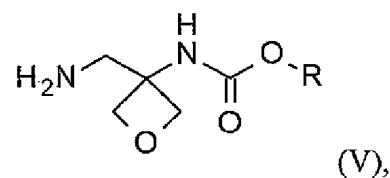


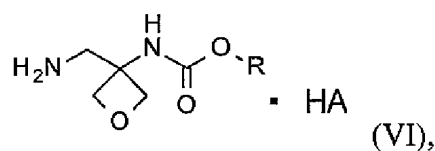
wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-, and wherein x is an integer selected from 1 to 6;

step c) amination of a compound of formula (IV) to form a compound of formula (V)



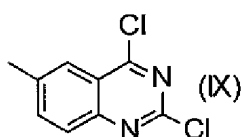
5 wherein R is as defined above;

step d) salt formation of a compound of formula (V) with an acid to form a compound of formula (VI)

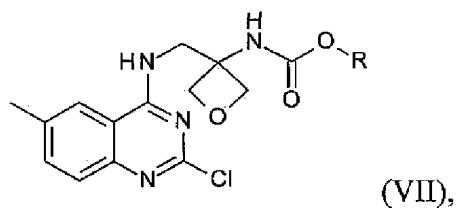


wherein R is as defined above;

10 step e) substitution reaction of a compound of formula (VI) with a compound of formula (IX)

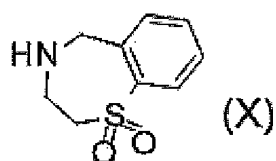


to give a compound of formula (VII)

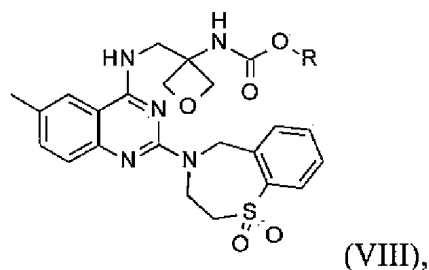


wherein R is as defined above;

step f) substitution reaction of a compound of formula (VII) with a compound of formula (X)

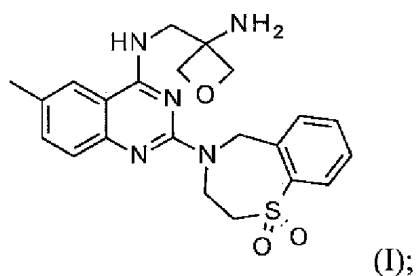


to give a compound of formula (VIII)



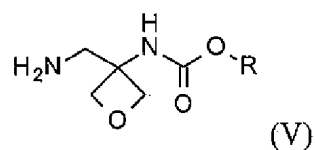
5 wherein R is as defined above;

step g) comprises deprotection of a compound of formula (VIII) to give a compound of formula (I)



and if necessary, form a pharmaceutically acceptable addition salt.

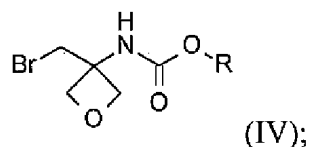
10 In another aspect, there is provided a process for the preparation of a compound of the formula (V):



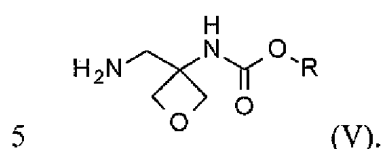
wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-, and wherein x is an integer selected from 1 to 6,

comprising the following steps:

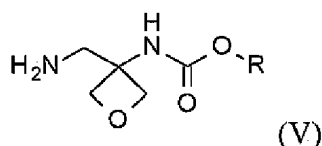
Step a) Conversion of carboxy group to carbamate to form a compound of formula (IV)



Step b) Amination of a compound of formula (IV) to form a compound of formula (V)

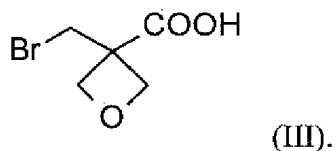


In another aspect, there is provided a compound of formula (V):



wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-, and wherein x is an integer selected from 1 to 6.

10 In another aspect, there is provided a compound of formula (III):



DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the term “C₁₋₆alkyl” signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 5 carbon atoms, for example as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, tert-butyl, n-pentyl, 3-methylbutyl, 1,1-dimethylpropyl, n-hexyl, 2-ethylbutyl and the like. Particular “C₁₋₆alkyl” groups are tert-butyl and 1,1-dimethylpropyl.

15

The term " C_xH_{2x} " signifies a saturated, linear- or branched chain alkyl group containing 1 to 6, particularly 1 to 4 carbon atoms.

The term " C_{1-6} alkoxy" signifies a group C_{1-6} alkyl-O-, wherein the " C_{1-6} alkyl" is as defined above, for example methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, 2-butoxy, tert-butoxy
5 and the like. Particular " C_{1-6} alkoxy" groups are methoxy and ethoxy and more particularly methoxy.

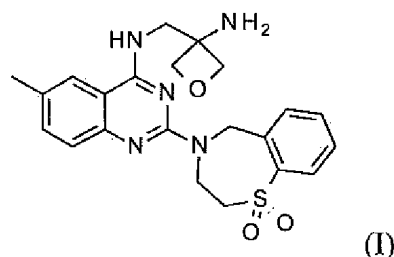
The term " C_{1-6} alkoxyphenyl" signifies a phenyl substituted by C_{1-6} alkoxy group as defined above at ortho, meta or para position. Particular " C_{1-6} alkoxyphenyl" group is 4-methoxyphenyl.

The term "amino" refers to primary ($-NH_2$), secondary ($-NH-$) or tertiary amino ($-N<$).

10 The term "hydroxy" refers to the group -OH.

Claims

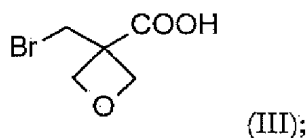
1. Process for the preparation of a compound of the formula (I):



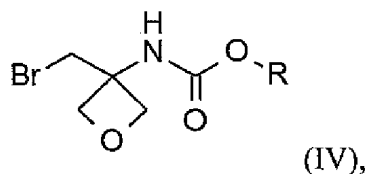
and pharmaceutically acceptable addition salts thereof,

5 comprising the following steps:

step a) oxidation of [3-(bromomethyl)oxetan-3-yl]methanol of formula (II) to form a compound of formula (III)

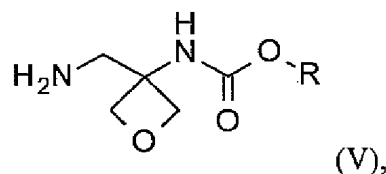


10 step b) conversion of carboxy group of a compound of formula (III) to carbamate to form a compound of formula (IV)



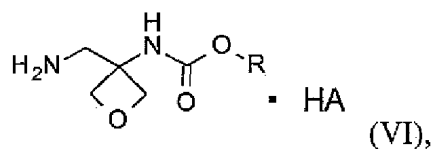
wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-, and wherein x is an integer selected from 1 to 6;

15 step c) amination of a compound of formula (IV) to form a compound of formula (V)



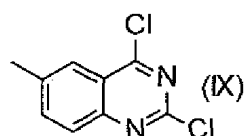
wherein R is as defined above;

step d) salt formation of a compound of formula (V) with an acid to form a compound of formula (VI)

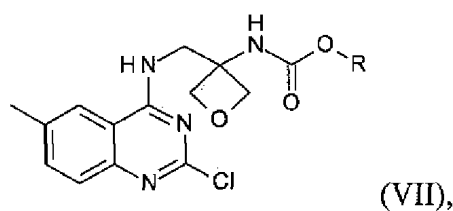


wherein R is as defined above;

5 step e) substitution reaction of a compound of formula (VI) with a compound of formula (IX)

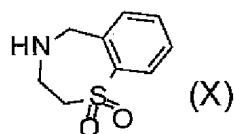


to give a compound of formula (VII)

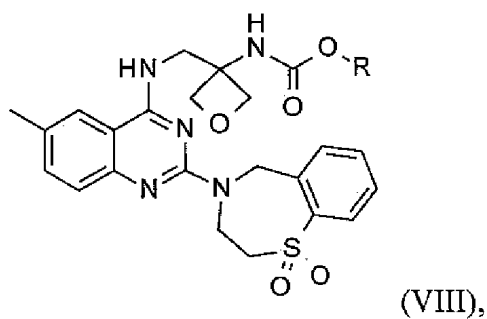


wherein R is as defined above;

10 step f) substitution reaction of a compound of formula (VII) with a compound of formula (X)

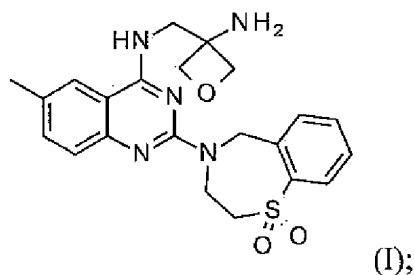


to give a compound of formula (VIII)



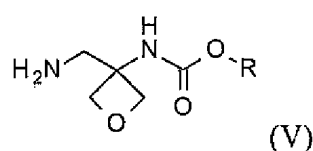
wherein R is as defined above;

step g) comprises deprotection of a compound of formula (VIII) to give a compound of formula (I)



and if necessary, form a pharmaceutically acceptable addition salt.

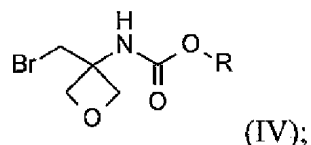
2. Process for the preparation of a compound of the formula (V):



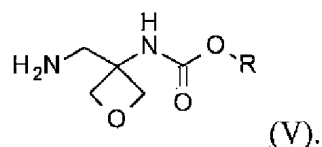
5 wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-, and wherein x is an integer selected from 1 to 6,

comprising the following steps:

Step a) Conversion of carboxy group to carbamate to form a compound of formula (IV)



10 Step b) Amination of a compound of formula (IV) to form a compound of formula (V)



3. A process according to claim 1 or 2, wherein R is tert-butyl, 1,1-dimethylpropyl, benzyl or 4-methoxyphenylmethyl.

15 4. A process according to claim 1, wherein step a) is performed with an oxidant at a reaction temperature range between 0°C and 100°C, particularly between 15°C to 25°C.

5. A process according to claim 1, wherein step a) is performed in a solvent selected from water, acetonitrile, dichloromethane, ethyl acetate and isopropyl acetate; or a co-solvent

which is a mixture of two or more kinds of solvents selected from water, acetonitrile, dichloromethane, ethyl acetate and isopropyl acetate. More particular solvent is a co-solvent of water and acetonitrile.

- 5 6. A process according to claim 4, wherein the oxidant is selected from sodium hypochlorite, potassium permanganate, 2,2,6,6-tetramethylpiperidinoxy and pyridinium chlorochromate; or a co-oxidant which is a mixture of two or more kinds of oxidants selected from sodium hypochlorite, potassium permanganate, 2,2,6,6-tetramethylpiperidinoxy and pyridinium chlorochromate, particularly the oxidant is a co-oxidant of 2,2,6,6-tetramethylpiperidinoxy and sodium hypochlorite.
- 10 7. A process according to any one of claims 1 or 2, wherein step b) of claim 1 or step a) of claim 2 is performed with an azide reagent and a base in an organic solvent and followed by adding an alcohol at temperature range of 0 °C and 100 °C, particularly 80°C.
8. A process according to claim 7, wherein the azide reagent is diphenylphosphoryl azide.
- 15 9. A process according to claim 7, wherein the base used is triethylamine, diisopropylethylamine or 4-methyl morpholine, more particularly 4-methylmorpholine.
10. A process according to any one of claim 7, wherein the solvent used is acetonitrile, toluene, chlorobenzene or dichloromethane, more particularly is toluene.
- 20 11. A process according to any one of claim 7, wherein the alcohol used is tert-butanol, 2-methyl-2-butanol, benzyl alcohol or 4-methoxyphenylmethanol, more particularly is 4-methoxyphenylmethanol.
12. A process according to claim 1, wherein step c) is performed with an amination agent, at reaction temperature range of 0 °C and 60 °C, particularly in the range of 25°C and 30°C.
13. A process according to claim 12, wherein the amination agent used in step c) is liquid ammonia.

14. A process according to claim 1, wherein step d) is performed in a solvent with an organic or inorganic acid at a temperature range of 0°C and 60°C, particularly in the range of 15°C and 25°C.

15. A process according to claim 14, wherein the solvent used in step d) is tetrahydrofuran, 2-methyltetrahydrofuran, acetonitrile, ethylacetate or methyl tert-butyl ether, more particularly in methyl tert-butyl ether.

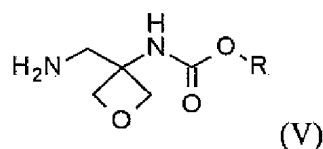
16. A process according to claim 14 or 15, wherein the acid used in step d) is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, L-tartaric acid, citric acid, L-lactic acid, maleic acid, fumaric acid, succinic acid, methanesulfonic acid, benzenesulfonic acid, benzoic acid, p-toluenesulfonic acid, oxalic acid, p-nitrobenzoic acid, salicylic acid or 4-chlorobenzoic acid, more particularly 4-chlorobenzoic acid.

17. A process according to claim 1, wherein step e) is performed in an organic solvent, particularly in tetrahydrofuran at reaction temperature range between 10°C and 30°C.

18. A process according to claim 1, wherein step f) is performed in an organic solvent with acid catalyst in temperature range between 0°C and 100°C, particularly between 60°C and 80°C.

19. A process according to claim 1, wherein step g) is performed in an organic solvent with acid in temperature range between 0°C and 100°C, particularly between 10°C and 40°C.

20. A compound of formula (V):



wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-, and wherein x is an integer selected from 1 to 6.

21. A compound of formula (III):