CHEMOKINE INHIBITING PIPERAZINE DERIVATIVES AND THEIR USE TO TREAT MYOCARDITIS

This application claims the benefit of U.S. Provisional Application Serial No. 60/497,380, filed August 22, 2003, which is incorporated herein in full by reference.

FIELD OF THE INVENTION

The present invention is directed to the use of piperazine derivatives to treat myocarditis.

BACKGROUND OF THE INVENTION

Myocarditis is an inflammatory process involving the heart often caused by an infectious agent. In North America and Europe, viruses are the most common cause, whereas in Central and South America, the parasitic protozoan Trypanosoma cruzi is more common and accounts for the majority of cases of myocarditis worldwide. Virtually any infectious agent can cause myocarditis. Other causes include drugs, toxins, allergic reactions, and certain systemic diseases associated with vasculitis. While myocarditis is an insidious process and is usually asymptomatic, it can result in heart failure and postmortum studies suggest that myocarditis may account for up to 20% of cases of sudden, unexpected death in young adults. Recent data has also further strengthened the suspected causal link between viral myocarditis and later development of idiopathic dilated cardiomyopathy.

Current understanding of the basic mechanisms of myocarditis derives largely from experimental models in which mice are infected with a cardiotropic virus. The primary mechanism for cardiac damage in myocarditis is thought to be a cell mediated immunological reaction to antigens associated with the pathogenic agent itself or to changes in the myocyte cell surface induced by the agent. Humoral autoimmunity has also been shown toalso be involved. The initial cellular response is characterized by infiltration of natural killer cells and macrophages with subsequent release of pro-inflammatory cytokines including interleukins 1and 2, tumor necrosis factor and interferon gamma. Later in the course of experimental myocarditis, cytotoxic T lymphocytes can be found as well as B lymphocytes with production of anti-myocardial antibodies.

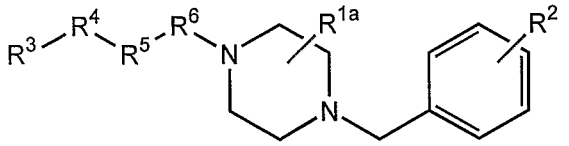
Findings in patients with myocarditis further support immunologic mechanisms for the observed cardiac damage and subsequent development of heart failure. These include: an imbalance between cytotoxic and helper T cells; increased myocardial expression of major histocompatibility antigens in biopsy specimens; overexpression of cell adhesion molecules on myocytes; and circulating autoantibodies directed against myocardial proteins some of which cross react with viral antigens (molecular mimicry). The effects of the immune reaction in the heart will depend on whether the response is self limited resulting in effective clearance of the etiologic agent and repair of cardiac injury or whether the response is prolonged and exaggerated resulting in progressive myocyte necrosis, fibrosis and pathologic remodeling.

The clinical features of myocarditis are quite variable. Most patients with focal inflammation are relatively asymptomatic and may demonstrate only minor electrocardiographic abnormalities. Others with more extensive inflammation can present with ventricular dilatation and mild to moderate heart failure. A smaller subset of patients manifest rapidly progressive dilated cardiomyopathy and severe, fulminant heart failure. Still others will present with atrial or ventricular arrhythmias, or atrio-ventricular heart block.

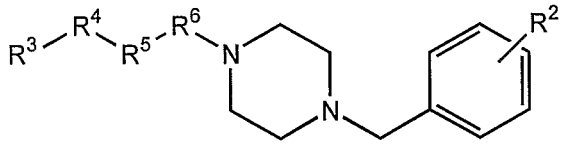
Treatment of myocarditis is largely supportive and directed at the systemic manifestations of the disease. All patients with suspected myocarditis and signs and symptoms of heart failure should be hospitalized and treated in a unit equipped with continuous electrocardiographic monitoring. Treatment of heart failure includes use of diuretics, angiotensin converting enzyme inhibitors or receptor antagonists, and beta-blockers after initial patient stabelization. In patients with moderate to severe heart faiure, supportive care may include use of parenteral inotropic and vasodilator drugs and possibly implantation of a temporary mechanical ventricular assist device. Antiarrhythmic drugs may be needed to suppress serious atrial or ventricular arrhythmias and a pacemaker may be required in cases of complete heart block. Since the long term consequences of myocarditis are attributed to an exaggerated cellular and humoral immune reaction, immunosuppressive and anti-inflammatory drugs could be of benefit. While uncontrolled clinical studies of immunosuppressive agents supports such an approach, to date, placebo controlled trials of prednisone alone and in combination with cyclosporine and of intravenous immune globulin have failed to demonsrate a beneficial effect on ventricular function. It is hoped that better understanding of the etiologic agents and immune response in myocarditis will lead to more selective

pharmacologic approaches to prevent progressive heart failure and development of dilated cardiomyopathy in the near future.

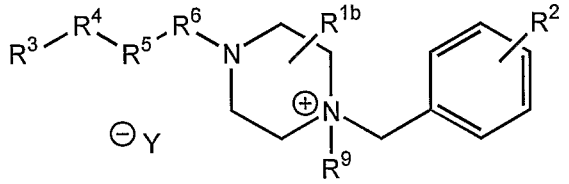
Piperazine derivatives of formulae Ia, Ib, Ic and Id are disclosed in U.S. Patent No. 6,207,665 and WO 98/56771 (the entirety of each of these documents is incorporated herein by reference) as being useful as anti-inflamatory agents in view of their ability to inhibit chemokines, MIP-1α and RANTES:



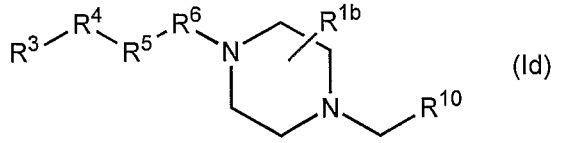
(Ia)



(Ib)



(Ic)



(Id)

enantiomers, diasteriomers and pharmaceutically acceptable salts thereof 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, 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;

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 $-N(R^7)_2$;

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;

Y is a pharmaceutically acceptable counterion:

R^{1b} is one or more substituents independently selected from the group consisting of hydrogen, 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; and

R^9 is alkyl, aralkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkylcarbonylalkyl, alkylcarbonylaminoalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, hetereocyclylalkyl, or cycloalkylalkyl;

R^{10} is a heterocyclyl 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, and monobenzylureido;

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.

Compounds of formulae Ia, Ib, Ic and Id are disclosed in U.S. Patent No. 6,207,665 and WO 98/56771 as being useful in treating various inflammatory disorders including multiple sclerosis, leukoencephalopathy, encephalomyelitis, Alzheimer's disease, Guillian-Barre syndrome, acute cell-mediated renal transplant rejection, allograft rejection, rheumatoid arthritis, atherosclerosis, uricaria, angioderma, allergic conjunctivitis, atopic dermatitis, allergic contact dermatitis, drug or insect sting allergy or systemic anaphylaxis.

DETAILED DESCRIPTION OF THE INVENTION

We have discovered that compounds of formulae Ia, Ib, Ic and Id are useful in treating myocarditis.

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 where R_a is an alkyl radical as defined above, *e.g.*, acetyl, ethylcarbonyl, *n*-propylcarbonyl, and the like.

"Alkylcarbonylalkyl" 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.*, acetylaminomethyl, 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 -$C(O)OR_a$ where 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 where 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 where 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-(ethoxycarbonyl)ethyl)ureido)ethyl, 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 $-N(H)-R_a-NH_2$ where 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, carboxyalkyl, 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.

"Arylsulfonyl" 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-nitrophenyl)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 $-R_cR_b$ 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 $-OR_b$ where 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 $-R_aC(O)OR_d$ where R_a is an alkyl radical as defined above and R_d 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 $-R_a-OR_d$ where 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 $-R_aOR_a$ 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 where 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 where 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.*, (phenylamino)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 in need of such administration, is sufficient to effect treatment, as defined below, for myocarditis. The amount of a compound of formula (I) which constitutes a "therapeutically effective amount" will vary depending on the compound, the severity of the disorder, and the age of the human 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 myocarditis in a human; and include:

(i) preventing the disorder from occurring in a human, in particular, when such human 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.

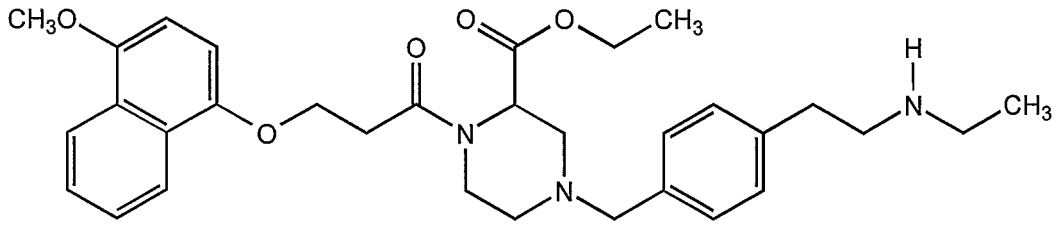
"Ureido" refers to a radical of the formula -N(H)-C(O)-NH_2.

"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.

Utility and Administration

A. Utility

As supported by the Examples by the examples herein, compounds of the type disclosed herein are useful in treating myocarditis.

B. Testing Procedures

Animals

Male Lewis rats (7-weeks-old; body weights 200 to 250 g) were purchased from Sankyo Laboratories. They were fed a standard diet and water and were maintained in compliance with animal welfare guide lines of the Institute of Experimental Animals, Tokyo Medical and Dental University.

Antigen and Immunization

Purified porcine cardiac myosin (Sigma Chemical Co.) was dissolved in 0.01 M phosphate-buffered saline (PBS) and emulsified with an equal volume of complete Freund's adjuvant (Difco) supplemented with *Mycobacterium tuberculosis* H37RA (Difco) at a concentration of 10 mg/mL. On day 0, rats were injected in the footpads subcutaneous with 0.2 mL of emulsion, yielding an immunizing dose of 1.0 mg/body of cardiac myosin per rat.

Preparation of stock solution of piperazine derivative

A 25mg/ml sterile saline solution of (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine in 40% cyclodextrin(Sigma) was prepared by dissolving the compound into 40% cyclodextrin in saline. The mixture was shaken followed by the addition of HCl. The mixture was stirred to dissolve the solute. After dissolution was complete, 1_MKOH was added to raise the pH to 4.5.

Treatment

Rats were administered subcutaneously with stock solution of (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine, from day 0 (group BX0) or from day 14 (group BX14) every day (50mg/kg, twice per day) and were sacrificed on day 21. As controls, groups C1 and C2 were treated with 40% cyclodextrin/saline.

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, 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 myocarditis.

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 disease-state, 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.

D. Combinations

The compounds of the present invention can be administered alone or in combination with one or more additional other therapeutic agents including:

Diuretics;

ACE Inhibitors;

Angiotensin Receptor Antagonists;

Beta Adrenoreceptor Blockers;

Carvedilol and Labetolol (mixed beta-blocker with alpha-1 blocking properties);

Vasodilators (e.g., Sodium Nitroprusside);

Positive Inotropic Agents (e.g., Dobutamine)

E. Preferred compounds

Preferred compounds of the present invention include all the preferred compounds identified in U.S. Patent No. 6,207,665 and WO 98/56771.

More preferred compounds include compounds of formula Ia 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)methyl-piperazine;
(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;

(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-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.

The most preferred compound is (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine.

EXAMPLES

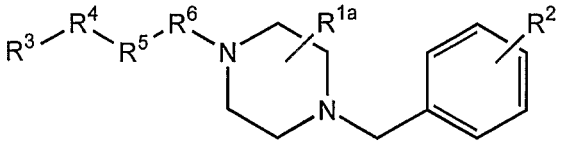
Example 1

Following the Testing Procedures outlined above, the heart weight to body weight ratio (H/B) of sacrificed rats was measured and histological examination and echocardiograms were performed to evaluate the severity of the disease. Myocarditis-affected areas in the treated groups were suppressed compared to those in the control groups (group BX0 or group BX14 vs controls: area ratio; 1.0±1.1%vs51.8±8.3% or 11.8±2.9%vs52.4±9.3%, respectively $P<0.05$). Cardiac function in the treated groups was improved (group BX0 or group BX14 vs controls: FS; 46.7±3.6%vs20.8±2.6% or 39.4±4.1%vs22.0±5.9%, respectively $P<0.05$). H/B showed similar reduction in the treated groups.

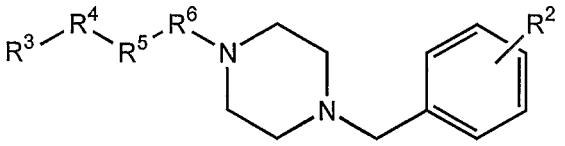
The CCR1 antagonist reduced the severity of EAM.

We Claim:

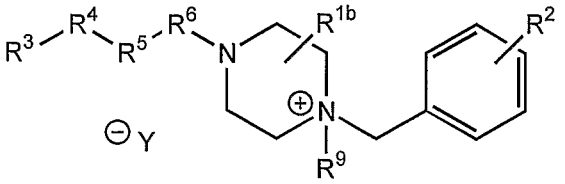
1. A method of treating myocarditis comprising administrating an effective amount of at least one compound of formula Ia, Ib, Ic or Id to a patient in need thereof



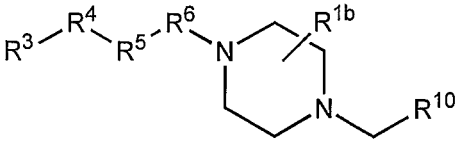
(Ia)



(Ib)



(Ic)



(Id)

enantiomers, diasteriomers and pharmaceutically acceptable salts thereof 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, 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;

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 $-N(R^7)_2$;

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;

Y is a pharmaceutically acceptable counterion:

R^{1b} is one or more substituents independently selected from the group consisting of hydrogen, 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; and

R^9 is alkyl, aralkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, alkylcarbonylalkyl, alkylcarbonylaminoalkyl, aminocarbonylalkyl, monoalkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, hetereocyclylalkyl, or cycloalkylalkyl;

R^{10} is a heterocyclyl 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, and monobenzylureido;

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.

2. A method of claim 1 wherein the compound is a compound of formula Ia.

3. A method of claim 2 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.

4. A method of claim 3 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.

5. A method of claim 4 wherein

R^4 is -O-;

R^5 is methylene; and

R^6 is -C(O)-.

6. A method of claim 5 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.

7. A method of claim 6 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.

8. A method of claim 7 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.

9. A method of claim 8 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.

10. A method of claim 9 wherein the compound is selected from
(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
enantiomers, diastereomers, salts and solvates thereof.

11. A method of claim 10 wherein the compound is (2*R*)-1-((4-chloro-2-(ureido)phenoxy)methyl)carbonyl-2-methyl-4-(4-fluorobenzyl)piperazine enantiomers, diastereomers, salts and solvates thereof.

12. A method of claim 1 wherein the compound of formula Ia, Ib, Ic or Id is administered in combination with at least one additional therapeutic agent selected from
Diuretics;
ACE Inhibitors;
Angiotensin Receptor Antagonists;
Beta Adrenoreceptor Blockers;
Carvedilol and Labetolol;
Vasodilators; and
Positive Inotropic Agents.