PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 45/06, 31/485, 38/04, 31/13 // (A61K 38/04, 31:485)

A1

(11) International Publication Number: **WO 99/07413**

(43) International Publication Date: 18 February 1999 (18.02.99)

(21) International Application Number: PCT/US98/10707

(22) International Filing Date: 26 May 1998 (26.05.98)

(30) Priority Data:
60/055,233 11 August 1997 (11.08.97) US

(71) Applicant *(for all designated States except US)*: ALGOS PHARMACEUTICAL CORPORATION [US/US]; Collingwood Plaza, 4900 Route 33, Neptune, NJ 07753 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CARUSO, Frank, S. [US/US]; 2 Bowling Green, Colts Neck, NJ 07722 (US).

(74) Agents: DILWORTH, Peter, G. et al.; Dilworth & Barrese, 333 Earle Ovington Boulevard, Uniondale, NY 11553 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUBSTANCE P INHIBITORS IN COMBINATION WITH NMDA–BLOCKERS FOR TREATING PAIN

(57) Abstract

The analgesic effectiveness of a substance P receptor antagonist is significantly potentiated by administering a substance P receptor antagonist with a nontoxic NMDA receptor antagonist and/or a nontoxic substance that blocks at least one major intracellular consequence of NMDA receptor activation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

SUBSTANCE P INHIBITORS IN COMBINATION WITH NMDA-BLOCKERS FOR TREATING PAIN

BACKGROUND OF THE INVENTION

This invention relates to an analgesic composition and method for alleviating pain. More particularly, this invention is concerned with alleviating pain by administration of an analgesic composition comprising a substance P receptor antagonist and, as a potentiator of the substance P receptor antagonist, a nontoxic N-methyl-D-aspartate (NMDA) receptor antagonist and/or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation.

The expression "substance P receptor antagonist" shall be understood to be synonymous with and/or inclusive of neurokinin-1, or NK-1, receptor antagonist. Substance P is a naturally occurring undecapeptide that belongs to the tachykinin family of peptides. Specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals. Its characteristic amino acid sequence is illustrated in U.S. Patent No. 4,680,283. The neuropeptide receptors for substance P are distributed throughout the mammalian nervous system, e.g., the brain and spinal ganglia, the circulatory system and peripheral tissues such as the duodenum and jejunum.

Substance P is believed to be involved in the transmission of pain. A large number of substance P receptor antagonists have been described in the patent literature as suitable for alleviating pain and/or ameliorating any of a variety of disorders that are commonly accompanied by pain. See, e.g., U.S. Patent Nos. 3,862,114, 3,912,711, 4,472,305, 4,481,139, 4,680,283, 4,839,465, 5,102,667, 5,162,339, 5,164,372, 5,166,136, 5,232,929, 5,300,648, 5,310,743, 5,338,845, 5,340,822, 5,378,803, 5,410,019, 5,411,971, 5,420,297, 5,422,354, 5,446,052,

5,451,586, 5,525,712, 5,527,811, 5,536,737, 5,541,195, 5,561,113, 5,576,317, 5,604,247, 5,624,950 and 5,635,510; World Patent Application Nos. WO 90/05525, WO 91/09844, WO 91/12266, WO 92/06079, WO 92/12151, WO 92/15585, WO 92/20661, WO 92/20676, WO 92/21677, WO 92/22569, WO 93/00330, WO 93/00331, WO 93/01159, WO 93/01160, WO 93/01165, WO 93/01169, WO 93/01170, WO 93/06099, WO 93/10073, WO 93/14084, WO 93/19064, WO 93/21155, WO 94/04496, WO 94/08997 and WO 95/11895; European Patent Application Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 443132, 446706, 484719, 499313, 512901, 512902, 514273, 514275, 520555, 522808, 528495 and 532456; and GB 2216529.

SUMMARY OF THE INVENTION

In accordance with the present invention, an analgesic composition is provided which comprises (a) an analgesically effective amount of at least one substance P receptor antagonist and (b) a substance P receptor antagonist-potentiating amount of at least one substance P receptor antagonist potentiator selected from the group consisting of nontoxic N-methyl-D-aspartate receptor and nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation.

Further in accordance with this invention, a method for alleviating pain is provided with comprises administering to a mammal exhibiting pain (a) an analgesically effective amount of at least one substance P receptor antagonist and (b) a substance P receptor antagonist-potentiating amount of at least one substance P receptor antagonist potentiator selected from the group consisting of nontoxic N-methyl-D-aspartate receptor antagonist and nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation.

The expression "N-methyl-D-aspartate receptor" shall be understood to include all of the binding site subcategories associated with the NMDA receptor, e.g., the glycine-binding site, the phenylcyclidine (PCP)-binding site, etc., as well as the NMDA channel. Thus, the invention herein contemplates the use of nontoxic substances that block an NMDA receptor binding site, e.g., dextromethorphan, or that block the NMDA channel, e.g., a source of magnesium such as magnesium sulfate.

The term "nontoxic" as used herein shall be understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established regulatory criteria and practice, is susceptible to approval by the FDA for administration to humans. The term "nontoxic" is also used herein to distinguish the NMDA receptor antagonists, or blockers, that are useful in the practice of the present invention from NMDA receptor antagonists such as MK 801 (the compound 5-methyl-10,11-dihydro-SH-dibenze[a,d] cyclohepten-5,10-imine), CPP (the compound 3-[2-carboxypiperazin-4-yl] propyl-1-phosphonic acid) and PCP (the compound 1-(1-phenylcyclohexyl)piperidine) whose toxicities effectively preclude their therapeutic use.

The terms "potentiate" and "potentiating" are used herein in their art-recognized sense, i.e., as referring to a significant increase in the level of analgesic activity for the combination of substance P receptor antagonist and nontoxic NMDA receptor antagonist and/or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation compared with that which could have been expected based on the activities of the substance P receptor antagonist administered alone and nontoxic NMDA receptor antagonist and/or nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation administered alone.

The expression "analgesically effective amount" as applied to the substance P receptor antagonist employed in the analgesic composition and method of this invention shall be understood to mean an amount of substance P receptor antagonist which when administered by itself or in combination with the nontoxic NMDA receptor antagonist and/or substance that blocks a major intracellular consequence of NMDA receptor activation provides effective analgesia.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Any of the substance P receptor antagonists heretofore used to treat pain and/or a disorder exhibiting a pain component, e.g., muscular pain, musculoskeletal pain, chronic pain, neuropathic pain, migraine, etc., can be used herein. Specific substance P receptor antagonists that can be used herein are disclosed in aforementioned U.S. Patent Nos. 3,862,114, 3,912,711, 4,472,305, 4,481,139, 4,680,283, 4,839,465, 5,102,667, 5,162,339, 5,164,372, 5,166,136, 5,232,929, 5,300,648, 5,310,743, 5,338,845, 5,340,822, 5,378,803, 5,410,019, 5,411,971, 5,420,297, 5,422,354, 5,446,052, 5,451,586, 5,525,712, 5,527,811, 5,536,737, 5,541,195, 5,561,113, 5,576,317, 5,604,247, 5,624,950 and 5,635,510; World Patent Application Nos. WO 90/05525, WO 91/09844, WO 91/12266, WO 92/06079, WO 92/12151, WO 92/15585, WO 92/20661, WO 92/20676, WO 92/21677, WO 92/22569, WO 93/00330, WO 93/00331, WO 93/01159, WO 93/01160, WO 93/01165, WO 93/01169, WO 93/01170, WO 93/06099, WO 93/10073, WO 93/14084, WO 93/19064, WO 93/21155, WO 94/04496, WO 94/08997 and WO 95/11895; European Patent Application Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 443132, 446706, 484719, 499313, 512901, 512902, 514273, 514275, 520555, 522808, 528495 and 532456; and GB 2216529, the contents of which are incorporated by reference herein.

More particularly, useful substance P receptor antagonists include the substance P analogs of U.S. Patent No. 3,862,114, e.g., compounds having the L-amino acid sequence G-L-M-NH_2, O-G-L-M-NH_2, F-G-L-M-NH_2 and the like; the undecapeptides of U.S. Patent No. 3,912,711, e.g., L-arginyl-L-prolyl-L-lysyl-L-prolyl-L-glutaminyl-L-glutaminyl-L-phenylalanyl-L-glycyl-L-leucyl-L-methionine amide and the like; the hexapeptide amides of U.S. Patent No. 4,472,305, e.g., HPro-Phe-Phe-DAla-Leu-MetNH_2, HPro-Phe-MePhe-Gly-Leu-MetNH_2, HPro-Phe-Phe-Gly-DLeu-MetNH_2 and the like; the undecapeptides of U.S. Patent No. 4,481,139, e.g., [D-Phe^5, D-Trp^7, D-Trp^9, Leu^{11}]-SP, [Glp^5, D-Trp^7, D-Trp^9, Thr^{11}]-SP_{5-11}, [D-Ang^1, D-Trp^7, D-Trp^9, Leu^{11}]-SP and the like; the substance P analogs of U.S. Patent No. 4,680,283, e.g., pyroglutamyl-ohenylalanyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl]methionine amide, pyroglutamyl-phenylalanyl-N-methyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl]methionine amide and the like; the di-(D-tryptophyl and/or tetra-hydropyridoindolylcarbonyl)-containing peptide amides of U.S. Patent No. 4,839,465, e.g., H-trp-Phe-trp-Leu-Met-NH_2, H-Pro-trp-Phe-trp-Leu-Phe-NH_2, H-tpi-Phe-trp-Leu-Met-NH_2 and the like; the isoindolones of U.S. Patent No. 5,102,667, e.g., 2-[l-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,7aR) or (3aR,7aRS) forms, 7,7-diphenyl-2-[2-(2-dimethylaminophenyl)acetyl]-4-perhydro-isoindolone in its (3aR,7aR) or (3aRS,7aRS) forms, 7,7-diphenyl-2-[(R)-2-(2-methoxyphenyl)propionyl]-4-perhydroisoindolone in its (3aR,7aR) or (3aRS,7aRS) forms and the like; the quinuclidines of U.S. Patent No. 5,162,339 and World Patent Application No. WO 90/05525, e.g., cis-3-[(2-chlorophenyl)methylamino]-2-benz-hydrylquinuclidine, cis-3-[(2-trifluoromethylphenyl)methylamino]-2-benzhydryl-quinuclidine, cis-3-[(2-methoxyphenyl)methylamino]-2-benzhydrylquinuclidine and the like; the peptides of U.S. Patent No. 5,164,372, e.g., the compounds of Examples 1-63 and the like; the spirolactams of U.S. Patent No. 5,166,136 and European Patent

Application No. EP 360390, e.g., 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester, 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid phenylmethyl ester, 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, (1,1-dimethyl)ethyl ester and the like; the 3-aminopiperidines and related nitrogen containing heterocycles of U.S. Patent No. 5,232,929, e.g., cis-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-1-allyl-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-1-ethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine and the like; the dialkylenepiperidinos of U.S. Patent Nos. 5,300,648 and 5,446,052, e.g., N-[4-(1-benzyl-4-piperidinyl)-2-(3,4-dichlorophenyl)-butyl]-4-fluoronaphtalene carboxamide hydrochloride, N-[4-[1-(fluorobenzyl)-4-piperidinyl]-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride, N-methyl-N-[4-(1-benzyl-4-piperidinyl)-2-(3,4-dichlorophenyl)-butyl]3-isopropoxy-phenylacetamide hydrochloride and the like; the 1-acylpiperidines of U.S. Patent Nos. 5,310,743 and 5,541,195, e.g., (2R,4S) and (2R,4R)-2-benzyl-1-(3,5-dimethyl-benzoyl)-N-(2-phenethyl)-4-piperidinamine hydrochloride, (2R*,4S*)-2-benzyl-1-(2-naphthoyl)-N-(4-quinolylmethyl)-4-piperidinamine, (2R*,4S*)-2-benzyl-1-(3-tri-fluoromethylbenzoyl)-N-(4-quinolylmethyl)-4-piperidinamine and the like; the cyclic dimeric dipeptide derivatives of U.S. Patent No. 5,338,845, e.g., the compounds of Table 1 and the like; the polycyclic amines of U.S. Patent No. 5,340,822, e.g., 4-[2-(4-benzylpiperidin-1-yl)ethyl]-4-(3-methylphenyl)-1-(3-chlorophenyl)acetylpiperidine hydrochloride, 3-[2-(4-benzylpiperidin-1-yl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetylpiperidine hydrochloride, 5-[2-(4-Benzylpiperidin-1-yl)ethyl]-5-(3,4-dichlorophenyl)-1-benzylpiperidinone hydrochloride and the like; the azole-fused peptides of U.S. Patent No. 5,378,803, e.g., the compounds of Examples 1-28 and the like; the peptides of U.S. Patent No. 5,410,019, e.g., H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leuψ[CH_2-NH]Leu-NH_2, H-D-Arg-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-D-Trpψ[CH_2-

NH]Leu-Nle-NH_2, H-D-Arg-Pro-Lys-Pro-Gln-Gln-D-Trpψ[CH_2-NH]Phe-D-Trp-Leu-Nle-NH_2 and the like; the N-alkylenepiperidinos of U.S. Patent No. 5,411,971, e.g., N-[2-(3,4-dichlorophenyl)-4-(4-(2-pyridylthio)-1-piperidinyl)butyl]-2,4-dichlorobenzamide, N-[4-(4-N'-acetylanilino-1-piperidinyl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide, N-[4-(1-methyl-2-imidazolyl)-4-thio-1-piperidinyl)-2-naphthylbutyl]-2,4-dimethoxybenzamide and the like; the peptides of U.S. Patent No. 5,420,297, e.g., Boc-Phe (p-CH_3)-OH, Boc-Phe(p-F)-OH and the like; the quinuclidines of U.S. Patent No. 5,422,354, e.g., 8-(diphenylmethyl)-N-((2-methoxyphenyl)methyl))-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine, 8-(diphenylmethyl)-N-(phenylmethyl)-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine, 8-(diphenylmethyl)-N-((2-chlorophenyl)methyl))-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine and the like; the 3-amino-2-arylquinuclidines of U.S. Patent No. 5,451,586, e.g., trans-2-phenyl-N-(2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine, cis-2-phenyl-N-(phenyl-methyl)-1-azabicyclo[2.2.2]octan-3-amine, 2-(1-naphthyl)-N-((2-methoxy-phenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine and the like; the isoquinolinyls of U.S. Patent No. 5,527,811, e.g., N-[(6-chloro-1,2-dihydro-2-methyl-1-oxo-4-phenylisoquinolin-3-yl)methyl]-N′-(3-isopropoxyphenyl)urea, N-[(1,2-dihydro-2,6,7-trimethyl-1-oxo-4-phenylisoquinolin-3-yl)methyl]-N′-(3-methylphenyl)urea, N-[(1,2-dihydro-2-methyl-1-oxo-4-phenylisoquinolin-3yl)methyl]-N′-(3-methylphenyl)urea and the like; the prolyl endopeptidase inhibitor compounds of U.S. Patent No. 5,536,737, e.g., (S)-2-[[(S)-2-(acetoxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide, (S)-2-[[(S)-2-(hydroxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide, (S)-2-[[(S)-2-[(benzoyloxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide and the like; the pseudopeptides of U.S. Patent No. 5,561,113, e.g., {1-[4-(1H-tetrazol-5-yl)-butyl)indol-3-yl}carbonyl-Hyp-Nal-NMeBzl, {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Tna-NMeBzl, {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-

Thn-NMeBzl and the like; the piperidines of U.S. Patent No. 5,576,317, e.g., (2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3-trifluoromethoxyphenyl)piperidine (2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine, (2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine and the like; the chromone compounds of U.S. Patent No. 5,604,247, e.g., (2R,4S)-N-[1-(3,5-bis-trifluoromethylbenzoyl)-2-(4-chlorobenzyl)piperidin-4-yl]-4-oxo-4H-1-benzopyrane-2-carboxamide, (2R,4S)-N-[1-(3,5-bistrifluormethylbenzoyl)-2-benzylpiperidin-4-yl]-4-oxo-4H-1-benzopyrane-2-carboxamide, (2R,4S)-N-[1-(3,5-bistrifluoromethylbenzoyl)-2-(4-chlorobenzyl)piperidin-4-yl]-6-fluoro-4-oxo-4H-1-benzopyrane-2-carboxamide and the like; the perhydroisoindoles of U.S. Patent No. 5,624,950, e.g., 7,7-dimethyl-4-(2-methoxyphenyl)-2-[2-(S)-(2-methoxyphenyl)propionyl]-4,5-perhydroisoindolediol, 4-(2-methoxyphenyl)-2-[2-(S)-(2-methoxyphenyl)proponyl]-5-methyl-4-perhydro-isoindolol, 2-[2-(S)-(2-hydroxyphenyl)propionyl]-4-(2-methoxyphenyl)-6-methyl-4-perhydroisoindolol and the like; the substituted pyrrolidin-3-yl-alkyl-piperidines of U.S,. Patent No. 5,635,510, e.g., (+)-or(-)-1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide, (+)-or(-)-1-[2-[3-(3,4-dichlorophenyl)-1-(2,6-dimethoxybenzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide, (+)-or(-)-1-[2-[3-(3,4-dichloro-phenyl)-1(3,4,5-trimethoxybenzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide and the like; the 3-amino-piperidines of World Patent Application No. WO 91/09844, e.g., cis-3-(2-chlorobenzylamino)-2-phenyl-piperidine, cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine, cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine and the like; the peptides of World Patent Application No. WO 91/12266, e.g., the compounds of Examples 1-34 and the like; the fused ring analogs of nitrogen containing heterocycles of World Patent Application No. WO 92/06079, e.g., [1α,3α,4α,5α]-4-(2-methoxybenzyl)-amino-3-phenyl-2-azabicyclo[3.3.0]octane, 4-(2-methoxybenzyl)amino-3-phenyl-2-

azabicyclo[4.4.0]decane, 4-(2-methoxybenzyl)amino-4-benzhydryl-3-azabicyclo-[4.1.0]heptane and the like; the N-alkyl quinuclidinium salts of World Patent Application No. WO 92/12151, e.g., (2S,3S)-cis-1-methyl-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine iodide, (2S,3S)-cis-1-(4-carbethoxybutyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo-[2.2.2]octan-3-amine iodide, (2S,3S)-cis-1-(4-carboethoxyphenylmethyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine iodide and the like; the 1-azabicyclo[3.2.2]nonan-3 amines of World Patent Application No. WO 92/15585, e.g., 2-(diphenylmethyl)-N-((2-methoxyphenyl)-methyl)-1-azabicyclo[3.2.2]nonan-3-amine, 2-(diphenylmethyl)-N-((2-chlorophenyl)-methyl)-1-azabicyclo[3.2.2]nonan-3-amine, 2-(diphenylmethyl)-N-((2,4-dimethoxy-phenyl)methyl)-1-azabicyclo[3.2.2]nonan-3-amine and the like; the N,N-diacyl-piperazines of World Patent Application No. WO 92/20661, e.g., 1,4-bis(N,N-diphenylcarbamoyl)piperazine-2-carboxylic acid, 1,4-bis(N,N-diphenylcarbamoyl)-2-methyl-piperazine, 1-(N,N-di-n-pentylcarbamoyl)-4-(N,N-diphenylcarbamoyl)-piperazine-2-carboxylic acid and the like; the substituted 3-aminoquinuclidines of World Patent Application No. WO 92/20676, e.g., (3R,4S,5S,6S)-N,N-diethyl-5-(2,5-dimethoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo-[2.2.2]octane-3-carboxylic acid, (3R,4S,5S,6S)-5-(2-methoxy-2-methylthiobenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid and the like; the quinuclidines of World Patent Application No. WO 92/21677, e.g., (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenyl-methyl-1-azabicyclo-[2.2.2]octan-3-amine, (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenyl-methyl-1-azabicyclo[2.2.2]octan-3-amine and the like; the peptides of World Patent Application No. WO 92/22569, e.g., the compounds of Examples 1-22 and the like;

the azanorbornane compounds of World Patent Application No. WO 93/00330, e.g., (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxyphenyl)methylamino]-bicyclo[2.2.1]heptane, (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]bicyclo[2.2.1]heptane, (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]bicyclo[2.2.1]heptane and the like; the fluoroalkoxybenzylamino derivatives of nitrogen containing heterocycles of World Patent Application No. WO 93/000331, e.g., (2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxy)-benzyl]aminopiperidine, 2-(diphenylmethyl)-N-((2-difluoromethoxy)phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-trifluoromethoxy-phenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-amine and the like; the fused tricyclics of World Patent Application No. WO 93/01159, e.g., 1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine, N-acetamido-1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine, 1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine and the like; the aromatic compounds of World Patent Application No. WO 93/01160, e.g., 2-ammonium-1-((3,5-dimethylphenyl)methyloxy)-3,3-diphenylpropane, 2-dimethylammonium-1-((3,5-dimethylphenyl)methyloxy)-3,3-diphenylpropane, 2-t-butoxycarbonylamino-3,3-diphenylpropanoyl-(2-methoxyphenyl)methylamide and the like; the aromatic compounds of World Patent Application No. WO 93/01165, e.g., L-1-((3,5-bis(trifluoromethyl)-phenyl)methyloxy)-2-(t-butoxycarbonylamino)-2-phenylethane, 1-((3,5-dimethylphenyl)methyloxy)-2(S)-2-(((carbomethoxy)methyl)amino)-2-phenylethane, (2S)-2-(((carboxamido)methyl)ammonium)-1-((3,5-dimethylphenyl)methyloxy)-2-phenylethane and the like; the aromatic compounds of World Patent Application No. WO 93/01169, e.g., 3,5-dimethylbenzyl 2-(1,1-dimethylethoxycarbonylamino)-3-(3-indolyl)propionate, 3,5-dimethylbenzyl 2-acetamido-3-(3-indolyl)propionate; 3,5-dimethylbenzyl 2-cyclohexanecarboxamido-3-(3-indolyl)propionate and the like; the 3-aminopiperidines

of World Patent Application No. WO 93/01170, e.g., (2S,3S)-3-(4,5-difluoro-2-methoxybenzyl)amino-2-phenylpiperidine, (2S,3S)-3-(2-cyclopentyl-oxy-5-methoxybenzyl)amino-2-phenylpiperidine, (2S,3S)-3-(5-sec-butyl-2-methoxy-benzyl)amino-2-phenylpiperidine and the like; the fused tricyclic nitrogen containing heterocycles of World Patent Application No. WO 93/06099, e.g., (+)-cis-9-diphenylmethyl-N-((2-methoxyphenyl)methyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine, (+)-cis-9-diphenylmethyl-N-(2-methoxy-5-chlorophenyl)-10-azatricyclo-[4.4.1.$0^{5,7}$]undecan-8-amine, (+)-cis-9-diphenylmethyl-N-(2-trifluoromethoxyphenyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine and the like; the acyclic ethylenediamines of World Patent Application No. WO 93/10073, e.g., 1-amino-1-phenyl-2-[(2-methoxy)-phenylmethylamino]propane, (1R',2S')-1-cyclohexylamino-1-phenyl-2-[(2-methoxy)-phenylmethylamino]propane, 1-N-cyclohexyl-1-phenyl-2-N'-[(2-methoxy-5-trifluoro-methoxyphenyl)methyl]-1,2-ethanediamine and the like; the piperidines of World Patent Application No. WO 93/14084, e.g., 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[((2-methyl)phenylsulfinyl)methyl]-4-piperidinol, 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[((4-methyl)phenylsulfinyl)methyl]-4-piperidinol, 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfinyl)methyl]-4-piperidinol and the like; the quinuclidines of World Patent Application No. WO 93/19064, e.g., (3R,4S,5S,6S)-N-carbamoylmethyl-5-(5-iso-propyl-2-methoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-N-carboxymethyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-3-(2-carbamoylpyrrolidin-1-yl)carbonyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane and the like; the perhydroisoindoles of World Patent Application No. WO 93/21155, e.g., diphenyl-7,7 (methoxy-2 phenyl)-4[(methoxy-2 phenyl)-2 propionyl]-2 perhydroisoindolol-4, diphenyl-7,7 (methoxy-2 phenyl)-4 [(methoxy-2 phenyl)-2 propionyl]-2 perhydroisoindolediol-4,5, diphenyl-7,7 (methoxy-2 phenyl)-4 [(hydroxy-2 phenyl)-2 acetyl]-2 perhydroisoindolol-4 and the

like; the substituted benzylamino nitrogen containing non-aromatic heterocycles of World Patent Application No. WO 94/04496, e.g., (2S,3S)-N-(2-methoxy-5-methyl-sulfonylphenyl)-methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-methylthiophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-dimethylaminophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine and the like; the substituted benzylaminoquinuclidines of World Patent Application No. WO 94/08997, e.g., (2S,3S)-N-(5-isopropenyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2,2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-vinylphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2,2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-4,5-dimethylphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine and the like; the N-benzoyl-4-oxy/thio-2-substituted piperidines of World Patent Application No. 95/11895, e.g., (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolylmethoxy)-piperidine, (2R*,4S*)-quinoline-3-carboxylic acid [2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl]ester, (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine and the like; the compounds of European Patent Application No. EP 327009, e.g., the compounds of Examples 1-5 and the like; the peptides of European Patent Application No. EP 333174, e.g., Boc-Gin-D-Trp(CHO)-Phe-Nmebzl, Boc-Thr-D-Trp(CHO)-Phe-NMeBzl, Boc-Glu(NMe_2)-D-Trp(CHO)-Phe-NMeBzl and the like; the peptides of European Patent Application No. EP 336230, e.g., the compounds of Example 1-22 and the like; the peptides of European Patent Application No. EP 394989, e.g., the compounds of Examples 1-63 and the like; the aromatic amines of European Patent Application No. 428434, e.g., N[(benzyl-4-piperidinyl-1)-4(dichloro-3,4 phenyl)-2 butyl]-dichloro-2,4 benzamide, N[(benzyl-4 piperidinyl-1)-4(difluoro-3,4 phenyl)-2 butyl]-dichloro-2,4 benzamide, N[(benzyl-4 piperidinyl-1)-4(dichloro-3,4 phenyl)-2 butyl]fluoro-4 naphthalene-1 carboxamide and the like; the isoindolones of European Patent Application No. EP 429366, e.g., diphenyl-7,7[dimethylamino-2 phenyl)-2

acetyl]-2 perhydroisoindolone-4, diphenyl-7,7[methoxy-2 phenyl)-2 propionyl-(R)]-2 perhydroisoindolone-4, [(5)-carboxy benzylimino-1 (methoxy-2 phenyl)-2 ethyl]-2 diphenyl-7,7 perhydroisoindolone-4 and the like; the peptides of European Patent Application No. EP 443132, e.g., the compounds of Examples 1-9 and the like; the azabicyclics of European Patent Application No. EP 499313, e.g., trans-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane, trans-3-[3,5-dimethoxybenzyloxy]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane, trans-2-(diphenylmethyl)-3-(3-phenoxybenzyloxy)-1-azabicyclo[2.2.2]octane and the like; the polycyclic amines of European Patent Application No. EP 512901, e.g., chlorhydrate of 5-[2-(4-benzyl-1-piperidinyl)ethyl]-5-(3,4-dichlorophenyl)-1-benzyl-piperidinone, chlorohydrate of 3-[2-(4-benzyl-1-piperidinyl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetylpiperidine, chlorohydrate of 3-[2-(4-benzyl-1-piperidinyl)ethyl]-3-(3,4-dichlorophenyl)-1-(3-isopropoxyphenyl)acetylazepine and the like; the dialkylenepiperidinos of European Patent Application No. EP 512902, e.g., chlorohydrate of N-[{4-[1-benzyl-piperidin-4-yl]-2-(3,4-dichlorophenyl)}-butyl]-4-fluoronaphtalenecarboxamide, chlorohydrate of N-[{2-(3,4-dichlorophenyl)-4-[1-(4-fluorobenzyl)-piperidin-4-yl]}-butyl]-2,4-dichlorobenzamide, chlorohydrate of N-methyl-N-{{4-[1-benzyl-piperidine-4-yl]-2-(3,4-dichlorophenyl)}-butyl]-3-isopropoxyphenylacetamide and the like; the perhydroisoindoles of European Patent Application No. EP 514273, e.g., {{[(pyrrolidinyl-1)-3 propoxy-2]phenyl}acetyl-2 diphenyl-4,4 fluoro-7 perhydroisoindole, diphenyl-4,4 fluoro-7 [(methoxy-2 phenyl)-2 propionyl-(S)]-2 perhydroisoindole, [(dimethylamino-3 propoxy)-2 phenyl]acetyl-2 diphenyl-4,4 fluoro-7 perhydroisoindole and the like; the thiopyranipyrroles of European Patent Application No. EP 514275, e.g., {[(dimethylamino-3 propoxy-2) phenyl]acetyl)-6 diphenyl-4,4-oxyde-1 perhydrothiopyrano[2,3-c]pyrrole, {[(pyrrolidinyl-1)-3 propoxy-2] phenyl} acetyl}-6 diphenyl-4,4 oxyde-1 perhydrothiopyrano[2,3-c]pyrrole, [{methoxy-2 phenyl)-2 propionyl-(S)]-6 diphenyl-

4,4 oxyde-1 perhydrothiopyrano[2,3-c]pyrrole and the like; the azabicyclics of European Patent Application No. EP 520555, e.g., 3-[(3,5-dimethylphenyl)methoxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane, 3-[(3,5-bistrifluoromethylphenyl)methoxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane, 3-[(3,5-bistrifluoromethylphenyl)methyloxy]-2-[1-(1-(4-methoxyphenyl)-2-phenyl)ethyl]-1-azabicyclo[2.2.2]octane and the like; the aromatic compounds of European Patent Application No. EP 522808, e.g., 2-ammonium-3,3-diphenylpropanoyl-(2-methoxyphenyl)methylamide, (3,5-dimethyl-phenyl)methyl-2-ammonium-3,3-diphenylpropanoate, 2-methylammonium-1-((3,5-dimethylphenyl)methyloxy)-3,3-diphenylpropane and the like; the azacyclics of European Patent Application No. EP 528495, e.g., cis-2-(diphenylmethyl-3-(3,5-dimethylbenzyloxy)-1-methylpyrrolidine, cis-3-((3,5-dimethylphenyl)methyloxy)-2-phenylpiperidine, cis-3-((3,5-dimethylphenyl)methyloxy-1-methyl-2-phenylpiperidine and the like; the 1-acylpiperidins of European Patent Application No. EP 532456, e.g., (2R*,4S*)-2-benzyl-1-(2-naphthoyl)-N-(4-chinolylmethyl)-4-piperidinamin, (2R*,4S*)-2-benzyl-1-(3-trifluoromethylbenzoyl)-N-(4-chinolylmethyl)-4-piperidinamin, (2R*,4S*)-2-benzyl-1-(3,5-bis-(trifluoromethyl)-benzoyl)-N-(4-chinolylmethyl)-4-piperidinamin and the like; and the peptides of GB 2216529, e.g., cyclo(Gln-Trp-Phe-(R)Gly[ANC-2]Leu-Met, cyclo(Gln-Npa-Phe-(R)Gly[ANC-2]Leu-Met, cyclo(Gln-Trp-Phe-Gly-Leu-Met and the like.

Among the nontoxic substances that block the NMDA receptor and as such are useful for enhancing the analgesic activity of a substance P receptor antagonist in accordance with this invention are dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) and its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), their mixtures and their pharmaceutically acceptable salts. Other useful nontoxic substances that block the NMDA receptor include amantadine (1-aminoadamantine), memantine (3,5-dimethylaminoadamantone), pyrroloquinoline

quinone and cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid. Of the nontoxic NMDA receptor antagonists, dextromethorphan in the form of its hydrobromide salt is preferred for use herein due to its ready availability and its established use in over-the-counter medications where it functions as a cough suppressant. While dextrorphan and its pharmaceutically acceptable salts will also provide excellent results, it is not known to be in commercial manufacture at this time.

In addition to, or in place of, a blocker for the NMDA receptor, at least one nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation can also be used. Activation of the NMDA receptor, a subtype of excitatory amino acid receptors, induces a number of changes in the functional activity of nerve cells and, in particular, their capacity for excitability or inhibition in the presence of an addictive substance via an increase in intracellular Ca++ concentration. The major consequences of NMDA receptor activation include the following sequences, or cascades, of events occurring within nerve cells:

a) translocation and activation of protein kinases such as protein kinase C → phosphorylation of substrate proteins such as cytosolic enzymes, channel proteins, receptor proteins, etc. → changes in functional activity;

b) initiation of early gene (c-*fos, c-jun, zif*-268, etc.) expression by either increased intracellular Ca++ or Ca++-activated protein kinases → expression of functional genes responsible for production of cellular enzymes (such as protein kinases), receptor proteins (such as the NMDA receptor), ion channel proteins (such as K+, Na+, Ca++ channels), neuropeptides (such as dynorphin), etc. → changes in functional activity;

c) Ca++/calmodulin (or other Ca++ binding proteins) induced activation of enzymes and other cellular components → activation of Ca++/calmodulin-protein kinase systems such as Ca++/calmodulin kinase II →

autophosphorylation of enzymes (e.g., Ca++/calmodulin kinase II) or other functional proteins → changes in functional activity;

d) Ca++/calmodulin induced activation of constitutive nitric oxide synthase as well as induction of inducible nitric oxide synthase → production of nitric oxide → i) production of cyclic guanosine monophosphate via activation of guanosine cyclase resulting in activation of protein kinases and early gene expression; ii) direct protein modification such as enzymes, receptor and/or channel proteins; iii) lipid membrane modification and/or nucleic acid modification via scavenge of free radicals; iv) induction of neurotoxicity at higher nitric oxide levels; v) retrograde actions in adjacent neurons or glial cells such as facilitation of glutamate release/NMDA receptor activation and/or inhibition of post-synaptic NMDA receptors → changes in functional activity;

e) interactions with the cyclic adenosine monophosphate/protein kinase A system, the phospholipase C-inositol triphosphate-Ca++/diacylglycerol-protein kinase system, the phospholipase A2-arachidonic acid/prostanoids/ leukotrienes system → changes in functional activity induced by second messenger systems other than NMDA receptor/Ca^{++}/Ca^{++}-calmodulin/protein kinase systems; and,

f) interactions with other excitatory amino acid receptor subtypes including non-NMDA receptors and metabotropic receptors as well as intracellular events subsequent to the activation of these excitatory amino acid receptor subtypes → changes in functional activity induced by the non-NMDA and metabotropic receptor activation.

A substance that blocks the NMDA receptor will effectively prevent all of the foregoing major intracellular sequences of events from taking place. However, even with activation of the NMDA receptor, it is still possible to alleviate pain in accordance with this invention by administering the substance P receptor antagonist and a nontoxic substance that blocks at least one of the foregoing major intra-cellular

sequences of events brought about by activation of the NMDA receptor. Thus, e.g., a substance that interferes with translocation and activation of protein kinase C or with calmodulin induced activation of constitutive nitric oxide synthase as well as induction of inducible nitric oxide synthase is also useful for the practice of this invention.

Nontoxic substances that block a major intracellular consequence of NMDA receptor activation and are therefore useful in the practice of the invention include inhibitors of protein kinase C, e.g., gangliosides such as ganglioside GM_1 (monosialoganglioside) and ganglioside GT_b (trisialoganglioside); amphipathic long chain bases such as sphingosine, N,N,N-trimethylsphingosine, sphinganine and psychosine; quinolyloxazole-2-ones such as 4-methyl-5-(3-quinolinyl)-2-(3H)-oxazolone and phenyl-5-(2-quinolinyl)-2-3(3H)-oxazolone; 1,4-bis-(amino-hydroxyalkylamino)-anthraquinones such as 1,4-bis-(3-propylamino-2-hydroxypropylamino)-9,10 anthracenedione and 1,4-bis-(3-benzylamino-2-hydroxypropylamino)-9,10 anthracenedione; and, mixtures and pharmaceutically acceptable salts of any of the foregoing.

Additional nontoxic substances that block a major intracellular consequence of NMDA receptor activation and as such are useful in the practice of the invention include inhibitors of calmodulin such as the phenothiazines, in particular, chlorpromazine, chlorpromazine sulfoxide, prochlorperazine dimaleate, perphenazine, trifluoperazine, fluphenazine, fluphenazine enanthate, fluphenazine decanoate, thioridazine, mesoridazine besylate, piperacetazine, acetophenazine dimaleate, carphenazine dimaleate, butaperazine dimaleate and phenothiazine sulfoxide; naphthalenesulfonamides such as N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide, N-(6-aminohexyl)-5-chloro-2-naphthalenesulfonamide and N-(6-aminohexyl)-5-bromo-2-naphthalenesulfonamide; 4-substituted-4H,6H-pyrrolo[1,2-a][4,1] benzoxazepines such as 1,3-dihydro-1-{1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1] benzoxazepin-4-yl)methyl]-4-piperidinyl}-2H-benzimidazol-2-one; benzhydryls such as N-

[2](diphenylmethylthioethyl]-2-(trifluoromethyl)-benzeneethanamine, N-[2-(bis(4-fluorophenyl)methylthio)- ethyl]-2-(trifluoromethyl)benzeneethanamine and N-[2-(bis(4-fluorophenyl)methylthio)ethyl]-3-(trifluoromethyl)benzene-ethanamine; tricyclic antidepressant drugs such as imipramine, 2-chloroimipramine and amitriptyline; penfluridol; haloperidol; pimozide; clozapine; calmidazolin; and, mixtures and pharmaceutically acceptable salts of any of the foregoing.

Of the two groups of substance P receptor antagonist potentiators the nontoxic NMDA receptor antagonists are preferred and of these, dextromethorphan is preferred for the reasons previously stated.

With regard to dosage levels, the substance P receptor antagonist must be present in an analgesically effective amount, e.g., at a level corresponding to the generally recommended adult human dosages for a particular substance P receptor antagonist, and the nontoxic NMDA receptor antagonist or substance that blocks a major intracellular consequence of NMDA activation must be present at a level that potentiates the therapeutic effectiveness of the substance P receptor antagonist. Given the wide variations in dosage level of the substance P receptor antagonist which depends to a large extent on the specific substance P receptor antagonist being administered, there can similarly be a wide variation in the dosage level of the nontoxic NMDA receptor antagonist or substance that blocks a major intracellular consequence of NMDA receptor activation. These amounts can be determined for a particular drug combination in accordance with this invention employing routine experimental testing.

While the substance P receptor antagonist and nontoxic NMDA receptor antagonist and/or substance that blocks a major intracellular consequence of NMDA receptor activation need not be administered together, they must both be present in the patient at effective levels at the same time. While it is within the scope of the invention to administer the substance P receptor antagonist and nontoxic NMDA receptor antagonist and/or substance that blocks a major intracellular consequence of NMDA

receptor activation separately, as a matter of convenience, it is preferred that they be coadministered as a single analgesic composition. All modes of administrations are contemplated, e.g., orally, rectally, parenterally, topically, or by intravenous, intramuscular, intrastemal or subcutaneous injection or in a form suitable by inhalation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy.

An analgesic composition containing the substance P receptor antagonist and nontoxic NMDA receptor antagonist and/or substance that blocks a major intracellular consequence of NMDA receptor activation will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, the analgesic composition can be formulated as a liquid, powder, elixir, injectable solution, etc. Formulations for oral use can be provided as tablets or hard capsules wherein the pharmacologically active ingredients are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are mixed with water or miscible solvents such as propylene glycol; PEG's and ethanol, or an oleaginous medium, e.g., peanut oil, liquid paraffin or olive oil.

For topical administration in the mouth, the analgesic composition herein can take the form of a buccal or sublingual tablet, drops or lozenges formulated in a known or conventional manner.

For topical administration, the analgesic composition of the invention can be formulated as a cream, gel, ointment or lotion or as a transdermal patch. Such composition can, for example, be formulated with an aqueous or oily base with the addition of suitable thickening, gelling, emulsifying, stabilizing, dispersing, suspending and/or coloring agents.

The analgesic composition of the invention can also be formulated as a sustained release preparation. Such long acting formulations can be administered by

implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the analgesic composition can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The analgesic composition of the invention can be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example, by bolus injection or continuous intravenous infusion. Formulations for injection can be presented in unit dosage, e.g., in ampoules or in multi-dose containers, with an added preservative. The analgesic composition can take a variety of forms such as a suspension, solution or emulsion in an oily or aqueous vehicle and can contain one or more formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the analgesic composition can be provided in powder form for dissolution in a suitable vehicle, e.g. sterile pyrogen-free water, before administration.

The analgesic composition of the invention can also be formulated as a rectal composition, e.g., a suppository or retention enema containing conventional suppository bases such as cocoa butter or other glyceride(s).

For administration by inhalation, the analgesic composition is conveniently delivered in the form of an aerosol spray by means of a pressurized container or a nebulizer employing a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide, and the like. In the case of a pressurized aerosol delivery system, the dosage unit can be regulated by means of a metering valve.

Aqueous suspensions can include pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose,

hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monoleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monoleate. The aqueous suspensions can also contain one or more preservatives, e.g., ethyl-or-n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

In addition to the substance P receptor antagonist and nontoxic NMDA receptor antagonist and/or substance that blocks a major intracellular consequence of NMDA receptor activation, the analgesic composition herein can contain at least one other pharmacologically active substance, e.g., a non-narcotic analgesic such as tramadol, acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin, zomepirac, and the like, or a narcotic analgesic such as codeine, oxycodone, dihydrocodeine, hydrocodone, levorphanol, morphine, and the like.

EXAMPLES 1-35

The following unit dosage forms are illustrative of the therapeutic drug combinations in accordance with the present invention:

Example	Substance P Receptor Antagonist (mg)	Nontoxic NMDA Receptor Blocker (mg)	Additional Active Component (mg)
1	pyroglutamyl-phenylalanyl-N-methyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl] methionine amide (25) [U.S. Patent No. 4,680,283]	dextromethorphan hydrobromide (30)	
2	pyroglutamyl-phenylalanyl-N-methyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl] methionine amide (25) [U.S. Patent No. 4,680,283]	dextromethorphan hydrobromide (30)	acetaminophen (325)
3	pyroglutamyl-phenylalanyl-N-methyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl] methionine amide (25) [U.S. Patent No. 4,680,283]	dextrorphan hydrobromide (30)	

Example	Substance P Receptor Antagonist (mg)	Nontoxic NMDA Receptor Blocker (mg)	Additional Active Component (mg)
4	2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,3aR) or (3aR,7aRS) forms (25) [U.S. Patent No. 5,102,667]	dextromethorphan hydrobromide (30)	
5	2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,3aR) or (3aR,7aRS) forms (25) [U.S. Patent No. 5,102,667]	dextromethorphan hydrobromide (30)	ibuprofen (200)
6	2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,3aR) or (3aR,7aRS) forms (25) [U.S. Patent No. 5,102,667]	dextrorphan hydrobromide (30)	
7	2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,3aR) or (3aR,7aRS) forms (25) [U.S. Patent No. 5,102,667]	amantadine (30)	
8	2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,3aR) or (3aR,7aRS) forms (25) [U.S. Patent No. 5,102,667]	memantine (30)	
9	cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (25) [U.S. Patent No. 5,162,339]	dextromethorphan hydrobromide (30)	
10	cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (25) [U.S. Patent No. 5,162,339]	dextromethorphan hydrobromide (30)	acetaminophen (325)
11	cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (25) [U.S. Patent No. 5,162,339]	dextrorphan hydrobromide (30)	
12	cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (25) [U.S. Patent No. 5,162,339]	amantadine (30)	
13	cis-3-[(2-chlorophenyl)methylamino]-2-benzhydrylquinuclidine (25) [U.S. Patent No. 5,162,339]	memantine (30)	

Example	Substance P receptor antagonist (mg)	Nontoxic NMDA Receptor Blocker (mg)	Additional Active Component (mg)
14	7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester (25) [U.S. Patent No. 5,166,136]	dextromethorphan hydrobromide (30)	
15	7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester (25) [U.S. Patent No. 5,166,136]	dextromethorphan hydrobromide (30)	acetaminophen (325)
16	7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester (25) [U.S. Patent No. 5,166,136]	dextrorphan hydrobromide (30)	
17	7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester (25) [U.S. Patent No. 5,166,136]	amantadine (30)	
18	7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester (25) [U.S. Patent No. 5,166,136]	memantine (30)	
19	cis-3-(2-methoxybenzylamino)-2-phenylpiperidine (25) [U.S. Patent No. 5,232,929]	dextromethorphan hydrobromide (30)	
20	cis-3-(2-methoxybenzylamino)-2-phenylpiperidine (25) [U.S. Patent No. 5,232,929]	dextromethorphan hydrobromide (30)	aspirin (325)
21	cis-3-(2-methoxybenzylamino)-2-phenylpiperidine (25) [U.S. Patent No. 5,232,929]	dextrorphan hydrobromide (30)	
22	cis-3-(2-methoxybenzylamino)-2-phenylpiperidine (25) [U.S. Patent No. 5,232,929]	amantadine (30)	
23	cis-3-(2-methoxybenzylamino)-2-phenylpiperidine (25) [U.S. Patent No. 5,232,929]	memantine (30)	
24	N-[4-[1-(fluorobenzyl)-4-piperidinyl]-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride (25) [U.S. Patent No. 5,300,648 and 5,446,052]	dextromethorphan hydrobromide (30)	

Example	Substance P receptor antagonist (mg)	Nontoxic NMDA Receptor Blocker (mg)	Additional Active Component (mg)
25	N-[4-[1-(fluorobenzyl)-4-piperidinyl]-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride (25) [U.S. Patent No. 5,300,648 and 5,446,052]	dextromethorphan hydrobromide (30)	acetaminophen (325)
26	N-[4-[1-(fluorobenzyl)-4-piperidinyl]-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride (25) [U.S. Patent No. 5,300,648 and 5,446,052]	dextrorphan hydrobromide (30)	
27	N-[4-[1-(fluorobenzyl)-4-piperidinyl]-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride (25) [U.S. Patent No. 5,300,648 and 5,446,052]	amantadine (30)	
28	N-[4-[1-(fluorobenzyl)-4-piperidinyl]-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride (25) [U.S. Patent No. 5,300,648 and 5,446,052]	memantine (30)	
29	3-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetyl-piperidine hydrochloride (25) [U.S. Patent No. 5,340,822]	dextromethorphan hydrobromide (30)	
30	3-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetyl-piperidine hydrochloride (25) [U.S. Patent No. 5,340,822]	dextromethorphan hydrobromide (30)	ibuprofen (200)
31	3-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetyl-piperidine hydrochloride (25) [U.S. Patent No. 5,340,822]	dextrorphan hydrobromide (30)	
32	N-[4-(4-N'-Acetylanilino-1-piperidinyl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide (25) [U.S. Patent No. 5,411,971]	dextromethorphan hydrobromide (30)	
33	8-(diphenylmethyl)-N-((2-methoxyphenyl) methyl))-9-azatricyclo[4.3.1.$0^{4,9}$] decan-7-amine (25) [U.S. Patent No. 5,422,354]	dextromethorphan hydrobromide (30)	

Example	Substance P receptor antagonist (mg)	Nontoxic NMDA Receptor Blocker (mg)	Additional Active Component (mg)
34	trans-2-phenyl-N-(2-methoxyphenyl) methyl)-1-azabicyclo[2.2.2]octan-3-amine (25) [U.S. Patent No. 5,451,586]	dextromethorphan hydrobromide (30)	
35	{1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl} carbonyl-Hyp-Thn-Nmebzl (25) [U.S. Patent No. 5,561,113]	dextromethorphan hydrobromide (30)	

In each of these dosage units, the nontoxic NMDA receptor antagonist dextromethorphan hydrobromide significantly potentiates the analgesic activity of the substance P receptor antagonist.

WHAT IS CLAIMED IS:

1. An analgesic composition which comprises (a) an analgesically effective amount of at least one substance P receptor antagonist and (b) a substance P receptor antagonist-potentiating amount of at least one substance P receptor antagonist potentiator selected from the group consisting of N-methyl-D-aspartate receptor nontoxic antagonist and nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation.

2. The analgesic composition of Claim 1 wherein the substance P receptor antagonist is selected from the group consisting of a substance P analog, undecapeptide, hexapeptide amide, di-(D-tryptophyl and/or tetra-hydropyridoindolylcarbonyl)-containing peptide amide, isoindolone, quinuclidine, peptide, spirolactam, 3-aminopiperidine and related nitrogen containing heterocycle, dialkylenepiperidino, 1-acylpiperidine, cyclic dimeric dipeptide derivative, polycyclic amine, azole-fused peptide, N-alkylenepiperidino, 3-amino-2-arylquinuclidine, isoquinolinyl, prolyl endopeptidase inhibitor compound, pseudopeptide, piperidine, chromone compound, perhydroisoindole, substituted pyrrolidin-3-yl-alkyl-piperidine, fused ring analog of nitrogen containing heterocycle, N-alkyl quinuclidinium salt, 1-azabicyclo[3.2.2]nonan-3-amine, N-N-diacyl-piperazine, substituted 3-amino-quinuclidine, azanorbornane compound, fluoroalkoxybenzylamino derivative of nitrogen containing heterocycle, fused tricyclic, aromatic compound, fused tricyclic nitrogen containing heterocycle, acyclic ethylenediamine, perhydroisoindole, substituted benzylamino nitrogen containing non-aromatic heterocycle, substituted benzylaminoquinuclidine, N-benzoyl-4-oxy/thio-2-substituted piperidine, aromatic amine, azabicyclic, thiopyranipyrrole and azacyclic.

3. The analgesic composition of Claim 2 wherein the substance P analog is selected from the group consisting of L-amino acid sequence G-L-M-NH_2, O-G-L-M-NH_2, F-G-L-M-NH_2, pyroglutamyl-ohenylalanyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl]methionine amide and pyroglutamyl-phenylalanyl-N-methyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl]methionine amide, undecapeptide is selected from the group consisting of L-arginyl-L-prolyl-L-lysyl-L-prolyl-L-glutaminyl-L-glutaminyl-L-phenylalanyl-L-glycyl-L-leucyl-L-methionine amide, [D-Phe^5, D-Trp^7, D-Trp^9, Leu^{11}]-SP, [Glp^5, D-Trp^7, D-Trp^9, Thr^{11}]-SP_{5-11}, and [D-Arg^1, D-Trp^7, D-Trp^9, Leu^{11}]-SP, hexapeptide amide is selected from the group consisting of Hpro-Phe-Phe-DAla-Leu-MetNH_2, HPro-Phe-MePhe-Gly-Leu-MetNH_2 and HPro-Phe-Phe-Gly-DLeu-MetNH_2, di-(D-tryptophyl and/or tetrahydropyridoindolylcarbonyl)-containing peptide amide is selected from the group consisting of H-trp-Phe-trp-Leu-Met-NH_2, Hpro-trp-Phe-trp-Leu-Phe-NH_2 and H-tpi-Phe-trp-Leu-Met-NH_2, isoindolone is selected from the group consisting of 2-[l-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,7aR) or (3aR,7aRS) forms, 7,7-diphenyl-2-[2-(2-dimethylaminophenyl)acetyl]-4-perhydro-isoindolone in its (3aR,7aR) or (3aRS,7aRS) forms, 7,7-diphenyl-2-[(R)-2-(2-methoxy-phenyl)propionyl]-4-perhydroisoindolone in its (3aR,7aR) or (3aRS,7aRS) forms, diphenyl-7,7[dimethylamino-2 phenyl)-2 acetyl]-2 perhydroisoindolone-4, diphenyl-7,7[methoxy-2 phenyl)-2 propionyl-(R)]-2 perhydroisoindolone-4 and [(5)-carboxy benzylimino-1 (methoxy-2 phenyl)-2 ethyl]-2 diphenyl-7,7 perhydro-isoindolone-4, quinuclidine is selected from the group consisting of cis-3-[(2-chlorophenyl)-methylamino]-2-benzhydrylquinuclidine, cis-3-[(2-trifluoro-methylphenyl)methyl-amino]-2-benzhydrylquinuclidine, cis-3-[(2-methoxy-phenyl)methylamino]-2-benz-hydrylquinuclidine, 8-(diphenylmethyl)-N-((2-methoxyphenyl)methyl))-9-azatricyclo-[4.3.1.$0^{4,9}$]decan-7-amine, 8-(diphenylmethyl)-N-(phenylmethyl)-9-azatricyclo-[4.3.1.$0^{4,9}$]decan-7-amine, 8-(diphenylmethyl)-N-((2-chlorophenyl)methyl))-9-

azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine, (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2,2.2]octan-3-amine, (3R,4S,5S,6S)-N-carbamoylmethyl-5-(5-isopropyl-2-methoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-N-carboxymethyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]-octane-3-carboxamide and (3R,4S,5S,6S)-3-(2-carbamoylpyrrolidin-1-yl)carbonyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane, the peptide is selected from the group consisting of H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leuψ[CH_2-NH]Leu-NH_2, H-D-Arg-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-D-Trpψ[CH_2-NH]Leu-Nle-NH_2, H-D-Arg-Pro-Lys-Pro-Gln-Gln-D-Trpψ[CH_2-NH]Phe-D-Trp-Leu-Nle-NH_2, Boc-Phe-(p-CH_3)-OH, Boc-Phe-(p-F)-OH, Boc-Gin-D-Trp(CHO)-Phe-NMe-Bzl, Boc-Thr-D-Trp(CHO)-Phe-NMeBzl, Boc-Glu(NMe_2)-D-Trp(CHO)-Phe-NMeBzl, cyclo(Gln-Trp-Phe-(R)Gly-[ANC-2]Leu-Met, cyclo(Gln-Npa-Phe-(R)Gly[ANC-2]Leu-Met and cyclo(Gln-Trp-Phe-Gly-Leu-Met), spirolactam is selected from the group consisting of 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diaza-spiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester, 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid phenylmethyl ester, 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro-[4.4]nonane-1-carboxylic acid and (1,1-dimethyl)ethyl ester, 3-aminopiperidine and related nitrogen containing heterocycle is selected from the group consisting of cis-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-1-allyl-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-1-ethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-3-(2-chlorobenzylamino)-2-phenylpiperidine, cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine, cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine, (2S,3S)-3-(4,5-difluoro-2-methoxybenzyl)amino-2-phenyl-piperidine, (2S,3S)-3-(2-

cyclopentyloxy-5-methoxybenzyl)amino-2-phenylpiperidine and (2S,3S)-3-(5-sec-butyl-2-methoxybenzyl)amino-2-phenyl-piperidine, dialkylenepiperidino is selected from the group consisting of N-[4-(1-benzyl-4-piperidinyl)-2-(3,4-dichlorophenyl)-butyl]-4-fluoronaphtalene carboxamide hydrochloride, N-[4-[1-(fluorobenzyl)-4-piperidinyl-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride, N-methyl-N-[4-(1-benzyl-4-piperidinyl)-2(3,4-dichlorophenyl)-butyl]3-isopropoxyphenylacetamide hydrochloride, chlorohydrate of N-[{4-[1-benzyl-piperidin-4-yl]-2-(3,4-dichloro-phenyl)}-butyl]-4-fluoronaphtalenecarboxamide, chlorohydrate of N-[{2-(3,4-dichloro-phenyl)-4-[1-(4-fluorobenzyl)-piperidin-4-yl]}-butyl]-2,4-dichlorobenzamide and chlorohydrate of N-methyl-N-{{4-[1-benzyl-piperidine-4-yl]-2-(3,4-dichlorophenyl)}-butyl]-3-isopropoxyphenylacetamide, the 1-acylpiperidine is selected from the group consisting of (2R,4S) and (2R,4R)-2-benzyl-1-(3,5-dimethylbenzoyl)-N-(2-phenethyl)-4-piperidinamine hydrochloride, (2R*,4S*)-2-benzyl-1-(2-naphthoyl)-N-(4-quinolyl-methyl)-4-piperidinamine, (2R*,4S*)-2-benzyl-2-(3-trifluoro-methylbenzoyl)-N-(4-quinolylmethyl)-4-piperidinamine, (2R*,4S*)-2-benzyl-1-(2-naphthoyl)-N-(4-chinolyl-methyl)-4-piperidinamin, (2R*,4S*)-2-benzyl-1-(3-trifluoromethylbenzoyl)-N-(4-chinolylmethyl)-4-piperidinamin and (2R*,4S*)-2-benzyl-1-(3,5-bis-(trifluoromethyl)-benzoyl)-N-(4-chinolylmethyl)-4-piperidinamin, polycyclic amine is selected from the group consisting of 4-[2-(4-benzylpiperidin-1-yl)ethyl]-4-(3-methylphenyl)-1-(3-chlorophenyl)acetylpiperidine hydrochloride, 3-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetylpiperidine hydrochloride, 5-[2-(4-benzylpiperidin-1-yl)ethyl]-5-(3,4-dichlorophenyl)-1-benzylpiperidinone hydrochloride, chlorhydrate of 5-[2-(4-benzyl-1-piperidinyl)ethyl]-5-(3,4-dichlorophenyl)-1-benzyl-piperidinone, chlorohydrate of 3-[2-(4-benzyl-1-piperidinyl)ethyl]-3-(3,4-dichlorophenyl)-1-phenyl-acetylpiperidine, chlorohydrate of 3-[2-(4-benzyl-1-piperidinyl)ethyl]-3-(3,4-dichlorophenyl)-1-(3-isopropoxy-phenyl)acetylazepine, the N-alkylenepiperidino is selected from the group consisting of N-[2-(3,4-dichlorophenyl)-4-(4-(2-pyridylthio)-1-

piperidinyl)butyl]-2,4-dichlorobenzamide, N-[4-(4-N'-acetylanilino-1-piperidinyl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide and N-[4-(1-methyl-2-imidazolyl)-4-thio-1-piperidinyl)-2-naphthylbutyl]-2,4-dimethoxybenzamide, 3-amino-2-aryl-quinuclidine is selected from the group consisting of trans-2-phenyl-N-(2-methoxy-phenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine, cis-2-phenyl-N-(phenylmethyl)-1-azabicyclo-[2.2.2]octan-3-amine and 2-(1-naphthyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine, isoquinolinyl is selected from the group consisting of N-[(6-chloro-1,2-dihydro-2-methyl-1-oxo-4-phenylisoquinolin-3-yl)methyl]-N'-(3isopropoxyphenyl)urea, N-[(1,2-dihydro-2,6,7-trimethyl-1-oxo-4-phenylisoquinolin-3-yl)methyl]-N'-(3-methylphenyl)urea and N-[(1,2-dihydro-2-methyl-1-oxo-4-phenyl-isoquinolin-3yl)methyl]-N'-(3-methylphenyl)urea, prolyl endopeptidase inhibitor compound is selected from the group consisting of (S)-2-[[(S)-2-(acetoxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide, (S)-2-[[(S)-2-(hydroxyacetyl)-1-pyrrolidinyl]carbonyl]-N-phenylmethyl-1-pyrrolidinecarboxamide and (S)-2-[[(S)-2-[(benzoyloxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide, pseudopeptide is selected from the group consisting of {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Nal-NMeBzl, {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Tna-NMeBzl and {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Thn-NMeBzl, piperidine is selected from the group consisting of (2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3trifluoromethoxyphenyl)piperidine, (2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine, (2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine, 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[((2-methyl)phenylsulfinyl)methyl]-4-piperidinol, 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[((4-methyl)phenylsulfinyl)methyl]-4-piperidinol and 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfinyl)methyl]-4-piperidinol, chromone compound is selected from the group consisting of (2R,4S)-N-[1-(3,5-bistrifluoromethylbenzoyl)-2-(4-chlorobenzyl)piperidin-4-yl]-4-oxo-4H-1-benzopyrene-2-carboxamide, (2R,4S)-N-[1-

(3,5-bistrifluormethylbenzoyl)-2-benzylpiperidin-4-yl]-4-oxo-4H-1-benzopyrene-2-carboxamide and (2R,4S)-N-[1-(3,5-bistrifluoromethylbenzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-6-fluoro-4-oxo-4H-1-benzopyrene-2-carboxamide, perhydroisoindole is selected from the group consisting of {{[(pyrrolidinyl-1)-3 propoxy-2]phenyl}acetyl}-2 diphenyl-4,4 fluoro-7 perhydroisoindole, diphenyl-4,4 fluoro-7 [(methoxy-2 phenyl)-2 propionyl-(S)]-2 perhydroisoindole, [(dimethylamino-3 propoxy)-2 phenyl]acetyl-2 diphenyl-4,4 fluoro-7 perhydroisoindole, 7,7-dimethyl-4-(2-methoxyphenyl)-2-[2-(S)-(2-methoxyphenyl)propionyl]-4,5-perhydroisoindolediol, 4-(2-methoxyphenyl)-2-[2-(S)-(2-methoxyphenyl)proponyl]-5-methyl-4-perhydro-isoindolol, 2-[2-(S)-(2-hydroxy-phenyl)propionyl]-4-(2-methoxyphenyl)-6-methyl-4-perhydroisoindolol, diphenyl-7,7 (methoxy-2 phenyl)-4[(methoxy-2 phenyl)-2 propionyl]-2 perhydroisoindolol-4, diphenyl-7,7 (methoxy-2 phenyl)-4 [(methoxy-2 phenyl)-2 propionyl]-2 perhydroiso-indolediol-4,5 and diphenyl-7,7 (methoxy-2 phenyl)-4 [(hydroxy-2 phenyl)-2 acetyl]-2 perhydroisoindolol-4, substituted pyrrolidin-3yl-alkyl-piperidine is selected from the group consisting of (+)-or(-)-1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide, (+)-or(-)-1-[2-[3-(3,4-dichloro-phenyl)-1(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide and (+)-or(-)-1-[2-[3-(3,4-dichloro-phenyl)-1(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide, fused ring analog of nitrogen containing heterocycle is selected from the group consisting of [1α,3α,4α,5α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo-[3.3.0]octane, 4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane and 4-(2-methoxybenzyl)amino-4-benzhydryl-3-azabicyclo[4.1.0]heptane, N-alkyl quinuclidinium salt is selected from the group consisting of (2S,3S)-cis-1-methyl-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine iodide, (2S,3S)-cis-1-(4-carbethoxybutyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)-methyl-1-azabicyclo[2.2.2]octan-3-amine iodide and (2S,3S)-cis-1-(4-carboethoxy-phenylmethyl)-

2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]-octan-3-amine iodide, 1-azabicyclo[3.2.2] nonan-3-amine is selected from the group consisting of 2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-azabicyclo[3.2.2]-nonan-3-amine, 2-(diphenylmethyl)-N-((2-chlorophenyl)methyl)-1-azabicyclo[3.2.2]-nonan-3-amine and 2-(diphenylmethyl)-N-((2,4-dimethoxyphenyl)methyl)-1-azabicyclo-[3.2.2]nonan-3-amine, N,N-diacyl-piperazine is selected from the group consisting of 1,4-bis(N,N-diphenyl-carbamoyl)piperazine-2-carboxylic acid, 1,4-bis(N,N-diphenyl-carbamoyl)-2-methyl-piperazine and 1-(N,N-di-n-pentylcarbamoyl)-4-(N,N-diphenyl-carbamoyl)piperazine-2-carboxylic acid, substituted 3-aminoquinuclidine is selected from the group consisting of (3R,4S,5S,6S)-N,N-diethyl-5-(2,5-dimethoyxbenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid and (3R,4S,5S,6S)-5-(2-methoxy-2-methylthiobenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid, azanorbornane compound is selected from the group consisting of (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxyphenyl)methylamino]bicyclo[2.2.1]heptane, (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-bicyclo-[2.2.1]heptane and (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]bicyclo[2.2.1]heptane, fluoroalkoxybenzylamino derivative of nitrogen containing heterocycle is selected from the group consisting of (2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxy)-benzyl]aminopiperidine, 2-(diphenyl-methyl)-N-((2-difluoromethoxy)phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine and (2S,3S)-N-(2-methoxy-5-trifluoro-methoxyphenyl)methyl-2-diphenylmethyl-1-aza-bicyclo[2.2.2]octane-3-amine, fused tricyclic is selected from the group consisting of 1-(5H-dibenzo[a.d]cyclohepten-5-yl)-2-)3,5-dimethylbenzyloxy)ethylamine, N-acetamido-1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine and 1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-2-(3,5-dimethylbenzyl-

oxy)ethylamine, aromatic compound is selected from the group consisting of 2-ammonium-1-((3,5-dimethylphenyl)-methyloxy)-3,3-diphenylpropane, 2-dimethyl-ammonium-1-((3,5-dimethylphenyl)-methyloxy)-3,3-diphenylpropane, 2-t-butoxy-carbonylamino-3,3-diphenylpropanoyl-(2-methoxyphenyl)methylamide, L-1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-(t-butoxycarbonylamino)-2-phenylethane, 1-((3,5-dimethylphenyl)methyloxy)-2(S)-2-(((carbomethoxy)methyl)amino)-2-phenyl-ethane, (2S)-2-(((carboxamido)methyl)-ammonium-1-((3,5-dimethylphenyl)methyloxy)-2-phenylethane, 3,5-dimethylbenzyl 2-(1,1-dimethylethoxycarbonylamino)-3-(3-indolyl)propionate, 2-methoxybenzyl 2-(1,1-dimethylethoxycarbonylamino)-3-(3-indolyl)propionate, 3,5-dimethylbenzyl 2-acetamido-3-(3-indolyl)propionate, 3,5-dimethylbenzyl 2-cyclohexanecarboxamido-3-(3-indolyl)propionate, 2-ammonium-3,3-diphenylpropanoyl-(2-methoxyphenyl) methylamide, (3,5-dimethylphenyl)methyl-2-ammonium-3,3-diphenylpropanoate and 2-methylammonium-1-((3,5-dimethylphenyl)-methyloxy)-3,3-diphenylpropane, fused tricyclic nitrogen containing heterocycle is selected from the group consisting of (±)-cis-9-diphenylmethyl-N-((2-methoxyphenyl)-methyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine (±)-cis-9-diphenylmethyl-N-(2-methoxy-5-chlorophenyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine and (±)-cis-9-diphenylmethyl-N-(2-trifluoromethoxyphenyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine, acyclic ethylenediamine is selected from the group consisting of 1-amino-1-phenyl-2-[(2-methoxy)phenylmethylamino]propane, (1R′,2S′)-1-cyclohexylamino-1-phenyl-2-[(2-methoxy)-phenylmethylamino]propane and 1-N-cyclohexyl-1-phenyl-2-N′-[(2-methoxy-5-trifluoromethoxyphenyl)methyl]-1,2-ethanediamine, substituted benzylamino nitrogen containing non-aromatic heterocycle is selected from the group consisting of (2S,3S)-N-(2-methoxy-5-methylsulfonylphenyl)-methyl-2-diphenylmethyl-1-azabicyclo-[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-methylthiophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine and (2S,3S)-N-(2-methoxy-5-dimethylaminophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine,

substituted benzylaminoquinuclidine is selected from the group consisting of (2S,3S)-N-(5-isopropenyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-vinylphenyl)methyl-2-diphenylmethyl-1-azabicyclo-[2.2.2]octan-3-amine and (2S,3S)-N-(2-methoxy-4,5-dimethylphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, N-benzoyl-4-oxy/thio-2-substituted piperidine is selected from the group consisting of (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl-4-(4-quinolylmethoxy)-piperidine, (2R*,4S*)-quinoline-3-carboxylic acid[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl]ester and (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl-4-(3-quinolylmethoxy)-piperidine, aromatic amine is selected from the group consisting of N[(benzyl-4-piperidinyl-1)-4(dichloro-3,4 phenyl)-2 butyl]-dichloro-2,4 benzamide, N[(benzyl-4 piperidinyl-1)-4(difluoro-3,4 phenyl)-2 butyl]-dichloro-2,4 benzamide and N[(benzyl-4 piperidinyl-1)-4(dichloro-3,4 phenyl)-2 butyl]fluoro-4 naphthalene-1 carboxamide, azabicyclic is selected from the group consisting of trans-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane, trans-3-(3,5-dimethoxybenzyloxy)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane, trans-2-(diphenylmethyl)-3-(3-phenoxy-benzyloxy)-1-azabicyclo[2.2.2]octane, 3-[(3,5-dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane and 3-[(3,5-bistrifluoromethylphenyl)-methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane, 3-[(3,5-bistri-fluoromethylphenyl)methyloxy]-2-[1-(1-(4-methoxyphenyl)-2-phenyl)ethyl]-1-aza-bicyclo[2.2.2]octane, thiopyranipyrrole is selected from the group consisting of {[(dimethylamino-3 propoxy-2) phenyl]acetyl)-6 diphenyl-4,4-oxyde-1 perhydro-thiopyrano[2,3-c]pyrrole, {[(pyrrolidinyl-1)-3 propoxy-2] phenyl} acetyl}-6 diphenyl-4,4 oxyde-1 perhydrothiopyrano[2,3-c]pyrrole and [{methoxy-2 phenyl)-2 propionyl-(S)]-6 diphenyl-4,4 oxyde-1 perhydrothiopyrano[2,3-c]pyrrole and the azabicyclic is selected from the group consisting of cis-2-(diphenylmethyl-3-(3,5-dimethyl-

benzyloxy)-1-methylpyrrolidine, cis-3-((3,5-dimethylphenyl)methyloxy)-2-phenyl-piperidine and cis-3-((3,5-dimethylphenyl)methyloxy-1-methyl-2-phenylpiperidine.

4. The analgesic composition of Claim 1 containing a therapeutically effective amount of at least one other pharmacologically active substance (c).

5. The analgesic composition of Claim 4 wherein the pharmacologically active substance (c) is selected from the group consisting of non-narcotic analgesics and narcotic analgesics.

6. The analgesic composition of Claim 5 wherein the non-narcotic analgesic is selected from the group consisting of tramadol, acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin and zomepirac.

7. The analgesic composition of Claim 5 wherein the narcotic analgesic is selected from the group consisting of codeine, dihydrocodeine, heroin, hydrocodone, levorphanol, morphine and oxycodone.

8. The analgesic composition of Claim 1 wherein the nontoxic N-methyl-D-aspartate receptor antagonist is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salts thereof.

9. The analgesic composition of Claim 2 wherein the nontoxic N-methyl-D-aspartate receptor antagonist is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salts thereof.

10. The analgesic composition of Claim 1 wherein (a) and (b) are present in sustained release dosage form.

11. A method of treating pain which comprises administering to a mammal exhibiting pain (a) an analgesically effective amount of at least one substance P receptor antagonist and (b) a substance P receptor antagonist-potentiating amount of at least one substance P receptor antagonist potentiator selected from the group consisting of nontoxic N-methyl-D-aspartate receptor antagonist and nontoxic substance that blocks a major intracellular consequence of N-methyl-D-aspartate receptor activation.

12. The method of Claim 11 wherein the substance P receptor antagonist is selected from the group consisting of a substance P analog, undecapeptide, hexapeptide amide, di-(D-tryptophyl and/or tetra-hydropyridoindolylcarbonyl)-containing peptide amide, isoindolone, quinuclidine, peptide, spirolactam, 3-aminopiperidine and related nitrogen containing heterocycle, dialkylenepiperidino, 1-acylpiperidine, cyclic dimeric dipeptide derivative, polycyclic amine, azole-fused peptide, N-alkylenepiperidino, 3-amino-2-arylquinuclidine, isoquinolinyl, prolyl endopeptidase inhibitor compound, pseudopeptide, piperidine, chromone compound, perhydroisoindole, substituted pyrrolidin-3-yl-alkyl-piperidine, fused ring analog of nitrogen containing heterocycle, N-alkyl quinuclidinium salt, 1-azabicyclo[3.2.2]nonan-3-amine, N-N-diacyl-piperazine, substituted 3-aminoquinuclidine, azanorbornane compound, fluoroalkoxybenzylamino derivative of nitrogen containing heterocycle, fused tricyclic, aromatic compound, fused tricyclic nitrogen containing heterocycle, acyclic ethylenediamine, perhydroisoindole, substituted benzylamino nitrogen containing non-aromatic heterocycle, substituted benzylaminoquinuclidine, N-benzoyl-4-oxy/thio-2-substituted piperidine, aromatic amine, azabicyclic, thiopyranipyrrole and azacyclic.

13. The method of Claim 12 wherein the substance P analog is selected from the group consisting of L-amino acid sequence G-L-M-NH_2, O-G-L-M-NH_2, F-G-L-M-NH_2, pyroglutamyl-ohenylalanyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl]methionine amide and pyroglutamyl-phenylalanyl-N-methyl-phenylalanyl-[(R)-3-amino-2-oxo-1-pyrrolidine-(S)-4-methyl-2-pentanoyl]methionine amide, undecapeptide is selected from the group consisting of L-arginyl-L-prolyl-L-lysyl-L-prolyl-L-glutaminyl-L-glutaminyl-L-phenylalanyl-L-glycyl-L-leucyl-L-methionine amide, [D-Phe^5, D-Trp^7, D-Trp^9, Leu^{11}]-SP, [Glp^5, D-Trp^7, D-Trp^9, Thr^{11}]-SP_{5-11}, and [D-Arg^1, D-Trp^7, D-Trp^9, Leu^{11}]-SP, hexapeptide amide is selected from the group consisting of Hpro-Phe-Phe-Dala-Leu-MetNH_2, HPro-Phe-

MePhe-Gly-Leu-MetNH_2 and HPro-Phe-Phe-Gly-DLeu-MetNH_2, di-(D-tryptophyl and/or tetrahydropyridoindolylcarbonyl)-containing peptide amide is selected from the group consisting of H-trp-Phe-trp-Leu-Met-NH_2, Hpro-trp-Phe-trp-Leu-Phe-NH_2 and H-tpi-Phe-trp-Leu-Met-NH_2, isoindolone is selected from the group consisting of 2-[1-imino-2-(2-methoxyphenyl)ethyl]-7,7-diphenyl-4-perhydroisoindolone in its (3aR,7aR) or (3aR,7aRS) forms, 7,7-diphenyl-2-[2-(2-dimethylaminophenyl)acetyl]-4-perhydro-isoindolone in its (3aR,7aR) or (3aRS,7aRS) forms, 7,7-diphenyl-2-[(R)-2-(2-methoxy-phenyl)propionyl]-4-perhydroisoindolone in its (3aR,7aR) or (3aRS,7aRS) forms, diphenyl-7,7[dimethylamino-2 phenyl)-2 acetyl]-2 perhydroisoindolone-4, diphenyl-7,7[methoxy-2 phenyl)-2 propionyl-(R)]-2 perhydroisoindolone-4 and [(5)-carboxy benzylimino-1 (methoxy-2 phenyl)-2 ethyl]-2 diphenyl-7,7 perhydro-isoindolone-4, quinuclidine is selected from the group consisting of cis-3-[(2-chlorophenyl)-methylamino]-2-benzhydrylquinuclidine, cis-3-[(2-trifluoro-methylphenyl)methyl-amino]-2-benzhydrylquinuclidine, cis-3-[(2-methoxy-phenyl)methylamino]-2-benz-hydrylquinuclidine, 8-(diphenylmethyl)-N-((2-methoxyphenyl)methyl))-9-azatricyclo-[4.3.1.$0^{4,9}$]decan-7-amine, 8-(diphenylmethyl)-N-(phenylmethyl)-9-azatricyclo-[4.3.1.$0^{4,9}$]decan-7-amine, 8-(diphenylmethyl)-N-((2-chlorophenyl)methyl))-9-azatricyclo[4.3.1.$0^{4,9}$]decan-7-amine, (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(5-ethyl-2-methoxy-phenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2,2.2]octan-3-amine, (3R,4S,5S,6S)-N-carbamoylmethyl-5-(5-isopropyl-2-methoxybenzyl-amino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-N-carboxy-methyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]-octane-3-carboxamide and (3R,4S,5S,6S)-3-(2-carbamoylpyrrolidin-1-yl)carbonyl-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane, the peptide is selected from the group consisting of H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-

Gly-Leuψ[CH_2-NH]Leu-NH_2, H-D-Arg-Pro-Lys-Pro-Gln-Gln-D-Trp-Phe-D-Trpψ[CH_2-NH]Leu-Nle-NH_2, H-D-Arg-Pro-Lys-Pro-Gln-Gln-D-Trpψ[CH_2-NH]Phe-D-Trp-Leu-Nle-NH_2, Boc-Phe-(p-CH_3)-OH, Boc-Phe-(p-F)-OH, Boc-Gin-D-Trp(CHO)-Phe-NMe-Bzl, Boc-Thr-D-Trp(CHO)-Phe-NMeBzl, Boc-Glu(NMe_2)-D-Trp(CHO)-Phe-NMeBzl, cyclo(Gln-Trp-Phe-(R)Gly-[ANC-2]Leu-Met, cyclo(Gln-Npa-Phe-(R)Gly[ANC-2]Leu-Met and cyclo(Gln-Trp-Phe-Gly-Leu-Met), spirolactam is selected from the group consisting of 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diaza-spiro[4.4]nonane-1-carboxylic acid, phenylmethyl ester, 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid phenylmethyl ester, 7-[(1S)-(1-methoxycarbonyl)-3-methylbutyl]-6-oxo-(5S)-1,7-diazaspiro-[4.4]nonane-1-carboxylic acid and (1,1-dimethyl)ethyl ester, 3-aminopiperidine and related nitrogen containing heterocycle is selected from the group consisting of cis-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-1-allyl-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-1-ethyl-3-(2-methoxybenzylamino)-2-phenylpiperidine, cis-3-(2-chlorobenzylamino)-2-phenylpiperidine, cis-3-(2-trifluoromethylbenzylamino)-2-phenylpiperidine, cis-3-(2-methoxybenzylamino)-2-(2-fluorophenyl)-piperidine, (2S,3S)-3-(4,5-difluoro-2-methoxybenzyl)amino-2-phenyl-piperidine, (2S,3S)-3-(2-cyclopentyloxy-5-methoxybenzyl)amino-2-phenylpiperidine and (2S,3S)-3-(5-sec-butyl-2-methoxybenzyl)amino-2-phenyl-piperidine, dialkylenepiperidino is selected from the group consisting of N-[4-(1-benzyl-4-piperidinyl)-2-(3,4-dichlorophenyl)-butyl]-4-fluoronaphtalene carboxamide hydrochloride, N-[4-[1-(fluorobenzyl)-4-piperidinyl-2-(3,4-dichlorophenyl)-butyl]-2,4-dichlorobenzamide hydrochloride, N-methyl-N-[4-(1-benzyl-4-piperidinyl)-2(3,4-dichlorophenyl)-butyl]3-isopropoxyphenylacetamide hydrochloride, chlorohydrate of N-[{4-[1-benzyl-piperidin-4-yl]-2-(3,4-dichloro-phenyl)}-butyl]-4-fluoronaphtalenecarboxamide, chlorohydrate of N-[{2-(3,4-dichloro-phenyl)-4-[1-(4-fluorobenzyl)-piperidin-4-yl]}-butyl]-2,4-dichlorobenzamide and chlorohydrate of N-methyl-N-{{4-[1-benzyl-piperidine-4-yl]-2-(3,4-dichlorophenyl)}-

butyl]-3-isopropoxyphenylacetamide, the 1-acylpiperidine is selected from the group consisting of (2R,4S) and (2R,4R)-2-benzyl-1-(3,5-dimethylbenzoyl)-N-(2-phenethyl)-4-piperidinamine hydrochloride, (2R*,4S*)-2-benzyl-1-(2-naphthoyl)-N-(4-quinolyl-methyl)-4-piperidinamine, (2R*,4S*)-2-benzyl-2-(3-trifluoro-methylbenzoyl)-N-(4-quinolylmethyl)-4-piperidinamine, (2R*,4S*)-2-benzyl-1-(2-naphthoyl)-N-(4-chinolyl-methyl)-4-piperidinamin, (2R*,4S*)-2-benzyl-1-(3-trifluoromethylbenzoyl)-N-(4-chinolylmethyl)-4-piperidinamin and (2R*,4S*)-2-benzyl-1-(3,5-bis-(trifluoromethyl)-benzoyl)-N-(4-chinolylmethyl)-4-piperidinamin, polycyclic amine is selected from the group consisting of 4-[2-(4-benzylpiperidin-1-yl)ethyl]-4-(3-methylphenyl)-1-(3-chlorophenyl)acetylpiperidine hydrochloride, 3-[2-(4-Benzylpiperidin-1-yl)ethyl]-3-(3,4-dichlorophenyl)-1-phenylacetylpiperidine hydrochloride, 5-[2-(4-benzylpiperidin-1-yl)ethyl]-5-(3,4-dichlorophenyl)-1-benzylpiperidinone hydrochloride, chlorhydrate of 5-[2-(4-benzyl-1-piperidinyl)ethyl]-5-(3,4-dichlorophenyl)-1-benzyl-piperidinone, chlorohydrate of 3-[2-(4-benzyl-1-piperidinyl)ethyl]-3-(3,4-dichlorophenyl)-1-phenyl-acetylpiperidine, chlorohydrate of 3-[2-(4-benzyl-1-piperidinyl)ethyl]-3-(3,4-dichlorophenyl)-1-(3-isopropoxy-phenyl)acetylazepine, the N-alkylenepiperidino is selected from the group consisting of N-[2-(3,4-dichlorophenyl)-4-(4-(2-pyridylthio)-1-piperidinyl)butyl]-2,4-dichlorobenzamide, N-[4-(4-N'-acetylanilino-1-piperidinyl)-2-(3,4-dichlorophenyl)butyl]-N-methylbenzamide and N-[4-(1-methyl-2-imidazolyl)-4-thio-1-piperidinyl)-2-naphthylbutyl]-2,4-dimethoxybenzamide, 3-amino-2-aryl-quinuclidine is selected from the group consisting of trans-2-phenyl-N-(2-methoxy-phenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine, cis-2-phenyl-N-(phenylmethyl)-1-azabicyclo-[2.2.2]octan-3-amine and 2-(1-naphthyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine, isoquinolinyl is selected from the group consisting of N-[(6-chloro-1,2-dihydro-2-methyl-1-oxo-4-phenylisoquinolin-3-yl)methyl]-N'-(3isopropoxyphenyl)urea, N-[(1,2-dihydro-2,6,7-trimethyl-1-oxo-4-phenylisoquinolin-3-yl)methyl]-N'-(3-methylphenyl)urea and N-[(1,2-dihydro-2-methyl-1-oxo-4-phenyl-

isoquinolin-3yl)methyl]-N′-(3-methylphenyl)urea, prolyl endopeptidase inhibitor compound is selected from the group consisting of (S)-2-[[(S)-2-(acetoxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide, (S)-2-[[(S)-2-(hydroxyacetyl)-1-pyrrolidinyl]carbonyl]-N-phenylmethyl-1-pyrrolidinecarboxamide and (S)-2-[[(S)-2-[(benzoyloxyacetyl)-1-pyrrolidinyl]carbonyl]-N-(phenylmethyl)-1-pyrrolidinecarboxamide, pseudopeptide is selected from the group consisting of {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Nal-NMeBzl, {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Tna-NMeBzl and {1-[4-(1H-tetrazol-5-yl)butyl]indol-3-yl}carbonyl-Hyp-Thn-NMeBzl, piperidine is selected from the group consisting of (2S,3S)-3-(5-tert-butyl-2-methoxybenzyl)amino-2-(3trifluoromethoxyphenyl)piperidine, (2S,3S)-3-(2-isopropoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine, (2S,3S)-3-(2-ethoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine, 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[((2-methyl)phenylsulfinyl)methyl]-4-piperidinol, 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-4-[((4-methyl)phenylsulfinyl)methyl]-4-piperidinol and 1-[2-(5-Fluoro-1H-indol-3-yl)ethyl]-4-[(phenylsulfinyl)methyl]-4-piperidinol, chromone compound is selected from the group consisting of (2R,4S)-N-[1-(3,5-bistrifluoromethylbenzoyl)-2-(4-chlorobenzyl)piperidin-4-yl]-4-oxo-4H-1-benzopyrene-2-carboxamide, (2R,4S)-N-[1-(3,5-bistrifluormethylbenzoyl)-2-benzylpiperidin-4-yl]-4-oxo-4H-1-benzopyrene-2-carboxamide and (2R,4S)-N-[1-(3,5-bistrifluoromethylbenzoyl)-2-(4-chloro-benzyl)-piperidin-4-yl]-6-fluoro-4-oxo-4H-1-benzopyrene-2-carboxamide, perhydroisoindole is selected from the group consisting of {{[(pyrrolidinyl-1)-3 propoxy-2]phenyl}acetyl}-2 diphenyl-4,4 fluoro-7 perhydroisoindole, diphenyl-4,4 fluoro-7 [(methoxy-2 phenyl)-2 propionyl-(S)]-2 perhydroisoindole, [(dimethylamino-3 propoxy)-2 phenyl]acetyl-2 diphenyl-4,4 fluoro-7 perhydroisoindole, 7,7-dimethyl-4-(2-methoxyphenyl)-2-[2-(S)-(2-methoxyphenyl)propionyl]-4,5-perhydroisoindolediol, 4-(2-methoxyphenyl)-2-[2-(S)-(2-methoxyphenyl)proponyl]-5-methyl-4-perhydro-isoindolol, 2-[2-(S)-(2-hydroxy-phenyl)propionyl]-4-(2-methoxyphenyl)-6-methyl-4-perhydroisoindolol, diphenyl-7,7

(methoxy-2 phenyl)-4[(methoxy-2 phenyl)-2 propionyl]-2 perhydroisoindolol-4, diphenyl-7,7 (methoxy-2 phenyl)-4 [(methoxy-2 phenyl)-2 propionyl]-2 perhydroiso-indolediol-4,5 and diphenyl-7,7 (methoxy-2 phenyl)-4 [(hydroxy-2 phenyl)-2 acetyl]-2 perhydroisoindolol-4, substituted pyrrolidin-3yl-alkyl-piperidine is selected from the group consisting of (+)-or(-)-1-(2-[3-(3,4-dichloro-phenyl)-1-[2-(2-methoxy-phenyl)-acetyl]-pyrrolidin-3-yl]-ethyl)-4-phenyl-piperidine-4-carboxylic acid amide, (+)-or(-)-1-[2-[3-(3,4-dichloro-phenyl)-1(2,6-dimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide and (+)-or(-)-1-[2-[3-(3,4-dichloro-phenyl)-1(3,4,5-trimethoxy-benzoyl)-pyrrolidin-3-yl]-ethyl]-4-phenyl-piperidine-4-carboxylic acid amide, fused ring analog of nitrogen containing heterocycle is selected from the group consisting of [1α,3α,4α,5α]-4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo-[3.3.0]octane, 4-(2-methoxybenzyl)amino-3-phenyl-2-azabicyclo[4.4.0]decane and 4-(2-methoxybenzyl)amino-4-benzhydryl-3-azabicyclo[4.1.0]heptane, N-alkyl quinuclidinium salt is selected from the group consisting of (2S,3S)-cis-1-methyl-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine iodide, (2S,3S)-cis-1-(4-carbethoxybutyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)-methyl-1-azabicyclo[2.2.2]octan-3-amine iodide and (2S,3S)-cis-1-(4-carboethoxy-phenylmethyl)-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]-octan-3-amine iodide, 1-azabicyclo[3.2.2] nonan-3-amine is selected from the group consisting of 2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-azabicyclo[3.2.2]-nonan-3-amine, 2-(diphenylmethyl)-N-((2-chlorophenyl)methyl)-1-azabicyclo[3.2.2]-nonan-3-amine and 2-(diphenylmethyl)-N-((2,4-dimethoxyphenyl)methyl)-1-azabicyclo-[3.2.2]nonan-3-amine, N,N-diacyl-piperazine is selected from the group consisting of 1,4-bis(N,N-diphenyl-carbamoyl)piperazine-2-carboxylic acid, 1,4-bis(N,N-diphenyl-carbamoyl)-2-methyl-piperazine and 1-(N,N-di-n-pentylcarbamoyl)-4-(N,N-diphenyl-carbamoyl)piperazine-2-carboxylic acid, substituted 3-aminoquinuclidine is selected from the group consisting of (3R,4S,5S,6S)-N,N-diethyl-5-(2,5-dimethoyxbenzyl-amino)-6-diphenylmethyl-1-

azabicyclo[2.2.2]octane-3-carboxamide, (3R,4S,5S,6S)-5-(5-isopropyl-2-methoxybenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid and (3R,4S,5S,6S)-5-(2-methoxy-2-methylthiobenzylamino)-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxylic acid, azanorbornane compound is selected from the group consisting of (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxyphenyl)methylamino]bicyclo[2.2.1]heptane, (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-(1,1-dimethylethyl)phenyl)methylamino]-bicyclo-[2.2.1]heptane and (1SR,2SR,3SR,4RS)-1-aza-2-diphenylmethyl-3-[(2-methoxy-5-trifluoromethoxyphenyl)methylamino]bicyclo[2.2.1]heptane, fluoroalkoxybenzylamino derivative of nitrogen containing heterocycle is selected from the group consisting of (2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxy)-benzyl]aminopiperidine, 2-(diphenyl-methyl)-N-((2-difluoromethoxy)phenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine and (2S,3S)-N-(2-methoxy-5-trifluoro-methoxyphenyl)methyl-2-diphenylmethyl-1-aza-bicyclo[2.2.2]octane-3-amine, fused tricyclic is selected from the group consisting of 1-(5H-dibenzo[a.d]cyclohepten-5-yl)-2-)3,5-dimethylbenzyloxy)ethylamine, N-acetamido-1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine and 1-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)-2-(3,5-dimethylbenzyl-oxy)ethylamine, aromatic compound is selected from the group consisting of 2-ammonium-1-((3,5-dimethylphenyl)-methyloxy)-3,3-diphenylpropane, 2-dimethyl-ammonium-1-((3,5-dimethylphenyl)-methyloxy)-3,3-diphenylpropane, 2-t-butoxy-carbonylamino-3,3-diphenylpropanoyl-(2-methoxyphenyl)methylamide, L-1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-(t-butoxycarbonylamino)-2-phenylethane, 1-((3,5-dimethylphenyl)methyloxy)-2(S)-2-(((carbomethoxy)methyl)amino)-2-phenyl-ethane, (2S)-2-(((carboxamido)methyl)-ammonium-1-((3,5-dimethylphenyl)methyloxy)-2-phenylethane, 3,5-dimethylbenzyl 2-(1,1-dimethylethoxycarbonylamino)-3-(3-indolyl)propionate, 2-methoxybenzyl 2-(1,1-dimethylethoxycarbonylamino)-3-(3-indolyl)propionate, 3,5-dimethylbenzyl 2-acetamido-3-(3-indolyl)propionate, 3,5-

dimethylbenzyl 2-cyclohexanecarboxamido-3-(3-indolyl)propionate, 2-ammonium-3,3-diphenylpropanoyl-(2-methoxyphenyl) methylamide, (3,5-dimethylphenyl)methyl-2-ammonium-3,3-diphenylpropanoate and 2-methylammonium-1-((3,5-dimethylphenyl)-methyloxy)-3,3-diphenylpropane, fused tricyclic nitrogen containing heterocycle is selected from the group consisting of (±)-cis-9-diphenylmethyl-N-((2-methoxyphenyl)-methyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine (±)-cis-9-diphenylmethyl-N-(2-methoxy-5-chlorophenyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine and (±)-cis-9-diphenylmethyl-N-(2-trifluoromethoxyphenyl)-10-azatricyclo[4.4.1.$0^{5,7}$]undecan-8-amine, acyclic ethylenediamine is selected from the group consisting of 1-amino-1-phenyl-2-[(2-methoxy)phenylmethylamino]propane, (1R′,2S′)-1-cyclohexylamino-1-phenyl-2-[(2-methoxy)-phenylmethylamino]propane and 1-N-cyclohexyl-1-phenyl-2-N′-[(2-methoxy-5-trifluoromethoxyphenyl)methyl]-1,2-ethanediamine, substituted benzylamino nitrogen containing non-aromatic heterocycle is selected from the group consisting of (2S,3S)-N-(2-methoxy-5-methylsulfonylphenyl)-methyl-2-diphenylmethyl-1-azabicyclo-[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-methylthiophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine and (2S,3S)-N-(2-methoxy-5-dimethylaminophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, substituted benzylaminoquinuclidine is selected from the group consisting of (2S,3S)-N-(5-isopropenyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, (2S,3S)-N-(2-methoxy-5-vinylphenyl)methyl-2-diphenylmethyl-1-azabicyclo-[2.2.2]octan-3-amine and (2S,3S)-N-(2-methoxy-4,5-dimethylphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine, N-benzoyl-4-oxy/thio-2-substituted piperidine is selected from the group consisting of (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl-4-(4-quinolylmethoxy)-piperidine, (2R*,4S*)-quinoline-3-carboxylic acid[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl]ester and (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl-4-(3-quinolylmethoxy)-piperidine, aromatic amine is selected from the group consisting of N[(benzyl-4-piperidinyl-1)-

4(dichloro-3,4 phenyl)-2 butyl]-dichloro-2,4 benzamide, N[(benzyl-4 piperidinyl-1)-4(difluoro-3,4 phenyl)-2 butyl]-dichloro-2,4 benzamide and N[(benzyl-4 piperidinyl-1)-4(dichloro-3,4 phenyl)-2 butyl]fluoro-4 naphthalene-1 carboxamide, azabicyclic is selected from the group consisting of trans-3-[3,5-bis(trifluoromethyl)benzyloxy]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane, trans-3-(3,5-dimethoxybenzyloxy)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane, trans-2-(diphenylmethyl)-3-(3-phenoxybenzyloxy)-1-azabicyclo[2.2.2]octane, 3-[(3,5-dimethylphenyl)methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane and 3-[(3,5-bistrifluoromethylphenyl)-methyloxy]-2-(1,2-diphenylethyl)-1-azabicyclo[2.2.2]octane, 3-[(3,5-bistrifluoromethylphenyl)methyloxy]-2-[1-(1-(4-methoxyphenyl)-2-phenyl)ethyl]-1-azabicyclo[2.2.2]octane, thiopyranipyrrole is selected from the group consisting of {[(dimethylamino-3 propoxy-2) phenyl]acetyl)-6 diphenyl-4,4-oxyde-1 perhydrothiopyrano[2,3-c]pyrrole, {[(pyrrolidinyl-1)-3 propoxy-2] phenyl} acetyl}-6 diphenyl-4,4 oxyde-1 perhydrothiopyrano[2,3-c]pyrrole and [{methoxy-2 phenyl)-2 propionyl-(S)]-6 diphenyl-4,4 oxyde-1 perhydrothiopyrano[2,3-c]pyrrole and the azabicyclic is selected from the group consisting of cis-2-(diphenylmethyl-3-(3,5-dimethylbenzyloxy)-1-methylpyrrolidine, cis-3-((3,5-dimethylphenyl)methyloxy)-2-phenylpiperidine and cis-3-((3,5-dimethylphenyl)methyloxy-1-methyl-2-phenylpiperidine.

14. The method of Claim 11 containing a therapeutically effective amount of at least one other pharmacologically active substance (c).

15. The method of Claim 14 wherein the pharmacologically active substance (c) is selected from the group consisting of non-narcotic analgesics and narcotic analgesics.

16. The method of Claim 15 wherein the non-narcotic analgesic is selected from the group consisting of tramadol, acetaminophen, aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen,

indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin and zomepirac.

17. The method of Claim 15 wherein the narcotic analgesic is selected from the group consisting of codeine, dihydrocodeine, hydrocodone, levorphanol, morphine and oxycodone.

18. The method of Claim 11 wherein the nontoxic N-methyl-D-aspartate receptor antagonist is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salts thereof.

19. The method of Claim 12 wherein the nontoxic N-methyl-D-aspartate receptor antagonist is at least one member selected from the group consisting of dextromethorphan, dextrorphan, amantadine, memantine and pharmaceutically acceptable salts thereof.

20. The method of Claim 11 wherein (a) and (b) are coadministered.

21. The method of Claim 18 wherein (a) and (b) are coadministered as a sustained release dosage form.

22. The method of Claim 11 wherein the pain is muscular pain, musculoskeletal pain, chronic pain, neuropathic pain or migraine.

INTERNATIONAL SEARCH REPORT

Interr. ıal Application No
PCT/US 98/10707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/485 A61K38/04 A61K31/13 //(A61K38/04, 31:485)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REN ET AL.: "An isobolographic analysis of N-methyl-D-aspartate and NK1 Tachykinin receptor antagonists on inflammatory hyperalgesia in the rat" BRIT. J. PHARMACOL., vol. 117, no. 1, January 1996, pages 196-202, XP002075553 * see in particular the abstract, Figs 2-3 and Table 2 *	1-3,8,9, 11-13, 18,19,22
Y		4-6, 14-16

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 1998	11.09.98

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

2

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

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/US 98/10707

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OKANO ET AL.: "Effects of inthrathecally injected glutamate and substance P antagonists on repeated cold stress induced hyperalgesia in rats" BIOL. PHARMACEUT. BULL., vol. 18, no. 1, January 1995, pages 42-44, XP002075554 * see in particular the abstract, p. 44 and Fig. 2 *	1-3, 11-13, 20,22
X	MURRAY ET AL.: "Neurokinin and NMDA antagonists (but not a kainic acid antagonist) are antinociceptive in the mouse formalin model" PAIN, vol. 44, no. 2, February 1991, pages 179-185, XP002075555 * see in particular the abstract and Tables II & III *	1-3, 11-13, 20,22
X	US 5 292 726 A (ASHTON WALLACE T ET AL) 8 March 1994 cited in the application *see col. 17, l.49 - col. 19, l. 14 *	1-3
Y	PRICE D D ET AL: "EFFECTS OF THE COMBINED ORAL ADMINISTRATION OF NSAIDS AND DEXTROMETHORPHAN ON BEHAVIORAL SYMPTOMS INDICATIVE OF ARTHRITIC PAIN IN RATS" PAIN, vol. 68, no. 1, November 1996, pages 119-127, XP002061724 *see in particular abstract and ultimate paragraph at page 126*	4-6, 14-16

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/10707

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2 ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3 ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds, which are defined by the general definition in the claims 1-4,11-14 the search had to be restricted for economic reasons. The search was limited to the combinations for which pharmacological data was given, and to the general idea underlying the application. (see PCT Guidelines, Chapter III, paragraph 2.3 & 3.6).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No
PCT/US 98/10707

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5292726 A	08-03-1994	WO 9220661 A	26-11-1992