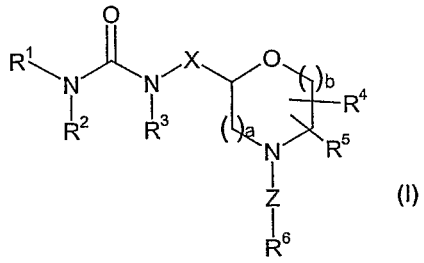
PROCESS FOR THE PREPARATION OF MORPHOLINE DERIVATIVES AND INTERMEDIATES THEREFORE

Novel Process

This invention relates to novel processes, in particular to processes for preparing certain morpholine derivatives.

Co-pending International Patent Application number PCT/GB01/04530 (Glaxo Group Limited) relates to certain morpholine urea derivatives of formula (I)



(I)

wherein:

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, aryl- SO_2-Y^1-, C_{1-6} alkyl-G-Y^1-, heteroaryl-G-aryl-Y^1-, J^1-SO_2-Y^1-, $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, $R^{17}NHCO$-Y^1-, $R^{17}NHSO_2$-Y^1-, C_{2-6} alkynyl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which C_{2-6} alkynyl and C_{2-6} alkynyl-Y^1 may be optionally substituted with a $-OR^{17}$ group, which C_{2-6} alkenyl may be optionally substituted by one or more $-COOR^{17}$ groups and which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

R^2 represents hydrogen or C_{1-6} alkyl optionally substituted by a hydroxy group;

R^3 represents hydrogen or C_{1-6} alkyl;

or R^1 and R^2 may together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2;

t represents 0 or 1;

X represents ethylene or a group of formula CR^eR^f wherein R^e and R^f independently represent hydrogen or C_{1-4} alkyl or R^e and R^f may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group;

R^4 and R^5 independently represent hydrogen or C_{1-4} alkyl;

Z represents a bond, CO, SO_2, $CR^{10}R^7(CH_2)_n$, $(CH_2)_nCR^{10}R^7$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, $CHR^7(CH_2)_nCO$, $COCHR^7(CH_2)_n$ or $SO_2CHR^7(CH_2)_n$;

R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl-C_{2-6} alkenyl-, -CN or a group of formula $-Y^2-J^3$;

R^7 represents hydrogen, C_{1-4} alkyl, $CONR^8R^9$ or $COOC_{1-6}$ alkyl;

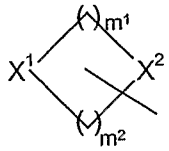
a and b represent 1 or 2, such that a+b represents 2 or 3;

G represents $-SO_2-$, $-SO_2NR^{18}-$, $-NR^{18}SO_2-$, $-NR^{18}CO-$, CO or $-CONR^{18}-$;

n represents an integer from 0 to 4;

M represents a C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-COC_{3-8}$ cycloalkyl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{15}R^{16}$, $-Y^3-CONR^{15}R^{16}$, hydroxy, oxo, $-Y^3-SO_2NR^{15}R^{16}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{13}C_{1-6}$ alkyl, $-Y^3-NR^{13}SO_2C_{1-6}$ alkyl, $-Y^3-NR^{13}CONR^{15}R^{16}$, $-Y^3-NR^{13}COOR^{14}$ or $-Y^3-OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen or C_{1-6} alkyl;

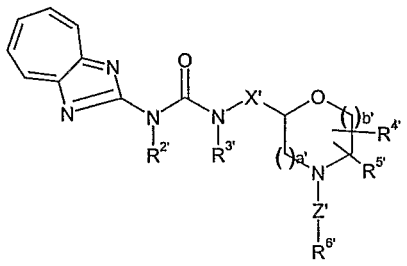
R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or R^{15} and R^{16} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

R^{17} and R^{18} independently represent hydrogen or C_{1-6} alkyl;

W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-6} alkyl, halogen or hydroxy groups;

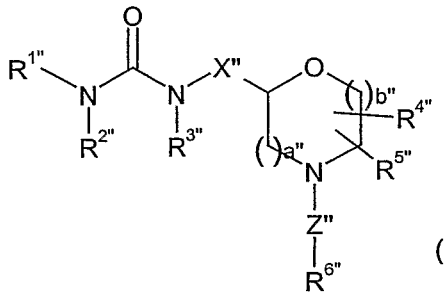
Y^1, Y^2 and Y^3 independently represent a bond or a group of formula $-(CH_2)_pCR^cR^d(CH_2)_q-$ wherein R^c and R^d independently represent hydrogen or C_{1-4} alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5;

and salts and solvates thereof;
with the provisos that;
the compound of formula (I) is not a compound of formula (I)[a]:



(I)[a]

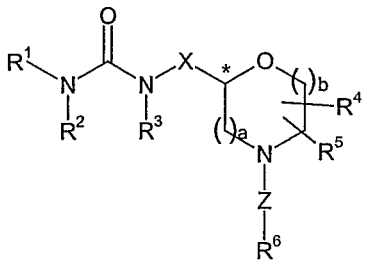
wherein $R^{2'}$ represents hydrogen or lower alkyl (specifically C_{1-4} alkyl); $R^{3'}$ represents hydrogen; X' represents methylene or ethylene; a' and b' both represent 1; $R^{4'}$ and $R^{5'}$ both represent hydrogen; and wherein the moiety $-Z'-R^{6'}$ represents halobenzyl, and;
the compound of formula (I) is not a compound of formula (I)[b]:



(I)[b]

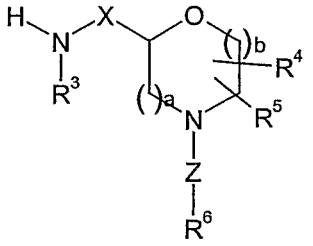
wherein $R^{1"}$ represents a hydrogen atom, a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{3-6} cycloalkylC_{1-4} alkyl group, an aryl group or an arylC_{1-4} alkyl group (particularly wherein aryl represents phenyl or naphthyl) in which the aryl moiety of the aryl group or arylC_{1-4} alkyl group may be optionally substituted with a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group or an amino group; $R^{2"}$ represents hydrogen; $R^{3"}$ represents hydrogen or C_{1-6} alkyl; X" represents methylene; a" and b" both represent 1; $R^{4"}$ and $R^{5"}$ both represent hydrogen; and wherein the moiety $-Z"-R^{6"}$ represents a C_{1-6} alkyl group, an arylC_{1-4} alkyl group (particularly wherein aryl represents phenyl or naphthyl), a heteroarylC_{1-4} alkyl group (particularly wherein heteroaryl represents 2-pyridyl, 3-pyridyl, 4-pyridyl or 1H-indol-3-yl), an aryloxyC_{2-5} alkyl group or a pyrrolidinylcarbonylC_{1-4} alkyl group in which the aryl moiety of the said groups may be optionally substituted with a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group or an amino group.

Compounds of formula (I) possess a chiral carbon atom at the position marked '*' and may therefore exist as enantiomers.



(I)

PCT/GB01/04530 also discloses a process for the preparation of compounds of formula (I) wherein enantiomers thereof may be prepared by a combination of an achiral synthesis with a resolution step. Examples of such a resolution step are preparative chiral high performance liquid chromatography (preparative chiral HPLC) and the fractional crystallisation of diastereoisomeric salts. In particular, it is disclosed in PCT/GB01/04530 that an enantiomer of a compound of formula (I) may be prepared by the resolution of a racemic modification of a compound of formula (III)

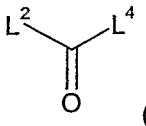


(III)

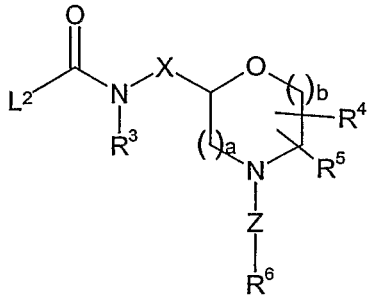
wherein;

R^3, a, b, R^4, R^5, Z, and R^6 are as defined in formula (I) above;

by fractional crystallisation of a diastereisomeric salt thereof, followed by reaction of the resolved enantiomer of the compound of formula (III) with a compound of formula (X) to give a compound of formula (IV)



(X)

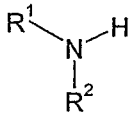


(IV)

wherein;

L^2 and L^4 are leaving groups, and R^3, a, b, R^4, R^5, Z, and R^6 are as defined in formula (I) above;

followed by reaction of a compound of formula (IV) with a compound of formula (V)



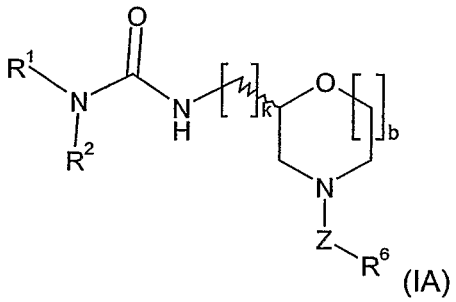
(V)

wherein;

R^1 and R^2 are as defined in formula (I) above;

to give a compound of formula (I).

Alternative processes for preparing an enantiomer of certain compounds of formula (I), being of formula (IA)



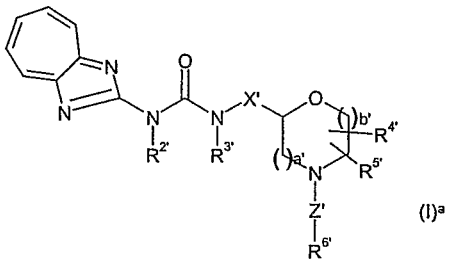
(IA)

wherein;

R^1, R^2, b, Z, and R^6 are as defined for formula (I), and;

k is 1 or 2;

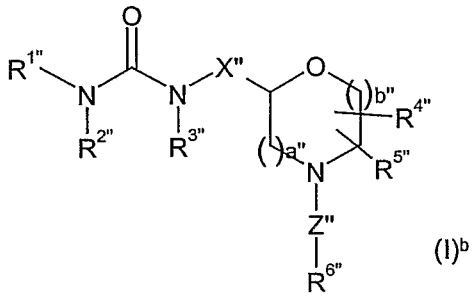
and salts and solvates thereof has now been discovered, with the provisos that; the compound of formula (IA) is not a compound of formula $(I)^a$:



$(I)^a$

wherein $R^{2'}$ represents hydrogen or lower alkyl (specifically C_{1-4} alkyl); $R^{3'}$ represents hydrogen; X' represents methylene or ethylene; a' and b' both represent 1; $R^{4'}$ and $R^{5'}$ both represent hydrogen; and wherein the moiety $-Z'-R^{6'}$ represents halobenzyl, and;

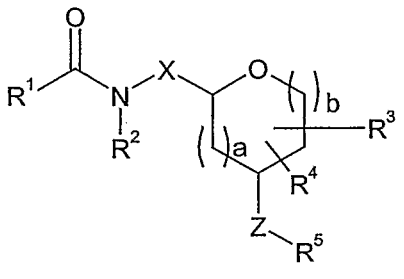
the compound of formula (IA) is not a compound of formula $(I)^b$:



$(I)^b$

wherein $R^{1''}$ represents a hydrogen atom, a C_{1-6} alkyl group, a C_{3-6} cycloalkyl group, a C_{3-6} cycloalkylC_{1-4} alkyl group, an aryl group or an arylC_{1-4} alkyl group (particularly wherein aryl represents phenyl or naphthyl) in which the aryl moiety of the aryl group or arylC_{1-4} alkyl group may be optionally substituted with a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group or an amino group; $R^{2''}$ represents hydrogen; $R^{3''}$ represents hydrogen or C_{1-6} alkyl; X'' represents methylene; a'' and b'' both represent 1; $R^{4''}$ and $R^{5''}$ both represent hydrogen; and wherein the moiety $-Z''-R^{6''}$ represents a C_{1-6} alkyl group, an arylC_{1-4} alkyl group (particularly wherein aryl represents phenyl or naphthyl), a heteroarylC_{1-4} alkyl group (particularly wherein heteroaryl represents 2-pyridyl, 3-pyridyl, 4-pyridyl or 1H-indol-3-yl), an aryloxyC_{2-5} alkyl group or a pyrrolidinylcarbonylC_{1-4} alkyl group in which the aryl moiety of the said groups may be optionally substituted with a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a C_{1-6} alkoxycarbonyl group or an amino group.

Co-pending International Patent Application publication WO 02/26722 (Glaxo Group Limited) discloses certain compounds of formula (Ip)

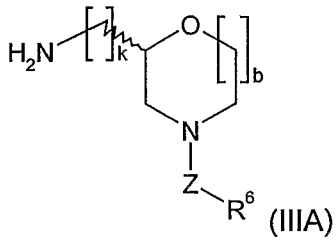


(Ip)

and processes for their preparation, including processes for the preparation of enentiomers of compounds of formula (Ip).

These processes involve the chiral synthesis of certain compounds of formula (III).

Accordingly, in a first aspect, there is provided a process for the preparation of a compound of formula (IIIA)



(IIIA)

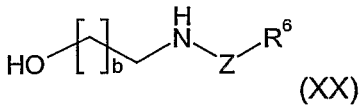
or a salt thereof;

wherein;

b, Z, and R^6 are as defined for formula (I) above, and;

k is 1 or 2;

which process comprises the reaction of a compound of formula (XX)

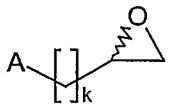


(XX)

wherein;

b, Z, and R^6 are as defined for formula (I);

with an enantiomer of a compound of formula (XXI)



(XXI)

wherein;

A is a protected amino group and k is 1 or 2;

followed by deprotection of the amino group to give a compound of formula (IIIA).

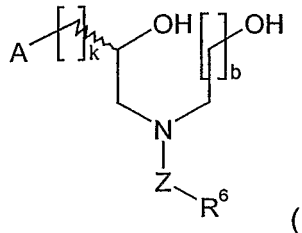
Suitable protecting groups for amines include phthalimido.

The compound of formula (IIIA) is typically prepared from the compounds of formulae (XX) and an enantiomer of a compound (XXI) under the Mitsonobu conditions as follows:

Typically, a mixture of the compound of formula (XX) and an enantiomer of a compound of formula (XXI) in a suitable solvent, such as tetrahydrofuran or toluene, is stirred, suitably for 2-36 hours at a suitable temperature, suitably the reflux temperature of the mixture, under an inert atmosphere, suitably an atmosphere of nitrogen. Further solvent, suitably toluene or tetrahydrofuran, is then added and the mixture cooled, suitably to 0-40°C. A phosphine, suitably triphenyl phosphine, is added and the mixture stirred until all the solid is dissolved. An azodicarboxylate, suitably diisopropylazodicarboxylate, is then added over a period of time, suitably 5-120 min, while maintaining the temperature at <40°C. The mixture is stirred at a suitable temperature, suitably 20-40°C. If necessary, further phosphine and azodicarboxylate reagents can be added. After a further period, the reaction mixture is concentrated to low volume. A suitable alcohol, suitably methanol or *iso*-propyl alcohol, is added and the concentration step repeated. This may be repeated as necessary. Further alcohol is then added and the mixture may be heated to a temperature suitably between 55-75°C. After a suitable period, suitably 20-45 minutes, the resultant slurry is cooled, suitably to 15-25°C, and then allowed to stand, suitably for 1.5-3 hours, after which time the product is isolated by filtration. The filter bed is washed with more alcohol and then dried *in vacuo* at 35-45°C to yield the protected compound of formula (IIIA).

The protected compound of formula (IIIA) may be deprotected to yield the compound of formula (IIIA) using standard conditions suitable for the removal of the particular protecting group, for example those conditions described in *P J Kocienski, Protecting Groups, (1994), Thieme.*

In a further aspect, the process for the preparation of the protected compound of formula (IIIA) described above may also be undertaken in two stages, in which an intermediate compound of formula (IIIB);



(IIIB)

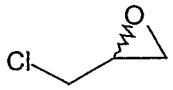
wherein;

k, Z, R^6, and b are as hereinbefore defined for formula (IIIA), and A is as hereinbefore defined for formula (XXI);

is isolated.

Typically, a mixture of the compound of formula (XX) and an enantiomer of a compound of formula (XXI) in a suitable solvent, such as tetrahydrofuran, C_{3-4} alkanol, toluene, N-methylpyrrolidinone and N,N-dimethylformamide , is stirred, suitably for 2-36 hours at a suitable temperature, suitably the reflux temperature of the mixture under an inert atmosphere, suitably an atmosphere of nitrogen. Further compound of formula (XX) is added as necessary and the mixture heated at a suitable temperature, suitably the reflux temperature of the mixture, under an inert atmosphere, suitably an atmosphere of nitrogen, for a suitable period of time. The reaction mixture is then cooled, suitably to 20-25°C, and the compound precipitated by means of addition of a suitable co-solvent, suitably diisopropyl ether. The compound of formula (IIIB) is isolated by filtration, washed with further co-solvent and dried *in vacuo*.

Alternatively, a compound of formula (IIIB) may be prepared by reaction of a compound of formula (XXII)



(XXII)

with a compound of formula (XX).

Accordingly, there is further provided a process for the preparation of a compound of formula (IIIB) which process comprises the reaction of a compound of formula (XXII) with a compound of formula (XX).

Typically, a mixture of the compound of formula (XX) and a compound of formula (XXII) in a suitable solvent, such as methyl tert-butyl ether, C_{1-4} alkanol, toluene, N-methylpyrrolidinone and N,N-dimethylformamide, is stirred, suitably for 2-36 hours at a suitable temperature, suitably room temperature, under an inert atmosphere, suitably an atmosphere of nitrogen. An aqueous work-up may be used at this point. A suitable solvent, suitably N-methylpyrrolidinone and N,N-dimethylformamide, is added to the reaction mixture, followed by potassium phthalimide. The mixture is stirred, suitably for 2-6 hours, at a suitable temperature, suitably 90-110°C. The reaction mixture is then cooled, suitably to 50-80°C, and the compound is crystallised by addition of suitable co-solvents, suitably a mixture of C_{1-4} alkanol and water. The reaction mixture is then cooled, suitably to 0-10°C. The compound of formula (IIIB) is isolated by filtration, washed with further co-solvent and dried in vacuo.

A protected compound of formula (IIIA) may then be prepared from a compound of formula (IIIB) using the process described previously.

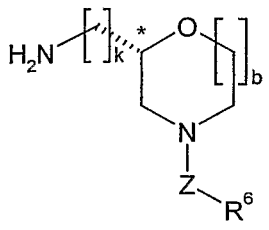
The compounds of formulae (XX) and the enantiomers of a compound of formula (XXI) and (XXII) are known, commercially available compounds, or may be prepared by analogy with known procedures, for examples those disclosed in

standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

The compound of formula (IIIA) is known and is disclosed in *J. Med. Chem., 1991, 34(2), 616-624.*

The enantiomer of the compound of formula (IIIA), being the compound of formula (IIIAS) may also be isolated from a mixture of the compound of formula (IIIAS) and its antipode, typically a racemic modification, by enzymatic resolution. A mixture of the compound of formula (IIIAS) and its antipode may be prepared by using a mixture of the enantiomers of a compound of formula (XXI) in the processes hereinbefore described. A racemic modification of the enantiomers of the compound of formula (XXI) may be prepared using procedures well known in the art.

Accordingly, there is provided in a still further aspect, a process for the separation of a compound of formula (IIIAS);



(IIIAS)

wherein;

k, b, Z, and R^6 are as hereinbefore defined for formula (IIIA);

from its antipode, which process comprises reaction of the mixture of a compound of formula (IIIAS) and its antipode with an enzyme and a suitable enzyme donor, such as an alkyl ester of a C_{4-8} alkanoic acid. A suitable enzyme is Lipase PS-C "Amano" II.

Typically, to a solution of a mixture of a compound of formula (IIIAS) and its antipode and a mixture of a suitable solvent, suitably *tert*-butyl methyl ether, and a suitable acyl donor, suitably ethyl octanoate, is added the enzyme, suitably Lipase PS-C "Amano" II, under an inert atmosphere, suitably an atmosphere of nitrogen. The mixture is stirred at elevated temperature, suitably 25-35°C for a suitable period of time, suitably 6-8hours. The enzyme is removed by vacuum filtration. To the filtrate is added de-ionised water, the resultant bi-phasic solution pH adjusted to pH 4-5 and the layers separated. To the aqueous phase is added a suitable non-polar solvent, suitably dichloromethane, and the resultant bi-phasic mixture pH adjusted to pH 6-7. The layers are then separated. To the aqueous phase is added a suitable non-polar solvent, suitably dichloromethane, and the pH of the resultant bi-phasic mixture adjusted to 9-10.

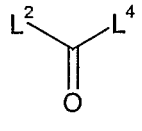
The layers are then separated and the non-polar solvent removed in vacuo to give a compound of formula (IIIAS).

For any of the hereinbefore described reactions or processes, conventional methods of heating and cooling may be employed, for example electric heating mantles and ice/salt baths respectively.

Suitably, the absolute stereochemistry of a compound of formula (IIIA) at the position marked "*" is as shown in formula (IIIAS).

Compounds of formula (IA) may then be prepared from compounds of formula (IIIA) as follows:

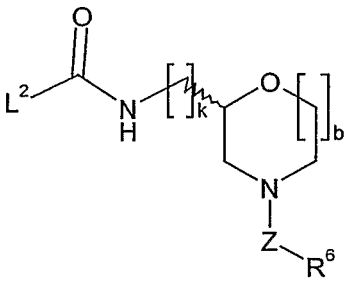
The compound of formula (IIIA) is reacted with a compound of formula (XA)



(XA)

wherein;

L^2 and L^4 represent leaving groups wherein L^2 and L^4 are the same or L^4 represents a leaving group which is more labile than L^2, to form a compound of formula (IVA)



(IVA)

wherein;

L^2, k, b, Z, and R^6 are as hereinbefore defined.

The compound of formula (IVA) is in turn is reacted with with a compound of formula (VA)

$$R^1—NHR^2 \quad (VA)$$

wherein R^1 and R^2 are as defined in formula (I) above, to give a compound of formula (IA).

Compounds of formulae (XA), and (VA) are also known, commercially available compounds, or may be prepared by analogy with known procedures,

for examples those disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

Suitable salts of the compounds of formula (IIIA) are those which may be useful in terms of isolation or handling of the compound of formula (IIIA) or those which may be useful in the preparation of compounds of formula (IA) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example tartrates, hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates. Salts of the compounds of formula (IIIA) may be prepared by procedures well known to those skilled in the art.

It is considered that the compound of formula (IIIB) is novel.

Accordingly, in an additional aspect, there is provided a compound of formula (IIIB) or a salt thereof.

Suitable salts of the compounds of the invention are those which may be useful in terms of isolation or handling of the compounds of the invention. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example tartrates, hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates. Salts of the compounds of the invention may be prepared by procedures well known to those skilled in the art.

A compound of formula (IA) may be prepared from a compound of formula (IIIA) as follows.

Typically, a compound of formula (IIIA) in a suitable first solvent is reacted with N,N'-carbonyldiimidazole in the same solvent at reduced temperature, suitably a temperature in the range –10 - 20 °C over a suitable period of time, for example 5-60 minutes. Suitable solvents include tetrahydrofuran, dichloromethane, C_{3-4} alkanol, isopropyl acetate, N-methylpyrrolidinone and N,N-dimethylformamide. The mixture is warmed to a suitable temperature, suitably 5-30°C and held at this temperature for a suitable period of time, for example 10-60 minutes. The compound of formula (VA) is then added, the mixture heated to a suitable elevated temperature, for example a temperature in the range 40-65°C, and stirred for a suitable period of time, for example 60-360 minutes. The reaction is then cooled to a suitable temperature, and a suitable second solvent, for example isopropyl acetate, added, followed by a aqueous solution of a suitable acidic salt, such as potassium dihydrogen phosphate or acetic acid. The solution is clarified if necessary, the lower

aqueous layer removed and the upper organic layer washed with further acidic salt solution, followed by water. The organic phase is distilled at atmospheric pressure to remove the first solvent and leave a slurry or solution of the compound of formula (IA) in the second solvent. The compound of formula (IA) may be isolated by filtration or evaporation of the solvent as appropriate.

A compound of formula (Ip) may be prepared from a compound of formula (IIIA) and a compound of formula R^1-COOH wherein R^1 is as defined for formula (Ip) as follows.

Typically, a solution of a compound of formula R^1-COOH in N,N-dimethylformamide in an inert atmosphere, suitably an atmosphere of nitrogen, is treated with O-(7-azabenzotriazol-1-yl)-N,N,N'N'-tetramethylammonium hexafluorophosphate and N,N-diisopropylethylamine followed by a solution of a compound of formula (IIIA) in a suitable solvent, for example N,N-dimethylformamide, and the mixture stirred at 18-30°C for 2-8 hours. The solvent is removed in vacuo and the residue dissolved in a suitable solvent, for example ethyl acetate. The solution is washed with 10% aqueous citric acid, brine, saturated aqueous sodium hydrogen carbonate, and brine dried over magnesium sulphate and evaporated in vacuo.

Suitable salts of the compounds of formulae (IA) and (Ip) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formulae (IA) and (Ip) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates. Examples of solvates include hydrates.

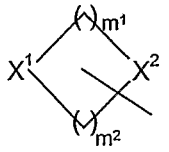
Salts and solvates of the compounds of formulae (IA) and (Ip)may be prepared by procedures well known to those skilled in the art.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected, for example those methods discussed in standard reference texts of synthetic methodology such as *P J Kocienski, Protecting Groups, (1994), Thieme.*

Suitably, the variable R^1 of compounds of formulae (IA) and (VA) represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, aryl- SO_2-Y^1-, C_{1-6} alkyl-G-Y^1-, J^1-SO_2-Y^1-, $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, C_{2-6} alkynyl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-

Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which C_{2-6} alkynyl and C_{2-6} alkynyl-Y^1 may be optionally substituted with a $-OR^{17}$ group and which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

J^1, J^2 and J^3 independently represent a moiety of formula (K):



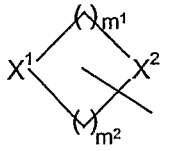
(K)

wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{15}R^{16}$, -Y^3-$CONR^{15}R^{16}$, hydroxy, oxo, -Y^3-$SO_2NR^{15}R^{16}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{13}C_{1-6}$ alkyl, -Y^3-$NR^{13}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{13}CONR^{15}R^{16}$, -Y^3-$NR^{13}COOR^{14}$ or -Y^3-$OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

Suitably, the variable R^2 of compounds of formulae (IA) and (VA) represents hydrogen or C_{1-6} alkyl.

More suitably, the variable R^1 of compounds of formulae (IA) and (VA) represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, -Y^1-J^1, -Y^1-CO-J^1 or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups;

J^1, J^2 and J^3 independently represent a moiety of formula (K):



(K)

wherein X^1 represents oxygen, nitrogen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, nitrogen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3, m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to

5, also provided that when X^2 represents oxygen, nitrogen, NR^{12} or sulphur, $m^1$and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) -Y^3-aryl, -Y^3-heteroaryl, -Y^3-CO-aryl, -Y^3-CO-heteroaryl, -C_{1-6} alkyl, -Y^3-$COOC_{1-6}$ alkyl, -Y^3-COC_{1-6} alkyl, -Y^3-W, -Y^3-CO-W, -Y^3-$NR^{15}R^{16}$, -Y^3-$CONR^{15}R^{16}$, hydroxy, oxo, -Y^3-$SO_2NR^{15}R^{16}$, -Y^3-SO_2C_{1-6} alkyl, -Y^3-SO_2aryl, -Y^3-SO_2heteroaryl, -Y^3-$NR^{13}C_{1-6}$ alkyl, -Y^3-$NR^{13}SO_2C_{1-6}$ alkyl, -Y^3-$NR^{13}CONR^{15}R^{16}$, -Y^3-$NR^{13}COOR^{14}$ or -Y^3-$OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring.

More suitably, the variable R^2 of compounds of formulae (IA) and (VA) represents hydrogen or C_{1-6} alkyl.

Preferred values of Z for compounds of formulae (IIIA), (XX), and (IA) are those wherein Z represents a bond, CO, SO_2, $CR^{10}R^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, or $CHR^7(CH_2)_nCO$.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) and references to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-3 hetero atoms selected from nitrogen, oxygen and sulphur. References to 'heteroaryl' may also be extended to include references to mono- and bicyclic heterocyclic aromatic rings containing 4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. pyridinyl, pyrimidinyl, thiophenyl, furanyl, pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl. Further examples of monocyclic heterocyclic aromatic rings include pyrazinyl, tetrazolyl or imidazolyl. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl or indolyl. Further examples of bicyclic heterocyclic aromatic rings include benzimidazolyl. Yet further examples of bicyclic heterocyclic aromatic rings include dihydrobenzofuranyl and pyrrolopyridinyl. Carbocyclic and heterocyclic aromatic rings may be optionally substituted, e.g. by one or more C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, cyano, hydroxy, nitro, amino, W, -$N(CH_3)_2$, -$NHCOC_{1-6}$ alkyl, -OCF_3, -CF_3, -$COOC_{1-6}$ alkyl, -$OCHF_2$, -SCF_3, -$CONR^{19}R^{20}$, -$SO_2NR^{19}R^{20}$ (wherein R^{19} and R^{20} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl), -$NHSO_2CH_3$, -SO_2CH_3 or -SCH_3 groups. A further substituent of carbocyclic and heterocyclic aromatic rings may be –COOH. Yet further substituents of carbocyclic and heterocyclic aromatic rings may be -$CH_2N(CH_3)_2$ or one or more –SH groups, wherein it will be appreciated that said group may tautomerise to form an =S group.

Examples of group M include tetrahydronaphthalenyl.

Examples of group W include piperidinyl, pyrrolidinyl, morpholinyl and piperazinyl which may be optionally substituted with one or more C_{1-6} alkyl, halogen, or hydroxy groups.

Examples of group J^1 include N-($COOCH_2CH_3$)-piperidin-4-yl, N-(CH_3)-piperidin-4-yl, N-($COCH_3$)-piperidin-4-yl, pyrrolidin-1-yl, tetrahydropyran-4-yl or N-morpholinyl. Further examples of group J^1 include N-(cyclopropylcarbonyl)-piperidin-4-yl, N-(methylsulphonyl)-piperidin-4-yl, thiopyranyl and tetrahydrothienyl.

Examples of group J^2 include (4-phenyl)-piperidin-1-yl, (4-$COOCH_2CH_3$)-piperazin-1-yl, (2-(3-hydroxy-pyrrolidin-1-yl-methyl))-piperidin-1-yl, N-morpholinyl, (4-$N(CH_3)_2$)-piperidin-1-yl, (4-(3-fluorophenyl))-piperazin-1-yl, (4-(4-fluorophenyl))-piperazin-1-yl, (4-pyrimidinyl)-piperazin-1-yl, (4-CH_3)-piperazin-1-yl, (4-$CONH_2$)-piperidin-1-yl, (3,3-dimethyl)-piperidin-1-yl, (4-$COCH_3$)-piperazin-1-yl, (4-(1-pyrrolidinyl-carbonylmethyl))-piperazin-1-yl, (4-hydroxy)-piperidin-1-yl, (4-methyl)-piperidin-1-yl, (4-(2-furanyl-carbonyl))-piperazin-1-yl, (4-benzyl)-piperazin-1-yl or (3-$CH_3SO_2CH_2$-)-morpholin-1-yl. Further examples of group J^2 include thiomorpholinyl, pyrrolidinyl and benzazepinyl.

Examples of group J^3 include indolinyl, which may be optionally substituted.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkylene and alkoxy shall be interpreted similarly. References to C_{3-8} cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl.

Preferably, R^1 represents C_{1-6} alkyl (particularly propyl), C_{2-6} alkenyl (particularly wherein said C_{2-6} alkenyl is substituted by one or more -$COOR^{17}$ groups, eg. –HC=CH-COOH), C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1- (particularly wherein heteroaryl represents thiazolyl, indolyl, furanyl, dihydrobenzofuran, oxoimidazolyl, isoxazolyl, thienyl, thioxodihydroimidazolyl, tetrazolyl, pyrazinyl, pyrrolopyridinyl), aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1- (particularly wherein aryl represents phenyl and heteroaryl represents thiadiazolyl, pyrazolyl or isoxazolyl), heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1- (particularly wherein aryl represents phenyl), heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1- (particularly wherein C_{1-6} alkyl represents ethyl, propyl, -$CH(CH_3)_2$ or -$C(CH_3)_3$), M-Y^1-, J^1-Y^1-, J^1-CO-Y^1-, aryl-SO_2-Y^1-, C_{1-6} alkyl-G-Y^1- (particularly wherein C_{1-6} alkyl represents methyl and G represents -$NR^{18}CO$-, –$CONR^{18}$-, –$NR^{18}SO_2$- or –SO_2NR^{18}-), heteroaryl-G-aryl-Y^1- (particularly wherein aryl represents phenyl and heteroaryl represents thiazolyl and G represents -$NR^{18}SO_2$-), J^1-SO_2-Y^1- (particularly wherein J^1 represents 1-pyrrolidinyl), $R^{17}O(CO)$-C_{2-6} alkenyl-Y^1-, $R^{17}NHCO$-Y^1- (particularly wherein R^{17} represents hydrogen), C_{2-6} alkynyl-Y^1- (particularly -C≡CH or wherein said C_{2-6} alkynyl is substituted with a –OR^{17} group, eg. $HOCH_2$-C≡C-), aryl-CO-Y^1- (particularly wherein aryl represents phenyl), C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-,

which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups and which C_{2-6} alkynyl-Y^1- may be optionally substituted with a $-OR^{17}$ group.

More preferred R^1 groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl-Y^1-, heteroaryl-Y^1-, aryl-$(O)_t$-aryl-Y^1-, aryl-$(O)_t$-heteroaryl-Y^1-, heteroaryl-$(O)_t$-aryl-Y^1-, heteroaryl-$(O)_t$-heteroaryl-Y^1-, C_{2-6} alkenyl-Y^1-, aryl-O-Y^1-, heteroaryl-O-Y^1-, C_{1-6} alkyl-SO_2-Y^1-, M-Y^1-, J^1-Y^1-, J^1-CO-Y^1- or C_{3-8} cycloalkyl-Y^1- or C_{3-8} cycloalkenyl-Y^1-, which cycloalkyl or cycloalkenyl may be optionally substituted by one or more hydroxyl or C_{1-6} alkyl groups.

Yet more preferably, R^1 represents aryl-Y^1-, heteroaryl-Y^1, aryl-$(O)_t$-aryl-Y^1-, C_{3-8} cycloalkyl-Y^1-, C_{2-6} alkenyl-Y^1- or C_{1-6} alkyl-SO_2-Y^1- especially wherein aryl represents phenyl or naphthyl optionally substituted by one or more C_{1-6} alkyl (especially methyl), halogen (especially chlorine, fluorine and bromine), CH_3O-, CH_3S-, F_2CHO-, $CH_3OC(O)$-, -CN, $-CF_3$, CF_3-S-, CF_3-O-, or $(CH_3)_2N$-, groups, and wherein heteroaryl represents pyridinyl optionally substituted by one or more halogen atoms (especially chlorine) and wherein cycloalkyl represents cyclohexyl. Further preferred substituents of phenyl include $-NHCOCH_3$ and $-CONH_2$. Yet further preferred substituents of phenyl include $-SO_2NH_2$, $-CONHCH_3$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, -COOH, $-CON(CH_3)_2$, $-SO_2CH_3$, $-CONHCH_2CH_3$, -CONHcyclopropyl and $-SO_2$NHcyclopropyl. Also preferably, R^1 represents C_{2-6} alkynyl-Y^1-. A series of particularly preferred compounds are those wherein R^1 represents aryl-Y^1- wherein aryl represents phenyl optionally substituted by one or more C_{1-6} alkyl (especially methyl), halogen (especially chlorine, fluorine and bromine), CH_3O-, CH_3S-, F_2CHO-, $CH_3OC(O)$-, -CN or $-CF_3$ groups. Further most preferred substituents of phenyl include $-NHCOCH_3$ and $-CONH_2$. A yet further most preferred substituent of phenyl includes SO_2NH_2. Most preferably, R^1 will also represent C_{2-6} alkenyl-Y^1- (particularly CH_2=CH-Y^1-), C_{3-8} cycloalkyl-Y^1- (particularly cyclohexyl-Y^1-) and C_{1-6} alkyl-SO_2Y^1- (particularly CH_3SO_2-Y^1-). Also most preferably, R^1 represents C_{2-6} alkynyl-Y^1- (particularly HC≡C-Y^1).

Especially preferred R^1 groups are aryl-Y^1- and heteroaryl-Y^1-, most especially wherein aryl represents phenyl and heteroaryl represents a 5 membered monocyclic heterocyclic aromatic ring (most particularly tetrazolyl) each of which may be optionally substituted as indicated above.

Preferred substituents of heteroaryl include $-CH_3$, $-CONH_2$, $-CH_2N(CH_3)_2$, halogen (particularly chlorine), $-OCH_3$, $-COOCH_3$ and $-NH_2$.

Most especially preferred compounds are those wherein R^1 represents phenyl-Y^1- which phenyl is substituted with a $-CONH_2$ or $-CONHCH_3$ group, preferably $-CONH_2$, and tetrazolyl-Y^1- which tetrazolyl is substituted with a methyl group.

Preferably, Y^1 represents a bond or C_{1-6} alkylene, more preferably a bond, methylene or ethylene, propylene, $-C(CH_3)_2-$ or $-CH(CH_3)-$, particularly a bond, methylene or ethylene, most preferably a bond or methylene, especially methylene.

Preferably, Y^2 represents a bond.

Preferably, Y^3 represents a bond.

Preferably, R^2 represents hydrogen, methyl or hydroxypropyl, more preferably hydrogen or methyl, especially hydrogen.

Also preferably, R^1 and R^2 together with the nitrogen atom to which they are attached form a group of formula J^2 wherein said nitrogen atom substitutes for either X^1 or X^2.

Preferably, R^4 and R^5 independently represent hydrogen or methyl. Most preferably, R^4 and R^5 represent hydrogen.

Preferably, Z represents a bond, CO, SO_2, $CR^{10}R^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$ or $CHR^7(CH_2)_nCO$.

More preferably, Z represents CO, $CHR^7(CH_2)_n$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$ or $CHR^7(CH_2)_nCO$, especially CH_2CO, $(CH_2)_2$, $(CH_2)_2S$, $(CH_2)_2O$, $(CH_2)_2OCO$, $(CH_2)_3CO$, CO, CHR^7, particularly CH_2, $CHCH_3$ or CH_2CO, most particularly CH_2 or CH_2CO, especially CH_2.

Preferably, R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl, CN, aryl, heteroaryl or a group of formula $-Y^2-J^3$, more preferably R^6 represents phenyl (optionally substituted with one or more halogen, phenyl or C_{2-6} alkenyl groups), naphthyl, C_{1-6} alkyl, C_{2-6} alkenyl, CN or a 5 membered aromatic heterocyclic ring containing 1 to 3 heteroatoms selected from O, N or S optionally substituted by halogen or C_{1-6} alkyl. Especially, R^6 represents phenyl (optionally substituted with one or more halogen (especially chlorine, fluorine or iodine), phenyl or 3–$CH=CH_2$ groups), naphthyl, indolinyl, methyl, $-CH=CH_2$, -CN or thiophenyl optionally substituted by halogen (especially chlorine). Most preferred R^6 represents indolinyl (especially indolin-1-yl) or else represents phenyl substituted by one or more halogen (eg. chlorine or fluorine) groups, particularly dichlorophenyl, 3-chlorophenyl, 5-chlorothiophenyl, 4-fluorophenyl and 3,4-difluorophenyl, most particularly dichlorophenyl, especially 3,4-dichlorophenyl.

Preferably, R^7 represents hydrogen, methyl, $COOC_{1-6}$ alkyl or $CONR^8R^9$, more preferably hydrogen, $COOC_{1-6}$ alkyl or $CONR^8R^9$ most preferably hydrogen, COOEt or $CONR^8R^9$, especially hydrogen.

Preferably, R^8 and R^9 represent hydrogen.

Preferably, R^{10} represents hydrogen.

Preferably, R^{11} and R^{12} independently represent hydrogen or methyl.

Preferably, R^{13} and R^{14} independently represent hydrogen or methyl.

Preferably, R^{15} and R^{16} independently represent hydrogen or methyl or R^{15} and R^{16} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring, especially hydrogen or methyl.

Preferably, R^{17} represents hydrogen.

Preferably, R^{18} represents hydrogen.

Preferably, R^{19} and R^{20} independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl, especially hydrogen, cyclopropyl or methyl. Particularly, R^{19} and R^{20} represent hydrogen.

Preferably, R^c represents hydrogen or methyl, particularly hydrogen.

Preferably, R^d represents hydrogen or methyl, particularly hydrogen.

Preferably, b represents 1.

Preferably, n represents 0, 1 or 2.

Preferably, p + q equals an integer from 0 to 2, more preferably, p and q independently represent 0 or 1 such that p + q equals an integer from 0 to 1.

Preferably, t represents 0.

Preferably, W represents pyrrolidinyl or piperidinyl, especially pyrrolidinyl.

Preferably, X^1 represents oxygen, nitrogen or NR^{11}.

Preferably, X^2 represents CH_2, oxygen, nitrogen or NR^{12}.

Preferably, m^1 and m^2 independently represent an integer from 1 to 2, such that $m^1 + m^2$ is in the range from 3 to 4.

Preferably, J^1 represents piperidinyl (particularly piperidin-4-yl) or tetrahydropyranyl (particularly tetrahydropyran-4-yl) optionally substituted by one or two $-COOCH_2CH_3$, -COOtBu, $-CH_3$, $-COCH_3$, $-SO_2N(CH_3)_2$, $-SO_2CH_3$, -COPhenyl or 3, 5-dimethylisoxazol-4-ylsulphonyl groups. Also preferably, J^1 represents morpholinyl, thiopyranyl or tetrahydrothienyl which may be optionally substituted as above (particularly dioxidotetrahydrothienyl).

Preferred substituents for J^1 include $-CH_2$-aryl (particularly wherein aryl represents phenyl optionally substituted with one or more halogen atoms, eg. dichlorophenyl), -COcyclopropyl or $-Y^3$-SO_2heteroaryl (particularly wherein heteroaryl represents dimethylisoxazolyl).

Preferably, J^2 represents piperidinyl (particularly piperidin-1-yl), morpholinyl (particularly N-morpholinyl) or piperazinyl (particularly piperazin-1-yl) optionally substituted by one or two phenyl, $-COOCH_2CH_3$, $-N(CH_3)_2$, fluorophenyl, $-CH_3$, $-CONH_2$, $-COCH_3$, $-CH_2CO$-(N-pyrrolidinyl), hydroxy, -CO-(2-furan), benzyl or $-CH_2SO_2CH_3$. Preferably, J^2 also represents thiomorpholinyl, pyrrolidinyl or benzazepinyl optionally substituted in a similar manner.

Other preferred substituents for J^2 include halogen (particularly fluorine), $-COOCH_2CH_3$, -CO-furoyl, $-SO_2CH_3$, –pyridinyl-CH_3 or oxo groups.

Preferably, J^3 represents indolinyl, particularly indolin-1-yl.

In a most preferred aspect, the variables R^1 and R^2 of compounds of formulae (IA) and (VA) represent 4-amidobenzyl or 2-methyltetrazol-5-ylmethyl, and hydrogen respectively; the variables b, Z, and R^6 for the compounds of formulae (IIIA), (XX), (IVA), and (IA) represent 1, $-CH_2-$, and 3,4-dichlorophenyl respectively; and the variable k for the compounds of formulae (IIIA), (XXI), and (IA) represents 1.

Suitable salts of the compounds of formula (IA) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates. Examples of solvates include hydrates. Salts and solvates of the compounds of formula (IA) may be prepared by procedures well known to those skilled in the art.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The following Examples illustrate the invention but do not limit it in any way.

General experimental details

NMR

Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker DPX250 or DPX400 instrument.

LC/MS System A

The following Liquid Chromatography Mass Spectroscopy (LCMS) system was used: 3mm ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents: A – 0.1% formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3ml per minute. The following gradient profile was used: 100% A for 0.7min; A + B mixtures, gradient profile 0 – 100% B over 3.5min; hold at 100%B for 1.1min; return to 100% A over 0.2min.

LC/MS System B

3μm Phenomenex Luna (50 x 2mm i.d.) column, eluting with solvents: A – 0.05% trifluoroacetic acid in water, B – 0.05% trifluoroacetic acid in acetonitrile, at 40°C and at a flow rate of 1ml per minute. The following linear gradient was used: 0 to 95% B over 8 minutes.

Analytical HPLC column, conditions and eluent

Reverse-phase high performance liquid chromatography was carried out using a Luna 3mm C18(2) (50 x 2.0mm i.d.) column eluting with solvents: A – 100% water, 0.05% TFA; and B – 100% acetonitrile, 0.05%TFA, at a flow rate of 2ml per minute, and at 60°C. The following gradient profile was used:0-95% B over 2.00min, return to 0% B over 0.01min.

Chiral analytical HPLC

(Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Examples

Example 1: Preparation of [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine – enzyme method

To a solution of [4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine (6g) and ethyl octanoate (17.2ml) in *tert*-butyl methyl ether (60ml) was added enzyme Lipase PS-C "Amano" II (6g), under an atmosphere of nitrogen. The mixture was stirred at 200rpm and heated to 30°C. The mixture was stirred at 30°C for a further 6h. The enzyme was removed by vacuum filtration and washed with *tert*-butyl methyl ether. Deionised water (30ml) was added to the filtrate and the resultant bi-phasic solution was pH adjusted to pH 5.7 and the layers were separated. To the aqueous phase was added dichloromethane (30ml) and the resultant bi-phasic mixture was pH adjusted to pH 6.6. The aqueous phase was separated, diluted with dichloromethane and the pH was adjusted to >pH 9. The layers were separated and solvent was evaporated in vacuo to give the title compound as a yellow oil (2.1g, 99%a/a, 96%ee)

LC/MS (System A) R_t 1.77 min, Mass Spectrum *m/z* 275 [MH^+].

Example 2: Preparation of 2-{[(2*R*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.038 g) and (S)-2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (N-(2,3-epoxypropyl)-phthalimide) (2.032g) in tetrahydrofuran (3.3ml) was stirred and heated at reflux under nitrogen. After 21.5h more tetrahydrofuran (12.5ml) was added and the mixture was cooled to 3°. Triphenyl phosphine (2.793g) was added and the mixture was stirred until all

the solid had dissolved. Diisopropylazodicarboxylate (2.1ml) was then added over 12min maintaining the temperature at <7°. After 2.25h the mixture was allowed to warm to 22°. After 5.3h more triphenylphosphine (121mg) and diisopropylazodicarboxylate (0.09ml) were added. After 22.5h the reaction mixture was concentrated to near dryness. Propan-2-ol (12ml) was added and the concentration repeated, this was repeated once more. More propan-2-ol (12ml) was added and the mixture was heated to 70°. After 0.5h the slurry was cooled to 22° and then after a further 2h the product was collected. The bed was washed with propan-2-ol (2x4ml) and then dried *in vacuo* at 40° to give the title compound (2.622g).

NMR (DMSO d-6): 1.93δ (1H) d of d, J=11.0Hz, 8.8Hz; 2.10δ (1H) d of t, J=3.5Hz, 11.3Hz; 2.52δ (1H) broad d, J=11.3Hz; 2.77δ (1H) broad d, J=11.3Hz; 3.3 – 3.8δ (7H) m; 7.31δ (1H) d of d, J=8.2Hz, 1.9Hz; 7.55δ (1H) d, J=1.9Hz; 7.68δ (1H) d, J=8.2Hz; 7.86δ (4H) m.

Preparation of [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine

A slurry of 2-{[(2*R*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (1.00g) in water(8.5ml) was heated to 75° and then treated dropwise with concentrated sulphuric acid (2.5ml). The mixture was then heated at reflux. After 23h the reaction mixture was cooled to 22° and then treated with dichloromethane (6ml). 880 Ammonia solution (7ml) was then added dropwise with cooling. More dichloromethane (10ml) was added. The aqueous phase was separated and extracted with more dichloromethane (10ml). The combined organic phase was washed with water (5ml) and then evaporated to dryness. The residue was reevaporated from DCM to give the title compound as an oil (662mg).

LC/MS (System A) R_t 1.77 min, Mass Spectrum *m/z* 275 [MH^+].

Example 3: Preparation of [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine – enzyme method

To a solution of [4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine (3g) and ethyl octanoate (5.8ml) in *tert*-butyl methyl ether (30ml) was added enzyme Lipase PS-C "Amano" II (3g), under an atmosphere of nitrogen. The mixture was stirred at 200rpm and heated to 30°C. The mixture was stirred at 30°C for a further 6.5h. The enzyme was removed by vacuum filtration. To the filtrate was added de-ionised water (15ml). The resultant bi-phasic solution was pH adjusted to pH 5.5 and the layers were separated. To the aqueous phase was added DCM (15ml) and the resultant bi-phasic mixture was pH adjusted to pH 6.5. The layers were separated and solvent was evaporated in vacuo to give the title compound as a yellow oil (1.0g, 98.9%a/a, 94.8%ee)

LC/MS (System A) R_t 1.77 min, Mass Spectrum *m/z* 275 [MH^+].

Example 4: Preparation of 2-{[(2*R*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (400g g) and (S)-2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (N-(2,3-epoxypropyl)-phthalimide) (399.6g) in toluene (1150ml) was stirred and heated at 103-107°C under nitrogen. After 22.5h the mixture was cooled to <60°C and charged with tetrahydrofuran (2800ml). Triphenyl phosphine (548g) was added and the mixture was stirred until all the solid had dissolved, then cooled to 5-9°C. Diisopropylazodicarboxylate (412ml) was then added over 70min maintaining the temperature at <12°. The mixture was warmed to 21-25° and stirred for 1.5h. The reaction mixture was concentrated by distillation to a final volume of 2800ml. Methanol (2800ml) was added and the concentration repeated to a volume of 2800ml. More methanol (2000ml) was added and the mixture was heated to 55°. After 0.75h the slurry was cooled to 18° and then after a further 1h the product was collected. The bed was washed with methanol (2x1200ml) and then dried *in vacuo* at 40° to give the title compound (526.9g).

Example 5: Preparation of 2-{(2*R*)-3-[(3,4-dichlorobenzyl)(2-hydroxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione

To a solution of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.8g) in tetrahydrofuran (6.2 ml) is added (S)-2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (3.1g) with stirring, under a nitrogen atmosphere. The mixture was heated to 90 °C over 1 h, then held at this temperature for 18 h. Further 2-[(3,4-dichlorobenzyl)amino]ethanol (0.14g) is added, and the reaction mixture heated to 90 °C for a further 5h. The reaction mixture is cooled to 22 °C, and diisopropyl ether (21ml) added, and the product isolated by vacuum filtration. The filter cake is washed with diisopropyl ether (3 ml) and dried in vacuo at 40 ° to give the title compound as a white solid (4.79g).
LC/MS (System B) R_t 3.85min, Mass Spectrum m/z 423 [MH^+]

Example 6: 2-{(2*R*)-3-[(3,4-dichlorobenzyl)(2-hydroxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione (alternative method)

A suspension of of 2-[3,4-dichlorobenzyl)amino]ethanol (10.0g) and (*R*)-(-)-epichlorohydrin (3.6ml) in 1-propanol (2.5ml) was stirred at 15-25°C for 20h. The mixture was diluted with methyl tert-butyl ether (50ml) and treated with 2N hydrochloric acid (50ml). The layers were separated, and the organic phase was washed with further 2N hydrochloric acid (20ml). The combined aqueous phases were treated with 10N sodium hydroxide (17ml) and extracted with

methyl tert-butyl ether (50ml). Further 10N sodium hydroxide (3ml) was added to the aqueous phase, and this was extracted with methyl tert-butyl ether (20ml). The combined organic phases were washed with water (40ml), and then concentrated to an oil. This was diluted with N,N-dimethylformamide (30ml) and treated with potassium phthalimide (8.3g). The mixture was heated for 3h at 110°C, cooled to 80°C and diluted with 1-propanol (30ml) and water (50ml). After cooling to 60°C, further water (20ml) was added, and the mixture was seeded with authentic 2-{(2*R*)-3-[(3,4-dichlorobenzyl)(2-hydroxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione. The suspension was cooled to 0-5°C, isolated by filtration and washed with aqueous 1-propanol (2 x 30ml). The cake was dried in vacuo at 40° to give the title compound as a white solid (7.5g).

Example 7: Preparation of 2-{[(2*R*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione

A suspension of 2-{(2*R*)-3-[(3,4-dichlorobenzyl)(2-hydroxyethyl)amino]-2-hydroxypropyl}-1*H*-isoindole-1,3(2*H*)-dione (5.0g) and triphenylphosphine (3.57g) in tetrahydrofuran (25ml) was treated with a solution of diisopropylazodicarboxylate (2.67ml) in tetrahydrofuran (3ml) at 8-13°C over 18min. The reagent was rinsed in with tetrahydrofuran (2ml), and the mixture was warmed to 15-25°C and stirred for 1 hour. The reaction mixture was concentrated *in vacuo* to a paste, and resuspended in methanol (30ml) at 55-65°C. The suspension was stirred for 30min at this temperature, cooled to 5-10°C over 90min, and held at this temperature for 40min. The product was collected by filtration, washed with chilled methanol (15ml) and dried *in vacuo* at 40° to give the title compound as a white solid (4.08g).

Description 1: Preparation of 4-({[({[(2*S*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}amino)carbonyl]amino}methyl)benzamide benzenesulfonate hydrate

A solution of [(2*S*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine (5g) in THF (10ml) is added to a slurry of N,N'-carbonyldiimidazole (3.2g) in THF (30ml) at 5-10 °C over ca. 10 min. The mixture is warmed to 15±3° and held at this temperature for ca. 15min. 4-Aminomethyl benzamide (3.0g) is then added, the mixture heated to 60±3° and stirred at this temp for 75 min.

The reaction is cooled to 22±3° and isopropyl acetate (40ml) added, followed by a solution of potassium dihydrogen phosphate (5% w/v, 40ml). The solution is filtered through celite (2g), the lower aqueous layer is removed and the upper organic layer washed with potassium dihydrogen phosphate (5% w/v, 2x40ml) then water (40ml). The organic phase is distilled at atmospheric pressure to remove THF and leave a slurry of 4-({[({[(2*S*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl} amino)carbonyl]amino}methyl)benzamide in isopropyl acetate (ca

60ml). This is cooled to 50±3° and isopropanol (30ml) is added, followed by an aqueous solution of benzene sulfonic acid (32% w/v, 10ml). The mixture is cooled to 22±3° over ca 1h, seeded with authentic 4-({[({[(2*S*)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl} amino)carbonyl]amino}methyl)benzamide hydrate and aged at 22±3° for 72 h. The contents are cooled to 0±3° over 1h and filtered. The filter cake is washed with a 4:1:0.1 mixture of isopropyl acetate/isopropyl alcohol/water (2.5ml) and dried in vacuo at 25±5° to give the title compound as a white solid (6.9g).

NMR (DMSO d-6): 2.81δ (1H) broad t; 3.0 – 3.4δ (5H) m; 3.67δ (2H) m; 4.02δ (1H) d of d, J=12.7Hz, 2.5Hz; 4.25δ (1H) d, 5.9Hz; 4.37δ (2H) m; 6.24δ (1H) t, J=5.6Hz; 6,58δ (1H) t, J=5.9Hz; 7.3δ (6H) m; 7.48δ (1H) d of d, J=8.3Hz, 2.0Hz; 7.61δ (2H) m [benzene sulphonate]; 7.75δ (1H) d, J=8.3Hz; 7.81δ (1H) d, 2.0Hz; 7.82δ (2H) m; 7.91δ (1H) broad s; 9.85 (1H) broad s [NH^+].

Description 2: Preparation of N-{[(2S)-4-(3,4-dichlorobenzyl)-2-morpholinyl]methyl}-N'-[(2-methyl-2H-tetrazol-5yl)methyl]

A suspension of 1-[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamine, 1:1 salt with D-tartaric acid (70g) in water (350ml) and dichloromethane (420ml) was treated with 35% aqueous ammonia (35ml) at <10°C. The aqueous phase was washed with further dichloromethane (70ml), and the combined organic phases were washed with water (70ml). The organic solution was concentrated to low volume, diluted with tetrahydrofuran (420ml) and reconcentrated to low volume. This solution in tetrahydrofuran was added to a suspension of carbonyl diimidazole (29.8g) in tetrahydrofuran (455ml) over *ca* 20min at 0 – 5°C. The mixture was warmed to 10-15°C, and held for 30min. Isopropanol (21ml) was added over 5min, and the mixture was stirred for a further 20min at 10-15°C. 1-(2-Methyl-2H-tetrazol-5yl)methanamine hydrochloride (25.2g) was added, and the mixture was heated to 55-60°C, and held for 5h. Tetrahydrofuran (200ml) was removed by distillation, and the mixture was cooled to 40-45°C. The mixture was treated with 12% aqueous potassium dihydrogen phosphate (350ml), and the aqueous phase was removed. The organic phase was diluted with ethyl acetate (175ml) and washed with 3%w/w aqueous sodium chloride (175ml). The organic phase was warmed to 40-45°C, filtered and washed with tetrahydrofuran (70ml). The solution was concentrated to low volume by distillation, diluted with isopropanol (595ml), and concentrated to low volume by distillation. Further isopropanol (770ml) was added, the mixture was heated to 75°C and cooled to 60-65°C. The solution was seeded, heated at 30-60°C for 18h, and then cooled to 10-15°C. The product was isolated by filtration, washed with isopropanol and dried in vacuo to give the title compound as a white solid (54.4g).

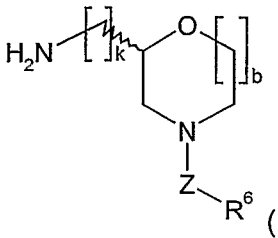
LC-MS (System A) Rt 2.21min, mass spectrum 414/416, MH+

Description 3: N-{[(2*S*)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl}-2-(5-phenyl-2H-tetraazol-2-yl)acetamide

A solution of (5-phenyl-2H-tetraazol-2-yl)acetic acid (0.082g) in N,N-dimethylformamide (2ml) under nitrogen was treated with O-(7-azabenzotriazol-1-yl)-N,N,N'N'-tetramethylammonium hexafluorophosphate (0.152g) and N,N-diisopropylethylamine (0.139ml) followed by a solution of 1-[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methanamine (0.110g) in N,N-dimethylformamide (3ml), and the mixture was stirred at 22°C for 4h. The solvent was removed in vacuo and the residue dissolved in ethyl acetate (20ml). The solution was washed with 10% aqueous citric acid (20ml), brine (20ml), saturated aqueous sodium hydrogen carbonate (20ml) and brine (20ml), dried ($MgSO_4$) and evaporated in vacuo. Purification by flash chromatography on silica gel (Merck 9385), eluting with ethyl acetate, followed by trituration of the resultant product with diethyl ether, gave the title compound as a white solid (0.184g).
LC-MS (System A): Rt 2.85min. Mass Spectrum *m/z* 461 [MH^+].

Claims

1. A process for the preparation of a compound of formula (IIIA)



(IIIA)

or a salt thereof;

wherein;

Z represents a bond, CO, SO_2, $CR^{10}R^7(CH_2)_n$, $(CH_2)_nCR^{10}R^7$, $CHR^7(CH_2)_nO$, $CHR^7(CH_2)_nS$, $CHR^7(CH_2)_nOCO$, $CHR^7(CH_2)_nCO$, $COCHR^7(CH_2)_n$ or $SO_2CHR^7(CH_2)_n$;

R^6 represents C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, aryl-C_{2-6} alkenyl-, -CN or a group of formula $-Y^2-J^3$;

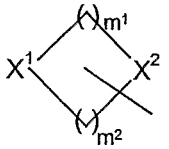
R^7 represents hydrogen, C_{1-4} alkyl, $CONR^8R^9$ or $COOC_{1-6}$ alkyl;

a and b represent 1 or 2, such that a+b represents 2 or 3;

n represents an integer from 0 to 4;

M represents a C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group fused to a monocyclic aryl or monocyclic heteroaryl group;

J^3 represents a moiety of formula (K):



(K)

wherein X^1 represents oxygen, NR^{11} or sulphur, X^2 represents CH_2, oxygen, NR^{12} or sulphur, m^1 represents an integer from 1 to 3 and m^2 represents an integer from 1 to 3, provided that m^1+m^2 is in the range from 3 to 5, also provided that when both X^1 and X^2 represent oxygen, NR^{11}, NR^{12} or sulphur, m^1 and m^2 must both not equal less than 2, wherein K is optionally substituted by one or more (eg. 1 or 2) $-Y^3$-aryl, $-Y^3$-heteroaryl, $-Y^3$-CO-aryl, $-COC_{3-8}$ cycloalkyl, $-Y^3$-CO-heteroaryl, $-C_{1-6}$ alkyl, $-Y^3-COOC_{1-6}$ alkyl, $-Y^3-COC_{1-6}$ alkyl, $-Y^3$-W, $-Y^3$-CO-W, $-Y^3-NR^{15}R^{16}$, $-Y^3-CONR^{15}R^{16}$, hydroxy, oxo, $-Y^3-SO_2NR^{15}R^{16}$, $-Y^3-SO_2C_{1-6}$ alkyl, $-Y^3-SO_2$aryl, $-Y^3-SO_2$heteroaryl, $-Y^3-NR^{13}C_{1-6}$ alkyl, $-Y^3-NR^{13}SO_2C_{1-6}$ alkyl, -

Y^3-$NR^{13}CONR^{15}R^{16}$, -Y^3-$NR^{13}COOR^{14}$ or -Y^3-$OCONR^{15}R^{16}$ groups, and is optionally fused to a monocyclic aryl or heteroaryl ring;

R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen or C_{1-6} alkyl;

R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or R^{15} and R^{16} together with the nitrogen atom to which they are attached may form a morpholine, piperidine or pyrrolidine ring;

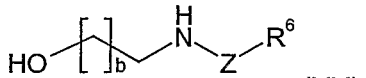
R^{17} and R^{18} independently represent hydrogen or C_{1-6} alkyl;

W represents a saturated or unsaturated, non-aromatic 5-7 membered ring containing between 1 and 3 heteroatoms selected from nitrogen, oxygen or sulphur, optionally substituted with one or more C_{1-6} alkyl, halogen or hydroxy groups;

Y^1, Y^2 and Y^3 independently represent a bond or a group of formula -$(CH_2)_pCR^cR^d(CH_2)_q$- wherein R^c and R^d independently represent hydrogen or C_{1-4} alkyl or R^c and R^d may together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl group, and p and q independently represent an integer from 0 to 5 wherein p + q is an integer from 0 to 5;, and;

k is 1 or 2;

which process comprises the reaction of a compound of formula (XX)

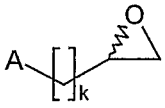


(XX)

wherein;

b, Z, and R^6 are as defined for formula (IIIA);

with an enantiomer of a compound of formula (XXI)



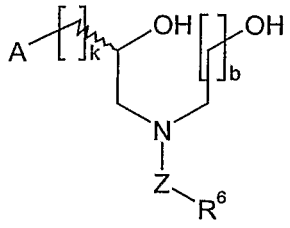
(XXI)

wherein;

A is a protected amino group and k is 1 or 2;

followed by deprotection of the amino group to give a compound of formula (IIIA).

2. A process according to claim 1 wherein an intermediate compound of formula of formula (IIIB);

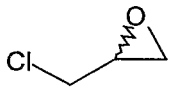


(IIIB)

wherein;

k, Z, R^6, and b are as hereinbefore defined for formula (IIIA) in claim 1, and A is a protected amino group;
is isolated.

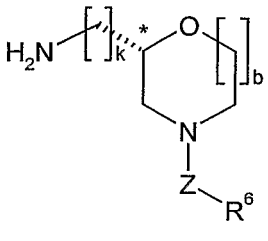
3. A process for the preparation of a compound of formula (IIIB) as defined in claim 2, which process comprises the reaction of a compound of formula (XXII)



(XXII)

with a compound of formula (XX) as defined in claim 1.

4. A process for the separation of a compound of formula (IIIAS);

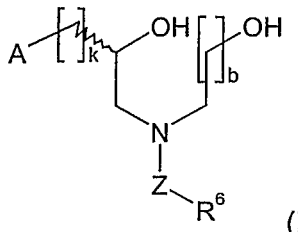


(IIIAS)

wherein;

k, b, Z, and R^6 are as defined for formula (IIIA) in claim 1;
from its antipode, which process comprises reaction of the mixture of a compound of formula (IIIAS) and its antipode with an enzyme and a suitable enzyme donor.

5. A compound of formula (IIIB)



(IIIB)

wherein;

k, Z, R^6, and B are as defined for formula (IIIA) in claim 1 and A isa protected amino group;

or a salt thereof.