QUATERNARY SALT CCR2 ANTAGONISTS

BACKGROUND OF THE INVENTION

The invention is directed to quaternary salt compounds which are antagonists to the chemoattractant cytokine receptor 2 (CCR2), pharmaceutical compositions, and methods for use thereof. More particularly, the CCR2 antagonists are phenylamino substituted quaternary salt compounds used in ameliorating or treating CCR2 mediated inflammatory disorders.

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 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, 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.

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.

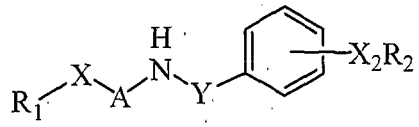
MCP-1 has been implicated in the pathogenesis of seasonal and chronic allergic rhinitis, having been found in the nasal mucosa of most patients with dust mite allergies. MCP-1 has also been found to induce histamine release from basophils *in vitro*. During allergic conditions, both allergens and histamines 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 quaternary salt compounds of Formula (I)

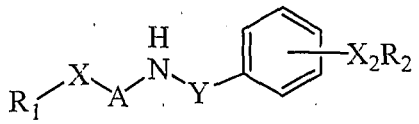


or pharmaceutically acceptable forms thereof, which are CCR2 antagonists and are useful in preventing, treating or ameliorating CCR2 mediated inflammatory syndromes, disorders or diseases in a subject in need thereof.

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 composition or medicament thereof.

DETAILED DESCRIPTION OF THE INVENTION

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



and pharmaceutically acceptable forms thereof, wherein

A is carbonyl, thiocarbonyl or sulfonyl;

X is a bond or -CH=CH-;

R_1 is selected from

(1). aryl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, alkoxycarbonyl, cyano, halogen or phenyl optionally substituted by lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, alkoxycarbonyl, cyano or halogen;

(2). C_5-C_{15} cycloalkyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen; or,

(3). heterocyclyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, aryl-lower alkyl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen;

n is 0, 1, 2, 3 or 4;

Y is a bond or $-CH_2-$;

X_2 is $-(CH_2)_m-$ wherein m is 1 or 2;

R_2 is $-N^+(R_4R_5)-ZR_3$;

Z is $-(CH_2)_p-$ wherein p is 0, 1 or 2;

R_3 is selected from

(1). aryl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen;

(2). C_5-C_{15} cycloalkyl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen; or,

(3). heterocyclyl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen; wherein, when heterocyclyl is attached via a carbon atom ring member and a heteroatom ring member is adjacent to said carbon atom, then p is 1 or 2;

R_4 and R_5 are each individually lower alkyl or lower alkenyl;

alternatively, R_4 and R_5 combine with the nitrogen atom of Formula (I) to form a heterocyclyl ring of 5 to 9 total ring atoms optionally containing one of an oxygen or sulfur ring atom, wherein the heterocyclyl ring nitrogen atom is substituted with one of lower alkyl or lower alkenyl to form a quaternary salt, and wherein $-ZR_3$ is absent and the heterocyclyl ring is optionally substituted with aryl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein A is carbonyl; X is a bond; R_1 is selected from aryl substituted by one or more lower alkyl or halogen, C_5-C_{15} cycloalkyl optionally substituted by one or more halogen, or heterocyclyl optionally substituted by one or more lower alkyl or halogen; Y is a bond; X_2 is $-CH_2-$; R_2 is $-N^+(R_4R_5)-R_3$; R_3 is selected from C_5-C_{15} cycloalkyl or heterocyclyl and R_4 and R_5 are each individually lower alkyl.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein A is carbonyl, X is a bond, R_1 is aryl optionally substituted by one or more halogen, Y is a bond, X_2 is $-CH_2-$, R_2 is $-N^+(R_4R_5)-R_3$, R_3 is heterocyclyl and R_4 and R_5 are each individually lower alkyl.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein A is carbonyl.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_1 is selected from

(1). aryl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano, halogen or phenyl optionally substituted by lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano or halogen;

(2). C_5-C_{15} cycloalkyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano or halogen; or,

(3). heterocyclyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, aryl-lower alkyl, halogen-substituted aryl or halogen.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein n is 0.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein p is 0 or 1.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_3 is C_5-C_{15} cycloalkyl or heterocyclyl; wherein, when heterocyclyl is attached via a carbon atom ring member and a heteroatom ring member is adjacent to said carbon atom, then p is 1.

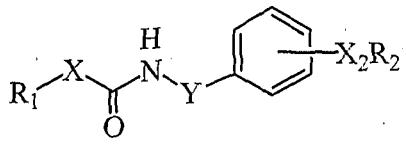
An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_4 and R_5 are each individually lower alkyl or lower allyl.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_4 and R_5 combine with the nitrogen atom of Formula (I) to form a heterocyclyl ring of 5 to 9 total ring atoms optionally containing one of an oxygen or sulfur ring atom, wherein the heterocyclyl ring nitrogen atom is substituted with lower alkyl to form a quaternary salt, and wherein $-ZR_3$ is absent and the heterocyclyl ring is optionally substituted with aryl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano or halogen.

An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof, wherein R_4 and R_5 combine with the nitrogen atom of Formula (I) to form a heterocyclyl ring of 5 to 9 total ring atoms optionally containing one of an oxygen or

sulfur ring atom, wherein the heterocyclyl ring nitrogen atom is substituted with lower alkyl to form a quaternary salt, and wherein $-ZR_3$ is absent and the heterocyclyl ring is optionally substituted with aryl optionally substituted with lower alkoxy.

An example of the invention is a compound of Formula (Ia)



or a pharmaceutically acceptable form thereof, wherein R_1, X, Y and X_2R_2 are dependently selected from

Cpd	R_1	X	Y	X_2R_2
1	3-Br-phenyl	-CH=CH-	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
2	3-Br-phenyl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
3	3-CF_3-phenyl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
4	3,4-Cl_2-phenyl	-CH=CH-	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
5	3-Br-phenyl	-CH=CH-	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
6	phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
7	3,4-Cl_2-phenyl	bond	bond	3-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
8	3-Br-phenyl	bond	bond	3-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
9	2,3-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
10	2,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
11	2,5-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
12	2,6-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
13	2-Cl-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
14	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-bicyclo[2.2.1]hept-2-yl,
15	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-(2*S*)-CH_2-tetrahydro-furan-2-yl,
16	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-(2*R*)-CH_2-tetrahydro-furan-2-yl,
17	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
18	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-CH_2-tetrahydro-pyran-4-yl,
19	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-thien-3-yl,
20	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-thiopyran-4-yl,
21	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+[(CH_3)(CH_2CH_3)]$-tetrahydro-pyran-4-yl,
22	3,4-Cl_2-phenyl	bond	bond	4-CH_2-$N^+\{(CH_3)[(CH_2)_2CH_3)]\}$-tetrahydro-pyran-4-yl,
23	3,5-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
24	3-Br-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,

Cpd	R_1	X	Y	X_2R_2
25	2-CH_3-3-Cl_2-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
26	3-Cl-4-F-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
27	3-Cl-4-OCH_3-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
28	3-Cl-4-CH_3-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
29	3-Cl-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
30	3-CN-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
31	3-OCH_3-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
32	2-CH_3-4-Cl-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
33	3-CF_3-4-Cl-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
34	4-Cl-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
35	2-CH_3-5-Cl-phenyl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
36	3,4-Cl_2-phenyl	bond	bond	4-$(CH_2)_2$-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
37	3-Br-phenyl	bond	bond	4-$(CH_2)_2$-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
38	3-Br-phenyl	-CH=CH-	bond	3-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
39	3,4-Cl_2-phenyl	bond	-CH_2-	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
40	3,4-Cl_2-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
41	3,4-Cl_2-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-thiopyran-4-yl,
42	3,5-F_2-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
43	3-Br-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
44	3-Br-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-thiopyran-4-yl,
45	3-Cl-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
46	3-F-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
47	4-Br-phenyl	-CH=CH-	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
48	3,4-Cl_2-phenyl	-CH=CH-	-CH_2-	4-CH_2-(1-CH_3-piperidinium),
49	3-Br-phenyl	-CH=CH-	-CH_2-	4-CH_2-(1-CH_3-piperidinium),
50	3,4-Cl_2-phenyl	bond	bond	4-CH_2-(1-CH_3-piperidinium),
51	3,4-Cl_2-phenyl	bond	bond	4-CH_2-(1-CH_3-pyrrolidinium),
52	3-Br-phenyl	-CH=CH-	bond	3-CH_2-(1-CH_3-piperidinium),
53	3,4-Cl_2-phenyl	-CH=CH-	bond	4-CH_2-(1-CH_3-piperidinium),
54	3,4-Cl_2-phenyl	-CH=CH-	bond	4-CH_2-[4-(2-OCH_3-phenyl)-1-CH_3-piperazin-1-ium],
55	3-Br-phenyl	-CH=CH-	bond	4-CH_2-(1-CH_3-piperidinium),
56	3-CF_3-phenyl	bond	bond	3-CH_2-(1-CH_3-piperidinium),
57	3-CF_3-phenyl	-CH=CH-	bond	4-CH_2-(1-CH_3-piperidinium),
58	3,4-Cl_2-phenyl	-CH=CH-	-CH_2-	4-CH_2-(4-CH_3-morpholin-4-ium),
59	3,4-Cl_2-phenyl	bond	bond	4-CH_2-(4-CH_3-morpholin-4-ium),
60	3,4-Cl_2-phenyl	-CH=CH-	bond	4-CH_2-(4-CH_3-morpholin-4-ium),
61	3-Br-phenyl	-CH=CH-	bond	4-CH_2-(4-CH_3-morpholin-4-ium),
62	3-CF_3-phenyl	-CH=CH-	-CH_2-	4-CH_2-(4-CH_3-morpholin-4-ium),

Cpd	R_1	X	Y	X_2R_2
63	3-Br-phenyl	-CH=CH-	bond	4-CH_2-N^+[(CH_3)($CH_2CH=CH_2$)]-tetrahydro-thiopyran-4-yl,
64	3-CF_3-phenyl	-CH=CH-	-CH_2-	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
65	3-CF_3-phenyl	bond	bond	3-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
66	3-CH_3-phenyl	-CH=CH-	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
67	3-CF_3-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
68	3-CF_3-phenyl	-CH=CH-	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
69	3-CH_3-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
70	3,4-Cl_2-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cycloheptyl,
71	3,4-Cl_2-phenyl	-CH=CH-	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
72	3-Br-phenyl	-CH=CH-	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
73	3-Br-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
74	3-CF_3-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
75	3,4-Cl_2-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
76	3-Cl-4-F-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
77	2,3-Cl_2-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
78	2,6-Cl_2-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
79	3-Cl-4-OCH_3-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
80	3-Cl-4-CH_3-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
81	2,5-Cl_2-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
82	3,4-Cl_2-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclopentyl,
83	3,4-Cl_2-phenyl	-CH=CH-	bond	3-CH_2-N^+(CH_3)$_2$-cyclohexyl,
84	4-F-phenyl	-CH=CH-	bond	3-CH_2-N^+(CH_3)$_2$-cyclohexyl,
85	3-(4-CF_3-phenyl)-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
86	3-(4-CH_3-phenyl)-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
87	3-(4-CH_3-phenyl)-phenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
88	4-biphenyl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
89	1-naphthalene	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
90	2-naphthalene	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
91	2-naphthalene	bond	bond	4-CH_2-N^+[(CH_3)(CH_2CH_3)]-tetrahydro-pyran-4-yl,
92	2-naphthalene	bond	bond	4-CH_2-N^+{(CH_3)[(CH_2)$_2CH_3$)]}-tetrahydro-pyran-4-yl,
93	7-Br-naphthalen-2-yl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
94	7-Br-naphthalen-2-yl	bond	bond	4-CH_2-N^+(CH_3)$_2$-cyclohexyl,
95	6-Br-2H-chromen-3-yl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,
96	6-Cl-2H-chromen-3-yl	bond	bond	4-CH_2-N^+(CH_3)$_2$-tetrahydro-pyran-4-yl,

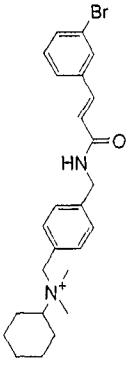
Cpd	R_1	X	Y	X_2R_2
97	6-Br-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
98	6-Cl-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
99	6-Br-2H-chromen-3-yl	bond	-CH_2-	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
100	5,7-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
101	5,7-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
102	6,8-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
103	6-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
104	6-OCH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
105	6-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
106	6-OCH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
107	6,8-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
108	6-Cl-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-(2*R*)-CH_2-tetrahydro-furan-2-yl,
109	6-Cl-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-(2*S*)-CH_2-tetrahydro-furan-2-yl,
110	6-Cl-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-(2*S*)-bicyclo[2.2.1]hept-2-yl,
111	6,8-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-bicyclo[2.2.1]hept-2-yl,
112	8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
113	8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
114	6-Cl-8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
115	6-Cl-8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
116	7,8-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
117	6-Cl-8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-bicyclo[2.2.1]hept-2-yl,
118	6-Cl-8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cycloheptyl,
119	6-Cl-8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclopentyl,

Cpd	R_1	X	Y	X_2R_2
120	6-Cl-8-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-thien-3-yl,
121	6-Cl-8-CH_3-2H-chromen-3-yl	bond	-CH_2-	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
122	6,8-Cl_2-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-thien-3-yl,
123	6-F-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
124	5-F-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
125	6-CF_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
126	8-F-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
127	7-CH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
128	7-OCH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
129	6-OCH_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
130	6-CF_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-thien-3-yl,
131	4-F-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-thien-3-yl,
132	5-F-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-thien-3-yl,
133	4-CF_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
134	8-CF_3-2H-chromen-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
135	3H-benzo[f]chromen-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
136	3H-benzo[f]chromen-2-yl	bond	bond	4-CH_2-(1-CH_3-pyrrolidinium),
137	3H-benzo[f]chromen-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
138	3H-benzo[f]chromen-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-thiopyran-4-yl,
139	3H-benzo[f]chromen-2-yl	bond	bond	4-CH_2-(4-CH_3-morpholin-4-ium),
140	3H-benzo[f]chromen-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-CH_2-tetrahydro-pyran-4-yl,

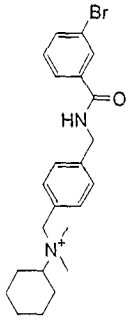
Cpd	R_1	X	Y	X_2R_2
141	3H-benzo[f]chromen-2-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
142	3-Br-8,9-dihydro-7H-benzocyclohepten-6-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
143	3-Br-8,9-dihydro-7H-benzocyclohepten-6-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
144	3-Br-8,9-dihydro-7H-benzocyclohepten-6-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
145	8,9-dihydro-7H-benzocyclohepten-6-yl	bond	bond	4-CH_2-(1-CH_3-pyrrolidinium),
146	8,9-dihydro-7H-benzocyclohepten-6-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
147	8,9-dihydro-7H-benzocyclohepten-6-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
148	8,9-dihydro-7H-benzocyclohepten-6-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
149	(2-CH_3-5-phenyl)-furan-3-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
150	[5-(4-Cl-phenyl)-2-CH_3]-furan-3-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
151	(2-CH_3-5-phenyl)-furan-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
152	benzofuran-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
153	[5-(4-Cl-phenyl)-2-CF_3]-furan-3-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
154	[5-(4-Cl-phenyl)-2-CF_3]-furan-3-yl	bond	$-CH_2-$	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
155	5-Cl-benzofuran-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
156	5-Cl-benzofuran-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
157	benzofuran-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
158	1-CH_3-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
159	5-Cl-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
160	5-Br-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
161	1-CH_3-1*H*-indol-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,

Cpd	R_1	X	Y	X_2R_2
162	(1-CH_2-phenyl)-1*H*-indol-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
163	1-CH_3-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
164	5-Cl-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
165	5-Cl-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-(2*S*)-CH_2-tetrahydro-furan-2-yl,
166	5-Cl-1*H*-indol-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-CH_2-bicyclo[2.2.1]hept-2-yl,
167	7,8-Cl_2-2,3-dihydro-benzo[b]oxepin-4-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
168	7,8-Cl_2-2,3-dihydro-benzo[b]oxepin-4-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
169	7,8-Cl_2-2,3-dihydro-benzo[b]oxepin-4-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-bicyclo[2.2.1]hept-2-yl,
170	7,8-Cl_2-2,3-dihydro-benzo[b]oxepin-4-yl	bond	-CH_2-	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
171	7,8-Cl_2-2,3-dihydro-benzo[b]oxepin-4-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-thien-3-yl,
172	5-Br-pyridin-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
173	2-Cl-pyridin-4-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
174	3-Cl-benzo[b]thien-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
175	2,5-Cl_2-thien-3-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
176	benzo[b]thien-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-tetrahydro-pyran-4-yl,
177	benzo[b]thien-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,
178	3-Cl-benzo[b]thien-2-yl	bond	bond	4-CH_2-$N^+(CH_3)_2$-cyclohexyl,

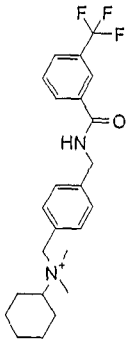
An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof represented as follows:



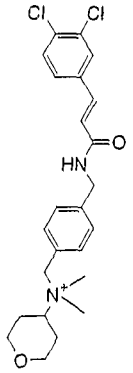
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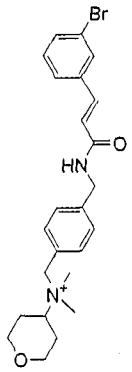
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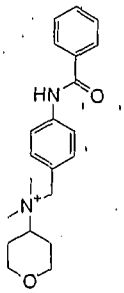
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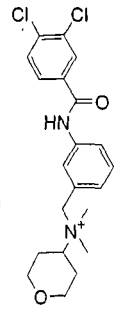
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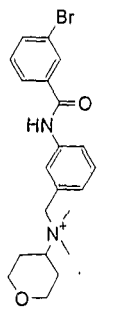
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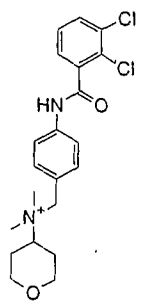
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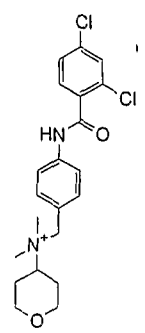
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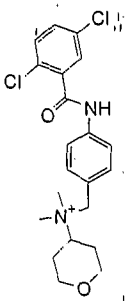
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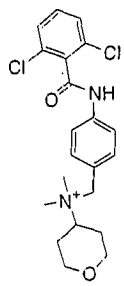
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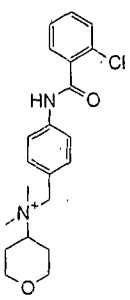
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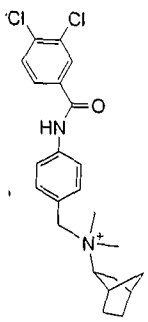
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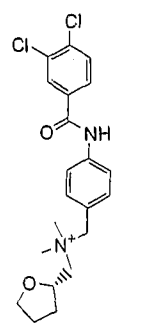
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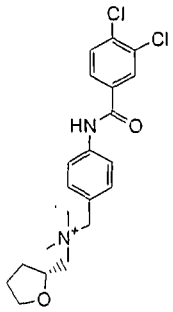
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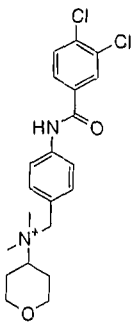
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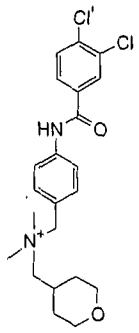
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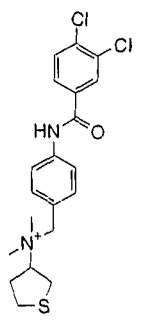
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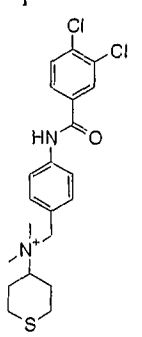
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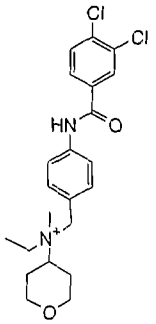
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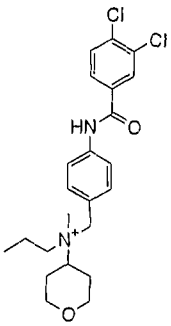
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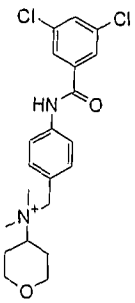
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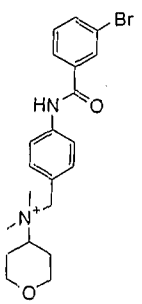
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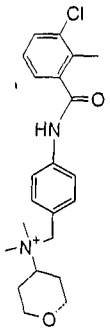
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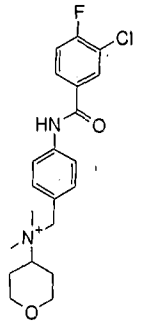
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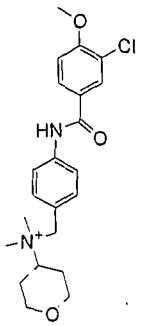


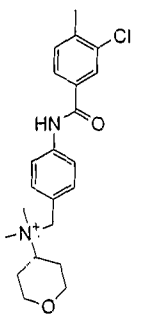
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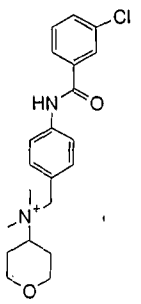


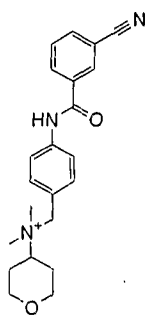
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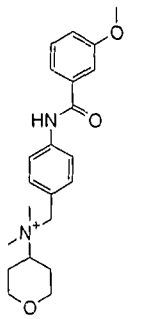

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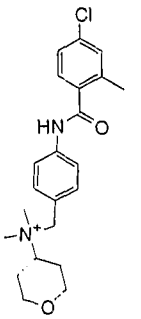

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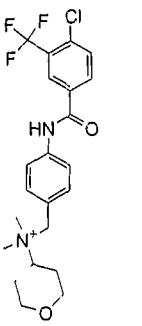

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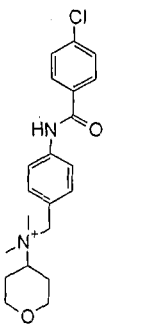

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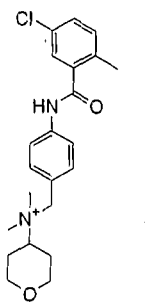

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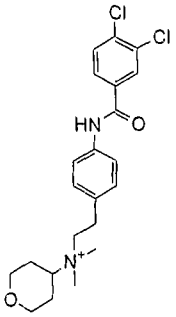

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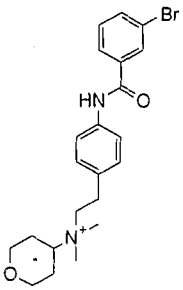

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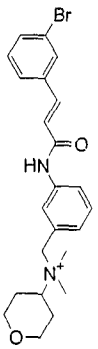

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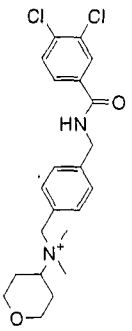

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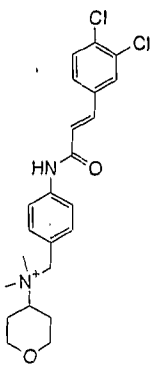

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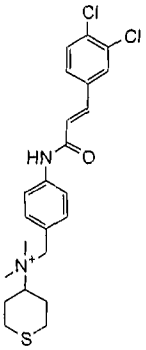

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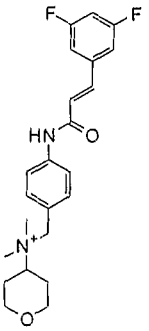

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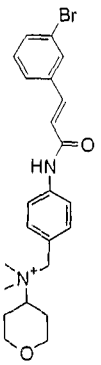

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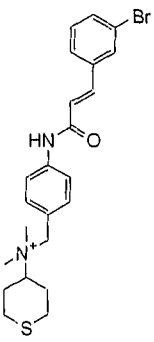

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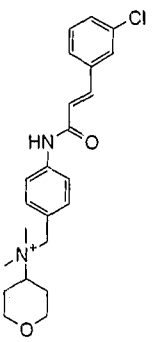

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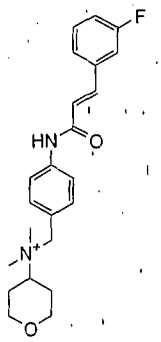

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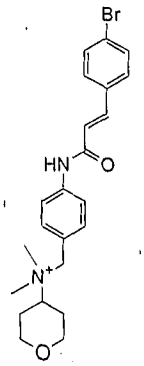

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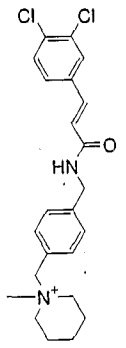

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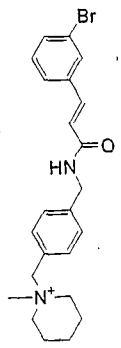
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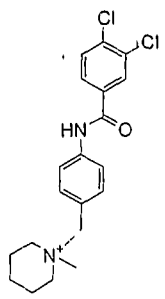
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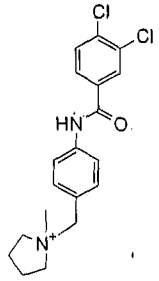
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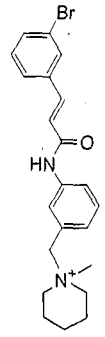
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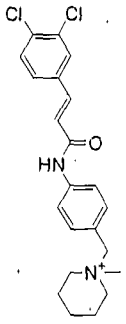
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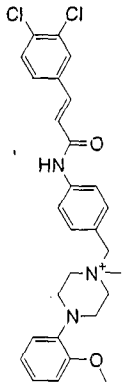
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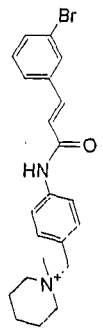
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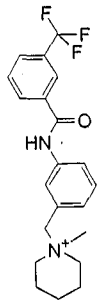
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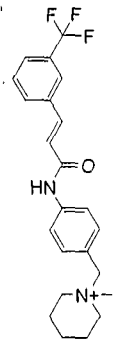
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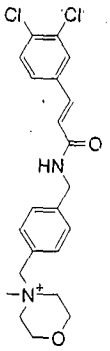
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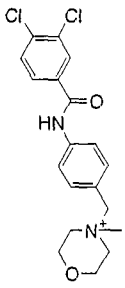
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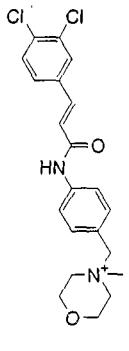
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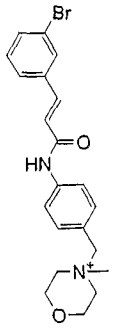
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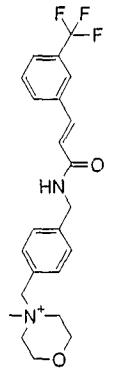
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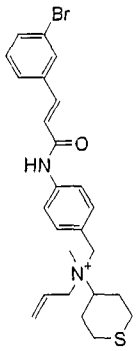
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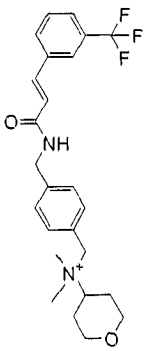
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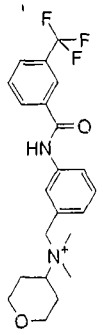
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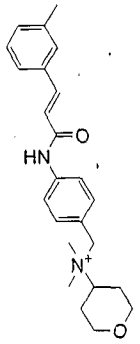
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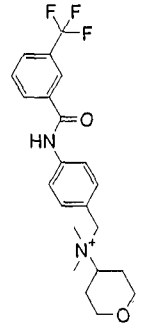
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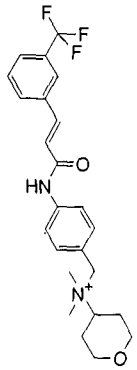
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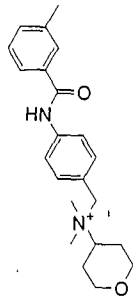
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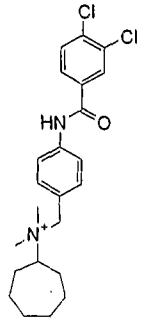
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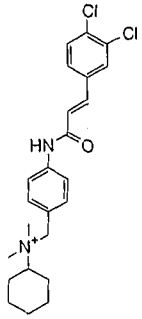
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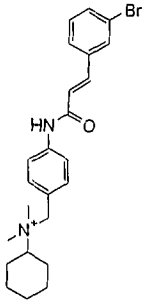
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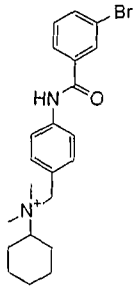
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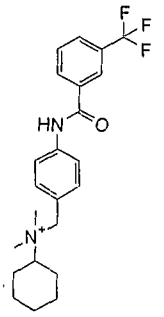
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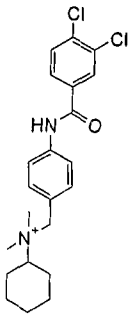
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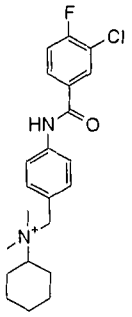
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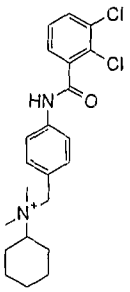
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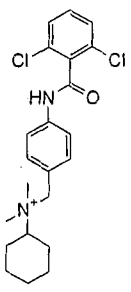
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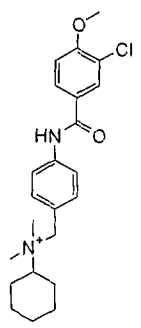
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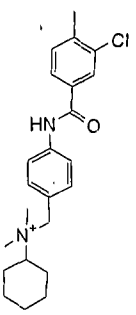
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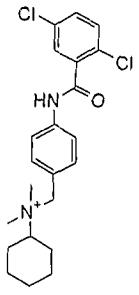
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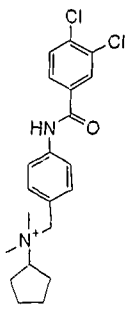
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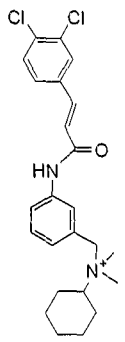
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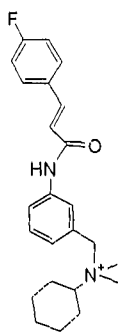
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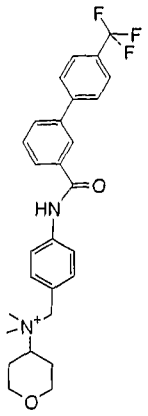
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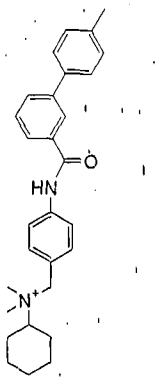
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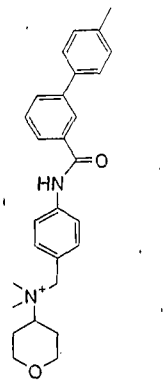


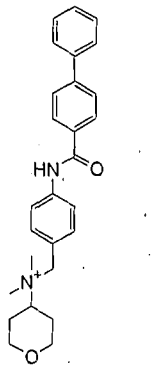
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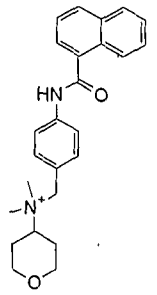


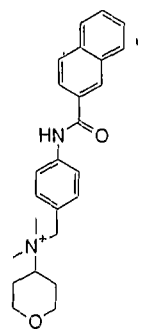
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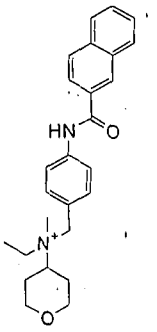

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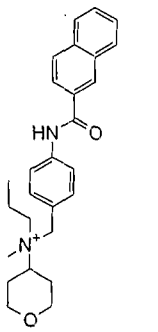

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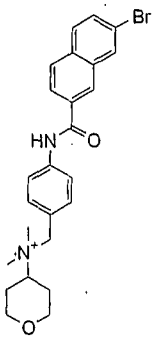

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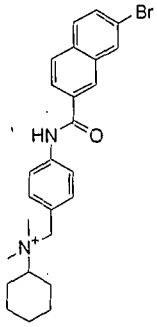

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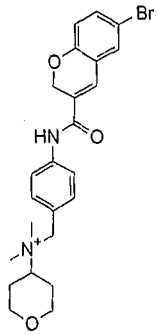

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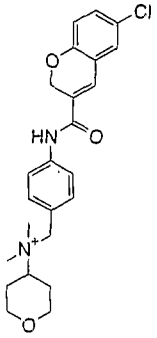

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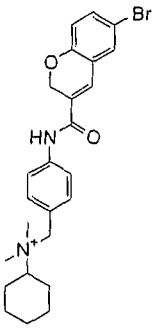

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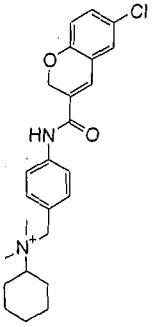

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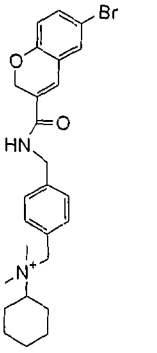

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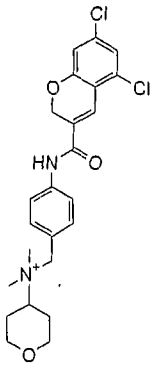

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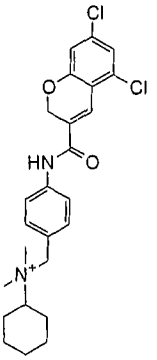

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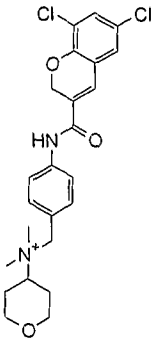

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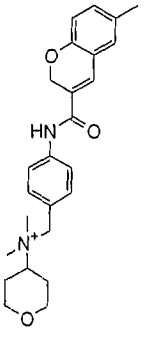

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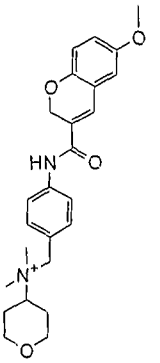

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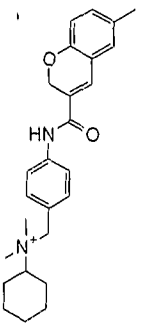

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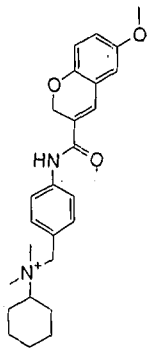

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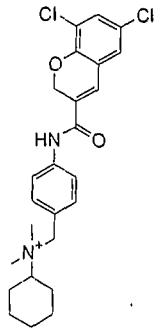

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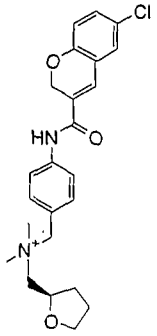

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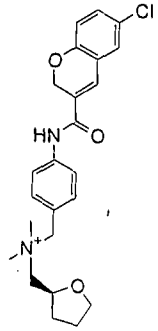
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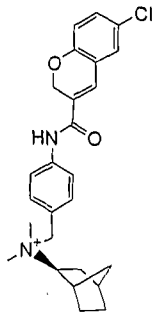
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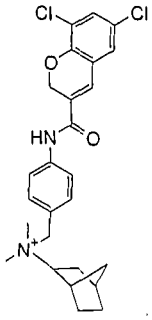
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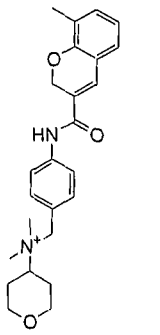
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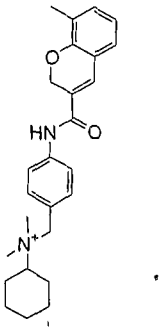
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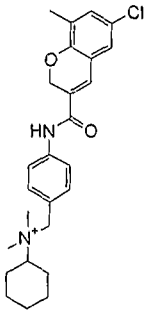
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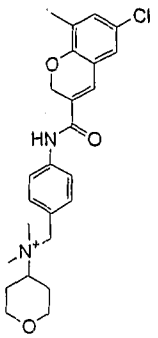
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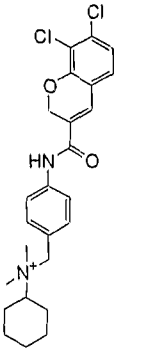
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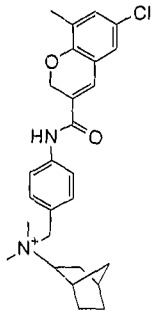
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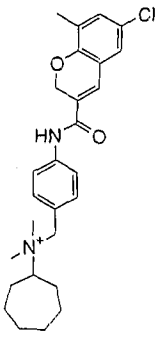
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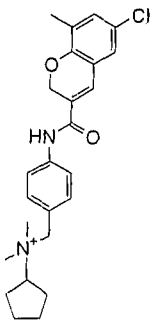
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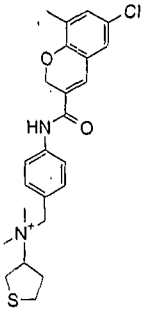
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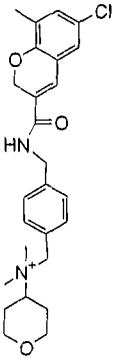
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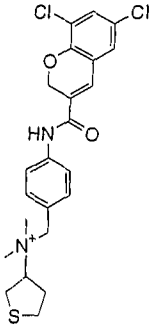
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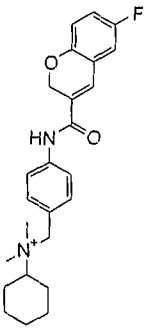
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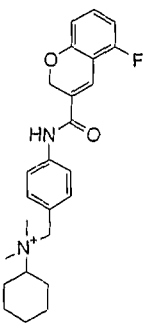
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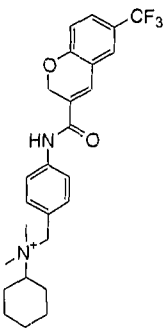
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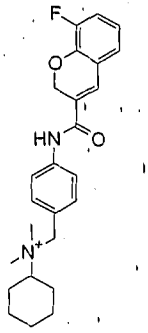
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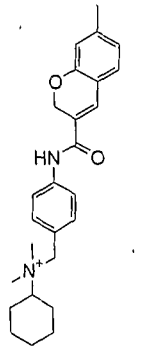
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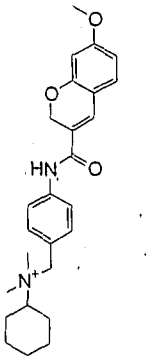
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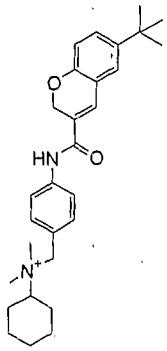
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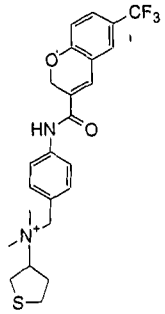
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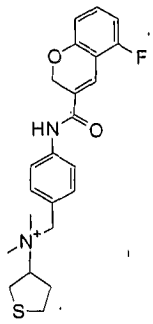
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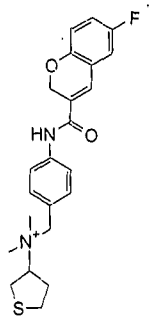
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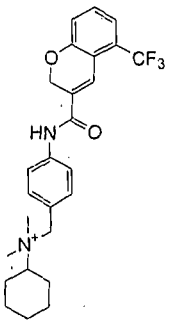
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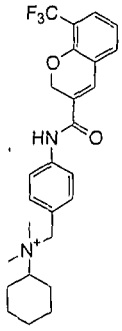
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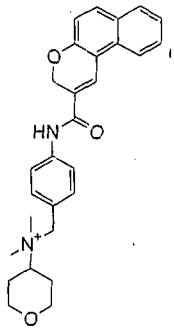
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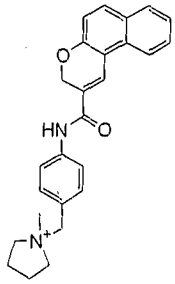
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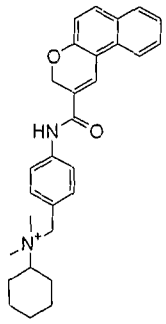
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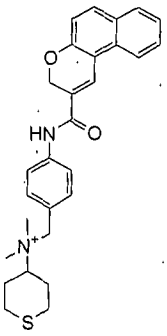
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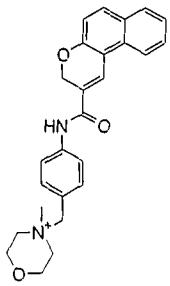
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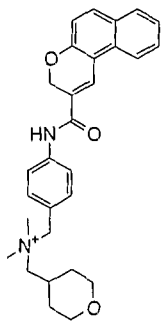
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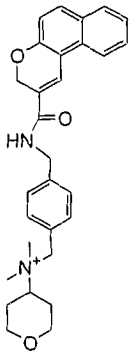
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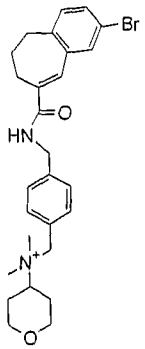
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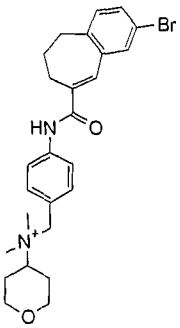
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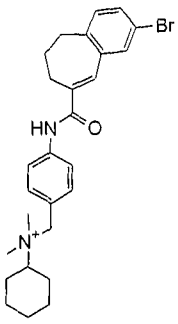
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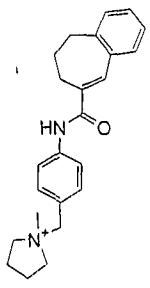
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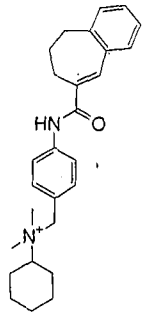
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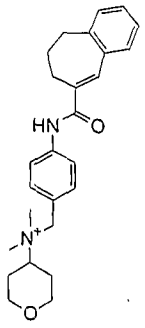
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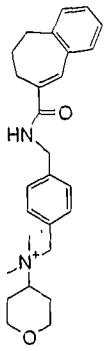
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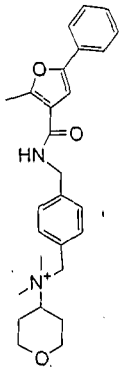
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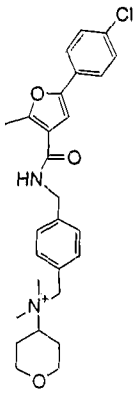
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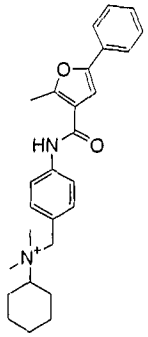
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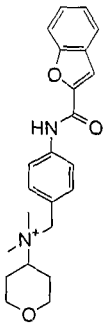
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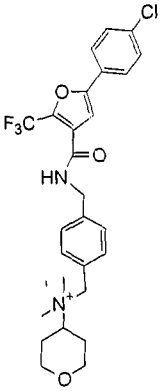
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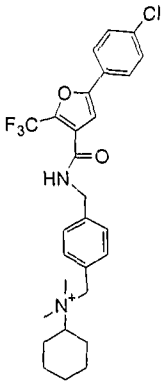
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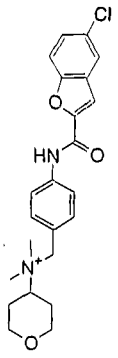
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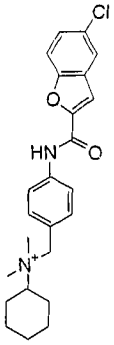
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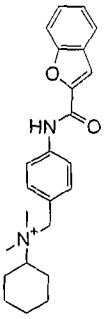
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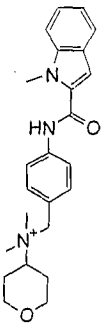
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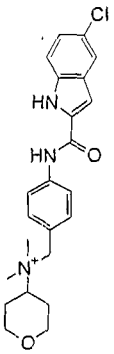
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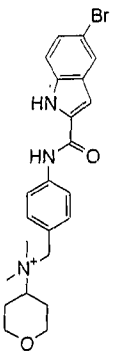
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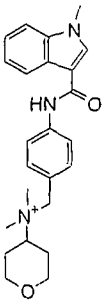
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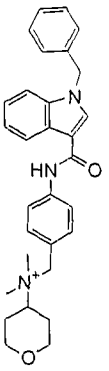
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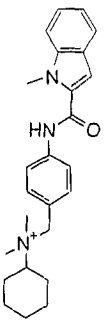
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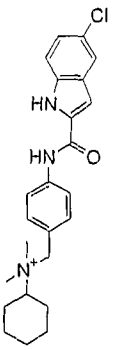
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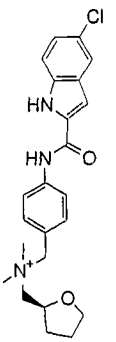
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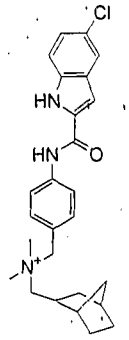
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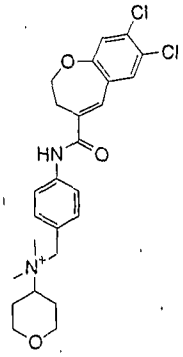
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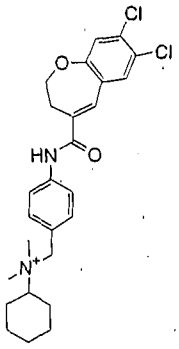
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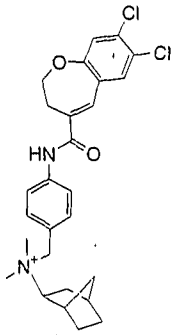
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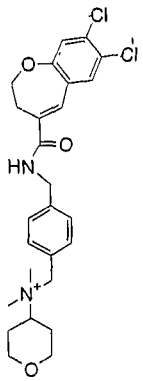
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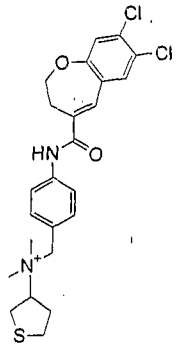
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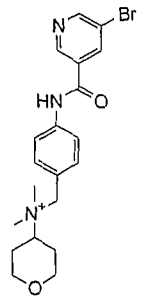
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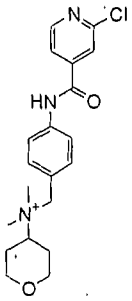
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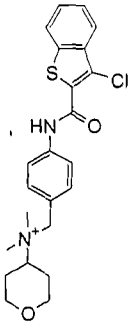
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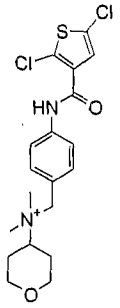
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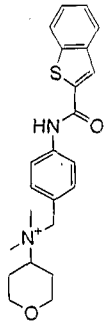
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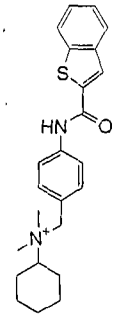
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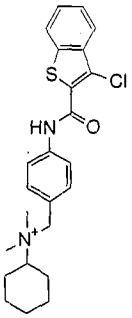
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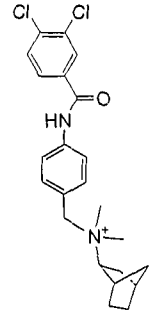


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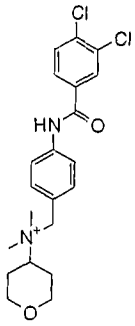


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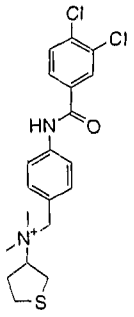
An example of the invention is a compound of Formula (I) and pharmaceutically acceptable forms thereof selected from:



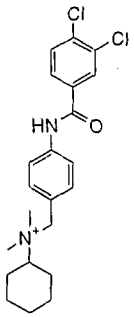
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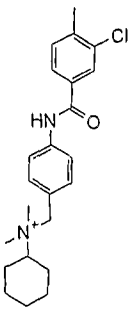
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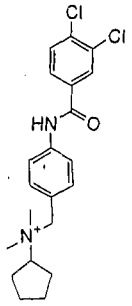
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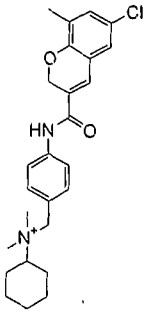
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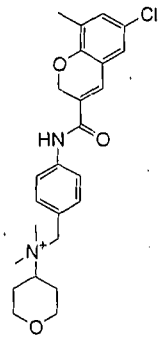
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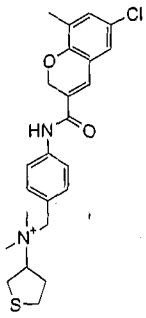
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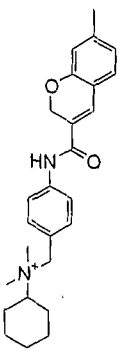
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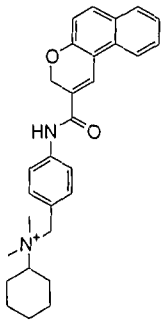
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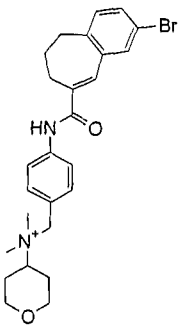
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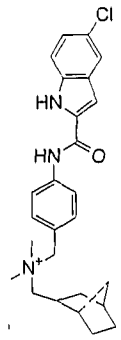
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Cpd 137



Cpd 143



Cpd 166

Definitions

Bond lines drawn into a ring system from a substituent variable indicate that the substituent may be attached to any of the substitutable ring atoms.

As used herein, the following terms are intended to have the following definitions.

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, ethyl, propyl, butyl, pentyl, hexyl 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 substituent having at least one double bond derived by the removal of one hydrogen atom from each of two adjacent carbon atoms in the chain. The term includes, without limitation, vinyl, vinylidene, allyl, allylidene, isopropenyl, prenyl, methallyl 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 1-4 carbon atoms.

The term "alkoxy" means an alkyl radical or linking group substituent attached through an oxygen-linking atom. 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 monovalent saturated or partially unsaturated monocyclic, polycyclic or bridged hydrocarbon ring system radical or linking group substituent. A ring of 3 to 20 carbon atoms may be designated by C_{3-20} cycloalkyl; a ring of 5 to 15 carbon atoms may be designated by C_{5-15} cycloalkyl; a ring of 3 to 8 carbon atoms may be designated by C_{3-8} cycloalkyl and the like. The term includes, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1*H*-indenyl, indanyl, 1,2,3,4-tetrahydro-naphthalenyl, 5,6,7,8-tetrahydro-naphthalenyl, 8,9-dihydro-7H-benzocyclohepten-6-yl, 6,7,8,9-tetrahydro-5*H*-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 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, isoindolyl, 3*H*-indolyl, indolinyl, benzofuranyl, benzo[*b*]thienyl, 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), 2,3-dihydro-1,4-benzodioxinyl (also known as 1,4-ethylenedioxyphenyl), 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 "independently selected" refers to two or more substituents that may be selected from a substituent variable group, wherein the selected substituents may be the same or different.

The term "dependently selected" refers to one or more substituent variables that are specified in an indicated combination for substitution in a core molecule (e.g., variables that refer to groups of substituents appearing in a tabular list of compounds).

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

The term "thiocarbonyl" means a linking group having the formula -C(S)- or -C(=S)-.

The term "sulfonyl" means a linking group having the formula $-SO_2-$.

The term "alkoxycarbonyl" means a radical having the formula -C(O)O-alkyl.

Pharmaceutically Acceptable Forms

Pharmaceutically acceptable forms according to the invention may, alternatively or in addition to a compound of Formula (I), comprise a pharmaceutically acceptable salt of a compound of Formula (I) or a prodrug or pharmaceutically active metabolite of such a compound or salt.

The compounds of the invention may be present in the form of pharmaceutically acceptable salts. 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 and triethiodide salts.

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 or trifluoroacetic acid.

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) or zinc.

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" or "chair" configuration, the substituents are on opposite sides in relationship to the carbon- carbon double bond; in the "Z" or "boat" 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

Pharmaceutically acceptable forms of a compound of Formula (I) or a composition or medicament thereof in accordance with the invention are CCR2 antagonists. Said composition or medicament may contain a compound of Formula (I) having a mean inhibition constant (IC_{50}) against MCP-1 binding to CCR2 of between about 5 μM to about 1 nM; between about 1 μM to about 1 nM; between about 800 nM to about 1 nM; between about 200 nM to about 1 nM; between about 100 nM to about 1 nM; between about 80 nM to about 1 nM; between about 20 nM to about 1 nM; between about 10 nM to about 1 nM; or about 1 nM.

A compound of Formula (I) or a composition or medicament thereof reduces MCP-1 induced monocyte chemotaxis. Said composition or medicament may contain a compound of Formula (I) having an IC_{50} for reduction in MCP-1 induced monocyte chemotaxis of between about 5 μM to about 1 nM; between about 1 μM to about 1 nM; between about 800 nM to about 1 nM; between about 200 nM to about 1 nM; between about 100 nM to about 1 nM; between about 80 nM to about 1 nM; between about 20 nM to about 1 nM; between about 10 nM to about 1 nM; or about 1 nM.

A compound of Formula (I) or a composition or medicament thereof reduces MCP-1 intracellular calcium mobilization. Said composition or medicament may contain a compound of Formula (I) having an IC_{50} for reduction in MCP-1 induced intracellular calcium mobilization of between about 5 μM to about 1 nM; between about 1 μM to about 1 nM; between about 800 nM to about 1 nM; between about 200 nM to about 1 nM; between about 100 nM to about 1 nM; between about 80 nM to about 1 nM; between about 20 nM to about 1 nM; between about 10 nM to about 1 nM; or about 1 nM.

Accordingly, a compound of Formula (I) or a 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 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 composition or medicament thereof.

The term "administering," with respect to the methods of the invention, means a method for preventing, treating or ameliorating a syndrome, disorder or disease as described herein with a compound of Formula (I) or composition or medicament thereof. Such methods include administering an effective amount of said compound, 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" as used herein, means an animal, typically a mammal, typically a human, typically a patient with 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 0.001 mg/kg/day to about 300 mg/kg/day.

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 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 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 carrier" 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 composition or medicament 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 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 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 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 composition or medicament thereof in a combination therapy with one or more anti-inflammatory agents (such as a small molecule, antibiotic, corticosteroid, steroid, and the like), anti-infective agents or immunosuppressive agents.

The term "combination therapy" refers to the use of a compound of Formula (I) or composition or medicament thereof in combination with an anti-inflammatory, anti-infective, or immunosuppressive agent for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease.

For preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease using a compound of Formula (I) or composition or medicament thereof and an anti-inflammatory, anti-infective or immunosuppressive agent in a combination therapy 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.

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 0.001 mg to about 5000 mg (preferably, from about 0.001 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 0.001 mg to about 300 mg/kg of body weight per day. A contemplated range also includes from about 0.003 to about 100 mg/kg of body weight per day. Another contemplated range includes from about 0.005 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., 0.01, 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 will vary depending on factors associated with the particular patient being treated (e.g., age, weight, diet, and time of administration), the severity of the condition being treated, the compound being employed, the mode of administration, and the strength of the preparation. 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. Preferably the compositions are sterile and aqueous based, using purified water. In addition to the compound of the invention, an ophthalmic composition may contain one or more of: a) a surfactant such as a polyoxyethylene fatty acid ester; b) a thickening agents such as cellulose, cellulose derivatives, carboxyvinyl polymers, polyvinyl polymers, and polyvinylpyrrolidones, typically at a concentration n the range of about 0.05 to about 5.0% (wt/vol); c) (as an alternative to or in addition to storing the composition in a container containing nitrogen and optionally including a free oxygen absorber such as Fe), an anti-oxidant such as butylated hydroxyanisol, ascorbic acid, sodium thiosulfate, or butylated hydroxytoluene at a concentration of about 0.00005 to about 0.1% (wt/vol); d) ethanol at a concentration of about 0.01 to 0.5% (wt/vol); and e) other excipients such as an isotonic agent, buffer, preservative, and/or pH-controlling agent. The pH of the ophthalmic composition is desirably within the range of 4 to 8.

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. All commercially

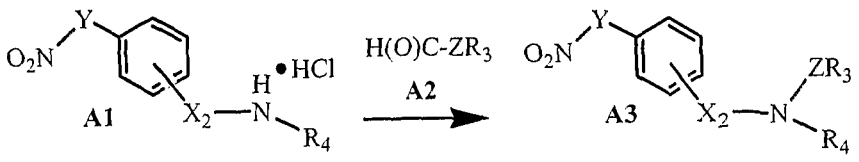
available chemicals were obtained from commercial suppliers and used without further purification. Particular equipment components used in the examples such as reaction vessels and the like are also commercially available.

The following abbreviations have the indicated meanings:

Cpd	compound
Boc	tert-butoxy carbonyl or t-butoxy carbonyl
Boc_2O	di-t-butyl-dicarbonate
conc.	concentrated
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM or CH_2Cl_2	dichloromethane
DMAP	(4,4-dimethylamino)-pyridine
DMF	N,N-dimethyl formamide
EDIC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Et_2O	ethoxy-ethane or ether
EtOAc	ethylacetate
EtOH	ethanol
HCOH	formaldehyde
HOBt	1-hydroxybenzotriazole hydrate
MeI or CH_3I	methyl iodide
MeOH	methanol
min(s)/hr(s)/d(s)	minute(s)/hour(s)/day(s)
$Pd(dppf)_2$	{[1,1'-bis(diphenylphosphino)-ferrocene] dichloropalladium(II)}
RT/rt/r.t.	room temperature
$NaB(OAc)_3H$	sodium triacetoxyborohydride
TEA or Et_3N	triethylamine
THF	tetrahydrofuran

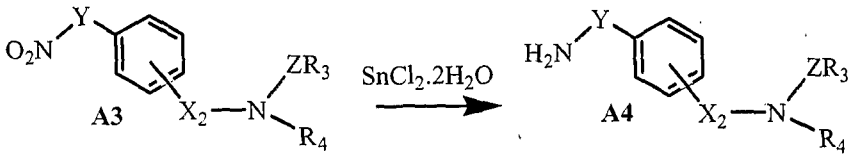
Scheme A

The synthetic method provided by Scheme A, depending on the starting materials used or when certain reaction conditions are desired, is used to prepare a compound of Formula (I).

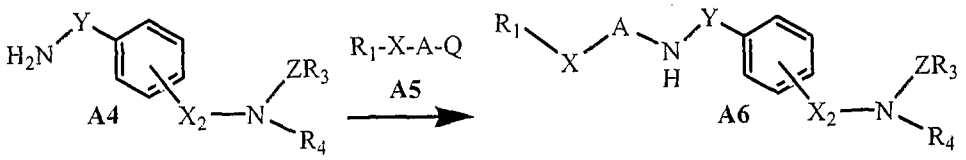


A mixture of a nitrophenylamine hydrochloride Compound **A1** and a solution of an aldehyde or ketone Compound **A2** (in a solvent such as CH_2Cl_2 and the like) is cooled to 0°C, then Et_3N is added followed by $NaB(OAc)_3H$. The resulting suspension is stirred and allowed to warm to r.t. for about 8-12 hrs (adapted from Shiroshi, et al., *J. Med. Chem.*, 2000, 43, 2049).

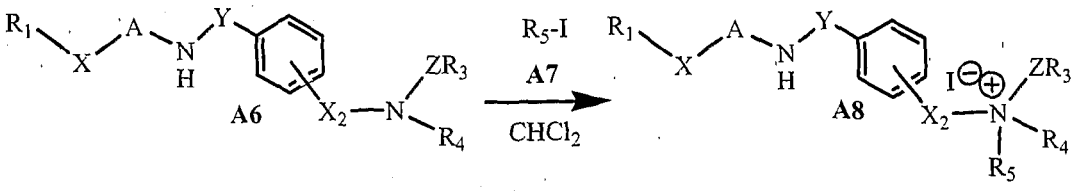
An aldehyde (such as formaldehyde and the like) in aqueous solution is added, followed by $NaB(OAc)_3H$ added in one portion while cooling the reaction vessel with ice. The reaction mixture is stirred at r.t. for about 12 hrs, then made basic (using a solution of 2N NaOH and the like) and extracted (with a solvent such as CH_2Cl_2 and the like). The organic layer is washed using brine, then separated and dried over Na_2SO_4. The drying agent is filtered and the solvent is removed *in vacuo* to yield a disubstituted nitrophenylamine Compound **A3** (adapted from Hashimoto et al., *Org. Proc. R&D*, 2002, 6, 70).



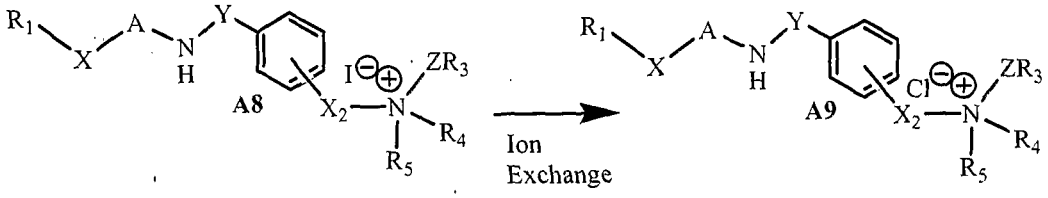
$SnCl_2.2H_2O$ in conc. HCl is added in small portions to a solution of Compound **A3** (in a solvent such as THF and the like) at r.t. The mildly exothermic reaction is maintained at r.t. using an ice-cooled water bath and stirred for about 1 hr. The round bottom flask containing the reaction mixture is placed in a warm water bath for about 30 min to allow the reaction to reach completion. The mixture is sequentially diluted with a solvent (such as THF and the like) and water, then made basic (using a solution of 2N NaOH and the like). The layers are separated and the aqueous layer is extracted (using a solvent such as Et_2O and the like). The combined organic layers were dried over $MgSO_4$, then filtered and the solvent was removed *in vacuo*. The solid obtained was further dried (by pressing the solid on an absorbent surface such as a filter paper) to provide a disubstituted aminophenylamine Compound **A4**.



A solution of a R_1 substituted Compound **A5** (wherein Q represents a leaving group such as chloride or hydroxy) is added dropwise via a dropping funnel over a period of about 20 min to a solution of Compound **A4** (in a solvent mixture such as Et_3N in THF and the like). The resulting suspension is allowed to warm to r.t. over a period of about 8-12 hrs, then made basic (using a solution of 2N NaOH and the like). The organic and aqueous layers are separately extracted (using a solvent such as EtOAc and the like). The organic layer is washed with brine, then dried (using $MgSO_4$, Na_2SO_4 and the like) and filtered. The solvent is removed *in vacuo* to yield a crude product which may be purified by either flash column chromatography (in a solvent ratio 15:1 EtOAc:MeOH to 6:1 EtOAc:MeOH) or preparative TLC (using a solvent mixture in a ratio of EtOAc:MeOH) to provide a substituted benzamide Compound **A6**.



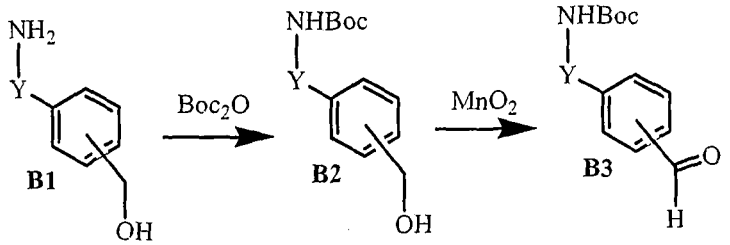
An R_5 substituted iodo Compound **A7** is added to a solution of Compound **A6** (in a solvent mixture such as acetone and acetonitrile and the like) at r.t. The resulting solution is stirred for about 8-12 hrs to form a precipitate. The solvent is removed *in vacuo* and the solid is sequentially washed (using EtOAc and Et_2O and the like), then dried in a vacuum oven for about 12 hrs to provide a quaternary salt Compound **A8**.



A solution of Compound **A8** (in a solvent:water ratio mix such as a 1:1 MeOH:H_2O) is passed through a column packed with an ion-exchange resin (such as ~300 g of Bio-Rad analytical grade anion exchange resin. AG 1-X8, 50-100 mesh, chloride form) into a flask. The column is then washed (such as with MeOH and the like) and solvents (such as acetone and Et_2O and the like) are added to the filtered product in the flask. The solvent is removed *in vacuo* and the product dried in a vacuum oven for about 8-12 hrs to provide a target Compound **A9** of Formula (I) wherein R_2 is $N^+(R_4R_5)$-ZR_3 and pharmaceutically acceptable anionic salt forms thereof.

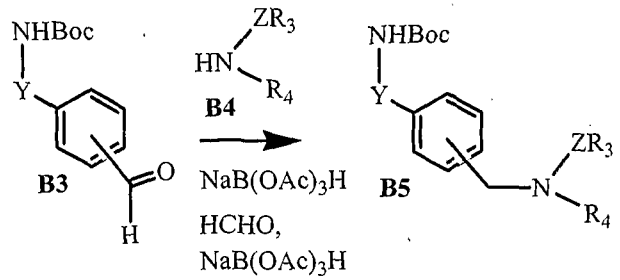
Scheme B

The synthetic method provided by Scheme B, depending on the starting materials used or when certain reaction conditions are desired, is used as an alternative to Scheme A to prepare a compound of Formula (I).

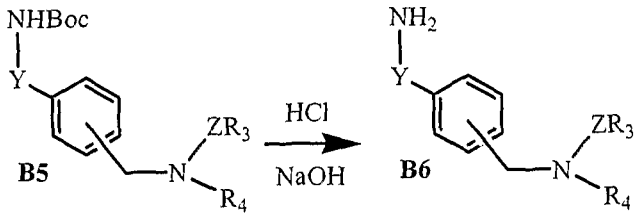


Di-t-butyl-dicarbonate is added in one portion at r.t. to a solution of Compound **B1** (in a solvent such as CH_2Cl_2 and the like) and the solution is stirred for about 48 hrs. The reaction mixture is sequentially washed with an acidic solution (using a 10% citric acid solution and the like) and brine. The organic layer is separated, dried over Na_2SO_4 and filtered. The solvent is

removed *in vacuo* to provide a protected Compound **B2** that is used in the next step without further purification. A reagent (such as MnO_2 and the like) is added to a solution of Compound **B2** (in a solvent such as chloroform and the like) to form a black suspension, which is stirred at r.t. for about 8-12 hrs, then filtered through a pad of celite. The solvent was evaporated *in vacuo* to provide Compound **B3**, which is used in the next step without further purification.



$NaB(OAc)_3H$ is added to a mixture of Compound **B3** and Compound **B4** (in a solvent such as CH_2Cl_2 and the like) and the suspension is stirred at r.t. for a period of time. After the reaction is complete, an aldehyde (such as formaldehyde and the like) in aqueous solution is added, followed by $NaB(OAc)_3H$ added in one portion while the reaction vessel is cooled with ice. The reaction mixture is stirred at r.t. for about 12 hrs, then made basic (using a solution of 2N NaOH and the like) and extracted (with a solvent such as CH_2Cl_2 and the like). The organic layer is washed using brine, then separated and dried over Na_2SO_4. The drying agent is filtered and the solvent is removed *in vacuo* to yield a crude product which was purified by column chromatography (using an eluent ratio of about 4:1 and a solvent mixture such as CH_2Cl_2:MeOH and the like) to provide a disubstituted phenylamine Compound **B5**.



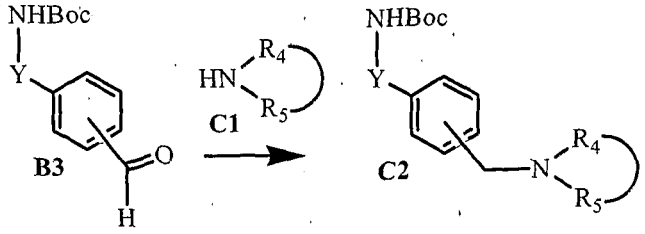
An HCl solution (in a solvent such as dioxane and the like) is added to a solution of Compound **B5** (in a solvent such as CH_2Cl_2 and the like) and the mixture is stirred at r.t. for about 12 hrs. The solvent is removed and the residue is made basic (using a base such as a 2N NaOH solution) then extracted (with a solvent such as EtOAc). The organic layer is washed with brine, then separated and dried over Na_2SO_4. The drying agent is filtered and the solvent is removed *in vacuo* to provide a Compound **B6**.

Accordingly, using the procedure of Scheme A to provide additional compounds of the present invention, Compound **B6** is used in place of Compound **A4** and carried forward to

provide a target compound of Formula (I) wherein X_2 is $-CH_2-$ and pharmaceutically acceptable anionic salt forms thereof.

Scheme C

The synthetic method provided by Scheme C, depending on the starting materials used or when certain reaction conditions are desired, is used as an alternative to Scheme B to prepare a compound of Formula (I).

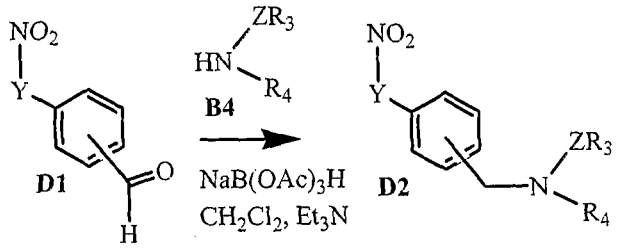


Using the procedure of Scheme B, Compound **C1** is used in place of Compound **B4** and coupled with Compound **B3** to provide Compound **C2**.

Accordingly, using the procedure of Scheme B to provide additional compounds of the present invention, Compound **C2** is used in place of Compound **B5** and carried forward to provide a target compound of Formula (I) wherein X_2 is $-CH_2-$ and R_4 and R_5 are taken together with the nitrogen atom of Formula (I) to form a heterocyclyl ring and pharmaceutically acceptable anionic salt forms thereof.

Scheme D

The synthetic method provided by Scheme D, depending on the starting materials used or when certain reaction conditions are desired, is used as an alternative to Scheme A or B to prepare a compound of Formula (I).

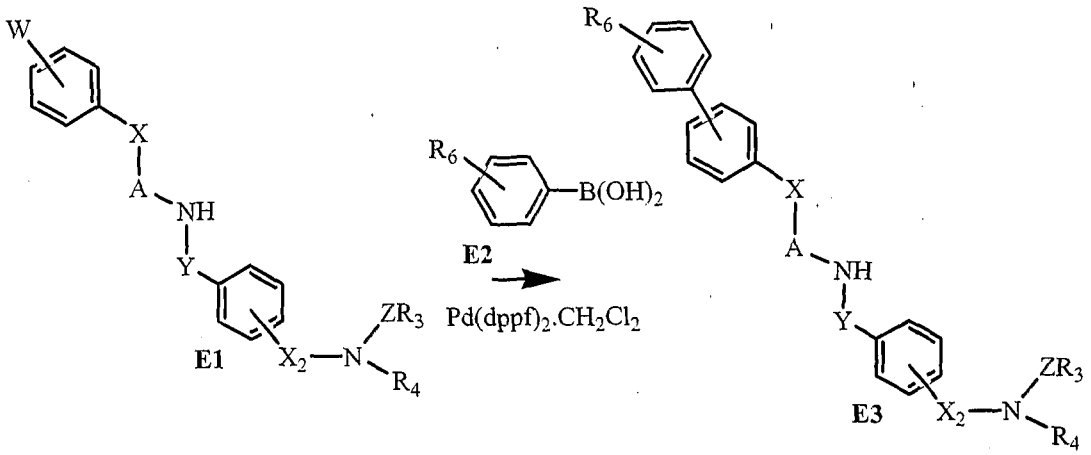


Using the procedure of Scheme B, Compound **D1** and Compound **B4** are coupled to provide Compound **D2**.

Accordingly, using the procedure of Scheme A to provide additional compounds of the present invention, Compound **D2** is used in place of Compound **A3** and carried forward to provide a target compound of Formula (I) wherein X_2 is $-CH_2-$ and pharmaceutically acceptable anionic salt forms thereof.

Scheme E

The synthetic method provided by Scheme E, depending on the starting materials used or when certain reaction conditions are desired, is used to prepare a compound of Formula (I).



Compound **E1** (wherein W_1 is a suitable leaving group such as a halogen atom) was reacted with Compound **E2** to provide a further substituted Compound **E3**, wherein R_6 is hydrogen, lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, alkoxycarbonyl, cyano or halogen.

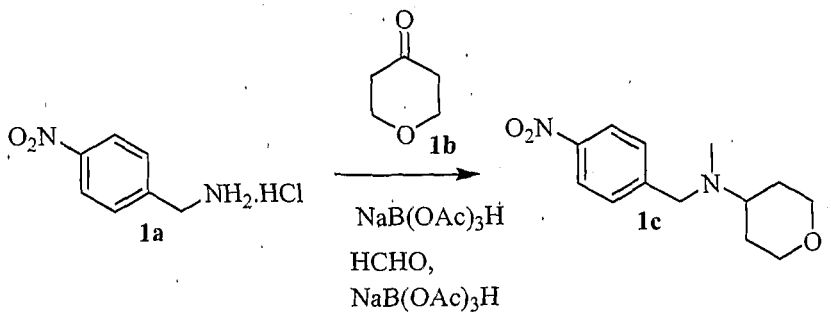
To provide additional compounds of the present invention, Compound **J3** was used to replace Compound **A6** and carried forward using the method of Scheme A to provide a target compound of Formula (I) and pharmaceutically acceptable anionic salt forms thereof.

Accordingly, using the procedure of Scheme A to provide additional compounds of the present invention, Compound **E3** is used in place of Compound **A6** and carried forward to provide a target compound of Formula (I) and pharmaceutically acceptable anionic salt forms thereof.

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

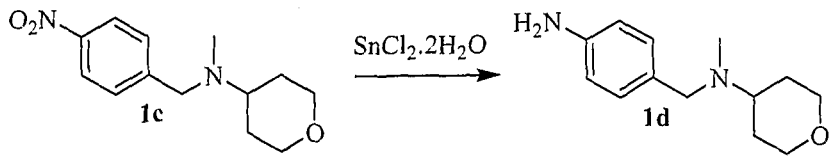
Example 1

[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium chloride (Cpd **17**)



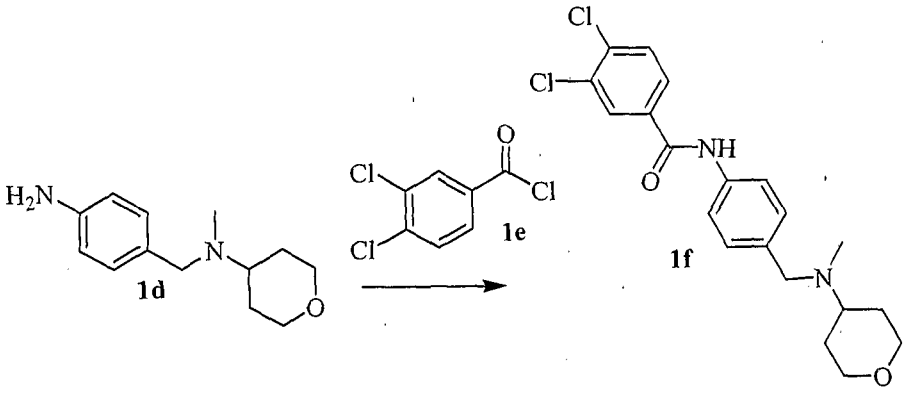
After cooling a mixture of 4-nitrobenzylamine hydrochloride Compound **1a**, (22.12 mmol, 4.18 g) and tetrahydro-4*H*-pyran-4-one Compound **1b** (22.25 mmol, 2.48 g) in CH_2Cl_2 (50 mL) to 0°C, Et_3N (22.43 mmol, 3.13 mL) was added, followed by $NaB(OAc)_3H$ (31.0 mmol, 6.58 g). The resulting suspension was allowed to warm to r.t. with stirring overnight. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 237, 100%). This portion of the procedure of Example 1 was adapted from Shiroshi, et al., *J. Med. Chem.*, 2000, 43, 2049.

An aqueous solution of formaldehyde (37% solution, 24.32 mmol, 1.98 mL) was combined with Compound **1c**, followed by $NaB(OAc)_3H$ (31.0 mmol, 6.58 g) added in one portion under ice cooling. The reaction mixture was stirred at r.t. for 12 hrs, then made basic using a 2N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, then separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to yield methyl-(4-nitro-benzyl)-(tetrahydro-pyran-4-yl)-amine Compound **1c** as a orange-yellow thick oil (5.58 g), which was used in the next step without further purification. This portion of the procedure of Example 1 was adapted from Hashimoto et al., *Org. Proc. R&D*, 2002, 6, 70. MS *m/e* 251 (M^+H, 100%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.82 (m, 4H), 2.21 (s, 3H), 2.59-2.78 (m, 1H), 3.38 (dt, J = 3.2 Hz, J = 11.2 Hz, 2H), 3.68 (s, 2H), 4.02-4.10 (m, 2H), 7.50 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.8 Hz, 2H).

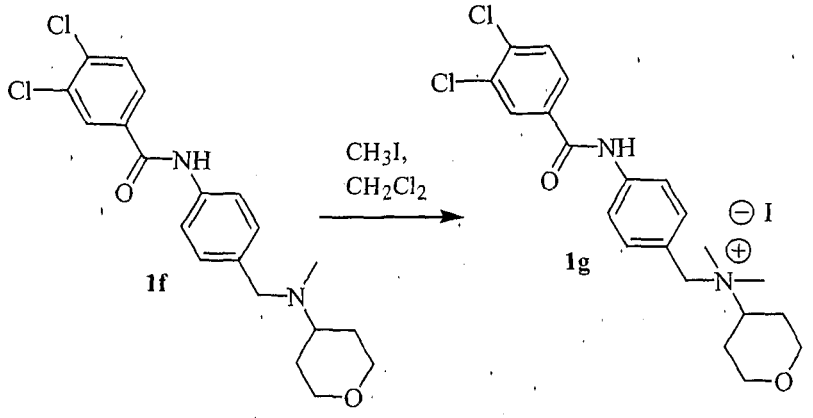


$SnCl_2.2H_2O$ (71.2 mmol, 16.07 g) in conc. HCl (14 mL) was added in small portions to a solution of Compound **1c** (22.12 mmol, 5.58 g) in THF (10 mL) at r.t. A mild exotherm was observed and the reaction mixture was placed in a water bath cooled with just enough ice to maintain r.t. The resulting yellow solution was stirred for 1 hr. TLC analysis [9:1

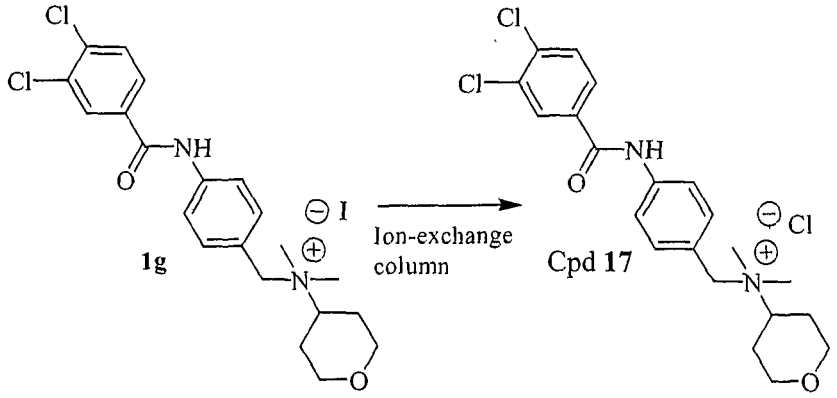
CH_2Cl_2:MeOH; R_f 0.6 (Compound **1c**) and R_f 0.2 (Compound **1d**)] showed a trace of starting material (Compound **1c**). The round bottom flask containing the reaction mixture was then placed in a warm water bath for 30 min to allow the reaction to reach completion. The mixture was diluted with THF (50 mL) and water (30 mL) and made basic with 2N NaOH solution. The layers were separated and the aqueous layer was extracted with Et_2O (2 X 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to obtain (4-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **1d** as a pale yellow solid. The solid was further dried by pressing it on a filter paper to obtain the product as an off-white powder (4.22 g, 86% yield over 3 steps). MS *m/e* 221 (M^+H, 100%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.52-1.70 (m, 4H), 2.11 (s, 3H), 2.50-2.61 (m, 1H), 3.29 (dt, J = 3.2 Hz, J = 11.2 Hz, 2H), 3.42 (s, 2H), 3.54 (br , 2H), 3.91-3.98 (m, 2H), 6.58 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H).



A solution of 3,4-dichlorobenzoyl chloride Compound **1e** (14.4 mmol, 3.01 g) was added dropwise via a dropping funnel over 20 min to a solution of Compound **1d** (13.64 mmol, 3.0 g) and Et_3N (27.28 mmol, 3.8 mL) in THF (100 mL) at 0°C. The resulting suspension was allowed to warm to r.t. overnight, then made basic using a 2N NaOH solution and extracted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 X 50 mL). The organic layers were washed with brine, then dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to yield 3,4-dichloro-N-(4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-benzamide Compound **1f** as a yellow solid. The product was purified by flash column chromatography (15:1 EtOAc:MeOH to 6:1 EtOAc:MeOH) to yield a white powder (4.6 g, 86%). Mp 135-136°C; MS *m/e* 393 (M^+H, 100%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.83 (m, 4H), 2.21 (s, 3H), 2.58-2.61 (m, 1H), 3.38 (dt, J = 3.1 Hz, J = 11.0 Hz, 2H), 3.58 (s, 2H), 4.01-4.09 (m, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.53-7.60 (m, 3H), 7.68-7.74 (m, 2H), 7.98 (d, J = 3.0 Hz, 1H); Anal. Calcd. for $C_{20}H_{22}Cl_2N_2O_2$: C 61.08, H 5.64, N 7.12, Cl 18.03; Found C 61.09, H 5.57, N 6.93, Cl 17.91.



Iodomethane (29.9 mmol, 18.6 mL) was added to a solution of Compound **1f** (10.2 mmol, 4.0 g) in acetone (250 mL) and acetonitrile (100 mL) at r.t. The resulting solution was stirred overnight, after which a white precipitate was observed. The solvent was removed *in vacuo* and the off-white solid was washed with EtOAc (20 mL) and Et_2O (100 mL) then dried in a vacuum oven for 12 hrs to obtain [4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide Compound **1g** as a white solid (5.0 g, 91.7%). Mp 210-213°C; MS *m/e* 407 (M, 100%); ^{1}H NMR (300 MHz, CD_3OD) δ 1.92-2.10 (m, 2H), 2.19-2.28 (m, 2H), 2.98 (s, 6H), 3.48 (t, J = 11.4 Hz, 2H), 3.65-3.77 (m, 1H), 4.10-4.19 (m, 2H), 4.54 (s, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.86-7.94 (m, 3H), 8.12 (d, J = 2.1 Hz, 1H); Anal. Calcd. for $C_{21}H_{25}Cl_2IN_2O_2$: C 47.12, H 4.71, N 5.23, I 23.71; Found C 46.83, H 4.57, N 5.18, I 23.38.



A solution of Compound **1g** (5.0 g) in 1:1 mixture of MeOH/H_2O was passed through a column packed with ~300 g of anion-exchange resin (Bio-Rad, analytical grade anion exchange resin. AG 1-X8, 50-100 mesh, chloride form). The column was washed with MeOH and some acetone and Et_2O were added to the flask. The solvent was removed *in vacuo* and the product was dried in a vacuum oven overnight to provide Compound **17** as a white powder (3.9 g, 95%). Mp 227-232°C; MS *m/e* 407 (M, 100%); ^{1}H NMR (400 MHz, CD_3OD) δ 1.95-2.01 (m, 2H), 2.22-2.25 (m, 2H), 2.97 (s, 6H), 3.48 (t, J = 11.7 Hz, 2H), 3.65-3.72 (m, 1H), 4.14-4.18 (m, 2H), 4.53 (s, 2H), 7.58 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.86-7.92 (m, 3H),

8.12 (d, J = 2.1 Hz, 1H); Anal. Calcd. for $C_{21}H_{25}Cl_3N_2O_2$: C 56.83, H 5.68, N 6.31, Cl 23.97; Found C 56.93, H 5.72, N 6.02, Cl 23.67 (%I was found to be < 0.1%).

Using the procedure of Example 1 and known appropriate reagents and starting materials, other compounds of the present invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

Cpd	Name	MS
6	(4-benzoylamino-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	429
9	[4-(2,3-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	407
10	[4-(2,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	407
11	[4-(2,5-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	407
12	[4-(2,6-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	407
13	[4-(2-chloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	373
14	bicyclo[2.2.1]hept-2-yl-[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	417
19	[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-thien-3-yl)-ammonium iodide	409
20	[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-thiopyran-4-yl)-ammonium iodide	423
21	[4-(3,4-dichloro-benzoylamino)-benzyl]-ethyl-methyl-(tetrahydro-pyran-4-yl)-ammonium iodide	421
22	[4-(3,4-dichloro-benzoylamino)-benzyl]-methyl-propyl-(tetrahydro-pyran-4-yl)-ammonium iodide	435
23	[4-(3,5-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	407
24	[4-(3-bromo-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	417
25	[4-(3-chloro-2-methyl-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	387
26	[4-(3-chloro-4-fluoro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	391
27	[4-(3-chloro-4-methoxy-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	403
28	[4-(3-chloro-4-methyl-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	387
29	[4-(3-chloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	359
30	[4-(3-cyano-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	364

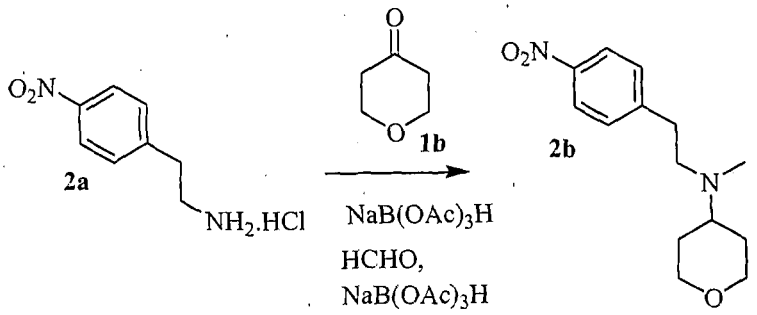
Cpd	Name	MS
31	[4-(3-methoxy-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	369
32	[4-(4-chloro-2-methyl-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	387
34	[4-(4-chloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	373
35	[4-(5-chloro-2-methyl-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	387
40	{4-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	419
41	{4-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-thiopyran-4-yl)-ammonium iodide	449
42	{4-[3-(3,5-difluoro-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	401
43	{4-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	443
44	{4-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-thiopyran-4-yl)-ammonium iodide	459
45	{4-[3-(3-chloro-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	399
46	{4-[3-(3-fluoro-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	383
47	{4-[3-(4-bromo-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	443
50	1-[4-(3,4-dichloro-benzoylamino)-benzyl]-1-methyl-piperidinium iodide	377
51	1-[4-(3,4-dichloro-benzoylamino)-benzyl]-1-methyl-pyrrolidinium iodide	363
54	1-{4-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-4-(2-methoxy-phenyl)-1-methyl-piperazin-1-ium iodide	510
55	1-{4-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-1-methyl-piperidinium iodide	413
57	1-methyl-1-{4-[3-(3-trifluoromethyl-phenyl)-acryloylamino]-benzyl}-piperidinium iodide	403
59	4-[4-(3,4-dichloro-benzoylamino)-benzyl]-4-methyl-morpholin-4-ium iodide	379
60	4-{4-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-4-methyl-morpholin-4-ium iodide	405
61	4-{4-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-4-methyl-morpholin-4-ium iodide	415
63	allyl-{4-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-methyl-(tetrahydro-thiopyran-4-yl)-ammonium iodide	487
66	dimethyl-(tetrahydro-pyran-4-yl)-[4-(3-m-tolyl-acryloylamino)-benzyl]-ammonium iodide	379
67	dimethyl-(tetrahydro-pyran-4-yl)-[4-(3-trifluoromethyl-benzoylamino)-benzyl]-ammonium iodide	407
68	dimethyl-(tetrahydro-pyran-4-yl)-{4-[3-(3-trifluoromethyl-phenyl)-acryloylamino]-benzyl}-ammonium iodide	433
69	dimethyl-[4-(3-methyl-benzoylamino)-benzyl]-(tetrahydro-pyran-4-yl)-ammonium iodide	353

Cpd	Name	MS
70	cycloheptyl-[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	419
71	cyclohexyl-{4-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-dimethyl-ammonium iodide	431
72	{4-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	443
74	cyclohexyl-dimethyl-[4-(3-trifluoromethyl-benzoylamino)-benzyl]-ammonium iodide	405
75	cyclohexyl-[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	405
76	[4-(3-chloro-4-fluoro-benzoylamino)-benzyl]-cyclohexyl-dimethyl-ammonium iodide	389
77	cyclohexyl-[4-(2,3-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	405
78	cyclohexyl-[4-(2,6-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	405
79	[4-(3-chloro-4-methoxy-benzoylamino)-benzyl]-cyclohexyl-dimethyl-ammonium iodide	401
80	[4-(3-chloro-4-methyl-benzoylamino)-benzyl]-cyclohexyl-dimethyl-ammonium iodide	385
81	cyclohexyl-[4-(2,5-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	405
82	cyclopentyl-[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-ammonium iodide	391
89	dimethyl-{4-[(naphthalene-1-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	389
90	dimethyl-{4-[(naphthalene-2-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	389
91	ethyl-methyl-{4-[(naphthalene-2-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	403
92	methyl-{4-[(naphthalene-2-carbonyl)-amino]-benzyl}-propyl-(tetrahydro-pyran-4-yl)-ammonium iodide	417
93	{4-[(7-bromo-naphthalene-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	467
94	{4-[(7-bromo-naphthalene-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	465
151	dimethyl-{4-[(2-methyl-5-phenyl-furan-3-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	419
152	{4-[(benzofuran-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	379
155	{4-[(5-chloro-benzofuran-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	413
156	{4-[(5-chloro-benzofuran-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	411
157	{4-[(benzofuran-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	437

Cpd	Name	MS
172	{4-[(5-bromo-pyridine-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	420
173	{4-[(2-chloro-pyridine-4-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	374

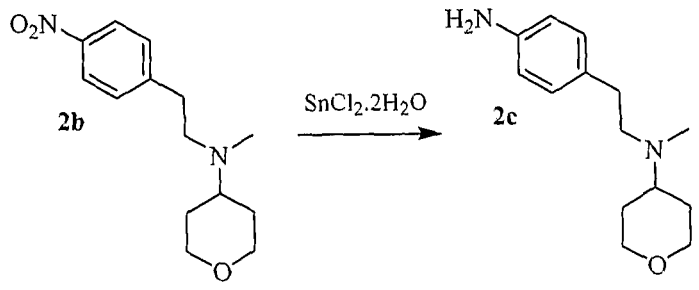
Example 2

{2-[4-(3,4-dichloro-benzoylamino)-phenyl]-ethyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide (Cpd **36**)



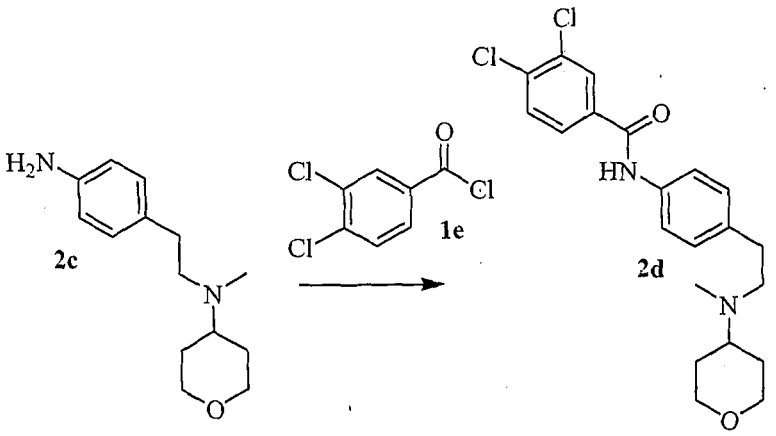
$NaB(OAc)_3H$ (2.33 mmol, 0.5 g) was added to a mixture of 2-(4-nitro-phenyl)-ethylamine Compound **2a** (2.25 mmol, 0.45 g) and tetrahydro-4*H*-pyran-4-one Compound **1b** (2.25 mmol, 0.21 mL) and Et_3N (2.25 mmol, 0.31 mL) in CH_2Cl_2 (25 mL). The resulting suspension was stirred at r.t. for 12 hrs. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 251, 100%).

An aqueous solution of formaldehyde (37% solution, 8.6 mmol, 0.7 mL) was added, followed by $NaB(OAc)_3H$ (2.33 mmol, 0.5 g) and the reaction mixture was stirred at r.t. for 12 hrs. The mixture was made basic using a 2N NaOH solution, extracted with CH_2Cl_2 and the organic layer was washed with brine, then separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to yield methyl-[2-(4-nitro-phenyl)-ethyl]-(tetrahydro-pyran-4-yl)-amine Compound **2b** as a yellow oil. The product was purified by flash column chromatography (10:1 CH_2Cl_2:MeOH; R_f 0.8) to yield a yellow oil (0.58 g, 97%). MS *m/e* 265 (M^+H, 100%).

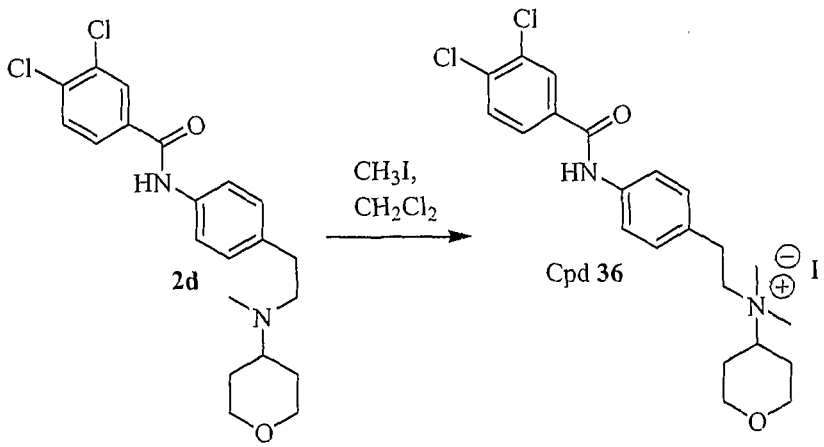


$SnCl_2.2H_2O$ (10.0 mmol, 2.25 g) was added to a solution of Compound **2b** (2.19 mmol, 0.58 g) in EtOH (10 mL) at r.t. A mild exotherm was observed. The resulting yellow solution

was stirred for 12 hrs and the solvent was removed *in vacuo*. The residue was made basic using a 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic layers were dried over Na_2SO_4 and filtered, then the solvent was removed *in vacuo* to obtain [2-(4-amino-phenyl)-ethyl]-methyl-(tetrahydro-pyran-4-yl)-amine Compound **2c** as an orange-yellow oil (0.4 g) used in the next step without purification. MS *m/e* 235 (M^+H, 100%).



A solution of 3,4-dichlorobenzoyl chloride Compound **1e** (0.25 mmol, 0.06 g) in THF (1 mL) was added dropwise over 2 min to a solution of Compound **2c** (0.2 mmol, 0.05 g) and Et_3N (0.4 mmol, 0.06 mL) in THF (4 mL) at 0 °C. The resulting suspension was allowed to warm to r.t. overnight, then made basic with a 2N NaOH solution and extracted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 X 10 mL). The organic layers were washed with brine, then dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* to yield 3,4-dichloro-N-(4-{2-[methyl-(tetrahydro-pyran-4-yl)-amino]-ethyl}-phenyl)-benzamide Compound **2d** as a yellow solid. The product was purified by preparative TLC (10:1 EtOAc:MeOH) (0.06 g, 73%). MS *m/e* 407 (M^+H, 100%);



Iodomethane (0.5 mL, excess) was added to a solution of Compound **2d** (0.07 mmol, 0.03 g) in acetone (1.0 mL) and acetonitrile (1.0 mL) at r.t. The resulting solution was stirred

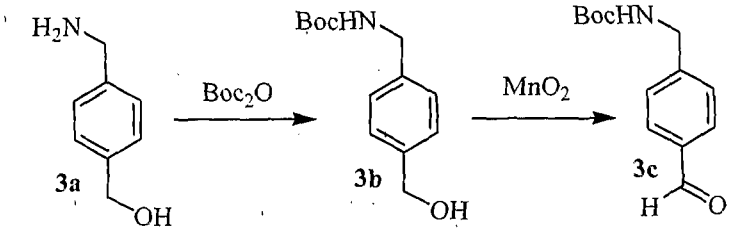
overnight, after which a yellow precipitate was observed. The solvent was removed *in vacuo* and the off-white solid was washed with Et_2O (2 X 5 mL) to provide Compound **36** as a pale yellow solid (0.03 g, 82%). MS *m/e* 548 (M, 100%).

Using the procedure of Example 2 and known appropriate reagents and starting materials, other compounds of the present invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

Cpd	Name	MS
37	{2-[4-(3-bromo-benzoylamino)-phenyl]-ethyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	431

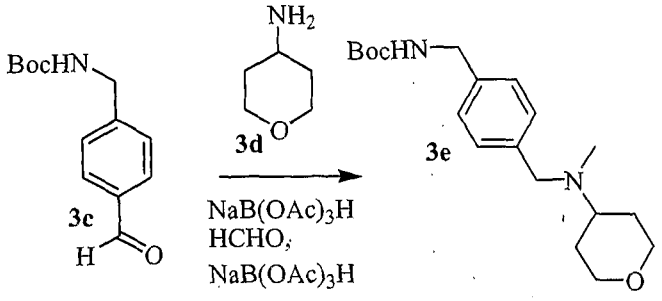
Example 3

dimethyl-(tetrahydro-pyran-4-yl)-(4-{[3-(3-trifluoromethyl-phenyl)-acryloylamino]-methyl}-benzyl)-ammonium iodide (Cpd **64**)

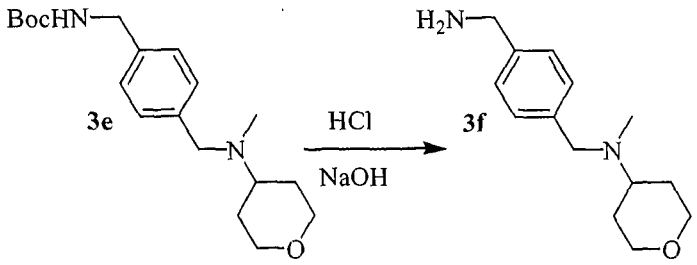


Boc_2O was added in one portion at r.t. to a solution of (4-aminomethyl-phenyl)-methanol Compound **3a** (21.2 mmol, 2.9 g) in CH_2Cl_2 (100 mL). The resulting solution was stirred for 48h, then washed with a 10% citric acid solution (50 mL) followed by brine. The organic layer was separated, then dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* to obtain (4-hydroxymethyl-benzyl)-carbamic acid tert-butyl ester Compound **3b** as a white solid (5.2 g, 99% yield), which was used in the next step without further purification.

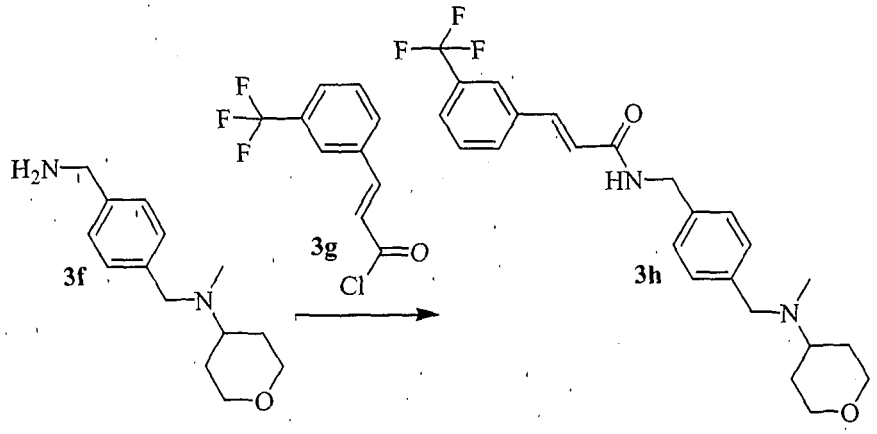
MnO_2 (9.6 g) was added to a solution of Compound **3b** (21.2 mmol, 5.2 g) in chloroform (60 mL), forming a black suspension that was stirred at r.t. overnight then filtered through a pad of celite. The solvent was evaporated *in vacuo* to obtain (4-formyl-benzyl)-carbamic acid tert-butyl ester Compound **3c** as a white solid (4.3 g, 87% yield), which was used in the next step without purification.



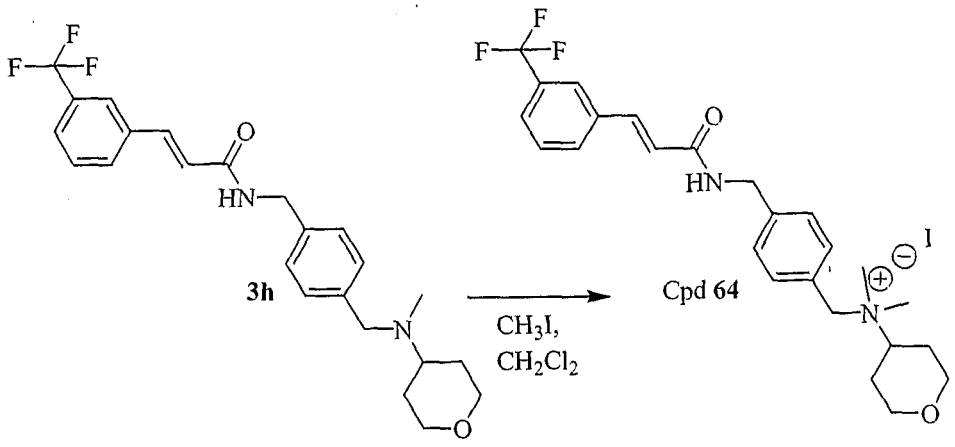
$NaB(OAc)_3H$ (2.8 mmol, 0.58 g) was added to a mixture of Compound **3c** (2.6 mmol, 0.6 g) and tetrahydro-pyran-4-ylamine Compound **3d** (2.6 mmol, 0.26 g) in CH_2Cl_2 (25 mL) and the resulting suspension was stirred at r.t. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 321; 100%). An aqueous solution of formaldehyde (37% solution, 8.6 mmol, 0.7 mL) was added to the reaction mixture, followed by $NaB(OAc)_3H$ (2.8 mmol, 0.58 g) added in one portion under ice cooling. The reaction mixture was stirred at r.t. for about 2h, then made basic with a 2N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, then separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to yield (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-benzyl)-carbamic acid tert-butyl ester Compound **3e** as a pale yellow oil. MS *m/e* 235 (M^+H, 100%). The product was purified by column chromatography (4:1 CH_2Cl_2:MeOH) to yield a colorless oil (0.52 g, 59% yield).



Compound **3e** was dissolved in CH_2Cl_2, then HCl in dioxane was added and the mixture was stirred at r.t. for 12 hrs. The solvent was removed and the gummy residue was made basic with 2N NaOH and extracted with EtOAc. The organic layer was washed with brine, then separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to obtain (4-aminomethyl-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **3f** as a pale yellow oil (0.3 g, 83% yield). MS *m/e* 235 (M^+H, 100%).



A solution of 3-(3-trifluoromethyl-phenyl)-acryloyl chloride Compound **3g** (0.3 mmol, 0.07 g) in THF (2 mL) was added dropwise to a solution of Compound **3f** (0.2 mmol, 0.05 g) and Et_3N (0.8 mmol, 0.14 mL) in THF (10 mL) at 0°C. The resulting suspension was allowed to warm to r.t. overnight. The reaction mixture was made basic with a 2N NaOH solution and extracted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (2 X 10 mL) and the organic layers were washed with brine, then dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* to yield a yellow solid (with methane) as the product. The crude product was purified by preparative TLC (9:1 EtOAc:MeOH, Rf = 0.2) to yield N-(4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-benzyl)-3-(3-trifluoromethyl-phenyl)-acrylamide Compound **3h** (0.06 g, 49% yield). MS *m/e* 433 (M^+H, 100%).



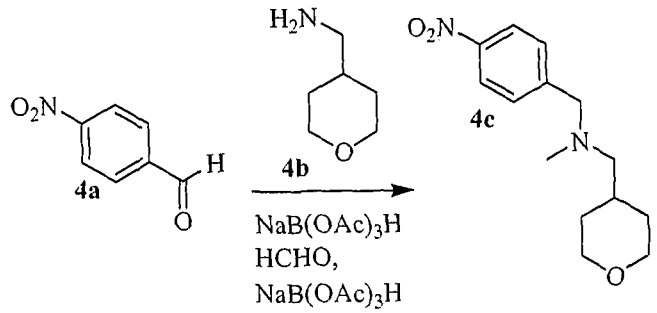
MeI (0.08 mL, 1.28 mmol) was added dropwise to a solution of Compound **3h** (0.07 mmol, 0.03 g) in a mixture of acetone:acetonitrile (2 mL). The resulting solution was stirred at r.t. for 24h to provide a residue. The residue was washed with ether (2× 1 mL) and dried under a high vacuum to provide Compound **64** (0.04 g, 93% yield) as an iodide salt. MS *m/e* 584 (M^+H, 100%).

Using the procedure of Example 3 and the appropriate known reagents and starting materials, other compounds of the invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

Cpd	Name	MS
1	(4-{[3-(3-bromo-phenyl)-acryloylamino]-methyl}-benzyl)-cyclohexyl-dimethyl-ammonium iodide	455
2	{4-[(3-bromo-benzoylamino)-methyl]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	429
3	cyclohexyl-dimethyl-{4-[(3-trifluoromethyl-benzoylamino)-methyl]-benzyl}-ammonium iodide	419
4	(4-{[3-(3,4-dichloro-phenyl)-acryloylamino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	447
5	(4-{[3-(3-bromo-phenyl)-acryloylamino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	457
39	{4-[(3,4-dichloro-benzoylamino)-methyl]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	421
48	1-(4-{[3-(3,4-dichloro-phenyl)-acryloylamino]-methyl}-benzyl)-1-methyl-piperidinium iodide	417
49	1-(4-{[3-(3-bromo-phenyl)-acryloylamino]-methyl}-benzyl)-1-methyl-piperidinium iodide	427
58	4-(4-{[3-(3,4-dichloro-phenyl)-acryloylamino]-methyl}-benzyl)-4-methyl-morpholin-4-ium iodide	419
149	dimethyl-(4-{[(2-methyl-5-phenyl-furan-3-carbonyl)-amino]-methyl}-benzyl)-(tetrahydro-pyran-4-yl)-ammonium iodide	433
150	[4-({[5-(4-chloro-phenyl)-2-methyl-furan-3-carbonyl]-amino}-methyl)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	467
153	(4-{[5-(4-chloro-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	507
154	(4-{[5-(4-chloro-phenyl)-2-trifluoromethyl-furan-3-carbonyl]-amino}-benzyl)-cyclohexyl-dimethyl-ammonium iodide	506

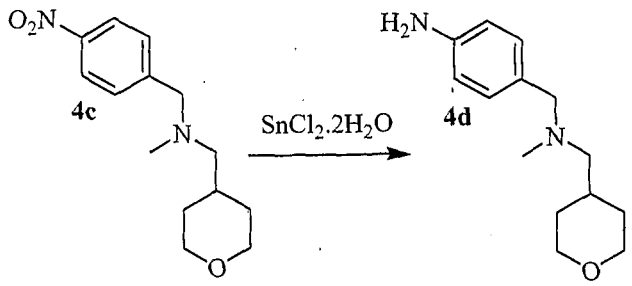
Example 4

[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium iodide (Cpd **18**)

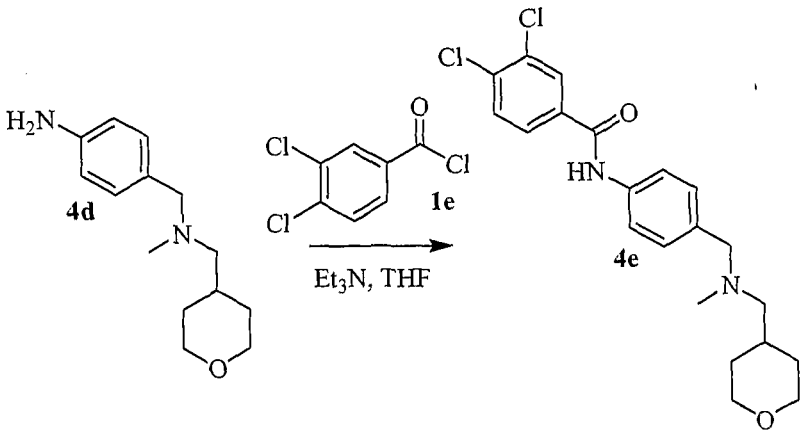


$NaB(OAc)_3H$ (3.5 mmol, 0.75 g) was added to a mixture of 4-nitro-benzaldehyde Compound **4a** (2.8 mmol, 0.42 g), (tetrahydro-pyran-4-yl)-methylamine Compound **4b** (3.0

mmol, 0.35 g) and glacial acetic acid (3 drops) in CH_2Cl_2 (50 mL) and the resulting suspension was stirred at r.t. overnight. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 251; 100%). An aqueous solution of formaldehyde (37% solution, 9.6 mmol, 0.8 mL) was added, followed by $NaB(OAc)_3H$ (3.5 mmol, 0.75 g). The reaction mixture was stirred at r.t. for 2h, then made basic with a 2N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, then separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to yield methyl-(4-nitro-benzyl)-(tetrahydro-pyran-4-ylmethyl)-amine Compound **4c** as yellow oil (0.63 g, 85% yield). MS *m/e* 265 (M^+H, 100%).

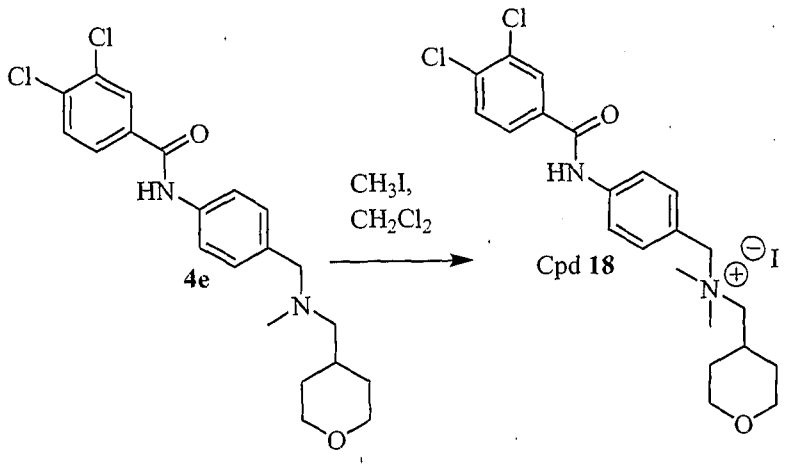


$SnCl_2.2H_2O$ (1.78 mmol, 0.4 g) was added to a solution of Compound **4c** (1.13 mmol, 0.3 g) in EtOH (20 mL) at r.t. The resulting yellow solution was stirred for 2 days then the solvent was removed *in vacuo*. The residue was made basic with a 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic layers were dried over Na_2SO_4 and filtered, then the solvent was removed *in vacuo* to obtain 4-{[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenylamine Compound **4d** as an orange-yellow oil (0.25 g, 94%) used in the next step without purification. MS *m/e* 235 (M^+H, 100%).



A solution of 3,4-dichlorobenzoyl chloride Compound **1e** (0.29 mmol, 0.06 g) in THF (1.0 mL) was added dropwise via syringe to a solution of Compound **4d** (0.19 mmol, 0.04 g) and Et_3N (0.36 mmol, 0.05 mL) in THF (4 mL) at 0 °C. The resulting suspension was allowed to warm to r.t. overnight, then made basic with a 2N NaOH solution and extracted with EtOAc

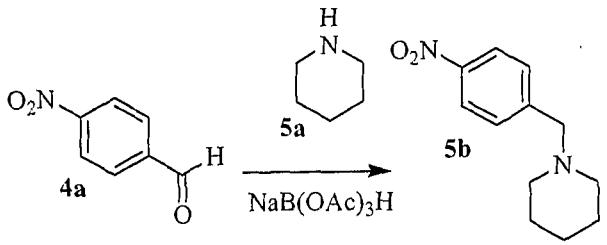
(15 mL). The aqueous layer was extracted with EtOAc (2 X 10 mL). The organic layers were washed with brine, dried over Na_2SO_4 and then filtered. The solvent was removed *in vacuo* to yield 3,4-dichloro-N-(4-{[methyl-(tetrahydro-pyran-4-ylmethyl)-amino]-methyl}-phenyl)-benzamide Compound **4e** as a yellow solid. The product was purified by preparative TLC (10:1 EtOAc:MeOH; Rf 0.4) (0.04 g, 52%). MS *m/e* 407 (M^+H, 100%).



Iodomethane (0.5 mL) was added to a solution of Compound **4e** (0.07 mmol, 0.03 g) in acetone (1.0 mL) and acetonitrile (1.0 mL) at r.t. The resulting solution was allowed to stand overnight, after which a yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O (2 X 1 mL) to obtain Compound **18** as a yellow solid (0.03 g, 96%). MS *m/e* 421 (M, 100%).

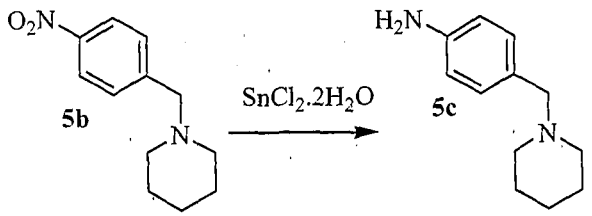
Example 5

1-{4-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-1-methyl-piperidinium iodide (Cpd **53**)

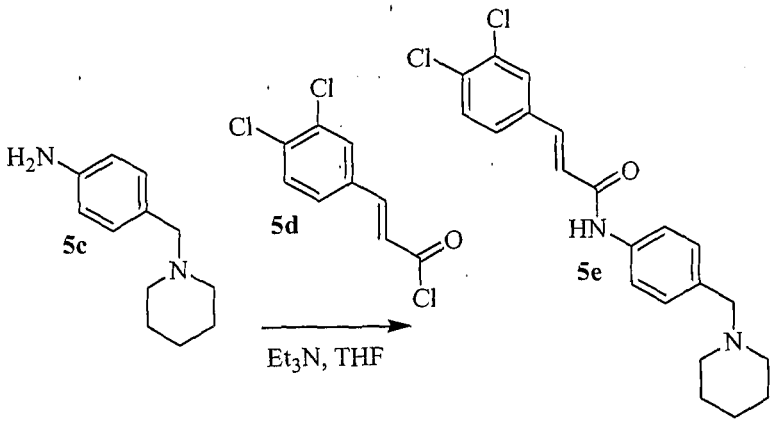


$NaB(OAc)_3H$ (6.6 mmol, 1.4 g) was added to a mixture of 4-nitro-benzaldehyde Compound **4a** (6.0 mmol, 0.9 g), piperidine Compound **5a** (9.0 mmol, 0.9 mL) and glacial acetic acid (5 drops) in CH_2Cl_2 (50 mL) and the resulting suspension was stirred at r.t. overnight. The reaction mixture was made basic with a 2N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, then separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo*. The product was purified by

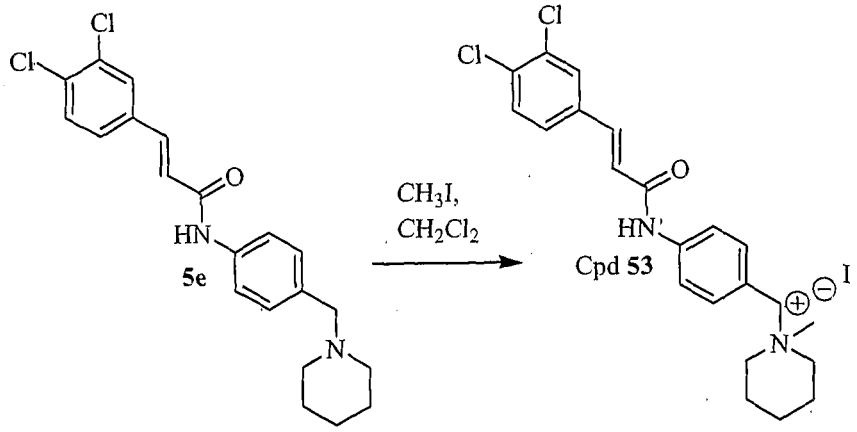
flash column chromatography (10:1 EtOAc:MeOH) to yield 1-(4-nitro-benzyl)-piperidine Compound **5b** as a yellow oil (0.89 g, 67% yield). MS *m/e* 221 (M^+H, 100%).



$SnCl_2.2H_2O$ (10.0 mmol, 2.25 g) was added to a solution of Compound **5b** (5.0 mmol, 1.1 g) in EtOH (25 mL) at r.t. and a mild exotherm was observed. The resulting yellow solution was stirred for 2 days then the solvent was removed *in vacuo*. The residue was made basic with a 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic layers were dried over Na_2SO_4 then filtered and the solvent was removed *in vacuo* to provide 4-piperidin-1-ylmethyl-phenylamine Compound **5c** as an orange-yellow oil (0.8 g, 84% yield), which was used in the next step without further purification. MS *m/e* 191 (M^+H, 100%).



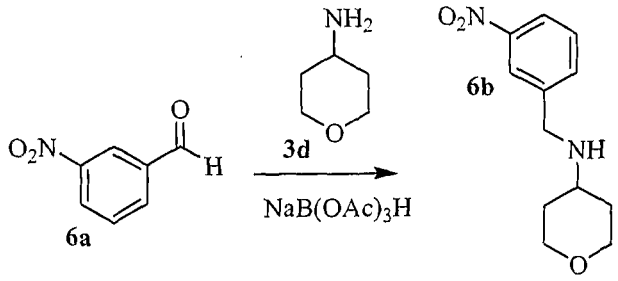
A solution of 3-(3,4-dichloro-phenyl)-acryloyl chloride Compound **5d** (0.21 mmol, 0.05 g) in THF (1.0 mL) was added dropwise via syringe to a solution of Compound **5c** (0.21 mmol, 0.04 g) and Et_3N (5.1 mmol, 0.7 mL) in THF (4 mL) at 0°C. The resulting suspension was allowed to warm to r.t. overnight, then made basic with a 2N NaOH solution and extracted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (2 X 10 mL). The organic layers were washed with brine, dried over Na_2SO_4 and then filtered. The solvent was removed *in vacuo* to yield 3-(3,4-dichloro-phenyl)-N-(4-piperidin-1-ylmethyl-phenyl)-acrylamide Compound **5e** as a yellow solid. The product was purified by preparative TLC (10:1 EtOAc:MeOH; Rf 0.4) to yield a yellow oil which was converted to the hydrochloride salt by dissolving a solution of Compound **5e** in CH_2Cl_2 with a solution of HCl in Et_2O, followed by removal of the solvent (0.05 g, 60%). MS *m/e* 389 (M^+H, 100%)..



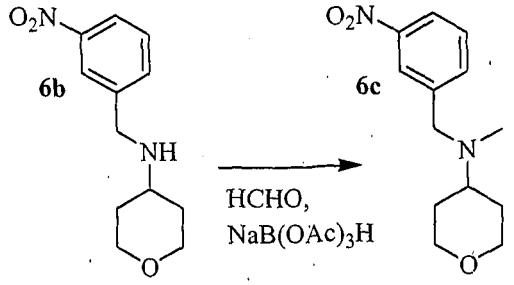
Iodomethane (0.5 mL) was added to a solution of Compound **5e** (0.06 mmol, 0.025 g) in acetone (1.0 mL) and acetonitrile (1.0 mL) at r.t. The resulting solution was allowed to stand overnight, after which a yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O (2 X 1 mL) to provide Compound **53** as a yellow solid (0.03 g, 89%). MS *m/e* 530 (M, 100%).

Example 6

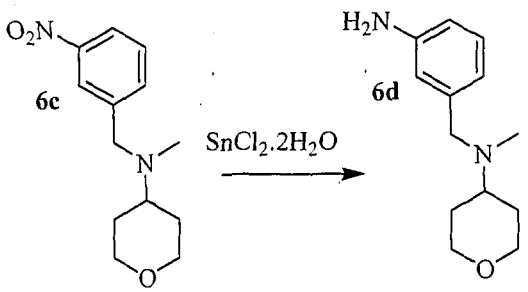
[3-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide (Cpd 7)



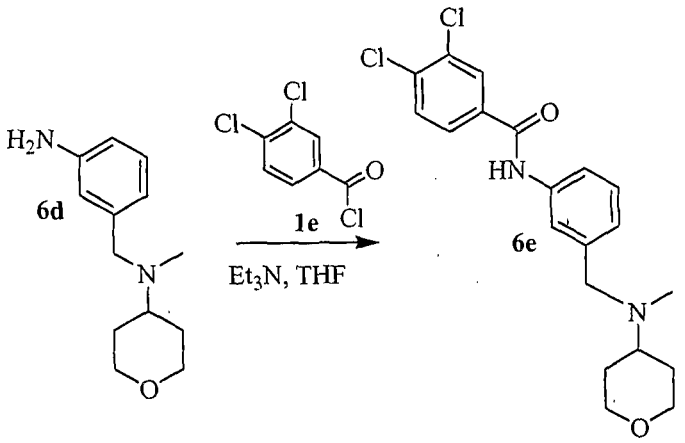
$NaB(OAc)_3H$ (11.87 mmol, 2.52 g) was added to a mixture of 3-nitrobenzaldehyde Compound **6a** (9.89 mmol, 1.49 g) and 4-amino-tetrahydro-pyran Compound **3d** (9.89 mmol, 1.00 g) in CH_2Cl_2 (50 mL) and the resulting suspension was stirred overnight at r.t. The reaction mixture was made basic with a 2N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, then separated and dried over $MgSO_4$. The drying agent was filtered and the solvent was removed *in vacuo*. The product was purified by flash column chromatography (9:1 CH_2Cl_2:MeOH) to yield (3-nitro-benzyl)-(tetrahydro-pyran-4-yl)-amine Compound **6b** as a yellow oil (1.91 g, 82%). (This portion of Example 6 was adapted from Shiroshi, et al., *J. Med. Chem.*, 2000, 43, 2049). MS *m/e* 237 (M^+H, 100%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.53 (m, 4H), 1.82-1.95 (d, 2H), 2.65-2.8 (m, 1H), 3.38 (dt, J = 3.2 Hz, J = 11.2 Hz, 2H), 3.92-4.05 (m, 4H), 7.45-7.54 (t, 1H), 7.65-7.72 (d, 1H), 8.07-8.15 (d, 1H), 8.22 (s, 1H).



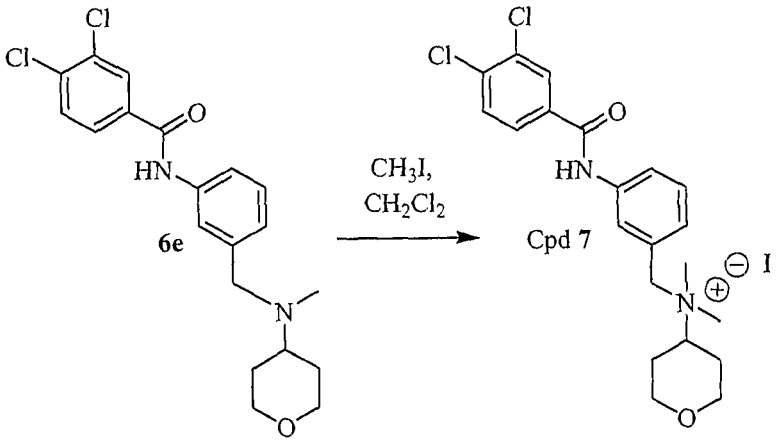
An aqueous solution of formaldehyde (37% solution, 9.4 mmol, 0.70 mL) was added to a solution of Compound **6b** (8.09 mmol, 1.91 g) in CH_2Cl_2, followed by $NaB(OAc)_3H$ (9.70 mmol, 2.06 g) added in one portion. The reaction mixture was stirred at r.t. for 12 hrs. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 251, 100%). The reaction mixture was made basic with a 2N NaOH solution and extracted with CH_2Cl_2. The organic layer was washed with brine, then separated and dried over $MgSO_4$. The drying agent was filtered and the solvent was removed *in vacuo* to yield methyl-(3-nitro-benzyl)-(tetrahydro-pyran-4-yl)-amine Compound **6c** as a yellow oil (1.87 g), which was used in the next step without further purification. MS *m/e* 251 (M^+H, 100%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60-1.82 (m, 4H), 2.21 (s, 3H), 2.60-2.75 (m, 1H), 3,38 (dt, J = 3.2 Hz, J = 11.2 Hz, 2H), 3.68 (s, 2H), 4.02-4.10 (m, 2H), 7.45-7.54 (t, 1H), 7.65-7.72 (d, 1H), 8.07-8.15 (d, 1H), 8.22 (s, 1H).



$SnCl_2.2H_2O$ (14.868 mmol, 3.35 g) was added to a solution of Compound **6c** (3.72 mmol, 0.930 g) in absolute ethanol (30 mL) at r.t. The reaction mixture was stirred overnight at 40°C. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 221, 100%). The solvent was removed *in vacuo* to obtain an orange solid, which was made basic to pH 9 with a 1N NaOH solution. The product was extracted with EtOAc, then dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to obtain (3-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **6d** as a yellow oil (0.490 g). MS *m/e* 221 (M^+H, 100%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-1.80 (m, 4H), 2.22 (s, 3H), 2.57-2.68 (m, 1H), 3.36 (dt, J = 3.2 Hz, J = 11.2 Hz, 2H), 3.50 (s, 2H), 3.65 (br, 2H), 3.98-4.10 (d, 2H), 6.55-6.62 (d, 1H), 6.70 (m, 2H), 7.05-7.12 (t, 1H).



A solution of 3,4-dichlorobenzoyl chloride Compound **1e** (0.250 mmol, 0.0523 g) was added dropwise to a solution of Compound **6d** (0.227 mmol, 0.0500 g) and Et_3N (0.250 mmol, 0.04 mL) in THF (10 mL) at 0 °C. The resulting suspension was allowed to warm to r.t. overnight. An aliquot of the reaction mixture showed the formation of product (MS *m/e* 393, 100%). The reaction mixture was made basic with a 2N NaOH solution and extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$ and then filtered. The solvent was removed *in vacuo* to yield 3,4-dichloro-N-(3-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-benzamide Compound **6e**. The product was purified by preparative TLC (9:1 EtOAc:MeOH) to yield a yellow solid (0.0380 g, 43%). MS *m/e* 393 (M^+H, 100%); ^1H NMR (300 MHz, $CDCl_3$) δ 1.58-1.83 (m, 4H), 2.21 (s, 3H), 2.61-2.75 (m, 1H), 3.35 (dt, J = 3.1 Hz, J = 11.0 Hz, 2H), 3.57 (s, 2H), 4.01-4.09 (m, 2H), 7.10 (d, J = 1H), 7.25-7.32 (t, 1H), 7.45-7.52 (d, 1H), 7.55-7.65 (d, 2H), 7.65-7.72 (m, 1H), 7.95 (m, 1H), 8.25 (s, 1H).



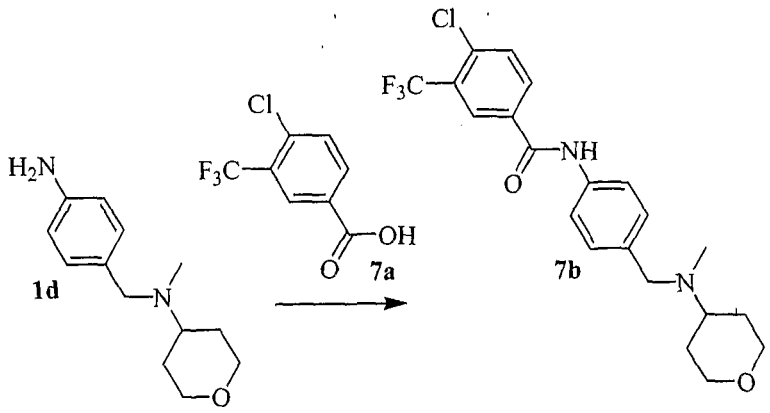
Iodomethane (0.0161 mol, 1.0 mL) was added to a solution of Compound **6e** (0.0674 mmol, 0.0265 g) in acetonitrile (3 mL) and acetone (3 drops) at r.t. The resulting solution was stirred overnight, then the solvent was removed *in vacuo*. The product was washed with Et_2O (10 mL) and dried in a vacuum oven for 12 hrs to provide Compound **7** as an orange solid (0.0326 g, 90.3%). MS *m/e* 407 (M, 100%).

Using the procedure of Example 6 and appropriate known reagents and starting materials, other compounds of the present invention may be prepared including, but not limited to (MS: Mass Spec data as MS *m/e* M^+H):

Cpd	Name	MS
8	[3-(3-bromo-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	419
38	{3-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	445
52	1-{3-[3-(3-bromo-phenyl)-acryloylamino]-benzyl}-1-methyl-piperidinium iodide	415
56	1-methyl-1-[3-(3-trifluoromethyl-benzoylamino)-benzyl]-piperidinium iodide	377
65	dimethyl-(tetrahydro-pyran-4-yl)-[3-(3-trifluoromethyl-benzoylamino)-benzyl]-ammonium iodide	407
83	cyclohexyl-{3-[3-(3,4-dichloro-phenyl)-acryloylamino]-benzyl}-dimethyl-ammonium iodide	431
84	cyclohexyl-{3-[3-(4-fluoro-phenyl)-acryloylamino]-benzyl}-dimethyl-ammonium iodide	381

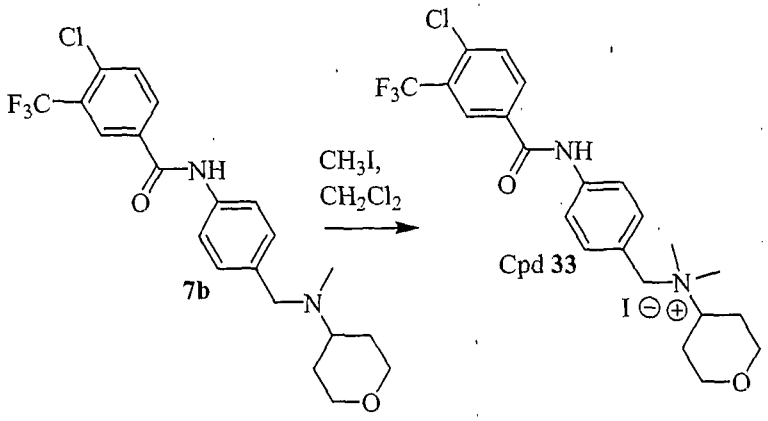
Example 7

[4-(4-chloro-3-trifluoromethyl-benzoylamino)-benzyl]-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide (Cpd **33**)



EDIC hydrochloride (0.33 mmol, 0.07 g) was added in one portion to a suspension of (4-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **1d** (0.25 mmol, 0.06 g), 4-chloro-3-trifluoromethyl-benzoic acid Compound **7a** (0.22 mmol, 0.05 g) and HOBt (0.22 mmol, 0.03 g) in DMF (5.0 mL) at 0°C. The resulting suspension was warmed to r.t. and a crystal of DMAP and Et_3N (0.65 mmol, 0.1 mL) were added. The mixture was stirred overnight and produced an orange-yellow suspension. The suspension was poured into water and the aqueous layer was extracted with EtOAc (25 mL). The organic layer was washed with water (2 X 20 mL), then a solution of 5% NaOH (10 mL) and brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* to yield a

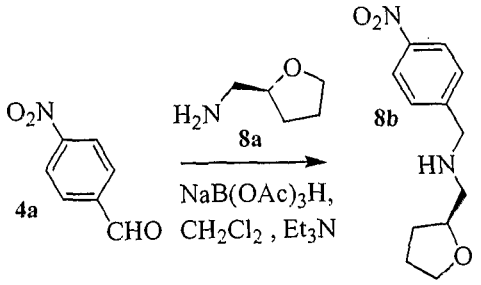
residue, which was purified via preparative TLC (15:1 CH_2Cl_2:MeOH) to provide 4-chloro-N-(4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-3-trifluoromethyl-benzamide Compound **7b** (0.06 g, 63%) as a pale yellow solid. MS m/e 427 (M^+H, 100%).



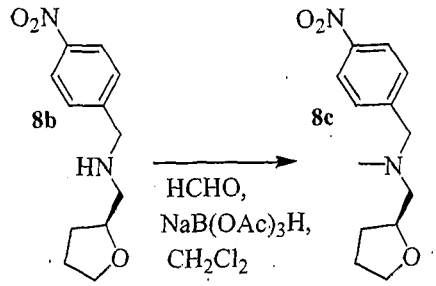
Iodomethane (0.5 mL) was added to a solution of Compound **7b** (0.07 mmol, 0.03 g) in CH_2Cl_2 (1.0 mL) at r.t. The resulting solution stood overnight, after which a pale yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O (2 X 1 mL) to provide Compound **33** as a yellow solid (0.03 g, 96%). MS *m/e* 441 (M^+H, 100%).

Example 8

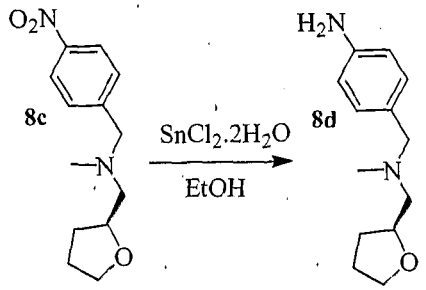
(2*S*)-[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-furan-2-ylmethyl)-ammonium iodide (Cpd **15**)



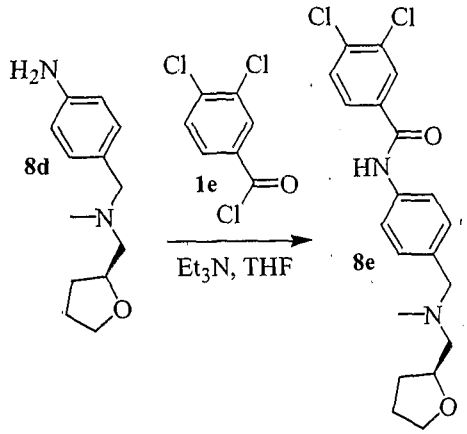
$NaB(OAc)_3H$ (3.5 mmol, 0.75 g) was added to a mixture of 4-nitro-benzaldehyde Compound **4a** (2.8 mmol, 0.42 g), (S)-(+)-(tetrahydro-furan-2-yl)-methylamine Compound **8a** (3.0 mmol, 0.3 mL) and glacial acetic acid (2 drops) in CH_2Cl_2 (25 mL) and the resulting suspension was allowed to stir at room temperature for 12 hrs. An aliquot of the reaction mixture showed the formation of (S)-(4-nitro-benzyl)-(tetrahydro-furan-2-ylmethyl)-amine Compound **8b** (MS m/e 237, 100%).



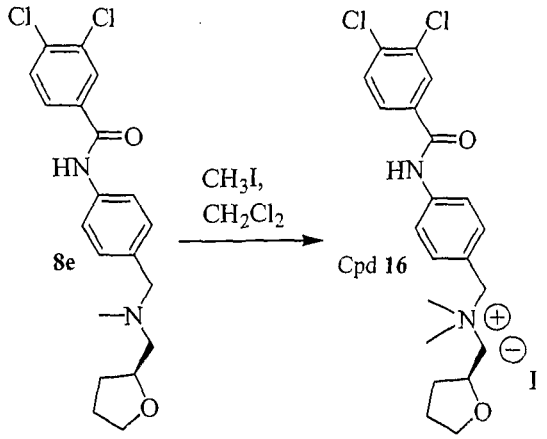
An aqueous solution of formaldehyde (37% solution, 9.6 mmol, 0.8 mL) was added to the reaction mixture followed by $NaB(OAc)_3H$ (3.5 mmol, 0.75 g) and the reaction mixture was allowed to stir at r.t. for 2 hrs. The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo*. The gummy residue thus obtained was spectroscopically characterized to be (S)-methyl-(4-nitro-benzyl)-(tetrahydro-furan-2-ylmethyl)-amine Compound **8c** (0.74 g). MS m/e 251 (M^+H, 100%).



$SnCl_2.2H_2O$ (10.0 mmol, 2.35 g) was added to a solution of Compound **8c** (2.8 mmol, 0.74 g) in EtOH (25 mL) at r.t. and the resulting yellow solution was stirred overnight. The solvent was removed in vacuo. The residue was basified with 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to obtain (S)-4-{[methyl-(tetrahydro-furan-2-ylmethyl)-amino]-methyl}-phenylamine Compound **8d** as a thick yellow oil (0.54 g, 88% yield), which was used in the next step without purification. MS m/e 221 (M^+H, 100%).



A solution of 3,4-dichlorobenzoyl chloride Compound **1e** (0.25 mmol, 0.05 g) in THF (5 mL) was added to a solution of Compound **8d** (0.25 mmol, 0.06 g) and Et_3N (0.5 mmol, 0.07 mL) in THF (3 mL) at 0°C and the reaction mixture was stirred overnight. The pale yellow suspension was poured in water and was extracted with EtOAc (20 mL). The organic layer was washed with water (2 X 20 mL) followed by brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the resulting residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to yield (S)-3,4-dichloro-N-(4-{[methyl-(tetrahydro-furan-2-ylmethyl)-amino]-methyl}-phenyl)-benzamide Compound **8e** as a pale yellow solid (0.06 g, 61%). M.S. m/e 393 (M^+H, 100%).



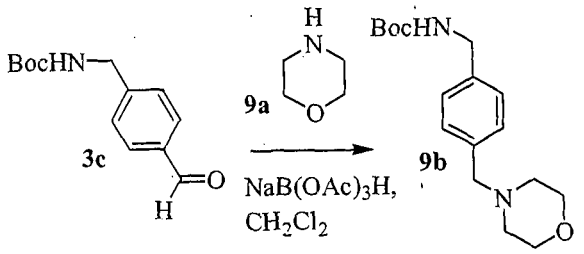
Iodomethane (0.5 mL) was added to a solution of Compound **8e** (0.07 mmol, 0.03 g) in CH_2Cl_2 (1.0 mL) at r.t. and the resulting solution was allowed to stand overnight. A yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O to obtain Compound **15** as a off-white powder (0.04 g, 97%). MS m/e 534 (M, 100%).

Using the procedure of Example 8 and the appropriate known reagents and starting materials, other compounds of the invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

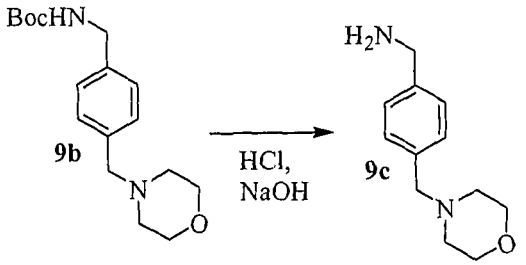
Cpd	Name	MS
16	(2*R*)-[4-(3,4-dichloro-benzoylamino)-benzyl]-dimethyl-(tetrahydro-furan-2-ylmethyl)-ammonium iodide	407
165	(2*S*)-{4-[(5-chloro-1H-indole-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-furan-2-ylmethyl)-ammonium iodide	412

Example 9

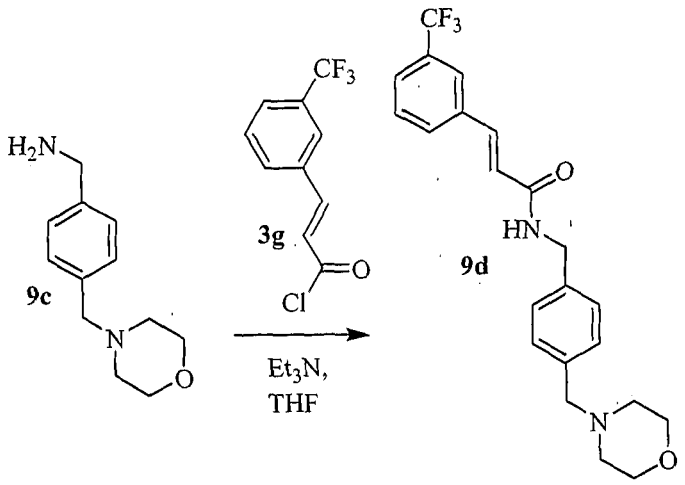
4-methyl-4-(4-{[3-(3-trifluoromethyl-phenyl)-acryloylamino]-methyl}-benzyl)-morpholin-4-ium iodide (Cpd **62**)



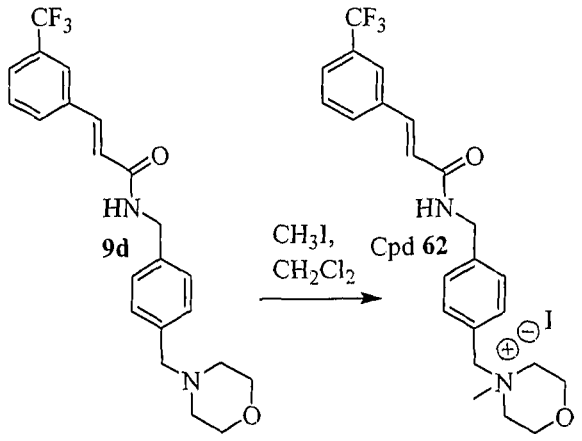
$NaB(OAc)_3H$ (0.82 mmol, 0.17 g) was added to a mixture of (4-formyl-benzyl)-carbamic acid tert-butyl ester Compound **3c** (0.75 mmol, 0.17 g) and morpholine Compound **9a** (0.75 mmol, 0.07 mL) in CH_2Cl_2 (20 mL) and the resulting suspension was stirred at room temperature for 6 hrs. The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to a crude product as a pale yellow oil. MS m/e 307 (M^+H, 100%). The product was purified by prep TLC (10:1 CH_2Cl_2/MeOH, Rf = 0.5) to yield (4-morpholin-4-ylmethyl-benzyl)-carbamic acid tert-butyl ester Compound **9b**.



Compound **9b** was dissolved in CH_2Cl_2 and was stirred with HCl in dioxane at r.t. for 12 hrs. The solvent was removed to obtain a gummy residue, which was basified with 2N NaOH and extracted with EtOAc. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to obtain 4-morpholin-4-ylmethyl-benzylamine Compound **9c** as pale yellow oil (wt. 0.09 g, 58% yield). MS m/e 207 (M^+H, 100%).



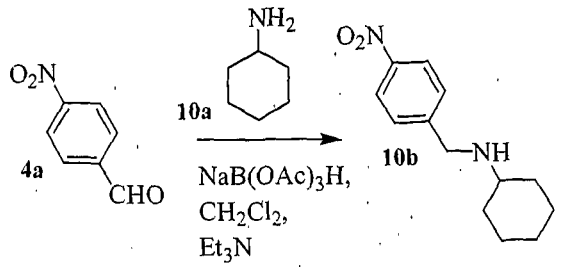
A solution of 3-(3-trifluoromethyl-phenyl)-acryloyl chloride Compound **3g** (0.3 mmol, 0.07 g) in THF (2 mL) was added dropwise to a solution of Compound **9c** (0.19 mmol, 0.04 g) and Et_3N (0.8 mmol, 0.14 mL) in THF (10 mL) at 0°C. The resulting suspension was allowed to warm to r.t. overnight. The reaction mixture was basified with 2N NaOH solution and was extracted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (2 X 10 mL). The organic layers were washed with brine, then dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the resulting yellow gummy oil was purified by preparative TLC (10:1 CH_2Cl_2/MeOH, Rf = 0.5) to yield N-(4-morpholin-4-ylmethyl-benzyl)-3-(3-trifluoromethyl-phenyl)-acrylamide Compound **9d** as a pale yellow solid (0.06 g , 77%). MS m/e 405 (M^+H, 100%).



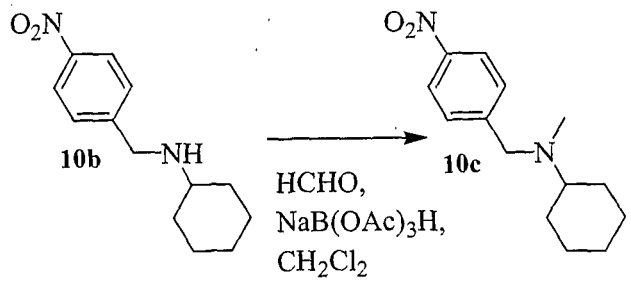
MeI (1.28 mmol, 0.08 mL) was added dropwise to a solution of Compound **9d** (0.07 mmol, 0.03 g) in a mixture of acetone/acetonitrile (2 mL). The solution was stirred at room temperature for 24 hrs and concentrated. The resulting residue was washed with ether (2×1 mL) and dried under high vacuum to give Compound **62** (0.03 g, 78%). MS m/e 546 (M).

Example 10

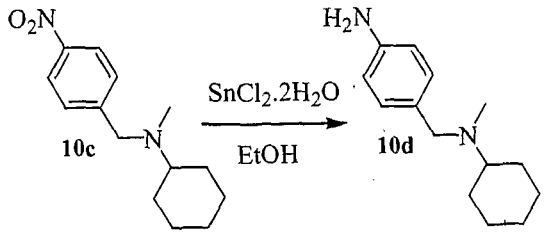
[4-(3-bromo-benzoylamino)-benzyl]-cyclohexyl-dimethyl-ammonium iodide (Cpd **73**)



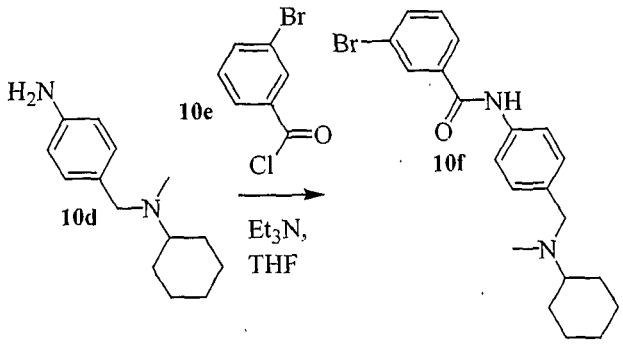
$NaB(OAc)_3H$ (11.0 mmol, 2.33 g) was added to a mixture of 4-nitro-benzaldehyde Compound **4a** (10.0 mmol, 1.51 g), cyclohexylamine Compound **10a** (10.5 mmol, 1.2 mL) and glacial acetic acid (5 drops) in CH_2Cl_2 (40 mL) and the resulting suspension was allowed to stir at room temperature for 12 hrs. An aliquot of the reaction mixture showed the formation of product (MS m/e 235, 100%). The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to yield cyclohexyl-(4-nitro-benzyl)-amine Compound **10b** as yellow oil (1.56 g, 67% yield), which was used in the next step without purification.



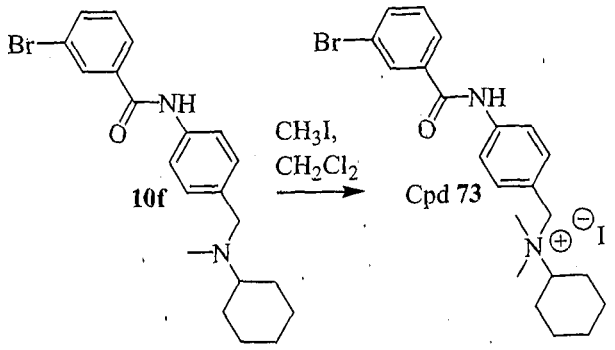
An aqueous solution of formaldehyde (37% solution, 9.6 mmol, 0.8 mL) was added to a solution of Compound **10b** (3.41 mmol, 0.8 g) in CH_2Cl_2 followed by $NaB(OAc)_3H$ (7.0 mmol, 1.5 g) and the mixture was allowed to stir at r.t. for 2 hrs. The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo*. The gummy residue was purified by column chromatography (9:1 EtOAc/MeOH) to yield cyclohexyl-methyl-(4-nitro-benzyl)-amine Compound **10c** as yellow oil (0.8 g, 94% yield). MS m/e 249 (M^+H, 100%).



$SnCl_2.2H_2O$ (16.0 mmol, 3.6 g) was added to a solution of Compound **10c** (3.2 mmol, 0.8 g) in EtOH (40 mL) at r.t. and the resulting yellow solution was stirred overnight. The solvent was removed *in vacuo*. The residue was basified with 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo to obtain 4-[(cyclohexyl-methyl-amino)-methyl]-phenylamine Compound **10d** as a thick yellow oil (0.69 g, 98% yield), which was used in the next step without purification. MS m/e 219 (M^+H, 100%).



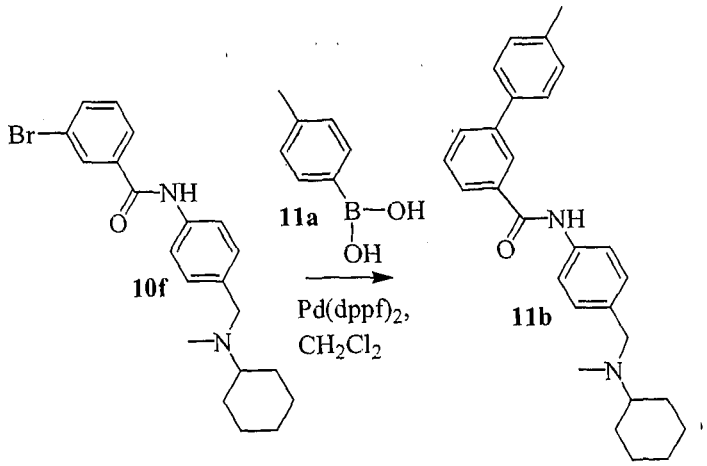
A solution of 3-bromobenzoyl chloride Compound **10e** (0.8 mmol, 0.15 g) was added to a solution of Compound **10d** (0.7 mmol, 0.2 g) and Et_3N (0.8 mmol, 0.14 mL) in THF (15 mL) in THF (5 mL) at 0°C and the reaction mixture was stirred overnight. The pale yellow suspension was poured in water and was extracted with EtOAc (30 mL). The organic layer was washed with water (2 X 20 mL) followed by 5% NaOH solution (10 mL) and brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the resulting residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to yield 3-bromo-N-{4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-benzamide Compound **10f** as a pale yellow solid (0.21 g, 75%). MS m/e 401 (M^+H, 100%).



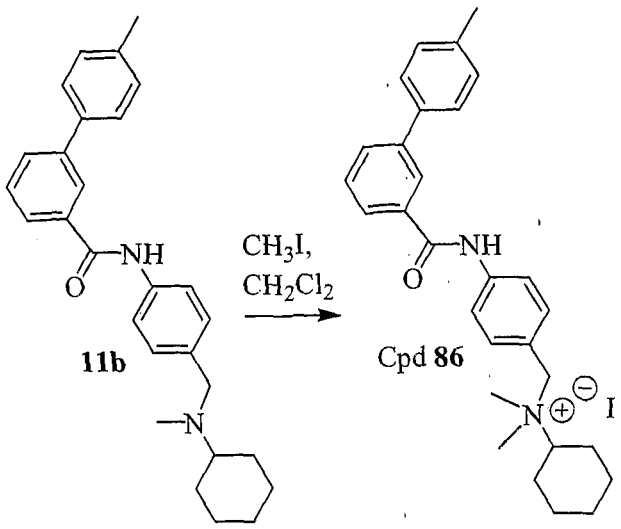
Iodomethane (0.5 mL) was added to a solution of Compound **10f** (0.07 mmol, 0.03 g) in CH_2Cl_2 (1.0 mL) at r.t. and the resulting solution was allowed to stand overnight. A yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O to provide Compound **73** as a pale yellow solid (0.04 g, 99%). MS m/e 542 (M, 100%).

Example 11

cyclohexyl-dimethyl-{4-[(4'-methyl-biphenyl-3-carbonyl)-amino]-benzyl}-ammonium iodide (Cpd **86**)



K_2CO_3 (0.2 mmol, 0.03 g) and a $Pd(dppf)_2$ catalyst:DCM complex (1:1) (0.03 mmol , 0.02 g) was added to a mixture of 3-bromo-N-{4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-benzamide Compound **10f** (0.1 mmol , 0.04 g) and p-tolylboronic acid Compound **11a** (0.12 mmol, 0.02 g) in a mixed solution of toluene/ethanol/water (7 mL/1 mL/1 mL). The resulting suspension was heated to reflux for 5 hrs, concentrated and purified with preparative TLC (10%MeOH/2% Et_3N/88%EtOAc) to yield 4'-methyl-biphenyl-3-carboxylic acid {4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}amide Compound **11b** (0.02 g, 48%). MS m/e 413 (M+1).



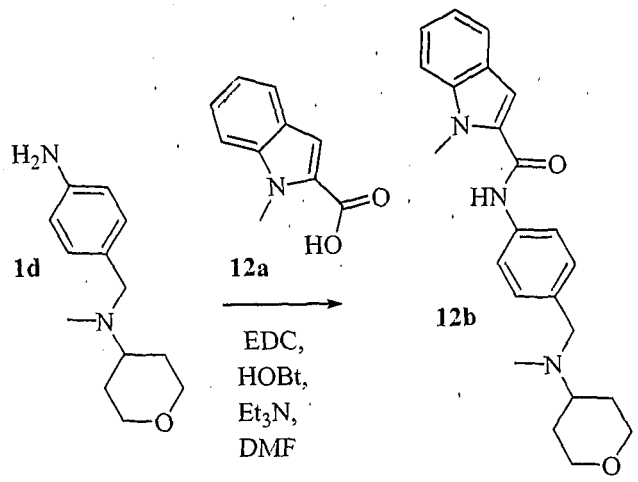
Iodomethane (0.32 mmol , 0.02 mL) was added dropwise to a solution of Compound **11b** (0.012 mmol , 0.005 g) in acetone/acetonitrile (1 mL, 0.5 mL/0.5 mL). The resulting solution was stirred at room temperature for 48 hrs and concentrated. The obtained residue was washed with ether (2×1 mL) and dried under a high vacuum to give Compound **86** (0.01 g, 89%). MS m/e 427 (M^+H).

Using the procedure of Example 11 and known appropriate reagents and starting materials, other compounds of the present invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

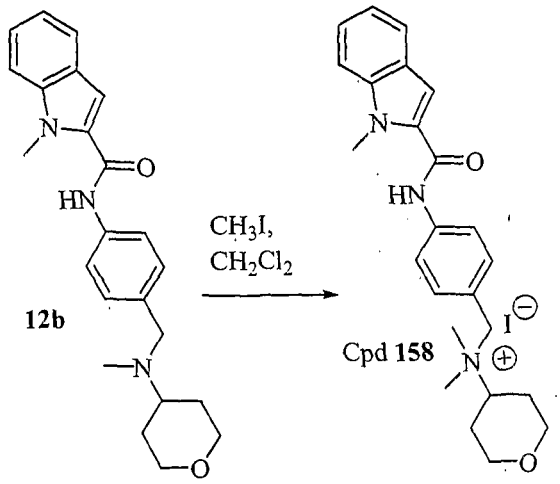
Cpd	Name	MS
85	dimethyl-(tetrahydro-pyran-4-yl)-{4-[(4'-trifluoromethyl-biphenyl-3-carbonyl)-amino]-benzyl}-ammonium iodide	483
87	dimethyl-{4-[(4'-methyl-biphenyl-3-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	429
88	{4-[(biphenyl-4-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	415

Example 12

dimethyl-{4-[(1-methyl-1H-indole-2-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide (Cpd **158**)



EDIC (0.33 mmol, 0.07 g) was added in one portion to a mixture of (4-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **1d** (0.25 mmol, 0.06 g), 1-methyl-1H-indole-2-carboxylic acid Compound **12a** (0.22 mmol, 0.04 g) and HOBt (0.22 mmol, 0.03 g) in DMF (5.0 mL) at 0°C. The resulting suspension was warmed to r.t. and then a crystal of DMAP and Et_3N (0.65 mmol, 0.1 mL) was added and the reaction mixture was stirred overnight. The resulting orange-yellow suspension was poured in water and was extracted with EtOAc (25 mL). The organic layer was washed with water (2 X 20 mL) followed by 5% NaOH solution (10 mL) and brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed in vacuo and the resulting residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to yield 1-methyl-1H-indole-2-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-amide Compound **12b** as a pale yellow solid (0.05 g, 60%). MS m/e 378 (M^+H, 100%).



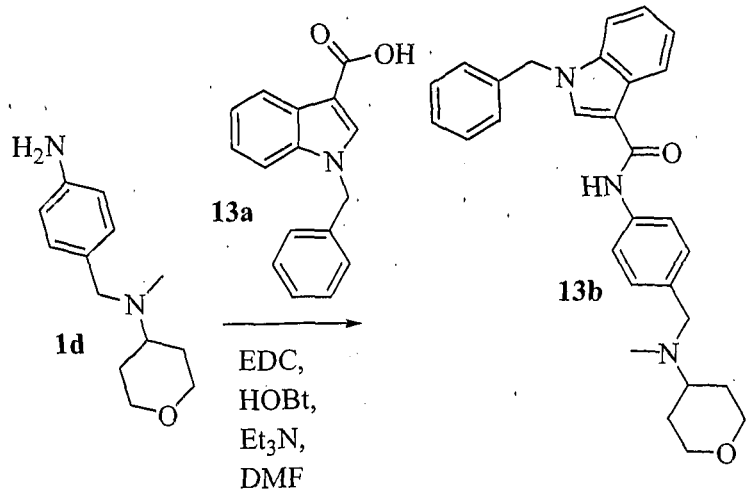
Iodomethane (0.5 mL) was added to a solution of Compound **12b** (0.08 mmol, 0.03 g) in CH_2Cl_2 (1.0 mL) at r.t. The mixture was allowed to stand overnight and a yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O to obtain Compound **158** as a yellow solid (0.03 g, 77%). MS m/e 391 (M^+H, 100%).

Using the procedure of Example 12 and known appropriate reagents and starting materials, other compounds of the present invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

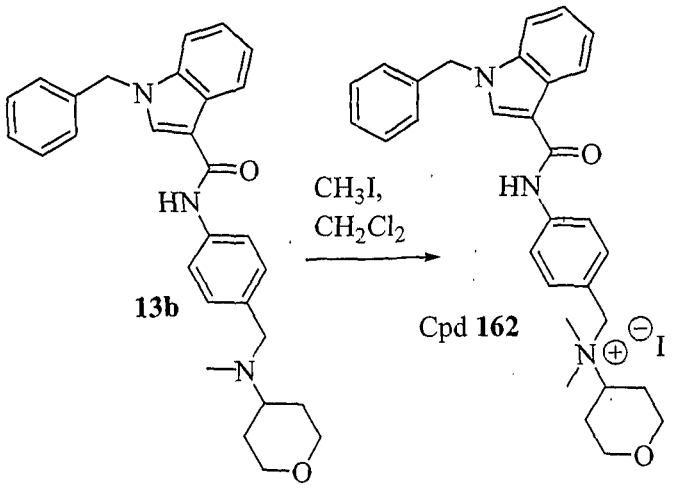
Cpd	Name	MS
159	{4-[(5-chloro-1H-indole-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	412
160	{4-[(5-bromo-1H-indole-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	456
161	dimethyl-{4-[(1-methyl-1H-indole-3-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	392
163	cyclohexyl-dimethyl-{4-[(1-methyl-1H-indole-2-carbonyl)-amino]-benzyl}-ammonium iodide	390
166	bicyclo[2.2.1]hept-2-ylmethyl-{4-[(5-chloro-1H-indole-2-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	422
174	{4-[(3-chloro-benzo[b]thiophene-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	429
175	{4-[(2,5-dichloro-thiophene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	413
176	{4-[(benzo[b]thiophene-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	395
177	{4-[(benzo[b]thiophene-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	393
178	{4-[(3-chloro-benzo[b]thiophene-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	427

Example 13

{4-[(1-benzyl-1H-indole-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide (Cpd **162**)



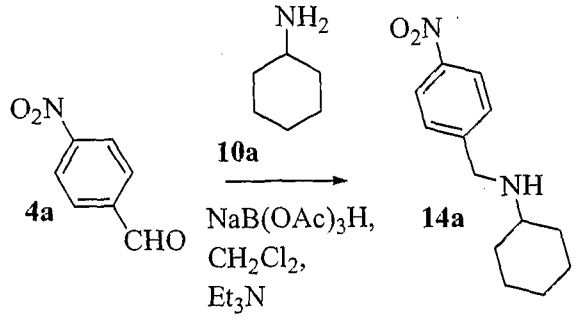
EDCI (0.33 mmol, 0.07 g) was added in one portion to a suspension of (4-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **1d** (0.25 mmol, 0.06 g), 1-benzyl-1H-indole-3-carboxylic acid Compound **13a** (0.22 mmol, 0.06 g) and HOBt (0.22 mmol, 0.03 g) in DMF (5.0 mL) at 0°C. The resulting suspension was warmed to r.t. and then a crystal of DMAP and Et_3N (0.65 mmol, 0.1 mL) was added and the reaction mixture was stirred overnight. The orange-yellow suspension was poured in water and was extracted with EtOAc (25 mL). The organic layer was washed with water (2 X 20 mL) followed by 5% NaOH solution (10 mL) and brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the resulting residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to yield Compound **13b** as a pale yellow solid (0.07 g, 71%). MS m/e 454 (M^+H, 100%).



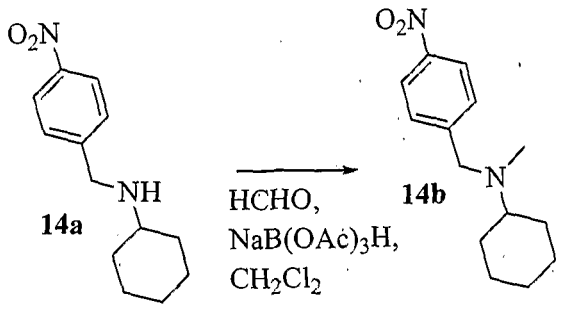
Iodomethane (0.5 mL) was added to a solution of Compound **13b** (0.08 mmol, 0.04 g) in CH_2Cl_2 (1.0 mL) at r.t. The mixture was allowed to stand overnight and a yellow precipitate was observed. The solvent was removed *in vacuo* and the yellow solid was washed with Et_2O to obtain Compound **162** as a yellow solid (0.05 g, 84%). MS m/e 469 (M^+H, 100%).

Example 14

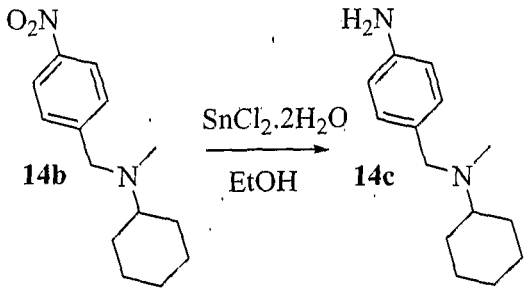
{4-[(5-chloro-1H-indole-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide (Cpd **164**)



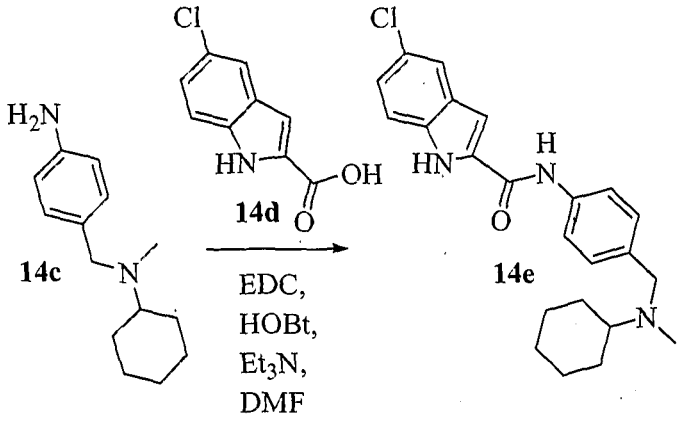
Sodium triacetoxyborohydride (11.0 mmol, 2.33 g) was added to a mixture of 4-nitro-benzaldehyde Compound **4a** (10.0 mmol, 1.51 g), cyclohexylamine Compound **10a** (10.5 mmol, 1.2 mL) and glacial acetic acid (5 drops) in CH_2Cl_2 (40 mL) and the resulting suspension was allowed to stir at room temperature for 12 hrs. An aliquot of the reaction mixture showed the formation of product (MS m/e 235, 100%). The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to yield cyclohexyl-(4-nitro-benzyl)-amine Compound **14a** (1.56 g, 67%) as a yellow oil, which was used in the next step without further purification.



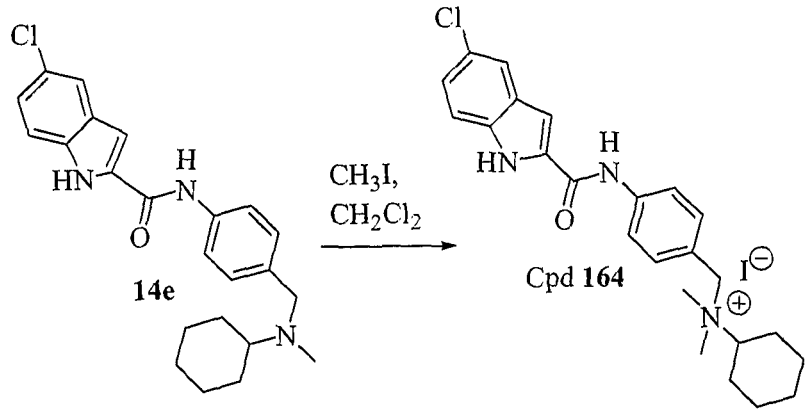
An aqueous solution of formaldehyde (37% solution, 9.6 mmol, 0.8 mL) was added to a solution of Compound **14a** (3.41 mmol, 0.8 g) in CH_2Cl_2, followed by sodium triacetoxyborohydride (7.0 mmol, 1.5 g). The mixture was allowed to stir at r.t. for 2 hrs. The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo*. The resulting gummy residue was purified by column chromatography (9:1 EtOAc/MeOH) to yield cyclohexyl-methyl-(4-nitro-benzyl)-amine Compound **14b** (0.8 g, 94%) as a yellow oil. MS m/e 249 (M^+H, 100%).



$SnCl_2.2H_2O$ (16.0 mmol, 3.6 g) was added to a solution of Compound **14b** (3.2 mmol, 0.8 g) in EtOH (40 mL) at r.t.. The resulting yellow solution was stirred overnight and the solvent was removed *in vacuo*. The resulting residue was basified with 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to obtain 4-[(cyclohexyl-methyl-amino)-methyl]-phenylamine Compound **14c** (0.69 g, 98%) as a thick yellow oil, which was used in the next step without further purification. MS m/e 219 (M^+H, 100%).



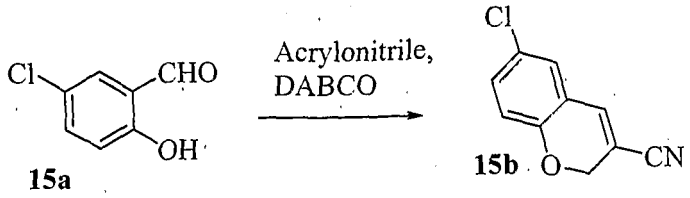
EDCI (0.33 mmol, 0.07 g) was added in one portion to a suspension of Compound **14c** (0.25 mmol, 0.05 g), 5-chloro-1H-indole-2-carboxylic acid Compound **14d** (0.22 mmol, 0.04 g) and HOBt (0.22 mmol, 0.03 g) in DMF (5.0 mL) at 0°C. The resulting suspension was warmed to r.t. and then a crystal of DMAP and Et_3N (0.65 mmol, 0.1 mL) was added and the reaction mixture was stirred overnight. The resulting orange-yellow suspension was poured in water and was extracted with EtOAc (25 mL). The organic layer was washed with water (2 X 20 mL) followed by 5% NaOH solution (10 mL) and brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the resulting residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to yield 5-chloro-1H-indole-2-carboxylic acid {4-[(cyclohexyl-methyl-amino)-methyl]-phenyl}-amide Compound **14e** (0.06 g, 68%) as a pale yellow solid. MS m/e 396 (M^+H, 100%).



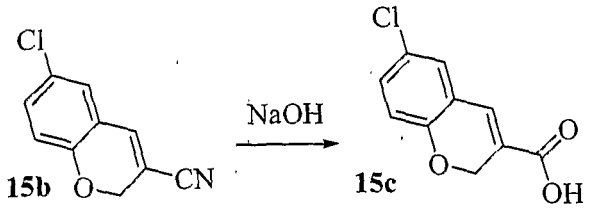
Iodomethane (0.5 mL) was added to a solution of Compound **14e** (0.08 mmol, 0.03 g) in CH_2Cl_2 (1.0 mL) at r.t. The resulting solution was allowed to stand overnight and a yellow precipitate was observed. The solvent was removed *in vacuo* and the resulting yellow solid was washed with Et_2O to obtain Compound **167** as a yellow solid (0.04 g, 72%). MS m/e 410 (M^+H, 100%).

Example 15

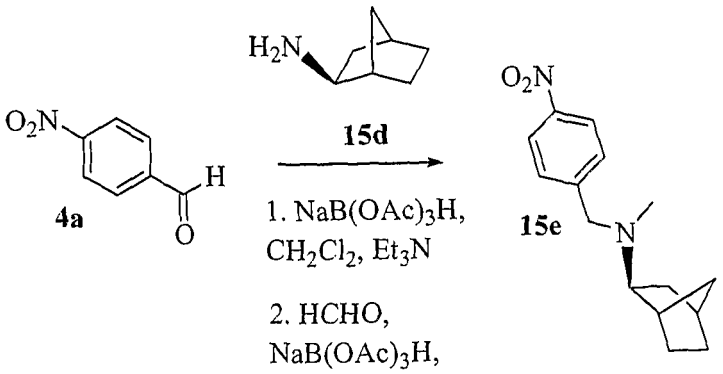
(2*S*)-bicyclo[2.2.1]hept-2-yl-{4-[(6-chloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide (Cpd **110**)



5-chloro-2-hydroxy-benzaldehyde Compound **15a** (10.0 mmol, 1.7 g), acrylonitrile (50.0 mmol, 2.14 mL) and DABCO (2.33 mmol, 0.26 g) were mixed together and heated to reflux overnight using an oil bath. After the flask was cooled to room temperature, Et_2O (100 mL) was added and the Et_2O layer was washed with 10% NaOH solution followed by 1N HCl and brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuo to obtain 6-chloro-2H-chromene-3-carbonitrile Compound **15b** as a yellow solid (1.42 g, 74%), which was used in the next step without further purification (the preceding was described in Wise, L. et al. *J. Med. Chem.*, **1988**, 31, 688).

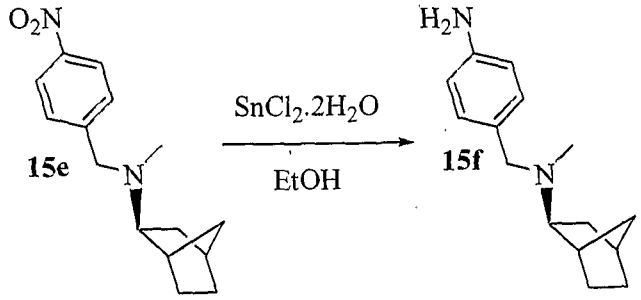


THF (2 mL) and 10% NaOH solution (100 mL) was added to a round bottom flask containing Compound **15b** (7.43 mmol, 1.42 g). The solution was heated to reflux for 4 hrs. The flask was immersed in an ice-bath and the solution was acidified by careful addition of conc. HCl. The resulting pale yellow solid was filtered and dried in a vacuum oven to obtain 6-chloro-2H-chromene-3-carboxylic acid Compound **15c** (1.02 g, 65%).

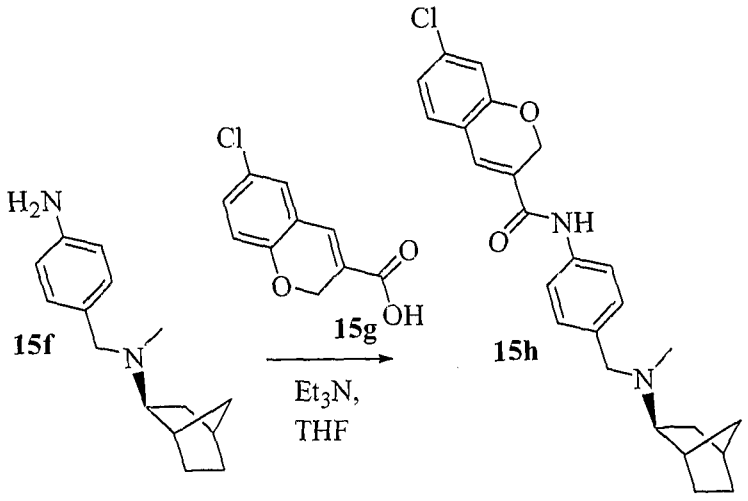


Sodium triacetoxyborohydride (3.5 mmol, 0.75 g) was added to a mixture of 4-nitro-benzaldehyde Compound **4a** (2.8 mmol, 0.42 g), (2*S*)-bicyclo[2.2.1]hept-2-ylamine Compound

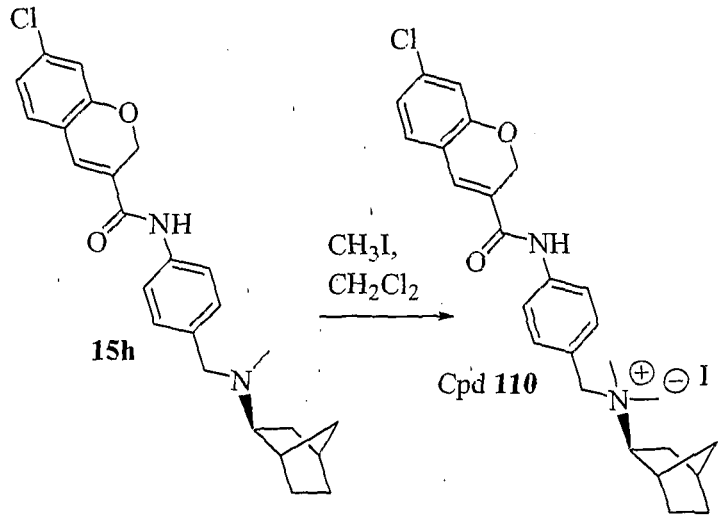
15d (3.0 mmol, 0.33 g) and glacial acetic acid (3 drops) in CH_2Cl_2 (40 mL). The resulting suspension was allowed to stir at room temperature for 12 hrs. An aliquot of the reaction mixture showed the formation of product (MS m/e 247, 100%). An aqueous solution of formaldehyde (37% solution, 9.6 mmol, 0.8 mL) was added to the reaction mixture followed by sodium triacetoxyborohydride (3.5 mmol, 0.75 g) and the mixture was allowed to stir at r.t. for 2 hrs. The reaction mixture was basified with 2N NaOH solution and was extracted with CH_2Cl_2. The organic layer was washed with brine, separated and dried over Na_2SO_4. The drying agent was filtered and the solvent was removed *in vacuo* to obtain (2*S*)-bicyclo[2.2.1]hept-2-yl-methyl-(4-nitro-benzyl)-amine Compound **15e** (0.72 g, 98%) as an orange oil. MS m/e 261 (M^+H, 100%), which was used in the next step without further purification.



$SnCl_2.2H_2O$ (10.4 mmol, 2.35 g) was added to a solution of Compound **15e** (2.76 mmol, 0.72 g) in EtOH (25 mL) at r.t. The resulting yellow solution was stirred for 2 days. The solvent was removed *in vacuo* and the resulting residue was basified with 2N NaOH solution and the aqueous layer was extracted with CH_2Cl_2 (2 X 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo to obtain (2*S*)-(4-amino-benzyl)-bicyclo[2.2.1]hept-2-yl-methyl-amine Compound **15f** (0.54 g, 85% yield) as a thick yellow oil. MS m/e 231 (M^+H, 100%), which was used in the next step without further purification.



EDCI (0.33 mmol, 0.07 g) was added in one portion to a suspension of Compound **15f** (0.24 mmol, 0.06 g), 6-chloro-2H-chromene-3-carboxylic acid Compound **15g** (0.22 mmol, 0.04 g) and HOBt (0.22 mmol, 0.03 g) in DMF (5.0 mL) at 0°C. The resulting suspension was warmed to r.t. and then a crystal of DMAP and Et_3N (0.65 mmol, 0.1 mL) was added and the reaction mixture was stirred overnight. The orange-yellow suspension was poured in water and was extracted with EtOAc (25 mL). The organic layer was washed with water (2 X 20 mL) followed by 5% NaOH solution (10 mL) and brine. The organic layer was separated, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the resulting residue was purified by preparative TLC (15:1 CH_2Cl_2/MeOH) to yield 6-chloro-2H-chromene-3-carboxylic acid (2*S*)-{4-[(bicyclo[2.2.1]hept-2-yl-methyl-amino)-methyl]-phenyl}-amide Compound **15h** (0.06 g, 61%) as a pale yellow solid. MS m/e 423 (M^+H, 100%).



Iodomethane (0.5 mL) was added to a solution of Compound **15h** (0.08 mmol, 0.03 g) in CH_2Cl_2 (1.0 mL) at r.t. and the resulting solution was allowed to stand overnight. A yellow precipitate was observed and the solvent was removed *in vacuo*. The resulting yellow solid was washed with Et_2O to obtain Compound **110** (0.05 g, 96%) as a yellow solid. MS m/e 437 (M^+H, 100%).

Using the procedure of Example 15 and known appropriate reagents and starting materials, other compounds of the present invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

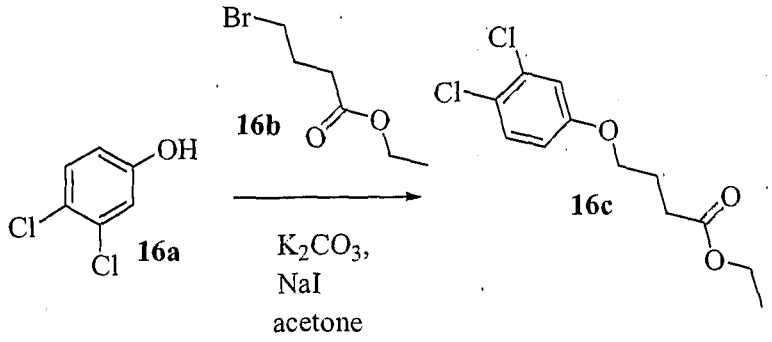
Cpd	Name	MS
95	{4-[(6-bromo-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	471
96	{4-[(6-chloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	427

Cpd	Name	MS
97	{4-[(6-bromo-2H-chromene-3-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	469
98	{4-[(6-chloro-2H-chromene-3-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	425
99	(4-{[(6-bromo-2H-chromene-3-carbonyl)-amino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	485
100	{4-[(5,7-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	461
101	cyclohexyl-{4-[(5,7-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	459
102	{4-[(6,8-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	461
103	dimethyl-{4-[(6-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	407
104	{4-[(6-methoxy-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	423
105	cyclohexyl-dimethyl-{4-[(6-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	405
106	cyclohexyl-{4-[(6-methoxy-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	421
107	cyclohexyl-{4-[(6,8-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	459
108	(2*R*)-{4-[(6-chloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-furan-2-ylmethyl)-ammonium iodide	427
109	(2*S*)-{4-[(6-chloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-furan-2-ylmethyl)-ammonium iodide	427
111	bicyclo[2.2.1]hept-2-yl-{4-[(6,8-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	471
112	dimethyl-{4-[(8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-(tetrahydro-pyran-4-yl)-ammonium iodide	407
113	cyclohexyl-dimethyl-{4-[(8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	405
114	{4-[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	439
115	{4-[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	441
116	cyclohexyl-{4-[(7,8-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	459
117	bicyclo[2.2.1]hept-2-yl-{4-[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	451
118	{4-[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-cycloheptyl-dimethyl-ammonium iodide	453
119	{4-[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-cyclopentyl-dimethyl-ammonium iodide	425
120	{4-[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-thiophen-3-yl)-ammonium iodide	443

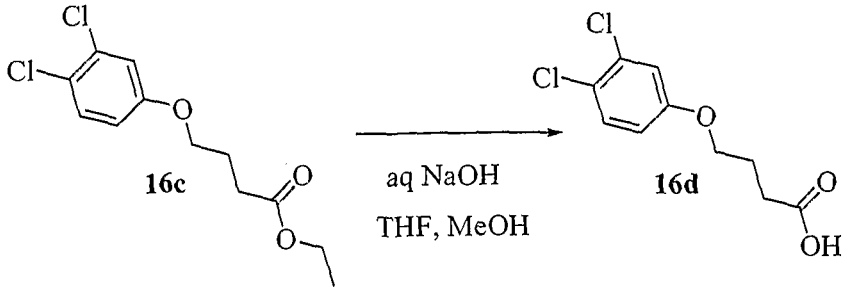
Cpd	Name	MS
121	(4-{[(6-chloro-8-methyl-2H-chromene-3-carbonyl)-amino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	455
122	{4-[(6,8-dichloro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydrd-thiophen-3-yl)-ammonium iodide	463
123	cyclohexyl-{4-[(6-fluoro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	409
124	cyclohexyl-{4-[(5-fluoro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	409
125	cyclohexyl-dimethyl-{4-[(6-trifluoromethyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	459
126	cyclohexyl-{4-[(8-fluoro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	409
127	cyclohexyl-dimethyl-{4-[(7-methyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	405
128	cyclohexyl-{4-[(7-methoxy-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	421
129	{4-[(6-tert-butyl-2H-chromene-3-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	447
130	dimethyl-(tetrahydro-thiophen-3-yl)-{4-[(6-trifluoromethyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	463
131	{4-[(5-fluoro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-thiophen-3-yl)-ammonium iodide	413
132	{4-[(6-fluoro-2H-chromene-3-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-thiophen-3-yl)-ammonium iodide	413
133	cyclohexyl-dimethyl-{4-[(5-trifluoromethyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	459
134	cyclohexyl-dimethyl-{4-[(8-trifluoromethyl-2H-chromene-3-carbonyl)-amino]-benzyl}-ammonium iodide	459
135	{4-[(3H-benzo[f]chromene-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	443
136	1-{4-[(3H-benzo[f]chromene-2-carbonyl)-amino]-benzyl}-1-methyl-pyrrolidinium iodide	399
137	{4-[(3H-benzo[f]chromene-2-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	441
138	{4-[(3H-benzo[f]chromene-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-thiopyran-4-yl)-ammonium iodide	459
139	4-{4-[(3H-benzo[f]chromene-2-carbonyl)-amino]-benzyl}-4-methyl-morpholin-4-ium iodide	415
140	{4-[(3H-benzo[f]chromene-2-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium iodide	457
141	(4-{[(3H-benzo[f]chromene-2-carbonyl)-amino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	457

Example 16

{4-[(7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide (Cpd **167**)

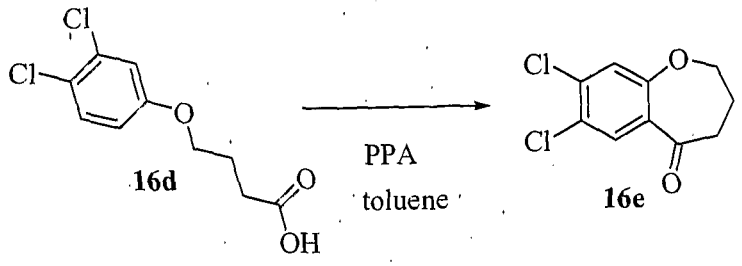


Potassium carbonate (27.5 mmol, 3.75 g) and sodium iodide (0.3333 mmol, 0.0500 g) were added to a reaction mixture of 3,4-dichloro-phenol Compound **16a** (30.25 mmol, 4.93 g) and 4-bromo-butyric acid ethyl ester Compound **16b** (27.5 mmol, 5.36g) in acetone (60 mL). The reaction mixture was stirred overnight at room temperature. TLC analysis (4:1 hexane:EtOAc) showed no formation of product. The reaction mixture was refluxed for 3 hrs and TLC analysis (4:1 hexane:EtOAc) showed trace of starting material Compound **16a**. The reaction mixture was refluxed overnight, then basified with 1N NaOH solution and extracted with CH_2Cl_2. The organics were dried over $MgSO_4$. The drying agent was filtered and the solvent was removed *in vacuo* to yield 4-(3,4-dichloro-phenoxy)-butyric acid ethyl ester Compound **16c** (6.9 g, 90.7%) as a pale pink oil, which was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21-1.31 (q, 3H), 2.12-2.25 (m, 2H), 2.45-2.53 (t, 2H), 3.95-4.02 (t, 2H), 4.10-4.20 (q, 2H), 6.71-6.78 (dd, 1H), 6.94-6.96 (d, 1H), 7.28-7.31 (d, 1H).

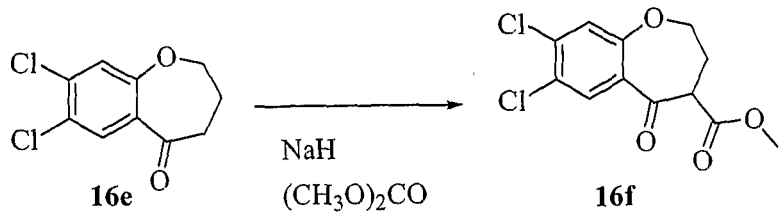


A 1N NaOH solution (20 mL) was added to a solution of Compound **16c** (7.22 mmol, 2.00 g) in THF (20 mL) and MeOH (10 mL). The reaction mixture stirred overnight at room temperature. The THF and MeOH were removed *in vacuo* and the remaining aqueous solution was acidified with 1N HCl. A precipitate was collected and dried in a vacuum oven overnight to yield 4-(3,4-dichloro-phenoxy)-butyric acid Compound **16d** (1.65 g, 92%) as a white solid,

which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05-2.18 (m, 2H), 2.52-2.60 (t, 2H), 3.95-4.05 (t, 2H), 6.70-6.79 (dd, 1H), 6.95-7.12 (d, 1H), 7.24-7.35 (t, 1H).

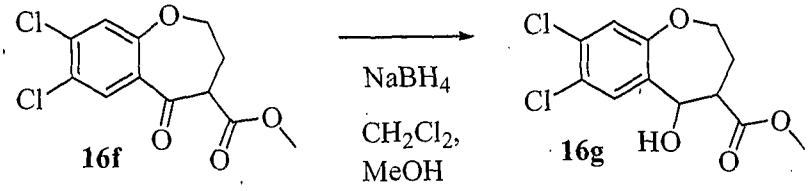


Polyphosphoric acid (10 equivalents by weight, 51.2 g) was added to a solution of Compound **16d** (0.0206 mol, 5.12 g) in toluene (51.5 mL). The mixture was heated to between 95 and 100°C (bath temperature). The reaction mixture was allowed to cool to room temperature and poured into a beaker of ice water. The aqueous layer was extracted with Et_2O. The organics were washed with water and dried with $MgSO_4$. The drying agent was filtered and the solvent was removed *in vacuo*, yielding a brown solid (3.7 g), which was purified by flash column chromatography (2% EtOAc/Hexane to 10% EtoAc/Hexane) to yield 7,8-dichloro-3,4-dihydro-2H-benzo[b]oxepin-5-one Compound **16e** (1.52 g, 32%) as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18-2.28 (m, 2H), 2.84-2.95 (t, 2H), 4.21-4.32 (t, 2H), 7.18 (s, 1H), 7.80 (s, 1H).

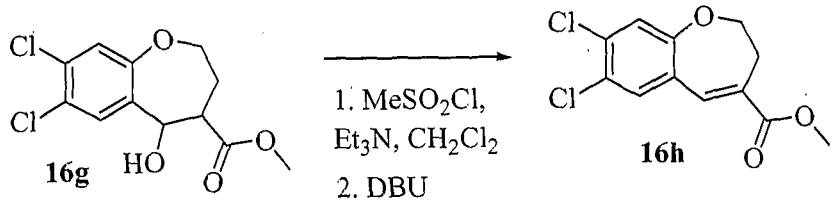


Sodium hydride (60% dispersion in mineral oil) (7.754 mmol, 0.3102 g) and dimethyl carbonate (37.41 mmol, 3.15 mL) were added to a reaction vessel. Compound **16e** (3.877 mmol, 1.0 g) was dissolved in dimethyl carbonate (2 mL) and added dropwise to the vessel. The mixture was refluxed for 2 hrs. TLC analysis showed a trace of the starting material Compound **16e** and the reaction mixture was allowed to cool and stirred overnight at room temperature. 2N HCl solution (25 mL) was added to the mixture, which was then extracted with EtOAc. The organics were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to yield a brown solid (1.27 g) which was taken up in Et_2O to yield a tan precipitate. TLC analysis (30% Et_2O/Hexane) showed the precipitate to be pure (0.800 g). The remainder of the brown solid was purified by flash column chromatography (30% Et_2O/Hexane) to yield 7,8-dichloro-5-oxo-2,3,4,5-tetrahydro-benzo[b]oxepine-4-carboxylic acid methyl ester

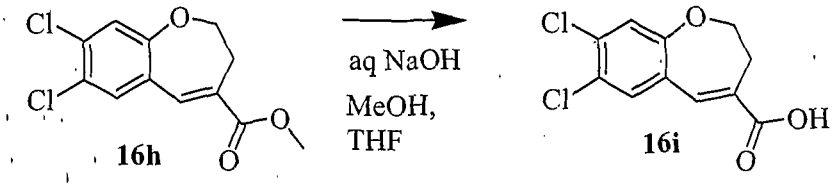
Compound **16f** (0.231 g) as a tan solid. ^{1}H NMR of precipitate (300 MHz, $CDCl_3$) δ 2.68-2.75 (t, 2H), 3.85 (s, 3H), 4.32-4.38 (t, 2H), 7.12 (s, 1H), 8.08 (s, 1H), 13.15 (s, 1H).



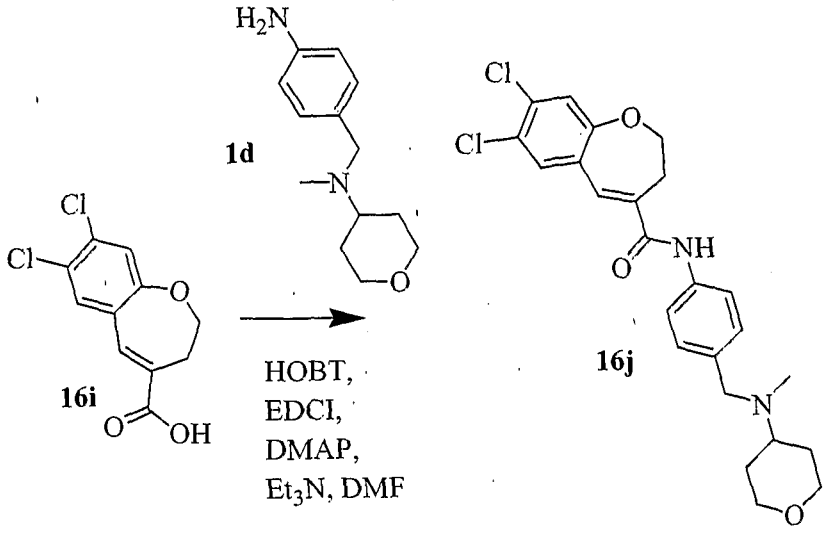
A solution of Compound **16f** (1.713 mmol, 0.4951 g) in CH_2Cl_2 (5 mL) was cooled to -15 °C while stirring. MeOH (0.75 mL) was added, followed by sodium borohydride (2.213 mmol, 0.0837 g) in two portions. The reaction mixture was stirred at –10 °C for 1 hr. TLC analysis (30% Et_2O/Hexane) of the reaction mixture showed complete formation of product, with no trace of starting material. The reaction mixture was washed with water and dried over $MgSO_4$. The drying agent was filtered and the solvent was removed *in vacuo* yielding 7,8-dichloro-5-hydroxy-2,3,4,5-tetrahydro-benzo[b]oxepine-4-carboxylic acid methyl ester Compound **16g** (0.488 g, 97.8%) as a yellow oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02-2.14 (m, 3H), 2.30-2.40 (m, 1H), 3.65 (s, 3H), 3.96-4.09 (m, 2H), 4.20-4.28 (m, 1H), 7.35 (s, 1H), 7.56 (s, 1H).



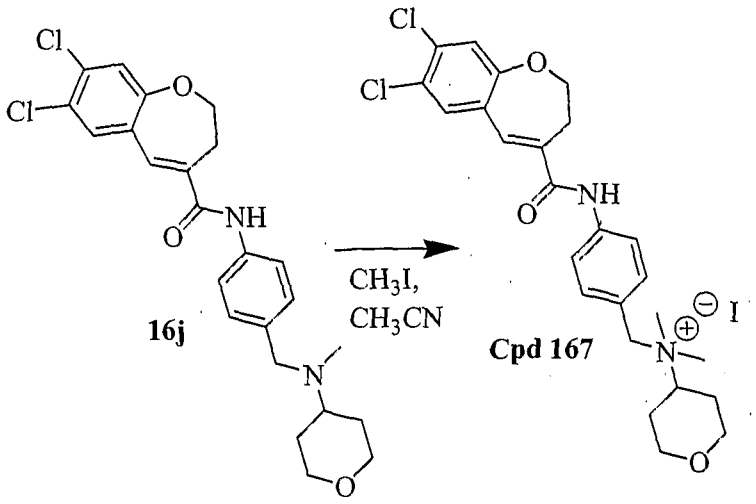
A solution of Compound **16g** (1.676 mmol, 0.4880 g) in CH_2Cl_2 (8 mL) was cooled to 0 °C while stirring. Triethylamine (5.018 mmol, 0.70 mL) was added, followed by the dropwise addition of methanesulfonyl chloride (2.506 mmol, 0.19 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. TLC analysis (30% Et_2O/Hexane) showed formation of product with no trace of starting material. The mixture was cooled to 0 °C and DBU (6.052 nmol, 0.90 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 30 mins. An aliquot of the reaction mixture was washed with water, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. NMR analysis showed complete formation of product. The remainder of the mixture was washed with water and dried over $MgSO_4$. The drying agent was filtered and the solvent was removed *in vacuo* to provide 7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carboxylic acid methyl ester Compound **16h** (0.408 g, 86.1%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95-3.00 (t, 2H), 3.82 (s, 3H), 4.22-4.28 (t, 2H), 7.10 (s, 1H), 7.40 (s, 1H), 7.48 (s, 1H).



A solution of Compound **16h** (1.494 mmol, 0.408 g), THF (20 mL), MeOH (10 mL) and a solution of 1N NaOH (20 mL) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the resulting aqueous solution was acidified with concentrated HCl until an off-white precipitate formed. The solid was filtered and dried in a vacuum oven overnight to provide 7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carboxylic acid Compound **16i** (0.373 g, 96.4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90-3.02 (t, 2H), 4.25-4.31 (t, 2H), 7.10 (s, 1H), 7.42 (s, 1H), 7.51 (s, 1H).



EDCI (0.3293 mmol, 0.0631 g) was added in one portion to a solution of Compound **16i** (0.2138 mmol, 0.0554 g), (4-amino-benzyl)-methyl-(tetrahydro-pyran-4-yl)-amine Compound **1d** (T10) (0.2459 mmol, 0.0541 g) and HOBT (0.2138 mmol, 0.0289 g) in DMF (6 mL) at 0°C. The mixture was warmed to room temperature and a catalytic amount of DMAP and triethylamine (0.6414 mmol, 0.09 mL) were added. The reaction mixture was stirred overnight at room temperature, then water was added and the mixture was extracted with EtOAc. The organics were washed with water, 1 N NaOH solution and brine and dried over $MgSO_4$. The drying agent was filtered and the solvent was removed in vacuo to yield a yellow oil which was purified by TLC prep plate (9:1 EtoAc: MeOH) to yield 7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carboxylic acid (4-{[methyl-(tetrahydro-pyran-4-yl)-amino]-methyl}-phenyl)-amide Compound **16j** (0.040 g, 41%) as a yellow solid. MS m/e 461 (M^+H, 90%), (M^+Na, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58-1.80 (m, 5H), 2.16 (s, 3H), 2.58-2.69 (m, 1H), 3.00-3.08 (m, 2H), 3.30-3.41 (m, 2H), 3.52 (s, 2H), 4.00-4.08 (m, 2H), 4.25-4.31 (m, 2H), 7.02 (s, 1H), 7.10 (s, 1H), 7.28-7.38 (t, 3H), 7.50-7.55 (d, 2H).



Iodomethane (0.0161 mol, 1.0 mL) was added to a solution of Compound **16j** (0.0433 mmol, 0.020 g) in acetonitrile (2 mL), acetone (2 drops) and dichloromethane (2 drops) at room temperature and the resulting solution was stirred overnight. The solvent was removed *in vacuo* and the resulting orange solid was washed with Et_2O and dried in a vacuum oven for 12 hrs to provide Compound **167** (0.0123 g, 78.5%). MS m/e 475 (M^+H, 100%); MS m/e 477 (M^+H, 75%).

Using the procedure of Example 16 and known appropriate reagents and starting materials, other compounds of the present invention may be prepared including, (MS: Mass Spec data as MS *m/e* M^+H):

Cpd	Name	MS
142	(4-{[(3-bromo-8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	497
143	{4-[(3-bromo-8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	483
144	{4-[(3-bromo-8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-benzyl}-cyclohexyl-dimethyl-ammonium iodide	481
145	1-{4-[(8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-benzyl}-1-methyl-pyrrolidinium iodide	361
146	cyclohexyl-{4-[(8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	403
147	{4-[(8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	405
148	(4-{[(8,9-dihydro-7H-benzocycloheptene-6-carbonyl)-amino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	419
168	cyclohexyl-{4-[(7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	473
169	bicyclo[2.2.1]hept-2-yl-{4-[(7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carbonyl)-amino]-benzyl}-dimethyl-ammonium iodide	485
170	(4-{[(7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carbonyl)-amino]-methyl}-benzyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium iodide	489

Cpd	Name	MS
171	{4-[(7,8-dichloro-2,3-dihydro-benzo[b]oxepine-4-carbonyl)-amino]-benzyl}-dimethyl-(tetrahydro-thiophen-3-yl)-ammonium iodide	477

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 17

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.

Table 2 lists inhibition values obtained for test compounds for MCP-1 binding to CCR2. The inhibition values (%) were obtained at a test concentration of 25 µM, unless indicated otherwise.

Table 1

Mean Ligand Binding (IC_{50} µM)

Cpd	IC_{50} (µM)	Cpd	IC_{50} (µM)
1	2.3	93	0.9
2	5.5	94	1.3
3	4.3	95	0.18
4	3.1	96	0.11
5	8.3	97	0.45
6	5	98	0.27

Cpd	IC_{50} (μM)
7	6.3
10	6.6
11	3.1
14	0.06
15	2
16	0.85
17	0.005; 0.01; 0.009
18	1.8
19	0.005
20	0.16
21	0.15
22	1.6
23	0.9
24	0.29; 0.19
26	0.28
27	0.75
28	0.46
29	0.33
30	4.2
31	11.4
32	3.4
33	0.4
34	2.4
35	0.4
37	10.2
38	5
39	6.4
40	1.6
42	5.7
43	0.34
44	14.6
45	0.26
46	1.3
47	3.7
48	8.4
49	11.9
50	2.6
51	2.7
52	2.6
53	3.2
55	5.4

Cpd	IC_{50} (μM)
100	0.52
101	1.1
102	0.19
103	0.82
104	1.9
105	0.32
106	1.1
107	0.17
108	3.1
109	5.3
110	0.32
111	2
112	0.15
113	0.53
114	0.06
115	0.05
116	0.6
117	0.12
118	0.2
119	0.1
120	0.03
122	0.58
126	0.91
127	0.08
128	0.6
129	0.15
130	0.3
131	0.33
132	0.13
133	3.3
134	0.47
135	0.91
136	4.6
137	0.08
138	2.4
139	9.8
140	1
143	0.007
144	0.33
146	0.71
147	1.2

Cpd	IC_{50} (μM)
56	11.8
57	13.3
59	10
61	2.7
63	3.5
66	1.7
67	2.5
68	1.5
69	6.4
70	0.11
71	0.17; 0.32
72	0.58
73	0.44
74	1.5
75	0.02
76	0.16
78	13.4
79	0.31
80	0.03
81	3
82	0.05
83	1.2
84	3.2
85	5.2
86	6
87	3.8
88	0.87
90	0.22
91	4.1
151	0.26
152	1.6
153	2.1
154	4.6
155	0.49
156	0.18
157	0.69
158	0.4
159	0.19
160	0.29
162	1.6
163	0.62
164	0.2
165	3.3
166	0.11
167	0.24
168	1
169	0.24
171	0.56
173	8.1
175	1.5
176	0.26
177	0.17
178	8.8

Table 2

% Inhibition Ligand Binding

Cpd	% Inhibition
8	34
9	65
12	38
13	29
25	15
36	49
41	87
58	53
60	20
99	34
121	37
123	100
124	100
125	100
141	-21
142	-18
145	36
148	7

Cpd	% Inhibition	Cpd	% Inhibition
62	9	149	58
64	63	150	27
65	61	161	33
77	53	170	36
89	29	172	17
92	54	174	52

Example 18

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 x 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 which had migrated to the bottom chamber was taken and counted then compared to vehicle.

Test compounds of the invention inhibited MCP-1 induced chemotaxis with IC_{50} values of from about 10 μM to about 1 nM.

Example 19

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 $[Ca^{2+}]_i$ upon addition of 0.2 μM MCP-1 is determined using FLIPR and compared to vehicle.

Test compounds of the invention inhibited MCP-1 induced influx of Ca^{2+} ions with IC_{50} values of from about 10 μM to about 1 nM.

Example 20

Inhibition of uveitis in mice

The lipopolysaccharide (LPS bacterial endotoxin) induced uveitis mouse model is used to test a compound of the invention for inhibition of MCP-1 induced inflammation in the anterior of the eye (Tuaillon N, Shen de F, Berger RB, Lu B, Rollins BJ and Chan CC, MCP-1 expression in endotoxin-induced uveitis, *Invest. Ophthalmol. Vis. Sci.*, 2002 May, 43(5): 1493-8).

After intraocular injection directly into the anterior chamber of the eye with LPS, a measurable amount of MCP-1 is found in the eye's aqueous humor within a few hours. The degree of inflammation is quantified by counting the number of leukocytes within the aqueous humor of the anterior chamber (including a differential count), determining the protein concentration in the aqueous humor and confirming the inhibition of inflammation by histological examination.

Procedure

A test compound was dissolved in saline (5 mg/mL), and 10 μL (50 μg) was applied topically to the injected eye at 0, 4, and 8 hr relative to the LPS injection. The control group was treated topically with a saline vehicle (no test compound). One hour after the last dose of the compound (i.e., 9 hours post-injection), the mice were sacrificed and leukocyte, neutrophil and mononuclear cell counts and protein concentration inside the eye were measured.

Results

In two trials, the compound inhibited leukocyte infiltration by 66% (±1%). The accumulation of protein was inhibited by 52% (±14%). Cell differential counts indicated that neutrophil influx into the eye was inhibited by 67% while mononuclear cell influx was inhibited by 40%. Histological examination confirmed the inhibition of cellular influx.

Based on the binding data for inhibition of MCP-1 induced inflammation and the data for inhibition of MCP-1 induced anterior uveitis, an effective dose per day for a compound of the invention for treating anterior uveitis is in a range of from about 50 μg to about 0.5 ng. An embodiment of an effective dose for a compound of the invention for the treatment of anterior uveitis is from about 5 μg to about 0.5 ng. Another embodiment of an effective dose for such treatment is from about 1 μg to about 1 ng. Another embodiment of an effective dose is from about 0.5 μg to about 1 ng. An embodiment of an effective dose is also from about 0.1 μg to about 1 ng.

Example 21

Inhibition Of Ovalbumin (Ova)-Induced Asthma In Mice

Test compounds of the present invention were active in two different models of ovalbumin (OVA)-induced asthma in mice.

Mast Cell-Dependent Model

Mice were sensitized by i.p. injection with OVA in saline (10 μg) on alternate days (Day 0, 2, 4, 6, 8, 10, 12). Groups of mice were each challenged by intranasal injection of OVA (Day 40, 43, 46). Compound 17 was administered by i.p. injection (30 mg/kg) on

consecutive days (Day 42, 43, 44, 45, 46). Compared to vehicle, leukocyte influx was inhibited by 95% and 55% (in two separate assays), LTC_4 influx was inhibited by 90% and IL-4 influx was inhibited by 85%.

Mast Cell-Independent Model

Mice were sensitized by i.p. injection of OVA emulsified in adjuvant (Day 1 and 14). Groups of mice were each challenged by intranasal injection of OVA (Day 25, 26, 27). Compound 17 was administered by i.p. injection (10 and 30 mg/kg) before each intranasal challenge (Day 25, 26, 27). Compared to vehicle, leukocyte influx was dose-dependently inhibited by 40% and 70%, respectively.

Example 22

Inhibition of ovalbumin-induced allergic rhinitis in mice

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

Prophylactic effect

Compound 17 (in PBS) was 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). The histamine receptor antagonist Astelin® was used as a positive control.

Compared to vehicle, Compound 17 dose-dependently inhibited nasal symptoms by 64/57% (sneezing/rubbing) and 82/71% (sneezing/rubbing), respectively. Compared to vehicle, the positive control inhibited nasal symptoms by 51/89% (sneezing/rubbing).

Therapeutic effect

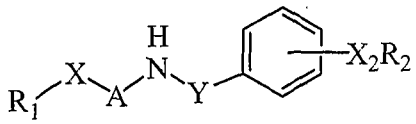
The dosing of Compound 17 was delayed until the symptoms of rhinitis had appeared (Day 29). Compound 17 (in PBS) was then administered by intranasal injection (10 μg/nostril) to both nostrils four times per day prior to intranasal challenge (Days 29-38). The anti-histamine Pyralimine and the mast cell-stabilizing agent Ketotifen were used as positive controls.

Compared to vehicle, Compound 17 inhibited nasal symptoms by 0/42% (sneezing/rubbing). Compared to vehicle, Pyralimine and Ketotifen inhibited nasal symptoms by 60/85% (sneezing/rubbing) and 50/81% (sneezing/rubbing), respectively.

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)



and pharmaceutically acceptable forms thereof, wherein

A is carbonyl, thiocarbonyl or sulfonyl;

X is a bond or -CH=CH-;

R_1 is selected from

(1). aryl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, alkoxycarbonyl, cyano, halogen or phenyl optionally substituted by lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, alkoxycarbonyl, cyano or halogen;

(2). C_5-C_{15} cycloalkyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen; or,

(3). heterocyclyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, aryl-lower alkyl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen;

n is 0, 1, 2, 3 or 4;

Y is a bond or $-CH_2-$;

X_2 is $-(CH_2)_m-$ wherein m is 1 or 2;

R_2 is $-N^+(R_4R_5)-ZR_3$;

Z is $-(CH_2)_p-$ wherein p is 0, 1 or 2;

R_3 is selected from

(1). aryl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen;

(2). C_5-C_{15} cycloalkyl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen; or,

(3). heterocyclyl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen; wherein, when heterocyclyl is attached via a carbon atom ring member and a heteroatom ring member is adjacent to said carbon atom, then p is 1 or 2;

R_4 and R_5 are each individually lower alkyl or lower alkenyl;

alternatively, R_4 and R_5 combine with the nitrogen atom of Formula (I) to form a heterocyclyl ring of 5 to 9 total ring atoms optionally containing one of an oxygen or sulfur ring atom, wherein the heterocyclyl ring nitrogen atom is substituted with one of lower alkyl or lower alkenyl to form a quaternary salt, and wherein $-ZR_3$ is absent and the heterocyclyl ring is optionally substituted with aryl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, halogen-substituted aryl, alkoxycarbonyl, cyano or halogen.

2. The compound of claim 1, wherein A is carbonyl; X is a bond; R_1 is selected from aryl substituted by one or more lower alkyl or halogen, C_5-C_{15} cycloalkyl optionally substituted by one or more halogen, or heterocyclyl optionally substituted by one or more lower alkyl or halogen; Y is a bond; X_2 is $-CH_2-$; R_2 is $-N^+(R_4R_5)-R_3$; R_3 is selected from C_5-C_{15} cycloalkyl or heterocyclyl and R_4 and R_5 are each individually lower alkyl.

3. The compound of claim 1, wherein A is carbonyl, X is a bond, R_1 is aryl optionally substituted by one or more halogen, Y is a bond, X_2 is $-CH_2-$, R_2 is $-N^+(R_4R_5)-R_3$, R_3 is heterocyclyl and R_4 and R_5 are each individually lower alkyl.

4. The compound of claim 1, wherein A is carbonyl.

5. The compound of claim 1, wherein R_1 is selected from

(1). aryl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano, halogen or phenyl optionally substituted by lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano or halogen;

(2). C_5-C_{15} cycloalkyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano or halogen; or,

(3). heterocyclyl optionally substituted by one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, aryl, aryl-lower alkyl, halogen-substituted aryl or halogen.

6. The compound of claim 1, wherein n is 0.

7. The compound of claim 1, wherein p is 0 or 1.

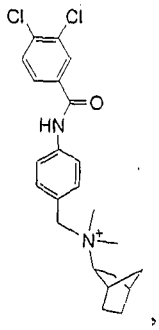
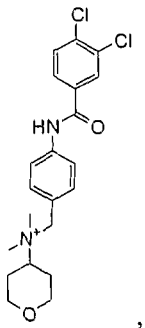
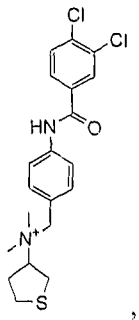
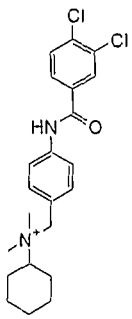
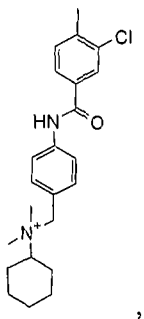
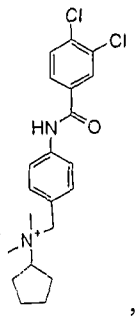
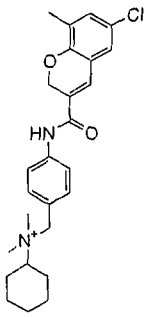
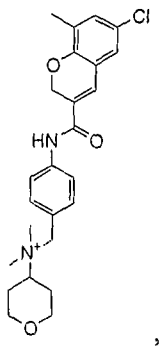
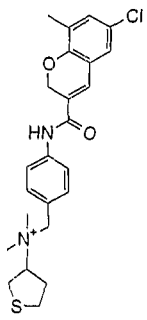
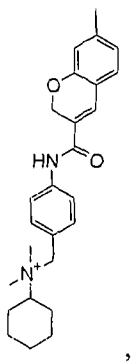
8. The compound of claim 1, wherein R_3 is C_5-C_{15} cycloalkyl or heterocyclyl; wherein, when heterocyclyl is attached via a carbon atom ring member and a heteroatom ring member is adjacent to said carbon atom, then p is 1.

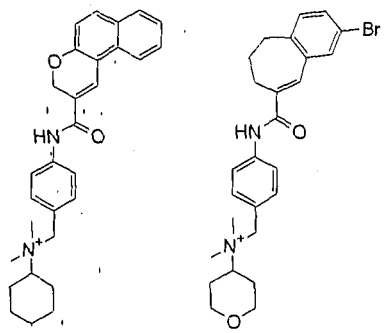
9. The compound of claim 1, wherein R_4 and R_5 are each individually lower alkyl or lower allyl.

10. The compound of claim 1, wherein R_4 and R_5 combine with the nitrogen atom of Formula (I) to form a heterocyclyl ring of 5 to 9 total ring atoms optionally containing one of an oxygen or sulfur ring atom, wherein the heterocyclyl ring nitrogen atom is substituted with lower alkyl to form a quaternary salt, and wherein $-ZR_3$ is absent and the heterocyclyl ring is optionally substituted with aryl optionally substituted with one or more lower alkyl, $-(CH_2)_n-CF_3$, lower alkoxy, cyano or halogen.

11. The compound of claim 1, wherein R_4 and R_5 combine with the nitrogen atom of Formula (I) to form a heterocyclyl ring of 5 to 9 total ring atoms optionally containing one of an oxygen or sulfur ring atom, wherein the heterocyclyl ring nitrogen atom is substituted with lower alkyl to form a quaternary salt, and wherein $-ZR_3$ is absent and the heterocyclyl ring is optionally substituted with aryl optionally substituted with lower alkoxy.

12. A compound and pharmaceutically acceptable forms thereof selected from


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and

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

14. The composition of claim 13 selected from a topically applied composition, an intranasally applied composition or an ocularly applied composition.

15. A process for preparing the composition of claim 13 comprising the step of admixing the compound of claim 1 and a pharmaceutically acceptable carrier.

16. 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.

17. The method of claim 16, wherein the effective amount is from about 0.001 mg/kg/day to about 300 mg/kg/day.

18. The method of claim 16, 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.

19. The method of claim 16, 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.

20. The method of claim 16, 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.

21. The method of claim 20, wherein the ophthalmic disorder is selected from uveitis or allergic conjunctivitis and the periodontal disease is selected from periodonitis, gingivitis or gum disease.

22. The method of claim 21, wherein uveitis is selected from acute, recurring or chronic uveitis.

23. The method of claim 21, wherein uveitis is selected from anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis.

24. The method of claim 16, 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.

25. The method of claim 16, 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.