PIPERAZINE UREA DERIVATIVES FOR THE TREATMENT OF ENDOMETRIOSIS

DESCRIPTION

Field of the Invention

The present invention is directed to piperazine derivatives and their pharmaceutically acceptable salts, which inhibit the activity of the chemokines, MIP-1α and RANTES being antagonists of Human Chemokine "C-C" receptor 1 (CCR1) thereby being useful for the treatment of endometriosis. It also relates to pharmaceutical compositions containing the derivatives or their pharmaceutically acceptable salts, and methods of their use.

BACKGROUND OF THE INVENTION

Chemokine receptors are expressed on leukocytes and process the signals following the binding of the chemokine whereby such signals are eventually transduced into migration or activation of the leukocytes towards the source of the chemokine. Therefore, by regulating the migration and activation of leukocytes from the peripheral blood to extravascular sites in organs, skin, articulations or connective, tissue, chemokines play a critical role in the maintenance of host defense as well as in the development of the immune response.

Human Chemokine "C-C" receptor 1 (CCR1) has been shown to respond to a number of human CC chemokines in a variety of assays including calcium mobilization, inhibition of adenylyl cyclase increase in extracellular acidification and chemotaxis. The range of chemokines that can signal through CCR1 is broad and includes MIP-1 alpha, RANTES, MCP-3, amongst others. All of these ligands are potent agonists for human CCR1 (EC50's < 10 nM). In addition, human CCR1 is also able to bind human MIP-1ß and MCP-1 with low affinity (>100 nM) but neither ligand is able to signal (1). Using polyclonal antibodies to CCR1 the receptor has been shown to be expressed in monocytes, and lymphocytes but not in neutrophils (2).

Molecules inhibiting the activity of CCR1 have been reported to be beneficial in treating diseases such as multiple sclerosis, rheumatoid arthritis and other chronic inflammatory diseases.

Endometriosis is a chronic inflammatory disease, characterized by implantation and growth of endometrial tissue outside the uterine cavity (3). It is classically described as the presence of endometrial tissue (glandular epithelium and stroma) outside the

uterine cavity. Endometriosis is a benign chronic disease, that affects 15–20% of all women in their reproductive life.

The symptoms of endometriosis are chronic pelvic pain, progressive dysmenorrhea, dyspareunia as well as infertility.

The treatment of endometriosis involves surgical resection and / or medication with hormonal agents such as gonadotropin-releasing hormone (GnRH) agonists and androgens. However, long-term medication with hormonal agents is undesirable because of side effects such as menopausal disorders (hot flushes), genital bleeding and bone demineralization.

The clinical control of endometriosis is often very difficult and the recurrence rate is high after discontinuation of medication.

The role of CCR1 and its ligands in endometriosis arises from the fact that retrograde menstruation is postulated as the initiating event in the pathogenesis of the disease. Furthermore, this is accompanied by an intraperitonial infiltration of macrophages and T cells in endometriotic lesions. The recruitment of these leukocytes into the endometrial lesions is initiated by the local production of chemokines the most notable example the CC chemokine RANTES (3-7), which is, amongst others, a ligand for the chemokine receptors CCR1, and CCR5.. The expression of RANTES is up-regulated in endometriotic lesions and in peritoneal fluid from patients with endometriosis. In comparison to other chemokines, RANTES plays an important role in the pathogenessis of endometriosis.

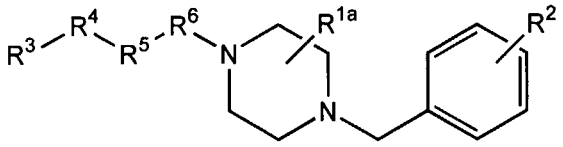
Related Disclosures

Piperazine derivatives of the type similar to the compounds of the invention are known in the literature as being useful for a variety of pharmaceutical indications, particularly as cardiotonic, neurotropic or anti- inflammatory agents. For example, published European Patent Application 0 702 010 (Adir) describes certain piperazine derivatives as being useful as central nervous system depressants and in the treatment of Alzheimer's and other diseases of immunological origin, such as arthritis and intestinal peristaltism. Published European Patent Application 0 655 442 (Fujisawa) describes similar piperazine derivatives as tachykinin antagonists useful in treating inflammatory diseases such as rheumatoid arthritis and osteoarthritis. A Czech published patent application. 260089, and related article, Valenta, V. *et al.*, *Collection Czechoslovak Chem. Commun.* (1987), Vol. 52, pp. 3013-3023, disclose piperazine derivatives as potential neurotropic and cardiovascular agents. European Published Patent Application 0 252 422 (Mitsubishi) and German Published Patent Application 3614363

(Hoechst) describe piperazine derivatives as being useful as cardiotonic agents.
European Published Patent Application 0 190 685 (G. D. Searle) describes piperazine derivatives which block the 5- lipoxygenase pathway of the arachidonic acid cascade, thereby being useful in the treatment of allergic and hypersensitivity reactions and inflammation. PCT Published Patent Application, WO 96/34864 (Schering Plough) discloses piperazine derivatives useful as neurokinin antagonists.
European Published Patent Application 1 254 899 (Schering AG) discloses the piperazine derivatives comprised in the present application for the treatment of an inflammatory disorder.
PCT patent application WO02/36581 (Schering AG) discloses also piperazine derivatives comprised in the present application for the diagnosing Alzheimer's disease.
All of the above references are incorporated herein in full by reference.
None of the above references describe the piperazine derivatives comprised in the present application for the treatment of endometriosis in human females, said piperazine derivatives being antagonists of Human Chemokine "C-C" receptor 1 (CCR1).

SUMMARY OF THE INVENTION

This invention is directed to the use of a compound of the following formula (Ia) or its pharmaceutically acceptable salt for the treatment and prevention of edometriosis in human wherein the treatment comprises administering to a human female in need of such treatment a therapeutically effective amount of said compound.
Accordingly, in one aspect, this invention provides compounds of the following formula (Ia):



(Ia)

wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, formyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl,

alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkylthioalkyl, aminoalkyl monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, azidoalkyl, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, (alkoxycarbonylalkyl) ureidoalkyl, alkoxycarbonylaminoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, alkoxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, aralkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, arylsulfonyl, heterocyclyl and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hyaroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl) (alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino,

ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl;

R^3 is

a carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, arylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, hydroxyalkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, aminoalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy) cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy) aralkyl, (monoalkylamino) aralkyl, (hydroxyalkyl)hioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkylamino, heterocyclylamino, (cycloalkylalkyl)amino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl) aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, (hydroxyalkoxy)carbonyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, dialkylaminocarbonyloxyalkyl, alkylcarbonylalkyl, arylcarbonylalkyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, (aminocarbonylalkyl) aminocarbonyl, (monoalkylaminocarbonylalkyl) aminocarbonyl, (carboxyalkyl) aminocarbonyl, (alkoxycarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino,

hydroxyamidino, guanidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, monohaloalkylureido, (monoalkyl)(monoaryl)ureido, dialkylureido, diarylureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl) ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl) glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido. arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, glycinamidoalkyl, alaninamido, monoalkylalaninamido, alaninamidoalkyl, heterocyclyl and heterocyclylalkyl;

or R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkylsufonyl, arylsulfonyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, haloalkoxy, alkenyl, alkynyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl) aminoalkyl, alkoxycarbonylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, guanidino, ureido, monoalkylureido, ureidoalkyl, monoalkylureidoalkyl, and glycinamido;

R^4 is

-O-, $-N(R^7)-$, $-C(R^8)_2-$ or a bond;

R^5 is

an alkylene chain or an alkylidene chain, or, if R^4 is a bond, R^5 is an alkylidene chain optionally substituted by aryl or $-N(R^7)_2$;

or R^4 and R^5 together are a -CH=CH-

R^6 is

-C(O)-, - C(S)-, $-CH_2-$ or a bond;

each R^7

is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl; and

each R^8

is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl) (alkyl)amino, aralkylcarbonylamino, (aralkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, aralkylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, (aralkylcarbonyl)(alkyl)aminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl;

provided that when R^4 is $-N(R^7)-$, R^3 can not be a heterocyclic ring system containing 4-8 members consisting of carbon atoms and only one nitrogen atom; and provided that when R^4 is $-C(R^8)_2$ or a bond, R^3 can not be a bridged saturated heterocyclic ring system containing 4-6 members consisting of carbon atoms and two nitrogen atoms, and as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof. The provisio was made to exclude compounds disclosed in prior art document WO 96/34864.

The patent application WO2004/037796 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compound according to the general formula I, II, IIa and III as defined in WO2004/037796 for the production of a medicament for the treatment

and prevention of edometriosis. Particularly favourable embodiments of the present invention are the following compounds as reported in WO2004/037796:

(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oXopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oxopropenyl] phenyl)-methanesulfonamide,

(5-Chloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-methanesulfonamide,

(5-Chloro-2- {(E)-3-[4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-phenyl)-acetic acid methyl ester,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-benzoic acid,

(5-chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-urea,

(5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxopropenyl}-4-trifluoromethoxy-phenyl)-urea,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oXo-propenyl}-4-methoxy-benzoic acid methyl ester.

The patent application WO03/035627 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds under the general formula 1 as defined in claim 1 of WO03/035627 for the treatment and prevention of edometriosis. Particularly favourable embodiments of the present invention are the following compounds as reported in WO03/035627:

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-propionic acid,

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4- (4-chloro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(3, 4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acrelic acid,

N-[(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-methanesulfonamide,

N- (5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzoyl)-methanesulfonamide,

N- [(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-C,C,C-trifluoro-methanesulfonamide,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-oxo-acetic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-acetic acid,

2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yll-2-oxo-ethoxy}-phenoxy)-2-methyl-propionic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-difluoro-acetic acid

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide

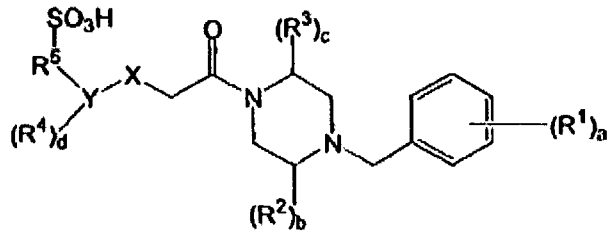
The patent application WO01/72728 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds under the general formula 1 as defined in page 2 of WO01/72728 as pablished for the treatment and prevention of edometriosis.

Particularly favourable embodiments of the present invention are the following compounds as reported in WO01/72728:

N-[5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]phenyl-trifluoromethanesulfonamide,

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]- benzenesulfonamide.

The patent application WO02/102787 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds of the formula I- WO02/102787



(I- WO02/102787)

or the pharmaceutical acceptable salts and prodrugs thereof; wherein

a = 0, 1, 2, 3, 4 or 5; b = 0, 1 or 2; c = 0, 1 or 2; d = 0, 1,2, 3 or 4;

X is -O-, -S-, -CH2- or -NR6-

Y is(C6-C10) aryl, or(C2-C9) heteroaryl,

each R1 is independently selected from the group consisting of: H-, HO-, halo-, (C1-C8) alkyl- optionally substituted with 1-3 fluorine atoms, (C1-C8) alkyl-O- wherein the alkyl group is optionally substituted with 1-3 fluorine atoms, HO-(C1-C8) alkyl-, NC-,H2N-, H2N-(C1-C8) alkyl-, HO-(C=O)-, (C1-C8)alkyl-(C=O)-, (C1-C8)alkyl-(C=O)-(C1-C8)alkyl-, H2N-(C=O)-, H2(C=O)-(C1-C8) alkyl-;

each R2 and R3 is independently selected from the group consisting of: H-, oxo, (C1-C8) alkyl- optionally substituted with 1-3 fluorine atoms, (C1-C8) alkyl-, (C6-C10) aryl-, (C6-C10)aryl-(C1-C8)alkyl-, HO-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C1-C8)alkyl, H2N-(C1-C8)alkyl, (C1-C8)alkyl-NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C2-C9)heterocyclyl-(C1-C8)alkyl, (C1-C8)alkyl-(C=O)-NH-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C=O)-NH-(C1-C8)alkyl, H2N-

(C=ONH-(C1-C8)alkyl, (C1-C8)alkyl-SO2-NH-(C1-C8)alkyl, (C2-C9)heteroaryl-(C1-C8)alkyl, H2N-(C=O)-,H2N- (C=O)- (CI-C8) alkyl-;

each R4 is independently selected from the group consisting of: H-, HO-, halo-, NC-, HO-(C=O-, H2N-, (C1-C8)alkyl-NH-, [(C1-C8)alkyl]2N-, (C1-C8)alkyl- optionally substituted with 1-3 fluorine atoms,(C1-C8) alkyl-O- wherein the alkyl group is optionally substituted with 1-3 fluorine atoms, HO-(C1-C8)alkyl-, (C1-C8)alkyl-O-(C1-C8)alkyl-, H2N-(C1-C8)alkyl-, (C1-C8)alkyl NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C1-C8)alkyl-(C=O)-, (C1-C8)alkyl-(C=O)-(CC8) alkyl-, (C6-C10)aryl-, (C2-Cg) heteroaryl-, (C6-C10) aryloxy, H2N-(C=O), H2N-(C=O)-(CC8) alkyl, (C1-C8)alkyl-NH-(C=O)-, (C1-C8)alkyl-NH-(C=O)-(C1-C8)alkyl-, [(C1-C8)alkyl]2N (C=O)-, [(C1-C8)alkyl]2-N-(C=O)-(C1-C8)alkyl-, (C3-C8)cycloalkyl-, (C1-C8)alkyl-SO2-, NC-(C C8)alkyl-, (C1-C8) alkyl-(C=O)-NH-, H2N-(C=O)-NH-, H2N-(C=O)-NH-(C1-C8) alkyl-;

R5 is (C1-C8) alkyl-.

for the treatment and prevention of edometriosis.

Particularly favourable embodiments of the present invention are the following compounds as reported in WO01/72728:

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

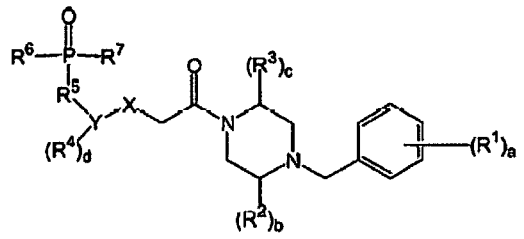
(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

The patent application WO2004/055031 in its entireties is hereby incorporated by reference to the present application. Advantageous forms of embodiment according to the present invention are the compounds of the formula I- WO2004/055031



(I-WO2004/055031)

a prodrug thereof, or a pharmaceutical acceptable salt of the compound or the prodrug thereof; wherein

a = 0, 1, 2, 3, 4 or 5; b = 0, 1 or 2; c = 0, 1 or 2; d = 0, 1,2, 3 or 4;

X is O, S, CH2 or NR6;

Y is (C6-C10) aryl or(C2-C9) heteroaryl ;

each R1 is independently: hydroxy, halo,(C1-C8) alkyl optionally substituted with 1 to 3 fluorine atoms,(C1-C8) alkoxy optionally substituted with 1-3 fluorine atoms, HO(C1-C8) alkyl-, cyano, amino, H2N (C1-C8) alkyl-, carboxy,acyl, (C1-C8) alkyl(C=O)(C1-C8)alkyl-, H2N(C=O)-, or H2N (C=O)(C1-C8) alkyl-;

each R2 and R3 are independently: oxo,(C1-C8) alkyl optionally substituted with 1-3 fluorine atoms, (C3-C8) cycloalkyl-, (C3-C8)cycloalkyl-(C1-C8)alkyl-, (C6-C10) aryl-, (C6-C10) aryl(C1-C8)alkyl-, HO(C1-C8) alkyl-,(C1-C8) alkyl-O-(C1-C8)alkyl-, H2N(C1-C8) alkyl-, (C1-C8)alkyl-NH-(C1-C8)alkyl-, [(C1-C8)alkyl]2N-(C1-C8)alkyl-, (C2-C9) heterocyclyl(C1-C8)alkyl-, (C1-C8)alkyl(C=O) NH(Ci-C8) alkyl-, (C1-C8)alkyl-O-(C=O) NH (C1-C8) alkyl-, H2N(C=O) NH(C1-C8) alkyl-, (C1-C8)alkyl-SO2-NH(C1-C8)alkyl-, (C2- C9) heteroaryl(C1-C8) alkyl-, H2N (C=O), or H2N (C=O) (C1-C8)alkyl-;

each R4 is independently: HO-,halo-, NC-, HO(C=O)-, H2N-, (C1-C8)alkyl NH-, [(C1-C8)alkyl] 2N-,(Ci-C8) alkyl-, optionally substituted with 1-3 fluorine atoms, (C1-C8) alkoxy optionally substituted with 1-3 fluorine atoms, HO (C1-C8) alkyl-, (C1-C8) alkyl-O-(C1-C8)alkyl-, H2N(C1-C8)alkyl--, (C1-C8)alkylNH(C1-C8)alkyl-, [(C1-C8)alkyl] 2N (C1- C8) alkyl-, (C1-C8)alkyl(C=O)-, (C1-C8)alkyl(C=O)(C1-C8)alkyl-, (C6-C10)aryl-, (C2-Cg) heteroaryl-, (C6-C10) aryloxy-, H2N(C=O)-, H2N (C=O)(Ci-C8)alkyl-, (C1-

C8) alkylNH(C=O)-, (C1-C8)alkyl-NH(C=O)(C1-C8)alkyl-, [(C1-C8)alkyl]2N(C=O)-, [(C1-C8) alkyl] 2N (C=O) (C1-C8) alkyl-, (C3-C8) cycloalkyl-, (C1-C8)alkylSO2-, NC(C1-C8)-alkyl(C=O)NH-, H2N(C=O)NH- or H2N(C=O)NH-(C1-C8)-alkyl-;

R5 is abound or a (C1-C8)-alkyl-;

R6 is independently: hydroxy, amine or (C1-C8)-alkyl-NH; and

R7 is independently: hydrogen, hydroxyl, (C1-C8)-alkyloxy or (C1-C8)-alkyl-

for the treatment and prevention of edometriosis.

Particularly favourable embodiments of the present invention are the following compounds as reported in WO2004/055031:

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzvl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzvl) phosphonic acid monoethyl ester,

5-Chloro-2-{2-[4-(4-fluoro-benzvl)-(2R5S)-2,5-dimethYl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid

In another aspect, this invention provides pharmaceutical compositions useful in treating endometriosis in a human female in need of such treatment, which composition comprises a therapeutically effective amount of a compound of formula (Ia) as described above, and a pharmaceutically acceptabe excipient.

In another aspect, this invention provides a method of treating and preventing endometriosis in a human female, which method comprises administering to a human female in need of such treatment a therapeutically effective amount of a compound of formula (Ia) as described above.

In another aspect, this invention provides compounds of formula (Ia) for the preparation of a medicament for the treatment of endometriosis.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e.g.*, methyl, ethyl, *n*- propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), *n* -heptyl, and the like.

"Alkylcarbonyl" refer to a radical of the formula -C(O)-R_a wnere R_a is an alkyl radical as defined above, *e.g.*, acetyl, ethylcarbonyl, *n*-propylcarbonyl, and the like.

"Alkylcarbonylalkyi" refers to a radical of the formula - R_a-C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (acetyl)methyl, 2-(acetyl)ethyl, 4- (ethylcarbonyl)butyl, and the like.

"Alkylcarbonylamino" refers to a radical of the formula -N(H)-C(O)-R_a where R_a is an alkyl radical as defined above, *e.g.*, acetylamino, ethylcarbonylamino, n-propylcarbonylamino, and the like.

"(Alkylcarbonyl)(alkyl) amino" refers to a radical of the formula -N(R_a)-C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, *N*-methyl-*N*-acetylamino, *N*-ethyl-*N*- (ethylcarbonyl)amino, and the like.

"Alkylcarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, acetylammomethyl, 2- (acetylamino)ethyl, 4-(ethylcarbonylamino)butyl, and the like.

"(Alkylcarbonyl)(alkyl)aminoalkyl" refers to a radical of the formula -R_a-N(R_a)-C(O)-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (*N*-methyl-*N*-acetylamino)methyl, 2-(*N*-ethyl-*N*-(ethylcarbonyl)amino) propyl, and the like.

"Alkylthio" refers to a radical of the formula -S-R_a where R_a is an alkyl radical as defined above, *e.g.*, methylthio, ethylthio, *n*- propylthio, and the like.

"Alkylsulfinyl" refers to a radical of the formula -S(O)R_a where R_a is an alkyl radical as defined above, *e.g.*, methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, and the like.

"Alkylsulfonyl" refers to a radical of the formula -$S(O)_2R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylsulfonyl, ethylsulfonyl, *n*- propylsulfonyl, and the like.

"Alkylthioalkyl" refers to a radical of the formula - R_a-S-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, methylthiomethyl, 2-methylthioethyl, 2-ethylthiopropyl, and the like.

"Alkylsulfinylalkyl" refers to a radical of the formula -R_a-S(O)-R_a where where each R_a is independently an alkyl radical as defined above, *e.g.,* methylsulfinylmethyl, 2-methylsulfinylethyl, 2- ethylsulfinylpropyl, and the like.

"Alkylsulfonylalkyl" refers to a radical of the formula $-R_a-S(O)_2-R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, methylsulfonylmethyl, 2-methylsulfonylethyl, 2-ethylsulfonylpropyl, and the like.

"Alkylsulfonylamino" refers to a radical of the formula $-N(H)-S(O)_2-R_a$ where R_a is an alkyl radical as defined above, *e.g.*, methylsulfonylamino, ethylsulfonylamino, *iso*-propylsulfonylamino, and the like.

"Alkylsulfonylaminoalkyl" refers to a radical of the formula $-R_a-N(H)-S(O)_2-R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, methylsulfonylaminomethyl, 2- (ethylsulfonylamino) ethyl, 3-(*iso*-propylsulfonylamino)propyl, and the like.

"(Alkylsulfonyl)(alkyl)aminoalkyl" refers to a radical of the formula $-R_a-N(R_a)-S(O)_2-R_a$ where each R_a is independently an alkyl radical as defined above, *e.g.*, (methylsulfonyl)(methyl)aminomethyl, 2-((ethylsulfonyl)(methyl)amino) ethyl, 3-((*iso*-propylsulfonyl)(ethyl)amino)propyl, and the like.

"Alkenyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one double bond and having from two to eight carbon atoms, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1- enyl, penta-1,4-dienyl, and the like.

"Alkenylcarbonylamino" refers to a radical of the formula $-N(H)-C(O)-R_c$ where R_c is an alkenyl radical as defined above, *e. g.*, ethenylcarbonylamino, prop-2-enylcarbonylamino, but-2- enylcarbonylamino, and the like.

"Alkynyl" refers to a straight or branched chain monovalent or divalent radical consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to eight carbon atoms, *e. g.*, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl, and the like.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above. *e.g.*, methoxy, ethoxy, *n*-propoxy, 1-methylethoxy (*iso*-propoxy), *n*-butoxy, *n*-pentoxy. 1,1- dimethylethoxy (*t*-butoxy), and the like.

"Alkoxycarbonyl" refers to a radical of the formula $-C(O)OR_a$ wnere R_a is an alkyl radical as defined above, *e.g.*, methoxycarbonyl, ethoxycarbonyl, *n*- propoxycarbonyl, and the like.

"Alkoxycarbonylalkyl" refers to a radical of the formula $-R_a-C(O)OR_a$ where each R_a is independently an alkyl radical as defined above, e.g., methoxycarbonylmethyl, 2-(ethoxycarbonyl)ethyl, 2- (methoxycarbonyl)propyl, and the like.

"Alkoxyalkylcarbonyloxyalkyl" refers to a radical of the formula $-R_a-OC(O)-R_a-OR_a$ wnere each R_a is independently an alkyl radical as defined above, *e.g.*,

methoxymethylcarbonyloxymethyl, 2-(2-(2- (ethoxy)ethylcarbonyloxy)ethyl) ethyl, 2-(3-(2-(ethoxy)ethylcarbonyloxy) propyl)ethyl, and the like.

"Alkoxycarbonylamino" refers to a radical of the formula -N(H)-C(O)-OR_a wnere R_a is an alkyl radical as defined above, *e.g.*, methoxycarbonylamino, ethoxycarbonylamino, *iso*propoxycarbonylamino, and the like.

"(Alkoxycarbonyl)(alkyl)amino" refers to a radical of the formula -$N(R_a)(C(O)OR_a)$ where each R_a is independently an alkyl radical as defined above, *e.g.*, *N*-methyl-*N*- methoxycarbonylamino, *N*-ethyl-*N*-ethoxycarbonylamino, and the like.

"Alkoxycarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-OR_a where each R_a is independently an alkyl radical as defined above, *e.g.*, methoxycarbonylaminomethyl, 2-(ethoxycarbonylamino) ethyl, *iso*propoxycarbonylaminomethyl, and the like.

"(Alkoxycarbonyl)(alkyl)aminoalkyl" refers to a radical of the formula - R_a-$N(R_a)(C(O)OR_a)$ where each R_a is independently an alkyl radical as defined above, *e.g.*, *N*-methyl-*N*-methoxycarbonylaminomethyl, 2-(*N*-ethyl- *N*-ethoxycarbonylamino)ethyl, and the like.

"(Alkoxy)aralkyl" refers to an aralkyl radical wherein the alkyl group therein is substituted by an alkoxy radical as defined above, *e.g.*, 2-phenyl- 1-methoxyethyl, phenyl(methoxy)methyl, and the like.

"Alkoxyalkylcarbonylamino" refers to a radical of the formula -N(H)-C(O)- R_a-O-R_a where each R_a is an alkyl radical as defined above, e.g., methoxymethylcarbonylamino, ethoxyethylcarbonylamino, methoxyethylcarbonylamino, and the like.

"Alkoxycarbonylalkylcarbonylamino" refers to a radical of the formula - N(H)-C(O)-R_a-$C(O)OR_a$ where each R_a is independently an alkyl radical as defined above, *e.g.* ethoxycarbonylmethylcarbonylamino, methoxycarbonylmethylcarbonylamino, (2-ethoxycarbonylethyl)carbonylamino, (2-methoxycarbonylethyl)carbonylamino, and the like.

"Alkoxycarbonylalkylcarbonylaminoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-R_a-C(O) OR_a where each R_a is independently an alkyl radical as defined above, *e.g.*, ethoxycarbonylmethylcarbonylaminomethyl, 2-(methoxycarbonylmethylcarbonylamino)ethyl, 1-((2-ethoxycarbonylethyl) carbonylamino)ethyl, (2-methoxycarbonylethyl)carbonylaminomethyl, and the like.

"(Alkoxycarbonylalkyl)aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-C(O)-OR_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (methoxycarbonylmethyl) aminocarbonyl, (2-

(ethoxycarbonyl)ethyl)aminocarbonyl, (1- (methoxycarbonyl)ethyl)aminocarbonyl, and the like.

"(Alkoxycarbonylalkyl)ureidoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-N(H)-R_a-C(O)-OR_a where each R_a is independently an alkyl radical as defined above and where the nitrogen to which -R_a- C(O)-OR_a is attached is indicated as "*N*", *e.g.*, (ethoxycarbonylmethyl)ureidomethyl, (2-(ethoxycarbonyl)ethyl)ureidomethyl, 2-((2-(ethoxycarbonylmethyl) ureidomethyl, and the like.

"(Alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido" refers to a radical of the formula - N(H)-C(O)-CH_2-N(R_a)-C(O)-R_a- C(O)-OR_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (methoxycarbonylmethylcarbonyl)(methyl) glycinamido, ((2-ethoxycarbonylethyl)carbonyl)(ethyl)glycinamido, and the like.

"(Alkoxyalkylcarbonyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H)-C(O)-R_a-O-R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (methoxyacetyl)glycinamido, (ethoxyacetyl)glycinamido, and the like.

"Alkylene chain" refers to straight or branched chain divalent radical consisting solely of carbonyl and hydrogen, containing no unsaturation and having from one to eight carbon atoms, *e.g.* , methylene, ethylene, propylene, *n*-butylene, and the like.

"Alkylidene chain" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from one to eight carbon atoms, wherein the unsaturation is present only as double bonds and wherein a double bond can exist between the first carbon of the chain and the rest of the molecule, *e.g.*, ethylidene, propylidene, *n*-butylidene, and the like.

"Amino" refers to the radical -NH_2.

"Aminoalkyl" refers to a radical of the formula -R_aNH_2 where R_a is an alkyl radical as defined above, *e. g.*, aminomethyl, 2-aminoethyl, 3-aminopropyl, 2-aminopropyl, and the like.

"Aminoalkylamino" refers to a radical of the formula -N(H)- R_a-NH_2 wnere R_a is an alkyl radical as defined above, *e.g.*, aminomethylamino, (2-aminoethyl)amino, (2-aminopropyl)amino, and the like.

"Aminoalkoxy" refers to a radical of a formula -OR_a- NH_2 where R_a is an alkyl radical as defined above, *e.g.*, aminomethoxy, 2- aminoethoxy, 3-aminopropoxy, 2-aminopropoxy, 4-aminobutoxy, and the like.

"Aminocarbonyl" refers to the radical -C(O)NH_2.

"Aminocarbonylglycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H)-C(O)-NH_2.

"(Aminocarbonyl)(alkyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(R_a)-C(O)-NH_2 where R_a is an alkyl radical as defined above and where the nitrogen with the R_a substituent is designated as "*N*" , *e.g.*, (aminocarbonyl)(*N'*-methyl)glycinamido, (aminocarbonyl)(*N'*- ethyl)glycinamido, and the like.

"Aminocarbonylalkyl" refers to a radical of the formula - R_a-C(O)NH_2 where R_a is an alkyl radical as defined above, *e.g.*, aminocarbonylmethyl, 2-(aminocarbonyl)ethyl, 2-(aminocarbonyl)propyl, and the like.

"(Aminocarbonylalkyl)aminocarbonyl" refers to a radical of the formula - C(O)-N(H)-R_a-C(O)-NH_2 where R_a is an alkyl radical as defined above, *e.g.*, (aminocarbonylmethyl)aminocarbonyl, (2-aminocarbonylethyl)aminocarbonyl, (1-aminocarbonylethyl)aminocarbonyl, and the like.

"(Aminoalkyl) aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a -NH_2 where R_a is an alkyl radical as defined above, *e.g.*, (aminomethyl) aminocarbonyl, (2-aminoethyl)aminocarbonyl, (1-aminoethyl)aminocarbonyl, and the like.

"Amidino" refers to the radical -C(NH)NH_2.

"Aryl" refers to a phenyl or naphthyl radical. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents selected from the group consisting of hydroxy, mercapto, halo, alkyl, alkenyl, alkynyl, phenyl, phenylalkyl, phenylalkenyl, alkoxy, phenoxy, phenylalkoxy, haloalkyl, haloalkoxy, formyl, nitro, cyano, amidino, cycloalkyl, hydroxyalkyl, alkoxyalkyl, phenoxyalkyl, phenylalkoxyalkyl, amino, monoalkylamino, dialkylamino, monophenylamino, monophenylalkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monophenylaminoalkyl, monophenylalkylaminoalkyl, alkylcarbonyl, carboxy, alkoxycarbonyl, carpoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, as defined herein.

"Arylcarbonyl" refers to a radical of the formula -C(O)R_b where R_b is an aryl radical as defined above, *e.g.*, phenylcarbonyl and naphthalen-2-ylcarbonyl, and the like.

"Arylcarbonylalkyl" refers to a radical of the formula -R_aC(O)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, phenylcarbonylmethyl, 2-(phenylcarbonyl)ethyl, 3-(naphthalen-2-ylcarbonyl) propyl, and the like.

"Arylcarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g*

., (4-methoxyphenyl)carbonylaminomethyl, 2-((4-fluorophenyl)carbonylamino) ethyl, 1-((4-chlorophenyl)carbonylamino)ethyl, and the like.

"Arylsuffonyl" refers to a radical of the formula $-S(O)_2-R_b$ where R_b is an aryl radical as defined above, *e.g.*, phenylsulfonyl, (4- chlorophenyl)sulfonyl, (3-nitrophenyl)sulfonyl, and the like.

"Arylsulfonylamino" refers to a radical of the formula $-N(H)-S(O)_2-R_b$ where R_b is an aryl radical as defined above, *e.g.*, phenylsulfonylamino, (4-chlorophenyl)sulfonylamino, (4-fluorophenyl)sulfonylamino, (3-nitrophenyl) sulfonylamino), and the like.

"Arylsulfonylaminoalkyl" refers to a radical of the formula $-R_a-N(H)-S(O)_2-R_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, phenylsulfonylaminomethyl, (4-chlorophenyl) sulfonylaminomethyl, 2-((4-fluorophenyl)sulfonylamino)ethyl, 1-((3- nitropnenyl)sulfonylamino)ethyl, and the like.

"(Arylsulfonyl) (alkyl)aminoalkyl" refers to a radical of the formula $-R_a-N(R_a)-S(O)_2-R_b$ where each R_a is independently an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, (phenylsulfonyl)(methyl) aminomethyl, ((4-chlorophenyl)sulfonyl)(ethyl)aminomethyl, 2-(((4-fluorophenyl)sulfonyl)(methyl)amino)ethyl, 1-(((3-nitrophenyl)sulfonyl) (ethyl)amino)ethyl, and the like.

"(Alkoxycarbonylaminoalkylcarbonyl)glycinamido" refers to a radical of the formula $-N(H)-C(O)-CH_2-N(H)-C(O)-N(H)-C(O)-OR_a$ where R_a is an alkyl radical as defined above, *e.g.*, (ethoxycarbonylaminocarbonyl)glycinamido, (methoxycarbonylaminocarbonyl)glycinamido, and the like.

"Arylcarbonylglycinamido" refers to a radical of the formula $-N(H)-C(O)-CH_2-N(H)-C(O)-R_b$ where R_b is an aryl radical as defined above, e.g., phenylcarbonylglycinamido, (4-fluoro-3-trifluoromethylphenyl) carbonylglycinamido, (4-fluorophenyl)carbonylglycinamido, and the like.

"(Arylcarbonyl)(alkyl)glycinamido" refers to a radical of the formula $-N(H)-C(O)-CH_2-N(R_a)-C(O)-R_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above and the nitrogen to which the R_a radical is attached is designated as "*N*", *e.g.*, (phenylcarbonyl)(*N'*-methyl) glycinamido, ((4-fluoro-3-trifluoromethylphenyl)carbonyl) (*N'*-ethyl)glycinamido, ((4-fluorophenyl)carbonyl)(*N'*-methyl) glycinamido, and the like.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, benzyl, and the like.

"Aralkylcarbonyl" refers to a radical of the formula -C(O)-R_d where R_d is an aralkyl radical as defined above, *e.g.*, benzylcarbonyl, 1-(phenyl)ethylcarbonyl, and the like.

"Aralkylcarbonylalkyl" refers to a radical of the formula -R_aC(O)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzylcarbonylmethyl, 2-(1-(phenyl)ethylcarbonyl)ethyl, and the like.

"Aralkenyl" refers to a radical of the formula -$R_c$$R_b$ where R_b is an aryl radical as defined above and R_c is an alkenyl radical as defined above, *e.g.*, 3-phenylpropylid-1-enyl, and the like.

"Aryloxy" refers to a radical of the formula -OR_b wnere R_b is an aryl radical as defined above, *e.g.*, phenoxy and naphthoxy, and the like.

"Aralkoxycarbonyl" refers to a radical of the formula -C(O)OR_d where R_d is an aralkyl radical as defined above, *e.g.*, benzyloxycarbonyl, and the like.

"Aralkoxycarbonylalkyl" refers to a radical of the formula -R_a C(O)OR_d wnere R_a is an alkyl radical as defined above and R_a is an aralkyl radical as defined above, *e.g.*, benzyloxycarbonylmethyl, 2- (benzyloxycarbonyl)ethyl, 3-((naphthalen-2-yl)oxy)carbonyl)propyl, and the like.

"Aryloxyalkyl" refers to a radical of the formula - R_a-OR_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above. *e.g.*, phenoxymethyl, 2-(phenoxy) ethyl, 3-(phenoxy)propyl, and the like.

"Aryloxyalkylcarbonyloxyalkyl" refers to a radical of the formula -R_a-OC(O)-R_a- OR_b where each R_a is independently an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, phenoxymethylcarbonyloxymethyl, (2-phenoxyethyl)carbonyloxymethyl, 3-((2-phenoxyethyl)carbonyloxy)propyl, and the like.

"Aralkoxy" refers to a radical of the formula - OR_d where R_d is an aralkyl radical as defined above, *e.g.*, benzyloxy, and the like.

"Aralkoxylalkyl" refers to a radical of the formula -R_a-OR_d wnere R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzyloxymethyl, 2- phenylethoxymethyl, and the like.

"Aralkoxyalkylcarbonyloxyalkyl" refers to a radical of the formula -R_a-OC(O)-R_a-OR_d where each R_a is independently an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzyloxymethylcarbonyloxymethyl, (2-(phenyl) ethoxymethyl)carbonyloxymethyl, 2-((2-(phenyl)ethoxymethyl)carbonyloxy) ethyl, and the like.

"Alkoxyalkyl" refers to a radical of the formula -R_a OR_a where each R_a is independently an alkyl radical as defined above, *e.g.*, methoxyethyl, ethoxymethyl, propoxymethyl, propoxyethyl, and the like.

"Alaninamido" refers to a radical of the formula -N(H)- C(O)-$C(CH_3)$H-NH_2.

"Alanimamidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-$C(CH_3)$H-NH_2 where R_a is an alkyl radical as defined above, *e.g.* , alaninamidomethyl, 2-(alaninamido)ethyl, 1-(alaninamido)ethyl, 3- (alaninamido)propyl, and the like.

"Azidoalkyl" refers to radical of the formula -R_a-N_3 where R_a is an alkyl radical as defined above, *e.g.* , 2-azidoethyl, 3-azidopropyl, 2-azidopropyl, 4-azidobutyl, and the like.

"Benzyl" refers to a radical of the formula -CH_2-R_h where R_h is a phenyl radical optionally substituted by one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, alkenyl, nitro, cyano, amino, monoalkylamino, dialkylamino, alkylcarbonyl, carboxy, alkoxycarbonyl, and aminocarbonyl.

"Benzylcarbonyl" refers to a radical of the formula -C(O)-CH_2- R_h where R_h is a phenyl radical as defined above, *e.g.*, (4-methoxybenzyl)carbonyl, (3-fluorobenzyl)carbonyl, and the like.

"Carboxy" refers to the radical -C(O)OH.

"Carboxyalkyl" refers to the radical of the formula -R_a-C(O)OH where R_a is an alkyl radical as defined above, *e.g.*, carboxymethyl, 2- carboxyethyl, 3-carboxypropyl, and the like.

"(Carboxyalkyl) aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-C(O)OH where R_a is an alkyl radical as defined above, *e.g.*, (carboxymethyl)aminocarbonyl, (2- carboxyethyl)aminocarbonyl, (1-carboxyethyl)aminocarbonyl, and the like.

"Carbocyclic ring system" refers to a stable 3- to 15-membered ring radical consisting solely of carbon and hydrogen atoms. For purposes of this invention, the carbocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring system, and may include fused or bridged ring systems, and the ring system may be partially or fully saturated or aromatic, and the carbon atoms in the ring system may be optionally oxidized. Examples of such carbocyclic ring system radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclohexyl, norbornane, norbornene, adamantyl, bicyclo[2.2.2]octane, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, and the like.

"Cycloalkyl" refers to a stable 3- to 10-membered monocyclic or bicyclic radical which is saturated, and which consist solely of carbon and hydrogen atoms, *e.g.*, cyclopropyl, cyclobutyl, cyclobutyl, cyclohexyl, decalinyl and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, halo, hydroxy, amino, nitro, alkoxy, carboxy, phenyl and alkoxycarbonyl.

"Cycloalkylalkyl" refers to a radical of the formula $-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e.g.*, cyclopropylmethyl, 2- cyclobutylethyl, 3-cyclohexylpropyl, and the like.

"Cycloalkylamino" refers to a radical of the formula $-N(H)-R_e$ where R_e is a cycloalkyl radical as defined above, *e.g.*, cyclopropylamino, cyclobutylamino, cyclohexylamino, and the like.

"Cycloalkylaminoalkyl" refers to a radical of the formula $-R_a-N(H)-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e. g.*, cyclopropylaminomethyl, 2-(cyclobutylamino)ethyl, cyclohexylaminomethyl, and the like.

"(Cycloalkylalkyl)amino" refers to a radical of the formula $-N(H)-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e.g.*, (cyclopropylmethyl)amino, (2-cyclobutylethyl) amino, (3-cyclohexylpropyl)amino, and the like.

"(Cycloalkylalkyl)aminoalkyl" refers to a radical of the formula $-R_a-N(H)-R_a-R_e$ where each R_a is independently an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e.g.,* (cyclopropylmethyl)aminomethyl, 2-((2-cyclobutylethyl)amino)ethyl, (3-cyclohexylpropyl)aminomethyl, and the like.

"Cycloalkylcarbonylamino" refers to a radical of the formula $-C(O)-N(H)-R_e$ where R_e is a cycloalkyl radical as defined above, *e.g.*, cyclopropylcarbonylamino, (2-phenylcyclopropyl)carbonylamino, cyclohexylcarbonylamino, 4-cyanodecalinylcarbonylamino. cyclopentylcarbonylamino, and the like.

"Cycloalkylcarbonylaminoalkyl" refers to a radical of the formula $-R_a-C(O)-N(H)-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above, *e.g.*, cyclopropylcarbonylaminomethyl, 2-((2- phenylcyclopropyl) carbonylamino)ethyl, 1-(cyclohexylcarbonylamino)ethyl, (3-phenylcyclopentyl)carbonylaminomethyl, and the like.

"Cycloalkylalkylcarbonylamino" refers to a radical of the formula $-C(O)-N(H)-R_a-R_e$ where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as

defined above, *e.g.*, (cyclopropylmethyl) carbonylamino, ((2-phenylcyclopropyl)methyl)carbonylamino, (2- cyclohexylethyl)carbonylamino, (1-cyclohexylethyl)carbonylamino, and the like.

"Cyano" refers to the radical -CN.

"Cyanoalkyl" refers to a radical of the formula -R_aCN where R_a is an alkyl radical as defined above, cyanomethyl, 2- (cyano)ethyl, 3-(cyano)propyl, and the like.

"DMF" refers to N,N- dimethylformamide.

"DMSO" refers to dimethylsulfoxide.

"Dialkylamino" refers to a radical of the formula -N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

"Dialkylaminoalkyl" refers to a radical of the formula -R_a-N(R_a) R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminomethyl, methyethylaminomethyl, 2-diethylaminoethyl, 3-dipropylaminopropyl, and the like.

"Dialkylaminocarbonyl" refers to a radical of the formula -C(O)N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminocarbonyl, methylethylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, ethylpropylaminocarbonyl, and the like.

"Dialkylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, dimethylaminocarbonylmethyl, 2-(methylethylaminocarbonyl)ethyl, 3-(diethylaminocarbonyl)propyl, 2- (dipropylaminocarbonyl)propyl, and the like.

"Dialkylaminocarbonyloxyalkyl" refers to a radical of the formula -R_a-O-C(O)-N(R_a)R_a where each R_a is independently an alkyl radical as defined above, *e.g*, dimethylaminocarbonyloxymethyl, 2- (methylethylaminocarbonyloxy)ethyl, 3-(diethylaminocarbonyloxy)propyl, 2- (dipropylaminocarbonyloxy)propyl, and the like.

"Dialkylureido" refers to a radical of the formula -N(H)- C(O)- N(R_a)(R_a) or a radical of the formula -N(R_a)-C(O)-N(R_a)H where each R_a is independently an alkyl radical as defined above and the attaching nitrogen is designated as "N" and the other nitrogen is designated as "N", *e.g.*, *N'*,*N'*-di(methyl) ureido, *N'*-methyl-*N'*-ethylureido, *N'*,*N'*-di(ethyl) ureido, *N'*,*N'*-di(propyl)ureido, *N*-methyl-*N'*- ethylureido, and the like.

"Diarylureido" refers to a radical of the formula -N(H)-C(O)-N(R_b)(R_b) or a radical of the formula -N(R_b)-C(O)-N(R_b)H where each R_b is independently an aryl radical as defined above and the attaching nitrogen is designated as "*N*" and the other

nitrogen is designated as "*N*", *e.g.* , *N',N'*-di(phenyl)ureido, *N'*-phenyl-*N'*-(3-nitro) phenylureido, *N',N'*-di(4-methoxyphenyl)ureido, *N',N'*-di(4- chlorophenyl) ureido, *N*-4-chlorophenyl-*N'*-(3-chlorophenyl) ureido and the like.

"Dialkylureidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-N(R_a) (R_a) or a radical of the formula -R_a-N(R_a)-C(O)-N(R_a)H where each R_a is independently an alkyl radical as defined above and the attached nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*"', *e.g.*, *N',N'*- di(methyl) ureidomethyl, 2-(*N'*-methyl-*N'*-ethylureido)ethyl, 1-(*N',N'*-di(ethyl)ureido)ethyl, 3-(*N',N'*-di(propyl)ureido)propyl, 2-(*N*-methyl-*N'*-ethylureido)ethyl, and the like.

"Formyl" refers to the radical -C(O)H.

"Formylalkyl" refers to a radical -R_a-C(O)H wnere R_a is an alkyl radical as defined above, *e.g.*, formylmethyl, 2-(formyl)ethyl, 3-(formyl)propyl, and the like.

"Glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2 -NH_2.

"Glycinamidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)- CH_2- NH_2 wnere R_a is an alkyl radical as defined above, *e.g.*, glycinamidomethyl. 2-(glycinamido)ethyl, 1-(glycinamido)ethyl, 3- (glycinamido)propyl, and the like.

"Guanidino" refers to the radical -N(H)-C(NH)-NH_2.

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo- 2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkoxy" refers to a radical of the formula -OR_f where R_f is an haloalkyl radical as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3- bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like.

"Haloalkylcarbonylamino" refers to a radical of the formula -N(H)-C(O) -R_f where R_f is an haloalkyl radical as defined above, *e.g.,* trifluoromethylcarbonylamino, trifluoromethylcarbonylamino, 2-bromoethylcarbonylamino, and the like.

"(Haloalkylcarbonyl)ureido" refers to a radical of the formula - N(H)-C(O)-N(H)-C(O)-R_f where R_f is a haloalkyl radical as defined above, *e.g.,* (trichloromethylcarbonyl)ureido, (3-fluoropropylcarbonyl)ureido, and the like.

"(Haloalkyl)(alkyl)ureidoalkyl" refers to a radical of the formula -R_a-N(R_a)-C(O)-N(H)-R_f or a a radical of the formula -R_a- N(R_f)-C(O)-N(H)-R_a or a radical of the formula -R_a-N(H)-C(O)-N(R_a) R_f where each R_a is independently an alkyl radical as defined above and R_f is an haloalkyl radical as defined above and terminal nitrogen is

designated as "*N*" and the other nitrogen is designated as "*N*', *e.g.*, *N*'-(2-chloroethyl)-*N*-(methyl)ureidomethyl, and 2-(*N*'-(2- chloroethyl)-*N*-(methyl)ureido)ethyl, and the like.

"Haloalkylcarbonylaminoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-R_f where R_a is an alkyl radical as defined above and R_f is an haloalkyl radical as defined above, *e.g.*, trifluoromethylcarbonylaminomethyl, 2-(trifluoromethylcarbonylamino)ethyl, and the like.

"Hydroxy" refers to the radical -OH.

"Hydroxyalkyl" refers to a alkyl radical as defined above that is substituted by a hydroxy radical, *e.g.*, hydroxymethyl, 2- hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl, 3- hydroxybutyl, and the like.

"(Hydroxyalkyl)aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-OH where R_a is an alkyl radical as defined above, *e.g.*, hydroxymethylaminocarbonyl, (2-hydroxyethyl)aminocarbonyl, (1- hydroxyethyl)aminocarbonyl, and the like.

"Hydroxyalkoxy" refers to a radical of the formula -OR_a-OH where R_a is an alkyl radical as defined above, *e.g.*, 2- hydroxyethoxy, 2-hydroxypropoxy, 4-hydroxybutoxy, 3-hydroxybutoxy, and the like.

"(Hydroxyalkoxy)carbonyl" refers to a radical of the formula - C(O)-OR_a-OH where R_a is an alkyl radical as defined above, *e.g.*, (2-hydroxyethoxy)carbonyl, (2-hydroxypropoxy)carbonyl, (4-hydroxybutoxy)carbonyl, (3-hydroxybutoxy) carbonyl, and the like.

"(Hydroxy)aralkyl" refers to an aralkyl radical as defined above wherein the alkyl radical therein is substituted by a hydroxy radical, *e.g.*, (phenyl)(hydroxy)methyl, 2-phenyl-1- hydroxyethyl, 2-phenyl-3-hydroxypropyl, and the like.

"(Hydroxyalkylthio) alkyl" refers to an alkylthioalkyl radical as defined above that is substituted by an hydroxy radical, *e.g.*, 2- hydroxyethylthiomethyl, 2-(hydroxymethylthio)ethyl, and the like.

"Hydroxyalkenyl" refers to an alkenyl radical as defined above that is substituted by a hydroxy radical, *e.g.*, 3-hydroxyprop-1-enyl, 4- hydroxybut-1-enyl, 4-hydroxypent-1- enyl, 5-hydroxypenta-1,3-dienyl, and the like.

"Hydroxyalkynyl" refers to an alkynyl radical as defined above that is substituted by a hydroxy radical, e.g., 3- hydroxyprop-ynyl, 4-hydroxypent-2-ynyl, 1-hydroxybut-3-ynyl, and the like.

"(Hydroxy)cycloalkylalkyl" refers to a radical of the formula - R_a(OH)-R_e where R_a is an alkyl radical as defined above and R_e is a cycloalkyl radical as defined above and

where the OH radical is a substituent on any carbon of the R_a radical, *e.g.*, 2-cyclopropyl-1-hydroxyethyl, (4-hydroxycyclohexyl)methyl, and the like.

"Hydroxyalkylaminoalkyl" refers to a monoalkylaminoalkyl radical as defined below that is substituted by a hydroxy radical, *e. g.*, 2-hydroxyethylaminomethyl, 2-(3-hydroxypropylamino)ethyl, and the like.

"Hydroxyamidino" refers to a radical of the formula - $C(NH_2)$=NOH.

"Heterocyclic ring system" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclic ring system radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclic ring system radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclic ring system may be partially or fully saturated or aromatic. The heterocyclic ring system may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furanyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, triazinyl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone.

"Heterocyclyl" refers to a heterocyclic ring system as defined above. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include a heterocyclic ring system as defined above which is optionally substituted by one or more substituents selected from the group consisting of hydroxy, mercapto, halo, alkyl, alkenyl, alkynyl, phenyl, phenylalkyl, phenylalkenyl, alkoxy, phenoxy, phenylalkoxy, haloalkyl, haloalkoxy, formyl, nitro,

cyano, amidino, cycloalkyl, hydroxyalkyl, alkoxyalkyl, phenoxyalkyl, phenylalkoxyalkyl, amino, monoalkylamino, dialkylamino, monophenylamino, monophenylalkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monophenylaminoalkyl, monophenylalkylaminoalkyl, carboxy, alkoxycarbonyl, phenylcarbonyl, benzylcarbonyl, alkylcarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, phenylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, ureido, monoalkylureido, monophenylureido, monobenzylureido, as defined herein.

"Heterocyclylalkyl" refers to a radical of the formula $-R_aR_g$ where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e.g.*, indolinylmethyl or imidazolylmethyl, and the like.

"Heterocyclylamino" refers to a radical of the formula - N(H)- R_g where R_g is a heterocyclyl radical as defined above, *e.g.*, oxazol-2-ylamino; piperidin-4- ylamino, and the like.

"Heterocyclylaminoalkyl" refers to a radical of the formula $-R_a$-N(H)-R_g where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e.g.* , oxazol-2-ylaminomethyl, 2-(oxazol-2-ylamino)ethyl, piperidin-4-ylaminomethyl, 2-(piperidin-4-ylamino)ethyl, and the like.

"Heterocyclylcarbonylamino" refers to a radical of the formula -N(H)-C(O)- R_g where R_g is a heterocyclyl radical as defined above, *e.g.*, piperidin-4-ylcarbonylamino, furan- 2-ylcarbonylamino, morpholin-4-ylcarbonylamino, and the like.

"Heterocyclylcarbonylaminoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-R_g where R_a is an alkyl radical as defined above and R_g is a heterocyclyl radical as defined above, *e.g.*, piperidin-4- ylcarbonylaminomethyl, 2-(furan-2-ylcarbonylamino)ethyl, 1-(morpholin-4- ylcarbonylamino)ethyl, and the like.

"Mercapto" refers to the radical -SH.

"Mercaptoalkyl" refers to a radical of the formula - R_a-SH where R_a is an alkyl radical as defined above, *e.g.*, mercaptomethyl, 2-mercaptoethyl, 3- mercaptopropyl, 2-mercaptobutyl and the like.

"Monoalkylamino" refers to a radical of the formula -N(H)R_a where R_a is an alkyl radical as defined above, *e.g.*, methylamino, ethylamino, propylamino, and the like.

"Monoalkylaminoalkyl" refers to a radical of the formula $-R_a$-N(H)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, methylaminomethyl, ethylaminomethyl, 2-(propylamino)ethyl, and the like.

"(Monoalkylamino)aralkyl" refers to a radical of the formula - R_d-N(H)R_a where R_a is an alkyl radical a defined above and R_d is an aralkyl radical as defined above, *e.g.*, (methylamino) (phenyl) methyl, 1-(ethylamino)-1-(4-methoxyphenyl)ethyl, 2-(isopropylamino)-3-(3-chlorophenyl)propyl, and the like.

"Monoarylamino" refers to a radical of the formula -N(H)R_b where R_b is an aryl radical as defined above, *e.g.*, phenylamino, (4-methoxyphenyl)amino, (3,4,5-trimethoxyphenyl) amino and the like.

"Monoarylaminoalkyl" refers to a radical fo the formula - R_a-N(H)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, phenylaminomethyl, 2-((4- methoxyphenyl)amino)ethyl, 3-((3,4,5-trimethoxyphenyl)amino)propyl, and the like.

"Monoaralkylamino" refers to a radical of the formula - N(H)R_d where R_d is an aralkyl radical as defined above, *e.g.*, benzylamino, (3,4,5- trimethoxybenzyl)amino, (4-chlorobenzyl)amino,and the like.

"Monoaralkylaminoalkyl" refers to a radical of the formula -R_a-N(H)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzylaminomethyl, (3- phenylpropyl)aminomethyl, 2-(benzylamino)ethyl, and the like.

"Monoalkylaminocarbonyl" refers to a radical of the formula -C(O)N(H)R_a where R_a is an alkyl radical as defined above, *e.g.*, methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, and the like.

"Monoalkylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(H)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, methylaminocarbonylmethyl, 2- (ethylaminocarbonyl)ethyl, 3-(propylaminocarbonyl)propyl, and the like.

"Monoarylaminocarbonyl" refers to a radical of the formula -C(O) N(H)R_b where R_b is an aryl radical as defined above, *e.g.*, phenylaminocarbonyl,(3,4,5-*tris*(trifluoromethoxy)phenyl)-aminocarbonyl, (4-chlorophenyl) aminocarbonyl, and the like.

"Monoarylaminocarbonylalkyl" refers to a radical of the formula -R_a-C(O)N(H)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, *e.g.*, phenylaminocarbonylmethyl, 2-((4-chlorophenyl) aminocarbonyl)ethyl, 3-((3,4,5-trimethoxyphenyl)aminocarbonyl)propyl, and the like.

"Monoaralkylaminocarbonyl" refers to a radical of the formula -C(O)N(H)R_d where R_d is an aralkyl radical as defined above, *e.g.*, benzylaminocarbonyl, (3, 4,5-

tris(trifluoromethoxy)benzyl)-aminocarbonyl, (4-chlorobenzyl) aminocarbonyl, and the like.

"Monoaralkylaminocarbonylalkyl" refers to a radical of the formula $-R_a-C(O)N(H)R_d$ where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above, *e.g.*, benzylaminocarbonylmethyl, 2-((4-chlorobenzyl) aminocarbonyl)ethyl, 3-((3,4,5-trimethoxybenzyl)aminocarbonyl)propyl, and the like.

"(Monoalkylaminocarbonylalkyl)aminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_a-C(O)-N(H)R_a where each R_a is independently an alkyl radical as defined above, *e.g.*, (methylaminocarbonylmethyl)aminocarbonyl, (2-(methylaminocarbonyl)ethyl)aminocarbonyl, (1-(ethylaminocarbonyl)ethyl) aminocarbonyl, and the like.

"Monoalkylalaninamido" refers to radical of the formula -N(H)-C(O)-C(CH_3)H-N(H)R_a where R_a is an alkyl radical as defined above and the attached nitrogen is designated as "*N*" and the other nitrogen (having the R_a substituent) is designated as "*N*", *e.g.*, *N'*-methylalanimido, *N'*-ethylalanimido, and the like.

"Monoalkylglycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H) R_a where R_a is an alkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen (having the R_a substituent) is designated as "*N*", *e.g.*, *N'*-methylglycinamido. *N'*-ethylglycinamido, and the like.

"(Monoarylaminocarbonyl) glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2- N(H)-C(O)-N(H)R_b where R_b is an aryl radical as defined above, *e.g.*, ((4-phenoxyphenyl)aminocarbonyl)glycinamido, ((4-chlorophenyl)aminocarbonyl) glycinamido, (phenylaminocarbonyl)glycinamido, and the like.

"(Monoarylaminocarbonyl)(alkyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(R_a)-C(O)- N(H)R_b where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above and the nitrogen to which R_a is attached is designated as "*N*", *e.g.*, ((4-phenoxyphenyl) aminocarbonyl)(*N'*-methyl)glycinamido, ((4-chlorophenyl) aminocarbonyl)(*N'*-ethyl)glycinamido, (phenylaminocarbonyl)(*N'*-methyl)glycinamido, and the like.

"(Monoaralkylaminocarbonyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2-N(H)-C(O)-N(H)R_d where R_d is an aralkyl radical as defined above, *e.g.*, ((4-phenoxybenzyl)aminocarbonyl)glycinamido, ((4-chlorobenzyl)aminocarbonyl)glycinamido, (benzylaminocarbonyl)glycinamido, and the like.

"(Monoaralkylaminocarbonyl)(alkyl)glycinamido" refers to a radical of the formula -N(H)-C(O)-CH_2- N(R_a)-C(O)- N(H)R_d where R_a is an alkyl radical as defined above and R_d is an aralkyl radical as defined above and the nitrogen to which the R_a is attached is designated as "*N* ", *e.g.*, ((4-phenoxybenzyl)aminocarbonyl)(*N'*-methyl) glycinamido, ((4-chlorobenzyl)aminocarbonyl)(*N'*-ethyl)glycinamido, (benzylaminocarbonyl)(*N'*-methyl)glycinamido, and the like.

"Monoalkylureido" refers to a radical of the formula -N(H)-C(O)-N(H) R_a or a radical of the formula -N(R_a)-C(O)-NH_2 where R_a is an alkyl radical as defined above and the attaching nitrogen is designated as " *N*" and the other nitrogen is designated as "*N*", *e. g.*, *N'*-methylureido, *N'*-ethylureido, *N'*- propylureido, *N*-methylureido, *N*-ethylureido, *N*- propylureido, and the like.

"Monophenylureido" refers to a radical of the formula -N(H)-C(O)-N(H)R_h where R_h is a phenyl radical as defined above, and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.* , *N'*-phenylureido, *N'*-(4-nitrophenyl)ureido, *N'*-(3-chlorophenyl)ureido, and the like.

"Monobenzylureido" refers to a radical of the formula -N(H)-C(O)-N(H)- CH_2-R_h where R_h is a phenyl radical as defined above, and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as " *N*"", *e. g.*, *N'*-benzylureido, *N'*-(4-nitrobenzyl) ureido, *N'*-(3-chlorobenzyl)ureido, and the like.

"Monohaloalkylureido" refers to a radical of the formula -N(H)-C(O)-N(H) R_f or a radical of the formula -N(R_f)-C(O)-NH_2 where R_f is a haloalkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N* ", *e.g.*, *N'*-chloromethylureido, *N'*-(2,2- difluoroethyl)ureido, *N'*-(3-chloropropyl)ureido, *N*- (trifluoromethyl)ureido, *N*-(pentafluoroethyl)ureido, *N*-(3- iodopropyl)ureido, and the like.

"Monoarylureido" refers to a radical of the formula -N(H)-C(O)-N(H)R_b or a radical of the formula -N(R_b) -C(O)-NH_2 where R_b is an aryl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.* , *N'*-phenylureido, *N'*- (4-methoxyphenyl)ureido, *N'*-(3-chlorophenyl)ureido, *N*- phenylureido, *N*-(2-trifluoromethylphenyl)ureido, *N*-(4-chlorophenyl) ureido, and the like.

"Monoaralkylureido" refers to a radical of the formula -N(H)-C(O)-N(H)R_d or a radical of the formula -N(R_d) -C(O)-NH_2 where R_d is an aralkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.*, *N'*- benzylureido, *N'*-(4-methoxybenzyl) ureido, *N'*-(3-

chlorobenzyl)ureido, *N*-benzylureido, *N*-(2- trifluoromethylbenzyl)ureido, *N*-(4-chlorobenzyl)ureido, and the like.

"(Monoalkyl)(monoaryl)ureido" refers to a radical of the formula -N(R_a)-C(O)-N(R_b)H, or a radical of the formula -N(R_b)-C(O)-N(R_a)H, or a radical of the formula -N(H)-C(O)-N(R_a)(R_b) where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above, and where the attaching nitrogen is designated as "*N* " and the other nitrogen is designated as *"N"*, e.g., *N*-methyl- *N'*-phenylureido, *N*-phenyl-*N'*-ethylureido, *N*- methyl-*N'*-(4-fluorophenyl)ureido, *N'*-ethyl-*N'*-(3-cyanophenyl)ureido, and the like.

"Monoalkylureidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-N(H)R_a or a radical of the formula -R_a- N(R_a)-C(O)-NH_2 where R_a is an alkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.* , *N'*-methylureidomethyl, 2-(*N'*- ethylureido)ethyl, 1-(*N'*-propylureido)ethyl, *N*- methylureidomethyl, 2-(*N*-ethylureido)ethyl, 1-(*N*-propylureido)ethyl, and the like.

"Monohaloalkylureidoalkyl" refers to a radical of the formula - R_a-N(H)-C(O)-N(H) R_f or a radical of the formula -R_a -N(R_f)-C(O)-NH_2 where R_a is an alkyl radical as defined above and R_f is a haloalkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.*, *N'*- chloromethylureidomethyl, 2-(*N'*-(2,2-difluoroethyl)ureido)ethyl, 1- (*N'*-(3-chloropropyl)ureido)ethyl, *N*-(trifluoromethyl) ureidomethyl, 2-(*N*-(pentafluoroethyl)ureido)ethyl, 1-(*N*-(3- iodopropyl)ureido)ethyl, and the like.

"Monoarylureidoalkyl" refers to a radical of the formula -R_a-N(H)-C(O)-N(H) R_b or a radical of the formula -R_a -N(R_b)-C(O)-NH_2 where R_a is an alkyl radical as defined above and R_b is an aryl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.*, *N'*-phenylureidomethyl, 2-(*N'*-(4- methoxyphenyl)ureido)ethyl, 1-(*N'*-(3-chlorophenyl)ureido)ethyl, *N*-phenylureidomethyl, 2-(*N*-(2-trifluoromethylphenyl)ureido) ethyl, 1-(*N*-(4-chlorophenyl)ureido)ethyl, and the like.

"Monoaralkylureidoalkyl" refers to a radical of the formula -R_a -N(H)-C(O)-N(H)R_d or a radical of the formula -R_a-N(R_d)-C(O)-NH_2 where R_a is an alkyl radical as defined above and R_b is an aralkyl radical as defined above and the attaching nitrogen is designated as "*N*" and the other nitrogen is designated as "*N*", *e.g.*, *N'*-benzylureidomethyl, 2-(*N'*-(4-methoxybenzyl)ureido)ethyl, 1-(*N'*-(3-

chlorobenzyl)ureido)ethyl, *N*- benzylureidomethyl, 2- (*N*-(2-trifluoromethylbenzyl)ureido)ethyl, 1-(*N*-(4- chlorobenzyl)ureido)ethyl, and the like.

"Monophenylamino" refers to an amino radical substituted by a phenyl radical as defined herein.

"Monophenylalkylamino" refers to an amino radical substituted by a phenylalkyl group as defined below, *e.g.*, benzylamino, 2-(benzyl)butylamino, and the like.

"Monophenylaminoalkyl" refers to an alkyl radical as defined above substituted by a monophenylamino group as defined above, *e.g.,* (phenytamino)methyl, 2-(1-(phenyl)ethylamino) ethyl, and the like.

"Monophenylalkylaminoalkyl" refers to an alkyl radical as defined above substituted by a monophenylalkylamino group as defined above, *e.g.*, (benzylamino)methyl, 2-(2-benzyl)butylamino)ethyl, and the like.

"Nitro" refers to the radical $-NO_2$.

"Oxo" refers to the subsituent =O.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Phenyl" refers to the benzene radical optionally substituted by one or more substituents selected from the group consisting of hydroxy, halo, alkyl, haloalkyl, alkoxy, alkenyl, nitro, cyano, amino, monoalkylamino, dialkylamino, alkylcarbonyl, carboxy, alkoxycarbonyl, and aminocarbonyl.

"Phenoxy" refers to the radical of the formula $-OR_h$ where R_h is phenyl as defined above.

"Phenylalkyl" refers to an alkyl radical as defined above substituted by a phenyl radical, *e.g.*, benzyl, and the like.

"Phenylalkenyl" refers to an alkenyl radical as defined above substituted by a phenyl radical, *e.g.*, 3-phenylprop-2-enyl, and the like.

"Phenylalkoxy" refers to a radical of the formula $-OR_i$ where R_i is a phenylalkyl radical as defined above, *e.g.*, benzyloxy, and the like.

"Phenylalkoxyalkyl" refers to an alkyl radical as defined above substituted by a phenylalkoxy radical as defined above, *e.g.*, benzyloxymethyl, and the like.

"Phenylcarbonyl" refers to a radical of the formula -C(O)-R_h where R_h is a phenyl radical as defined above, *e.g.*, (4-chlorophenyl) carbonyl, (4-fluorophenyl)carbonyl, and the like.

"Phenylaminocarbonyl" refers to a radical of the formula -C(O)-N(H)-R_h where R_h is a phenyl radical as defined above, *e.g.*, (4-chlorophenyl)aminocarbonyl, (4-methoxyphenyl)aminocarbonyl, and the like.

"Pharmaceutically acceptable counterion" " refers to those anions which retain the biological effectiveness and properties of the parent compound. which are not biologically or otherwise undesirable. Examples of such anions may be found in Berge, S.M. *et al.*, *Journal of Pharmaceutical Sciences* (1977), Vol. 66, No. 1, pp. 1-19.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, pyruvic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, zinc, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2- diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*- ethylpiperidine, polyamine resins and the like.

Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"THF" refers to tetrahydrofuran.

"Therapeutically effective amount" refers to that amount of a compound of formula (I) which, when administered to a human female in need of such administration, is sufficient to effect treatment, as defined below, for endometriosis which are alleviated by the CCR-1 antagonist activity. The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the disorder and its severity, and the age of the human female to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein cover the treatment of endometriosis disorder in a human female; and include:

(i) preventing the disorder from occurring in a human female, in particular, when such human female is predisposed to the disorder but has not yet been diagnosed as having it;

(ii) inhibiting the disorder, *i.e.,* arresting its development; or

(iii) relieving the disorder, *i.e.,* causing regression of the disorder.

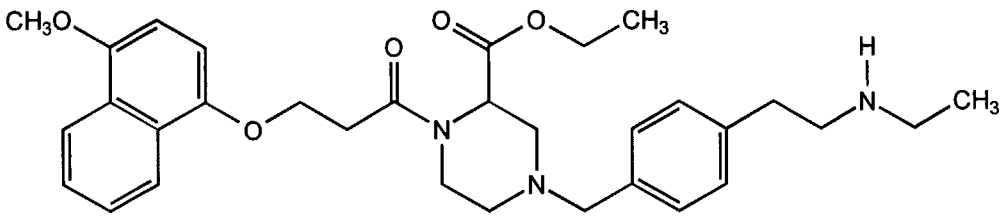
"Ureido" refers to a radical of the formula -N(H)-C(O)-NH_2.

"Ureidoalkyl" refers to a radical of the formula -R_a-N(H)C(O)NH_2 where R_a is an alkyl radical as defined above, *e.g.*, ureidomethyl, 2- (ureido)ethyl, 3-(ureido)propyl, and the like.

It is understood from the above definitions and examples that for radicals containing a substituted alkyl group any substitution thereon can occur on any carbon of the alkyl group.

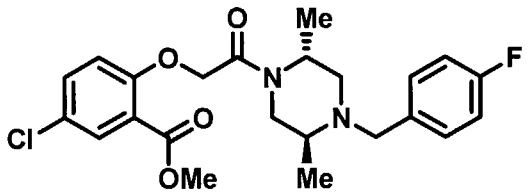
The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms in their structure. The compounds of the invention and their pharmaceutically acceptable salts may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of this invention. Absolute configuration of certain carbon atoms within the compounds, if known, are indicated by the appropriate absolute descriptor *R* or *S*. The descriptor "*trans*" is used to indicate that the R^{1a} or the R^{1b} substituents are on opposite sides of the piperazine plane. The descriptor "*cis*" is used to indicate that the R^{1a} or the R^{1b} substituents are on the same side of the piperazine plane.

The nomenclature used herein is a modified form of the I.U.P. A.C. system wherein the compounds of the invention are named as piperazine derivatives. For example, a compound of formula (Ia) wherein R^6 is -C(O)-, R^5 is ethylene, R^4 is -O-, R^{1a} is in the 2-position of the piperazine ring and is ethoxycarbonyl, R^2 is 2-(ethylamino)ethyl in the 4-position of the phenyl ring and R^3 is naphthalen-1-yl substituted at the 4-position by methoxy, *i.e.*, the compound of the following formula:



is named herein as 1-(2-((4-methoxynaphthalen-1-yl)oxy)ethyl)carbonyl-2-ethoxycarbonyl-4-(4-(2-(ethylamino)ethyl)benzyl)piperazine or with the nomenclature according to the following example:

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester



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Utility and Administration

A. Utility

The CCR1 antagonists according to the present invention are potent inhibitor of disease score in animal models and cell culture models of endometriosis.

The compounds of the invention inhibit the chemokine (MIP-1α and RANTES) induced migration of monocytes and macrophages and are therefore useful in the treatment and prevention of endometriosis in human females.

Clinical studies are performed to investigate the benefit of the CCR1 antagonists according to the present invention in the treatment and prevention of endometriosis.

B. Testing

To demonstrate that the compounds inhibit the activity of MIP-1α or RANTES several assays may be employed. One assay utilizes a microphysiometer, which uses a patented silicon-based light addressable potentiometric sensor to continuously monitor subtle changes in extracellular pH levels. These changes result from the generation of acidic metabolites excreted by living cells into their immediate microenvironment during basal and stimulated conditions. It has been previously demonstrated by microphysiometry that THP-1 cells, which have been shown to express the chemokine receptors, CCR1 and CCR2, respond dose-responsively to their respective chemokines, including MIP-1α, RANTES and MCP-1 (a ligand for CCR2). See, *e.g.,* Hirst, M. *et al.,* "Chemokine receptors," *Journal of NIH Research* (1995), Vol. 80. Another assay which may be used to demonstrate the ability of the compounds to inhibit the activity of MIP- 1α and RANTES is based on the measurement of intracellular Ca^{2+} concentrations and/or increases in intracellular [^{3}H] inositol phosphate release from MIP-1α and RANTES stimulated cells. Ligand binding to the CCR1 receptor results in G- protein induced activation of phospholipase C, which leads to the conversion of phosphatidyl inositol phosphate to inositol phosphate and diacyglycerol. Inositol phosphate in turn binds to a receptor located at intracellular sites to release Ca^{2+} into the cytoplasm. In addition to Ca^{2+} concentration increases due to release from intracellular stores, binding of inositol phosphate to its receptor leads to an increased flux of extracellular calcium across the membrane and into the cell. Thus the activation of the CCR1 receptor by MIP-1α and RANTES and, subsequently, inhibition of the activation by the compounds of the invention can be determined by assaying for an increase in free intracellular Ca^{2+} levels. Typically this can be achieved by the use of calcium-sensitive fluorescent probes such as quin-2, fura-2 and indo-1. Alternatively, functional activation or inhibition of the activation of the CCR1 receptor can be measured by quantitation of [^{3}H] inositol phosphate release from the cell pre-labeled with [^{3}H] inositol.

Standard *in vitro* binding assays may be employed to demonstrate the affinity of the compounds for the CCR1 receptor (thereby inhibiting the activity of MIP- 1α and RANTES by competitive binding to the receptor). See, *e.g.* , Neote, K. *et al.*, Cell (1993), Vol. **72**, pp. 415-425. One particular assay employs the use of HEK293 cells which have been stably transfected to express human CCR1 receptor.

Endometriosis cell culture models with human U937 cells and primary human peritoneal macrophages in combination with a peritoneal fluid pool from patients with endometriosis are used as tools to investigate the effects of CCR1 antagonists on inhibition and reduction of chemokine induced monocites/macrophages migration.

Determination of CCR1 mRNA in endometrial and endometriotic tissue samples can be performed for example by real-time quantitative RT-PCR analysis.

Standard *in vivo* assays which may be employed to demonstrate the compounds usefulness in the treatment of endometriosis is for example the animal model of surgically induced endometriosis in intact cycling rats as also reported in the literature (15).

Other very important models to assay the compounds usefulness *in vivo* in the treatment of endometriosis are models in primates.

In comparison to rodents, primates (Baboon, Cynomolgous, Rhesus monkeys) have a menstrual cycle, are continuos breeders and develop spontaneous endometriosis. In addition, endometriosis can also be induced for example by the inoculation of menstrual tissue or by autologous transplantation of endometrial tissue into the peritoneal cavity (9, 10). Furthermore it is possible to isolate and characterize their peritoneal fluid.

Own experimental data show for example that non human primates express the receptor CCR1. As in human, it could be shown that CCR1 is localized on tissue infiltrating immune cells in endometriotic lesions /grafts. By immunohistochemical staining and cell counting it could be demonstrated, that the number of CCR1-positive cells is up-regulated in endometriotic grafts of Rhesus monkey (see Figure 6). The advantage of the non human primate model is the morphology of endometriotic lesions (red lesions, white lesions, endometrioma) resembling those found in women and reflecting the human situation. Studies in non human primate are performed to evaluate activity of CCR1 antagonist according to the present invention.

C. General Administration

Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out *via* any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally, topically, transdermally, or rectally, sublingually, intramuscular, subcutaneously, intravaginally or intravenously in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the

invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of one or more suitable pharmaceutical excipient(s). Preferably, the composition will be about 5% to 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

The preferred route of administration is oral, using a convenient daily dosage regimen which can be adjusted according to the degree of severity of the disease- state to be treated. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, is formed by the incorporation of any of the normally employed excipients.

Such excipients include non- toxic and chemically compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers, and the like, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, cyclodextrin, propyl gallate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.

Preferably such compositions will take the form of capsule, caplet or tablet and therefore will also contain a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as croscarmellose sodium or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose ether derivatives, and the like.

The compounds of the invention, or their pharmaceutically acceptable salts, may also be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier that slowly dissolves within the body, *e.g.*, polyoxyethylene glycols and polyethylene glycols (PEG), *e.g.*, PEG 1000 (96%) and PEG 4000 (4%), and propylene glycol.

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., a compound(s) of the invention (about 0.5% to about 20%), or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in

a carrier, such as, for example, water, saline, aqueous dextrose, aqueous cyclodextrin, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences,* 18th Ed., (Mack Publishing Company, Easton, Pennsylvania, 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of edometriosis alleviated by the inhibition of the activity of the chemokines, MIP-1α and RANTES.

The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease- states, and the host undergoing therapy.

Generally, a therapeutically effective daily dose is from about 0.014 mg to about 14.0 mg/kg of body weight per day of a compound of the invention, or a pharmaceutically acceptable salt thereof; preferably, from about 0.14 mg to about 10.0 mg/kg of body weight per day; and most preferably, from about 1.4 mg to about 7.0 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 1.0 mg to about 1.0 gram per day of a compound of the invention, or a pharmaceutically acceptable salt thereof, preferably from about 10 mg to about 700 mg per day, and most preferably from about 100 mg to about 500 mg per day.

Description of the drawings

Other features and advantages of the invention will become apparent from the following description of some favourable forms of embodiment of the invention, provided purely as a non-restricting example, with reference to the accompanying drawings, in which:

Figure 1 shows the localization of CCR1 in endometriotic lesions and endometrial tissue.

In endometriotic-peritoneal lesions the chemokine receptor CCR1 is localized on tissue infiltrating immune cells (A-D). CCR1 expressing immune cells were not detected in endometrium of patients with endometriosis (E) as well as in endometrium of non endometriotic controls (G). Negative control (F, H).

Figure 2 shows analysis data of CCR1 mRNA expression in endometriotic lesions and endometrium from patients with endometriosis.
Controls: line 1, 2 and 3 represent endometrium from non endometriotic women. In these tissue samples the CCR1 mRNA expression is low. Lanes 4-9 are tissue samples from women with endometriosis.
In brackets: endometrium and endometriotic lesion from the same patient.
The CCR1 mRNA expression is up-regulated in endometriotic lesions (lines 5, 7, 9) in comparison to the samples of endometrium (lines 4, 6, 8).

Figure 3 shows the characterization of immune cells expressing CCR1.
Co-immunostainings with monoclonal antibodies for CCR1 (Fig. A and D), CD4 (Fig. 4 B) and CD68 (Fig. 4 E) confirm that the chemokine receptor CCR1 is expressed on monocytes, and macrophages (CD 68) T helper cells (CD4) (Fig.4 C and F).

Figure 4 shows the effects of the CCR1 antagonist on area and volume of peritoneal endometriotic lesions in rats with experimental induced endometriosis.
Controls: White bar: animals were treated 4 weeks with vehicle, propylene glycol (0.5 mg/kg). Dotted bar: Animals received an anti estrogen (11β-Fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10thia-6azapentadecyl)-estra-1,3,5(10)-triene-3,17β-diol) (1 mg/kg). Striped bar: Treatment of animals with a CCR1 antagonist according to the present application and particularly with (2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as sulphate salt (50 mg/kg). In comparison to the vehicle control, the data show that compounds according to the present invention reduce effects on area and volume of peritoneal endometriotic cysts in rat.

Figure 5a and 5b CCR1 mRNA expression in endometriosis rat model.

Figure 5a shows the expression of CCR1 mRNA in endometriotic cysts of mesenterium and peritoneum. Operated rat uterus and rat ovary were used as controls (1-3 animal 1; 4-7 animal 2). In comparison to uterus and ovary, CCR1 mRNA expression is up-regulated in cysts of peritoneum and mesenterium.

Figure 5b shows the expression of CCR1 ligand RANTES in treated and untreated animals. Control group (untreated animals): RANTES is highly expressed in mesenterial and peritoneal lesions. The treatment with CCR1 antagonists induces after 3 weeks of treatment a significant downregulation of RANTES mRNA in peritoneal and mesenterial cysts of rat. Results represent mean values from three animals.

Figure 6 a and 6b: Number and localization of CCR1 stained cells in endometrium and endometriotic grafts / lesions of Rhesus monkey.

Figure 6A: CCR1 positive cell counts. The cell counts represent the average number of CCR1 positive cells per section counted with an ocular grid . The cells were identified by immunohistochemical staining. Six sections were counted n=3 animals. The number of CCR1 expressing cells is up-regulated in endometriotic grafts during the menstrual cycle in rhesus monkey.

Figure 6b: Localisation of CCR1 stained cells in endometriotic grafts/ lesions and in endometrium. In comparison to the endometrium, the number of CCR1 expressing cells is enhanced in endometriotic grafts/lesions.

Preferred Embodiments

One aspect of the invention are the compounds of formula (Ia) as defined above in the Summary of the Invention. Of these compounds, a preferred group of compounds of formula (Ia) is that group of compounds wherein:

R^3 is

a carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, arylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, hydroxyalkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy,

aminoalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy) cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy) aralkyl, (monoalkylamino)aralkyl, (hydroxyalkyl)hioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkylamino, heterocyclylamino, (cycloalkylalkyl)amino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl) aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, (hydroxyalkoxy)carbonyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, dialkylaminocarbonyloxyalkyl, alkylcarbonylalkyl, arylcarbonylalkyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, (aminocarbonylalkyl) aminocarbonyl, (monoalkylaminocarbonylalkyl) aminocarbonyl, (carboxyalkyl) aminocarbonyl, (alkoxycarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, hydroxyamidino, guanidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, monohaloalkylureido, (monoalkyl)(monoaryl)ureido, dialkylureido, diarylureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl) ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl) glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido,

(alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, glycinamidoalkyl, alaninamido, monoalkylalaninamido, alaninamidoalkyl, heterocyclyl and heterocyclylalkyl.

Of this group of compounds, a preferred subgroup of compounds is that group of compounds wherein:

R^4 is

-O-, -N(R^7)- or -C(R^8)-;

R^5 is

an alkylene chain;

R^7 is

selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, aralkylcarbonylamino, (aralkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, aralkylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, (aralkylcarbonyl)(alkyl)aminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, dialkylureido. ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl.

Of this subgroup of compounds, a preferred class of compounds is that group of compounds wherein:

R^4 is

-O-;

R^5 is

methylene; and

R^6 is

-C(O)-.

Of this class of compounds, a preferred subclass of compounds is that group of compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, aminoalkoxy, cycloalkyl, cycloalkylaminoalkyl, aralkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy)carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl) aminocarbonyl,

(aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonylalkyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido (monoarylaminocarbonyl) (alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

Preferred compounds within this subclass of compounds are selected from the group consisting of the following compounds:

(2*S*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1- ((phenoxy)methyl)carbonyl-2-ethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- (methoxymethyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-((acetylamino)methyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((4-fluorobenzyl)amino)ethyl)4- (4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl- 2-(2-((methyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methyl-5- methylpiperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(ethoxycarbonyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(methoxycarbonyl)methylpiperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((methoxy) methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-(methoxy)ethyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxypropyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-hydroxybut-4-ynyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(2-hydroxyethyl)piperazine ;

1-((4- chlorophenoxy)methyl)carbonyl-3-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;

(2*S*, 5*R*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(2*S*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*,5*S*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(2-methylthio)ethylpiperazine;

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy) methylpiperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((2-hydroxyethyl)thio) methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-(*N'*-(ethoxycarbonylmethyl) ureido)methyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-((amino)carbonyloxy)methyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((acetyl) methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl) piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxybutyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)-5-((diethylamino)methyl)piperazine;

(2*R*, 5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) -5-((dimethylamino)methyl)piperazine;

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine;

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1- yl)methyl)piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6- dimethylpiperazine;

1-((phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

1-((2-(acetylamino)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxypropyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut-3-enyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-3- trifluoromethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)- 1-((4-chloro-2-((4-(2,5-di(trifluoromethyl)phenylcarbonyl)piperazin-1-yl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

Of this subclass of compounds, a preferred group of compounds is that group of compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, hydroxyalkenyl, cyanoalkyl, alkoxyalkyl, monoalkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, aryloxyalkylcarbonyloxyalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, alkyl, alkoxy, formyl, nitro, cyano, aminoalkoxy, cycloalkylaminoalkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl,

alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy) carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido, (monoarylaminocarbonyl) (alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

Preferred compounds within this group of compounds in this subclass group of compounds are selected from the group consisting of the following compounds:

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-ethylpiperazine;

(2*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

(2*S*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

4-(4-fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl) spiro[cyclopropane-1,2'-piperazine];

1-((4-chlorophenoxy)methyl) carbonyl-2-hydroxymethyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-(methoxy)ethyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2- methylpropyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5- methylpiperazine;

(2*R*)-1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

(2*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- (hydroxymethyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(((methyl)ureido) methyl)piperazine;

(2*R*,3*R*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;

(*cis*)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4- fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5- methylpiperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((hydroxy)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((methoxy)methyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine;

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxyethyl)piperazine;

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyprop-3-enyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl) piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl)piperazine;

(3*S*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3,5-dimethylpiperazine; 1-((4-chloro-3-nitrophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-hydroxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((ethyl) (1-methylbutyl)aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(benzylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((1-methylbutyl)amino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*iso*- propylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-nitrophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-methylphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (acetylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(phenylsulfonyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- ((methyl)(ethyl)amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (dimethylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(oxazol-2-ylaminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- (morpholin-4-ylmethyl)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-bromo-2-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2-methoxycarbonylphenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methyl-2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methyl-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine:

(*trans*)-1-((3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-nitro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl- 2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- nitro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-4,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl)piperazine;

(*trans*)-1-((4- methyl-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((3-chloro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2- (2-azidoethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(phthalimido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(maleimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4- (benzylcarbonyl)piperazin-1-yl)methyl)phenoxy)methyl)-carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((4-((2,3,4-trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2,6-difluorophenyl)ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (ethenylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (cyclopropylcarbonylamino)phenoxy)methyl)carbonyl-2.5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (cyclopentylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((furan-2- yl)carbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methoxyphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*- (methoxycarbonylmethylcarbonyl)-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2-methoxycarbonylethyl)carbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl) aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(3-trifluoromethyl-4-fluorophenyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4-methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-chlorophenyl)carbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4-fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,3- difluorophenylcarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-diflurophenylcarbonyl)glycinamido) phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl) aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(3- chloropropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'* -(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((3-fluorophenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'* -(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(2*S*)-1-((4-chloro- 2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine.

A more preferred group of compounds in this subclass group of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl and hydroxyalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxy, formyl, nitro, cycloalkylaminoalkyl, hydroxyalkyl, amino, alkylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, alkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, hydroxyamidino, ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, alaninamido, and heterocyclylalkyl.

Preferred compounds within this more preferred group of compounds in this subclass group of compounds are selected from the group consisting of the following compounds:

(*trans*)-1-((4- chloro-3-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2 *S*,5*R*)-1-((4-bromo-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1- ((3-hydroxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*S*,5*R*)-1-((4-nitro-3- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2R)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(2-hydroxyethyl)piperazine;

(*trans*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro- 3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine;

(2*R*,6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,6-dimethylpiperazine;

(*trans*)-1-((4-chloro-2- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-hydroxyethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- (acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino- 4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2- (methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2R)-1-((4-chloro-2-(glycinamido) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-ethyluredio)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-amino-5-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochforide salt;

(*trans*)-1-((4-chloro-2- (((ethyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(((diethyl)amino) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((cyclopropyl)amino)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((dimethyl)amino)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((methyl)amino)methyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4- methylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylamino)ethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylsulfonyl)(methyl)aminoethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5 *S*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(imidazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(triazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(tetrazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((morpholin-4-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2- aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4- chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2- aminoethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-aminocarbonylphenyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (hydroxyamidino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(methoxymethylcarbonyl)glycinamido)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

The most preferred group of compounds within this subclass group of compounds are those compounds wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4- position with chloro and at the 2-position by aminocarbonyl, ureido, or glycinamido.; namely, the compounds selected from the group consisting of the following compounds:

(2*R*,5*S*)- 1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2- (ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

Of the subgroup of compounds as set forth above, another preferred class of compounds are those compounds wherein:

R^4 is

-N(R^7)-;

R^5 is

methylene;

R^6 is

-C(O)-; and

R^7 is

selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl.

Of this class of compounds, a preferred subclass of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, aminoalkoxy, cycloalkyl, cycloalkylaminoalkyl, aralkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino. dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl) aminoalkyl, alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy)carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonylalkyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl) glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

A preferred group of compounds in this subclass group of compounds is that group wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, hydroxyalkenyl, cyanoalkyl, alkoxyalkyl, monoalkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, aryloxyalkylcarbonyloxyalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, alkyl, alkoxy, formyl, nitro, cyano, aminoalkoxy, cycloalkylaminoalkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy) carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido, (monoarylaminocarbonyl) (alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

A more preferred group in this subclass group of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl and hydroxyalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxy, formyl, nitro, cycloalkylaminoalkyl, hydroxyalkyl, amino, alkylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, alkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, hydroxyamidino, ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, alaninamido, and heterocyclylalkyl.

An even more preferred group of compounds in this subclass group of compounds are those compounds wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido. Preferred compounds in this group selected from the group consisting of the following compounds:

(*trans*)-1-((4-chlorophenylamino)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine

1-((4-chloro-2-(aminocarbonyl) phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; and

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

Of the subgroup of compounds as set forth above, another preferred class of compounds are those compounds wherein:

R^4 is

- $C(R^8)_2$-;

R^5 is

methylene;

R^6 is

- C(O)-; and

each R^8 is

independently selected from the group consisting of hydrogen, alkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, ureidoalkyl, monoalkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, and dialkylaminoalkyl.

A preferred subclass of compounds of this class of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, aminoalkoxy, cycloalkyl, cycloalkylaminoalkyl, aralkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl) aminoalkyl, (cycloalkyalkyl)aminoalkyl,

alkoxycarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl)(alkyl)aminoalkyl, heterocyclylaminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy)carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl) aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonylalkyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

A preferred group of compounds within this preferred subclass of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl, cycloalkyl, hydroxyalkyl, hydroxyalkenyl, cyanoalkyl, alkoxyalkyl, monoalkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, aryloxyalkylcarbonyloxyalkyl, and heterocyclylalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, alkyl, alkoxy, formyl, nitro, cyano, aminoalkoxy, cycloalkylaminoalkyl, hydroxyalkyl, (monoalkylamino)aralkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, monoaralkylamino, alkylcarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino,

alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, (cycloalkyalkyl)aminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, carboxy, alkoxycarbonyl, alkylcarbonyl, (hydroxyalkoxy) carbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, hydroxyamidino, ureido, monoalkylureido, monoarylureido, monoaralkylureido, (monoalkyl)(monoaryl)ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl)glycinamido, (monoarylaminocarbonyl) glycinamido, (monoarylaminocarbonyl)(alkyl)glycinamido, alaninamido, heterocyclyl and heterocyclylalkyl.

A more preferred group of compounds within this subclass of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of alkyl and hydroxyalkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, alkyl, alkoxy, formyl, nitro, cycloalkylaminoalkyl, hydroxyalkyl, amino, alkylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, alkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, monoarylaminocarbonyl, (aminocarbonylalkyl)aminocarbonyl, (aminoalkyl)aminocarbonyl, hydroxyamidino,

ureido, (haloalkylcarbonyl)ureido, ureidoalkyl, glycinamido, monoalkylglycinamido, aminocarbonylglycinamido, (alkoxyalkylcarbonyl)glycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, alaninamido, and heterocyclylalkyl.

An even more preferred group of compounds of this subclass group of compounds are those compounds wherein:

R^2 is

4-fluoro;

R^3 is

phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido; and

one R^8

is hydrogen and the other R^8 is selected from the group consisting of amino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, ureidoalkyl, monoalkylureidoalkyl, monohaloalkylureidoalkyl, and aminoalkyl.

Preferred compounds in this even more preferred group are those compounds selected from the group consisting of the following compounds:

(*trans*)-1-(2-(4-chlorophenyl)-3-(methylsulfonylamino)propyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- (methylsulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(acetylamino) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(amino)ethyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)- 2-(ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(ureido)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(amino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*t*- butoxycarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- ((ethoxycarbonylmethylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- (*N'*-iso-propylureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(*N'*-(2- chloroethyl)ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-((2- nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- ((2,4-dinitrophenyl)sulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- (cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-((2- cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- ((2-methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (*t*-butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (ethyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl) ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

Of the compounds of formula (Ia), another preferred group of compounds are those compounds wherein:

R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, alkyl, alkylsufonyl, arylsulfonyl, alkoxy, hydroxyalkoxy, haloalkyl, formyl, nitro, cyano, haloalkoxy, alkenyl, alkynyl, aryl, aralkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, alkylcarbonylamino, alkoxycarbonylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, (alkoxycarbonyl)(alkyl)amino, alkylsulfonylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl) aminoalkyl, alkoxycarbonylaminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, guanidino, ureido, monoalkylureido, ureidoalkyl, monoalkylureidoalkyl, and glycinamido.

Of this group of compounds, a preferred subgroup of compounds is that group of compounds wherein:

R^4 is

-O-, - $N(R^7)$- or -$C(R^8)$-;

R^5 is

an alkylene chain;

R^7 is

selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkylcarbonyl, alkylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, and alkoxycarbonyl; and

each R^8

is independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, amino, monoalkylamino, dialkylamino, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkylalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylcarbonylamino, alkoxycarbonylalkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, aralkylcarbonylamino, (aralkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, cycloalkylcarbonylaminoalkyl, alkoxycarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, aralkylcarbonylaminoalkyl, heterocyclylcarbonylaminoalkyl, (aralkylcarbonyl)(alkyl)aminoalkyl,

arylsulfonylamino, alkylsulfonylaminoalkyl, ureido, monoalkylureido, monohaloalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, monohaloalkylureidoalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, and dialkylaminocarbonylalkyl.

Of this subgroup of compounds, a preferred class of compounds are those compounds wherein:

R^4 is

-O-;

R^5 is

methylene; and

R^6 is

-C(O)-.

Of this class of compounds, a preferred subclass group of compounds are those compounds wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, alkyl, cycloalkyl, cycloalkylaminoalkyl, haloalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, alkoxyalkyl, aralkoxyalkyl, alkylthioalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, azidoalkyl, monoalkylureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, and heterocyclylalkyl; and

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo.

A preferred group of compounds in this preferred subclass group of compounds are those compounds wherein R^3 is selected from the group consisting of azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnofinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-

oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone.

A more preferred group of compounds in this preferred subclass of compounds are those compounds wherein R^3 is benzopyranyl, benzopyranonyl, benzfuranyl, benzofuranonyl, quinolinyl, indolyl, indolinyl, oxazolyl, imidazolyl, or benzothienyl.

A preferred compound in this more preferred group is (*trans*)-1-((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine.

Another aspect of the invention is a method of treating edometriosis in a human female, which method comprises administering to a human female in need of such treatment a therapeutically effective amount of a compound of formula (Ia) as described above.

Preparation of Compounds of The Invention

The following Reaction Schemes are directed to the preparation of compounds of formula (Ia). It is understood that those compounds of the invention which are not specifically prepared in the following Reaction Schemes may be prepared by similar synthetic processes with the appropriately substituted starting materials and reagents. It is also understood that in the following descriptions, combinations of the various substituents (*e.g.* , R^{1a}, R^2 and R^3 substituents) on the depicted formulae are permissible only if such combinations result in stable compounds.

For the purposes of convenience only, preparation of compounds of the invention where R^3 is only phenyl are illustrated below. It is understood that other R^3 groups (including other carbocyclic and heterocyclic ring systems) may be prepared in a similar manner.

It is also understood that during the preparation of the compounds of the invention, as described below, additional reactive groups (for example, hydroxy, amino or carboxy groups) on the intermediate compounds utilized in the preparation may be protected as needed by the appropriate protecting group by treating the intermediate compound prior to the desired reaction with the appropriate protecting group precursor by methods known to those of ordinary skill in the art. The protecting groups may then be removed as desired by methods known to those of ordinary skill in the art, for example, by acidic or basic hydrolysis. Such protecting groups and methods are described in detail in Greene, T.W. and Wuts, P.G.M., "Protective Groups in Organic Synthesis", 2nd

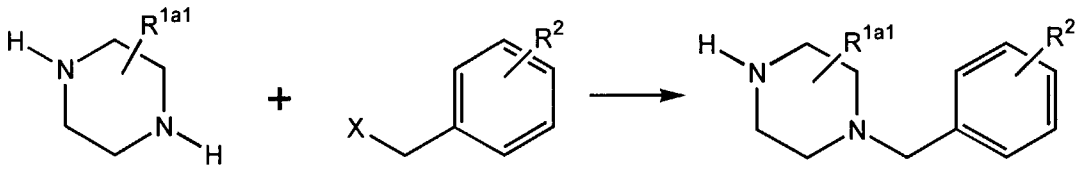
Edition, 1991, John Wiley & Sons. Also, dimethylpiperazines can be prepared in an asymmetric synthesis according to the method outlined in Mickelson, J.W., Belonga, K.L., Jacobsen, E.J., *Journal of Organic Chemistry* (1995), Vol. 60, pp. 4177-4123.

It should be noted that the only difference in the two groups of compounds covered by formula (Ia) and formula (Ib) as described below is the required substitution of the piperazine ring in the compounds of formula (Ia). Accordingly, it is understood that, unless otherwise indicated, the following Reaction Schemes directed to the preparation of the compounds of formula (Ib) may be used to prepare compounds of formula (Ia) .

A. Preparation of Compounds of Formula (C)

Compounds of formula (C) are intermediates in the preparation of the compounds of the invention. They are prepared according to the following Reaction Scheme 1 wherein R^{1a1} is one or more independently selected R^{1a} substituents as described above in the Summary of the Invention for compounds of formula (Ia) (except that R^{1a1} can not be aminoalkyl or monoalkylaminoalkyl unless appropriately protected); X is chloro, bromo or iodo; and R^2 is as described above for compounds of formula (Ia):

Reaction Scheme 1



(A) (B) (C)

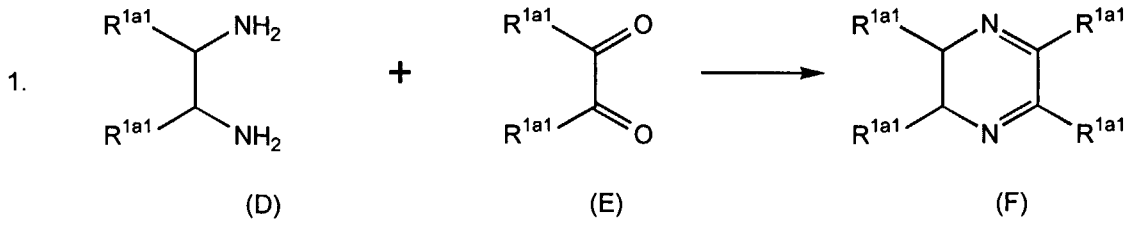
The compounds of formula (A) and formula (B) are commercially available, *e.g.*, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared according to methods known to those of ordinary skill in the art.

In general, the compounds of formula (C) are prepared by treating a compound of formula (A) in an organic solvent, such as methylene chloride, with an equimolar amount of a compound of formula (B). The reaction mixture is stirred for about 10 to 20 hours at ambient temperature. The reaction mixture is then concentrated to afford a residue which is dissolved in an organic solvent. The compound of formula (C) is isolated from the solution by standard isolation techniques, for example, by filtration, concentration and flash column chromatography.

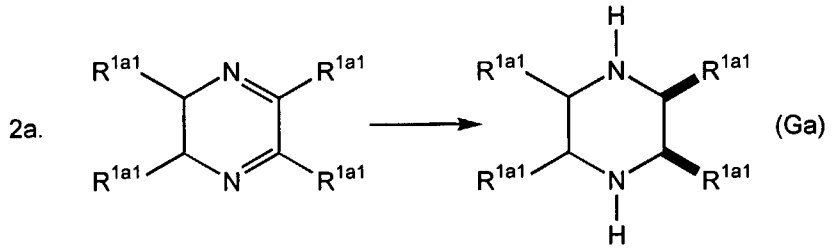
B. Preparation of Compounds of Formula (Ga) and Formula (Gb)

Compounds of formula (Ga) and formula (Gb) are intermediates in the preparation of compounds of the invention. They are prepared as illustrated in the following Reaction Scheme 2 wherein each R^{1a1} is independently selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylaminoalkyl, (cycloalkylalkyl)aminoalkyl, haloalkyl, alkenyl, alkynyl, aralkyl, aralkenyl, formylalkyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy) aralkyl, (hydroxy)cycloalkylalkyl, mercaptoalkyl, cyanoalkyl, haloalkylcarbonylaminoalkyl, (alkoxy)aralkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkylthioalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, alkoxycarbonylaminoalkyl, hydroxyalkylaminoalkyl, aryloxyalkylcarbonyloxyalkyl, alkoxyalkylcarbonyloxyalkyl, aralkoxyalkylcarbonyloxyalkyl, alkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, heterocyclyl and heterocyclylalkyl (except that R^{1a1} can not be aminoalkyl or monoalkylaminoalkyl unless appropriately protected):

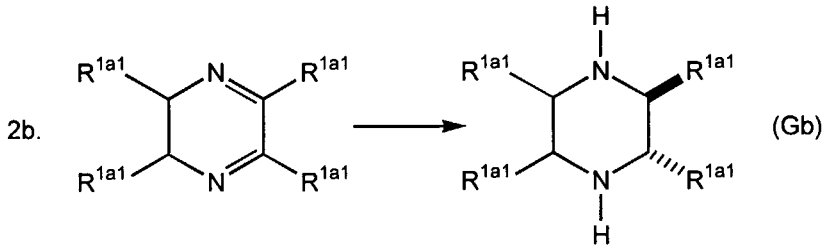
Reaction Scheme 2



(D) (E) (F)



(F)



(F)

Compounds of formula (D) and formula (E) are commercially available, *e.g.*, from Aldrich Chemical Co. or Sigma Chemical Co., or may be made from methods known to those of ordinary skill in the art.

In general, compounds of formula (Ga) and formula (Gb) are prepared by first treating a compound of formula (D) in an anhydrous aprotic solvent, such as anhydrous ether, with an equimolar amount of a compound of formula (E) in an anhydrous aprotic solvent, such as anhydrous ether, over a period of time, for example, over a two hour period. The resulting reaction mixture is stirred for about 2 to about 4 hours, preferably for about 3 hours, at ambient temperature. The compound of formula (F) is isolated from the reaction mixture by standard isolation techniques, such as concentration of the product and purification by vacuum distillation.

To a solution of a strong reducing agent, such as lithium aluminum hydride, in an anhydrous polar aprotic solvent, such as tetrahydrofuran, is added the compound of formula (F). The resulting mixture is stirred at ambient temperature for about 30 minutes to about 2 hours, preferably for about 1 hour. The mixture is then heated to

reflux to complete the reaction. Upon completion, the compound of formula (Ga) is isolated from the reaction mixture by standard isolation techniques, such as quenching by water and a mild base, followed by filtration.

Alternatively, to a solution of formula (F) in a polar protic solvent, such as absolute ethanol, is added a solid alkaline metal, such as sodium metal over a period of time, such as over a 3 hour period. The resulting mixture is heated to reflux for about 2 to about 4 hours, preferably for about 3 hours. The compound of formula (Gb) is distilled from the reaction mixture by the addition of water to the reaction mixture. The distillate is then treated with an aqueous acid, such as hydrochloric acid, to form the salt of the compound of formula (Gb).

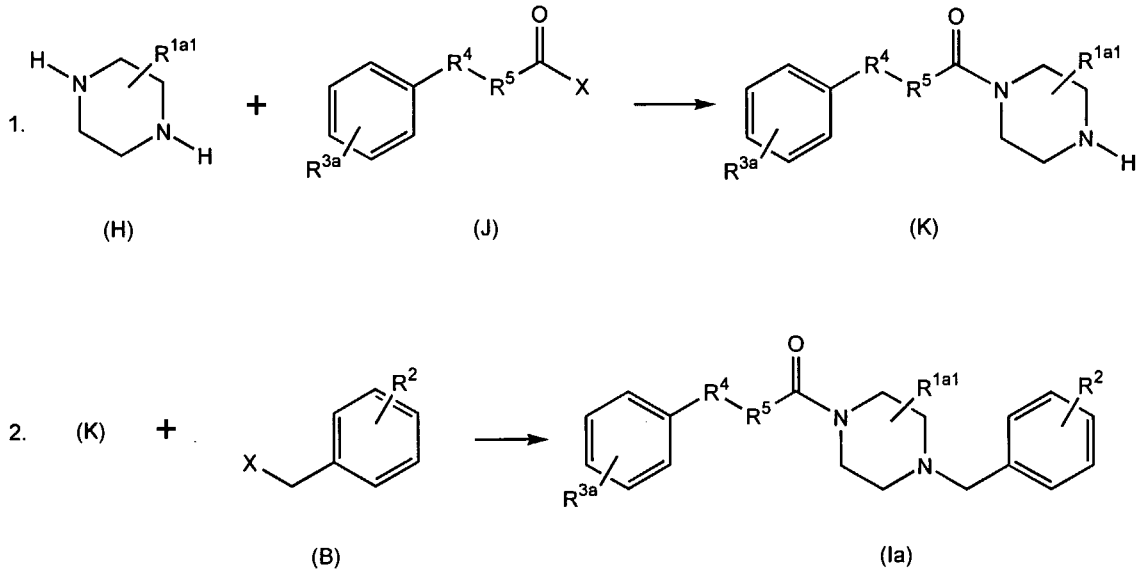
Compounds of formula (Ga) and formula (Gb) may then be treated with compounds of formula (B) in a manner similar to that described above in Reaction Scheme 1 to produce compounds of the invention wherein the relative orientation of the R^{1a} substituents is fixed.

C. Preparation of Compounds of Formula (Ia)

The compounds of formula (Ia) are compounds of the invention and they are prepared as illustrated in the following Reaction Scheme 3 wherein each X is independently chloro or bromo; R^{1a1} is one or more independently selected R^{1a} substituents as described above in the Summary of the Invention for compounds of formula (Ia) (except that R^{1a1} can not contain a primary or secondary amine unless appropriately protected); R^2, R^4 and R^5 are as described in the Summary of the Invention for compounds of formula (Ia) (except that R^4 and R^5 can not contain a primary or secondary amine unless adequately protected); and R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cyctoalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl carboxy, alkoxycarbonyl,

aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl; and R^4 and R^5 are as described above in the Summary of the Invention:

Reaction Scheme 3



The compounds of formula (B), formula (H) and formula (J) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared according to methods known to those of ordinary skill in the art.

In general, compounds of formula (Ia) are prepared by the foregoing Reaction Scheme by first treating a compound of formula (H) in a polar solvent, such as methanol, with an equimolar amount of a compound of formula (J) in an anhydrous polar solvent, such as anhydrous ether. The resulting reaction mixture is stirred at ambient temperature for about 5 minutes to about 24 hours in the presence of an acid-scavenging base, such as triethylamine. The compound of formula (K) is then isolated from the reaction mixture by standard isolation techniques, such as organic phase extraction, evaporation of solvents and purification by flash column chromatography.

The compound of formula (K) in an aprotic polar solvent, such as tetrahydrofuran, is treated with an excess molar amount of a compound of formula (B) in the presence of a mild base, such as triethylamine and, optionally, a catalytic amount of sodium iodide. The resulting mixture is stirred at ambient temperature for about 1 to 5 days, preferably for about 2 days. The compound of formula (Ia) is then isolated from the reaction mixture by standard isolation techniques such as filtration, concentration of volatiles and purification by flash column chromatography.

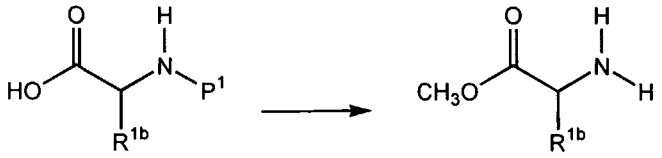
Alternatively, compounds of formula (Ga) and formula (Gb), as prepared above in Reaction Scheme 2, may be used in place of compounds of formula (H) in this Reaction Scheme to produce compounds of the invention wherein the relative orientation of the R^{1a} substituents is fixed.

D. Preparation of Compounds of Formula (Ia)

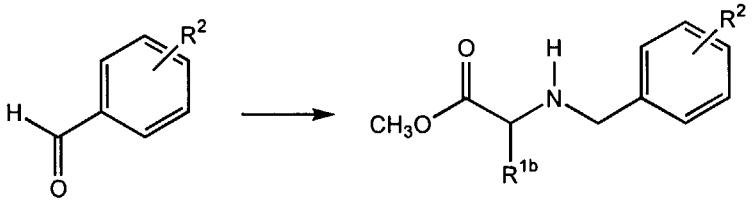
Compounds of formula (Ia) are compounds of the invention and they are prepared as illustrated in the following Reaction Scheme 4 wherein X is chloro, bromo or an activated ester; P^1 and P^2 are independently nitrogen-protecting groups, such as *t*-butoxycarbonyl (P^1 can also be hydrogen); R^{1a}, R^2, R^4 and R^5 are as described above in the Summary of the Invention; R^{1b} is as described above in the Summary of the Invention for compounds of formula (Ic) and (Id); and R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl,

dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl:

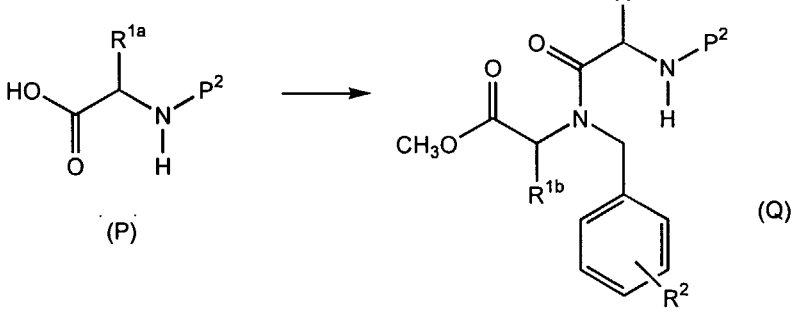
Reaction Scheme 4

1. 

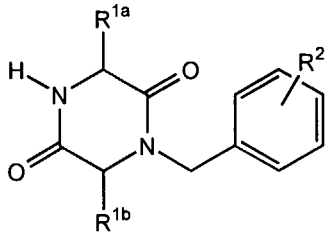
(L) (M)

2. (M) + 

(N) (O)

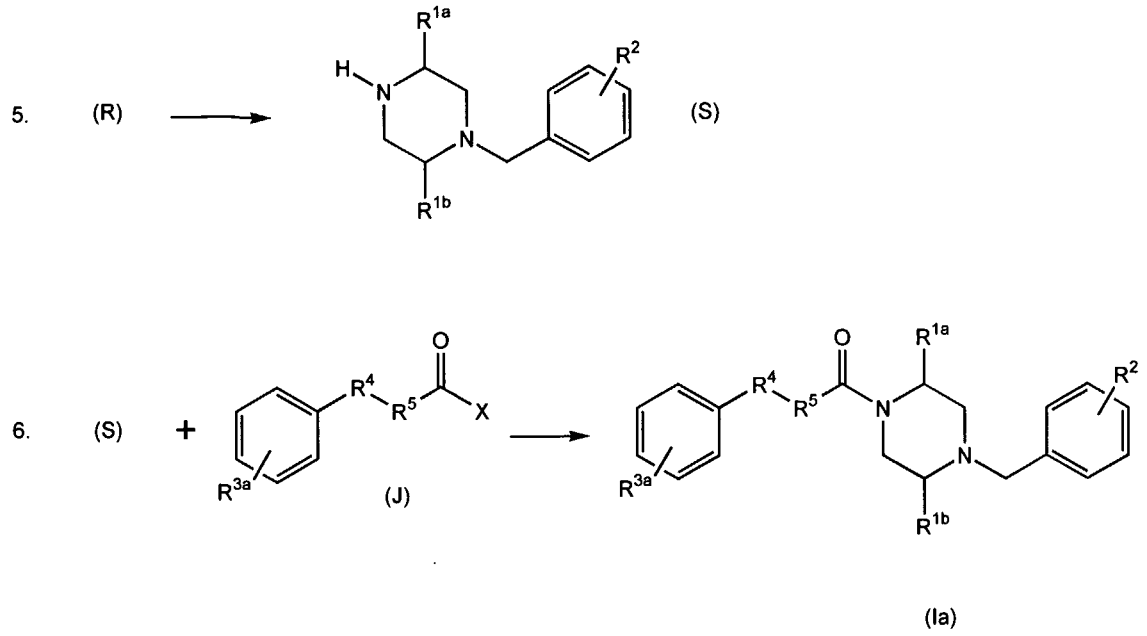
3. (O) + 

(P) (Q)

4. (Q) → 

(R)

Reaction Scheme 4 continued



Compounds of formula (L), formula (N), formula (P) and formula (J) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared according to methods known to one of ordinary skill in the art.

Compounds of formula (L) wherein the R^{1b} substituent contains an un-protected hydroxy group may be protected with the appropriate oxygen-protecting group prior to the synthesis of the compound of formula (M). Removal of the protecting group may be performed as desired.

in general, the compounds of formula (Ia) are prepared by first esterifying a compound of formula (L) by treating the compound with an excess molar amount of a lower alkanol, preferably methanol, in the presence of an acid, preferably hydrochloride gas, at about 0°C to ambient temperature. The resulting mixture is then stirred at about 0°C to reflux temperature, preferably at ambient temperature, for about 4 hours to about 18 hours. The mixture is then concentrated by removal of solvents to produce the compound of formula (M) .

To a solution of the compound of formula (M) in an organic solvent, such as methanol, at about 0°C to ambient temperature, is added an excess molar amount of a compound of formula (N), and then treated with a mild acid, such as acetic acid, and stirred at ambient temperature for about 2 hours to about 4 hours, preferably for about 3 hours, to form an intermediate imine. The imine is then reduced *in situ* by treatment with a reducing agent, such as sodium cyanoborohydride, to produce a compound of formula

(O), which is isolated from the reaction mixture by standard isolation techniques, such as filtration and purification by flash column chromatography.

To a solution of a compound of formula (P) in a polar aprotic solvent, such as anhydrous tetrahydrofuran, is added an acid scavenging mild base, such as *N*-methylmorpholine, followed by the addition of an acid coupling reagent, such as isobutylchloroformate. The resulting mixture is stirred at about 0°C to ambient temperature for about 15 minutes to about 2 hours, preferably for about 15 minutes at 0°C and then for about an hour at ambient temperature, to form an intermediate active ester of the compound of formula (P). The intermediate is then treated *in situ* with a compound of formula (O) in anhydrous polar aprotic solvent, such as anhydrous tetrahydrofuran and the resulting mixture is stirred at ambient temperature for about 10 hours to about 24 hours, preferably for about 15 hours. The compound of formula (Q) is isolated from the reaction mixture by standard isolation techniques, such as concentration, organic phase separation and purification by flash column chromatography.

The compound of formula (Q) in an aprotic solvent, such as methylene chloride, at about 0°C, is then treated with a strong organic acid, such as trifluoroacetic acid. for a period of about 2 to about 4 hours, preferably for about 2 hours, to remove the protecting group on the nitrogen atom, followed by spontaneous cyclization to form the compound of formula (R), which is isolated from the reaction mixture by standard isolation techniques, such as neutralization with a mild base, filtration and concentration.

The compound of formula (R) in an anhydrous polar aprotic solvent, such as anhydrous tetrahydrofuran, at about 0°C is treated with a strong reducing agent, such as lithium aluminum hydride. The resulting mixture is then heated to reflux for about 12 hours to about 24 hours, preferably for about 15 hours. The mixture is then cooled to ambient temperature and the reaction quenched with water, followed by aqeous base, preferably aqueous potassium hydroxide. The resulting mixture is allowed to stir at ambient temperature for about 30 minutes to an hour. The compound of formula (S) is then isolated from the reaction mixture by filtration and concentration.

The compound of formula (S) in a polar aprotic solvent, such as methylene chloride, in the presence of excess amount of an acid scavenging base, such as triethylamine, is added a slighly excess molar amount of a compound of formula (J) in a polar aprotic solvent, such as methylene chloride. The resulting mixture is stirred at ambient temperature for about 15 minutes to about 1 hour, preferably for about 15 minutes. The compound of formula (Ia) is then isolated from the reaction mixture by standard

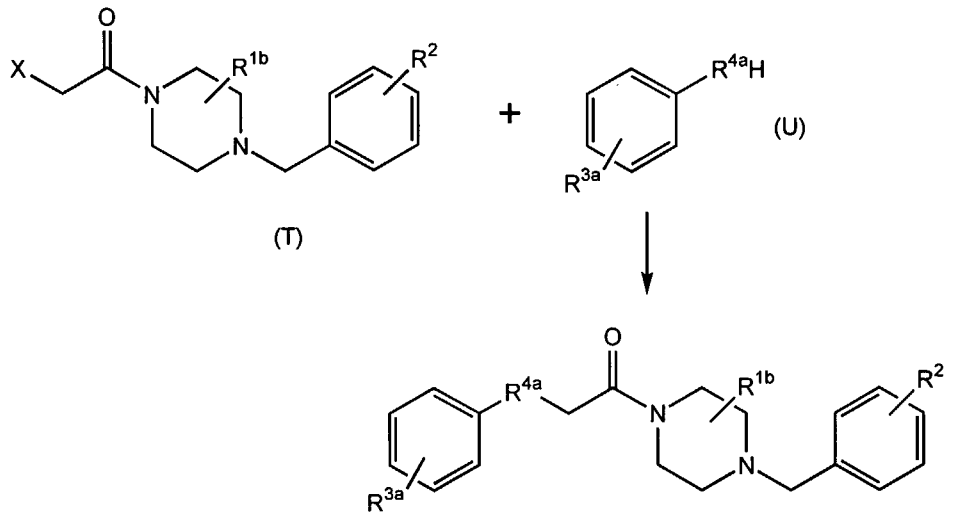
isolation techniques, such as extraction, concentration and flash column chromatography.

E. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) are prepared as illustrated below in Reaction Scheme 5 where X is chloro or bromo; R^{1b} is as described above in the Summary of the Invention for R^{1a} of compounds of formula (Ia) and hydrogen; and R^2 is as described above in the Summary of the Invention for compounds of formula (Ia); R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, halo, alkyl, alkoxy, aryloxy, haloalkyl, formyl, nitro, cyano, aralkoxy, haloalkoxy, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, cycloalkylaminoalkyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, aryloxycarbonylalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, arylsulfonyl, hydroxyalkoxy, aminoalkoxy, (monoalkylamino)aralkyl, aminoalkylamino, heterocyclylamino, alkenylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, haloalkylcarbonylamino, alkoxyalkylcarbonylamino, alkoxycarbonylalkylcarbonylamino, alkylsulfonylamino, arylcarbonylaminoalkyl, alkoxycarbonylalkylcarbonylaminoalkyl, alkylsulfonylaminoalkyl, (alkylsulfonyl)(alkyl)aminoalkyl, arylsulfonylaminoalkyl, (arylsulfonyl) (alkyl)aminoalkyl, heterocyclylaminoalkyl, (hydroxyalkoxy)carbonyl, (aminocarbonylalkyl)aminocarbonyl, (monoalkylaminocarbonylalkyl) aminocarbonyl, (carboxyalkyl)aminocarbonyl, (alkoxycarbonylalkyl) aminocarbonyl, (aminoalkyl)aminocarbonyl, (hydroxyalkyl)aminocarbonyl, dialkylaminocarbonyloxyalkyl, monoarylureido, monoaralkylureido, monohaloalkylureido, (monoalkyl)(monoaryl)ureido, diarylureido, (haloalkylcarbonyl)ureido, monoarylureidoalkyl, monoaralkylureidoalkyl, monohaloalkylureidoalkyl, (haloalkyl)(alkyl)ureidoalkyl, (alkoxycarbonylalkyl)ureidoalkyl, glycinamido, monoalkylglycinamido, (alkoxyalkylcarbonyl)glycinamido, aminocarbonylglycinamido, (aminocarbonyl)(alkyl)glycinamido, (alkoxycarbonylalkylcarbonyl)(alkyl) glycinamido, (alkoxycarbonylaminoalkylcarbonyl)glycinamido, arylcarbonylglycinamido, (arylcarbonyl)(alkyl)glycinamido, (monoaralkylaminocarbonyl)glycinamido, (monoaralkylaminocarbonyl)(alkyl) glycinamido, (monoarylaminocarbonyl)glycinamido, (monoarylaminocarbonyl) (alkyl)glycinamido, glycinamidoalkyl, alaninamido,

monoalkylalaninamido, alaninamidoalkyl, heterocyclyl and heterocyclylalkyl; and R^{4a} is -O- or -N(R^{7a})- where R^{7a} is hydrogen, alkyl, aryl or aralkyl:

Reaction Scheme 5



Compounds of formula (U) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared according to methods known to those of ordinary skill in the art. Compounds of formula (T) may be prepared according to the methods described herein for compounds of formula (C) or for compounds of formula (K), or by acylating the compounds of formula (C) as prepared herein by standard methods known to those of ordinary skill in the art.

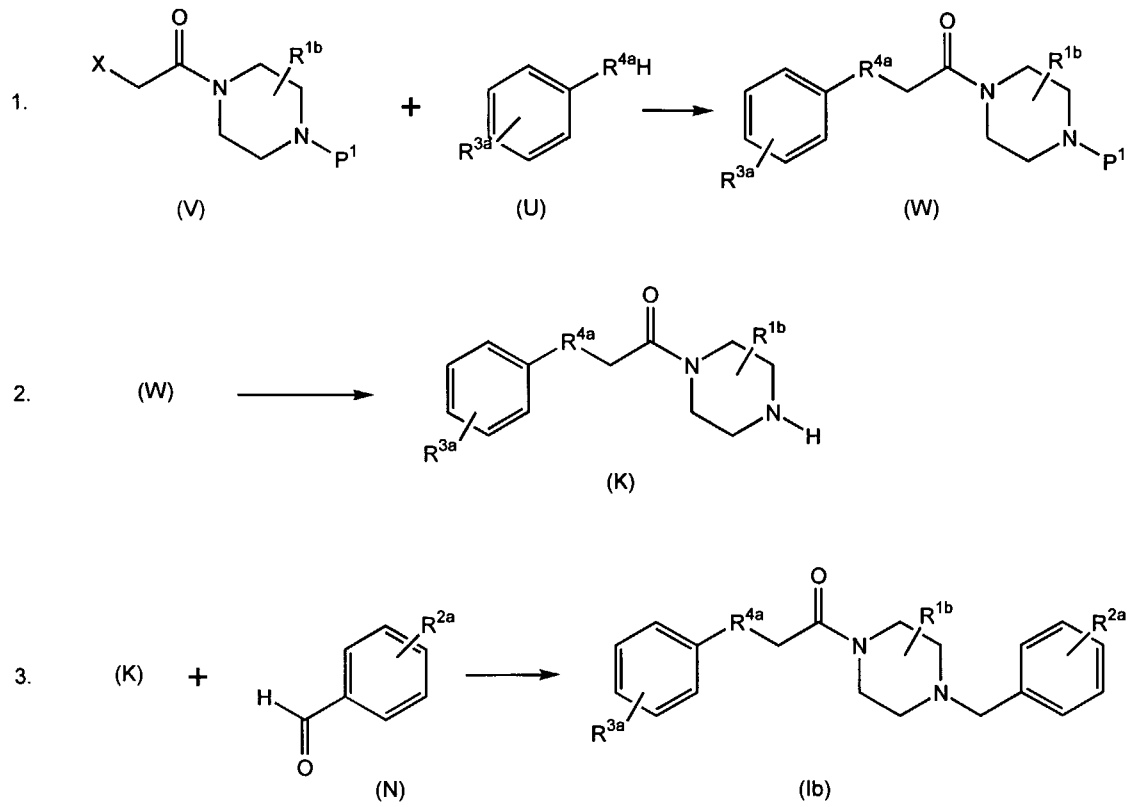
In general, the compounds of formula (Ib) are prepared by the foregoing Reaction Scheme by first treating a compound of formula (T) in an anhydrous aprotic solvent, such as anhydrous dimethylformamide, with a slightly excess molar amount of a compound of formula (U) in the presence of a mild base, such as potassium carbonate. The resulting mixture is stirred at about 50°C for about 10 hours to about 24 hours, preferably for about 15 hours. The compound of formula (Ib) is then isolated from the reaction mixture by standard isolation techniques, such as extraction, filtration and precipitation.

F. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) may also be prepared as illustrated in the following Reaction Scheme 6 where X is chloro, bromo or an activated ester; P^1 is a nitrogen-

protecting group, such as *t*- butoxycarbony; R^{1b} is as described above in the Summary of the Invention for compounds of formula (Ic) and formula (Id); R^{2a} is as described above in the Summary of the Invention for R^2 in compounds of formula (Ic) except that R^{2a} can not be formyl or formylalkyl; R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido, ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl; and R^{4a} is -O- or -N(R^{7a})- where R^{7a} is hydrogen, alkyl, aryl or aralkyl:

Reaction Scheme 6



Compounds of formula (U) and formula (N) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared according to methods known to those of ordinary skill in the art. Compounds of formula (V) may be prepared according to the method described above for compounds of formula (K) in Reaction Scheme 3.

In general, compounds of formula (Ib) as prepared in the foregoing Reaction Scheme 6 are prepared by first treating a compound of formula (U) in an aprotic solvent, such as dimethylformamide, at about 0°C, with a strong base, such as potassium hexamethyldisilazide, to deprotonate the compound. The resulting mixture is stirred for about 20 minutes to an hour, preferably for about 20 minutes, at about 0°C. An equimolar amount of a compound of formula (V) in an aprotic solvent, such as dimethylformamide is then added to the mixture and the resulting mixture is stirred at ambient temperature for about 1 to 24 hours, preferably for about 2 hours. The compound of formula (W) is then isolated from the reaction mixture by standard isolation techniques, such as extraction and concentration.

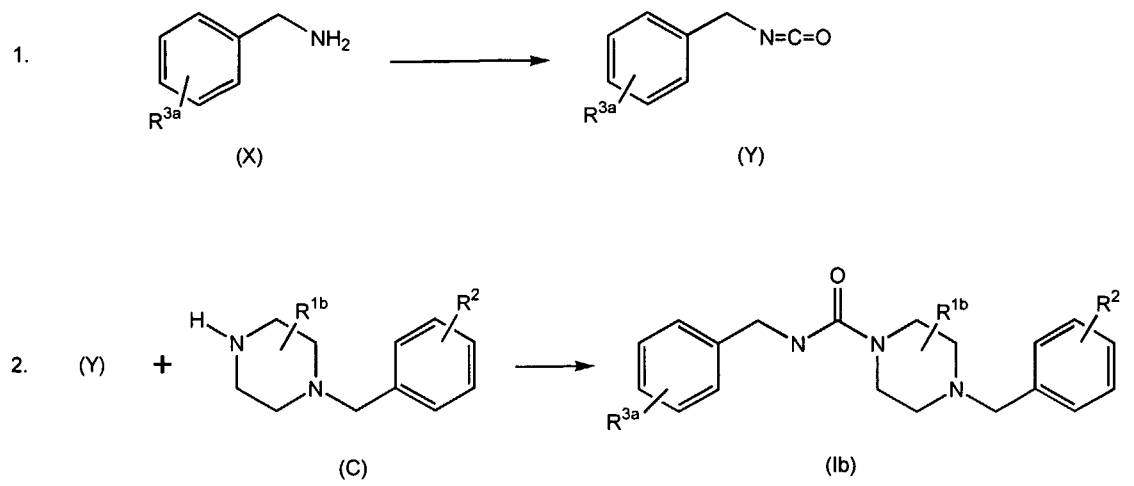
The P^1 protecting group is then removed from the compound of formula (W) to form a compound of formula (K) by standard amine-deprotecting procedures, such as treating the compound of formula (W) with a strong acid, such as trifluoroacetic acid.

To a solution of the compound of formula (K) in a polar solvent, such as methanol, at about 0°C to ambient temperature, was added an excess molar amount of a compound of formula (N) , and then treated with a mild acid, such as acetic acid, and stirred at ambient temperature for about 2 hours to about 4 hours, preferably for about 3 hours, to form an intermediate imine. The imine is then reduced *in situ* by treatment with a reducing agent, such as sodium cyanoborohydride, to produce a compound of formula (Ib), which is isolated from the reaction mixture by standard isolation techniques, such as filtration and purification by flash column chromatography.

G. Preparation of Compounds of Formula (Ib)

Compounds of formula (Ib) may also be prepared as illustrated in the following Reaction Scheme 7 where R^{1b} is as described above in the Summary of the Invention for compounds of formula (Ic) and formula (Id); and R^2 is as described above in the Summary of the Invention for the compounds of formula (Ib); and R^{3a} is one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, alkyl, mercapto, mercaptoalkyl, alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, alkoxy, aryloxy, haloalkyl, formyl, formylalkyl, nitro, nitroso, cyano, aralkoxy, haloalkoxy, cycloalkyl, cycloalkylalkyl, (hydroxy)cycloalkylalkyl, cycloalkylamino, cycloalkylaminoalkyl, (cycloalkylalkyl)amino, (cycloalkyalkyl)aminoalkyl, cyanoalkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, hydroxyalkyl, (hydroxy)aralkyl, hydroxyalkylthioalkyl, hydroxyalkenyl, hydroxyalkynyl, alkoxyalkyl, (alkoxy)aralkyl, aryloxyalkyl, aralkoxyalkyl, amino, monoalkylamino, dialkylamino, monoarylamino, monoaralkylamino, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, hydroxyalkylaminoalkyl, monoarylaminoalkyl, monoaralkylaminoalkyl, alkylcarbonylamino, (alkylcarbonyl)(alkyl)amino, alkylcarbonylaminoalkyl, (alkylcarbonyl)(alkyl)aminoalkyl, alkoxycarbonylamino, (alkoxycarbonyl)(alkyl)amino, alkoxycarbonylaminoalkyl, (alkoxycarbonyl)(alkyl)aminoalkyl, carboxy, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylcarbonylalkyl, aralkylcarbonyl, aralkylcarbonylalkyl, carboxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, alkoxyalkylcarbonyloxyalkyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, monoarylaminocarbonyl, monoaralkylaminocarbonyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, monoarylaminocarbonylalkyl, monoaralkylaminocarbonylalkyl, amidino, guanidino, ureido, monoalkylureido, dialkylureido. ureidoalkyl, monoalkylureidoalkyl, dialkylureidoalkyl, heterocyclyl and heterocyclylalkyl:

Reaction Scheme 7



Compounds of formula (X) are commercially available, for example, from Aldrich Chemical Co. or Sigma Chemical Co., or may be prepared acccording to methods known to those of ordinary skill in the art. Compounds of formula (C) may be prepared according to methods described herein.

In general , the compounds of formula (Ib) prepared by this Reaction Scheme are prepared by first treating a compound of formula (X) in an organic solvent, such as toluene. with phosgene for a period of time from about 1 hour to about 24 hours, preferably for about 2 hours, at reflux temperature to form the isocyanate of formula (Y), which is isolated from the reaction mixture by standard isolation techniques, such as concentration and filtration.

The compound of formula (Y) in an anhydrous aprotic polar solvent, such as tetrahydrofuran, is then treated with an equimolar amount of a compound of formula (C). The resulting mixture is stirred at ambient temperature for about 10 hours to about 48 hours, preferably for about 20 hours. The compound of formula (Ib) is then isolated from the reaction mixture by standard isolation techniques, such as concentration and evaporation of solvents.

In addition to the foregoing Reaction Schemes 1 through 7, other compounds of invention may be made by reactions known to one skilled in the art. For example, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein at least one R^{1a} substituent or at least one R^{1b} substituent is selected from the group consisting of hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy)aralkyl, (hydroxy)cycloalkylalkyl, hydroxyalkylthioalkyl, and hydroxyalkylaminoalkyl, may be dissolved in an aprotic polar solvent, such as methylene chloride, in the presence of a mild acid scavenging base and then treated

with a slightly excess molar amount of a sulfonyl halide, such as sulfonyl chloride, to form an intermediate compound containing a sulfonate leaving group. The compound may then be dissolved in an anhydrous aprotic solvent, such as dimethylformamide, and treated, in the presence of a mild base, with the appropriate nucleophilic reagent to form compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein the R^{1a} substituent or the R^{1b} substituent (depending on the nucleophilic reagent utilized) may be selected from the group consisting of heterocyclylalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, cycloalkylamino, cyanoalkyl, (cycloalkylalkyl)aminoalkyl, or hydroxyalkylthioalkyl.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains a hydroxy group, such as hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy) aralkyl, (hydroxy) cycloalkylalkyl, hydroxyalkylthioalkyl, and hydroxyalkylaminoalkyl, may be treated with a mild oxidizing agent, such as oxalyl chloride, which is dissolved in an inert organic solvent, such as methylene chloride, to which DMSO is added over a period of time at about -60°C to about 0°C, preferably at about -50°C. The reaction mixture is stirred at about -60°C to about 0°C for about 15 minutes to about an hour, preferably for about 15 minutes, and then a mild base, such as triethylamine, is added to the mixture. The mixture is allowed to gradually warm to ambient temperature, at which point the oxidized compound (*i.e.*, the corresponding aldehyde) of formula (Ia), or any appropriately substituted starting material or intermediate thereof, is isolated from the reaction mixture by standard isolation techniques.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an aldehyde or a ketone group, such as formyl, alkylcarbonyl or alkylcarbonylalkyl, may be treated with the appropriate organometallic reagent, such as an organomagnesium or organolithium, under standard Grignard synthesis reaction conditions to form the corresponding hydroxy-substituted compounds.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains a hydroxy group, such as hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, (hydroxy) aralkyl, (hydroxy)cycloalkylalkyl, hydroxyalkylthioalkyl, and hydroxyalkylaminoalkyl, in an anhydrous polar solvent, such as anhydrous ether, in the presence of a strong base, such as sodium hydride, may be treated with an alkyl halide, such as methyl iodide, at ambient temperatures, to form the corresponding alkoxy-substituted compounds.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein at least one R^{1a} substituent or at least one R^{1b} substituent is formyl or formylalkyl, may be reacted with a primary or secondary amine, under the reductive amination conditions as described above for the preparation of the compounds of formula (O) or the compounds of formula (Ib) as prepared in Reaction Scheme 6 to form the corresponding compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein the R^{1a} substituent or the R^{1b} substituent is monoalkylaminoalkyl, dialkylaminoalkyl, monoaralkylaminoalkyl, or hydroxyalkylaminoalkyl.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an ester group, such as an alkoxycarbonyl, aryloxycarbonyl or aralkoxycarbonyl group, may be subjected to standard basic hydrolysis conditions, to form the corresponding compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an acid group, *i.e.* a carboxy group.

Alternatively, a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is -C(O)- may be reduced to the corresponding compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is $-CH_2-$ by methods known to those of ordinary skill in the art, for example, by the method described above for compounds of formula (S).

In addition, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is -C(O)- may be converted to a compound of formula (Ia), or any appropriately substituted starting material or intermediate thereof, wherein R^6 is -C(S)- by treatment with Lawesson's Reagent under standard conditions known to those of ordinary skill in the art.

In addition, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain an unoxidized sulfur atom may be oxidized with the appropriate sulfur oxidizing agent according to methods known to those skilled in the art, such as using hydrogen peroxide, to produce the corresponding compounds which contain a sulfinyl or a suffonyl group in place thereof.

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a carboxy group can be converted to compounds containing the corresponding amide group by first converting the carboxy group into an activated ester or mixed anhydride using, for example, isobutyl chlorofarmate in the presence of a mild base, such as *N*- methylmorpholine, in an

aprotic solvent, such as THF, and then treating the ester with the appropriately substituted primary or secondard amine in an aprotic solvent, such as THF.

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a cyano group can be converted to the compounds containing a hydroxyamidino group by reaction with the an hydroxyamine in a polar solvent, such as DMSO. The hydroxyamine may be prepared *in situ* by first treating the hydrochloride salt of the hydoxyamine with a base, such as triethylamine.

Alternatively, of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a hydroxy group may be converted to the compounds containing the corresponding azide group by treating the compound with triphenylphosphine and an alkyl azodicarboxylate, for example. diethylazodicarboxylate, in an aprotic solvent, such as THF, and then displacing the activated oxygen so formed with an azide source, such as diphenylphosphorylazide, in an aprotic solvent, such as THF.

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a $-NH_2$ group or a $-R_a-NH_2$ group may be converted to compounds containing a corresponding $-R_a-N(H)-C(O)-$ group by reacting the compound with appropriately substituted acid halide under standard acylation conditions.

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a acid halide group (-C(O)-X where X is halo) or an activated ester group can be converted to compounds containing the corresponding -C(O)-N(H)- group by reacting the compound with the appropriately substituted primary or secondardy amine under standard acylation or amide bond formation conditions.

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contains an primary or secondary amine group can be converted to compounds containing the corresponding aminoalkyl group in a manner similar to the conversion of formula (M) to formula (O) in Reaction Scheme 4. In particular, the amine is reacted with an appropriately substituted aldehyde to form the intermediate imine, which is then reduced by treatment with an appropriate reducing agent, such as sodium cyanoborohydride.

Alternatively, compounds of formula (Ia), or any appropriately substituted starting material or intermediate thereof, which contain a primary or secondary amine can be converted to the compounds containing the corresponding ureido group by reacting the compound with phosgene in a manner similar to Reaction Scheme 7 above (in an

aprotic solvent) to form the corresponding isocyanate, which is then reacted with the appropriately substituted primary or secondary amine.

In addition, all compounds of the invention that exist in free base form or free acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic acid, or by the appropriate inorganic or organic base. Salts of the compounds of the invention can also be converted to the free base form or to the free acid form or to another salt by methods known to those skilled in the art.

The following specific Preparations and Examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

In the following Preparation and Examples, all NMR data refers to ^{1}H NMR spectrum data and is given in the format of "(multiplicity, number of hydrogens)". The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

PREPARATION 1

Compounds of Formula (C)

A. To a solution of 2-methylpiperazine (0.10 g, 1 mmol) in CH_2Cl_2 (2 mL) was added 4-fluorobenzyl bromide (0.125 mL, 1 mmol). The resultant mixture was stirred at ambient temperature. After 15 hours, the mixture was concentrated *in* vacuo to afford a solid. This solid was dissolved in CH_2Cl_2 and washed sequentially with water, aqueous $NaHCO_3$ solution, then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to an oil. Purification by flash column chromatography afforded 0.025 g (12% yield) of 1-(4-fluorobenzyl)-3-methylpiperazine, a compound of formula (C), as a colorless oil; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (m, 2), 3.4 (s, 2), 3.0-2.6 (m, 5), 2.0 (br s, 2), 1.6 (t, 1), 1.0 (d, 3) ppm.

B. In a similar manner, the following compounds of formula (C) were made:

(2*R*,5*S*)-1-(chloro)acetyl-4-(4-fluorobenzyl)-2,5- dimethylpiperazine-1-(4-fluorobenzyl)piperazine;

(*trans*)- 1-(4-fluorobenzyl)-2,5-dimethylpiperazine;

(*cis*)-1-(4- fluorobenzyl)-2,3-dimethylpiperazine;

(*trans*)-1-(4- fluorobenzyl)-2,3-dimethylpiperazine; and

(*cis*)-1-(4- fluorobenzyl)-3,5-dimethylpiperazine.

C. In a similar manner, other compounds of formula (C) are made.

PREPARATION 2

Compounds of Formula (F)

A. To a solution of ethylene diamine (13 g, 216 mmol) in anhydrous ether (600 mL) was added 2,3-butanedione (18.6 g, 216 mmol, in 200 mL anhydrous ether) dropwise over 2 hours. The resulting mixture was stirred at ambient temperature. After 3 hours, the clear solution was concentrated *in vacuo* to afford a brown oil. Purification by vacuum distillation afforded 16.6 g (70% yield) of 5,6-dimethyl-2,3-dihydropyrazine, a compound of formula (F), as clear, yellow oil; b.p. 60°C /16 mm Hg, NMR ($CDCl_3$) 3.3 (br s, 4), 2.1 (s, 6) ppm.

B. In a similar manner, other compounds of formula (F) are made.

PREPARATION 3

Compounds of formula (Ga)

A. To a solution of lithium aluminum hydride (0.36 g, 10 mmol) in anhydrous tetrahydrofuran (50 mL) was carefully added 5,6-dimethyl-2,3- dihydropyrazine (1.0 g, 9 mmol, in 10 mL of anhydrous tetrahydrofuran). The resulting mixture was stirred at ambient temperature for 1 hour, then heated to reflux. After the reaction was completed, as determined by thin layer chromatographic analysis of reaction mixture, the reaction mixture was cooled to ambient temperature and quenched by sequential addition of 0.4 mL of water, 0.4 mL of 15% aqueous NaOH solution, then 1.2 mL of water. After brief shaking, the mixture was filtered through a fritted funnel. Filtrate was concentrated *in vacuo* to 0. 92 g (90% yield) of (*cis*)-2,3-dimethylpiperazine, a compound of formula (Ga), as clear, yellow oil; NMR ($CDCl_3$) 2.7 (m, 4), 2.5 (m, 2), 0.9 (d, 6) ppm.

B. In a similar manner, other compounds of formula (Ga) are made.

PREPARATION 4

Compounds of formula (Gb)

A. To a solution of 5,6-dimethyl-2, 3-dihydropyrazine (2.3 g, 21 mmol) in absolute ethanol (60 mL) was added sodium metal (6.5 g, 280 mmol) in small portions over a 3 hour period. The resulting mixture was heated to reflux. After 3 hours at reflux, the product was distilled from the mixture while 200 mL of water was added gradually to reaction vessel. The distillate was treated with 1 N aqueous HCl solution and concentrated *in vacuo* to afford a semi-solid. Titration with acetone afforded 0.78 g (20% yield) of (*trans*)-2,3- dimethylpiperazine, a

compound of formula (Gb), as an orange solid; NMR (DMSO-d_6) 9.8 (br s, 4), 3.5-3.2 (m, 6), 1.2 (s, 6) ppm.

B. In a similar manner, other compounds of formula (Gb) are made.

PREPARATION 5

Compounds of Formula (K)

A. To a solution of (*cis*)-2,6- dimethylpiperazine (0.115 g, 1.1 mmol) in methanol (35 mL) was added 4- chlorophenoxyacetyl chloride (0.205 g, 1.0 mmol, in solution of 6 mL of anhydrous ether). The resulting mixture was stirred at ambient temperature for 10 minutes and then triethylamine (0.10 mL, 0.72 mmol) was added. After 30 minutes, the mixture was concentrated *in vacuo* to afford an oily residue. This was taken up in ether and washed with saturated aqueous $NaHCO_3$ solution, then brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an oil. Purification by flash column chromatography afforded 0.202 g (80% yield) of (*cis*)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine, a compound of formula (K), as a clear, colorless oil; NMR ($CDCl_3$) 7.3 (d, 2), 6.9 (d, 2), 4.7 (d, 1), 4.6 (d, 1), 4.4 (d, 1), 3.8 (d, 1), 2.7 (m, 3) , 2.2 (t, 1), 1.1 (m, 6) ppm.

B. In a similar manner, the following compounds of formula (I) were made:
(3*S*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-3,5- dimethylpiperazine; and
(3*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine.

C. In a similar manner, other compounds of formula (K) are made.

PREPARATION 6

Compounds of Formula (M)

A. A solution of (2*R*)-3-benzyloxy-2-(*N* -(*t*-butoxycarbonyl)amino) propanoic acid (23 g, 78 mmol, $[\alpha]_D$ -4.4° (c = 2, H_2O)) in methanol (250 mL) was cooled to 0°C and HCl (g) bubbled into the solution until saturated. The resulting mixture was stirred at ambient temperature for 17 hours and then concentrated *in vacuo* to afford 17 g (100% yield) of (2*R*)-3-benzyloxy-2-aminopropanoic acid methyl ester, a compound of formula (M), as a white solid; NMR (DMSO- d_6) 8.7 (br s, 3), 7.4-7.3 (m, 5), 4.5 (q, 2), 4.4 (br s, 1), 3.8 (s, 2), 3.7 (s, 3) ppm.

B. In a similar manner, other compounds of formula (M) are made.

PREPARATION 7

Compounds of Formula (O)

A. A solution of (2*R*)-3-benzyloxy-2- aminopropanoic acid methyl ester (19 g, 78 mmol) in methanol (350 mL) under N_2 was cooled to 0°C and acetic acid (2 g, pH 2) was added, followed by the addition of 4-fluorobenzaldehyde, a compound of formula (N) (12.5 mL, 117 mmol) and sodium cyanoborohydride (7.3 g, 117 mmol) and 3 Å molecular sieves (15 g). The resulting mixture was stirred at ambient temperature for 3 hours, then filtered through Celite (MeOH). The filtrate was concentrated *in vacuo* to afford a clear liquid. This was taken up in ethyl acetate and washed sequentially with 10% aqueous Na_2CO_3 solution, water, then brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography on silica gel afforded 14.7 g (60% yield) of (2*R*)-3- benzyloxy-2-(*N*-(4-fluorobenzyl)amino)propanoic acid methyl ester, a compound of formula (O), as a clear, colorless oil; NMR ($CDCl_3$) 7.4-7.2 (m, 7), 7.0 (dd, 2), 4.5 (d, 2), 3.9-3.5 (m, 8) ppm, MS (LSIMS) 317.

B. In a similar manner, the following compounds of formula (O) were made:

(2*R*)- 2-(*N*-(4-fluorobenzyl)amino)propanoic acid methyl ester;

(2*S*)-2-(*N*-(4-fluorobenzyl)amino)propanoic acid methyl ester;

(2*R*)-2-(*N*-(4-fluorobenzyl)amino)4- methylthiobutanoic acid methyl ester;

(2*R*)-2-(*N*-(4- fluorobenzyl)amino)-3-methoxypropanoic acid methyl ester;

(2 *R*)-2-(*N*-(4-fluorobenzyl)amino)-3-((2-hydroxyethyl)thio) propanoic acid methyl ester; and

(2*R*)-2-(*N*-(4- fluorobenzyl)amino)-3-methylbutanoic acid methyl ester.

C. In a similar manner, the following compounds of formula (O) are made:

(2*S*)-2-(*N*-(4-fluorobenzyl) amino)-4-methylthiobutanoic acid methyl ester;

(2*S*)-2-(*N*-(4-fluorobenzyl)amino)-3-methoxypropanoic acid methyl ester;

(2*S*)-2(*N*-(4-fluorobenzyl)amino)-3-((2-hydroxyethyl)thio) propanoic acid methyl ester;

(2*S*)-2-(*N*-(4- fluorobenzyl)amino)-3-methylbutanoic acid methyl ester;

(2 *R*)-2-(*N*-(4-fluorobenzyl)amino)butanoic acid ethyl ester;

(2*S*)-2-(*N*-(4-fluorobenzyl)amino)butanoic acid ethyl ester;

(2*R*)-2-(*N*-(4-chlorobenzyl)amino)butanoic acid methyl ester;

(2*S*)-2-(*N*-(4-chlorobenzyl)amino) butanoic acid methyl ester;

(2*R*)-2-(*N*-(4- chlorobenzyl)amino)-4-methylthiobutanoic acid methyl ester;

(2 *R*)-2-(*N*-(4-chlorobenzyl)amino)-3-methoxypropanoic acid methyl ester;

(2*R*)-2-(*N*-(4-chlorobenzyl)amino)-3-((2- hydroxyethyl)thio)propanoic acid methyl ester; and

(2*R*)-2- (*N*-(4-chlorobenzyl)amino)-3-methylbutanoic acid methyl ester.

D. In a similar manner, other compounds of formula (O) are made.

PREPARATION 8

Compounds of Formula (Q)

A. To a solution of *N*-*t*-butoxycarbonyl-D-alanine (5.6 g, 30 mmol, $[\alpha]_D$ +23° (c=2, CH_3CO_2H)) in anhydrous tetrahydrofuran (150 mL) under N_2 at 0°C was added *N*-methylmorpholine (3.0 g, 30 mmol), followed by the addition of isobutylchloroformate (3.7 mL, 30 mmol) , resulting in the formation of a white solid. The resulting suspension was stirred at 0°C for 15 minutes, and then at ambient temperature for 1 hour. A solution of (2*R*)-3-benzyloxy-2-(*N*-(4-fluorobenzyl)- amino)propanoic acid methyl ester (7.5 g, 24 mmol, in 50 mL of anhydrous tetrahydrofuran) was added to the mixture and the resulting mixture was stirred at ambient temperature. After 15 hours, the mixture was filtered through Celite (tetrahydrofuran). The filtrate was concentrated *in vacuo* to afford a yellow liquid, which was dissolved in ethyl acetate, washed with water and then with brine. The organic phase was separated then dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography on silica gel afforded 7.3 g (63% yield) of (2*R*)-3-benzyloxy-2-(*N*-(4- fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxy-carbonylamino) ethyl)carbonyl)amino)propanoic acid methyl ester, a compound of formula (Q), as a clear oil; NMR ($CDCl_3$) 7.4-7.2 (m, 7), 7.0 (dd, 2), 5.3 (d, 2), 4.9-4,.3 (m, 5), 4.1-3.7 (m, 4), 1.6 (s, 9), 1.0 (d, 3) ppm.

B. In a similar manner, the following compounds of formula (Q) were made:

(2*R*)-2-(*N*- (4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino) ethyl)carbonyl)amino)propanoic acid methyl ester;

(2*S*)-2- (*N*-(4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)propanoic acid methyl ester;

(2*R*)-2-(*N*-(4-fluorobenzyl)-*N*-(((1*R*)- 1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)propanoic acid methyl ester;

(2*S*)-2-(*N*-(4-fluorobenzyl)-*N*- (((1*R*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino) propanoic acid methyl ester;

(2*R*)-2-(*N*-(4- fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino) ethyl)carbonyl)amino)-4-methylthiobutanoic acid methyl ester;

(2*R*)-2-(*N*-(4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)-3-methoxypropanoic acid methyl ester;

(2*R*)-2-(*N*-(4- fluorobenzyl)- *N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)- 3-((2-hydroxyethyl)thio)propanoic acid methyl ester;

(2*R*)- 2-(*N*-(4-fluorobenzyl)-*N*-(((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino)-3-methylbutanoic acid methyl ester; and

(2*R*)-2-(*N*-(4-fluorobenzyl)-*N*- (((1*S*)-1-(*t*-butoxycarbonylamino)-2-(ethoxycarbonyl)ethyl)- carbonyl)amino)propanoic acid methyl ester.

C. In a similar manner, other compounds of formula (Q) are made.

PREPARATION 9 Compounds of Formula (R)

A. To a solution of (2*R*)-3-benzyloxy-2-(*N*-(4-fluorobenzyl)-*N*- (((1*S*)-1-(*t*-butoxycarbonylamino)ethyl)carbonyl)amino) propanoic acid methyl ester (2.0 g, 4 mmol) in CH_2Cl_2 (25 mL) was cooled to 0°C and trifluoroacetic acid (25 mL) was added dropwise over 2 hours. At the end of the addition, the ice bath was removed and the mixture was stirred at ambient temperature. After 2 hours, the mixture was concentrated *in vacuo.* The residual yellow oil was taken up in ethyl acetate and washed with 1 N aqueous $NaHCO_3$ solution. The organic layer was separated then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 1.2 g (83% yield) of (2*R*, 5*S*)-1-(4-fluorobenzyl)-2-(benzyloxy)methyl-5-methylpiperazine-3,6- dione, a compound of formula (R), as a clear oil; NMR ($CDCl_3$) 7.4-7.2 (m, 7), 7.0 (dd, 2), 5.0 (d, 1), 4.5-4.0 (m, 4), 3.9-3.5 (m, 4), 1.5 (d, 3) ppm, MS (LSIMS) 356.

B. In a similar manner, the following compounds of formula (R) were made:

(2*R*,5*S*)-1-(4-fluorobenzyl)-2,5-dimethylpiperazine-3,6- dione;

(2*S*,5*S*)-1-(4-fluorobenzyl)-2,5- dimethylpiperazine-3,6-dione;

(2*R*,5*R*)-1-(4- fluorobenzyl)-2,5-dimethylpiperazine-3,6-dione;

(2*S*,5 *R*)-1-(4-fluorobenzyl)-2,5-dimethylpiperazine-3,6-drone;

(2 *R*,5*S*)-1-(4-fluorobenzyl)-2-(2-methylthioethyl)-5- methylpiperazine-3,6-dione;

(2*R*,5*S*)-1-(4- fluorobenzyl)-2-(methoxymethyl)-5-methylpiperazine-3,6-dione;

(2*R*,5*S*)-1-(4-fluorobenzyl)-2-((2-hydroxyethyl)thiomethyl)-5- methylpiperazine-3,6-dione;

(2*R*,5*S*)-1-(4- fluorobenzyl)-2-(1-methylethyl)-5-methylpiperazine-3,6-dione; and

(2*R*,5*S*)-1-(4-fluorobenzyl)-2-methyl-5-(ethoxycarbonyl) methylpiperazine-3,6-dione.

C. In a similar manner, other compounds of formula (R) are made:

PREPARATION 10

Compounds of Formula (S)

A. To a suspension of (2*R*,5*S*)-1-(4- fluorobenzyl)-2-(hydroxy)methyl-5-methylpiperazine-3,6-dione (2.0 g, 7.5 mmol) in anhydrous tetrahydrofuran (50 mL) under N_2 at 0°C was carefully added lithium aluminum hydride (2.2 g, 60 mmol). The resulting suspension was heated to reflux. After 15 hours, the mixture was cooled to ambient temperature and carefully quenched with water (2 mL) , then 1 N aqueous KOH solution (6 mL). The resulting suspension was stirred at ambient temperature for 30 minutes, then filtered through Celite (ethyl acetate). The filtrate was concentrated *in vacuo* to afford 1.6 g (90% yield) of (2*R*,5*S*)-1-(4-fluorobenzyl)-2- (hydroxy)methyl-5- methylpiperazine, a compound of formula (S), as a white solid; NMR ($CDCl_3$) 7.3 (dd, 2), 7.0 (dd, 2), 4.2-4.0 (m, 2), 3.5 (d, 1) 3.0 (m, 2), 2.7 (m, 2), 1.7 (m, 1), 1.0 (d, 3).

B. In a similar manner, the following compounds of formula (S) were made:

(2*R*,5*S*)-1-(4- fluorobenzyl)- 2,5-dimethylpiperazine;

(2*S*,5*S*)-1-(4-fluorobenzyl)- 2,5-dimethylpiperazine;

(2*R*,5*R*)-1-(4-fluorobenzyl)- 2,5-dimethylpiperazine;

(2*S*,5*R*)-1-(4-fluorobenzyl)- 2,5-dimethylpiperazine;

(2*R*,5*S*)-1-(4-fluorobenzyl)- 2-(2-methylthioethyl)-5-methylpiperazine;

(2*R*,5*S*)- 1-(4-fluorobenzyl)-2-(methoxymethyl)-5-methylpiperazine;

(2 *R*,5*S*)-1-(4-fluorobenzyl)-2-((2-hydroxyethyl)thiomethyl)-5- methylpiperazine;

(2*R*,5*S*)-1-(4-fluorobenzyl)-2-(1- methylethyl)-5-methylpiperazine; and

(2*R*,5*S*)-1-(4- fluorobenzyl)-2-methyl-5-(ethoxycarbonyl)methylpiperazine.

C. In a similar manner, other compounds of formula (S) are made.

PREPARATION 11

Compounds of formula (W)

A. To a solution of 3,4,5-trimethoxyphenol (2.8 g, 15 mmol) in DMF (60 mL) at 0°C was added potassium hexamethyldisilazide (32 mL, 16 mmol, 0.5 M solution in toluene). The resulting mixture was stirred at 0°C. After 20 minutes, 1-(chloro)acetyl- 4-(*t*-butoxycarbonyl)piperazine (4.6 g, 15 mmol, in 15 mL of DMF) was added and the mixture stirred at ambient temperature. After 2 hours the mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 6.5 g (100% yield) of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(*t*-

butoxycarbonyl) piperazine, a compound of formula (W), as a yellow solid; NMR ($CDCl_3$) 7.2 (m, 2), 4.6 (s, 2), 3.8 (m, 9), 3.6 (m, 4), 3.4 (m, 4), 1.5 (s, 9) ppm.

B. In a similar manner, the following compounds of formula (W) were made:

1-((4- chlorophenyl)methyl)carbonyl-4-(*t*-butoxycarbonyl)piperazine;

(3*R*)-1-((4-chlorophenyl)methyl)carbonyl-3-methyl-4-(*t*-butoxycarbonyl)piperazine;

(3*S*)-1-((4-chlorophenyl)methyl) carbonyl-3-methyl-4-(*t*-butoxycarbonyl)piperazine; and

1- ((4-chlorophenyl)methyl)carbonyl-3-(2-((((4-chlorophenoxy)methyl)carbonyl) oxy)ethyl)-4-(*t*-butoxycarbonyl)piperazine.

C. In a similar manner, other compounds of formula (W) are made.

PREPARATION 12 Compounds of formula (Y)

A. To a solution of 4-chlorobenzylamine (0.50 g, 3.5 mmol) in toluene (15 mL) was added phosgene (7.3 mL, 14 mmol, 1.93 M solution in toluene). The resulting mixture was stirred at ambient temperature for 15 minutes, then heated to reflux. After 2 hours at reflux, the mixture was cooled to ambient temperature and concentrated *in vacuo* to afford 0.70 g (100% yield) of 4-chlorobenzylisocyanate, a compound of formula (Y), as a yellow liquid; NMR ($CDCl_3$) 7.4-7.2 (m, 4), 4.4 (m, 2) ppm.

B. In a similar manner, other compounds of formula (Y) are made.

EXAMPLE 1

Compounds of Formula (Ia) and Formula (Ib)

A. To a solution of (2*R*,5*S*)-1-(4- fluorobenzyl)-2-(hydroxy)methyl-5-methylpiperazine (1.6 g, 6.7 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (excess) and 4-chlorophenoxyacetyl chloride (1.5 g, 7.4 mmol, dropwise in 10 mL solution of CH_2Cl_2). The resultant mixture was stirred at ambient temperature. After 20 minutes, analysis by analytical TLC showed complete consumption of starting material had occurred. The mixture was concentrated of volatiles *in vacuo* and the residue taken up in CH_2Cl_2. This was washed with saturated aqueous $NaHCO_3$ solution, then water, then brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel afforded 2.16 g (79% yield) of (2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((hydroxy) methyl)piperazine, as a solid yellow foam: NMR (DMSO-d_6) 7.7 (br s, 2), 7.3 (m, 4), 6.9 (d, 2), 5.0-4.2 (m, 5), 4.0-3.2 (m, 7), 1. 2 (m, 3) ppm; MS (LSIMS) 406.

B. In a similar manner, other compounds of formula (Ia) were made:

1- ((4-chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5-methylpiperazine, trifluoroacetic acid salt; NMR (DMSO-d_6) 7.6 (m, 2), 7.3 (m, 4), 6.9 (m, 2), 5.0-3.8 (m, 6), 3.5-2.8 (m, 5), 1.4 (m, 3) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- ethylpiperazina;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-methylpiperazine;

4-benzyl-1-((4-chlorophenoxy)methyl) carbonyl-2-phenylpiperazine;

(2*R*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(1-methylethyl)piperazine;

4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(methoxymethyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-ethylpiperazine-3-one;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-ethylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 4.4 (m, 1), 3.7 (m, 1), 3.4 (m, 2), 2.8 (m, 2), 2.0-1.7 (m, 5), 0.9 (m, 3) ppm;

(2*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-methylpropyl)piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (m, 2), 4.2 (m, 1), 3.6-3.0 (m, 5), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-benzylpiperazine;

4-(benzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-phenylpiperazine-3-one;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.7 (m, 3) , 3.8-3. 2 (m,5), 2.8 (m, 2), 2.2 (m, 2), 2.0 (m, 2), 1.7 (m, 2) ppm;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl) carbonyl-2,6-dimethylpiperazine; NMR (DMSO-d_6) 7.6 (m, 2), 7.3 (m, 4), 6.9 (d, 2), 4.8 (m, 3), 4.4 (m, 3), 3.3 (d, 2), 3.0 (m, 2), 1. 4 (m, 6) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(1-methylpropyl)piperazine;

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-methylpiperazine, hydrochloride salt;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (m, 2), 4.2 (m, 1), 3.6-3.0 (m, 5), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-(2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(butyl)piperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (m, 2), 4.6 (m, 3), 3.5 (m, 5), 3.2 (dt, 1), 3.0 (m, 1), 2.8 (dd, 1), 2.2 (m, 2), 1.6 (m, 2), 1.0 (d, 3) ppm;

(2 *S*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2, 5-dimethylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (m, 2), 4.2 (m, 1), 3.6-3.0 (m, 5), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*S*,5*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine, hydrochoride salt; NMR (DMSO-d_6) 7.6 (m, 2), 7.2 (m, 4), 6.9 (d, 2), 4.8 (m, 2), 4.4 (m, 1), 4.1 (t, 1), 3.9-2.9 (m, 6), 1.5-1. 2 (m, 6) ppm;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine hydrochloride salt; NMR (DMSO-d_6) 7.6 (m, 2), 7.2 (m, 4), 6.9 (d, 2), 4.8 (m, 2), 4.4 (m, 1), 4.1 (t, 1), 3.9-2.9 (m, 6), 1.5-1.2 (m, 6) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(1,1-dimethylethyl)piperazine;

(2*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-methylpropyl)piperazine;

(2 *R*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- (2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5-methylpiperazine; NMR ($CDCl_3$) 7.2 (m, 6), 7.0 (m, 2), 6.8 (m, 4), 4.7-4.0 (m, 7), 3.6 (m, 2), 3.4 (m, 1), 3.1 (m, 1), 2.6 (m, 1), 2.3 (m, 2), 2.0 (m, 2), 1. 0 (d, 3) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(methoxycarbonyl)methylpiperazine;

(2*S*)- 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl) carbonyl-2,3-dimethylpiperazine, hydrochloride salt; NMR (DMSO-d_6) 7.6 (m, 2), 7.2 (m, 4), 6.9 (m, 2), 5.0-4.1 (m, 6), 3. 5-2.9 (m, 4), 1.5-1.2 (m, 6) ppm;

(2*R*)-4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-benzylpiperazine;

(2 *R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- propylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (m, 2), 4.4 (m, 1), 3.7 (m,

1), 3.4 (m, 2), 3.0 (m, 1), 2. 7 (m,2), 2.0-1.6 (m, 4), 1.2 (m, 2), 0.9 (m, 3) ppm ;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxyethyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 4), 7.0 (t, 2), 6.9 (dd, 2), 4.7 (d, 2), 4.0-3.4 (m, 8), 2.8 (m, 2), 2.3 (m, 1), 1.8 (m, 3) ppm;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(hydroxymethyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (t, 2), 4.7 (d, 2), 3.9-3. 2 (m, 7), 2.8-2.2 (m, 4) ppm;

(2*S*)-4-(4-fluorobenzyl)1- ((4-chlorophenoxy)methyl)carbonyl-2-butylpiperazine;

(2*R*, 6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine, hydrochloride salt; NMR ($CDCl_3$) 7. 7 (br s, 2), 7.2 (m, 4), 6.8 (d, 2), 4.6 (s, 2), 4.4 (m, 3), 3.9 (m, 1), 3. 5 (m, 1), 3.2 (m, 1), 2.8 (m, 2), 1.6 (s, 6) ppm;

(2*S*, 6*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine, hydrochloride salt; NMR ($CDCl_3$) 7. 7 (br s, 2), 7.2 (m, 4), 6.8 (d, 2), 4.6 (s, 2), 4.4 (m, 3), 3.9 (m, 1), 3. 5 (m, 1), 3.2 (m, 1), 2.8 (m, 2), 1.6 (s, 6) ppm;

4-(4- fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl)spiro[cyclopropane-1, 2'-piperazine]; NMR ($CDCl_3$) 7.3 (m, 4), 7.0-6.8 (m, 4) , 4.6 (m, 4), 2.8 (m, 2), 2.2-1.6 (m, 4) ppm;

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-(trifluoromethyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-5-(2-methylthio)ethylpiperazine, hydrochloride salt;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methylpiperazine;

(2*S*)- 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 3.8 (m, 2), 3.4 (m, 2), 3.2 (m, 2), 2.6 (m, 1), 2.4 (m, 1), 2.2 (m, 1), 1.6-1. 3 (m, 4), 0.9 (m, 3) ppm;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine; NMR (DMSO-d_6) 7.6 (m, 2), 7.3 (m, 4), 6.9 (d, 2), 5.0-4.2 (m, 6), 3. 5-3.1 (m, 4), 2.2 (m, 1), 1.2 (d, 3), 0.9 (d, 6) ppm;

(2*S*) -4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-methylpropyl) piperazine;

(2*R*,3*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine, hydrochloride salt; NMR (DMSO-d_6) 7.8 (m, 2), 7.3 (m, 4), 6.9 (d, 2), 5.1- 3.6 (m, 6), 3.2 (m, 4), 1.5-1.2 (m, 6) ppm;

(3*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-butylpiperazine;

(3*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- (1-methylpropyl)piperazine;

(3*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-methylpropyl)piperazine;

(3 *R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- butylpiperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy)methylpiperazine; NMR ($CDCl_3$) 7.3 (m, 8), 6.8 (m,, 5), 4.5 (m, 6), 3.6 (m, 5), 3.0 (m, 1), 2.7 (dd, 1), 2.3 (d, 1), 1.2 (d, 3) ppm;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl) piperazine dihydrochloride salt;

(2*R*)-4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-2-methylpiperazine hydrochloride salt;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((4-acetylpiperazin-1-yl)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-((trifluoroacetylamino)methyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl)methylpiperazine hydrochloride salt;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine, hydrochloride salt;

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino-4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine; NMR (DMSO-d_6) 9.5 (br s, 1), 8.1 (br s, 1), 7.7 (m, 2), 7.3 (m, 2), 7.0 (m, 2), 5.0 (m, 2), 4.3 (m, 3), 3.8-2.9 (m, 5), 2.1 (s,3), 1.2 (m, 6) ppm;

4-(4-fluorobenzyl)-1-((2-((acetylamino)methyl)-4- chlorophenoxy)methyl)carbonyl-2,5-methylpiperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.1 (dd, 1), 7.0 (t, 2), 6.7 (d, 1), 4.7 (m, 2), 4.2-3.4 (m, 10), 3.0 (br s, 1), 2.7 (dd, 1), 2.5 (q, 4), 2.2 (d, 1), 2.0 (m, 4), 1.3 (m, 3), 0.9 (m, 3) ppm;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(((*t*-butoxycarbonyl)amino)methylpiperazine;

1-((4-chloro-2- (acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 10.9 (d, 1), 9.5 (s, 1), 8. 1 (s, 1), 7.6 (d, 2), 7.3 (t, 2), 7.0 (m, 2), 5.0 (q, 2), 4.7 (m, 1), 4.3 (m, 2), 3.9-2. 8 (m, 6), 2.1 (s, 3), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm;

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.5 (d, 1), 8.2 (s, 1), 7.8 (t, 2), 7.3 (t, 2), 7.0 (dt, 2), 6.8 (dq, 1), 6.4 (d, 1), 5.2-4.3 (m, 5), 3.9-2.8 (m, 5), 1.8 (d, 3), 1.3 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(*iso*- propylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.5 (d, 1), 8. 2 (s, 1), 7.8 (t, 2), 7.3 (t, 2), 7.0 (m, 2), 5.2-4.3 (m, 5), 3.9-2.7 (m, 6) , 1.4-1.1 (m, 12) ppm;

(*trans*)-1-((4-chloro-2- (methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.3 (s, 1), 8. 2 (s, 1), 7.8 (t, 2), 7.3 (t, 2), 7.1 (m, 2), 5.3-4.2 (m, 5), 4.0 (s, 2), 3. 9-2.8 (m, 8), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((4-chloro- 2-(2-(methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.5 (s. 1), 8.1 (s, 1), 7.8 (t, 2), 7.3 (t, 2), 7.0 (m, 2), 5.2-4.2 (m, 5) , 3.8 (q, 1), 3.7-3.2 (m, 5), 2.9-2.6 (m, 6), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.6 (s. 1), 8.1 (s, 1), 7.8 (t, 2), 7.3 (t, 2), 7.0 (m, 2), 5.2-4.2 (m, 5), 4.0 (q, 2), 3.8 (q, 1), 3.6-3.2 (m, 3), 2. 8- 2.6 (m, 5), 1.4-1.2 (m, 9) ppm;

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.9 (d, 1), 9. 3 (s. 1), 7.7 (d, 2), 7.3-7.2 (m, 4), 7.0 (d, 1), 5.0 (m, 2), 4.7 (m, 1), 4. 4 (m, 3), 3.9 (m, 1), 3.6 (m, 1), 3.4-2.8 (m, 6), 1.4 (d, 1.5), 1.2 (d, 1.5) ppm;

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.0 (s. 1), 8.4 (s, 1), 7.3 (m, 2), 7.0 (m, 3), 6.9 (m, 1), 4.7 (m, 3), 4.0 (s, 2), 3.8-3.1 (m, 5), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (br d, 3), 1.0 (br s, 3) ppm;

(*trans*)-1-((4-chloro-2- (ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.4 (s, 1), 8.5 (s, 1), 7.3 (m, 2), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 3.5 (m, 3), 3.1 (m, 2) , 2.7 (dd, 1), 2.5 (q, 1), 2.2 (d, 1), 1.3 (m, 6), 10 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(acetylaminomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.0 (br s, 1), 7.3 (m, 3), 7.1 (dd, 1), 7.0 (m, 2), 6. 8 (br d, 1), 4.7 (m, 3), 4.4 (d, 1), 3.8-3.0 (m, 6), 2.7 (m, 1), 2.2 (m, 1), 2.0 (s, 3), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-(1-(methylsulfonyl)(methyl)aminoethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (m, 1), 5.6 (q, 1), 4.7 (m, 3), 4.2 (m, 1), 3. 7 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.1 (m, 1), 2.8 (d, 3), 2.7 (d, 3), 2.3 (br d, 1), 1.6 (d, 3), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*) -1-((4-chloro-2-(1-(phenylsulfonyl)(methyl)aminoethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (d, 2), 7.3 (m, 6), 6.9 (t, 2), 6.8 (t, 1), 5.6 (q, 1), 4.6 (m, 3), 4.2 (m, 1), 3.6 (m, 2), 3.4 (d, 1), 3.0 (m, 1), 2.6 (m, 4), 2. 4 (s, 3), 2.3 (m, 1), 1.3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl)aminoethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 4), 7.0 (t, 2), 6.8 (m, 1), 6.0 (m, 1), 5.4 (q, 1), 4.6 (m, 3), 4.2 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3,0 (m, 1), 2.6 (m, 4), 2. 2 (m, 3), 1.3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-(2- (4-chlorophenyl)-3-(methylsulfonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (t, 4), 7.2 (br d, 2), 7.0 (t, 2), 5.0 (br s, 1), 4.6 (br s, 1), 4.0 (m, 1), 3.4 (m, 5), 3.0 (m, 2), 2.8 (s, 3), 2.6 (m, 2), 2.2 (br d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.2 (br d, 2), 7.0 (t, 2), 5.2 (m, 1), 4.6 (br s, 1), 4.2 (m, 1), 3.8 (m, 1), 3.4 (m, 5), 3.0 (m, 1), 2.8 (s, 3), 2. 6 (m, 2), 2.2 (m, 1), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2- (methylsulfonylamino) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 5), 7.0 (t, 2), 6.6 (m, 1), 4.9 (q, 1), 4.6 (m, 0.5), 4.2 (br d, 0.5), 3.8 (m, 1), 3.5 (m, 1), 3.4 (m, 1), 3.0 (m, 2), 2. 7 (m, 6), 2.2 (m, 1), 1.2 (m, 3), 0.8 (m, 3) ppm;

(*trans*)- 1-(2-(4-chlorophenyl)-2-(acetylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.8 (m, 1), 7.3 (m, 5), 7.0 (t, 2), 5.3 (m, 1), 4.6 (m, 0.5), 4.1 (t, 0.5), 3.5 (m, 1), 3. 4 (m, 1), 3.0 (m, 3), 2.6 (m, 2), 2.2 (m, 1), 2.0 (m, 4), 1.2 (m, 3), 0.8 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((4-(2,5- di(trifluoromethyl)phenylcarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-

fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (m, 1), 8.1 (m, 2), 7.9 (t, 1), 7.7. (m, 1), 7.4 (d, 1), 7.3 (m, 2), 7.2 (m, 1), 5.4 (m, 1), 5.0 (m, 2), 4.4 (m, 6), 3.4 (m, 9) , 3.0 (m, 1), 2.8 (m, 1), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((4-(benzylcarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (m, 1), 7.9 (t, 2), 7.7. (t, 1), 7.6, (s, 1), 7.5 (d, 1), 7.3 (m, 4), 7.2 (m, 3), 5.4 (m, 1), 5.0 (m, 2), 4.4 (m, 6) , 3.7 (m, 2), 3.4 (m, 6), 3.0 (m, 2), 2.8 (m, 1), 1.4 (dd, 3), 1.2 (dd, 3) ppm;

(*trans*)-1-((4-chloro-2-((4-((2,3,4- trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine: NMR (DMSO-d_6) 11.0 (m, 1), 9.0 (s, 1), 7,9 (t, 2), 7.7. (m, 1), 7.6 (s, 1), 7.5 (m, 1), 7.2 (m, 4), 5.4 (m, 1), 5.0 (m, 2), 4.4 (m, 6), 3.4 (m, 8) , 3.1 (m, 2), 2.8 (m, 1), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 11.0 (m, 1), 8.6 (s, 1), 7. 9 (t, 2), 7.7. (m, 1), 7.6 (s, 1), 7.4 (d, 1), 7.3 (m, 1), 7.3 (t, 2), 7. 2 (m, 3), 5.4 (m, 1), 5.0 (m, 2), 4.3 (m, 6), 3.4 (m, 9), 3.1 (m, 2), 2.8 (m, 1), 1.4 (dd, 3), 1.2 (dd, 3) ppm;

(*trans*)-1-((4- chloro-2-((*N'*-(2,6-difluorophenyl)ureido)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.6 (br s, 1), 8.6 (s, 1), 7.4 (quin, 1), 7.3 (t, 2), 7.0 (m, 5), 6.9 (d, 1), 4.7 (m, 3), 4.1 (brs, 0.5), 3.8 (br s, 0.5), 3.5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2.6 (dd, 1), 2.2 (d, 1), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(ethenylcarbonylamino) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.8 (d, 1), 8.6 (s, 1), 7.3 (m, 3), 7.0 (t, 3), 6.9 (d, 1), 6.4 (dd, 2), 5.8 (dd, 1), 4.7 (m, 3), 3.6 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (dd, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(cyclopropylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.7 (br s, 1), 8.4 (s, 1), 7.3 (m, 2), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 3.7 (m, 1), 3.5 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (dd, 1), 1.7 (m, 1), 1.3 (m, 3), 1.0 (m, 5), 0.8 (m, 2) ppm;

(*trans*)-1-((4-chloro-2-(cyclopentylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.3 (br s, 1), 8.5 (s, 1), 7.3 (t, 2), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 3.7 (m, 1), 3.5 (q, 2), 3.1 (m, 2),

2.8 (quin, 1), 2. 7 (dd, 1), 2.2 (dd, 1), 1.9 (m, 3), 1.8 (m, 1), 1.6 (m, 3), 1.3 (m, 3), 0. 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((furan-2-yl) carbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 10.4 (br s, 1), 9.7 (br d, 1), 8.2 (br s, 1), 7.9 (s, 1), 7.7 (m, 2), 7.3 (m, 3), 7.2 (s, 2), 6.7 (d, 1), 5.3 (br d, 1), 5.0 (m, 2), 4.7 (m, 0.5), 4.5 (m, 0.5), 4.2 (m, 3), 3. 6 (m, 1) , 3.4 (m, 1), 2.8 (m, 1), 1.3 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.0 (s, 1), 8.6 (s, 1), 8.1 (d, 2), 7.5 (m, 3), 7.3 (t, 2), 7.0 (t, 3), 6.8 (d, 1), 4.7 (m, 3), 37 (m, 1), 35 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (dd, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-((ethoxycarbonylmethylcarbonylamino) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.6 (m, 1), 7.2 (s, 6), 7.0 (t, 2), 5.4 (m, 1), 4.2 (q, 2), 3.8 (m, 1), 3.5 (m, 1), 3.4 (m, 3), 3.0 (m, 3), 2.6 (m, 2), 2.2 (m, 2), 1. 3. (m, 4.5), 1.1. (m, 1.5), 0.9 (dd, 1.5), 0.7 (dd, 1.5) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-(*N'*-iso-propylureido) ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7.0 (t, 2), 5.2 (t, 1), 4.6 (m, 0.5), 4.4 (m, 1), 4.2 (t, 0.5), 3.8 (m, 1), 3.5 (m, 1), 3.4 (m, 1), 3.0 (m, 3), 2.6 (m, 1), 2.2 (m, 1), 1.1 (m, 9), 0.9 (dd, 1.5), 0.8 (dd, 1.5) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-(*N'*-(2-chloroethyl) ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7.0 (t, 2), 5.2 (t, 2), 4.6 (m, 0. 5), 4.2 (t, 0.5), 3.5 (m, 6), 3.0 (m, 4), 2.6 (m, 1), 2.2 (m,1), 1.1 (m, 3), 0. 9 (dd, 1.5), 0.8 (dd, 1.5) ppm;

(*trans*)-1-(2-(4- chlorophenyl)-2- ((2-nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.1 (d, 1), 7.7 (q, 1), 7.6 (t, 2), 7.3 (m, 6), 7.0 (t, 2), 5.6 (m, 1), 4.6 (m, 0.5), 4.1 (t, 0.5), 3.7-3.2 (m, 3), 3.0 (m, 4), 2.6 (m, 1), 2.2 (m, 1), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 8), 7.0 (t, 2), 6.9 (d, 2), 5.3 (m, 1), 4.6 (m, 0.5), 4.1 (t, 0.5), 3.8 (s, 3), 3. 5 (m, 3), 3.4-2.8 (m, 6), 2.6 (m, 1), 2.2 (m, 1), 1.2 (m, 3), 0.8 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-((2,4-dinitrophenyl) sulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.6 (s, 1), 8.2 (d, 1), 7.8 (m, 1), 7.3 (m, 4), 7.0 (t, 2), 6.9 (t, 2), 5.0 (m, 1), 4.6 (m, 0.5), 4.1 (m,

0.5), 3. 5 (m, 1), 3.4 (m, 1), 3.0 (m, 5), 2.6 (m, 1), 2.2 (m, 1), 1.1 (m, 3), 0.8 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2- (cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7.0 (t, 2), 5.2 (m, 1), 4.6 (m, 0.5), 4.2 (m, 0.5), 3.5 (m, 2), 3.4 (m, 1), 3.0 (m, 3), 26 (m, 2), 2.2 (m, 1), 1.5 (m, 1), 1.2 (m, 3), 0.9 (m, 3.5), 0.7 (m, 3.5) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2-((2-cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7.0 (t, 2), 5.4 (m, 1), 4.6 (m. 0.5), 4.2 (m, 0.5), 3.6 (m, 2), 3.4 (m, 1), 3. 0 (m, 4), 2.6 (m, 1), 2.2 (m, 2), 1.6 (m, 10), 1.2 (m, 3), 1.1 (m, 2), 0. 8 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-((2- methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;; NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d, 2), 7.0 (t, 2), 6.0 (br s, 1), 4.6 (m, 0.5), 4.2 (m, 0.5), 3.6 (m, 2), 3.4 (m, 3), 3. 0 (m, 2), 2.6 (m, 3), 2.2 (d, 1), 2.0 (m, 4), 1.2 (m, 3), 0.9 (m, 9) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d, 2), 7.0 (t, 2), 6.0 (br s, 1), 4.6 (m, 0.5), 4.2 (m, 0.5), 3.6 (m, 2), 3.4 (m, 3), 3.0 (m, 2), 2.6 (m, 3), 2.4 (m, 1), 2.2 (d, 1), 1.6 (m, 8), 1.1. (m, 4), 0.9 (m, 4) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(*t*- butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d, 2), 7.0 (t, 2), 4.6 (m, 1.5), 4.2 (m, 0.5), 3.6 (m, 2), 3.4 (m, 4), 3.2 (m, 1), 3.0 (m, 1), 2. 6 (m, 2), 2.2 (d, 1), 1.3 (s, 9), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(ethyl)ureido)propyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d, 2), 7.0 (t, 2), 5.1 (m, 1), 4.9 (m, 1), 4.6 (m, 0.5), 4.2 (m, 0.5), 3.6 (m, 2), 3.4 (m, 4), 3.2 (m, 3), 3.0 (m, 1) , 2.6 (m, 3), 2.2 (m, 1), 1.1 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl)ureido) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d, 2), 7.0 (t, 2), 5.6 (br s, 1), 5.9 (s, 1), 4.6 (m, 0.5), 4.2 (m, 0.5), 3.6 (m, 5), 3.4 (m, 5), 3.2 (m, 1), 3. 0 (m, 1), 2.6 (m, 3), 2.2 (d, 1), 2.0 (t, 2), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (d, 4), 7.2 (d,

2), 7.0. (t, 2), 5.8 (br d, 1), 4.6 (m, 0.5), 4.2 (m, 0.5), 3.6 (m, 6), 3.4 (m, 4), 3.3 (t, 4), 3.0 (m, 2) , 2.6 (m, 3), 2.2 (m, 1), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(methoxycarbonylmethylcarbonyl)- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.6 (br s, 1), 8. 4 (d, 1), 7.3 (dd, 2), 7.0 (t, 3), 6.8 (d, 1), 4.7 (m, 3), 4.3 (s, 2), 3. 8 (s, 3), 3.6 (m, 4), 3.5 (m, 2), 3.1 (m, 4), 2.7 (dd, 1), 2.2 (d, 1), 1. 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(2-methoxycarbonylethyl)carbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.6 (br s, 1), 8.4 (d, 1), 7.3 (dd, 2), 7.0 (t, 3), 6. 8 (d, 1), 4.7 (m, 3), 4.3 (s, 3), 3.8 (s, 3), 3.6 (q, 2), 3.2 (s, 3), 3.1 (s, 2) , 2.7 (m, 5), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl) aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9. 6 (br s, 1), 8.4 (d, 1), 7.3 (dd, 2), 7.2 (t, 1), 7.0 (m, 6), 6.8 (d, 1), 5. 4 (t, 1), 4.6 (m, 3), 4.4 (d, 2), 4.3 (s, 2), 3.8 (m, 1), 3.5 (q, 2), 3. 1 (m, 5), 2.6 (m, 1), 2.3 (s, 3), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(3- trifluoromethyl-4- fluorophenyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.8 (br s, 1), 8.4 (d, 1), 8.1 (br s, 1), 7.6 (m, 2), 7.3 (dd, 2), 7.0 (m, 4), 6.8 (d, 1), 4.7 (m, 3), 4.3 (t, 2), 3.7 (m, 1), 3.6 (q, 2), 3.2 (s, 3), 3.1 (m, 2), 2.7 (m, 1), 2.2 (d, 1), 1.3 (m, 3), 0. 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(4- methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.6 (br s, 1), 8.4 (d, 1), 7.3 (m, 2), 7.2 (d, 2), 7.1 (d, 2), 7.0 (m, 3), 6.8 (d, 1), 5.4 (t, 1), 4.7 (m, 3),4.4 (d, 2), 4.2 (d, 2), 3.8 (m, 1), 3.6 (q, 2), 3.1 (m, 5), 2.7 (m, 1), 2.3 (s, 3), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2- ((*N'*-(3-chlorophenyl)carbonyl-*N'*-(methyl)glycinamido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.9 (br s, 1), 8.4 (d, 1), 7.5 (s, 1), 7.3 (m, 5), 7.0 (t, 3), 6.8 (d, 1), 4.7 (m, 3), 4.4 (br s, 2), 4.1 (m, 1), 3.6 (m, 1), 3.5 (q, 2), 3.2 (m, 3), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'* -(4-fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.7 (br s, 1), 8.4 (s, 1), 7.3 (m, 4), 7.0 (m, 5), 6.8 (d, 1), 5.5 (t, 1), 4.7 (m, 2) 4.4 (d, 2), 4.2 (m, 2), 3.6 (m, 1), 3.5 (q, 2), 3.1 (m, 5), 2.7 (m, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(methoxymethylcarbonyl) glycinamido)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 10.1 (br s, 1), 8.4 (d, 1), 7. 3 (t, 3), 7.0 (t, 3), 6.8 (d, 1), 4.7 (m, 3), 4.2 (d, 2), 4.0 (s, 2), 3.6 (m, 1), 3.5 (q, 2), 3.4 (s, 3), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonylaminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9. 9 (br s, 1), 8.4 (m, 2), 7.3 (m, 3), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 4. 4 (m, 6), 3.6 (m, 1), 3.5 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10. 4 (br s, 1), 8.4 (d, 1), 7.9 (d, 1), 7.5 (d, 1), 7.4 (t, 1), 7.3 (m, 2), 7.1 (t, 1), 7.0 (t, 3), 6.8 (m, 2), 4. 7 (m, 3), 4.4 (d, 2), 3.6 (m, 1), 3.5 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2. 2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-(*N'*-(2,3-difluorophenylcarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.3 (br s, 1), 8.4 (d, 1), 7.8 (t, 1), 7.5 (quin, 1), 7.3 (m, 3), 7.2 (m, 1), 7.0 (t, 3), 6.8 (d, 1), 4.7 (m, 3), 4.4 (d, 2), 36 (m, 1), 3.5 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0. 9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9. 9 (br s, 1), 8.3 (br s, 1), 7.3 (m, 6), 7.0 (t, 6), 6.8 (m, 3), 6.5 (m, 1) , 4.7 (m, 3), 4.4 (m, 2), 3.6 (m, 1), 3.5 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-(*N'*-(2,4-diflurophenylcarbonyl)glycinamido)phenoxy)methyl) -carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.3 (br s, 1), 8.4 (d, 1), 8.1 (q, 1), 7.5 (m, 1), 7. 3 (m, 2), 7.0 (t, 3), 6.8 (m, 3), 4.7 (m, 3), 4.4 (d, 2), 3.6 (m, 1), 3.5 (q, 2), 3.1 (m, 2), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.0 (m, 1), 7.8 (d, 1), 7.3 (m, 5), 7.2 (dd, 1), 7.0 (m, 3), 6.8 (d, 1), 4.8 (m, 3), 4.6 (d, 2), 4.4 (m, 0.5), 3.9 (m, 0.5), 3.5 (q, 2) , 3.1 (m, 2), 2.6 (m, 1), 2.2 (m, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2- ((ethoxycarbonylmethylcarbonyl)aminomethyl)phenoxy)-methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8. 4 (br s, 1), 7.3 (m, 3), 7.2 (dd, 1), 7.0 (m, 2), 6.8 (d, 1), 4.8 (m, 3), 4. 5 (d, 2), 4.2 (m, 3), 3.6 (m, 1), 3.5 (q, 2), 3.3 (s, 2), 3.1 (m, 1), 2. 6 (m, 1), 2.2 (d, 1), 1.3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)- 1-((4-chloro-2-(*N'*-(3-chloropropyl)ureidomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.2 (dd, 1), 7.0 (m, 2), 6.8 (d, 1), 4.8 (m, 4), 4.4 (d, 2), 4.2 (m, 1), 3.6 (m, 5), 3.3 (m, 3), 3.1 (m, 1), 2.6 (m, 1), 2. 2 (d, 1), 1.9 (quin, 2), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.2 (m, 1), 7.3 (m, 6), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4,8 (m, 3), 4.4 (d, 2), 3.8 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.1 (m, 1), 2.6 (m, 1), 2.2 (m, 1), 1. 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((3-fluorophenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.6 (m, 1), 7.8 (t, 2), 7.3 (m, 4), 7.2 (dd, 1), 7.1 (dt, 1), 7.0 (t, 2), 6.8 (d, 1), 4.8 (m, 3), 4.6 (d, 2), 3.8 (m, 1), 3.5 (q, 2), 31 (m, 2), 2.6 (m, 1), 2.2 (d, 1), 1. 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2- (*N'*-(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.9 (m, 1), 6.8 (d, 1), 5.1 (m, 1), 4.8 (m, 3), 4.4 (d, 2), 4.1 (q, 2), 3.6 (m, 2), 3.4 (m, 3), 3.2 (m, 1), 3. 1 (m, 2), 2.7 (m, 1), 2.5 (t, 2), 2.2 (d, 1), 1.3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl) carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.9 (m, 1), 7.8 (m, 2), 7.2 (s, 1), 7.3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.8 (m, 3), 4.6 (d, 2), 4.4 (m, 0.5), 3.9 (m, 0.5), 3.5 (q, 2), 3.1 (m, 2), 2. 6 (m, 1), 2.2 (m, 1), 1.3 (m, 3), 0.9 (m, 3) ppm; and

(*trans*)-1-((4-chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 8), 7.0 (m, 3), 6.8 (d, 1), 4.9 (s, 1) , 4.6 (d, 2), 4.4 (m, 2), 3.8 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2.7 (m, 2), 2. 2 (m, 1), 2.0 (m, 1), 1.3 (m, 5), 0.9 (m, 3) ppm.

C. In a similar manner, the following compounds of formula (Ib) were made:

1-(2- (4-chlorophenyl)ethenyl) carbonyl-4-(4-fluorobenzyl)piperazine;

1-(2-(4-chlorophenyl) ethyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-(1-(*t*- butoxycarbonyl)amino-2-(4-chlorophenyl)ethyl)carbonyl-4-(benzyl) piperazine;

1-(3-(*t*-butoxycarbonyl)amino-2-(4- chlorophenyl)propyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 8), 4.8 (m, 1), 3.6-3.3 (m, 8), 2.6 (m, 2), 2. 3 (m, 3), 2.1 (m, 1), 1.4 (s, 9) ppm;

1-(2-(3,4,5- trimethoxyphenyl)ethenyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (d, 1), 7.3 (m, 4), 6.7 (m, 3), 3.9-3.6 (m, 13), 3. 5 (s, 2), 2.5 (m, 4) ppm;

1-(1-(3,4-dimethoxyphenyl)- 2-(4-chlorophenyl)ethenyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(2-(3,4,5-trimethoxyphenyl)ethyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((acetyl)amino)(4-chlorophenyl)methyl)carbonyl-4-(4- fluorobenzyl)piperazine, hydrochloride salt.

EXAMPLE 2

Compounds of Formula (Ia)

A. To a solution of (2*R*,5*S*)-1-(chloro)acetyl-4-(4-fluorobenzyl)-2, 5-dimethylpiperazine (0.29 g, 1 mmol) in anhydrous DMF (5 mL) was added 4- hydroxy-3-methoxyphenylacetonitrile (0.20 g, 1.2 mmol) and potassium carbonate (0.28 g, 2 mmol, powdered). The resultant mixture was stirred at 50°C. After 15 hours analysis by analytical HPLC (HPLC on a C18 Vydac column with 20-70% acetonitrile in water gradient with 0.1% trifluoroacetic acid) showed complete consumption of starting material had occurred. The mixture was poured into water and extracted with three portions of ethyl acetate. The combined organic extracts were washed sequentially with 0.5 N aqueous KOH solution, water, then brine. It was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. This was dissolved in ethyl acetate and treated with a solution of HCl in anhydrous ether. Filtration of the resultant solid afforded 0.38 g (85% yield) of

(2*R*,5*S*)-1- ((4-(cyano)methyl-2-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)-2,5- dimethylpiperazine, hydrochloric acid salt as a white solid: NMR (DMSO- d_6) 11.5 (br s, 1), 7.6 (m, 4), 6.9 (m, 3), 4.8 (br s, 2), 4.4 (br s, 3), 4.0 (m, 1), 3.9 (s, 2), 3.8 (s, 3), 3.6 (m, 1), 3.3 (m, 2), 3. 2-2.9 (m, 3) ppm.

B. In a similar manner, other compounds of formula (Ia) were made:

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.4 (br d, 1), 7.7 (m, 2), 7.2 (m, 4), 6.9 (br s, 1), 5.0 (m, 1), 4.8 (m, 2), 4.3 (m, 3) , 3. 7 (m, 2), 3.3 (m, 2), 2.9 (m, 1), 1.4-1.2 (m, 6) ppm;

1-((2- acetylaminophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.6 (br s, 1), 9.4 (s, 1), 8.0 (d, 1), 7.8 (br s, 2) , 7.2 (t, 2), 6.9 (m, 3), 5.0 (m, 3), 4.3 (m, 3), 3.8 (q, 1), 3. 6 (br s, 1), 3. 4 (m, 1), 2.8 (m, 1), 2.1 (s, 3), 1.3 (dd, 3), 1.2 (d, 3) ppm;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2- (methoxycarbonyl)methyl-4-(4-fluorobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-2-(ethoxycarbonyl)-4-(4-fluorabenzyl) piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6.2 (s, 2), 4.7-4. 2 (m, 4), 3.8 (m, 9), 3.5 (s, 2), 2.6 (d, 2), 2.2 (dd, 2), 1.3 (m, 6) ppm;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6.2 (s, 2), 4.6 (s, 3), 4.4 (m, 1), 4.1 (m, 1), 3.8 (s, 6), 3.85 (s, 3), 3.5 (m, 2), 2.8 (d, 1), 2.6 (d, 1), 2.1 (m, 2), 1.3 (m, 3) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 4.4 (m, 1), 4.1 (m, 1), 3.7 (m, 1), 3.4 (m, 2), 2.8 (m, 1), 2. 6 (d, 1), 2.0 (m, 2), 1.3 (m, 3) ppm;

1-((4- chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2) , 4.0 (m, 2), 3.7 (m, 1), 3.4-2.9 (m, 3), 2.7 (m, 1), 2.5 (m, 1), 2.1 (m, 1) , 1.1 (m, 3) ppm;

(2*S*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 4.4 (m, 1), 4.1 (m, 1), 3.7 (m, 1), 3.4 (m, 2), 2.8 (m, 1), 2.6 (d, 1), 2.0 (m, 2), 1.3 (m, 3) ppm;

4-((4-chiorophenoxy)methyl) carbonyl-3-(((4-chlorophenyl)amino)carbonyl)methyl-1-(benzyl)piperazin-2- one;

1-((phenoxy)methyl)carbonyl-2-ethyl-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-hydroxymethyl- 4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.7-4.5 (m, 3), 4.2-3.3 (m, 5), 3.2-2.7 (m, 2), 2. 3- 2.0 (m, 4) ppm;

1-(1-(4-chlorophenoxy)-1-methylethyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine;

(2*S*,5*R*)-1- ((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6.2 (s, 2), 4.6 (m, 34), 4.2 (m, 1), 3.8 (m, 6), 3.5 (m, 3), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 4), 0.9 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6.2 (s, 2), 4.6 (m, 3), 4.2 (m, 1), 3.8 (m, 6), 3. 5 (m, 3), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6.3 (s, 2), 4.7 (m, 2), 4.2 (m, 1), 3.8 (s, 6), 3.5 (m, 4), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*S*,5*R*)-1-((4-bromo-3,5-dimethoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.7 (d, 1), 7.8 (m, 2), 7.3 (m, 2), 6.3 (s, 2), 4.9 (m, 2), 4.3 (m, 2), 4.0-2.8 (m, 12), 1.4-1.2 (m, 6) ppm;

(2*S*,5*R*)-1-((4-nitro-3-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.4 (s, 1), 8.2 (d, 1), 7.3 (m, 4), 7.0 (t, 2), 4.8 (m, 3), 4.2-2.3 (m, 7), 1.3 (m 3), 1.0 (m, 3) ppm;

(*trans*) -1-((4-chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.2 (br s, 1), 8. 2 (s, 1), 7.4 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 5.9 (s, 1), 5.0-4.0 (m, 3), 3. 8-3.0 (m, 5), 2.8 (d, 1), 2.3 (d, 1), 1.3 (m, 3), 1.0 (br s, 3) ppm;

(2*R*,5*S*)-1-((4-chloro-2-(aminocarbonyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.2 (br s, 1), 8.2 (s, 1), 7.4 (m, 4), 7.0 (t, 2), 6.8 (d, 1), 5.8 (s, 1), 4.7 (m, 2), 3.7-3.1 (m, 5), 2.8 (d, 1), 2.3 (d, 1), 1. 3 (d, 3), 1.0 (br s, 3) ppm;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-((amino)carbonyloxy)methyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 11 (br d, 1), 7.9 (br s, 1), 7.6 (m, 2), 7.3 (m, 4), 5.2 (d, 1), 5.0 (m, 2), 4.3 (m, 4), 4. 0 (m, 1), 3.6 (m, 2), 1.3 (m, 6) ppm;

(*trans*)-1-((4- chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.9 (br d, 1), 7.9 (br s, 2), 7.6 (m, 1), 7.3 (m, 4), 5.0 (m, 2), 4.5 (s, 2), 4.3 (m, 2), 3.7-3.3 (m, 6), 1.3 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt; NMR (DMSO-d_6) 7.7 (br s, 3), 7.3 (m, 5), 5.2 (d, 1), 5.0 (m, 2), 47-4.2 (m, 4), 3.9-3.4 (m, 3), 1.3 (m, 6) ppm;

(*trans*)-1-((2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 9.1 (br s, 1), 8.2 (d, 1), 7.4 (dd, 1), 7. 3 (br s, 2), 7.1 (t, 1), 7.0 (m, 2), 6.9 (d, 1), 5.8 (br s, 1), 4.7 (m, 2) , 4.2 (m, 1), 3.7-3.4 (m, 3), 3.0 (br s, 1), 2.7 (br s, 1), 2.3 (d, 1), 1. 3 (m, 3), 1.0 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-amino-5- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt; NMR ($CDCl_3$) 10.9 (br d, 1), 7.8 (m, 2), 7.5 (dd, 1), 7.3 (m, 2), 6.8 (s, 1), 5.0 (m, 3), 4.3-3.2 (m, 7), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((4-methyl-2-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.9 (br d, 1), 10.4 (s, 1), 7.9 (s, 2), 7.5 (m, 2), 7.3 (m, 2), 7.0 (d, 1), 5.2 (m, 1), 5.0 (m, 2), 4.6 (m, 1), 4.3 (m, 3), 3.6 (m, 2), 2.8 (m, 1), 2.5 (s, 3), 1.4-1.1 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.9 (br d, 1), 10.4 (s, 1), 7.8 (s, 1), 7.5 (dd, 1), 7.3 (dd, 2), 7.0 (m, 3), 4.8 (m, 3), 4.1 (m, 1), 3.5 (m, 3), 3.0 (br s, 1), 2.7 (dd, 1), 2. 5 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine hydrochloride salt; NMR (DMSO-d_6) 11.0 (d, 1), 7.8 (t, 2), 7.3 (t, 2), 7.1 (m, 2), 6.8 (m, 2), 4.9-3.3 (m, 9), 2.8 (t, 1), 2.2 (s, 3) , 1.4-1.1 (m, 6) ppm;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 11.0 (d, 1), 7.8

(t, 2), 7.3 (m, 3), 7.1 (t, 1), 6.9 (m, 2), 5.0-3.2 (m, 11), 2.8 (t, 1), 1.4- 1.1 (m, 6) ppm;

(*trans*)-1-((3-chloro-5-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.8 (d, 1), 7.8 (m, 2), 7.3 (t, 2), 6.6 (s, 2), 6.5 (br s, 1), 5.0-3.2 (m, 12), 2.8 (m, 1), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 11.1 (d, 1), 7.9 (m, 2), 7.7 (br s, 1), 7.2 (m, 4), 5.2-3.3 (m, 12), 2.8 (t, 1), 1.4-1.2 (m, 6) ppm;

1- ((phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 (br d, 1), 7.7 (m, 2), 7.3 (m, 4), 6.9 (m, 3), 4. 9 (m, 3), 4.3 (m, 3), 4.0-2.8 (m, 5), 1.4 (d, 1.5), 1.2 (d, 1.5) ppm;

(*trans*)-1-((4-chlorophenylamino)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6). 7.4 (dd, 2), 7.1 (m, 4), 6.6 (d, 2), 5.8 (t, 1), 4.5 (br s, 0.5), 4.0 (br m, 1.5), 3.8 (br m, 1), 3.8-3.3 (m, 3), 3.0 (m, 2), 2.6 (m, 1), 2.2 (d, 1), 1.1 (br d, 3), 0.9 (br d, 3) ppm;

(*trans*)-1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11 (br d, 1), 7.7 (m, 4), 7.3 (m, 3), 5.0 (q, 2), 4.7 (m, 0.5), 4.4 (m. 2.5), 3.8 (m, 0.5), 3.6-2.9 (m, 6), 1.4 (d, 1.5), 1. 3 (d, 1.5) ppm;

(*trans*)-1-((4-chloro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.8 (br d, 1), 7.9-6.8 (m, 7), 5.1-2.8 (m, 10), 2.2 (s, 3), 1.3 (m, 6) ppm;

(*trans*)-1-((4-chloro- 2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (t, 2), 6.8 (m, 3), 4.8 (br s, 3). 4.1 (br s, 1), 3.5 (q, 3), 3.2 (q, 4), 3.0 (br s, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (br s, 3), 1 (m. 9) ppm;

(*trans*)-1-((4-chloro-2-hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7. 0-6.7 (m, 5), 4.9 (m, 0.5), 4.6 (br s, 2), 4.2 (m, 0.5), 3.6-3.2 (m, 3), 3.0 (br d, 1), 2.7 (br d, 1), 2.2 (d, 2), 1.3 (m, 3), 0.9 (m, 3) ppm;

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.8 (d, 1), 7.7 (m, 2), 7.3 (m, 4), 6.9 (d, 1), 5.0-4.3 (m, 6), 3.9-2.9 (m, 7), 1.4 (d, 1. 5), 1.2 (d, 1.5) ppm;

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0-6.7 (m, 3), 4. 7 (m, 4), 4.1 (m, 1), 3.5 (m, 2.5), 3.2 (m, 0.5), 3.0 (s, 1), 2.7 (dd, 1), 2.2 (d, 1), 2.1 (m, 1), 1.2 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(ureidomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.4 (m, 2), 7.1 (m, 4), 6.9 (d, 1), 6.4 (t, 1), 5.6 (s, 2), 5.0-4.0 (m, 4) , 3.5 (m, 2), 3.3 (d, 2), 3.0 (m, 2), 2.2 (m, 2), 1.2 (br d , 3), 0.9 (br d, 3) ppm;

1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2-methyl- 4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br d, 1), 7.7 (m, 2), 7.3 (t, 2), 6.9 (m, 3), 5.0-4.2 (m, 5), 3.9 (m, 1), 3. 6 (m, 1), 3.4 (m, 1), 3.0 (m, 3), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm;

1-((4-chloro-3-aminophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br d, 1), 7.8 (br s, 2), 7.3 (t, 2), 7.0 (d, 1), 6.4 (s, 1), 6.2 (d, 1), 4.8-4.2 (m, 5), 4.0 (m, 1), 3.6 (m, 1), 3.4 (d, 1), 3.2-2.9 (m, 4), 1.3 (m, 3) ppm;

(2*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9. 0 (s, 1), 8.2 (s, 1), 7.3 (t, 1), 7.0 (t, 3), 6.8 (q, 3), 5.0 (s, 2), 4.6 (dt, 2), 4.4 (d, 0.5), 3.7 (br s, 0.5), 3.4 (m, 2.5), 3.0 (t, 0.5), 2.8 (m, 1), 2.6 (d, 1), 2.1 (m, 3), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm;

(2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.0 (s, 1), 8.2 (s, 1), 7.3 (t, 1), 7.0 (t, 3), 6.8 (q, 3), 5.0 (s, 2), 4.6 (dt, 2), 4.4 (d, 0.5), 3.7 (br s, 0.5), 3.4 (m, 2.5), 3.0 (t, 0.5), 2.8 (m, 1), 2.6 (d, 1), 2.1 (m, 3), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm;

(*trans*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.8 (br s, 1), 8.2 (br s, 2), 7.8 (br s, 2), 7.7 (br s, 1), 7.3 (m, 2), 6.8 (br s , 2), 5.2- 4.3 (m, 5), 3.9-3.1 (m, 5), 2.8 (t, 1), 1.5-1.1 (m, 6) ppm;

(2*R*,5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9. 0 (s, 1), 8.3 (s, 1), 7.3 (t, 1), 7.0 (t, 3), 6.8 (m, 3), 5.0 (s, 2), 4.6 (m, 2), 4.2 (d, 0.5), 3.7-3.4 (m, 2.5), 3.2 (m, 2), 2.7 (d, 1), 2.5(m, 1), 2.2 (d, 1), 1.3 (br d, 3), 1.0 (br d, 3) ppm;

(*trans*)-1- ((4-bromo-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 10.4 (s, 1), 8.0 (s, 1), 7.6 (dd, 1), 7.3 (m, 2), 7.0 (m, 3), 4.8 (m, 3), 4.1 (br d, 1), 3.5 (m, 3), 3. 0 (m, 1), 2.7 (dd, 1), 2.3 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

1- ((4-chloro-2-methoxycarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (br d, 1), 7.7 (m, 3), 7.6 (dd, 1), 7.3 (t, 2), 7.0 (d, 1), 5.0 (do, 2), 4.7 (m, 1), 4.4 (m, 3), 3.8 (m, 4), 3.4 (m, 2), 3.0 (m, 2), 1.4 (d, 1.5), 1.2 (d, 1. 5) ppm;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.9 (br s, 2), 7.8 (s, 1), 7.4 (m, 1), 7.1 (t, 2), 7.0 (d, 1), 4.8 (m, 3), 4.4 (m, 2), 3.9 (m, 4), 3.5 (m, 2), 2.8 (m, 2), 1.6 (m, 3) , 1.3 (m, 3) ppm;

1-((4-chloro-2-aminocarbonylphenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.6 (br s, 1), 8.0 (s, 1), 7.6 (dd, 1), 7.4 (dd, 2), 7. 2 (t, 2), 6.9 (d, 1), 5.0 (m, 3), 4.4 (m, 2), 4.0 (m, 1), 3.8 (m, 2), 3.6 (m, 1), 3.1 (m, 1), 2. 9 (m, 1) , 1.6 (d, 1.5), 1.4 (d, 1.5) ppm;

1-((4-chloro-2- (aminocarbonyl) phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br s, 1), 7.9 (br s, 1), 7.7 (m, 3), 7.2 (m, 2), 6.6 (d, 1), 4.8 (br s, 1), 4.4-3.9 (m, 6), 3.4 (d, 1), 3.0 (m, 3), 1.4 (m, 3) ppm;

(2*R*)-1-((4-chloro-2- aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 9.1 (s, 1), 8.2 (s, 1), 7.4 (dd, 1), 7.3 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 5.8 (br s, 1), 4.8 (m, 3), 3. 5 (m, 3), 2.9 (d, 1), 2.7 (d, 1), 2.2 (m, 2), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (br d, 1), 10.4 (s, 1), 7.6 (m, 4), 7.3 (t, 2), 7.2 (d, 1), 5.2 (m, 2), 4.7 (m, 1), 4.3 (m, 3), 3.9 (m, 1), 3.6 (m, 1), 3.1 (m, 3), 1.5 (d, 1.5), 1.3 (d, 1.5) ppm;

(2*R*,5*S*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.5 (s, 1), 7.8 (s, 1), 7.5 (d, 1), 7.3 (m, 2), 7.0 (t, 3), 4.8 (m, 3), 41 (m, 1), 3.5 (m, 3), 3.1 (br s, 1), 2.7 (dd, 1), 2. 3 (dd, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*R*)-1-((4-chloro- 2-formylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.4 (s, 1), 7.8 (s, 1), 7.5 (d, 1), 7.3 (m, 2), 7.0 (t, 3), 4.8 (br s, 2), 4.7 (m, 1), 4.2 (m, 1), 3.4 (m, 3), 3. 1 (m, 1) , 2.8 (br d, 1), 2.6 (br d, 1), 2.1 (m, 1), 2.0 (dd, 1), 1.3 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-cyanophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.5 (dd, 1), 7.3 (m, 2), 7.0 (m, 4), 4.8 (m, 3), 4.1 (m, 1), 3.5 (m, 3), 3.0 (m, 1), 2.7 (m, 1), 2.2 (m, 1), 1.3 (m, 3), 0.8 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.8 (br d, 1), 7.8 (s, 2), 7.5 (m, 2), 7.3 (m, 3), 7. 2 (m, 1), 5.3 (m, 1), 5.0 (s, 2), 4.3 (m, 3), 4.0 (m, 1), 3.8-3.3 (m, 2), 2. 8 (m, 1), 2.6 (s, 3), 1.4 (dd, 3), 1.3 (m, 3) ppm;

1-((2- (acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 11.0 (br s, 1), 9.4 (s, 1), 8.0 (d, 1), 7.6 (d, 2), 7.3 (t, 2), 7.0 (m, 3), 4.9 (q, 2), 4.7 (m, 1), 4. 3 (m, 3), 3.9 (m, 1), 3.6-2.8 (m, 4), 2.1 (s, 3), 1.4 (d, 1.5), 1.3 (d, 1. 5) ppm;

(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (br d, 1), 7.9 (s, 2), 7.5-7.3 (m, 6), 5.2 (d, 1), 4.9 (m, 2), 4.3 (m, 3), 3.6 (m, 2) , 3.2 (m, 1), 2.8 (m, 1), 1.5-1.2 (m, 6) ppm;

(2*R*, 5*S*)-1-((3-hydroxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6)10.5 (br d, 1), 9.3 (s, 1), 7.8 (s, 2), 7.2 (m, 2), 6.2 (s, 2), 6.1 (s, 1), 4.7 (m, 4) , 4.3 (m, 3), 3.8 (m, 1), 3.6 (m, 1), 2.8 (m, 1), 2.2 (s, 3), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-methyl-2-aminophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 11.0 (br m, 1), 7.8 (s, 2), 7.2 (m, 5), 5.3 (m, 1), 5. 0 (m, 2), 4.3 (m, 3), 4.0 (m, 1), 3.5 (m, 2), 2.8 (m, 1), 2.2 (s, 3), 1.3 (m, 6) ppm;

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (br d, 1), 10.0 (s, 1), 7.9 (s, 2), 7.5 (m, 2), 7.3 (m, 3), 6.9 (m, 1), 5. 2 (m, 1), 4.9 (m, 2), 4.3 (m, 3), 4.0 (m, 1), 3.6 (m, 2), 2.8 (m, 1) , 1.3 (m, 6) ppm;

(*trans*)-1-((4-methyl-2-acetylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.5 (s, 1), 7.3(m, 3), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 3), 4.2 (br d, 1), 3.6 (m, 1), 3.5 (q, 2), 3.0 (br s, 1), 2.7 (m, 4), 2. 2 (m, 4), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((2- methoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 12.1 (s, 1), 7.8 (m, 3), 7.3 (br s, 1), 7.0 (br s, 4), 4.8 (m, 2), 4.3 (m, 3), 3.9 (m, 5), 3.6 (m, 1), 2.8 (m, 1), 2.4 (m, 1), 1.6 (m, 3), 1.3 (m, 3) ppm;

(*trans*)-1-((3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 10.8 (br d, 1), 7.8 (m, 3), 7.7 (m, 1), 7.6 (t, 1), 7.4 (d, 1), 7.3 (t, 2), 5.2 (m, 1), 5.0 (m, 2), 4. 7 (m, 1), 4.3 (m, 3), 4.0 (m, 1), 3.6 (m, 1), 2.8 (m, 1), 1.4 (m, 3), 1.3 (m, 3) ppm;

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 9.7 (br d, 1), 8.6 (s, 1), 8.5 (s, 1), 8.1 (d, 1), 7.8 (s, 1), 7.6 (br s, 3), 7.3 (t, 3), 5.4 (d, 1), 5.1 (m, 2), 4.6 (m, 1), 4. 3 (s, 2),4.2 (m, 1), 3.7 (m, 1), 3.4 (m, 1), 3.0 (m, 1), 2.6 (s, 3), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl) carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br d, 1), 8.0 (m, 3), 7.3 (m, 2), 7.0 (m, 2), 5.3 (d, 1), 5.0 (m, 2) , 4. 3 (m, 3), 3.7-3.3 (m, 2), 3.0 (m, 1), 2.8 (m, 1), 2.6 (s, 3), 1.4 (m, 3), 1.3 (m, 3) ppm;

(*trans*)-1-((5-nitro-2-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 10.5 (br d, 1), 7.7 (m, 4), 7.4 (d, 1), 7.3 (t, 2), 5. 3 (d, 1), 5.1 (m, 2), 4.7 (m, 1), 4.3 (m, 2), 3.9 (q, 1), 3.6 (br d, 1), 3. 4 (m, 1), 2.9 (dd, 1), 2.3 (s, 3), 1.4 (m, 3), 1.3 (m, 3) ppm;

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br d, 1), 7.9 (t, 2), 7.3 (m, 4), 7.0 (d, 1), 4.8 (m, 3), 4.3 (m, 3), 3.9 (m, 1) , 3.6 (m, 1), 3.2 (m, 1), 2.8 (t, 1), 1.4 (dd, 3), 1.3 (dd, 3) ppm;

(*trans*)-1-((5-nitro-2-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br d, 1), 7.9 (t, 2), 7.7 (d, 1), 7.6 (s, 1), 7.3 (t, 2), 6.7 (d, 1) , 5. 0 (m, 3), 4.7 (m, 1), 4.3 (m, 2), 4.0 (q, 1), 3.6 (m, 1), 3.3 (m, 1), 2.8 (t, 1) , 1.4 (dd, 3), 1.3 (dd, 3) ppm;

(*trans*)-1-((2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.3 (m, 1), 7.9 (br s, 2), 7.8 (br m, 1), 7.3 (m, 4), 7.0 (t, 1), 5.3 (m, 1), 5.0 (m, 2), 4.6 (m, 1), 4.3 (m, 2) , 3.6 (m, 3), 2.8 (m, 1), 1.3 (m, 6) ppm;

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.5 (br d, 1), 7.8 (s, 2), 7.3 (m, 2), 7.1 (t, 1), 6.5 (m, 3), 4.8 (m, 2), 4.3 (m, 3), 3.8 (m, 1), 3.6 (m, 1), 3. 4 (m, 2), 2.8 (t, 1), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)- 1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;; NMR (DMSO-d_6) 11.2 (br s, 1) , 7.9 (br s, 2), 7.3 (m, 3), 7.1 (s, 2), 5.2 (d, 1), 4.9 (s, 2), 4.3 (m, 3), 3.9-3.4 (m, 9), 2.8 (m, 1), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((5-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.2 (br d, 1), 7.9 (dd, 2), 7.6 (m,

1), 7.3 (t, 2), 6.6 (q, 2), 5.3 (d, 1), 5.0 (s, 2), 4.3 (m, 3), 3.8 (s, 3), 3.4 (m, 3), 2.8 (m, 1), 2.6 (s, 3), 1.5-1.2 (m, 6) ppm;

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.8 (br d, 1), 9.1 (br s, 1), 7.9 (d, 1), 7.8 (br s, 2), 7.4 (t, 1), 7.2 (m, 3), 7.0 (t, 1), 5.2 (d, 1), 5.0 (m, 2), 4. 3 (m, 3), 3.9-3.4 (m, 7), 2.8 (dd, 1), 14-1.2 (m, 6) ppm;

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.0 (br s), 7.7 (m, 3), 7.4 (t, 1), 7.3 (t, 2), 7.0 (dd, 2), 5.0 (m, 2), 4.5 (m, 1), 4.2 (m, 5), 3.8 (q, 1), 3.6 (t, 2), 3.4 (m, 2) , 2.9 (m, 1), 1.3 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1- ((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.5 (br d, 1), 7.8 (t, 2), 7.3 (t, 2), 6.9 (m, 4), 4.8 (m, 3), 4.4 (m, 1), 4.3 (m, 2), 3.9 (m, 3), 3.6 (m, 3), 3.4 (m, 1), 2.8 (m, 1), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((2-acetyl-4,5-dimethylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.4 (br s, 1), 7.8 (m, 2), 7.4 (s, 1), 7.2 (t, 2), 6. 8 (m, 1), 5.2 (d, 1), 4.9 (s, 2), 4.3 (m, 3), 3.8 (m, 1), 3.6 (m, 1), 3.4 (m, 1), 2.8 (m, 1), 2.6 (s, 3), 2.2 (s, 3), 2.1 (s, 3), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((5-methoxy-2-(methoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.0 (br d, 1), 7.9 (br s, 2), 7.7 (d, 1), 7.3 (m, 2), 6.6 (m, 2), 5.0 (m, 3), 4.3 (m, 3), 3.8 (s, 3), 3.7 (s, 3), 3. 6 (m, 1), 3.4 (m, 2), 2.8 (dd, 1), 1.4 (dd, 3), 1.2 (dd, 3) ppm;

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 7.4 (t, 2), 7.15 (t, 2), 7. 1 (d, 2), 6.6 (d, 2), 5.8 (t, 1), 4.5 (m, 1), 4.2 (m, 1), 3.9 (m, 1), 3.7 (m, 1), 3.4 (m, 1), 3.3 (m, 1), 2.9 (m, 1), 2.8 (d, 1), 2.6 (d, 1), 2.0 (m, 2), 1.3 (d, 1.5), 1.1 (d, 1.5) ppm;

(*trans*)-1- ((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (d, 1), 7.4 (d, 1), 7.3 (m, 2), 7.0 (m, 3), 6.8 (s, 1), 6.3 (d, 1), 4.7 (m, 3), 4.1 (m, 1) , 3.6 (m, 3), 3.0 (br s, 1), 2.7 (br d, 1), 2.2 (d, 1), 1.3 (m, 3), 1.0 (m, 3) ppm;

(*trans*)-1-((2-chloro-4-carboxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((1-nitroso-3,6-di(hydroxysulfonyl)naphthalen-2-yloxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-nitroso-4-hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,6-di(hydroxysulfonyl)naphthalen-1- yloxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-hydroxysulfonyl-6-aminonaphthalen-1-yloxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-hydroxysulfonyl-7-aminonaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((5- hydroxysulfonylquinolin-8-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dinitro-7- hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4- hydroxysulfonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-amino-4-hydroxysulfonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-formyl-2,6-di-*t*-butylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- (morpholin-4-yl)methyl-2,5-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((4- (methoxycarbonyl)-2,6-dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((4-(hydroxysulfonyl) naphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3,6-di(hydoxysulfonyl)-8- aminonaphthalen-1-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-5-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-trifluromethyl-2,3,5,6,-tetrafluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-formyl-5-(2-hydroxy-3-methoxy-5-formylphenyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-carboxy-2,3,5,6-tetrafluorophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-(adamant-1-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(adamant-1-yl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-di((1-methyl-1-phenyl)ethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetyl-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-*t*- butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetyl-4-chloro-5-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-4-chloro-6-nitrophenxoy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-4,6- dibromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-formyl-4,6-di(*t*-butyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3,5-dinitrophenoxy)methyl)carbonyl-2,5-dimethyt-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2,6-dichloro-4- ethoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-ethoxycarbonyl-4-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-6-(prop-3-enyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- fluoro-4-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-acetyl-4-methyl-6-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methylbenzothiazol-5-yloxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(4-(trifluoromethyl)phenoxy)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(1*H*-pyrazol-3-yl)-4-chloro-5-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2- (1*H*-pyrazol-3-yl)-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(((2-phenyl-4-oxo-7- hydroxy-4*H*-1-benzopyran-3-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-chloro-3- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-methoxy-4-(butoxymethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((6-hydroxyquinolin-2-yloxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxycarbonyl- 6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2,5-di(*t*-butyl)-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-formyl-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(2 *H*-benzotriazol-2-yl)-4-(2-hydroxyethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(methylthio)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5- di(*t*-butyl)-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dibromo-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-diiodo-4-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- nitro-4-methoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(ethoxycarbonyl)indol-5-yloxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-(2-carboxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dinitro-4- (carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-3-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((6-carboxynaphthalen-2-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-difluoro-4- ethylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(2-(methoxycarbonyl)ethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(prop-3-enyl)-4-acetylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- oxo-2*H*- benzofuran-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6-tribromo-3,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(heptylcarbonyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-nitro-4-phenylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methoxy-4-(eth-2-enyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((2-chloro-4- methoxycarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2,6-diiodo-4-cyanophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-diiodo-4-carboxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- phenyl-4-oxo-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-phenyl-4-oxo- 7-methoxy-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-(((2-phenyl-4-oxo-7- methoxy-2,3-dihydro-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- octylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((4-phthalimid-1-ylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-(morpholin-4-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-chloro-4- bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-7-methoxy-2*H*-1-benzopyran-8-yl) oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-5-fluorophenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(1- methylcyclohex-1-yl)-4-methyl-6-(2-hydroxy-3-(1-methylcyclohex-1-yl)-5- methylbenzyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-formyl-3-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4-carboxy-6- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethyl-4-carboxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-(2-(carboxy)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4-(hydroxymethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-dibromo-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- (ethoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-amino-4-(methoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-(4-nitrophenyl)eth-2-enyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-acetyl-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(*t*- butyl)-4-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- (ethoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-cyclohexyl-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethyl-4-chlorophenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-ethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-*n*-butylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((3-carboxy-1-bromonaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- bromo-4-nitro-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dichloro-4-(ethoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((4-methyl-2-oxo-2*H*-1-benzopyran- 6-yl) oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dibromo-4-formyl-6-methoxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- (2-(4-nitrophenyl)eth-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,4,6-tribromo-3- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-benzyl-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2- (bezothiazol-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-6-fluorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-ethoxy-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-bromo-4,6-di(*t*-butyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(pyrrolidin-1-yl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(morpholin-4-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(piperidin-1-yl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-4-chloro-6-bromophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((4,7- dimethoxy-5-formylbenzofuran-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-4-methyl-8- nitro-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4-bromo-6-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dimethyl-6-*t*-butylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((2-nitro-4-(hydroxysulfonyl)naphthalen-1-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (hydroxysulfonyl)-6-aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (hydroxysulfonyl)-7-aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (methoxycarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-*n*-butylcarbonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-ethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(((2-ethyl)hexoxy) carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-((*n*-pentoxy)carbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-5-(methoxycarbonyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2, 4,6-tribromo-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methoxy-4-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2- (phenyl)eth-2-enyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(1,2,4-triazol-1-yl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-chloro-5-methylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(*n*-hexoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- formyl-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-4-(2-(ethoxycarbonyl) ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,4,6-tetrachlorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- ((2-methylpropoxy)carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-(*n*- butoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(phenylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-hydroxymethyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-mercaptophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine:

(trans)-1-((2-nitro-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-di(1-methylbutyl) phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-trifluoromethyl-4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dibromo-4-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-6- acetyl)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxycarbonyl-4-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- formyl-4-bromo-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,6-diformyl-4-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2, 6-dinitro-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-4-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-formyl-4-nitro-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(aminocarbonyl) methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxycarbonyl-4-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((2-phenyl-4-oxo-4*H*-1-benzopyran-6-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- chloro-4-trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-3-methyl-6- isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((5,7-dibromo-2-methylquinolin-8- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,7-dichloro-2-methylquinolin-8-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-dinitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4-(1,1-dimethylpropyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-diphenyl-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-3- methyl-6-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-4-(carboxy)methyl-2*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-4-trifluoromethyl-2*H* -1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-d imethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-*t*-butyl-4-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-6-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxycarbonyl- 4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-bromo-5-fluorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4- di(1,1-dimethylpropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methyl-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,4-trifluorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5- difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-5-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- methyl-3-(ethoxycarbonyl)indol-5-yl)oxy)methyl)carbonyl-2, 5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-aminocarbonyl-4- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dinitro-3-*t*-butylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-fluoro-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-3- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(2-ethylhexoxy)carbonylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,4,6-tribromo-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((4-(4-bromophenyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(4- carboxypheny)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3,6-trifluorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,4,5-trifluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6- trifluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-fluoro-5-trifluoromethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2,4-dinitronaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3,6- di(hydroxysulfonyl)-8-aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- acetyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-dimethyl-4-(1-(3,5-dimethyl-4- hydoxyphenyl)-1-methylethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(3-(4- hydroxyphenyl)hex-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((6-(hydroxysulfonyl) naphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-chloro-4-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-bromo-4,5-difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2- (methoxycarbony)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2,6-diphenyl-4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2- amino-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-4-fluorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methyl-4-iodophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-6- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-3-isopropyl-6-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-carboxy-3,4,6-trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-6- isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(piperidin-1-yl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2,3-dihydro-2,2-dimethylbenzofuran-7-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(*t*-butyl)-4-(1-methylpropyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-methyl-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((phenanthren-9-yl) oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-3- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-chloro-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-4-bromo-6- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-(acetyl)methylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(5-mercaptotetrazol-1-yl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6-triiodo-3- (2-carboxy)butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-hydroxymethyl-4-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,5,6-tetrafluoro-4-(2,3,4,5,6-pentafluorophenyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(benzotriazol-2-yl)-4,6-di(1,1-dimethylpropyl) phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenyl-3-hydroxy-4-oxo-4*H*-1-benzopyran-6- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((indanonyl)oxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-3-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(2,4-dinitrophenyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methyl-4- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dibromo-4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- diiodo-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine:

(trans)-1-((2-formyl-4-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-amino-5-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-amino-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- amino-4-*t*-butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-3-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-5-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-methyl-4-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,5-dimethyl-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dibromo-4- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- aminocarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-aminocarbonyl-4-chlorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6- tri(dimethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-hydroxymethyl-6-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(methoxycarbonyl)- 5-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-4-(methoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4-(prop-3-enyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-acetyl-5-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetyl-4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetyl-3-methoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-dimethoxy-4-acetylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(*t*-butyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4- di(*t*-butyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3,5-di(*t*-butyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(isopropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- (ethoxycarbony)methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((2-ethoxy-5-prop-2- enylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-5-prop-2-enylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-di(1-methylpropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-difluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-diphenylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-3- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-cyclopentyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-cyclopentylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-difluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans)*-1-((2-carboxy-6-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- amino-4-chloro-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,4-difluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-6-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2,4- dicarboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3-dimethoxy-5-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-bromo-4-fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dichoro-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methyl-4-isopropylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1- (((fluoren-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-diethylaminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)- 1-((2-amino-3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-3,4,8- trimethyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-acetyl-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-4-bromophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- (methylcarbonyl)amino-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((1-acetylnaphthalen- 2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- methyl-5-isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-4-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1- aminonaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-aminonaphthalen-1-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methoxy-4-(1,2-dihydroxyethyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-(2- aminoethyl)indolin-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5-chloroquinolin-8- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-(2-(amino)ethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(2-(amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-(2- (amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4-diaminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(diethylamino)methyl-4- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-5-(2-aminobutyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-bromo-6-fluorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- iodophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(2-carboxyethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dibromo-3-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-dichloro-3-carboxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-carboxyethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(2- hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-(2-hydroxyethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(2-hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-(2- hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4-dibromo-6-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-6- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-diiodo-6-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-6-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-ethoxy-6-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-5-(diethylamino)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-formyl-5-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formyl-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-formyl-4-bromophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-formyl-4-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((4-methoxynapthalen- 1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-5,6-dimethoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- nitro-4-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((fluoren-9-on-1-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((4-hydroxy-1,2,3,4-tetrahydronaphthalen-8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2, 3,4,5,6-pentabromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-3,4,5,6- tetrabromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3,4-trichlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methyl-4-bromo-6-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6-triiodophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- formyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1-bromonaphthalen-2-yl)oxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1,6- dibromonapthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((1-nitrosonaphthalen-2-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2,4-dichloronaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- nitronaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-carboxynaphthalen-1-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-methylnaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3- (hydroxysulfonyl)-7-(dimethylamino)naphthalen-1-yl)oxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((4- methoxynaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((1-formylnapthalen-2-yl)oxy) methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1-carboxynaphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1- amino-4-(hydroxysulfonyl)naphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(naphthalen-2- yl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-aminonaphthalen-2-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- fluoro-4-(carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4-(carboxymethyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methoxy-4-(carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- hydroxymethylphenxoy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(hydroxymethyl)-4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((2,6-di(hydroxymethyl)-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((4-mercaptophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-carboxyindol-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-(((3-carboxyindol-5- yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((indol-4-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((indol-5-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(benzoxazol-2-yl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-(((2-methylquinolin- 8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,7-dibromoquinolin-8-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,7- diiodoquinolin-8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((5-nitroquinolin-8-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((quinolin-5-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5-(hydroxysulfonyl)- 7-iodoquinolin-8-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-2,5,7,8-tetramethyl-2,3- dihydro-1- benzopyran-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-3-chloro-4-methyl-2*H* -1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-3-(diethylamino)methyl)-4- methyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-6-methoxy-2 *H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-2*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-4-formyl-6-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-formyl-6-iodophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-ethoxy-4-formylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-carboxy-4-formylphenox)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-6- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dinitro-6-formylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4- dinitro-6-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4-dinitro-6-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5-dinitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dinitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- nitro-4-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitro-4-formyl-6-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dinitro-4-methylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- nitro-4-(carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dichlorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methoxy-5-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((4-cyanophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(1-methyl-1-phenylethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (ethylamino)-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-acetylnaphthalen- 1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(carboxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- (carboxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((benzotriazol-1-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((quinolin-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,4- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4,6-tri(*t*-butyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethoxy-4-(methoxycarbonyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-trifluoromethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-5- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(4-cyanophenyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- nitro-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-methylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- methylphenox)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(methoxycarbonyl)methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((carbazol-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2-oxo-1,3- benzothiol-2-on-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-3-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((2-oxo-4-methyl-2*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine,

(trans)-1-((3- carboxy-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-5-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-6-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((quinolin-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-diaminophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(hydroxysulfonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-(((fluorenon-9-on-2-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5,6,7, 8-tetrahydronaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-(((5,6,7,8- tetrahydronaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-9-((2,4,6- tribromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dibromo-4-cyanophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine:

(trans)-1-((2,3,5,6-tetrafluorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3-dichlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,6- trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine

(trans)-1-((2-chloro-4,5-dimethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5-dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(methylcarbonyl)aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-isopropoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(benzyloxy)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-ethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-(ethoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(ethylcarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(*t*-butyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(1-methylpropyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,3-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3,5- trimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3,6-trimethylphenxoy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,4-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,6-trimethoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-5-isopropylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,5-dimethyl-4-(diethylamino)methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(*t*-butyl)-6-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-prop-3-enyl-6-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-prop-2-enylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-ethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-*n*-propylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((3-fluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-difluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-chloro-4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dichlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- iodophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-(phenylamino)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-phenylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-trifluoromethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- *t*-butylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-isopropylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-methyl-4-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,4-dimethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-*t*-butyl-5-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- isopropyl-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-ethylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dimethyl-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-dibromo-4-fluorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-bromo-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-isopropyl-4-chloro-5-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(methylcarbonyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-ethoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-propoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-*n*- butoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-*n*-hexoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- *n*-heptoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(propoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(ethylcarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(1,1,3,3-tetramethylbutyl)phenoxy) methyl) carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(1,1-dimethylpropyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(1-methylpropyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- acetyl-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine,

(trans)-1-((2-(*t*-butyl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-(ethylamino)-4-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-(methoxycarbonyl)methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-ethylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-*n*-propylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4,6-dibromophenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4,6- dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4,6-diiodophenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-6-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-6-methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-carboxy-5-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-5-methoxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-4-bromophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-carboxy-4-fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-carboxy-4-iodophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- carboxy-4-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-chlorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,3, 4-trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,3,4,5,6-pentachlorophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,4,5-trichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methoxyphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((3-(ethoxycarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dimethyl-4- bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dimethyl-4-bromophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- methyl-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-isopropyl-4-chloro-5-methylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-ethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(*t*-butyl)-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-formyl-4-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-prop-3-enylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(1-phenyethyl)-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(ethoxycarbonyl)methylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-trifluoromethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-fluoro-4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-fluoro-4-chlorophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((7- methoxynaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-benzyloxy-4-cyanophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-chloro-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-bromo-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3,5-dimethoxy-4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dibromo-3,5-dimethoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-methyl-3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dimethoxyphenoxy)methyl)carbonyl-2, 5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- nitro-3-carboxy-6-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-cyanophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-5- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-(carboxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-5-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(dimethylamino)methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-(dimethylamino)ethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((naphthalen-1-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((5- aminonaphthalen-1-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-nitro-4-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,6-di(*t*-butyl)-4-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- carboxy-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-5-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-nitro-4-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(benzyloxy)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((3,5- di(trifluoromethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4-dibromophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dibromo-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,4-dichlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3,5-dimethyl-4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dicarboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-dichloro-4-carboxyphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((2- carboxyquinolin-4-yl)oxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-dimethyl-4-formylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6-di(*t*-butyl)-4-carboxyphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- amino-5-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2,6-di(*t*-butyl)-4- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((4-carboxyquinolin-2-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-nitro-4-chlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-ethyl-4-chloro-5- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-di(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(morpholin-4-yl)methyl-4-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-cyanophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- chloro-4-bromophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-trifluoromethylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methyl-4-acetylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-(dimethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-methyl-4- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dimethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- phenylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(ethoxycarbonyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-benzylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-carboxynaphthalen-2-yl)oxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-(((quinolin-8-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((3,5-dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(cyclohexyl) phenoxy)methyl)carbonyl-2,5-dlmethyl-4-(4-fluorobenzyl)plperazine;

(trans)-1-(((quinolin-6-yl)oxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((2,4-dichloro-3-methylphenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2, 5-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-bromophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (methylcarbonyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-acetylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3-trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(trans)-1-((4-bromophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-5- formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((tropinon-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-5- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-5-formylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- formyl-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-carboxy-5-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-amino-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-amino-3- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-aminophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dichloro-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-fluoro-4-nitrophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2,3-difluoro-6-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-chloro-4- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-nitro-4-cyanophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- bromo-4-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((3-chlorophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)plperazine;

(trans)-1-((3,4-dichlorophenoxy)methyl)carbonyl-2, 5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5- dichlorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,4,5-trimethylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((3,5-dimethyl-4-chlorophenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(methoxycarbonyl)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4- trifluoromethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-*t*-butylphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-isopropylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((naphthalen-2-yl)oxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((6-bromonaphthalen-2-yl)oxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(trans)-1-((3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-methoxy-5-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((1,3-benzodioxolan-5-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2,6- dimethyl-4-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-nitrophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- methoxy-4-(amino)methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((3-(aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-ffluorobenzyl)piperazine;

(trans)-1-((3-(methoxycarbonyl)methylphenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-(4-phenylcarbonyl)-4-fluorophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((2-(1-methyl)cyclohexyl-2,4-dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2- (benzyloxycarbanyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(4-(methyl)phenylcarbonyl)-5- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonyl-5-octoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-octylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(2-(carboxy)phenylcarbonyl-5- di(*n*-butyl)aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonyl-5- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-methoxy-4-(3-hydroxyprop-2-enyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-(((3-(phenylaminocarbonyl)naphthalen-2-yl)oxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-(((6-(phenylcarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-((2- phenylethyl)carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(trans)-1-((4-((4-fluorophenyl) carbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((2-(phenylamino)carbonylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonyl-4- chloro-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(trans)-1-((4-(4-chlorophenyl)carbonylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-benzylcarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((2-phenylcarbonyl-4- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-(2-methylcarbonylethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans) -1-((4-phenylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fiuorobenzyl)piperazine; and

(trans)-1-((3- phenylcarbonylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine.

C. In a similar manner, the following compounds of formula (Ib) were made:

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.6 (m, 3), 7.5 (m, 4), 6.2 (s, 2), 4.6 (m, 4), 4.2 (m, 4), 3.8 (m, 9), 3.4 (m, 1), 2.6 (m, 1) ppm;

1-((3- methoxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 5), 6.5 (m, 4), 4.6 (s, 2), 3.8-3.5 (m, 9), 2. 4 (m, 4) ppm;

1-((3,4-dimethoxyphenoxy)methyl)carbonyl-4-(benzyl) piperazine; NMR ($CDCl_3$) 7.8 (m, 2), 7.4 (m, 3), 6.8 (d, 1), 6.6 (d, 1), 6.4 (dd, 1), 4.8 (d, 2), 4.3 (m, 3), 4.0 (m, 1), 3.7 (s, 3), 3.65 (s, 3), 3.6-3.3 (m, 8), 3.2-2.9 (m, 3) ppm;

1- ((phenoxy)methyl)carbonyl-4-(benzyl)piperazine and 1-(chloro)acetyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 7), 7.0 (m, 3) , 4.7 (s, 2), 3.6 (m, 6), 2.4 (m, 4) ppm;

1-((4-chlorophenoxy) methyl)carbonyl-4-(benzyl)piperazine and 1-(chloro)acetyl-4-(benzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 7), 6.9 (m, 2), 4.6 (s, 2), 3.6 (m, 6), 2.4 (m, 4) ppm;

1-((3-cyanophenoxy)methyl) carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (m, 4), 6.8 (m, 3), 4.4 (q, 2), 4.2 (d, 1), 3.9 (d, 2), 3.6 (m, 3), 3.0 (m, 3), 2.6 (m, 2) ppm;

1-((4-cyanophenoxy)methyl)carbonyl-4- (benzyl)piperazine; NMR ($CDCl_3$) 7.6 (m, 4), 7.4 (m, 3) , 7.0 (d, 2), 4.9 (q, 2), 4.6 (d, 1), 4.3 (d, 2), 4.0 (d, 2), 3.6 (t, 1), 3. 4 (d, 2), 3.0 (m, 2) ppm;

1-((3-(1-methylimidazolin-2yl) phenoxy)methyl)carbonyl-4-(benzyl)piperazine; NMR ($CDCl_3$) 7.5 (m, 6), 7.2 (m, 3), 5.0 (d, 2), 4.0 (m, 4), 3.3 (q, 4), 3.0 (m, 6) ppm;

1-((4-chloro-2-aminocarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine; NMR (DMSO-d_6) 8.7 (s, 1), 7. 8 (s, 1), 7.7 (s, 1), 7.6 (dd, 1), 7.4 (q, 3), 7.2 (d, 1), 5.0 (s, 2), 3. 4 (br d, 4), 3.3 (s, 2), 2.4 (br d, 4) ppm;

1-((5-chloroquinolin- 8-yloxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.0 (s, 1), 8.5 (d, 1), 7.75 (dd, 1), 7.65 (d, 1), 7.4 (q, 2), 7.1 (d, 1), 5.1 (s, 2), 3.5 (m, 6), 2.4 (br d, 4) ppm;

1- ((3-trifluoromethoxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-(3-(3,4,5-trimethoxyphenoxy)propyl)carbonyl-4-(benzyl)piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)propyl)carbonyl-4-(benzyl) piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)pentyl)carbonyl-4- (benzyl) piperazine;

1-((4-methoxyphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3-chlorophenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)ethyl)carbonyl- 4-(benzyl) piperazine;

1-((3,4-dichlorophenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3,5-dichlorophenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((3,4,5-trimethylphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((4-nitrophenoxy)methyl)carbonyl-4-(benzyl) piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)septyl)carbonyl-4- (benzyl) piperazine;

1-(1-(3,4,5-trimethoxyphenoxy)-2- methylpropyl)carbonyl-4-(benzyl)piperazine;

1-(1-(3,4,5- trimethoxyphenoxy)butyl)carbonyl-4-(benzyl)piperazine;

1-((4- bromophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- fluorophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- trifluoromethylphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1- (((4-chlorophenyl)thio)methyl)carbonyl-4-(benzyl)piperazine;

1- ((2-chlorophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (benzyloxy)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (methoxycarbonyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1- ((4-(amino)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- hydroxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4-(1- methylethyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4-(2,2-dimethylethyl)phenoxy)methyl)carbonyl-4- (benzyl) piperazine;

1-((4-(acetyl)phenoxy)methyl)carbonyl-4-(benzyl) piperazine;

1-((napthalenyl-2-oxy)methyl)carbonyl-4-(benzyl) piperazine;

1-((4-chloro-3,5-dimethylphenoxy)methyl)carbonyl-4- (benzyl)piperazine;

1-((1,3-benzodioxolyl-5-oxy)methyl)carbonyl- 4-(benzyl)piperazine;

1-((2,4,6-trichlorophenoxy)methyl)carbonyl- 4-(benzyl)piperazine;

1-((2,3,4,5,6-pentafluorophenoxy)methyl) carbonyl-4-(benzyl)piperazine;

1-((2-(benzyloxy)-4-cyanophenoxy) methyl)carbonyl-4-(benzyl)piperazine;

1-((2-chloro-4- bromophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((3- bromophenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((3,5- trifluoromethylphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1- (((5-oxo-6,7,8-trihydronaphthalen-1-yl)oxy)methyl)carbonyl-4-(benzyl) piperazine;

1-(((2-oxo-2*H*-1-benzopyran-4-yl)oxy)methy) carbonyl-4-(benzyl)piperazine;

1-((2-cyanophenoxy)methyl) carbonyl-4-(benzyl)piperazine;

1-((4-methyl-3,5-dibromophenoxy) methyl)carbonyl-4-(benzyl)piperazine;

1-((quinolinyl-6-oxy) methyl)carbonyl-4-(benzyl)piperazine;

1-(((diphenyl)methoxy) methyl)carbonyl-4-(benzyl)piperazine;

1-((3-(morpholin-4-yl) phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((2-bromophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine, hydrochloride salt;

1-((pyridinyl-3-oxy)methyl)carbonyl-4-(benzyl)piperazine;

1- ((2-(benzyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (benzyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4- (formyl)phenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((2- (prop-3-enyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((benzothiazolyl-2-oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-cyclohexylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-(benzyloxy)carbonylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((5-chloroquinolinyl-8- oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- (imidazol-1-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-chloro-5-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-carboxyphenoxy)methyl)carbonyl-4-(benzyl)piperazine;

1-((4-iodophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 7.6 (m, 6), 6.8 (d, 2), 4.9 (d, 2), 4.4 (m, 3), 4.0 (m, 1), 3.6 (m, 1), 3.4-2.9 (m, 6) ppm;

1-((2-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dimethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-methylquinolinyl-4-oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2,3-dihydro-1*H* -inden-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((coumarin-4-yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-chlorobenzyloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((4-chlorophenyl)amino)methyl)carbonyl-4-(4-chlorobenzyl) piperazine, hydrochloride salt; NMR (DMSO-d_6) 11.4 (br s, 1), 7.6 (dd, 4), 7.1 (d, 2), 6.6 (d, 2), 4.4 (m, 4), 4.0 (m, 4); 3. 6-2.9 (m, 4) ppm;

1-((4-chloronaphthalenyl-1-oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-(((4-chlorophenyl)(methyl)amino) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((di(4-chloro) phenyl)methoxy)methyl)carbonyl-4-(chlorobenzyl)piperazine;

1-((3, 5-dimethoxy-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (q, 4), 6.2 (s, 2), 4.7 (s, 2), 3.9 (s, 6), 3.6 (m, 4), 3.5 (s, 2), 2.4 (m, 4) ppm;

1-((5,7- dichloroquinolinyl-8-oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((6-hydroxycoumarin-4-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-fluoro-4-chlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine, hydrochloride salt; NMR (DMSO- d_6) 11.8 (s, 1), 7.5 (m, 5), 7.1 (d, 1), 6.8 (d, 1), 5.0 (q, 2) , 4.3 (m, 3), 3.9 (m, 1), 3.6-2.9 (m, 6) ppm;

1-((2- (hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine; NMR (DMSO-d_6) 7.6 (m, 6), 7. 3 (d, 1), 5.0 (q, 2), 4.3 (m, 3), 3.9 (m, 1), 3.5-2.9 (m, 6) ppm;

1-((4-bromo-2-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine; NMR (DMSO-d_6) 11.4 (br s, 1), 7.8 (m, 2), 7.5 (m, 4), 7.2 (d, 1), 5.2 (q, 2), 4.4 (m, 3), 4.0 (m, 1), 3.6-2.9 (m, 6) ppm;

1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((4-bromo-2-chlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine hydrochloride salt;

1-((2- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine hydrochloride salt;

1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine hydrochloride salt;

1-((2-aminocarbonyl-4- chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 8.7 (br s, 1), 7.8 (s, 1), 7.7 (s, 1), 7.6 (dd, 1) , 7.2 (m, 3), 7.2 (d, 1), 5.0 (s, 2), 3.5 (m, 6), 2.4 (m, 4) ppm;

1-((3,5-dimethoxy-4-bromophenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 6.2 (s, 2), 4.7 (s, 2), 3.9 (s, 6), 3.6 (m, 4), 3.5(s, 2), 2.4 (m, 4) ppm;

1-((3- formyl-4-nitrophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.5 (s, 1), 8.2 (d, 1), 7.3 (m, 6), 4.9 (s, 2), 3.6 (m, 2), 3.5 (m, 4), 2.4 (m, 4) ppm;

1-((2-chloro-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((1-nitroso-3,6-di(hydroxysulfonyl)naphthalen-2-yloxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-nitroso-4- hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,6-di(hydroxysulfonyl)naphthalen-1-yloxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-hydroxysulfonyl-6- aminonaphthalen-1-yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-hydroxysulfonyl-7-aminonaphthalen-1-yloxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((5-hydroxysulfonylquinolin-8- yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,3- dinitro-7-hydroxysulfonylnaphthalen-1-yloxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-4-hydroxysulfonylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-4- hydroxysulfonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-formyl-2,6-di-*t*-butylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-(morpholin-4-yl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- (methoxycarbonyl)-2,6-dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-(hydroxysulfonyl)naphthalen-1-yloxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,6-di(hydoxysulfonyl)-8-aminonaphthalen-1-yloxy) methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-5- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- trifluromethyl-2,3,5,6,-tetrafluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-formyl-5-(2-hydroxy-3- methoxy-5-formylphenyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-carboxy-2,3,5,6-tetrafluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(adamant-1-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- (adamant-1-yl)-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,4-di((1-methyl-1-phenyl)ethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- nitro-4-*t*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-acetyl-4-chloro-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-4-chloro-6- nitrophenxoy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- acetyl-4,6-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-4,6-di(*t*-butyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3,5-dinitrophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2,6-dichloro-4- ethoxycarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-ethoxycarbonyl-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-6-(prop-3-enyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-fluoro-4- cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- acetyl-4-methyl-6-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-methylbenzothiazol-5-yloxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-carboxy-4-(hydroxysulfonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(4- (trifluoromethyl)phenoxy)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-(1*H*-pyrazol-3-yl)-4-chloro-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-(1*H*-pyrazol-3-yl)-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2-phenyl-4-oxo-7-hydroxy-4*H*- 1-benzopyran-3-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-chloro-3-trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(butoxymethyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((6-hydroxyquinolin-2-yloxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxycarbonyl-6- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,5-di(*t*-butyl)-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(2*H*- benzotriazol-2-yl)-4-(2-hydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-(methylthio)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,5-di(*t*-butyl) -4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((3,5-dibromo-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-diiodo-4-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-nitro-4-methoxycarbonylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- (ethoxycarbonyl)indol-5-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3-(2-carboxyethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,6-dinitro-4-(carboxymethyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- nitro-3-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((6-carboxynaphthalen-2-yloxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-difluoro-4-ethylcarbonylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(2-(methoxycarbonyl) ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-(prop-3-enyl)-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((3-oxo-2*H*-benzofuran-6-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4,6-tribromo-3,5- dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((4-(heptylcarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-nitro-4-phenylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-methoxy-4-(eth-2-enyl)phenoxy) methyl)carbonyl-4-(4-chlorobenryl)piperazine;
1-((2-chloro-4- methoxycarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-diiodo-4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,6-diiodo-4-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-phenyl-4-oxo-7-methoxy-4*H*-1-benzopyran-5-yl) oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-phenyl-4- oxo-7-methoxy-2,3-dihydro-4*H*-1-benzopyran-5-yl)oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((4-octylcarbonylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4-phthalimid-1- ylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- (morpholin-4-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-chloro-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((2-oxo-7-methoxy-2*H*-1-benzopyran-8-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-acetyl-5- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-(1-methylcyclohex-1-yl)-4-methyl-6-(2-hydroxy-3-(1-methylcyclohex-1- yl)-5-methylbenzyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-3-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-chloro-4-carboxy-6-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethyl-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-4-(2-(carboxy)ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dimethoxy-4-(hydroxymethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dibromo-4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-nitro-4-(ethoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-amino-4-(methoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2-(4-nitrophenyl) eth-2-enyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-di(*t*-butyl)-4-(methoxycarbonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- methoxy-4-(ethoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-cyclohexyl-4-chlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2,6-dimethyl-4-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4- ethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- *n*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((3-carboxy-1-bromonaphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-bromo-4-nitro-6-formylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-4-chlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((2,6-dichloro-4-(ethoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((4-methyl-2-oxo-2 *H*-1-benzopyran-6-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,3-dibromo-4-formyl-6-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2-(4-nitrophenyl)eth-2-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4,6- tribromo-3-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-benzyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-(bezothiazol-2-yl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-nitro-6-fluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethoxy-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-bromo-4,6-di(*t*-butyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-(pyrrolidin-1-yl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(morpholin-4-yl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(piperidin-1-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- formyl-4-chloro-6-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((4,7-dimethoxy-5-formylbenzofuran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-oxo-4- methyl-8-nitro-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-bromophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-bromo-6- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,4-dimethyl-6-*t*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((2-nitro-4-(hydroxysulfonyl)naphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3- (hydroxysulfonyl)-6-aminonaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3-(hydroxysulfonyl)-7- aminonaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3-(methoxycarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-(hydroxysulfonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- *n*-butylcarbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-ethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(((2-ethyl)hexoxy)carbonyl)phenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((4-((*n*-pentoxy)carbonyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- nitro-5-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,4,6-tribromo-3-methylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-methoxy-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-methoxy-4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-(2-(phenyl)eth-2-enyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-(1,2,4-triazol-1-yl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-nitro-4-chloro-5-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(*n*- hexoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-chloro-4-formyl-6-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(2-(ethoxycarbonyl) ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,3,4,6-tetrachlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-((2-methylpropoxy)carbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(*n*-butoxycarbonyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(phenylamino) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- hydroxymethyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-mercaptophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((2-nitro-6-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-di(1-methylbutyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3- trifluoromethyl-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dibromo-4-(methoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-dichloro-6-acetyl) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- methoxycarbonyl-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-formyl-4-bromo-6-methoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-diformyl-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,6-dinitro-4-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-nitro-4-acetylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-formyl-4-nitro-6-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- (aminocarbonyl)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxycarbonyl-4-methoxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-6-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-chloro-4-trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-3-methyl-6- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- (((5,7-dibromo-2-methylquinolin-8-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((5,7-dichloro-2-methylquinolin-8-yl) oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6- dinitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-nitro-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-4-(1,1-dimethylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-Biphenyl-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-dichloro-3-methyl- 6-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- (((2-oxo-4-(carboxy)methyl-2*H*-1-benzopyran-7-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2-oxo-4- trifluoromethyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-*t*-butyl-4-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-formyl-6- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methoxycarbonyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-bromo-5-fluorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,4-di(1,1-dimethylpropyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-methyl-4- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,3,4-trifluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,5-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-methyl-5-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-(((2-methyl-3-(ethoxycarbonyl)indol-5- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- aminocarbonyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dinitro-3-*t*-butylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-fluoro-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- carboxy-3-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(2-ethylhexoxy)carbonylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4,6-tribromo-4-carboxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(4-bromophenyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((4-(4-carboxypheny)phenoxy)methyl)carbanyl-4-(4- chlorobenzyl)piperazine;

1-((2,3,6-trifluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4,5- trifluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,4,6-trifluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-fluoro-5-trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2,4-dinitronaphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((3,6- di(hydroxysulfonyl)-8-aminonaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-4-chlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dimethyl-4-(1-(3, 5-dimethyl-4-hydoxyphenyl)-1-methylethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-(3-(4-hydroxyphenyl)hex-2-yl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((6- (hydroxysulfonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-chloro-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-bromo-4,5-difluorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-chloro-4- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methoxy-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2-(methoxycarbony)ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-diphenyl-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-amino-3- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methyl-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine
1-((2-methyl-4-iodophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-fluoro-6-methoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-carboxy-3-isopropyl-6- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-carboxy-3,4,6-trichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-6-isopropylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-(piperidin-1-yl)-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- (((2,3-dihydro-2,2-dimethylbenzofuran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-di(*t*-butyl)-4-(1- methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-methyl-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((phenanthren-9-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2-nitro-4-bromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-fluoro-3-trifluoromethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-5- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-chloro-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4-bromo-6-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-(acetyl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(5- mercaptotetrazol-1-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4,6-triiodo-3-(2-carboxy)butylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-hydroxymethyl-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2, 3,5,6-tetrafluoro-4-(2,3,4,5,6-pentafluorophenyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(benzotriazol-2-yl)-4,6-di(1, 1-dimethylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-phenyl-3-hydroxy-4-oxo-4*H*-1-benzopyran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((indanonyl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-nitro-4- (hydroxysulfonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-nitro-3-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-(2,4-dinitrophenyl)aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-methyl-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2, 6-dibromo-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-diiodo-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-formyl-4-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-amino-5-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-amino-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-4-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-amino-4-*t*-butylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-amino-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methyl-3-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((2-carboxy-5-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-methyl-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,5-dimethyl-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2, 6-dibromo-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-aminocarbonylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-aminocarbonyl-4-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2- aminoethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4,6-tri(dimethylamino)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-hydroxymethyl-6-methoxyphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2,3-dimethoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(methoxycarbonyl)-5- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methoxy-4-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dimethoxy-4-(prop-3-enyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-5- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-acetyl-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-3-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-methoxy-4-acetylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,6-dimethoxy-4-acetylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-di(*t* -butyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,4-di(*t*-butyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,5-di(*t*-butyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2,6-di(isopropyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4- (ethoxycarbony)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-ethoxy-5-prop-2-enylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-5-prop-2-enylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-di(1- methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-diphenylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-nitro-3-trifluoromethylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-cyclopentyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-cyclopentylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,3-difluorophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-6-aminophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-4- chloro-5-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,4-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-6-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,4-dicarboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,3-dimethoxy-5-formylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-bromo-4- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2,6-dichoro-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3-methyl-4-isopropylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-(((fluoren-2-yl)oxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-diethylaminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-3- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- (((2-oxo-3,4,8-trimethyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-acetyl-4-fluorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-fluoro-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- (methylcarbonyl)amino-5-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((1-acetylnaphthalen-2-yl)oxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-methoxy-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-methyl-5- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methyl-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((1-aminonaphthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-aminonaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(1,2- dihydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((3-(2-aminoethyl)indalin-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((5-chloroquinolin-8-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(2-(amino) ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-(2-(amino)ethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(2-(amino)ethyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2,4-diaminophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((4-aminophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-(diethylamino)methyl-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- methyl-5-(2-aminobutyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-(benzotriazol-2-yl)-4-(1,1,3,3- tetramethylbutyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4-bromo-6-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-iodophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(2-carboxyethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,6-dibromo-3-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,6-dichloro-3-carboxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-methoxy-4-carboxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethoxy- 4-carboxyphenoxylmethyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((4-(2-carboxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(2-hydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3-(2-hydroxyethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-(2-hydroxyethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-(2- hydroxyethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dibromo-6-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-fluoro-6-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4-dichloro-6-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-diiodo-6- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-6-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethoxy-6-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-formyl-5-(diethylamino)phenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((2-formyl-5-methoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-3,5- dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine ;
1-((2-formyl-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4-methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((4-methoxynapthalen-1-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-carboxy-5,6-dimethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-nitro-4- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- (((fluoren-9-on-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4-hydroxy-1,2,3,4-tetrahydronaphthalen-8-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3,4,5,6- pentabromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methyl-3,4,5,6-tetrabromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,3,4-trichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-methyl-4-bromo-6-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,4,6-triiodophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-formyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3-formylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-(((1-bromonaphthalen-2-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1,6-dibromonapthalen- 2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1- nitrosonaphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2,4-dichloronaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-nitronaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-carboxynaphthalen- 1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2- methylnaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3-(hydroxysulfonyl)-7-(dimethylamino)naphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((4- methoxynaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1-formylnapthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((1-carboxynaphthalen-1-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((1-amino-4- (hydroxysulfonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(naphthalen-2-yl)aminophenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-(((3-aminonaphthalen-2-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-fluoro-4- (carboxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-(carboxymethyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-methoxy-4-(carboxymethyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- hydroxymethylphenxoy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(hydroxymethyl)-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-di(hydroxymethyl)-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-methoxy-4-(hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-mercaptophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-(((2-carboxyindol-5-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((3-carboxyindol-5-yl) oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((indol-4- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((indol- 5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- (benzoxazol-2-yl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2-methylquinolin-8-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((5,7-dibromoquinolin-8-yl)oxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-(((5,7-diiodoquinolin-8-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((5- nitroquinolin-8-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((quinolin-5-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((5-(hydroxysulfonyl)-7-iodoquinolin-8-yl)oxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-(((2-phenyl-4-oxo-4*H*-1- benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-carboxy-2,5,7,8-tetramethyl-2,3-dihydro-1-benzopyran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2-oxo-3- chloro-4-methyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2-oxo-3-(diethylamino)methyl)-4- methyl-2*H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((2-oxo-6-methoxy-2*H*-1-benzopyran-7-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((2-oxo-2 *H*-1-benzopyran-7-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-formyl-6-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-4-formyl-6-iodophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-ethoxy-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-formylphenox)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2,4-dichloro-6-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4-dinitro-6-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dinitro-6- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine:
1- ((2,4-dinitro-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,5-dinitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((2-nitro-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,4-dinitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-nitro-4-formyl-6-methoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-nitro-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dinitro-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-nitro-4-(carboxymethyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6- dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((3-methoxy-5-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(1-methyl-1-phenylethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-(ethylamino)-4-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2- acetylnaphthalen-1-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(carboxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(carboxymethyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-(((benzotriazol-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((quinolin-2-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,6-dimethoxy-4-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,4-dimethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4,6-tri(*t*-butyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethoxy- 4-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-trifluoromethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-methyl-5-aminophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-((4-(4-cyanophenyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-nitro-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-methylphenox) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- (methoxycarbonyl)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((carbazol-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;
1-(((2-oxo-1,3-benzothiol-2-on-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-phenyl-4- oxo-4*H*-1-benzopyran-3-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((2-oxo-4-methyl-2*H*-1-benzopyran-7-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-nitrophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-carboxy-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-5-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((2-phenyl-4-oxo-2,3-dihydro-4*H*-1-benzopyran-6-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((quinolin-6-yl) oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3- diaminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((4-(hydroxysulfonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((fluorenon-9-on-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((5,6,7,8-tetrahydronaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((5,6,7,8- tetrahydronaphthalen-2-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4,6-tribromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,6-dibromo-4-cyanophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-fluorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3,5,6- tetrafluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3-dichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,3,6-trichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-chloro-4,5-dimethylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,5-dichlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(methylcarbonyl)aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-isopropoxyphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;
1-((2-(benzyloxy)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- phenylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-(methoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine,
1-((2-(ethaxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-acetylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(ethylcarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(*t*-butyl) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-(1-methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,3,5-trimethylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,3,6-trimethylphenxoy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4-dimethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,4,6- trimethoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- methyl-5-isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,5-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,5-dimethyl-4-(diethylamino)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(*t*- butyl)-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-prop-3-enyl-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-prop-2-enylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-ethylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-*n*- propylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((3-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,5-difluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-chloro-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,5-dichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-iodophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-(phenylamino)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((3-(diethylamino)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-phenylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((3-acetylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((3-trifluoromethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-*t*- butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3- isopropylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((3-methyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,4-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-*t*-butyl-5-methylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)piperazine;

1-((2-isopropyl-5-methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-ethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dimethyl-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2, 6-dibromo-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-bromo-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-methyl-4-chlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-isopropyl-4-chloro-5- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-(methylcarbonyl)aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-ethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((4-propoxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl) piperazine;

1-((4-*n*-butoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-*n*- hexoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-*n*-heptoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(propoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-(ethylcarbonyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((4-(1,1,3,3-tetramethylbutyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(1,1- dimethylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(1-methylpropyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-methoxy-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-acetyl-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(*t*-butyl)-4- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-(ethylamino)-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-(methoxycarbonyl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-ethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-*n*- propylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4,6-dibromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-4,6-dichlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-carboxy-4,6-diiodophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-6- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-carboxy-6-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-5-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-5-methoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-carboxy-5-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4- bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- carboxy-4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-carboxy-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-carboxy-4-iodophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-carboxy-4-methoxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,3,4- trichlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2,3,4,5,6-pentachlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2,4,5-trichlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3-methoxyphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((3-(methoxycarbonyl)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- (ethoxycarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,6-dimethyl-4-bromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((3,5-dimethyl-4-bromophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-methyl-4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-isopropyl-4-chloro-5-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-ethoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(*t*-butyl)-4-methylphenoxy)methyl)carbonyl-4- (4- chlorobenzyl)piperazine;
1-((3-formyl-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-4-prop-3- enylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- (1-phenyethyl)-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-(ethoxycarbonyl)methylphenoxy)methyl)carbonyl- 4-(4-chlorobenzyl)puperazine;
1-((4-trifluoromethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-fluoro-4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-fluoro-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((7-methoxynaphthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-benzyloxy-4-cyanophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-bromo-3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3,5-dimethoxy-4-bromophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2,6-dibromo-3,5-dimethoxyphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((3-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methyl-3-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-nitro-3-carboxy-6-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-cyanophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-methoxy-5- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2- nitro-5-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-(carboxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-methoxy-5-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-(dimethylamino)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(2- (dimethylamino)ethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-(((naphthalen-1-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-(((5-aminonaphthalen-1-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-nitro-4- aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2, 6-di(*t*-butyl)-4-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3-carboxy-4-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((2-methyl-5-carboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-nitro-4-aminophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-(benzyloxy)phenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- (aminocarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,5-di(trifluoromethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,4-dibromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2,6-dibromo-4-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,4-dichlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3- methoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((3,5-dimethyl-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,5-dicarboxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-chloro-4-carboxyphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dichloro-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- (((2-carboxyquinolin-4-yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2,6-dimethyl-4-formylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2,6-di(*t*-butyl)-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-amino-5-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-di(*t*-butyl)-4-(hydroxymethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((4-carboxyquinolin-2- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-nitro- 4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((3-ethyl-4-chloro-5-methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3,5-di(methoxycarbonyl)phenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((2-(morpholin-4-yl)methyl-4- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine
1- ((2-methoxy-4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-chloro-4-bromophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((2-trifluoromethylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-methylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-methyl-4-acetylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-(dimethylamino) phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- methyl-4-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-dimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((4-phenylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-(ethoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4-acetylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- benzylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-methoxy-4-carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((3-carboxynaphthalen-2-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-(hydroxymethyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((quinolin-8-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-aminophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((4- (aminocarbonyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3,5-dimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-(cyclohexyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-(((quinolin-6-yl)oxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2,4-dichloro-3-methylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2,5-dimethylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-bromophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3- (methylcarbonyl)aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((3-acetylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;
1-((3-trifluoromethylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((4-bromophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;
1-((2-formylphenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;
1-((2-methoxy-5-formylphenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;
1-(((tropinon-yl)oxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1-((2-nitro-5- fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;
1- ((2-nitro-5-formylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3-formyl-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-carboxy-5-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((2-amino-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-amino-3- carboxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((2-nitro-4-aminophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dichloro-4-nitrophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-fluoro-4-nitrophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,3-difluoro-6- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- chloro-4-nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-nitro-4-cyanophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((2-bromo-4-methylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-chlorophenoxy)methyl)carbonyl-4- (4-chlorobenzyl)piperazine;

1-((3,4-dichlorophenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,5-dichlorophenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,4,5- trimethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1- ((4-fluorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3,5-dimethyl-4-chlorophenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-methoxyphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-((4-(methoxycarbonyl)phenoxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4- trifluoromethylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((4-*t*-butylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((4-isopropylphenoxy)methyl)carbonyl-4-(4- chlorobenzyl) piperazine;

1-(((naphthalen-2-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((6-bromonaphthalen-2- yl)oxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((3- (hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-methoxy-5-(hydroxymethyl)phenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-(((1,3-benzodioxolan-5-yl)oxy)methyl) carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2,6-dimethyl-4- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- nitrophenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2- methoxy-4-(amino)methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine;

1-((3-(aminocarbonyl)phenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine;

1-((3-(methoxycarbonyl)methylphenoxy) methyl)carbonyl-4-(4-chlorobenzyl)piperazine;

1-((2-(4- phenylcarbonyl)-4-fluorophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((2-(1-methyl)cyclohexyl-2,4- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((2-(benzyloxycarbonyl)phenoxy)methyl)carbonyl-4-(4- fluorobenzyl)piperazine;

1-((2-(4-(methyl)phenylcarbonyl)-5- methoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1- ((2-phenylcarbonyl-5-octoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

1-((4-octylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

1-((2-(2-(carboxy)phenylcarbonyl-5-di(*n*-butyl) aminophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2- phenylcarbonyl-5-methoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

1-((2-methoxy-4-(3-hydroxyprop-2-enyl)phenoxy)methyl) carbonyl-4-(4-fluorobenzyl)piperazine;

1-(((3- (phenylaminocarbonyl)naphthalen-2-yl)oxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-(((6-(phenylcarbonyl)naphthalen-2-yl) oxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2-((2- phenylethyl)carbonyl)phenaxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4-((4-fluorophenyl)carbonyl)phenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine

1-((2-(phenylamino)carbonylphenoxy) methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2- phenylcarbonylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2-phenylcarbonyl-4-chloro-5-methylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4-(4-chlorophenyl)carbonylphenoxy) methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4- benzylcarbonyl)phenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((2-phenylcarbonyl-4-methylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4-(2-methylcarbonylethyl)phenoxy) methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((4- phenylcarbonylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; and

1-((3-phenylcarbonylphenoxy)methyl)carbonyl-4-(4-fluorobenzyl) piperazine;

D. In a similar manner the following compounds of formula (Ia) or (Ib) were made:

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 0.86-1.02 (m, 3H), 1.04-1.36 (m, 3H), 2.16 (m, 1H), 2.62 (m, 1H), 2.94 (m, 1H), 3.08 (m, 0.5H), 3.42 (m, 1H), 3.58 (m, 1H), 3.76 (s, 3H), 3.98 (m, 1H), 4.40 (s, 0.5H), 4.82 (m, 1.5H), 5.02 (m, 0.5H), 6.98 (s, 1H), 7.14 (m, 2H), 7.38 (m, 2H), 7.56 (m, 1H), 7.62 (s, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 0.90 (m, 3H), 1.30 (m, 3H), 2.25 (d, 1H), 2.68 (d, 1H), 3.00 (m, 1H), 3.20 (m, 1H), 3.40 (m, 1H), 3.50 (m, 2H), 3.62 (s, 2H), 3.68 (s, 3H), 4.65 (m, 3H), 6.80 (m, 1H), 7.00 (t, 2H), 7.30 (m, 4H).

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1.30 (m, 3H), 2.00 (m, 1H), 2.10 (m, 1H), 2.60 (d, 1H), 2.80 (m, 1H), 3.45 (m, 2H), 3.60 (m, 2H), 3.62 (s, 3H), 4.30 (m, 1H), 4.65 (m, 2H), 4.75 (d, 2H), 6.78 (d, 1H), 7.00 (t, 2H), 7.30 (m, 4H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester; . ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0.76-0.98 (m, 3H), 1.08-1.30 (m, 3H), 2.16 (m, 1H), 2.62 (m, 1H), 2.94 (m, 1H), 3.08 (m, 0.5H), 3.58 (m, 3H), 3.73 (s, 3H), 4.00 (m, 1H), 4.40 (s, 0.5H), 4.88 (m, 1.5H), 5.08 (m, 0.5H), 6.96 (m, 1H), 7.14 (m, 2H), 7.36 (m, 2H), 7.66 (m, 1H), 7.84 (m, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0.76-0.97 (m, 3H), 1.08-1.32 (m, 3H), 2.16 (m, 1H), 2.62 (m, 1H), 2.94 (m, 1H), 3.08 (m, 1H), 3.40 (m, 1.5H), 3.58 (m, 1H), 3.73 (s, 3H), 3.87 (s, 3H), 4.00 (m, 1H), 4.40 (s, 0.5H), 4.92 (m, 1.5H), 5.08 (m, 0.5H), 6.68 (m, 1H), 7.14 (m, 2H), 7.36 (m, 2H), 7.86 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester; ^{1}H NMR (500 MHz, DMSO-d_6):δ/ppm = 0.90 (m, 3H), 1.25 (m, 3H), 2.23 (m, 1H), 2.75 (m, 2H), 2.94 (m, 1H), 3.35 (m, 1H), 3.45 (m, 1H), 3.63 (m, 1H), 3.77 (s, 3H), 3.92

(s, 3H), 4.31 (s, 1H), 4.92 (m, 2H), 6.81 (s, 1H), 7.12 (m, 2H), 7.37 (m, 2H), 7.72 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid methyl ester; ^{1}H NMR (400MHz, $CDCl_3$):δ/ppm = 0.78-0.98(m, 3H), 1.18-1.36 (m, 3H), 2.22 (m, 1H), 2.38 (s, 3H), 2.66 (m, 1H), 3.00 (m, 1H), 3.10-4.20 (m, 4H), 3.86 (s, 3H), 4.24-4.86 (m, 3H), 6.94-7.02 (m, 3H), 7.29 (m, 2H), 7.81 (s, 1H).

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 0.91 (d, 3H), 1.29 (d, 3H), 2.24 (d, 1H), 2.69 (dd, 1H), 3.02 (br, 1H), 3.41 (d, 1H), 3.47-3.71 (m, 2H), 3.87 (s, 3H), 4.10-4.22 (m, 1H), 4.60-4.86 (m, 3H), 7.00 (dd, 2H), 7.18 (br, 1H), 7.30 (dd, 2H), 7.91 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid methyl ester; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1.00 (m, 3H), 1.30 (m, 3H), 2.25 (d, 1H), 2.70 (dd, 1H), 3.05 (m, 1H), 3.20 (m, 1H), 3.50 (m, 2H), 3.68 (m, 1H), 3.95 (s, 3H), 4.20 (m, 1H), 4.80 (m, 2H), 7.00 (t, 2H), 7.30 (m, 3H), 7.90 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid methyl ester; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0.62 (m - rotamer, 1.25H), 0.73 (t - rotamer, 3.5H), 0.85 (m - rotamer, 1.25H), 1.23 (m, 1H), 1.37 (m, 1H), 1.55 (m, 1H), 1.70 (m, 1H), 1.83 (m, 1H), 2.26 (t, 1H), 2.55 (d, 1H), 2.75 (d – rotamer, 1H), 3.45 (dd, 1H), 3.47 (t, 1H), 3.60 (m, 1H), 3.78 (s, 3H), 4.20 (d, 1H), 4.90 (m – rotamer, 2H), 6.99 (d, 1H), 7.13 (t, 2H), 7.35 (t, 2H), 7.55 (dd, 1H), 7.64 (d, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester; . ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0.60-0.90 (m, 6H), 1.06-1.60 (m, 3H), 1.62-1.82 (m, 1.5H), 2.16 (m, 1H), 2.60 (m, 2H), 2.88 (m, 1H), 3.46 (m, 1H), 3.60 (m, 1.5H), 3.76 (s, 3H), 3.85 (s, 3H), 4.22 (m, 1H), 4.92 (m, 1H), 5.12 (m, 1H), 6.68 (m, 1H), 7.12 (m, 2H), 7.34 (m, 2H), 7.86 (s, 1H).

5-bromo-2-[2-[(2*R*)-4-[(5-chloro-2-thienyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1.30 (m, 3H), 2.05 (m, 1H), 2.15 (m, 1H), 2.75 (m, 1H), 2.90 (m, 1H), 3.05 (m, 1H), 3.45 (m, 1H), 3.60 (m, 2H), 3.65 (s, 2H), 3.70 (s, 3H), 4.35 (m, 1H), 4.68 (m, 2H), 6.65 (d, 1H), 6.72 (d, 1H), 6.80 (dd, 1H), 7.35 (m, 2H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid; ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 0.73-0.88 (m, 3H), 1.12-1.25 (m, 3H), 2.05-2.20 (m, 1H), 2.65 (m, 1H), 2.90 (m, 1H), 3.08 (m, 0.5H), 3.50 (m, 3H), 3.97 (m, 0.5H), 4.40 (m, 1H), 4.75 (m, 1.5H), 4.94 (m, 0.5H), 6.93 (m, 1H), 7.12 (m, 3H), 7.34 (m, 3H), 7.57 (m, 1H).

5-chloro-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid; . ^{1}H NMR (400 MHz, DMSO-d_6 + TFA): δ/ppm = 1.16 (d, 3H), 1.32 (d, 3H), 2.76-3.50 (m, 5H), 4.24-4.52 (m, 3H), 4.60-5.00 (m, 3H), 6.50 (m, 1H), 7.23 (m, 2H), 7.30 (m, 1H), 7.54 (m, 2H), 7.67 (m, 1H), 9.50 (br, 1H).

EXAMPLE 3

Compounds of Formula (Ia) and Formula (Ib)

A. To a solution of 1- ((3,4,5-trimethoxyphenoxy)methyl)carbonylpiperazine (0.22 g, 0.70 mmol) in 1% acetic acid in methanol (6 mL) was added 4-cyanobenzaldehyde (0.33 g, 2.5 mmol) and sodium cyanoborohydride (0.093 g, 1.4 mmol). The resultant mixture was stirred at ambient temperature for 1.5 hours and the mixture was then concentrated of volatiles *in vacuo*. Residue was taken up in ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution, water, and then brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography on silica gel afforded 0.21 g of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-cyanobenzyl)piperazine, a compound of formula (Ib), as a clear oil: NMR ($CDCl_3$) 7.6 (d, 2), 7.4 (d, 2), 6.2 (s, 2), 4.6 (s, 2), 3.8 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3.5 (s, 2), 2.2 (m, 4) ppm.

B. In a similar manner, other compounds of formula (Ib) were made:

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(3,4-dimethoxybenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-methoxybenzyl) piperazine,

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- chlorobenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(3-trifluoromethylbenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(2,3-dimethyl-4-methoxybenzyl) piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- phenoxybenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(4-(dimethylamino)benzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-(methylthio)benzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-methoxy3-methylbenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(2-chlorobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(3-nitrobenzyl)piperazine;

1- ((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-hydroxybenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3,5-dibromo-4-hydroxybenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(2-fluorobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0 (m, 2), 6.2 (s, 2), 4.6 (s, 2) , 3.9 (m, 9), 3.6 (m, 4), 3.4 (s, 2), 2.4 (m, 4) ppm;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-bromobenzyl)piperazine; NMR ($CDCl_3$) 7.4 (d, 2), 7.2 (d, 2), 6.2 (s, 2), 4.6 (s, 2) , 3.85 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3.4 (s, 2), 2.4 (m, 4) ppm;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2-bromobenzyl) piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- fluorobenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(3-bromobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(3-cyanobenzyl)piperazine;

1- ((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2,4-difluorobenzyl) piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2,3- difluorobenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl) carbonyl-4-(3,4-difluorobenzyl)piperazine;

NMR ($CDCl_3$) 7.3-7.0 (m, 3), 6.2 (s, 2), 4.6 (s, 2), 3.85 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3.5 (s, 2), 2.4 (m, 4) ppm;

1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-4-(2,6-difluorobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-chlorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 4), 6.2 (s, 2), 4.6 (s, 2), 3.85 (s, 6), 3.75 (s, 3), 3.6 (m, 4), 3.5 (s, 2), 2.4 (m, 4) ppm;

1-((3,4, 5-trimethoxyphenoxy)methyl)carbonyl-4-(3-chloro-4-fluorobenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(4-trifluoromethylbenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-4-(4-nitrobenzyl)piperazine;

1-((3,4,5- trimethoxyphenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(2,5-difluorobenzyl) piperazine;

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3- nitro-4-hydroxybenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7. 2 (m, 4), 7.0 (t, 2), 6.8 (d, 2). 4.6 (s, 2), 3.6 (m, 4), 3.4 (s, 2), 2.4 (m, 4) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-4-(4- chlorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 6), 6.8 (d, 2), 4.6 (s, 2), 3.6 (m, 4), 3.5 (s, 2), 2.4 (m, 4) ppm;

1- ((3,4,5-trimethoxyphenoxy)methyl)carbonyl-4-(3-(benzyloxy)benzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-4-(3,4,5- trimethoxybenzyl)piperazine;

C. In a similar manner, the following compounds of formula (Ia) were made:

(3*S*)-1-((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 4.0 (m, 2), 3.7 (m, 1), 3.4-2.9 (m, 3), 2. 7 (m, 1), 2.5 (m, 1), 2.1 (m, 1), 1.1 (m, 3) ppm;

(3*R*)-1- ((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (s, 2), 4.0 (m, 2), 3.7 (m, 1), 3.4-2.9 (m, 3), 3.2 (m, 1), 3.0 (m, 1), 2. 7 (m, 1), 2.5 (m, 1), 2.1 (m, 1), 1.1 (m, 3) ppm;

1-((4- chlorophenoxy)methyl)carbonyl-3-(2-((((4-chlorophenoxy)methyl)carbonyl) oxy)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-hydroxyethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2- ((2-methylpropyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.1 (m, 4), 6.9 (t, 2), 6.7 (d, 2), 4.6 (s, 2), 4.4 (d, 1), 3.6 (d, 1), 3.3 (m, 3), 2.7-2.3 (m, 6), 2.0-1.7 (m, 5) , 0.8 (t, 6) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((4- fluorobenzyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine, hydrochloride salt;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2-hydroxyethyl) amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-(2-((methyl)amino)ethyl)4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-3-(2-((4-fluorobenzyl)amino) ethyl)-4-(4-fluorobenzyl)piperazine, hydrochloride salt;

1-((4- chlorophenoxy)methyl)carbonyl-3-(2-((methyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-3- (2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-((2-methylpropyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((ethyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (d, 2), 6.9 (t, 1), 6.4 (br s, 2), 5.0-4.6 (m, 3), 4.0 (m, 3), 3.7-3.2 (m, 4), 3.0-2. 7 (m, 3) , 2.2 (m, 1), 1.3 (m, 6), 1.0 (br d, 3) ppm;

(*trans*)-1-((4-chloro-2-(((diethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.5 (d, 1), 7.3 (m, 2), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 3), 4.2 (m, 1), 3.6-3.4 (m, 4), 3.2 (m, 1), 3.0 (m, 1), 2.7 (dd, 1), 2.6 (q, 2), 2.2 (d, 1), 1.3 (m, 3), 1.0 (m, 9) ppm;

(*trans*)-1-((4- chloro-2-(((cyclopropyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (d, 2), 6.8 (t, 1), 4.8-4.0 (m, 6), 3.7-3.2 (m, 3), 3.0 (br s, 1), 2. 7 (d, 1), 2.2 (m, 2), 1.3 (m, 3), 0.9 (m, 3), 0.5 (m, 4) ppm;

(*trans*)-1-((4-chloro-2-(((dimethyl)amino)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 3), 4.1 (m, 1), 3.6-3.4 (m, 4), 3.0 (br s, 1), 2.7 (dd, 1), 2.2 (m, 8) , 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(((methyl)amino)methyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 2), 4.1 (m, 1), 3.7-3.4 (m, 5), 3.0 (br s, 1), 2.7 (dd, 1), 2.4 (s, 3) , 2.2 (m, 2), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-((amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6.7 (d, 1), 4.7 (m, 2), 3.8 (d, 1), 3.5 (m, 4), 3.0 (br s, 1), 2.7 (dt, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((4-methylpiperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 4), 4.2 (m, 1), 3.8 (m, 1), 3.6-3.0 (m, 8), 2.9 (t, 1), 2.7 (m, 1), 2. 5-2.2 (m, 6), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.9 (m, 3), 7.7 (s, 2). 7.4 (t, 1), 7.2 (m, 2), 5.4 (d, 1), 5.0 (m, 2), 4.3 (m, 4), 3. 6- 3.1 (m, 12), 2.8 (m, 1), 1.5-1.0 (m, 6) ppm;

(*trans*)-1- ((4-chloro-2-(((2-hydroxyethyl)amino)methyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 4), 7.1 (dd, 1), 7.0 (t, 2), 6.7 (d, 1), 4.7 (m, 2), 4.2-3.4 (m, 6), 3.0 (br s, 2), 2.7 (m, 4), 2.2 (d, 2), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((morpholin-4-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.1 (dd, 1), 7.0 (t, 2), 6.7 (d, 1), 4.7 (m, 2), 4.1-3.4 (m, 11), 3.0 (br s, 1), 2.7 (dd, 1), 2.5 (t, 4), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2- (ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (m, 1), 4.7 (m, 2), 4.1 (m, 1), 3.8 (s, 2), 3.6 (m, 1), 3.5 (q, 2) , 3.0 (m, 1), 2.7 (m, 3), 2.6 (q, 2), 1.3 (m, 3), 1.1 (t, 3), 1.0 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-((ethyl)(1-methylbutyl) aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR (DMSO-d_6) 7.9 (m, 1), 7.7 (m, 2), 7.5 (m, 1), 7.2 (m, 3), 5.1 (m, 1), 4.6 (d, 1), 4.3 (m, 2), 3.7-2.8 (m, 6), 2. 5 (s, 2), 1.5- 1.2 (m, 19), 0.8 (s, 3) ppm;

(*trans*)-1-((4-chloro-2-(benzylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 7), 7.0 (t, 2), 6.7 (d, 1), 6.6 (m, 2), 4.7 (d, 2), 4.4 (s, 2), 4.2-3.0 (m, 8), 2.6 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.9 (m, 2), 7.3 (t, 2), 7.1 (m, 1), 6.9 (d, 2), 5.2 (d, 1), 4.9 (m, 2), 4.6 (m, 1), 4.5-3.2 (m, 6), 2.8 (t, 1), 2.5 (s, 1) , 1.7-1.2 (m, 9), 0.9 (d, 6) ppm;

(*trans*)-1-((4- chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 3). 7.1 (dd, 1), 7.0 (t, 2), 6.8 (br d, 1), 4.7 (m, 2), 3.8 (s, 2), 3. 6 (m, 1), 3.5 (q, 2), 3.0 (m, 2), 2.7 (dd, 1), 2.4 (m, 3), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 4), 0.4 (m, 2), 0.1 (m, 2) ppm;

(*trans*)-1-((4-chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.8 (m, 2) , 7.4 (m, 8), 7.2 (m, 2), 5.4 (d, 1), 5.0 (m, 2), 4.7 (m, 1), 4.5 (s, 2), 4. 3 (m, 2), 3.9-3.4 (m, 4), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(1-((methyl)(ethyl)amino)ethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.4 (s, 1), 7.3 (m,

2), 7.1 (dd, 1), 7.0 (t, 2), 6.8 (br d, 1), 4.6 (br s, 3), 4.0 (m, 2), 3.6 (d, 1), 3.4 (d, 1), 3.0 (m, 1), 2.7 (dd, 1), 2.5 (d q, 1), 2.4 (d q, 1), 2.2 (s, 3), 1.3 (m, 6), 1.0 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(1-(dimethylamino)ethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (CD_3OD) 7.6 (m, 3), 7.5 (d, 1), 7.3 (m, 3), 5.1 (m, 3) , 4.4 (m, 2), 3.8 (dd, 2), 3.6 (m, 1), 3.4 (m, 1), 3.0 (m, 1), 2.6 (m, 7), 1.6 (m, 6), 1.3 (m, 3) ppm;

(2R)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 2), 4.4 (m, 1), 3.5 (m, 10), 3.0 (m, 1), 2.8 (m, 1), 2.6 (m, 2), 1.4 (m, 12), 1.2 (m, 3) ppm;

(*trans*)- 1-((4-chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.8 (m, 2), 7,6 (s, 1), 7.5 (m, 1), 7.3 (t, 2), 7.2 (m, 1), 5.4 (d, 1), 5.0 (m, 2), 4.7 (m, 1), 4.3 (m, 6), 4.0 (m, 2), 3.8-3.1 (m, 8) , 2.9 (m, 1), 1.4 (m, 12), 1.2 (m, 3) ppm;

1-((4-chloro-2-(morpholin-4-ylmethyl)phenoxy)methyl) carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11. 5 (br d, 1), 10.6 (m, 1), 7.7 (m, 2), 7.6 (s, 1), 7.5 (dd, 1), 7.3 (t, 2), 7.2 (d, 1), 5.2 (q d, 2), 4.7 (m, 1), 4.4 (m, 4), 3.9-3.7 (m, 4), 3.5 (m, 1), 3.4 (m, 4), 3.0 (m, 4), 2.8 (m, 1), 1.5 (d, 1.5), 1.3 (d, 1.5) ppm.

5-chloro-4-(dimethylamino)-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 1.10-1.30 (m, 6H), 2.82 (s, 6H), 3.00 (m, 1H), 3.21 (m, 0.5), 3.40 (m, 1H), 3.58-3.70 (m, 2H), 4.20-4.40 (m, 3H), 4.70 (m, 0.5H), 4.90-5.10 (m, 2H), 6.62 (s, 1H), 7.30 (t, 2H), 7.60 (m, 2H), 7.68 (m, 1H).

EXAMPLE 4

Compounds of Formula (Ia)

A. To a solution of (2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fiuorobenzyl)-5-((hydroxy) methyl)piperazine (0.17 g, 0.42 mmol) in CH_2Cl_2 (50 mL) at 0°C was added triethylamine (excess) and methane sulfonyl chloride (0.050 mL, 0.5 mmol). The resultant mixture was stirred at 0°C until consumption of alcohol was observed by TLC analysis. The mixture was concentrated of volatiles *in vacuo*. Residue was taken up in anhydrous DMF (5 mL) and K_2CO_3 (excess) added, followed by tetrazole (0.050 g, 0.71 mmol). The resulting mixture

was stirred at ambient temperature for 3 days and filtered. The filtrate was concentrated *in vacuo* and the residue taken up in ethyl acetate. This was washed with water then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography on silica gel afforded 25 mg of (2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl) piperazine as a white solid: NMR ($CDCl_3$) 7.3 (m, 5), 7.0 (m, 4), 4.8-4.1 (m, 5), 3.8 (m, 3), 3.2 (m, 2), 2.8 (dd, 1), 2.5 (dd, 1), 1.4 (d, 3) ppm, MS (ESI) 458.

B. In a similar manner, the following compounds of formula (Ia) were made:

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl)piperazine; NMR ($CDCl_3$) 7.9 (s, 1), 7.3(m, 5), 6.9 (m, 4), 4.7 (m, 3), 4.4-3.4 (m, 5), 3.1-2.7 (m, 2), 2.4 (t, 1), 2.0 (d, 1), 1.2 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4.7-4. 1 (m, 5), 3.9-3.4 (m, 9), 3.2-2.7 (m, 3), 2.3 (m, 2), 2.0 (m, 1), 1.2 (m, 3) ppm;

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1-yl)methyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)-5-((diethylamino)methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.7 (m, 3) , 3.9-3. 4 (m, 4), 2.8-2.3 (m, 7), 1.2 (m, 3), 0.9 (t, 6) ppm;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-(((ethyl)amino)methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.7 (m, 3), 4.2-3.4 (m, 5), 2. 8-2.3 (m, 6), 1.3-1.0 (m, 6) ppm;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((4-methylpiperazin-1-yl)methyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.7 (m, 3), 3.9-3.4 (m, 4), 2.8-2.2 (m, 14), 1.2 (m, 3) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-4-(4- fluorobenzyl)-3-(2-(4-(*t*-butoxycarbonyl)piperazin-1-yl)ethyl) piperazine, hydrochloride salt

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((dimethylamino)methyl)piperazine

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (m, 4), 4.6 (m, 4), 4.2-3.2 (m, 4), 2.6-2.2 (m, 4), 1.2 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-((((cyclopropyl)methyl)amino)methyl)piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5-(((2-hydroxyethyl)thio)methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4.7 (m, 3), 4.1-3. 5 (m, 5), 3.1-2.3 (m, 8), 1.3 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-(imidazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.3 (m, 1), 9. 4 (s, 1), 7.9 (s, 3), 7.6 (s, 2), 7.4 (m, 1), 7.3 (m, 3), 7.1 (m, 1), 5.4 (m, 2), 4.9 (m, 1), 4.2 (m, 2), 3.8-3.2 (m, 6), 2.7 (m, 1), 1.4-1.2 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (s, 1), 7.3 (m, 2), 7.2 (dd, 1), 7.0 (m, 5), 6.8 (d, 1), 5.8 (q, 1), 4.6 (m, 3), 4.2 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2. 7 (dd, 1), 2.2 (dd, 1), 2.0 (br s, 1), 1.8 (dd, 3), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(triazol-1- ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 8.4 (s, 1), 7.9 (s, 1), 7.3 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 5.4 (s, 2), 4.6 (m, 3), 4.2 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2.9 (dd, 1), 2.2 (dd, 1), 1.3 (m, 3), 0.9 (m, 3) ppm; and

(*trans*)-1-((4-chloro-2-(tetrazol-1- ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 9.4 (s, 1), 7.4 (s, 1), 7.3 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 5.6 (s, 2), 4.7 (m, 3), 4.2 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3. 0 (m, 1), 2.9 (dd, 1), 2.2 (dd, 1), 1.3 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 5

Compounds of Formula (Ia)

A. To a solution of oxalyl chloride (0.62 g, 5 mmol) in CH_2Cl_2 (20 mL) at -50°C was added DMSO (0.85 g, 11 mmol, in solution of 5 mL of CH_2Cl_2) over 2 minutes. 4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine (1.85 g, 4.5 mmol, in solution of 5 mL of CH_2Cl_2) was added. The resulting mixture was stirred at -50°C for 15 minutes, then triethylamine (2.3 g, 22 mmol) was added. After 5 minutes at -50°C, the mixture was gradually warmed to ambient temperature. At that time the mixture was diluted with CH_2Cl_2 and washed with water, then brine. The organic layer was

then dried over $MgSO_4$ and concentrated *in vacuo* to afford 1.7 g of 4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-((formyl)methyl)piperazine as a yellow oil; NMR ($CDCl_3$) 9.8 (d, 1) 7.3 (m, 4), 7.0 (m, 4), 4.6 (m, 3), 3.8-3.2 (m, 7), 2.7-2.2 (m, 4) ppm.

B. In a similar manner, the following compounds of formula (Ia) were made:

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-((acetyl)methyl)piperazine, hydrochloride salt; NMR ($CDCl_3$) 7.3 (m, 4), 6.9 (m, 4), 4.6 (m, 2), 3.8-3.3 (m, 7), 2. 4 (m, 4), 2.1 (d, 3) ppm; and

(2*R*,5*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-formylpiperazine.

EXAMPLE 6

Compounds of Formula (Ia)

A. To a solution of 4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((formyl)methyl) piperazine (0.31 g, 0.77 mmol) in anhydrous THF (20 mL) was added methyl magnesium bromide (0.26 mL, 0.77 mmol, 3.0 M solution in ether). The resultant mixture was stirred overnight at ambient temperature. At that time the mixture was poured into 5% aqueous NH_4Cl solution and extracted with two portions of ether. The combined organic extracts were washed with brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography on silica gei afforded 0.29 g of 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxypropyl)piperazine, as a clear, colorless oil, which was converted to its hydrochloride salt; NMR ($CDCl_3$) 7.6 (m, 2), 7. 2 (m, 4), 6.9 (m, 2), 4.7 (m, 2), 4.4-3.0 (m, 10), 2.4-1.4 (m, 2). 1.3-1. 0 (m, 3) ppm.

B. In a similar manner, the following compounds of formula (Ia) were made:

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2-phenylethyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 9), 7.0 (t, 2), 6.8 (d, 2), 4.9 (m, 1), 4.8 (m, 2), 4.1 (m, 1), 3.8-3.3 (m, 6), 2.8 (m, 2), 2.2 (m, 1), 2. 0 (m, 2) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxypentyl)piperazine; NMR ($CDCl_3$) 7. 8 (m, 2), 7.3 (m, 4), 6.9 (d, 2), 4.8 (d, 2), 4.5-3.0 (m, 16) 2.2-1.2 (m, 8) , 0.9 (m, 3) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(2-hydroxybut-4-enyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 5.7 (m, 1), 5.2

(dd, 1), 5.1 (t, 1), 4.6 (m, 2), 4.2-3.3 (m, 7), 2.9 (m, 2), 2.4 (m, 1), 1.9-1.5 (m, 2) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-hydroxyprop-2-enyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.1 (b s, 1), 7.6 (m, 2), 7.3 (d, 4), 6.9 (d, 2), 6.1 (m, 1), 5.9 (m, 1), 5.4 (m, 2), 4.8 (m, 2), 4.4 (m, 4), 3. 7-3.1 (m, 5), 1.1 (m, 3) ppm;

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxybutyl)piperazine, hydrochloride salt; NMR (DMSO-d_6) 10.3 (b s, 1), 7.6 (m, 2), 7.3 (m, 4), 6.9 (d, 2), 5.6 (m, 1), 4.9 (m, 2), 4.4 (m, 3), 3.9-3.1 (m, 5), 1.4 (m, 4), 1.1 (d, 3), 0. 8 (t, 3) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxybut-4-ynyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2-cyclohexylethyl) piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyethyl)piperazine hydrochloride salt; NMR (DMSO-d_6) 10.3 (b s, 1), 7.6 (m, 2), 7.3(m, 4), 6.9 (d, 2), 5.6 (b s, 1), 4.9 (m, 2), 4.6-4.0 (m, 6), 3.2 (m, 3), 1.2 (d, 3), 1.1 (d, 3) ppm;

(2*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl)piperazine, hydrochloride salt;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.2-6.8 (m, 4), 5. 1 (m, 1), 4.7 (m, 2), 4.2-3.0 (m, 9), 2.7 (dd, 1), 2.3 (d, 1), 1.5 (d, 3), 1.3 (br m, 3), 0.9 (br m, 3) ppm;

1-((4-chlorophenoxy)methyl) carbonyl-2-(1-hydroxyethyl)-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.2 (m, 4), 7.0 (m, 2), 6.8 (dd, 2), 4.7 (m, 3), 4.2 (m, 1), 3.8 (m, 1), 3.4 (s, 2), 3.2 (m, 1), 2.3 (dd, 1), 2.1 (m, 1), 1.1 (m, 3) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2- hydroxypropyl)-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.6 (br s, 2), 7.3 (d, 4), 6.9 (q, 2), 4.9 (m, 3), 4.3 (m, 3), 3. 9 (m, 3) , 3.3. (m, 2), 3.0 (m, 1), 2.2 (t, 1), 1.8 (m, 1), 1.5 (m, 1), 1. 1 (d, 1.5) , 1.0 (d, 1.5) ppm; and

1-((4-chlorophenoxy)methyl) carbonyl-2-(2-hydroxybut-3-enyl)-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 7.6 (dt, 2), 7.3 (m, 4), 6.9 (t, 2), 5.8 (m, 1), 5.2 (dd, 1), 5.0 (dt, 2), 4.8 (dt, 1), 4.4 (m, 2), 3.9 (m, 1), 3.4 (m, 3), 3.0 (m, 3), 2.2 (m, 1) , 1.8 (m, 1), 1.6 (m, 1) ppm.

EXAMPLE 7

Compounds of Formula (Ia)

A. To a solution of 4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxy-2- phenylethyl)piperazine (0.051 g, 0.11 mmol) in anhydrous ether (5 mL) was added sodium hydride (0.006 g, 0.15 mmol). The resultant mixture was stirred at ambient temperature for 30 minutes, then methyl iodide (0.016 g, 0.11 mmol) was added. Once thin layer chromatography analysis showed complete consumption of 4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxy-2-phenylethyl)piperazine had occurred, the mixture was poured into water and extracted with two portions of ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 0.046 g of 4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-methoxy-2-phenylethyl)piperazine as a yellow oil: NMR ($CDCl_3$) 7. 3 (m, 9), 7.0 (m, 2), 6.9 (m, 2), 4.8 (m, 3), 4.2 (m, 2), 3.9-3.2 (m, 5), 3. 1 (d, 2), 3.0 (s, 1), 2.9 (s, 1), 2.6 (m, 1), 2.4 (m, 1), 1.9 (m, 1) ppm.

B. In a similar manner, other compounds of the invention were made:

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-((methoxy) methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.6 (m, 3), 3.8-3.1 (m, 9), 3.0 (br s, 1), 2.7 (dd, 1), 2.3 (t, 1) , 1.2 (m, 3) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-2-(2-(methoxy)ethyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (d, 2), 4.7 (m, 3), 4.1 (m, 1), 3.7 (m, 1), 3.4-3.2 (m, 6), 2.8 (m, 3), 2.0 (m, 4) ppm;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) methylpiperazine-2-one;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonylpiperazine-2-one;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-3-((methoxy)methyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.9 (dd, 2), 4.7 (d, 2), 3.9-3. 3 (m, 11), 2.6 (m, 2), 2.2 (m, 1) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3- (2-(methoxy)ethyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7. 0 (t, 2), 6.9 (dd, 2), 4.7 (d, 2), 3.8-3.3 (m, 11), 2.6 (m, 2), 2.2 (m, 1) , 1.8 (m, 2) ppm;

4-(4-fluorobenzyl)-1-(2-(4-chlorophenoxy)ethyl) piperazin-2-one; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4.2 (t, 2), 3.8 (t, 2), 3.5 (m, 4), 3.2 (s, 2), 2.6 (t, 2) ppm;

4-(4-fluorobenzyl)-1-(2-(4-chlorophenoxy)ethyl)-3-((ethoxycarbonyl)methyl)piperazin-2-one, hydrochloride salt; NMR ($CDCl_3$) 7.2 (m, 2), 7.1 (m, 4), 6.8 (d, 2), 4.2 (m, 9), 3.5 (m, 5), 2.9 (br s, 1), 1.3 (t, 3) ppm;

(*trans*)-1-((4-chloro- 2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0-6.8 (m, 5), 4. 7 (br m, 2.5), 4.2 (br s, 0.5), 3.8 (s, 3), 3.6-3.2 (m, 4), 3.0 (br s, 1), 2.7 (m, 1), 2. 2 (d, 1), 1.2 (br m, 3), 1.9 (br m, 3) ppm; and

(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 2), 7.0-6.8 (m, 5), 4.7 (br m, 2.5), 4.2 (br s, 0.5), 3.8 (s, 3), 3.6-3.2 (m, 4), 3.0 (br s, 1), 2.7 (m, 1), 2.2 (d, 1), 1.2 (br m, 3), 1.9 (br m, 3) ppm.

EXAMPLE 8

Compounds of formula (Ia)

A. To a solution of 4-chlorobenzylisocyanate (0.59 g, 3.5 mmol) in anhydrous THF (15 mL) at 0°C was added 1-(4-chlorobenzyl) piperazine (0.74 g, 3.5 mmol). The resultant mixture was stirred at ambient temperature. After 20 hours the mixture was concentrated of volatiles. The resulting solid was washed with ethyl acetate and dried *in vacuo* to afford 0.72 g of 1-(((4-chlorobenzyl)amino)carbonyl)-4-(4-chlorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.4 (m, 4), 7.3 (m, 2), 7.2 (m, 2), 4.4-4.1 (m, 6), 3.6 (m, 4), 3.0 (m, 2) ppm.

B. In a similar manner, other compounds of formula (Ia) were made:

4-(4-fluorobenzyl)-1- ((4- chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl) piperazine; NMR ($CDCl_3$) 7.2 (m, 4), 7.0 (t, 2), 6.8 (dd, 2), 5.7 (br s, 1), 5.2 (m, 1), 5.0 (m, 1), 4.8-2.0 (m, 15) ppm;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- (*N'*-(ethoxycarbonylmethyl) ureido)methyl)piperazine; NMR (DMSO-d_6) 7.3 (m, 4), 7.1 (t, 2), 6.8 (d, 2), 6.5 (t, 2), 4.8 (m, 2), 4.1-1.8 (m, 15), 1.1 (m, 3) ppm;

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.8 (br s, 1), 8.3 (s, 1), 7.3 (m, 2), 7.0 (m, 3), 6.8 (d, 1), 6.0 (br s, 1), 5.0 (m, 2), 4.8 (m, 2), 4.1 (m, 3), 3.6 (m, 3), 3.1 (m, 2), 2.7 (d, 1), 2.3 (d, 1), 0.9 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR ($DMSO-d_6$) 9.8 (br m, 1), 9.4 (s, 1), 8.2 (s, 1), 7.6 (m, 2), 7.3 (m, 2), 7.0 (m, 2), 6.0 (br m, 2), 5.0 (m, 3), 4.3 (br m, 3), 4.0 (s, 2), 3.7-3.2 (m, 4), 2.8 (s, 3), 1.3 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-ethyluredio)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 8.8 (s, 1), 8.4 (s, 1), 7.3 (m, 2), 7.0 (m, 2), 6.8 (m, 3), 4.7 (m, 2), 4.1 (m, 2), 3.6-3.3 (m, 4), 3. 0 (br s, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 5), 0.9 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($DMSO-d_6$) 10.4 (br d, 1), 9.2 (s, 1), 9.1 (s, 1), 8.2 (s, 1), 8.1 (d, 1), 7.7 (m, 2), 7.3 (m, 3), 6.9 (m, 2), 5.0 (m, 2), 4.7 (m, 1) , 4.3 (m, 3), 3.8 (q, 1), 3.6 (m, 1), 3.4 (m, 1), 2.9 (t, 1), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*- (4-nitrophenyl)ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.1 (s, 1), 8.4 (s, 1), 8.3 (s, 1), 8.2 (s, 1), 7.9 (d, 1), 7.8 (d, 1), 7.3 (m, 3), 7.0 (t, 2) , 6.8 (d, 1), 6.7 (m, 1), 4.7 (m, 2), 3.6 (m, 4), 3.1 (m, 1), 2.8 (m, 1), 2.3 (d, 1), 1.4 (m, 3), 1.0 (m, 3) ppm;

(*trans*)-1- ((4-chloro-2-(*N'*-(4-methylphenyl)ureido)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($DMSO-d_6$) 10.5 (br d, 1), 9.6 (s, 1), 8.5 (d, 1), 8.2 (s, 1), 7.8 (m, 2), 7.3 (m, 4), 7. 1 (d, 2), 6.9 (s, 1), 5.0 (m, 2), 4.3 (m, 3), 3.9 (s, 1), 3.6 (m, 1) , 3.4 (m, 1), 2.8 (dd, 1), 2.2 (s, 3), 1.4 (m, 3), 1.2 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.0 (s, 1), 8.4 (s, 1), 7.3 (m, 8), 7.0 (t, 2), 6.8 (q, 2), 5.6 (t, 1), 4.6 (m, 4), 3.6 (m, 3), 3.0 (m, 1), 2.7 (m, 1), 2.2 (m, 2), 1. 3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 1), 5.6 (m, 1), 5.4 (br

d, 1) 4.7 (m, 2), 3.5 (q, 2), 3.2 (m, 4), 3.0 (m, 1), 2.7 (m, 4), 2.2 (d, 1), 1.4 (d, 3), 1.3 (m, 9), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(oxazol-2-ylaminomethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 3), 4.4 (s, 2), 4.3 (t, 2), 3.9 (m, 1), 3.8 (t, 2), 3.5 (q, 2), 3.3 (m, 1), 3. 0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(ureido)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.3 (m, 4), 7.2 (m, 2), 7.1 (t, 2), 5.8 (br s, 1), 5.4 (br s, 2), 4.0 (m, 1), 3.4 (m, 2), 3.2 (m, 3), 2.9 (m, 1), 2.5 (m, 2), 2.1 (m, 1), 1.1 (m, 3), 0.8 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-2- (ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.3 (m, 5), 7.1 (t, 2), 6.6 (q, 1), 5.6 (br s, 2), 5.0 (m, 1), 4.4 (m, 0.5), 4.0 (m, 0.5), 3.5 (m, 2), 3.3 (m, 2), 2. 8 (m, 2), 2.7 (m, 1), 2.5 (m, 1), 2.1 (d, 1), 1.2 (m, 3), 0.8 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methoxyphenyl) ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.2 (br s, 1), 9.5 (s, 1), 8.5 (br s, 1), 8.2 (s, 1), 7.7 (m, 2), 7.2 (m, 4), 7.0 (s, 3), 6.5 (dd, 1), 5.0 (m, 2), 4.3 (m, 3), 3.7 (m, 5), 3.4 (m, 1), 2.9 (m, 1), 1.4 (s, 3), 1.2 (s, 3) ppm; and

(*trans*)-1-((4-chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.5 (s, 1), 9.0 (m, 1), 8.3 (s, 1), 7.3 (m, 2), 7.0 (m, 4), 4.8 (m, 3), 4.2 (m, 1), 3.6 (m, 2) , 3.4 (m, 1), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 9

Compounds of formula (Ia)

A. To a solution of (*cis*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine (0.20 g, 0.71 mmol) in anhydrous THF (2 mL) was added 4-fluorobenzylbromide (0.11 mL, 0.85 mmol), diisopropylethylamine (0.15 mL, 0.85 mmol) and sodium iodide (0.042 g, 0.28 mmol). The resultant mixture was stirred at ambient temperature for 2 days. At that time the mixture was poured into ether and washed with 5% aqueous $NaHCO_3$ solution, then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash column chromatography on silica gel afforded 0.17 g of (*cis*)-

1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4- fluorobenzyl)piperazine as a pink oil; which was converted to its hydrochoride salt; NMR ($CDCl_3$) 7.6 (m, 2), 7.3 (m, 4), 7.0-6.8 (m, 2), 5.0-2.8 (m, 10), 1.5-1.3 (m, 6) ppm.

B. In a similar manner, the following compounds of formula (Ia) were made:

1-((4- chlorophenoxy)methyl)carbonyl-2- ((((cyclopropyl)methyl)amino)methyl)-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4.5 (s, 2) , 3.4 (m, 4), 3.0 (m, 1), 2.5 (m, 4), 2.2 (t, 1), 2.0 (m, 2), 16 (s, 2), 0.8 (m. 1), 0. 5 (m, 2), 0.1 (m, 2) ppm;

(3*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine, hydrochloride salt; NMR ($CDCl_3$) 13.3 (m,1), 7.9 (q, 2), 7.2 (m, 4), 6.9 (d, 2), 6.8 (d, 2), 4.8-3.3 (m, 10), 1.7 (d, 3), 1.2-1.0 (m, 3) ppm;

(3*S*,5*S*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3,5-dimethylpiperazine, hydrochloride salt; NMR ($CDCl_3$) 13.3 (m,1), 7.9 (q, 2) , 7.2 (m, 4), 6.9 (d, 2), 6.8 (d, 2), 4.8-3.3 (m, 10), 1.7 (d, 3), 1.2-1. 0 (m, 3) ppm;

1-((4-chlorophenoxy)methyl)carbonyl-2-(((4- fluorobenzyl)amino)methyl)-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(((methyl)amino)methyl)-4-(4-fluorobenzyl) piperazine: NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (d, 2), 4.5 (q, 2), 3.6 (m, 4), 3.1 (m, 2), 2.8 (m, 3), 2.6 (s, 3), 2.5-2. 3 (m, 3) ppm; and

1-((4-chlorophenoxy)methyl)carbonyl-3- trifluoromethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6.8 (dd, 2), 4.6 (m, 2), 4.2 (m, 1), 3.8 (m, 3), 3.6 (dd, 1), 3.3 (m, 2), 3.0 (m, 1), 2.6 (m, 1) ppm.

EXAMPLE 10

Compounds of Formula (Ia)

A. To a solution of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2-(methoxycarbonyl)methyl-4-(4-fluorobenzyl)piperazine (0.20 g, 0.42 mmol) in a methanol/water solution (20 mL, 3:1) was added lithium hydroxide, monohydrate (0.40 mL, 9.5 mmol). The resultant mixture was stirred at ambient temperature for 30 min. At that time HPLC analysis showed complete conversion had occurred. The mixture was poured into ethyl acetate and washed sequentially with an aqueous acetic acid/water solution (pH < 4) , water, and brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 0.

060 g of 1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2-(carboxy)methyl-4- (4-fluorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.4 (m, 2), 7.1 (m, 2), 6.2 (m, 2), 5.1 (m, 1), 4.7 (m, 3), 4.0 (m, 2), 3. 8 (d, 9), 3.3-3.1 (m, 4), 2.6 (m, 2), 2.4 (m, 2) ppm, MS (ESI) 476.

B. In a similar manner, the following compounds of the invention were made:

1-((4-chlorophenoxy)methyl) carbonyl-3-(carboxy)methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 7.4 (t, 2), 7.3 (d, 2), 7.1 (t, 2), 6.9 (d, 2), 4.7 (m, 2), 4.0 (d, 2), 3.7 (m, 2), 3.5 (m, 3), 3.2 (m, 1), 2.8-2.4 (m, 3) ppm;

1-((4-chloro-2-carboxyphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 8.0 (s, 1), 7.4 (dd, 1), 7.3 (m, 3), 7.0 (t, 1), 6.9 (d, 1), 5.0 (m, 2), 4.6 (m, 1), 4.3 (m, 1) , 3.7 (m, 1), 3.4 (m, 2), 2.8 (d, 1), 2.6 (m, 1), 2.1 (m, 1), 1.4 (d, 1.5), 1.3 (d, 1.5) ppm; and

(*trans*)-1-((4-chloro-2- carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.4 (br s, 1), 8.0 (m, 1), 7.5 (m, 3), 7. 2 (m, 2), 7.0 (d, 1), 5.0 (m, 2), 4.6 (m, 1), 4.3 (m, 3), 3.7 (m, 2), 3.4 (m, 1) , 3.3 (m, 1), 1.4-1.3 (m, 6) ppm.

EXAMPLE 11

Compounds of formula (Ia)

A. To a solution of lithium aluminum hydride (0.29 g, 7 mmol) in a solution of anhydrous THF (16 mL) was added 1-((4-chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)piperazine (0.36 g, 1.0 mmol, in 3 mL of THF). The resultant mixture was stirred at ambient temperature for 9 hours. At that time 0.3 mL of water and 0.3 mL of 15% aqueous NaOH solution were added and the resulting mixture stirred at ambient temperature. After 18 hours, the mixture was filtered through a short column of Celite (THF) and the filtrate concentrated *in vacuo* to afford 0.12 g of 1-(2-(4- chlorophenoxy)ethyl)-4-(4-fluorobenzyl)piperazine as a clear oil; NMR ($CDCl_3$) 7.2 (m, 4), 7.0 (m, 2), 6.8 (m, 2), 4.0 (m, 2) , 3.4 (m, 2), 2.8-2.4 (m, 10) ppm.

B. In a similar manner the following compounds of formula (Ia) or (Ib) were made:

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0.84-0.98 (m, 3H), 1.16-1.28 (m, 3H), 2.16 (m, 1H), 2.70 (m, 1H), 2.88 (m, 1H), 3.08 (m, 0.5H), 3.40 (m, 1.5H), 3.58 (m, 1.5H), 4.0 (m, 1H), 4.40 (s, 0.5H), 4.94 (m, 1.5H), 5.18 (m, 0.5H), 7.12 (m, 3H), 7.36 (m, 2H), 7.54 (m, 1H), 7.62 (s, 1H)5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-

oxoethoxy]benzeneacetic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1.00 (m, 3H), 1.30 (m, 3H), 2.05 (d, 1H), 2.68 (dd, 1H), 2.80 (m, 1H), 3.05 (m, 1H), 3.25 (m, 1H), 3.60 (m, 4H), 4.10 (m, 1H), 4.65 (m, 2H), 6.78 (m, 1H), 7.00 (t, 2H), 7.33 (m, 4H).

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 1.30 (m, 3H), 2.05 (m, 1H), 2.20 (m, 1H), 2.65 (d, 1H), 2.85 (m, 1H), 3.50 (m, 4H), 3.65 (m, 2H), 4.35 (m, 1H), 4.70 (m, 2H), 6.72 (d, 1H), 7.00 (t, 2H), 7.30 (m, 4H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6):δ/ppm = 0.80-0.98 (m, 3H), 1.16-1.28 (m, 3H), 2.16 (m, 1H), 2.55 (m, 0.5H), 2.70 (m, 0.5H), 2.95 (m, 1H), 3.08 (m, 0.5H), 3.40 (m, 1.5H), 3.58 (m, 1.5H), 4.00 (m, 1H), 4.40 (s, 0.5H), 4.94 (m, 1.5H), 5.18 (m, 0.5H), 7.12 (m, 3H), 7.36 (m, 2H), 7.64 (m, 1H), 7.74 (s, 1H).

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm = 0.84-0.98 (m, 3H), 1.16-1.28 (m, 3H), 2.16 (m, 1H), 2.70 (m, 1H), 3.08 (m, 2H), 3.50 (m, 2H), 3.72 (m, 1H), 3.92 (s, 3H), 4.20 (s, 0.5H), 4.94 (m, 2.5H), 6.54 (s, 1H), 7.00 (m, 2H), 7.34 (m, 2H), 8.24 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid; ^{1}H NMR (500 MHz, DMSO-d_6):δ/ppm = 0.90 (m, 3H), 1.25 (m, 3H), 2.23 (m, 1H), 2.75 (m, 1H), 3.35 (m, 1H), 3.45 (m, 1H), 3.62 (m, 1H), 3.77 (m, 2H), 3.95 (s, 3H), 4.30 (s, 1H), 5.02 (m, 2H), 6.91 (s, 1H), 7.10 (m, 2H), 7.37 (m, 2H), 7.75 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid; ^{1}H NMR (400MHz, DMSO-d_6 + D_2O):δ/ppm = 0.90-1.10 (m, 3H), 1.20-1.45 (m, 3H), 2.27 (m, 1H), 2.40 (s, 3H), 2.73 (m, 1H), 3.00-4.30 (m, 5H), 4.60-5.10 (m, 3H), 6.84 (s, 1H), 7.02 (m, 2H), 7.30 (m, 2H), 7.98 (s, 1H);

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (400 MHz, DMSO-d_6, 120°C):δ/ppm = 0.94 (d, 3H), 1.24 (d, 3H), 2.25 (d, 1H), 2.75 (dd, 1H), 2.95-3.00 (m, 1H), 3.34 (d, 1H), 3.47 (d, 1H), 3.61 (d, 1H), 3.73 (d, 1H), 4.24-4.30 (m, 1H), 4.94 (d, 1H), 5.03 (d, 1H), 7.09 (dd, 2H), 7.37 (dd, 2H), 7.41 (s, 1H), 7.81 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid; ^{1}H NMR (400 MHz, $CDCl_3$):δ/ppm =

1.00 (m, 3H), 1.30 (m, 3H), 2.30 (m, 1H), 2.70 (m, 1H), 3.10 (m, 1H), 3.25 (m, 1H), 3.60 (m, 2H), 3.70 (m, 1H), 4.65 (m, 1H), 5.00 (m, 2H), 7.00 (t, 2H), 7.30 (m, 3H), 8.05 (s, 1H).

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid; ^{1}H NMR (500 MHz, DMSO-d_6, 120°C):δ/ppm = 0.62 (t - rotamer, 1.25H), 0.73 (t - rotamer, 3.5H), 0.86 (t - rotamer, 1.25H), 1.24 (m, 1H), 1.37 (m, 1H), 1.54 (m, 1H), 1.69 (m, 1H), 1.84 (m, 1H), 2.26 (t, 1H), 2.57 (d, 1H), 2.66 (dd, 1H), 2.90 (dd, 1H), 3.52 (m, 3H), 4.20 (d, 1H), 4.99 (m – rotamers, 2H), 7.09 (m, 3H), 7.35 (t, 2H), 7.55 (dd, 1H), 7.63 (d, 1H), 13.12 (br, 1H);

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid; ^{1}H NMR (500 MHz, DMSO-d_6):δ/ppm = 0.80 (m, 6H), 1.25 (m, 0.5H), 1.40 (m, 1H), 1.70 (m, 4H), 1.94 (m, 1H), 3.08 (m, 4H), 3.90 (m, 3.5H), 4.20 (br, 1H), 4.90 (m, 1H), 5.10 (m, 1H), 6.80 (m, 1H), 7.20 (m, 2H), 7.54 (m, 2H), 7.90 (s, 1H);

5-chloro-4-ethoxy-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

4-amino-5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

4-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-5-methylbenzoic acid;

EXAMPLE 12

Compounds of Formula (Ib)

A. To a solution of 1-(1-(*t*-butoxycarbonyl)amino-2-(4-chlorophenyl)ethyl) carbonyl-4-(benzyl)piperazine (0.20 g, 0.44 mmol) in a solution of CH_2Cl_2 (3 mL) was added trifluoroacetic acid (3 mL). The resultant mixture was stirred at ambient temperature. After 18 hours, the mixture was concentrated *in vacuo* to afford a

yellow oil. This was dissolved in ethyl acetate and washed with an aqueous $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 0.17 g of a clear, colorless film. This was dissolved in ether and treated with an ethereal solution of HCl, resulting in formation of a white precipitate. Concentration afforded 0. 18 g of 1-(1-amino-2-(4-chlorophenyl)ethyl)carbonyl-4-(benzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.4 (m, 7), 7.1 (m, 2), 4.0 (t, 1), 3.7-3.1 (m, 4), 2.8 (m, 2), 2.4-2.2 (m, 5), 1.8 (m, 1) ppm.

B. In a similar manner, the following compounds of formula (Ib) were made:

1-(3-amino-2-(4-chlorophenyl)propyl) carbonyl-4-(4-chlorobenzyl)piperazine; NMR ($CDCl_3$) 7. 2 (m, 8), 3.8 (s, 3), 3.6-3.3 (m, 8), 3.0 (m, 2), 2.6 (dq, 2), 2.4-2.1 (m, 4) ppm; and

1-(1-amino-2-(4-chlorophenyl)ethyl)carbonyl-4-(4- chlorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7.1 (d, 2), 4.0 (t, 1), 3.6-3.1 (m, 6), 2.8 (dq, 2), 2.6 (br s, 2), 2.4 (m, 3) , 1.8 (m, 1) ppm.

C. In a similar manner, the following compounds of formula (Ia) were made:

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 3), 7.2 (dd, 1), 7.0 (t, 2), 6.8 (br d, 1), 4.7 (m, 2), 3.9 (s, 2), 3. 5 (m, 3), 3.0 (br s, 1), 2.7 (m, 1), 2.2 (m, 4), 1.3 (m, 3), 0.9 (m, 3) ppm;

(trans)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10.1 (s, 1), 8.5 (s, 1), 7.3 (t, 3), 7.0 (t, 3), 6.8 (d, 1), 4.7 (m, 3), 4.2-3. 4 (m, 5), 3.2 (m, 1), 3.0 (br s, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.3 (m, 3), 0.9 (m, 3) ppm;

(2*R*,5*S*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 10.0 (s, 1), 8.2 (m, 3), 7.6 (s, 1), 7.3 (m, 2), 7.1 (dd, 1), 6.9 (m, 1), 5.2-4.2 (m, 5), 3.8-2.9 (m, 7), 1.2 (m, 6) ppm;

(2*R*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11. 4 (br s, 1), 10.0 (s, 1), 8.3 (br s, 2), 8.1 (s, 1), 7.8 (m, 2), 7.4 (t, 2), 7.1 (d, 1), 7.0 (d, 1) 5.0 (q, 2), 4.7 (m, 1), 4.3 (m, 3), 3.9 (m, 3), 3.6 (m, 1), 3.1 (m, 3), 1.5 (d, 1.5), 1.3 (d, 1.5) ppm;

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.9 (s, 1), 8.5 (s, 1),

7.3 (m, 3), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 4.2-3.9 (m, 1), 3.6-3.3 (m, 5), 3.0 (br s, 1), 2.7 (dd, 1), 2. 5 (s, 3), 2.3 (d, 1), 1.3 (m, 3), 1.0 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 10. 2 (s, 1), 8.5 (s, 1), 7.3 (m, 3), 7.0 (m, 3), 6.8 (d, 1), 4.7 (m, 3), 4.2- 3.9 (m, 1), 3.6-3.2 (m, 5), 3.0 (m, 1), 2.7 (dd, 1), 2.2 (d, 1), 1.4 (d, 3), 1.3 (m, 3), 1.0 (br s, 3) ppm;

(*trans*)-1-((4-chloro-2- (1-(methylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 3), 7.1 (dd, 1), 7.0 (t, 2), 6.8 (br d, 1), 4.7 (m, 3), 4.0 (q, 2), 3.6 (q, 2), 3. 2 (m, 1), 3.0 (m, 1), 2.7 (dd, 1), 2.3 (m, 4), 1.3 (m, 6), 0.9 (m, 3) ppm;

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.6 (br d, 1), 74-7.1 (m, 8), 7.0 (t, 2), 6.8 (m, 1), 5.0 (d, 1), 4.6 (m, 3), 4.2 (m, 1), 3.5 (t, 1), 3.4-3.0 (m, 4), 2. 8 (m, 1), 24 (s, 3), 2.2 (m, 1), 1.2 (m, 3), 0.8 (m, 3) ppm;

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazineNMR (DMSO-d_6) 9.2 (br s, 1), 7.6 (m, 4), 7.3 (t, 2), 7.2 (d, 1), 5.2 (dd, 1), 5. 0 (d, 1), 4.8 (m, 1), 4.4 (d, 4), 3.9 (d, 1), 3.4 (m, 11), 1.4 (d, 1.5), 1. 2 (d, 1.5) ppm;

(2*R*,5*S*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.8 (br s, 1), 9.2 (br s, 1), 7.6 (s, 3), 7.5 (dd, 1), 7.3 (t, 2), 7.2 (d, 1), 5.4 (m, 1) , 5.0 (m, 3), 4.7 (m, 1), 4.5 (s, 2), 4.3 (m, 3), 3.7-3.1 (m, 11), 1.4-1. 1 (m, 6) ppm;

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO- d_6) 11.3 (br d, 1), 9.7 (m, 2), 7.9 (m, 2), 7.7 (m, 2), 7. 4-7.2 (m, 3), 5.4 (m, 1), 5.0 (m, 2), 4.6 (m, 1), 4.2 (m, 3), 3.8-3.2 (m, 10), 2.8 (dd, 1), 1.7 (m, 3), 1.4 (dd, 3), 1.2 (m, 3) ppm;

(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7. 2 (d, 2), 7.0 (t, 2), 4.8 (m, 1), 4.2 (m, 1), 3.9 (m, 1), 3.5-3.2 (m, 3), 2. 9 (m, 3), 2.6 (m, 2), 2.2 (m, 1), 1.2 (m, 3), 0.8 (m, 3) ppm; and

(*trans*)-1-(2-(4-chlorophenyl)-2-(amino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7. 3 (m, 6), 7.0 (t, 2), 4.7 (m, 0.5), 4.5 (m, 1), 4.2 (d, 0.5), 3.5 (q, 2), 3. 2 (m, 1), 3.0 (m, 1), 2.6 (m, 2), 2.5 (m, 2), 2.2 (m, 1), 1.2 (m, 3), 0. 9 (m, 3) ppm.

EXAMPLE 13

Compounds of Formula (Ia)

A. To a solution of (*trans*)- 1-((4-chloro-2-carboxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine (0.217 g, 0.50 mmol) in a solution of tetrahydroduran (5 mL) at 0°C was added isobutyl chloroformate (0.075 g, 0.55 mmol) and *N*-methylmorpholine (0.0556 g, 0.55 mmol). The resulting mixture was stirred at 0°C for 20 min, resulting in formation of a white precipitate. A solution of methylamine in tetrahydrofuran (0. 25 mL, 2.0 M, 0.50 mmol) was then added and the mixture stirred for 30 min more, at which time it was concentrated of volatiles *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed with water, then brine, dried over $MgSO_4$, filtered and concentrated to 0.208 g of a foam. This was dissolved in ethyl acetate and treated with 1 M ethereal HCl solution (excess). The resulting solid was collected by filtration and washed with ethyl acetate. Drying *in vacuo* afforded 0.19 g of (*trans*)-1-((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine as a white solid; NMR (DMSO-d_6) 10.8 (br d, 1), 9.2 (br s, 1), 7.8 (s, 2), 7.7 (m, 1), 7.6 (m, 1), 7.3 (m, 3), 5.4 (d, 1), 5.0 (m, 2), 4.7 (m, 1), 4.3 (m, 3), 4.0 (m, 1), 3.6 (m, 2), 2. 8 (s, 3), 1.4 (m, 3), 1.3 (m, 3) ppm.

B. In a similar manner, the following compounds of formula (Ia) were made:

(*trans*)-1-((4-chloro-2-((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 9.4 (br s, 1), 7.8 (s, 1), 7.6 (dd, 1), 7.4 (m, 2), 7.2 (d, 1), 7.1 (t, 2), 7.0 (s, 1), 5.3 (m, 1), 5.0 (m, 2), 4.4 (m, 1), 4.0 (m, 1), 3.8 (d, 2), 3.5 (m, 2) , 3.0 (m, 1), 2.7 (m, 1), 2.2 (br d, 1), 1.2 (br d, 3), 0.9 (br d, 3) ppm;

(*trans*)-1-((4-chloro-2-((2-aminoethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 9.4 (br s, 1), 8.2 (s, 1), 7.3 (m, 3), 7.0 (t, 2), 6.8 (d, 1), 4.7 (m, 3), 4.2 (m, 1) 3.6 (m, 5), 3.1 (m, 3), 2.7 (br d, 1), 2.3 (d, 1), 1.3 (br d, 3), 1.0 (m, 2) ppm;

(*trans*)-1- ((4-chloro-2-((4-aminocarbonylphenyl)aminocarbonyl)phenoxy)methyl) carbonyl-2.5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR (DMSO-d_6) 11.4 (s, 1), 7.9 (m, 5), 7.7 (d, 1), 7.4 (m, 3), 7.1 (t, 2), 5.4 (d, 1), 5.1 (m, 2), 4.6 (br s, 1), 4.0 (m, 1), 3.5 (m, 3), 3. 0 (m, 1) , 2.2 (m, 1), 1.3 (m, 3), 0.9 (m, 3) ppm; and

(*trans*)-1-(2-(4-chlorophenyl)-3-(*t*-butoxycarbonylamino)propyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 4), 7.2 (d, 2),

7.0 (t, 2), 4.8 (br s, 1), 4.6 (m, 1), 4.0 (m, 1), 3.4 (m, 6), 3.0 (m, 1), 2.6 (m, 2), 2.1 (m, 1), 1.4 (s, 9) , 1.2 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 14

Compounds of formula (Ia)

A. To a solution of hydroxylamine, hydrochloride (0.17 g, 2.5 mmol) in DMSO (3 mL) was added triethylamine (0.252 g, 2.5 mmol). The mixture was stirred at ambient temperature for 10 minutes, then filtered and washed with THF. The filtrate was concentrated *in vacuo* to remove the THF then treated with (*trans*)-1-((4-chloro-2-cyanophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine (0.200 g, 0.48 mmol). The resulting mixture was heated to 75°C for 20 hours. At that time the mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water, then brine, dried over $MgSO_4$, filtered concentrated *in vacuo* to afford 0.21 g of an oil. 0.030 g of this oil was dissolved in ethyl acetate and treated with 1 M ethereal HCl solution (excess). The resulting solid was collected by filtration and washed with ethyl acetate. Drying *in vacuo* afforded 0.027 g of (*trans*)-1-((4-chloro-2-(hydroxyamidino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.6 (s, 1), 7.3 (t, 2), 7.2 (dd, 1) , 7.0 (t, 2), 6.7 (br d, 1), 6.1 (br s, 2), 4.7 (m, 3), 3.7 (br d, 1), 3. 5 (q, 2), 3.2 (m, 1), 3.0 (m, 1), 2.7 (m, 1), 2.2 (t, 1), 1.3 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 15

Compounds of Formula (Ia)

A. To a solution of 4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)piperazine (0.134 g, 0.33 mmol) and triphenylphosphine (0.100 g) in THF (6 mL) at 0°C was added diethyl azodicarboxylate (0.060 mL) and diphenylphosphoryl azide (0.081 mL). The mixture was stirred at ambient temperature for 2 days, then concentrated of volatiles *in vacuo*. Purification by flash column chromatography on silica gel afforded 0.047 g of 1-((4-chlorophenoxy) methyl)carbonyl-2-(2-azidoethyl)-4-(4-fluorobenzyl)piperazine as a clear, colorless oil; NMR ($CDCl_3$) 7.3 (m, 4), 7.0 (t, 2), 6. 9 (d, 2), 4.7 (m, 3), 4.4 (br d, 1), 4.3 (m, 1), 4.1 (m, 1), 3.5-3.1 (m, 4), 2.8 (d, 1), 2.7 (d, 1), 2.1 (m, 2), 1.8 (m, 1) ppm.

EXAMPLE 16

Compounds of Formula (Ia)

A. To a solution of (*trans*)-1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine (0.169 g, 0.416 mol) in 10 mL of methylene chloride was added phthallic anhydride (0.074 g, 0.499 mol) and several 4Å molecular sieves. The mixture was stirred at ambient temperature for 3 hours, then at 70°C for 3 hours. At that time the mixure was cooled to 0°C and treated with oxalyl chloride (0.064 g, 0.499 mol). This was stirred at ambient temperature for 3 hours then partitioned between methylene chloride and water. The organic layer was concentrated to give an oil. Purification by flash column chromatography on silica gel afforded 0.058 g of a clear oil. This was dissolved in ethyl acetate and treated with 1 M ethereal HCl solution (excess). The resulting solid was collected by filtration and washed with ethyl acetate. Drying *in vacuo* afforded 0.045 g of (*trans*)-1-((4-chloro-2-(phthalimido)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine as a white solid; NMR ($CDCl_3$) 7.9 (m, 2), 7.8 (m, 2), 7.4 (d, 1), 7.3 (m, 3) , 7.05 (d, 1), 7.0 (t, 2), 4.6 (m, 3), 4.0 (m, 1), 3.5 (m, 1), 3.4 (m, 2), 2.9 (m, 1), 2.6 (m, 1), 2.2 (m, 1), 1.2 (m, 3), 0.9 (m, 3) pppm.

B. In a similar manner, the following compound of formula (Ia) was made:

(*trans*)-1-((4-chloro-2-(maleimido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; NMR ($CDCl_3$) 7.3 (m, 6), 7.0 (t, 2), 6.8 (s, 1), 4.6 (m, 3) , 4.0 (m, 1), 3.5 (q, 2), 3.2 (m, 1), 3.0 (br s, 1), 2.6 (dd, 1), 2.2 (br d, 1), 1.2 (m, 3), 0.9 (m, 3) ppm.

EXAMPLE 17

This example illustrates the preparation of representative pharmaceutical compositions for oral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 1-((2- methylphenoxy)methyl)carbonyl-4-(4-chlorobenzyl) piperazine hydrochloride salt:

A. Ingredients	% wt./wt.
Compound of the invention	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

The above ingredients are mixed and dispensed into hard-shell gelatin capsules containing 100 mg each, one capsule would approximate a total daily dosage.

B. Ingredients	% wt./wt.
Compound of the invention	20.0%
Magnesium stearate	0.9%

Starch	8.6%
Lactose	69.6%
PVP (polyvinylpyrrolidine)	0.9%

The above ingredients with the exception of the magnesium stearate are combined and granulated using water as a granulating liquid. The formulation is then dried, mixed with the magnesium stearate and formed into tablets with an appropriate tableting machine.

C. Ingredients

Compound of the invention	0.1 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g
Polysorbate 80	1.0 g
Water	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of water is then added with stirring to provide 100 mL of the solution which is filtered and bottled.

D. Ingredients	% wt. /wt.
Compound of the invention	20.0%
Peanut Oil	78. 0%
Span 60	2.0%

The above ingredients are melted, mixed and filled into soft elastic capsules.

E. Ingredients	%wt./wt.
Compound of the invention	1.0%
Methyl or carboxymethyl cellulose	2.0%
0.9% saline	q.s. 100 mL

The compound of the invention is dissolved in the cellulose/saline solution, filtered and bottled for use.

EXAMPLE 18

This example illustrates the preparation of a representative pharmaceutical formulation for parenteral administration containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e. g.*, 4- (4-fluorobenzyl)-1-((2-((acetylamino)methyl)-4-chlorophenoxy)methyl) carbonyl-2,5-methylpiperazine:

Ingredients

Compound of the invention	0.02 g
Propylene glycol	20.0 g
Polyethylene glycol 400	20.0 g

Polysorbate 80	1.0 g
0.9% Saline solution	q.s. 100 mL

The compound of the invention is dissolved in propylene glycol, polyethylene glycol 400 and polysorbate 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2 m membrane filter and packaged under sterile conditions.

EXAMPLE 19

This example illustrates the preparation of a representative pharmaceutical composition in suppository form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 4- (4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl) piperazine:

Ingredients	% wt./wt.
Compound of the invention	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

EXAMPLE 20

This example illustrates the preparation of a representative pharmaceutical formulation for insufflation containing a compound of the invention, or a pharmaceutically acceptable salt thereof, e.g., (2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,5-dimethylpiperazine:

Ingredients	% wt./wt.
Micronized compound of the invention	1.0%
Micronized lactose	99.0%

The ingredients are milled, mixed, and packaged in an insufflator equipped with a dosing pump.

EXAMPLE 21

This example illustrates the preparation of a representative pharmaceutical formulation in nebulized form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 1-(((4- chlorophenyl)amino)methyl)carbonyl-4-(4-chlorobenzyl)piperazine:

Ingredients	% wt./wt.

Compound of the invention	0.005%
Water	89.995%
Ethanol	10.000%

The compound of the invention is dissolved in ethanol and blended with water. The formulation is then packaged in a nebulizer equipped with a dosing pump.

EXAMPLE 22

This example illustrates the preparation of a representative pharmaceutical formulation in aerosol form containing a compound of the invention, or a pharmaceutically acceptable salt thereof, *e.g.*, 1-((4-chloro-2-(((ethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine:

Ingredients	% wt./wt.
Compound of the invention	0.10%
Propellant 11/12	98.90%
Oleic acid	1. 00%

The compound of the invention is dispersed in oleic acid and the propellants. The resulting mixture is then poured into an aerosol container fitted with a metering valve.

In the following examples, 293MR cells are utilized. These are human embryonic kidney cells (HEK293) which were stably transfected to express human CCR1 receptor by the following procedure: HEK293 cells were obtained from the American Type Culture Collection (ATCC CRL 1573). Human CCR1 cDNA was provided through collaboration with Dr. Stephen Peiper of the University of Louisville, Kentucky. The CCR1 gene was subcloned using standard techniques (see, e *.g., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring* Harbor Laboratory Press, 1989) into a standard plasmid containing the SV40 promoter and enhancer. The plasmid also contained hygromycin and puromycin resistance genes. Calcium phosphate transfection standard protocols were used to insert the plasmid into the HEK293 cells. Cells were selected for stable expression of CCR1 using hygromycin and puromycin selection. Cells were tested for the ability to bind ^{125}I- labelled RANTES or MIP-1α with high affinity.

EXAMPLE 23

In Vitro Assay: Calcium Flux

Since the CCR1 receptor, in common with other seven transmembrane G-protein coupled receptors, responds to the binding of its ligand, *e.g.*, MIP-1α and RANTES, by mobilizing free intracellular calcium, one can measure biological activity by calcium flux assays using the fluorescent dye Fura 2. In the following assay, the ability of the compounds of the invention to block this biologic response is measured.

Protocol:

1) Two flasks of 293MR cells were detached, washed and resuspended in Hanks Ca^{2+} (50 mL Hanks, 1.0 mL 1 M Hepes, 1.6 mL 500 mM $CaCl_2$, pH 7.4). The cells were washed twice in this media.
2) The cells were counted CCR1 = 28 x 10^6 cells made to 2 x 10^6 cells/mL by suspending into 14 mL Hanks Ca^{2+}.
3) To 10 mL of the cells (20 x 10^6) was added 30 mL of media (containing 50 µg of Fura in 50 µL of DMSO). Final cell concentration was 1.0 x 10^6 cells/mL. Final Fura concentration was 1.25 µM.
4) The cells were incubated at 37°C for 30 minutes in the presence (or absence) of increasing concentrations of compounds of the invention. Cells were washed as above to remove free Fura. Cells were resuspended at 1 x 10^6 cells/mL. Cells were then aliquoted (2.0 mL) in a cuvette and placed in a spectrofluorimeter. The cells were then stimulated with either MIP-1α or RANTES (Peprotech Inc.) and Ca^{2+} release was measured in the spectrofluorimeter.
5) The data were corrected for nM Ca^{2+} released by adding 100 µL of 0.1 % Triton X-100 (for maximum values) followed by 100 µL of 500 mM EGTA, pH 8.5 (for minimum values).

The compounds of the invention, when tested in this assay, demonstrated the ability to inhibit the Ca^{2+} mobilization in response to binding of MIP-1α and RANTES to the CCR1 receptor.

EXAMPLE 26

In Vitro Assay

The assays were performed in a microphysiometer to investigate the functional activity of the antagonist of interest. The microphysiometer assesses cellular response through the use of a silicon-based potentiometric sensor that can measure small changes on solution pH (Hafeman *et al., Science* (1988), Vol. 240, pp. 1182-1185; Parce *et al., Science* (1989), Vol. 246, pp. 243-247). It has been shown that the microphysiometer can be used for measuring metabolic rates of living cells (Parce *et al.*, 1989). The activation of cell membrane receptors can alter the rate of extracellular acidification

(Owicki *et al., Proc. Natl. Acad. Sci.* (1989), Vol. 87, pp. 4007-4011). The following assay demonstrates that activation of CCR1 receptors endogenously expressed on human THP-1 cells with MIP-1α and RANTES induced physiological changes resulting in an increase in metabolic rates and that the compounds of the invention inhibit this effect in a dose-dependent manner.

Materials:

1. Cytosensor Capsule Kit (Molecular Devices Cat #R8013).
2. Agarose Entrapment Medium (Molecular Devices Cat # R8023)
3. Cytosensor Modified RPMI 1640 Medium, low buffered (Molecular Devices Cat #R8023)
4. Cytosensor Sterilant Kit (Molecular Devices Cat# R8017)
5. Reference Electrode Maintenance Kit (Molecular Devices Cat# 0310-2805)
6. MIP-1α or RANTES (Peprotech Inc.) working solution: 10 μM in Modified RPMI 1640 medium (Molecular Devices Cat# R8016) supplemented with 1 mg/mL BSA (bovine serum albumin),100 units/mL penicillin, and 100 μg/mL streptomycin). This working solution is hereinafter referred to as "modified culture medium".
7. MCP-1 working solution: 10 μM in modified culture medium.
8. Compounds of the invention stock solution: 1 mM in DMSO (stored at ambient temperature).
9. Cell Culture:
    a. THP- 1 (ATCC Cat #TIB202)
    b. Tissue culture medium: RPMI 1640 supplemented with 10% FBS (fetal bovine serum). This medium is hereinafter referred to as "growth medium".

Assay Procedure:

THP-1 cells were grown in T-25 cm^2 flasks in growth medium at 37° C, 5.0% CO_2, 95% air to a cell density of $1x10^6$ cells/mL. The cells were harvested by centrifugation (5 minutes at 20 G) and resuspended in modified growth medium. Trypan blue dye exclusion cell count was performed and cells were ≥ 90% viable. Cells were centrifuged again, the supernatant was removed, and the resulting pellet was resuspended to final cell concentration of 1×10^6 /0.1 mL. Agarose cell entrapment reagent was melted and placed into a 37°C water bath. Cell suspension was prepared: 0.15 mL of the THP-1 cells were added to a 1.5 mL centrifuge tube with 50 μL of the melted agarose solution. Addition to the capsule cups: the capsule cups were placed in a 12 well microtiter plate, a spacer was added to the capsule cup, and 7 μL of cell/agarose suspension was pipetted into the center of the cup. After three minutes, 1 mL of modified growth medium was pipetted to the outside of the capsule cup, and 200 μL of modified growth

medium was pipetted to the inside. The capsule insert was then placed into the cup with sterile forceps and 500 µL of modified culture medium was pipetted into the insert. Completed capsule were loaded into the chambers of the microphysiometer. The chambers were perfused at a rate of 100 µL/minute with modified culture medium. The pump cycle was 50 seconds on and 40 seconds off. Multiple data points representing metabolic rate were taken and used as baseline. Cells were exposed to the compounds of the invention for 30 minutes prior to addition of chemokine agonists at a final concentration of 10 nM. Treated and non-treated cells were challenged with agonist for 100 seconds and data was collected.

When tested in this assay, the compounds of the invention demonstrated the ability to inhibit the activation of the CCR1 receptor by MIP-1α or RANTES.

EXAMPLE 25

In vitro assay for CCR1 receptor antagonists.

This assay demonstrates the affinities of the compounds of the invention for binding to the CCR1 receptor. The binding affinities of the compounds for the CCR1 receptor were determined by their abilities to compete with ^{125} I-MIP-1α or ^{125}I-RANTES for binding to the CCR1 receptor.

Reagents and Solutions; MIP-1α and RANTES (Peprotech Inc.)

Cells:

293MR cells (K_D=1-3 nM and B_{max}=2-3 x 10^6 sites/cell) were detached by trypsinization and plated into flasks at least 48 hours prior to the experiment.

Ligand:

^{125}I-MIP- 1α and ^{125}I-RANTES from New England Nuclear (specific activity is 2200 Ci/mmol, 25 µCi/vial) was reconstituted in 1 mL H_2O.

Assay buffer:

130 mM NaCl, 5 mM KCl, 1 mM $MnCl_2$, 50mM Tris, 30 µg/ml bacitracin, 0. 1% BSA, pH 7.4.

Wash buffer:

Phosphate buffer solution (PBS)

Compounds of the Invention:

The stock solution of the compounds was 1 mM in 100% DMSO. The highest concentration in the assay was 10 µM and may vary depending on the potency of the compounds. A serial 1:3 dilution from the highest concentration was made with assay buffer. Six concentrations of each compound were usually being screened to generate a dose curve from which the K_i value was determined.

Assay procedure:

Assays were performed in 96-well v-bottom microtiter plates in a total volume of 100 µl. 293MR cells was detached from T225 cm^2 flask in PBS by shaking. The cells were washed once in PBS and resuspended in the assay buffer to about 1.1 x 10^5 cells/mL. Cells (about 8000 cells/assay) were incubated with either ^{125}I-MIP-1α or ^{125}I- RANTES (about 15,000-20,000 cpm/assay) in the presence and absence of different concentrations of compounds at ambient temperature for 30-40 minutes.

The reactions were terminated by harvesting through a GF/B filter plate presoaked with 0.3% PEI (Sigma # P- 3143) plus 0.5% BSA and washing 5 times with cold PBS. The radioactivities in each well were determined by scintilation counting following addition of 50 µl of scintillation fluid.

The nonspecific binding was defined by the binding in the presence of 100 nM of unlabeled MIP-1α or RANTES. The CCR1 receptor concentration used in the assay was 0.4 nM and ^{125}I- MIP-1α or ^{125}I-RANTES was 0.06 nM. The concentrations of compounds in the assay is typically from 10 µM to 30 nM in 1:3 dilution and the concentrations for more potent compounds were lower depending on the potency.

Calculations:

The dose curves of each compound with 6 concentration points were generated and IC_{50} values were determined by fitting the data to the log-logit equation (linear) with an EXCEL spread-sheet. The K_i values were then calculated by dividing the IC_{50} by 1.025, to correct for concentration of labelled ligand.

The compounds of the invention, when tested in this assay, demonstrated their affinity to bind to the CCR1 receptor.

The data given in Table 2 show that the compounds listed bind to CCR1 receptor and compete with MIP-1α and RANTES. The K_i values are in the range of 1-172 nM. Table 2 is only a selection of compounds tested.

A comparison with other known piperazine compounds is given in Table 1. The compounds according to the present application (No. 10-12) have superior binding affinities to the CCR1 receptor compared to compounds which are alkylated at α-carbon (No. 1-6, 13) and compounds which have no substitution on the piperazine ring (No. 1-9). For example compounds 1-6 have K_i values of grater than 10 µM.

Examle 26

Effects of a CCR-1 antagonist on cell migration/chemotaxis will be analyzed on human U937 cells and peritoneal macrophages, isolated from peritoneal fluid from patients with endometriosis and controls.

Chemotaxis will be assayed in Boyden chambers containing permeable 0.4 µm pore size polyethylene terephthalate (P.E.T.) track-etched membranes (Becton Dickinson, Franklin Lakes, NJ). In this assay, a human histiocytic cell line (U937) that can be induced to display monocytic differentiation and chemotactic responsiveness after treatment with 1 mM 8-bromo-cyclic adenosine monophosphate (cAMP) (Kay et al. 1983).

U937 cells are cultured at 37°C with 5% CO_2 in RMPI medium supplemented with 10% fetal calf serum and penicillin G (100 U/mL), streptomycin (100 µg/mL) and gentamicin (50 µg/mL) and incubated with 1 mM 8-bromo-cAMP (Sigma, St. Louis, MO) every 24 hours for a total of 48 hours. The presence of CCR-1 protein in U937 cells and peritoneal macrophages will be confirmed by Western Blot analysis: 50 µg of protein lysates from U937 cells will be subjected to SDS-PAGE and the proteins will be blotted to nitrocellulose paper as described (Hornung et al. 1997). Mouse IgG monoclonal antibodies will be raised against the human RANTES receptor CCR-1.

A peritoneal fluid pool of 16 patients with moderate or severe endometriosis will be prepared. The protein amount of RANTES will be measured with specific ELISAs (R&D Systems). Samples are diluted 1:4 in PBS with 0.1% BSA and placed in the bottom wells of the Boyden chambers (600 µL per well). P.E.T track-etched membranes are then fixed in place in 24 well plates to separate bottom from top compartments and 500.000 cells in 200 µL of PBS containing 0.1% BSA will be added to the upper wells. Before the experiments starts, cells will be preincubated for 30 min with CCR1 antagonist. As control, cells will be treated with PBS. The loaded chambers will be incubated at 37°C in humidified air with 5% CO_2 for 120 minutes. Nonmigrating cells will be removed by several washes with PBS and migrating cells will be fixed to the membrane with absolute methanol overnight at 4°C and stained with Crystal Violet (Sigma, St. Louis, MO). Optical absorption at a wavelenght of 570nm is used to quantify monocyte chemotaxis. The same peritoneal fluid pool will always be used as a positive control and values normalized to 100% in each set of experiments. PBS alone will always be used as a negative control.

To evaluate the inhibitory effects of CCR-1 antagonist, the same peritoneal fluid pool of 16 patients with moderate or severe endometriosis will be used. CCR1 antagonist will be added at concentrations of 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7} or 10^{-6} molar.

Apoptosis ELISA

Programmed cell death by apoptosis is characterized by formation of multinucleosomal-sized genomic DNA fragments. DNA fragments are multiples of 180 bp subunits associated with core histones. The levels of DNA released in the cytosol of apoptotic cells will be measured using the Cell Death Detection ELISA kit (Roche, Mannheim, Germany). This is a quantitative sandwich-enzyme-linked-immunoassay using antibodies against DNA and histones. Extent of DNA fragmentation is expressed as an enrichment factor, calculated by dividing the absorbance of a given sample by the absorbance of the corresponding 10% FCS control.

Assessment of apoptosis in CCR-1 treated U937 cells

One potential mechanism of chemotaxis inhibition is via monocyte apoptosis. To exclude this potential mechanism, we will use a DNA fragmentation ELISA. U937 cells will be cultured for 24h in 10% (control) and 2.5% FCS. Samples in 2.5% FCS will be incubated with CCR-1 antagonist (ZK811752). Cells treated with TNF-alpha in 2.5% FCS will be used as a positive control.

Statistical analyses

All experiments will be repeated three times and results will be expressed as the mean ± SD. Normally distributed data will be analyzed by paired t-test or ANOVA. Nonparametric data will be analyzed by the Kruskal-Wallis and Mann-Whitney statistics. Significant differences will be accepted when two-tailed analyses yield $P<0.05$.

Example 27

Determination of CCR1 mRNA in endometrial and endometriotic tissue samples by real-time quantitative RT-PCR analysis.

Total RNA from endometrium and endometriotic lesions was extracted using Trizol Reagent (Life Technologies,cat.no:15596-026). Afterwards 20 µg of total RNA was used to enrich poly (A) +RNA (Medcalf et al.; EMBO. J. 1986; 5, 2217).

The cDNA synthesis was performed by using SuperScript First-Strand Synthesis System (Invitrogen). Quantification of mRNA abundance was performed by real-time PCR detection using an ABI PRISM 7700 Sequence Detection System (PE Biosystems, Inc. , Weiterstadt, Germany) and SYBRGreen as double stranded DNA-specific fluorescent dye (SYBRGreen PCR Master MIX, PE Biosystems). For

quantification of amplified transcripts, 0.2 µl first strand cDNA was used. Relative Quantification with data from the ABI PRISM 7700 sequence Detection System was performed using the comparative CT method.

Specific primer pair for CCR1 detection : 5`-CTC-CGT-GCC-AGA-AGG-TGA-AC-3´ and 5`-CCA-GGA-CCA-CCA-GGA-TGT-TT-3´. Internal control and reference gene was the housekeeping gene cyclophilin (Primer pair: 5'-GAA-GTT-GGC-CGC-ATG-AAG-A-3' and 5'-GCC-TAA-AGT-TCT-CGG-CCG-T-3'). PCR reaction: 10 min 95°C, 15 sec 95°C, 1 min 62°C (40 cycles). The purity of amplification products were controlled by melting curves.

Example 28

Immunohistochemical analysis of CCR1 in endometriotic lesions and in endometrium. Biopsies were frozen at the point of collection and stored at –80°C. For cutting, tissues were first embedded in TissueTek (Sakura) and equilibrated at –20°C. Before immunostaining, frozen slides were thawed and air-dried for 2 hours at room temperature.

For immunohistochemical analysis tissue sections were then cut using a Leica Kryotome and mounted on SuperFrost Plus glass slides. Cryosections of 5 µm were performed and fixed for 10 min in Aceton at 4°C. The fixed cryosections were washed in TBS and blocked with peroxidase block solution (DAKO). After a next washing procedure the tissue slides were blocked for 15 min with protein block solution from DAKO.

Tissue from peritoneal lesions and endometrium were incubated for 30 min with a monoclonal CCR1 antibody (clone 53504.111, R&D Systems) in a concentration of 0.8 µg/ml. Immunohistochemical stainings were performed with goat anti-mouse DAKO EnVision System, Peroxidase (AEC) Kit (DAKO: K4004). The samples were washed and incubated with EnVision-System peroxidase labelled polymer (DAKO). After 15 min AEC-Chromogen incubation the samples were washed and incubated for 5 min in Haematoxilin. Stained tissues were embedded in Fluoromount G (Dunn Labortechnik GmbH). For characterization of CCR1 expressing immune cells, the samples were stained with antibodies for CD4/CD14 and CD68 (Dako) and Alexa 568 (Molecular Probes). Stained tissues were examined with an Axioplan imaging microscope. Pictures were taken with the AxioCam Camera System, Axiovision 3.1, KS400 (Carl Zeiss). All images were taken with the same exposure time.

Example 29

Effects of compounds according to the present invention on surgically induced endometriosis in intact cycling rats.

Surgical procedure: Endometriosis was induced surgically in female Wistar rats (200g-250 g body weight) showing a normal 4 day oestrous cycle. All procedures were carried out under sterile conditions. During the first laparotomy, a 2 cm portion of the right uterine horn was resected and placed in PBS at 37°C. The uterine segment was opened longitudinally, and the endometrium was peeled from the myometrium. One segment was transplanted to the parietal peritoneum of the right abdominal wall and the other segment to the arterial cascades of the intestinal mesentery. The segments were sutured using non-absorbable silk suture at four corners, with the endometrial surface facing the lumen of the peritoneal cavity. At 4 weeks after the induction of endometriosis, the animals underwent a second laparotomy to evaluate the size and viability of the ectopic endometrial tissue. Macroscopically, this laparotomy revealed the formation of cystic structures (endometriosis-like foci) in ~90% of the animals. The surface area in length X width (mm^2) was measured using a calliper. Only animals in which the ectopic endometrium had formed endometriosis-like foci at both locations were used for the experiment. The animals were divided into 4 groups (n=10 animals per group). Group 1 animals (controls) received vehicle only. Group 2 animals were treated with an anti estrogen (positive control reference) (dose 1 mg/kg) daily. Group 3 received 50 mg/kg with (2R)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as chloride salt two times daily. Group 4 sham operated animals. Groups 1-3 were treated with daily s.c. injections for 4 weeks.

Evaluation: The animals were killed with a CO2 atmosphere after 4 weeks of treatment. During autopsy, the number of animals with or without persistent endometriotic lesions was calculated and the and the surface area and the volume was measured in situ. The mRNA expression of CCR1 and RANTES in rat uterus, ovary, peritoneal and mesenterial endometriotic cysts was analysed and quantified as described in Example 27.

Example 30

Endometriosis is experimentally induced by the inoculation of menstrual endometrium or by autologous transplantation as described in the literature. (11, 12, 13, 14). Immunoistochemical analysis of CCR1 in endometriotic grafts/lesions were performed as described in Example 28.

First part of the study: Endometriosis treatment. After induction of endometriosis, primates were treated with different concentrations of CCR1 antagonist for 2-3 weeks. As control, animals will be treated with vehicle, GnRH antagonist and Placebo. A videolaparoscopy will be performed to document the number, surface, volume and revised American Fertility Society (rAFS) score and stage of endometriotic lesions. All laparoscopies were performed by a single investigator. Serum and blood samples were taken and analyzed before induction of the disease and during treatment. In the second part of the study, animals were treated with CCR1 antagonist before endometriosis was induced, particularly with (2R)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as sulphate salt. At study end, endometriotic lesions were subjected to immunohistochemical and molecularbiological analysis.

Example 31

Efficacy of CCR1 antagonist according to the invention in the treatment of symptomatic endometriosis.

The following clinical study is performed to examine the efficacy of CCR-1 antagonists according to the invention, particularly (2R)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine as sulphate salt for the treatment of endometriosis and associated pelvic pain.

A multi-center, placebo-controlled, randomized, double-blind in parallel-groups study is designed with a population of young fertile women with historically confirmed endometriosis in the age of 18 – 45 years, with or without infertility.

The study will be Placebo-controlled, randomized, double-blind in parallel-groups. The duration of the treatment is of three months.

The primary efficacy variable is change of pelvic pain by visual analogue scale.

Secondary efficacy variables: Reduction of intake of co-medication for pelvic pain.

Safety parameters: Physical and gynaecological examination incl. breast, safety laboratory, bleeding patterns (patient diary).

The invention is described above with reference to preferred forms of embodiment. It is nevertheless clear that the invention is susceptible to numerous variations within the framework of technical equivalents.

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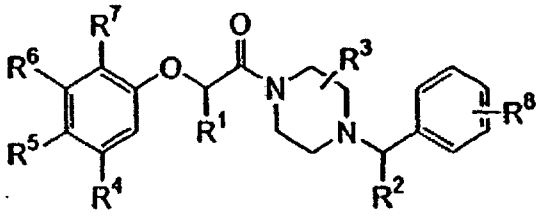
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TABLE 1

Test Compounds

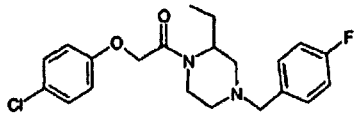
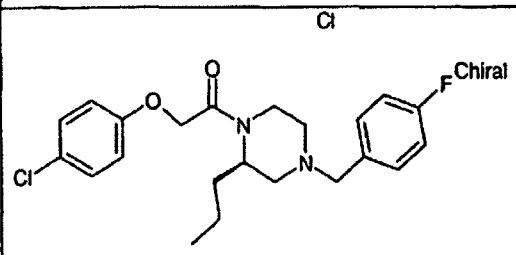
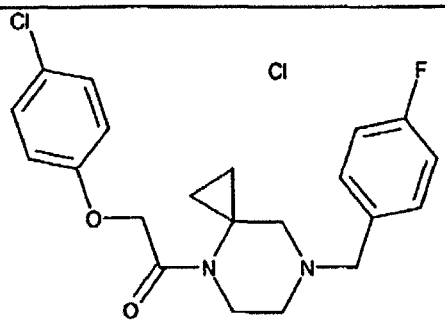
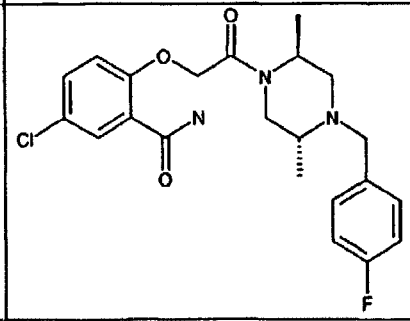
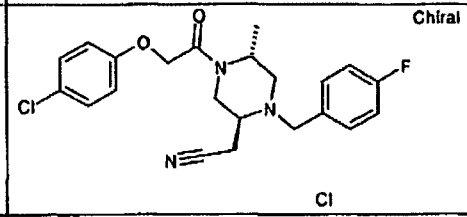
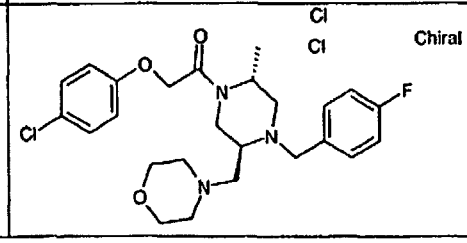


Cpd #	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	K_i (nM)
1	methyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 μM
2	ethyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 μM
3	isopropyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 μM
4	propyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 μM
5	butyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 μM
6	hexyl	H	H	methoxy	methoxy	methoxy	H	H	> 10 μM
7	H	H	H	methoxy	methoxy	methoxy	H	H	328 nM
8	H	H	H	methoxy	H	H	H	H	> 10 μM
9	H	H	H	H	methoxy	H	H	H	> 10 μM
10	H	H	methyl	methoxy	methoxy	methoxy	H	F	18 nM
11	H	H	methyl	H	Cl	H	H	F	10 nM
12	H	H	2,5-dimethyl	H	Cl	H	H	F	4 nM
13	dimethyl	H	methyl	H	Cl	H	H	F	> 10 μM

Table 2

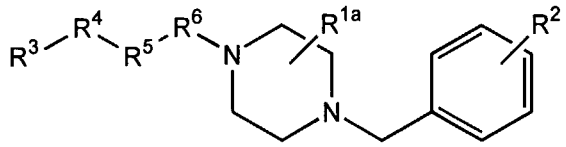
Nr.	Compound	Ki (nM)
1	1-((phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	108
2	(*trans*)-1-((4-chlorophenylamino)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	16
3	(*trans*)-1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	11
4	(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	56
5	(*trans*)-1-((4-chloro-2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	32
6	(*trans*)-1-((4-chloro-2-hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	11
7	(*trans*)-1-((4-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	10
8	(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	15
9	1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	3
10	(2*R*,5*S*)-1-((4-chloro-3-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	3
11	(*trans*)-1-((4-chloro-2-(1-hydroxyethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5
12	(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5
13	(*trans*)-1-((4-chloro-2-((ethyl)(1-methylbutyl)aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	41
14	(*trans*)-1-((4-chloro-2-(ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	2
15	1-((4-chloro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	9
16	1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	21
17	(*trans*)-1-((4-chloro-2-(benzylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	42
18	(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	87
19	1-((4-chloro-2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	5
20	(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	7
21	(*trans*)-1-((4-chloro-2-(*iso*-propylcarbonylamino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	13
22	(*trans*)-1-((4-chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	3
23	(*trans*)-1-((4-chloro-2-(2-(methoxycarbonyl)ethylcarbonylamino)-phenoxy)-methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5

	Compound	Ki (nM)
24	(*trans*)-1-((4-chloro-2-(methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	6
25	(2*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	1
26	(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	1
27	(*trans*)-1-((4-chloro-2-((aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	2
28	(*trans*)-1-((4-chloro-2-(1-((methyl)(ethyl)amino)ethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	18
29	(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	6
30	(*trans*)-1-((4-chloro-2-((2-aminoethyl)aminocarbonyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	9
31	1-((2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine	106
32	(*trans*)-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	68
33	(2*R*,5*S*)-1-((3-hydroxy-5-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	5
34	(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	31
35	1-((4-chlorophenoxy)methyl)carbonyl-2-(1-hydroxyethyl)-4-(4-fluorobenzyl)piperazine	13
36	1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut-3-enyl)-4-(4-fluorobenzyl)piperazine	172
37	1-((4-chlorophenoxy)methyl)carbonyl-3-trifluoromethyl-4-(4-fluorobenzyl)piperazine	148
38	1-((4-chlorophenoxy)methyl)carbonyl-2-(2-azidoethyl)-4-(4-fluorobenzyl)piperazine	49
39	(*trans*)-1-((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	18
40	(*trans*)-1-((4-chloro-2-(phthalimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	64
41	(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	56
42	(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	26
43	(*trans*)-1-(2-(4-chlorophenyl)-2-(methylsulfonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine	32

No	compound	Ki (nM)
44		15
45		75
46		74
47		3
48		38
49		109

Claims:

1. Use of a compound of the following formula (Ia):



(Ia)

for the production of a medicament for the treatment and the prevention of edometriosis in human wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of oxo, halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl) amino(C1-C8)alkyl, halo(C1-C8)alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2- C8)alkenyl, formyl, formyl(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2- C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, mercapto(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8) alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, azido(C1-C8)alkyl, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8) alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1- C8)alkyl, (C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or

naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8) alkyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (C1- C8)alkylthio(C1-C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8) alkylsulfonyl(C1-C8)alkyl, (C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy, halo(C1-C8) alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy)(C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10) cycloalkylamino(C1-C8)alkyl, ((C3-C10)cycloalkyl(C1-C8)alkyl)amino, ((C3- C10)cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, cyano(C1-C8)alkyl, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-

C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8) alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1- C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8) alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkoxycarbonylamino(C1-C8) alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxycarbonyl, (C1-C8)alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbony((C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1- C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C7-C8) alkylaminocarbonyl(C1-C8)alkyl, amidino, guanidino, ureido, mono(C1-C8) alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and

sulfur and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^3 is

a carbocylic 3- to 15-membered ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8) alkenyl, hydroxy(C1-C8)alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1- C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, amino(C1-C8)alkylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino, alkylcarbonylamino, (C1-C8) alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-

C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, ((C1-C8) alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1- C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, ((C3-C10) cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyt(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, di(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl,

aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureidoalkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mona(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

or R^3 is

a 3-15 membered heterocyclic ring system consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen,

oxygen and sulfur, substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkylsufonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8)alkoxy, (C2-C8) alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, amino, mono(C1- C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl(C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, monoalkylamino(C1-C8)alkyl, di(C1- C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1- C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido;

R^4 is

-O-, -N(R^7)-, -C(R^8)$_2$- or a bond;

R^5 is

an (C1-C8) alkylene chain or an (C1-C8) alkylidene chain, or, if R^4 is a bond, R^5 is an (C1-C8) alkylidene chain optionally substituted by (optionally substituted phenyl or naphthyl) or -N(R^7)$_2$;

or R^4 and R^5 together are –HC=CH-

R^6 is

-C(O)-, -C(S)-, $-CH_2-$ or a bond;

each R^7

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkylcarbonyl, (C1-C8) alkylcarbonyl(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1- C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8)alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl}((C1-C8)alkyl) aminoalkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, dl(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl,

mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl;

provided that when R^4 is $-N(R^7)-$, R^3 cannot be a heterocyclic ring system containing 4-8 members consisting of carbon atoms and only one nitrogen atom; and provided that when R^4 is $-C(R^8)_2$ or a bond, R^3 cannot be a bridged saturated heterocyclic ring system containing 4-6 members consisting of carbon atoms and two nitrogen atoms, and as a single stereoisomer or a mixture thereof; or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein:

R^3 is

a 3- to 15- membered carbocylic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, hydroxysulfonyl, halo, (C1-C8)alkyl, mercapto, mercapto(C1-C8) alkyl, (C1-C8)alkylthio, (C1-C8)alkylsulfinyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl)sulfonyl, (C1-C8)alkylthio(C1- C8)alkyl, (C1-C8)alkylsulfinyl(C1-C8)alkyl, (C1-C8)alkylsulfonyl(C1-C8) alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, (optionally substituted phenyl or naphthyl)oxy, halo(C1-C8)alkyl, formyl, formyl(C1-C8)alkyl, nitro, nitroso, cyano, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy, halo(C1-C8)alkoxy, amino(C1-C8)alkoxy, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C8)alkyl, (hydroxy) (C3-C10)cycloalkyl(C1-C8)alkyl, (C3-C10)cycloalkylamino, (C3-C10)cycloalkylamino(C1-C8)alkyl, cyano(C1-C8) alkyl, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C2-C8)alkenyl, hydroxy(C1-C8) alkyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (hydroxy(C1-C8)alkyl)thio(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (C1-C8)alkoxy(C1-C8)alkyl, ((C1-C8)alkoxy) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8) alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino,

amino(C1-C8)alkylamino, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, amino, ((C3-C10)cycloalkyl(C1- C8)alkyl) amino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, dl(C1-C8) alkylaminocarbonyloxy(C1-C8)alkyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8) alkyl,

aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (mono(C1-C8) alkylaminocarbonyl(C1-C8)alkyl)aminocarbonyl, (carboxy(C1-C8)alkyl) aminocarbonyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, amidino, hydroxyamidino, guanidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, monohalo(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, di(C1-C8)alkylureido, di(optionally substituted phenyl or naphthyl)ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, glycinamido(C1-C8)alkyl, alaninamido, mono(C1-C8) alkylalaninamido, alaninamido(C1-C8)alkyl, 3-15 membered heterocyclyl consisting of carbon

atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

3. The compound of Claim 2 wherein:

R^4 is

-O-, -N(R^7)- or -C(R^8)-;

R^5 is

an (C1-C8)alkylene chain;

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8) alkyl,

((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl) ((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8)alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8) alkyl, carboxy(C1-C8)alkyl, (C1-C8)alkoxycarbony4(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylamlnocarbonyl(C1-C8)alkyl, and di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl.

4. The compound of Claim 3 wherein:

R^4 is

-O-;

R^5 is

methylene; and

R^6 is

-C(O)-.

5. The compound of Claim 4 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2- C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, hydroxy(C1-C8)alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-

C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamlno(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalky(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-CS)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamlno(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)

sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy) carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl) ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

6. The compound of Claim 5 selected from the group consisting of the following compounds:

(2*S*)-1-((4-chlorophenoxy)methyl)carbonyl- 2-methyl-4-(4-fluorobenzyl)piperazine;

1-((phenoxy)methyl) carbonyl-2-ethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl) -1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(methoxymethyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-((acetylamino)methyl)piperazine;

1-((4-chlorophenoxy) methyl)carbonyl-2-(2-((4-fluorobenzyl)amino)ethyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((methyl)amino)ethyl)-4- (4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl- 2-(2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-((((4-chlorophenoxy)methyl)carbonyl)oxy)methyl-5-methylpiperazine;

4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(ethoxycarbonyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(methoxycarbonyl)methylpiperazine;

4-(4-fluorobenzyl)- 1-((4-chlorophenoxy)methyl)carbonyl-3-((methoxy)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-(methoxy) ethyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxy-2-(4-methylphenyl)ethyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxypropyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxybut-4-ynyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-5-(2-hydroxy-2-methylpropyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(2-hydroxyethyl)piperazine ;

1-((4-chlorophenoxy)methyl)carbonyl-3- (2-((2-hydroxyethyl)amino)ethyl)-4-(4-fluorobenzyl)piperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,3-dimethylpiperazine;

(2*S*,5*R*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*S*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(2-methylthio)ethylpiperazine;

(2*R*,5*R*)-4- (4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(benzyloxy)methylpiperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((2- hydroxyethyl)thio)methyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(*N'*-(ethoxycarbonylmethyl) ureido) methyl)piperazine;

(2*R*,5*S*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-5-((amino)carbonyloxy)methyl-4-(4-fluorobenzyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-((acetyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-hydroxy-1-(phenyl)methyl)piperazine;

(2*R*,5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-5-(1-hydroxybutyl)piperazine;

(2*R*,5 *S*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((diethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((dimethylamino)methyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-(((cyclopropyl)amino)methyl)piperazine;

(2*R*,5*S*)-1- ((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((morpholin-4-yl)methyl)piperazine;

(2*R*,5*R*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((piperazin-1- yl)methyl)piperazine;

(*cis*)-1-((3,4,5-trimethoxyphenoxy) methyl)carbonyl-2,6-dimethyl-4-(4-fluorobenzyl)piperazine;

(*cis*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,6-dimethylpiperazine;

1-((phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

1-((2-(acetylamino)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxypropyl)-4-(4-fluorobenzyl) piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxybut- 3-enyl)-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-trifluoromethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-((4-(2,5-di(trifluoromethyl)phenylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

7. The compound of Claim 5 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8) alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3- C10)cycloalkylcarbonylamino, (optionally

substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally

substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8) alkyl.

8. The compound of Claim 7 selected from the group consisting of the following compounds:

1-((3,4,5-trimethoxyphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-ethylpiperazine;

(2*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

(2*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-propylpiperazine;

4-(4- fluorobenzyl)-1-(((4-chlorophenoxy)methyl)carbonyl)spiro[cyclopropane-1, 2'-piperazine];

1-((4-chlorophenoxy)methyl)carbonyl-2- hydroxymethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1- ((4-chlorophenoxy)methyl)carbonyl-2-(2-(methoxy)ethyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2-(2-((2-methylpropyl)amino)ethyl) -4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

1-((4- chlorophenoxy)methyl)carbonyl-4-(4-fluorobenzyl)-5-methylpiperazine;

(2*R*)-1-((4-chlorophenoxy)methyl)carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

(2*S*)-1-((4-chlorophenoxy)methyl) carbonyl-3-methyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-3-(hydroxymethyl) piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-3-(2-hydroxyethyl)piperazine;

4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(((methyl)ureido)methyl)piperazine;

(2*R*,3*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,3-dimethylpiperazine;

(*cis*)-1-((4- chlorophenoxy)methyl)carbonyl-3,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-(((4-chlorophenoxy)methyl)carbonyl)oxy)ethyl-5-methylpiperazine;

(2 *R*,5*R*)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)-5((hydroxy)methyl)piperazine;

(2*R*,5*R*) -4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-((methoxy)-methyl)piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy) methyl)carbonyl-2-methyl-5-(1-methylethyl)piperazine;

(2*R*, 5*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2- methyl-5-(1-hydroxyethyl)piperazine;

(2*R*,5*R*)-4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-methyl-5-(1-hydroxyprop-3-enyl)piperazine;

(2*R*,5*S*)-1-((4- chlorophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((cyano) methyl)piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy) methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((1,2,4-triazol-2-yl)methyl) piperazine;

(2*R*,5*R*)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)-5-((tetrazolyl)methyl)piperazine;

(3*S*,5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy) methyl)carbonyl-3,5-dimethylpiperazine;

1-((4-chloro-3- nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-methylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(diethylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- hydroxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-chloro-2-methoxyphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((ethyl)(1-methylbutyl)aminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2- aminophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-3-nitrophenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (benzylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((1-methylbutyl)amino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*iso*-propylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,4-dichlorophenyl)ureido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-nitrophenyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(4-methylphenyl)ureido) phenoxy)methyl)carbonyl-2,5-dlmethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-benzylureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((cyclopropylmethyl)aminomethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(phenylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (acetylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((methylamino)(phenyl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(phenylsulfonyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(acetyl)(methyl) aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(*N*-methyl- *N'*-ethylureido)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- ((methyl)(ethyl)amino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (dimethylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-((4-*t*- butoxycarbonylpiperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- ((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(oxazol-2- ylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-(morpholin-4-ylmethyl)phenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(trans)-1- ((4-bromo-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-fluoro-3-chlorophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-methoxycarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-methoxycarbonylphenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-carboxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans)*-1-((3-cyanophenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methyl-2- aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methyl-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxycarbonylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-acetyl-2-(aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-nitro-3-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-nitro-2- methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-amino-3-nitrophenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- nitro-2-aminophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-aminophenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((3- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-methoxy-2-acetylphenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5- methoxy-2-acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((2-((2-hydroxyethyl)aminocarbonyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-((2-hydroxyethoxy)carbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(2-hydroxyethoxy)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-acetyl-4,5- dimethylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((5-methoxy-2-(methoxycarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(*N'*-methylureido)amino)methyl)piperazine;

(*trans*)-1-((4- methyl-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((3-chloro-5-methoxyphenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methoxy-5-nitrophenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(hydroxymethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-methylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chlorophenoxy)methyl)carbonyl-2- (2-azidoethyl)-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-chloro-2-(phthalimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (maleimido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((4-(benzylcarbonyl) piperazin-1-yl)methyl)phenoxy)methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2,3, 4-trifluorophenyl)aminocarbonyl)piperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-((2-fluorophenyl)aminocarbonyl)piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2,6-difluorophenyl)ureido) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(ethenylcarbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(cyclopropylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(cyclopentylcarbonylamino)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((furan-2-yl)carbonylamino)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(phenylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(3-methoxyphenyl)ureido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(methoxycarbonylmethylcarbonyl)-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(2- methoxycarbonylethyl)carbonyl-*N'*-(methyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-methylbenzyl)aminocarbonyl- *N'*-(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-trifluoromethyl-4-fluorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4- methylbenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(3-chlorophenyl)carbonyl-*N'*-(methyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-(4- fluorobenzyl)aminocarbonyl-*N'*-(methyl)glycinamido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2-iodophenylcarbonyl)glycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(2,3-difluorophenylcarbonyl) glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-((4-phenoxyphenyl)aminocarbonyl)glycinamido)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(2,4-difluorophenylcarbonyl)glycinamido)phenoxy)methyl) -carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(trans)-1-((4-chloro-2-((2-iodophenylcarbonyl)aminomethyl) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((ethoxycarbonylmethylcarbonyl) aminomethyl)phenoxy)-methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(3-chloropropyl)ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'* -(2-fluoro-6-trifluoromethylphenyl)ureidomethyl)phenoxy)-methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((3-fluorophenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(*N'*-(2-(ethoxycarbonyl)ethyl)ureidomethyl)phenoxy)-methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*S*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((2,5-di(trifluoromethyl)phenyl)carbonylaminomethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4- chloro-2-(*N'*-(2-(phenyl)cyclopropyl)ureidomethyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

9. The compound of Claim 7 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8)alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)

alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

10. The compound of Claim 9 selected from the group consisting of the following compounds:

(*trans*)-1-((4-chloro-3-nitrophenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*S*,5*R*)-1-((4-bromo-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((3-hydroxy-5-methylphenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2 *S*,5*R*)-1-((4-nitro-3-formylphenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(2R)-1-((4-chlorophenoxy)methyl) carbonyl-2-methyl-4-(4- fluorobenzyl)piperazine;

4-(4- fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl) piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(2*R*, 5*S*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-1-((4-chloro-3,5- dimethoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*,5*S*)-4-(4-fluorobenzyl)-1-((4- chlorophenoxy)methyl)carbonyl-2-(2-hydroxyethyl)-5-methylpiperazine;

(2*R*,6*R*)-4-(4-fluorobenzyl)-1-((4-chlorophenoxy)methyl) carbonyl-2,6-dimethylpiperazine;

(*trans*)-1-((4-chloro-2- methoxyphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro-2-(hydroxymethyl)phenoxy)methyl)carbonyl-2-methyl-4- (4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-3- (hydroxymethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-hydroxyethyl)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(aminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (ureidomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-aminophenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(acetylamino)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-4-(4-fluorobenzyl)-1-((2-acetylamino- 4-chlorophenoxy)methyl)carbonyl-2,5-dimethylpiperazine;

(*trans*)-1-((4-chloro-2-(propylcarbonylamino)phenoxy)methyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(methoxymethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2- (methoxycarbonyl)ethylcarbonylamino)phenoxy)-methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(2-(ethoxycarbonyl)ethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (methylsulfonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (bromomethylcarbonylamino)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(2*R*)-1-((4-chloro-2-(glycinamido) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((*N'*-methylglycinamido)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(alaninamido)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((aminocarbonyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((aminocarbonyl)(methyl)glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-ethyluredio)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ethylcarbonylamino) phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-amino-5-nitrophenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine, dihydrochloride salt;

(*trans*)-1-((4-chloro-2-(((ethyl)amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((diethyl)amino)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(((cyclopropyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- (((dimethyl)amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(((methyl) amino)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-((amino)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-methylpiperazin-1-yl)methyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(ethylaminomethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1- (methylamino)ethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(1-(methylsulfonyl) (methyl)aminoethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-((piperazin-1-yl)methyl) phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4-chloro-2-((piperazin-1-yl)methyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4-*t*-butoxycarbonylpiperazin-1-yl) methyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(imidazol-1-ylmethyl)phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(1-(imidazol-1-yl)ethyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-(triazol-1-ylmethyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(tetrazol-1-ylmethyl) phenoxy) methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((morpholin-4-yl)methyl)phenoxy)methyl)carbonyl- 2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)-1-((4- chloro-2-aminocarbonylphenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

1-((4-chloro-2-formylphenoxy)methyl)carbonyl-2- methyl-4-(4-fluorobenzyl)piperazine;

(2*R*,5*S*)-1-((4- chloro-2-formylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(2*R*)-1-((4-chloro-2-formylphenoxy)methyl) carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1- ((4-chloro-2-(methylaminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((aminocarbonylmethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((2- aminoethyl)aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-((4- aminocarbonyloptionally substituted phenyl)aminocarbonyl)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(hydroxyamidino)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2- acetylphenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((2-(aminocarbonyl)phenoxy)methyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4- chloro-2-((*N'*-(trichloromethylcarbonyl)ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-((4-chloro-2-(*N'*-(methoxymethylcarbonyl)glycinamido)phenoxy) methyl)-carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-((4-chloro-2-(*N'*-(ethoxycarbonyiaminocarbonyl) glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine.

11. The compound of Claim 9 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4-position with chloro and at the 2-position by aminocarbonyl, ureido, or glycinamido; namely, the compound selected from the group consisting of the following compounds:

(2*R*,5*S*)-1-((4-chloro-2- (aminocarbonyl)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(glycinamido)phenoxy) methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-((4-chloro-2-(ureido)phenoxy)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(2*R*, 5*S*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine; and

(2*R*,5*S*)-1-((4- chloro-2-(glycinamido)phenoxy)methyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine.

12. The compound of Claim 9 wherein the most preferred compound is:

(2*R*)- 1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine;

13. The compound of Claim 3 wherein:

R^4 is

-N(R^7)-;

R^5 is

methylene;

R^6 is

-C(O)-; and

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl.

14. The compound of Claim 13 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8)

alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1-C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1- C8)alkoxy, hydroxy(C1-C8) alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8)alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8) alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8) alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)

alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy) carbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl) aminocarbonyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group

of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur) (C1-C8)alkyl.

15. The compound of Claim 14 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1- C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8) alkoxy, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl) (c1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(c1- C8)alkylamino, (C1-C8)alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-

C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8) alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(c1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

16. The compound of Claim 15 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8) alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (3C-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8) alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl) aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8) alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl) ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1- C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

17. The compound of Claim 16 wherein R^2 is 4-fluoro and R^3 is phenyl substituted at the 4- position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido.

18. The compound of Claim 17 selected from the group consisting of the following compounds:

(*trans*)-1-((4-chlorophenylamino)methyl) carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

1-((4-chloro- 2-(aminocarbonyl)phenylamino)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl) piperazine; and

1-((4-chlorophenylamino)methyl)carbonyl-2-methyl- 4-(4-fluorobenzyl)piperazine.

19. The compound of Claim 3 wherein:

R^4 is

$-C(R^8)_2-$;

R^5 is

methylene;

R^6 is

-C(O)-; and

each R^8

is independently selected from the group consisting of hydrogen, (C1- C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1- C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, and di(C1-C8)alkylamino(C1- C8)alkyl.

20. The compound of Claim 19 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkylamino(C1-C8) alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkyl, (C1-C8) alkylthio(C1-C8)alkyl, hydroxy(C1-C8)alkylthio(C1-C8)alkyl, amino(C1-C8) alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)

alkyl, azido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo;

R^3 is

phenyl optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, hydroxy(C1-C8)alkyl, (mono(C1-C8) alkylamino) (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1- C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8) alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8) alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-

C8)alkoxycarbonylamino(C1- C8)alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)amino(C1-C8) alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8) alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl, (amino(C1-C8)alkyl) aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, di(C1-C8) alkylaminocarbonyl(C1-C8) alkyl, hydroxyamidino, ureido, mono(C1-C8) alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, dl(C1-C8)alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8) alkyl)ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8) alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8) alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl) glycinamido, (optionally substituted phenyl or naphthyl) carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl) ((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylaminocarbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl) aminocarbonyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8)alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur

and (3-15membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

21. The compound of Claim 20 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl, (C3-C10)cycloalkyl, hydroxy(C1-C8)alkyl, hydroxy(C2-C8)alkenyl, cyano(C1-C8)alkyl, (C1-C8)alkoxy(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, and (3- 15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of hydroxy, halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, cyano, amino(C1-C8)alkoxy, (C3-C10)cycloalkylamino(C1-C8) alkyl, hydroxy(C1-C8) alkyl, (mono(C1-C8)alkylamino)(optionally substituted phenyl or naphthyl)(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino, (C1-C8) alkylcarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10) cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl) carbonylamino, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8) alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1- C8)alkyl)amino(C1-C8)alkyl, (cycloalkyl(C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkoxycarbonyl(C1-

C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkylsulfonylamino(C1-C8)alkyl, ((C1-C8)alkylsulfonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl) sulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (C1-C8)alkylcarbonyl, (hydroxy(C1-C8)alkoxy)carbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl)aminocarbonyl; (amino(C1-C8)alkyl)aminocarbonyl, (hydroxy(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, mono(C1-C8)alkylureido, mono(optionally substituted phenyl or naphthyl)ureido, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylureido, (mono(C1-C8)alkyl)(mono(optionally substituted phenyl or naphthyl))ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8) alkylureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl) ureido(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, (halo(C1-C8)alkyl)((C1-C8)alkyl) ureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1- C8)alkoxy(C1-C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonyl)((C1-C8)alkyl) glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, (optionally substituted phenyl or naphthyl)carbonylglycinamido, ((optionally substituted phenyl or naphthyl)carbonyl)((C1-C8)alkyl) glycinamido, (mono(optionally substituted phenyl or naphthyl)(C1-C8) alkylaminocarbonyl)((C1-C8)alkyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)glycinamido, (mono(optionally substituted phenyl or naphthyl)aminocarbonyl)((C1-C8) alkyl)glycinamido, alaninamido, 3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

22. The compound of Claim 21 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of (C1-C8) alkyl and hydroxy(C1-C8)alkyl;

R^2 is

one or more substituents independently selected from the group consisting of hydrogen, chloro or fluoro;

R^3 is

phenyl substituted by one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C1-C8)alkoxy, formyl, nitro, (C3-C10)cycloalkylamino(C1-C8)alkyl, hydroxy(C1-C8)alkyl, amino, (C1-C8)alkylcarbonylamino, halo(C1-C8)alkylcarbonylamino, (C1-C8) alkoxy(C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonyl(C1-C8) alkylcarbonylamino, (C1-C8)alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, ((C1-C8) alkylsulfonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, (aminocarbonyl(C1-C8)alkyl) aminocarbonyl, (amino(C1-C8)alkyl)aminocarbonyl, hydroxyamidino, ureido, (halo(C1-C8)alkylcarbonyl)ureido, ureido(C1-C8)alkyl, glycinamido, mono(C1-C8)alkylglycinamido, aminocarbonylglycinamido, ((C1-C8)alkoxy(C1- C8)alkylcarbonyl)glycinamido, (aminocarbonyl)((C1-C8)alkyl)glycinamido, ((C1-C8)alkoxycarbonylamino(C1-C8)alkylcarbonyl)glycinamido, alaninamido, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl.

23. The compound of Claim 22 wherein:

R^2 is

4- fluoro;

R^3 is

phenyl substituted at the 4-position with chloro and optionally substituted at the 2-position by aminocarbonyl, ureido, or glycinamido; and

one R^8 is

hydrogen and the other R^8 is selected from the group consisting of amino, (C1-C8) alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10) cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8) alkylsulfonylamino, (optionally substituted phenyl or naphthyl)

carbonylamino, (C1-C8)alkoxycarbonyl(C1-C8)alkylcarbonylamino, (C1-C8) alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8) alkyl, (C1-C8)alkoxycarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur) carbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, and amino(C1-C8)alkyl.

24. The compound of Claim 23 selected from the group consisting of the following compounds:

(*trans*)-1-(2-(4-chlorophenyl)-3- (methylsulfonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(acetylamino) propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(methylsulfonylamino)ethyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(acetylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2- (amino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-2-(ureido)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(amino)propyl)carbonyl-2, 5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-3-(*t*-butoxycarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((ethoxycarbonylmethylcarbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'-iso*-propylureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(*N'*-(2-chloroethyl)ureido)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2-nitrophenyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl- 4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((4-methoxyphenylmethyl)carbonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-((2,4-dinitrophenyl)sulfonylamino)ethyl)carbonyl-2,5- dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4- chlorophenyl)-2-(cyclopropylcarbonylamino)ethyl)carbonyl-2,5-dimethyl-4- (4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)- 2-((2-cyclopropylethyl)carbonylamino)ethyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- ((2-methylpropyl)carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4- fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3- (cycloppentylcarbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (*t*-butyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl) piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*- (ethyl)ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine;

(*trans*)-1-(2-(4-chlorophenyl)-3-(*N'*-(3-choropropyl) ureido)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine; and

(*trans*)-1-(2-(4-chlorophenyl)-3-((morpholin-4-yl) carbonylamino)propyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

25. The compound of Claim 1 wherein:

R^3 is

a heterocyclic ring system substituted by one or more substituents independently selected from the group consisting of hydrogen, hydroxy, halo, (C1-C8) alkyl, (C1-C8)alkylsulfonyl, (optionally substituted phenyl or naphthyl) sulfonyl, (C1-C8)alkoxy, hydroxy(C1-C8)alkoxy, halo(C1-C8)alkyl, formyl, nitro, cyano, halo(C1-C8) alkoxy, (C2-C8)alkenyl, (C2-C8)alkynyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8)alkylamino, mono(optionally substituted phenyl or naphthyl)amino,

mono(optionally substituted phenyl or naphthyl) (C1-C8)alkylamino, (C1-C8)alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C2-C8)alkenylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, halo(C1-C8) alkylcarbonylamino, (C1-C8)alkoxy(C1-C8)alkylcarbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, ((C1-C8)alkoxycarbonyl)((C1-C8)alkyl)amino, (C1-C8) alkylsulfonylamino, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)carbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl)amino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, carboxy, (C1-C8)alkoxycarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxycarbonyl, (C1-C8) alkylcarbonyl, (optionally substituted phenyl or naphthyl)carbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, aminocarbonyl, mono(C1-C8)alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, di(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)aminocarbonyl(C1-C8)alkyl, guanidino, ureido, mono(C1-C8) alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, and glycinamido.

26. The compound of Claim 25 wherein:

R^4 is

-O-, - $N(R^7)$- or -$C(R^8)$-;

R^5 is

an (C1-C8) alkylene chain;

R^7 is

selected from the group consisting of hydrogen, (C1-C8)alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkyl, (C1-C8) alkylcarbonyl, (C1-C8)alkylcarbonyl(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl(C1-C8)alkyl, aminocarbonyl, mono(C1-C8) alkylaminocarbonyl, di(C1-C8)alkylaminocarbonyl, and (C1-C8) alkoxycarbonyl; and

each R^8 is

independently selected from the group consisting of hydrogen, (C1-C8) alkyl, optionally substituted phenyl or naphthyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkyl, hydroxy, (C1-C8)alkoxy, hydroxy(C1-C8) alkyl, (C1-C8)alkoxy(C1-C8)alkyl, amino, mono(C1-C8)alkylamino, di(C1-C8) alkylamino, (C1-C8)alkylcarbonylamino, (C3-C10)cycloalkylcarbonylamino, (C3-C10)cycloalkyl(C1-C8) alkylcarbonylamino, (C1-C8)alkoxycarbonylamino, (C1-C8)alkylsulfonylamino, (optionally substituted phenyl or naphthyl)carbonylamino, (C1-C8) alkoxycarbonyl(C1-C8)alkylcarbonylamino, ((C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino, ((optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonyl)((C1-C8)alkyl)amino, (C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C3-C10)cycloalkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxycarbonylamino(C1-C8)alkyl, ((C1-C8)alkylcarbonyl)((C1-C8)alkyl) amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkylcarbonylamino(C1-C8)alkyl, (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)carbonylamino(C1-C8)alkyl, ((optionally substituted phenyl or naphthyl)(C1-C8)alkylcarbonyl)((C1-C8) alkyl)amino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl) sulfonylamino, (C1-C8)alkylsulfonylamino(C1-C8)alkyl, ureido, mono(C1-C8) alkylureido, monohalo(C1-C8)alkylureido, di(C1-C8)alkylureido, ureido(C1-C8)alkyl, mono(C1-C8)alkylureido(C1-C8)alkyl, di(C1-C8)alkylureido(C1-C8) alkyl, monohalo(C1-C8)alkylureido(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1- C8)alkylamino(C1-C8)alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, carboxy(C1-C8) alkyl, (C1-C8)alkoxycarbonyl(C1-C8)alkyl, aminocarbonyl(C1-C8)alkyl, mono(C1-C8)alkylaminocarbonyl(C1-C8)alkyl, and di(C1-C8) alkylaminocarbonyl(C1-C8)alkyl.

27. The compound of Claim 26 wherein:

R^4

is -O-;

R^5

is methylene; and

R^6

is -C(O)-.

28. The compound of Claim 26 wherein:

R^{1a} is

one or more substituents independently selected from the group consisting of halo, (C1-C8)alkyl, (C3-C10) cycloalkyl, (C3-C10)cycloalkylamino(C1-C8)alkyl, halo(C1-C8)alkyl, hydroxy(C1-C8) alkyl, hydroxy(C2-C8)alkenyl, hydroxy(C2-C8)alkynyl, (hydroxy)(optionally substituted phenyl or naphthyl)(C1-C8)alkyl, cyano(C1-C8)alkyl, halo(C1-C8)alkylcarbonylamino(C1-C8)alkyl, (C1-C8) alkoxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8) alkoxy(C1-C8)alkyl, (C1-C8)alkylthio(C1-C8)alkyl, hydroxy(C1-C8) alkylthio(C1-C8)alkyl, amino(C1-C8)alkyl, mono(C1-C8)alkylamino(C1-C8) alkyl, di(C1-C8)alkylamino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)amino(C1-C8)alkyl, mono(optionally substituted phenyl or naphthyl)(C1-C8)alkylamino(C1-C8)alkyl, azido(C1-C8)alkyl, mono(C1-C8) alkylureido(C1-C8)alkyl, ((C1-C8)alkoxycarbonyl(C1-C8)alkyl)ureido(C1-C8)alkyl, hydroxy(C1- C8) alkylamino(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)oxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (optionally substituted phenyl or naphthyl)(C1-C8)alkoxy(C1-C8)alkylcarbonyloxy(C1-C8)alkyl, (C1-C8) alkylcarbonyl(C1-C8)alkyl, (C1-C8)alkoxycarbonyl, (C1-C8) alkoxycarbonyl(C1-C8)alkyl, and (3-15 membered heterocyclyl consisting of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur)(C1-C8)alkyl; and

R^2 is

one or more substituents independently selected from the group consisting of hydrogen and halo.

29. The compound of Claim 28 wherein R^3 is selected from the group consisting of azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl, carbazolyl, cinnolinyl, decahydroisoquinolyl, dioxolanyl, furyl, isothiazolyl, quinuclidinyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indanyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, piperazinyl, 4- piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl,

tetrahydrofuryl, tetrahydropyranyl, thienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone.

30. The compound of Claim 29 wherein R^3 is benzopyranyl, benzopyranonyl, benzfuranyl, benzofuranonyl, quinolinyl, indolyl, indolinyl, oxazolyl, imidazolyl, or benzothienyl.

31. The compound of Claim 30, namely, (*trans*)-1-((benzo[b]pyran-2-on-7-yloxy)methyl)carbonyl-2,5-dimethyl-4-(4-fluorobenzyl)piperazine.

32. The compounds

(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oXopropenyl]- phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(R)-4-(4-fluorobenzyl)-2-methylpiperazin-1-yl]-3-oxopropenyl] phenyl)-methanesulfonamide,

(5-Chloro-2-[(E)-3-[(2R, 5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-urea,

N-(5-Chloro-2-[(E)-3-[(2R,5S)-4-(4-fluorobenzyl)-2, 5-dimethylpiperazin-1-yl]-3-oxopropenyl]-phenyl)-methanesulfonamide,

(5-Chloro-2- {(E)-3-[4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-phenyl)-acetic acid methyl ester,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-benzoic acid,

(5-chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxo-propenyl}-4-methoxy-phenyl)-urea,

(5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oxopropenyl}-4-trifluoromethoxy-phenyl)-urea,

5-Chloro-2-{(E)-3-[(R)-4-(4-fluoro-benzyl)-2-methyl-piperazin-1-yl]-3-oXo-propenyl}-4-methoxy-benzoic acid methyl ester

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-propionic acid,

(5-Chloro-2-{2-[4-(3,4-difluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(4-chloro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Bromo-2-{2-[(2R)-2-ethyl-4-(4-fluoro-benzyl)-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4- (4-chloro-benzyl)- (2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

(5-Chloro-2-{2-[4-(3, 4-difluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetic acid,

3-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acrelic acid,

N-[(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-methanesulfonamide,

N- (5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzoyl)-methanesulfonamide,

N- [(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-acetyl]-C,C,C-trifluoro-methanesulfonamide,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-oxo-acetic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-acetic acid,

2-(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yll-2-oxo-ethoxy}-phenoxy)-2-methyl-propionic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenoxy)-difluoro-acetic acid

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonamide

N-[5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]phenyl-trifluoromethanesulfonamide,

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]- benzenesulfonamide.

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Bromo-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5- Bromo -2-{2-[4-(4-fluoro-benzyl)-(2R)-2-methyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-methanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-phenyl)-ethanesulfonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R,5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonic acid,

(5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R, 5S)-2,5-dimethyl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl) phosphonic acid monoethyl ester,

5-Chloro-2-{2-[4-(4-fluoro-benzyl)-(2R5S)-2,5-dimethYl-piperazin-1-yl]-2-oxo-ethoxy}-benzyl)-phosphonamidic acid

5-chloro-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester;

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid methyl ester;

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid methyl ester;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid methyl ester;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid methyl ester

5-bromo-2-[2-[(2*R*)-4-[(5-chloro-2-thienyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid methyl ester

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzenesulfonic acid;

5-chloro-4-(dimethylamino)-2-[2-[(2R,5S)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzeneacetic acid

5-bromo-2-[2-[(2*R*)-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzeneacetic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-methylbenzoic acid

4,5-dichloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid.

5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-4-(trifluoromethyl)benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]benzoic acid;

5-bromo-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-4-ethoxy-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

4-amino-5-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]benzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-5-ethyl-4-[(4-fluorophenyl)methyl]-2-methylpiperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

5-chloro-2-[2-[(2*R*,5*S*)-2,5-diethyl-4-[(4-fluorophenyl)methyl]piperazinyl]-2-oxoethoxy]-4-methoxybenzoic acid;

4-chloro-2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]benzoic acid;

2-[2-[(2*R*,5*S*)-4-[(4-fluorophenyl)methyl]-2,5-dimethylpiperazinyl]-2-oxoethoxy]-5-methylbenzoic acid

for the production of a medicament for the treatment and the prevention of edometriosis in human

33. A pharmaceutical composition useful in treating endometriosis in a human female in need of such treatment, which composition comprises a therapeutically effective amount of a compound according to claim 1.