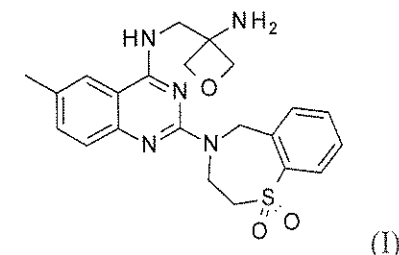


compound of formula (I) by hydrogenation with palladium on carbon will lead to heavy metal residual issue, which is not suitable for process chemistry and large scale manufacture. In addition, another intermediate, tert-butyl [(3-aminooxetan-3-yl)methyl] carbamate, for synthesizing compound of formula (I) suffers from instability as the primary amine.

- 5 In this invention, a simple and effective synthetic approach is developed to synthesize compounds of formula (I). This synthetic approach can be applied on technical scale and allows to obtain the product in a good yield, desired purity and stable form without using heavy metal catalyst.

SUMMARY

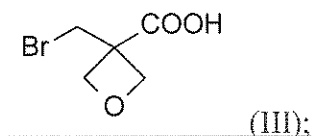
- 10 In one aspect, there is provided a process for the preparation of a compound of the formula (I):



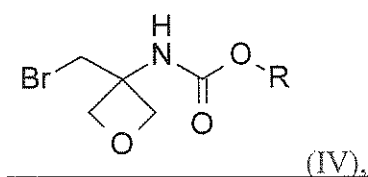
and pharmaceutically acceptable addition salts thereof.

comprising the following steps:

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

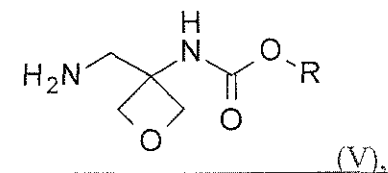


step b) conversion of carboxy group of a compound of formula (III) to carbamate to form a compound of formula (IV)



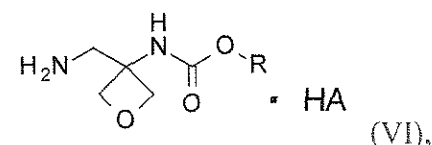
wherein R is C₁₋₆alkyl, C₁₋₆alkoxyphenyl-C_xH_{2x}- or phenyl-C_xH_{2x}-;

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



wherein R is as defined above;

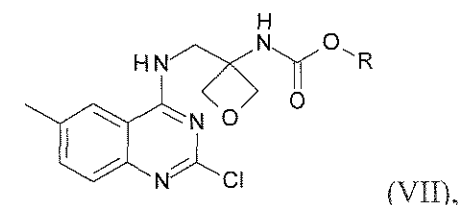
- 5 step d) salt formation of a compound of formula (V) with an acid to form a compound of formula (VI)



wherein R is as defined above;

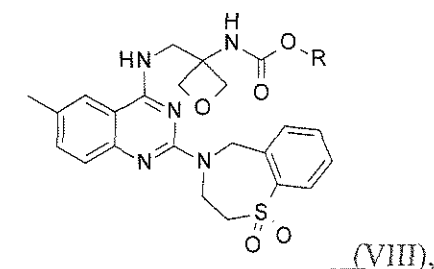
step e) substitution reaction of a compound of formula (VI) with a compound of formula (IX) to

- 10 give a compound of formula (VII)



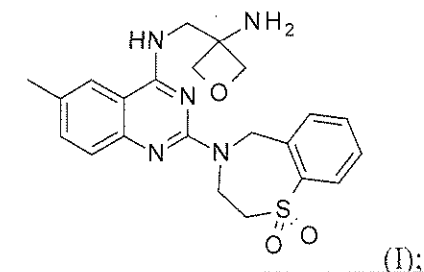
wherein R is as defined above;

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



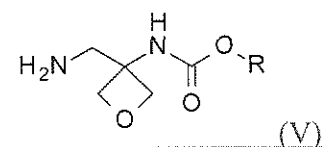
wherein R is as defined above;

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



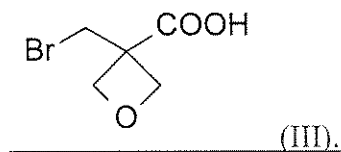
5 and if necessary, form a pharmaceutically acceptable addition salt.

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}-.

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



10

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,
15 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.

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 “C₁₋₆alkoxy” signifies a group C₁₋₆alkyl-O-, wherein the “C₁₋₆alkyl” is as defined above, for example methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, 2-butoxy, tert-butoxy
5 and the like. Particular “C₁₋₆alkoxy” groups are methoxy and ethoxy and more particularly methoxy.

The term “C₁₋₆alkoxyphenyl” signifies a phenyl substituted by C₁₋₆alkoxy group as defined above at ortho, meta or para position. Particular “C₁₋₆alkoxyphenyl” group is 4-methoxyphenyl.

The term “amino” refers to primary (-NH₂), secondary (-NH-) or tertiary amino ().

10 The term “hydroxy” refers to the group -OH.