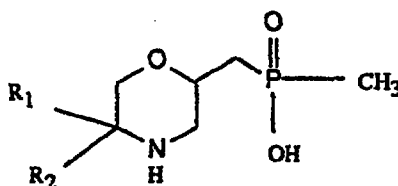


Substituted Phosphinic Compounds and their Use as Pharmaceuticals

This invention relates to chemical compounds which are substituted phosphinic acids or salts or esters thereof, their preparation and their use as pharmaceuticals.

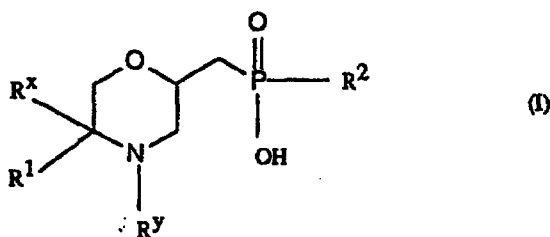
In WO 94/22843 there are described phosphinic acids of formula



where R_1 and R_2 are both H, R^1 and R^2 are both methyl or R^1 and R^2 together with the attached carbon atom are cyclopentyl. These compounds are said to act as $GABA_B$ antagonists.

It has now been found that compounds having remarkably high $GABA_B$ receptor binding affinity can be provided by preparing novel substituted phosphinic acids containing a morpholine ring.

Accordingly, the present invention provides compounds which are substituted phosphinic acids of formula



or salts or esters thereof,

where R^1 is a monovalent aromatic or araliphatic group connected through a carbon atom thereof to the indicated carbon atom, R^2 is an unsubstituted or substituted hydrocarbyl group, R^x is hydrogen or an unsubstituted or substituted hydrocarbyl group, R^y is hydrogen, R^y_a or a NH- protecting group, and R^y_a is an unsubstituted or substituted

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hydrocarbyl group.

R^1 as an aromatic group may have up to 40 carbon atoms and may be an aryl group such as a phenyl, tolyl, xylyl or naphthyl group or a heterocyclic aromatic group such as a thienyl, furyl, indolyl or pyridyl group, which groups may be unsubstituted or substituted by one or more substituents such as halogen, hydroxy, C_1 to C_4 alkoxy, carboxyl, functionally modified carboxyl including esterified carboxyl, amidated carboxyl and cyano, carboxy- C_1 - C_8 alkyl, functionally modified carboxy- C_1 - C_8 alkyl or nitro.

Preferably, R^1 as an aromatic group is an aryl group of 6 to 15 carbon atoms which may be unsubstituted or substituted in one or more positions by halogen, carboxyl, functionally modified carboxyl, carboxy- C_1 - C_8 alkyl, functionally modified carboxy- C_1 - C_8 alkyl or nitro, or R^1 as an aromatic group is a 5 to 10-membered heterocyclic aromatic group having one or two nitrogen atoms in the ring system. More preferably, R^1 as unsubstituted or substituted aryl is phenyl or phenyl substituted in one or more of the meta and para positions, with respect to the carbon atom thereof linked to the indicated morpholine ring, by halogen, carboxyl, functionally modified carboxyl, or nitro. Examples of such substituted phenyl groups include phenyl mono- or di-substituted by chloro; bromo; iodo; carboxyl; $-\text{COOR}^3$ where R^3 is C_1 to C_8 alkyl such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl optionally substituted by halogen, hydroxy or C_1 to C_4 alkoxy; carbamoyl; N- C_1 - C_4 alkyl carbamoyl, such as methyl- or ethyl-carbamoyl, N, N-di(C_1 - C_4 alkyl) carbamoyl such as dimethyl- or diethyl-carbamoyl; cyano; carboxy- C_1 - C_4 alkyl such as carboxymethyl; C_1 to C_8 alkoxy-carbonyl- C_1 - C_4 alkyl such as methoxy- or ethoxy- carbonylmethyl; carbamoyl- C_1 - C_4 alkyl such as carbamoylmethyl; N- C_1 - C_4 alkylcarbamoyl- C_1 - C_4 alkyl such as methyl- or ethyl-carbamoylmethyl; N,N-di(C_1 - C_4 alkyl)carbamoyl- C_1 - C_4 alkyl such as dimethyl- or diethyl-carbamoylmethyl; cyano- C_1 - C_4 alkyl such as cyanomethyl; or nitro. More preferably, R^1 as a heterocyclic aromatic group is a 5 to 10-membered heterocyclic group having a nitrogen atom as the only ring hetero atom, e.g. pyridyl or indolyl.

R^1 as an araliphatic group may have 7 to 40 carbon atoms and may be phenyl-lower alkyl, for example benzyl or 2-phenylethyl, α , α -diphenyl-lower alkyl such as diphenylmethyl, or α -naphthyl-lower alkyl such as naphthylmethyl, any of which groups may be unsubstituted or substituted in one or more positions, which may be ortho, meta or para positions, by a substituent chosen from those hereinbefore specified for R^1 as an aromatic group. Preferably, R^1 as an araliphatic group is α -phenyl- C_1 - C_4 alkyl, which is unsubstituted or substituted in one or more positions by halogen, carboxyl, functionally modified carboxyl or nitro.

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In especially preferred compounds of the invention, R^1 is phenyl, 3-iodophenyl, 3, 4-dichlorophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-nitrophenyl, benzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl.

R^2 as an unsubstituted or substituted hydrocarbonyl group may, in general, have 1 to 40 carbon atoms. It may be for example an alkyl, cycloalkyl, alkenyl or alkynyl group or an alkyl, cycloalkyl or alkenyl group substituted by one or more substituents such as halogen, hydroxy, C_1 to C_8 alkoxy, thio, C_1 to C_8 alkylthio, cyano, acylamino, C_3 to C_8 cycloalkyl, C_3 to C_8 cycloalkyl substituted for example by one or more substituents such as hydroxy, C_1 to C_8 alkoxy, thio or C_1 to C_8 alkylthio, C_3 to C_8 cycloalkenyl, C_6 to C_{15} aryl, C_6 to C_{15} aryl substituted for example by one or more substituents such as hydroxy, C_1 to C_8 alkoxy, halogen or trifluoromethyl, heteroaryl or heteroaryl substituted by one or more substituents such as halogen.

Aliphatic radicals R^2 are, for example, lower alkyl, lower alkenyl, lower alkynyl, oxo-lower alkyl, hydroxy- or dihydroxy-lower alkyl, hydroxy-lower alkenyl, mono-, di- or poly-halo-lower alkyl, mono-, di- or poly-halo-lower alkenyl, mono-, di- or poly-halo-(hydroxy)-lower alkyl, mono-, di- or poly-halo(hydroxy)-lower alkenyl, lower alkoxy-lower alkyl, di-lower alkoxy-lower alkyl, lower alkoxy(hydroxy)-lower alkyl, lower alkoxy(halo)-lower alkyl, lower alkylthio-lower alkyl and di-lower alkylthio-lower alkyl.

Cycloaliphatic radicals R^2 are, for example, cycloalkyl, hydroxycycloalkyl, oxa-, dioxo-, thia- and dithia-cycloalkyl.

Cycloaliphatic-aliphatic radicals R^2 are, for example, cycloalkyl-lower alkyl, cycloalkenyl-lower alkyl, cycloalkyl(hydroxy)-lower alkyl and (lower alkylthio)cycloalkyl-(hydroxy)-lower alkyl.

Araliphatic radicals R^2 are, for example, phenyl-lower alkyl radicals that are unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl, preferably α -phenyl-lower alkyl substituted as indicated or unsubstituted α,α -diphenyl- or α -naphthyl-lower alkyl.

Heteroarylaliphatic radicals R^2 are, for example, thienyl-, furyl- or pyridyl-lower alkyl radicals that are unsubstituted or substituted, especially mono- or di-substituted, by halogen, preferably unsubstituted α -thienyl-, α -furyl- or α -pyridyl-lower alkyl.

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Hereinbefore and hereinafter, lower radicals and compounds are to be understood, for example, as those containing up to and including 7, preferably up to and including 4, carbon atoms.

Lower alkyl is, for example, C₁-C₇alkyl, preferably C₁-C₄alkyl, such as methyl, ethyl, propyl, isopropyl or butyl, but may also be isobutyl, sec-butyl, tert-butyl or a C₅-C₇alkyl group, such as a pentyl, hexyl or heptyl group.

Lower alkenyl is, for example, C₂-C₄alkenyl, such as vinyl, allyl or but-2-enyl, but may also be a C₅-C₇alkenyl group, such as a pentenyl, hexenyl or heptenyl group.

Lower alkynyl is, for example, C₂-C₇alkynyl, preferably C₃-C₅alkynyl, that carries the double bond in a position higher than the α,β -position, for example 2-propynyl (propargyl), but-3-yn-1-yl, but-2-yn-1-yl or pent-3-yn-1-yl.

Oxo-lower alkyl carries the oxo group preferably in a position higher than the α -position and is, for example, oxo-C₂-C₇alkyl, especially oxo-C₃-C₆alkyl, such as 2-oxopropyl, 2- or 3-oxobutyl or 3-oxopentyl.

Phenyl-lower alkyl is, for example, benzyl, 1-phenylethyl, 2-phenylprop-2-yl or, in the second place, 2-phenylethyl, 2-phenylprop-1-yl or 3-phenylprop-1-yl.

Thienyl-, furyl- or pyridyl-lower alkyl is, for example, thienyl-, furyl- or pyridyl-methyl, 1-thienyl-, 1-furyl- or 1-pyridyl-ethyl, 2-thienyl-, 2-furyl- or 2-pyridyl-prop-2-yl, or, in the second place, 2-thienyl-, 2-furyl- or 2-pyridyl-ethyl, 2-thienyl-, 2-furyl- or 2-pyridyl-prop-1-yl or 3-thienyl-, 3-furyl- or 3-pyridyl-prop-1-yl.

Hydroxy-lower alkyl carries the hydroxy group preferably in the α - or β -position and is, for example, corresponding hydroxy-C₂-C₇alkyl, such as 1-hydroxyethyl, 1- or 2-hydroxypropyl, 2-hydroxyprop-2-yl, 1- or 2-hydroxybutyl, 1-hydroxyisobutyl or 2-hydroxy-3-methylbutyl.

Dihydroxy-lower alkyl carries the hydroxy groups especially in the α,β -position and is, for example, α,β -dihydroxy-C₃-C₇alkyl, such as 1,2-dihydroxyprop-2-yl.

Hydroxy-lower alkenyl carries the hydroxy groups preferably in the α -position and the double bond preferably in a position higher than the α,β -position and is, for example,

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corresponding α -hydroxy- C_3 - C_5 alkenyl, for example 1-hydroxybut-2-enyl.

Mono-, di- or poly-halo-lower alkenyl is, for example, mono- di- or tri-fluoro- C_2 - C_5 -alkenyl, such as 1-fluorobut-2-enyl.

Mono-, di- or polyhalo(hydroxy)-lower alkyl carries the hydroxy group preferably in the α -position and the halogen atoms preferably in a position higher than the α -position and is, for example, corresponding mono- di- or tri-fluoro- α -hydroxy- C_2 - C_7 alkyl, such as 4,4,4-trifluoro-1-hydroxybutyl.

Mono-, di- or poly-halo-lower alkyl is, for example, mono- di- or tri-fluoro- C_2 - C_5 alkyl, such as 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, 1- or 2-fluorobutyl or 1,1-difluorobutyl.

Lower alkoxy is, for example, C_1 - C_7 alkoxy, preferably C_1 - C_4 alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy or butoxy, but may also be isobutoxy, sec-butoxy, tert-butoxy or a C_5 - C_7 alkoxy group, such as a pentyloxy, hexyloxy or heptyloxy group.

Acylamino-lower alkyl is, for example C_1 - C_4 alkylcarbonylamino- C_1 - C_4 alkyl such as acetylaminopropyl or C_6 - C_{10} arylcarbonylamino- C_1 - C_4 alkyl such as benzoylaminomethyl.

Cyano-lower alkyl is, for example cyano- C_1 - C_4 alkyl, such as cyanomethyl or 2-cyanoethyl.

Mono-, di- or poly-halo(hydroxy)-lower alkenyl carries the hydroxy group preferably in the α -position and the halogen atoms preferably in a position higher than the α -position and is, for example, corresponding mono-, di- or tri-fluoro- α -hydroxy- C_2 - C_5 alkenyl, such as 2-fluoro-1-hydroxybuten-2-yl.

Lower alkoxy-lower alkyl is, for example, C_1 - C_4 alkoxy- C_1 - C_4 alkyl, such as methoxy- or ethoxy-methyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxy- or 3-ethoxy-propyl or 1- or 2-methoxybutyl.

Di-lower alkoxy-lower alkyl is, for example, di- C_1 - C_4 -alkoxy- C_1 - C_4 alkyl, for example dimethoxymethyl, dipropoxymethyl, 1,1- or 2,2-diethoxyethyl, diisopropoxymethyl, dibutoxymethyl or 3,3-dimethoxypropyl.

Lower alkoxy(hydroxy)-lower alkyl is, for example, C_1 - C_4 alkoxy- C_2 - C_7 -(hydroxy)alkyl,

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such as 2-hydroxy-3-methoxyprop-2-yl.

Lower alkoxy(halo)-lower alkyl is, for example, C₁-C₄alkoxy-C₂-C₅-(halo)alkyl, such as 2-fluoro-3-methoxybutyl.

Lower alkylthio-lower alkyl is, for example, C₁-C₄alkylthio-C₁-C₄alkyl, such as methylthio- or ethylthio-methyl, 2-methylthioethyl, 2-ethylthioethyl, 3-methylthio- or 3-ethylthio-propyl or 1- or 2-methylthiobutyl.

Di-lower alkylthio-lower alkyl is, for example, di-C₁-C₄alkylthio-C₁-C₄alkyl, for example dimethylthiomethyl, dipropylthiomethyl, 1,1- or 2,2-diethylthioethyl, diisopropylthiomethyl, dibutylthiomethyl or 3,3-dimethylthiopropyl.

Halogen is halogen having an atomic number of up to and including 53, i.e. fluorine, chlorine, bromine or iodine.

Cycloalkyl is, for example, C₃-C₈cycloalkyl, especially C₃-C₆cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Hydroxycycloalkyl is, for example, α -hydroxy-C₃-C₆cycloalkyl, such as 1-hydroxycyclopropyl, 1-hydroxycyclobutyl or 1-hydroxycyclohexyl.

Oxa- or thia-cycloalkyl is, for example, oxa- or thia-C₃-C₈cycloalkyl, especially oxa- or thia-C₃-C₆cycloalkyl, such as 2-oxacyclopropyl (oxiranyl), 2- or 3-oxacyclobutyl (oxetan-yl), 2- or 3-thiacyclobutyl (thietanyl), 2- or 3-oxacyclopentyl (tetrahydrofuranyl), 2- or 3-thiacyclopentyl (thiolanyl) or 2-oxacyclohexyl (tetrahydropyranyl).

Dioxacycloalkyl is, for example, 1,3-dioxá-C₃-C₈cycloalkyl, such as 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl.

Dithiacycloalkyl is, for example, 1,3-dithia-C₃-C₈cycloalkyl, such as 1,3-dithiolan-2-yl or 1,3-dithian-2-yl.

Cycloalkyl-lower alkyl is, for example, C₃-C₈-cycloalkyl-C₁-C₄alkyl, especially C₃-C₆-cycloalkyl-C₁-C₄alkyl, such as α -(C₃-C₆cycloalkyl)-C₁-C₄alkyl, for example cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

Cycloalkenyl-lower alkyl is, for example, C₃-C₈cycloalkenyl-C₁-C₄alkyl, especially

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C₃-C₆cycloalkenyl-C₁-C₄alkyl, such as α -(C₃-C₆cycloalkenyl)-C₁-C₄alkyl, for example cyclopent-1-enylmethyl, cyclopent-2-enylmethyl, cyclopent-3-enylmethyl, cyclohex-1-enylmethyl, cyclohex-2-enylmethyl or cyclohex-3-enylmethyl.

Cycloalkyl(hydroxy)-lower alkyl is, for example, C₃-C₆cycloalkyl-C₁-C₄(hydroxy)alkyl, such as α -(C₃-C₆cycloalkyl)- α -hydroxy-C₁-C₄alkyl, for example cyclopropyl(hydroxy)-methyl, cyclobutyl(hydroxy)methyl, or cyclohexyl(hydroxy)methyl.

(Lower alkylthiocycloalkyl)(hydroxy)-lower alkyl is, for example, 1-(C₁-C₄alkylthio-C₃-C₆cycloalkyl)-1-hydroxy-C₁-C₄alkyl, such as (2-methylthiocycloprop-1-yl)hydroxymethyl.

In preferred compounds of the invention, R² is lower alkyl, lower alkenyl, lower alkynyl, oxo-lower alkyl, hydroxy- or dihydroxy-lower alkyl, hydroxy-lower alkenyl, mono-, di- or poly-halo-lower alkyl, mono-, di- or poly-halo-lower alkenyl, mono-, di- or poly-halo-(hydroxy)-lower alkyl, mono-, di- or poly-halo(hydroxy)-lower alkenyl, lower alkoxy-lower alkyl, di-lower alkoxy-lower alkyl, lower alkoxy(hydroxy)-lower alkyl, lower alkoxy(halo)-lower alkyl, lower alkylthio-lower alkyl, di-lower alkylthio-lower alkyl, cyano-lower alkyl, acylamino-lower alkyl, cycloalkyl, hydroxycycloalkyl, oxa-, dioxo-, thia- and dithia-cycloalkyl, cycloalkyl-lower alkyl, cycloalkenyl-lower alkyl, cycloalkyl-(hydroxy)-lower alkyl, (lower alkylthio)cycloalkyl(hydroxy)-lower alkyl, or mono- or diphenyl-lower alkyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, halogen, hydroxy and/or by trifluoromethyl, naphthyl-lower alkyl or unsubstituted or halo-substituted thienyl-, furyl- or pyridyl-lower alkyl.

In more preferred compounds of formula I, R² is C₁-C₇alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl, α,α -di-C₁-C₄alkoxy-C₁-C₄alkyl, especially α,α -di-C₁-C₄alkoxy-methyl or ethyl, such as dimethoxy- or diethoxy-methyl or 1,1-diethoxyethyl, cyano-C₁-C₄ alkyl such as cyanomethyl or 2-cyanoethyl, acylamino-C₁-C₅ alkyl such as acetylaminomethyl, acetylaminopropyl, acetylaminopentyl or benzoylaminomethyl, C₃-C₆cycloalkyl-C₁-C₄alkyl, such as cyclopropyl- or cyclohexyl-methyl, C₃-C₆cycloalkenyl-C₁-C₄alkyl, such as cyclohex-3-enylmethyl, or is phenyl-C₁-C₄alkyl, such as benzyl, that is unsubstituted or mono-, di- or tri-substituted by C₁-C₄alkyl, such as methyl, C₁-C₄alkoxy, such as methoxy, hydroxy and/or by halogen, such as fluorine, chlorine or iodine.

In more preferred compounds of the invention, R² is C₁-C₅ alkyl such as methyl, ethyl or butyl, α,α -di-(C₁-C₄ alkoxy)methyl such as diethoxymethyl, α,α -di-(C₁-C₄ alkoxy)ethyl

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such as 1, 1-diethoxyethyl, C₃-C₆ cycloalkyl-C₁-C₄ alkyl such as cyclopropylmethyl or cyclohexylmethyl, benzyl or 4-methoxybenzyl. In especially preferred compounds, R² is cyclohexylmethyl or 4-methoxybenzyl.

R^x as an unsubstituted or substituted hydrocarbyl group may have up to 40 carbon atoms and may be a C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₃ to C₈ cycloalkyl, C₄ to C₁₃ cycloalkylalkyl, C₆ to C₁₀ aryl or C₇ to C₁₃ aralkyl group, any of which groups may be substituted by one or more substituents chosen from those hereinbefore specified for R¹. Preferably R^x is hydrogen, lower alkyl, C₃ to C₆ cycloalkyl, C₆ to C₈ aryl or C₇ to C₉ aralkyl, especially hydrogen or isopropyl.

R^y as an unsubstituted or substituted hydrocarbyl group R^y_a may have up to 40 carbon atoms and may be, for example, a C₁ to C₁₀ alkyl, C₃ to C₈ cycloalkyl or C₇ to C₁₃ aralkyl group, any of which groups may be unsubstituted or substituted by hydroxy or C₁ to C₄ alkoxy. R^y as a NH-protecting group may be, for example, an acyl group such as acetyl, trifluoroacetyl, benzoyl or p-nitrobenzoyl or an alkoxycarbonyl or aralkoxycarbonyl group such as tert-butoxycarbonyl or benzyloxycarbonyl. Preferably R^y is hydrogen, lower alkyl, C₇ to C₉ aralkyl, acetyl, benzoyl, tert-butoxycarbonyl or benzyloxycarbonyl, especially hydrogen, methyl, ethyl, benzyl, acetyl, benzoyl, tert-butoxycarbonyl or benzyloxycarbonyl.

Specific especially preferred compounds of the invention are those of formula I in which R¹ is phenyl, 3-iodophenyl, 3, 4-dichlorophenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-carboxyphenyl, 3-nitrophenyl, benzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl, R² is cyclohexylmethyl or 4-methoxybenzyl, R^x is hydrogen or isopropyl and R^y is hydrogen, methyl or benzyloxycarbonyl, and salts and esters thereof.

The compounds of formula I may be in the form of internal salts and can form both acid addition salts and salts with bases by conventional salt-forming reactions.

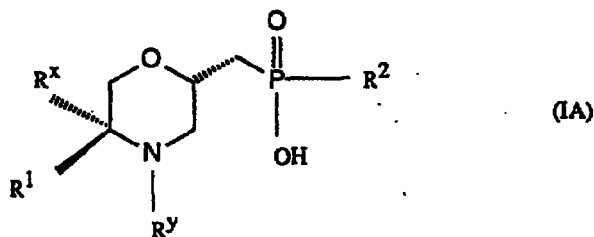
Acid addition salts of compounds of formula I are, for example, their pharmaceutically acceptable salts with suitable mineral acids, such as hydrohalic acids, sulfuric acid or phosphoric acid, for example hydrochlorides, hydrobromides, sulfates, hydrogen sulfates or phosphates, or salts with suitable aliphatic or aromatic sulfonic acids or N-substituted sulfamic acids, for example methanesulfonates, benzenesulfonates, p-toluenesulfonates or N-cyclohexylsulfamates (cyclamates).

Salts of compounds of formula I with bases are, for example, their salts with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, for example alkali metal salts, especially sodium or potassium salts, alkaline earth metal salts, especially calcium or magnesium salts, and also ammonium salts with ammonia or organic amines or quaternary ammonium bases, such as unsubstituted or C-hydroxylated aliphatic amines, especially mono-, di- or tri-lower alkylamines, for example methyl-, ethyl- or diethyl-amine, mono-, di- or tri-(hydroxy-lower alkyl)amines, such as ethanol-, diethanol- or triethanol-amine, tris(hydroxymethyl)methylamine or 2-hydroxy-tert-butylamine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkylamines or N-(polyhydroxy-lower alkyl)-lower alkylamines, such as 2-(dimethylamino)ethanol or D-glucamine, or quaternary aliphatic ammonium hydroxides, for example tetrabutylammonium hydroxide.

As well as forming salts with bases, the hydroxy group attached to phosphorus in formula I may also be esterified. Thus, the invention includes compounds of formula I in the form of their esters with an alcohol, which may be a C₁ to C₁₀ alkanol in which the alkyl radical is unsubstituted or substituted, for example by halogen, cyano or C₁ to C₄ alkoxy, such as methanol, ethanol, isopropanol, isobutanol, 2-ethylhexanol, 2-chloroethanol, 2-cyanoethanol, 2-ethoxyethanol or 2-n-butoxyethanol, a C₃ to C₈ cycloaliphatic alcohol such as cyclopropanol, cyclobutanol, cyclopentanol, cyclohexanol, cycloheptanol, methylcyclohexanol or cyclooctanol, or a C₇ to C₁₃ araliphatic alcohol such as benzyl alcohol.

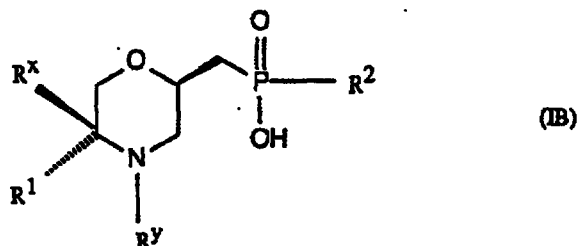
Provided asymmetric carbon atoms are present, the compounds according to the invention may be in the form of isomeric mixtures, especially in the form of racemates, or in the form of pure isomers, especially optical antipodes.

Preferred isomers of compounds of formula I are those in which R¹ and the group attached to the 2- position of the indicated morpholine ring are trans with respect to each other, i.e. those of formula



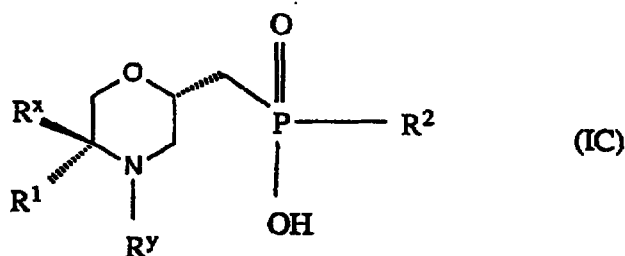
or of formula

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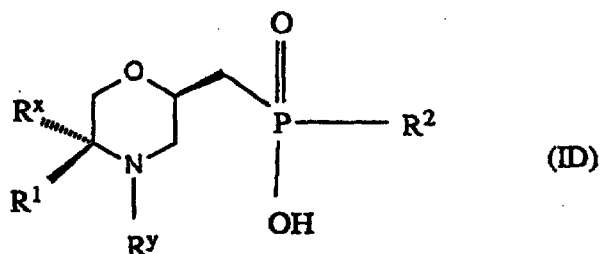


where R^1 , R^2 , R^x and R^y are as hereinbefore defined.

Other preferred isomers of formula I are those in which R^1 and the group attached to the 2-position of the indicated morpholine ring are cis with respect to each other, i.e. those of formula



or of formula



where R^1 , R^2 , R^x and R^y are as hereinbefore defined.

Examples of specific compounds of formula I are

3-((3R*,6R*)-6-[(5-acetylaminoethyl)hydroxyphosphinoylmethyl]morpholin-3-yl)benzoic acid,

3-((3R*,6R*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]morpholin-3-yl)benzoic acid,

3-((3R*,6R*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]morpholin-3-yl)benzoic acid,

3-[(3R*,6R*)-6-(butylhydroxyphosphinoylmethyl)-

morpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-
morpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-(benzylhydroxyphosphinoylmethyl)-
morpholin-3-yl]benzoic acid,
diethoxymethyl-[(2R*,5R*)-5-[(3-methoxycarbonyl)phenyl]-
morpholin-2-ylmethyl]phosphinic acid,
cyclohexylmethyl-[(2R*,5R*)-5-phenylmorpholin-2-ylmethyl]-
phosphinic acid,
diethoxymethyl-[(2R*,5R*)-5-(3-nitrophenyl)-
morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5R*)-5-(3-iodophenyl)morpholin-2-ylmethyl]-
phosphinic acid,
[(2R*,5R*)-5-(3-cyanophenyl)morpholin-2-ylmethyl]-
phenylmethylphosphinic acid,
5-acetylaminopentyl-[(2R*, 5R*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
phosphinic acid,
cyclohexylmethyl-[(2R*,5R*)-5-(3,4-dichlorophenyl)-
morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5R*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
phosphinic acid,
benzyl-[(2R*,5R*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-phosphinic acid,
[(2R*,5R*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
pyridin-2-ylmethylphosphinic acid,
[(2R*,5R*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
diethoxymethylphosphinic acid,
[(2R*,5R*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
4-methoxyphenylmethylphosphinic acid,
[(2R*,5R*)-5-benzylmorpholin-2-ylmethyl]-4-methoxyphenyl-
methylphosphinic acid,
4-[(3R*,6R*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6R*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoyl-
methyl]morpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6R*)-6-(benzylhydroxyphosphinoylmethyl)-
morpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6R*)-6-(butylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl]benzoic acid,

4-[(3R*,6R*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
cyclohexylmethyl-[(2R*,5R*)-5-(4-iodobenzyl)morpholin-2-ylmethyl]phosphinic acid,
[(2R*,5R*)-5-(4-iodobenzyl)morpholin-2-ylmethyl]-4-methoxyphenylmethylphosphinic acid,
cyclohexylmethyl-[(2R*,5R*)-5-[4-ethoxycarbonyl]phenylmethyl]morpholin-2-ylmethyl phosphinic acid,
4-[(3R*,6R*)-6-(butylhydroxyphosphinoylmethyl)-N-methylmorpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6R*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-N-benzyloxycarbonylmorpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6R*)-[(5-acetylaminopentyl)hydroxyphosphinoylmethyl]-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-(butylhydroxyphosphinoylmethyl)-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-(benzylhydroxyphosphinoylmethyl)-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6R*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-3-methylmorpholin-3-yl]benzoic acid,
5-acetylaminopentyl-[(2R*,5R*)-5-(6-oxo-1,6-dihydropyridin-3-yl)-morpholin-2-ylmethyl]phosphinic acid,
cyclohexylmethyl-[(2R*,5R*)-5-(6-oxo-1,6-dihydropyridin-3-yl)-morpholin-2-ylmethyl]-phosphinic acid,
butyl-[(2R*,5R*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
benzyl-[(2R*,5R*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
4-methoxyphenylmethyl-[(2R*,5R*)-5-(6-oxo-1,6-dihydropyridin-3-yl)-morpholin-2-ylmethyl]phosphinic acid,
diethoxymethyl-[(2R*,5R*)-5-(6-oxo-1,6-dihydropyridin-3-yl)-morpholin-2-ylmethyl]phosphinic acid,

cyclohexylmethyl-[(2R*,5R*)-5-(2-oxo-1,2-dihydropyridin-4-yl)-morpholin-2-ylmethyl]phosphinic acid,
5-acetylamino-pentyl-[(2R*,5R*)-5-(2-oxo-1,2-dihydropyridin-4-yl)-morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5R*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
diethoxymethyl-[(2R*,5R*)-5-(2-oxo-1,2-dihydropyridin-4-yl)-morpholin-2-ylmethyl]phosphinic acid,
benzyl-[(2R*,5R*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
4-methoxyphenylmethyl-[(2R*,5R*)-5-(2-oxo-1,2-dihydropyridin-4-yl)-morpholin-2-ylmethyl]phosphinic acid,

2-[(3R*,6R*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
2-[(3R*,6R*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
2-[(3R*,6R*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
2-[(3R*,6R*)-6-[(5-acetylamino-pentyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
2-[(3R*,6R*)-6-(butylhydroxyphosphinoylmethyl)morpholin-3-ylmethyl]benzoic acid,
2-[(3R*,6R*)-6-(benzylhydroxyphosphinoylmethyl)morpholin-3-ylmethyl]benzoic acid,

3-[(3R*,6R*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6R*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]morpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6R*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6R*)-6-[(5-acetylamino-pentyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6R*)-6-(butylhydroxyphosphinoylmethyl)morpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6R*)-6-(benzylhydroxyphosphinoylmethyl)morpholin-3-ylmethyl]benzoic acid,

benzyl-((2R*,5R*)-5-[4-((1,3,4)oxadiazol-2-yl)phenyl]morpholin-2-ylmethyl]phosphinic acid,
butyl-((2R*,5R*)-5-[4-(5-trifluoromethyl-[1,2,4]oxadiazol-3-yl)-phenyl]morpholin-2-ylmethyl]phosphinic acid,
1-(4-((3R*,6R*)-6-[(4-methoxybenzyl)hydroxyphosphinoylmethyl]-morpholin-3-yl)phenyl)-1H-[1,2,4]triazole-3-carboxylic acid,
((2R*,5R*)-5-[4-(3-amino-[1,2,4]oxadiazol-5-yl)phenyl]morpholin-2-ylmethyl)cyclohexylmethylphosphinic acid,
[(2R*,5R*)-5-[3-(3-amino-[1,2,4]oxadiazol-5-yl)phenyl]morpholin-2-ylmethyl)cyclohexylmethylphosphinic acid,
diethoxymethyl-((2R*,5R*)-5-[3-(1H-tetrazol-5-yl)phenyl]morpholin-2-ylmethyl]phosphinic acid,

3-((3R*,6S*)-6-[(5-acetylamino)pentyl]hydroxyphosphinoylmethyl)morpholin-3-yl]benzoic acid,
3-((3R*,6S*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-morpholin-3-yl]benzoic acid,
3-((3R*,6S*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]morpholin-3-yl]benzoic acid,
3-((3R*,6S*)-6-(butylhydroxyphosphinoylmethyl)-morpholin-3-yl]benzoic acid,
3-((3R*,6S*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-morpholin-3-yl]benzoic acid,
3-[(3R*,6S*)-6-(benzylhydroxyphosphinoylmethyl)morpholin-3-yl]benzoic acid,
diethoxymethyl-((2R*,5S*)-5-[(3-methoxycarbonyl)phenyl]-morpholin-2-ylmethyl]phosphinic acid,
cyclohexylmethyl-[(2R*,5S*)-5-phenylmorpholin-2-ylmethyl]-phosphinic acid,
diethoxymethyl-[(2R*,5S*)-5-(3-nitrophenyl)morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5S*)-5-(3-iodophenyl)morpholin-2-ylmethyl]-phosphinic acid,
[(2R*,5S*)-5-(3-cyanophenyl)morpholin-2-ylmethyl]phenylmethylphosphinic acid,
5-acetylamino)pentyl-[(2R*, 5S*)-5-(3,4-dichlorophenyl)-morpholin-2-ylmethyl]phosphinic acid,

cyclohexylmethyl-[(2R*,5S*)-5-(3,4-dichlorophenyl)-
morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5S*)-5-(3,4-dichlorophenyl)-
morpholin-2-ylmethyl]phosphinic acid,
benzyl-[(2R*,5S*)-5-(3,4-dichlorophenyl)-
morpholin-2-ylmethyl]phosphinic acid,
[(2R*,5S*)-5-(3,4-dichlorophenyl)morpholin-
2-ylmethyl]pyridin-2-ylmethylphosphinic acid,
[(2R*,5S*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
diethoxymethylphosphinic acid,
[(2R*,5S*)-5-(3,4-dichlorophenyl)morpholin-2-ylmethyl]-
4-methoxy-phenylmethylphosphinic acid,
[(2R*,5S*)-5-benzylmorpholin-2-ylmethyl]-4-methoxyphenyl-
methylphosphinic acid,
4-[(3R*,6S*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6S*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoyl-
methyl]morpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6S*)-6-(benzylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl]benzoic acid,
4-[(3R*,6S*)-6-(butylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl]benzoic acid,
4-[(3R*,6S*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl]benzoic acid,
cyclohexylmethyl-[(2R*,5S*)-5-(4-iodobenzyl)morpholin-
2-ylmethyl]phosphinic acid,
[(2R*,5S*)-5-(4-iodobenzyl)morpholin-2-ylmethyl]-
4-methoxyphenylmethylphosphinic acid,
cyclohexylmethyl-[(2R*,5S*)-5-[4-ethoxycarbonyl]phenyl-
methyl]morpholin-2-ylmethyl]phosphinic acid,
4-[(3R*,6S*)-6-(butylhydroxyphosphinoylmethyl)-
N-methylmorpholin-3-ylmethyl]benzoic acid,
4-[(3R*,6S*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-
N-benzylloxycarbonylmorpholin-3-ylmethyl]benzoic acid,
3-[(3R*,6S*)-6-[(5-acetylaminopentyl)hydroxyphosphinoyl-
methyl]-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6S*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-
3-methylmorpholin-3-yl]benzoic acid,

3-[(3R*,6S*)-6-(butylhydroxyphosphinoylmethyl)-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6S*)-6-(benzylhydroxyphosphinoylmethyl)-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6S*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]-3-methylmorpholin-3-yl]benzoic acid,
3-[(3R*,6S*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-3-methylmorpholin-3-yl]benzoic acid,

5-acetylaminopentyl-[(2R*,5S*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
cyclohexylmethyl-[(2R*,5S*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5S*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
benzyl-[(2R*,5S*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
4-methoxyphenylmethyl-[(2R*,5S*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,
diethoxymethyl-[(2R*,5S*)-5-(6-oxo-1,6-dihydropyridin-3-yl)morpholin-2-ylmethyl]phosphinic acid,

cyclohexylmethyl-[(2R*,5S*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
5-acetylaminopentyl-[(2R*,5S*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
butyl-[(2R*,5S*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
diethoxymethyl-[(2R*,5S*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
benzyl-[(2R*,5S*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,
4-methoxyphenylmethyl-[(2R*,5S*)-5-(2-oxo-1,2-dihydropyridin-4-yl)morpholin-2-ylmethyl]phosphinic acid,

2-[(3R*,6S*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-morpholin-3-ylmethyl]benzoic acid,
2-[(3R*,6S*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]-

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morpholin-3-ylmethyl} benzoic acid,
2-[(3R*,6S*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl} benzoic acid,
2-[(3R*,6S*)-6-[(5-acetylamino)pentyl]hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl} benzoic acid,
2-[(3R*,6S*)-6-(butylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl} benzoic acid,
2-[(3R*,6S*)-6-(benzylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl} benzoic acid,

3-[(3R*,6S*)-6-[(cyclohexylmethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl} benzoic acid,
3-[(3R*,6S*)-6-[(4-methoxyphenylmethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl} benzoic acid,
3-[(3R*,6S*)-6-[(diethoxymethyl)hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl} benzoic acid,
3-[(3R*,6S*)-6-[(5-acetylamino)pentyl]hydroxyphosphinoylmethyl]-
morpholin-3-ylmethyl} benzoic acid,
3-[(3R*,6S*)-6-(butylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl} benzoic acid,
3-[(3R*,6S*)-6-(benzylhydroxyphosphinoylmethyl)morpholin-
3-ylmethyl} benzoic acid,

benzyl-[(2R*,5S*)-5-[4-[(1,3,4)oxadiazol-2-yl]phenyl]morpholin-
2-ylmethyl} phosphinic acid,
butyl-[(2R*,5S*)-5-[4-(5-trifluoromethyl-1,2,4)oxadiazol-3-yl]-
phenyl]morpholin-2-ylmethyl} phosphinic acid,
1-[4-[(3R*,6S*)-6-[(4-methoxybenzyl)hydroxyphosphinoylmethyl]-
morpholin-3-yl]phenyl]-1H-[1,2,4]triazole-3-carboxylic acid,
[(2R*,5S*)-5-[4-(3-amino-1,2,4)oxadiazol-5-yl]phenyl]morpholin-
2-ylmethyl} cyclohexylmethylphosphinic acid,
[(2R*,5S*)-5-[3-(3-amino-1,2,4)oxadiazol-5-yl]phenyl]morpholin-
2-ylmethyl} cyclohexylmethylphosphinic acid,
diethoxymethyl-[(2R*,5S*)-5-[3-(1H-tetrazol-5-yl)phenyl]morpholin-
2-ylmethyl} phosphinic acid.

It has been found that the compounds of formula I and their pharmaceutically acceptable salts have valuable pharmacological properties. They exhibit an effective binding to the

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GABA_B receptor and have been found to be antagonists of GABA (γ -aminobutyric acid) at that receptor. With regard to the mechanism, antagonism at GABA_B receptors can increase the release of rapid stimulant amino acid transmitters, that is to say, glutamate and aspartate, and thus improve information processing in the brain. This is in keeping with the finding that the late post-synaptic inhibition potential in the hippocampus, which is attributed to a GABA_B mechanism, is broken down by the antagonists and thus permits a faster nerve impulse transmission sequence.

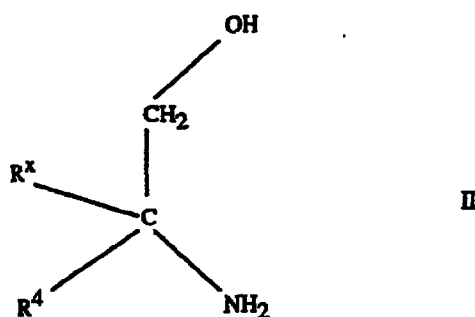
It has also been found that chronic treatment with anti-depressants and repeated electric shocks increase the number of GABA_B receptors in the cerebral cortex of rats. In accordance with receptor theories, chronic treatment with GABA_B antagonists should have the same effect. For this and other reasons, GABA_B antagonists can accordingly act as anti-depressants.

The GABA_B antagonists according to the invention interact at the GABA_B receptor with IC₅₀ values from 10⁻⁷ to 10⁻¹⁰M (mole/litre) on cerebral cortex membranes of rats. In contrast to GABA_B agonists, such as baclofen, they do not potentiate the stimulation by noradrenalin of adenylate cyclase on sections of the cerebral cortex of rats but act as antagonists of the baclofen action. The antagonists not only exhibit antagonism towards baclofen but also have an independent action as antagonists of endogenous GABA.

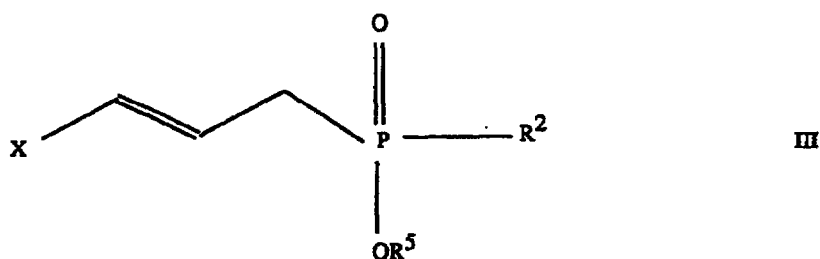
In view of their excellent GABA_B antagonistic properties, the compounds of the invention are suitable for use in the treatment or prevention of conditions characterised by stimulation of GABA_B receptors. Thus they are suitable for use as nootropics, antidepressants and anxiolytics, for example in the treatment of central nervous system disorders such as anxiety, depression, cerebral insufficiency, epilepsy of the "petit mal" type, i.e. absence epilepsy in children and adolescents, atypical absences such as the Lennox-Gastaut syndrome, in the treatment of conditions requiring enhancement of cognitive performance and as an antidote to baclofen.

Compounds of formula I where R^y is hydrogen may be prepared by reacting a compound of formula

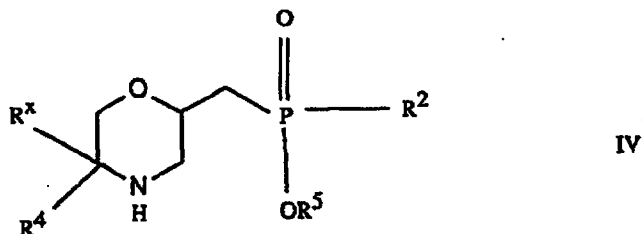
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where R^4 is R^1 as hereinbefore defined except that R^4 may not be substituted by carboxyl, and R^x is as hereinbefore defined except that it may not be substituted by carboxyl with a compound of formula



where R^2 is as hereinbefore defined, X is halogen, e.g. chlorine or bromine, and R^5 is C_1 to C_8 alkyl, e.g. n-hexyl, n-octyl, preferably C_1 to C_4 alkyl such as methyl, ethyl, isopropyl or isobutyl, especially ethyl, in the presence of a base, to give a compound of formula

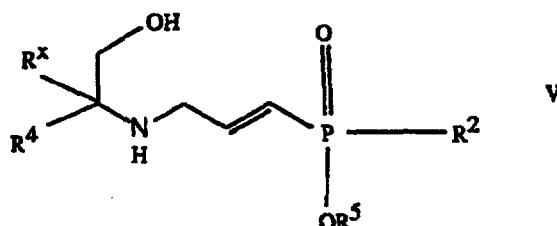


where R^4 and R^x are as defined in formula II, followed, where required, by one or more substitution reactions to change the nature of a substituent in R^4 and/or R^x and/or by hydrolysis of an ester substituent in R^4 and/or R^x to carboxyl and/or by conversion of the ester group $-OR^5$ to $-OH$.

By appropriate selection of the base and reaction conditions, the reaction of compounds of formulae II and III, which proceeds by monoalkylation of the amino group followed by cyclisation, may be effected in a one-step procedure. Preferably, to avoid complications resulting from dialkylation of the amino group, the reaction is carried out in two stages. In the first stage, a weak base, for example a hindered amine such as 1, 8-diazabicyclo[5.4.0]undec-7-ene (DBU) is added slowly to a mixture of the

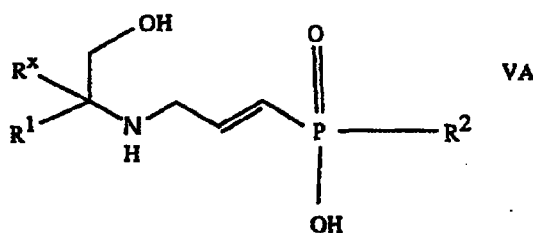
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compounds of formulae II and III in a solvent, preferably a hydrocarbon such as benzene, toluene or xylene, at a temperature of 70 to 110°C, to give a novel intermediate product of formula



where R^2 , R^4 , R^5 and R^x are as hereinbefore defined. This intermediate is then treated with a base under harsher conditions than those employed in its formation, for example with a similar base at a higher temperature or, preferably, with a stronger base such as an alkali metal hydride at a temperature from 10 to 50°C. The treatment of the intermediate with base may be carried out in a solvent, preferably a hydrocarbon such as toluene, benzene or xylene.

Intermediate compounds of formula V may also themselves be used as pharmaceuticals, for example in the treatment or prevention of a condition characterised by stimulation of a GABA_B receptor, particularly in de-esterified form, i.e. where R^5 as alkyl has been replaced by hydrogen and any carboxylic ester group in R^4 and/or R^x has been converted into a carboxyl group. Accordingly, the invention includes novel compounds of formula



where R^1 , R^2 and R^x are as hereinbefore defined, or salts or esters thereof.

Compounds of formula I or IV in which R^x and/or R^1 or R^4 respectively contains a cyano substituent on an aryl or heteroaryl ring may be prepared by reacting an alkali metal cyanide with a compound of formula I or IV where R^x and/or R^1 or R^4 respectively contains a halogen substituent on an aryl or heteroaryl ring, which compound may be prepared by diazotisation, followed by reaction with an alkali metal halide, of a compound of formula I or IV where R^x and/or R^1 or R^4 respectively contains an amino group on an aryl or heteroaryl ring, which compound may be prepared by reduction of a compound of formula I or IV in which R^x and/or R^1 or R^4 respectively contains a nitro group on an aryl

or heteroaryl ring. All of these reactions can be effected using known procedures.

Compounds of formula I or IV in which R^x and/or R¹ or R⁴ respectively contains an esterified carboxyl substituent can also be prepared from other compounds of formula I or IV respectively. For example, they may be prepared by reacting a compound of formula I or IV in which R^x and/or R¹ or R⁴ respectively contains a halogen substituent on an aryl or heteroaryl ring with carbon monoxide and an alcohol in the presence of a palladium complex as catalyst, using known procedures.

Compounds of formula I in which R^x and/or R¹ contains a carboxyl substituent may be prepared by hydrolysis of a compound of formula I or IV in which R^x and/or R¹ or R⁴ respectively contains an esterified carboxyl substituent using conventional hydrolysis procedures.

Where, in a compound of formula IV or V, R⁴ contains an esterified carboxyl group, this may be hydrolysed to a free carboxyl group using conventional methods. Where R⁴ in the compound of formula IV contains a nitro group on an aryl or heteroaryl ring, this group may be converted in turn to amino by reduction, to halo by diazotisation of amino followed by reaction with an alkali metal halide, to cyano by reaction of halo with an alkali metal cyanide and thence to carboxyl by hydrolysis of cyano, these reactions conveniently being carried out using known procedures.

The conversion of the ester group -OR⁵ in a compound of formula IV or V into -OH can be effected by treatment with a suitable basic or acidic agent, such as an alkali metal hydroxide, for example sodium hydroxide or lithium hydroxide, an alkali metal halide, especially an alkali metal bromide or iodide, such as lithium bromide or sodium iodide, thiourea, an alkali metal thiophenolate, such as sodium thiophenolate, or a protonic acid or a Lewis acid, such as a mineral acid, for example hydrochloric acid, or a tri-lower alkyl-halosilane, for example trimethylchlorosilane. The replacement reaction can be effected in the absence or presence of a solvent and, if necessary, with heating or with cooling in a closed vessel and/or under an inert gas atmosphere.

The conversion of -OR⁵ in a compound of formula IV or V into -OH can also be carried out by treatment with an acid under hydrolytic conditions, especially with a mineral acid, such as a hydrohalic acid, for example hydrochloric acid, which is used in dilute or concentrated aqueous form, or by treatment with an organic silyl halide, such as trimethylsilyl iodide or bromide, and, if necessary, by subsequent hydrolysis. The reaction is preferably carried out at elevated temperature, for example by maintaining the reaction

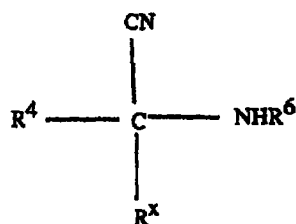
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mixture at reflux temperature, and, where appropriate, using an organic diluent in a closed vessel and/or under an inert gas atmosphere.

Compounds of formula II are in some instances commercially available, e.g. (R) - and (S) - phenyl glycinols. Compounds of formula II may be prepared by reduction of an aminocarboxylic acid of formula $R^4C(R^x)(NH_2)COOH$, where R^4 and R^x are as hereinbefore defined in formula II, by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex such as boron trifluoride diethyl etherate. This reaction may be carried out using known procedures. Novel compounds of formula II, where (i) R^4 is iodobenzyl, particularly 4-iodobenzyl, and R^x is hydrogen and (ii) R^4 is phenyl and R^x is isopropyl, may be prepared by this method.

The compounds of formula II where R^4 is substituted by nitro may be prepared from an aminocarboxylic acid of formula $R^4C(R^x)(NH_2)COOH$ where R^4 is otherwise unsubstituted by nitration to introduce a nitro group into R^4 , converting the amino group in the product into a protected amino group, for example by reaction with di-tert-butyl dicarbonate to form a tert-butylcarbamate group, esterifying the carboxyl group in the protected product for example by conversion into a methyl ester, then reducing the ester group to $-CH_2OH$ by treatment with an appropriate reducing agent such as an alkali metal borohydride and finally removing the amino-protecting group by treatment with acid to re-form a free amino group. These reactions may be carried out using known procedures or minor modifications thereof. The known compound of formula II where R^4 is nitrophenyl may be prepared by such a reaction sequence.

Compounds of formula II may also be prepared by a Strecker synthesis in which an aldehyde or ketone of formula $R^4C(=O)R^x$, where R^4 and R^x are as hereinbefore defined, is reacted with a compound of formula R^6NH_2 , where R^6 is hydrogen or an alkyl group of 1 to 8 carbon atoms optionally substituted by a C_6 to C_{10} aryl group which is unsubstituted or substituted, for example by hydroxy or C_1 to C_4 alkoxy, and an alkali metal cyanide to give a compound of formula

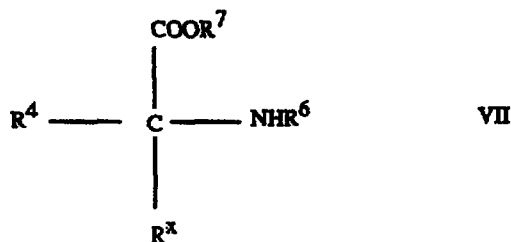


VI

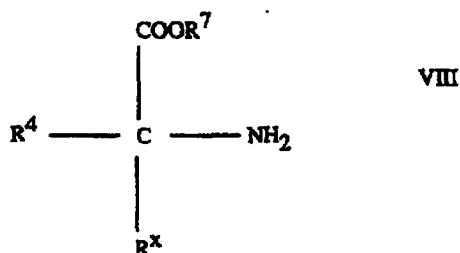
where R^4 , R^6 and R^x are as hereinbefore defined, reacting the compound of formula VI

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with an alcohol of formula R^7OH , where R^7 is an alkyl group of 1 to 10 carbon atoms, e.g. n-hexyl, 2-ethylhexyl, n-octyl or decyl, preferably C_1 to C_4 alkyl such as methyl, ethyl, isopropyl or n-butyl, especially methyl or ethyl, in the presence of an acid to form a compound of formula



where R^4 , R^6 , R^7 and R^x are as hereinbefore defined, removing R^6 , when this is other than hydrogen, from the compound of formula VII using, for example, known procedures to give a compound of formula



where R^4 , R^7 and R^x are as hereinbefore defined, for example, where R^6 is an optionally substituted benzyl group, by catalytic hydrogenation in the presence of an organic acid, e.g. acetic acid, to give a compound of formula VIII in the form of a salt thereof with the organic acid, reacting the compound of formula VIII with an amino-protecting agent such as tert-butyl dicarbonate to convert the amino group into a protected amino group, reducing the ester group $-\text{COOR}^7$ in the protected compound to $-\text{CH}_2\text{OH}$ by reaction with an appropriate reducing agent such as an alkali metal borohydride, and finally removing the protecting group to form a free amino group. This sequence of reactions may be carried out using known procedures, or minor modifications thereof. Where R^4 is substituted by a carboxylic ester group, the protected amino group formed should be a group such as a tert-butyl carbamate group which will permit the ester group $-\text{COOR}^7$ to be reduced to $-\text{CH}_2\text{OH}$ while leaving the ester group in R^4 and then be removable by a reaction, for example in a non-aqueous medium, which leaves the ester group in R^4 .

In a modification of the Strecker synthesis hereinbefore described, the compound of formula VI may be subjected to acid hydrolysis, for example using conventional procedures, to convert the indicated cyano group to carboxyl and the resulting

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aminocarboxylic acid may be reduced to a compound of formula II by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex such as boron trifluoride diethyl etherate, for instance using known procedures.

Compounds of formula II, VI, VII or VIII in which R^4 is 3-methoxycarbonylphenyl, which may be prepared from an aldehyde or ketone of formula $R^4C(=O)R^x$ by the reaction sequence as hereinbefore described, are believed to be novel per se. Compounds of formula II or VIII where R^4 is 3,4-dichlorophenyl and R^7 is C_1 - C_{10} alkyl are also believed to be novel.

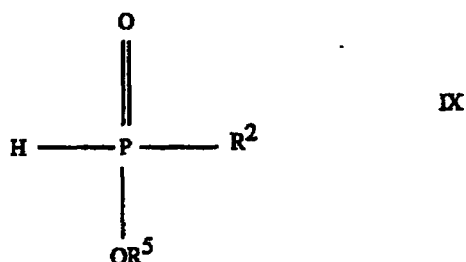
Compounds of formula II in which R^4 is a monovalent aromatic group as hereinbefore defined and R^x is an unsubstituted or substituted hydrocarbyl group are believed to be novel, with the exception of compounds of formula II in which R^4 is phenyl and R^x is methyl, chloromethyl, ethyl, $-(CH_2)_3SCH_3$, allyl or methylol, compounds of formula II in which R^x is aminomethyl and R^4 is phenyl, p-hydroxyphenyl or p-methoxyphenyl, compounds of formula II in which R^x is methylol and R^4 is 4-decylphenyl or 5-[(7-chloro-4-quinoliny)amino]-2-hydroxyphenyl, a compound of formula II in which R^4 is 4-methoxyphenyl and R^x is ethyl, and a compound of formula II in which R^4 is 2,4-dichlorophenyl and R^x is N-triazolymethyl.

Compounds of formula II in which R^4 is a monovalent araliphatic group as hereinbefore defined and R^x is an unsubstituted or substituted hydrocarbyl group as hereinbefore defined other than methylol are believed to be novel, with the exception of compounds of formula II where R^x is methyl and R^4 is benzyl, 4-chlorobenzyl, 3,4-dichlorobenzyl, 3,4-dimethoxybenzyl, 2-phenylethyl, 1,3-benzodioxol-5-methyl, 3-phenyl-1-aminopropyl, α -hydroxybenzyl, α -hydroxy- α -methylbenzyl, or α -hydroxy- α -methyl-4-nitrobenzyl, and with the exception of compounds of formula II where R^4 is benzyl and R^x is allyl or $-CH_2CH_2SCH_3$.

Compounds of formula II in which R^4 is iodobenzyl, particularly 4-iodobenzyl, and R^x is hydrogen or an unsubstituted or substituted hydrocarbyl group, as hereinbefore defined are also believed to be novel.

Compounds of formula III which, with the exception of the compound where R^2 is methyl and R^5 is ethyl, are believed to be novel, particularly those where R^2 is cycloalkylalkyl such as cyclohexylmethyl, may be prepared by reacting a compound of formula

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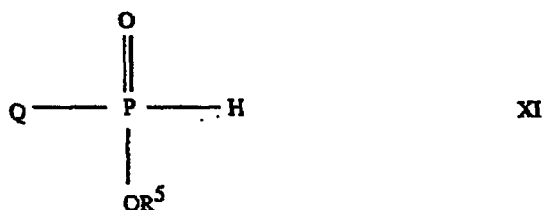


with a compound of formula



where R^2 , R^5 and X are as hereinbefore defined, in the presence of a silylating agent such as a bis(trialkylsilyl) derivative of an amide, which agent undergoes reaction with the compound of formula IX to form a P(III) silyl compound which then reacts with the compound of formula X. The reaction may be carried out at a temperature from 0 to 50°C ; it is preferably carried out in a solvent, for example a hydrocarbon such as toluene or a halohydrocarbon such as dichloromethane.

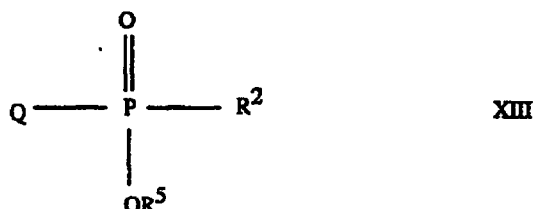
Esters of formula IX may be prepared by reacting a protected phosphinate ester of formula



where R^5 is as hereinbefore defined and Q is a P-H-protecting group, with a compound of formula



where R^2 is as hereinbefore defined and Z is a leaving moiety, to give a compound of formula



and then replacing the protecting group Q in the compound of formula XIII by hydrogen.

The leaving moiety Z may be, for example, a halogen atom or an organic sulphonate group. Preferably Z is chlorine, bromine, iodine, or a methanesulphonate, trifluoromethanesulphonate or p-toluenesulphonate group. The reaction between the compounds of formulae XI and XII and the deprotection reaction on the compound of formula XIII may be carried out using known procedures, for example as described in EP 0569333.

Protected phosphinate esters of formula XI may be prepared by known methods, for example as described in US 4 933 478. Compounds of formula XII are either commercially available or may be prepared by known procedures.

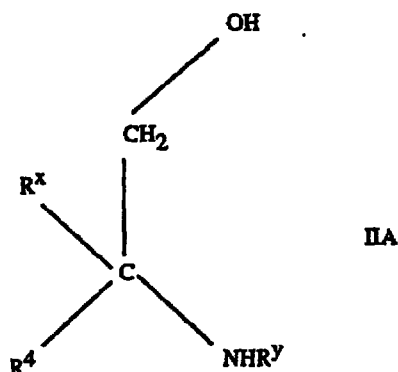
Compounds of formula X are dihaloalkenes which are either commercially available or may be prepared using known methods.

Compounds of formula I where R^Y is R^Y_a may be prepared by reacting a compound of formula I where R^Y is hydrogen with a compound of formula R^Y_aZ , where R^Y_a and Z are as hereinbefore defined, or by reductive alkylation using an aldehyde of formula R^Y_bCHO , where R^Y_b is hydrogen or R^Y_a as hereinbefore defined, and a reducing agent which reduces imines to amines, for example sodium cyanoborohydride. Such reactions may be carried out using conventional procedures.

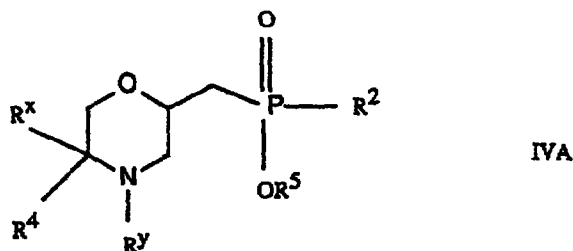
Compounds of formula I where R^Y is a NH-protecting group may be prepared by reacting a compound of formula I where R^Y is hydrogen with a reagent known to introduce the desired protecting group. For example, where the protecting group is an acyl group, the compound of formula I where R^Y is hydrogen may be reacted with an acyl halide or carboxylic acid anhydride such as acetyl chloride, acetic anhydride or benzoyl chloride, for instance using known procedures. Where the protecting group is an alkoxycarbonyl or aralkoxycarbonyl group, the compound of formula I where R^Y is hydrogen may be reacted with an alkoxycarbonyl or aralkoxycarbonyl halide or an alkyl or aralkyl dicarbonate such as benzyl chloroformate or di-tert-butyl dicarbonate, for example using known procedures.

In general, compounds of formula I where R^Y is R^Y_a or a NH-protecting group may also be prepared by the method hereinbefore described for the preparation of compounds of formula I where R^Y is hydrogen, in which method the compound of formula II is replaced by a compound of formula

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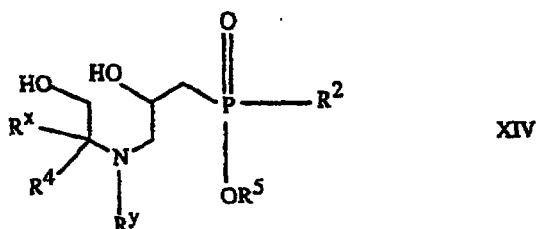


where R^4 and R^x are as hereinbefore defined in formula II and R^y is R^y_a or a NH-protecting group, the reaction of the compound of formula II A with the compound of formula III in the presence of a base giving directly a compound of formula



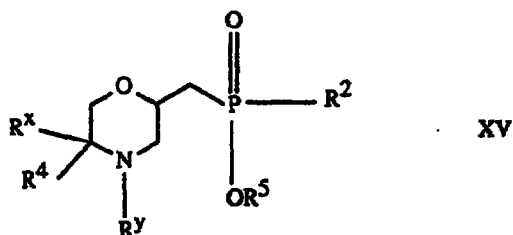
where R^4 and R^x are as defined in formula II, R^2 and R^5 are as hereinbefore defined and R^y is R^y_a as hereinbefore defined or a NH-protecting group. This reaction may be carried out in a solvent, usually a hydrocarbon such as benzene, toluene or xylene, and is generally carried out under harsher conditions than those used for the reaction of compounds of formulae II and III, for example using sodium hydride as the base and at a temperature of 10°C to 70°C. This reaction may be followed, where required, by one or more substitution reactions to change the nature of a substituent in R^4 and/or R^x and/or by hydrolysis of an ester substituent in R^4 and/or R^x to carboxyl and/or by conversion of the ester group $-OR^5$ to $-OH$.

Compounds of formula I may also be prepared by reacting a compound of formula



to convert the indicated primary hydroxyl group into a leaving moiety Z as hereinbefore

defined, thereby effecting cyclisation to give a compound of formula



where R^2 , R^4 , R^5 , R^x and R^y are as hereinbefore defined followed, where required, by replacement of R^y as an NH-protecting group by hydrogen and/or by one or more substitution reactions to change the nature of a substituent in R^4 and/or R^x and/or by hydrolysis of an ester substituent in R^4 and/or R^x to carboxyl and/or by conversion of the ester group $-OR^5$ to $-OH$.

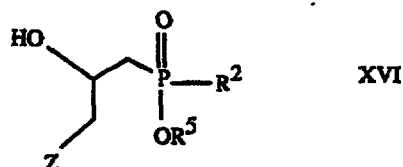
The conversion of the primary hydroxyl group in the compound of formula XIV into Z may be carried out using known procedures. For example, where Z is an iodine atom, the conversion may be effected by reacting the compound of formula XIV with triphenylphosphine, imidazole and iodine in a solvent such as acetonitrile or tetrahydrofuran at 0°C to 50°C , and where Z is a trifluoromethanesulphonate group, the conversion may be effected by reacting the compound of formula XIV with trifluoromethanesulphonic anhydride in pyridine at -100°C to 50°C .

The replacement of R^y as an NH-protecting group by hydrogen may be carried out using known procedures for removal of the NH-protecting group. For example, where R^y is an acyl group such as acetyl or benzoyl, replacement by hydrogen may be effected by reaction with aqueous hydrochloric acid, while where R^y is trifluoroacetyl, replacement by hydrogen may be effected by reaction with aqueous potassium carbonate.

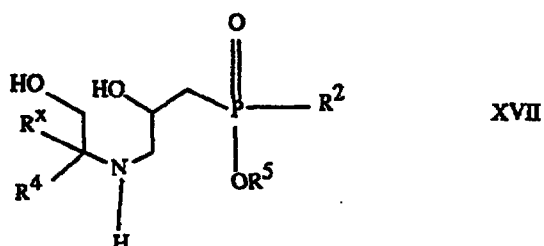
The other optional subsequent reactions of compounds of formula XV may be carried out as hereinbefore described for corresponding reactions of compounds of formula IV.

Compounds of formula XIV, which are themselves believed to be novel, may be prepared by reacting a compound of formula II with a compound of formula

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where R^2 , R^5 and Z are as hereinbefore defined, in the presence of a hindered base, to give a compound of formula

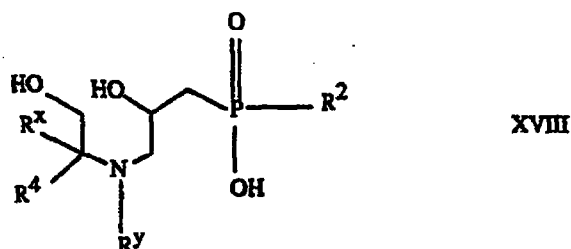


where R^2 , R^4 , R^5 and R^x are as hereinbefore defined, and replacing the indicated hydrogen attached to nitrogen by a NH-protecting group R^y as hereinbefore defined, for example using known procedures such as those hereinbefore described. The reaction between the compounds of formula II and XVI may be carried out, for example, at a temperature of 20 to 100°C, preferably in an organic solvent such as an alcohol, especially ethanol. The hindered base may be, for example, a diazabicyclo compound such as 1,5-diazabicyclo [4.3.0]non-5-ene or 1,8-diazabicyclo [5.4.0]undec-7-ene or preferably, a tertiary amine such as dicyclohexyl(ethyl)amine or, especially, diisopropylethylamine.

Compounds of formula XVI may be prepared using the procedures described in J. Med. Chem, 1995, 38, 3313.

Compounds of formula XIV or XVII may themselves be used as pharmaceuticals, for example in the treatment or prevention of a condition characterised by stimulation of a $GABA_B$ receptor, particularly in de-esterified form, i.e. where R^5 as alkyl has been replaced by hydrogen and any carboxylic ester group in R^4 and/or R^x has been converted into a carboxyl group, for example using known procedures. Accordingly, the invention includes novel compounds of formula

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where R^1 , R^2 , R^x and R^y are as hereinbefore defined, or salts or esters thereof.

Compounds of the invention obtained as salts can be converted into the free compounds in a manner known per se, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned hereinbefore, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned hereinbefore.

Salts of the invention can be converted into different salts of the invention in a manner known per se; for example, acid addition salts can be converted by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of another acid in a suitable solvent in which an inorganic salt being formed is insoluble and is thus excluded from the reaction equilibrium, and base salts can be converted by freeing the free acid and converting into a salt again.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

Owing to the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter the free compounds and their salts are also optionally to be understood as being the corresponding salts and free compounds, respectively, where appropriate and where the context so allows.

For compounds of formula I, and intermediates in the preparation thereof, diastereoisomeric mixtures and mixtures of racemates can be separated in known manner into the pure diastereoisomers and racemates, respectively, on the basis of the physico-chemical differences between their constituents, for example by chromatography and/or fractional crystallisation.

Resulting racemates can also be resolved into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of micro-

organisms or, by reaction of the resulting diastereoisomeric mixture or racemate with an optically active auxiliary compound, for example according to the acidic, basic or functionally modifiable groups contained in compounds of formula I, with an optically active acid, base or an optically active alcohol, into mixtures of diastereoisomeric salts or functional derivatives, such as esters, separation of the same into the diastereoisomers from which the desired enantiomer can be freed in customary manner. Suitable bases, acids and alcohols for the purpose are, for example, optically active alkaloid bases, such as strychnine, cinchonine or brucine, or D- or L-(1-phenyl)ethylamine, 3-pipecoline, ephedrine, amphetamine and similar bases that can be obtained by synthesis, optically active carboxylic or sulfonic acids, such as quinic acid or D- or L-tartaric acid, D- or L-di-o-toluoyletartaric acid, D- or L-malic acid, D- or L-mandelic acid, or D- or L-camphor-sulfonic acid, or optically active alcohols, such as borneol or D- or L-(1-phenyl)ethanol.

Compounds of formula I, VA or XVIII may be isotopically labelled, particularly with ^{11}C , ^{14}C , ^2H , ^3H or ^{125}I , for use in diagnostics.

The compounds of formula I, VA or XVIII may be used, for example, in the form of pharmaceutical compositions that comprise a therapeutically effective amount of the active ingredient, where appropriate together with pharmaceutically acceptable carriers that are suitable for enteral, for example oral, or parenteral administration, which carriers may be solid or liquid and organic or inorganic. For example, tablets or gelatin capsules are used that contain the active ingredient together with diluents, for example lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets may also contain binders, for example magnesium aluminium silicate, starches, such as corn, wheat, rice or arrowroot starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, for example sodium alginate, and/or effervescent mixtures, or absorbents, colourings, flavourings and sweeteners. The compounds of formula I can also be used in the form of parenterally administrable compositions or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, for example in the case of lyophilised compositions that comprise the active ingredient on its own or together with a carrier, for example mannitol, can be prepared before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical compositions which, if desired, may comprise other pharmacologically active substances, may be prepared in a

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manner known per se, for example by conventional mixing, granulating, confectioning, dissolving or lyophilising processes, and may comprise approximately from 0.1 % to 100 %, especially from approximately 1 % to approximately 50 %, and, in the case of lyophilisates, up to approximately 100 %, active ingredient.

The invention relates also to the use of the compounds of formula I, VA or XVIII, or salts or esters thereof, preferably in the form of pharmaceutical compositions.

The dose may depend on various factors, such as the mode of administration, species, age and/or individual condition. The doses to be administered daily may, in the case of oral administration, be from approximately 1 to approximately 50 mg/kg, especially from 5 to approximately 25 mg/kg, and, in the case of warm-blooded animals having a body weight of approximately 70 kg, preferably from approximately 70 mg to approximately 3500 mg, especially from approximately 350 to approximately 1750 mg, expediently divided into from 2 to 6, for example 3 or 4, single doses.

The invention accordingly includes a method of treating or preventing a condition in warm-blooded mammals, particularly humans, characterised by stimulation of a GABA_B receptor which comprises administering to the warm-blooded mammal a compound of formula I, VA or XVIII, or a pharmaceutically acceptable salt or ester thereof.

The invention is illustrated by the following Examples.

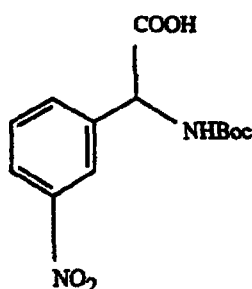
Compound D used in the Examples is prepared as follows. In subsequent formulae, Boc denotes tert-butoxycarbonyl.

Phenyl glycine (42g) is dissolved in concentrated sulphuric acid (210ml) and the solution is cooled to 0°C. Fuming nitric acid (15.5ml) is added dropwise to the cooled solution over 30 minutes and the mixture is stirred for a further 30 minutes at 0°C, then 18 hours at room temperature. The solution obtained is poured over 1 litre of ice and carefully adjusted to pH7 by adding approximately 875ml of 10M aqueous sodium hydroxide whilst keeping the temperature of the solution below 20°C. The resulting mixture is stirred for 3 hours at room temperature and the precipitate obtained is filtered off. The precipitate is washed three times with water and recrystallized from 1 litre of water to afford 3-nitrophenylglycine, mpt 165-6°C.

3-Nitrophenyl glycine (5g) is added to a mixture of methanol (200ml) and triethylamine (20ml) and the mixture is stirred vigorously for 10 minutes at room temperature.

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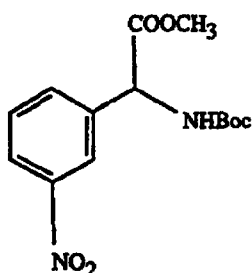
Di-tert-butyl dicarbonate (11.13g) is added and the reaction mixture is heated under reflux for 2 hours. The solution obtained is cooled to room temperature and then concentrated to dryness under reduced pressure to afford a dark orange residue. The residue is purified by flash chromatography [silica gel, CH₂Cl₂ (95%), CH₃OH (2.5%), CH₃COOH (2.5%)] to afford Compound A as an orange foam.



Compound A

¹³Cnmr (100MHz; CDCl₃): δ (ppm) 27.9 (q), 58.2(d), 82.6(s), 122.4(d), 123.0(d), 129.5(d), 133.0(d), 140.4(s), 148.2(s), 156.8(s), 172.1(s).

A solution of Compound A (14.54g) and p-toluenesulphonic acid (1.87g) in methanol (200ml) is stirred at room temperature for 24 hours. Ethyl acetate and saturated aqueous NaHCO₃ are added, the organic phase is separated, dried over MgSO₄ and filtered, and the filtrate is evaporated under reduced pressure. The product obtained is purified by flash chromatography [silica gel, hexane:ethyl acetate (2:1)] to yield Compound B as a yellow solid, mpt = 86°C,

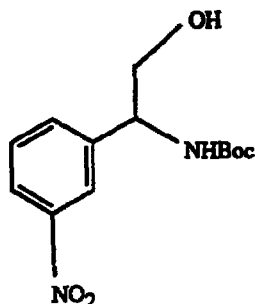


Compound B

Analysis: calculated for C₁₄H₁₈N₂O₆; C, 54.19; H, 5.85; N, 9.03%.
Found, C, 54.32; H, 6.00; N, 8.93%.

A solution of sodium borohydride (2.33g) in absolute ethanol (30ml) is added dropwise to a stirred solution of Compound B (9.57g) in absolute ethanol (120ml) at room temperature. The reaction mixture is stirred for 18 hours at room temperature, after which excess sodium borohydride is destroyed by adding glacial acetic acid. The solvents are removed under reduced pressure and the residue is triturated with ethyl acetate (3 x 50ml). The combined ethyl acetate phases are evaporated to dryness and the residue is then

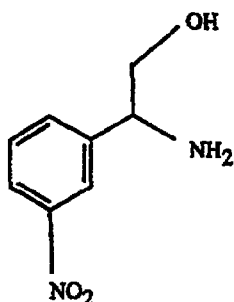
co-evaporated with toluene (3 x 50ml). The resultant residue is purified by flash chromatography [silica gel, ethyl acetate: hexane (1:1)] to afford Compound C, m.p. 100°C.



Compound C

Analysis: calculated for $C_{13}H_{18}N_2O_5$; C, 55.31; H, 6.43; N, 9.92%. Found, C, 55.25; H, 6.63; N, 9.76%.

Trifluoroacetic acid (60ml) is added to a flask containing Compound C (5g) cooled to 0°C. The resulting solution is stirred for 20 minutes at 0°C, then allowed to warm to room temperature and stirred for a further 3 hours. The solvent is removed under reduced pressure and the residue is purified by ion exchange chromatography (Dowex 50WX 2-200 (H⁺ form) resin, elutant 3% aqueous ammonium hydroxide solution) to afford Compound D as a pale brown foam.



Compound D

Analysis: calculated for $C_8H_{10}N_2O_3$; C, 52.74; H, 5.53; N, 15.38%.
Found, C, 53.12; H, 5.75; N, 15.07%.

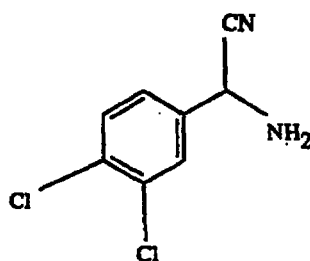
¹³C nmr (100MHz; MeOH): δ (ppm) 58.0(d), 68.2(t), 122.8(d), 123.1(d), 130.4(d), 134.5(d), 146.3(s), 149.6(s).

Compound G used in the Examples is prepared as follows:

Sodium cyanide (4.9g, 0.1M) and ammonium chloride (5.88g, 0.1M) are stirred in water (20ml) at room temperature. A solution of 3,4-dichlorobenzaldehyde (17.5g, 0.1M) in methanol (30ml) is added dropwise over one minute. Aqueous ammonia solution (10ml,

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specific gravity 0.88) is added and the reaction is stirred for 3 hours at room temperature. Ethyl acetate is added and the organic phase separated, dried over magnesium sulphate, filtered and evaporated. The residue is dissolved in ethyl acetate and repeatedly extracted with 2N hydrochloric acid. The combined aqueous layers are adjusted to pH9 using aqueous ammonia solution and re-extracted repeatedly with ethyl acetate. The combined organic layers are dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford an orange oil which is purified by flash chromatography on silica using hexane:ethyl acetate (1:1) as eluant to afford Compound G. m.p. 64-65°C



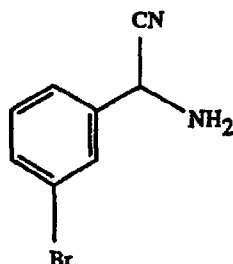
Compound G

Found: C, 47.81; H, 2.99; N, 13.92%.

$C_8H_6Cl_2N_2$ requires C, 47.79; H, 3.01; N, 13.93%.

Compound J used in the Examples is prepared as follows:

Using substantially the same procedure as described for the preparation of compound G, a mixture of 3-bromo-benzaldehyde (18.5g, 0.1M), sodium cyanide (4.9g, 0.1M), ammonium chloride (5.9g, 0.11M) and aqueous ammonia solution (10ml, specific gravity 0.88) in methanol/water (30ml/20ml) is reacted for 24 hours at room temperature to afford Compound H as a red/brown waxy solid.



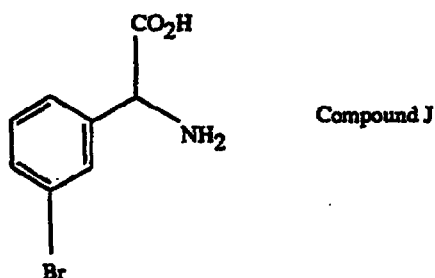
Compound H

^{13}C nmr (100 MHz; $CDCl_3$): δ (ppm) 46.6 (d), 120.4 (S), 122.9 (S), 125.2 (d), 129.7 (d), 130.5 (d), 132.1(d), 138.3 (S).

A mixture of Compound H (10.5g, 49.8mM) in 6M hydrochloric acid (200ml) is heated under reflux for 68 hours. The supernatant is decanted off, cooled to room temperature

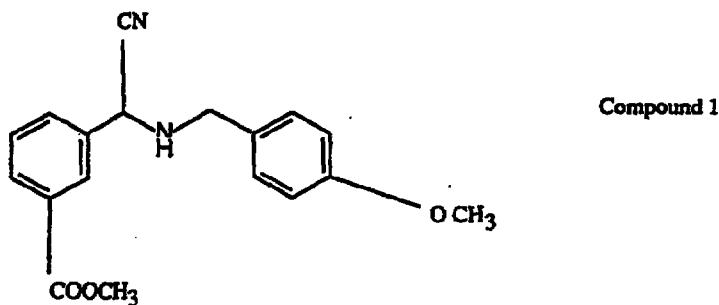
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and adjusted to pH7 using aqueous ammonia solution. The precipitated product is collected by filtration, washed with water and dried. Trituration with ethyl acetate followed by drying affords Compound J as a brown solid. m.p. 201-204°C (dec).



^{13}C nmr (100MHz; CD_3OD): δ (ppm) 56.9 (d), 124.0 (S), 128.1 (d), 132.2 (2 x d), 134.0 (d), 136.0 (S), 170.1 (S).

Example 1



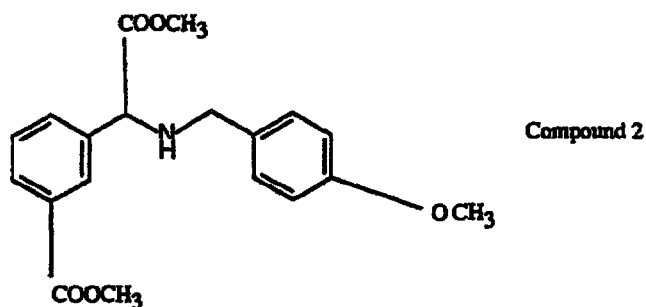
3-methoxycarbonylbenzaldehyde (1.6g, 10.0mM) in methanol (10ml) is added to a solution of 4-methoxybenzylamine hydrochloride (1.7g, 10.0mM) and sodium cyanide (0.490g, 10.0mM) in water (10ml) and the mixture is stirred for 3 hours at room temperature. Water (20ml) is added and the mixture extracted with dichloromethane. The organic phase is washed with brine, dried (MgSO_4) and evaporated to dryness to afford an oil which is purified by silica gel chromatography using 20% ethyl acetate in hexane as eluant to afford Compound 1.

Analysis: calculated for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$; C, 69.66; H, 5.85; N, 9.03%.

Found, C, 69.40; H, 5.94; N, 8.73%.

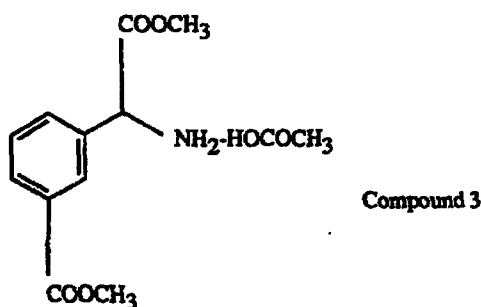
^{13}C nmr (100MHz; CDCl_3): δ (ppm) 50.6(t), 52.2(q), 52.8(d), 55.2(q), 114.0(d), 118.3(s), 128.3(d), 129.0(d), 129.6(d), 129.8(s), 130.1(d), 130.9(s), 131.6(d), 135.3(s), 159.1(s), 166.2(s).

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Example 2

A solution of Compound 1 (7g, 22.56mM) in methanol (75ml) is cooled to 0°C and saturated with hydrogen chloride gas. Once saturated, the reaction mixture is stored at -20°C for 4 days and then concentrated under reduced pressure to a quarter of its original volume. Ethyl acetate and saturated aqueous sodium bicarbonate solution are added and the organic phase is separated, washed with water and brine, dried over magnesium sulphate, filtered and evaporated to give an oil. Purification by flash chromatography on silica using hexane: ethyl acetate (1:1) as eluant affords Compound 2 as an oil.

^{31}C nmr (100MHz; CDCl_3): δ (ppm) 50.7 (t), 52.1(q), 52.3(q), 55.2(q), 63.8(d), 113.7(d), 128.69(d), 128.72(d), 129.2(d), 129.4(d), 130.5(s), 131.2(s), 132.0(d), 138.5(s), 158.7(s), 166.7(s), 172.9(s).

Example 3

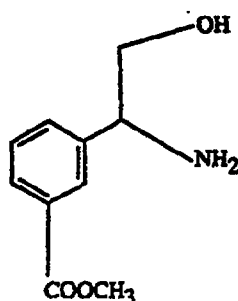
A mixture of Compound 2 (8.0g, 23.3mM) and palladium black (2.0g) in glacial acetic acid (50ml) and methanol (50ml) is hydrogenated for 4 hours at room temperature. After checking completion of the reaction by thin layer chromatography (tlc), the mixture is filtered and the filtrate evaporated under reduced pressure. The residue is co-evaporated three times with toluene (3 x 20ml) and then purified by flash chromatography on silica using ethyl acetate as eluant to afford Compound 3 as a pale yellow oil.

Analysis: calculated for $\text{C}_{13}\text{H}_{17}\text{NO}_6$; C, 55.12; H, 6.05; N, 4.94%.

Found; C, 55.46; H, 5.99; N, 5.05%

^{13}C nmr (100MHz; CDCl_3): δ (ppm) 20.8 (q), 52.1(q), 52.5(q), 57.9(d), 127.9(d), 128.9(d), 129.3(d), 130.7(s), 131.4(d), 139.9(s), 166.6(s), 173.5(s), 175.9(s).

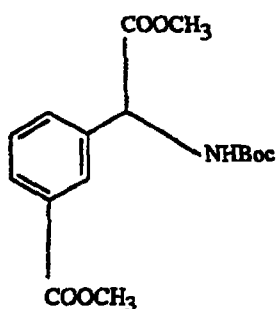
Example 4



Compound 4

Step 1

A solution of di-tert-butyl-dicarbonate (4.5g, 20.83mM) in methanol (10ml) is added to a vigorously stirred solution of Compound 3 (3.1g, 10.9mM) and triethylamine (10ml, 71.75mM) in methanol (40ml). The mixture is then heated at 60°C for 30 minutes, cooled to room temperature and evaporated under reduced pressure. The residue is purified by flash chromatography on silica using hexane: ethyl acetate (4:1) as eluant to afford Compound E m.p. 88-90°C.



Compound E

Analysis: calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_6$: C, 59.43; H, 6.55; N, 4.33%.

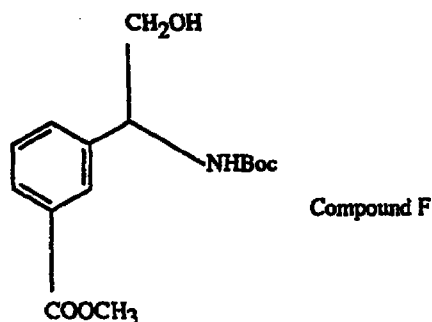
Found, C, 59.54; H, 6.72; N, 4.32%.

Step 2

Sodium borohydride (800mg, 21.2mM) is added in eight equal portions, at 30 minute intervals, to a stirred solution of Compound E (3.2g, 9.9mM) in methanol (50ml). On completion of the reaction (tlc), the remaining sodium borohydride is destroyed with glacial acetic acid and the reaction mixture evaporated under reduced pressure to afford an

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oily solid. This residue is co-evaporated with toluene (2 x 20ml) and triturated with ethyl acetate. Evaporation of the ethyl acetate extracts under reduced pressure affords a colourless oil which is purified by flash chromatography on silica using hexane: ethyl acetate (1:1) as eluant to afford Compound F, m.p. 102-104°C.



Analysis: calculated for $C_{15}H_{21}NO_5$; C, 61.01; H, 7.17; N, 4.74%.

Found; C, 61.11; H, 7.23; N, 4.70%.

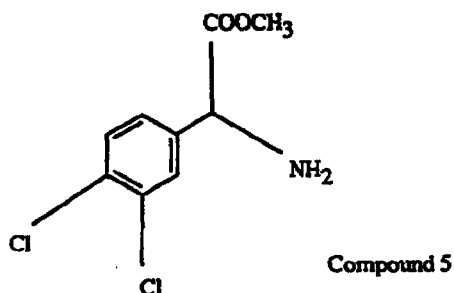
Step 3

Trifluoroacetic acid (3.0ml, 39.17mM) is added to a stirred solution of Compound F (2.2g, 7.45mM) in dry dichloromethane (25ml) under argon at room temperature. The mixture is stirred for 5 hours at room temperature. On completion of the reaction (tlc), the mixture is evaporated under reduced pressure without heating and the residue is co-evaporated with chloroform (2 x 20ml). After drying under high vacuum, the residue is purified by ion exchange chromatography on Amberlyst A21 resin using water as eluant to afford Compound 4 as a colourless oil.

Found: C, 58.98; H, 6.73; N, 6.53%.

$C_{10}H_{13}NO_3 \cdot \frac{1}{2}H_2O$ requires C, 58.8; H, 6.91; N, 6.86%.

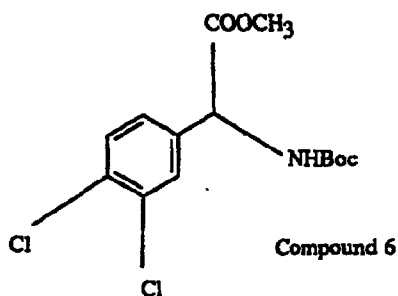
^{13}C nmr (100 MHz; CD_3OD): δ (ppm) 52.6(q), 58.1(d), 67.4(t), 129.1(d), 129.8(2 x d), 131.6(s), 132.9(d), 142.4(s), 168.2(s).

Example 5

A solution of Compound G (1.4g, 5.98mM) in methanol (20ml) is cooled to 0°C and saturated with hydrogen chloride gas. Once saturated, the reaction mixture is stored at -20°C for 2 days. The solvent is removed under reduced pressure and the residue co-evaporated with methanol (3 x 20ml). The residue is suspended in ethyl acetate and the organic phase is washed successively with saturated aqueous sodium bicarbonate solution, water and brine. The organic layers are dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford an oil which is purified by flash chromatography on silica using hexane: ethyl acetate (1:1) as eluant to afford Compound 5.

Found: C, 46.12; H, 3.85; N, 6.09%. $C_9H_9Cl_2NO$ requires C, 46.18; H, 3.88; N, 5.98%.

^{13}C nmr (100MHz; $CDCl_3$): δ (ppm) 52.5(q), 57.5(d), 126.2(d), 128.9(d), 130.8(d), 131.9(s), 132.6(s), 140.2(s), 173.4(s).

Example 6

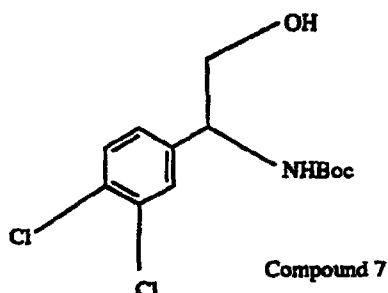
Compound 5 (6.0g, 25.63mM), di-tert-butyl dicarbonate (11.19g, 51.26mM) and

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triethylamine (20ml, 143.50mM) are reacted in methanol (200ml) using substantially the same procedure as described for the preparation of Compound E in Example 4. The crude product is purified by chromatography on silica using 20% ethyl acetate in hexane as eluant to afford Compound 6 as a yellow solid. m.p. 90-92°C.

Found: C, 50.55; H, 5.16; N, 4.08%. $C_{14}H_{17}Cl_2NO_4$ requires C, 50.32; H, 5.13; N, 4.19%.

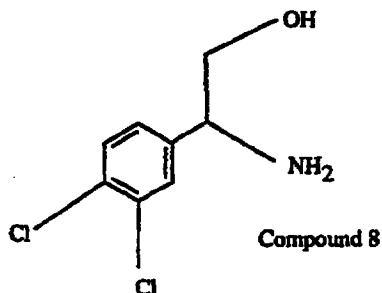
Example 7



To a solution of Compound 6 (6.78g, 20.28mM) in absolute ethanol (100ml) is dropwise added a solution of sodium borohydride (1.15g, 30.43mM) in absolute ethanol (30ml). The reaction is stirred for 6 hours at room temperature and then left to stand for 48 hours at room temperature. The solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica using hexane: ethyl acetate (1:1) as eluant to afford Compound 7 as a white solid. m.p. 113-114°C.

Found: C, 51.21; H, 5.69; N, 4.43%. $C_{13}H_{17}Cl_2NO_3$ requires C, 51.00; H, 5.60; N, 4.57%.

Example 8



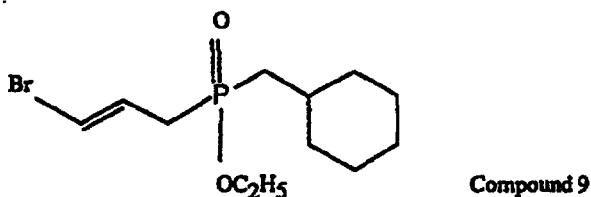
Compound 7 (4.7, 15.35mM) is reacted with trifluoroacetic acid (75ml) using substantially

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the same procedure as described for the preparation of Compound D from Compound C. The crude product is purified by ion exchange chromatography on Dowex 50WX 2-200 (H^+ form) resin using methanol: water: aqueous ammonia solution (50%: 47%: 3%) as eluant to afford Compound 8 as a cream coloured solid. m.p. 65-67°C.

Found: C, 46.61; H, 4.37; N, 6.59%. $C_8H_9Cl_2NO$ requires C, 46.63; H, 4.40; N, 6.80%.

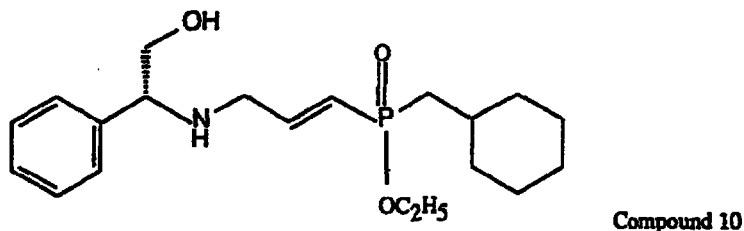
Example 9



Bis(trimethylsilyl)acetamide (28.51ml) is added dropwise to a solution of 18.22g of ethyl cyclohexylmethylphosphinate, prepared as described in EP 0569333, in 100ml of dry CH_2Cl_2 under argon. The solution is stirred at room temperature for 1 hour, then trimethyl phosphate (13.42ml) is added, followed by 1,3-dibromopropene (mixture of cis/trans isomers) (9.57ml). After stirring the solution at room temperature for 18 hours, it is poured into saturated aqueous $NaHCO_3$ solution (100ml) and stirred for 10 minutes. The product is extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic extracts are washed with brine, then dried with $MgSO_4$ and filtered. The filtrate is evaporated under reduced pressure, then excess trimethyl phosphate is removed by evaporation at 80°C at 0.45mm Hg. The residue is purified by flash chromatography (silica gel, ethyl acetate) to yield Compound 9 as a mixture of cis and trans isomers.

^{31}P nmr (162MHz, $CDCl_3$): δ (ppm) 51.1 and 52.2.

Example 10



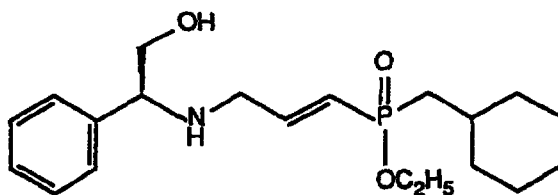
A mixture of (R)-2-amino-2-phenylethanol (0.88g, 6.47mM) and Compound 9 (1.0g, 3.23mM) in toluene (10ml) is heated under reflux. 1, 8-Diazabicyclo[5.4.0]undec-7-ene

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(0.48ml, 3.23mM) is added in ten aliquots at 30 minute intervals. The reaction is heated under reflux for a further hour and allowed to stand overnight at room temperature. The mixture is filtered and the filtrate evaporated under reduced pressure to afford a yellow oil which is purified by flash chromatography on silica using 5% methanol in dichloromethane as eluant to afford Compound 10 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P nmr (162Hz; CDCl_3): δ (ppm) 43.49 and 43.55.

Example 11

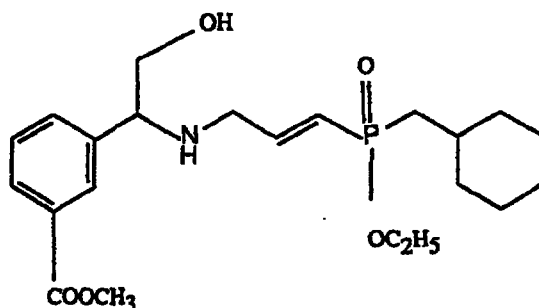


Compound 11

(S)-2-amino-2-phenyl ethanol (2.66g, 19.4mM), Compound 9 (3.0g, 9.7mM) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.40g, 9.7mM) are reacted in toluene (30ml) using the procedure described for the preparation of Compound 10. The crude product is purified by flash chromatography on silica using 5% methanol in dichloromethane as eluant to afford Compound 11 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P nmr (162MHz; CDCl_3): δ (ppm) 43.37 and 43.43.

Example 12



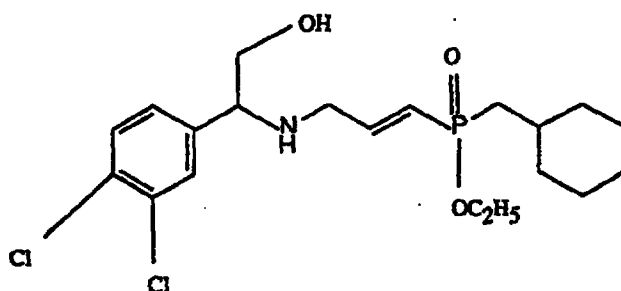
Compound 12

A mixture of Compound 4 (1.3g, 6.66mM) and Compound 9 (2.06g, 6.66mM) in toluene/THF (25ml, 1:1 mixture) is heated to 80°C under argon. A solution of 1,8-diazabicyclo [5.4.0]undec-7-ene (1.52g, 9.95mM) in toluene/THF (15ml, 1:1 mixture) is

added over 5 hours. The mixture is cooled to room temperature and allowed to stand for 18 hours. The mixture is filtered and the filtrate evaporated under reduced pressure to afford a yellow oil which is purified by flash chromatography on silica using 5% methanol in dichloromethane as eluant to give Compound 12 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P (162MHz; CDCl_3): δ (ppm) 43.53 and 43.58.

Example 13

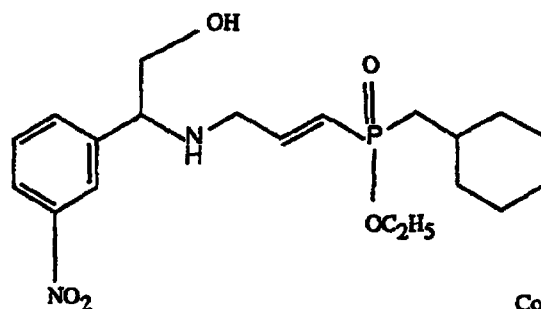


Compound 13

Using substantially the same procedure as described for the preparation of Compound 12, a mixture of Compound 8 (2.76g, 13.39mM) and Compound 9 (4.14g, 13.39mM) in toluene/THF (50ml/4ml) is reacted with a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (2.03g, 13.39mM) in THF (6ml) at 110°C to afford Compound 13 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P nmr (162MHz; CDCl_3): δ (ppm) 43.73 and 43.82.

Example 14



Compound 14

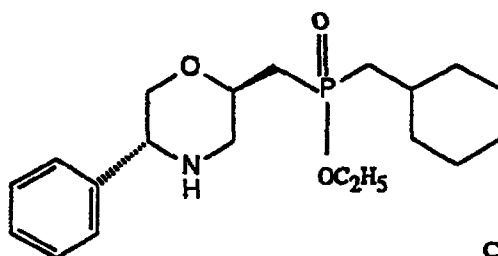
Using substantially the same procedure as described for the preparation of Compound 12, a mixture of Compound D (3.19g, 17.50mM) and Compound 9 (5.41g, 17.50mM) in toluene/THF (50ml/4ml) is reacted with a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene

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(2.66g, 17.5mM) in THF (6ml) at 110°C to afford Compound 14 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P nmr (162MHz; CDCl_3): δ (ppm) 43.60 and 43.66.

Example 15



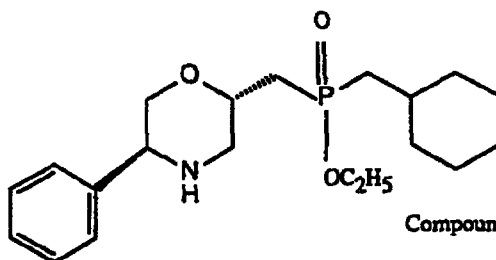
Compound 15

A suspension of sodium hydride (0.079g, 3.31mM) in dry toluene (10ml) is stirred at 0°C. A solution of Compound 10 (1.1g, 3.01mM) in dry toluene (20ml) is added dropwise. The reaction mixture is allowed to warm to room temperature and stirred for 20 hours. Saturated aqueous ammonium chloride solution (5ml) is added, then the reaction mixture is partitioned between ethyl acetate and water. The aqueous layer is extracted with ethyl acetate and the combined organic phases are dried over magnesium sulphate, filtered and evaporated. The residue is purified by flash chromatography on silica using 5% methanol in dichloromethane as eluant to afford Compound 15 as a mixture of diastereomers at phosphorus.

Mass spec. (FAB): $(m+1)^+ m/z = 366$.

^{31}P nmr (162MHz; CDCl_3): δ (ppm) 54.05 and 54.63.

Example 16



Compound 16

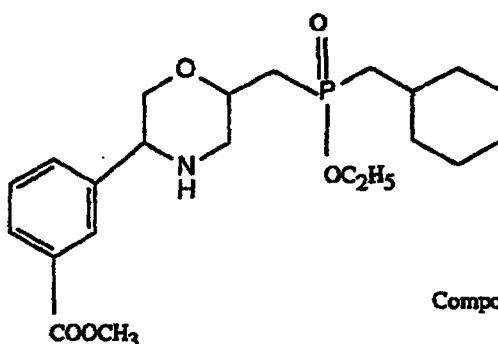
Using substantially the same procedure as described for the preparation of Compound 15, Compound 11 (1.20g, 3.28mM) and sodium hydride (0.086g, 3.61mM) are reacted in toluene (40ml) to afford Compound 16 as a mixture of diastereomers at phosphorus.

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Found: C, 63.39; H, 8.75; N, 3.70%. $C_{20}H_{32}NO_3P \cdot 0.75 H_2O$ requires C, 63.39; H, 8.91; N, 3.70%.

^{31}P (162MHz; $CDCl_3$): δ (ppm) 54.08 and 54.65.

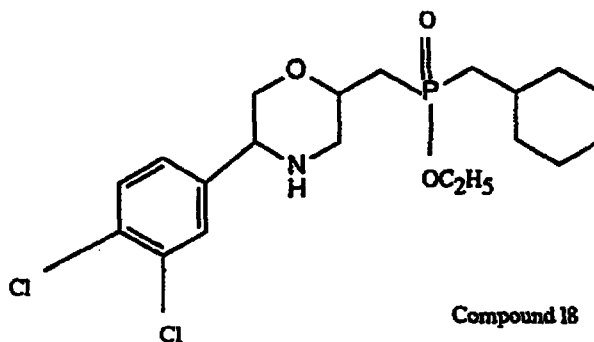
Example 17



Compound 17

A solution of Compound 12 (50mg, 0.12mM) in dry toluene (0.5ml) is stirred at room temperature. A suspension of sodium hydride (6.2mg, 0.26mM) in toluene (0.5ml) is added in one portion and the reaction mixture is stirred for 3 hours at room temperature. The reaction is then quenched with glacial acetic acid and the product is extracted with ethyl acetate. The combined organic phases are washed with water and brine, then dried over magnesium sulphate, filtered and evaporated. The residue is purified by flash chromatography on silica using 5% methanol in dichloromethane as eluant to afford trans-2,5-disubstituted morpholine racemic Compound 17 as a mixture of diastereomers at phosphorus.

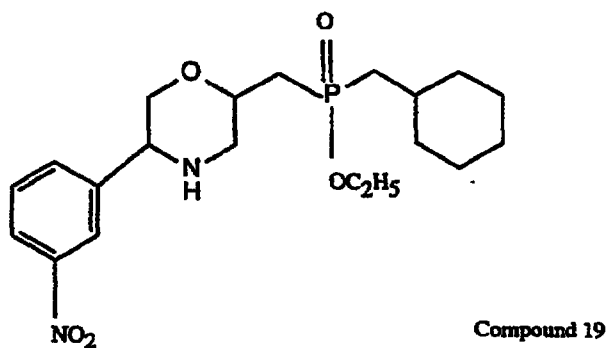
^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 54.06 and 54.64.

Example 18

Using substantially the same procedure as described for the preparation of Compound 15, Compound 13 (2.24g, 5.15mM) and sodium hydride (0.136g, 5.67mM) are reacted in toluene (80ml) to afford trans-2,5-disubstituted morpholine racemic Compound 18 as a mixture of diastereomers at phosphorus.

Analysis: Found, C, 54.21; H, 7.08; N, 3.11%. $C_{20}H_{30}Cl_2NO_3P \cdot 0.5H_2O$ requires C, 54.18; H, 7.05; N, 3.16%.

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 53.80 and 54.40.

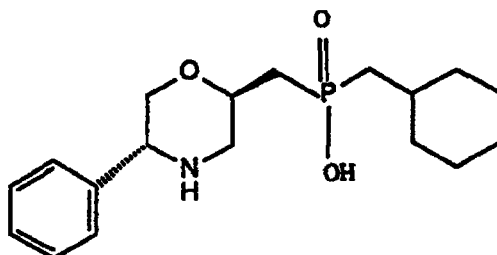
Example 19

Using substantially the same procedure as described for the preparation of Compound 15, Compound 14 (5.38g, 13.1mM) and sodium hydride (0.346g, 14.41mM) are reacted in toluene (150ml) to afford trans-2,5-disubstituted morpholine racemic Compound 19 as a mixture of diastereomers at phosphorus.

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^{31}P nmr (162MHz, CDCl_3): δ (ppm) 53.73 and 54.33.

Example 20



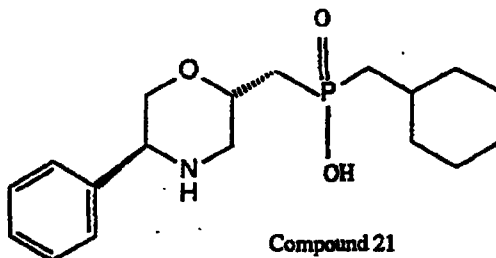
Compound 20

To a stirred solution of Compound 15 (650mg, 1.78mM) in dichloromethane (25ml) under argon is added dropwise bromotrimethylsilane (0.939ml, 7.12mM). The reaction mixture is stirred for 24 hours at room temperature. The reaction is then quenched by the addition of a mixture of methanol: water (95:5). The solvent is removed under reduced pressure to afford an oily residue which is purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: water: aqueous ammonia solution (50% : 47% : 3%) as eluant. The resulting product is dried under high vacuum ($< 0.05\text{mm Hg}$) to afford Compound 20 as a white solid. m.p. $> 250^\circ\text{C}$. $[\alpha]_D = +10.8^\circ$ ($\text{C}=1$, CH_3OH).

Found: C, 63.72; H, 8.44; N, 4.02%. $\text{C}_{18}\text{H}_{28}\text{NO}_3\text{P}$ requires C, 64.08; H, 8.36; N, 4.15%.

^{31}P nmr (162MHz, D_2O): δ (ppm) 55.22.

Example 21



Compound 21

Using the same procedure as described for the preparation of Compound 20, Compound 16 (670mg, 1.83mM) and bromotrimethylsilane (1.1g, 7.3mM) are reacted in dichloromethane (20ml) to afford Compound 21. m.p. $> 250^\circ\text{C}$. $[\alpha]_D = -10.5^\circ$ ($\text{C} = 1$,

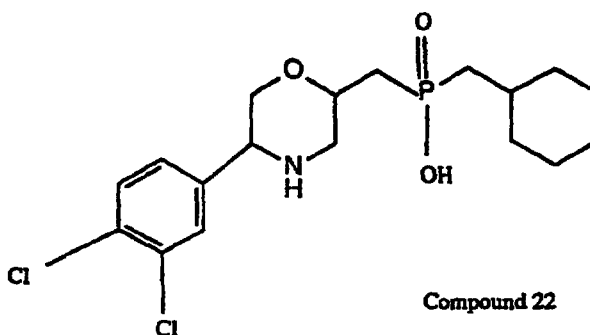
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CH₃OH).

Found: C, 63.62; H, 8.50; N, 4.05%. C₁₈H₂₈NO₃P requires C, 64.08; H, 8.36; N, 4.15%.

³¹P nmr (162MHz; D₂O/DCl): δ (ppm) 55.36.

Example 22



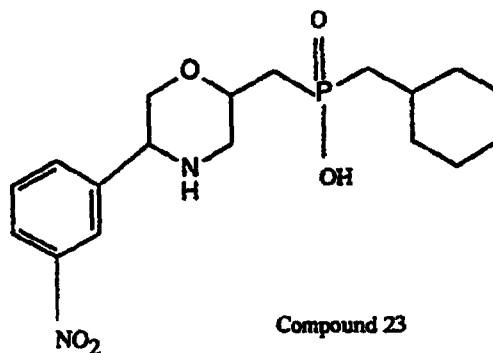
Using the same procedure as described for the preparation of Compound 20, Compound 18 (0.979g, 2.25mM) and bromotrimethylsilane (0.89ml, 6.76mM) are reacted in dichloromethane (40ml) to afford trans-2,5-disubstituted morpholine racemic Compound 22. m.p. > 200°C (dec).

Found: C, 52.45; H, 6.53; N, 3.29%. C₁₈H₂₆Cl₂NO₃P · 0.25H₂O requires C, 52.63; H, 6.50; N, 3.41%.

³¹P nmr (202.5MHz; d₄-acetic acid): δ (ppm) 45.45.

Sodium salt, ³¹P nmr (162MHz; D₂O/DCl): δ (ppm) 41.89.

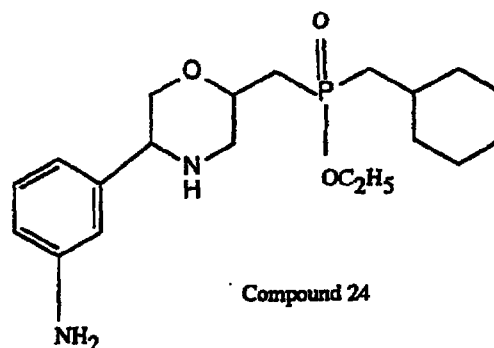
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Example 23

Using the same procedure as described for the preparation of Compound 20, Compound 19 (0.50g, 1.20mM) and bromotrimethylsilane (0.48ml, 3.65mM) are reacted in dichloromethane (25ml) to afford trans-2,5-disubstituted morpholine the racemic Compound 23. m.p. 128-130°C.

Found: C, 54.23; H, 7.25; N, 6.93%. $C_{18}H_{27}N_2O_5P \cdot H_2O$ requires C, 53.99; H, 7.30; N, 7.00%.

^{31}P nmr (162MHz; CD_3OD): δ (ppm) 37.64.

Example 24

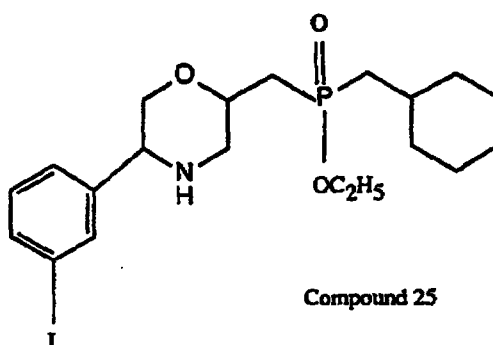
A mixture of Compound 19 (2.98g, 7.26mM) and 10% palladium on activated charcoal (0.5g) in absolute ethanol (150ml) is hydrogenated for 18 hours. The mixture is filtered and the filtrate is evaporated. The residue is purified by flash chromatography on silica using 10% methanol in dichloromethane as eluant to afford trans-2,5-disubstituted morpholine racemic Compound 24 as a mixture of diastereomers at phosphorus. m.p. 115-118°C.

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Found: C, 62.52; H, 8.88; N, 7.18%. $C_{20}H_{33}N_2O_3P \cdot 0.25 H_2O$ requires C, 62.40; H, 8.77; N, 7.31%.

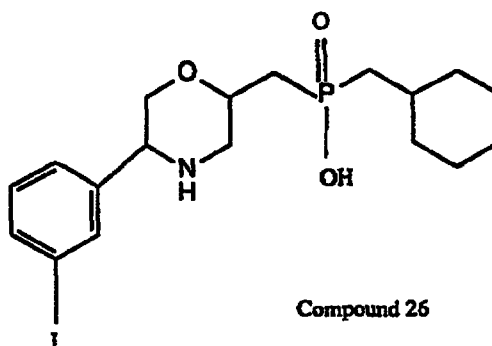
^{31}P (162MHz; $CDCl_3$): δ (ppm) 54.16 and 54.72.

Example 25



Crushed ice (15g) is added to a stirred solution of Compound 24 (2.43g, 6.38mM) in concentrated hydrochloric acid (50ml) and the resulting mixture is cooled to 0°C. A solution of sodium nitrite (0.48g, 7.02mM) in water (25ml) is added dropwise and the resulting mixture is stirred for 10 minutes at 0°C. The resulting solution is then added dropwise to a solution of potassium iodide (11.13g, 67.01mM) in water (200ml). The reaction mixture is stirred for a further 2½ hours at room temperature and then allowed to stand overnight at room temperature. Ethyl acetate is added and the two phases separated. The aqueous phase is neutralized by addition of solid sodium bicarbonate and extracted with ethyl acetate. These ethyl acetate extracts are combined with the original organic phase and the combined organic phases are washed with aqueous 10% sodium hydroxide solution followed by aqueous 5% sodium bisulphite solution then water. The organic phase is dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue is purified by flash chromatography on silica using 10% methanol in ethyl acetate as eluant to afford trans-2,5-disubstituted morpholine racemic Compound 25 as a mixture of diastereomers at phosphorus. Mass spec. (CI/NH₃): (m+1)⁺ m/z = 492.

^{31}P nmr (162MHz; $CDCl_3$): δ (ppm) 54.21 and 54.77.

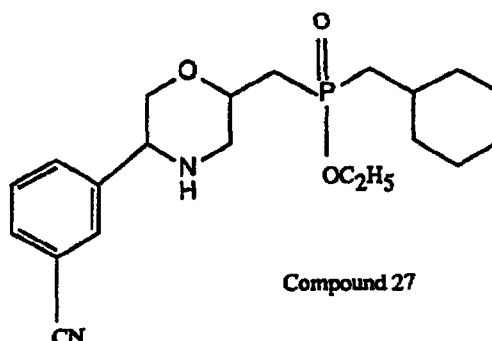
Example 26

Compound 26

Using substantially the same procedure as described for the preparation of Compound 20, Compound 25 (0.1g, 0.20mM) and bromotrimethylsilane (0.427ml, 3.20mM) are reacted in dichloromethane (10ml) for 78 hours at room temperature. The crude product is purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H⁺ form) using methanol: water: aqueous ammonia solution (50% : 47% : 3%) as eluant and the product is dried under high vacuum (< 0.05 mm Hg) to afford trans-2,5-disubstituted morpholine racemic Compound 26. m.p. > 230°C (dec).

Found: C, 44.48; H, 5.70; N, 2.95%. C₁₈H₂₇INO₃P · 1.2H₂O requires C, 44.59; H, 6.11; N, 2.89%.

³¹P nmr (162MHz; CD₃OD/DCl): δ (ppm) 53.08.

Example 27

Compound 27

Sodium cyanide impregnated alumina (5mM NaCN per gram of alumina) is prepared by the procedure of S. L. Regen, S. Quici and S. J. Liaw described in the Journal Organic Chemistry, 1979, 44(12), 2029. To a mixture of tris (dibenzylideneacetone) dipalladium

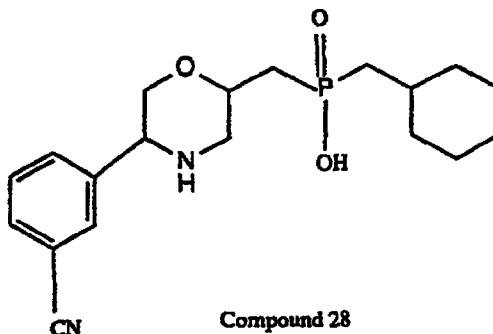
- 53 -

(O) [0.17g, 0.18mM], sodium cyanide impregnated alumina (4.7g) and tri(2-furyl)phosphine (0.34g, 1.45mM) under argon is added a solution of Compound 25 (0.89g, 1.8mM) in dry degassed toluene (50ml). The reaction is heated at 80°C for 12 hours. The reaction is monitored by tlc and if required further tris(dibenzylideneacetone) dipalladium (0) [0.17g, 0.18mM] and tri(2-furyl)phosphine (0.34g, 1.45mM) are added and the reaction heated for 8 hours at 80°C. On completion of the reaction, the mixture is filtered and the solids washed with ether. The combined filtrate is evaporated under reduced pressure and the residue is purified by flash chromatography on silica using 10% methanol in ethyl acetate as eluant to afford trans-2,5-disubstituted morpholine racemic Compound 27 as a mixture of diastereomers at phosphorus.

Mass spec. (CI/NH₃) : (M+1)⁺ m/z = 391.

³¹P nmr (162MHz; CDCl₃): δ (ppm) 53.95 and 54.57.

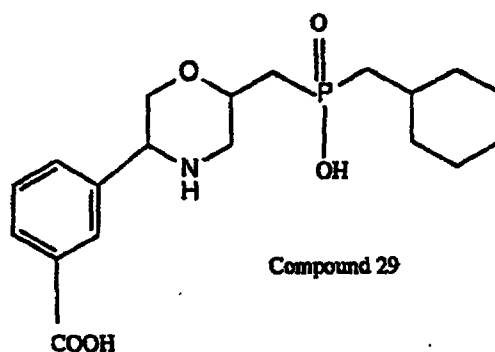
Example 28



Using substantially the same procedure as described for the preparation of Compound 20, Compound 27 (0.16g, 0.41mM) and bromotrimethylsilane (0.81ml, 6.14mM) are reacted in dichloromethane to afford trans-2,5-disubstituted morpholine racemic Compound 28.

Mass spec. (CI, NH₃) : M⁺ m/z = 362.

³¹P nmr (162MHz; D₂O/DCl): δ (ppm) 55.31.

Example 29

A mixture of Compound 27 (0.09g, 0.23mM), 6M hydrochloric acid solution (10ml) and ethanol (1ml) is heated under reflux for 72 hours. On completion of the reaction (^{31}P nmr), the solvent is removed under reduced pressure. The residue is purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: water: aqueous ammonia solution (50%: 47%: 3%) as eluant and the product is dried under high vacuum ($\leq 0.05\text{mm Hg}$) to afford trans-2,5-disubstituted morpholine racemic Compound 29. m.p. $> 260^\circ\text{C}$.

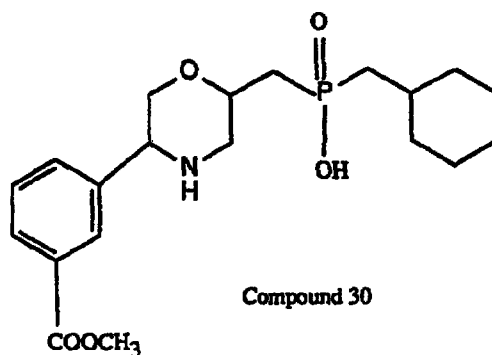
^{31}P nmr (162MHz; D_2O): δ (ppm) 40.67.

Example 30

A mixture of Compound 17 (0.50g, 1.18mM), 6M hydrochloric acid solution (25ml) and glacial acetic acid (5ml) is heated at 100°C for 16 hours. On completion of the reaction (^{31}P nmr), the solvent is removed under reduced pressure. The residue is purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: water: aqueous ammonia solution (50%: 47%: 3%) as eluant and the product is dried under high vacuum ($\leq 0.05\text{mm Hg}$) to afford trans-2,5-disubstituted morpholine racemic Compound 29.

Found: C, 58.68; H, 7.35; N, 3.71%. $\text{C}_{19}\text{H}_{28}\text{N O}_5\text{P} \cdot 0.5\text{H}_2\text{O}$ requires C, 58.45; H, 7.49; N, 3.59%.

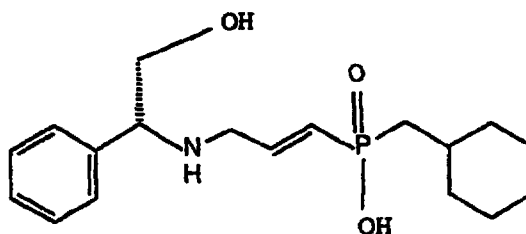
^{31}P nmr (162MHz; D_2O): δ (ppm) 40.71.

Example 31

A solution of Compound 29 (317mg, 0.83mM) in methanol (20ml) is saturated with gaseous hydrogen chloride and the reaction mixture stirred for 16 hours at room temperature. The solvent is removed under reduced pressure and the residue is purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: water: aqueous ammonia solution (50%: 47%: 3%) as eluant. The product is dried under high vacuum (≤ 0.05 mm Hg) to afford trans-2,5-disubstituted morpholine racemic Compound 30.

Found: C, 60.26; H, 7.57; N, 3.45%. $C_{20}H_{30}NO_5P \cdot 0.25 H_2O$ requires C, 60.01; H, 7.68; N, 3.50%.

^{31}P nmr (162MHz; CD_3OD): δ (ppm) 37.21.

Example 32

Using substantially the same procedure as described for the preparation of Compound 20, Compound 10 (90mg, 0.246mM) and bromotrimethylsilane (200 μ l, 1.57mM) are reacted in

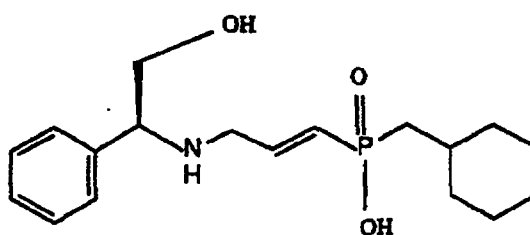
- 56 -

dichloromethane (2ml) to afford Compound 31.

$[\alpha]_D -38.5^\circ$ (C = 0.6, CH₃OH)

³¹P nmr (162MHz; CD₃OD): δ (ppm) 29.00.

Example 33



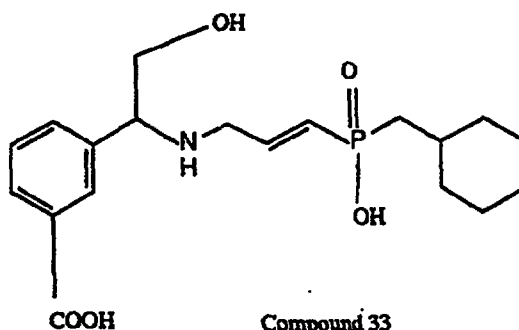
Compound 32

Using substantially the same procedure as described for the preparation of Compound 20, Compound 11 (90mg, 0.246mM) and bromotrimethylsilane (200 μ l, 1.57mM) are reacted in dichloromethane to afford Compound 32.

$[\alpha]_D +41.3^\circ$ (C = 0.6, CH₃OH)

³¹P nmr (162MHz; CD₃OD): δ (ppm) 28.84.

Example 34



Compound 33

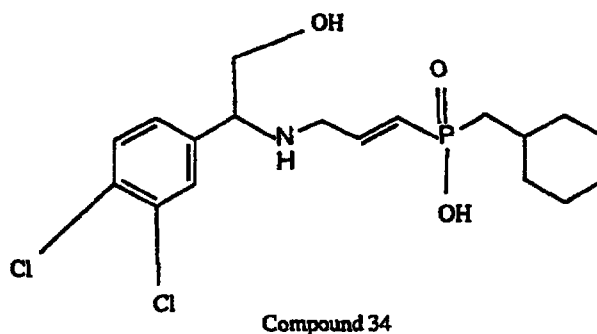
To a stirred solution of Compound 12 (100mg, 0.24mM) in dichloromethane (2ml) under argon is added bromotrimethylsilane (300 μ l, 2.4mM) and the reaction is stirred for 24

- 57 -

hours at room temperature. The solvent is removed under reduced pressure and the residue is co-evaporated with a 1:1 mixture of methanol: water. The resulting residue is then dissolved in a mixture of 6M hydrochloric acid (5ml) and methanol (0.3ml) and the mixture is heated under reflux for 4 hours. The solvent is removed under reduced pressure and the residue is co-evaporated three times with water. The resulting residue is purified by ion exchange chromatography on Dowex 50WX 2-200 resin using methanol: water: aqueous ammonia solution (50% : 47% : 3%) as eluant to afford Compound 33.

^{31}P nmr (162MHz; CD_3OD): δ (ppm) 29.28.

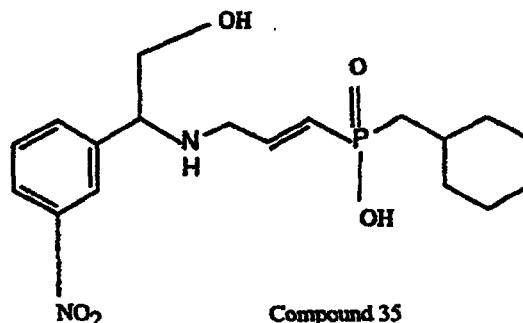
Example 35



Using substantially the same procedure as described for the preparation of Compound 20, Compound 13 (0.5g, 1.15mM) and bromotrimethylsilane (0.91ml, 6.9mM) are reacted in dichloromethane (15ml) to afford Compound 34.

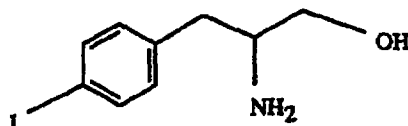
^{31}P nmr (162MHz; CD_3OD): δ (ppm) 29.06.

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Example 36

Using substantially the same procedure as described for the preparation of Compound 20, Compound 14 (90mg, 0.219mM) and bromotrimethylsilane (200 μ l, 1.57mM) are reacted in dichloromethane (2ml) to afford Compound 35.

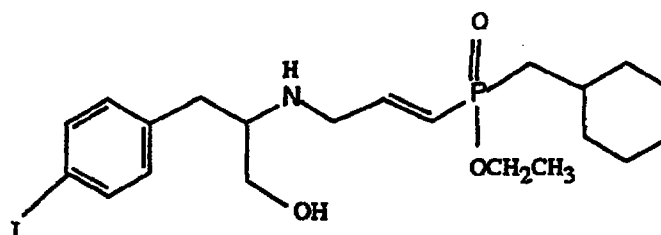
^{31}P nmr (162MHz; CD_3OD): δ (ppm) 29.57.

Example 37

Boron trifluoride ethyl etherate (1.25ml, 10mM) is added dropwise to a suspension of 2-amino-3-(4-iodophenyl)propionic acid (2.9g, 10mM) in THF (10ml) over 20 minutes. The mixture is heated under reflux for 2 hours, then borane dimethyl sulphide complex (1.1ml, 11mMol) is added dropwise over 1 hour whilst maintaining the mixture at reflux. The mixture is heated under reflux for a further 5 hours and then stirred for 15 hours at room temperature.

A 1:1 mixture of water and THF (20ml) is added followed by 5N sodium hydroxide solution (7.5ml). The reaction mixture is heated under reflux for 7 hours, cooled to room temperature and filtered. The filter cake is washed with THF (2 x 10ml) and the filtrate is evaporated to 25% of its original volume and then extracted with dichloromethane. The combined organic layers are dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford a pale yellow solid which is recrystallised from hexane: ethyl acetate (1:2) to afford Compound 36, m.p. 105-107°C.

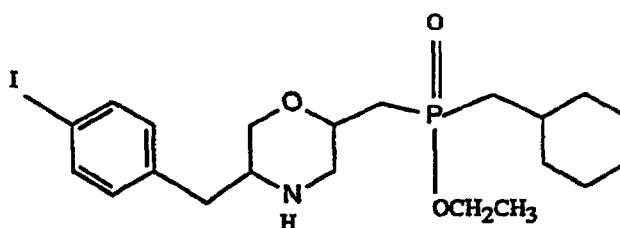
Found: C, 38.69; H, 4.40; N, 4.92%. $\text{C}_9\text{H}_{12}\text{INO}$ requires C, 39.01; H, 4.37; N, 5.06%.

Example 38

Compound 37

Using substantially the same procedure as described for the preparation of Compound 12, a mixture of Compound 36 (2.40g, 8.66mM) and Compound 9 (2.7g, 8.66mM) in toluene (20ml) is reacted with a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.30g, 8.66mM) in THF (10ml) at 75°C to afford Compound 37 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P nmr (202MHz; CDCl_3) δ (ppm) 43.69 and 43.72.

Example 39

Compound 38 [trans]

Compound 39 [cis]

A suspension of sodium hydride (0.105g, 4.4mM) in dry toluene (5ml) is added portionwise over 30 seconds to a stirred solution of Compound 37 (2.0g, 4.0mM) in dry toluene (25ml). The mixture is stirred for 30 minutes at 0°C and then for 3 hours at room temperature. Glacial acetic acid (1ml) is added, then the reaction mixture is diluted with ethyl acetate (75ml). The organic phase is washed with saturated sodium bicarbonate solution, water and then brine. The combined organic phases are dried over magnesium sulphate, filtered and evaporated. The residue is purified by flash chromatography on silica using 20% methanol in ethyl acetate as eluant to afford trans-2, 5-disubstituted morpholine racemic Compound 38 and cis-2, 5-disubstituted morpholine racemic

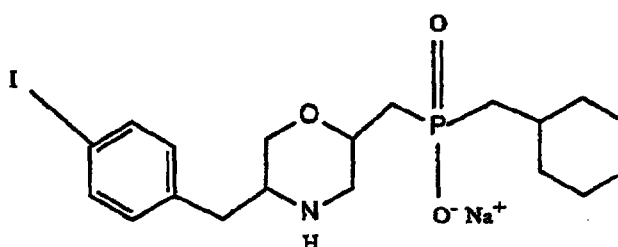
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Compound 39 each as a mixture of diastereomers at phosphorus.

Compound 38: ^{31}P nmr (162MHz; CDCl_3) δ (ppm) 53.93 and 54.60

Compound 39: ^{31}P nmr (162MHz; CDCl_3) δ (ppm) 54.25 and 54.82 ppm.

Example 40

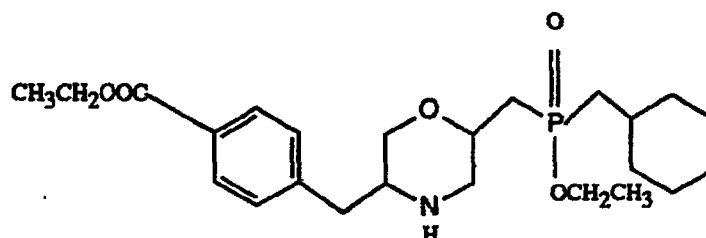


Compound 40

To a stirred solution of Compound 38 (180 mg, 0.356 mM) in dichloromethane (5ml) under argon is added dropwise bromotrimethylsilane (0.20ml, 1.52mM). The reaction mixture is stirred for 20 hours at room temperature. The solvent is removed under reduced pressure and the residue coevaporated with 1:1 water:methanol (2 x 0.5ml). The residue is purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: 2% sodium hydroxide solution (1:1) to elute the product. The resulting product is further purified by gel filtration on a Bio-Gel P2 column using water as eluant to afford trans-2, 5-disubstituted morpholine racemic Compound 40, m.p. $>250^\circ\text{C}$ (dec).

Found: C, 41.42; H, 5.40; N, 2.42%. $\text{C}_{19}\text{H}_{28}\text{INO}_3\text{P.Na. } 3\text{H}_2\text{O}$ requires C, 41.20; H, 6.10; N, 2.53%.

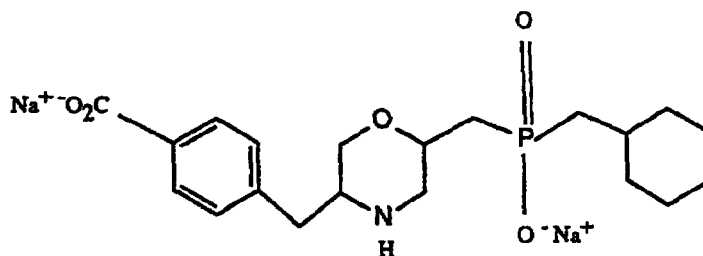
^{31}P nmr (161MHz; D_2O): δ (ppm) 41.81.

Example 41

Compound 41

A mixture of Compound 38 (0.180g, 0.36mM) and bis triphenylphosphine palladium (II) chloride (0.200g, 0.28mM) in absolute ethanol (2ml) and triethylamine (1ml) is degassed by sparging with argon for 5min. The mixture is heated under reflux and vigorously stirred under an atmosphere of carbon monoxide for 3 hours. The mixture is cooled to room temperature and the solvent is removed under reduced pressure to afford an oily solid which is triturated with ethyl acetate. The combined ethyl acetate washings are evaporated under reduced pressure and the residue is purified by flash chromatography on silica using 10% methanol in chloroform as eluant to afford trans-2, 5-disubstituted morpholine racemic Compound 41 as a mixture of diastereomers at phosphorus.

^{31}P nmr (161 MHz; CDCl_3): δ (ppm) 53.93 and 54.60.

Example 42

Compound 42

A mixture of Compound 41 (0.095g, 0.21mM) and 6M hydrochloric acid solution (4ml) is heated under reflux for 20 hours. On completion of the reaction (^{31}P nmr) the solvent is removed under reduced pressure and the residue is purified by ion exchange

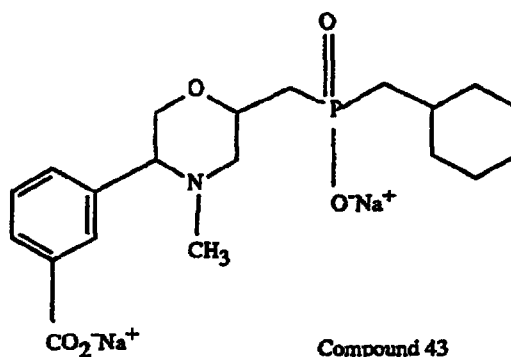
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chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: 2% sodium hydroxide solution (1:1) to elute the product. The resulting product is further purified by gel filtration on a BIO-GEL P2 column using water as eluant to afford trans-2, 5-disubstituted morpholine racemic Compound 42, m.p. $>250^\circ C$ (dec).

Found: C, 50.53; H, 7.40; N, 2.96%. $C_{20}H_{28}NO_5P \cdot Na \cdot 2H_2O$ requires C, 50.52; H, 6.79; N, 2.95%.

^{31}P nmr (202MHz, D_2O) : δ (ppm) 42.38.

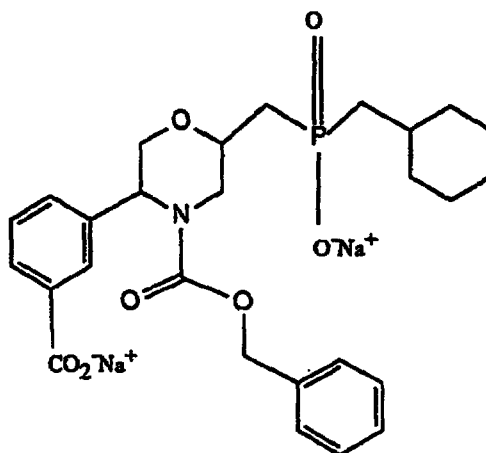
Example 43



A buffered stock solution of formaldehyde is prepared by dissolving sodium acetate (1.8g, 21.4mM), acetic acid (1.3ml, 22.7mM) and 40% aqueous formaldehyde solution (7.0ml; 101mM) in water (5ml). An aliquot (10ml) of the above stock solution is added to a mixture of Compound 29 (0.10g, 0.262mM) in methanol (2ml) and the mixture is stirred for 10 minutes at room temperature. Sodium cyanoborohydride (0.165g, 2.62mM) is added portionwise over 2 minutes. The mixture is stirred for 24 hours at room temperature. The solvent is removed under reduced pressure and the residue purified by ion exchange chromatography on Dowex 50WX 2-200 resin (H^+ form) using methanol: 2% sodium hydroxide solution (1:1) to elute the product. The resulting product is further purified by gel filtration on a BIO-GEL P2 column using water as eluant to afford the trans-2, 5- disubstituted morpholine racemic Compound 43, m.p. $>250^\circ C$ (dec).

Found: C, 52.60; H, 6.82; N, 3.10%. $C_{20}H_{28}NO_5P \cdot 2Na \cdot H_2O$ requires C, 52.52; H, 6.61; N, 3.06%.

^{31}P nmr (202 MHz; D_2O) δ (ppm) 41.93.

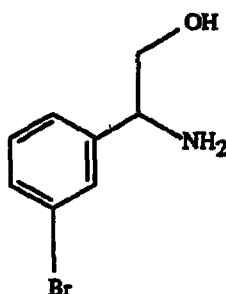
Example 44**Compound 44**

Compound 29 (0.25g, 0.66mM) is dissolved in a 1:1 mixture of dioxan: water (4ml) and the pH of the resulting solution is adjusted to pH 9 by the addition of 0.1M sodium hydroxide solution. The mixture is vigorously stirred and benzyl chloroformate (0.188ml, 1.32mM) is added dropwise over 15 minutes. The pH of the mixture is adjusted to pH9 by further addition of 0.1M sodium hydroxide solution and the mixture is stirred for 20 hours at room temperature. The mixture is concentrated under reduced pressure to one half of its original volume and acidified with concentrated hydrochloric acid. The mixture is extracted with ethyl acetate and the combined organic phases are washed with water then brine, dried over magnesium sulphate, filtered and evaporated. The residue is purified by flash chromatography on silica using acetic acid: methanol: chloroform (2% :10%: 88%) as eluant. The product is further purified by ion exchange chromatography on Dowex 50 WX 2-200 resin (H⁺ form) using THF: water (3:1) as eluant. The resulting product is dissolved in 1% sodium hydroxide solution (2.5ml) and purified by gel filtration on a BIO-GEL P2 column using water as eluant to afford trans-2, 5-disubstituted morpholine racemic Compound 44, m.p. > 250°C (dec).

Found: C, 52.27; H, 6.00; N, 2.24%. C₂₇ H₃₂ N O₇ P. 2 Na. 3H₂O requires C, 52.85; H, 6.24; N, 2.28%.

³¹P nmr (161 MHz; D₂O) δ (ppm) 41.75.

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Example 45

Compound 45

Boron trifluoride ethyl etherate (75.0ml, 0.61M) is added dropwise to a suspension of compound J (70.2g, 0.31M) in THF (350ml) over 20 minutes. The mixture is heated under reflux for 2 hours, then borane dimethyl sulphide complex (57.9ml, 0.61M) is added dropwise over 1.5 hours whilst maintaining the mixture at reflux. The mixture is heated under reflux for a further 3 hours and then stood for 18 hours at room temperature.

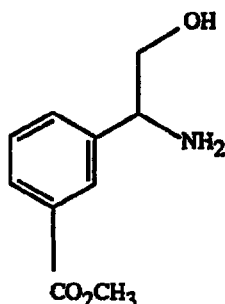
A 1:1 mixture of water and THF (350ml) is added followed by 5M sodium hydroxide solution (350ml). The reaction mixture is heated under reflux for 5 hours then cooled to room temperature. The two layers are separated and the aqueous layer extracted with ethyl acetate. The combined organic phases are washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford a brown oil.

This residue is triturated with diethyl ether/hexane then recrystallised from ethyl acetate to afford compound 45, m.p. 74-76°C.

Found C, 44.40; H, 4.67; N, 6.35%.

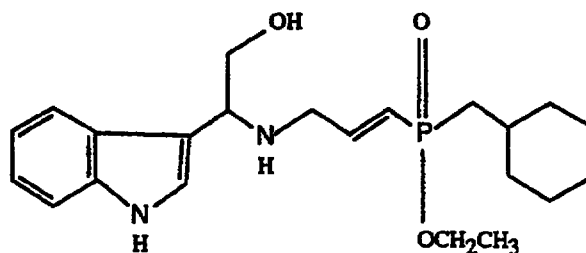
C₈H₁₀Br NO requires C, 44.46; H, 4.67; N, 6.48%.

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Example 46**Compound 4**

A mixture of compound 45 (15.0g, 69.4mM) and bis(triphenylphosphine) palladium (II) chloride (4.0g, 5.70mM) in methanol (100ml) and triethylamine (25ml) is degassed by sparging with argon for 5 minutes. The mixture is saturated with carbon monoxide and then pressurised to 30 psi in a pressure vessel. The mixture is slowly heated to 100°C whilst maintaining the pressure below 50psi for 5 hours. The mixture is cooled to room temperature, filtered and evaporated. The residue is triturated with ethyl acetate and the filtrate evaporated. The residue is purified by flash chromatography on silica using a gradient from 10% to 20% methanol in chloroform as eluant to afford compound 4.

¹³C nmr (100MHz; CD₃OD): δ(ppm) 52.6 (q), 58.3 (d), 68.1 (t), 129.0 (d), 129.5 (d), 129.7 (d), 131.5 (s), 132.9 (d), 143.6 (s), 168.4 (s).

Example 47**Compound 46**

(2R/S)-2-amino-2-(1H-indol-3-yl)ethanol is prepared by the procedure of A.H. Katz *et al* described in the Journal Medicinal Chemistry, 1988, 31, 1244.

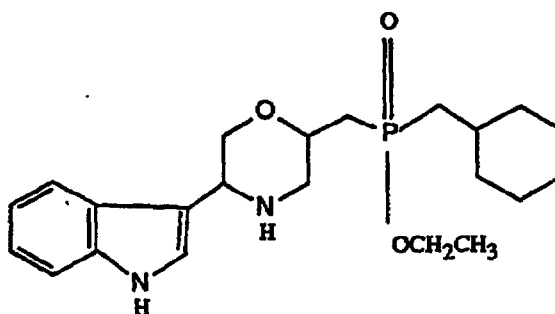
Using substantially the same procedure as described for the preparation of Compound 12, a mixture of (2R/S)-2-amino-2-(1H-indol-3-yl) ethanol (0.39g, 2.21mM) and Compound 9

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(0.68g, 2.20mM) in toluene/THF (10ml/15ml) is reacted with a solution of 1,8-diazabicyclo [5.4.0]undec-7-ene (0.33g, 2.17mM) in toluene (5ml) at 75°C to afford Compound 46 as a 1:1 mixture of diastereomers at phosphorus.

^{31}P nmr (162 MHz; CDCl_3) : $\delta(\text{ppm})$ 43.25 and 43.43.

Example 48



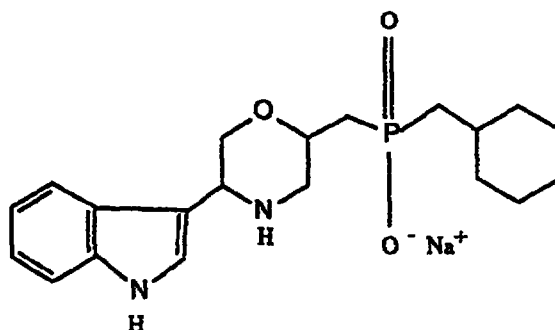
Compound 47

A suspension of sodium hydride (0.014g, 0.59mM) in dry toluene (10ml) is stirred at 0°C. A solution of Compound 46 (0.200g, 0.49mM) in dry toluene (7ml) is added dropwise. The reaction mixture is allowed to warm slowly to room temperature and stirred for 4 hours. Glacial acetic acid is added to quench the reaction, then the mixture is filtered and evaporated. The residue is purified by flash chromatography on silica using 20% methanol in ethyl acetate as eluant to afford trans-2,5-disubstituted morpholine racemic Compound 47 as a mixture of diastereomers at phosphorus.

Mass spec. (CI/NH_3) : $(\text{M}+1)^+$ m/z = 405.

^{31}P nmr (162 MHz; CDCl_3) : $\delta(\text{ppm})$ 54.44 and 55.32.

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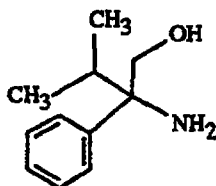
Example 49

Compound 48

Using substantially the same procedure as described for the preparation of Compound 40, Compound 47 (0.115g, 0.28mM) and bromotrimethylsilane (0.15ml, 1.13mM) are reacted in dichloromethane (5ml) for 3 days at room temperature to afford trans-2,5-disubstituted morpholine racemic Compound 48.

^{13}C nmr (100MHz; D_2O) δ (ppm) 28.6 (t), 28.7 (t), 35.1 (d), 37.6 (t), 37.7 (t), 37.9 (t), 38.3 (t), 41.6 (t), 53.8 (d), 54.2 (t), 74.7 (t), 75.6 (d), 114.8 (d), 115.6 (s), 121.3 (d), 122.3 (d), 125.0 (d), 125.4 (d), 128.3 (s), 138.8 (s).

^{31}P nmr (202 MHz; D_2O) δ (ppm) 42.6.

Example 50

Compound 49

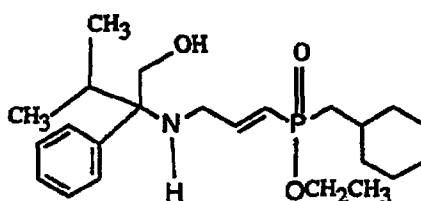
Using substantially the same procedure as described in Example 37, DL-2-amino-3-methyl-2-phenylbutyric acid (10.0g, 51.8mM), boron trifluoride ethyl etherate (6.4ml, 51.8mM) and borane dimethyl sulphide complex (4.9ml, 51.8mM) are reacted in dry THF (50ml) to afford Compound 49.

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Mass spec. (CI, NH₃): (m+1)⁺ m/z = 180.

¹³C nmr (100MHz; CDCl₃) 16.8 (q), 17.4 (q) 34.8 (d), 61.7 (s), 69.2 (t), 126.2 (d), 126.4 (d), 127.8 (d), 144.2 (s).

Example 51



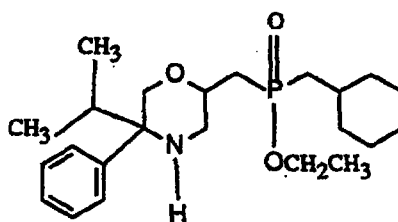
Compound 50

Using substantially the same procedure as described in Example 12, a mixture of Compound 49 (1.07g, 6.0mM) and Compound 9 (1.86g, 6.0mM) in toluene (20ml) is reacted with a solution of 1, 8 - diazabicyclo [5.4.0]undec-7-ene (1.1g, 7.2mM) in toluene (5ml) at 75°C to afford Compound 50 as a 1:1 mixture of diastereomers at phosphorus.

Mass spec. (CI, NH₃) : (m + 1)⁺ m/z = 408.

³¹P (202.5 MHz; CDCl₃) δ (ppm) 44.22 and 44.25.

Example 52



(2R*, 5R*)

Compound 51

(2R*, 5S*)

Compound 52

Using substantially the same procedure as described in Example 39, Compound 50 (200mg, 0.49mM) and sodium hydride (12mg, 0.49mM) and sodium hydride (12mg, 0.49mM) are reacted in dry toluene (3ml). The crude product is purified by flash chromatography on silica using 10% methanol in ethyl acetate as eluant to afford (2R*, 5R*) morpholine racemic Compound 51 and (2R*, 5S*) morpholine racemic Compound

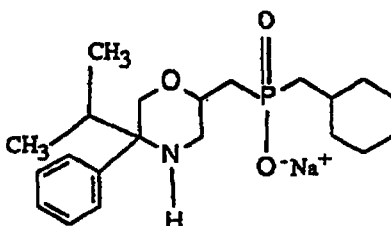
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52 each as a mixture of diastereomers at phosphorus.

Compound 51: ^{31}P nmr (162MHz; CDCl_3) δ (ppm) 54.3 and 55.0.

Compound 52: ^{31}P nmr (162MHz; CDCl_3) δ (ppm) 54.2 and 55.5.

Example 53

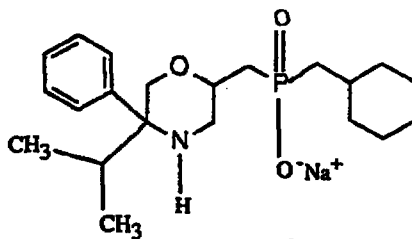


Compound 53

Using substantially the same procedure as described in Example 40, Compound 51 (40mg, 0.1mM) and bromotrimethylsilane (0.066ml, 0.5mM) are reacted in dry dichloromethane (1 ml) to afford (2R*, 3R*) morpholine racemic Compound 53.

^{31}P nmr (202.5MHz; D_2O) δ (ppm) 42.5.

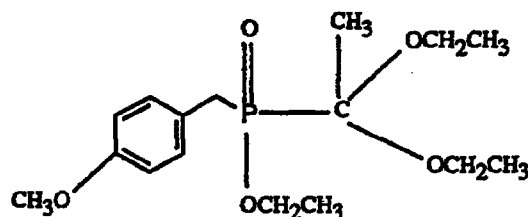
Example 54



Compound 54

Using substantially the same procedure as described in Example 40, Compound 52 (180mg, 0.2mM) and bromotrimethylsilane (0.132ml, 1.0mM) are reacted in dry dichloromethane (2 ml) to afford (2R*, 5S*) morpholine racemic Compound 54.

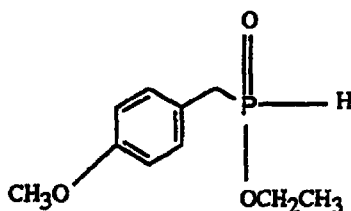
^{31}P nmr (202.5MHz; D_2O) δ (ppm) 42.2.

Example 55

Compound 55

A 0.5M solution of potassium bis(trimethylsilyl)amide in toluene (50ml, 25mM) is added dropwise to a cooled (-70°C) solution of ethyl 1,1-diethoxyethylphosphinate (5.25g, 25mM) in dry THF (30ml). The mixture is stirred for 0.5 hours at -70°C . The resulting solution is added dropwise over ten minutes to a cooled solution of 4-methoxybenzyl chloride (3.9g, 25mM) in THF (30ml). The resulting mixture is stirred for 1 hour at -70°C and then allowed to warm to room temperature. Reaction is stirred for 18 hours at room temperature. Glacial acetic acid is added and the reaction is evaporated. The residue is partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic phase is separated and washed with water then brine, dried over magnesium sulphate, filtered and evaporated. The residue is purified by flash chromatography on silica using ethyl acetate: hexane (2:1) as eluant to afford Compound 55.

^{31}P nmr (162MHz; CDCl_3) δ (ppm) 44.6.

Example 56

Compound 56

Chlorotrimethylsilane (3.8ml, 30.3mM) is added to a solution of Compound 55 (1.0g, 3.03mM) in a 9:1 mixture of chloroform: ethanol (10ml) and the mixture is stirred for 18 hours at room temperature. The mixture is evaporated under reduced pressure and the residue is co-evaporated with chloroform. After drying under high vacuum, the residue is

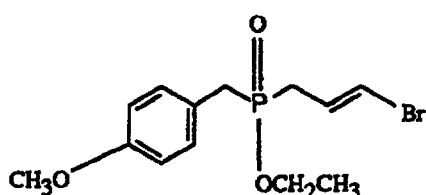
- 71 -

purified by flash chromatography on silica using ethyl acetate as eluant to afford Compound 56 as a colourless oil.

Mass spec. (CI, NH₃): (m + NH₄)⁺ m/z = 232.

³¹P nmr (162MHz; CDCl₃): δ (ppm) 37.3.

Example 57

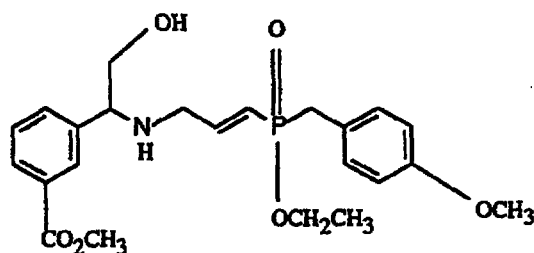


Compound 57

Using substantially the same procedure as described in Example 9, Compound 56 (0.5g, 2.33mM), bis(trimethylsilyl)acetamide (0.69ml, 2.80mM), trimethyl phosphate (0.33ml, 2.80mM) and 1,3-dibromopropene (mixture of cis/trans isomers) (0.23ml, 2.33mM) are reacted in dry dichloromethane (10ml) to afford Compound 57 as a mixture of cis and trans isomers.

³¹P nmr (162MHz; CDCl₃) δ (ppm) 47.2 and 48.1.

Example 58



Compound 58

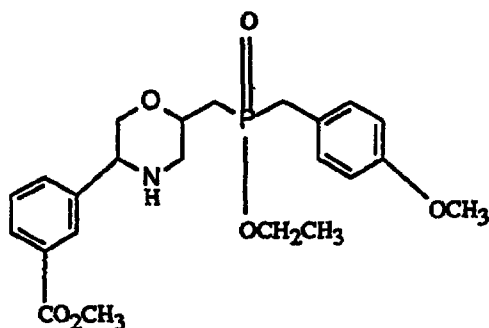
Using substantially the same procedure as described in Example 12, a mixture of Compound 4 (0.193g, 0.99mM) and Compound 57 (0.330g, 0.99mM) in toluene/THF (10ml, 4:1 mixture) is reacted with a solution of 1,8-diazabicyclo [5.4.0]undec-7-ene (0.181g, 1.19mM) in toluene (2ml) at 80°C to afford Compound 58 as a 1:1 mixture of diastereomers at phosphorus.

Mass spec. (CI, NH₃): (m+1)⁺ m/z = 448.

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^{31}P nmr (162MHz; CDCl_3) δ (ppm) 39.40 and 39.49.

Example 59

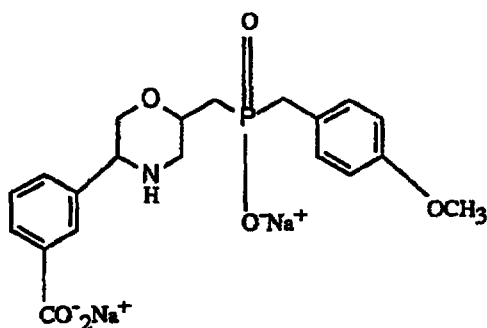


Compound 59

Using substantially the same procedure as described in Example 39, Compound 58 (200mg, 0.45mM) and sodium hydride (10.8mg, 0.45mM) are reacted in toluene (2ml) to afford trans-2,5-disubstituted morpholine racemic Compound 59 as a mixture of diastereomers at phosphorus.

^{31}P nmr (162MHz; CDCl_3) δ (ppm) 50.0 and 50.8.

Example 60



Compound 60

Bromotrimethylsilane (0.074ml, 0.55mM) is added to a solution of Compound 59 (50mg, 0.11mM) in dichloromethane (1 ml) and the reaction is stirred for 24 hours at room temperature. The solvent is removed under reduced pressure and the residue is co-evaporated with a 1:1 mixture of methanol: water. The resulting residue is dissolved in 6M hydrochloric acid (2ml) and the mixture is heated under reflux for 4 hours. The solvent is removed under reduced pressure and the residue is co-evaporated three times with water. The resulting residue is purified by ion exchange chromatography on Dowex

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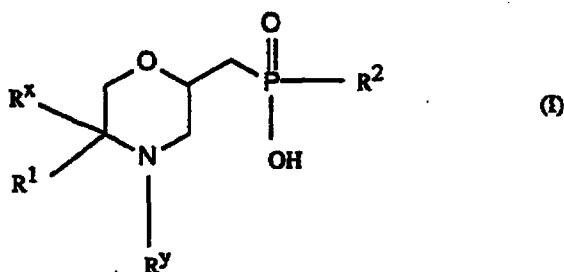
50 WX 2-200 resin (H^+ form) using methanol : 2% sodium hydroxide solution (1:1) to elute the product. The resulting product is further purified by gel filtration on a BIO-GEL P2 column using water as eluant to afford the trans-2,5-disubstituted morpholine racemic Compound 60.

^{31}P nmr (202.5MHz; D_2O) δ (ppm) 37.4.



Claims

1. A compound which is a substituted phosphinic acid of formula



or a salt or ester thereof,

where R^1 is a monovalent aromatic or araliphatic group connected through a carbon atom thereof to the indicated carbon atom, R^2 is an unsubstituted or substituted hydrocarbyl group, R^x is hydrogen or an unsubstituted or substituted hydrocarbyl group, R^y is hydrogen, R^y_a or a NH-protecting group and R^y_a is an unsubstituted or substituted hydrocarbyl group.

2. A compound according to claim 1, in which R^1 is an aryl group of 6 to 15 carbon atoms which is unsubstituted or substituted in one or more positions by halogen, hydroxy, C_1 to C_4 alkoxy, carboxyl, functionally modified carboxyl, carboxy - C_1 - C_8 alkyl, functionally modified carboxy - C_1 - C_8 - alkyl or nitro, or R^1 is a 5 to 10-membered heterocyclic aromatic group having one or two nitrogen atoms in the ring system.
3. A compound according to claim 1, in which R^1 is phenyl or phenyl substituted in one or more of the meta and para positions, with respect to the carbon atom thereof linked to the indicated morpholine ring, by halogen, carboxyl, functionally modified carboxyl or nitro, or R^1 is a 5 to 10-membered heterocyclic aromatic group having a nitrogen atom as the only ring hetero atom.
4. A compound according to claim 1, in which R^1 is a phenyl-lower alkyl, α , α -diphenyl - lower alkyl or α -naphthyl-lower alkyl group, said group being unsubstituted or substituted in one or more positions by halogen, hydroxy, C_1 to C_4 alkoxy, carboxyl, functionally modified carboxyl, carboxy - C_1 - C_8 alkyl,



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functionally modified carboxy - C₁-C₈ alkyl or nitro.

5. A compound according to claim 1, in which R¹ is α -phenyl - C₁-C₄ alkyl which is unsubstituted or substituted in one or more positions by halogen, carboxyl, functionally modified carboxyl or nitro.
6. A compound according to claim 1, in which R¹ is phenyl, 3-iodophenyl, 3,4-dichlorophenyl, 3-carboxyphenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-nitrophenyl, benzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl.
7. A compound according to any of the preceding claims, in which R² is lower alkyl, lower alkenyl, lower alkynyl, oxo-lower alkyl, hydroxy- or dihydroxy-lower alkyl, hydroxy-lower alkenyl, mono-, di- or poly-halo-lower alkyl, mono-, di- or poly-halo-lower alkenyl, mono-, di- or poly-halo(hydroxy)-lower alkyl, mono-, di- or poly-halo(hydroxy)-lower alkenyl, lower alkoxy-lower alkyl, di-lower alkoxy-lower alkyl, lower alkoxy(hydroxy)-lower alkyl, lower alkoxy(halo)-lower alkyl, lower alkylthio-lower alkyl, di-lower alkylthio-lower alkyl, cyano-lower alkyl, acylamino-lower alkyl, cycloalkyl, hydroxycycloalkyl, oxa-, dioxo-, thia- and dithia-cycloalkyl, cycloalkyl-lower alkyl, cycloalkenyl-lower alkyl, cycloalkyl-(hydroxy)-lower alkyl, (lower alkylthio)cycloalkyl(hydroxy)-lower alkyl, or mono- or di-phenyl-lower alkyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, halogen, hydroxy and/or by trifluoromethyl, naphthyl-lower alkyl or unsubstituted or halo-substituted thienyl-, furyl- or pyridyl-lower alkyl.
8. A compound according to claim 7, in which R² is C₁-C₇alkyl, α,α -di-C₁-C₄alkoxy-C₁-C₄alkyl, cyano-C₁-C₄ alkyl, acylamino-C₁-C₅ alkyl, C₃-C₆cycloalkyl-C₁-C₄-alkyl, C₃-C₆cycloalkenyl-C₁-C₄alkyl, or is phenyl-C₁-C₄alkyl that is unsubstituted or mono-, di- or tri-substituted by C₁-C₄alkyl, C₁-C₄alkoxy, hydroxy and/or by halogen.
9. A compound according to claim 7, in which R² is C₁-C₅ alkyl, α,α -di-(C₁-C₄ alkoxy)methyl, α,α -di-(C₁-C₄ alkoxy)ethyl, C₃-C₆ cycloalkyl-C₁-C₄ alkyl, benzyl or 4-methoxybenzyl.
10. A compound according to claim 7, in which R² is cyclohexylmethyl or 4-methoxybenzyl.

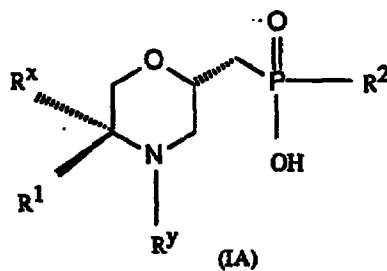


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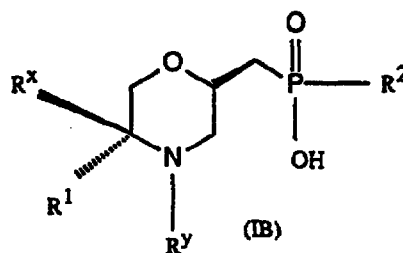
11. A compound according to any of the preceding claims, in which R^x as unsubstituted or substituted hydrocarbyl is a C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_3 to C_8 cycloalkyl, C_4 to C_{13} cycloalkylalkyl, C_6 to C_{10} aryl or C_7 to C_{13} aralkyl group, said group being unsubstituted or substituted by halogen, hydroxy, C_1 to C_4 alkoxy, carboxyl, functionally modified carboxyl, carboxy - C_1 - C_8 alkyl, functionally modified carboxy - C_1 - C_8 alkyl or nitro.
12. A compound according to any of the preceding claims, in which R^x is hydrogen, lower alkyl, C_3 to C_6 cycloalkyl, C_6 to C_8 aryl or C_7 to C_9 aralkyl.
13. A compound according to claim 12, in which R^x is hydrogen or isopropyl.
14. A compound according to any of the preceding claims, in which R^y is R^y_a and is a C_1 to C_{10} alkyl, C_3 to C_8 cycloalkyl or C_7 to C_{13} aralkyl group, said group being unsubstituted or substituted by hydroxy or C_1 to C_4 alkoxy.
15. A compound according to any of claims 1 to 13, in which R^y is a NH-protecting group and is an acyl, alkoxycarbonyl or aralkoxycarbonyl group.
16. A compound according to any of claims 1 to 13, in which R^y is hydrogen, lower alkyl, C_7 to C_9 aralkyl, tert-butoxycarbonyl or benzyloxycarbonyl.
17. A compound according to claim 1, in which R^1 is phenyl, 3-iodophenyl, 3,4-dichlorophenyl, 3-cyanophenyl, 3-(methoxycarbonyl)phenyl, 3-carboxyphenyl, 3-nitrophenyl, benzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-iodobenzyl, 4-carboxybenzyl, 4-ethoxycarbonylbenzyl or indol-3-yl, R^2 is cyclohexylmethyl or 4-methoxybenzyl, R^x is hydrogen or isopropyl and R^y is hydrogen, methyl or benzyloxycarbonyl.
18. A compound according to any of the preceding claims, which is of formula



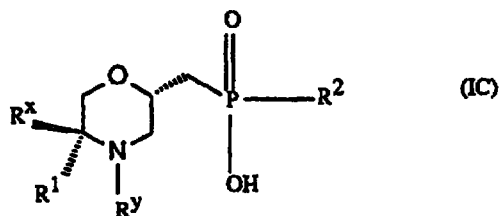
- 77 -



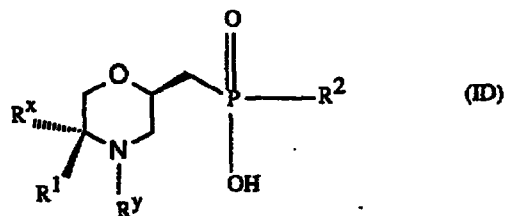
or



or



or

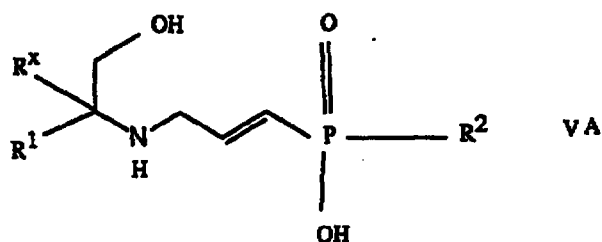


where R^1 is as defined in any of claims 1 to 6, R^2 is as defined in any of claims 1 and 7 to 10, R^x is as defined in any of claims 1 and 11 to 13 and R^y is as defined in any of claims 1 and 14 to 16.

19. A compound of formula

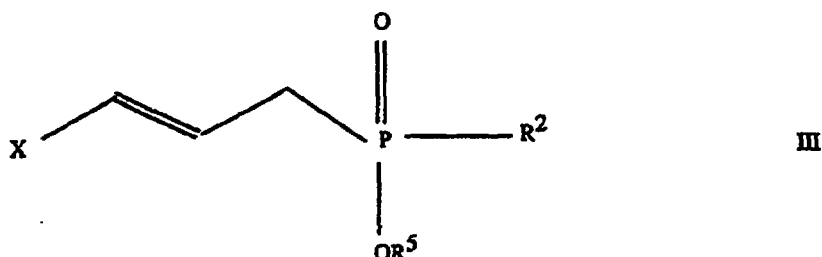


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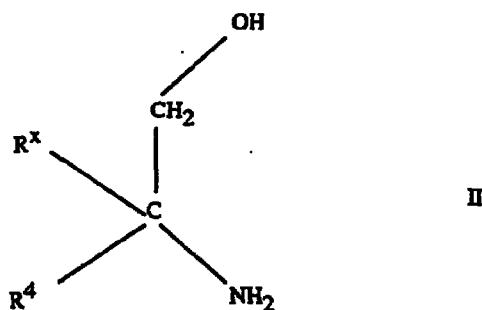
where R^1 is as defined in any of claims 1 to 6, R^2 is as defined in any of claims 1 and 7 to 10 and R^x is as defined in any of claims 1 and 11 to 13, or a salt or ester thereof.

20. A compound of formula

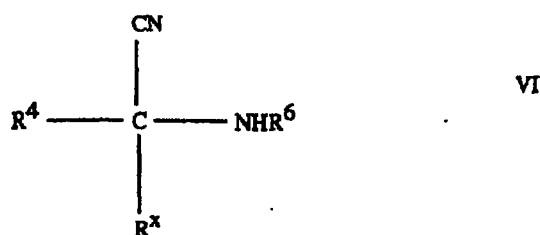


where R^2 is as defined in any of the claims 1 and 7 to 10, X is halogen and R^5 is C_1 to C_8 alkyl, provided that R^2 is not methyl when R^5 is ethyl.

21. A compound of formula



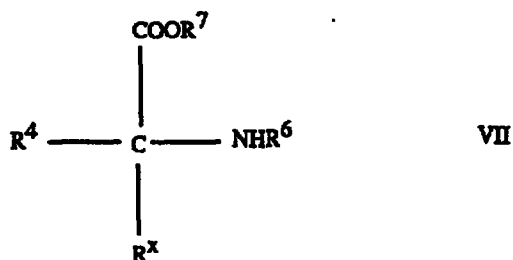
or



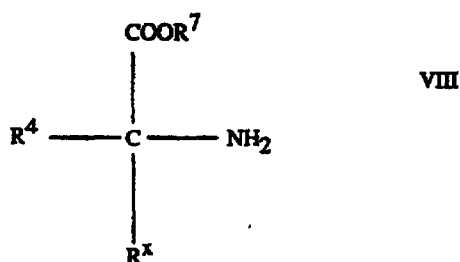
or



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or

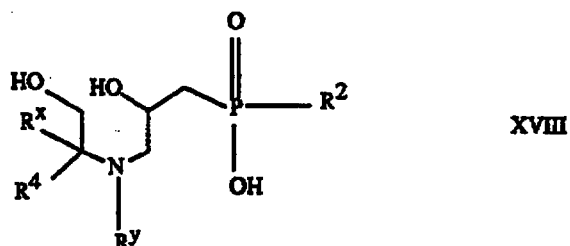


where R^4 is 3-methoxycarbonylphenyl, R^6 is hydrogen or an alkyl group of 1 to 8 carbon atoms which is unsubstituted or substituted by an unsubstituted or substituted C_6 to C_{10} aryl group, R^7 is an alkyl group of 1 to 10 carbon atoms and R^x is hydrogen or unsubstituted or substituted hydrocarbyl, or a compound of formula II or VIII where R^4 is 3, 4-dichlorophenyl and R^7 is an alkyl group of 1 to 10 carbon atoms, or a compound of formula II in which R^4 is a monovalent aromatic group connected through a carbon atom thereof to the indicated carbon atom and R^x is an unsubstituted or substituted hydrocarbyl group with the provisos that when R^4 is phenyl R^x is not methyl, ethyl, $-(\text{CH}_2)_3\text{SCH}_3$, allyl or methylol, that when R^x is aminomethyl R^4 is not phenyl, p-hydroxyphenyl or p-methoxyphenyl and that when R^4 is 2,4-dichlorophenyl, R^x is not N-triazolylmethyl, or a compound of formula II in which R^4 is iodobenzyl and R^x is hydrogen or an unsubstituted or substituted hydrocarbyl group, or a compound of formula II in which R^4 is a monovalent araliphatic group R^1 as defined in any of claims 1 and 4 to 6 and R^x is an unsubstituted or substituted hydrocarbyl group as defined in any of claims 1 and 11 to 13 other than methylol, with the provisos that when R^x is methyl, R^4 is not benzyl, 4-chlorobenzyl, 3,4-dichlorobenzyl, 3,4-dimethoxybenzyl, 2-phenylethyl, 1,3-benzodioxol-5-methyl, 3-phenyl-1-aminopropyl, α -hydroxybenzyl, α -hydroxy- α -methylbenzyl or α -hydroxy- α -methyl-4-nitrobenzyl, and that when R^4 is benzyl, R^x is not allyl or $-\text{CH}_2\text{CH}_2\text{SCH}_3$.

22. A compound of formula

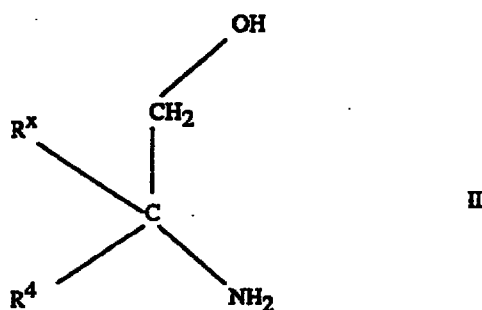


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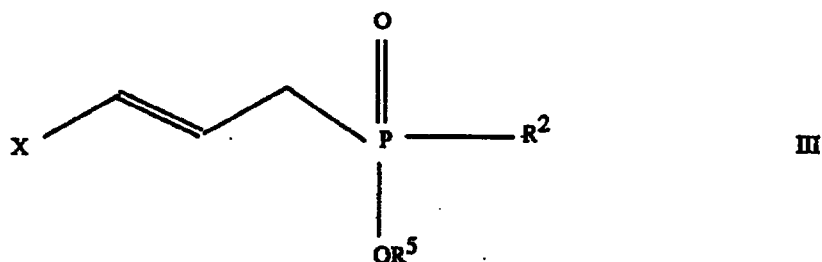


where R^1 is as defined in any of claims 1 to 6, R^2 is as defined in any of claims 1 and 7 to 10, R^3 is as defined in any of claims 1 and 11 to 13 and R^5 is as defined in any of claims 1 and 14 to 16, or a salt or ester thereof.

23. A method of preparing a compound according to claim 1 where R^5 is hydrogen which comprises reacting a compound of formula



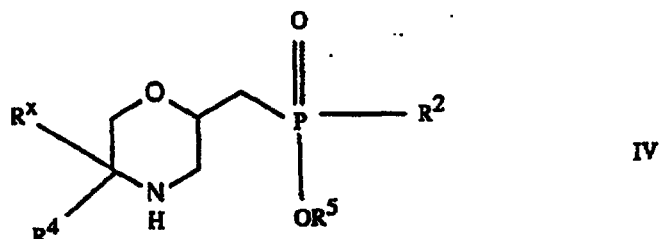
where R^4 is R^1 as defined in any of claims 1 to 6, with the proviso that R^4 is not substituted by carboxyl, and R^3 is as defined in any of claims 1 and 11 to 13 with the proviso that it is not substituted by carboxyl, with a compound of formula



where R^2 is as defined in any of claims 1 and 7, to 10, X is halogen and R^5 is C_1 to C_8 alkyl, in the presence of a base to give a compound of formula

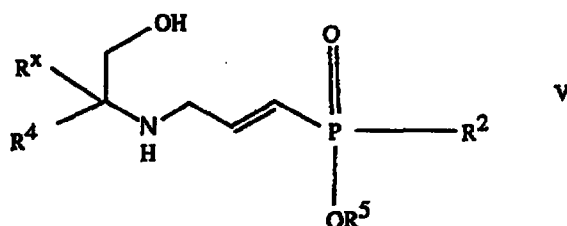


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where R^4 and R^x are as defined in formula II, followed, where required, by one or more substitution reactions to change the nature of a substituent in R^4 and/or R^x and/or by hydrolysis of an ester substituent in R^4 and/or R^x to carboxyl and/or by conversion of the ester group $-OR^5$ to $-OH$.

24. A method according to claim 23, in which the reaction of the compounds of formulae II and III is carried out by adding a weak base to a mixture of the compounds of formulae II and III in a solvent to give an intermediate of formula

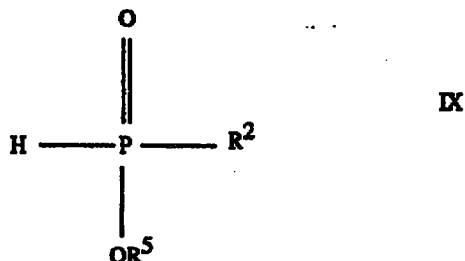


where R^2 , R^4 , R^5 and R^x are as defined in claim 23, and then treating the intermediate with base under harsher conditions than those employed in its formation.

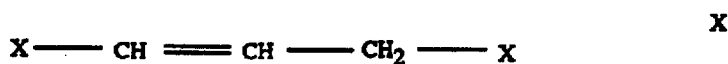
25. A method according to claim 23 or 24, in which R^4 in the compound of formula IV contains a nitro group on an aryl or heteroaryl ring and this group is converted in turn to amino by reduction, to halo by diazotisation of amino followed by reaction with an alkali metal cyanide and thence to carboxyl by hydrolysis of cyano.
26. A method of preparing a compound according to claim 20 which comprises reacting a compound of formula



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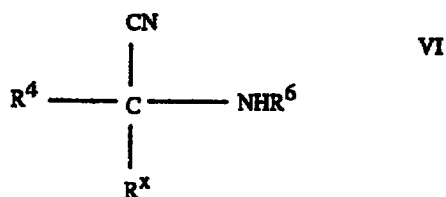


with a compound of formula

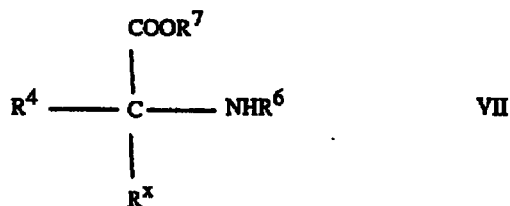


where R^2 , R^5 and X are as defined in claim 20, in the presence of a silylating agent which undergoes reaction with the compound of formula IX to form a P(III) silyl compound which then reacts with the compound of formula X.

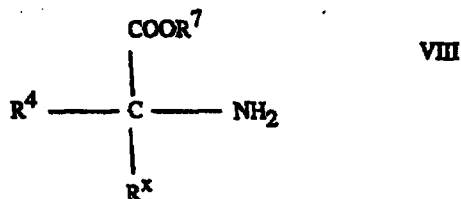
27. A method of preparing a compound of formula II according to claim 21, which comprises reacting an aldehyde or ketone of formula $\text{R}^4\text{C}(=\text{O})\text{R}^x$ with an amine of formula R^6NH_2 and an alkali metal cyanide to give a compound of formula



and either(a) reacting the compound of Formula VI with an alcohol of Formula R^7OH in the presence of an acid to form a compound of formula



removing R^6 , when R^6 is other than hydrogen, from the compound of formula VII to give a compound of formula

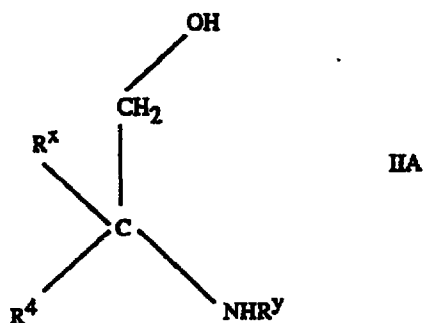


reacting the compound of formula VIII with an amino-protecting agent to convert the amino group into a protected amino group, reducing the ester group $-\text{COOR}^7$ in the protected compound to $-\text{CH}_2\text{OH}$ and removing the protecting group to form a free amino group, where R^4 , R^6 , R^7 and R^x are as defined in claim 21; or (b) subjecting the compound of formula VI to acid hydrolysis to convert the indicated cyano group to carboxyl and reducing the resulting aminocarboxylic acid by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex.

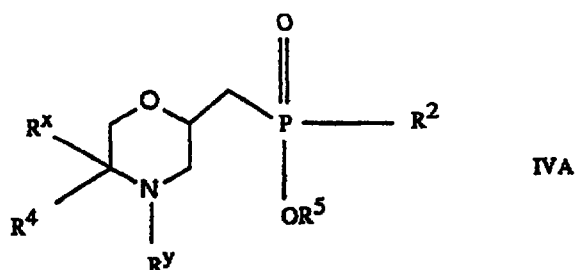
28. A method of preparing a compound of formula II according to claim 21, which comprises reducing an aminocarboxylic acid of formula $\text{R}^4\text{C}(\text{R}^x)(\text{NH}_2)\text{COOH}$, where R^4 and R^x are as defined in claim 21, by reaction with borane dimethyl sulphide in the presence of a boron trifluoride complex.
29. A method of preparing a compound according to claim 1 in which R^y is R^y_a which comprises reacting a compound of formula I as defined in claim 1 where R^y is hydrogen with either (a) a compound of formula R^y_aZ where R^y_a is as defined in claim 1 and Z is a leaving moiety or (b) an aldehyde of formula R^y_bCHO , where R^y_b is hydrogen or R^y_a as defined in claim 1, and a reducing agent which reduces imines to amines.
30. A method of preparing a compound according to claim 1 in which R^y is a NH-protecting group which comprises reacting a compound according to claim 1 in which R^y is a NH-protecting group which comprises reacting a compound according to claim 1 in which R^y is hydrogen with an acyl halide, a carboxylic acid anhydride, an alkoxycarbonyl or aralkoxycarbonyl halide or an alkyl or aralkyl dicarbonate.
31. A method of preparing a compound according to claim 1 in which R^y is R^y_a or a NH-protecting group, which comprises reacting a compound of formula



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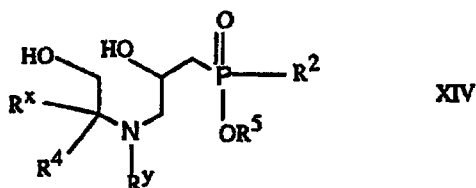


with a compound of formula III as defined in claim 23 in the presence of a base to give a compound of formula

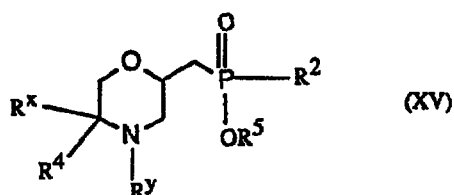


where R^4 , R^x , R^2 and R^5 are as defined in claim 23 and R^y is R^y_a or a NH-protecting group as defined in any of claims 1 and 14 to 16 followed, where required, by one or more substitution reactions to change the nature of a substituent in R^4 and/or R^x and/or by hydrolysis of an ester substituent in R^4 and/or R^x to carboxyl and/or by conversion of the ester group $-OR^5$ to $-OH$.

32. A method of preparing a compound according to claim 1 which comprises reacting a compound of formula



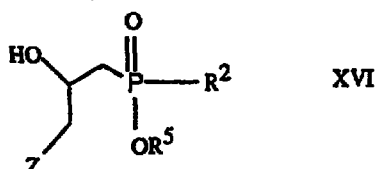
to convert the indicated primary hydroxyl group into a leaving moiety, thereby effecting cyclisation to give a compound of formula



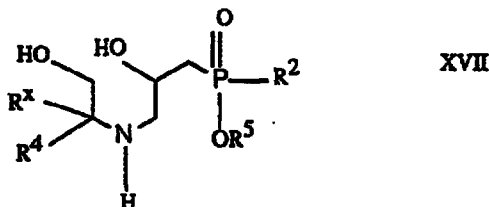


where R^2 , R^4 , R^x and R^y are as defined in claim 1 and R^5 is as defined in claim 23, followed, where required, by replacement of R^y as a NH-protecting group by hydrogen and/or by one or more substitution reactions to change the nature of a substituent in R^4 and/or R^x and/or by hydrolysis of an ester substituent in R^4 and/or R^x to carboxyl and/or by conversion of the ester group $-OR^5$ to $-OH$.

33. A method of preparing a compound of formula XIV as defined in claim 32 which comprises reacting a compound of formula II as defined in claim 23 with a compound of formula



where R^2 and R^5 are as defined in claim 32, and Z is a leaving moiety, in the presence of a hindered base, to give a compound of formula



where R^2 , R^4 , R^5 and R^x are as defined in claim 32, and replacing the indicated hydrogen attached to nitrogen by a NH-protecting group.

34. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 19 or 22, optionally together with a pharmaceutically acceptable carrier.
35. A compound according to any of claims 1 to 19 or 22 for use in a therapeutic method of treating a warm-blooded animal.
36. Use of a compound according to any of claims 1 to 19 or 22 in the preparation of a medicament for the treatment or prevention of a condition characterised by stimulation of a $GABA_B$ receptor.
37. A method of treating or preventing a condition in a warm-blooded mammal



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characterised by stimulation of a GABA_B receptor which comprises administering to the mammal a compound according to any of claims 1 to 19 or 22.