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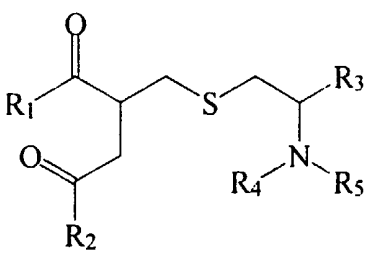
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WO 01/40187 A2

(54) Title: NEUROPROTECTIVE AGENTS AND METHODS RELATED THERETO



(I)

(57) Abstract: Neuroprotective agents are disclosed having structure (I) wherein R_1, R_2, R_3, R_4 and R_5 are as defined herein. Such compounds have utility in the treatment of conditions which benefit from administration of neuroprotective agents generally, including treatment of central and peripheral nervous condition as well as for promoting nerve cell differentiation. Methods of treating such conditions are also disclosed, as are pharmaceutical compositions containing one or more of the compounds of this invention.

DESCRIPTION

NEUROPROTECTIVE AGENTS AND METHODS RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATION

This applications claims the benefit of U.S. Provisional Application No. (awaiting) filed July 25, 2000; which provisional application was originally filed as U.S. Application No. 09/450,245 filed November 29, 1999 and converted to the above-identified provisional application by Petition mailed July 25, 2000.

TECHNICAL FIELD

This invention is generally directed to neuroprotective agents, pharmaceutical compositions containing the same, as well as to methods related to the use of such neuroprotective agents.

BACKGROUND OF THE INVENTION

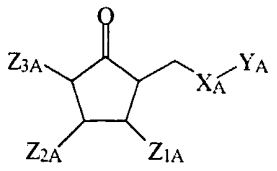
Neurotrophic factors are a group of proteinaceous compounds that participate in differentiation induction of neurons to maintain the existence and survival of cells, of which nerve growth factors (NGFs) are a representative class. NGFs are involved in the differentiation, existence, maintenance and/or repair of neurons in both the central and peripheral nervous systems of animals and represent a series of proteins having molecular weights of approximately 50,000 daltons.

Damage to nerves caused by either aging or internal/external factors often develop paphological symptoms. In the central nervous system, such damage is found to cause, for example, Alzheimer's disease, dementia induced by cerebro-vascular disorders, disturbance of consciousness due to cerebral contusion, and tremor or muscle rigidity associated with Parkinson's disease. Similarly, damage to the peripheral nervous system is associated with a number of conditions, such as amyotropic lateral sclerosis, spinal muscle atrophy, motor function disturbances due to neuron damage, neuropathy induced by diabetes mellitus, uremia, vitamin B_1 or B_{12} deficiency, chronic liver disease, sarcoidosis, amyloidosis, hypothyrea, cancer, angiopathy, Sjögren symptoms, immunopathy

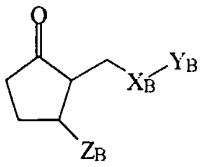
accompanied by infections, hereditary disease, physical compression, certain types of drugs (*e.g.*, carcinostatic, tuberculostatic and/or anti-epileptic agents), or upon exposure to, for example, arsenic, thallium or carbon disulfide.

Since neurons may suffer damage from numerous events, indentification of a neurotropic factor which can regenerate and/or repair of damaged neurons is highly desirably. To this end, a recent attempt has involved the clinical application of NGF to conditions such as Alzheimer's disease, neural damage or spinal injury. For example, when NGF is present, PC 12 cells terminate cell proliferation and differentiate into neuron-like cells with neurites. This has allowed screening for active substances which have NGF-like neuron differentiation/promoting activity. Substances identified in this manner include antibiotic staurosporin and certain cystacycline compounds. Unfortunately, both of these substances have drawbacks with respect to toxicity and kinetics.

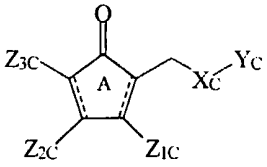
More recently, compounds with neuron differentiation promoting activity have been reported in published PCT WO 99/05091 (Nippon Kayaku Co. Ltd.). Such compounds of this published PCT encompass a wide range of structures, including compounds of the following formulas (1A) through (1F):



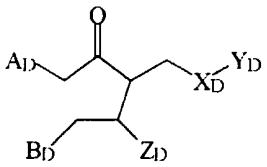
(1A)



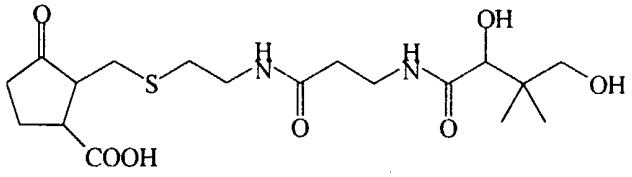
(1B)



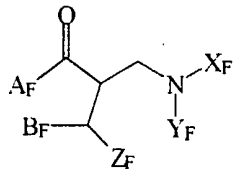
(1C)



(1D)



(1E)



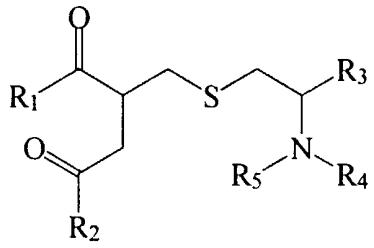
(IF)

While significant advances have been made in this field, there is still a need in the art for novel neuroprotective agents, particularly low molecular weight compounds, as well as related compositions and methods of use. The present invention fulfills these needs and provides further related advantages.

SUMMARY OF THE INVENTION

In brief, the present invention is directed to compounds having activity as neuroprotective agents (also referred to herein as simply "compounds"), as well as to compositions and methods related thereto. As used herein, the term "neuroprotective agent" means a compound that prevents neuron cell death.

The compounds of the present invention have the following structure (I):



(I)

wherein R_1, R_2, R_3, R_4 and R_5 are as defined below, including stereoisomers and pharmaceutically acceptable salts thereof.

The present invention is also directed to methods for treating a variety of conditions by administering an effective amount of a neuroprotective agent of this invention to an animal or subject in need thereof (referred to herein as a "patient"), typically a warm-blooded animal (including a human). Prior to administration, the compounds of this invention are preferably formulated as a pharmaceutical composition which contains an effective dosage amount of one or more neuroprotective agents in combination with one (or more) pharmaceutically acceptable carrier(s).

Conditions that may be treated by the compounds of this invention, or a pharmaceutical composition containing the same, include any condition which may benefit from administration of neuroprotective agents generally, and are particularly useful for the prevention and/or treatment of various conditions including (but not limited to) increased intracraniel pressure and cerebral herniation, cerebral edema, hydrocephalus, meningintis, encephalitis, ischemic encephalopathy, cerebral infarction, intracranial hemorrhage, epidermal hematoma, subdural hematoma, parenchymal injuries, Alzheimer's deasease, Huntington's disease, Parkinsonism, amytrophic lateral sclerosis, multiple sclerosis, hepatic encephalopathy, leukodystrophy, acute idiopathic neuropathy, neurilemmoma, and/or neurofibroma.

These and other aspects of this invention will be apparent upon reference to the following detailed description. To that end, certain patent and other documents are cited herein to more specifically set forth various aspects of this invention. Each of these documents are hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

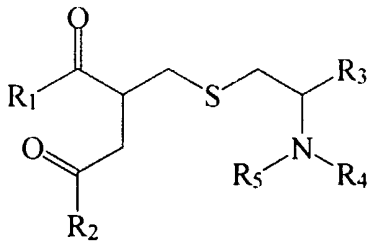
Figure 1 shows the effect of a representative compound according to the present invention in a rat taxol-induced neuropathy model.

Figure 2 shows the effects of representative compounds according to the present invention on a rat taxol-induced neuropathy model.

Figure 3 shows the effects of representative compounds according to the present invention on a rat taxol-induced neuropathy model.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is directed to compounds which have activity as neuroprotective agents, as well as to compositions and methods relating to the same. The compounds of this invention have the following structure (I):



(I)

and stereoisomers and pharmaceutically acceptable salts thereof,

wherein:

R_1 is alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl;

R_2 is $-OR_{2a}$ or $-NR_{2b}R_{2c}$;

R_3 is hydrogen, keto, $-C(=O)OR_{3a}$, or $-C(=O)NR_{3b}R_{3c}$;

R_4 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-C(=O)R_{4a}$, $-C(=O)OR_{4b}$, $-C(=O)NR_{4c}R_{4d}$, $-OC(=O)NR_{4c}R_{4d}$ or $-SO_2R_{4e}$.

or wherein R_3 and R_4 taken together form a heterocyclic ring or substituted heterocyclic ring; and

R_5 is hydrogen, alkyl or substituted alkyl;

and wherein:

R_{2a} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, or substituted heterocyclealkyl;

R_{2b} and R_{2c} are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or a radical of the formula $-OR_{2d}$, $-C(=O)R_{2d}$ or $-SO_2R_{2d}$ wherein R_{2d} is alkyl, substituted alkyl, aryl or substituted aryl, or R_{2b} and R_{2c} taken together with the nitrogen atom to which they are attached from a heterocyclic ring or substituted heterocyclic ring;

R_{3a}, R_{3b} and R_{3c} are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substitued arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, or a radical of the formula $-Y_3-Z_3-R_{3d}$, where Y_3 is alkanediyl, substitute alkanediyl or a direct bond, Z_3 is -O-, -S-, $-SO_2-$, $-N(R_{3e})-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -NHC(=O)-, $-C(=O)N(R_{3e})-$ or a direct bond, and wherein R_{3d} and R_{3e} are the same or different and independently hydrogen, amino, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl; or R_{3b} and R_{3c} taken together with the nitrogen atom to which they are attached from a heterocyclic ring or substituted heterocyclic ring; and

R_{4a}, R_{4b}, R_{4c}, R_{4d} and R_{4e} are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, or a radical of the formula $-Y_4-Z_4-R_{4f}$, where Y_4 is alkanediyl, substitute alkanediyl or a direct bond, Z_4 is -O-, -S-, $-SO_2-$, $-N(R_{4g})-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -NHC(=O)-, $-C(=O)N(R_{4g})-$ or a direct bond, and wherein R_{4f} and R_{4g} are the same or different and independently hydrogen, amino, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl, or R_{4f} and R_{4g} taken together with the nitrogen atom to which they are attached form a heterocycle or substituted heterocycle,

or R_{4c} and R_{4d} taken together with the nitrogen atom to which they are attached from a heterocyclic ring or substituted heterocyclic ring.

As used herein, the terms used above having following meaning.

"Alkyl" means a straight chain or branched, saturated or unsaturated alkyl, cyclic or non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (also referred to as an "alkenyl" or "alkynyl", respectively).

Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cycloalkyls are also referred to herein as "carbocyclic" rings systems, and include bi- and tri-cyclic ring systems having from 8 to 14 carbon atoms such as a cycloalkyl (such as cyclo pentane or cyclohexane) fused to one or more aromatic (such as phenyl) or non-aromatic (such as cyclohexane) carbocyclic rings. .

"Alkanediyl" means a divalent alkyl group having two hydrogen atoms taken from the same carbon atom or different carbon atoms of the alkyl, such as $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2-$, $CH_2CH(CH_3)CH_2-$, -(cyclohexyl)-, and the like.

"Halogen" means fluorine, chlorine, bromine or iodine.

"Keto" means a carbonyl group (*i.e.*, =O).

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atoms replaced with an aryl moiety, such as benzyl, $-(CH_2)_2$phenyl, $-(CH_2)_3$phenyl, $-CH(phenyl)_2$, and the like.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls are pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as -CH_2pyridinyl, -CH_2pyrimidinyl, and the like."Heterocycle" means a heterocyclic ring containing from 5 to 10 ring atoms

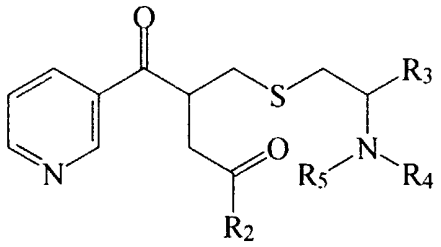
"Heterocycle" means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the heteroaryls listed above, heterocycles also include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclealkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2morpholinyl, and the like.

The term "substituted" as used herein means any of the above groups (*i.e.*, alkyl, alkanediyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocyclealkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent ("C(=O)") two hydrogen atoms are replaced. Substituents include halogen, hydroxy, alkyl, substituted alkyl (such as haloalkyl, mono- or di-substituted aminoalkyl, alkyloxyalkyl, and the like), aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, -NR_aR_b, -$NR_aC(=O)R_b$, -$NR_aC(=O)NR_aR_b$, -$NR_aC(=O)OR_b$ -$NR_aSO_2R_b$, -OR_a, -$C(=O)R_a$ -$C(=O)OR_a$ -$C(=O)NR_aR_b$, -$OC(=O)R_a$, -$OC(=O)OR_a$, -$OC(=O)NR_aR_b$, -$NR_aSO_2R_b$, or a radical of the formula -Y-Z-R_a where Y is alkanediyl, substitute alkanediyl, or a direct bond, Z is -O-, -S-, -SO_2-, -$N(R_b)$-, -C(=O)-, -C(=O)O-, -OC(=O)-, -$N(R_b)C(=O)$-, -$C(=O)N(R_b)$- or a direct bond, wherein R_a and R_b are the same or different

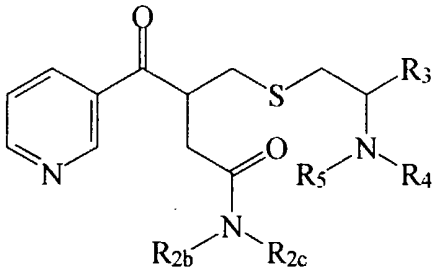
and independently hydrogen, amino, alkyl, substituted alkyl (including halogenated alkyl), aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl, or wherein R_a and R_b taken together with the nitrogen atom to which they are attached form a heterocycle or substituted heterocycle.

In one embodiment of this invention, R_1 is pyridinyl. In a more specific embodiment of this aspect, R_1 is pyridin-3-yl, and compounds of this invention have the following structure:



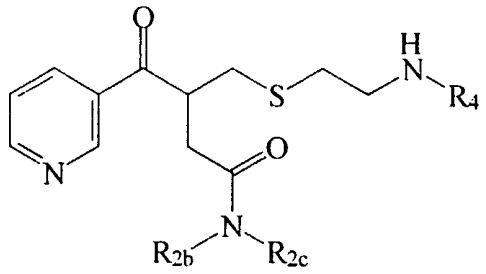
(II)

In a further embodiment of structure (II), R_2 is $-NR_{2b}R_{2c}$, and compounds of this invention have the following structure (III):



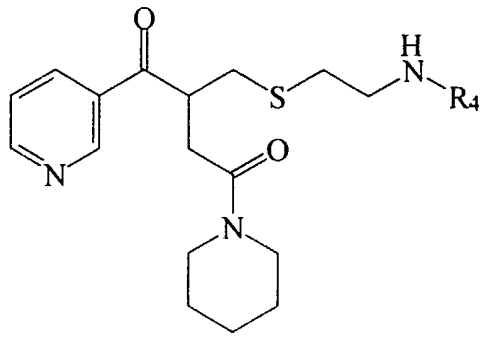
(III)

In still a further embodiment of structure (III), R_3 and R_5 are hydrogen, and compounds of this invention have the following structure (IV):



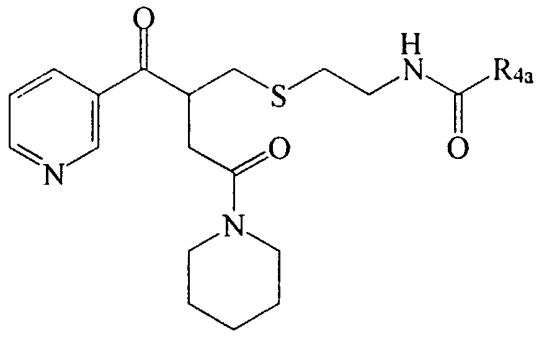
(IV)

In yet a further embodiment of structure (V), R_{2b} and R_{2c} taken together with the nitrogen atom to which they are attached form piperidyl, and the compounds of this invention have the following structure (V):

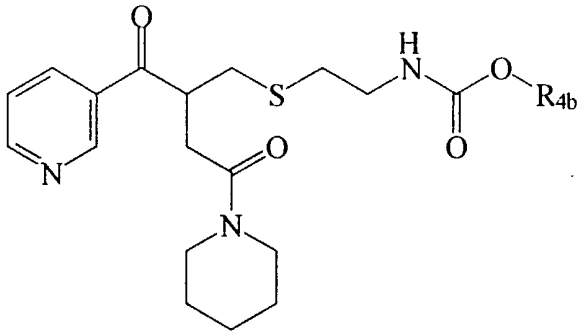


(V)

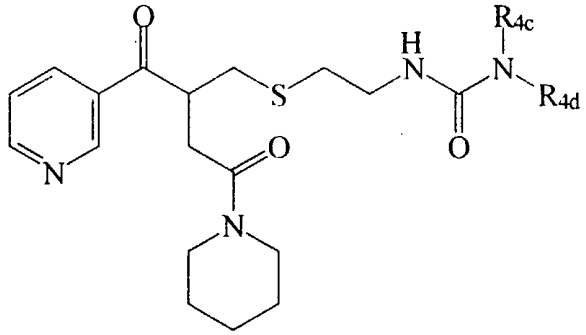
In a more specific embodiment of structure (V), R_4 is , $-C(=O)R_{4a}$, $-C(=O)OR_{4b}$ or $-C(=O)NR_{4c}R_{4d}$, and compounds of this invention have the following structures (VI), (VII) or (VIII), respectively:



(VI)

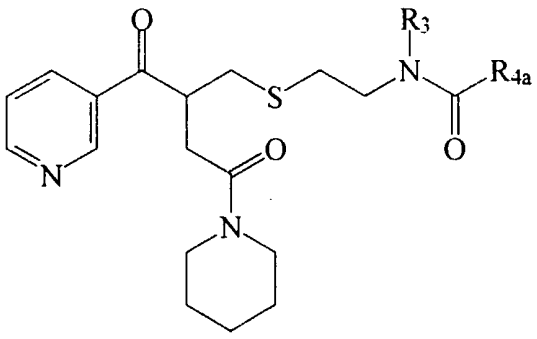


(VII)



(VIII)

In a further embodiment of structure (I), compounds of this invention have the following structure (IX):



(IX)

wherein R_3 is, in one embodiment, alkyl or substituted alkyl.

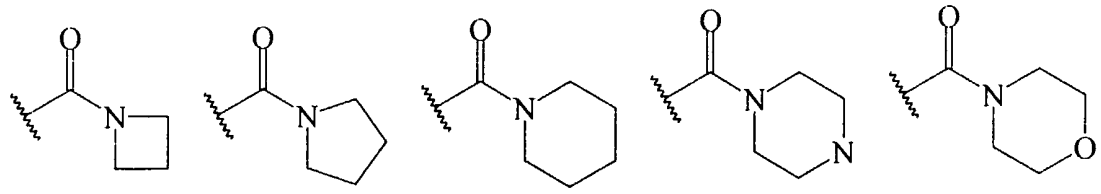
In one representative embodiment, R_1 is heterocycle and, more specifically, an aromatic heterocycle (*i.e.*, heteroaryl) such as pyridin-2-yl or pyridin-3-yl. In another embodiment, R_1 is aryl such as phenyl, or alkyl (including cycloalkyl). In still a further embodiment, R_1 is heteroaryl such as thiazolyl.

In another representative embodiment, R_2 is $-OR_{2a}$ wherein R_{2a} is hydrogen or an alkyl group such as methyl, ethyl, n-propyl, n-butyl, t-butyl or $-CH_2$(cyclopropyl), or a substituted alkyl such as $-(CH_2)_2NH_2$, $-CH_2(OC(=O)$t-butyl). In another embodiment, R_{2a} is aryl such as phenyl or substituted aryl such as 4-chlorophenyl, or arylalkyl, such as benzyl (*i.e.*, $-CH_2$phenyl) or $-(CH_2)_2$phenyl. In a further embodiment, R_{2a} is heterocyclealkyl, such as $-(CH_2)_2$morpholinyl, $-(CH_2)_2$indolyl, $-(CH_2)_{2-3}$piperidinyl, $-(CH_2)_3$pyridinyl or $-(CH_2)_2$thiophenyl.

In a further representative embodiment, R_2 is $-NR_{2b}R_{2c}$, wherein R_{2b} is hydrogen and R_{2c} is alkyl, substituted alkyl (*e.g.*, $(CH_2)_3OCH_3$), arylalkyl (*e.g.* benzyl) or heteroarylalkyl (*e.g.* $-CH_2$pyridinyl or $-CH_2$thiophenyl). In another embodiment , R_{2c} is $-OR_{2d}$ or $-SO_2R_{2d}$ wherein R_{2d} is alkyl such as methyl, aryl such as phenyl or arylalkyl such as benzyl. In a further embodiment, R_{2b} and R_{2c} are both alkyl such as methyl or ethyl. In still a further embodiment, R_{2b} and R_{2c} taken together form a heterocycle ring such as pyrrolidinyl, piperidinyl and morpholinyl.

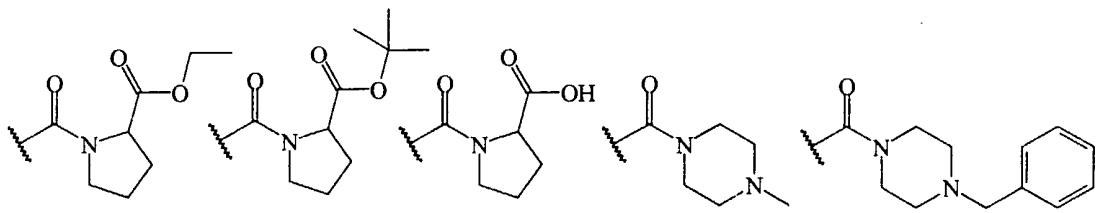
In still a further representative embodiment, R_3 is hydrogen or keto (*i.e.*, =O). In another embodiment, R_3 is carbonyl (*i.e.*, -COOH) or an alkyl ester of the formula

-C(=O)OR_{3a}, such as methyl ester (*i.e.*, -C(=O)OMe) or ethyl ester (*i.e.*, -C(=O)OEt). In still a further embodiment, R_3 is an amide of the formula -C(=O)$NR_{3b}R_{3c}$, such as dialkylamide (*e.g.*, -C(=O)$N(CH_3)_2$), cycloalkylamide (*e.g.*, -C(=O)NH(cyclohexyl)), arylalkylamide (*e.g.*, -C(=O)$NH(CH_2)_3$phenyl), heterocycle alkylamide (*e.g.*, -C(=O)$N(CH_2)_3$imidazolyl, -C(=O)$N(CH_2)_2$pyridinyl, -C(=O)$NH(CH_2)_3$morpholinyl), substituted alkylamide (*e.g.*, -C(=O)$N(CH_3)(CH_2)_{2-3}N(Me)_2$ or -C(=O)$N(CH_3)(CH_2)_2N(Et)_2$, or wherein R_{3b} and R_{3c} taken together form a heterocyclic ring such as the following structures (i) through (v):



(i) (ii) (iii) (iv) (v)

or wherein R_{3b} and R_{3c} taken together form a substituted heterocyclic ring such as the following structures (vi) through (x):

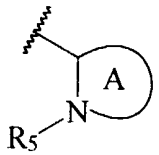


(vi) (vii) (viii) (ix) (x)

Representative R_4 moieties of this invention include (but are not limited to) those listed in Table 1 of Example 45. For example, one representative embodiment, R_4 is hydrogen, alkyl such as methyl or ethyl, aryl such as phenyl or naphthyl, or arylalkyl such as benzyl. In another embodiment, R_4 is -C(=O)R_{4a}. In this embodiment, representative R_{4a} groups include alkyl and substituted alkyl, as well as aryl, substituted aryl, arylalkyl

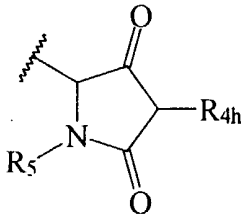
and substituted arylalkyl. Further representative R_{4a} groups include heterocycle, substituted heterocycle, heterocyclealkyl and substituted heterocyclealkyl. In another embodiment, R_4 is $-C(=O)OR_{4b}$. In this embodiment, representative R_{4b} groups include alkyl, substituted alkyl, aryl and substituted aryl. In still another embodiment, R_4 is $-C(=O)NR_{4c}R_{4d}$ or $-OC(=O)NR_{4c}R_{4d}$. In this embodiment, representative R_{4c} and R_{4d} groups include alkyl, substituted alkyl, aryl, and substituted aryl. In yet a further embodiment, R_4 is $-SO_2R_{4e}$. In this embodiment, representative R4e groups include alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, and substituted arylalkyl, as well as heterocycle and substituted heterocycle.

In a further representative embodiment, R_3 and R_4 taken together form a substituted or unsubstituted heterocyclic ring of the following structure (xi):

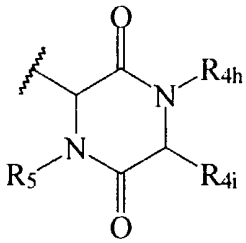


(xi)

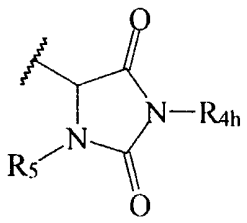
wherein ring A represents a heterocyclic ring as defined above. Representative heterocyclic rings in this regard include pyrrolyl, imidazolyl, pyrazolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, and the like, as well as keto-substituted heterocycles such as hydantinyl, ketopiperazinyl, diketopiperazinyl, and the like. In one representative embodiment, R_3 and R_4 are taken together to form a substituted heterocyclic ring having the following structures (xii), (xiii) or (xiv):



(xii)



(xiii)



(xiv)

wherein R_{4h} and R_{4i} represents the same or difference substituents as defined above, such as hydrogen or alkyl.

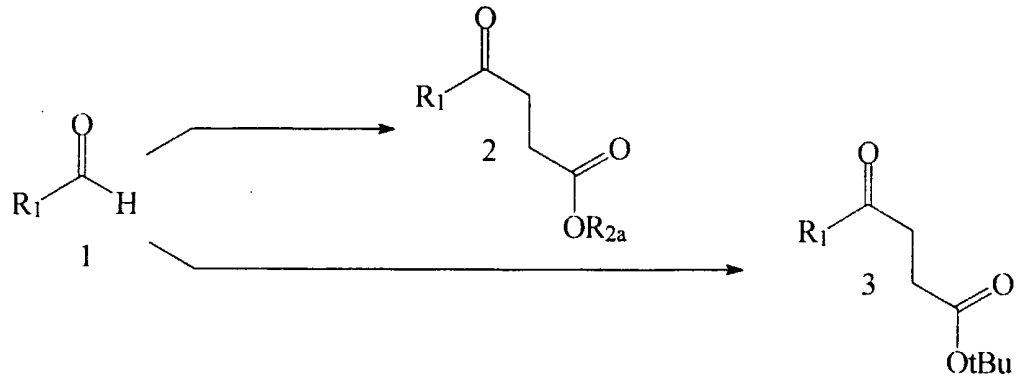
In another representative embodiment, R_5 is hydrogen. In another emobiment, R_5 is alkyl such as methyl, ethyl, n-propyl, n-butyl and cyclohexyl.

Pharmaceutically acceptable salts of compounds of structure (I) are also within the scope of this invention. To this end, the compound may generally be utilized as the free base. Alternatively, the compounds may be used in the form of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, 1,2-ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, benzenesulfonic, p-tolyenesulfonic, hippuric, sebacic, 2-hydroxy-1-naphthoic and perchloric acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of a compound of structure (I) is intended to encompass any and all acceptable salt forms.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as recemates, reacemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention. In addition, some of the compounds of structure (I) may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

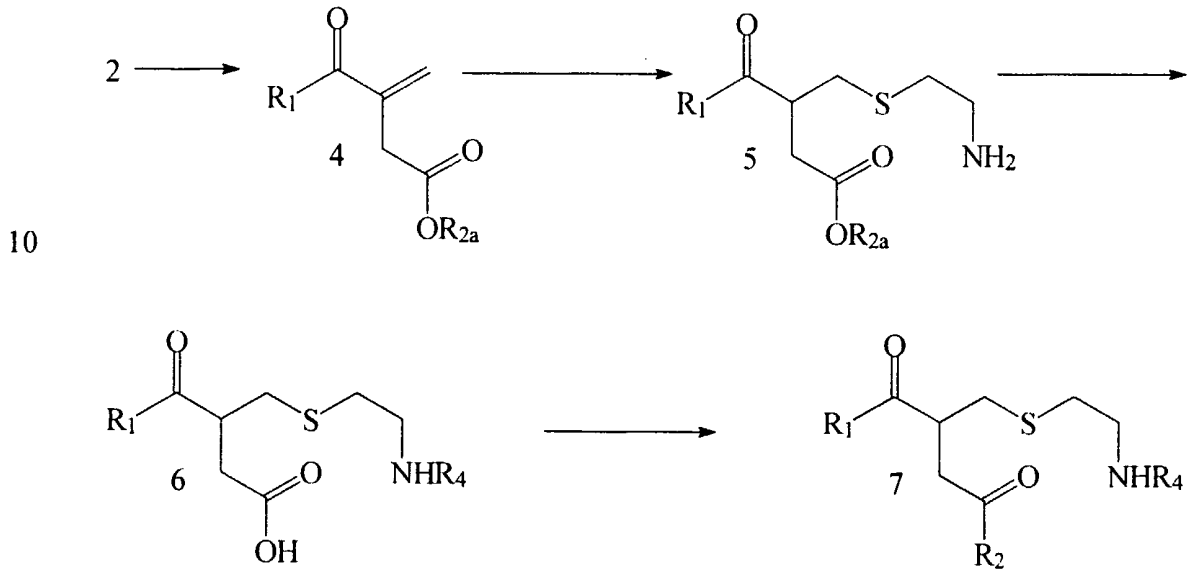
The compounds of this invention may generally be made by organic synthesis techniques known to those skilled in the art, as well as by the following general techniques and by the procedures set forth in the Examples. To that end, the compounds of this invention may be made according to the following Reaction Schemes.

Reaction Scheme 1



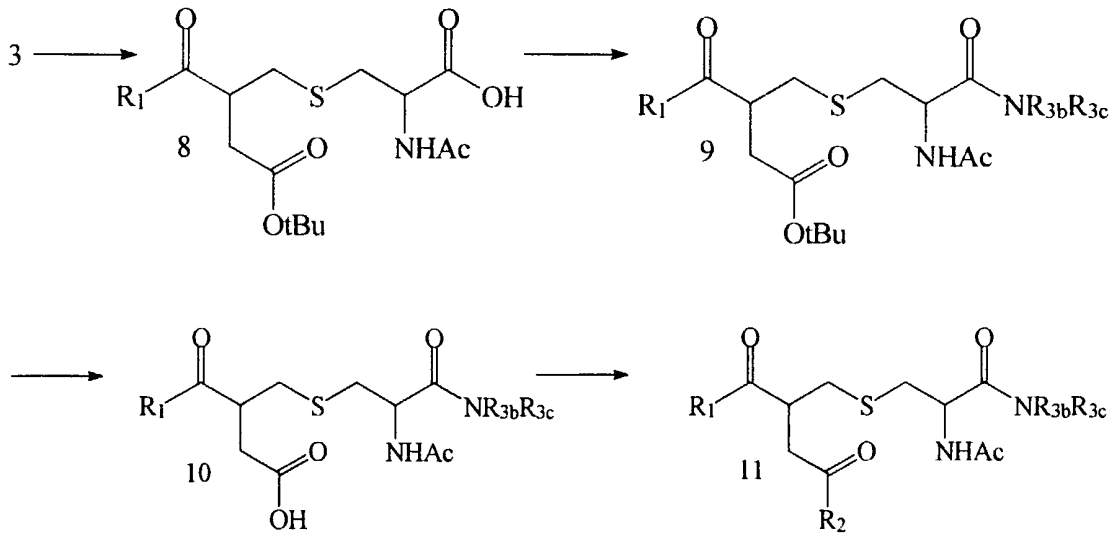
In Reaction Scheme 1, compound 2 may be prepared by treating aldehyde 1 with an acrylate ester in the presence of sodium cyanide in dimethylformamide solvent. Similarly, compound 3 can be prepared from aldehyde 1 using the above conditions.

Reaction Scheme 2



In Reaction Scheme 2, compound may be prepared from compound 2 by treating it with piperidine and aqueous formaldehyde in tetrahydrofuran. The piperidyl adduct intermediate can be treated with hydrochloric acid to give compound 4. Treatment of compound 4 with 2-aminoethanethiol in tetrahydrofuran will result in compound 5. The amine group in compound 5 can be converted to amides (by treating with acid chloride), carbamates (by treating with chloroformates) and ureas (by treating with isocyanates) in dichloromethane or tetrahydrofuran. Once the amine group was converted to NHR_4, the ester group OR_{2a} can by hydrolyzed either under basic (using sodium hydroxide) or acidic (hydrochloric acid) to give compound 6. The acid group in compound 6 can be functionalized to an amide by standard coupling conditions using a carbodiimide (such as ethyl diisopropyl carbodiimide) in a suitable solvent (such as tetrahydrofuran or dichloromethane).

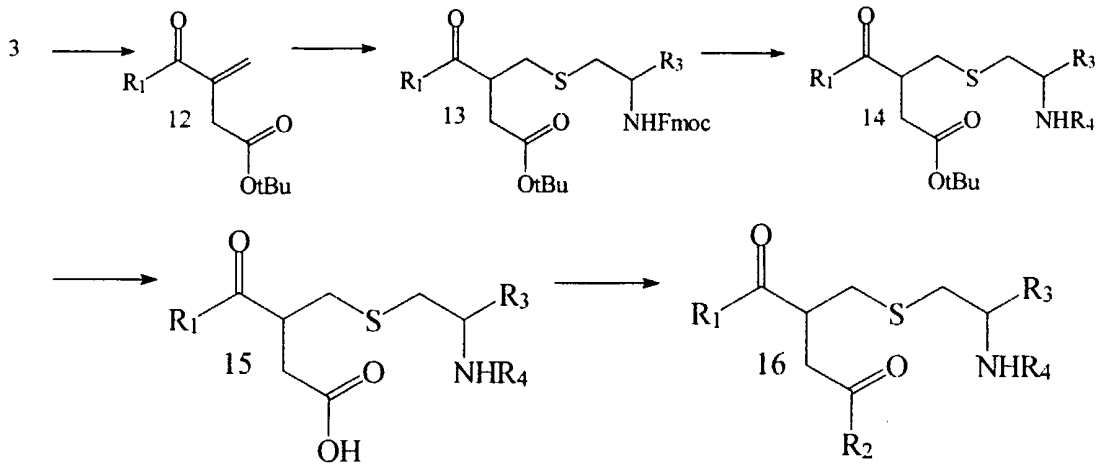
Reaction Scheme 3



In Reaction Scheme 3, compound 8 can be prepared from compound 3 by treatment with piperidine and aqueous formaldehyde in tetrahydrofuran. The intermediate piperidyl adduct can be treated with N-acetyl cysteine in tetrahydrofuran or ethanol to give

compound 8. The acid group in compound 8 can be further functionalized to an amide by treating with an amine and a suitable carbodiimide (such as ethyl diisopropyl carbodiimide) in dichloromethane or tetrahydrofuran. The t-butyl ester in compound 9 can be hydrolyzed to an acid, as in compound 10, using an acid (such as hydrochloric acid). The acid group in compound 10 can be converted to an ester ($R_2 = OR_{2a}$ in compound 11) by treating with an alkyl halide, triethylamine in dimethylformamide or to an amide ($R_2 = NR_{2b}R_{2c}$ in compound 11) by using an amine and standard carbodiimide coupling procedure.

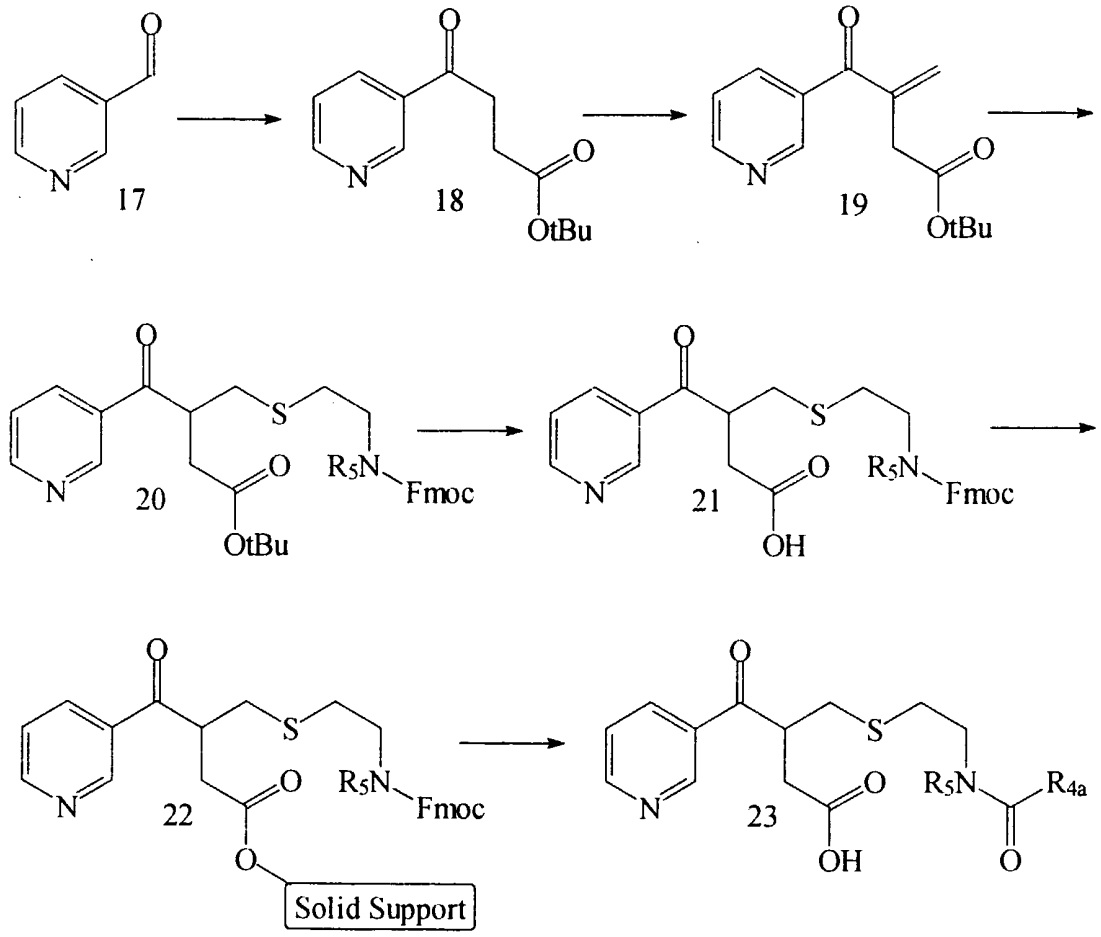
Reaction Scheme 4



In Reaction Scheme 4, compound 12 can be prepared from compound 3 by treating it with piperidine and aqueous formaldehyde in tetrahydrofuran. The piperidyl adduct intermediate can be treated with a limited amount of hydrochloric acid to give compound 12. Treatment of compound 12 with an appropriately substituted thiol in tetrahydrofuran resulted in compound 13. The Fmoc group on compound 13 can be cleaved with piperidine in dimethylformamide to give the free amine. This free amine can be functionalized to an amide ($R_4 = C(=O)R_{4a}$ in compound 14) using an acid chloride, or to a carbamate ($R_4 = C(=O)OR_{4b}$ in compound 14) using a chloroformate or to a urea ($R_4 = C(=O)NR_{4c}R_{4d}$ in compound 14) using an isocyanate. The t-butyl ester in compound 14

can be cleaved to a free acid using hydrochloric acid in water-tetrahydrofuran solvent system to give compound 15. The acid group in compound 15 can be functionalized to an amide by standard coupling conditions using a carbodiimide (such as ethyl diisopropyl carbodiimide) in a suitable solvent (such as tetrahydrofuran or dichloromethane), or to an ester by treating with an alkyl halide, triethylamine in dimethylformamide.

Reaction Scheme 5



In Reaction Scheme 5, treatment of compound 17, 3-pyridinecarboxaldehyde, with sodium cyanide and t-butyl acrylate in dimethylformamide

results in compound 18. Compound 18 may be converted to compound 19 using piperidine and aqueous formaldehyde in tetrahydrofuran to give a piperidyl adduct. The intermediate piperidyl adduct can be treated with limited amount of hydrochloric acid to give compound 19. Compound 19 can be converted to compound 20 using N-Fmoc-protected cysteamine in tetrahydrofuran. The t-butyl group in compound 20 can be cleaved to give free acid 21 using trifluoroacetic acid in dichloromethane. The acid 21 can be attached to a solid phase resin (such as 2-chlorotrityl resin) in the presence of diisopropylethylamine to give compound 22. The FMOC group in compound 22 can be cleaved using piperidine in dimethylformamide to give free amine, which can be treated with either an acid chloride to give an amide, or a chloroformate to give a carbamate, or to an isocyanate to give a urea. Compound 23 can be cleaved off the resin using trifluoroacetic acid in dichloromethane.

In another embodiment of the invention, pharmaceutical compositions containing one or more compounds of this invention are disclosed. For purpose of administration, a compound of structure (I) is preferably formulated as a pharmaceutical composition. Pharmaceutical compositions of the present invention comprise a compound of this invention and a pharmaceutically acceptable carrier, wherein the compound is present in the composition in an amount which is effective to treat the condition of interest. Preferably, the pharmaceutical compositions of the present invention include a compound of structure (I) in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more typically from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

Pharmaceutically acceptable carriers are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a compound of this invention, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the compounds of this invention in an appropriate manner, and in accordance

with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, PA 1990.

In another embodiment, the present invention provides a method for treating a variety of conditions by administering an effective amount of a compound of structure (I) to a patient in need thereof. As used herein, treatment includes preventative administration, as well as "rescue" treatment when, for example, a patient has already developed neuropathy. Conditions that may be treated by the compounds of this invention, or a pharmaceutical composition containing the same, include any condition which is responsive to treatment by a neuroprotective agent generally and, more specifically, for treatment of central or peripheral nervous disorders, or for promoting nerve cell differentiation. Representative conditions in this regard include (but not limited to) increased intracraniel pressure and cerebral herniation, cerebral edema, hydrocephalus, meningintis, encephalitis, ischemic encephalopathy, cerebral infarction, intracranial hemorrhage, epidermal hematoma, subdural hematoma, parenchymal injuries, Alzheimer's deasease, Huntington's disease, Parkinsonism, amytrophic lateral sclerosis, multiple sclerosis, hepatic encephalopathy, leukodystrophy, acute idiopathic neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, HIV-induced neuropathy, neurilemmoma, and/or neurofibroma.

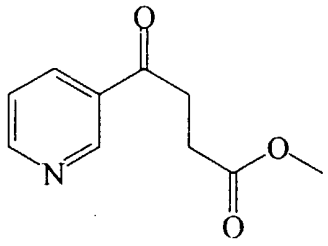
The methods of this invention include systemic administration of a compound of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration encompasses both oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

The following examples are offered by way of illustration, not limitation.

EXAMPLES

EXAMPLE 1

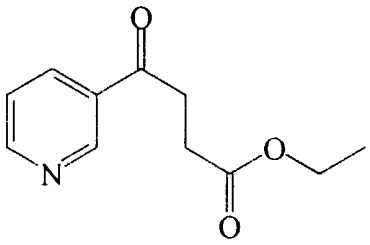
METHYL 4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of 3-pyridinecarboxyaldehyde (10.7 g) in dimethyl formamide (DMF, 20 mL) was added over 10 min. to a stirred suspension of sodium cyanide (2.45 g) in DMF (80 mL) at room temperature under dry nitrogen. The solution was stirred for 30 min. and methyl acrylate (18.6 g) in DMF (80 mL) was added dropwise over 50 min. The reaction mixture was stirred for 3 h. Acetic acid (6.6 mL) and water (30 mL) were added and stirring was continued for 5 minutes. The mixture was concentrated, dissolved in water (360 mL), and pH was adjusted to 7.5 with sodium bicarbonate. The aqueous layer was extracted with chloroform (3 X 300 mL). The chloroform layers were combined, washed with saturated sodium chloride solution (brine), dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (SiO2, 30% ethyl acetate in hexanes) to yield 4.3 g (22%) of the title compound; ESMS $(M+1)^+$ 194.

EXAMPLE 2

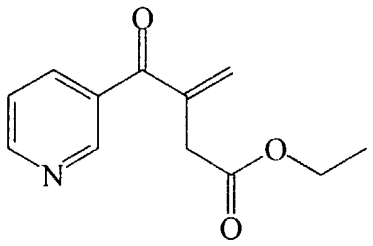
ETHYL 4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from 3-pyridinecarboxyaldehyde (20 g) and ethyl acrylate (22.4 g) as described in Example 1 to yield 5.1 g, ESMS (M+1)+ 208.

EXAMPLE 3

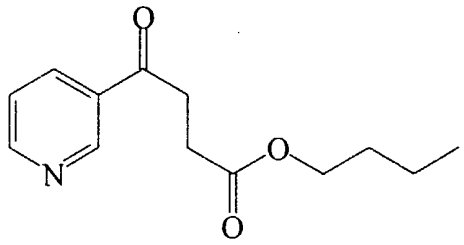
ETHYL 3-(3-PYRIDYLCARBONYL)BUT-3-ENOATE



A solution of ethyl 4-oxo-4-(3-pyridyl)butanoate (4 g), 37% aqueous formaldehyde (2.46 g) and piperidine (2.46 g) was stirred at room temperature for 18 h. The reaction mixture was diluted with 200 mL of ethyl acetate and washed with water (2X100 mL). The reaction mixture was concentrated and dissolved in ethanol (10 mL) and treated with 4N HCl/dioxane (4 mL) at 80°C for 12 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 X 100 mL), saturated sodium bicarbonate solution (2 X 100 mL), concentrated and purified on flash chromatography (20% Ethyl acetate to 80% ethyl acetate in hexane) to give 2.28 g of the title compound, ESMS (M+1)+ 220.

EXAMPLE 4

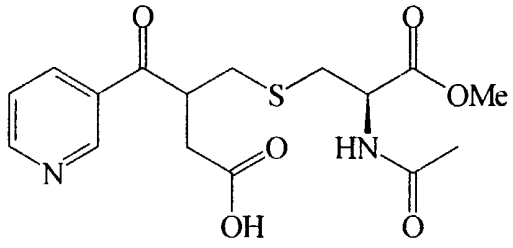
BUTYL 4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of 3-pyridinecarboxyaldehyde (26.8 g) in dimethyl formamide (DMF, 100 mL) was added over 10 min. to a stirred suspension of sodium cyanide (7.0 g) in DMF (200 mL) at room temperature under dry nitrogen. The solution was stirred for 30 min. and n-butyl acrylate (32 g) in DMF (200 mL) was added dropwise over 60 min. The reaction mixture was stirred for 3 h. Acetic acid (20 mL) and water (80mL) were added and stirring was continued for 10 minutes. The solution was concentrated under reduced pressure, dissolved in ethyl acetae (600 mL), washed with water (3 X 200 mL), brine (200 mL) and dried (Na_2SO_4). The solution was filtered, concentrated and distilled at 140°C at 0.5 mm/Hg to give 18.2 g of the title compound as an oil; ESMS $(M+1)^+$ 236.

EXAMPLE 5

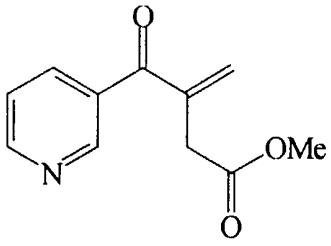
3-{[(2R)-2-(ACETYLAMINO)-2-(METHOXYCARBONYL)ETHYLTHIO]-METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



A solution of 4-oxo-3-(piperidylmethyl)-4-(3-pyridyl)butanoic acid (5.0g), methyl N-acetyl-L-cysteine ester (4.7 g) in ethanol (44 mL) was heated at reflux for 2 h. The solution was concentrated under reduced pressure and purified on flash chromatography (SiO_2, $CHCl_3$: MeOH : CH_3COOH = 20:1:0.5) to afford the title compound in 85% yield; ESMS $(M+1)^+$ 369.

EXAMPLE 6

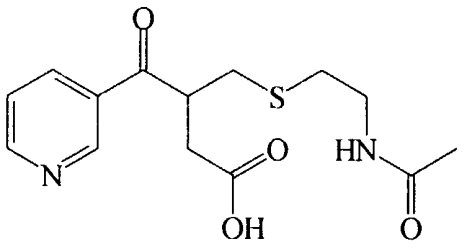
METHYL 3-(3-PYRIDYLCARBONYL)BUT-3-ENOATE



A solution of methyl 4-oxo-3-(piperidylmethyl)-4-(3-pyridyl)butanoate (4 g) in ethanol (10 mL) and 4N HCl/dioxane (4.0 mL) was heated at 80°C for 12 hrs. The reaction mixture was concentrated and purified on flash chromatography (SiO_2, $CHCl_3$: MeOH: CH_3COOH = 10:1:0.5) to give 2.28 g of the title compound.

EXAMPLE 7

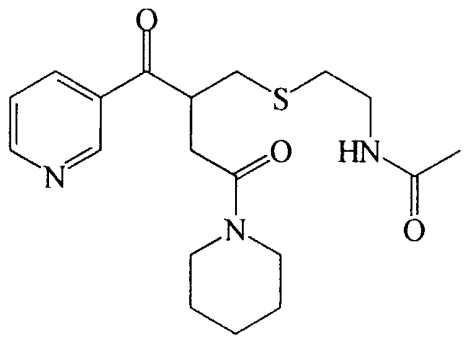
3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL-4-OXO-4-(3-PYRIDYL)-BUTANOIC ACID



A solution of 4-oxo-4-(3-pyridyl)butanoic acid (7.0 g) in ethanol (25 mL) was heated with piperidine (3.65 g) and 37% formaldehyde in water (3.5 g) at 80°C for 3 hrs. A solution of n-acetylcysteamine (4.65 g) in ethanol (30 mL) was added to the reaction mixture and heated at 80°C with stirring for 3 h. The solution was concentrated and purified by flash chromatography (SiO_2, $CHCl_3$:MeOH:CH_3COOH = 20:1:0.5) to give 7.3 g of the title compound.

EXAMPLE 8

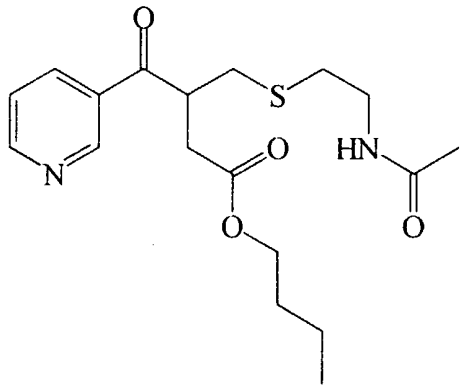
4-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)-BUTYLTHIO]ETHYL}-ACETAMIDE



Ethylchloroformate (1.54 g) was added to a stirred solution of 3-{[2-(acetylamino)ethylthio]methyl-4-oxo-4-(3-pyridyl)butanoic acid (4.0 g), triethylamine (1 eq) in tetrahydrofuran (100 mL) at 0°C. Piperidine (1.21 g) was added to the reaction mixture and stirred at room temperature for 2 hrs. The reaction mixture was concentrated, and purified on HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 2.6 g (53%) of the title compound; ESMS, (M+1), 378.

EXAMPLE 9

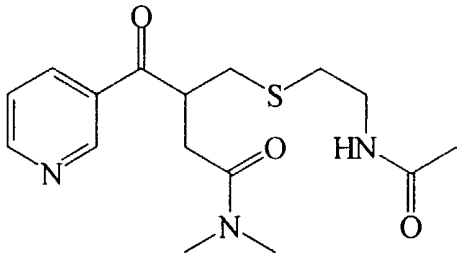
BUTYL 3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYLBUTANOATE



A solution of butyl 4-oxo-4-(3-pyridyl)butanoate (6.0 g), 37% formaldehyde in water (2.06 g) and piperidine (2.17 g) in ethanol (25 mL) was heated at 80°C for 2 hrs. N-Acetylcysteamine (3.03 g) was added to the reaction mixture. The reaction mixture was heated at 80°C with stirring for 3 hrs. The solution was concentrated and purified on HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 5.60 g of the title compound; ESMS $(M+1)^+$ 367.

EXAMPLE 10

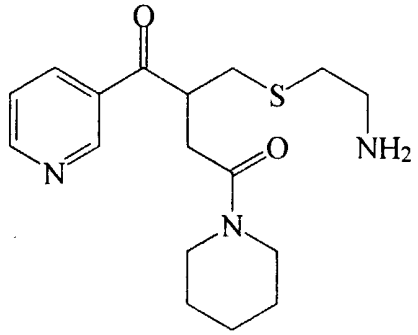
3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-N,N-DIMETHYL-4-OXO-4-(3-PYRIDYL)BUTANAMIDE



Ethyl chloroformate (3.85g) was added to a solution of 3-{[2-(acetylamino)-ethylthio]methyl-4-oxo-4-(3-pyridyl)-butanoic acid (10g) and triethylamine (4.88 g) in tetrahydrofuran (THF, 150 mL) at 0°C. The reaction mixture was stirred for 5 min. A 2M solution of dimethylamine in THF (17.7 mL) was added to the reaction mixture and stirred at room temperature for 2 hrs. The reaction mixture was concentrated and purified on HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 5.1 g of the title compound; ESMS $(M+1)^+$ 338.

EXAMPLE 11

2-[(2-AMINOETHYLTHIO)METHYL]-4-PIPERIDYL-1-(3-PYRIDYL)BUTANE-1,4-DIONE

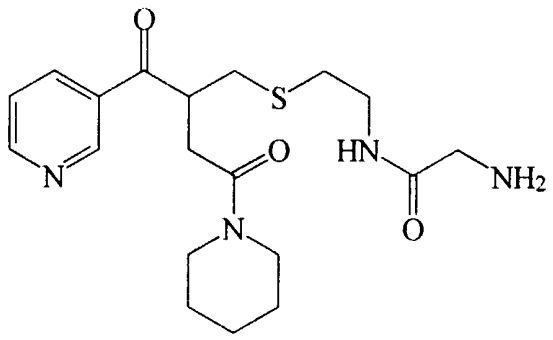


Ethyl chloroformate (8.07 g) was added over 10 min to a solution of 4-oxo-4-(3-pyridyl)butanoic acid (11.1 g) and triethylamine (7.5 g) in dichloromethane (300 mL) at 0°C with constant stirring. Piperidine (5.27 g) was added to the reaction mixture and stirred at room temperature for 1h. The reaction mixture was washed with water and the organic layer was concentrated to an oil. The oil was dissolved in ethanol (80 mL), 37% aqueous formaldehyde (6.85 g) and piperidine (6.85 g). The reaction mixture was heated at 80°C for 3 h. (tert-Butoxy)-N-(2-sulfanylethyl)carboxamide (10.97 g) was added to the reaction mixture and stirred at 80°C for 2 h. The reaction mixture was concentrated and purified by flash chromatography (50% ethyl acetate in hexanes to 100% ethyl acetate) to give (tert-butoxy)-N-{2-[4-oxo-4-piperidyl-2-(3-

pyridylcarbonyl)butylthio]ethyl}carboxamide. This compound was dissolved in dioxane (80 mL) and treated with 4N HCl/dioxane (60 mL) for 30 min. at r.t. The reaction mixture was concentrated to give 63% yield of the title compound as hydrochloride salt; ESMS $(M+1)^+$ 336.

EXAMPLE 12

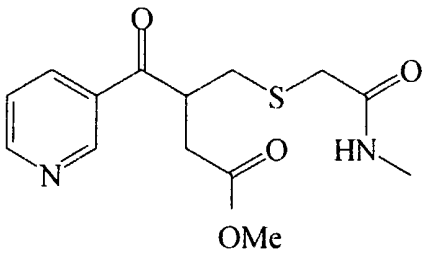
2-AMINO-N-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)-BUTYLTHIO]-ETHYL}ACETAMIDE



Ethyl chloroformate (2.93 g) was added to a solution of 2-[(tert-butoxy)-carbonylamino]acetic acid (4.73 g) and triethylamine (4.09 g) in dichloromethane (150 mL) at 0 _C. The solution was stirred for 20 min. and 2-[(2-aminoethylthio)methyl]-4-piperidyl-1-(3-pyridyl)butane-1,4-dione (10 g), triethylamine (4.1 g) and dichloromethane (150 mL) were added to the reaction mixture and stirred at room temperature for 1h. The reaction mixture was washed with water, concentrated under reduced pressure and purified on flash chromatography (50% ethyl acetate in hexanes to 100% ethyl acetate) to give 35% of 2-[(tert-butoxy)carbonylamino]-N-{2-[4-oxo-4-piperidyl-2-(3-pyridylcarbonyl)butylthio]ethyl}acetamide. This intermediate (4.22 g) was treated with 4N HCl/dioxane (15 mL) in dioxane (25 mL) for 30 min. The solution was purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water) to give 2.8 g of the title compound, ESMS, $(M+1)^+$ 393.

EXAMPLE 13

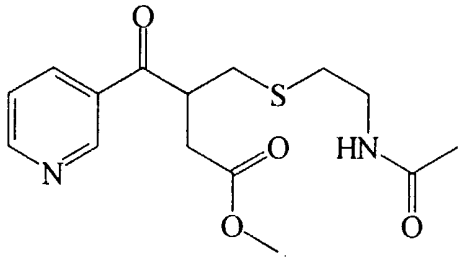
METHYL 3-{[(N-METHYLCARBAMOYL)METHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of methyl 3-(3-pyridylcarbonyl)but-3-enoate in dichloromethane (0.5 mL, 0.1 mM), triethylamine in dichloromethane (0.5 mL, 0.1 mM) and N-methyl-2-sulfanylacetamide (0.6 mL, 0.12 mmol) was stirred for 24 h. PS isocyanate resin (60 mg) was added to the reaction mixture and stirred for 24 h. The solution was filtered and concentrated to give the title compound in quantitative yield, ESMS, $(M+1)^+$ 311.

EXAMPLE 14

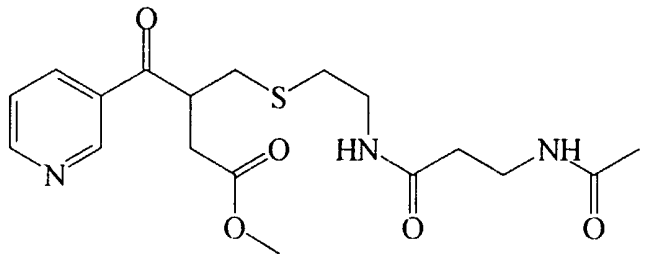
METHYL 3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from methyl 3-(3-pyridylcarbonyl)but-3-enoate and N-(2-sulfanylethyl)acetamide as described in Example 13 in quantitative yield, ESMS, $(M+1)^+$ 325.

EXAMPLE 15

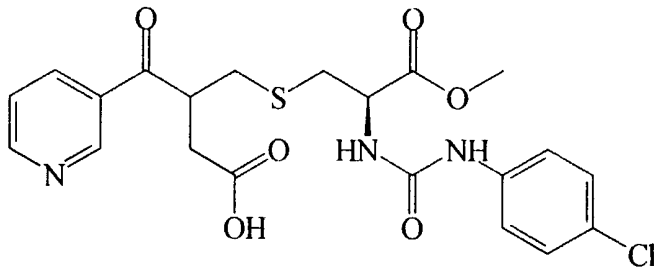
METHYL 3-({2-[3-(ACETYLAMINO)PROPANOYLAMINO]ETHYLTHIO}-METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of methyl 3-[(2-aminoethylthio)methyl]-4-oxo-4-(3-pyridyl)butanoate (747 mg), 3-(acetylamino)propanoic acid (302 mg), dicyclohexylcarbodiimide (433 mg), 1-hydroxybenzotriazole (567 mg) and N-methylmorpholine (402 mg) in dichloromethane (10 mL) were stirred at room temperature overnight. The solution was concentrated and purified by flash chromatography (SiO2, chloroform:methanol = 9:1) to give the title compound in 75% yield; ESMS $(M+1)^+$ 396.

EXAMPLE 16

3-[((2R)-2-{[(4-CHLOROPHENYL)AMINO]CARBONYLAMINO}-2-(METHOXYCARBONYL)ETHYLTHIO)METHYL]-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID

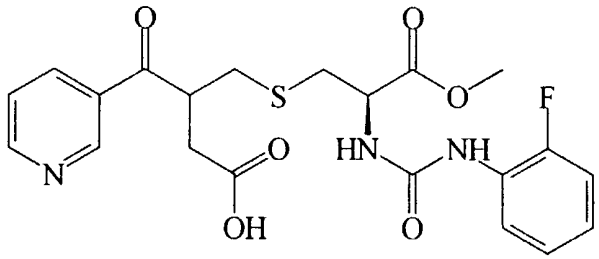


Wang resin (100-200 mesh, 0.66 mmol/g, 70 mg) was treated with triphenylphosphine (34.5 mg), diethyl azodicarboxylate (20.8 μL) and 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-

pyridyl)butanoic acid (72.3 mg) in THF (0.5 mL) at room temperature for 3 days. The resin was filtered, washed with dimethyl formamide, isopropanol, dichloromethane and ether and dried. The resin was treated with 20% piperidine-dichloromethane (1 mL) solution for 1 h. The resin was filtered, and washed with dimethyl formamide, isopropanol, dichloromethane and ether and dried. The resin was treated with 10 eq of 4-chlorophenyl isocyanate in dichloromethane (6 mL) for two days. The resin was washed with washed with dimethyl formamide, isopropanol, dichloromethane and ether and dried. The resin was treated with 20% trifluoroacetic acid in dichloromethane (5 mL). The solution was filtered, concentrated and purified on HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 12% of the title compound; ESMS, $(M+1)^+$ 480.

EXAMPLE 17

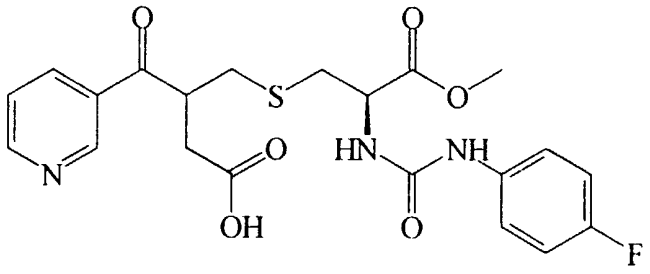
3-[((2R)-2-{[(2-FLUOROPHENYL)AMINO]CARBONYLAMINO}-2-(METHOXYCARBONYL)ETHYLTHIO)METHYL]-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and 2-fluorophenyl isocyanate as described in Example 16 in a 13% yield; ESMS, $(M+1)^+$ 464.

EXAMPLE 18

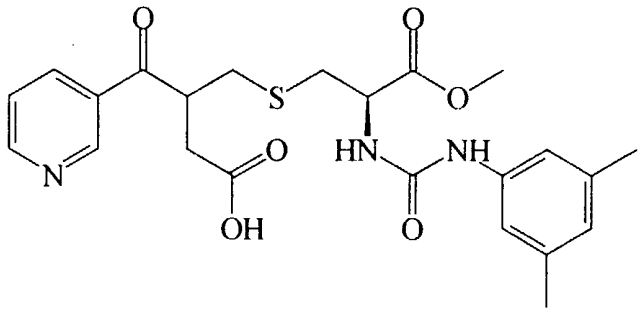
3-[((2R)-2-{[(4-FLUOROPHENYL)AMINO]CARBONYLAMINO}-2-(METHOXYCARBONYL)ETHYLTHIO)METHYL]-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and 4-fluorophenyl isocyanate as described in Example 16 in a 5% yield; ESMS, $(M+1)^+$ 464.

EXAMPLE 19

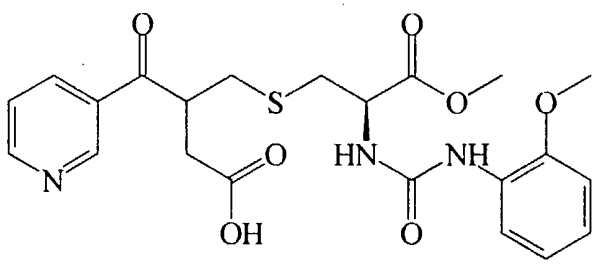
3-[((2R)-2-{[(3,5-DIMETHYLPHENYL)AMINO]CARBONYLAMINO}-2-(METHOXYCARBONYL)ETHYLTHIO)METHYL]-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and 3,5-dimethylphenyl isocyanate as described in Example 16 in a 2.4% yield; ESMS, $(M+1)^+$ 474.

EXAMPLE 20

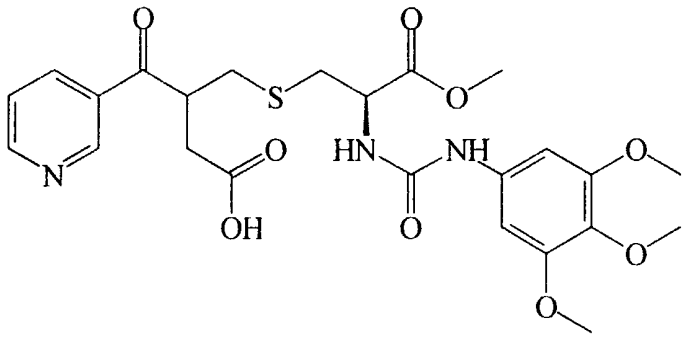
3-[((2R)-2-{[(2-METHOXYPHENYL)AMINO]CARBONYLAMINO}-2-(METHOXYCARBONYL)ETHYLTHIO)METHYL]-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and 2-methoxyphenyl isocyanate as described in Example 16 in a 14% yield: ESMS, $(M+1)^+$ 476.

EXAMPLE 21

3-[((2R)-2-{[(3,4,5-TRIMETHOXYPHENYL)AMINO]CARBONYLAMINO}-2-(METHOXYCARBONYL)ETHYLTHIO)METHYL]-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID

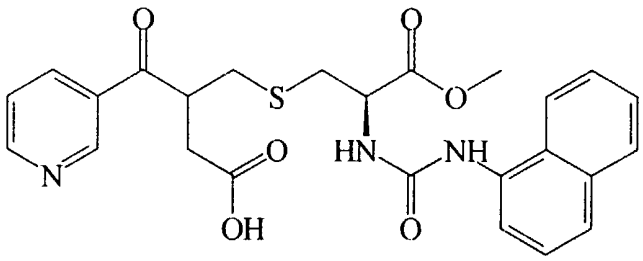


The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-

pyridyl)butanoic acid and 3,4,5-trimethoxyphenyl isocyanate as described in Example 16 in a 7.2% yield; ESMS, $(M+1)^+$ 536.

EXAMPLE 22

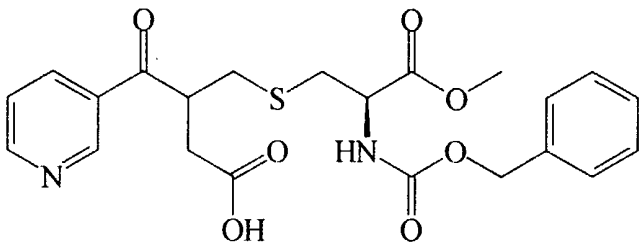
3-({(2R)-2-(METHOXYCARBONYL)-2-[(NAPHTHYLAMINO)CARBONYLAMINO]ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and 1-naphthyl isocyanate as described in Example 16 in a 12% yield; ESMS, $(M+1)^+$ 496.

EXAMPLE 23

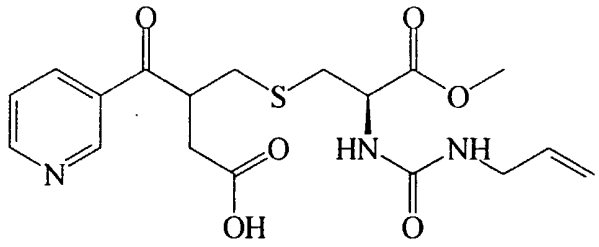
3-({(2R)-2-(METHOXYCARBONYL)-2-[(PHENYLMETHOXY)CARBONYLAMINO]ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and benzyl chloroformate as described in Example 16 at 12% yield; ESMS, $(M+1)^+$ 460.

EXAMPLE 24

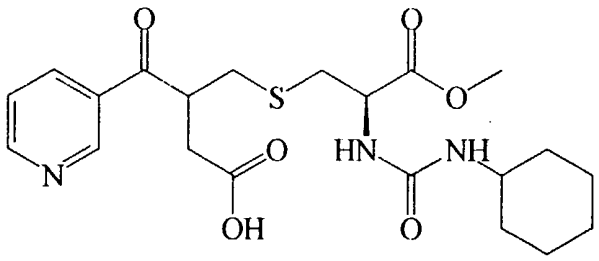
3-({(2R)-2-(METHOXYCARBONYL)-2-[(PROP-2-ENYLAMINO)CARBONYLAMINO]ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and allyl isocyanate as described in Example 23 to provide the desired compound in a 10.4% yield; ESMS, $(M+1)^+$ 410.

EXAMPLE 25

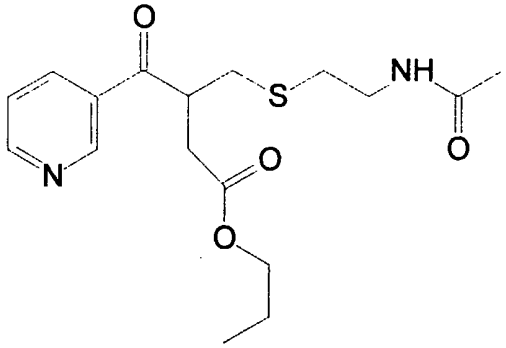
3({(2R)-2-[(CYCLOHEXYLAMINO)CARBONYLAMINO]-2-(METHOXYCARBONYL) ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOIC ACID



The title compound was prepared from 3-({(2R)-2-[(fluoren-9-ylmethoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid and cyclohexyl isocyanate as described in Example 16 in a 6% yield; ESMS, $(M+1)^+$ 452.

EXAMPLE 26

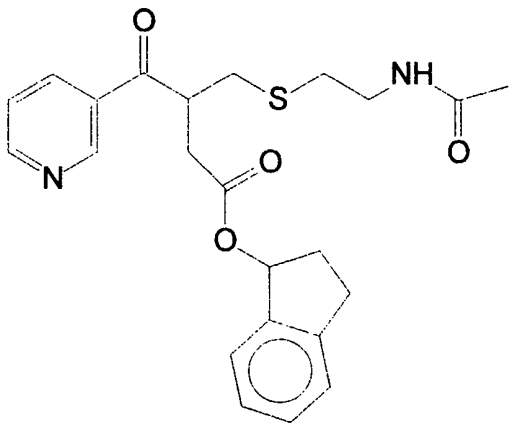
PROPYL 3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of 3-{[2-(acetylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid (0.1 g), 1[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (68.1 mg), n-propanol (1.0 eq) and 4-dimethylaminopyridine (0.1 eq) in dimethyl formamide (2 mL) was stirred for 24 h. The solution was purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 0.085 g (75%) of the title compound; ESMS $(M+1)^+$ 353.

EXAMPLE 27

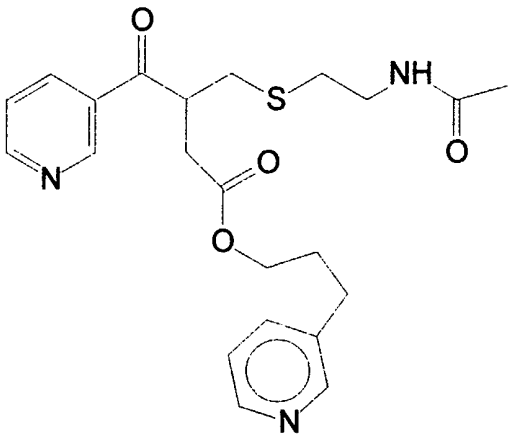
INDANYL 3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from 3-{[2-(acetylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid and indanol as described in the above Example 26 in 55% yield; ESMS ($M+1^+$) 427.

EXAMPLE 28

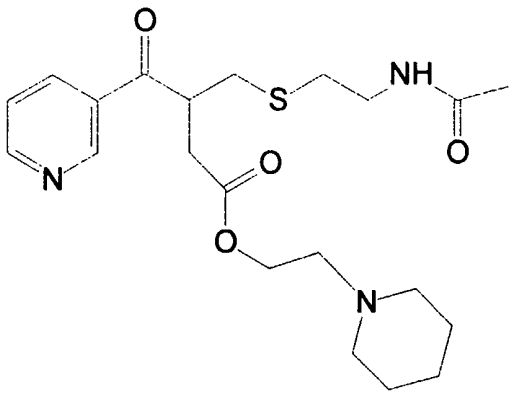
3-(3-PYRIDYL)PROPYL 3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from 3-{[2-(acetylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid and 3-(3-pyridyl)propan-1-ol as described in the above Example 26 in 65% yield; ESMS ($M+1^+$) 430.

EXAMPLE 29

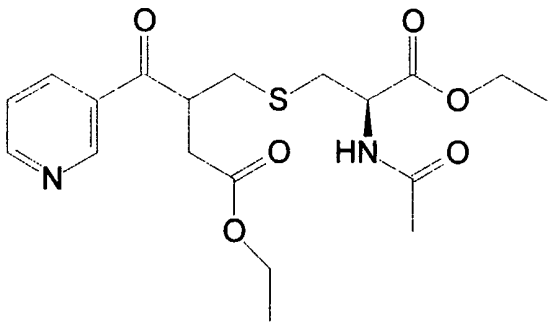
2-PIPERIDYLETHYL 3-{[2-(ACETYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from 3-{[2-(acetylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid and 3-(3-pyridyl)propan-1-ol as described in the above Example 26 in 35% yield; ESMS ($M+1^+$) 422.

EXAMPLE 30

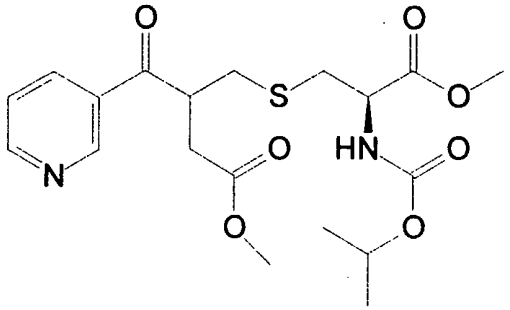
ETHYL 3-{[(2R)-2-(ACETHYLAMINO)-2-(ETHOXYCARBONYL)ETHYLTHIO]METHYL}-4-OXO-(3-PYRIDYL)BUTANOATE



A solution of ethyl 4-oxo-4-(3-pyridyl)butanoate (0.30 g), piperidine (0.15 g) and 37% aqueous formaldehyde (0.14 g) in ethanol (2 mL) was stirred at 90 °C for 2 h. A solution of ethyl (2R)-2(acetylamino)-3-sulfanylpropanoate (0.28 g) in ethanol (5 mL) was added to the reaction mixture and heated at 80 °C for 3 h. The reaction mixture was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 0.19 g of the title compound; ESMS $(M+1)^+$ 411.

EXAMPLE 31

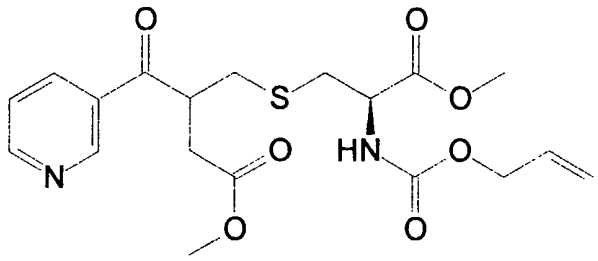
METHYL 3-({(2R)-2-(METHOXYCARBONYL)-2-[(METHYLETHOXY)CARBONYLAMINO]-ETHYLTHIO}METHYL-4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of 3-({(2R)-2-(methoxycarbonyl)-2-{(methylethoxy) carbonylamino]-ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid (15 mg), triethylamine (35 μL) and trimethylsilyl diazomethane (10 eq) in dichloromethane (1 mL) and dimethyl formamide (1 mL) was stirred at room temperature overnight. The reaction mixture was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 6.7 mg of the title compound; ESMS $(M+1)^+$ 427.

EXAMPLE 32

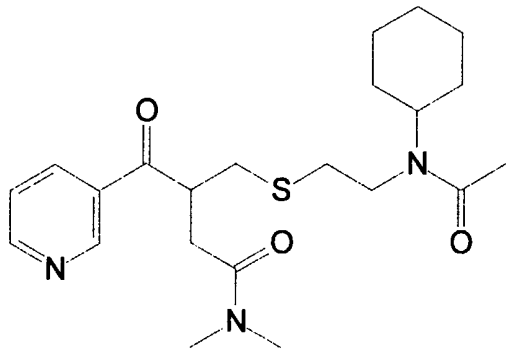
METHYL 3-({(2R)-2-(METHOXYCARBONYL)-2-[(PROP-2-ENYLOXYCARBONYLAMINO]-ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from 3{[2-(butylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid and trimethylsilyl diazomethane as described in the above Example 31 in 55% yield; ESMS ($M+1^+$) 425.

EXAMPLE 33

3-{[2-(N-CYCLOHEXYLACETYLAMINO)ETHYLTHIO]METHYL}-N,N-DIMETHYL-4-OXO--4-(3-PYRIDYL)BUTANAMIDE

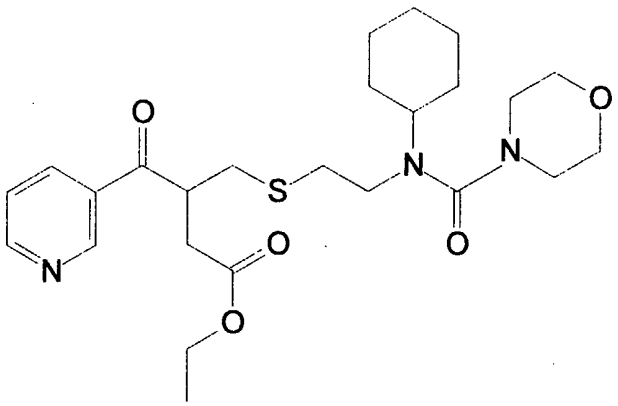


Triethylamine (14.7 μL) was added to a solution of 3-{[2-(N-cyclohexylacetylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid (44.6 mg) in dichloromethane (1.1 mL) and stirred for 30 min. The solution was cooled to 0 °C and ethyl chloroformate (10.5 μL) was added and stirred for 10 minutes. Dimethylamine in tetrahydrofuran (2M, 53 μL) was added and stirred at room temperature overnight. The

solution was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetronitrile in water both containing 0.1% TFA) to give 6.8 mg of the title compound; ESMS $(M+1)^+$ 420.

EXAMPLE 34

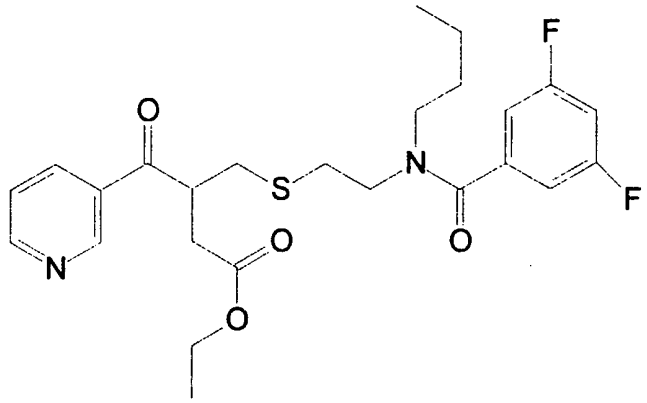
ETHYL 3-{[2-(N-CYCLOHEXYLMORPHOLIN-4-YLCARBONYLAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of ethy 3-{[2-(cyclohexylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoate (47.2 mg) and triethylamine (17.4 μL) in dichloromethane (1.3 mL) was treated with morpholine-4-carbony chloride (14.9 μL) at room temperature for 1 h. The solution was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 11 mg of the tile compound; ESMS $(M+1)^+$ 492.

EXAMPLE 35

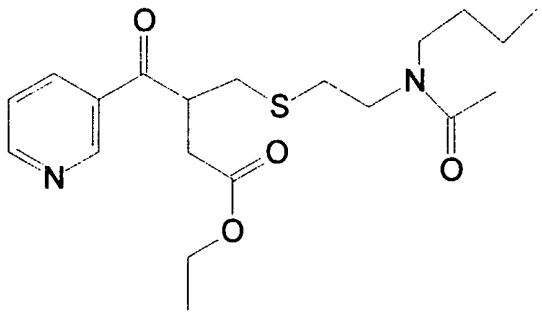
ETHYL 3-({2-[3,5-DIFLUOROPHENYL)-N-BUTYLCARBONYLAMINO]ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOATE



A solution of ethyl 3{[2-(butylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoate (100 mg), 3,5-difluorobenzoyl chloride (50 mg) and triethylamine (28 mg) in dichloromethane (3 mL) was stirred at room temperature overnight. The solution was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 57 mg of the title compound; ESMS $(M+1)^+$ 493.

EXAMPLE 36

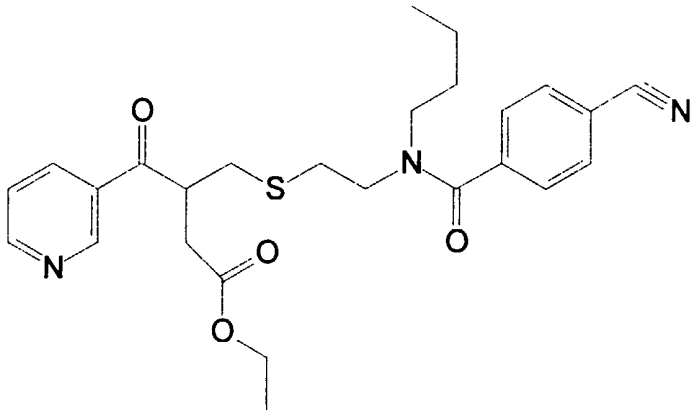
ETHYL 3-{[2-N-BUTYLACETAMINO)ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from ethyl 3{[2-(butylamino) ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoate and acetyl chloride as described in the above Example 35 in 49% yield; ESMS ($M+1^+$) 395.

EXAMPLE 37

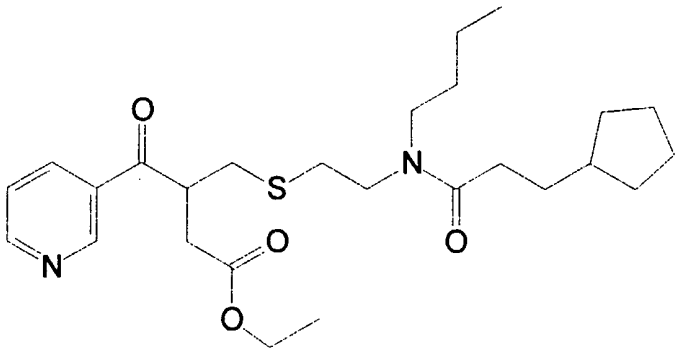
ETHYL 3-({2-[N-BUTYL(4-CYANOPHENYL) CARBONYLAMINO]ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from ethyl 3{[2-butylamino) ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoate and 4-cyano benzoyl chloride as described in the above Example 35 in 38% yield; ESMS ($M+1^+$) 482.

EXAMPLE 38

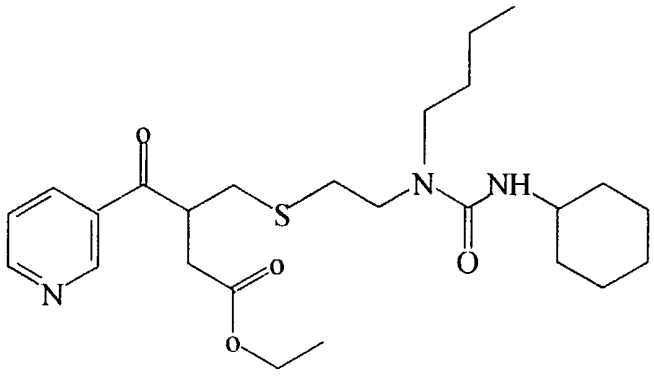
ETHYL 3-{[2-(N-BUTYL-3-CYCLOPENTYLPROPANOYLAMINO) ETHYLTHIO]METHYL}-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from ethyl 3{[2-(butylamino)ethylthio] methyl}-4-oxo-4-(3-pyridyl)butanoate and cyclopentylpropionyl chloride as described in the above Example 35 in 35% yield; ESMS ($M+1^+$) 477.

EXAMPLE 39

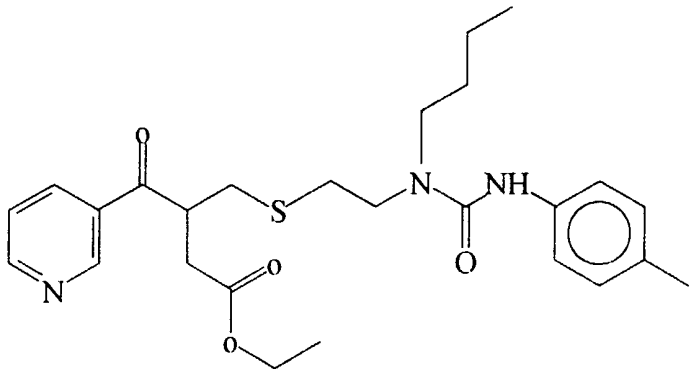
ETHYL 3-({2-[N-BUTYL(CYCLOHEXYLAMINO)CARBONYLAMINO] ETHYLTHIO}METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from ethyl 3{[2-(butylamino)ethylthio] methyl}-4-oxo-4-(3-pyridyl)butanoate and cyclohexylisocyanate as described in the above Example 35 in 48% yield; ESMS ($M+1^+$) 478.

EXAMPLE 40

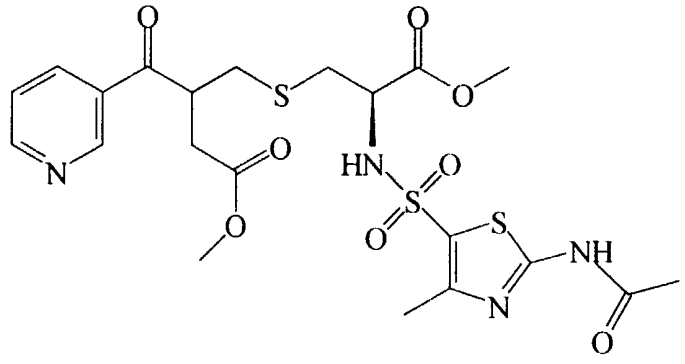
ETHYL 3-[(2-{N-BUTYL(4-METHYLPHENYL)AMINO]CARBONYLAMINO}
ETHYLTHIO)METHYL)-4-OXO-4-(3-PYRIDYL)BUTANOATE



The title compound was prepared from ethyl 3{[2-(butylamino)ethylthio] methyl}-4-oxo-4-(3-pyridyl)butanoate and 4-methylphenyl isocyanate as described in the above Example 35 in 48% yield; ESMS ($M+1^+$) 486.

EXAMPLE 41

METHYL 3-{[(2R)-2-({[2-(ACETYLAMINO)-4-METHYL(1,3-THIAZOL-5-
YL)]SULFONYL}AMINO-2-(METHOXYCARBONYL)ETHYLTHIO]METHYL}-4-OXO-4-(3-
PYRIDYL)BUTANOATE

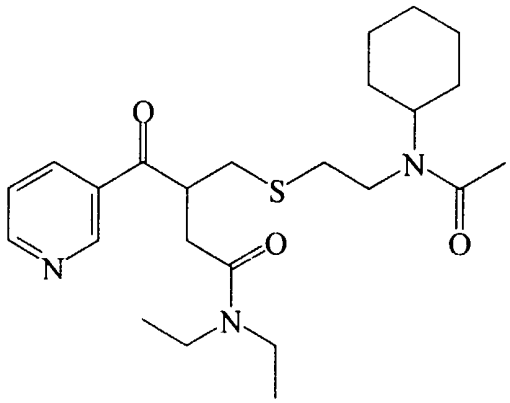


A solution of methyl 3-{[(2R)-2-amino-2-(methoxycarbonyl)ethylthio] methyl}-4-oxo-4-(3-pyridyl)butanoate hydrochloride (20.7 mg), N-[5-(chlorosulfonyl)-4-

methyl-1,3-thiazol-2-yl]acetamide (1.5 eq) and triethylamine (1.5 eq) in dichloromethane (1 mL) was stirred at room temperature overnight. The solution was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 19.1 mg of the title compound; ESMS $(M+1)^+$ 559.

EXAMPLE 42

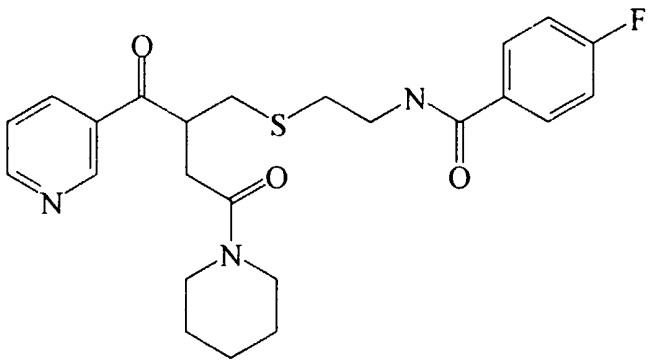
3-{[(2-(N-CYCLOHEXYLACETYLAMINO)ETHYLTHIO]METHYL}N,N-DIETHYL-4-OXO-4-4(3-PYRIDYL)BUTANAMIDE



A solution of 3-{[(2-(N-cyclohexylacetylamino)ethylthio]methyl}-4-oxo-4-(3-pyridyl)butanoic acid (49 mg), triethylamine (13 mg), ethyl chloroformate (14 mg) in dichloromethane (1 mL) were stirred at room temperature under anhydrous conditions for 15 min. Diethylamine (9 mg) was added and the reaction mixture was stirred overnight. The solution was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 49 mg of the title compound; ESMS $(M+1)^+$ 448.

EXAMPLE 43

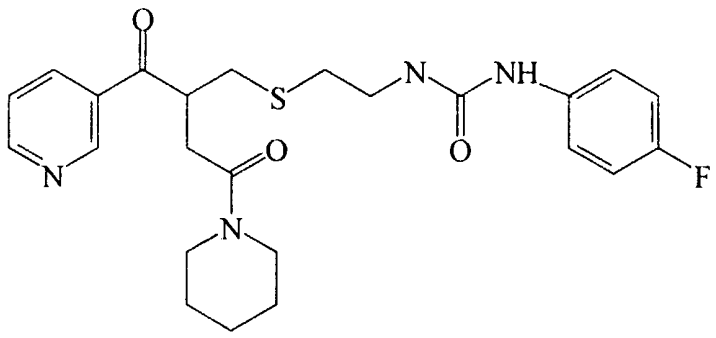
(4-FLUOROPHENYL)-N-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)BUTYLTHIO]ETHYL}CARBOXAMIDE



A solution of ethyl 3-({2-[(4-fluorophenyl)carbonylamino]ethylthio} methyl)-4-oxo-4-(3-pyridyl)butanoate (100 mg) and lithium hydroxide (1 eq) was stirred at room temperature in ethanol-water (1:1, 2 mL) till the starting material disappeared. The solution was acidified and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 91 mg of 3-({2-[(4-fluorophenyl)carbonylamino]ethylthio}methyl)-4-oxo-4-(3-pyridyl)butanoic acid. The acid (91 mg) was treated with ethyl chloroformate (1.1 eq) and triethylamine (1.1 eq) in tetrahydrofuran (2.5 mL) at room temperature for 10 minutes. Piperidine (1.1 eq) was added to the reaction mixture and stirred at room temperature overnight. The solution was concentrated and purified on preparative HPLC (C-18 prep column, 10% to 90% acetonitrile in water both containing 0.1% TFA) to give 66 mg of the title compound; ESMS $(M+1)^+$ 458.

EXAMPLE 44

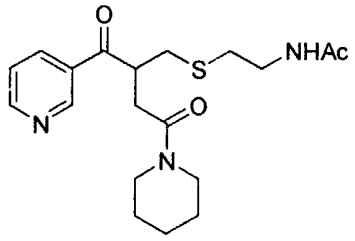
[(4-FLUOROPHENYL)-AMINO]-N-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)BUTYLTHIO]ETHYL}CARBOXAMIDE



The title compound was prepared from ethyl 3-[({2-{[(4-fluorophenyl)amino] carbonylamino}ethylthio)methyl]-4-oxo-4-(3-pyridyl)butanoate and piperidine as described in the above Example 43 in 29% yield; ESMS ($M+1^+$) 473.

EXAMPLE 45

4-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)-BUTYLTHIO]ETHYL}- ACETAMIDE IN PURE CRISTAL FORM



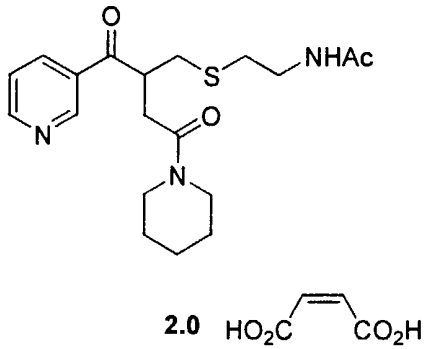
in pure crystal form

Piperidine (41.0 ml), 1-hydroxybenzotriazole hydrate (55.7 g, 0.41 mol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (79.0 g, 0.41 mol) were added to a mixture of 3-{[2-(acetylamino)ethylthio]}methyl-4-oxo-4-(3-pyridyl)butanoic acid (116.3 g, 0.37 mol) in tetrahydrofuran (1500 ml) at room temperature. After being

stirred for 2 h, the reaction mixture was filtered by Celite and the filtrate was evaporated. The residue was poured into H_2O (900 ml) and extracted with AcOEt (700 ml) three times. After the organic layer was washed with sat. $NaHCO_3$ (900 ml), the solvent was dried over $MgSO_4$ and evaporated to give the title compound (118.7 g, 85%) as a yellow oil. The crude yellow oil (79.6 g, 0.21 mol) was dissolved with AcOEt (350 ml) and the mixture was stirred vigorously at room temperature. After being stirred for 12 h, separated crystals were collected. The crystals were recrystallized from AcOEt (350 ml) to give the title compound (67.1 g, 84%) as an off white solid of mp 86-90°C. Anal. Calcd for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21; N, 11.13. Found : C, 60.36; H, 7.02; N, 11.08. ^{1}H-NMR(CD_3OD) ppm: 1.42-1.52 (2H, m), 1.56-1.70 (4H, m), 1.90 (3H, s), 2.60 (2H, t, J=7 Hz), 2.73 (1H, dd, J=7 and 13 Hz), 2.81-2.91 (2H, m), 3.08 (1H, dd, J=10 and 16 Hz), 3.26-3.32 (2H, m), 3.41 (2H, t, J=5 Hz), 3.46-3.53 (2H, m), 4.16 (1H, m), 7.58 (1H, ddd, J=1, 5 and 8 Hz), 8.44 (1H, dt, J=2 and 8 Hz), 8.73 (1H, dd, J=2 and 5 Hz), 9.15 (1H, dd, J=1 and 2 Hz).

EXAMPLE 46

4-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)-BUTYLTHIO]ETHYL}-ACETAMIDE 2 MALEATE

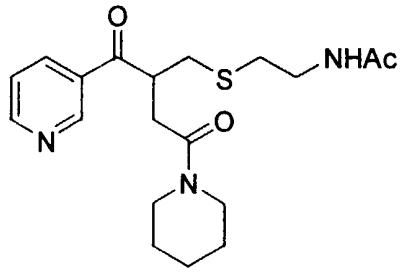


A solution of maleic acid (88.7 g, 0.765 mol) in acetone (700 ml) was added to a solution of 4-{2-[4-oxo-4-piperidyl-2-(3-pyridylcarbonyl)-butylthio]ethyl}-acetamide (96.2 g, 0.255 mol) in acetone (600 ml) at room temperature. After the mixture was stood for overnight, the crystals were collected to give the title compound (142.5 g, 92%) as a

white solid of mp 115-117°C. Anal. Calcd for $C_{23}H_{31}N_3O_7S$: C, 53.19; H, 5.79; N, 6.89. Found : C, 53.17; H, 5.63; N, 6.89. ^{1}H-NMR(CD_3OD) ppm: 1.42-1.51 (2H, m), 1.56-1.70 (4H, m), 1.90 (3H, s), 2.60 (2H, t, J=7 Hz), 2.75 (1H, dd, J=7 and 13 Hz), 2.81-2.94 (2H, m), 3.10 (1H, dd, J=10 and 16 Hz), 3.25-3.32 (2H, m), 3.41 (2H, t, J=5 Hz), 3.47-3.53 (2H, m), 4.17 (1H, m), 6.31 (4H, s), 7.73 (1H, ddd, J=1, 5 and 8 Hz), 8.58 (1H, dt, J=2 and 8 Hz), 8.78 (1H, dd, J=2 and 5 Hz), 9.21 (1H, dd, J=1 and 2 Hz).

EXAMPLE 47

4-{2-[4-Oxo-4-Piperidyl-2-(3-Pyridylcarbonyl)-Butylthio]Ethyl}-Acetamide 1.5 Maleate

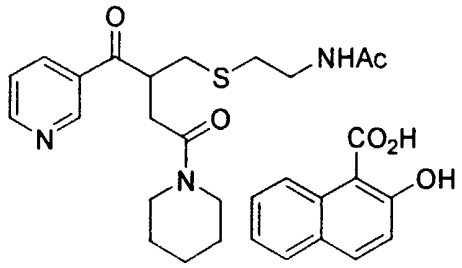


1.5 HO_2C CO_2H

A solution of maleic acid (116 mg, 1 mmol) in acetone (2 ml) was added to a solution of 4-{2-[4-oxo-4-piperidyl-2-(3-pyridylcarbonyl)-butylthio]ethyl}-acetamide (377 mg, 1 mmol) in acetone (2 ml) at room temperature. After the mixture was stood for overnight, the crystals were collected to give the title compound (208 mg, 61%) as a white solid of mp 113-115° C. Anal. Calcd for $C_{50}H_{66}N_6O_{18}S_2$: C, 54.44; H, 6.03; N, 7.62. Found : C, 54.18; H, 5.97; N, 7.54. ^{1}H-NMR(CD_3OD) ppm: 1.42-1.51 (2H, m), 1.56-1.70 (4H, m), 1.90 (3H, s), 2.60 (2H, t, J=7 Hz), 2.74 (1H, dd, J=7 and 13 Hz), 2.81-2.94 (2H, m), 3.10 (1H, dd, J=10 and 16 Hz), 3.25-3.34 (2H, m), 3.41 (2H, t, J=6 Hz), 3.47-3.54 (2H, m), 4.17 (1H, m), 6.31 (3H, s), 7.69 (1H, ddd, J=1, 5 and 8 Hz), 8.58 (1H, dt, J=2 and 8 Hz), 8.78 (1H, dd, J=2 and 5 Hz), 9.21 (1H, dd, J=1 and 2 Hz).

EXAMPLE 48

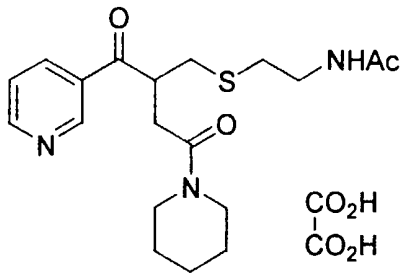
4-{2-[4-Oxo-4-Piperidyl-2-(3-Pyridylcarbonyl)-Butylthio]Ethyl}-Acetamide 2-Hydroxy-1-Naphthoate



2-Hydroxy-1-naphthoic acid (376 mg, 2 mmol) was added to a solution of 4-{2-[4-oxo-4-piperidyl-2-(3-pyridylcarbonyl)-butylthio]ethyl}-acetamide (754 mg, 2 mmol) in EtOH (2 ml) at room temperature. After the mixture was stood for overnight, the crystals were collected and recrystallized from (acetone-hexane) to give the title compound (896 mg, 79%) as a white solid of mp 105-107°C. Anal. Calcd for $C_{30}H_{35}N_3O_6S$: C, 63.70; H, 6.24; N,7.43. Found : C, 63.40; H, 6.06; N, 7.33. ^{1}H-NMR(CD_3OD) ppm: 1.42-1.52 (2H, m), 1.56-1.70 (4H, m), 1.90 (3H, s), 2.60 (2H, t, J=7 Hz), 2.72 (1H, dd, J=7 and 13 Hz), 2.80-2.91 (2H, m), 3.09 (1H, dd, J=10 and 16 Hz), 3.27-3.33 (2H, m), 3.41 (2H, t, J=5 Hz), 3.46-3.53 (2H, m), 4.16 (1H, m), 7.12 (1H, d, J=9 Hz), 7.32 (1H, m), 7.53 (1H, m), 7.59 (1H, ddd, J=1, 5 and 8 Hz), 7.78 (1H, d, J=8 Hz), 7.94 (1H, d, J=9 Hz), 8.12 (1H, br s), 8.45 (1H, dt, J=2 and 8 Hz), 8.73 (1H, dd, J=2 and 5 Hz), 8.88 (1H, d, J=9 Hz), 9.15 (1H, d, J=2 Hz).

EXAMPLE 49

4-{2-[4-OXO-4-PIPERIDYL-2-(3-PYRIDYLCARBONYL)-BUTYLTHIO]ETHYL}-ACETAMIDE OXALATE



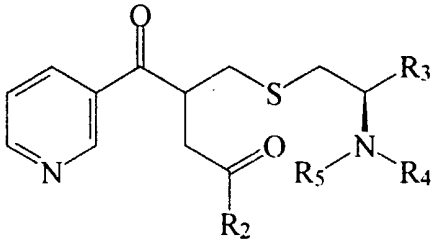
A solution of oxalic acid (87 mg, 0.97 mmol) in acetone (1 ml) was added to a solution of 4-{2-[4-oxo-4-piperidyl-2-(3-pyridylcarbonyl)-butylthio]ethyl}-acetamide (366 mg, 0.97 mmol) in acetone (2 ml) at room temperature. After the mixture was stood for overnight, the crystals were collected to give the title compound (345 mg, 74%) as a white solid of mp 129-130°C. Anal. Calcd for $C_{21}H_{29}N_3O_7S$: C, 53.95; H, 6.25; N, 8.99. Found: C, 53.97; H, 6.34; N, 8.88. ^{1}H-NMR(CD_3OD) ppm: 1.42-1.52 (2H, m), 1.56-1.70 (4H, m), 1.90 (3H, s), 2.60 (2H, t, J=7 Hz), 2.73 (1H, dd, J=7 and 13 Hz), 2.81-2.93 (2H, m), 3.08 (1H, dd, J=10 and 16 Hz), 3.26-3.33 (2H, m), 3.42 (2H, t, J=5 Hz), 3.46-3.53 (2H, m), 4.16 (1H, m), 7.67 (1H, ddd, J=1, 5 and 8 Hz), 8.54 (1H, dt, J=2 and 8 Hz), 8.78 (1H, dd, J=2 and 5 Hz), 9.20 (1H, dd, J=1 and 2 Hz).

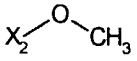
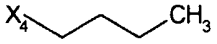
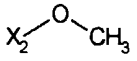
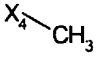
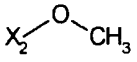
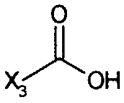
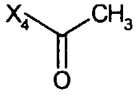
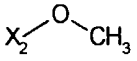
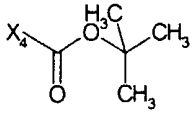
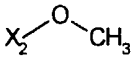
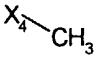
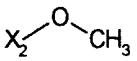
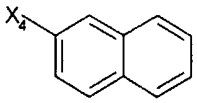
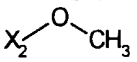
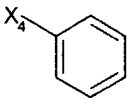
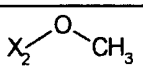
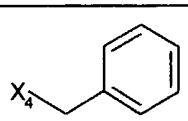
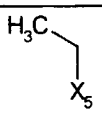
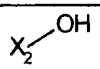
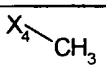
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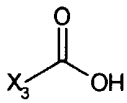
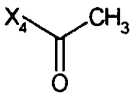
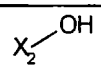
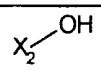
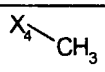
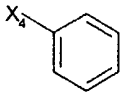
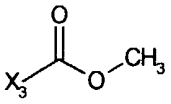
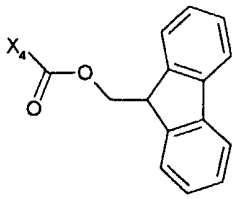
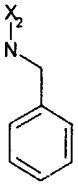
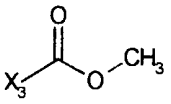
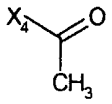
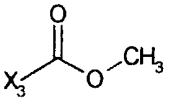
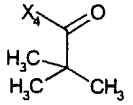
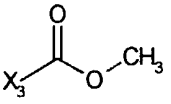
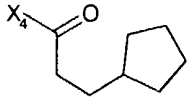
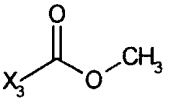
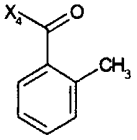
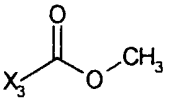
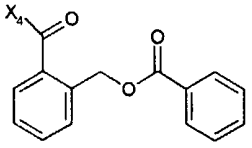
REPRESENTATIVE COMPOUNDS

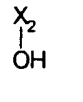
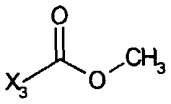
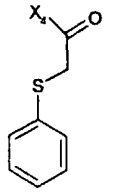
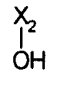
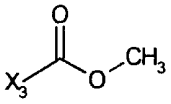
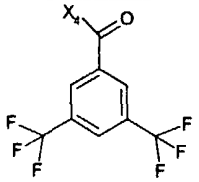
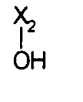
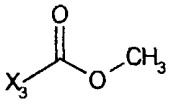
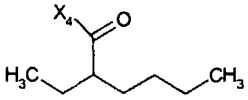
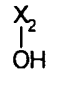
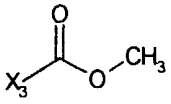
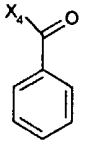
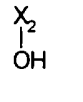
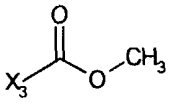
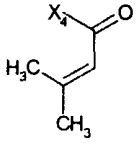
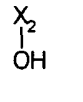
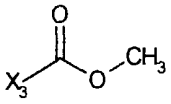
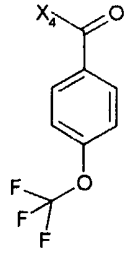
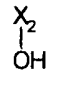
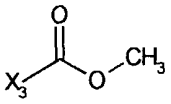
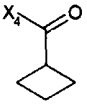
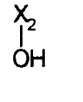
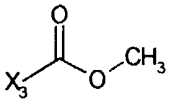
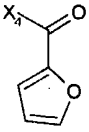
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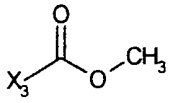
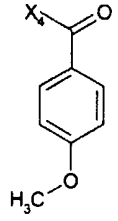
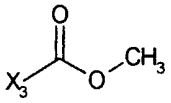
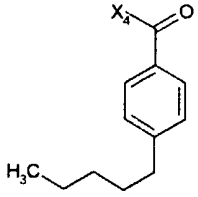
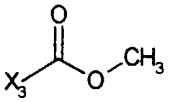
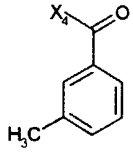
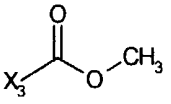
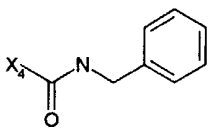
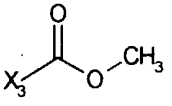
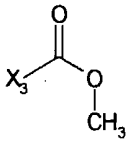
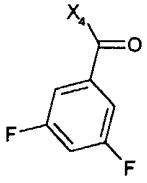
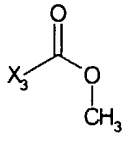
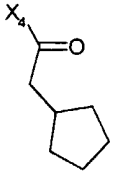
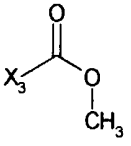
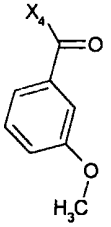
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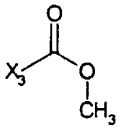
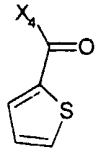
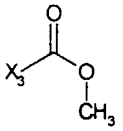
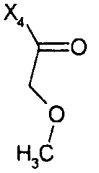
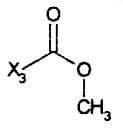
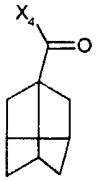
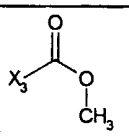
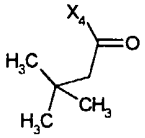
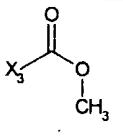
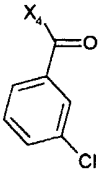
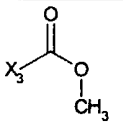
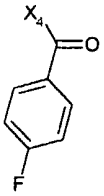
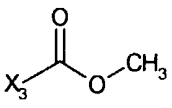
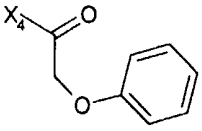
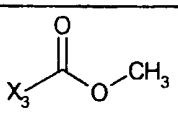
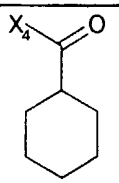


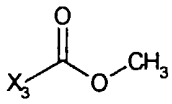
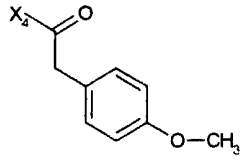
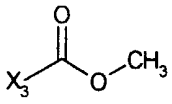
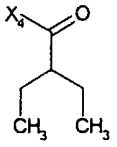
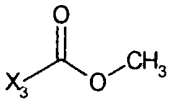
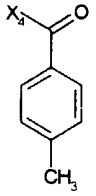
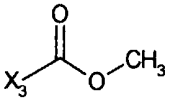
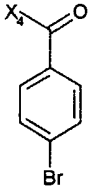
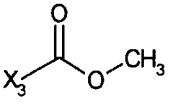
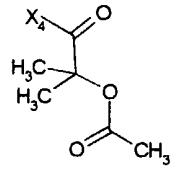
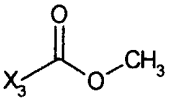
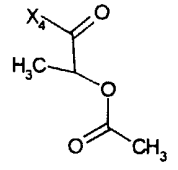
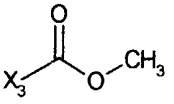
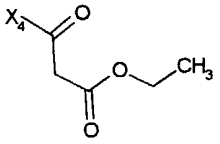
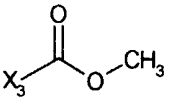
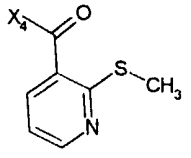
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2		H			310
3				H	368
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5				H	310
6				H	423
7				H	372
8		H			401
9		H			296

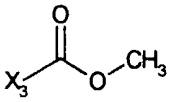
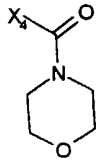
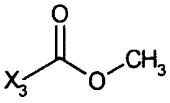
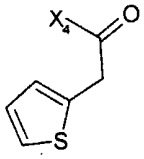
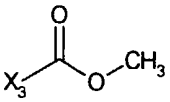
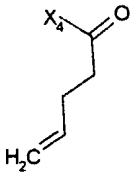
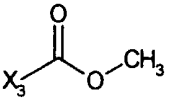
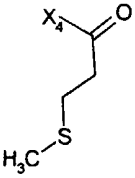
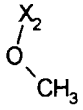
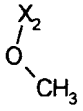
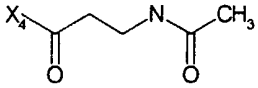
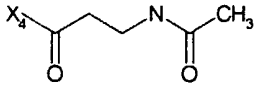
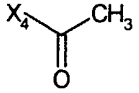
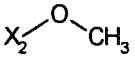
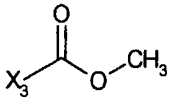
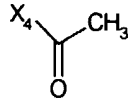
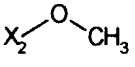
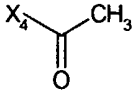
No.	R_2	R_3	R_4	R_5	MW (M^+)
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11		H	H	H	268
12				H	296
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19				H	565

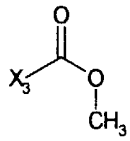
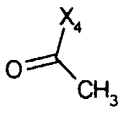
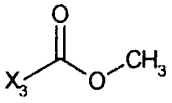
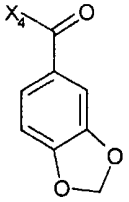
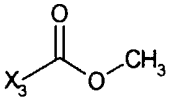
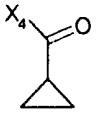
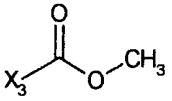
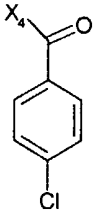
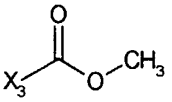
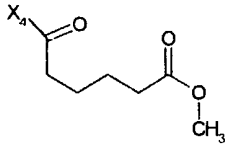
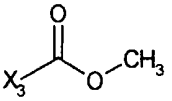
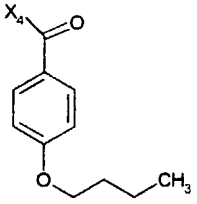
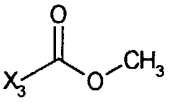
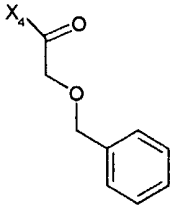
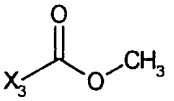
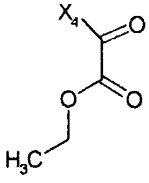
No.	R_2	R_3	R_4	R_5	MW (M^+)
20				H	477
21				H	566
22				H	453
23				H	430
24				H	408
25				H	514
26				H	408
27				H	420

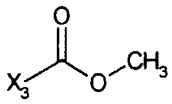
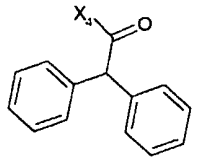
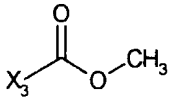
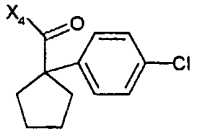
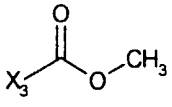
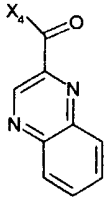
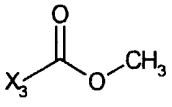
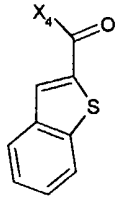
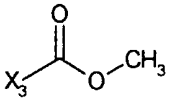
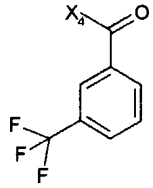
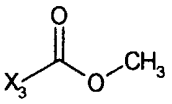
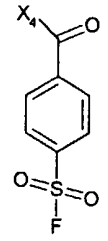
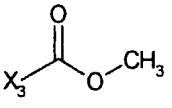
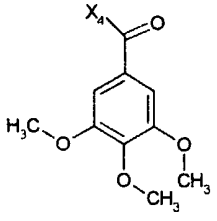
No.	R_2	R_3	R_4	R_5	MW (M^+)
28				H	461
29				H	501
30				H	445
31				H	460
32			H	H	326
33				H	466
34				H	437
35				H	461

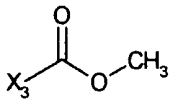
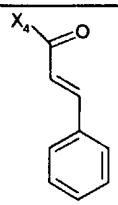
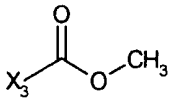
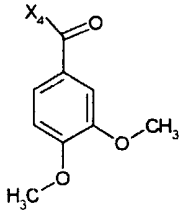
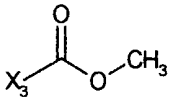
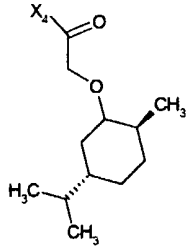
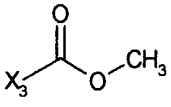
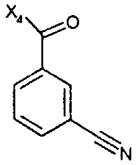
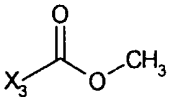
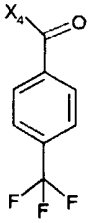
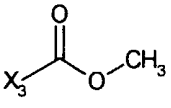
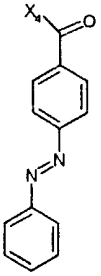
No.	R_2	R_3	R_4	R_5	MW (M^+)
36				H	437
37				H	398
38				H	489
39				H	425
40				H	465
41				H	448
42				H	461
43				H	437

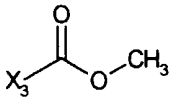
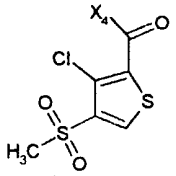
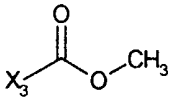
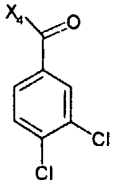
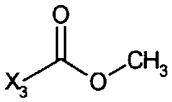
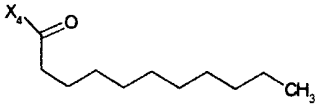
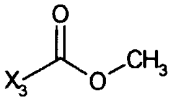
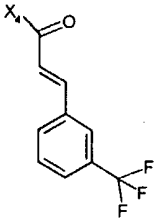
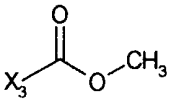
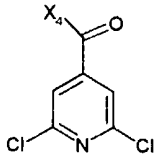
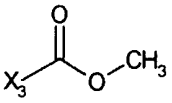
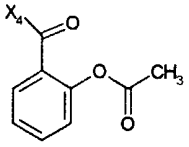
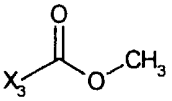
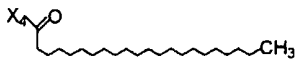
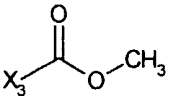
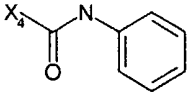
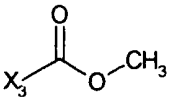
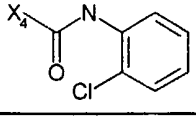
No.	R_2	R_3	R_4	R_5	MW (M^+)
44				H	475
45				H	425
46				H	445
47				H	509
48				H	454
49				H	440
50				H	440
51				H	478

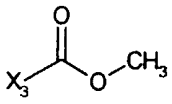
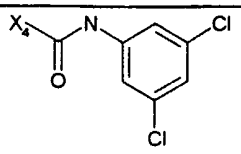
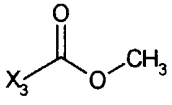
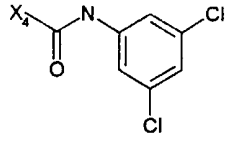
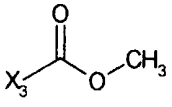
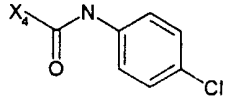
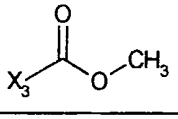
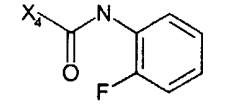
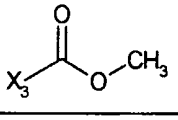
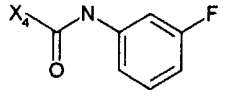
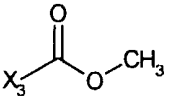
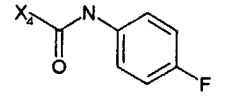
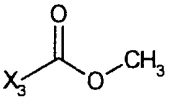
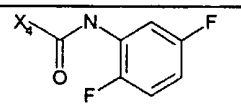
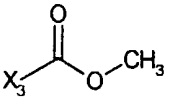
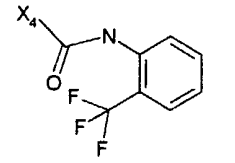
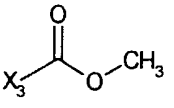
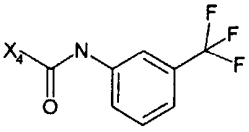
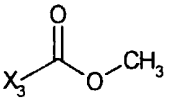
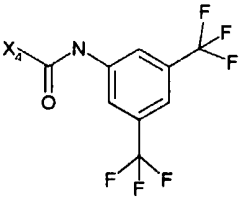
No.	R_2	R_3	R_4	R_5	MW (M^+)
52				H	439
53				H	451
54				H	408
55				H	429
56		H	H	H	282
57		H		H	395
58		H		H	381
59		H		H	310
60				H	382
61		H		H	324

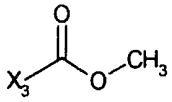
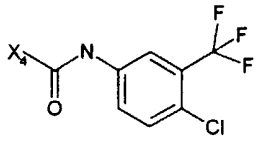
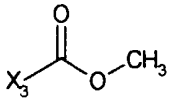
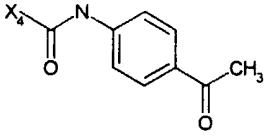
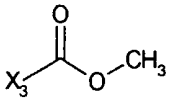
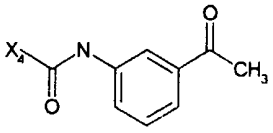
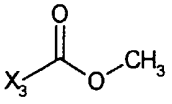
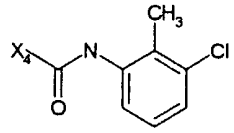
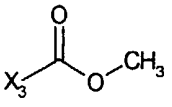
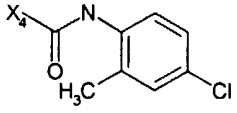
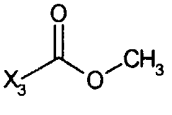
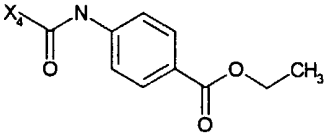
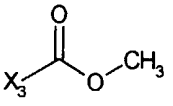
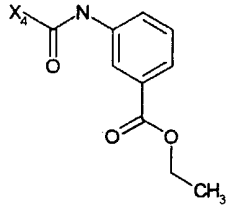
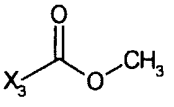
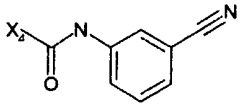
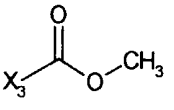
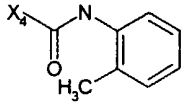
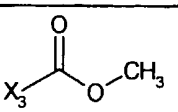
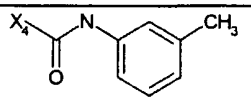
No.	R_2	R_3	R_4	R_5	MW (M^+)
62				H	368
63				H	474
64				H	394
65				H	465
66				H	469
67				H	503
68				H	475
69				H	426

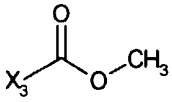
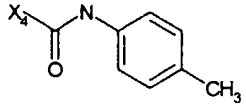
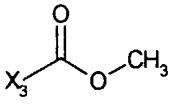
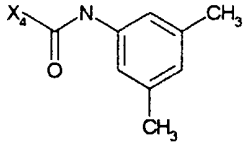
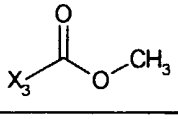
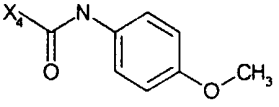
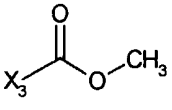
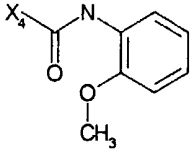
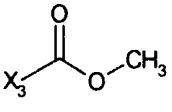
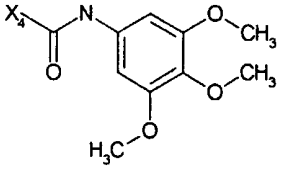
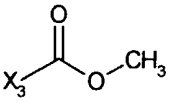
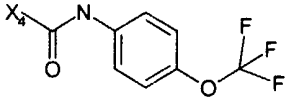
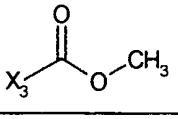
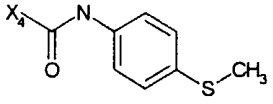
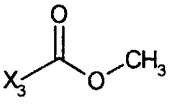
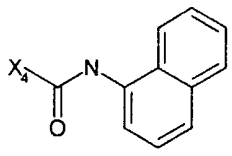
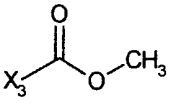
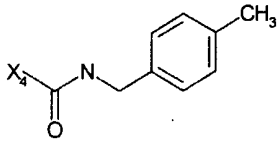
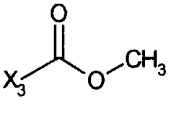
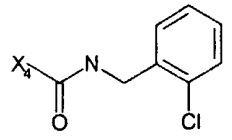
No.	R_2	R_3	R_4	R_5	MW (M^+)
70				H	521
71				H	533
72				H	483
73				H	487
74				H	498
75				H	513
76				H	521

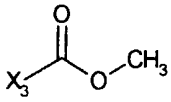
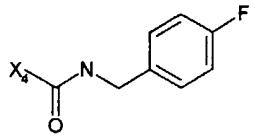
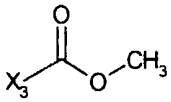
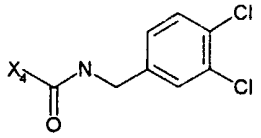
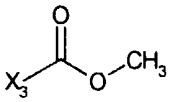
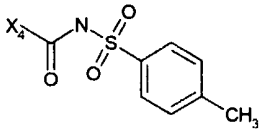
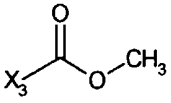
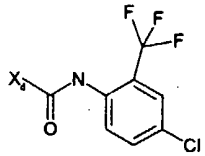
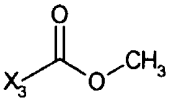
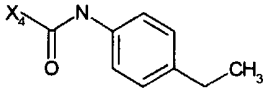
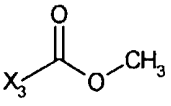
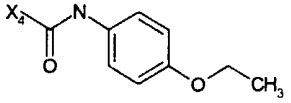
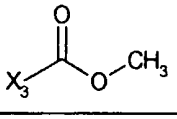
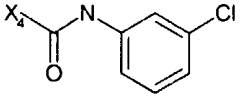
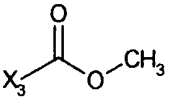
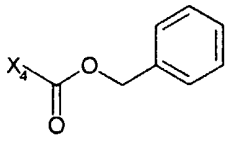
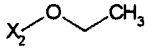
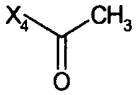
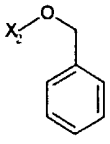
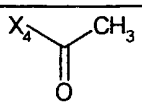
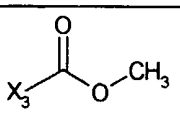
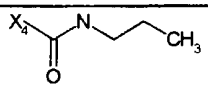
No.	R_2	R_3	R_4	R_5	MW (M^+)
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78				H	491
79				H	523
80				H	455
81				H	498
82				H	535

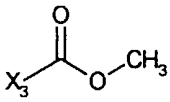
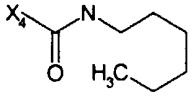
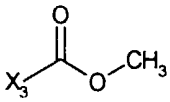
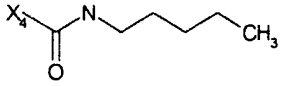
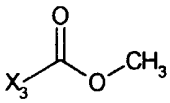
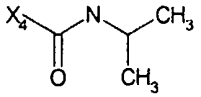
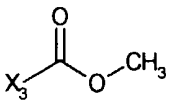
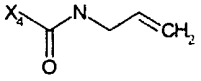
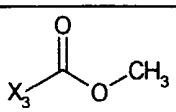
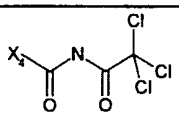
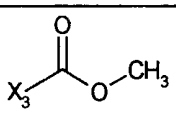
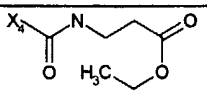
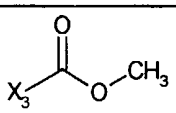
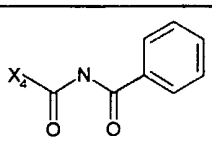
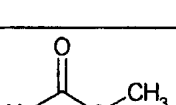
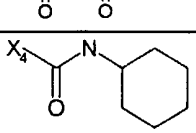
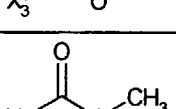
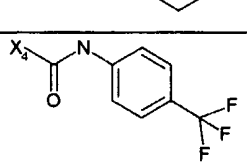
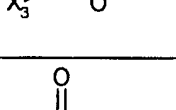
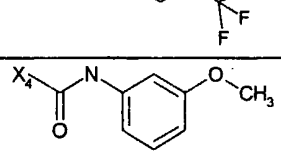
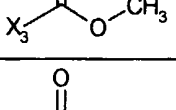
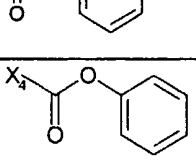
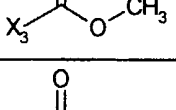
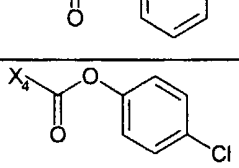
No.	R_2	R_3	R_4	R_5	MW (M^+)
83				H	549
84				H	499
85				H	495
86				H	525
87				H	500
88				H	489
89				H	649
90				H	445
91				H	480

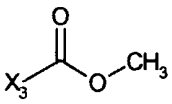
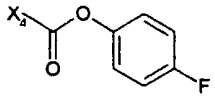
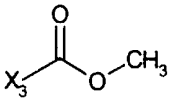
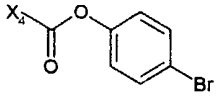
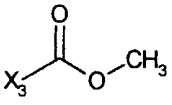
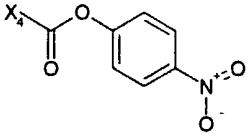
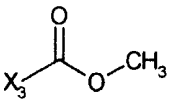
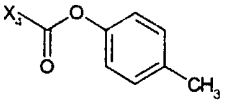
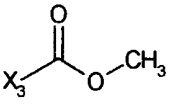
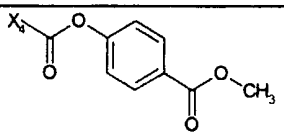
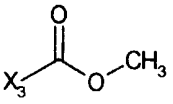
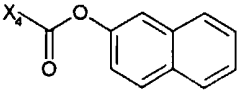
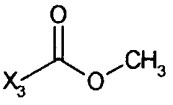
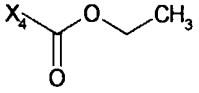
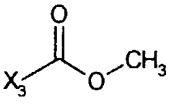
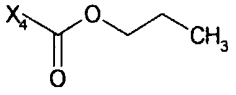
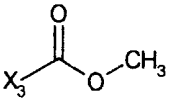
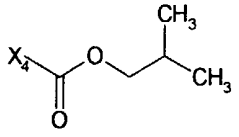
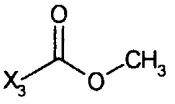
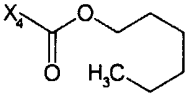
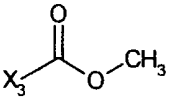
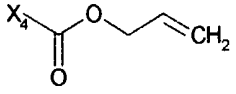
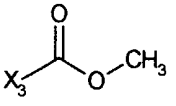
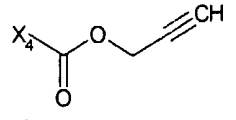
No.	R_2	R_3	R_4	R_5	MW (M^+)
92				H	514
93				H	514
94				H	480
95				H	463
96				H	463
97				H	463
98				H	481
99				H	513
100				H	513
101				H	581

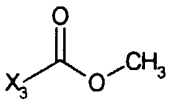
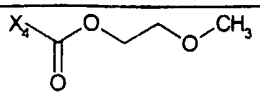
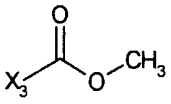
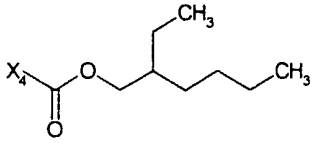
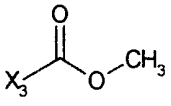
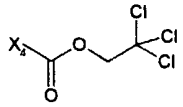
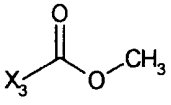
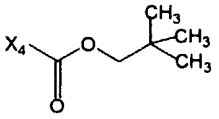
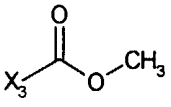
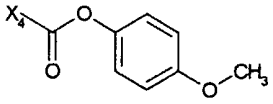
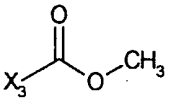
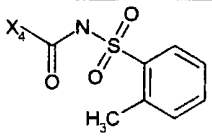
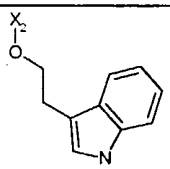
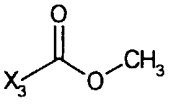
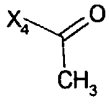
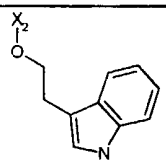
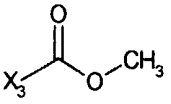
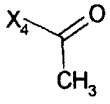
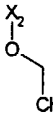
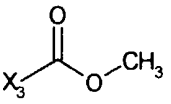
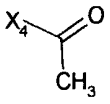
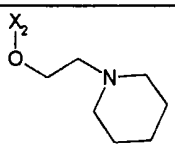
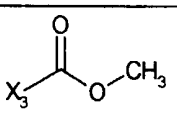
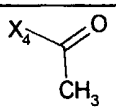
No.	R_2	R_3	R_4	R_5	MW (M^+)
102				H	548
103				H	488
104				H	488
105				H	494
106				H	494
107				H	518
108				H	518
109				H	471
110				H	460
111				H	460

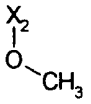
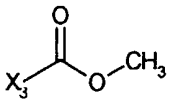
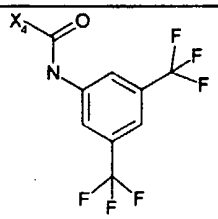
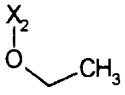
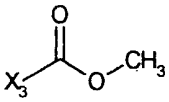
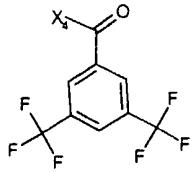
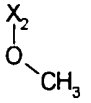
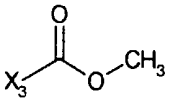
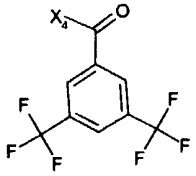
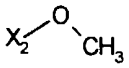
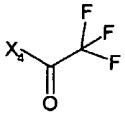
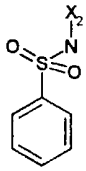
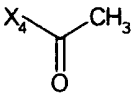
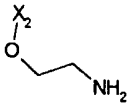
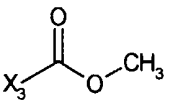
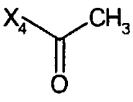
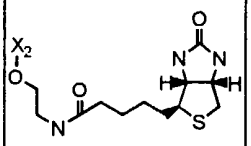
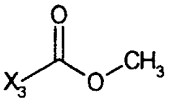
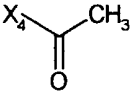
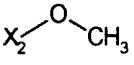
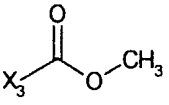
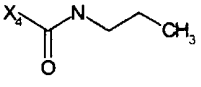
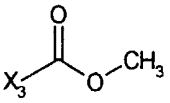
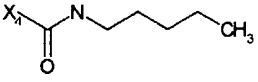
No.	R_2	R_3	R_4	R_5	MW (M^+)
112				H	460
113				H	474
114				H	476
115				H	476
116				H	536
117				H	529
118				H	492
119				H	496
120				H	474
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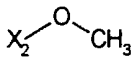
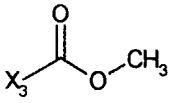
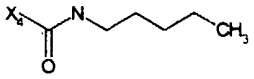
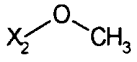
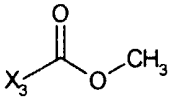
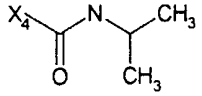
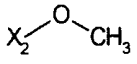
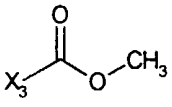
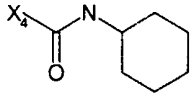
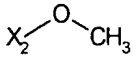
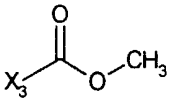
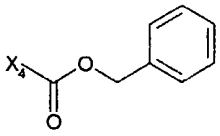
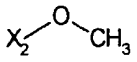
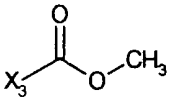
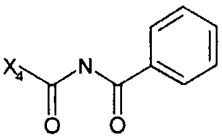
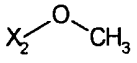
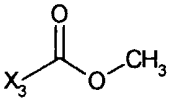
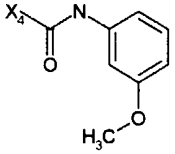
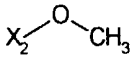
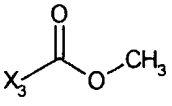
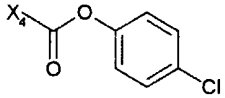
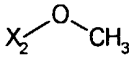
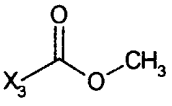
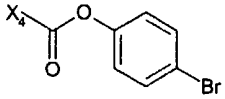
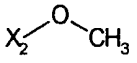
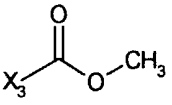
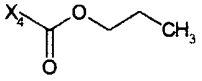
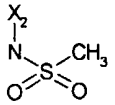
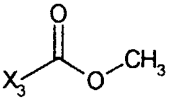
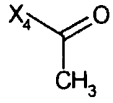
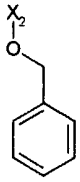
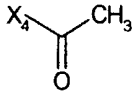
No.	R_2	R_3	R_4	R_5	MW (M^+)
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123				H	528
124				H	524
125				H	548
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129				H	461
130		H		H	338
131		H		H	400
132				H	411

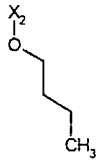
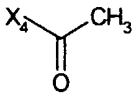
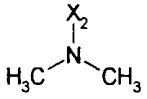
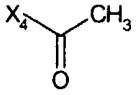
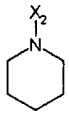
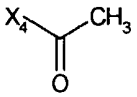
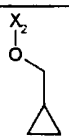
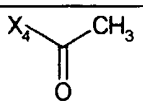
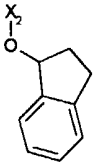
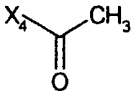
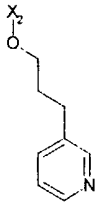
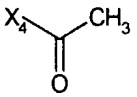
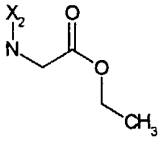
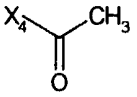
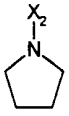
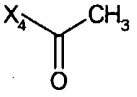
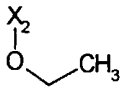
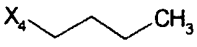
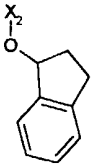
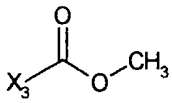
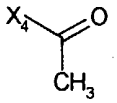
No.	R_2	R_3	R_4	R_5	MW (M^+)
133				H	454
134				H	440
135				H	411
136				H	409
137				H	515
138				H	470
139				H	474
140				H	452
141				H	513
142				H	476
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144				H	481

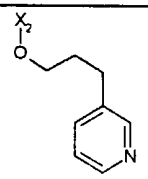
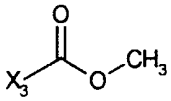
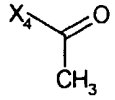
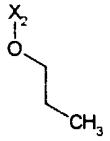
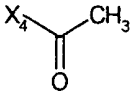
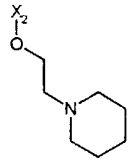
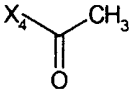
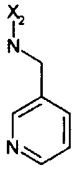
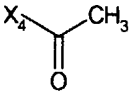
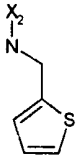
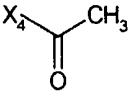
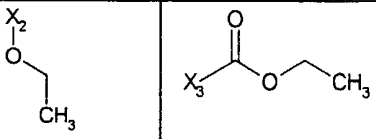
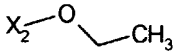
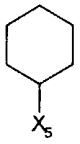
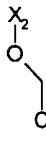
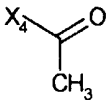
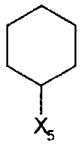
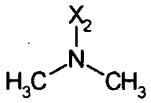
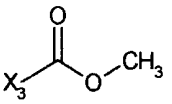
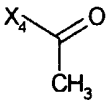
No.	R_2	R_3	R_4	R_5	MW (M^+)
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146				H	525
147				H	491
148				H	461
149				H	505
150				H	497
151				H	398
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153				H	426
154				H	455
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156				H	408

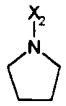
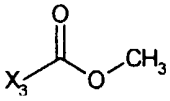
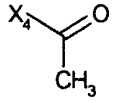
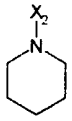
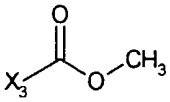
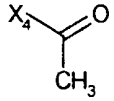
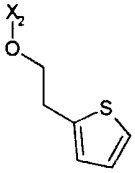
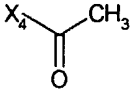
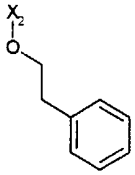
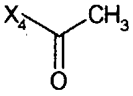
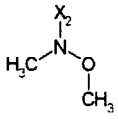
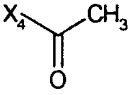
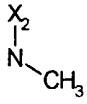
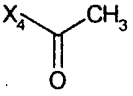
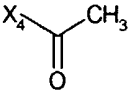
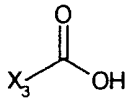
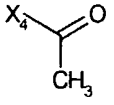
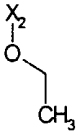
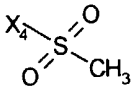
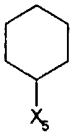
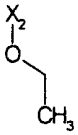
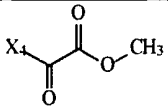
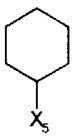
No.	R_2	R_3	R_4	R_5	MW (M^+)
157				H	428
158				H	483
159				H	502
160				H	441
161				H	477
162				H	524
163				H	512
164				H	396
165				H	482
166				H	480

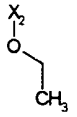
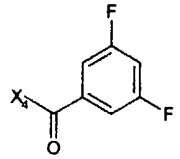
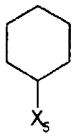
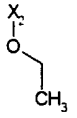
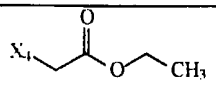
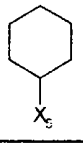
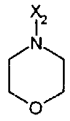
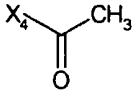
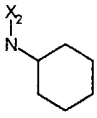
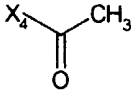
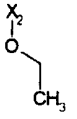
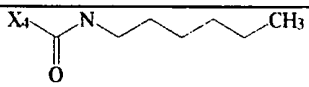
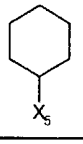
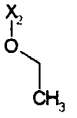
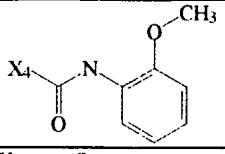
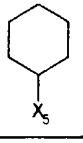
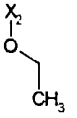
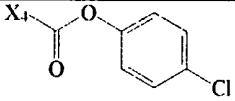
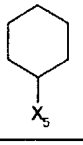
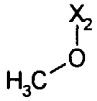
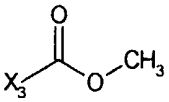
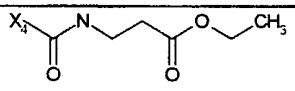
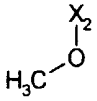
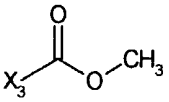
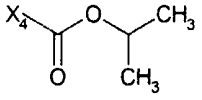
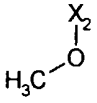
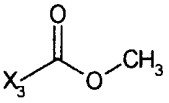
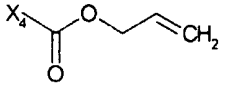
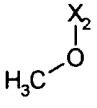
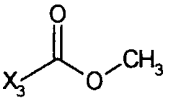
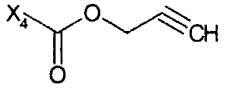
No.	R_2	R_3	R_4	R_5	MW (M^+)
167				H	596
168				H	595
169				H	581
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171		H		H	450
172				H	411
173				H	638
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175				H	454

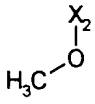
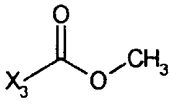
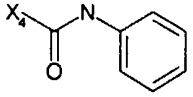
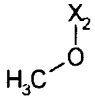
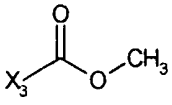
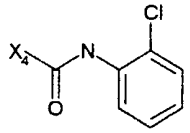
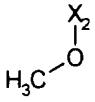
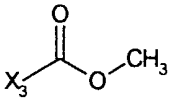
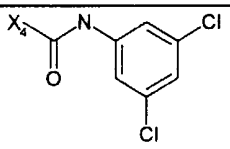
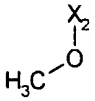
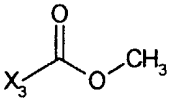
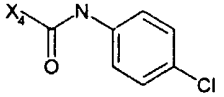
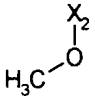
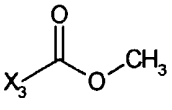
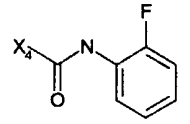
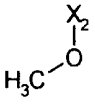
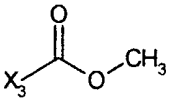
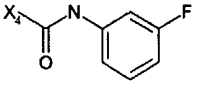
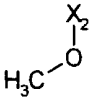
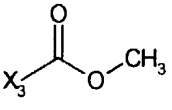
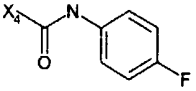
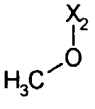
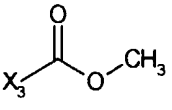
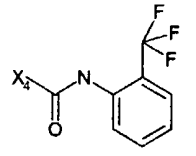
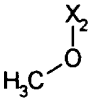
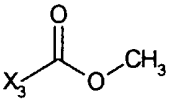
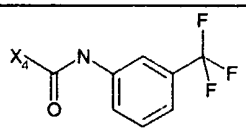
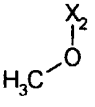
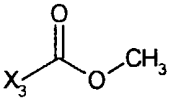
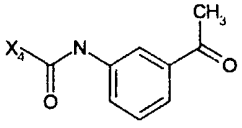
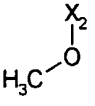
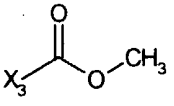
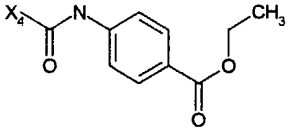
No.	R_2	R_3	R_4	R_5	MW (M^+)
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177				H	426
178				H	466
179				H	475
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181				H	490
182				H	495
183				H	539
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186		H		H	400

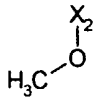
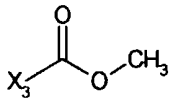
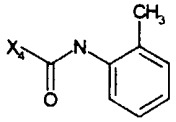
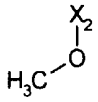
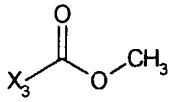
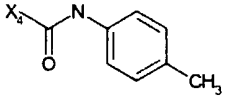
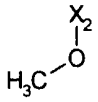
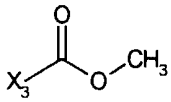
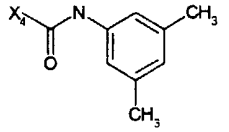
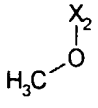
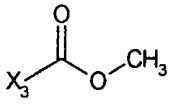
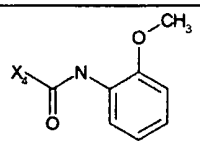
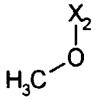
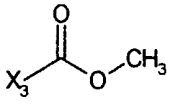
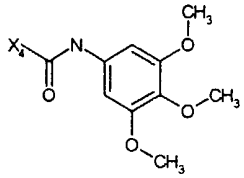
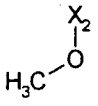
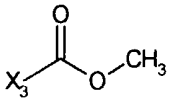
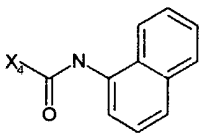
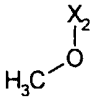
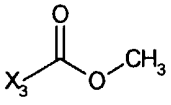
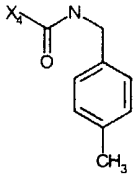
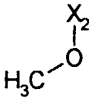
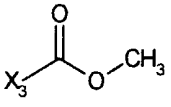
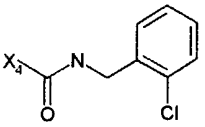
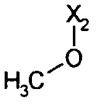
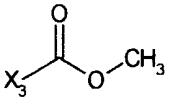
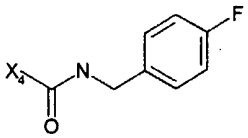
No.	R_2	R_3	R_4	R_5	MW (M^+)
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188		H		H	337
189		H		H	378
190		H		H	364
191		H		H	427
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196				H	485

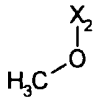
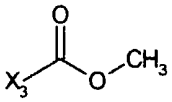
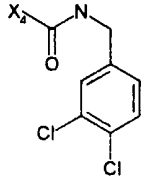
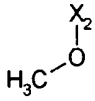
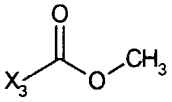
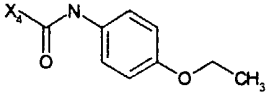
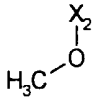
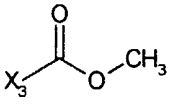
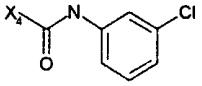
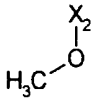
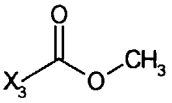
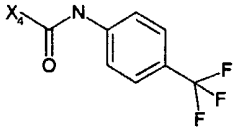
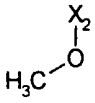
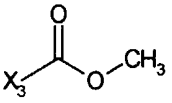
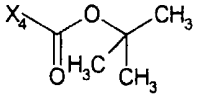
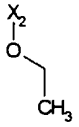
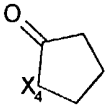
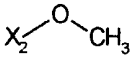
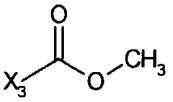
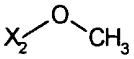
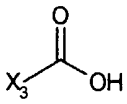
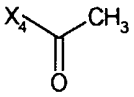
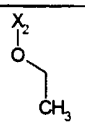
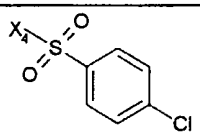
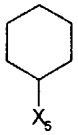
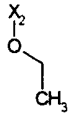
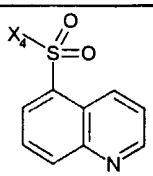
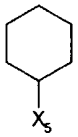
No.	R_2	R_3	R_4	R_5	MW (M^+)
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198		H		H	352
199		H		H	422
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201		H		H	406
202				H	410
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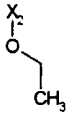
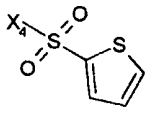
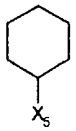
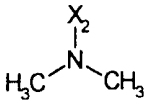
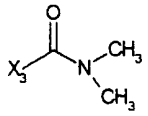
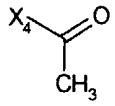
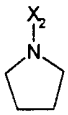
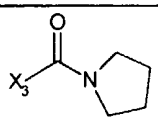
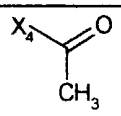
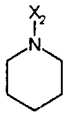
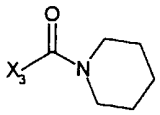
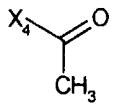
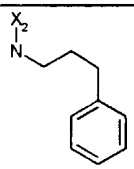
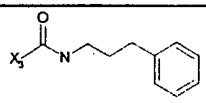
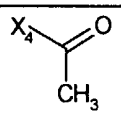
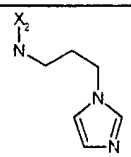
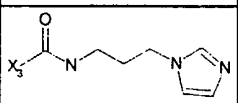
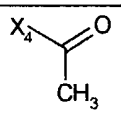
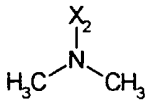
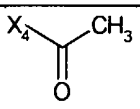
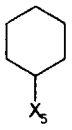
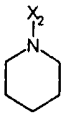
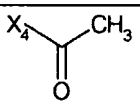
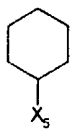
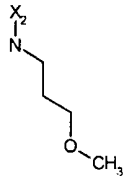
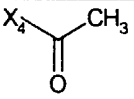
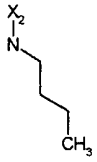
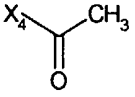
No.	R_2	R_3	R_4	R_5	MW (M^+)
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208		H		H	421
209		H		H	415
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211		H		H	323
212		H		H	450
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215		H			465

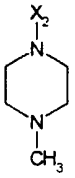
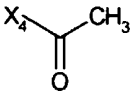
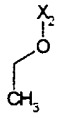
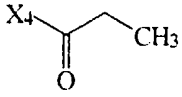
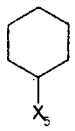
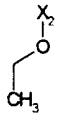
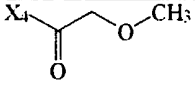
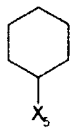
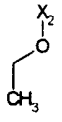
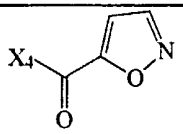
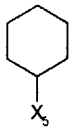
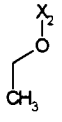
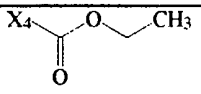
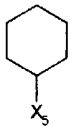
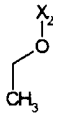
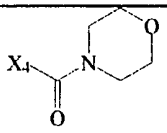
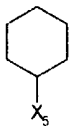
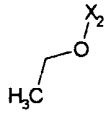
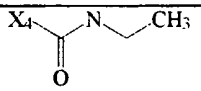
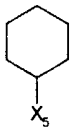
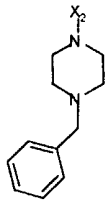
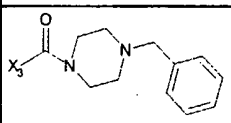
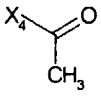
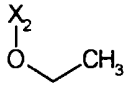
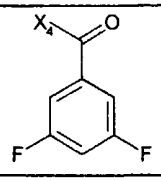
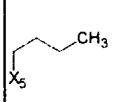
No.	R_2	R_3	R_4	R_5	MW (M^+)
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217		H			465
218		H		H	379
219		H		H	392
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221		H			528
222		H			533
223				H	484
224				H	426
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226				H	422

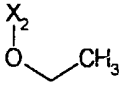
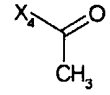
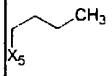
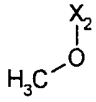
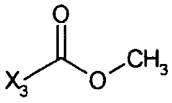
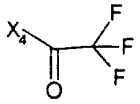
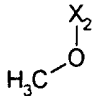
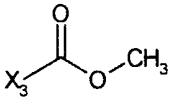
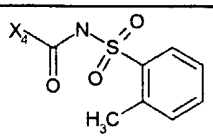
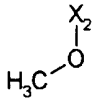
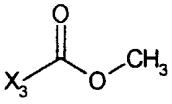
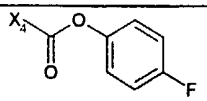
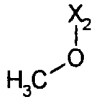
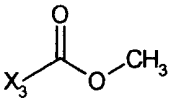
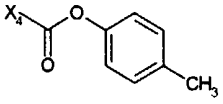
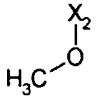
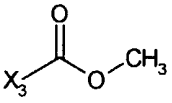
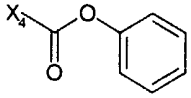
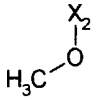
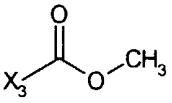
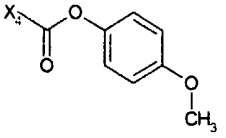
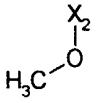
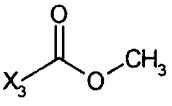
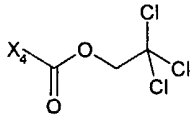
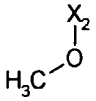
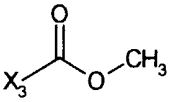
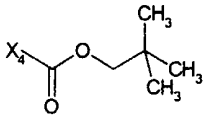
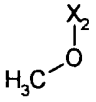
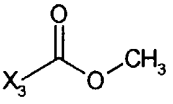
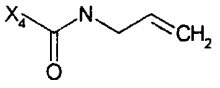
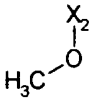
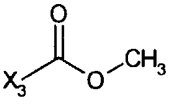
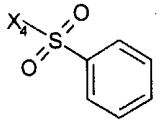
No.	R_2	R_3	R_4	R_5	MW (M^+)
227				H	460
228				H	494
229				H	528
230				H	494
231				H	478
232				H	478
233				H	478
234				H	528
235				H	528
236				H	502
237				H	532

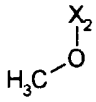
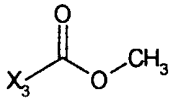
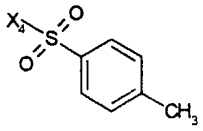
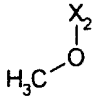
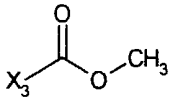
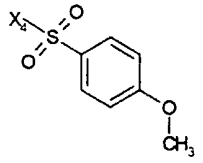
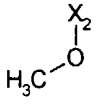
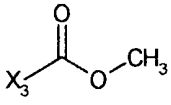
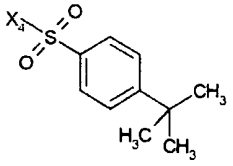
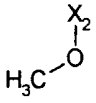
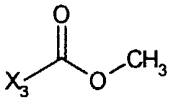
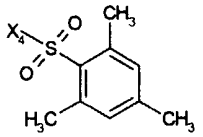
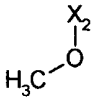
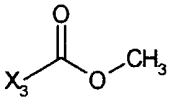
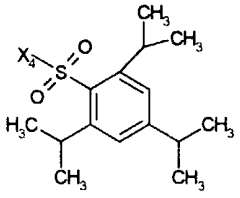
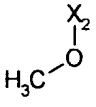
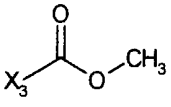
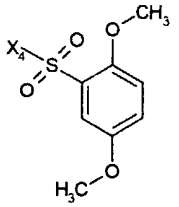
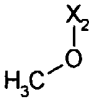
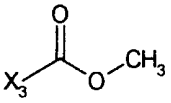
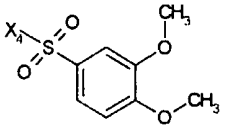
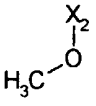
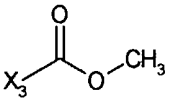
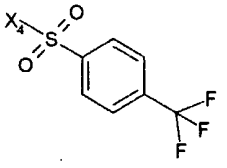
No.	R_2	R_3	R_4	R_5	MW (M^+)
238				H	474
239				H	474
240				H	488
241				H	490
242				H	550
243				H	510
244				H	488
245				H	508
246				H	492

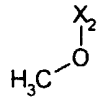
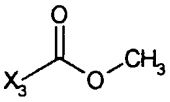
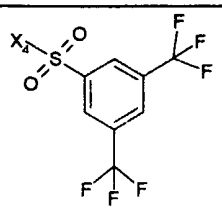
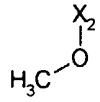
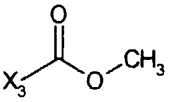
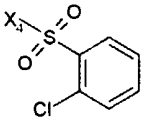
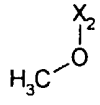
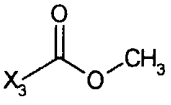
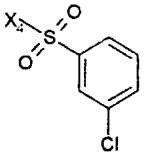
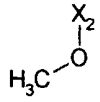
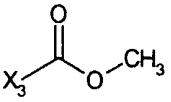
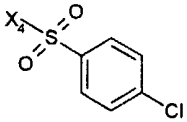
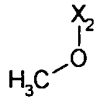
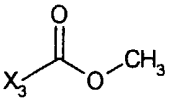
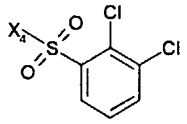
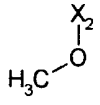
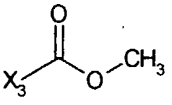
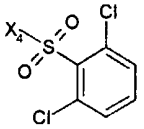
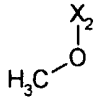
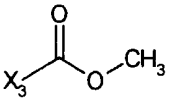
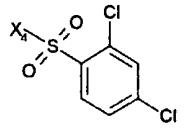
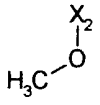
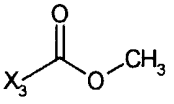
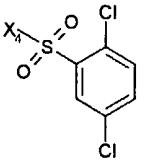
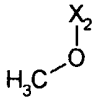
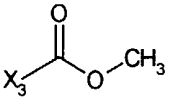
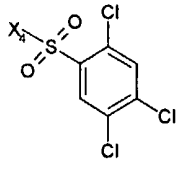
No.	R_2	R_3	R_4	R_5	MW (M^+)
247				H	542
248				H	504
249				H	494
250				H	528
251				H	441
252		H		H	364
253			H	H	340
254				H	368
255		H			553
256		H			570

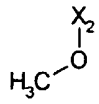
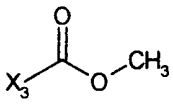
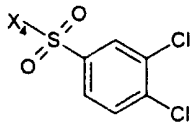
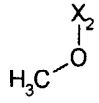
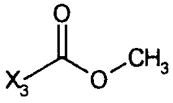
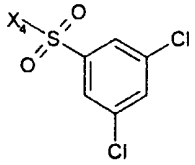
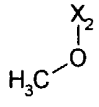
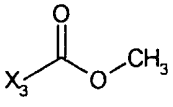
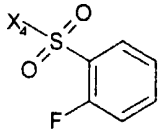
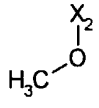
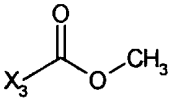
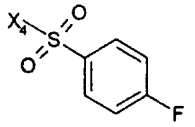
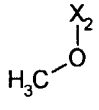
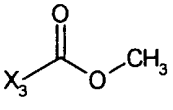
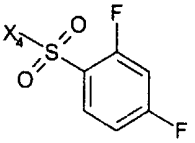
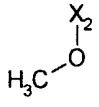
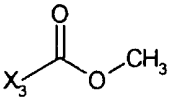
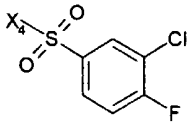
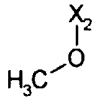
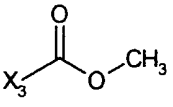
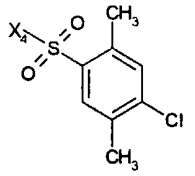
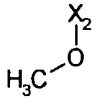
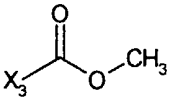
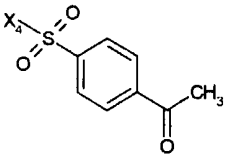
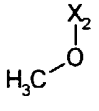
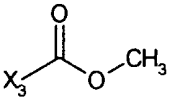
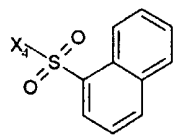
No.	R_2	R_3	R_4	R_5	MW (M^+)
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259				H	461
260				H	489
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265		H		H	381
266		H		H	365

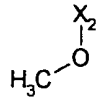
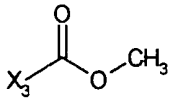
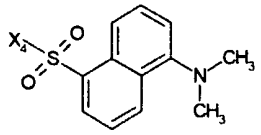
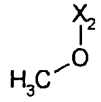
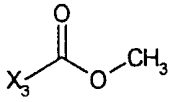
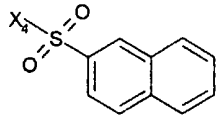
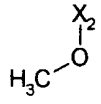
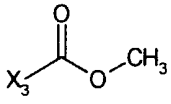
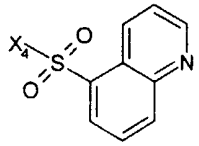
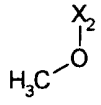
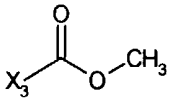
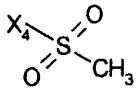
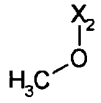
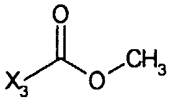
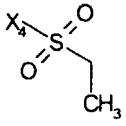
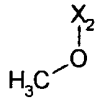
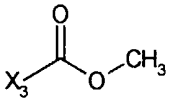
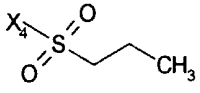
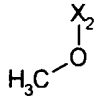
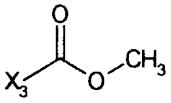
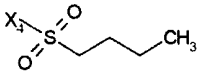
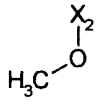
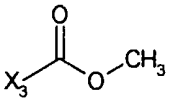
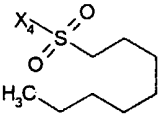
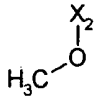
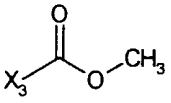
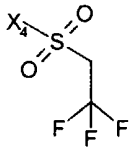
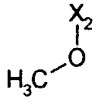
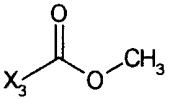
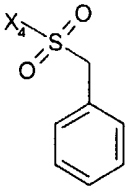
No.	R_2	R_3	R_4	R_5	MW (M^+)
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268		H			435
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275		H			493

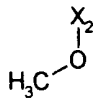
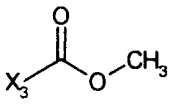
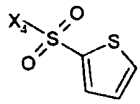
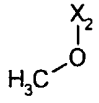
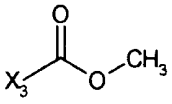
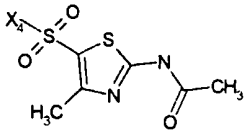
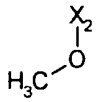
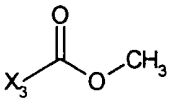
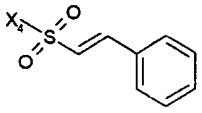
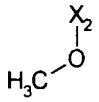
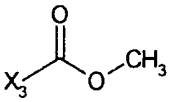
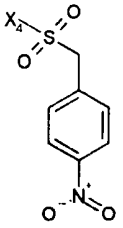
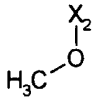
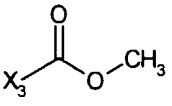
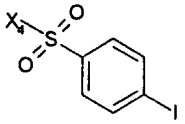
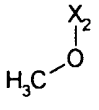
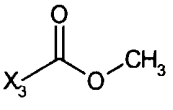
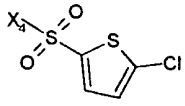
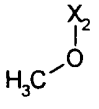
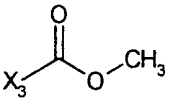
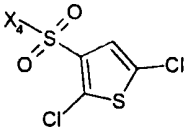
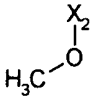
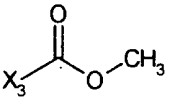
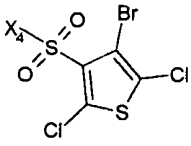
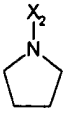
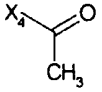
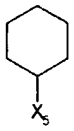
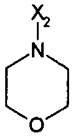
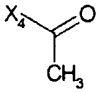
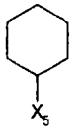
No.	R_2	R_3	R_4	R_5	MW (M^+)
276		H			395
277				H	436
278				H	538
279				H	478
280				H	475
281				H	461
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283				H	516
284				H	455
285				H	423
286				H	481

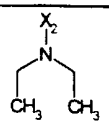
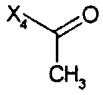
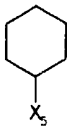
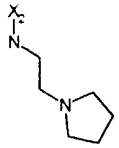
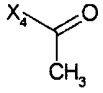
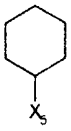
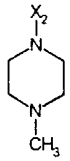
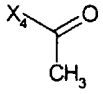
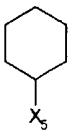
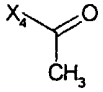
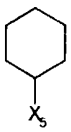
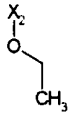
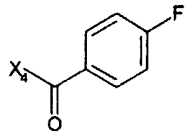
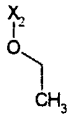
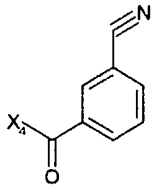
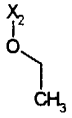
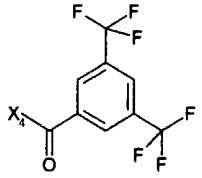
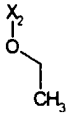
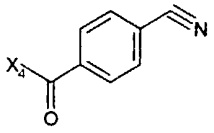
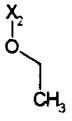
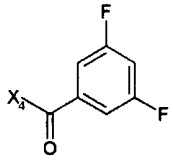
No.	R_2	R_3	R_4	R_5	MW (M^+)
287				H	495
288				H	511
289				H	537
290				H	523
291				H	607
292				H	541
293				H	541
294				H	549

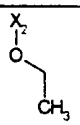
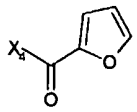
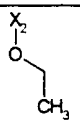
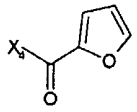
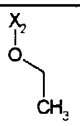
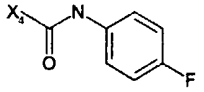
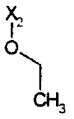
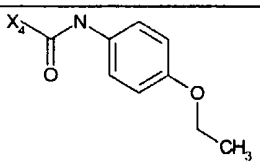
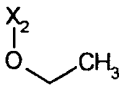
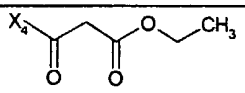
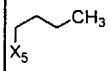
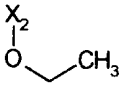
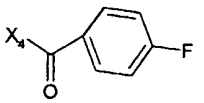
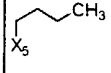
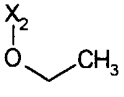
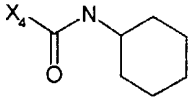
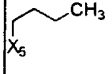
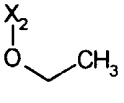
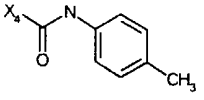
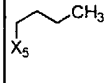
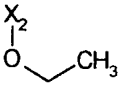
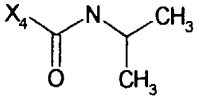
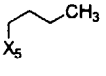
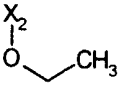
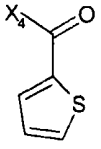
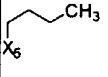
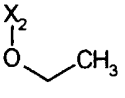
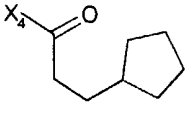
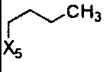
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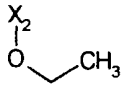
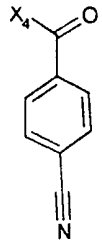
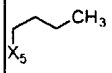
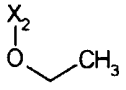
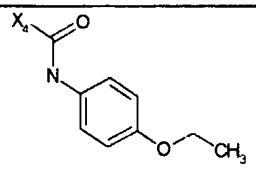
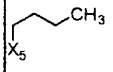
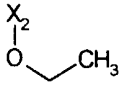
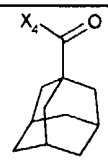
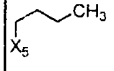
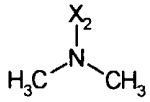
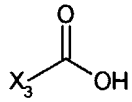
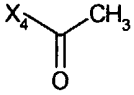
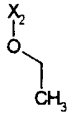
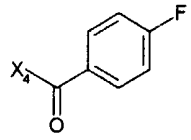
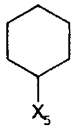
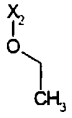
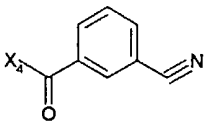
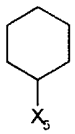
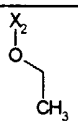
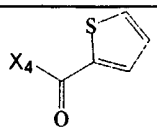
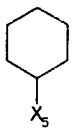
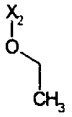
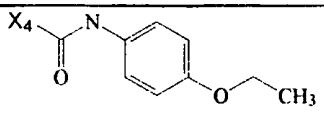
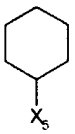
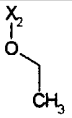
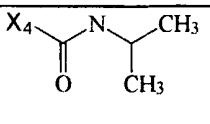
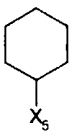
No.	R_2	R_3	R_4	R_5	MW (M^+)
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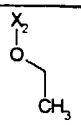
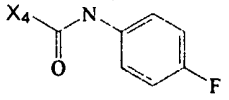
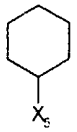
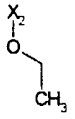
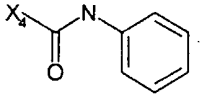
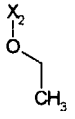
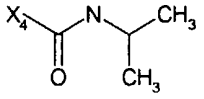
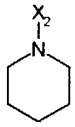
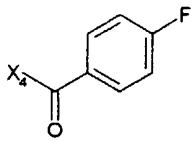
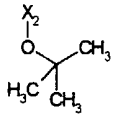
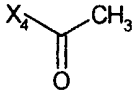
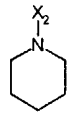
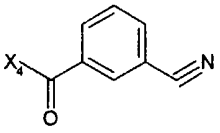
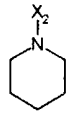
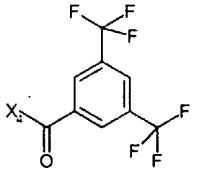
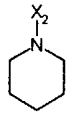
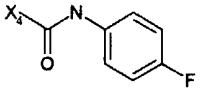
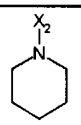
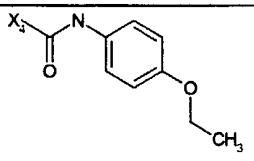
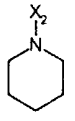
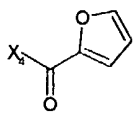
No.	R_2	R_3	R_4	R_5	MW (M^+)
313				H	574
314				H	531
315				H	532
316				H	418
317				H	433
318				H	447
319				H	461
320				H	517
321				H	486
322				H	495

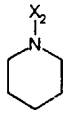
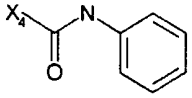
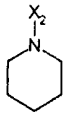
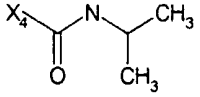
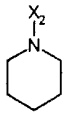
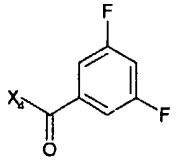
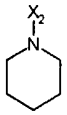
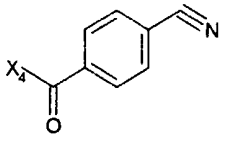
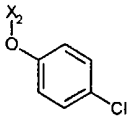
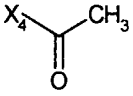
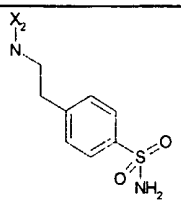
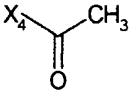
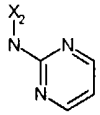
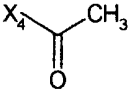
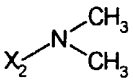
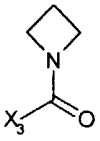
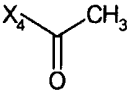
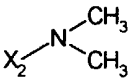
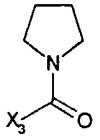
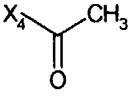
No.	R_2	R_3	R_4	R_5	MW (M^+)
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324				H	559
325				H	507
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327				H	606
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330				H	634
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332		H			462

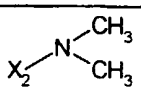
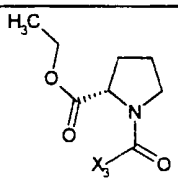
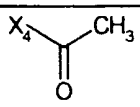
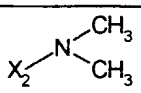
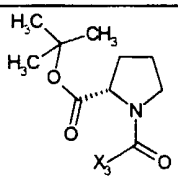
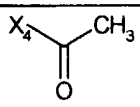
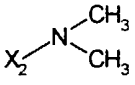
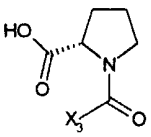
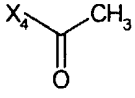
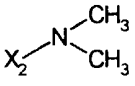
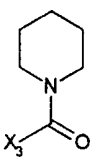
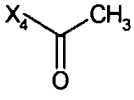
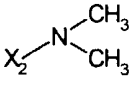
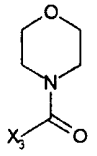
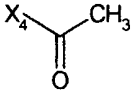
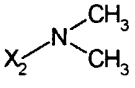
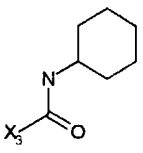
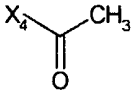
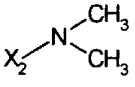
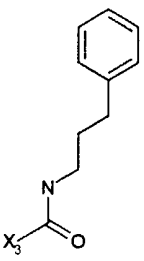
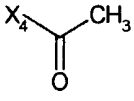
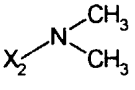
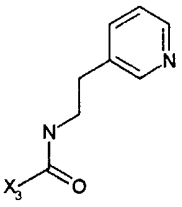
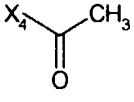
No.	R_2	R_3	R_4	R_5	MW (M^+)
333		H			448
334		H			489
335		H			475
336		H			393
337		H		H	418
338		H		H	426
339		H		H	536
340		H		H	426
341		H		H	436

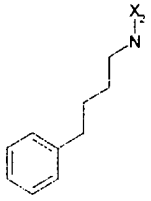
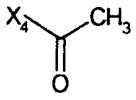
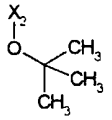
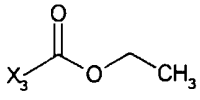
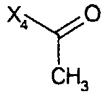
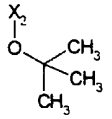
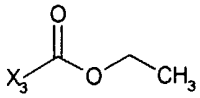
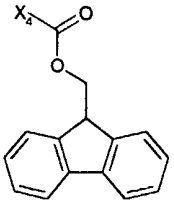
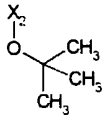
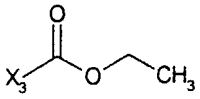
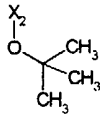
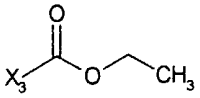
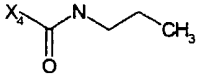
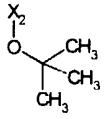
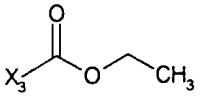
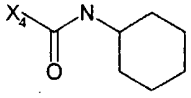
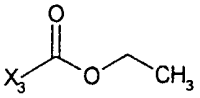
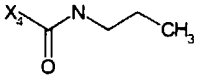
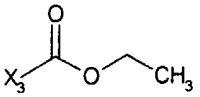
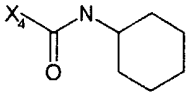
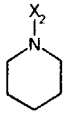
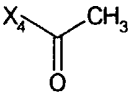
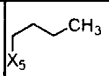
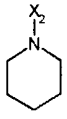
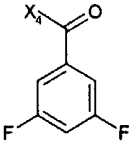
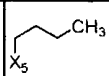
No.	R_2	R_3	R_4	R_5	MW (M^+)
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344		H		H	434
345		H		H	460
346		H			467
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348		H			478
349		H			486
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352		H			477

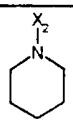
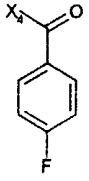
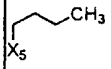
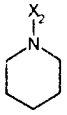
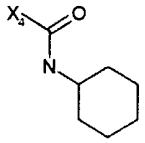
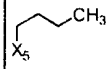
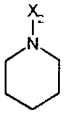
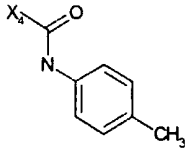
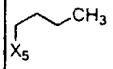
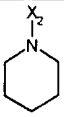
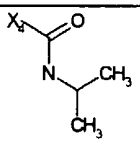
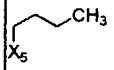
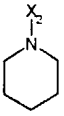
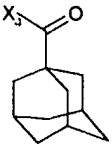
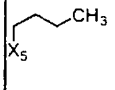
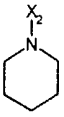
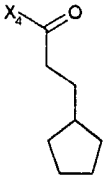
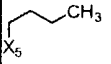
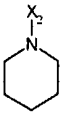
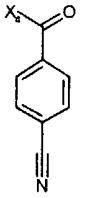
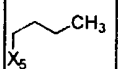
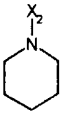
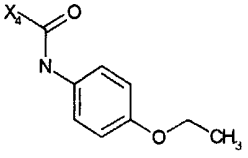
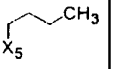
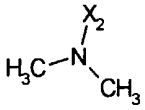
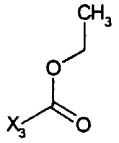
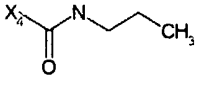
No.	R_2	R_3	R_4	R_5	MW (M^+)
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354		H			516
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357		H			501
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361		H			464

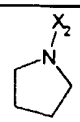
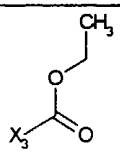
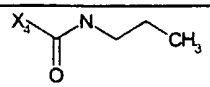
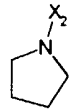
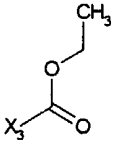
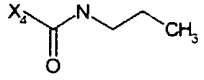
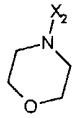
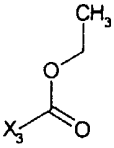
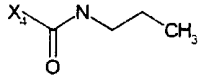
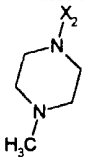
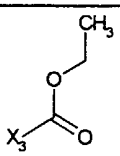
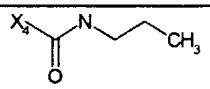
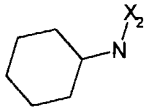
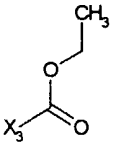
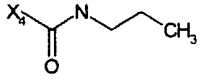
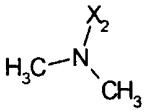
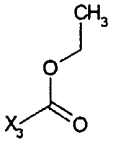
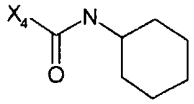
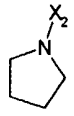
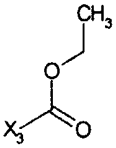
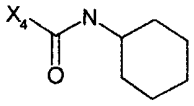
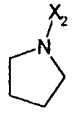
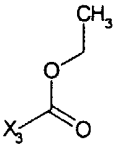
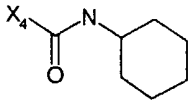
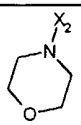
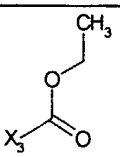
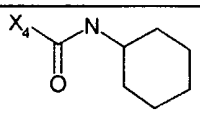
No.	R_2	R_3	R_4	R_5	MW (M^+)
362		H			516
363		H		H	416
364		H		H	381
365		H		H	458
366		H		H	366
367		H		H	465
368		H		H	576
369		H		H	473
370		H		H	499
371		H		H	430

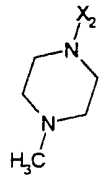
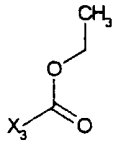
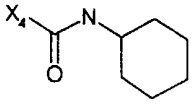
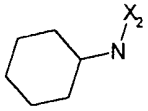
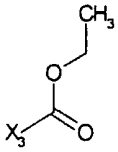
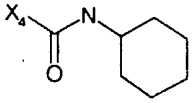
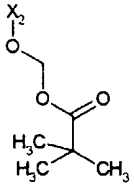
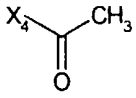
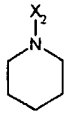
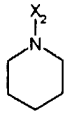
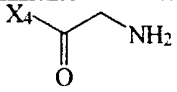
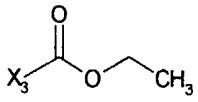
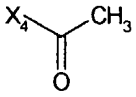
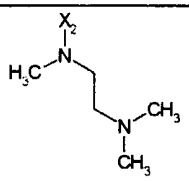
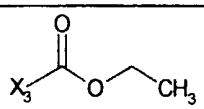
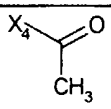
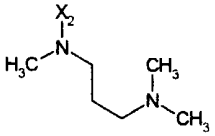
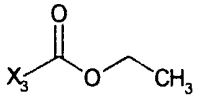
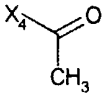
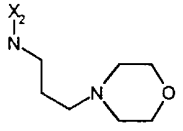
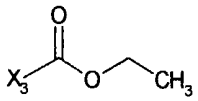
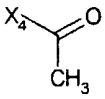
No.	R_2	R_3	R_4	R_5	MW (M^+)
372		H		H	455
373		H		H	421
374		H		H	476
375		H		H	465
376		H		H	421
377		H		H	493
378		H		H	387
379				H	421
380				H	435

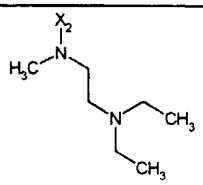
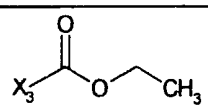
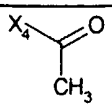
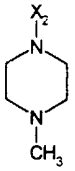
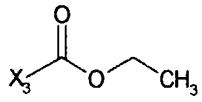
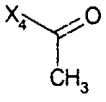
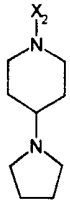
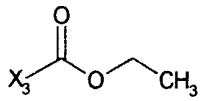
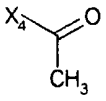
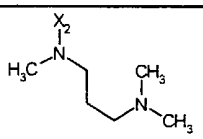
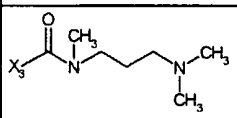
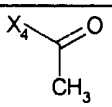
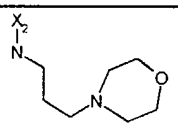
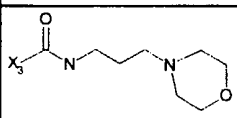
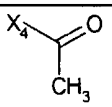
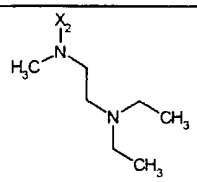
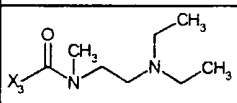
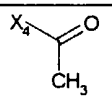
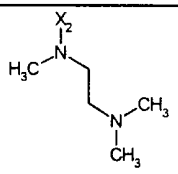
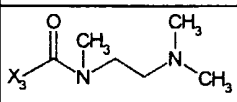
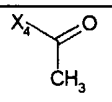
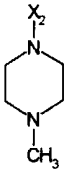
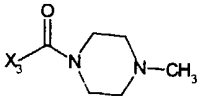
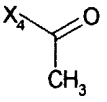
No.	R_2	R_3	R_4	R_5	MW (M^+)
381				H	507
382				H	535
383				H	479
384				H	449
385				H	451
386				H	463
387				H	499
388				H	486

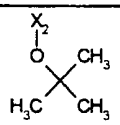
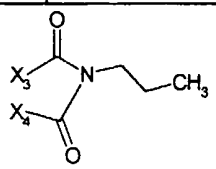
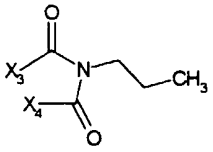
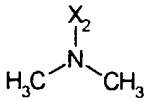
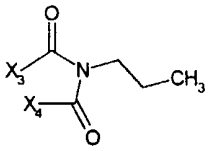
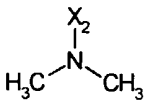
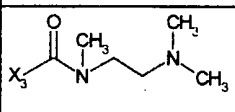
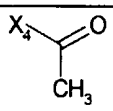
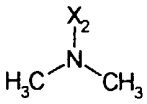
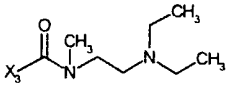
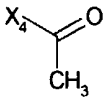
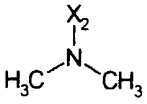
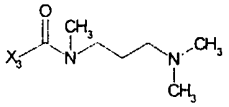
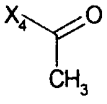
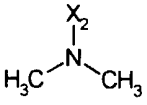
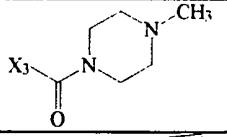
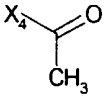
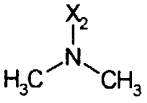
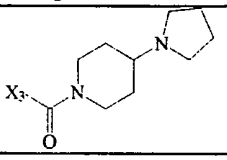
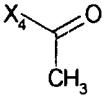
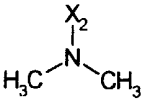
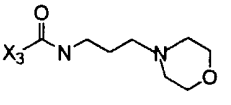
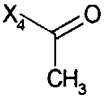
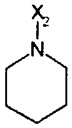
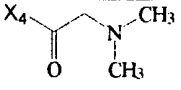
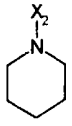
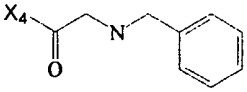
No.	R_2	R_3	R_4	R_5	MW (M^+)
389		H		H	442
390				H	439
391				H	619
392			H	H	397
393				H	482
394				H	522
395				H	426
396				H	466
397		H			434
398		H			532

No.	R_2	R_3	R_4	R_5	MW (M^+)
399		H			514
400		H			517
401		H			525
402		H			477
403		H			554
404		H			516
405		H			521
406		H			555
407				H	453

No.	R_2	R_3	R_4	R_5	MW (M^+)
408				H	479
409				H	493
410				H	495
411				H	508
412				H	507
413				H	493
414				H	519
415				H	533
416				H	535

No.	R_2	R_3	R_4	R_5	MW (M^+)
417				H	548
418				H	547
419		H		H	425
420		H	H	H	336
421		H		H	393
422				H	382
423				H	467
424				H	481
425				H	509

No.	R_2	R_3	R_4	R_5	MW (M^+)
426				H	495
427				H	465
428				H	519
429				H	551
430				H	607
431				H	579
432				H	523
433				H	519

No.	R_2	R_3	R_4	R_5	MW (M^+)
434				H	436
435				H	379
436				H	407
437				H	466
438				H	494
439				H	480
440				H	464
441				H	518
442				H	508
443		H		H	421
444		H		H	438

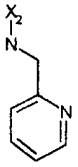
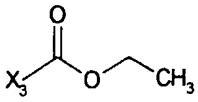
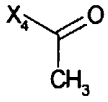
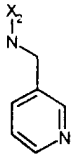
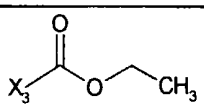
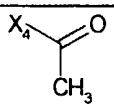
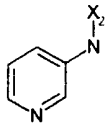
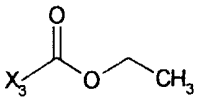
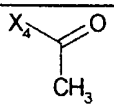
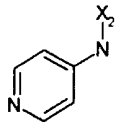
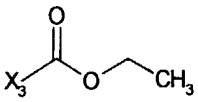
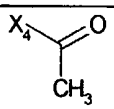
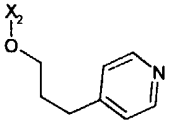
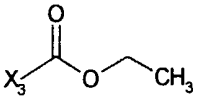
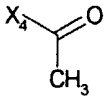
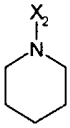
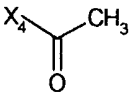
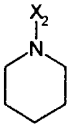
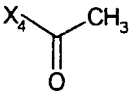
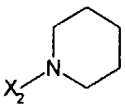
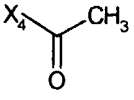
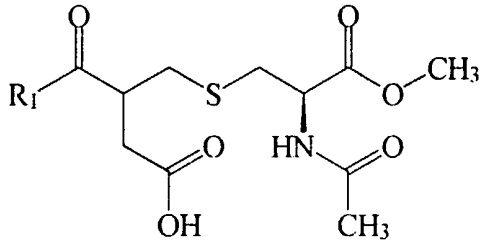
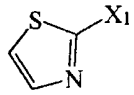
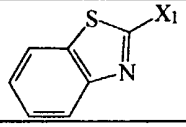
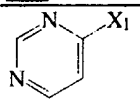
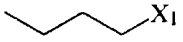
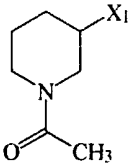
No.	R_2	R_3	R_4	R_5	MW (M^+)
445				H	473
446				H	473
447				H	459
448				H	459
449				H	502
450		H		H	378
451		H		H	378
452		H		H	410

Table 2



No.	R_1	MW (M^+)
462		374
463		424
464		369
465		347
466		416

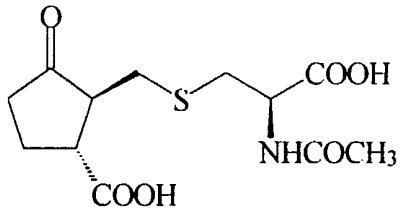
EXAMPLE 51

PC12 CELL PROTECTION AGAINST TAXOL ASSAY

Differentiated PC12 (rat pheochromocytoma) cells are utilized to model taxol-damaged neurons. Differentiated PC12 have nerve-like morphology which is disrupted by administration of taxol. Quantification of damage to differentiated PC12 cells by taxol is measured by the release of LDH that occurs upon cell necrosis.

Method

PC12 cells are differentiated with NGF (100 mg/ml) for 29 hours. Compounds are added for 19 hours (pre-treatment), then taxol (0.24 mM) is added. 72 hours (3 days) after taxol addition, cell survival is assayed by LDH release. Complete cellular protection (100%) is defined as the protection derived from 30 mM NK5805. NK5805 is a reference compound for neuronal protection. It was originally identified by Nippon Kayaku Co. Ltd. in published PCT WO99/05091 and has the following structure:



NK5805

LDH values were quantified by calculating the following % survival, relative to 30 mM NK5805, according to Equation (1):

$$\frac{100 \times \{(\text{LDH for taxol}) - (\text{LDH for taxol + test compound})\}}{(\text{LDH for taxol}) - (\text{LDH for taxol + 30 mM NK5805})} \quad \text{Eq. (1)}$$

In this example, a 100% protection level is equivalent to the group given no taxol.

Results

Table 2 identifies preferred compounds with significant protection of differentiated PC12 from taxol damage. To this end, preferred compounds (from Table 1 above) having a protection level of at least 50% at 10 μM concentration in this assay are as follows: 5, 8, 24, 32, 58, 60, 61, 74, 81, 90-92, 94, 95, 97-102, 105, 106, 110-113, 115-117, 121-123, 125-129, 132, 136, 140, 164, 169, 170, 174-184, 187-189, 195, 196, 198, 202,

204-208, 214-226, 240, 244, 246, 249, 251-253, 257, 259, 260, 263, 264, 268-273, 275, 277-282, 285, 335, 337-345, 355, 357-375, 378-388, 420-426, 432-435 and 444.

EXAMPLE 52

RAT SUPERIOR CERVICAL GANGLION CELL PROTECTION AGAINST TAXOL ASSAY

Rat superior cervical ganglion (SCG) neurons have been used extensively to model neuronal systems. This assay utilizes SCG neurons to identify potential protective agents against taxol-induced neuropathy.

Method

Neonatal rat SCG neurons are cultured with 2.5 ng/ml NFG and the test compounds. After 36 hours 1 mM taxol is added. 72 hours (3 days) after taxol addition, cell survival is assayed by LDH release. Complete cellular protection (100%) is defined as the protection derived from 30 mM. LDH values were quantified by calculating the following % survival, relative to 30 mM NK5805 as noted in Equation (1) above.

Results

Table 3 identifies preferred compounds with significant protection of rat SCG from taxol damage. To this end, preferred compounds (from Table 1 above having a protection level of at least 50% at 10 μM concentration in this assay are as follows: 1, 2, 8, 25, 30, 32, 59-61, 74, 77, 120, 129, 130, 132-135, 139, 140, 143-146, 148, 152, 153, 159, 162-164, 168, 169, 175, 187-189, 194, 196, 197, 206, 218, 223, 226, 258, 259, 263, 356, 370, 378-388, 395, 396, 407, 410, 413, 416, 421, 422 and 435-442.

EXAMPLE 53

EFFICACY OF REPRESENTATIVE COMPOUNDS IN RAT TAXOL NEUROPATHY MODEL

In vivo efficacy of representative compounds were tested with rat taxol induced neuropathy model reported by Cliffer et al. (*Ann. Neurol. 43*:46-55, 1998).

Method

Sprague-Dawley female rats (215-225g) were used. One week prior to the initiation of dosing with test compounds, base line electrophysiological recording were obtained. Dosing of the test compounds was initiated one day prior to the first injection of taxol (A.G. Scientific). Beginning on Day 2 animals were injected with total of two doses of 15 mg/kg paclitaxel giving 3 days apart, for a cumulative dose of 30 mg/ml.

On Day 1 of the study, all rat were randomized into groups of 10 each and weighed. Dosing with test compounds was initiated on Day 1 and continued for a total of 45 days. Test compounds were administered by intraperitoneal (i.p.) injection or by post orum (p.o.) gavage in conscious once daily. Paclitaxel was administered on Day 2 and 5 by tail vein injection at 6 mg/ml in 50% saline /25%Cremophore /25% ethanol. One group was given the paclitaxel vehicle alone in an equivalent volume. Test compounds were formulated for dosing daily, immediately prior to dosing. The compounds were formulated by adding 15% of the final volume of pure PEG400 to the compounds and mixed on an orbital shaker for 40 minutes. Following dissolution, saline was added and the solution was vortexed. Taxol (A.G. Scientific) is solvated with Cremophore-ethanol vehicle at 12 mg/ml and then diluted 50/50 with saline. The test compounds are solvated with saline at appropriate concentration.

Sensory and motor nerve conduction velocities were evaluated using a method based in the protocol described by De Koning and Gispen (*Peptides 8*:415-422, 1987). Electrophysiological evaluation was carried out as a double blind study. Animals were anesthetized with isofluorane. In order to maintain body temperature, anesthetized animals were placed on Deltaphase™ Isothermal Pads and rectal temperatures were monitored. Stimulating needle electrodes were inserted close to the sciatic nerve at the sciatic notch and the tibial nerve near the ankle. Subcutaneous recording electrodes were placed over the distal lumbricales foot muscles. Stimuli were supramaximal square-waves of 0.1 msec duration generated with a Grass S88 Stimulator through a Grass stimulation isolation unit. An ETH-260 Bride/Bio Amplifier (CB Sciences Inc), computer (Macintosh Iici), and data acquisition system (MacLab/200) were used for the recordings. The motor

and sensory nerve conduction velocities were calculated by measuring the distance between the sciatic notch and ankle sites, and the latency between the M-wave and the H-reflex. The electrophysiological evaluations were conducted 2 weeks later. Statistical analysis was carried out using unpaired t-tests and repeated measures of analysis of variance (ANOVA) using Statview. In all cases 5% was chosen as the level of statistical significance in two-tailed tests.

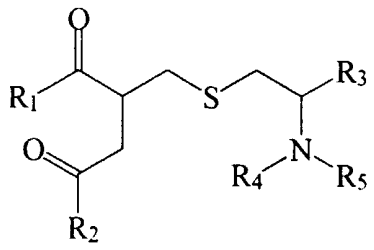
Results

Compound No. 60 was active to ameliorate the taxol-induced retardation of sensory nerve conduction velocity by i.p. administration at 10 mg/kg (*see* Figure 1, 3). Compound No.188 (40 mg/kg), compound No. 440 and compound No. 438 (20 mg/kg) were active to ameliorate the taxol-induced retardation of sensory nerve conduction velocity by p.o. administration (*see* Figure 2, 3). Compound No. 189 was active to ameliorate the taxol-induced retardation of sensory nerve conduction velocity by i.p. administration at 2.5 mg/kg (*see* Figure 2) and p.o. administration at 20 mg/kg (*see* Figure 3). Thus, representative compounds of this invention, such as compound No. 60, compound No. 188, compound No. 440, compound No. 438 and compound No. 189, are effective in this *in vivo* rat neuropathy model.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. A compound having the structure:



and stereoisomers and pharmaceutically acceptable salts thereof,

wherein:

R_1 is alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl;

R_2 is $-OR_{2a}$ or $-NR_{2b}R_{2c}$;

R_3 is hydrogen, keto, $-C(=O)OR_{3a}$, or $-C(=O)NR_{3b}R_{3c}$;

R_4 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, $-C(=O)R_{4a}$, $-C(=O)OR_{4b}$, $-C(=O)NR_{4c}R_{4d}$, $-OC(=O)NR_{4c}R_{4d}$ or $-SO_2R_{4e}$.

or wherein R_3 and R_4 taken together form a heterocyclic ring or substituted heterocyclic ring; and

R_5 is hydrogen, alkyl or substituted alkyl;

and wherein:

R_{2a} is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, or substituted heterocyclealkyl;

R_{2b} and R_{2c} are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl or a radical of the formula $-OR_{2d}$, $-C(=O)R_{2d}$ or $-SO_2R_{2d}$ wherein R_{2d} is alkyl, substituted alkyl, aryl or substituted

aryl, or R_{2b} and R_{2c} taken together with the nitrogen atom to which they are attached from a heterocyclic ring or substituted heterocyclic ring;

R_{3a}, R_{3b} and R_{3c} are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substitued arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl, substituted heterocyclealkyl, or a radical of the formula $-Y_3-Z_3-R_{3d}$, where Y_3 is alkanediyl, substitute alkanediyl or a direct bond, Z_3 is -O-, -S-, $-SO_2-$, $-N(R_{3e})-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -NHC(=O)-, $-C(=O)N(R_{3e})-$ or a direct bond, and R_{3d} and R_{3e} are the same or different and independently hydrogen, amino, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl, or R_{3d} and R_{3e} taken together with the nitrogen atom to which they are attached form a heterocycle or substituted heterocycle; or R_{3b} and R_{3c} taken together with the nitrogen atom to which they are attached from a heterocyclic ring or substituted heterocyclic ring; and

R_{4a}, R_{4b}, R_{4c}, R_{4d} and R_{4e} are the same or different and independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, or a radical of the formula $-Y_4-Z_4-R_{4f}$, where Y_4 is alkanediyl, substitute alkanediyl or a direct bond, Z_4 is -O-, -S-, $-SO_2-$, $-N(R_{4g})-$, -C(=O)-, -C(=O)O-, -OC(=O)-, -NHC(=O)-, $-C(=O)N(R_{4g})-$ or a direct bond, and R_{4f} and R_{4g} are the same or different and independently hydrogen, amino, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocyclealkyl or substituted heterocyclealkyl, or R_{4f} and R_{4g} taken together with the nitrogen atom to which they are attached form a heterocycle or substituted heterocycle; or R_{4c} and R_{4d} taken together with the nitrogen atom to which they are attached from a heterocyclic ring or substituted heterocyclic ring.

2. The compound of claim 1 wherein R_1 is heterocycle.

3. The compound of claim 2 wherein heterocycle is pyridyl.

4. The compound of claim 3 wherein pyridyl is pyrid-3-yl.

5. The compound of claim 1 wherein R_2 is $-OR_{2a}$.

6. The compound of claim 5 wherein R_{2a} is hydrogen or alkyl.

7. The compound of claim 5 wherein R_{2a} is methyl, ethyl, propyl or butyl.

8. The compound of claim 1 wherein R_2 is $-NR_{2b}R_{2c}$.

9. The compound of claim 8 wherein R_{2b} and R_{2c} are alkyl.

10. The compound of claim 8 wherein R_{2b} and R_{2c} taken together with the nitrogen atom to which they are attached form a heterocyclic ring.

11. The compound of claim 10 wherein the heterocyclic ring is piperidyl.

12. The compound of claim 1 wherein R_3 is hydrogen.

13. The compound of claim 1 wherein R_3 is keto.

14. The compound of claim 1 wherein R_3 is $-C(=O)OR_{3a}$.

15. The compound of claim 14 wherein R_{3a} is alkyl.

16. The compound of claim 14 wherein R_{3a} is methyl or ethyl.

17. The compound of claim 1 wherein R_3 is $-C(=O)NR_{3b}R_{3c}$.

18. The compound of claim 17 wherein R_{3b} and R_{3c} are the same or different and independently hydrogen, alkyl or substituted alkyl.

19. The compound of claim 17 wherein R_{3b} and R_{3c} taken together with the nitrogen atom to which they are attached form a heterocyclic ring or substituted heterocyclic ring.

20. The compound of claim 1 wherein R_4 is alkyl or aryl.

21. The compound of claim 1 wherein R_4 is $-C(=O)R_{4a}$.

22. The compound of claim 21 wherein R_{4a} is alkyl or substituted alkyl.

23. The compound of claim 22 wherein R_{4a} is methyl.

24. The compound of claim 21 wherein R_{4a} is aryl or substituted aryl.

25. The compound of claim 1 wherein R_4 is $-C(=O)OR_{4b}$.

26. The compound of claim 25 wherein R_{4b} is alkyl or substituted alkyl.

27. The compound of claim 25 wherein R_{4b} is aryl, substituted aryl, arylalkyl or substituted arylalkyl.

28. The compound of claim 1 wherein R_4 is $-C(=O)NR_{4c}R_{4d}$.

29. The compound of claim 28 wherein R_{4c} is hydrogen.

30. The compound of claim 28 wherein R_{4d} is alkyl.

31. The compound of claim 28 wherein R_{4d} is aryl, substituted aryl, arylalkyl or substitute arylalkyl.

32. The compound of claim 1 wherein R_4 is $-SO_2R_{4e}$.

33. The compound of claim 32 wherein R_{4e} is aryl or substituted aryl.

34. The compound of claim 1 wherein R_5 is hydrogen.

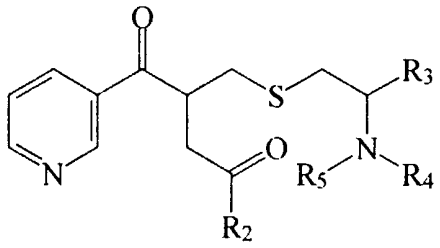
35. The compound of claim 1 wherein R_5 is alkyl or cycloalkyl.

36. The compound of claim 35 wherein R_5 is methyl, ethyl, n-propyl or n-butyl.

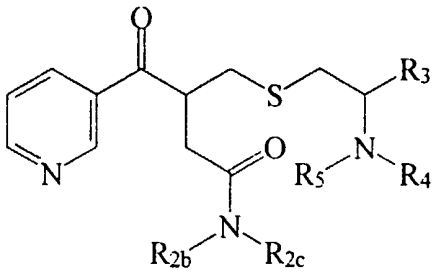
37. The compound of claim 35 wherein R_5 is cyclohexyl.

38. The compound of claim 1 wherein R_3 and R_5 are both hydrogen.

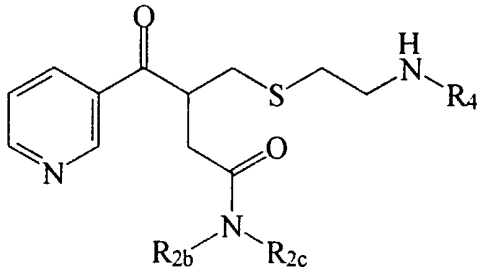
39. The compound of claim 1 having the structure:



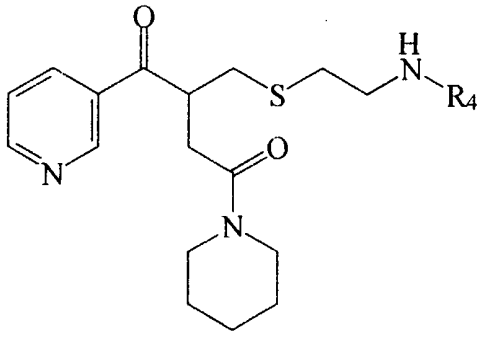
40. The compound of claim 1 having the structure:



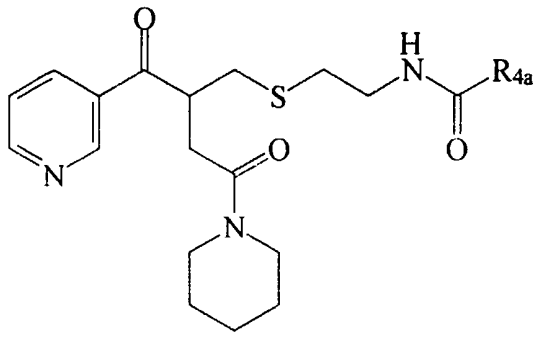
41. The compound of claim 1 having the structure:



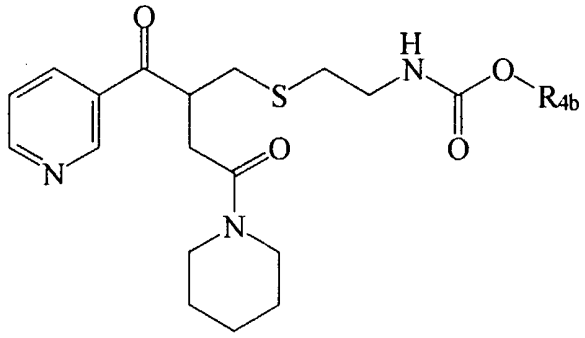
42. The compound of claim 1 having the structure:



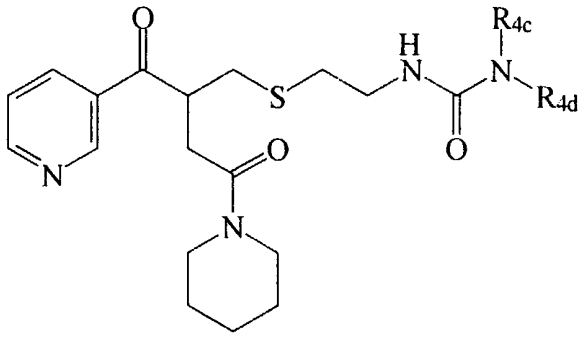
43. The compound of claim 1 having the structure:



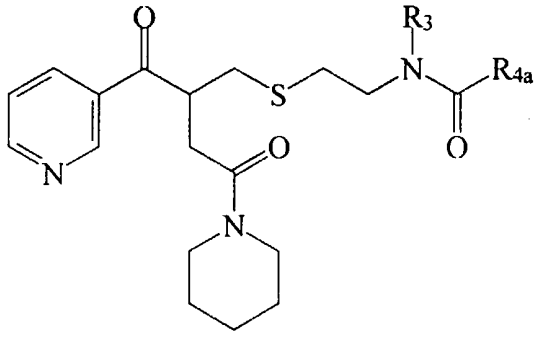
44. The compound of claim 1 having the structure:



45. The compound of claim 1 having the structure:



46. The compound of claim 1 having the structure:



47. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

48. A method for treating a nervous system disorder, comprising administering to a patient in need thereof an effective amount of the composition of claim 47.

49. The method of claim 48 wherein the nervous system disorder is caused by a chemotherapeutic agent.

50. The method of claim 48 wherein the nervous system disorder is caused by a chemical agent.

51. The method of claim 48 wherein the disorder is a central nervous system disorder.

52. The method of claim 51 wherein the central nervous system disorder is increased intracraniel pressure and cerebral herniation, cerebral edema, hydrocephalus, meningintis, encephalitis, ischemic encephalopathy, cerebral infarction, intracranial hemorrhage, epidermal hematoma, subdural hematoma, parenchymal injuries, Alzheimer's deasease,

Huntington's disease, Parkinsonism, amytrophic lateral sclerosis, multiple sclerosis, hepatic encephalopathy or leukodystrophy

53. The method of claim 48 wherein the disorder is a peripheral nervous system disorder.

54. The method of claim 53 wherein the peripheral nervous system disorder is acute idiopathic neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, HIV-induced neuropathy, neurilemmoma or neurofibroma.

55. A method for promoting nerve cell differentiation, comprising administering to a patient in need thereof an effective amount of the composition of claim 47.

Fig.1 Effect in rat taxol neuropathy model

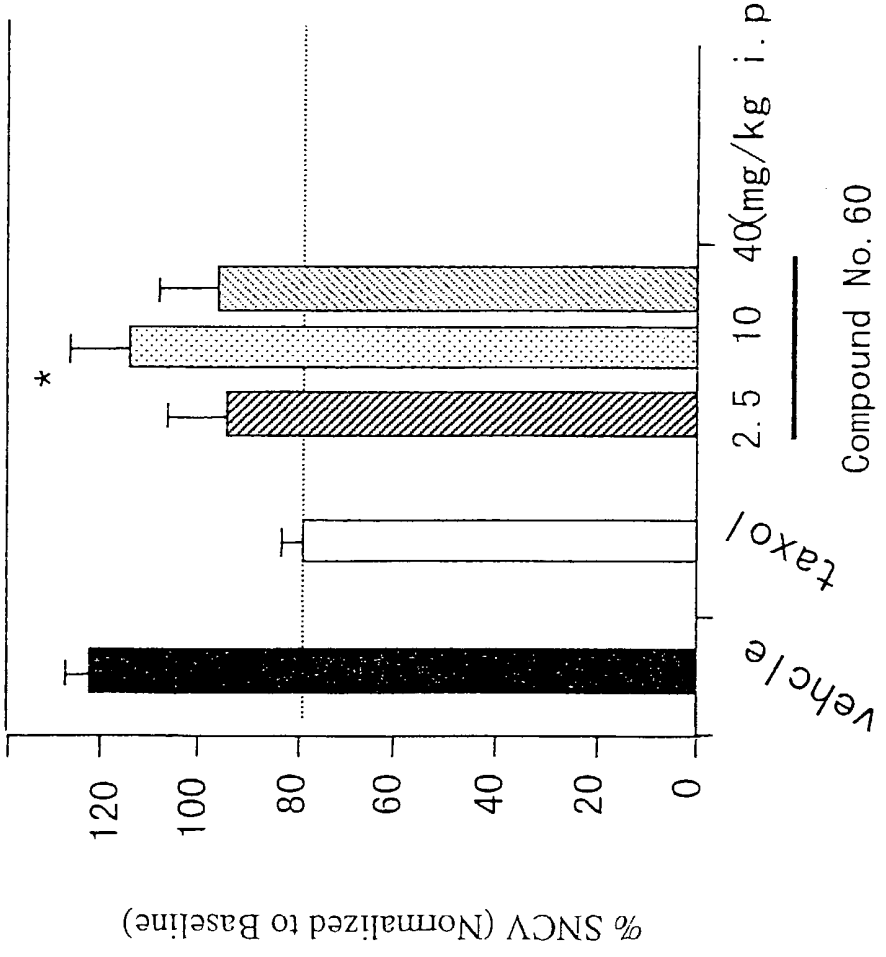


Fig. 2 Effect in rat taxol neuropathy model

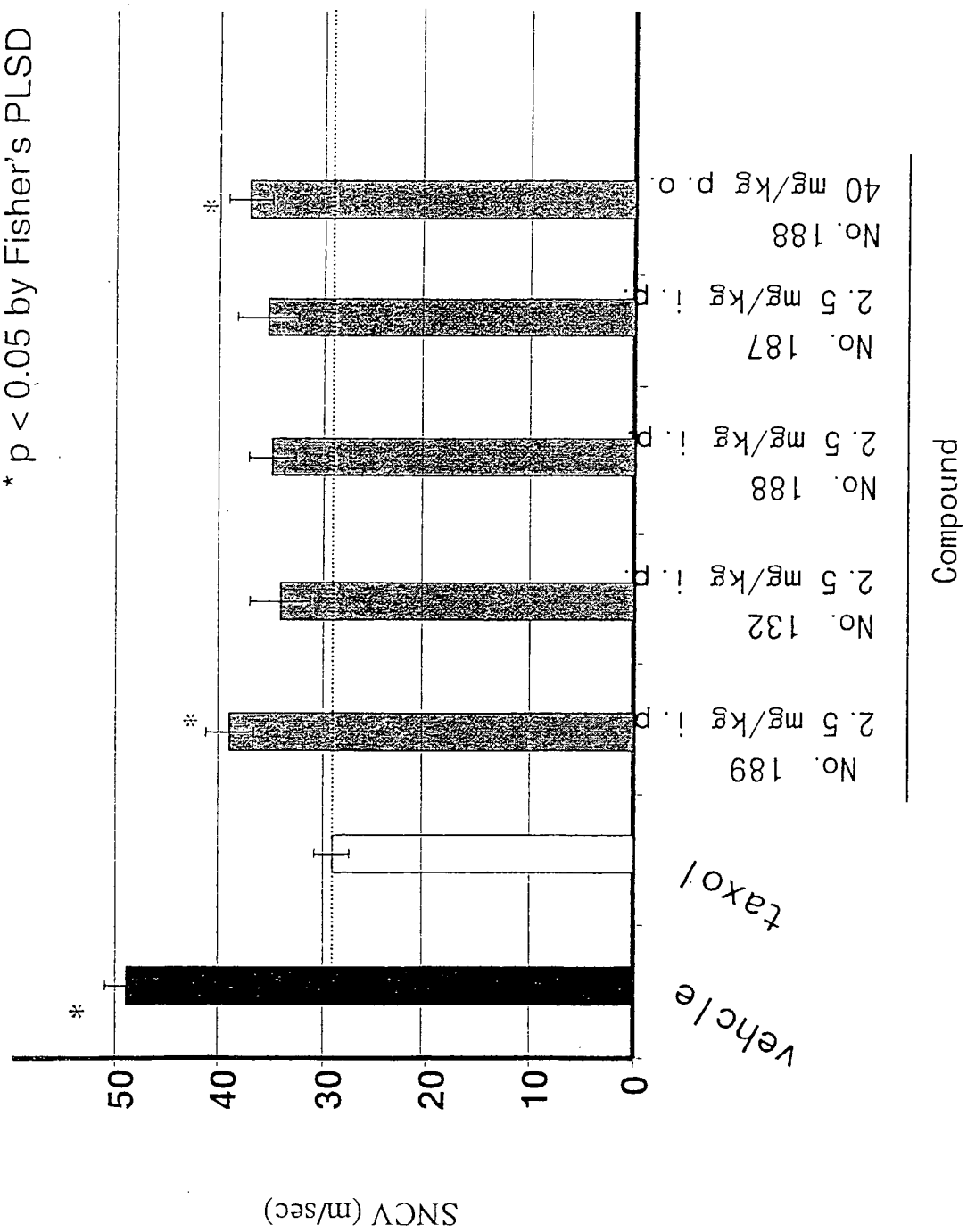


Fig. 3 Effect in rat taxol neuropathy model

