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(54) Title: NITRATE ESTERS AND THEIR USE FOR NEUROLOGICAL CONDITIONS

(57) Abstract

Compounds and methods for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject are described. Neurological or cognitive conditions are treated by administering to a subject an effective amount of a therapeutic compound comprising a nitrate ester, or a pharmaceutically acceptable salt or ester thereof.

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NITRATE ESTERS AND THEIR USE FOR NEUROLOGICAL CONDITIONS

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FIELD OF THE INVENTION

This invention relates to nitrate esters and use thereof in effecting neuroprotection, mitigating neurodegeneration and/or effecting cognition enhancement. More particularly, this invention relates to organic nitrates having therapeutic utility as neuroprotective agents and/or cognition enhancers. The invention still more particularly relates to nitrate esters bearing a sulfur or phosphorus atom β or γ to a nitrate group and their congeners which have therapeutic utility as neuroprotective agents and/or cognition enhancers.

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BACKGROUND OF INVENTION

The nitrate ester glyceryl trinitrate (GTN) or nitroglycerin, has been used as a vasodilator in the treatment of angina pectoris for over a hundred years, and the dominant contemporary belief is that GTN exerts its therapeutic effect through *in vivo* release of nitric oxide (NO). Other organic nitrates, such as isosorbide dinitrate, have also been identified as effective and clinically important vasodilators. NO itself has been identified as Endothelium Derived Relaxing Factor (EDRF) and several classes of compounds, for example nitrosothiols, in addition to organic nitrates, have been proposed as NO donors or NO prodrugs. Well-known examples of these classes of compound and one nitrate, GTN itself, have been suggested to demonstrate neurotoxic or neuroprotective effects by dint of interactions with the redox modulatory site of the *N*-methyl-D-aspartate (NMDA) excitatory amino acid receptor. Thus GTN is firstly a potent vasodilator and secondly possesses

potential neuroprotective properties. Several attempts have been made to increase the efficacy or potency of alternative organic nitrates as vasodilators relative to GTN, for example, by incorporation of propanolamine or cysteine functionalities. However, no attempt has been made to separately regulate the vasodilatory and neuroprotective effects of GTN. Indeed, postural hypotension, weakness and other signs of cerebral ischemia are adverse effects, associated with the vasodilatory effects of GTN and observed in treatment, which are highly contraindicative of GTN itself, and by extrapolation GTN derivatives (1,2,3-trinitratorpropane derivatives), as clinically useful neuroprotective therapeutic agents.

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OBJECTS AND SUMMARY OF THE INVENTION

In as much as the potent vasodilatory effects of organic nitrates may prove (a) deleterious to, or alternatively (b) synergistic with the neuroprotective effects of GTN, it is postulated herein that regulation of these two effects is required for development of new and useful neuroprotective therapeutic agents. Further, it is postulated that such regulation may be achieved through use of an appropriate organic nitrate, such as, for example, nitrate esters incorporating sulfur-containing or phosphorus-containing functionalities into the structure of the nitrate esters or through use of their congeners. Interaction of organic nitrates with amino acid neurotransmitter receptors, including the NMDA receptor, will provide examples of compounds with neuroprotective properties, but modulation of the γ -aminobutyric acid type A (GABA_A) receptor response will provide examples of organic nitrates capable of cognition enhancement. Stimulation of cerebral soluble guanylyl cyclase (GCCase) by organic nitrates, in particular selectively over arterial GCCase, will provide examples of compounds with neuroprotective properties. Organic nitrates bearing antioxidant functionalities and those capable of inhibiting apoptosis will also provide examples of compounds with neuroprotective properties. These postulates are based, in part, on bioassay data on such compounds. Thus, there is a need for synthetic organic nitrates, such as, for example, nitrate esters containing sulfur or phosphorus functionalities or their congeners, as new and useful therapeutic agents for use in effecting neuroprotection, mitigating neurodegeneration and/or effecting cognition enhancement. It will be appreciated, therefore, that these compounds can be used for

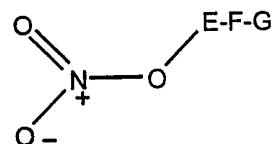
treatment conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; 5 myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin; dementias of all type, trauma, drug-induced brain damage, aging.

It is an object of the present invention to provide novel organic nitrates, including 10 aliphatic nitrate esters bearing a sulfur or phosphorus moiety β or γ to a nitrate group, or congeners thereof. Another object of the present invention is to provide methods for making such novel organic nitrates. Another object of the invention is to provide methods for effecting neuroprotection, mitigating neurodegeneration and /or effecting cognition enhancement employing organic nitrates. Another object of the present invention is to 15 provide novel drugs as neuroprotective agents. Yet another object of the present invention is to provide novel drugs for use in cognition enhancement.

This invention provides novel compounds, methods and pharmaceutical compositions which are useful in the treatment of neurological disorders requiring 20 mitigation of neurodegeneration, neuroprotection and/or cognition enhancement. Methods of the invention involve administering to a subject in need thereof a therapeutic compound which provides neuroprotection or cognition enhancement. Accordingly, the compositions and methods of the invention are useful for effecting neuroprotection or cognition enhancement in disorders in which neurotoxic damage occurs. The methods of 25 the invention can be used therapeutically to treat conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral 30 vascular hemorrhage; hemorrhage;

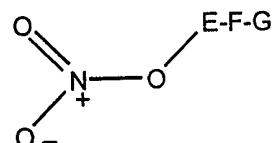
environmental excitotoxins; dementias of all type, trauma, drug-induced brain damage, and aging or can be used prophylactically in a subject susceptible or predisposed to these conditions. In certain embodiments, a therapeutic compound used in the method of the invention preferably can interact with GCase effecting neuroprotection and/or cognition enhancement. In other embodiments, a therapeutic compound used in the method of the invention preferably can modulate glutamate and/or non-glutamate neuroreceptor interactions effecting neuroprotection and/or cognition enhancement.

The invention relates to organic nitrates, i.e., nitrate esters. In one aspect, the invention provides a method including the step of administering to a subject an effective amount of a therapeutic compound having the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions, such that neurodegeneration is mitigated in the subject.

In another aspect, the invention provides a method including the step of administering to a subject an effective amount of a therapeutic compound having the



formula (Formula I):

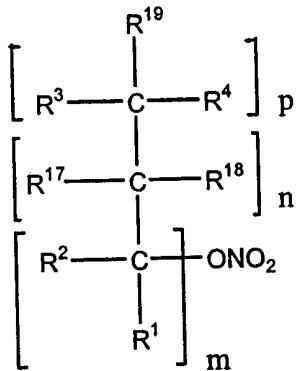
wherein E, F, G are organic radicals which may contain inorganic counterions, such that cognition enhancement is effected.

In a further aspect, the invention provides use of therapeutic compounds that mitigate neurodegeneration, effect neuroprotection and/or effect cognition enhancement in a subject to

which the therapeutic compound is administered, the compounds having the formula (Formula II):

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in which: m and n and p are integers from 0 to 10;

R^{3,17} are each independently hydrogen, a nitrate group, or A;

R^{1,4} are each independently hydrogen or A;

15 where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring,

20 optionally bearing from 1 to 4 hydroxy, nitrate, or amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate,

25 amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted 30 aryl group; a heterocyclic group; amino (including alkylamino,

dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R^2, R^5, R^{18}, R^{19} are optionally hydrogen, A, or X-Y;

5 where X is F, Br, Cl, NO_2 , CH_2 , CF_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR⁷, SO_2M , S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO_2HM , PO_3HM , PO_3M_2 , P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO_2M , CO_2H , CO_2R^{11} , C(O), C(O)R¹², C(O)(OR¹³), PO_2H , PO_2M , P(O)(OR¹⁴),

10 P(O)(R¹³), SO, SO_2 , C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH_3 , CF_2H , CF_3 , OH, NH₂, NHR⁶, NR^6R^7 , CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR⁷, SO_2M , S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO_2HM , PO_3M_2 , P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO_2M ,

15 CO_2H , CO_2R^{11} , C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or C₁-C₆ connections to R¹ - R⁴ in cyclic derivatives, or are each independently hydrogen, a nitrate group, or W;

20 M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso that, when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups; that R⁴ is not H or C₁ - C₃ alkyl.

25 Preferred therapeutic compounds for use in the invention include compounds in which R¹⁹ is X-Y. In some preferred embodiments: R¹⁹ is X-Y and R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents, or C₁ or C₂ connections to R¹ - R³ in cyclic derivatives; R¹ and R³ are the same or different and selected from H, C₁-C₄ alkyl chains, which may include one O, linking R¹ and R³ to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which

5 rings optionally bear hydroxyl substituents; R² and R⁴ are the same or different and selected from H, a nitrate group, C₁-C₄ alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R⁵); and R⁷, R¹¹ are the same or different C₁-C₈, alkyl or acyl.

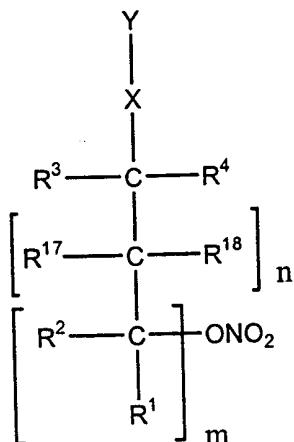
10 5 In certain embodiments in which R¹⁹ is X-Y, m, p = 1, and n = 0.

15 In other embodiments in which R¹⁹ is X-Y, X is selected from: CH₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, 10 S(O)₂OR⁹, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), and SSR⁴.

20 In other embodiments in which R¹⁹ is X-Y, Y is selected from CN, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, SCN, SCN₂H₂(R¹⁵)₂, SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SR⁴, SO₂M, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(SR¹³), SR⁵, SSR⁵, or does not exist.

25 In certain embodiments, X and/or Y contain a sulfur-containing functional group. 20 In some embodiments, a compound of the invention according to Formula II comprises a heterocyclic functionality, more preferably, a nucleoside or nucleobase. In further embodiments, a compound of the invention comprises a carbocyclic functionality, more preferably, a steroidal or carbohydrate moiety.

30 25 In another aspect, a therapeutic compound which is employed in methods of the invention is represented by the formula (Formula III):



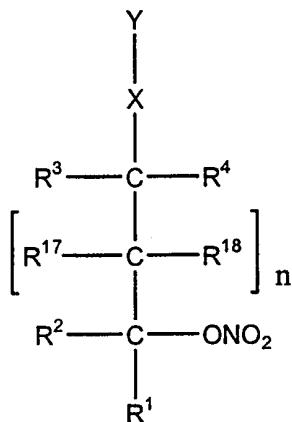
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in which: m is 1-10; R¹⁻¹⁸, X, and Y have the meaning as defined above. In some embodiments, R⁶ - R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents, or C₁ - C₆ connections to R¹ - R⁴ in cyclic derivatives. In certain preferred embodiments, R¹⁸ is A and n = 1.

In another aspect, the invention provides novel compounds useful for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement which are represented by the structures of Formula 3.

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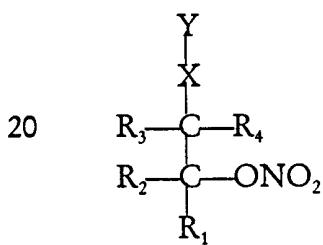
In a further aspect, a therapeutic compound according to the invention is represented by the formula (Formula IV):



in which: $R^3, R^1 = H$; $n, R^2 R^{4-18}$, X, and Y have the meaning as defined above. In certain preferred embodiments, X is CH_2 or does not exist, and Y is selected from: F, Br, 5 Cl, CH_3 , CF_2H , CF_3 , OH, NH_2 , NHR_6 , NR_6R_7 , CN, $NHOH$, N_2H_3 , $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3 , S, SCN, $SCN_2H_2(R_{15})_2$, $SCN_2H_3(R_{15})$, $SC(O)N(R_{15})_2$, $SC(O)NHR_{15}$, SO_3M , SH, SR_7 , SO_2M , $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_2HM , PO_3M_2 , $P(O)(OR_{15})(OR_{16})$, $P(O)(OR_{16})(OM)$, $P(O)(R_{15})(OR_8)$, $P(O)(OM)R_{15}$, CO_2M , CO_2H , CO_2R_{11} , $C(O)R_{12}$, $C(O)(OR_{13})$, $C(O)(SR_{13})$, SR_5 , SSR_7 , and SSR_5 . In certain embodiments, 10 R_2 and R_4 are optionally H, a nitrate group or a connection to R_5-R_{16} in cyclic derivatives.

By one particular aspect of this invention there is provided an aliphatic nitrate ester containing at least one nitrate group, in which a S or P atom is situated β or γ to a nitrate group, or congeners thereof, having the general formula (Formula IV*):

15



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where X is CH_2 , O, NH, NMe , CN, $NHOH$, N_2H_3 , $N_2H_2R_{13}$, $N_2HR_{13}R_{14}$, N_3 , S, SCN, $SCN_2H_2(R_5)_2$, $SCN_2H_3(R_5)$, $SC(O)N(R_5)_2$, $SC(O)NHR_5$, SO_3M , SH, SR_7 , SO_2M , $S(O)R_8$, $S(O)_2R_9$, $S(O)OR_8$, $S(O)_2OR_9$, PO_3M_2 , $P(O)(OR_5)(OR_6)$, $P(O)(OR_6)(OM)$, $P(O)(R_5)(OR_8)$,

P(O)(OM)R₅, CO₂M, CO₂H, CO₂R₁₁, C(O), C(O)R₁₂, C(O)(OR₁₃), PO₂M, P(O)(OR₁₄), P(O)(R₁₃), SO, SO₂, C(O)(SR₁₃), SR₄, or SSR₄;

Y is SCN, SCN₂H₂(R₅)₂, SC(O)NHR₅, SC(O)N(R₅)₂, SR₄, SR₁₀, SSR₁₀, SO₂M,

SO₃M, PO₃HM, PO₃M₂, P(O)(OR₅)(OR₆), or P(O)(OR₆)(OM), CN, N₃, N₂H₂R₁₃,

5 N₂HR₁₃R₁₄, CO₂M, CO₂H, CO₂R₁₁, C(O)R₁₂, C(O)(SR₁₃), or does not exist;

R₅, R₆, R₈, R₉, R₁₀, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, are the same or different alkyls containing 1-12 carbon atoms which may contain 1-4 ONO₂ substituents or C₁ or C₂ connections to R₁ - R₃ in cyclic derivatives;

R₇, R₁₁ are C₁ - C₈, alkyl or acyl;

10 R₂ and R₄ are the same or different and selected from H, ONO₂, C₁-C₄ alkyl optionally bearing 1-3 nitrate groups, and acyl groups (-C(O)R₁₀);

R₁ and R₃ are the same or different and selected from H, C₁-C₄ alkyl and chains, which may rings optionally bear hydroxyl substituents; and

M is H, Na⁺, K include one O, linking R₁ and R₃ to form pentosyl, hexosyl,

15 cyclopentyl or cyclohexyl rings, which ⁺, NH₄⁺ or N⁺H_nR_{11(4-n)} where n is 0-3;

with the proviso that, when X is O, Y is not COR₁₂; and

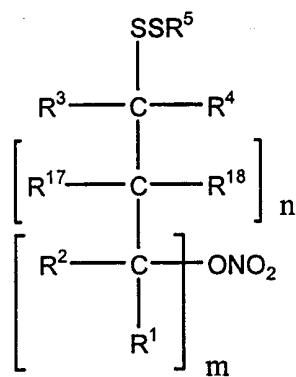
with the proviso that, when R₃ is H, R₆ is not ethyl or n-butyl;

and pharmaceutically acceptable salts thereof.

20 The invention further provides a pharmaceutical composition comprising an effective amount of nitrate ester of Formula IV*, in admixture with a physiologically acceptable carrier therefor. The invention still further provides a method for effecting neuroprotection in a subject in need thereof comprising administering to said subject an effective amount of a nitrate ester of Formula IV*.

25

In yet another aspect of the invention, compounds according to the invention are represented by the formula (Formula V):



where m, n, R¹⁻¹⁸, X, and Y have the meaning as defined above.

5 In another aspect, the invention provides methods for preparing organic nitrates represented by the structures of Formula V.

The therapeutic compounds of the invention are administered to a subject by a route which is effective for mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement. Suitable routes of administration include sublingual, 10 oral, buccal, transdermal, nasal, subcutaneous, intravenous, intramuscular and intraperitoneal injection. Preferred routes of administration are intravenous, subcutaneous and transdermal administration, particularly for effecting neuroprotection. In addition, for effecting cognition enhancement, oral administration may be preferred. The therapeutic compounds can be administered with a pharmaceutically acceptable vehicle.

15

The invention also provides methods for treating a disease state associated with neurodegeneration by administering to a subject an effective amount of a therapeutic compound having a formula as set forth above, such that a disease state associated with neurodegeneration is treated.

20

The invention provides methods for effecting neuroprotection and/or cognition enhancement by administering to a subject an effective amount of a therapeutic compound

having a formula described above, such that neuroprotection and/or cognition enhancement is effected.

5 The invention further provides pharmaceutical compositions for treating neurodegeneration. The pharmaceutical compositions include a therapeutic compound of the invention in an amount effective to mitigate neurodegeneration in admixture with a pharmaceutically acceptable carrier therefor.

10 The invention also provides packaged pharmaceutical compositions for treating neurodegeneration. The packaged pharmaceutical compositions include a therapeutic compound of the invention and instructions for using the pharmaceutical composition for treatment of neurodegeneration.

15 **BRIEF DESCRIPTION OF DRAWINGS**

Figure 1 is a graph showing the effect of GTN with added L-cysteine (2mM) on soluble guanylyl cyclase (GCase) activity in rat aorta homogenate. Bars represent the mean \pm standard errors calculated separately for each point.

20 Figure 2 is a graph showing the effect of IVd neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate normalized to the maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

25 Figure 3 is a graph showing the effect of IVg neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to the maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

Figure 4 is a graph showing the effect of IVb neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

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Figure 5 is a graph showing the effect of IVf neat (diamonds); with added L-cysteine (2mM, triangles; 5mM circles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

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Figure 6 is a graph showing the effect of IVe neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

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Figure 7 is a graph showing the effect of IVj neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

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Figure 8 is a graph showing the effect of IVa neat (diamonds); with added L-cysteine (2mM, triangles); with added dithiothreitol (2mM, DTT, squares); on soluble GCase activity in rat aorta homogenate, normalized to maximal GTN response. Bars represent the mean \pm standard errors calculated separately for each point.

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Figure 9 is a graph showing a comparison of GTN (squares), IIIm (circles) and IVh (triangles) with added L-cysteine (1 mM) on soluble GCase activity in rat aorta homogenate (a), and rat hippocampus homogenate (b). Data points represent the mean of duplicate determinations carried out in identical GCase preparations.

Figure 10 is a graph showing a comparison of GTN (squares), Va (circles) and Vb (triangles) with added L-cysteine(1 mM) on soluble GCase activity in rat aorta homogenate homogenate (a), and rat hippocampus homogenate (b). Data points represent the mean \pm standard errors calculated separately for each point (n=8-11).

5

Figure 11 is a graph showing a comparison of cyclic GMP accumulation in isolated rat aorta induced by diluent (Basal, open bar), GTN (filled bar), Va (stippled bar), or IIIm (hatched bar). Segments of rat aorta were exposed to diluent, 1 μ M drug (a), or 10 μ M drug (b) for 1 min. and cyclic GMP content determined by radioimmunoassay. Data are the mean \pm standard errors (a, n=8; b, n=5).

Figure 12 is a graph showing a comparison of cyclic GMP accumulation in isolated rat aorta induced by diluent (Basal, open bar), GTN (filled bar), IVk (stippled bar), Vb (cross-hatched bar), or Vc (hatched bar). Segments of rat aorta were exposed to diluent, 1 μ M drug (a), or 10 μ M drug (b) for 1 min and cyclic GMP content determined by radioimmunoassay. Data are the mean \pm standard errors (a, n=5; b, n=4).

Figure 13 is a graph showing cyclic GMP accumulation in rat hippocampal slices induced by diluent (Basal, open bar), GTN (filled bar), and Va (stippled bar). Sections of rat hippocampus (400 μ m) were prepared and exposed to diluent, 10 μ M drug (a) or 100 μ M drug (b) for 3 min and cyclic GMP content determined by radioimmunoassay. Data are the mean \pm standard errors (a, n=4; b, n=5).

Figure 14 is a graph showing a comparison of relaxation of isolated rat aorta induced by GTN (squares), Va (open triangles), compound IVc (diamonds), compound IVd (open squares), compound IVf (triangles), and compound IVg (open diamonds). Data points represent the mean \pm standard errors (n=5-8).

Figure 15 is a graph showing a comparison of relaxation of isolated rat aorta induced by GTN (squares), IVk (open triangles), Vb (diamonds), IIIm (open squares), Vc (triangles), and IVh (open diamonds). Data points represent the mean \pm standard errors (n=3-8).

5

Figure 16 is a graph showing relaxation induced by t-Bu nitrosothiol in isolated rat aorta. Data points represent the mean \pm standard deviation (n=3).

Figure 17 is a graph showing relaxation induced by compound Ivd (a) and IVc (b) in 10 untreated (squares) and GTN-tolerant (triangles) isolated rat aorta. Aortae were made tolerant by treatment with 0.5 mM GTN for 30 min. Data points represent the mean \pm standard deviation (n= 3-6).

Figure 18 is a graph showing a comparison of the percent change in mean arterial 15 pressure in conscious unrestrained rats after subcutaneous administration of 400 μ mol/kg GTN (squares) or Va (open circles). Data points represent the mean \pm standard errors (n=6).

Figure 19 is a graph showing a comparison of the percent change in mean arterial 20 pressure in Inactin anaesthetized rats after intravenous bolus injection of GTN (squares) or Va (open circles). Data points represent the mean \pm standard errors (n=4).

Figure 20 is a graph showing plasma levels (μ M) of Vb (circles) and its mononitrate 25 metabolite Vc (open squares) after subcutaneous administration of 200 μ mol/kg Vb in conscious unrestrained rats. Data points represent the mean of two experiments.

Figure 21 is a graph showing the effect of compound Va on lactate dehydrogenase (LDH) release from rat hippocampal slices after a 30-min period of *in vitro* ischemia. Data are the mean \pm standard errors (n=8). *, P<0.05 compared to ischemia.

Figure 22 is a graph showing the effect of delayed administration of Va on lactate dehydrogenase (LDH) release from rat hippocampal slices after a 30-min period of *in vitro* ischemia. Data are the mean \pm standard errors (n=6). *, P<0.05 compared to ischemia.

5 Figure 23 is a graph showing the effect of blocking guanylyl cyclase with ODQ on the neuroprotective properties of Va in rat hippocampal slices subjected to a 30-min period of *in vitro* ischemia. Data are the mean \pm standard errors (n=4).

10 Figure 24 is a graph showing viable neurons in the CA1 region of the gerbil hippocampus after global cerebral ischemia. Data are the mean \pm standard error for the number of animals in parentheses. *, P<0.05 compared to vehicle control.

15 Figure 25 is a graph showing the total and cerebral cortical infarct volume of rat brain after a 2-hour period of focal cerebral ischemia. Data are the mean \pm standard errors (n=10).

Figure 26 is a graph showing the effect of GTN (0.2. or 0.4 mg/hr by subcutaneous patch) on NMDA-induced loss of striatal tyrosine hydroxylase (TH) activity in the rat.

20 Figure 27 is a graph showing the effect of GTN (0.4 mg/hr by subcutaneous patch) implanted one hour after an infusion of NMDA into the substantia nigra on striatal TH activity. ** P < 0.05 compared to animals receiving NMDA alone.

25 Figure 28 is a graph showing the percent decrease in striatal TH activity in rats pretreated with GTN compared to Losartan, a drug that decreases systemic blood pressure through a mechanism different from that of GTN. Animals pretreated with GTN showed significant amounts of neuroprotection; whereas, animals pretreated with Losartan did not show any evidence of neuroprotection.

Figure 29 is a graph showing the blood pressure profiles of animals administered (a) GTN (0.4 mg/hr by subcutaneous patch), or (b) losartan (30 mg/kg by intraperitoneal injection).

5 Figure 30 is a graph showing the effect of compound IVd (Bunte salt, 10-100 μ M) on GABA receptor-activated membrane current recorded in an oocyte expressing the $\alpha 1\beta 2\gamma 2L$ isoform of the GABA_A receptor.

10 Figure 31 is a graph showing that nitric oxide donors have no effect on GABA_A receptors expressed in *Xenopus* oocytes.

Figure 32 is a graph showing that the concentration-response relationship for activation of the GABA_A receptor is altered in a non-competitive manner by compound IVd (Bunte salt).

15

DETAILED DESCRIPTION OF INVENTION

This invention pertains to methods and compositions useful for treating neurodegeneration. The methods of the invention involve administering to a subject a therapeutic compound which effects neuroprotection and/or cognition enhancement.

20

Neuroprotection and/or cognition enhancement can be effected, for example, by modulating an interaction with guanylyl cyclase (GCase), a glutamate or non-glutamate neuroreceptor or attenuating free radical damage. GCase is the enzyme responsible for cGMP production in various areas of the brain.

25

According to certain aspects of the invention, neurodegeneration is mitigated by stimulating cerebral GCase. One of the major targets for organic nitrates is GCase activation, resulting in the production of cGMP. Experimental evidence obtained in a number of *in vitro* model systems supports the notion that elevated levels of cGMP help to prevent apoptotic (programmed) cell death. Thus, a cGMP-dependent mechanism 30 significantly increases the

survival of trophic factor-deprived PC12 cells and rat sympathetic neurons (Farinelli et al., 1996), and of primary cultures of rat embryonic motor neurons (Estevez et al., 1998). The mechanism of action for organic nitrates in preventing apoptotic cell death may be inhibition of caspase-3 activation indirectly through elevations in cGMP levels or directly via protein S-nitrosylation of the enzyme by an NO-intermediate (Kim et al., 1997).

5 Caspase-3 is a member of the cysteine protease family of enzymes that are essential for the execution step in apoptosis (Cohen, 1997; Nicholson and Thornberry, 1997). Activation of caspase-3 is required for apoptotic cell death in trophic factor-deprived PC12 cells (Haviv et al., 1997) and in glutamate-mediated apoptotic cell death of cultured cerebellar granule

10 neurons (Du et al., 1997). In animal models of cerebral ischemia, caspase-3 activity is induced and may be responsible for the apoptotic component of delayed neuronal cell death (Chen et al., 1998; Namura et al., 1998; Ni et al., 1998). Inhibitors of caspase-3 significantly decrease the apoptotic component of delayed neuronal cell death in response to ischemic injury both *in vitro* (Gottron et al., 1997) and *in vivo* (Endres et al., 1998). A

15 secreted region of the Alzheimer's disease β -amyloid precursor protein lowers intracellular calcium levels and provides neuroprotective effects on target cells through increases in cGMP levels and activation of protein kinase G (Barger et al., 1995; Furukawa et al., 1996).

In preferred embodiments of the methods of the invention, nitrated molecules that have the capacity to activate GCCase directly or via release of an NO-containing intermediate are

20 used to modulate GCCase activity.

According to certain other aspects of the invention, cognition enhancement (e.g., improved memory performance) is achieved by stimulating cerebral GCCase. Several lines of experimental evidence support the notion that GCCase and cGMP are involved in the formation and retention of new information. cGMP has been directly implicated in both long-term potentiation (LTP) and long-term depression (LTD), which are proposed cellular models for learning and memory (Arancio et al., 1995; Wu et al., 1998). In animal models, elevation of hippocampal cGMP levels leading to increased protein kinase G activity has been shown to be important for retention and consolidation of new learning (Bernabeu et al., 1996, 1997). Thus, stimulation of cerebral GCCase activity is expected to improve learning and

memory performance in individuals in whom cognitive abilities are impaired by injury, disease, or aging.

We have shown that novel organic nitrate esters have differential effects to activate
5 soluble GCCase and to cause cGMP accumulation in vascular and brain tissue. There is a clear dissociation between the vascular relaxation effects of organic nitrate esters and ability to effect neuroprotection. Activation of GCCase and accumulation of cGMP have been shown to be important in the neuroprotection of hippocampal brain slices subjected to a period of *in vitro* ischemia.

10

Cerebral ischemia results in marked increases in the release of the excitatory amino acid glutamate in the affected brain region (Bullock et al., 1998; Huang et al., 1998; Yang et al., 1998). In both humans (Bullock et al., 1998) and experimental animals (Huang et al., 1998; Goda et al., 1998; Yang et al., 1998), the amount of glutamate released during

15 ischemia is positively correlated with the extent of brain injury. In experimental animal models of cerebral ischemia, decreased release of glutamate during ischemia (Goda et al., 1998) or blockade of glutamate receptors with antagonists (Ibarrola et al., 1998; O'Neill et al., 1998; Umemura et al., 1997) significantly reduces the extent of brain injury. However, these interventions are only effective when given prior to or during the ischemic insult.

20 To be broadly useful, a therapeutic intervention is preferably effective when administered after the period of ischemia. We have designed a class of novel organic nitrate esters having high efficacy in effecting neuroprotection *in vivo* in models of transient global and focal cerebral ischemia when given after the ischemic insult. It will be appreciated, therefore, that these organic nitrates can be used for treatment of conditions including but not

25 limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular

hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin; and the like.

The direct effects of organic nitrates on amino acid neurotransmitter receptors has
5 been tested using the *Xenopus* oocyte expression system and two-electrode voltage-clamp recording methods. Organic nitrates were found to have direct, modulatory effects on GABA_A receptor function (see Working Examples below). These allosteric modulatory effects of organic nitrates were not shared by direct NO-generating compounds, indicating a novel mechanism of action for organic nitrates to interact with GABA_A receptors. In
10 behavioural models of learning and memory, drugs which decrease GABA_A receptor function improve performance on learning and memory tasks (Venault et al., 1992). Thus, the behavioural effect of organic nitrates, developed to act as modulators of GABA_A receptor function, will be to improve memory performance and cognition in patient populations. It will be appreciated, therefore, that these organic nitrates can be used for
15 treatment of conditions including but not limited to: stroke; dementias of all type; trauma; drug-induced brain damage; and aging.

According to certain aspects of the invention, neurodegeneration is mitigated by inhibition of free radical damage. Reoxygenation and reperfusion after a period of
20 ischemia contributes significantly to the development of brain injury. Oxygen radicals, especially superoxide and peroxynitrite, formed in the period after an ischemic event may initiate processes such as breakdown of membrane lipids (lipid peroxidation), leading to loss of cell membrane integrity and inhibition of mitochondrial function (Macdonald and Stoodley, 1998; Gaetani et al, 1998). Oxidative stress is also believed to be one factor
25 involved in initiation of apoptotic neuronal cell death (Tagami et al., 1998). In experimental animal models of ischemic brain injury, free radical scavengers and enhanced activity of superoxide dismutase have been found to reduce the extent of neuronal injury and cell death (Chan et al., 1998; Mizuno et al., 1998; Tagami et al., 1998). In preferred embodiments of the methods of the invention, nitrated molecules which have the capacity
30 to inhibit production of free radicals and/or which act as free radical scavengers are used to attenuate the brain injury that occurs

after a period of cerebral ischemia. It will be appreciated by those skilled in the art, that any organic nitrate in which vasodilatory potency is reduced and neuroprotective potency increased, represents a new and useful therapeutic agent for use in neuroprotection, particularly in treatment of conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant, animal and marine origin. GTN itself, proposed as a neuroprotective agent, has no clinical utility as a neuroprotective agent in therapy owing to its extraordinarily high vasodilatory potency. Similarly, by extrapolation, 1,2,3-trinitraptopropane (GTN) derivatives are not expected to have clinical utility as neuroprotective agents in therapy owing to their especially high vasodilatory potency.

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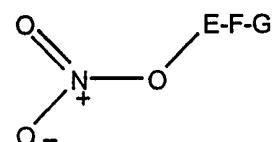
It will additionally be appreciated by those skilled in the art, that the use in therapy of any organic nitrate in cognition enhancement, represents a new and useful treatment for cognition enhancement, particularly in treatment of conditions including but not limited to: stroke; dementias of all type, trauma, drug-induced brain damage, and aging.

20

“Mitigating neurodegeneration” as use herein involves effecting neuroprotection, inhibiting or preventing neurodegeneration, and/or ameliorating the manifestations or impact of neurodegeneration. Such amelioration includes effecting cognition enhancement, as is quantified by tests known in the art (e.g., Venault et al., 1992, incorporated herein by reference). “Modulating” a biological process as used herein (for example, modulating the activity of the non-glutamate neuroreceptors), encompasses both increasing (positively modulating) and decreasing (negatively modulating) such activity, and thus inhibition, potentiation, agonism, and antagonism of the biological process.

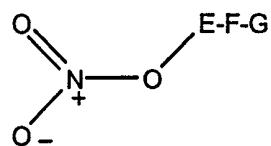
In particular, the therapeutic compounds of the invention comprise at least one nitrate group. The nitrate groups(s) can optionally be covalently bound to a carrier moiety or molecule (e.g., an aromatic group, an aliphatic group, peptide, steroid, nucleoside, peptidomimetic, steroidomimetic, or nucleoside analogue, or the like). In addition to functioning as a carrier for the nitrate functionality, the carrier moiety or molecule can enable the compound to traverse biological membranes and to be biodistributed preferentially, without excessive or premature metabolism. Further, in addition to functioning as a carrier for the nitrate functionality, the carrier moiety or molecule can enable the compound to exert amplified neuroprotective effects and/or cognition enhancement through synergism with the nitrate functionality.

In one aspect, the invention provides a method of treating a neurological condition and/or preventing an undesirable mental condition (e.g., memory loss) including the step of administering to a subject an effective amount of a therapeutic compound capable of mitigating neurodegeneration which has at least one nitrate group. In one embodiment, the therapeutic compound is capable of effecting neuroprotection. In another embodiment of the invention, the therapeutic compound is capable of effecting cognition enhancement. The therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions; so that a neurological condition is treated.

In another aspect, the invention provides a pharmaceutical composition including a physiologically acceptable carrier and a compound having the formula (Formula I):



wherein: E, F, G are organic radicals which may contain inorganic counterions; such that neurodegeneration is mitigated. The composition is employed for mitigating neurodegeneration, effecting neuroprotection and /or effecting cognition enhancement.

5 In another aspect, therapeutic compounds of the invention that effect neuroprotection and/or effect cognition enhancement in a subject to which the therapeutic compound is administered have the formula (Formula II):



in which: m, n, p are integers from 0 to 10; R^{3,17} are each independently hydrogen, a nitrate group, or A; R^{1,4} are each independently hydrogen or A, where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains 20 O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety 25 constituting a linkage of from 0 to 5

carbons, between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g., C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and 5 alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy ; R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y; where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), 10 P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵; Y is F, Br, 15 Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, 20 P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist; R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁ - C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or A; M is 25 H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(+k) where k is 0-3, or other pharmaceutically acceptable counterion.

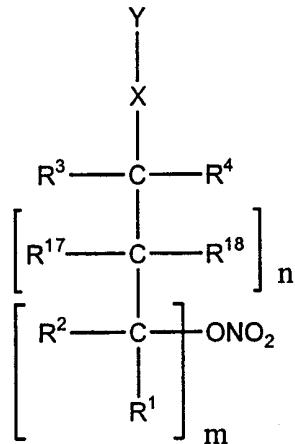
Pharmaceutical compositions comprising a compound of Formula II in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting europrotection and/or 30 effecting cognition enhancement in a subject comprising the step of administering a

compound of Formula II to a subject such that said mitigation and /or said neuroprotection an/or cognition enhancement occurs.

According to this aspect of the invention, preferred therapeutic compounds for 5 effecting neuroprotection and/or cognition enhancement in a subject to which the compound is administered include compounds in which R¹⁹ is X-Y. In some preferred embodiments: R¹⁹ is X-Y and R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents, or C₁ or C₂ connections to R¹ – R³ in cyclic derivatives; R¹ and R³ are the 10 same or different and selected from H, C₁-C₄ alkyl chains, which may include one O, linking R¹ and R³ to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents; R² and R⁴, are the same or different and selected from H, a nitrate group, C₁-C₄ alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R⁵); and R⁷, R¹¹ are the same or different C₁ – C₈, alkyl or acyl.

15 In certain embodiments in which R¹⁹ is X-Y, m, p = 1, and n = 0. In other embodiments in which R¹⁹ is X-Y, X is selected from: CH₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵)₂, SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₃HM, 20 PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SSR⁴. In certain other embodiments in which R¹⁹ is X-Y, Y is selected from CN, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, SCN, SCN₂H₂(R¹⁵)₂, SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SR⁴, SO₂M, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), 25 P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(SR¹³), SR⁵, SSR⁵, or does not exist. In some embodiments, X and/or Y contains a sulfur-containing functional group. In certain embodiments, the compound of the invention comprises a heterocyclic functionality, more preferably, a nucleoside or nucleobase. In other embodiments, the compound of the invention comprises a carbocyclic functionality, more preferably, a 30 steroidal or carbohydrate moiety.

In another aspect of the invention, a therapeutic compound of the invention is represented by the formula (Formula III):

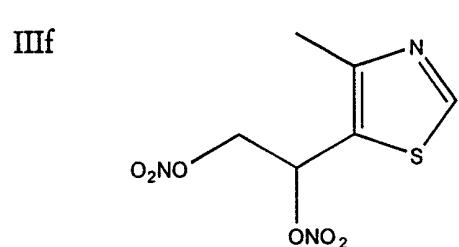
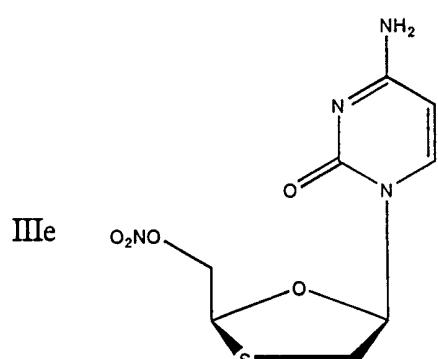
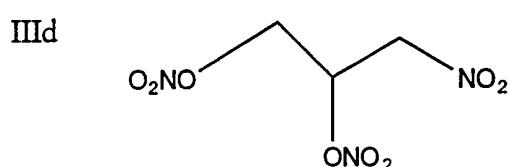
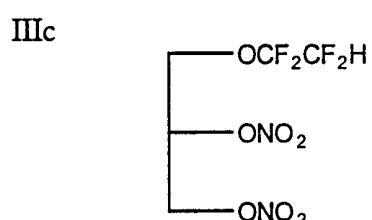
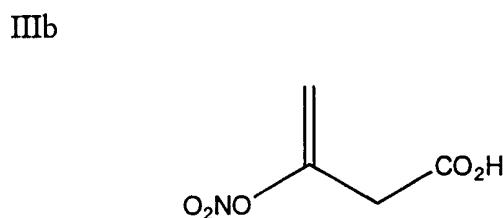
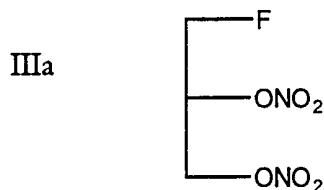


5 in which: m, n are 1-10; R¹⁻¹⁸, X, and Y have the meaning as defined above. In certain preferred embodiments, R⁶ - R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents, or C₁ - C₆ connections to R¹ - R⁴ in cyclic derivatives. In certain preferred embodiments, R¹⁸ is A and m = n = 1.

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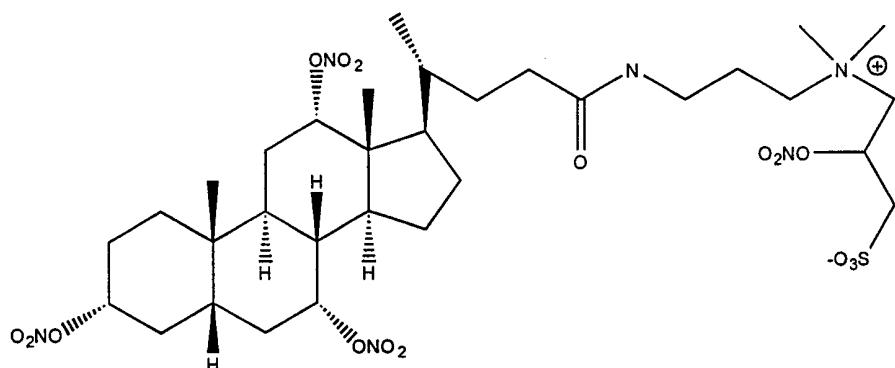
Pharmaceutical compositions comprising a compound of Formula III in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step 15 of administering a compound of Formula III to a subject such that said mitigation and / or said neuroprotection and/or cognition enhancement occurs.

Examples and preferred embodiments of compounds of the invention according to Formula III are set forth below:



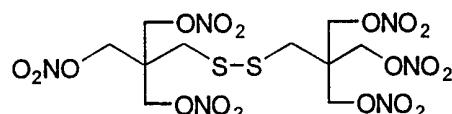
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IIIg



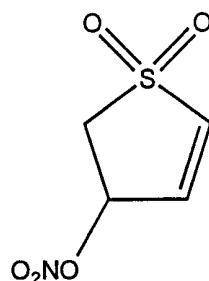
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IIIh



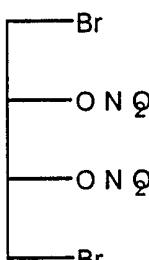
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IIIi



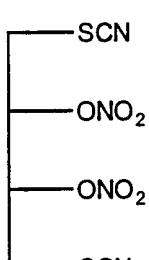
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IIIj



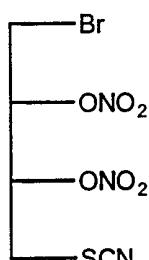
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IIIk



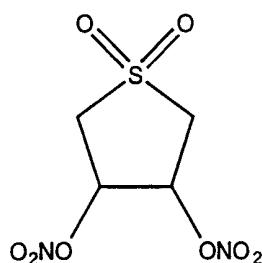
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IIIl



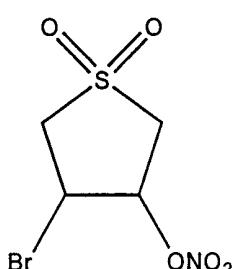
IIIm

5



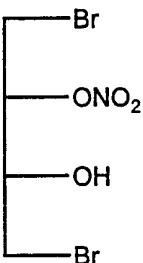
III n

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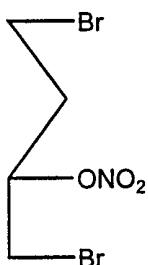
III o

15



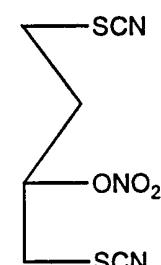
III p

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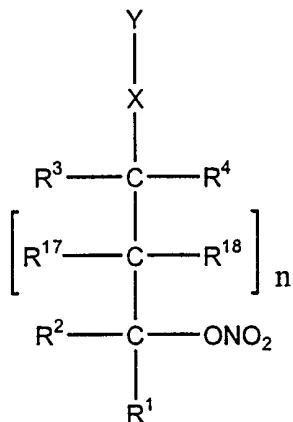


III q

25



In another aspect of the invention, a therapeutic compound of the invention can be represented by the formula (Formula IV):

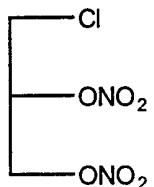


in which $n = 0$, X is CH_2 or does not exist, and Y is selected from F, Br, Cl, CH_3 ,
 5 CF_2H , CF_3 , OH, NH_2 , NHR_6 , NR_6R_7 , CN, NHOH , N_2H_3 , $\text{N}_2\text{H}_2\text{R}_{13}$, $\text{N}_2\text{HR}_{13}\text{R}_{14}$, N_3 , S,
 SCN, $\text{SCN}_2\text{H}_2(\text{R}_{15})_2$, $\text{SCN}_2\text{H}_3(\text{R}_{15})$, $\text{SC(O)N(R}_{15})_2$, SC(O)NHR_{15} , SO_3M , SH, SR_7 , SO_2M ,
 S(O)R₈, $\text{S(O)}_2\text{R}_9$, S(O)OR_8 , $\text{S(O)}_2\text{OR}_9$, PO_2HM , PO_3M_2 , $\text{P(O)(OR}_{15})(\text{OR}_{16})$,
 P(O)(OR₁₆)(OM), $\text{P(O)(R}_{15})(\text{OR}_8)$, P(O)(OM)R_{15} , CO_2M , CO_2H , CO_2R_{11} , C(O)R_{12} ,
 C(O)(OR₁₃), $\text{C(O)(SR}_{13})$, SR_5 , SSR_7 or SSR_5 . R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} ,
 10 R_{15} , and R_{16} are as defined above. In certain preferred embodiments, R_2 and R_4 are
 optionally H, a nitrate group or a connection to $\text{R}_5\text{-R}_{16}$ in cyclic derivatives.

15 Pharmaceutical compositions comprising a compound of Formula IV in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step of administering a compound of Formula IV to a subject such that said mitigation and / or said neuroprotection and/or cognition enhancement occurs.

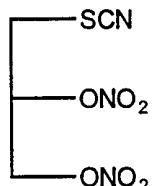
20 Examples and preferred embodiments of compounds of the invention according to Formula IV are set forth below:

IVa 3



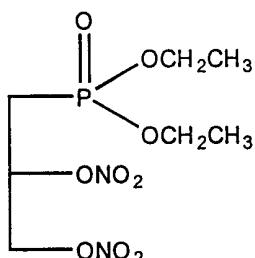
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IVb 5



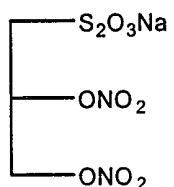
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IVc 8



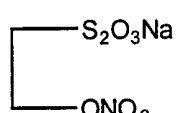
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IVd 9

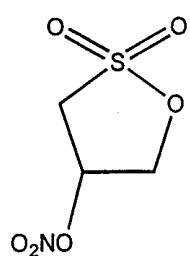


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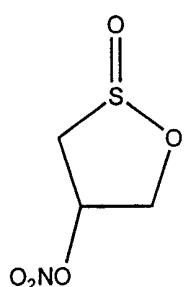
IVe 10



25 IVf 16

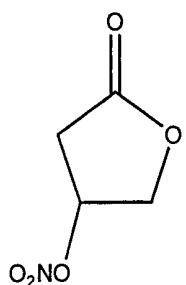


IVg 17



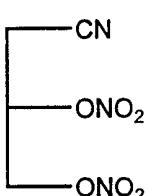
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IVh 18



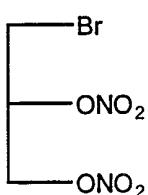
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IVi



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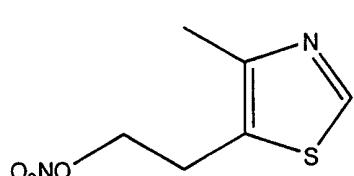
IVj



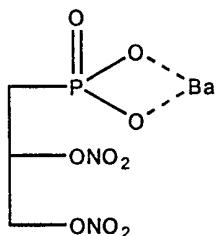
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IVk 61

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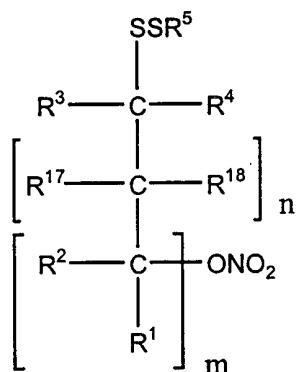
IVl



IVm

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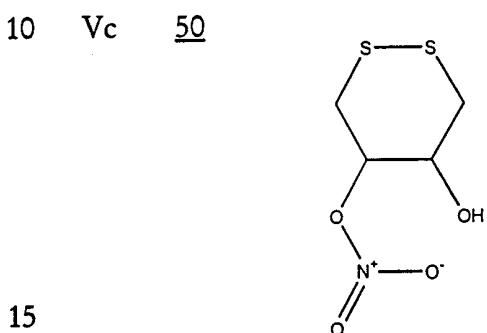
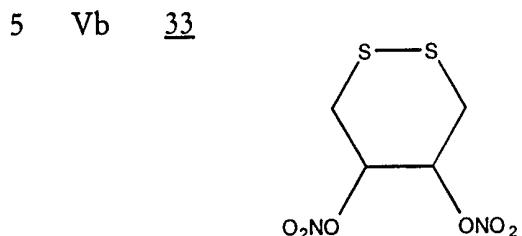
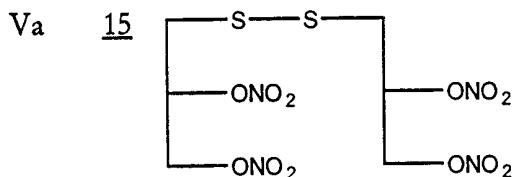
In yet another aspect of the invention, a compound of the invention can be represented by the formula (Formula V):



in which R_2 is optionally H or a connection to R_5 in cyclic derivatives, R_4 is H or a nitrate group, and R_5 is as described above.

10 Pharmaceutical compositions comprising a compound of Formula V in admixture with a pharmaceutically acceptable carrier therefor are provided by the invention. The invention further provides methods of mitigating neurodegeneration, effecting neuroprotection and/or effecting cognition enhancement in a subject comprising the step 15 of administering a compound of Formula V to a subject such that said mitigation and /or said neuroprotection and/or cognition enhancement occurs.

20 Examples and preferred embodiments of compounds of the invention according to formula V (Formulae Va-c) are set forth below:



15 Table 1 lists data determined for compounds of the invention per art-recognized characterization techniques.

Table 1	¹ H NMR	¹³ C NMR
IIIa	(CDCl ₃): 5.34-5.57 (1H, dm, ³ J _{HF} 20.6), 4.53-4.87 (4H, superposition several multiplets, O ₂ NO-CH ₂ + CH ₂ F, ² J _{HF} 46.7, ⁴ J _{HF} 0.66)	(CDCl ₃): 79.47 (d, ¹ J _{CF} 177), 76.73 (d, ² J _{CF} 20.6), 67.84 (d, ³ J _{CF} 6.87)
IIIb	(CDCl ₃): δ	(CDCl ₃): δ
IIIc	(CDCl ₃): δ 5.7 (1H, t, ² J _{HF} 54), 5.45 (1H, m), 4.5-4.9 (2H, m), 4.15-4.35 (1H, m)	(CDCl ₃): δ 75.55, 68.05, 60.76
IIId	(CDCl ₃): δ 5.46 (1H, m), 4.80-4.87 (1H, dd, J 3.5, 12.9), 4.65-4.72 (1H, dd, J 6.2, 12.9), 3.7-3.8 (2H, m)	(CDCl ₃): δ 77.24, 68.57, 39.86
IIIf	(CDCl ₃) δ 8.72 (s, 1H), 5.38 (t, 1H), 4.6 (d, 2H), 2.45 (s, 3H)	-
II Ig	(DMSO _d ₆) CH ₂ ONO ₂ only: δ 4.8-5.8	(DMSO _d ₆) CONO ₂ only: δ 85.68, 84.17, 82.47, 76.50

IIIh	(CD ₃ OD) δ 4.85 (3H, m), 3.5 (1H, m)	(CD ₃ OD) δ 70.61, 36.74
IIIi	(CDCl ₃): δ 6.95 (dd, 1H), 6.71 (dd, 1H), 6.09 (m, 1H), 3.80 (dd, 1H), 3.32 (dd, 1H)	(CDCl ₃): δ 137.9, 132.5, 76.6, 52.9
IIIj	(CDCl ₃): δ 5.62 (2H, m), 3.60 (4H, m)	(CDCl ₃): δ 77.87, 25.22
IIIk	(CD ₃ CN): δ 3.45 (m, 2H), 5.72 (m, 2H)	(CD ₃ CN): δ 79.98, 28.87
IIIl	-	(CD ₃ CN): δ 79.48, 33.45, 28.47
IIIm	(DMSO ₄ ^d): δ 5.97 (m, 2H), 3.80 (m, 4H)	(DMSO ₄ ^d): δ 78.84, 52.60
IIIn	(CDCl ₃): δ 5.73 (m, 1H), 4.62 (m, 1H), 3.96-3.77 (m, 1H), 3.58-3.32 (m, 1H)	(CDCl ₃): δ 81.47, 57.85, 53.50, 38.75
IIIo	-	(CDCl ₃): δ 81.24, 69.79, 33.26, 27.24
IIIp	(CDCl ₃): δ 5.36 (m, 1H), 3.11-3.60 (m, 4H), 2.33 (m, 2H)	(CDCl ₃): δ 78.92, 33.66, 30.64, 27.36
IIIq	(CDCl ₃): δ 5.47 (m, 1H), 3.53-3.05 (m, 4H), 2.29 (m, 2H)	(CDCl ₃): δ 81.32, 37.12, 32.97, 30.98
IVi	(CDCl ₃): δ 5.45 (1H, m), 4.83 (1H, dd), 4.65 (1H, dd), 2.9 (2H, m)	(CD ₃ OD): δ 116.44, 75.37, 71.20, 19.19
IVk	(CDCl ₃): δ 8.55 (s, 1H), 4.55 (t, 2H), 3.15 (t, 2H), 2.37 (s, 3H)	(CDCl ₃): δ 150.9, 150.7, 125.3, 72.53, 24.47, 15.18
IVm	(CDCl ₃): δ 7.5-8.0 (arom, 5H), 5.7 (1H, m), 4.94 (1H, dd), 4.62 (1H, dd), 3.5 (2H, m)	(CDCl ₃): δ 135.45, 134.79, 129.81, 27.95, 73.08, 70.04, 54.73
Vb	(CDCl ₃): δ 5.56 (m, 2H), 3.38-2.95 (m, 4H)	(CD ₃ OD): δ 85.93, 32.77
Vc	(CDCl ₃): δ 5.85-5.91 (1H, m), 4.50-4.58 (1H, m), 3.22-3.29 (1H, dd, J 5.47, 12.78), 2.97-3.05 (1H, dd, J 4.6, 11.88), 2.82-2.90 (1H, dd, J 2.87, 12.78), 2.74-2.83 (1H, dd, J 3.15, 11.9)	(CDCl ₃): δ 87.6, 74.96, 36.20, 31.54

Methods for preparing organic nitrates represented by the structures of Formula III are provided by the invention and taught herein, particularly in the Working Examples below.

5

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers (e.g., enantiomers, diastereomers) arising from such asymmetry are included within the scope of this invention. Such isomers can be obtained in substantially pure form by classical separation techniques and by asymmetric synthesis. For the purposes of this application, unless 10

expressly noted to the contrary, a compound shall be construed to include both the R and S stereoisomers at each stereogenic center.

In certain embodiments, a therapeutic compound of the invention comprises a cation (i.e., in certain embodiments, one of X or Y includes a cation, e.g., in the compound of formula IVd). If the cationic group is a proton, then the compound is considered an acid. If the proton is replaced by a metal ion or its equivalent, the compound is a salt. Pharmaceutically acceptable salts of the therapeutic compound are within the scope of the invention. For example, M can be a pharmaceutically acceptable alkali metal (e.g. Li, Na, K), ammonium, alkaline earth metal (e.g. Ca, Ba, Mg), higher valency cation, or polycationic counter ion (e.g., polyammonium cation) (see e.g., Berge et al., 1977). It will be appreciated that the stoichiometry of an anionic portion of the compound to a salt-forming cation will vary depending on the charge of the anionic portion of the compound and the charge of the counterion. Preferred pharmaceutically acceptable salts include a sodium, potassium, or calcium salt, but other salts are also contemplated within their pharmaceutically acceptable range.

The therapeutic compound of the invention can be administered in a pharmaceutically acceptable vehicle. As used herein "pharmaceutically acceptable vehicle" includes any and all solvents, excipients, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like which are compatible with the activity of the compound and are physiologically acceptable to the subject. An example of the pharmaceutically acceptable vehicle is buffered normal saline (0.15 M NaCl). The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the therapeutic compound, use thereof in the compositions suitable for pharmaceutical administration is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Carrier or substituent moieties useful in the present invention may also include moieties which allow the therapeutic compound to be selectively delivered to a target organ. For example, delivery of the therapeutic compound to the brain may be enhanced by a carrier moiety using either active or passive transport (a "targeting moiety").

5 Illustratively, the carrier molecule may be a redox moiety, as described in, for example, U.S. Patents 4,540,654 and 5,389,623, both to Bodor. These patents disclose drugs linked to dihydropyridine moieties which can enter the brain, where they are oxidized to a charged pyridinium species which is trapped in the brain. Thus drugs accumulate in the brain. Other carrier moieties include compounds, such as amino acids or thyroxine, which

10 can be passively or actively transported *in vivo*. Such a carrier moiety can be metabolically removed *in vivo*, or can remain intact as part of an active compound. Structural mimics of amino acids (and other actively transported moieties) including peptidomimetics, are also useful in the invention. As used herein, the term "peptidomimetic" is intended to include peptide analogues which serve as appropriate substitutes for peptides in interactions with,

15 for example, receptors and enzymes. The peptidomimetic must possess not only affinity, but also efficacy and substrate function. That is, a peptidomimetic exhibits functions of a peptide, without restriction of structure to amino acid constituents. Peptidomimetics, methods for their preparation and use are described in Morgan et al. (1989), the contents of which are incorporated herein by reference. Many targeting moieties are known, and

20 include, for example, asialoglycoproteins (see e.g., Wu, U.S. Patent 5,166,320) and other ligands which are transported into cells via receptor-mediated endocytosis (see below for further examples of targeting moieties which may be covalently or non-covalently bound to a target molecule).

25 In the methods of the invention, neurodegeneration in a subject is mitigated, and/or neuroprotection and/or cognition enhancement is effected, by administering a therapeutic compound of the invention to the subject. The term "subject" is intended to include living organisms in which the particular neurological condition to be treated can occur. Examples of subjects include humans, apes, monkeys, cows, sheep, goats, dogs, cats, mice, rats, and

30 transgenic species thereof. As would be apparent to a person of skill in the art, the animal

subjects employed in the working examples set forth below are reasonable models for human subjects with respect to the tissues and biochemical pathways in question, and consequently the methods, therapeutic compounds and pharmaceutical compositions directed to same. As evidenced by Mordenti (1986) and similar articles, dosage forms for 5 animals such as, for example, rats can be and are widely used directly to establish dosage levels in therapeutic applications in higher mammals, including humans.

In particular, the biochemical cascade initiated by cerebral ischemia is generally accepted to be identical in mammalian species (Mattson and Scheff, 1994; Higashi et al., 10 1995). In light of this, pharmacological agents that are neuroprotective in animal models such as those described herein are believed to be predictive of clinical efficacy in humans, after appropriate adjustment of dosage. Specifically, there are comparable memory-deficit patterns between brain-damaged rats and humans, which indicates that the rat can serve as an excellent animal model to evaluate the efficacy of pharmacological treatments or brain 15 damage upon memory (Kesner, 1990). The only approved drug for the clinical treatment of occlusive stroke in humans is tissue plasminogen activator, which is administered at a dose of 0.9 mg/kg by intravenous injection (Wittkowsky, 1998). This drug is also effective in protecting the rat brain subjected to cerebral ischemia by occlusion of the middle cerebral artery, when administered at a dose of 10 mg/kg intravenously (Jiang et al., 1998). 20 Thus, the rat model of focal cerebral ischemia used in the development of the novel organic nitrate esters described herein has been shown to be predictive of clinical efficacy with at least one other class of pharmacological agents.

As would also be apparent to a person skilled in the art, the invention further 25 encompasses methods of the invention employed *ex vivo* or *in vitro*. For example, the Working Examples describe studies utilizing tissue homogenates according to the invention. Furthermore, diagnostic tests or studies of efficacy of selected compounds may conveniently be performed *ex vivo* or *in vitro*, including in animal models. Such tests, studies and assays are within the scope of the invention.

Administration of the compositions of the present invention to a subject to be treated can be carried out using known procedures, at dosages and for periods of time effective to mitigate neurodegeneration, and/or to effect neuroprotection and./or cognition enhancement in the subject. An effective amount of the therapeutic compound necessary to achieve a therapeutic effect may vary according to factors such as the amount of neurodegeneration that has already occurred at the clinical site in the subject, the age, sex, and weight of the subject, and the ability of the therapeutic compound to mitigate neurodegeneration and/or to effect neuroprotection and/or cognition enhancement in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response.

5 For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A non-limiting example of an effective dose range for a therapeutic compound of the invention (e.g., Va) is between 0.5 and 500 mg/kg of body weight per day. In an aqueous composition, preferred concentrations for the active compound (i.e., the therapeutic

10 compound that can mitigate neurodegeneration and /or effect neuroprotection and /or cognition enhancement) are between 5 and 500 mM, more preferably between 10 and 100 mM, and still more preferably between 20 and 50 mM.

15

The therapeutic compounds of the invention can be effective when administered orally. Accordingly, a preferred route of administration is oral administration.

20 Alternatively, the active compound may be administered by other suitable routes such as transdermal, subcutaneous, intraocular, intravenous, intramuscular or intraperitoneal administration, and the like (e.g., by injection). Depending on the route of administration, the active compound may be coated in a material to protect the compound from the action

25 of acids, enzymes and other natural conditions which may inactivate the compound.

The compounds of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB, they

can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Patents 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs ("targeting moieties"), thus providing targeted drug delivery (see, e.g., Ranade et al., 1989).

5 Exemplary targeting moieties include folate and biotin (see, e.g., U.S. Patent 5,416,016 to Low et al.); mannosides (Umezawa et al., 1988); antibodies (Bloeman et al., 1995; Owais et al., 1995); and surfactant protein A receptor (Briscoe et al., 1995). In a preferred embodiment, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety.

10

Delivery and *in vivo* distribution can also be affected by alteration of an anionic group of compounds of the invention. For example, anionic groups such as phosphonate or carboxylate can be esterified to provide compounds with desirable pharmocokinetic, pharmacodynamic, biodistributive, or other properties. Exemplary compounds include

15 IVI and pharmaceutically acceptable salts or esters thereof.

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be 20 administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan et al., 1984).

25 The therapeutic compound may also be administered parenterally (e.g., intramuscularly, intravenously, intraperitoneally, intraspinally, or intracerebrally). Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Pharmaceutical compositions suitable for injectable use include 30 sterile aqueous solutions (where water soluble) or dispersions and sterile powders

for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and

5 fungi. The vehicle can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants.

10

Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In some cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the

15 composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yield a powder of the active ingredient (i.e., the therapeutic compound) optionally plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the 5 therapeutic compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

10

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to 15 produce the desired therapeutic effect in association with the required pharmaceutical vehicle. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of neurological conditions in 20 subjects.

Therapeutic compositions can be administered in time-release or depot form, to obtain sustained release of the therapeutic compounds over time. The therapeutic compounds of the invention can also be administered transdermally (e.g., by providing the 25 therapeutic compound, with a suitable carrier, in patch form).

Active compounds are administered at a therapeutically effective dosage sufficient to mitigate neurodegeneration and/or to effect neuroprotection and/or cognition enhancement in a subject. A "therapeutically effective dosage" preferably mitigates 30 neurodegeneration by about 20%, more preferably by about 40%, even more preferably by about 60%, and still more

preferably by about 80% relative to untreated subjects. The ability of a compound to mitigate neurodegeneration can be evaluated in model systems that may be predictive of efficacy in mitigating neurodegeneration in human diseases, such as animal model systems known in the art (including, e.g., the method of transient middle cerebral artery occlusion in the rat) or by *in vitro* methods, (including, e.g., the assays described herein).

It will be appreciated that the ability of a compound of the invention to mitigate neurodegeneration will, in certain embodiments, be evaluated by observation of one or more symptoms or signs associated with neurodegeneration *in vivo*. Thus, for example, the ability of a compound to mitigate neurodegeneration may be associated with an observable improvement in a clinical manifestation of the underlying neurodegeneration-related disease state or condition, or a slowing or delay in progression of symptoms of the condition. Thus, monitoring of clinical manifestations of disease can be useful in evaluating the neurodegeneration-mitigating efficacy of a compound of the invention.

15

The method of the invention is useful for treating neurodegeneration associated with any disease in which neurodegeneration occurs. Clinically, neurodegeneration can be associated with conditions including but not limited to: stroke; Parkinson's disease; Alzheimer's disease; Huntington's disease; multiple sclerosis; amyotrophic lateral sclerosis; AIDS-induced dementia; epilepsy; alcoholism; alcohol withdrawal; drug-induced seizures; viral/bacterial/fever-induced seizures; trauma to the head; hypoglycemia; hypoxia; myocardial infarction; cerebral vascular occlusion; cerebral vascular hemorrhage; hemorrhage; environmental excitotoxins of plant; animal and marine origin; dementias of all type; trauma; drug-induced brain damage; and aging; or result from surgical procedures such as cardiac bypass.

Novel compounds according to the invention can be synthesized by methods set forth herein (see, e.g., Working Examples) or in our patents U.S. No. 5,807,847 and U.S. No. 5,883,122. Various compounds for use in the methods of the invention are commercially

available and/or can be synthesized by standard techniques. In general, nitrate esters can be prepared from the corresponding alcohol, oxirane or alkene by standard methods, that include: nitration of alcohols and oxiranes, mixed aqueous/organic solvents using mixtures of nitric and sulfuric acid and/or their salts, with temperature control (see Yang et al., 1996); nitration of alcohols and oxiranes in acetic anhydride using nitric acid or its salts with or without added acid catalyst, with temperature control (see, e.g., Louw et al., 1976); nitration of an alcohol with a nitronium salt, e.g. a tetrafluoroborate; nitration of an alkene with thallium nitrate in an appropriate solvent (see Ouellette et al., 1976).

10 The following Examples further illustrate the present invention and are not intended to be limiting in any respect. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

15

Working Examples

Example 1

Characterization of guanylyl cyclase activation

20 Activation of soluble guanylyl cyclase (GCase) by nitrates III^m, IV^a, IV^b, IV^d, IV^e, IV^f, IV^g, IV^j, Va, Vb, and GTN was assayed employing partially purified enzyme freshly prepared from the 105,000g supernatant fraction of rat aorta homogenates, using the radioimmunoassay method described by Bennett et al. (1992), the disclosure of which is incorporated herein by reference. Dose-response curves were obtained for
25 GCase activation by nitrates IV^a, IV^b, IV^d, IV^e, IV^f, IV^g, IV^j, and GTN in the presence and absence of cysteine and dithiothreitol (DTT; both 2mM). In all cases, data were normalized to the maximal GTN response carried out in identical GCase preparations. Experimental incubations were performed at 37°C for 10 min. The data from these curves are summarized in Figures 1-8, which give: concentrations of
30 nitrates required to give a response equivalent to the maximal response seen for GTN+cysteine; the maximal response measured for each nitrate, and; where applicable, potency. The GCase assay data show that IV^d activates GCase, with a

submillimolar EC₅₀ in the absence of any added thiol, in contrast to GTN which requires added cysteine (Figs 1,2). Compounds IVd and IVg also activate GCCase in the presence of DTT in contrast to GTN (Figs 2,3). Activation of GCCase by IVb was cysteine-dependent and the response was very low (EC₅₀ > 1mM) (Fig. 4). Activation of GCCase by compound 5 IVf was cysteine-dependent and much greater than that achieved by GTN (Fig. 5). Activation of GCCase by compound IVe was very low under all conditions tested (Fig. 6). Activation of GCCase by compounds IVj and IVa was cysteine-dependent and approximately equivalent to GTN (Figs. 7,8). Relative to GTN itself, a wide range of 10 potencies was observed for the nitrate esters of the invention. No activation of GCCase by glycerol mononitrates was observed in this assay at the concentrations of nitrate employed.

To test for potential differences in GCCase activation by nitrates, the effects of IIIm, IVh, Va, Vb, and GTN were assayed in brain and vascular tissue. IVh had no effect on GCCase activity in either rat aorta or rat hippocampus (Fig. 9). IIIm had greater efficacy to 15 stimulate GCCase activity compared to GTN in both rat aorta and rat hippocampus (Fig. 9). Vb was found to be equivalent to GTN in efficacy and potency for activation of GCCase in both rat aorta and rat hippocampus (Fig. 10). Va was found to have greater efficacy, but equal potency, to GTN in rat aorta (Fig. 10a). In contrast, Va had greater efficacy and greater potency to stimulate GCCase in rat hippocampus (Fig. 10b). These data illustrate 20 that nitrates have differential effects on GCCase activation that are dependent on both structure of the compound and the tissue assayed for GCCase activity, supporting the notion that neuroprotective and cardiovascular effects of nitrates are separable.

Example 2

25 Characterization of cyclic GMP accumulation

In order to extend the GCCase data further, the effects of nitrates Va, IIIm, Vb, Vc, and IVk on cyclic GMP accumulation in intact isolated rat aorta were examined (Figs. 11,12). Thoracic aortic strips were prepared from male Sprague-Dawley rats (Charles-River, Canada) as described in McGuire et al. (1994) and Stewart et al. (1989), both 30 incorporated herein by

reference. Tissues were contracted submaximally with phenylephrine (0.1 μ M) and exposed to various concentrations of drug for 1 min. Cyclic GMP accumulation was determined using the radioimmunoassay method described by Bennett et al. (1992). At concentrations of 1 μ M and 10 μ M, GTN and IVk significantly increased cGMP accumulation (Figs. 11, 5 12). At a concentration of 1 μ M, Va, IIIm, Vb, and Vc did not significantly increase cyclic GMP accumulation (Figs. 11a, 12a). At a concentration of 10 μ M, Va, Vb, and IVk significantly increased cyclic GMP accumulation, whereas IIIm and Vc did not (Figs. 11b, 12b).

10 Sections of rat hippocampus (400 μ m) were prepared and incubated in oxygenated Krebs solution at 37°C. After a 60-min equilibration period, the brain slices were stimulated with different concentrations of Va or GTN for 3-min. Cyclic GMP accumulation was determined as described above for aortic strips. Figure 13 shows that Va causes a concentration-dependent increase in the tissue levels of cGMP in rat hippocampal 15 brain slices *in vitro* and that, at high concentration (100 μ M), Va is more effective than GTN in elevating cGMP levels in hippocampal brain slices *in vitro*. These data are in very good agreement with the differential effects of Va and GTN on hippocampal GCase activity shown in Figure 10b.

20 *Example 3*

Characterization of relaxation of isolated blood vessels

In order to extend the GCase data, the relaxing effects of nitrates IIIm, IVc, IVd, IVf, 25 IVg, IVh, IVk, Va, Vb, and Vc on rat aortic tissue were examined. Thoracic aortic strips were prepared from male Sprague-Dawley rats (Charles-River, Canada) as described in McGuire et al. (1994), and Stewart et al. (1989). Tissues were contracted submaximally with phenylephrine (0.1 μ M) and exposed to various concentrations of nitrovasodilator to obtain concentration-response curves. In this intact tissue assay, all of the nitrates were observed to cause relaxation of the tissue with a maximal relaxant response equal to that obtained with GTN. However, the compounds differed in potency with EC₅₀ (effective concentration for 50% of the subjects) 30 values of 7.87 nM, 94.3 nM, 6.59 μ M, 25.2 μ M, 11.0 μ M, and 0.203 μ M, for GTN and compounds Va, IVd, IVg, IVf, and IVc, respectively (Fig. 14). In another series

of experiments, the EC₅₀ values for relaxation were 0.61 nM, 3.19 nM, 8.40 nM, 0.153 μ M, 0.437 μ M and 6.89 μ M for GTN, IVk, Vb, IIIm, Vc, and IVh, respectively (Fig. 15). The EC₅₀ value for a nitrosothiol (*tert*-butyl nitrosothiol, Fig.16) was 11.2 μ M. Compounds IVd and IVc were tested for their ability to cause vascular relaxation in tissues that had been
5 made tolerant to the relaxant effect of GTN. GTN tolerance was induced by incubating tissues with high concentrations of GTN (0.5mM GTN for 30 min). Under these conditions, the maximal relaxant effects of IVd (Fig.17a) and IVc (Fig.17b) were not significantly different from their effects for untreated tissue. The EC₅₀ for relaxation was increased approximately threefold, but the difference was not statistically significant.

10

Example 4

Characterization of blood pressure changes in the whole animal

To test for differential effects of nitrates on blood pressure responses, Va and GTN were injected into rats in which the abdominal aorta was cannulated for blood pressure recording. In the first experiment, Va and GTN were injected subcutaneously at a dose of 400 μ mol/kg body weight into conscious, freely moving animals. GTN caused a small and transient decrease in blood pressure in these animals, whereas Va had no discernable effect on arterial blood pressure (Fig. 18). Va and GTN were subsequently tested in anesthetized rats in which the abdominal vena cava was also cannulated to allow for bolus intravenous injection of drugs. In this preparation, GTN caused a substantial and dose-dependent decrease in arterial blood pressure. In contrast, Va at equal doses had very modest effects on blood pressure at doses lower than 2 μ mol/kg body weight (Fig. 19). These data are in very good agreement with the results obtained for these two agents using the isolated blood vessel preparation.

25

The plasma levels of nitrates Vb and Vc (the denitrated metabolite of Vb) were measured to gain insight into the handling of these molecules in the body. Cannulas were placed in the abdominal aorta for blood sampling. After a two-day recovery period, a single subcutaneous dose of Vb (200 μ mol/kg) was administered and blood samples
30 collected over a period of six hours. Samples were centrifuged, the plasma collected, and the concentrations of

Vb and Vc determined by gas-liquid chromatography by the method of McDonald and Bennett (1990). The data obtained for Vb and Vc indicate that nitrates achieve maximal plasma levels within 30 minutes after subcutaneous injection, and thereafter decline at a steady rate (Fig. 20). These data suggest that nitrates have excellent bioavailability after 5 subcutaneous injection.

Example 5

Characterization of neuroprotection in brain slices

In order to test for potential neuroprotective properties, the effects of Va were 10 tested in an *in vitro* model of cerebral ischemia. Rat hippocampal slices were subjected to 30 minutes of ischemia by incubation in a buffered salt solution lacking glucose and oxygen. Sections of rat hippocampus (400 μ m) were prepared and incubated in oxygenated Krebs solution at 37°C. Slices were then either untreated or subjected to a 30-minute period of ischemia by incubation in Krebs solution lacking oxygen and glucose. Slices 15 were then incubated for a further 4 hours in oxygenated Krebs solution in the presence of drug vehicle or 200 μ M Va. At the end of the 4-hr re-oxygenation period, release of the cytosolic enzyme lactate dehydrogenase (LDH) from the tissue was used an index of neuronal cell injury. Some hippocampal slices were treated with Va (200 μ M) after the 30- minute period of ischemia. Figure 21 shows that Va significantly reduced the release of 20 LDH from ischemic brain slices when administered immediately after the period of ischemia. Figure 22 shows that Va was still effective at protecting ischemic brain slices *in vitro* when drug exposure was delayed for up to 1 hour after re-oxygenation of the tissue.

To test the mechanism of this neuroprotection, rat hippocampal brain slices made 25 ischemic for 30 minutes *in vitro* were exposed to the guanylyl cyclase inhibitor ODQ 5-min prior to administration of 200 μ M Va. The concentration of ODQ used was known to completely block the production of cGMP induced by Va. Blockade of guanylyl cyclase by ODQ completely eliminated the neuroprotective effect of Va in ischemic rat hippocampal

slices, showing that elevations in cGMP levels are directly related to the neuroprotective properties of Va *in vitro* (Fig. 23).

Example 6

5 *Characterization of neuroprotection in the whole animal*

To test the efficacy of nitrates in animal models of cerebral ischemia, two different approaches were taken. In the first, Mongolian gerbils were subjected to 5 minutes of global forebrain ischemia by occlusion of the common carotid arteries under halothane anesthesia. This period of ischemia produces a selective neuronal cell death in the CA1 10 region of the hippocampus that develops over several days. Surgical procedures, and control of brain and body temperature during the occlusion, were as described in Nurse and Corbett (1996), incorporated herein by reference. Animals were given two 15 subcutaneous injections of drug vehicle, or 400 μ mol/kg IVh, Vb or Va at 5-min and 90 min after the occlusion. Sham-treated animals had the carotid arteries exposed but not 20 occluded. Seven days later, the brains were fixed by transcardiac perfusion with 4% paraformaldehyde, dissected out, embedded in paraffin, and 5 μ m sections were cut and stained with cresyl violet. Viable neurons in 100 square μ m blocks of the CA1 region were counted to obtain an index of neuronal cell damage. The results obtained with nitrates IVh, Vb, and Va are shown in Figure 24. Both Va and Vb produced a statistically 25 significant neuroprotection against 5 minutes of global forebrain ischemia in the gerbil.

The second animal model tested was transient focal cerebral ischemia in the rat induced by occlusion of the middle cerebral artery. Under halothane anesthesia, a filament was advanced into the right internal carotid artery until the origin of the right middle 25 cerebral artery was occluded. The filament was secured, the animal allowed to regain consciousness, and two hours later the filament was removed under halothane anesthesia. Animals were given five subcutaneous doses of drug vehicle or 200 μ mol/kg Va at 2, 3, 4, 6, and 8 hr post-occlusion. At 24 hr post-occlusion the animals were sacrificed, the brain 30 removed, cut into 2-mm coronal sections and stained for viable tissue with 2,3,5-triphenyltetrazolium. Infarct

volume of whole brain and cerebral cortex was quantitated by computer-assisted image analysis. A 2-hour episode of cerebral ischemia followed by recirculation produces a large infarct in the cerebral cortex and subcortical structures on the affected side. The volumes of the total and cerebral cortical infarct in the rat brain were very similar to those reported by other groups using the same procedure (e.g., Sydserff et al., 1995; Morikawa et al., 1998). Figure 25 shows the results obtained with nitrate Va in this model. A series of subcutaneous injections of Va at a dose of 200 μ mol/kg body weight at 2, 3, 4, 6, and 8 hours after the onset of cerebral ischemia resulted in a statistically significant neuroprotection when assayed 24 hours after ischemia. Collectively, these data indicate that delayed administration of Va is neuroprotective in two different animal models of cerebral ischemia.

In a separate series of experiments, the effects of organic nitrates on focal excitotoxic lesions induced by localized application of NMDA in the rat brain were determined. Male Sprague-Dawley rats were stereotactically infused with NMDA into the right substantia nigra as described in Connop et al. (1995), incorporated herein by reference. Four days later, both striata were dissected and assayed for tyrosine hydroxylase (TH) activity. Loss of TH activity in the striata is a quantitative index of NMDA-induced neuronal cell death in the substantia nigra. The striata of each animal were compared to express neurotoxicity as a percent decrease in TH activity of the ipsilateral striatum as compared to the contralateral striatum. Pretreatment of these animals with GTN (administered as a subcutaneous patch inserted under halothane anesthesia one hour prior to the NMDA infusion) at doses of 0.2 and 0.4 mg/hr produced a dose-dependent reduction in the loss of TH activity from the ipsilateral striatum (Fig. 26). Figure 27 shows that delaying the administration of GTN until one hour after the NMDA infusion was equally effective at preventing NMDA-induced neuronal cell death in the substantia nigra. Losartan, a drug that decreases systemic blood pressure through a mechanism different from that of GTN, had no neuroprotective effects (Fig. 28). This shows that any vasorelaxation caused by GTN is not the mechanism of the neuroprotection against excitotoxic cell death induced by NMDA. Figure 29 shows that the doses of losartan and GTN used in these studies caused an equivalent decrease in systemic blood pressure. Male

Sprague-Dawley rats with aortic catheters were connected to pressure transducers which recorded blood pressure for 4 to 8 hours. The animals treated with subcutaneous 0.4 mg/hour GTN patches implanted in the dorsal neck region, showed a 15% decrease in MAP 250 minutes post implantation. Animals treated with a single 30 mg/kg 5 intraperitoneal injection of Losartan showed a 20% decrease in MAP 250 minutes after injection. From these data, treatment protocols for the NMDA infusion experiments shown in Figure 28 were generated.

Example 7

10 *Characterization of neuroreceptor interactions*

The direct effects of organic nitrates on amino acid neurotransmitter receptors has been tested using the *Xenopus* oocyte expression system and two-electrode voltage-clamp recording methods. Human recombinant γ -aminobutyric acid type A (GABA_A) receptors composed of $\alpha 1\beta 2\gamma 2L$ subunits were expressed in *Xenopus* oocytes as described in 15 Reynolds et al. (1996), incorporated herein by reference. GABA_A receptor-activated membrane current was recorded in individual oocytes, and modulation of this current by GTN and organic nitrates described herein was assessed. GABA (10 μ M) was applied until the peak steady-state current response was obtained. IVd (Bunte salt) was pre-applied for 30 seconds prior to exposure of the oocyte to GABA. At 100 μ M, IVd produced a 55% 20 inhibition of the response to 10 μ M GABA (Fig. 30). This effect appears to be unrelated to the production or release of nitric oxide, as diethylamine nonoate salt (DEA) and *t*-butylnitrosothiol (*t*-BuSNO) which both spontaneously release nitric oxide in aqueous solution, had no effect on GABA receptor-activated membrane current in an oocyte expressing the $\alpha 1\beta 2\gamma 2L$ isoform of the GABA_A receptor. In contrast, nitroglycerin (GTN) 25 produced a reversible inhibition of the GABA response (Fig. 31). Organic nitrates such as GTN and IVd do not compete with GABA for binding to the GABA_A receptor. Rather, they are believed to produce an allosteric modulation of the receptor that decreases the maximal current without changing the apparent affinity of the receptor for GABA. For example, compound IVd (Bunte salt, pre-applied for 30 seconds) decreased the peak current 30 amplitude in an oocyte from 302 nA to 150 nA. However, the EC₅₀ concentration (GABA concentration producing 50% of the maximal

response) for GABA was not changed (Fig. 32). Other organic nitrates described herein have been found to have similar inhibitory effects on GABA_A receptor-activated membrane current.

5 *Example 8*

Synthesis of IIIe

To acetic anhydride (3 mL) was added gradually, with stirring, 70% nitric acid (0.26 mL), while keeping the temperature between 20-30° by external cooling. With continuous vigorous stirring the mixture was cooled to -30-35° and 2',3'-dideoxy-3-thiocytosine (0.25 g) 10 was added. After 10 min. at -35°, the reaction mixture was heated up to -20° and then stirred at -20-10° for 15 min, and 10 min at 0°. The resulting reaction mixture was poured into ice-water, stirred for 1 hr, then NaHCO₃ was added by portions until CO₂ evolution ceased. The water solution was extracted with 3x20 mL of ethyl acetate. Combined extracts were dried (MgSO₄) and concentrated. 0.38 g of slightly yellowish oil was 15 obtained. The oil crystallized in a day and was recrystallized from CHCl₃. Yield 52%. Conversion to the nitrate was evidenced by the significant downfield shift of the C5' proton multiplet from δ 3.6 to 4.85 ppm.

Example 9

20 *Synthesis of nitrate IIIf*

0.26 mL (4.15 mmol) conc. HNO₃ was added to 2 mL acetic anhydride such that the temperature did not exceed 25 - 30 °C. The mixture was cooled at 0 - 5 °C and 0.3 g (1.88 mmol) of 5-(1,2-dihydroxyethyl)-4-methylthiazole was added in several portions, the temperature being kept below 5 °C. The reaction mixture was stirred at 0 - 5 °C for 45 25 min and then 0.45 mL water was added. The mixture was stirred for 30 min and then rotary evaporated. The residue was neutralized by adding 5 mL of saturated NaHCO₃ solution and the organic product was extracted with ethyl acetate. The organic layer was concentrated and the dinitrate IIIf was purified through column chromatography (silica gel/ ethyl acetate eluant). A slightly yellow solid was obtained. Yield: 0.150 g (32 %).

*Example 10**Synthesis of nitrate IIIi*

Nitrate IIIi was obtained by two routes. Route I proceeded from the elimination reaction of IIIm in basic solution. Route II proceeded from nitration of *trans*-3-bromo-4-hydroxytetrahydrothiophene-1,1-dioxide, yielding nitrate IIIn, followed by reaction with a weak base, e.g., sodium thiocyanate in 2-butanone. Purification is achieved with silica flash column chromatography using 1:1 hexane:ethyl acetate as eluant.

*Example 11**Synthesis of nitrate IIIj*

1,4-Dibromo-2,3-butanediol is nitrated: (a) using a nitration mixture prepared from HNO_3 and H_2SO_4 over 2 days; or (b) using acetyl nitrate reacting for 2 hours. Work-up requires quenching of the reaction mixture in ice-water for an hour, extraction, drying, and evaporation. Successful purification of the title compound by silica gel column chromatography is achieved on a 25 g scale using a mixture of 70% hexane and 30% CH_2Cl_2 as eluent.

*Example 12**Synthesis of nitrate IIIk and IIIl*

Synthesis from dinitrate IIIj proceeded by refluxing with sodium or potassium thiocyanate (2 eq.) in 2-butanone for 8 hr. After cooling, a precipitate was removed by filtration and the filtrate was concentrated. Nitrates IIIk and IIIl were separated by silica flash column chromatography with hexane/dichloromethane as eluent.

*Example 13**Synthesis of nitrate IIIm*

3,4-Epoxytetrahydrothiophene-1,1-dioxide (250 mg, 1.9 mmol) was refluxed for 24 hrs in 10 mL of water and 25mg of toluenesulfonic acid. After the first 6 hrs, another 25 mg of

the acid was added. The reaction was monitored by thin layer chromatography (5% MeOH in dichloromethane). Purification was by silica flash column chromatography using 5% MeOH/CH₂Cl₂ as eluent to afford 200 mg of diol. The diol was nitrated in a cooled solution of conc. sulfuric acid (2 mol eq.), nitric acid (70%, 2 mol eq.) in an ice bath.

5 The temperature was maintained as close to 0 °C as possible. The ice bath was removed and the mixture was allowed to stir for 1 hour (reaction was monitored by thin layer chromatography, 100% CH₂Cl₂ eluent). The acid layer was removed and the organic layer washed with: (i) water; (ii) 10% sodium carbonate; (iii) 10% urea; (iv) water. Drying over sodium sulfate, filtration and concentration, yielded crude product which was purified by

10 flash column chromatography, with dichloromethane as eluent. An alternative route involves direct nitration of 3,4-epoxytetrahydrothiophene-1,1-dioxide in a similar nitration mixture.

Example 14

15 *Synthesis of nitrate IVk*

1.17 mL (18.2 mmol) concentrated HNO₃ was added, under stirring and cooling (0 – 5 °C), to 1 mL (18.2 mmol) concentrated H₂SO₄ and then 2 g (14 mmol) of 4-methyl-5-(2-hydroxyethyl)thiazole was added dropwise into the nitration mixture, the temperature being kept under 10 °C. The mixture was stirred for 3 hours at room temperature, diluted 20 with 10 mL of water and neutralized with solid NaHCO₃. The organic product was extracted with ethyl acetate and purified by column chromatography (silica gel/ ethyl acetate eluant) to produce a colorless oily product. Yield: 1.18 g (45%).

Example 15

25 *Synthesis of nitrate Ivi*

0.03 g (0.035 ml) of allyl cyanide was added to a stirred suspension of 0.22 g (0.5 mmol) of Tl (NO₃)₃.3H₂O in 2 mL of pentane. After 20 min of vigorous stirring, the pentane solution was decanted and evaporated to dryness. After evaporation the residual oil (0.44 g) was columned (CH₂Cl₂, Rf 0.64 (CH₂Cl₂)). Clean oil immediately crystallized during an attempt to 30 dissolve it in CDCl₃. Yield 0.065 g (76%). The structure of IVn was confirmed by

X-ray analysis. IR (film): 1297.03, 1678.91, 2258.91 (CN). Mass spec. m/z (Cl⁺, fragment, %): 191.9 (M+H, 2.44), 129.0 (16.41), 81.9 (100). Calculated for C₄H₅N₃O₆ 191.02.

Example 16

5 *Synthesis of nitrate IVn*

0.9 g (0.75 mL, 4.92 mmol) of allylphenyl sulfone was added dropwise to a stirred suspension of 2.43 g (5.47 mmol) of Tl (NO₃)₃·3H₂O in 10 mL of pentane. The resulting mixture was stirred overnight. The pentane solution was decanted. 2x10 mL of MeOH (methanol) were added to the reaction mixture, stirred for 10 minutes and extracts were 10 added to the pentane solution. The combined extracts were evaporated to dryness and purified by silica flash column chromatography using CH₂Cl₂ as eluant. Yield 0.08 g (15%). IR (KBr): 1152.39, 1290.91, 1273.12, 1353.83, 1646.08. Mass spec. m/z (Cl⁺, fragment, %): 307.0 (M+1, 66.5), 244.0 (100%). Calculated for C₉H₁₀N₂O₈S 306.02.

15 *Example 17*

Synthesis of nitrate Va

2.2 g (7.3 mmol) of nitrate IVd was dissolved in 5 g of cold H₂O₂ (30%, 0°C) and then 1 g of 10 % H₂SO₄ was added. The mixture was stirred at 0-5 °C until a white oil separated (ca. 30-60 min). The aqueous layer was discarded and the oil was dissolved in 20 dichloromethane, washed successively with water, then NaHCO₃ solution and finally water. The organic solution was dried over MgSO₄. Removal of the solvent produced 1.3 g of the crude product which was purified by column chromatography (Silicagel, CH₂Cl₂/hexanes : 70/30). Yield: 0.650 g (45 %).

25 *Example 18*

Synthesis of nitrate Vc.

3 g (8.88 mmol) of 1,4-dibromo-2,3-dinitrobutanediol and 2.81 g (18 mmol) of Na₂S₂O₃·5H₂O were dissolved in a mixture of 100 mL of MeOH and 45 mL of H₂O. The resulting solution was heated during 4 days at 40-45°. After this time the reaction mixture was

partially evaporated to reduce the volume of solvents. The resulting mixture was extracted 4x50 mL of ethyl ether. The extracts were combined, washed (H_2O), dried ($MgSO_4$) and evaporated to minimum. Column chromatography afforded the title compound in 10% yield, separated from Vb, the major product.

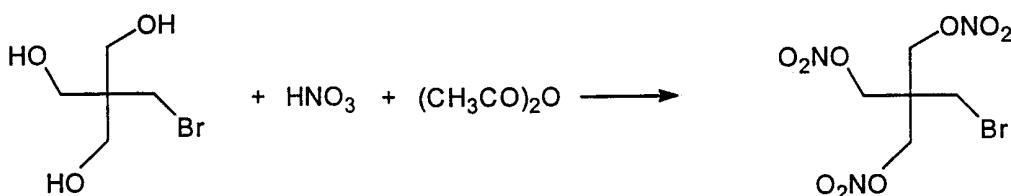
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Example 19

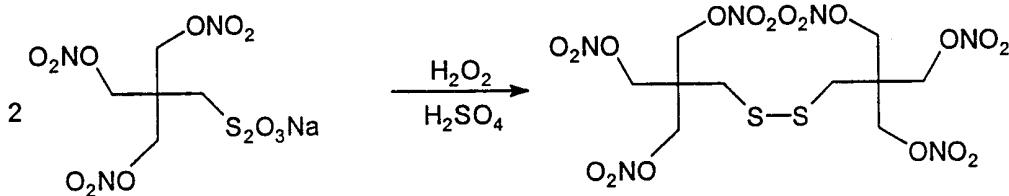
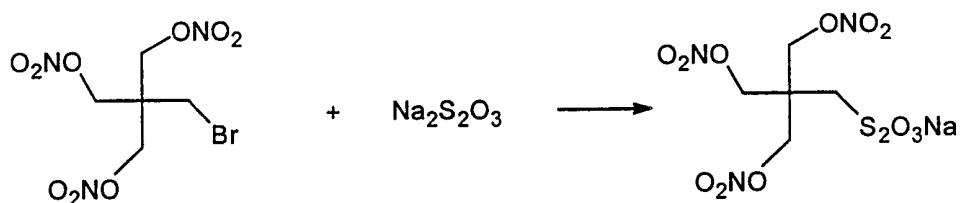
Synthesis of nitrate IIIh

The synthetic route employed for synthesis of the hexanitrate IIIh is shown in the Scheme:

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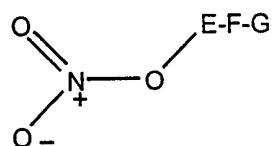
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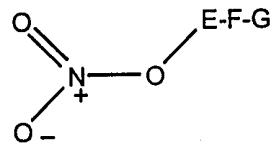
What is claimed is:

1. A method for effecting cognition enhancement in a subject in need thereof comprising administering to said subject an effective amount of a therapeutic compound such that cognition enhancement occurs, wherein the therapeutic compound has the formula (Formula I):



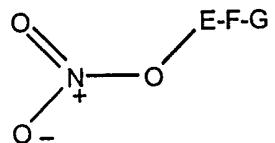
wherein E, F, G are organic radicals which may contain inorganic counterions.

2. A method for mitigating cellular damage due to ischemia in a subject in need thereof comprising administering to said subject an effective amount of a therapeutic compound such that cellular damage is mitigated, wherein the therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions.

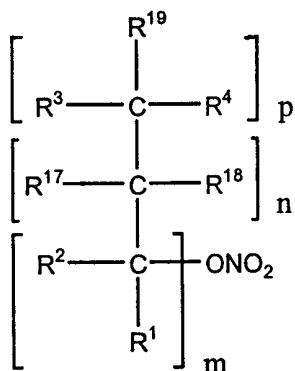
15 3. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein the therapeutic compound has the formula (Formula I):



wherein E, F, G are organic radicals which may contain inorganic counterions,

with the proviso that when E is methylene, F and G are not both C, organic radicals each bearing one nitrate group.

4. A method for mitigating neurodegeneration in a subject, comprising administering to
 5 said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein the therapeutic compound has the formula (Formula II):



in which: m, n, p are integers from 0 to 10;

R^{3,17} are each independently hydrogen, a nitrate group, or A;

R^{1,4} are each independently hydrogen or A;

20 where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the
 25 aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or
 30 aryl, or heterocyclic groups); a

substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl,

5 or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

10 where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

15 Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M,

20 CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

R⁶, R⁷, R⁸, R⁹, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁-C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or A; and

25 M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(4-k) where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso,

when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups;

that R⁴ is not H or C₁ - C₃ alkyl.

5. The method of claim 4, wherein:

R¹⁹ is X-Y.

5 6. The method of claim 5, wherein:

R¹ and R³ are the same or different and selected from H, C₁-C₄ alkyl chains, which may include one O, linking R¹ and R³ to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

10 R² and R⁴, are the same or different and selected from H, a nitrate group, C₁-C₄ alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R⁵);

R⁷, R¹¹ are the same or different C₁-C₈, alkyl or acyl;

R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁ or C₂ connections to R¹ - R³ in cyclic derivatives; and

15 M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(4-k) where k is 0-3.

7. The method of claim 6, wherein:

m = 1, n = 0, p = 1.

20 8. The method of claim 7, wherein:

X is CH₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³),

25 PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SSR⁴; and

Y is CN, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, SCN, SCN₂H₂(R¹⁵)₂, SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SR⁴, SO₂M, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(SR¹³), SR⁵, SSR⁵, or does not exist.

30

9. The method of claim 6, wherein:

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

5 X is $CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8,$
 $S(O)_2OR^9, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), PO_3HM$ or
 $P(O)(OM)R^{15}$; and

Y is $SO_2M, SO_3M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), SR^5, SR^4$
or SSR^5 , or does not exist.

10. The method of claim 3, wherein the therapeutic compound is administered orally,

10 intravenously, buccally, transdermally or subcutaneously.

11. The method of claim 3, further comprising administering the therapeutic compound in
a pharmaceutically acceptable vehicle.

15 12. The method of claim 3, wherein administering the therapeutic compound to the
subject modulates an activity of the glutamate neuroreceptor.

13. The method of claim 3, wherein administering the therapeutic compound to the
subject modulates an activity of a non-glutamate neuroreceptor.

20 14. The method of claim 3, wherein administering the therapeutic compound to the
subject modulates cerebral guanylyl cyclase activity.

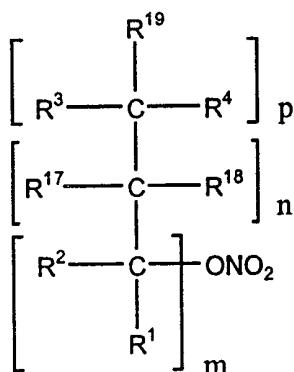
25 15. The method of claim 3, wherein administering the therapeutic compound to the
subject modulates apoptosis.

16. The method of claim 3, wherein administering the therapeutic compound to the
subject modulates cerebral free radical damage.

17. A method for treating a disease state associated with neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that a disease state associated with neurodegeneration is treated, wherein the therapeutic compound has the formula (Formula II):

5

10



in which: m, n, p are integers from 0 to 10;

15

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$R^{1,4}$ are each independently hydrogen or A;

20

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR^6 and unsaturations in the chain, optionally

bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR^6 and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4 , which optionally contains O, S, NR^6 and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages

(e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties),

5 arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂,

10 SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃,

15 N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

20 R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁-C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(4-k) where k is 0-3, or other pharmaceutically acceptable counterion;

25 and with the proviso,

when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups;

that R⁴ is not H or C₁ - C₃ alkyl.

18. The method of claim 17, wherein:

30 R¹⁹ is X-Y.

19. The method of claim 18, wherein:

R^1 and R^3 are the same or different and selected from H, C_1 - C_4 alkyl chains, which may include one O, linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

5 R^2 and R^4 , are the same or different and selected from H, a nitrate group, C_1 - C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups (- $C(O)R^5$);

R^7 , R^{11} are the same or different C_1 - C_8 , alkyl or acyl;

10 R^5 , R^6 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^1 - R^3 in cyclic derivatives; and

M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

20. The method of claim 19, wherein:

$m = 1$, $n = 0$, $p = 1$.

15

21. The method of claim 20, wherein:

X is CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$,
20 $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$,
 PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, SSR^4 ; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$,
 $SC(O)NHR^{15}$, SO_3M , SR^4 , SO_2M , PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$,
 $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5 , SSR^5 , or

25 does not exist.

22. The method of claim 20, wherein:

R^5 , R^6 , R^8 , R^9 , R^{10} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is CH_2 , O, NH, NMe, S, SO_3M , SH, SR^7 , SO_2M , S(O)R^8 , $\text{S(O)}_2\text{R}^9$, S(O)OR^8 , $\text{S(O)}_2\text{OR}^9$, PO_3M_2 , $\text{P(O)(OR}^{15}\text{)(OR}^{16}\text{)}$, $\text{P(O)(OR}^{16}\text{)(OM)}$, $\text{P(O)(R}^{15}\text{)(OR}^8\text{)}$, PO_3HM or P(O)(OM)R^{15} ; and

Y is SO_2M , SO_3M , PO_3HM , PO_3M_2 , $\text{P(O)(OR}^{15}\text{)(OR}^{16}\text{)}$, $\text{P(O)(OR}^{16}\text{)(OM)}$, SR^5 , SR^4

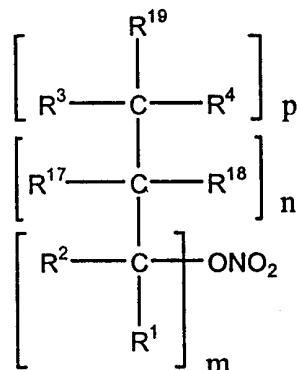
5 or SSR^5 , or does not exist.

23. The method of claim 2, wherein administering the therapeutic compound to the subject modulates levels of cyclic nucleotide cGMP and/or cAMP.

10 24. The method of claim 17, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

25. The method of claim 17 further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

15 26. A method for effecting neuroprotection in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that neuroprotection occurs, wherein the therapeutic compound has the formula (Formula II):



in which: m, n and p are integers from 0 to 10;

$\text{R}^{3,17}$ are each independently hydrogen, a nitrate group, or A;

$\text{R}^{1,4}$ are each independently hydrogen or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, 5 between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally 10 contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; 15 alkoxy; a substituted or unsubstituted aryloxy;

20 R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, 25 PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, 30 PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

$R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO_2 substituents; or $C_1 - C_6$ connections to $R^1 - R^4$ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W ; and

5 M is $H, Na^+, K^+, NH_4^+, N^+H_kR^{11}_{(4-k)}$ where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso,

when $m = n = p = 1; R^{19}, R^2, R^{18}, R^1 = H; R^{17}, R^3$ are nitrate groups;
that R^4 is not H or $C_1 - C_3$ alkyl.

10

27. The method of claim 26, wherein:

R^{19} is $X-Y$.

28. The method of claim 27, wherein:

15 R^1 and R^3 are the same or different and selected from H, C_1-C_4 alkyl chains which may include one O , linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R^2 and R^4 , are the same or different and selected from H , a nitrate group, C_1-C_4 alkyl optionally bearing 1-3 nitrate group, and acyl groups $(-C(O)R^5)$;

20 R^7, R^{11} are the same or different $C_1 - C_8$, alkyl or acyl;

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; and

M is $H, Na^+, K^+, NH_4^+, N^+H_kR^{11}_{(4-k)}$ where k is 0-3.

25

29. The method of claim 28, wherein:

$m = 1, n = 0, p = 1$.

30. The method of claim 29, wherein:

X is CH₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³),

5 PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SSR⁴; and

Y is CN, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, SCN, SCN₂H₂(R¹⁵)₂, SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SR⁴, SO₂M, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(SR¹³), SR⁵, SSR⁵, or does not exist.

10

31. The method of claim 28, wherein:

R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyls containing 1-12 carbon atoms; or C₁ or C₂ connections to R¹ or R³ in cyclic derivatives;

X is CH₂, O, NH, NMe, S, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸,

15 S(O)₂OR⁹, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), PO₃HM or P(O)(OM)R¹⁵; and

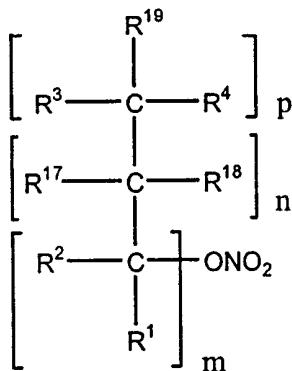
Y is SO₂M, SO₃M, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), SR⁵, SR⁴ or SSR⁵, or does not exist.

20 32. The method of claim 26, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

33. The method of claim 26, further comprising administering the therapeutic compound in a pharmaceutically acceptable vehicle.

25

34. A method for effecting cognition enhancement in a subject comprising administering to said subject an effective amount of a organic nitrate, or therapeutically acceptable salt thereof, having the formula (Formula II):



in which: m, n, p are integers from 0 to 10;

10 R^{3,17} are each independently hydrogen, a nitrate group, or A;

R^{1,4} are each independently hydrogen, or A;

where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted

15 cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and unsaturations in the linkage, and optionally bearing

20 from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or 25 unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

R², R⁵, R¹⁸, R¹⁹ are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃,

30 N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M,

SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

5 Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

10 R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁-C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a nitrate group, or W; and

M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(4-k) where k is 0-3, or other pharmaceutically acceptable counterion;

15 and with the proviso,
when m = n = p = 1; R¹⁹, R², R¹⁸, R¹ = H; R¹⁷, R³ are nitrate groups;
that R⁴ is not H or C₁ - C₃ alkyl.

20 35. The method of claim 34, wherein:

R¹⁹ is X-Y.

36. The method of claim 35, wherein:

25 R¹ and R³ are the same or different and selected from H, C₁-C₄ alkyl chains which may include one O, linking R¹ and R³ to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R² and R⁴, are the same or different and selected from H, a nitrate group, C₁-C₄ alkyl optionally bearing 1-3 nitrate group, and acyl groups (-C(O)R⁵);

R⁷, R¹¹ are the same or different C₁ - C₈, alkyl or acyl;

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to $R^1 - R^3$ in cyclic derivatives; and

M is $H, Na^+, K^+, NH_4^+, N^+H_kR^{11}_{(4+k)}$ where k is 0-3.

5

37. The method of claim 36, wherein:

$m = 1, n = 0, p = 1;$

X is $CH_2, O, NH, NMe, CN, NHOH, N_2H_3, N_2H_2R^{13}, N_2HR^{13}R^{14}, N_3, S, SCN, SCN_2H_2(R^{15})_2, SCN_2H_3(R^{15}), SC(O)N(R^{15})_2, SC(O)NHR^{15}, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8, S(O)_2OR^9, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), P(O)(OM)R^{15}, CO_2M, CO_2H, CO_2R^{11}, C(O), C(O)R^{12}, C(O)(OR^{13}), PO_2M, P(O)(OR^{14}), P(O)(R^{13}), SO, SO_2, C(O)(SR^{13}), SSR^4;$ and

Y is $CN, N_2H_2R^{13}, N_2HR^{13}R^{14}, N_3, SCN, SCN_2H_2(R^{15})_2, SC(O)N(R^{15})_2, SC(O)NHR^{15}, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), P(O)(OM)R^{15}, CO_2M, CO_2H, CO_2R^{11}, C(O)R^{12}, C(O)(SR^{13}), SR^5, SSR^5,$ or does not exist.

38. The method of claim 36, wherein:

$m = 1, n = 0, p = 1;$

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyls containing 1-12 carbon atoms; or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives;

X is $CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, S(O)R^8, S(O)_2R^9, S(O)OR^8, S(O)_2OR^9, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), P(O)(R^{15})(OR^8), PO_3HM$ or $P(O)(OM)R^{15};$ and

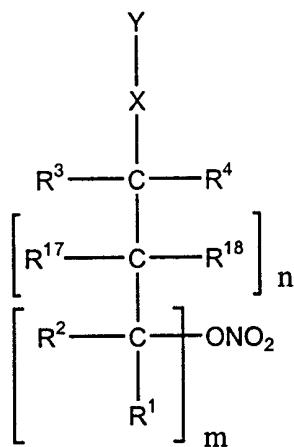
Y is $SO_2M, SO_3M, PO_3HM, PO_3M_2, P(O)(OR^{15})(OR^{16}), P(O)(OR^{16})(OM), SR^5, SR^4$ or $SSR^5,$ or does not exist.

39. A method for mitigating neurodegeneration in a subject, comprising administering to said subject an effective amount of a therapeutic compound such that mitigation of neurodegeneration occurs, wherein guanylyl cyclase is activated and cGMP level is increased.

40. The method of claim 34, wherein the therapeutic compound is administered orally, intravenously, buccally, transdermally or subcutaneously.

41. The method of claim 34, further comprising administering the therapeutic compound
5 in a pharmaceutically acceptable vehicle.

42. Organic nitrates containing at least one nitrate group having the general formula
(Formula III):



10 in which: m is an integer from 1 to 10; n is an integer from 0 to 10;
 $R^{3,4,17}$ are each independently hydrogen, a nitrate group, or A;
 where A is selected from: a substituted or unsubstituted aliphatic group (preferably
 a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the
 chain, which optionally contains O, S, NR⁶ and unsaturations in the chain, optionally
 15 bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an
 unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the
 aliphatic ring, which optionally contains O, S, NR⁶ and unsaturations in the ring,
 optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an
 unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons,
 20 between R¹ and R³ and/or between R¹⁷ and R⁴, which optionally contains O, S, NR⁶ and
 unsaturations in the linkage,

and optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR⁶ and

5 unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

10 R², R⁵, R¹⁸, are optionally hydrogen, A, or X-Y;

where X is F, Br, Cl, NO₂, CH₂, CF₂, O, NH, NMe, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM, PO₃HM, PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵,

15 CO₂M, CO₂H, CO₂R¹¹, C(O), C(O)R¹², C(O)(OR¹³), PO₂H, PO₂M, P(O)(OR¹⁴), P(O)(R¹³), SO, SO₂, C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵;

Y is F, Br, Cl, CH₃, CF₂H, CF₃, OH, NH₂, NHR⁶, NR⁶R⁷, CN, NHOH, N₂H₃, N₂H₂R¹³, N₂HR¹³R¹⁴, N₃, S, SCN, SCN₂H₂(R¹⁵)₂, SCN₂H₃(R¹⁵), SC(O)N(R¹⁵)₂, SC(O)NHR¹⁵, SO₃M, SH, SR⁷, SO₂M, S(O)R⁸, S(O)₂R⁹, S(O)OR⁸, S(O)₂OR⁹, PO₂HM,

20 PO₃M₂, P(O)(OR¹⁵)(OR¹⁶), P(O)(OR¹⁶)(OM), P(O)(R¹⁵)(OR⁸), P(O)(OM)R¹⁵, CO₂M, CO₂H, CO₂R¹¹, C(O)R¹², C(O)(OR¹³), C(O)(SR¹³), SR⁵, SSR⁷ or SSR⁵, or does not exist;

R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶ are the same or different alkyl or acyl groups containing 1-24 carbon atoms which may contain 1-4 ONO₂ substituents; or C₁-C₆ connections to R¹ - R⁴ in cyclic derivatives; or are each independently hydrogen, a

25 nitrate group, or W; and

M is H, Na⁺, K⁺, NH₄⁺, N⁺H_kR¹¹_(+k) where k is 0-3, or other pharmaceutically acceptable counterion;

and with the proviso that,

when m=0; n=1;

R^{18} and R^3 are the same or different and selected from H, a nitrate group, $C_1 - C_4$ alkyl and chains, which may include one O, linking R^{18} and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings optionally bear hydroxyl substituents;

R^{17} and R^4 , are the same or different and selected from H, a nitrate group, C_1-C_4

5 alkyl optionally bearing 1-3 nitrate group, and acyl groups $(-C(O)R^5)$;

$R^5, R^6, R^8, R^9, R^{10}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$ are the same or different alkyl groups containing 1-12 carbon atoms which may contain 1-4 ONO_2 substituents; or C_1 or C_2 connections to R^{18}, R^{17} , or R^3 in cyclic derivatives;

R^7, R^{11} are $C_1 - C_8$ alkyl or acyl;

10 M is H, Na^+ , K^+ , NH_4^+ , $N^+H_kR^{11}_{(4-k)}$ where k is 0-3;

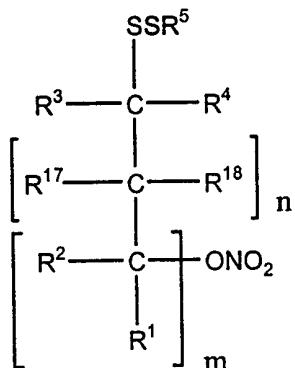
X is CH_2 , O, NH, NMe, CN, NHOH, N_2H_3 , $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SR^7 , SO_2M , $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM , PO_3M_2 , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)$, $C(O)R^{12}$, $C(O)(OR^{13})$,

15 PO_2M , $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2 , $C(O)(SR^{13})$, or SSR^4 ;

that Y is not CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3 , SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M , SH, SO_2M , PO_3M_2 , PO_3HM , $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(OM)R^{15}$, CO_2M , CO_2H , CO_2R^{11} , $C(O)R^{12}$, $C(O)(SR^{13})$, SR^4 , SR^5 , or SSR^5 , or does not exist.

20

43. A method for preparing a compound represented by the formula (Formula V):



in which m, n = 0 - 10;

R⁴ is hydrogen, a nitrate group, or A;

R³, R¹⁷, R¹⁸ are each independently hydrogen or A;

and R⁵ is A;

5 where A is selected from: a substituted or unsubstituted aliphatic group (preferably a branched, or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally contains O, S, NR₆ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the 10 aliphatic ring, which optionally contains O, S, NR₆ and unsaturations in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R₁ and R₃ and/or between R₂ and R₄, which optionally contains O, S, NR₆ and unsaturations in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino or 15 aryl, or heterocyclic groups); a substituted or unsubstituted aliphatic group (preferably a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain), containing carbonyl linkages (e.g. C=O, C=S, C=NOH), which optionally contains O, S, NR₆ and unsaturations in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino or aryl, or heterocyclic groups; a substituted or unsubstituted aryl 20 group; a heterocyclic group; amino (including alkylamino, dialkylamino (including cyclic amino, diamino and triamino moieties), arylamino, diarylamino, and alkylarylamino); hydroxy; alkoxy; a substituted or unsubstituted aryloxy;

the method comprising:

reacting an appropriate halo-alcohol with a nitrating reagent selected from a 25 mixture of nitric and sulfuric acid in a mixture of water and a selected organic solvent, acetyl nitrate, nitronium tetrafluoroborate, or reacting an appropriate halo-alkene with thallium nitrate in pentanes, under conditions such that an appropriate halo-organic nitrate is formed;

reacting an appropriate halo-organic nitrate with a thiolsulfonate salt so as to 30 produce a selected Bunte salt;

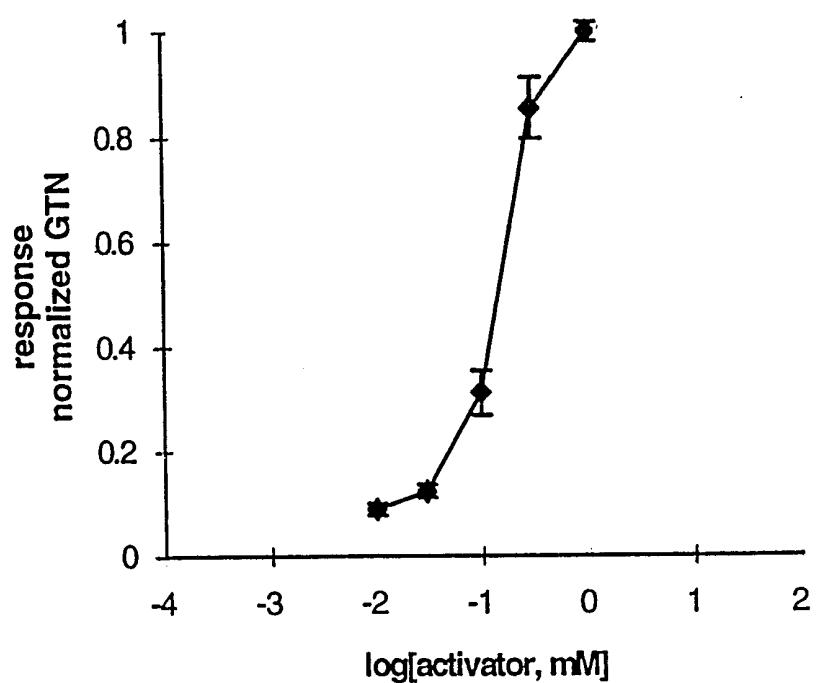
reacting an appropriate Bunte salt, optionally with an oxidizing agent (e.g. 30% hydrogen peroxide) in the presence of an appropriate catalyst (e.g. sulfuric acid), under conditions such that the compound of Formula 5 is prepared;

5 reacting an appropriate disulfide in a thiol/disulfide exchange reaction with an organic thiolate salt, under conditions such that a compound of Formula 5 is formed.

44. The method of claim 2, wherein administering the therapeutic compound to the subject modulates cellular free radical damage.

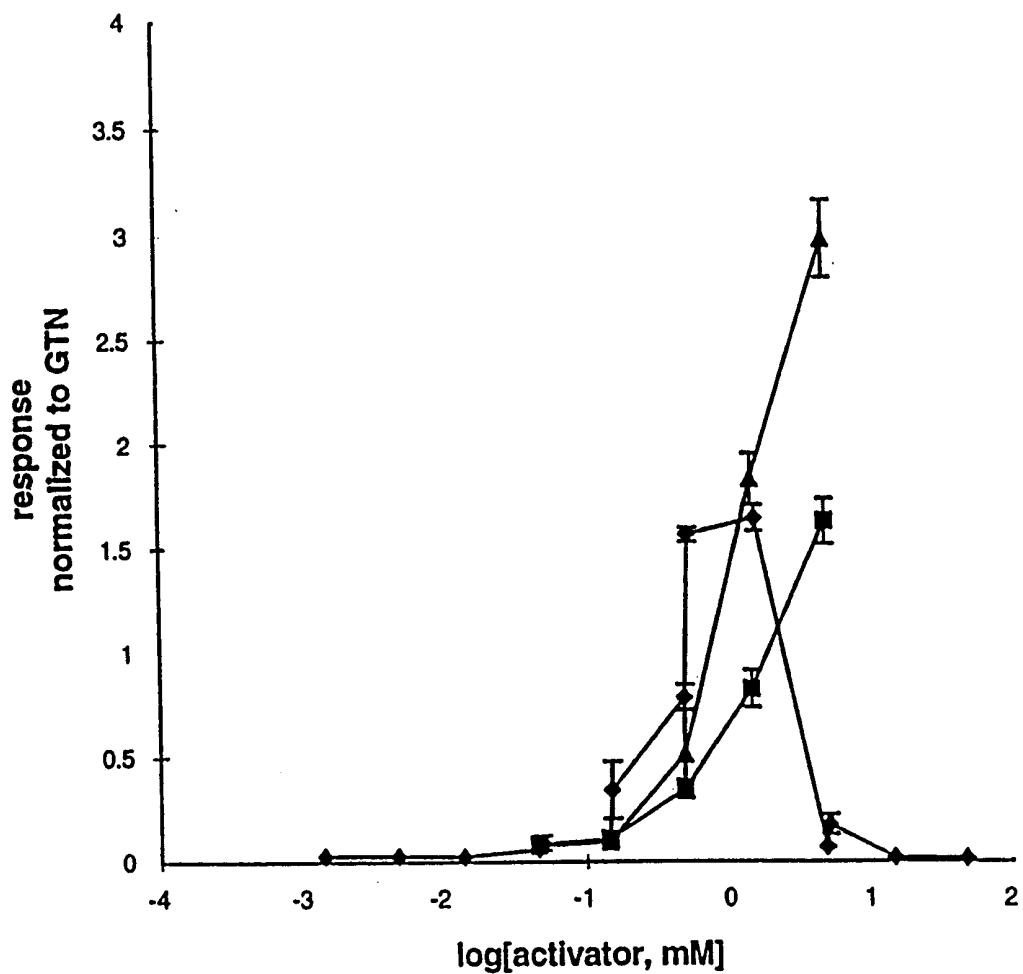
1/32

FIGURE 1



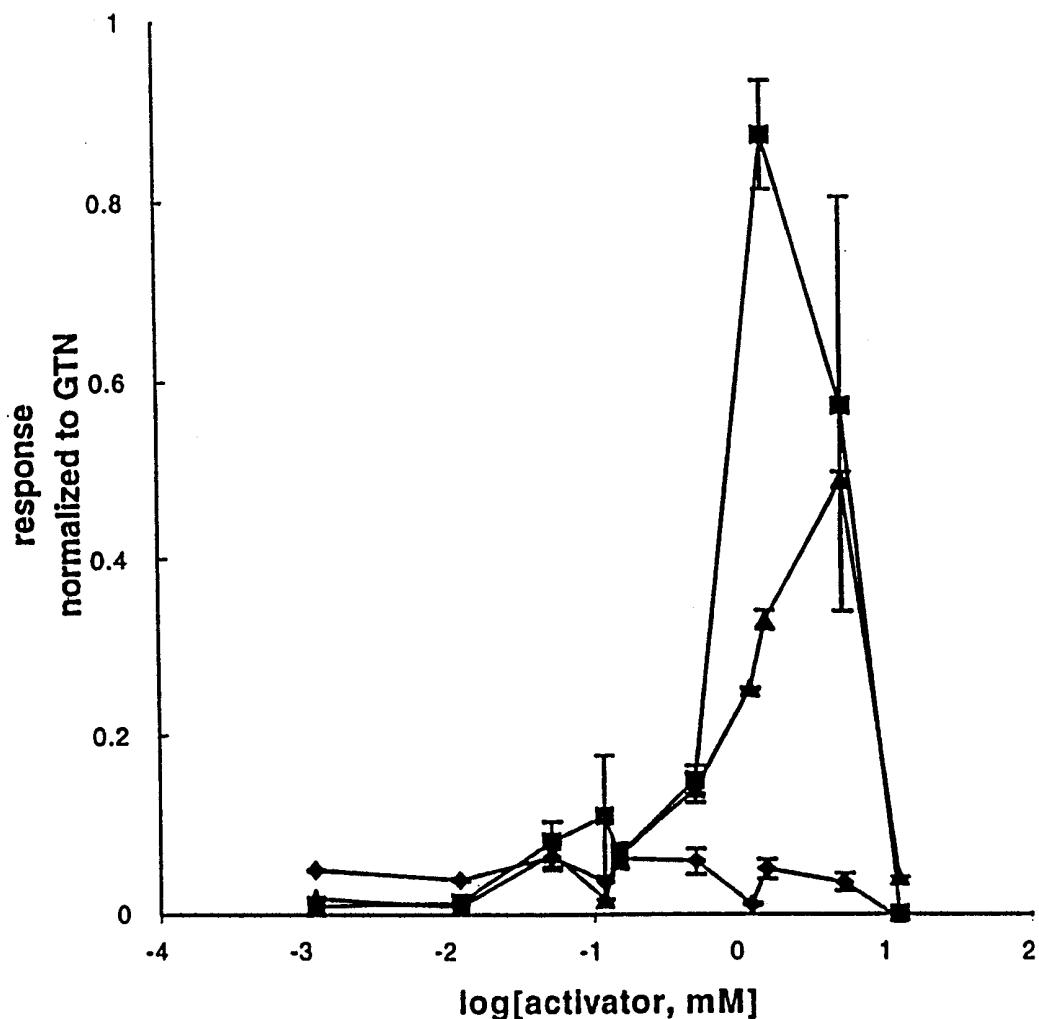
2/32

FIGURE 2



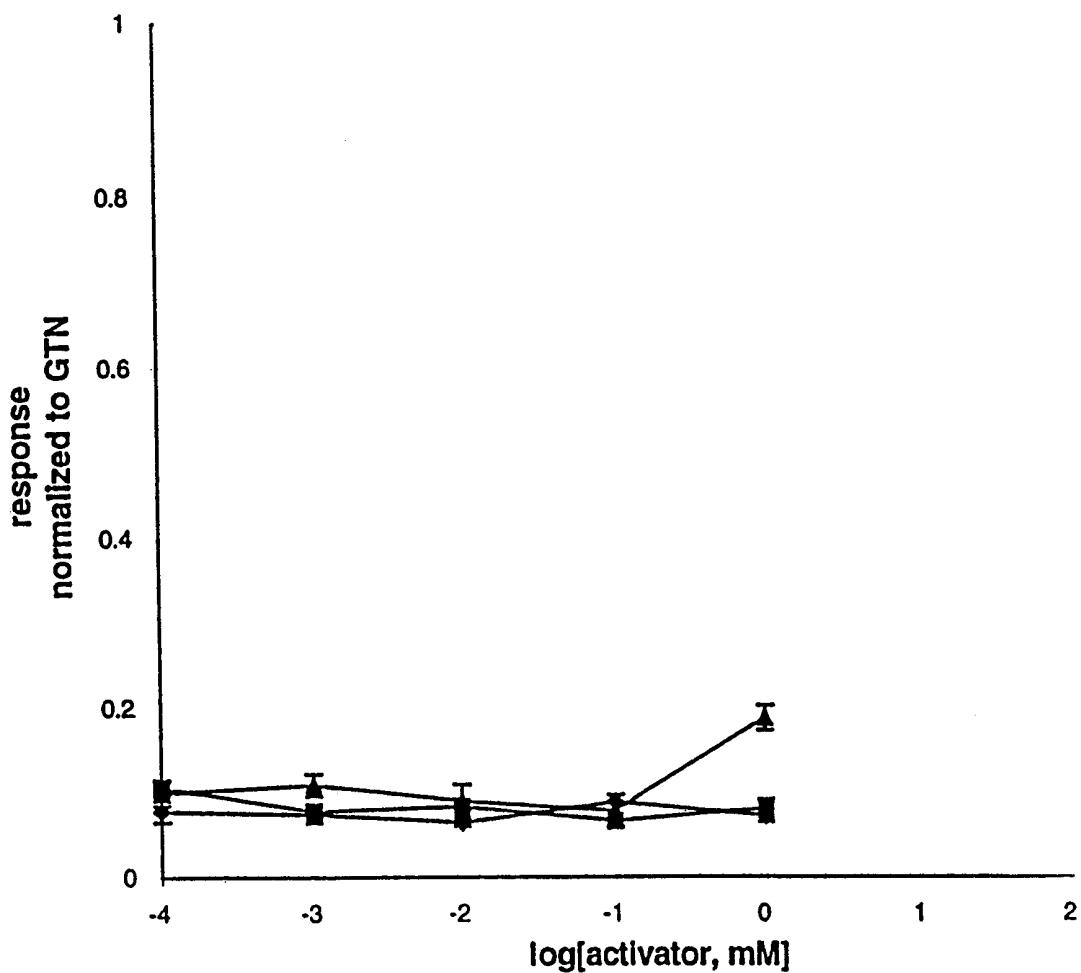
3/32

FIGURE 3



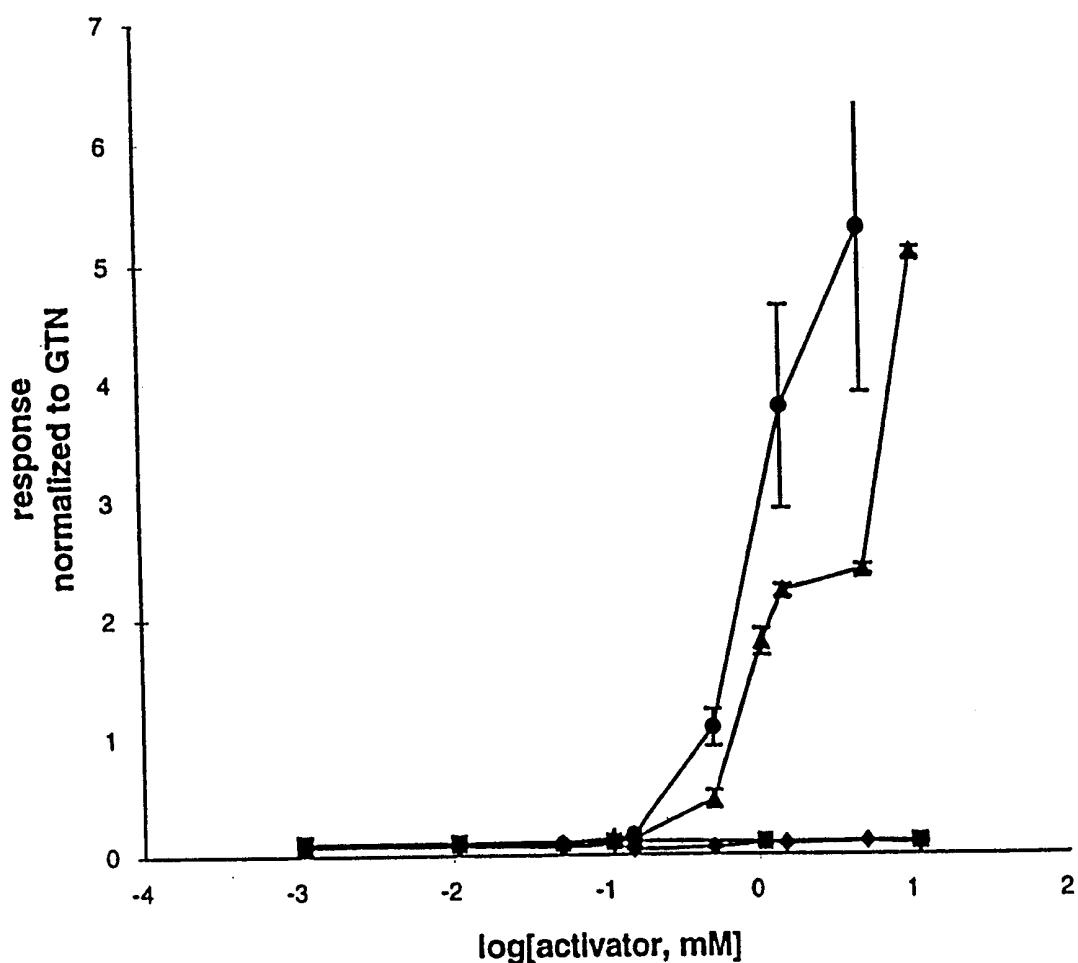
4/32

FIGURE 4



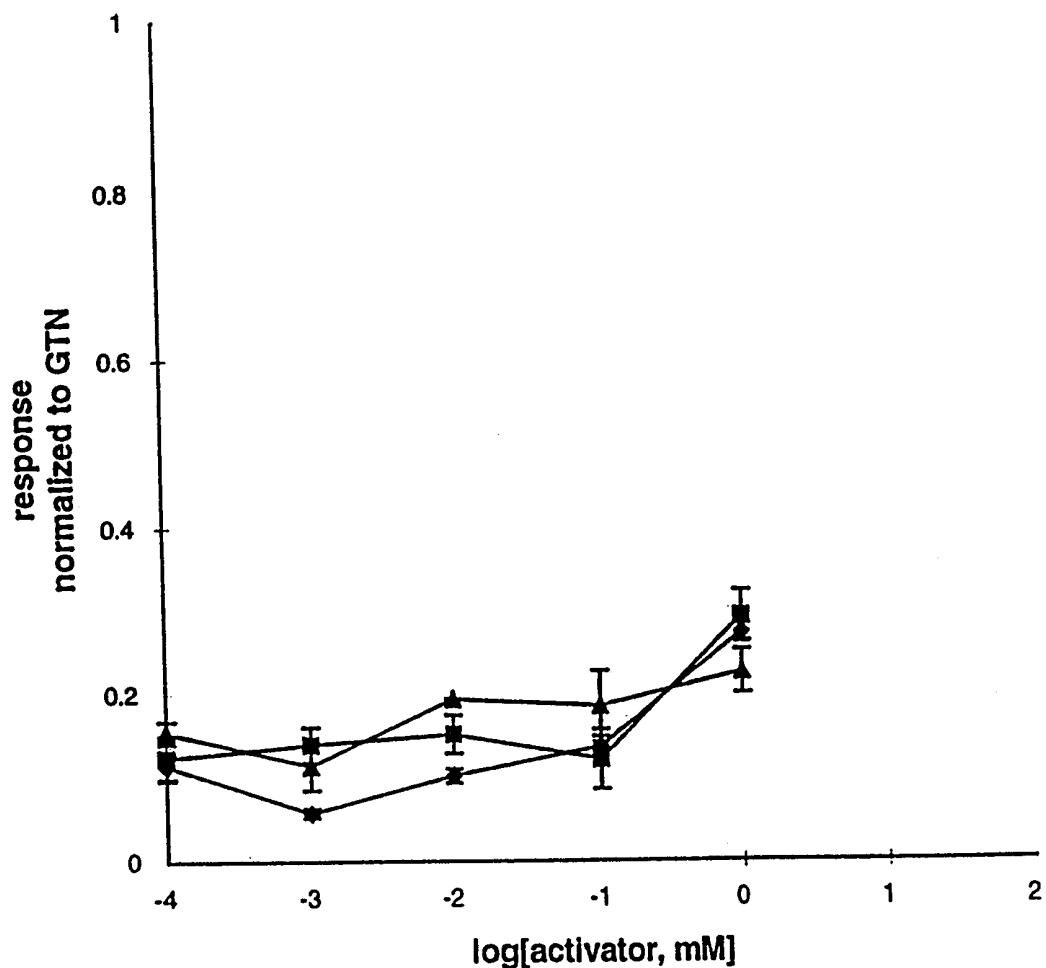
5/32

FIGURE 5



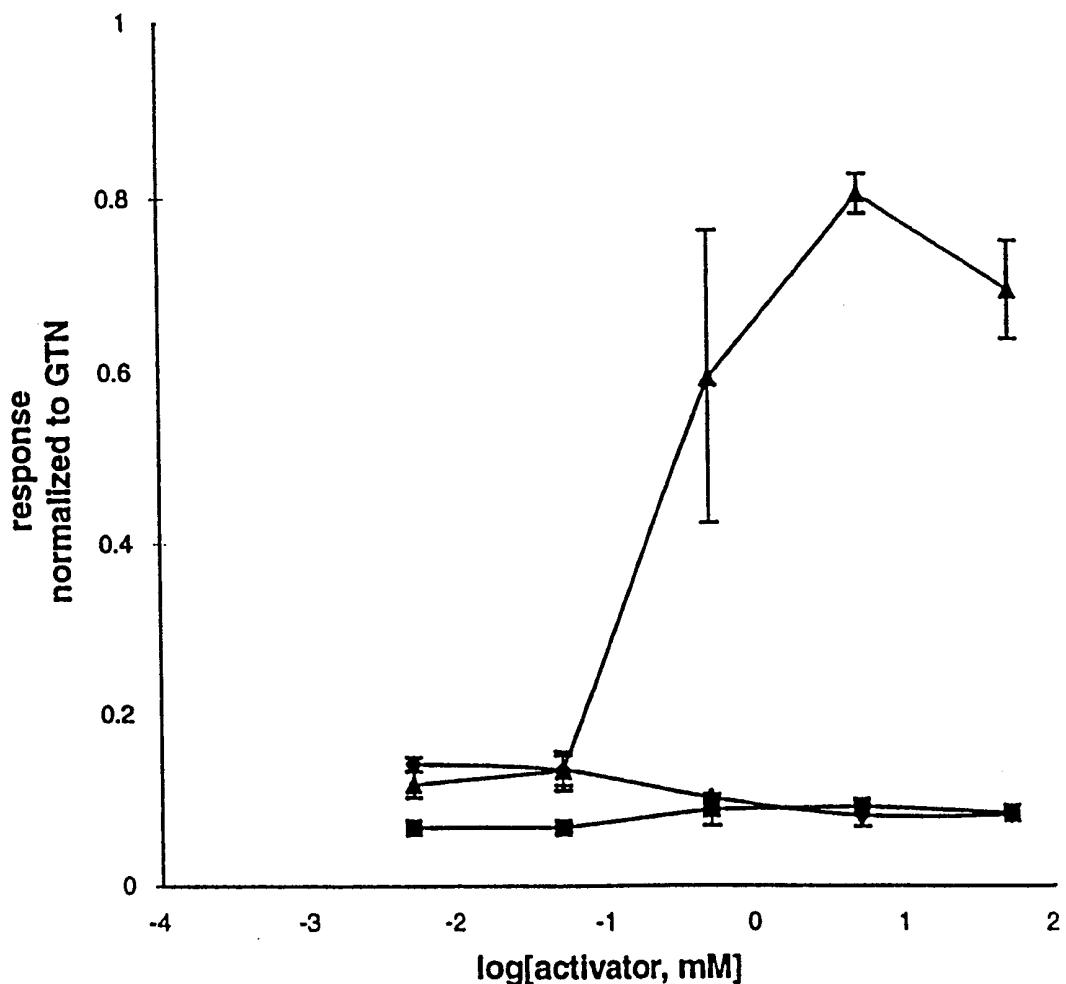
6/32

FIGURE 6



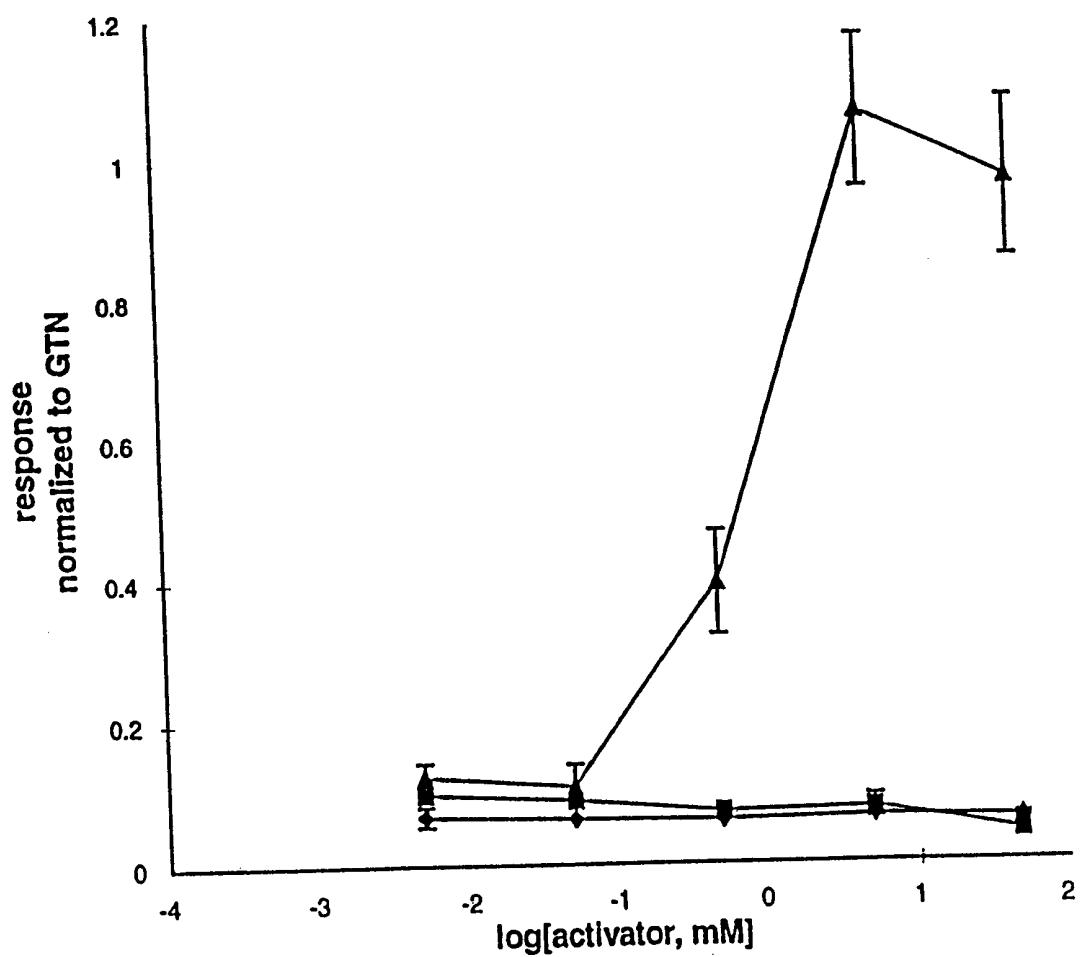
7/32

FIGURE 7



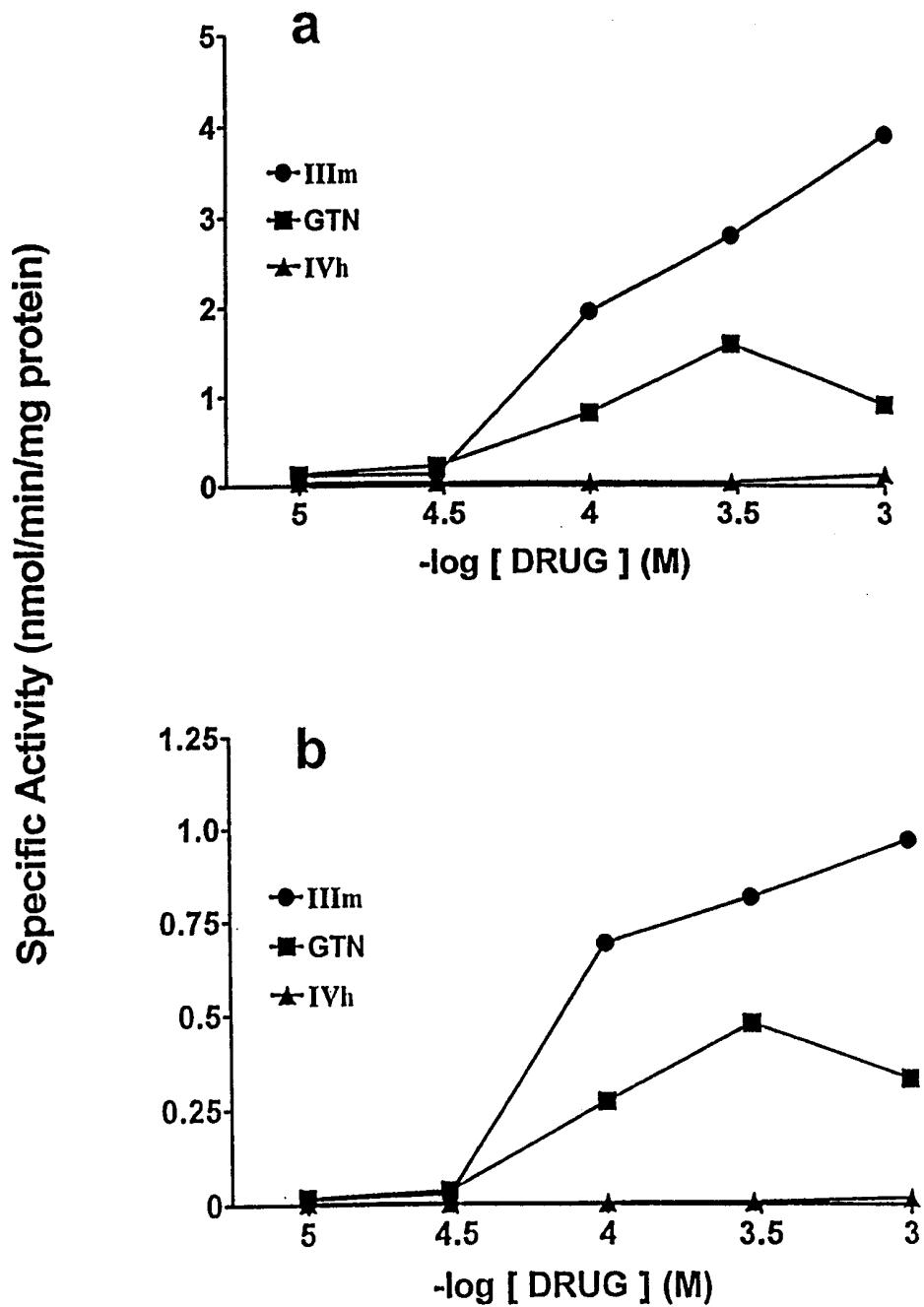
8/32

FIGURE 8



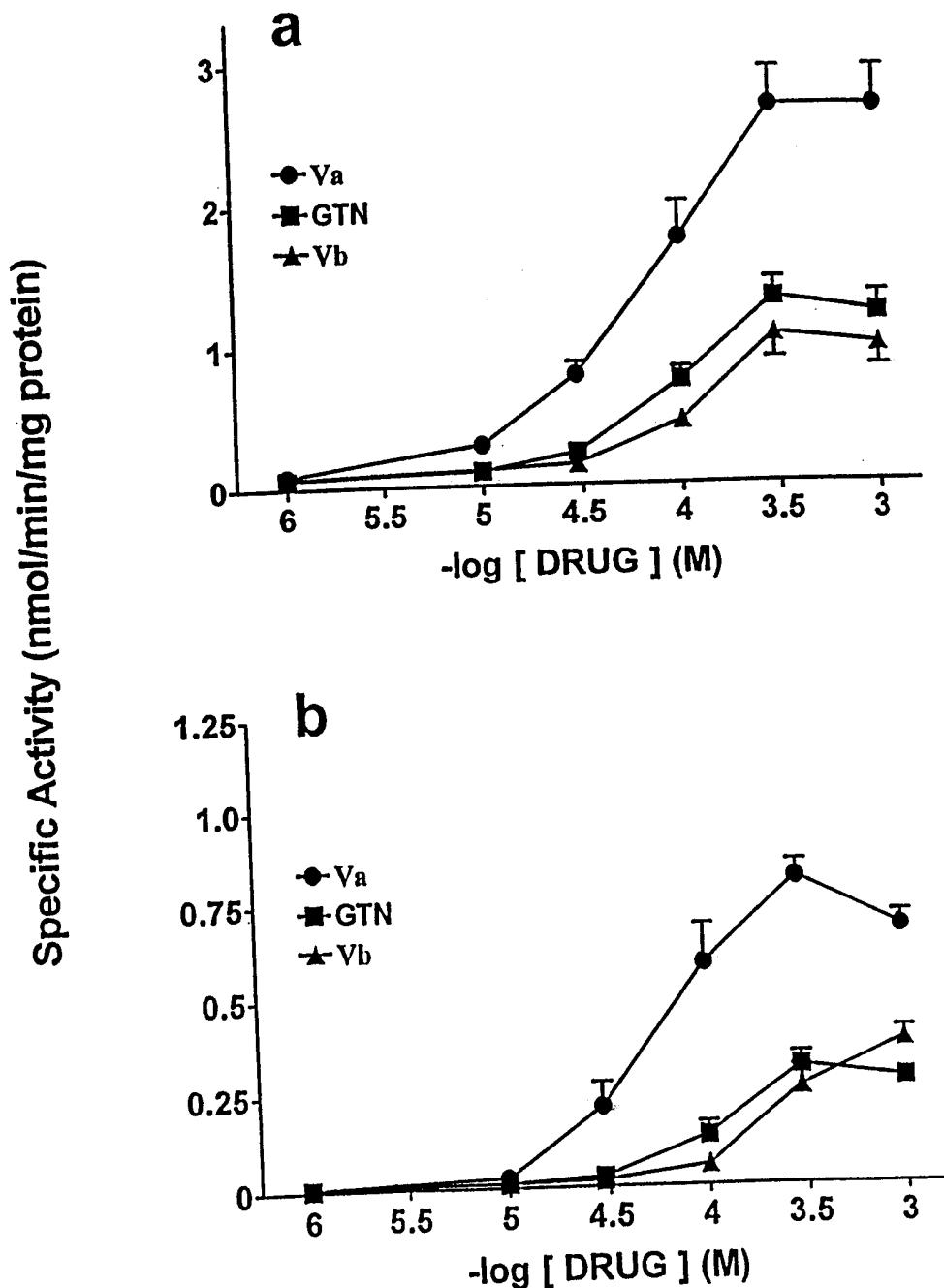
9/32

FIGURE 9



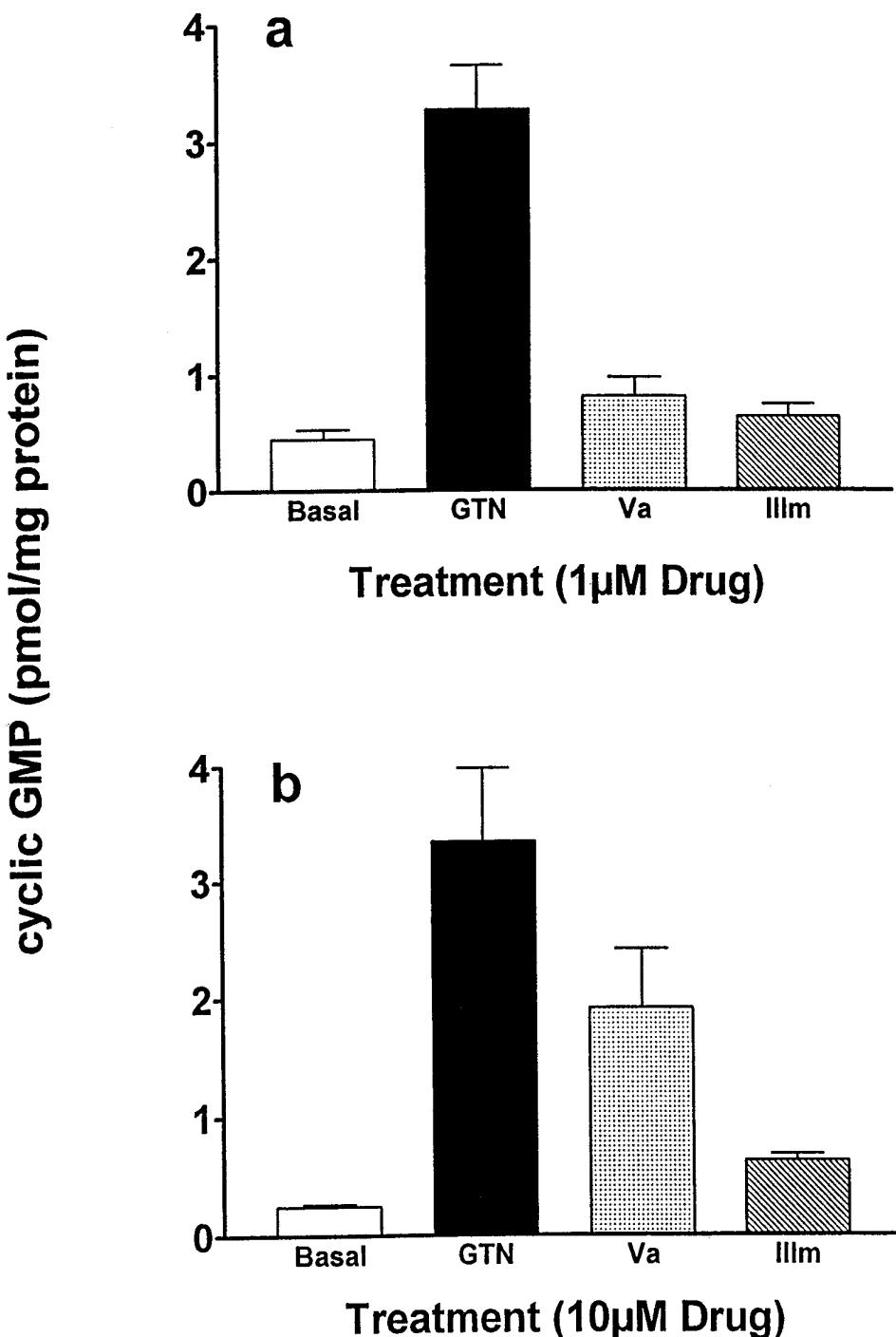
10/32

FIGURE 10



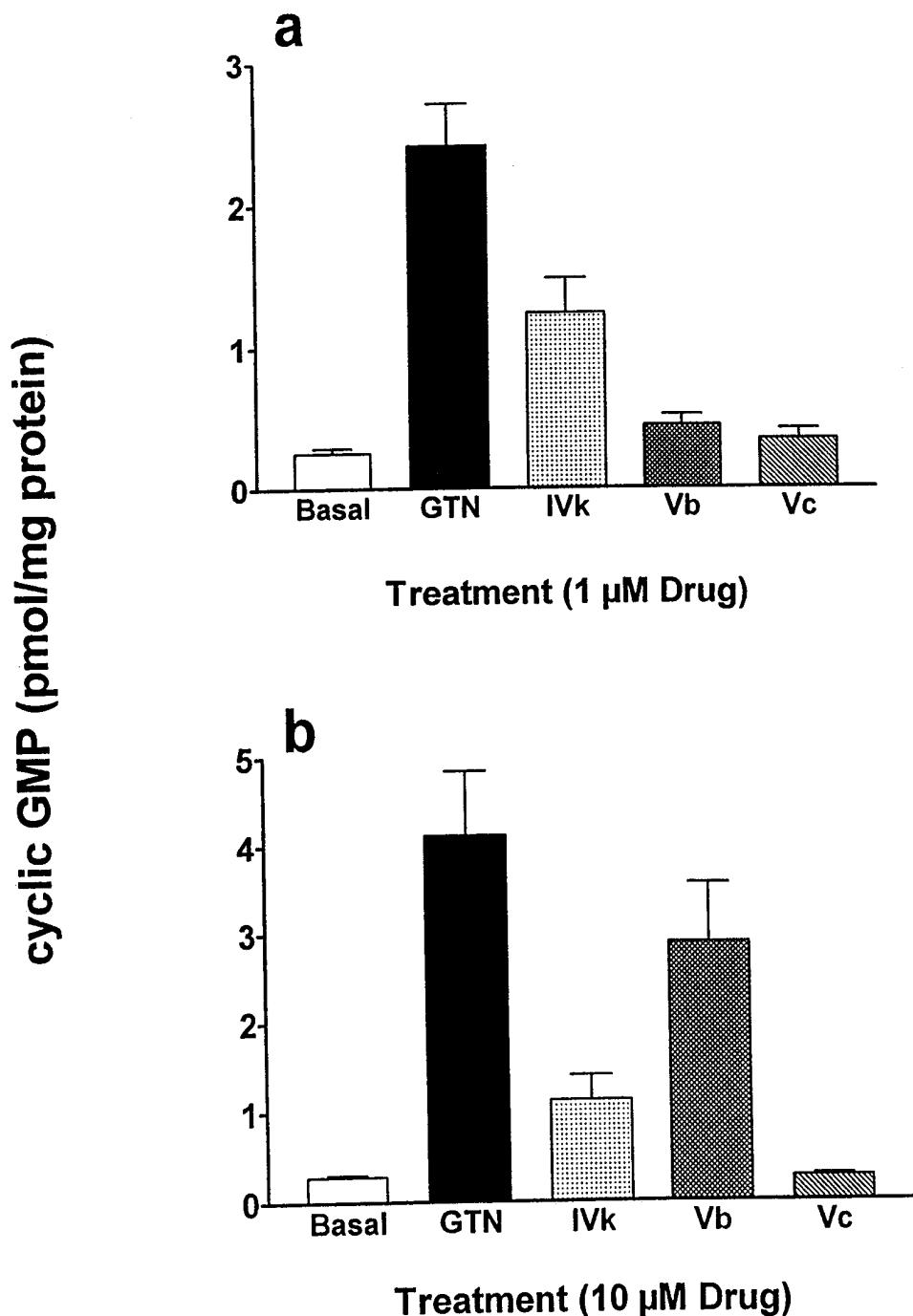
11/32

FIGURE 11



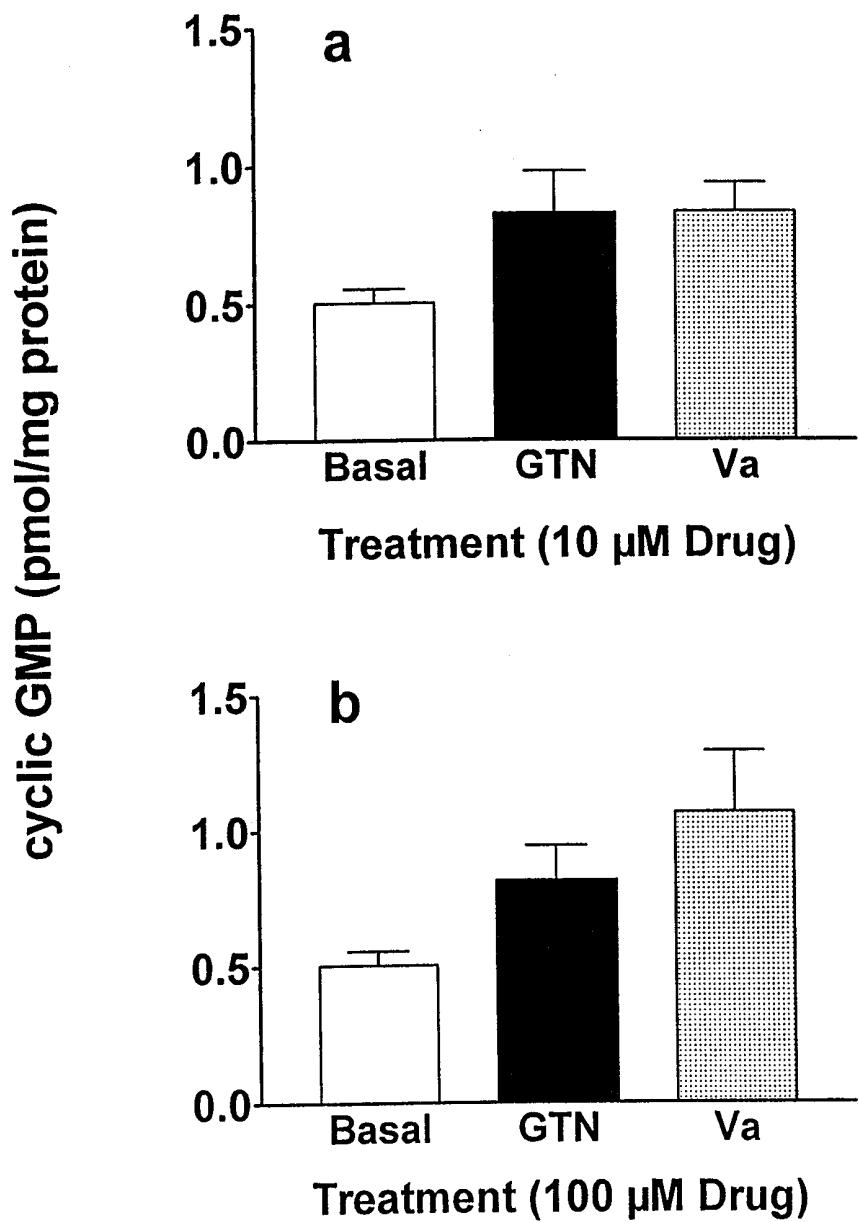
12/32

FIGURE 12



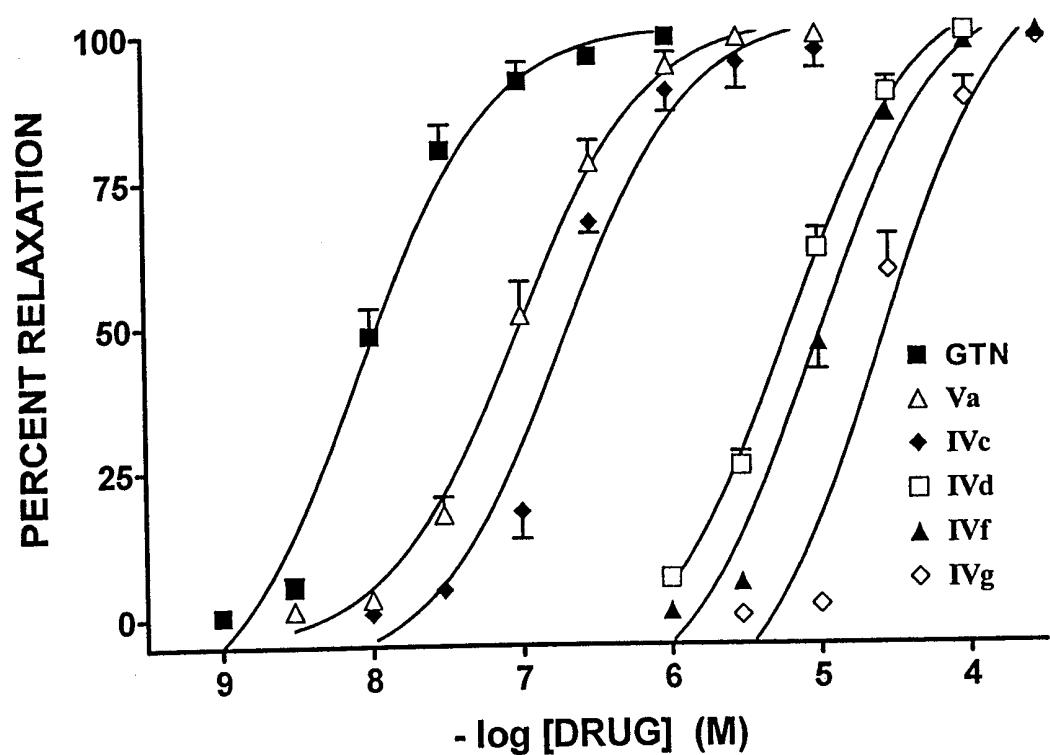
13/32

FIGURE 13



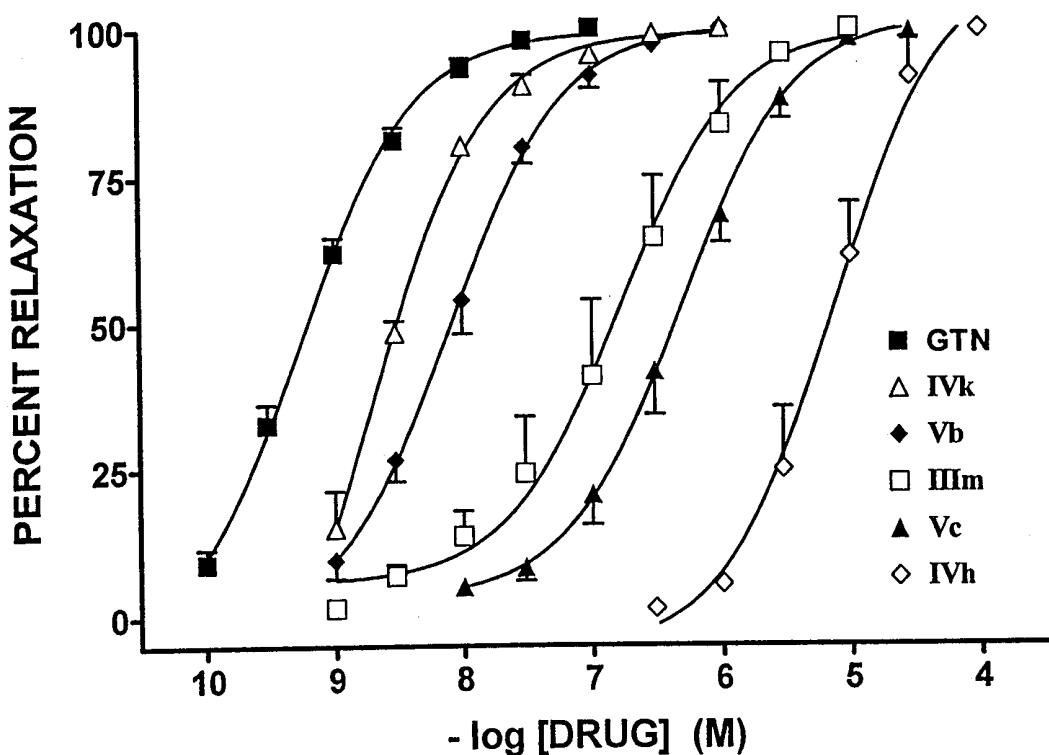
14/32

FIGURE 14



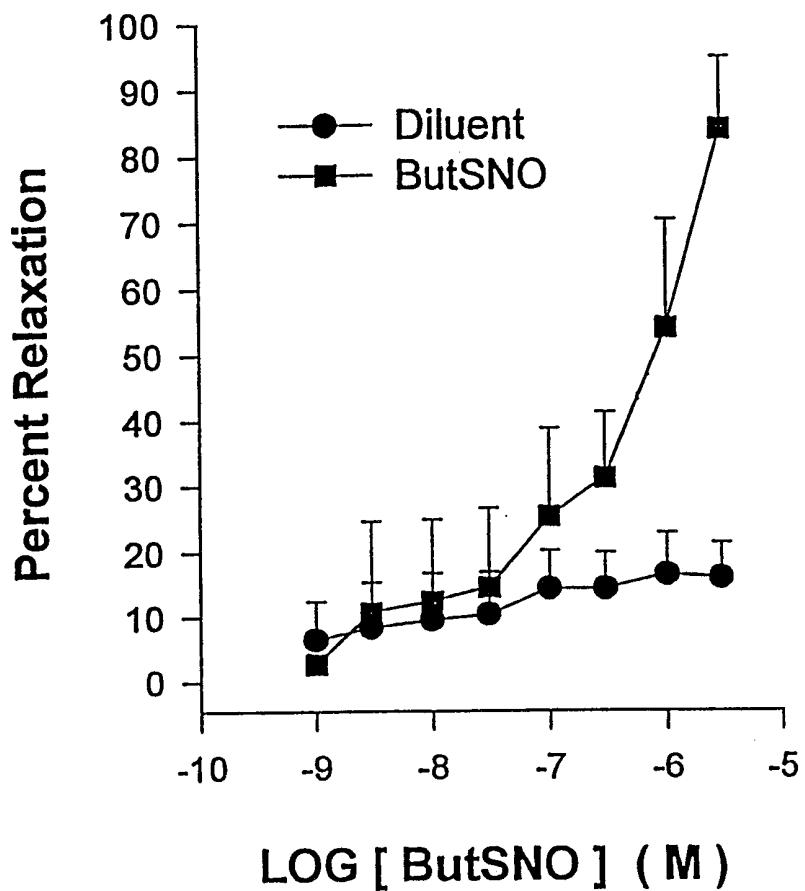
15/32

FIGURE 15



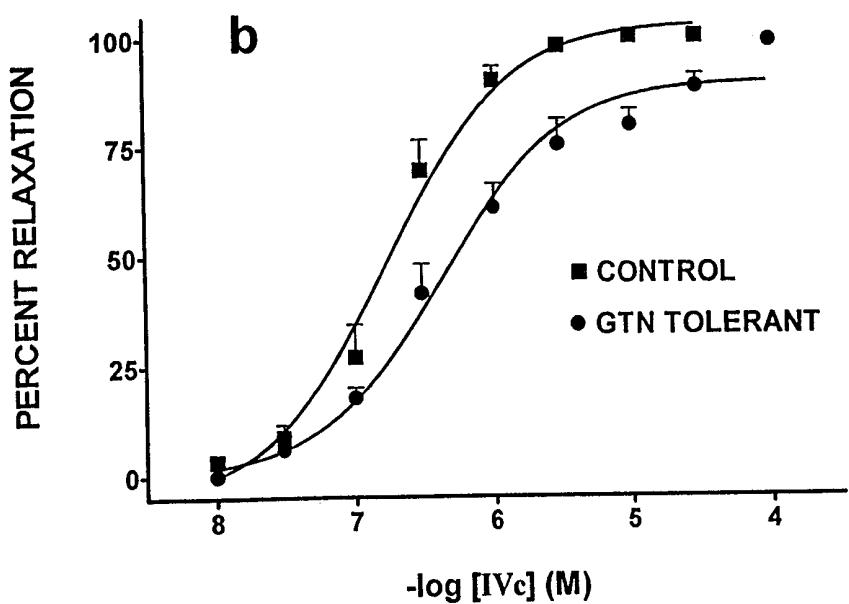
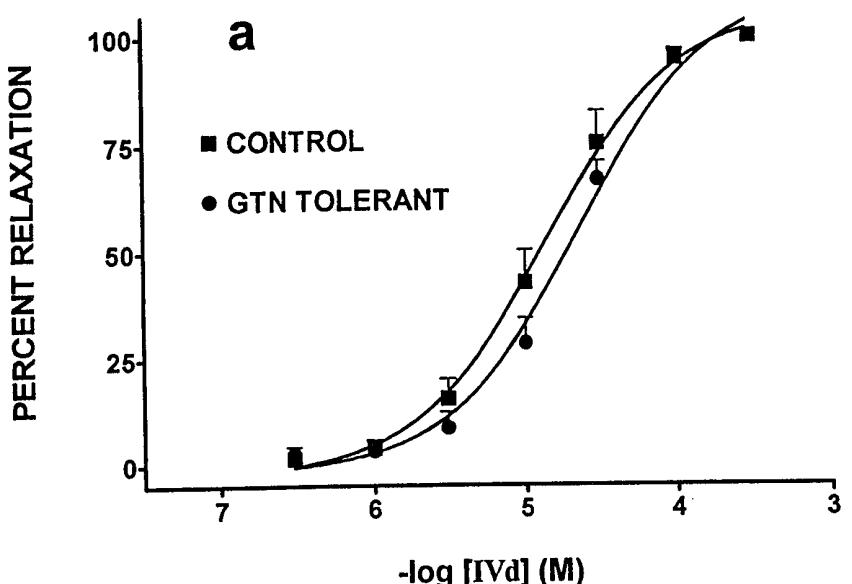
16/32

FIGURE 16



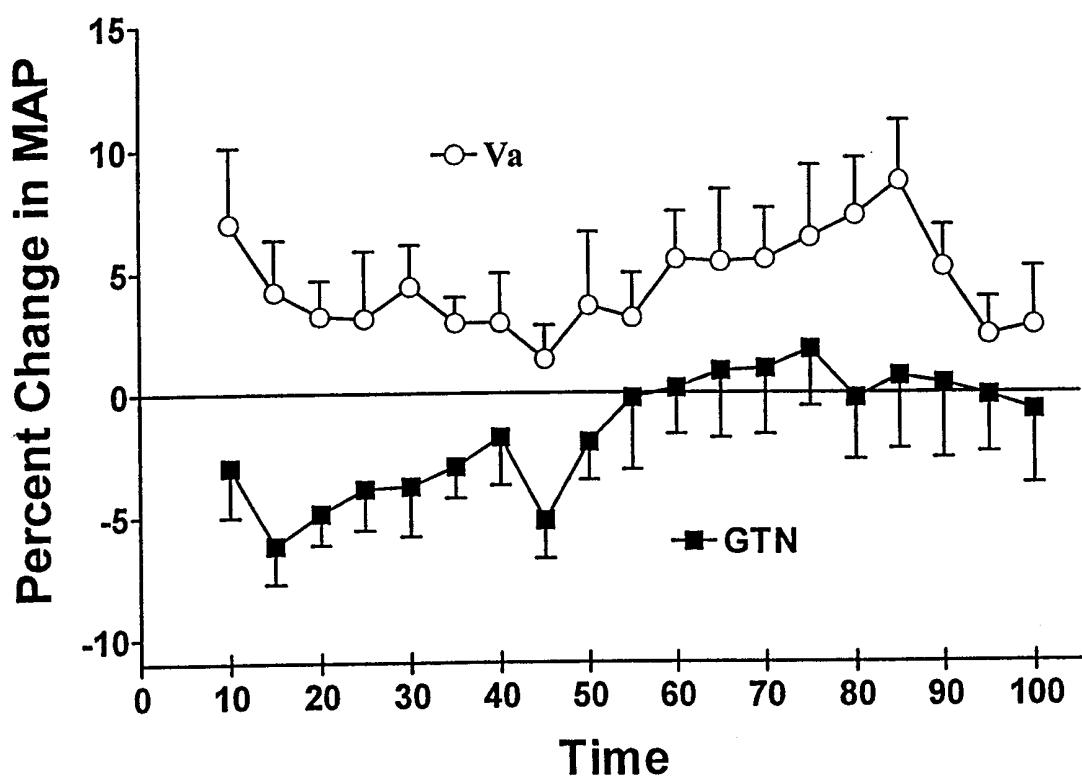
17/32

FIGURE 17



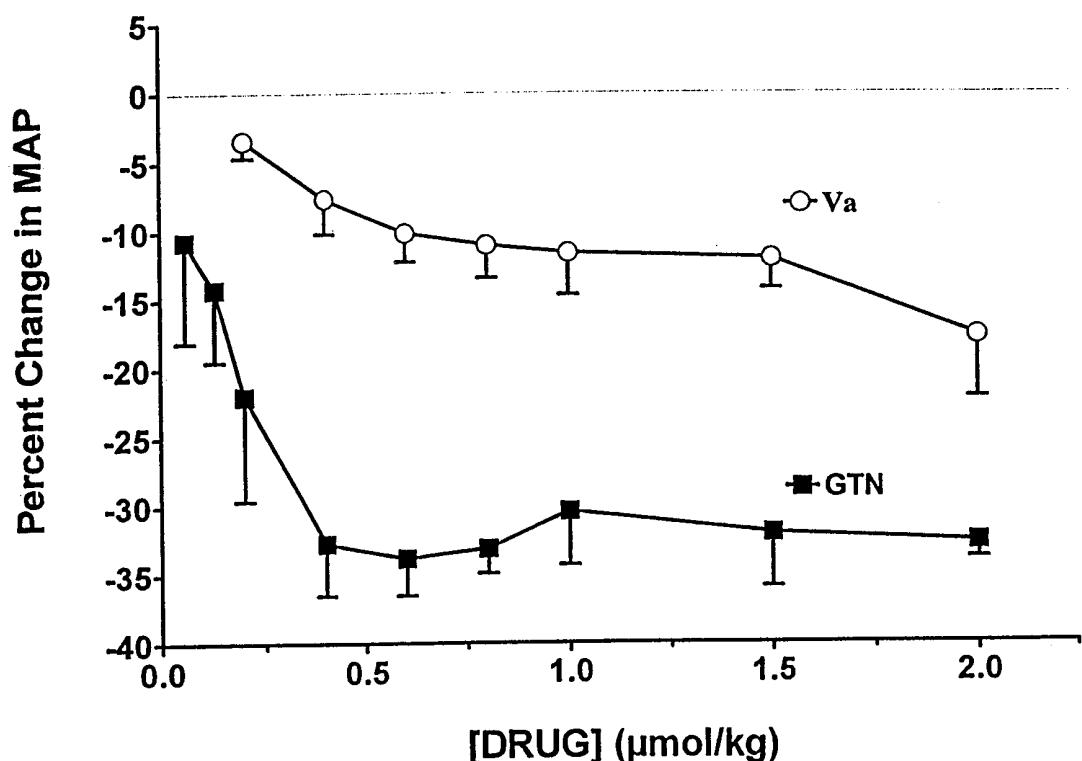
18/32

FIGURE 18



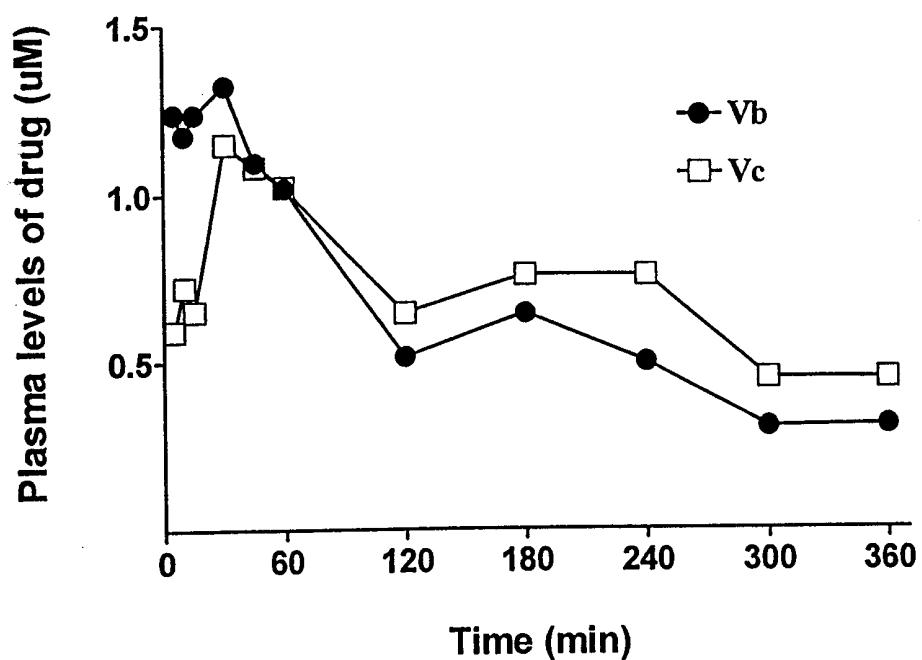
19/32

FIGURE 19



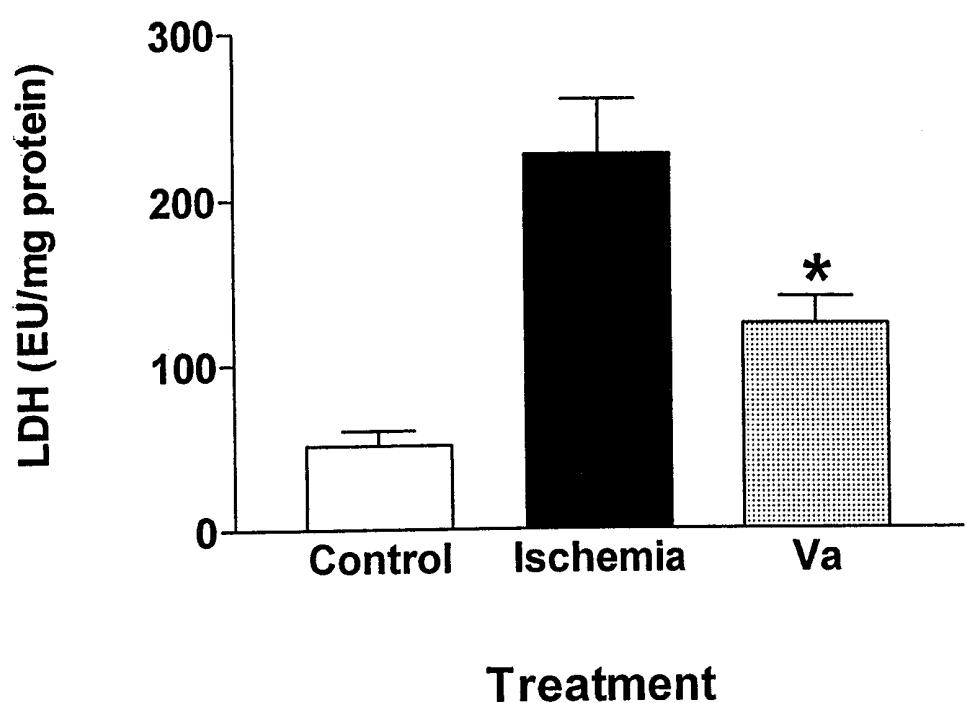
20/32

FIGURE20



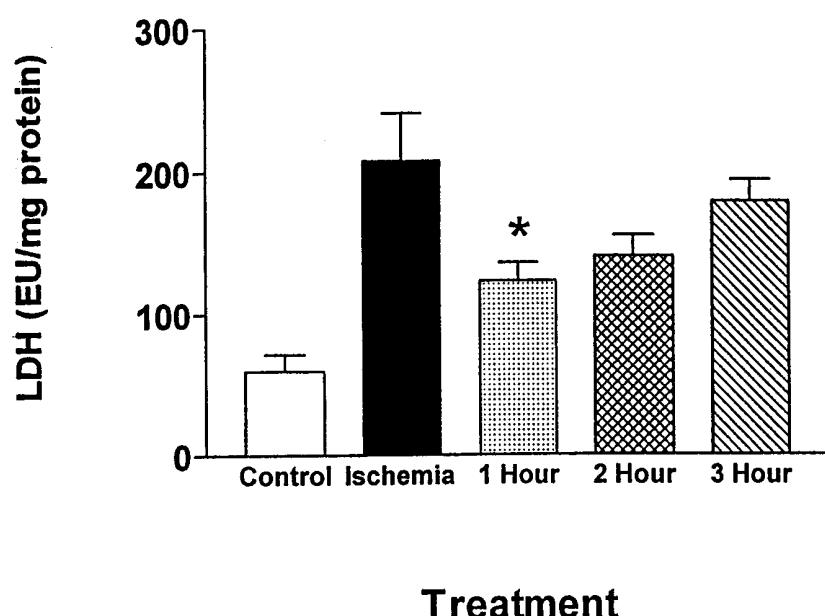
21/32

FIGURE 21



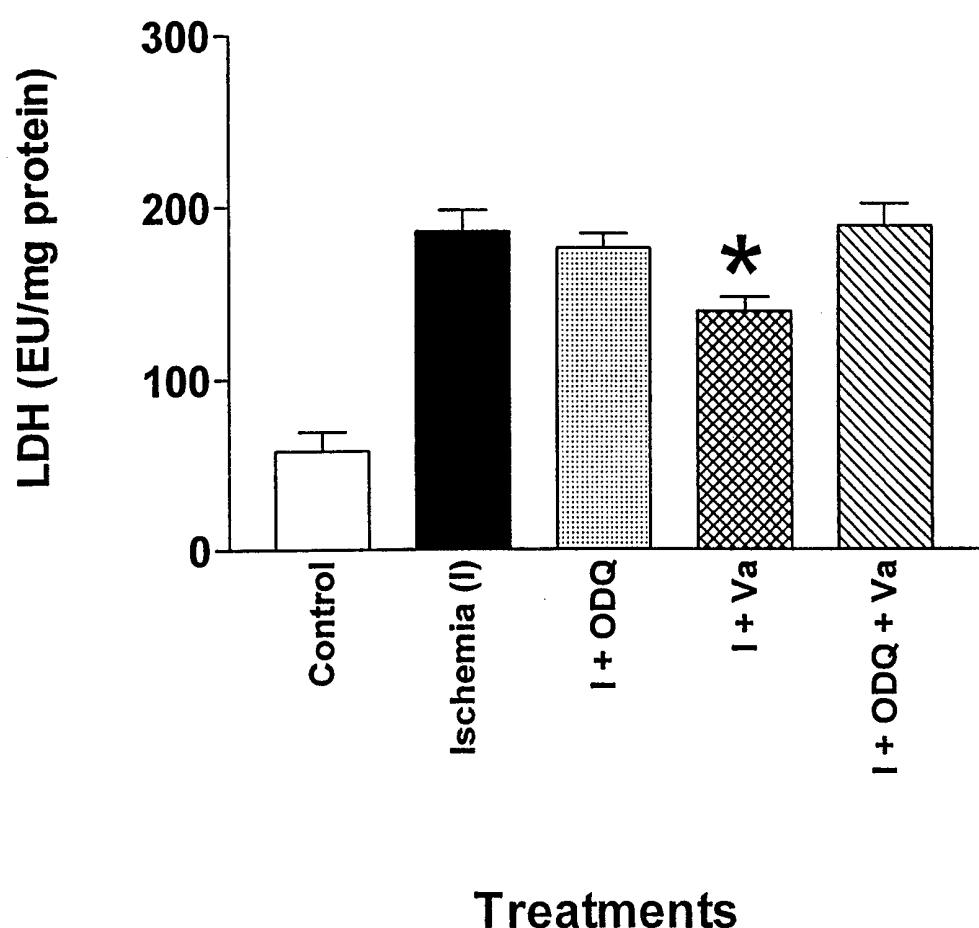
22/32

FIGURE 22



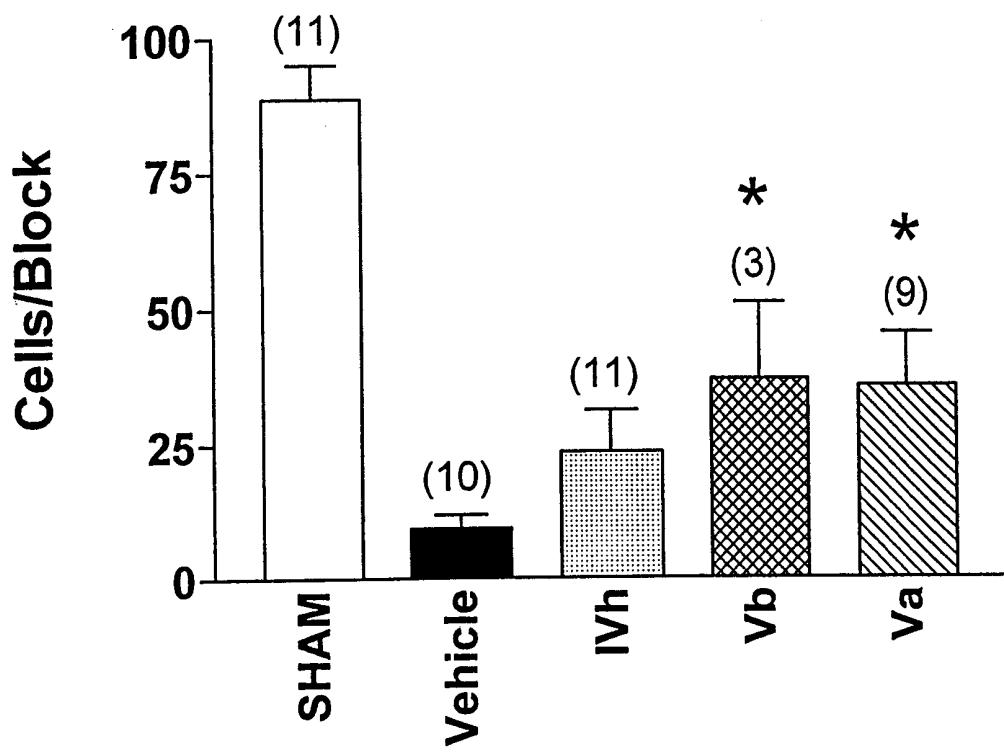
23/32

FIGURE 23



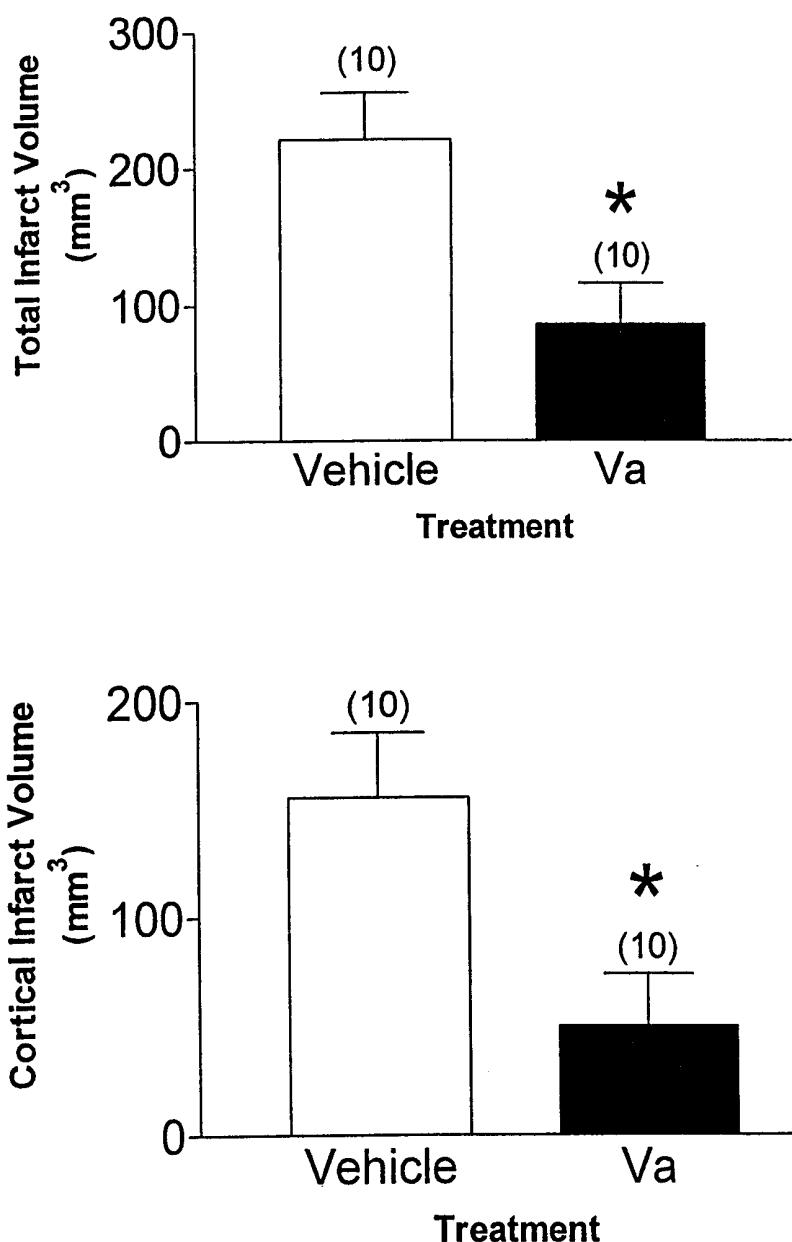
24/32

FIGURE 24



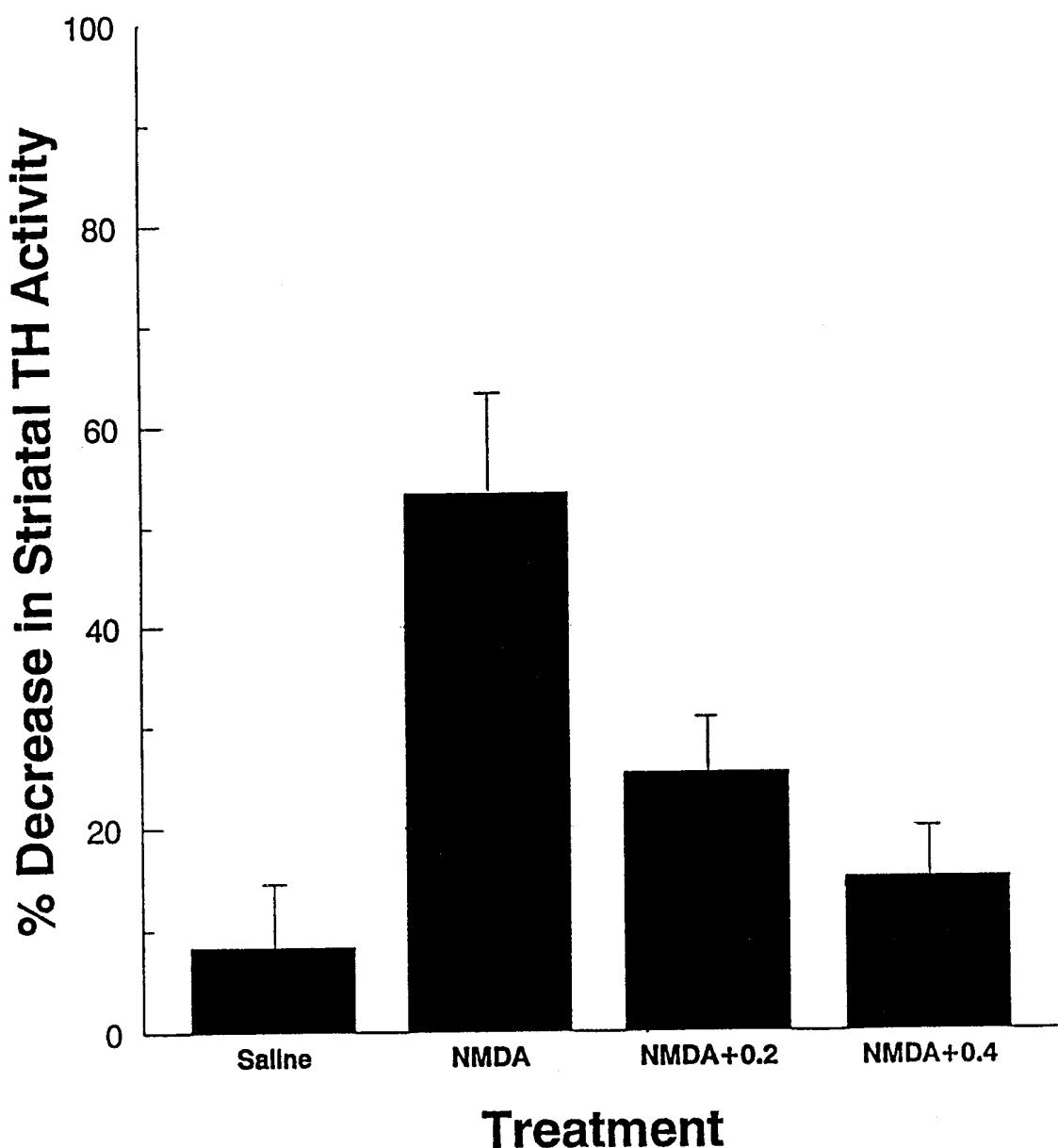
25/32

FIGURE 25



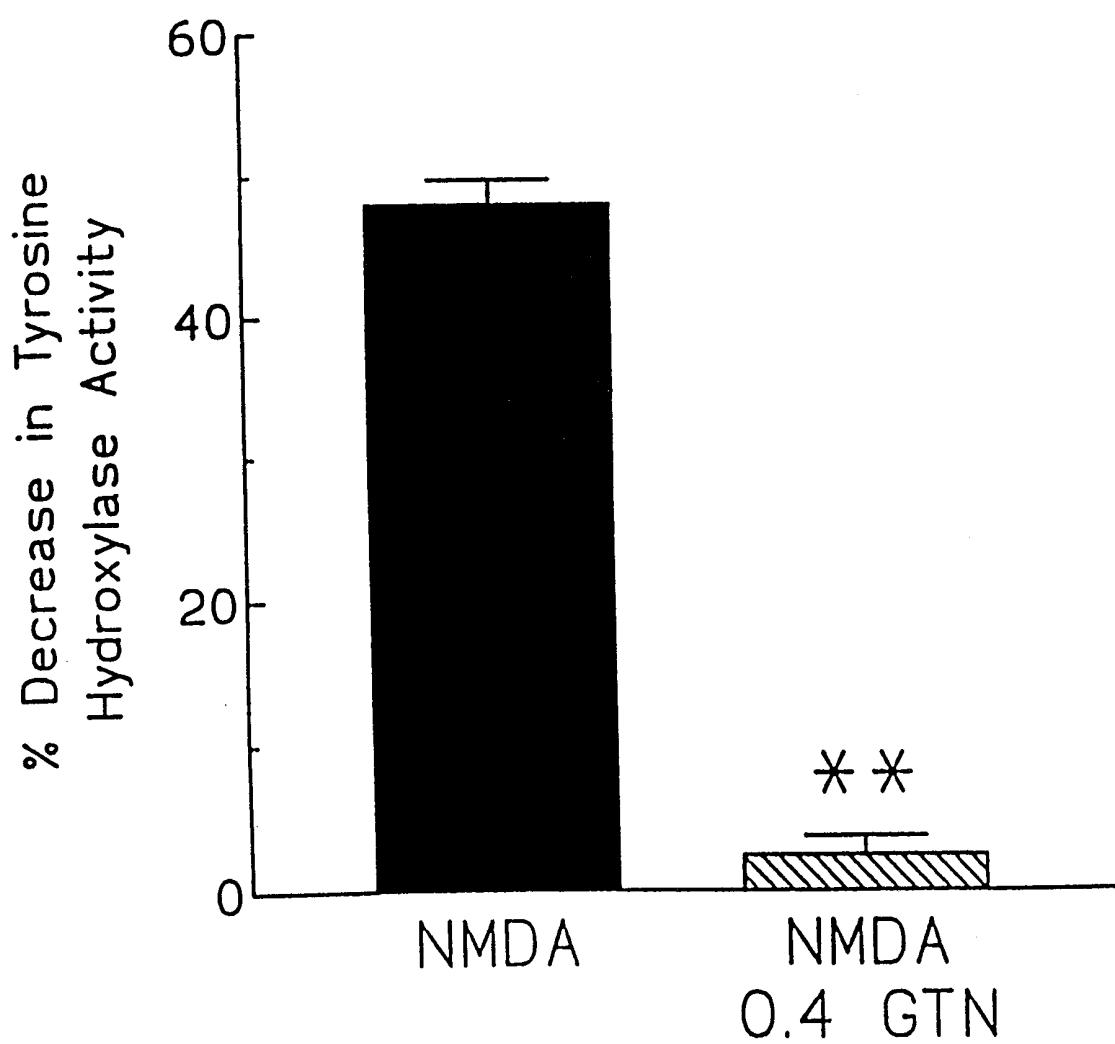
26/32

FIGURE 26



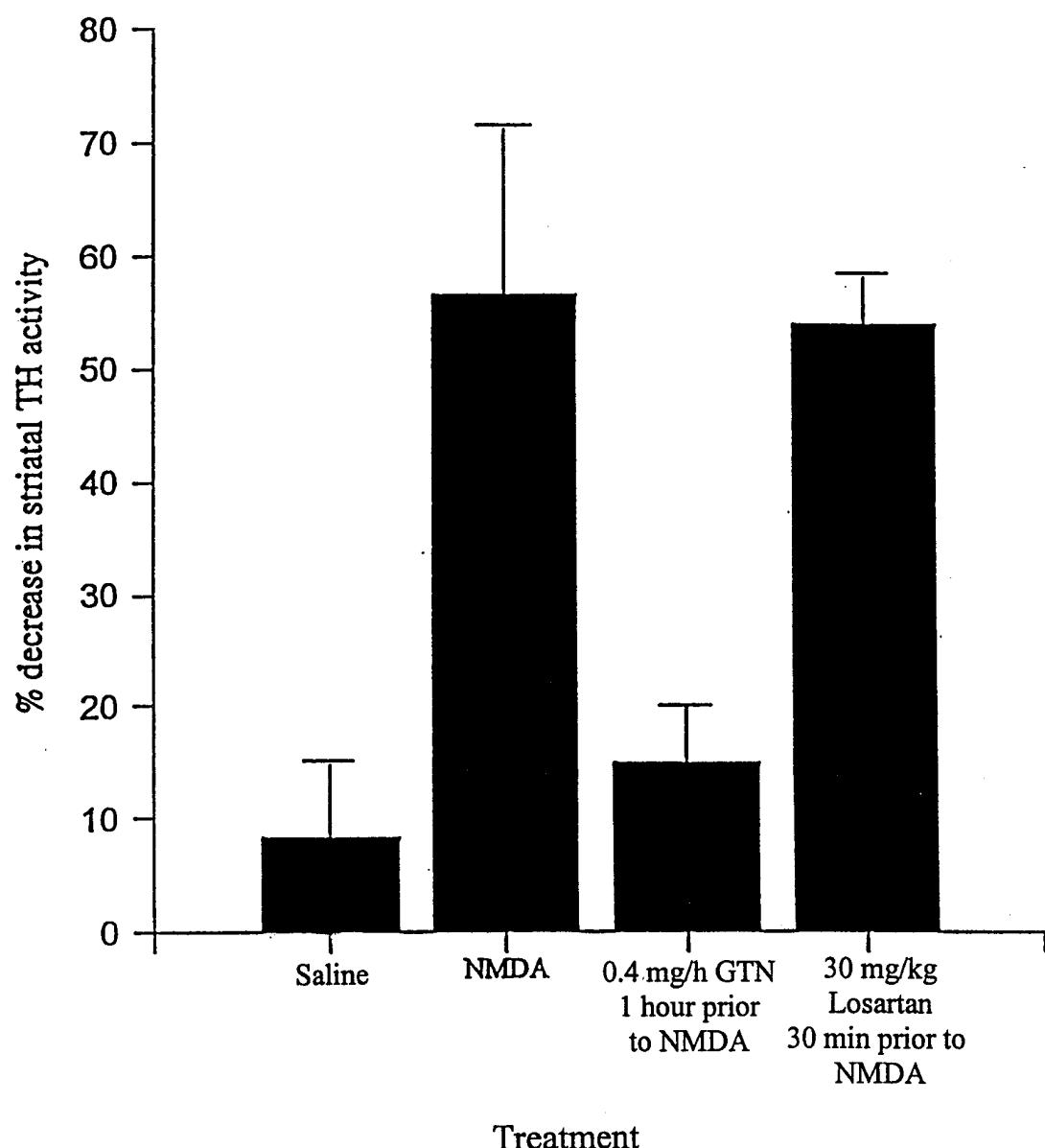
27/32

FIGURE 27



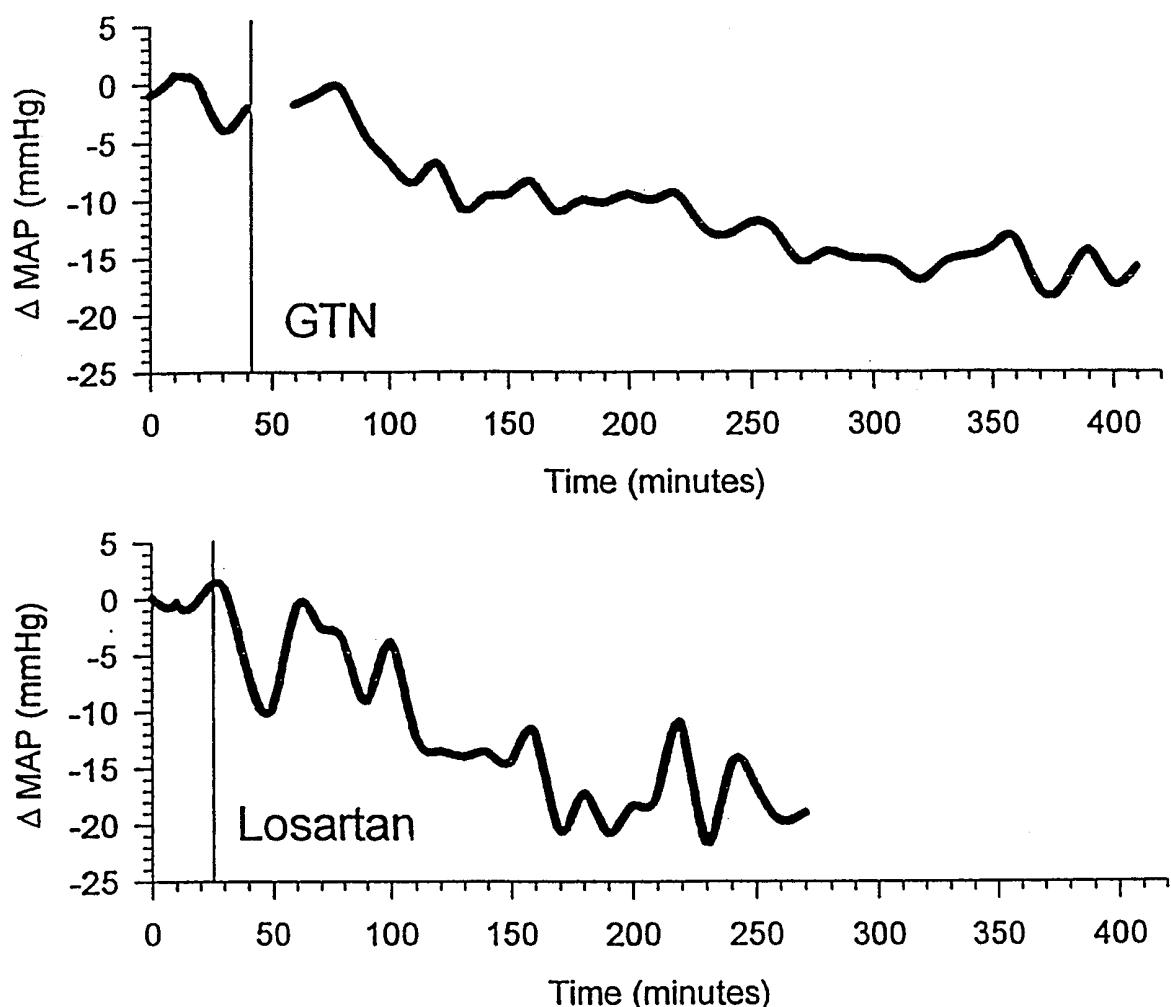
28/32

FIGURE 28



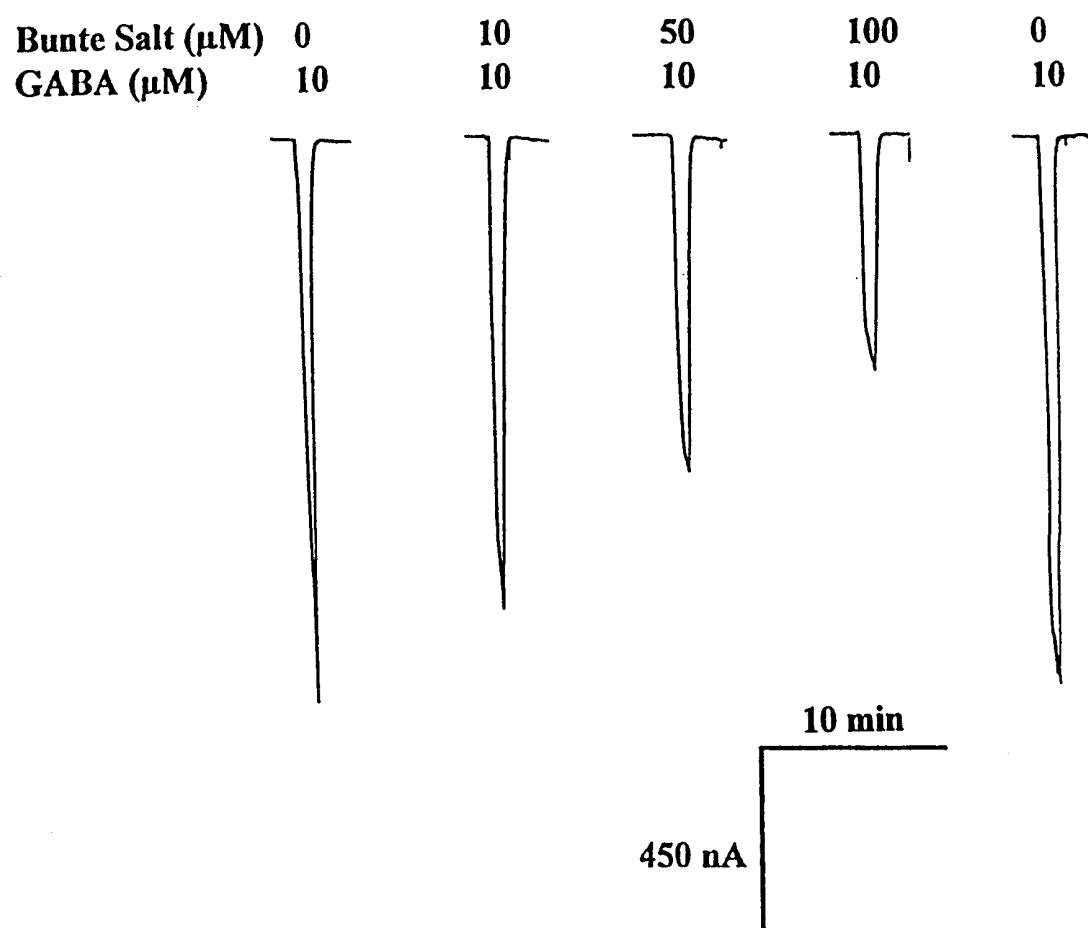
29/32

FIGURE 29



30/32

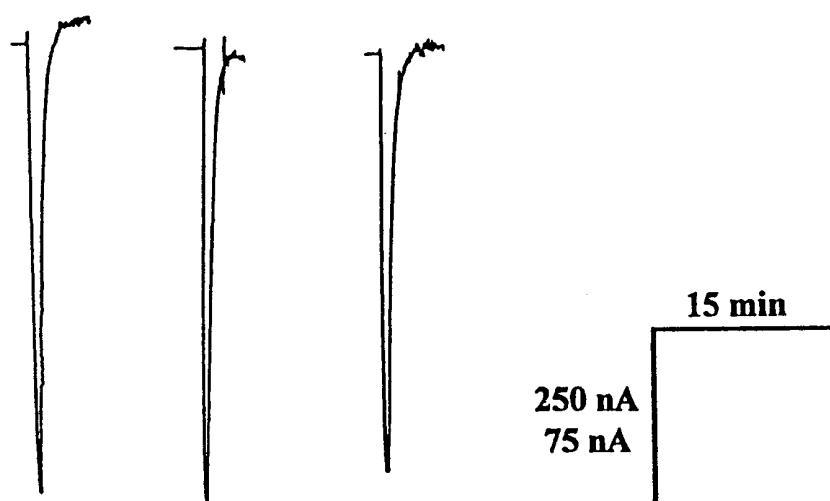
FIGURE 30



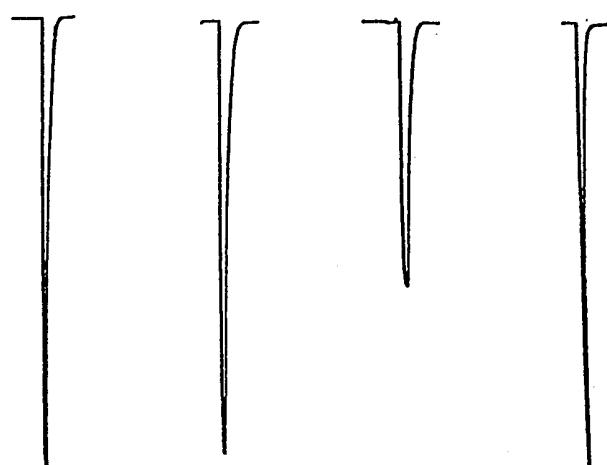
31/32

FIGURE 31

DEA (μM)	0	25	100
GABA (μM)	20	20	20



tBuSNO (μM)	0	44	0	0
GTN (μM)	0	0	44	0
GABA (μM)	20	20	20	20



32/32

FIGURE 32

