COMPOSITION FOR TREATING PAIN

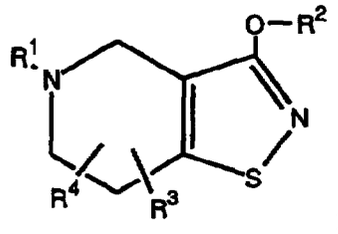
The present invention relates to a method for using a combination of compounds for treating pain.

This invention relates to a therapeutic combination of compounds to provide analgesic activity.

More active analgesic combinations effects are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages, thereby diminishing the expected side effects and toxicity that would otherwise result from higher dosages. It would be particularly desirable to acquire a synergistic combination effect. Such a composition is the subject of the present invention.

The composition of this invention provides a surprising synergistically effective treatment for pain using compounds which are independently known in the art. The synergistic effect of the present composition provides a means for treating pain using a lower dosage of each compound in the composition, thus providing a treatment with a more desirable side effect profile.

The present invention provides a composition useful for the treatment of pain, comprising a compound selected from the group consisting of:

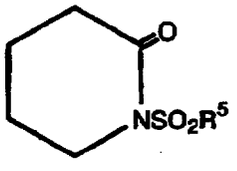


I

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

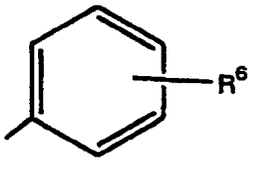
R^2 is C_1-C_6alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, branched or unbranched with 1-6 carbon atoms inclusive, which group may be optionally substituted with fluoro, hydroxy or phenyl optionally substituted with fluoro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy;

R^3 and R^4 are independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl optionally substituted with halogen triflurormethyl, C_1-C_4 alkyl, hydroxy, or C_1-C_4 alkoxy, or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

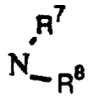


II;

in which R^5 represents the radical

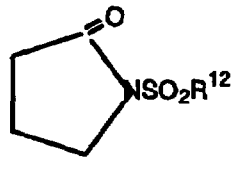


in which R^6 at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical



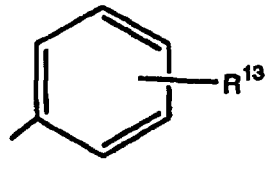
in which R^7 and R^8 which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical

optionally containing another heteroatom, or the radical OR^9, R^9 representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{10} or $S(O)R^{11}$, R^{10} and R^{11} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^5 represents naphthyl optionally substituted with $R^{6'}$, $R^{6'}$ being defined above for R^6;

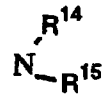


III

in which R^{12} represents the radical

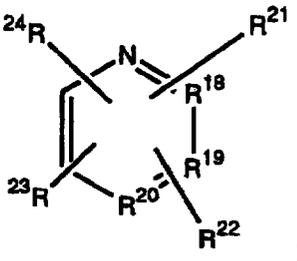


in which R^{13} at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical



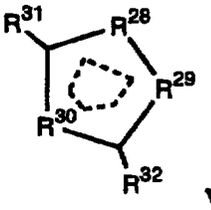
in which R^{14} and R^{15} which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical or NO_2, or $OR^{12'}$, $R^{12'}$ representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{16} or $S(O)R^{17}$, R^{16} and R^{17} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^{12} represents

naphthyl optionally substituted with $R^{13'}$, $R^{13'}$ being defined above for R^{13};



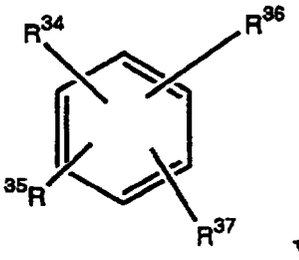
IV

wherein, one of R^{18}, R^{19}, and R^{20} represents nitrogen and the remainder represent carbon atoms; substituted on one of the ring carbon atoms with a R^{24} substituent represented by a non-aromatic azacyclic or azabicyclic ring system and independently substituted on each of the other ring carbon atoms with R^{23}, R^{21}, or R^{22} substituent of low lipophilicity or a hydrocarbon having a maximum of 20 carbon atoms;



V;

wherein one of R^{28}, R^{29} or R^{30} is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R^{31} represents a non-aromatic '927azacycle or '927azabicyclic ring system; and R^{32} represents a substituent which is convertable in vivo to an amino group;

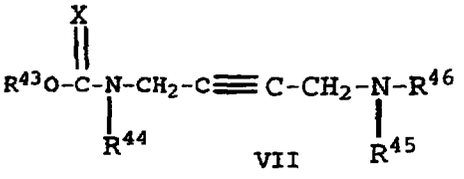


VI;

wherein R^{34} represents a non-aromatic; non-fused 1-azabicyclic ring system; and

R^{35}, R^{36}, and R^{37} independently represent hydrogen, F, Cl, Br, $-CF_3$, $-OR^{38}$, $-NR^{38}R^{39}$, $-NHOR^{38}$, $-NHNH_2$, $-CN$, COR^{40}, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group, provided that at least one of R^{35}, R^{36}, and R^{37} is other than hydrogen or a hydrocarbon group, or R^{35} and R^{36} or R^{37} taken together form a C_{1-6}alkylenedioxy ring,

wherein R^{38} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, R^{39} is hydrogen, C_{1-6} alkyl,or $-COCH_3$, and R^{40} represents OH, $-OR^{38}$, NHR^{39}, or $-NR^{38}R^{39}$



VII

wherein R^{43} is

alkyl of from one to six carbon atoms,

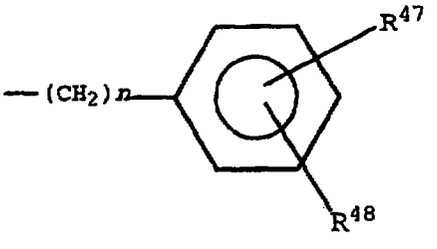
alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from two to six carbon atoms,

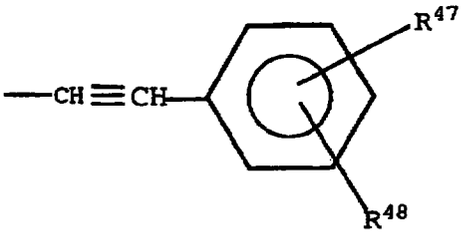
alkenyl of from two to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from two to six carbon atoms,

alkynyl of from two to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms, cycloalkyl of from three to six carbon atoms,



wherein n is zero or an integer of one to eight and R^{47} and R^{48} are independently hydrogen, fluorine, chlorine, bromine, hydroxy, alkyl of from one to three carbon atoms, or alkoxy of from one to three carbon atoms, or alkoxy of from one to four carbon atoms, or



wherein

R^{47} and R^{48} are as defined above;

X is oxygen or sulfur;

R^{44} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

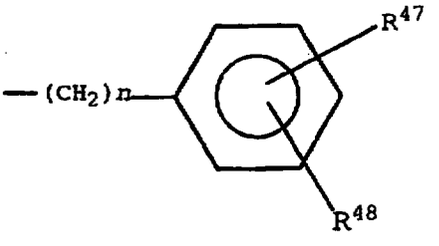
alkenyl of from three to six carbon atoms

alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or



wherein n, R47 and R48 are as defined above R45 and R46 are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

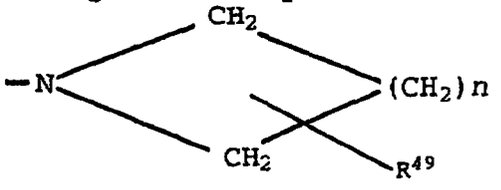
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

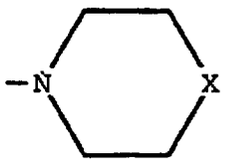
cycloalkyl of from three to eight carbon atoms,

phenyl,

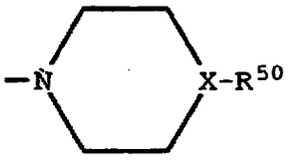
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^{45} and R^{46} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



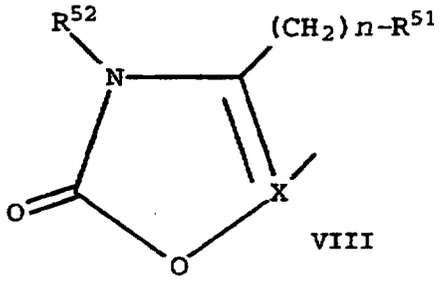
wherein R^{49} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms and n is as defined above,



wherein X is defined above or

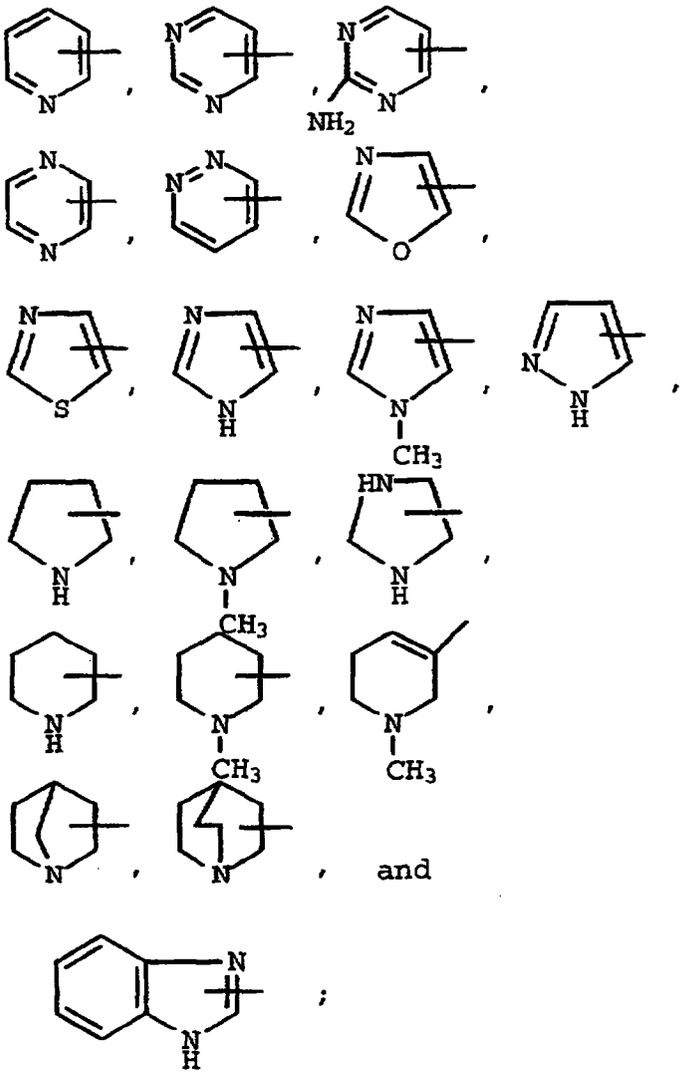


wherein R^{50} is hydrogen or alkyl of from one to six carbon atoms,

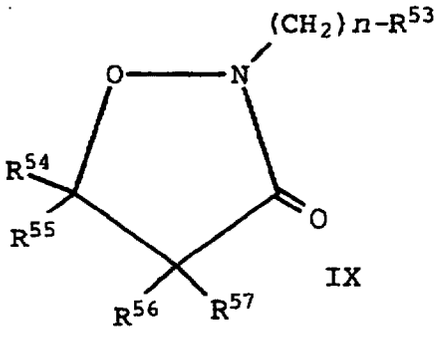


VIII

wherein R^{51} is selected from the group consisting of

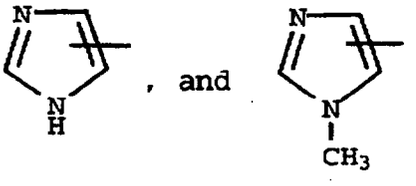


R^{52} is hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; n' is zero or an integer of one or two; X' is carbon or nitrogen; and ..... represents a single or double bond with the proviso that when, ... represents a double bond X' is nitrogen and when ..... represents a single bond X' is CH_2;

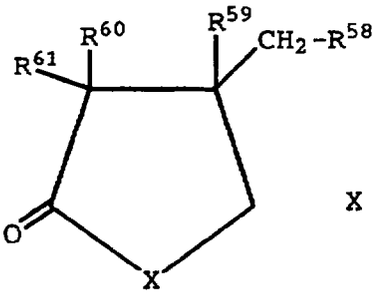


IX

wherein R^{53} is selected from the group consisting

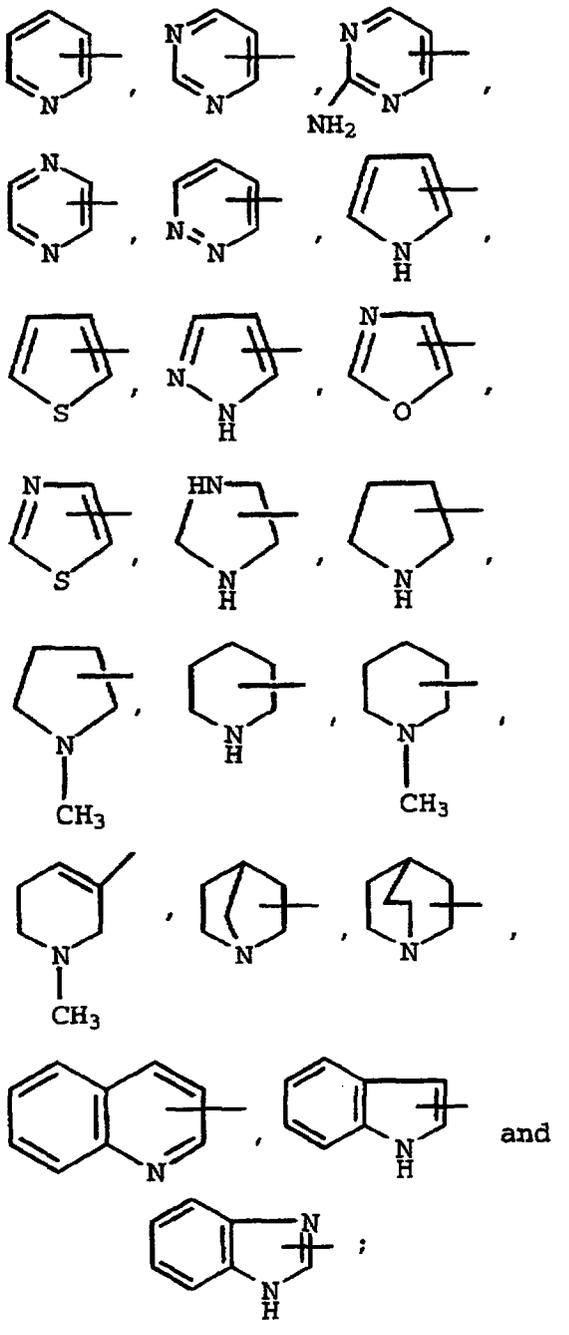


R54, R55, R56, and R57 are each independenty hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from C1-C10 alkyl, alkoxy, C1-C10 halogen or trifluoromethyl; n' is an interger of one or two;



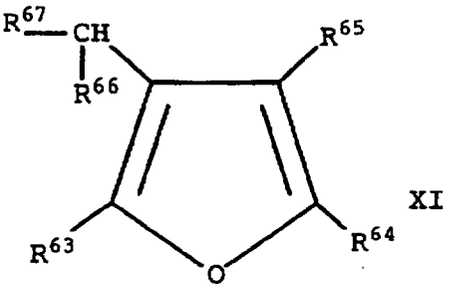
X

wherein X is oxygen, sulfur, or -N-R^{62}, wherein R^{62} is hydrogen or alkyl of from one to ten carbon atoms; R^{58} is selected from the group consisting of



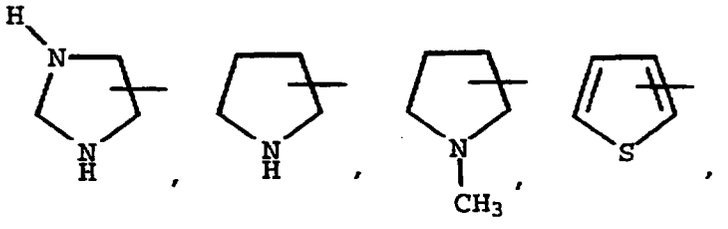
and

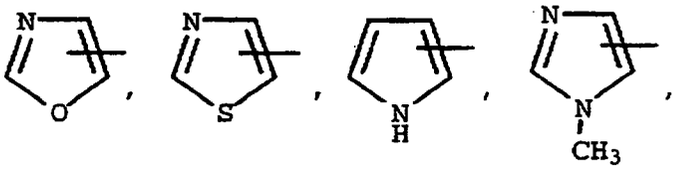
R^{59}, R^{60}, and R^{61} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; --- represents a single or double bond with the proviso that when --- represents a double bond R^{57} and R^{60} are absent;

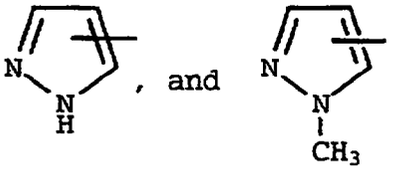


XI

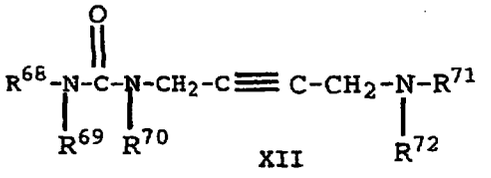
wherein R^{63}, R^{64}, and R^{65} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from the group consisting of alkyl, alkoxy, thioalkoxy, halogen, and trifluoromethyl; R^{66} is hydrogen, hydroxy or alkoxy of from one to ten carbon atoms; and R^{67} is selected from the group consisting of







; or



XII

wherein

R^{69} is hydrogen and R^{67} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

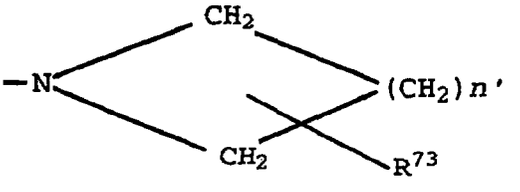
alkenyl of from three to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{68} and R^{69} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



wherein n' is zero or an integer from one to eight and R^{73} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms or alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms;

R^{70} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of form one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

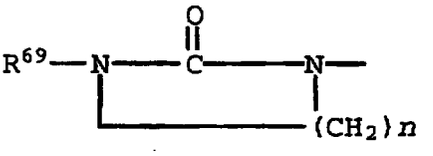
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{70} when taken together with R^{68} forms a ring denoted by



wherein n is an integer from one to three and R68 are as defined above;

R^{71} and R^{72} are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

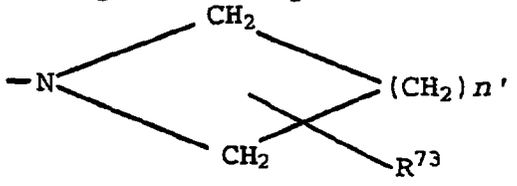
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with dydroxy or alkoxy of from one to four carbon atoms,

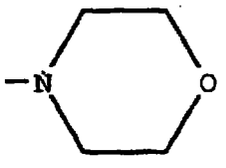
cycloalkyl of from three to eight carbon atoms,

phenyl,

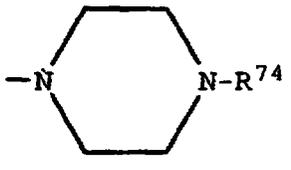
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^3 and R^4 are taken together with the nitrogen atom to which they are attached to form a ring denoted by



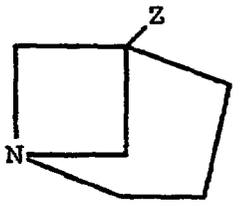
wherein n' and R^{73} are ad defined above,



wherein X is defined above or

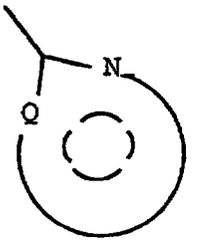


wherein R^{74} is hydrogen or alkyl of from one to six carbon atoms,

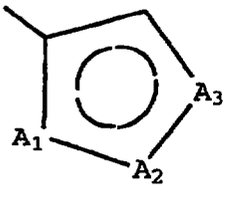


XIII

in which Z is a heterocyclic group

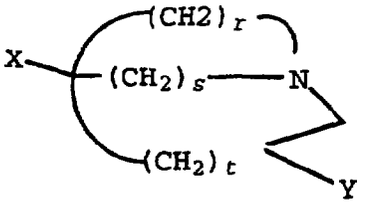


in which Q represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, or three nitrogen atoms, any amino nitrogen being substituted by a C_{1-2} alkyl, cyclopropyl or propargyl group, and any ring carbon atom being optionally substituted by a group R_1; or a group

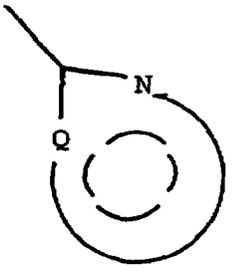


in which A_1, A_2 and A_3 complete a 5-membered aromatic ring and A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_2 and the other is nitrogen or CR_3, or A_2 is oxygen or sulphur, one of A_1 and A_3 is CR_2 and the other is CR_3; and R_1, R_2 and R_3 are independently selected from hydrogen, halogen, CN, OR_4, SR_4, $N(R_4)_2$, $NHCOR_4$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR_4$, $NHNH_2$, NO_2, COR_4, COR_5, cyclopropyl, C_{2-5} straight chain alkenyl, C_{2-5} straight chain alkynyl or C_{1-5} straight chain alkyl optionally terminally substituted with OR_4, $N(R_4)_2$, SR_4, CO_2R_4, $CON(R_4)_2$ or one, two or three halogen atoms, in which each R_4 is independently hydrogen or C_{1-3} alkyl and R_5 is OR_4, NH_2 or NHR_4; or in which Z is a group $-C(R_7)=NR_6$ in which R_6 is a group OR_8, where R_8 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a group $OCOR_9$ where R_9 is hydrogen or R_8, or a group NHR_{10} or $NR_{11}R_{12}$ where R_{10}, R_{11} and R_{12} are independently C_{1-2} alkyl and R_7 is hydrogen or C_{1-4} alkyl, subject to the

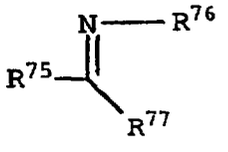
proviso that when R_6 is a group OCOR9 or NHR_{10}, R_7 is C1-4 alkyl



in which one of X and Y represents hydrogen and the other represents Z, and Z' is a group

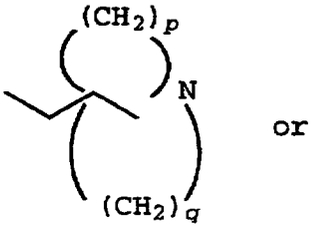


in which Q' represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises two or three nitrogen atoms, any amino nitrogen being substituted by a C1-2 alkyl, cyclopropyl or propargyl group, r represents the integer of 2 or 3, s represents an integer of 1 or 2 and t represents 0, with the proviso that when Y is hydrogen s is 1;

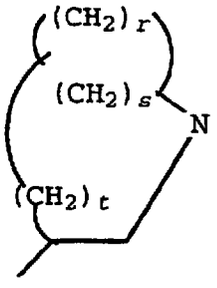


XV

wherein R^{75} represents



or



in which

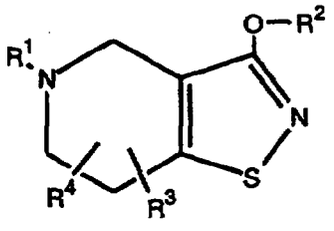
each of p and q independently represents an integer of 2 to 4, r represents an integer of 2 to 4, s represents 1 or 2 and t represents 0 or 1;

R^{76} is a group OR^{78}, where R^{78} is C_{1-4} alkenyl, C_{2-4} alkynyl, a group $OCOR^{79}$ where R^{79} is hydrogen or R^{78}, or a group NHR^{80} or NR^{81}, R^{82}, where R^{80}, R^{81} and R^{82} are independently C_{1-2} alkyl; and R^{77} is hydrogen or C_{1-4}alkyl, subject to the proviso that when R^{76} is a group $OCOR^{79}$ or a group NHR^{80}, R^{77} is alkyl;

(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane; or a pharmaceutically acceptable salt or solvate thereof;

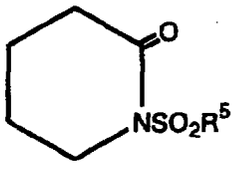
and one or more Synergistic Analgesics in a weight ratio of Compound to Synergistic Analgesic of from about 1 to about 1000.

The present invention provides a method for treating pain comprising administering to a patient in need thereof, an anagesic composition comprising a compound selected from the group consisting of:



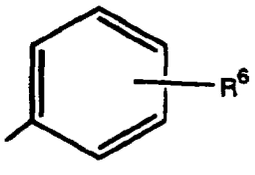
I

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;
R^2 is C_1-C_6alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, branched or unbranched with 1-6 carbon atoms inclusive, which group may be optionally substituted with fluoro, hydroxy or phenyl optionally substituted with fluoro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy;
R^3 and R^4 are independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl optionally substituted with halogen trifluroromethyl, C_1-C_4 alkyl, hydroxy, or C_1-C_4 alkoxy, or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;



II;

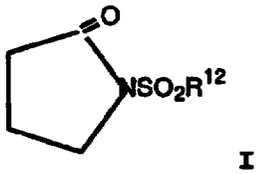
in which R^5 represents the radical



in which R^6 at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical

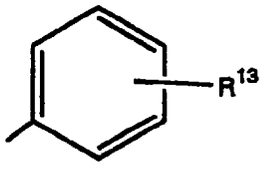


in which R^7 and R^8 which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical OR^9, R^9 representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up tc 14 carbon atoms, or the radical SR^{10} or $S(O)R^{11}$, R^{10} and R^{11} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^5 represents naphthyl optionally substituted with $R^{6'}$, $R^{6'}$ being defined above for R^6;

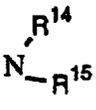


III

in which R^{12} represents the radical

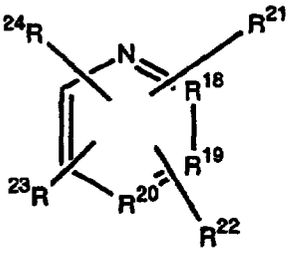


in which R^{13} at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical



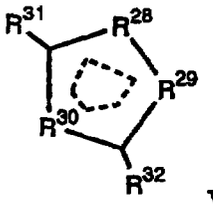
in which R^{14} and R^{15} which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which

they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical or NO_2, or $OR^{12'}$, $R^{12'}$ representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{16} or $S(O)R^{17}$, R^{16} and R^{17} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^{12} represents naphthyl optionally substituted with $R^{13'}$, $R^{13'}$ being defined above for R^{13};



IV

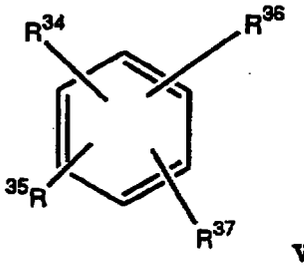
wherein, one of R^{18}, R^{19}, and R^{20} represents nitrogen and the remainder represent carbon atoms; substituted on one of the ring carbon atoms with a R^{24} substituent represented by a non-aromatic azacyclic or azabicyclic ring system and independently substituted on each of the other ring carbon atoms with R^{23}, R^{21}, or R^{22} substituent of low lipophilicity or a hydrocarbon having a maximum of 20 carbon atoms;



V;

wherein one of R^{28}, R^{29} or R^{30} is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R^{31} represents a non-aromatic '927azacycle or '927azabicyclic ring system; and

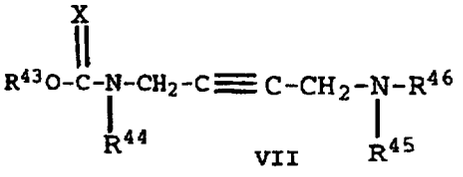
R^{32} represents a substituent which is convertable in vivo to an amino group;



VI;

wherein R^{34} represents a non-aromatic; non-fused 1-azabicyclic ring system; and

R^{35}, R^{36}, and R^{37} independently represent hydrogen, F, Cl, Br, $-CF_3$, $-OR^{38}$, $-NR^{38}R^{39}$, $-NHOR^{38}$, $-NHNH_2$, $-CN$, COR^{40}, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group, provided that at least one of R^{35}, R^{36}, and R^{37} is other than hydrogen or a hydrocarbon group, or R^{35} and R^{35} or R^{37} taken together form a C_{1-6}alkylenedioxy ring, wherein R^{38} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, R^{39} is hydrogen, C_{1-6} alkyl,or $-COCH_3$, and R^{40} represents OH, $-OR^{38}$, NHR^{39}, or $-NR^{38}R^{39}$



VII

wherein R^{43} is

alkyl of from one to six carbon atoms,

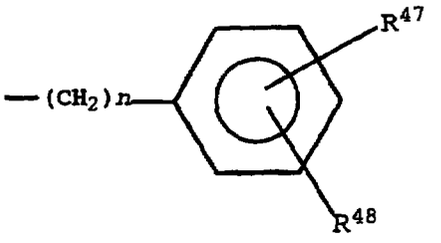
alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from two to six carbon atoms,

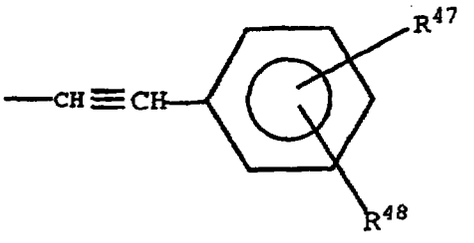
alkenyl of from two to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from two to six carbon atoms,

alkynyl of from two to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms, cycloalkyl of from three to six carbon atoms,



wherein n is zero or an integer of one to eight and R^{47} and R^{48} are independently hydrogen, fluorine, chlorine, bromine, hydroxy, alkyl of from one to three carbon atoms, or alkoxy of from one to three carbon atoms, or alkoxy of from one to four carbon atoms, or



wherein

R^{47} and R^{48} are as defined above;

X is oxygen or sulfur;

R^{44} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

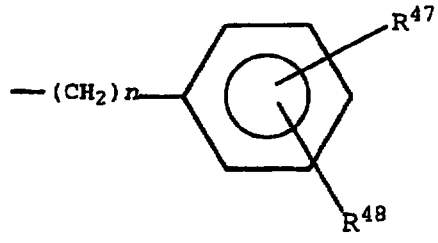
alkenyl of from three to six carbon atoms

alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or



wherein n, R47 and R48 are as defined above R45 and R46 are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

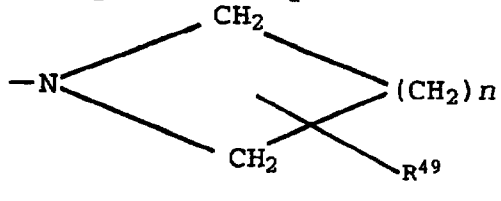
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to eight carbon atoms,

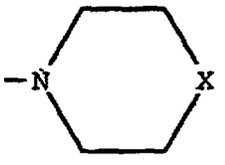
phenyl,

phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^{45} and R^{46} are taken together with the nitrogen atom to which they are attached to form a ring denoted by

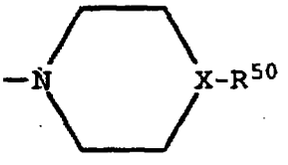


wherein R^{49} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with

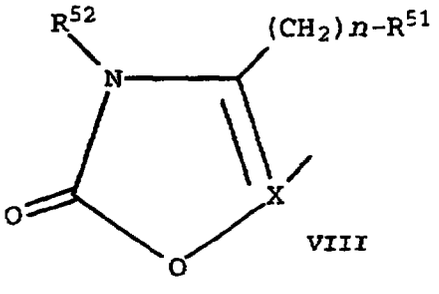
hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms and n is as defined above,



wherein X is defined above or

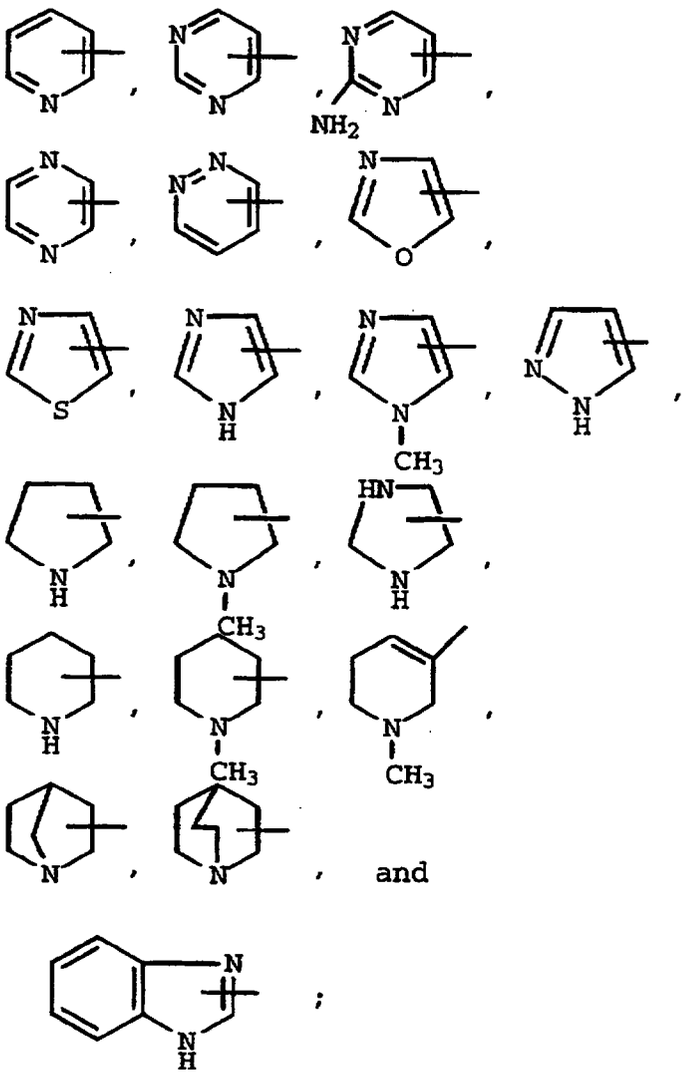


wherein R^{50} is hydrogen or alkyl of from one to six carbon atoms,

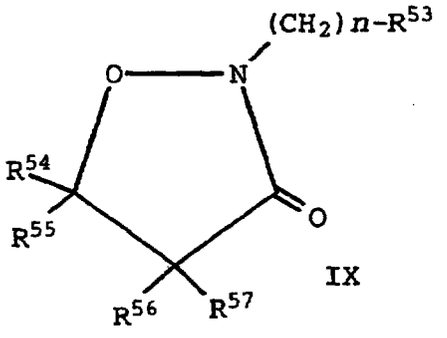


VIII

wherein R^{51} is selected from the group consisting of

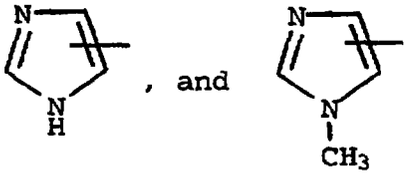


R^{52} is hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; n' is zero or an integer of one or two; X' is carbon or nitrogen; and ... represents a single or double bond with the proviso that when, ... represents a double bond X' is nitrogen and when ... represents a single bond X' is CH_2;



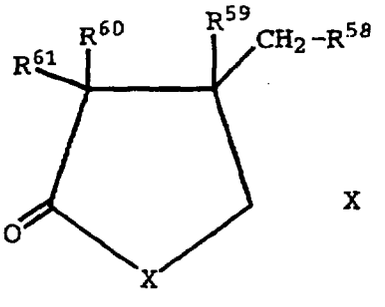
IX

wherein R^{53} is selected from the group consisting



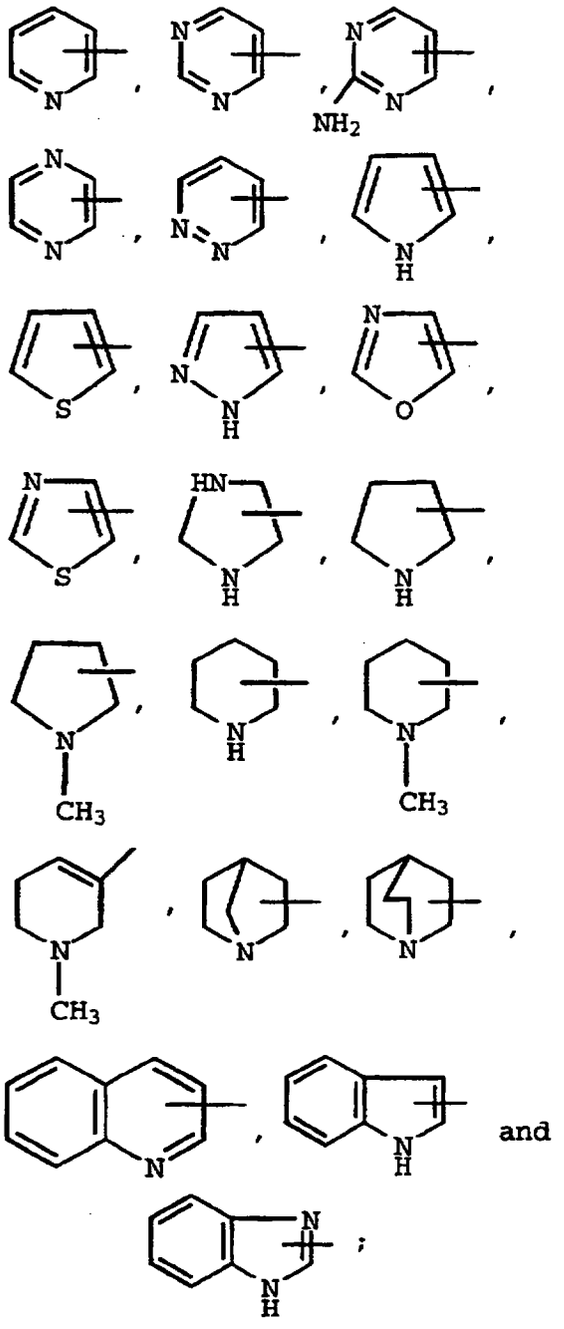
,

R54, R55, R56, and R57 are each independenty hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from C1-C10 alkyl, alkoxy, C1-C10 halogen or trifluoromethyl; n' is an interger of one or two;



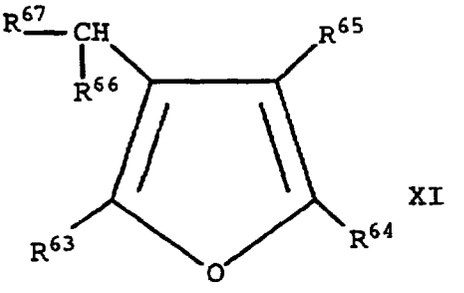
X

wherein X is oxygen, sulfur, or -N-R^{62}, wherein R^{62} is hydrogen or alkyl of from one to ten carbon atoms; R^{58} is selected from the group consisting of



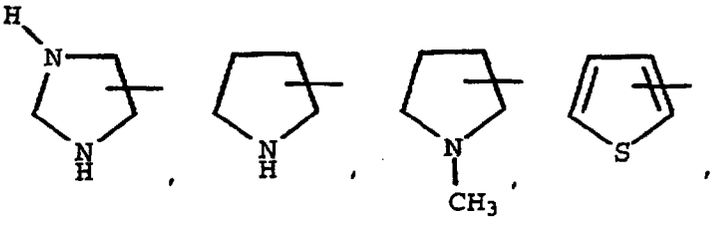
and

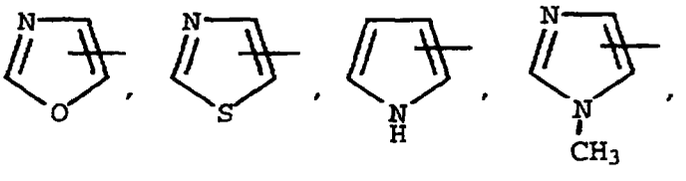
R^{59}, R^{60}, and R^{61} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; --- represents a single or double bond with the proviso that when --- represents a double bond R^{57} and R^{60} are absent;

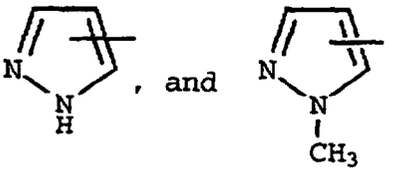


XI

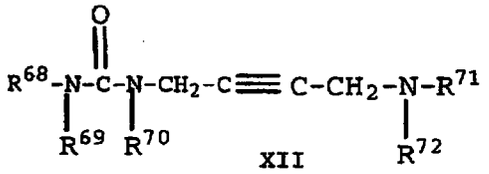
wherein R^{63}, R^{64}, and R^{65} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from the group consisting of alkyl, alkoxy, thioalkoxy, halogen, and trifluoromethyl; R^{66} is hydrogen, hydroxy or alkoxy of from one to ten carbon atoms; and R^{67} is selected from the group consisting of







; or



XII

wherein

R^{69} is hydrogen and R^{67} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

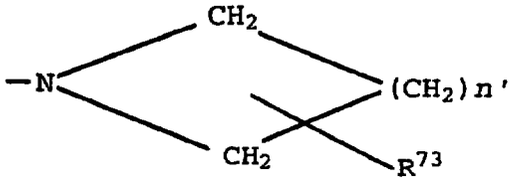
alkenyl of from three to six carbon atoms,

alkenyl of from three to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or R^{68} and R^{69} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



wherein n' is zero or an integer from one to eight and R^{73} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms or alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms;

R^{70} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of form one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

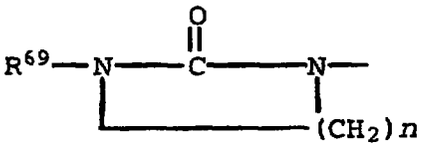
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{70} when taken together with R^{68} forms a ring denoted by



wherein n is an integer from one to three and R68 are as defined above;

R^{71} and R^{72} are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

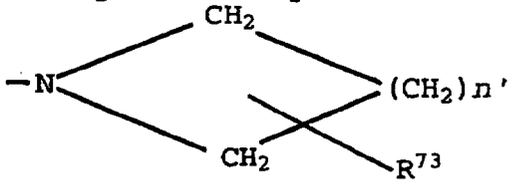
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with dydroxy or alkoxy of from one to four carbon atoms,

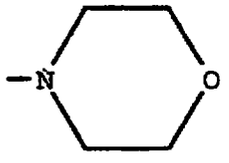
cycloalkyl of from three to eight carbon atoms,

phenyl,

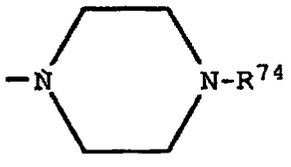
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^3 and R^4 are taken together with the nitrogen atom to which they are attached to form a ring denoted by



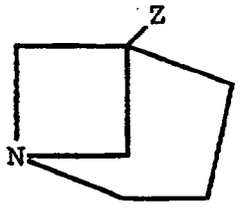
wherein n' and R^{73} are ad defined above,



wherein X is defined above or

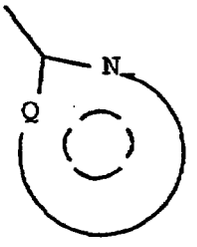


wherein R^{74} is hydrogen or alkyl of from one to six carbon atoms,

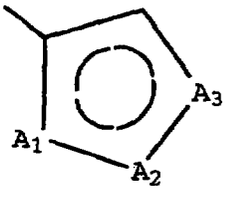


XIII

in which Z is a heterocyclic group

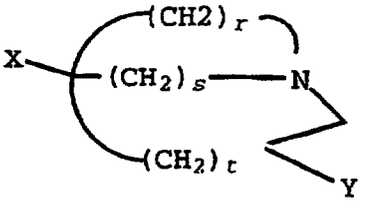


in which Q represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, or three nitrogen atoms, any amino nitrogen being substituted by a C_{1-2} alkyl, cyclopropyl or propargyl group, and any ring carbon atom being optionally substituted by a group R_1; or a group

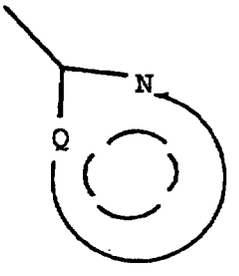


in which A_1, A_2 and A_3 complete a 5-membered aromatic ring and A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_2 and the other is nitrogen or CR_3, or A_2 is oxygen or sulphur, one of A_1 and A_3 is CR_2 and the other is CR_3; and R_1, R_2 and R_3 are independently selected from hydrogen, halogen, CN, OR_4, SR_4, $N(R_4)_2$, $NHCOR_4$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR_4$, $NHNH_2$, NO_2, COR_4, COR_5, cyclopropyl, C_{2-5} straight chain alkenyl, C_{2-5} straight chain alkynyl or C_{1-5} straight chain alkyl optionally terminally substituted with OR_4, $N(R_4)_2$, SR_4, CO_2R_4, $CON(R_4)_2$ or one, two or three halogen atoms, in which each R_4 is independently hydrogen or C_{1-3} alkyl and R_5 is OR_4, NH_2 or NHR_4; or in which Z is a group $-C(R_7)=NR_6$ in which R_6 is a group OR_8, where R_8 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a group $OCOR_9$ where R_9 is hydrogen or R_8, or a group NHR_{10} or $NR_{11}R_{12}$ where R_{10}, R_{11} and R_{12} are independently C_{1-2} alkyl and R_7 is hydrogen or C_{1-4} alkyl, subject to the

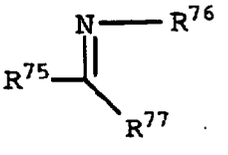
proviso that when R_6 is a group OCOR9 or NHR10, R_7 is C_{1-4} alkyl



in which one of X and Y represents hydrogen and the other represents Z, and Z' is a group

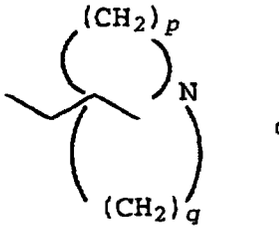


in which Q' represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises two or three nitrogen atoms, any amino nitrogen being substituted by a C1-2 alkyl, cyclopropyl or propargyl group, r represents the integer of 2 or 3, s represents an integer of 1 or 2 and t represents 0, with the proviso that when Y is hydrogen s is 1;

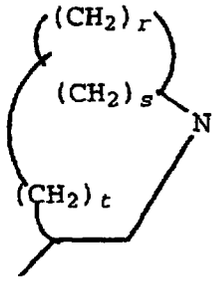


XV

wherein R^{75} represents



or



in which

each of p and q independently represents an integer of 2 to 4, r represents an integer of 2 to 4, s represents 1 or 2 and t represents 0 or 1;

R^{76} is a group OR^{78}, where R^{78} is C_{1-4} alkenyl, C_{2-4} alkynyl, a group $OCOR^{79}$ where R^{79} is hydrogen or R^{78}, or a group NHR^{80} or NR^{81}, R^{82}, where R^{80}, R^{81} and R^{82} are independently C_{1-2} alkyl; and R^{77} is hydrogen or C_{1-4}alkyl, subject to the proviso that when R^{76} is a group $OCOR^{79}$ or a group NHR^{80}, R^{77} is alkyl;

(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane; or a pharmaceutically acceptable salt or solvate thereof; and

one or more Synergistic Analgesics in a weight ratio of Compound to Synergistic Analgesic of from about 1 to about 1000.

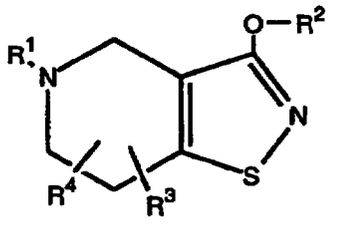
As noted hereinbefore, the compounds employed in the method of the present invention are known. The compounds, methods of preparing the compounds, as well as pharmaceutical formulations containing the compounds, are taught in U.S. Pat. Nos. 4,923,880, 5,110,828, 5,041,436, 5,278,170, 7,177,084, 4,992,436, 5,260,293, 4996,201, 5,066,662, 5,066,665, 5,066,663, 4,988,688, 5,106,853,

5,192,765, 5,041,455, 5,043,345, 5,260,314, 5,310,911, 5,106,851, 5,068,237, 5,318,978, 5,242,927, 5,300,516, 5,089,505, 5,302595, 5,219,871, 5,096,890, 5,164,386, 5,164,514, 5,157,160, 5,217,975, and 5,081,130 herein incorporated by reference.

It is to be understood that the invention extends to the use of each of the stereoisomeric forms of the compounds of the present invention as well as the pure diastereomeric, pure enantiomeric, and racemic forms of the named compounds.

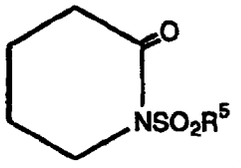
As used herein, the terms "Synergistic Analgesic" and "Synergistic Analgesics" refer to the group consisting of Nonsteroidal anti-inflammatory drugs (NSAIDS), acetaminophen, alpha-adrenergic compounds, and opioids.

As used herein, the term "Selected Muscarinic Compound" and "Selected Muscarinic Compounds" refers to a compound selected from the group consisting of



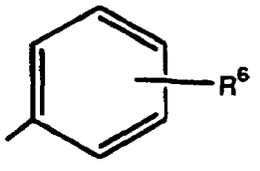
I

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;
R^2 is C_1-C_6alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, branched or unbranched with 1-6 carbon atoms inclusive, which group may be optionally substituted with fluoro, hydroxy or phenyl optionally substituted with fluoro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy;
R^3 and R^4 are independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl optionally substituted with halogen trifluroromethyl, C_1-C_4 alkyl, hydroxy, or C_1-C_4 alkoxy, or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

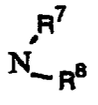


II;

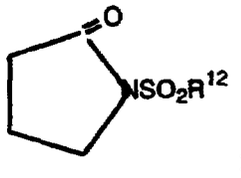
in which R^5 represents the radical



in which R^6 at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical

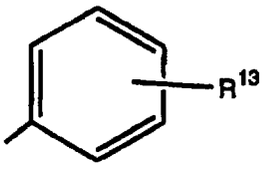


in which R^7 and R^8 which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical OR^9, R^9 representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{10} or $S(O)R^{11}$, R^{10} and R^{11} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^5 represents naphthyl optionally substituted with $R^{6'}$, $R^{6'}$ being defined above for R^6;

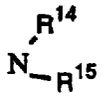


III

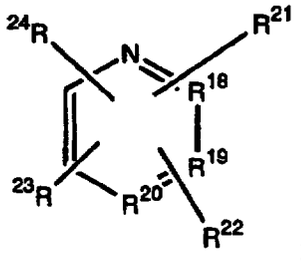
in which R^{12} represents the radical



in which R^{13} at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical



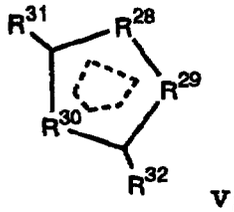
in which R^{14} and R^{15} which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical or NO_2, or $OR^{12'}$, $R^{12'}$ representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{16} or $S(O)R^{17}$, R^{16} and R^{17} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^{12} represents naphthyl optionally substituted with $R^{13'}$, $R^{13'}$ being defined above for R^{13};



IV

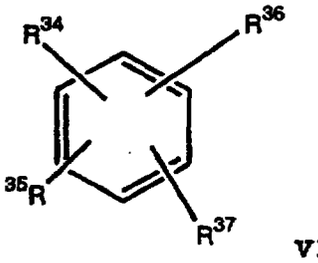
wherein, one of R^{18}, R^{19}, and R^{20} represents nitrogen and the remainder represent carbon atoms; substituted on one of the ring carbon atoms with a R^{24} substituent represented by a non-aromatic azacyclic or azabicyclic ring system and

independently substituted on each of the other ring carbon atoms with R^{23}, R^{21}, or R^{22} substituent of low lipophilicity or a hydrocarbon having a maximum of 20 carbon atoms;



V;

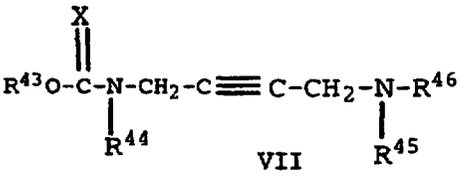
wherein one of R^{28}, R^{29} or R^{30} is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R^{31} represents a non-aromatic '927azacycle or '927azabicyclic ring system; and R^{32} represents a substituent which is convertable in vivo to an amino group;



VI;

wherein R^{34} represents a non-aromatic; non-fused 1-azabicyclic ring system; and

R^{35}, R^{36}, and R^{37} independently represent hydrogen, F, Cl, Br, $-CF_3$, $-OR^{38}$, $-NR^{38}R^{39}$, $-NHOR^{38}$, $-NHNH_2$, -CN, COR^{40}, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group, provided that at least one of R^{35}, R^{36}, and R^{37} is other than hydrogen or a hydrocarbon group, or R^{35} and R^{36} or R^{37} taken together form a C_{1-6}alkylenedioxy ring, wherein R^{38} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, R^{39} is hydrogen, C_{1-6} alkyl,or $-COCH_3$, and R^{40} represents OH, $-OR^{38}$, NHR^{39}, or $-NR^{38}R^{39}$



VII

wherein R^{43} is

alkyl of from one to six carbon atoms,

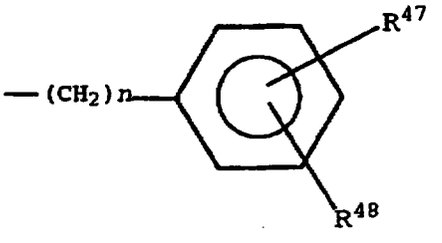
alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from two to six carbon atoms,

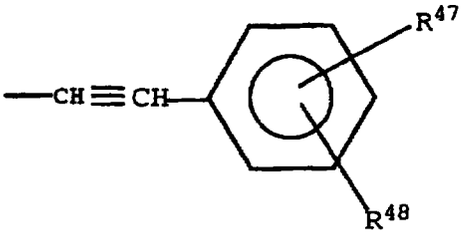
alkenyl of from two to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from two to six carbon atoms,

alkynyl of from two to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms, cycloalkyl of from three to six carbon atoms,



wherein n is zero or an integer of one to eight and R^{47} and R^{48} are independently hydrogen, fluorine, chlorine, bromine, hydroxy, alkyl of from one to three carbon atoms, or alkoxy of from one to three carbon atoms, or alkoxy of from one to four carbon atoms, or



wherein

R^{47} and R^{48} are as defined above;

X is oxygen or sulfur;

R^{44} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

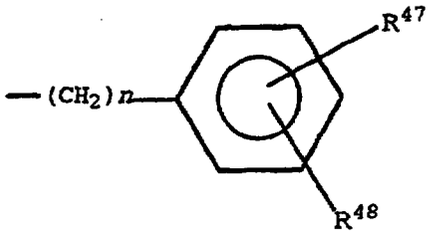
alkenyl of from three to six carbon atoms

alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or



wherein n, R47 and R48 are as defined above R45 and R46 are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

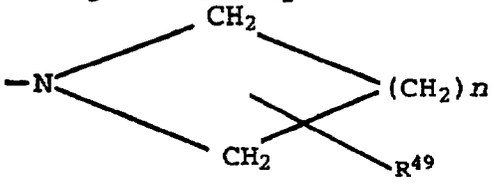
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

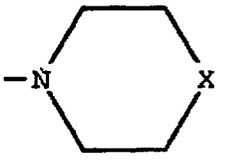
cycloalkyl of from three to eight carbon atoms,

phenyl,

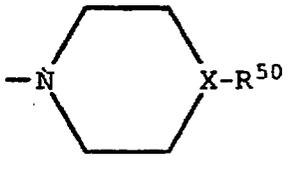
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^{45} and R^{46} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



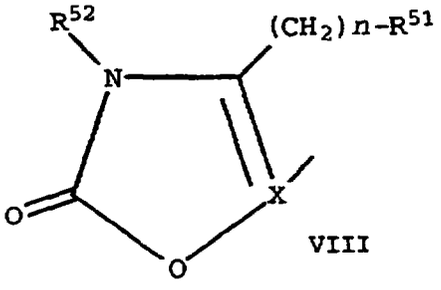
wherein R^{49} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms and n is as defined above,



wherein X is defined above or

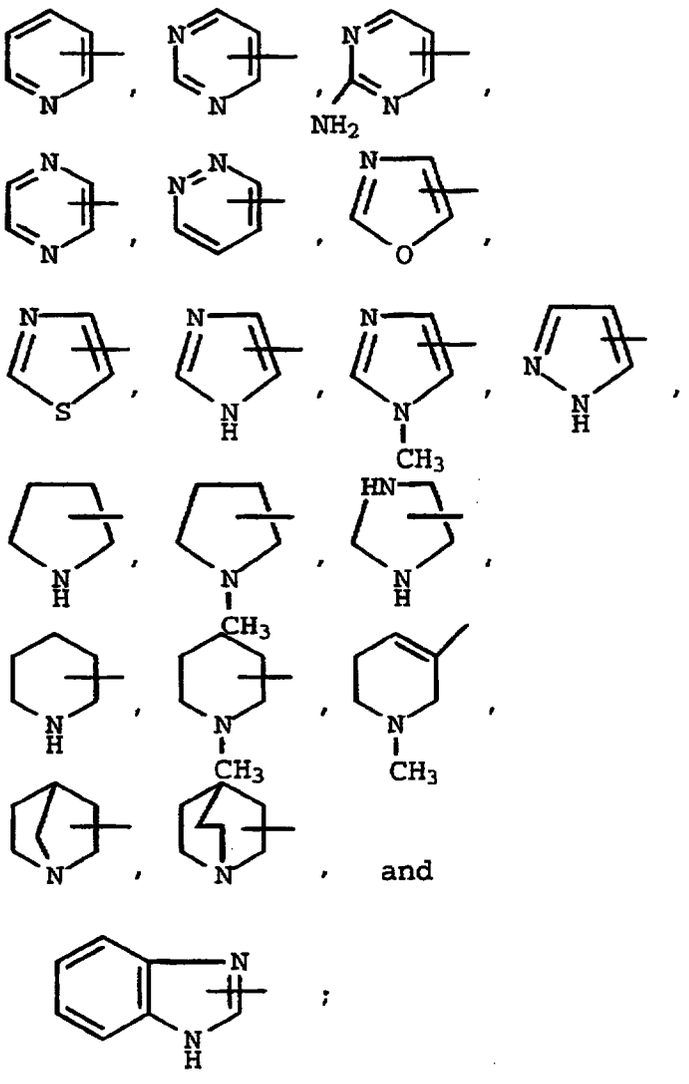


wherein R^{50} is hydrogen or alkyl of from one to six carbon atoms,



VIII

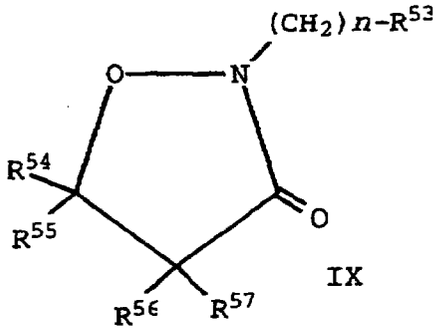
wherein R^{51} is selected from the group consisting of



and

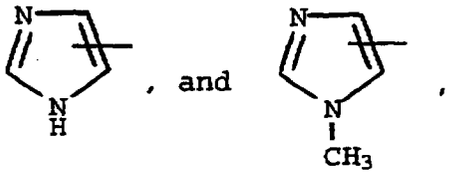
;

R^{52} is hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; n' is zero or an integer of one or two; X' is carbon or nitrogen; and ..... represents a single or double bond with the proviso that when, ... represents a double bond X' is nitrogen and when ..... represents a single bond X' is CH_2;

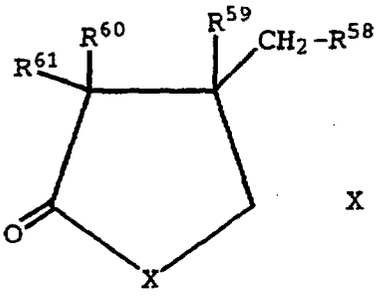


IX

wherein R^{53} is selected from the group consisting

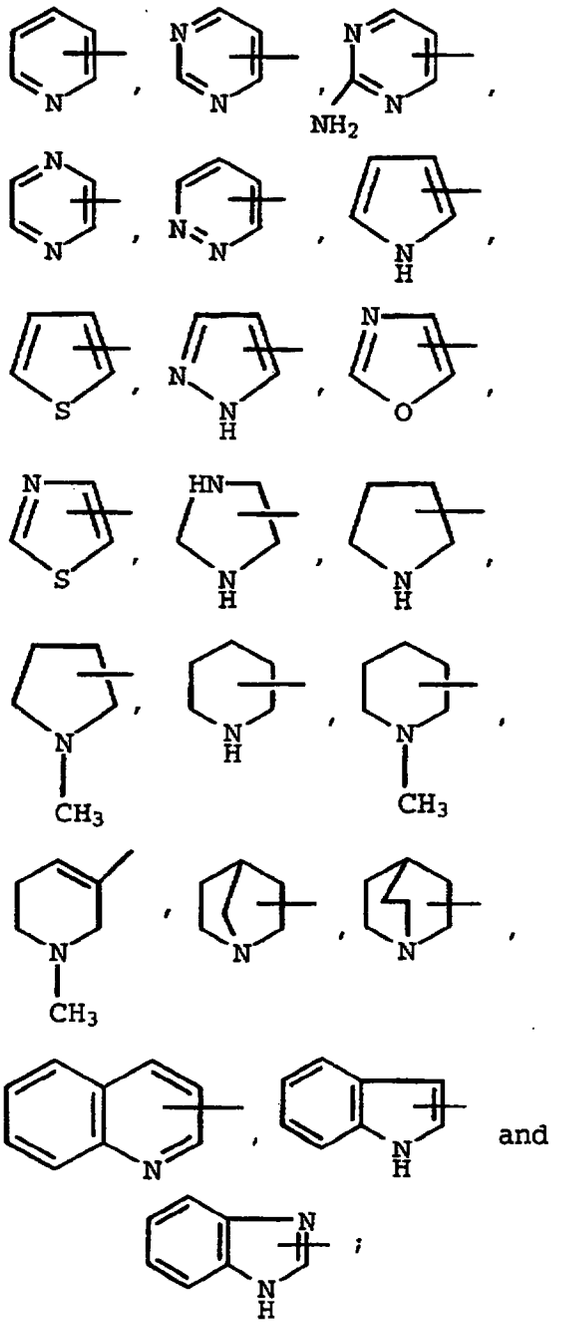


R54, R55, R56, and R57 are each independenty hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from C1-C10 alkyl, alkoxy, C1-C10 halogen or trifluoromethyl; n' is an interger of one or two;



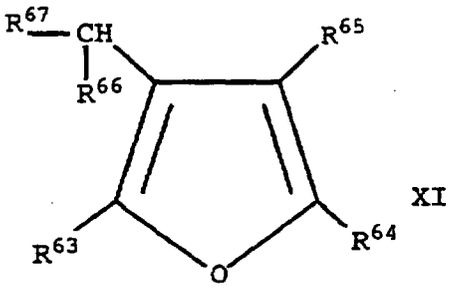
X

wherein X is oxygen, sulfur, or -N-R^{62}, wherein R^{62} is hydrogen or alkyl of from one to ten carbon atoms; R^{58} is selected from the group consisting of



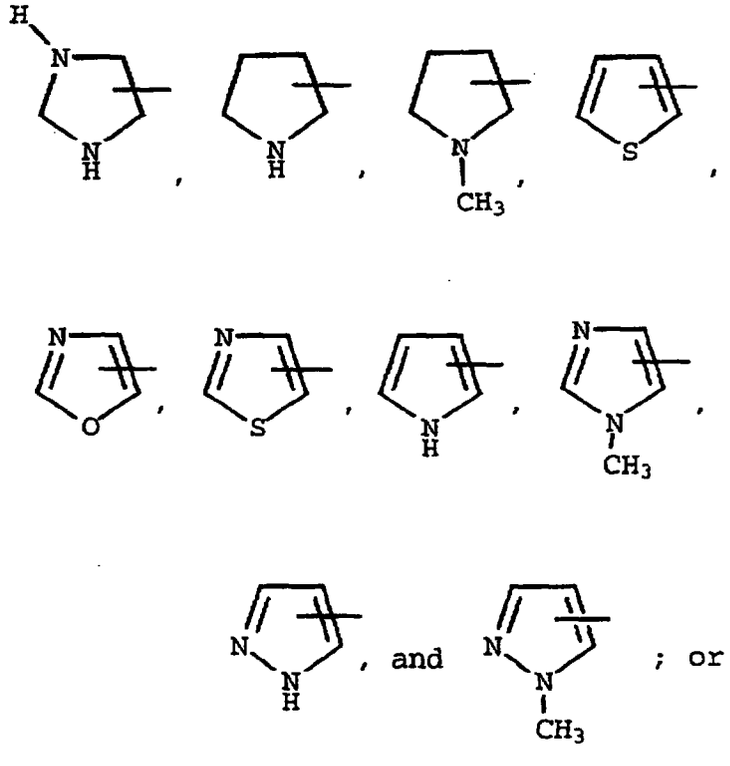
and

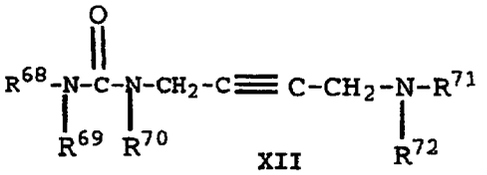
R^{59}, R^{60}, and R^{61} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; --- represents a single or double bond with the proviso that when --- represents a double bond R^{57} and R^{60} are absent;



XI

wherein R^{63}, R^{64}, and R^{65} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from the group consisting of alkyl, alkoxy, thioalkoxy, halogen, and trifluoromethyl; R^{66} is hydrogen, hydroxy or alkoxy of from one to ten carbon atoms; and R^{67} is selected from the group consisting of





XII

wherein

R^{69} is hydrogen and R^{67} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

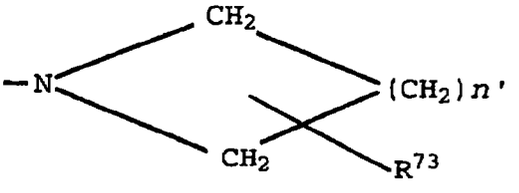
alkenyl of from three to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{68} and R^{69} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



wherein n' is zero or an integer from one to eight and R^{73} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms or alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms;

R^{70} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of form one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

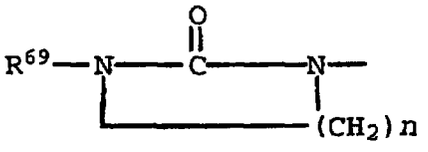
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{70} when taken together with R^{68} forms a ring denoted by



wherein n is an integer from one to three and R68 are as defined above;

R^{71} and R^{72} are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

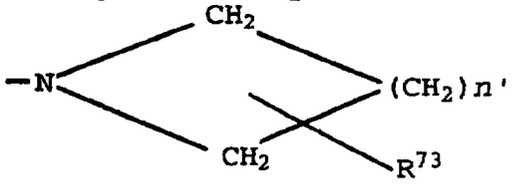
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with dydroxy or alkoxy of from one to four carbon atoms,

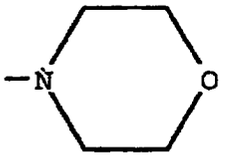
cycloalkyl of from three to eight carbon atoms,

phenyl,

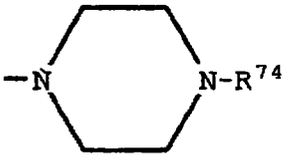
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^3 and R^4 are taken together with the nitrogen atom to which they are attached to form a ring denoted by



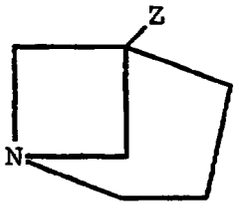
wherein n' and R^{73} are ad defined above,



wherein X is defined above or

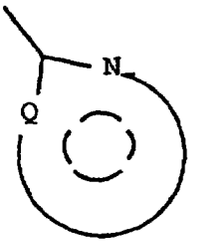


wherein R^{74} is hydrogen or alkyl of from one to six carbon atoms,

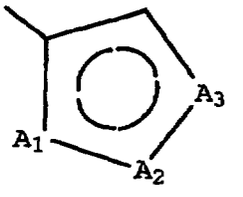


XIII

in which Z is a heterocyclic group

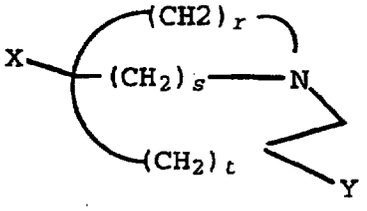


in which Q represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, or three nitrogen atoms, any amino nitrogen being substituted by a C_{1-2} alkyl, cyclopropyl or propargyl group, and any ring carbon atom being optionally substituted by a group R_1; or a group

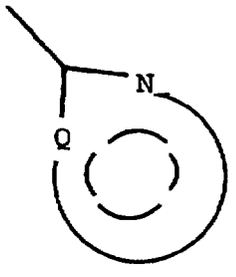


in which A_1, A_2 and A_3 complete a 5-membered aromatic ring and A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_2 and the other is nitrogen or CR_3, or A_2 is oxygen or sulphur, one of A_1 and A_3 is CR_2 and the other is CR_3; and R_1, R_2 and R_3 are independently selected from hydrogen, halogen, CN, OR_4, SR_4, $N(R_4)_2$, $NHCOR_4$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR_4$, $NHNH_2$, NO_2, COR_4, COR_5, cyclopropyl, C_{2-5} straight chain alkenyl, C_{2-5} straight chain alkynyl or C_{1-5} straight chain alkyl optionally terminally substituted with OR_4, $N(R_4)_2$, SR_4, CO_2R_4, $CON(R_4)_2$ or one, two or three halogen atoms, in which each R_4 is independently hydrogen or C_{1-3} alkyl and R_5 is OR_4, NH_2 or NHR_4; or in which Z is a group $-C(R_7)=NR_6$ in which R_6 is a group OR_8, where R_8 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a group $OCOR_9$ where R_9 is hydrogen or R_8, or a group NHR_{10} or $NR_{11}R_{12}$ where R_{10}, R_{11} and R_{12} are independently C_{1-2} alkyl and R_7 is hydrogen or C_{1-4} alkyl, subject to the

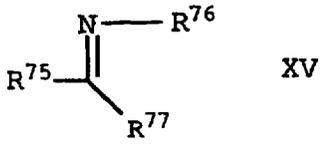
proviso that when R_6 is a group OCOR9 or NHR_{10}, R_7 is C_{1-4} alkyl



in which one of X and Y represents hydrogen and the other represents Z, and Z' is a group

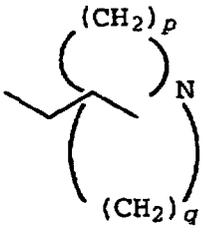


in which Q' represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises two or three nitrogen atoms, any amino nitrogen being substituted by a C1-2 alkyl, cyclopropyl or propargyl group, r represents the integer of 2 or 3, s represents an integer of 1 or 2 and t represents 0, with the proviso that when Y is hydrogen s is 1;

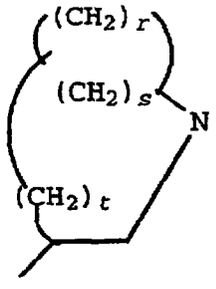


XV

wherein R^{75} represents



or



in which

each of p and q independently represents an integer of 2 to 4, r represents an integer of 2 to 4, s represents 1 or 2 and t represents 0 or 1;

R^{76} is a group OR^{78}, where R^{78} is C_{1-4} alkenyl, C_{2-4} alkynyl, a group $OCOR^{79}$ where R^{79} is hydrogen or R^{78}, or a group NHR^{80} or NR^{81}, R^{82}, where R^{80}, R^{81} and R^{82} are independently C_{1-2} alkyl; and R^{77} is hydrogen or C_{1-4}alkyl, subject to the proviso that when R^{76} is a group $OCOR^{79}$ or a group NHR^{80}, R^{77} is alkyl;

(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane; or a pharmaceutically acceptable salt or solvate thereof.

The term "low lipophilicity" refers to hydrogen, halogen, $-CF_3$, $-OR^{25}$, $-NR^{25}R^{26}$, $-NHOR^{25}$, $-NHNH_2$, -CN, COR^8, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group; wherein R^{25} is hydrogen, C_1-C_6 alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl; R^{26} is hydrogen, alkyl or $-COCH_3$, and R27 represents $-OR^{25}$ or $-NR^{25}R^{26}$;

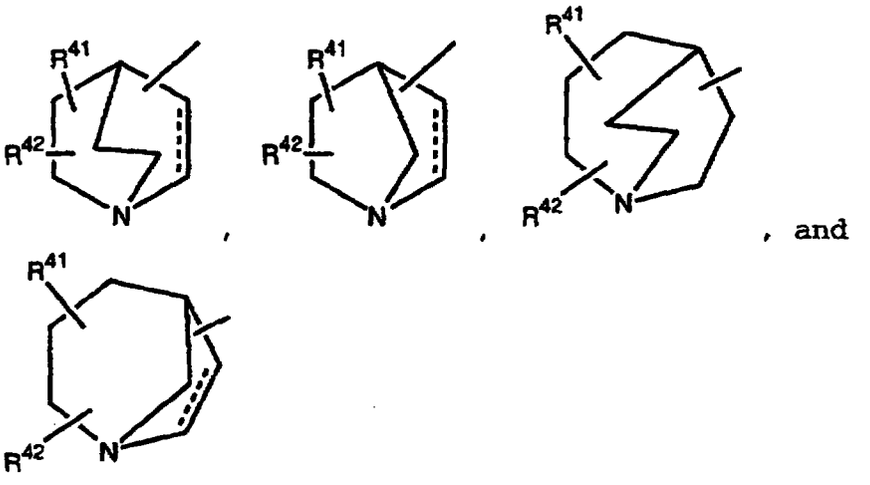
The term azacyclic or azabicyclic ring system is a non-aromatic ring system containing one nitrogen atom as the sole heteroatom. Sutably, the ring system contains from 4-10 ring atoms, preferably from 5-8 ring atoms. Preferably, the

ring system contains a tertiary amino nitrogen atom in a caged structure. The bicyclic systems may be fused, spiro, or birdged. Preferably, the nitrogen atom is at a bridgehead in a bicyclic system. Examples of such heteroatoms include the heteroatoms described in U.S. Patent 5,260,293, columns 2-3, which has been incorporated by reference.

The term "'927 azacyclic or '927 azabicyclic" refers to a non-aromatic ring system containing one nitrogen atom as the sole heteroatom. Suitably the ring contains from 4 to 10 ring atoms. Preferably from 5-8 ring atoms. The bicyclic systems may be fused, spiro or bridged. Examples of such heteroatoms include the bicyclic heteroatoms described in U.S. Patent 5,242,927 column 2, which has been incorporated by reference. The most preferred '927azabicyclic or '927azacyclic systems include pyrrolidine, 1,2,5,6-tetrahydropyridine, quinuclidine or 1-azabicyclo[2.2.1]heptane ring, optionally substituted with methyl or hydroxy. An especially preferred '927 azabicyclic ring is quinuclidine, which is substituted by hydrogen, methyl or hydroxy at any available atom.

Groups which are converted in vivo to an amino group on the compounds claimed herein for treating pain may be ascertained by administering the compound to a human or an animal and detecting, by conventional analytical techniques, the presence of the corresponding compound having an amino substituent in the urine of a human or animal. Examples of such groups include groups which are hydrolysable in vivo to an amino group, such as amido, urethan substituents. In particular a group of the formula -NH.Q whererin Q represents CHO, COR^{33} or CO_2R^{33}, and R^{33} represents an optionally substituted hydrocarbon group. The term hydrocarbon group includes groups having up to 20 carbon atoms, suitably up to 10, and conveniently up to 8 carbon atoms. Suitable hydrocarbon groups include C_{1-8} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl and arylC_{1-6}alkyl.

Suitable R^{34} groups include the following:



wherein the broken line represents an otpional chemical bond; and R^{41} and R^{42} may be present at any position, including the point of attachment to the benzene ring, and independently represent hydrogen, C_{1-4}alkyl, F, Br, Cl, C_{1-4} alkoxy, hydroxy, carboxy, or C_{1-4}alkyoxycarbonyl or R^{41} and R^{42} together represent cabonyl. The nitrogen atom may be substituted by hydrogen or C_{1-4} alkyl.

The term "phenyl-C_1-C_4 alkyl" designates an alkyl group which is substituted with a phenyl group. Preferred phenyl-alkyl groups include benzyl, 1- and 2-phenylethyl, 1-, 2-, 3-phenyla propyl and 1-methyl-1-phenylethyl. The phenyl group may be optionally be substituted with from 1-3 independently selected named substituents.

The term "form together with the nitrogen atom to which they are joined, a heterocyclic radical" means that a heterocyclic radical optionally containing another heteroatom, for example, S or O. Such groups include, but are not limited to, piperidyl, piperazynyl, morpholinyl, and pyrrolidinyl.

The term "alkyl" refers to the number of carbon atoms indicated; however, when no number is specified, the term refers to C_{1-6} alkyl. The alkyl may be linear or branched unless specified.

The term "halogen" refers to chloro, bromo, and fluoro substituents.

The term "alkynyl" has its accepted meaning; however, if the number of carbon atoms are unspecified, it refers to C_{2-10} alkynyl. The alkynyl group may be linear or branched unless specified.

The term alkoxy refers to C_{1-4} alkoxy unless specified.

The term "analgesic dose", as used herein, represents an amount of compound necessary to prevent or treat a human susceptible to or suffering from pain following administration to such human. The active compounds are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.005 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 0.05 to about 100 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally to humans susceptible to or suffering from anxiety, the compounds may also be administered by a variety of other rcutes such as the transdermal, parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may be designed to provide delayed or controlled release using formulation techniques which are known in the art.

The term "NSAIDS", as used herein, represents a nonsteroidal anti-inflammatory drug which can be identified as such by the skilled artisan. For example, the Merck

Manual, 16th Edition, Merck Research Laboratories (1990) pp 1308 - 1309 provide well known examples of NSAIDS. The term is intended to include, but is not limited to salicylates such as aspirin, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac. Especially preferred NSAIDS include aspirin, ibuprofen, and naproxen. Alternative preferred NSAIDS are indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac. Particularly preferred NSAIDS include aspirin and ibuprofen. The salicylates may include acetylsalicylic acid, sodium acetylsalicylic acid, calcium acetylsalicylic acid, salicylic acid, and sodium salicylate. An especially preferred NSAID is ibuprofen.

The term "acetaminophen", as used herein, shall have the art accepted meaning and refers to N-(4-Hydroxyphenyl)acetamide and 4'-hydroxyacetanilide. The compound is claimed in U.S. Patent No. 2,998,450 and is known to the skilled artisan.

The term "central alpha-adrenergic active compounds", as used herein, represents a compound having central alpha-adrenergic receptor activity. The most preferred central alpha-adrenergic active compound is clonidine or a pharmaceutically acceptable salt thereof having the chemical name: 2-(2,6-dichlorophenylamino)-2-imidazoline.

Clonidine is known to be useful for treating hypertension. *see* Physicians' Desk Reference, 45th Ed. (1991) p. 673.

The term "opioid", as used herein, represents opioid analgesics and antagonists including natural opioid analgesics, synthetic opioid analgesics, opioid antagonists and opioid agonist-antagonists. Preferred an opioid compounds are selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone,

brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine. More preferred opioid compounds are selected from the group consisting of codeine, nabuphine, naloxone, and naltrexone.

Preferred an opioid compounds are morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine.

Especially preferred opioid compounds are selected from the group consisting of hydromorphone, hydrocodone, meperidone, buprenorphine, butorphenol, nalbuphine, pentazocine, oxymorphine, oxycodone, levorphanol, fentanyl, and alphaprodine.

Particularly preferred opioid compounds are selected from the group consisting of propoxyphene, methadone, morphine, hydrocodone, hydromorphine, and codeine. The especially particularly preferred opioid ccmpounds are selected from morphine and codeine.

As used herein, the phrase "one or more" most preferredly refers to one; however, two, three, or more may be used.

We have discovered that a group of compounds having muscarinic cholinergic activity can be particular useful for treating pain when used in combination with non-steroidal antiinflammatory agents (NSAIDS). More specifically, the invention provides a method of treating pain in humans using a specified known compounds (collectively referred to herein as "selected muscarinic compounds") in combination with a NSAIDS to provide a synergistic effect. The Selected Muscarinic Compounds are believed to be active based on activity at muscarinic cholinergic receptors; however, the present invention is in no way limited by the mechanism of action.

There are many NSAIDS known in the literature and to the skilled artisan.

We have discovered that a group of compounds having muscarinic cholinergic activity can be particular useful for treating pain when used in combination with acetaminophen. More specifically, the invention provides a method of treating pain in humans using a specified Selected Muscarinic Compounds in combination with acetaminophen to provide a synergistic effect.

Further, we have discovered that a group of compounds having muscarinic cholinergic activity can be particularly useful for treating pain when used in combination with central alpha-adrenergic active compounds. More specifically, the invention provides a method of treating pain in humans using Selected Muscarinic Compounds in combination with a central alpha-adrenergic active compound to provide a synergistic effect.

Oral combinations of aspirin with codeine or other narcotic analgesics are known to provide additive analgesic effects in man. The Pharmacological Basis of Therapeutics, 5th edition, Macmillan Publishing Co., 1975, pp 325-358.

The present invention further envisions that one or more Selected Muscarinic Compounds may be used at one time in the composition of this invention to provide the desired analgesic effect.

In the composition of this invention a Selected Muscarinic Compound and NSAIDS compound are combined in a weight ratio of Compound to NSAIDS of from about 1 to about 1000.

A preferred composition is a weight ratio of Compound to NSAIDS of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

In the composition of this invention a Selected Muscarinic Compound and acetaminophen are combined in a weight ratio of Selected Muscarinic Compound to acetaminophen of from about 1 to about 1000.

A preferred composition is a weight ratio of Selected Muscarinic Compound to acetaminophen of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The Selected Muscarinic Compounds are effective over a wide dosage range; however, it is desirable to administer a dosage that is as low as possible. The amount of NSAIDS present in the composition is adjusted as described above in ratio to the Selected Muscarinic Compound dosage. The amount of acetaminophen present in the composition is adjusted as described above in ratio to the Selected Muscarinic compound dosage.

In the composition of this invention a Selected Muscarinic Compound selected and one or more opioid compounds are combined in a weight ratio of Selected Muscarinic Compound to opioid compound of from about 1 to about 1000.

A preferred composition is a weight ratio of Selected Muscarinic Compound to opioid compound of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The amount of opioid compound present in the composition is adjusted as described above in ratio to the Selected Muscarinic Compound dosage.

However, for each composition claimed herein, it will be understood that the amount of the Selected Muscarinic Compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of Selected Muscarinic Compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration,

and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally to humans susceptible to or suffering from pain, the compounds may also be administered by a variety of other routes such as the transdermal, parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may be designed to provide delayed or controlled release using formulation techniques which are known in the art.

Transdermal formulations containing the composition claimed herein most preferably deliver the active substances in an effective amount for from about three days to about seven days. However, for chronic pain such as arthritis or cancer pain, a transdermal delivery of from about three days to up to about two weeks is desirable. Alternatively, it may be preferred to deliver the claimed compositions transdermally in an effective amount for from about one day to about three days.

As used herein the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established or alleviation of the characteristic symptoms of such condition.

The Selected Muscarinic Compounds employed in the invention are not believed to act via the GABA/benzodiazepine, 5HT1A, or D1 receptor systems in humans. Rather, the activity of the present Selected Muscarinic Compounds as analgesic agents is believed to be based upon modulation of muscarinic cholinergic receptors. However, the mechanism by which the present compounds function is not necessarily the mechanism stated *supra.*, and the present invention is not limited by any mode of operation.

Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate,

fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, **66**, 2 (1977) which are known to the skilled artisan. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, depot, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

The dosage administered will, of course, vary depending on known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of the symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 100 mg/kg of body weight Selected Muscarinic Compound and from about 0.6 to about 200 mg/kg of NSAIDS.

Compositions suitable for internal administration contain from about one half (0.5) milligrams to about 600 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of from about 0.5% to about 95% by weight based on the total weight of the composition.

For compositions containing acetaminophen, usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 500 mg/kg of body weight Selected

Muscarinic Compound and from about 0.6 to about 200 mg/kg of acetaminophen.

Typical compositions include a compound of Selected Muscarinic Compound and one or more NSAIDSs, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

Typical compositions include a Selected Muscarinic Compound and acetaminophen, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a

capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used, as described above.

A preferred composition is a weight ratio of Selected Muscarinic Compound to central alpha-adrenergic active compound of from about 1 to about 100. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

The Selected Muscarinic Compounds are effective over a wide dosage range; however, it is desirable to administer a dosage that is as low as possible. The amount of central alpha-adrenergic active compound present in the composition is adjusted as described above in ratio to the Selected Muscarinic Compound dosage.

Usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 500 mg/kg of body weight Selected Muscarinic ompound and from about 0.6 to about 200 mg/kg of central alpha-adrenergic active compound.

Typical compositions include a Selected Muscarinic Compound and one or more central alpha-adrenergic active compounds, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the compositions of this invention are dispensed in unit form comprising from about 0.1 to about 300 mg in a pharmaceutically acceptable carrier per unit dosage.

The compositions of this invention may be suitable for administration to an animal. Such animals include both domestic animals, for example livestock, laboratory animals, and household pets, and non-domestic animals such as wildlife. More preferredly, the animal is a vertebrate. Most preferredly, a composition of this invention shall be administered to a mammal. It is especially preferred that the animal is a domestic mammal or a human. The most preferred mammal is a human. For such domestic animal purposes, a composition of this invention may be administered as a feed additive.

The following models and assays are useful for illustrating the effectiveness of the compositions claimed herein.

Nociceptive pain model:

Acetic acid-induced writhing: A standard procedure for detecting and comparing the analgesic activity of different classes of analgesic drugs for which there is a good correlation with human analgesic activity is the prevention

of acetic acid-induced writhing in mice. Mice, are subcutaneously administered various doses of the claimed composition and are injected injected intraperitoneally with acetic acid (0.5% solution, 10 ml/kg) 5 min prior to a designated observation period. For scoring purposes a "writhe" is indicated by whole body stretching or contraction of the abdomen during the observation period beginning 5 min after receiving the acetic acid. Inhibition of writhing behavior is demonstrative of analgesic activity.

See, Haubrich, D.R., Ward, S.J., Baizman, E., Bell, M.R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A.K., Saelens, J.K. and Luttinger, D.: Pharmacology of pravadoline: a new analgesic agent. The Journal of Pharmacology and Experimental Therapeutics 255 (1990) 511-522.

Neuropathic pain model:

Sciatic nerve ligation model: Rats are anesthetized and a nerve ligation procedure performed. The common sciatic nerve is exposed and 4 ligatures tied loosely around it with about 1 mm spacing. One day to 10 weeks after surgery, the nociceptive testing is performed. Responses to noxious heat are determined by placing the rats in a chamber with a clear glass floor and aiming at the plantar surface of the affected foot a radiant heat source from beneath the floor. Increased latency to withdraw the hindpaw is demonstrative of analgesic activity. Responses to normally innocuous mechanical stimuli is determined by placing the rats in a chamber with a screen floor and stimulating the plantar surface of the hind paw with graduated von Frey hairs which are calibrated by the grams of force required to bend them. Rats with sciatic nerve ligation respond to lower grams of mechanical stimulation by reflexive withdrawal of the foot than uncperated rats. This response to stimuli which are normally innocuous is termed allodynia. Increases in the grams of mechanical force required to produce foot withdrawal is demonstrative of antiallodynic activity.

See, Bennett, G.J. and Xie, Y.-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33 (1988) 87-107. See also, Lee, Y.-W., Chaplan, S.R. and Yaksh, T.L.: Systemic and supraspinal, but not spinal, opiates suppress allodynia in a rat neuropathic pain model. Neuroci Lett 186 (1995) 111-114.

Formalin paw test: Rats are anesthetized and when there is a loss of spontaneous movement the rats are injected subcutaneously in the dorsal surface of the hindpaw with 50 ul of 5% formalin solution using a 30 gauge needle. Rats are then individually placed in an open Plexiglas chamber for observation, and within a maximum interval of 1 to 2 min, the animal displays recovery from anesthesia with spontaneous activity and normal motor function. Pain behavior is quantified by periodically counting the incidents of spontaneous flinching/shaking of the injected paw. The flinches are counted for 1-min periods at 1- to 2-, 5- to 6- and 5min intervals during the interval from 10 to 60 min. Inhibition of the pain behavior is demonstrative of an analgesic activity.

See, Malmberg, A.B. and Yaksh, T.L.: Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. The Journal of Pharmacology and Experimental Therapeutics 263 (1992) 136-146.

Inflammatory pain model:

Brewer's yeast-induced hyperalgesia (Randall-Selitto Test): To assess nociceptive threshold in rats, ascending pressure is applied gradually to the paw with a motor driven weight of a Ugo Basile Analgesy Meter. Rats respond to the pressure by either pulling free of the device, struggling or vocalizing. Hyperalgesia is induced by a hind paw subplantar injection of 0.1 ml of 1% suspension of brewer's yeast in 0.9% saline. The composition of this invention is administered at varying times (0 - 4 hr) after injection of brewer's yeast and pressure threshold for the inflamed paw

again determined at varying times. Increases in the pressure which produces a behavioral response is demonstrative of analgesic activity.

See, Haubrich, D.R., Ward, S.J., Baizman, E., Bell, M.R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A.K., Saelens, J.K. and Luttinger, D.: Pharmacology of pravadoline: a new analgesic agent. The Journal of Pharmacology and Experimental Therapeutics 255 (1990) 511-522.

Utility Test Methods

The unexpectedly enhanced analgesic activity of the composition of the invention is evidenced by tests intially conducted on mice. Male mice are fasted for 16-22 hours and weighed. Mice weighing from about 18-22 grams at the time of testing are used for the following studies. All mice are dosed sequentially by the oral route with suspensions of a composition of this invention. Doses are coded using a code unknown to the observer.

A stock suspension of the test composition is prepared by mixing the active ingredients with about 40 mL of an aqueous vehicle containing about 2% Tween 80 (R), a pharmacological dispersant and containing 100% polysorbate 80, and 1% by weight Methocel (R) MC powder, and containing 100% methylcellulose, in distilled water. The mixture may be sonicated for about 10 to about 15 seconds using an ultrasound sytem. All dosing suspensions are prepared by dilution of the stock suspension with Methocel/Tween 80. All suspensions are used within two hours of preparation.

Mouse Writhing Test

An accepted standard for detecting and comparing the analgesic activity of different classes of analgesic compounds for which there is a good correlation with human analgesic activity is the prevention of phenyl-p-benzoquinone induced writhing in mice. [H. Blumberg et al. Proc. Soc. Exp. biol. Med., 118, 763-766 (1965)].

Mice, treated with various doses of Selected Muscarinic Compound, composition or vehicle are injected intraperitoneally with a standard challenge dose of phenyl-p-benzoquinone 5 minutes prior to a designated observation period. The pheyl-p-benzoquinone is prepared as about 0.1 mg/ml solution in about 5% by volume of ethanol in water. The writhing dose is 1.25 mg/kg injected at a volume of about 0.25ml/10g. For scoring purposes a "writhe" is indicated by whole body stretching or contracting of the abdomen during an observation period beginning about five minutes after the phenyl-p-benzoquinone dose.

All ED50 values and their 95% confidence limits are determined using accepted numerical methods. For example, *see* W.F. Thompson, Bacteriological Rev., **11**, 115-145 (1947). The interaction of the dosages on phenyl-p-benzoquinone induced writhing in mice is demonstrated by the Loewe isobologram (S. Loewe, Pharm. Rev. 9, 237-242 (1957).

The solid line connecting the ED50 dosages of Selected Muscarinic Compound (alone) and Synergistic Analgesic as claimed herein (alone) represents the "ED50 addition line" which indicates the expected location of the ED50's for Selected Muscarinic Compound and classical analagesic combinations if simple additivity were to describe their combined effects. The 95% confidence range for the ED50 addition line is shown by the area between the broken lines above and below the ED50 addition line.

According to Loewe's isobolic theory, if the analgesic effects are simply additive to one another, then the expected location of the ED50's of the Selected Muscarinic Compound and Synergistic Analgesic component of each fixed dosage ratio would be contained within or overlap the region of the ED50 addition line. Combination ED50's located significantly below the ED50 addition line would represent unexpectedly enhanced analgesic activity and combination ED50's located above the line would represent unexpected diminished analgesic effect.

One method to establish the significance of such unexpected enhanced or diminished activity is to calculate the best fitting polynomial regression line to the observed ED50's using standard mathematical techniques.

Such experiments demonstrate that compositions comprised of a Selected Muscarinic Compound and one or more Synergistic Analgesics provides a statistically significant synergistic analgesic effect.

Preferred compounds for use in treating pain include:
(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane and compounds of Formulae IV, V, VIII, IX, XIII, XIV, and XV; or
a pharmaceutically acceptable salt thereof.

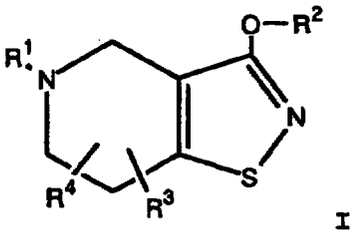
Especially preferred compounds include the following:
compounds of Formulae XIII, XIV, and XV.

Examples of preferred compounds include, but are not limited to, 3-[2-(6-hydroxypyrazin)yl]-1-azabicyclo[2.2.2]octane, 3-(2-pyrazinyl)-1-azabicyclo[2.2.1]heptane, 6-(2-pyrazinyl)-1-azabicyclo[3.2.1]octane, 6-(2-pyrazinyl)-1-azabicyclo[3.2.1]octan-6-ol, 3-fluoro-3-(2-pyrazinyl)-1-azabicyclo[2.2.1]heptane, 1-methyl-3-(2-pyrazinyl)pyrrolidine, 3-[2-(3-methylpyrazin)yl]-1-azabicyclo[2.2.2]octan-3-ol,3-[2-(3,6-dimethylpyrazin)yl]-1-azabicyclo[2.2.1]heptane, 3-[2-(6-allyloxypyrazin)yl]-1-azabicyclo[2.2.1]heptane,3-[2-(6-methoxypyrazin)yl]-1-azabicyclo[2.2.2]octane, 3-[2-(6-chloropyrazin)yl]-1,2,5,6-tetrahydropyridine, 3-[5-(3-octanyloxycarbonylamino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptane, 3-[5-(3-cyclohexylcarbonylamino-1,2,3-oxadiazol)-yl]quinuclidine, 3-[5-(3-(1-(3-n-pentyloxycarbonyl)-1-ethoxycarbonylamino)-1,2,4-oxadiazol)-yl]quinuclidine, 3-[5-(3-octanoylamino-1,2,4-oxadiazol)-yl]quinuclidine, 3-[(1-methyl-1H-imidazol-5-yl)methyl]1,2,4-oxadiazol-5(4H)-one, 4-methyl-3-[(1-methyl-1H-imidazol-4-yl)-methyl]1,2,4-oxadiazol-5(4H)-one, 4-ethyl-

3[(1-methyl-1H-imidazol-4-yl)-methyl]-1,2,4-oxadiazol-5(4H)-one, N-[4-(hexahydro-1H-azaepin-1-yl)-2-butynyl]-N,N-dimethyl urea, N-[4-1-pyrrolidinyl)-2-butynyl]-urea, 5-acetyl-1-azabicyclo[3.1.1]heptane, 1-azabicyclo[3.1.1]hept-5-ylcarboxaldehyde, 3-(2-methyltetrazol-5-yl)-1-azabicyclo[2.2.1]heptane, 3-(2-methyl-1,2,3-triazol-4-yl)-1-azabicyclo-[2.2.2]octane, 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1]heptane, and a pharmaceutically acceptable salt or solvate thereof.

We Claim:

1. A composition for treating pain comprising an analgesic dose of a Compound selected from the group consisting of:

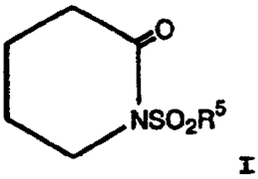


I

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

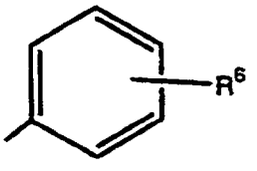
R^2 is C_1-C_6alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, branched or unbranched with 1-6 carbon atoms inclusive, which group may be optionally substituted with fluoro, hydroxy or phenyl optionally substituted with fluoro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy;

R^3 and R^4 are independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl optionally substituted with halogen trifluroromethyl, C_1-C_4 alkyl, hydroxy, or C_1-C_4 alkoxy, or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

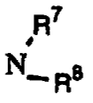


II;

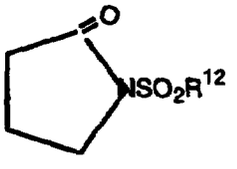
in which R^5 represents the radical



in which R^6 at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical

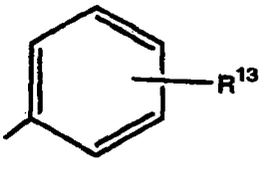


in which R^7 and R^8 which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical OR^9, R^9 representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{10} or $S(O)R^{11}$, R^{10} and R^{11} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^5 represents naphthyl optionally substituted with $R^{6'}$, $R^{6'}$ being defined above for R^6;

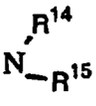


III

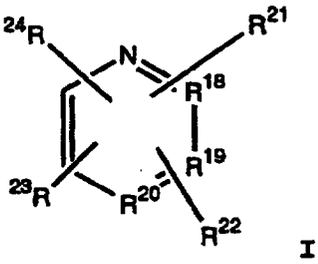
in which R^{12} represents the radical



in which R^{13} at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical

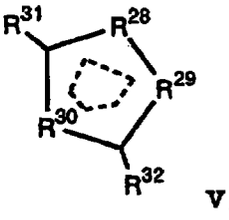


in which R^{14} and R^{15} which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical or NO_2, or $OR^{12'}$, $R^{12'}$ representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{16} or $S(O)R^{17}$, R^{16} and R^{17} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^{12} represents naphthyl optionally substituted with $R^{13'}$, $R^{13'}$ being defined above for R^{13};



IV

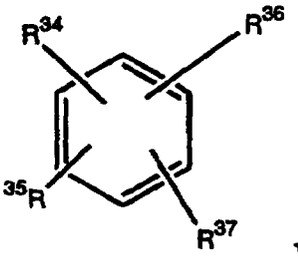
wherein, one of R^{18}, R^{19}, and R^{20} represents nitrogen and the remainder represent carbon atoms; substituted on one of the ring carbon atoms with a R^{24} substituent represented by a non-aromatic azacyclic or azabicyclic ring system and independently substituted on each of the other ring carbon atoms with R^{23}, R^{21}, or R^{22} substituent of low lipophilicity or a hydrocarbon having a maximum of 20 carbon atoms;



V;

wherein one of R^{28}, R^{29} or R^{30} is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a

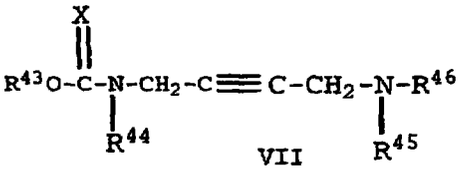
1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R^{31} represents a non-aromatic '927azacycle or '927azabicyclic ring system; and R^{32} represents a substituent which is convertable in vivo to an amino group;



VI;

wherein R^{34} represents a non-aromatic; non-fused 1-azabicyclic ring system; and

R^{35}, R^{36}, and R^{37} independently represent hydrogen, F, Cl, Br, $-CF_3$, $-OR^{38}$, $-NR^{38}R^{39}$, $-NHOR^{38}$, $-NHNH_2$, $-CN$, COR^{40}, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group, provided that at least one of R^{35}, R^{36}, and R^{37} is other than hydrogen or a hydrocarbon group, or R^{35} and R^{36} or R^{37} taken together form a C_{1-6}alkylenedioxy ring, wherein R^{38} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, R^{39} is hydrogen, C_{1-6} alkyl,or $-COCH_3$, and R^{40} represents OH, $-OR^{38}$, NHR^{39}, or $-NR^{38}R^{39}$



VII

wherein R^{43} is

alkyl of from one to six carbon atoms,

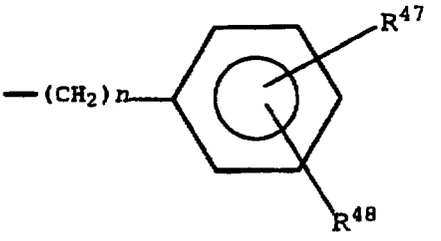
alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from two to six carbon atoms,

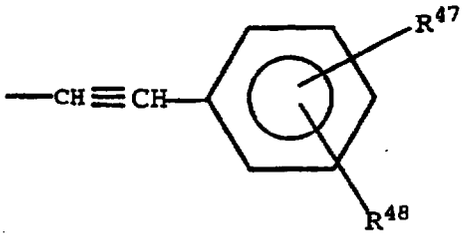
alkenyl of from two to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from two to six carbon atoms,

alkynyl of from two to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms, cycloalkyl of from three to six carbon atoms,



wherein n is zero or an integer of one to eight and R^{47} and R^{48} are independently hydrogen, fluorine, chlorine, bromine, hydroxy, alkyl of from one to three carbon atoms, or alkoxy of from one to three carbon atoms, or alkoxy of from one to four carbon atoms, or



wherein

R^{47} and R^{48} are as defined above;

X is oxygen or sulfur;

R^{44} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

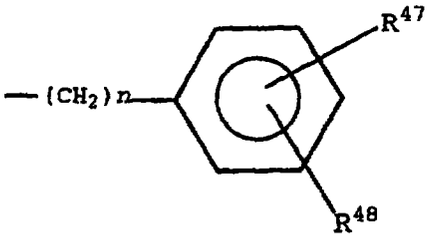
alkenyl of from three to six carbon atoms

alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or



wherein n, R47 and R48 are as defined above R45 and R46 are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

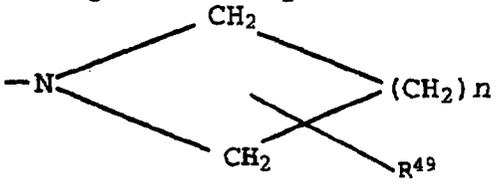
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

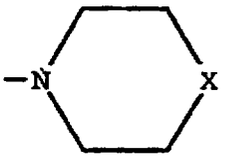
cycloalkyl of from three to eight carbon atoms,

phenyl,

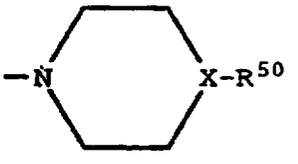
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^{45} and R^{46} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



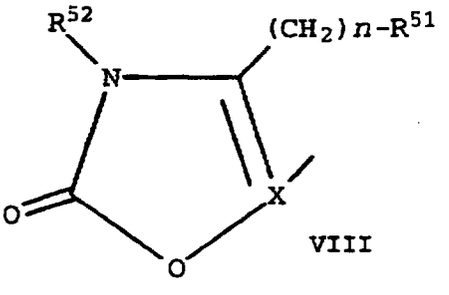
wherein R^{49} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms and n is as defined above,



wherein X is defined above or

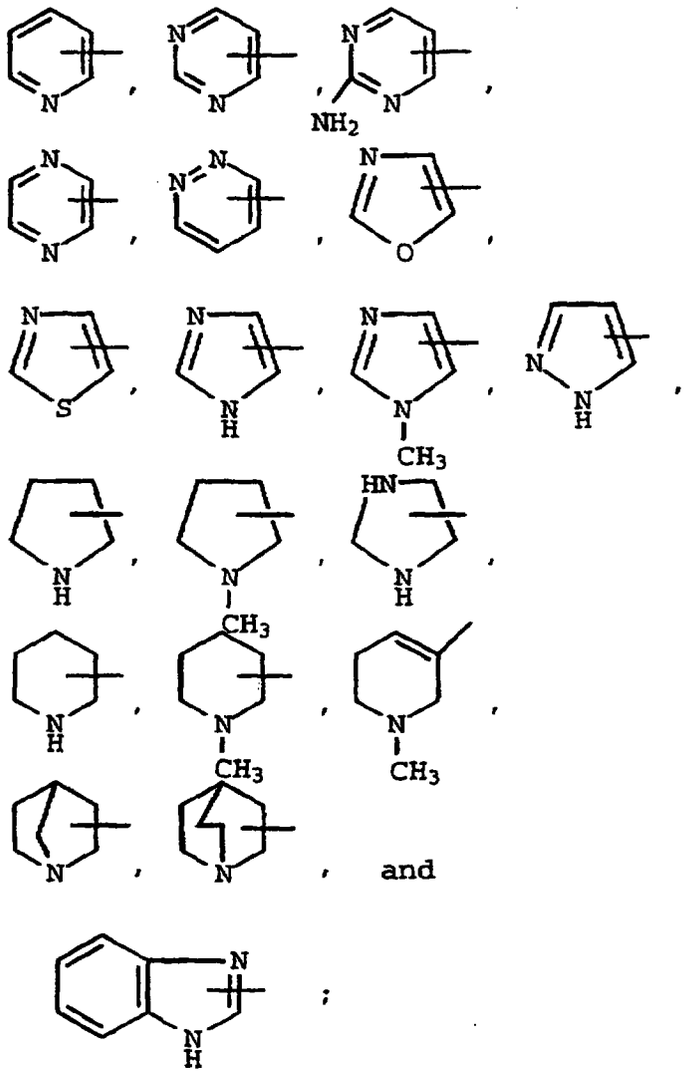


wherein R^{50} is hydrogen or alkyl of from one to six carbon atoms,



VIII

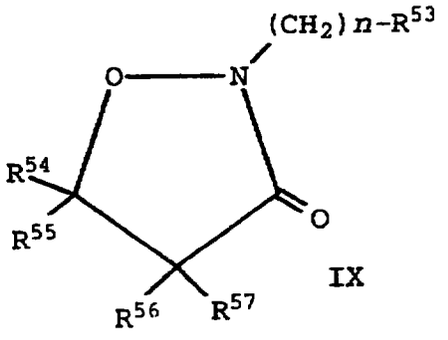
wherein R^{51} is selected from the group consisting of



and

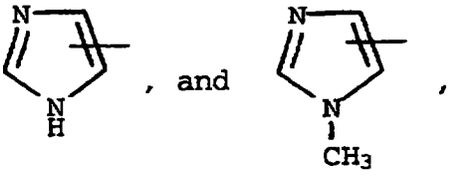
;

R^{52} is hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; n' is zero or an integer of one or two; X' is carbon or nitrogen; and ____represents a single or double bond with the proviso that when, ___ represents a double bond X' is nitrogen and when ___ represents a single bond X' is CH_2;

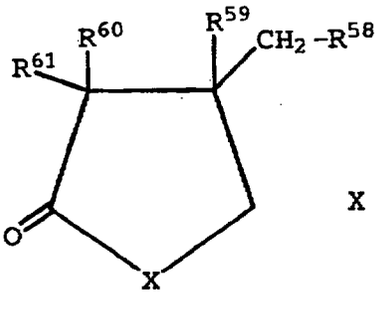


IX

wherein R^{53} is selected from the group consisting

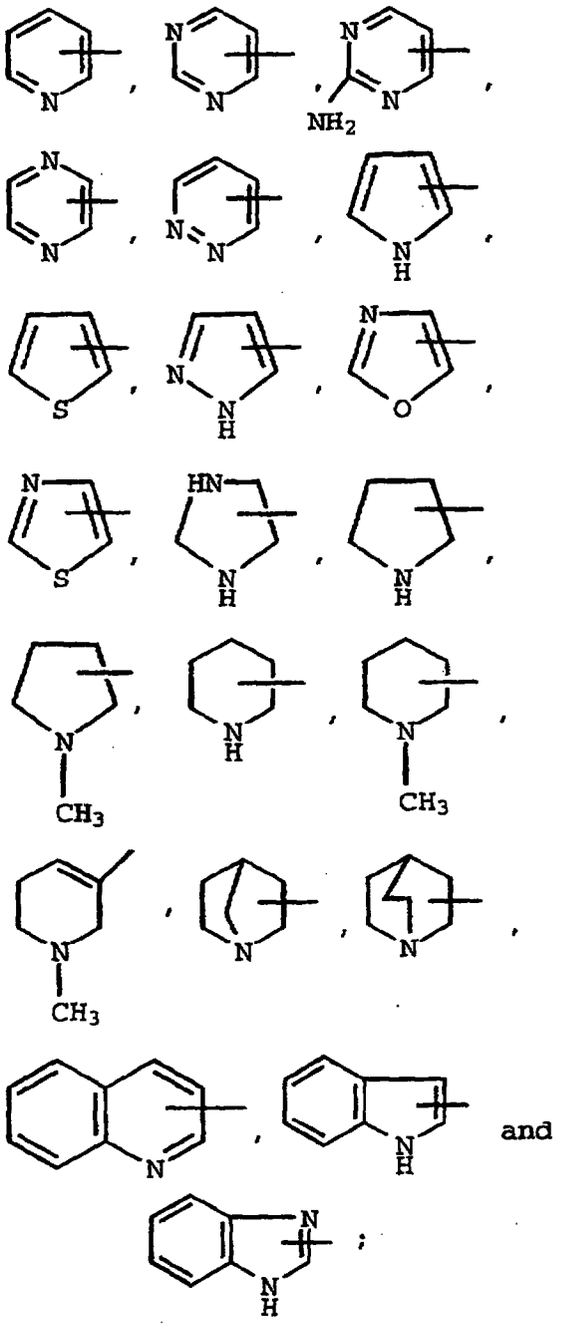


R^{54}, R^{55}, R^{56}, and R^{57} are each independenty hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from C1-C10 alkyl, alkoxy, C1-C10 halogen or trifluoromethyl; n' is an interger of one or two;



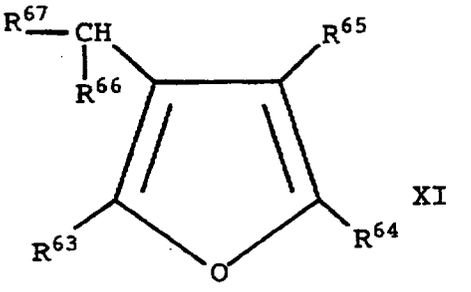
X

wherein X is oxygen, sulfur, or -N-R^{62}, wherein R^{62} is hydrogen or alkyl of from one to ten carbon atoms; R^{58} is selected from the group consisting of



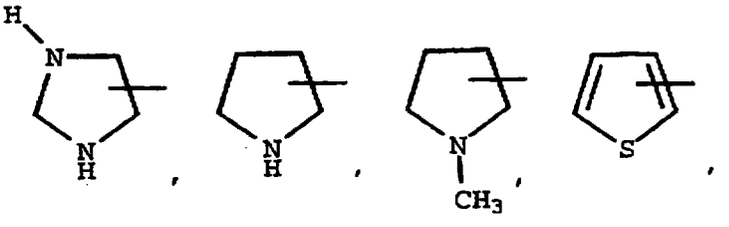
and

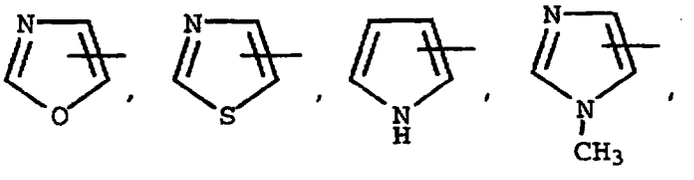
R^{59}, R^{60}, and R^{61} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; --- represents a single or double bond with the proviso that when --- represents a double bond R^{57} and R^{60} are absent;

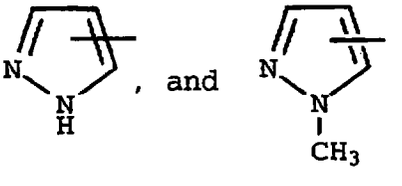


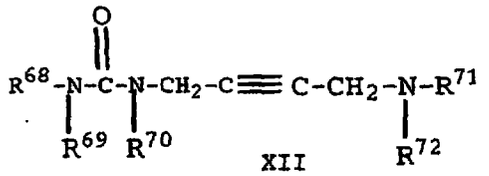
XI

wherein R^{63}, R^{64}, and R^{65} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from the group consisting of alkyl, alkoxy, thioalkoxy, halogen, and trifluoromethyl; R^{66} is hydrogen, hydroxy or alkoxy of from one to ten carbon atoms; and R^{67} is selected from the group consisting of









XII

wherein

R^{69} is hydrogen and R^{67} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

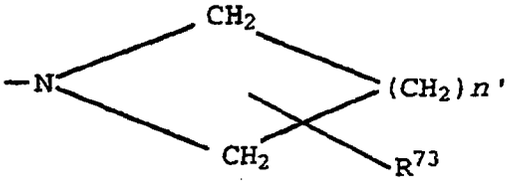
alkenyl of from three to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{68} and R^{69} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



wherein n' is zero or an integer from one to eight and R^{73} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms or alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms;

R^{70} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of form one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

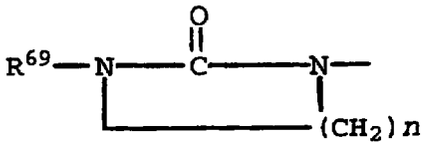
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{70} when taken together with R^{68} forms a ring denoted by



wherein n is an integer from one to three and R68 are as defined above;

R^{71} and R^{72} are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

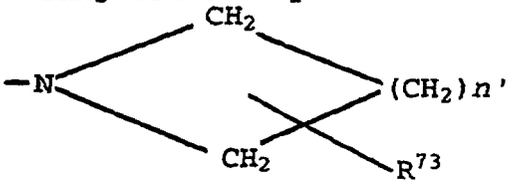
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with dydroxy or alkoxy of from one to four carbon atoms,

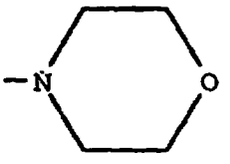
cycloalkyl of from three to eight carbon atoms,

phenyl,

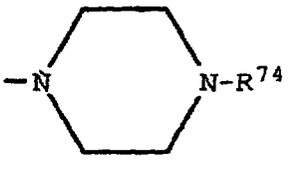
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^3 and R^4 are taken together with the nitrogen atom to which they are attached to form a ring denoted by



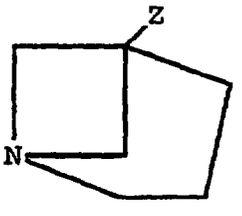
wherein n' and R^{73} are ad defined above,



wherein X is defined above or

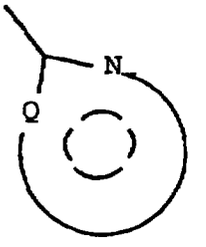


wherein R^{74} is hydrogen or alkyl of from one to six carbon atoms,

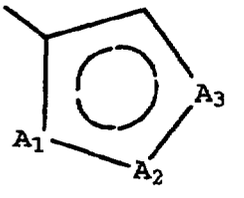


XIII

in which Z is a heterocyclic group

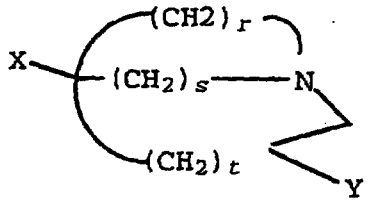


in which Q represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, or three nitrogen atoms, any amino nitrogen being substituted by a C_{1-2} alkyl, cyclopropyl or propargyl group, and any ring carbon atom being optionally substituted by a group R_1; or a group

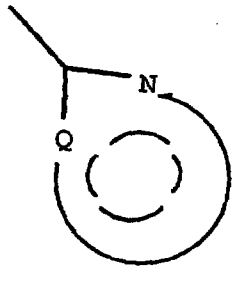


in which A_1, A_2 and A_3 complete a 5-membered aromatic ring and A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_2 and the other is nitrogen or CR_3, or A_2 is oxygen or sulphur, one of A_1 and A_3 is CR_2 and the other is CR_3; and R_1, R_2 and R_3 are independently selected from hydrogen, halogen, CN, OR_4, SR_4, $N(R_4)_2$, $NHCOR_4$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR_4$, $NHNH_2$, NO_2, COR_4, COR_5, cyclopropyl, C_{2-5} straight chain alkenyl, C_{2-5} straight chain alkynyl or C_{1-5} straight chain alkyl optionally terminally substituted with OR_4, $N(R_4)_2$, SR_4, CO_2R_4, $CON(R_4)_2$ or one, two or three halogen atoms, in which each R_4 is independently hydrogen or C_{1-3} alkyl and R_5 is OR_4, NH_2 or NHR_4; or in which Z is a group $-C(R_7)=NR_6$ in which R_6 is a group OR_8, where R_8 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a group $OCOR_9$ where R_9 is hydrogen or R_8, or a group NHR_{10} or $NR_{11}R_{12}$ where R_{10}, R_{11} and R_{12} are independently C_{1-2} alkyl and R_7 is hydrogen or C_{1-4} alkyl, subject to the

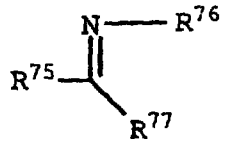
proviso that when R_6 is a group $OCOR_9$ or NHR_{10}, R_7 is C_{1-4} alkyl



in which one of X and Y represents hydrogen and the other represents Z, and Z' is a group

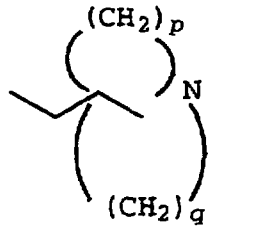


in which Q' represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises two or three nitrogen atoms, any amino nitrogen being substituted by a C1-2 alkyl, cyclopropyl or propargyl group, r represents the integer of 2 or 3, s represents an integer of 1 or 2 and t represents 0, with the proviso that when Y is hydrogen s is 1;

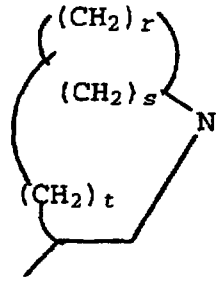


XV

wherein R^{75} represents



or



in which

each of p and q independently represents an integer of 2 to 4, r represents an integer of 2 to 4, s represents 1 or 2 and t represents 0 or 1;

R^{76} is a group OR^{78}, where R^{78} is C_{1-4} alkenyl, C_{2-4} alkynyl, a group $OCOR^{79}$ where R^{79} is hydrogen or R^{78}, or a group NHR^{80} or NR^{81}, R^{82}, where R^{80}, R^{81} and R^{82} are independently C_{1-2} alkyl; and R^{77} is hydrogen or C_{1-4}alkyl, subject to the proviso that when R^{76} is a group $OCOR^{79}$ or a group NHR^{80}, R^{77} is alkyl;

(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane; or

a pharmaceutically acceptable salt or solvate thereof;

and one or more Synergistic Analgesics in a weight ratio of Compound to Synergistic Analgesic of from about 1 to about 1000.

2. A composition as claimed by **Claim** 1 wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

3. A composition as claimed by **Claim** 1 wherein the Synergistic Analgesic is a nonsteroidal anti-inflammatory drug.

4. A composition as claimed by **Claim 3** wherein the nonsteroidal anti-inflammatory drug is selected from the group consisting of indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac.

5. A composition as claimed by **Claim 3** wherein the nonsteroidal anti-inflammatory drug is ibuprofen.

6. A composition as claimed by **Claim 3** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

7. A composition as claimed by **Claim 1** wherein the Synergistic Analgesic is an opioid.

8. A composition as claimed by **Claim 7** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

9. A composition as claimed by **Claim 8** wherein the Compound is selected from the group consisting of 1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone, 1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone, 3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile, 1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide, 1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide, 1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide, (methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and 1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or a pharmaceutically acceptable salt thereof.

10. A composition as claimed by **Claim 8** wherein the opioid is selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine.

11. A composition as claimed by **Claim 8** wherein the opioid is selected from the group consisting of hydromorphone, hydrocodone, meperidone, buprenorphine, butorphenol, nalbuphine, pentazocine, oxymorphine, oxycodone, levorphanol, fentanyl, and alphaprodine.

12. A composition as claimed by **Claim 8** wherein the opioid is selected from the group consisting of propoxyphene, methadone, hydrocodone, hydromorphine, and codeine.

13. A composition as claimed by **Claim 1** wherein the Compound is selected from the group consisting of Formula I, II, and III; or a pharmaceutically acceptable salt or solvate thereof.

14. A composition as claimed by **Claim 1** wherein the Compound is selected from the group consisting of Formula XIV and XV; or a pharmaceutically acceptable salt or solvate thereof.

15. A composition as claimed by **Claim 14** wherein the Compound is selected from the group consisting of 1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone, 1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone, 3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile, 1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide, 1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide, 1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide, (methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and 1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or a pharmaceutically acceptable salt thereof.

16. A composition as claimed by **Claim 1** wherein the Synergistic Analgesic is acetaminophen.

17. A composition as claimed by **Claim 15** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

18. A composition as claimed by **Claim 17** wherein the Compound is selected from the group consisting of

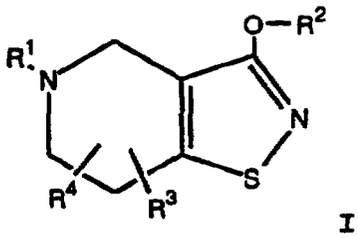
1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone,
1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone,
3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile,
1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide,
1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide,
1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide,
(methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile,
oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and
1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or
a pharmaceutically acceptable salt thereof.

19. A composition as claimed by **Claim 1** wherein the Synergistic Analgesic is an alpha-adrenergic compound.

20. A composition as claimed by **Claim 19** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

21. A composition as claimed by **Claim 20** wherein the Compound is selected from the group consisting of
1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone,
1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone,
3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile,
1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide,
1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide,
1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide,
(methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile,
oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and
1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or
a pharmaceutically acceptable salt thereof.

22. A method for treating pain comprising administering an analgesic dose of a composition comprising a compound a Compound selected from the group consisting of:

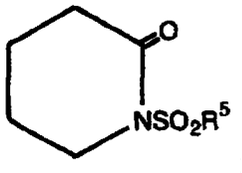


I

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

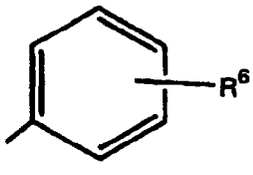
R^2 is C_1-C_6alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, branched or unbranched with 1-6 carbon atoms inclusive, which group may be optionally substituted with fluoro, hydroxy or phenyl optionally substituted with fluoro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy;

R^3 and R^4 are independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl optionally substituted with halogen trifluroromethyl, C_1-C_4 alkyl, hydroxy, or C_1-C_4 alkoxy, or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

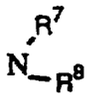


II;

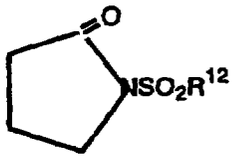
in which R^5 represents the radical



in which R^6 at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical

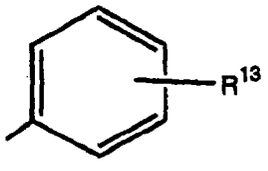


in which R^7 and R^8 which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical OR^9, R^9 representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{10} or $S(O)R^{11}$, R^{10} and R^{11} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^5 represents naphthyl optionally substituted with $R^{6'}$, $R^{6'}$ being defined above for R^6;

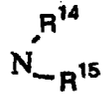


III

in which R^{12} represents the radical



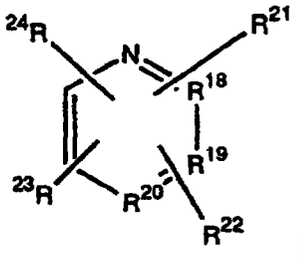
in which R^{13} at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical



in which R^{14} and R^{15} which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which

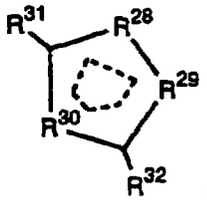
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they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical or NO_2, or $OR^{12'}$, $R^{12'}$ representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{16} or $S(O)R^{17}$, R^{16} and R^{17} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^{12} represents naphthyl optionally substituted with $R^{13'}$, $R^{13'}$ being defined above for R^{13};



IV

wherein, one of R^{18}, R^{19}, and R^{20} represents nitrogen and the remainder represent carbon atoms; substituted on one of the ring carbon atoms with a R^{24} substituent represented by a non-aromatic azacyclic or azabicyclic ring system and independently substituted on each of the other ring carbon atoms with R^{23}, R^{21}, or R^{22} substituent of low lipophilicity or a hydrocarbon having a maximum of 20 carbon atoms;

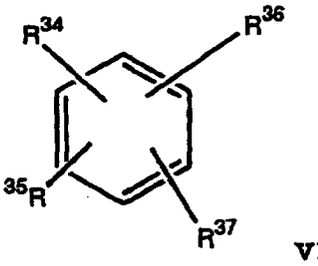


V;

wherein one of R^{28}, R^{29} or R^{30} is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R^{31} represents a non-aromatic '927azacycle or '927azabicyclic ring system; and

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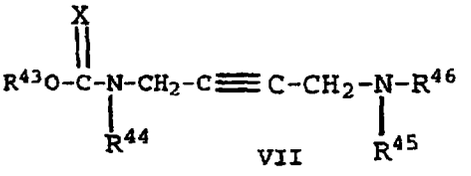
R^{32} represents a substituent which is convertable in vivo to an amino group;



VI;

wherein R^{34} represents a non-aromatic; non-fused 1-azabicyclic ring system; and

R^{35}, R^{36}, and R^{37} independently represent hydrogen, F, Cl, Br, $-CF_3$, $-OR^{38}$, $-NR^{38}R^{39}$, $-NHOR^{38}$, $-NHNH_2$, -CN, COR^{40}, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group, provided that at least one of R^{35}, R^{36}, and R^{37} is other than hydrogen or a hydrocarbon group, or R^{35} and R^{36} or R^{37} taken together form a C_{1-6}alkylenedioxy ring, wherein R^{38} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, R^{39} is hydrogen, C_{1-6} alkyl,or $-COCH_3$, and R^{40} represents OH, $-OR^{38}$, NHR^{39}, or $-NR^{38}R^{39}$



VII

wherein R^{43} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

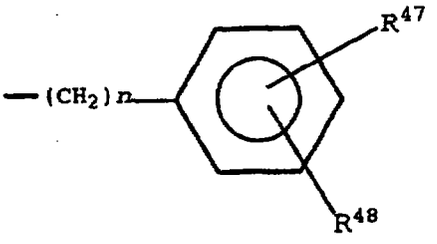
alkenyl of from two to six carbon atoms,

alkenyl of from two to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

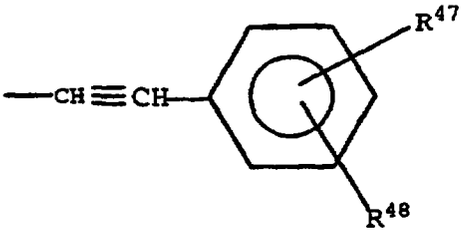
alkynyl of from two to six carbon atoms,

alkynyl of from two to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms, cycloalkyl of from three to six carbon atoms,

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wherein n is zero or an integer of one to eight and R^{47} and R^{48} are independently hydrogen, fluorine, chlorine, bromine, hydroxy, alkyl of from one to three carbon atoms, or alkoxy of from one to three carbon atoms, or alkoxy of from one to four carbon atoms, or



wherein

R^{47} and R^{48} are as defined above;

X is oxygen or sulfur;

R^{44} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms

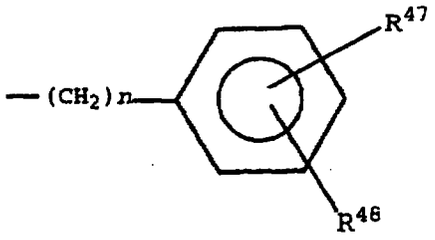
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

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wherein n, R47 and R48 are as defined above R45 and R46 are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

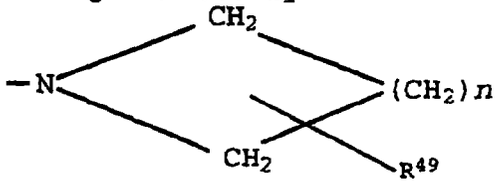
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to eight carbon atoms,

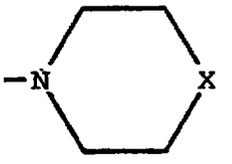
phenyl,

phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^{45} and R^{46} are taken together with the nitrogen atom to which they are attached to form a ring denoted by

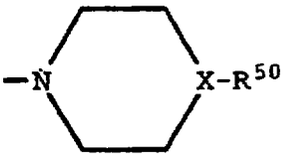


wherein R^{49} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with

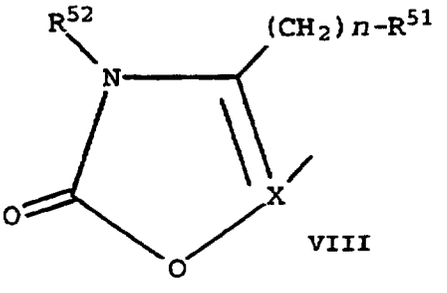
hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms and n is as defined above,



wherein X is defined above or



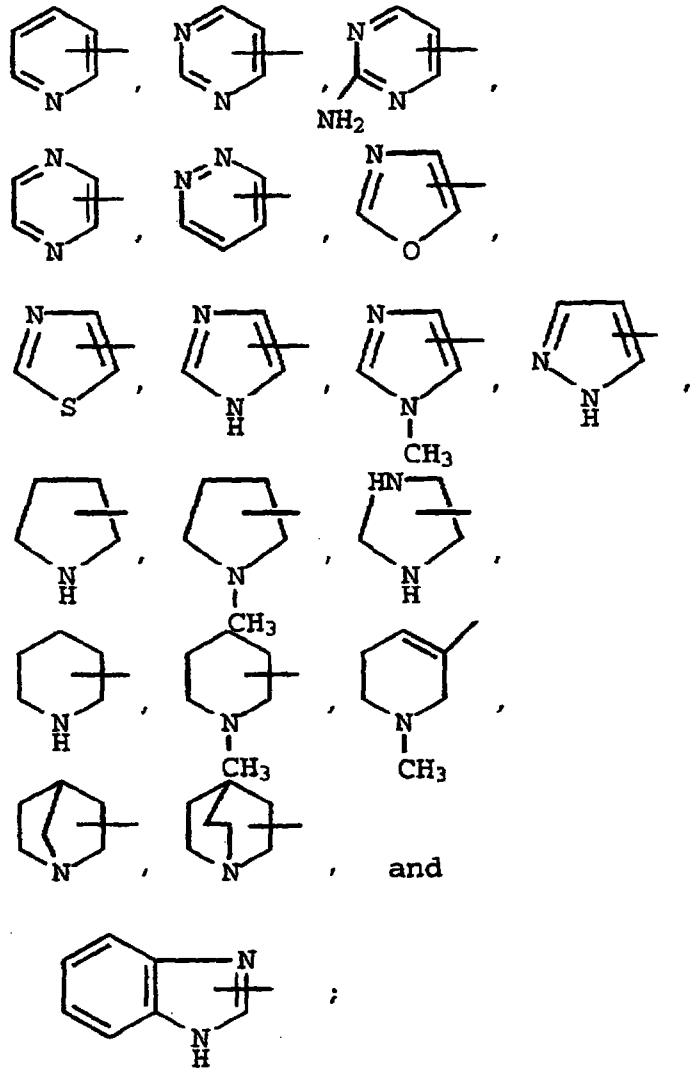
wherein R^{50} is hydrogen or alkyl of from one to six carbon atoms,



VIII

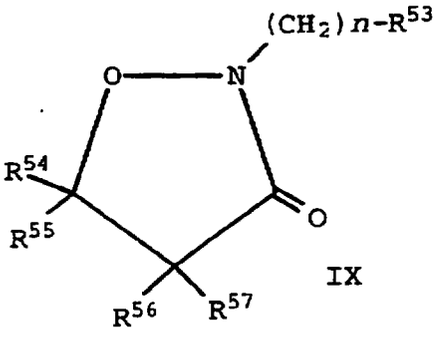
wherein R^{51} is selected from the group consisting of

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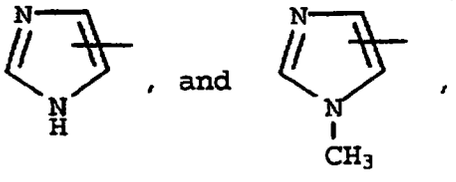
and

R^{52} is hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; n' is zero or an integer of one or two; X' is carbon or nitrogen; and ---represents a single or double bond with the proviso that when, --- represents a double bond X' is nitrogen and when --- represents a single bond X' is CH_2;

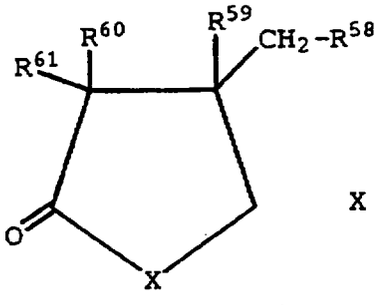


IX

wherein R^{53} is selected from the group consisting



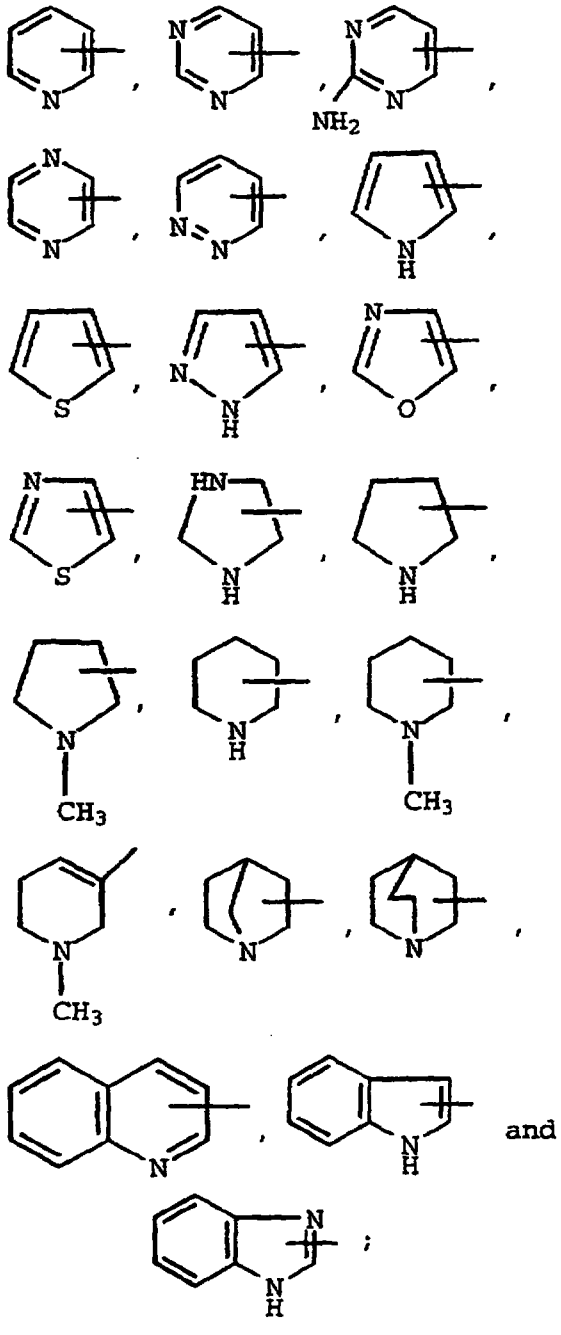
R54, R55, R56, and R57 are each independenty hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from C1-C10 alkyl, alkoxy, C1-C10 halogen or trifluoromethyl; n' is an interger of one or two;



X

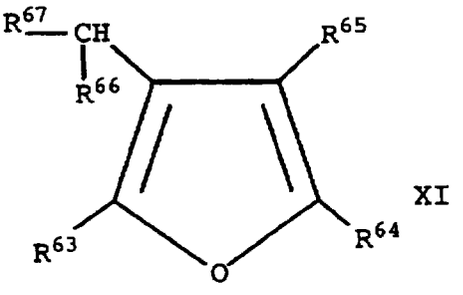
wherein X is oxygen, sulfur, or -N-R^{62}, wherein R^{62} is hydrogen or alkyl of from one to ten carbon atoms; R^{58} is selected from the group consisting of

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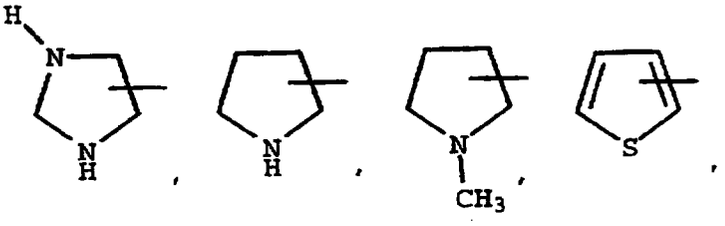
and

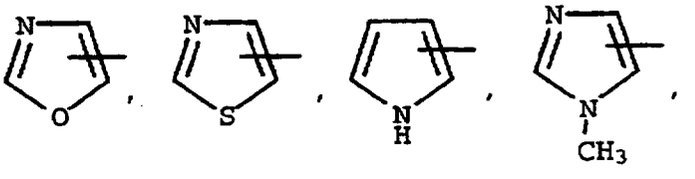
R^{59}, R^{60}, and R^{61} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; --- represents a single or double bond with the proviso that when --- represents a double bond R^{57} and R^{60} are absent;

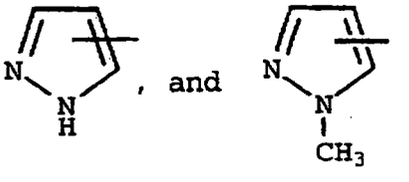


XI

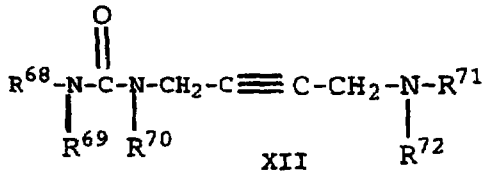
wherein R^{63}, R^{64}, and R^{65} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from the group consisting of alkyl, alkoxy, thioalkoxy, halogen, and trifluoromethyl; R^{66} is hydrogen, hydroxy or alkoxy of from one to ten carbon atoms; and R^{67} is selected from the group consisting of







; or



XII

wherein

R^{69} is hydrogen and R^{67} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

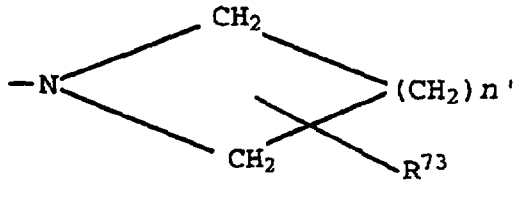
alkenyl of from three to six carbon atoms,

alkenyl of from three to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or R^{68} and R^{69} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



wherein n' is zero or an integer from one to eight and R^{73} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms or alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms;

R^{70} is hydrogen,

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alkyl of from one to six carbon atoms,

alkyl of form one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

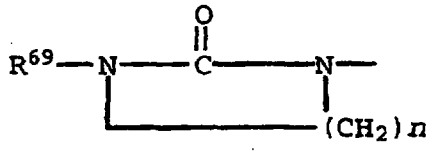
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{70} when taken together with R^{68} forms a ring denoted by



wherein n is an integer from one to three and R68 are as defined above;

R^{71} and R^{72} are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with dydroxy or alkoxy of from one to four carbon atoms,

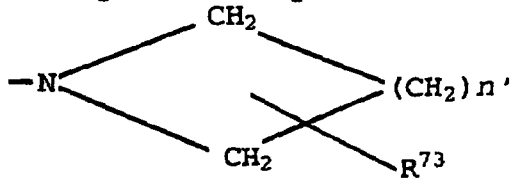
cycloalkyl of from three to eight carbon atoms,

phenyl,

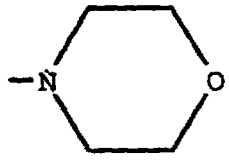
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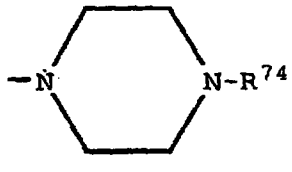
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^3 and R^4 are taken together with the nitrogen atom to which they are attached to form a ring denoted by



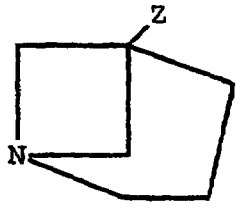
wherein n' and R^{73} are as defined above,



wherein X is defined above or



wherein R^{74} is hydrogen or alkyl of from one to six carbon atoms,

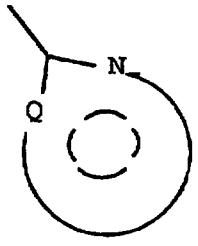


XIII

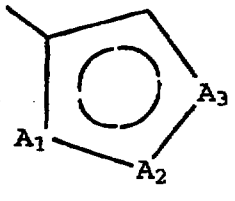
in which Z is a heterocyclic group

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in which Q represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, or three nitrogen atoms, any amino nitrogen being substituted by a C_{1-2} alkyl, cyclopropyl or propargyl group, and any ring carbon atom being optionally substituted by a group R_1; or a group

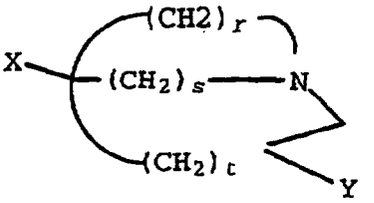


in which A_1, A_2 and A_3 complete a 5-membered aromatic ring and A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_2 and the other is nitrogen or CR_3, or A_2 is oxygen or sulphur, one of A_1 and A_3 is CR_2 and the other is CR_3; and R_1, R_2 and R_3 are independently selected from hydrogen, halogen, CN, OR_4, SR_4, $N(R_4)_2$, $NHCOR_4$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR_4$, $NHNH_2$, NO_2, COR_4, COR_5, cyclopropyl, C_{2-5} straight chain alkenyl, C_{2-5} straight chain alkynyl or C_{1-5} straight chain alkyl optionally terminally substituted with OR_4, $N(R_4)_2$, SR_4, CO_2R_4, $CON(R_4)_2$ or one, two or three halogen atoms, in which each R_4 is independently hydrogen or C_{1-3} alkyl and R_5 is OR_4, NH_2 or NHR_4; or in which Z is a group $-C(R_7)=NR_6$ in which R_6 is a group OR_8, where R_8 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a group $OCOR_9$ where R_9 is hydrogen or R_8, or a group NHR_{10} or $NR_{11}R_{12}$ where R_{10}, R_{11} and R_{12} are independently C_{1-2} alkyl and R_7 is hydrogen or C_{1-4} alkyl, subject to the

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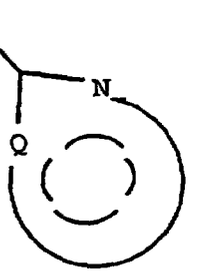
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proviso that when R_6 is a group $OCOR_9$ or NHR_{10}, R_7 is C1-4 alkyl;

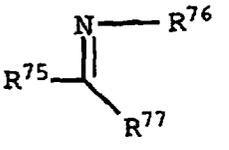


XIV

in which one of X and Y represents hydrogen and the other represents Z, and Z' is a group



in which Q' represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises two or three nitrogen atoms, any amino nitrogen being substituted by a C1-2 alkyl, cyclopropyl or propargyl group, r represents the integer of 2 or 3, s represents an integer of 1 or 2 and t represents 0, with the proviso that when Y is hydrogen s is 1;

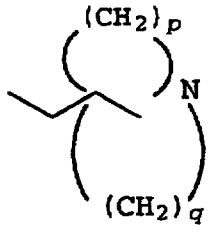


XV

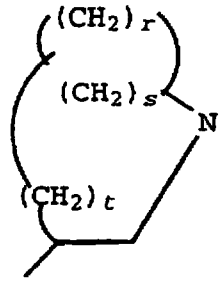
wherein R^{75} represents

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or



in which

each of p and q independently represents an integer of 2 to 4, r represents an integer of 2 to 4, s represents 1 or 2 and t represents 0 or 1;

R^{76} is a group OR^{78}, where R^{78} is C_{1-4} alkenyl, C_{2-4} alkynyl, a group $OCOR^{79}$ where R^{79} is hydrogen or R^{78}, or a group NHR^{80} or NR^{81}, R^{82}, where R^{80}, R^{81} and R^{82} are independently C_{1-2} alkyl; and R^{77} is hydrogen or C_{1-4}alkyl, subject to the proviso that when R^{76} is a group $OCOR^{79}$ or a group NHR^{80}, R^{77} is alkyl;

(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane; or

a pharmaceutically acceptable salt or solvate thereof;

and one or more Synergistic Analgesics in a weight ratio of Compound to Synergistic Analgesic of from about 1 to about 1000.

23. A method as claimed by **Claim 22** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

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24. A method as claimed by **Claim 22** wherein the Synergistic Analgesic is a nonsteroidal anti-inflammatory drug.

25. A method as claimed by **Claim 24** wherein the nonsteroidal anti-inflammatory drug is selected from the group consisting of indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac.

26. A method as claimed by **Claim 24** wherein the nonsteroidal anti-inflammatory drug is ibuprofen.

27. A method as claimed by **Claim 24** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

28. A method as claimed by **Claim 22** wherein the Synergistic Analgesic is an opioid.

29. A method as claimed by **Claim 28** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

30. A method as claimed by **Claim 29** wherein the Compound is selected from the group consisting of 1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone, 1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone, 3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile, 1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide, 1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide, 1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide, (methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and 1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or

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a pharmaceutically acceptable salt thereof.

31. A method as claimed by **Claim 29** wherein the opioid is selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, naloxone, naltrexone, pentazocine, butorphanol, nabuphine, and buprenorphine.

32. A method as claimed by **Claim 29** wherein the opioid is selected from the group consisting of hydromorphone, hydrocodone, meperidone, buprenorphine, butorphenol, nalbuphine, pentazocine, oxymorphine, oxycodone, levorphanol, fentanyl, and alphaprodine.

33. A method as claimed by **Claim 29** wherein the opioid is selected from the group consisting of propoxyphene, methadone, hydrocodone, hydromorphine, and codeine.

34. A method as claimed by **Claim 22** wherein the Compound is selected from the group consisting of Formula I, II, and III; or a pharmaceutically acceptable salt or solvate thereof.

35. A method as claimed by **Claim 22** wherein the Compound is selected from the group consisting of Formula XIV and XV; or a pharmaceutically acceptable salt or solvate thereof.

36. A method as claimed by **Claim 35** wherein the Compound is selected from the group consisting of 1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone, 1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone, 3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile, 1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide, 1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide, 1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide, (methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile,

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oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and 1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or a pharmaceutically acceptable salt thereof.

37. A method as claimed by **Claim 22** wherein the Synergistic Analgesic is acetaminophen.

38. A method as claimed by **Claim 37** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

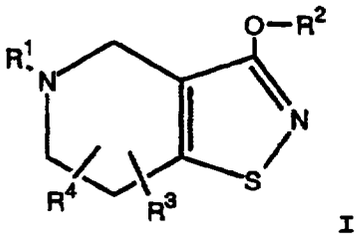
39. A method as claimed by **Claim 22** wherein the Synergistic Analgesic is an alpha-adrenergic compound.

40. A method as claimed by **Claim 39** wherein the Compound is selected from the group consisting of Formula IV, V, VIII, IX, XIII, XIV, and XV; or a pharmaceutically acceptable salt or solvate thereof.

41. A method as claimed by **Claim 40** wherein the Compound is selected from the group consisting of 1-azabicyclo[2.2.2]oct-3-yl cyclopropyl ketone, 1-azabicyclo[2.2.1]hept-3-yl cyclopropyl ketone, 3-oxo-3-(1-azabicyclo[2.2.1]hept-3-yl)propionitrile, 1-azabicyclo[2.2.2]oct-3-yl-N-methoxycarboxamide, 1-azabicyclo[3.2.1]oct-5-yl-N-methoxycarboxamide, 1-azabicyclo[2.2.1]hept-3-yl-N-methoxycarboxamide, (methoxyimino)-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, oximino-(1-azabicyclo[2.2.2]oct-3-yl)acetonitrile, and 1-azabicyclo[2.2.2]oct-3-ylidecyanoacetic acid; or a pharmaceutically acceptable salt thereof.

42. The use of a First Compound selected from the group consisting of

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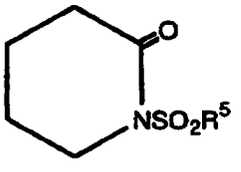


I

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;

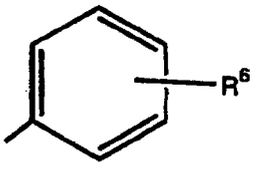
R^2 is C_1-C_6alkyl, C_3-C_6 alkenyl, C_3-C_6 alkynyl, branched or unbranched with 1-6 carbon atoms inclusive, which group may be optionally substituted with fluoro, hydroxy or phenyl optionally substituted with fluoro, trifluoromethyl, lower alkyl, hydroxy, or lower alkoxy;

R^3 and R^4 are independently hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, phenyl optionally substituted with halogen triflurorомethyl, C_1-C_4 alkyl, hydroxy, or C_1-C_4 alkoxy, or phenyl-C_1-C_4 alkyl, in which the phenyl group may be substituted with halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy;



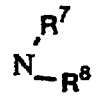
II;

in which R^5 represents the radical

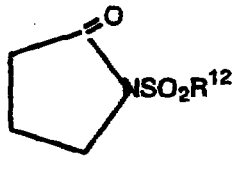


in which R^6 at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical

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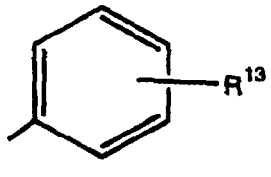


in which R^7 and R^8 which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical OR^9, R^9 representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{10} or $S(O)R^{11}$, R^{10} and R^{11} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^5 represents naphthyl optionally substituted with $R^{6'}$, $R^{6'}$ being defined above for R^6;

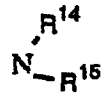


III

in which R^{12} represents the radical



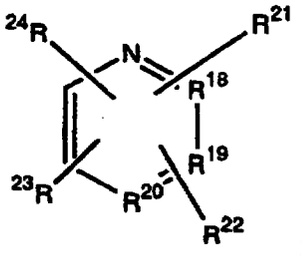
in which R^{13} at any position on the benzene ring represents linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or the radical



in which R^{14} and R^{15} which may be identical or different represent hydrogen, linear C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or form together with the nitrogen atom to which

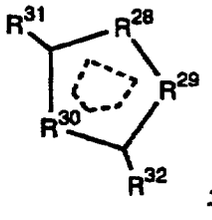
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they are attached a carbonaceous hetercyclic radical optionally containing another heteroatom, or the radical or NO_2, or $OR^{12'}$, $R^{12'}$ representing hydrogen, linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl or aryl containing up to 14 carbon atoms, or the radical SR^{16} or $S(O)R^{17}$, R^{16} and R^{17} represent linear, branched or cyclic C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl, or R^{12} represents naphthyl optionally substituted with $R^{13'}$, $R^{13'}$ being defined above for R^{13};



IV

wherein, one of R^{18}, R^{19}, and R^{20} represents nitrogen and the remainder represent carbon atoms; substituted on one of the ring carbon atoms with a R^{24} substituent represented by a non-aromatic azacyclic or azabicyclic ring system and independently substituted on each of the other ring carbon atoms with R^{23}, R^{21}, or R^{22} substituent of low lipophilicity or a hydrocarbon having a maximum of 20 carbon atoms;



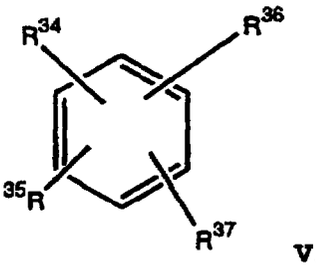
V;

wherein one of R^{28}, R^{29} or R^{30} is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds) thus forming a 1,3,4-oxadiazole or 1,2,4-oxadiazole nucleus; R^{31} represents a non-aromatic '927azacycle or '927azabicyclic ring system; and

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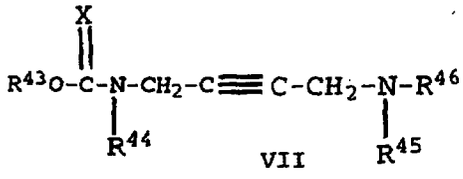
R^{32} represents a substituent which is convertable in vivo to an amino group;



VI;

wherein R^{34} represents a non-aromatic; non-fused 1-azabicyclic ring system; and

R^{35}, R^{36}, and R^{37} independently represent hydrogen, F, Cl, Br, $-CF_3$, $-OR^{38}$, $-NR^{38}R^{39}$, $-NHOR^{38}$, $-NHNH_2$, $-CN$, COR^{40}, or a substituted or unsubstituted, saturated or unsaturated hydrocarbon group, provided that at least one of R^{35}, R^{36}, and R^{37} is other than hydrogen or a hydrocarbon group, or R^{35} and R^{36} or R^{37} taken together form a C_{1-6}alkylenedioxy ring, wherein R^{38} is C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl, R^{39} is hydrogen, C_{1-6} alkyl,or $-COCH_3$, and R^{40} represents OH, $-OR^{38}$, NHR^{39}, or $-NR^{38}R^{39}$



VII

wherein R^{43} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from two to six carbon atoms,

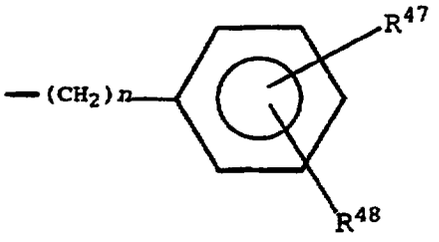
alkenyl of from two to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from two to six carbon atoms,

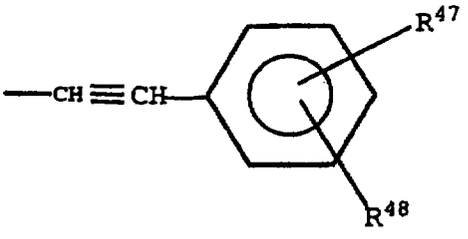
alkynyl of from two to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms, cycloalkyl of from three to six carbon atoms,

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wherein n is zero or an integer of one to eight and R^{47} and R^{48} are independently hydrogen, fluorine, chlorine, bromine, hydroxy, alkyl of from one to three carbon atoms, or alkoxy of from one to three carbon atoms, or alkoxy of from one to four carbon atoms, or



wherein

R^{47} and R^{48} are as defined above;

X is oxygen or sulfur;

R^{44} is

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms

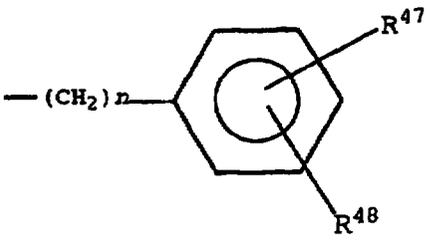
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

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wherein n, R47 and R48 are as defined above R45 and R46 are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

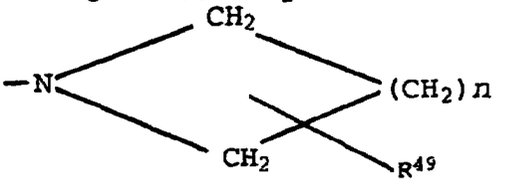
alkynyl of from three to twenty carbon atoms,

alkynyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to eight carbon atoms,

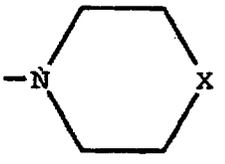
phenyl,

phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^{45} and R^{46} are taken together with the nitrogen atom to which they are attached to form a ring denoted by

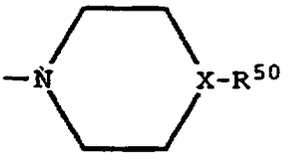


wherein R^{49} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with

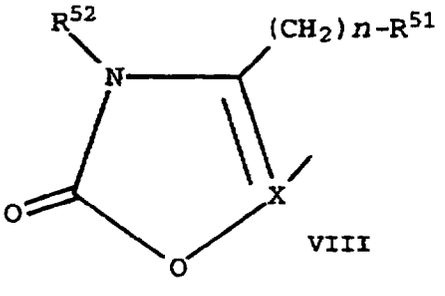
hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms and n is as defined above,



wherein X is defined above or



wherein R^{50} is hydrogen or alkyl of from one to six carbon atoms,

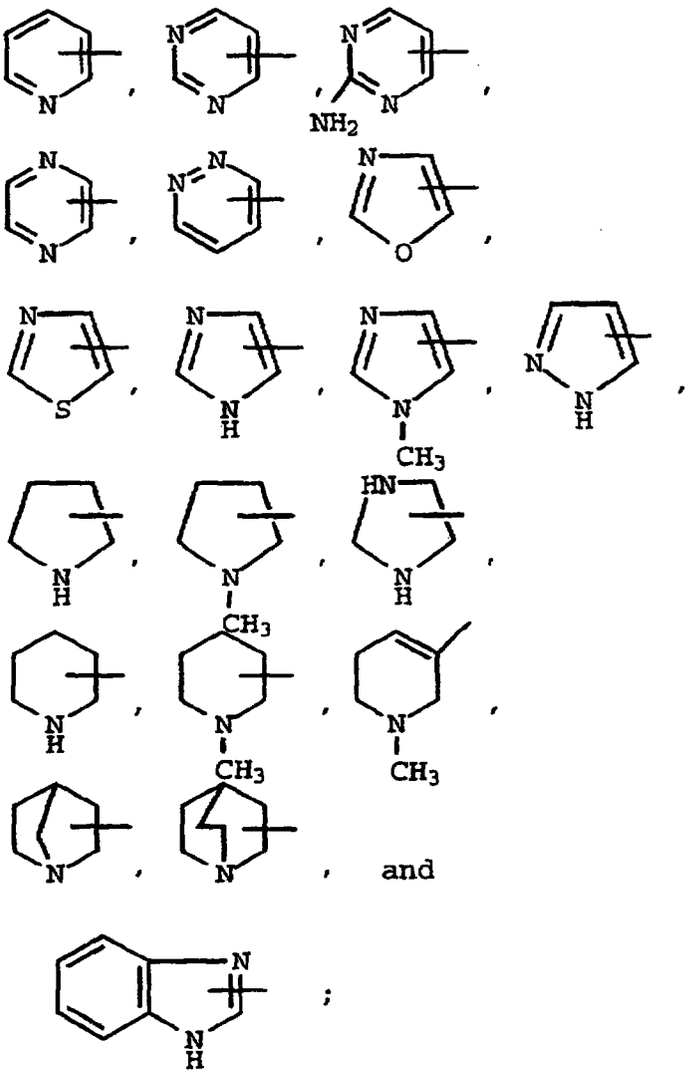


VIII

wherein R^{51} is selected from the group consisting of

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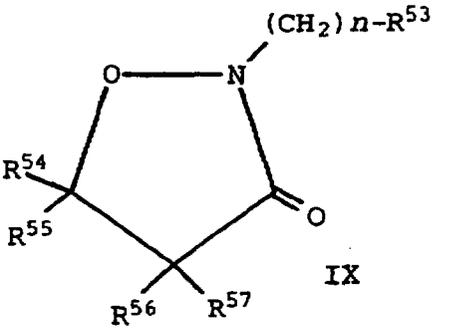
and

;

R^{52} is hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; n' is zero or an integer of one or two; X' is carbon or nitrogen; and ... represents a single or double bond with the proviso that when, ... represents a double bond X' is nitrogen and when ... represents a single bond X' is CH_2;

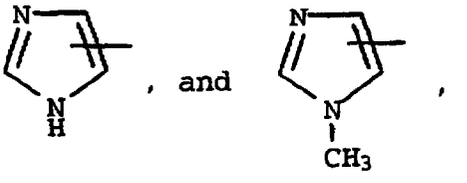
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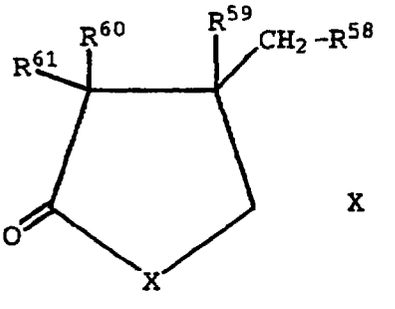


IX

wherein R^{53} is selected from the group consisting



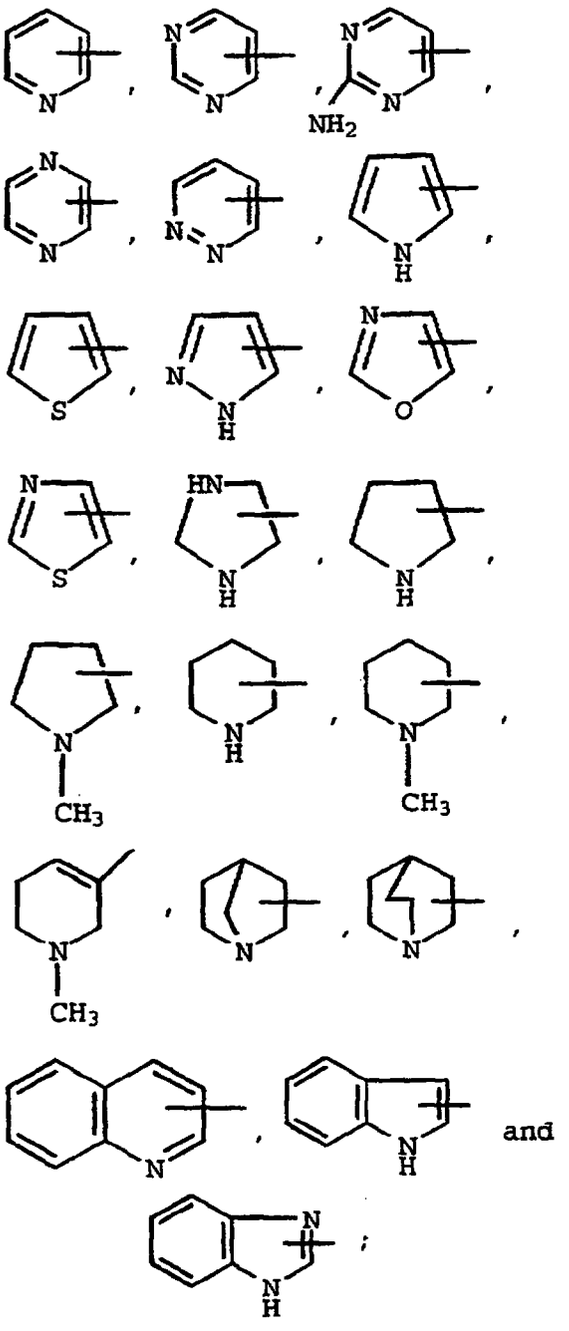
R^{54}, R^{55}, R^{56}, and R^{57} are each independenty hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from C1-C10 alkyl, alkoxy, C1-C10 halogen or trifluoromethyl; n' is an interger of one or two;



X

wherein X is oxygen, sulfur, or -N-R^{62}, wherein R^{62} is hydrogen or alkyl of from one to ten carbon atoms; R^{58} is selected from the group consisting of

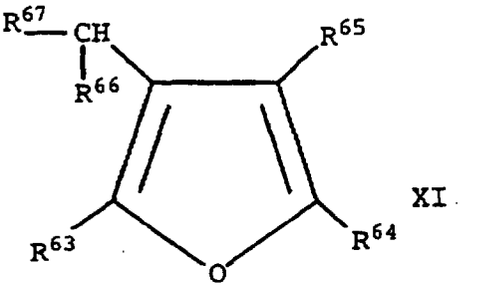
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and

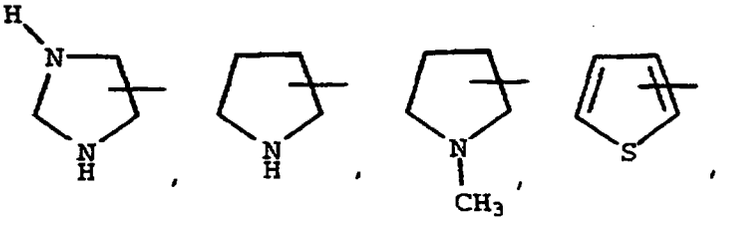
R^{59}, R^{60}, and R^{61} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms or aryl; --- represents a single or double bond with the proviso that when --- represents a double bond R^{57} and R^{60} are absent;

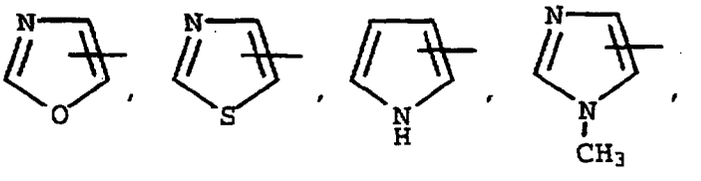
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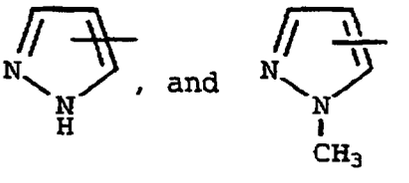


XI

wherein R^{63}, R^{64}, and R^{65} are each independently hydrogen, alkyl of from one to ten carbon atoms, alkynyl of from two to ten carbon atoms, phenyl or phenyl substituted by one to four substituents selected from the group consisting of alkyl, alkoxy, thioalkoxy, halogen, and trifluoromethyl; R^{66} is hydrogen, hydroxy or alkoxy of from one to ten carbon atoms; and R^{67} is selected from the group consisting of



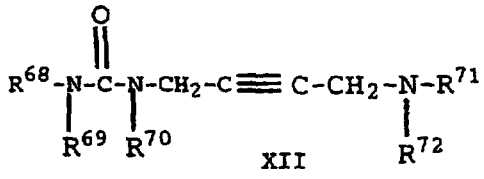




; or

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XII

wherein

R^{69} is hydrogen and R^{67} is hydrogen,

alkyl of from one to six carbon atoms,

alkyl of from one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

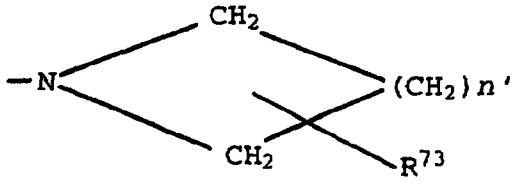
alkenyl of from three to six carbon atoms,

alkenyl of from three to six carbon atoms, substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or R^{68} and R^{69} are taken together with the nitrogen atom to which they are attached to form a ring denoted by



wherein n' is zero or an integer from one to eight and R^{73} is hydrogen, alkyl of from one to ten carbon atoms, alkyl of from one to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkenyl of from two to ten carbon atoms, alkenyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkynyl of from two to ten carbon atoms or alkynyl of from two to ten carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms;

R^{70} is hydrogen,

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alkyl of from one to six carbon atoms,

alkyl of form one to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to six carbon atoms,

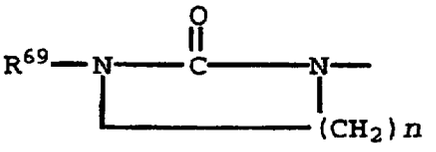
alkenyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to six carbon atoms,

alkynyl of from three to six carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to six carbon atoms, or

R^{70} when taken together with R^{68} forms a ring denoted by



wherein n is an integer from one to three and R68 are as defined above;

R^{71} and R^{72} are each independently hydrogen,

alkyl of from one to twenty carbon atoms,

alkyl of from one to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkenyl of from three to twenty carbon atoms,

alkenyl of from three to twenty carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms,

alkynyl of from three to twenty carbon atoms,

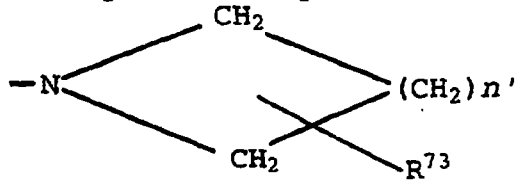
alkynyl of from three to twenty carbon atoms substituted with dydroxy or alkoxy of from one to four carbon atoms,

cycloalkyl of from three to eight carbon atoms,

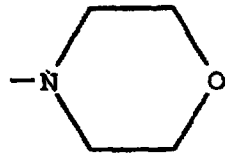
phenyl,

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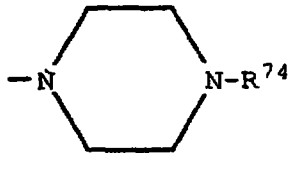
phenyl substituted with alkyl of from one to four carbon atoms, alkyl of from one to four carbon atoms substituted with hydroxy or alkoxy of from one to four carbon atoms, alkoxy of from one to four carbon atoms, chlorine, bromine, hydroxy, nitro or trifluoromethyl of R^3 and R^4 are taken together with the nitrogen atom to which they are attached to form a ring denoted by



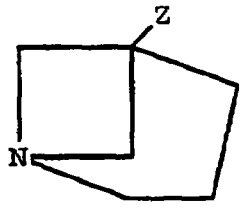
wherein n' and R^{73} are ad defined above,



wherein X is defined above or



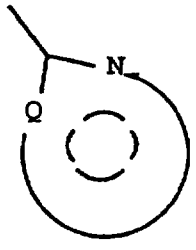
wherein R^{74} is hydrogen or alkyl of from one to six carbon atoms,



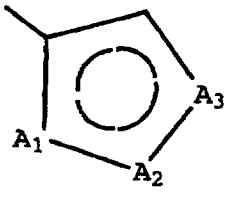
XIII

in which Z is a heterocyclic group

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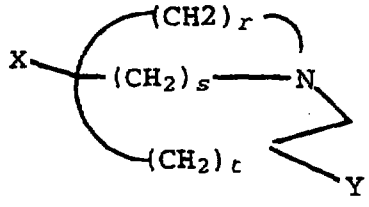
in which Q represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises one or two heteroatoms selected from oxygen, nitrogen and sulphur, or three nitrogen atoms, any amino nitrogen being substituted by a C_{1-2} alkyl, cyclopropyl or propargyl group, and any ring carbon atom being optionally substituted by a group R_1; or a group



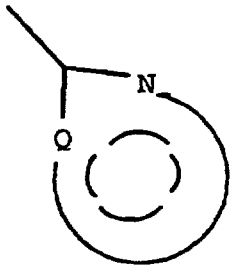
in which A_1, A_2 and A_3 complete a 5-membered aromatic ring and A_1 is oxygen or sulphur, one of A_2 and A_3 is CR_2 and the other is nitrogen or CR_3, or A_2 is oxygen or sulphur, one of A_1 and A_3 is CR_2 and the other is CR_3; and R_1, R_2 and R_3 are independently selected from hydrogen, halogen, CN, OR_4, SR_4, $N(R_4)_2$, $NHCOR_4$, $NHCOOCH_3$, $NHCOOC_2H_5$, $NHOR_4$, $NHNH_2$, NO_2, COR_4, COR_5, cyclopropyl, C_{2-5} straight chain alkenyl, C_{2-5} straight chain alkynyl or C_{1-5} straight chain alkyl optionally terminally substituted with OR_4, $N(R_4)_2$, SR_4, CO_2R_4, $CON(R_4)_2$ or one, two or three halogen atoms, in which each R_4 is independently hydrogen or C_{1-3} alkyl and R_5 is OR_4, NH_2 or NHR_4; or in which Z is a group $-C(R_7)=NR_6$ in which R_6 is a group OR_8, where R_8 is C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, a group $OCOR_9$ where R_9 is hydrogen or R_8, or a group NHR_{10} or $NR_{11}R_{12}$ where R_{10}, R_{11} and R_{12} are independently C_{1-2} alkyl and R_7 is hydrogen or C_{1-4} alkyl, subject to the

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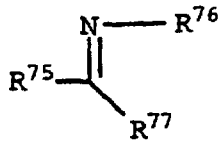
proviso that when R_6 is a group $OCOR_9$ or NHR_{10}, R_7 is C_{1-4} alkyl



in which one of X and Y represents hydrogen and the other represents Z, and Z' is a group



in which Q' represents a 3-membered divalent residue completing a 5-membered aromatic ring and comprises two or three nitrogen atoms, any amino nitrogen being substituted by a C1-2 alkyl, cyclopropyl or propargyl group, r represents the integer of 2 or 3, s represents an integer of 1 or 2 and t represents 0, with the proviso that when Y is hydrogen s is 1;

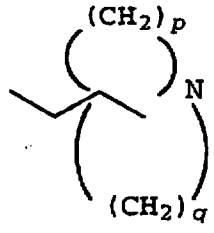


XV

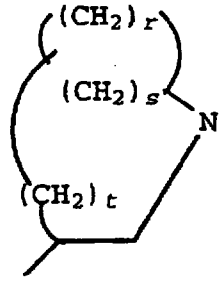
wherein R^{75} represents

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or



in which

each of p and q independently represents an integer of 2 to 4, r represents an integer of 2 to 4, s represents 1 or 2 and t represents 0 or 1;

R^{76} is a group OR^{78}, where R^{78} is C_{1-4} alkenyl, C_{2-4} alkynyl, a group $OCOR^{79}$ where R^{79} is hydrogen or R^{78}, or a group NHR^{80} or NR^{81}, R^{82}, where R^{80}, R^{81} and R^{82} are independently C_{1-2} alkyl; and R^{77} is hydrogen or C_{1-4}alkyl, subject to the proviso that when R^{76} is a group $OCOR^{79}$ or a group NHR^{80}, R^{77} is alkyl;

(3R,4R)-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-azabicyclo[2.2.1heptane; or

a pharmaceutically acceptable salt or solvate thereof; and one or more Synergistic Analgesics in a weight ratio of First Compound to Synergistic Analgesic of from about 1 to about 1000 for a manufacture of a medicament for therapeutic application in the treatment of pain.

43. A use as claimed by **Claim 42** wherein the Synergistic Analgesic is an opioid.

44. A use as claimed by **Claim 42** wherein the Synergistic Analgesic is acetaminophen.

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45. A use as claimed by **Claim 42** wherein the Synergistic Analgesic is a nonsteroidal anti-inflammatory drug.

46. A use as claimed by **Claim 42** wherein the Synergistic Analgesic is an alpha-adrenergic compound.

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