SUBSTITUTED DIPIPERIDINE CCR2 ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This present application claims benefit of U.S. Provisional Patent Application Serial No. 60/613922, filed September 28, 2004, which is incorporated herein by reference in its entirety and for all purposes.

FIELD OF THE INVENTION

The invention is directed to substituted dipiperidine compounds, which are antagonists to the chemoattractant cytokine receptor 2 (CCR2), pharmaceutical compositions, and methods for use thereof. More particularly, the CCR2 antagonists are substituted dipiperidine carboxylic acid, alcohol and ester compounds useful for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease.

BACKGROUND OF THE INVENTION

CCR2 is a member of the GPCR family of receptors, as are all known chemokine receptors, and are expressed by monocytes and memory T-lymphocytes. The CCR2 signaling cascade involves activation of phospholipases ($PLC\beta_2$), protein kinases (PKC), and lipid kinases (PI-3 kinase).

Chemoattractant cytokines (i.e., chemokines) are relatively small proteins (8-10 kD), which stimulate the migration of cells. The chemokine family is divided into four subfamilies based on the number of amino acid residues between the first and second highly conserved cysteines.

Monocyte chemotactic protein-1 (MCP-1) is a member of the CC chemokine subfamily (wherein CC represents the subfamily having adjacent first and second cysteines) and binds to the cell-surface chemokine receptor 2 (CCR2). MCP-1 is a potent chemotactic factor, which, after binding to CCR2, mediates monocyte and lymphocyte migration (i.e., chemotaxis) toward a site of inflammation. MCP-1 is also expressed by cardiac muscle cells, blood vessel endothelial cells, fibroblasts, chondrocytes, smooth muscle cells, mesangial cells, alveolar cells, T-lymphocytes, marcophages, and the like.

After monocytes enter the inflammatory tissue and differentiate into macrophages, monocyte differentiation provides a secondary source of several proinflammatory modulators, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-8 (a member of the CXC chemokine subfamily, wherein CXC represents one amino acid residue between the first and second cysteines), IL-12, arachidonic acid metabolites (e.g., PGE_2 and LTB_4), oxygen-derived free radicals, matrix metalloproteinases, and complement components.

Animal model studies of chronic inflammatory diseases have demonstrated that inhibition of binding between MCP-1 and CCR2 by an antagonist suppresses the inflammatory response. The interaction between MCP-1 and CCR2 has been implicated (see Rollins BJ, Monocyte chemoattractant protein 1: a potential regulator of monocyte recruitment in inflammatory disease, *Mol. Med. Today*, 1996, 2:198; and Dawson J, *et al.*, Targeting monocyte chemoattractant protein-1 signaling in disease, *Expert Opin. Ther. Targets*, 2003 Feb, 7(1):35-48) in inflammatory disease pathologies such as psoriasis, uveitis, atherosclerosis, rheumatoid arthritis, multiple sclerosis, Crohn's Disease, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, tuberculosis, sarcoidosis, invasive staphylococcia, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, Chronic Obstructive Pulmonary Disease (COPD), allergic asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, and stomach.

Monocyte migration is inhibited by MCP-1 antagonists (either antibodies or soluble, inactive fragments of MCP-1), which have been shown to inhibit the development of arthritis, asthma, and uveitis. Both MCP-1 and CCR2 knockout (KO) mice have demonstrated that monocyte infiltration into inflammatory lesions is significantly decreased. In addition, such KO mice are resistant to the development of experimental allergic encephalomyelitis (EAE, a model of human MS), cockroach allergen-induced asthma, atherosclerosis, and uveitis. Rheumatoid arthritis and Crohn's Disease patients have improved during treatment with TNF-α antagonists (e.g., monoclonal antibodies and soluble receptors) at dose levels correlated with decreases in MCP-1 expression and the number of infiltrating macrophages.

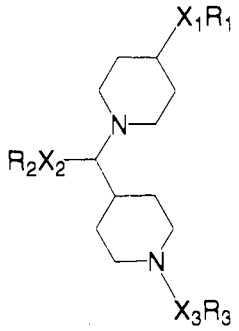
MCP-1 has been implicated in the pathogenesis of seasonal and chronic allergic rhinitis, having been found in the nasal mucosa of most patients with dust mite allergies. MCP-1 has also been found to induce histamine release from basophils *in vitro*. During allergic conditions, both allergens and histamines have been shown to trigger (i.e., to up-regulate) the expression of MCP-1 and other chemokines in the nasal mucosa of people with allergic rhinitis, suggesting the presence of a positive feedback loop in such patients.

There remains a need for small molecule CCR2 antagonists for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease resulting from MCP-1 induced monocyte and lymphocyte migration to a site of inflammation.

All documents cited herein are incorporated by reference.

SUMMARY OF THE INVENTION

The invention provides substituted dipiperidine compounds of Formula (I)

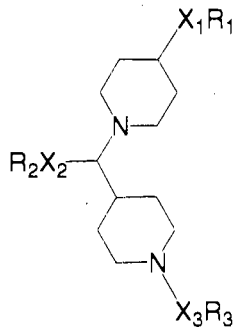


or a salt, isomer, prodrug, metabolite or polymorph thereof, which are CCR2 antagonists and are useful in preventing, treating or ameliorating CCR2 mediated inflammatory syndromes, disorders or diseases in a subject in need thereof.

The present invention also provides a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or a form, composition or medicament thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of Formula (I)



or a salt, isomer, prodrug, metabolite or polymorph thereof wherein

X_1 is absent, alkyl, carbonyl, alkylcarbamoyl or alkylcarbamoylalkyl,

R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, hydroxyalkyl, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy,

alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, alkylamino, alkylaminoalkyl, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl,

X_2 is absent or alkyl,

R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), cyano, nitro, alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacylaryl, oxyacrylyl, oxyacrylylaryl (optionally substituted on aryl with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, nitro, amino or aminoalkyl), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl, carbamoylalkyl, urea or ureaalkyl,

X_3 is carbonyl, carboxyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, alkylcarbamoyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present, and

R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or aryl (optionally substituted on aryl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_1 is absent, alkyl or alkylcarbamoylalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_1 is alkyl or alkylcarbamoylalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_1 is absent.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_1 is phenyl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein phenyl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, alkylhydroxy, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, alkylamino,

alkylaminoalkyl, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, alkylhydroxy, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl or carbonylalkoxy.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_1 is phenyl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein phenyl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, alkylhydroxy, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl or carbonylalkoxy.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy or sulfonylalkyl), carboxy, acyl or carbonylalkoxy.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_1 is phenyl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein phenyl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy or sulfonylalkyl), carboxy, acyl or carbonylalkoxy.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_2 is absent.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_2 is alkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), cyano, nitro, alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacylaryl, oxyacrylyl, oxyacrylylaryl (optionally substituted on aryl with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, nitro, amino or aminoalkyl), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl, carbamoylalkyl, urea or ureaalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacrylylaryl (optionally substituted on aryl with one or more of halogen or nitro), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl or ureaalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacrylylphenyl (optionally substituted on phenyl with one or more of halogen or nitro), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl or ureaalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_3 is carbonyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_3 is carbonyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or phenyl (optionally substituted on phenyl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl, phenyl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or aryl (optionally substituted on aryl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl, phenyl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or phenyl (optionally substituted on phenyl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo, carbonylalkoxy or aryl (optionally substituted on aryl with one or more halogen).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl, phenyl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo, carbonylalkoxy or aryl (optionally substituted on aryl with one or more halogen).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl optionally substituted with aryl,

wherein aryl is optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is cycloalkyl optionally substituted with aryl, wherein aryl is optionally substituted with one or more of halogen.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is aryl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is phenyl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is aryl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo or carbonylalkoxy.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is phenyl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo or carbonylalkoxy.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is heterocyclyl optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino or aminoalkyl.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein R_3 is heterocyclyl optionally substituted with one or more of halogen.

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein

X_1 is absent, alkyl or alkylcarbamoylalkyl,

R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy or sulfonylalkyl), carboxy, acyl or carbonylalkoxy,

X_2 is absent or alkyl,

R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacrylylaryl (optionally substituted on aryl with one or more of halogen or nitro), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl or ureaalkyl,

X_3 is carbonyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present, and

R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo, carbonylalkoxy or aryl (optionally substituted on aryl with one or more halogen).

An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof, wherein X_2R_2, X_1R_1, and X_3R_3 are dependently selected from

Cpd	X_2R_2	X_1R_1	X_3R_3
1	CO_2H	-4-Cl-phenyl	C(O)CH=CH-3,4-Cl_2-phenyl
2	CO_2H	-4-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
3	$C(O)OCH_3$	-4-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
4	CO_2H	-4-Cl-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl
5	CO_2H	-4-OCH_3-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl
6	CO_2H	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
7	CO_2H	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
8	CO_2H	-5-F-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
9	CO_2H	-5-F-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
10	CO_2H	-indol-1-yl	C(O)CH=CH-3,4,5-F_3-phenyl
11	CO_2H	-CH_2-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
12	CO_2H	-CH_2-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl

Cpd	X_2R_2	X_1R_1	X_3R_3
13	(*S*)-CO_2H	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
14	(*R*)-CO_2H	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
15	CO_2H	-5-OH-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
198 16	CO_2H	-5-OH-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
17	CO_2H	-5-NHC(O)CH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
18	CO_2H	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
19	CO_2H	-5-F-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
20	CO_2H	-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
21	CO_2H	-1-C(O)CH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
22	CO_2H	-indol-3-yl	C(O)CH=CH-3,4-F_2-phenyl
23	CO_2H	-indol-3-yl	C(O)CH=CH-4-CF_3-phenyl
24	CO_2H	-6-F-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
25	CO_2H	-6-Cl-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
26	CO_2H	-5-OCH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
27	CO_2H	-indol-3-yl	C(O)CH=CH-phenyl
28	CO_2H	-indol-3-yl	C(O)NH-3,5-F_2-phenyl
29	CO_2H	-5-NHSO_2CH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
30	CO_2H	-5-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
31	CO_2H	-6-Cl-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
32	CO_2H	-indol-3-yl	C(O)NH-phenyl
33	CO_2H	-indol-3-yl	C(O)NH-3,5-Cl_2-phenyl
34	CO_2H	-indol-3-yl	C(O)CH=CH-4-Cl-phenyl
35	CO_2H	-indol-3-yl	C(O)CH=CH-3-CF_3-phenyl
36	CO_2H	-indol-3-yl	C(O)CH=CH-3-Br-4-F-phenyl
37	CO_2H	-indol-3-yl	C(O)CH=CH-4-OCH_3-phenyl
38	CO_2H	-6-OCH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
39	CO_2H	-6-F-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
40	CO_2H	-indol-3-yl	C(O)NH-3,4-F_2-phenyl
41	CO_2H	-4-OCH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
42	CO_2H	-7-OCH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
43	CO_2H	-indol-3-yl	C(=S)NH-phenyl
44	CO_2H	-indol-3-yl	C(=S)NH-2,4-F_2-phenyl
45	CO_2H	-indol-3-yl	C(=S)NH-3,5-Cl_2-phenyl
46	CO_2H	-6-Cl-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
47	CO_2H	-5-OCH_3-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
48	CO_2H	-indol-3-yl	C(O)NH-3-Cl-4-F-phenyl
49	CO_2H	-indol-3-yl	C(O)NH-3-Cl-4-CH_3-phenyl

Cpd	X_2R_2	X_1R_1	X_3R_3
50	CO_2H	-indol-3-yl	C(=NH)NHC(O)-3,4-Cl_2-phenyl
51	CO_2H	-indol-3-yl	C(=NH)NHC(O)-3,5-F_2-phenyl
52	CO_2H	-indol-3-yl	C(=NH)NHC(O)-3,4,5-F_3-phenyl
53	CO_2H	-5-$NHSO_2CH_3$-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
54	CO_2H	-indol-3-yl	C(=NH)NHC(O)-3-F-phenyl
55	CO_2H	-indol-3-yl	C(=S)NH-3,5-F_2-phenyl
56	CO_2H	-indol-3-yl	C(=S)NH-3-Br-phenyl
57	CO_2H	-indol-3-yl	C(O)NH-3-CF_3-4-Cl-phenyl
58	CO_2H	-indol-3-yl	C(O)NH-3-CF_3-4-F-phenyl
59	CO_2H	-indol-3-yl	C(O)CH=CH-4-NO_2-phenyl
60	CO_2H	-indol-3-yl	C(O)CH=CH-4-Br-phenyl
61	CO_2H	-indol-3-yl	C(O)CH=CH-4-CH_3-phenyl
62	CO_2H	-indol-3-yl	C(O)CH=CH-3-F-phenyl
63	CO_2H	-indol-3-yl	C(O)CH=CH-3,4-$(OCH_3)_2$-phenyl
64	CO_2H	-indol-3-yl	C(=S)NH-3,4-Cl_2-phenyl
65	CO_2H	-indol-3-yl	C(O)NH-3-CF_3-5-F-phenyl
66	CO_2H	-indol-3-yl	C(O)NH-3,4-$(OCH_3)_2$-phenyl
67	CO_2H	-indol-3-yl	C(O)NH-3-Cl-4-OCH_3-phenyl
68	CO_2H	-indol-3-yl	C(O)NH-4-$C(O)OCH_3$-phenyl
69	CO_2H	-indol-3-yl	C(O)NH-4-OCH_3-phenyl
70	CO_2H	-indol-3-yl	C(O)CH=CH-3-CH_3-phenyl
71	CO_2H	-indol-3-yl	C(O)CH=CH-3-Br-phenyl
72	CO_2H	-indol-3-yl	C(O)CH=CH-3-OCH_3-phenyl
73	CO_2H	-indol-3-yl	C(=NH)NHC(O)-3-CF_3-phenyl
74	CO_2H	-indol-3-yl	C(O)CH=CH-3-F-4-CH_3-phenyl
75	CO_2H	-indol-3-yl	C(O)CH=CH-3-F-4-CF_3-phenyl
76	CO_2H	-indol-3-yl	C(O)CH=CH-3-Cl-4-F-phenyl
77	CO_2H	-indol-3-yl	C(O)CH=CH-4-F-phenyl
78	CO_2H	-indol-3-yl	C(=S)NH-4-CH_3-phenyl
79	CO_2H	-indol-3-yl	C(=S)NH-3-CF_3-phenyl
80	CO_2H	-indol-3-yl	C(=S)NH-4-CF_3-phenyl
81	CO_2H	-5-NHC(O)O-$C(CH_3)_3$-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
82	CO_2H	-6-$NHSO_2CH_3$-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
83	CO_2H	-5-NH_2-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
84	CO_2H	-indol-3-yl	C(O)$NHCH_2$-3,4-Cl_2-phenyl
85	CO_2H	-indol-3-yl	C(O)NH-3-Br-phenyl
86	CO_2H	-indol-3-yl	C(O)NH-3-Cl-phenyl

Cpd	X_2R_2	X_1R_1	X_3R_3
87	$C(O)OCH_3$	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
88	CO_2H	-indol-3-yl	C(O)NH-4-Cl-phenyl
89	CO_2H	-indol-3-yl	C(O)NH-4-Br-phenyl
90	CO_2H	-indol-3-yl	C(O)NH-4-F-phenyl
91	CO_2H	-indol-3-yl	C(O)NH-3-F-phenyl
92	CO_2H	-indol-3-yl	C(O)CH=CH-3-NO_2-phenyl
93	CO_2H	-indol-3-yl	C(O)CH=CH-3-Cl-phenyl
94	CO_2H	-5-OCH_3-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
95	CO_2H	-6-OCH_3-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
96	CO_2H	-indol-3-yl	C(O)NH-4-CF_3-phenyl
97	CO_2H	-indol-3-yl	C(O)NH-3-CF_3-phenyl
98	CO_2H	-indol-3-yl	C(O)NH-3-CH_3-phenyl
99	CO_2H	-indol-3-yl	C(O)NH-4-CH_3-phenyl
100	CO_2H	-indol-3-yl	C(O)NH-3,4-$(CH_3)_2$-phenyl
101	CO_2H	-indol-3-yl	C(O)NH-3-CH_3-4-Br-phenyl
102	CO_2H	-indol-3-yl	C(O)NH-3-CH_3-4-F-phenyl
103	CO_2H	-indol-3-yl	C(O)CH=CH-thien-2-yl
104	CO_2H	-indol-3-yl	C(O)CH=CH-thien-3-yl
105	CO_2H	-indol-3-yl	C(O)NH-3-F-4-CH_3-phenyl
106	CO_2H	-indol-3-yl	C(O)NH-3-CF_3-4-CH_3-phenyl
107	$C(O)NH_2$	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
108	CO_2H	-7-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
109	CO_2H	-5-$NHSO_2CH_3$-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
110	CO_2H	-indol-3-yl	C(O)NH-2,3-Cl_2-phenyl
111	CO_2H	-indol-3-yl	C(O)NH-2,4-Cl_2-phenyl
112	CH_2OH	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
113	CH_2OH	-indol-3-yl	C(O)CH=CH-3,4-F_2-phenyl
114	CO_2H	-indol-3-yl	C(O)CH_2O-3,4-Cl_2-phenyl
115	CO_2H	-indol-3-yl	C(O)$(CH_2)_2$-3,4-Cl_2-phenyl
116	CH_2OH	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
117	CO_2H	-indol-3-yl	C(O)NH-2-F-4-Cl-phenyl
118	$C(O)OCH_3$	-7-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
119	CH_2OH	-indol-3-yl	C(O)CH=CH-3-CF_3-phenyl
120	CH_2OH	-indol-3-yl	C(=S)NH-3-CF_3-phenyl
121	CH_2OH	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
122	CH_2OH	-indol-3-yl	C(=S)NH-3,4-Cl_2-phenyl
123	CH_2OH	-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl

Cpd	X_2R_2	X_1R_1	X_3R_3
124	CH_2OH	-indol-3-yl	C(=S)NH-3,5-F_2-phenyl
125	CO_2H	-indol-3-yl	C(O)NH-2,3,4-F_3-phenyl
126	CO_2H	-indol-3-yl	C(O)NH-2,4,5-Cl_3-phenyl
127	CO_2H	-indol-3-yl	C(O)NH-4-SCH_3-phenyl
128	CH_2OH	-indol-3-yl	C(=NH)NHC(O)-3,4-Cl_2-phenyl
129	CH_2OH	-indol-3-yl	C(O)NH-3,5-F_2-phenyl
130	$CH_2N(CH_3)_2$	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
131	CH_2OH	-7-OCH_3-indol-3-yl	C(O)$OC(CH_3)_3$
132	CH_2OH	-6-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
133	CH_2OH	-7-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
134	CH_2N-$(SO_2CH_3)_2$	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
135	CO_2H	-indol-3-yl	C(O)NH-3,5-$(CH_3)_2$-phenyl
136	CO_2H	-indol-3-yl	C(O)NH-3,5-$(CF_3)_2$-phenyl
137	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
138	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3,4-F_2-phenyl
139	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3,4-Cl_2-phenyl
140	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-2,4,5-F_3-phenyl
141	CH_2OH	-4-OCH_3-phenyl	C(O)NH-3,4-F_2-phenyl
142	CO_2H	-indol-3-yl	C(O)NH-4-SCF_3-phenyl
143	CO_2H	-indol-3-yl	C(O)NH-4-OCF_3-phenyl
144	CO_2H	-indol-3-yl	C(O)NH-3-SCH_3-phenyl
145	CO_2H	-4-C(O)OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
146	CO_2H	-5-C(O)OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
147	CO_2H	-5-CO_2H-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
148	CO_2H	-CH_2C(O)NH-benzyl	C(O)CH=CH-3,5-F_2-phenyl
149	CO_2H	-CH_2C(O)NH-benzyl	C(O)CH=CH-3,4,5-F_3-phenyl
150	CO_2H	-pyrrol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
151	CO_2H	-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
152	C(O)O-CH_2CH_3	-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
153	CH_2OH	-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
154	CH_2OH	-indol-3-yl	C(O)-benzo[*b*]furan-2-yl
155	CH_2OH	-pyrazol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
156	CH_2OH	-pyrazol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
157	CH_2OH	-indol-3-yl	C(O)-5-Cl-benzo[*b*]furan-2-yl
158	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl

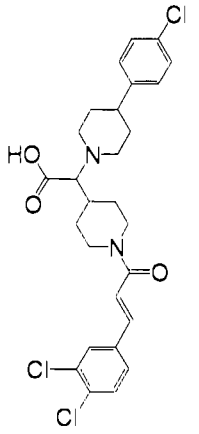
Cpd	X_2R_2	X_1R_1	X_3R_3
159	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-phenyl
160	CH_2OH	-4-OCH_3-phenyl	C(O)-5-Cl-benzo[*b*]furan-2-yl
161	CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3-Br-4-F-phenyl
162	CH_2OH	-5-OCH_3-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
163	CH_2OH	-6-OCH_3-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
164	CH_2OH	-5-OCH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
165	CH_2OH	-6-OCH_3-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
166	CH_2OH	-5-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
167	CH_2OH	-6-OCH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
168	CH_2OH	-5-F-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
169	CH_2OH	-5-F-indol-3-yl	C(O)CH=CH-4-F-phenyl
170	CH_2OH	-5-F-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
171	CH_2OH	-5-F-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
172	CH_2OH	-5-F-indol-3-yl	C(O)CH=CH-3-Br-4-F-phenyl
173	CH_2OH	-indazol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
174	CH_2OH	-benzoimidazol-2-yl	C(O)CH=CH-3,5-F_2-phenyl
175	CH_2OH	-benzoimidazol-2-yl	C(O)CH=CH-3,4,5-F_3-phenyl
176	CH_2OH	-benzoimidazol-2-yl	C(O)CH=CH-3,4-Cl_2-phenyl
177	CO_2H	-indazol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
178	CO_2H	-5-NH_2-1H-pyrrolo[3,2-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
179	CO_2H	-5-NH_2-1H-pyrrolo[2,3-c]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
180	(*S*)-CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
181	(*R*)-CH_2OH	-4-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
182	CH_2OH	-pyridin-4-yl	C(O)CH=CH-3,5-F_2-phenyl
183	CH_2OH	-pyridin-4-yl	C(O)CH=CH-3,4,5-F_3-phenyl
184	CH_2OH	-pyridin-4-yl	C(O)CH=CH-3-CF_3-phenyl
185	CH_2OH	-pyridin-4-yl	C(O)CH=CH-3,4-Cl_2-phenyl
186	CH_2OH	-pyridin-4-yl	C(O)CH=CH-3-Br-4-F-phenyl
187	(*S*)-CH_2OH	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
188	(*R*)-CH_2OH	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
189	CH_2OH	-benzo[1,3]dioxol-5-yl	C(O)CH=CH-3,4,5-F_3-phenyl
190	CH_2OH	-benzo[1,3]dioxol-5-yl	C(O)CH=CH-3,5-F_2-phenyl
191	CH_2OH	-5-NH_2-1H-pyrrolo[3,2-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
192	CH_2OH	-4-F-phenyl	C(O)CH=CH-3,5-F_2-phenyl
193	CH_2OH	-4-F-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl

Cpd	X_2R_2	X_1R_1	X_3R_3
194	CH_2OH	-thiazol-2-yl	C(O)CH=CH-3,5-F_2-phenyl
195	CH_2OH	-thiazol-2-yl	C(O)CH=CH-3,4,5-F_3-phenyl
196	CH_2OH	-thiazol-2-yl	C(O)CH=CH-3,4-Cl_2-phenyl
197	CH_2OH	-3-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
198	CH_2OH	-5-$NHSO_2CH_3$-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
199	$CH_2OC(O)$-CH=CH-3,5-F_2-phenyl	-5-$NHSO_2CH_3$-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
200	CH_2OH	-pyridin-2-yl	C(O)CH=CH-3,5-F_2-phenyl
201	CH_2OH	-5-$NHSO_2CH_3$-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
202	CH_2OH	-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,5-F_2-phenyl
203	CH_2OH	-2-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
204	CO_2H	-2-CH_3-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
205	CH_2OH	-7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,5-F_2-phenyl
206	CO_2H	-4-$NHSO_2CH_3$-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl
207	CO_2H	-1H-pyrrolo[3,2-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
208	CH_2OH	-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
209	CH_2OH	-4-$NHSO_2CH_3$-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl
210	CH_2OH	-4-$NHSO_2CH_3$-phenyl	C(O)CH=CH-3,4-Cl_2-phenyl
211	CO_2H	-6-F-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
212	CH_2OH	-indol-3-yl	C(O)-2-(3,4-Cl_2-phenyl)-cyclopropyl
213	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
214	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
215	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
216	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3-CH_3-phenyl
217	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
218	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3-CF_3-phenyl
219	CH_2NH-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-thien-3-yl
220	CH_2NH-C(O)H	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl

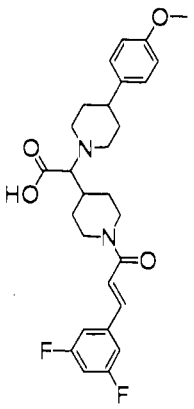
Cpd	X_2R_2	X_1R_1	X_3R_3
221	CH_2NH-C(O)H	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
222	CH_2NH-C(O)H	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
223	CH_2NH-C(O)H	-indol-3-yl	C(O)CH=CH-3-CH_3-phenyl
224	CH_2NH-C(O)H	-indol-3-yl	C(O)CH=CH-3-CF_3-phenyl
225	CH_2NH-C(O)H	-indol-3-yl	C(O)CH=CH-thien-3-yl
226	CH_2NH-C(O)H	-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
227	$C(O)NH_2$	-1H-pyrrolo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
228	CH_2NH-C(O)NH-CH_2CH_3	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
229	CH_2NH-C(O)NH-CH_2CH_3	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
230	CH_2NH-C(O)NH-CH_2CH_3	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
231	CH_2NH-C(O)NH-CH_2CH_3	-indol-3-yl	C(O)CH=CH-3-CH_3-phenyl
232	CH_2NH-C(O)NH-CH_2CH_3	-indol-3-yl	C(O)CH=CH-3-CF_3-phenyl
233	CH_2NH-C(O)NH-CH_2CH_3	-indol-3-yl	C(O)CH=CH-3-Br-4-F-phenyl
234	CH_2O-$C(O)CH_3$	-indol-3-yl	$C(O)OC(CH_3)_3$
235	CH_2O-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
236	CH_2O-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
237	CH_2O-$C(O)CH_3$	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
238	CH_2NH-$C(O)OCH_3$	-indol-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
239	CH_2NH-$C(O)OCH_3$	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl

Cpd	X_2R_2	X_1R_1	X_3R_3
240	CH_2NH-$C(O)OCH_3$	-indol-3-yl	C(O)CH=CH-3,4-Cl_2-phenyl
241	CH_2NH-$C(O)OCH_3$	-indol-3-yl	C(O)CH=CH-3-CH_3-phenyl
242	CH_2O-$C(O)CH_3$	-indol-3-yl	C(O)NH-3,4-Cl_2-phenyl
243	CH_2O-$C(O)CH_3$	-{5-N[$C(O)CH_3$-SO_2CH_3]}-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
244	CH_2OH	-4-Cl-phenyl	C(O)CH=CH-3,4-Cl_2-phenyl
245	CH_2Cl	-4-Cl-phenyl	C(O)CH=CH-3,4-Cl_2-phenyl
246	CH_2OH	-4-Cl-phenyl	C(O)CH=CH-3,4,5-F_3-phenyl
247	CH_2Cl	-4-Cl-phenyl	C(O)CH=CH-4-CF_3-phenyl
248	CH_2OH	-furo[2,3-b]pyridin-3-yl	C(O)CH=CH-3,4,5-F_3-phenyl
249	CH_2OH	-4-Cl-phenyl	C(O)CH=CH-3,5-F_2-phenyl
250	CH_2O-$C(O)OCH_3$	-4-Cl-phenyl	C(O)CH=CH-3,5-F_2-phenyl
251	$CH_2OC(O)$-CH=CH-4-NO_2-phenyl	-indol-3-yl	C(O)CH=CH-4-NO_2-phenyl
252	CH_2NH-$C(O)CH_2$-$N(CH_3)_2$	-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl
253	CH_2OH	-4-OCH_3-phenyl	C(O)CH≡CH-3,4,5-F_3-phenyl
254	CH_2OH	-5-F-indol-3-yl	C(O)CH=CH-3,4-F_2-phenyl
255	CH_2OCH_3	-4-OCH_3-phenyl	C(O)CH=CH-3,5-F_2-phenyl
256	CH_2OH	-5,6-Cl_2-1H-benzoimidazol-2-yl	C(O)CH=CH-3,5-F_2-phenyl
257	CH_2OH	-5,6-Cl_2-1H-benzoimidazol-2-yl	C(O)CH=CH-3,4,5-F_3-phenyl
258	CH_2OH	-4-Cl-phenyl	C(O)CH=CH-4-Cl-phenyl
259	CH_2OH	-5-OH-indol-3-yl	C(O)CH=CH-3,5-F_2-phenyl

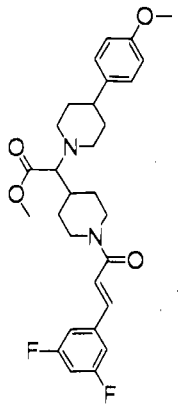
An example of the invention is a compound of Formula (I) and a salt, isomer, prodrug, metabolite or polymorph thereof represented as follows:



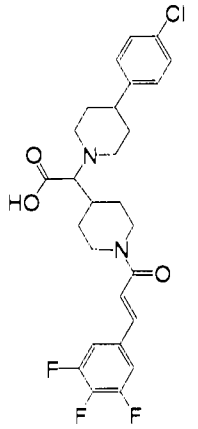
Cpd 1



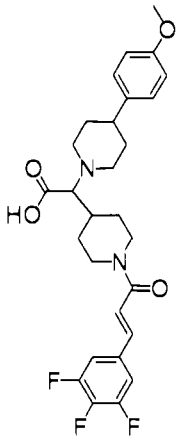
Cpd 2



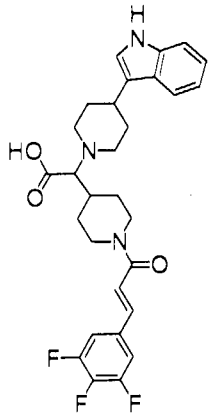
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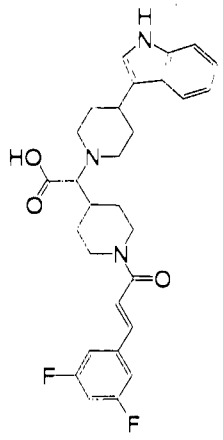
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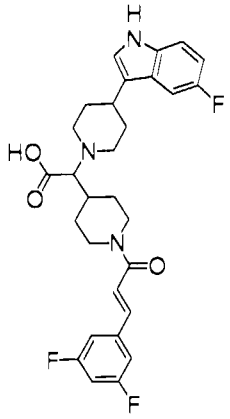
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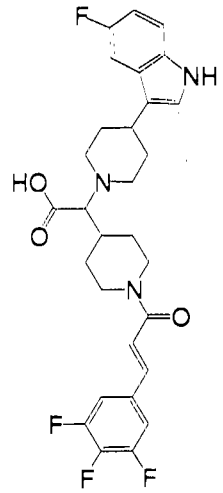
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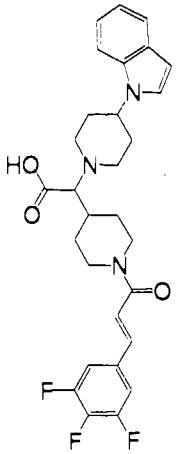
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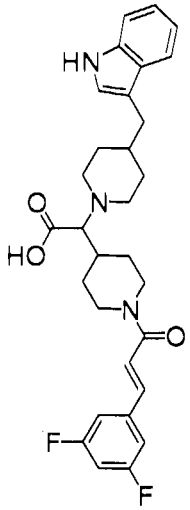
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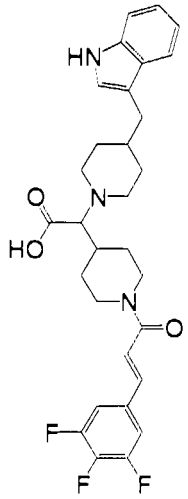
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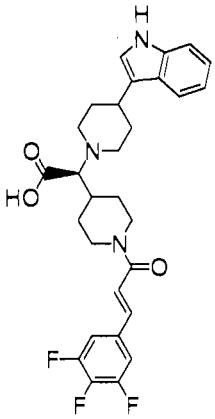
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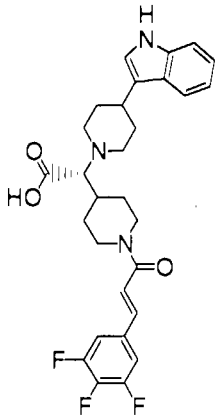
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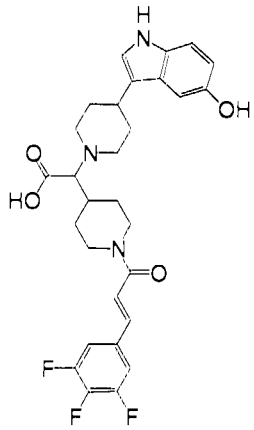
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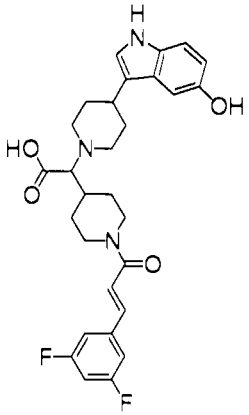
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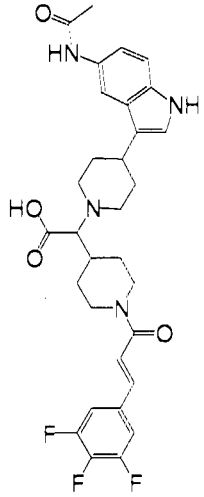
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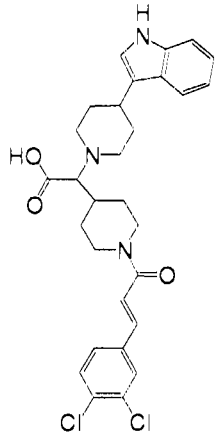
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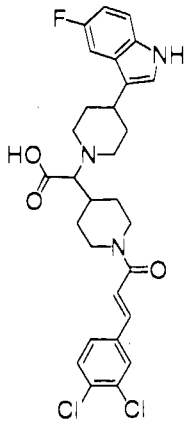
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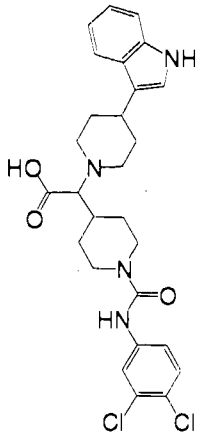
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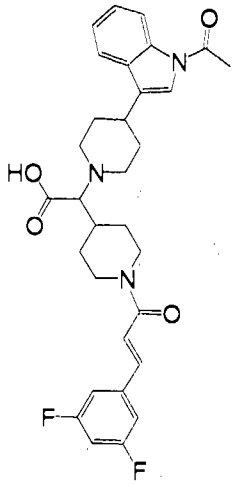
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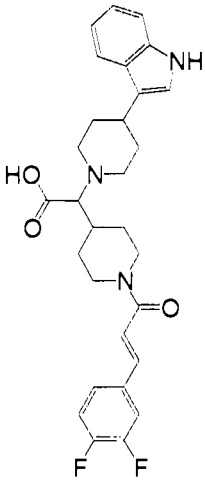
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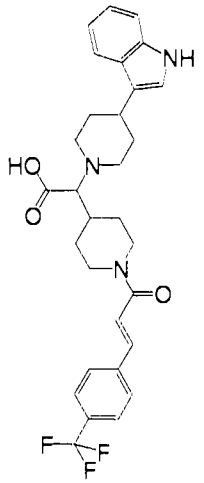
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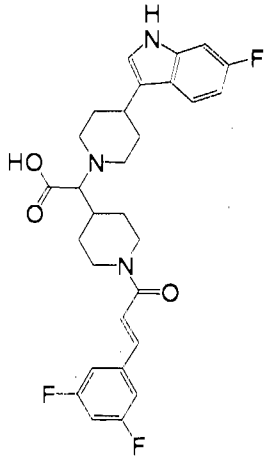
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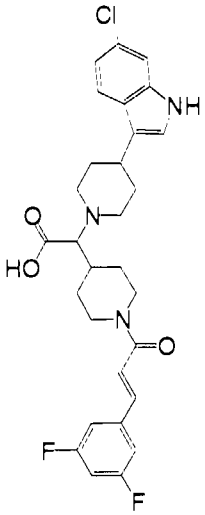
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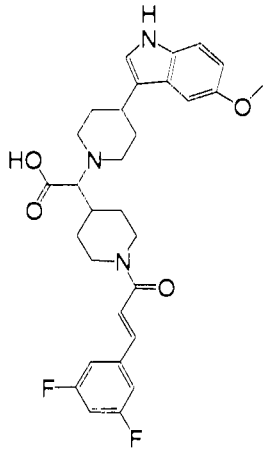
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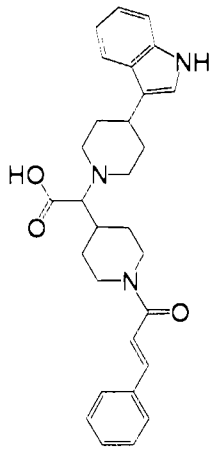
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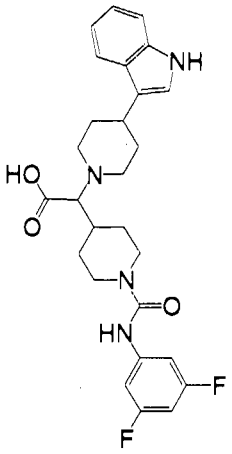
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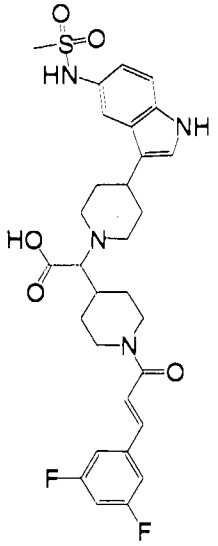
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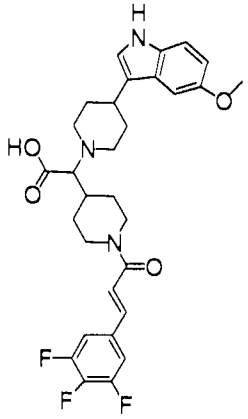
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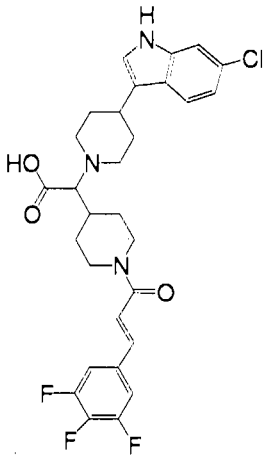
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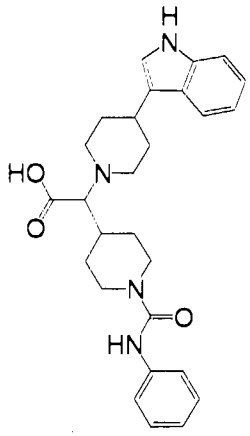
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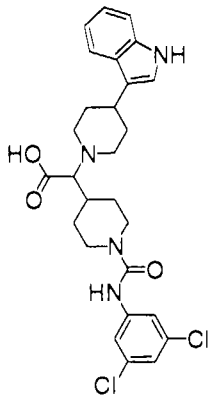
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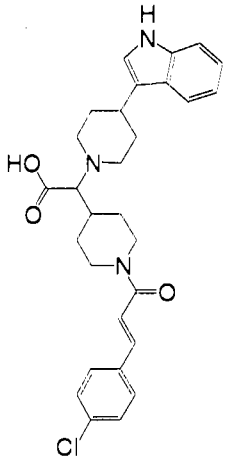
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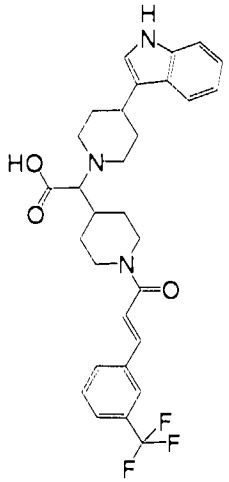
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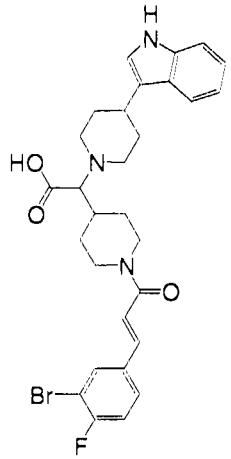
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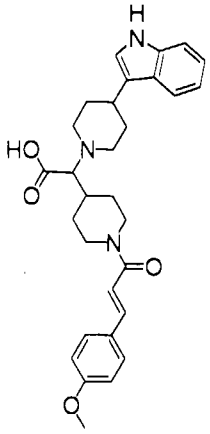
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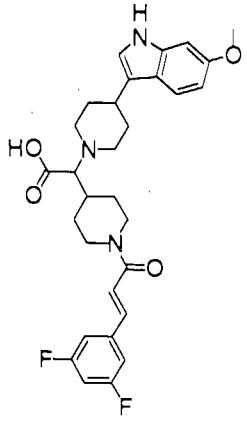
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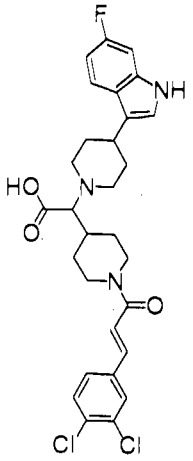
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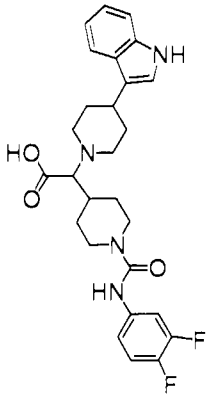
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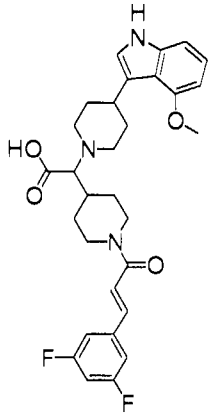
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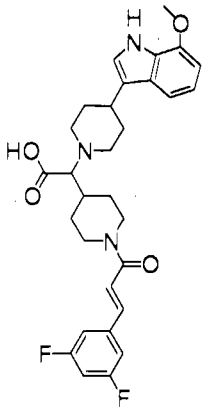
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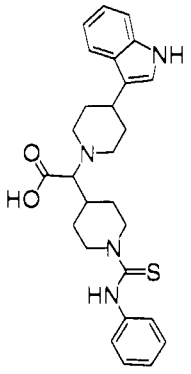
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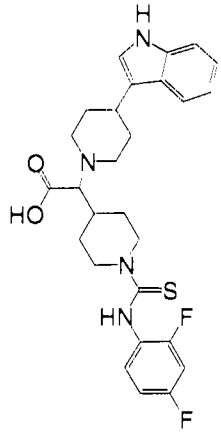
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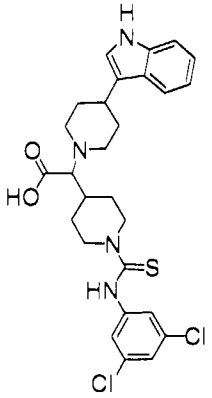
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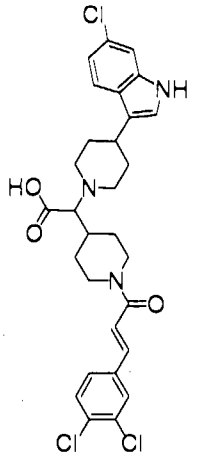
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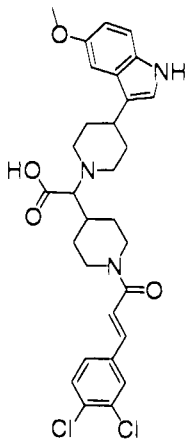
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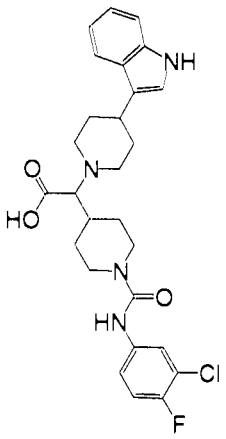
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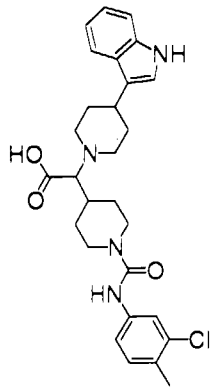
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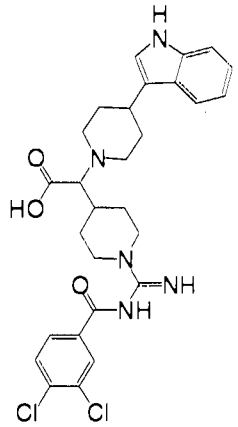
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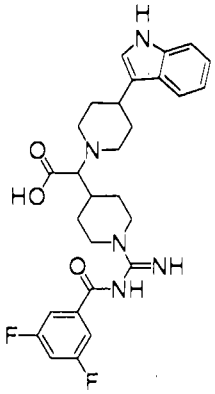
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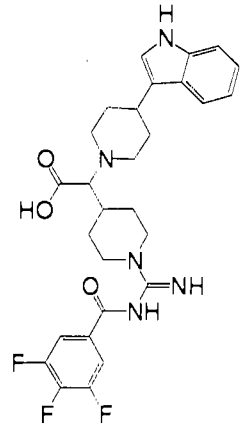
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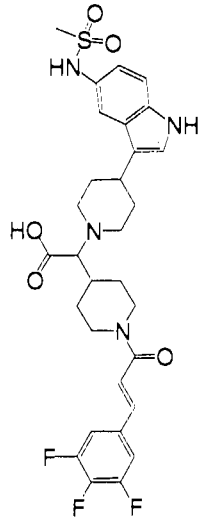
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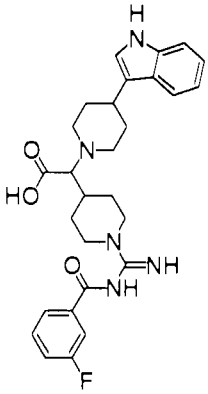
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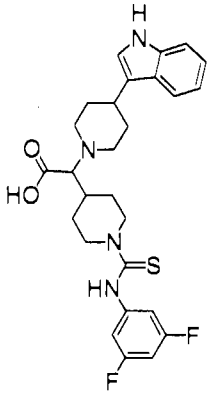
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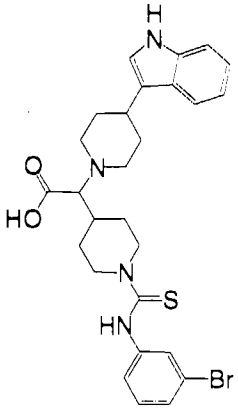
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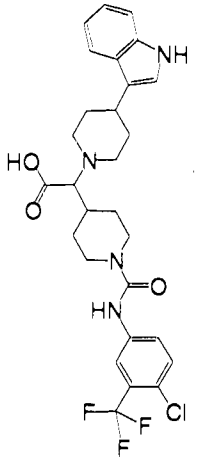
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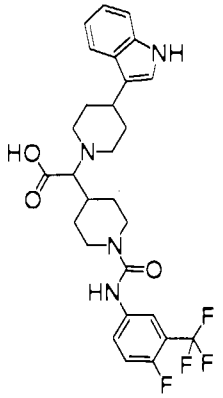
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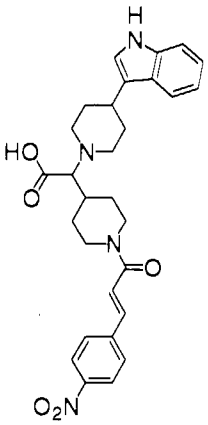
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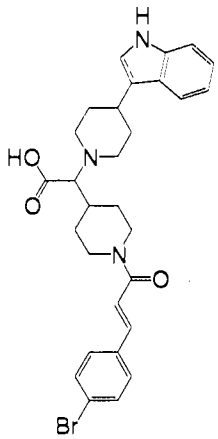
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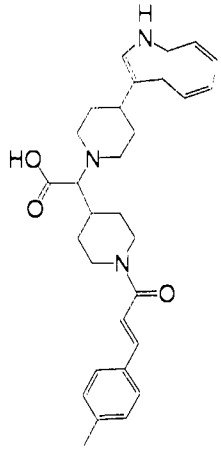
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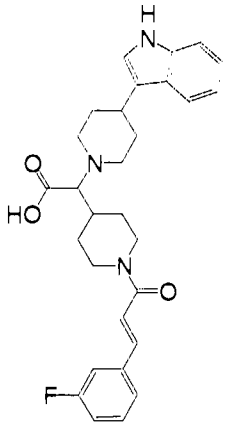
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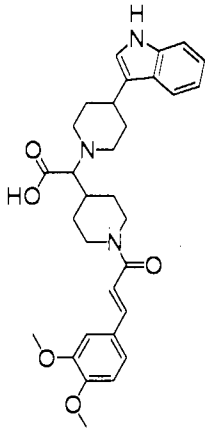
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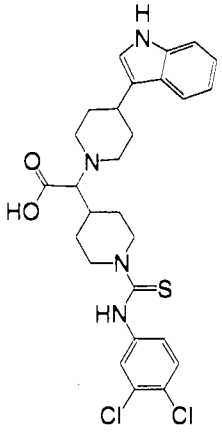
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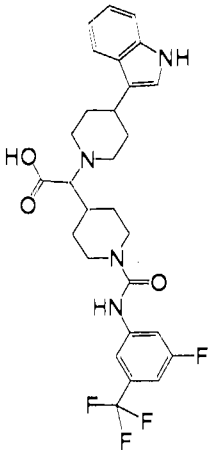
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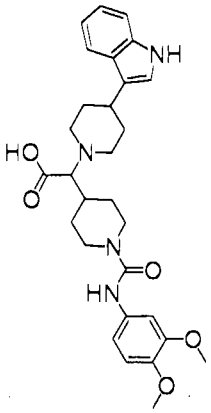
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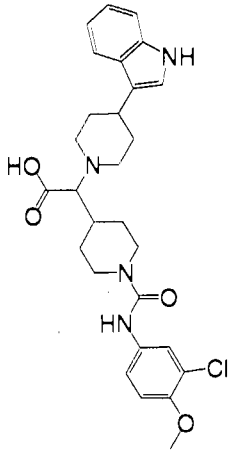
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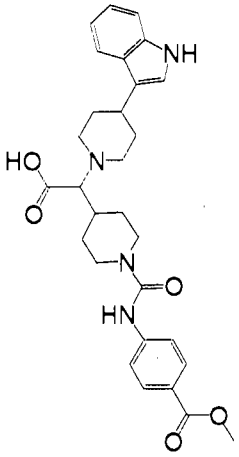
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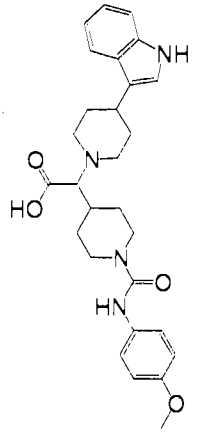
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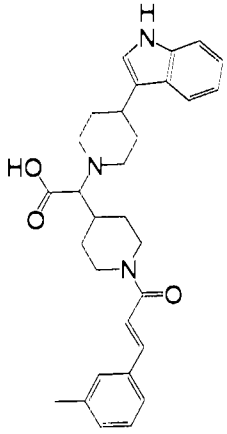
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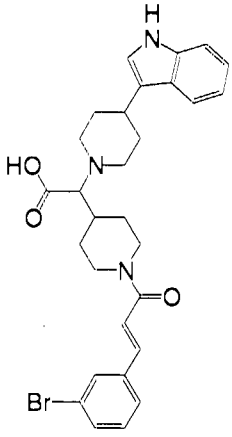
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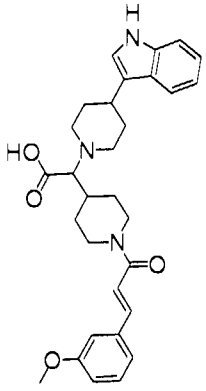
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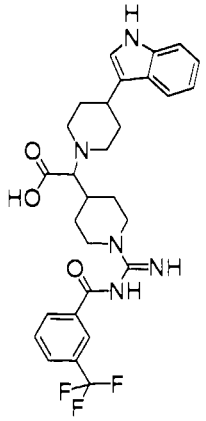
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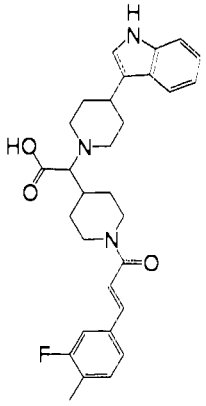
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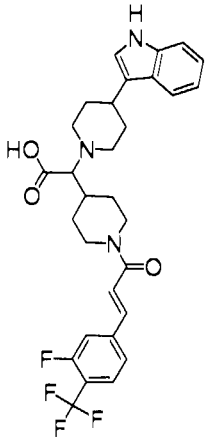
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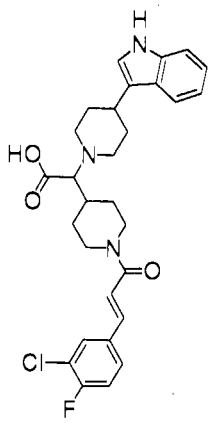
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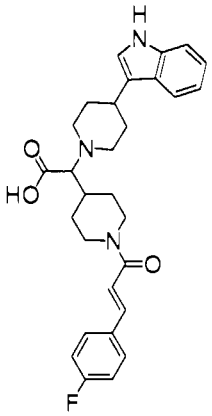
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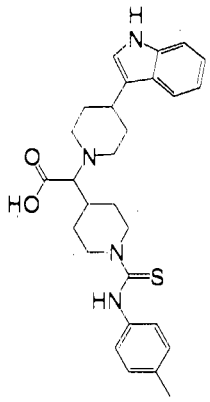
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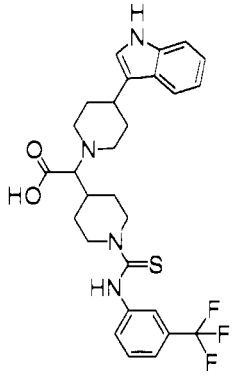
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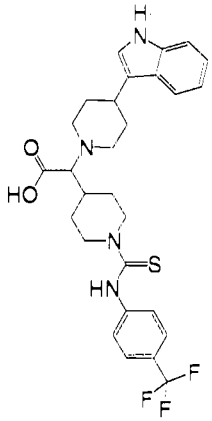
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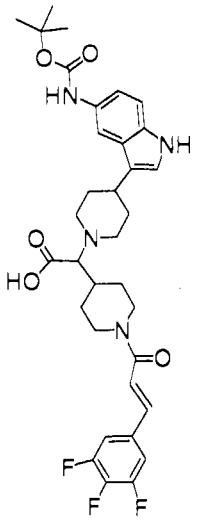
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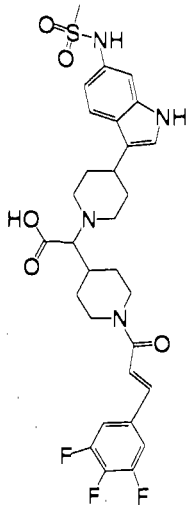
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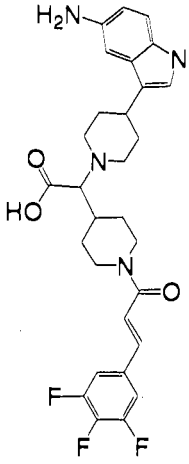
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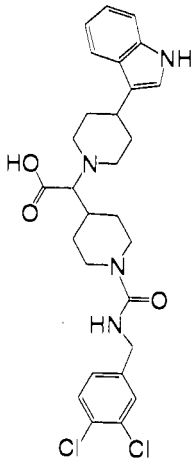
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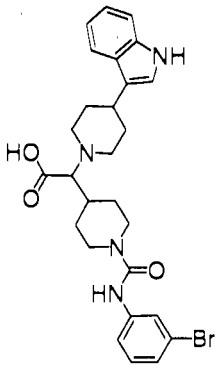
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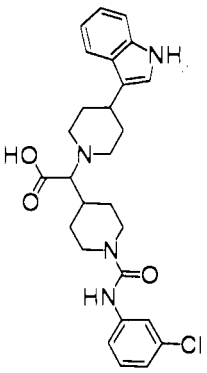
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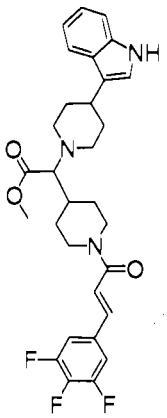
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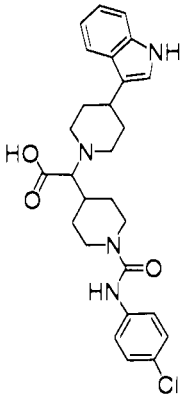
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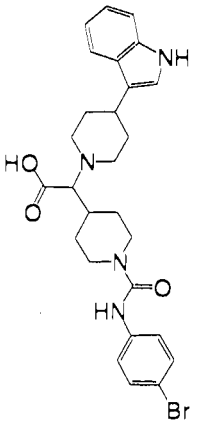
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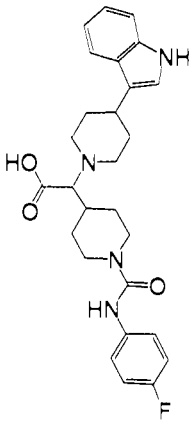
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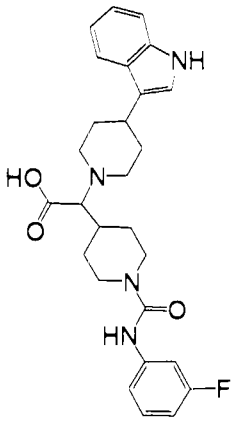
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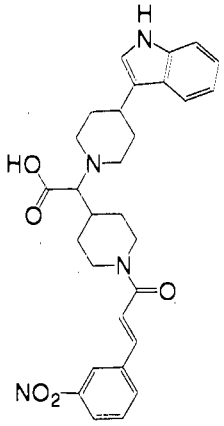
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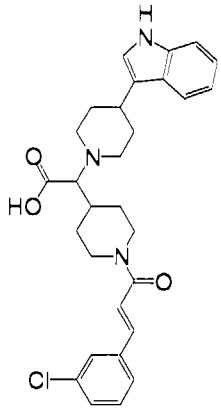
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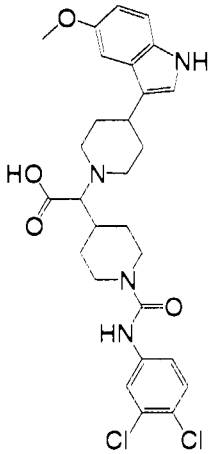
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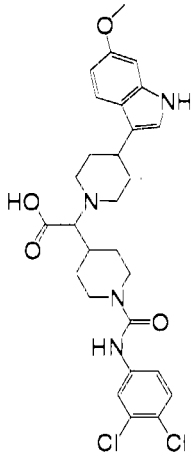
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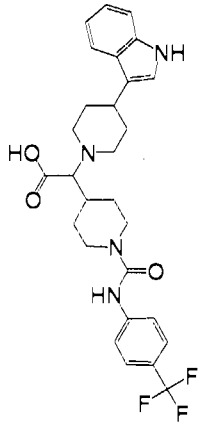
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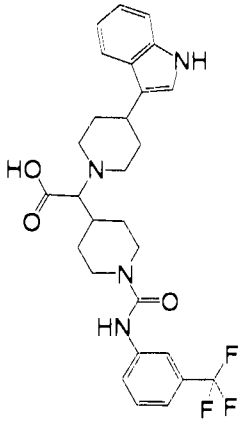
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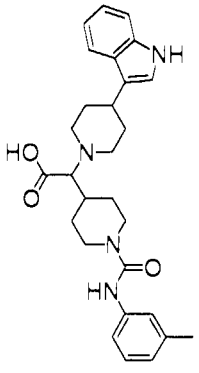
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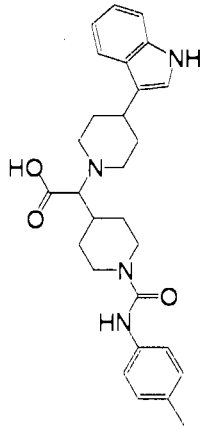
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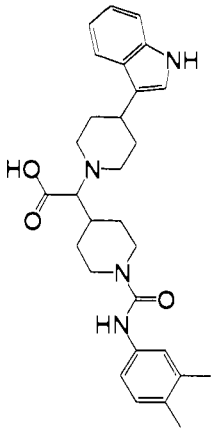
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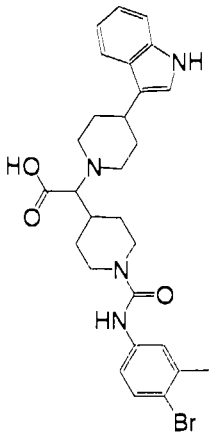
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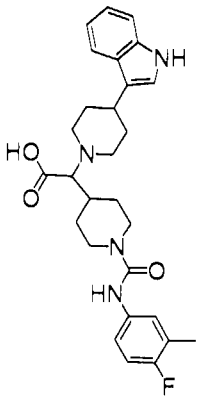
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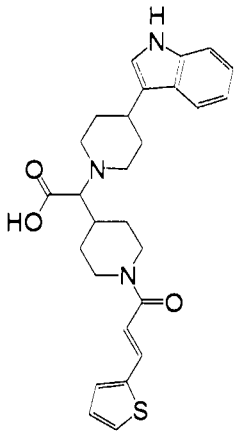
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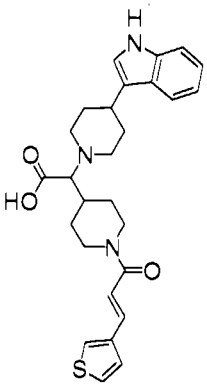
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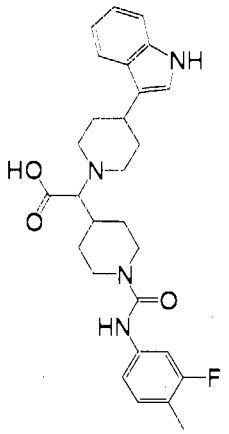
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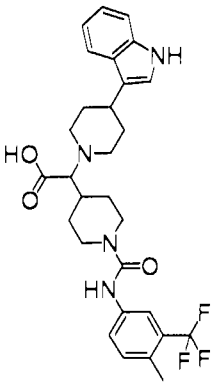
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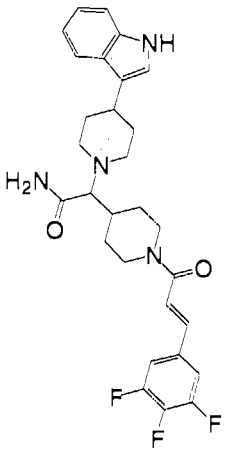
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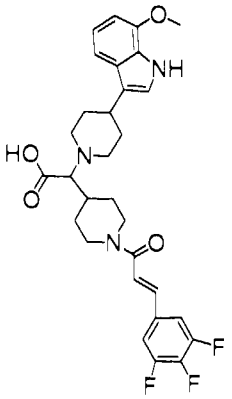
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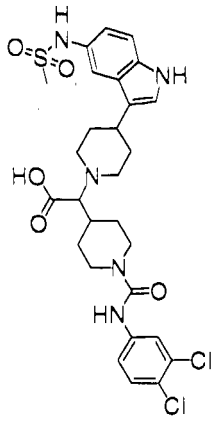
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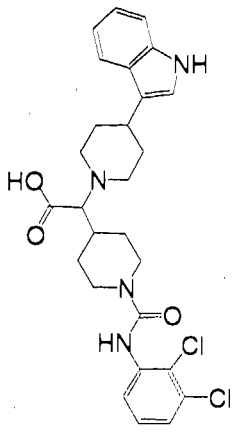
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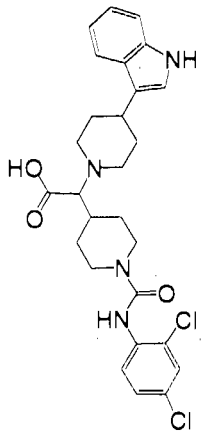
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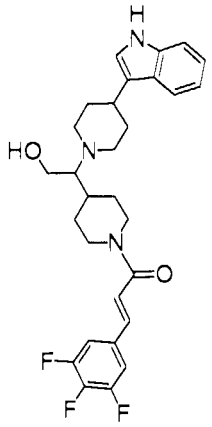
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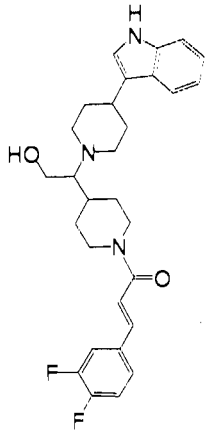
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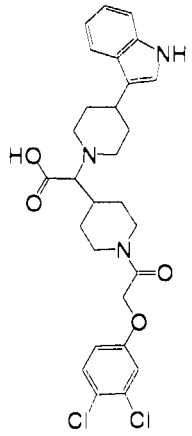
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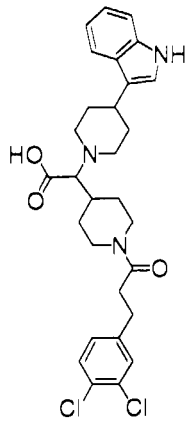
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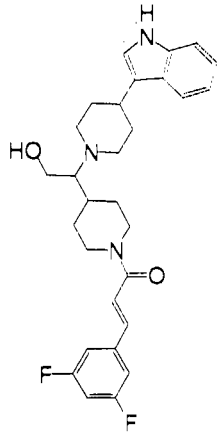
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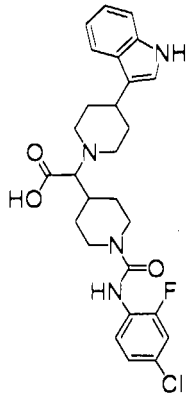
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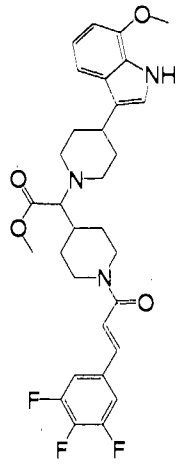
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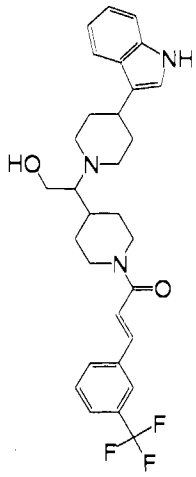
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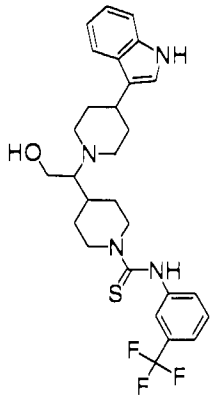
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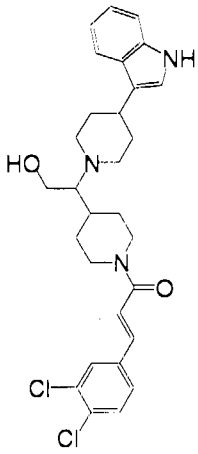
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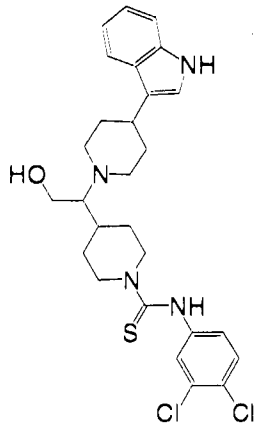
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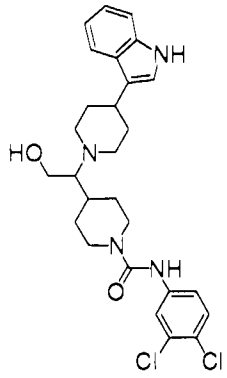
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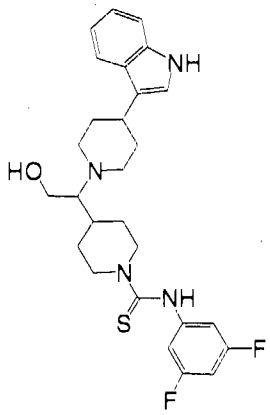
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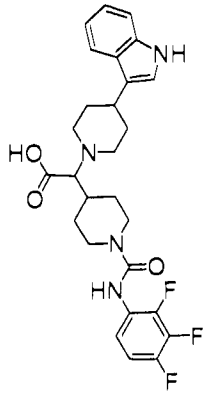
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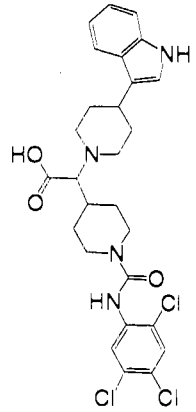
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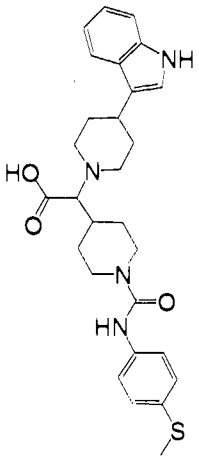
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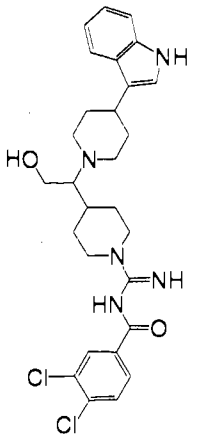
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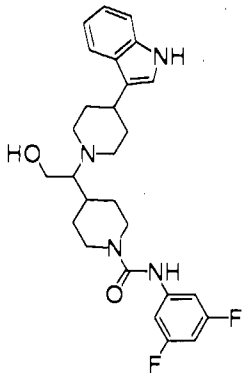
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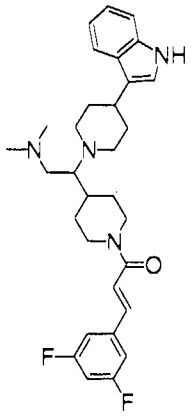
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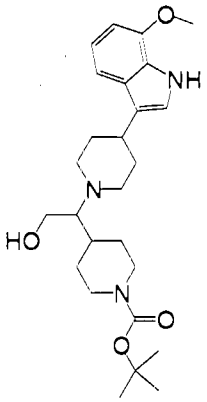
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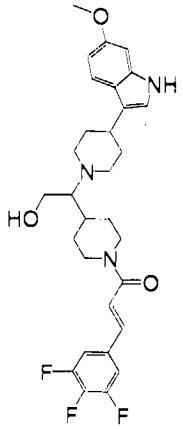
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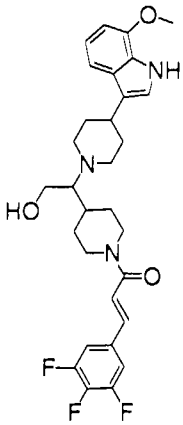
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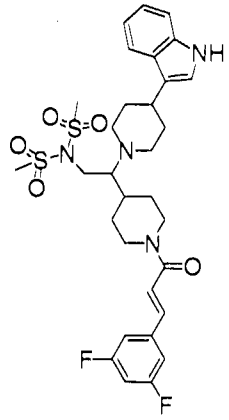
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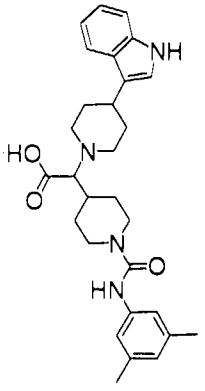
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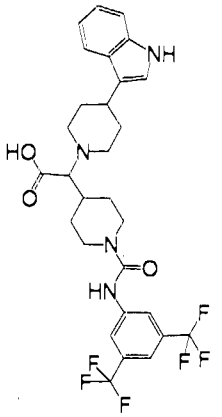
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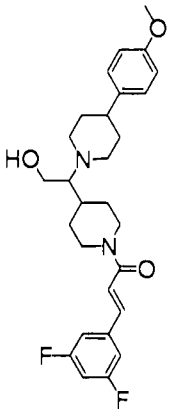
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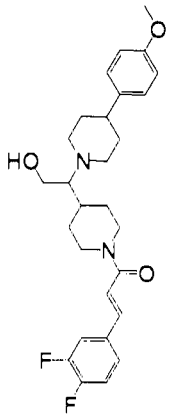
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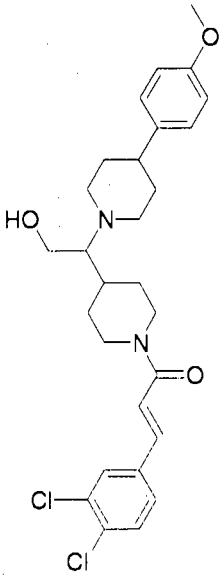
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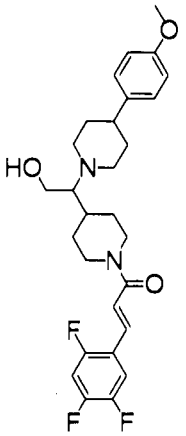
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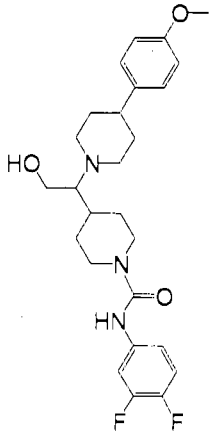
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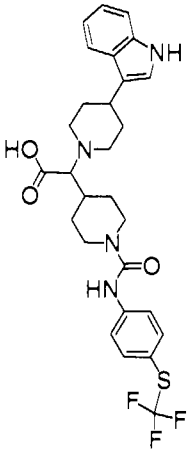
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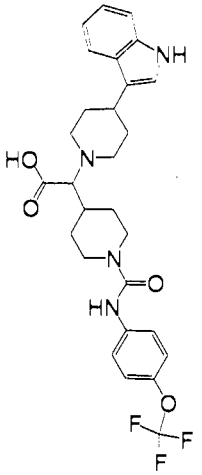
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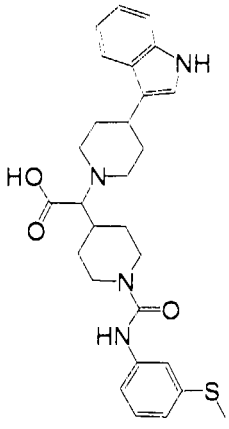
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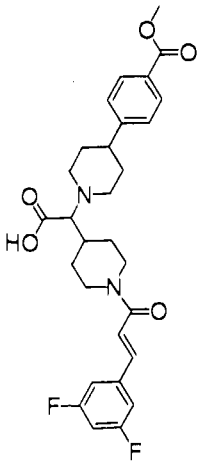
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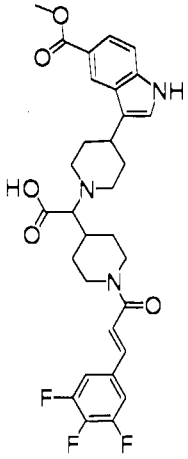
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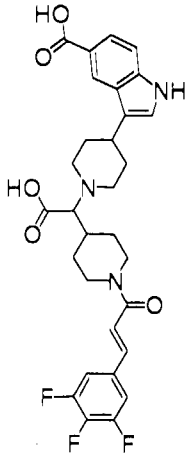
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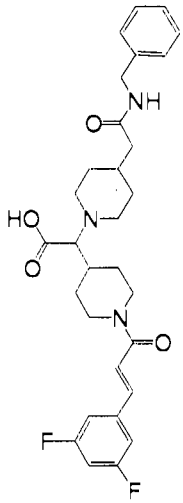
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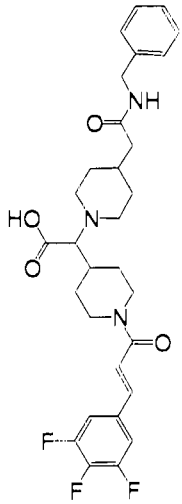
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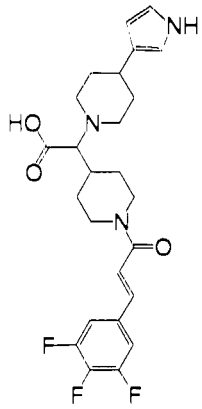
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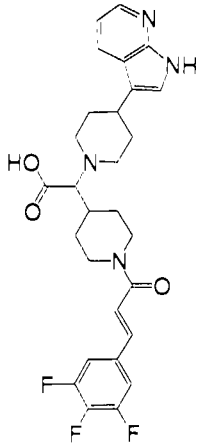
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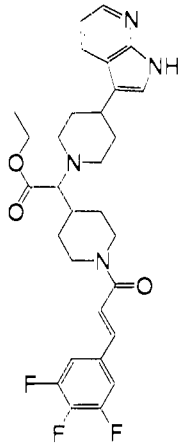
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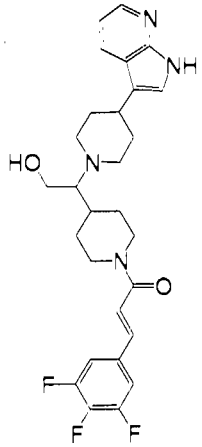
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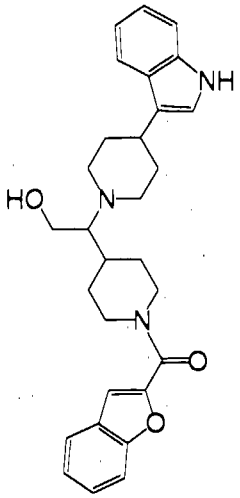
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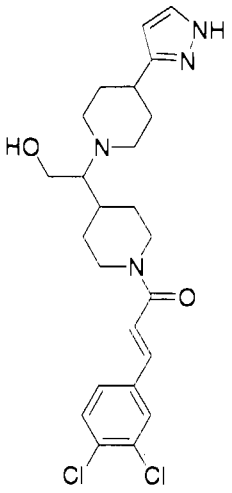
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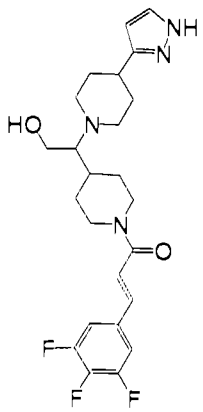
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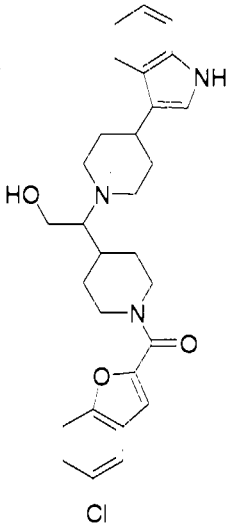
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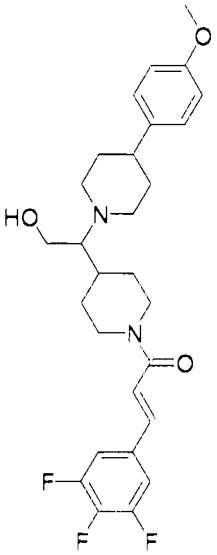
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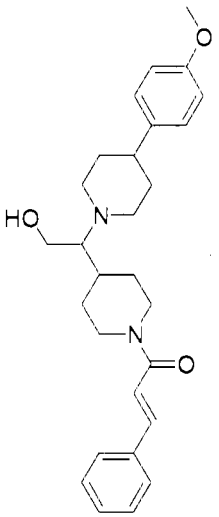
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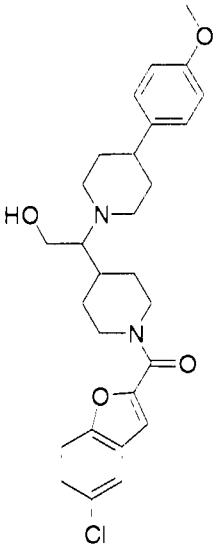
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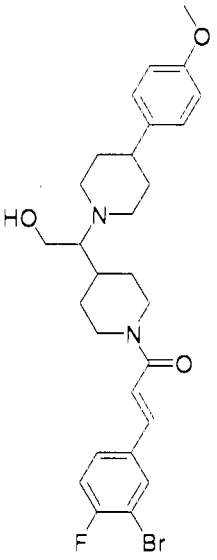
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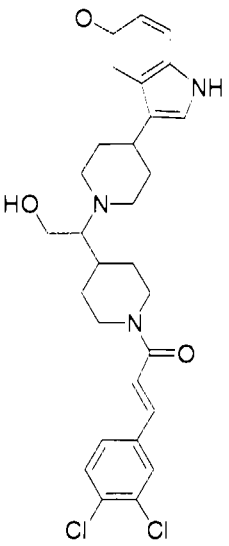
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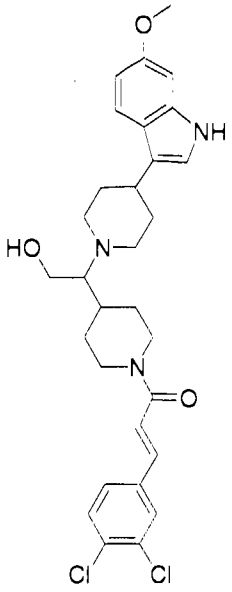
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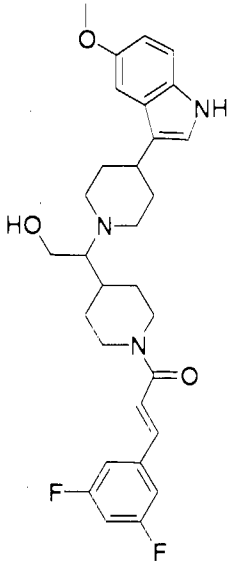
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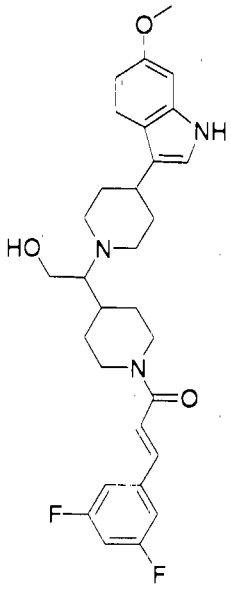
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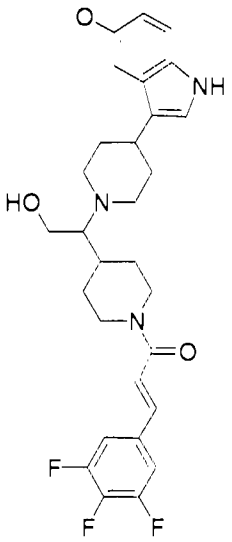
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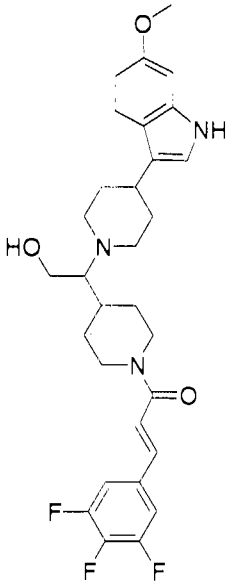
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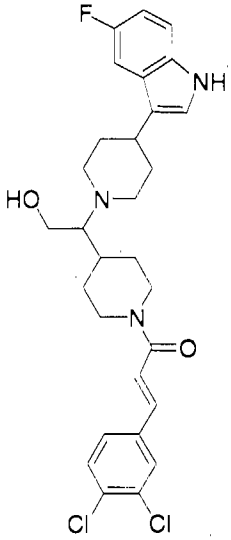
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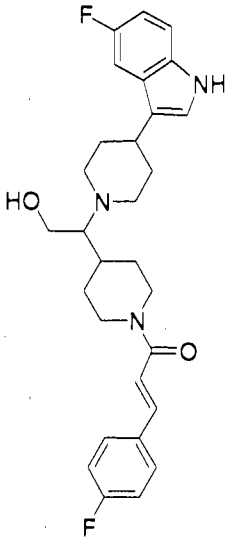
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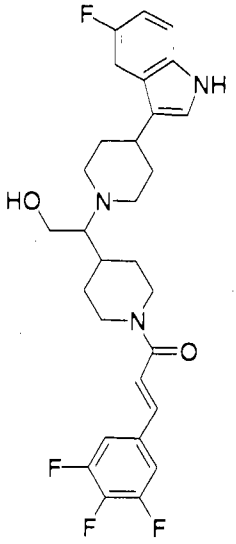
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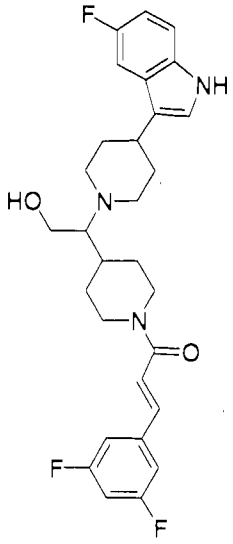
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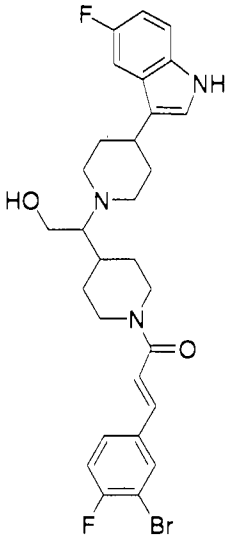
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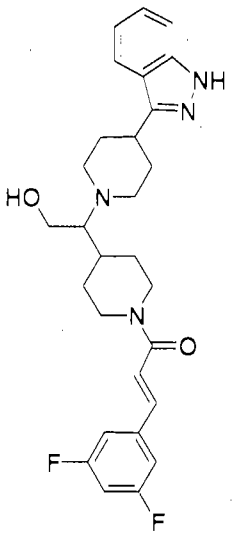
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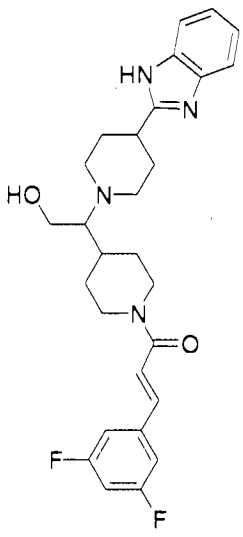
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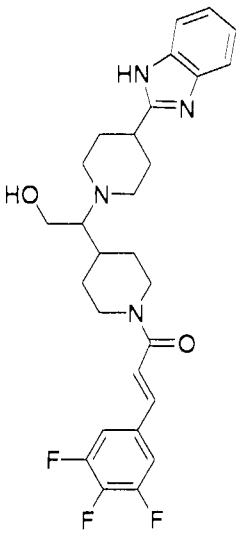
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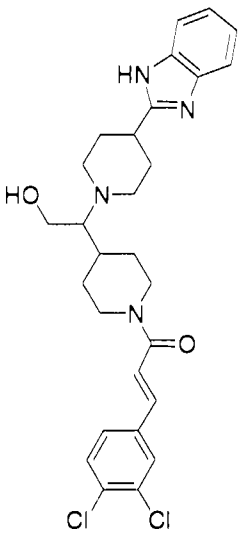
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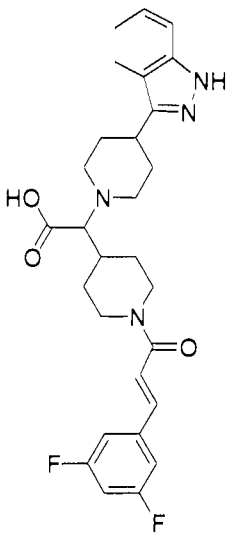
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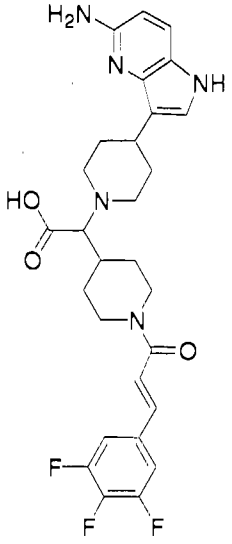
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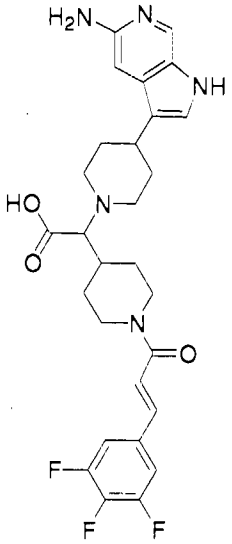
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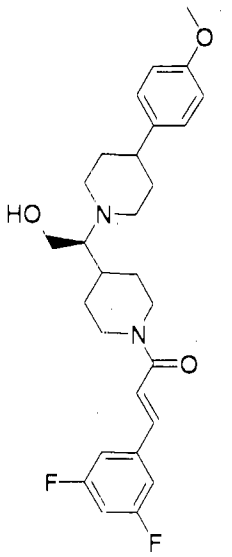
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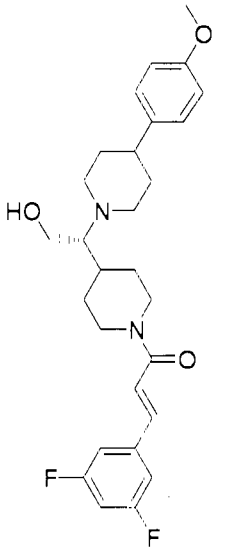
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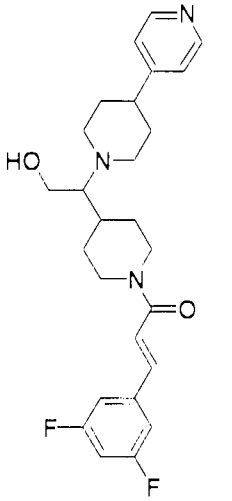
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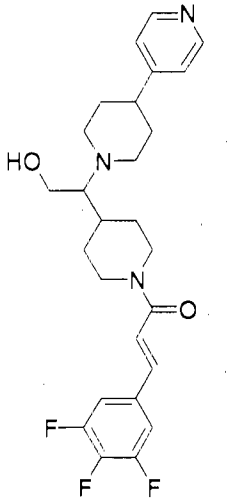
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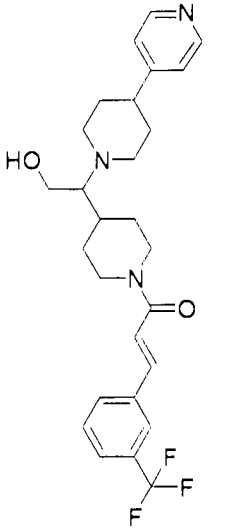
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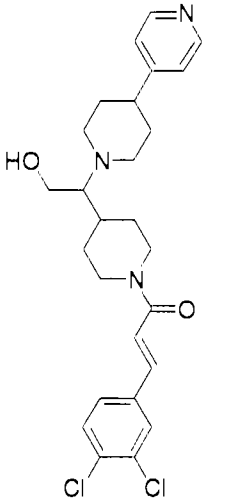
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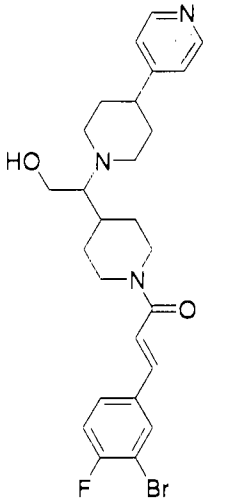
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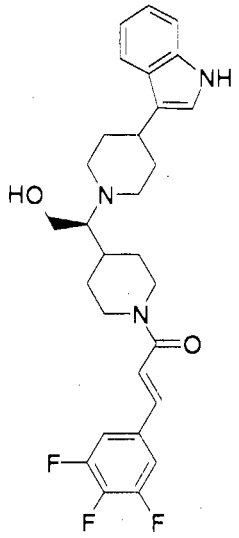
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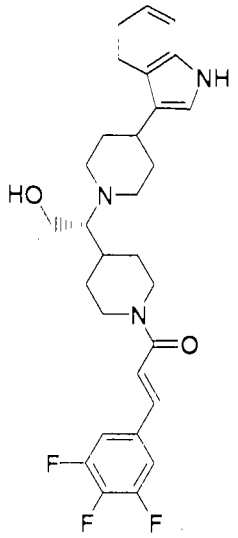
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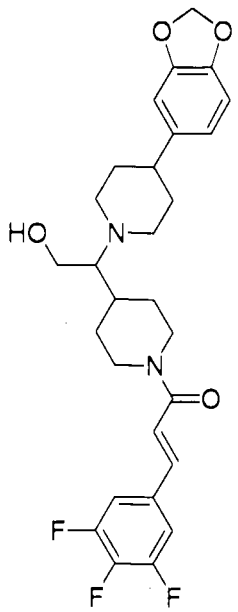
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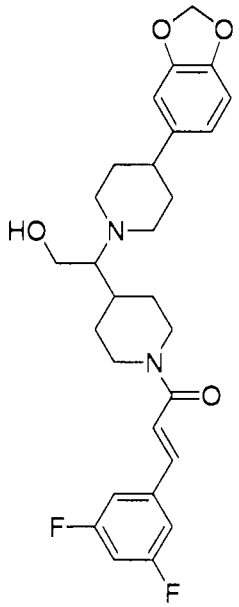
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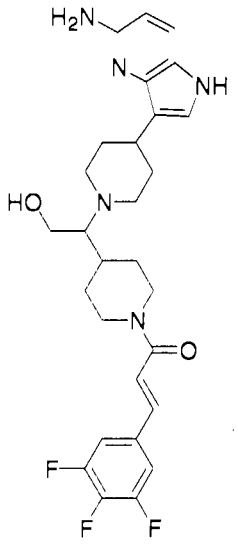
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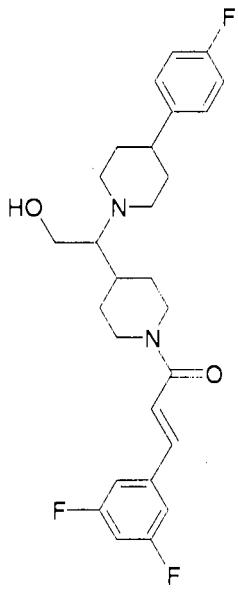
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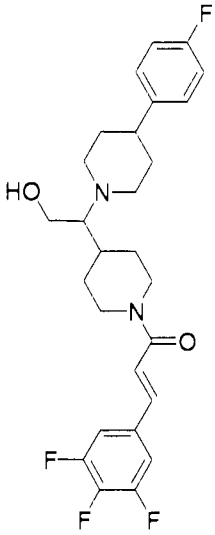
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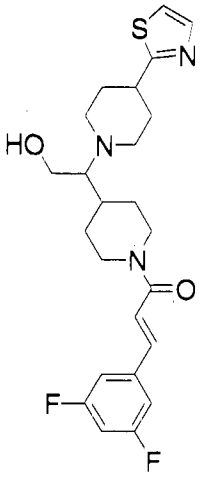
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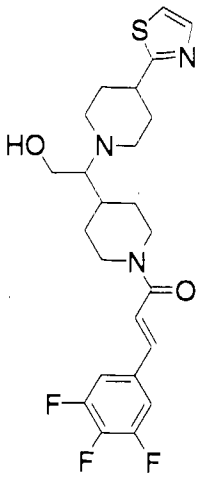
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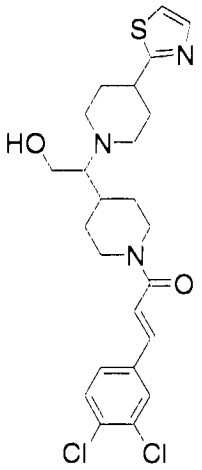
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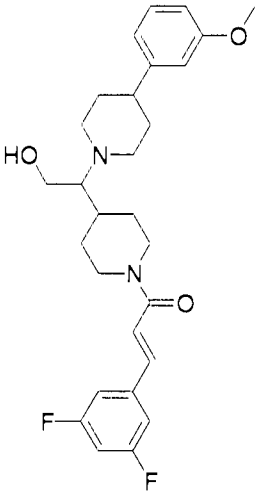
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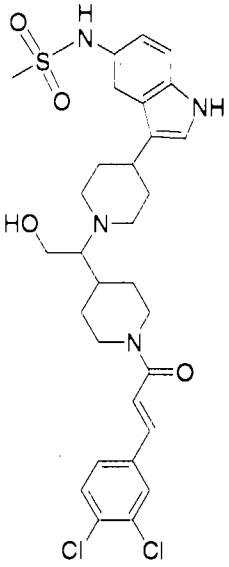
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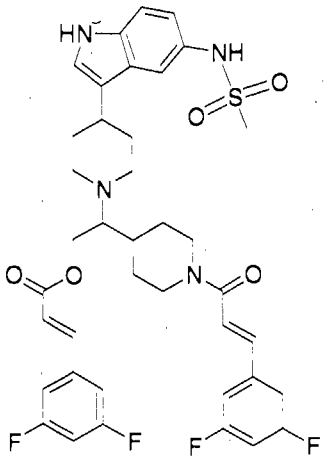
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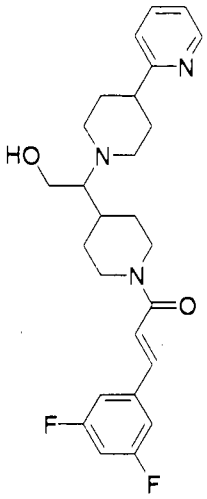
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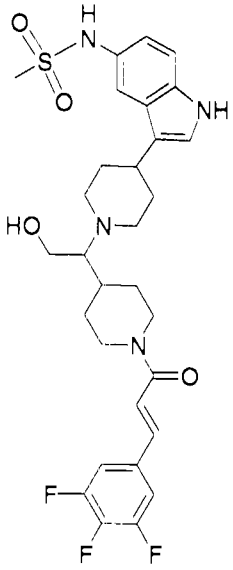
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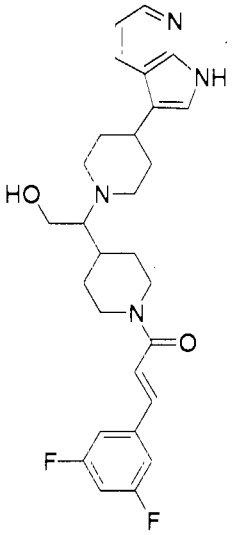
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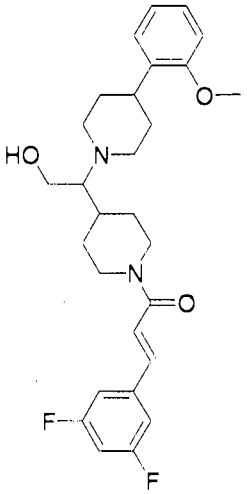
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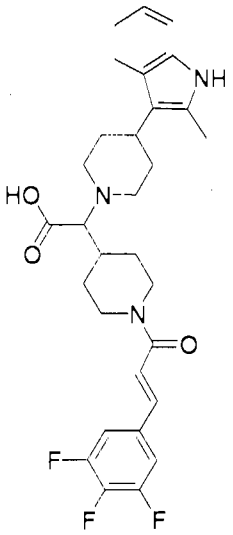
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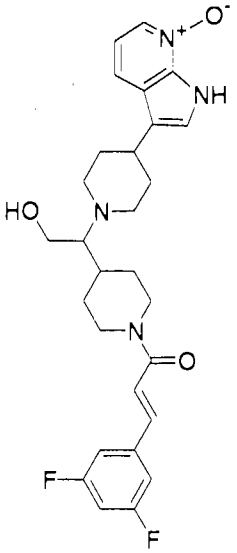
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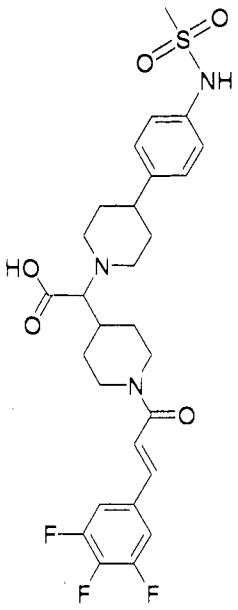
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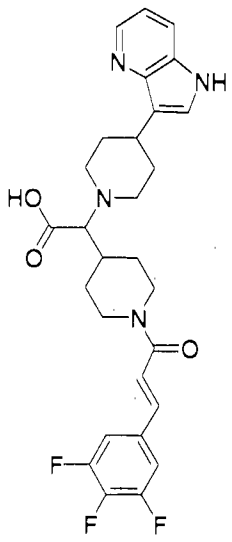
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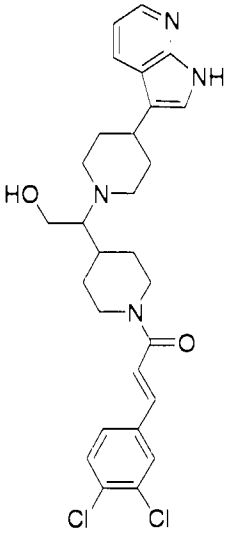
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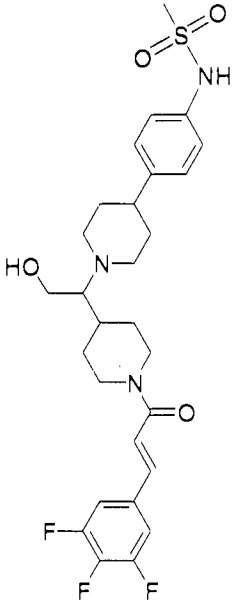
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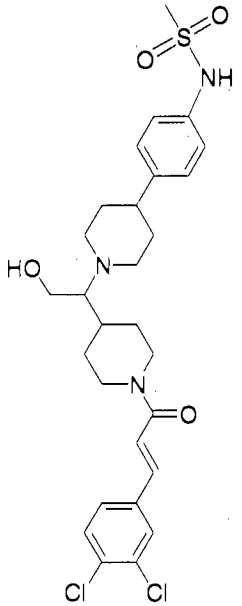
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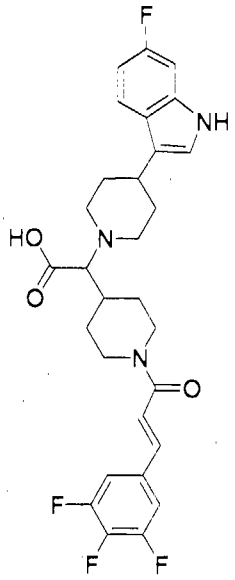
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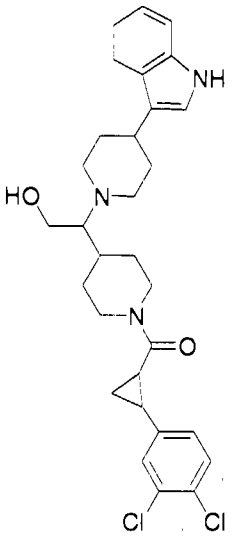
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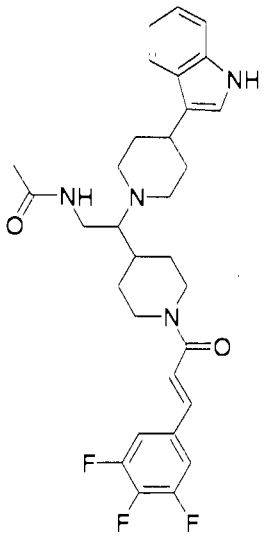
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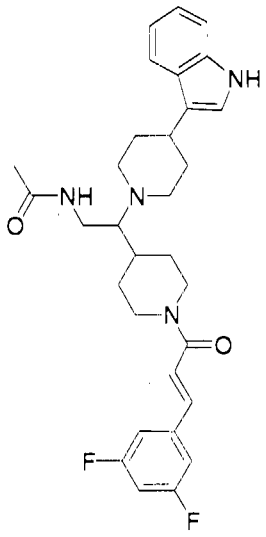
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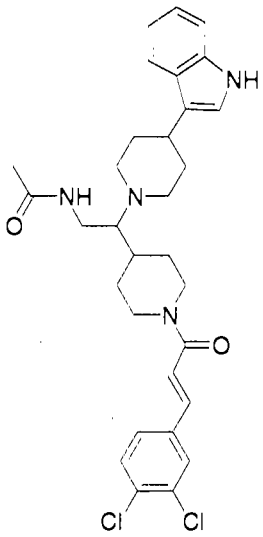
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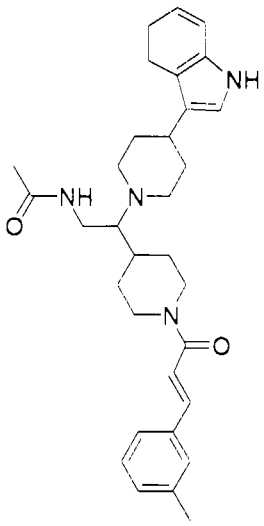
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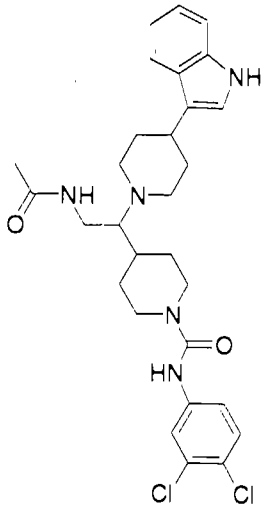
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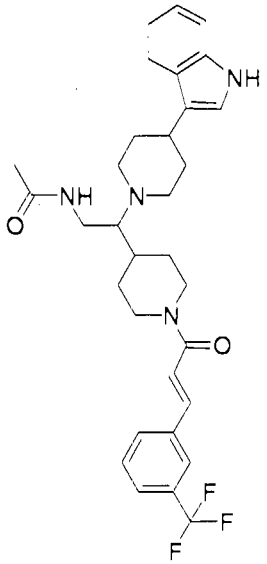
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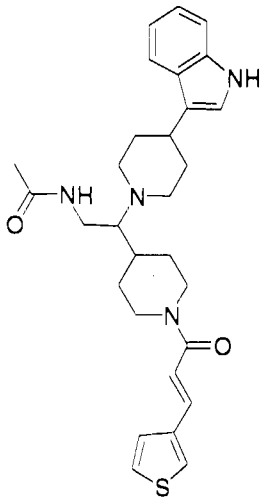
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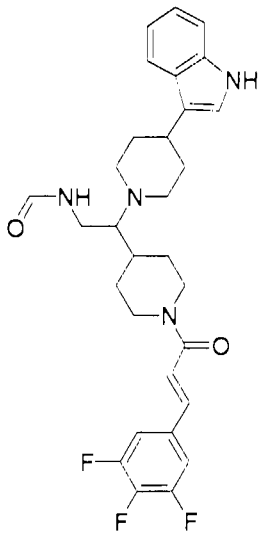
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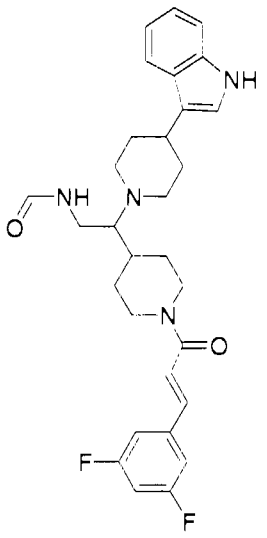
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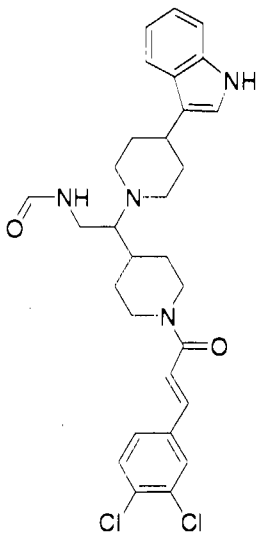
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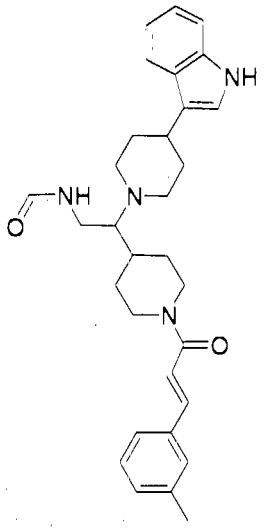
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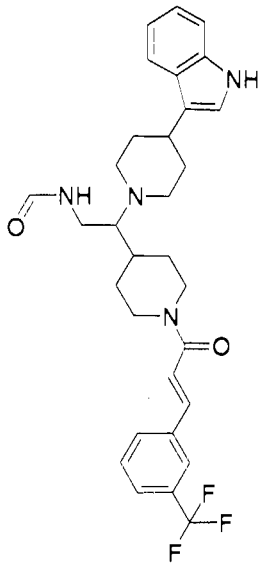
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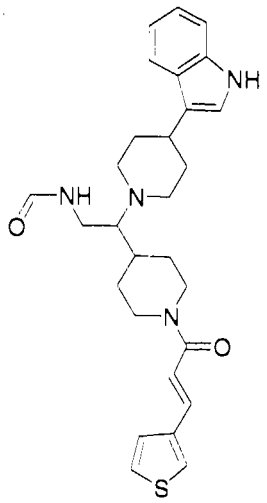
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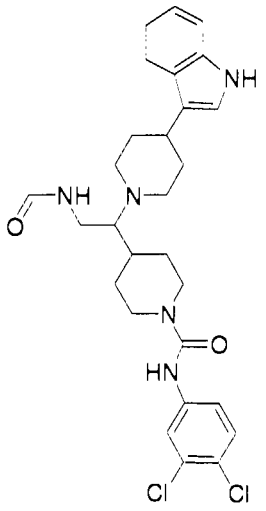
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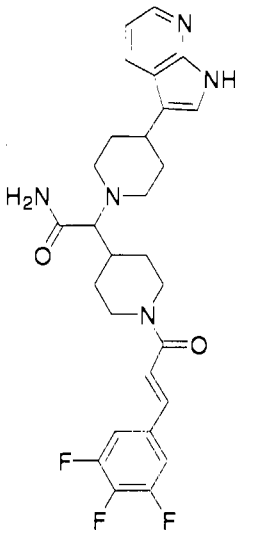
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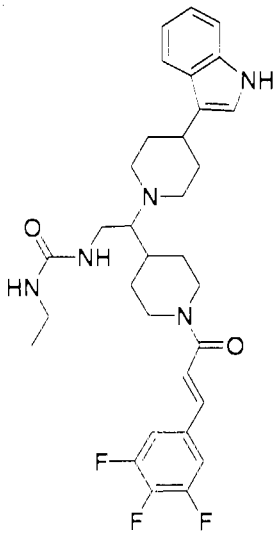
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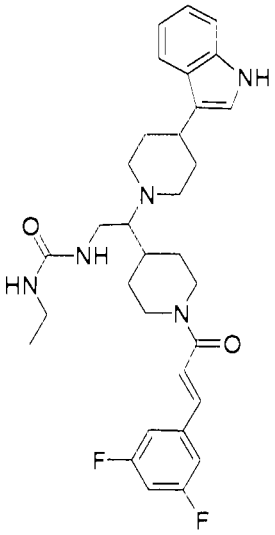
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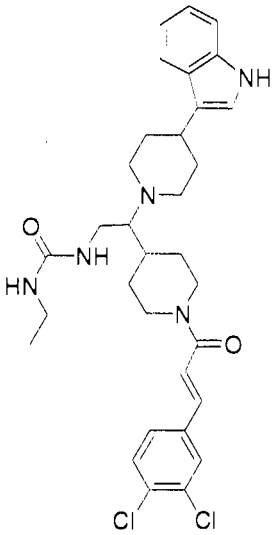
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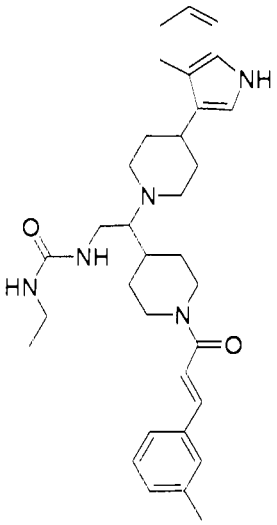
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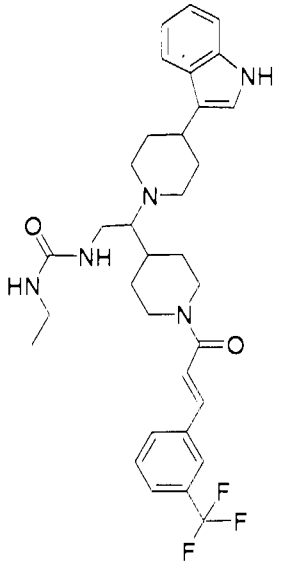
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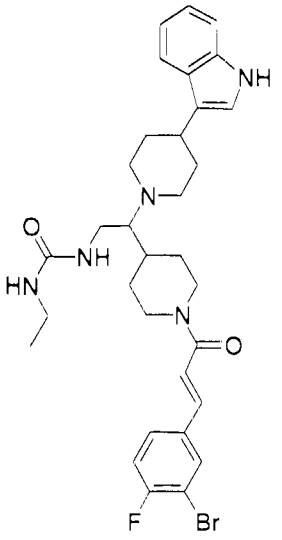
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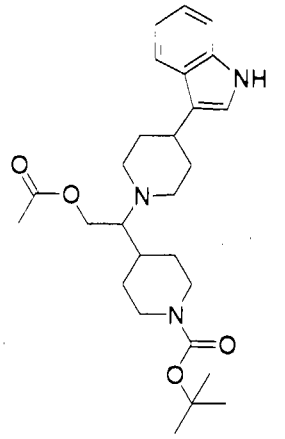
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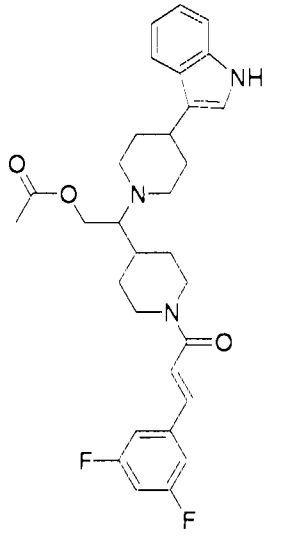
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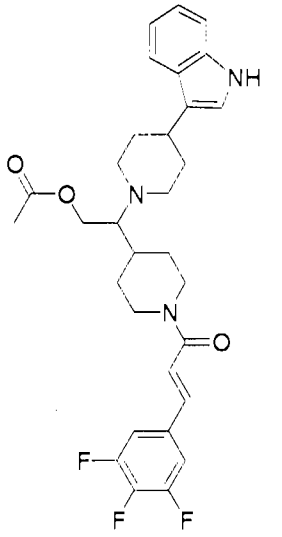
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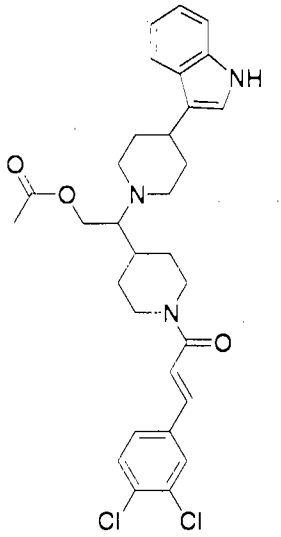
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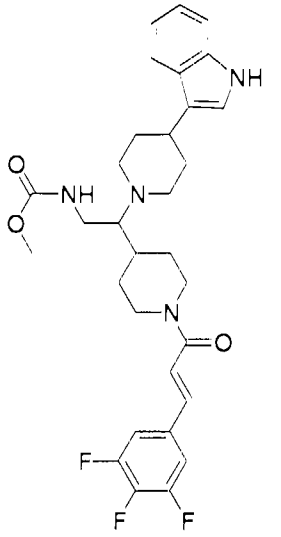
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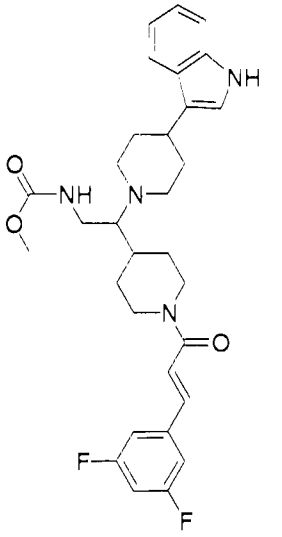
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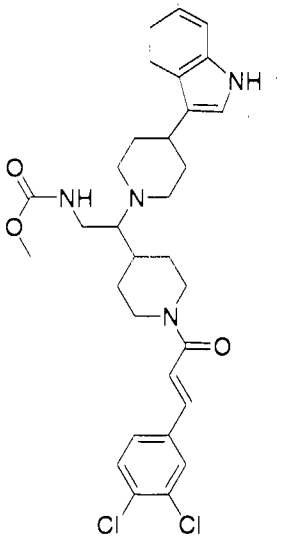
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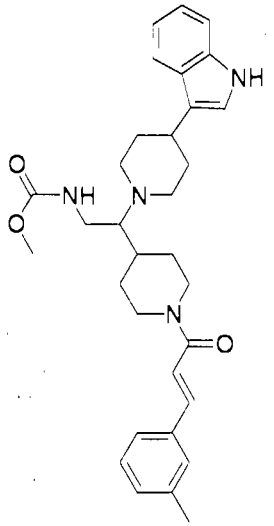
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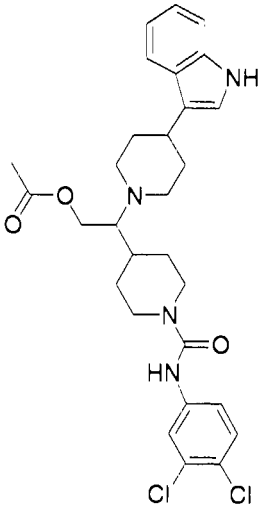
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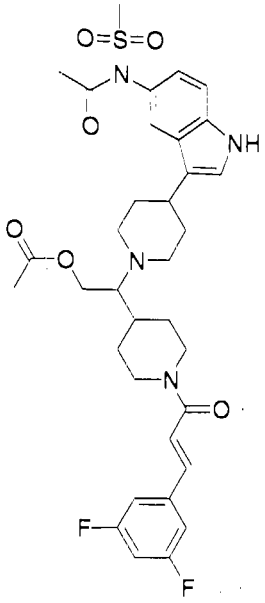
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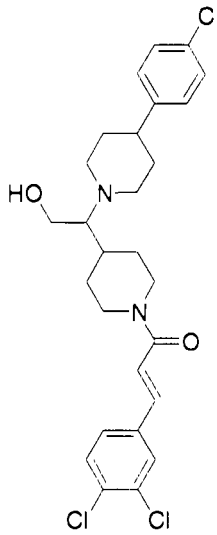
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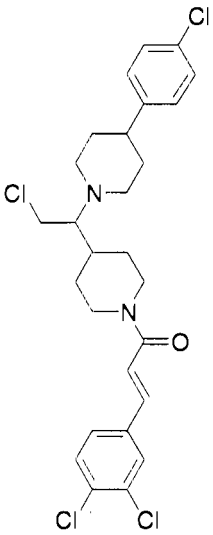
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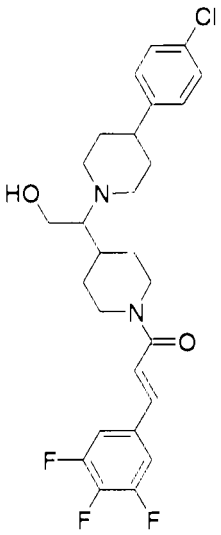
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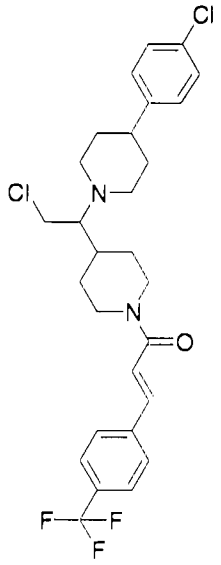
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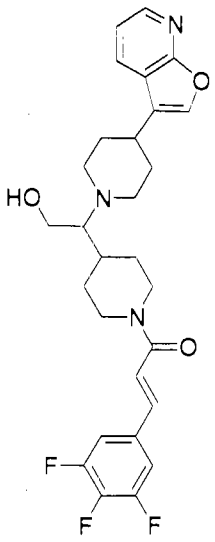
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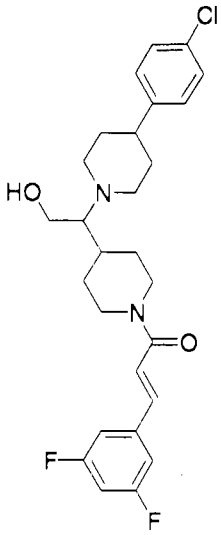
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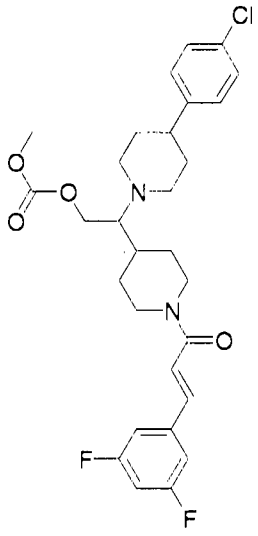
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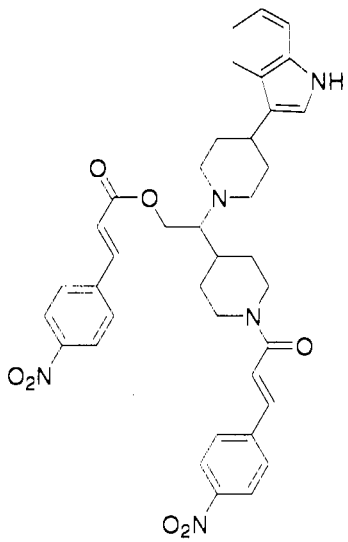
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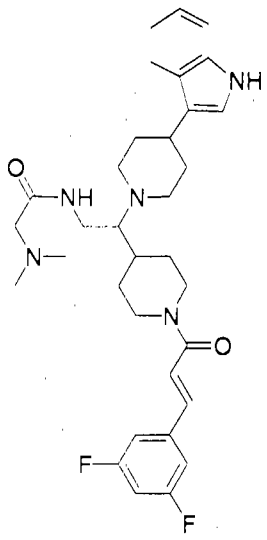
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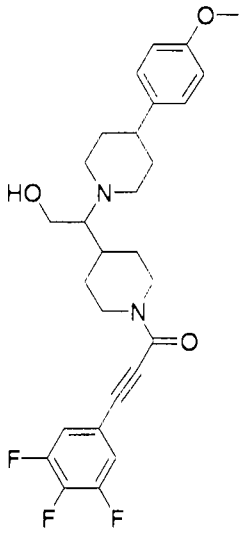
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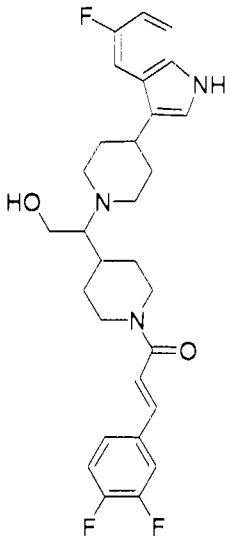
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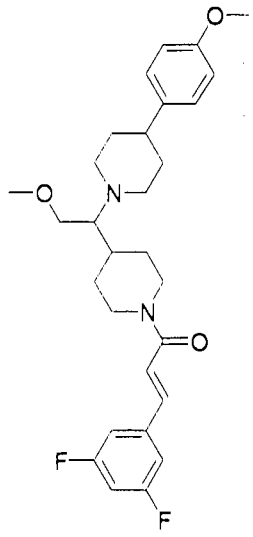
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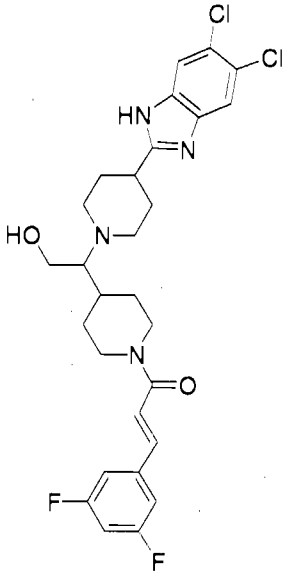
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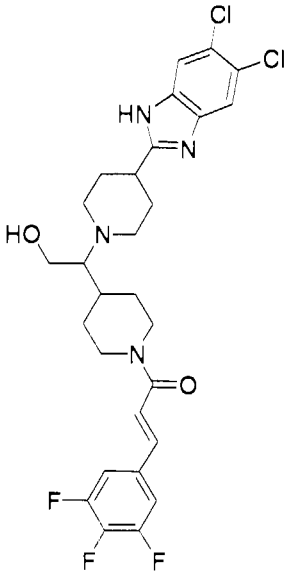
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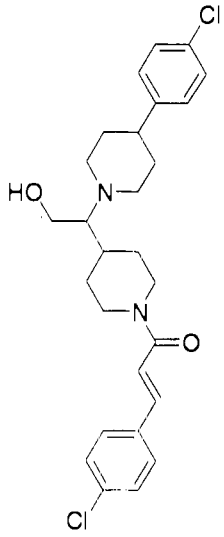
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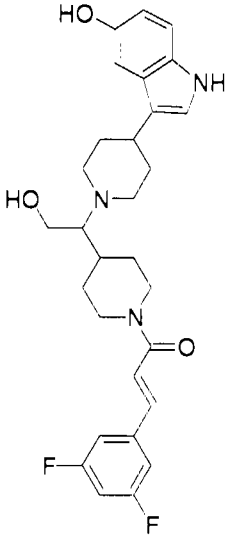
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Chemical Definitions

As used herein, the following terms have the following meanings.

The term "alkyl" means a saturated aliphatic branched or straight-chain monovalent hydrocarbon radical or linking group substituent having from 1-8 carbon atoms, wherein the radical is derived by the removal of one hydrogen atom from a carbon atom and the linking group is derived by the removal of one hydrogen atom from each of two carbon atoms in the chain. The term includes, without limitation, methyl, methylene, ethyl, ethylene, propyl, propylene, isopropyl, isopropylene, n-butyl, n-butylene, t-butyl, t-butylene, pentyl, pentylene, hexyl, hexylene and the like. An alkyl substituent may be attached to a core molecule via a terminal carbon atom or via a carbon atom within the chain. Similarly, any number of

substituent variables may be attached to an alkyl substituent when allowed by available valences. The term "lower alkyl" means an alkyl substituent having from 1-4 carbon atoms.

The term "alkenyl" means a partially unsaturated alkyl radical or linking group substituent having at least at least two carbon atoms and one double bond derived by the removal of one hydrogen atom from each of two adjacent carbon atoms in the chain. Atoms may be oriented about the double bond in either the *cis* (E) or *trans* (Z) conformation. The term includes, without limitation, methylidene, vinyl, vinylidene, allyl, allylidene, propylidene, isopropenyl, iso-propylidene, prenyl, prenylene (3-methyl-2-butenylene), methallyl, methallylene, allylidene (2-propenylidene), crotylene (2-butenylene), and the like. An alkenyl substituent may be attached to a core molecule via a terminal carbon atom or via a carbon atom within the chain. Similarly, any number of substituent variables may be attached to an alkenyl substituent when allowed by available valences. The term "lower alkenyl" means an alkenyl substituent having from 2-4 carbon atoms.

The term "alkynyl" means a partially unsaturated alkyl radical or linking group substituent having at least two carbon atoms and one triple bond derived by the removal of two hydrogen atom from each of two adjacent carbon atoms in the chain. The term includes, without limitation, ethinyl, ethinylidene, propargyl, propargylidene and the like. An alkynyl substituent may be attached to a core molecule via a terminal carbon atom or via a carbon atom within the chain. Similarly, any number of substituent variables may be attached to an alkynyl substituent when allowed by available valences. The term "lower alkynyl" means an alkynyl substituent having from 2-4 carbon atoms.

The term "alkoxy" means an alkyl radical or linking group substituent attached through an oxygen-linking atom, wherein a radical is of the formula -O-alkyl and a linking group is of the formula -O-alkyl-. The term includes, without limitation, methoxy, ethoxy, propoxy, butoxy and the like. An alkoxy substituent may be attached to a core molecule and further substituted where allowed.

The term "cycloalkyl" means a saturated or partially unsaturated monocyclic, polycyclic or bridged hydrocarbon ring system radical or linking group. A ring of 3 to 20 carbon atoms may be designated by C_{3-20} cycloalkyl; a ring of 3 to 12 carbon atoms may be designated by C_{3-12} cycloalkyl, a ring of 3 to 8 carbon atoms may be designated by C_{3-8} cycloalkyl and the like.

The term cycloalkyl includes, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthalenyl, 5,6,7,8-tetrahydro-naphthalenyl, 6,7,8,9-tetrahydro-*5H*-benzocycloheptenyl, 5,6,7,8,9,10-hexahydro-benzocyclooctenyl, fluorenyl, bicyclo[2.2.1]heptyl,

bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octyl, bicyclo[3.1.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octenyl, bicyclo[3.2.1]octenyl, adamantanyl, octahydro-4,7-methano-1*H*-indenyl, octahydro-2,5-methano-pentalenyl (also referred to as hexahydro-2,5-methano-pentalenyl) and the like. A cycloalkyl substituent may be attached to a core molecule and further substituted where allowed.

The term "aryl" means an unsaturated, conjugated π electron monocyclic or polycyclic hydrocarbon ring system radical or linking group substituent of 6, 9, 10 or 14 carbon atoms. The term includes, without limitation, phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, anthracenyl and the like. An aryl substituent may be attached to a core molecule and further substituted where allowed.

The term "heterocyclyl" means a saturated, partially unsaturated (such as those named with the prefix dihydro, trihydro, tetrahydro, hexahydro and the like) or unsaturated monocyclic, polycyclic or bridged hydrocarbon ring system radical or linking group substituent, wherein at least one ring carbon atom has been replaced with one or more heteroatoms independently selected from N, O or S. A heterocyclyl substituent further includes a ring system having up to 4 nitrogen atom ring members or a ring system having from 0 to 3 nitrogen atom ring members and 1 oxygen or sulfur atom ring member. Alternatively, up to two adjacent ring members may be a heteroatom, wherein one heteroatom is nitrogen and the other is selected from N, O or S. A heterocyclyl radical is derived by the removal of one hydrogen atom from a single carbon or nitrogen ring atom. A heterocyclyl linking group is derived by the removal of one hydrogen atom from two of either a carbon or nitrogen ring atom. A heterocyclyl substituent may be attached to a core molecule by either a carbon atom ring member or by a nitrogen atom ring member and further substituted where allowed.

The term heterocyclyl includes, without limitation, furanyl, thienyl, 2*H*-pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, pyrrolyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2-imidazolinyl (also referred to as 4,5-dihydro-1*H*-imidazolyl), imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, tetrazolinyl, tetrazolidinyl, 2*H*-pyranyl, 4*H*-pyranyl, thiopyranyl, pyridinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, azetidinyl, azepanyl, indolizinyl, indolyl, 4-aza-indolyl (also referred to as 1H-pyrrolo[3,2-b]pyridin-3-yl), 6-aza-indolyl (also referred to as 1H-pyrrolo[2,3-c]pyridin-3-yl), 7-aza-indolyl (also referred to as 1H-pyrrolo[2,3-b]pyridin-3-yl), isoindolyl, 3*H*-indolyl, indolinyl, benzo[*b*]furanyl, furo[2,3-b]pyridin-3-yl, benzo[*b*]thienyl, indazolyl (also referred to as 1*H*-indazolyl), benzoimidazolyl, benzothiazolyl, purinyl, 4*H*-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl,

1,8-naphthyridinyl, pteridinyl, quinuclidinyl, 2H-chromenyl, 3H-benzo[f]chromenyl, tetrahydro-furanyl, tetrahydro-thienyl, tetrahydro-pyranyl, tetrahydro-thiopyranyl, tetrahydro-pyridazinyl, hexahydro-1,4-diazepinyl, hexahydro-1,4-oxazepanyl, 2,3-dihydro-benzo[b]oxepinyl, 1,3-benzodioxolyl (also known as 1,3-methylenedioxyphenyl or benzo[1,3]dioxolyl), 2,3-dihydro-1,4-benzodioxinyl (also known as 1,4-ethylenedioxyphenyl or benzo[1,4]dioxinyl), benzo-dihydro-furanyl (also known as 2,3-dihydro-benzofuranyl), benzo-tetrahydro-pyranyl, benzo-dihydro-thienyl, 5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thienyl, 5,6,7-trihydro-4*H*-cyclohexa[*b*]thienyl, 5,6-dihydro-4*H*-cyclopenta[*b*]thienyl, 2-aza-bicyclo[2.2.1]heptyl, 1-aza-bicyclo[2.2.2]octyl, 8-aza-bicyclo[3.2.1]octyl, 7-oxa-bicyclo[2.2.1]heptyl, pyrrolidinium, piperidinium, piperazinium, morpholinium and the like.

The term "acrylyl" means a linking group of the formula -C(O)C=C-.

The term "acyl" means a radical of the formula -C(O)-alkyl, or a linking group of the formula -C(O)-alkyl-.

The term "acyloxy" means a linking group of the formula -C(O)-alkyl-O-.

The term "alkoxycarbonylalkoxy" means a radical of the formula -O-alkyl-C(O)O-alkyl, or a linking group of the formula -O-alkyl-C(O)O-alkyl-.

The term "alkoxycarboxy" means a radical of the formula -O-alkyl-CO_2H or -O-alkyl-C(O)OH.

The term "alkylamino" means a radical of the formula -alkyl-NH_2, or a linking group of the formula -alkyl-NH-.

The term "alkylaminoalkyl" means a radical of the formula -alkyl-NH-alkyl or -alkyl-N(alkyl)$_2$, or a linking group of the formula -alkyl-NH-alkyl- or -alkyl-N(alkyl)-alkyl-.

The term "alkylcarbamoyl" means a radical of the formula -alkyl-C(O)NH_2, or a linking group of the formula -alkyl-C(O)NH-.

The term "alkylcarbamoylalkyl" means a radical of the formula -alkyl-C(O)NH-alkyl or -alkyl-C(O)N(alkyl)$_2$, or a linking group of the formula -alkyl-C(O)NH-alkyl- or -C(O)N(alkyl)-alkyl-.

The term "alkylcarbonylalkoxy" means a radical of the formula -alkyl-C(O)O-alkyl, or a linking group of the formula -alkyl-C(O)O-alkyl-.

The term "alkylcarboxy" means a radical of the formula -alkyl-CO_2H or -alkyl-C(O)OH.

The term "alkylsulfonylamino" means a radical of the formula -alkyl-SO_2-NH_2.

The term "alkylsulfonylaminoalkyl" means a radical of the formula -alkyl-SO_2-NH-alkyl or -alkyl-SO_2-N(alkyl)$_2$, or a linking group of the formula -alkyl-SO_2-NH-alkyl- or -alkyl-SO_2-N(alkyl)-alkyl-.

The term "amino" means a radical of the formula -NH_2.

The term "aminoacylamino" means a radical of the formula -NH-C(O)-alkyl-NH_2, or a linking group of the formula -NH-C(O)-alkyl-NH-.

The term "aminoacylaminoalkyl" means a radical of the formula -NH-C(O)-alkyl-NH-alkyl or -NH-C(O)-alkyl-N(alkyl)$_2$, or a linking group of the formula -NH-C(O)-alkyl-NH-alkyl- or -NH-C(O)-alkyl-N(alkyl)-alkyl-.

The term "aminoalkyl" means a radical of the formula -NH-alkyl or -N(alkyl)$_2$, or a linking group of the formula -NH-alkyl- or -N(alkyl)-alkyl-.

The term "carbamoyl" means a radical of the formula -C(O)NH_2, or a linking group of the formula -C(O)NH-.

The term "carbamoylalkyl" means a radical of the formula -C(O)NH-alkyl or -C(O)N(alkyl)$_2$, or a linking group of the formula -C(O)NH-alkyl- or -C(O)N(alkyl)-alkyl-.

The term "carbonyl" means a linking group of the formula -C(O)- or -C(=O)-.

The term "carbonylalkoxy" means a radical of the formula -C(O)O-alkyl, or a linking group of the formula -C(O)O-alkyl-.

The term "carboxy" means a radical of the formula -C(O)OH or -CO_2H.

The term "carboxyl" means a linking group of the formula -C(O)O-.

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

The term "iminomethylaminocarbonyl" means a linking group having the formula -C(NH)NHC(O)- or -C(=NH)NHC(O)-.

The term "oxyacyl" means a radical of the formula -OC(O)-alkyl, or a linking group of the formula -OC(O)-alkyl-.

The term "oxyacylaryl" means a radical of the formula -OC(O)-alkyl-aryl.

The term "oxyacrylyl" means a radical of the formula -OC(O)-alkenyl, or a linking group of the formula -OC(O)-alkenyl-.

The term "oxyacrylylaryl" means a radical of the formula -OC(O)-alkenyl-aryl.

The term "oxycarbonylalkoxy" means a radical of the formula -OC(O)-O-alkyl, or a linking group of the formula -OC(O)-O-alkyl-.

The term "sulfonylalkyl" means a radical of the formula -SO_2-alkyl, or a linking group of the formula -SO_2-alkyl-.

The term "sulfonylamino" means a radical of the formula -SO_2-NH_2.

The term "sulfonylaminoalkyl" means a radical of the formula -SO_2-NH-alkyl or -SO_2-N(alkyl)$_2$, or a linking group of the formula -SO_2-NH-alkyl- or -SO_2-N(alkyl)-alkyl-.

The term "thioalkyl" means a radical of the formula -S-alkyl, or a linking group of the formula -S-alkyl-.

The term "thiocarbamyl" means a radical of the formula -C(S)NH_2 or -C(=S)NH_2, or a linking group of the formula --C(S)NH-.

The term "urea" means a radical of the formula -NH-C(O)-NH_2.

The term "ureaalkyl" means a radical of the formula -NH-C(O)-NH-alkyl or -NH-C(O)-N(alkyl)$_2$.

The term "substituted" means one or more hydrogen atoms on a core molecule have been replaced with one or more radicals or linking groups, wherein the linking group, by definition is also further substituted.

The term "dependently selected" means one or more substituent variables are present in a specified combination (e.g. groups of substituents commonly appearing in a tabular list).

The substituent nomenclature used in the disclosure of the present invention was derived using nomenclature rules well known to those skilled in the art (e.g., IUPAC).

Compound Forms

The compounds of the invention may be present in a form which may, alternatively or in addition to a compound of Formula (I), comprise a salt of a compound of Formula (I) or a prodrug or active metabolite of such a compound or salt.

The compounds of the invention may be present in a salt form. For use in medicines, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." FDA-approved pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Pharmaceutically acceptable acidic/anionic salts include, without limitation, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate,

napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide trifluoroacetate salts and the like.

Organic or inorganic acids also include, and are not limited to, hydroiodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic, trifluoroacetic acid and the like.

Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tromethane or "TRIS"), ammonia, benzathine, *t*-butylamine, calcium, calcium gluconate, calcium hydroxide, chloroprocaine, choline, choline bicarbonate, choline chloride, cyclohexylamine, diethanolamine, ethylenediamine, lithium, LiOMe, L-lysine, magnesium, meglumine, NH_3, NH_4OH, N-methyl-D-glucamine, piperidine, potassium, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, sodium, sodium carbonate, sodium-2-ethylhexanoate (SEH), sodium hydroxide, triethanolamine (TEA), zinc and the like.

The compounds of the invention may be present in the form of pharmaceutically acceptable prodrugs and metabolites thereof. In general, such prodrugs and metabolites will be functional derivatives of the compounds that are readily convertible *in vivo* into an active compound.

The term "prodrug" means a pharmaceutically acceptable form of a functional derivative of a compound of the invention (or a salt thereof), wherein the prodrug may be: 1) a relatively active precursor which converts *in vivo* to an active prodrug component; 2) a relatively inactive precursor which converts *in vivo* to an active prodrug component; or 3) a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo* (i.e., as a metabolite). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The term "metabolite" means a pharmaceutically acceptable form of a metabolic derivative of a compound of the invention (or a salt thereof), wherein the derivative is a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo*.

The present invention also contemplates compounds of Formula (I) in various stereoisomeric or tautomeric forms. The invention encompasses all such CCR2 inhibiting

compounds, including active compounds in the form of essentially pure enantiomers, racemic mixtures and tautomers or pharmaceutically acceptable forms thereof.

The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. Such substances have the same number and kind of atoms but differ in structure. The structural difference may be in constitution (geometric isomers) or in an ability to rotate the plane of polarized light (stereoisomers).

The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are stereoisomers wherein an asymmetrically substituted carbon atom acts as a chiral center. The term "chiral" refers to a molecule that is not superposable on its mirror image, implying the absence of an axis and a plane or center of symmetry. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superposable. The term "diastereomer" refers to stereoisomers that are not related as mirror images. The symbols "*R*" and "*S*" represent the configuration of substituents around a chiral carbon atom(s). The symbols "*R**" and "*S**" denote the relative configurations of substituents around a chiral carbon atom(s). .

The term "racemate" or "racemic mixture" refers to a compound of equimolar quantities of two enantiomeric species, wherein the compound is devoid of optical activity. The term "optical activity" refers to the degree to which a chiral molecule or nonracemic mixture of chiral molecules rotates the plane of polarized light.

The term "geometric isomer" refers to isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring or to a bridged bicyclic system. Substituent atoms (other than H) on each side of a carbon-carbon double bond may be in an E or Z configuration. In the "E" configuration, the substituents are on opposite sides in relationship to the carbon-carbon double bond; in the "Z" configuration, the substituents are oriented on the same side in relationship to the carbon-carbon double bond.

Substituent atoms (other than H) attached to a hydrocarbon ring may be in a cis or trans configuration. In the "cis" configuration, the substituents are on the same side in relationship to the plane of the ring; in the "trans" configuration, the substituents are on opposite sides in relationship to the plane of the ring. Compounds having a mixture of "cis" and "trans" species are designated "cis/trans". Substituent atoms (other than H) attached to a bridged bicyclic system may be in an "endo" or "exo" configuration. In the "endo" configuration, the substituents attached to a bridge (not a bridgehead) point toward the larger of the two remaining bridges; in the "exo" configuration, the substituents attached to a bridge point toward the smaller of the two remaining bridges.

It is to be understood that the various substituent stereoisomers, geometric isomers and mixtures thereof used to prepare compounds of the present invention are either commercially available, can be prepared synthetically from commercially available starting materials or can be prepared as isomeric mixtures and then obtained as resolved isomers using techniques well-known to those of ordinary skill in the art.

The isomeric descriptors "R," "S," "S*," "R*," "E," "Z," "cis," "trans," "exo", and "endo", where used herein, indicate atom configurations relative to a core molecule and are intended to be used as defined in the literature.

The compounds of the present invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the free base of each isomer of an isomeric pair using an optically active salt (followed by fractional crystallization and regeneration of the free base), forming an ester or amide of each of the isomers of an isomeric pair (followed by chromatographic separation and removal of the chiral auxiliary) or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

Furthermore, compounds of the present invention may have a plurality of polymorph or amorphous crystalline forms and, as such, are intended to be included in the scope of the invention. In addition, some of the compounds may form a plurality of solvates with water (i.e., hydrates) or common organic solvents, such are also intended to be encompassed within the scope of this invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Therapeutic Use

Compounds of Formula (I) or a form, composition or medicament thereof in accordance with the present invention are CCR2 antagonists. A compound of Formula (I) or a form, composition or medicament thereof may have a mean inhibition constant (IC_{50}) against MCP-1 binding to CCR2 of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between

about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; or, between about 10 nM to about 0.01 nM.

A compound of Formula (I) or a composition or medicament thereof reduces MCP-1 induced monocyte chemotaxis. A compound of Formula (I) or a form, composition or medicament thereof may have an IC_{50} for reduction in MCP-1 induced monocyte chemotaxis of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; or, between about 10 nM to about 0.01 nM.

A compound of Formula (I) or a composition or medicament thereof reduces MCP-1 intracellular calcium mobilization. A compound of Formula (I) or a form, composition or medicament thereof may have an IC_{50} for reduction in MCP-1 induced intracellular calcium mobilization of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 10μM to about 0.01 nM; between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; or, between about 10 nM to about 0.01 nM.

Accordingly, a compound of Formula (I) or a form, composition or medicament thereof is useful in a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or form, composition or medicament thereof.

The present invention is directed to a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or a form, composition or medicament thereof.

The term "administering" with respect to the methods of the invention, means a method for therapeutically or prophylactically preventing, treating or ameliorating a syndrome, disorder or disease as described herein by using a compound of Formula (I) or a form, composition or medicament thereof. Such methods include administering an effective amount of said compound, compound form, composition or medicament at different times during the course of a therapy or concurrently in a combination form. The methods of the invention are to be understood as embracing all known therapeutic treatment regimens.

The term "subject" refers to a patient, which may be animal, typically a mammal, typically a human, which has been the object of treatment, observation or experiment and is at risk of (or susceptible to) developing a syndrome, disorder or disease that is associated with elevated MCP-1 expression or MCP-1 overexpression, or a patient with an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression.

The term "effective amount" means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes preventing, treating or ameliorating the symptoms of a syndrome, disorder or disease being treated.

The effective amount of a compound of the invention in such a therapeutic method is from about 0.1 ng/kg/day to about 300 mg/kg/day.

Examples of compounds of Formula (I) or a form, composition or medicament thereof useful in a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof is selected from the group consisting of:

6 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

7 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

8 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

9 [4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

13 (*S*)-{[4-(1H-indol-3-yl)-piperidin-1-yl]}-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

15 [4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

16 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

18 {1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

19 {1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

20 [1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

22 {1-[(2*E*)-3-(3,4-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

23 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

24 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

25 [4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

26 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

27 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-phenyl-acryloyl]-piperidin-4-yl}-acetic acid;

29 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

30 [4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

31 [4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

34 {1-[(2*E*)-3-(4-chloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

35 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

36 {1-[(2*E*)-3-(3-bromo-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

38 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

39 {1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

40 [1-(3,4-difluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

41 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(4-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

42 {1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

45 [1-(3,5-dichloro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

46 [4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

47 {1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

48 [1-(3-chloro-4-fluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

49 [1-(3-chloro-4-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

50 {1-[(3,4-dichloro-benzoylamino)-imino-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

52 {1-[imino-(3,4,5-trifluoro-benzoylamino)-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

53 [4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

57 [1-(4-chloro-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

59 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-nitro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

60 {1-[(2*E*)-3-(4-bromo-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

62 {1-[(2*E*)-3-(3-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

64 [1-(3,4-dichloro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

70 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-m-tolyl-acryloyl]-piperidin-4-yl}-acetic acid;

71 {1-[(2*E*)-3-(3-bromo-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

72 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-methoxy-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

74 {1-[(2*E*)-3-(3-fluoro-4-methyl-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

75 {1-[(2*E*)-3-(3-fluoro-4-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

76 {1-[(2*E*)-3-(3-chloro-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

77 {1-[(2*E*)-3-(4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

79 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-trifluoromethyl-phenylthiocarbamoyl)-piperidin-4-yl]-acetic acid;

80 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethyl-phenylthiocarbamoyl)-piperidin-4-yl]-acetic acid;

81 [4-(1H-pyrrol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

83 [4-(6-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

88 [1-(4-chloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

92 [4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-nitro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

93 {1-[(2*E*)-3-(3-chloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

94 [1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

95 [1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

96 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

101 [1-(4-bromo-3-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

106 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-methyl-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

108 [4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

109 [1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

112 (2*E*)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

113 (2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

116 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

119 (2*E*)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3-trifluoromethyl-phenyl)-propenone;

121 (2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

122 4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carbothioic acid (3,4-dichloro-phenyl)-amide;

123 4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide;

129 4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,5-difluoro-phenyl)-amide;

132 (2*E*)-1-(4-{2-hydroxy-1-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

133 (2*E*)-1-(4-{2-hydroxy-1-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

136 [1-(3,5-bis-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

137 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

139 (2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

142 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

143 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethoxy-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

144 [4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-methylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

146 3-[1-(carboxy-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-methyl)-piperidin-4-yl]-1H-indole-5-carboxylic acid methyl ester;

151 [4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

153 (2*E*)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

158 (2*E*)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

162 (2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

166 (2*E*)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

170 (2*E*)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

171 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone;

180 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{(1*S*)-2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

181 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{(1*R*)-2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

187 (2*E*)-1-(4-{(1*S*)-2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

188 (2*E*)-1-(4-{(1*R*)-2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

198 N-{3-[1-(1-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-hydroxy-ethyl)-piperidin-4-yl]-1H-indol-5-yl}-methanesulfonamide;

201 N-{3-[1-(2-hydroxy-1-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-piperidin-4-yl]-1H-indol-5-yl}-methanesulfonamide;

202 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

205 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

208 (2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

211 [4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

213 *N*-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-acetamide;

238 (2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-carbamic acid methyl ester;

243 acetic acid 2-{4-[5-(acetyl-methanesulfonyl-amino)-1H-indol-3-yl]-piperidin-1-yl}-2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl ester; and

259 (2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone.

The invention includes the use of an instant compound for the preparation of a composition or medicament for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof, wherein the composition or medicament comprises a mixture one or more compounds of the invention and an optional pharmaceutically acceptable carrier.

The term "composition" means a product comprising at least a compound of the invention, such as a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from such combinations of the specified ingredients in the specified amounts and one or more pharmaceutically acceptable carriers or any such alternatives to a compound of the invention and a pharmaceutically acceptable carrier therefor.

The term "medicament" means a product for use in preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease.

The term "pharmaceutically acceptable" means molecular entities and compositions that are of sufficient purity and quality for use in the formulation of a composition or medicament of the invention and that, when appropriately administered to an animal or a human, do not produce an adverse, allergic, or other untoward reaction. Since both human and veterinary use is included within the scope of the invention, a pharmaceutically acceptable formulation includes a compound of Formula (I) or a form, composition or medicament thereof for either human or veterinary use.

The term "CCR2 mediated inflammatory syndrome, disorder or disease" means, without limitation, syndromes, disorders or diseases associated with elevated MCP-1 expression, MCP-1 overexpression or inflammatory conditions that accompany syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression.

The terms "elevated MCP-1 expression" or "MCP-1 overexpression" mean unregulated or up-regulated CCR2 activation as a result of MCP-1 binding.

The term "unregulated" means unwanted CCR2 activation in a multicellular organism resulting in harm (such as discomfort or decreased life expectancy) to the multicellular organism.

The term "up-regulated" means: 1). increased or unregulated CCR2 activity or expression, or 2). increased CCR2 expression leading to unwanted monocyte and lymphocyte migration. The existence of an inappropriate or abnormal level of MCP-1 or activity of CCR2 is determined by procedures well known in the art.

CCR2 mediated inflammatory syndromes, disorders or diseases include, without limitation, ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, invasive staphyloccocia, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach.

The term "uveitis" generically refers to any inflammatory disease involving the eye. Uveitis can be divided into clinically distinct subtypes based on the part of the eye in which the inflammation is present (percentages correspond to patients known to fit these categories): anterior (51%), intermediate (13%), posterior (20%), or panuveitis (16%) and, according to the course of the disease, as either acute (16%), recurring (26%), or chronic (58%). Those with anterior uveitis (~19%) eventually develop irreparable vision damage despite aggressive treatment such as unilateral blindness (9%), bilateral blindness (2%), or unilateral or bilateral vision impairment (8%). Most cases of uveitis are idiopathic, but known causes include infection (e.g., toxoplasmosis, cytomegalovirus, and the like) or development as a component of a systemic inflammatory and/or autoimmune disorder (e.g., juvenile RA, HLA-B27-associated spondyloarthropathies, sarcoidosis, and the like).

Patients with anterior uveitis have MCP-1 present in large quantities in the aqueous humor of the eye. The amount of MCP-1 correlates with the severity of the clinical symptoms and the large number of mononuclear cells present in the cellular infiltrate. Uveitis is also a potential complication resulting from cataract surgery and prophylactic use of antibiotics and corticosteroids is common for such patients. Currently, most patients with anterior uveitis are first treated with topical corticosteroids. Injected or oral steroids may be used in severe cases, or if the disease is recurrent or chronic. If steroids are ineffective, immunosuppressive agents (e.g., cyclosporine, methotrexate, azathioprine, cyclophosphamide, and the like) are used, particularly if the patient's vision is in danger. All of these drugs have potentially severe side-effects, particularly in children, and there is general agreement that there is an unmet medical need for safe and effective steroid substitutes or steroid-sparing agents.

An example of the invention is a method for preventing, treating or ameliorating CCR2 mediated ophthalmic disorders (such as uveitis, allergic conjunctivitis and the like), rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, chronic obstructive pulmonary disease, allergic rhinitis, asthma, allergic asthma, periodontal diseases (such as periodonitis, gingivitis, gum disease and the like) in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or a form, composition or medicament thereof.

Another example of the invention is a method for preventing, treating or ameliorating CCR2 mediated uveitis, wherein uveitis includes, without limitation, acute, recurring or chronic uveitis (such as anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis and the like) in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or a form, composition or medicament thereof.

An example of the invention is a method for preventing, treating or ameliorating CCR2 mediated acute uveitis, recurring uveitis, chronic uveitis, allergic conjunctivitis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, chronic obstructive pulmonary disease, allergic rhinitis, asthma, allergic asthma, periodonitis, gingivitis or gum disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or a form, composition or medicament thereof.

The invention includes a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I) or a form, composition or medicament thereof in a combination product with one or more therapeutic agents.

The term "combination product" refers to a compound of Formula (I) or a form, composition or medicament thereof in admixture with a therapeutic agent and an optional carrier for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease.

The term "therapeutic agent" refers to one or more anti-inflammatory agents (such as a small molecule, antibiotic, corticosteroid, steroid, and the like), anti-infective agents or immunosuppressive agents.

For preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease using a compound of Formula (I) or a form, composition or medicament thereof and a therapeutic agent in a combination product includes, without limitation, co-administration of the compound and the agent, sequential administration of the compound and the agent, administration of a composition containing of the compound and the agent or

simultaneous administration of separate compositions containing of the compound and the agent.

As those skilled in the art will appreciate, the effective amounts of the components comprising the combination product may be independently optimized and combined to achieve a synergistic result whereby the pathology is reduced more than it would be if the components of the combination product were used alone.

Pharmaceutical Compositions

The present invention includes a pharmaceutical composition or medicament comprising one or more of the instant compounds and an optional pharmaceutically acceptable carrier.

The present invention further includes a process for making a pharmaceutical composition or medicament comprising mixing one or more of the instant compounds and an optional pharmaceutically acceptable carrier; and, includes those compositions or medicaments resulting from such a process. Contemplated processes include both conventional and unconventional pharmaceutical techniques.

The composition or medicament may take a wide variety of forms to effectuate mode of administration ocularly, intranasally (by inhalation or insufflation), sublingually, orally, parenterally or rectally including, without limitation, ocular (via a delivery device such as a contact lens and the like), intranasal (via a delivery device), transdermal, topical with or without occlusion, intravenous (both bolus and infusion), injection (intraperitoneally, subcutaneously, intramuscularly, intratumorally, or parenterally) and the like.

The composition or medicament may be in a dosage unit such as a tablet, pill, capsule, powder, granule, liposome, biodegradable carrier, ion exchange resin, sterile solution and the like (facilitating immediate release, timed release, or sustained release), parenteral solution or suspension, metered aerosol or liquid spray, drop, ampoule, auto-injector device or suppository.

Compositions or medicaments suitable for oral administration include solid forms such as pills, tablets, caplets, capsules (each including immediate release, timed release, and sustained release formulations), granules and powders and liquid forms such as solutions, syrups, elixirs, emulsions and suspensions. Forms useful for nasal administration include sterile solutions or nasal delivery devices. Forms useful for ocular administration include sterile solutions or ocular delivery devices. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

Alternatively, the composition or medicament may be administered in a form suitable for once-weekly or once-monthly administration. For example, an insoluble salt of the active

compound may be adapted to provide a depot preparation for intramuscular injection (e.g., a salt form) or to provide a solution for nasal or ocular administration (e.g., a quaternary ammonium salt).

The dosage form (tablet, capsule, powder, solution, contact lens, patch, liposome, ion exchange resin, suppository, teaspoonful, and the like) containing the composition or medicament thereof contains an effective amount of the active ingredient necessary to provide a therapeutic effect.

The composition or medicament may contain an effective amount of from about 0.0001 mg to about 5000 mg (preferably, from about 0.0001 to about 500 mg) of a compound of the present invention or a pharmaceutically acceptable form thereof and may be constituted into any form suitable for the mode of administration selected for a subject in need.

A contemplated range of the effective amount includes from about 0.0001 mg to about 300 mg/kg of body weight per day. A contemplated range also includes from about 0.0003 to about 100 mg/kg of body weight per day. Another contemplated range includes from about 0.0005 to about 15 mg/kg of body weight per day. The composition or medicament may be administered according to a dosage regimen of from about 1 to about 5 times per day.

For oral administration, the composition or medicament is preferably in the form of a tablet containing, e.g., 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, time of administration and concomitant diseases, will result in the need to adjust dosages. The use of either daily administration or post-periodic dosing may be employed.

For ocular administration, the composition is preferably in the form of an ophthalmic composition. The ophthalmic compositions are preferably formulated as eye-drop formulations and filled in appropriate containers to facilitate administration to the eye, for example a dropper fitted with a suitable pipette.

For ocular administration, the composition is preferably in the form of an ophthalmic composition. The ophthalmic compositions are preferably formulated as eye-drop formulations and filled in appropriate containers to facilitate administration to the eye, for example a dropper fitted with a suitable pipette.

Synthetic Methods

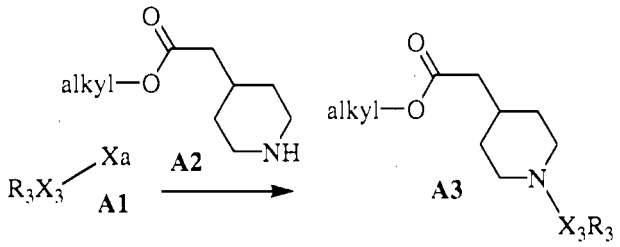
Representative compounds of the present invention can be synthesized in accordance with the general synthetic schemes described below and are illustrated more particularly in the specific examples that follow. The general schemes and specific examples are offered by way of illustration; the invention should not be construed as being limited by the chemical reactions and conditions expressed. The methods for preparing the various starting materials used in the schemes and examples are well within the skill of persons versed in the art.

The following abbreviations and formulas have the indicated meanings:

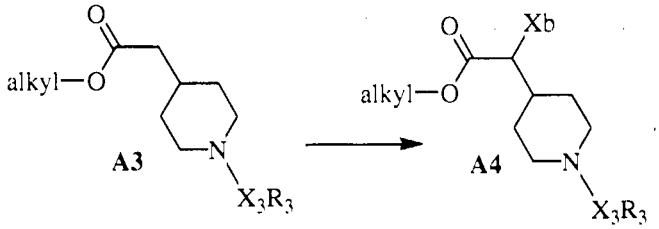
Boc	tert-butoxy carbonyl or t-butoxy carbonyl
Ac_2O	acetic anhydride
CH_2Cl_2 or DCM	methylene chloride or dichloromethane
$CHCl_3$	chloroform
CH_3CN or MeCN	acetonitrile
COPD	chronic obstructive pulmonary disease
Cpd	compound
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethyl formamide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_2O	ether
EtOAc or CH_3CO_2Et	ethylacetate
FLIPR	fluorometric imaging plate reader
$LiAlH_4$	lithium aluminum hydride
LHMDS	lithium bis(trimethylsilyl)amide
LiOH	lithium hydroxide
MeOH/CH_3OH	methanol
MsCl	methanesulfonyl chloride
min(s)/hr(s)/d(s)	minute(s)/hour(s)/day(s)
MS	mass spectrum, refers to data shown as m/z $(M+H)^+$
NH_4Cl	ammonium chloride
N(*i*-Pr)$_2$Et	dissopropylethylamine
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaN_3	sodium azide

NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
psi	pounds per square inch
PTLC	preparative thin layer chromatography
RPMI	Roswell Park Memorial Institute
RT/rt/r.t.	room temperature
$SOCl_2$	thionyl chloride
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane or trimethylsilyl chloride

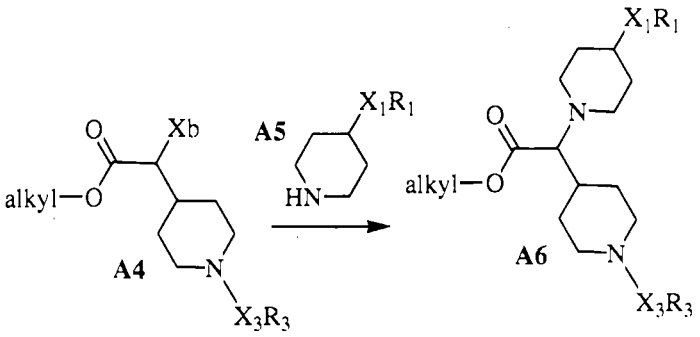
Scheme A



Compound **A1** (wherein Xa is a suitable leaving group such as halogen) is reacted with a solution of Compound **A2** (in a solvent or mixture of solvents such as TEA, methylene chloride and the like) at about 0°C and stirred for about 8-10 hrs at room temperature to give a disubstituted piperidine Compound **A3** (representative of an intermediate compound of Formula (I) wherein X_2 is absent and R_2 is carbonylalkoxy).

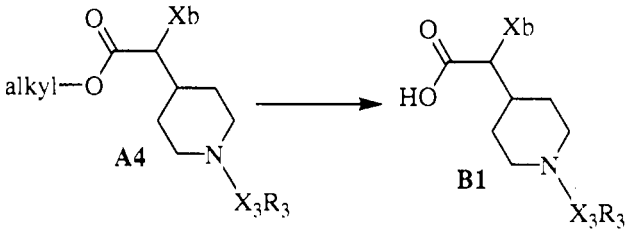


A solution of Compound **A3** is added dropwise to a reagent solution (such as LHMDS in a solvent such as THF and the like) at about -78°C and is stirred for about 3-4 hrs at about -78°C. A reagent (such as TMSCl and the like) is added dropwise to the mixture at about -78°C. The mixture is stirred for about 1 hr, then a halogen reagent solution is added (such as NBS, NCS, bromine and the like in a solvent such as THF and the like) dropwise at about -78°C. The mixture is stirred for about 2 hrs, then transferred to an ice-water bath and stirred for about 30 min. to provide Compound **A4** as a racemate (wherein Xb is a suitable leaving group such as halogen).

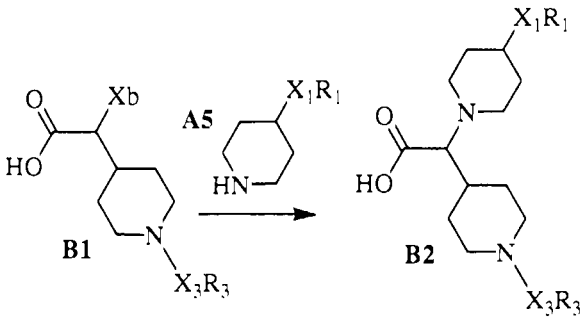


A solution of Compound **A5** (commercially available or prepared according to methods well known to one skilled in the art; in a solvent such as CH_3CN and the like) and TEA are reacted at reflux for about 5 hrs with a solution of Compound **A4** (in a solvent such as acetonitrile and the like) to provide a racemate Compound **A6** (representative of a compound of Formula (I) wherein X_2 is absent and R_2 is carbonylalkoxy). The racemate Compound **A6** may be chromatographically separated using conventional resolution techniques known to those skilled in the art.

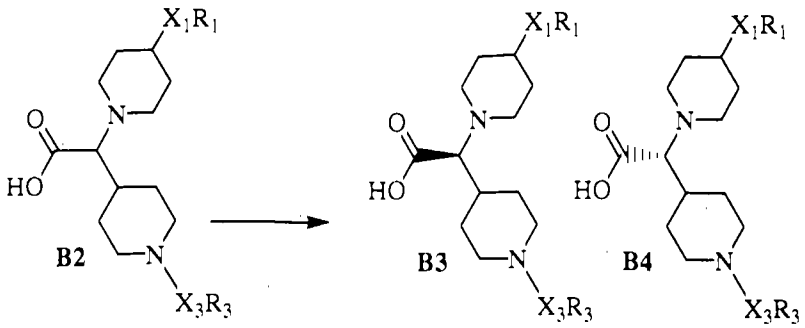
Scheme B



A solution of Compound **A4** (wherein Xb is a suitable leaving group such as halogen) is reacted with an aqueous reagent solution (such as LiOH in a solvent such as THF, MeOH, and the like or mixtures thereof) at about room temperature. The reaction mixture is stirred at about room temperature for about 4 hrs then acidified (using an acid such as HCl and the like) to provide Compound **B1**.



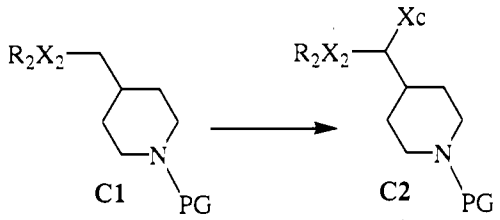
Using the procedure of Scheme A, Compound **B1** is used in place of Compound **A4**. Compound **B1** is reacted with Compound **A5** to provide a racemate Compound **B2** (representative of a compound of Formula (I) wherein X_2 is absent and R_2 is carboxy).



The racemate Compound **B2** may be chromatographically separated using conventional resolution techniques known to those skilled in the art to provide the separate enantiomers Compound **B3** and Compound **B4**.

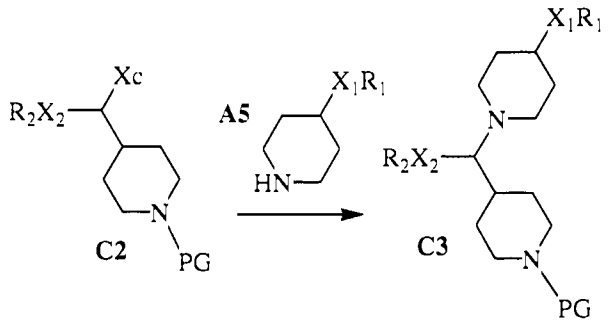
For Compound **B2**, **B3** or **B4**, substitutions with other functional groups may be made using techniques known to those skilled in the art to provide compounds that are representative of the scope of the present invention.

Scheme C



Using the procedure of Scheme A, Compound **C1** (wherein PG is a protecting group, representing that X_3 is carbonylalkoxy and R_3 is not present and the like) is used in place of Compound **A3**.

Compound **C1** is reacted with a halogen reagent solution to provide Compound **C2** (wherein Xc is a suitable leaving group such as halogen) as a racemate. The racemate Compound **C2** may be separated into two enantiomers using conventional resolution techniques known to those skilled in the art.



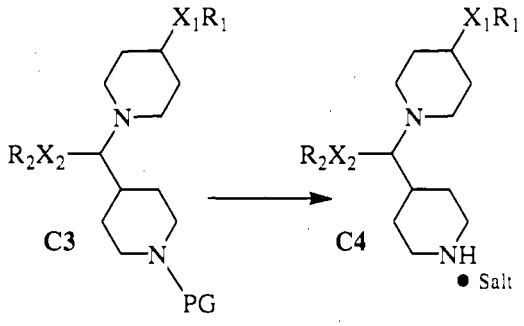
Using the procedure of Scheme A, Compound **C2** is used in place of Compound **A4**.

Compound **C2** is reacted with Compound **A5** to provide Compound **C3** as a racemate.

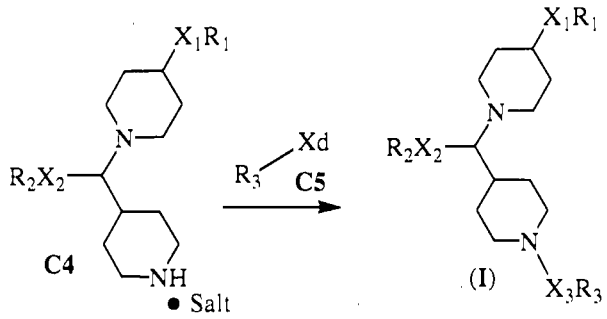
Compound **C3** (wherein X_2 is absent and R_2 is selected from carbonylalkoxy or carboxy) is reacted with a reducing agent (such as lithium aluminum hydride and the like) to provide intermediates wherein X_2 is alkyl and R_2 is hydroxy.

The racemate Compound **C3** may be separated into two enantiomers using conventional resolution techniques known to those skilled in the art.

For Compound **C3**, either before or after resolution, conversions to other functional groups may be made using techniques known to those skilled in the art to provide compounds that are representative of the scope of the present invention.



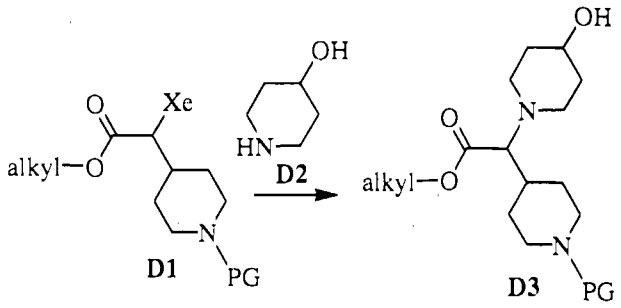
At a suitable point, the protecting group may be removed and converted to a salt form using means known to those skilled in the art to provide an intermediate Compound **C4** made amendable for further substitution.



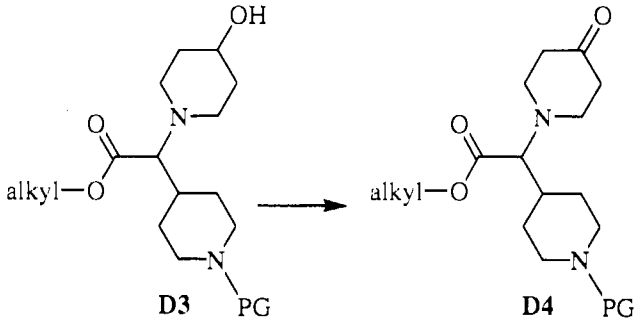
A solution of Compound **C4** (in a suitable solvent such as CH_2Cl_2, CH_3CN, DMF and the like or mixtures thereof) in the presence of a suitable base (such as Et_3N, DIPEA and the like) is reacted under suitable conditions with an Xd substituted Compound **C5** (wherein Xd is a suitable reaction group such as isocyanato, isothiocyanato, *N*-(imino-pyrazol-1-yl-methyl)-aminocarbonyl, acrylylchloride and the like, wherein certain portions of Xd are incorporated into X_3 as a product of the reaction) to provide a compound of Formula (I).

Included within the scope of the present invention are art known functional group transformations for any of the foregoing intermediates or compounds described in the present invention.

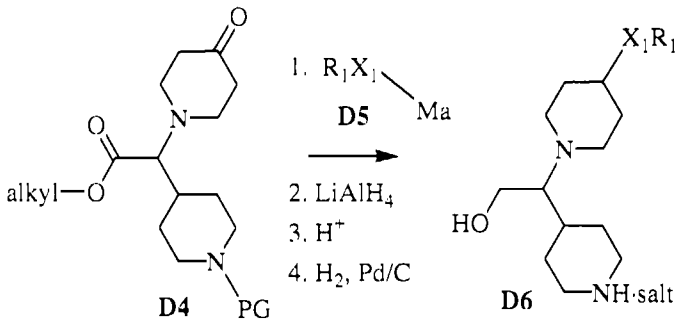
Scheme D



A solution of commercially available Compound **D2** and Compound **D1** (wherein Xe is a suitable leaving group such as halogen) is refluxed (in a solvent such as acetonitrile and the like) in the presence of a reagent (such as DIPEA and the like) to provide Compound **D3** as a racemate.



A solution of Compound **D3** is oxidized (using an oxidizing agent such as oxalyl chloride, DMSO and TEA in CH_2Cl_2 and the like) to provide Compound **D4**.



In Step 1 of the reaction sequence, Compound **D4** is reacted with a Compound **D5** (wherein X_1 is absent or alkyl and Ma represents a magnesium halide or other metal or metal halide group and the like) to provide an R_1 substituted intermediate (wherein a tertiary hydroxyl group is present at the point of attachment of X_1R_1 on the piperidine ring).

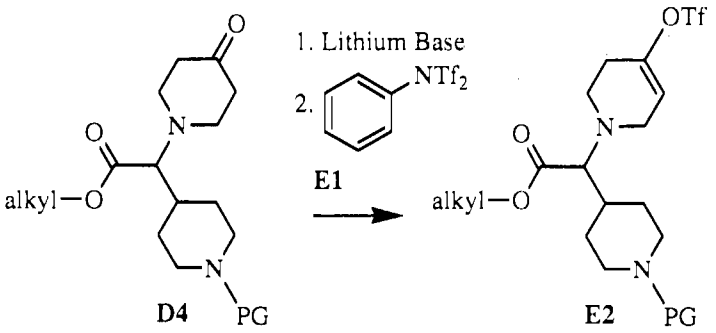
In Step 2 of the reaction sequence, the Compound **D4** R_2 ester group is reacted with a reducing reagent (such as lithium aluminum hydride and the like), whereby the ester is converted to a hydroxymethyl group.

In Step 3 of the reaction sequence, the Compound **D4** protecting group is removed and converted to an acid salt form and the tertiary hydroxyl is simultaneously eliminated with an acid (such as trifluoroacetic acid or hydrochloric acid and the like).

In Step 4 of the reaction sequence, a Compound **D4** double bond resulting from the tertiary hydroxyl elimination is hydrogenated in the presence of a suitable catalyst (such as palladium on carbon and the like).

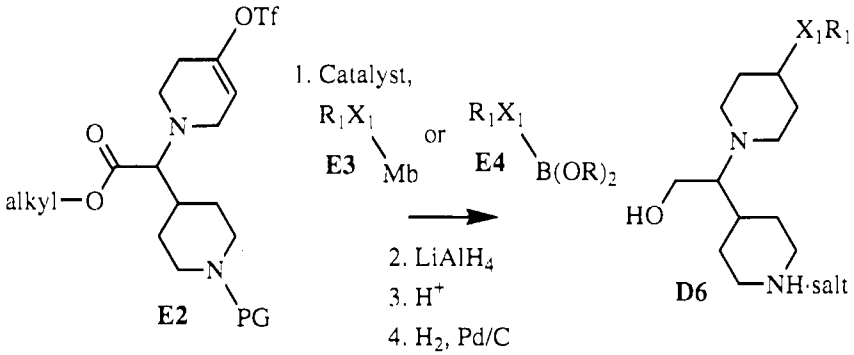
Using the procedure of Scheme C and Compound **D6** in place of Compound **C4** enables one skilled in the art to prepare other compounds representative of the scope of the present invention.

Scheme E



In Step 1 of the reaction sequence, Compound **D4** is enolized using a suitable lithiated amine base (such as LHMDS and the like in a solvent such as THF and the like) at –78°C.

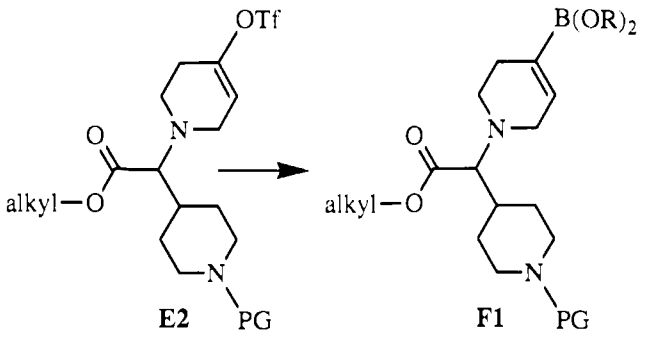
In Step 2 of the reaction sequence, the enolized intermediate is reacted with *N*-phenyl-trifluoromethanesulfonimide to provide the vinyl triflate Compound **E2**.



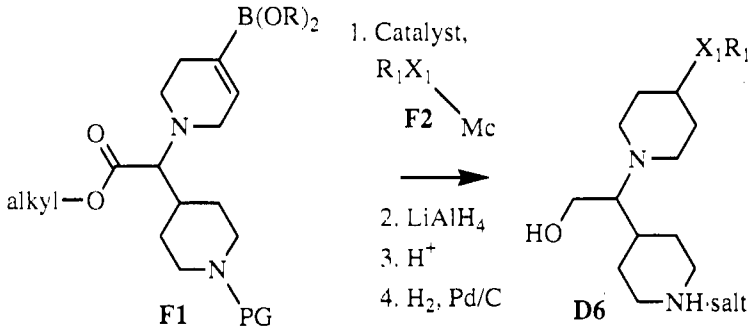
In Step 1 of the reaction sequence, Compound **E2** is coupled with either Compound **E3** (wherein X_1 is absent or $-CH_2-$ and Mb represents a zinc halide or other metalated group and the like) or Compound **E4** (wherein X_1 is absent and $B(OR)_2$ represents a boronic ester or acid group and the like) in the presence of a transition metal catalyst (such as tetrakis (triphenylphosphine)palladium and the like) to provide an intermediate product which is then

carried forward in Reactions 2-4, according to the procedure of Scheme D, to provide Compound **D6** (wherein X_1 is as defined respectively for Compound **E3** or Compound **E4**).

Scheme F



Compound **E2** is reacted with a diborane [such as 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (also referred to as bis-pinacolato-diboron) and the like] and a palladium catalyst (such as dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium and the like) to provide Compound **F1**.

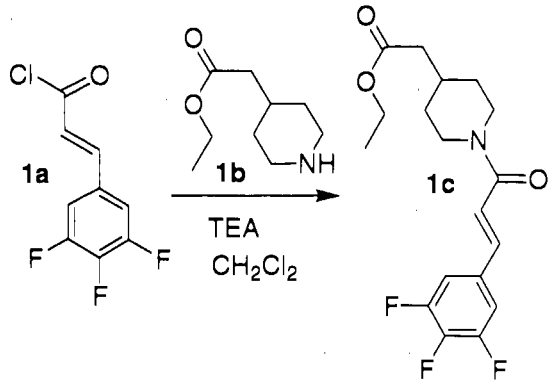


In Reaction 1, Compound **F1** is coupled with Compound **F2** (wherein X_1 is absent and Mc represents triflate, halide and the like) in the presence of a transition metal catalyst (such as tetrakis (triphenylphosphine)palladium and the like) to provide an intermediate product which is then carried forward in Reactions 2-4, according to the procedure of Scheme D, to provide Compound **D6** (wherein X_1 is absent).

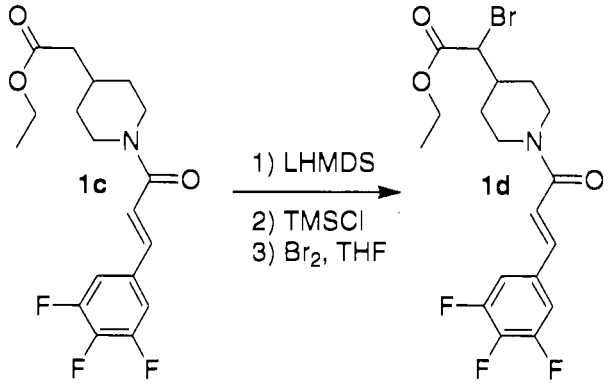
The invention is further defined by reference to the following examples, which are merely intended to be illustrative and not limiting.

Example 1

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid (Cpd **6**)

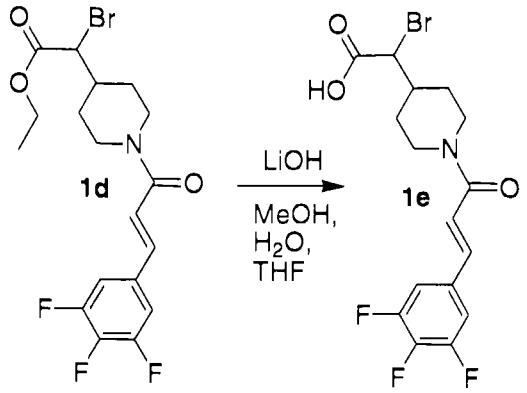


3-(3,4,5-trifluoro-phenyl)-acryloyl chloride Compound **1a** (1.50 g, 6.80 mmol) was added to the solution of piperidin-4-yl-acetic acid ethyl ester Compound **1b** (1.28 g, 7.49 mmol) and TEA (triethylamine) (1.89 mL, 13.56 mmol) in CH_2Cl_2 (30 mL) at 0°C. The mixture was stirred overnight at room temperature, diluted with methylene chloride (20 mL) and washed with 1 N HCl (10 mL) and water (10 mL), then dried over Na_2SO_4 and concentrated. The crude product was purified by chromatography (50% EtOAc/hexane) to give {1-[3,4,5-trifluoro-phenyl)acryloyl]-piperidin-4-yl}-acetic acid ethyl ester Compound **1c** (1.80 g, 75% yield). MS: m/z 356 $(M+H)^+$.

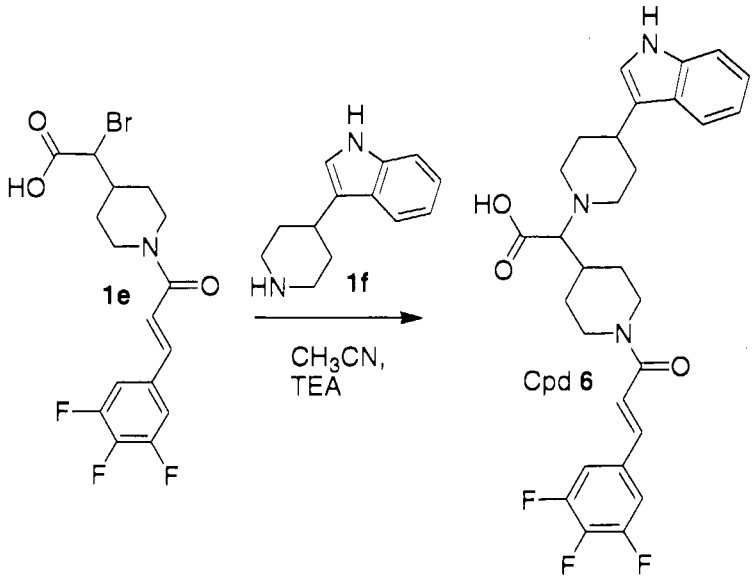


To a solution of LHMDS in THF (1.0 M, 4.9 mL) at -78°C was added dropwise a solution of Compound **1c** (0.96g, 2.70 mmol) in THF (8 mL). The resulting reaction mixture was stirred at -78°C for 3.5 hrs. TMSCl (0.62 mL, 4.88 mmol) was added dropwise to the reaction mixture at -78°C, then the mixture was stirred for 1 hr and Br_2 (0.17 mL, 3.3 mmol) was added dropwise at the same temperature. The reaction mixture was stirred at -78°C for 2 hrs, then stirred in an ice-water bath for 0.5 hr. The reaction mixture was poured into a mixture of EtOAc (100 mL) and $NaHCO_3$ (100 mL). The organic layer was washed with water (1×100 mL) and brine (1×100 mL), then dried over Na_2SO_4, filtered and concentrated. The resulting

crude product was purified on a silica gel column with 50% EtOAc/hexane to give bromo-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid ethyl ester Compound **1d** (0.7 g, 59.8%). MS: m/z 434 $(M+H)^+$.



To a solution of Compound **1d** (0.7 g, 1.62 mmol) in MeOH (18 mL) and THF (6 mL) at room temperature was added LiOH (0.2 g, 8.3 mmol) in water (6 mL). The resulting reaction mixture was stirred at room temperature for 4 hrs and concentrated by evaporating the MeOH and THF solvents. The aqueous solution was acidified to pH 1 with 1M HCl solution and extracted with EtOAc. The organic layer was washed with brine (1×100 mL), dried over Na_2SO_4, then filtered and concentrated to give bromo-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid Compound **1e** (0.64 g, 98%). MS: m/z 406 $(M+H)^+$.



To a solution of Compound **1e** (0.26g, 0.64 mmol) in acetonitrile (10 mL) was added 3-piperidin-4-yl-1*H*-indole Compound **1f** (152 mg, 0.64 mmol) and TEA (0.18 mL, 1.29 mmol). The resulting reaction mixture was refluxed for 5 hrs, then concentrated and cooled to provide a white precipitate. The precipitate was washed with EtOAc and water to give Compound **6** (0.23g, 67%) as a racemate. MS *m/z* 526 $(M+H)^+$. ^1H NMR (DMSO-d6, 400 MHz) δ 12.11 (br

s, 1H), 10.85 (s, 1H), 7.81 (q, J = 7.2 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.37 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.04 (m, 2H), 6.95 (q, J = 7.0 Hz, 1H), 4.47 (m, 1H), 4.31 (m, 1H), 3.10 (m, 1H), 2.96 (d, J = 10.8 Hz, 1H), 2.88 (m, 2H), 2.65 (m, 3H), 2.35 (m, 1H), 2.06 (m, 1H), 1.94 (m, 3H), 1.69 (m, 1H), 1.61 (m, 2H), 1.09 (m, 2H).

Using the procedure of Example 1 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
1	[4-(4-chloro-phenyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	535
2	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(4-methoxy-phenyl)-piperidin-1-yl]-acetic acid	499
4	[4-(4-chloro-phenyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	521
5	[4-(4-methoxy-phenyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	517
7	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	508
8	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	526
9	[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	544
10	(4-indol-1-yl-piperidin-1-yl)-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	526
11	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-ylmethyl)-piperidin-1-yl]-acetic acid	522
12	[4-(1H-indol-3-ylmethyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	540
15	[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	542
16	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	524
17	[4-(5-acetylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	583
18	{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	540
19	{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	558
22	{1-[(2*E*)-3-(3,4-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	508
23	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	540
24	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	526

Cpd	Name	MS
25	[4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	542
26	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	538
27	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-phenyl-acryloyl]-piperidin-4-yl}-acetic acid	472
29	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	601
30	[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	556
31	[4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	560
34	{1-[(2*E*)-3-(4-chloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	506
35	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	540
36	{1-[(2*E*)-3-(3-bromo-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	568
37	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-methoxy-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	502
38	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	538
39	{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	558
41	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(4-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	538
42	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	538
46	[4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	574
47	{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	570
53	[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	619
59	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-nitro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	517
60	{1-[(2*E*)-3-(4-bromo-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	550
61	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-p-tolyl-acryloyl]-piperidin-4-yl}-acetic acid	486
62	{1-[(2*E*)-3-(3-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	490
63	{1-[(2*E*)-3-(3,4-dimethoxy-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	532

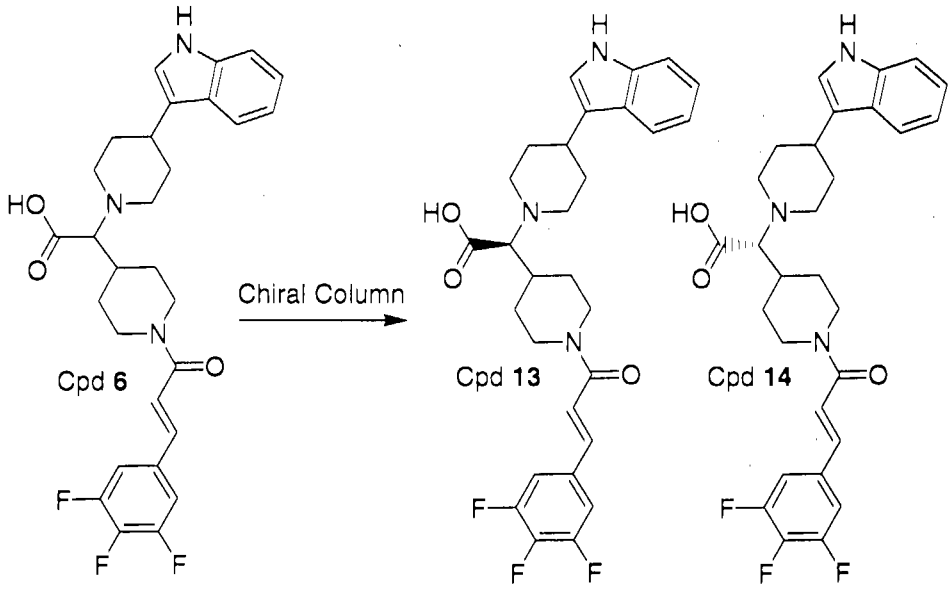
Cpd	Name	MS
70	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-m-tolyl-acryloyl]-piperidin-4-yl}-acetic acid	486
71	{1-[(2*E*)-3-(3-bromo-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	550
72	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-methoxy-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	502
74	{1-[(2*E*)-3-(3-fluoro-4-methyl-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	504
75	{1-[(2*E*)-3-(3-fluoro-4-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	558
76	{1-[(2*E*)-3-(3-chloro-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	524
77	{1-[(2*E*)-3-(4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	490
81	[4-(1H-pyrrol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	641
82	[4-(5-tert-butoxycarbonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	619
83	[4-(6-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	541
92	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-nitro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	517
93	{1-[(2*E*)-3-(3-chloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	506
103	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-thiophen-2-yl-acryloyl]-piperidin-4-yl}-acetic acid	478
104	[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-thiophen-3-yl-acryloyl]-piperidin-4-yl}-acetic acid	478
108	[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	556
114	{1-[2-(3,4-dichloro-phenoxy)-acetyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	544
115	{1-[3-(3,4-dichloro-phenyl)-propionyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	542
145	4-[1-(carboxy-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-methyl)-piperidin-4-yl]-benzoic acid methyl ester	527
146	3-[1-(carboxy-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-methyl)-piperidin-4-yl]-1H-indole-5-carboxylic acid methyl ester	584
147	3-[1-(carboxy-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-methyl)-piperidin-4-yl]-1H-indole-5-carboxylic acid	570
151	[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	527
177	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indazol-3-yl)-piperidin-1-yl]-acetic acid	509

Cpd	Name	MS
178	[4-(5-amino-1H-pyrrolo[3,2-b]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	542
179	[4-(5-amino-1H-pyrrolo[2,3-c]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	542
204	[4-(2-methyl-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	540
206	[4-(4-methanesulfonylamino-phenyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	580
207	[4-(1H-pyrrolo[3,2-b]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	527
211	[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	544

Example 2

(*S*)-{[4-(1H-indol-3-yl)-piperidin-1-yl]}-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid (Cpd **13**)

(*R*)-{[4-(1H-indol-3-yl)-piperidin-1-yl]}-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid (Cpd **14**)



The racemate [4-(1*H*-indol-3-yl)-piperidin-1-yl]-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid Compound **6** (255 mg, 0.49 mmol) was separated into two enantiomers Compound **13** (110 mg, 86.3%) and Compound **14** (110 mg, 86.3%) with a chiralpak AD column (eluted with CH_3CN/CH_3OH 85 /15).

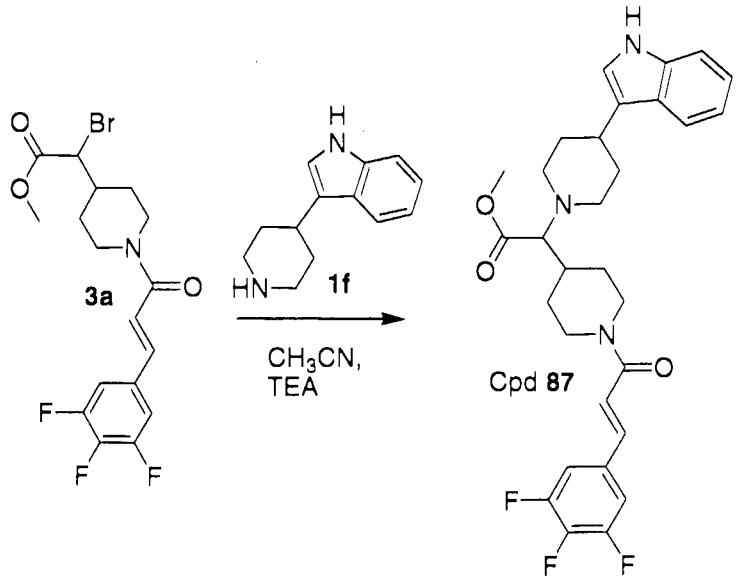
Compound **13**: MS *m/z* 526 $(M+H)^+$, 548 $(M+Na)^+$. ^1H NMR (DMSO-d6, 400 MHz) δ 11.95 (br s, 1H), 10.78 (s, 1H), 7.81 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.37 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.04 (m, 2H), 6.95 (q, J = 7.0 Hz, 1H), 4.47 (m, 1H), 4.31 (m, 1H), 3.10 (m,

1H), 2.90 (m, 3H), 2.65 (m, 3H), 2.35 (m, 1H), 2.06 (m, 1H), 1.94 (m, 3H), 1.69 (m, 1H), 1.61 (m, 2H), 1.09 (m, 2H).

Compound **14**: MS *m/z* 526 $(M+H)^+$, 548 $(M+Na)^+$. ^1H NMR (DMSO-d6, 400 MHz) δ 12.02 (br s, 1H), 10.73 (s, 1H), 7.81 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.37 (m, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.04 (m, 2H), 6.95 (q, J = 7.0 Hz, 1H), 4.46 (m, 1H), 4.31 (m, 1H), 3.10 (m, 1H), 2.90 (m, 3H), 2.65 (m, 3H), 2.35 (m, 1H), 2.06 (m, 1H), 1.94 (m, 3H), 1.69 (m, 1H), 1.61 (m, 2H), 1.09 (m, 2H).

Example 3

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid methyl ester (Cpd **87**)



The procedure of Example 1 and piperidin-4-yl-acetic acid methyl ester was used in place of piperidin-4-yl-acetic acid ethyl ester Compound **1f** to provide bromo-{1-[(2*E*)3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid methyl ester Compound **3a**.

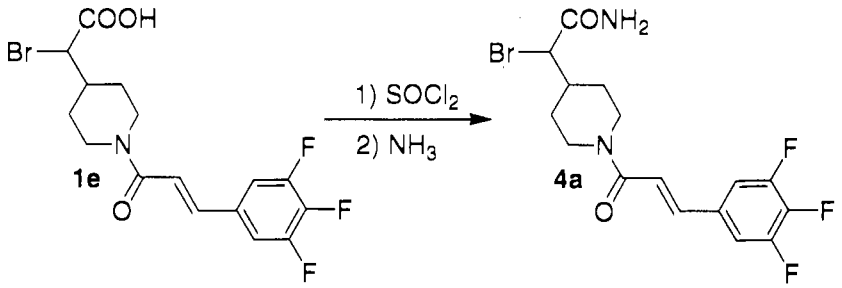
3-piperidin-4-yl-1*H*-indole Compound **1f** (1.0 g, 5.0 mmol) and TEA (0.6 g, 5.9 mmol) were added to a solution of Compound **3a** (2.1 g, 5.0 mmol) in acetonitrile (70 mL). The mixture was refluxed for 48 hrs and then concentrated *in vacuo*. The residue was chromatographed (5% $CH_3OH/CHCl_3$) to give Compound **87** (1.5 g, 56%). MS *m/z* 540 $(M+H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (br s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 15.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.10 (m, 4H), 6.96 (br s, 1H), 6.81 (m, 1H), 4.69 (m, 1H), 4.08 (m, 1H), 3.76 (s, 3H), 3.13 (m, 1H), 2.93 (m, 2H), 2.82 (m, 3H), 2.59 (m, 1H), 2.29 (m, 1H), 2.08 (m, 4H), 1.79 (m, 1H), 1.65 (m, 2H), 1.21 (m, 2H).

Using the procedure of Example 3 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

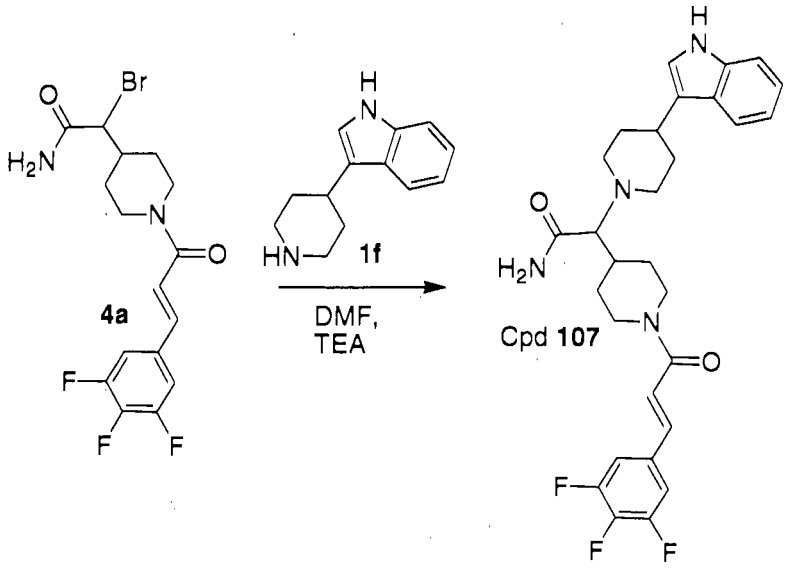
Cpd	Name	MS
3	{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(4-methoxy-phenyl)-piperidin-1-yl]-acetic acid methyl ester	513
118	[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid methyl ester	570
152	[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid ethyl ester	555

Example 4

2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetamide (Cpd **107**)



To a solution of bromo-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid Compound **1e** (0.38 g, 0.93 mmol) in CH_2Cl_2 (4 mL) was added $SOCl_2$ (1 mL). The resulting reaction mixture was refluxed for 3 hrs, the concentrated *in vacuo* to give an acid chloride intermediate (0.39 g, 98.9%). A solution of the intermediate (0.39g, 0.92 mmol) in acetone (10 mL) was added dropwise to a solution of ammonium hydroxide (39 mL). The reaction mixture was stirred at room temperature for 2 hrs and extracted with EtOAc (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, then filtered and concentrated to give 2-bromo-2-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetamide Compound **4a** (0.38 g, 94%). MS *m/z* 405 $(M+H)^+$.



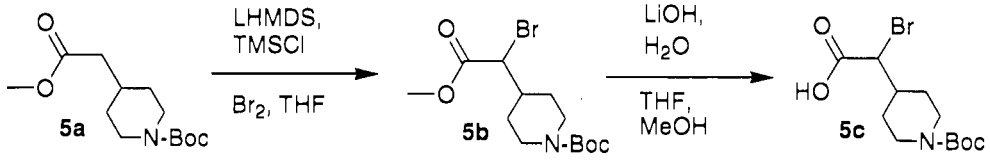
To a solution of Compound **4a** (25 mg, 0.065 mmol) in DMF (4 mL) was added 3-piperidin-4-yl-1*H*-indole Compound **1f** (13 mg, 0.065 mmol) and TEA (0.05 mL, 0.36 mmol). The reaction mixture was refluxed for 4 hrs and then concentrated *in vacuo*. The residue was purified using preparative TLC (70% CH_3CO_2Et/hexane) to give Compound **107** (8 mg, 25%). MS *m/z* 525 $(M+H)^+$; ^1H NMR (CD_3OD, 300 MHz) δ: 7.38-7.61 (m, 5H), 7.18-7.31 (m, 2H), 6.92-7.10 (m, 4H), 4.62 (m, 1H), 4.39 (m, 1H), 4.12 (m, 1H), 3.79 (m, 1H), 3.10-3.40 (m, 4H), 2.79 (m, 1H), 2.61 (m, 1H), 2.08-2.39 (m, 4H), 1.81 (m, 2H), 1.25-1.49 (m, 2H).

Using the procedure of Example 4 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
227	2-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetamide	526

Example 5

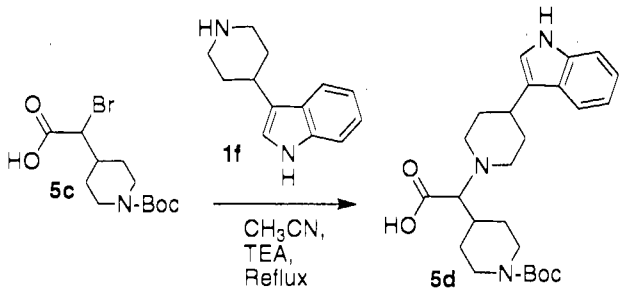
[1-(4-fluoro-3-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid (Cpd **102**)



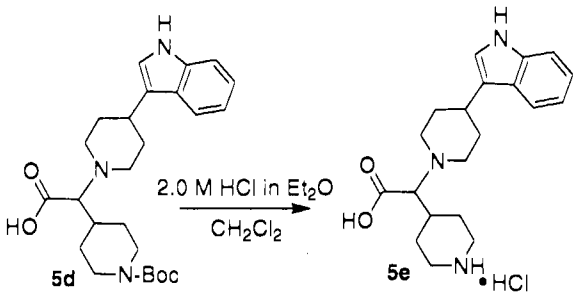
A solution of 4-methoxycarbonylmethyl-piperidine-1-carboxylic acid tert-butyl ester Compound **5a** (1.0 g, 3.9 mmol) in THF (5 mL) was added to LHMDS (1.0 M in THF) (7.0 mL, 7.0 mmol) at -78°C and the reaction mixture was stirred at -78°C for 3 hrs. TMSCl (0.89 mL, 7.0 mmol) was added dropwise and the mixture was stirred for 1 hr at -78°C then Br_2 (0.24 mL, 4.7 mmol) was added dropwise. The mixture was stirred at -78°C for 2 hrs, then allowed

to warm to 0°C and stirred for an additional 30 min. The mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution, then washed with H_2O. The organics were dried over Na_2SO_4, then the drying agent was filtered and solvent removed *in vacuo* to yield a yellow solid. The crude product was purified by flash column chromatography (50% EtOAc/hexane) to yield 4-(bromo-methoxycarbonyl-methyl)-piperidine-1-carboxylic acid tert-butyl ester Compound **5b** as a pale yellow oil (1.0 g, 77%). MS *m/z* 358 $(M+Na)^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (br, 2H), 4.01 (d, J = 8.5 Hz, 1H), 3.80 (s, 3H), 2.65-2.78 (br s, 2H), 2.04 (m, 2H), 1.61 (m, 1H), 1.45 (s, 9H), 1.21 (m, 2H).

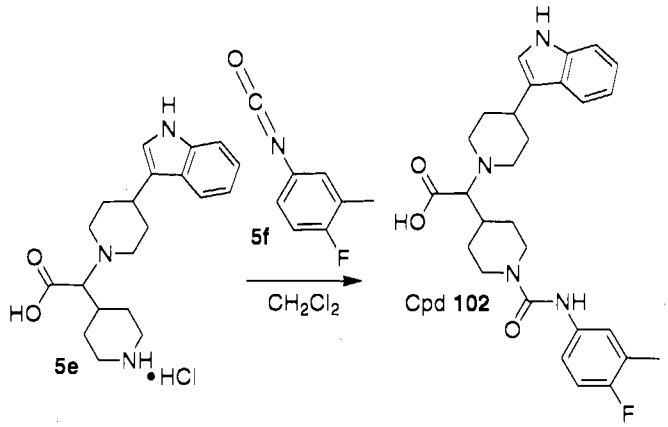
An aqueous LiOH solution (0.624 g, 14.87 mmol in 7 mL H_2O) was added to a solution of Compound **5b** (1.0 g, 2.97 mmol) in MeOH (21 mL) and THF (7 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo to provide a white solid, which was acidified with 1 N HCl. A crude product was extracted with ethyl acetate and the organics were washed with brine and dried over Na_2SO_4. The drying agent was filtered and the solvent removed *in vacuo*, yielding 4-(bromo-carboxy-methyl)-piperidine-1-carboxylic acid tert-butyl ester Compound **5c** (0.663 g, 66%) as a white solid. The product (>90% purity by NMR) was used in the next step without further purification. MS *m/z* 344; 346 $(M+Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 4.0-4.2 (m, 3H), 2.6-2.8 (br s, 2H), 1.9-2.1 (m, 2H), 1.64-1.75 (m, 1H), 1.45 (s, 9H), 1.2-1.3 (m, 2H).



A solution of Compound **5c** (0.335 g, 1.040 mmol), 3-piperidin-4-yl-1*H*-indole Compound **1f** (0.208 g, 1.040 mmol) and TEA (0.29 mL, 2.080 mmol) in CH_3CN was refluxed for 5 hrs. The solvent was removed *in vacuo* to provide a yellow solid. The product was washed with a minimal amount of methanol to removing residual starting material to obtain 4-{carboxy-[4-(1H-indol-3-yl)-piperidin-1-yl]-methyl}-piperidine-1-carboxylic acid tert-butyl ester Compound **5d** (27%, 0.459 g) as a white solid. MS *m/z* 442 $(M+H)^+$.



2.0 M HCl in Et_2O (5 mL, 10 mmol) was added to a solution of Compound **5d** (0.125 g, 0.283 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* to provide a tan solid product. The product was washed with CH_2Cl_2 to obtain [4-(1*H*-indol-3-yl)-piperidin-1-yl]-piperidin-4-yl-acetic acid Compound **5e** (0.108 g, 100%) as a tan solid. MS *m/z* 342 $(M+H)^+$.



To a solution of Compound **5e** (28.8 mg, 0.07 mmol) and Et_3N (0.02 mL, 0.14 mmol) in CH_2Cl_2 at 0°C was added 1-fluoro-4-isocyanato-2-methyl-benzene Compound **5f** (10.6 mg, 0.07 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo*, leaving an off-white solid. The solid was washed with H_2O, which was decanted and then with 50% EtOAc/ hexane, which was decanted to provide Compound **102** (76%, 0.026 g) as an off-white solid. MS *m/z* 493 $(M+H)^+$; ^1H NMR (400 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.40 (s, 1H), 7.55 (m, 1H), 7.35 (m, 2H), 7.25 (m, 1H), 7.05 (m, 4H), 4.15 (m, 2H), 2.60-3.05 (m, 8H), 2.20 (s, 3H), 1.85-2.05 (m, 4H), 1.65 (m, 5H), 1.15 (m, 2H).

Using the procedure of Example 5 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

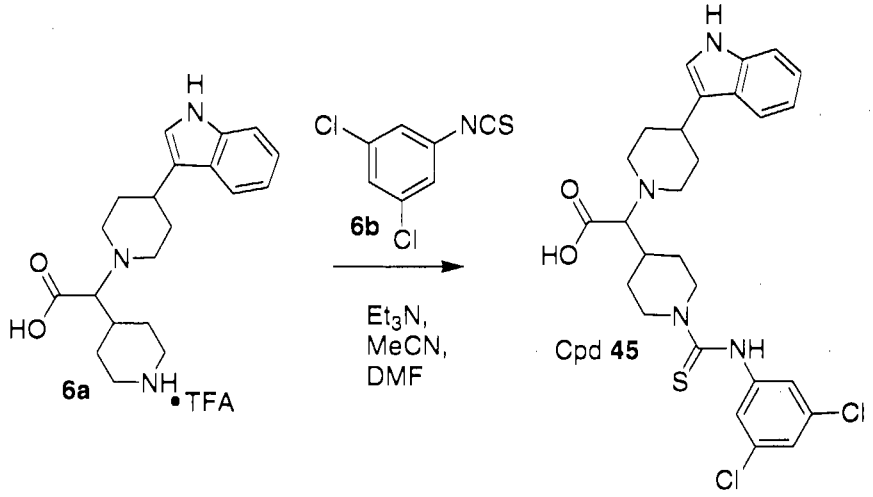
Cpd	Name	MS
20	[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	529

Cpd	Name	MS
28	[1-(3,5-difluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	497
32	[4-(1H-indol-3-yl)-piperidin-1-yl]-(1-phenylcarbamoyl-piperidin-4-yl)-acetic acid	461
33	[1-(3,5-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	529
40	[1-(3,4-difluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	497
48	[1-(3-chloro-4-fluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	513
49	[1-(3-chloro-4-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	509
57	[1-(4-chloro-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	563
58	[1-(4-fluoro-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	547
65	[1-(3-fluoro-5-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	547
66	[1-(3,4-dimethoxy-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	521
67	[1-(3-chloro-4-methoxy-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	525
68	4-[(4-{carboxy-[4-(1H-indol-3-yl)-piperidin-1-yl]-methyl}-piperidine-1-carbonyl)-amino]-benzoic acid methyl ester	519
69	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-methoxy-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	491
84	[1-(3,4-dichloro-benzylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	543
85	[1-(3-bromo-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	539
86	[1-(3-chloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	495
88	[1-(4-chloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	495
89	[1-(4-bromo-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	539
90	[1-(4-fluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	479
91	[1-(3-fluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	479
94	[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	559
95	[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	559

Cpd	Name	MS
96	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	529
97	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	529
98	[4-(1H-indol-3-yl)-piperidin-1-yl]-(1-m-tolylcarbamoyl-piperidin-4-yl)-acetic acid	475
99	[4-(1H-indol-3-yl)-piperidin-1-yl]-(1-p-tolylcarbamoyl-piperidin-4-yl)-acetic acid	475
100	[1-(3,4-dimethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	489
101	[1-(4-bromo-3-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	553
105	[1-(3-fluoro-4-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	493
106	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-methyl-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	543
109	[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-acetic acid	622
110	[1-(2,3-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	529
111	[1-(2,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	529
117	[1-(4-chloro-2-fluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	513
125	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(2,3,4-trifluoro-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	515
126	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(2,4,5-trichloro-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	563
127	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-methylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	507
135	[1-(3,5-dimethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	489
136	[1-(3,5-bis-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	597
142	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	561
143	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethoxy-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	545
144	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-methylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid	507

Example 6

[1-(3,5-dichloro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid (Cpd **45**)



A solution of a TFA salt of [4-(1*H*-indol-3-yl)-piperidin-1-yl]-piperidin-4-yl-acetic acid Compound **6a** (35 mg, 0.076 mmol, 1 eq) and Et_3N (32 µL, 0.23 mmol, 3 eq) in DMF (1 mL) and MeCN (1 mL) was treated with 3,5-dichloro-phenylisothiocyanate Compound **6b** (22 mg, 0.11 mmol, 1.5 eq). The mixture was stirred for 16 hrs and then diluted with MeCN resulting in the formation of a tan precipitate. The precipitate was collected by filtration, washed with MeCN and dried to provide Compound **45** (30 mg, 73%) as a tan solid. MS: m/z 545 $(M+H)^+$; ^1H NMR (d^6-DMSO, 400 MHz) δ: 10.76 (1H, s), 9.41 (1H, s), 7.55 (1H, d, J=7.7 Hz), 7.43 (1H, s), 7.43 (1H, s), 7.32 (1H, d, J=8.3 Hz), 7.27 (1H, app t, J=1.6 Hz), 7.08 (1H, d, J=2.0 Hz), 7.05 (1H, app t, J=6.9 Hz), 6.95 (1H, app t, J=7.4 Hz), 4.70 (2H, m), 3.14 (3H, m), 2.93 (3H, m), 2.75 (1H, m), 2.62 (1H, app t, J=12.8 Hz), 2.36 (1H, app t, J=11.2 Hz), 2.13 (1H, m), 1.95 (3H, m), 1.73 (1H, m), 1.63 (2H, m), 1.26 (2H, m).

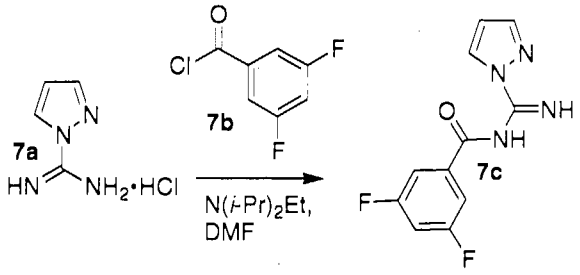
Using the procedure of Example 6 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
43	[4-(1H-indol-3-yl)-piperidin-1-yl]-(1-phenylthiocarbamoyl-piperidin-4-yl)-acetic acid	477
44	[1-(2,4-difluoro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	513
55	[1-(3,5-difluoro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	513
56	[1-(3-bromo-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	555
64	[1-(3,4-dichloro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	545

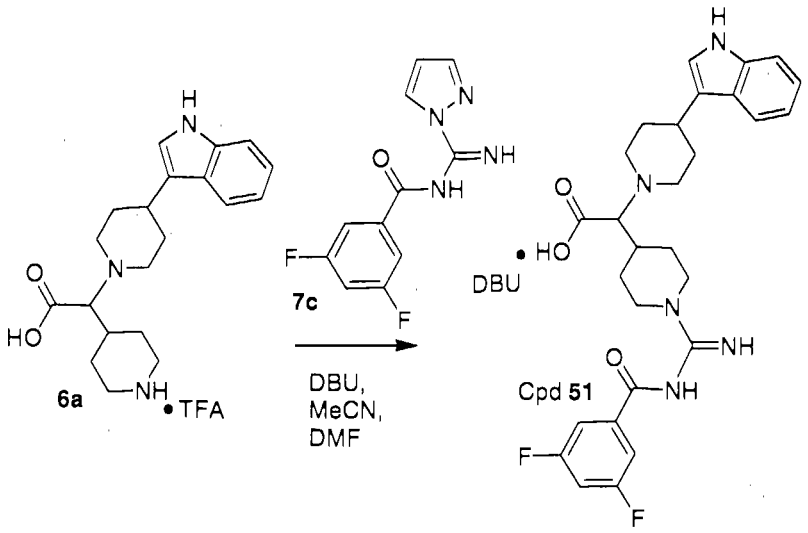
Cpd	Name	MS
78	[4-(1H-indol-3-yl)-piperidin-1-yl]-(1-p-tolylthiocarbamoyl-piperidin-4-yl)-acetic acid	491
79	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-trifluoromethyl-phenylthiocarbamoyl)-piperidin-4-yl]-acetic acid	545
80	[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethyl-phenylthiocarbamoyl)-piperidin-4-yl]-acetic acid	545

Example 7

{1-[(3,5-difluoro-benzoylamino)-imino-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid (Cpd **51**)



DIPEA (348 µL, 2.00 mmol, 2 eq) was added to a solution of pyrazole-1-carboxamidine Compound **7a** (146 mg, 1.00 mmol, 1 eq) in DMF (2 mL), then 3,5-difluoro-benzoyl-chloride Compound **7b** (126 µL, 1.00 mmol, 1 eq) was added with stirring. After 48 hrs, the mixture was poured into EtOAc and a dilute NH_4Cl solution. The aqueous layer was removed, the organic layer was washed twice with brine then dried over anhydrous Na_2SO_4. The solid was removed by filtration and the filtrate was evaporated to provide an off-white solid. The crude product was heated in a minimal amount of 3:2:1 CH_2Cl_2:hexanes:EtOAc and then cooled to room temperature. A precipitate formed and was collected by filtration to provide 3,5-difluoro-*N*-(imino-pyrazol-1-yl-methyl)-benzamide Compound **7c** (105 mg, 42%) as a white solid. MS *m/z* 251 $(M+H)^+$.



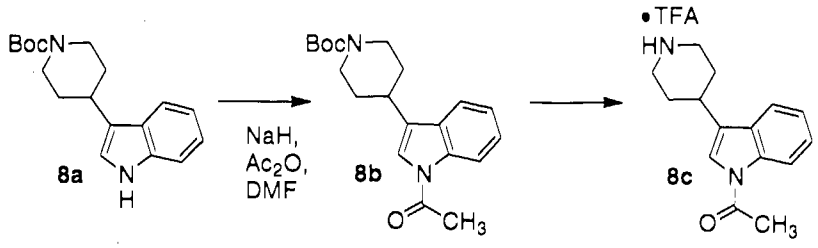
A solution of the TFA salt of [4-(1*H*-indol-3-yl)-piperidin-1-yl]-piperidin-4-yl-acetic acid Compound **6a** (34 mg, 0.075 mmol, 1 eq) and DBU (26 μL, 0.17 mmol, 2.2 eq) in DMF (1 mL) and MeCN (1 mL) was treated with Compound **7c** (19 mg, 0.075 mmol, 1 eq) and stirred for 24 hrs. The reaction was then diluted with MeCN, resulting in the formation of a tan precipitate. The precipitate was collected by filtration, washed with MeCN and dried to provide a DBU salt of Compound **51** (28 mg, 55%) as a tan solid. MS *m/z* 524 $(M+H)^+$; 546 $(M+Na)^+$; ^{1}H NMR (d^6-DMSO, 400 MHz) δ: 10.76 (1H, s), 7.63 (1H, d, J=8.8 Hz), 7.62 (1H, d, J=8.6 Hz), 7.51 (1H, d, J=7.8 Hz), 7.33 (1H, m), 7.31 (1H, d, J=7.9 Hz), 7.01-7.05 (2H, m), 6.94 (1H, app t, J=7.2 Hz), 3.49 (2H, m), 3.42 (2H, m), 3.24 (2H, m), 2.94-2.80 (3H, m), 2.77-2.59 (5H, m), 2.49 (obscured)-2.40 (1H, m), 1.99-1.82 (6H, m), 1.74 (1H, m), 1.70-1.48 (8H, m), 1.08 (2H, m).

Using the procedure of Example 7 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
50	{1-[(3,4-dichloro-benzoylamino)-imino-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	556
52	{1-[imino-(3,4,5-trifluoro-benzoylamino)-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	542
54	{1-[(3-fluoro-benzoylamino)-imino-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	506
73	{1-[imino-(3-trifluoromethyl-benzoylamino)-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid	556

Example 8

[4-(1-acetyl-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid (Cpd **21**)



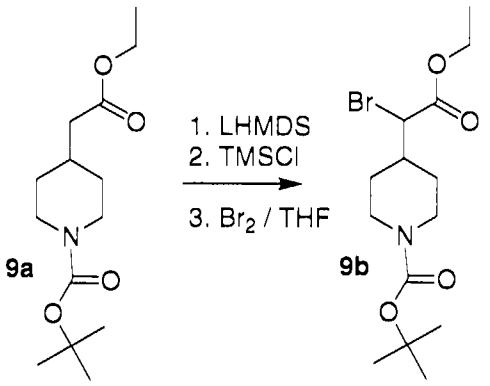
A solution of 4-(1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester Compound **8a** (95 mg, 0.32 mmol, 1 eq) in DMF (3 mL) was treated with NaH (17 mg, 0.35 mmol, 1.1 eq) and stirred for 30 min. Acetic anhydride (33 μL, 0.35 mmol, 1.1 eq) was added and the reaction mixture was stirred for 3 hrs. The mixture was partitioned between EtOAc and water and the aqueous layer was discarded. The organic layer was washed with brine, dried over Na_2SO_4, then filtered and the filtrate was evaporated. Purification of the crude residue by silica gel chromatography (2:1 hexanes:EtOAc) provided 4-(1-acetyl-1*H*-indol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester Compound **8b** (98 mg, 89%) as an oil. MS: m/z 365 $(M+Na)^+$.

A solution of Compound **8b** (59 mg, 0.17 mmol, 1 eq) in CH_2Cl_2 (1.5 mL) was cooled to 0°C and treated with TFA (0.5 mL) with stirring. After stirring for 4 hrs, the reaction mixture was allowed to warm to room temperature, the volatiles were removed to provide a TFA salt of 4-(1-acetyl-1*H*-indol-3-yl)-piperidine Compound **8c** as an oil, which was used in the next step without further purification. MS *m/z* 243 $(M+H^+)$.

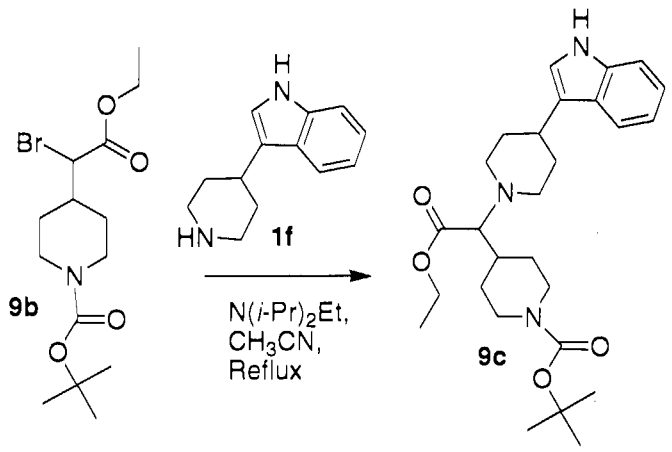
Using the procedure of Example 1, Compound **8c** was used in place of Compound **1f** and carried forward to provide Compound **21**. MS *m/z* 550 $(M+H)^+$.

Example 9

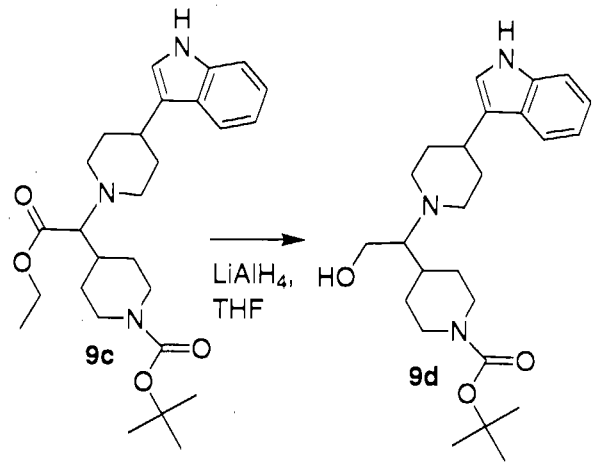
(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone (Cpd **112**)



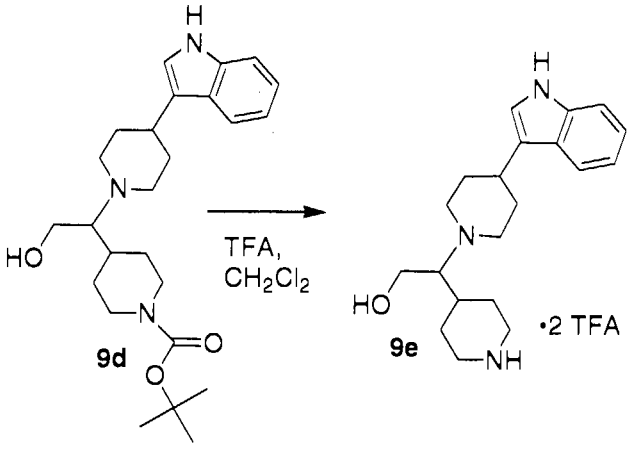
4-ethoxycarbonylmethyl-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9a** (12.4 g, 45.7 mmol, 1 eq) was dissolved in THF (40 mL) and cooled to –78°C. LHMDS (1M solution in THF, 82 mL, 82.3 mmol, 1.8 eq) was added dropwise with stirring. After 45 min, TMSCl (10.4 mL, 82.3 mmol, 1.8 eq) was added to the lithium enolate, and the resulting solution was stirred at –78°C for 1 hr. Bromine (2.3 mL, 45.7 mmol, 1 eq) was then added, and the reaction was stirred for 2 hrs at –78°C. The mixture was then warmed to room temperature over 30 min, quenched with saturated aqueous $NaHCO_3$ and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was removed and extracted again with EtOAc. The organic layers were combined and washed twice with brine. The organic layer was dried over anhydrous sodium sulfate, the filtered and evaporated to provide a dark orange oil which was purified by silica gel chromatography (4:1 to 1:1 hexanes:EtOAc) to provide 4-(bromo-ethoxycarbonyl-methyl)-piperidine-1-carboxylic acid tert-butyl ester Compound **9b** (12.3 g, 82%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.06 (2H, q, J=6.9 Hz); 3.96 (2H, broad m); 3.81 (1H, d, J=8.5 Hz); 2.53 (2H, m); 1.86 (2H, m); 1.47 (1H, m); 1.28 (9H, s); 1.13 (3H, t, J=6.9 Hz); 1.14-0.96 (2H, m).



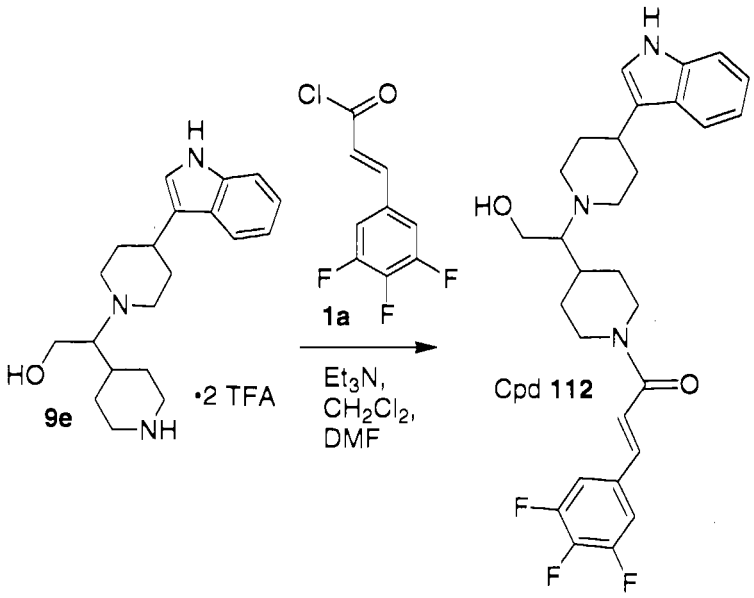
Compound **9b** (7.25 g, 20.7 mmol, 1 eq), 3-piperidin-4-yl-1H-indole Compound **1f** (4.14 g, 20.7 mmol, 1 eq) and diisopropylethylamine (10.8 mL, 62.1 mmol, 3 eq) were added to MeCN (60 mL) and the resulting solution was heated at reflux for 48 hrs. The reaction was then cooled to room temperature to precipitate unreacted Compound **1f** from the solution. The precipitate was removed by filtration and the filtrate evaporated. Silica gel chromatography (3:2:1 to 3:1.5:1 CH_2Cl_2:hexanes:EtOAc) provided 4-{ethoxycarbonyl-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9c** (4.73 g, 49%) as a pale foam. MS: m/z 470 $(M+H)^+$, 492 $(M+Na)^+$.



Compound **9c** (646 mg, 1.38 mmol, 1 eq) was dissolved in THF (12 mL) and the solution was cooled to 0°C. A 1M solution of $LiAlH_4$ (2.06 mmol, 1.5 eq) in THF (2 mL) was added dropwise to the solution of Compound **9c**. The mixture was stirred for 1.5 hrs, additional $LiAlH_4$ solution (0.5 mL) was added and the reaction mixture was stirred for an additional 1 hr. The reaction was quenched by sequential addition of water (0.1 mL), 15% NaOH (0.1 mL) and water (0.3 mL). The mixture was stirred for 30 min to form a precipitate. The precipitate was removed by filtration through a pad of celite. The pad was then washed with EtOAc, and the resulting filtrate washed twice with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate was evaporated to provide 4-{2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9d** (492 mg, 83%) as a white foam, used in the next step without further purification. MS *m/z* 428 $(M+H)^+$.



Compound **9d** (273 mg, 0.64 mmol, 1 eq) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0°C. TFA (0.5 mL) was added dropwise with stirring and the reaction was allowed to slowly warm to room temperature. After 3 hrs, the volatiles were removed *in vacuo* to provide the bis-trifluoroacetate salt of 2-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-2-piperidin-4-yl-ethanol Compound **9e** as an orange oil that was used in the next step without further purification. MS *m/z* 328 $(M+H)^+$.



Compound **9e** (805 mg, 1.45 mmol, 1 eq) was dissolved in CH_2Cl_2 (10 mL) and DMF (2 mL) and cooled to 0°C. TEA (0.8 mL, 5.80 mmol, 4 eq) was added, followed by slow addition of a solution of 3,4,5-trifluoro-cinnamoyl chloride Compound **1a** (320 mg, 1.45 mmol, 1 eq) in CH_2Cl_2 (2 mL) and DMF (3 mL). After stirring overnight, the reaction was allowed to warm to room temperature, the volatiles were removed *in vacuo* and the resulting residue dissolved in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with anhydrous Na_2SO_4 and filtered to remove the solid. The filtrate was evaporated and the resulting residue chromatographed using PTLC (8% MeOH in CH_2Cl_2). Isolation of the product band was followed by elution with 10-15% MeOH in CH_2Cl_2. The solvent was removed *in vacuo* and the residue triturated with methanol to provide Compound **112** (154 mg, 21%) as a white solid. MS *m/z* 512 $(M+H)^+$; 534 $(M+Na)^+$; ^1H NMR (d^6-DMSO, 400 MHz) δ: 10.74 (1H, s), 7.81 (2H, m), 7.52 (1H, d, J=7.9 Hz), 7.39 (2H, s), 7.32 (1H, d, J=7.8 Hz), 7.09-7.01 (2H, m), 6.95 (1H, app t, J=7.4 Hz), 4.47 (1H, broad t, J=11.3 Hz), 4.35-4.27 (2H, m), 3.70-3.62 (1H, m), 3.62-3.54 (1H, m), 3.05 (1H, m), 2.94-2.81 (2H, m), 2.77-2.59 (3H, m), 2.55 (1H, t (partially obscured), J=11.3 Hz), 2.22 (1H, m), 2.03 (1H, m), 1.96-1.74 (4H, m), 1.70-1.50 (2H, m), 1.25-0.99 (2H, m).

Using the procedure of Example 9 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
113	(2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	494
116	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	494

Cpd	Name	MS
119	(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3-trifluoromethyl-phenyl)-propenone	526
121	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	526
123	4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	515
129	4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,5-difluoro-phenyl)-amide	483
131	4-{2-hydroxy-1-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester	458
132	(2*E*)-1-(4-{2-hydroxy-1-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	542
133	(2*E*)-1-(4-{2-hydroxy-1-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	542
137	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	485
138	(2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	485
139	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	517
140	(2*E*)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(2,4,5-trifluoro-phenyl)-propenone	503
141	4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,4-difluoro-phenyl)-amide	474
153	(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	513
154	benzofuran-2-yl-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-methanone	472
155	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrazol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	477
156	(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-pyrazol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	463
157	(5-chloro-benzofuran-2-yl)-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-methanone	506
158	(2*E*)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	503
159	(2*E*)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-phenyl-propenone	449
160	(5-chloro-benzofuran-2-yl)-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-methanone	497
161	(2*E*)-3-(3-bromo-4-fluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	545
162	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	556

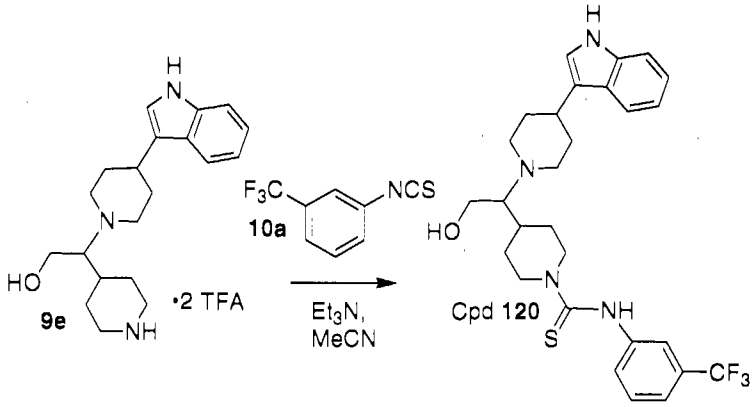
Cpd	Name	MS
163	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	556
164	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	524
165	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	524
166	(2*E*)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	542
167	(2*E*)-1-(4-{2-hydroxy-1-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	542
168	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone	544
169	(2*E*)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(4-fluoro-phenyl)-propenone	494
170	(2*E*)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	530
171	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone	512
172	(2*E*)-3-(3-bromo-4-fluoro-phenyl)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone	572
173	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indazol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	495
174	(2*E*)-1-(4-{1-[4-(1H-benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-propenone	495
175	(2*E*)-1-(4-{1-[4-(1H-benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	513
176	(2*E*)-1-(4-{1-[4-(1H-benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4-dichloro-phenyl)-propenone	527
182	(2*E*)-3-(3,5-difluoro-phenyl)-1-{4-[2-hydroxy-1-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethyl]-piperidin-1-yl}-propenone	456
183	(2*E*)-1-{4-[2-hydroxy-1-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethyl]-piperidin-1-yl}-3-(3,4,5-trifluoro-phenyl)-propenone	474
184	(2*E*)-1-{4-[2-hydroxy-1-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethyl]-piperidin-1-yl}-3-(3-trifluoromethyl-phenyl)-propenone	488
185	(2*E*)-3-(3,4-dichloro-phenyl)-1-{4-[2-hydroxy-1-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethyl]-piperidin-1-yl}-propenone	488
186	(2*E*)-3-(3-bromo-4-fluoro-phenyl)-1-{4-[2-hydroxy-1-(3,4,5,6-tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethyl]-piperidin-1-yl}-propenone	516
191	(2*E*)-1-(4-{1-[4-(5-amino-1H-pyrrolo[3,2-b]pyridin-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	528
198	N-{3-[1-(1-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-hydroxy-ethyl)-piperidin-4-yl]-1H-indol-5-yl}-methanesulfonamide	619

Cpd	Name	MS
201	N-{3-[1-(2-hydroxy-1-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-piperidin-4-yl]-1H-indol-5-yl}-methanesulfonamide	605
202	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	495
205	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	511
208	(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	527
209	N-{4-[1-(2-hydroxy-1-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-piperidin-4-yl]-phenyl}-methanesulfonamide	566
210	N-{4-[1-(1-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-hydroxy-ethyl)-piperidin-4-yl]-phenyl}-methanesulfonamide	580
212	[2-(3,4-dichloro-phenyl)-cyclopropyl]-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-methanone	540
244	(2*E*)-1-(4-{1-[4-(4-chloro-phenyl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4-dichloro-phenyl)-propenone	521
246	(2*E*)-1-(4-{1-[4-(4-chloro-phenyl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	507
251	(2*E*)-3-(4-nitro-phenyl)-acrylic acid 2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(4-nitro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl ester	678
253	1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propynone	501
254	(2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone	512
256	(2*E*)-1-(4-{1-[4-(5,6-dichloro-1H-benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-propenone	563
257	(2*E*)-1-(4-{1-[4-(5,6-dichloro-1H-benzoimidazol-2-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	581
258	(2*E*)-3-(4-chloro-phenyl)-1-(4-{1-[4-(4-chloro-phenyl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone	487
259	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	510

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Example 10

4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carbothioic acid (3-trifluoromethyl-phenyl)-amide (Cpd **120**)



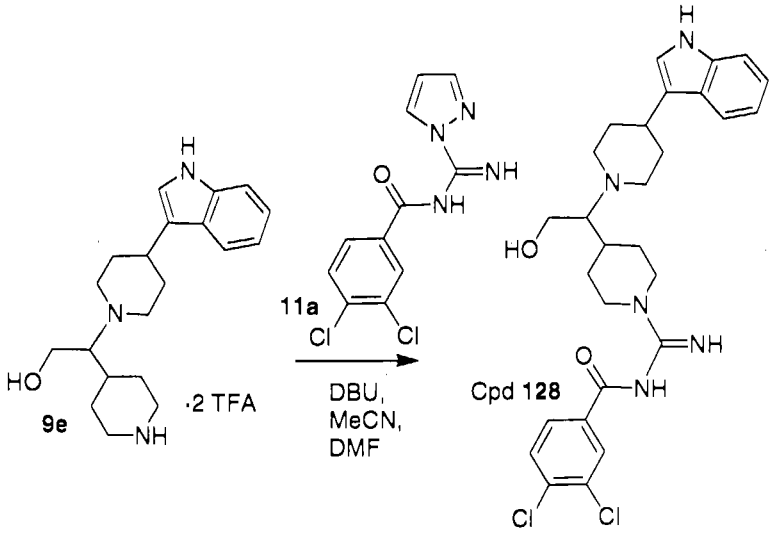
2-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-2-piperidin-4-yl-ethanol, bis-trifluoroacetate salt Compound **9e** (61 mg, 0.11 mmol, 1 eq) and TEA (46 µL, 0.33 mmol, 3 eq) were dissolved in acetonitrile (1 mL). 3-trifluoromethyl-phenylisothiocyanate Compound **10a** (17 µL, 0.11 mmol, 1 eq) was added and the mixture stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed once with saturated aqueous $NaHCO_3$ and washed twice with brine. The organic layer was dried over anhydrous Na_2SO_4. The solids were removed by filtration and the filtrate evaporated to provide an oil that was chromatographed using PTLC (8% MeOH in CH_2Cl_2). Isolation of the product band was followed by elution with 10-15% MeOH in CH_2Cl_2. The solvent was removed *in vacuo* to provide Compound **120** (35 mg, 60%) as a yellow solid. MS *m/z* 531 $(M+H)^+$.

Using the procedure of Example 10 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd		MS
122	4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carbothioic acid (3,4-dichloro-phenyl)-amide	531
124	4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carbothioic acid (3,5-difluoro-phenyl)-amide	499

Example 11

3,4-dichloro-N-[(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-imino-methyl]-benzamide (Cpd **128**)

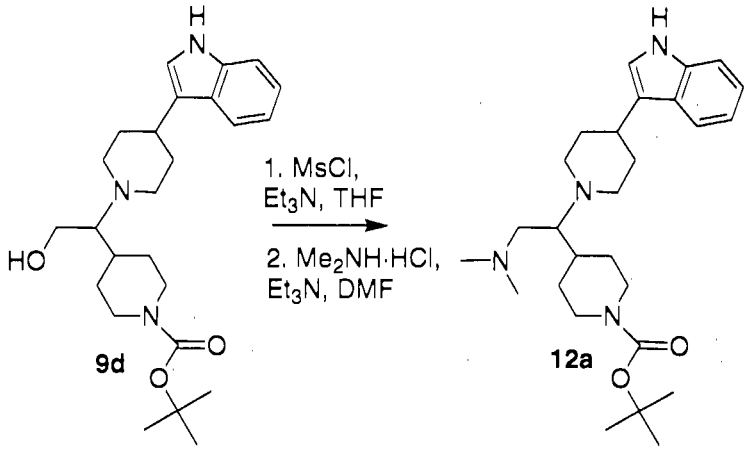


2-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-2-piperidin-4-yl-ethanol, bis-trifluoroacetate salt Compound **9e** (56 mg, 0.10 mmol, 1 eq) and DBU (49 µL, 0.33 mmol, 3.3 eq) were dissolved in DMF (1 mL). 3,4-dichloro-*N*-(imino-pyrazol-1-yl-methyl)-benzamide Compound **11a** (31 mg, 0.11 mmol, 1.1 eq) was added, and the mixture was stirred overnight at room temperature. The volatiles were removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ and twice with brine. The organic layer was dried with anhydrous Na_2SO_4 then filtered to remove the solid. The filtrate was evaporated and the resulting residue chromatographed using PTLC (8% MeOH in CH_2Cl_2). Isolation of the product band was followed by elution with 10-15% MeOH in CH_2Cl_2. The solvent was removed *in vacuo* to provide Compound **128** as an oil.

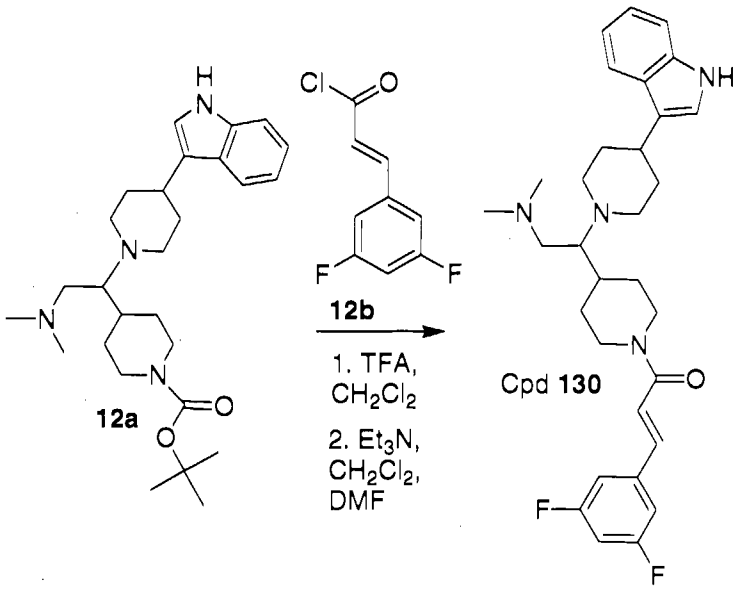
The oil was dissolved with CH_2Cl_2 and 4N HCl in dioxane was added to form a precipitate which was collected by filtration and washed with dichloromethane to provide the hydrochloride salt of Compound **128** (28 mg, 48%) as a white solid. MS *m/z* 542 $(M+H)^+$.

Example 12

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-dimethylamino-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone (Cpd **130**)



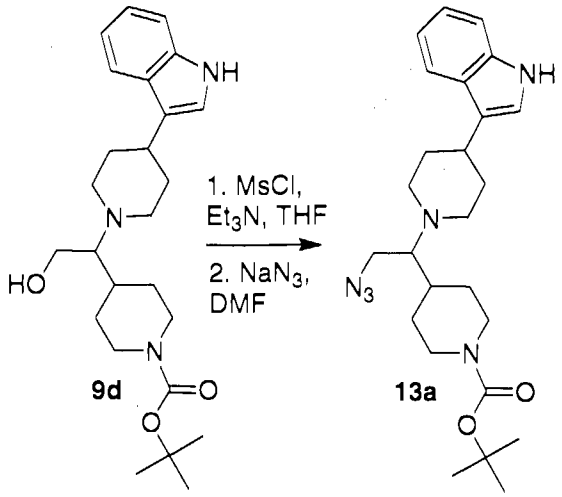
4-{2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9d** (91 mg, 0.21 mmol, 1 eq) and Et_3N (88 µL, 0.63 mmol, 3 eq) were dissolved in THF (2 mL) and cooled to 0°C. MsCl (18 µL, 0.23 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred for 1.5 hrs. The solvent was removed *in vacuo* and the residue dissolved in DMF (2 mL). Et_3N (88 µL, 0.63 mmol, 3 eq) and dimethylamine hydrochloride (43 mg, 0.53 mmol, 2.5 eq) were added, and the mixture was stirred for 16 hrs. The volatiles were removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2. After washing with saturated aqueous $NaHCO_3$ and brine, the organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated to provide a crude oil which was purified by silica gel column chromatography (10% 2N methanolic ammonia in CH_2Cl_2) to provide 4-{2-dimethylamino-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **12a** (59 mg, 62%) as an oil. MS *m/z* 455 $(M+H)^+$.



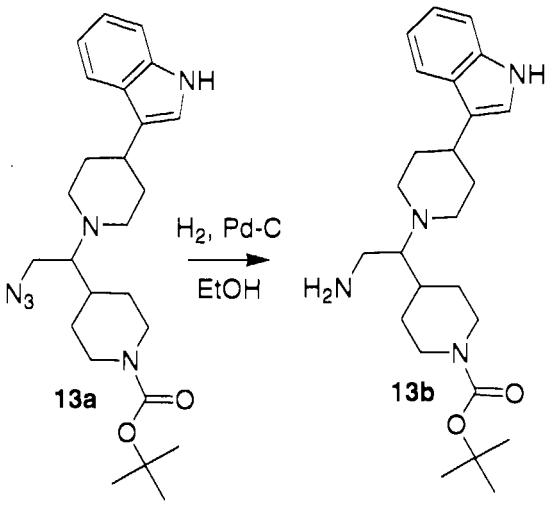
Compound **12a** (59 mg, 0.13 mmol, 1 eq) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0°C. TFA (0.5 mL) was added dropwise with stirring and the reaction was allowed to warm to room temperature over 3 hrs. The volatiles were removed in vacuo and the resulting residue dissolved in DMF (1 mL) and CH_2Cl_2 (1 mL). Et_3N (54 μL, 0.39 mmol, 3 eq) was added and the solution was cooled to 0°C. 3-(3,5-difluoro-phenyl)-acryloyl chloride Compound **12b** (26 mg, 0.13 mmol, 1 eq) was added and the mixture was stirred for 48 hrs. The reaction mixture was allowed to warm to room temperature, the solvents were removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ and twice with brine, then the organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to provide a crude oil, which was purified by silica gel chromatography (10-15% 2N methanolic ammonia in CH_2Cl_2) to provide Compound **130** (30 mg, 44%) as a pale foam. MS *m/z* 521 $(M+H)^+$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, s), 7.64 (1H, d, J=7.9 Hz), 7.53 (1H, d, J=15.4 Hz), 7.36 (1H, d, J=.1 Hz), 7.18 (1H, ddd, J=1.1, 8.2, 8.2 Hz), 7.10 (1H, ddd, J=1.0, 8.2, 8.2), 7.04-6.94 (3H, m), 6.78 (1H, m), 4.69 (1H, broad s), 4.08 (1H, d, J=12.7 Hz), 3.11 (1H, app t, J=12.3 Hz), 2.95 (1H, m), 2.87-2.75 (3H, m), 2.70 (1H, m), 2.61-2.43 (2H, m), 2.43-2.32 (1H, m), 2.23 (6H, s), 2.27-2.15 (1H, m), 2.12-1.94 (3H, m), 1.93-1.82 (1H, m), 1.80-1.58 (3H, m), 1.47-1.23 (2H, m).

Example 13

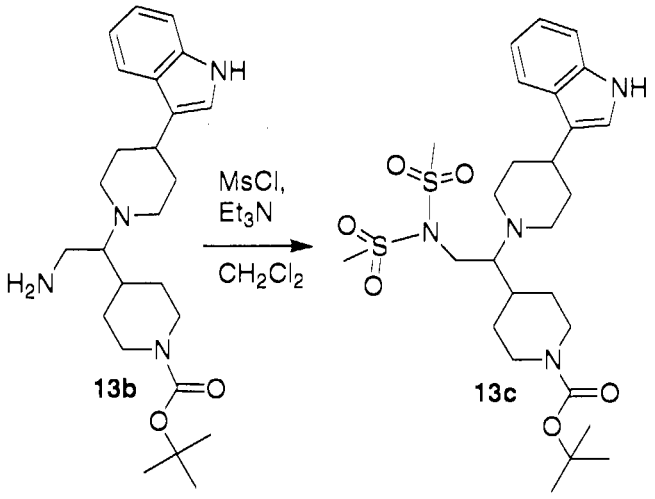
N-{2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-*N*-methanesulfonyl-methanesulfonamide (Cpd **134**)



4-{2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9d** (869 mg, 2.03 mmol, 1 eq) and Et_3N (854 µL, 6.09 mmol, 3 eq) were dissolved in THF (21 mL) and cooled to 0°C. MsCl (172 µL, 2.22 mmol, 1.1 eq) was added dropwise and the mixture was stirred for 2 hrs. The solvent was removed *in vacuo* and the residue dissolved in DMF (7 mL). Sodium azide (330 mg, 5.08 mmol, 2.5 eq) was added and the reaction mixture was stirred for 16 hrs at room temperature. The solvent was removed *in vacuo* and the resulting residue dissolved in CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$ and brine, then the organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated to provide a crude oil, which was purified by silica gel column chromatography (3:1.5:1 to 3:1:1.5 CH_2Cl_2:hexanes:EtOAc) to provide 4-{2-azido-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester Compound **13a** (560 mg, 61%) as a pale foam. MS *m/z* 453 $(M+H)^+$.

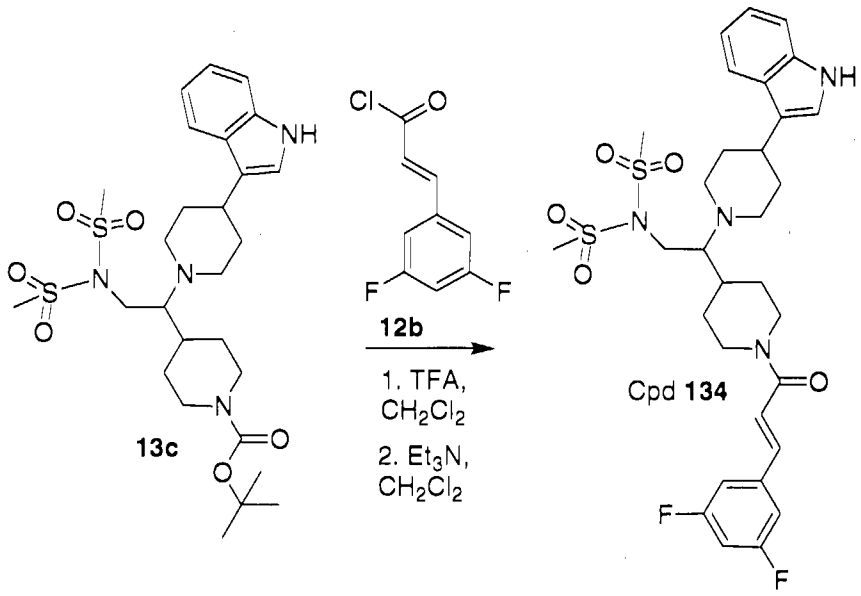


A solution of Compound **13a** (560 mg, 1.24 mmol, 1 eq) in absolute ethanol (20 mL) in a bottle was purged with nitrogen for 10 min. Pd-C (palladium on carbon) (10% by weight, 264 mg, 0.25 mmol, 0.2 eq) was added and the bottle was pressurized to 60 psi with hydrogen. The pressure was released and the bottle was refilled again to 60 psi with hydrogen. The pressurization and release was repeated twice more, then the bottle was shaken at 60 psi H_2 for 4 hrs at room temperature. After release of the hydrogen pressure, the solution was purged with nitrogen and filtered through celite. Evaporation of the solvent *in vacuo* provided 4-{2-amino-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **13b** (510 mg, 96%) as a pale foam, used in the next step without further purification. MS *m/z* 427 $(M+H)^+$.



Compound **13b** (79 mg, 0.19 mmol, 1 eq) and Et_3N (53 µL, 0.38 mmol, 2 eq) were dissolved in CH_2Cl_2 (1 mL). The mixture was cooled to 0°C and MsCl (16 µL, 0.20 mmol, 1.1 eq) was added dropwise with stirring. The reaction mixture was stirred for 48 hrs, then the volatiles were removed *in vacuo* and the residue subjected to silica gel chromatography (3:1:1 CH_2Cl_2:EtOAc:hexanes) to provide 4-{1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-2-

(dimethanesulfonyl)-amino-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **13c** (81 mg, 73%) as a yellow foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (1H, s), 7.61 (1H, d, J=7.8 Hz), 7.36 (1H, d, J=8.0 Hz), 7.19 (1H, app dt, J=0.9, 7.8, 7.8 Hz), 7.10 (1H, app dt, J=0.9, 7.8, 7.8 Hz), 6.94 (1H, d, J=2.0 Hz), 4.25-4.07 (1H, broad m), 4.05 (1H, dd, J=15.4, 11.1 Hz), 3.46 (6H, s), 3.17 (1H, d, J=10.4 Hz), 2.97 (1H, app t, J=11.7), 2.92-2.78 (3H, m), 2.78-2.59 (2H, m), 2.45 (1H, t, J=10.1 Hz), 2.19-2.04 (2H, app t), 1.99-1.84 (1H, m), 1.81-1.50 (5H, m), 1.51-1.37 (1H, m (obscured by 9H singlet)), 1.47 (9H, s), 1.35-1.17 (2H, m).

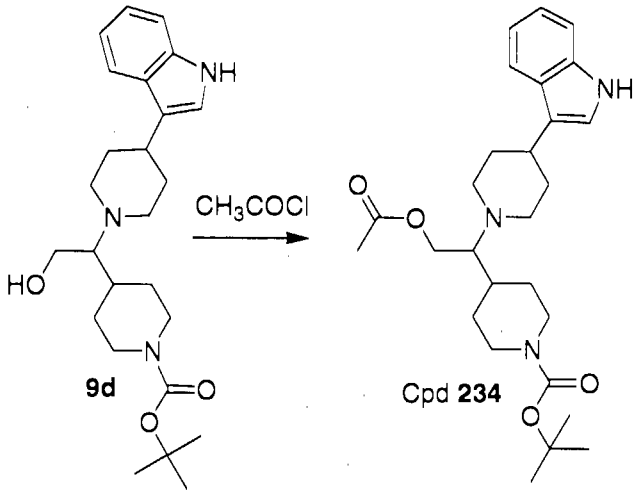


Compound **13c** (75 mg, 0.13 mmol, 1 eq) was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. TFA (1 mL) was added dropwise with stirring and the reaction was allowed to warm to room temperature over 3 hrs. The volatiles were removed *in vacuo* to provide an oil that was used in the subsequent reaction without further purification. The deprotected Compound **13c** (41 mg, 0.065 mmol, 1 eq) was dissolved in CH_2Cl_2 (1 mL). Et_3N (27 μL, 0.20 mmol, 3 eq) was added to the solution followed by 3-(3,5-difluoro-phenyl)-acryloyl chloride Compound **12b** (17 mg, 0.085 mmol, 1.3 eq). After stirring overnight, the reaction was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 then filtered and the filtrate was evaporated to provide a crude oil, which was chromatographed using PTLC (3:2.5:1 CH_2Cl_2:EtOAc:hexanes). Isolation of the product band was followed by elution with 3:2 CH_2Cl_2:EtOAc. The solvent was removed *in vacuo* to provide Compound **134** (21 mg) as a pale foam. MS *m/z* 649 $(M+H)^+$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (1H, s), 7.61 (1H, d, J=7.8 Hz), 7.56 (1H, d, J=15.4 Hz), 7.37 (1H, d, J=8.1 Hz), 7.19 (1H, ddd, J=7.1, 7.1, 1.1 Hz), 7.10 (1H, ddd, J=7.8, 7.8, 1.1 Hz), 7.02 (2H, m), 6.95 (1H, d, J=2.2 Hz), 6.89 (1H, d, 15.2 Hz), 6.80 (1H, m), 4.76 (1H, broad t, J=11.5 Hz), 4.20-4.10 (1H, m), 4.06 (1H, dd, J=14.9, 10.9 Hz), 3.45 (6H, s), 3.25-3.08 (2H, m), 3.04-2.78

(4H, m), 2.68 (1H, m), 2.48 (1H, m), 2.11 (3H, m), 1.85 (1H, m), 1.81-1.61 (3H, m), 1.55 (1H, m), 1.35 (1H, m).

Example 14

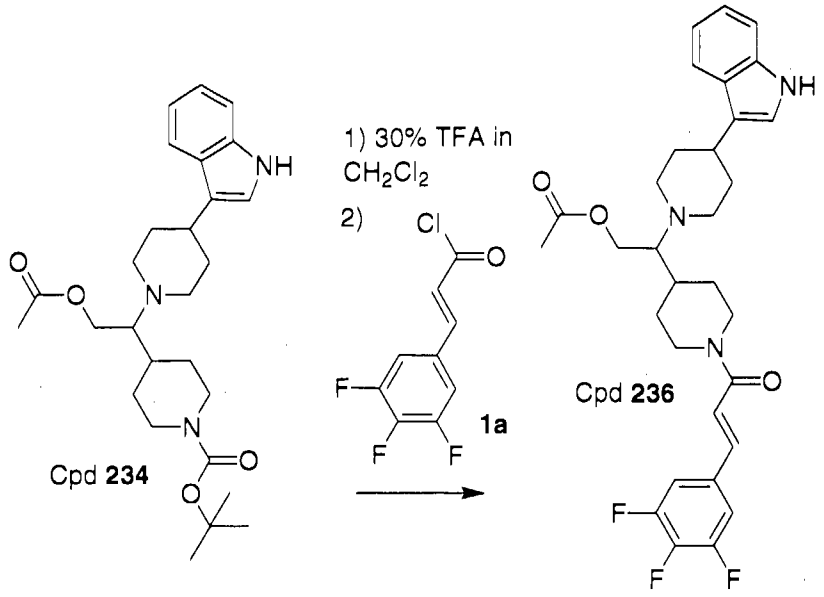
4-{2-acetoxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (Cpd **234**)



TEA (0.2 g, 2.0 mmol) and acetyl chloride (0.1 mL, 1.4 mmol) were added to a solution of 4-{2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9d** (0.43 g, 1.0 mmol) in methylene chloride (15.0 mL). The mixture was stirred for 2 hrs at r.t. then the reaction was quenched with water. The organic layer was washed with 0.5N HCl (5.0 mL), water (5.0 mL) and brine (5.0 mL), then dried over Na_2SO_4. The methylene chloride was evaporated to provide Compound **234** (0.47 g, 99%) as a white solid. MS *m/z* 470 $(M+H)^+$.

Example 15

acetic acid 2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl ester (Cpd **236**)



TFA (3.0 mL) was added to a solution of Compound **234** (0.1 g, 0.21 mmol) in methylene chloride (7.0 mL). The mixture was stirred for 2 hrs and then concentrated in vacuo. The resulting residue was dissolved in methylene chloride (10.0 mL) and TEA (0.1 g) and 3-(3,4,5-trifluoro-phenyl)-acryloyl chloride Compound **1a** (0.05 g, 0.23 mmol) was added. A crude product was prepared then purified with chromatography (eluted with 50% EtOAc in hexane) to provide Compound **236** (0.08 g, 68%). MS *m/z* 554 $(M+H)^+$.

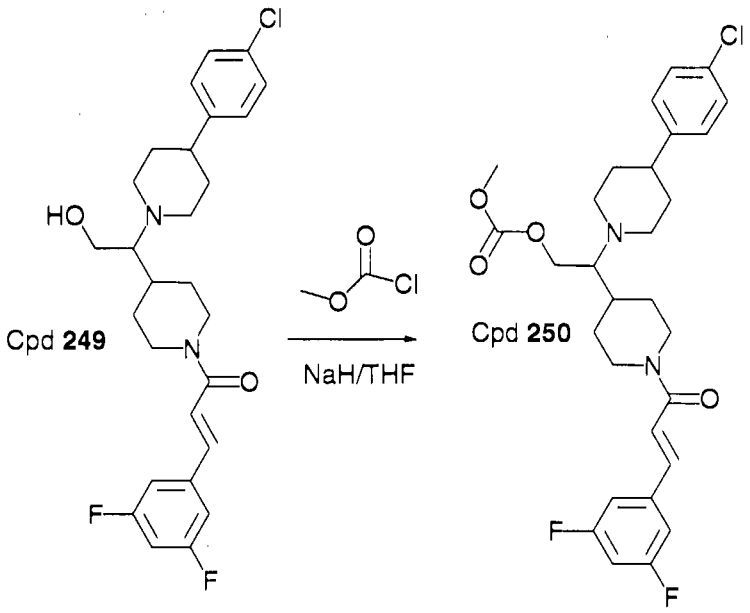
Using the procedure of Example 15 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
199	(2*E*)-3-(3,5-difluoro-phenyl)-acrylic acid 2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-ethyl ester	753
235	acetic acid 2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl ester	536
237	acetic acid 2-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl ester	568
242	acetic acid 2-[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl ester	557
243	acetic acid 2-{4-[5-(acetyl-methanesulfonyl-amino)-1H-indol-3-yl]-piperidin-1-yl}-2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl ester	671

Example 16

(2*E*)-1-(4-{1-[4-(4-chloro-phenyl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-propenone (Cpd **249**)

carbonic acid 2-[4-(4-chloro-phenyl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl ester methyl ester (Cpd **250**)

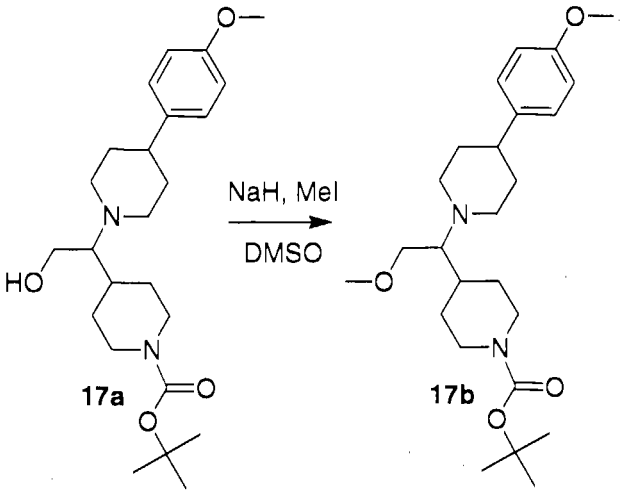


Compound **249** was prepared using the procedure of Example 9 and 4-(4-chloro-phenyl)-piperidine in place of 3-piperidin-4-yl-1H-indole Compound **1f**. MS *m/z* 489 $(M+H)^+$.

NaH (5 mg, 0.21 mmol) and methyl chloroformate(10 mg, 0.11 mmol) were added to a solution of Compound **249** (40 mg, 0.082 mmol) in THF (8 mL). The mixture was refluxed for 24 hrs, then concentrated in vacuo for 0.5 hrs. The resulting residue was purified via preparative TLC (in 50% EtOAc/Hexane) to provide Compound **250** (15 mg, 33%). MS *m/z* 547 $(M+H)^+$.

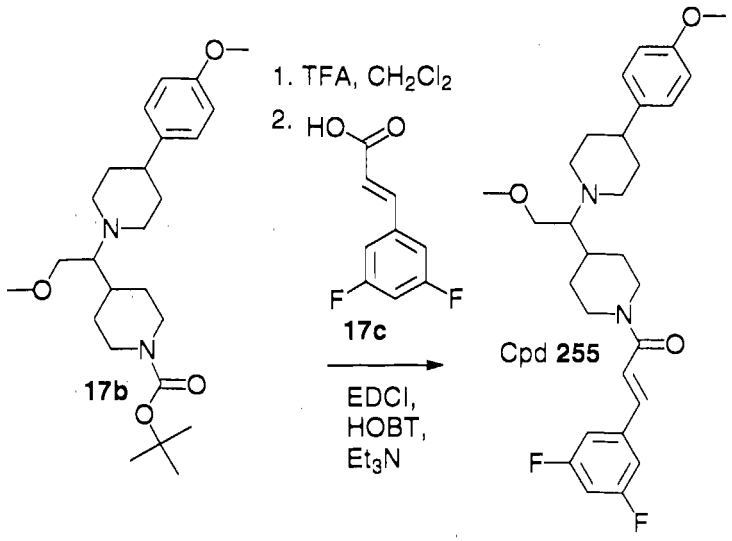
Example 17

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-methoxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone (Cpd **255**)



4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester Compound **17a** was prepared using the procedure of Example 9 and 4-(4-methoxy-phenyl)-piperidine in place of 3-piperidin-4-yl-1H-indole Compound **1f**.

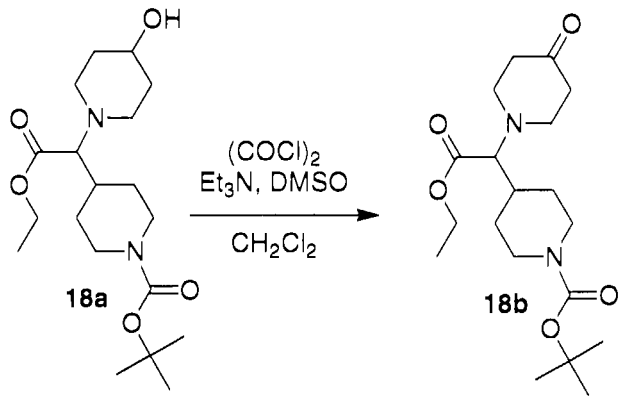
Compound **17a** (150 mg, 0.36 mmol, 1 eq) was dissolved in DMSO (3 mL) under nitrogen. Sodium hydride (50% in mineral oil, 22 mg, 0.47 mmol, 1.3 eq) was added at r.t. and the resulting suspension was stirred for 30 mins. Methyl iodide (29 µL, 0.47 mmol, 1.3 eq) was added and the solution was stirred for 16 hrs. An additional amount of sodium hydride (22 mg, 1.3 eq) was added, followed by additional methyl iodide (29 µL, 0.47 mmol, 1.3 eq) and the mixture was stirred for 1 hr. A final portion of sodium hydride (22 mg, 1.3 eq) was added and the suspension was stirred for 1 hr. The reaction mixture was partitioned between brine and EtOAc. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with dilute brine and dried over sodium sulfate, then filtered and evaporated. The residue was purified via silica gel (1:1 hexanes:EtOAc to 100% EtOAc) to provide 4-{2-methoxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **17b** (47 mg, 30%) as a viscous oil. MS *m/z* 433 $(M+H)^+$.



Compound **17b** (47 mg, 0.11 mmol, 1 eq) was dissolved in CH_2Cl_2 (2 mL) and treated dropwise with TFA (500 µL). The mixture was stirred for 2 hrs and the solvent was evaporated to provide a crude residue that was used in the next step without further purification. The residue was dissolved in CH_2Cl_2 (1 mL) and DMF (100 µL). The solution was cooled to 0°C and 3-(3,5-difluoro-phenyl)-acrylic acid Compound **17c** (20 mg, 0.11 mmol, 1 eq) was added, followed by HOBt (16 mg, 0.12 mmol, 1.1 eq), Et_3N (46 µL, 0.33 mmol, 3 eq) and EDCI (23 mg, 0.12 mmol, 1.1 eq). The reaction was allowed to slowly warm to r.t. and stirred for 3 days. The solvent was evaporated to provide a residue that was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic layer was removed, then washed with brine and dried over anhydrous Na_2SO_4. The solution was filtered, then the filtrate was concentrated and purified via silica gel chromatography (1:1 to 1:3 hexanes:EtOAc) to provide Compound **255** (41 mg, 82%) as a pale foam. MS *m/z* 499 $(M+H)^+$.

Example 18

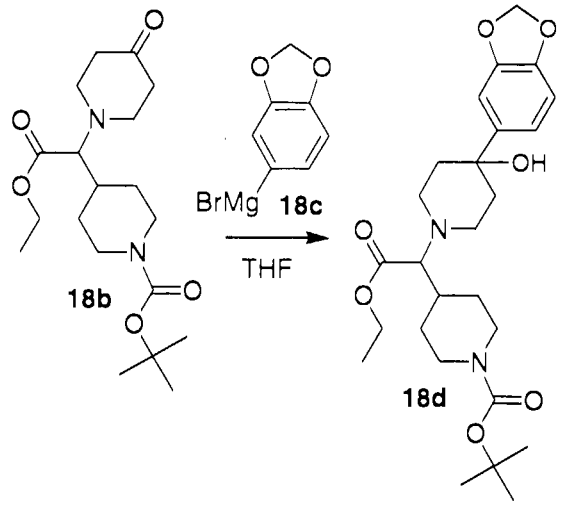
(2*E*)-1-{4-[1-(4-benzo[1,3]dioxol-5-yl-piperidin-1-yl)-2-hydroxy-ethyl]-piperidin-1-yl}-3-(3,4,5-trifluoro-phenyl)-propenone (Cpd **189**)



A solution of DMSO (493 μL, 6.95 mmol, 4.4 eq) in CH_2Cl_2 (10 mL) was cooled to -78°C. Oxalyl chloride (276 μL, 3.16 mmol, 2 eq) was added dropwise and the mixture was stirred for 25 mins.

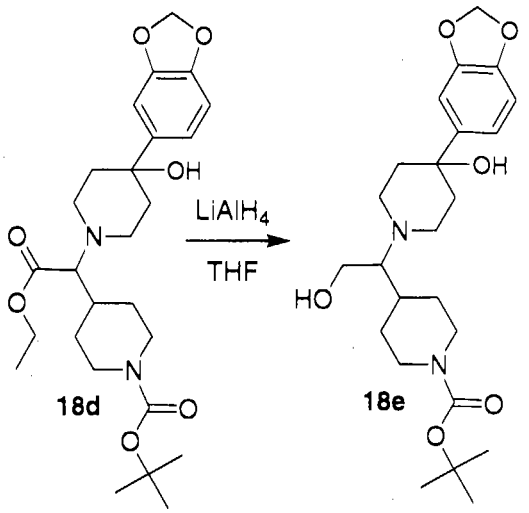
4-[ethoxycarbonyl-(4-hydroxy-piperidin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **18a** was prepared using the procedure of Example 9 and piperidin-4-ol in place of 3-piperidin-4-yl-1H-indole Compound **1f**.

A solution of Compound **18a** (586 mg, 1.58 mmol, 1 eq) in CH_2Cl_2 (5 mL) was added dropwise to the solution of oxalyl chloride in DMSO at –78°C. The mixture was stirred for 20 mins and Et_3N (1.3 mL, 9.48 mmol, 6 eq) was added dropwise. The mixture was warmed to room temperature and then partitioned between CH_2Cl_2 and brine. The organic layer was removed and the aqueous layer was made more basic with 2.5N NaOH and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and dried over sodium sulfate, then filtered and evaporated to provide a crude residue that was purified by silica gel chromatography (3:1 hexanes:EtOAc to 2:3 hexanes:EtOAc) to provide 4-[ethoxycarbonyl-(4-oxo-piperidin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **18b** (503 mg, 86%) as a crystalline solid. MS *m/z* 387 $(M+H+H_2O)^+$.

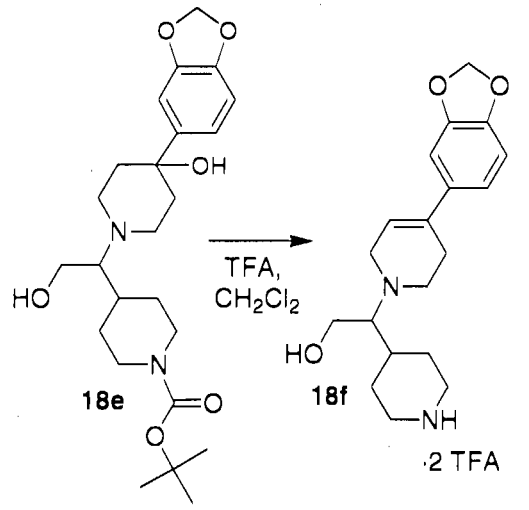


A solution of benzo[1,3]dioxol-5-yl magnesium bromide Compound **18c** (1M in 1:1 toluene:THF, 1.03 mL, 1.03 mmol, 1 eq) was added dropwise to a stirred solution of Compound **18b** (378 mg, 1.03 mmol, 1 eq) in THF (6 mL) at 0°C. After 1 hr, additional Compound **18c** (600 μL) was added and the mixture was stirred for another 30 mins. The reaction was quenched with saturated NH_4Cl and partitioned between saturated $NaHCO_3$ and EtOAc. The organic layer was removed and the aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate, then filtered and evaporated to provide a crude product which was purified via silica gel

chromatography (2:1 hexanes:EtOAc to 50:50 hexanes:EtOAc) to provide 4-[(4-benzo[1,3]dioxol-5-yl-4-hydroxy-piperidin-1-yl)-ethoxycarbonyl-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **18d** (335 mg, 66%). MS *m/z* 491 $(M+H)^+$.

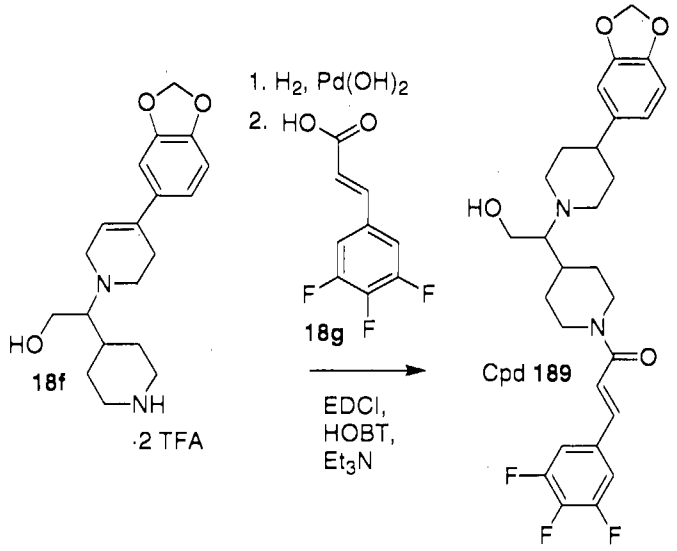


A solution of Compound **18d** (163 mg, 0.33 mmol, 1 eq) in THF (2.5 mL) was cooled to 0°C and treated with $LiAlH_4$ (1M in THF, 500 µL, 0.50 mmol, 1.5 eq). The mixture was stirred for 2 hrs, during which time the ice bath melted, and the reaction was sequentially quenched with water (22 µL), 15% NaOH (22 µL) and water (66 µL). The quenched reaction mixture was stirred for 30 mins, then the solids were removed by filtration through celite and subsequent washing with EtOAc. The filtrate was evaporated and the crude residue was purified via silica gel chromatography (5% to 10% 2M $MeOH/NH_3$ in CH_2Cl_2) to provide 4-[1-(4-benzo[1,3]dioxol-5-yl-4-hydroxy-piperidin-1-yl)-2-hydroxy-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **18e** (72 mg, 49%) as an oil. MS *m/z* 449 $(M+H)^+$.



TFA (0.5 mL) was added to a solution of Compound **18e** (72 mg, 0.16 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min, then evaporated to provide a bis-

trifluoroacetate salt of 2-(4-benzo[1,3]dioxol-5-yl-3,6-dihydro-2H-pyridin-1-yl)-2-piperidin-4-yl-ethanol Compound **18f** (89 mg, quant) as a yellow oil that was used in the next step without further purification. MS *m/z* 331 $(M+H)^+$.



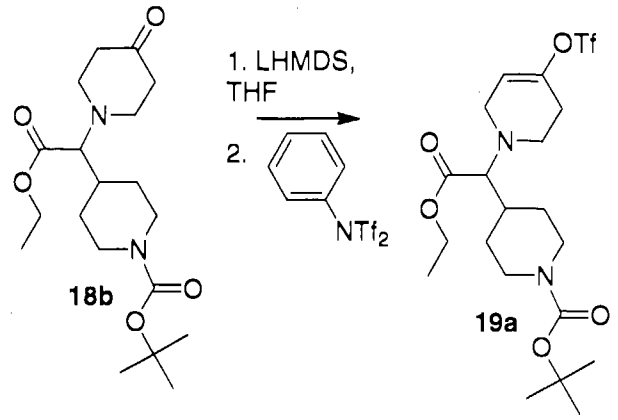
A solution of Compound **18f** (89 mg, 0.16 mmol, 1 eq) was dissolved in methanol (10 mL) and charged with palladium hydroxide (20% on carbon, 50% w/w with water, 40 mg, 0.028 mmol, 0.2 eq). The mixture was sequentially purged with nitrogen and hydrogen, then shaken under hydrogen (50 psi) for 4 hrs. After purging with nitrogen, the mixture was filtered through celite and the filtrate was evaporated to provide a viscous oil. A portion of the crude product (45 mg, 0.08 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.5 mL) and DMF (0.5 mL). 3-(3,4,5-trifluoro-phenyl)-acrylic acid Compound **18g** (16 mg, 0.08 mmol, 1 eq) was added, followed by HOBt (12 mg, 0.088 mmol, 1.1 eq), Et_3N (45 µL, 0.32 mmol, 4 eq) and EDCI (17 mg, 0.088 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 16 hrs, then the solvents were evaporated. The resulting residue was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic layer was removed and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, then filtered and evaporated. The resulting residue was purified via silica gel chromatography (4% to 12% 2M NH_3·MeOH in CH_2Cl_2) to provide Compound **189** (24 mg, 58%) as a tan foam. MS *m/z* 517 $(M+H)^+$.

Using the procedure of Example 18 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

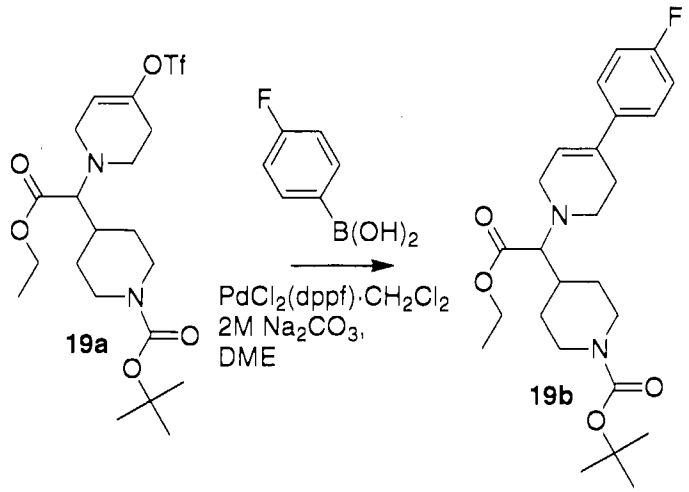
Cpd	Name	MS
190	(2*E*)-1-{4-[1-(4-benzo[1,3]dioxol-5-yl-piperidin-1-yl)-2-hydroxy-ethyl]-piperidin-1-yl}-3-(3,5-difluoro-phenyl)-propenone	499

Example 19

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{1-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone
(Cpd **192**)

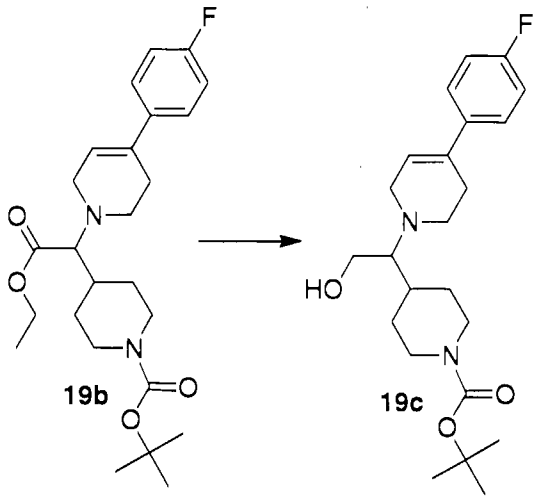


4-[ethoxycarbonyl-(4-oxo-piperidin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **18b** (503 mg, 1.37 mmol, 1 eq) was dissolved in THF (10.5 mL) and cooled to -78°C. Lithium bis(trimethylsilyl)amide (1M in THF, 1.5 mL, 1.5 mmol, 1.1 eq) was added dropwise to the Compound **18b** solution and stirred for 20 mins at –78°C. A solution of *N*-phenyl-trifluoromethanesulfonimide (536 mg, 1.5 mmol, 1.5 eq) in THF (5 mL) was added dropwise with stirring. The resulting mixture was warmed to 0°C and stirred for 3 hrs at 0°C. The solvents were removed *in vacuo*, and the resulting residue purified by chromatography on neutral alumina (3:1 hexanes:EtOAc) to provide 4-[ethoxycarbonyl-(4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **19a** (432 mg, 63%) as a viscous oil. MS *m/z* 523 $(M+Na)^+$.

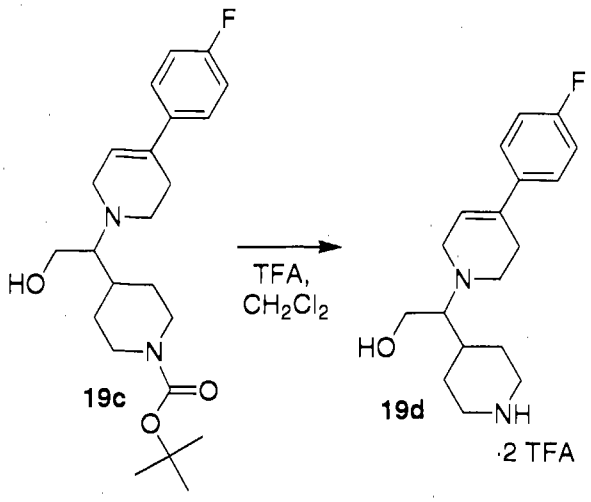


A solution of Compound **19a** (170 mg, 0.34 mmol, 1 eq) and 4-fluoro-phenyl boronic acid (52 mg, 0.37 mmol, 1.1 eq) in DME (3.3 mL) was charged with 2M Na_2CO_3 (0.68 mL) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (20 mg,

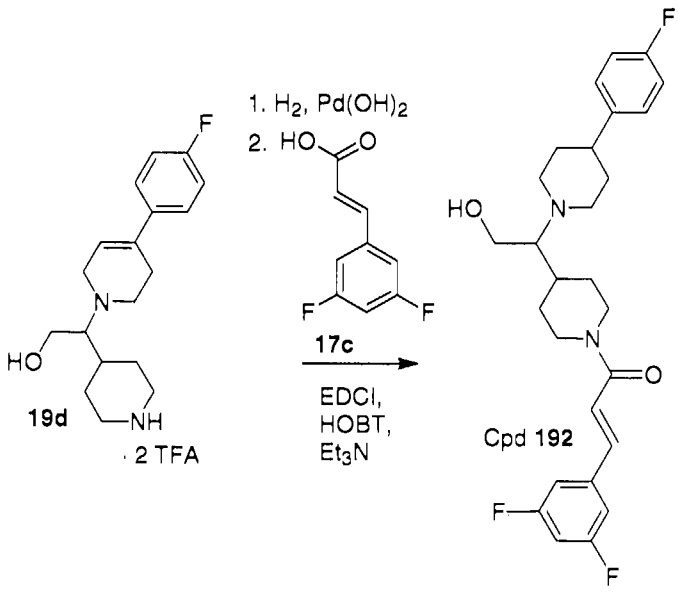
0.027 mmol, 0.08 eq). The mixture was heated to reflux for 2.5 hrs, then cooled and partitioned between EtOAc and brine. The organic layer was removed and the aqueous layer was extracted again with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated, then purified via silica gel chromatography (4:1 hexanes:EtOAc to 1:1 hexanes:EtOAc) to provide 4-{ethoxycarbonyl-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **19b** (79 mg, 52%) as a viscous oil. MS *m/z* 447 $(M+H)^+$.



A solution of Compound **19b** (79 mg, 0.18 mmol, 1 eq) in THF (1.4 mL) was treated with $LiAlH_4$ (1M in THF, 270 µL, 0.27 mmol, 1.5 eq) and stirred for 2 hrs, then water (13 µL), 15% NaOH (13 µL) and water (39 µL) were sequentially added. The reaction mixture was stirred for 1 hr, then the quenched reaction mixture was filtered through a celite pad and the pad was washed with EtOAc. The combined filtrates were evaporated to provide 4-{1-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-hydroxy-ethyl}-piperidine-1-carboxylic acid tert-butyl ester Compound **19c** (65 mg (89%), which was used in the next step without further purification. MS *m/z* 405 $(M+H)^+$.



A solution of Compound **19c** (65 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was treated with TFA (0.5 mL). The mixture was stirred for 3 hrs, then the solvent was removed in vacuo to provide the bis-trifluoroacetate salt of 2-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-piperidin-4-yl-ethanol Compound **19d** (88 mg, quant.) as a viscous oil that was used without further purification. MS *m/z* 305 $(M+H)^+$.



A solution of Compound **19d** (88 mg, 0.16 mmol, 1 eq.) and palladium hydroxide (40 mg, 0.029 mmol, 0.18 eq) in methanol (10 mL) was sequentially purged with nitrogen and hydrogen, then shaken under hydrogen (50 psi) for 16 hrs. After nitrogen purging, the reaction mixture was filtered through celite and the filtrate was evaporated to provide the bis-trifluoroacetate salt of 2-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-piperidin-4-yl-ethanol Compound **19e**, which was used in the next step without further purification. A portion of Compound **19e** (43 mg, 0.08 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.5 mL) and DMF (0.5 mL). 3-(3,5-difluoro-phenyl)-acrylic acid Compound **17c** (15 mg, 0.08 mmol, 1 eq) was added,

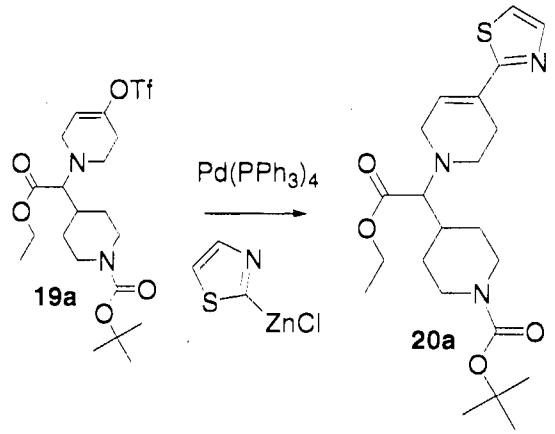
followed by HOBt (12 mg, 0.088 mmol, 1.1 eq), Et_3N (45 μL, 0.32 mmol, 4 eq) and EDCI (17 mg, 0.088 mmol, 1.1 eq). The mixture was stirred at room temperature for 72 hrs. The solvent was evaporated to provide a residue that was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic layer was removed and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, then filtered and evaporated. The resulting residue was purified by silica gel chromatography (4% to 12% 2M NH_3·MeOH in CH_2Cl_2) to provide Compound **192** (11 mg, 29%) as a tan foam. MS *m/z* 473 $(M+H)^+$.

Using the procedure of Example 19 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
193	(2*E*)-1-(4-{1-[4-(4-fluoro-phenyl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone	491
197	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(3-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	507 (M+Na)

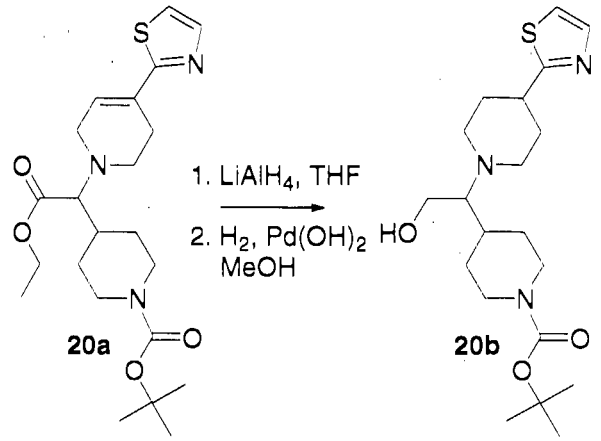
Example 20

(2*E*)-3-(3,5-difluoro-phenyl)-1-{4-[2-hydroxy-1-(4-thiazol-2-yl-piperidin-1-yl)-ethyl]-piperidin-1-yl}-propenone
(Compound **194**)

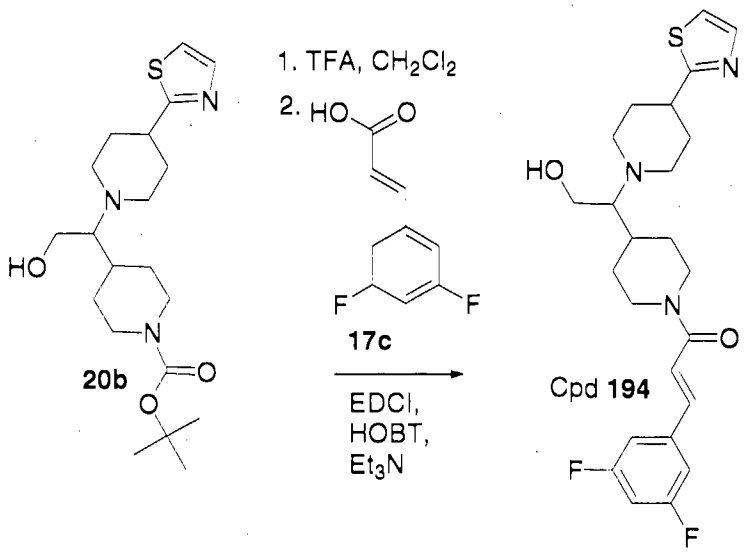


A solution of *n*-butyl lithium (1.05M in hexanes, 695 mL, 1.7 eq) was added dropwise to a solution of thiazole (43 μL, 0.60 mmol, 1.4 eq) in THF (1 mL) at –78°C and the mixture was stirred for 20 mins. Freshly powdered zinc chloride (246 mg, 1.81 mmol, 4.2 eq) was added and the mixture was warmed to room temperature with stirring. A solution of 4-[ethoxycarbonyl-(4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **19a** (216 mg, 0.43 mmol, 1 eq) in THF (2 mL) and tetrakis triphenylphosphine palladium (50 mg, 0.043 mmol, 0.1 eq) were added to the solution. The mixture was heated at reflux for 1 hr, then cooled and partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was removed and the aqueous layer was

extracted with EtOAc. The organic layers were combined and dried over anhydrous sodium sulfate, then filtered and evaporated. The resulting residue was purified via silica gel chromatography (3:2 to 2:3 hexanes:EtOAc) to provide 4-[ethoxycarbonyl-(4-thiazol-2-yl-3,6-dihydro-2H-pyridin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **20a** (174 mg, 93%) as a yellow foam. MS *m/z* 438 $(M+H)^+$.



A solution of Compound **20a** (165 mg, 0.38 mmol, 1 eq) in THF (3 mL) was cooled to 0°C and treated with $LiAlH_4$ (1M in THF, 570 µL, 1.5 eq) with stirring. The mixture was stirred for 1 hr, then warmed to room temperature and stirred for an additional 1 hr. The reaction was sequentially quenched with water (30 µL), 15% NaOH (30 µL) and water (90 µL). The quenched reaction mixture was stirred for 30 mins, then filtered through a celite pad and the pad was washed with EtOAc. The filtrate was evaporated and the resulting residue purified via silica gel chromatography (4% to 12% 2M $MeOH{\cdot}NH_3$ in CH_2Cl_2) to provide an inseparable mixture of crude products. The product mixture was dissolved in of MeOH and $Pd(OH)_2$ (35 mg, 0.025 mmol, 0.12 eq) and purged with nitrogen. Hydrogen was bubbled through the mixture, and the mixture was stirred under hydrogen for 3 hrs. The mixture was purged with nitrogen, then filtered through celite and evaporated to provide (in 2 steps) 4-[2-hydroxy-1-(4-thiazol-2-yl-piperidin-1-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **20b** (82 mg, 55%) as a pale foam that was used in the next step without further purification. MS *m/z* 396 $(M+H)^+$.



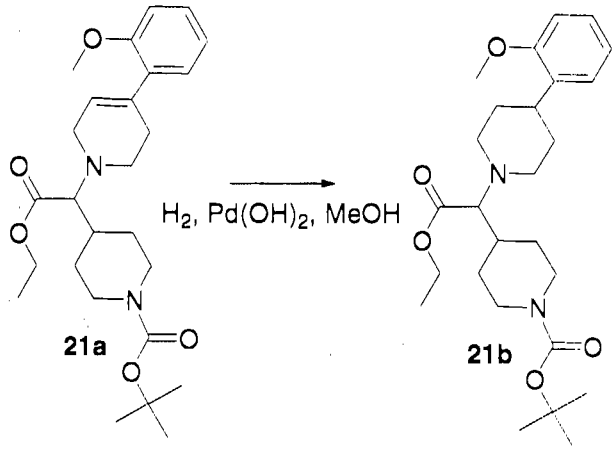
Compound **20b** (82 mg, 0.21 mmol, 1 eq) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C with stirring. TFA (0.5 mL) was added dropwise and the mixture was stirred for 3 hrs while warming to room temperature. The solvent was removed *in vacuo* to provide a crude residue, which was used in the next step without further purification. A portion of the residue (37 mg, 0.07 mmol, 1 eq) was dissolved in CH_2Cl_2 (0.5 mL) and DMF (0.5 mL). 3-(3,5-difluoro-phenyl)-acrylic acid Compound **17b** (13 mg, 0.07 mmol, 1 eq) was added, followed by HOBt (10 mg, 0.077 mmol, 1.1 eq), Et_3N (39 µL, 0.28 mmol, 4 eq) and EDCI (15 mg, 0.077 mmol, 1.1 eq). The mixture was stirred at room temperature for 16 hrs, then the solvent was evaporated. The resulting residue was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic layer was removed and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, then filtered and evaporated. The resulting residue was purified via silica gel chromatography (2% to 10% 2M NH_3·MeOH in CH_2Cl_2) to provide Compound **194** (11 mg, 34%) as a tan foam. MS *m/z* 462 $(M+H)^+$.

Using the procedure of Example 20 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
195	(2*E*)-1-{4-[2-hydroxy-1-(4-thiazol-2-yl-piperidin-1-yl)-ethyl]-piperidin-1-yl}-3-(3,4,5-trifluoro-phenyl)-propenone	480
196	(2*E*)-3-(3,4-dichloro-phenyl)-1-{4-[2-hydroxy-1-(4-thiazol-2-yl-piperidin-1-yl)-ethyl]-piperidin-1-yl}-propenone	494

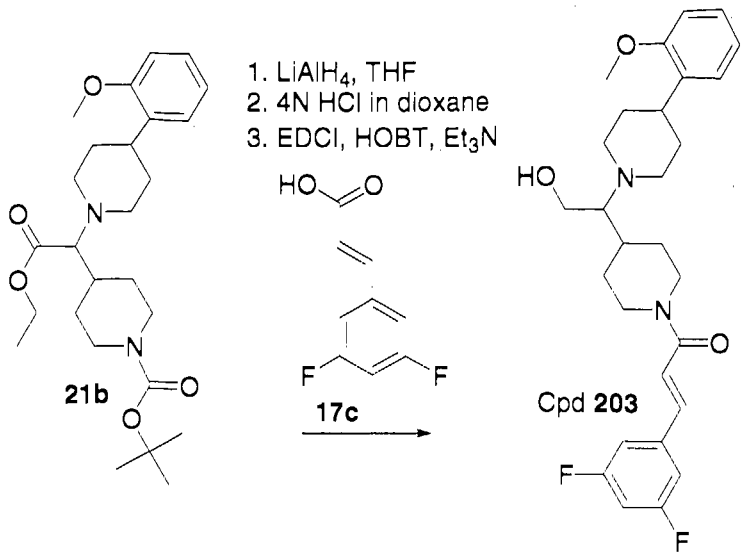
Example 21

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(2-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone (Compound **203**)



The procedure of Example 20 and 2-methoxy-phenyl and zinc iodide in place of thiazol-2-yl and zinc chloride were used to prepare 4-{ethoxycarbonyl-[4-(2-methoxy-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methyl}-piperidine-1-carboxylic acid tert-butyl ester Compound **21a**.

A solution of Compound **21a** (200 mg, 0.44 mmol, 1 eq) and palladium hydroxide (20% on carbon, 50 wt. % H_2O, 70 mg, 0.05 mmol, 0.11 eq) in methanol (3 mL) was sequentially purged with nitrogen and hydrogen, then pressurized under hydrogen (50 psi), the mixture was shaken for 24 hrs. After purging with nitrogen, the reaction mixture was filtered through celite and the filtrate was evaporated. The resulting residue was filtered through a plug of silica (3:2:1 to 3:1:1 CH_2Cl_2:hexanes:EtOAc) to provide 4-{ethoxycarbonyl-[4-(2-methoxy-phenyl)-piperidin-1-yl]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **21b** (58 mg, 29%) as a viscous oil. MS *m/z* 462 $(M+H)^+$.



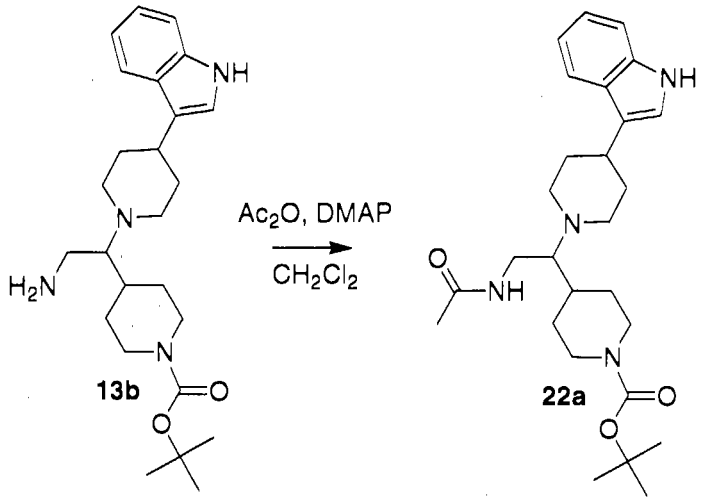
A solution of Compound **21b** (58 mg, 0.13 mmol, 1 eq) in THF (1 mL) was cooled to 0°C and treated with $LiAlH_4$ (1M in THF, 190 µL, 1.5 eq) with stirring. After 1 hr, the mixture was warmed to room temperature and stirred for an additional 1 hr. The reaction was sequentially quenched with water (9 µL), 15% NaOH (9 µL) and water (27 µL). The mixture was stirred for 30 mins, then filtered through a celite pad and the pad was washed with EtOAc. The filtrates were evaporated and dissolved in methanol (2 mL). A solution of 4N HCl in dioxane was added dropwise with stirring. The mixture was stirred for 3 hrs, then the solvent was removed *in vacuo* and the residue dissolved in DMF (1 mL). 3-(3,5-difluoro-phenyl)-acrylic acid Compound **17c** (20 mg, 0.11 mmol, 1 eq) was added, followed by HOBt (16 mg, 0.12 mmol, 1.1 eq), Et_3N (46 µL, 0.33 mmol, 3 eq) and EDCI (23 mg, 0.12 mmol, 1.1 eq). The mixture was stirred at room temperature for 16 hrs. The solvent was evaporated to provide a residue that was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic layer was removed and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, then filtered and evaporated. The resulting residue was purified by silica gel chromatography (2% to 10% 2M NH_3·MeOH in CH_2Cl_2) to provide Compound **203** (12 mg, 23%) as a pale foam. MS *m/z* 485 $(M+H)^+$.

Using the procedure of Example 21 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

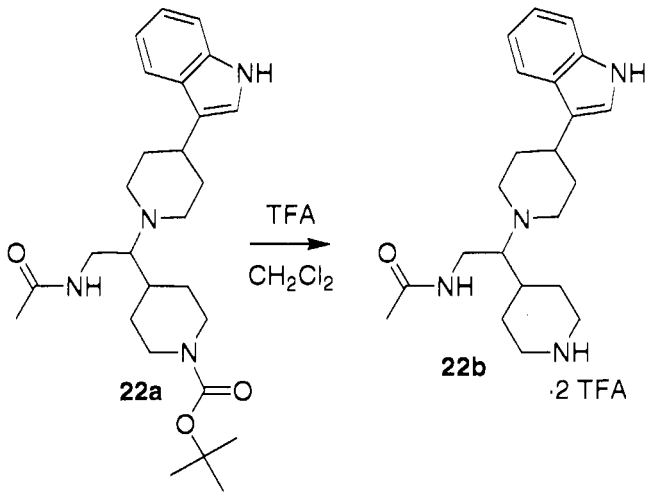
Cpd	Name	MS
200	3-(3,5-difluoro-phenyl)-1-{4-[2-hydroxy-1-(3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-yl)-ethyl]-piperidin-1-yl}-propenone	456

Example 22

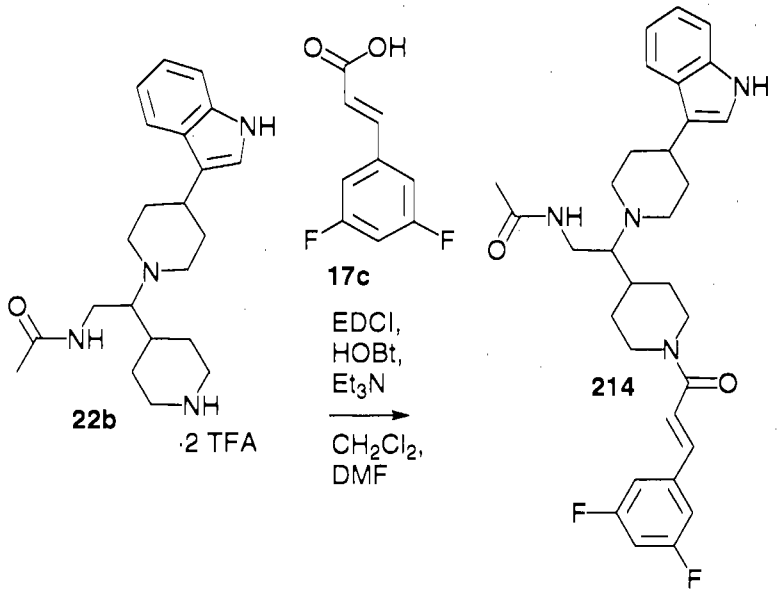
N-{2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-acetamide (Cpd **214**)



A solution of 4-{2-amino-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **13b** (431 mg, 1.01 mmol, 1 eq) in CH_2Cl_2 (5 mL) was treated with dropwise addition of acetic anhydride (572 µL, 6.06 mmol, 6 eq) followed by addition of DMAP (12 mg, 0.1 mmol, 0.1 eq). After stirring overnight at room temperature, the volatiles were removed *in vacuo* and the resulting residue dissolved in CH_2Cl_2. After washing with saturated sodium bicarbonate, the organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated. The crude residue was subjected to silica gel chromatography (2% to 10% 2M MeOH·NH_3 in CH_2Cl_2) to provide 4-{2-acetylamino-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **22a** (385 mg, 81%) as a white foam. MS *m/z* 469 $(M+H)^+$.



A solution of Compound **22a** (352 mg, 0.75 mmol) in CH_2Cl_2 (6 mL) was treated with TFA (1 mL) and the reaction mixture was stirred for 4 hrs at room temperature. The mixture was evaporated to dryness to provide *N*-{2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-piperidin-4-yl-ethyl}-acetamide, bis-trifluoroacetate salt Compound **22b** (442 mg, 99%) as a dark oil that was used in the next step without further purification. MS *m/z* 369 $(M+H)^+$.



A solution of Compound **22b** (66 mg, 0.11 mmol, 1 eq) and 3-(3,5-difluoro-phenyl)-acrylic acid Compound **17c** (24 mg, 0.12 mmol, 1.1 eq) in CH_2Cl_2 (1 mL) and DMF (0.5 mL) was treated with triethylamine (61 µL, 0.44 mmol, 4 eq), HOBt (16 mg, 0.12 mmol, 1.1 eq), and EDCI (23 mg, 0.12 mmol, 1.1 eq) and the reaction was stirred for 16 hrs at room temperature. The solvents were removed in vacuo, and the resulting residue partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was removed, and the aqueous layer extracted with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to provide a crude residue that was purified via silica gel chromatography (2% to 10% gradient of 2M MeOH·NH_3 in CH_2Cl_2) to afford Compound **214** (29 mg, 49%) as a tan foam. MS *m/z* 535 $(M+H)^+$.

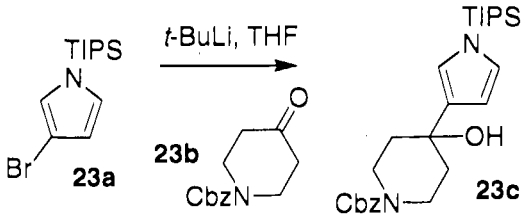
Using the procedure of Example 22 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
213	*N*-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-acetamide	553
215	N-{2-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-acetamide	567
216	*N*-({2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-*m*-tolyl-acryloyl]-piperidin-4-yl}-ethyl)-acetamide	513

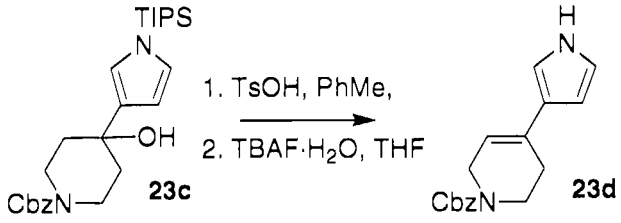
Cpd	Name	MS
217	4-{2-acetylamino-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	556
218	N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-acetamide	567
219	N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-thiophen-3-yl-acryloyl]-piperidin-4-yl}-ethyl)-acetamide	505
220	N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-formamide	539
221	N-{2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-formamide	521
222	N-{2-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-formamide	553
223	N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-m-tolyl-acryloyl]-piperidin-4-yl}-ethyl)-formamide	499
224	N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-formamide	553
225	N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-thiophen-3-yl-acryloyl]-piperidin-4-yl}-ethyl)-formamide	491
226	4-{2-formylamino-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide	542
228	1-ethyl-3-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-urea	582
229	1-{2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3-ethyl-urea	564
230	1-{2-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3-ethyl-urea	596
231	1-ethyl-3-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-m-tolyl-acryloyl]-piperidin-4-yl}-ethyl)-urea	542
232	1-ethyl-3-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-urea	596
233	1-{2-{1-[(2*E*)-3-(3-bromo-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-3-ethyl-urea	624
238	(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-carbamic acid methyl ester	569
239	{2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-carbamic acid methyl ester	551
240	{2-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-carbamic acid methyl ester	583
241	(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-m-tolyl-acryloyl]-piperidin-4-yl}-ethyl)-carbamic acid methyl ester	529
252	N-{2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-2-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-2-dimethylamino-acetamide	578

Example 23

[4-(1H-pyrrol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid (Cpd **150**)

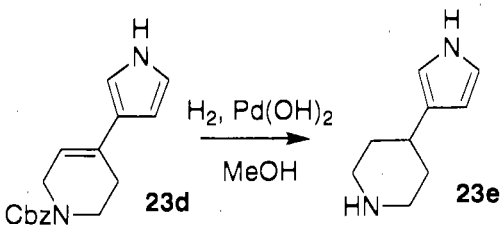


A solution of 3-bromo-1-triisopropylsilanyl-1H-pyrrole Compound **23a** (2.42 g, 8.00 mmol, 1 eq) in THF (80 mL) was cooled to –78°C. *tert*-butyl lithium (1.7M in pentane, 9.6 mL, 16.00 mmol, 2 eq) was added dropwise with stirring. The mixture was stirred for 20 min and 4-oxo-piperidine-1-carboxylic acid benzyl ester Compound **23b** (1.87 g, 8.00 mmol, 1 eq) was added and the mixture was stirred for an additional 20 mins. The solution was warmed to room temperature with stirring for 1.5 hrs. The reaction was partitioned between EtOAc and water and the aqueous layer was removed. Extraction of the aqueous layer with EtOAc was followed by combination of the organic layers, and washing twice with brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered. The filtrate was evaporated and the crude product was purified via silica gel chromatography (2:1 hexanes:EtOAc) to provide 4-hydroxy-4-(1-triisopropylsilanyl-1*H*-pyrrol-3-yl)-piperidine-1-carboxylic acid benzyl ester Compound **23c** (2.71 g, 74%) as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.28 (5H, m), 6.72 (1H, dd, J=2.6, 2.6 Hz), 6.68 (1H, dd, J=1.7, 1.7 Hz), 6.27 (1H, dd, J=3.0, 1.5 Hz), 5.14 (2H, s), 3.84 (2H, broad s), 3.46 (2H, app t, J=10.3 Hz), 2.04-1.81 (4H, m), 1.42 (3H, m), 1.08 (18H, d, J=7.5 Hz).

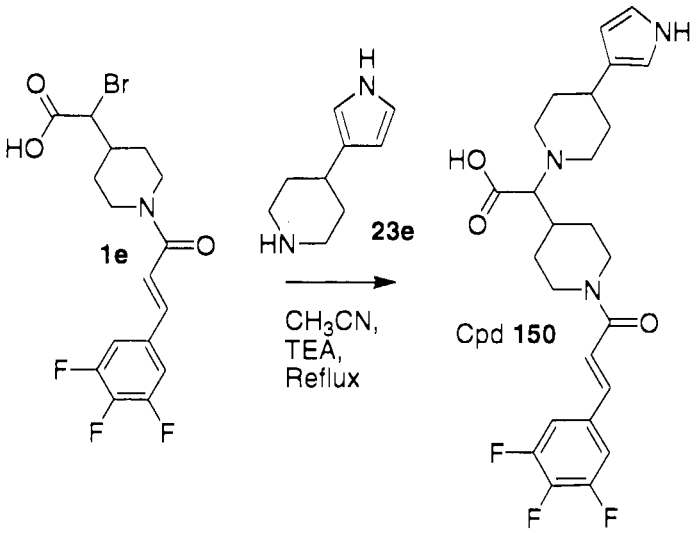


A solution of Compound **23c** (557 mg, 1.21 mmol, 1 eq) in toluene (36 mL) was treated with $TsOH·H_2O$ (19 mg, 0.098 mmol, 0.08 eq) and stirred for 30 mins at room temperature. The reaction was then partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the aqueous layer was discarded. The organic layer was washed twice with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to provide a brown oil that was used without further purification. The oil (0.61 mmol, 1 eq) was dissolved in THF (10 mL) and treated with $TBAF·H_2O$ (190 mg, 0.73 mmol, 1.2 eq). The mixture was stirred for 30 mins at room temperature, then between EtOAc and water. The aqueous layer was discarded

and the organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to provide a tan oil that was purified by silica gel chromatography (3:2 hexanes:EtOAc) to provide 4-(1*H*-pyrrol-3-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester Compound **23d** (150 mg, 87%) in two steps as an oil. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.38-7.26 (5H, m), 6.75 (1H, s), 6.67 (1H, dd, J=2.0, 2.7 Hz), 6.23 (1H, dd, J=1.4, 2.8 Hz), 5.78 (1H, s), 5.13 (2H, s), 4.05 (2H, s), 3.63 (2H, s), 2.40 (2H, s).



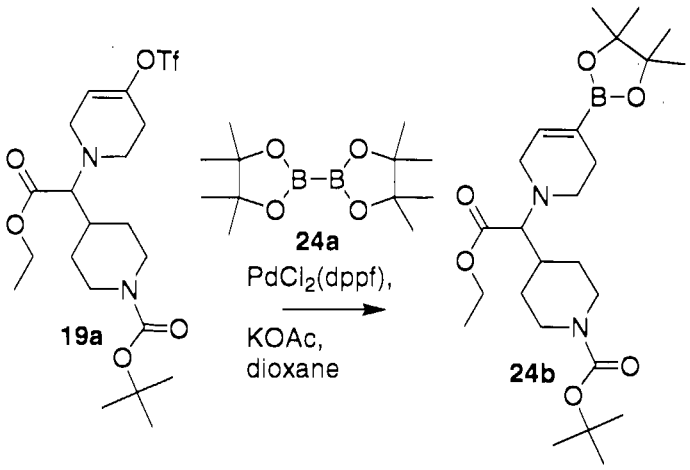
A solution of Compound **23d** (64 mg, 0.23 mmol, 1 eq) and $Pd(OH)_2$ (20 wt. % on carbon, 40 mg, 0.057 mmol, 0.25 eq) in MeOH (13 mL) was sequentially purged with nitrogen (10 mins) and hydrogen, then pressurized with hydrogen (60 psi) and shaken for 16 hrs. The pressure was released and the solution was purged with nitrogen, then filtered through Celite and evaporated to provide 4-(1*H*-pyrrol-3-yl)-piperidine Compound **23d** (32 mg, 94%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ: 6.63 (1H, s), 6.53 (1H, s), 5.99 (1H, s), 3.13 (2H, m), 2.78 (2H, m), 2.62 (1H, m), 1.93 (2H, m), 1.58 (2H, m).



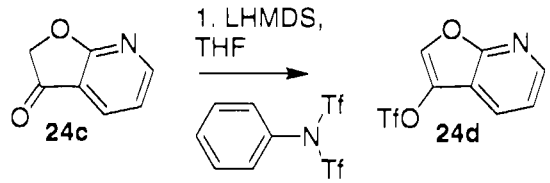
The procedure of Example 1 and Compound **23d** in place of bromo-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid Compound **1e** were used to provide Compound **150**. MS *m/z* 476 $(M+H)^+$.

Example 24

(2*E*)-1-{4-[1-(4-furo[2,3-b]pyridin-3-yl-piperidin-1-yl)-2-hydroxy-ethyl]-piperidin-1-yl}-3-(3,4,5-trifluoro-phenyl)-propenone (Cpd **248**)

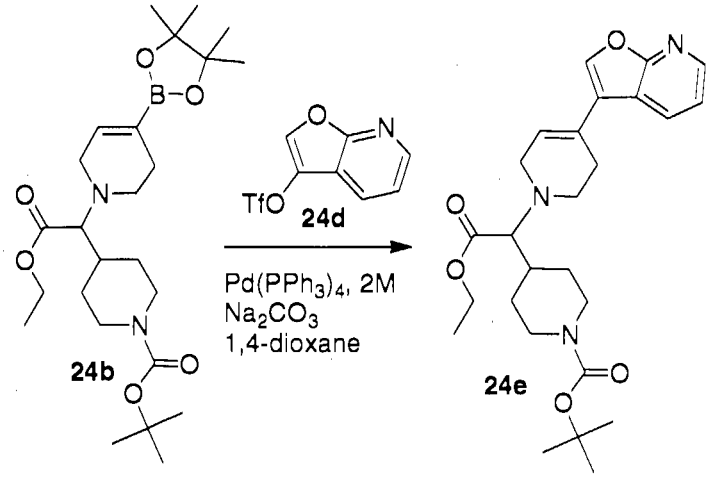


A solution of 4-[ethoxycarbonyl-(4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **19a** (200 mg, 0.40 mmol, 1 eq), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (also referred to as bis-pinacolato-diboron) Compound **24a** (112 mg, 0.44 mmol, 1.1 eq), potassium acetate (118 mg, 1.20 mmol, 3 eq) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (10 mg, 0.012 mmol, 0.03 eq) in 1,4-dioxane (3 mL) was heated at 80°C for 4 hrs. The reaction mixture was cooled and partitioned between EtOAc and brine. The organic layer was removed and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over anhydrous sodium sulfate, then filtered and evaporated to provide a crude residue that was purified via silica gel chromatography (3:1 to 2:1 hexanes:EtOAc) to provide 4-{ethoxycarbonyl-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridin-1-yl]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **24a** (137 mg, 72%) as a viscous oil. MS *m/z* 479 $(M+H)^+$.

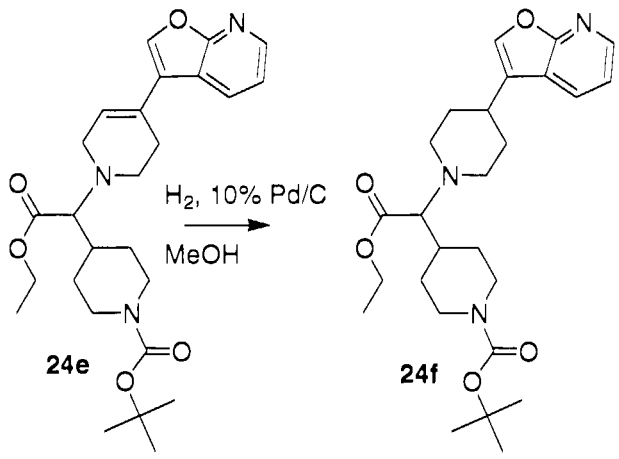


A solution of furo[2,3-b]pyridin-3-one Compound **24c** (124 mg, 0.92 mmol, 1 eq) in THF (7.5 mL) was cooled to –78°C and treated with dropwise addition of LHMDS (1M in THF, 1 mL, 1.01 mmol, 1.1 eq). The mixture was stirred for 30 min, then *N*-phenyl-trifluoromethanesulfonimide (361 mg, 1.01 mmol, 1.1 eq) was added and the reaction was warmed to 0°C. The mixture was then stirred for 1 hr at 0°C, then evaporated to dryness. The

resulting crude residue was purified by neutral alumina chromatography (3:1 hexanes:EtOAc) to provide trifluoro-methanesulfonic acid furo[2,3-b]pyridin-3-yl ester Compound **24d**, which was used immediately in the next step.

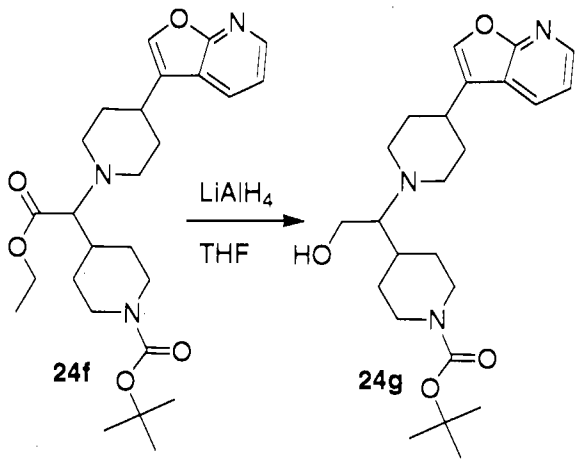


A solution of Compound **24b** (94 mg, 0.20 mmol, 1 eq), Compound **24d** (70 mg, 0.26 mmol, 1.3 eq), and tetrakis(triphenylphosphine) palladium (10 mg, 0.0087 mmol, 0.04 eq) in 2M sodium carbonate (0.4 mL) and 1,4-dioxane (2 mL) were added to a microwave reaction vessel. The solution was subjected to microwave irradiation (250W pMax, 110°C, 4.5 min ramp, 5 min hold) and then cooled. The reaction was partitioned between EtOAc and saturated NaHCO3 and the organic layer removed. The aqueous layer was extracted with EtOAc and the organic layers were combined and dried over anhydrous sodium sulfate, then filtered and evaporated. The resulting residue was subjected to silica gel chromatography (1:1 hexanes:EtOAc) to provide 4-[ethoxycarbonyl-(4-furo[2,3-b]pyridin-3-yl-3,6-dihydro-2*H*-pyridin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **24e** (51 mg, 54%). MS *m/z* 470 $(M+H)^+$.

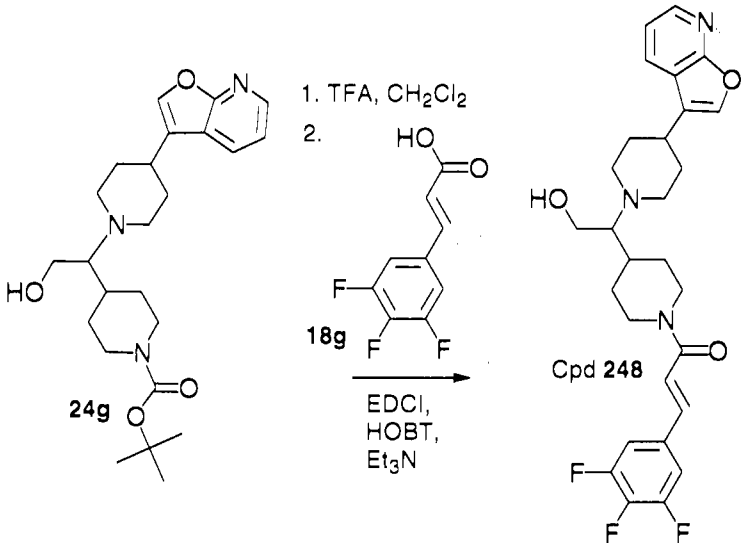


A solution of Compound **24e** (51 mg, 0.11 mmol, 1 eq) and 10% palladium on carbon (50 mg, 0.047 mmol, 0.43 eq) in MeOH (2 mL) was sequentially purged with nitrogen and

hydrogen and stirred under a balloon atmosphere of hydrogen for 16 hrs. The reaction mixture was purged with nitrogen, filtered through celite, then evaporated and subjected to silica gel chromatography (1:1:1 CH_2Cl_2:hexanes:EtOAc) to provide 4-[ethoxycarbonyl-(4-furo[2,3-b]pyridin-3-yl-piperidin-1-yl)-methyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **24f** (14 mg, 27%) as an oil. MS *m/z* 472 $(M+H)^+$.



Compound **24f** (14 mg, 0.030 mmol, 1 eq) was dissolved in THF and cooled to 0°C. A solution of lithium aluminum hydride (1M in THF, 0.045 mL, 0.045 mmol, 1.5 eq) was added dropwise with stirring, followed by additional lithium aluminum hydride solution (0.075 mL) over a 2 hr period. The reaction was quenched by successive addition of water (5 µL), 15% NaOH (5 µL), and water (15 µL). The solution was stirred for 1 hr, then filtered through celite and the solids were washed with EtOAc. The combined filtrates were evaporated to provide 4-[1-(4-furo[2,3-b]pyridin-3-yl-piperidin-1-yl)-2-hydroxy-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester Compound **24g** (13 mg, quant) as a clear film that was used in the next step without further purification. MS *m/z* 430 $(M+H)^+$.

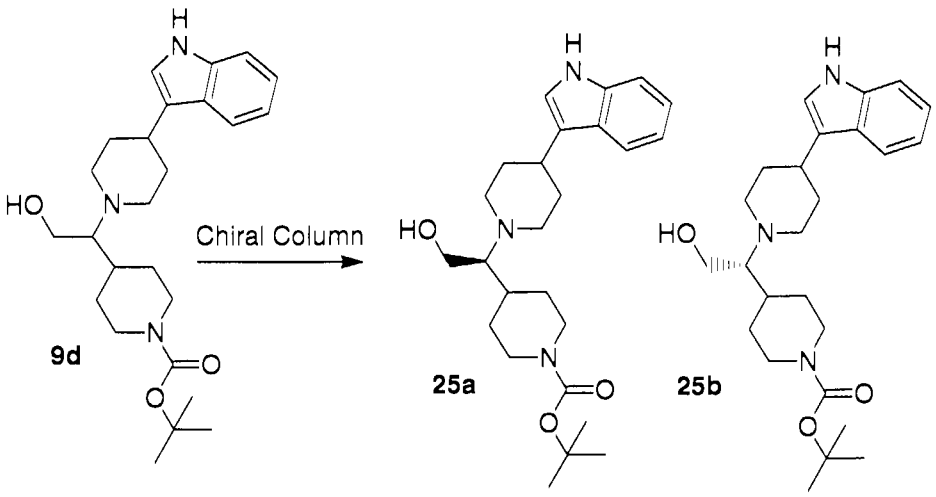


A solution of Compound **24g** (13 mg, 0.030 mmol, 1 eq) in CH_2Cl_2 (4 mL) was cooled to 0°C. TFA (1 mL) was added and the reaction mixture was stirred at 0°C for 1 hr, then room temperature for 2 hrs. The solvents were removed in vacuo and the resulting residue was dissolved in CH_2Cl_2 (1 mL) and DMF (0.2 mL). Triethylamine (0.017 mL, 0.12 mmol, 4 eq), HOBt (4 mg, 0.033 mmol, 1.1 eq), and 3-(3,4,5-trifluoro-phenyl)-acrylic acid Compound **18g** (6 mg, 0.030 mmol, 1 eq) were added and the reaction was cooled to 0°C. EDCI (7 mg, 0.036 mmol, 1.2 eq) was added and the reaction mixture was stirred for 16 hrs, slowly warming to room temperature. The solvents were removed in vacuo, then the resulting residue was dissolved in CH_2Cl_2 and partitioned with saturated NaHCO3. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous sodium sulfate, then filtered and evaporated to provide a crude residue, which was purified via silica gel chromatography to provide Compound **248** (7 mg, 45%) as a pale foam.

Example 25

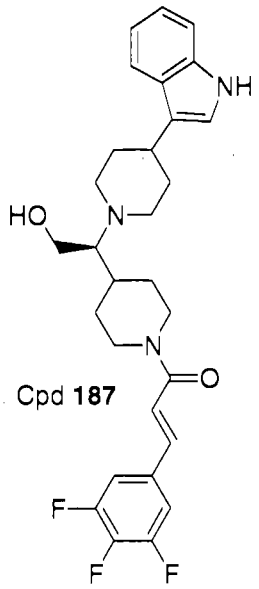
(2*E*)-1-(4-{(1*S*)-2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone (Cpd **187**)

(2*E*)-1-(4-{(1*R*)-2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone (Cpd **188**)



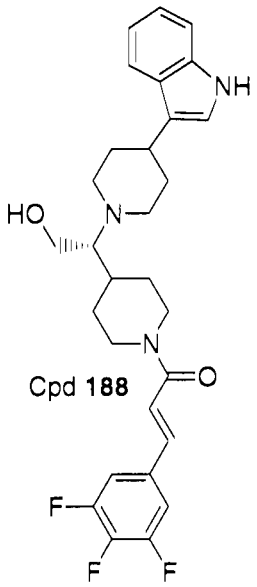
The racemic 4-{2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **9d** (220 mg) was enantiomerically separated to provide a 4-{(1*S*)-2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound **25a** (60 mg, 55%) and a 4-{(1*R*)-2-hydroxy-1-[4-(1*H*-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid *tert*-butyl ester Compound

25b (60 mg, 55%) via chiral HPLC chromatography using a Chiralpak AD column (Mobile phase: 15% heptane in ethanol). MS *m/z* 428 $(M+H)^+$ (for each enantiomer).



Cpd **187**

The procedure of Example 9 and Compound **25a** in place of Compound **9d** were used to provide Compound **187**. MS *m/z* 512 $(M+H)^+$.



Cpd **188**

The procedure of Example 9 and Compound **25b** in place of Compound **9d** were used to provide Compound **188**. MS *m/z* 512 $(M+H)^+$.

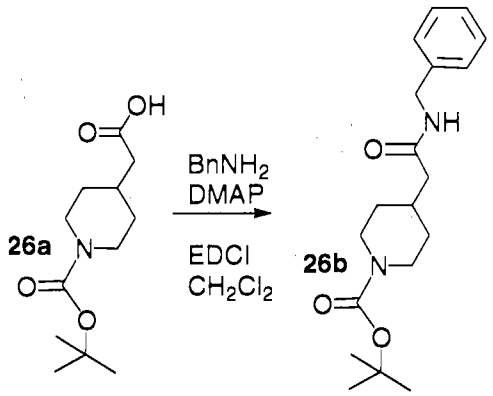
Using the procedure of Example 25 (with the exception of the mobile phase being changed from 15% heptane in ethanol to 15% ethanol in heptane) and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS

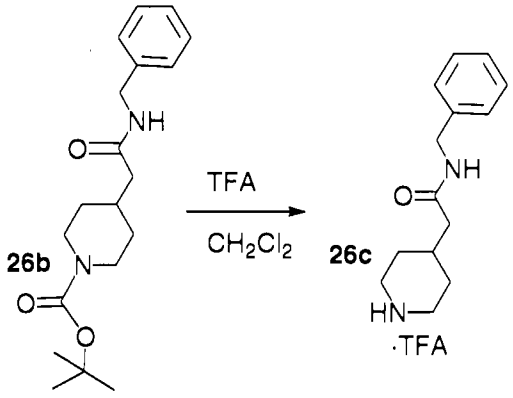
Cpd	Name	MS
180	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{(1*S*)-2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	485
181	(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{(1*R*)-2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone	485

Example 26

[4-(benzylcarbamoyl-methyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid (Cpd **148**)

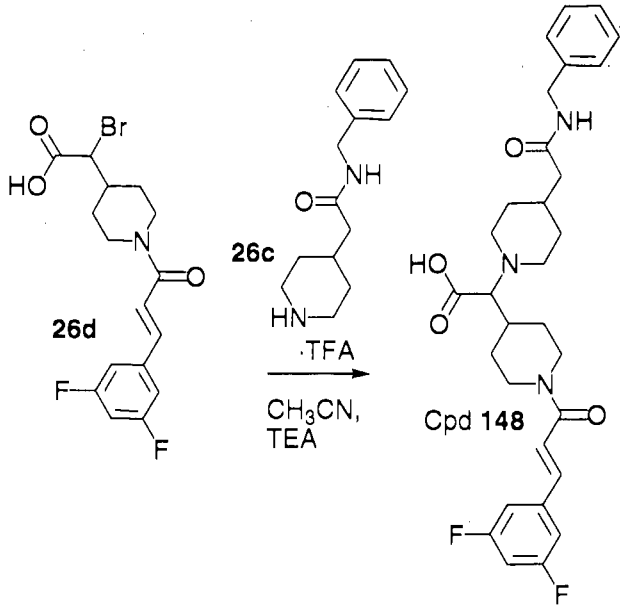


A solution of benzylamine (655 mL, 6.00 mmol, 3 eq), 4-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester Compound **26a** (487 mg, 2.00 mmol, 1 eq) and DMAP (24 mg, 0.20 mmol, 0.1 eq) in CH_2Cl_2 (5 mL) was treated with EDCI (422 mg, 2.20 mmol, 1.1 eq). The mixture was stirred for 16 hrs, then the reaction mixture was poured into EtOAc and sequentially washed with 1N HCl, brine, saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous sodium sulfate, then filtered and evaporated to provide 4-(benzylcarbamoyl-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester Compound **26b** (455 mg, 69%) as a white solid that was used in the next step without further purification. MS *m/z* 355 $(M+H)^+$.



A solution of Compound **26b** (93 mg, 0.28 mmol) in CH_2Cl_2 (1.5 mL) was cooled to 0°C with stirring. TFA (0.5 mL) was added dropwise and the reaction mixture was stirred for 4

hrs. The solvents were removed *in vacuo* to provide *N*-benzyl-2-piperidin-4-yl-acetamide, trifluoroacetate salt Compound **26c** (96 mg, 99%) as a clear oil that was used in the next step without further purification.



The procedure of Example 1 and 3-(3,5-difluoro-phenyl)-acryloyl chloride Compound **12b** in place of 3-(3,4,5-trifluoro-phenyl)-acryloyl chloride Compound **1a** was used to prepare bromo-{1-[3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid Compound **26d**.

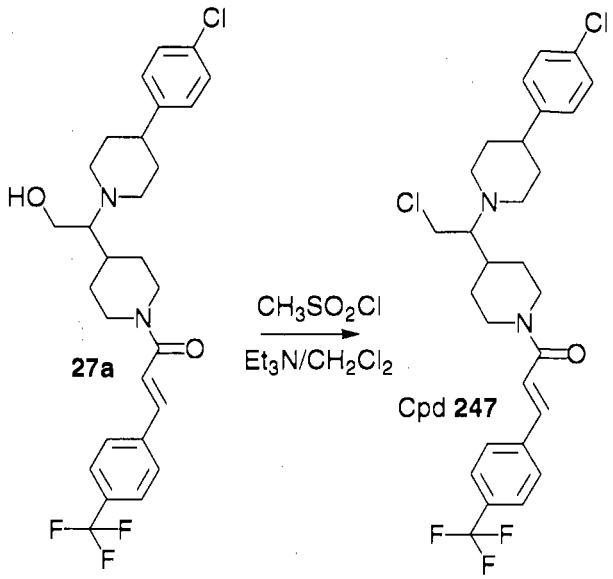
The procedure of Example 1, Compound **26c** in place of bromo-{1-[3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid Compound **1e** and Compound **26c** in place of 3-piperidin-4-yl-1H-indole Compound **1f** were used to provide Compound **148**. MS *m/z* 540 $(M+H)^+$.

Using the procedure of Example 26 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
149	[4-(benzylcarbamoyl-methyl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid	558

Example 27

(2*E*)-1-(4-{2-chloro-1-[4-(4-chloro-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(4-trifluoromethyl-phenyl)-propenone
(Cpd **247**)



Et_3N (0.02 mL, 0.14 mmol) and methanesulfonyl chloride (10 mg, 0.088 mmol) were added to a solution of Compound **27a** (20 mg, 0.041 mmol) in DCM (3 mL). The mixture was stirred at room temperature for 2 hrs, then concentrated in vacuo for 0.5 hrs. The resulting residue was purified via preparative TLC with 50% EtOAc/Hexane to provide Compound **247** (7 mg, 32%). MS *m/z* 539 $(M+H)^+$.

Using the procedure of Example 27 and known appropriate reagents and starting materials, the following compounds of the invention were prepared:

Cpd	Name	MS
245	(2*E*)-1-(4-{2-chloro-1-[4-(4-chloro-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4-dichloro-phenyl)-propenone	539

Biological Activity

Compounds of the invention were subjected to various representative biological tests. The results of these tests are intended to illustrate the invention in a non-limiting fashion.

Example 28

MCP-1 Receptor Binding Assay in THP-1 Cells

THP-1 cells were obtained from American Type Culture Collection (Manassas, VA, USA). The THP-1 cells were grown in RPMI-1640 supplemented with 10% fetal bovine serum

in a humidified 5% CO_2 atmosphere at 37°C. The cell density was maintained between 0.5×10^6 cells/mL.

THP-1 cells were incubated with 0.5 nM ^{125}I labeled MCP-1 (Perkin-Elmer Life Sciences, Inc. Boston, MA) in the presence of varying concentrations of either unlabeled MCP-1 (R & D Systems, Minneapolis, MN) or test compound for 2 hours at 30° C in a 96 well plate. Cells were then harvested onto a filter plate, dried, and 20 µL of Microscint 20 was added to each well. Plates were counted in a TopCount NXT , Microplate Scintillation & Luminescence Counter (Perkin-Elmer Life Sciences, Inc. Boston, MA). Blank values (buffer only) were subtracted from all values and drug treated values were compared to vehicle treated values. 1 µM cold MCP-1 was used for nonspecific binding.

Table 1 lists IC_{50} values for inhibition of MCP-1 binding to CCR2 obtained for test compounds of the invention. Where an IC_{50} value was not obtained for a particular compound, the percent inhibition is provided at a test concentration of 25 µM.

Table 1

Inhibition of MCP-1 Binding IC_{50} (µM)

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
1	0.253	87	2.802	173	0.43
2	1.83	88	0.02	174	0.15
3	3.8	89	0.095	175	0.188
4	0.37	90	0.48	176	0.07
5	0.84	91	0.305	177	3
6	0.002	92	0.04	178	0.09
7	0.02	93	0.004	179	0.23
8	0.065	94	0.01	180	0.07
9	0.035	95	0.02	181	0.04
10	8.6	96	0.12	182	0.33
11	2.167	97	0.25	183	0.47
12	0.41	98	0.89	184	1.6
13	0.001	99	0.81	185	0.84
14	0.364	100	0.43	186	0.36
15	0.015	101	0.02	187	0.0006
16	0.03	102	0.26	188	0.0295
17	0.16	103	0.07	189	0.17
18	0.004	104	0.09	190	0.21
19	0.01	105	0.09	191	0.1
20	0.024	106	0.02	192	0.22
21	3.4	107	1.8	193	0.14

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
22	0.025	108	0.003	194	2.3
23	0.015	109	0.02	195	3.3
24	0.01	100	6.8	196	5.7
25	0.007	111	11.2	197	1.2
26	0.02	112	0.004	198	0.0006
27	0.08	113	0.006	199	0.02
28	0.1	114	0.35	200	2
29	0.024	115	0.32	201	0.001
30	0.017	116	0.0006	202	0.0193
31	0.008	117	1	203	0.51
32	1.1	118	3.2	204	0.004
33	0.72	119	0.01	205	0.04
34	0.01	120	0.08	206	2
35	0.008	121	0.0002	207	0.21
36	0.008	122	0.04	208	0.215
37	0.655	123	0.009	209	52%
38	0.02	124	0.13	210	5
39	0.002	125	1.7	211	0.02
40	0.05	126	2.1	212	58%
41	0.014	127	0.76	213	0.08
42	0.007	128	0.32	214	0.07
43	1.1	129	0.04	215	0.09
44	2.7	130	8.55	216	0.25
45	0.14	131	3.9	217	0.21
46	0.001	132	0.05	218	0.37
47	0.01	133	0.010	219	0.34
48	0.03	134	0.3	220	0.44
49	0.025	135	0.94	221	0.41
50	0.03	136	0.08	222	0.68
51	0.3	137	0.03	223	4.1
52	0.03	138	0.172	224	54%
53	0.006	139	0.02	225	1.3
54	1.4	140	1.6	226	2.1
55	0.115	141	0.34	227	0.96
56	0.06	142	0.005	228	2.4
57	0.02	143	0.01	229	1.7
58	0.09	144	0.05	230	2.1

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
59	0.21	145	5.85	231	4.6
60	0.04	146	0.007	232	4
61	0.12	147	0.15	233	0.66
62	0.08	148	8.8	234	11.2
63	1.61	149	16.6	235	0.03
64	0.02	150	1.6	236	0.02
65	0.353	151	0.01	237	0.215
66	17.70	152	1.9	238	2.4
67	0.845	153	0.003	239	3
68	3.55	154	0.27	240	4.6
69	14.2	155	0.207	241	58%
70	0.003	156	0.08	242	0.23
71	0.02	157	0.44	243	0.09
72	0.03	158	0.1	244	0.26
73	0.15	159	0.27	245	2.17
74	0.005	160	56%	246	0.07
75	0.004	161	0.05	247	53%
76	0.002	162	0.007	248	1.9
77	0.07	163	0.03	249	0.02
78	0.14	164	0.01	250	2.9
79	0.008	165	0.08	251	0.39
80	0.078	166	0.006	252	5.8
81	0.03	167	0.073	253	42%
82	0.11	168	0.02	254	0.12
83	0.004	169	0.057	255	2.4
84	2.9	170	0.04	256	25%
85	0.17	171	0.0045	258	0.2
86	0.21	172	0.032	259	0.002

Example 29

MCP-1 Induced Calcium Mobilization in THP-1 Cells

THP-1 cells were plated at a density of 8 x 10^5 cells/ mL (100 µL/well) into poly-D lysine coated clear bottom, black 96 well plates. The cells were loaded with 5 µM fluo-3 for 45 minutes. The fluo-3 was washed off and cells were incubated with varying concentrations of test compound for 15 minutes. The change in calcium ion concentration upon addition of 0.2 µM MCP-1 was determined using FLIPR and compared to vehicle.

Table 2 lists IC_{50} values for inhibition of MCP-1 induced influx of calcium ions. Where an IC_{50} value was not obtained for a particular compound, the percent inhibition is provided at a test concentration of 25 μM.

Table 2

Inhibition of MCP-1 Induced Calcium Ion Influx IC_{50} (μM)

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
6	0.005	137	0.21	187	0.00005
9	0.002	138	1.29	188	0.01
13	0.004	139	0.04	189	0.16
14	1.13	141	6.9	190	0.25
65	0.12	142	0.03	191	0.17
87	0.36	143	0.08	192	0.17
88	0.41	144	1.3	193	0.14
89	0.47	146	0.05	198	0.00002
91	0.89	147	0.6	199	0.004
96	0.14	153	0.007	201	0.0006
97	0.97	154	4.8	202	0.008
98	1.85	155	0.94	203	5
99	1.6	156	50%	204	0.005
100	0.48	157	0.32	205	0.02
101	0.13	158	0.14	207	0.11
102	0.86	159	2.1	208	0.0008
103	0.49	160	33%	211	0.005
104	1.01	161	0.18	213	0.09
105	0.13	162	0.002	214	0.18
106	0.11	163	0.01	215	0.02
108	0.01	164	0.009	216	1.8
109	0.03	165	0.11	217	2
112	0.0006	166	0.008	218	1.9
113	0.001	167	0.03	219	52%
114	0.21	168	0.01	220	0.96
115	0.18	169	0.17	227	0.87
116	0.002	170	0.01	233	1.8
119	0.008	171	0.007	235	0.02
120	0.001	172	0.02	236	0.03
121	0.0001	173	21%	237	0.07
122	0.0008	175	2.30	242	0.04
123	0.004	176	2.61	244	0.08

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
124	0.07	178	2.35	245	0.4
127	0.82	179	2.06	246	0.02
128	0.02	180	0.12	251	0.56
129	0.02	181	0.16	253	3.9
132	0.003	182	7.87	254	0.03
133	0.0008	183	9.25	256	11
134	0.01	184	14%	258	2.3
135	7.1	185	4.6	259	88%
136	0.13	186	6.1		

Example 30

MCP-1 Induced Chemotaxis in THP-1 Cells

MCP-1 induced chemotaxis was run in a 24-well chemotaxis chamber. MCP-1 (0.01 μg/mL) was added to the lower chamber and 100 μL of THP-1 cells (1×10^7 cell/mL) was added to the top chamber. Varying concentrations of test compound were added to the top and bottom chambers. Cells were allowed to chemotax for 3 hours at 37 °C and 5% CO_2. An aliquot of the cells that had migrated to the bottom chamber was taken and counted then compared to vehicle.

Table 3 lists IC_{50} values for inhibition of MCP-1 induced chemotaxis. Where an IC_{50} value was not obtained for a particular compound, the percent inhibition is provided at a test concentration of 25 μM.

Table 3

Inhibition of MCP-1 Induced Chemotaxis IC_{50} (μM)

Cpd	IC50	Cpd	IC50	Cpd	IC_{50}
2	1.81	85	0.19	159	0.86
6	0.008	86	0.28	161	0.09
7	0.008	87	1	162	0.02
8	0.01	88	0.24	163	0.15
9	0.02	89	0.21	164	0.04
13	0.006	91	0.27	165	0.025
14	0.07	92	0.1	166	0.03
15	0.006	93	0.02	167	0.03
16	0.02	94	0.01	168	0.04
17	0.02	95	0.02	169	0.055
18	0.008	96	0.08	170	0.009
19	0.004	97	0.23	171	0.006

Cpd	IC50	Cpd	IC50	Cpd	IC_{50}
20	0.01	98	2.2	172	0.03
22	0.004	99	2.5	173	0.13
23	0.003	100	0.94	174	0.45
24	0.0007	101	0.14	175	0.3
25	0.01	102	0.23	176	0.09
26	0.03	103	0.09	178	0.18
27	0.01	104	0.16	179	0.14
28	0.43	105	0.01	180	0.09
29	0.0004	106	0.21	181	0.07
30	0.001	108	0.02	182	0.35
31	0.002	109	0.03	183	0.4
33	0.61	112	0.004	185	0.34
34	0.006	113	0.095	186	0.96
35	0.03	114	0.29	187	0.002
36	0.0004	115	0.46	188	0.02
37	0.38	116	0.0004	189	0.72
38	0.004	119	0.01	190	0.2
39	0.0019	121	0.012	191	0.15
40	0.03	123	0.005	192	0.35
41	0.04	127	0.75	193	1.3
42	0.0008	129	0.08	198	0.0002
46	0.0002	132	0.07	199	0.03
47	0.0002	133	0.04	201	0.003
48	0.04	134	0.09	202	0.015
49	0.004	135	0.77	203	1.2
53	0.0007	136	0.14	204	0.01
57	0.003	137	0.08	205	0.04
58	0.13	138	0.217	207	0.19
59	0.09	139	0.05	208	0.013
60	0.07	141	0.76	211	0.008
61	0.08	142	0.06	213	0.17
62	0.18	143	0.08	214	0.19
65	1.6	144	0.5	215	0.46
70	0.02	146	0.053	216	0.7
71	0.007	147	0.04	217	0.62
72	0.03	151	0.03	235	0.008
74	0.006	153	0.009	236	0.02

Cpd	IC50	Cpd	IC50	Cpd	IC_{50}
75	0.009	154	0.16	237	0.11
76	0.01	155	0.13	242	0.27
77	0.06	156	0.12	251	0.17
81	0.03	157	0.46	254	0.02
82	0.21	158	0.1	259	0.005
83	0.03				

Example 31

Collagen-Induced Arthritis Model

In a collagen-induced arthritis model in mice, DBA1 mice were immunized with bovine type II collagen on day 0, injected (*sc*) with lipopolysaccharide (LPS) on day 21, and dosed (*ip, bid*) with a test compound at either 25, 50 or 100 mg/kg from day 20 to day 35. Body weight was monitored, and clinical disease score recorded every 2-3 days starting on day 20.

Test compound was dosed in one of two vehicles:

1) 10% Pharmasolve:20% PEG-400:70% of a 1% solution of Tween-80 in water; or,

2) 30% PEG-400:20% Solutol:50% of a 0.1 N solution of $NaHCO_3$.

At a dose of 100 mg/kg, Compound 6 (in either vehicle) inhibited the development of arthritis (clinical disease score on day 35) by greater than 90%.

Compound 13 (Pharmasolve vehicle only) inhibited the development of arthritis (clinical disease score on day 35) by 23%, 50% and 79% at the 25, 50, and 100 mg/kg doses, respectively. Histological analyses showed that the compounds significantly inhibited infiltration of monocytes and lymphocytes into the joints, but did not significantly affect infiltration by polymorphonuclear leukocytes.

Example 32

Adjuvant-Induced Arthritis Model (Dosing from Day 0-14)

In the adjuvant-induced arthritis model, 7-week old male Lewis rats are injected in the right hind footpad with a mixture of heat-killed *Mycobacterium Butyricum* (0.5 mg) in liquid paraffin oil (50 µL). An increase in volume of the contralateral (non-injected) hind paw is a measure of arthritis severity.

Body weight and hind paw volume (as measured by mercury plethysmography volume displacement) are typically recorded on days 0, 3, 7, 10, 12, 14, and 16. Animals were dosed with test Compound 6 (*ip, bid*, 100 mg/kg) from days 0-14, or with a vehicle control. As a

positive control for inhibition, a separate group of rats was injected with indomethacin (orally, once per day, 3 mg/kg) from days 10-14.

Animals dosed with Compound 6 demonstrated insignificant swelling of the contralateral paws and a 40% decrease in swelling in the injected paws. Indomethacin inhibited contralateral paw swelling by 72% and swelling in the adjuvant-injected paws by 38%.

Example 33

Adjuvant-Induced Arthritis Model (Prophylactic Dosing from Day 7-14)

Following the procedure of Example 32, animals were dosed with test Compound 13 (*ip, bid*, 100 mg/kg), or with vehicle alone, from days 7-14. Under these conditions, Compound 13 inhibited swelling of the contralateral paws by 94%.

Example 34

Adjuvant-Induced Arthritis Model (Therapeutic Dosing from Day 12-16)

Following the procedure of Example 32, animals were dosed with test Compound 6 (*ip, bid*, 100 mg/kg), or with vehicle alone, from days 12-16 (after the contralateral paws had already started to swell as a result of the arthritis). Again, indomethacin (orally, once per day, 3 mg/kg) was used as a positive control.

Under these conditions, Compound 6 inhibited contralateral paw swelling by 51% and decreased swelling in the injected paw by 40%. Indomethacin inhibited contralateral paw swelling by 69% and inhibited adjuvant-injected paw swelling by 40%.

Example 35

Mouse Model of Allergic Asthma:

An allergic asthma model in mice was used to test compounds of the invention for therapeutic effect on asthmatic response as a function of airway inflammation and hyperresponsiveness (Malaviya, et al., *J. Phar. Exp. Ther.*, **2000**, 295: 912-926). Airway hyperresponsiveness in asthmatic patients is a cardinal feature of allergic asthma and is maintained as a result of persistent airway inflammation. Eosinophils are the prominent cells involved in airway inflammation and are found in large numbers in sputum and bronchoalveolar lavage fluids.

Airway responsiveness was measured in unrestrained mice by noninvasive whole body plethysmography using a BioSystem plethysmography instrument (BUXCO, Troy, NY). Each animal was individually placed in the plethysmography instrument chamber and chamber pressure was used as a measure of the difference between thoracic volume expansion or

contraction and air volume removed or added to the chamber during breathing. The differential of this function with respect to time produced a pseudo flow value that was proportionate to the difference between the rate of the thoracic volume expansion and nasal air flow (Hamelmann, et al., *J. Respir. Crit. Care Med.*, **1997**, 156: 766-775).

Animals and Method:

Three treatment groups of BALB/c female mice (6-8 weeks old) were tested in the 32 day study:

Group 1: vehicle control phosphate buffered saline (PBS)-sensitized and PBS-challenged mice;
Group 2: positive control ovalbumin (OVA)-sensitized and OVA-challenged mice; and,
Group 3: OVA-sensitized and OVA-challenged mice treated with Compound 13.

The vehicle used was a mixture of 20% Solutol, 30% PEG400 and 50% 0.1N $NaHCO_3$.

Day 0 and 14:

Group 1 mice were sensitized by injection (ip) with PBS; and,
Group 2 mice were OVA sensitized by injection (ip) with OVA (20 μg) dissolved in PBS adsorbed on 2.25 mg alum.

Day 28, 29 and 30:

Challenge Phase

Group 1 mice were challenged with PBS by ultrasonic nebulization for 20 min.

A first subset of Group 2 mice was OVA-challenged by ultrasonic nebulization of OVA (5 mg/mL) for 20 min.
A second subset of Group 2 mice was also OVA-challenged by ultrasonic nebulization of OVA (5 mg/mL) for 20 min.

Treatment Phase

Group 1 mice were treated by injection (*ip*) with vehicle at 30 min before and at 6 hr after the PBS challenge.
Group 2 (first subset) mice were treated by injection (*ip*) with vehicle at 30 min before and at 6 hr after the OVA challenge.
Group 2 (second subset) mice were treated by injection (*ip*) with Compound 13 (100 mg/kg) at 30 min before and at 6 hr after the OVA challenge. The second subset was then designated as treatment Group 3.

Day 31:

Group 1 and Group 2 (first subset) mice were dosed twice with vehicle alone, the second dose for each group was administered 6 hr after the first dose; and,

Group 3 mice were dosed twice with Compound 13 (100 mg/kg), the second dose was administered 6 hr after the first dose.

Day 32:

The three treatment groups were challenged via airway by means of methacholine inhalation and asthmatic response was measured as a function of airway hyper-responsiveness.

Baseline Phase

A baseline reading over a 5 min period for each of the mice in the three treatment groups was taken in the plethysmography instrument, then the baseline readings were averaged.

Challenge Phase

Group 1 mice were nebulized with saline at increasing doses (1-30 mg/ml) over a 2 min period.

Group 2 (first subset) and Group 3 mice were nebulized with methacholine at increasing doses (1-30 mg/ml) over a 2 min period.

Post-Challenge Phase

A 5 min post-challenge reading for each of the mice was taken and the readings were averaged.

Reduction in airway hyperresponsiveness was calculated according to the following formula:

$$(100\%) \times \left[1 - \frac{(\text{Treated Reading}^{Avg} - \text{Veh. Control Reading}^{Avg})}{(\text{Positive Control Reading}^{Avg} - \text{Veh. Control Reading}^{Avg})} \right]$$

Airway inflammation was measured by eosinophil cell count in bronchoalveolar saline lavage samples (1 mL) of the mice from the three groups. The lavage fluid was centrifuged and the supernatant was removed. The cell pellet was resuspended in saline containing 0.1% BSA, then cytospin smears were made from the cell suspension and stained with Giemsa. The number of eosinophils was counted and the cell concentration adjusted to 0.1×10^6/mL.

Airway Hyperresponsiveness Results:

Group 1 mice (661±80; n=4);

Group 2 mice (1425±128; n=7); and,

Group 3 mice (1147±49; n=4).

The result for the mice treated with Compound 13 represents an approximate average of 36% reduction in airway hyperresponsiveness compared to the non-treated mice.

Eosinophil Infiltration Results:

Group 1 mice ($0\pm0 \times 10^5$/mL; n=4);

Group 2 mice ($0.8\pm0.2 \times 10^5$/mL; n=9); and,

Group 3 mice ($0.2\pm0.1 \times 10^5$/ml; n=3).

The result for the mice treated with Compound 13 represents an average 75% reduction in airway inflammation compared to the non-treated mice.

Example 36

Inhibition of ovalbumin-induced allergic rhinitis in mice

BALB/c mice are sensitized by i.p. injection of OVA emulsified in alum (Day 0, 5, 14, 21). Groups of mice are each challenged by intranasal injection of OVA (Day 22-35, 38). Control group mice receive an equal volume of vehicle by intranasal injection. Nasal symptoms (number of sneezes and episodes of nose rubbing by the front paws) are counted during the 5 min period following the last intranasal injection (Day 38).

Prophylactic effect

A test compound (in PBS) is administered by intranasal injection (10 and 30 μg/nostril) to both nostrils twice daily 1 hr and 6 hrs prior to intranasal challenge (Days 22-35), once per day prior to intranasal challenge (Days 36, 37) then 1 hr and 6 hrs prior to intranasal challenge (Day 38). One or more suitable anti-allergen agents are used as a positive control.

Compared to vehicle and the positive control, a test compound inhibits nasal symptoms (sneezing/rubbing).

Therapeutic effect

The dosing of test compound is delayed until the symptoms of rhinitis have appeared (Day 29). A test compound (in PBS) is then administered by intranasal injection (10 μg/nostril) to both nostrils four times per day prior to intranasal challenge (Days 29-38). One or more suitable anti-allergen agents are used as a positive control.

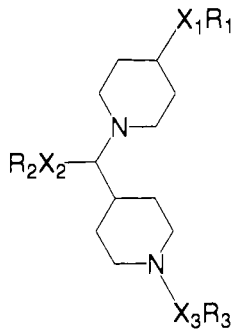
Compared to vehicle and positive control, a test compound inhibits nasal symptoms (sneezing/rubbing).

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the

invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



or a salt, isomer, prodrug, metabolite or polymorph thereof wherein

X_1 is absent, alkyl, carbonyl, alkylcarbamoyl or alkylcarbamoylalkyl,

R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, hydroxyalkyl, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, alkylamino, alkylaminoalkyl, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl,

X_2 is absent or alkyl,

R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), cyano, nitro, alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacylaryl, oxyacrylyl, oxyacrylylaryl (optionally substituted on aryl with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, nitro, amino or aminoalkyl), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl, carbamoylalkyl, urea or ureaalkyl,

X_3 is carbonyl, carboxyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, alkylcarbamoyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present, and

R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy,

carbamoyl, carbamoylalkyl or aryl (optionally substituted on aryl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

2. The compound of claim 1, wherein X_1 is absent, alkyl or alkylcarbamoylalkyl.

3. The compound of claim 1, wherein X_1 is alkyl or alkylcarbamoylalkyl.

4. The compound of claim 1, wherein X_1 is absent.

5. The compound of claim 1, wherein R_1 is phenyl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein phenyl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, alkylhydroxy, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, alkylamino, alkylaminoalkyl, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl.

6. The compound of claim 1, wherein R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, alkylhydroxy, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl or carbonylalkoxy.

7. The compound of claim 1, wherein R_1 is phenyl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein phenyl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, alkylhydroxy, nitro, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy, sulfonylalkyl, alkylcarboxy or alkylcarbonylalkoxy), alkylcarboxy, alkylcarbonylalkoxy, alkoxycarboxy, alkoxycarbonylalkoxy, sulfonylamino, sulfonylaminoalkyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, carboxy, acyl or carbonylalkoxy.

8. The compound of claim 1, wherein R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or

more of alkyl, alkoxy, halogen, hydroxy, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy or sulfonylalkyl), carboxy, acyl or carbonylalkoxy.

9. The compound of claim 1, wherein R_1 is phenyl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein phenyl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy or sulfonylalkyl), carboxy, acyl or carbonylalkoxy.

10. The compound of claim 1, wherein X_2 is absent.

11. The compound of claim 1, wherein X_2 is alkyl.

12. The compound of claim 1, wherein R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), cyano, nitro, alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacylaryl, oxyacrylyl, oxyacrylylaryl (optionally substituted on aryl with one or more of alkyl, alkoxy, cyano, halogen, hydroxy, nitro, amino or aminoalkyl), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl, carbamoylalkyl, urea or ureaalkyl.

13. The compound of claim 1, wherein R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacrylylaryl (optionally substituted on aryl with one or more of halogen or nitro), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl or ureaalkyl.

14. The compound of claim 1, wherein R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacrylylphenyl (optionally substituted on phenyl with one or more of halogen or nitro), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl or ureaalkyl.

15. The compound of claim 1, wherein X_3 is carbonyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present.

16. The compound of claim 1, wherein X_3 is carbonyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present.

17. The compound of claim 1, wherein R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or phenyl (optionally substituted on phenyl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

18. The compound of claim 1, wherein R_3 is cycloalkyl, phenyl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or aryl (optionally substituted on aryl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

19. The compound of claim 1, wherein R_3 is cycloalkyl, phenyl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, cyano, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl, carbamoylalkyl or phenyl (optionally substituted on phenyl with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl).

20. The compound of claim 1, wherein R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo, carbonylalkoxy or aryl (optionally substituted on aryl with one or more halogen).

21. The compound of claim 1, wherein R_3 is cycloalkyl, phenyl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo, carbonylalkoxy or aryl (optionally substituted on aryl with one or more halogen).

22. The compound of claim 1, wherein R_3 is cycloalkyl optionally substituted with aryl, wherein aryl is optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, nitro, amino or aminoalkyl.

23. The compound of claim 1, wherein R_3 is cycloalkyl optionally substituted with aryl, wherein aryl is optionally substituted with one or more of halogen.

24. The compound of claim 1, wherein R_3 is aryl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl,

alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl.

25. The compound of claim 1, wherein R_3 is phenyl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, hydroxy, nitro, amino, aminoalkyl, alkylamino, alkylaminoalkyl, thioalkyl, thioalkyltrihalo, carboxy, acyl, carbonylalkoxy, carbamoyl or carbamoylalkyl.

26. The compound of claim 1, wherein R_3 is aryl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo or carbonylalkoxy.

27. The compound of claim 1, wherein R_3 is phenyl optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo or carbonylalkoxy.

28. The compound of claim 1, wherein R_3 is heterocyclyl optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino or aminoalkyl.

29. The compound of claim 1, wherein R_3 is heterocyclyl optionally substituted with one or more of halogen.

30. The compound of claim 1, wherein

X_1 is absent, alkyl or alkylcarbamoylalkyl,

R_1 is aryl or heterocyclyl, wherein heterocyclyl has an optionally present nitrogen atom and wherein the nitrogen atom is optionally oxidized, and wherein aryl and heterocyclyl are each optionally substituted with one or more of alkyl, alkoxy, halogen, hydroxy, amino (optionally substituted with one or more of alkyl, acyl, carbonylalkoxy or sulfonylalkyl), carboxy, acyl or carbonylalkoxy,

X_2 is absent or alkyl,

R_2 is hydroxy, halogen, amino (optionally substituted with one or more of alkyl, formyl, acyl, sulfonylalkyl or carbonylalkoxy), alkoxy, carboxy, carbonylalkoxy, oxyacyl, oxyacrylylaryl (optionally substituted on aryl with one or more of halogen or nitro), oxycarbonylalkoxy, aminoacylamino, aminoacylaminoalkyl, carbamoyl or ureaalkyl,

X_3 is carbonyl, acyl, acyloxy, acrylyl, carbonylalkynyl, carbonylalkoxy, carbamoyl, carbamoylalkyl, thiocarbamyl or iminomethylaminocarbonyl, wherein when X_3 is carbonylalkoxy, then R_3 is optionally present, and

R_3 is cycloalkyl, aryl or heterocyclyl each optionally substituted with one or more of alkyl, alkoxy, halogen, alkyltrihalo, alkoxytrihalo, nitro, thioalkyl, thioalkyltrihalo, carbonylalkoxy or aryl (optionally substituted on aryl with one or more halogen).

31. A compound selected from the group consisting of

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

(*S*)-{[4-(1H-indol-3-yl)-piperidin-1-yl]}-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,4-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-phenyl-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

[4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(4-chloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3-bromo-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3,4-difluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(4-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3,5-dichloro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(6-chloro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3-chloro-4-fluoro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3-chloro-4-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(3,4-dichloro-benzoylamino)-imino-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[imino-(3,4,5-trifluoro-benzoylamino)-methyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

[1-(4-chloro-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(4-nitro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(4-bromo-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3,4-dichloro-phenylthiocarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-m-tolyl-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3-bromo-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-methoxy-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3-fluoro-4-methyl-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3-fluoro-4-trifluoromethyl-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(3-chloro-4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

{1-[(2*E*)-3-(4-fluoro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-trifluoromethyl-phenylthiocarbamoyl)-piperidin-4-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethyl-phenylthiocarbamoyl)-piperidin-4-yl]-acetic acid;

[4-(1H-pyrrol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

[4-(6-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

[1-(4-chloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3-nitro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

{1-[(2*E*)-3-(3-chloro-phenyl)-acryloyl]-piperidin-4-yl}-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

[1-(4-bromo-3-methyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-methyl-3-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

[1-(3,4-dichloro-phenylcarbamoyl)-piperidin-4-yl]-[4-(5-methanesulfonylamino-1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3-trifluoromethyl-phenyl)-propenone;

(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carbothioic acid (3,4-dichloro-phenyl)-amide;

4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,4-dichloro-phenyl)-amide;

4-{2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidine-1-carboxylic acid (3,5-difluoro-phenyl)-amide;

(2*E*)-1-(4-{2-hydroxy-1-[4-(6-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-1-(4-{2-hydroxy-1-[4-(7-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

[1-(3,5-bis-trifluoromethyl-phenylcarbamoyl)-piperidin-4-yl]-[4-(1H-indol-3-yl)-piperidin-1-yl]-acetic acid;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-3-(3,4-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(4-trifluoromethoxy-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

[4-(1H-indol-3-yl)-piperidin-1-yl]-[1-(3-methylsulfanyl-phenylcarbamoyl)-piperidin-4-yl]-acetic acid;

3-[1-(carboxy-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-methyl)-piperidin-4-yl]-1H-indole-5-carboxylic acid methyl ester;

[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

(2*E*)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-1-(4-{2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-1-(4-{2-hydroxy-1-[4-(5-methoxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{1-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-2-hydroxy-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{(1*S*)-2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{(1*R*)-2-hydroxy-1-[4-(4-methoxy-phenyl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-1-(4-{(1*S*)-2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

(2*E*)-1-(4-{(1*R*)-2-hydroxy-1-[4-(1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-3-(3,4,5-trifluoro-phenyl)-propenone;

N-{3-[1-(1-{1-[(2*E*)-3-(3,4-dichloro-phenyl)-acryloyl]-piperidin-4-yl}-2-hydroxy-ethyl)-piperidin-4-yl]-1H-indol-5-yl}-methanesulfonamide;

N-{3-[1-(2-hydroxy-1-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-piperidin-4-yl]-1H-indol-5-yl}-methanesulfonamide;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(7-oxy-1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

(2*E*)-3-(3,4-dichloro-phenyl)-1-(4-{2-hydroxy-1-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone;

[4-(6-fluoro-1H-indol-3-yl)-piperidin-1-yl]-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-acetic acid;

N-(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-acetamide;

(2-[4-(1H-indol-3-yl)-piperidin-1-yl]-2-{1-[(2*E*)-3-(3,4,5-trifluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl)-carbamic acid methyl ester;

acetic acid 2-{4-[5-(acetyl-methanesulfonyl-amino)-1H-indol-3-yl]-piperidin-1-yl}-2-{1-[(2*E*)-3-(3,5-difluoro-phenyl)-acryloyl]-piperidin-4-yl}-ethyl ester; and

(2*E*)-3-(3,5-difluoro-phenyl)-1-(4-{2-hydroxy-1-[4-(5-hydroxy-1H-indol-3-yl)-piperidin-1-yl]-ethyl}-piperidin-1-yl)-propenone.

32. A composition comprising an effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

33. The composition of claim 32 selected from a topically applied composition, an intranasally applied composition or an ocularly applied composition.

34. A process for preparing the composition of claim 33 comprising the step of admixing the compound of claim 1 and a pharmaceutically acceptable carrier.

35. A method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof comprising administering to the subject an effective amount of the compound of claim 1 or composition or medicament thereof.

36. The method of claim 35, wherein the effective amount is from about 0.1 ng/kg/day to about 300 mg/kg/day.

37. The method of claim 35, wherein the syndrome, disorder or disease is associated with elevated MCP-1 expression or MCP-1 overexpression, or is an inflammatory condition

that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression.

38. The method of claim 35, wherein the syndrome, disorder or disease is selected from ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, invasive staphyloccocia, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, or carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach.

39. The method of claim 35, wherein the method further comprises preventing, treating or ameliorating CCR2 mediated ophthalmic disorders, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, chronic obstructive pulmonary disease, allergic rhinitis, asthma, allergic asthma, periodontal diseases in a subject in need thereof comprising administering to the subject an effective amount of the compound of claim 1 or composition or medicament thereof.

40. The method of claim 39, wherein the ophthalmic disorder is selected from uveitis or allergic conjunctivitis and the periodontal disease is selected from periodonitis, gingivitis or gum disease.

41. The method of claim 40, wherein uveitis is selected from acute, recurring or chronic uveitis.

42. The method of claim 40, wherein uveitis is selected from anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis.

43. The method of claim 35, wherein the method further comprises preventing, treating or ameliorating CCR2 mediated acute uveitis, recurring uveitis, chronic uveitis, allergic conjunctivitis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, chronic obstructive pulmonary disease, allergic rhinitis, asthma, allergic asthma, periodonitis, gingivitis or gum disease in a subject in need thereof comprising

administering to the subject an effective amount of the compound of claim 1 or composition or medicament thereof.

44. The method of claim 35, wherein the method further comprises preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease in a subject in need thereof comprising administering to the subject an effective amount of the compound of claim 1 or composition or medicament thereof in a combination therapy with one or more anti-inflammatory agents, anti-infective agents or immunosuppressive agents.