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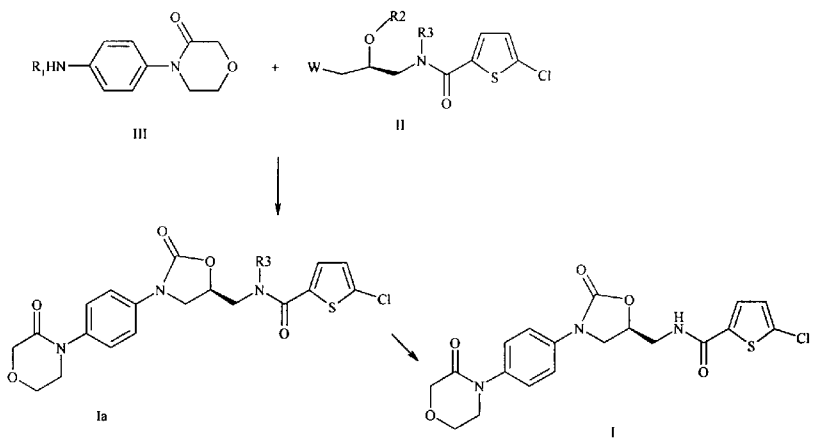
(54) **Title**: PROCESSES FOR THE PREPARATION OF 5-CHLORO-N-({(5S)-2-OXO-3-[4-(3-OXO-4-MORPHOLINYL) PHENYL]-1,3-OXAZOLIDIN-5-YL}METHYL)-2-THIOPHENE-CARBOXAMIDE AND INTERMEDIATES THEREOF



(57) **Abstract**: TThe present invention provides processes for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I) and intermediates thereof. Also provides novel intermediates and their use in the synthesis of oxazolidine derivatives.

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PROCESSES FOR THE PREPARATION OF 5-CHLORO-N-({(5S)-2-OXO-3-[4-(3-OXO-4-MORPHOLINYL) PHENYL]-1,3-OXAZOLIDIN-5-YL}METHYL)-2-THIOPHENE-CARBOXAMIDE AND INTERMEDIATES THEREOF

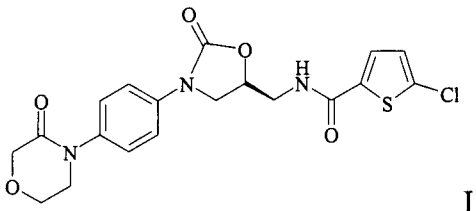
BACKGROUND OF THE INVENTION

1. Technical Field

The present invention relates to processes for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide and intermediates thereof.

2. Description of the Related Art

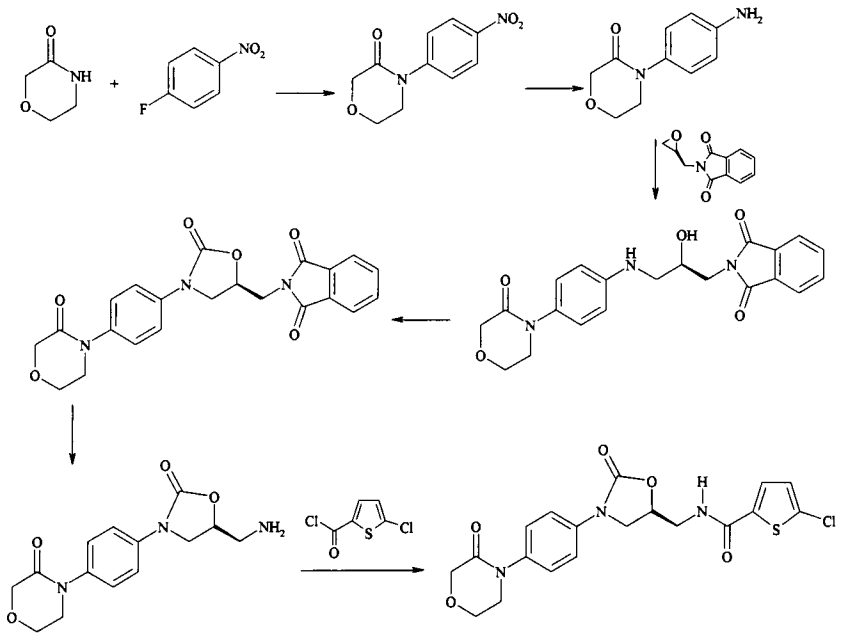
Rivaroxaban is a novel anticoagulant approved in US and Europe and several other countries for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. Rivaroxaban is structurally related to the antibacterial compound Linezolid (Zyvox) is enantiomerically pure. Rivaroxaban is available in the market under the brand name Xarelto® as 10 mg tablets in Europe. Rivaroxaban is chemically described as 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (herein after referred as rivaroxaban) and is represented by the structural formula I shown below:



I

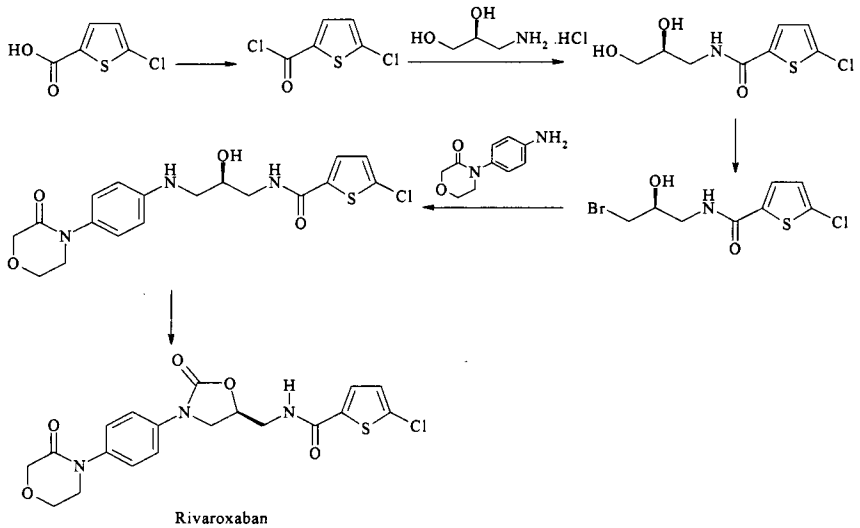
U.S. Patent No. US 7,585,860 describes morpholinyl oxazolidinone thiophene carboxamides including rivaroxaban or pharmaceutically acceptable acid addition salts thereof, a pharmaceutical composition and a method of treatment.

The US'860 patent also discloses a process for the preparation of rivaroxaban which is illustrated by scheme below:



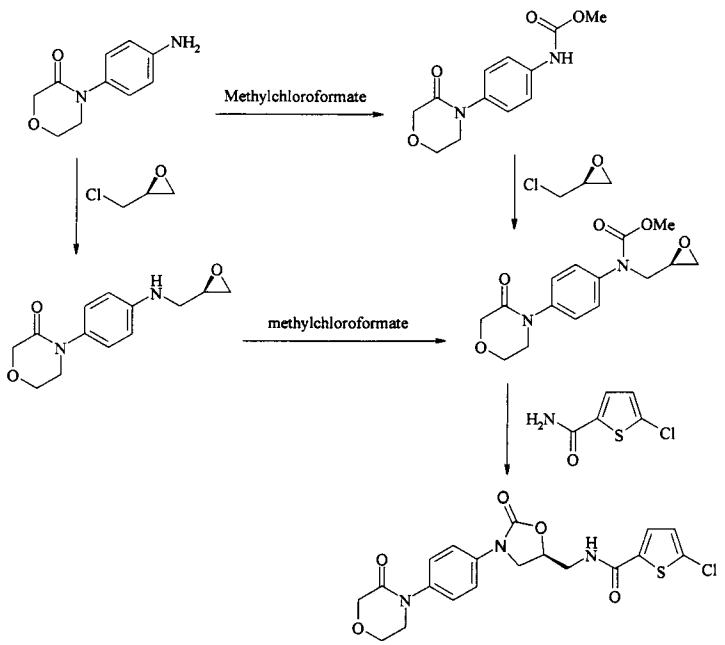
Rivaroxaban

U.S. Publication application US2007/0149522A1 and Drugs of the future 2006, 31(6), 484-493 discloses a process for the preparation of rivaroxaban which is illustrated by scheme below:

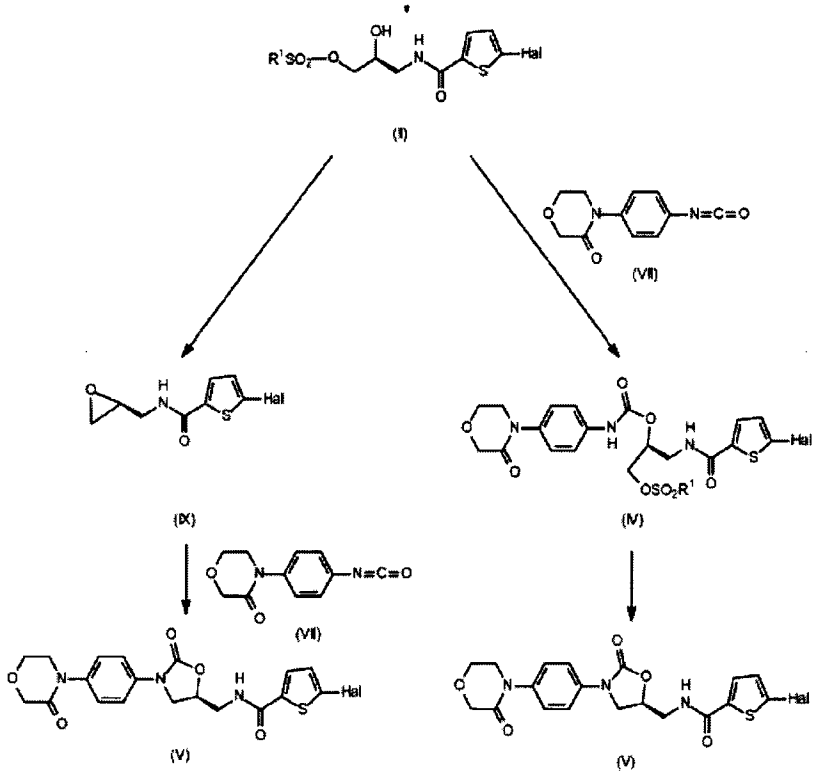


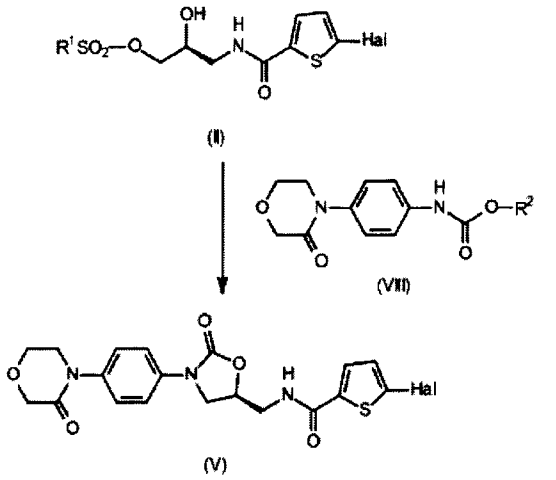
Rivaroxaban

U.S. Patent No. US 7,816,355 B1 describes a process for the preparation of rivaroxaban which is illustrated by below scheme:



European publication application EP 2354128A1 discloses processes for rivaroxaban and its intermediates which are illustrated by scheme below:





The process disclosed in the patent US'860 patent has various disadvantages in the reaction management which has particularly unfavourable effects for preparation of the compound of the formula (I) on the industrial scale.

The alternate process disclosed in the U.S. Publication application US '522A1 involves the usage of toxic solvents and reagents. This is disadvantageous per se, and in addition these toxic substances must be removed from the final product (I) until below the maximum limit permissible in each case and may require additional process steps which makes the process expensive and unsuitable on commercial scale.

The process disclosed in the US patent US '355 employs haloformates intermittently which are hazardous, corrosive and difficult to handle on industrial scale moreover the process has scope for formation of impurities, bye products leading to low yield and purity of final compounds thus making the process expensive and not suitable on commercial scale.

The aforementioned processes entail the use of hazardous and expensive reagents thus leading to the formation of various bye products and impurities prompting them to incorporate additional purification steps intermittently thus end up with low yields and purities of the final product thus rendering the processes unsuitable on commercial scale.

In view of potentiality of the compound rivaroxaban, there is a need in the art to provide improved processes for the preparation of rivaroxaban, which can avoid the use of potentially hazardous, expensive chemicals, the formation of isomeric and other process related impurities while affording the desired product rivaroxaban in high yield and purity.

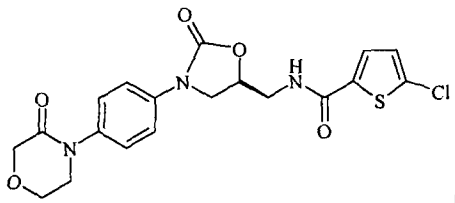
The reaction steps of the present invention using the intermediate compounds of formulae II, IV, VI, IX and X for the preparation of rivaroxaban (I) have not reported in the literature.

The processes of the present invention are simple, eco-friendly, cost-effective, reproducible, robust and are well amenable on industrial scale.

SUMMARY OF THE INVENTION

The present invention relates to processes for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I) and intermediates thereof.

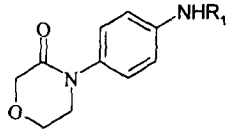
In one aspect, the present invention relates to a process for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I),



(I)

comprising:

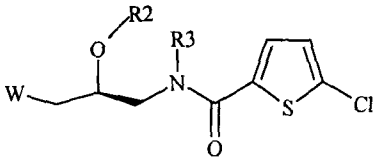
a) reacting the compound of formula (III) or a salt thereof



(III)

Where R_1 is H or $-C(=O)-OR4$ where R4=C_{1-4} alkyl straight chain or branched optionally substituted with 1to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub /unsub arylalkyl, C_{2-6} alkenyl, cycloalkyl.

with the compound of formula (II)

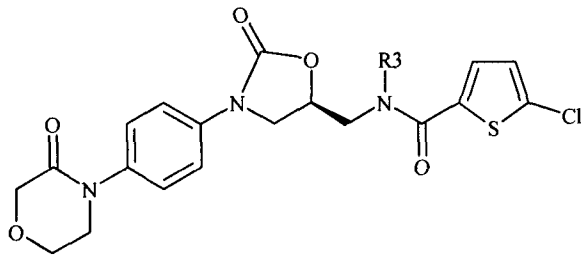


(II)

Where W= halogen (Cl, Br,I), -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl; Where R_2 is H or –CO-R5 where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched chain;

to provide the compound of formula (Ia) ,



(Ia)

Where R3 is H or a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched chain;

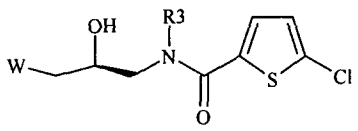
b) deprotection of the compound of formula (Ia) (when R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched chain) using a suitable reagent provides the compound of formula I.

The above process is schematically represented by Fig. 1.

In another aspect, the present invention relates to another process for the preparation of compound of formula I,

comprising:

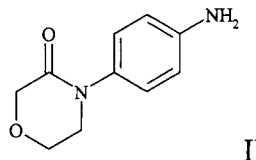
a) reacting the compound of formula IIa



IIa

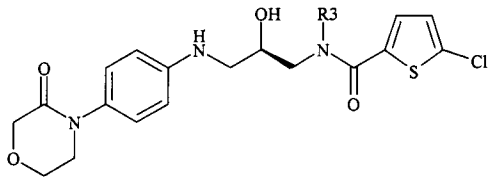
Where W is same as defined above and R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched chain;

with a compound of formula IIIb



IIIb

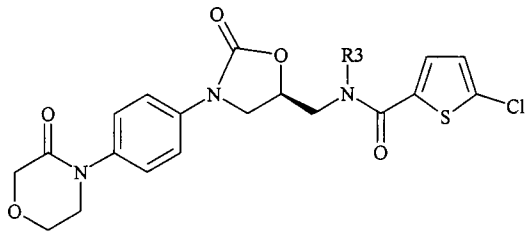
in the presence of a suitable reagent to obtain the compound of formula V



V

Where R3 is same as defined above,

b) carbonylation of the compound of formula V by using suitable reagent provides the compound of formula Ia

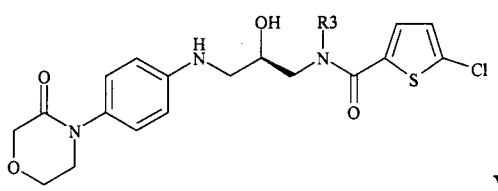


(Ia)

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched chain;

c) deprotection of the compound of formula (Ia) using suitable reagent provides the compound of formula I.

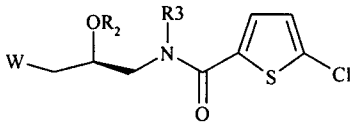
In yet another aspect, the present invention relates to an alternate process for the preparation of compound of formula V



V

Where R3 is protecting group such as sub or unsub benzyl, trityl, C $_{3-10}$ alkenyl straight Chain or branched chain

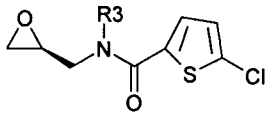
a) reacting the compound of formula IIa



II

Where W, R2 are same as defined above and R3 is protecting group such as sub or unsub benzyl, trityl, C $_{3-10}$ alkenyl straight or branched chain;

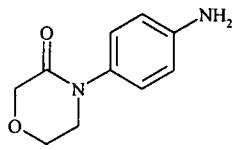
with a suitable reagent to provide the compound of formula IV



IV

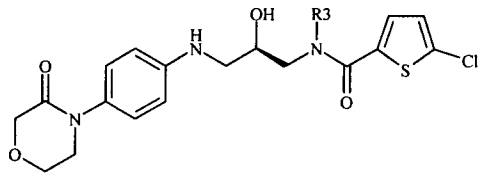
Where R3 is protecting group such as sub or unsub benzyl, trityl, C $_{3-10}$ alkenyl straight or branched chain;

b) reacting the compound of formula IV with the compound of formula IIIb



IIIb

in the presence of a suitable solvent to obtain the compound of formula V



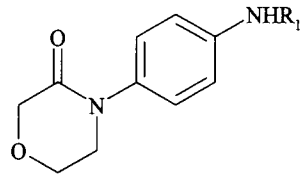
V

The above process is schematically represented by Fig. 2.

In yet still another aspect, the present invention relates to an alternate process for the preparation of compound of formula I

comprising:

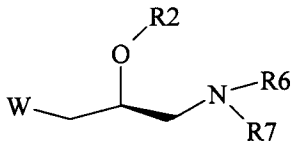
a) reacting the compound of formula III



III

Where R_1=-H or –C-OOR$_4$ where R_4 =C_{1-12} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl, C_{2-6} alkenyl, cycloalkyl.

with the compound of formula VI



VI

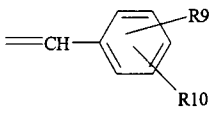
W= halogen atom (Cl, Br,I) or –OSO_2R- Where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group.

Where R2 = -H or –CO-R5 where R5=C $_{1-12}$ alkyl straight chain or branched optionally sub with 1-3 halogen atom(F, Cl, Br), C_{1-12} alkoxy straight or branched which are optionally sub. with 1-3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub phenyloxy, sub or unsub arylalkoxy, sub or unsub arylalkyl group;

R6, R7= independently selected from the group consisting of H or amino protecting group.

a) R6, R7= -H or –CO-OR8 where R8 = C_{1-12} alkyl straight or branched which are optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl group, sub or unsub aryl alkyl group.

b) R6, R7=



Where R9, R10 = independently selected from H or group consisting of Cl, Br, F, I , C_{1-10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl. Br), C_{1-10} alkoxy straight or branched which are optionally sub with 1 to 3 halogen atom (F, Cl, Br), -NO_2, -CN, -alkyl sulfonyl, arylsulfonyl.

c) R6, R7 = -H or –CO-R^{11} where R^{11}= H or C $_{1-10}$ alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl group.

d) –N R 6 R7 = sub or unsub phthalimido group

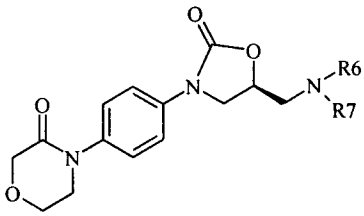
e) –N R 6 R7 = Azido group

f) –N R6 R7= sub or unsub. pyrrole ring

g) –R6 , R7 = -H or trityl group

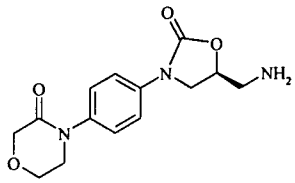
h) R6 = R7 = Sub or unsub benzyl group.

in the presence of suitable reagent to provide the compound of formula VII



VII

b) deprotection of compound of formula VII using a suitable reagent to provide the compound of formula VIII

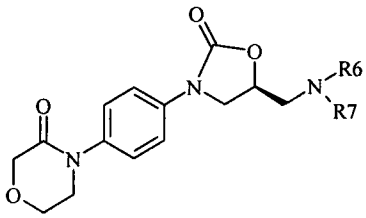


VIII

The compound of formula VIII obtained can be converted into rivaroxaban (I) by known processes reported in the literature.

The above process is schematically represented by Fig. 3.

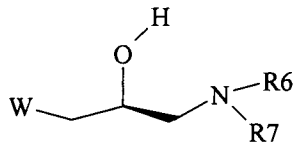
In yet still further aspect, the present invention relates to alternate process for the preparation of compound of formula VII



VII

comprising:

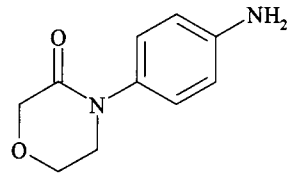
a) reacting the compound of formula VIa



VIa

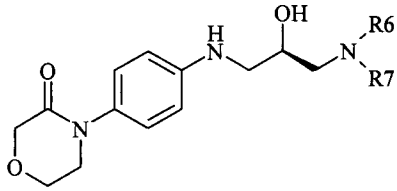
Where W, R6 and R7 are same as defined above.

with the compound of formula IIIb



IIIb

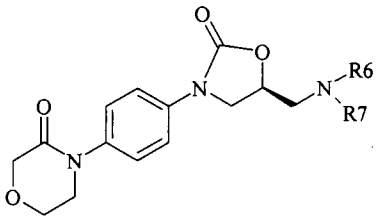
in the presence of suitable reagent to provide the compound of formula IX



IX

Where R6 and R7 are same as defined above

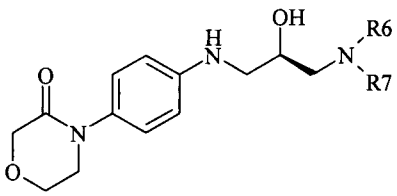
b) carbonylation of the compound of formula IX using a suitable reagent to obtain the compound of formula VII



VII

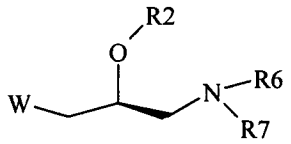
Where R6 and R7 are same as defined above.

In another embodiment, the present invention provides an alternate process for the preparation of compound of formula IX



IX

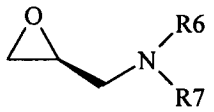
reacting the compound of formula VI



VI

Where W, R2, R6 and R7 are same as defined above.

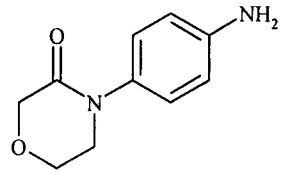
with a suitable reagent to form the compound of formula X



X

Where R6 and R7 are same as defined above

b) reacting the compound of formula X with the compound of formula IIIb

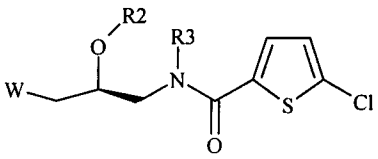


IIIb

to provide the compound of formula IX.

The above process is schematically represented by Fig. 4.

In another aspect, the present invention relates to a method for synthesis of compound having the formula II



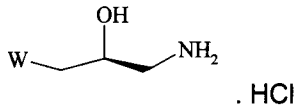
(II)

Where W= halogen atom (Cl, Br, I) or $-OSO_2R-$ Where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group; R2= -H or $\overset{O}{\overset{\|}{-C-R5}}$; where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched chain;

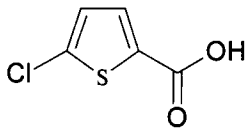
comprising:

a) reacting the compound having the formula XI



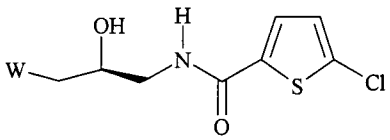
XI

with a compound having the formula XII



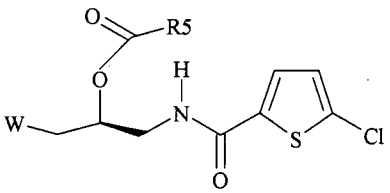
XII

in the presence of a suitable reagent to provide the compound having the formula IIa



IIa

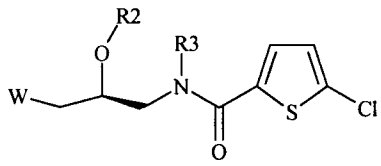
b) reacting the compound of formula IIa with a suitable reagent gives the compound of formula IIb



IIb

c) reacting the compound of formula IIb with a suitable reactant or reagent to provide the compound of formula II.

In another aspect, the present invention relates to an alternate method for the synthesis of compound having the formula II



(II)

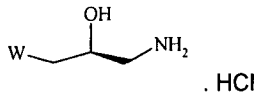
Where W= halogen atom (Cl, Br,I) or $-OSO_2R$- Where R= C_1-C_4 alkyl, sub or unsub phenyl, arylalkyl group; R2= -H or $-C(=O)-R5$;

where R5 is C_1-C_{12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched;

comprising:

a) reacting the compound of formula XI

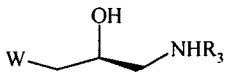


XI

with R3-X in the presence of a suitable reagent

R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chainor branched and X is a leaving group such as halogen atom (Cl, Br,I) or $-OSO_2R$- Where R= C_1-C_4 alkyl, sub or unsub phenyl, arylalkyl group or CHO group,

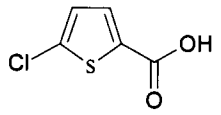
to provide the compound of formula XIII



XIII

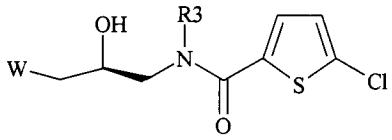
Where R3 is same as defined above

b) reacting the compound having the formula XIII with the compound of formula XII



XII

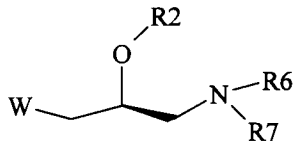
in the presence of a suitable reagent to provide the compound having the formula IIc



IIc

c) reacting the compound of formula IIc with a suitable reactant to give the compound of formula II.

In another aspect, the present invention relates to a method for synthesis of compound of formula VI

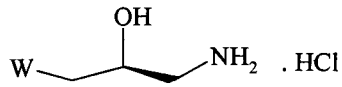


VI

Where W, R2, R6, R7 are same as defined in above aspects.

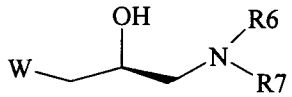
comprising:

a) reacting the compound of formula XI



XI

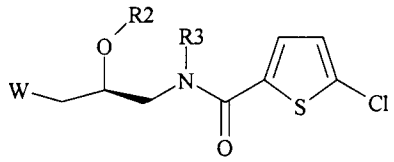
with a suitable protecting agent to provide the compound of formula VIa



VIa

b) reacting the compound of formula VIa with a suitable reactant to provide the compound of formula VI.

In another aspect, the present invention provides a compound having the formula II



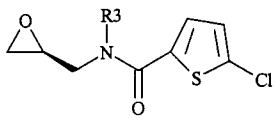
(II)

where W= halogen atom (Cl, Br,I), -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl; R2= -H or  ;

R5 is C_1-C_{12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

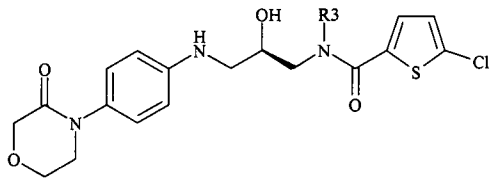
In yet another aspect, the present invention provides a compound having the formula IV



IV

Where R3 = protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched.

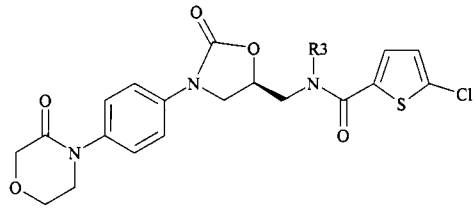
In yet another aspect, the present invention provides a compound having the formula V



V

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched ;

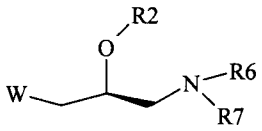
In yet another aspect, the present invention provides a compound having the formula Ia



Ia

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched chain.

In yet another aspect, the present provides a compound having the formula VI



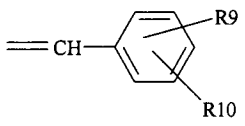
VI

Where W= halogen atom (Cl, Br, I) or $-SO_2R$- Where R= C_{1-4} alkyl, sub or unsub.phenyl, arylalkyl group;

R2 = -H or –CO-R5 where R5=C_{1-12} alkyl straight chain or branched optionally sub with 1-3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight or branched which are optionally sub. with 1-3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub phenyloxy, sub or unsub arylalkoxy, sub or unsub arylalkyl group.

R6, R7= independently selected from the group consisting of H or amino protecting group.

a) R6, R7= -H or –CO-OR8 where R8 = C_{1-12} alkyl straight or branched which are optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl group, sub or unsub aryl alkyl group.

b) R6, R7= 

Where R9, R10 = independently selected from H or group consisting of Cl, Br, F, I , C_1 –C_{10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl. Br), C_1-C_{10} alkoxy straight chain or branched which are optionally sub with 1 to 3 halogen atom (F, Cl, Br), -NO_2, -CN, -alkyl sulfonyl, arylsulfonyl.

c) R6, R7 = -H or –CO-R^{11} where R^{11}= H or C $_{1-10}$ alkyl straight or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl group.

d) –N R 6 R7 = sub or unsub.phthalimido group

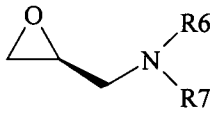
e) –N R 6 R7 = Azido group

f) –N R6 R7= sub. or unsub. pyrrole ring.

g) –R6 , R7 = -H or trityl group

h) R6 = R7 = Sub or unsub benzyl group.

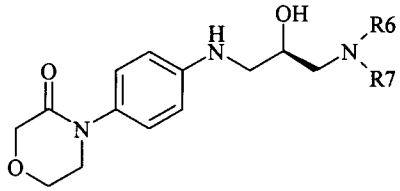
In yet another aspect, the present invention provides a compound having the formula X



X

Where R6 and R7 are same as defined for compound of formula VI.

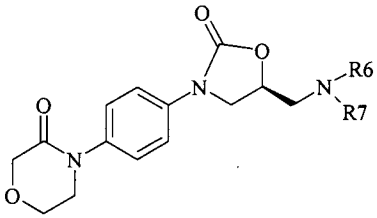
In yet another aspect, the present invention provides a compound having the formula IX



IX

Where R6 and R7 are same as defined for compound of formula VI.

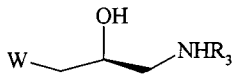
In another aspect, the present invention provides a compound having the formula VII



VII

Where R6 and R7 are same as defined for compound of formula VI.

In another aspect, the present invention provides a compound having the formula XIII



XIII

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight or branched same as defined above.

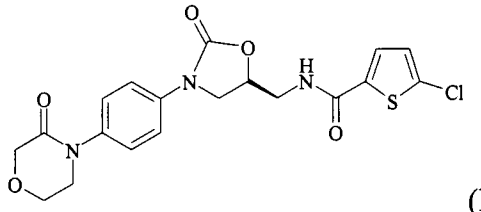
BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 to 4: are schematic representations of the processes of present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to processes for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I) and intermediates thereof.

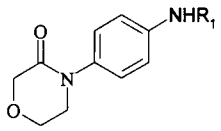
In one embodiment, the present invention provides a process for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene carboxamide (I),



(I)

comprising:

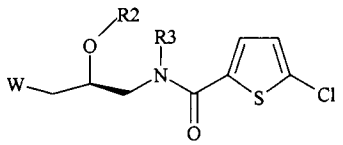
a) reacting the compound of formula (III) or a salt thereof



(III)

Where R_1 is H or  where R_4=C_{1-4} alkyl straight chain or branched optionally substituted with 1to 3 halogen atom (F, Cl, Br), sub or unsub. phenyl, sub or unsub arylalkyl, C_{2-6} alkenyl, cycloalkyl;

with the compound of formula (II)



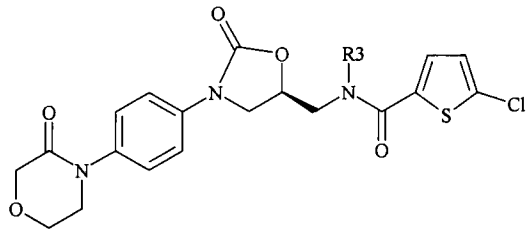
(II)

Where W= halogen (Cl, Br,I) or $-OSO_2R$- Where R= C_{1-4} alkyl, sub or unsub.phenyl, arylalkyl group;

R2 is H or –CO-R5 where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched;

in the presence of a base and an organic solvent to provide the compound of formula (Ia) ,



(Ia)

Where R3 is same as defined above.

b) deprotection of the compound of formula (Ia) using a suitable reagent in the presence of a suitable organic solvent provides the compound of formula I.

When in the compound of formula Ia where R3 is H the reaction step b) will not take place.

The use of base in step a) is not critical but the base should be capable of deprotection of carbamate group of compound of formula III. The bases that can be used in step a) is selected from base having an alkoxide group with C_1 –C_7 carbon atoms; C_{1-4} alkyl carbanion such as methyl, sec-butyl, butyl or tert-butyl carbanion; a conjugate base of a carbamate; lithium diisopropyl amide, lithium amide; inorganic bases like metal hydroxides such as sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; or mixture thereof, preferably a base with alkoxide group having C_{4-5} carbon atoms.

More preferably lithium tert-amylate or lithium t-butoxide or potassium carbonate is being used.

The most preferred bases containing a lithium cation and an alkoxide group such as tert-amylate or tert-butoxide.

When a base does not contain a lithium cation (bases for ex. Sodium, potassium or tetra alkyl ammonium salt), mixing such a base with lithium salt, such as lithium chloride, lithium bromide, lithium iodide, lithium acetate, lithium tetraflouroborate and other lithium inorganic salts can be used to form the lithium cation and base in situ.

Optionally the reaction step a) is carried out using a nucleophile.

The use of nucleophile is not critical. An example of a nucleophile is an alkoxide group, linear or branched, having C_{1-7} atoms. Preferred nucleophile is methoxide or ethoxide or isopropoxide or isobutoxide or 2-ethoxyethyl, 2-(N,N-dimethylamino) ethoxide or 2,2,2-trichloroethoxide or 2,2,2-trifluoroethoxide.

Commercial alkoxide salts such as lithium, sodium or potassium methoxide, ethoxide or isopropoxide can be used or the alkoxide formed insitu by reacting a base as referred above with a corresponding alcohol such as methanol, ethanol or isopropanol. Where a lithium alkoxide is used as a nucleophile and a base, the lithium cation, the base and the nucleophile required may be from the same chemical substance and atleast two equivalents of such chemical substance are needed for reaction.

The solvents that can be used in step a) should be neutral but are not limited to alcohols such as methanol, tert-amyl alcohol, tert-butyl alcohol and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile and the like; or mixture thereof. Preferably N,N-dimethylformamide (DMF) or tetrahydrofuran (THF) or mixture thereof.

The reaction step a) can be carried out at a temperature range from about -40°C to the boiling point of the solvent(s) used, preferably from about -20°C to about 80°C.

The time required for the reaction to complete may also vary widely, depending on various factors, notably the reaction temperature, the nature of the reagent and the solvents employed, a period of from about 2 hour to about 24 hours, preferably from about 10 hour to about 21 hours.

In the reaction step (b) when R3 is amide nitrogen protecting group

The use of deprotecting reagents depends upon the protecting group present.

The suitable deprotection reagents used is selected from the group consisting of p-toluene sulfonic acid, N-bromosuccinimide, trifluoro acetic acid, hydrogenation catalysts like

palladium-carbon, platinum oxide and the like; inorganic acids such as HCl, HBr, sulfuric acid, phosphoric acid and the like or mixture thereof.

The solvents that can be used in deprotection step b) include but are not limited to water, alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, chlorobenzene and the like; esters such as ethyl acetate and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF) and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), acetonitrileand the like; or mixture thereof. Preferably hydrocarbon solvent toluene is being used.

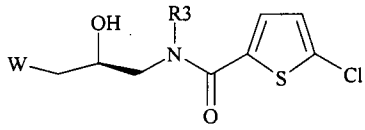
The reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 25°C to about boiling point of the solvent(s) used.

The time required for the reaction to complete may also vary widely, depending upon various factors like reaction temperature, the nature of the reagent and the solvents employed, a period of from about 30 minutes to about 24 hours, preferably from about 1 hour to about 5 hours is being sufficient.

In another embodiment, the present invention provides an alternate process for the preparation of compound of formula I

comprising:

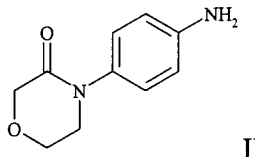
a) reacting the compound of formula IIa



IIa

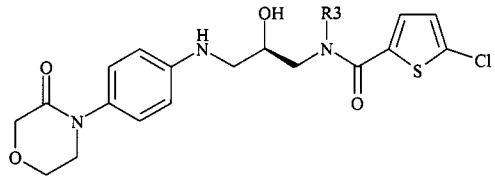
Where W is same as defined above and R3 is protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight or branched;

with the compound of formula IIIb



IIIb

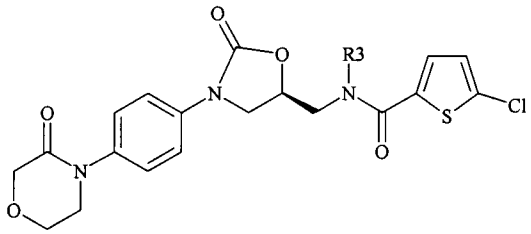
in the presence of a suitable reagent to obtain the compound of formula V



V

Where R3 is same as defined above;

b) carbonylation of the compound of formula V by using suitable reagent provides the compound of formula Ia



(Ia)

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight or branched not H.

c) deprotection of the compound of formula (Ia) using suitable reagent provides the compound of formula I.

The reaction step a) can be carried out under any suitable method and condition, one option is to carry out in presence of a base, here any suitable base include but not limited to inorganic such as alkali or alkaline earth metal carbonates, bicarbonates, hydroxides or ammonium cations or bases such as C $_{1-8}$ alkoxides of alkali metals and alkaline earth metals or organic bases such as tri (C $_{1-6}$ alkyl) amines and collidine and the like; or mixture thereof.

The solvents that can be used should be neutral include but are not limited to alcohols such as methanol, ethanol and the like; hydrocarbons such as toluene, xylene and the like; halogenated solvents such as dichloromethane, chloroform and the like; ethers such as

tetrahydrofuran (THF), 1,4-dioxane and the like; nitriles such as acetonitrile and the like; or mixture thereof. Preferably methanol or toluene.

The reaction can be performed at a temperature range from about 30°C to about 200°C, preferably from about 70°C to about 120°C.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 24 hours, preferably from about 30 minutes to about 5 hours is being sufficient.

The carbonylation step b) involving the reaction of the compound of formula V with a suitable carbonylating agent to give compound of formula Ia is carried out by using carbonylating agents selected from the group consisting of phosgene or phosgene equivalent such as diphosgene, triphosgene and like; carbon monoxide equivalents such as N,N-carbonyldiimidazole (CDI), diethyl carbonate and the like; mixture thereof. Preferably N,N-carbonyldiimidazole (CDI) is being used.

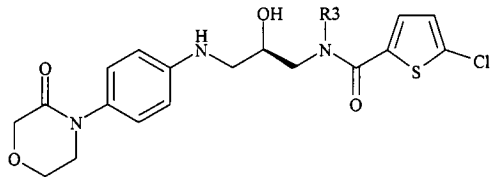
The suitable solvents that can be used can be any solvent that is neutral and which can make the reaction mixture into homogenous and is selected from the group consisting of hydrocarbons such as toluene and the like; halogenated solvent such as dichloromethane, chloroform and the like; nitriles such as acetonitrile and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF and the like; polar aprotic solvent such as N,N-dimethyl formamide(DMF) and the like or mixture thereof. Preferably dichloromethane is being used.

The reaction can be performed at any suitable temperature, specifically at a range from about 20°C to the boiling temperature of the solvent(s) used. Preferably from about 25 °C to about boiling temperature of the solvent(s) used.

The duration of time for the reaction to complete may also vary widely, depending upon various factors, typically a period of from about 30 minutes to about 48 hours, preferably from about 2 hours to about 24 hours is being used.

The reaction step c) of converting compound of formula Ia to the compound of formula I by using suitable deprotecting agents can be carried out in a similar method as described above.

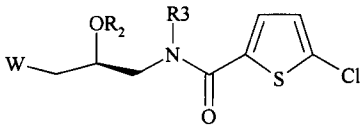
In yet further embodiment, the present invention provides a process for the preparation of compound of formula V



V

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched;

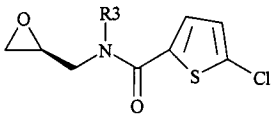
a) reacting the compound of formula IIa



IIa

Where W, R_2 are same as defined above, R3 is protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched;

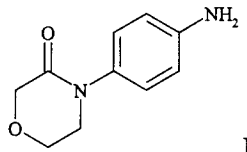
with a suitable base to provide the compound of formula IV



IV

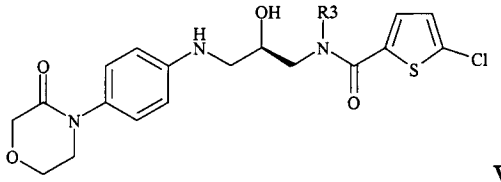
Where R3 is protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched ;

b) reacting the compound of formula IV with the compound of formula IIIb



IIIb

in the presence of an organic solvent to obtain the compound of formula V



V

The obtained compound of formula V is converted into the compound of formula I by following the process as described above.

The reaction step a) can be carried out under any suitable method and condition, one option is to carry out in presence of a base, here any suitable base include but not limited to inorganic such as alkali or alkaline earth metal carbonates, bicarbonates, hydroxides or ammonium cations or bases such as C_{1-8} alkoxides of alkali metals and alkaline earth metals.

The pH of the reaction mixture should be adjusted to about 8 so as to favour the complete conversion of IIa to the formula IV.

The solvents that can be used include but are not limited to alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF), 1,4-dioxane and the like; nitriles such as acetonitrile and the like; or mixture thereof. Preferably methanol.

The reaction can be performed at a temperature range from about -30°C to about 50°C, preferably from about -10°C to about 35°C.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours is being sufficient.

The reaction step b) is usually performed in the presence of solvent(s).

The suitable solvents that can be used is selected from the group consisting of alcohols such as methanol, ethanol and like; hydrocarbons such as toluene and the like; nitriles such as acetonitrile and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) and the like; or mixture thereof. Preferably ethanol or aqeous ethanol.

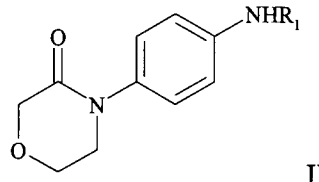
The reaction can be performed at a temperature range from about 30°C to the boiling temperature of the solvent(s) used. Preferably at boiling temperature of the solvent(s) used.

The duration of time for the reaction to complete may also vary widely, depending upon various factors, typically a period of from about 4 hours to about 48 hours, preferably from about 8 hours to about 24 hours is being sufficient.

In yet still another embodiment, the present invention provides an alternate process for the preparation of compound of formula I

comprising:

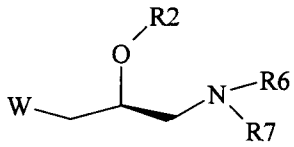
a) reacting the compound of formula III



III

Where R_1=-H or –C-OOR$_4$ where R_4 =C_1 –C_{12} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl, C_2-C_6 alkenyl, cycloalkyl.

with the compound of formula VI



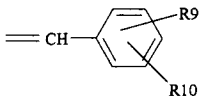
VI

Where W= halogen atom (Cl, Br, I) or –SO_2R- Where R= C_{1-4} alkyl, sub or unsub phenylgroup, arylalkyl group;

R2 = -H or –CO-R5 where R5=C $_{1-12}$ alkyl straight chain or branched optionally sub with 1-3 halogen (F, Cl, Br), C_1 – C_{12} alkoxy straight or branched which are optionally sub. with 1-3 halogen (F, Cl, Br), sub or unsub phenyl, sub or unsub phenyloxy, sub or unsub arylalkoxy, sub or unsub arylalkyl group;

R6, R7= independently from the group consisting of H or amino protecting group.

R6, R7= -H or –CO-OR8 where R8 = C_{1-12} alkyl straight or branched which are optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl group, sub or unsub aryl alkyl group;

R6, R7= 

Where R9, R10 = independently selected from H or group consisting of Cl, Br, F, I , C_{1-10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl. Br), C_{1-10} alkoxy straight or branched which are optionally sub with 1 to 3 halogen atom (F, Cl, Br), -NO_2, -CN, -alkyl sulfonyl, arylsulfonyl;

R6, R7 = -H or –CO-R^{11} where R^{11}= H or C $_{1-10}$ alkyl straight or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl group;

–N R 6 R7 = sub or unsub phthalimido group;

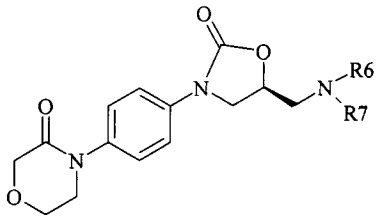
–N R 6 R7 = Azido group;

–N R6 R7= sub. or unsub. pyrrole ring;

–R6 , R7 = -H or trityl group;

R6 = R7 = Sub or unsub benzyl group;

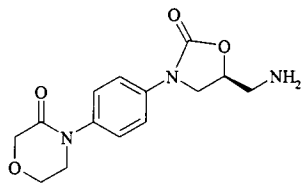
in the presence of a suitable base and an organic solvent to provide the compound of formula VII



VII

Where R6, R7 are same as defined above.

b) deprotection of compound of formula VII using a suitable reagent to obtain the compound of formula VIII



VIII

The compound of formula VIII obtained can be converted into rivaroxaban (I) by known processes reported in the literature.

The use of base in step a) is not critical, the bases that can be used is selected from base having an alkoxide group with C_{1-7}; C_{1-4} alkyl carbanion such as methyl, sec-butyl, butyl or tert-butyl carbanion; a conjugate base of a carbamate; lithium diisopropyl amide, lithium amide; inorganic bases like metal hydroxides such as sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; or mixture thereof, preferably a base with alkoxide group having C_{4-5} carbon atoms, More preferably tert-amylate or butoxide is being used.

The most preferred bases containing a lithium cation and an alkoxide group such as tert-amylate or tert-butoxide or potassium carbonate.

When a base does not contain a lithium cation (bases for ex. Sodium, potassium or tetra alkyl ammonium salt), mixing such a base with lithium salt, such as lithium chloride, lithium bromide, lithium iodide, lithium acetate, lithium tetraflouroborate and other lithium inorganic salts can be used to form the lithium cation and base in situ.

Optionally the reaction step a) is carried out using a nucleophile.

The use of nucleophile is not critical. An example of a nucleophile is an alkoxide group, linear or branched, having C_{1-7} atoms. Preferred nucleophile is methoxide or ethoxide or isopropoxide or isobutoxide or 2-ethoxyethyl, 2-(N,N-dimethylamino) ethoxide or 2,2,2-trichloroethoxide or 2,2,2-trifluoroethoxide.

Commercial alkoxide salts such as lithium, sodium or potassium methoxide, ethoxide or isopropoxide can be used or the alkoxide may be formed insitu by reacting a base as referred above with a corresponding alcohol such as methanol, ethanol or isopropanol. Where a lithium alkoxide is used as a nucleophile and a base, the lithium cation , the base and the nucleophile required may be from the same chemical substance and atleast two equivalents of such chemical substance are needed for reaction.

The solvents that can be used in step a) include but are not limited to alcohols such as methanol, tert-amyl alcohol, tert-butyl alcohol and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile and the like; or mixture thereof. Preferably DMF or THF or mixture thereof.

The reaction step a) can be carried out at a temperature range from about -40°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 80°C.

The time required for the reaction to complete may also vary widely, depending on various factors, notably the reaction temperature, the nature of the reagent and the solvents employed, a period of from about 1 hour to about 24 hours, preferably from about 8 hour to about 21 hours.

The reaction step b) can be carried out by using any suitable deprotecting agent reported in the art and capable of disassociating the desired protecting group.

The use of suitable deprotecting reagents depends upon the protecting group present.

The suitable deprotection reagents used is selected from the group consisting of triflouro acetic acid and the like; inorganic acids such as HCl, HBr, sulfuric acid, phosphoric

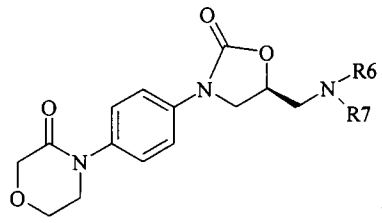
acid, hydroxyl amine, hydrazine hydrate, catalytic hydrogenation, ammonium formate, methyl amine and the like or mixture thereof.

The solvents that can be used in deprotection step b) include but are not limited to water, acetic acid, alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, chloroform and the like; esters such as ethyl acetate and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF) and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), acetonitrile and the like; or mixture thereof.

The reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 25°C to about boiling point of the solvent(s) used.

The time required for the reaction to complete may also vary widely, depending upon various factors like reaction temperature, the nature of the reagent and the solvents employed, a period of from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 8 hours is being sufficient.

In yet still further embodiment, the present invention provides an alternate process for the preparation of compound of formula VII

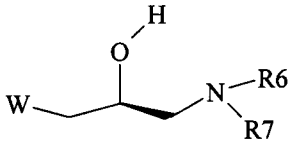


VII

Where R6, R7 are same as defined above

comprising:

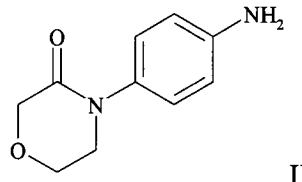
a) reacting the compound of formula VIa



VIa

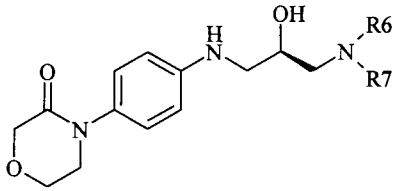
Where W, R6 and R7 are same as defined above.

with the compound of formula IIIb



IIIb

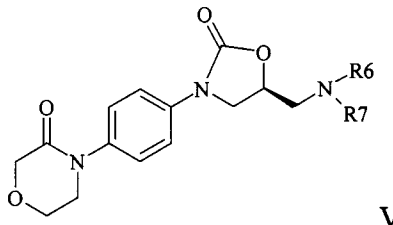
in the presence of suitable base and an organic solvent to provide the compound of formula IX



IX

Where R6 and R7 are same as defined above

b) cyclization of the compound of formula IX using a suitable reagent to obtain the compound of formula VII



VII

Where R6 and R7 are same as defined above

The solvents that can be used should be neutral they include but are not limited to alcohols such as methanol, ethanol and the like; hydrocarbons such as toluene and the like; nitriles such as acetonitrile and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile and the like; or mixture thereof. Preferably hydrocarbon solvent toluene is being used.

The use of base may enhance the conversion , the bases that can used optionally include but are not limited to organic bases such as tri (C_{1-6} alkyl) amines, collidine, pyridine and the like; inorganic bases such as alkali, alkaline earth metal carbonates, bicarbonates, alkali metal hydroxides and the like; preferably collidine.

The reaction can be performed at a temperature range from about 30°C to about 200°C, preferably from about 70°C to about 120°C.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 1 hour to about 8 hours, preferably from about 2 hrs minutes to about 6 hours is being sufficient.

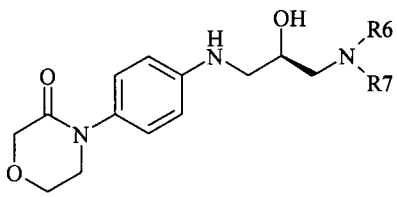
The carbonylation step b) involving the reaction of the compound of formula IX with a suitable carbonylating agent to give compound of formula VII is carried out by using carbonylating agents selected from the group consisting of phosgene or phosgene equivalent such as diphosgene, triphosgene and like; carbon monoxide equivalents such as N,N-carbonyldiimidazole (CDI), diethyl carbonate and the like; mixture thereof. Preferably N,N-carbonyldiimidazole (CDI) is being used.

The suitable solvents that can be used can be any solvent that is neutral and which can make the reaction mixture into homogenous and is selected from the group consisting of alcohols such as methanol, ethanol and the like; hydrocarbons such as toluene and the like; halogenated solvent such as dichloromethane, ethylene dichloride, chloroform and the like; nitriles such as acetonitrile and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) and the like; or mixture thereof. Preferably dichloromethane is being used.

The reaction can be performed at any suitable temperature, specifically at a range from about 20°C to the boiling temperature of the solvent(s) used. Preferably from about 25 °C to about boiling temperature of the solvent(s) used.

The duration of time for the reaction to complete may also vary widely, depending upon various factors, typically a period of from about 30 minutes to about 48 hours, preferably from about 2 hours to about 24 hours is being used.

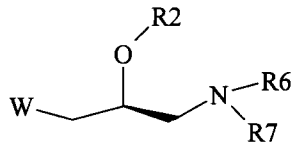
In another embodiment, the present invention provides an alternate process for the preparation of compound of formula IX



IX

Where R6 and R7 are same as defined above

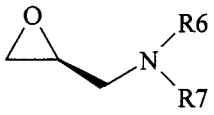
a) reacting the compound of formula VI



VI

Where W, R2, R6 and R7 are same as defined above.

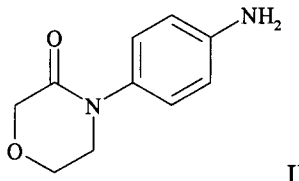
with a suitable reagent to form the compound of formula X



X

Where R6 and R7 are same as defined above

b) reacting the compound of formula X with the compound of formula IIIb



IIIb

to provide the compound of formula IX.

The reaction step a) can be performed under any suitable conditions to afford the cyclized product X.

One option to perform the cyclization is in the presence of a base.

Any base that suits the cyclization process can be used. the bases that can used include but are not limited to alkali, alkaline earth metal carbonates, bicarbonates, alkali metal hydroxides or ammonium cations, C $_{1-8}$ alkoxides of alkali metals and alkaline earth metals. Preferably lithium tert-butoxide.

The pH of the reaction mixture should be adjusted to above 8 so as to enable the conversion of the compound of formula VI to the compound of formula X to maximum extent.

The solvents that can be used should be neutral they include but are not limited to alcohols such as methanol, ethanol and the like; halogenated solvent such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF,and the like; hydrocarbons such as toluene and the like; nitriles such as acetonitrile and the like or mixture thereof. Preferably methanol.

The reaction can be performed at a temperature range from about -30°C to about 50°C, preferably from about 0°C to about 50°C.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 120 hours, preferably from about 30 minutes to about 85 hrs.

The reaction step b) can be performed using any suitable method reported under any suitable conditions to afford the desired product IX.

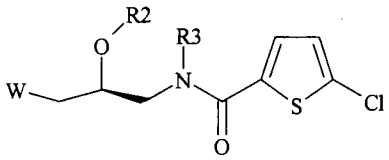
The reaction step b) can be performed in any inert solvent or mixture of solvents.

The suitable solvents that can be used herein include but are not limited to alcohols such as methanol, ethanol and the like; nitriles such acetonitrile and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF and the like; hydrocarbons such as toluene, xylene and the like;aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and the like; or mixture thereof. Preferably ethanol is being used.

The reaction can be performed at a temperature range from about 30°C to about boiling point of the solvent(s) used, preferably at boiling points of the solvent(s).

The duration of time for the reaction to complete may also vary widely, typically a period of from about 1 hour to about 48 hours, preferably from about 8 hours to about 24 hrs.

In yet another embodiment, the present invention provides a method of synthesis of compound having the formula II



(II)

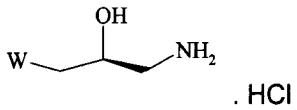
Where W= halogen atom (Cl, Br,I) or $-OSO_2R$- Where R= C_{1-4} alkyl, sub or unsub phenylgroup or arylalkyl group.

R2 is H or –CO-R5 where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

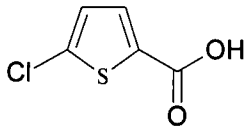
comprising:

a) reacting the compound having the formula XI



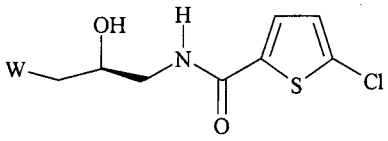
XI

with a compound having the formula XII



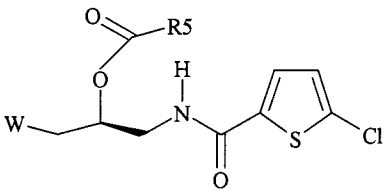
XII

in the presence of a suitable base, coupling agent and an organic solvent to provide the compound having the formula IIa



IIa

b) reacting the compound of formula IIa with a suitable reactant in the presence of suitable solvents and a base gives the compound of formula IIb



IIb

c) reacting the compound of formula IIb with a suitable reactant and an organic solvent t to provide the compound of formula II.

The compounds of formula XI and XII used herein can be prepared by any method known in the art.

The reaction step a) is performed by reacting the compound of formula XI with the compound of formula XII or with its corresponding carbonyl halides, preferably carbonyl chloride or with the corresponding symmetric or mixed carboxylic anhydrides of the

carboxylic acids of the compound formula XII defined above solvents, if appropriate in the presence of an activating or coupling agent and or a base to the compound of formula IIa.

The solvents that can be used in step a) should be inert include but are not limited to water, alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, chloroform and the like; hydrocarbon solvents such as toluene and the like; ethers such as diethyl ether, tetrahydrofuran (THF) and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile, pyridine, hexamethyl phosphoric triamide and the like; or mixture thereof. Preferably dichloromethane or toluene.

The suitable coupling agents used in step a) include but are not limited to N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide. HCl, N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole monohydrate and the like.

The bases that can be employed is selected from alkali bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; organic bases such as triethyl amine, diisopropyl ethylamine, diisopropyl amine, 4.N,N-dimethylaminopyridine or pyridine or mixture thereof, preferably sodium bicarbonate or triethylamine.

The reaction step a) can be carried out at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C.

The time required for the reaction to complete may also vary widely, depending on various factors, notably the reaction temperature, the nature of the reagent and the solvents employed, a period of from about 1 hour to about 24 hours, preferably from about 2 hour to about 4 hours.

The suitable agents that can be used in step b) include acid halides of general formula

Preferably acid chlorides or acid anhydrides of general formula $(R5CO)_2O$.

Where R5 is C_1-C_{12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

The suitable organic solvents that can be used in step b) is selected from the group to water, halogenated solvents such as dichloromethane, chloroform and the like; esters such as ethyl acetate, n-butyl acetate and the like; hydrocarbon solvents such as toluene and the like; ethers such as diethyl ether, tetrahydrofuran (THF) and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), acetonitrile and the like; or mixture thereof. Preferably dichloromethane.

The bases that can be employed in step b) is selected from alkali bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; organic bases such as triethyl amine, diisopropyl ethylamine, diisopropyl amine, 4.N,N-dimethylaminopyridine or pyridine or mixture thereof, preferably pyridine.

The reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C.

The time required for the reaction step b) to complete may also vary widely, depending upon various factors like reaction temperature, the nature of the reagent and the solvents employed, a period of from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 8 hours is being sufficient.

The reaction step c) is performed by reacting the compound IIb with the compound of general formula R3-X in the presence of an organic solvent and optionally in the presence of a base.

Where R3= amide nitrogen protecting group, for example sub or unsub benzyl group, trityl group, isoalkenyl group, preferably trityl group;

X= leaving group for example halogen atom (Cl, Br), sulfonyloxy group or hydroxyl group;

The suitable bases that can be used in step c) is selected from the group like alkali or alkaline earth metal hydroxides such as sodium hydroxide, barium hydroxide and the like alkali carbonates such as sodium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; alkali metal alkoxides such as sodium methoxide, lithium tertiary butoxide and the like; amides such as sodium amide, lithium bis (trimethylsilyl)amide or lithium diisopropyl ethylamide, diisopropylamide and the like; or mixtures thereof. Preferably sodium hydroxide.

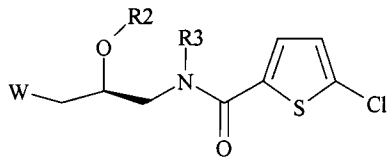
Optionally the reaction step c) can be performed by employing a catalyst for ex. P-toluene sulfonic acid.

The solvents that can be used in step c) include but are not limited to alcohols such as methanol, ethanol and the like; halogenated solvents such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF) and the like; esters such as ethyl acetate and the like; hydrocarbon solvents such as toluene and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), acetonitrile and the like; or mixture thereof. Preferably toluene.

The reaction step c) can be performed at a temperature range from about -70°C to the boiling point of the solvent used, preferably from about 0°C to the boiling point of the solvent used.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours is being sufficient.

In yet further embodiment, the present invention provides an alternate method for the synthesis of compound having the formula II



II

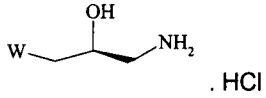
Where W= halogen atom (Cl, Br, I) or $-OSO_2R$- Where R= C_{1-4} alkyl, sub or unsub phenylgroup or arylalkyl group; R2 = -H or  ;

R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched;

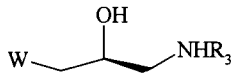
comprising:

a) reacting the compound of formula XI



XI

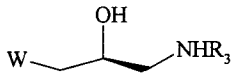
with R3-X in the presence of a suitable reagent to provide the compound of formula XIII



XIII

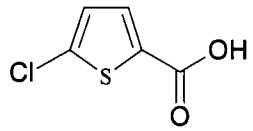
R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched

b) reacting the compound of formula XIII



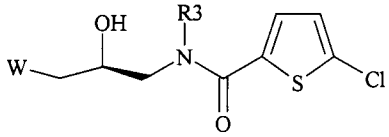
XIII

with a compound having the formula XII



XII

in the presence of a suitable reactant to provide the compound having the formula IIc



IIc

c) reacting the compound of formula IIc with a suitable reagent gives the compound of formula II.

In the reaction step a) the compound having the formula (XIII) prepared by reacting compound having the formula (XI) with R^3- X in the presence of suitable reagent.

Suitable bases for carrying out the reaction are inorg.bases such as ammonia,alkali, or alkaliearth metal hydroxides such as Sod. Hydroxide, carbonates such as Sodium carbonate;bicarbonates such as Sodium bicarbonate .Org. bases such as tri(C_{1-6} alkyl)amines, Collidine, Pyridine etc. Preferably triethylamine.

Suitable solvents for carryingout the reaction are alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, trichloromethane, hydrocarbons such as

toluene, nitriles such as acetonitrile, aprotic polar solvents such as DMF, esters such as ethyl acetate , preferably methanol (or) toluene.

Temp: 0°C to boling point of the solvent used. Preferably at 25-50°C.

When X = aldehyde (-CHO) group, the intermediate compound (imine) can be reduced to compound (XIII) with a suitable reducing agent.

Suitable reducing agents are hydrogenation catalysts like Pd/C, PtO_2,Raney-Ni,metal hydrides such as Sodium borohydride, Sodium cyanoborohydride, Zinc borohydride. Preferably Sodium cyanoborohydride.

Optionally the reduction step can be carried out in presence of a base such as Ammonia.

The reduction step can be carried out with a hydrogen pressure of 5-12 kg and a Temp from about 25°C to about 55°C and for a period of 30 mins to about 12 hours.

Optionally the formation of imine & reduction of imine to compound of formula (XIII) can be carried out in one pot.

The reaction step b) is carried out by reacting the compound of formula XIII with the compound of formula XII or with the corresponding carbonyl halides preferably carbonyl chlorides or with the corresponding symmetric or mixed carboxylic anhydrides of the carboxylic acids of the formula XII defined above in the presence of solvents and an activating or coupling agent and / or a base to afford the compound of formula IIc.

The suitable bases that can be used in step b) is selected from the group like alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; amines such as triethyl amine, diisopropyl amine, diisopropylethylamine, N,N-dimethylamino-pyridine, pyridine and the like; or mixtures thereof, preferably triethyl amine or sodium bicarbonate.

The suitable activating or coupling agents include but are not limited to N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide.HCl, N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole monohydrate and the like;

The solvents that can be used in step b) is selected from the group consisting of water, halogenated solvents such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF) and the like; alcohols such as methanol, ethanol and the like;

hydrocarbon solvents such as toluene and the like; nitriles such as acetonitrile and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), pyridine, hexamethylphosphoric triamide and the like; or mixture thereof. Preferably dichloromethane or toluene.

The reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours is being sufficient.

The suitable reactants that can be used in step c) include acid halides of general formula

Preferably acid chlorides or acid anhydrides of general formula $(R5CO)_2O$.

Where R5 is C_1-C_{12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

The suitable solvents that can be used in step c) is selected from the group to water, halogenated solvents such as dichloromethane, chloroform and the like; esters such as ethyl acetate and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF) and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), acetonitrile and the like; or mixture thereof. Preferably dichloromethane.

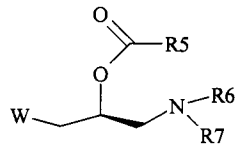
The bases that can be employed in step c) is selected from alkali bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; organic bases such as triethyl amine, diisopropyl ethylamine, 4.N,N-dimethylaminopyridine or pyridine or mixture thereof, preferably pyridine.

The reaction step c) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C.

The time required for the reaction step c) to complete may also vary widely, depending upon various factors like reaction temperature, the nature of the reagent and the solvents

employed, a period of from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 8 hours is being sufficient.

In yet another embodiment, the present invention provides a method for synthesis of compound of formula VI

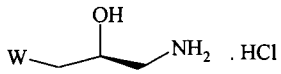


VI

Where W, R5,R6,R7 are same as defined in above aspects.

comprising:

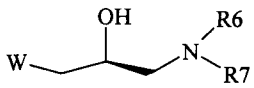
a) reacting the compound of formula XI



XI

Where W is same as defined above

with a suitable protecting agent to provide the compound of formula VIa



VIa

Where W, R6 and R7 are same as defined above

b) reacting the compound of formula VIa with a suitable acylating agent in the presence of a base and an organic solvent to provide the compound of formula VI.

The suitable protecting groups that can be used in step a) is selected from the group consisting of carbamates, imino, amides, phthalimides, azido, pyrrole ring, trityl or dibenzyl group.

Other protecting groups that are suitable herein are also contemplated within this process of invention.

The reaction step a) is essentially performed in the presence of a base.

The suitable bases that can be used in step a) is selected from the group inorganic bases like alkali, alkaline earth metal carbonates such as sodium carbonate, magnesium carbonate and the like; bicarbonates such as sodium bicarbonate and the like; hydroxides such as sodium

hydroxide, magnesium hydroxide and the like; organic bases such as triethyl amine, diisopropylethylamine, pyridine and the like; or mixtures thereof, preferably triethyl amine.

The solvents that can be used in step a) is selected from the group consisting of alcohols such as methanol, ethanol and the like; esters such as ethyl acetate and the like; halogenated solvents such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF) and the like; hydrocarbon solvents such as toluene and the like; nitriles such as acetonitrile and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF) and the like; or mixture thereof.

The reaction step a) can be performed at a temperature range from about -40°C to the boiling point of the solvent(s) used, preferably at about 25°C to about boiling point of the solvent (s) used.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 24 hours is being sufficient.

The suitable acylating agents that can be used in step b) can be selected from

 or $(R_5CO)_2O$. where R5 is same as defined above.

The suitable bases that can be used in step b) is selected from the group inorganic bases like alkali, alkaline earth metal carbonates such as sodium carbonate, magnesium carbonate and the like; bicarbonates such as sodium bicarbonate and the like; organic bases such as triethyl amine, diisopropylethylamine, collidine and the like; or mixtures thereof, preferably pyridine.

The suitable solvents that can be used in step b) is selected from the group consisting of halogenated solvents such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF) and the like; hydrocarbon solvents such as toluene and the like; nitriles such as acetonitrile or mixture thereof. Preferably dichloromethane.

The reaction step b) can be performed at a temperature range from about -10°C to the boiling point of the solvent(s) used, preferably at about 0°C to about 50°C.

The duration of time for the reaction to complete may also vary widely, typically a period of from about 30 minutes to about 12 hours, preferably from about 30 minutes to about 2 hours is being sufficient.

The reaction steps described above can be performed at atmospheric, elevated or reduced pressure in the range of about 0.5 to 5 bar. In general, the reactions are carried out at atmospheric pressure.

The starting intermediate compounds of III, XI, XII are commercially available or can be prepared by processes reported in the literature.

The intermediate compounds formed in various stages are optionally isolated from the reaction mixtures by conventional methods such as evaporation of solvents or by cooling or by adding antisolvents or by extractions using solvents. Furthermore the intermediate compounds are optionally purified if required at various stages by methods for eg.washing, drying and / or by recrystallization in protic or apolar polar solvents or mixture thereof.

Optionally the process steps of present invention can be carried out by one pot synthesis independently.

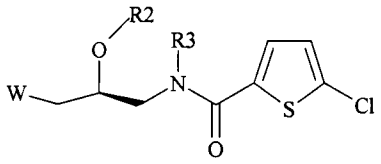
The reported processes aforementioned involves hazardous and expensive reagents like haloformates and bromine derivatives making them difficult to handle on commercial scale and also requires additional purification steps thus ending up with low yields and purities of the final product thus rendering the process not amenable on commercial scale.

Compared to the processes reported in the art for rivaroxaban (I) the processes of present invention are advantageous because they involves simple and less no. of reaction steps, nonhazardous reagents or solvents, commercially available cheaper raw materials are being used thus making the processes easy to handle on industrial scale and more economic.Furthermore, the yields and purities of the intermediates and final product are surprisingly higher.

The processes of present invention are especially valuable for the following reasons:
it makes it possible to obtain the intermediate compounds on an industrial scale in excellent yields, starting from a simple, low-cost starting materials, involve simple process steps and reagents thus making processes more cost effective than reported processes.

Advantageously, the processes of present invention do not involve purification steps thus provides the intermediates of rivaroxaban with higher yields and purities.

In an embodiment of the present invention, there is provided compound having the formula II



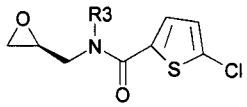
(II)

Where W= halogen (Cl, Br, I) or $-OSO_2R$- Where R= C_{1-4} alkyl, sub or unsub.phenyl, arylalkyl group;

R2 is H or –CO-R5 where R5 is C_1-C_{12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

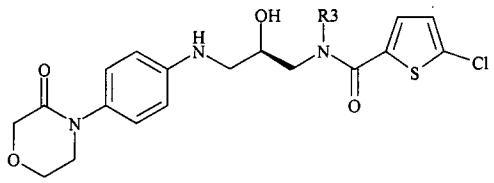
In another embodiment, the present invention provides compound having the formula IV



IV

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched;

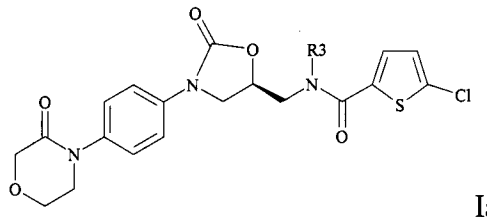
In yet another embodiment, the present invention provides a compound having the formula V



V

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;.

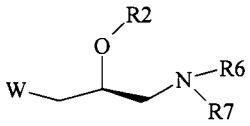
In yet another embodiment, the present invention provides compound having the formula Ia



Ia

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched ;

In yet another embodiment, the present invention provides compound having the formula VI



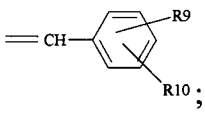
VI

Where W= halogen (Cl, Br,I) or $-OSO_2R$- Where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group;

R2 = -H or –CO-R5 where R5=C_{1-12} alkyl straight chain or branched optionally sub with 1-3 halogen (F, Cl, Br), C_{1-12} alkoxy straight or branched which are optionally sub. with 1-3 halogen (F, Cl, Br), sub or unsub phenyl, sub or unsub phenyloxy, sub or unsub arylalkoxy, sub or unsub arylalkyl group.

R6, R7= independently selected from the group consisting of H or amino protecting group.

a) R6, R7= -H or –CO-OR8 where R8 = C_{1-12} alkyl straight or branched which are optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl group, sub or unsub aryl alkyl group.

b) R6, R7=  ;

Where R9, R10 = independently selected from H or group consisting of Cl, Br, F, I , C_{1-10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl. Br), C_{1-10} alkoxy straight chain or branched which are optionally sub with 1 to 3 halogen atom (F, Cl, Br), $-NO_2$, -CN, -alkyl sulfonyl, arylsulfonyl;

c) R6, R7 = -H or $-CO-R^{11}$ where R^{11}= H or C_{1-10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl group;

d) –N R 6 R7 = sub or unsub phthalimido group;

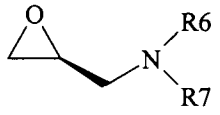
e) –N R 6 R7 = Azido group;

f) –N R6 R7= sub or unsub pyrrole ring;

g) –R6 , R7 = -H or trityl group;

h) R6 = R7 = Sub or unsub benzyl group;

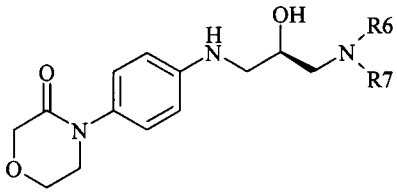
In yet further embodiment, the present invention provides compound having the formula X



X

Where R6 and R7 are same as defined above for the compound of formula VI.

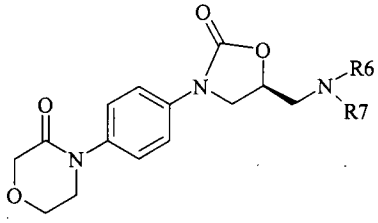
In yet another embodiment, the present provides compound having the formula IX



IX

Where R6 and R7 are same as defined above for the compound of formula VI.

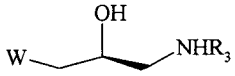
In another embodiment, the present invention provides compound having the formula VII



VII

Where R6 and R7 are same as defined for compound of formula VI.

In another embodiment, the present invention provides compound having the formula XIII



XIII

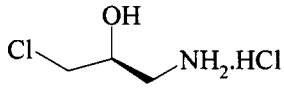
Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched same as defined above.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the

specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

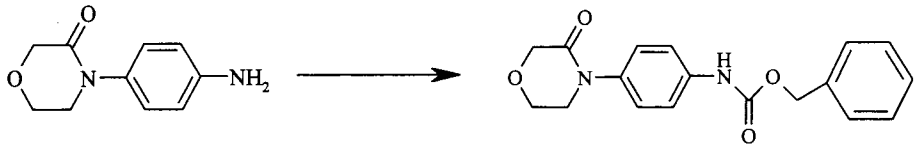
EXAMPLES

Example 1: Preparation of (S)-1-amino-3-chloro-2-propanol hydrochloride



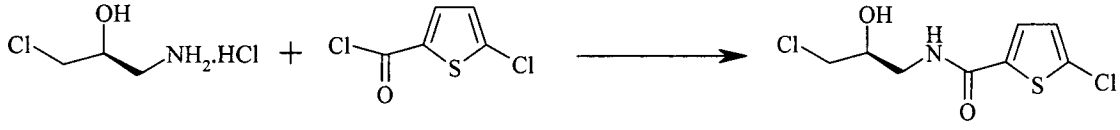
The starting material (S)-1-amino-3-chloro-2-propanol hydrochloride was prepared by the method disclosed in the US patent US 6,362,334B1.

Example 2: Preparation of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (Compound III ,R^1= -CO-OCH2Ph)



To a solution of 4-(4-aminophenyl)morpholin-3-one(3.73 g,19.40 mmol) in acetone (80ml) were added water (40 ml) and $NaHCO_3$ (3.26g, 38.80 mmol). The mixture was cooled to 0°C and benzyl chloro formate (50% in toluene, 20.60 mmol) was added dropwise. The mixture was stirred at R.T for 4 hrs and poured into ice/water. The product was filtered, washed with water and hexane and dried, affording the title compound as a white solid (6.2 g, 98%).

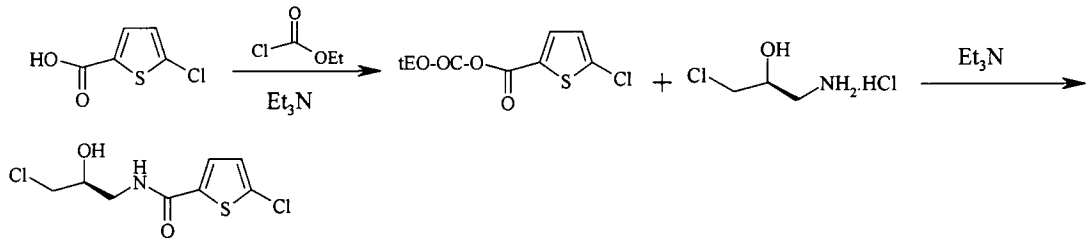
Example 3: Preparation of N-[(2S)-3-chloro-2-hydroxypropyl]-5-chlorothiophene-2-carboxamide(comp-II where R^2 = H, R^3 =H ,w = - Cl)



461g of Sodiumhydrogen carbonate and 350 g of (2S)-1-amino-3-chloro-2-propanol hydrochloride are initially charged at 13-15°C in 2.1 lit of water and admixed with 950 ml of 2-methyl tetrahydrofuran. 444g (1eq) of 5-chlorothiophene-3-carbonyl chloride (prepared from

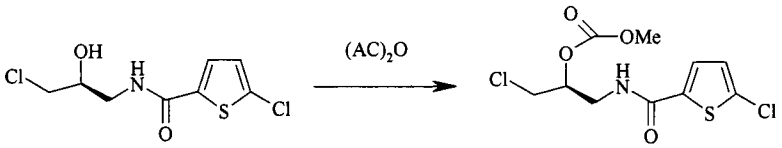
5-chlorothiophene-2-carboxylic acid and thionyl chloride) in 180 ml of toluene are added drop-wise to this mixture with cooling from 15-18°C over a period of 2 hrs. For work up, the phases are separated and the org. phase is washed with water and distilled completely under reduced pressure to yield brown colored solid. After re-crystallization from isopropyl alcohol and hexane yields the title compound as a light brown to off-white colored solid. (Yield = 456 gms, corresponds to 75% of the theory).

Example 4: Alternative Preparation of N-[(2S)-3-chloro-2-hydroxypropyl]-5-chlorothiophene-2-carboxamide (comp-II where W=Cl, $R^2 = R^3 = H$)



To 54.5 gms of 5-chlorothiophene-2-carboxylic acid (commercially available) in 500 ml of dichloromethane added 41 gms (1.6 eq) of tri ethyl amine and cooled to 0°C. To the resultant solution added ethyl chloro formate (41 gms,1.1 eq) by drop-wise at 0°C. After stirring for 30 min, added 37.5 g of tri ethyl amine (1.46 eq) and 300 ml of dichloromethane, added (2S)-3-chloro-2-hydroxypropylamine.HCl by portions at 0°C. After stirring for 30 min at 0° C, raise the temperature to about 30°C and stirred for another 30 min. For workup, added 227 ml of water and separated the layers. Washed the org. layer with 1M HCl solution (227 ml), 5% sodium bicarbonate solution (227ml x 2) and water (227 ml). After drying the org. layer with 5 g of sodium sulfate, distilled off solvent completely to give brownish solid, re-crystallized from IPA & hexane to yield title compound as a off-white crystalline solid. (Yield = 30 g, 35% of theory).

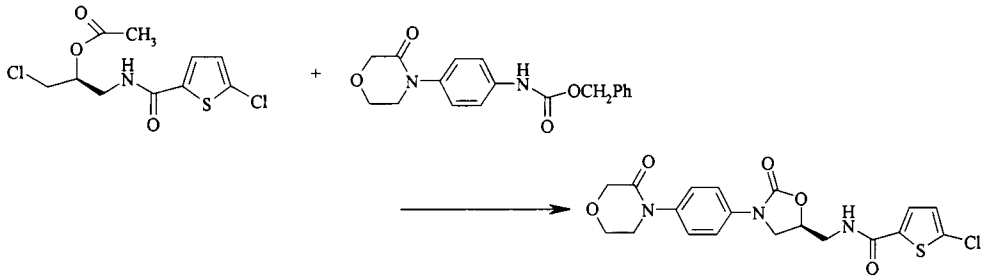
Example 5: Preparation of N-[(2S)-3-chloro-2-(acetyloxy)propyl]-5-chlorothiophene-2-carboxamide(comp-II where R^2 = -CO-CH3,R3 = -H, w = - Cl)



A mixture of 9.0 g (4.5 eq) of acetic acid anhydride and 6.0 g (3.75 eq) of pyridine was cooled to 0° C .At this temperature, 5.0 gms (19.68 mmol) of N-[(2S)-3-chloro-2-

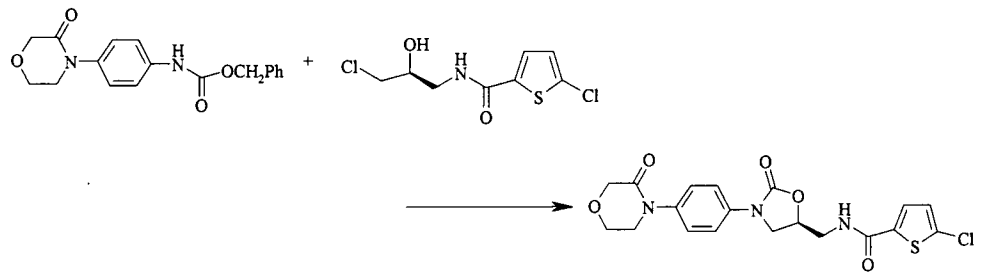
hydroxypropyl]-5-chlorothiophene-2-carboxamide (prepared in Ex. 3 or 4) was added . After stirring for 1 hr at this temperature the reaction mix. was poured into 150 ml of dichloromethane and 50 ml of water, separated the aq. & org. layers and then the aq. Layer extracted with 20 ml x 2 dichloromethane. After washing the MDC layer with 50 ml of saturated NaHCO3 solution and 50 ml of sat. brine solution and dried over Sodium sulfate, distill-off solvent completely and proceed to next steps without further purification. (Yield = 5 g, correspond to 86% of theory).

Example 6: Preparation of Rivaroxaban (I)



To a solution of [4-(3-oxo-morpholin-4-yl)phenyl carbamic acid benzyl ester (prepared in Ex.2) (5g,15.3 mmol) in N,N – dimethyl formamide (15ml) and methanol (1.0 g, 2 eq) at 20°C is added a solution of lithium-t-butoxide (3.6 g, 3 eq) in 20 ml THF while keeping less than 24°C with an ice-bath. The solution is cooled to 5 °C and N-[(2S)-3-chloro-2-(acetyloxy) propyl]-5-chlorothiophene-2-carboxamide (9 gms, 2 eq) (prepared in Ex.5) is added. The resulting solution is allowed to stand for 21 hrs at 21 ° C .Saturated. amm. chloride solution (25 ml) is added followed by water (50 ml), sat. Sodium chloride solution (25 ml) and methylene chloride (50 ml).The phases are separated and the aq. Washed with methylene chloride (3 x 25 ml). The organic layers are dried on magnesium sulfate and concentrated in vacuo to yield semi-solid and re-crystallized from ethanol to yield title compound as a white solid (Yield = 3. 34 gms, 50% of theory).

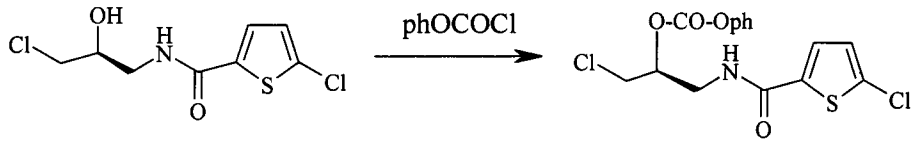
Example 7: Alternative Preparation of Rivaroxaban (I):



To a solution of [4-(3-oxo-morpholin-4-yl) phenyl carbamic acid benzyl ester] (5g,15.3 mmol) (prepared in Ex.2) and N-[(2S)-3-chloro-2-hydroxypropyl]-5-chlorothiophene-2-carboxamide (5.0 gms , 1.28 eq) (prepared in Ex. 3 or 4) in DMF (15 ml) in an icebath was added a solution of lithium tert. Butoxide (3.0 gms, 2.45 eq) in THF (16.5 ml). The resultant mix. was allowed to stand at 20 ° C for 44 hrs. Saturated aq. amm. Chloride (25 ml), water (50 ml) and methylene chloride (60 ml) were added and the phases separated. The aq. was washed with methylene chloride (60 ml) and the combined org. were dried on magnesium sulfate and concentrated to get a crude compound. After re-crystallization from acetic acid, yields a title compound as white crystalline solid (Yield = 3.0 g , corresponds to 45% of the theory).

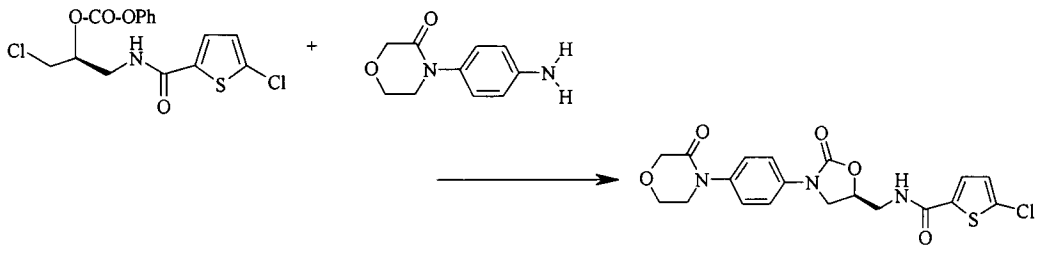
Example 8: Alternative Preparation of Rivaroxaban (I):

Step- I : Preparation of N-[(2S)-3-chloro-2-((phenoxy carbonyl)-oxy)propyl]-5-chlorothiophene-2-carboxamide(comp-II where R^2 = -CO-Oph,R^3 = -H, w = - Cl)



To a solution of N-[(2S)-3-chloro-2-hydroxypropyl]-5-chlorothiophene-2-carboxamide (5.0 g, 19.68 mmol), pyridine (2.5 g, 1.6 eq) and dichloromethane (50 ml), phenyl chloroformate (3.5gms , 1.13 eq)was added drop-wise at 0°C . After stirring at 0°C for 1 hour, the reaction mix. was poured into water and the org. layer was separated . The aq. layer was extracted with dichloromethane (100 ml) and the combined org. extract was washed with dil. HCl (50 ml) followed by water (2x 50 ml) and concentrated to get crude compound. This compound is directly used for the next step. (Yield = 7.0 gms, 95 % of the theory).

Step- II : Preparation of Rivaroxaban (I):

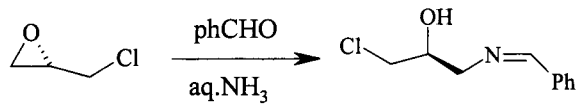


To a solution of N-[(2S)-3-chloro-2-((phenyloxycarbonyl)-oxy)propyl]-5-chlorothiophene-2-carboxamide (7.0 gms, 18.7 mmol) (prepared in step – I) and 4-(4-aminophenyl)morpholin-3-one (4.5 gms , 1.25eq) commercially available) in DMF (35 ml),

Potassium carbonate (6.5 gms, 2.5 eq) and catalytic amount of triethylbenzyl amm.chloride were added and stirred at 80°C for 12 hrs. The reaction mixture was poured into water (150 ml) and extracted with dichloromethane (3 x 50 ml). The combined org. extract was washed with water (2 x 50 ml) and evaporated to get the crude compound. Upon recrystallization from acetone to yield a title compound as a white crystalline solid (Yield = 1.63 gms, 20 % of the theory).

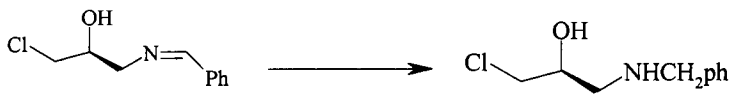
Example 9: Preparation of N-[(2S)-3-chloro-2-(acetyloxy)propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide(comp-II where W= Cl, R^2 = -$COCH_3$,R3 = CH_2ph)

Step- I : Preparation of (S)-1-benzalimino-3-chloro-2-propanol:



(S)-Epichlorohydrin (44.978 gm, 486.1 mmol, 98.9% enantiomeric excess) is added to a mix. of benzaldehyde (50.0 ml, 492 mmol, 1.012 eq) ethanol (163 ml) and aq ammonia (29.8 wt %) (50 ml, 787.4 mmol,1.62 eq) at 18 ° C over 10 min with an exotherm to 22° C. The reaction mix. is permitted to exotherm to 34° C over 1.5 hrs ,warmed to 42 ° C, stirred at 20 -25 ° C for 20.5 hrs , then warmed to 74 ° C and immediately allowed to cool. The mix. is concentrated under reduced pressure. To the residue, added 200 ml methylene chloride and 100 ml water. Separated the aq. layer & org. layer and the org. layer washed with water (50 ml). Distilled off the org. layer completely to give the title compound as a light brownish liquid. (Yield = 90 g, 93.7% of the theory).

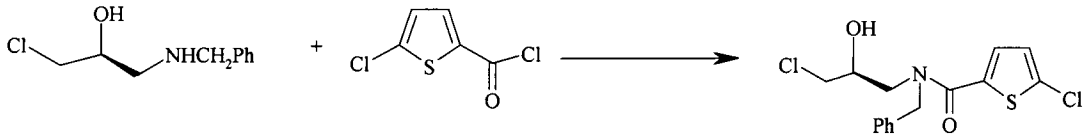
Step- II: Preparation of (2S)-1-benzylamino-3-chloro-2-propanol (Comp: XIII, where W=Cl, R3=-CH_2Ph)



To a solution of the (S)-1-benzalimino-3-chloro-2-propanol (5.0 gms) (25.38 mmol) (prepared in step – I) in 50 ml of methanol ,added sodiumborohydride (0.964 gm, 1 eq) by portions by maintaining the temperature at 25- 30 ° C , stirred for 15 min at 25- 30 ° C and distill-off the solvent under reduced pressure to yield a semi-solid . Added 50 ml water and extracted into methylene chloride (50 ml x 2) . Washed the methylene chloride layer with 25

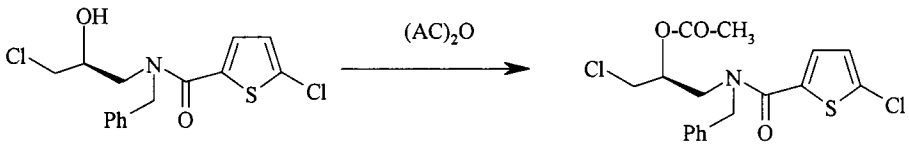
ml x 1 water and concentrated to get the title compound as oil. (Yield = 4.0 gms, 80 % of the theory).

Step-III: Preparation of N-[(2S)-3-chloro-2-hydroxypropyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide(comp-II where R^2 = -H,R3 = CH2ph, w = Cl):



12.6 gms of sodium bicarbonate and 19.9 gm(0.1 mol) of (2S)-1-(benzylamino)-3-chloro-2-propanol (prepared in step II) are initially charged at from 13 to 15 ° C in 60 ml of water and admixed with 30 ml of the 2-methyl THF. 18.5 gm (1.02 eq) of 5-chlorothiophene-2-carbonyl chloride in 30 ml of toluene are added drop-wise with cooling at from 15 to 18 ° C over a period of 2 hrs . For work up, the phases are separated and the org. phase is washed with water and distilled completely under reduced pressure to yield a crude compound . After re-crystallisation form isopropyl alcohol- n- hexane mix. yield a title compound as a light cream colored solid. (Yield = 24 gms, 70% of the theory).

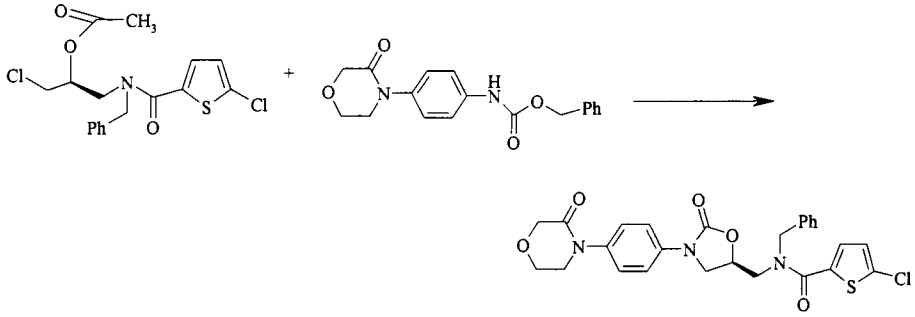
Step-IV: Preparation of N-[(2S)-3-chloro-2-(acetyloxy)propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide:



A mix. of 28.5 gms (4 eq) of acetic acid anhydride and 16.5 gms (3 eq) of pyridine was cooled to 0° C. At this temperature 24 gms (69.86 mmol) of N-[(2S)-3-chloro-2-hydroxypropyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (prepared in step –III) was added. After stirring for 1 hr at this temp. the reaction mixture was poured into 300 ml of dichloromethane and 100 ml water, separated the aq. & org. layers and the org. layer is extracted with 50 ml x 2 dichloromethane . After washing the org. layer with 50 ml of saturated sodium bicarbonate solution and the 50 ml of the saturated brine solution and dried over Sodium sulfate , distill- off solvent completely and proceed to the next step without further purification . (Yield = 22. 9 gms, corresponds to 85% of the theory)

Example 10: Preparation of Rivaroxaban (I):

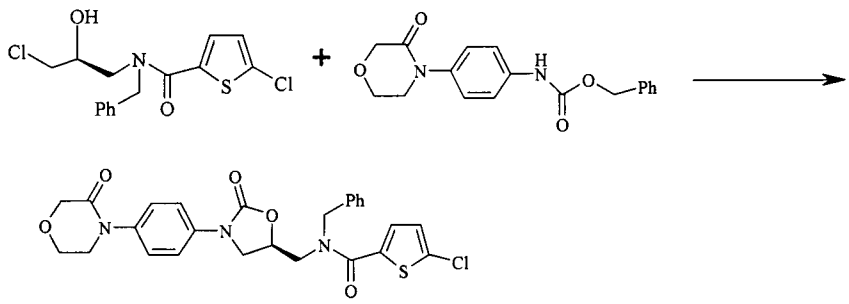
Step-I: Preparation of 5-Chloro-N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-thiophene carboxamide (Compound – Ia where R^3= benzyl):



To a solution of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 gms, 10 mmol) in 10 ml DMF and methanol (0.64 g, 2 eq)at 20 ° C is added a solution of Lithium –ter- butoxide (2.4 gms, 3eq) in THF (13.5 ml) while keeping less than 24 ° C with an ice – bath. The solution is cooled to 5° C N-[(2S)-3-chloro-2-(acetyloxy)propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (7.73 gms, 2 eq) (prepared in Ex.9) is added . The resulting solution is allowed to stand for 21 hrs at 21°C .Sat. ammonium chloride solution (20 ml) is then added followed by water (30 ml) , sat. aq. NaCl solution (20 ml) and the MDC (50 ml). The phases are separated and the aqueous. was washed with MDC (25 ml x 3). The org are dried on magnesium sulphate and concentrated in vacuum to yield a semisolid and re-crystallized from ethanol to yield a title compound as a white crystalline solid.

(Yield = 1. 65 gms, correspond to 38 % of theory).

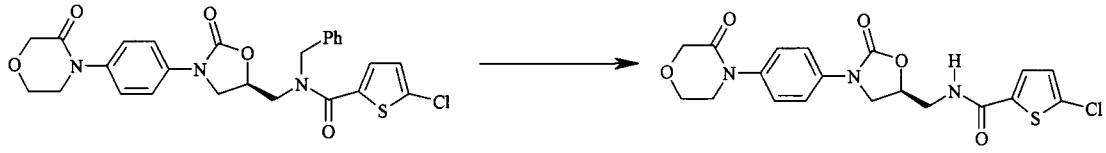
Alternative Preparation of 5-Chloro-N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-thiophene carboxamide (Compound Ia):



To a solution of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 gms , 10 mmol) and N-[(2S)-3-chloro-2-hydroxypropyl]-N^1-benzyl-5-chlorothiophene-2-

carboxamide (4.95 gms, 1.28 eq) (prepared in the Ex. 9 of step – III) in DMF (10 ml) in an ice-bath was added a solution of the Lithium – ter- butoxide (1.96 gms , 2.45 eq) in THF (11 ml).The resultant mix. was allowed to stand at 20 ° C for 44 hrs. saturated aqueous ammonium chloride solution (20 ml) water (25 ml), and methylene chloride (50 ml) were added and the phases are separated . The aqueous was washed with methylenedichloride (30 ml) and the combined organics were dried on magnesium sulphate and concentrated to get a crude compound. After recrystallization from acetone to yield the title compound as a white crystalline solid (Yield = 1.85 gms , corresponds to 42 % of the theory).

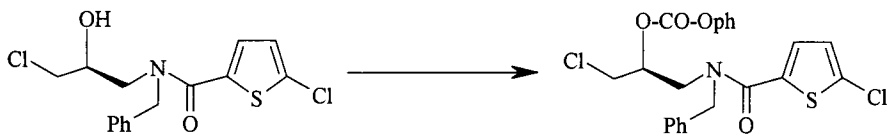
Step II: Debenzylation of 5-Chloro-N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-h carboxamide (Preparation of Rivaroxaban(I)):



To a suspension of 5-Chloro N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-thiophene carboxamide (prepared in step –I) (5.26 gms , 10 mmol) in $CHCl_3$ (100 ml), N-methylacetamide (0.73 gms , 0.2 eq) and N-bromosuccinimide (4.45 gms, 2.5eq) were added at about 30°C and the resulting mix.was stirred at reflux for 18 hrs . The solvent was evaporated under vacuum and dichloromethane (100 ml) and aq. Sodium hydroxide (1M, 50 ml) were added and the phases are separated .The aq. was extracted with dichloromethane (25 ml x 3) and the combined organics washed with water (20 ml x 2), brine(1 X 10 ml) and dried over sodium sulphate. The solvent was evaporated under vacuum and the solid obtained was re-crystallized from acetic acid. (Yield = 2.66 gms, 61 % of the theory).

Example.11: Alternative Preparation of Rivaroxaban (I) :

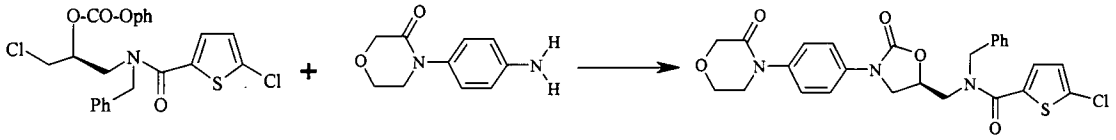
Step- I : Preparation of N-[(2S)-3-chloro-2-{(phenyloxy carbonyl)-oxy }propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide(comp-II where W=Cl, R^2 = -CO-Oph,R^3 = benzyl)



To a solution of N-[(2S)-3-chloro-2-hydroxypropyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (3.45 gms, 10 mmol), pyridine (1.264 gms, 1.6 eq) and dichloromethane (35

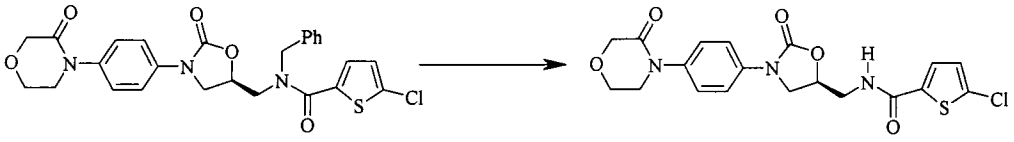
ml), phenylchloroformate (1.72 gms, 1.1 eq) was added drop-wise at 0 ° C . After stirring at 0° C for 1 hour , the reaction mixture was poured into water and the org. layer was separated . The aq. layer was extracted with DCM (50 ml) and the combined organic extract was washed with dil. HCl (20 ml) followed by water (2 x 20 ml) and then concentrated to get a title compound (4.2 gms , 90% of the theory). This compound is used for step – II without further purification.

Step- II: Preparation of 5-Chloro N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholin-4yl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-thiophene carboxamide (Compound Ia, where R3=benzyl)



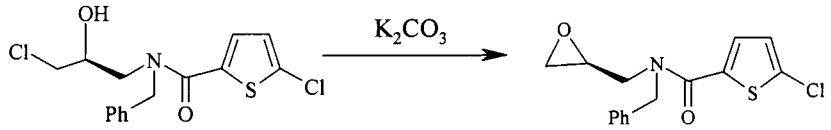
To a solution of N-[(2S)-3-chloro-2-{(phenyloxy carbonyl)-oxy} propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (4.2 gms, 9 mmol) (prepared in step –I) and 4-(4-aminophenyl)-morpholin-3-one (2.17 gms, 1.25 eq) in DMF (20 ml), potassium carbonate (3.07 gms , 2.5 eq) and catalytic amount of triethyl benzyl ammonium chloride were added and stirred at 80 ° C for 12 hours. The reaction mixtures was poured into water (100 ml) and then extracted with dichloromethane (25 ml x 3). The combined organic extract was washed with dil. HCl (2 x20ml) and water (2x 50 ml) and then evaporated to get crude compound, upon re-crystallization from acetone to yield title compound as off- white crystalline powder (Yield: 0.95 gms, 18.1% of theory).

Step- III : Preparation of Rivaroxaban (I):



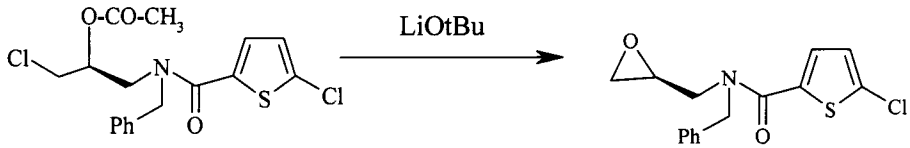
To a solution of 5.26 gms of 5-Chloro-N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolin-5-yl}methyl]-N^1-benzyl-2-thiophene carboxamide (prepared in step-II) in toluene (50 ml) was added paratoluenesulphonic acid (6.88 gms , 4 eq) and refluxed for 5 hrs. Cool the reaction mixture to about 30 °C and the product isolated by filtration. Re-crystallize the solid obtained from the acetic acid to yield pure title compound as a white-crystalline solid. (Yield = 3.35 gms, 77% of the theory).

Example.12: Preparation of N-(S) (1-oxiranylmethyl)-N^1-benzyl-5-chlorothiophene-2-carboxamide (compound- IV where R^3 = benzyl):



8.6 gms of powdered potassium carbonate (4.3 eq) was added to a solution of N-[(2S)-3-chloro-2-hydroxypropyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide(5.0gms,14.5 mmol, 1eq) (prepared in Ex.9 of step-III) in 250 ml of methylene chloride under an atmosphere of nitrogen. The reaction mixture was stirred at R.T for 3- days, then the suspension was filtered and the filter cake was washed with methylene chloride. Filterate and the wash liquid were combined and then concentrated in the vacuum at about 30°C to afford 3.13gms (70 %) of the title compound. The resulting material was used in the following reaction without any further purification.

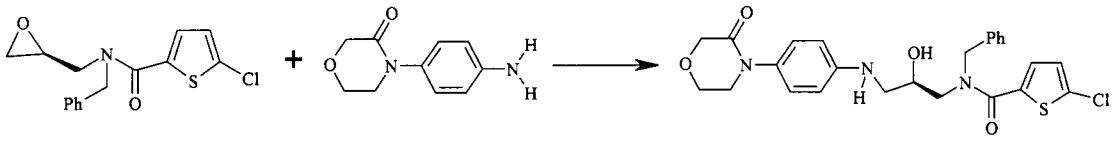
Example.13: Alternative Preparation of N-(S) (1-Oxiranylmethyl)-N^1-benzyl-5-chlorothiophene-2-carboxamide:



To a solution of N-[(2S)-3-chloro-2-(acetyloxy)propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (3.865 gms,10 mmol) in methanol (10 ml) at 13 ° C was added Lithium-tert-butoxide (1.0 gms ,1.25 eq) while maintaining less than 22° C . The mixture was stirred at 8-20° C for a period of 30 min, and water (100 ml) and dichloromethane (100 ml) were added. The phases are separated and the aq. phase was washed with methylene chloride (50 ml). The combined organics were dried on magnesium sulphate and then concentrated to afford 2.30 gms (75%) of the title compound . The compound was used in the further reactions without any further purification.

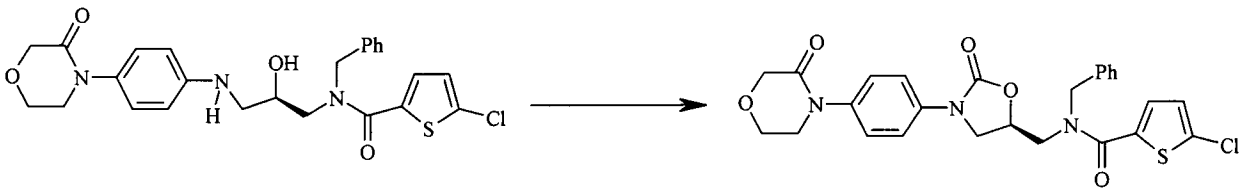
Example.14: Alternative Preparation of Rivaroxaban (I):

Step –I: Preparation of N-[(R)-2-hydroxy-3-{4-(3-oxomorpholin-4-yl)phenylamino}propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide)(Compound V where R^3 = benzyl):



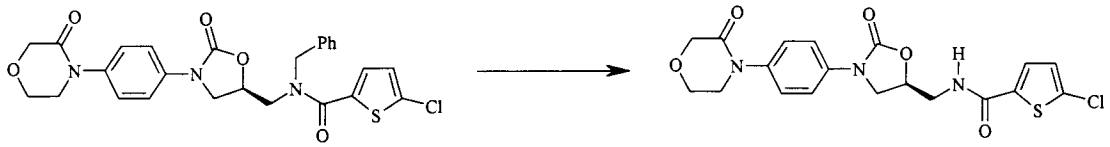
To a suspension of 19.2 gms (0.1 mol) of 4-(4-aminophenyl morpholin-3-one) in ethanol (200 ml) added N-(S)-(1- oxiranylmethyl)-N^1-benzyl-5-chlorothiophene-2-carboxamide (32 gms , 1.05 eq) (prepared in the example 12 or 13) and refluxed for a period of 24 hrs . Distill off the solvent under vacuum and re-crystallized from ethyl acetate afford the title compound as a off – white crystalline solid. (42.4 gms, 85% of the theory).

Step –II: Preparation of 5-chloro-N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-thiophenecarboxamide (Compound – Ia where R^3= benzyl):



To a suspension of 49.95 (0.1 mol) of N-[(R)-2-hydroxy -3-{4-(3-oxomorpholin-4-yl)phenylamino}propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (prepared in step –I) in dichloromethane (250 ml) added N,N^1- carbonyldiimidazole (17.8 gms, 1.1 eq) and stirred the mixture at 33- 35 ° C for a period of 48 hrs. Then the mixture was cooled to 25°C , and the product was isolated by the filtration and washed with 50 ml of dichloromethane and 50 ml water . The wet product was dried and re-crystallized from acetic acid to yield the title product as white crystalline solid.(47.3 gms, 90% of the theory).

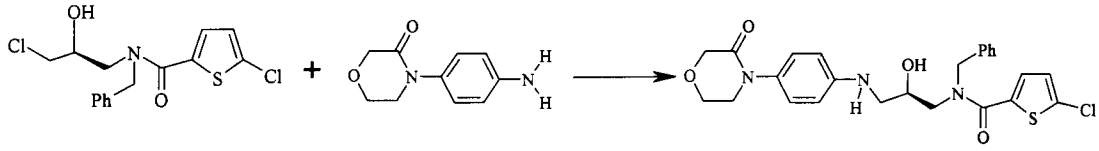
Step – III: Preparation of Rivaroxaban (I):



A solution of 5-chloro –N- [{(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl]-N^1-benzyl-2-thiophene carboxamide (5.26 gms, 10 mmol) (prepared in the Step –II) in chlorobenzene (50 ml) containing N-bromosuccinimide (1.78 gms, 1 eq) and AIBN (0.33 gms , 0.2 eq) was heated to reflux under a nitrogen atmosphere. After 4 hrs further AIBN (0.1 eq) and NBS (0.2 eq) were added. The solution was heated overnight then

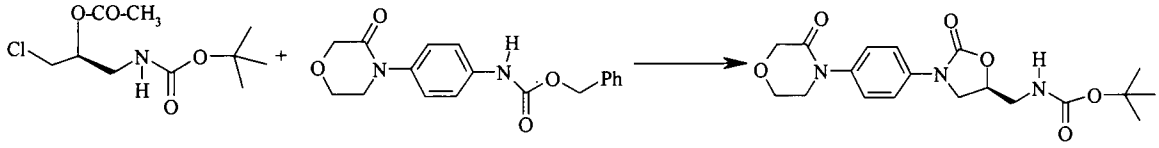
cooled , filtered and concentrated water (50 ml) and ethanol (100 ml) ware added and stirred for 1 hr at R.T . Filtered the product and washed with ethanol. Re-crystallized from acetic acid to yield pure title compound. (Yield =3.1 gms , 71% of the theory).

Example 15: Alternative preparation of N-[(R)-2-hydroxy-3-{4-(3-oxomorpholin-4-yl)phenylamino}propyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide) (Compound V, R^3=benzyl:



To a suspension of 19.2 gms (0.1 mole) of 4-(4-amino-phenyl morpholin-3-one) and N-[(2S)-3-chloro-2-hydroxypropyl]-N^1-benzyl-5-chlorothiophene-2-carboxamide (34.0 gms ,0.1 mol , 1 eq) in 100 ml toluene added 11.5 gms collidine and 45.6 ml ethanol. The reaction mixture was heated to 105 ° C and then stirred for a period of 3 hrs at that temp. then 39 ml of n- butanol were added and the reaction mix. was cooled to 22 ° C . After stirring for atleast1 hr at the ambient temperature the product was isolated by the filtration and then washed with toluene and water. The wet product was dried and then re-crystallized from methanol to yield 24.9 gms (50%) of the title compound.

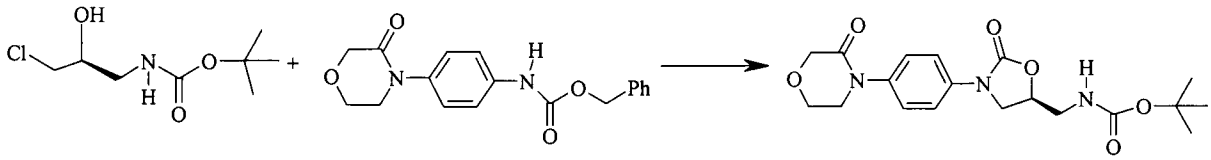
Example 16: Preparation of tert-butyl – { (5S)-3-[4-(3-oxo-4-morpholinyl)phenyl]-2-oxo- 1,3-oxazolidin-5-yl}methylcarbamate (Compound – VII; R^6= - H, R^7= -CO-O-tBu):



To a solution of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 gms , 10 mmol) (prepared in Ex.2) and (1S)-2- [(tert-butoxycarbonyl)amino]-1-(chloromethyl)ethylacetate (3.06 gms , 1.22 eq) (prepared as per US 6,998,420 B2) in DMF (7ml) and methanol (0.39 gms, 1.22 eq) at 0° C was added Lithium-tert-butoxide (1.768 gms, 2.21 eq) . The solution was allowed to stand at 20-25° C for 18 hrs. acetic acid (1.2 gms,2 eq) was added. The mixture was diluted to 250 ml total volume with methanol. Distilled – off solvent completely and re-crystallized from ethyl acetate yield title compound as white crystalline solid (2.5 gms, 63.8% of the theory).

Example 17: Alternative Preparation of tert-butyl – { (5S)-3-[4-(3-oxo-morpholin-4-

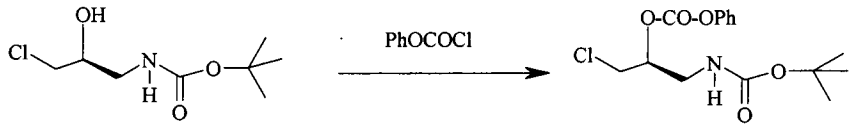
yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate (Compound –VII; where R6=H, R7=COO-tert-butyl):



To a suspension of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 gms, 10 mmol) (prepared in Ex.2) and tert-butyl (2S)-3- chloro-2-hydroxypropyl carbamate (2.64 gms, 1.26 eq) (prepared as per US6,998,420 B2) in DMF(7 ml) in an ice bath was added a solution of Lithium-t-butoxide (1.956 gms, 2.4 eq) in THF (10. 7 ml) . The resultant solution was allowed to stand at 20° C for the period of 44 hrs . Sat aq. ammonium chloride (25 ml), water (50 ml) and methylene chloride (50 ml) were added and the phases were separated. The aq. layer was washed with methylene chloride (50 ml) and the combined organic layers dried on magnesium sulphate and then concentrated to yield a crude compound. After recrystallisation from ethyl acetate to yield title compound as a white crystalline solid. (Yield = 2. 74 gms , 70 % of the theory).

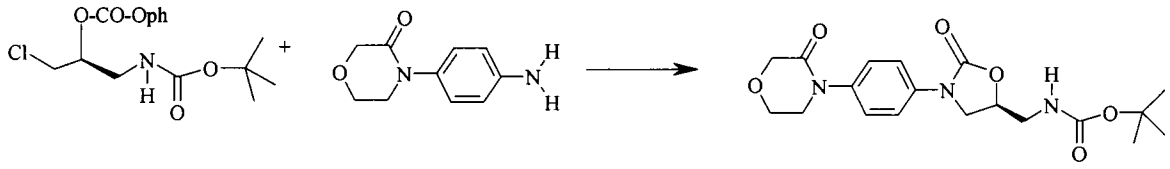
Example 18: Alternative Preparation of tert-butyl–{(5S)-3-[4-(3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate(Compound –VII; R6=-H, R7= CO_2tBu):

Step-I: Preparation of tert-butyl (2S) -3-chloro -2- ((phenyloxy carbonyl) oxy) propyl carbamate (compound VI , R^2 = - CO-OPh, R^6 = -H,R^7= -CO-Ot.Bu, w=Cl):



To a solution of tert-butyl-(2S)-3-chloro-2-hydroxypropyl carbamate (20.95gms ,0.1moles) (prepared as per US6,998,420 B2) pyridine (12.64 gms, 1.6 eq) and dichloromethane (200 ml) . phenyl chloroformate (17.25 gms , 1.1 eq) was added drop-wise at 0°C . After stirring for 1 hour at 0°C , the reaction mixture was poured into the water and the org. layer was separated and the aq. was extracted with dichloromethane (200 ml) and the combined extract was washed with the dil.HCl (50 ml) followed by water (100 ml x 2) and then concentrated the organic layer to get the crude compound (27.5 gms, 83.5 % of the theory). The compound is directly used for the next step without any further purification.

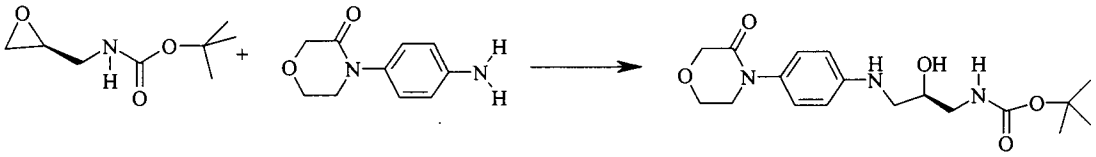
Step –II: Preparation of tert-butyl-{(5S)-3-[4-(3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate:



To a solution of tert-butyl-(2S)-3-chloro-2-((phenyloxy carbonyl)oxy)propyl carbamate (3.295 gms , 10 mmol) (prepared in Step –I) and 4-(4-aminophenyl) morpholin -3-one (2.4 gms, 1.25 eq) in DMF (25 ml) . potassium carbonate (3.45 gms, 2.5 eq) and catalytic amount of triethylbenzyl ammonium chloride were added and then stirred at 80 °C for 12 hrs. The reaction mixture was poured into water (100 ml) and extracted with dichloromethane (25 ml x 3) . The combined organics were washed with dil. HCl (10 ml x 2) and water (20 ml x 2) . Distill-off solvent completely and recrystallized from methanol to yield title compound as white-crystalline solid (0.784 gms, 21 % of the theory).

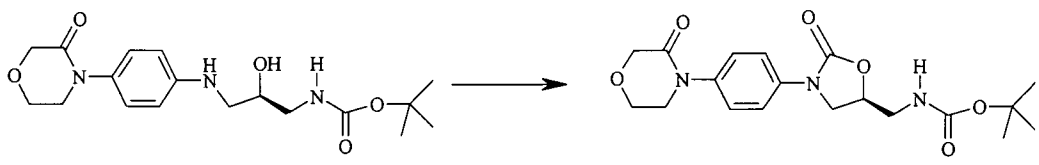
Example 19: Alternative Preparation of tert-butyl – { (5S)-3-[4-(3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate(Compound –VII where in R^6 = -H, R^7= -CO_2tBu-):

Step – I: Preparation of tert. Butyl –N- [(R)-2-hydroxy-3-{4-(3-oxomorpholin-4-yl)phenylamino}propyl]carbamate (compound – IX, R^6= -H, R^7= -CO-Ot Bu):



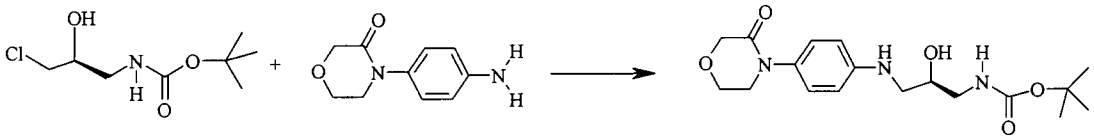
To a suspension of 4-(4-aminophenyl)-morpholin-3-one (19.2 gms 0.1 mol) in ethanol (200 ml) added tert-butyl-(2S)-oxiranyl methyl carbamate (17. 3 gms, 0.1 mol, 1 eq) (prepared as per US6,998,420 B2) and refluxed for 24 hrs . Distill – off solvent completely and used for the next reaction without further purification (Yield =36.5 gms, 100 % of the theory).

Step:II: Preparation of tert-butyl – { (5S)-3-[4-(3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methylcarbamate:



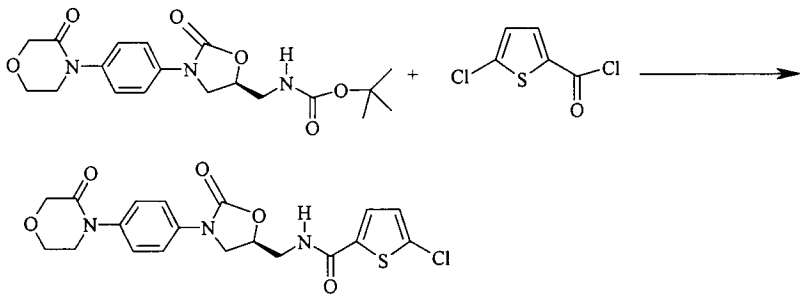
To a solution of tert-butyl-N-[(R)-2-hydroxy-3-{4-(3-oxomorpholin-4-yl)phenyl amino}propyl]carbamate (36.5 gms, 0.1 mol) in dichloromethane (200 ml) was added N,N^1-carbonyldiimidazole (16.85 gms, 1.04 eq) at once and the solution was stirred for 44 hrs at ambient temp. water (200 ml) added and phases were separated . washed the organics with water (100 ml) and distill-off completely under reduced pressure to yield a title compound as off-white crystalline solid (37.25 ,95% of the theory).

Example 20: Alternative Preparation of tert. Butyl –N- [(R)-2-hydroxy-3-{4-(3-oxomorpholin-4-yl)phenylamino}propyl]carbamate (compound – VII, R^6= -H, R^7= -CO_2tBu):



To a suspension of 19.2 gms (0.1 mol) of 4-(4-aminophenyl)-morpholin-3-one and tert.butyl-(2S)-3-chloro-2-hydroxypropyl carbamate (23 gms, 1.05 eq) in ethanol (200 ml) was added potassium carbonate(27.6 gms, 2 eq) and refluxed for 24 hrs. Filter the undissolved solid and washed with ethanol (50 ml). Distill off the solvent completely and to the semi solid added water (200 ml) and adjusted pH = 2 with dil. HCl and washed the aq. layer with 50 ml of dichloromethane. Acidic aq. layer taken and pH =10 adjusted with 10 % NaOH solution and then extracted with dichloromethane (100 ml x 2) and washed dichloromethane layer with water (50 ml x 2).Distill off the solvent and then used for the further reactions without further purifications.(Yield=23 gms, 63% of the theory).

Example 21: Preparation of Rivaroxaban (I)



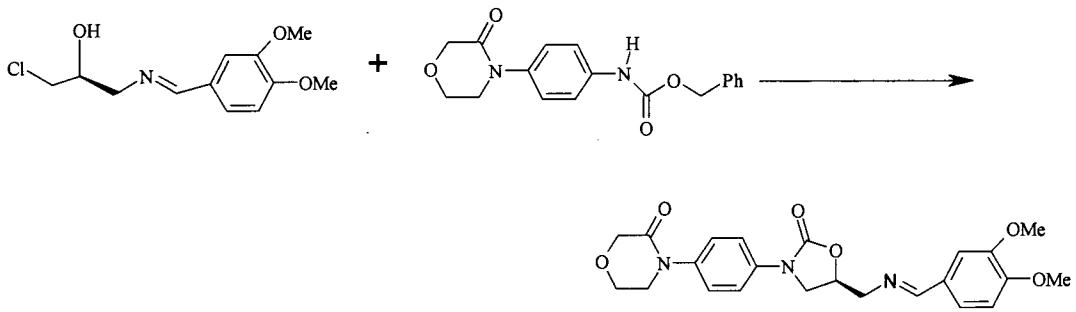
5-chlorothiophene-2-carbonyl chloride(9.5 gms, 52.5 mmol, 4.13 eq) was added to a solution of tert- butyl- {(5S)-3-[4-(3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl]methyl carbamate (prepared in above examples(5.0 gms, 12.75 mmol, 1 eq), methanol (1.0 gm, 31.25 mmol,2.45 eq) and Sodium iodide (4 gms, 26.6 mmol,2.1 eq) in acetonitrile(250

ml). The yellow heterogenous mix. was stirred fot about 20 min at R.T. N,N-Diisopropylamine (6.5 gms, 4 eq) was added at 0°C and the heterogenous mix. was stirred at R.T for 4 hrs.It was quenched with 10% HCl (100 ml) and the product isolated by the filteration and then recrystallized from acetic acid(Yield = 4.2 gms,76.4 % of the theory).

Example 22: Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl]-morpholin-3-one. Hydrochloride (Compound VIII):

39.2 gms (0.1 mol) of tert-butyl-{(5S)-3-[4-[3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl carbamate (prepared in the above examples) added 300 ml of methanolic hydrochloric acid (having 8-12 % assay) and stirred for about 1 hr at R.T Distill off the solvent completely under the reduced pressure and to the white solid added 50 ml dichloromethane and stirred for about 20 min and filtered to get title compound as a white-crystalline solid. (Yield = 26.5 gms, 80.6% of the theory).

Example 23: Preparation of (S)-5-{[3,4-dimethoxy-benzylidene)-amino]methyl}-3-[4-(3-oxo-morpholin-4-yl)phenyl]-1,3-oxazolidin-2-one (Compound –VII, where R6, R7= 3,4-dimethylbenzylidene group.



To [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 g, 10 mmol) in dichloromethane (10 ml) added Lithium-tert-butoxide (2.0 g, 2.5 eq) and the mix. stirred at about 30°C.To the resultant suspension is added (S)-1-chloro-3-[(3,4-dimethyoxy-benzylidene)-amino]-propan-2-ol) (3.85 g, 1.5 eq) (prepared as per WO2007/116284) in DCM (10 ml)in one portion. The resulting thin suspension is heated to reflux for about 21 hrs. After cooling to R.T , the organic. Layer is washed with water (1 x 50 ml, 1x 25 ml). These aq. phases are then discarded. The organic phase is concentrated in vacuo to about ½ volume , at

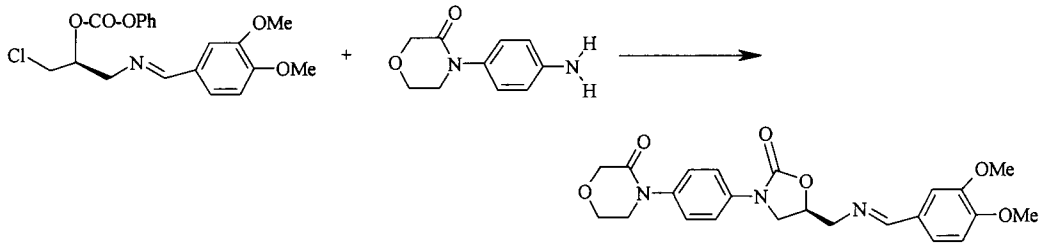
which time isopropyl alcohol (100 ml) is then added and the concentration continued to a volume of less than 100 ml. The resultant suspension is cooled to -10°C to -20°C and the solids isolated by the filtration and then washed with cold isopropyl alcohol.(Yield = 0.878 g 20 % of the theory).

Example 24: Alternative Preparation of (S)-5-{[3,4-dimethoxy-benzylidene)-amino]methyl}-3-[4-(3-oxo-morpholin-4-yl)phenyl]-1,3-oxazolidin-2-one (Compound – VII):

Step-I: Preparation of (S)-3-chloro-2-((phenyloxy carbonyl)oxy)-1-[(3,4-dimethoxy benzalidene)amino]propane (Compound –VI, R^2= -H,w = -Cl R6,R7=3,4-dimethoxybenzylidene group)

To a solution of (S)-1-chloro-3-[(3,4-dimethoxy-benzalidene amino]-propan-2-ol (25.75 g, 0.1 moles) (prepared as per WO 20007/116284) in dichloromethane (250 ml) and pyridine (12. 64 g, 1.6 eq), phenylchloroformate (17.25 g, 1.1eq) was added drop-wise at 0°C. After stirring for 1 hr at 0°C, the reaction mixture was poured into the water and the organic layer was separated and the aq. was extracted with DCM (200 ml) and the combined extracts was washed with dil. HCl (50 ml) followed by water (100 ml x 2) and then concentrated under reduced pressure to get the title compound as a oily liquid .(Yield = 30.0 g, 83 % of the theory)

Step-II: Preparation of (S)-5-{[3,4-dimethoxy-benzalidene)-amino]methyl}-3-[4-(3-oxo-morpholin-4-yl)phenyl]-1,3-oxazolidin-2-one:

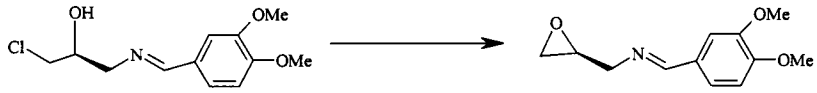


To a solution of (S)-3-chloro-2-((phenyloxy carbonyl)oxy)-1-[(3,4-dimethoxy benzalidene)amino]-propane (3.77g,10mmol) (prepared in step- I) and 4-(4-aminophenyl)mopholin-3-one (2.4 g, 12.5 mmol, 1.25 eq) in DMF (20 ml) potassium carbonate (3.45 g, 25 mmol, 2.5 eq) and catalytic amount of triethylbenzyl amm. Chloride were added and then stirred at about 80°C for 12 hrs. The reaction mixture was poured into

water (150 ml) and then extracted with DCM (25 ML X 3) . The combined organics washed with dil. HCl (10 ml x 2) and water (20 ml x 2) . Distill off the solvent completely to yield a title compound as light brownish solid. (Yield = 0.439 , 10 % of the theory)

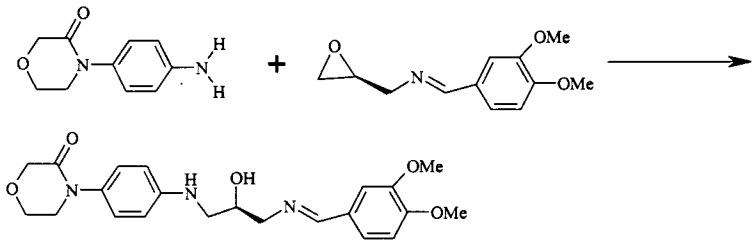
Example 25: Alternative Preparation of (S)-5-{[(3,4-dimethoxy-benzylidene)-amino]methyl}-3-[4-(3-oxo-morpholin-4-yl)phenyl]-1,3-oxazolidin-2-one (Compound –VII):

Step-I: Preparation of (S)-(3,4-dimethoxy benzylidene oxiranyl methyl amine (Compound – X, where R6,R7= 3,4-dimethoxybenzylidene group)



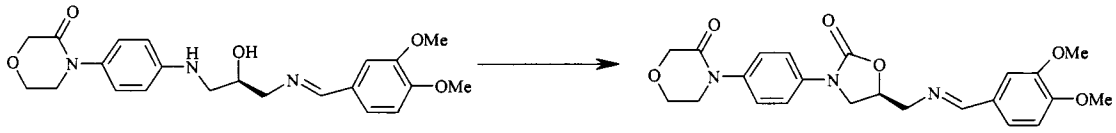
To a solution of (S)-1-chloro-3-[(3,4-dimethoxy-benzylidene)amino]-propan-2-ol (25. 75 g, 0.1 moles) in methanol (50 ml) at 13°C was added lithum-tert- butoxide (8.8 gms, 1.1 eq) while maintaining less than 22°C. The mix. was stirred at 8-20°C for about 30 min and water (200 ml) and DCM (200 ml) were added. The phases are separated and the aq. was washed with DCM (200 ml) . The combined organics dried over MgSO4 and then concentrated under reduced pressure to yield a title compound as a oily liquid (Yield = 16. 65 g, 71% of the theory).

Step-II: Preparation of 4-{4-[(R)-2-hydroxy-3-(3,4-dimethoxy benzylidene)amino)propyl amino]phenyl}-morpholin-3-one (Compound – IX, where R6,R7= 3,4-dimethoxybenzylidene group)



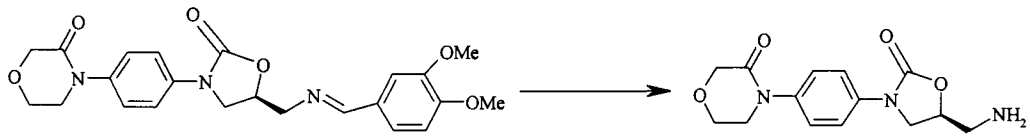
To a suspension of 4-(4-aminophenyl)-morpholin-3-one (19. 2 g, 0.1 moles) in ethanol (200 ml) was added (S)-(3,4-dimethoxy benzylidene oxiranyl methyl amine (22.5 gms, 0.102 moles) (prepared in step I) and then refluxed for about 24 hrs . Distill off the solvent and used for the next reactions without further purification.(Yield = 41 g, 99% of the theory)

Step –III: Preparation of (S)-5-{[(3,4-dimethoxy-benzylidene)amino]-methyl}-3-]4-(3-oxo-morpholin-4-yl)phenyl]-1,3-oxazolidin-2-one:



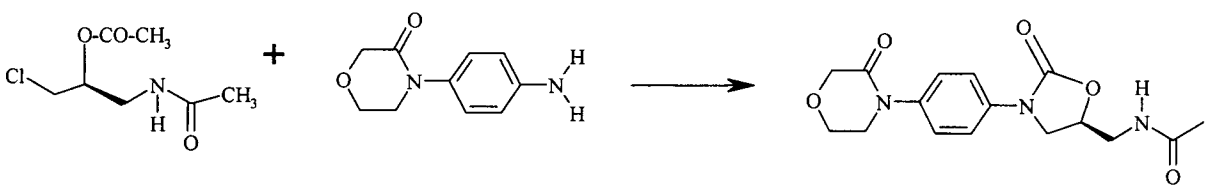
To a solution of 4-{4-[(R)-2-hydroxy-3-((3,4-dimethoxy benzylidene) amino) propylamino]phenyl}morpholin-3-one (prepared in Step –II) (41.3 ,0.1 mol) in dichoromethane (250 ml) added N,N'-carbonyldiimidazole (17.82 gms, 1.1eq) at once and the solution was stirred at ambient temperature for about 44 hrs. water (250 ml) added and the phases are separated and the org. layer washed with water (100 ml) and then distill-off the solvent completely and then re-crystallized from isopropyl alcohol to yield title compound as a off-white crystalline solid (38.6 g, 88% of the theory).

Example 26: Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound –VIII):



To (S)-5-{[(3,4-dimethoxy-benzylidene)amino]-methyl}-3-[4-(3-oxo-morpholin-4-yl)phenyl]-oxazolidin-2-one (prepared in the above examples of 23, 24 or 25) (43. 9 gms, 0.1 mol) is added ethylacetate (300 ml) .To the mix. is added 12M aq. HCl(85 ml) and the R.M is stirred for about 2 hrs at the ambient temperature . The phases are separated, the org. layer is washed with the ethyl acetate (100 ml) , Dichloromethane (200 ml) is added and adjusted to pH 9-10 with 50% aq. NaOH solution and separated the org. layer and distilled completely to yield pure title compound as a white- crystalline solid. (Yield = 23 g, 68.9% of the theory).

Example.27: Preparation of (S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-1,3-Oxazolidin-5yl}methyl]acetamide (Compound- VII, R^6 = -H,R^7= -CO CH3):



To a suspension of [4-(3-oxo-morpholin-yl)phenyl]carbamic acid benzyl ester (3.26 gms,10 mmol) in DMF (10 ml) and methanol (0.64 g, 20 mmol, 2 eq) at 20° C is added to a

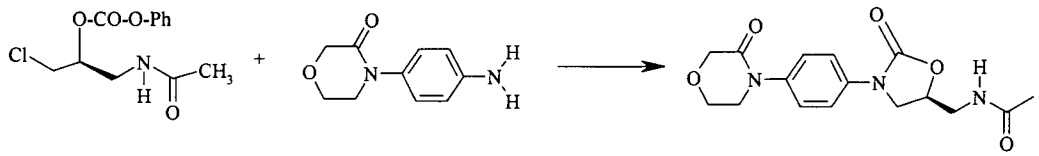
solution of Lithium-t-Butoxide (2.4 g, 30mmol, 3 eq) in THF (13.5 ml) while keeping less than 24°C . The suspension is cooled to about 5°C, and (S)-N-[2-(acetyloxy)-3-chloropropyl]acetamide (3.87g, 20 mmol, 2 eq) (prepared as per US7,087,784B2). The resulting suspension is allowed to stand at about 21°C for 21 hrs. Sat. NH4Cl solution (25 ml) is added followed by water (30 ml), sat.aq. NaCl (25 ml) and methylene chloride (50 ml). The phases are separated and the aq. washed with DCM (20 ml x3) . The organics are dried on MgSO4 and concentrated in the vacuum and then recrystallized from methanol to yield a title compound as a white-crystalline solid. (Yield = 1.072 g, 32% of the theory).

Example 28: Alternative Preparation of (S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-1,3-oxazolidin-5yl}methyl]acetamide (Compound- VII) (R6= H, R7= $COCH_3$):

Step- I: Preparation of (S)-N-[2-((Phenyloxy carbonyl)oxy)-3-chloropropyl]acetamide (Compound – VI, R^2= -CO-OPh, R^6= -H, R^7 = -COCH3, w = -Cl):

To a solution of (S)-N[2-hydroxy-3-chloropropyl]acetamide (prepared as per US 6,362,334B1) (15.15 g, 0.1 moles) pyridine (12.64 g, 1.6 eq) in DCM (200 ml), phenyl chloroformate(17.2 g, 1.1eq) added drop-wise at 0°C. After stirring at 0°C for 1 hr the reaction mix. was poured into the water and the organic layer was separated and the aq. was extracted with DCM (100ml)and the combined extracts were washed with dil.HCl (50 ml) and water (50 ml x 2) . concentrated under reduced pressure and used for the next step without further purification. (Yield = 24. 9 g, 92% of the theory).

Step-II: Preparation of (S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl}methyl]acetamide:

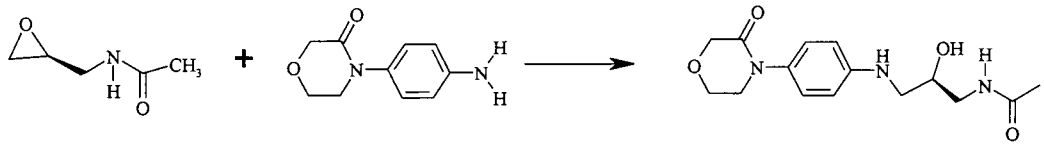


To a solution of (S)-N [2-((phenyloxycarbonyl) oxy)-3-chloro propyl]acetamide (2.715 g, 10 mmol) (prepared in the step – I) and4-(4-aminophenyl)-morpholin-3-one (2.4 g, 12.5 mmol,1.25 eq) in DMF (20 ml) , potassium carbonate (3.45 g, 25 mmol, 2.5 eq) and

catalytic amount of tri ethyl benzyl ammo.chloride were added and stirred at 80°C for about 12 hrs. The reaction mix. was poured into water (150 ml) and then extracted with dichloromethane (25 ml x 3). The combined organics were washed with dil. HCl (10 ml x 2) and water (20 ml x 2) Distill – off the solvent completely and then re-crystallized from ethanol to yield a title compound as a white crystalline solid (Yield = 0.737g, 22% of the theory).

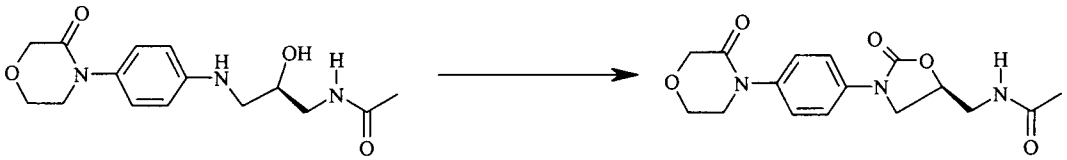
Example 29: Alternative Preparation of (S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl}methyl]acetamide (Compound- VII) (R6=H, R7=$COCH_3$):

Step-I: Preparation of N-[(R)-2-hydroxy-3-{4-(3-oxo-morpholin-4-yl)phenylamino}propyl]acetate (Compound – IX, wherein R^6 = -H,R^7 = -COCH3):



To suspension of 4-(4-aminophenyl)-morpholin-3-one (19.2 g, 0.1 mol) in ethanol (200 ml) was added (S) – glycidylacetamide (12. 65 gms, 1.1 eq) (prepared as per US6,362,334B1) at once and then refluxed for about 24 hrs. Distill- off solvent completely under reduced pressure and then used for the next step without further purification. (Yield = 30.7 g, corresponds to 100 % of the theory).

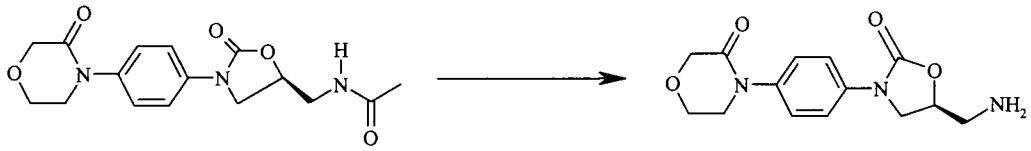
Step – II: Preparation of (S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl}methyl]acetamide:



To a solution of N-[(R)-2-hydroxy-3-{4-(3-oxo-morpholin-4-yl)phenylamino}propyl]-acetamide (30. 7 g, 0.1 mol) (prepared in step I) in dichloromethane (200 ml) was added N,N^1- carbonyl diimidazole (17.82 g, 0.11 mol, 1.1 eq) and stirred for about 44 hrs at ambient temperature added water (200 ml) and the phases are separated and washed the org. layer with water (100 ml) and distill-off the solvent completely to get a crude compound . Re-

crystallized from methanol yield a title compound as a white – crystalline solid. (Yield = 29. 4 g, 87 % of the theory).

Example 30: Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound – VIII):



To a solution of(S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl}methyl]acetamide (3.38 g, 10 mmol) in pyridine (56 ml) and ethanol (7 ml) was added hydroxylamine. Hydrochloride (4.5 g, 6.5 eq) and refluxed for about 24 hrs . After cooling to R.T, added water (200 ml) and then extracted into MDC (50 ml x 2).washed the org. layer with dil.HCl (10 ml x 2) and the org. layer discarded . Washed the aq. layer with (10 ml) dichloromethane. To the aq. layer added 50 ml DCM and pH = 9- 10 adjusted with 10 % NaOH solution. Separated the phases and the org. layer washed with the water (10 ml x 1). Distill- off the solvent completely to yield a title compound as a white crystalline solid. (Yield = 0.52 g, 18 % of the theory).

Alternative Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound VIII):

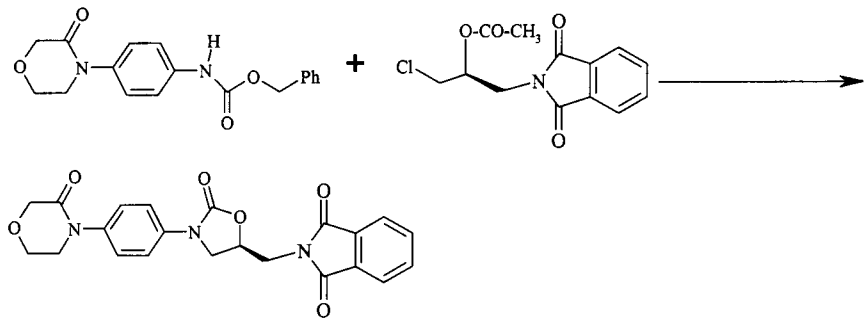
To a suspension of the (S)-N-[{3-(4-(3-oxo-morpholin-4-yl)phenyl)-2-oxo-5-oxazolidinyl}methyl]acetamide (3.38g, 10 mmol) in methanol (20 ml)hydrazine hydrate (80 %) (3ml) and refluxed for 2 hrs. After cooling to R.T, added DCM (20 ml) and filtered the by-product and washed with the DCM (10 ml). Distilled-off the solvent completely and re-crystallize the crude compound from methanol to yield title compound as a white-crystalline solid .(Yield = 2.5 g, 86 % of theory).

Example 31: Preparation of 2-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1H-isoindole-1,3(2H)- dione (Compound –VII NR6R7= Phthalimido group)

Step I: Preparation of (S)-2-Phthalimido-1-(chloromethyl)ethyl acetate (compound VI; wherein W=Cl, R2=-COCH3, NR6R7=Phthalimido group)

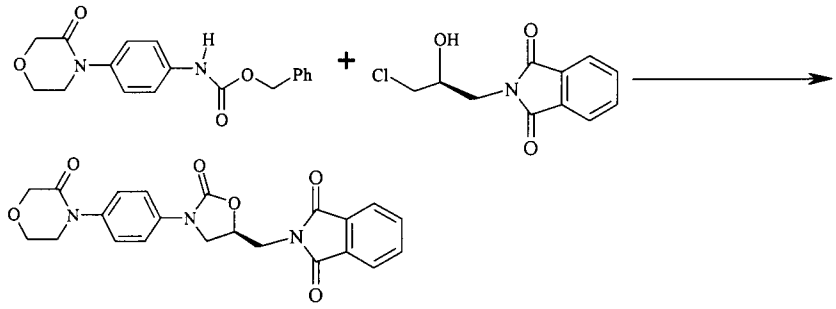
To a solution of (S)-1-Phthalimido-3-chloro-propan-2-ol (23.9 g, 0.1 mol)(prepared as US 6,362,334 B1) in dichloromethane (125ml) was added acetic anhydride (42.4 g, 4 eq) at once and refluxed for overnight. 100 ml of water was added and the phases are separated and washed the aqeous phase with dichloromethane (2x50 ml) and washed dichloromethane layer with dil HCl sol. (2x50ml) and water (2x50ml). Distilled off the solvent completely and used for next reaction without further purification. (Yield 19.98 g. (71% of theory)

Step II: Preparation of 2-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]1,3-oxazolidin-5yl}methyl)-1H-isoindole;1,3(2H)-dione



To a solution of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 g, 1mmol) in DMF (10 ml) and methanol (0.64 g, 20 mmol) at 20 ° C is added a solution of Lithium-t-butoxide (2.4 g, 30 mmol, 3eq) in THF (15ml) while keeping less than 24°C with an ice-bath . The solution is cooled to 5°C, (S)-2-phthalimido-1-(chloromethyl) ethylacetate (5.63 g,2eq) (prepared in step I) solution is added. The resulting solution is allowed to stand at 21 ° C for 21 hrs. Sat. aq.NH_4Cl (25 ml),water (30 ml) , Sat. NaCl(25 ml) and DCM (50 ml) were added and the phases are separated and the aq. washed with DCM(20 ml x3) . The organics are dried on $MgSO_4$ and concentrated to get crude compound .Re-crystallize from acetone to yield a title compound as a white – crystalline solid (Yield= 0.92 g, 22 % of the theory).

Example 32: Alternative Preparation of 2-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1H-isoindole-1,3(2H)-dione (Compound – VII) NR6R7= Phthalimido group):



To a solution of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26 g, 10 mmol) and (S)-1-phthalimido-3-chloro-propan-2-ol(3.02 g, 1.26 eq) (prepared as per US6,362,334B1) in DMF (10 ml) in an ice-bath was added a solution of Lithium-t-Butoxide (1.956 g, 2.4 eq) in THF (15 ml) . The resultant solution was allowed to stand at 20° C for 44 hrs. Sat. aq. ammo. chloride (25 ml) , water (30 ml) and DCM (50 ml) was added and the phases are separated . The organics dried on MgSO4 and distill off the solvent completely to yield title compound as a off- white crystalline solid. Re-crystallized from acetone to yield a title compound as a white crystalline solid. (Yield = 2.0 g, 48 % of the theory).

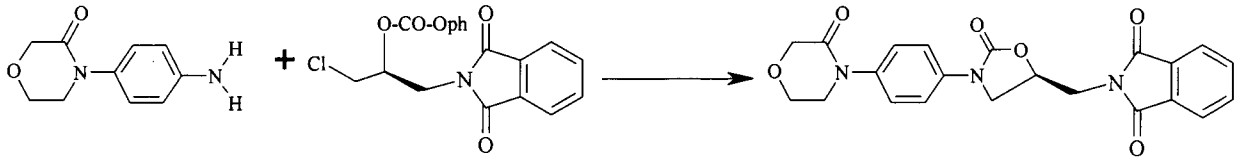
Example 33: Alternative Preparation of 2-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1H-isoindole-1,3(2H)-dione (Compound – VII) NR6R7= Phthalimido group):

Step-I: Preparation of (S)-1-phthalimido-2-((phenyloxycarbonyl)oxy)-3-propylchloride (Compound- VI, R^2= -CO-OPh, w= -Cl; NR6R7= Phthalimido group):

To a solution of (S)-phthalimido-3-chloro-propan-2-ol (23.95g, 0.1mol),pyridine (12.64 g, 1.6 eq) in DCM (200ml) added phenylchloroformate (17.2 g, 1.1 eq) by drop-wise at 0°C.After stirring for an hr at 0°C, the reaction mix. was poured into water and the org. layer was separated and the aq. was extracted with DCM(100 ml) . The combined extracts were washed with Dil. HCl (50 ml) and water (50 ml x 2) concentrated under reduced pressure and used for the next step without further purification (Yield = 31.6 g, 87.8 % of theory)

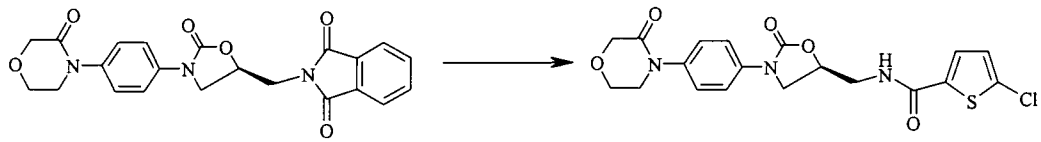
Step- II: Preparation of 2-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-

oxazolidin-5-yl}methyl)-1H-isoindole-1,3(2H)-dione (Compound – VII):



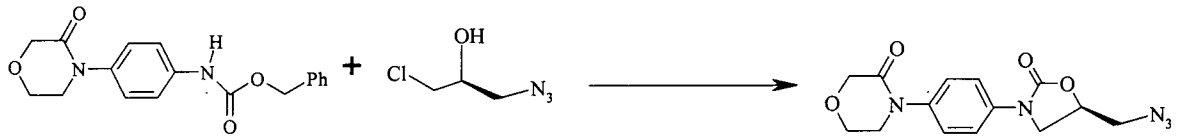
To a suspension of (S)-1-phthalimido-2-((phenyloxycarbonyl) oxy)-3-propylchloride (3.595g, 10 mmol) (prepared in Step- I) and 4-(4-aminophenyl)morpholin-3-one (2.4g, 12.5 mmol, 1.25 eq) in DMF (20 ml). Potassium carbonate (3.45 gms, 25 mmol, 2.5 eq) and catalytic amount of triethylbenzyl ammonium chloride were added and then stirred for about 18 hrs at 80°C .The reaction mix. is poured into the water (50 ml) and then extracted with the DCM (25 ml x 3). The combined organics are washed with Dil.HCl (10 ml x2) and water (10 ml x 2). Distill off the solvent under reduced pressure to yield a title compound.((Yield = 0.5 g, 12 % of the theory).

Example.34: Preparation of Rivaroxaban (I)



The above compound is prepared same as in the Reference: US 7,351,823 B2.

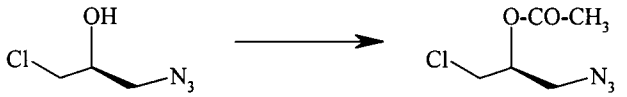
Example 35: Preparation of 4-{4-[(5R)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (Compound – VII, wherein N,R^6,R^7 = $-N_3$):



To a solution of [4-(3-oxo-morpholin-4-ylphenyl] carbamic acid benzyl ester (3.26 g, 10 mmol) and (S)-1-azido-3-chloro-propan-2-ol (1.7 g, 1.26 eq) (prepared by method reported) in DMF (10 ml) in an ice- bath was added a solution of Lithium–t- Butoxide (1.956g, 2.4 eq) in THF (15 ml). The resultant solution was allowed to stirred at about 20 °C for about 44 hrs. Sat. aq. NH4Cl solution (25 ml), water (30 ml) and DCM (50 ml) were added and the phases are separated . The organics are dried on MgSO4 and then distilled completely to yield a title compound as a light brownish colored solid and then re-crystallized from ethyl acetate to yield title compound as a white crystalline solid.(Yield = 0.89 g, 22.2% of the theory).

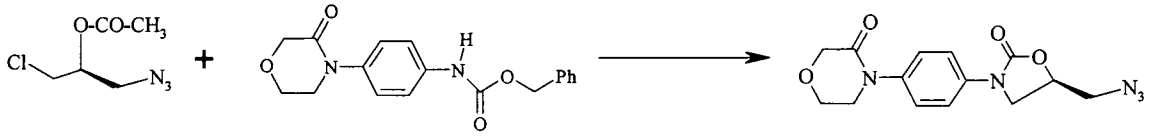
Example 36: Alternate Preparation of 4-{4-[(5R)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (Compound – VII, wherein N,R^6,R^7 = -N_3):

Step- I: Preparation of (1S)-2-azido-1-(chloromethyl)ethyl acetate.(Compound-VI, wherein w= -Cl, R^2 = -COCH3,NR^6R^7= -N_3):



To solution of (S)-1-azido-3-chloro-propan-2-ol (13.55 g, 0.1 mol) in dichloromethane (50 ml) was added acetic anhydride (15.3 g, 1.5 eq) at once and then refluxed for about 5hrs. Pour the R.M into the water (100 ml) and then separated the aq. layer and then extracted with DCM (25 ml x 2). Combined organics dried over sodium sulphate and distilled under vacuum to give title compound as a colorless liquid (15. 0 g, 84. 6 % of the theory).

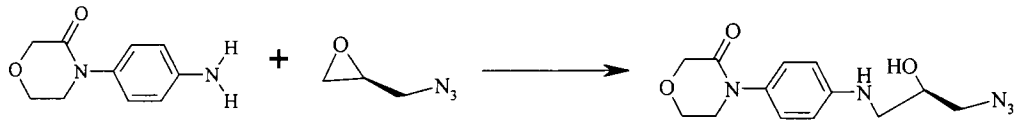
Step.II: Preparation of 4-{4-[(5R)-(5-azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one:



To a solution of [4-(3-oxo-morphoin-4-yl)phenyl]carbamic acid benzyl ester (3.26 g, 0.1 mol) in DMF (10 ml) and methanol (0.64g, 20 m mol , 2eq) at 20°C is added a solution Lithium-t-Butoxide (2.4 g, 30 mmol, 3eq) in THF (15 ml) while maintaining the temperature. less than 24°C. The solution is cooled to 5°C, and then (1S)-2-azido-1-(chloromethyl) ethyl acetate (3.55 g, 20 mmol, 2 eq) (prepared in Step – I) is added. The resulting solution is then allowed to stand at 21°C for about 21 hrs. Sat.ammo.chloride solution (25 ml), water(30 ml), Sat. NaCl solution(25 ml) and DCM (50 ml) were added and the phases are separated . The aq. washed with DCM (20 ml x 3) and the organics dried over $MgSO_4$ and then concentrated Re-crystallize from toluene to yield a title compound as a white crystalline – solid (Yield = 1.48 g, 37% of the theory).

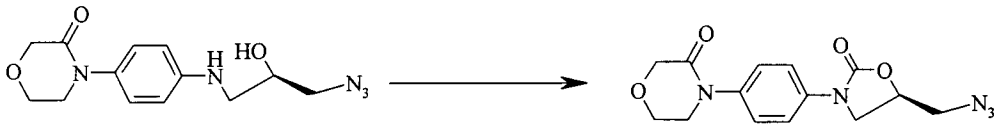
Example 37: Alternative Preparation of 4-{4-[(5R)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound – VII, wherein N,R^6,R^7 = -N_3):

Step.I: Preparation of 4-[4-{(R)-2-hydroxy-3-azidopropylamino}phenyl]morpholin-3-one(Compound – IX, wherein N,R^6,R^7 = -N_3):



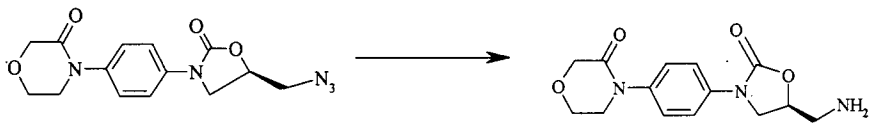
To a suspension of 4-(4-aminophenyl) morpholin-3-one (19.2 g, 0.1 mol) in ethanol (200 ml) added glycidyl azide (9.9g, 1 eq) (prepared as per JOC, vol-21, P-382,1955) and then refluxed for 22 hrs. Distill-off the solvent completely and used for the next reaction without further purification (Yield = 29 g, 99% of the theory).

Step- II: Preparation of 4-{4-[(5R)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one:



To a solution of 4-[4-{(R)-2-hydroxy-3-azido propyl amino} phenyl]-morpholin-3-one (29.1 g, 0.1 mol) in DCM (200 ml) added N,N^1-carbonyldiimidazole (17.82g,0.11 mol, 1.1 eq) and stirred for about 44 hrs at the ambient temperature. water (200 ml) added the phases are separated . Washed the organics with water (100 ml) and then distilled completely and then re-crystallized from isopropyl alcohol to yield title compound as a white- crystalline solid. (Yield = 29.2 g,92% of the theory).

Example 38: Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (Compound- VIII):



To a solution of azido compound (prepared in the above examples 35, 36 or 37) (31.8 g) in 400 ml of ethyl acetate, added 2.5 g, of 5% Pd/C and hydrogenated the mix. at 45-50 °C at 6-8 kg of Hydrogen pressure for 8 – 12 hrs . After reaction has been completed (as indicated by the TLC), filtered off the catalyst and washed with ethylacetate (50 ml). Distill-off the solvent completely and then re-crystallized from methanol (Yield = 25. 7 g, 88% of the theory).

Example 39: Preparation of (1S)-2-(triphenylmethyl amino)-1-(chloromethyl) ethyl acetate (or) Preparation of (1S)-2-(aminotrityl)-1-(chloromethyl)-ethylacetate (Compound-VI, w= -Cl,R^6= -H,R^7= trityl group):

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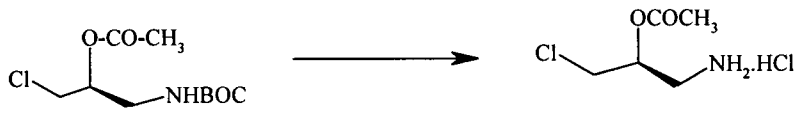
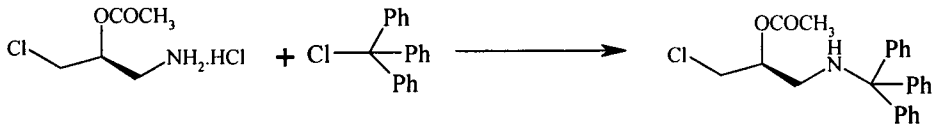
Step.I: Preparation of (1S)-2-amino-1-(chloromethyl)ethylacetate.hydrochloride:



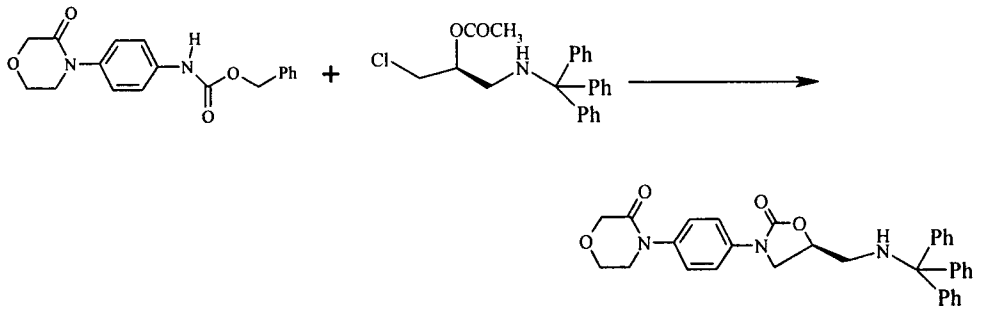
(1S)-2[(tert-butyloxy carbonyl) amino]-1-(chloromethyl) ethyl acetate (prepared as in US,6,998,420B2) (25.15g) added 150 ml of methanolic hydrochloride (having assay 8-12%) and stirred for 1 hr at ambient temperature and distill-off the solvent completely and added 50 ml of DCM and then stirred for about 30 min at 25°C and the product isolated by the filteration. (Yield = 14.3g, 77% of the theory).

Step.II: Preparation of (1S)-2-(aminotrityl)-1-(chloromethyl)ethylacetate:



To a solution of (1S)-2-amino-1-(chloromethyl) ethyl acetate hydrochloride (1.86g,10 mmol) in pyridine (30 ml) was added triphenylmethylchloride (or trityl chloride) (2.785g, 190mmol, 1eq) and then refluxed for 8 hrs . Pour the R.M into ice-water and the product is isolated by filtration. Re-crystallized the wet material from ethanol yield title compound as a white–crystalline solid. (Yield = 2.67 g, 68.2 % of the theory).

Example 40: Preparation of 4-{4-[(5S)-5-(trityl amino methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound –VII, wherein R^6= -H, R^7= trityl group



To solution of [4-(3-oxo-morpholin-4-yl) phenyl] carbamic acid benzyl ester (3.26g, 10mmol) in DMF (15 ml) and methanol (0.64g,20 mmol, 2 eq) at 20°C is added a solution of Lithium-t-Butoxide (2.4g,30 mmol,3eq) in THF (15 ml)while keeping less than 24°C. The mix. is cooled to about 5°C, and then (S)-2-(tritylamino)-1-(chloromethyl)ethylacetate (prepared in Ex 39) is added. The resulting mix. was stirred at 21°C for 24 hrs. Sat. aq. NH_4Cl

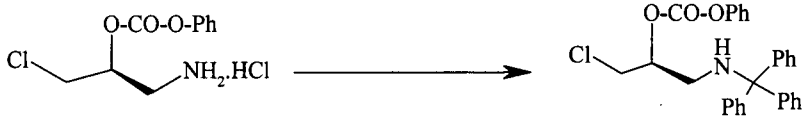
solution (25 ml), water (30ml), Sat.aq. NaCl solution (25 ml) and DCM (50 ml) were added and the phases are separated. The aq. was washed with DCM (20 ml x 2). Combined organics dried over $MgSO_4$ and then distilled under reduced pressure to yield semi-solid. Upon re-crystallization from ethanol yield title compound as a white crystalline solid. (Yield = 1.49 g, 28% of the theory).

Example 41: Alternative Preparation of 4-{4-[(5S)-5-(trityl amino methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound –VII) (where R6=H, R7= trityl):

Step.I: Preparation of (2S)-3-chloro-2-((phenyloxycarbonyl)oxy)propylamine. Hydrochloride:

To 3.29 g (0.1 mol) of tert-butyl (2S)-3-chloro-2-((phenyloxy carbonyl) oxy) propyl carbamate (prepared in the Ex 18 step II.) added methanolic . HCl (20 ml) and then stirred for about 1 hr at R.T. Distill off the solvent and added DCM (20 ml) and the product isolated by the filteration. (Yield =1.12g,42 % of the theory).

Step.II: Preparation of (2S)-N-[3-chloro-2-((phenyloxy carbonyl) oxy) propyl]trityl amine.(Compound- VI, w= -Cl,R^2= -COOPh, R^6= -H,R^7= trityl group):



To a solution of (2S)-3-chloro-2-((phenyloxy carbonyl) oxy) propylamine.HCl(prepared in Step- I) (2.66 g, 10m.mol) in 30 ml of pyridine was added tritylchloride (10 mmol) and then refluxed for about 12 hrs . Pour the R.M into the ice-water and the product isolated by the filtration. Re-crystallize the wet material from ethanol to yield a title compound as a white- crystalline solid. (Yield=3.19 g, 68% of the theory).

Step.III: Preparation of 4-{4-[(5S)-5-(trityl amino methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one:

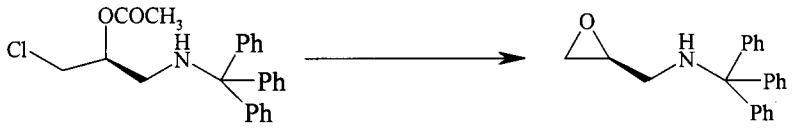
To a solution of (2S)-N-[3-chloro-2-((phenyloxycarbonyl)oxy)propyl] tritylamine (4.695g, 10 mmol) (prepared in Step-II) and 4-(4-aminophenyl) morphlin-3-one (2.4g, 1.25eq) in DMF (30 ml). Potassium carbonate (3.45 g, 2.5 eq) and catalytic amount of triethylbenzyl ammonium chloride were added and then stirred at 80°C for 16 hrs. Pour the R.M into water (50 ml) and extracted into DCM(50 ml x 3). Washed the organics with dil.HCl (10 ml x 2) and water (20 ml x 2) . Distill off the solvent completely and re-crystallized from ethanol to yield title compound as a white crystalline solid (Yield= 0.854g, 16.2% of the theory).

Example 42: Alternative Preparation of 4-{4-[(5S)-5-(trityl amino methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound –VII, wherein R^6= -H, R^7= trityl group):

Step.I: Preparation of (S)-Oxiranylmethyltritylamine

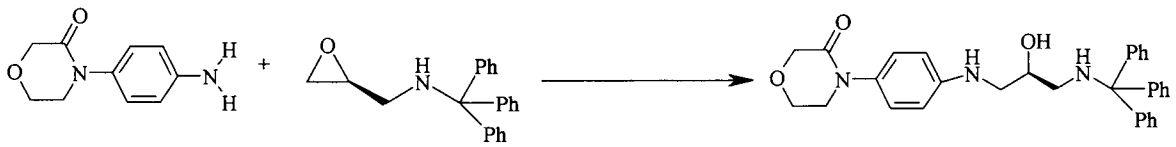
(Compound –X where R6 =-H;

R7=trityl):



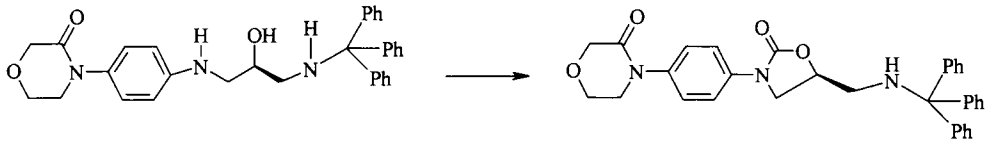
To a solution of (S)-2-(aminotrityl)-1-chloromethyl) ethyl acetate (3.91g, 10 mmol) in methanol (10 ml) was added Lithium-t-Butoxide (0.88g, 1.1eq) while keeping less than 22°C. After stirring for about 30 min at 13- 18 °C, added water (100 ml) and then DCM (100 ml) and the phases are separated. Washed the aq. with DCM (50 ml) and the organics dried over Na_2SO_4 and distilled off completely. This compound is used for the next reaction without any further purification.(Yield = 2.77g, 88 % of the theory).

Step.II: Preparation of 4-[4-{(S)-2-hydroxy-3-(aminotrityl) propylamino} phenyl] morpholin-3-one (Compound-IX, wherein R^6= -H, R^7= trityl group):



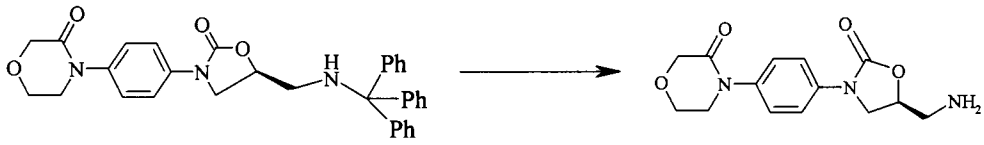
To a suspension of 4-(4-aminophenyl) morpholin-3-one (19.2g, 0.1 mol) in ethanol (200 ml) added(S)-oxiranylmethyltrityl amine (31.5 g, 0.1 mol) (prepared in Step – I) and then refluxed for 32 hrs. Distill- off the solvent completely and used for further reactions without further purifications. (Yield = 50. 7 g, 100% of the theory).

Step-III: Preparation of 4-{4-[(5S)-5-(tritylamino methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one:



To a solution of 4-{4-[(S)-2-hydroxy-3-(aminotrityl) propyl amino]phenyl}-morpholin-3-one (54.7g,0.1 mol) (prepared in Step-II) in DCM (300 ml) was added N,N^1-carbonyl diimidazole (17.82g, 1.1 eq) and then stirred for 48 hrs at ambient temperature. water (300 ml) added and the phases are separated . The aq. was washed with DCM (100 ml) and then combined organics were dried and distilled completely. Re-crystallized the crude compound from ethanol to yield a title compound as a white crystalline solid (Yield = 48.6 g, 91.1% of the theory).

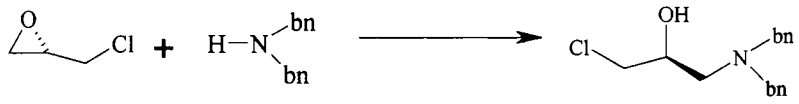
Example 43: Preparation of 4-{4-[(5S)-5-(amino methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morphlin-3-one (Compound-VIII):



A solution of 4-{4-[(5S)-5-(aminotrityl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (5.34g, 10mmol) in 50 ml of acetic acid is prepared by warming on the steam batch. The solution is then cooled to approximately 10°C, 5ml of a saturated solution of dry hydrogen bromide in acetic acid was added, and the reaction mixture was stirred for 10 mins. The trityl bromide formed during the reaction was removed by filtration and the filtrate was poured immediately into 250ml of cold water and adjusted the pH to 9-10 with 50% sodium hydroxide solution. The aqeous layer was washed with chloroform (3x50ml) and organic layer was washed with water (2x20ml) and distilled off the solvent completely and recrystallized from methanol (Yield 1.6 g, 55% of theory).

Example 44: Preparation of (S)-2-(dibenzylamino)-1-(chloromethyl)ethyl acetate (Compound-VI, wherein w= -Cl, R^2= -COCH3, R^6=R^7= Benzyl):

Step.I: Preparation of (S)-3-chloro-2-hydroxypropyl dibenzylamine (Compound VI, w=Cl, R2=H, R6=R7=benzyl):

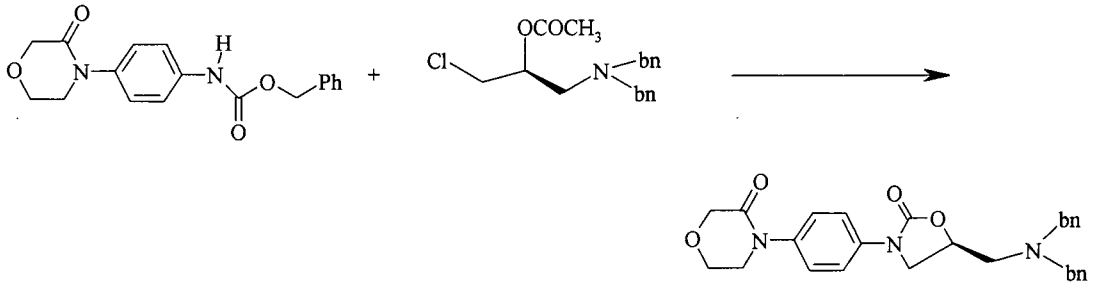


To a solution of (S)-epichlorohydrin (9.25 g, 0.1mol) in ethanol (100 ml) was added dibenzylamine (19.7 g, 0.1mol) and then refluxed for about 6 hrs. Distill-off the solvent completely under reduced pressure and then used for the next reaction without further purification. (Yield = 28.30g, corresponds to 98% of the theory).

Step.II: Preparation of (S)-2-(dibenzylamino)-1-(chloromethyl)ethyl acetate:

To solution of (S)-3-chloro-2-hydroxypropyldibenzyl amine (28.95 g, 0.1 mol) in ethyl acetate (150 ml)was added acetic anhydride (16.32 g, 1.6 eq) and then maintained at about 40-50°C for 2 hrs . Pour the R.M into the water (100ml) and the phases are separated. washed the aq. with ethyl acetate (50 ml x 2) and the combined organics washed with water (50 ml x 2) . Distill- off the solvent completely to yield crude title compound. Re-crystallize from toluene and hexane yield pure title compound as off-white crystalline solid. (Yield =27.8g, 84% of the theory).

Example 45: Preparation of 4-{4-[(5S)-5-(Dibenzylaminomethyl)-2-oxo-1,3-oxazolidin-3-yl}phenyl]-morpholin-3-one (Compound-VII, wherein R^6=R^7= Benzyl group):



To a suspension of [4-(3-oxo-morpholin-yl) phenyl] carbamic acid benzyl ester(3.26g,10 mmol) in DMF (10 ml) and methanol (0.64g,2eq) at 20 °C is added a solution of Lithium-t-Butoxide (2.4g,3eq) in THF (15 ml) while keeping less than24 °C. The mix. is cooled to 5°C and (S)-2-(di benzyl amino)-1-(chloro methyl)ethyl acetate (6.63 g,2 eq) and the resultant mix. stirred at 21°C for 24 hrs. Sat aq. NH_4Cl solution (25 ml), water (30 ml) ,aq. NaCl solution (25 ml) and DCM(50 ml) were added and the phases were separated . The aq. was washed with DCM(20 ml x 2) and the combined organics dried over $MgSO_4$ and distilled

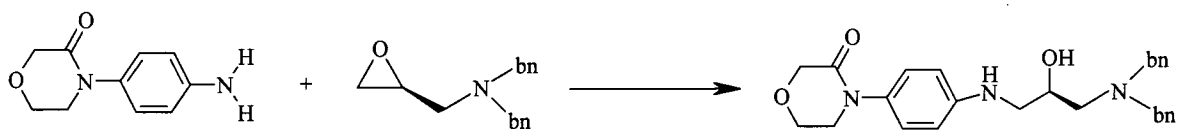
under reduced pressure and recrystallized from acetone to yield title compound as a white – crystalline solid.(Yield = 2.45g, 52 % of the theory).

Example 46: Alternative Preparation of 4-{4-[(5S)-5-(Dibenzylaminomethyl)-2-oxo-1,3-oxazolidin-3-yl}phenyl]-morpholin-3-one (Compound-VII, wherein R^6=R^7= Benzyl group):

Step.I: Preparation of (S)-Dibenzyloxiranylmethylamine (Compound X, where R6=R7=benzyl):

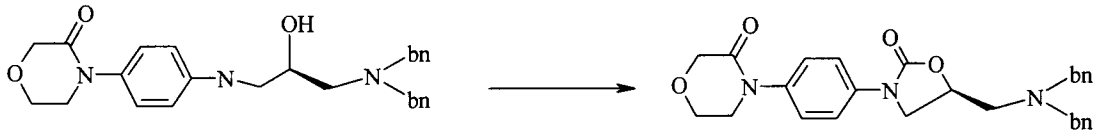
To a solution of (S)-3-Chloro-2-hydroxy propyldibenzylamine (2.895g, 10 mmol) in methanol (10 ml) added Lithium-t-butoxide (1.0 gm, 1.25 eq) while keeping less than 22°C. After stirring for 13-22°C for ½ hr, water (100m l) and DCM (100 ml) were added and the phases were separated .Washed the aq. layer with DCM (50 ml). combined organics dried with Sodium Sulfate and then distill- off the solvent completely and used for the next step without further purification. (Yield= 2.2g, 87 % of the theory).

Step.II: Preparation of 4-[4-{(R)-2-hydroxy-3-(dibenzylamino)propylamino}phenyl morpholin-3-one (Compound IX, wherein R^6=R^7= Benzyl group):



To a suspension of 4-(4-aminophenyl)morpholin-3-one (19.2 g,0.1 mol) in isopropyl alcohol (200 ml) was added (S)-dibenzyl-oxiranyl methylamine (25.3g, 0.1 mol) (prepared in Step- I) and refluxed for 24 hrs. Distill-off solvent and used for the next reaction without further purification (44 g, 98.8% of the theory).

Step.III: Preparation of 4-{4-[(5S)-5-dibenzylaminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}- morpholin-3-one:



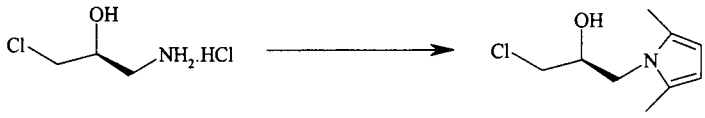
To a solution of 4-[4-{(S)-2-hydroxy-3-(dibenzyl amino) propyl amino} phenyl]morpholin-3-one (44.5 g,0.1 mol) in DCM(300 ml) was added N,N^1-carbonyldiimidazole (17.82 g,1.1 eq) and then stirred for 44 hrs at ambient temperature. water (200 ml) added and

the phases are separated . The aq. washed with DCM (100 ml) and the combined organics, washed with water (100 ml). Distill off the solvent completely and then re-crystallized from acetone to yield title compound as a white crystalline solid. (Yield = 42.95 g, 92% of the theory).

Example 47: Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-one (Compund-VIII):

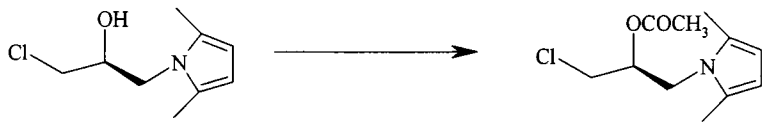
To a solution of 4-{4-[(5S)-5-(dibenzylamino) methyl-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (4.17g, 10mmol) in methanol (100ml) and acetic acid (5 ml) was added 10% Pd/C (1.0g). Then passed the hydrogen gas of about 5.6 kgs/cm^2 at about 50°C until the reaction completes as indicated by TLC. The reaction suspension was filtered on celite and washed with methanol. The filtrate was distilled off to half of the total volume and cooled to about 0°C for about 30 mins. The separated solid was filtered and washed with methanol. (Yield = 2.56 g ; 88% of theory).

Example 48: Preparation of 1-((2S)-3-chloro-2-hydroxypropyl)-2,5-dimethyl pyrrole (Compound-VI wherein w= -Cl, R^2= -H, NR6R7=2,5-dimethylpyrrole ring)



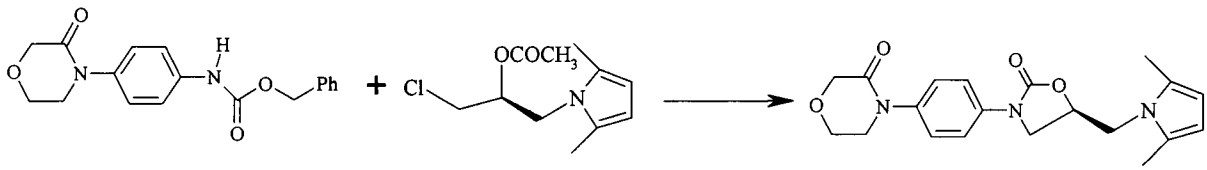
To a solution of (2S)-3-chloro-2-hydroxypropylamine.HCl(14.6 g, 0.1 mol) (prepared in Ex.1) and Sodium acetate (16.4 g, 0.2 mol) in acetic acid (150 ml) was added 2,5-hexanedione (12.54g, 0.11 mol) and then refluxed for 2 hrs. Pour the R.M into water (500 ml) and then extracted with DCM (100 ml x3).Washed DCM layer with sat. aq. Sodium bicarbonate solution (50 ml x 2) and water (50 ml x 2) . Distill- off the solvent under reduced pressure to yield title compound (Yield = 17.5 g, 92.2% of the theory).

Example.49: Preparation of 1-[(2S)-3-chloro-2-(acetyloxy) propyl]-2,5-dimethyl pyrrole (Compound-VI wherein w= -Cl, R^2= -COCH3, NR6R7=2,5-dimethyl pyrrole Ring)



To a solution of 1-((2S)-3-chloro-2-hydroxypropyl)-2,5-dimethyl pyrrole (18.75 g, 0.1 mol) (prepared in ex 48) in DCM (100ml) was added acetic acid anhydride (20.4 g,0.2 mol) and the solution was refluxed for 4 hrs. Pour the R.M into ice-water and the phases are separated. washed the aq. layer with DCM (50 ml x 2) . Combined organics washed with the sat. Sodium bicarbonate solution (50 ml) followed by water (50 ml) . Distill-off the solvent under reduced pressure to yield title compound. This compound is directly used for the next reaction without any further purification.(Yield = 20.2 g, 88 % of the theory).

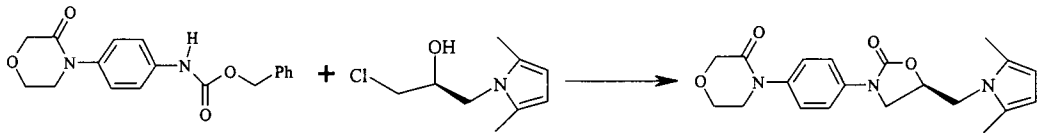
Example 50: Preparation of 4-{4-[(5S)-5-(2,5-dimethyl-pyrrol-1-yl methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound VII wherein NR6R7=2,5-dimethyl pyrrole ring)



To a suspension of [4-(3-oxo-morpholin-yl)phenyl]carbamic acid benzyl ester (3.26g,10mmol) in DMF (10 ml) and methanol (0.64g,2 eq) at 20°C is added a solution of Lithium-t-Butoxide (2.4g,3eq) in THF (15 ml) while keeping temperature at less than 24°C. The mix.is cooled to 5°C, and then 1-[(2S)-3-chloro-2-(acetyloxy) propyl]-2,5-dimethyl pyrrole (4.6g,2eq) (prepared in ex 49) and the resultant mix. is stirred at 21°C for about 24 hrs. Sat.aq.NH4Cl solution (25ml), water(30 ml). Sat. aq.NaCl solution (25 ml) and DCM(50 ml) were added and the phases are separated .The aq.was washed with DCM (20 ml x2) and the combined organics dried over $MgSO_4$ and then distilled under reduced pressure and then re-crystallized from methanol to yield title compound as a white crystalline solid.

(Yield = 1.55g, 33 % of the theory).

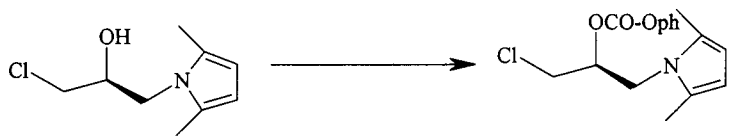
Example 51: Alternative Preparation of 4-{4-[(5S)-5-(2,5-dimethyl-pyrrol-1-yl methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound VII) where N6R7=2,5-dimethyl pyrrole ring:



To a suspension of [4-(3-oxo-morpholin-4-yl)phenyl]carbamic acid benzyl ester (3.26g, 10mmol) and 1-[(2S)-3-chloro-2-hydroxypropyl]-2,5-dimethylpyrrole (2.89 g,1.26 eq) (prepared in Example 48) in DMF (10 ml) in an ice-bath was added a solution of the Lithium-t-Butoxide (1.92 g,2.4 eq) in THF (12ml). The resultant mixture was allowed to stand at 21°C for about 48 hrs. Sat.aq. NH_4Cl solution (25ml), water (30 ml), and DCM (50 ml) were added and the phases are separated . The aq. layer was washed with DCM (50 ml) and the combined organics dried on $MgSO_4$ and then concentrated to yield crude title compound. Upon re-crystallization from acetone yield pure title compound as a white crystalline solid (Yield=2.585g, 55 % of the theory).

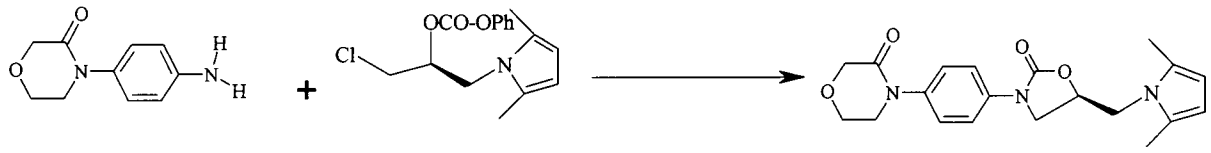
Example 52: Alternative Preparation of 4-{4-[(5S)-5-(2,5-dimethyl-pyrrol-1-yl methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one (Compound VII where NR6R7=2,5-dimethyl pyrrole ring.

Step.I: Preparation of 1-[(2S)-3-chloro-2((phenyloxy carbonyl)oxy)propyl]-2,5-dimethyl pyrrole (Compound-VI, wherein W=-Cl,R^2= -CO-OPh, NR6R7=2,5-dimethylpyrrole)



To solution of 1-[(2S)-3-chloro-2-hydroxypropyl-2,5-dimethyl pyrrole (18.75 g, 0.1 mol and pyridine (12.64g,1.6 eq) in DCM(200ml). Phenyl chloroformate (17.16 g, 1.1eq) added at 0°C. After stirring for about 1 hr at 0°C The R.M was poured into the water and the phases are separated. The aq. washed with DCM (100 ml). Combined organics washed with dil.HCl(100ml) an water (100 ml x 2). Concentrated the org. layer to yield the title compound and used as such for the next reaction without any further purification. (Yield = 26. 75, 87 % of the theory).

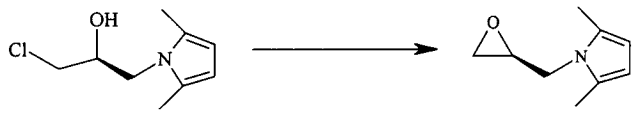
Step-II: Preparation of 4-{4-[(5S)-5-(2,5-dimethyl-pyrrol-1-yl methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one :



To solution of 1-[(2S)-3-chloro-2((phenyloxy carbonyl)oxy)propyl]-2,5-dimethyl pyrrole(3.075g,10mmol) (prepared in Step-I) and 4-(4-aminophenyl) morpholin-3-one (2.4g,1.25 eq) in DMF (20 ml) . Potassium carbonate (3.45g, 2.5 eq) and catalytic amount of triethyl benzylamm. Chloride were added and then stirred at 80°C for about 22 hrs. Pour the R.M into the water (150 ml) and then extracted into the DCM(30ml x 3) .washed DCM layer with (10 ml x 2) dil. HCl and water (10 ml x 3). Distill-off the solvent completely and then purified by re-crystallization from ethyl acetate.(Yield = 0.52 g, 11.2 % of the theory).

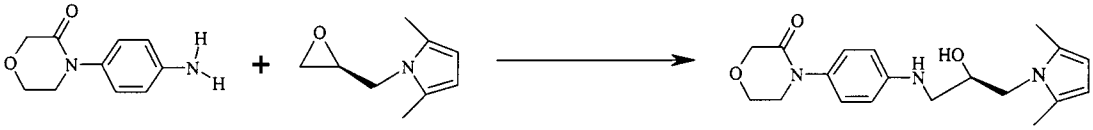
Example 53: Alternative Preparation of 4-{4-[(5S)-5-(2,5-dimethyl-pyrrol-1-yl methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one(Compound VII wherein NR6R7=2,5-dimethylpyrrole ring.

Step. I: Preparation of (S)-2,5-dimethyl-1-oxiranylmethyl-1H-pyrrole (Compound X Where NR6R7=2,5-dimethyl pyrrole ring):



To solution of 1-[(2S)-3-chloro-2-hydroxypropyl]2,5-dimethyl pyrrole (1.875g, 10 mmol) in methanol (5 ml) was added Lithium-t-Butoxide (0.88g, 1.1 eq) while keeping the temperature less than 22°C. After stirred for about 30 min at 20-25°C dilute the R.M with water (50 ml) and DCM(50 ml) and the phases are separated . washed the aq. with DCM (25 ml) and then combined organics dried over MgSO4 and then concentrated to get title compound (Yield = 1.13g, 75 % of the theory). The compound is used directly for the next reaction without any further purification.

Step.II: Preparation of 4-{4-[(R)-2-hydroxy-3-(2,5-dimethyl pyrrol-1-yl)propyl amino]phenyl }-morpholin-3-one(Compound IX wherein NR6R7= 2,5-dimethylpyrrole ring



To a suspension of 4-(4-amino phenyl)-morpholin-3-one (1.92 g,1 eq) in ethanol (20 ml) was added (S)-2,5-dimethyl-1-oxiranyl methyl-1H-pyrrole (1.51g,1eq) (prepared in Step-I) and refluxed for 24 hrs. Distill-off the solvent completely and then used for the next reaction without any further purification.(Yield – 3.43 g, 100 % of the theory).

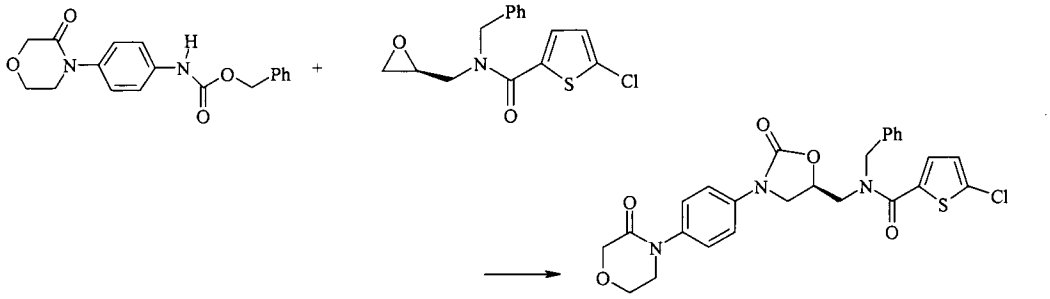
Step.III: Preparation of 4-{4-[(5S)-5-(2,5-dimethyl-pyrrol-1-yl methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one.:

To a solution of 4-{4-[(R)-2-hydroxy-3-(2,5-dimethyl pyrrol-1-yl)propyl amino] phenyl}-morpholin-3-one (3.43 g, 10 mmol) (prepared in Step-II) in DCM (30 ml) was added N,N^1-carbonyldiimidazole (1.8 g, 1.12 eq) and then stirred for 38 hrs at ambient temperature water (30 ml) was added the phases are separated . The aq. was extracted with DCM (15 ml) and the combined organics washed with water (10 ml x 2) and then distilled completely and then recrystallized from acetone to yield title compound as a white crystalline solid. (Yield = 4.3 g, 91.5% of the theory).

Example 54: Preparation of 4-{4-[(5S)-5-(aminoethyl)-2-oxo-1,3-oxazolidin-3yl]phenyl}-morpholin-3-one (Compound VIII)

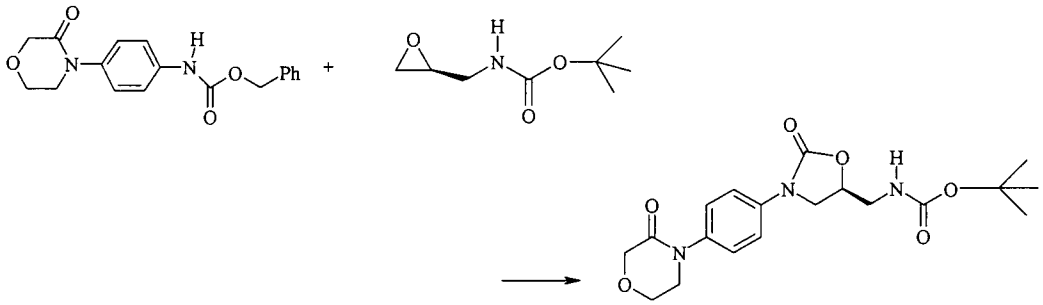
To a solution of 4-{4-[(5S)-5-(2,5-dimethyl pyrrol-1yl methyl)-3-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (3.69 g, 10mmol) in pyridine (50 ml) and ethanol (7 ml) was added hydroxyl amine HCl (4.17 g, 6 eq) and refluxed for 6 hrs. After cooled to RT added water (200ml) and extracted with DCM (3X50ml). washed the organic layer with dil.HCl (2x10 ml) followed by water (1oml). Organic layer discarded. To the aqeous layer added 50 ml DCM and pH =9-10 adjusted with 10% NaOH solution and separated the phases and washed the aqueous layer with DCM (2X25 ml) and washed the organic layer with water (2x20ml). Distilled off the solvent completely and recrystalized from acetone (Yield=1.18 gms, 42% of theory).

Example 55: Preparation of 5-chloro-N-[{(5S)-2-oxo-3-[4-(3-oxo-4-morpholidin-5-yl}methyl-N^1-benzyl-2-thiophene carboxamide (Compound-Ia wherein R^3 = Benzyl):



To a suspension of [4-(3-oxo-morpholin-4-yl)-phenyl] carbamic acid benzyl ester (3.26 g, 10 mmol) and N-(S)-(1-oxiranylmethyl)-N^1-benzyl-5-chloro thiophene-2-carboxamide (3.843g, 1.26 eq) (prepared in Ex. 12 or 13) in DMF (10 ml)in an ice bath was added a solution of Lithium-tert-Butoxide (1.6 g, 2 eq) in THF (8 ml). The resultant mix. was allowed to stand at 20°C for 44 hrs. Sat. aq. ammonium chloride solution (20 ml), water (25 ml) and DCM (50 ml) were added and the phases are separated . The aq. was washed with DCM (30 ml) and the combined organics were dried on $MgSO_4$ and then concentrated to get a crude compound. After re-crystallization from the acetone yielded title compound of a white crystalline solid.(Yield = 2.78g, 63 % of the theory).

Example 56: Preparation of tert-butyl-{(5S)-3-[4-(3-oxo-morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl carbamate (Compound VII, wherein R^6 = -H, R^7 = -CO_2tBu):

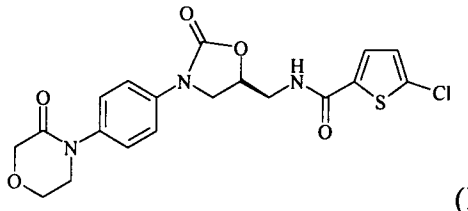


To a suspension of [4-(3-oxo-morpholin-4-yl)-phenyl]carbamic acid benzyl ester (3.26g, 10 mmol) and tert-butyl(2S)-oxiranylmethyl carbamate (prepared as per US 6,998,420B2) (2.23g, 1.29 eq) in THF (15 ml) at 0°C was added a solution of Lithium-t-butoxide (1.04g, 1.3 eq) in THF(5 ml). After standing for 2 days at 20- 25 °C, DCM(25 ml) ,

then acetic acid (1.15 ml, 2 eq) followed by water (10 ml) was added. The phases were separated and the aq. washed with DCM (25 ml). The combined organics dried over MgSO4 and then concentrated. Re-crystallized from methanol to yield title compound as a white solid. (Yield = 2.97 g, 76 % of the theory).

We Claim:

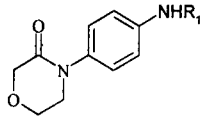
1) A process for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I),



(I)

comprising:

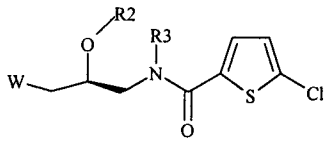
a) reacting the compound of formula (III) or a salt thereof



(III)

Where R_1 is H or $-C(=O)-OR4$ where R4=C_{1-4} alkyl straight chain or branched optionally substituted with 1to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub arylalkyl, C_2-C_6 alkenyl, cycloalkyl;

with the compound of formula (II)

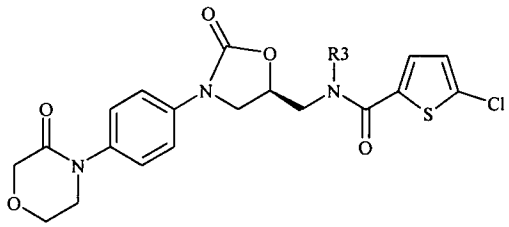


(II)

Where W= halogen (Cl, Br,I), -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl;

R2 is H or –CO-R5 where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to 3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or unsub.phenyl, sub or unsub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched, in the presence of a base to provide the compound of formula (Ia),



(Ia)

Where R3 is same as defined above,

b) deprotection of the compound of formula (Ia) (when R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched chain) using a suitable reagent provides the compound of formula I.

2) The process of claim 1, wherein the bases that can be used in step a) is selected from base having an alkoxide group with C_{1-7} carbon atoms; C_{1-4} alkyl carbanion such as methyl, sec-butyl, butyl or tert-butyl carbanion; a conjugate base of a carbamate; lithium diisopropyl amide, lithium amide; inorganic bases like metal hydroxides such as sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate and the like; or mixture thereof, preferably a base with alkoxide group having C_{4-5} carbon atoms, more preferably lithium tert-amylate or lithium t-butoxide or potassium carbonate is being used.

3) The process of claim 1, wherein the nucleophile used in step a) is an alkoxide group, linear or branched, having C_{1-7} atoms. Preferred nucleophile is methoxide or ethoxide or isopropoxide or isobutoxide or 2-ethoxyethyl, 2-(N,N-dimethylamino) ethoxide or 2,2,2-trichloroethoxide or 2,2,2-trifluoroethoxide.

4) The process of claim 1, wherein the solvents that can be used in step a) is selected from the group consisting of alcohols like methanol, tert-amyl alcohol, tert-butyl alcohol and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF), 2-methyl THF, and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile, and the like; or mixture thereof, preferably N,N-dimethylformamide (DMF) or tetrahydrofuran (THF) or mixture thereof.

5) The process of claim 1, wherein reaction step a) can be carried out at a temperature range

to about 80°C and a time period from about 2 hour to about 24 hours, preferably from about 10 hour to about 21 hours.

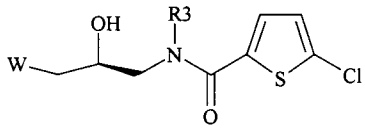
6) The process of claim 1, wherein the suitable deprotection reagents used in step b) is selected from the group consisting of p-toluene sulfonic acid, N-bromosuccinimide, triflouro acetic acid;hydrogenation catalysts like palladium on carbon, platinum oxide and the like; inorganic acids such as HCl, HBr, sulfuric acid, phosphoric acid and the like or mixture thereof.

7) The process of claim 1, wherein the suitable solvents that can be used in step b) is selected from the group consisting of water, alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, esters such as ethyl acetate, hydrocarbon solvents such as toluene, ethers such as diethyl ether, tetrahydrofuran (THF), 1,4-dioxane, aprotic polar solvents such as N,N-dimethylformamide (DMF),dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), acetonitrile and the like; or mixture thereof. Preferably hydrocarbon solvent toluene is being used.

8) The process of claim 7, wherein the reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 25°C to about boiling point of the solvent(s) used and the time period is from about 30 minutes to about 24 hours, preferably from about 1 hour to about 5 hours.

9) An alternate process for the preparation of compound of formula I comprising:

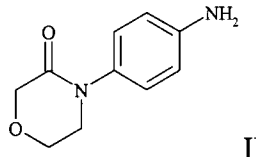
a) reacting the compound of formula IIa



IIa

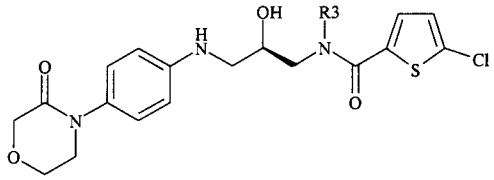
Where W is same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

with a compound of formula IIIb



IIIb

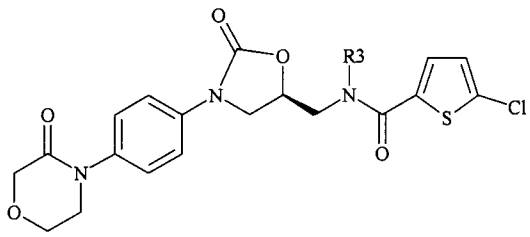
in the presence of a base to provide the compound of formula V,



V

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched

b) carbonylation of the compound of formula V by using a suitable reagent provides the compound of formula Ia



(Ia)

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched.

c) deprotection of the compound of formula (Ia) using suitable reagent provides the compound of formula I.

10) The process of claim 9, wherein the suitable base used in step a) is selected from inorganic base like alkali or alkaline earth metal carbonates, bicarbonates, hydroxides or ammonium cations or bases such as C_{1-8} alkoxides of alkali metals and alkaline earth metals or organic bases such as tri (C_{1-6} alkyl) amines and collidine or mixture thereof.

11) The process of claim 9, wherein the solvents that can be used in step a) is selected from the group consisting of alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane,chloroform, hydrocarbons such as toluene, ethers such as tetrahydrofuran (THF), nitriles acetonitrile or mixture thereof. Preferably methanol or toluene.

12) The process of claim 9, wherein the reaction step a) can be performed at a temperature range from about 30°C to about 200°C, preferably from about 70°C to about 120°C, and a time period of from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours.

13) The process of claim 9, wherein the suitable carbonylating agent used in step b is selected from the group consisting of phosgene or phosgene equivalent such as diphosgene, triphosgene, carbon monoxide equivalents such as N,N-carbonyldiimidazole (CDI), diethyl carbonate and the like; mixture thereof. Preferably N,N-carbonyldiimidazole (CDI) is being used.

14) The process of claim 9, wherein the suitable solvent used in step b) is selected from the group consisting of hydrocarbons such as toluene, halogenated solvents such as dichloromethane,chloroform, nitriles such as acetonitrile, ethers such as tetrahydrofuran (THF), 2-methyl THF, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) or mixture thereof. Preferably dichloromethane is being used.

15) The process of claim 9, wherein the reaction step b) can be performed at any suitable temperature, specifically at a range from about 20°C to the boiling temperature of the solvent(s) used. Preferably from about 25 °C to about boiling temperature of the solvent(s) used and a time period from about 30 minutes to about 48 hours, preferably from about 2 hours to about 24 hours.

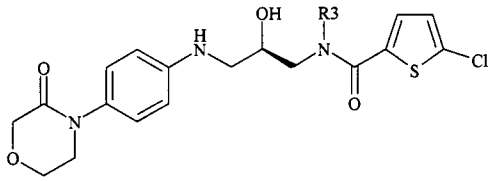
16) The process of claim 9, wherein the reaction step c) of converting compound of formula Ia to the compound of formula I by using suitable deprotecting agents selected from selected from the group consisting of p-toluene sulfonic acid, N-bromosuccinimide, triflouro acetic acid and the like; hydrogenation catalysts like palladium on carbon, platinum oxide inorganic acids such as HCl, HBr, sulfuric acid, phosphoric acid and the like.

17) The process of claim 9, wherein the suitable solvents that can be used in step c) is selected from the group consisting of water, alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, chlorobenzene, esters such as ethyl acetate, butyl acetate, isopropyl acetate,hydrocarbon solvents such as toluene, ethers such as diethyl ether, tetrahydrofuran (THF), aprotic polar solvents such as N,N-

dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile, and the like; or mixture thereof. Preferably hydrocarbon solvent toluene is being used.

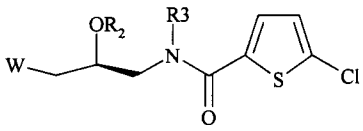
18) The process of claim 9, wherein the reaction step c) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 25°C to about boiling point of the solvent(s) used and the time period is from about 30 minutes to about 24 hours, preferably from about 1 hour to about 5 hours.

19) A process for the preparation of compound of formula V



V

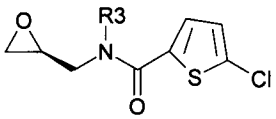
a) reacting the compound of formula II



II

Where W, R2 are same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

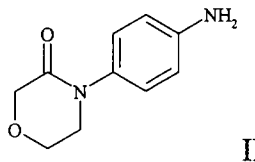
with a suitable reagent to provide the compound of formula IV



IV

Where R3 is same as defined above,

b) reacting the compound of formula IV with the compound of formula IIIb



IIIb

to provide the compound of formula V.

20) The process of claim 19, wherein the reaction step a) is carried out in presence of a base, selected from inorganic such as alkali or alkaline earth metal carbonates, bicarbonates, hydroxides or ammonium cations or bases such as C $_{1-8}$ alkoxides of alkali metals and alkaline earth metals or mixture thereof, preferably potassium carbonate or lithium tert-butoxide.

21) The process of claim 19, wherein the solvents used in step a) is selected from alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, ethers such as tetrahydrofuran (THF), nitriles such as acetonitrile, hydrocarbons like toluene or mixture thereof, preferably methanol.

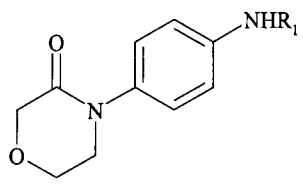
22) The process of claim 19, wherein reaction step a) can be performed at a temperature range from about -30°C to about 50°C, preferably from about -10°C to about 35°C and duration of time can be from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours is being sufficient.

23) The process of claim 19, wherein the suitable solvent in reaction step b) is selected from alcohols such as methanol, ethanol, isopropanol, hydrocarbons such as toluene, nitriles such as acetonitrile, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile, or mixture thereof. Preferably ethanol.

24) The process of claim 19, wherein the reaction step b) can be performed at a temperature range from about 30°C to the boiling temperature of the solvent(s) used, preferably at boiling temperature of the solvent(s) used and duration of time can be from about 4 hours to about 48 hours, preferably from about 8 hours to about 24 hours.

25) An alternate method for the synthesis of compound of formula I comprising:

a) reacting the compound of formula III

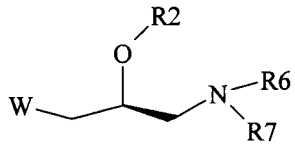


III

Where R_1=-H or –$COOR_4$ where R_4 =C_{1-12} alkyl straight chain or branched optionally

sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl, C_{2-6} alkenyl, cycloalkyl;

with the compound of formula VI



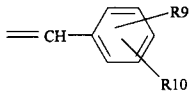
VI

Where W= halogen atom (Cl, Br, I), -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl;

R2 = -H or –CO-R5 where R5=C_{1-12} alkyl straight chain or branched optionally sub with 1-3 halogen atom (F, Cl, Br), $C_1 - C_{12}$ alkoxy straight chain or branched which are optionally sub. with 1-3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub phenyloxy, sub or unsub arylalkoxy, sub or unsub arylalkyl group;

R6, R7= independently selected from the group consisting of H or amino protecting group.

a) R6, R7= -H or –CO-OR8 where R8 = C_{1-12} alkyl straight chain or branched which are optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl group, sub or unsub aryl alkyl group;

b) R6, R7= 

Where R9, R10 = independently selected from H or group consisting of Cl, Br, F, I , $C_1 -_{10}$ alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl. Br), C_{1-10} alkoxy straight or branched which are optionally sub with 1 to 3 halogen atom (F, Cl, Br), -NO_2, -CN, -alkyl sulfonyl, arylsulfonyl;

c) R6, R7 = -H or –CO-R^{11} where R^{11}=H or C_{1-10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl group;

d) –N R 6 R7 = sub or unsub phthalimido group;

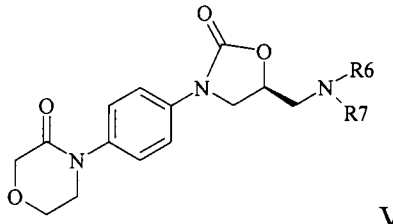
e) –N R 6 R7 = Azido group;

f) –N R6 R7= sub or unsub pyrrole ring;

g) –R6,R7 = -H or trityl group;

h) R6 = R7 = sub or unsub benzyl group;

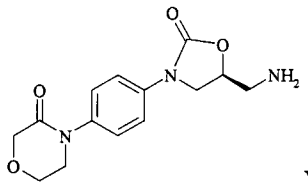
in the presence of a suitable reagent to provide the compound of formula VII



VII

Where R6, R7 are same as defined above.

b) deprotection of compound of formula VII using a suitable reagent to provide the compound of formula VIII



VIII

and conversion of compound of formula VIII into rivaroxaban (I).

26) The process of claim 25, wherein the step a) is performed in using a base selected from base having an alkoxide group with C_1 –C_7; C_{1-4} alkyl carbanion such as methyl, sec-butyl, butyl or tert-butyl carbanion; a conjugate base of a carbamate; lithium diisopropyl amide, lithium amide; inorganic bases like metal hydroxides such as sodium hydroxide, potassium hydroxide,alkali metal carbonates such as sodium carbonate, potassium carbonate, metal bicarbonates likesodium bicarbonate, potassium bicarbonate or mixture thereof, preferably a base with alkoxide group having C_{4-5} carbon atoms, More preferably tert-amylate or tert-butoxide, most preferred base is lithium tert-butoxide or potassium carbonate.

27) The process of claim 25, wherein the nucleophile used in step a) is selected from nucleophile of an alkoxide group, linear or branched, having C_{1-7} atoms. Preferred nucleophile is methoxide or ethoxide or isopropoxide or isobutoxide or 2-ethoxyethyl, 2-(N,N-dimethylamino) ethoxide or 2,2,2-trichloroethoxide or 2,2,2-trifluoroethoxide.

28) The process of claim 25, wherein the solvent in step a) is selected from alcohols such as methanol, tert-amyl alcohol, tert-butyl alcohol, hydrocarbon solvents such as toluene, ethers such as tetrahydrofuran (THF), 2-methyl THF, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA),

acetonitrile or mixture thereof. Preferably DMF or THF or mixture thereof.

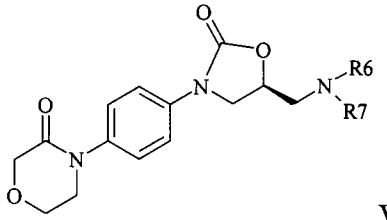
29) The process of claim 25, wherein reaction step a) can be carried out at a temperature range from about -40°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 80°C. and the time required is from about 1 hour to about 24 hours, preferably from about 8 hour to about 21 hours.

30) The process of claim 25, wherein the reaction step b) can be carried out by using any suitable deprotecting agent, the suitable deprotection reagents is selected from triflouro acetic acid and the like; inorganic acids such as HCl, HBr, sulfuric acid, phosphoric acid, hydroxyl amine, hydrazine hydrate, hydrogenation catalysts like palladium on carbon, platinum oxide, ammonium formate, methyl amine and the like or mixture thereof.

31) The process of claim 25, wherein the solvents used in deprotection step b) is selected from water, acetic acid, alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, esters such as ethyl acetate, hydrocarbon solvents such as toluene, ethers such as diethyl ether, tetrahydrofuran (THF), aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) or mixture thereof.

32) The process of claim 25, wherein the reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 25°C to about boiling point of the solvent(s) used and time required can be from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 8 hours is being sufficient.

33) A process for the preparation of compound of formula VII

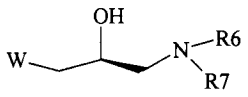


VII

Where R6, R7 are same as defined above.

comprising:

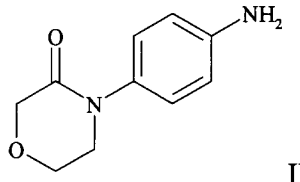
a) reacting the compound of formula VIa



VIa

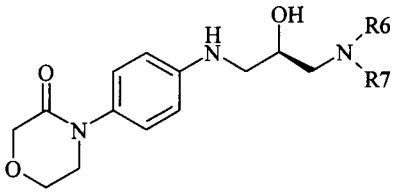
Where W, R6 and R7 are same as defined above.

with the compound of formula IIIb



IIIb

in the presence of suitable base to provide the compound of formula IX



IX

Where R6 and R7 are same as defined above

b) carbonylation of the compound of formula IX using a suitable reagent to obtain the compound of formula VII.

34) The process of claim 33, wherein the step a) is carried out using a base selected from organic bases such as tri (C_{1-6} alkyl) amines, collidine, pyridine, inorganic bases such as alkali, alkaline earth metal carbonates, bicarbonates, alkali metal hydroxides , C_{1-8} alkoxides of alkali and alkaline earth metals or mixture thereof, preferably collidine.

35) The process of claim 33, wherein the suitable solvent used in step a) is selected from alcohols such as methanol, ethanol, hydrocarbons such as toluene, xylene, nitriles such as acetonitrile, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile or mixture thereof. Preferably hydrocarbon solvent toluene is being used.

36) The process of claim 33, wherein the step a) can be performed at a temperature range from about 30°C to about 200°C, preferably from about 70°C to about 120°C and a time period of from about 1 hour to about 8 hours, preferably from about 2 hours to about 6 hours.

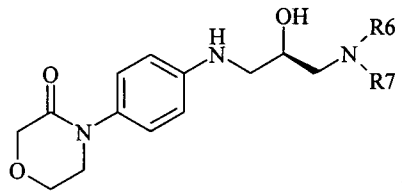
37) The process of claim 33, wherein carbonylation step b) is carried out by using

carbonylating agents selected from the group consisting of phosgene or phosgene equivalent such as diphosgene, triphosgene, carbon monoxide equivalents such as N,N-carbonyldiimidazole (CDI), diethyl carbonate or mixture thereof. Preferably N,N-carbonyldiimidazole (CDI) is being used.

38) The process of claim 33, wherein the suitable solvents that can be used in step b) is selected from the group consisting of alcohols such as methanol, ethanol, hydrocarbons such as toluene, halogenated solvent such as dichloromethane, chloroform, nitriles such as acetonitrile, ethers such as tetrahydrofuran (THF), 2-methyl THF, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA) or mixture thereof. Preferably dichloromethane.

39) The process of claim 33, wherein reaction step b) is performed at a temperature, specifically at a range from about 20°C to the boiling temperature of the solvent(s) used. Preferably from about 25 °C to about boiling temperature of the solvent(s) used and time period can be from about 30 minutes to about 48 hours, preferably from about 2hours to about 24 hours.

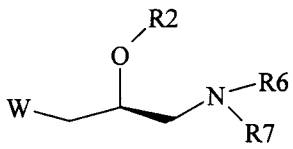
40) An alternate process for the preparation of compound of formula IX



IX

Where R6 and R7 are same as defined above

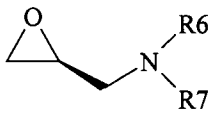
a) reacting the compound of formula VI



VI

Where W, R2, R6 and R7 are same as defined above.

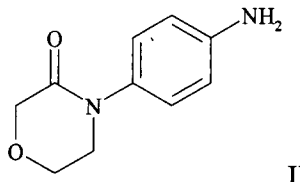
with a suitable reagent to form the compound of formula X



X

Where R6 and R7 are same as defined above

b) reacting the compound of formula X with the compound of formula IIIb



IIIb

to provide the compound of formula IX.

41) The process of claim 40, wherein the step a) is performed using a base selected from alkali, alkaline earth metal carbonates, bicarbonates, alkali metal hydroxides or ammonium cations, C $_{1-8}$ alkoxides of alkali metals and alkaline earth metals. Preferably lithium tert-butoxide.

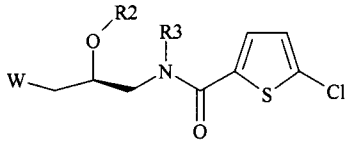
42) The process of claim 40, wherein the suitable solvent used in step a) is selected from alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, ethers such as tetrahydrofuran (THF), 2-methyl THF, hydrocarbons such as toluene or mixture thereof. Preferably methanol.

43) The process of claim 40, wherein the reaction step a) is carried out at a temperature range from about -30°C to about 50°C, preferably from about 0°C to about 50°C. and a time period from about 30 minutes to about 120 hours, preferably from about 30 minutes to about 85 hrs.

44) The process of claim 40, wherein the suitable solvent in reaction step b) is selected from alcohols such as methanol, ethanol, nitriles such acetonitrile, ethers such as tetrahydrofuran (THF), 2-methyl THF, hydrocarbons such as toluene, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile, or mixture thereof. Preferably ethanol is being used.

45) The process of claim 40, wherein the reaction step b) is carried out at a temperature range from about 30°C to about boiling point of the solvent(s) used, preferably at boiling points of the solvent(s) and a time period of from about 1 hour to about 48 hours, preferably from about 8 hours to about 24 hrs.

46) A method of synthesis of compound having the formula II



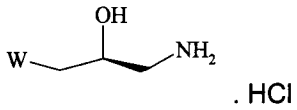
(II)

where W= halogen atom (Cl, Br, I) or -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group; R2 =-H or –CO-R5; R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to 3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched;

comprising:

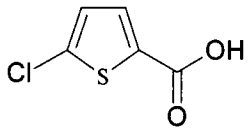
a) reacting the compound of formula XI



XI

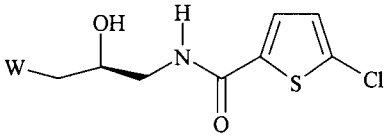
Where W is same as defined above,

with a compound of formula XII



XII

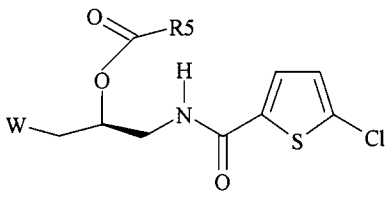
in the presence of a suitable reagent to provide the compound of formula IIa



IIa

Where W is same as defined above,

b) reacting the compound of formula IIa with a suitable reacatant to provide the compound of formula IIb



IIb

c) reacting the compound of formula IIb with a suitable reacatant to provide the compound of formula II.

47) The process of claim 46, wherein the reaction step a) is performed by reacting the compound of formula XI with the compound of formula XII or with its corresponding carbonyl halides, preferably carbonyl chloride or with the corresponding symmetric or mixed carboxylic anhydrides of the carboxylic acids of the compound formula XII defined above, if appropriate in the presence of an activating or coupling agent and or a base to the compound of formula IIa.

48) The process of caim 46, wherein the suitable solvents that can be used in step a) is selected from water, alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, hydrocarbon solvents such as toluene, ethers such as tetrahydrofuran (THF), aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N- dimethylacetamide (DMA), acetonitrile, pyridine, hexamethyl phosphoric triamide or mixture thereof. Preferably dichloromethane or toluene.

49) The process of claim 46, wherein the suitable coupling agents used in step a) is selected from the group consisting of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide. HCl, N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole monohydrate or mixture thereof

50) The process of claim 46, wherein the bases that can be employed in step a) is selected from alkali bicarbonates such as sodium bicarbonate, potassium bicarbonate, organic bases such as triethyl amine, diisopropyl ethylamine, diisopropyl amine, 4.N,N-dimethylaminopyridine or pyridine or mixture thereof, preferably sodium bicarbonate or triethylamine.

51) The process of claim 46, wherein the reaction step a) can be carried out at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C and a time period from about 1 hour to about 24 hours, preferably from about 2 hour to about 4 hours.

52) The process of claim 46, wherein the suitable reactants that can be used in step b) include acid halides of general formula

Preferably acid chlorides or acid anhydrides of general formula $(R5CO)_2O$.

Where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

53) The process of claim 46, wherein the suitable solvents used in step b) is selected from water, halogenated solvents such as dichloromethane, chloroform, chlorobenzene, esters such as ethyl acetate, isopropyl acetate, hydrocarbon solvents such as toluene, ethers such as tetrahydrofuran (THF), 1,4-dioxane, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N- dimethylacetamide (DMA),acetonitrile or mixture thereof. Preferably dichloromethane.

54) The process of claim 46, wherein the suitable bases employed in step b) is selected from alkali bicarbonates such as sodium bicarbonate, potassium bicarbonate; organic bases such as triethyl amine, diisopropyl ethylamine, diisopropyl amine, 4.N,N-dimethylaminopyridine, pyridine or mixture thereof, preferably pyridine.

55) The process of claim 46, wherein the reaction step b) can be perrformed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C and a time period from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 8 hours.

56) The process of claim 46, wherein the reaction step c) is performed by reacting the compound of formula IIb with the compound of general formula R3-X

Where R3= amide nitrogen protecting group, for example sub or unsub benzyl group, trityl group, C3-10 alkenyl straight chain or branched, preferably trityl group;

X= leaving group for example halogen atom (Cl, Br), sulfonyloxy group or hydroxyl group;

57) The process of claim 46, wherein the suitable bases that can be used in step c) is selected from alkali or alkaline earth metal hydroxides such as sodium hydroxide,

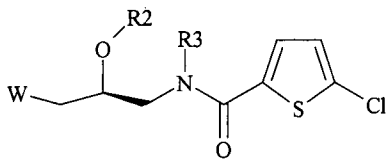
barium hydroxide; alkali carbonates such as sodium carbonate; alkali metal bicarbonates such as sodium bicarbonate, ; alkali metal alkoxides such as sodium methoxide, lithium tertiary butoxide; amides such as sodium amide, lithium bis (trimethylsilyl)amide or lithium diisopropyl ethylamide, diisopropylamide; or mixtures thereof.
Preferably sodium hydroxide.

58) The process of claim 46, wherein the reaction step c) is optionally performed by employing a catalyst such as para-toluene sulfonic acid.

59) The process of claim 46, wherein suitable solvents that can be used in step c) is slected from alcohols such as methanol, ethanol,halogenated solvents such as dichloromethane, chloroform, ethers such as tetrahydrofuran (THF), esters such as ethyl acetate, hydrocarbon solvents such as toluene, aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA),acetonitrile,or mixture thereof. Preferably toluene.

60) The process of claim 46, wherein the reaction step c) can be performed at a temperature range from about -70°C to the boiling point of the solvent used, preferably from about 0°C to the boiling point of the solvent used and a time period of from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours.

61) An alternate method for the synthesis of compound of formula II



(II)

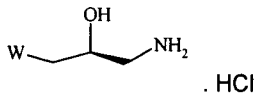
where W= halogen atom (Cl, Br, I) or -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group; R2 = -H or –CO-R5;

R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to 3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched;

comprising:

a) reacting the compound of formula XI

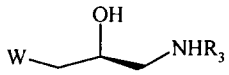


XI

with R3-X in the presence of a suitable reagent

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched and X is halogen atom (Cl, Br, I) or -O-SO_2R where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group or CHO group,

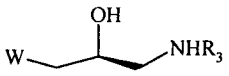
to provide the compound of formula XIII



XIII

Where R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched

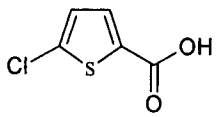
b) reacting the compound of formula XIII



XIII

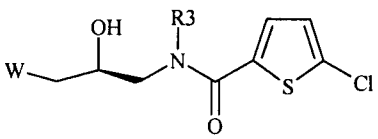
Where R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched,

with a compound having the formula XII



XII

in the presence of a suitable reagent to provide the compound having the formula IIc



IIc

Where W is same as defined above and R_3 Where R3 is protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched,

c) reacting the compound of formula IIc with a suitable reactant gives the compound of formula II.

62) The process of claim 61, wherein the suitable bases used in step a) is selected from inorganic bases such as ammonia,alkali, or alkaliearth metal hydroxides such as sodium hydroxide, carbonates such as sodium carbonate, metal bicarbonates such as sodium bicarbonate , organic bases such as tri(C_{1-6} alkyl)amines, collidine, pyridine or mixtuere thereof. Preferably triethylamine.

63) The process of claim 61, wherein the suitable solvents used in step a) is selected from alcohols such as methanol, ethanol, halogenated solvents such as dichloromethane, chloroform, hydrocarbons such as toluene, nitriles such as acetonitrile, aprotic polar solvents such as DMF, esters such as ethyl acetate or mixture thereof, preferably methanol (or) toluene.

64) The process of claim 61, wherein the suitable temperature for reaction step a) is from about 0°C to boling point of the solvent(s) used. Preferably from about 25°C to about 50°C.

65) The process of claim 61, wherein reaction step b) is carried out by reacting the compound of formula XIII with the compound of formula XII or with the corresponding carbonyl halides preferably carbonyl chlorides or with the corresponding symmetric or mixed carboxylic anhydrides of the carboxylic acids of the formula XII defined above.

66) The process of claim 61, wherein the suitable bases used in step b) is selected from the group consisting of alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate like; amines such as triethyl amine, diisopropyl amine, diisopropylethylamine, N,N-dimethylaminopyridine, pyridine or mixtures thereof, preferably triethyl amine or sodium bicarbonate.

67) The process of claim 61, wherein the suitable activating or coupling agents used in step a) is selected from N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide.HCl, N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole monohydrate

68) The process of claim 61, wherein the suitable solvents used in step b) is selected from the group consisting of water, halogenated solvents such as dichloromethane, chloroform, ethers such as tetrahydrofuran (THF),alcohols such as methanol,

ethanol, hydrocarbon solvents such as toluene, nitriles such as acetonitrile; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile, pyridine, hexamethylphosphoric triamide or mixture thereof. Preferably dichloromethane or toluene.

69) The process of claim 61, wherein the reaction step b) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C and at a time period of from about 30 minutes to about 72 hours, preferably from about 30 minutes to about 5 hours is being sufficient.

70) The process of claim 61, wherein the suitable reagents that can be used in step c) include acid halides of general formula

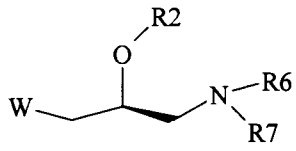
Preferably acid chlorides or acid anhydrides of general formula $(R5CO)_2O$.
Where R5 is C_1-C_{12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_1-C_{12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group.

71) The process of claim 61, wherein suitable solvents used in step c) is selected from the group to water, halogenated solvents such as dichloromethane, chloroform, and the like; esters such as ethyl acetate and the like; hydrocarbon solvents such as toluene and the like; ethers such as tetrahydrofuran (THF) and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), acetonitrile and the like; or mixture thereof. Preferably dichloromethane.

72) The process of claim 61, wherein the bases that can be employed in step c) is selected from alkali bicarbonates such as sodium bicarbonate, potassium bicarbonate like; organic bases such as triethyl amine, diisopropyl ethylamine, diisopropyl amine, 4.N,N-dimethylaminopyridine or pyridine or mixture thereof, preferably pyridine.

73) The process of claim 61, wherein the reaction step c) can be performed at a temperature range from about 0°C to the boiling point of the solvent(s) used, preferably from about 0°C to about 50°C and at a time period of from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 8 hours is being sufficient.

74) A method for synthesis of compound of formula VI

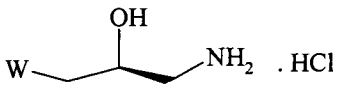


VI

Where W, R2, R6, R7 are same as defined above.

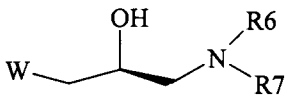
comprising:

a) reacting the compound of formula XI



XI

with a suitable protecting agent to provide the compound of formula VIa



VIa

Where W, R6,R7 are same as defined above,

b) reacting the compound of formula VIa with a suitable acylating agent to provide the compound of formula VI.

75) The process of claim 74, wherein the suitable protecting agents that can be used in step a) is selected from the group consisting of carbamates, imino, amides, phthalimides, azido, pyrrole ring, trityl or dibenzyl group.

76) The process of claim 74, wherein the reaction step a) is essentially performed in the presence of a base and is selected from the group consisting of inorganic bases like alkali, alkaline earth metal carbonates such as sodium carbonate, magnesium carbonate; metal bicarbonates such as sodium bicarbonate, hydroxides such as sodium hydroxide, magnesium hydroxide; organic bases such as triethyl amine, diisopropylethylamine, pyridine or mixtures thereof, preferably triethyl amine.

77) The process of claim 74, wherein the solvents that can be used in step a) is selected from the group consisting of alcohols such as methanol, ethanol, esters such as ethyl acetate, halogenated solvents such as dichloromethane, chloroform, ethers such as tetrahydrofuran (THF), hydrocarbon solvents such as toluene,nitriles such as

acetonitrile; aprotic polar solvents such as N,N-dimethylformamide (DMF), or mixture thereof.

78) The process of claim 74, wherein reaction step a) can be performed at a temperature range from about -40°C to the boiling point of the solvent(s) used, preferably at about 25°C to about boiling point of the solvent (s) used and a time period of from about 30 minutes to about 48 hours, preferably from about 30 minutes to about 24 hours is being sufficient.

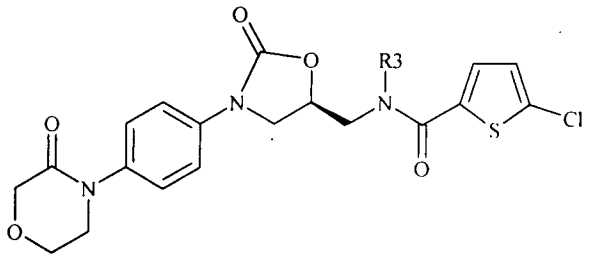
79) The process of claim 74, wherein the suitable acylating agents that can be used in step b) can be selected from $R5\text{-}\overset{\overset{O}{\|}}{C}\text{-}X$ or $(R_5CO)_2O$. where R5 is same as defined above.

80) The process of claim 74, wherein the suitable bases that can be used in step b) is selected from the group inorganic bases like alkali, alkaline earth metal carbonates such as sodium carbonate, magnesium carbonate, metal bicarbonates such as sodium bicarbonate, organic bases such as triethyl amine, diisopropylethylamine, pyridine, collidine or mixtures thereof, preferably pyridine.

81) The process of claim 74, wherein the suitable solvents that can be used in step b) is selected from the group consisting of halogenated solvents such as dichloromethane, chloroform and the like; ethers such as tetrahydrofuran (THF) and the like; hydrocarbon solvents such as toluene and the like; nitriles such as acetonitrile or mixture thereof. Preferably dichloromethane.

82) The process of caim 74, wherein the reaction step b) can be performed at a temperature range from about -10°C to about boling point of the solvent(s) used, preferably from about 0°C to 50°C and duration of time is from about 30 minutes to about 12 hours, preferably from about 30 minutes to about 2 hours.

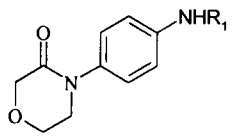
83) A process for the preparation of compound of formula Ia ,



(Ia)

Where R3 is H or a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched,

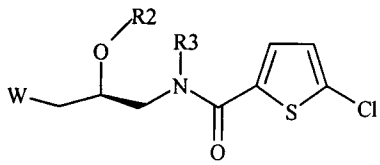
reacting the compound of formula (III) or a salt thereof



(III)

Where R_1 is H or  where R4=C_{1-4} alkyl straight chain or branched optionally substituted with 1to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub arylalkyl, C_{2-6} alkenyl, cycloalkyl;

with the compound of formula (II)



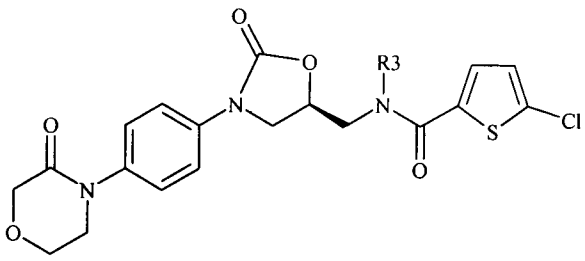
(II)

Where W= halogen atom (Cl, Br, I), -O-SO_2R where R= C_{1-4} alkyl, sub or un sub phenyl, arylalkyl;

R2 is H or –CO-R5 where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to 3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or unsub.phenyl, sub or unsub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched,

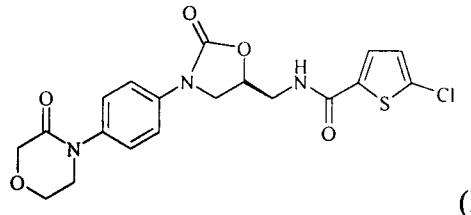
in the presence of a base and optionally in the presence of a nucleophile to provide the compound of formula (Ia).



(Ia)

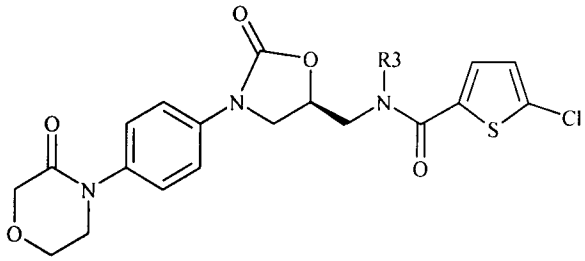
Where R3 is H or a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight or branched,

84) A process for the preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide (I),



(I)

by deprotection of the compound of formula (Ia)

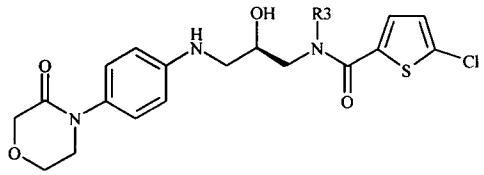


Ia

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

using a suitable reagent to provide the compound of formula I.

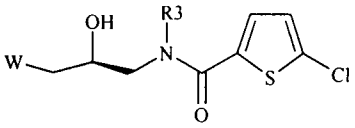
85) A process for the synthesis of compound having the formula V



V

R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

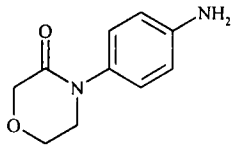
by reacting the compound of formula IIa



IIa

Where W is same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

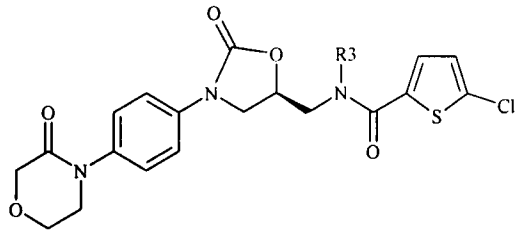
with a compound of formula IIIb



IIIb

in the presence of a suitable reagent to provide the compound of formula V.

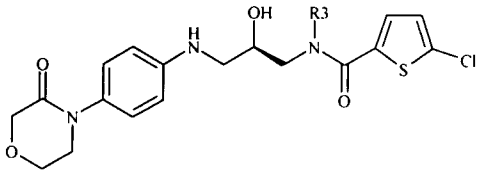
86) A process for the preparation of compound of formula Ia



(Ia)

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

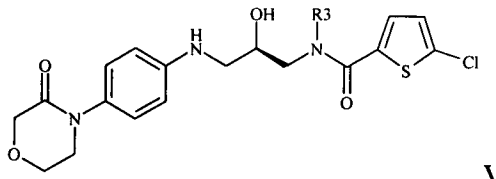
by carbonylation of the compound of formula V



V

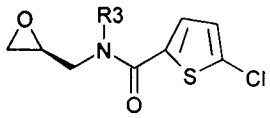
using a suitable reagent to provide the compound of formula Ia.

87) A process for the preparation of compound of formula V



V

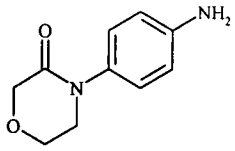
by reacting the compound of formula IV



IV

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched ;

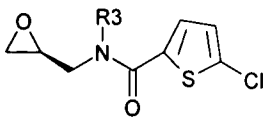
with the compound of formula IIIb



IIIb

to provide the compound of formula V.

88) A process for the preparation of compound of formula IV

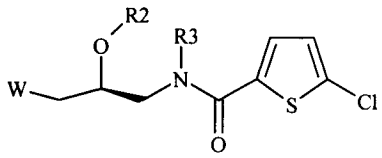


IV

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight

chain or branched ;

by reacting the compound of formula of formula II

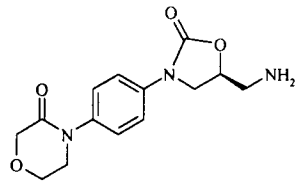


(II)

Where W, R2, R3 are same as defined above

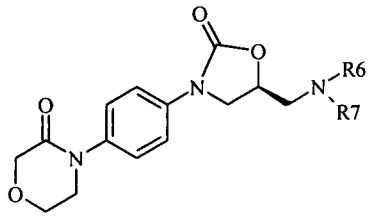
with a suitable base to provide compound of formula II

89) A method for the synthesis of compound having the formula VIII



VIII

by deprotection of compound of formula VII

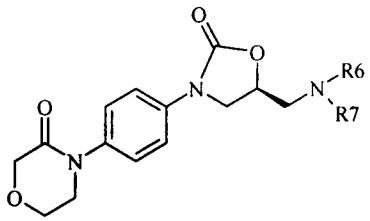


VII

Where R6, R7 are same as defined above.

using a suitable reagent to provide compound of formula VIII.

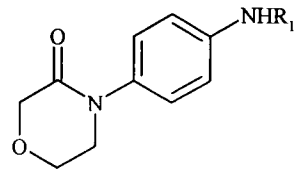
90) A method for the synthesis of compound having the formula VII



VII

Where R6, R7 are same as defined above.

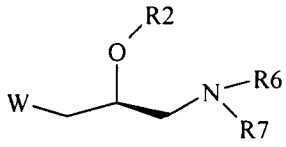
by reacting the compound of formula III



III

Where R_1 is same as defined above,

with the compound of formula VI

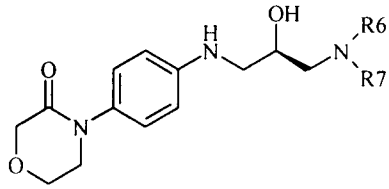


VI

Where W, R2, R6, R7 are same as defined above,

to provide the compound of formula VII.

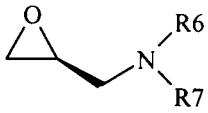
91) A process for the preparation of compound of formula IX



IX

Where R6 and R7 are same as defined above,

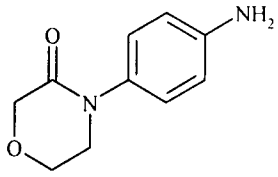
by reacting the compound of formula X



X

Where R6 and R7 are same as defined above,

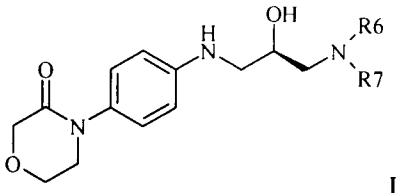
with the compound of formula IIIb



IIIb

to provide the compound of formula IX.

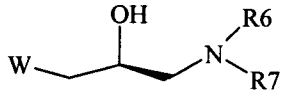
92) An process for the preparation of compound of formula IX



IX

Where R6 and R7 are same as defined above,

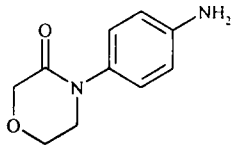
by reacting the compound of formula VIa



VIa

Where W, R6, R7 are same as defined above

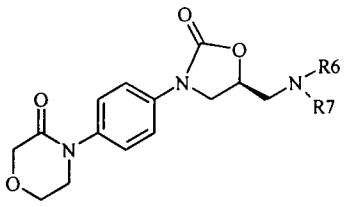
with the compound of formula IIIb



IIIb

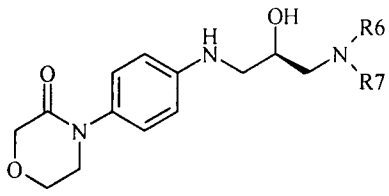
to give compound of formula IX.

93) A process for the preparation of compound of formula VII



VII

by reacting the compound of formula IX

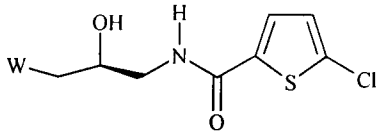


IX

Where R6 and R7 are same as defined above,

with a suitable carbonylating agent.

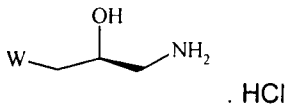
94) A method for the synthesis of compound of formula IIa



IIa

Where W is same as defined above,

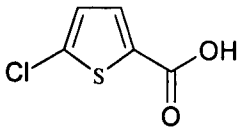
reacting the compound of formula XI



XI

Where W is same as defined above,

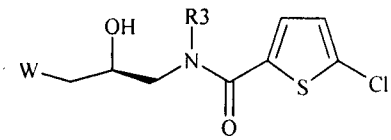
with a compound of formula XII



XII

in the presence of a suitable coupling agent and a base to provide the compound of formula IIa.

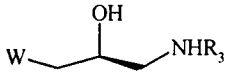
95) A method for the synthesis of compound of formula IIc



IIc

Where W is same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched ,

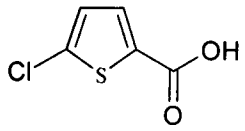
reacting the compound of formula XIII



XIII

Where W is same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched

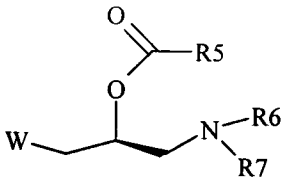
with a compound of formula XII



XII

in the presence of a suitable coupling agent and a base to provide the compound of formula IIc.

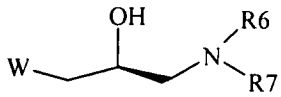
96) A method for synthesis of compound having the formula VI



VI

Where W, R5, R6, R7 are same as defined above,

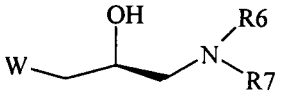
by reacting the compound of formula VIa



VIa

with a suitable acylating agent to provide the compound of formula VI.

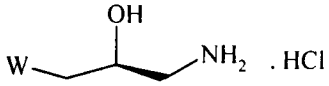
97) A method for synthesis of compound having the formula VIa



VIa

Where W, R6,R7 are same as defined above,

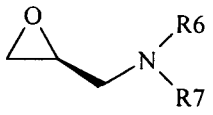
by reacting the compound of formula XI



XI

with a suitable protecting agent and a base to provide the compound of formula VIa.

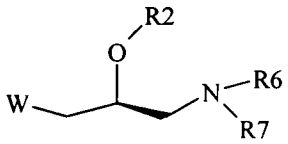
98) A process for the synthesis of compound having the formula X



X

Where R6 and R7 are same as defined above

by reacting the compound of formula VI

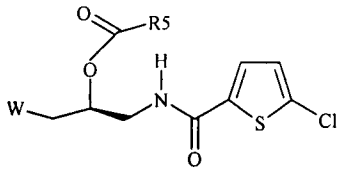


VI

Where W, R2, R6 and R7 are same as defined above.

in the presence of base to form the compound of formula X.

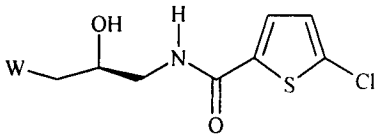
99) A method for synthesis of compound having the formula IIb



IIb

Where W, R5 are same as defined above

by reacting the compound of formula IIa

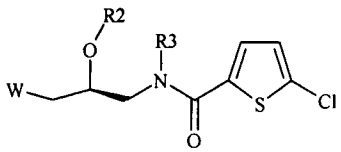


IIa

Where W is same as above

with a suitable reactant to provide compound of formula IIb

100) A method of synthesis of compound having the formula II

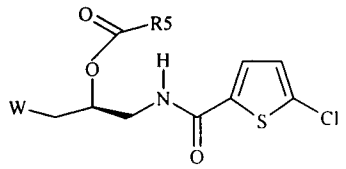


(II)

Where W, R2 are same as defined above and R3 is a protecting group such as sub or unsub

benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched;

by reacting the compound of formula IIb



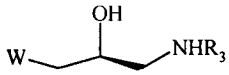
IIb

Where W, R5 are same as defined above

with R3-X to provide compound of formula II.

Where R3 and X are same as defined above.

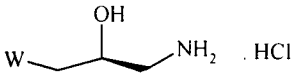
101) A method of synthesis of compound of formula XIII



XIII

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight or branched ;

by reacting the compound of formula XI

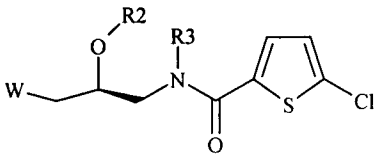


XI

with R3-X to provide the compound of formula XIII.

Where R3 and X are same as defined above.

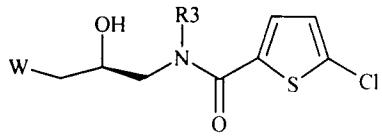
102) A method of synthesis of compound of formula II



(II)

Where W, R2 are same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched ;

by reacting the compound of formula IIc

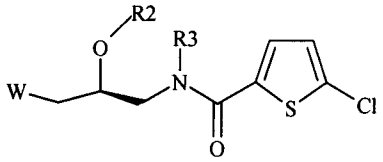


IIc

Where W and R3 are same as defined above

with a suitable reagent to provide the compound of formula II.

103) A compound having the formula II



(II)

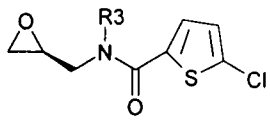
Where W= halogen (Cl, Br, I) or $-OSO_2R$- Where R= C_1-C_4 alkyl, sub or unsub phenyl , arylalkyl group;

R2 is H or –CO-R5 where R5 is C_{1-12} alkyl straight chain or branched optionally substituted with 1 to3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight chain or branched optionally substituted with 1 to 3 halogen atom (F,Cl,Br), sub or un sub.phenyl, sub or un sub phenyloxy, sub or unsub aryl alkyl, sub or unsub arylalkoxy group;

R3 is H or protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched;

and its use in the synthesis of oxazolidines having biological activity.

104) A compound having the formula IV

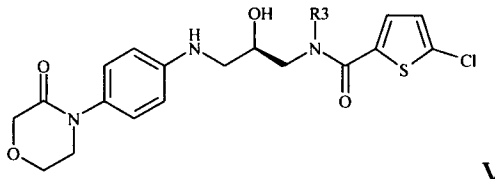


IV

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched;

and its use in the synthesis of oxazolidines having biological activity.

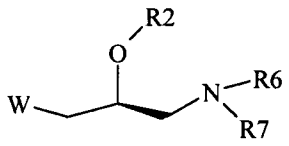
105) A compound having the formula V



V

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_{3-10} alkenyl straight chain or branched and its use in the synthesis of oxazolidines having biological activity.

106) A compound having the formula VI



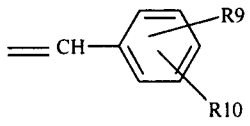
VI

Where W= halogen (Cl, Br, I) or $-OSO_2R$- Where R= C_{1-4} alkyl, sub or unsub phenyl, arylalkyl group;

R2 = -H or –CO-R5 where R5=C_{1-12} alkyl straight chain or branched optionally sub with 1-3 halogen atom (F, Cl, Br), C_{1-12} alkoxy straight or branched which are optionally sub. with 1-3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub phenyloxy, sub or unsub arylalkoxy, sub or unsub arylalkyl group.

R6, R7= independently selected from the group consisting of H or amino protecting group.

a) R6, R7= -H or –CO-OR8 where R8 = C_{1-12} alkyl straight or branched which are optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl group, sub or unsub aryl alkyl group.

b) R6, R7= 

Where R9, R10 = independently selected from H or group consisting of Cl, Br, F, I , C_1 –C_{10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl. Br), C_{1-10} alkoxy straight chain or branched which are optionally sub with 1 to 3 halogen atom (F, Cl, Br), $-NO_2$, -CN, -alkyl sulfonyl, arylsulfonyl.

c) R6, R7 = -H or –CO-R^{11} where R^{11}= H or C_{1-10} alkyl straight chain or branched optionally sub. with 1 to 3 halogen atom (F, Cl, Br), sub or unsub phenyl, sub or unsub aryl alkyl group.

d) –N R 6 R7 = sub or unsub phthalimido group

e) –N R 6 R7 = Azido group

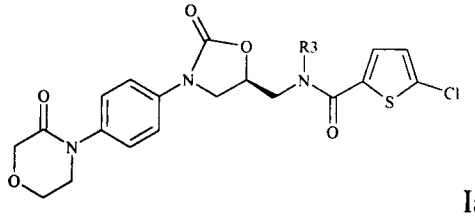
f) –N R6 R7= sub or unsub pyrrole ring

g) –R6 , R7 = -H or trityl group

h) R6 = R7 = Sub or unsub benzyl group.

and its use in the synthesis of oxazolidines having biological activity.

107) A compound having the formula Ia

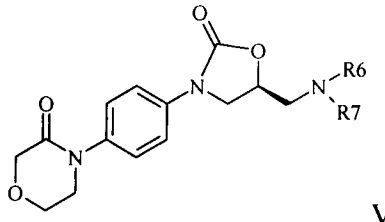


Ia

Where R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight chain or branched ;

and its use in the synthesis of oxazolidines having biological activity.

108) A compound having the formula VII

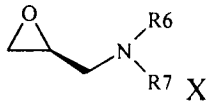


VII

Where R6 and R7 are same as defined for compound of formula VI.

and its use in the synthesis of oxazolidines having biological activity.

109) A compound having the formula X

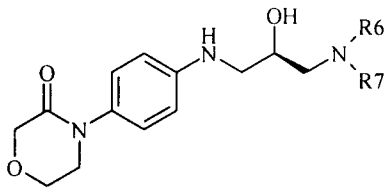


X

Where R6 and R7 are same as defined for compound of formula VI.

and its use in the synthesis of oxazolidines having biological activity.

110) A compound having the formula IX

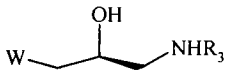


IX

Where R6 and R7 are same as defined for compound of formula VI

and its use in the synthesis of oxazolidines having biological activity.

111) A compound having the formula XIII



XIII

Where W is same as defined above and R3 is a protecting group such as sub or unsub benzyl, trityl, C_3-C_{10} alkenyl straight or branched ;

and its use in the synthesis of oxazolidines having biological activity.

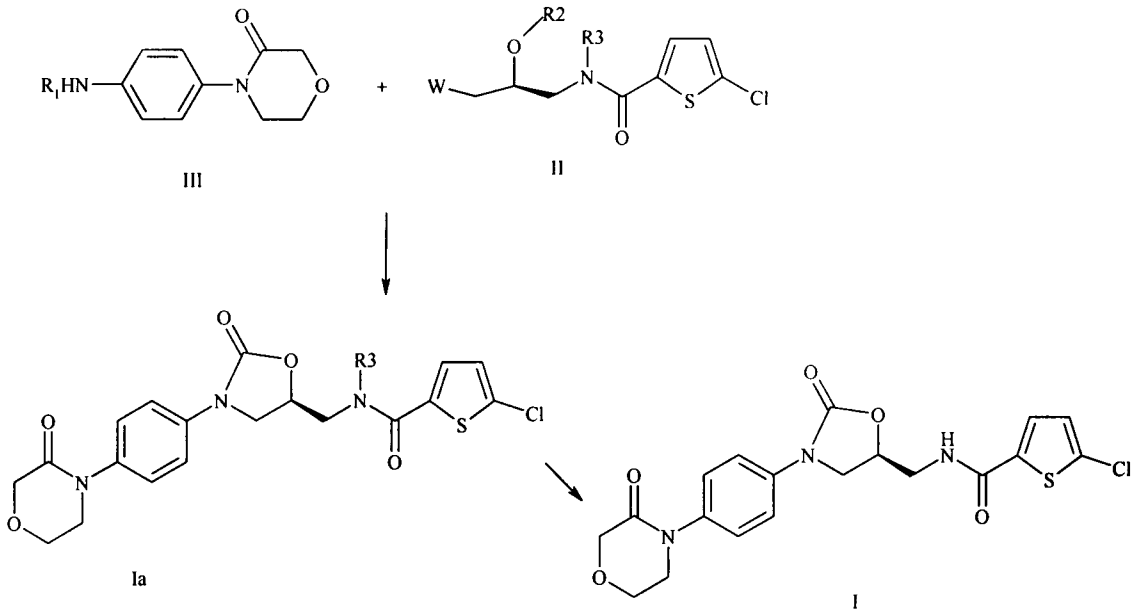


Fig 1

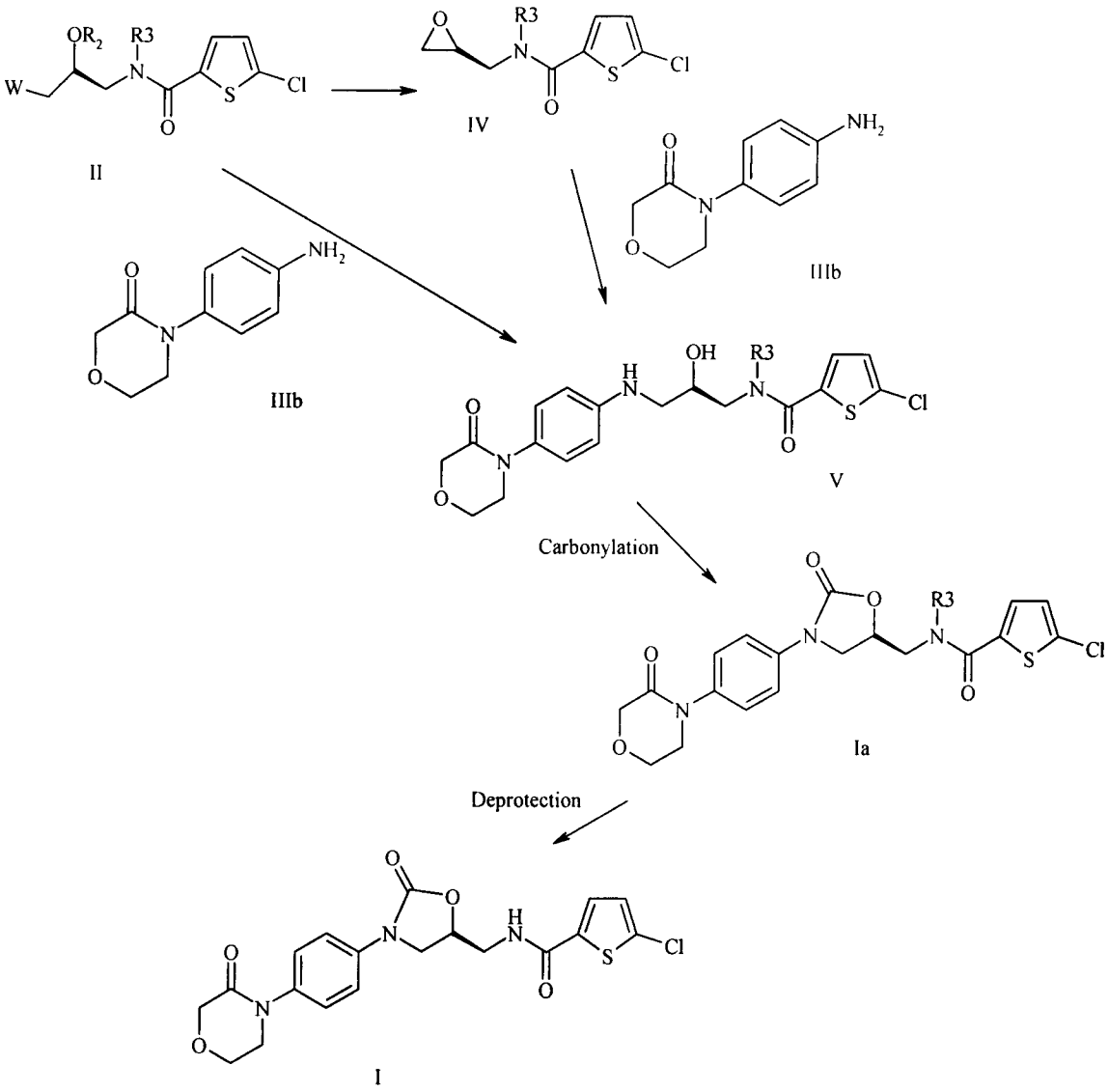


Fig. 2

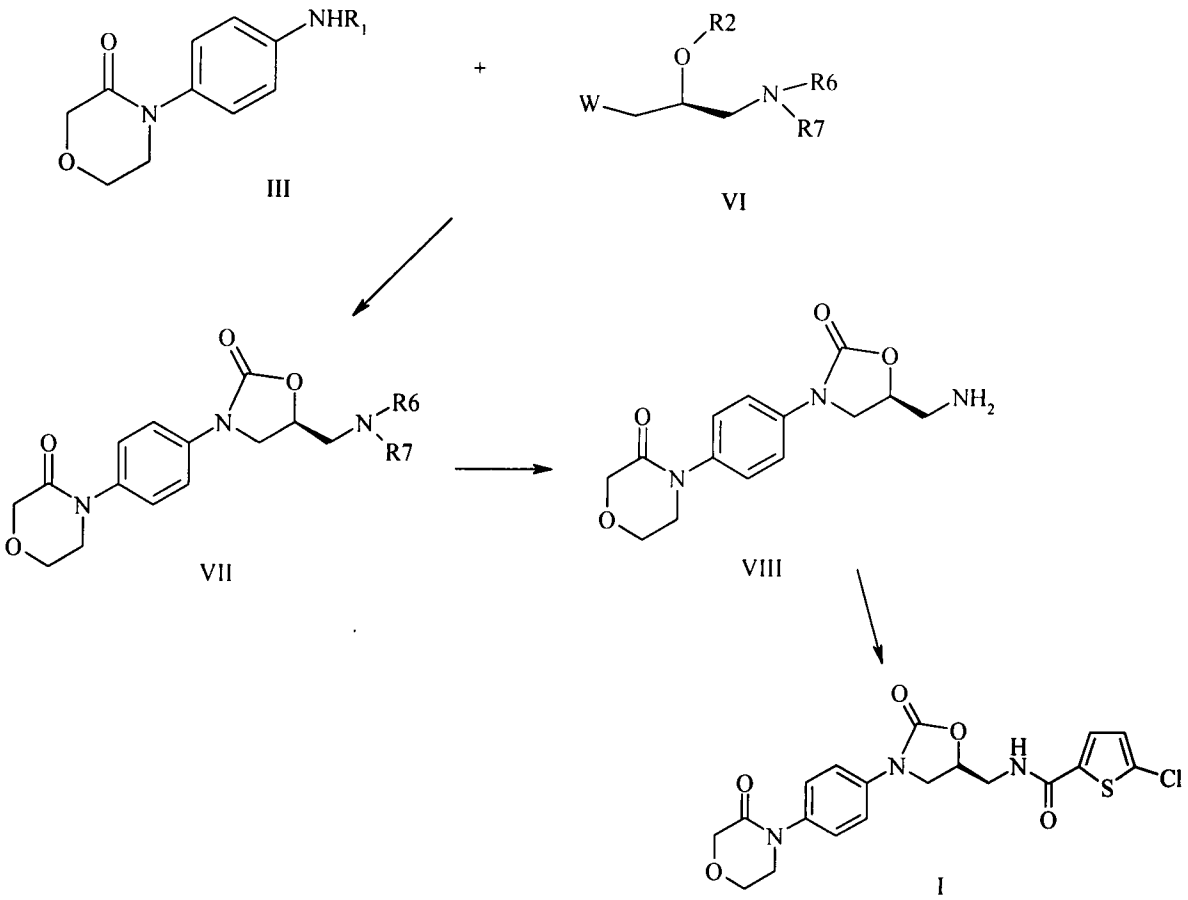

NHR1
O
N
O
III
+
R2
O
W
N
R6
R7
VI
O
O
N
O
N
R6
R7
O
VII
O
O
N
NH2
O
N
O
VIII
O
O
N
H
N
S
Cl
O
O
N
O
I

Fig. 3

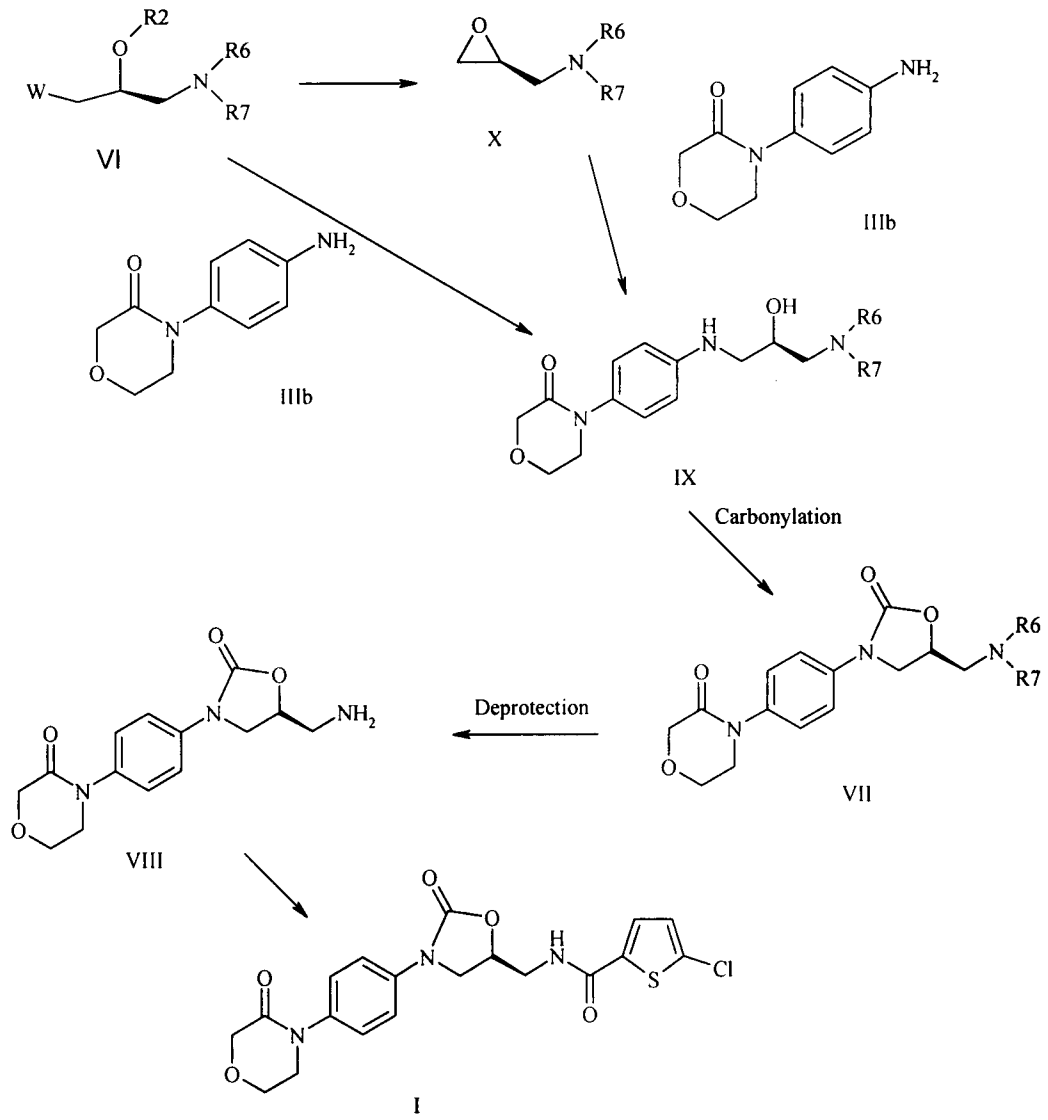


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 11/00670

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/425; A61K 31/535 (2012.01)
USPC - 514/365; 514/237.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/365; 514/237.5 (see search terms below)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/376; 514/417; 544/369; 548/200; 548/202; 548/203; 548/204; 548/205; 548/225; 548/229; 548/234 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: oxazolidinones, process, preparing, 3-oxo-4-morpholinyl, 1,3-oxazolidin-5-yl, 2-thiophenecarboxamide, 4-(4-aminophenyl)-3-morpholinone, epoxide, isocyanate, epibromohydrin, cyclization, phosgene, 2-oxazolidinone, linezolid, synthesis, carbonylation, carbonyldiimidazole. INTERNET search - Google - sam

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 7,585,860 B2 (STRAUB et al.) 08 September 2009 (08.09.2009), col 2, ln 66 - col 3, ln 14; col 3, ln 20-32; col 8, ln 34-35; col 8, ln 44 - col 9, ln 22; col 18, ln 1-54; col 19, ln 5-61; col 20, ln 11-15; col 22, ln 1-38; col 23, ln 1-40; col 44, ln 1-20, 44-59; col 44, ln 66 - col 45, ln 10.	104-105 and 107 --- 1-103, 106 and 108-111
Y	MADHUSUDHAN et al., A Novel and Short Convergent Approach for N-Aryl-5-aminomethyl- -2-oxazolidinone Derivatives Linezolid and DUP-721, Ind J Chem., 2005, 44B, pp 1236-1238. pg 1237, Scheme 1; pg 1238, col 1, para 4 - pg 1238, col 2, para 1.	1-103, 106 and 108-111
Y	CIACCIO, Diastereospecific Synthesis of an Epoxide, J Chem Ed 72(11), pp 1037-1039, 1995, pg 1037, col 2, para 2. Downloaded from: http://courses.chem.psu.edu/chem431/400Expts/EX478.pdf	19-24, 40-45, 87-88, 91, 98 and 109
Y	OILA et al., Synthesis of a novel carboxy functionalized PyOX-ligand, Tetrahedron Letters 46, pp 967-969, 2005, pg 967, col 2, para 1; pg 968, Scheme 1. Downloaded from: http://lib.tkk.fi/Diss/2008/isbn9789512289608/article1.pdf	46-83, 85-86, 94-95, 99-102 and 111

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2012 (10.03.2012)	26 MAR 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)