Title: NOVEL HYDROXYAMIDINO CARBOXYLATE DERIVATIVES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

Abstract

The current invention discloses novel hydroxyamidino carboxylate derivatives useful as nitric oxide synthase inhibitors. Compounds of particular interest are defined by Formula (I) wherein X, Y, A, J, R1, R2, R3, R4, R5 and R6 are as described in the specification.
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NOVEL HYDROXYAMIDINO CARBOXYLATE DERIVATIVES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

Background of the Invention

Field of the Invention

The present invention relates to novel hydroxamidino carboxylate derivatives and their use in therapy, in particular their use as nitric oxide synthase inhibitors.

Related Art

It has been known since the early 1980's that the vascular relaxation caused by acetylcholine is dependent on the presence of the vascular endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for well over 100 years. In addition, NO is the active component of amyl nitrite, glyceryltrinitrate and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesized from the amino acid L-arginine by the enzyme NO synthase.

Nitric oxide is the endogenous stimulator of the soluble guanylate cyclase. In addition to endothelium-dependent relaxation, NO is involved in a number of biological actions including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al., Biochemical Pharmacology, 38, 1709-1715, 1989; Moncada et al., Pharmacological Reviews,
43, 109-142, 1991). Excess NO production appears to be involved in a number of pathological conditions, particularly conditions which involve systemic hypotension such as toxic shock, septic shock and therapy with certain cytokines (Kerwin et al., J. Medicinal Chemistry, 38, 4343-4362, 1995).

The synthesis of NO from L-arginine can be inhibited by the L-arginine analogue, L-N-monomethyl-arginine (L-NMMA) and the therapeutic use of L-NMMA for the treatment of toxic shock and other types of systemic hypotension has been proposed (WO 91/04024 and GB-A-2240041). The therapeutic use of certain other NO synthase inhibitors apart from L-NMMA for the same purpose has also been proposed in WO 91/04024 and in EP-A-0446699.

It has recently become apparent that there are at least three types of NO synthase as follows:

(i) a constitutive, Ca++/calmodulin dependent enzyme, located in the endothelium, that releases NO in response to receptor or physical stimulation.

(ii) a constitutive, Ca++/calmodulin dependent enzyme, located in the brain, that releases NO response to receptor or physical stimulation.

(iii) a Ca++ independent enzyme which is induced after activation of vascular smooth muscle, macrophages, endothelial cells, and a number of other cells by endotoxin and cytokines. Once expressed this inducible NO synthase generates NO continuously for long periods.

The NO released by the two constitutive enzymes acts as a transduction mechanism underlying several physiological responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading
microorganisms. It also appears that the adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result largely from the effects of NO synthesized by the inducible NO synthase (Knowles and Moncada, Biochem J., 298, 249-258, 1994; Billiar et al., Annals of Surgery, 221, 339-349, 1995; Davies et al., 1995).

There is also a growing body of evidence that NO may be involved in the degeneration of cartilage which takes place in certain conditions such as arthritis and it is also known that NO synthesis is increased in rheumatoid arthritis and in osteoarthritis (McInnes et al., J. Exp. Med., 184, 1519-1524, 1996; Sakurai et al., J. Clin. Investig., 96, 2357-2363, 1995). Accordingly, conditions in which there is an advantage in inhibiting NO production from L-arginine include autoimmune and/or inflammatory conditions affecting the joints, for example arthritis, and also inflammatory bowel disease, cardiovascular ischemia, diabetes, congestive heart failure, myocarditis, atherosclerosis, migraine, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, asthma, bronchiectasis, hyperalgesia (alldynia), cerebral ischemia (both focal ischemia, thrombotic stroke and global ischemia (secondary to cardiac arrest), multiple sclerosis and other central nervous system disorders mediated by NO, for example Parkinson’s disease and Alzheimer’s disease, and other disorders mediated by NO including opiate tolerance in patients needing protracted opiate analgesics, and benzodiazepine tolerance in patients taking benzodiazepines, and other addictive behaviour, for example, nicotine and eating disorders (Kerwin et al., J. Medicinal Chemistry, 38, 4343-4362, 1995; Knowles and Moncada, Biochem J., 298, 249-258, 1994; Davies et al., 1995; Pfeilschifter et al., Cell Biology International, 20, 51-58, 1996).
Further conditions in which there is an advantage in inhibiting NO production from L-arginine include systemic hypotension associated with septic and/or toxic shock induced by a wide variety of agents; therapy with cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy (E. Kelly et al., J. Partent. Ent. Nutri., 19, 234-238, 1995; S. Moncada and E. Higgs, FASEB J., 9, 1319-1330, 1995; R. G. Kilbourn et al, Crit. Care Med., 23, 1018-1024, 1995).

Some of the NO synthase inhibitors proposed for therapeutic use so far, and in particular L-NMMA, are non-selective; they inhibit both the constitutive and the inducible NO synthases. Use of such a non-selective NO synthase inhibitor requires that great care be taken in order to avoid the potentially serious consequences of over-inhibition of the constitutive NO-synthase including hypertension and possible thrombosis and tissue damage. In particular, in the case of the therapeutic use of L-NMMA for the treatment of toxic shock it has been recommended that the patient must be subject to continuous blood pressure monitoring throughout the treatment. Thus, while non-selective NO synthase inhibitors have therapeutic utility provided that appropriate precautions are taken, NO synthase inhibitors which are selective in the sense that they inhibit the inducible NO synthase to a considerably greater extent than the constitutive isoforms of NO synthase would be of even greater therapeutic benefit and easier to use (S. Moncada and E. Higgs, FASEB J., 9, 1319-1330, 1995).

oxide synthase. The disclosures of which are hereby incorporated by reference in their entirety as if written herein.

5 Summary of the Invention

In a broad aspect, the present invention is directed to novel compounds, pharmaceutical compositions and methods of using said compounds and compositions for inhibiting or modulating nitric oxide synthesis in a subject in need of such inhibition or modulation by administering a compound which preferentially inhibits or modulates the inducible isoform of nitric oxide synthase over the constitutive isoforms of nitric oxide synthase. It is also another object of the present invention to lower nitric oxide levels in a subject in need of such lowering.

Compounds of the present invention are represented by Formula I and II:

I

II

and pharmaceutically acceptable salts thereof, wherein;

J is selected from the group consisting of O, NR\textsuperscript{22}, and S;
J can be $R^{29}$, wherein $R^{29}$ is a group selected from
OR$^{28}$, OR$^{28}$S, SR$^{28}$, OR$^{28}$NR$^{24}$ and SR$^{28}$NR$^{24}$ provided that A
is R$^{26}$;

J$^{1}$ and J$^{2}$ are independently selected from OR$^{23}$, SR$^{23}$,
NHR$^{24}$ and N(R$^{24}$)R$^{25}$ provided that A is R$^{26}$;

G is selected from O, S, CH$_2$, CHR$^{15}$, C(R$^{15}$)$_2$, NH and
NR$^{15}$;

A is selected from the group consisting of O, N(R$^{5}$), S
and heterocyclyl with the proviso that J is selected from
other than O and A is selected from other than O, S and
heterocyclyl unless R$^{8}$ is other than hydrogen,
hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl, or R$^{7}$ is
selected from other than aryl, heteroaryl, aralkyl,
heteroaralkyl, H, alkyl, alkenyl, CH$_2$OC(=O)GR$^{15}$,
hydroxyalkyl, polyhydroxyalkyl, amino,
hydroxy,(poly)acyloxyalkyl and carboxyalkyl where G is
selected from the group consisting from O, S, CH$_2$, CHR$^{15}$,
C(R$^{15}$)$_2$, NH, and NR$^{15}$ and R$^{15}$ is selected from hydrogen,
alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and
heteroaryl;

A is selected from the group consisting of O, N(R$^{5}$)
and S connected to the point of attachment of R$^{3}$ by a
spacer selected from a group consisting of a covalent bond
and a linear moiety having a chain length of 1 to 3 atoms
to form C7 to C10 heterocyclyl with the proviso that when J
is selected from O and A is selected from O and S, R$^{1}$ is
selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)R¹⁵ and C(O)R¹⁵ where C(O)R¹⁵ can represent natural and synthetic amino acids and where R¹⁵ is selected from substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino and cycloalkoxy, R² is selected from other than H, alkanoyl and aroyl, or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

A can be selected from the group selected from O, N(R⁵) and S connected to the point of attachment of R⁴ by a spacer group selected from a group consisting of a covalent bond and a linear moiety having a chain length of 1 to 4 atoms to form C₆ to C₁₀ heterocyclyl provided that the linear moiety is selected from other than O and S;

A can be selected from the group selected from O, N(R⁵) and S connected to the point of attachment of any one of R¹ and R² by a spacer group selected from a linear moiety having a chain length of 1 to 6 atoms to form C₅ to C₁₀ heterocyclyl provided that, when A is N(R⁵), R¹ is selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)R¹⁵ and C(O)R¹⁵ where C(O)R¹⁵ may represent natural and synthetic amino acids and where R¹⁵ is selected from substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino and cycloalkoxy, or R² is selected from other than H, alkanoyl and aroyl or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

A can be selected from the group consisting of O, N(R⁵) and S connected to the points of attachment of R¹ and
R² by a spacer group selected from a linear moiety having a chain length of 1 to 6 to form C5 to C10 heterocyclyl;

A can be selected from the group consisting of O, N(R⁵) and S connected to X through substituent selected from hydroxyl, sulhydryl, amino, carboxyl, and carbonyl substituents of group X by a spacer selected from a covalent bond and a linear moiety having a chain length of 1 to 4 atoms to form C5 to C10 heterocyclyl;

A can be R² with the proviso that when R² is H, R⁸ is selected from other than hydrogen, or R¹ is selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)R¹⁵ and C(O)R¹⁵ wherein C(O)R¹⁵ can represent natural and synthetic amino acids and wherein R¹⁵ is selected from substituted dihydropyridyl, alkyl, alkylthio and alkoxy, or R² is selected from other than H, alkanoyl and aroyl, or J is selected from other than O;

A can be R²⁷, wherein R²⁷ is selected from the group consisting of N(R⁵)OR⁷, N(R⁵) N(R⁷)R²⁵, N(R⁵)SO₂R¹³, N(R⁵)C(O)R¹⁵, N(R⁵)C(S)R¹⁵, R¹⁹(R²⁰)C=N-N(R⁵), R¹⁹(R²⁰)C=N-O, natural and synthetic amino acids, N(R⁵)PO(O)(OR¹³)₁R⁶ and N(R⁵)PO(O)(OR¹³)₂;

R¹ and R² are independently selected from the group consisting of hydrogen, hydroxyl, sulhydryl, OR⁶, SR⁶, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carboxamidocycloalkyl,
dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl,
carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl,
formylalkyl, acylalkyl, CH₂SO₃⁻ M⁺, CH₂CH₂SO₃⁻ M⁺, CH₂PO₃⁻

2M⁺, CH₂CH₂PO₃⁻ 2M⁺, CH(OR)₆CF₃, S(O)R¹³, SO₂R¹³,
P(O)R³⁰R³¹, P(O)(R⁻)₂R⁺, C(O)R¹⁵, C(S)R¹⁵, CH₂OC(O)R¹⁵,
CH₂NR²⁻ C(O)R¹⁵, CH₂NR²⁻ C(S)R¹⁵, CH₂SC(O)R¹⁵, CH₂SC(S)R¹⁵,
CH₂OC(O)GR¹⁵, CH₂NR²⁻ C(O)GR¹⁵, CH₂NR²⁻ C(S)GR¹⁵,
CH₂OC(S)GR¹⁵, CH₂SC(S)GR¹⁵, OSO₂R¹³, OS(O)R¹³, OC(S)R¹⁵,
SC(S)R¹⁵, OC(S)GR¹⁵, SC(S)GR¹⁵, OC(O)R¹⁵, SC(O)R¹⁵,
OC(O)GR¹⁵, SC(O)GR¹⁵ and R¹⁹(R²⁰)CH, provided that R¹ is
selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)⁻R¹⁵
and C(O)R¹⁵ where C(O)R¹⁵ can represent natural and
synthetic amino acids and where R¹⁵ is selected from
substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino
and cycloalkoxy, unless J is selected from NR²⁻, R²⁹ and S,
R² is selected from other than H, alkanoyl and aroyl, R²⁶ is
present, A is R²⁷, or R⁸ is selected from other than
hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl or
provided that R² is selected from other than H, alkanoyl
and aroyl, unless R¹ is selected from other than H,
S(O)R¹³, SO₂R¹³, CH₂OC(O)R¹⁵ and C(O)R¹⁵ where C(O)R¹⁵ can
represent natural and synthetic amino acids where R¹⁵ is
selected from substituted dihydropyridyl, alkyl, alkylthio,
alkoxy, amino and cycloalkoxy, J is selected from NR²⁻, R²⁹
and S, R²⁶ is present, A is R²⁷, or R⁸ is selected from
other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl or haloalkyl;

\[ R^1 \text{ and } R^2 \text{ can be taken together forming group selected from a group consisting of } R^{19}(R^{20})C=, D(C(R^{30})R^{31})_2D \]

where \( z \) is 2 to 5 and \( D \) is selected from the group consisting of oxygen, C=O, C=S, S(O)\( m \) where \( m \) is 0 to 2, OP(OR\( m \))\( R^{30} \), P(O)\( R^{30} \), P(S)\( R^{30} \) and Si(R\( 19 \))\( R^{20} \),

\[ D((R^{19})R^{20}C)EW(C(R^{19})R^{20})_2D \text{ where } E \text{ is 1 to 2, } k \text{ is 1 to 2,} \]

with the proviso that only one \( D \) can be oxygen or sulfur at any time, and \( W \) is selected from the group consisting of oxygen, C=O, C=S, S(O)\( m \), Se(O)\( m \) where \( m \) is 0 to 2, P(O)\( R^{30} \), P(S)\( R^{30} \), N(R\( 19 \)), and Si(R\( 19 \))\( R^{20} \), cycloalkyl radicals, cycloalkenyl radicals wherein said cycloalkyl radicals and cycloalkenyl radicals may be optionally substituted with one or more \( R^{30} \) or \( R^{31} \) substituents, aryl radicals, heteroaryl radicals, saturated heterocyclic radicals and partially saturated heterocyclic radicals where said radicals are 1,2-disubstituted and said 1,2-substituents are independently selected from the group consisting of C=O, C=S, C(R\( 19 \))\( R^{32} \), S(O), S(O)\( 2 \), OP(OR\( 31 \))\( R^{30} \), P(O)\( R^{30} \),
P(S)\( R^{30} \), and Si(R\( 19 \))\( R^{20} \), cis-1,2-disubstituted alkanes and cis-1,2-disubstituted alkenes where said 1,2-substituents are independently selected from C=O, C=S, C(R\( 19 \))\( R^{32} \), S(O), S(O)\( 2 \), OP(OR\( 31 \))\( R^{30} \), P(O)\( R^{30} \), P(S)\( R^{30} \), and Si(R\( 19 \))\( R^{20} \) and said alkyl and alkenyl may be optionally substituted with one or more \( R^{30} \) or \( R^{31} \) substituents;
R³ and R⁴ are independently selected from the group consisting of hydrogen, hydroxyl, sulphydryl, OR⁶, SR⁶, CH₂SO₃⁻, CH₂CH₂SO₃⁻, M⁺, CH₃PO₃⁻², 2M⁺, CH₂CH₂PO₃⁻², 2M⁺, CH(OR)⁶CF₃, S(O)R¹³, SO₂R¹³, P(O)R³⁰R³¹, P(O)(R³⁰)₂R³¹, C(O)R¹⁵, C(S)R¹⁵, CH₂OC(O)R¹⁵, CH₂NR¹⁹C(O)R¹⁵, CH₂NR¹⁹C(S)R¹⁵, CH₂SC(O)R¹⁵, CH₂SC(S)R¹⁵, CH₂OC(O)GR¹⁵, CH₂NR¹⁹C(O)GR¹⁵, CH₂NR¹⁹C(S)GR¹⁵, CH₂OC(S)GR¹⁵, CH₂SC(S)GR¹⁵, OSO₂R¹³, OS(O)R¹³, OC(S)R¹⁵, SC(S)R¹⁵, OC(S)GR¹⁵, SC(S)GR¹⁵, OC(O)R¹⁵, SC(O)R¹⁵, OC(O)GR¹⁵ and SC(O)GR¹⁵ with the proviso that R³ and R⁴ are selected from other than H, OH, SH, OR⁶, SR⁶, OC(=O)R¹⁵, SC(=O)R¹⁵, CH₂OC(=O)GR¹⁵, OC(=O)GR¹⁵, SC(=O)GR¹⁵, OSO₂R¹³ and OS(O)R¹³ where R⁶, R¹³ and R¹⁵ are independently selected from the group selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl unless J is selected from NR²², R²⁹ and S, R¹ and R² are taken together, R²⁶ is present, A is R²⁷, or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

R⁵ is selected from the group consisting of hydrogen, ary1, heteroaralkyl, hydroxy, alkyl, alkenyl, alkynyl, amino, cyanooalkyl, dicyanoalkyl, carboxamidoalkyl, hydroxyalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, carboxalkoxycyanocycloalkyl, dicarboxalkoxycyanocycloalkyl, formylalkyl, acylalkyl, heteroaryl polyhydroxyalkyl.
polyacycloalkyl, carboalkoxy, S(O)R$_{13}$, SO$_2$R$_{13}$, P(O)R$_{30}^{31}$, P(O)(R')$_2$R$_{31}$, C(O)R$_{15}$, C(S)R$_{15}$, CH$_2$OC(O)R$_{15}$, CH$_2$NR$^+$C(O)R$_{15}$, CH$_2$NR$^+$C(S)R$_{15}$, CH$_2$SC(O)R$_{15}$, CH$_2$SC(S)R$_{15}$, CH$_2$OC(O)GR$_{15}$, CH$_2$NR$^+$C(O)GR$_{15}$, CH$_2$NR$^+$C(S)GR$_{15}$,  

CH$_2$OC(S)GR$_{15}$, CH$_2$SC(S)GR$_{15}$, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, halooalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino and sulfonylalkylamino;

with the proviso that R$_5$ is selected from other than the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxyalkyl, polyhydroxyalkyl, amino, hydroxy, polyacyloxyalkyl, carboalkoxy and CH$_2$OC(O)GR$_{15}$ where G is independently selected from O, S, CH$_2$, CHR$_{15}$, C(R$_{15}$)$_2$, NH, and NR$_{15}$ and where R$_{15}$ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl unless J is selected from NR$_{22}$, R$_{29}$ and S, R$_1$ and R$_2$ are taken together, R$^{26}$ is present, A is R$^{27}$, or R$^8$ is selected.
from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

\[ \text{R}^5, \text{R}^1 \text{ and R}^2 \text{ can be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form C5 to C8 heterocyclyl;} \]

\[ \text{R}^5 \text{ can be a heterocyclyl radical in which there is at least one carbon in one ring and in which 1 to about 4 members of said ring are heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur and said heterocyclyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, loweralkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylamidino, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkeny1, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, arylhaloalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,} \]
dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, carboxalkoxy cycloalkyl, dicarboxalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxy phosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino and acylamino with the proviso that $R^8$ is selected from other than H when A is N($R^5$) unless $R^1$ and $R^2$ are taken together;

$R^6$ is selected from the group selected from hydrogen, heterocyclic, heteroaryl, hydroxyalkyl, minoalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxy cyanocycloalkyl, carboxalkoxy cycloalkyl, dicarboxalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl, 
diaralkoxyphosphonoalkyl, sulfonylalkyl, 
alkoxysulfonylalkyl, aralkoxysulfonylalkyl, 
alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, 
sulfonylalkylamino, natural and synthetic amino acids and 
polyhydroxy compounds of carbon with the proviso that \( R^6 \) is 
selected from other than hydrogen, alkyl, alkenyl, alkynyl, 
cycloalkyl, heterocyclic, aryl and heteroaryl unless \( J \) is 
selected from the group consisting of NR\(^{22} \), R\(^{29} \) and S, R\(^{26} \) 
is present, \( A \) is R\(^{27} \), R\(^1 \) and R\(^2 \) are taken together, or R\(^8 \) 
is selected from other than hydrogen, hydroxyalkyl, 
alkoxyalkyl, alkyl and haloalkyl;

\( R^7 \) is selected from the group consisting of hydrogen, 
aryl, heteroaralkyl, hydroxy, alkyl, alkenyl, alkynyl, 
amino, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, 
hydroxyalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, 
carboalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, 
dicyanocycloalkyl, carboxamidocycloalkyl, 
dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, 
carboalkoxy(cycloalkyl), dicarboxalkoxy(cycloalkyl), 
formylalkyl, acylalkyl, S(O)R\(^{13} \), SO\(_2\)R, P(O)R\(^{30} \)R\(^{31} \), 
P(O)(R\(^{30} \))\(^2 \)R\(^{31} \), C(O)R\(^{15} \), C(S)R\(^{15} \), CH\(_2\)OC(O)R\(^{15} \), 
CH\(_2\)NR\(^{19} \)C(O)R\(^{15} \), CH\(_2\)NR\(^{19} \)C(S)R\(^{15} \), CH\(_2\)SC(O)R\(^{15} \), CH\(_2\)SC(S)R\(^{15} \), 
CH\(_2\)OC(O)GR\(^{15} \), CH\(_2\)NR\(^{19} \)C(O)GR\(^{15} \), CH\(_2\)NR\(^{19} \)C(S)GR\(^{15} \), 
CH\(_2\)OC(S)GR\(^{15} \), CH\(_2\)SC(S)GR\(^{15} \), heteroaryloxyalkyl, aralkyl, 
aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, 
alkylsulfonylalkyl, aralkylthioalkyl, 
heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, 
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, 
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, 
cycloalkenylalkyl, haloalkyl, haloalkenyl, haloalkylcycloalkyl,
aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, 5
carboalkoxyalkyl, dialkoxyphosphonoalkyl,  
diaralkoxyphosphonoalkyl, phosphonoalkyl,  
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,  
phosphonoalkylamino, dialkoxyphosphonoalkyl,  
diaralkoxyphosphonoalkyl, sulfonylalkyl,  
alkoxysulfonylalkyl, aralkoxysulfonylalkyl,  
alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino and  
sulfonylalkylamino with the proviso that \( R^7 \) is selected  
from other than the group consisting of hydrogen, alkyl,  
alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl,  
hydroxyalkyl, polyhydroxyalkyl, amino, hydroxy,  
polyacyloxyalkyl, carboxyalkoxy and \( \text{CH}_2\text{OC(O)GR}^{15} \) where \( G \) is  
selected from the group consisting of O, S, CH\(_2\), CHR\(_{15}\),  
C(R\(_{15}\))\(_2\), NH, and NR\(_{15}\) and wherein \( R^{15} \) is selected from  
hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,  
heterocyclic, aryl and heteroaryl unless \( J \) is selected  
from NR\(_{22}\), \( R^{29} \) and S, \( R^{26} \) is present, \( A \) is \( R^{27} \), \( R^1 \) and \( R^2 \)  
are taken together, or \( R^8 \) is selected from other than  
hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;  
or

\[ R^7, R^1 \text{ and } R^2 \]  
can be taken together to form a spacer group selected from a linear moiety having a chain length  
of 1 to 4 atoms to form a C5 to C8 heterocycyl;  

\( R^7 \) can be a heterocycyl radical in which there is at  
least one carbon in one ring and in which 1 to about 4  
members of said ring are heteroatoms independently selected  
from oxygen, nitrogen and sulfur and said heterocycyl radical  
may be optionally substituted with heteroarylamino,  
N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino,  
haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy,
cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro,
lower alkylamino, alkylthio, alkythioalkyl, aroylamino,
aralkylamino, aralkylthio, alkylsulfinyl, alkylsulfonyl,
alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl,
monoalkyl amidosulfonyl, dialkyl amidosulfonyl,
monoarylaminosulfonyl, arylsulfonamido,
diarylaminosulfonyl, monoalkyl monoaryl amidosulfonyl,
aryl sulfinyl, arylsulfonyl,
heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl,
alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl,
heteroaralkanoyl, haloalkanoyl, alky1, alkenyl, alkynyl,
alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl,
lower cycloalkylalkyl, lower cycloalkenylalkyl, halo,
haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyarylalkyl,
hydroxyalkyl, hydroxyheteroarylalkyl, haloalkoxyalkyl, aryl,
aralkyl, aroyl, aralkoxy, aryloxyalkyl, saturated
heterocyclyl, partially saturated heterocyclyl, heteroaryl,
heteroaryloxy, heteroaryloxyalkyl, arylalkyl,
heteroarylalkyl, arylalkenyl, heteroaryllalkenyl,
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyanocarboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carboxamidocycloalkyl,
dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl,
carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl,
formylalkyl, acylalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy,
phosphonoalkoxy, dialkoxyphosphonoalky lamino,
diaralkoxyphosphonoalkylamino, phosphonoalkylamino,
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,
guanidino, amidino and acylamino with the proviso that \( A \) is
selected from other than \( O \) and \( S \) unless \( J \) is selected from
NR\(^{22}\), R\(^{29}\) and \( S \) or \( J^1 \) and \( J^2 \) are selected from two groups
independently selected from OR\textsuperscript{23}, SR\textsuperscript{23}, NHR\textsuperscript{24} and
N(R\textsuperscript{24})R\textsuperscript{25}, R\textsuperscript{1} and R\textsuperscript{2} are taken together when A is R\textsuperscript{26}, or
provided that R\textsuperscript{8} is selected from other than H when A is
N(R\textsuperscript{5});

5 \[ R^{8} \text{ is selected from hydrogen, hydroxyalkyl, haloalkyl, } \]
alkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl,
aliphaticalkyl, cyanoalkyl, sulfhydrylalkyl, formyl, C(O)A-
R\textsuperscript{7}, C(S)A-R\textsuperscript{7}, CH\textsubscript{2}OC(O)A-R\textsuperscript{7}, CH\textsubscript{2}NR\textsuperscript{19}C(O)A-R\textsuperscript{7}, CH\textsubscript{2}NR\textsuperscript{19}C(S)A-
R\textsuperscript{7}, CH\textsubscript{2}SC(O)A-R\textsuperscript{7}, CH\textsubscript{2}SC(S)A-R\textsuperscript{7}, CH\textsubscript{2}OC(O)GR\textsuperscript{15},
CH\textsubscript{2}NR\textsuperscript{19}C(O)GR\textsuperscript{15}, CH\textsubscript{2}NR\textsuperscript{19}C(S)GR\textsuperscript{15}, CH\textsubscript{2}OC(S)GR\textsuperscript{15}, CH\textsubscript{2}SC(S)GR\textsuperscript{15}
and acyl with the proviso that R\textsuperscript{8} is selected from other
than hydrogen, hydroxyalkyl, haloalkyl, alkylationalkyl
unless J\textsuperscript{1} and J\textsuperscript{2} are selected from NR\textsuperscript{22}, R\textsuperscript{29} and S, R\textsuperscript{26} is
present, R\textsuperscript{1} and R\textsuperscript{2} are taken together, or A is R\textsuperscript{27};

15 \[ R^{13} \text{ is independently selected from aryloxy, amino, } \]
alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl,
alkoxy, aliphaticalkyl, arythio, alkyl, alkenyl, alkynyl, aryl,
aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfanylalkyl,
aliphaticalkyl, aralkythioalkyl,
heteroaralkythioalkyl, aryloxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkeny, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkeny,
haloaryloxyalkyl, aralkylsulfanylalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
carboxycarboxyalkyl, carboxycarboxyalkyl,
dicarboxyalkyl, cyanoxyalkyl, dicyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboxalkoxy cyanocycloalkyl, carboxalkoxy cycloalkyl, dicarboxalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyposphonoalkyl, dialkoxy phosphonoalkyl, phosphonoalkyl, dialkoxy phosphonoalkoxy, diaralkoxy phosphonoalkoxy, phosphonoalkoxy, dialkoxy phosphonoalkylamino, diaralkoxy phosphonoalkylamino, phosphonoalkylamino, dialkoxy phosphonoalkyl, diaralkoxy phosphonoalkyl, sulfonlalkyl, alkoxy sulfonlalkyl, aralkoxy sulfonlalkyl, alkoxy sulfonlalkoxy, aralkoxy sulfonlalkoxy, sulfonlalkoxy, alkoxy sulfonlalkylamino, aralkoxy sulfonlalkylamino, sulfonlalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon;

\[ R^{15} \] is independently selected from hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonlalkyl, aralkylthioalkyl, hetero aralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonlalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalcoxyalkyl, carboxalcoxyalkyl, dicarboxalcoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalcoxy cyanocycloalkyl, carboxalcoxy cycloalkyl, icarboxalcoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyposphonoalkyl, dialkoxy phosphonoalkyl, phosphonoalkyl, dialkoxy phosphonoalkoxy, diaralkoxy phosphonoalkoxy, phosphonoalkoxy, dialkoxy phosphonoalkylamino, diaralkoxy phosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,  
diaralkoxyphosphonoalkyl, sulfonylalkyl,  
alkoxysulfonylalkyl, aralkoxysulfonylalkyl,  
alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy,  
sulfonylalkoxy, alkoxyalkylamino,  
aralkoxyalkylamino, sulfonylalkylamino, natural and  
synthetic amino acids and polyhydroxy compounds of carbon;  

\( M^+ \) is a pharmaceutically acceptable cation;  

X is selected from the group consisting of alkylene,  
alkenylene, and alkylnylene groups which may be optionally  
substituted from the group consisting of alkyl, alkoxy,  
hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano  
and amino; or  

X can be \(-{(CH_2)}_pQ{(CH_2)}_r^-\) wherein p is 1 to 3, r is 1 to 3  
and Q is selected from oxygen, C=O, S(O)\(_t\), Se(O)\(_t\) wherein \( t \) is 0 to 2, P(O)\(_{21}\) wherein \( R^{21} \) is hydroxyl or alkyl which  
may be optionally substituted with one of the group  
consisting of alkyl, alkoxy, hydroxy, halogen,  
trifluoromethyl, nitro, cyano, amino, carboxy, and N\(_{12}\)  
where n is 1 to 2 and \( R^{12} \) is selected from the group  
consisting of hydrogen, oxy, hydroxyl and alkyl which may  
be optionally substituted from the group consisting of  
alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro,  
cyano and amino;  

X can be \(-{(CH_2)}_sT{(CH_2)}_v^-\) wherein s is 0 to 2, v is 0 to 2  
and T is selected from a 3 to 6 membered carbocyclic  
radical, aryl radical and a heterocyclic radical where all  
said radicals may be optionally substituted with alkyl,
alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

Y is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, alkylthioalkyl, alkylaminoalkyl and NR<sup>9</sup>R<sup>10</sup> where R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclyl and aralkyl;

R<sup>9</sup> and R<sup>10</sup> can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclyl;

R<sup>19</sup> and R<sup>20</sup> are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkoxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylmethyl, heteroaryloxyalkyl, heteroarylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycyanocycloalkyl, dicarboalkoxycyanocycloalkyl, formylalkyl, acylalkyl,
aryl sulfinylalkyl, aryl sulfonylalkyl, aralkyl sulfinyl, cycloalkyl sulfinylalkyl, cycloalkyl sulfonylalkyl, heteroaryl sulfonylealkyl, heteroaryl sulfonylalkyl, aralkyl sulfinylalkyl, aralkyl sulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl and diaralkoxyphosphonoalkyl with the proviso that only one of R^{19} and R^{20} is hydrogen;

R^{19} and R^{20} can be taken together to form a linear moiety spacer group having a chain length of 2 to 7 atoms to form a group consisting of C3 to C8 cycloalkyl, C3 to C8 cycloalkenyl and C3 to C8 heterocycyl;

R^{22} and R^{23} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aralkoxyalkyl, alkoxyalkyl, alkyl sulfinylalkyl, alkyl sulfonylealkyl, heteroaralkyl-thioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkythioalkyl, arythioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenylalkoxyalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylothioalkyl, heteroaralkylthioalkyl, aryloxyalkyl, aryloxyalkyl, aralkyl sulfinylalkyl, aralkyl sulfonylealkyl, cycloalkyl sulfinylalkyl, cycloalkyl sulfonylalkyl, heteroaryl sulfonylealkyl, heteroaryl sulfonylalkyl, aralkyl sulfinylalkyl and aralkyl sulfonylalkyl;

R^{24} and R^{25} are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkoxyalkyl, aralkoxyalkyl, alkoxy, alkyl sulfinylalkyl, alkyl sulfonylalkyl,
aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,
arylthioalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkenyl; cycloalkenyl, cycloalkenylalkyl,
haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl,
haloalkoxyalkyl, haloalkenylxyalkyl, cycloalkoxy,
halocycloalkoxyalkyl, halocycloalkenylxyalkyl,
perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl,
heteroaryl, heteroarylalkyl, heteroarylmethyl,
heteroarylthioalkyl,
heteroarylthioalkyl, arylsulfanylalkyl,
aryl sulfonylalkyl, cycloalkylsulfanylalkyl,
cycloalkylsulfonylalkyl, heteroaryl sulfonylalkyl,
heteroaryl sulfanylalkyl, aralkylsulfanylalkyl and
aralkylsulfonylalkyl;

\[ R^{24} \] and \[ R^{25} \] can be taken together to form a spacer
group independently selected from a linear moiety having a
chain length of 4 to 7 atoms to form C5 to C8 heterocyclyl;

\[ R^{26} \] is independently selected from hydrogen, formyl,
hydroxyalkyl, alkenyl, alkynyl, acyl, aroyl, aralkanoyl,
heteroaroyl, alkylsulfanylalkyl, alkylsulfonlalkyl,
heteroarylthioalkyl, alkoxyalkyl, alkenyloxyalkyl,
alkylthioalkyl, cycloalkylalkenyl, cycloalkenyl, haloalkyl,
haloalkenyl, haloalkoxyalkyl, haloalkenylxyalkyl,
halocycloalkenylxyalkyl, cyanoalkyl, carboxy, carboxamido,
carboxalkoxy, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyanocarboxalkoxyalkyl,
carboxalkoxyalkyl, dicarboxalkoxyalkyl, formylalkyl and
acylalkyl with the proviso that \( J \) is selected from other
than 0 unless \[ R^8 \] is other than hydrogen;
$R^{28}$ is independently selected from a group consisting of CH($R^{23}$)CH$_2$, CH($R^{23}$)CH$_2$CH$_2$, CH$_2$CH($R^{23}$)CH$_2$, cycloalkylene and heterocyclylene;

$R^{30}$ and $R^{31}$ independently selected from the group selected from hydroxy, thiol, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, aralkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkylalkenyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, dialkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, dialkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, dialkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, dialkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonyl alkoxyl, aralkoxy sulfonyl alkoxyl, sulfonylalkoxy, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids, and polyhydroxy compounds of carbon;
$R^{30}$ and $R^{31}$ can be together to form a linear moiety spacer group having a chain length of 2 to 7 atoms selected from the group consisting of C3 to C8 cycloalkyl, C3 to C8 cycloalkenyl, and C3 to C8 heterocyclyl substituted independently and optionally with one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups.

It is an object of the present invention to provide compounds that have usefulness as inhibitors of nitric oxide synthase. These compounds also preferentially inhibit the inducible form over the constitutive form by at least 3 fold.

It is an advantage of the present invention that the compounds are more selective than those known in the art.

It is an object of the present invention to provide compounds that also are more selective than those known in the art.

It is also an advantage in that compounds of the present invention have preferred physical properties as compared to compounds known in the art. In contrast, NIL, which is disclosed in WO 93/13055 when the hydrochloride salt can be isolated as a colorless crystal, but has the property of deliquescence. The compound quickly becomes a very viscous sticky oil upon exposure to moisture in normal room air which makes it difficult to handle.

Also included in the family of compounds of Formula I and II are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is
pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula 1 may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid.

Suitable pharmaceutically-acceptable base addition salts of compounds of Formula 1 include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethlenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound of Formula 1 by reacting, for example, the appropriate acid or base with the compound of Formula 1.

While it may be possible for the compounds of formula (1) to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition.

According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (1) or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be
acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula (1) or a pharmaceutically acceptable salt or solvate thereof (lactive ingredient) with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a
suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.
Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.001 to 2500 mg/kg per day. The dose range for adult humans is generally from 0.005 mg to 10 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The compounds of Formula I and II are preferably administered orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

The use of generic terms in the description of the compounds are herein defined for clarity.

As utilized herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylthio", means an acyclic alkyl radical containing from 1 to about
10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Said alkyl radicals may be optionally substituted with groups as defined below. Examples of such radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, oxopropyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl and the like.

The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Said alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propylenyl, 2-chloropropylenyl, buten-1-yl, isobutenyl, pentenylene-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Said alkynyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a "hydroxyl" radical, one hydrido radical may be attached to a carbon atom to form
a "methine" radical (—CH—), or two hydrido radicals may be attached to a carbon atom to form a "methylene" (—CH₂⁻) radical.

The term "carbon" radical denotes a carbon atom without any covalent bonds and capable of forming four covalent bonds.

The term "cyano" radical denotes a carbon radical having three of four covalent bonds shared by a nitrogen atom.

The term "hydroxyalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with a hydroxyl as defined above. Specifically embraced are monohydroxyalkyl, dihydroxyalkyl and polyhydroxyalkyl radicals.

The term "alkanoyl" embraces radicals wherein one or more of the terminal alkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylalkyl and dicarbonylalkyl radicals. Examples of monocarbonylalkyl radicals include formyl, acetyl, and pentanoyl. Examples of dicarbonylalkyl radicals include oxalyl, malonyl, and succinyl.

The term "alkylene" radical denotes linear or branched radicals having from 1 to about 10 carbon atoms and having attachment points for two or more covalent bonds. Examples of such radicals are methylene, ethylene, methylethylene, and isopropylidene.
The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyhaloalkyl" embraces radicals wherein any one or more of the haloalkyl carbon atoms is substituted with hydroxy as defined above.

The term "haloalkylene radical" denotes alkylene radicals wherein any one or more of the alkylene carbon atoms is substituted with halo as defined above. Dihalo alkylene radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkylene radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkylene radicals are "lower haloalkylene" radicals having one to about six
carbon atoms. Examples of "haloalkylene" radicals include difluoromethylene, tetrafluoroethylene, tetrachloroethylene, alkyl substituted monofluoromethylene, and aryl substituted trifluoromethylene.

The term "haloalkeny1" denotes linear or branched radicals having from 1 to about 10 carbon atoms and having one or more double bonds wherein any one or more of the alkenyl carbon atoms is substituted with halo as defined above. Dihaloalkeny1 radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkeny1 radicals may have more than two of the same halo atoms or a combination of different halo radicals.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy.

The term "haloalkoxyalkyl" also embraces alkyl radicals having one or more haloalkoxy radicals attached.
to the alkyl radical, that is, to form monohaloalkoxyalkyl and dihaloalkoxyalkyl radicals. The term "haloalkenyloxy" also embraces oxygen radicals having one or more haloalkenyloxy radicals attached to the oxygen radical, that is, to form monohaloalkenyloxy and dihaloalkenyloxy radicals. The term "haloalkenyloxyalkyl" also embraces alkyl radicals having one or more haloalkenyloxy radicals attached to the alkyl radical, that is, to form monohaloalkenyloxyalkyl and dihaloalkenyloxyalkyl radicals.

The term "alkylenedioxy" radicals denotes alkylene radicals having at least two oxygens bonded to a single alkylene group. Examples of "alkylenedioxy" radicals include methylenedioxy, ethylenedioxy, alkylsubstituted methylenedioxy, and arylsubstituted methylenedioxy. The term "haloalkylenedioxy" radicals denotes haloalkylene radicals having at least two oxy groups bonded to a single haloalkyl group. Examples of "haloalkylenedioxy" radicals include difluoromethylenedioxy, tetrafluoroethylenedioxy, tetrachloroethylenedioxy, alkylsubstituted monofluoromethylenedioxy, and arylsubstituted monofluoromethylenedioxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Said "aryl" group may have 1 to 3 substituents such as heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkythio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio.
alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido,
alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl,
5 monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl,
arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl,
alkenoyl, aroyl, heteroaroyl, aralkanoyl,
10 heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl,
alkylenedioxy, haloalkylenedioxy, cycloalkyl,
cycloalkenyl, lower cycloalkylalkyl, lower
cycloalkenylalkyl, halo, haloalkyl, haloalkoxy,
hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl,
15 hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl,
arloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl,
partially saturated heterocyclyl, heteroaryl,
heteroaryloxy, heteroaryloxyalkyl, arylalkyl,
heteroarylalkyl, arylalkenyl, heteroarylalkenyl,
carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.
The term "perhaloaryl" embraces aromatic radicals such as
phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl
wherein the aryl radical is substituted with 3 or more
halo radicals as defined above.
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The term "heterocyclyl" embraces saturated,
partially saturated and unsaturated heteroatom-containing
ring-shaped radicals, where the heteroatoms may be
selected from nitrogen, sulfur and oxygen. Examples of
30 saturated heterocyclic radicals include saturated 3 to 6-
membered heteromonocyclic group containing 1 to 4 nitrogen
atoms[e.g. pyrroolidinyl, imidazolidinyl, piperidino,
piperaziny1, etc.]; saturated 3 to 6-membered
heteromonocyclic group containing 1 to 2 oxygen atoms and
1 to 3 nitrogen atoms [e.g. morpholiny1, etc.]; saturated
3 to 6-membered heteromonomocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidiny1, etc.]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonomocycl1 group containing 1 to 4 nitrogen atoms, for example, pyrroly1, pyrroliny1, imidazoly1, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidy1, pyraziny1, pyridaziny1, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny1, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridaziny1 [e.g., tetrazolo [1,5-b]pyridaziny1, etc.], etc.; unsaturated 3 to 6-membered heteromonomocyclic group containing an oxygen atom, for example, pyrany1, 2-fury1, 3-fury1, etc.; unsaturated 5 to 6-membered heteromonomocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonomocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonomocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur
atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. Said "heterocyclyl" group may have 1 to 3 substituents as defined below. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. Non-limiting examples of heterocyclic radicals include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrrolinyl, 3-pyrrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiophenolyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazonyl, quinolinyl, tetrazolyl, and the like.

Said "heterocyclyl" group may have 1 to 3 substituents such as heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfanyl, alkylsulfonfyl, alkylsulfonamido, alkylaminosulfonfyl, amidosulfonfyl, monoalkyl amidosulfonfyl, dialkyl amidosulfonfyl, monoarylamidosulfonfyl, arylsulfonamido, diarylamidosulfonfyl, monoalkyl monoaryl amidosulfonfyl, arylsulfanyl, arylsulfonfyl, heteroarylhthio, heteroarylsulfanyl, heteroarylsulfonfyl, alkanoyl,
alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylendioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaryl, hydroxyalkyl, hydroxyheteroaryl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclic, partially saturated heterocyclic, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyloxy, carboxaralkoxy, cyano, and carbohaloalkoxy.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO₂-. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. "Alkylsulfonylalkyl", embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfonyl", embraces haloalkyl radicals attached to a sulfonyl radical, where haloalkyl is defined as above. "Haloalkylsulfonylalkyl", embraces haloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical.

The term "sulfinyl", whether used alone or linked to other terms such as alkylsulfinyl, denotes respectively divalent radicals -S(O)-. "Alkylsulfinyl", embraces alkyl radicals attached to a sulfinyl radical, where alkyl is defined as above. "Alkylsulfinylalkyl", embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfinyl", embraces haloalkyl radicals attached to a sulfinyl
radical, where haloalkyl is defined as above. "Haloalkylsulfinylalkyl", embraces haloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may have additional substituents such as heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonfyl, alkylsulfonamido, alkylaminosulfonfyl, amidosulfonfyl, monoalkyl amidosulfonfyl, dialkyl amidosulfonfyl, monoarylaminosulfonfyl, arylsulfonamido, diarylamidosulfonfyl, monoalkyl monoaryl amidosulfonfyl, arylsulfinyl, arylsulfonfyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonfyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alklynedioxy, haloalkylenedioxy, cycloalkyl, cycloalkeny1, lower cycloalkylalkyl, lower cycloalkeny1alkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylmethyl, arylalkenyl, heteroarylmethylenyl,
carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals wherein the heteroaralkyl radical may be additionally substituted with three or more substituents as defined above for aralkyl radicals. The term "perhaloaralkyl" embraces aryl-substituted alkyl radicals wherein the aralkyl radical is substituted with three or more halo radicals as defined above. The term "Aralkylsulfinyld" embraces aralkyl radicals attached to a sulfinyl radical, where aralkyl is defined as above. "Aralkylsulfinyldalkyl", embraces aralkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "Aralkylsulfonyld", embraces aralkyl radicals attached to a sulfonyl radical, where aralkyl is defined as above. "Aralkylsulfonyldalkyl", embraces aralkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include cyclohexylhexyl. The term "cycloalkenyl" embraces radicals having three to ten
carbon atoms and one or more carbon-carbon double bonds. Preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "halocycloalkyl" embraces radicals wherein any one or more of the cycloalkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkyl, dihalocycloalkyl and polyhalocycloalkyl radicals. A monohalocycloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhalocycloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred halocycloalkyl radicals are "lower halocycloalkyl" radicals having three to about eight carbon atoms. Examples of such halocycloalkyl radicals include fluorocyclopropyl, difluorocyclobutyl, trifluorocyclopentyl, tetrafluorocyclohexyl, and dichlorocyclopropyl. The term "halocycloalkenyl" embraces radicals wherein any one or more of the cycloalkenyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkenyl, dihalocycloalkenyl and polyhalocycloalkenyl radicals. The term "halocycloalkoxy" also embraces cycloalkoxy radicals having one or more halo radicals attached to the cycloalkoxy radical, that is, to form monohalocycloalkoxy, dihalocycloalkoxy, and polycycloalkoxy radicals.

The term "Cycloalkylsulfinyl", embraces cycloalkyl radicals attached to a sulfinyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfinylalkyl", embraces
cycloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "cycloalkylsulfonyl", embraces cycloalkyl radicals attached to a sulfonyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfonylalkyl", embraces cycloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. An example of "lower alkylthio" is methylthio (CH$_3$-S-). The term "alkylsulfanyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- atom.

The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical. The terms arylamino denotes "monoaryl氨基" and "diaryl氨基" containing one or two aryl radicals, respectively, attached to an amino radical. The term "Aralkylamino", embraces aralkyl radicals attached to an amino radical, where aralkyl is defined as above. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoaralkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

The term "arylsulfinyl" embraces radicals containing an aryl radical, as defined above, attached to a divalent
-S(=O)- atom. The term "arylsulfinylalkyl" denotes arylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms.

The term "Arylsulfonyl", embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. "Arylsulfonylalkyl", embraces arylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "heteroarylsulfinyl" embraces radicals containing an heteroaryl radical, as defined above, attached to a divalent -S(=O)- atom. The term "heteroarylsulfinylalkyl" denotes heteroarylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms. The term

"Heteroarylsulfonyl", embraces heteroaryl radicals attached to a sulfonyl radical, where heteroaryl is defined as above. "Heteroarylsulfonylalkyl", embraces heteroarylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The aryl in said aryloxy may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenylthio, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylothio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl,
alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylatedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboxaralkoxy, cyano, and carbohaloalkoxy.

The term "aroyl" embraces aryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include benzoyle and toluoyl. The aroyl in said aroyl may be additionally substituted with heteroarylalino, N-aryl-N-alkylalino, N-heteroarylalino-N-alkylalino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenylalino. hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylalino, aralkylalino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyldiamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylatedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl,
hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "aralkanoyl" embraces aralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, phenylacetyl. The aryl in said aralkanoyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaalkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonfyl, amidosulfonfyl, monoalkyl amidosulfonfyl, dialkyl amidosulfonfyl, monoarylamidosulfonfyl, arylsulfonamido, diarylamidosulfonfyl, monoaryl monoaryl amidosulfonfyl, arylsulfinyl, arylsulfonfyl, heteroarylamino, heteroarylsulfinyl, heteroarylsulfonfyl, alkanoyl, alkenoyl, aryl, heteroaryl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylendioxy, haloalkylendioxy, cycloalkyl, cycloalkenyloxy, lower cycloalylalkyl, lower cycloalkenyloxyalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.
The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The aryl in said aralkoxy radicals may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfanyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonfyl, amidosulfonfyl, monoalkyl amidosulfonfyl, dialkyl amidosulfonfyl, monoarylamidosulfonfyl, arylosulfonamido, diarylamidosulfonfyl, monoalkyl monoaryl amidosulfonfyl, arylsulfanyl, arylosulfonfyl, heteroarylthio, heteroarylsulfanyl, heteroarylsulfonfyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyarylalkyl, hydroxyheteroarylalkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, aylalkyl, heteroarylalkyl, aylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl. The aryl in said
aryloxyalkyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arythio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, dialkyl amidosulfonyl,
monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenyalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclic, partially saturated heterocyclic, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "haloaryloxyalkyl" embraces aryloxyalkyl radicals, as defined above, wherein one to five halo radicals are attached to an aryloxy group. The term "heteroaryloxy" embraces heteroaryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include pyridyloxy and furylloxy. The heteroaryl in said heteroaryloxy may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy,
alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfanyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfanyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenyalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroaryllalkyl, arylalkenyl, heteroaryllalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "heteroaroyl" embraces heteroaryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include furoyl and nicotinyl. The heteroaryl in said heteroaroyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfanyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl
amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenediexo, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroalkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "heteroaralkanoyl" embraces heteroaralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, pyridylacetyl and furylbutyryl. The heteroaryl in said heteroaralalkanoyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxyl, heteroaralkoxy, cycloalkoxy, cycloalkenoyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoaryl amidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl.
heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl; halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyarylalkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxyl, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "heteroaralkoxy" embraces oxy-containing heteroaralkyl radicals attached through an oxygen atom to other radicals. More preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having heteroaryl radicals attached to lower alkoxy radical as described above. The heteroaryl in said heteroaralkoxy radicals may be additionally substituted with heteroarylamino, N-arylamino, N-alkyl-N-heteroarylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenylthio, hydroxy, amino, thio, nitro, lower alkylthio, alkylthioalkyl, arylthio, aralkylthio, arylthioalkyl, alkylsulfonyl, alkylsulfoxonamido, alklyaminoalkyl, amidosulfonamido, monoalkyl amidosulfonamido, diarylamidosulfonamido, monoaryl amidosulfonamido, diarylamidosulfonamido, monoalkyl monoaryl amidosulfonamido, arylsulfinyl, arylylamidosulfonamido, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy,
hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, 
hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, 
aryloxy, aralkoxy, aralkoxyalkyl, saturated heterocyclyl, 
partially saturated heterocyclyl, heteroaryl, 
heteroaryloxy, heteroaryloxyalkyl, arylalkyl, 
heteroaryllalkyl, arylalkeny1, heteroaryllalkeny1, 
carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy. 
The term "heteroaryloxyalkyl" embraces heteroaryloxy 
radicals, as defined above, attached to an alkyl group. 

Examples of such radicals include pyridyloxymethyl. The 
heteroaryl in said heteroaryloxyalkyl may be additionally 
substituted with heteroarylamino, N-aryl-N-alkylamino, N-
heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, 
alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkeny1oxy, 
hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, 
alkylthioalkyl, arylamino, aralkylamino, ary1thio, 
alysulfiny1, alkylsulfeny1, alkylsulfonamido, 
alysulfinosulfon1, amidosulfon1, monoalkyl 
amidosulfon1, dialky1 amidosulfon1, 
monoarylamidosulfon1, arylsulfonamido, 
diarylamidosulfon1, monoalkyl monoaryl amidosulfon1, 
arlylsulfiny1, arylsulfeny1, heteroary1thio, 
heteroarylsulfiny1, heteroarylsulfon1, alkanoy1, 
alkeny1, aroy1, heteroaroy1, aralkeny1, 
heteroaralkeny1, haloalkanoy1, alkyl, alkenyl, alkynyl, 
alky1enedioxy, haloalky1enedioxy, cycloalkyl, 
cycloalkeny1, lower cycloalkylalkyl, lower 
cycloalkeny1lalkyl, halo, haloalkyl, haloalkoxy, 
hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, 
hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, 
aryloxy, aralkoxy, aralkoxyalkyl, saturated heterocyclyl, 
partially saturated heterocyclyl, heteroaryl, 
heteroaryloxy, heteroaryloxyalkyl, arylalkyl, 
heteroaryllalkyl, arylalkeny1, heteroaryllalkeny1, 
carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.
The term "haloheteroaryloxyalkyl" embraces heteroaryloxyalkyl radicals, as defined above, wherein one to four halo radicals are attached to an heteroaryloxy group.

The term "arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio. The aryl in said arylthio may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkythio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulphonamido, alkylaminosulfonfyl, amidosulfonfyl, monoalkyl amidosulfonfyl, dialkyl amidosulfonfyl, monoarylamidosulfonfyl, arylsulfonamido, diarylamidosulfonfyl, monoalkyl monoaryl amidosulfonfyl, arylsulfinyl, arylsulfonyl, heteroarylamthio, heteroarylsulfinyl, heteroarylsulfonfyl, alkanoyl, alkenoyl, aryl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkeny1, lower cycloalkylalkyl, lower cycloalkenylalkyl, hal0, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocycyl, partially saturated heterocycyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.
The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl. The aryl in said arylthioalkyl may be additionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonfyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroalkyl, haloalkoxyalkyl, aryl, aralkyl, arloxy, aralkoxy, arloxyalkyl, saturated heterocycl, partially saturated heterocycl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboaralkoxy, cyano, and carbohaloalkoxy.

The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl.
The term "carbonyl" denotes a carbon radical having two of the four covalent bonds shared with an oxygen atom. The term "carboxy" embraces a hydroxyl radical, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboxamide" embraces amino, monoalkylamino, and dialkylamino radicals, attached to one of two unshared bonds in a carbonyl group. The term "carboxamidoalkyl" embraces carboxamide radicals, as defined above, attached to an alkyl group. The term "carboxyalkyl" embraces a carboxy radical, as defined above, attached to an alkyl group. The term "carboalkoxy" embraces alkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboaralkoxy" embraces aralkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "monocarboalkoxyalkyl" embraces one carboalkoxy radical, as defined above, attached to an alkyl group. The term "dicarboalkoxyalkyl" embraces two carboalkoxy radicals, as defined above, attached to an alkylene group. The term "monocyanooalkyl" embraces one cyano radical, as defined above, attached to an alkyl group. The term "dicyanoalkylene" embraces two cyano radicals, as defined above, attached to an alkyl group. The term "carboalkoxycyanooalkyl" embraces one cyano radical, as defined above, attached to an alkylene group.

The term "acyl", alone or in combination, means a carbonyl or thionocarbonyl group bonded to a radical selected from, for example, hydrido, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkoxyalkyl, haloalkoxy, aryl, heterocyclyl, heteroaryl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylthio, arylthio, amino, alkylamino, dialkylamino, aralkoxy, arylthio, and alkylthioalkyl.
Examples of "acyl" are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotinyl, and the like. The term "haloalkanoyl" embraces one or more halo radicals, as defined herein, attached to an alkanoyl radical as defined above. Examples of such radicals include, for example, chloroacetyl, trifluoroacetyl, bromopropanoyl, and heptafluorobutyryl. The alkanoyl in said haloalkanoyl may be additionally substituted with hydroxy, amino, thio, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylaminosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroaryl sulfinyl, heteroaryl sulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aroyl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboxaralkoxy, cyano, and carbohaloalkoxy.

The term "phosphono" embraces a pentavalent phosphorus attached with two covalent bonds to an oxygen radical. The term "diaralkoxyphosphono" denotes two alkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "diaralkoxyphosphono" denotes two
aralkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "dialkoxyphosphonoalkyl" denotes dialkoxyphosphono radicals, as defined above, attached to an alkyl radical. The term "diaralkoxyphosphonoalkyl" denotes diaralkoxyphosphono radicals, as defined above, attached to an alkyl radical.

The structural term, H(W)C=C(K)E, alone or in combination, means cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, cyanocarboalkoxy cycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, or acylalkyl wherein at least one of W, E, and K are independently selected from carboxy, thionocarboxy, thiolcarboxy, cyano, carboxamido, thionocarboxamido, carboalkoxy, thiono carboalkoxy, thiocarboalkoxy, acyl, thionoacyl, formyl or thionoformyl provided any two of W, E, or K may be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 saturated carbocyclyl, a C5 to C8 partially saturated carbocyclyl, a C5 to C8 saturated heterocyclyl or a C5 to C8 partially saturated heterocyclyl substituted independently and optionally with, for example, one or more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and halo groups.

The term "spacer" can include a covalent bond and a linear moiety having a backbone of 1 to 7 continuous atoms. The spacer may have 1 to 7 atoms of a univalent or multivalent chain. Univalent chains may be constituted by a radical selected from =C(H)-, =C(R')-, -O-, -S-, -S(O)-,
$S(O)_2^-$, $-\text{NH}^-$, $-\text{N}(R^6)^-$, $-\text{N}=\text{N}$, $-\text{CH(OH)}^-$, $=\text{C(OH)}^-$, $-\text{CH(O)}^-$, $-\text{C(OR)}^-$, $=\text{C(OR)}^-$, and $-\text{C(O)}^-$. Multi-valent chains may consist of a straight chain of 1 or 2 or 3 or 4 or 5 or 6 or 7 atoms or a straight chain of 1 or 2 or 3 or 4 or 5 or 6 or 7 atoms with a side chain. The chain may be constituted of one or more radicals selected from: lower alkylene, lower alkenyl, $-\text{O}^-$, $-\text{O}-\text{CH}_2^-$, $-\text{S}-\text{CH}_2^-$, $-\text{CH}_2\text{CH}_2^-$, ethenyl, $-\text{CH}^=\text{CH(OH)}^-$, $-\text{OCH}_2\text{O}^-$, $-\text{O}(\text{CH}_2)_2\text{O}^-$, $-\text{NHCH}_2^-$, $-\text{OCH(}R^6\text{)O}^-$, $-\text{O}(\text{CH}_2\text{CH}^R\text{)}\text{O}^-$, $-\text{OCF}_2\text{O}^-$, $-\text{O}(\text{CF}_2)_2\text{O}^-$, $-\text{S}^-$, $-\text{S}(\text{O})^-$, $-\text{S}(\text{O})_2^-$, $-\text{N(}H\text{)}^-$, $-\text{N(}H\text{)O}^-$, $-\text{N}(R^6)^-$, $-\text{N}(R^6)^-$, $-\text{C(O)}^-$, $-\text{C(O)NH}^-$, $-\text{C(O)NR}^6^-$, $-\text{N}^-$, $-\text{OCH}_2^-$, $-\text{SCH}_2^-$, $\text{S(O)CH}_2^-$, $-\text{CH}_2\text{C(O)}^-$, $-\text{CH(OH)}^-$, $=\text{C(OH)}^-$, $-\text{CH(O)}^-$, $-\text{C(OR)}^-$, $=\text{C(OR)}^-$, $\text{S(O)CH}_2^-$, and $-\text{NR}^6\text{CH}_2^-$ and many others radicals defined above or generally known or ascertained by one of skill-in-the art. Side chains may include substituents such as heteroarylamino, $N$-aryl-$N$-alkylamino, $N$-heteroarylamino-$N$-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonynamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfoxamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylthioalkoxy, haloalkylthioalkoxy, cycloalkyl, cycloalkenylyl, lower cycloalkylalkyl, lower cycloalkenyalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl,
aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboalkoxy, carboxaralkoxy, cyano, and carbohaloalkoxy.

The term "prodrug" refers to a compound that is made more active in vivo.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

Compounds of the present invention can exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention. Pharmaceutically acceptable sales of such tautomeric, geometric or stereoisomeric forms are also included within the invention.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have two higher ranking groups on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans"). Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.
Some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

Some of the compounds described herein may contain one or more ketonic or aldehydic carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each aldehyde and ketone group present. Compounds of the present invention having aldehydic or ketonic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms.

Some of the compounds described herein may contain one or more imine or enamine groups or combinations thereof. Such groups may exist in part or principally in the "imine" form and in part or principally as one or more "enamine" forms of each group present. Compounds of the present invention having said imine or enamine groups are meant to include both "imine" and "enamine" tautomeric forms.

The following general synthetic sequences are useful in making the present invention. Abbreviations used in the schemes are as follows: "AA" represents amino acids, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate, "Bz" represents a benzyl group, "CMR-Cl" represents a chloromethylation or bromomethylation reagent such as CH$_2$OC(O)R$^{15}$, CH$_2$NR$_2$C(O)R$^{15}$, CH$_2$NR$_2$C(S)R$^{15}$, CH$_2$SC(O)R$^{15}$, CH$_2$SC(S)R$^{15}$, CH$_2$OC(O)GR$^{15}$, CH$_2$NR$_2$C(O)GR$^{15}$, CH$_2$NR$_2$C(S)GR$^{15}$, CH$_2$OC(S)GR$^{15}$, or CH$_2$SC(S)GR$^{15}$, "DCC" represents 1,3-dicyclohexylcarbodiimide, "DIBAH" represents...
diisobutylaluminum hydride, "DIPEA" represents diisopropylethylamine, "DMF" represents dimethylformamide, "DMSO" represents dimethylsulfoxide, "Fmoc" represents 9-fluorenylethoxycarbonyl, "LDA" represents lithium diisopropyramide, "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzylxocarbonyl, "PTC" represents a phase transfer catalyst, "p-TsOH" represents paratoluenesulfonic acid, "TBTU" represents 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, "TEA" represents triethylamine, "THF" represents tetrahydrofuran, and "Z" represents benzyloxy carbonyl.

Disclosed are fifty-three synthetic processes useful in the preparation of the compounds of the present invention. The use of "E" in the structures of these preparatory methods refers to the substituent "E" as defined in structural term, H(W)C=C(K)E, above. The use of "Z" in the structures of these preparatory methods refers to the use of "Z" refers to the benzyloxy carbonyl group as defined in the paragraph immediately above.

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.
Scheme 1

(a) $R^3\text{-NH}_2$ (aa) N-chlorosuccimide, DMF
(b) BOP, DIPEA, DMF
(c) Pd, $H_2$, Ethanol/Acetic Acid
(d) $H_2O$, pH 9-10
(e) HCl, dioxane or trifluoroacetic acid.
Scheme 2

(a) HCl, Methanol
(b) BOP, DIPEA, DMF
(c) Pd, H2, Ethanol/Acetic Acid
(d) TEA, DMF
(e) HCl, dioxane or trifluoroacetic acid
Scheme 3

1. a  
2. aa

(a) $R_3$-NH$_2$ (aa) N-chlorosuccimide, DMF
(b) BOP, DIPEA, DMF
(c) HCl, dioxane or trifluoroacetic acid
(d) $H_2$O, pH 9-10  
(e) Pd, $H_2$, Ethanol/Acetic Acid
Scheme 4

(a) HCl, Methanol
(b) BOP, DIPEA, DMF
(c) HCl, dioxane or trifluoroacetic acid
(d) TEA, DMF
(e) Pd, H₂, Ethanol/Acetic Acid
Scheme 5

(a) t-Butoxycarbonyl azide, H2O, dioxane, MgO
(b) Pd, H2, Ethanol/Acetic Acid
(c) TEA, 0-80 °C
Scheme 6

(a) TEA, 0-80 °C
(b) HCl, dioxane
Scheme 7

(R^1 = hydroxyl, sulfhydryl, OR 6 or SR^6)

(a) 1. t-butoxycarbonylazide, H_20, dioxane, MgO
2. acetic anhydride, TEA (b) BOP, DIPEA, DMF

(c) 1 equiv. NaOH, ethanol (d) DMSO, DCC, H_3PO_4
(e) R^1-NH_2, ethanol, sodium carbonate
Scheme 8

(R^1 = hydroxyl, sulfhydryl, OR^6 or SR^6)  (a) BH_3, THF
(b) Acylation with R^2: a carboxylic acid chlor ide
or anhydride, a chloroformate, an isocyanate, a
sulfonyl chloride, sulfinyl chloride, or phosphating
or phosphonating reagent with standard conditions
(c) HCl, dioxane or trifluoroacetic acid
(d) H_2O, pH 9-10 with (2) or TEA, DMF with (2b)
Scheme 9

(a) 1. t-butoxycarbonylazide, H₂O, dioxane, MgO
2. acetic anhydride, TEA
(b) BOP, DIPEA, DMF
(c) 1 equiv. NaOH, ethanol
(d) DMSO, DCC, H₃PO₄
(e) R²-NH₂ (R² = hydroxyl, sulfhydryl, OR⁶ or SR⁶), ethanol, sodium carbonate
Scheme 10

(R² = hydroxyl, sulfhydryl, OR⁶ or SR⁶) (a) BH₃, THF
(b) Acylation with R¹: a carboxylic acid chloride
or anhydride, a chloroformate, an isocyanate, a
sulfonyl chloride, sulfinyl chloride, or phosphating
or phosphonating reagent with standard conditions
(c) HCl, dioxane or trifluoroacetic acid
(d) H₂O, pH 9-10 with (2) or TEA, DMF with (2b)
Scheme 11

(a) $R^3$-NH$_2$ (aa) N-chlorosuccinimide, DMF
(b) HCl, dioxane or trifluoroacetic acid
(c) Acylation with $R^1$: a carboxylic acid chloride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, or phosphating or phosphonating reagent with standard conditions
(d) Pd, H$_2$, Ethanol/Acetic Acid (e) H$_2$O, pH 9-10
Scheme 12

(a) HCl, Methanol
(b) HCl, dioxane or trifluoroacetic acid
(c) Acylation with R^1: a carboxylic acid chloride or anhydride, a chloroformate, an isocyanate, a sulfonyl chloride, sulfinyl chloride, or phosphating or phosphonating reagent with standard conditions
(d) Pd, H₂, Ethanol/Acetic Acid
(e) TEA, DMF
Scheme 13

(a) $R^3\text{-NH}_2$ (aa) N-chlorosuccimide, DMF
(b) HCl, dioxane or trifluoroacetic acid
(c) Acylation with $R^2$: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride, sulfinyl chloride, or phosphating or phosphonating agent with standard conditions
(d) Pd, $H_2$, Ethanol/Acetic Acid
(e) $H_2O$, pH 9-10
(a) HCl, methanol
(b) HCl, dioxane or trifluoroacetic acid
(c) Acylation with R²: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride, sulfinyl chloride, or phosphating or phosphonating reagent with standard conditions
(d) Pd, H₂, Ethanol/Acetic Acid
(e) TEA, DMF
(a) Benzyl chloroformate, Na₂CO₃, THF, Water
(b) HCl, dioxane or trifluoroacetic acid
(c) catalytic p-TsOH, hexane or toluene, azeotropic distillation (d) Pd, H₂, Ethanol/Acetic Acid
(e) Acylation with R¹ or R²: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride or sulfinyl chloride with standard conditions.
(a) catalytic p-TsOH, hexane or toluene, azeotropic distillation

(b) Pd, H₂, Ethanol/Acetic Acid

(c) Acylation with R¹ or R²: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride or sulfinyl chloride with standard conditions.
Scheme 17

(a) NaO₃SCH₂OH, pH 10-11 [see L. Maier, Phosphorus, Sulfur Silicon Related Elements (1990), 47, 43-46]

(b) 1. Aldehyde, acetal with trace of acid, or ketone, methanol or ethanol, 2. NaCNBH₃, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]
Scheme 18

(a) Trichloroethyl chloroformate, Na₂CO₃, H₂O, THF [see D. Gravel et al., Canadian Journal of Chemistry, 50, 3846 (1972)]
(b) Lawesson's Reagent, [Jones and Bradshaw, Chem. Reviews (1984), 84, 17-30 and cited references.
(c) 1. Zinc dust, Acetic Acid, 2. Na₂CO₃, H₂O
(d) Acylation with R¹: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride, or sulfinyl chloride with standard conditions.
(e) Acylation with R² with (d)-conditions.
Scheme 19

(a) catalytic p-TsOH, hexane or toluene, azeotropic distillation
(b) NaCNBH₃, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]
(c) Acylation with R¹ or R²: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride, or sulfinyl chloride with standard conditions.
Scheme 20

(a) 2 equivalents of Lithium Diisopropylamide, THF, C(O)Cl₂ or C(S)Cl₂
(b) HCl, dioxane or trifluoroacetic acid
(c) 1. Lithium Diisopropylamide, THF,
2. 2-haloalkanoate ester (R)
(d) Na₂CO₃, toluene, heat
Scheme 21

(a) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanal
(b) HCl, dioxane or trifluoroacetic acid
(c) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanone
Scheme 22

1. a  2. aa

Y
(1)  R³

N
R³

(2)

Y
Cl

R³

(66)

R⁴-HN

1. b  2. c

R⁴

(5)

H₂N

BoHN

(67)

R⁴

BoHN

(68)

R⁴

H₂N

(a) R³-NH₂ (aa) N-chlorosuccimide, DMF
(b) an aldehyde or ketone precursor to R⁴, catalytic p-TsOH, hexane or toluene, azeotropic distillation
(c) NaCNBH₃, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]
(d) H₂O, pH 9-10
(e) HCl, dioxane or trifluoroacetic acid
Scheme 23

(a) Na$_2$CO$_3$, aqueous dioxane; Acylation with a carboxylic acid chloride or anhydride
(b) Na$_2$CO$_3$, aqueous dioxane; sulfonation with a sulfonyl chloride or sulfinyl chloride with standard conditions
(a) Na₂CO₃, aqueous dioxane; Acylation with carboxylic acid chloride or anhydride
(b) Na₂CO₃, aqueous dioxane; sulfonation with sulfonyl chloride or sulfinyl chloride with standard conditions
(c) trifluoroacetic acid anhydride
(d) NaBH₄, R⁶-OH, aprotic polar solvent
Scheme 25

(a) TEA, DMF
(b) benzyl chloroformate, Na₂CO₃, dioxane, water
(c) NaOH, H₂O
(d) BOP, DIPEA, DMF
(e) DMF, heat
(f) Pd, H₂, Ethanol
Scheme 26

(a) TEA, DMF

(b) an aldehyde or ketone precursor to $R^4$, catalytic p-TsOH, hexane or toluene, azeotropic distillation

(c) NaCNBH$_3$, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]

(d) Pd, H$_2$, Ethanol

(e) TEA, 0-80 °C (f) Acylation with $R^2$: carboxylic acid chloride or anhydride, chloroformate, isocyanate, sulfonyl chloride, sulfinyl chloride, or phosphating or phosphonation reagent with standard conditions
Scheme 27

(a) Phthallic anhydride, THF at reflux
(b) LDA, THF, then Alkylation with a chloromethylation reagent (CMR-Cl)
(c) Pd, H₂, Ethanol
(d) H₂O, pH 9-10
(e) Hydrazine, methanol, reflux.
Scheme 28

(a) Phthalic anhydride, THF at reflux
(b) LDA, THF Alkylation with a chloromethylation reagent (CMR-C1)
(c) Hydrazine, methanol, reflux
(d) H₂O, pH 9-10
(e) Pd, H₂, Ethanol
(a) A t-Butoxycarbonyl amino acid (Boc-AA), BOP, DIPEA, DMF
(b) A 4-nitrobenzyloxycarbonyl amino acid (pnZ-AA), BOP, DIPEA, DMF
(c) Pd, H₂, Ethanol
(d) HCl, dioxane, H₂O
Scheme 30

(a) LDA, THF Alkylation with a chloromethylation reagent (CMR-Cl)
(b) Hydrazine, methanol, reflux
(c) H₂O, pH 9-10
(d) Pd, H₂, Ethanol
Scheme 31

(6: A = O or S; R^7 = H)

(a) 2 equivalents of Lithium Diisopropylamide, THF, C(O)Cl_2 or C(S)Cl_2
(b) HCl, dioxane or trifluoroacetic acid
(c) 1. Lithium Diisopropylamide, THF,
2. 2-haloalkanoate ester (R)
(d) Na_2CO_3, toluene, heat
Scheme 32

\[ (11: A = O \text{ or } S; R^7 = H) \]

\[ (108) \]

\[ \text{1. b, 2. d} \]

(a) 2 equivalents of Lithium Diisopropylamide, THF, C(O)Cl₂ or C(S)Cl₂
(b) Pd, H₂, ethanol/acetic acid
(c) 1. Lithium Diisopropylamide, THF,
2. 2-haloalkanoate ester (R)
(d) Na₂CO₃, toluene, heat
Scheme 33

(a) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanone
(b) HCl, dioxane or trifluoroacetic acid
(c) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanone
Scheme 34

(a) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanal
(b) Pd, H₂, ethanol/acetic acid
(c) Lithium Diisopropylamide, THF, then dialkyl acetal of a bromoalkanone
Scheme 35

(a) Pd, H₂, Ethanol/Acetic Acid
(b) Heat up to 150 °C to decarboxylate
(c) BH₃ in Tetrahydrofuran (d) DMSO, DCC, H₃PO₄
(e) p-TsOH, R²³-OH, hexane, heat
(f) BF₃ etherate with an R²³-OH or R²³-SH in an aprotic solvent
(g) 1. Aqueous Na₂CO₃ wash, 2. thoroughly dry, then 3. HCl in dioxane
Scheme 36

(a) H₂O, pH 9-10
(b) Hydrazine, methanol, reflux
Scheme 37

(a) BF₃ etherate with HOR²⁸OH, HOR²⁸SH, HSR²⁸SH, HOR²⁸NR²⁴H, or HSR²⁸NR²⁴H in an aprotic solvent or, with HOR²⁸OH, p-TsOH, R²³-OH, hexane, heat
(b) HCl, dixoane or trifluoroacetic acid
(c) H₂O, pH 9-10 (d) Hydrazine, methanol, reflux
Scheme 38

(a) HCl/dioxane or trifluoroacetic acid, then SOCl₂/DMF
(b) 1 equivalent DIBAH/THF at -78 °C
(c) p-TsOH, R²³-OH, hexane, heat
(d) 1. 1 equivalent NaOH/alcohol, 2. HCl (1 mole), dry  
   3. BOP, DIPEA, DMF, 4. H-A-R⁷
(e) BF₃ etherate with an R²³-OH or R²³-SH  
in an aprotic solvent
Scheme 39

(a) Pd, H₂, ethanol/acetic acid
(b) H₂O, pH 9-10
(c) Hydrazine, methanol, reflux
(a) 1 equivalent NaOH in ethanol, then 1 equivalent of HCl, then heat to 150 °C to decarboxylate

(b) Hydrazine, methanol, reflux

(c) Intermediate (2) or (2b), pH 9-10, H₂O

(d) R⁷-SH, CH₂Cl₂, -10 °C, HCl

(e) R⁷-OH, CH₂Cl₂, -10 °C, HCl
Scheme 40

(a) 1 equivalent NaOH in ethanol, then 1 equivalent of HCl, then heat to 150 °C to decarboxylate

(b) Hydrazine, methanol, reflux

(c) Intermediate (2) or (2b), pH 9-10, H₂O

(d) R⁷-SH, CH₂Cl₂, -10 °C, HCl

(e) R³-OH, CH₂Cl₂, -10 °C, HCl
Scheme 41

(a) Hydrazine, ethanol, reflux
(b) Intermediate (2) or (2b), pH 9-10, H₂O
(c) R⁷-SH, CH₂Cl₂, -10 °C, HCl
(d) R⁷-OH, CH₂Cl₂, -10 °C, HCl
(a) H-NR$_5^-$R$_7^-$, toluene, reflux
(b) R$^7$-OH, CH$_2$Cl$_2$, -10 °C, HCl
(c) R$^7$-SH, CH$_2$Cl$_2$, -10 °C, HCl
(d) 1. 1 equivalent NaOH in ethanol, 2. 1 equivalent of HCl, 3. BOP, DIPEA, DMF, H-NR$_5^-$R$_7^-$
(a) Pd, H₂, Ethanol/Acetic Acid
(b) Intermediate (2) or (2b), pH 9-10, H₂O
(c) H₂, Pt, Acetic acid
(d) Cl-C(O)R₁₅, triethylamine
(e) 1. Hydrazine, methanol, reflux, 2. HCl, dioxane
Scheme 44

(a) 1. 1 equivalent LDA/THF at -78 °C,
    2. bromoacetal (166)
(b) 1. 1 equivalent LDA/THF at -78 °C,
    2. Br-CH₂CH₂O-Bz
(c) catalytic p-TsOH, H₂O, 0-5 °C
(d) H₂N-R⁴, NaCNBH₃, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]
(a) Intermediate (2) or (2b), pH 9-10, H$_2$O
(b) HCl/Acetic acid
(c) 1. BOP, DIPEA, DMF, 2. H-A-R$_7$
(d) Pd, H$_2$, Ethanol/Acetic Acid
(e) Hydrazine, methanol, reflux
Scheme 46

(a) Tosyl Chloride (TsCl), Pyridine, H2O, 0-5 °C
(b) 1. NaCN, DMF, heat, 2. Hydrazine, methanol, reflux
(c) 1. Sodium thioacetate, DMF, heat, 2. Hydrazine, methanol, reflux, 3. Hydrolysis with TsOH
(d) 1. Sodium thioacetate, DMF, heat, 2. Hydrolysis with 1 equiv. NaOH, 3. CMR-Cl, 4. Hydrazine, methanol, reflux
(a) 1. HCl, dioxane, 2. BOP, DIPEA, DMF, 3. HOCH₂CCl₃
(b) 1. 1 equivalent LDA/THF at -78 °C, 2. CMR-Cl
(c) catalytic p-TsOH, H₂O, 0-5 °C
(d) H₂N-R⁴, NaCNBH₃, methanol, KOH [see R. F. Borch, Organic Synthesis, 52, 124 (1972)]
Scheme 48

(a) Intermediate (2) or (2b), pH 9-10, H2O
(b) Zinc dust/THF
(c) 1. BOP, DIPEA, DMF, 2. H-A-R7
(d) Hydrazine, methanol, reflux
Scheme 49

(a) 1. 1 equivalent LDA/THF at -78 °C, 2. alkylation with an R^8-reagent such as R^8-Br, R^8-OTs, R^8-oxirane, thiirane, or aziridine, or CMR-Cl
(b) catalytic p-TsOH, H_2O, 0-5 °C
(c) H_2N-R^4, NaCNBH_3, methanol, KOH
(d) Intermediate (2) or (2b), pH 9-10, H_2O
Scheme 50

(a) HCl in dioxane or ethyl acetate
(b) 1. BOP, DIPEA, DMF, 2. H-R \(^{27}\) such as HN(R\(^{22}\))OR\(^{6}\), HN(R\(^{22}\))N(R\(^{24}\))R\(^{25}\), R\(^{19}\)(R\(^{20}\))C=N-N(R\(^{22}\))H, R\(^{19}\)(R\(^{20}\))C=N-OH
(c) Hydrazine, methanol, reflux
(d) 1. ClCO\(_2\)Et, TEA, THF, -10 °C, 2. CH2Cl2, PTC, NaOH, H-R \(^{27}\) such as HN(R\(^{22}\))SO\(_2\)R\(^{13}\), HN(R\(^{22}\))C(O)R\(^{15}\), HN(R\(^{22}\))C(S)R\(^{15}\), HN(R\(^{22}\))P(O)(OR\(^{13}\))\(_n\)R\(^{6}\)
Scheme 51

(a) 1. BOP, DIPEA, DMF,
2. t-butyl ester of amino acid with t-butoxycarbonyl protected OH or SH group (H₂N-AA)
(b) Hydrazine, methanol, reflux
(c) HCl in dioxane or ethyl acetate
(d) 1. BOP, DIPEA, DMF,
2. t-butyl N-t-butoxycarbonyl amino acid
   with unprotected OH or SH group (HO/S-AA)
Scheme 52

(a) 1 equivalent LDA/THF at -78 °C (b) R_{26}^2 C(O)Cl acylation
(c) R^8-reagent such as R^8-Br, R^8-OTs, R^8-oxirane,
(d) HCl in dioxane or ethyl acetate
(e) Intermediate (2) or (2b), pH 9-10, H_2O
(f) BF_3 etherate with an R_{23}^{23} -OH or R_{23}^{23} -SH
(g) BF_3 etherate with HOR_{28}^{28} OH, HOR_{28}^{28} SH, HSR_{28}^{28} SH,
    HOR_{28}^{28} NR_{24}^{24} H, or HSR_{28}^{28} NR_{24}^{24} H
(h) H_2, Pd/C, Ammonium Formate
(a) t-Butoxycarbonyl azide, H₂O, dioxane, MgO
(b) H₂O, phosphoric acid
(c) R²²-NH₂, catalytic p-TsOH, toluene, azeotropic distillation
(d) N-chlorosuccinimide, DMF
(e) R⁷-OH, toluene, reflux (f) HCl, dioxane

Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent.
Therefore the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. Compounds containing multiple variations of the structural modifications illustrated in the preceding schemes or the following Examples are also contemplated. It should also be noted that some numerical measurements (e.g. molarity, time, temperature, mass etc.) in the Examples may be estimates, therefore minor experimentation is contemplated for exact values.

All experiments are performed under either dry nitrogen or argon. All solvents and reagents are used without further purification unless otherwise noted. The routine work-up of the reactions involved the addition of the reaction mixture to a mixture of either neutral, or acidic, or basic aqueous solutions and organic solvent. The aqueous layer is extracted n times (x) with the indicated organic solvent. The combined organic extracts is washed n times (x) with the indicated aqueous solutions, dried over anhydrous Na₂SO₄, filtered, concentrated in vacuo, and purified as indicated. Separations by column chromatography are achieved with conditions described by Still. (Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separation with Moderate Resolution. J. Org. Chem., 1978, 43, 2923-2925.)

The hydrochloride salts are made from 1N HCl, HCl in ethanol (EtOH), 2 N in MeOH, or 6 N HCl in dioxane. Thin layer chromatograms are run on 0.25 mm EM precoated plates of silica gel 60 F254. High performance liquid chromatograms (HPLC) are obtained from C-8 or C-18 reverse phase columns which are obtained from several vendors. Analytical samples are dried in an Abderhalden apparatus at either 56°C or 78°C. ¹H NMR spectra are obtained from either General Electric QE-300 or Varian VXR 400 MHz spectrometer. ¹³C NMR spectra is obtained from a Varian spectrometer at 125.8 MHz.
EXAMPLE 1

Ex-1a) To a stirring DMF solution of e-Z-a-Boc-2-methyl-L-Lysine (3.94 g, 10.0 mmol), N-(2-cyanoethyl)-2-aminothiazole (1.46 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-cyanoethyl)-N-(2-thiazolyl)-e-Z-a-Boc-2-methyl-L-Lysinamide.

Ex-1b) N-(2-cyanoethyl)-N-(2-thiazolyl)-e-Z-a-Boc-2-methyl-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-cyanoethyl)-N-(2-thiazolyl)-a-Boc-2-methyl-L-Lysinamide.

Ex-1c) To a 125 mL flask is added 2.60 g (0.01 mol) of N-(2-cyanoethyl)-N-(2-thiazolyl)-a-Boc-2-methyl-L-Lysinamide and 70 mL of water. This solution is adjusted to pH = 9.5
by addition of 2.5 N NaOH. To this solution is added portion wise, 2.15 g of O-methyl chloroacetaldoxime which is prepared immediately prior to use by the reaction of 5.38 g (0.05 mol) of O-methyl acetaldoxime with 8 g (0.060 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The O-methyl chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with MgSO₄, filtration and concentration under 30°C affords the O-methyl chloroacetaldoxime as a pale yellow oil. During the O-methyl chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product is then eluted with 10% aqueous pyridine.

After concentrating, the product produced in Ex-1c is deprotected by allowing it to stand in 2N HCl at 25°C for two hours. Concentrating in vacuo affords L-N-(2-cyanoethyl)-N-(2-thiazolyl)-e-N-(methoxyiminoethyl)-2-methyllysianamide dihydrochloride.

EXAMPLE 2
**Ex-2a)**  To a stirring DMF solution of e-Z-a-Boc-2-methyl-L-Lysine (3.94 g, 10.0 mmol), N,N-dimethyl-N’-(2-pyridyl)hydrazine dihydrochloride (2.31 g, 10.5 mmol), 2.53 g triethylamine (0.025 mol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-dimethylamino)-N-(2-pyridyl)-e-Z-a-Boc-2-methyl-L-Lysinamide.

**Ex-2b)**  N-(2-dimethylamino)-N-(2-pyridyl)-e-Z-a-Boc-2-methyl-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-dimethylamino)-N-(2-pyridyl)-a-Boc-2-methyl-L-Lysinamide.

**Ex-2c)**  To a 125 mL flask is added 2.60 g (0.01 mol) of N-(2-dimethylamino)-N-(2-pyridyl)-a-Boc-2-methyl-L-Lysinamide and 70mL of DMF. To this solution is added 2.19 g of methyl acetimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) was added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product, is then eluted with 10% aqueous pyridine.
After concentrating, the product produced in **Ex-2c** is deprotected by allowing it to stand in 2N HCl at 25°C for two hours. Concentrating in vacuo afforded L-N-(2-dimethylamino)-N-(2-pyridyl)-e-N-(iminoethyl)-2-methyl-L-lysaminamide tetrahydrochloride.

![Chemical structure]

**EXAMPLE 3**

10 **Ex-3a)** To a stirring DMF solution of a-Z-S-(N-Boc-2-aminoethyl)-2-methyl-L-Cysteine (4.12 g, 10.0 mmol), N-(2-hydroxyethyl)-N-(2-thiazolyl)amine (1.39 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(N-Boc-2-aminoethyl)-2-methyl-L-Cysteinamide.

**Ex-3b)** N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(N-Boc-2-aminoethyl)-2-methyl-L-Cysteinamide is then dissolved in trifluoroacetic acid and allowed to stand at room
temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-aminoethyl)-2-methyl-L-Cysteinamide trifluoroacetate.

5 **Ex-3c** To a 125 mL flask is added (10 mmol) of N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-aminoethyl)-2-methyl-L-Cysteinamide and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.34 g of chloroacetaldoxime which is prepared immediately prior to use by the reaction of 3.55 g (0.06 mol) of acetaldoxime with 10.4 g (0.078 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with MgSO₄,

filtration and concentration under 30°C affords the chloroacetaldoxime as a pale yellow oil. During the chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Z-protected product is then eluted with 10% aqueous pyridine and lyophilized to remove solvent.

**Ex-3d** N-(2-hydroxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-(N-oximinoethyl)amino)ethyl)-2-methyl-L-Cysteinamide is dissolved in 25 ml of acetic anhydride containing a 0.1 g pyridine. After standing at room temperature for 2 hours, the reaction mixture is concentrated in vacuo to give N-(2-acetoxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide.

N-(2-acetoxyethyl)-N-(2-thiazolyl)-a-Z-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide is dissolved in 30% HBr in acetic acid to remove the Z-
function generating the amino product \( N-(2\text{-acetoxyethyl})-N-(2\text{-thiazolyl})-S-(2-(N-(2\text{-acetoxyiminoethyl})amino)ethyl)-2\text{-methyl-L-Cysteinamide.} \)

**EXAMPLE 4**

**Ex-4a)** To a stirring DMF solution of \( a-Z-S-(N\text{-Boc-2-aminoethyl})-2\text{-methyl-L-Cysteine} \) (4.12 g, 10.0 mmol), 4-aminopyridine (1.00 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added \([(N,N\text{-dimethylamino)propyl} ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving \( N-(4\text{-pyridyl})- a-Z-S-(N\text{-Boc-2-aminoethyl})-2\text{-methyl-L-Cysteinamide.} \)

**Ex-4b)** \( N-(4\text{-pyridyl})- a-Z-S-(N\text{-Boc-2-aminoethyl})-2\text{-methyl-L-Cysteinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give \( N-(4\text{-pyridyl})- a-Z-S-(2\text{-aminoethyl})-2\text{-methyl-L-Cysteinamide trifluoroacetate.} \)

**Ex-4c)** To a 125 mL flask is added (10 mmol) of \( N-(4\text{-pyridyl})- a-Z-S-(2\text{-aminoethyl})-2\text{-methyl-L-Cysteinamide} \) and 70 mL of DMF. To this solution is added 4.14 g of methyl \( N-\)
Z-acetimidate. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Z-protected product is then eluted with 10% aqueous pyridine.

Ex-4d) N-(4-pyridyl)-α-Z-S-(2-(N-(N-Z-iminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide (0.005 mol) is thoroughly dried and dissolved in 25 ml of anhydrous THF. To the THF solution cooled to -78°C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of acetyl chloride is added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-acetyl-N-(4-pyridyl)-α-Z-S-(2-(N-(N-Z-iminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide.

N-acetyl-N-(4-pyridyl)-α-Z-S-(2-(N-(N-Z-iminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-functions generating the amino product N-acetyl-N-(4-pyridyl)-S-(2-(iminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide.
**Example 5**

**Ex-5a)** To a stirring DMF solution of a-Z-e-Boc-2-methyl-L-Lysine (3.94 g, 10.0 mmol), N-(phenyl)-2-aminoimidazole (1.67 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(phenyl)-N-(2-imidazolyl)-a-Z-e-Boc-2-methyl-L-Lysinamide.

**Ex-5b)** N-(phenyl)-N-(2-imidazolyl)-a-Z-e-Boc-2-methyl-L-Lysinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(phenyl)-N-(2-imidazolyl)-a-Z-2-methyl-L-Lysinamide trifluoroacetate.

To a 125 mL flask is added (10 mmol) of N-(phenyl)-N-(2-imidazolyl)-a-Z-2-methyl-L-Lysinamide and 70mL of DMF. To this solution is added 1.50g of methyl acetimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction
mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-(phenyl)-N-(2-imidazolyl)-a-Z-e-(1-iminoethyl)-2-methyl-L-Lysinamide dihydrochloride is then eluted with 10% aqueous pyridine.


Ex-5d) N-(phenyl)-N-(2-imidazolyl)-a-Z-e-(N-Boc-1-iminoethyl)-2-methyl-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(phenyl)-N-(2-imidazolyl)-e-(N-Boc-1-iminoethyl)-2-methyl-L-Lysinamide.

N-(phenyl)-N-(2-imidazolyl)-e-(N-Boc-1-iminoethyl)-2-methyl-L-Lysinamide is dissolved in ethanol. The solution is cooled in an ice bath. Triethylamine (TEA) (1 mL) is added, followed by 1,1-dicyanoethene. The reaction is allowed to warm to room temperature. Upon completion, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column giving, N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(N-Boc-1-iminoethyl)-2-methyl-L-Lysinamide. This material is used in example 6.
Example 6

After concentrating, N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(N-Boc-1-iminoethyl)-2-methyl-L-Lysinamide (prepared in example 5) is deprotected by allowing it to stand in dioxane and 2N HCl at 25°C for three hours. The reaction mixture is then concentrated in vacuo to give N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(1-iminoethyl)-2-methyl-L-lysinamide trihydrochloride.

Example 8

Ex-8a) e-Amino-a-hydroxyhexanoic acid (1.47 g, 10 mmol) is allowed to stir with t-butoxycarbonylazide (1.49 g, 10.5 mmol) and MgO (0.47 g, 10.5 mmol) in dioxane/water.
solution. Upon completion, the magnesium salts are removed by filtration. The e-(N-Boc-amino)-a-hydroxy hexanoic acid solution is cooled in an ice bath and treated with acetic anhydride (1.07 g, 10.5 mmol) and triethyl amine (TEA) (1.06 g, 10.5 mmol) and stirred. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving e-(N-Boc-amino)-a-(acetoxy)hexanoic acid.

**Ex-8b)** To a stirring DMF solution of e-(N-Boc-amino)-a-(acetoxy) hexanoic acid (2.68 g, 9 mmol), N-5-tetrazoyl-N-methoxyamine hydrochloride (1.53 g, 9.5 mmol), and 1-hydroxybenzotriazole hydrate (1.31 g, 9.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.74 g, 9.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methoxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-(acetoxy) hexanamide.

**Ex-8c)** N-methoxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-(acetoxy) hexanamide (2.82 g, 8 mmol) is dissolved in ethanol and treated with sodium hydroxide (0.3 g, 8 mmol). When the acetyl group is removed the mixture is concentrated in vacuum and passed through a reverse phase chromatographic column, giving N-methoxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-hydroxyhexanamide.

**Ex-8d)** N-methoxy-N-(5-tetrazoyl)-e-(N-Boc-amino)-a-hydroxy hexanamide (2.32 g, 8 mmol) is dissolved in DMSO and treated with 1,3-dicyclohexylcarbodiimide (DCC) (1.6 g, 8 mmol) and phosphoric acid. The reaction is stirred at room temperature. Upon completion, methylene chloride is added to the mixture and it is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer
is dried over MgSO₄, filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column, giving N-methoxy-N-((5-tetrazoyl)-e-(N-Boc-amino)-2-oxohexanamide.

Ex-8e) N-methoxy-N-((5-tetrazoyl)-e-(N-Boc-amino)-2-oxohexanamide (2.22 g, 8 mmol) is dissolved in ethanol and treated with hydroxylamine hydrochloride (0.6 g, 8 mmol) and sodium carbonate (1 g). The reaction mixture is filtered and concentrated in vacuum, giving crude N-methoxy-N-((5-tetrazoyl)-e-(N-Boc-amino)-2-oximinohexanamide.

Ex-8f) N-methoxy-N-((5-tetrazoyl)-e-(N-Boc-amino)-2-oximino hexanamide is cooled in an ice bath and 1.0M borane-tetrahydrofuran complex (8.5 mL) added dropwise. When addition is complete, the reaction is allowed to warm to room temperature. Upon complete reduction 1 mL of water is added. The reaction is concentrated at reduced pressure. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. N-methoxy-N-((5-tetrazoyl)-e-(N-Boc-amino)-2-oximinohexanamide is then eluted with 10% aqueous pyridine.

Ex-8g) After concentrating, the product is treated with one equivalent of acetic anhydride (0.82 g, 8 mmol) and triethyl amine (TEA) (0.80 g, 8 mmol) and stirred. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-methoxy-N-((5-tetrazoyl)-e-(N-Boc-amino)-a-(N-hydroxy-N-acetamido)hexanamide.

To a 125 mL flask is added 2.08 g (7 mmol) N-methoxy-N-(5-tetrazoyl)-e-amino-a-(N-hydroxy-N-acetamido)hexanamide hydrochloride and 50 mL of DMF. To this solution is added 1.05 g of methyl acetimidate hydrochloride. Triethylamine (TEA) (2.03 g, 20 mmol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-methoxy-N-(5-tetrazoyl)-e-(N-(1-iminoethyl))amino-a-(N-hydroxy-N-acetamido)hexanamide is then eluted with 10% aqueous pyridine and solvents removed and compound dried.

Example 10

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\begin{align*}
\text{Example 10}
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e-(N-Boc-amino)-a-(acetoxy)hexanoic acid is prepared as in example 8.

\textbf{Ex-10a)} To a stirring DMF solution of e-(N-Boc-amino)-a-(acetoxy) hexanoic acid (2.97 g, 10 mmol), 2-aminothiazole (1.05 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After
stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-a-(acetoxy)hexanamide.

Ex-10b) N-(2-Thiazolyl)-e-(N-Boc-amino)-a-(acetoxy)hexanamide (3.5 g, 10 mmol) is dissolved in ethanol and treated with sodium hydroxide (4.0 g, 10 mmol). When the acetyl group is removed, the mixture is concentrated in vacuum and passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-a-(hydroxy)hexanamide.

Ex-10c) N-(2-Thiazolyl)-e-(N-Boc-amino)-a-(hydroxy)hexanamide (3.0 g, 9 mmol) is dissolved in DMSO and treated with 1,3-dicyclohexylcarbodiimide (DCC) (1.8 g, 9 mmol) and phosphoric acid. The reaction is stirred at room temperature. Upon completion, methylene chloride is added to the mixture, and it is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer is dried over MgSO4, filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-2-oxohexanamide.

Ex-10d) N-(2-Thiazolyl)-e-(N-Boc-amino)-2-oxohexanamide (2.8 g, 9 mmol) is dissolved in ethanol and treated with methoxyamine hydrochloride (0.78 g, 9 mmol) and sodium carbonate (1 g). Upon completion, the reaction mixture is filtered and concentrated in vacuum, giving crude N-(2-thiazolyl)-e-(N-Boc-amino)-2-methoxyiminohexanamide.

Ex-10e) N-(2-Thiazolyl)-e-(N-Boc-amino)-2-methoxyiminohexanamide (prepared in example 9) is cooled in an ice bath and 1.0M borane-tetrahydrofuran complex (9.5 mL) added dropwise. When addition is complete, the reaction is allowed to warm to room temperature. Upon complete reduction 1 mL of water is added. The reaction is
concentrated in vacuum. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. N-(2-thiazolyl)-e-(N-Boc-amino)-2-methoxyaminohexanamide is then eluted with 10% aqueous pyridine.

**Ex-10f** After concentrating, the product is cooled in an ice bath, treated with one equivalent of acetic anhydride (0.92 g, 9 mmol) and triethyl amine (TEA) (0.90 g, 9 mmol), stirred, and allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-(2-thiazolyl)-e-(N-Boc-amino)-a-(N-methoxyacetamido)hexanamide.

**Ex-10g** N-(2-Thiazolyl)-e-(N-Boc-amino)-a-(N-methoxy-N-acetamido)hexanamide is deprotected by allowing it to stand in dioxane and 2N HCl at 25°C for two hours. Concentrating in vacuo affords N-(2-thiazolyl)-e-(amo)-a-(N-methoxyacetamido)hexanamide hydrochloride.

To a 125 mL flask is added 3.01 g (8 mmol) of afforded N-(2-thiazolyl)-e-(amo)-a-(N-methoxyacetamido)hexanamide hydrochloride and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.49 g of chloroacetaldoxime which is prepared immediately prior to use by the reaction of 5.38 g (0.05 mol) of acetaldoxime with 8 g (0.060 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with MgSO₄, filtration and concentration under 30°C afforded the chloroacetaldoxime as a pale yellow oil. During the chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH =
7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-[(2-thiazolyl)-e-(N-(1-oximinoethyl)amino)-a-(N-methoxyacetamido)hexanamide is then eluted with 10% aqueous pyridine. The solvents are removed, and the compound dried.

Example 11

10 **Ex-11a** a-[(N-Boc)-S-(N-Z-2-aminoethyl)-2-methyl-D,L-Homocysteine (4.55 g, 11 mmol) is coupled with 2-aminoimidazole (0.95 g, 11.5 mmol) following the procedure used in **Ex-1a**. The result is N-[(2-imidazolyl)- a-[(N-Boc)-S-(N-Z-2-aminoethyl)-2-methyl-D,L-Homocysteinateamide.

15 **Ex-11b** N-[(2-Imidazolyl)- a-[(N-Boc)-S-(N-Z-2-aminoethyl)-2-methyl-D,L-homocysteinateamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed.
The reaction mixture is then concentrated in vacuo to give N-(2-imidazoly1)-S-(N-Z-2-aminoethyl)-2-methyl-D,L-Homocysteinamide trifluoroacetate.

Ex-11c) N-(2-Imidazolyl)-S-(N-Z-2-aminoethyl)-2-methyl-D,L-homocysteinamide (10 mmol) is cooled in an ice bath and treated with 4-morpholinomethylbenzoyl chloride (2.50 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol) and stirred. The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-(2-imidazolyl)-S-(N-Z-2-aminoethyl)-a-N-(4-morpholinomethylbenzoyl)-2-methyl-D,L-homocysteinamide.

Ex-11d) N-(2-imidazolyl)-S-(N-Z-2-aminoethyl)-a-N-(4-morpholinomethylbenzoyl)-2-methyl-D,L-homocysteinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-imidazolyl)-S-(2-aminoethyl)-a-N-(4-morpholinomethylbenzoyl)-2-methyl-D,L-homocysteinamide.

To a 125 mL flask is added 4.43 g (10 mmol) of afforded N-(2-imidazolyl)-S-(2-aminoethyl)-a-N-(4-morpholinomethylbenzoyl)-2-methyl-D,L-homocysteinamide and 70mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.23 g of 1-chloro-2-fluoroacetaldoxime which is prepared immediately prior to use by the reaction of 5.38 g (0.05 mol) of 2-fluoroacetaldoxime with 8 g (0.060 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The 1-chloro-2-fluoroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with MgSO₄, filtration and concentration under 30°C affords 1-chloro-2-fluoro
acetaldoxime as a pale yellow oil. During 1-chloro-2-fluoroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-[(2-imidazoly1)-S-(2-(N-(2-fluoro-1-oximinoethyl)amino)ethyl)-a-N-(4-morpholinomethylbenzoyl)]-2-methyl-D,L-homocysteinamide is then eluted with 10% aqueous pyridine. The solvents are removed, and the compound dried.

Example 12

Ex-12a) d-Z-a-(N-Boc)-D,L-2,5-Dimethylornithine (4.19 g, 11 mmol) is coupled with 3-aminoquinucilidine (1.45 g, 11.5 mmol) following the procedure used in Ex-1a. The result is N-(3-quiniclidinyl)-d-Z-a-(N Boc)-D,L-2,5-dimethylornithinamide.

Ex-12b) N-(3-Quiniclidinyl)-d-Z-a-(N-Boc)-D,L-2,5dimethylornithinamide is then dissolved in trifluoroacetic acid and allowed to stand at room
temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-\((3\text{-quiniclidinyl})\)-d-Z-D,L-2,5-dimethylornithinamide trifluoroacetate.

**Ex-12c** The product N-\((3\text{-quiniclidinyl})\)-d-Z-D,L-2,5-dimethylornithinamide (10 mmol) is cooled in an ice bath and treated with methylchloroformate (0.97 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving N-\((3\text{-quiniclidinyl})\)-d-Z-a-(N-methoxyformyl)-D,L-2,5-dimethylornithinamide.

**Ex-12d** N-\((3\text{-quiniclidinyl})\)-d-Z-a-(N-methoxyformyl)-D,L-2,5-dimethylornithinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-\((3\text{-quiniclidinyl})\)-a-(N-methoxyformyl)-D,L-2,5-dimethylornithinamide.

To a 125 mL flask is added 3.02 g (9 mmol) N-\((3\text{-quiniclidinyl})\)-a-(N-methoxyformyl)-D,L-2,5-dimethylornithinamide and 50 mL of DMF. To this solution is added 2.57 g of methyl cyclopropylformimidate hydrochloride. Triethylamine (TEA) (1.82 g, 18 mmol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. N-\((3\text{-quiniclidinyl})\)-d-N-(1-imino-1-cyclopropylmethyl)-a-(N-methoxyformyl)-D,L-2,5-
dimethylornithinamide is then eluted with 10% aqueous pyridine and solvents removed and compound dried.

Example 13

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Ex-13a) a-(N-Boc)-ortho-(N-Z-aminomethyl)-2-methylphenylalanine (4.70 g, 11 mmol) is coupled with a-amino-g-butyrolactone hydrobromide (2.07 g, 11.5 mmol) following the procedure used in Ex-1a. The result is N-(2-g-butyrolactone)-a-(N-Boc)-ortho-(N-Z-aminomethyl)-2-methylphenylalaninamide.

Ex-13b) N-(2-g-Butyrolactone)-a-(N-Boc)-ortho-(N-Z-aminomethyl)-2-methylphenylalaninamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-g-butyrolactone)-ortho-(N-Z-aminomethyl)-2-methylphenylalaninamide trifluoroacetate.

Ex-13c) N-(2-g-Butyrolactone)-ortho-(N-Z-aminomethyl)-2-methylphenylalaninamide (10 mmol) is cooled to -78°C and treated with methanesulfonyl chloride (1.20 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material
is passed through a reverse phase chromatographic column, giving N-(2-g-butyrolactone)-a-(N-methansulfonyl)-ortho-(N-Z-aminomethyl)-2-methylphenylalaninamide.

**Ex-13d)** N-(2-g-Butyrolactone)-a-(N-methansulfonyl)-ortho-(N-Z-aminomethyl)-2-methylphenylalaninamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-g-butyrolactone)-a-(N-methansulfonyl)-ortho-(aminomethyl)-2-methylphenylalaninamide.

To a 125 mL flask is added 3.68 g (10 mmol) of afforded N-(2-g-butyrolactone)-a-(N-methansulfonyl)-ortho-(aminomethyl)-2-methylphenylalaninamide and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.34 g of chloroacetaldoxime which is prepared immediately prior to use by the reaction of 3.55 g (0.06 mol) of acetaldoxime with 10.4 g (0.078 mol) of N-chlorosuccinimide in 65 mL of N,N-dimethylformamide at 0°C. The chloroacetaldoxime is isolated after three hours by extracting into diethyl ether and washing with aqueous NaCl. Drying with MgSO₄, filtration and concentration under 30°C affords chloroacetaldoxime as a pale yellow oil. During chloroacetaldoxime addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-(2-g-butyrolactone)-a-(N-methansulfonyl)-ortho-(N-(1-oximoethyl))aminomethyl)-2-methylphenylalaninamide is then eluted with 10% aqueous pyridine. The solvents are removed, and the compound dried.
**Example 14**

**Ex-14a** 3-(5-(N-Z-Aminomethyl)thiophenyl)-2-(N-Boc-amino)-2-methylpropionic acid (4.78 g, 11 mmol) is coupled with 2-aminopyrimidine (1.09 g, 11.5 mmol) following the procedure used in **Ex-1a**. The result is N-(2-pyrimidinyl)-3-(5-(N-Z-Aminomethyl)thiophenyl)-2-(N-Boc-amino)-2-methylpropionamide.

**Ex-14b** N-(2-pyrimidinyl)-3-(5-(N-Z-Aminomethyl)thiophenyl)-2-(N-Boc-amino)-2-methylpropionamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-(2-pyrimidinyl)-3-(5-(N-Z-Aminomethyl)thiophenyl)-2-amino-2-methylpropionamide trifluoroacetate.

**Ex-14c** The product N-(2-pyrimidinyl)-3-(5-(N-Z-Aminomethyl)thiophenyl)-2-amino-2-methylpropionamide trifluoroacetate is cooled in an ice bath and treated with methoxyacetyl chloride (1.14 g, 10.5 mmol) and triethyl amine (TEA) (2.1 g, 21 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed
through a reverse phase chromatographic column, giving the product N-(2-pyrimidinyl)-3-(5-(N-Z-
Aminomethyl)thiophenyl)-2-acetamido-2-methylpropionamide.

Ex-14d) N-(2-pyrimidinyl)-3-(5-(N-Z-
Aminomethyl)thiophenyl)-2-acetamido-2-methylpropionamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-(2-
pyrimidinyl)-3-(5-(aminomethyl)thiophenyl)-2-acetamido-2-
methylpropionamide.

To a 125 mL flask is added 3.02 g (9 mmol) N-(2-
pyrimidinyl)-3-(5-(aminomethyl)thiophenyl)-2-acetamido-2-
methylpropionamide and 50 mL of DMF. To this solution is added 1.97 g of methyl acetimidate hydrochloride.
Triethylamine (TEA) (2.74 g, 27 mmol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product N-(2-pyrimidinyl)-3-(5-(N-(1-
iminoethyl)amino)methyl)thiophenyl)-2-acetamido-2-
methylpropionamide is then eluted with 10% aqueous pyridine and solvents removed and compound dried.
Ex-15a) To a stirring DMF solution of α-Boc-O-(2-(N-Z-amino)ethyl)-2-methyl-L-serine (3.96 g, 10.0 mmol), 2-methylaminopyridine (1.14 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-Z-amino)ethyl)-2-methyl-L-serinamide.

Ex-15b) N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-Z-amino)ethyl)-2-methyl-L-serinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product N-methyl-N-(2-pyridyl)-α-Boc-O-(2-aminoethyl)-2-methyl-L-serinamide.

Ex-15c) To a 125 mL flask was added 2.83 g (0.008 mol) of N-methyl-N-(2-pyridyl)-α-Boc-O-(2-aminoethyl)-2-methyl-L-serinamide and 70mL of DMF. To this solution was added 4.14
g of methyl N-Z-acetimidate. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product is then eluted with 10% aqueous pyridine.

**Ex-15d)** N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide (1.97 g, 0.005 mol) is added to 50 ml of THF containing 1.01 grams of triethylamine. Carbobenzoxy chloride (Z-Cl; 1.03 g, 0.006 mol) is added and stirred at room temperature for 24 hours. The reaction mixture is concentrated in vacuo to remove THF and slurried with 50 ml. methylene chloride. The methylene chloride is washed with water, concentrated in vacuo at 50 °C, and residue purified by chromatography to afford N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide.

**Ex-15e)** N-methyl-N-(2-pyridyl)-α-Boc-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide is then dissolved in trifluoroacetic acid and allowed to stand at room temperature with spectroscopic monitoring until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give N-methyl-N-(2-pyridyl)-O-(2-(N-(N-Z-iminoethyl)amino)ethyl)-2-methyl-L-serinamide trifluoroacetate.

**Ex-15f)** N-methyl-N-(2-pyridyl)-O-(2-(N-(N-Z-iminoethyl)amino)ethyl)-2-methyl-L-serinamide trifluoroacetate is added to 50 ml of toluene in 100 ml reaction flask. After adding 0.761 g of p-toluenesulfonic acid and 0.504 g (0.006 mol) cyclopentanone, the reaction
mixture is refluxed with azeotropic distillation complete removal of water using a Dean-Stark trap. After cooling, the solvent and excess cyclopentanone is removed in vacuo to give an essentially quantitative yield of the imine N-methyl-N-(2-pyridyl)-α-(N-cyclopentylene)-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide toluenesulfonate salt.

**Ex-15g)** N-methyl-N-(2-pyridyl)-α-(N-cyclopentylene)-O-(2-(N-(N-Z-1-iminoethyl)amino)ethyl)-L-serinamide is placed in a mixture with anhydrous toluene, a hydrogenation catalyst such as palladium on carbon, and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to reduce the imine and remove the Z-function generating the p-toluenesulfonate salt of the amino product N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide.

The p-toluenesulfonate salt of N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide (0.003 mol) is placed in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78 °C, 3,3,3-trifluoropropanoic anhydride (0.762g, 0.0032 mol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-α-N-(3,3,3-trifluoropropanoyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide which can be purified if needed chromatographically.
**EXAMPLE 16**

**Ex-16a**) To a stirring DMF solution of α-Z-O-(2-(N-Boc-amino)ethyl)-2-methyl-L-serine (3.96 g, 10.0 mmol), 4-methylaminoimidazole (1.01 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-Boc-amino)ethyl)-2-methyl-L-serinamide.

**Ex-16b**) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-Boc-amino)ethyl)-2-methyl-L-serinamide is dissolved in trifluoroacetic acid and allowed to stand at room temperature with spectroscopic monitoring until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give the amino product N-methyl-N-(4-imidazolyl)-α-Z-O-(2-aminoethyl)-2-methyl-L-serinamide trifluoroacetate.
Ex-16c) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-aminoethyl)-2-
methyl-L-serinamide is converted to N-methyl-N-(4-
imidazolyl)-α-Z-O-(2-(N-(1-oximinoethyl))amino)ethyl)-2-
methyl-L-serinamide as described for the conversion of
product of Ex-2b to product of Ex-2c.

Ex-16d) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-
oximinoethyl)amino)ethyl)-2-methyl-L-serinamide (2.12 g,
0.005 mol) is added to 50 ml of THF containing 1.01 grams
of triethylamine. Methyl chloroformate (0.567 g, 0.006 mol)
is added and stirred at room temperature for 24 hours. The
reaction mixture is concentrated in vacuo to remove THF and
slurried with 50 ml. methylene chloride. The methylene
chloride is washed with water, concentrated in vacuo at 50
°C, and residue purified by chromatography to afford N-
methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-(O-
(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-
serinamide.

Ex-16e) N-methyl-N-(4-imidazolyl)-α-Z-O-(2-(N-(1-(O-
(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-
serinamide is then dissolved in ethanol and is combined
with a hydrogenation catalyst such as palladium on carbon
and hydrogen. This reaction is shaken under pressure for
an extended period of time in a standard Parr hydrogenation
apparatus to give N-methyl-N-(4-imidazolyl)-O-(2-(N-(1-(O-
(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-
serinamide.

Ex-16f) N-methyl-N-(4-imidazolyl)-O-(2-(N-(1-(O-
(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-
serinamide (1.40 g, 0.004 mol) is added to 50 ml of toluene
in 100 ml. reaction flask. After adding 0.761 g of p-
toluenesulfonic acid and 0.546 g (0.005 mol) 2-
acetylpyrrole, the reaction mixture is refluxed with
azeotropically distilled complete removal of water using a
Dean-Stark trap. After cooling, the solvent is removed in
vacuo to give an essentially quantitative yield of the
imine N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrrolylethyleny1))-O-2-N-(1-0-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-2-methyl-L-serinamide toluenesulfonate salt.

5 Ex-16g) N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrrolylethyleny1))-O-2-N-(1-0-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-serinamide toluenesulfonate salt is placed in a mixture with anhydrous toluene, a hydrogenation catalyst such as palladium on carbon, and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to reduce the imine generating the p-toluensulfonate salt of the amino product N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrrolylethyleny1))-O-2-N-(1-0-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-serinamide.

The p-toluensulfonate salt N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrrolylethyleny1))-O-2-N-(1-0-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-2-methyl-L-serinamide (0.003 mol) is placed in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78 °C, ethanesulfonyl chloride (0.412 g, 0.0032 mol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrrolylethyleny1))-O-2-N-(1-0-(methoxycarbonyl) oximino)ethyl)amino)ethyl)-α-(N-ethanesulfonyl)-2-methyl-L-serinamide which can be purified if needed chromatographically.
**Example 17**

**Ex-17a)** \(\alpha\)-Z-O-(2-(N-Boc-amino)ethyl)-2-methyl-L-serine (3.96 g, 10.0 mmol) is reacted with 4-methylaminothiazole (1.20 g, 10.5 mmol) as described in Example 16 to yield N-methyl-N-(4-thiazolyl)-\(\alpha\)-Z-O-(2-(N-Boc-amino)ethyl)-2-methyl-L-serinamide.

**Ex-17b)** N-(4-thiazolyl)-\(\alpha\)-Z-O-(2-(N-Boc-amino)ethyl)-2-methyl-L-serinamide is converted to N-methyl-N-(4-thiazolyl)-\(\alpha\)-Z-O-(2-aminoethyl)-2-methyl-L-serinamide as described in Example 16.

**Ex-17c)** N-methyl-N-(4-thiazolyl)-\(\alpha\)-Z-O-(2-aminoethyl)-2-methyl-L-serinamide is converted to N-methyl-N-(4-thiazolyl)-\(\alpha\)-Z-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide using methyl 2-fluoroacetimidate hydrochloride as described in **Ex-2c**.

**Ex-17d)** N-methyl-N-(4-thiazolyl)-\(\alpha\)-Z-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide is then dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to give N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide.
N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide (1.25 g, 0.004 mol) is reacted with sodium hydroxymethanesulfonate in aqueous solution at a pH of 10 using a procedure described by L. Maier (Phosphorus, Sulfur, Silicon Related Elements (1990), vol. 47, pages 43-46) to form sodium α-N-(N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamido) methanesulfonate.

Example 18

**Ex-18a)** e-Z-a-Boc-2-methyl-L-Lysine (4.56 g, 12 mmol) is reacted with 3(N-methylamino)oxacycloheptane (1.61 g, 12.5 mmol) as described in **Ex-2a** to yield N-methyl-N-(3-oxacycloheptyl)-e-Z-a-Boc-2-methyl-L-Lysinamide.

**Ex-18b)** N-Methyl-N-(3-oxacycloheptyl)-e-Z-a-Boc-2-methyl-L-Lysinamide is then subjected to conditions to remove the Z protecting group as described in **Ex-2b** to give N-methyl-N-(3-oxacycloheptyl)-a-Boc-2-methyl-L-Lysinamide.

**Ex-18c)** The resulting N-methyl-N-(3-oxacycloheptyl)-a-Boc-2-methyl-L-Lysinamide (3.93 g, 11 mmol) is reacted with methyl but-3-eneiminate hydrochloride (2.90 g) as described
in Ex-2c in Example 2 to yield N-methyl-N-(3-oxacycloheptyl)-a-Boc-e-N-(1-imino-3-butenyl)-2-methyl-L-Lysinamide.

Ex-18d) N-Methyl-N-(3-oxacycloheptyl)-a-Boc-e-N-(1-imino-3-butenyl)-2-methyl-L-Lysinamide is then subjected to conditions to remove the Boc protecting group as described in Ex-2d to give N-methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-Lysinamide.

Ex-18e) N-Methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-Lysinamide (3.57 g, 11 mmol) is treated with one equivalent 2,2,2-trichloroethyl chloroformate (2.22 g, 11 mmol) and sodium carbonate in aqueous tetrahydrofuran under the conditions described by D. Gravel in Canadian Journal of Chemistry, 50, 3846, 1972 to give N-methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxyformyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-Lysinamide.

Ex-18f) N-Methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxyformyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-Lysinamide (5.24 g, 10 mmol) is treated with Lawesson's Reagent under the conditions described in Chem. Reviews, 84, 17-30, 1984 and references cited therein. To yield N-methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxythioformyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-thionolysinamide.

Ex-18g) N-Methyl-N-(3-oxacycloheptyl)-a-N-(2,2,2-trichloroethoxythioformyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-thionolysinamide (5.03 g, 10 mmol) is dissolved in acetic acid and treated with zinc dust (0.65g, 10 mmol). After stirring two hours, saturated aqueous sodium carbonate is added. The solids are removed by filtration. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange
column. The column is washed with water. The product N-methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-thionolysinamide is then eluted with 10% aqueous pyridine.

After concentration, the product N-methyl-N-(3-oxacycloheptyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-thionolysinamide is cooled in an ice bath and treated with one equivalent of 2-furanylacetyl chloride (1.4 g, 10 mmol) and stirred at room temperature for 24 hours. The reaction mixture is concentrated in vacuo and slurried with 50 ml methylene chloride. The methylene chloride is washed with water, concentrated in vacuo at 50 °C, and residue purified by chromatography to afford N-methyl-N-(3-oxacycloheptyl)-a-N-(2-furanylacetyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-thionolysinamide.

**Example 19**

20 **Ex-19a)** e-(N-Z-Amino)-a-(N-boc-amino)-2-methylhex-4-eneoic acid (4.54 g, 12 mmol) is reacted with 4-(N-ethylamino)-1,2,3-triazole (1.40 g, 12.5 mmol) using the conditions to prepare as describe in **Ex-1a** in Example 1 to
yield N-ethyl-N-(4-(1,2,3-triazolyl))-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhex-4-enamide.

**Ex-19b)** N-ethyl-N-(4-(1,2,3-triazolyl))-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhex-4-enamide is then subject to conditions to remove the Z protecting group as described in **Ex-1b** to N-ethyl-N-(4-(1,2,3-triazolyl))-e-amino-a-(N-Boc-amino)-2-methylhex-4-enamide.

**Ex-19c)** The resulting N-ethyl-N-(4-(1,2,3-triazolyl))-e-amino-a-(N-Boc-amino)-2-methylhex-4-enamide (3.95 g, 11 mmol) is reacted with chloro 1-(2-fluorocyclopropyl)formaldoxime (3.08 g) using the process described in **Ex-1c** to yield N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-(N-Boc-amino)-2-methylhex-4-enamide.

**Ex-19d)** N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-a-(N-Boc-amino)-2-methylhex-4-enamide is then subject to conditions to remove the Boc protecting group as described in **Ex-1d** to give N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-amino-2-methylhex-4-enamide.

**Ex-19e)** N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-amino-2-methylhex-4-enamide (4.87 g, 11 mmol) is treated with one equivalent trichloroethyl chloroformate (2.29 g, 11 mmol) and sodium carbonate in aqueous tetrahydrofuran under the conditions described by D. Gravel in Canadian Journal of Chemistry, 50, 3846, 1972 to give N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(2,2,2-trichloroethoxyformyl)amino-2-methylhex-4-enamide.
Ex-19f) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(2,2,2-trichloroethoxyformyl)amino-2-methylhex-4-enamide (6.29 g) is treated with Lawesson's Reagent under the conditions described in Chem. Reviews, 84, 17-30, 1984 and references cited therein, to yield N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(2,2,2-trichloroethoxythionoformyl)amino-2-methyl-thionohex-4-enamide.

Ex-19g) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(2,2,2-trichloroethoxythionoformyl)amino-2-methyl-thionohex-4-enamide (5.40 g, 10 mmol) is dissolved in acetic acid and treated with zinc dust (0.65 g, 10 mmol). After stirring two hours, saturated aqueous sodium carbonate is added. The solids are removed by filtration. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-amino-2-methyl-thionohex-4-enamide is then eluted with 10% aqueous pyridine.

Ex-19h) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-amino-2-methyl-thionohex-4-enamide (3.32 g, 9 mmol) is added to 50 mL of toluene in 100 mL reaction flask. After adding 1.71 g of p-toluenesulfonic acid and 2.17 g (14 mmol) 3-cyclopentenyl (thiomethyl)methyl ketone, the reaction mixture is refluxed with azeotropic distillation for complete removal of water using a Dean-Stark trap. After cooling, the solvent and excess 3-cyclopentenyl methoxymethyl ketone are removed in vacuo to give an essentially quantitative yield of the imine N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(1-cyclopentyl-2-methylthioethenyl)amino-2-methyl-thionohex-4-enamide toluenesulfonate salt.
Ex-19i) N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(1-(1-cyclopentyl-2-methylthioethenyl))amino-2-methyl-thionohex-4-enamide toluenesulfonate salt is dissolved in methanol and treated with 1.0M sodium cyanoborohydride in THF (9.1 mL) and potassium hydroxide using the conditions described by R. F. Borch in *Organic Synthesis, 52, 124, 1972* to give, the product N-ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(1-(1-cyclopentyl-2-methylthioethyl))amino-2-methyl-thionohex-4-enamide.

N-Ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(1-(1-cyclopentyl-2-methylthioethyl))amino-2-methyl-thionohex-4-enamide (3.94g, 0.008 mol) is place in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling in an ice bath, 2-cyanoproponyl chloride (0.99 g, 8.5 mmol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-Ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopropyl)oximinomethyl)amino-2-N-(1-(1-cyclopentyl-2-methylthioethyl))-2-cyanopropanamido-2-methyl-thionohex-4-enamide which can be purified if needed chromatographically.
Ex-20a) e-(N-Z-Amino)-a-(N-Boc-amino)-2-methylpent-3-ynoic acid (3.99 g, 11 mmol) is reacted with 5-aminotetrazole hydrochloride (1.40 g, 11.5 mmol) using the processed described in Ex-1a to yield N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylpent-3-ynameide.

Ex-20b) N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylpent-3-ynameide is then subject to conditions to remove the Z protecting group as described in Ex-1b to give N-(5-tetrazolyl)-e-amino-a-(N-Boc-amino)-2-methylpent-3-ynameide.

Ex-20c) The resulting N-(5-tetrazolyl)-e-amino-a-(N-Boc-amino)-2-methylpent-3-ynameide (3.24 g, 10 mmol) is reacted with chloroacetaldoxime (1.63 g) using the processed described in Ex-1c to yield N-(5-tetrazolyl)-e-N-(1-oximinoethyl)amino-a-(N-Boc-amino)-2-methylpent-3-ynameide.

Ex-20d) N-(5-tetrazolyl)-e-N-(1-oximinoethyl)amino-a-(N-Boc-amino)-2-methylpent-3-ynameide is dissolved in 30 mL of propionic anhydride containing 0.1 g of pyridine. After standing at room temperature for 2 hours, the reaction mixture is concentrated in vacuo to give N-(5-tetrazolyl)-e-N-(1-(O-propionyloximino)ethyl)amino-a-(N-Boc-amino)-2-methylpent-3-ynameide.
Ex-20e) N-(5-tetrazolyl)-e-N-(1-(O-propionylximino)ethyl)amino-a-(N-Boc-amino)-2-methylpent-3-ynamide (4.10 g, 10 mmol) is dissolved in THF and cooled to -78°C. Two equivalents of lithium diisopropylamine (LDA) 2.0M solution (10 mL) is added dropwise over a period of 20 minutes. Phosgene (0.998 g, 10.1 mmol) is added through a gas inlet tube over 30 minutes. After the mixture is allowed to warm to room temperature, 1 mL of water is added. The solvents are removed in vacuo and the product purified by chromatography to give 3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionylximino)ethyl)amino)prop-1-ynyl)-5-methyl-1-(N-Boc)-hydantoin.

3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionylximino)ethyl)amino)prop-1-ynyl)-5-methyl-1-(N-Boc)-hydantoin is then dissolved in trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give 3-N-(5-tetrazolyl)-5-(3-(N-(1-(O-propionylximino)ethyl)amino)prop-1-ynyl)-5-methyl-hydantoin trifluoroacetate.

![Chemical Structure]

Example 21
Ex-21a) a-(N-Boc)-O-(N-Z-2-aminoethyl)-2-methyl-L-serine (4.21 g, 11 mmol) is reacted with 2-aminoimidazole (0.95 g, 11.5 mmol) using the process described in Ex-2a to yield N-(2-imidazolyl)-a-(N-boc)-O-(N-Z-2-aminoethyl)-2-methyl-L-serinamide.

Ex-21b) N-(2-Imidazolyl)-a-(N-Boc)-O-(N-Z-2-aminoethyl)-2-methyl-L-serinamide is then subjected to conditions to remove the Z protecting group as described in Ex-2b to give N-(2-imidazolyl)-a-(N-Boc)-O-(2-aminoethyl)-2-methyl-L-serinamide.

Ex-21c) The resulting N-(2-imidazolyl)-a-(N-Boc)-O-(2-aminoethyl)-2-methyl-L-serinamide (3.36 g, 10 mmol) is reacted with methyl acetimidate hydrochloride (1.13 g) using the process in Ex-2c to yield N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide.

Ex-21d) N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide (3.68 g, 10 mmol) is dissolved in THF and cooled to -78°C. To the cooled mixture is added one equivalent of 2.0M lithium diisopropylamide solution (5 mL) over 30 minutes. One equivalent of 2-bromo-1,1-dimethoxy-4-thiomethylbutane (2.43 g, 10 mmol) dissolved in THF is added to the cooled mixture over 20 minutes. The mixture is allowed to warm to room temperature and 1 mL of water is added. The solvents are removed in vacuo and the product purified by chromatography to give N-(1-dimethoxy-4-thiomethyl-2-butyl)-N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide.

N-(1-dimethoxy-4-thiomethyl-2-butyl)-N-(2-imidazolyl)-a-(N-boc)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide (5 mmol) is then placed in 50 ml of aqueous 2N HCl. After standing at room temperature until the t-butoxycarbonyl and methoxy groups are removed, the reaction mixture is then concentrated in vacuo to give 1-N-
(2-imidazolyl)-3-(2-(N-(1-iminoethyl)amino)ethoxy)methyl)-3-methyl-6-(2-methiothioethyl)-2-oxo-3,6-dihydropyrazine trihydrochloride.

Example 22

Ex-22a) a-(N-Boc)-S-(N-Z-aminoethyl)-2-methyl-L-cysteine (4.38 g, 11 mmol) is reacted with 5-methylaminotetrazole hydrochloride (1.53 g, 11.5 mmol) using the process described in Ex-2a to yield N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(N-Z-aminoethyl)-2-methyl-L-cysteinamide.

Ex-22b) N-Methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(N-Z-aminoethyl)-2-methyl-L-cysteinamide is then subject to conditions to remove the Z protecting group as described in Ex-2b to give N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(aminoethyl)-2-methyl-L-cysteinamide.

Ex-22c) The resulting N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(aminoethyl)-2-methyl-L-cysteinamide (2.44 g, 10 mmol) is added to 50 mL of water in a 200 mL reaction flask and the pH adjusted to 6-7 with hydrochloric acid. After forming an equilibrium concentration of the imine, N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethyleneamino)ethyl)-2-methyl-L-cysteinamide, by addition of 10 mmol of disodium formylphosphonate while
maintaining a pH of 6-7, 50 ml of methanol is added. The reaction mixture is treated with 1.0M sodium cyanoborohydride in THF (40 mL). The excess borohydride is destroyed, the reaction mixture concentrated to remove organic solvents, and the residue purified by passing it through a reverse phase chromatographic column to give the product N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethylamino)ethyl)-2-methyl-L-cysteinamide.

**Ex-22d**  N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethylamino)ethyl)-2-methyl-L-cysteinamide (8 mmol) is reacted with methyl acetimidate hydrochloride (1.75 g) using the process described in **Ex-2c** to yield N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-2-methyl-L-cysteinamide. N-methyl-N-(5-tetrazolyl)-a-(N-Boc)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-2-methyl-L-cysteinamide is then placed in 50 ml of aqueous 2N HCl. After standing at room temperature until the t-butoxycarbonyl group is removed, the reaction mixture is then concentrated in vacuo to give N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-2-methyl-L-cysteinamide hydrochloride.

N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-2-methyl-L-cysteinamide hydrochloride (5 mmol) is placed in 50 ml water and stirred vigorously with a mixture of 5mmol of N,N-dimethyloctadecylamine in 75 ml of toluene. The aqueous layer is separated and two equivalents of NaOH (10 mmol) is added to generate the disodium salt of N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-2-methyl-L-cysteinamide.
**Example 23**

**Ex-23a)** e-(N-Z-Amino)-a-(N-Boc-amino)-2-methylhexanoic acid (4.56 g, 12 mmol) is reacted with 5-(N-methylamino)tetrazole (1.06 g, 12.5 mmol) using the conditions to prepare on Page 94 in Example 1 to yield N-methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-23b)** N-Methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhexanamide is then subject to conditions to remove the Z protecting group as described in **Ex-1b** to yield N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-23c)** The resulting N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-2-methylhexanamide (3.89 g, 11 mmol) is reacted with methyl acetimidate hydrochloride (2.49 g) using the process in **Ex-2c** to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-23d)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)-2-methylhexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-2d** to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-amino-2-methylhexanamide.
**Ex-23e)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-amino-2-methylhexanamide (3.05 g, 11 mmol) is treated with one equivalent trichloroethyl chloroformate (2.29 g) and sodium carbonate in aqueous tetrahydrofuran under the conditions described by D. Gravel in Canadian Journal of Chemistry 50, 3846, 1972 to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-(N-(2,2,2-trichloroethoxyformyl))amino-2-methylhexanamide.

**Ex-23g)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-(N-(2,2,2-trichloroethoxyformyl))amino-2-methylhexanamide (4.65 g) is treated with Lawesson's Reagent under the conditions described in Chem. Reviews, 84, 17-30, 1984 and references cited therein to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-(N-(2,2,2-trichloroethoxythionoformyl))amino-2-methylthionohexanamide.

**Ex-23g)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-(N-(2,2,2-trichloroethoxythionoformyl))amino-2-methylthionohexanamide (4.84 g, 10 mmol) is dissolved in acetic acid and treated with zinc dust (0.65g, 10 mmol). After stirring two hours, saturated aqueous sodium carbonate is added. The solids are removed by filtration. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-amino-2-methyl-thionohexanamide is then eluted with 10% aqueous pyridine.

N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-amino-2-methyl-thionohexanamide (2.65 g, 9 mmol) is placed in 20 ml of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78 °C, ethyl chloroformate (0.98 g, 9 mmol) in 10 ml anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is
removed in vacuo, 50 ml methylene chloride added along with 20 ml of water. The methylene chloride layer is separated, back washed with water, and concentrated to afford N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-((N-ethoxycarbonyl)amino)-2-methyl-thionohexanamide.

![Molecular structure](image)

**Example 24**

**Ex-24a)**  e-(N-Z-Amino)-a-(N-Boc-amino)-2-methylhexanoic acid (4.56 g, 12 mmol) is reacted with 5-(N-methylamino)tetrazole (1.06 g, 12.5 mmol) using the process in **Ex-2a** to yield N-methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-24b)** N-Methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhexanamide is then subject to conditions to remove the Z protecting group as described in **Ex-2b** to give N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-24c)** The resulting N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-2-methylhexanamide (3.88 g, 11 mmol) is reacted with methyl 2-fluoroacetimidate hydrochloride (2.07) using the process in **Ex-2c** to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)-2-methylhexanamide.
**Ex-24d)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)-2-methylhexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-24d** to N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-amino-2-methylhexanamide.

**Ex-24e)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-amino-2-methylhexanamide (3.09 g, 10 mmol) is placed in 20 mL of anhydrous THF containing 1.01 grams of triethylamine. After cooling to -78°C, trifluoroacetic anhydride (2.17 g, 10.3 mmol) in 10 mL anhydrous THF is added over 20 minutes. After warming to room temperature, the solvent is removed in vacuo to afford N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-trifluoroacetamido-2-methylhexanamide trifluoroacetate.

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-trifluoroacetamido-2-methylhexanamide trifluoroacetate (9 mmol) is dissolved in ethanol and treated with two equivalents of sodium borohydride (0.74 g, 20 mmol). After stirring several hours, the ethanol is removed in vacuo. Upon completion, 50 mL methylene chloride is added along with 20 mL of water. The methylene chloride layer is separated, back washed with water, dried over MgSO₄, and concentrated to afford N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-(N-(2,2,2-trifluoro-1-ethoxyethyl))amino-2-methylhexanamide.
Example 25

**Ex-25a)** a-(N-Z)-S-(N-hydroxy-2-aminoethyl)-2-methyl-L-cysteine methyl ester (3.28 g, 10 mmol) is treated with methyl (N-(benzoyloxyethyl)acetimidate hydrochloride (4.14 g) as described in **Ex-2c** to give a-(N-Z)-S-(2-(1-(N-(benzoyloxyethyl)imino)ethyl)-N-hydroxy)aminoethyl)-2-methyl-L-cysteine methyl ester.

**Ex-25b)** a-(N-Z)-S-(2-(1-(N-(benzoyloxyethyl)imino)ethyl)-N-hydroxy)aminoethyl)-2-methyl-L-cysteine methyl ester (4.63 g, 9 mmol) is dissolved in DMF and treated with N-methyl-5-amino-tetrazole (0.93 g, 9.5 mmol). The mixture is heated until replacement of the methoxy is observed. Upon completion, the reaction mixture is concentrated. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-tetrazolyl)-a-(N-Z)-S-(2-(1-(N-(benzoyloxyethyl)imino)ethyl)-N-hydroxy)aminoethyl)-2-methyl-L-cysteine amide.

N-methyl-N-(5-tetrazolyl)-a-(N-Z)-S-(2-(1-(N-(benzoyloxyethyl)imino)ethyl)-N-hydroxy)aminoethyl)-2-methyl-L-cysteine amide is then subject to conditions to remove the Z protecting group as described in **Ex-2b** to give...
N-methyl-N-(5-tetrazolyl)-S-(2-(1-(N-(benzoyloxy)methyl)imino)ethyl)-N-hydroxy)aminoethyl)-2-methyl-L-cysteinamide.

**Example 26**

**Ex-26a**) a-(N-Z)-e-(N-Boc)-2-methyl-L-Lysine (3.80 g, 10 mmol) is treated with N-methyl-5-amino-tetrazole (0.89 g, 10.5 mmol) using the conditions to prepare **Ex-3a** to yield N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-(N-Boc)-2-methyl-L-Lysine.

**Ex-26b**) N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-(N-Boc)-2-methyl-L-Lysine is then subject to conditions to remove the Boc protecting group as described in **Ex-3b** to give N-methyl-N-(5-tetrazolyl)-a-(N-Z)-2-methyl-L-Lysine.

**Ex-26c**) N-Methyl-N-(5-tetrazolyl)-a-(N-Z)-2-methyl-L-Lysine (3.51 g, 10 mmol) is added to 50 mL of toluene in 100 mL reaction flask. After adding 1.89 g of p-toluenesulfonic acid and 0.93 g (16 mmol) propionaldehyde the reaction mixture is refluxed with azeotropic
distillation for complete removal of water using a Dean-
Stark trap. After cooling, the solvent is removed in vacuo
to give the iminium salt, N-methyl-N-(5-tetrazolyl)-a-(N-

**Ex-26d)** N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-
propylene)-2-methyl-L-Lysine p-toluenesulfonate (9 mmol) is
dissolved in methanol and treated with 1.0M sodium
cyanoborohydride in THF (19 mL) and potassium hydroxide
using the conditions and work-up described by R. F. Borch
in *Organic Synthesis*, 52, 124, 1972 to give the product, N-
methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-propyl)-2-methyl-L-
Lysine.

**Ex-26e)** N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(1-propyl)-
2-methyl-L-Lysine (3.38 g, 8 mmol) is treated with methyl
(N-(benzoyloxymethyl)acetimidate hydrochloride (3.70 g) as
described in **Ex-2c** to give N-methyl-N-(5-tetrazolyl)-a-(N-
Z)-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-
propyl)-2-methyl-L-Lysine.

**Ex-26f)** N-methyl-N-(5-tetrazolyl)-a-(N-Z)-e-N-(2-(1-(N-
(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-2-methyl-L-
Lysine is then subject to conditions to remove the Z
protecting group as in **Ex-2b** to give N-methyl-N-(5-
tetrazolyl)-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-2-methyl-L-Lysine.

N-methyl-N-(5-tetrazolyl)-e-N-(2-(1-(N-
(benzoyloxymethyl)imino)ethyl))- e-N-(1-propyl)-2-methyl-L-
Lysine (3.30 g, 7 mmol) is placed in 20 mL of anhydrous THF
containing 1.01 grams of triethylamine. After cooling to
-78°C, benzoyl chloride (1.01 g, 7.2 mmol) in 10 mL
anhydrous THF is added over 20 minutes. After warming to
room temperature, the solvent is removed in vacuo, 50 mL
methylen chloride is added along with 20 mL of water. The
methylen chloride layer is separated, back washed with
water, dried over MgSO₄, and concentrated to afford N-
methyl-N-(5-tetrazolyl)- a-N-benzoyl- e-N-(2-(1-(N-
(benzoyloxyethyl)iminomethyl)ethyl))- e-N-(1-propyl)-2-methyl-L-Lysine.

**EXAMPLE 27**

**Ex-27a)** To a stirring DMF solution of ε-pnZ-α-Boc-2-methyl-L-Lysine (4.64 g, 10.0 mmol), 1-(4-nitrobenzyloxyethyl)-5-methylaminotetrazole (2.77 g, 10.5 mmol), 2.53 g triethylamine (0.025 mol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-(4-nitrobenzyloxyethyl)tetrazolyl)-ε-pnZ-α-Boc-2-methyl-L-Lysinamide.

**Ex-27b)** N-methyl-N-(5-(4-nitrobenzyloxyethyl)tetrazolyl)-ε-pnZ-α-Boc-2-methyl-L-Lysinamide is then dissolved in 25 mL anhydrous trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is concentrated to dryness.
in vacuo, aqueous sodium carbonate added to neutralize residual acid, and the aqueous solution extracted with methylene chloride to yield N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-2-methyl-L-
LYsinamide.

Ex-27c) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-2-methyl-L-Lysinamide (4.68 g, 8.0 mmol) is placed in admixture with tetrahydrofuran (50 mL) and phthalic anhydride (1.19 g, 8.0 mmol) and heated at reflux until the reaction is complete. Removal of the tetrahydrofuran afforded the phthalimide of N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-ε-pnZ-2-methyl-L-Lysinamide.

Ex-27d) Phthalimide is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of N-chloromethyl-N,N′-trimethylurea was added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-N-phthaloyl-ε-pnZ-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide.

Ex-27e) N-methyl-N-(5-(4-nitrobenzyloxymethyl)tetrazolyl)-α-N-phthaloyl-ε-pnZ-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the pnZ-functions generating the amino product N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide.

Ex-27g) To a 125 mL flask is added 2.36 g (0.005 mol) of N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(N,N′-
trimethylureido-N-methylene)-2-methyl-L-Lysinamide is converted to N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide as described in Ex-17c.

N-methyl-N-(5-(tetrazolyl)-α-N-phthaloyl-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide (1.64 g, 0.003 mol) is dissolved in 25 mL methanol and hydrazine (0.96 g, 0.003 mol) added. After refluxing for 6 hours, the methanol is removed, aqueous 10% hydrochloric acid added to the residue in an ice bath until the pH was 3 to 4, and the precipitated hydrazide removed by filtration. The aqueous solution is concentrated in vacuo to give the dihydrochloride of N-methyl-N-(5-(tetrazolyl)-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide.

**EXAMPLE 28**

**Ex-28a** To a stirring DMF solution of ε-Boc-α-pnZ-2-methyl-L-Lysine (4.64 g, 10.0 mmol), 1-(4-nitrobenzoxymethyl)-5-methylaminotetrazole (2.77 g, 10.5 mmol), 2.53 g triethylamine (0.025 mol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-
dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-(4-nitrobencyloxy)methyl)tetrazolyl)-ε-Boc-α-pnZ-2-methyl-L-Lysinamide.

**Ex-28b)** N-methyl-N-(5-(4-nitrobencyloxy)methyl)tetrazolyl)-ε-Boc-α-pnZ-2-methyl-L-Lysinamide is then dissolved in 25 mL anhydrous trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is concentrated to dryness in vacuo, aqueous sodium carbonate added to neutralize residual acid, and the aqueous solution extracted with methylene chloride to yield N-methyl-N-(5-(4-nitrobencyloxy)methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide.

**Ex-28c)** N-methyl-N-(5-(4-nitrobencyloxy)methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide (4.68 g, 8.0 mmol) is placed in admixture with tetrahydrofuran (50 mL) and phthalic anhydride (1.19 g, 8.0 mmol) and heated at reflux until the reaction is complete. Removal of the tetrahydrofuran affords the phthalimide of N-methyl-N-(5-(4-nitrobencyloxy)methyl) tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide.

**Ex-28d)** Phthalimide is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of N-chloromethyl-N,N′N′-trimethylurea is added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-methyl-N-(5-(4-nitrobencyloxy)methyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-α-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide.
Ex-28e) N-methyl-N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-
ε-N-phthaloyl-α-pnZ-α-N-(N,N′N′-trimethylureido-N-
methylene)-2-methyl-L-Lysinamide is dissolved in 25 mL
methanol and one equivalent of hydrazine added. After
refluxing for 6 hours, the methanol is removed, aqueous 10
% hydrochloric acid added to the residue in an ice bath
until the pH is 7, and the precipitated hydrazide removed
by filtration. The aqueous solution is concentrated in
vacuo to give N-methyl-N-(5-(4-
nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-α-N-(N,N′N′-
trimethylureido-N-methylene)-2-methyl-L-Lysinamide
hydrochloride.

Ex-28f) The N-methyl-N-(5-(4-
nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-α-N-(N,N′N′-
trimethylureido-N-methylene)-2-methyl-L-Lysinamide is
converted to N-methyl-N-(5-(4-nitrobenzyloxy)methyl)
tetrazolyl)-α-pnZ-ε-N-(2-fluoro-1-iminoethyl)-α-N-(N,N′N′-
trimethylureido-N-methylene)-2-methyl-L-Lysinamide as
described in Ex-17c.

N-methyl-N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-ε-N-
(2-fluoro-1-iminoethyl)-α-N-(N,N′N′-trimethylureido-N-
methylene)-2-methyl-L-Lysinamide is dissolved in ethanol
and is combined with a hydrogenation catalyst such as
palladium on carbon and hydrogen. This reaction is shaken
under pressure for an extended period of time in a standard
Parr hydrogenation apparatus to remove the pnZ-functions
generating the amino product N-methyl-N-(5-tetrazolyl)-ε-N-
(2-fluoro-1-iminoethyl)-α-N-(N,N′N′-trimethylureido-N-
methylene)-2-methyl-L-Lysinamide.
**Example 29**

**Ex-29a)** e-(N-Z-Amino)-a-(N-Boc-amino)-2-methylhexanoic acid (3.80 g, 10 mmol) is reacted with 5-(N-methylamino)tetrazole (0.89 g, 10.5 mmol) using the process described in Ex-2a to yield N-methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-29b)** N-Methyl-N-(5-tetrazolyl)-e-(N-Z-amino)-a-(N-Boc-amino)-2-methylhexanamide is then subject to conditions to remove the Z protecting group as described in Ex-2b to N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-29c)** The resulting N-methyl-N-(5-tetrazolyl)-e-(amino)-a-(N-Boc-amino)-2-methylhexanamide (3.14 g, 9 mmol) is reacted with methyl 2-fluoroacetimidate hydrochloride (1.67 g) using the process described in Ex-2c in Example 2 to yield N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)-2-methylhexanamide.

**Ex-29d)** N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-a-(N-Boc-amino)-2-methylhexanamide is then subject to conditions to remove the Boc protecting group as described in Ex-2d to give N-methyl-N-(5-
tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-amino-2-methylhexanamide.

**Ex-29e)** To a stirring DMF solution of N-Boc-phenylalanine (2.25 g, 8.5 mmol), N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-amino-2-methylhexanamide (2.28 g, 8 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl] ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-(N-(N-Boc-phenylalaninyl)amino)-2-methylhexanamide.

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-(N-(N-Boc-phenylalaninyl)amino)-2-methylhexanamide is then subject to conditions to remove the Boc protecting group as described in **Ex-2d** to give in Example 2 to give N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-(N-(phenylalaninyl)amino)-2-methylhexanamide.

**EXAMPLE 30**
Ex-30a) ε-Boc-α-pnZ-2-methyl-L-Lysine (4.64 g, 10.0 mmol) and 1-(4-nitrobenzyloxy)methyl)aminotetrazole (2.62 g, 10.5 mmol) is converted to N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-ε-Boc-α-pnZ-2-methyl-L-Lysinamide analogous to that described in Example 28.

Ex-30b) N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-ε-Boc-α-pnZ-2-methyl-L-Lysinamide is then converted to N-(5-(4-nitrobenzyloxy methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide analogous to that described in Example 28.

Ex-30c) N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide (4.68 g, 8.0 mmol) is then converted to the phthalimide of N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide analogous to that described in Example 28.

Ex-30d) Phthalimide is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of chloromethyl acetate is added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give N-acetoxyethyl-N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-2-methyl-L-Lysinamide

Ex-30e) N-acetoxyethyl-N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-ε-N-phthaloyl-α-pnZ-2-methyl-L-Lysinamide is converted to N-acetoxyethyl-N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide analogous to that described in Example 28.

Ex-30f) N-acetoxyethyl-N-(5-(4-nitrobenzyloxy)methyl)tetrazolyl)-α-pnZ-2-methyl-L-Lysinamide is converted to N-acetoxyethyl-N-(5-(4-
nitrobenzyloxyethyl)tetrazolyl)-α-pnZ-ε-N-(iminoethyl)-2-methyl-L-Lysinamide as described in Ex-2c.

N-acetoxyethyl-N-(5-(4-nitrobenzyloxyethyl)tetrazolyl)-α-pnZ-ε-N-(iminoethyl)-2-methyl-L-Lysinamide is dissolved in ethanol and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the pnZ-functions generating the amino product N-acetoxyethyl-N-(5-tetrazolyl)-ε-N-(iminoethyl)-2-methyl-L-Lysinamide.

(31)

Example 31

Ex-31a) To a 125 mL flask is added 3.14 g (0.011 mol) of e-amino-a-(N-Boc-amino)-2-(cyanomethyl)hexanoic acid and 70 mL of DMF. To this solution is added 2.41 g of methyl aceticidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product e-(N-(1-iminoethyl)amino)-
a-(N-Boc-amino)-2-(cyanomethyl)hexanoic acid is then eluted with 10% aqueous pyridine and thoroughly dried.

**Ex-31b** e-(N-(1-Iminoethyl)amino)-a-(N-Boc-amino)-2-(cyanomethyl)hexanoic acid (3.33 g, 10 mmol) is dissolved in THF and cooled to -78°C. One equivalent of lithium diisopropylamine (LDA) 2.0M solution (5.0 mL) is added dropwise over a period of 20 minutes. Ethyl 2-bromopropionate (1.85 g, 10.3 mmol) is added over 30 minutes. The mixture is allowed to warm to room temperature. The solvents are removed in vacuo, and the product purified by chromatography to give (1-ethoxycarbonyl)ethyl e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)-2-(cyanomethyl)hexanoate.

(1-Ethoxycarbonyl)ethyl e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)-2-(cyanomethyl)hexanoate is then dissolved in anhydrous trifluoroacetic acid and allowed to stand at room temperature until the t-butoxycarbonyl group is removed. The reaction mixture is then concentrated in vacuo to give (1-ethoxycarbonyl)ethyl e-(N-(1-iminoethyl)amino)-a-amin-2-(cyanomethyl)hexanoate trifluoroacetate. This product is refluxed in toluene and sodium carbonate (3 equivalents) to give the cyclized product 3-(4-(N-(1-iminoethyl)amino)butyl)-3-cyanomethyl-6-methylmorpholine-2,5-dione.
Example 32

Ex-32a) To a 125 mL flask is added 3.21 g (0.01 mol) of e-amino-a-(N-Z-amino)-2-(N,N-dimethylaminomethyl)hexanoic acid and 70 mL of DMF. To this solution is added 2.54 g of methyl 2-fluoroacetimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Z-protected product is then eluted with 10% aqueous pyridine.

Ex-32b) e-(N-(2-Fluoroiminoethyl)amino)-a-(N-Z-amino)-2-(N,N-dimethylaminomethyl)hexanoic acid (3.5 g, 9 mmol) is dissolved in THF and cooled to -78°C. Two equivalents of lithium diisopropylamine (LDA) 2.0M solution (9.2 mL) is added dropwise over a period of 20 minutes. Phosgene (0.9 g, 9.3 mmol) is added through a gas inlet tube over 30 minutes. The mixture is allowed to warm to room temperature. The solvents are removed in vacuo, and the product purified by chromatography to give 3-(4-(N-(2-fluoroiminoethyl)amino)butyl)-4-(N-Z)-3-(N,N-dimethylaminomethyl)oxazolidine-2,5-dione.

3-(4-(N-(2-fluoroiminoethyl)amino)butyl)-4-(N-Z)-3-(N,N-dimethylaminomethyl)oxazolidine-2,5-dione is dissolved in ethyl acetate and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function generating the amino product 3-(4-(N-(2-fluoroiminoethyl)amino)butyl)-3-(N,N-dimethylaminomethyl)oxazolidine-2,5-dione.
**Example 33**

**Ex-33a**) To a 125 mL flask is added 3.20 g (0.010 mol) of e-aminoo-a-(N-Boc-amino)-2-(2-methylthioethyl)hexanoic acid and 70 mL of DMF. To this solution is added 2.19 g of methyl acetimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The Boc-protected product e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)-2-(2-methylthioethyl)hexanoic acid is then eluted with 10% aqueous pyridine.

e-(N-(1-iminoethyl)amino)-a-(N-Boc-amino)-2-(2-methylthioethyl)hexanoic acid (3.29 g, 9 mmol), 2-hydroxycyclohexanone dimer (1.03 g, 9 mmol) and 30 mmol of 2,2-dimethoxypropane are dissolved in 50 mL of 2.0M HCl in dioxane. After standing at room temperature for 12 hours, the solvent is removed in vacuo to afford 3-(4-(N-(1-
iminoethyl)amino)butyl)-3-(2-methylthioethyl)-3H,5H,6H,7H,8H-1,4-benzoxazin-2-one dihydrochloride.

Example 34

10 **Ex-34a** e-(N-(2-Fluoroiminoethyl)amino)-a-(N-Z-amino)-2-(N,N-dimethylaminomethyl)hexanoic acid prepared in example 32 (3.82 g, 10 mmol) is dissolved in acetic acid and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the Z-function. The catalyst is removed by filtration and the solvent removed in vacuo to afford the amino product e-(N-(2-fluoroiminoethyl)amino)-a-amino)-2-(N,N-dimethylaminomethyl)hexanoic acid.

15 e-(N-(2-fluoroiminoethyl)amino)-a-amino)-2-(N,N-dimethylaminomethyl)hexanoic acid (10 mmol), 2-hydroxypropanol (0.74 g, 10 mmol) and 30 mmol of 2,2-dimethoxypropane are dissolved in 50 mL of 2.0M HCl in dioxane. After standing at room temperature for 12 hours, the solvent is removed in vacuo to afford 3-(4-(N-(2-fluoroiminoethyl)amino)butyl)-3-(N,N-dimethylaminomethyl)-6-methyl-3H,6H-1,4-oxazin-2-one dihydrochloride.
Example 36

Ex-36a) Dibenzyl 2-(2-(N-Boc-amino)ethoxymethyl)-2-phthalimidomalonate (6.02 g, 10 mmol) is dissolved in ethanol/acetic acid and is combined with a hydrogenation catalyst palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the benzyl esters to give 2-(2-(N-Boc-amino)ethoxymethyl)-2-phthalimidomalonic acid.

Ex-36b) 2-(2-(N-Boc-amino)ethoxymethyl)-2-phthalimidomalonic acid is heated to 150°C until decarboxylation is complete to give 3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropionic acid.

Ex-36c) 3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropionic acid (3.36 g, 9 mmol) is cooled in an ice bath and 1.0M borane-tetrahydrofuran complex (18 mL) added dropwise. When addition is complete, the reaction is allowed to warm to room temperature. When the reduction is complete, excess reagent is destroyed by addition of acetic acid. The reaction is concentrated at reduced pressure. The
crude product is purified by column chromatography on silica gel to yield 3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropanol.

**Ex-36d** 3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropanol (2.8 g, 8 mmol) is dissolved in DMSO and treated with 1,3-dicyclohexylcarbodiimide (DCC) (1.6 g, 8 mmol) and phosphoric acid. The reaction is stirred at room temperature. Upon completion, methylene chloride is added to the mixture and it is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer is dried over MgSO₄, filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column, giving 3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropanol.

**Ex-36e** 3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropanol (1.81 g, 7 mmol) is added to 50 mL of hexane in 100 mL reaction flask. After adding 0.1 g of p-toluenesulfonic acid and 1.6 g (14 mmol) 2-(thiethyl)methanol, the reaction mixture is refluxed with azeotropic distillation for removal of water using a Dean-Stark trap. After cooling, dilute aqueous sodium carbonate (20 mL) is added, the hexane separated, and then concentrated in vacuo to afford 1,1-bis-(2-thienylmethoxy)-3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropane.

**Ex-36f** 1,1-Bis-(2-thienylmethoxy)-3-(2-(N-Boc-amino)ethoxy)-2-phthalimidopropanol is dissolved in 2.0M HCl in acetic acid. The reaction is allowed to stand at 25°C until the Boc group is removed to give, after concentrating in vacuo, 2-(3,3-Bis-(2-thienylmethoxy)-2-phthalimidopropoxy)ethanamine hydrochloride.

**Ex-36g** To a 125 mL flask is added 2.83 g (6 mmol) of 2-(3,3-Bis-(2-thienylmethoxy)-2-phthalimidoproproxy)ethanamine hydrochloride and 70 mL of water. This solution is
adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.15 g of methyl 2-fluroacetimidate. During methyl 2-fluroacetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product N-(2-fluoro-1-iminoethyl)-2-(3,3-Bis-(2-thienylmethoxy)-2-phthalimidopropoxy)ethanamine is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water.

The N-(2-fluoro-1-iminoethyl)-2-(3,3-Bis-(2-thienylmethoxy)-2-phthalimidopropoxy)ethanamine (2.55 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate and is heated to reflux. After complete removal of the phthaloyl protecting group and filtering to remove the phthaloylhydrazide, the methanolic solution is then adjusted to pH = 7.5 with aqueous hydrochloric acid and poured onto a Dowex 50 Cation exchange column. The column is washed with water, and the product N-(2-fluoro-1-iminoethyl)-2-(3,3-Bis-(2-thienylmethoxy)-2-aminopropoxy)ethanamine is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water.

Example 37
**Ex-37a)** Diethyl 2-(4-(N-Boc-amino)but-2-enyl)-2-phthalimidomalonate (10 mmol) is dissolved in ethanol and sodium hydroxide (0.78g, 20 mmol) is added. When the ethyl esters have hydrolyzed, two equivalents of HCl are added through a gas inlet tube. The solvent is removed in vacuo. The sodium chloride is removed by washing with water, and the residue is dried at reduced pressure to give 2-(4-(N-Boc-amino)but-2-enyl)-2-phthalimidomalonic acid.

**Ex-37b)** 2-(4-(N-Boc-amino)but-2-enyl)-2-phthalimidomalonic acid is heated to 150°C until decarboxylation is complete to give 6-(N-Boc-amino)-2-phthalimido-hex-4-enoic acid.

**Ex-37c)** 6-(N-Boc-amino)-2-phthalimido-hex-4-enoic acid (3.34 g, 9 mmol) is cooled in an ice bath and 1.0M borane-tetrahydrofuran complex (18 mL) added dropwise. When addition is complete, the reaction is allowed to warm to room temperature. When the reduction is complete, excess reagent is destroyed by addition of acetic acid. The reaction is concentrated at reduced pressure. The crude product is purified by column chromatography on silica gel to yield 6-(N-Boc-amino)-2-phthalimido-hex-4-enol.

**Ex-37d)** 6-(N-Boc-amino)-2-phthalimido-hex-4-enol (2.7 g, 8 mmol) is dissolved in DMSO and treated with 1,3-dicyclohexylcarbodiimide (DCC) (1.6 g, 8 mmol) and phosphoric acid. The reaction is stirred at room temperature. Upon completion, methylene chloride is added to the mixture and it is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer is dried over MgSO₄, filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column, giving 6-(N-Boc-amino)-2-phthalimido-hex-4-enal.

**Ex-37e)** 6-(N-Boc-amino)-2-phthalimido-hex-4-enal (2.50 g, 7 mmol) is added to 50 mL of cyclohexane in 100 mL reaction
flask. After adding 0.1 g of p-toluenesulfonic acid and 1.0 g (7 mmol) 1,2-benzenedithiol, the reaction mixture is refluxed with azeotropic distillation for removal of water using a Dean-Stark trap. After cooling, dilute aqueous sodium carbonate (20 mL) is added, the hexane separated, and then concentrated in vacuo to afford 2-(6-(N-Boc-amino)-2-phthalimido-hex-4-enyl)-3-thia-2H,3H-benzo thiophene.

Ex-37f) 2-(6-(N-Boc-amino)-2-phthalimido-hex-4-enyl)-3-thia-2H,3H-benzo thiophene is dissolved in trifluoroacetic acid. The reaction is allowed to stand at 25 °C until the Boc group is removed to give, after concentrating in vacuo, to give 2-(6-amino-2-phthalimido-hex-4-enyl)-3-thia-2H,3H-benzo thiophene trifluoroacetate.

Ex-37g) To a 125 mL flask is added 6 mmol of the 2-(6-amino-2-phthalimido-hex-4-enyl)-3-thia-2H,3H-benzo thiophene trifluoroacetate and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.31 g of methyl acetimidate. During methyl acetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product 2-(6-(N-(1-iminoethyl)amino)-2-phthalimido-hex-4-enyl)-3-thia-2H,3H-benzo thiophene is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water.

2-(6-(N-(1-iminoethyl)amino)-2-phthalimido-hex-4-enyl)-3-thia-2H,3H-benzo thiophene (1.90 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate and is heated to reflux. After complete removal of the phthaloyl protecting group and filtering to remove the phthaloylhydrazide, the
methanolic solution is then adjusted to pH = 7.5 with aqueous hydrochloric acid and poured onto a Dowex 50 Cation exchange column. The column is washed with water, and the product 2-(6-(N-(1-iminoethyl)amino)-2-amino-hex-4-enyl)-3-thia-2H,3H-benzothiophene is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water.

![Chemical Structure](image)

(39)

**Example 39**

**Ex-39a** Diethyl 2-(4-(N-Boc-amino)but-2-enyl)-2-phthalimidomalonate (10 mmol) is dissolved in ethanol and sodium hydroxide (0.78 g, 10 mmol) is added. When one ethyl ester is hydrolyzed, the reaction mixture is then concentrated in vacuo, 50 ml anhydrous cyclohexane is added, and then is added (1.25 g, 10.5 mmol) of thionyl chloride. After the formation of the acid chloride is complete, sodium chloride is removed by filtration, and the mixture is concentrated in vacuo to give ethyl 2-(4-(N-Boc-amino)but-2-enyl)-2-phthalimido-3-chloro-3-oxopropionate.

**Ex-39b** Ethyl 2-(4-(N-Boc-amino)but-2-enyl)-2-phthalimido-3-chloro-3-oxopropionate (9 mmol) is dissolved in tetrahydrofuran, cooled to -78°C and treated with one equivalent (9 mL) of 1.0 M diisobutylaluminum hydride in THF. Acetic acid is added and the reaction is warmed to
room temperature to generate the aldehyde. After the mixture is concentrated in vacuo, methylene chloride is added. The methylene chloride layer is washed with 10% aqueous sodium bicarbonate, water and brine. The methylene chloride layer is dried over MgSO\(_4\), filtered and solvents removed in vacuo. The product is passed through a reverse phase chromatographic column giving ethyl 2-((4-((N-Boc-amino)but-2-enyl)-2-phthalimido-3-oxopropionate.

**Ex-39c** Ethyl 2-((4-((N-Boc-amino)but-2-enyl)-2-phthalimido-3-oxopropionate (8 mmol) is added to 50 mL of hexane in 100 mL reaction flask. After adding 0.1 g of p-toluene sulfonic acid and 1.30 g (17 mmol) 1,3-propanediol, the reaction mixture is refluxed with azeotropic distillation for removal of water using a Dean-Stark trap. After cooling, dilute aqueous sodium carbonate (20 mL) is added, the hexane separated, and then concentrated in vacuo to afford ethyl 2-((4-((N-Boc-amino)but-2-enyl)-2-phthalimido-3-(2-(1,3-dioxanyl))acetate.

**Ex-39d** Ethyl 2-((4-((N-Boc-amino)but-2-enyl)-2-phthalimido-3-((2-(1,3-dioxanyl))acetate (7 mmol) is dissolved in ethanol and treated with one equivalent of sodium hydroxide (0.26 g, 7 mmol). When the ester group is removed, the mixture is concentrated in vacuum. The residue is dissolved in 10 mL of thionyl chloride and warmed. The excess thionyl chloride is removed in vacuo, anhydrous toluene added and removed in vacuo, and 20 mL of toluene containing phenol (0.71 g, 7.5 mmol) and triethylamine (1.01 g, 10 mmol) is added. After stirring at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column giving phenyl 2-((4-((N-Boc-amino)but-2-enyl)-2-phthalimido-3-(2-(1,3-dioxanyl))acetate.
**Ex-39e)** Phenyl 2-[(N-Benzylamino)but-2-enyl]-2-phthalimido-3-[(2-(1,3-dioxanyl))acetate is dissolved in anhydrous trifluoroacetic acid to remove the Boc-function generating the amino product; phenyl 2-[(4-aminobut-2-enyl)]-2-phthalimido-3-[(2-(1,3-dioxanyl))acetate trifluoroacetate, after removal of solvent.

**Ex-39f)** To a 125 mL flask is added (6 mmol) phenyl 2-[(4-aminobut-2-enyl)]-2-phthalimido-3-[(2-(1,3-dioxanyl))acetate trifluoroacetate and 70 mL of DMF. To this solution is added 2.19 g of methyl aceticimidate hydrochloride. Triethylamine (TEA) (3.04 g, 0.03 mol) is added. After the addition is complete, the solution is allowed to stand at 25°C for 16 hours. The reaction mixture is filtered from triethylamine hydrochloride, and the filtrate is concentrated in vacuum. The residue is dissolved in 50% acetic acid and lyophilized. The crude product is purified by then adjusting the pH to 7.5 and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product Phenyl 2-[(4-aminobut-2-enyl)]-2-phthalimido-3-[(2-(1,3-dioxanyl))acetate is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

Phenyl 2-[(4-aminobut-2-enyl)]-2-phthalimido-3-[(2-(1,3-dioxanyl))acetate (2.38 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. After complete removal of the phthaloyl protecting group and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give the product.
**Example 40**

**Ex-40a)** Ethyl 6-phthalimido-2-cyano-2-(N-Boc-amino)hexanoate (4.29 g, 10 mmol) is dissolved in ethanol and treated with sodium hydroxide (0.38 g, 10 mmol). When the ethyl ester group is hydrolyzed, one equivalent of HCl (0.36 g, 10 mmol) is added through a gas inlet tube. The solvent is removed in vacuo and the residue is heated to 150°C until decarboxylation is complete. The crude product is passed through a reverse phase chromatographic column giving 6-phthalimido-2-(N-Boc-amino)hexanenitrile.

**Ex-40b)** 6-Phthalimido-2-(N-Boc-amino)hexanenitrile (3.21 g, 9 mmol) is dissolved in methanol and 0.9 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give the product 6-amino-2-(N-Boc-amino)hexanenitrile.

**Ex-40c)** To a 125 mL flask is added 1.82 g (8 mmol) of 6-amino-2-(N-Boc-amino)hexanenitrile and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N
NaOH. To this solution is added portion wise, 2.11 g of methyl 2-fluoroacetimidate. During methyl 2-fluoroacetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product 6-(N-(2-Fluoro-1-iminoethyl)amino)-2-(N-Boc-amino)-hexanenitrile is then eluted with 10% aqueous pyridine.

6-(N-(2-Fluoro-1-iminoethyl)amino)-2-(N-Boc-amino)-hexanenitrile (2.12 g, 7 mmol) is dissolved in methylene chloride and (0.98 g, 8 mmol) 2-piperazinylmethanethiol is added at with cooling to -10°C. HCl (1.9 g) gas is added by gas inlet tube. The reaction is allowed to warm to room temperature. When the reaction is completed, the solvent is removed in vacuo to yield 6-(N-(2-fluoro-1-iminoethyl)amino)-1-imino-1-(2-piperazinylmethylthio)-2-hexanamine pentahydrochloride.

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**Example 41**

**Ex-41a)** Ethyl 6-phthalimido-2-cyano-2-(N-Boc-amino)hexanoate (4.29 g, 10 mmol) is dissolved in methanol and 1.0 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group and filtering to remove the phthaloylhydrazide, the
methanolic solution is then concentrated to dryness in an ice bath to give the product ethyl 6-amino-2-cyano-2-(N-Boc-amino)hexanoate.

**Ex-41b)** To a 125 mL flask is added 2.69 g (9 mmol) of ethyl 6-amino-2-cyano-2-(N-Boc-amino)hexanoate and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.05 g of methyl acetimidate. During methyl acetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product Ethyl 6-(N-(1-iminoethyl)amino)-2-cyano-2-(N-Boc-amino)hexanoate is then eluted with 10% aqueous pyridine.

Ethyl 6-(N-(1-iminoethyl)amino)-2-cyano-2-(N-Boc-amino)hexanoate (2.73 g, 8 mmol) is dissolved in methylene chloride and 10 mL anhydrous ethanol is added. The mixture is cooled to -10°C and (1.2 g) HCl gas is added by gas inlet tube. The reaction is allowed to warm to room temperature. When the reaction is completed, the solvent is removed in vacuo to yield ethyl 6-(N-(1-iminoethyl)amino)-2-(ethoxyiminomethyl)-2-aminohexanoate trihydrochloride.
Example 42

**Ex-42a**) Ethyl 6-({N-(1-iminoethyl)amino}-2-cyano-2-({N-Boc-amino})hexanoate (Ex-41c) (3.41 g, 10 mmol) is dissolved in ethanol and treated with one equivalent of sodium hydroxide (0.37 g, 10 mmol). When the ester group is removed, p-toluenesulfonic acid (10 mmol) is added. The mixture is concentrated in vacuum. The residue is dissolved in 60 mL of DMF. 5-methylaminotetrazole hydrochloride (1.40 g, 10.5 mmol) and 1-hydroxybenzotriazole hydrate (1.46 g, 10.5 mmol) are added. The mixture is cooled in an ice bath then is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-((5-tetrazolyl)-6-((N-(1-iminoethyl)amino)-2-cyano-2-({N-Boc-amino})hexanamide.

N-Methyl-N-((5-tetrazolyl)-6-((N-(1-iminoethyl)amino)-2-cyano-2-({N-Boc-amino})hexanamide (3.15 g, 8 mmol) is dissolved in methylene chloride and (0.26 g, 8 mmol) methanol is added. The mixture is cooled to -10°C and (1.9 g) HCl gas is added by gas inlet tube. The reaction is allowed to warm to room temperature. When the reaction is completed, the solvent is removed in vacuo to yield N-
methyl-N-(5-tetrazolyl)-6-(N-(1-iminooethyl)amino)-2- (methoxyiminomethyl)-2-aminohexanamide.

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Example 43

Ex-43a) tert-Butyl 6-(N-Z-amino)-2-cyano-2-
phthalimidohexanoate is dissolved in ethanol/acetic acid
and is combined with a hydrogenation catalyst such as
palladium on carbon and hydrogen. This reaction is shaken
under pressure for an extended period of time in a standard
Parr hydrogenation apparatus to remove the Z-function
generating the amino product tert-butyl 6-amino-2-cyano-2-
phthalimidohexanoate acetate.

Ex-43b) To a 125 mL flask is added 3.57 g (0.01 mol) of
tert-butyl 6-amino-2-cyano-2-phthalimidohexanoate acetate
and 70 mL of DMF. To this solution is added 2.19 g of
methyl acetimidate hydrochloride. Triethylamine (TEA)
(3.04 g, 0.03 mol) is added. After the addition is
complete, the solution is allowed to stand at 25°C for 16
hours. The reaction mixture is filtered from triethylamine
hydrochloride, and the filtrate is concentrated in vacuum.
The residue is dissolved in 50% acetic acid and
lyophilized. The crude product is purified by then
adjusting the pH to 7.5 and poured onto a Dowex 50 Cation
exchange column. The column is washed with water. The
product tert-Butyl 6-(N-(1-iminoethyl)amino)-2-cyano-2-phthalimidohexanoate is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

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Ex-43c) tert-Butyl 6-(N-(1-iminoethyl)amino)-2-cyano-2-phthalimidohexanoate is dissolved in acetic acid and is combined with a hydrogenation catalyst such as platinum on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to reduce the nitrile. When the reaction is complete, the crude product is purified by then adjusting the pH to 7.5 and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product tert-Butyl 6-(N-(1-iminoethyl)amino)-2-aminomethyl-2-phthalimidohexanoate is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

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Ex-43d) tert-Butyl 6-(N-(1-iminoethyl)amino)-2-aminomethyl-2-phthalimidohexanoate (3.22 g, 8 mmol) is cooled in an ice bath and treated with N-Boc-glycyl chloride (1.39 g, 8.5 mmol) and triethyl amine (TEA) (0.8 g, 8 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum. The resulting material is passed through a reverse phase chromatographic column, giving tert-butyl 6-(N-(1-iminoethyl)amino)-2-(N-(N-Boc-glycyl))aminomethyl-2-phthalimidohexanoate.

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tert-Butyl 6-(N-(1-iminoethyl)amino)-2-(N-(N-Boc-glycyl))aminomethyl-2-phthalimidohexanoate (7 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then
concentrated to dryness. The product is taken up and allowed to stand in 2N HCl and dioxane at 25 °C for two hours. Concentrating in vacuo affords the unprotected product 6-[(N-(1-iminoethyl)amino)-2-[(N-glycylaminomethyl)-5 2-phthalimidoehxanoic acid trihydrochloride.

Example 45

Ex-45a) tert-Butyl 2-phthalimidoacetate (2.61 g, 10 mmol) is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents (1.11 g, 11 mmol) of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents (2.15 g, 11 mmol) of 2-(3-bromopropyl)-1,3-dioxolane is added. After warming to room temperature, the reaction mixture is concentrated in vacuo, 50 mL methylene chloride is added, the solvent is washed with water, and the methylene chloride is dried over anhydrous K₂CO₃ and is taken to dryness to give, after chromatographic purification, the tert-butyl 2-phthalimido-5-(1,3-dioxolanyl)pentanoate.

Ex-45b) tert-Butyl 2-phthalimido-5-(1,3-dioxolanyl)pentanoate (3.38 g, 9 mmol) is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents (1.01 g, 10 mmol) of diisopropylamine followed by 1 equivalent on n-
butyl lithium in hexane. Subsequently, 1.1 equivalents (2.15 g, 10 mmol) of 2-benzylxyloxy-1-bromoethane is added. After warming to room temperature, the reaction mixture is concentrated in vacuo, 50 mL methylene chloride is added, the solvent is washed with water, and the methylene chloride is dried over anhydrous K₂CO₃ and is taken to dryness. The crude product is purified by reverse phase chromatography to give tert-butyl 2-phthalimido-2-(2-benzyloxyethyl)-5-(1,3-dioxolanyl)pentanoate.

Ex-45c) The tert-butyl 2-phthalimido-2-(2-benzyloxyethyl)-5-(1,3-dioxolanyl)pentanoate is treated with 0.5 g of p-toluenesulfonic acid in 20 mL of ice water. The mixture is stirred and is allowed to warm to room temperature until the aldehyde is regenerated. The water mixture is extracted with methylene chloride. The methylene chloride is dried and concentrated to give tert-butyl 2-phthalimido-2-(2-benzyloxyethyl)-6-oxohexanoate.

Ex-45d) tert-Butyl 2-phthalimido-2-(2-benzyloxyethyl)-6-oxohexanoate (3.72 g, 8 mmol) and ammonia are dissolved in methanol and treated with 1.0M sodium cyanoborohydride in THF and potassium hydroxide using the conditions and work-up described by R. F. Borch in Organic Synthesis, 52, 124, 1972 to give the product tert-butyl 2-phthalimido-2-(2-benzyloxyethyl)-6-aminohexanoate.

Ex-45e) To a 125 mL flask is added 3.24 g (7 mmol) of tert-butyl 2-phthalimido-2-(2-benzyloxyethyl)-6-aminohexanoate and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.57 g of methyl acetimidate. During methyl acetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column
is washed with water. The protected product tert-Butyl 2-phthalimido-2-(2-benzyl oxyethyl)-6-(N-(1-iminoethyl)amino)hexanoate is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

Ex-45f) tert-Butyl 2-phthalimido-2-(2-benzyl oxyethyl)-6-(N-(1-iminoethyl)amino)hexanoate is then dissolved in 2.0M HCl in acetic acid and allowed to stand at room temperature until the t-butyl group is removed. The reaction mixture is then concentrated in vacuo to give 2-phthalimido-2-(2-benzyl oxyethyl)-6-(N-(1-iminoethyl)amino)hexanoic acid hydrochloride.

Ex-45g) To a stirring DMF solution of 2-phthalimido-2-(2-benzyl oxyethyl)-6-(N-(1-iminoethyl)amino)hexanoic acid hydrochloride (2.71 g, 6 mmol), 5-(2'-N-methyl)hydrazinotetrazole (0.76 g, 6.5 mmol), and 1-hydroxybenzotriazole hydrate (0.90 g, 6.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.20 g, 6.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column, giving N-methyl-N-(N-(5-tetrazoyl)amino)-2-phthalimido-2-(2-benzyl oxyethyl)-6-(N-(1-iminoethyl)amino)hexanamide.

Ex-45h) N-methyl-N-(N-(5-tetrazoyl)amino)-2-phthalimido-2-(2-benzyl oxyethyl)-6-(N-(1-iminoethyl)amino)hexanamide is dissolved in ethanol/acetic acid and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the benzyl group generating, after filtering to remove catalyst and concentration in vacuo, N-
methyl-N-(N-(5-tetrazoyl)amino)-2-phthalimido-2-(2-hydroxyethyl)-6-(N-(1-iminoethyl)amino)hexanamide.

N-Methyl-N-(N-(5-tetrazoyl)amino)-2-phthalimido-2-(2-hydroxyethyl)-6-(N-(1-iminoethyl)amino)hexanamide (2.29 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give N-Methyl-N-(N-(5-tetrazoyl)amino)-2-amino-2-(2-hydroxyethyl)-6-(N-(1-iminoethyl)amino)hexanamide.

Example 46

Ex-46a) To a stirring DMF solution of 2-phthalimido-2-(2-benzzyloxyethyl)-6-(N-(1-iminoethyl)amino)hexanoic acid hydrochloride (Ex-45f; prepared in example 45) (4.51 g, 10 mmol), glycine tert-butyl ester hydrochloride (1.76 g, 10.5 mmol) and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column giving tert-butyl N-(2-phthalimido-
2-(2-benzzyloxyethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate.

**Ex-46b** tert-Butyl N-(2-phthalimido-2-(2-benzzyloxyethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate is dissolved in ethanol/acetic acid and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to remove the benzyl-function generating tert-Butyl N-(2-phthalimido-2-(2-hydroxyethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate.

**Ex-46c** tert-Butyl N-(2-phthalimido-2-(2-hydroxyethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate (3.79 g, 8 mmol) in 50 mL THF is cooled in an ice bath and is treated with tosyl chloride (1.62 g, 8.5 mmol) and triethyl amine (TEA) (1.6 g, 16 mmol). The mixture is allowed to warm to room temperature. Upon completion the mixture is concentrated in vacuum to give tert-Butyl N-(2-phthalimido-2-(2-tosyloxyethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate.

**Ex-46d** tert-Butyl N-(2-phthalimido-2-(2-tosyloxyethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate (2.96 g, 7 mmol) is treated with sodium cyanide (0.5 g, 7.5 mmol) in 20 mL of dimethylformamide and heated. When the substitution is complete, the reaction is concentrated. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column giving tert-Butyl N-(2-phthalimido-2-(2-cyanoethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate.

**Ex-46e** tert-Butyl N-(2-phthalimido-2-(2-cyanoethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetate is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl
protecting group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give tert-Butyl N-(2-amino-2-(2-cyanoethyl)-6-(N-(1-iminoethyl)amino)hexanoyl)aminoacetate.

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\text{tert-Butyl N-(2-amino-2-(2-cyanoethyl)-6-(N-(1-iminoethyl)amino)hexanoyl)aminoacetate is allowed to stand in 2N HCl and dioxane at 25°C for two hours. The solution is then concentrated to dryness to give N-(2-amino-2-(2-cyanoethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetic acid hydrochloride.}
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**Example 48**

**Ex-48a** tert-Butyl 2-phthalimido-5-(1,3-dioxolanyl)pentanoate (Ex-45b; prepared in scheme 45) (3.76 g, 10 mmol) is dissolved in dry 2.0 M HCl in dioxane. The reaction is stirred until the t-butyl group is removed, and then the reaction is concentrated. DMF (70 mL), 2,2,2-trichloroethanol (1.56 g, 10.5 mmol), and 1-hydroxybenzotriazole hydrate (1.45 g, 10.5 mmol) are added and the mixture is cooled in an ice bath. When cold [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.93 g, 10.5 mmol) is added. After stirring 55 h at ambient
temperature, the reaction mixture is concentrated in vacuum. The resulting material is then purified by column chromatography giving 2,2,2-trichloroethyl 2-phthalimido-5-(1,3-dioxolanyl)pentanoate.

Ex-48b) 2,2,2-Trichloroethyl 2-phthalimido-5-(1,3-dioxolanyl) pentanoate (4.06 g, 9 mmol) is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents (0.75 g) of chloroacetonitrile is added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo. The resulting material is then purified by column chromatography giving 2,2,2-trichloroethyl 2-cyanomethyl-2-phthalimido-6-(1,3-dioxolanyl)pentanoate.

Ex-48c) 2,2,2-Trichloroethyl 2-cyanomethyl-2-phthalimido-6-(1,3-dioxolanyl)pentanoate (3.92 g, 8 mmol) is added to ice water with 0.1 g of p-toluenesulfonic acid, is stirred and is allowed to warm to room temperature to generate the aldehyde. The resulting solution is extracted with methylene chloride, the extracting is dried over MgSO₄, and is concentrated in vacuo to give 2,2,2-trichloroethyl 2-cyanomethyl-2-phthalimido-6-oxopentanoate.

Ex-48d) 2,2,2-Trichloroethyl 2-cyanomethyl-2-phthalimido-6-oxopentanoate (3.02 g, 7 mmol) is dissolved in methanol and is treated with ammonia (0.13 g, 7.5 mmol), and 1.0M sodium cyanoborohydride in THF (8 mL) and potassium hydroxide using the conditions and work-up described by R. F. Borch in Organic Synthesis, 52, 124, 1972 to give the product
2,2,2-trichloroethyl 2-cyanomethyl-2-phthalimido-6-aminohexanoate.

**Ex-48e)** To a 125 mL flask is added 4.32 g (10 mmol) of 2,2,2-trichloroethyl 2-cyanomethyl-2-phthalimido-6-aminohexanoate and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 2.19 g of methyl acetimidate. During methyl acetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product 2,2,2-trichloroethyl 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoate is then eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

**Ex-48f)** 2,2,2-trichloroethyl 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoate (4.26 g, 9 mmol) is dissolved in tetrahydrofuran. Zinc dust (1.17 g) is added, and the mixture is allowed to stir. When the trichloroethyl protecting group is completely removed, the reaction mixture is acidified with 2 N HCl. The solids are filtered for removal, and the solvent is removed in vacuo. The resulting material is purified by reverse phase chromatography to give 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino) hexanoic acid.

**Ex-48g)** To a stirring solution of 2-cyanomethyl-2-phthalimido-6-(N(1-iminoethyl)amino)hexanoic acid (2.74 g, 8 mmol), 5-(N-methylsulfonylmethylamino)tetrazole (1.50 g, 8.5 mmol), and 1-hydroxybenzotriazole hydrate (1.17 g, 8.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.56 g, 8.5 mmol). After stirring 55 h at
ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and is passed through a reverse phase chromatographic column, giving N-methylsulfonylmethyl-N-(5-tetrazolyl)-2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanamide.

N-methylsulfonylmethyl-N-(5-tetrazolyl)-2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanamide (3.61 g, 7 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give N-methylsulfonylmethyl-N-(5-tetrazolyl)-2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanamide.

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**Example 49**

**Ex-49a** tert-Butyl 2-phthalimido-5-(1,3-dioxolanyl)pentanoate (**Ex-45b**: prepared in scheme 45) (3.76 g, 10 mmol) is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1
equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of chloroacetonitrile is added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and is concentrated in vacuo. The resulting material is then purified by column chromatography giving tert-Butyl 2-cyanomethyl-2-phthalimido-5-(1,3-dioxolanyl)pentanoate.

**Ex-49b)** tert-Butyl 2-cyanomethyl-2-phthalimido-5-(1,3-dioxolanyl) pentanoate (3.74 g, 9 mmol) is added to ice water with 0.1 g of p-toluenesulfonic acid, is stirred and is allowed to warm to room temperature to generate the aldehyde. The resulting solution is extracted with methylene chloride, the extractant is dried over MgSO₄, and is concentrated in vacuo to give tert-Butyl 2-cyanomethyl-2-phthalimido-6-oxohexanoate.

**Ex-49c)** tert-Butyl 2-cyanomethyl-2-phthalimido-6-oxohexanoate (2.98 g, 8 mmol) is dissolved in methanol and is treated with ammonia (0.15 g, 8.5 mmol) and 1.0M sodium cyanoborohydride in THF (8 mL) and potassium hydroxide using the conditions and work-up described by R. F. Borch in *Organic Synthesis*, 52, 124, 1972 to give the product tert-Butyl 2-cyanomethyl-2-phthalimido-6-aminohexanoate.

To a 125 mL flask is added 2.60 g (7 mmol) of tert-Butyl 2-cyanomethyl-2-phthalimido-6-aminohexanoate and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.53 g of methyl aceticamide. During methyl aceticamide addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and is poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product tert-Butyl 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoate is then
eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{H}_3C & \quad \text{CH}_3 \\
\text{NC} & \quad \text{SO}_2 \\
\text{NH}_2 & \quad \text{CH}_3 \\
\text{O} & \quad \text{O}
\end{align*}
\]

(50)

Example 50

10 **Ex-50a)** tert-Butyl 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoate (Ex-49) is deprotected by allowing it to stand in 2N HCl and dioxane at 25°C for two hours. Concentrating in vacuo affords 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoic acid hydrochloride.

**Ex-50b)** 2-Cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoic acid hydrochloride (6 mmol) is dissolved in tetrahydrofuran, is cooled in an ice bath and is treated with ethylchloroformate (0.70 g, 6.5 mmol) and triethylamine (TEA) (1.3 g, 13 mmol). The mixture is allowed to warm to room temperature. The resulting material is treated with O-methoxymethyl-N-methanesulfonylmethylhydroxylamine (1.10 g, 6.5 mmol). The mixture is stirred vigorously until the substitution is complete. The solvent is removed in vacuo, the residue is dissolved in water, is adjusted to pH = 7.5 with 1N HCl, and is poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product N-Methanesulfonylmethyl-N-(O-methoxymethoxy)-2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanamide is then
eluted with a solvent of 10% pyridine, 50% methanol and 40% water and taken to dryness in vacuo.

N-Methanesulfonylmethyl-N-(O-methoxymethoxy)-2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanamide (2.54 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give N-methanesulfonylmethyl-N-(methoxymethoxy)-2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanamide.

![Chemical Structure](image)

**Example 51**

**Ex-51a** To a stirring DMF solution of 2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoic acid hydrochloride (Ex-50a; prepared in example 50) (2.14 g, 6 mmol), t-butyl alanine hydrochloride (1.19 g, 6.5 mmol), and 1-hydroxybenzotriazole hydrate (0.90 g, 10.5 mmol) in 75 mL of dimethylformamide (DMF) cooled in an ice bath is added [(N,N-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.19 g, 10.5 mmol). After stirring 55 h at ambient temperature, the reaction mixture is concentrated in vacuum. The resulting material is dissolved in aqueous acetonitrile and passed through a reverse phase chromatographic column giving t-butyl N-(2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoyl)alaninate.
Ex-51b) t-Butyl N-(2-cyanomethyl-2-phthalimido-6-(N-(1-iminoethyl)amino)hexanoyl)alaninate (2.42 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give t-Butyl N-(2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanoyl)alaninate.

t-Butyl N-(2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanoyl)alaninate is dissolved and allowed to stand in 2.0M HCl in dioxane at 25°C for two hours. Concentrating in vacuo affords N-(2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanoyl)alanine dihydrochloride.

Example 52

Ex-52a) N-Boc-5-nitropentanamine (2.31 g, 10 mmol) is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of 2-butanoyl chloride is added. After warming to room temperature, the reaction mixture is filtered to remove the
precipitant and concentrated in vacuo to give 1-(N-Boc-amino)-4-nitrononan-5-one which is purified by chromatography.

**Ex-52b)** 1-(N-Boc-amino)-4-nitrononan-5-one (2.67 g, 9 mol) is thoroughly dried and dissolved in 25 mL of anhydrous THF. To the THF solution cooled to -78 °C, is added 1.1 equivalents of diisopropylamine followed by 1 equivalent on n-butyl lithium in hexane. Subsequently, 1.1 equivalents of bromoacetonitrile is added. After warming to room temperature, the reaction mixture is filtered to remove the precipitant and concentrated in vacuo to give 1-(N-Boc-amino)-4-nitro-4-cyanomethyl-nonan-5-one.

**Ex-52c)** 1-(N-Boc-amino)-4-nitro-4-cyanomethylnonan-5-one is dissolved in 50 mL anhydrous cyclohexane, is treated with 2 mL BF₃ etherate and 1,2-propanediol (9 mmol), and is allowed to stir until the ketal forms. The reaction mixture is washed with aqueous sodium carbonate, and the cyclohexane is dried over anhydrous potassium carbonate. Evaporation of the solvent and chromatography gave 2-(5-(N-Boc-amino)-1-nitro-1-cyanomethylpentyl)-2-propyl-4-methyl-1,3-dioxolane.

**Ex-52d)** 2-(5-(N-Boc-amino)-1-nitro-1-cyanomethylpentyl)-2-propyl-4-methyl-1,3-dioxolane is deprotected by allowing it to stand in anhydrous trifluoroacetic acid at 25°C for two hours. Concentrating in vacuo affords 2-(5-amino-1-nitro-1-cyanomethylpentyl)-2-propyl-4-methyl-1,3-dioxolane trifluoroacetate.

**Ex-52e)** To a 125 mL flask is added 8 mmol of 2-(5-amino-1-nitro-1-cyanomethylpentyl)-2-propyl-4-methyl-1,3-dioxolane trifluoroacetate and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.75 g of methyl acetimidate. During methyl acetimidate addition, the pH is
kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product is then eluted with 10% aqueous pyridine.

The 2-(5-(N-(1-iminoethyl)amino)-1-nitro-1-cyanomethylpentyl)-2-propyl-4-methyl-1,3-dioxolane is dissolved in ethanol with 30 mmol ammonium formate and is combined with a hydrogenation catalyst such as palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus. The solvent is removed and 50 mL of water added. The solution is then adjusted to pH = 7.5 with 1N HCl and is poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product is then eluted with 10% aqueous pyridine and is taken to dryness to give 2-(5-(N-(1-iminoethyl)amino)-1-amino-1-cyanomethylpentyl)-2-propyl-4-methyl-1,3-dioxolane.

![Diagram](attachment:image.png)

**Example 53**

**Ex-53a)** 6-(N-Boc-amino)-2-phthalimido-hex-4-enal (**Ex-37d**) (10 mmol) is added to 50 mL of cyclohexane in 100 mL reaction flask. After adding 0.1 g of p-toluenesulfonic acid and 0.70 g (10 mmol) ethylene glycol, the reaction mixture is refluxed with azeotropic distillation for removal of water using a Dean-Stark trap. After cooling,
the solvent is removed in vacuo to give 2-(5-(N-Boc-amino)-1-phthalimido-pent-3-enyl)-1,3-dioxolane.

**Ex-53b**) 2-(5-(N-Boc-amino)-1-phthalimido-pent-3-enyl)-1,3-dioxolane is dissolved in ethanol and is combined with a hydrogenation catalyst palladium on carbon and hydrogen. This reaction is shaken under pressure for an extended period of time in a standard Parr hydrogenation apparatus to reduce the alkenyl group. Evaporation of the solvent gives 2-(5-(N-Boc-amino)-1-phthalimido-pentyl)-1,3-dioxolane.

**Ex-53c**) 2-(5-(N-Boc-amino)-1-phthalimido-pentyl)-1,3-dioxolane (7 mmol) is dissolved in anhydrous acetic acid with 2.5 g of dry HCl added through a gas inlet tube. The reaction is allowed to stand at 25°C until the Boc group is removed to give 2-(5-amino-1-phthalimido-pentyl)-1,3-dioxolane hydrochloride.

**Ex-53d**) To a 125 mL flask is added 2.04 g (6 mmol) of 2-(5-amino-1-phthalimido-pentyl)-1,3-dioxolane hydrochloride and 70 mL of water. This solution is adjusted to pH = 9.5 by addition of 2.5 N NaOH. To this solution is added portion wise, 1.31 g of methyl acetimidate. During methyl acetimidate addition, the pH is kept at 9.5 via concomitant addition of 2.5 N NaOH. After the addition is complete, the solution is allowed to stand at 25°C for 25 minutes. The solution is then adjusted to pH = 7.5 with 1N HCl and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The protected product 2-(5-(N-(1-Iminoethyl)amino)-1-phthalimidopentyl)-1,3-dioxolane is then eluted with 10% aqueous pyridine.

**Ex-53e**) 2-(5-(N-(1-Iminoethyl)amino)-1-phthalimidopentyl)-1,3-dioxolane (1.73 g, 5 mmol) is dissolved in methanol and 0.5 g hydrazine monohydrate. The mixture is heated to reflux. After complete removal of the phthaloyl protecting
group, cooling and filtering to remove the phthaloylhydrazide, the methanolic solution is then concentrated to dryness to give 2-(5-(N-(1-
iminoethyl)amino)-1-aminopentyl)-1,3-dioxolane.

Ex-53f) 2-(5-(N-(1-iminoethyl)amino)-1-aminopentyl)-1,3-dioxolane (0.86 g, 4 mmol) is allowed to stir with t-butoxycarbonylazide (0.64 g, 4.5 mmol) and MgO (0.20 g, 4.5 mmol) in dioxane/water solution. Upon completion, the magnesium salts are removed by filtration. The resulting material is passed through a reverse phase chromatographic column giving 2-(5-(N-(1-iminoethyl)amino)-1-(N-Boc-amino)pentyl)-1,3-dioxolane.

Ex-53g) 2-(5-(N-(1-iminoethyl)amino)-1-(N-Boc-amino)pentyl)-1,3-dioxolane is treated with 30 mL of water with 5 mL of phosphoric acid added and allowed to stir until the acetal is cleaved. The solution is then adjusted to pH = 7.5 and poured onto a Dowex 50 Cation exchange column. The column is washed with water. The product is then eluted with 10% aqueous pyridine and taken to dryness to give to give 6-(N-(1-iminoethyl)amino)-2-(N-Boc-aminohexanal.

Ex-53h) 6-(N-(1-iminoethyl)amino)-2-(N-Boc-aminohexanal (0.95 g, 3.5 mmol) is added to 50 mL of cyclohexane in 100 mL reaction flask. After adding 1.33 g (7 mmol) of p-toluenesulfonic acid and 0.26 g (3.5 mmol) butylamine, the reaction mixture is refluxed with azeotropic distillation complete removal of water using a Dean-Stark trap. After cooling, the solvent is removed in vacuo to give an essentially quantitative yield of 6-(N-butylimino)-N-(1-iminoethyl)-2-(N-Boc-aminohexanamine di-para-toluenesulfonate.

Ex-53i) 6-(N-Butylimino)-N-(1-iminoethyl)-2-(N-Boc-aminohexanamine di-para-toluenesulfonate (1.14 g, 3.5 mmol)
is dissolved in 10 mL dimethylformamide and treated with (0.54 g, 4 mmol) of N-chlorosuccinimide. The reaction is stirred until complete. 40 mL of toluene was added to precipitate the succinimide which is removed. The toluene solvent is removed in vacuo, and the DMF solution is used in the next step without isolation of resulting 6-(N-butylimino)-6-chloro-N-(1-iminoethyl)-2-(N-Boc-aminohexanamine di-para-toluenesulfonate.

**Ex-53j** 6-(N-butylimino)-6-chloro-N-(1-iminoethyl)-2-(N-Boc-aminohexanamine di-para-toluenesulfonate (3.5 mmol) solution is added to 50 mL of anhydrous methanol in 100 mL reaction flask. After the reaction mixture is stirred, the solvent and methanol are removed in vacuo to give 6-(N-butylimino)-6-methoxy-N-(1-iminoethyl)-2-(N-Boc-aminohexanamine di-para-toluenesulfonate.

6-(N-butylimino)-6-methoxy-N-(1-iminoethyl)-2-(N-Boc-aminohexanamine di-para-toluenesulfonate is deprotected by allowing it to stand in 2N HCl in methyl acetate at 25°C for two hours. Concentrating in vacuo affords 6-(N-butylimino)-6-methoxy-N-(1-iminoethyl)-1,2-hexanediamine di-para-toluenesulfonate hydrochloride.

**Biological Data**

The subject compounds of formula I and II are expected to be found to inhibit nitric oxide synthase and posses useful pharmacological properties as demonstrated in one or more of the following assays:

**Citrulline Assay for Nitric Oxide Synthase**
NOS activity is measured by monitoring the conversion of L-[2,3-3H]-arginine to L-[2,3-3H]-citrulline. Mouse inducible NOS (miNOS) is prepared from an extract of LPS-treated mouse RAW 264.7 cells and rat brain constitutive NOS (rnNOS) is prepared from an extract of rat cerebellum. Both preparations are partially purified by DEAE-Sepharose chromatography. Enzyme (10 m L) is added to 40 mL of 50 mM Tris (pH 7.6) and the reaction initiated by the addition of 50 mL of a solution containing 50 mM Tris (pH 7.6), 2.0 mg/mL bovine serum albumin, 2.0 mM DTT, 4.0 mM CaCl₂, 20 mM FAD, 100 &M tetrahydrobiopterin, 2.0 mM NADPH and 60 mM L-arginine containing 0.9 mCi of L-[2,3-3H]-arginine. For constitutive NOS, calmodulin was included at a final concentration of 40 nM. Following incubation at 37°C for 15 minutes, the reaction is terminated by addition of 300 mL cold buffer containing 10 mM EGTA, 100 mM HEPES (pH 5.5) and 1.0 mM L-citrulline. The [3H]-citrulline is separated by chromatography on Dowex 50W X-8 cation exchange resin and radioactivity quantified with a liquid scintillation counter.

**Raw Cell Nitrite Assay**

RAW 264.7 cells are plated to confluency on a 96-well tissue culture plate grown overnight (17h) in the presence of LPS to induce NOS. A row of 3-6 wells are left untreated and served as controls for subtraction of nonspecific background. The media is removed from each well and the cells are washed twice with Kreb-Ringers-Hepes (25mM, pH 7.4) with 2 mg/ml glucose. The cells are then placed on ice and incubated with 50mL of buffer containing L-arginine (30mM) +/- inhibitors for 1h. The assay is initiated by warming the plate to 37°C in a water bath for 1h. Production of nitrite by intracellular iNOS is linear.
with time. To terminate the cellular assay, the plate of cells is placed on ice and the nitrite-containing buffer removed and analyzed for nitrite using a previously published fluorescent determination for nitrite. T. P. Misko et al, *Analytical Biochemistry*, 214, 11-16 (1993). All values are the average of triplicate wells and are compared to a background-subtracted induced set of cells (100% value).

**In Vivo Assay**

Rats are treated with an intraperitoneal injection of 10mg/kg of endotoxin (LPS) with or without oral administration of the nitric oxide synthase inhibitors. Plasma nitrites are measured 5 hours post-treatment. The results show that the administration of the nitric oxide synthase inhibitor decreases the rise in plasma nitrites, a reliable indicator of the production of nitric oxide, induced by endotoxin.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.
We Claim:

1. A compound having the Formula I or II:

\[ \text{I} \]

\[ \text{II} \]

and pharmaceutically acceptable salts thereof, wherein;

- \( J \) is selected from the group consisting of \( \text{O}, \text{NR}^2_2 \), and \( \text{S} \);

- \( J \) can be \( \text{R}^2_9 \), wherein \( \text{R}^2_9 \) is a group selected from \( \text{OR}^2_8 \), \( \text{SR}^2_8 \), \( \text{NR}^2_8 \), and \( \text{SR}^2_8 \) \( \text{NR}^2_8 \) provided that \( A \) is \( \text{R}^2_6 \);

- \( J^1 \) and \( J^2 \) are independently selected from the group consisting of \( \text{OR}^2_3 \), \( \text{SR}^2_3 \), \( \text{NHR}^2_4 \) and \( \text{N}(\text{R}^2_4)\text{R}^2_5 \) provided that \( A \) is \( \text{R}^2_6 \);

- \( G \) is selected from the group consisting of \( \text{O}, \text{S}, \text{CH}_2, \text{C}(\text{R}^1_1), \text{C}(\text{R}^1_1)_2, \text{NH} \) and \( \text{NR}^1_1 \).
A is selected from the group consisting of O, N(R\textsuperscript{5}), S and heterocyclyl with the proviso that J is selected from other than O, and A is selected from other than O, S and heterocyclyl unless \( R^8 \) is other than hydrogen,

\( R^7 \) is hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl, or \( R^7 \) is selected from other than aryl, heteroaryl, aralkyl, heteroaralkyl, H, alkyl, alkenyl, CH\textsubscript{2}OC\textsubscript{2}(=O)GR\textsubscript{15}, hydroxyalkyl, polyhydroxyalkyl, amino, hydroxy, (poly)acyloxyalkyl and carboxyalkyl wherein \( G \) is independently selected from the group consisting from O, S, CH\textsubscript{2}, CHR\textsubscript{15}, C(R\textsubscript{15})\textsubscript{2}, NH, and NR\textsubscript{15} and \( R^{15} \) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl, with the proviso that when \( A \) is H, \( R^7 \) is not present.

\( R^3 \) is connected to the point of attachment of \( R^3 \) by a spacer selected from a group consisting of a covalent bond and a linear moiety having a chain length of 1 to 3 atoms to form C\textsubscript{7} to C\textsubscript{10} heterocyclyl with the proviso that when \( J \) is selected from O and A is selected from O and S, \( R^1 \) is selected from other than H, S(O)R\textsubscript{13}, SO\textsubscript{2}R\textsubscript{13}, CH\textsubscript{2}OC(O)R\textsubscript{15} and C(O)R\textsubscript{15} wherein C(O)R\textsubscript{15} can represent natural and synthetic amino acids and wherein \( R^{15} \) is selected from substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino and cycloalkoxy, \( R^2 \) is selected from other than H, alkanoyl and aroyl, or \( R^8 \) is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

A can be selected from the group selected from O, N(R\textsuperscript{5}) and S connected to the point of attachment of \( R^4 \) by a
spacer group selected from a group consisting of a covalent bond and a linear moiety having a chain length of 1 to 4 atoms to form C6 to C10 heterocyclyl provided that the linear moiety is selected from other than O and S;

5 A can be selected from the group selected from 0, N(R⁵) and S connected to the point of attachment of any one of R¹ and R² by a spacer group selected from a linear moiety having a chain length of 1 to 6 atoms to form C5 to C10 heterocyclyl provided that, when A is N(R⁵), R¹ is selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)R¹⁵ and C(O)R¹⁵ wherein C(O)R¹⁵ may represent natural and synthetic amino acids and wherein R¹⁵ is selected from substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino and cycloalkoxy, or R² is selected from other than H, alkanoyl and aroyl or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

A can be selected from the group consisting of O, N(R⁵) and S connected to the points of attachment of R¹ and R² by a spacer group selected from a linear moiety having a chain length of 1 to 6 to form C5 to C10 heterocyclyl;

A can be selected from the group consisting of O, N(R⁵) and S connected to X through substituent selected from hydroxyl, sulfhydryl, amino, carboxyl, and carbonyl substituents of group X by a spacer selected from a covalent bond and a linear moiety having a chain length of 1 to 4 atoms to form C5 to C10 heterocyclyl;
A can be $R^{26}$ with the proviso that when $R^{26}$ is H, $R^8$ is selected from other than hydrogen, or $R^1$ is selected from other than H, S(O)R$_{13}$, SO$_2$R$_{13}$, CH$_2$OC(O)R$_{15}$ and C(O)R$_{15}$ wherein C(O)R$_{15}$ can represent natural and synthetic amino acids and wherein R$_{15}$ is selected from substituted dihydropyridyl, alkyl, alkythio and alkoxy, or $R^2$ is selected from other than H, alkanoyl and aroyl, or J is selected from other than O;

A can be $R^{27}$, wherein $R^{27}$ is selected from the group consisting of N($R^5$)OR$_7$, N($R^5$)N($R^7$)R$_{25}$, N($R^5$)SO$_2$R$_{13}$,

N($R^5$)C(O)R$_{15}$, N($R^5$)C(S)R$_{15}$, R$_{19}$ (R$_{20}$)C=N-N($R^5$), R$_{19}$ (R$_{20}$)C=N-O, natural and synthetic amino acids, N($R^5$)P(O)(OR$_{13}$)$_1$R$_6$ and N($R^5$)P(O)(OR$_{13}$)$_2$;

$R^1$ and $R^2$ are independently selected from the group consisting of hydrogen, hydroxyl, sulfhydryl, OR$_6$, SR$_6$, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, formylalkyl, acylalkyl, CH$_2$SO$_3^-$ M$^+$, CH$_2$CH$_2$SO$_3^-$ M$^+$, CH$_2$PO$_3^{-2}$

2M$^+$, CH$_2$CH$_2$PO$_3^{-2}$ 2M$^+$, CH(OH)$_6$CF$_3$, S(O)R$_{13}$, SO$_2$R$_{13}$,

P(O)R$_{30}$, P(O)(R$^{30}$)$_2$R$_{31}$, C(O)R$_{15}$, C(S)R$_{15}$, CH$_2$OC(O)R$_{15}$,

CH$_2$NR$_{19}$ C(O)R$_{15}$, CH$_2$NR$_{19}$ C(S)R$_{15}$, CH$_2$SC(O)R$_{15}$, CH$_2$SC(S)R$_{15}$,

CH$_2$OC(O)GR$_{15}$, CH$_2$NR$_{19}$ C(O)GR$_{15}$, CH$_2$NR$_{19}$ C(S)GR$_{15}$,
CH₂OC(S)GR¹⁵, CH₂SC(S)GR¹⁵, OSO₂R¹³, OS(O)R¹³, OC(S)R¹⁵, SC(S)R¹⁵, OC(S)GR¹⁵, SC(S)GR¹⁵, OC(O)R¹⁵, SC(O)R¹⁵, OC(O)GR¹⁵, SC(O)GR¹⁵ and R¹⁹(R²⁰)CH provided that R¹ is selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)₆R¹⁵ and C(O)R¹⁵ wherein C(O)R¹⁵ can represent natural and synthetic amino acids and wherein R¹⁵ is selected from substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino and cycloalkoxy, unless J is selected from NR²², R²⁹ and S, R² is selected from other than H, alkanoyl and aroyl, R²⁶ is present, A is R²⁷, or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl or provided that R² is selected from other than H, alkanoyl and aroyl, unless R¹ is selected from other than H, S(O)R¹³, SO₂R¹³, CH₂OC(O)₆R¹⁵ and C(O)R¹⁵ wherein C(O)R¹⁵ can represent natural and synthetic amino acids wherein R¹⁵ is selected from substituted dihydropyridyl, alkyl, alkylthio, alkoxy, amino and cycloalkoxy, J is selected from NR²², R²⁹ and S, R²⁶ is present, A is R²⁷, or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl or haloalkyl;

R¹ and R² can be taken together forming a group selected from a group consisting of R¹⁹(R²⁰)C=, D(C(R³⁰)(R³¹))₂D wherein z is 2 to 5 and D is selected from the group consisting of oxygen, C=O, C=S, S(O)ₘ wherein m is 0 to 2, OP(OR⁻)₃₀, P(O)R₃₀, P(S)R₃₀ and Si(R¹⁹)R²⁰, D((R⁻)R²⁰C)ₑW(C(R¹⁹)R²₀)ₖD wherein e is 1 to 2, k is 1 to
2, with the proviso that only one D can be oxygen or sulfur at any time, and W is selected from the group consisting of oxygen, C=O, C=S, S(O)\(_m\), Se(O)\(_m\) wherein m is 0 to 2, 
P(O)\(^{30}\), P(S)\(^{30}\), N(R')\(^{19}\), and Si(R')\(^{19}\)\(^{20}\), cycloalkyl radicals, cycloalkenyl radicals wherein said cycloalkyl radicals and cycloalkenyl radicals may be optionally substituted with one or more R\(^{30}\) or R\(^{31}\) substituents, aryl radicals, heteroaryl radicals, saturated heterocyclic radicals and partially saturated heterocyclic radicals wherein said radicals are 1,2-disubstituted and said 1,2-substituents are independently selected from the group consisting of C=O, C=S, C(R')\(^{32}\), S(O), S(O)\(_2\), OP(OR')\(^{31}\)\(^{30}\), P(O)\(^{30}\), P(S)\(^{30}\), and Si(R')\(^{20}\), cis-1,2-disubstituted alkanes and cis-1,2-disubstituted alkenes wherein said 1,2-substituents are independently selected from C=O, C=S, C(R')\(^{32}\), S(O), S(O)\(_2\), OP(OR')\(^{31}\)\(^{30}\), P(O)\(^{30}\), P(S)\(^{30}\), and Si(R')\(^{20}\) and said alkyl and alkenyl may be optionally substituted with one or more R\(^{30}\) or R\(^{31}\) substituents;

R\(^3\) and R\(^4\) are independently selected from the group consisting of hydrogen, hydroxyl, sulphydryl, OR\(^6\), SR\(^6\), 
CH\(_2\)SO\(_3\)^-M\(^+\), CH\(_2\)CH\(_2\)SO\(_3\)^- M\(^+\), CH\(_2\)PO\(_3\)^-2 2M\(^+\), CH\(_2\)CH\(_2\)PO\(_3\)^-2 2M\(^+\), 
CH(OR')\(^6\)CF\(_3\), S(O)\(_R\)\(^{13}\), SO\(_2\)\(^{13}\), P(O)\(^{30}\)\(^{31}\) R\(^{30}\), P(O)\(^{30}\) R\(^{30}\), P(O)\(^{30}\) R\(^{30}\), 
C(O)\(^{15}\), C(S)\(^{15}\), CH\(_2\)OC(O)\(^{15}\), CH\(_2\)NR\(^{19}\)C(O)\(^{15}\), 
CH\(_2\)NR\(^{19}\)C(S)\(^{15}\), CH\(_2\)SC(O)\(^{15}\), CH\(_2\)SC(S)\(^{15}\), CH\(_2\)SC(S)GR\(^{15}\), 
CH\(_2\)NR\(^{19}\)C(O)GR\(^{15}\), CH\(_2\)NR\(^{19}\)C(S)GR\(^{15}\), CH\(_2\)OC(S)GR\(^{15}\), 
CH\(_2\)SC(S)GR\(^{15}\), OSO\(_2\)\(^{13}\), OS(O)\(^{13}\), OC(S)\(^{15}\), SC(S)\(^{15}\),
OC(S)GR fifteen, SC(S)GR fifteen, OC(O)R fifteen, SC(O)R fifteen, OC(O)GR fifteen and
SC(O)GR fifteen with the proviso that R^3 and R^4 are selected from
other than H, OH, SH, OR six, SR six, OC (=) O R fifteen, SC (=) O R fifteen,
CH2OC (=) O GR fifteen, OC (=) O GR fifteen, SC (=) O GR fifteen, OSO2R thirteen and OS(O)R thirteen
wherein R six, R thirteen and R fifteen are independently selected from the
group selected from hydrogen, alkyl, alkenyl, alkynyl,
cycloalkyl, heterocyclic, aryl and heteroaryl unless J is
selected from NR two, R twenty-nine and S, R one and R two are taken together,
R twenty-six is present, A is R twenty-seven, or R eight is selected from other than
hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

R five is selected from the group consisting of hydrogen,
aryl, heteroaralkyl, hydroxy, alkyl, alkenyl, alkynyl,
amino, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,
hydroxyalkyl, dicarboxamidoalkyl, cyano,carboxalkoxyalkyl,
carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carboxamidocycloalkyl,
dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl,
carboxalkoxyycycloalkyl, dicarboxalkoxyycycloalkyl,
formylalkyl, acylalkyl, heteroaryl polyhydroxyalkyl,
polyacycloalkyl, carboxalkoxy, S(O)R thirteen, SO2R thirteen, P(O)R thirty, R nineteen,
P(O)R thrity-one, C(O)R fifteen, C(S)R fifteen, CH2OC(O)R fifteen,
CH2NR nineteen C(O)R fifteen, CH2NR nineteen C(S)R fifteen, CH2SC(O)R fifteen,
CH2SC(S)R fifteen, CH2OC(O)GR fifteen, CH2NR nineteen C(O)GR fifteen, CH2NR nineteen C(S)GR fifteen,
CH2OC(S)GR fifteen, CH2SC(S)GR fifteen, heteroaryloxyalkyl, aralkyl,
arloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl,
alkeysulfonylalkyl, aralkylthioalkyl,
heteroaralkoxythioalkyl, alkoxalkyl, heteroaryloxyalkyl,
alkenlyoxyalkyl, alkylthioalkyl, aryloxyalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl,
aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl,
carboalkoxyalkyl, dialkoxyphosphonoalkyl,
diaryloxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkylamino, diaryloxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaryloxyphosphonoalkyl, sulfonylalkyl,
alkoxysulfonylalkyl, aralkoxysulfonylalkyl,
alcoxyalxylalkylamino, aralkoxysulfonylalkylamino and
sulfonylalkylamino;

with the proviso that \( R^5 \) is selected from other than the

\[ \text{group consisting of hydrogen, alkyl, alkenyl, aryl,} \]
\[ \text{heteroaryl, aralkyl, heteroaralkyl, hydroxyalkyl,} \]
\[ \text{polyhydroxyalkyl, amino, hydroxy, polyaclyoxyalkyl,} \]
\[ \text{carboalkoxy and CH}_2\text{OC(O)GR}^{15} \]
\[ \text{wherein G is independently} \]
\[ \text{selected from O, S, CH}_2, \text{CHR}^{15}, \text{C(R}^{15})_2, \text{NH, and NR}^{15} \]
\[ \text{and} \]
\[ \text{wherein R}^{15} \text{is selected from hydrogen, alkyl, alkenyl,} \]
\[ \text{alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl} \]
\[ \text{unless J is selected from NR}^{22}, \text{R}^{29}, \text{R}^1 \text{and R}^2 \text{are} \]
\[ \text{taken together, R}^{26} \text{is present, A is R}^{27}, \text{or R}^8 \text{is selected} \]
\[ \text{from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl} \]
\[ \text{and haloalkyl;} \]

\[ \text{R}^5, \text{R}^1 \text{and R}^2 \text{can be taken together to form a spacer} \]
\[ \text{group selected from a linear moiety having a chain length} \]
\[ \text{of 1 to 4 atoms to form C5 to C8 heterocyclyl;} \]

\[ \text{R}^5 \text{can be a heterocyclyl radical in which there is at} \]
\[ \text{least one carbon in one ring and in which 1 to about 4} \]
\[ \text{members of said ring are heteroatoms independently selected} \]
\[ \text{from the group consisting of oxygen, nitrogen and sulfur} \]
and said heterocyclyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino,

N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenylxoy, hydroxy, amino, thio, nitro, loweralkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfanyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonfyl, amidosulfonyl, monoalkyl amidosulfonfyl, dialkyl amidosulfonfyl, monoarylamidosulfonfyl, arylsulfonamido, diarylamidosulfonfyl, monoalkyl monoaryl amidosulfonfyl, arylsulfanyl, arylsulfonfyl, heteroarylythio, heteroarylsulfanyl, heteroarylsulfonfyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkenyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryI, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroaryllalkyl, arylalkenyl, heteroaryllkenenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicroboxamidoalkyl, cyanocarboxalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxyycycloalkyl, dicarboalkoxyycycloalkyl, formylalkyl, acylalkyl, dialkoxypshosphonoalkyl, diaralkoxypshphonoalkyl, phosphonoalkyl, dialkoxypshphonoalkoxy, diaralkoxypshphonoalkoxy, phosphonoalkoxy, dialkoxypshphonoalkylamino, diaralkoxypshphonoalkylamino, phosphonoalkylamino, dialkoxypshphonoalkyl, diaralkoxypshphonoalkyl, guanidino, amidino and acylamino with the proviso that that
$R^8$ is selected from other than H when A is $N(R^5)$ unless $R^1$ and $R^2$ are taken together;

$R^6$ is selected from the group selected from hydrogen, heterocyclic, heteroaryl, hydroxyalkyl, minoalkyl, heteroaryloxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfanylalkyl, alkylsulfonylealkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aralkylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfonylealkyl, alkylsulfonylealkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylealkyl, alkoxyalkylsulfonylealkyl, aralkoxyalkylsulfonylealkyl, alkoxyalkylamino, aralkoxyalkylamino, sulfonylealkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon with the proviso that $R^6$ is selected from other than hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl unless J is selected from the group consisting of $NR^{22}$, $R^{29}$ and S, $R^{26}$ is present, $A$ is $R^{27}$, $R^1$ and $R^2$ are taken together, or $R^8$
is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl;

\[ R^7 \] is selected from the group consisting of hydrogen, aryl, heteroaralkyl, hydroxy, alkyl, alkenyl, alkynyl, amino, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, hydroxyalkyl, dicarboxamidoalkyl, cyanocarbalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxy cyanocycloalkyl, formylalkyl, acylalkyl, \( S(O)R^{13} \), \( SO_2R^{13} \), \( P(O)R^{30}R^{31} \), \( P(O)(R^{30})_2R^{31} \), \( C(O)R^{15} \), \( C(S)R^{15} \), \( CH_2OC(O)R^{15} \), \( CH_2NR^C(O)R^{15} \), \( CH_2NR^C(S)R^{15} \), \( CH_2SC(O)R^{15} \), \( CH_2SC(S)R^{15} \), \( CH_2OC(O)GR^{15} \), \( CH_2NR^C(O)GR^{15} \), \( CH_2NR^C(S)GR^{15} \), \( CH_2OC(S)GR^{15} \), \( CH_2SC(S)GR^{15} \), heteroaralkoxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfanylalkyl, alkylsulfonylalkyl, alkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfanylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino and sulfonylalkylamino with the proviso that \( R^7 \) is selected from other than the group consisting of hydrogen, alkyl,
alkenyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxyalkyl, polyhydroxyalkyl, amino, hydroxy, polyacyloxyalkyl, carboalkoxy and CH₂OC(O)GR¹⁵ wherein G is selected from the group consisting of O, S, CH₂, CHR¹⁵, C(R¹⁵)₂, NH, and NR¹⁵ and wherein R¹⁵ is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl unless J is selected from NR²², R²⁹ and S, R²⁶ is present, A is R²⁷, R¹ and R² are taken together, or R⁸ is selected from other than hydrogen, hydroxyalkyl, alkoxyalkyl, alkyl and haloalkyl; or

R⁷, R¹ and R² can be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form a C5 to C8 heterocycyl;

R⁷ can be a heterocycyl radical in which there is at least one carbon in one ring and in which 1 to about 4 members of said ring are heteroatoms independently selected from oxygen, nitrogen and sulfur and said heterocycyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralklamino, arylthio, alkylsulfanyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfanyl, arylsulfonyl, heteroarylthio,

teroaryl sulfanyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl,
haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy,  
haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower  
cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl,  
haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl,  
hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl,  
aryl, aralkoxy, aralkyl, aralkoxyalkyl, saturated heterocyclyl,  
partially saturated heterocyclyl, heteroaryl,  
heteroarylalkyl, heteroaryloxyalkyl, arylalkyl,  
heteroarylylalkyl, arylalkenyl, heteroarylgalkenyl,  
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,  
dicarboxamidoalkyl, cyanoarcoalkoxyalkyl,  
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,  
dicyanoxyalkyl, carboxamidocycloalkyl,  
dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl,  
carboalkoxy cycloalkyl, dicarboalkoxycycloalkyl,  
formylalkyl, acylalkyl, dialkoxyporphonooalkyl,  
diaralkoxyphosphonooalkyl, phosphonooalkyl,  
dialkoxyporphonooalkoxy, diaralkoxyphosphonoalkoxy,  
phosphonooalkyl, dialkoxyporphonoalkylamino,  
diaralkoxyphosphonoalkylamino, phosphonooalkylamino,  
dialkoxyporphonoalkyl, diaralkoxyphosphonoalkyl,  
guanidino, amidino and acylamino with the proviso that A is  
selected from other than O and S unless J is selected from  
NR\(^2\), R\(^2\) and S or J\(^1\) and J\(^2\) are selected from two groups  
independently selected from OR\(^2\), SR\(^2\), NHR\(^2\) and  
N(R\(^\cdot\))R\(^1\), R\(^1\) and R\(^2\) are taken together when A is R\(^2\), or  
provided that R\(^8\) is selected from other than H when A is  
N(R\(^5\));  
\[ R^8 \]  
is selected from hydrogen, hydroxalkyl, haloalkyl,  
alkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl,  
alkylthioalkyl, cyanoalkyl, sulfhydrylalkyl, formyl, C(O)A-
R^7, C(S)A-R^7, CH_2OC(O)A-R^7, CH_2NR^19C(O)A-R^7, CH_2NR^19C(S)A-
R^7, CH_2SC(O)A-R^7, CH_2SC(S)A-R^7, CH_2OC(O)GR^{15},
CH_2NR^19C(O)GR^{15}, CH_2NR^19C(S)GR^{15}, CH_2OC(S)GR^{15}, CH_2SC(S)GR^{15}
and acyl with the proviso that R^8 is selected from other
than hydrogen, hydroxyalkyl, haloalkyl, alkyl, alkoxyalkyl
unless J^1 and J^2 are selected from NR^{22}, R^{29} and S, R^{26} is
present, R^1 and R^2 are taken together, or A is R^{27};

R^{13} is independently selected from aryloxy, amino,
alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl,
alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aroyl,
aralkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,
aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenylalkoxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl,
haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
cyanoarboxamidoalkyl, carboxaloxyalkyl,
dicarboxaloxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboxaloxyccanocycloalkyl, carboxaloxyccycloalkyl,
dicarboxaloxyccycloalkyl, formylalkyl, acylalkyl,
dialkoxyphosphonoalkyl, dianalkoxyphosphonoalky_,
phosphonoalkyl, dialkoxyphosphonoalky_, phosphonoalky_,
dialkoxyphosphonoalkylamino, dianalkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalky_,
dialkoxyphosphonoalkylamino, dianalkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalky_,
dialkoxyphosphonoalkylamino, dianalkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalky_,
dialkoxyphosphonoalkylamino, dianalkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalky_,
dialkoxyphosphonoalkylamino, dianalkoxyphosphonoalkylamino,
sulfonylalkoxy, alkoxy sulfonetylalkylamino, aralkoxy sulfonetylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon;  

\[ R^+ \] is independently selected from hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroarylxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfynylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroarylxythioalkyl, alkoxyalkyl, heteroarylxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aroylxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloarylxyalkyl, aralkylsulfynylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxoxyalkyl, carboxoxyalkyl, dicarboxoxyalkyl, cyano cycloalkyl, dicyano cycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxoxy cyanocycloalkyl, carboxoxy cycloalkyl, carboxoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxy phosphonoalkyl, diaralkoxy phosphonoalkyl, phosphonoalkyl, dialkoxy phosphonoalkoxy, diaralkoxy phosphonoalkoxy, phosphonoalkoxy, dialkoxy phosphonoalkylamino, diaralkoxy phosphonoalkylamino, phosphonoalkylamino, dialkoxy phosphonoalkyl, diaralkoxy phosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkoxy, aralkoxy sulfonylalkoxy, sulfonylalkoxy, aralkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon;  

\[ M^+ \] is a pharmaceutically acceptable cation;
X is selected from the group consisting of alkylene, alkenylene, and alkynylene groups which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano and amino; or

\[ -(CH_2)_pQ(CH_2)_r^- \] wherein \( p \) is 1 to 3, \( r \) is 1 to 3 and \( Q \) is selected from oxygen, C=O, S(O)_t, Se(O)_t wherein \( t \) is 0 to 2, \( P(O)R_{21}^{21} \) wherein \( R_{21}^{21} \) is hydroxyl or alkyl which may be optionally substituted with one of the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, and \( N(R_{12}^{12})_n \) wherein \( n \) is 1 to 2 and \( R_{12}^{12} \) is selected from the group consisting of hydrogen, oxy, hydroxyl and alkyl which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\[ -(CH_2)_sT(CH_2)_v^- \] wherein \( s \) is 0 to 2, \( v \) is 0 to 2 and \( T \) is selected from a 3 to 6 membered carbocyclic radical, aryl radical and a heterocyclic radical wherein all said radicals may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

Y is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, alkylthioalkyl, alkylaminoalkyl and \( NR_{9}^{9}R_{10}^{10} \) wherein \( R_{9}^{9} \) and \( R_{10}^{10} \) are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclic, and aralkyl;
$R^9$ and $R^{10}$ can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclyl:

$R^{19}$ and $R^{20}$ are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenxyoalkyl, halocycloalkoxyalkyl, halocycloalkenxyoalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxaloxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxyxycycloalkyl, dicarboalkoxyxycycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfanylalkyl, aralkylsulfonylalkyl, dialkoxyphosphono, dialkoxyphosphonoalkyl and dialkoxyphosphonoalkyl with the proviso that only one of $R^{19}$ and $R^{20}$ is hydrogen;

$R^{19}$ and $R^{20}$ can be taken together to form a linear moiety spacer group having a chain length of 2 to 7 atoms.
to form a group consisting of C3 to C8 cycloalkyl, C3 to C8 cycloalkenyl and C3 to C8 heterocyclyl;

\( R^{22} \) and \( R^{23} \) are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, aralkylsulfinylalkyl and aralkylsulfonylalkyl;

\( R^{24} \) and \( R^{25} \) are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkoxy, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenyloxyalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, cycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaryalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl,
cycloalkylsufonylalkyl, heteroarylsulfonylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl and aralkylsulfonylalkyl;

\( R^{24} \) and \( R^{25} \) can be taken together to form a spacer
group independently selected from a linear moiety having a chain length of 4 to 7 atoms to form C5 to C8 heterocyclyl;

\( R^{26} \) is independently selected from hydrogen, formyl, hydroxyalkyl, alkenyl, alkynyl, acyl, aroyl, aralkanoyl, heteroaroyl, alkylsulfinylalkyl, alkylsulfonylalkyl, heteroaralkylthioalkyl, alkoxyalkyl, alkenyloxyalkyl, alkylthioalkyl, cycloalkylalkeny1, cycloalkenyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkenyloxyalkyl, cyanoalkyl, carboxy, carboxamido, carboxaloxy, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyanocarboxaloxyalkyl, carboxaloxyalkyl, dicarboxaloxyalkyl, formylalkyl and acylalkyl with the proviso that \( J \) is selected from other than 0 unless \( R^{8} \) is other than hydrogen;

\( R^{28} \) is independently selected from a group consisting
of CH\((R^{23})CH_2\), CH\((R^{23})CH_2\)CH\(_2\)H, CH\(_2\)CH\((R^{23})CH_2\), cycloalkylene
and heterocyclylene;

\( R^{30} \) and \( R^{31} \) are independently selected from the group consisting of hydroxy, thiol, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylothio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylothioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkeny1, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl, halooralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl,
5 dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboalkoxycyanocycloalkyl, carboalkoxyycyloalkyl, dicarboalkoxyycyloalkyl, formylalkyl, acylalkyl,
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,
10 phosphonoalkyl, dialkoxyphosphonoalkoxy,
diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
15 alkoxyalkyl, aralkoxyalkyl, alkoxyalkylalkoxy, aralkoxyalkylalkoxy, sulfonylalkoxy, alkoxyalkylamino, alkoxyalkylamino, sulfonylalkylamino, natural and
synthetic amino acids, and polyhydroxy compounds of carbon;

20 \[ R_{30} \text{ and } R_{31} \] can be taken together to form a linear
moiety spacer group having a chain length of 2 to 7 atoms
selected from the group consisting of C3 to C8 cycloalkyl,
C3 to C8 cycloalkenyl, and C3 to C8 heterocyclyl
substituted independently and optionally with one or more
alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy,
haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and
halo groups.

2. A compound having the Formula:
and pharmaceutically acceptable salts thereof, wherein:

R^1 and R^2 are independently selected from the group

consisting of hydroxyl, sulfhydryl, OR^6, SR^6, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
cyanocarboxamidoalkyl, carboalkoxyalkyl,
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl,
dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, CH_2SO_3^- M^+,
CH_2CH_2SO_3^- M^+, CH_2PO_3^- 2M^+, CH_2CH_2PO_3^- 2M^+, CH(OR^6)CF_3,
P(O)R^3 R^4, P(O)(R^3)R^2 R^1, C(S)R^15, CH_2SC(O)R^15,
CH_2SC(S)R^15, CH_2OC(O)GR^15, CH_2OC(S)GR^15, CH_2SC(S)GR^15,
OSO_2R^13, OS(O)R^13, OC(S)R^15, SC(S)R^15,
OC(S)GR^15, SC(S)GR^15, OC(O)R^15, SC(O)R^15, OC(O)GR^15, SC(O)GR^15
wherein R^6 is selected from the group consisting of
hydroxyalkyl, aminoalkyl, heteroaryloxyalkyl, aralkyl,
aryloxyalkyl, aryloxyalkyl, alkylsulfinylalkyl,
alkylsulfonylalkyl, aralkylthioalkyl,
heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl,
halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl,
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,(dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl; carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diarylalkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diarylalkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diarylalkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, \( R^{13} \) is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alky1, alkenyl, alkylnyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloalkylsulfinylalkyl, aralkylsulfinylalkyl, cyanalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diarylalkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diarylalkoxyphosphonoalkoxy, dialkoxyphosphonoalkylamino, diarylalkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl, 
diaralkoxyphosphonoalkyl, sulfonylalkyl, 
alkoxysulfonylealkyl, aralkoxysulfonylealkyl, 
alkoxysulfonylealkoxy, aralkoxysulfonylealkoxy, 
sulfonylalkoxy, alkoxy sulfonylealkylamino, 
aralkoxysulfonylealkylamino, sulfonylalkylamino, natural and 
synthetic amino acids and polyhydroxy compounds of carbon, 
$R^{15}$ is selected from the group consisting of hydrido, 
aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, 
heteroaryloxyalkyl, alkoxy, alkylthio, arythio, alkyl, 
alkenyl, alkynyl, aryl, aralkyl, arloxyalkyl, 
aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylealkyl, 
aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, 
heteroaryloxyalkyl, alkényloxyalkyl, alkylthioalkyl, 
arlyloalkyl, cycloalkyl, cycloalkylalkyl, 
cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, 
haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, 
aralkylsulfonylalkyl, carbonyl, cyanoalkyl, dicyanoalkyl, 
carboxamidoalkyl, dicarboxamidoalkyl, 
cyanocarboalkoxyalkyl, carboalkoxyalkyl, 
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, 
carboxamidocycloalkyl, dicarboxamidocycloalkyl, 
carboalkoxyalkenyalkyl, carboalkoxyalkylalkyl, 
araalkoxyalkyl, araalkoxyalkylalkyl, aralkoxyalkyl, 
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, 
phosphonoalkyl, dialkoxyphosphonoalkoxyl 
diaralkoxyphosphonoalkoxy, phosphonoalkoxy, 
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, 
phosphonoalkylamino, diaralkoxyphosphonoalkyl, 
diaralkoxyphosphonoalkyl, sulfonylalkyl, 
alkoxy sulfonylealkyl, aralkoxysulfonylealkyl, 
alkoxy sulfonylealkoxy, aralkoxysulfonylealkoxy, 
sulfonylalkoxy, alkoxy sulfonylealkylamino, 
aralkoxysulfonylealkylamino, sulfonylalkylamino, natural and 
synthetic amino acids and polyhydroxy compounds of carbon,
\(R^1\) and \(R^2\) are independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyln, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylamyl, heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, carboxalkoxy cycloalkyl, dicarboxalkoxy cycloalkyl, formylalkyl, acylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaralkoxyphosphono, dialkoxyphosphonoalkyl and diaralkoxyphosphonoalkyl with the proviso that only one of \(R^1\) and \(R^2\) is hydrogen, \(R^3\)

and \(R^3\) are independently selected from the group consisting of hydroxy, thiol, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alky1, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl,
haloarylalkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicycloamidoalkyl,
cyanocarboalkoxyalkyl, carboalkoxyalkyl,
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboalkoxycyanocycloalkyl, carboalkoxy,cycloalkyl,
dicarboalkoxy,cycloalkyl, formylalkyl, acylalkyl,
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,
phosphonoalkyl, dialkoxyphosphonoalkoxy,
diaralkoxyphosphonoalkoxy, phosphonoalkoxy,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
akoxysulfonylalkyl, aralkoxysulfonylalkyl,
akoxysulfonylalkoxy, aralkoxysulfonylalkoxy,
sulfonylalkoxy, alkoxysulfonylalkylamino,
aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and
synthetic amino acids, and polyhydroxy compounds of carbon,
wherein R<sup>30</sup> and R<sup>31</sup> can be taken together to form a linear
moiety spacer group having a chain length of 2 to 7 atoms
selected from the group consisting of C3 to C8 cycloalkyl,
C3 to C8 cycloalkenyl, and C3 to C8 heterocyclyl
substituted independently and optionally with one or
more alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl,
alkoxy, haloalkoxy, cyano, carboalkoxy, hydroxy,
hydroxyalkyl, and halo groups, M<sup>+</sup> is a pharmaceutically
acceptable cation; and G is selected from the group
consisting of O, S, CH<sub>2</sub>, CHR<sup>15</sup>, C(R<sup>15</sup>)<sub>2</sub>, NH and NR<sup>15</sup>
wherein R<sup>15</sup> is selected from the group consisting of hydrogen,
alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and
heteroaryl
R$^3$ and R$^4$ are independently selected from the group consisting of CH$_2$SO$_3^-$ M$^+$, CH$_2$CH$_2$SO$_3^-$ M$^+$, CH$_2$PO$_3^{2-}$ 2M$^+$, CH$_2$CH$_2$PO$_3^{2-}$ 2M$^+$, CH(OH)$_6$CF$_3$, S(O)R$^{13}$, SO$_2$R$^{13}$, P(O)R$^{30}$R$^{31}$, P(O)(R$^-$)$_2$R$^{31}$, C(O)R$^{15}$, C(S)R$^{15}$, CH$_2$OC(O)R$^{15}$, CH$_2$NR$^{19}$C(O)R$^{15}$, CH$_2$NR$^{19}$C(S)R$^{15}$, CH$_2$SC(O)R$^{15}$, CH$_2$SC(S)R$^{15}$, CH$_2$NR$^{19}$C(O)GR$^{15}$, CH$_2$NR$^{19}$C(S)GR$^{15}$, CH$_2$OC(S)GR$^{15}$, CH$_2$SC(S)GR$^{15}$, OC(S)R$^{15}$, SC(S)R$^{15}$, OC(S)GR$^{15}$, SC(S)GR$^{15}$;

R$^7$ is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxyxyanocycloalkyl, carboalkoxyxycycloalkyl, dicarboalkoxyxycycloalkyl, formylalkyl, acylalkyl, S(O)R$^{13}$, SO$_2$R$^{13}$, P(O)R$^{30}$R$^{31}$, P(O)(R$^-$)$_2$R$^{31}$, C(O)R$^{15}$, C(S)R$^{15}$, CH$_2$OC(O)R$^{15}$, CH$_2$NR$^{19}$C(O)R$^{15}$, CH$_2$NR$^{19}$C(S)R$^{15}$, CH$_2$SC(O)R$^{15}$, CH$_2$SC(S)R$^{15}$, CH$_2$NR$^{19}$C(O)GR$^{15}$, CH$_2$NR$^{19}$C(S)GR$^{15}$, CH$_2$OC(S)GR$^{15}$, CH$_2$SC(S)GR$^{15}$, heteroaryloxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, dialkoxyphosphonoalkyl, phosphonoalkyl, phos.
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxyalkylsulfonylalkyl, aralkoxyalkylsulfonylalkyl, alkoxyalkylsulfonylalkyl, aralkoxyalkylsulfonylalkylamino and sulfonylalkylamino;

R^7 can be a heterocyclyl radical in which there is at least one carbon in one ring and in which 1 to about 4 members of said ring are heteroatoms independently selected from oxygen, nitrogen and sulfur and said heterocyclyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenylxloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylamid, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyarylalkyl, hydroxyalkyl, hydroxyheteroarylalkyl, haloalkoxyalkyl, ary1, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, 
dicyanocycloalkyl, carboxamidocycloalkyl, 
dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, 
carboxalkoxyalkyl, dicarboxalkoxyalkyl, 
formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, 
diaralkoxyphosphonoalkyl, phosphonoalkyl, 
dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, 
phosphonoalkoxy, dialkoxyphosphonoalkylamino, 
diaralkoxyphosphonoalkylamino, phosphonoalkylamino, 
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, 
guanidino, amidino and acylamino with the proviso that A is 
selected from other than 0 and S or provided that R^8 is 
selected from other than H when A is N(R^5); 

R^7, R^1 and R^2 can be taken together to form a spacer 
group selected from a linear moiety having a chain length 
of 1 to 4 atoms to form a C5 to C8 heterocyclyl; 

R^8 is selected from the group consisting of 
aminoalkyl, alkylaminoalkyl, alkylthioalkyl, cyanoalkyl, 
sulphhydrylalkyl, formyl, C(O)A-R^7, C(S)A-R^7, CH\_2OC(O)A-R^7, 
CH\_2NR\_19C(O)A-R^7, CH\_2NR\_19C(S)A-R^7, CH\_2SC(O)A-R^7, CH\_2SC(S)A-R^7, 
CH\_2OC(O)GR\_15, CH\_2NR\_19C(O)GR\_15, CH\_2NR\_19C(S)GR\_15, 
CH\_2OC(S)GR\_15, CH\_2SC(S)GR\_15 and acyl; 

X is selected from the group consisting of alkylene, 
alkenylene, and alkynylene groups which may be optionally 
substituted from the group consisting of alkyl, alkoxy, 
hydroxy, sulphhydryl, halogen, trifluoromethyl, nitro, cyano 
and amino;
X can be \(-(\text{CH}_2)_p\text{Q(\text{CH}_2)}_r\) wherein \(p\) is 1 to 3, \(r\) is 1 to 3 and \(Q\) is selected from oxygen, C=O, S(O)\(_t\), Se(O)\(_t\) wherein \(t\) is 0 to 2, \(P(O)R^{21}\) wherein \(R^{21}\) is hydroxyl or alkyl which may be optionally substituted with one of the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, and \(N(R^{12})\)_n wherein \(n\) is 1 to 2 and \(R^{12}\) is selected from the group consisting of hydrogen, oxy, hydroxyl and alkyl which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\[X\text{ can be } -(\text{CH}_2)_sT(\text{CH}_2)_v\] wherein \(s\) is 0 to 2, \(v\) is 0 to 2 and \(T\) is selected from a 3 to 6 membered carbo cyclic radical, aryl radical and a heterocyclic radical where all said radicals may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\(Y\) is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenylxoy, alkenyloxyalkyl, alkylthioalkyl, alkylaminoalkyl and \(NR^9R^{10}\) wherein \(R^9\) and \(R^{10}\) are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclicl, and aralkyl;

\(R^9\) and \(R^{10}\) can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclicl;
A is selected from the group consisting of O, N(R^5), S and heterocyclic with the proviso that J is selected from other than O, wherein R^5 is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, carboxalkoxyycycloalkyl, dicarboxalkoxyycycloalkyl, formylalkyl, acylalkyl, S(O)R^{13}, SO_2R^{-}, P(O)R^{30,31}, P(O)(R')_2R^{-}, C(O)R^{-}, C(S)R^{-}, CH_2OC(O)R^{-}, CH_2NR^{-}C(O)R^{-}, CH_2NR^{-}C(S)R^{-}, CH_2SC(O)R^{-}, CH_2SC(S)R^{-}, CH_2NR^{-}C(O)GR^{-}, CH_2NR^{-}C(S)GR^{-}, CH_2OC(S)GR^{-}, CH_2SC(S)GR^{-}, heteroaryloxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboxalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonioalkyl, alkoxyalkylsulfonylalkyl, aralkoxyalkylsulfonylalkyl, aralkoxyalkylsulfonylalkylamino, aralkoxyalkylsulfonylalkylamino and sulfonioalkylamino;

A can be selected from the group consisting of O, N(R^5) and S connected to X through substituent selected
from hydroxyl, sulfhydryl and substituents of group X by a spacer selected from a covalent bond and a linear moiety having a chain length of 1 to 4 atoms to form C5 to C10 heterocyclyl;

5 A can be $^R_{27}$, wherein $^R_{27}$ is selected from the group consisting of $N(R^5)OR^7$, $N(R^5)NR^7R^{25}$, $N(R^5)SO_2R^{13}$, $N(R^5)C(O)R^{15}$, $N(R^5)C(S)R^{15}$, $R^{19}(R^{20})C=N-N(R^5)$, $R^{19}(R^{20})C=N-O$, natural and synthetic amino acids, $N(R^5)P(O)(OR^{13})_1R^6$ and $N(R^5)P(O)(OR^{13})_2$ wherein $R^{25}$ is independently selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkoxy, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, cycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heteroaralkylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroaryl sulfinylalkyl, heteroaryl sulfonylalkyl, alkenylsulfinylalkyl and alkenylsulfonylalkyl;

$R^1$ and $R^2$ can be taken together to form a group independently selected from a group consisting of $R^{19}(R^{20})C=, D(C(R^{30})(R^{31}))_2D$ where z is 2 to 5 and D is
selected from the group consisting of oxygen, C=O, C=S, S(O)m where m is 0 to 2, OP(OR)31R30, P(O)R30, P(S)R30 and Si(R19)R20, D((R19)R20)C=WN(C(R19)R20)kD where e is 1 to 2, k is 1 to 2, with the proviso that only one D can be oxygen or sulfur at any time, and W is selected from the group consisting of oxygen, C=O, C=S, S(O)m, Se(O)m where m is 0 to 2, P(O)R30, P(S)R30, N(R19), and Si(R19)R20;  

R1, R2 and R3 can be taken together to form a spacer group selected from a linear moiety having a chain length of 1 to 4 atoms to form C5 to C8 heterocycl; 

J is selected from the group consisting of O, NR22, 

and S wherein R22 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkynylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkoxyalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, aralkylsulfinylalkyl and aralkylsulfonylalkyl; 

R19 and R20 can be taken together to form a linear moiety spacer group having a chain length of 2 to 7 atoms.
to form a group consisting of C3 to C8 cycloalkyl, C3 to C8 cycloalkenyl and C3 to C8 heterocyclyl.

3. The compound and pharmaceutically acceptable salts as recited in Claim 2 wherein:

R¹ and R² are independently selected from the group consisting of hydroxyl, sulfhydryl, OR¹⁶, SR¹⁶, CH₂SO₃⁻, CH₂SO₃⁺, CH₂CH₂SO₃⁻, CH₂PO₃⁻, CH₂CH₂PO₃⁻, 2M⁺, P(O)R¹⁰₋₁³, P(O)(R¹⁰)₂R¹³, C(S)R¹⁵⁻, CH₂SC(O)R¹⁵⁻, CH₂SC(S)R¹⁵⁻, CH₂OC(O)GR¹⁵⁻, CH₂OC(S)GR¹⁵⁻, CH₂SC(S)GR¹⁵⁻, OSO₂R¹₃⁻, OS(O)R¹₃⁻, OC(S)R¹⁵⁻, SC(S)R¹⁵⁻, OC(S)GR¹⁵⁻, SC(S)GR¹⁵⁻, OC(O)R¹⁵⁻, SC(O)R¹⁵⁻, OC(O)GR¹⁵⁻, and SC(O)GR¹⁵⁻, wherein R⁶ is selected from the group consisting of hydroxyalkyl, aminoalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylealkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, halocycaralkylsulfonylealkyl, cyanoalkyl, dicynoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, carboxalkoxycyanocycloalkyl, dicarboxalkoxycyanocycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxysulfonylalkyl, alkoxy sulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, $R^{13}$ is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyld, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicyanoalkoxyalkyl, cyanocycloalkyl, dicyano cycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonooalkyl, diaralkoxyphosphonooalkyl, phosphonoalkyl, dialkoxy phosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonooalkylamino, diaralkoxyphosphonooalkylamino, phosphonoalkylamino, dialkoxy phosphonoalkyl, diaralkoxy phosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxysulfonylalkyl, alkoxy sulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxy sulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, $R^{15}$ is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl,
heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, arylalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaryloxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkeny1, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkeny1, haloarylsulfinylalkyl, haloarylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxy cyanocycloalkyl, carboxalkoxy cycloalkyl, icarboxalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxyposphonoalkyl, diarylkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyposphonoalkoxy, dialkoxyposphonoalkoxy, phosphonoalkoxy, dialkoxyposphonoalkylamino, dialkoxyposphonoalkylamino, phosphonoalkylamino, dialkoxyposphonoalkyl, diarylkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon;

$R^{30}$ and $R^{31}$ are independently selected from the group consisting of hydroxy, thiol, aryl, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, arylalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaryloxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl,
haloarylalkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
cyanocarboalkoxyalkyl, carboalkoxyalkyl,
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl,
dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl,
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,
phosphonoalkyl, dialkoxyphosphonoalkoxy,
diaralkoxyphosphonoalkoxy, phosphonoalkoxy,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
alkoxysulfonylalkyl, aralkoxysulfonylalkyl,
alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy,
sulfonylalkoxy, alkoxy, sulfonylalkylaminoo,
laralkoxysulfonylalylamino, sulfonylalkylamino, natural and
synthetic amino acids, and polyhydroxy compounds of carbon,
wherein $R^{30}$ and $R^{31}$ can be taken together to form a linear
moiety spacer group having a chain length of 2 to 7 atoms
selected from the group consisting of C3 to C8 cycloalkyl,
C3 to C8 cycloalkenyl, and C3 to C8 heterocyclyl
substituted independently and optionally with one or more
alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy,
haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and
halo groups, $M^{+}$ is a pharmaceutically acceptable cation;
and G is selected from the group consisting of O, S, CH$_2$,
CHR$^{15}$, C(R$^{15}$)$_2$, NH and NR$^{15}$ wherein R$^{15}$ is selected from the
group consisting of hydrogen, alkyl, alkenyl, alkynyl,
cycloalkyl, heterocyclic, aryl and heteroaryl;
R^3 and R^4 are independently selected from the group consisting of CH_2SO_3^- M^+, CH_2CH_2SO_3^- M^+, CH_2PO_3^- 2M^+,
CH_2CH_2PO_3^- 2M^+, CH(OR^6)CF_3, S(O)R^13, SO_2R^13, P(O)R^30R^31,
P(O)R^30R^31, C(O)R^15, C(S)R^15, CH_2OC(O)R^15,
CH_2NR^19C(O)R^15, CH_2NR^19C(S)R^15, CH_2SC(O)R^15, CH_2SC(S)R^15,
CH_2NR^19C(O)GR^15, CH_2NR^19C(S)GR^15, CH_2OC(S)GR^15,
CH_2SC(S)GR^15, OC(S)R^15, SC(S)R^15, OC(S)GR^15, SC(S)GR^15;

R^7 is selected from the group consisting of alkynyl,
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyanocarboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carboxamidocycloalkyl,
dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl,
carboalk oxy cycloalkyl, dicarboalkoxy cycloalkyl,
formylalkyl, acylalkyl, S(O)R^13, SO_2R^13, P(O)R^30R^31,
P(O)R^30R^31, C(O)R^15, C(S)R^15, CH_2OC(O)R^15,
CH_2NR^19C(O)R^15, CH_2NR^19C(S)R^15, CH_2SC(O)R^15, CH_2SC(S)R^15,
CH_2NR^19C(O)GR^15, CH_2NR^19C(S)GR^15, CH_2OC(S)GR^15,
CH_2SC(S)GR^15, heteroaryloxyalkyl, aryloxyalkyl,
aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,
aralkylthioalkyl, heteroaralkylthioalkyl, alkox yalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,
arlythioalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl,
haloalkyl, haloalkenyl, halocycloalkyl,
aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl,
carboalkoxyalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
alkoxysulfonylealkyl, aralkoxysulfonylealkyl,
5 alkoxyisulfonylealkylamino, aralkoxyisulfonylealkylamino and
sulfonylealkylamino wherein R\(^{19}\) is selected from the group
consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl,
alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl,
10 aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfinylalkyl,
alkylsulfonylealkyl, aralkylthioalkyl,
heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl,
15 haloalkenyl, haloalkoxyalkyl, haloalkoxyalkenyl,
haloalkycycloalkoxyalkyl, haloalkycycloalkoxyalkenyl,
haloalkycycloalkenyoxyalkyl, perhaloaryl, perhaloaralkyl,
perhaloaryloxyalkyl, heteroaryl, heteroaralkyl,
heteroarylthioalkyl, heteroaralkylthioalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
20 cyanocarboxalkoxyalkyl, carboxalkoxyalkyl,
dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboxalkoxycyanocycloalkyl, carboxalkoxyycycloalkyl,
dicarboxalkoxyycycloalkyl, formylalkyl, acylalkyl,
25 arylsulfinylalkyl, arylsulfonylealkyl, aralkylsulfinyl,
cycloalkylsulfinylalkyl, cycloalkylsulfonylealkyl,
heteroarylsulfonylealkyl, heteroarylsulfinylalkyl,
aralkylsulfinylalkyl, aralkylsulfonylealkyl, carboxy,
dialkoxyphosphono, diaralkoxyphosphono,
30 dialkoxyphosphonoalkyl and diaralkoxyphosphonoalkyl;

R\(^{7}\) can be a heterocyclyl radical in which there is at
least one carbon in one ring and in which 1 to about 4
members of said ring are heteroatoms independently selected
from oxygen, nitrogen and sulfur and said heterocyclic radical may be optionally substituted with heteroarylmino, N-aryl-N-alkylamino, N-heteroarylmino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arythio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkeny, lower cycloalkylalkyl, lower cycloalkenyalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclic, partially saturated heterocyclic, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkeny, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicycloalkyl, cyanocarboxalcohol, dicarboxamidoalkyl, carboalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dircarboxamidocycloalkyl, carboalkoxyycycloalkyl, dicarboalkoxyycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,
guanidino, amidino and acylamino with the proviso that A is selected from other than O and S or provided that \( R^8 \) is selected from other than H when A is N(R^5);

\( R^8 \) is selected from the group consisting of aminoalkyl, alkylaminoalkyl, alkylthioalkyl, cyanoalkyl, sulfhydroxyalkyl, formyl, C(O)A-R^7, C(S)A-R^7, CH_2OC(O)A-R^7, CH_2NR(C(O)A-R^7, CH_2NR(C(S)A-R^7, CH_2SC(O)A-R^7, CH_2SC(S)A-R^7, CH_2OC(O)GR^{15}, CH_2NR(C(O)GR^{15}, CH_2NR(C(S)GR^{15}, CH_2OC(S)GR^{15}, CH_2SC(S)GR^{15} and acyl;

\( R^8 \) can be selected from the group consisting of hydrogen, hydroxyalkyl, haloalkyl, alkyl and alkoxyalkyl with the proviso that J is NR^{22} or S;

X is selected from the group consisting of alkenylene, alkenylene, and alkynylene groups which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, sulfhydroxyl, halogen, trifluoromethyl, nitro, cyano and amino;

X can be \(-(CH_2)_pQ(CH_2)_r-\) wherein p is 1 to 3, r is 1 to 3 and Q is selected from oxygen, C=O, S(O)\(_t\), Se(O)\(_t\) wherein t is 0 to 2, P(O)R^{21} wherein R^{21} is hydroxyl or alkyl which may be optionally substituted with one of the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, and N(R^{12})\(_n\) wherein n is 1 to 2 and R^{12} is selected from the group consisting of hydrogen, oxy, hydroxyl and alkyl which may be optionally substituted from the group consisting of
alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

X can be \(-(\text{CH}_2)_s\text{T(\text{CH}_2)}_v\)\n\ \text{wherein s is 0 to 2, v is 0 to 2 and T is selected from a 3 to 6 membered carbocyclic radical, aryl radical and a heterocyclyl radical where all said radicals may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;}

Y is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxalkyl, alkylthioalkyl, alkylaminoalkyl and \(\text{NR}^9\text{R}^{10}\)\n\ \text{wherein R}^9\text{ and R}^{10}\text{ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, ary1, heterocyclyl, and aralkyl;}

\(\text{R}^9\text{ and R}^{10}\text{ can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclyl;}

A is selected from the group consisting of O, N(R)^5, S and heterocyclyl with the proviso that J is selected from other than O, where \(\text{R}^5\text{ is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl,}

dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, S(O)\text{R}^{13},

SO_2\text{R}^{13}, \text{P(O)R}^{30}\text{R}^{31}, \text{P(O)(R}^{30}\text{)R}^{31}, \text{C(O)R}^{15}, \text{C(S)R}^{15},

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CH₂OC(O)R¹⁵, CH₂NR¹⁹C(O)R¹⁵, CH₂NR¹⁹C(S)R¹⁵, CH₂SC(O)R¹⁵,
CH₂SC(S)R¹⁵, CH₂NR¹⁹C(O)GR¹⁵, CH₂NR¹⁹C(S)GR¹⁵, CH₂OC(S)GR¹⁵,
CH₂SC(S)GR¹⁵, heteroaryloxyalkyl, aryloxyalkyl,
aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,
aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkythioalkyl,
arylthioalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl,
haloalkyl, haloalkenyl, halocycloalkyl,
aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl,
carboxyalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonlalkyl,
alkoxysulfonylalkyl, aralkoxysulfonylalkyl,
alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino and
sulfonlalkylamino;

A can be selected from the group consisting of O,
N(R⁵) and S connected to X through substituent selected
from hydroxyl, sulfhydryl and substituents of group X by a
spacer selected from a covalent bond and a linear moiety
having a chain length of 1 to 4 atoms to form C₅ to C₁₀
heterocyclyl;

A can be R²⁷, wherein R²⁷ is selected from the group
consisting of N(R⁵)OR⁷, N(R⁵)N(R⁷)R²⁵, N(R⁵)SO₂R¹³,
N(R⁵)C(O)R¹⁵, N(R⁵)C(S)R¹⁵, R¹⁹(R²⁰)C=N=N(R⁵), R¹⁹(R²⁰)C=N-
O, natural and synthetic amino acids, N(R⁵)P(O)(OR¹³)₁R⁶ and
N(R⁵)P(O)(OR¹³)₂ wherein R²⁵ is selected from the group
consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl,
alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkoxy, alkylsulfanylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylothioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkylsulfanylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, cycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylothioalkyl, arylsulfanylalkyl, arylnesulfanylalkyl, cycloalkylsulfanylalkyl, cycloalkylsulfynlalkyl, heteroarylsulfynlalkyl, and aralkylsulfynlalkyl and $R^{20}$ is selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, acyl, aroyl, aralkanoyl, heteroaroyl, aralkoxyalkyl, alkylsulfynlalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylothioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkylalkenyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylothioalkyl, heteroaralkylthioalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyano carboxamidoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxamidoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxamidoalkyl, dicyanocycloalkyl, dicarboxamidoalkyl, dicarboxamidoalkyl, dicarboxamidoalkyl, dicarboxamidoalkyl, carboxamidoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, formylalkyl, acylalkyl,
arylsulfinylalkyl, arylsufonylalkyl, aralkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, dialkoxyphosphono, diaalkoxyphosphonoalkyl and dialkoxyphosphonoalkyl;  

$R^1$ and $R^2$ can be taken together to form a group independently selected from a group consisting of  

$R^{19} (R^{20})C=, D(C(R^{30})(R^{31}))_zD$ where $z$ is 2 to 5 and $D$ is  

selected from the group consisting of oxygen, C=O, C=S, S(O)$_m$ where $m$ is 0 to 2, OP(OR$^{31}$)$_R^{30}$, P(O)$_R^{30}$, P(S)$_R^{30}$ and  

$Si(R^{19})R^{20}$, D((R$^{19}$)R$^{20}$C)$_e$W(C(R$^{19}$)R$^{20}$)$_kD$ where $e$ is 1 to 2, $k$ is 1 to 2, with the proviso that only one $D$ can be oxygen or sulfur at any time, and $W$ is selected from the group consisting of oxygen, C=O, C=S, S(O)$_m$, Se(O)$_m$ where $m$ is 0 to 2, P(O)$_R^{30}$, P(S)$_R^{30}$, N(R$^{19}$), and Si(R$^{19}$)R$^{20}$;  

J is selected from the group consisting of O, NR$^{22}$, and S wherein R$^{22}$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl, halocycloalkenylalkyl, perhaloaryloxyalkyl, heteroaryl, heteroarylalkyl arylsulfinylalkyl, arylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl.
heteroaryl sulfonylalkyl, heteroaryl sulfinylalkyl, aralkyl sulfinylalkyl and aralkyl sulfonylalkyl; heteroaryl thioalkyl, heteroaralkyl thioalkyl,

19 $R^1$ and $R^2$ can be taken together to form a linear moiety spacer group having a chain length of 2 to 7 atoms to form a group consisting of C3 to C8 cycloalkyl, C3 to C8 cycloalkenyl and C3 to C8 heterocyclyl.

4. The compound and pharmaceutically acceptable salts as recited in Claim 2 wherein:

$R^1$ and $R^2$ are independently selected from the group consisting of hydroxyl, sulfhydryl, OR, SR, P(O)R, P(O)(OR)$^{30}$, P(O)(OR)$^{31}$, C(S)R$^{15}$, OSO$_2$R$^{13}$, O(S)R$^{13}$, OC(S)R$^{15}$, SC(S)R$^{15}$, OC(S)GR$^{15}$, SC(S)GR$^{15}$, OC(O)R$^{15}$, SC(O)R$^{15}$, OC(O)GR$^{15}$, and SC(O)GR$^{15}$, wherein $R^6$ is selected from the group consisting of hydroxyalkyl, aminoalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkythioalkyl, heteroaralkythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycaralkyl sulfinylalkyl, aralkyl sulfonylalkyl, cyanoalkyl, dicyanoalkyl, carbamidoalkyl, dicarbamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl, dicarboxalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxy phosphonoalkyl.
dialkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, $R^{13}$ is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, aroyloxy, alkyl, alkenyl, alkylnyl, aryl, aralkyl, aralkoxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aroyloxyalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, dialkoxy phosphonoalkyl, diaralkoxy phosphonoalkoxy, phosphonoalkyl, dialkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkoxy, aralkoxy sulfonylalkoxy, sulfonylalkoxy, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon,
$R^{15}$ is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, aralkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, icarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxyalkylsulfonylalkyl, aralkoxyalkylsulfonylalkyl, alkoxyalkyl, alkoxyalkylamino, aralkoxyalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, $R^{30}$ and $R^{31}$ are independently selected from the group consisting of hydroxy, thiol, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl,
heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenylalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl,
5 haloalkylsulfenylalkyl, aralkylsulfonylalkyl, cyanoalkyl,
dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
cyanocarboalkoxyalkyl, carboalkoxyalkyl,
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
10 carboalkoxycyanocycloalkyl, carboalkoxydicycloalkyl,
dicarboalkoxydicycloalkyl, formylalkyl, acylalkyl,
dialkoxycarbophonoalkyl, dialkoxycarbophonoalkyl,
phosphonoalkyl, dialkoxycarbophonoalkoxy,
dialkoxycarbophonoalkoxy, phosphonoalkoxy,
15 dialkoxycarbophonoalkylamino, dialkoxycarbophonoalkylamino,
phosphonoalkylamino, dialkoxycarbophonoalkyl,
dialkoxycarbophonoalkyl, sulfonylealkyl,
alkoxysulfonylealkyl, aralkoxysulfonylealkyl,
alkoxysulfonylealkoxy, aralkoxysulfonylealkoxy,
20 sulfonylealkoxy, alkoxyalkylamino,
aralkoxysulfonylealkylamino, sulfonylealkylamino, natural and
synthetic amino acids, and polyhydroxy compounds of carbon,
wherein $R^{30}$ and $R^{31}$ can be taken together to form a linear
moiety spacer group having a chain length of 2 to 7 atoms
selected from the group consisting of C3 to C8 cycloalkyl,
C3 to C8 cycloalkenyl, and C3 to C8 heterocyclyl
substituted independently and optionally with one or more
alkyl, haloalkyl, aryl, heteroaryl, alkoxyalkyl, alkoxy,
haloalkoxy, cyano, carboalkoxy, hydroxy, hydroxyalkyl, and
30 halo groups, $M^+$ is a pharmaceutically acceptable cation;
and G is selected from the group consisting of O, S, CH$_2$,

$\text{CHR}^{15}$, $\text{C}(\text{R}^{15})_2$, NH and $\text{NR}^{15}$ wherein $\text{R}^{15}$ is selected from the
group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl

\[ R^3 \text{ and } R^4 \text{ are independently selected from the group } \]
consisting of \( S(O)R^{13} \), \( \text{SO}_2R^{13} \), \( P(O)R^{30}R^{31} \), \( P(O)(R^{30})_2R^{31} \),
\( C(O)R^{15} \), \( C(S)R^{15} \), \( \text{OC(S)}R^{15} \), \( \text{SC(S)}R^{15} \), \( \text{OC(S)}\text{GR}^{15} \), \( \text{SC(S)}\text{GR}^{15} \);

\[ R^7 \text{ is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxyxcycloalkyl, dcarboalkoxyxcycloalkyl, formylalkyl, acylalkyl, S(O)R^{13} \), \( \text{SO}_2R^{13} \), \( P(O)R^{30}R^{31} \), \( P(O)(R^{30})_2R^{31} \), \( C(O)R^{15} \), \( C(S)R^{15} \), \( \text{HC}_{2}\text{OC(S)}R^{15} \), \( \text{CH}_2\text{SC(S)}R^{15} \), \( \text{CH}_2\text{OC(S)}\text{GR}^{15} \), \( \text{CH}_2\text{SC(S)}\text{GR}^{15} \), heteroaryloxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonooalkyl, diaralkoxyphosphonooalkyl, phosphonoalkyl, dialkoxyphosphonooalkylamino, diaralkoxyphosphonooalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino and

sulfonylalkylamino;
$R^7$ can be a heterocyclyl radical in which there is at least one carbon in one ring and in which 1 to about 4 members of said ring are heteroatoms independently selected from oxygen, nitrogen and sulfur and said heterocyclyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylamino, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkeny1, lower cycloalkylalkyl, lower cycloalkanylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxylarkyl, hydroxyalkyl, hydroxyheteroalkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxybicycloalkyl, dicarboalkoxybicycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy,
phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, guanidino, amidino and acylamino with the proviso that \( A \) is selected from other than \( O \) and \( S \) or provided that \( R^8 \) is selected from other than \( H \) when \( A \) is \( \text{N}(R^5) \);

\( R^8 \) is selected from the group consisting of hydrogen, hydroxyalkyl, haloalkyl, alkyl and alkoxyalkyl with the proviso that \( J \) is \( \text{NR}^{22} \) or \( S \);

\( X \) is selected from the group consisting of alkylenes, alkenylene, and alkynylene groups which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano and amino;

\( X \) can be \( -(\text{CH}_2)_p\text{Q(}\text{CH}_2)_r- \) wherein \( p \) is 1 to 3, \( r \) is 1 to 3 and \( \text{Q} \) is selected from oxygen, \( \text{C}=\text{O} \), \( \text{S}(\text{O})_t \), \( \text{Se}(\text{O})_t \) wherein \( t \) is 0 to 2, \( \text{P(O)}R^{21} \) wherein \( R^{21} \) is hydroxyl or alkyl which may be optionally substituted with one of the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, and \( \text{N}(R^{12})_n \) wherein \( n \) is 1 to 2 and \( R^{12} \) is selected from the group consisting of hydrogen, oxy, hydroxyl and alkyl which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\( X \) can be \( -(\text{CH}_2)_s\text{T(}\text{CH}_2)_v- \) wherein \( s \) is 0 to 2, \( v \) is 0 to 2 and \( T \) is selected from a 3 to 6 membered carbocyclic radical, aryl radical and a heterocyclicyl radical where all
said radicals may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

Y is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, alkylthioalkyl, alkylaminoalkyl and NR\textsuperscript{9}R\textsuperscript{10} wherein R\textsuperscript{9} and R\textsuperscript{10} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclyl, and aralkyl;

R\textsuperscript{9} and R\textsuperscript{10} can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclyl;

A is selected from the group consisting of O, N(R\textsuperscript{5}), S and heterocyclyl with the proviso that J is selected from other than O, wherein R\textsuperscript{5} is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicycarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicycarboalkoxyalkyl, cyanocycloalkyl, dicycyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxyxycycloalkyl, dicycarboalkoxyxycycloalkyl, formylalkyl, acylalkyl, S(O)R\textsuperscript{13}, SO\textsubscript{2}R\textsuperscript{13}, P(O)R\textsuperscript{30}R\textsuperscript{31}, P(O)(R\textsuperscript{30})\textsuperscript{2}R\textsuperscript{31}, C(O)R\textsuperscript{15}, C(S)R\textsuperscript{15}, C\textsubscript{2}H\textsubscript{2}OC(O)R\textsuperscript{15}, C\textsubscript{2}H\textsubscript{2}SC(O)R\textsuperscript{15}, C\textsubscript{2}H\textsubscript{2}SC(S)R\textsuperscript{15}, C\textsubscript{2}H\textsubscript{2}OC(S)GR\textsuperscript{15}, C\textsubscript{2}H\textsubscript{2}SC(S)GR\textsuperscript{15}, heteroaryloxyalkyl, arloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,
arylthioalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkeny1, cycloalkeny1, cycloalkenylalkyl,
haloalkyl, haloalkeny1, halocycloalkyl,
aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl,
carboalkoxyalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl,
alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino and sulfonylalkylamino;

A can be \( R^{27} \), wherein \( R^{27} \) is selected from the group consisting of \( N(R^5)OR^7 \), \( N(R^5)N(R^5)R^{25} \), \( N(R^5)SO_2R^{13} \), \( N(R^5)C(O)R^{15} \), \( N(R^5)C(S)R^{15} \), natural and synthetic amino acids, \( N(R^5)P(O)(OR^{13})_1R^6 \) and \( N(R^5)P(O)(OR^{13})_2 \) wherein \( R^{25} \) is selected from the group consisting of hydrogen, hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkoxy, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkeny1, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkeny1, halocycloalkyl, halocycloalkeny1, haloalkoxyalkyl, cycloalkoxy, halocycloalkoxyalkyl,
halocycloalkeny1oxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroaryloxyalkyl, heteroarylthioalkyl, heteroaralkylthioalkyl,
aralkylsulfinylalkyl, aralkylsulfonylalkyl, cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroaryl sulfonlalkyl, heteroarylsulfinylalkyl, aralkylsulfinylalkyl and aralkylsulfonylalkyl;
R¹ and R² can be taken together to form a group independently selected from a group consisting of
D(C(R³⁰)(R³¹))₂D where z is 2 to 5 and D is
selected from the group consisting of oxygen, C=O, C=S,
S(O)ᵐ where m is 0 to 2, OP(OR³¹)R³⁰, P(O)R³⁰, P(S)R³⁰;
J is selected from the group consisting of O, NR²²,
and S wherein R²² is selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl,
aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,
aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,
arlythioalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkeny1, cycloalkeny1, cycloalkeny1alkyl,
haloalkyl, haloalkeny1, halocycloalkyl, halocycloalkeny1,
haloalkoxyalkyl, haloalkeny1oxyalkyl, halocycloalkoxyalkyl,
halocycloalkeny1oxyalkyl, perhaloaryloxyalkyl, heteroaryl,
heteroaryalkyl arylsulfinylalkyl, arylsulfonylalkyl,
cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl,
heteroarylsulfinylalkyl, heteroarylsulfonylalkyl,
aralkylsulfinylalkyl and aralkylsulfonylalkyl;
5. The compound and pharmaceutically acceptable salts as recited in Claim 2 wherein:
R¹ and R² are independently selected from the group consisting of
hydroxyl, sulfhydryl, OR⁶, SR⁶, OSO₂R¹³,
OS(O)R¹³, OC(S)R¹⁵, SC(S)R¹⁵, OC(S)GR¹⁵, SC(S)GR¹⁵,
OC(O)R¹⁵, SC(O)R¹⁵, OC(O)GR¹⁵ and SC(O)GR¹⁵, wherein R⁶ is
selected from the group consisting of hydroxyalkyl,
aminoalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl,
aralkoxyalkyl, alkylsulfonylalkyl, alkylsulfonilalkyl,
aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,
arlythioalkyl, cycloalkylalkyl, cycloalkylalkenyl,
cycloalkenyl, cycloalkylalkynyl, haloalkyl, haloalkenyl,
halocycaralkylsulfonylalkyl, aralkylsulfonylalkyl,
cyanoalkyl, dicyanoalkyl, carbonamidoalkyl,
dicarboxamidoalkyl, cyanocarboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carbonamidocycloalkyl,
dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl,
carboalkoxyglycycloalkyl, dicarboalkoxyglycycloalkyl,
formylalkyl, acylalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkylamino,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
aldehydeysilfonylalkyl, aralkoxy-sulfonylalkyl,
aldehydesilfonylalkylamino, aralkoxy-sulfonylalkylamino,
sulfonylalkylamino, natural and synthetic amino acids and
polyhydroxy compounds of carbon, R₁³ is selected from the
group consisting of aryloxy, amino, alkylamino,
dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy,
alkylthio, arythio, alkyl, alkenyl, alkynyl, aryl,
aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfonylalkyl,
aldehydesilfonylalkyl, aralkylthioalkyl,
heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arythioalkyl, cycloalkyl,
cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkylalkynyl, haloalkyl, haloalkenyl,
haloaralkylsulfonylalkyl, aralkylsulfonylalkyl, cyanoalkyl,
dicyanoalkyl, carbonamidoalkyl, dicarboxamidoalkyl,
cyanocarboalkoxyalkyl, carboalkoxyalkyl,
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxyycycloalkyl, dicarboalkoxyycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkoxy, aralkoxy sulfonylalkoxy, sulfonylalkoxy, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon,

R^{15} is selected from the group consisting of hydrido, aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamoidoalkyl, dicarboxamoidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxyycycloalkyl, icarboalkoxyycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy, phosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylekkoxy, aralkoxy sulfonylekkoxy, sulfonylalkoxy, alkoxy sulfonylekkoxylamino, aralkoxy sulfonylekkoxylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon,

$M^+$ is a pharmaceutically acceptable cation; and G is selected from the group consisting of O, S, CH$_2$, CHR$^{15}$, C(R$^{15}$)$_2$, NH and NR$^{15}$ wherein R$^{15}$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclic, aryl and heteroaryl.

R$^3$ and R$^4$ are independently selected from the group consisting of S(O)R$^{13}$, SO$_2$R$^{13}$, OC(S)R$^{15}$, SC(S)R$^{15}$, OC(S)GR$^{15}$, SC(S)GR$^{15}$;

R$^7$ is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxyycycloalkyl, dicarboalkoxyycycloalkyl, formylalkyl, acylalkyl, S(O)R$^{13}$, SO$_2$R$^{13}$, P(O)R$^{30}$R$^{31}$, P(O)(R$^{15}$)$_2$R$^{31}$, C(O)R$^{15}$, C(S)R$^{15}$, CH$_2$OC(O)R$^{15}$, CH$_2$SC(O)R$^{15}$, CH$_2$SC(S)R$^{15}$, Heteroaryloxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxyssulfonylalkyl, aralkoxyssulfonylalkyl, alkoxyssulfonylalkylamino, aralkoxyssulfonylalkylamino and sulfonylalkylamino;

$R^7$ can be a heterocyclyl radical in which there is at least one carbon in one ring and in which 1 to about 4 members of said ring are heteroatoms independently selected from oxygen, nitrogen and sulfur and said heterocyclyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoaryl monoamyl amidosulfonyl, arylsulfinyl, aryalsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkylalkyl, halo, haloalkyl, haloalkoxy, hydroxyhaloalkyl, hydroxylaralkyl, hydroxyalkyl, hydroxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl,
aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl,
partially saturated heterocyclyl, heteroaryl,
heteroaryloxy, heteroaryloxyalkyl, arylalkyl,
heteroarylmethyl, arylalkenyl, heteroarylmethylenyl,
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyanocarboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carboxamidocycloalkyl,
dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl,
carboalkoxyxycycloalkyl, dicarboalkoxyxycycloalkyl,
formylalkyl, acylalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkoxy, diaralkoxyphosphonoalkoxy,
phosphonoalkoxy, dialkoxyphosphonoalkylamino,
diaralkoxyphosphonoalkylamino, phosphonoalkylamino,
dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl,
guanidino, amidino and acylamino with the proviso that A is
selected from other than O and S or provided that R^8 is
selected from other than H when A is N(R^5);

R^8 is selected from the group consisting of hydrogen,
hydroxyalkyl, haloalkyl, alkyl and alkoxyalkyl with the
proviso that J is NR^22 or S;

X is selected from the group consisting of alkylene,
alkenylene, and alkynylene groups which may be optionally
substituted from the group consisting of alkyl, alkoxy,
hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano
and amino;

X can be -(CH_2)_pQ(CH_2)_r- wherein p is 1 to 3, r is 1 to
3 and Q is selected from oxygen, C=O, S(O)_t, Se(O)_t wherein
t is 0 to 2, P(O)R^{21} wherein R^{21} is hydroxyl or alkyl which
may be optionally substituted with one of the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, and \( N(R_{12})_n \)

wherein \( n \) is 1 to 2 and \( R_{12} \) is selected from the group consisting of hydrogen, oxy, hydroxyl and alkyl which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\[ X = -(CH_2)_sT(CH_2)_v^- \] wherein \( s \) is 0 to 2, \( v \) is 0 to 2 and \( T \) is selected from a 3 to 6 membered carbocyclic radical, aryl radical and a heterocyclic radical where all said radicals may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\( Y \) is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, alkylthioalkyl, alkylaminoalkyl and \( NR^9 R^{10} \) wherein \( R^9 \) and \( R^{10} \) are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclic, and aralkyl;

\( R^9 \) and \( R^{10} \) can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclic;

\( A \) is selected from the group consisting of O, \( N(R^5) \), S and heterocyclic with the proviso that \( J \) is selected from other than O, wherein \( R^5 \) is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl,
cyanocarboalkoxyalkyl, carboalkoxyalkyl,
dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboalkoxycyanocycloalkyl, carboalkoxyycycloalkyl,
dicarboalkoxyycycloalkyl, formylalkyl, acylalkyl, S(O)R^{13},
SO_{2}R^{13}, C(O)R^{15}, C(S)R^{15}, CH_{2}OC(O)R^{15}, CH_{2}SC(O)R^{15},
CH_{2}SC(S)R^{15}, CH_{2}OC(S)GR^{15}, CH_{2}SC(S)GR^{15},
heteroaryloxyalkyl, aryloxyalkyl, aralkoxyalkyl,
alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl,
heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl,
cycloalkylalkeny1, cycloalkenyl, cycloalkenylalkyl, halooalkyl,
haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl,
carboalkoxyalkyl, dialkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, diaralkoxyphosphonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,
alkoxysulfonylalkyl, aralkoxysulfonylalkyl,
alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino and
sulfonylalkylamino;

A can be R^{27}, wherein R^{27} is selected from the group
consisting of N(R')OR^{7}, N(R')N(R')R^{25}, N(R')SO_{2}R^{13},
N(R')C(O)R^{15}, N(R')C(S)R^{15}, natural and synthetic amino
acids, N(R')P(O)(OR^{13})_{1}R^{6} and N(R')P(O)(OR^{13})_{2}
wherein R^{25}
is selected from the group consisting of hydrogen,
hydroxyalkyl, alkyl, alkenyl, alkynyl, aryl, aralkyl,
aryloxyalkyl, aralkoxyalkyl, alkoxy, alkylsulfinylalkyl,
alkeylsulfonylalkyl, aralkylthioalkyl,
heteroaralkylthioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl,
cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl,
cycloalkoxy, halocycloalkoxyalkyl,
halocycloalkenyloxyalkyl, perhaloaryl, perhaloaralkyl, perhaloaryloxyalkyl, heteroaryl, heteroaryloalkyl,
heteroarylhthioalkyl, heteroarylaralkylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl,
cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl,
aralkylsulfinylalkyl and aralkylsulfonylalkyl;

J is selected from the group consisting of O, NR\(^{22}\),
and S wherein R\(^{22}\) is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl,
aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroarylaralkylthioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl,
arylthioalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl,
haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkenyl, haloalkoxyalkyl, haloalkenyloxyalkyl, halocycloalkoxyalkyl,
halocycloalkenyloxyalkyl, perhaloaryloxyalkyl, heteroaryl, heteroaryloalkyl arylsulfinylalkyl, arylsulfonylalkyl,
cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl,
aralkylsulfinylalkyl and aralkylsulfonylalkyl;

6. The compound and pharmaceutically acceptable salts as recited in Claim 2 wherein:
R¹ and R² are independently selected from the group consisting of hydroxyl, sulfhydryl, OR⁶, SR⁶, OSO₂R¹³, OS(O)R¹³, OC(S)R¹⁵, SC(S)R¹⁵, OC(S)GR¹⁵, SC(S)GR¹⁵, OC(O)R¹⁵, SC(O)R¹⁵, OC(O)GR¹⁵, and SC(O)GR¹⁵, wherein R⁶ is selected from the group consisting of hydroxyalkyl, aminoalkyl, heteroaryloxyalkyl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenyalkyl, haloalkyl, haloalkenyl, halocycaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl, dicarboalkoxycycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl,

alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, R¹³ is selected from the group consisting of aryloxy, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroaryloxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl,
alkenyloxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkeny1, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkeny1, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboxalkoxycyanocycloalkyl, carboxalkoxyacycloalkyl, dicarboxalkoxyacycloalkyl, formylalkyl, acylalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkoxy, dialralkoxyphosphonoalkoxy, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxysulfonylalkyl, alkoxy sulfonylalkoxy, aralkoxysulfonylalkoxy, sulfonylalkoxy, aralkoxysulfonylalkylamino, aralkoxy sulfonylalkylamino, sulfonylalkylamino, natural and synthetic amino acids and polyhydroxy compounds of carbon, R^15 is selected from the group consisting of hydrido, aryls, amino, alkylamino, dialkylamino, hydroxyalkyl, heteroarylxyalkyl, alkoxy, alkylthio, arylthio, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroarylxyalkyl, alkenoxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkeny1, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkeny1, haloaralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxy, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboxalkoxyalkyl, carboxalkoxyalkyl, dicarboxalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl,
carboxamidocycloalkyl, dicarboxamidocycloalkyl,
carboalkoxycyanocycloalkyl, carboalkoxycycloalkyl,
icarboalkoxyalkyl, formylalkyl, acylalkyl,
dialkoxypyrophonoalkyl, diaralkoxyphosphonoalkyl,
phosphonoalkyl, dialkoxypyrophonoalkoxy,
diaralkoxyphosphonoalkoxy, phosphonoalkoxy,
dialkoxypyrophonoalkylamino, diaralkoxyphosphonoalkylamino,
phosphonoalkylamino, dialkoxypyrophonoalkyl,
diaralkoxyphosphonoalkyl, sulfonylalkyl,

10 alkoxysulfonylalkyl, aralkoxysulfonylalkyl,
alkoxysulfonylalkoxy, aralkoxysulfonylalkoxy,
sulfonylalkoxy, alkoxysulfonylalkylamino,
aralkoxysulfonylalkylamino, sulfonylalkylamino, natural and
synthetic amino acids and polyhydroxy compounds of carbon,

15 $M^+$ is a pharmaceutically acceptable cation, and $G$ is
selected from the group consisting of $O$, $S$, $CH_2$, $CHR^{15}$,
$C(R^{15})_2$, $NH$ and $NR^{15}$ wherein $R^{15}$ is selected from the group
consisting of hydrogen, alkyl, alkenyl, alkynyl,
cycloalkyl, heterocyclic, aryl and heteroaryl;

20 $R^3$ and $R^4$ are independently selected from the group
consisting of $OC(S)R^{15}$, $SC(S)R^{15}$, $OC(S)GR^{15}$, $SC(S)GR^{15}$;

$R^7$ is selected from the group consisting of alkynyl,
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyanocarboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyano cycloalkyl, carboxamidocycloalkyl,
dicarboxamidocycloalkyl, carboalkoxycyanocycloalkyl,
carboalkoxycycloalkyl, dicarboalkoxycycloalkyl,
formylalkyl, acylalkyl, $S(O)R^{13}$, $SO_2R^{13}$, $P(O)R^{30}R^R^{31}$,
$P(O)(R^{30})_2R^{31}$, $C(O)R^{15}$, $C(S)R^{15}$, $CH_2OC(O)R^{15}$, $CH_2SC(O)R^{15}$,
\( \text{CH}_2\text{SC(S)}\text{R}^{15}, \text{CH}_2\text{OC(S)}\text{GR}^{15}, \text{CH}_2\text{SC(S)}\text{GR}^{15}, \text{heteroaryloxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkoxythioalkyl, alkoxyalkyl, heteroaryloxyalkyl, alkenyloxyalkyl, alkylthioalkyl, aralkylthioalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxy sulfonylalkyl, aralkoxy sulfonylalkyl, alkoxy sulfonylalkylamino, aralkoxy sulfonylalkylamino and sulfonylalkylamino; }$

\( R^7 \) can be a heterocyclyl radical in which there is at least one carbon in one ring and in which 1 to about 4 members of said ring are heteroatoms independently selected from oxygen, nitrogen and sulfur and said heterocyclyl radical may be optionally substituted with heteroarylamino, N-aryl-N-alkylamino, N-heteroarylamino-N-alkylamino, haloalkylthio, alkanoyloxy, alkoxy, heteroaralkoxy, cycloalkoxy, cycloalkenylthio, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylosulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylothio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkylenedioxy,
haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower
cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl,
haloalkoxy, hydroxyhaloalkyl, hydroxyarylalkyl, hydroxyalkyl,
hydroxyheteroarylalkyl, haloalkoxyalkyl, aryl, aralkyl,
aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl,
partially saturated heterocyclyl, heteroaryl,
heteroaryloxy, heteroaryloxyalkyl, arylalkyl,
heteroarylmethyl, arylalkenyl, heteroarylmethenyl,
cyanoalkyl, dicyanoalkyl, carboxamidoalkyl,
dicarboxamidoalkyl, cyano-carboalkoxyalkyl,
carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl,
dicyanocycloalkyl, carboxamido-cycloalkyl,
dicarboxamidocycloalkyl, carboalkoxy-cyanocycloalkyl,
carboalkoxy-cycloalkyl, dicarboalkoxy-cycloalkyl,
formylalkyl, acylalkyl, dialkoxy-phosphonoalkyl,
dialkoxyphosphonoalkyl, phosphonoalkyl,
dialkoxyphosphonoalkoxy, dialkoxyphosphonoalkoxy,
phosphonoalkoxy, dialkoxy-phosphono-alkylamino,
dialkoxyphosphonoalkylamino, phosphonoalkylamino,
dialkoxyphosphonoalkyl, dialkoxyphosphonoalkyl,
guanidino, amidino and acylamino with the proviso that A is
selected from other than O and S or provided that R^8 is
selected from other than H when A is N(R^5);

R^8 is selected from the group consisting of hydrogen,
hydroxyalkyl, haloalkyl, alkyl and alkoxyalkyl with the
proviso that J is NR^{22} or S;

X is selected from the group consisting of alkylene,
alkenylene, and alkynylene groups which may be optionally
substituted from the group consisting of alkyl, alkoxy,
hydroxy, sulfhydryl, halogen, trifluoromethyl, nitro, cyano
and amino;
X can be \(-(CH_2)_pQ(\text{CH}_2)_r\)- wherein \(p\) is 1 to 3, \(r\) is 1 to 3 and \(Q\) is selected from oxygen, \(\text{C} = \text{O}\), \(\text{S}(\text{O})_t\), \(\text{Se}(\text{O})_t\) wherein \(t\) is 0 to 2, \(P(\text{O})R^{21}\) wherein \(R^{21}\) is hydroxyl or alkyl which may be optionally substituted with one of the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano, amino, carboxy, and \(N(R^{12})_n\) wherein \(n\) is 1 to 2 and \(R^{12}\) is selected from the group consisting of hydrogen, oxy, hydroxyl and alkyl which may be optionally substituted from the group consisting of alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

X can be \(-(CH_2)_sT(\text{CH}_2)_v\)- wherein \(s\) is 0 to 2, \(v\) is 0 to 2 and \(T\) is selected from a 3 to 6 membered carbocyclic radical, aryl radical and a heterocyclic radical where all said radicals may be optionally substituted with alkyl, alkoxy, hydroxy, halogen, trifluoromethyl, nitro, cyano and amino;

\(Y\) is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkenyl, cycloalkenyloxy, alkenyloxyalkyl, alkylthioalkyl, alkylaminoalkyl and \(NR^9R^{10}\) wherein \(R^9\) and \(R^{10}\) are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, nitro, amino, hydroxy, alkoxy, aryl, heterocyclyl, and aralkyl;

\(R^9\) and \(R^{10}\) can be taken together to form a spacer group selected from a linear moiety having a chain length of 2 to 7 atoms to form a C3 to C8 heterocyclyl;
A is selected from the group consisting of O, N(R^5), S and heterocycyl with the proviso that J is selected from other than O, wherein R^5 is selected from the group consisting of alkynyl, cyanoalkyl, dicyanoalkyl, carboxamidoalkyl, dicarboxamidoalkyl, cyanocarboalkoxyalkyl, carboalkoxyalkyl, dicarboalkoxyalkyl, cyanocycloalkyl, dicyanocycloalkyl, carboxamidocycloalkyl, dicarboxamidocycloalkyl, carboalkoxy cyanocycloalkyl, carboalkoxy cycloalkyl, dicarboalkoxy cycloalkyl, formylalkyl, acylalkyl, S(O)R^{13}, SO_2R^{13}, C(O)R^{15}, C(S)R^{15}, CH_2OC(O)R^{15}, CH_2SC(O)R^{15}, CH_2SC(S)R^{15}, CH_2OC(S)GR^{15}, CH_2SC(S)GR^{15}, heteroaryl carboxyalkyl, aryloxyalkyl, alkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkylthioalkyl, heteroarylalkoxythioalkyl, alkoxyalkyl, heteroaryl oxyalkyl, alkenyloxyalkyl, alkylthioalkyl, arythioalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkenyl, cycloalkenylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, carboxyalkyl, carboalkoxyalkyl, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, phosphonoalkyl, dialkoxyphosphonoalkylamino, diaralkoxyphosphonoalkylamino, phosphonoalkylamino, dialkoxyphosphonoalkyl, diaralkoxyphosphonoalkyl, sulfonylalkyl, alkoxysulfonylalkyl, aralkoxysulfonylalkyl, alkoxysulfonylalkylamino, aralkoxysulfonylalkylamino and sulfonylalkylamino;

A can be R^{27}, wherein R^{27} is selected from the group consisting of N(R^5)OR^7, N(R^5)SO_2R^{13}, N(R^7)C(O)R^{15}. 

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N(R\(^5\))C(S)R\(^{15}\), natural and synthetic amino acids,
N(R\(^5\))P(O)(OR\(^{13}\))\(_1\)R\(^6\) and N(R\(^5\))P(O)(OR\(^{13}\))\(_2\);

J is selected from the group consisting of O, NR\(^{22}\),
and S wherein R\(^{22}\) is selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryloxyalkyl,
aralkoxyalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,
aralkylthioalkyl, heteroaralkylthioalkyl, alkoxyalkyl,
heteroaryloxyalkyl, alkenoxyalkyl, alkylthioalkyl,
arythioalkyl, cycloalkyl, cycloalkylalkyl,
cycloalkylalkeny1, cycloalkeny1, cycloalkeny1alkyl,
haloalkyl, haloalkeny1, halocycloalkyl, halocycloalkeny1,
haloalkoxyalkyl, haloalkeny1oxyalkyl, halocycloalkoxyalkyl,
halocycloalkeny1oxyalkyl, perhaloaryloxyalkyl, heteroaryl,
heteroarylp1alkyl arylsulfinylalkyl, arylsulfonylalkyl,
cycloalkylsulfinylalkyl, cycloalkylsulfonylalkyl,
heteroarylsulfinylalkyl, heteroarylsulfonylalkyl,
aralkylsulfinylalkyl and aralkylsulfonylalkyl; heteroarylthioalkyl, heteroaralkylthioalkyl.

7. A compound as recited in claim 2 wherein said compound
is selected from the group consisting of:

L-N-(2-cyanoethyl)-N-(2-thiazolyl)- e-N-(methoxyiminoethyl)-2-methyllysine amide dihydrochloride;

L-N-(2-dimethylamino)-N-(2-pyridyl) - e-N-(iminoethyl)-2-methyl-L-lysine amide tetrahydrochloride;

N-(2-acetoxyethyl)-N-(2-thiazolyl)-S-(2-(N-(2-acetoxyiminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide;

N-acetyl-N-(4-pyridyl)-S-(2-(N-(iminoethyl)amino)ethyl)-2-methyl-L-Cysteinamide;
N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(N-Boc-1-iminoethyl)-2-methyl-L-Lysinamide;

N-(phenyl)-N-(2-imidazolyl)-a-N-(2,2-dicyanoethyl)-e-(1-iminoethyl)-2-methyl-L-lysinamide trihydrochloride;

N-methoxy-N-(5-tetrazoyl)-e-amino- a-(N-hydroxy-N-acetamido)hexanamide hydrochloride;

N-(2-thiazolyl)-e-(amino)-a-(N-methoxyacetamido)hexanamide hydrochloride;

N-(2-imidazolyl)-S-(2-aminoethyl)- a-N-(4-morpholinomethylbenzoyl)-2-methyl-D,L-homocysteinamide;

N-(3-quiniclidinyl)-a-(N-methoxyformyl)-D,L-2,5-dimethylornithinamide;

N-(2-g-butyrolactone)-a-(N-methansulfonyl)-ortho-(aminomethyl)-2-methylphenylalaninamide;

N-(2-pyrimidinyl)- 3-(5-(aminomethyl)thiophenyl)-2-acetamido-2-methylpropionamide;

N-methyl-N-(2-pyridyl)-α-(N-cyclopentyl)-α-N-(3,3,3-trifluoropropanoyl)-O-(2-(N-(1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide;

N-methyl-N-(4-imidazolyl)-α-(N-(1-pyrrolylethylene)))-O-(2-(N-(1-(O-(methoxycarbonyl)oximino)ethyl)amino)ethyl)-2-methyl-L-serinamide;

N-methyl-N-(4-thiazolyl)-O-(2-(N-(2-fluoro-1-iminoethyl)amino)ethyl)-2-methyl-L-serinamide;

N-methyl-N-(3-oxacycloheptyl)-a-N-(2-furanylacetyl)-e-N-(1-imino-3-butenyl)-2-methyl-L-thionolysinamide;
N-Ethyl-N-(4-(1,2,3-triazolyl))-e-N-(1-(2-fluorocyclopentyl)oximinomethyl)amino-2-N-(1-cyclopentyl-2-methylthioethyl))-2-cyanopropanamido-2-methyl-thionohex-4-enamide;

3-N-(5-tetrazolyl)-5-(3-(N-(1-(0-propionyloximino)ethyl)amino)prop-1-ynyl)-5-methyl-hydantoin trifluoroacetate;

1-N-(2-imidazolyl)-3-(2-(N-(1-iminoethyl)amino)ethoxy)methyl)-3-methyl-6-(2-methiothioethyl)-2-oxo-3,6-dihydropyrazine trihydrochloride;

N-methyl-N-(5-tetrazolyl)-S-(2-(N-phosphonomethyl-N-(1-iminoethyl)amino)ethyl)-2-methyl-L-cysteinate hydrochloride;

N-methyl-N-(5-tetrazolyl)-e-(N-(1-iminoethyl)amino)-2-((N-ethoxycarbonyl)amino)-2-methyl-thionohexanamide;

N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-(N-(2,2,2-trifluoro-1-ethoxyethyl))amino-2-methylhexanamide;

N-methyl-N-(5-tetrazolyl)-S-(2-(1-(N-(benzoyloxymethyl)imino)ethyl)-N-hydroxy)aminoethyl)-2-methyl-L-cysteinate hydrochloride;

N-methyl-N-(5-tetrazolyl)-a-N-benzoyl-e-N-(2-(1-(N-(benzoyloxymethyl)imino)ethyl))-e-N-(1-propyl)-2-methyl-L-Lysine;

N-methyl-N-(5-(tetrazolyl)-ε-N-(2-fluoro-1-iminoethyl)-ε-N-(N,N′-trimethylureido-N-methylene)-2-methyl-L-Lysinamide;
N-methyl-N-(5-tetrazolyl)-e-(N-(1-imino-2-fluoroethyl)amino)-2-(N-(phenylalaninyl)amino)-2-methylhexanamide;

N-acetoxyemethyl-N-(5-tetrazolyl)-e-N-(iminoethyl)-2-methyl-L-Lysinamide, 3-(4-(N-(1-iminoethyl)amino)butyl)-3-cyanomethyl-6-methylmorpholine-2,5-dione;

3-(4-(N-(2-fluoroiminoethyl)amino)butyl)-3-(N,N-dimethylaminomethyl)oxazolidine-2,5-dione;

3-(4-(N-(1-iminoethyl)amino)butyl)-3-(2-methylthioethyl)-3H,5H,6H,7H,8H-1,4-benzoxazin-2-one dihydrochloride;

6-(N-(2-fluoro-1-iminoethyl)amino)-1-imino-1-(2-piperazinylmethylthio)-2-hexanamine pentahydrochloride;

ethyl 6-(N-(1-iminoethyl)amino)-2-(ethoxyiminemethy)-2-aminohexanoate trihydrochloride;

N-methyl-N-(5-tetrazolyl)-6-(N-(1-iminoethyl)amino)-2-(methoxyiminomethyl)-2-aminohexanamide;

6-(N-(1-iminoethyl)amino)-2-(N-glycaminomethyl)-2-phthalimidohexanoic acid trihydrochloride;

N-Methyl-N-(N-(5-tetrazolyl)amino)-2-amino-2-(2-hydroxyethyl)-6-(N-(1-iminoethyl)amino)hexanamide;

N-(2-amino-2-(2-cyanoethyl)-6-(N-(1-iminoethyl)amino)hexanoyl) aminoacetic acid hydrogen chloride;

N-methylsulfonfylmethyl-N-(5-tetrazolyl)-2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanamide;

tert-Butyl 2-cyanomethyl-2-phthalimidono-6-(N-(1-iminoethyl)amino)hexanoate;

N-methanesulfonfylmethyl-N-(methoxymethoxy)-2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanamide;
N-(2-cyanomethyl-2-amino-6-(N-(1-iminoethyl)amino)hexanoyl)alanine dihydrochloride; and
6-(N-butylimino)-6-methoxy-N-(1-iminoethyl)-1,2-hexanediamine di-para-toluenesulfonate hydrochloride.

8. A method of inhibiting nitric oxide synthesis in a subject in need of such inhibition by administering a therapeutically effective amount of a compound of Claims 1, 2, 3, 4, 5, 6 or 7.

9. A method of selectively inhibiting nitric oxide synthesis produced by inducible NO synthase over nitric oxide produced by the constitutive forms of NO synthase in a subject in need of such selective inhibition by administering a therapeutically effective amount of a compound of Claims 1, 2, 3, 4, 5, 6 or 7.

10. A method of lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a compound of Claims 1, 2, 3, 4, 5, 6 or 7.

11. A pharmaceutical composition comprising a compound of Claims 1, 2, 3, 4, 5, 6 or 7 together with one or more pharmaceutically acceptable carriers.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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<th>C07D257/06</th>
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
  
  *A* document defining the general state of the art which is not considered to be of particular relevance
  
  *E* earlier document published on or after the international filing date
  
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  
  *O* document referring to an oral disclosure, use, exhibition or other means
  
  *P* document published prior to the international filing date but later than the priority date claimed
  
  *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  
  *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  
  *Z* document member of the same patent family

Date of the actual completion of the international search: 13 June 2000

Date of mailing of the international search report: 27/06/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5018 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

page 1 of 3
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPCG 7  C07D265/36  C07D333/16  C07D333/06  C07D319/06  C07D241/04  C07C257/14  C07D209/48  C07C317/28  C07D317/30  A61K31/16  A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

**D. DATE**

Date of the actual completion of the international search: 13 June 2000

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 MV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Allard, M

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page 2 of 3
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Continuation of Box I.2

Claims Nos.: 1-6 (partly), 8-11 (partly)

Present claims 1-6 and partly 8-11 insofar they concern claims -6, relate to an extremely large number of possible compounds and their use. In fact, said claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of said claims impossible. In particular, claim 1 contains so many cascading provisos that a meaningful comparison with the documents of the prior art is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the compounds recited in claim 7 and/or the examples of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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</tr>
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