

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
6 April 2006 (06.04.2006)

PCT

(10) International Publication Number
WO 2006/036994 A2

(51) International Patent Classification:

A61K 31/53 (2006.01) A61K 31/496 (2006.01)
 A61K 31/501 (2006.01) C07D 209/42 (2006.01)
 A61K 31/497 (2006.01) C07D 417/02 (2006.01)
 A61K 31/541 (2006.01) C07D 413/02 (2006.01)
 A61K 31/5377 (2006.01)

(21) International Application Number:

PCT/US2005/034702

(22) International Filing Date:

27 September 2005 (27.09.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

10/951,542 27 September 2004 (27.09.2004) US
 11/028,896 3 January 2005 (03.01.2005) US
 11/183,626 18 July 2005 (18.07.2005) US

(71) Applicant (for all designated States except US): **MICRO-BIA, INC.** [US/US]; 320 Bent Street, Cambridge, MA 02141 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BARTOLINI, Wilmin** [US/US]; 3 Cottage Lane, Amesbury, MA 01913 (US). **CALI, Brian, M.** [US/US]; 100 Hillside Avenue, Arlington, MA 02476 (US). **CHEN, Barbara** [US/US]; 41 Oakland Street, Watertown, MA 02472 (US). **CHEN, Yueh-Tyng** [US/US]; 219 Webster Street, Newton, MA 02465 (US). **CURRIE, Mark, G.** [US/US]; 18 Hall

Avenue, Sterling, MA 01564 (US). **MILNE, G., Todd** [US/US]; 169 Mason Terrace, Brookline, MA 02146 (US). **PEARSON, James, Philip** [US/US]; 14 Gray Street, Cambridge, MA 02138 (US). **TALLEY, John, Jeffrey** [US/US]; 96 North Street, Somerville, MA 02144 (US). **YANG, Jing Jing** [CN/US]; 104 Burroughs Road, Boxborough, MA 01719 (US). **ZIMMERMAN, Craig** [US/US]; 31 North Street, Topsfield, MA 01983 (US).

(74) Agents: **MEIKLEJOHN, Anita, L.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, MN 55440-1022 (US).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: MODULATORS OF CRTH2, COX-2 AND FAAH

Row	IUPAC name	COX-1 IC50 (μM)	COX-2 IC50 (μM)
1	[6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl]acetic acid	3.3	0.29
2	[1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	5	0.2
3	[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	3.22
4	[6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	6.3	0.32
5	[6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl]acetic acid	16.3	0.41
6	[6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl]acetic acid	27.3	0.23
7	[1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	35	0.2
8	[1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	85, 90	0.56 0.6
9	[1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10
10	[1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	2.8
11	[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	>100	8.9
12	[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid	>100	>22.2
13	[1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid	>100	>10%
14	[1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>10%
15	[1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100
16	[1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	>100
17	[1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	3.03
18	[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.4
19	[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	>100	0.8

(57) Abstract: Certain substituted indoles that are modulators of one or more of CRTH2, COX-2 AND FAAH are described. The compounds are useful for treatment of pain and/or inflammation as well as other disorders.



Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Attorney Docket No. 14184-055WO1

MODULATORS OF CRTH2, COX-2 AND FAAH**BACKGROUND**Cox Inhibitors

Cyclooxygenases play an essential role in prostaglandin synthesis. Cyclooxygenase-1 (COX-1) is constitutive and relatively long-lived, whereas cyclooxygenase-2 (COX-2) is inducible and relatively short-lived. COX-1 is thought to be responsible for maintaining basal level prostaglandin production, which is important for normal gastrointestinal and renal function. COX-2 is induced by certain inflammatory agents, hormones, growth factors, cytokines, and other agents. COX-2 plays a significant role in prostaglandin synthesis within inflammatory cells such as macrophages and monocytes, and prostaglandin production associated with COX-2 induction can have a deleterious effect on the body. Thus, to reduce unwanted inflammation and to treat certain other conditions, it can be desirable to inhibit COX-2 activity without significantly inhibiting COX-1 activity.

Many non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2. These non-selective inhibitors include indomethacin (Shen et al. 1963 *J Am Chem Soc* 85:4881; 4-chlorobenzoyl-5-methoxy-2-methyl-1*H*-indole-3-acetic acid). It is desirable to identify NSAIDs that inhibit COX-2 activity, but do not significantly inhibit COX-1 activity at physiological levels where COX-2 activity is significantly inhibited. Such selective inhibitors are expected to have the desirable anti-inflammatory, anti-pyretic, and analgesic properties associated with NSAIDs, while having reduced or no gastrointestinal or renal toxicity.

Subsequent to indomethacin administration, the unchanged parent compound, the desmethyl metabolite (O-desmethyindomethacin), the desbenzoyl metabolite (N-deschlorobenzoylindomethacin) and the desmethy-desbenzoyl metabolite (O-desmethy-N-deschlorobenzoylindomethacin) can be found in plasma in significant amounts (Strachman et al. 1964 *J Am Chem Soc* 86:799; Helleberg 1981 *Clin Pharmacokinet* 6:245), all in an unconjugated form (Harman et al. 1964 *J Pharmacol Exp Therap* 143:215). It has been reported that all three metabolites are devoid of

Attorney Docket No. 14184-055WO1

anti-inflammatory activity (Helleberg 1981 *Clin Pharmacokine.* 6:245 and Duggan et al. 1972 *Pharmacol and Exp Ther* 181:562), although it has also been reported that the desmethyl metabolite has some ability to inhibit prostaglandin synthesis (Shen et al. 1977 *Adv Drug Res* 12:90).

- 5 Indomethacin derivatives in which the benzoyl group has been replaced by a 4-bromobenzyl group or the acetic acid side chain has been extended exhibit greater selectivity for inhibition of COX-2 relative to COX-1 (Black et al. 1996 *Bioorganic & Medicinal Chem Lett* 6:725 and Black et al. 1997 *Advances in Experimental Medicine and Biology* 407:73). In addition, synthesis methodology has been demonstrated for
10 the preparation of indomethacin analogues, some of which do not inhibit cyclooxygenases (Touhey et al. 2002 *Eur J Cancer* 38:1661).

FAAH inhibitors

- Many fatty acid amides are known to have analgesic activity. A number of fatty acid amides (e.g., arachidonyl amino acids and anandamide) induce analgesia in animal
15 models of pain (see, for example, Walker et al. 1999 *Proc Natl Acad Sci* 96:12198, Friderie and Mechoulam 1993 *Eur J Pharmacol* 231:313). Anandamide and certain other fatty acid amides (e.g., N-palmitoyl ethanolamine, N-oleoyl ethanolamide, oleamide, 2-arachidonoylglycerol) are cleaved and inactivated by fatty acid amide hydrolase (FAAH) (Deutsch et al. 2003 *Prostaglandins Leukot Essent Fatty Acids*
20 66:201; and Cravatt and Lichtman 2003 *Current Opinion in Chemical Biology* 7:469).

- Inhibition of FAAH is expected to lead to an increase in the level of anandamide and other fatty acid amides. This increase in fatty acid amides may lead to an increase in the nociceptive threshold. Thus, inhibitors of FAAH are useful in the treatment of
25 pain. Such inhibitors might also be useful in the treatment of other disorders that can be treated using fatty acid amides or modulators of cannabinoid receptors (e.g., anxiety, eating disorders, and cardiovascular disorders). NPAA (N-palmitoylethanolamine acid anhydrolase) is a hydrolase that breaks down N-palmitoyl ethanolamine (PEA), a fatty acid amide. PEA is a naturally occurring substrate for

Attorney Docket No. 14184-055WO1

the cannabinoid receptor 2 (CB2 receptor). Inhibition of NPAA may lead to increased PEA levels. Accordingly, NPAA inhibitors may be useful in the treatment of inflammation and nociceptive pain control.

- 5 In addition, there is evidence (see, e.g., Weber et al. 2004 *J. Lipid Res.* 45:757) that when FAAH activity is reduced or absent, one of its substrates, anandamide, acts as a substrate for COX-2 that can be converted to a prostamide. Thus, certain prostamides may be elevated in the presence of an FAAH inhibitor. Given that certain prostamides are associated with reduced intraocular pressure and ocular
10 hypotensivity, FAAH inhibitors may be useful agents for treating glaucoma.

CRTH2 modulators

- CRTH2 is a $G_{\alpha i}$ protein-coupled receptor that is thought to be involved in both mediating PGD_2 -induced chemoattraction and in activation of specific cell types
15 involved in allergic inflammation. It has been reported that CRTH2 is expressed by Th2 cells, eosinophils and basophils, but not by Th1 cells, B cells or NK cells. (Nagata et al. 1999 *FEBS Letters* 459:195-199).

- PGD_2 is produced by allergen-activated mast cells and has been implicated in various allergic diseases as a pro-inflammatory mediator, although it may have anti-
20 inflammatory activity in certain situations (Ajuebor et al. 2000 *Am J Physiol Gastrointest Liver Physiol* 279:G238-44). CRTH2 receptor is a high affinity receptor for PGD_2 as is DP, a $G_{\alpha s}$ protein-coupled receptor.

- CRTH2 agonists activate eosinophils, basophils and Th2 cells *in vitro*, resulting in induction of actin polymerization, calcium influx, CD11b expression and chemotaxis
25 (Monneret et al 2003 *J Pharmacol Exp Ther* 304:349-55). An *in vivo* study has demonstrated that injection of a CRTH2 agonist can elicit transient recruitment of eosinophils from bone marrow into the blood (Shichijo 2003 *J Pharmacol Exp Ther* 307:518-525). A genetic study of African American and Chinese cohorts found that polymorphisms in CRTH2 were tightly associated with asthma susceptibility (Huang

Attorney Docket No. 14184-055WO1

et al. 2004 *Hum Mol. Genet* 2791). It has been suggested that modulators of CRTH2 may be useful in the prevention and/or treatment of allergic asthma and other allergic disorders (US 2002/0022218 A1 and WO 03/066047). Recruitment and/or activation of eosinophils, basophils and Th2 cells is a prominent feature of the changes that occur in the asthmatic lung. Similar activation of these cell types, or subsets thereof, are believed to play an important role in the etiology of other diseases, including eosinophilic esophagitis and atopic dermatitis (Arora and Yamakazi 2004 *Clin Gastroenterol Hepatol* 2:523-30; Kiehl et al. 2001 *Br J Dermatol* 145:720-729). This fact, combined with the fact that CRTH2 mediates PGD₂-induced chemotaxis, suggests that compounds that alter chemotaxis by modulating CRTH2 activity could be useful in controlling chronic airway inflammation, allergic rhinitis, atopic dermatitis, chronic obstructive pulmonary disease (COPD), or eosinophilic esophagitis. Thus, CRTH2 antagonists that reduce the ability of Th2 cells and eosinophils to respond to mast-cell derived PGD₂ could be useful for preventing and/or treating allergic disorders such as allergic rhinitis and asthma. Allergic rhinitis is classified as either seasonal (SAR) or perennial (PAR) depending upon the type of trigger and duration of symptoms. SAR symptoms occur in the spring, summer and/or early fall and can be triggered by outdoor allergens such as airborne tree, grass and weed pollens while PAR is usually persistent and chronic with symptoms occurring year-round and is commonly associated with indoor allergens such as dust mites, animal dander and/or mold spores. Symptoms of allergic rhinitis may include runny nose, nasal itching, sneezing, watery eyes and nasal congestion. CRTH2 modulators may be useful for treating SAR and/or PAR.

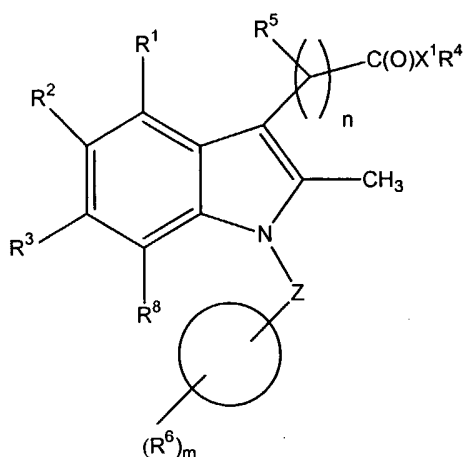
It is often found that agonists induce desensitization of the cell system by promoting internalization and down regulation of the cell surface receptor (*Int Immunol* 15:29-38, 2003). Therefore, certain CRTH2 agonists may be therapeutically useful because they can cause the desensitization of PGD₂-responsive cells. It has been shown that certain CRTH2 agonists can induce desensitization of PGD₂-responsive cells to subsequent activation by a CRTH2 agonist (see, e.g., Yoshimura-Uchiyama et al. 2004 *Clin Exp Allergy* 34:1283-1290). Importantly, CRTH2 agonists may also cause cross-desensitization. Cross-desensitization, which can occur in many cell-signaling

Attorney Docket No. 14184-055WO1

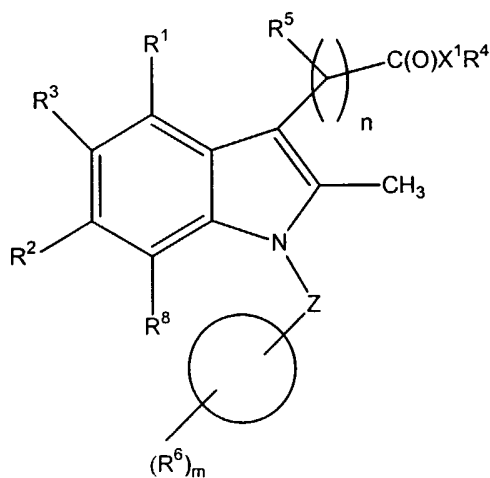
systems, refers to a phenomena whereby an agonist for one receptor can reduce or eliminate sensitivity of a cell type to an unrelated agonist/receptor signaling system. For example, it is known that treatment with the CRTH2 agonist indomethacin reduces expression of CCR3, the receptor for the chemoattractant, eotaxin (Stubbs et al. 2002, *J Biol Chem* 277:26012-26020).

SUMMARY

The invention features compounds having **Formula I** or **Formula II** or **Formula III**, pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising such compounds and methods for treating a patient by administering such pharmaceutical compositions alone or in combination with one or more other therapeutic agents. The invention features a compound having the formula:



or



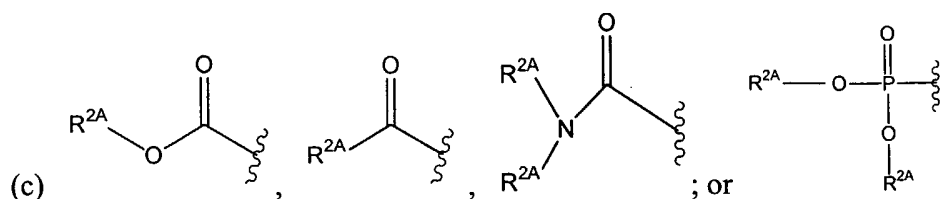
Attorney Docket No. 14184-055WO1

Formula I**Formula II**

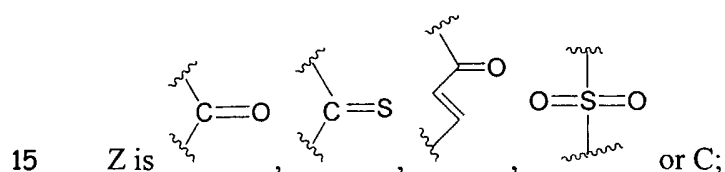
wherein:

 R^1 is: H or a halogen; R^2 is: H, a halogen, or $R^{2B}O$ - wherein5 R^{2B} is selected from:

(a) H;

(b) C_1 to C_6 alkyl or a C_2 to C_6 alkenyl that is optionally independently substituted with one or more halogen; -OH, -NH₂, -C(O)OH;

10 wherein each R^{2A} is independently: H, a C_1 to C_6 alkyl, a C_2 to C_6 alkenyl, a C_2 to C_6 alkynyl, a C_6 to C_{10} aryl, a C_3 to C_{10} cycloalkyl, or a C_7 to C_{20} arylalkyl optionally independently substituted with one or more halogen, -OH, -C(O)OH, or -NH₂;

 R^3 is H or a halogen; X^1 is -O-, -S-, -N(H)- or -N(H)S(O₂)-;

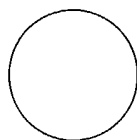
R^4 is H; a C_1 to C_{10} alkyl; a C_2 - C_{10} alkenyl; a C_2 - C_{10} alkynyl; a C_3 to C_8 cycloalkyl; a C_1 to C_6 hydroxyalkyl; a hydroxyl substituted C_6 to C_8 aryl; a primary, secondary or tertiary C_1 to C_6 alkylamino; primary, secondary or tertiary C_6 to C_8 arylamino; C_2 to C_6 alkylcarboxylic acid; a C_1 to C_6 alkylester; a C_6 to C_8 aryl; a C_6 to C_8

Attorney Docket No. 14184-055WO1

arylcarboxylic acid; a C₆ to C₈ arylester; a C₆ to C₈ aryl substituted C₁ to C₆ alkyl; a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, S(O)₂, N, and S(O); an alkyl-substituted or aryl-substituted a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, S(O)₂, N, and S(O), wherein one or more H within R⁴ can be substituted by a halogen, -OH, or -C(O)OH, -NH₂;

n is 1, 2, 3, 4 or 5;

Each R⁵ is independently: H, an optionally substituted C₁-C₄ alkyl, wherein the substituents are independently selected from a halogen and -OH;



10 represents a C₃-C₆ saturated carbocycle, a C₆ aryl, C₃-C₆ non-saturated, non-aromatic carbocycle, a 6-membered heteroaryl having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, S(O)₂, N, S(O) and N(R⁷) or a 3- to 7-membered saturated or non-saturated heterocycle having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, S(O)₂, N, S(O) and N(R⁷);

15 each R⁶ is independently H, a halogen, -CH₃, -CN, -OCH₃, -SCH₃, -SCF₃, -OCH₂CF₃ or -CH₂CH₃ wherein one or more H can be replaced by a halogen;

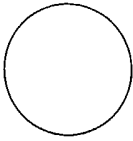
m = 1, 2, 3, 4, or 5;

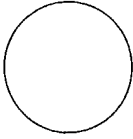
R⁷ is: H, a halogen, -CH₃, -CN, -OCH₃, -SCH₃, or -CH₂CH₃ wherein one or more H can be replaced by a halogen; and

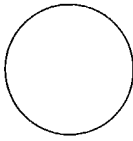
20 R⁸ is: H, a halogen or -CH₃, wherein one or more H can be replaced by a halogen.

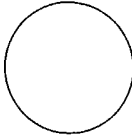
In certain embodiments, each R⁶ is independently a halogen, -CH₃, -CN, -OCH₃, -SCH₃, -SCF₃, -OCH₂CF₃ or -CH₂CH₃ wherein one or more H can be replaced by a halogen

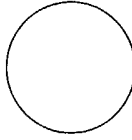
Attorney Docket No. 14184-055WO1

In certain embodiments,  represents a C₃-C₆ saturated carbocycle (e.g., cyclohexyl, cyclopentyl, cyclobutyl or cyclopropyl). In certain embodiments 4

 represents a C₃-C₆ non-saturated, non-aromatic carbocycle (e.g., cyclohexenyl, a cyclopentenyl, or cyclobutenyl). In certain embodiments

5  represents a 6-membered heteroaryl (e.g., pyrazine, pyridazine, triazine,

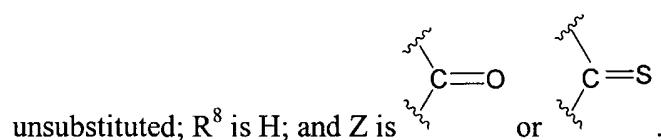
tetrazine, or pentazine). In certain embodiments  represents a 3- to 7-membered saturated heterocycle (e.g., piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, tetrahydropyran,

10  represents a 3- to 7-membered non-saturated heterocycle (e.g., thiophene, furan, pyrrole, thiazole, oxazole, imidazole, isothiazole, isoxazole, pyrazole, triazole, tetrazole, oxadiazole, oxatriazole or thiadiazole)

15 In various embodiments: R¹ is H; R¹ is a halogen (e.g., F or Cl); R² is R^{2B}O- and R^{2B} is a substituted C₁ to C₆ alkyl or a substituted C₂ to C₆ alkenyl; R² is R^{2B}O- and R^{2B} is not substituted; R² is R^{2B}O- and R^{2B} is a C₁ to C₆ alkyl or a C₂ to C₆ alkenyl optionally substituted with one or more halogen; R² is R^{2B}O- and R^{2B} is a C₁ to C₃ alkyl or alkenyl; R² is R^{2B}O- and R^{2B} is a C₁ to C₃ alkyl; R² is R^{2B}O- and R^{2B} is a methyl group or an ethyl group; R² is substituted only with a halogen; R² is H; R³ is a
20 halogen; R³ is Cl; R³ is F; X¹ is -O-; X¹ is -S-; X¹ is -N(H)-; X¹ is -N(H)S(O)₂-; R⁶ is selected from: -CH₃, -CF₂H, -CH₂F, -CF₃, -CN, -OCF₂H, -OCH₃, -SCF₃, -SCF₂H, -

Attorney Docket No. 14184-055WO1

SCH₃, -CH₂CH₃ and -OCF₃; R⁷ is selected from: -CH₃, -CF₂H, -CH₂F, -CF₃, -CN, -OCF₂H, -OCH₃, -SCF₃, -SCF₂H, -SCH₃, -CH₂CH₃ and -OCF₃; n is 1 or 2; m is 1 or 2; m is 1 or 2 and other than H; R⁵ is H; R⁵ is a methyl group or an ethyl group; X¹ is O and R⁴ is H; X¹ is O and R⁴ is other than H; R⁴ is an optionally independently substituted C₃ to C₁₀ branched alkyl; R⁴ is a C₁ to C₁₀ alkyl; R⁴ is a C₄ to C₈ cycloalkyl; R⁴ is a C₁ to C₆ hydroxy substituted alkyl; R⁴ is a hydroxyl substituted C₄ to C₈ aryl; R⁴ is a primary, secondary or tertiary C₁ to C₆ alkylamino; R⁴ is a primary, secondary or tertiary C₄ to C₈ arylamino; R⁴ is a C₂ to C₆ alkylcarboxylic acid; R⁴ is a C₁ to C₆ alkylester; R⁴ is a branched C₁ to C₆ alkylester; R⁴ is a C₄ to C₈ aryl; R⁴ is a C₄ to C₈ arylcarboxylic acid; R⁴ is a C₄ to C₈ arylester; R⁴ is C₄ to C₈ aryl substituted C₁ to C₆ alkyl; R⁴ is a C₄ to C₈ heterocyclic alkyl or aryl; R⁴ is an alkyl-substituted or aryl-substituted C₄ to C₈ heterocyclic alkyl or aryl; R⁴ is substituted; R⁴ is



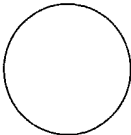
The invention also features: a pharmaceutical composition comprising any of the forgoing compounds and a pharmaceutically acceptable carrier; a method for treating inflammation comprising administering a composition comprising any of the forgoing compounds; a method for treating anxiety comprising administering any of the forgoing compounds; a method for treating a sleep disorder comprising administering any of the forgoing compounds; and a method for treating a respiratory disorder (e.g., asthma) comprising administering any of the forgoing compounds.

The invention features a method for inhibiting COX-2 activity in a patient, the method comprising administering any of the forgoing compounds (e.g., a compound of Formula I wherein X¹ is O and R⁴ is H).

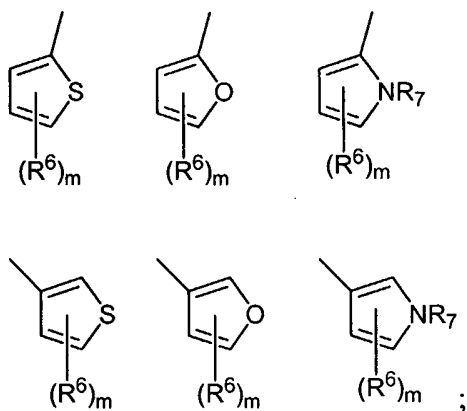
The invention features a method for inhibiting FAAH activity in a patient, the method comprising administering any of the forgoing compounds (e.g., a compound of Formula I wherein X¹ is O and R⁴ is other than H).

Attorney Docket No. 14184-055WO1

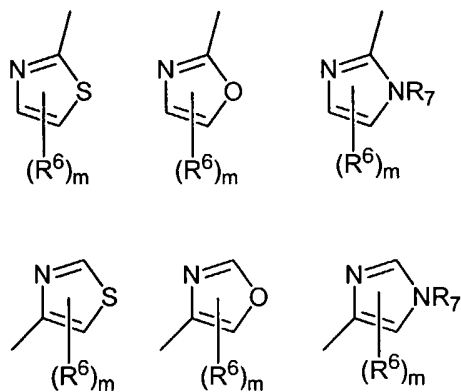
The invention features a method for modulating CRTH2 activity on a patient, the method comprising administering any of the forgoing compounds.

In the case of , suitable 5-membered ring heterocycles include:

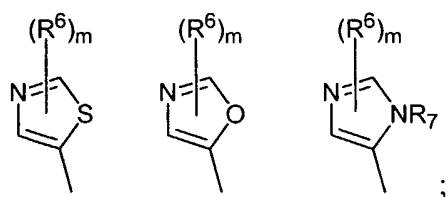
5 thiophene, furan, and pyrrole



10 thiazole, oxazole, and imidazole

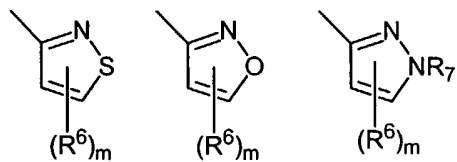


15

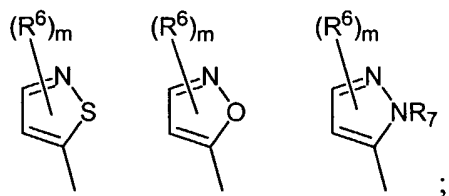
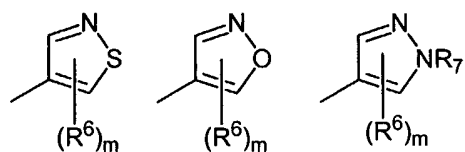


Attorney Docket No. 14184-055WO1

isothiazole, isoxazole, and pyrazole

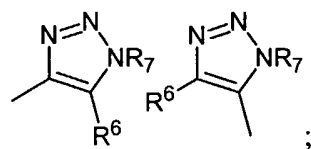


5

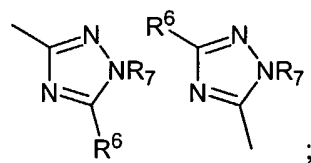


10

1,2,3-triazole

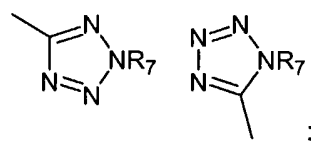


1,2,4-triazole



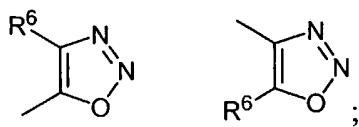
15

tetrazole

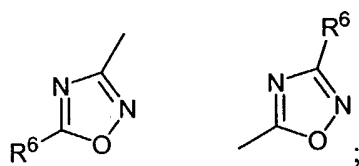


Attorney Docket No. 14184-055WO1

1,2,3-oxadiazole

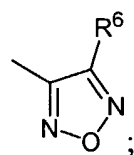


5 1,2,4-oxadiazole



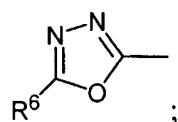
1,2,5-oxadiazole

10



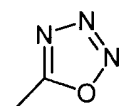
1,3,4-oxadiazole

15



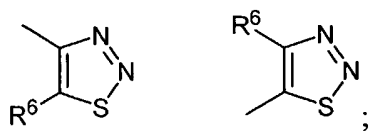
1,2,3,4-oxatriazole

20

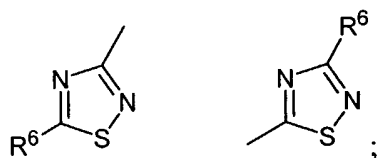


1,2,3-thiadiazole

Attorney Docket No. 14184-055WO1

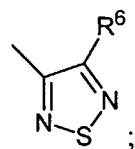


1,2,4-thiadiazole



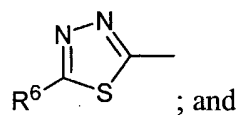
5

1,2,5-thiadiazole



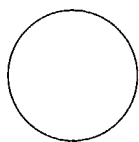
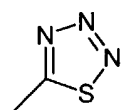
10

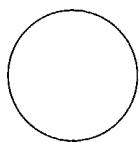
1,3,4-thiadiazole



1,2,3,4-thiadiazole

15

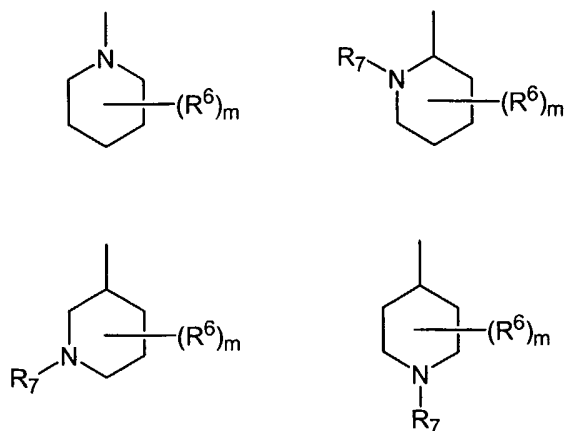


In the case of , suitable 5 and 6-membered ring saturated heterocycles include:

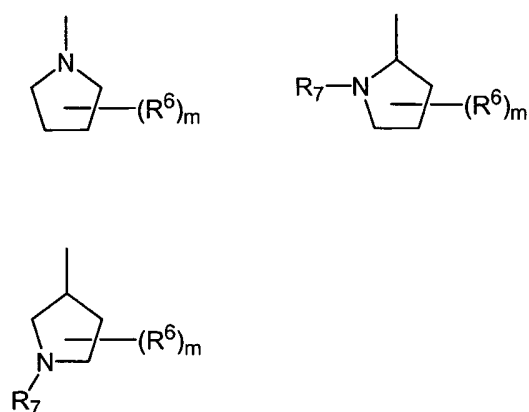
20

Piperidine and substituted piperidine

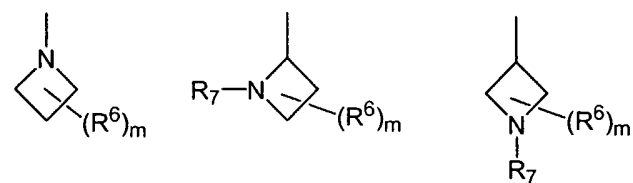
Attorney Docket No. 14184-055WO1



5 Pyrrolidine and substituted pyrrolidine

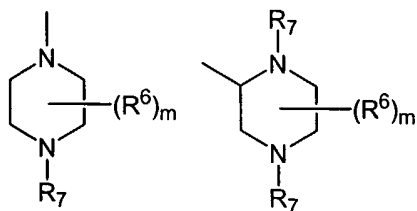


10 Azetidine and substituted azetidine

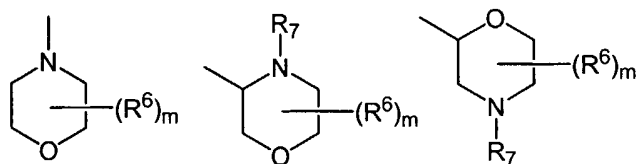


15 Piperazine and substituted piperazine

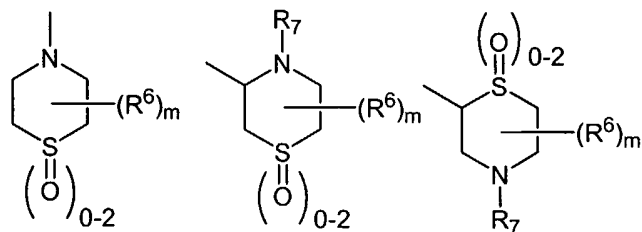
Attorney Docket No. 14184-055WO1



5 Morpholine and substituted morpholine

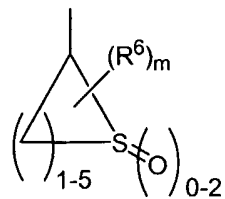


10 Thiomorpholine and substituted thiomorpholine and their sulfoxide and sulfone derivatives



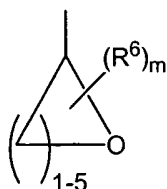
15

Thioethers, substituted thioethers, their sulfoxides and sulfones



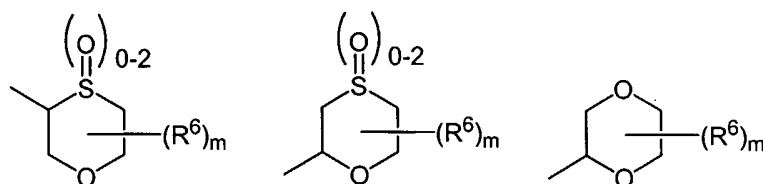
Attorney Docket No. 14184-055WO1

Ethers and substituted ethers



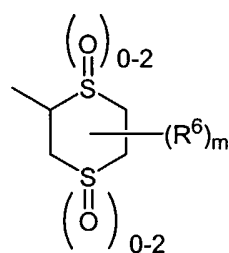
5

1,4-Thioether-ethers and 1,4-dioxane derivatives



10

1,4-bis-Thioethers, their sulfoxides and sulfones

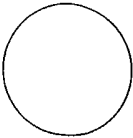


15

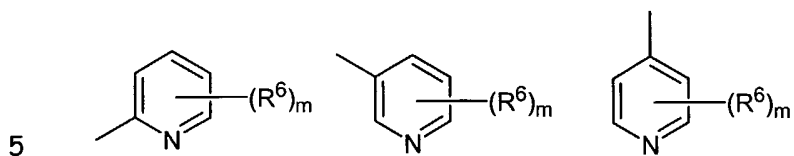
Also included are tetrahydrofuran, dihydrofuran, tetrahydrothiophene, dihydrothiophene, piperidine, dihydropyrrole, 1,3-dithiolane, 1,2-dithiolane, isoxazolidine, isothiazolidine, pyrazolidine, tetrahydro-2H-pyran, tetrahydro-2H-thiopyran, 3,6-dihydro-2H-thiopyran, 3,4-dihydro-2H-thiopyran, piperidine, 1,2,3,6-tetrahydropyridine, 1,2,3,4-tetrahydropyridine, morpholine, thiomorpholine, piperazine, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, and the like.

20

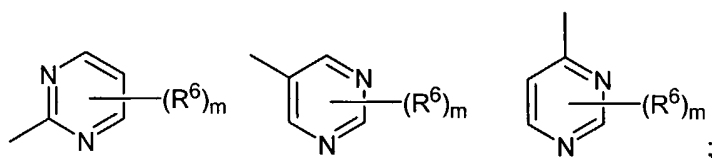
Attorney Docket No. 14184-055WO1

In the case of , suitable 6-membered ring heteroaryls include:

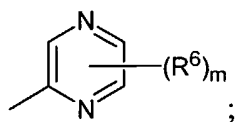
pyridine



pyrimidine

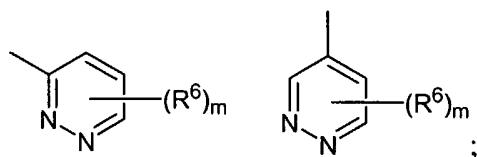


10 pyrazine



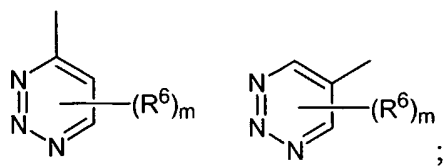
pyridazine

15

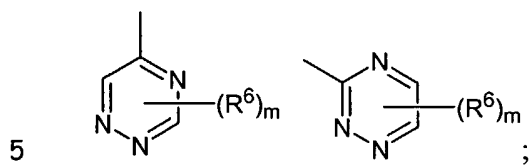


1,2,3-triazine

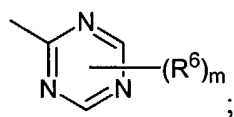
Attorney Docket No. 14184-055WO1



1,2,4-triazine

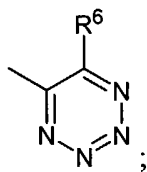


1,3,5-triazine



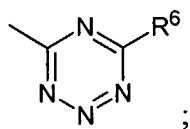
10

1,2,3,4-tetrazine



15

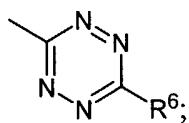
1,2,3,5-tetrazine



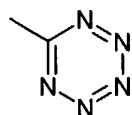
1,2,4,5-tetrazine

20

Attorney Docket No. 14184-055WO1



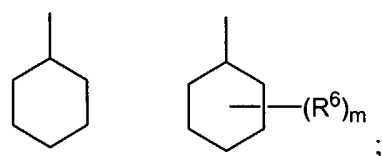
pentazine



5

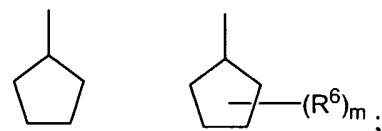
Suitable carbocycles include:

cyclohexyl and substituted cyclohexyl



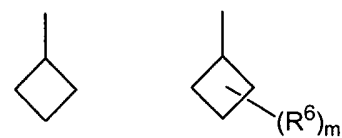
10

cyclopentyl and substituted cyclopentyl

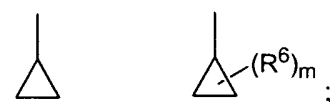


15

cyclobutyl and substituted cyclobutyl

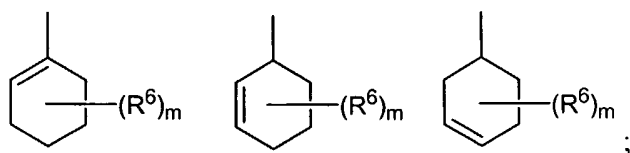


20 cyclopropyl and substituted cyclopropyl



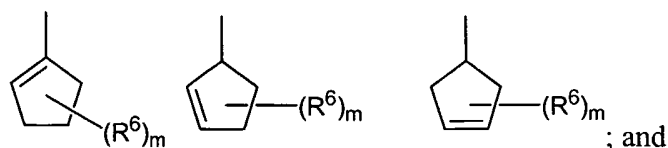
Attorney Docket No. 14184-055WO1

cyclohexenyl and substituted cyclohexenyl

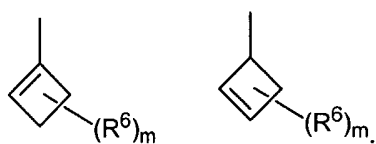


5

cyclopentenyl and substituted cyclopentenyl



10 cyclobutenyl and substituted cyclobutenyl



15 The compounds of the invention inhibit COX-2 or fatty acid amide hydrolase (FAAH) or both COX-2 and FAAH. Some of the compounds of the invention are modulators of CRTH2 activity, e.g., they are either agonists or antagonists of CRTH2. Some compounds may be partial agonists or inverse agonists (inhibitors of basal level activity) of CRTH2. In addition, certain of the compounds of the invention inhibit NPAA.

20 The compounds of the invention are useful in treating pain and inflammation as well as other disorders such as allergic rhinitis, asthma, atopic dermatitis, eosinophilic esophagitis, and other disorders associated with allergic inflammation.

Some of the compounds of the invention that inhibit COX-2 activity are relatively selective for COX-2 relative to COX-1. Thus, certain COX-2 inhibitors of the

Attorney Docket No. 14184-055WO1

invention do not substantially inhibit COX-1 at concentrations at which COX-2 is substantially inhibited. Some of the compounds of the invention that are relatively selective for FAAH do not substantially inhibit COX-2 at concentrations at which FAAH is substantially inhibited. Some compounds are relatively selective for COX-2 as compared to FAAH. These compounds do not substantially inhibit FAAH at concentrations at which COX-2 is substantially inhibited. Other compounds inhibit both COX-2 and FAAH at similar concentrations. These compounds are not particularly selective for COX-2 versus FAAH. Certain compounds of the invention are modulators of CRTH2. Of these compounds, some may also be inhibitors of COX-2 and/or FAAH.

Certain compounds having **Formula I** or **Formula II** are COX-2 inhibitors that are selective for inhibition of COX-2 over COX-1 and do not substantially inhibit FAAH. In these compounds R^4 is most often H and X^1 is O.

Certain compounds having **Formula I** or **Formula II** are FAAH inhibitors and are selective for inhibition of FAAH over both COX-2 and COX-1. In these compounds R^4 is most often other than H. In such compounds R^8 is often a halogen or $-CH_3$ substituted with one or more F.

Certain compounds having **Formula I** or **Formula II** are selective COX-2 inhibitors. In these compounds R^8 is often H. In some embodiments of **Formula I** or **Formula II**, R^2 is H. Many such compounds are CRTH2 antagonists. Some are not CRTH2 antagonists

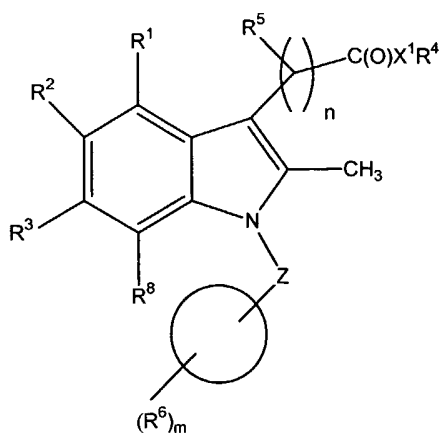
In some embodiments of **Formula I** or **Formula II**, R^2 is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen. Many such compounds are CRTH2 agonists. Some are not CRTH2 agonists.

Certain compounds having **Formula I** or **Formula II** are CRTH2 agonists; in some embodiments the compound has an EC_{50} for CRTH2 that is less than 20 μM ; the compound has an EC_{50} for CRTH2 that is less than 10 μM ; and the compound has an EC_{50} for CRTH2 that is less than 5 μM .

Attorney Docket No. 14184-055WO1

Certain compounds having **Formula I** or **Formula II** are CRTH2 antagonists; in some embodiments the compound has an IC_{50} for CRTH2 that is less than 20 μM ; the compound has an IC_{50} for CRTH2 that is less than 10 μM ; and the compound has an IC_{50} for CRTH2 that is less than 5 μM .

5 Certain CRTH2 antagonists have the formula:



10

Formula I

15 wherein:

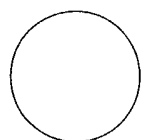
R^1 is H or F;

R^2 is a halogen (e.g., F) or $R^{2B}O-$ wherein R^{2B} is H or CH_3 ;

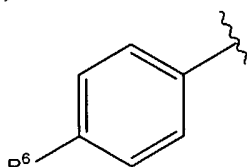
20

R^3 is H, F, or Cl;

Z is or C;



is

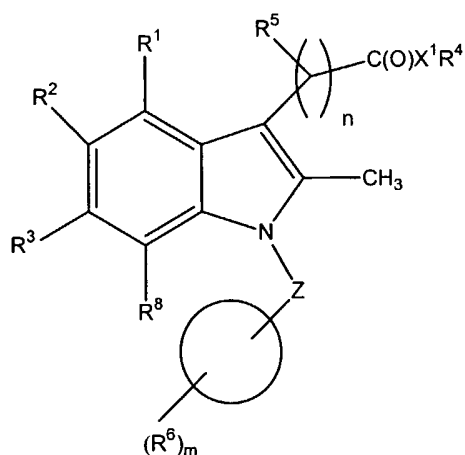


wherein R^6 is $-SCF_3$;

Attorney Docket No. 14184-055WO1

 R^8 is H; R^5 is H; n is 1; X^1 is O; and R^4 is H.

5 CRTH2 antagonists also include compounds having the formula:



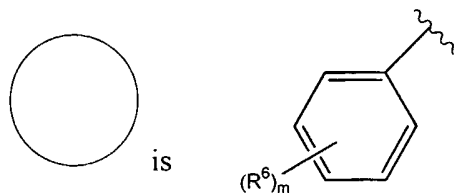
10

Formula I

wherein:

15 R^1 is H or F; R^2 is a halogen (e.g., F) or $R^{2B}O^-$ wherein R^{2B} is H or CH_3 ; R^3 is H, F, or Cl;

20 Z is ;



wherein m is 1 and R^6 at the 3 position is F or Cl or m is 2 and R^6 at the 3 and 4 positions are both Cl or F;

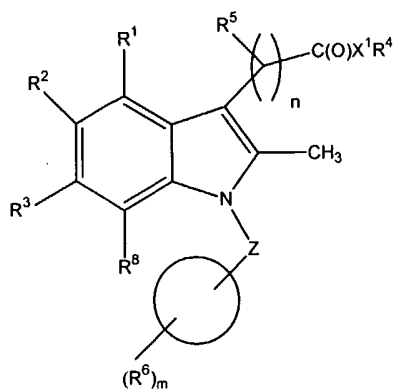
 R^8 is H;

Attorney Docket No. 14184-055WO1

 R^5 is H; n is 1; X^1 is O and R^4 is H.

CRTH2 antagonists also include compounds having the formula:

5



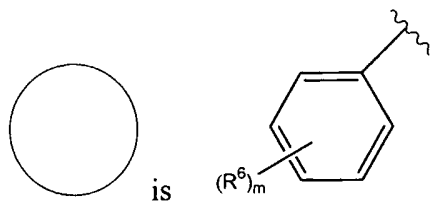
10

Formula I

wherein:

15 R^1 is H or F; R^2 is a halogen (e.g., F) or $R^{2B}O-$ wherein R^{2B} is H or CH_3 ; R^3 is H, F, or Cl;

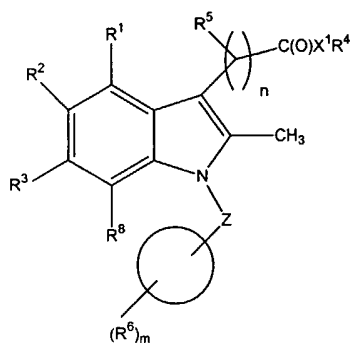
Z is C;

wherein m is 1, 2, 3, 4, or 5 and R^6 is F, Cl, Br, or $-OCF_3$;25 R^8 is H; R^5 is H; n is 1; and X^1 is O and R^4 is H.

Attorney Docket No. 14184-055WO1

In other embodiments: m is 2 and R⁶ at the 3 and 4 positions are both F or Cl; m is 1 and R⁶ is Cl at the 3 position; m is 1 and R⁶ is Br at the 4 position; m is 1 and R⁶ is F at the 4 position; and m is 1 and R⁶ is -OCF₃ at the 4 position.

5 CRTH2 antagonists also include compounds having the formula:



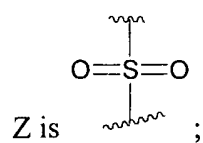
Formula I

wherein:

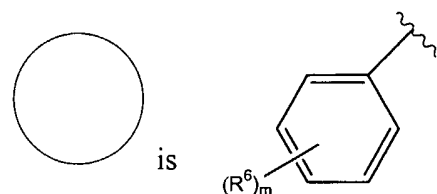
R¹ is H or F;

R² is a halogen (e.g., F) or R^{2B}O- wherein R^{2B} is H or CH₃;

R³ is H, F, or Cl;



Z is ;



Attorney Docket No. 14184-055WO1

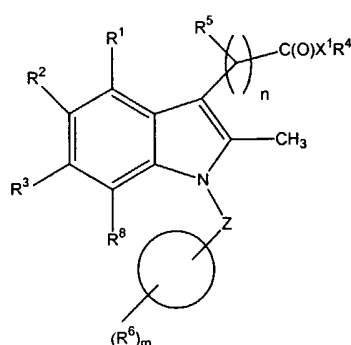
wherein m is 1 and R⁶ at the 3 or 4 position is Cl or F, or m is 2 and R⁶ at both the 3 and 4 positions is Cl or F, or m is 1 and R⁶ at the 4 position in -SCF₃, -OCH₃ or -OCF₃;

R⁸ is H;

5 R⁵ is H; n is 1;

X¹ is O; and R⁴ is H.

10 CRTH2 agonists include compounds having the formula:



Formula I

15 wherein:

R¹ is H or F;

R² is a halogen (e.g., F) or R^{2B}O- wherein R^{2B} is H or CH₃;

R³ is H, F, or Cl;

20 Z is ;

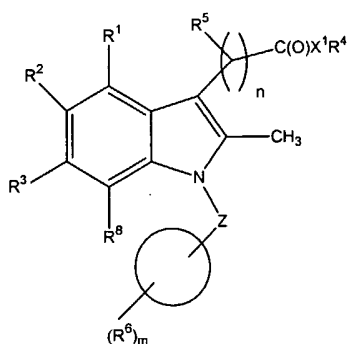
25 is

Attorney Docket No. 14184-055WO1

wherein R^6 is H, F, Cl, $-OCH_3$, $-CH_3$; R^8 is H; R^5 is H; n is 1 X^1 is O; and R^4 is H.

5

COX-2 antagonists include compounds having the formula:

10 **Formula I**

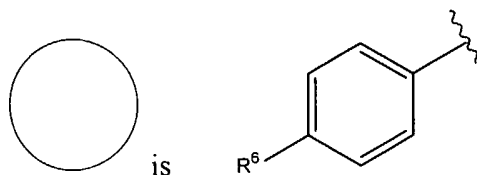
wherein:

 R^1 is H or F; R^2 is a halogen (e.g., F) or $R^{2B}O-$ wherein R^{2B} is H or CH_3 ; R^3 is H, F, or

15

Cl; Z is ;

20



25

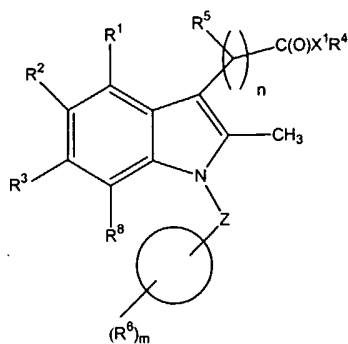
wherein R^6 is H, F, Cl, $-OCH_3$, $-CH_3$; R^8 is H,

Attorney Docket No. 14184-055WO1

 R^5 is H; n is 1; X^1 is O; and R^4 is H.

FAAH antagonists also include compounds having the formula:

5

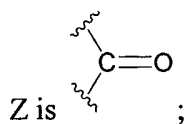


10

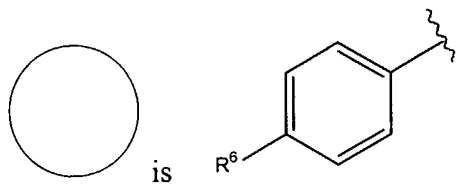
Formula I

wherein:

15 R^1 is H or F; R^2 is a halogen (e.g., F) or $R^{2B}O-$ wherein R^{2B} is H or CH_3 ; R^3 is H, F, or Cl;



20



30 wherein R^6 is H, F, Cl, $-OCH_3$, $-CH_3$;

 R^8 is H,

Attorney Docket No. 14184-055WO1

R⁵ is H; n is 1

X¹ is O or N(H); and R⁴ is a C₁ to C₈ alkyl optionally independently substituted with one or more -OH or -CO₂H.

The invention also features compositions comprising a compound having **Formula I**
5 or **Formula II**, wherein the composition contains no more than 0.0001%, 0.001%, 0.01%, 0.1%, 0.3%, 0.5%, 0.9%, 1.9%, 5.0%, or 10% by weight other compounds.

The invention also features a method of treating a disorder associated with unwanted
COX-2 activity or unwanted FAAH activity or both unwanted COX-2 activity and
10 unwanted FAAH activity. In some embodiments of the method: the disorder is an inflammatory disorder; and R²O- is a hydroxy group or a group that is metabolized to a hydroxy group, i.e., R²O- is a prodrug of a hydroxy group. In certain embodiments R²O- is an alkoxy group that is not rapidly metabolically converted to a hydroxy group or is not significantly metabolically converted to a hydroxy group. In other
15 embodiments, the invention includes a therapeutic method comprising administering a compound of the invention together with an agent for the treatment of inflammation, pain or fever, e.g., a NSAID.

The invention also features a compound having **Formula I** or **Formula II** wherein
20 the prodrug of a hydroxy moiety is selected from: (a) an ester having a C₁ to C₆ branched or straight chain alkyl group, (b) phosphate ester having C₁ to C₆ branched or straight chain alkyl groups, (c) a carbamate having C₁ to C₆ branched or straight chain alkyl groups, and (d) a carbonate group having a C₁ to C₆ branched or straight chain alkyl group.

25 The invention also features: a method for treating pain comprising administering a compound of the invention or a pharmaceutical composition comprising the compound; a method for treating inflammation comprising administering a compound of the invention or a pharmaceutical composition comprising the compound; a method for treating both pain and/or inflammation comprising administering a compound of
30 the invention or a pharmaceutical composition comprising the compound; a method

Attorney Docket No. 14184-055WO1

for treating anxiety comprising administering a compound of the invention or a pharmaceutical composition comprising the compound; and a method for treating a sleep disorder comprising administering a compound of the invention or a pharmaceutical composition comprising the compound.

5

The invention includes: a method for lowering COX-2 activity in a patient by administering the compound or a pharmaceutical composition comprising the compound; a method for lowering FAAH activity in a patient by administering the compound or a pharmaceutical composition comprising the compound; and a method
10 for lowering both FAAH activity and COX-2 activity in a patient by administering the compound or a pharmaceutical composition comprising the compound. In various embodiments administration of the compound or a composition comprising the compound does not lower COX-1 activity by more than 5% at a dosage that decreases COX-2 activity by at least 25%.

15

The invention also includes a method for treating a disorder characterized by imbalance of the Th1/Th2 ratio towards Th1, the method comprising administering a compound having **Formula I** or **Formula II**. In certain embodiments, the disorder is selected from: rheumatoid arthritis, Type I diabetes, psoriasis, gastritis, irritable bowel
20 disorder, multiple sclerosis, painless thyroiditis, lupus, and Crohn's Disease.

The invention also includes a method for treating a disorder characterized by imbalance of the Th1/Th2 ratio towards Th2, the method comprising administering a compound having **Formula I** or **Formula II**. In certain embodiments, the disorder is
25 selected from: asthma, atopic dermatitis, allergic rhinitis, allergy, and Grave's Disease.

The invention features a method for treating a disorder selected from asthma, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis, and other disorders associated
30 with allergic inflammation, the method comprising administering a compound having **Formula I** or **Formula II**. In some embodiments, the compound is a CRTH2

Attorney Docket No. 14184-055WO1

agonists. In certain embodiments, R^2 is $R^{2B}O^-$ and R^{2B} is H. In some embodiments, the method further comprises administering a second compound that is an anti-inflammatory agent.

5 The invention also features a method for treating a disorder characterized by undesirable activation of Th1 cells, the method comprising administering compound of **Formula I** or **Formula II**. The invention also features a method for treating a disorder characterized by undesirable activation of Th2 cells, the method comprising administering compound of **Formula I** or **Formula II**.

10

In some embodiments, the disorder is selected from: rheumatoid arthritis, Type I diabetes, psoriasis, gastritis, irritable bowel disorder, multiple sclerosis, painless thyroiditis, lupus, and Crohn's Disease. In other embodiments, the disorder is selected from: asthma, atopic dermatitis, allergic rhinitis, allergy, and Grave's

15

Disease. The invention also features a method for modulating CRTH2 activity in a patient, the method comprising administering a compound having **Formula I** or **Formula II** to a patient. In some embodiments, the compound is a CRTH2 agonist. In others it is an antagonist. In some embodiments, R^2 is $R^{2B}O^-$ and R^{2B} is H. In others R^{2B} is a C_1-C_3

20

alkyl, optionally independently substituted with one or more halogen.

The invention features a pharmaceutical composition comprising a compound of the invention (or a salt thereof, e.g., a TRIS or other salt thereof) and a pharmaceutically acceptable carrier.

25

The invention also features a method for treating a patient for a disorder characterized by an increased level of a cytokine produced by Th2 cells, e.g., a disorder characterized by increased (e.g., undesirably increased) IL-4, IL-10 and/or IL-13 in a patient, the method comprising administering to the patient a CRTH2 modulator

30

described herein.

Attorney Docket No. 14184-055WO1

The invention also features a method for treating a patient for a disorder characterized by an increased level of a cytokine produced by Th1, e.g., a disorder characterized by increased (e.g., undesirably increased) interferon- γ in a patient, the method comprising administering to the patient a CRTH2 modulator described herein.

5

The invention also features a method for decreasing the Th1 cell/Th2 cell ratio in a patient, the method comprising administering to the patient a CRTH2 modulator, e.g., a CRTH2 agonist.

10

The invention also features a method for increasing the Th1 cell/Th2 cell ratio in a patient, the method comprising administering to the patient a CRTH2 modulator, e.g., a CRTH2 antagonist.

15

In some embodiments the CRTH2 modulators are also inhibitors of cyclooxygenase-1 (COX-1) and/or cyclooxygenase-2 (COX-2). Among compounds that inhibit COX-2 and/or COX-1, those that are selective for COX-2 are preferred. Thus, in some embodiments: the compound exhibits an IC_{50} for COX-2 that is at least 20,000; 10,000; 1,000; 500; 100; 50; or 25 μ M, and have an IC_{50} for COX-1 that is even greater than the IC_{50} for COX-2. In some embodiments the COX-1 IC_{50} for a compound is at least 2, 5, 10, 25, 50, 100, 500, 1000 or more times the COX-1 IC_{50} for indomethacin in the same assay.

20

25

Some desirable compound having the structure of **Formula I** or **Formula II** have an EC_{50} for human CRTH2 that is less than 20, 10, 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μ M.

30

Some desirable compound having the structure of **Formula I** or **Formula II** have an IC_{50} for human CRTH2 that is less than 20, 10, 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μ M.

Attorney Docket No. 14184-055WO1

In some embodiments of the invention, the composition is administered to a patient that is not being treated with a non-selective NSAID, e.g., a patient that is not being treated with indomethacin.

5 In certain embodiments the compounds are administered in combination with a second compound useful for reducing inflammation or pain.

The subject can be a mammal, preferably a human. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

10 The term “treating” or “treated” refers to administering a compound described herein to a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect a disease, the symptoms of the disease or the predisposition toward the disease.

15 “An effective amount” refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.05 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the
20 possibility of co-usage with other agents.

The term “mammal” includes, for example, mice, hamsters, rats, cows, sheep, pigs, goats, and horses, monkeys, dogs (e.g., *Canis familiaris*), cats, rabbits, guinea pigs, and primates, including humans.

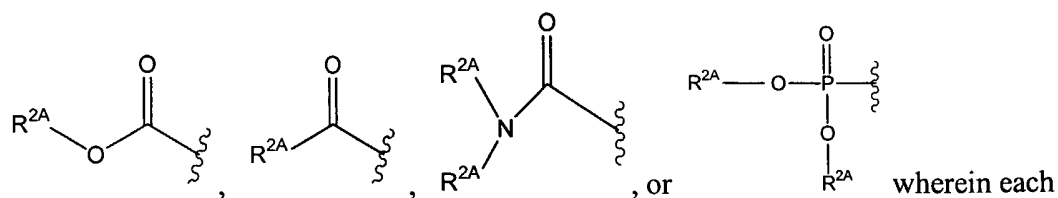
25 The term “prodrug” refers to compounds which are drug precursors which, following administration and absorption, release the drug *in vivo* through a metabolic process. Exemplary prodrugs include acyl amides of the amino compounds of this invention

Attorney Docket No. 14184-055WO1

such as amides of alkanolic (C_1 to C_6) acids, amides of aryl acids (e.g., benzoic acid) and alkane (C_1 to C_6) dioic acids.

- 5 The invention includes prodrugs that are converted *in vivo* so that $R^{2B}O^-$ becomes a hydroxyl group. Thus, in the prodrug form of the compounds of the invention $R^{2B}O^-$ is a group that is converted to a hydroxyl group. For example, in a prodrug form of the compounds of the invention, $R^{2B}O^-$ can be a carbonate, ester, carbamate, phosphate ester or a similar group.

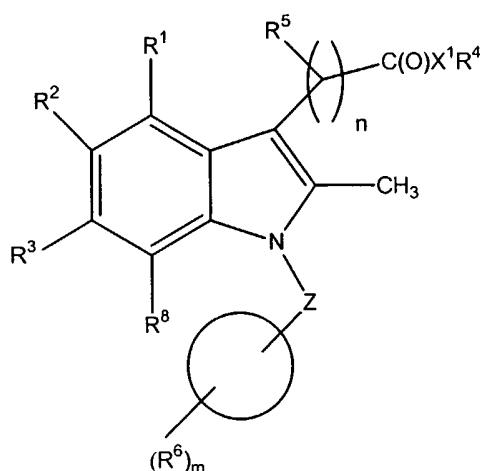
Thus, R^{2B} can be, for example,



- 10 R^{2A} is independently: H or a C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or arylalkyl optionally independently substituted with one or more halogen.

Particularly useful are compound in which R^{2A} is selected from: H and a substituted or unsubstituted C_1 alkyl, a C_2 alkyl, a C_3 alkyl or a C_4 alkyl.

Also featured is a compound having **Formula I**



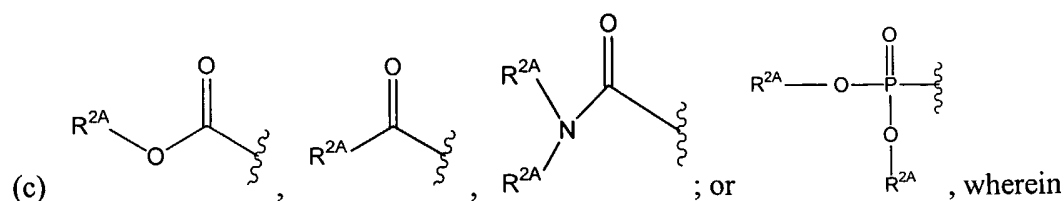
Attorney Docket No. 14184-055WO1

Formula I

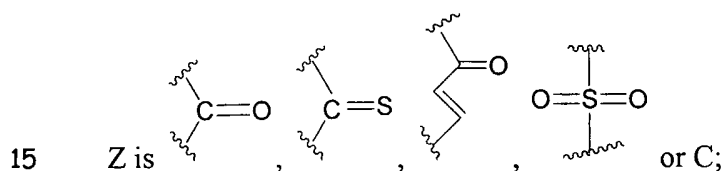
wherein:

 R^1 is: H or a halogen; R^2 is: H, a halogen, or $R^{2B}O-$ wherein5 R^{2B} is selected from:

(a) H;

(b) C_1 to C_6 alkyl or a C_2 to C_6 alkenyl that is optionally independently substituted with one or more halogen; -OH, -NH₂, -C(O)OH;

10 each R^{2A} is independently: H, a C_1 to C_6 alkyl, a C_2 to C_6 alkenyl, a C_2 to C_6 alkynyl, a C_6 to C_{10} aryl, a C_3 to C_{10} cycloalkyl, or a C_7 to C_{20} arylalkyl optionally independently substituted with one or more halogen, -OH, -C(O)OH, or -NH₂;

 R^3 is H or a halogen; X^1 is -O-, -S-, -N(H)- or -N(H)S(O₂)-;

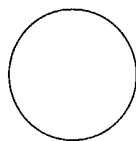
R^4 is H; a C_1 to C_{10} alkyl; a C_2 - C_{10} alkenyl; a C_2 - C_{10} alkynyl; a C_3 to C_8 cycloalkyl; a C_1 to C_6 hydroxyalkyl; a hydroxyl substituted C_6 to C_8 aryl; a primary, secondary or

Attorney Docket No. 14184-055WO1

5 tertiary C₁ to C₆ alkylamino; primary, secondary or tertiary C₆ to C₈ arylamino; C₂ to C₆ alkylcarboxylic acid; a C₁ to C₆ alkylester; a C₆ to C₈ aryl; a C₆ to C₈ arylcarboxylic acid; a C₆ to C₈ arylester; a C₆ to C₈ aryl substituted C₁ to C₆ alkyl; a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, S(O)₂, N, and S(O); an alkyl-substituted or aryl-substituted a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, S(O)₂, N, and S(O), wherein one or more H within R⁴ can be substituted by a halogen, -OH, or -C(O)OH, -NH₂;

n is 1, 2, 3, 4 or 5;

10 Each R⁵ is independently: H, an optionally substituted C₁-C₄ alkyl, wherein the substituents are independently selected from a halogen and -OH;



15 represents a C₃-C₆ saturated carbocycle, a C₆ aryl, C₃-C₆ non-saturated, non-aromatic carbocycle, a 6-membered heteroaryl having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, S(O)₂, N, S(O) and N(R⁷) or a 3- to 7-membered saturated or non-saturated heterocycle having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, S(O)₂, N, S(O) and N(R⁷);

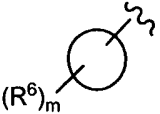
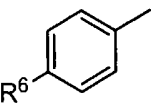
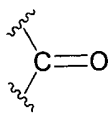
each R⁶ is independently H, a halogen, -CH₃, -CN, -OCH₃, -SCH₃, -SCF₃, -OCH₂CF₃ or -CH₂CH₃ wherein one or more H can be replaced by a halogen;

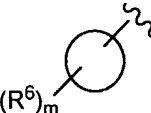
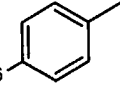
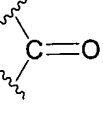
m = 1, 2, 3, 4, or 5;

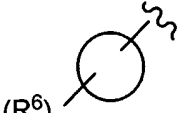
20 R⁷ is: H, a halogen, -CH₃, -CN, -OCH₃, -SCH₃, or -CH₂CH₃ wherein one or more H can be replaced by a halogen; and

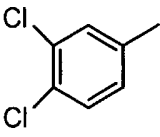
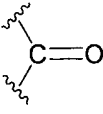
R⁸ is: H, a halogen or -CH₃, wherein one or more H can be replaced by a halogen;

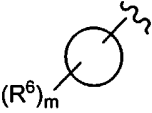
Attorney Docket No. 14184-055WO1

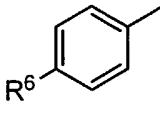
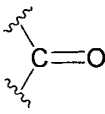
provided that when  is , $n = 1$, Z is , R^5 is H, R^1 is H, R^3 is H, R^8 is H, R^2 is $-\text{OCH}_3$, $-\text{C}(\text{O})\text{X}^1\text{R}^4$ is $-\text{COOH}$, then R^6 is not Cl, H, F, or

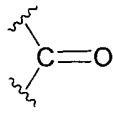
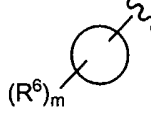
CF_3 ; further provided that when  is , $n = 1$, R^5 is H, R^1 is F, R^3 is H, R^2 is CH_3 , R^8 is H, Z is , $-\text{C}(\text{O})\text{X}^1\text{R}^4$ is $-\text{COOH}$, then R^6 is not H;

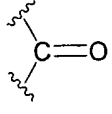
5 further provided that when  is

 $n = 1$, R^5 is H, Z is , R^1 is H, R^3 is H, R^8 is H, and $-\text{C}(\text{O})\text{X}^1\text{R}^4$ is

$-\text{COOH}$, then R^2 is not $-\text{OH}$; further provided that when  is

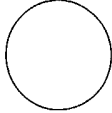
, $n = 1$, Z is , R^5 is H, R^1 is F, R^3 is H, R^8 is H, R^2 is $-\text{OCH}_3$, $-\text{C}(\text{O})\text{X}^1\text{R}^4$ is $-\text{COOH}$, then R^6 is not H; further provided that when R^1 , R^3 , R^5 and R^8

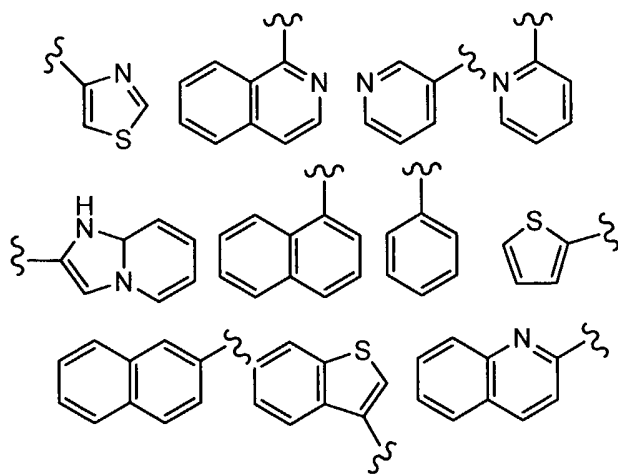
10 are all H, R^2 is F, $n = 1$, $-\text{C}(\text{O})\text{X}^1\text{R}^4$ is $-\text{COOH}$, Z is , then  is not a benzyl group that is para substituted with a halogen; further provided that when

R^1 , R^3 , R^5 and R^8 are all H, R^2 is $-\text{OCH}_3$, $n = 1$, $-\text{C}(\text{O})\text{X}^1\text{R}^4$ is $-\text{COOH}$, Z is ,

Attorney Docket No. 14184-055WO1

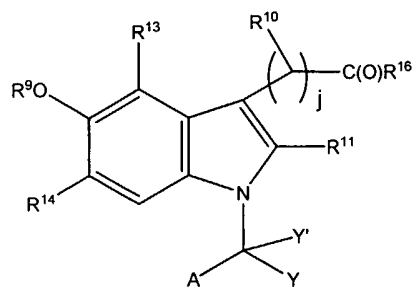
then  is not a benzyl group that is para substituted with a halogen; and further provided that when R^1 , R^3 , R^5 and R^8 are all H, R^2 is F, $n = 1$, $-C(O)X^1R^4$ is –

COOH, Z is C, then  is not selected from



- 5 . This compound, with or without the provisos is useful for treatment of the various conditions and disorders described herein. Also disclosed are pharmaceutical compositions comprising this compound.

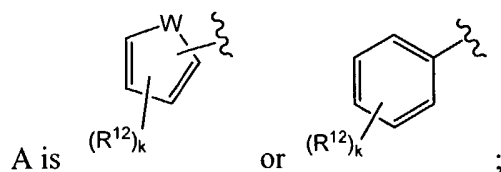
Also disclosed is a compound having the **Formula III**:



Formula III

- 10 wherein:

Attorney Docket No. 14184-055WO1



R^9 is H, a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

j is 1, 2, 3 or 4;

5 R^{10} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more -OH, - NH_2 , or halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more -OH, - NH_2 or halogen;

R^{11} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more halogen;

10 R^{12} is a halogen; -CN; -OH; -SH; a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; -OR^{12A}; -SR^{12A}; -SOR^{12A}; or -S(O)₂R^{12A}, wherein R_{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

k is 0, 1, 2, 3, 4 or 5;

R^{13} is H or a halogen;

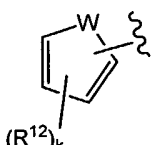
15 R^{14} is H or a halogen;

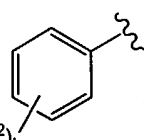
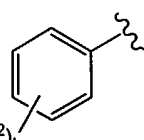
Y and Y' are both H; Y and Y' taken together are S; or Y and Y' taken together are O;

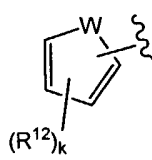
W is O, S, or -NR¹⁵, wherein R¹⁵ is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; and

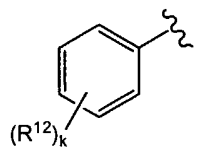
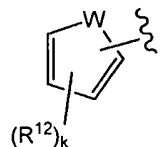
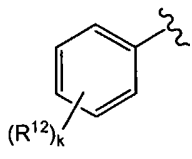
Attorney Docket No. 14184-055WO1

R^{16} is $-OH$, $-OR^{16A}$, or R^{16A} , wherein R^{16A} is: H or a C_1 to C_6 (C_1 , C_2 , C_3 , C_4 , C_5 , C_6) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or arylalkyl optionally independently substituted with one or more halogen $-OH$, $-C(O)OH$, or $-NH_3$.

5 In various embodiments of **Formula III**: A is , W is S; W is O; W is –


 NR¹⁵; A is ; k is 1; k is 2; k is 3; R¹² is F; Cl; $-CN$; $-OH$; $-SH$; a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl; $-OR^{12A}$; $-SR^{12A}$; $-SOR^{12A}$; or $-S(O)_2R^{12A}$, wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl; R¹² is F; Cl; $-CN$; $-OH$; $-SH$; a C_1 - C_3 alkyl,
 10 optionally independently substituted with one or more F or Cl; R¹² is $-OR^{12A}$; $-SR^{12A}$; $-SO R^{12A}$; or $-S(O)_2 R^{12A}$, wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl; R⁹ is H; R⁹ is a C_1 - C_3 alkyl, optionally

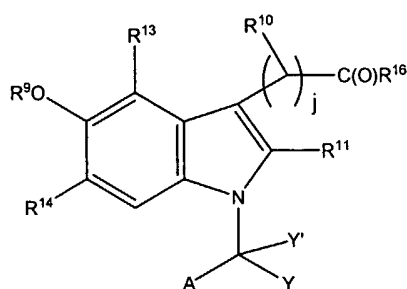
independently substituted with one or more halogen; wherein A is , A is

; A is ; wherein A is ; the compound
 15 is a CRTH2 agonist; the compound has an EC₅₀ for CRTH2 that is less than 20 μM ; the compound has an EC₅₀ for CRTH2 that is less than 10 μM ; the compound has an EC₅₀ for CRTH2 that is less than 5 μM ; the compound is a CRTH2 antagonist; the compound has an IC₅₀ for CRTH2 that is less than 20 μM ; the compound has an IC₅₀ for CRTH2 that is less than 10 μM ; the compound has an IC₅₀ for CRTH2 that is less
 20 than 5 μM ; wherein R⁹ is a C_1 - C_3 alkyl, optionally independently substituted with one

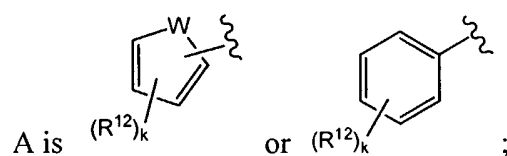
Attorney Docket No. 14184-055WO1

or more halogen; R^9 is H; wherein Y and Y' taken together are S; Y and Y' taken together are O; Y and Y' are both H; j is 1; j is 2; j is 3; j is 4; R^{13} is H, F or Cl; R^{14} is H, F or Cl; R^9 is H, a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl; R^{10} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more -OH, -NH₂, or F or Cl; or a C_1 - C_6 alkenyl optionally independently substituted with one or more -OH, -NH₂, F or Cl; R^{11} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more F or Cl; or a C_1 - C_6 alkenyl optionally independently substituted with one or more F or Cl; any halogen is selected from F and Cl.

Also disclosed is a compound having **Formula IV**:

**Formula IV**

wherein:



R^9 is H, a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

n is 1, 2, 3 or 4;

Attorney Docket No. 14184-055WO1

R^{10} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more -OH, - NH_2 , or halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more -OH, - NH_2 or halogen;

5 R^{11} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more halogen;

R^{12} is a halogen; -CN; -OH; -SH; a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; - OR^{12A} ; - SR^{12A} ; - SOR^{12A} ; or - $S(O)_2R^{12A}$, wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

10 m is 0, 1, 2, 3, 4, or 5;

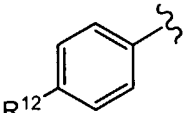
R^{13} is H or a halogen;

R^{14} is H or a halogen;

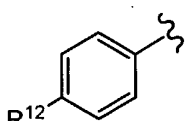
Y and Y' are both H; Y and Y' taken together are S; or Y and Y' taken together are O;

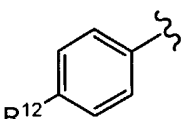
15 W is O, S, or - NR^{15} , wherein R^{15} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; and

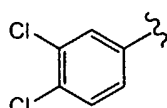
R^{16} is -OH, - OR^{16A} , or R^{16A} , wherein R^{16A} is: H or a C_1 to C_6 (C_1 , C_2 , C_3 , C_4 , C_5 , C_6) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or arylalkyl optionally independently substituted with one or more halogen -OH, - $C(O)OH$, or - NH_3 ;

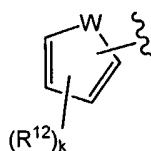
20 provided that if A is , j is 1, R^{10} is H, Y and Y' taken together are O, R^{11} is - CH_3 , R^{13} is H, R^{14} is H and R^9 is - CH_3 , then R^{12} is not: Cl, H, F or - CF_3 ;

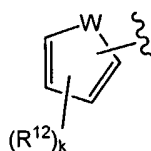
Attorney Docket No. 14184-055WO1

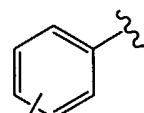
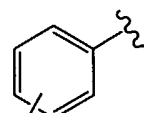
further provided that if A is , j is 1, R¹⁰ is H, Y and Y' taken together are O, R¹¹ is -CH₃, R¹³ is H, R¹⁴ is H, and R⁹ is H, then R¹² is not H; further provided

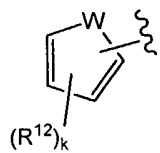
that when A is , j is 1, R¹⁰ is H, Y and Y' taken together are O, R¹¹ is -CH₃, R¹³ is F, R¹⁴ is H, R⁹ is -CH₃, R¹² is not H; and further provided that when A is

5 , j is 1, R¹⁰ is H, Y and Y' taken together are O, R¹¹ is -CH₃, R¹³ is H, R¹⁴ is H, then R⁹ is not H.

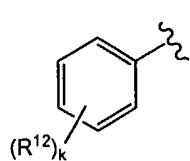


In various embodiments of **Formula IV**: A is ; W is S; W is O; W is -

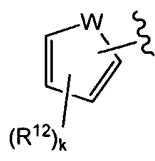
10  NR¹⁵; A is ; k is 1; k is 2; k is 3; R¹² is F; Cl; -CN; -OH; -SH; a C₁-C₃ alkyl, optionally independently substituted with one or more F or Cl; -O R^{12A}; -SR^{12A}; -SOR^{12A}; or -S(O)₂R^{12A}, wherein R^{12A} is a C₁-C₃ alkyl, optionally independently substituted with one or more F or Cl; R¹² is F; Cl; -CN; -OH; -SH; a C₁-C₃ alkyl, optionally independently substituted with one or more F or Cl; R¹² is -O R^{12A}; -S R^{12A}; -SO R^{12A}; or -S(O)₂ R^{12A}, wherein R^{12A} is a C₁-C₃ alkyl, optionally independently substituted with one or more F or Cl; R⁹ is H; R⁹ is a C₁-C₃ alkyl, optionally

15 independently substituted with one or more halogen; wherein A is , A is

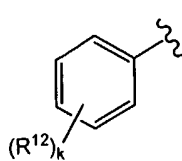
Attorney Docket No. 14184-055WO1



; A is



; wherein A is



; the compound

is a CRTH2 agonist; the compound has an EC_{50} for CRTH2 that is less than 20 μM ; the compound has an EC_{50} for CRTH2 that is less than 10 μM ; the compound has an EC_{50} for CRTH2 that is less than 5 μM ; the compound is a CRTH2 antagonist; the compound has an IC_{50} for CRTH2 that is less than 20 μM ; the compound has an IC_{50} for CRTH2 that is less than 10 μM ; the compound has an IC_{50} for CRTH2 that is less than 5 μM ; wherein R^9 is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; R^9 is H; wherein Y and Y' taken together are S; Y and Y' taken together are O; Y and Y' are both H; j is 1; j is 2; j is 3; j is 4; R^{13} is H, F or Cl; R^{14} is H, F or Cl; R^9 is H, a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl; R^{10} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more -OH, -NH₂, or F or Cl; or a C_1 - C_6 alkenyl optionally independently substituted with one or more -OH, -NH₂, F or Cl; R^{11} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more F or Cl; or a C_1 - C_6 alkenyl optionally independently substituted with one or more F or Cl; any halogen is selected from F and Cl.

Also disclosed are methods for treating certain disorders by administering a compound having **Formula III** or **Formula IV** and pharmaceutical compositions comprising compounds having **Formula III** or **Formula IV**. In various embodiments the disorders include: a disorder characterized by imbalance of the Th1/Th2 ratio towards Th1, a disorder selected from: rheumatoid arthritis, Type I diabetes, psoriasis, gastritis, irritable bowel disorder, multiple sclerosis, painless thyroiditis, lupus, and Crohn's Disease; a disorder characterized by imbalance of the Th1/Th2 ratio towards Th2; and a disorder selected from: asthma, atopic dermatitis, allergic rhinitis, allergy, and Grave's Disease; a disorder selected from asthma, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis, and other disorders associated with allergic inflammation; a disorder characterized by an increased level of one or more of IL-4, IL-10 and IL-13 in a patient.

Attorney Docket No. 14184-055WO1

The term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁-C₁₂ alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it (i.e., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12). The term "haloalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms "arylalkyl" or "aralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl and 9-fluorenyl groups.

The terms "alkylamino" and "dialkylamino" refer to -NH(alkyl) and -N(alkyl)₂ radicals respectively. The term "aralkylamino" refers to a -NH(aralkyl) radical. The term "alkoxy" refers to an -O-alkyl radical. The term "mercapto" refers to an SH radical. The term "thioalkoxy" refers to an -S-alkyl radical.

The term "aryl" refers to an aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system, wherein any ring atom capable of substitution can be substituted by a substituent. Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, and anthracenyl.

The term "cycloalkyl" as employed herein includes saturated monocyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 3 to 12 carbons, wherein any ring atom capable of substitution can be substituted by a substituent. Examples of cycloalkyl moieties include, but are not limited to, cyclopentyl, norbornyl, and adamantyl.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

Attorney Docket No. 14184-055WO1

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

5 The term "substituents" refers to a group "substituted" on an alkyl, cycloalkyl, alkenyl, alkynyl, heterocyclyl, heterocycloalkenyl, cycloalkenyl, aryl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation, alkyl, alkenyl, alkynyl, alkoxy, acyloxy, halo, hydroxy, cyano, nitro, amino, SO₃H, sulfate, phosphate, perfluoroalkyl, perfluoroalkoxy, methylenedioxy, ethylenedioxy, carboxyl, oxo, thioxo, imino (alkyl, aryl, aralkyl), S(O)_n alkyl (where n is 0-2), S(O)_n aryl (where n is 0-2), S(O)_n heteroaryl (where n is 0-2), S(O)_n heterocyclyl (where n is 0-2), amine (mono-, di-, alkyl, cycloalkyl, aralkyl, heteroaralkyl, and combinations thereof), ester (alkyl, aralkyl, heteroaralkyl), amide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof), sulfonamide (mono-, di-, alkyl, aralkyl, heteroaralkyl, and combinations thereof), unsubstituted aryl, unsubstituted heteroaryl, 10 unsubstituted heterocyclyl, and unsubstituted cycloalkyl. In one aspect, the substituents on a group are independently any one single, or any subset of the aforementioned substituents.

The invention includes salts, particularly physiologically acceptable salts, and solvates of the compounds having **Formula I** or **Formula II**. Solvates are forms of 20 the compounds in which the compound forms a complex with solvent molecules by coordination in the solid or liquid states. Hydrates are a special form of solvate in which the compound is coordinated with water.

Certain compounds having **Formula I** or **Formula II** may exist in stereoisomeric forms such as enantiomers, diastereomers and mixtures thereof. Mixtures can be 25 separated into stereoisomerically pure constituents.

Certain compounds having **Formula I** or **Formula II** may be tautomeric, and the invention encompasses the various tautomeric mixtures.

Attorney Docket No. 14184-055WO1

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims. The patents, patent applications, and publications referenced herein are hereby incorporated by reference in their entirety.

DESCRIPTION OF DRAWINGS

FIG. 1 is a table that provides COX-1 IC₅₀ (purified enzyme assay) and COX-2 IC₅₀ (purified enzyme assay) for a number of compounds. All numbers are in μ M units.

FIG 2a is a table that provides CRTH2 activity data for a number of compounds which are CRTH2 agonists. Compounds were tested for CRTH2 agonist activity at 10 and 1 μ M.

FIG 2b is a table that provides CRTH2 activity data for a number of compounds, some of which are CRTH2 antagonists. Compounds were tested for CRTH2 antagonist activity at 10 μ M.

DETAILED DESCRIPTION

The invention features compounds that inhibit COX-2 FAAH, and/or modulators of CRTH2. Certain COX-2 inhibitors are selective COX-2 inhibitors in that they are selective for inhibition of COX-2 as compared to COX-1. Certain of the FAAH inhibitors are selective for inhibition of FAAH relative to both COX-2 and COX-1. Certain of the COX-2 inhibitors, in addition to being selective for COX-2 relative to COX-1, are selective for COX-2 relative to FAAH. Certain compounds of the invention are modulators of CRTH2. Of these compounds, some may also be inhibitors of COX-2 and/or FAAH.

Certain compounds of the invention are expected to have an increased half-life in the human body compared to certain structurally related compounds. Certain compounds

Attorney Docket No. 14184-055WO1

of the invention are expected to have reduced renal and/or gastric toxicity compared to certain structurally related compounds.

Useful selective COX-2 inhibitors are those which inhibit COX-2 activity at

physiological concentrations where COX-1 activity is not significantly inhibited.

Thus, the compounds have an IC_{50} for COX-1 that is at least 2-, 5-, 10-, 15-, 20-, 100-, 500-, 1,000-fold greater than the IC_{50} for COX-2. Certain compounds do not significantly inhibit COX-1 at a therapeutically effective concentration, e.g., a concentration effective to reduce pain or inflammation attributable to COX-2

associated prostaglandin production. Useful compounds include those having an IC_{50} for COX-2 of less than about 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μ M, and have an IC_{50} for COX-1 of greater than about 1, 5, 10, 15, 20, 40 or 100 μ M. In certain embodiments the COX-2 IC_{50} for a compound is less than 20, 10, 5, 3, 2, 1, 0.5, 0.4, 0.3, 0.2, 0.1 or 0.05 times the COX-2 IC_{50} for indomethacin in the same assay. In certain embodiments the COX-1 IC_{50} for a compound is at least 2, 5, 10, 25, 50, 100, 500, 1000 or more times the COX-1 IC_{50} for indomethacin in the same assay. In certain embodiments, the selectivity for COX-2 over COX-1 for a compound is greater than 3, 5, 10, 50, 100, 200, 500 or 1000 times the selectivity of indomethacin in the same assays.

Certain useful selective FAAH inhibitors include those which inhibit FAAH activity at a physiological concentration at which COX-1 and COX-2 activity is not

significantly inhibited. Thus, the compounds have an IC_{50} for COX-1 and COX-2 that is at least 2-, 5-, 10-, 15-, 20-, 100-, 500-, 1,000-fold greater than the IC_{50} for

FAAH. Particularly desirable are compounds that do not measurably inhibit COX-1 and COX-2 at a therapeutically effective concentration, e.g., a concentration effective to reduce pain. Useful compounds include those having an IC_{50} for FAAH of less than about 80, 60, 40, 20, 10, 5, 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μ M, and have an IC_{50} for COX-1 and COX-2 of greater than about 1, 5, 10, 15, 20, 50, 100, 200, or 400 μ M. In certain embodiments, the IC_{50} for FAAH for

Attorney Docket No. 14184-055WO1

a compound is no more than about 5, 1, 0.1, 0.05, 0.01 or 0.001 times the IC_{50} for FAAH of indomethacin in the same assay.

Of course, other useful FAAH inhibitors also inhibit COX-2 at physiological concentrations at which COX-1 activity is not significantly inhibited. Particularly desirable are compounds that do not measurably inhibit COX-1 at a therapeutically effective concentration, e.g., a concentration effective to reduce pain. Useful compounds include those having an IC_{50} for FAAH of less than about 80, 60, 40, 20, 10, 5, 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μM , an IC_{50} for COX-2 of less than about 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μM , and an IC_{50} for COX-1 of greater than about 1, 5, 10, 15, or 20 μM . In certain embodiments the COX-2 IC_{50} for such a FAAH inhibitor is less than 20, 10, 5, 3, 2, 1, 0.5, 0.4, 0.3, 0.2, 0.1 or 0.05 times the COX-2 IC_{50} for indomethacin in the same assay. In certain embodiments the COX-1 IC_{50} for such a FAAH inhibitor is at least 2, 5, 10, 25, 50, 100, 500, 1000 or more times the COX-1 IC_{50} for indomethacin in the same assay.

Certain useful selective COX-2 inhibitors include those which inhibit COX-2 activity at physiological concentrations where FAAH activity is not significantly inhibited.

Particularly desirable are compounds that do not significantly inhibit FAAH at a therapeutically effective concentration, e.g., a concentration effective to reduce pain. Useful compounds include those having an IC_{50} for COX-2 of less than about 2.0, 1.5, 1.0, 0.5, 0.4, 0.3, 0.2, 0.1, 0.08, 0.06, 0.04, 0.02, or 0.01 μM , and have an IC_{50} for FAAH of greater than about 5, 10, 15, 20, 50, 100, 200 or 400 μM . Of course, other useful COX-2 inhibitors also inhibit FAAH at therapeutically relevant doses, i.e., they are not particularly selective for COX-2 over FAAH. In certain embodiments the COX-2 IC_{50} for a compound is less than 20, 10, 5, 3, 2, 1, 0.5, 0.4, 0.3, 0.2, 0.1 or 0.05 times the COX-2 IC_{50} for indomethacin in the same assay. In certain embodiments the COX-1 IC_{50} for a compound is at least 2, 5, 10, 25, 50, 100, 500, 1000 or more times the COX-1 IC_{50} for indomethacin in the same assay.

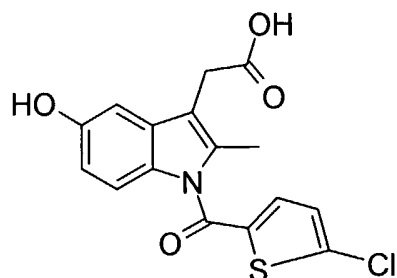
Attorney Docket No. 14184-055WO1

Certain compounds having **Formula I** or **Formula II**, e.g., those in which X^1 is $-O-$ and R^4 is a C_1 to C_6 alkyl are effective FAAH inhibitors, but are not particularly effective COX-2 inhibitors. However, many such compounds are metabolized to a form in which X^1 is $-O-$ and R^4 is H. Many of these metabolites are effective COX-2 inhibitors, but are not highly effective FAAH inhibitors, although they can inhibit FAAH to some extent. Thus, compounds having **Formula I** or **Formula II** which are FAAH inhibitors and in which X^1 is $-O-$ and R^4 is a C_1 to C_6 alkyl can exhibit two different phases of activity when administered to a patient—an initial, relatively high FAAH inhibition phase characterized by little or no significant COX-2 inhibition followed by a COX-2 inhibition phase characterized by reduced FAAH inhibition.

Examples

Certain useful compounds are described below.

{1-[(5-chlorothiophen-2-yl)carbonyl]-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid

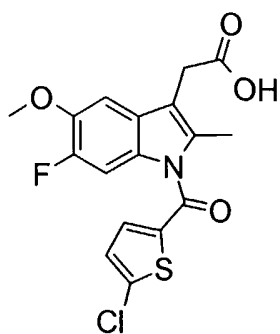


mp 195 °C

^1H NMR (CDCl_3 /300 MHz) 7.43 (d, 1H, $J = 4.2$ Hz), 7.13-7.10 (m, 2H), 6.87 (d, 1H, $J = 2.1$ Hz), 6.61 (dd, 1H, $J = 8.7, 2.1$ Hz), 3.66 (s, 2H), 2.38 (s, 3H).

{1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid

Attorney Docket No. 14184-055WO1

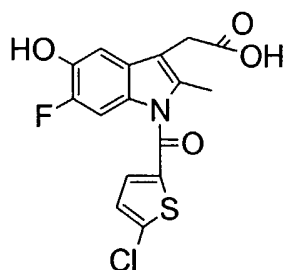


mp 169 °C

5 ¹H NMR (CDCl₃/300 MHz) 7.35 (d, 1H, *J* = 4.0 Hz), 7.09 (d, 1H, *J* = 11.7 Hz), 7.00 (d, 1H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 4.0 Hz), 3.93 (s, 3H), 3.70 (s, 2H), 2.42 (s, 3H).

{1-[(5-chlorothien-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid

10

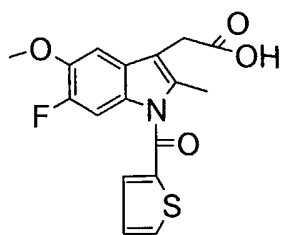


mp 174 °C

15 ¹H NMR (CDCl₃/300 MHz) 7.34 (d, 1H, *J* = 3.9 Hz), 7.13 (d, 1H, *J* = 11.1 Hz), 7.07 (d, 1H, *J* = 8.4 Hz), 6.98 (d, 1H, *J* = 3.9 Hz), 3.66 (s, 2H), 2.39 (s, 3H).

[6-fluoro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

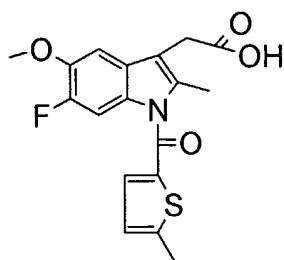
Attorney Docket No. 14184-055WO1



mp 137 °C

- 5 ¹H NMR (CDCl₃/300 MHz) 7.77 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.54 (dd, 1H, *J* = 3.9, 1.2 Hz), 7.15 (dd, 1H, *J* = 5.0, 3.9 Hz), 7.01 (d, 1H, *J* = 12.0 Hz), 7.00 (d, 1H, *J* = 8.1 Hz), 3.92 (s, 3H), 3.69 (s, 2H), 2.41 (s, 3H).

-
- 10 {6-fluoro-5-methoxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl}acetic acid

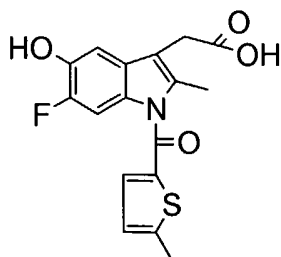


mp 152 °C

- 15 ¹H NMR (CDCl₃/300 MHz) 7.35 (d, 1H, *J* = 3.9 Hz), 7.06 (d, 1H, *J* = 12.3), 6.99 (d, 1H, *J* = 8.1 Hz), 6.81 (d, 1H, *J* = 3.9 Hz), 3.92 (s, 3H), 3.68 (s, 2H), 2.60 (s, 3H), 2.42 (s, 3H).

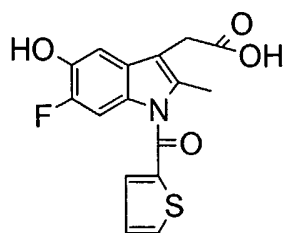
-
- 20 {6-fluoro-5-hydroxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl}acetic acid

Attorney Docket No. 14184-055WO1



mp 197 °C

5 ¹H NMR (CD₃OD/300 MHz) 7.40 (d, 1H, *J* = 4.0 Hz), 6.99 (d, 1H, *J* = 8.7 Hz), 6.98 (d, 1H, *J* = 11.7 Hz), 6.93 (d, 1H, *J* = 4.0 Hz), 3.64 (s, 2H), 2.62 (s, 3H), 2.34 (s, 3H).

[6-fluoro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

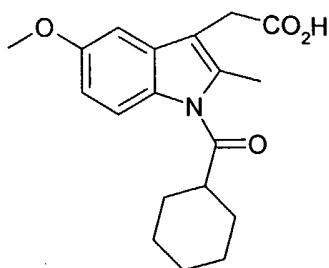
10

mp 219 °C

15 ¹H NMR (CD₃OD/300 MHz) 7.97 (dd, 1H, *J* = 5.1, 1.2 Hz), 7.59 (dd, 1H, *J* = 3.9, 1.2 Hz), 7.22 (dd, 1H, *J* = 5.1, 3.9 Hz), 7.00 (d, 1H, *J* = 8.7 Hz), 6.94 (d, 1H, *J* = 12.0 Hz), 3.65 (s, 2H), 2.32 (s, 3H).

[1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

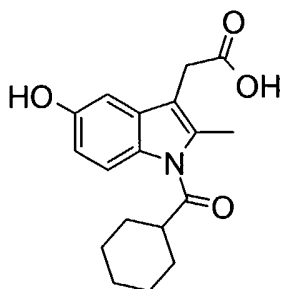
Attorney Docket No. 14184-055WO1



mp 129 °C

¹H NMR (CDCl₃/300 MHz) 7.62 (d, 1H, *J* = 9.0 Hz), 6.93 (d, 1H, *J* = 2.7), 6.86 (dd, 1H, *J* = 9.0, 2.7 Hz), 3.85 (s, 3H), 3.67 (s, 2H), 3.18 (m, 1H), 2.04-1.32 (m, 10H).

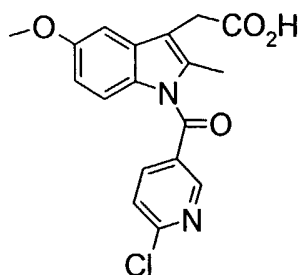
[1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid



¹H NMR (CDCl₃/300 MHz) 7.50 (d, 1H, *J* = 9.0 Hz), 6.95 (d, 1H, *J* = 2.1), 6.73 (dd, 1H, *J* = 9.0, 2.1 Hz), 3.53 (s, 2H), 3.12 (m, 1H), 2.49 (s, 3H), 2.00-1.05 (m, 10H).

{1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid

Attorney Docket No. 14184-055WO1

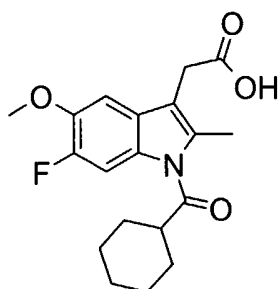


mp 153 °C

¹H NMR (CDCl₃/300 MHz) 8.71 (d, 1H, *J* = 2.7 Hz), 8.27 (dd, 1H, *J* = 8.1, 2.7 Hz),
5 7.98 (dd, 1H, *J* = 8.1, 2.7 Hz), 7.48 (d, 1H, *J* = 8.7 Hz), 6.97 (d, 1H, *J* = 2.4 Hz), 6.76
(dd, 1H, *J* = 8.7, 2.4 Hz), 3.84 (s, 3H), 3.71 (s, 2H), 2.41 (s, 3H).

[1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

10

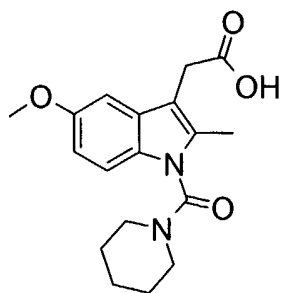


mp 104 °C

¹H NMR (CDCl₃/300 MHz) 7.72 (d, 1H, *J* = 12.9 Hz), 7.13 (d, 1H, *J* = 8.1), 3.91 (s,
15 3H), 3.69 (s, 2H), 3.23 (m, 1H), 2.56 (s, 3H), 2.05-1.27 (m, 10H).

[5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

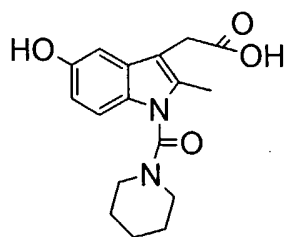
Attorney Docket No. 14184-055WO1



yellow oil

5 ^1H NMR (CDCl_3 /300 MHz) 7.16 (d, 1H, $J = 9.0$ Hz), 6.96 (d, 1H, $J = 2.7$), 6.81 (dd, 1H, $J = 9.0, 2.7$ Hz), 3.83 (s, 3H), 3.66 (s, 2H), 3.58-3.30 (m, 4H), 2.40 (s, 3H), 1.70-1.55 (m, 6H).

10 [5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]acetic acid



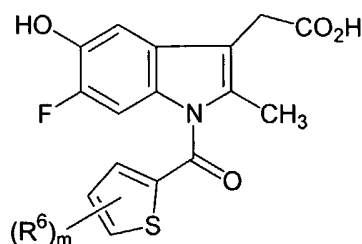
mp 235 °C

15 ^1H NMR (CDCl_3 /300 MHz) 6.99 (d, 1H, $J = 8.7$ Hz), 6.79 (s, 1H), 6.64 (d, 1H, $J = 8.7$ Hz), 3.47 (s, 2H), 3.47-3.30 (m, 4H), 2.33 (s, 3H), 1.72-1.43 (m, 6H).

Additional compounds include:

20 [6-fluoro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-1H-indol-3-yl]acetic acid
derivatives having the formula:

Attorney Docket No. 14184-055WO1



including:

- 5 [6-fluoro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;
 {6-fluoro-1-[(5-fluorothien-2-yl)carbonyl]-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;
 {1-[(5-chlorothien-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;
- 10 {1-[(5-bromothien-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;
 {6-fluoro-5-hydroxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;
 {6-fluoro-5-hydroxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;
- 15 {1-[(5-ethoxythien-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;
 (1-{[5-(difluoromethoxy)thien-2-yl]carbonyl}-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;
- 20 (6-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;
 (6-fluoro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;
 (6-fluoro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;
- 25 {6-fluoro-5-hydroxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl} acetic acid;

Attorney Docket No. 14184-055WO1

(1-{{5-(difluoromethyl)thien-2-yl}carbonyl}-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-hydroxy-2-methyl-1-{{5-(trifluoromethyl)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

5 (6-fluoro-5-hydroxy-2-methyl-1-{{5-(methylthio)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-2-yl}carbonyl)-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

10 [6-fluoro-5-hydroxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

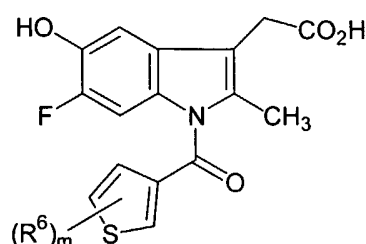
[6-fluoro-5-hydroxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[6-fluoro-5-hydroxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

15 {1-[(5-cyanothien-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid

[6-fluoro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

20 derivatives having the formula:



including:

25 [6-fluoro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

{6-fluoro-1-[(5-fluorothien-3-yl)carbonyl]-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

{1-[(5-chlorothien-3-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;

{1-[(5-bromothien-3-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;

5 {6-fluoro-5-hydroxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;

{6-fluoro-5-hydroxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;

10 {1-[(5-ethoxythien-3-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

15 (6-fluoro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

20 {6-fluoro-5-hydroxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethyl)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

25 (6-fluoro-5-hydroxy-2-methyl-1-{[5-(methylthio)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-3-yl}carbonyl)-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

30 [6-fluoro-5-hydroxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

Attorney Docket No. 14184-055WO1

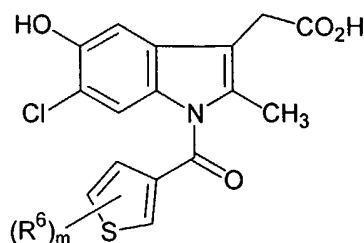
[6-fluoro-5-hydroxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[6-fluoro-5-hydroxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

- 5 {1-[(5-cyanothien-3-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid.

[6-chloro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

- 10 derivatives having the formula:



including:

- 15 [6-chloro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;
 {6-chloro-1-[(5-fluorothien-3-yl)carbonyl]-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;
 {1-[(5-chlorothien-3-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;
 20 {1-[(5-bromothien-3-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;
 {6-chloro-5-hydroxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;
 {6-chloro-5-hydroxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;
 25 {1-[(5-ethoxythien-3-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

(1-{{5-(difluoromethoxy)thien-3-yl}carbonyl}-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-hydroxy-2-methyl-1-{{5-(trifluoromethoxy)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

5 (6-chloro-5-hydroxy-2-methyl-1-{{5-(pentafluoroethoxy)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-hydroxy-2-methyl-1-{{5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

10 {6-chloro-5-hydroxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{{5-(difluoromethyl)thien-3-yl}carbonyl}-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-hydroxy-2-methyl-1-{{5-(trifluoromethyl)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

15 (6-chloro-5-hydroxy-2-methyl-1-{{5-(methylthio)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-3-yl}carbonyl)-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

20 [6-chloro-5-hydroxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

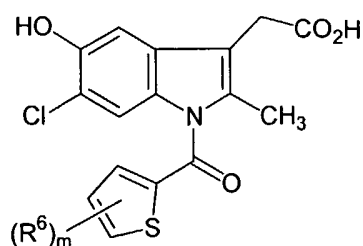
[6-chloro-5-hydroxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[6-chloro-5-hydroxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

25 {1-[(5-cyanothien-3-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid.

30 [6-chloro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid derivatives having the formula:

Attorney Docket No. 14184-055WO1



including:

- 5 [6-chloro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid;
 {6-chloro-1-[(5-fluorothien-2-yl)carbonyl]-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;
 {1-[(5-chlorothien-2-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;
- 10 {1-[(5-bromothien-2-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;
 {6-chloro-5-hydroxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl} acetic acid;
 {6-chloro-5-hydroxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl} acetic acid;
- 15 {1-[(5-ethoxythien-2-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;
 (1-{[5-(difluoromethoxy)thien-2-yl]carbonyl}-6-chloro-5-hydroxy-2-methyl-*1H*-indol-3-yl)acetic acid;
- 20 (6-chloro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-2-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;
 (6-chloro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-2-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;
 (6-chloro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;
- 25 {6-chloro-5-hydroxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-*1H*-indol-3-yl} acetic acid;

Attorney Docket No. 14184-055WO1

(1-{{5-(difluoromethyl)thien-2-yl}carbonyl}-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-hydroxy-2-methyl-1-{{5-(trifluoromethyl)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

5 (6-chloro-5-hydroxy-2-methyl-1-{{5-(methylthio)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-2-yl}carbonyl)-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

10 [6-chloro-5-hydroxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

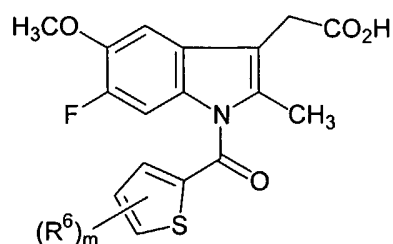
[6-chloro-5-hydroxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[6-chloro-5-hydroxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

15 {1-[(5-cyanothien-2-yl)carbonyl]-6-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid.

[6-fluoro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

20 derivatives having the formula:



including:

25 [6-fluoro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

{6-fluoro-1-[(5-fluorothien-2-yl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

{1-[(5-chlorothiien-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

{1-[(5-bromothiien-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

5 {6-fluoro-5-methoxy-1-[(5-hydroxythiien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;

{6-fluoro-5-methoxy-1-[(5-methoxythiien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;

10 {1-[(5-ethoxythiien-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethoxy)thiien-2-yl]carbonyl}-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thiien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

15 (6-fluoro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thiien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-methoxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thiien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

20 {6-fluoro-5-methoxy-2-methyl-1-[(5-methylthiien-2-yl)carbonyl]-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethyl)thiien-2-yl]carbonyl}-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-methoxy-2-methyl-1-{[5-(trifluoromethyl)thiien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

25 (6-fluoro-5-methoxy-2-methyl-1-{[5-(methylthio)thiien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thiien-2-yl} carbonyl)-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

30 [6-fluoro-5-methoxy-2-methyl-1-({5-[(trifluoromethyl)thio]thiien-2-yl} carbonyl)-1*H*-indol-3-yl]acetic acid;

Attorney Docket No. 14184-055WO1

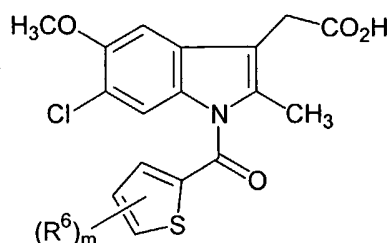
[6-fluoro-5-methoxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-*1H*-indol-3-yl]acetic acid;

[6-fluoro-5-methoxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-*1H*-indol-3-yl]acetic acid; and

5 {1-[(5-cyanothien-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid.

[6-chloro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid

10 derivatives having the formula:



15 including:

[6-chloro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid;

{6-chloro-1-[(5-fluorothien-2-yl)carbonyl]-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-chlorothien-2-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-bromothien-2-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{6-chloro-5-methoxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

{6-chloro-5-methoxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-2-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

(1-{{5-(difluoromethoxy)thien-2-yl}carbonyl}-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{{5-(trifluoromethoxy)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

5 (6-chloro-5-methoxy-2-methyl-1-{{5-(pentafluoroethoxy)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{{5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

10 {6-chloro-5-methoxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{{5-(difluoromethyl)thien-2-yl}carbonyl}-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{{5-(trifluoromethyl)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

15 (6-chloro-5-methoxy-2-methyl-1-{{5-(methylthio)thien-2-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-2-yl}carbonyl)-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

20 [6-chloro-5-methoxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[6-chloro-5-methoxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

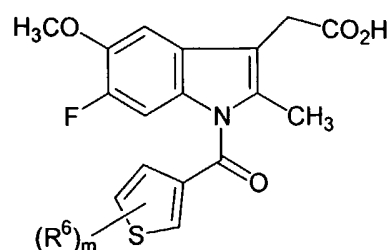
[6-chloro-5-methoxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

25 {1-[(5-cyanothien-2-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

[6-fluoro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

30 derivatives having the formula:

Attorney Docket No. 14184-055WO1



including:

[6-fluoro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

5 {6-fluoro-1-[(5-fluorothien-3-yl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

{1-[(5-chlorothien-3-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

{1-[(5-bromothien-3-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

10 {6-fluoro-5-methoxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;

{6-fluoro-5-methoxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl} acetic acid;

15 {1-[(5-ethoxythien-3-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

20 (6-fluoro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-methoxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

{6-fluoro-5-methoxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl} acetic acid;

25 (1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

Attorney Docket No. 14184-055WO1

(6-fluoro-5-methoxy-2-methyl-1-{{5-(trifluoromethyl)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-fluoro-5-methoxy-2-methyl-1-{{5-(methylthio)thien-3-yl}carbonyl}-1*H*-indol-3-yl)acetic acid;

5 [1-({5-[(difluoromethyl)thio]thien-3-yl}carbonyl)-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

[6-fluoro-5-methoxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

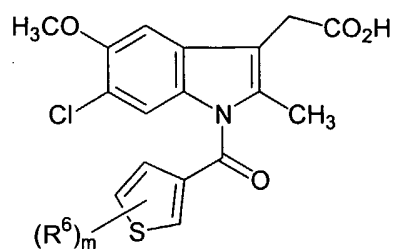
10 [6-fluoro-5-methoxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[6-fluoro-5-methoxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

{1-[(5-cyanothien-3-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

15

[6-chloro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid derivatives having the formula:



20

including:

[6-chloro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

{6-chloro-1-[(5-fluorothien-3-yl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

25

{1-[(5-chlorothien-3-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

{1-[(5-bromothiien-3-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{6-chloro-5-methoxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

5 {6-chloro-5-methoxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-3-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

10 (1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

15 (6-chloro-5-methoxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

{6-chloro-5-methoxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

20 (1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{[5-(trifluoromethyl)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(6-chloro-5-methoxy-2-methyl-1-{[5-(methylthio)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

25 [1-(5-{[5-(difluoromethyl)thio]thien-3-yl}carbonyl)-6-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

[6-chloro-5-methoxy-2-methyl-1-(5-{[5-(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

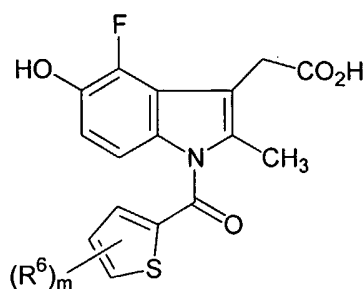
30 [6-chloro-5-methoxy-2-methyl-1-(5-{[5-(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

Attorney Docket No. 14184-055WO1

[6-chloro-5-methoxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-*1H*-indol-3-yl]acetic acid; and
 {1-[(5-cyanothien-3-yl)carbonyl]-6-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid.

5

[4-fluoro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid
 10 derivatives having the formula:



including:

15

[4-fluoro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid;
 {4-fluoro-1-[(5-fluorothien-2-yl)carbonyl]-5-hydroxy-2-methyl-*1H*-indol-3-yl}acetic acid;
 {1-[(5-chlorothien-2-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-*1H*-indol-3-yl}acetic acid;
 20 {1-[(5-bromothien-2-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-*1H*-indol-3-yl}acetic acid;
 {4-fluoro-5-hydroxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;
 25 {4-fluoro-5-hydroxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

{1-[(5-ethoxythien-2-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethoxy)thien-2-yl]carbonyl}-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

5 (4-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-fluoro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-fluoro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

10 {4-fluoro-5-hydroxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl} acetic acid;

(1-{[5-(difluoromethyl)thien-2-yl]carbonyl}-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

15 (4-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethyl)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-fluoro-5-hydroxy-2-methyl-1-{[5-(methylthio)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-(5-{[(difluoromethyl)thio]thien-2-yl}carbonyl)-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

20 [4-fluoro-5-hydroxy-2-methyl-1-(5-{[(trifluoromethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

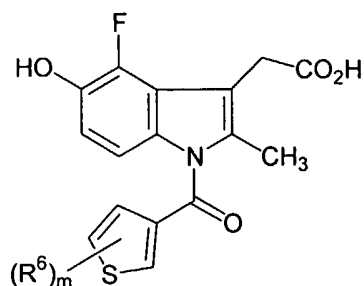
[4-fluoro-5-hydroxy-2-methyl-1-(5-{[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

25 [4-fluoro-5-hydroxy-2-methyl-1-(5-{[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

{1-[(5-cyanothien-2-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl} acetic acid

Attorney Docket No. 14184-055WO1

[4-fluoro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-*1H*-indol-3-yl]acetic acid derivatives having the formula:



5

including:

[4-fluoro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-*1H*-indol-3-yl]acetic acid;{4-fluoro-1-[(5-fluorothien-3-yl)carbonyl]-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;

10 {1-[(5-chlorothien-3-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;

{1-[(5-bromothien-3-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;

15 {4-fluoro-5-hydroxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-*1H*-indol-3-yl} acetic acid;

{4-fluoro-5-hydroxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-*1H*-indol-3-yl} acetic acid;{1-[(5-ethoxythien-3-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-*1H*-indol-3-yl} acetic acid;

20 (1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-4-fluoro-5-hydroxy-2-methyl-*1H*-indol-3-yl)acetic acid;

(4-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

25 (4-fluoro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

(4-fluoro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

Attorney Docket No. 14184-055WO1

{4-fluoro-5-hydroxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

5 (4-fluoro-5-hydroxy-2-methyl-1-{[5-(trifluoromethyl)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-fluoro-5-hydroxy-2-methyl-1-{[5-(methylthio)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

10 [1-(5-{[(difluoromethyl)thio]thien-3-yl}carbonyl)-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

[4-fluoro-5-hydroxy-2-methyl-1-(5-{[(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

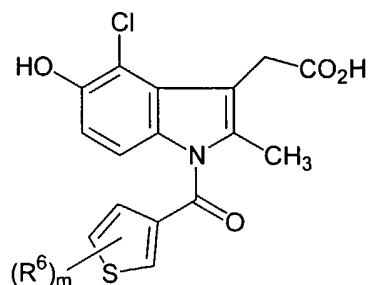
[4-fluoro-5-hydroxy-2-methyl-1-(5-{[(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

15 [4-fluoro-5-hydroxy-2-methyl-1-(5-{[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

{1-[(5-cyanothien-3-yl)carbonyl]-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid.

20

[4-chloro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid derivatives having the formula:



25

including:

[4-chloro-5-hydroxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

Attorney Docket No. 14184-055WO1

{4-chloro-1-[(5-fluorothien-3-yl)carbonyl]-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-chlorothien-3-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

5 {1-[(5-bromothien-3-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{4-chloro-5-hydroxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

10 {4-chloro-5-hydroxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-3-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

15 (4-chloro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

20 (4-chloro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

{4-chloro-5-hydroxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

25 (4-chloro-5-hydroxy-2-methyl-1-{[5-(trifluoromethyl)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(methylthio)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

30 [1-({5-[(difluoromethyl)thio]thien-3-yl}carbonyl)-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

Attorney Docket No. 14184-055WO1

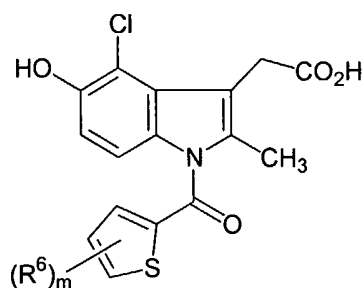
[4-chloro-5-hydroxy-2-methyl-1-(5-[(trifluoromethyl)thio]thien-3-yl)carbonyl)-1*H*-indol-3-yl]acetic acid;

[4-chloro-5-hydroxy-2-methyl-1-(5-[(pentafluoroethyl)thio]thien-3-yl)carbonyl)-1*H*-indol-3-yl]acetic acid;

- 5 [4-chloro-5-hydroxy-2-methyl-1-(5-[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl)carbonyl)-1*H*-indol-3-yl]acetic acid; and
 {1-[(5-cyanothien-3-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid.

10

[4-chloro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid derivatives having the formula:



including:

[4-chloro-5-hydroxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

{4-chloro-1-[(5-fluorothien-2-yl)carbonyl]-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

20

{1-[(5-chlorothien-2-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-bromothien-2-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

25

{4-chloro-5-hydroxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

{4-chloro-5-hydroxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-2-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid;

5 (1-{[5-(difluoromethoxy)thien-2-yl]carbonyl}-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(trifluoromethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-2-yl]carbonyl}-1*H*-
10 indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

{4-chloro-5-hydroxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

15 (1-{[5-(difluoromethyl)thien-2-yl]carbonyl}-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(trifluoromethyl)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-hydroxy-2-methyl-1-{[5-(methylthio)thien-2-yl]carbonyl}-1*H*-indol-3-
20 yl)acetic acid;

[1-(5-{[(difluoromethyl)thio]thien-2-yl}carbonyl)-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid;

[4-chloro-5-hydroxy-2-methyl-1-(5-{[(trifluoromethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

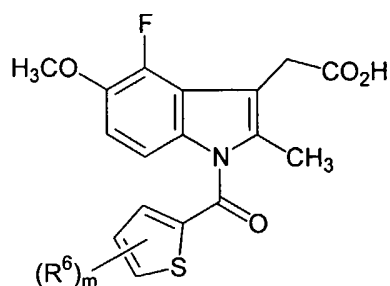
25 [4-chloro-5-hydroxy-2-methyl-1-(5-{[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[4-chloro-5-hydroxy-2-methyl-1-(5-{[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

{1-[(5-cyanothien-2-yl)carbonyl]-4-chloro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic
30 acid.

Attorney Docket No. 14184-055WO1

[4-fluoro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-*1H*-indol-3-yl]acetic acid derivatives having the formula:



including:

[4-fluoro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid;

{4-fluoro-1-[(5-fluorothien-2-yl)carbonyl]-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-chlorothien-2-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-bromothien-2-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{4-fluoro-5-methoxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

{4-fluoro-5-methoxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-2-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethoxy)thien-2-yl]carbonyl}-4-fluoro-5-methoxy-2-methyl-*1H*-indol-3-yl)acetic acid;

(4-fluoro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thien-2-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

(4-fluoro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-2-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

Attorney Docket No. 14184-055WO1

(4-fluoro-5-methoxy-2-methyl-1-{{5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl}carbonyl}-
1H-indol-3-yl)acetic acid;

{4-fluoro-5-methoxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-*1H*-indol-3-yl}acetic
 acid;

5 (1-{{5-(difluoromethyl)thien-2-yl}carbonyl}-4-fluoro-5-methoxy-2-methyl-*1H*-indol-
 3-yl)acetic acid;

(4-fluoro-5-methoxy-2-methyl-1-{{5-(trifluoromethyl)thien-2-yl}carbonyl}-*1H*-indol-
 3-yl)acetic acid;

10 (4-fluoro-5-methoxy-2-methyl-1-{{5-(methylthio)thien-2-yl}carbonyl}-*1H*-indol-3-
 yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-2-yl}carbonyl)-4-fluoro-5-methoxy-2-methyl-*1H*-
 indol-3-yl]acetic acid;

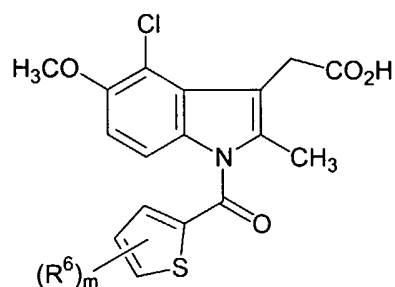
[4-fluoro-5-methoxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-2-yl}carbonyl)-*1H*-
 indol-3-yl]acetic acid;

15 [4-fluoro-5-methoxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-
1H-indol-3-yl]acetic acid;

[4-fluoro-5-methoxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-2-
 yl}carbonyl)-*1H*-indol-3-yl]acetic acid; and

20 {1-[(5-cyanothien-2-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic
 acid.

[4-chloro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-*1H*-indol-3-yl]acetic acid
 derivatives having the formula:



including:

Attorney Docket No. 14184-055WO1

[4-chloro-5-methoxy-2-methyl-1-(thien-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;
{4-chloro-1-[(5-fluorothien-2-yl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-chlorothien-2-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-bromothien-2-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{4-chloro-5-methoxy-1-[(5-hydroxythien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

{4-chloro-5-methoxy-1-[(5-methoxythien-2-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-2-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethoxy)thien-2-yl]carbonyl}-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

{4-chloro-5-methoxy-2-methyl-1-[(5-methylthien-2-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethyl)thien-2-yl]carbonyl}-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(trifluoromethyl)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(methylthio)thien-2-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

[1-({5-[(difluoromethyl)thio]thien-2-yl}carbonyl)-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

Attorney Docket No. 14184-055WO1

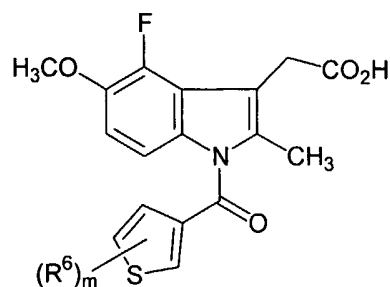
[4-chloro-5-methoxy-2-methyl-1-({5-[(trifluoromethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[4-chloro-5-methoxy-2-methyl-1-({5-[(pentafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

- 5 [4-chloro-5-methoxy-2-methyl-1-({5-[(1,1,2,2-tetrafluoroethyl)thio]thien-2-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and
 {1-[(5-cyanothien-2-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

10

[4-fluoro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid derivatives having the formula:



15

including:

[4-fluoro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid;

{4-fluoro-1-[(5-fluorothien-3-yl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

- 20 {1-[(5-chlorothien-3-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

{1-[(5-bromothien-3-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

- {4-fluoro-5-methoxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

- 25 {4-fluoro-5-methoxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-1*H*-indol-3-yl}acetic acid;

Attorney Docket No. 14184-055WO1

{1-[(5-ethoxythien-3-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

5 (4-fluoro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-fluoro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

10 (4-fluoro-5-methoxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

{4-fluoro-5-methoxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

15 (4-fluoro-5-methoxy-2-methyl-1-{[5-(trifluoromethyl)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-fluoro-5-methoxy-2-methyl-1-{[5-(methylthio)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

20 [1-(5-{[(difluoromethyl)thio]thien-3-yl}carbonyl)-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

[4-fluoro-5-methoxy-2-methyl-1-(5-{[(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

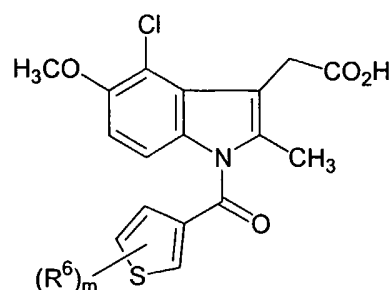
[4-fluoro-5-methoxy-2-methyl-1-(5-{[(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

25 [4-fluoro-5-methoxy-2-methyl-1-(5-{[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

{1-[(5-cyanothien-3-yl)carbonyl]-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

Attorney Docket No. 14184-055WO1

[4-chloro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-*1H*-indol-3-yl]acetic acid derivatives having the formula:



5 including:

[4-chloro-5-methoxy-2-methyl-1-(thien-3-ylcarbonyl)-*1H*-indol-3-yl]acetic acid;

{4-chloro-1-[(5-fluorothien-3-yl)carbonyl]-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

10 {1-[(5-chlorothien-3-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-bromothien-3-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

{4-chloro-5-methoxy-1-[(5-hydroxythien-3-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

15 {4-chloro-5-methoxy-1-[(5-methoxythien-3-yl)carbonyl]-2-methyl-*1H*-indol-3-yl}acetic acid;

{1-[(5-ethoxythien-3-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl}acetic acid;

20 (1-{[5-(difluoromethoxy)thien-3-yl]carbonyl}-4-chloro-5-methoxy-2-methyl-*1H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(trifluoromethoxy)thien-3-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(pentafluoroethoxy)thien-3-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

25 (4-chloro-5-methoxy-2-methyl-1-{[5-(1,1,2,2-tetrafluoroethoxy)thien-3-yl]carbonyl}-*1H*-indol-3-yl)acetic acid;

Attorney Docket No. 14184-055WO1

{4-chloro-5-methoxy-2-methyl-1-[(5-methylthien-3-yl)carbonyl]-1*H*-indol-3-yl}acetic acid;

(1-{[5-(difluoromethyl)thien-3-yl]carbonyl}-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid;

5 (4-chloro-5-methoxy-2-methyl-1-{[5-(trifluoromethyl)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

(4-chloro-5-methoxy-2-methyl-1-{[5-(methylthio)thien-3-yl]carbonyl}-1*H*-indol-3-yl)acetic acid;

10 [1-(5-{[(difluoromethyl)thio]thien-3-yl}carbonyl)-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid;

[4-chloro-5-methoxy-2-methyl-1-(5-{[(trifluoromethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

[4-chloro-5-methoxy-2-methyl-1-(5-{[(pentafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid;

15 [4-chloro-5-methoxy-2-methyl-1-(5-{[(1,1,2,2-tetrafluoroethyl)thio]thien-3-yl}carbonyl)-1*H*-indol-3-yl]acetic acid; and

{1-[(5-cyanothien-3-yl)carbonyl]-4-chloro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

20

[6-chloro-1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

[6-chloro-1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclohexylcarbonyl)-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclohexylcarbonyl)-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

25 [4-chloro-1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

[4-chloro-1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclohexylcarbonyl)-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

30

[4-fluoro-5-methoxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-hydroxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

- [4-chloro-5-hydroxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-methoxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-hydroxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-methoxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
5 [6-chloro-5-hydroxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-methoxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-hydroxy-2-methyl-1-(pyridin-2-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
-
- [4-fluoro-5-methoxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
10 [4-fluoro-5-hydroxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-methoxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-hydroxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-methoxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-hydroxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
15 [6-chloro-5-methoxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-hydroxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-methoxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-hydroxy-2-methyl-1-(pyridin-3-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
-
- 20 [4-fluoro-5-methoxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-fluoro-5-hydroxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-methoxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-hydroxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-methoxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
25 [6-fluoro-5-hydroxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-methoxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-hydroxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-methoxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-hydroxy-2-methyl-1-(pyridin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

30

Attorney Docket No. 14184-055WO1

[4-fluoro-5-methoxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-hydroxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

5 [4-chloro-5-methoxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-chloro-5-hydroxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

10 [6-fluoro-5-methoxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-fluoro-5-hydroxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-chloro-5-methoxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

15 [6-chloro-5-hydroxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[5-methoxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[5-hydroxy-2-methyl-1-(tetrahydro-2H-pyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

20

[4-fluoro-5-methoxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-hydroxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

25 [4-chloro-5-methoxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-chloro-5-hydroxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

30 [6-fluoro-5-methoxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

[6-fluoro-5-hydroxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-chloro-5-methoxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

5 [6-chloro-5-hydroxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[5-methoxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

10 [5-hydroxy-2-methyl-1-(tetrahydro-2H-thiopyran-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-methoxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-hydroxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-chloro-5-methoxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

15 [4-chloro-5-hydroxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-fluoro-5-methoxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-fluoro-5-hydroxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-chloro-5-methoxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[6-chloro-5-hydroxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

20 [5-methoxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[5-hydroxy-2-methyl-1-(piperidin-4-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-methoxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

25 [4-fluoro-5-hydroxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[4-chloro-5-methoxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

30 [4-chloro-5-hydroxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

[6-fluoro-5-methoxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[6-fluoro-5-hydroxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

5 [6-chloro-5-methoxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[6-chloro-5-hydroxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[5-methoxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

10 [5-hydroxy-2-methyl-1-[(1-methylpiperidin-4-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[4-fluoro-5-methoxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

15 [4-fluoro-5-hydroxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[4-chloro-5-methoxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

20 [4-chloro-5-hydroxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[6-fluoro-5-methoxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[6-fluoro-5-hydroxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

25 [6-chloro-5-methoxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[6-chloro-5-hydroxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

[5-methoxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

30 [5-hydroxy-2-methyl-1-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

- [4-fluoro-5-methoxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-fluoro-5-hydroxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-methoxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-hydroxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
5 [6-fluoro-5-methoxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-hydroxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-methoxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-hydroxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-methoxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
10 [5-hydroxy-2-methyl-1-(piperazin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

-
- [4-fluoro-5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-fluoro-5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[4-chloro-5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
15 [4-chloro-5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-fluoro-5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[6-chloro-5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
20 [5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid
[5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1*H*-indol-3-yl]acetic acid

-
- [6-chloro-1-(cyclopentylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid
[6-chloro-1-(cyclopentylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid
25 [1-(cyclopentylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid
[1-(cyclopentylcarbonyl)-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid
[1-(cyclopentylcarbonyl)-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid
[4-chloro-1-(cyclopentylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid
[4-chloro-1-(cyclopentylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid
30 [1-(cyclopentylcarbonyl)-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid
[1-(cyclopentylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

[1-(cyclopentylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid
 [6-chloro-1-(cyclobutylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

[6-chloro-1-(cyclobutylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclobutylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

5 [1-(cyclobutylcarbonyl)-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclobutylcarbonyl)-4-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

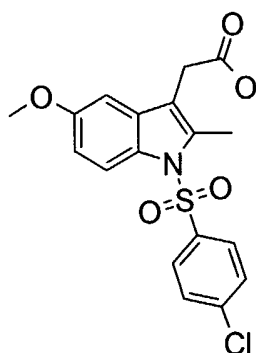
[4-chloro-1-(cyclobutylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid

[4-chloro-1-(cyclobutylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclobutylcarbonyl)-4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

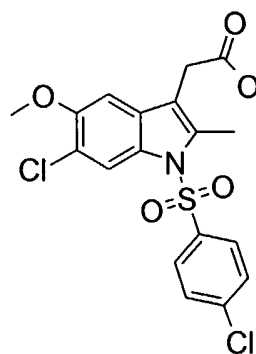
10 [1-(cyclobutylcarbonyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid

[1-(cyclobutylcarbonyl)-5-hydroxy-2-methyl-1*H*-indol-3-yl]acetic acid



15

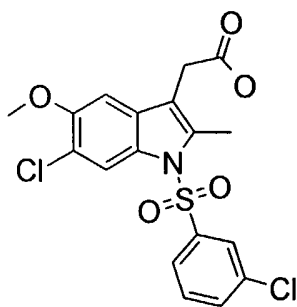
{1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid



20

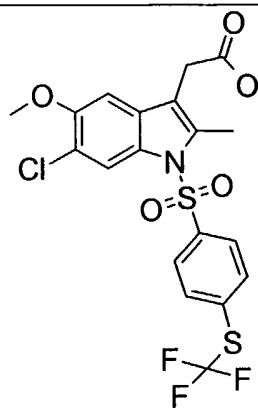
{6-chloro-1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid

Attorney Docket No. 14184-055WO1



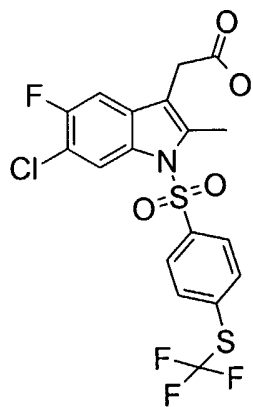
{6-chloro-1-[(3-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid

5



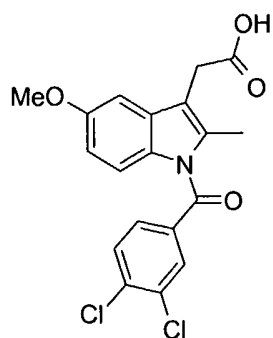
[6-chloro-5-methoxy-2-methyl-1-({4-[(trifluoromethyl)thio]phenyl}sulfonyl)-1H-indol-3-yl]acetic acid

10

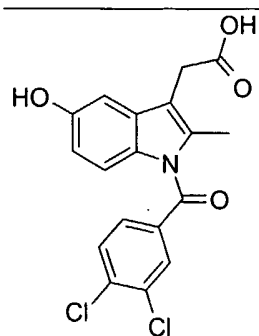


[6-chloro-5-fluoro-2-methyl-1-({4-[(trifluoromethyl)thio]phenyl}sulfonyl)-1H-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

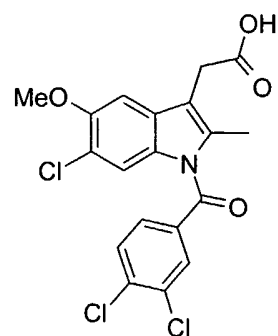


[1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid



5

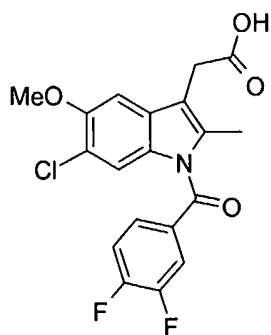
[1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid



10

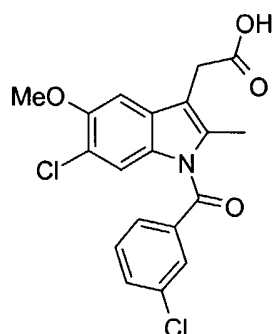
[6-chloro-1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1



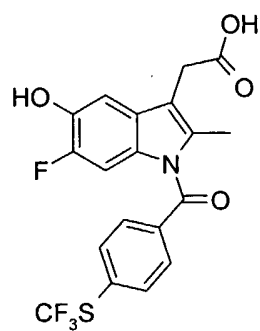
[6-chloro-1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

5



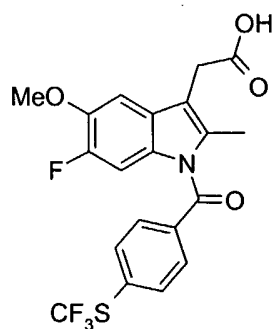
[6-chloro-1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

10

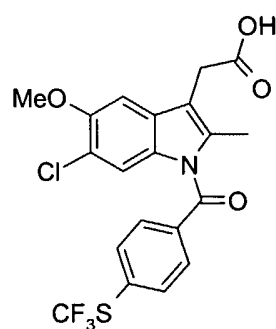


[1-(4-chlorobenzoyl)-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1

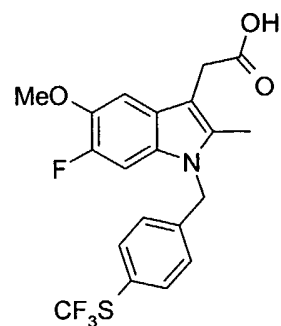


[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid



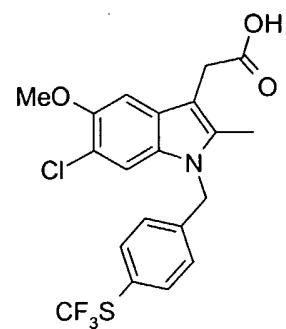
5

[6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid



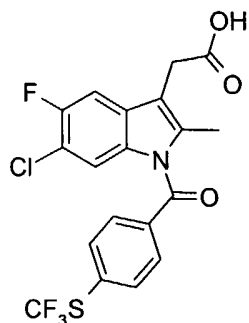
10

[1-(4-chlorobenzyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid



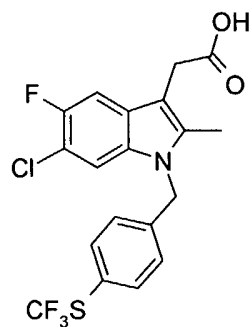
Attorney Docket No. 14184-055WO1

[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid



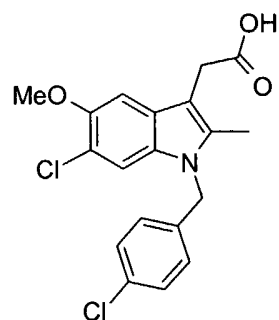
5

[6-chloro-1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid



10

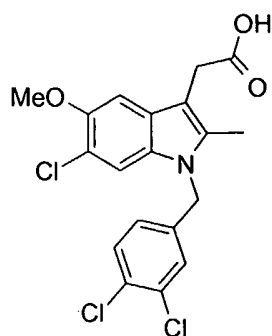
[6-chloro-1-(4-chlorobenzyl)-5-fluoro-2-methyl-1H-indol-3-yl]acetic acid



15

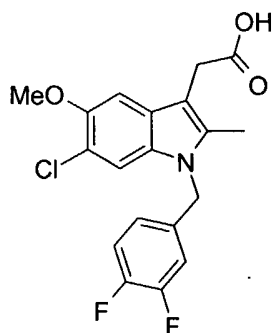
[6-chloro-1-(4-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

Attorney Docket No. 14184-055WO1



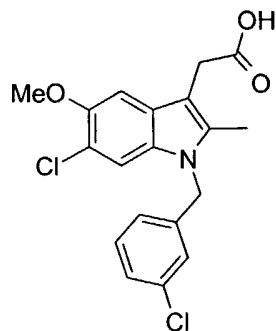
[6-chloro-1-(3,4-dichlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

5



[6-chloro-1-(3,4-difluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

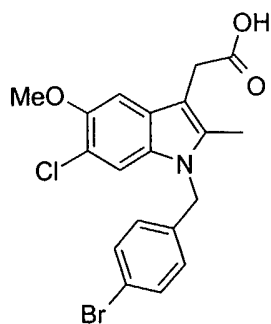
10



[6-chloro-1-(3-chlorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

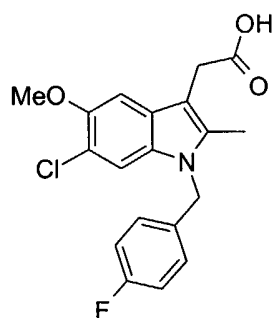
15

Attorney Docket No. 14184-055WO1



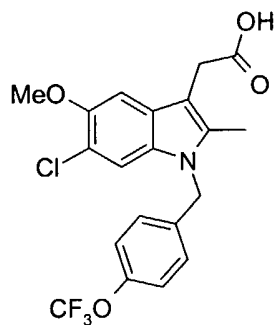
[1-(4-bromobenzyl)-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

5



[6-chloro-1-(4-fluorobenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

10



[6-chloro-1-(4-trifluoromethoxybenzyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

15

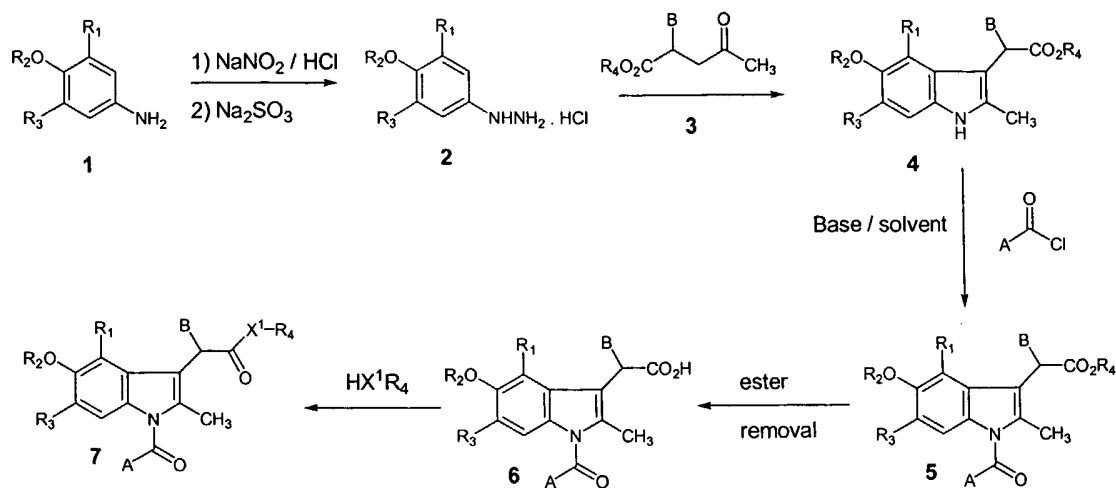
Synthesis Methods

Attorney Docket No. 14184-055WO1

Preparation of {1-[(5-chlorothien-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid

The preparation of this compound can be achieved as follows.

5



10 Step 1. Preparation of (3-fluoro-4-methoxyphenyl)hydrazine (2, $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{F}$).

3-Fluoro-4-methoxyaniline (1, $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{F}$) (95 g, 0.67 mol) was added to concentrated hydrochloric acid (250 mL), the suspension was stirred at ambient temperature for 18 h, then it was cooled to 0 °C and a solution of sodium nitrite (53.7 g, 0.78 mol) in water (200 mL) was added dropwise at 0-5 °C. When the addition was complete, the resulting solution was stirred at 0 °C for 1 h then it was added dropwise at 0-5 °C to a stirred solution of tin (II) chloride dihydrate (638.9 g, 2.83 mol) in concentrated hydrochloric acid (500 mL). The mixture was allowed to warm to ambient temperature then it was stored at 4 °C for 18 h. The resulting precipitate was collected by filtration, washed with water (400 mL), and ether (1000 mL) and dried *in vacuo*. The solid hydrochloride salt was basified by addition to 10% aqueous sodium hydroxide solution (800 mL), the free base was extracted into ether (2 X 400 mL), and the combined extracts were dried (MgSO_4) and the solvent removed *in vacuo* to give (3-fluoro-4-methoxyphenyl)hydrazine (2, $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$, $\text{R}_3 = \text{F}$) (51.9 g,

Attorney Docket No. 14184-055WO1

50%) as a yellow solid, mp 46-50 °C; ¹H-NMR (CDCl₃/250 MHz): 1.5 (s, 1H, NH-NH₂), 3.85 (s, 3H, OCH₃), 5.0 (s, 2H, NH-NH₂), 6.44 (m, 1H, phenyl 6-*H*), 6.60 (dd, 1H, phenyl 5-*H*), 6.79 (t, 1H, phenyl 2-*H*).

5 Step 2A. Preparation of (6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (4, R₁ = H, R₂ = CH₃, R₃ = F, R₄ = B = H) and (4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (4, R₁ = F, R₂ = CH₃, R₃ = H, R₄ = B = H).

Levulinic acid (3, B = R₄ = H) (38 mL, 354 mmol) and 3-fluoro-6-methoxy-phenylhydrazine hydrochloride (2, R₁ = H, R₂ = CH₃, R₃ = F) (67.5 g, 350 mmol) were combined and 150 mL of glacial acetic acid added and the slurry was stirred at 80 °C for 4 h. The reaction was cooled to room temperature and added to ice water (500 mL). The resulting aqueous solution was extracted with dichloromethane (3 X 500 mL) and the organics dried (MgSO₄) and concentrated to afford a thick semi-solid. Water (450-500 mL) was added and the slurry was stirred vigorously overnight while manually breaking up large solid pieces with a spatula. The fine tan solid that resulted was isolated by filtration and dried to afford a mixture of indoles 56.3 grams, 67% yield, ~ 93% pure by HPLC (7/1 ratio of (6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (4, R₁ = H, R₂ = CH₃, R₃ = F, R₄ = B = H) and (4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (4, R₁ = F, R₂ = CH₃, R₃ = H, R₄ = B = H) of by NMR). Major isomer ¹H-NMR (CDCl₃/300 MHz) 2.27 (s, 3H), 3.82 (s, 2H), 3.84 (s, 3H), 6.92-6.97 (m, 2H, ArH).

25 Step 2B. Preparation of 2-trimethylsilylethyl (6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (4, R₁ = B = H, R₂ = CH₃, R₃ = F, R₄ = CH₂CH₂Si(CH₃)₃).

The indoles from Step 2A (56.3 g, 238 mmol) were combined with 2-trimethylsilylethanol (41 mL, 1.25 eq.) and 4-(dimethylamino)pyridine (DMAP) (4 g) in dichloromethane (600 mL) and cooled to 0 °C. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (50.2 g, 1.1 eq.) was added in portions and the reaction was stirred for 30 min at 0 °C and then allowed to warm to room

Attorney Docket No. 14184-055WO1

temperature and stir overnight. The reaction mixture was diluted with dichloromethane (600 mL) and washed with water (2 X 200 mL), dried and concentrated to give a thick orange syrup which after triturating with hexanes induced solid formation, the solid was recrystallized from hexane-ethyl acetate to afford tan needles of 2-trimethylsilylethyl (6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (4, $R_1 = H = B$, $R_2 = CH_3$, $R_3 = F$, $R_4 = CH_2CH_2Si(CH_3)_3$), 52 g, 65% yield, >98% pure; 1H -NMR ($CDCl_3$ /300 MHz) 0.16 (s, 9H), 0.98 (m, 2H), 2.37 (s, 3H), 3.61 (s, 2H), 3.93 (s, 3H), 4.12 (m, 2H), 7.00-7.05 (m, 2H, ArH). The other regioisomer, 2-trimethylsilylethyl (4-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (4, $R_1 = F$, $R_3 = B = H$, $R_2 = CH_3$, $R_4 = CH_2CH_2Si(CH_3)_3$), may be isolated by concentration of the filtrate and purification by chromatography on silica gel.

Step 3. Preparation of 2-trimethylsilylethyl-{1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetate (5, $R_1 = H = B$, $R_2 = CH_3$, $R_3 = F$, $R_4 = CH_2CH_2Si(CH_3)_3$, A = 5-chlorothiophene).

In a dry flask 2-trimethylsilylethyl (6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (4, $R_1 = H = B$, $R_2 = CH_3$, $R_3 = F$, $R_4 = CH_2CH_2Si(CH_3)_3$), (1.0 g, 2.96 mmol) was dissolved in tetrahydrofuran (THF) (10 mL) and hexamethylphosphoramide (HMPA) (1 mL) and cooled to $-78^\circ C$. Potassium bis(trimethylsilyl)amide 0.5M in toluene (6.52 mL) was added and the reaction was stirred for 30 min. 5-Chlorothiophene-2-carbonyl chloride (562 mg, 3.1 mmol) in 3 mL of THF was added and the reaction was stirred for 0.5 h at $-78^\circ C$ and 0.5 h at $0^\circ C$, and then treated with saturated ammonium chloride (20 mL) and the reaction extracted with ethyl acetate (3 x 30 mL), dried over $MgSO_4$ and concentrated to give a thick oil which was purified by chromatography to afford 2-trimethylsilylethyl-{1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetate (5, $R_1 = H = B$, $R_2 = CH_3$, $R_3 = F$, $R_4 = CH_2CH_2Si(CH_3)_3$, A = 5-chlorothiophene). (600 mg, 1.24 mmol, 42%, >99% pure) as light yellow oil; 1H -NMR ($CDCl_3$ /300 MHz) consistent with the assigned structure.

Attorney Docket No. 14184-055WO1

Step 4. Preparation of {1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid (6, R₁ = H, R₂ = CH₃, R₃ = F, R₄ = H, A = 5-chlorothiophene).

5 A solution of the product from Step 3, 2-trimethylsilylethyl-{1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetate **5**, R₁ = H = B, R₂ = CH₃, R₃ = F, R₄ = CH₂CH₂Si(CH₃)₃, A = 5-chlorothiophene) (600 mg, 1.24 mmol) dissolved in 8 mL of THF was treated with a solution of tetrabutylammonium fluoride (1M, 3.1 mL, 3.1 mmol) in THF. The solution was stirred at room temperature until
10 the ester had been cleaved (ca. 1 h), and then the solution was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over MgSO₄ and concentrated to give a solid that was purified by chromatography eluting with hexanes and ethyl acetate to provide 280 mg, 59% of pure {1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-
15 indol-3-yl}acetic acid (**6**, R₁ = H, R₂ = CH₃, R₃ = F, R₄ = H, A = 5-chlorothiophene), mp 169 °C
¹H NMR (CDCl₃/300 MHz) 7.35 (d, 1H, *J* = 4.0 Hz), 7.09 (d, 1H, *J* = 11.7 Hz), 7.00 (d, 1H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 4.0 Hz), 3.93 (s, 3H), 3.70 (s, 2H), 2.42 (s, 3H).

20 Step 5. Preparation of {1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid (6, R₁ = H = B, R₂ = H, R₃ = F, A = 5-chlorothiophene).

The product from Step 3, 2-trimethylsilylethyl-{1-[(5-chlorothiophen-2-yl)carbonyl]-6-
25 fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl} acetate **5**, R₁ = H = B, R₂ = CH₃, R₃ = F, R₄ = CH₂CH₂Si(CH₃)₃, A = 5-chlorothiophene) (400 mg, 0.83 mmol) was dissolved in 10 mL of dry dichloromethane and cooled to -78 °C. The solution was then treated with boron tribromide (1M, 4.9 mL, 4.9 mmol) in dichloromethane and the solution allowed to warm to room temperature and stirred at that temperature for an additional
30 2 h. The solution was then poured into water and the phases separated and the aqueous phase extracted with dichloromethane. The combined extracts were washed

Attorney Docket No. 14184-055WO1

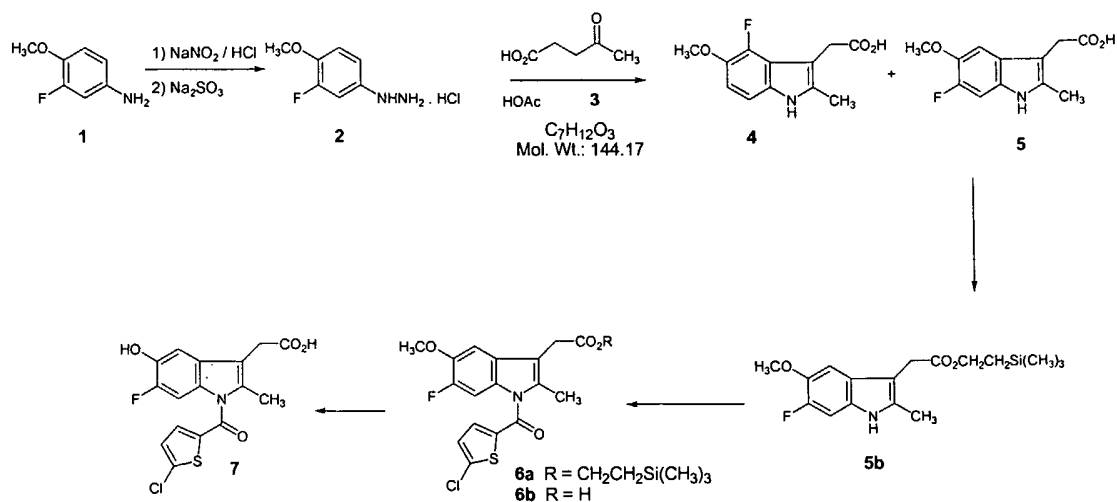
with brine, dried over MgSO_4 and concentrated to give a solid that was purified by chromatography eluting with methanol and dichloromethane to provide 150 mg, 49%, of pure {1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1*H*-indol-3-yl}acetic acid (**6**, $\text{R}_1 = \text{H} = \text{B}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{F}$, $\text{A} = 5\text{-chlorothiophene}$) mp 174 °C, ^1H NMR ($\text{CDCl}_3/300\text{ MHz}$) 7.34 (d, 1H, $J = 3.9\text{ Hz}$), 7.13 (d, 1H, $J = 11.1\text{ Hz}$), 7.07 (d, 1H, $J = 8.4\text{ Hz}$), 6.98 (d, 1H, $J = 3.9\text{ Hz}$), 3.66 (s, 2H), 2.39 (s, 3H).

Step 6. Preparation on derivatives of compound 6.

To prepare the compounds of the general formula 7, the free acid 6 can be coupled to HX^1R_4 in the presence of a dehydrating agent such as dicyclohexylcarbodiimide.

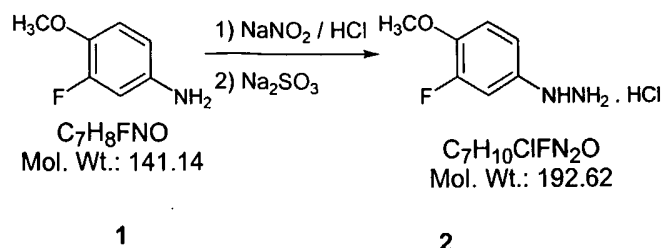
General Synthesis Scheme 1

The compounds of the present invention may be prepared by the general method outlined in Scheme 1.



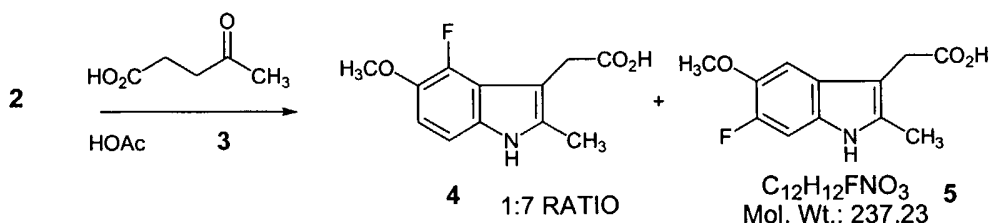
Step 1. Preparation of phenylhydrazines, representative example: (3-fluoro-4-methoxyphenyl)hydrazine (**2**).

Attorney Docket No. 14184-055WO1



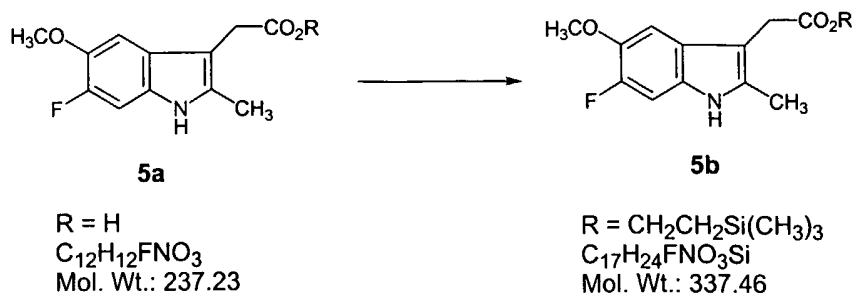
The preparation of phenylhydrazine derivatives (**2**) begins with treatment of commercially available anilines (**1**) with nitrous acid, generated from sodium nitrite and concentrated hydrochloric acid, to produce the corresponding diazonium salt. In the same reaction vessel the diazonium salt is treated with sodium sulfite and hydrochloric acid to produce the desired hydrazine hydrochloride (**2**) in 90% yield. Alternatively, the diazonium salt can be reduced with stannous chloride in hydrochloric acid.

Step 2. Preparation of indoles by the Fisher Indole synthesis, representative example: (6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid (**5**).



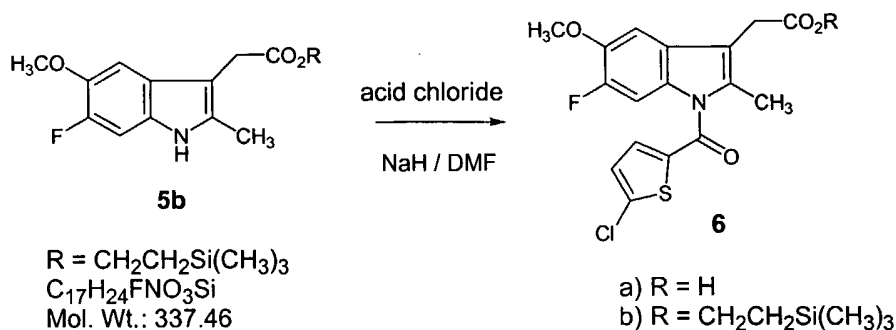
Condensation of hydrazine hydrochloride (**2**) with levulinic acid (**3**) in acetic acid results in the formation of two regioisomeric indole derivatives **4** and **5** in a 1:7 ratio. The major regioisomer **5** can be isolated in pure form by crystallization of the reaction mixture. Alternatively, the indole mixture can be esterified with an alcohol such as 2-trimethylsilylethanol to afford the corresponding esters that can then be separated by a number of means, for example by chromatography.

Attorney Docket No. 14184-055WO1



Step 3. Acylation of indole **5b**: preparation of 2-trimethylsilylethyl-{1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetate (**6b**).

5



Treatment of the indole ester **5b** with sodium hydride in dimethylformamide (DMF) followed by treatment with an acid chloride such as 5-chlorothiophene-2-carbonyl chloride affords the acylated indole derivative **6b** in 82% yield. The ester can then be removed by treatment with an acid such as trifluoroacetic acid to produce the corresponding acid, in this instance **6a**.

10

Step 4. Preparation of 5-hydroxy indole derivatives: preparation of {1-[(5-chlorothiophen-2-yl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid (**7**).

15

Attorney Docket No. 14184-055WO1



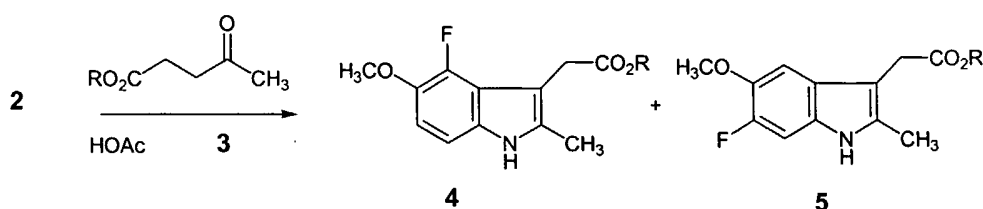
5 Esters such as **6b** upon treatment with excess boron tribromide in dichloromethane can be converted to the corresponding acid phenols, such as **7** in good yield. Under these reaction conditions both the ester and the 5-methoxy moieties are dealkylated to the acid and phenol respectively. If desired the carboxylic acids can be converted to their salt derivatives by treatment with a base such as sodium hydroxide.

Attorney Docket No. 14184-055WO1

General Synthesis Scheme 2

Compounds of the invention can also be prepared according to general synthesis scheme 2 as follows.

5



10

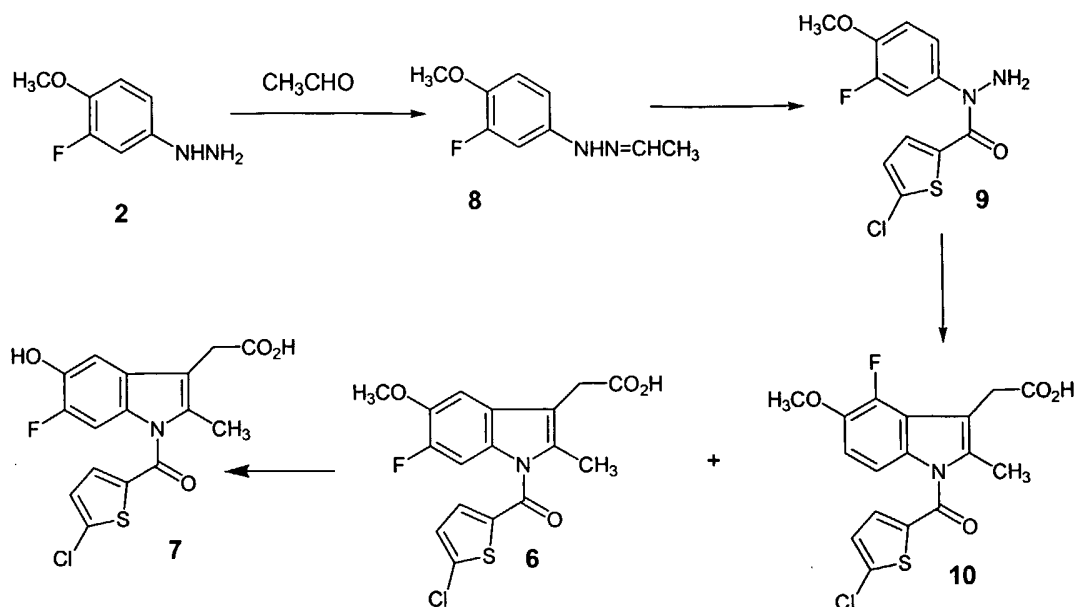
In the first step the hydrazine (2) is condensed with an ester of levulinic acid in acetic acid to afford a mixture of regioisomeric indole esters 4 and 5 (for example if one uses ethyl levulinate (3, R = Et) the products (4 and 5) will be the ethyl esters, R = Et). The esters can be separated and then acylated by the procedure outline in Scheme 1 to afford the corresponding acyl derivatives such as 6, R = Et in the present example. Hydrolysis of the ester affords the corresponding acid, 6a. If desired, the ester and the 5-methoxy groups can be removed in a single operation upon treatment with boron tribromide in dichloromethane to give phenols such as 7.

15

General Synthesis Scheme 3

Compounds of the invention can also be prepared according to general synthesis scheme below

Attorney Docket No. 14184-055WO1

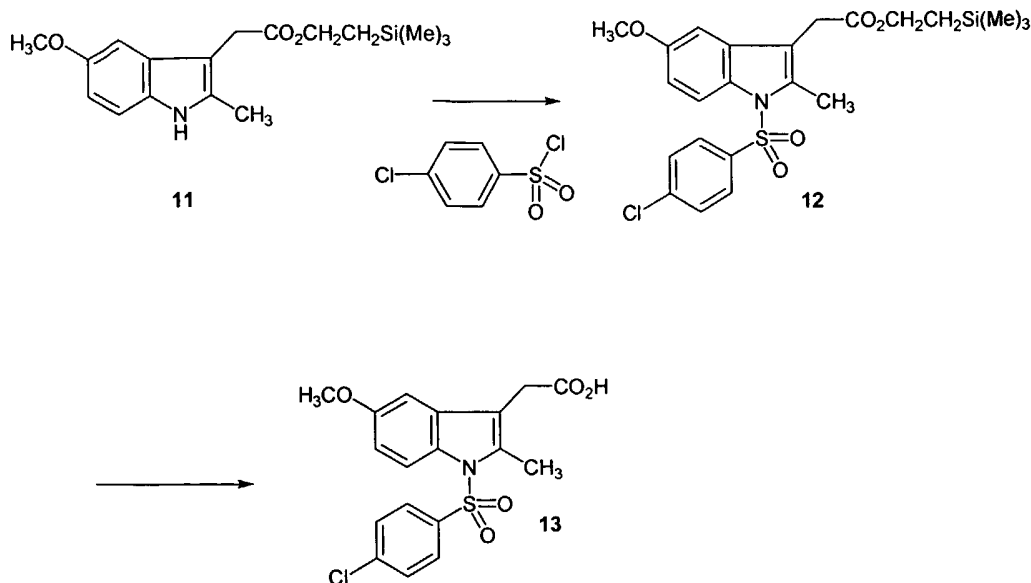


The route commences with the condensation of phenylhydrazine derivatives such as **2** with acetaldehyde to afford the corresponding hydrazone **8**. Acylation of **8** with an acid chloride, in the present example 5-chlorothiophene-2-carbonyl chloride, followed by treatment with gaseous hydrochloric acid in an alcohol such as methanol provides the desired acylated hydrazine **9** after neutralization of the excess acid. Condensation of **9** with levulinic acid provides a mixture of regioisomers that can then be separated to afford acylated indoles, in the present example, **6** and **10**. If desired, the 5-methoxy group can then be converted to the corresponding 5-hydroxy substituent by treatment with boron tribromide in dichloromethane for example to prepare **7**.

General Synthesis Scheme 4

Compounds of the invention can also be prepared according to general synthesis scheme 4 as follows.

Attorney Docket No. 14184-055WO1

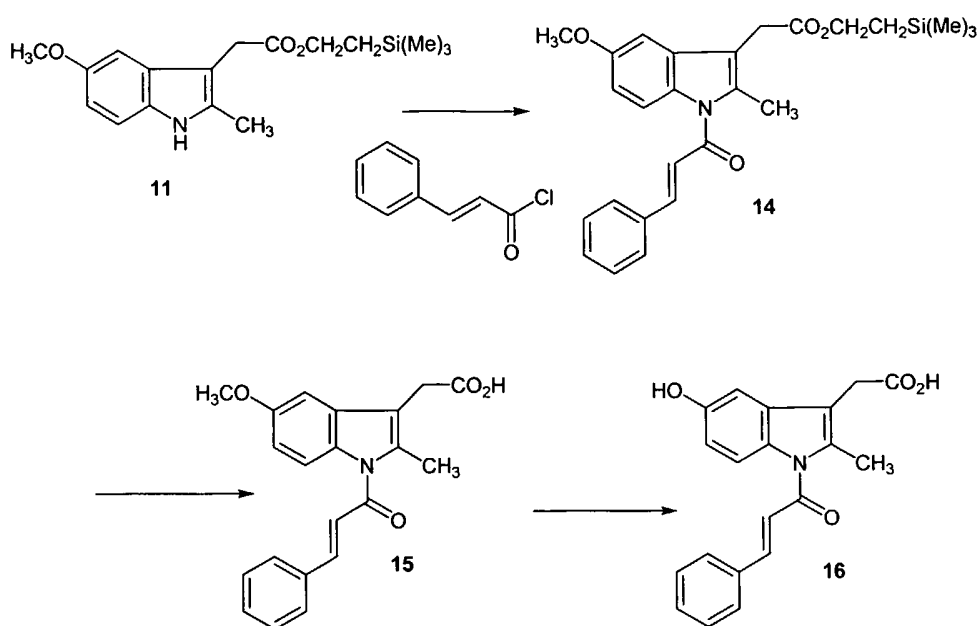


Treatment of the indole ester **11**, prepared from the corresponding indole acid by
 5 coupling with 2-trimethylsilylethanol in the presence of a dehydrating agent such as
 dicyclohexylcarbodiimide, with a strong base such as potassium
 bis(trimethylsilyl)amide in tetrahydrofuran generates the indole anion that can be
 condensed with a sulfonyl chloride to afford the *N*-sulfonyl derivatives such as **12**. In
 the present example 4-chlorobenzenesulfonyl chloride was used the sulfonyl chloride.
 10 In the second step the *N*-sulfonyl indole **12** is converted into the corresponding indole
 acid **13** upon treatment with tetrabutylammonium fluoride in tetrahydrofuran. If
 desired, the 5-methoxy substituent can be converted to the corresponding 5-hydroxy
 group upon treatment of **13** with boron tribromide in dichloromethane.

15 General Synthesis Scheme 5

Compounds of the invention can also be prepared according to general synthesis
 scheme 5 as follows

Attorney Docket No. 14184-055WO1

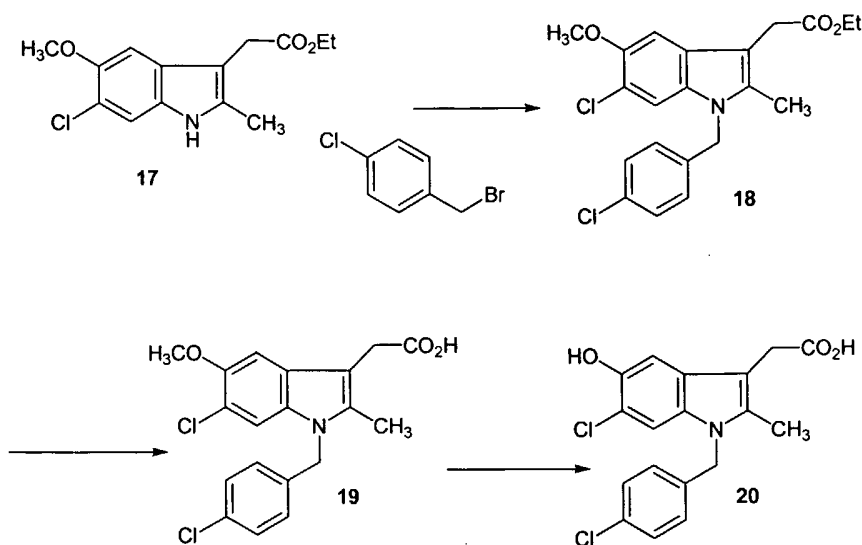


Treatment of the indole ester **11**, prepared from the corresponding indole acid by
 5 coupling with 2-trimethylsilylethanol in the presence of a dehydrating agent such as
 dicyclohexylcarbodiimide, with a strong base such as potassium
 bis(trimethylsilyl)amide in tetrahydrofuran generates the indole anion that can be
 condensed with a cinnamoyl chloride to afford the *N*-acyl derivative **14**. In the
 second step the *N*-acyl indole **14** is converted into the corresponding indole acid **15**
 10 upon treatment with tetrabutylammonium fluoride in tetrahydrofuran. If desired, the
 5-methoxy substituent can be converted to the corresponding 5-hydroxy group, **16**,
 upon treatment of **15** with boron tribromide in dichloromethane.

General Synthesis Scheme 6

15 Compounds of the invention can also be prepared according to general synthesis
 scheme 6 as follows

Attorney Docket No. 14184-055WO1



Treatment of the indole ester **17** with a strong base such as potassium

5 bis(trimethylsilyl)amide in tetrahydrofuran generates the indole anion that can be alkylated with 4-chlorobenzyl bromide to afford the *N*-benzyl derivative **18**. In the second step the *N*-benzyl indole **18** is converted into the corresponding indole acid **19** upon treatment with sodium hydroxide in aqueous tetrahydrofuran. If desired, the 5-methoxy substituent can be converted to the corresponding 5-hydroxy group, **20**, upon
10 treatment of **19** with boron tribromide in dichloromethane.

Labels

It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass
15 or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine, iodine and chlorine include ^3H , ^{14}C , ^{35}S , ^{18}F , ^{32}P , ^{33}P , ^{125}I , and ^{36}Cl , respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e. ^3H , and carbon-14, i.e., ^{14}C , radioisotopes are
20 particularly preferred for their ease in preparation and detectability. Radiolabeled compounds described herein and prodrugs thereof can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples

Attorney Docket No. 14184-055WO1

and Schemes by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent.

The labels can be primary labels (where the label comprises an element which is detected directly) or secondary labels (where the detected label binds to a primary label, e.g., as is common in immunological labeling). An introduction to labels, labeling procedures and detection of labels is found in Introduction to Immunocytochemistry, (2d ed.) Polak and Van Noorden,, Springer Verlag, N.Y. (1997) and in Handbook of Fluorescent Probes and Research Chemicals, Haugland (1996), a combined handbook and catalogue published by Molecular Probes, Inc., Eugene, Oreg. Primary and secondary labels can include undetected elements as well as detected elements. Useful primary and secondary labels in the present invention can include spectral labels, which include fluorescent labels such as fluorescent dyes (e.g., fluorescein and derivatives such as fluorescein isothiocyanate (FITC) and Oregon GreenTM, rhodamine and derivatives (e.g., Texas red, tetramethylrhodamine isothiocyanate (TRITC), etc.), digoxigenin, biotin, phycoerythrin, AMCA, CyDyesTM and the like), radiolabels (including those described above), enzymes (e.g., horseradish peroxidase, alkaline phosphatase etc.) spectral colorimetric labels such as colloidal gold or colored glass or plastic (e.g. polystyrene, polypropylene, latex, etc.) beads. The label may be coupled directly or indirectly to the compound of the invention according to methods well known in the art. As indicated above, a wide variety of labels may be used, with the choice of label depending on sensitivity required, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions. In general, a detector which monitors a protein/inhibitory agent interaction is adapted to the particular label which is used. Typical detectors include spectrophotometers, phototubes and photodiodes, microscopes, scintillation counters, cameras, film and the like, as well as combinations thereof. Examples of suitable detectors are widely available from a variety of commercial sources known to persons of skill.

Attorney Docket No. 14184-055WO1

Nonlimiting examples of labels include those which utilize 1) chemiluminescence (using horseradish peroxidase or alkaline phosphatase with substrates that produce photons as breakdown products) with kits being available, e.g., from Molecular Probes, Amersham, Boehringer-Mannheim, and Life Technologies/Gibco BRL; 2) color production (using both horseradish peroxidase or alkaline phosphatase with substrates that produce a colored precipitate) (kits available from Life Technologies/Gibco BRL, and Boehringer-Mannheim); 3) fluorescence (e.g., using Cy-5 (Amersham), fluorescein, and other fluorescent tags); 5) radioactivity. Other methods for labeling and detection will be readily apparent to one skilled in the art.

In one embodiment, the label is a fluorescent label. Fluorescent labels have the advantage of requiring fewer precautions in handling, and being amenable to high-throughput visualization techniques (optical analysis including digitization of the image for analysis in an integrated system comprising a computer). Preferred labels are typically characterized by one or more of the following: high sensitivity, high stability, low background, low environmental sensitivity and high specificity in labeling. Fluorescent moieties, which are incorporated into the labels of the invention, are generally known, including Texas red, digoxigenin, biotin, 1- and 2-aminonaphthalene, p,p'-diaminostilbenes, pyrenes, quaternary phenanthridine salts, 9-aminoacridines, p,p'-diaminobenzophenone imines, anthracenes, oxacarbocyanine, merocyanine, 3-aminoequilenin, perylene, bis-benzoxazole, bis-p-oxazolyl benzene, 1,2-benzophenazin, retinol, bis-3-aminopyridinium salts, hellebrigenin, tetracycline, sterophenol, benzimidazolylphenylamine, 2-oxo-3-chromen, indole, xanthen, 7-hydroxycoumarin, phenoxazine, calicylate, strophanthidin, porphyrins, triarylmethanes, flavin and many others. Many fluorescent tags are commercially available from the SIGMA chemical company (Saint Louis, Mo.), Molecular Probes, R&D systems (Minneapolis, Minn.), Pharmacia LKB Biotechnology (Piscataway, N.J.), CLONTECH Laboratories, Inc. (Palo Alto, Calif.), Chem Genes Corp., Aldrich Chemical Company (Milwaukee, Wis.), Glen Research, Inc., GIBCO BRL Life Technologies, Inc. (Gaithersburg, Md.), Fluka ChemicaBiochemika Analytika (Fluka

Attorney Docket No. 14184-055WO1

Chemie AG, Buchs, Switzerland), and Applied Biosystems (Foster City, Calif.), as well as many other commercial sources known to one of skill.

The labels may be covalently bound to the compounds of the invention by a tether group. The tether group can be any moiety capable of covalently linking to the inhibitors and to the labels. Preferred groups are substituted or unsubstituted alkylene, alkenylene or alkynylene of 1 to 10 carbon atoms, more preferably 1 to 4 carbon atoms. Particularly preferred groups are unsubstituted alkynylenes.

10 METHODS FOR ASSESSING ACTIVITY *IN VITRO* AND *IN VIVO*

COX RELATED ASSAYS

COX-1 and COX-2 Inhibition: Purified Enzyme Assays

15

The *in vitro* COX-1 and COX-2 inhibitory activity of the compounds described herein can be measured using a test kit available from Cayman Chemical (Ann Arbor, MI). Because COX-1 and COX-2 convert arachidonic acid to prostaglandin H₂ (PGH₂), one can assess COX inhibitory activity of a test compound by measuring the effect of the compound on PGH₂ production in the presence of purified COX-1 enzyme and in the presence of purified COX-2 enzyme. In this assay, the production of PGH₂ can be measured by reducing PGH₂ to prostaglandin F_{2α} (PGF_{2α}) with SnCl₂ and then detecting PGF_{2α} by enzyme immunoassay (EIA) using a suitable antibody. Figure 1 provides activity data for certain compounds tested for inhibition of Cox-1 and Cox-2 using the Cox-1 and Cox-2 purified enzyme assays.

25

COX-1 and COX-2 Inhibition: Human Whole Blood Assay

30 A human whole blood assay can also be used to measure the inhibitory activity of each compound on COX-1 and COX-2. Briefly, human whole blood is drawn from 3-6

Attorney Docket No. 14184-055WO1

healthy volunteers who had not taken NSAIDS the previous 2 weeks. To measure COX-1 activity in whole blood, 100 μ l of whole blood is combined with a 2 μ l aliquot of test compound in vehicle or vehicle alone and incubated for 1 hr at 37 °C as described by Berg et al. (1999 *Inflamm. Res.* 48, 369-379). Serum is isolated from the sample by centrifugation at 12,000g for 5 min at 4 °C and then assayed for thromboxane B2 (TXB2) levels using an ELISA assay (e.g., Cayman EIA Kit, Catalog Number 519031). To measure COX-2 activity in whole blood, 100 μ l of heparinized whole blood is combined with a 1 μ l aliquot of 10 mg/mL LPS (lipopolysaccharide) and a 2 μ l aliquot of test compound in vehicle or vehicle alone and incubated for 24 h at 37 °C as described by Berg et al. (*supra*). Serum is isolated from the sample by centrifugation at 12,000g for 5 min at 4 °C and assayed for prostaglandin E₂ (PGE₂) using an ELISA assay (e.g., Cayman EIA Kit, Catalog Number 514010).

FAAH RELATED ASSAYS

FAAH Inhibition: Human Whole Cell Assay and Rat and Human Brain Homogenate Assays

The ability of compounds to inhibit FAAH can be measured in human whole cell and human and rat brain homogenates as described herein.

FAAH Rat Brain Membrane (RBM) Homogenate Preparation

Adult rats (Charles River CD strain, female, 200 g) are anaesthetized with isoflurane and rapidly decapitated, respectively. Each brain is quickly removed and chilled in tubes (3 brains per tube) on ice. About 25 mL of "homogenization buffer" (20 mM HEPES buffer, pH 7.0, with 1 mM MgCl₂) is added to 15 to 20 g of brain. The brains are homogenized on ice for 1 min using an Omni GLH homogenizer (Omni International, Marietta, Georgia). The homogenates are transferred to three centrifuge tubes and centrifuged at 36,500g for 20 min at 4 °C. The supernatant is discarded and each pellet is re-suspended in 25 mL "homogenization buffer". The re-suspended

Attorney Docket No. 14184-055WO1

material is again centrifuged (36,500g, 20 min at 4 °C). Pellets are combined by resuspension in 10 mL of “homogenization buffer” and incubated in a 37 °C water bath for 15 min. The tubes are then placed on ice for 5 min followed by centrifugation at 36,500g for 20 min at 4 °C. The supernatant is discarded and the
5 membrane pellets are then re-suspended in 40 mL of “resuspension buffer” (50 mM Tris-HCl buffer, pH 7.4, containing 1 mM EDTA and 3 mM MgCl₂). A Bradford Protein assay is performed to determine protein concentration. The protein is aliquotted into screw cap Cryo tubes each containing ~ 400 µL, flash frozen in liquid nitrogen and stored at –80 °C until used for the assay.

10 FAAH Human Brain Membrane (HBM) Homogenate Preparation

About 10 g of frozen normal human brain cortex tissue is obtained (e.g., from (Analytical Biological Services (ABS), Inc. (Wilmington, Delaware)). The brain tissue is thawed and transferred to a large ceramic mortar on ice. 50 mL of ice-cold “homogenization buffer” (20 mM HEPES buffer, pH 7.0, with 1 mM MgCl₂) is added
15 to the mortar and the tissue is homogenized with a pestle. The homogenate is centrifuged at 36,500g for 20 min at 4 °C. The supernatants are discarded and the pellets are re-suspended in “homogenization buffer” and centrifuged as before. The supernatants are again discarded and the pellets are re-suspended in 30 mL homogenization buffer and incubated in a 37 °C water bath for 20 min. The
20 homogenate is then centrifuged as before. The supernatant is discarded and the membrane pellets are re-suspended in 30 mL “resuspension buffer” (50 mM Tris-HCl buffer, pH 7.4, containing 1 mM EDTA and 3 mM MgCl₂). A Bradford Protein assay is performed to determine protein concentration. The protein is aliquotted into screw cap Cryo tubes each containing ~ 200 µL, flash frozen in liquid nitrogen and stored at
25 –80 °C until used for the assay.

FAAH Human Carcinoma Cell Membrane (HCM) Homogenate Preparation

Human breast epithelial carcinoma MCF7 cells are obtained from the American Type Culture Collection (ATCC Number HTB-22, Manassas, Virginia) and cultured as essentially as described by ATCC. Briefly, cells are grown in Eagle’s Minimum

Attorney Docket No. 14184-055WO1

Essential Medium (ATCC catalog no. 30-2003) supplemented with 4 mM L-glutamine, 10% final volume of fetal bovine serum (ATCC catalog no. 30-2020), and 0.1 mg/mL human recombinant insulin (Sigma, St. Louis, Missouri). The cells are grown in 5% carbon dioxide in air. When cells reach ~80% confluency, adherent
5 cells are rinsed with Hanks Balanced Salts Solution (ATCC catalog no. 30-2213), scraped into suspension and collected by centrifugation in a clinical centrifuge at room temperature. Cell pellets are then washed by resuspension in Hanks Balanced Salts Solution followed by centrifugation. Cell pellets are then flash frozen in a dry ice and ethanol bath and stored at -80 °C. Cell pellets are thawed and 25 mL of
10 homogenization buffer is added. Membrane homogenates of MCF7 cells are then prepared as described above for rat brain homogenates. A Bradford Protein assay is performed to determine the protein concentration. The protein is aliquotted into screw cap Cryo tubes each containing ~ 200 µL, flash frozen in liquid nitrogen and stored at -80 °C until used for the assay.

Determination of FAAH Activity

FAAH activity is assayed in the respective homogenates (Rat brain, Human brain, or Human breast cell carcinoma MCF7 cell) using a modification of the method of Omeir et al. (1995 Life Sci 56:1999) and Fowler et al. (1997 J. Pharmacol Exp Ther 283:729). For assay of FAAH in rat brain membrane homogenates (RBM), RBM
20 homogenates (7 µg protein in 20 µl final volume of 10 mM Tris pH 6.5) are mixed with 180 µl of a mixture of the following: 2.0 µM unlabelled anandamide, 0.03 µCi radiolabeled anandamide [ethanolamine 1-³H] (40-60 Ci/mmol, product number ART-626, American Radiolabelled Chemicals, St. Louis, Missouri), 1 mg/mL Bovine Serum Albumin (fatty acid-free BSA, electrophoresis grade, Sigma, St. Louis
25 Missouri), 10 mM Tris-HCl (pH 6.5), and 1 mM EDTA in the presence and absence of inhibitors (vehicle was DMSO at a final concentration of 1%) and incubated for 10 min at 37 °C. Samples are placed on ice to terminate the reactions. ³H-ethanolamine product and un-reacted ³H-anandamide substrate are separated by either: (1) using chloroform/ methanol extraction or (2) by passing the reaction mixture through a glass
30 fiber filter containing activated charcoal. Samples are extracted with

Attorney Docket No. 14184-055WO1

chloroform/methanol by adding 0.4 mL of chloroform/methanol (1:1 v/v), vigorously mixing the samples, and separating of the aqueous and organic phases by centrifugation. Radioactivity (corresponding to FAAH-catalyzed breakdown of ^3H -anandamide) found in aliquots (0.2 mL) of the aqueous phase is determined by liquid
5 scintillation counting with quench correction. IC_{50} values are determined as described by Jonsson et al. (2001 *Br J Pharmacol* 133:1263). Alternatively, reactions are purified using a modification of the solid-phase extraction method described by Wilson et al (2003 *Anal Biochem* 318 : 270). This method can be modified as follows: after reactions were incubated at 37°C for 10 min and chilled on ice, the
10 reaction mixtures are acidified by adding 10 μL of sodium phosphate solution [0.5M (pH 2.0)]. 90 μL aliquots of the acidified reaction mixtures are applied to activated charcoal (that has been previously washed with methanol as described by Wilson et al.) containing 80 μL of water on top of a glass fiber filter, centrifuged, and the radioactivity in the eluate is counted as described previously by Wilson et al.

15 Whole cell anandamide hydrolysis assay

FAAH activity can be assayed in whole cells using methods disclosed previously (Maccarone et al. 1998 *J Biol Chem* 273:32332 and Bisogno et al. 1997 *J Biol Chem* 272 :3315). In addition to the cell lines described in Maccarone et al. and Bisogno et
20 al., MCF7 (ATCC designation HTB-22) and T84 (ATCC designation CCL-248) cell lines may be used in these assays.

Determination of Endogenous and Exogenous Anandamide Levels in Rat Plasma and Brain Tissue

25 The effects of test compounds on endogenous and exogenously dosed anandamide levels can be measured. Rats dosed with test article are sacrificed at various time points to determine the levels of anandamide both circulating and within the brain tissue. For experiments measuring exogenous levels of anandamide, the anandamide
30 (Cayman Chemical, Ann Arbor, MI or Sigma Chemical, St. Louis, MO) is dosed (in the range of 3-30 mg/kg) intraperitoneally (IP) 30 min post dosing of test compound. Animals are sacrificed at either 15, 30, or 60 min after anandamide administration

Attorney Docket No. 14184-055WO1

upon anesthesia administration followed by decapitation. Brains are immediately extracted and the plasma is recovered from the blood.

Anandamide is extracted from the plasma by first precipitating the proteins by adding an equal volume of cold acetone with 10 ng of d8-anandamide (Cayman Chemicals, Ann Arbor, MI) as an internal standard. The acetone is evaporated from the supernatant followed by an extraction with chloroform:methanol (2:1). The chloroform layer is collected and evaporated to dryness. The pellet containing the anandamide is resuspended into methanol:chloroform (3:1) and injected onto an Xterra IS 2.1x20 mm C8 column (Waters Corporation, Milford, MA) and followed by detection by a Waters Quattro Micro LCMSMS (Waters Corporation, Milford, MA). The HPLC method consists of a step gradient (mobile phase A: 10 mM ammonium hydroxide in water, mobile phase B: 20% methanol in Acetonitrile) starting at 25% B and stepping up to 90% B at 2.2 min and holding for 2 min. Quantities are measured against known standards spiked into blank plasma using MassLynx v.4.0 software (Waters Corporation, Milford, MA).

Levels of anandamide from brain tissue are determined as follows. Brain tissue is homogenized in ethyl acetate and water (3:1) with 10 ng of d8-anandamide (Cayman Chemicals, Ann Arbor, MI) as an internal standard. The ethyl acetate layer is collected and evaporated to dryness. The pellet containing anandamide is resuspended in methanol:chloroform (3:1) and analyzed by the same method as plasma and normalized against the fresh tissue weight.

CRTH2 RELATED ASSAYS

CRTH2 agonist assay

CRTH2 agonists increase the expression of CD11b on eosinophils. Neutrophils do not express CRTH2. They do, however, express receptors for other lipid mediators, including 5-oxo-6,8,11,14-eicosatetraenoic acid (5-oxo-ETE), leukotriene B4 (LTB4), and platelet activating factor (PAF). Therefore, any increased expression of CD11b

Attorney Docket No. 14184-055WO1

by neutrophils is likely to be caused by an activity other than activation of CRTH2. Accordingly, preferred compounds increase CD11b expression on eosinophils, but not on neutrophils.

- 5 The potential CRTH2 agonist activity of certain compounds was tested using a CD11b expression assay using essentially the method described by Monneret et al. (*J Pharmacol Exp Ther* 304:349-55, 2003), and the results of this analysis are presented in Figure 2a where the results of two separate experiments are reported.
- 10 Briefly, polymorphonuclear cells (0.5 ml; 10^6 /ml cells) in PBS containing 0.9 mM CaCl_2 and 0.5 mM MgCl_2) were incubated with a test compound at room temperature for 10 min. The incubations were terminated by the addition of ice-cold FACSFlow (BD Biosciences; Cat# 342003) and centrifugation (400 g for 5 min at 4°C). The cells were then incubated for 30 min at 4°C with a mixture of PE-labeled mouse anti-
- 15 human VLA-4 (5 μl ; BD Biosciences) and FITC-labeled mouse anti-human CD11b (10 μl ; Beckman Coulter). The cells were then incubated with Optilyse C (0.25 ml; Beckman Coulter) for 15 min, centrifuged, and then fixed in PBS (0.4 ml; calcium and magnesium free) containing 1% formaldehyde. The distribution of fluorescence intensities among 60,000 cells was measured by flow cytometry. Eosinophils were
- 20 gated out on the basis of their granularity (high side scatter) and labeling with VLA-4 (PE fluorescence). CD11b was then measured in the eosinophil region on the basis of fluorescence due to FITC. All data were corrected for the value obtained for the corresponding isotope control antibody.
- 25 The results presented in Figure 2a are reported as the percentage of CD11b expression as compared to the maximum response generated by the positive control 15R-methyl PGD_2 ((5E,9 α ,13E,15R)-9,15-dihydroxy-15-methyl-11-oxoprostano-5,13-dien-1-oic acid). Compounds with greater than 30% CD11b activity in this assay were considered to be CRTH2 agonists.

30

Attorney Docket No. 14184-055WO1

To confirm that the CD11b expression is caused by activation of the CRTH2 receptor certain controls were performed. Accordingly, effect of the compounds on CD11b expression in neutrophils was tested. If the compound increases CD11b expression in neutrophils, the mobilization in eosinophils is likely caused by an activity other than activation of the CRTH2 receptor. In all cases tested CD11b expression was only observed in eosinophils.

CRTH2 antagonist assay

The potential CRTH2 antagonist activity of certain compounds was tested using an assay that tests the ability of the compounds to block the CD11b expression in eosinophils by 15-R-methyl-PGD₂ using essentially the method described above for the agonist assay except that the cells were preincubated with various concentrations of compounds before they were challenged with the agonist 15R-Methyl-PGD₂. The results of this analysis are presented in Figure 2b. A CRTH2 antagonist should block CD11b expression by subsequently added 15-Methyl-PGD₂. The results presented in Figure 2b are reported as percentage of inhibition of the maximum response generated by 15R-Methyl-PGD₂. Ramatroban (3-((3R)-3-{{(4-fluorophenyl)sulfonyl}amino}-1,2,3,4-tetrahydro-9H-carbazol-9-yl)propanoic acid), a known CRTH2 antagonist was used as a positive control in this assay. Compounds with 85% or greater inhibition in this assay are considered to be CRTH2 antagonists.

Alternatively, the CRTH2 antagonist activities can also be determined by a calcium mobilization assays conducted as follows, adapted from the protocol described by Monneret et al. (*J Pharmacol Exp Ther* 304:349-55, 2003). Leukocytes (10⁷ cells/ml) are treated with the acetoxymethyl ester of fluo-3 (2 μ M; Molecular Probes, Eugene, Oregon) in the presence of Pluronic F-127 (0.02%; Molecular Probes) for 60 min at 23°C. The mixture is centrifuged at 200 x g for 10 min and the pellet resuspended in PBS to give a concentration of 5 x 10⁶ cells/ml. The leukocytes are treated with PC5-labeled mouse anti-human CD16 (3.3 μ l/10⁶ cells; Beckman-Coulter) for 30 min at 0°C. PBS (25 ml) is added, the mixture centrifuged as described above, and the pellet resuspended in PBS to give a concentration of 3x10⁶ leukocytes/ml. After incubation

Attorney Docket No. 14184-055WO1

at 23°C for 30 min, an aliquot (0.95 ml) of the leukocyte suspension is removed and treated with PBS (50 µl) containing Ca⁺⁺ (36 mM) and Mg⁺⁺ (20 mM). After 5 min, the cells are analyzed by flow cytometry using a FACSCalibur instrument (Becton-Dickinson, San Jose, CA). A total of approximately 10⁶ cells are counted over a
5 period of 3 to 4 min for each sample. Fluo-3 fluorescence is measured in eosinophils, neutrophils, and monocytes, which are gated out on the basis of CD16 staining and side scatter. Test compounds are added 2 min after the start of each run followed 2 min later by 15R-Methyl-PGD₂. Maximal calcium responses are determined by addition of the calcium ionophore, A23187 (10 µM) one minute after the addition of
10 15R-Methyl-PGD₂.

MEASUREMENT OF PHARMACOKINETIC PARAMETERS

To determine the various pharmacokinetic parameters, serum samples from animals dosed with a test compound are collected and analyzed by LC/MS. Briefly, samples are injected (10 µL) into a flow of 10% methanol in water onto a sample extraction
15 cartridge (Waters Oasis HLB Direct Connect). The sample is washed for 0.5 min followed by a column switch that places the sample extraction cartridge into the path of the HPLC. The sample is eluted onto a reverse phase HPLC column (Waters Xterra IS C₈ 2.1 x 20mm, 5 µm particle size) and is eluted with a gradient (Mobile Phase A: 10 mM NH₄OH in dH₂O; Mobile Phase B: 20% methanol in Acetonitrile).
20 Initial condition of 20% B, ramping to 90% B over 1.5 min, and holding for 0.5 min, then returning to initial conditions to re-equilibrate the column for 1 min, all at a flow rate of 0.4 mL/min.). A Micromass Quattro Micro (Waters Corp.; Milford, MA) triple quadrupole mass spectrometer operated in MRM mode is used to detect test compound as it elutes from the HPLC column. Concentrations are determined by
25 relative response to an internal standard and calculated based on a standard concentration curve of the test compound. MassLynx software (Waters, Corp.; Milford, MA) is used to calculate the absolute concentration of test compound in each serum sample. A concentration versus time plot is generated from the data in Microsoft Excel, Summit Software PK Solutions 2.0 or Graph Pad Prism (GraphPad
30 Software, Inc., San Diego, CA) to generate PK curves. From the generated curve, the

Attorney Docket No. 14184-055WO1

AUC_n (Area Under the Curve, n = length of experiment in h) is calculated by the software for both intravenous (IV) and orally dosed animals. Oral Bioavailability (F_n) is calculated using the equation: $F = AUC_{\text{oral}} / AUC_{\text{IV}}$. C_{max} and T_{max} are determined by visual inspection of the oral concentration curve. C_{max} is the maximum concentration of the test compound circulating in the blood through the duration of the experiment reported at time, T (T_{max}). The terminal half-life, t_{1/2}, is calculated using at least two data points on the IV curve representing the elimination phase. Thus, the t_{1/2} is calculated by inserting the slope (β) of the line generated by plotting the natural log of the test article concentration versus time (during the elimination phase) into the equation $t_{1/2} = 0.693/\beta$. The volume of distribution (Vd) is calculated using the equation $Vd = Cls/\beta$ (Cls = systemic clearance, β = slope from t_{1/2} equation). Cls are determined by dividing the dose by the AUC_{IV}.

ANIMAL MODELS

Animal Models For Assessing Anti-Inflammatory Activity

Any of a variety of animal models can be used to test the compounds of the invention for their effectiveness in reducing inflammation and treating pain. Useful compounds can exhibit effectiveness in reducing inflammation or pain in one or more animal models.

Carrageenan-induced foot pad edema model

The model is described, for example, by Winter et al. (1962 *Proc Soc Exp Biol Med* 111:544). Briefly, rats are fasted with free access to water for 17 to 19 h before oral treatment with up to three doses of a test compound, indomethacin or celecoxib, or a control vehicle (1% methylcellulose in deionized water). One h after the last treatment, paw edema is induced by injecting 0.05 mL of a 2 % carrageenan solution into the left hindpaw.) The left hindpaw volume of each rat is measured using a plethysmometer before oral treatment, at the time of carrageenan injection and at 1.5 h, 3 h, 4.5 h after the injection of carrageenan. The edema volume of each rat at each time point is expressed as the change from the volume at the time of oral treatment

Attorney Docket No. 14184-055WO1

and the anti-inflammatory effect in treated groups is expressed as % inhibition compared to the vehicle only group 1.5 h, 3 h and 4.5 h after the carrageenan injection. The significance of the difference between in edema different groups is assessed by a one-way analysis of variance (ANOVA) followed by the non-paired
5 Dunnett *t* test. In this model, hyperalgesic response and PGE₂ production can also be measured (Zhang et al. 1997 *J Pharmacol and Exp Therap* 283:1069).

Complete Freund's adjuvant (CFA) induced arthritis model

In this model arthritis is induced in groups of eight Lewis derived male rats weighing 160 ± 10 g by injecting a well-ground suspension of killed *Mycobacterium*
10 *tuberculosis* (0.3 mg in 0.1 mL of light mineral oil; Complete Freund's Adjuvant, CFA) into the subplantar region of the right hind paw on Day 1. Hind paw volumes are measured by water displacement on Days 0, 1 and 5 (right hind paw, with CFA), and on Days 0, 14 and 18 (left hind paw, without CFA); rats are weighed on Days 0 and 18. Test compounds, dissolved or suspended in 2% Tween 80, are prepared fresh
15 daily and administered orally twice daily for 5 consecutive days (Day 1 through Day 5) beginning one h before injection of CFA. For CFA-injected vehicle control rats, the increase in paw volume on Day 5 relative to Day 1 (Acute Phase of inflammation) is generally between 0.7 and 0.9 mL; and, that on Day 18 relative to day 14 (Delayed Phase of inflammation) is generally between 0.2 and 0.4 mL. Thus, anti-
20 inflammatory activity in this model may be denoted by values calculated during the Acute Phase as well as the Delayed Phase. Animals are also weighed on Day 0 and Day 18; CFA-injected vehicle control animals generally gain between 40 to 60 g body weight over this time period. A 30 percent or more reduction in paw volume relative to vehicle treated controls is considered of significant anti-inflammatory activity. The
25 mean ± SEM for each treatment group is determined and a Dunnett test is applied for comparison between vehicle and treated groups. Differences are considered significant at P<0.05. Polyarthritis of fore paw, tail, nose and ear can be scored visually and noted on the first day and final day, wherein positive (+) sign is for swelling response and negative (-) sign is normal. X-ray radiographies of the
30 hindpaws can also be performed for further radiological index determination of

Attorney Docket No. 14184-055WO1

arthritic symptoms. Hyperalgesia can also be measured in this model, allowing determination of analgesic effects of test compounds (Bertorelli et al. 1999 *Brit Journ Pharmacol* 128:1252).

Air-pouch model

5 This model is described by Masferrer et al. (1994 *Proc Natl Acad Sci USA* 91:3228). Briefly, male Lewis rats (175-200 g, Harlan Sprague-Dawley) are subcutaneously injected with 20 mL of sterile air into the intrascapular area of the back to create air cavities. An additional 10 mL of air is injected into the cavity every 3 days to keep the space open. Seven days after the initial air injection, 2 mL of a 1% solution of
10 carrageenan dissolved in sterile saline is injected directly into the pouch to produce an inflammatory response. In treated and untreated animals the volume of exudate is measured and the number of leukocytes present in the exudate is determined by Wright-Giemsa staining. In addition, PGE₂ and 6-keto-PGF_{1α} are determined in the pouch exudates from treated and untreated animals by specific ELISAs (Cayman
15 Chemicals, Ann Arbor, MI).

Animal Models for Assessing Analgesic Activity

Carrageenan-induced thermal hyperalgesia

This model is described by Hargreaves et al. (1988 *Pain* 32:77). Briefly, inflammation is induced by subplantar injection of a 2% carrageenan suspension
20 (0.1 mL) into the right hindpaw. Three h later, the nociceptive threshold is evaluated using a thermal nociceptive stimulation (plantar test). A light beam (44% of the maximal intensity) is focused beneath the hindpaw and the thermal nociceptive threshold is evaluated by the paw flick reaction latency (cut-off time: 30 sec). The pain threshold is measured in ipsilateral (inflamed) and in contralateral (control)
25 hindpaws, 1 h after the oral treatment with the test compound or a control. The results can be expressed as the nociceptive threshold in seconds (sec) for each hindpaw and the percentage of variation of the nociceptive threshold (mean ± SEM) for each rat from the mean value of the vehicle group. A comparison of the nociceptive threshold

Attorney Docket No. 14184-055WO1

between the inflamed paw and the control paw of the vehicle-treated group is performed using a Student's *t* test, a statistically significant difference is considered for $P < 0.05$. Statistical significance between the treated groups and the vehicle group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Phenylbenzoquinone-induced writhing model

This model is described by Siegmund et al. (1957 *Proc Soc Exp Bio Med* 95:729). Briefly, one h after oral dosing with a test compound, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5th to the 10th min after PBQ injection, and can also be counted between the 35th and 40th min and between the 60th and 65th min to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean $\pm$ SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

Kaolin-induced arthritis model.

This model is described by Hertz et al. (1980 *Arzneim Forsch* 30:1549). Briefly, arthritis is induced by injection of 0.1 mL of kaolin suspension into the knee joint of the right hind leg of a rat. Test compounds are administered subcutaneously after 15 min and again after two h. Reference compounds can be administered orally or subcutaneously. Gait is assessed every h from 1.5 h to 5.5 h after treatment and is scored as follows: normal gait (0), mild disability (1), intermittent raising of paw (2), and elevated paw (3). Results are expressed as the mean gait score (mean $\pm$ SEM) calculated from individual values at each time point and the percentage of variation of the mean score calculated from the mean value of the vehicle-treated group at 4.5 h and 5.5 h after treatment. The statistical significance of differences between the

Attorney Docket No. 14184-055WO1

treated groups and the vehicle-treated group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) at each time point.

Peripheral Mononeuropathy Model

This model is described by Bennett et al. (1988 *Pain* 33:87) and can be used to assess anti-hyperalgesic effect of an orally administered test compound in a model of peripheral mononeuropathy. The effect of the test substance can be compared to a no treatment control or reference substance, e.g., morphine. Peripheral mononeuropathy is induced by loose ligation of the sciatic nerve in anaesthetized male Sprague Dawley rats (pentobarbital; 45 mg/kg by intraperitoneal route). Fourteen days later, the nociceptive threshold is evaluated using a mechanical nociceptive stimulation (analgesimeter paw pressure test; Ugo Basile, Italy). The test and reference compounds and the vehicle are orally administered (10 mL/kg carried 1% methylcellulose). Increasing pressure is applied to the hindpaw of the animal until the nociceptive reaction (vocalization or paw withdrawal) is reached. The pain threshold (grams of contact pressure) is measured in ipsilateral (injured) and in contralateral (non injured) hindpaws, 60 min after treatment. The results are expressed as: the nociceptive threshold (mean $\pm$ SEM) in grams of contact pressure for the injured paw and for the non-injured paw (vehicle-treated group) and the percentage of variation the nociceptive threshold calculated from the mean value of the vehicle-treated group. A comparison of the nociceptive threshold between the non injured paw and the injured paw of the vehicle-treated group is performed using a Student's *t* test. The statistical significance of the difference between the treated groups and the vehicle group is determined for the injured hindpaw by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software (SigmaStat® v. 2.0.3 (SPSS Science Software, Erkrath GmbH)).

Diabetic Neuropathy Paw Pressure Test

Complete protocol details can be found in Rakieten et al. (1963 *Cancer Chemother Rep* 29:91). Briefly, diabetes is induced by intraperitoneal injection of streptozotocin in rats. Three weeks later, the nociceptive threshold is measured using the paw

Attorney Docket No. 14184-055WO1

pressure test to assess hyperalgesia. Test compound or controls are administered intraperitoneally 30 min prior to pain measurement.

Acetic Acid Writhing Test

Briefly, a test compound is administered orally one h before intraperitoneal injection of acetic acid (0.5%, 10 mL/kg) in rats. Reduction in the number of writhes by 50 percent or more (≥ 50) per group of animals observed during the 5 to 11 min period after acetic acid administration, relative to a vehicle treated control group, indicates possible analgesic activity. This assay is based on that described in Inoue, K. et al. (1991 *Arzneim. Forsch./Drug Res.* 41: 235).

Formalin test

Complete protocol details can be found in Hunskaar et al. (1985 *Neurosci. Meth.* 14:69). Briefly, 30 min after intraperitoneal administration of a test compound or a control, 20 μ L of a 5% formalin solution is injected by subplantar route into the right hindpaw of the rat. Hindpaw licking time is recorded during the early phase and the later phase after formalin injection.

Tail flick Test

Complete protocol details can be found in D'Amour and Smith (1941 *J Pharmacol. Exp Ther.* 72:74). Briefly, 30 min after intraperitoneal administration of a test compound or a control, a light beam is focused onto the tail of the rat. The nociceptive reaction latency, characterized by tail withdrawal, is recorded. The cutoff time is set to 15 seconds.

Tail Immersion Test

In this test the tail of the rat is immersed into a 50-60°C water bath. The nociceptive reaction latency, characterized by tail withdrawal, is measured (Haubrich et al. 1990 *J Pharmacol Exp Ther* 255:511 and Lichtman et al. 2004 *Pain* 109:319).

Attorney Docket No. 14184-055WO1

Hot plate test

Complete protocol details can be found in Eddy et al. (1950 *J Pharmacol. Exp. Ther.* 98:121). Briefly, 30 min after intraperitoneal administration of a test compound or a control, the mouse is placed on a metallic hot plate maintained at 52°C. The
5 nociceptive reaction latency, characterized by a licking reflex of the forepaws or by a jumping off the hot plate is recorded. The cut-off time is set to 30 seconds.

Assays for Assessing Anxiolytic Activity

Compounds of the invention that modulate FAAH activity, and thus fatty acid amide levels, may also have anxiolytic activity. Animal models to assess anxiolytic activity
10 include:

Elevated Plus Maze

The elevated plus maze consists of four maze arms that originate from a central platform, effectively forming a plus sign shape as described in van Gaalen and Steckler (2000 *Behavioural Brain Research* 115:95). The maze can be made of
15 plexiglas and is generally elevated. Two of the maze arms are unwallled (open) and two are walled (closed). The two open arms are well lit and the two enclosed arms are dark (Crawley 2000 *What's Wrong With My Mouse?: Behavioral Phenotyping of Transgenic and Knockout Mice*. Wiley-Liss, New York). The test is premised on the naturalistic conflict between the tendency of an animal to explore a novel
20 environment and the aversive properties of a brightly lit, open area (Pellow et al. 1985 *J. Neuroscience Methods*. 14:149).

Complete protocol details can be found in Fedorova et al. (2001 *J. Pharm. Exp. Ther.* 299: 332). Briefly, 15 min following intraperitoneal administration of test compound
25 or control, an animal is placed individually on the central platform, facing one of the open arms opposite to the observer. The number of open and closed arm entries, and the time spent in the different compartments of the maze by the animal (central platform, open and closed arms) is scored (as described in Gaalen et al. (*supra*)). An

Attorney Docket No. 14184-055WO1

arm visit is recorded when an animal moves all four paws into the arm as described in Simonin et al. (1998 *EMBO J.* 17: 886). Behavior is scored by an observer and/or via a video camera over a 5-min test session. A greater amount of time spent or entries made by the animal in the open versus the closed arms is an indicator of anxiolytic activity.

Elevated Zero Maze

The elevated zero maze is a modification of the elevated plus maze. The elevated zero maze consists of a plexiglas apparatus in the shape of a circle (i.e., a circular runway of 46 cm diameter and 5.5 cm runway width) with two open and two wall-enclosed sectors of equal size. It is elevated up to a meter above the ground. This apparatus is described in Simonin et al. (*supra*) and Crawley (*supra*).

Complete protocol details can be found in Kathuria et al (2003 *Nature Medicine* 9: 76). Briefly, 30 min following intraperitoneal administration of test compound or control, an animal is placed on one open sector in front of an enclosed sector. Time in a new sector is recorded as entry with all four paws. Behavior will be scored by an observer and/or via a video camera over a 5-min test session. A greater amount of time spent or entries made by the animal in the open versus the walled sector is an indicator of anxiolytic activity.

Any of a variety of animal models can be used to test the compounds of the invention for their effectiveness in reducing allergic and inflammatory activity. Useful compounds can exhibit effectiveness in reducing allergic response and inflammation in one or more animal models.

Animal Models Related to Allergic Response

Systemic Eosinophilia

The model is described, for example, by Shichijo et al. (2003 *J. Pharmacol. Exp. Ther.* 307:519-520). Briefly, seven week old male Brown Norway or Wistar rats are

Attorney Docket No. 14184-055WO1

intravenously injected with 250-300ug/rat of 13, 14-dihydro-15-keto-prostaglandin D₂ (DK-PGD₂), a CRTH2 agonist (dissolved in ethanol and PBS), or the corresponding volume of solvent. Rats are pretreated with or without intravenously injected 3-30 mg/kg Ramatroban [(+)-(3R)-3-(4-fluorobenzenesulfonamido)-1,2,3,4-tetra-
5 hydrocarbazole-9-propionic acid], a CRTH2/thromboxane A₂ antagonist (dissolved in NaOH, pH-neutralized by HCl addition, and dosed in a 10% Cremophor solution). Peripheral blood is collected at 0, 1, 2, 3, 4 and 5 hours post-injection for blood smears. Following blood collection, animals are euthanized by complete bleeding and the femoral head and condyles are removed from the left femur. Total white blood
10 cells are counted. Differential cell counts are performed on blood smears stained with May-Gruenwald's and Giemsa's solution based on standard morphologic and histological criteria.

Induction of Contact Hypersensitivity

In this model, induction of contact hypersensitivity (CHS) is created as described by
15 Takeshita et al. (2004. *Int. Immunol.* 16(7):947-59). On days 0 and 1, female Balb/c mice, 7-8 weeks of age are painted onto the shaved abdominal skin with 400μl of 0.5% fluorescein isothiocyanate (FITC) dissolved in acetone:dibutylphthalate (1:1, DBP). Six days later, mice are challenged by application of 20μl of 0.5% FITC in DBP onto both sides of the right ear. The solvent control (DBP) is applied to the left
20 ear. Challenge-induced increases in ear thickness are measured by an engineer's micrometer at 0, 24, 48 and 72 hours post-challenge. The CHS response is determined by challenge-induced increases in ear thickness. CHS response = [(right ear thickness post challenge- left ear thickness post challenge) – (right ear thickness pre challenge – left ear thickness pre challenge)].

25 To determine the presence of leukocyte infiltration, ears and back skins are fixed for 30 hours in zinc fixative at room temperature and embedded in paraffin for histological and immunohistochemical evaluation. For assessment of eosinophil peroxidase activity (EPO), skin sections are homogenized in 1 ml of ice cold buffer (0.05 M Tris-HCl pH 8.0 containing 0.1% Triton X-100). The tissue samples are

Attorney Docket No. 14184-055WO1

centrifuged at 10,000 g for 20 minutes at 4° C and supernatants are collected for measurement of EPO activity. In a 96 well microtiter plate, the substrate solution (100µl of 10mM o-phenylenediamine in 0.05 M Tris-HCl and 4mM H₂O₂) is added to the 20-fold diluted homogenate in buffer (100µl). The reaction mixture is incubated at room temperature for 1 hour before the reaction is stopped by the addition of 100µl of 2M sulfuric acid. The microtiter plate is measured for absorbance.

Evan's Blue Test

Complete protocol details can be found in Takeshita et al. (2004. *Int. Immunol.*

16(7):947-59). Briefly, female Balb/c mice, 7 weeks of age are injected at two locations intradermally on their shaved backs with increasing concentrations of 0.1-10ug/site of DK-PGD₂. This is followed by an intravenous injection of 0.25ml of saline containing 1.25 mg of Evan's blue dye. Four hours post-dye injection, mice are euthanized and the back skin is collected. Edema severity is assessed by measuring the density of the extravasated dye. Effects of pharmacological inhibition of the inflammatory reaction to DK-PGD₂ will also be assessed by treatment with CRTH2 antagonists, such as Ramatroban.

Allergen-Induced Airway Cell Proliferation and Inflammation

Complete protocol details can be found in Eynott et al. (2003. *J. Pharmacol. Ther.*

304:22-29). Briefly, Brown Norway rats are sensitized on days 1, 2, and 3 with intraperitoneal injections of 1 mg ovalbumin (OVA) with 100mg Al(OH)₃ in 1 mL 0.9% NaCl saline. Then they are exposed to either 0.9% NaCl saline (vehicle) or 1% OVA aerosol (1% OVA in 0.9% NaCl saline) every 3rd day on three occasions for 30 minutes. On those days are treated with either vehicle or compound 1 hour before and ~4-8 hours after allergen exposure. Airway inflammatory cell accumulation and proliferation of cells is measured by bronchoalveolar lavage (BAL) fluid collection and cell counts. Samples are collected 24 hours after final aerosol challenge. Serum OVA-specific IgE levels is measured by the Rat IgE ELISA Quantitation kit (Bethyl Laboratories, Inc., catalog # E101-85).

Attorney Docket No. 14184-055WO1

Airway hyperresponsiveness analysis using the FlexiVent system

8-10 wk old male BALB/c mice (n=10/experimental group) are quarantined for 14 days before immunization by intraperitoneal injection of a mixture of ovalbumin (OVA; 10 µg) and aluminum hydroxide (Alum; 2 mg) in sterile water or vehicle only (sterile water). Animal are immunized at Day 0 and Day 7. On days 13, 14, and 15 test compound (10 mg/kg), vehicle or dexamethasone (10 mg/kg positive control) is delivered by oral gavage (2X per day). On days 14 and 15, animals are exposed to aerosolized ovalbumin (OVA challenge with 1% heat aggregated grade V chicken egg ovalbumin; Sigma, St Louis, MO) for 3 hours each day. Twenty four hours following the second OVA challenge mice are anesthetized and airway hyperresponsiveness to increasing concentrations of methacholine (3, 6, 12, 25, 50 mg/ml nebulizer delivered via aerosol) is measure using a FlexiVent analyzer (SCIREQ, Montreal, Canada). Airway resistance is calculated for each concentration of methacholine. Following Flexivent analysis, animals are sacrificed and either bronchoalveolar lavage (BAL) is performed to collect cells and fluid or lungs are fixed and isolated for histopathological analyses.

Prostaglandin D₂-induced Eosinophilic Airway Inflammation

Complete protocol details can be found in Shiraishi et al (2004. *J. Pharmacol. Ther. epub as DOI:10.1124/jpet.104.078212*). Briefly, Brown Norway rats are intravenously injected with rat interleukin-5 or PBS, one hour prior to intratracheal administration of prostanoid receptor agonists. These agonists include the following; PGD₂, two CRTH₂-specific agonists, DK-PGD₂, and 11-deoxy-11-methylene-15-keto-PGD₂ (MK-PGD₂), a DP receptor-specific agonist BW 245C, a thromboxane A₂ receptor (TP)-specific agonist, I-BOP and Indomethacin. In some experiments, an orally delivered CRTH₂/TP antagonist, Ramatroban, an intravenously delivered DP antagonist, BW A868C, or an intravenously delivered TP antagonist are administered two hours prior to administration of agonists. Rats are euthanized at 2, 8 and 24 hours post-agonist administration. Inflammatory cell accumulation in the trachea and lungs is recovered by bronchoalveolar lavage for cell counts and lungs are evaluated by

Attorney Docket No. 14184-055WO1

histological examination. In a separate experiment, rats receive intravenous injection of IL-5 (0.2 ng/kg) or PBS one hour prior to intratracheal administration of PGD₂ (100 nmoles/animal) or vehicle. A peripheral blood sample is collected hourly post-dose of IL-5 for hematological evaluation.

5 Murine Allergic Inflammation

Complete protocol details are described in Fujitani et al. (2002 *J. Immunol* 168:443-449) and Matsuoka et al. (2000. *Science* 287: 2013-2017), Briefly, transgenic and wildtype mice are immunized with 10 µg OVA in 0.2 ml Alum on days 0 and 14. On day 21, the mice are exposed to aerosolized OVA (50mg/ml in sterile saline) for 20
10 minutes. On days 1 and 3 post-OVA challenge, mice are euthanized, bronchoalveolar lavaged, and the lavage fluid is assessed by differential cell counting.

Allergic Rhinitis in Anesthetized Rodents

In this model described, for example, by Arimura et al. (2001 *J. Pharmacol. Ther.* 298:411-419) guinea pigs are sensitized to OVA twice by inhalation of an aerosol solution of 1 % OVA for 10 minutes. At 7 days after the second sensitization, the animals are anesthetized and artificially ventilated through a tracheal cannula using a respirator. Another glass cannula is inserted into the nasopharynx from the side of the larynx, and a fixed amount of air is continuously insufflated into the nasal cavity via
20 the nasal cannula using another respirator. Insufflation pressure is monitored by a pressure transducer connected to the side arm of the nasal cannula as an indication of intranasal pressure. Nasal antigen challenge is performed by generating an aerosol of 3% OVA between the nasal cannula and the animal respirator for 3 minutes using an ultrasonic nebulizer, and then the intranasal pressure is measured for 30 minutes.
25 Nasal secretion and the nose are collected for further evaluation.

A biphasic allergic rhinitis model in conscious guinea pigs is also fully described in Arimura et al. (2001 *J. Pharmacol. Ther.* 298:411-419).

Attorney Docket No. 14184-055WO1

Allergic Conjunctivitis Model

Complete protocol details are described in Arimura et al. (2001 *J. Pharmacol. Ther.* 298:411-419). Briefly, a 2.5% OVA solution is applied topically to both eyes (10
5 μ l/eye) of conscious guinea pigs that have been sensitized as described in the
“Allergic Rhinitis Model in Anesthetized Guinea Pigs” protocol above. Immediately
following OVA application, Evan’s blue dye (20 mg/kg i.v.) is injected as a marker of
plasma exudation. The amount of Evan’s blue extravasated in the conjunctiva and
eyelid for 30 minutes is quantified. Independently, Histamine 0.001%, PGD₂ 0.01%,
10 or a combination of the two are applied to the eyes of nonsensitized guinea pigs, and
dye exudation is determined.

In the case of CRTH2 modulators useful for treating gastrointestinal disorders in
which inflammation plays a role there a number of useful animal models that can be
15 used in the testing of compounds.

TNBS Colitis in Rats:

Complete protocol details for one model can be found in Morris et al.
(Gastroenterology 96(3):795-803, 1989). Briefly, to induce chronic colonic
inflammation in rats, a rubber catheter is inserted rectally into the colon such that the
20 tip is 8 cm proximal to the anus. Next, 2,4,6-Trinitrobenzenesulfonic acid (TNBS 5-
30mg) dissolved in 50% ethanol is instilled into the lumen of the colon through the
rubber catheter. Rats are euthanized at various times (24 hours and 1-8 weeks)
following rectal TNBS administration and the colon tissue is examined for damage,
inflammation and ulceration. Colon weight and colonic myeloperoxidase (MPO)
25 activity is also assessed. Complete protocol details for an alternative model can
be found in Dohi et al. (Gastroenterology 119:724-733, 2000). Briefly, mice
(C57BL/6; 40 μ g/g and Balb/c 36 μ g/g) are given a solution of TNBS dissolved in a
mixture of phosphate-buffered saline and then mixed with an equal volume of ethanol
for a final concentration of 2% TNBS in 50% ethanol. On days 0 and 7, the TNBS
30 enema is administered to mice anesthetized with ketamine and xylazine via a glass

Attorney Docket No. 14184-055WO1

microsyringe equipped with a gastric intubation needle. Tissues and cells are assessed 3 days later (day 10).

Oxazolone Colitis in Mice:

Complete protocol details for this model can be found in Kojima et al. (J. Pharmacol. Sci. 96:307-313, 2004). Briefly, a metal catheter is inserted 4 cm into the lumen of the colon via the anus in the anesthetized mouse. Oxazolone solution (0.15 mL/mouse) is administered into the colon through the catheter. Colonic tissues from mice on days 0 (before colitis induction), 1, 2, 4 and 7 are collected and examined for evidence of colitis and myeloperoxidase (MPO) activity.

In general any model of colitis can be used, in particular, mouse or rat models in which a chemical, hapten or antigen is used to induce colitis.

Oral antigen-induced gastrointestinal allergy in mice

Complete protocol details for one model can be found in Hogan et al. (Nat Immunol. 2(4):353-60, 2001). Briefly, mice are sensitized by intraperitoneal injection with ovalbumin (50 µg) in alum (1mg) in 0.9% sterile saline on day 0. On days 12 and 15, mice are orally administered with encapsulated ovalbumin or placebo enteric-coated beads (20mg) followed by oral administration of acidified water (300 µL, pH 2.0). In some experiments, mice are intragastrically challenged with soluble ovalbumin (1 mg) in PBS (200 µL) or control PBS on days 12 and 15. Mice are euthanized and parameters are measured 72 hours after the last antigen challenge. The gastrointestinal tract tissue is examined for eosinophilic inflammation.

Complete protocol details for another model can be found in Forbes et al. (Gastroenterology 127:105-118, 2004). Briefly, mice are sensitized by an intraperitoneal injection of 50 µg of ovalbumin/1mg of alum in 200 µL of 0.9% sterile saline on day 0. On days 12, 14, and 16, mice are orally administered 20 mg of either encapsulated ovalbumin enteric coated beads or placebo beads, followed by 200µL of acidified water (pH 2.0). 72 hours after the last antigen challenge, mice are euthanized and disease parameters are measured in various ways. In some

Attorney Docket No. 14184-055WO1

experiments, mice are intraperitoneally injected on days 0, 1, and 3 with either rat IgG2b-depleting anti-D4 monoclonal antibody or rat IgG control antibody. Methacholine-induced bronchial hyperresponsiveness is determined on day 4..

5 Experimental oral allergen-induced diarrhea

Complete protocol details can be found in Brandt et al. (J. Clin. Invest. 112(11):1666-1677, 2003). Briefly, mice are sensitized twice, 2 weeks apart, with 50 µg of ovalbumin/1mg of aluminum potassium sulfate adjuvant by intraperitoneal injection. Two weeks later, mice are held in the supine position 3 times a week and orally
10 administered 250 µL of sterile saline that contains up to 50mg of ovalbumin. Before each intragastric challenge, mice are deprived of food for 3-4 hours with the aim of limiting antigen degradation in the stomach. Diarrhea is assessed by visually monitoring mice for up to 1 hour following intragastric challenge.

Other colitis models are described Elson et al. (Gastroenterology 109:1344-1367, 1995)
15 and Kim et al. (Scand. J. Gastroenterol 27:529-537, 1992).

Assays for Assessing Antinociception Mechanism

Compounds can be tested to determine if they influence pathways involved in nociception. The results of such assays can be used to investigate the mechanism by
20 which a test compound mediates its antinociceptive effect. In addition to the FAAH related assays, the following methods can be used to assess the mechanism by which a test compound mediates its antinociceptive effect.

Elevation of 3α,5α-THP

3α-hydroxy-5α-pregnan-20-one (3α,5α-THP or allopregnanolone) is a pregnane steroid
25 that acts as an agonist of the inhibitory GABA_A receptor subtype and is known to have both anxiolytic and analgesic effects in a variety of animal systems, with supportive evidence for a similar role in humans. Thus, compounds that elevate

Attorney Docket No. 14184-055WO1

3 α ,5 α -THP may have an antinociceptive effect. The level of 3 α ,5 α -THP in the brain of animals treated with a test compound can be measured as described by VanDoren et al. (1982 *J Neuroscience* 20:200) as follows. Briefly, steroids are extracted from individual cerebral cortical hemispheres dissected in ice-cold saline after euthanasia.

5 Cortices are frozen at -80 °C until use. Samples are digested in 0.3 N NaOH by sonication and extracted three times in 3 mL aliquots of 10% (v/v) ethyl acetate in heptane. The aliquots are combined and diluted with 4 mL of heptane. The extracts are applied to solid phase silica columns (Burdick & Jackson, Muskegon, MI), washed with pentane, and steroids of similar polarity to 3 α ,5 α -THP are eluted off of
10 the column by the addition of 25% (v/v) acetone in pentane. The eluant is then dried under N₂ and steroids are redissolved in 20% (v/v) isopropanol RIA buffer (0.1 M NaH₂PO₄, 0.9 M NaCl, 0.1% w/v BSA, pH 7.0). Extraction efficiency is determined in 50 μ l of the redissolved extract by liquid scintillation spectroscopy and the remaining sample is used in the determination of 3 α ,5 α -THP by radioimmunoassay.

15 Reconstituted sample extracts (75 μ l) and 3 α ,5 α -THP standards (5-40,000 pg in 6.25% v/v ethanol, 31% v/v isopropyl alcohol in RIA buffer) are assayed in duplicate by the addition of 725 μ l of RIA buffer, 100 μ l of [³H]3 α ,5 α -THP (20,000 dpm), and 100 μ l of anti-3 α ,5 α -THP antibody. Total binding is determined in the absence of
20 unlabeled 3 α ,5 α -THP, and nonspecific binding is determined in the absence of antibody. The antibody-binding reaction is allowed to equilibrate for 120 min at room temperature and is terminated by cooling the mixture to 4 °C. Bound 3 α ,5 α -THP is separated from unbound 3 α ,5 α -THP by incubation with 300 μ l of cold dextran coated charcoal (DCC; 0.04% dextran, 0.4% powdered charcoal in double-distilled H₂O) for 20 min. DCC is removed by centrifugation at 2000 x g for 10 min. Bound
25 radioactivity in the supernatant is determined by liquid scintillation spectroscopy. Sample values are compared to a concurrently run 3 α ,5 α -THP standard curve and corrected for extraction efficiency.

Cannabinoid Receptor Binding

Compounds may exert an antinociceptive effect via binding to either or both of the
30 cannabinoid receptors CB₁ and CB₂. CB₁ is expressed in the brain (Matsuda et al.

Attorney Docket No. 14184-055WO1

1990 *Nature* 346:561), and CB₂ is expressed by macrophages and in the spleen (Munro et al. 1993 *Nature* 365:61). Both of these receptors have been implicated in mediating analgesic effects through binding of agonists (see, for example, Clayton et al. 2002 *Pain* 96:253). Thus, test compounds can be assayed to determine whether they bind to one or both human cannabinoid receptors. An assay for CB₁ binding is described by Matsuda et al. (*supra*). This assay employs recombinant cells expressing CB₁. Binding to CB₂ can be determined in the same manner using recombinant cells expressing CB₂. Briefly, to measure the ability of a test compound to bind to CB₁, the binding of a labelled CB₁ ligand, e.g., [³H]WIN 55212-2 (2 nM for CB₁ and 0.8 nM for CB₂) to membranes isolated from HEK-293 cells expressing recombinant CB₁ is measured in the presence and absence of a compound. Non-specific binding is separately determined in the presence of several-fold excess of unlabelled WIN 55212-2 (5 µM for CB₁ and 10 µM for CB₂). The specific ligand binding to the receptors is defined as the difference between the total binding and the non-specific binding determined in the presence of an excess of unlabelled WIN 55212-2. The IC₅₀ values and Hill coefficients (n_H) are determined by non-linear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants (K_i) are calculated from the Cheng Prusoff equation ($K_i = IC_{50}/(1+(L/K_D))$, where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor).

Therapeutic Methods

Cox and FAAH related therapeutic methods

The compounds of the invention can be used, for example, to treat conditions or disorders in which it is considered desirable to reduce or eliminate COX-2 activity and/or FAAH activity. Thus, they can be used in any situation in which a COX-2 inhibitor or FAAH inhibitor is used as well as in other situations. For example, compounds of Formula I and related prodrugs can be used to treat an inflammatory disorder, including both disorders in which inflammation is considered a significant component of the disorder and those in which inflammation is considered a relatively minor component of the disorder, to treat acute and chronic pain (analgesic) and to

Attorney Docket No. 14184-055WO1

treat fever (antipyretic). Among the inflammatory disorders that can be treated are auto-immune disorders.

Disorders that can be treated with a composition comprising a compound having

Formula I or Formula II and related prodrugs thereof include: arthritis (including
5 rheumatoid arthritis, spondyloarthropathies, gouty arthritis, degenerative joint diseases (i.e. osteoarthritis), systemic lupus erythematosus, ankylosing spondylitis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin inflammation disorders (i.e. psoriasis, eczema, burns, dermatitis), enuresis, eosinophilic disease, gastrointestinal
10 disorders (including inflammatory bowel disease, peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis), and disorders ameliorated by a gastroprokinetic agent (i.e. ileus, for example post-operative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic
15 esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP)).

The compounds of the invention can also be used in the treatment of symptoms
20 associated with influenza or other viral infections, common cold, sprains and strains, myositis, neuralgia, synovitis, injuries such as sports injuries and those following surgical and dental procedures, coagulation disorders, kidney disease (e.g., impaired renal function), ophthalmic disorders (including glaucoma, retinitis, retinopathies, uveitis and acute injury to the eye tissue), liver diseases (i.e., inflammatory liver
25 disease including chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis and liver transplant rejection), and pulmonary inflammatory diseases (e.g., including asthma, allergic rhinitis, respiratory distress syndrome chronic bronchitis, and emphysema). Compositions comprising a compound having **Formula I or Formula**
30 **II** and related prodrugs thereof can also be used to treat, for example, inflammation associated with: vascular diseases, migraine headaches, tension headaches,

Attorney Docket No. 14184-055WO1

periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, multiple sclerosis, and ischemia (e.g., myocardial ischemia), and the like. The compounds
5 may be useful for treating neuroinflammation associated with brain disorders (e.g., Parkinson's disease and Alzheimer's disease) and chronic inflammation associated with cranial radiation injury. The compounds may be useful for treating acute inflammatory conditions (such as those resulting from infection) and chronic inflammatory conditions (such as those resulting from asthma, arthritis and
10 inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds can also be administered to those prior to surgery or taking anticoagulants. The compounds of the invention may reduce the risk of a thrombotic cardiovascular event which is defined as any sudden event of a type known to be
15 caused by platelet aggregation, thrombosis, and subsequent ischemic clinical events, including thrombotic or thromboembolic stroke, myocardial ischemia, myocardial infarction, angina pectoris, transient ischemic attack (TIA; amaurosis fugax), reversible ischemic neurologic deficits, and any similar thrombotic event in any vascular bed (splanchnic, renal, aortic, peripheral, etc.).

20 The compounds of the invention may inhibit uterus contraction caused by hormones and prostanoid-induced smooth muscle contraction. The compounds of the invention may be useful in treating premature labor, menstrual cramps, menstrual irregularity, and dysmenorrhea.

25 The compounds of the invention may inhibit cellular neoplastic transformations and metastatic tumor growth. The compounds of the invention may be associated with reducing the number of adenomatous colorectal polyps. Thus, compounds and prodrugs may also be useful in reducing the risk of certain cancers, e.g., solid tumor
30 cancers such as colon or colorectal cancer. The compounds and prodrugs may also be used in the treatment of prevention of all cancers including cancers of the bladder,

Attorney Docket No. 14184-055WO1

cancers associated with overexpression of HER-2/neu cervix, skin, esophagus, head and neck, lung including non small-cell lung cancers, kidney, pancreas, prostate, gall bladder and bile duct and endometrial cancers, gastric cancers, gliomas, hepatocellular carcinomas, colonic adenomas, mammary cancers, ovarian cancers and salivary cancers. In addition, the compounds and prodrugs may be useful in treating large intestine cancer and prostate cancer. The compounds may also be useful in cases where the patient is at risk for cancer including oral premalignant lesions, cervical intraepithelial neoplasia, chronic hepatitis, bile duct hyperplasia, atypical adenomatous hyperplasia of lung, prostatic, intraepithelial neoplasia, bladder dysplasia, actinic keratoses of skin, colorectal adenomas, gastric metaplasia, and Barrett's esophagus.

Compounds of the invention are also useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease (and precursors thereof), Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multiinfarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

Compounds of the invention may also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore are of use in the treatment of stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures). The compounds of the invention may be useful to control or suppress seizures (including those that are chemically induced).

The compounds of the invention can be used in treatment of all varieties of pain including pain associated with a cough condition, pain associated with cancer, preoperative pain, arthritic pain and other forms of chronic pain such as post-operative pain, lumbosacral pain, musculo-skeletal pain, headache, migraine, muscle

Attorney Docket No. 14184-055WO1

ache, lower back and neck pain, toothache and the like. The compounds of the invention are also useful for the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of the invention may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumor angiogenesis. The compounds of the invention may be used to inhibit angiogenesis, such as occurs in wet macular degeneration.

The compounds of the invention may also be used for treating sexual behavior problems and/or improving sexual performances.

Certain compounds are useful in the prevention and/or treatment of pain, in particular acute or chronic neurogenic pain, migraine, neuropathic pains including the forms associated with herpes virus and diabetes, acute or chronic pain associated with the inflammatory diseases: arthritis, rheumatoid arthritis, osteoarthritis, spondylitis, gout,

Attorney Docket No. 14184-055WO1

vascularitis, Crohn's disease, irritable bowel syndrome and acute/sharp or chronic pains at the periphery. The compounds can also be used to prevent and/or treat emesis, dizziness, vomiting, and nausea, especially after chemotherapy, food behavioral problems/feeding disorders (i.e. eating disorders, in particular anorexias and cachexias of various natures, weight loss associated with cancer and other wasting conditions, or bulimia), neurological pathologies, psychiatric tremors (e.g., dyskinesias, dystonia, spasticity, obsessive compulsive behavior, Tourette's syndrome, all forms of depression and anxiety of any nature and origin, mood disturbances, psychoses), acute or chronic neurodegenerative diseases (e.g., Parkinson's disease, Alzheimer's disease, senile insanity, Huntington's chorea, lesions related to cerebral ischemia and cranial and medullary traumas, epilepsy, sleep disorders (sleep apnea), cardiovascular diseases (in particular hypertension, cardiac arrhythmias, arteriosclerosis, heart attacks, cardiac ischemias, renal ischemia), cancers (benign tumors of the skin, papillomas and cerebral tumors, prostate tumors, cerebral tumors (glioblastomas, medullary epitheliomas, medullary blastomas, neuroblastomas, tumors of origin, astrocytomas, astroblastomas, ependymomas, oligodendrogliomas, plexus tumor, neuroepithelioma, epiphysis tumor, ependyblastomas, malignant meningiomas, sarcomatosis, malignant melanomas, schwann cell cancers), disorders of the immune system (in particular autoimmune diseases including psoriasis, erythematous lupus), diseases of conjunctive or connective tissue, Sjogren's syndrome, spondylarthritis anchylosis, undifferentiated spondylarthritis undifferentiated, Behcet's disease, autoimmune hemolytic anaemias, multiple sclerosis, amyotrophic side sclerosis, amyloses, graft rejection, and illnesses affecting the blastocytes, allergic diseases (i.e., immediate or delayed hypersensitivity, allergic rhinitis or conjunctivitis, contact dermatitis), viral or bacterial parasitic infectious diseases (i.e. AIDS, meningitis), inflammatory diseases (in particular arthritic diseases: arthritis, rheumatoid arthritis osteoarthritis, spondylitis, gout, vascularitis, Crohn's disease, irritable bowel syndrome, osteoporosis, psoriasis, ocular infections and disorders (i.e. ocular hypertension, glaucoma, wet macular degeneration), lung diseases (i.e. diseases of the respiratory tracts, bronchyospasms, cough, asthma, chronic bronchitis, chronic obstruction of the respiratory tracts,

Attorney Docket No. 14184-055WO1

emphysema), gastrointestinal disorders(i.e. irritable bowel syndrome, intestinal inflammatory disorders, ulcers, diarrheas, acid reflux), urinary incontinence, vesical inflammation, movement disorders, psychomotor disorders, hypertension, and AIDS-related complex. The compounds can be used as a sleep aid, to treat insomnia or to induce sleep. The compounds may be used to reduce or control body weight (or fat) or prevent and/or treat obesity or other appetite related disorders related to the excess consumption of food, ethanol and other appetizing substances. The compounds may be used to modulate lipid metabolism, reduce body fat (e.g., via increasing fat utilization) or reduce (or suppress) appetite (e.g., via inducing satiety). The compounds may be used to prevent, control or treat schizophrenia, paranoia or other related disorders, or other disorders of dopamine transmission.

The compounds of the invention can also be used to treat anxiety (including generalized anxiety disorder, panic disorder, and social anxiety Disorder) and depression.

CRTH2 related therapeutic methods

The compounds of the invention that are CRTH2 antagonists can be used, for example, to prevent and/or treat conditions or disorders in which it is considered desirable to reduce or eliminate CRTH2 activity. The compounds of the invention that are CRTH2 agonists can be used, for example, to prevent and/or treat conditions in which it is considered desirable to : (1) downregulate CRTH2 activity via desensitization; (2) downregulate non-CRTH2 chemokine receptor activity via cross-desensitization or (3) shift the balance of Th1 and Th2 cells towards Th2 via agonism at CRTH2. CRTH2 agonists are expected to be especially useful in the prevention and/or treatment of disease and disorders characterized by an imbalance of Th1/Th2 that is shifted towards Th1 cells, e.g., rheumatoid arthritis, Type I diabetes, psoriasis, gastritis, irritable bowel disorder, multiple sclerosis, painless thyroiditis, lupus, and Crohn's Disease.

Attorney Docket No. 14184-055WO1

Compounds that are CRTH2 antagonists or agonists may be used to aid in preventing and/or treating a disease or disorder mediated, regulated or influenced by, for example, Th2 cells, eosinophils, basophils, platelets, Langerhans cells, dendritic cells or mast cells. They also may be used to aid in the prevention or treatment of a disease or disorder mediated, regulated or influenced by PGD₂ and metabolites thereof, such as 13,14-dihydro-15- keto-PGD₂ and 15-deoxy-Δ^{12,14}-PGD₂.

CRTH2 antagonists are expected to be useful in the prevention and/or treatment of disease and disorders characterized by undesirable activation of Th2 cells, eosinophils, and basophils e.g., asthma, atopic dermatitis, allergic rhinitis, allergies (e.g., food allergies, dust allergies, pollen allergies, mold allergies), and Grave's Disease.

Compounds that are CRTH2 antagonists or agonists may be used to aid in preventing and/or treating the following types of diseases, conditions and disorders:

- (1) respiratory tract/obstructive airways diseases and disorders including: rhinorrhea, tracheal constriction, airway contraction, acute-, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofulous rhinitis, perennial allergic rhinitis, seasonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis), , asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)), bronchitis (including chronic and eosinophilic bronchitis), chronic inflammatory diseases of the lung which result in interstitial fibrosis, such as interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, or other autoimmune conditions), chronic obstructive pulmonary disease (COPD)(such as irreversible COPD), chronic sinusitis, conjunctivitis (e.g. allergic conjunctivitis), cystic fibrosis, extrinsic allergic alveolitis (like farmer's lung and related diseases), fibroid lung, hypersensitivity lung

Attorney Docket No. 14184-055WO1

diseases, hypersensitivity pneumonitis, idiopathic interstitial pneumonia, nasal congestion, nasal polyposis, otitis media, and cough (chronic cough associated with inflammation or iatrogenic induced), pleurisy, pulmonary congestion, emphysema, bronchiectasis,, sarcoidosis, lung fibrosis, including cryptogenic fibrosing alveolitis, fibrosis complicating anti-neoplastic therapy Is and chronic infection, including tuberculosis and aspergillosis and other fungal infections, vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension, acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

(2) systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies, and food related allergies which may have effects remote from the gut (such as migraine, rhinitis and eczema);

(3) bone and joint related diseases and disorders including: osteoporosis, arthritis (including rheumatic, infectious, autoimmune), seronegative spondyloarthropathies (such as ankylosing spondylitis, rheumatoid spondylitis, psoriatic arthritis, enthesopathy, Bechet's disease, Marie-Strumpell arthritis, arthritis of inflammatory bowel disease, and Reiter's disease), systemic sclerosis, osteoarthritis/osteoarthrosis, s both primary and secondary to e.g. congenital hip dysplasia, cervical and lumbar spondylitis, and low back and neck pain, Still's disease, reactive arthritis and undifferentiated spondartlopathy, septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Pott's disease and Poncet's syndrome, acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursar and synovial inflammation, primary and secondary Sjogren's syndrome, systemic sclerosis and limited scleroderma,, mixed connective tissue disease, and undifferentiated connective tissue

Attorney Docket No. 14184-055WO1

disease, inflammatory myopathies including, polymyalgia rheumatica, juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications, vasculitides including giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa, microscopic polyarteritis, and vasculitides to associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins, low back pain, Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease, drug-induced arthralgias, tendonitides, and myopathies;

- (4) skin and eye related diseases and disorders including: glaucoma, ocular hypertension, cataract, retinal detachment, psoriasis, eczematous diseases (like atopic dermatitis, contact dermatitis, and seborrheic dermatitis) , cutaneous eosinophilias, chronic skin ulcers, cutaneous lupus erythematosus, contact hypersensitivity/allergic contact dermatitis (including sensitivity to poison ivy, sumac, or oak), and eosinophilic folliculitis (Ofuji's disease), pruritus, drug eruptions, urticaria (acute or chronic, allergic or non-allergic), acne, erythema, dermatitis hepeticiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, pemphigus, pemphigoid, epidermolysis bullosa, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme, cellulitis, both, infective and non infective, panniculitis, cutaneous Lymphomas, non-melanoma skin cancer and other dysplastic lesions, blepharitis, iritis, anterior and posterior uveitis, choroiditis, autoimmune, degenerative or inflammatory disorders affecting the retina, ophthalmitis including sympathetic ophthalmitis, sarcoidosis, infections including viral, fungal, and bacterial;
- (5) gastrointestinal tract and abdominal related diseases and disorders including: Coeliac disease, cholecystitis, enteritis (including

Attorney Docket No. 14184-055WO1

- eosinophilic gastroenteritis), eosinophilic esophagitis, eosinophilic gastrointestinal inflammation, allergen induced diarrhea, enteropathy associated with seronegative arthropathies, gastritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), colitis, irritable
- 5 bowel syndrome, glossitis, gingivitis, periodontitis, oesophagitis, including reflex, proctitis, fibrosis and cirrhosis of the liver, pancreatitis, both acute and chronic, hepatitis (alcoholic, steatohepatitis and chronic viral), and gastrointestinal related allergic disorders;
- (6) transplant rejection related conditions including: acute and chronic
- 10 allograft rejection following solid organ transplant, for example, transplantation of kidney, heart, liver, lung, and cornea, chronic graft versus host disease, skin graft rejection, and bone marrow transplant rejection;
- (7) genitourinary related conditions including nephritis (interstitial and
- 15 glomerulonephritis), nephrotic syndrome, cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer, acute and chronic urethritis, prostatitis, epididymitis, oophoritis, salpingitis, vulvo vaginitis, Peyronie's disease, and erectile dysfunction;
- (8) CNS related diseases and disorders including: neurodegenerative
- 20 diseases, Alzheimer's disease and other cementing disorders including CJD and nvCJD, amyloidosis, and other demyelinating syndromes, cerebral atherosclerosis and vasculitis, temporal arteritis, myasthenia gravis, acute and chronic so pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain,
- 25 headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post- herpetic, and HIV-associated neuropathies, neurosarcoidosis, central and peripheral nervous system complications of malignant, infectious or autoimmune processes;
- (9) Inflammatory or immunological diseases or disorders including:
- 30 general inflammation (of the nasal, pulmonary, and gastrointestinal

Attorney Docket No. 14184-055WO1

- passages), mastocytosis (cutaneous, systemic, mast cell activation
 syndrome, and pediatric mast cell diseases), mastitis (mammary
 gland), vaginitis, vasculitis (e.g., necrotizing, cutaneous, and
 hypersensitivity vasculitis), myositis (including polyiniosis,
 5 dermatomyositis), basophil related diseases including basophilic
 leukemia and basophilic leukocytosis, and eosinophil related diseases
 such as Churg-Strauss syndrome, lupus erythematosus (such as,
 systemic lupus erythematosus, subacute cutaneous lupus
 erythematosus, and discoid lupus erythematosus), Hashimoto's
 10 thyroiditis, Grave's disease, type I diabetes, complications arising from
 diabetes mellitus, other immune disorders, eosinophilia fasciitis, hyper
 IgE syndrome, Addison's disease, antiphospholipid syndrome, acquired
 immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and
 paraneoplastic syndromes.
- 15 (10) cardiovascular diseases and disorders including: hypertension, cerebral
 trauma, occlusive vascular disease, stroke, cerebrovascular disorder,
 atherosclerosis, affecting the coronary and peripheral is circulation,
 pericarditis, myocarditis, inflammatory and auto-immune
 cardiomyopathies including myocardial sarcoid, endocarditis,
 20 valvulitis, and aortitis including infective (e.g. syphilitic), vasculitides,
 disorders of the proximal and peripheral veins including phlebitis and
 thrombosis, including deep vein thrombosis and complications of
 varicose veins;
- 25 (11) oncological diseases and disorders including: common cancers
 (prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach,
 skin and brain tumors), malignancies affecting the bone marrow
 (including the leukaemias) and lymphoproliferative systems, such as
 Hodgkin's and non- Hodgkin's Lymphoma, metastatic disease and
 tumour recurrences, and paraneoplastic syndromes; and
- 30 (12) other diseases and disorders including: pain, migraine, sleep disorders,
 fever, sepsis, idiopathic thrombocytopenia pupura, post-operative

Attorney Docket No. 14184-055WO1

adhesions, flushing, ischemic/reperfusion injury in the heart, brain, peripheral limbs, infection, viral infection, thrombosis, shock, thermal regulation including fever, Raynaud's disease, gangrene, diseases requiring anti-coagulation therapy, congestive heart failure, mucus secretion disorders, pulmonary hypotension, prostanoid-induced smooth muscle contraction associated with dysmenorrhea and premature labor. Compounds that are CRTH2 antagonists or agonists (and similarly, compounds that are DP-1 agonists or antagonists) may also be used to reduce hair (e.g. mammalian) growth.

10 Administration of Compounds

The compounds of the invention can be used alone or in combination with other compounds used to treat inflammatory disorders. Combination therapies are useful in a variety of situations, including where an effective dose of one or more of the agents used in the combination therapy is associated with undesirable toxicity or side effects when not used in combination. This is because a combination therapy can be used to reduce the required dosage or duration of administration of the individual agents.

Thus, the compounds of the invention can be used in a co-therapy with a second agent, e.g., an anti-inflammatory agent. Anti-inflammatory agents which can be used in co-therapy include: NSAIDs, 5-lipoxygenase (LO) inhibitors (e.g., masoprocol, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, and flezelastine hydrochloride, enazadrem phosphate, and bunaprolast), p38 inhibitors (e.g., SB203580 and Vertex compound VX745), LTB₄ antagonists and LTA₄ hydrolase inhibitors, CRTH2 modulators (e.g., ramatroban), steroids or corticosteroids (e.g., beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, bunedoside, butixocort, dexamethasone, flunisolide, fluocortin, fluticasone, hydrocortisone, methylprednisolone, mometasone, predonisolone, predonisone, tipredane, tixocortal, triamcinolone, and triamcinolone acetone), and other compounds including: Bayer compound BAY1005 (CA registry 128253-31-6), Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono

Attorney Docket No. 14184-055WO1

compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY-223982, LY-233469, and LY-255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SmithKline SKF-104493.

The compounds of the invention can be used in combination with selective COX-2 inhibitors, e.g., Celecoxib, Valdecoxib, Parecoxib, Rofecoxib, Etoricoxib, and Lumaricoxib.

The compounds of the invention can be used in a co-therapy with an agent used to treat an anxiety disorders, including: benzodiazepines (e.g., Xanax[®], Librium[®]), SSRIs (e.g., Prozac[®], Zoloft[®]), monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs, e.g., amitryptilline).

The compounds of the invention can be used in a co-therapy with an agent used to treat rheumatoid arthritis including etanercept (Enbrel[®]) and infliximab (Remicade[®]).

The compounds of the invention can also be used in a co-therapy with a second agent that has analgesic activity. Analgesics which can be used in co-therapy include, but are not limited to: NSAIDs (e.g., acetaminophen, acetyl salicylic acid, alclofenac, alminoprofen, apazone, aspirin, benoxaprofen, bezpiperylon, bucloxic acid, carprofen, clidanac, diclofenac, diclofenac, diflunisal, diflusinal, etodolac, fenbufen, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, flufenamic acid, flufenisal, flufenisal, fluprofen, flurbiprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketoprofen, ketorolac, meclofenamic acid, meclofenamic acid, mefenamic acid, mefenamic acid, miroprofen, mofebutazone, nabumetone oxaprozin, naproxen, naproxen, niflumic acid, oxaprozin, oxpinac, oxyphenbutazone, phenacetin, phenylbutazone, phenylbutazone, piroxicam, piroxicam, pirprofen, pranoprofen, sudoxicam, tenoxicam, sulfasalazine, sulindac, sulindac, suprofen, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, tolmetin, zidometacin, zomepirac,

Attorney Docket No. 14184-055WO1

and zomepirac), a non-narcotic analgesic such as tramadol, an opioid or narcotic analgesic (e.g., APF112, beta funaltrexamine, buprenorphine, butorphanol, codeine, cypridine, dezocine, dihydrocodeine, diphenyloxylate, enkephalin pentapeptide, fedotozine, fentanyl, hydrocodone, hydromorphone, levorphanol, loperamide, meperidine, mepivacaine, methadone, methyl nalozone, morphine, nalbuphine, nalmefene, naloxonazine, naloxone, naltrexone, naltrindole, nor-binaltorphimine, oxycodone, oxymorphone, pentazocine, propoxyphene, and trimebutine), NK1 receptor antagonists (e.g., ezlopitant and SR-14033, SSR-241585), CCK receptor antagonists (e.g., loxiglumide), NK3 receptor antagonists (e.g., talnetant, osanetant SR-142801, SSR-241585), norepinephrine-serotonin reuptake inhibitors (NSRI; e.g., milnacipran), vanilloid receptor agonists and antagonists, cannabinoid receptor agonists (e.g., arvanil), sialorphan, compounds or peptides that are inhibitors of neprilysin, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH₂; WO 01/019849 A1), Tyr-Arg (kyotorphin), CCK receptor agonists (e.g., caerulein), conotoxin peptides, peptide analogs of thymulin, dexloxiglumide (the R-isomer of loxiglumide; WO 88/05774), and analgesic peptides (e.g., endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, and substance P).

In addition, certain antidepressants can be used in co-therapy either because they have analgesic activity or are otherwise beneficial to use in combination with an analgesic. Examples of such anti-depressants include: selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine, sertraline), serotonin-norepinephrine dual uptake inhibitors, venlafaxine and nefazadone. Certain anti-convulsants have analgesic activity and are useful in co-therapy. Such anti-convulsants include: gabapentin, carbamazepine, phenytoin, valproate, clonazepam, topiramate and lamotrigine. Such agents are considered particularly useful for treatment of neuropathic pain, e.g., treatment of trigeminal neuralgia, postherpetic neuralgia, and painful diabetic neuropathy. Additional compounds useful in co-therapy include: alpha-2-adrenergic receptor agonists (e.g., tizanidine and clonidine), mexiletine, corticosteroids, compounds that block the NMDA (N-methyl-D-aspartate) receptor (e.g., dextromethorphan, ketamine, and amantadine), glycine antagonists, carisoprodol,

Attorney Docket No. 14184-055WO1

cyclobenzaprine, various opiates, nonopioid antitussive (e.g. dextromethorphan, carmiphen, caramiphen and carbetapentane), opioid antitussives (e.g. codeine, hydrocodone, metaxolone. The compounds of the invention can also be combined with inhalable gaseous nitric oxide (for treating pulmonary vasoconstriction or airway constriction), a thromboxane A2 receptor antagonist, a stimulant (i.e. caffeine), an H₂-antagonist (e.g. ranitidine), an antacid (e.g. aluminum or magnesium hydroxide), an anti-flatulent (e.g. simethicone), a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levodesoxyephedrine), a prostaglandin (e.g. misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol), a diuretic, a sedating or non-sedating histamine H₁ receptor antagonists/antihistamines (i.e. any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between histamine and its receptor) including but not limited to: - 4 astemizole, acrivastine, antazoline, astemizole, azatadine, azelastine, astemizole, bromopheniramine, bromopheniramine maleate, carbinoxamine, carebastine, cetirizine, chlorpheniramine, chlorpheniramine maleate, cimetidine, clemastine, cyclizine, cyproheptadine, descarboethoxyloratadine, dexchlorpheniramine, dimethindene, diphenhydramine, diphenylpyraline, doxylamine succinate, doxylamine, ebastine, efletirizine, epinastine, farnotidine, fexofenadine, hydroxyzine, hydroxyzine, ketotifen, levocabastine, levocetirizine, levocetirizine, loratadine, meclizine, mepyramine, mequitazine, methdilazine, mianserin, mizolastine, noberastine, norastemizole, noraztemizole, phenindamine, pheniramine, picumast, promethazine, pynlamine, pyrilamine, ranitidine, temelastine, terfenadine, trimeprazine, tripelenamine, and triprolidine; a 5HT₁ agonist, such as a triptan (e.g. sumatriptan or naratriptan), an adenosine A₁ agonist, an EP ligand, a sodium channel blocker (e.g. lamotrigine), a substance P antagonist (e.g. an NK antagonist), a cannabinoid, a 5-lipoxygenase inhibitor, a leukotriene receptor antagonist/leukotriene antagonists/LTD₄ antagonists (i.e., any compound that is capable of blocking, inhibiting, reducing or otherwise interrupting the interaction between leukotrienes and the Cys LTI receptor) including but not limited to: zafirlukast, montelukast, montelukast sodium (Singulair®), pranlukast, iralukast, pobilukast, SKB-106,203 and

Attorney Docket No. 14184-055WO1

compounds described as having LTD4 antagonizing activity described in US 5,565,473, a DMARD (e.g. methotrexate), a neurone stabilising antiepileptic drug, a mono-aminergic uptake inhibitor (e.g. venlafaxine), a matrix metalloproteinase inhibitor, a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor, an inhibitor of the release, or action, of tumor necrosis factor, an antibody therapy, such as a monoclonal antibody therapy, an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon), a local anaesthetic, a known FAAH inhibitor (e.g., PMSF, URB532, URB597, or BMS-1, as well as those described in those described in WO04033652, US6462054, US20030092734, US20020188009, US20030195226, and WO04033422), an antidepressant (e.g., VPI-013), a fatty acid amide (e.g. anandamide, N-palmitoyl ethanolamine, N-oleoyl ethanolamide, 2-arachidonoylglycerol, or oleamide), arvanil, analogs of anandamide and arvanil as described in US 20040122089, and a proton pump inhibitor (e.g., omeprazole, esomeprazole, lansoprazole, pantorazole and rabeprazole).

The compound of the invention can also be used in a co-therapy with a second agent that is a cannabinoid receptor antagonist to prevent and/or treat obesity and other appetite related disorders.

Agents of the invention may also be coadministered with one or more of the following:

inactivating antibodies (e.g., monoclonal or polyclonal) to interleukins (e.g., IL-4 and IL-5 (for example see Leckie et al. 2000 *Lancet* 356:2144));

soluble chemokine receptors (e.g. recombinant soluble IL-4 receptor (Steinke and Borish 2001 *Respiratory Research* 2:66));

chemokine receptor modulators including but not limited to antagonists of chemokine receptor superfamilies (e.g. CCR1 (e.g., CP-481,715 (Gladue et al. *J Biol Chem*

Attorney Docket No. 14184-055WO1

278:40473)), CCR2, CCR2A, CCR2B, CCR3 (e.g., UCB35625 (Sabroe et al. *J Biol Chem* 2000 275:25985), CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX3CR1 for the C-X3-C family, as well as the XC family.)

5 These modulators include those compounds described in WO0039125A1, WO02070523A1, WO03035627A1, WO03084954A1, WO04011443A1, WO04014875A1, WO04018425A1, WO04018435A1, WO04026835A1, WO04026880A1, WO04039376A1, WO04039377A1, WO04039787A1, WO04056773A1, WO04056808A1, WO05021513A1, and WO04056809A1,
10 EP1541563A1, WO05040167A1, WO05058881A1, WO05073192A1, WO05070903A2, and EP1571146A1;

PGD₂ receptor antagonists including, but not limited to, compounds described as having PGD₂ antagonizing activity in United States Published Applications
15 US20020022218, US20010051624, and US20030055077, PCT Published Applications W09700853, W09825919, WO03066046, WO03066047, WO03101961, WO03101981, WO04007451, WO0178697, WO04032848, WO03097042, WO03097598, WO03022814, WO03022813, and WO04058164, European Patent Applications EP945450 and EP944614, and those listed in: Torisu et al. 2004 *Bioorg*
20 *Med Chem Lett* 14:4557, Torisu et al. 2004 *Bioorg Med Chem Lett* 2004 14:4891, and Torisu et al. 2004 *Bioorg & Med Chem* 2004 12:4685;

VLA-4 antagonists;

25 P2X7 receptor antagonists;

immunosuppressants such as cyclosporine (cyclosporine A, Sandimmune® Neoral®), tacrolimus (FK-506, Prograf®), rapamycin (sirolimus, Rapamune®) and other FK-506 type immunosuppressants, and mycophenolate, e.g., mycophenolate mofetil
30 (CellCept®);

Attorney Docket No. 14184-055WO1

5 β -agonists including but not limited to: albuterol (Proventil[®], Salbutamol[®],
Ventolin[®]), bambuterol, bitoterol, clenbuterol, fenoterol, formoterol, isoetharine
(Bronkosol[®], Bronkometer[®]), metaproterenol (Alupent[®], Metaprel[®]), pitbuterol
(Maxair[®]), reproterol, rimiterol, salmeterol, terbutaline (Brethaire[®], Brethine[®],
Bricanyl[®]), adrenalin, isoproterenol (Isuprel[®]), epinephrine bitartrate (Primatene[®]),
ephedrine, orciprenaline, fenoterol and isoetharine;

10 β 2-agonist-corticosteroid combinations including but not limited to: salmeterol-
fluticasone (Advair[®]), formoterol-budesonid (Symbicort[®]);

a bronchodilator including but not limited to theophylline and aminophylline

a mast cell stabilizer including but not limited to cromolyn, cromolyn sodium,
nedocromil, and proxicromil

15 an anticholinergic including but not limited to: atropine, benztropine, biperiden,
flutropium, hyoscyamine, ilutropium, ipratropium, ipratropium bromide,
methscopolamine, oxybutinin, rispenzepine, scopolamine, and tiotropium;

20 an anti-tussive including but not limited to: dextromethorphan, codeine, and
hydromorphone;

a decongestant including but not limited to: pseudoephedrine and
phenylpropanolamine;

25 an expectorant including but not limited to: guaifenesin, guaicol sulfate, terpin,
ammonium chloride, glycerol guaicolate, and iodinated glycerol;

30 a PDE inhibitor including but not limited to: fluticasone, denbutyllene, piclamilast,
roflumilast, zardaverine, and rolipram;

Attorney Docket No. 14184-055WO1

a recombinant humanized monoclonal antibody including but not limited to Omalizumab (xolair®) and talizumab (tnx-901);

a lung surfactant including but not limited to dsc-104

5

antithrombotic agents, such as thrombolytic agents (e.g., streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β -blockers (e.g., atenolol), β -adrenergic agonists (e.g., isoproterenol), ACE inhibitors and vasodilators (e.g., sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enalaprilat);

10

anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (e.g., glyburide, meglitinide), biguanides, e.g., metformin (Glucophage®), α -glucosidase inhibitors (acarbose), thiazolidinone compounds, e.g., rosiglitazone (Avandia®), troglitazone (Rezulin®), ciglitazone, pioglitazone (Actos®) and englitazone;

15

preparations of interferon beta (interferon β - I α , interferon β - I β);

gold compounds such as auranofin and aurothioglucose;

20

cytokine inhibitors including but not limited to inhibitors of the production of TNF (e.g. etanercept (Enbrel®), antibody therapies such as orthoclone (OKT3), daclizumab (Zenapax®), basiliximab (Simulec®)), infliximab (Remicade®) and D2E6 TNF antibody) or interleukins (and compounds as described in WO05042502A1 and WO05061465A1);

25

lubricants or emollients such as petrolatum and lanolin, keratolytic agents, vitamin D₃ derivatives (e.g., calcipotriene and calcipotriol (Dovonex®)), PUVA, anthralin (Drithrocreme®), etretinate (Tegison®) and isotretinoin;

Attorney Docket No. 14184-055WO1

nicotinic acid or another nicotinic acid receptor agonist (for example, one can coadminister a CRTH2 or DP-1 antagonist to reduce, prevent or eliminate flushing associated with administration with nicotinic acid or a nicotinic receptor agonist);

- 5 multiple sclerosis therapeutic agents such as interferon β - I β (Betaseron®), interferon β - I α (Avonex®), azathioprine (Imurek®, Imuran®), glatiramer acetate (Capoxone®), a glucocorticoid (e.g., prednisolone) and cyclophosphamide; and

other compounds such as 5-aminosalicylic acid and prodrugs thereof

- 10 DNA-alkylating agents (e.g., cyclophosphamide, ifosfamide), antimetabolites (e.g., azathioprine, 6-mercaptopurine, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disruptors (e.g., vincristine, vinblastine, paclitaxel, colchicine, nocodazole and vinorelbine), DNA intercalators (e.g., doxorubicin, daunomycin and cisplatin), DNA synthesis inhibitors such as
- 15 hydroxyurea, DNA cross-linking agents, e.g., mitomycin C, hormone therapy (e.g., tamoxifen, and flutamide), and cytostatic agents, e.g., imatinib (STI571, Gleevec®) and rituximab (Rituxan®).

- Combination therapy can be achieved by administering two or more agents, each of
- 20 which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered
- 25 simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by min, h, days, or weeks. Thus, the two or more agents can be administered within min of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 h of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2,
- 30 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are

Attorney Docket No. 14184-055WO1

possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

Administration

10 The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert

15 excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

20 The agent can be in the form of a pharmaceutically acceptable salt. Such salts are prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Examples of salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. In some embodiments, the salt can

25 be an ammonium, calcium, magnesium, potassium, or sodium salt. Examples of salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. In some embodiments, the salt can be an ammonium, calcium, magnesium, potassium, or sodium salt. Examples of salts derived from

30 pharmaceutically acceptable organic non-toxic bases include salts of primary,

Attorney Docket No. 14184-055WO1

secondary, and tertiary amines, benethamine, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, diethanolamine, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, epolamine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, meglumine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and trolamine, tromethamine. Examples of other salts include tris, arecoline, arginine, barium, betaine, bismuth, chloroprocaine, choline, clemizole, deanol, imidazole, and morpholineethanol. Examples of salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, benethamine, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, diethanolamine, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, epolamine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, meglumine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and trolamine, tromethamine. Examples of other salts include arecoline, arginine, barium, betaine, bismuth, chloroprocaine, choline, clemizole, deanol, imidazole, and morpholineethanol. In one embodiment are tris salts.

The agents of the invention can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, pellet, gel, paste, syrup, bolus, electuary, slurry, capsule; powder; granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a liposomal formulation (see, e.g., EP 736299) or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents of the invention can

Attorney Docket No. 14184-055WO1

also be administered by captisol delivery technology, rectal suppository or parenterally.

5 A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

10 The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The pharmaceutical compositions may include a "pharmaceutically acceptable inert carrier", and this expression is intended to include one or more inert excipients, which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, 15 lubricants, binders, disintegrating agents, and the like. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques, "Pharmaceutically acceptable carrier" also encompasses controlled release means.

20 Compositions of the present invention may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, and the like. Any such optional ingredient must be compatible with the compound of the invention to insure the stability of the formulation.

25 The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and 30 betaine, and peptides and proteins, for example albumen.

Attorney Docket No. 14184-055WO1

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

5

BINDERS: alginic acid, cellulose and its derivatives (*e.g.* ethyl cellulose, cellulose acetate, carboxymethyl cellulose, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), citric acid monohydrate, corn starch, gelatin, guar gum, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™ such as AVICEL-PH-101™, -103™, and 105™ sold by FMC Corporation, Marcus Hook, PA USA), natural and synthetic gums such as acacia, other alginates, other starches, polyethylene oxide, polyvinyl alcohol, polyvinyl pyrrolidone, potato starch, powdered tragacanth, pre-gelatinized starch (*e.g.* STARCH 1500® and STARCH 1500 LM®, sold by Colorcon), sodium alginate, or mixtures thereof;

10

15

20

25

30

FILLERS: aluminum magnesium hydroxide, aluminum oxide, calcium carbonate (*e.g.* granules or powder), calcium dihydroxide, calcium sulfate (*e.g.* granules or powder), dextrates, dextrose, dibasic calcium phosphate, dibasic calcium phosphate anhydrous, fructose (granules or powder), honey, hydrous lactose, iron oxides (*e.g.* yellow, black, red, *e.g.* ferric oxide), kaolin, lactose, lactose and aspartame, lactose and cellulose, lactose and microcrystalline cellulose, lactose anhydrate, lactose monohydrate, magnesium aluminate, magnesium carbonate, magnesium hydroxide, maltodextrin, maltose, mannitol, microcrystalline cellulose, microcrystalline cellulose & guar gum, molasses, powdered cellulose, pre-gelatinized starch, silicic acid, silicic anhydride, silicified microcrystalline cellulose, sodium chlorate, sorbitol, soybean lecithin, starch, sucrose, talc, triacetin, tribasic calcium phosphate, xanthar gum, or mixtures thereof; talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof,

Attorney Docket No. 14184-055WO1

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, clays, croscarmellose sodium, crospovidone, gums (like gellan), lactose monohydrate, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, other algin, other celluloses, other starches, polacrilin potassium, potato or tapioca starch, povidone, pre-gelatinized starch, simethicone emulsion, sodium starch glycolate, or mixtures thereof agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algin, other celluloses, gums, or mixtures thereof,

SURFACTANTS: Tween 80 or polyoxyethylene-polyoxypropylene copolymer, polyoxyethylene sorbitan, or mixtures thereof;

LUBRICANTS: a coagulated aerosol of synthetic silica (Degussa Co. Plano TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), agar, calcium stearate, ethyl laurate, ethyl oleate, glycerin, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), light mineral oil, magnesium stearate, mannitol, mineral oil, other glycols, palmitic acid, polyethylene glycol, sodium lauryl sulfate, sodium stearyl fumarate, sorbitol, stearic acid, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), talc, vegetable based fatty acids lubricant, zinc stearate, or mixtures thereof; calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Degussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof,

Attorney Docket No. 14184-055WO1

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof,

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride,
5 benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, polysorbate, sorbic acid, thimersol, thymo, or mixtures thereof; benzalkonium
10 chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures
15 thereof, and

COATING AGENTS: candellilla wax, carnuba wax, cellulose acetate phthalate, ethylcellulose, gelatin, gellan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methylcellulose (hypromellose), maltodextrin,
20 methacrylates, methylcellulose, microcrystalline cellulose and carrageenan, microcrystalline wax, pharmaceutical glaze, polyethylene glycol (e.g. polyethylene glycol 8000, polyethylene glycol 3000), polyvinyl acetate phthalate, shellac, sodium carboxymethyl cellulose, sucrose, titanium dioxide, or mixtures thereof; sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin,
25 pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, or mixtures thereof.

COLORANTS: FD&C blue no.1, D&C yellow #10 aluminum lake, FD&C yellow
30 #6/sunset yellow FCF aluminum lake, FD&C carmine aluminum lake and FD&C blue #1, or mixtures thereof; and

Attorney Docket No. 14184-055WO1

ANTIOXIDANTS: butylated hydroxyanisole, sodium ascorbate, sodium metabisulfate, malic acid, citric acid, ascorbic acid, butylated hydroxytoluene, vitamin C, propyl gallate, or mixtures thereof.

5

The formulation can also include other excipients and categories thereof including but not limited to L-histidine, Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, permeability enhancers (e.g. lipids, sodium cholate, acylcarnitine, salicylates, mixed bile salts, fatty acid micelles, chelators, fatty acid, surfactants, medium chain glycerides), protease inhibitors (e.g. soybean trypsin inhibitor, organic acids), pH lowering agents and absorption enhancers effective to promote bioavailability (including but not limited to those described in US6086918 and US5912014), creams and lotions (like maltodextrin and carrageenans); materials for chewable tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spherization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD& C Yellow No. 6 aluminum lake, FD&C Blue #1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6

10
15
20
25
30

Attorney Docket No. 14184-055WO1

Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol, methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

- 10 Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS-1-7040), and black ink (S-1-8106).

The dose range for adult humans is generally from 0.005 mg to 10 g/day orally.

- 15 Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed
20 will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

- A dosage unit (e.g. an oral dosage unit) can include from, for example, 1 to 30 µg, 1 to 40 µg, 1 to 50 µg, 1 to 100 µg, 1 to 200 µg, 1 to 300 µg, 1 to 400 µg, 1 to 500 µg, 1 to 600 µg, 1 to 700 µg, 1 to 800 µg, 1 to 900 µg, 1 to 1000 µg, 10 to 30 µg, 10 to 40 µg, 10 to 50 µg, 10 to 100 µg, 10 to 200 µg, 10 to 300 µg, 10 to 400 µg, 10 to 500 µg, 10 to 600 µg, 10 to 700 µg, 10 to 800 µg, 10 to 900 µg, 10 to 1000 µg, 100 to 200 µg, 100 to 300 µg, 100 to 400 µg, 100 to 500 µg, 100 to 600 µg, 100 to 700 µg, 100 to 800 µg, 100 to 900 µg, 100 to 1000 µg, 100 to 1250 µg, 100 to 1500 µg, 100 to 1750 µg, 100 to 2000 µg, 100 to 2250 µg, 100 to 2500 µg, 100 to 2750 µg, 100 to 3000 µg, 200 to 300 µg, 200 to 400 µg, 200 to 500 µg, 200 to 600 µg, 200 to 700 µg, 200 to 800 µg,
- 25
30

Attorney Docket No. 14184-055WO1

200 to 900 µg, 200 to 1000 µg, 200 to 1250 µg, 200 to 1500 µg, 200 to 1750 µg, 200
to 2000 µg, 200 to 2250 µg, 200 to 2500 µg, 200 to 2750 µg, 200 to 3000 µg, 300 to
400 µg, 300 to 500 µg, 300 to 600 µg, 300 to 700 µg, 300 to 800 µg, 300 to 900 µg,
300 to 1000 µg, 300 to 1250 µg, 300 to 1500 µg, 300 to 1750 µg, 300 to 2000 µg, 300
5 to 2250 µg, 300 to 2500 µg, 300 to 2750 µg, 300 to 3000 µg, 400 to 500 µg, 400 to
600 µg, 400 to 700 µg, 400 to 800 µg, 400 to 900 µg, 400 to 1000 µg, 400 to 1250 µg,
400 to 1500 µg, 400 to 1750 µg, 400 to 2000 µg, 400 to 2250 µg, 400 to 2500 µg, 400
to 2750 µg, 400 to 3000 µg, 500 to 600 µg, 500 to 700 µg, 500 to 800 µg, 500 to 900
µg, 500 to 1000 µg, 500 to 1250 µg, 500 to 1500 µg, 500 to 1750 µg, 500 to 2000 µg,
10 500 to 2250 µg, 500 to 2500 µg, 500 to 2750 µg, 500 to 3000 µg, 600 to 700 µg, 600
to 800 µg, 600 to 900 µg, 600 to 1000 µg, 600 to 1250 µg, 600 to 1500 µg, 600 to
1750 µg, 600 to 2000 µg, 600 to 2250 µg, 600 to 2500 µg, 600 to 2750 µg, 600 to
3000 µg, 700 to 800 µg, 700 to 900 µg, 700 to 1000 µg, 700 to 1250 µg, 700 to 1500
µg, 700 to 1750 µg, 700 to 2000 µg, 700 to 2250 µg, 700 to 2500 µg, 700 to 2750 µg,
15 700 to 3000 µg, 800 to 900 µg, 800 to 1000 µg, 800 to 1250 µg, 800 to 1500 µg, 800
to 1750 µg, 800 to 2000 µg, 800 to 2250 µg, 800 to 2500 µg, 800 to 2750 µg, 800 to
3000 µg, 900 to 1000 µg, 900 to 1250 µg, 900 to 1500 µg, 900 to 1750 µg, 900 to
2000 µg, 900 to 2250 µg, 900 to 2500 µg, 900 to 2750 µg, 900 to 3000 µg, 1000 to
1250 µg, 1000 to 1500 µg, 1000 to 1750 µg, 1000 to 2000 µg, 1000 to 2250 µg, 1000
20 to 2500 µg, 1000 to 2750 µg, 1000 to 3000 µg, 2 to 500 µg, 50 to 500 µg, 3 to 100 µg,
5 to 20 µg, 5 to 100 µg, 50 µg, 100 µg, 150 µg, 200 µg, 250 µg, 300 µg, 350 µg, 400
µg, 450 µg, 500 µg, 550 µg, 600 µg, 650 µg, 700 µg, 750 µg, 800 µg, 850 µg, 900 µg,
950 µg, 1000 µg, 1050 µg, 1100 µg, 1150 µg, 1200 µg, 1250 µg, 1300 µg, 1350 µg,
1400 µg, 1450 µg, 1500 µg, 1550 µg, 1600 µg, 1650 µg, 1700 µg, 1750 µg, 1800 µg,
25 1850 µg, 1900 µg, 1950 µg, 2000 µg, 2050 µg, 2100 µg, 2150 µg, 2200 µg, 2250 µg,
2300 µg, 2350 µg, 2400 µg, 2450 µg, 2500 µg, 2550 µg, 2600 µg, 2650 µg, 2700 µg,
2750 µg, 2800 µg, 2850 µg, 2900 µg, 2950 µg, 3000 µg, 3250 µg, 3500 µg, 3750 µg,
4000 µg, 4250 µg, 4500 µg, 4750 µg, 5000 µg, 1 to 30 mg, 1 to 40 mg, 1 to 100 mg, 1
to 300 mg, 1 to 500 mg, 2 to 500 mg, 3 to 100 mg, 5 to 20 mg, 5 to 100 mg (e.g. 1
30 mg, 2 mg, 3 mg, 4mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg,
14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45

Attorney Docket No. 14184-055WO1

mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg) of a compound described herein. In certain embodiments the dosage unit and daily dose are equivalent. In various embodiments, the dosage unit is administered with food at
5 anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g. with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day.

10 Combining two or more active ingredients in single dosage form results in the possibility of chemical interactions between the active drug substances. For example, acidic and basic active ingredients can react with each other and acidic active ingredients can facilitate the degradation of acid labile substances. Thus, in certain dosage forms, acidic and basic substances can be physically separated as two distinct
15 or isolated layers in a compressed tablet, or in the core and shell of a press-coated tablet. Additional agents that are compatible with acidic as well as basic substances, have the flexibility of being placed in either layer. In certain multiple layer compositions at least one active ingredient can be enteric-coated. In certain
20 embodiments thereof at least one active ingredient can be presented in a controlled release form. In certain embodiments where a combination of three or more active substances are used, they can be presented as physically isolated segments of a compressed multilayer tablet, which can be optionally film coated.

The therapeutic combinations described herein can be formulated as a tablet or
25 capsule comprising a plurality of beads, granules, or pellets. All active ingredients including the vitamins of the combination are formulated into granules or beads or pellets that are further coated with a protective coat, an enteric coat, or a film coat to avoid the possible chemical interactions. Granulation and coating of granules or beads is done using techniques well known to a person skilled in the art. At least one active
30 ingredient can present in a controlled release form. Finally these coated granules or beads are filled into hard gelatin capsules or compressed to form tablets.

Attorney Docket No. 14184-055WO1

The therapeutic combinations described herein can be formulated as a capsule comprising microtablets or minitables of all active ingredients. Microtablets of the individual agents can be prepared using well known pharmaceutical procedures of tablet making like direct compression, dry granulation or wet granulation. Individual microtablets can be filled into hard gelatin capsules. A final dosage form may comprise one or more microtablets of each individual component. The microtablets may be film coated or enteric coated.

The therapeutic combinations described herein can be formulated as a capsule comprising one or more microtablets and powder, or one or more microtablets and granules or beads. In order to avoid interactions between drugs, some active ingredients of a said combination can be formulated as microtablets and the others filled into capsules as a powder, granules, or beads. The microtablets may be film coated or enteric coated. At least one active ingredient can be presented in controlled release form.

The therapeutic combinations described herein can be formulated wherein the active ingredients are distributed in the inner and outer phase of tablets. In an attempt to divide chemically incompatible components of proposed combination, few interacting components are converted in granules or beads using well known pharmaceutical procedures in prior art. The prepared granules or beads (inner phase) are then mixed with outer phase comprising the remaining active ingredients and at least one pharmaceutically acceptable excipient. The mixture thus comprising inner and outer phase is compressed into tablets or molded into tablets. The granules or beads can be controlled release or immediate release beads or granules, and can further be coated using an enteric polymer in an aqueous or non-aqueous system, using methods and materials that are known in the art.

The therapeutic combinations described herein can be formulated as single dosage unit comprising suitable buffering agent. All powdered ingredients of said

Attorney Docket No. 14184-055WO1

combination are mixed and a suitable quantity of one or more buffering agents is added to the blend to minimize possible interactions.

5 The agents described herein, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, 10 microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

15 The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, 20 polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by 25 other suitable means

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final 30 concentrations, depending on the intended use. The techniques of preparation are

Attorney Docket No. 14184-055WO1

generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, 1995.

Formulation

5 The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycolic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ϵ -caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used to implants that release
10 a compound or another agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations are described in EP 0 467 389 A2, WO 93/241150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2,
15 WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and. US20020019446. In such sustained release formulations microparticles of compound are combined with
20 microparticles of polymer. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (where PEG 300 and PEG 400 are most preferred) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled release of the agent within the GI tract. Additional controlled release formulations are described in WO
25 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

Controlled release formulations

30 In general, one can provide for controlled release of the agents described herein through the use of a wide variety of polymeric carriers and controlled release systems

Attorney Docket No. 14184-055WO1

including erodible and non-erodible matrices, osmotic control devices, various reservoir devices, enteric coatings and multiparticulate control devices.

5 Matrix devices are a common device for controlling the release of various agents. In such devices, the agents described herein are generally present as a dispersion within the polymer matrix, and are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of these devices may be dependent upon the solubility of the agent in the polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the pore network,
10 and the tortuosity of the network. In one instance, when utilizing an erodible polymeric matrix, the matrix imbibes water and forms an aqueous-swollen gel that entraps the agent. The matrix then gradually erodes, swells, disintegrates or dissolves in the GI tract, thereby controlling release of one or more of the agents described herein. In non-erodible devices, the agent is released by diffusion through an inert
15 matrix.

Agents described herein can be incorporated into an erodible or non-erodible polymeric matrix controlled release device. By an erodible matrix is meant aqueous-erodible or water-swella-ble or aqueous-soluble in the sense of being either erodible or
20 swella-ble or dissolvable in pure water or requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. When contacted with the aqueous environment of use, the erodible polymeric matrix imbibes water and forms an aqueous-swollen gel or matrix that entraps the agent described herein. The aqueous-swollen matrix gradually erodes, swells, disintegrates
25 or dissolves in the environment of use, thereby controlling the release of a compound described herein to the environment of use.

The erodible polymeric matrix into which an agent described herein can be incorporated may generally be described as a set of excipients that are mixed with the
30 agent following its formation that, when contacted with the aqueous environment of use imbibes water and forms a water-swollen gel or matrix that entraps the drug form.

Attorney Docket No. 14184-055WO1

Drug release may occur by a variety of mechanisms, for example, the matrix may disintegrate or dissolve from around particles or granules of the agent or the agent may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the device. One ingredient of this water-swollen matrix is the water-swallowable, erodible, or soluble polymer, which may generally be described as an osmopolymer, hydrogel or water-swallowable polymer. Such polymers may be linear, branched, or crosslinked. The polymers may be homopolymers or copolymers. In certain embodiments, they may be synthetic polymers derived from vinyl, acrylate, methacrylate, urethane, ester and oxide monomers. In other embodiments, they can be derivatives of naturally occurring polymers such as polysaccharides (e.g. chitin, chitosan, dextran and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum and scleroglucan), starches (e.g. dextrin and maltodextrin), hydrophilic colloids (e.g. pectin), phosphatides (e.g. lecithin), alginates (e.g. ammonium alginate, sodium, potassium or calcium alginate, propylene glycol alginate), gelatin, collagen, and cellulose.

Cellulose is a cellulose polymer that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeat units with a compound to form an ester-linked or an ether-linked substituent. For example, the cellulose ethyl cellulose has an ether linked ethyl substituent attached to the saccharide repeat unit, while the cellulose cellulose acetate has an ester linked acetate substituent. In certain embodiments, the cellulose for the erodible matrix comprises aqueous-soluble and aqueous-erodible cellulose can include, for example, ethyl cellulose (EC), methylcellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC). In certain embodiments, the cellulose comprises various grades of low viscosity (MW less than or equal to 50,000 daltons, for example, the Dow Methocel™ series E5, E15LV, E50LV and K100LY) and high viscosity (MW greater than 50,000 daltons, for example, E4MCR, E10MCR, K4M, K15M and K100M and the

Attorney Docket No. 14184-055WO1

Methocel™ K series) HPMC. Other commercially available types of HPMC include the Shin Etsu Metolose 90SH series.

5 The choice of matrix material can have a large effect on the maximum drug concentration attained by the device as well as the maintenance of a high drug concentration. The matrix material can be a concentration-enhancing polymer, for example, as described in WO05/011634.

10 Other materials useful as the erodible matrix material include, but are not limited to, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGITO, Rohm America, Inc., Piscataway, New Jersey) and other acrylic acid derivatives such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-
15 dimethylaminoethyl) methacrylate, and (trimethylaminoethyl) methacrylate chloride.

The erodible matrix polymer may contain a wide variety of the same types of additives and excipients known in the pharmaceutical arts, including osmopolymers, osmagens, solubility-enhancing or-retarding agents and excipients that promote
20 stability or processing of the device.

Alternatively, the agents of the present invention may be administered by or incorporated into a non-erodible matrix device. In such devices, an agent described herein is distributed in an inert matrix. The agent is released by diffusion through the
25 inert matrix. Examples of materials suitable for the inert matrix include insoluble plastics (e.g. methyl acrylate-methyl methacrylate copolymers, polyvinyl chloride, polyethylene), hydrophilic polymers (e.g. ethyl cellulose, cellulose acetate, crosslinked polyvinylpyrrolidone (also known as crospovidone)), and fatty compounds (e.g. carnauba wax, microcrystalline wax, and triglycerides). Such devices
30 are described further in Remington: The Science and Practice of Pharmacy, 20th edition (2000).

Attorney Docket No. 14184-055WO1

Matrix controlled release devices may be prepared by blending an agent described herein and other excipients together, and then forming the blend into a tablet, caplet, pill, or other device formed by compressive forces. Such compressed devices may be formed using any of a wide variety of presses used in the fabrication of pharmaceutical devices. Examples include single-punch presses, rotary tablet presses, and multilayer rotary tablet presses, all well known in the art. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000. The compressed device may be of any shape, including round, oval, oblong, cylindrical, or triangular. The upper and lower surfaces of the compressed device may be flat, round, concave, or convex.

In certain embodiments, when formed by compression, the device has a strength of at least 5 Kiloponds (Kp)/cm² (for example, at least 7 Kp/cm²). Strength is the fracture force, also known as the tablet hardness required to fracture a tablet formed from the materials, divided by the maximum cross-sectional area of the tablet normal to that force. The fracture force may be measured using a Schleuniger Tablet Hardness Tester, Model 6D. The compression force required to achieve this strength will depend on the size of the tablet, but generally will be greater than about 5 kP/cm².

Friability is a well-known measure of a device's resistance to surface abrasion that measures weight loss in percentage after subjecting the device to a standardized agitation procedure. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability. Devices having a strength of greater than 5 kP/cm² generally are very robust, having a friability of less than 0.5%. Other methods for forming matrix controlled-release devices are well known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

As noted above, the agents described herein may also be incorporated into an osmotic control device. Such devices generally include a core containing one or more agents as described herein and a water permeable, non-dissolving and non-eroding coating

Attorney Docket No. 14184-055WO1

surrounding the core which controls the influx of water into the core from an aqueous environment of use so as to cause drug release by extrusion of some or all of the core to the environment of use. In certain embodiments, the coating is polymeric, aqueous-permeable, and has at least one delivery port. The core of the osmotic device
5 optionally includes an osmotic agent which acts to imbibe water from the surrounding environment via such a semi-permeable membrane. The osmotic agent contained in the core of this device may be an aqueous-swallowable hydrophilic polymer or it may be an osmogen, also known as an osmagent. Pressure is generated within the device which forces the agent(s) out of the device via an orifice (of a size designed to
10 minimize solute diffusion while preventing the build-up of a hydrostatic pressure head). Nonlimiting examples of osmotic control devices are disclosed in U. S. Patent Application Serial No. 09/495,061.

Osmotic agents create a driving force for transport of water from the environment of
15 use into the core of the device. Osmotic agents include but are not limited to water-swallowable hydrophilic polymers, and osmogens (or osmagens). Thus, the core may include water-swallowable hydrophilic polymers, both ionic and nonionic, often referred to as osmopolymers and hydrogels. The amount of water-swallowable hydrophilic polymers present in the core may range from about 5 to about 80 wt% (including for
20 example, 10 to 50 wt%). Nonlimiting examples of core materials include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly (2-hydroxyethyl methacrylate), poly (acrylic) acid, poly (methacrylic) acid, polyvinylpyrrolidone (PVP) and crosslinked PVP, polyvinyl alcohol (PVA),
25 PVA/PVP copolymers and PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl cellulose (CEC), sodium
30 alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolat. Other materials include hydrogels comprising interpenetrating networks of polymers that

Attorney Docket No. 14184-055WO1

may be formed by addition or by condensation polymerization, the components of which may comprise hydrophilic and hydrophobic monomers such as those just mentioned. Water-swellaable hydrophilic polymers include but are not limited to PEO, PEG, PVP, sodium croscarmellose, HPMC, sodium starch glycolate, polyacrylic acid
5 and crosslinked versions or mixtures thereof.

The core may also include an osmogen (or osmagent). The amount of osmogen present in the core may range from about 2 to about 70 wt% (including, for example, from 10 to 50 wt%). Typical classes of suitable osmogens are water-soluble organic
10 acids, salts and sugars that are capable of imbibing water to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. Typical useful osmogens include but are not limited to magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate,
15 mannitol, xylitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose, lactose, citric acid, succinic acid, tartaric acid, and mixtures thereof. In certain embodiments, the osmogen is glucose, lactose, sucrose, mannitol, xylitol, sodium chloride, including combinations thereof.

The core may include a wide variety of additives and excipients that enhance the performance of the dosage form or that promote stability, tableting or processing. Such additives and excipients include tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, disintegrants, antioxidants, lubricants and flavorants. Nonlimiting examples of additives and excipients include
20 but are not limited to those described elsewhere herein as well as microcrystalline cellulose, metallic salts of acids (e.g. aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, zinc stearate), pH control agents (e.g. buffers, organic acids, organic acid salts, organic and inorganic bases), fatty acids, hydrocarbons and fatty alcohols (e.g. stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol),
25 fatty acid esters (e.g. glyceryl (mono- and di-) stearates, triglycerides, glyceryl (palmiticstearic) ester, sorbitan esters (e.g. sorbitan monostearate, saccharose
30

Attorney Docket No. 14184-055WO1

monostearate, saccharose monopalmitate, sodium stearyl fumarate), polyoxyethylene sorbitan esters), surfactants (e.g. alkyl sulfates (e.g. sodium lauryl sulfate, magnesium lauryl sulfate), polymers (e.g. polyethylene glycols, polyoxyethylene glycols, polyoxyethylene, polyoxypropylene ethers, including copolymers thereof), polytetrafluoroethylene), and inorganic materials (e.g. talc, calcium phosphate), cyclodextrins, sugars (e.g. lactose, xylitol), sodium starch glycolate). Nonlimiting examples of disintegrants are sodium starch glycolate (e. g., Explotab[™] CLV, (microcrystalline cellulose (e. g., Avicel[™]), microcrystalline silicified cellulose (e.g., ProSolv[™]), croscarmellose sodium (e. g., Ac-Di-Sol[™]). When the agent described herein is a solid amorphous dispersion formed by a solvent process, such additives may be added directly to the spray-drying solution when forming an agent described herein/concentration-enhancing polymer dispersion such that the additive is dissolved or suspended in the solution as a slurry, Alternatively, such additives may be added following the spray-drying process to aid in forming the final controlled release device.

A nonlimiting example of an osmotic device consists of one or more drug layers containing an agent described herein, such as a solid amorphous drug/polymer dispersion, and a sweller layer that comprises a water-swellaable polymer, with a coating surrounding the drug layer and sweller layer. Each layer may contain other excipients such as tableting aids, osmagents, surfactants, water-soluble polymers and water-swellaable polymers.

Such osmotic delivery devices may be fabricated in various geometries including bilayer (wherein the core comprises a drug layer and a sweller layer adjacent to each other), trilayer (wherein the core comprises a sweller layer sandwiched between two drug layers) and concentric (wherein the core comprises a central sweller agent surrounded by the drug layer). The coating of such a tablet comprises a membrane permeable to water but substantially impermeable to drug and excipients contained within. The coating contains one or more exit passageways or ports in communication with the drug-containing layer(s) for delivering the drug agent. The drug-containing

Attorney Docket No. 14184-055WO1

layer(s) of the core contains the drug agent (including optional osmagents and hydrophilic water-soluble polymers), while the sweller layer consists of an expandable hydrogel, with or without additional osmotic agents.

- 5 When placed in an aqueous medium, the tablet imbibes water through the membrane, causing the agent to form a dispensable aqueous agent, and causing the hydrogel layer to expand and push against the drug-containing agent, forcing the agent out of the exit passageway. The agent can swell, aiding in forcing the drug out of the passageway. Drug can be delivered from this type of delivery system either dissolved or dispersed
10 in the agent that is expelled from the exit passageway.

- The rate of drug delivery is controlled by such factors as the permeability and thickness of the coating, the osmotic pressure of the drug-containing layer, the degree of hydrophilicity of the hydrogel layer, and the surface area of the device. Those
15 skilled in the art will appreciate that increasing the thickness of the coating will reduce the release rate, while any of the following will increase the release rate: increasing the permeability of the coating; increasing the hydrophilicity of the hydrogel layer; increasing the osmotic pressure of the drug-containing layer; or increasing the device's surface area.

- 20 Other materials useful in forming the drug-containing agent, in addition to the agent described herein itself, include HPMC, PEO and PVP and other pharmaceutically acceptable carriers. In addition, osmagents such as sugars or salts, including but not limited to sucrose, lactose, xylitol, mannitol, or sodium chloride, may be added.

- 25 Materials which are useful for forming the hydrogel layer include sodium CMC, PEO (e.g. polymers having an average molecular weight from about 5,000,000 to about 7,500,000 daltons), poly (acrylic acid), sodium (polyacrylate), sodium croscarmellose, sodium starch glycolat, PVP, crosslinked PVP, and other high molecular weight hydrophilic materials.

30

Attorney Docket No. 14184-055WO1

In the case of a bilayer geometry, the delivery port(s) or exit passageway(s) may be located on the side of the tablet containing the drug agent or may be on both sides of the tablet or even on the edge of the tablet so as to connect both the drug layer and the sweller layer with the exterior of the device. The exit passageway(s) may be produced by mechanical means or by laser drilling, or by creating a difficult-to-coat region on the tablet by use of special tooling during tablet compression or by other means.

The osmotic device can also be made with a homogeneous core surrounded by a semipermeable membrane coating, as in US3845770. The agent described herein can be incorporated into a tablet core and a semipermeable membrane coating can be applied via conventional tablet-coating techniques such as using a pan coater. A drug delivery passageway can then be formed in this coating by drilling a hole in the coating, either by use of a laser or mechanical means. Alternatively, the passageway may be formed by rupturing a portion of the coating or by creating a region on the tablet that is difficult to coat, as described above. In one embodiment, an osmotic device comprises: (a) a single-layer compressed core comprising: (i) an agent described herein, (ii) a hydroxyethylcellulose, and (iii) an osmagent, wherein the hydroxyethylcellulose is present in the core from about 2.0% to about 35% by weight and the osmagent is present from about 15% to about 70% by weight; (b) a water-permeable layer surrounding the core; and (c) at least one passageway within the water-permeable layer (b) for delivering the drug to a fluid environment surrounding the tablet. In certain embodiments, the device is shaped such that the surface area to volume ratio (of a water-swollen tablet) is greater than 0.6 mm^{-1} (including, for example, greater than 1.0 mm^{-1}). The passageway connecting the core with the fluid environment can be situated along the tablet band area. In certain embodiments, the shape is an oblong shape where the ratio of the tablet tooling axes, i.e., the major and minor axes which define the shape of the tablet, are between 1.3 and 3 (including, for example, between 1.5 and 2.5). In one embodiment, the combination of the agent described herein and the osmagent have an average ductility from about 100 to about 200 Mpa, an average tensile strength from about 0.8 to about 2.0 Mpa, and an average

Attorney Docket No. 14184-055WO1

brittle fracture index less than about 0.2. The single-layer core may optionally include a disintegrant, a bioavailability enhancing additive, and/or a pharmaceutically acceptable excipient, carrier or diluent.

5 In certain embodiments, entrainment of particles of agents described herein in the extruding fluid during operation of such osmotic device is desirable. For the particles to be well entrained, the agent drug form is dispersed in the fluid before the particles have an opportunity to settle in the tablet core. One means of accomplishing this is by adding a disintegrant that serves to break up the compressed core into its particulate
10 components. Nonlimiting examples of standard disintegrants include materials such as sodium starch glycolate (e. g. , ExplotabTM CLV), microcrystalline cellulose (e. g., AvicelTM), microcrystalline silicified cellulose (e. g., ProSolTM) and croscarmellose sodium (e. g., Ac-Di-SolTM), and other disintegrants known to those skilled in the art. Depending upon the particular formulation, some disintegrants work better than
15 others. Several disintegrants tend to form gels as they swell with water, thus hindering drug delivery from the device. Non-gelling, non-swelling disintegrants provide a more rapid dispersion of the drug particles within the core as water enters the core. In certain embodiments, non-gelling, non-swelling disintegrants are resins, for example, ion-exchange resins. In one embodiment, the resin is AmberliteTM IRP 88 (available
20 from Rohm and Haas, Philadelphia, PA). When used, the disintegrant is present in amounts ranging from about 1-25% of the core agent.

Water-soluble polymers are added to keep particles of the agent suspended inside the device before they can be delivered through the passageway(s) (e.g., an orifice). High
25 viscosity polymers are useful in preventing settling. However, the polymer in combination with the agent is extruded through the passageway(s) under relatively low pressures. At a given extrusion pressure, the extrusion rate typically slows with increased viscosity. Certain polymers in combination with particles of the agent described herein form high viscosity solutions with water but are still capable of being
30 extruded from the tablets with a relatively low force. In contrast, polymers having a low weight-average, molecular weight (< about 300,000) do not form sufficiently

Attorney Docket No. 14184-055WO1

viscous solutions inside the tablet core to allow complete delivery due to particle settling. Settling of the particles is a problem when such devices are prepared with no polymer added, which leads to poor drug delivery unless the tablet is constantly agitated to keep the particles from settling inside the core. Settling is also problematic when the particles are large and/or of high density such that the rate of settling increases.

In certain embodiments, the water-soluble polymers for such osmotic devices do not interact with the drug. In certain embodiments the water-soluble polymer is a non-ionic polymer. A nonlimiting example of a non-ionic polymer forming solutions having a high viscosity yet still extrudable at low pressures is Natrosol™ 250H (high molecular weight hydroxyethylcellulose, available from Hercules Incorporated, Aqualon Division, Wilmington, DE; MW equal to about 1 million daltons and a degree of polymerization equal to about 3,700). Natrosol 250H™ provides effective drug delivery at concentrations as low as about 3% by weight of the core when combined with an osmagent. Natrosol 250H™ NF is a high-viscosity grade nonionic cellulose ether that is soluble in hot or cold water. The viscosity of a 1% solution of Natrosol 250H using a Brookfield LVT (30 rpm) at 25°C is between about 1, 500 and about 2,500 cps.

In certain embodiments, hydroxyethylcellulose polymers for use in these monolayer osmotic tablets have a weight-average, molecular weight from about 300,000 to about 1.5 million. The hydroxyethylcellulose polymer is typically present in the core in an amount from about 2.0% to about 35% by weight.

Another example of an osmotic device is an osmotic capsule. The capsule shell or portion of the capsule shell can be semipermeable. The capsule can be filled either by a powder or liquid consisting of an agent described herein, excipients that imbibe water to provide osmotic potential, and/or a water-swellaable polymer, or optionally solubilizing excipients. The capsule core can also be made such that it has a bilayer or

Attorney Docket No. 14184-055WO1

multilayer agent analogous to the bilayer, trilayer or concentric geometries described above.

Another class of osmotic device useful in this invention comprises coated swellable tablets, for example, as described in EP378404. Coated swellable tablets comprise a tablet core comprising an agent described herein and a swelling material, preferably a hydrophilic polymer, coated with a membrane, which contains holes, or pores through which, in the aqueous use environment, the hydrophilic polymer can extrude and carry out the agent. Alternatively, the membrane may contain polymeric or low molecular weight water-soluble porosigens. Porosigens dissolve in the aqueous use environment, providing pores through which the hydrophilic polymer and agent may extrude. Examples of porosigens are water-soluble polymers such as HPMC, PEG, and low molecular weight compounds such as glycerol, sucrose, glucose, and sodium chloride. In addition, pores may be formed in the coating by drilling holes in the coating using a laser or other mechanical means. In this class of osmotic devices, the membrane material may comprise any film-forming polymer, including polymers which are water permeable or impermeable, providing that the membrane deposited on the tablet core is porous or contains water-soluble porosigens or possesses a macroscopic hole for water ingress and drug release. Embodiments of this class of sustained release devices may also be multilayered, as described, for example, in EP378404.

When an agent described herein is a liquid or oil, such as a lipid vehicle formulation, for example as described in WO05/011634, the osmotic controlled-release device may comprise a soft-gel or gelatin capsule formed with a composite wall and comprising the liquid formulation where the wall comprises a barrier layer formed over the external surface of the capsule, an expandable layer formed over the barrier layer, and a semipermeable layer formed over the expandable layer. A delivery port connects the liquid formulation with the aqueous use environment. Such devices are described, for example, in US6419952, US6342249, US5324280, US4672850, US4627850, US4203440, and US3995631.

Attorney Docket No. 14184-055WO1

The osmotic controlled release devices of the present invention can also comprise a coating. In certain embodiments, the osmotic controlled release device coating exhibits one or more of the following features: is water-permeable, has at least one
5 port for the delivery of drug, and is non-dissolving and non-eroding during release of the drug formulation, such that drug is substantially entirely delivered through the delivery port(s) or pores as opposed to delivery primarily via permeation through the coating material itself. Delivery ports include any passageway, opening or pore whether made mechanically, by laser drilling, by pore formation either during the
10 coating process or *in situ* during use or by rupture during use. In certain embodiments, the coating is present in an amount ranging from about 5 to 30 wt% (including, for example, 10 to 20 wt%) relative to the core weight.

One form of coating is a semipermeable polymeric membrane that has the port(s)
15 formed therein either prior to or during use. Thickness of such a polymeric membrane may vary between about 20 and 800 μm (including, for example, between about 100 to 500 μm). The diameter of the delivery port (s) may generally range in size from 0.1 to 3000 μm or greater (including, for example, from about 50 to 3000 μm in diameter). Such port(s) may be formed post-coating by mechanical or laser drilling or
20 may be formed *in situ* by rupture of the coatings; such rupture may be controlled by intentionally incorporating a relatively small weak portion into the coating. Delivery ports may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the coating over an indentation in the core. In addition, delivery ports may be formed during coating, as in the case of asymmetric membrane
25 coatings of the type disclosed in US5612059 and US5698220. The delivery port may be formed *in situ* by rupture of the coating, for example, when a collection of beads that may be of essentially identical or of a variable agent are used. Drug is primarily released from such beads following rupture of the coating and, following rupture, such release may be gradual or relatively sudden. When the collection of beads has a
30 variable agent, the agent may be chosen such that the beads rupture at various times

Attorney Docket No. 14184-055WO1

following administration, resulting in the overall release of drug being sustained for a desired duration.

Coatings may be dense, microporous or asymmetric, having a dense region supported
5 by a thick porous region such as those disclosed in US5612059 and US5698220.

When the coating is dense the coating can be composed of a water-permeable material. When the coating is porous, it may be composed of either a water-permeable or a water-impermeable material. When the coating is composed of a porous water-
10 impermeable material, water permeates through the pores of the coating as either a liquid or a vapor. Nonlimiting examples of osmotic devices that utilize dense coatings include US3995631 and US3845770. Such dense coatings are permeable to the external fluid such as water and may be composed of any of the materials mentioned in these patents as well as other water-permeable polymers known in the art.

15 The membranes may also be porous as disclosed, for example, in US5654005 and US5458887 or even be formed from water-resistant polymers. US5120548 describes another suitable process for forming coatings from a mixture of a water-insoluble polymer and a leachable water-soluble additive. The porous membranes may also be
20 formed by the addition of pore-formers as disclosed in US4612008. In addition, vapor-permeable coatings may even be formed from extremely hydrophobic materials such as polyethylene or polyvinylidene difluoride that, when dense, are essentially water-impermeable, as long as such coatings are porous. Materials useful in forming the coating include but are not limited to various grades of acrylic, vinyls, ethers,
25 polyamides, polyesters and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration such as by crosslinking. Nonlimiting examples of suitable polymers (or crosslinked versions) useful in forming the coating include plasticized, unplasticized and reinforced cellulose acetate (CA), cellulose diacetate,
30 cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate

Attorney Docket No. 14184-055WO1

trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxiated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly (acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. In various embodiments, the coating agent comprises a cellulosic polymer, in particular cellulose ethers, cellulose esters and cellulose ester-ethers, i.e., cellulosic derivatives having a mixture of ester and ether substituents, the coating materials are made or derived from poly (acrylic) acids and esters, poly (methacrylic) acids and esters, and copolymers thereof, the coating agent comprises cellulose acetate, the coating comprises a cellulosic polymer and PEG, the coating comprises cellulose acetate and PEG.

Coating is conducted in conventional fashion, typically by dissolving or suspending the coating material in a solvent and then coating by dipping, spray coating or by pan-coating. In certain embodiments, the coating solution contains 5 to 15 wt% polymer. Typical solvents useful with the cellulosic polymers mentioned above include but are not limited to acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofuran, diglyme, water, and mixtures thereof. Pore-formers and non-solvents (such as water, glycerol and ethanol) or plasticizers (such as diethyl phthalate) may also be added in any amount as long as the polymer remains soluble at the spray temperature. Pore-formers and their use in fabricating coatings are described, for example, in US5612059. Coatings may also be hydrophobic microporous layers wherein the pores are substantially filled with a gas and are not wetted by the aqueous

Attorney Docket No. 14184-055WO1

medium but are permeable to water vapor, as disclosed, for example, in US5798119. Such hydrophobic but water-vapor permeable coatings are typically composed of hydrophobic polymers such as polyalkenes, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and
5 ethers, natural waxes and synthetic waxes. Hydrophobic microporous coating materials include but are not limited to polystyrene, polysulfones, polyethersulfones, polyethylene, polypropylene, polyvinyl chloride, polyvinylidene fluoride and polytetrafluoroethylene. Such hydrophobic coatings can be made by known phase inversion methods using any of vapor-quench, liquid quench, thermal processes,
10 leaching soluble material from the coating or by sintering coating particles. In thermal processes, a solution of polymer in a latent solvent is brought to liquid-liquid phase separation in a cooling step. When evaporation of the solvent is not prevented, the resulting membrane will typically be porous. Such coating processes may be conducted by the processes disclosed, for example, in US4247498, US4490431 and
15 US4744906. Osmotic controlled-release devices may be prepared using procedures known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

As further noted above, the agents described herein may be provided in the form of
20 microparticulates, generally ranging in size from about 10 μ m to about 2mm (including, for example, from about 100 μ m to 1mm in diameter). Such multiparticulates may be packaged, for example, in a capsule such as a gelatin capsule or a capsule formed from an aqueous-soluble polymer such as HPMCAS, HPMC or starch; dosed as a suspension or slurry in a liquid ; or they may be formed into a
25 tablet, caplet, or pill by compression or other processes known in the art. Such multiparticulates may be made by any known process, such as wet- and dry-granulation processes, extrusion/spheronization, roller-compaction, melt-congealing, or by spray-coating seed cores. For example, in wet-and dry- granulation processes, the agent described herein and optional excipients may be granulated to form
30 multiparticulates of the desired size. Other excipients, such as a binder (e. g., microcrystalline cellulose), may be blended with the agent to aid in processing and

Attorney Docket No. 14184-055WO1

forming the multiparticulates. In the case of wet granulation, a binder such as microcrystalline cellulose may be included in the granulation fluid to aid in forming a suitable multiparticulate. See, for example, Remington : The Science and Practice of Pharmacy, 20th Edition, 2000. In any case, the resulting particles may themselves
5 constitute the therapeutic composition or they may be coated by various film-forming materials such as enteric polymers or water-swellaable or water-soluble polymers, or they may be combined with other excipients or vehicles to aid in dosing to patients.

In certain embodiments, it may be desirable to provide for the immediate release of one or more of the agents described herein, and the controlled release of one or more
10 other agents. For example, in one embodiment, a compound described herein can be provided in an immediate release formulation together with a cotherapy agent described herein in a controlled release format. For example, in one embodiment, a compound described herein can be provided in a controlled release format together
15 with a cotherapy agent described herein in an immediate release format.

The agents can be incorporated into microemulsions, which generally are thermodynamically stable, isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules
20 (Encyclopedia of Pharmaceutical Technology (New York: Marcel Dekker, 1992), volume 9). For the preparation of microemulsions, surfactant (emulsifier), co-surfactant (co-emulsifier), an oil phase and a water phase are necessary. Suitable surfactants include any surfactants that are useful in the preparation of emulsions, e.g., emulsifiers that are typically used in the preparation of creams. The co-surfactant (or
25 "co-emulsifier") is generally selected from the group of polyglycerol derivatives, glycerol derivatives and fatty alcohols. Preferred emulsifier/co-emulsifier combinations are generally although not necessarily selected from the group consisting of: glyceryl monostearate and polyoxyethylene stearate; polyethylene glycol and ethylene glycol palmitostearate; and caprylic and capric triglycerides and
30 oleoyl macrogolglycerides. The water phase includes not only water but also, typically, buffers, glucose, propylene glycol, polyethylene glycols, preferably lower

Attorney Docket No. 14184-055WO1

molecular weight polyethylene glycols (e.g., PEG 300 and PEG 400), and/or glycerol, and the like, while the oil phase will generally comprise, for example, fatty acid esters, modified vegetable oils, silicone oils, mixtures of mono- di- and triglycerides, mono- and di-esters of PEG (e.g., oleoyl macrogol glycerides), etc.

5

The agents of the invention can be incorporated into pharmaceutically-acceptable nanoparticle, nanosphere, and nanocapsule formulations (Delie and Blanco-Prieto 2005 Molecule 10:65-80). Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland et al., 1987; Quintanar-Guerrero et al., 10 1998; Douglas et al., 1987). To avoid side effects due to intracellular polymeric overloading, ultrafine particles (sized around 0.1 μm) can be designed using polymers able to be degraded in vivo (e.g. biodegradable polyalkyl-cyanoacrylate nanoparticles). Such particles are described in the prior art (Couvreur et al, 1980; 1988; zur Muhlen et al., 1998; Zambaux et al. 1998; Pinto-Alphandry et al., 1995 and 15 U.S. Pat. No. 5,145,684).

The agents of the invention can be formulated with pH sensitive materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon 20 including those described in US4910021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175, 003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film- 25 forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane-coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a 30 pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally

Attorney Docket No. 14184-055WO1

about 5.0 or higher. The agents of the invention may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents of the invention may be formulated according to the methodology described in any of WO03105812 (extruded hydratable polymers); WO0243767 (enzyme cleavable
5 membrane translocators); WO03007913 and WO03086297 (mucoadhesive systems); WO02072075 (bilayer laminated formulation comprising pH lowering agent and absorption enhancer); WO04064769 (amidated peptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms);
10 US5007790 and US5972389 (sustained release dosage forms); WO04112711 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952, 314 (biopolymer); US5108758 (glassy amylose matrix delivery); US 5840860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat
15 gliadin or zein); US5866619 and US6368629 (saccharide containing polymer); US 6531152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (eg hydrophobic polymer-Eudragit)); US 6234464; US 6403130 (coating with polymer containing casein and high methoxy pectin; WO0174175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO04019872 (transferring fusion proteins). The agents of the invention may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a
20 controlled-release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents of the invention.

30 The agents of the invention can be formulated in an osmotic device including the ones disclosed in US4503030, US5609590 and US5358502. US4503030 discloses an

Attorney Docket No. 14184-055WO1

osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract.

More particularly, the invention relates to an osmotic device comprising a wall

formed of a semi-permeable pH sensitive composition that surrounds a compartment

containing a drug, with a passageway through the wall connecting the exterior of the

device with the compartment. The device delivers the drug at a controlled rate in the

region of the gastrointestinal tract having a pH of less than 3.5, and the device self-

destructs and releases all its drug in the region of the gastrointestinal tract having a pH

greater than 3.5, thereby providing total availability for drug absorption. U. S. Patent

Nos. 5,609, 590 and 5, 358,502 disclose an osmotic bursting device for dispensing a

beneficial agent to an aqueous environment. The device comprises a beneficial agent

and osmagent surrounded at least in part by a semi-permeable membrane. The

beneficial agent may also function as the osmagent. The semi-permeable membrane is

permeable to water and substantially impermeable to the beneficial agent and

osmagent. A trigger means is attached to the semi-permeable membrane (e. g. , joins

two capsule halves). The trigger means is activated by a pH of from 3 to 9 and

triggers the eventual, but sudden, delivery of the beneficial agent. These devices

enable the pH-triggered release of the beneficial agent core as a bolus by osmotic

bursting.

The agents of the invention may be formulated based on the invention described in U.

S. Patent No. 5,316, 774 which discloses a composition for the controlled release of

an active substance comprising a polymeric particle matrix, where each particle

defines a network of internal pores. The active substance is entrapped within the pore

network together with a blocking agent having physical and chemical characteristics

selected to modify the release rate of the active substance from the internal pore

network. In one embodiment, drugs may be selectively delivered to the intestines

using an enteric material as the blocking agent. The enteric material remains intact in

the stomach but degrades under the pH conditions of the intestines. In another

embodiment, the sustained release formulation employs a blocking agent, which

remains stable under the expected conditions of the environment to which the active

substance is to be released. The use of pH-sensitive materials alone to achieve site-

specific delivery is difficult because of leaking of the beneficial agent prior to the

Attorney Docket No. 14184-055WO1

release site or desired delivery time and it is difficult to achieve long time lags before release of the active ingredient after exposure to high pH (because of rapid dissolution or degradation of the pH-sensitive materials).

- 5 The agents may also be formulated in a hybrid system which combines pH-sensitive materials and osmotic delivery systems. These hybrid devices provide delayed initiation of sustained-release of the beneficial agent. In one device a pH-sensitive matrix or coating dissolves releasing osmotic devices that provide sustained release of the beneficial agent see U. S. Patent Nos. 4,578, 075, 4,681, 583, and 4,851, 231. A
- 10 second device consists of a semipermeable coating made of a polymer blend of an insoluble and a pH-sensitive material. As the pH increases, the permeability of the coating increases, increasing the rate of release of beneficial agent see U. S. Patent Nos. 4,096, 238, 4, 503,030, 4, 522, 625, and 4,587, 117.
- 15 The agents of the invention may be formulated in terpolymers according to U. S. Patent No. 5,484, 610 which discloses terpolymers which are sensitive to pH and temperature which are useful carriers for conducting bioactive agents through the gastric juices of the stomach in a protected form. The terpolymers swell at the higher physiologic pH of the intestinal tract causing release of the bioactive agents into the
- 20 intestine. The terpolymers are linear and are made up of 35 to 99 wt % of a temperature sensitive component, which imparts to the terpolymer LCST (lower critical solution temperature) properties below body temperatures, 1 to 30 wt % of a pH sensitive component having a pKa in the range of from 2 to 8 which functions through ionization or deionization of carboxylic acid groups to prevent the bioactive
- 25 agent from being lost at low pH but allows bioactive agent release at physiological pH of about 7.4 and a hydrophobic component which stabilizes the LCST below body temperatures and compensates for bioactive agent effects on the terpolymers. The terpolymers provide for safe bioactive agent loading, a simple procedure for dosage form fabrication and the terpolymer functions as a protective carrier in the acidic
- 30 environment of the stomach and also protects the bioactive agents from digestive enzymes until the bioactive agent is released in the intestinal tract.

Attorney Docket No. 14184-055WO1

The agents of the invention may be formulated in pH sensitive polymers according to those described in U. S. Patent No. 6,103, 865. U. S. Patent No. 6,103, 865 discloses pH-sensitive polymers containing sulfonamide groups, which can be changed in physical properties, such as swellability and solubility, depending on pH and which can be applied for a drug-delivery system, bio-material, sensor, and the like, and a preparation method therefore. The pH-sensitive polymers are prepared by introduction of sulfonamide groups, various in pKa, to hydrophilic groups of polymers either through coupling to the hydrophilic groups of polymers, such as acrylamide, N, N-dimethylacrylamide, acrylic acid, N-isopropylacrylamide and the like or copolymerization with other polymerizable monomers. These pH-sensitive polymers may have a structure of linear polymer, grafted copolymer, hydrogel or interpenetrating network polymer.

The agents of the invention may be formulated according U. S. Patent No. 5, 656, 292 which discloses a composition for pH dependent or pH regulated controlled release of active ingredients especially drugs. The composition consists of a compactable mixture of the active ingredient and starch molecules substituted with acetate and dicarboxylate residues. The preferred dicarboxylate acid is succinate. The average substitution degree of the acetate residue is at least 1 and 0. 2-1. 2 for the dicarboxylate residue. The starch molecules can have the acetate and dicarboxylate residues attached to the same starch molecule backbone or attached to separate starch molecule backbones. The present invention also discloses methods for preparing said starch acetate dicarboxylates by transesterification or mixing of starch acetates and starch dicarboxylates respectively.

The agents of the invention may be formulated according to the methods described in U. S. Patent Nos. 5,554, 147,5, 788, 687, and 6,306, 422 which disclose a method for the controlled release of a biologically active agent wherein the agent is released from a hydrophobic, pH-sensitive polymer matrix. The polymer matrix swells when the environment reaches pH 8.5, releasing the active agent. A polymer of hydrophobic

Attorney Docket No. 14184-055WO1

and weakly acidic comonomers is disclosed for use in the controlled release system. Also disclosed is a specific embodiment in which the controlled release system may be used. The pH-sensitive polymer is coated onto a latex catheter used in ureteral catheterization. A ureteral catheter coated with a pH-sensitive polymer having an
5 antibiotic or urease inhibitor trapped within its matrix will release the active agent when exposed to high pH urine.

The agents of the invention may be formulated in/with bioadhesive polymers according to US Patent No. 6,365, 187. Bioadhesive polymers in the form of, or as a
10 coating on, microcapsules containing drugs or bioactive substances which may serve for therapeutic, or diagnostic purposes in diseases of the gastrointestinal tract, are described in US6365187. The polymeric microspheres all have a bioadhesive force of at least 11 mN/cm^2 (110 N/m^2) Techniques for the fabrication of bioadhesive
15 microspheres, as well as a method for measuring bioadhesive forces between microspheres and selected segments of the gastrointestinal tract in vitro are also described. This quantitative method provides a means to establish a correlation between the chemical nature, the surface morphology and the dimensions of drug-
20 loaded microspheres on one hand and bioadhesive forces on the other, allowing the screening of the most promising materials from a relatively large group of natural and synthetic polymers which, from theoretical consideration, should be used for making
bioadhesive microspheres. Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple
nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to
25 generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The
Science and Practice of Pharmacy. Other devices for generating aerosols employ
compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are
30 mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

Attorney Docket No. 14184-055WO1

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasal (including using a cannula), or by other routes. The agents can be administered orally, e.g., as a tablet or cachet containing a predetermined amount of the active ingredient, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, granules, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299, WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886 or in some other form. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, and humectants. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisobornide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal administration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a transmembrane formulation as described in WO 90/07923. The agents can be administered non-invasively via the dehydrated particles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug

Attorney Docket No. 14184-055WO1

formulation as described in WO 02/49621. The agents can be administered intranasally using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 5 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents, alone or in combination with other suitable components, can be administered by pulmonary route utilizing several techniques including but not 10 limited to intratracheal instillation (delivery of solution into the lungs by syringe), intratracheal delivery of liposomes, insufflation (administration of powder formulation by syringe or any other similar device into the lungs) and aerosol inhalation. Aerosols (e.g., jet or ultrasonic nebulizers, metered-dose inhalers (MDIs), and dry-powder inhalers (DPIs)) can also be used in intranasal applications. Aerosol 15 formulations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium and can be placed into pressurized acceptable propellants, such as hydrofluoroalkanes (HFAs, i.e. HFA-134a and HFA-227, or a mixture thereof), dichlorodifluoromethane (or other chlorofluocarbon propellants such as a mixture of Propellants 11, 12, and/or 114), propane, nitrogen, and the like. Pulmonary 20 formulations may include permeation enhancers such as fatty acids, and saccharides, chelating agents, enzyme inhibitors (e.g., protease inhibitors), adjuvants (e.g., glycocholate, surfactin, span 85, and nafamostat), preservatives (e.g., benzalkonium chloride or chlorobutanol), and ethanol (normally up to 5% but possibly up to 20%, by weight). Ethanol is commonly included in aerosol compositions as it can improve 25 the function of the metering valve and in some cases also improve the stability of the dispersion. Pulmonary formulations may also include surfactants which include but are not limited to bile salts and those described in U.S. 6,524,557 and references therein. The surfactants described in U.S. 6,524,557, e.g., a C8-C16 fatty acid salt, a bile salt, a phospholipid, or alkyl saccharide are advantageous in that some of them 30 also reportedly enhance absorption of the compound in the formulation. Also suitable in the invention are dry powder formulations comprising a therapeutically effective

Attorney Docket No. 14184-055WO1

amount of active compound blended with an appropriate carrier and adapted for use in connection with a dry-powder inhaler. Absorption enhancers which can be added to dry powder formulations of the present invention include those described in U.S. 6,632,456. WO 02/080884 describes new methods for the surface modification of
5 powders. Aerosol formulations may include U.S. 5,230,884, U.S. 5,292,499, WO 017/8694, WO 01/78696, U.S. 2003019437, U. S. 20030165436, and WO 96/40089 (which includes vegetable oil). Sustained release formulations suitable for inhalation are described in U.S. 20010036481A1, 20030232019A1, and U.S. 20040018243A1 as well as in WO 01/13891, WO 02/067902, WO 03/072080, and WO 03/079885.

10 Pulmonary formulations containing microparticles are described in WO 03/015750, U.S. 20030008013, and WO 00/00176. Pulmonary formulations containing stable glassy state powder are described in U.S. 20020141945 and U.S. 6,309,671. Other aerosol formulations are described in EP 1338272A1 WO 90/09781, U. S. 5,348,730, U.S. 6,436,367, WO 91/04011, and U.S. 6,294,153 and U.S. 6,290,987 describes a
15 liposomal based formulation that can be administered via aerosol or other means. Powder formulations for inhalation are described in U.S. 20030053960 and WO 01/60341. The agents can be administered intranasally as described in U.S. 20010038824.

20 Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of
25 pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

30 The agent can be fused to immunoglobulins or albumin, or incorporated into a liposome to improve half-life. The agent can also be conjugated to polyethylene

Attorney Docket No. 14184-055WO1

glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. The agent can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, 1995.

Attorney Docket No. 14184-055WO1

Methods to increase chemical and/or physical stability of the agents the described herein are found in WO 00/04880, and WO 97/04796 and the references cited therein.

Methods to increase bioavailability of the agents described herein are found in U.S. 20030198619, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate
5 can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses Ulex europaeus I (UEAI) and UEAI mimetics which may be used to target the agents to the GI tract.

Kits

The compounds and pharmaceutical formulations described herein may be contained
10 in a kit. The kit may include single or multiple doses of two or more agents, each packaged or formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the
15 package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation. Thus, the kits can comprise:
a) a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier, vehicle or diluent; and b) a container or
20 packaging. The kits may optionally comprise instructions describing a method of using the pharmaceutical compositions in one or more of the methods described herein (e.g. preventing or treating one or more of the diseases and disorders described herein). The kit may optionally comprise a second pharmaceutical composition comprising one or more additional agents described herein for cotherapy use, a
25 pharmaceutically acceptable carrier, vehicle or diluent. The pharmaceutical composition comprising the compound described herein and the second pharmaceutical composition contained in the kit may be optionally combined in the same pharmaceutical composition.

Attorney Docket No. 14184-055WO1

A kit includes a container or packaging for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

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

It maybe desirable to provide a written memory aid containing information and/or instructions for the physician, pharmacist or subject regarding when the medication is to be taken. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule

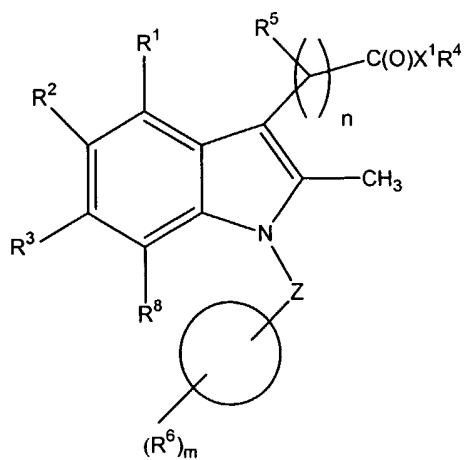
Attorney Docket No. 14184-055WO1

while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules. A kit can take the form of a dispenser designed to dispense the daily doses one at a time in the order of their intended use. The dispenser can be equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that have been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

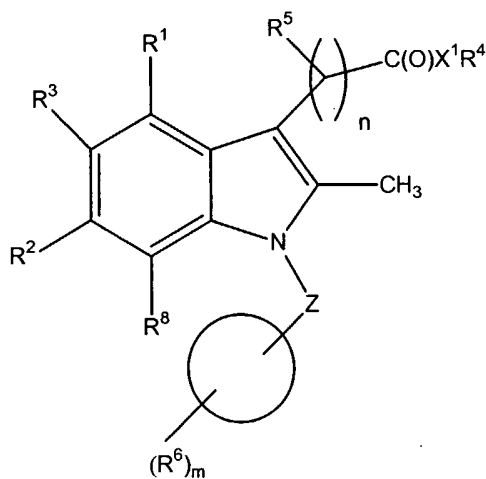
A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention.

Attorney Docket No. 14184-055WO1

1. A compound having the formula:



or

**Formula I****Formula II**

- 5 wherein:

R^1 is: H or a halogen;

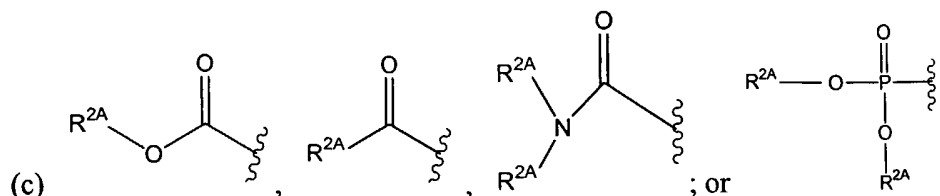
R^2 is: H, a halogen, or $R^{2B}O^-$ wherein

R^{2B} is selected from:

- (a) H;

Attorney Docket No. 14184-055WO1

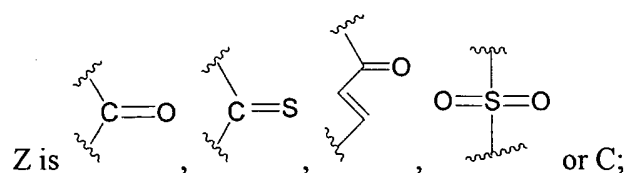
(b) C₁ to C₆ alkyl or a C₂ to C₆ alkenyl that is optionally independently substituted with one or more halogen; -OH, -NH₂, -C(O)OH;



wherein each R^{2A} is independently: H, a C₁ to C₆ alkyl, a C₂ to C₆ alkenyl, a C₂ to C₆ alkynyl, a C₆ to C₁₀ aryl, a C₃ to C₁₀ cycloalkyl, or a C₇ to C₂₀ arylalkyl optionally independently substituted with one or more halogen, -OH, -C(O)OH, or -NH₂;

R³ is H or a halogen;

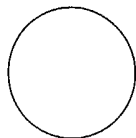
X¹ is -O-, -S-, -N(H)- or -N(H)S(O₂)-;



- 10 R⁴ is H; a C₁ to C₁₀ alkyl; a C₂-C₁₀ alkenyl; a C₂-C₁₀ alkynyl; a C₃ to C₈ cycloalkyl; a C₁ to C₆ hydroxyalkyl; a hydroxyl substituted C₆ to C₈ aryl; a primary, secondary or tertiary C₁ to C₆ alkylamino; primary, secondary or tertiary C₆ to C₈ arylamino; C₂ to C₆ alkylcarboxylic acid; a C₁ to C₆ alkylester; a C₆ to C₈ aryl; a C₆ to C₈ arylcarboxylic acid; a C₆ to C₈ aryylester; a C₆ to C₈ aryl substituted C₁ to C₆ alkyl; a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, S(O)₂, N, and S(O); an alkyl-substituted or aryl-substituted a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, S(O)₂, N, and S(O), wherein one or more H within R⁴ can be substituted by a halogen, -OH, or -C(O)OH, -NH₂;
- 15
- 20 n is 1, 2, 3, 4 or 5;

Attorney Docket No. 14184-055WO1

Each R⁵ is independently: H, an optionally substituted C₁-C₄ alkyl, wherein the substituents are independently selected from a halogen and -OH;



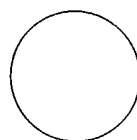
- 5 represents a C₃-C₆ saturated carbocycle, a C₆ aryl, C₃-C₆ non-saturated, non-aromatic carbocycle, a 6-membered heteroaryl having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, S(O)₂, N, S(O) and N(R⁷) or a 3- to 7-membered saturated or non-saturated heterocycle having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, S(O)₂, N, S(O) and N(R⁷);

each R⁶ is independently H, a halogen, -CH₃, -CN, -OCH₃, -SCH₃, -SCF₃, -OCH₂CF₃ or -CH₂CH₃ wherein one or more H can be replaced by a halogen;

- 10 m = 1, 2, 3, 4, or 5;

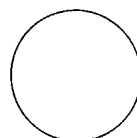
R⁷ is: H, a halogen, -CH₃, -CN, -OCH₃, -SCH₃, or -CH₂CH₃ wherein one or more H can be replaced by a halogen; and

R⁸ is: H, a halogen or -CH₃, wherein one or more H can be replaced by a halogen.



- 15 2. The compound of claim 1 wherein saturated carbocycle.

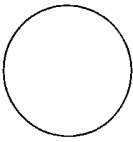
3. The compound of claim 2 wherein the C₃-C₆ saturated carbocycle is selected from cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl.



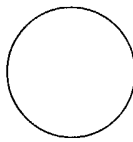
4. The compound of claim 1 wherein non-saturated, non-aromatic carbocycle.

Attorney Docket No. 14184-055WO1

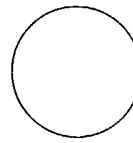
5. The compound of claim 4 wherein the C₃-C₆ non-saturated, non-aromatic carbocycle is selected from a cyclohexenyl, a cyclopentenyl, a cyclobutenyl.

6. The compound of claim 1 wherein  represents a 6-membered heteroaryl.

5 7. The compound of claim 6 wherein the 6-membered heteroaryl is selected from pyrazine, pyridazine, triazine, tetrazine, and pentazine.

8. The compound of claim 1 wherein  represents a 3- to 7-membered saturated heterocycle.

10 9. The compound of claim 8 wherein the 6-membered saturated heterocycle is selected from piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, tetrahydropyran, tetrahydrothiopyran, and dioxane.

15 10. The compound of claim 1 wherein  represents a 3- to 7-membered non-saturated heterocycle.

20 11. The compound of claim 10 wherein the 3- to 7-membered non-saturated heterocycle is selected from: thiophene, furan, pyrrole, thiazole, oxazole, imidazole, isothiazole, isoxazole, pyrazole, triazole, tetrazole, oxadiazole, oxatriazole and thiadiazole.

Attorney Docket No. 14184-055WO1

12. The compound of any of claims 1-11 wherein R^1 is H.
13. The compound of any of claims 1-11 wherein R^1 is a halogen.
- 5 14. The compound of claim 13 wherein R^1 is F or Cl.
15. The compound of any of claims 1-14 wherein R^{2B} is a substituted C_1 to C_6 alkyl or a substituted C_2 to C_6 alkenyl.
- 10 16. The compound of any of claims 1-14 wherein R^{2B} is not substituted.
17. The compound of any of claims 1-14 wherein R^{2B} is a C_1 to C_6 alkyl or a C_2 to C_6 alkenyl optionally substituted with one or more halogen.
- 15 18. The compound of any of claims 1-14 wherein R^{2B} is a C_1 to C_3 alkyl or alkenyl.
19. The compound of claim 18 wherein R^{2B} is a C_1 to C_3 alkyl.
- 20 20. The compound of claim 19 wherein R^{2B} is a methyl group or an ethyl group.
21. The compound of claim 1-15 wherein R^{2B} is substituted only with a halogen.
- 25 22. The compound of any of claims 1-21 wherein R^2 is H.
23. The compound of any of claims 1-22 wherein R^3 is a halogen.
- 30 24. The compound of any of claims 23 wherein R^3 is Cl.

Attorney Docket No. 14184-055WO1

25. The compound of any of claims 23 wherein R^3 is F.

26. The compound of any of claims 1-25 wherein $-C(O)X^1R^4$ is $-C(O)OR^4$.

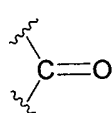
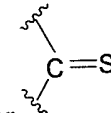
5

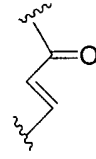
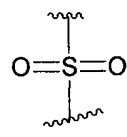
27. The compound of any of claims 1-25 wherein X^1 is $-S-$.

28. The compound of any of claims 1-25 wherein X^1 is $-N(H)-$.

10

29. The compound of any of claims 1-25 wherein X^1 is $-N(H)S(O)_2-$.

30. The compound of any of claims 1-29 wherein Z is  or .

31. The compound of any of claims 1-29 wherein Z is , ,
or C.

15

32. The compound of any of claims 1-30 wherein R^6 is selected from: $-CH_3$, $-CF_2H$, $-CH_2F$, $-CF_3$, $-CN$, $-OCF_2H$, $-OCH_3$, $-SCF_3$, $-SCF_2H$, $-SCH_3$, $-CH_2CH_3$ and $-OCF_3$.

20

33. The compound of any of claims 1-32 wherein R^7 is selected from: $-CH_3$, $-CF_2H$, $-CH_2F$, $-CF_3$, $-CN$, $-OCF_2H$, $-OCH_3$, $-SCF_3$, $-SCF_2H$, $-SCH_3$, $-CH_2CH_3$ and $-OCF_3$.

34. The compound of any of claims 1-33 wherein n is 1 or 2.

25

35. The compound of any of claims 1-34 wherein m is 1 or 2.

Attorney Docket No. 14184-055WO1

36. The compound of any of claims 1-35 wherein R^5 is H.

37. The compound of any of claims 1-35 wherein R^5 is a methyl group or an ethyl group.

5

38. The compound of any of claims 1-35 wherein R^5 is an unsubstituted methyl group or an unsubstituted ethyl group.

39. The compound of any of claims 1-38 wherein R^4 is H.

10

40. The compound of any of claims 1-26 and 30-39 wherein X^1 is O and R^4 is H.

41. The compound of any of claims 1-27 and 30-39 wherein X^1 is O and R^4 is other than H.

15

42. The compound of any of claims 1-39 and 41 wherein R^4 is an optionally independently substituted C_3 to C_{10} branched alkyl.

43. The compound of any of claims 1-39 and 41 wherein R^4 is a C_1 to C_{10} alkyl.

20

44. The compound of any of claims 1-39 and 41 wherein R^4 is a C_4 to C_8 cycloalkyl.

25

45. The compound of any of claims 1-39 and 41 wherein R^4 is a C_1 to C_6 hydroxy substituted alkyl.

46. The compound of claim 45 wherein R^4 is a hydroxyl substituted C_4 to C_8 aryl.

30

Attorney Docket No. 14184-055WO1

47. The compound of any of claims 1-39 and 41 wherein R⁴ is a primary, secondary or tertiary C₁ to C₆ alkylamino.

48. The compound of any of claims 1-39 and 41 wherein R⁴ is a primary, secondary or tertiary C₄ to C₈ arylamino.

49. The compound of any of claims 1-39 and 41 wherein R⁴ is a C₂ to C₆ alkylcarboxylic acid.

50. The compound of any of claims 1-39 and 41 wherein R⁴ is a C₁ to C₆ alkylester.

51. The compound of claim 50 wherein R⁴ is a branched C₁ to C₆ alkylester.

52. The compound of any of claims 1-39 and 41 wherein R⁴ is a C₄ to C₈ aryl.

53. The compound of any of claims 1-39 and 41 wherein R⁴ is a C₄ to C₈ arylcarboxylic acid.

54. The compound of any of claims 1-39 and 41 wherein R⁴ is a C₄ to C₈ arylester.

55. The compound any of claims 1-39 and 41 wherein R⁴ is C₄ to C₈ aryl substituted C₁ to C₆ alkyl.

56. The compound of any of claims 1-39 and 41 wherein R⁴ is a C₄ to C₈ heterocyclic alkyl or aryl.

Attorney Docket No. 14184-055WO1

57. The compound of any of claims 1-39 and 41 wherein R⁴ is an alkyl-substituted or aryl-substituted C₄ to C₈ heterocyclic alkyl or aryl.

58. The compound of any of claims 1-39 and 41 wherein R⁴ is substituted.

5

59. The compound of any of claims 1-39 and 41 wherein R⁴ is unsubstituted.

60. A pharmaceutical composition comprising the compound of any of claims 1-59 and a pharmaceutically acceptable carrier.

10

61. A method for treating inflammation comprising administering a composition comprising the compound of any of claims 1-59.

15

62. A method for treating anxiety comprising administering the compound of any of claims 1-59.

63. A method for treating a sleep disorder comprising administering the compound of any of claims 1-59.

20

64. A method for treating a respiratory disorder comprising administering the compound of any of claims 1-59.

65. The method of claim 64 wherein the respiratory disorder is asthma.

25

66. A method for inhibiting COX-2 activity in a patient, the method comprising administering the compound of any of claims 1-59.

67. A method for inhibiting FAAH activity in a patient, the method comprising administering the compound of any of claims 1-59.

30

Attorney Docket No. 14184-055WO1

68. The method of claim 65 wherein X^1 is O and R^4 is H.

69. The method of claim 66 wherein X^1 is O and R^4 is other than H.

5 70. A method for modulating CRTH2 activity on a patient, the method comprising administering the compound of any of claims 1-59.

71. The pharmaceutical composition of claim 60 further comprising an analgesic agent.

10

72. The pharmaceutical composition of claim 60 further comprising an anti-inflammatory agent.

73. The compound of any of claims 1-59 having **Formula I**.

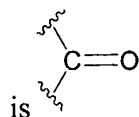
15

74. The compound of any of claims 1-59 having **Formula II**.

75. The compound of any of claims 1-59 and 74 wherein R^8 is H.

20 76. The compound of any of claims 1-59 having **Formula I** wherein R^8 is H.

77. The compound of any of claims 1-59 having **Formula I** wherein Z

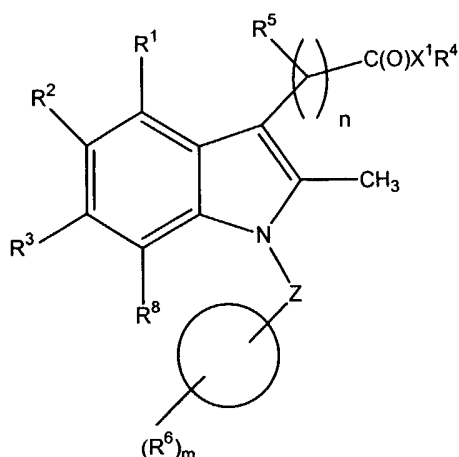


25

78. The compound of any of claims 1-59 having **Formula I** wherein Z is C.

79. A compound having the formula:

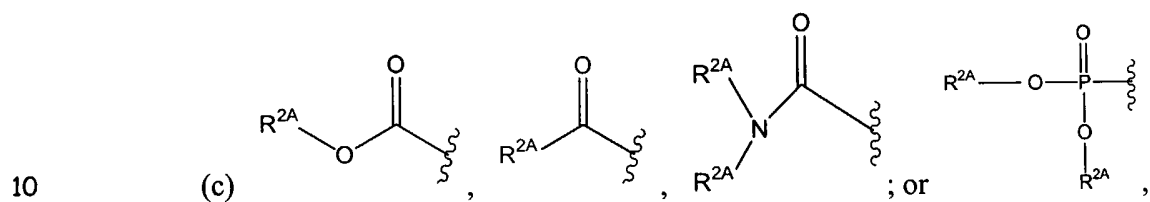
Attorney Docket No. 14184-055WO1

**Formula I**

wherein:

 R^1 is: H or a halogen;5 R^2 is: H, a halogen, or $R^{2B}O$ - wherein R^{2B} is selected from:

(a) H;

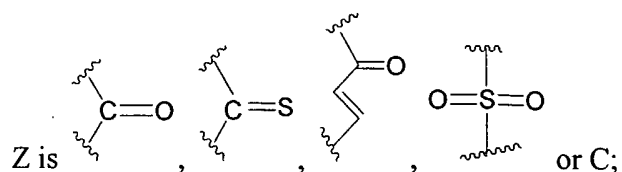
(b) C_1 to C_6 alkyl or a C_2 to C_6 alkenyl that is optionally independently substituted with one or more halogen; -OH, -NH₂, -C(O)OH;

wherein each R^{2A} is independently: H, a C_1 to C_6 alkyl, a C_2 to C_6 alkenyl, a C_2 to C_6 alkynyl, a C_6 to C_{10} aryl, a C_3 to C_{10} cycloalkyl, or a C_7 to C_{20} arylalkyl optionally independently substituted with one or more halogen, -OH, -C(O)OH, or -NH₂;

 R^3 is H or a halogen;

Attorney Docket No. 14184-055WO1

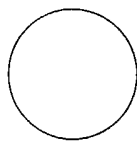
X^1 is $-O-$, $-S-$, $-N(H)-$ or $-N(H)S(O_2)-$;



R^4 is H; a C_1 to C_{10} alkyl; a C_2 - C_{10} alkenyl; a C_2 - C_{10} alkynyl; a C_3 to C_8 cycloalkyl; a C_1 to C_6 hydroxyalkyl; a hydroxyl substituted C_6 to C_8 aryl; a primary, secondary or tertiary C_1 to C_6 alkylamino; primary, secondary or tertiary C_6 to C_8 arylamino; C_2 to C_6 alkylcarboxylic acid; a C_1 to C_6 alkylester; a C_6 to C_8 aryl; a C_6 to C_8 arylcarboxylic acid; a C_6 to C_8 arylester; a C_6 to C_8 aryl substituted C_1 to C_6 alkyl; a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, $S(O)_2$, N, and S(O); an alkyl-substituted or aryl-substituted a 4 to 8 membered heterocyclic alkyl or heteroaryl wherein the heteroatoms are selected from O, S, $S(O)_2$, N, and S(O), wherein one or more H within R^4 can be substituted by a halogen, $-OH$, or $-C(O)OH$, $-NH_2$;

n is 1, 2, 3, 4 or 5;

Each R^5 is independently: H, an optionally substituted C_1 - C_4 alkyl, wherein the substituents are independently selected from a halogen and $-OH$;



represents a C_3 - C_6 saturated carbocycle, a C_6 aryl, C_3 - C_6 non-saturated, non-aromatic carbocycle, a 6-membered heteroaryl having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, $S(O)_2$, N, S(O) and $N(R^7)$ or a 3- to 7-membered saturated or non-saturated heterocycle having 1, 2, 3, 4 or 5 heteroatoms independently selected from O, S, $S(O)_2$, N, S(O) and $N(R^7)$;

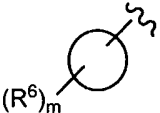
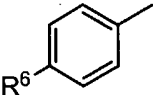
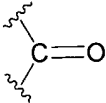
each R^6 is independently H, a halogen, $-CH_3$, $-CN$, $-OCH_3$, $-SCH_3$, $-SCF_3$, $-OCH_2CF_3$ or $-CH_2CH_3$ wherein one or more H can be replaced by a halogen;

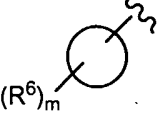
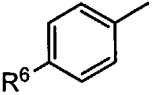
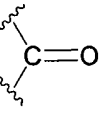
Attorney Docket No. 14184-055WO1

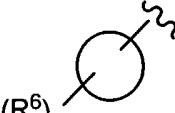
 $m = 1, 2, 3, 4, \text{ or } 5$;

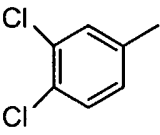
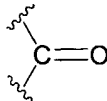
R^7 is: H, a halogen, $-\text{CH}_3$, $-\text{CN}$, $-\text{OCH}_3$, $-\text{SCH}_3$, or $-\text{CH}_2\text{CH}_3$ wherein one or more H can be replaced by a halogen; and

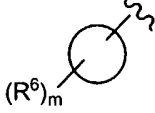
R^8 is: H, a halogen or $-\text{CH}_3$, wherein one or more H can be replaced by a halogen;

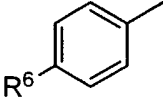
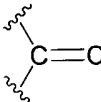
5 provided that when  is , $n = 1$, Z is , R^5 is H, R^1 is H, R^3 is H, R^8 is H, R^2 is $-\text{OCH}_3$, $-\text{C(O)X}^1\text{R}^4$ is $-\text{COOH}$, then R^6 is not Cl, H, F, or CF_3 ;

further provided that when  is , $n = 1$, R^5 is H, R^1 is F, R^3 is H, R^2 is CH_3 , R^8 is H, Z is , $-\text{C(O)X}^1\text{R}^4$ is $-\text{COOH}$, then R^6 is not H; further

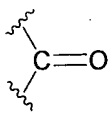
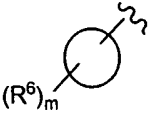
provided that when  is

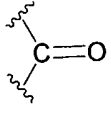
10  $n = 1$, R^5 is H, Z is , R^1 is H, R^3 is H, R^8 is H, and $-\text{C(O)X}^1\text{R}^4$ is

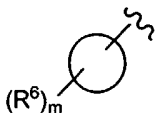
$-\text{COOH}$, then R^2 is not $-\text{OH}$; further provided that when  is

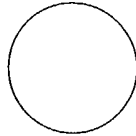
, $n = 1$, Z is , R^5 is H, R^1 is F, R^3 is H, R^8 is H, R^2 is $-\text{OCH}_3$, $-\text{C(O)X}^1\text{R}^4$ is $-\text{COOH}$, then R^6 is not H; further provided that when R^1 , R^3 , R^5 and R^8

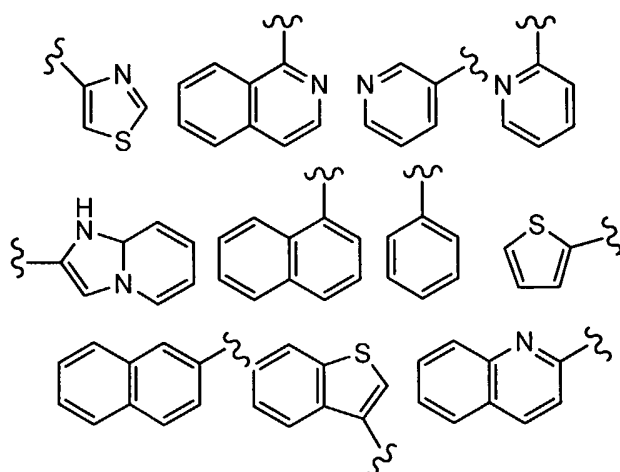
Attorney Docket No. 14184-055WO1

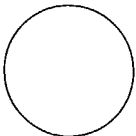
are all H, R^2 is F, $n = 1$, $-C(O)X^1R^4$ is $-COOH$, Z is , then $(R^6)_m$  is not a benzyl group that is para substituted with a halogen; further provided that when

R^1, R^3, R^5 and R^8 are all H, R^2 is $-OCH_3$, $n = 1$, $-C(O)X^1R^4$ is $-COOH$, Z is ,

then $(R^6)_m$  is not a benzyl group that is para substituted with a halogen; and further provided that when R^1, R^3, R^5 and R^8 are all H, R^2 is F, $n = 1$, $-C(O)X^1R^4$ is –

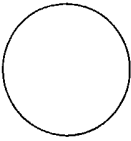
$COOH$, Z is C, then  is not selected from



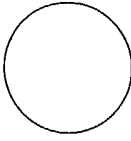
80. The compound of claim 79 wherein  represents a C_3 - C_6 saturated carbocycle.

10 81. The compound of claim 80 wherein the C_3 - C_6 saturated carbocycle is selected from cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl.

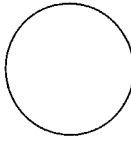
Attorney Docket No. 14184-055WO1

82. The compound of claim 79 wherein  represents a C₃-C₆ non-saturated, non-aromatic carbocycle.

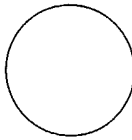
83. The compound of claim 82 wherein the C₃-C₆ non-saturated, non-aromatic carbocycle is selected from a cyclohexenyl, a cyclopentenyl, a cyclobutenyl.

5 84. The compound of claim 79 wherein  represents a 6-membered heteroaryl.

85. The compound of claim 84 wherein the 6-membered heteroaryl is selected from pyrazine, pyridazine, triazine, tetrazine, and pentazine.

10 86. The compound of claim 79 wherein  represents a 3- to 7-membered saturated heterocycle.

15 87. The compound of claim 86 wherein the 6-membered saturated heterocycle is selected from piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine sulfoxide, thiomorpholine sulfone, tetrahydropyran, tetrahydrothiopyran, and dioxane.

88. The compound of claim 79 wherein  represents a 3- to 7-membered non-saturated heterocycle.

Attorney Docket No. 14184-055WO1

89. The compound of claim 88 wherein the 3- to 7-membered non-saturated heterocycle is selected from: thiophene, furan, pyrrole, thiazole, oxazole, imidazole, isothiazole, isoxazole, pyrazole, triazole, tetrazole, oxadiazole, oxatriazole and thiadiazole.

5

90. The compound of any of claims 79-89 wherein R^1 is H.

91. The compound of any of claims 79-89 wherein R^1 is a halogen.

10

92. The compound of claim 91 wherein R^1 is F or Cl.

93. The compound of any of claims 79-92 wherein R^{2B} is a substituted C_1 to C_6 alkyl or a substituted C_2 to C_6 alkenyl.

15

94. The compound of any of claims 79-92 wherein R^{2B} is not substituted.

95. The compound of any of claims 79-92 wherein R^{2B} is a C_1 to C_6 alkyl or a C_2 to C_6 alkenyl optionally substituted with one or more halogen.

20

96. The compound of any of claims 79-92 wherein R^{2B} is a C_1 to C_3 alkyl or alkenyl.

97. The compound of claim 96 wherein R^{2B} is a C_1 to C_3 alkyl.

25

98. The compound of claim 97 wherein R^{2B} is a methyl group or an ethyl group.

99. The compound of any of claims 79-92 wherein R^{2B} is substituted only with a halogen.

30

Attorney Docket No. 14184-055WO1

100. The compound of any of claims 79-99 wherein R^2 is H.

101. The compound of any of claims 79-100 wherein R^3 is a halogen.

5 102. The compound of claim 101 wherein R^3 is Cl.

103. The compound of claim 101 wherein R^3 is F.

104. The compound of any of claims 79-103 wherein X^1 is -O-.

10

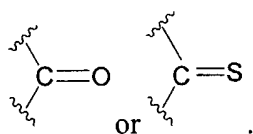
105. The compound of any of claims 79-103 wherein X^1 is -S-.

106. The compound of any of claims 79-103 wherein X^1 is -N(H)-

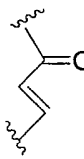
15

107. The compound of any of claims 79-103 wherein X^1 is -N(H)S(O)₂-.

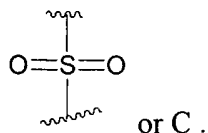
108. The compound of any of claims 79-107 wherein Z is



109. The compound of any of claims 79-107 wherein Z is



20



or C.

110. The compound of any of claims 79-109 wherein R^6 is selected from: -
 CH_3 , $-\text{CF}_2\text{H}$, $-\text{CH}_2\text{F}$, $-\text{CF}_3$, $-\text{CN}$, $-\text{OCF}_2\text{H}$, $-\text{OCH}_3$, $-\text{SCF}_3$, $-\text{SCF}_2\text{H}$, $-\text{SCH}_3$, $-\text{CH}_2\text{CH}_3$
 and $-\text{OCF}_3$.

25

Attorney Docket No. 14184-055WO1

111. The compound of any of claims 79-109 wherein R^7 is selected from: -
CH₃, -CF₂H, -CH₂F, -CF₃, -CN, -OCF₂H, -OCH₃, -SCF₃, -SCF₂H, -SCH₃, -CH₂CH₃
and -OCF₃.

5 112. The compound of any of claims 79-111 wherein n is 1 or 2.

113. The compound of any of claims 79-112 wherein m is 1 or 2.

114. The compound of any of claims 79-113 wherein R^5 is H.

10

115. The compound of any of claims 79-113 wherein R^5 is a methyl group
or an ethyl group.

116. The compound of any of claims 79-113 wherein R^5 is an unsubstituted
15 methyl group or an unsubstituted ethyl group.

117. The compound of any of claims 79-116 wherein R^4 is H.

118. The compound of any of claims 79-104 and 108-114 wherein X^1 is O
20 and R^4 is H.

119. The compound of any of claims 79-104 and 108-116 wherein X^1 is O
and R^4 is other than H.

25 120. The compound of any of claims 79-116 wherein R^4 is an optionally
independently substituted C₃ to C₁₀ branched alkyl.

121. The compound of any of claims 79-116 wherein R^4 is a C₁ to C₁₀ alkyl.

30 122. The compound of claim 121 wherein R^4 is a C₄ to C₈ cycloalkyl.

Attorney Docket No. 14184-055WO1

123. The compound of any of claims 79-116 wherein R^4 is a C_1 to C_6 hydroxy substituted alkyl.

5 124. The compound of any of claims 79-116 wherein R^4 is a hydroxyl substituted C_4 to C_8 aryl.

125. The compound of any of claims 79-116 wherein R^4 is a primary, secondary or tertiary C_1 to C_6 alkylamino.

10 126. The compound of any of claims 79-116 wherein R^4 is a primary, secondary or tertiary C_4 to C_8 arylamino.

127. The compound of any of claims 79-116 wherein R^4 is a C_2 to C_6 alkylcarboxylic acid.

15 128. The compound of any of claims 79-116 wherein R^4 is a C_1 to C_6 alkylester.

20 129. The compound of claim 50 wherein R^4 is a branched C_1 to C_6 alkylester.

130. The compound of any of claims 79-116 wherein R^4 is a C_4 to C_8 aryl.

25 131. The compound of any of claims 79-116 wherein R^4 is a C_4 to C_8 arylcarboxylic acid.

132. The compound of any of claims 79-116 wherein R^4 is a C_4 to C_8 arylester.

30 133. The compound any of claims 79-116 wherein R^4 is C_4 to C_8 aryl substituted C_1 to C_6 alkyl.

Attorney Docket No. 14184-055WO1

134. The compound of any of claims 79-116 wherein R^4 is a C_4 to C_8 heterocyclic alkyl or aryl.

5 135. The compound of any of claims 79-116 wherein R^4 is an alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl.

136. The compound of any of claims 79-116 wherein R^4 is substituted.

10 137. The compound of any of claims 79-116 wherein R^4 is unsubstituted.

138. The compound of any of claims 79-92 and 101-137 wherein R^2 is –
 OCH_3 or CH_3 .

15 139. The compound of any of claims 79-92 and 101-137 wherein R^2 is –
 OCH_3 or CH_3 .

140. The compound of any of claims 79-92 and 101-137 wherein R^1 is H
and R^8 is H

20 141. The compound of any of claims 79-140 wherein R^1 and R^8 are both is
H

142. The compound of any of claims 79-114 and 138-141 wherein $n = 1$, R^5
is H and $-C(O)X^1R^4$ is $-C(O)OH$.

25 143. The compound of any of claims 79-107 and 110-142 wherein Z is C.

144. A method for treating inflammation comprising administering a
composition comprising the compound of any of claims 79-143.

Attorney Docket No. 14184-055WO1

145. A method for treating anxiety comprising administering the compound of any of claims 79-143.

5 146. A method for treating a sleep disorder comprising administering the compound of any of claims 79-143.

147. A method for treating a respiratory disorder comprising administering the compound of any of claims 79-143.

10 148. The method of claim 64 wherein the respiratory disorder is asthma.

149. A method for inhibiting COX-2 activity in a patient, the method comprising administering the compound of any of claims 79-143.

15 150. A method for inhibiting FAAH activity in a patient, the method comprising administering the compound of any of claims 79-143.

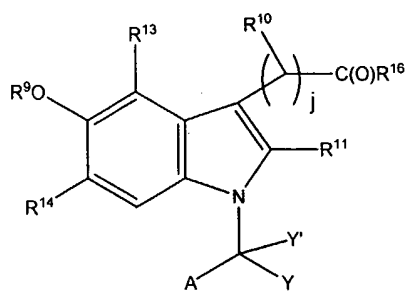
151. A method for modulating CRTH2 activity on a patient, the method comprising administering the compound of any of claims 79-143.

20 152. The pharmaceutical composition comprising the compound of any of claims 79-143.

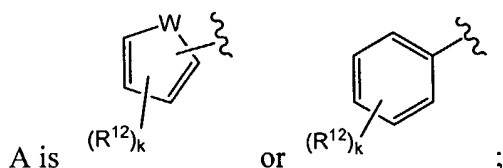
25 153. The pharmaceutical composition of claim 60 further comprising an anti-inflammatory agent or an analgesic agent.

154. A compound having the formula:

Attorney Docket No. 14184-055WO1



wherein:



R^9 is H, a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

j is 1, 2, 3 or 4;

R^{10} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more -OH, - NH_2 , or halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more -OH, - NH_2 or halogen;

R^{11} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more halogen;

R^{12} is a halogen; -CN; -OH; -SH; a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; - OR^{12A} ; - SR^{12A} ; - SOR^{12A} ; or - $S(O)_2R^{12A}$,

wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

k is 0, 1, 2, 3, 4 or 5;

R^{13} is H or a halogen;

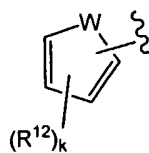
R^{14} is H or a halogen;

Y and Y' are both H; Y and Y' taken together are S; or Y and Y' taken together are O;

W is O, S, or - NR^{15} , wherein R^{15} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; and

Attorney Docket No. 14184-055WO1

R^{16} is $-OH$, $-OR^{16A}$, or R^{16A} , wherein R^{16A} is: H or a C_1 to C_6 (C_1 , C_2 , C_3 , C_4 , C_5 , C_6) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or arylalkyl optionally independently substituted with one or more halogen $-OH$, $-C(O)OH$, or $-NH_3$.



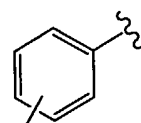
5 155. The compound of claim 154 wherein A is $(R^{12})_k$.

156. The compound of claim 154 or claim 155 wherein W is S.

157. The compound of claim 154 or claim 155 wherein W is O.

10

158. The compound of claim 154 or 155 wherein W is $-NR^{15}$.



159. The compound of claim 154 wherein A is $(R^{12})_k$.

15

160. The compound of any of claims 154-159 wherein k is 1.

161. The compound of any of claims 154-159 wherein k is 2.

162. The compound of any of claims 154-159 wherein k is 3.

20

163. The compound of any of claims 154-162 wherein R^{12} is F; Cl; $-CN$; $-OH$; $-SH$; a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl; $-OR^{12A}$; $-SR^{12A}$; $-SOR^{12A}$; or $-S(O)_2R^{12A}$, wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl.

25

164. The compound of claim 163 wherein R^{12} is F; Cl; $-CN$; $-OH$; $-SH$; a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl.

Attorney Docket No. 14184-055WO1

165. The compound of claim 163 wherein R^{12} is $-O R^{12A}$; $-S R^{12A}$; $-SO R^{12A}$; or $-S(O)_2 R^{12A}$, wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more F or Cl.

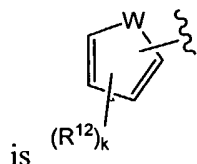
5

166. The compound of any of claims 154-165 wherein R^9 is H.

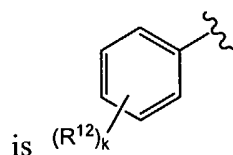
167. The compound of any of claims 154-165 wherein R^9 is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen.

10

168. The compound of any of claims 154, 156-158 and 160-167 wherein A

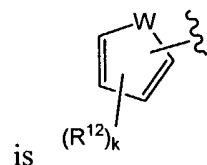


169. The compound of any of claims 154, 156-158 and 160-167 wherein A

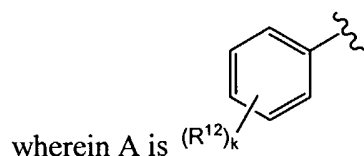


15

170. The compound of any of claims 154, 156-158 and 160-167 wherein A



171. The compound of claim of any of claims 154, 156-158 and 160-167



20

172. The compound of any of claims 154-171 wherein the compound is a CRTH2 agonist.

Attorney Docket No. 14184-055WO1

173. The compound of claim 172 wherein the compound has an EC₅₀ for CRTH2 that is less than 20 μM.

174. The compound of claim 172 wherein the compound has an EC₅₀ for CRTH2 that is less than 10 μM.

175. The compound of claim 172 wherein the compound has an EC₅₀ for CRTH2 that is less than 5 μM.

176. The compound of any of claims 154-171 wherein the compound is a CRTH2 antagonist.

177. The compound of claim 176 wherein the compound has an IC₅₀ for CRTH2 that is less than 20 μM.

178. The compound of claim 176 wherein the compound has an IC₅₀ for CRTH2 that is less than 10 μM.

179. The compound of claim 176 wherein the compound has an IC₅₀ for CRTH2 that is less than 5 μM.

180. The compound of any of claims 154-179 wherein R⁹ is a C₁-C₃ alkyl, optionally independently substituted with one or more halogen.

181. The compound of any of claims 154-179 wherein R⁹ is H.

182. The compound of any of claims 154-179 wherein Y and Y' taken together are S.

183. The compound of any of claims 154-179 wherein Y and Y' taken together are O.

184. The compound of any of claims 154-179 wherein Y and Y' are both H.

Attorney Docket No. 14184-055WO1

185. The compound of any of claims 154-179 wherein j is 1.

186. The compound of any of claims 154-179 wherein j is 2.

5 187. The compound of any of claims 154-179 wherein j is 3.

188. The compound of any of claims 154-179 wherein j is 4.

189. The compound of any of claims 154-179 wherein R¹³ is H, F or Cl.

10

190. The compound of any of claims 154-179 wherein R¹⁴ is H, F or Cl.

191. The compound of any of claims 154-179 wherein R⁹ is H, a C₁-C₃ alkyl, optionally independently substituted with one or more F or Cl.

15

192. The compound of any of claims 154-179 wherein R¹⁰ is H; a C₁-C₆ alkyl, optionally independently substituted with one or more -OH, -NH₂, or F or Cl; or a C₁-C₆ alkenyl optionally independently substituted with one or more -OH, -NH₂, F or Cl.

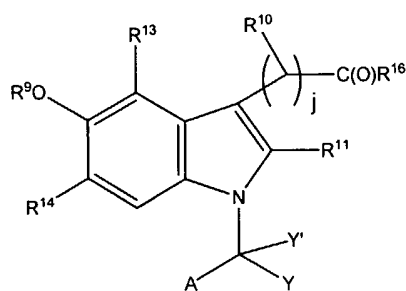
20

193. The compound of any of claims 154-179 wherein R¹¹ is H; a C₁-C₆ alkyl, optionally independently substituted with one or more F or Cl; or a C₁-C₆ alkenyl optionally independently substituted with one or more F or Cl.

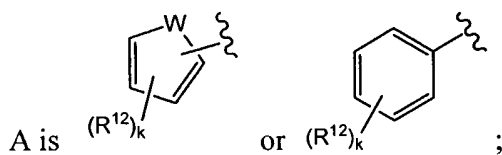
25 194. The compound of claim any of claims 154-179 wherein any halogen is selected from F and Cl.

195. A compound having the formula:

Attorney Docket No. 14184-055WO1



wherein:



R^9 is H, a C_1 - C_3 alkyl, optionally independently substituted with one or more

5 halogen;

n is 1, 2, 3 or 4;

R^{10} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more -OH, - NH_2 , or halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more -OH, - NH_2 or halogen;

10 R^{11} is H; a C_1 - C_6 alkyl, optionally independently substituted with one or more halogen; or a C_1 - C_6 alkenyl optionally independently substituted with one or more halogen;

R^{12} is a halogen; -CN; -OH; -SH; a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; - OR^{12A} ; - SR^{12A} ; - SOR^{12A} ; or - $S(O)_2R^{12A}$,

15 wherein R^{12A} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen;

m is 0, 1, 2, 3, 4, or 5;

R^{13} is H or a halogen;

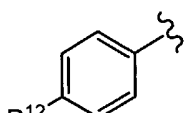
R^{14} is H or a halogen;

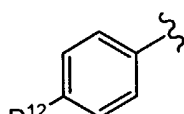
20 Y and Y' are both H; Y and Y' taken together are S; or Y and Y' taken together are O;

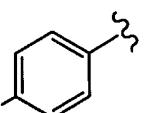
W is O, S, or - NR^{15} , wherein R^{15} is a C_1 - C_3 alkyl, optionally independently substituted with one or more halogen; and

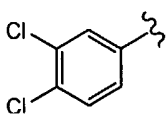
Attorney Docket No. 14184-055WO1

R^{16} is $-\text{OH}$, $-\text{OR}^{16A}$; or R^{16A} , wherein R^{16A} is: H or a C_1 to C_6 (C_1 , C_2 , C_3 , C_4 , C_5 , C_6) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or arylalkyl optionally independently substituted with one or more halogen $-\text{OH}$, $-\text{C}(\text{O})\text{OH}$, or $-\text{NH}_3$;

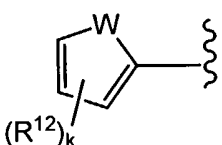
5 provided that if A is , j is 1, R^{10} is H, Y and Y' taken together are O, R^{11} is $-\text{CH}_3$, R^{13} is H, R^{14} is H and R^9 is $-\text{CH}_3$, then R^{12} is not: Cl, H, F or $-\text{CF}_3$;

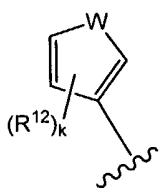
further provided that if A is , j is 1, R^{10} is H, Y and Y' taken together are O, R^{11} is $-\text{CH}_3$, R^{13} is H, R^{14} is H, and R^9 is H, then R^{12} is not H; further provided

that when A is , j is 1, R^{10} is H, Y and Y' taken together are O, R^{11} is $-\text{CH}_3$, R^{13} is F, R^{14} is H, R^9 is $-\text{CH}_3$, R^{12} is not H; and further provided that when A is

10 , j is 1, R^{10} is H, Y and Y' taken together are O, R^{11} is $-\text{CH}_3$, R^{13} is H, R^{14} is H, then R^9 is not H.

15 196. The compound of claim 195 wherein R^{12} is selected from: F, Cl, Br, OH, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCF}_2\text{H}$, $-\text{OCF}_3$, $-\text{OCF}_2\text{CF}_3$, $-\text{OCF}_2\text{CF}_2\text{H}$, $-\text{CH}_3$, $-\text{CF}_2\text{H}$, $-\text{CF}_3$, $-\text{SCH}_3$, $-\text{SCF}_2\text{H}$, $-\text{SCF}_3$, $-\text{SCF}_2\text{CF}_3$, $-\text{SCF}_2\text{CF}_2\text{H}$, and $-\text{CN}$.

197. The compound of claim 195 or 196 wherein A is .

198. The compound of claim 195 or 196 wherein A is .

Attorney Docket No. 14184-055WO1

199. The compound of any of claims 195-198 wherein R^{16} is $-OH$.

200. The compound of any of claims 195-198 wherein R^{16} is $-OR^{16A}$,
wherein R^{16A} is: a C_1 to C_6 ($C_1, C_2, C_3, C_4, C_5, C_6$) alkyl, alkenyl, alkynyl, aryl,
5 cycloalkyl, or arylalkyl optionally independently substituted with one or more
halogen $-OH$, $-C(O)OH$, or $-NH_3$.

201. The compound of of any of claims 195-198 wherein R^{16} is $-OR^{16A}$,
wherein R^{16A} is: a C_1 to C_6 ($C_1, C_2, C_3, C_4, C_5, C_6$) alkyl optionally independently
10 substituted with one or more halogen $-OH$, $-C(O)OH$, or $-NH_3$.

202. The compound of of any of claims 195-198 wherein R^{16} is R^{16A}
wherein R^{16} is: a C_1 to C_6 ($C_1, C_2, C_3, C_4, C_5, C_6$) alkyl optionally independently
15 substituted with one or more halogen $-OH$, $-C(O)OH$, or $-NH_3$.

203. The compound of any of claims 195-202 wherein R^{14} is Cl or F .

204. The compound of any of claims 195-202 wherein R^{14} is Cl .

205. The compound of any of claims 195-202 wherein R^{14} is F .

206. The compound of any of claims 195-205 wherein R^{11} is CH_3 .

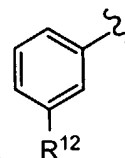
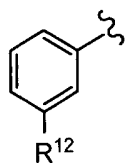
207. The compound of any of claims 195-206 wherein R^9 is CH_3 .

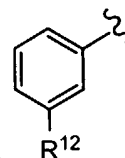
208. The compound of any of claims 195-207 wherein R^{13} is H .

209. The compound of any of claims 195-208 wherein R^{16} is $-OH$.

Attorney Docket No. 14184-055WO1

210. The compound of any of claims 195, 196 and 199-208 wherein A is



211. The compound of any of claims 195-208 wherein A is  and
5 R¹² is F, Cl, CH₃, -OCF₃, Br, CF₃, and Cl.

212. A pharmaceutical composition comprising the compound of any of claims 154-211 and a pharmaceutically acceptable carrier.

10 213. A method for treating a disorder characterized by imbalance of the Th1/Th2 ratio towards Th1, the method comprising administering the compound of any of claims 154-211.

15 214. The method of claim 51 wherein the disorder is selected from: rheumatoid arthritis, Type I diabetes, psoriasis, gastritis, irritable bowel disorder, multiple sclerosis, painless thyroiditis, lupus, and Crohn's Disease.

20 215. A method for treating a disorder characterized by imbalance of the Th1/Th2 ratio towards Th2, the method comprising administering the compound of any of claims 154-211.

216. The method of claim 215 wherein the disorder is selected from: asthma, atopic dermatitis, allergic rhinitis, allergy, and Grave's Disease.

25 217. A method for modulating CRTH2 activity in a patient, the method comprising administering the compound of any of claims 154-211.

Attorney Docket No. 14184-055WO1

218. A method for treating a disorder selected from asthma, allergic rhinitis, atopic dermatitis, eosinophilic esophagitis, and other disorders associated with allergic inflammation, the method comprising administering the compound of any of claims 154-211.

5

219. The method of claim 218 wherein the disorder is asthma.

220. The method of any of claims 213-219 further comprising administering a second compound that is an anti-inflammatory agent.

10

221. A method for increasing the Th1 cell/Th2 cell ratio in a patient, the method comprising administering to the patient the compound of any of claims 154-211.

15

222. A method for decreasing the Th1 cell/Th2 cell ratio in a patient, the method comprising administering to the patient the compound of any of claims 154-211.

20

223. The method of claim 221 wherein the compound is a CRTH2 antagonist.

224. The method of claim 222 wherein the compound is a CRTH2 agonist.

25

225. A method for treating a disorder characterized by an increased level of one or more of IL-4, IL-10 and IL-13 in a patient, the method comprising administering to the patient the compound of any of claims 154-211.

30

226. A method for treating a disorder characterized by an increased level of interferon- γ in a patient, the method comprising administering to the patient the compound of any of claims 154-211.

Row	IUPAC name	COX-1 IC50 (μm)	COX-2 IC50 (μm)
1	{6-fluoro-5-methoxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl}acetic acid	3.3	0.29
2	{1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	5	0.2
3	{1-(cyclohexylcarbonyl)-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	3.22
4	{6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl}acetic acid	6.3	0.32
5	{6-fluoro-5-hydroxy-2-methyl-1-[(5-methyl-2-thienyl)carbonyl]-1H-indol-3-yl}acetic acid	16.3	0.41
6	{6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl}acetic acid	27.3	0.23
7	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	35	0.2
8	{1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	85, 90	0.56 0.6
9	{1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10
10	{1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	2.8
11	{5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl}acetic acid	>100	8.9
12	{5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl}acetic acid	>100	>22.2
13	{1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl}acetic acid	>100	>10%
14	{6-chloro-1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>10%
15	{1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100
16	{1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	>100
17	{1-(cyclohex-1-en-1-ylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	3.03
18	{1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	0.4
19	{1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid	>100	0.8

FIG. 1

ROW	IUPAC name	CD11b agonist activity at 10 μ M (%)	CD11b agonist activity at 1 μ M (%)
1	[1-(4-chlorobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	91.5	100.7
2	[1-(4-chlorobenzoyl)-4-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	104.1	98
3	[5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid	35.9	45.1
4	[5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid	43.8	40.4
5	[5-methoxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid	48.6	35.9
6	[1-[(6-chloropyridin-3-yl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	35.7	30.1
7	[1-[(6-chloropyridin-3-yl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl]acetic acid	44.8	28.0
8	[1-(4-bromobenzoyl)-4,6-difluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	30.1	11.9
9	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethyl)benzoyl]-1H-indol-3-yl]acetic acid	49.7	61.5
10	[6-fluoro-5-hydroxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid	44.8	39.9
11	[1-(4-bromobenzoyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	93.0	129.4
12	[6-fluoro-5-hydroxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl]acetic acid	32.2	26.1
13	[6-fluoro-5-methoxy-2-methyl-1-[4-(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl]acetic acid	46	43.5
14	[4-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	55.3	46.8
15	[6-chloro-5-methoxy-2-methyl-1-[4-(trifluoromethoxy)benzoyl]-1H-indol-3-yl]acetic acid	46.8	65.4
16	[6-chloro-1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	35.3	16.2
17	[6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid	34.2	19.3
positive control	(5E,9 α ,13E,15R)-9,15-dihydroxy-15-methyl-11-oxoprostano-5,13-dien-1-ol-ic acid	95.6	100

FIG. 2A

Row	IUPAC name	CD11b antagonist activity at 10 μ M (% inhibition)
1	(1-benzyl-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	92.4
2	(1-benzyl-6-fluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	60.4
3	(1-(3,4-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	96.1
4	(1-(3,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	104.7
5	(1-(2,4-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	91.2
6	(1-(cyclohexylcarbonyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	51.7
7	(1-(2,3-dichlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	60.4
8	(1-(2,3-dichlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	75.2
9	(1-(3-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	82.5
10	(1-(3-chlorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	91.2
11	(1-(3,4-difluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	78.9
12	(1-(3,4-difluorobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	89.9
13	(1-(4-bromobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	96.1
14	(1-(4-bromobenzoyl)-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	101.0
15	(1-(4-bromobenzoyl)-4,6-difluoro-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	92.4
16	(1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	87.5
17	(1-[(5-chloro-2-thienyl)carbonyl]-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	86.2
18	(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	99.8
19	(1-(4-fluorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	77.6
20	(1-[(4-chlorophenyl)sulfonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	103.5
21	(1-[(4-chlorophenyl)sulfonyl]-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	103.5
22	(5-methoxy-2-methyl-1-[(2E)-3-phenylprop-2-enyl]-1H-indol-3-yl)acetic acid	83.8
23	(1-(4-cyanobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	48.0
24	(1-(cyclohexylcarbonyl)-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	91.2
25	(5-hydroxy-2-methyl-1-(2E)-3-phenylprop-2-enyl)-1H-indol-3-yl)acetic acid	98.6
26	(1-[(5-chloro-2-thienyl)carbonyl]-6-fluoro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	57.9
27	(5-methoxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl)acetic acid	6.2
28	(5-hydroxy-2-methyl-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl)acetic acid	46.8
29	(6-fluoro-5-hydroxy-2-methyl-1-[(trifluoromethyl)biobenzoyl]-1H-indol-3-yl)acetic acid	99.8
30	(5-hydroxy-2-methyl-1-(3-phenylprop-2-ynyl)-1H-indol-3-yl)acetic acid	102.3
31	(6-fluoro-5-methoxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	73.9
32	(6-fluoro-5-methoxy-2-methyl-1-(5-methyl-2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	89.9
33	(6-fluoro-5-hydroxy-2-methyl-1-(5-methyl-2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	89.9
34	(6-fluoro-5-hydroxy-2-methyl-1-(2-thienylcarbonyl)-1H-indol-3-yl)acetic acid	54.2
35	(6-fluoro-5-hydroxy-2-methyl-1-[(1,1,2,2-tetrafluoroethoxy)benzoyl]-1H-indol-3-yl)acetic acid	37.0
36	(6-chloro-1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	94.9
37	(5-methoxy-1-(4-methoxybenzoyl)-2-methyl-1H-indol-3-yl)acetic acid	39.4
38	(5-methoxy-2-methyl-1-[(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	80.1
39	(1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	80.1
40	(1-[(5-chloro-2-thienyl)methyl]-5-hydroxy-2-methyl-1H-indol-3-yl)acetic acid	86.2
41	(6-chloro-5-methoxy-2-methyl-1-[(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	80.1
42	(1-(4-chlorobenzoyl)-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	96.1
43	(6-chloro-5-hydroxy-2-methyl-1-[(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	89.9
44	(6-chloro-1-[(5-chloro-2-thienyl)methyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	72.7
45	(1-[(5-chloro-2-thienyl)methyl]-5-fluoro-2-methyl-1H-indol-3-yl)acetic acid	86.2
46	(5-fluoro-2-methyl-1-[(trifluoromethoxy)benzoyl]-1H-indol-3-yl)acetic acid	94.9
47	(1-benzyl-6-chloro-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	46.8
48	(5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl)acetic acid	91.2
49	(5-fluoro-1-(4-fluorobenzoyl)-2-methyl-1H-indol-3-yl)acetic acid	98.6
50	(6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	48
51	(6-chloro-1-[(5-chloro-2-thienyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid	48.0
positive control	3-[(3R)-3-[(4-fluorophenyl)sulfonylamino]-1,2,3,4-tetrahydro-9H-carbazol-9-yl]propanoic acid	88.7; 86.3

FIG. 2B