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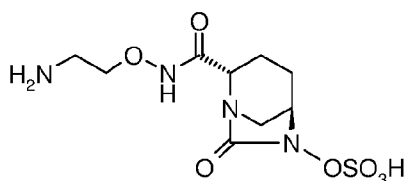
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(54) Title: A PROCESS FOR PREPARATION OF (2S, 5R)-N-(2-AMINO ETHOXY)-6-(SULFOOXY)-7-OXO-1,6- DIAZABICYCLO [3.2.1] OCTANE-2-CARBOXAMIDE



Formula (I)

(57) Abstract: A process for preparation of (2S,5R)-N-(2-aminoethoxy)-6-(sulfoxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide is disclosed. Formula (I)

A PROCESS FOR PREPARATION OF (2*S*, 5*R*)-*N*-(2-AMINO ETHOXY)-6-(SULFOOXY)-7-OXO-1,6-DIAZABICYCLO [3.2.1] OCTANE-2-CARBOXAMIDE

RELATED PATENT APPLICATIONS

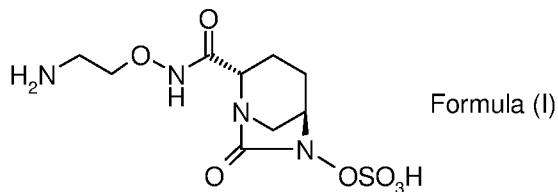
This application claims priority to Indian Patent Application No. 287/MUM/2015 filed on January 28, 2015, the disclosures of which are incorporated herein by reference in its entirety as if fully rewritten herein.

FIELD OF THE INVENTION

The invention relates to a process for preparation of (2*S*, 5*R*)-*N*-(2-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide.

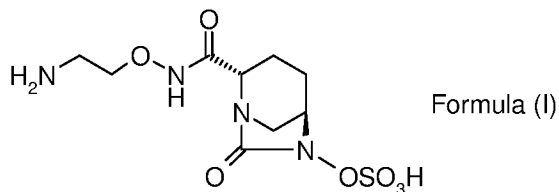
BACKGROUND OF INVENTION

A compound of Formula (I), chemically known as (2*S*, 5*R*)-*N*-(2-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide has antibacterial properties and is disclosed in PCT International Patent Application No. PCT/IB2013/053092, PCT/JP2013/064971 and PCT/IB2012/002675. The present invention discloses a process for preparation of a compound of Formula (I).

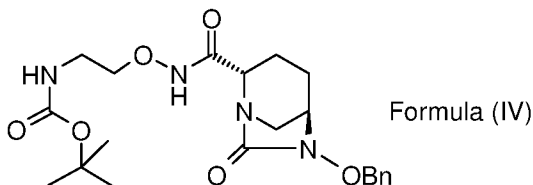
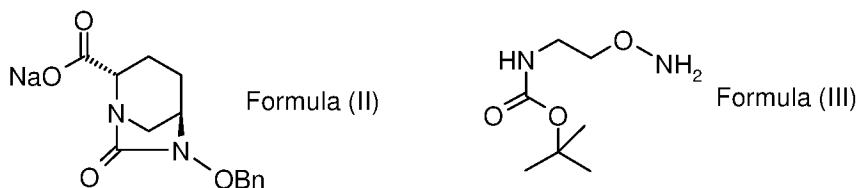


SUMMARY OF THE INVENTION

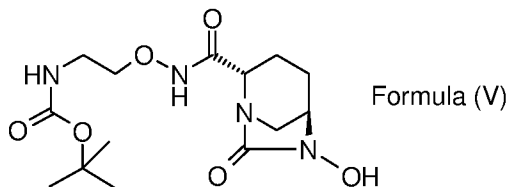
In one general aspect, there is provided a process for preparation of a compound of Formula (I), comprising:



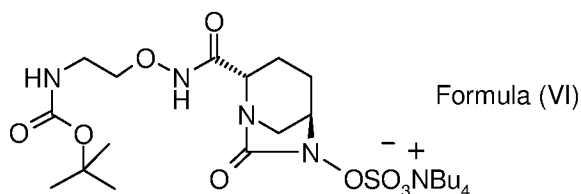
(a) reacting a compound of Formula (II) with a compound of Formula (III) to obtain a compound of Formula (IV);



(b) hydrogenolysis of a compound of Formula (IV) to obtain a compound of Formula (V);



(c) converting a compound of Formula (V) to a compound of Formula (VI); and



(d) converting a compound of Formula (VI) to a compound of Formula (I).

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the following description including claims.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows an X-ray powder diffraction pattern of a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made to the exemplary embodiments, and specific language will be used herein to describe the same. It should nevertheless be understood that no limitation of the scope of the invention is thereby intended. Alterations and further modifications of the inventive features illustrated herein, which would occur to one skilled in the relevant art and having possession of this disclosure, are to be considered within the scope of the invention. It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the content clearly dictates otherwise. All references including patents, patent applications, and literature cited in the specification are expressly incorporated herein by reference in their entirety.

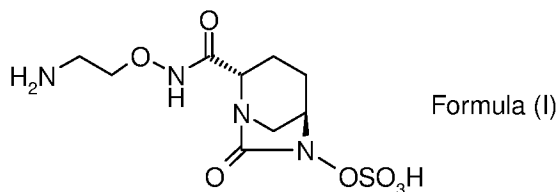
The term “OBn” as used herein refers to benzyloxy.

The term “EDC” as used herein refers to 1-ethyl-3-(3-dimethylamino propyl)carbodiimide.

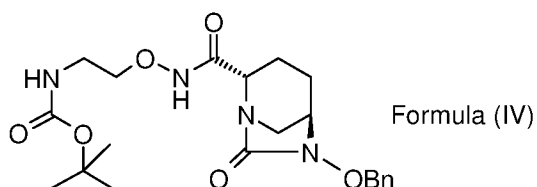
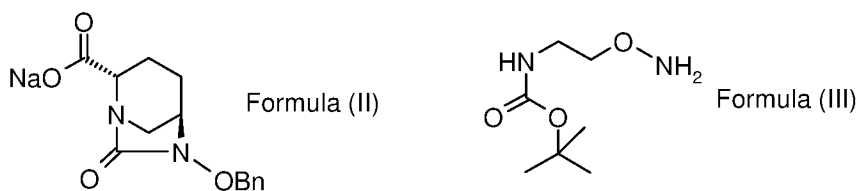
The term “HOBt” as used herein refers to 1-hydroxybenzotriazole.

The term “TBAA” as used herein refers to tetrabutylammonium acetate

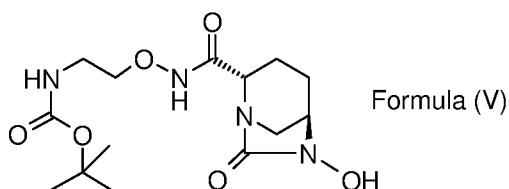
In one general aspect, there is provided a process for preparation of a compound of Formula (I), comprising:



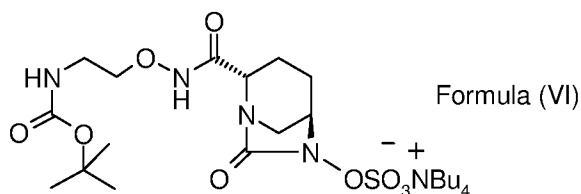
(a) reacting a compound of Formula (II) with a compound of Formula (III) to obtain a compound of Formula (IV);



(d) hydrogenolysis of a compound of Formula (IV) to obtain a compound of Formula (V);



(e) converting a compound of Formula (V) to a compound of Formula (VI); and



(d) converting a compound of Formula (VI) to a compound of Formula (I).

In some embodiments, compound of Formula (I) is prepared by using a general procedure described in Scheme 1. Typically, a compound of Formula (I) is prepared from sodium salt of 6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (II). The sodium salt of 6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxylic acid (II) is reacted with a compound of Formula (III) in presence of a coupling agent and a suitable solvent at a temperature ranging from about 15°C to about 60°C for about 1 hour to about 24 hours to provide an intermediate compound of Formula (IV). Typical, non-limiting examples of coupling agent include EDC hydrochloride, dicyclohexylcarbodiimide, diisopropylcarbodiimide (DIC), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumtetrafluoroborate (TBTU), O-(7-bzabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-(6-chlorobenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HCTU), O-(3,4-dihydro-4-oxo-1,2,3-benzotriazine-3-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TDBTU), 3-(diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT), carbonyldiimidazole (CDI), pivalyl chloride, HOBt and the like. Typical, non-limiting examples of suitable solvents include water, N,N-dimethylformamide, N,N - dimethylacetamide, 1,4 dioxane or a mixture thereof. In some embodiments, sodium salt of 6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxylic acid (II) is reacted with a compound of Formula (III) in presence of EDC hydrochloride and HOBt at a temperature ranging from 15°C to 35°C for about 10 to 20 hours to provide an intermediate compound of Formula (IV).

The compound of Formula (IV) is subjected for hydrogenolysis using hydrogen source in presence of a transition metal catalyst and a suitable solvent at a temperature ranging from about 25°C to about 60°C for about 1 hour to about 14 hours to provide a compound of Formula (V). Typical, non-

limiting examples of hydrogen source include hydrogen gas, ammonium formate, cyclohexene, lithium – liquid ammonia, ammonia – *tert*-butanol, sodium – liquid ammonia – *tert*-butanol, triethylsilyl hydride and the like. Typical, non-limiting examples of transition metal catalyst include 5% palladium on carbon, 10% palladium on carbon, 20% palladium hydroxide on carbon, Raney-Nickel and the like. Typical, non-limiting examples of suitable solvents include methanol, ethanol, dichloromethane, *N,N*-dimethylformamide or a mixture thereof. In some embodiments, compound of Formula (IV) is treated with 10% palladium on carbon and hydrogen gas at a temperature ranging from 25°C to 35°C for about 2 to 8 hours to provide a compound of Formula (V).

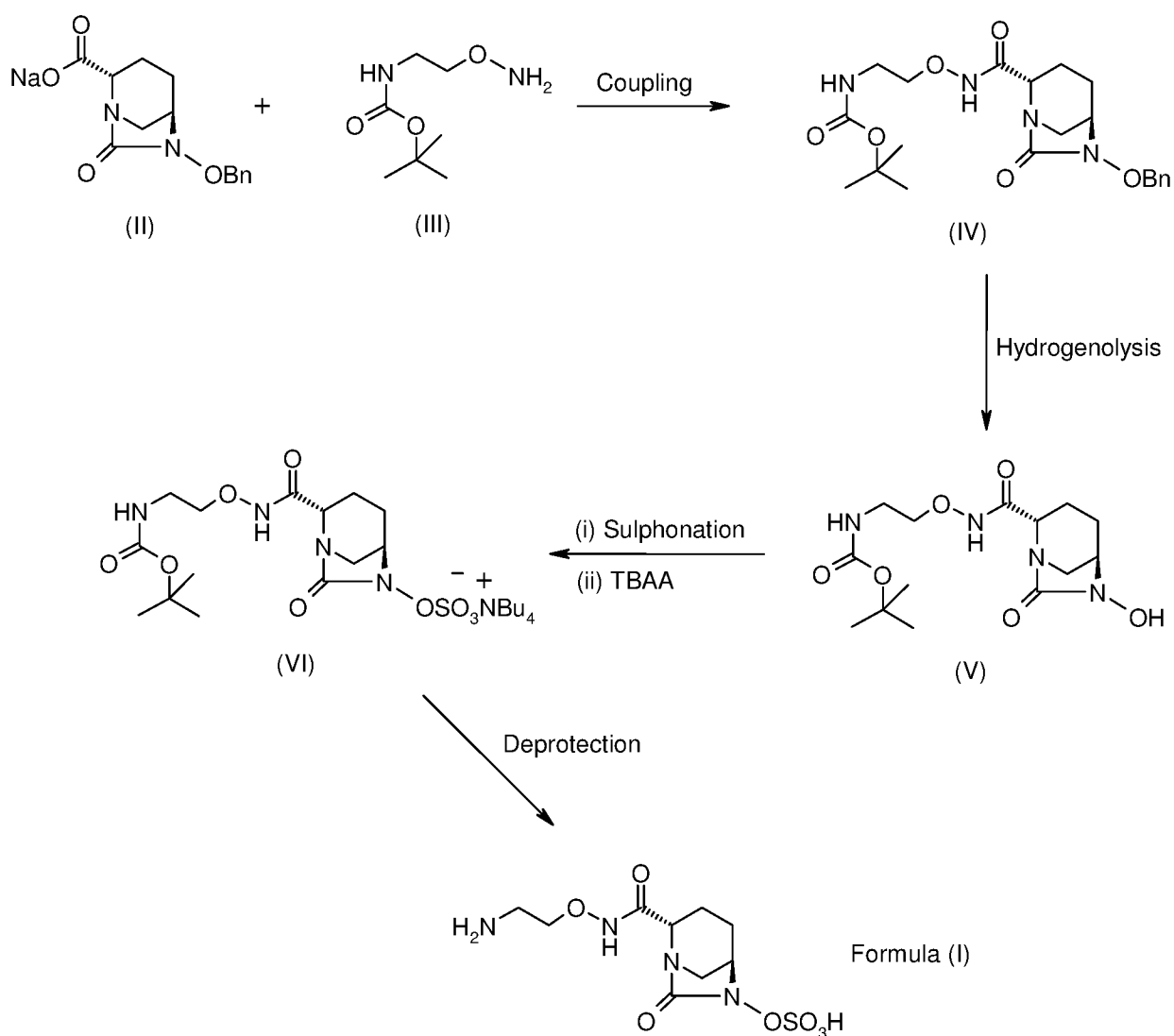
The compound of Formula (V) is sulfonated by reacting with a suitable sulfonating reagent in a suitable solvent at a temperature ranging from about 5°C to about 80°C for about 1 hour to 24 hours. Typical, non-limiting examples of sulfonating reagent include sulfur trioxide pyridine complex, sulfur trioxide trimethylamine complex, sulfur trioxide triethylamine complex, sulfur trioxide *N,N*-dimethylaniline complex, sulfur trioxide 2-methylpyridine complex, sulfur trioxide dioxane complex, sulfur trioxide thioxane complex, sulfur trioxide dimethyl sulfide complex, sulfur trioxide dimethylsulfoxide complex, or sulfur trioxide *N,N*-dimethylformamide complex. Typical, non-limiting examples of suitable solvents include dichloromethane, pyridine or *N,N*-dimethylformamide. In some embodiments, compound of Formula (V) is reacted with sulfur trioxide dimethylformamide complex at a temperature ranging from 5°C to 35°C for about 1 to 4 hours to provide sulfonic acid compound. The obtained sulfonic acid compound is treated with tetrabutylammonium acetate to provide tetrabutylammonium salt of sulfonic acid compound of Formula (VI).

The compound according to the invention is finally isolated as zwitterions, by treating intermediate compound of Formula (VI) with trifluoroacetic acid in a suitable solvent at a temperature ranging from -15°C to 40°C for about 0.5 to about 14 hour. Typical, non-limiting examples of suitable solvents include dichloromethane, chloroform or acetonitrile. In some embodiments, compound of Formula (VII) is treated with trifluoroacetic acid in presence of dichloromethane at a temperature ranging from -15°C to -5°C for about 1 to 4 hour to provide a compound of Formula (I).

In some embodiments, the obtained compound of Formula (I) is converted to corresponding salts. In some embodiments, compound of Formula (I) is dissolved in suitable solvent such as 10%

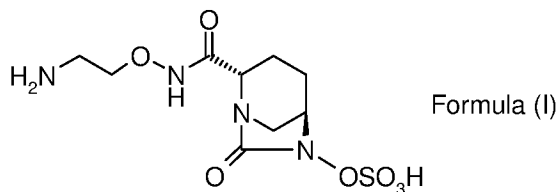
tetrahydrofuran: water mixture and is passed through the column packed with Dowex 50WX8 200 Na⁺ resin or passing through Indion 225 Na resin to provide sodium salt of compound of Formula (I). In some embodiments, compound of Formula (I) is dissolved in suitable solvent such as acetone, tetrahydrofuran, ethanol, isopropanol or acetonitrile and thereby treated with sodium ethylhexanoate or potassium ethylhexanoate to provide sodium or potassium salt of compound of Formula (I).

In some embodiments, a compound of Formula (I) is prepared using a process described in Scheme 1.

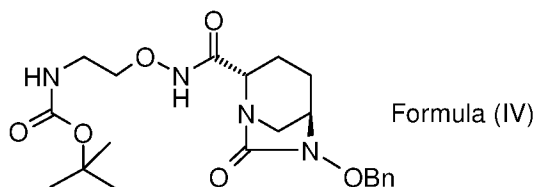
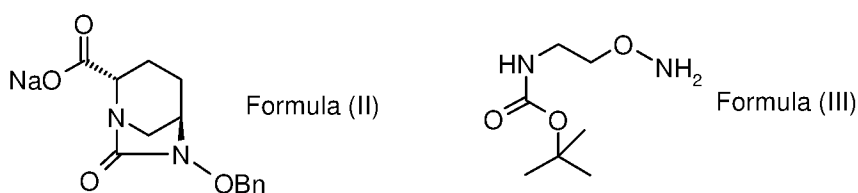


Scheme 1

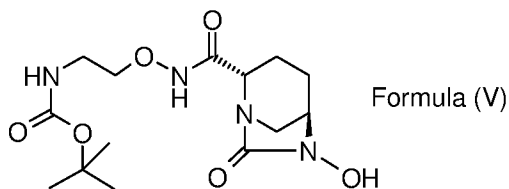
In some embodiments, there is provided a process for preparation of a compound of Formula (I), comprising:



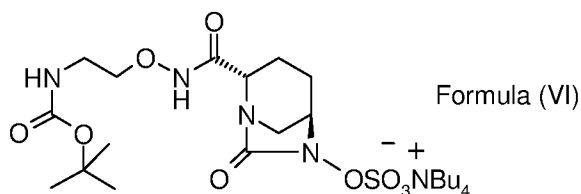
(a) reacting a compound of Formula (II) with a compound of Formula (III) in presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride to obtain a compound of Formula (IV);



(b) hydrogenolysis of a compound of Formula (IV) in presence of palladium on carbon and hydrogen gas to obtain a compound of Formula (V);



(c) sulphonating a compound of Formula (V) in presence of sulphur trioxide dimethylformamide complex, followed by treatment with tetrabutylammonium acetate to obtain a compound of Formula (VI); and



Formula (VI)

(d) treating a compound of Formula (VI) with trifluoroacetic acid to obtain a compound of Formula (I).

In some embodiments, there is provided a compound of Formula (I) in crystalline form.

In some embodiments, there is provided a compound of Formula (I) in a crystalline form and having an X-ray powder diffraction pattern comprising a peak selected from the group consisting of 8.78 (± 0.2), 9.48 (± 0.2), 10.65 (± 0.2), 12.04 (± 0.2), 14.81 (± 0.2), 15.63 (± 0.2), 16.09 (± 0.2), 16.68 (± 0.2), 17.17 (± 0.2), 17.48 (± 0.2), 17.66 (± 0.2), 18.33(± 0.2), 19.03 (± 0.2), 20.38 (± 0.2), 21.16 (± 0.2), 21.91 (± 0.2), 22.51 (± 0.2), 26.01 (± 0.2), 26.55(± 0.2), 29.45(± 0.2), 29.84 (± 0.2) degrees 2 theta

In some embodiments, there is provided a compound of Formula (I) in a crystalline form and having an X-ray powder diffraction pattern comprising a peak selected from the group consisting of 8.78 (± 0.2), 9.48 (± 0.2), 10.65 (± 0.2), 12.04 (± 0.2), 14.81 (± 0.2), 15.63 (± 0.2), 16.09 (± 0.2), 16.68 (± 0.2), 17.17 (± 0.2), 17.48 (± 0.2), 17.66 (± 0.2), 18.33(± 0.2), 19.03 (± 0.2), 20.38 (± 0.2), 21.16 (± 0.2) degrees 2 theta.

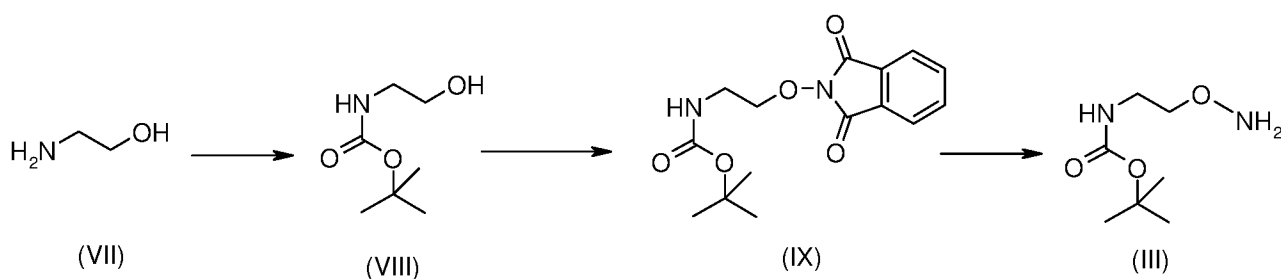
In some embodiments, there is provided a compound of Formula (I) in a crystalline form and having an X-ray powder diffraction pattern comprising a peak selected from the group consisting of 15.63 (± 0.2), 16.09 (± 0.2), 16.68 (± 0.2), 17.48 (± 0.2), 17.66 (± 0.2), 19.02 (± 0.2), 20.38(± 0.2) degrees 2 theta.

In some embodiments, there is provided a compound of Formula (I) in a crystalline form and having an X-ray powder diffraction pattern substantially the same as shown in Figure 1.

In some embodiments, there is provided a compound of Formula (I) having a purity of at least about 94% as determined by HPLC.

In some embodiments, there is provided a pharmaceutical composition comprising a compound of Formula (I) in a crystalline form and having an X-ray powder diffraction pattern substantially the same as shown in Figure 1. In some embodiments, there is provided a pharmaceutical composition comprising a compound of Formula (I) having a purity of at least about 94% as determined by HPLC. In some embodiments, the said pharmaceutical compositions may further comprise one or more pharmaceutically acceptable excipients.

In some embodiments, compound of Formula (III) is prepared using a general procedure described in Scheme 2. Typically, a compound of Formula (III) is prepared from ethanolamine (VII). Ethanolamine (VII) is reacted with a di-*tert*-butyl dicarbonate in presence of a suitable base and a suitable reaction solvent to obtain a compound of Formula (VIII). Typical, non-limiting examples of suitable base include triethylamine, pyridine or *N*-ethyldiisopropylamine. Typical, non-limiting examples of suitable solvents include dichloromethane, chloroform, dichloroethane or ethyl acetate. The compound of Formula (VIII) is further reacted with *N*-hydroxyphthalimide; in presence of diisopropyl azodicarboxylate, triphenylphosphine to obtain a compound of Formula (IX). The compound of Formula (IX) is finally treated with hydrazine hydrate in presence of dichloromethane to obtain a compound of Formula (III).



Scheme 2

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the

invention. For example, those skilled in the art will recognize that the invention may be practiced using a variety of different compounds within the described generic descriptions.

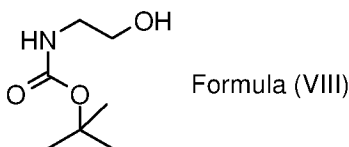
EXAMPLES

The following examples illustrate the embodiments of the invention that are presently best known. However, it is to be understood that the following are only exemplary or illustrative of the application of the principles of the present invention. Numerous modifications and alternative compositions, methods and systems may be devised by those skilled in the art without departing from the spirit and scope of the present invention. The appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity, the following examples provide further detail in connection with what are presently deemed to be the most practical and preferred embodiments of the invention.

Example 1

Synthesis of *tert*-butyl-[2-(aminooxy) ethyl]carbamate (III)

Step 1: Preparation of *tert*-butyl-2-hydroxy ethylcarbamate (VIII):

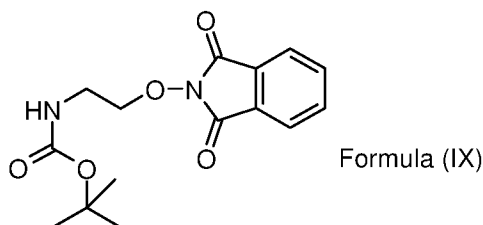


To a stirred solution of ethanolamine (50.0 g, 0.8186 mol) in dichloromethane (1000 ml), was added triethylamine (124 g, 1.228 mol) at 0°C. After 10 minutes, di-*tert*-butyl dicarbonate (VII, 214.15 g, 0.9823 mol) was added drop wise at 0°C under continuous stirring. Then reaction mass was allowed to warm to 25°C and stirred further for 3 hours. After completion of reaction, the resulting reaction mixture was poured into water (250 ml) and the organic layer was separated and dried over anhydrous sodium sulfate. The dried organic layer was concentrated under reduced pressure to obtain 130 g of the titled product as colorless oil in 98% yield.

Analysis:

Mass: 162 (M+1); for Molecular Weight of 161.2 and Molecular Formula of $C_7H_{15}NO_3$.

1H NMR (400MHz, $CDCl_3$): δ 4.92(br s,1H), 3.72-3.68(q,2H), 3.30-3.26(q,2H), 2.33(br s,1H), 1.44(s,9H).

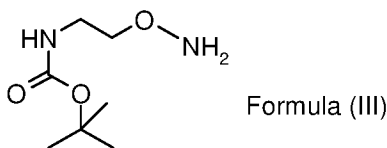
Step 2: Preparation of *N*-Boc-2-(2-aminoethoxy)isoindoline-1,3-dione (IX):

To a stirred solution of *tert*-butyl-2-hydroxy-ethylcarbamate (VIII, 50 g, 0.3106 mol) in tetrahydrofuran (500 ml), was added triphenylphosphine (89.5 g, 0.3416 mol) at 25°C. After stirring for 10 minutes, a solution of *N*-hydroxyphthalimide (50.66 g, 0.3106 mol) in dichloromethane (250 ml) was added to the reaction mass at 25°C over a period of 10 minutes. After stirring for further 10 minutes, diisopropyl azodicarboxylate (69.1 g, 0.3416 mol) was added to the reaction mass in small portions (exothermic reaction was observed up to 34°C). The resulting reaction mass was stirred further at 25°C. After 16 hours, the reaction mass was concentrated under reduced pressure to obtain colorless oily material. The oily residue was diluted with diisopropyl ether (200 ml) and stirred for 30 minutes. The separated solid was filtered under suction. The filtrate was evaporated under reduced pressure and the residue subjected to di-isopropyl ether treatment (200 ml). This procedure was repeated once again. The filtrate was concentrated to obtain a solid product. The obtained solid was washed with diisopropyl ether (50 ml) and dried under reduced pressure. This solid contains small amount of triphenylphosphine oxide, along with the product. This was used as such for the next reaction without further purification.

Analysis:

Mass: 307.2 (M+1); for Molecular Weight of 306.3 and Molecular Formula of $C_{15}H_{18}N_2O_5$;

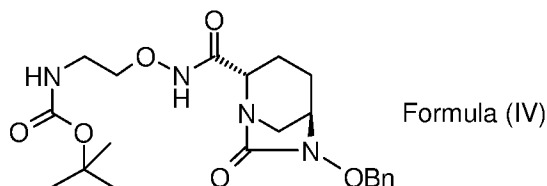
1H NMR of purified material (400MHz, $CDCl_3$): 7.85-7.25 (m,4H), 5.62(br s,1H), 4.26-4.23(t,2H), 3.46-3.42(q,2H), 1.46(s,9H).

Step 3: Preparation of *tert*-butyl-[2-(aminooxy) ethyl]carbamate (III):

To a stirred solution of *N*-Boc-2-(2-aminoethoxy)isoindoline-1,3-dione (IX, 97 g, 0.3167 mol) in dichloromethane (970 ml) was added hydrazine hydrate (31.7 g, 0.6334 mol), at 0°C, drop wise, over a period of 45 minutes and the stirring continued further. After 2 hours, the reaction mass was filtered under suction. Filtrate was washed with water (485 ml), and the organic layer was diluted with an aq. solution of 10% potassium hydrogen sulfate (485 ml) and stirred for 15 minutes. The aqueous layer was separated, neutralized with solid sodium hydrogen carbonate and extracted with dichloromethane (2 × 485 ml). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain colorless oil, this was used as such for further reaction immediately (28g, overall yield of step II and step III was 60%)

Analysis:

Mass: 177.2 (M+1) for Molecular Weight of 176.2 and Molecular Formula of C₇H₁₆N₂O₃.

Example 2**Synthesis of (2*S*,5*R*)-*N*-(2-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (I)****Step 1: Preparation of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(benzyloxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (IV):**

To a clear solution of sodium (2*S*,5*R*)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (II, 42.67 g, 0.143 mol; prepared according to the procedure disclosed in Indian Patent Application No. 699/MUM/2013) in water (426 ml) was added EDC.HCl (67.1 g, 0.349 mol) at 15°C

under stirring. After 10 minutes, a solution of *tert*-butyl-[2-(aminooxy) ethyl]carbamate (III, 28.0g, 0.159 mol; prepared as per the literature procedure depicted in Scheme 2) in dimethylformamide (56 ml) was added drop wise at 10°C under continuous stirring. The temperature of the reaction mass was allowed to warm to 25°C and then HOBt (21.5g, 0.159 mol) was added in small portions over a period of 15 minutes and the resulting mixture was further stirred at room temperature for 16 hours. The reaction was continuously monitored using thin layer chromatography using mixture of acetone and hexane (35:65) as solvent system. After completion of reaction, the resulting mixture was filtered and the residue was washed with water (130 ml). The obtained white residue was suspended in water (130 ml) and the mixture stirred at 50°C for 3 hours. The resulting suspension was filtered, the residue dried under reduced pressure to obtain 51 g of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(benzyloxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (IV) as off white solid in 73% yield.

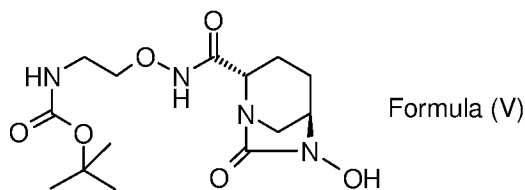
Analysis:

Mass: 433.4 (M-1); for Molecular Weight of 434.5 and Molecular Formula of C₂₁H₃₀N₄O₆;

¹H-NMR (400MHz, CDCl₃): δ 9.32 (br s, 1H), 7.41-7.26(m,5H), 5.41(br s, 1H), 5.06-4.88(dd, 2H), 3.98-3.96(d,1H), 3.91-3.90(m,2H), 3.39(m, 1H), 3.31-3.26(m, 2H), 3.04-3.01(d,1H), 2.77-2.74(d, 1H), 2.33-2.28(m, 1H), 2.03-1.93(m, 2H), 1.67-1.64(m, 1H), 1.44(s, 9H);

Purity as determined by HPLC: 99.4%.

Step 2: Preparation of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(hydroxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (V):



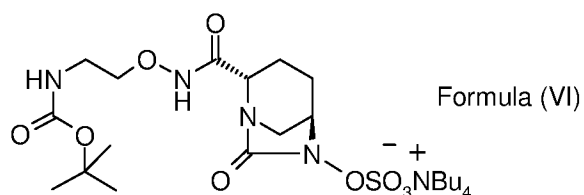
A solution of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(benzyloxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (IV, 38 g, 0.0875 mol) in a mixture of dimethylformamide and dichloromethane (2: 8, 76 ml: 304 ml), containing 10% Pd/C (7.6 g, 50% wet) was hydrogenated at 50 psi hydrogen atmosphere at 25°C for 3 hours. The resulting mixture was filtered through a celite pad. The residue was washed with dichloromethane (75 ml). The solvent from the combined filtrate was evaporated

under reduced pressure to obtain 30 g (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(hydroxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (V) as an oil, which was used as such for the next reaction without further purification.

Analysis:

Mass: 343.3 (M-1) for Molecular Weight of 344.3 and Molecular Formula of C₁₄H₂₄N₄O₆.

Step 3: Preparation of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide,tetrabutyl ammonium salt (VI):



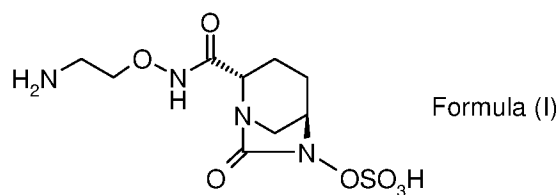
To a stirred solution of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(hydroxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (V, 30.0 g, 0.0875 mol) in dimethylformamide (150 ml) was added sulphur trioxide dimethylformamide complex (16.06 g, 0.105 mol) in one portion, at 10°C. The reaction mass was stirred at the same temperature for 30 minutes and then allowed to warm to room temperature. After 2 hours, a solution of tetrabutylammonium acetate (31.6 g, 0.105 mol) in water (95 ml) was slowly added to the reaction mixture and stirred for another 2 hours. The solvent from the reaction mixture was evaporated under reduced pressure to obtain an oily residue. The oily mass was co-evaporated with xylene (2 × 60 ml) to obtain thick mass. This mass was partitioned between 1: 1 mixture of dichloromethane (300 ml) and water (300 ml). The organic layer was separated and the aqueous layer re-extracted with dichloromethane (150 ml). The combined organic extracts were washed with water (3 × 150 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3 × 60 ml). Each time the ether layer was decanted and the residue was finally concentrated under reduced pressure to obtain the sticky mass. The so obtained material was purified by column chromatography over silica gel using mixture of methanol and dichloromethane as elution solvent. The solvent from the combined fractions was evaporated to obtain 47.5 g of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide,tetrabutyl ammonium salt as white foam in 70% yield.

Analysis:

Mass: 423.4 (M-1) as free sulphonic acid; for Molecular Weight of 665.9 and Molecular Formula of $C_{30}H_{59}N_5O_9S$;

1H - NMR (400MHz, $CDCl_3$): δ 9.52(br s, 1H), 5.53(br s, 1H), 4.33(s, 1H), 3.95-3.92(m, 3H), 3.37-3.27(m, 11H), 2.87-2.84(d, 1H), 2.35-2.30(m, 1H), 2.17(m, 1H), 1.96-1.88(m, 2H), 1.74-1.60(m, 8H), 1.47-1.40(m, 17H), 1.02-0.98(m, 12H).

Step 4: Preparation of (2*S*,5*R*)-*N*-(2-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide (I):



To a stirred solution of (2*S*,5*R*)-*N*-(2-Boc-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide, tetrabutyl ammonium salt (VI, 17 g, 0.0225 mol) in dichloromethane (85 ml) was added trifluoroacetic acid (85 ml) drop wise at $-10^\circ C$ over a period of 45 minutes. The resulting mass was further stirred at same temperature for 1 hour. The resulting reaction mixture was poured into cyclohexane (850 ml), stirred well for 30 minutes and the separated oily layer was collected. This procedure was repeated one more time and finally the separated oily layer was added to *tert*-butyl methyl ether (170 ml) under vigorous stirring at $25^\circ C$. The ether layer was removed by decantation from the precipitated solid. This procedure was repeated twice again with *tert*-butyl methyl ether (2×170 ml). The solid thus obtained was stirred with fresh dichloromethane (170 ml) for 30 minutes and filtered. The residual solid was dried at $45^\circ C$ under reduced pressure to yield 7.3g of the titled compound in crude form. The obtained solid was further dissolved in water, (7.3 ml) and to this solution was added basic resin (Amberlyst A-26 –OH ion exchange resin, 4.4 g) under stirring. After 0.5 hour, the resin was filtered and to the filtrate isopropanol (51 ml) was added slowly at $25^\circ C$. The solution was further stirred for 12 hours. The separated solid was filtered and washed with additional isopropanol (7.5 ml) and dried under reduced pressure to obtain 4.3 g of (2*S*,5*R*)-*N*-(2-aminoethoxy)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxamide as off-white solid in 52 % yield.

Analysis:

Mass: 323.1 (M-1); for Molecular Weight of 324.31 and Molecular Formula of $C_9H_{16}N_4O_7S$;

1H -NMR (400MHz, D_2O): δ 4.07-4.06(d, 1H), 4.05-4.03(t, 2H), 3.96-3.94(d, 1H), 3.20(br s, 1H), 3.16-3.13(t, 2H), 3.02-2.99(d, 1H), 2.04-1.68(m, 4H);

Purity as determined by HPLC: 94.88%.

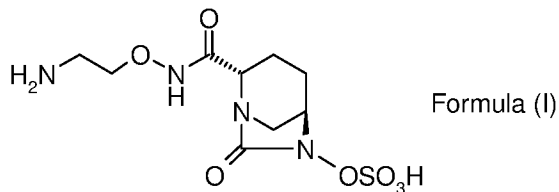
X-ray powder diffraction pattern (2 Theta Values): 8.78 (± 0.2), 9.48 (± 0.2), 10.65 (± 0.2), 12.04 (± 0.2), 14.81 (± 0.2), 15.63 (± 0.2), 16.09 (± 0.2), 16.68 (± 0.2), 17.17 (± 0.2), 17.48 (± 0.2), 17.66 (± 0.2), 18.33(± 0.2), 19.03 (± 0.2), 20.38 (± 0.2), 21.16 (± 0.2), 21.91 (± 0.2), 22.51 (± 0.2), 26.01 (± 0.2), 26.55(± 0.2), 29.45(± 0.2) and 29.84 (± 0.2)

Typical X-ray analysis was performed as follows. Pass the test substance through sieve #100 BSS or gently grind it with a mortar and pestle. Place the test substance uniformly on a sample holder having cavity surface on one side, press the sample and cut into thin uniform film using a glass slide in such a way that the surface of the sample should be smooth and even. Record the X-ray diffractogram using the following instrument parameters.

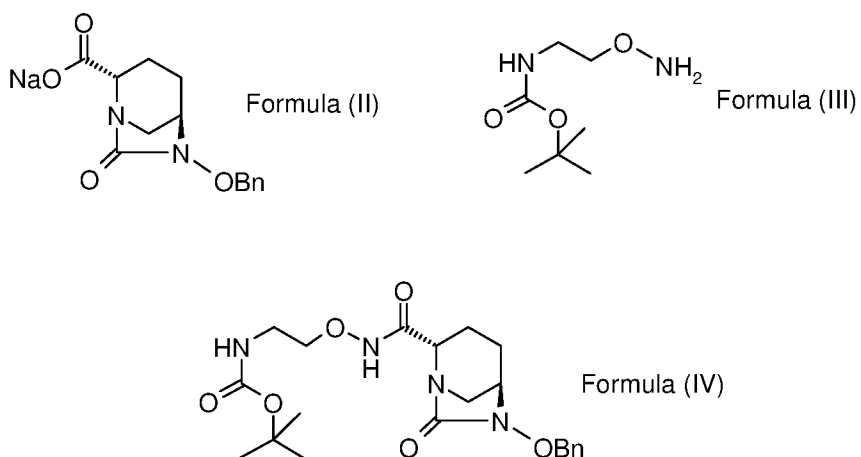
Instrument	: X-Ray Diffractometer (PANalytical, Model X'Pert Pro MPD)
Target source	: CuK(α)
Antiscattering slit (Incident beam)	: 1°
Programmable Divergent slit	: 10 mm (fixed)
Anti-scattering slit (Diffracted beam)	: 5.5 mm
Step width	: 0.02°
Voltage	: 40 kV
Current	: 40 mA
Time per step	: 30 seconds
Scan range	: 3 to 40°

CLAIMS

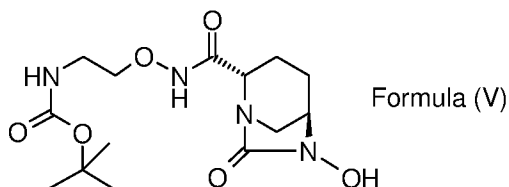
1. A process for preparation of a compound of Formula (I), comprising:



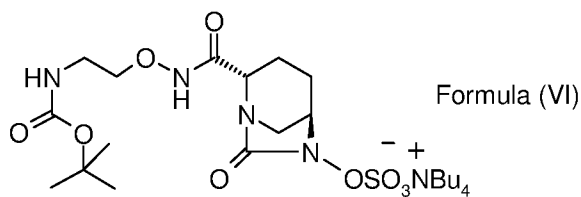
- (a) reacting a compound of Formula (II) with a compound of Formula (III) to obtain a compound of Formula (IV);



- (b) hydrogenolysis of a compound of Formula (IV) to obtain a compound of Formula (V);



- (c) converting a compound of Formula (V) to a compound of Formula (VI); and



(d) converting a compound of Formula (VI) to a compound of Formula (I).

2. A process according to Claim 1, wherein a compound of Formula (IV) is obtained by reacting a compound of Formula (II) with a compound of Formula (III) in presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

3. A process according to Claim 1, wherein a compound of Formula (V) is obtained by carrying out hydrogenolysis of a compound of Formula (IV) in presence of a transition metal catalyst and a hydrogen source.

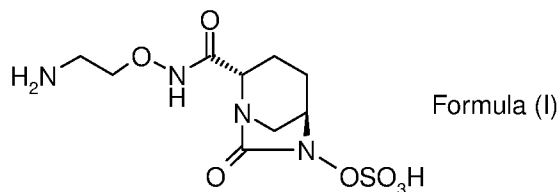
4. A process according to Claim 3, wherein the transition metal catalyst is palladium on carbon and hydrogen source is hydrogen gas.

5. A process according to Claim 1, wherein a compound of Formula (VI) is obtained by sulphonating a compound of Formula (V), followed by the treatment with tetrabutylammonium acetate.

6. A process according to Claim 5, wherein sulphonation is carried out in presence of sulphur trioxide dimethylformamide complex.

7. A process according to Claim 1, wherein a compound of Formula (VI) is converted to a compound of Formula (I) by treating a compound of Formula (VI) with trifluoroacetic acid.

8. A compound of Formula (I) in a crystalline form.



9. A compound of Formula (I) according to Claim 8, having an X-ray powder diffraction pattern comprising a peak selected from the group consisting of 8.78 ($\pm$ 0.2), 9.48 ($\pm$ 0.2), 10.65 ($\pm$ 0.2), 12.04 ($\pm$ 0.2), 14.81 ($\pm$ 0.2), 15.63 ($\pm$ 0.2), 16.09 ($\pm$ 0.2), 16.68 ($\pm$ 0.2), 17.17 ($\pm$ 0.2), 17.48 ($\pm$ 0.2).

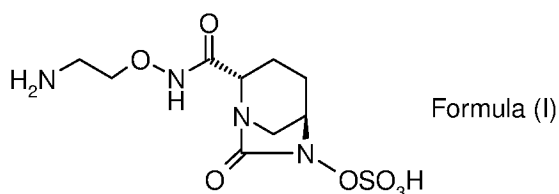
0.2), 17.66 (± 0.2), 18.33(± 0.2), 19.03 (± 0.2), 20.38 (± 0.2), 21.16 (± 0.2), 21.91 (± 0.2), 22.51 (± 0.2), 26.01 (± 0.2), 26.55(± 0.2), 29.45(± 0.2), and 29.84 (± 0.2) degrees 2 theta.

10. A compound of Formula (I) according to Claim 8, having an X-ray powder diffraction pattern comprising a peak selected from the group consisting of 8.78 (± 0.2), 9.48 (± 0.2), 10.65 (± 0.2), 12.04 (± 0.2), 14.81 (± 0.2), 15.63 (± 0.2), 16.09 (± 0.2), 16.68 (± 0.2), 17.17 (± 0.2), 17.48 (± 0.2), 17.66 (± 0.2), 18.33(± 0.2), 19.03 (± 0.2), 20.38 (± 0.2), and 21.16 degrees 2 theta.

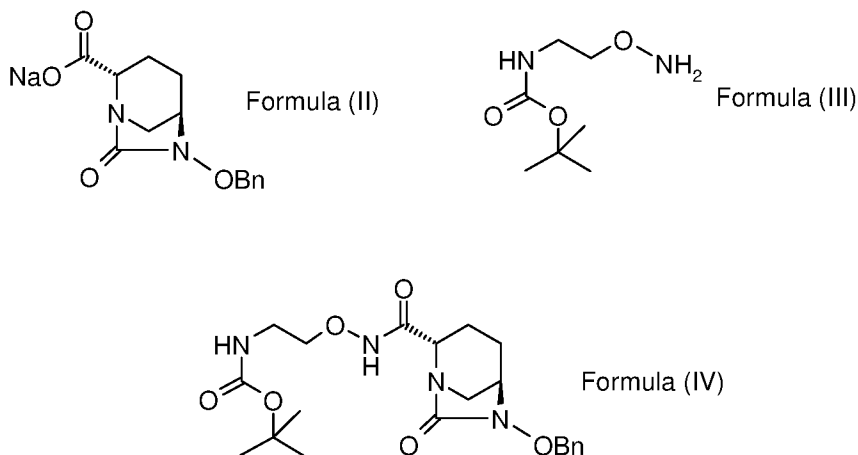
11. A compound of Formula (I) having purity of at least about 94% as determined by HPLC.

12. A pharmaceutical composition comprising a compound of Formula (I) according to any one of the Claims 8 to 11.

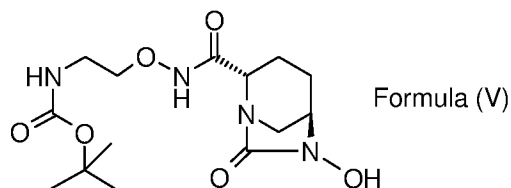
13. A process for preparation of a compound of Formula (I), comprising:



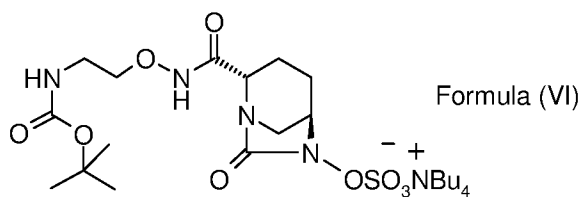
(a) reacting a compound of Formula (II) with a compound of Formula (III) in presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride to obtain a compound of Formula (IV);



(b) hydrogenolysis of a compound of Formula (IV) in presence of palladium on carbon and hydrogen gas to obtain a compound of Formula (V);



(c) sulphonating a compound of Formula (V) in presence of sulphur trioxide dimethylformamide complex, followed by treatment with tetrabutylammonium acetate to obtain a compound of Formula (VI); and



(d) treating a compound of Formula (VI) with trifluoroacetic acid to obtain a compound of Formula (I).

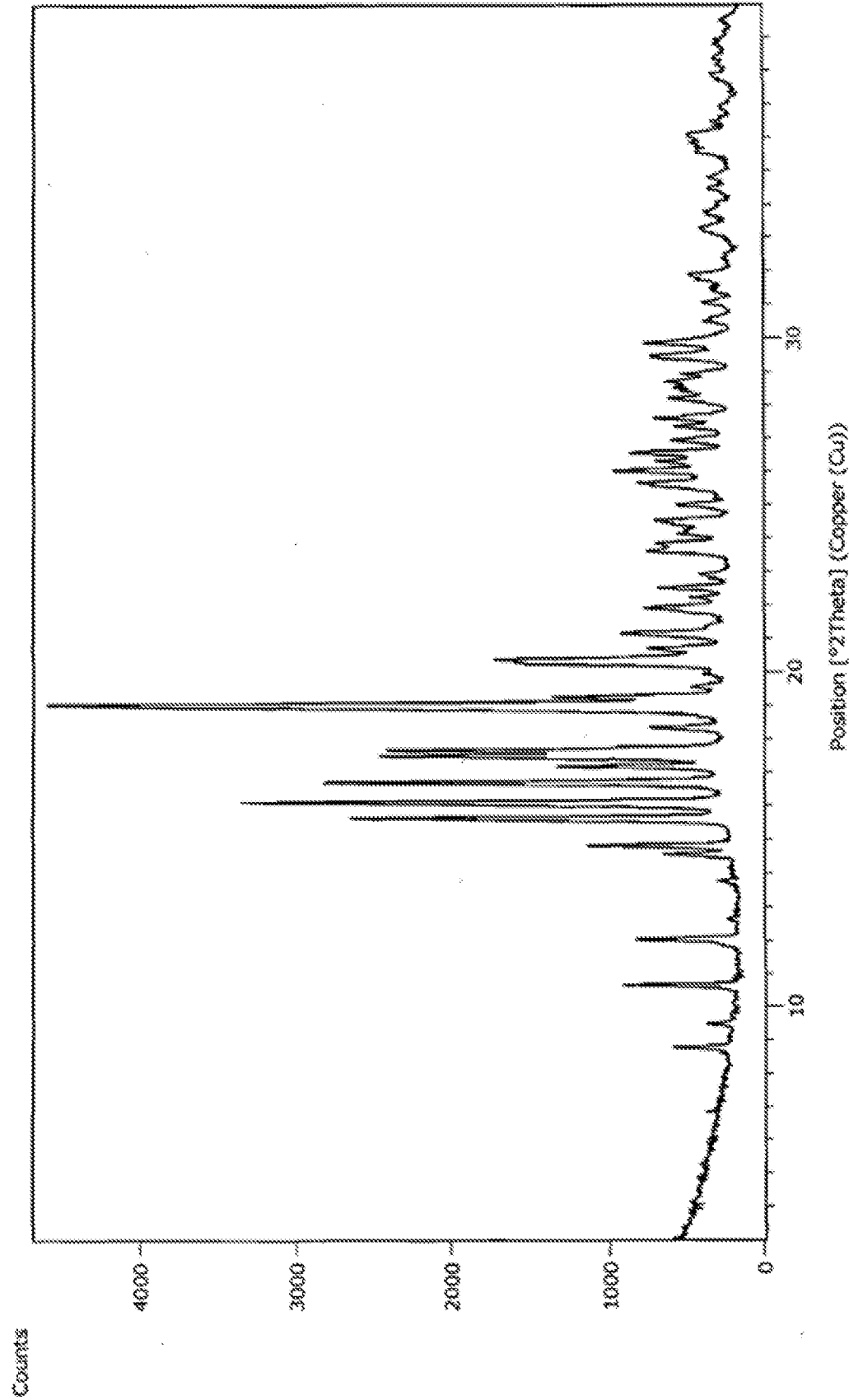


Figure 1

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2016/050264

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/08

ADD.

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)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/180197 A1 (MEIJI SEIKA PHARMA CO LTD [JP]) 5 December 2013 (2013-12-05) paragraph [0446] - paragraph [0455] -----	1-7,13
X	CA 2 874 279 A1 (MEIJI SEIKA PHARMA CO LTD [JP]) 5 December 2013 (2013-12-05) example 59 -----	1-7,13
A	WO 2014/091268 A1 (NAEJA PHARMACEUTICAL INC [CA]) 19 June 2014 (2014-06-19) example 9 -----	1-7,13
X	WO 2014/135930 A1 (WOCKHARDT LTD [IN]) 12 September 2014 (2014-09-12) formula (II) -----	1-7,13



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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

8 March 2016

Date of mailing of the international search report

14/06/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Baston, Eckhard

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/050264

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7, 13

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7, 13

Process for the preparation of a compound of formula (I)

2. claims: 8-12

Crystalline form of a compound of formula (I)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/050264

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2013180197	A1	05-12-2013	AR	091222 A1	21-01-2015
			AU	2013268415 A1	04-12-2014
			CA	2874279 A1	05-12-2013
			CL	2014003035 A1	30-01-2015
			CN	104334559 A	04-02-2015
			CO	7151513 A2	29-12-2014
			EP	2857401 A1	08-04-2015
			HK	1206746 A1	15-01-2016
			HK	1208862 A1	18-03-2016
			JP	W02013180197 A1	21-01-2016
			KR	20150015523 A	10-02-2015
			PH	12014502683 A1	26-01-2015
			TW	201408668 A	01-03-2014
			US	2015141401 A1	21-05-2015
			US	2016024090 A1	28-01-2016
			WO	2013180197 A1	05-12-2013

CA 2874279	A1	05-12-2013	AR	091222 A1	21-01-2015
			AU	2013268415 A1	04-12-2014
			CA	2874279 A1	05-12-2013
			CL	2014003035 A1	30-01-2015
			CN	104334559 A	04-02-2015
			CO	7151513 A2	29-12-2014
			EP	2857401 A1	08-04-2015
			HK	1206746 A1	15-01-2016
			HK	1208862 A1	18-03-2016
			JP	W02013180197 A1	21-01-2016
			KR	20150015523 A	10-02-2015
			PH	12014502683 A1	26-01-2015
			TW	201408668 A	01-03-2014
			US	2015141401 A1	21-05-2015
			US	2016024090 A1	28-01-2016
			WO	2013180197 A1	05-12-2013

WO 2014091268	A1	19-06-2014	AU	2012396338 A1	16-07-2015
			CA	2893804 A1	19-06-2014
			CR	20150359 A	20-08-2015
			EA	201500544 A1	30-12-2015
			EP	2931723 A1	21-10-2015
			JP	2016503000 A	01-02-2016
			KR	20150093809 A	18-08-2015
			PH	12015501303 A1	24-08-2015
			SG	11201504540T A	30-07-2015
			WO	2014091268 A1	19-06-2014

WO 2014135930	A1	12-09-2014	AU	2013380573 A1	10-09-2015
			WO	2014135930 A1	12-09-2014
