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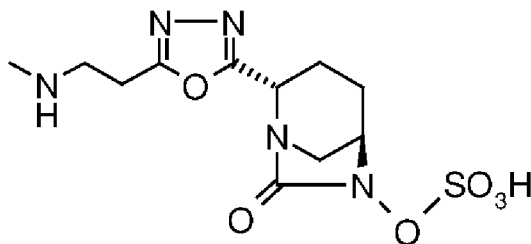
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(54) Title: A PROCESS FOR PREPARATION OF TRANS-SULFURIC ACID MONO-{2-[5-(2-METHYLAMINO-ETHYL)-[1,3,4]-OXADIAZOL-2-YL]-7-OXO-1,6-DIAZA-BICYCLO [3.2.1]OCT-6-YL} ESTER



Formula (I)

(57) Abstract: A process for preparation of compound of Formula (I) is disclosed.

**A PROCESS FOR PREPARATION OF *TRANS*-SULFURIC ACID
MONO-{2-[5-(2-METHYLAMINO-ETHYL)-[1,3,4]-OXADIAZOL-2-
YL]-7-OXO-1,6-DIAZA-BICYCLO [3.2.1]OCT-6-YL} ESTER**

RELATED PATENT APPLICATIONS

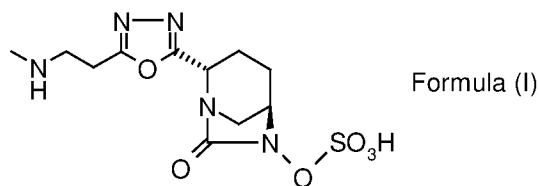
This application claims the priority to the Indian Patent Application No. 1636/MUM/2014 filed on May 14, 2014, the disclosures of which are incorporated herein by reference in its entirety as if fully rewritten herein.

FIELD OF THE INVENTION

The invention relates to a process for preparation of *trans*-sulfuric acid mono-{2-[5-(2-methylamino-ethyl)-[1,3,4]-oxadiazol-2-yl]-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl} ester.

BACKGROUND OF THE INVENTION

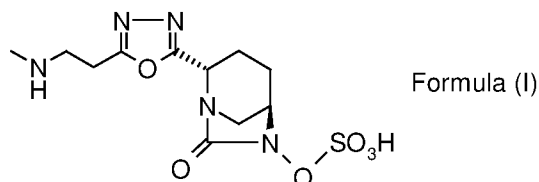
Several 1,6-diazabicyclo[3.2.1]octan-7-one derivatives have been described as antibacterial agents in PCT International Patent Application No. PCT/IB2012/054296. A compound of Formula (I), chemically known as *trans*-sulfuric acid mono-{2-[5-(2-methylamino-ethyl)-[1,3,4]-oxadiazol-2-yl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl} ester has antibacterial properties and is also disclosed in PCT International Patent Application No. PCT/US2013/034562. The present invention discloses a process for preparation of a compound of Formula (I).



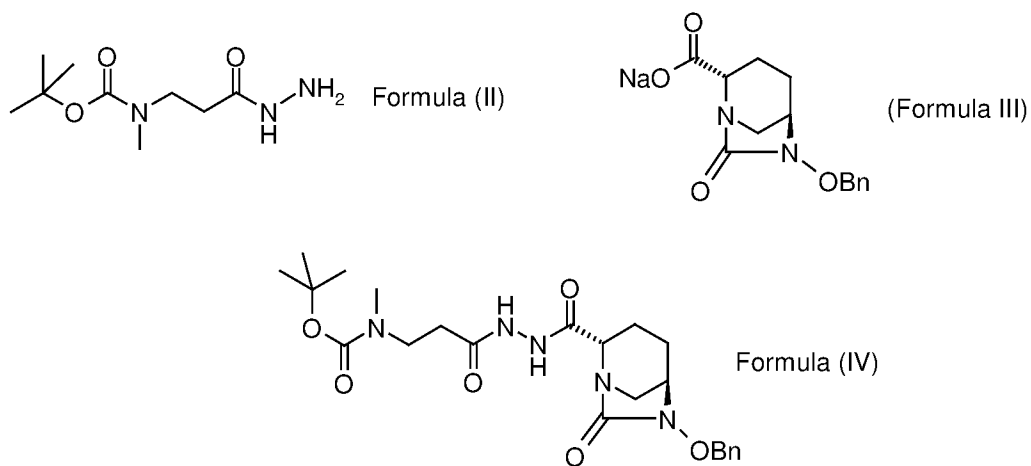
Formula (I)

SUMMARY OF THE INVENTION

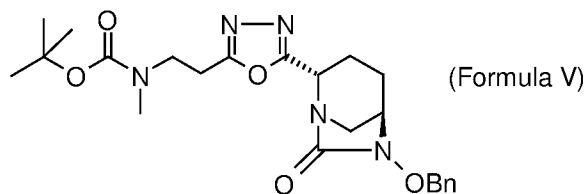
In one general aspect, there is provided a process for preparation of a compound of Formula (I), comprising:



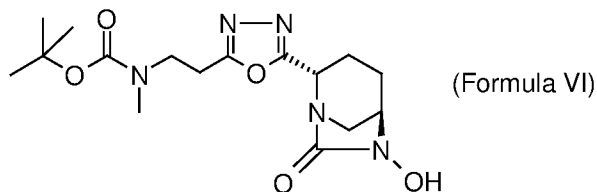
(a) reacting a compound of Formula (II) with a compound of Formula (III) to obtain a compound of Formula (IV);



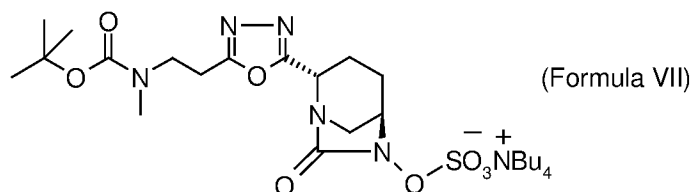
(b) cyclizing a compound of Formula (IV) to obtain a compound of Formula (V);



(c) hydrogenolysis of a compound of Formula (V) to obtain a compound of Formula (VI);



(d) sulfonating a compound of Formula (VI), followed by tetrabutylammonium salt formation to obtain a compound of Formula (VII); and



(e) deprotecting a compound of Formula (VII) to obtain a compound of Formula (I).

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

DETAILED DESCRIPTION OF THE INVENTION

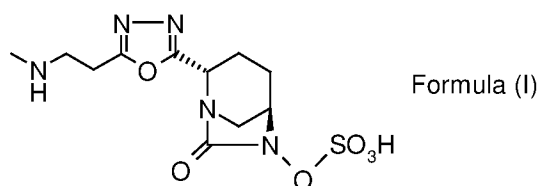
Reference will now be made to the exemplary embodiments, and specific language will be used herein to describe the same. It should nevertheless be understood that no limitation of the scope of the invention is thereby intended. Alterations and further modifications of the inventive features illustrated 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.

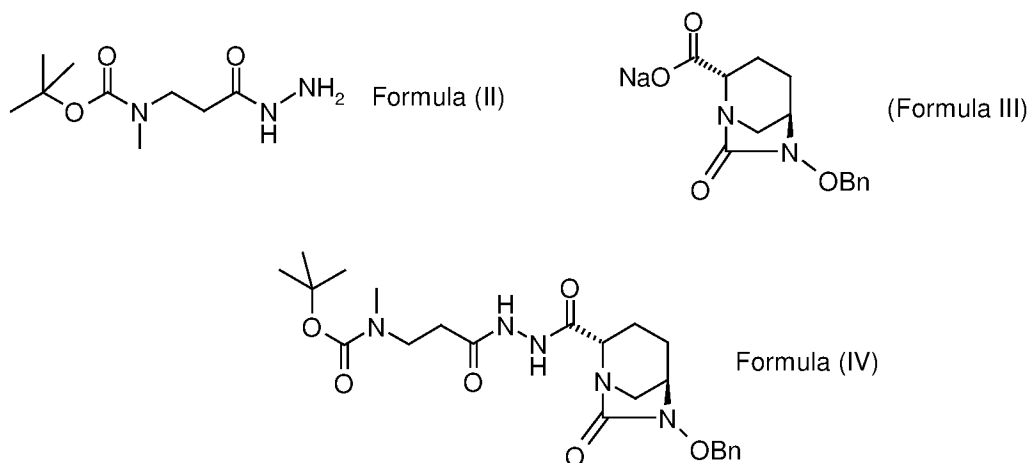
The term “EDC” as used herein refers to 1-ethyl-3-(3-dimethylamino propyl)carbodiimide.

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

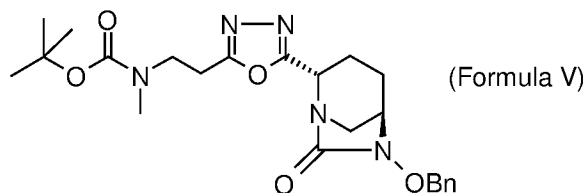
In one general aspect, there is provided a process for preparation of a compound of Formula (I), comprising:



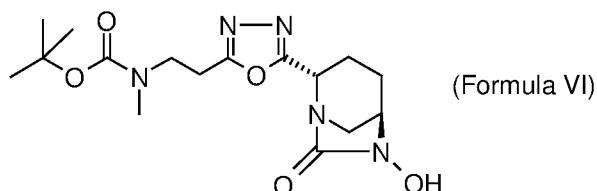
(a) reacting a compound of Formula (II) with a compound of Formula (III) to obtain a compound of Formula (IV);



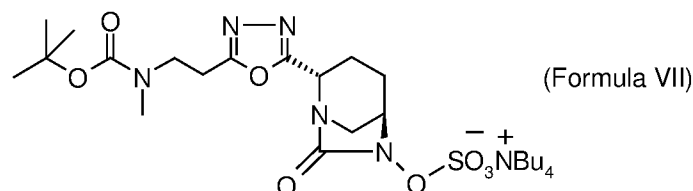
(b) cyclizing a compound of Formula (IV) to obtain a compound of Formula (V);



(c) hydrogenolysis of a compound of Formula (V) to obtain a compound of Formula (VI);



(d) sulfonating a compound of Formula (VI), followed by tetrabutylammonium salt formation to obtain a compound of Formula (VII); and



(e) deprotecting a compound of Formula (VII) to obtain a compound of Formula (I).

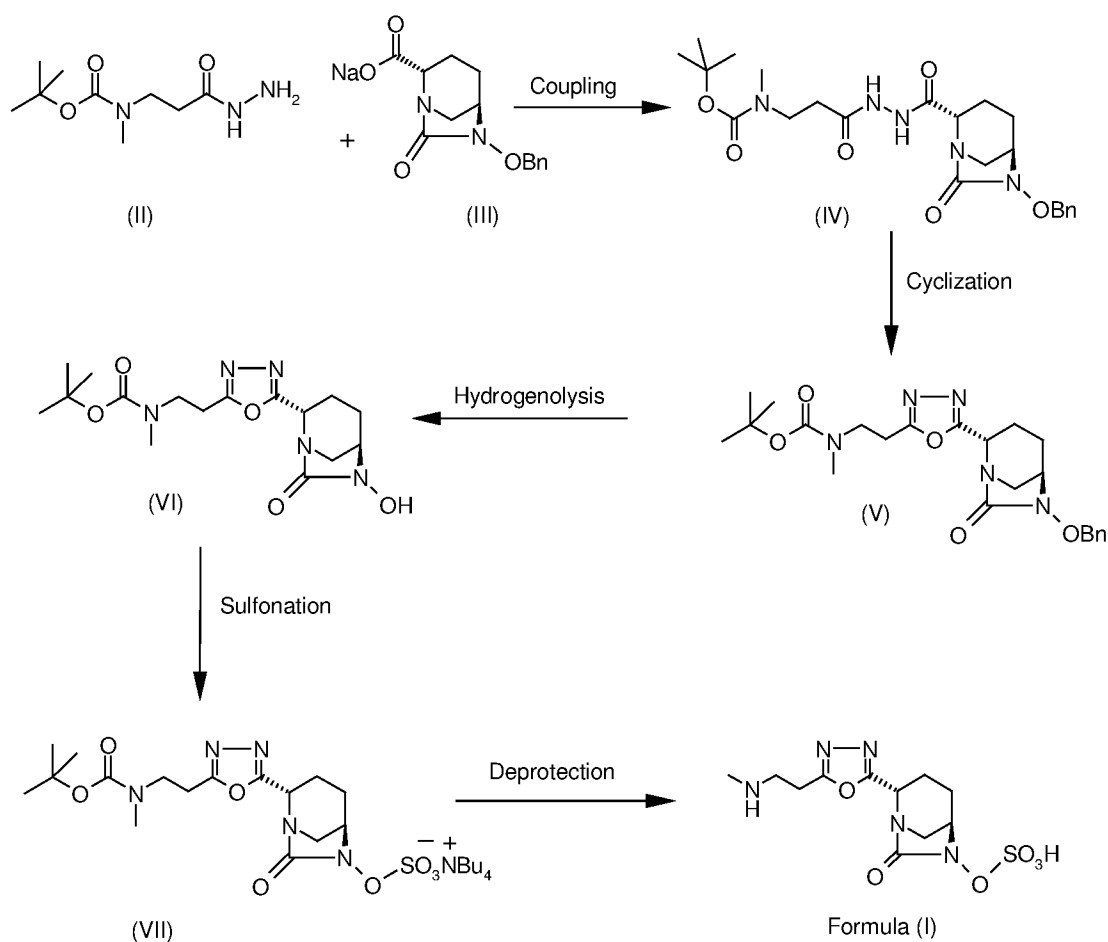
In some embodiments, a compound of Formula (I) is prepared by using a general procedure described in Scheme 1. Typically, a compound of Formula (I) is prepared from sodium salt of 6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (III). The sodium salt of 6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carboxylic acid (III) is reacted with (3-hydrazinocarbonyl-ethyl)-methyl-carbamic acid *tert*-butyl ester (II) in presence of coupling agent at a temperature ranging from -15°C to 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-Azabenzotriazol-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 or a mixture thereof. In some embodiments, a compound of Formula (II) is reacted with a compound of Formula (III) in presence of EDC hydrochloride and HOBt at a temperature of about 30°C for about 20 hours to provide an intermediate compound of Formula (IV). In some embodiments, a compound of Formula (II) is reacted with a compound of Formula (III) in presence of water as a solvent.

The compound of Formula (IV) is cyclized to provide a compound of Formula (V). The cyclization of a compound of Formula (IV) is effected by treating with a reagent such as *p*-toluene sulfonyl chloride, *p*-nitrobenzene sulfonyl chloride, methane sulfonyl chloride or triphenylphosphine in a suitable solvent such as toluene, chloroform, dichloromethane, or *N,N*-dimethyl formamide at a temperature ranging from 20°C to 75°C for about 15 minutes to about 4 hours to provide 1,3,4-oxadiazole intermediate compound of Formula (V). In some embodiments, compound of Formula (IV) is cyclized in presence of triphenylphosphine, iodine and triethylamine at a temperature of about 25°C for about 30 minutes to provide a compound of Formula (V). In some embodiments, a compound of Formula (IV) is cyclized to a compound of Formula (V) in presence of dichloromethane as a solvent.

The compound of Formula (V) is subjected for hydrogenolysis by using hydrogen source in presence of a transition metal catalyst in a suitable solvent such as methanol, ethanol, dichloromethane, *N,N*-dimethylformamide or a mixture thereof at a temperature ranging from 25°C to 60°C for about 1 hour to about 14 hours to provide a compound of Formula (VI). Typical, non-limiting examples of hydrogen source include hydrogen gas,

ammonium formate, cyclohexene, lithium – liquid ammonia, ammonia – *tert*-butanol, sodium – liquid ammonia – *tert*-butanol, triethyl silyl 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. In some embodiments, compound of Formula (V) is treated with 10% palladium on carbon in presence of hydrogen gas at 1 atmospheric pressure and at temperature of about 35°C for about 2 hours to provide a compound of Formula (VI). In some embodiments, a compound of Formula (V) is converted to a compound of Formula (VI) in presence of methanol as a solvent.

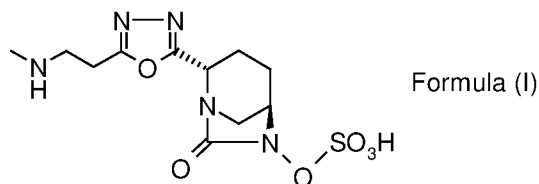
**Scheme 1**

The compound of Formula (VI) is sulfonated by reacting with suitable sulfonating reagent in a suitable solvent such as pyridine, dichloromethane or *N,N*-dimethylformamide, at a temperature ranging from 25°C to 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, sulfur trioxide-*N,N*-dimethylformamide complex and the like. In some embodiments, compound of Formula (VI) is reacted with sulfur trioxide-pyridine complex in presence of dichloromethane at a temperature of about 30°C for about 3 hours to provide pyridine salt of sulfonic acid compound. The obtained pyridine salt of sulfonic acid compound is treated with tetrabutylammonium hydrogen sulfate to provide tetrabutylammonium salt of sulfonic acid compound of Formula (VII).

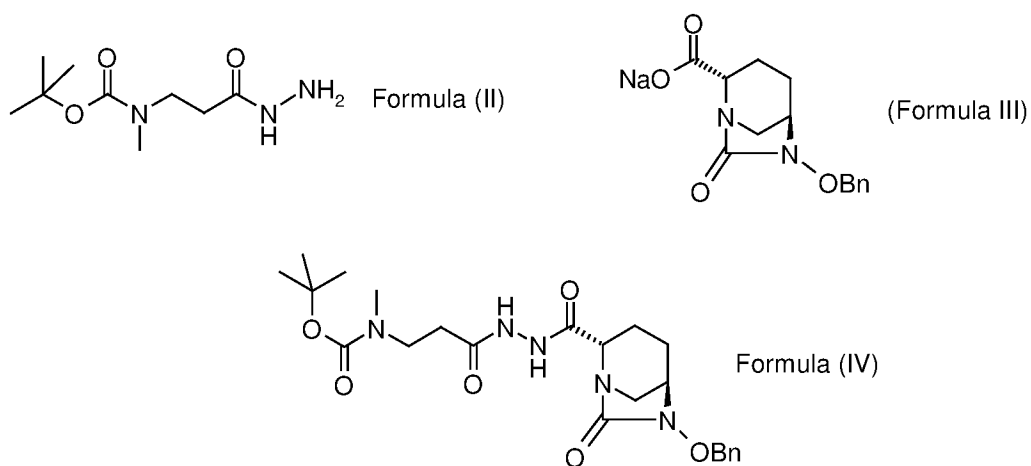
The compound according to the invention is finally isolated as zwitterions, by removing the protecting groups of a compound of Formula (VII). The compound of Formula (VII) is reacted with a suitable deprotecting agent such as trifluoroacetic acid in presence of a suitable solvent such as dichloromethane, chloroform or acetonitrile, at a temperature ranging from -15°C to 40°C for about 0.5 to about 14 hours. In some embodiments, a compound of Formula (VII) is treated with trifluoroacetic acid in presence of dichloromethane at a temperature of about 0°C to about -10°C for about 1 hour to provide a compound of Formula (I).

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

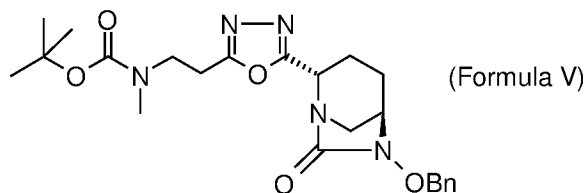
In some embodiments, there is provided a process for preparation of a compound of Formula (I), comprising:



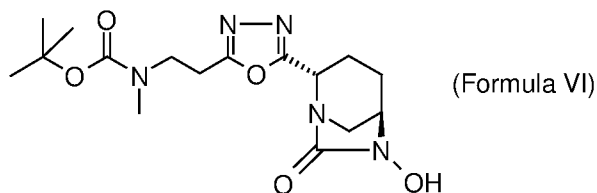
(a) reacting a compound of Formula (II) with a compound of Formula (III) in presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride to obtain a compound of Formula (IV);



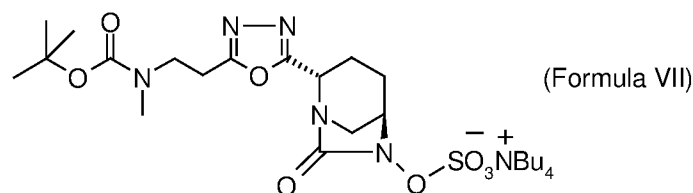
(b) cyclizing a compound of Formula (IV) in presence of triphenylphosphine, iodine and triethylamine to obtain a compound of Formula (V);



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



(d) sulfonating a compound of Formula (VI) in presence of sulfur trioxide-pyridine complex, followed by treatment with tetrabutylammonium hydrogen sulfate to obtain a compound of Formula (VII); and



(e) deprotecting a compound of Formula (VII) in presence of trifluoroacetic acid to obtain a compound of Formula (I).

In some embodiments, there is provided a compound of Formula (I) having a purity of at least about 95% as determined by HPLC.

In some embodiments, there is provided a process for preparation of compound of Formula (I) having a purity of at least about 95% as determined by HPLC.

In some embodiments, there is provided a pharmaceutical composition comprising a compound of Formula (I) having a purity of at least about 95% as determined by HPLC. In some embodiments, the said pharmaceutical composition may further comprise one or more pharmaceutically acceptable excipients.

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 *trans*-sulfuric acid mono-{2-[5-(2-methylamino-ethyl)-[1,3,4]-oxadiazol-2-yl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl} ester (I)

Step 1: Preparation of *trans*-{3-[N'-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)-hydrazino]-3-oxo-propyl}-methyl-carbamic acid *tert*-butyl ester (IV):

Sodium salt of 6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (III) (5.9 g, 0.02 mol; prepared using a method disclosed in Indian Patent Application No 699/MUM/2013) was dissolved in water (100 ml) to obtain a clear solution under stirring at 25°C. To the clear solution was added successively, (3-hydrazinocarbonyl-ethyl)-methyl-carbamic acid *tert*-butyl ester (II) (4.5 g, 0.02 mol), EDC. HCl (5.7 g, 1.5 mol), and HOBT (2.7 g, 0.02 mol) followed by water (20 ml) under stirring at 25°C. The reaction mixture was stirred at 30°C for 20 hours. As maximum precipitation was reached, thin layer chromatography (acetone: hexane, 35:65) showed

completion of reaction. The suspension was filtered under suction and the wet cake was washed with additional water (100 ml) and dried under vacuum at 45°C to furnish 5.5 g of *trans*-{3-[N'-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)-hydrazino]-3-oxo-propyl}-methyl-carbamic acid *tert*-butyl ester (IV) as a white powder in 58% yield.

Analysis:

Mass: 476.4 (M+1); for Molecular Formula: C₂₃H₃₃N₅O₆ and Molecular Weight: 475.2;

¹H NMR (CDCl₃): δ 7.43-7.35 (m, 5H), 5.04 (d, 1H), 4.90 (d, 1H), 4.01 (d, 1H), 3.54 (t, 2H), 3.33 (br s, 1H), 3.14-3.07 (m, 2H), 2.85 (s, 3H), 2.53 (br s, 2H), 2.33-2.30 (m, 1H), 2.07-1.94 (m, 2H), 1.64-1.61 (m, 4H), 1.40 (s, 9H), 1.25-1.17 (m, 2H).

Step 2: Preparation of *trans*-{2-[5-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (V):

To a solution of triphenylphosphine (3.3 g, 0.0126 mol) in dichloromethane (70 ml) at was added iodine (3.2 g, 0.0126 mol) and triethyl amine (7.0 ml, 0.0525 mol) under stirring at 25°C. Separately prepared solution of *trans*-{3-[N'-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)-hydrazino]-3-oxo-propyl}-methyl-carbamic acid *tert*-butyl ester (IV) (5.5 g, 0.0105 mol) dissolved in dichloromethane (30 ml) was added to above reaction mixture and the mixture was stirred at 25°C for 30 minutes. The reaction mixture was concentrated and to this ethyl acetate (100 ml) was added. The separated triphenylphosphine oxide was filtered off. The filtrate was concentrated and the residue purified by silica gel column chromatography using mixture of ethyl acetate and hexane, to afford 5 g of the titled compound.

Analysis:

Mass: 458.3 (M+1); for Molecular Formula: C₂₃H₃₁N₅O₅ and Molecular Weight: 457.53;

¹H NMR (CDCl₃): δ 7.44-7.35 (m, 5H), 5.04 (d, 1H), 4.93 (d, 1H), 4.70 (t, 1H), 3.62 (br s, 2H), 3.36 (s, 1H), 3.07 (t, 2H), 2.93 (br d, 1H), 2.85 (br s, 4H), 2.32-2.27 (m, 2H), 2.12 (br d, 2H), 1.95 (br s, 1H), 1.40 (s, 9H).

Step 3: Preparation of *trans*-{2-[5-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (VI):

To a solution of *trans*-{2-[5-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (V) (5 g, 0.0109 mol) in methanol (50 ml) was added 10% palladium on carbon (1.5 g) at 25°C. The reaction mixture was stirred under 1 atmospheric pressure of hydrogen at 35°C for 2 hours. The catalyst was removed by filtering the reaction mixture under suction over a celite bed. The celite bed was washed with methanol (50 ml). The combined filtrate was evaporated under vacuum below 35°C to provide 3.8 g of *trans*-{2-[5-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (VI) in 93% yield; it was used as such for the next reaction.

Step 4: Preparation of *trans*-tetrabutyl ammonium salt-methyl-{2-[5-(7-oxo-6-sulphooxy-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-carbamic acid *tert*-butyl ester (VII):

A solution of *trans*-{2-[5-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4] oxadiazol-2-yl]-ethyl}-methyl-carbamic acid *tert*-butyl ester (VI) (3.8 g, 9.8 mmol), in dichloromethane (38 ml) was charged with triethylamine (2.6 ml, 19.7 mmol) under stirring to provide a clear solution. To this clear solution was added sulfur trioxide-pyridine complex (2.35 g, 14.8 mmol) under stirring at 30°C. The reaction mixture was stirred for 3 hours and to this 0.5 M aqueous potassium dihydrogen phosphate (38 ml) was added followed by ethyl acetate (76 ml). The biphasic mixture was stirred for 15 minutes at 30°C. Aqueous layer was separated and re-extracted with dichloromethane and ethyl acetate mixture (1:2 v/v, 76 ml twice). To the aqueous layer was added solid tetrabutyl ammonium hydrogen sulfate (3 g, 8.8 mmol) and stirring was continued for 1

hour at room temperature. The reaction mixture was extracted with dichloromethane (3 × 50 ml). Layers were separated and dichloromethane layer dried over sodium sulfate and then evaporated under vacuum at 35°C to provide 2.8 g of *trans*-tetrabutyl ammonium salt-methyl-{2-[5-(7-oxo-6-sulphooxy-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-carbamic acid *tert*-butyl ester (VII). This was purified by column chromatography to afford 2.0 g of pure product in 29% yield.

Analysis:

Mass: 446.5 (M-1) as free sulfonic acid; for Molecular Formula: C₁₆H₂₅N₅O₈S.N (C₄H₉)₄ and Molecular Weight: 688.5;

¹H NMR (CDCl₃): δ 4.67 (d, 1H), 4.36 (br s, 1H), 3.33-3.29 (m, 8H), 3.23 (d, 1H), 3.08 (t, 2H), 2.87 (s, 3H), 2.83 (s, 1H), 2.28-2.22 (m, 3H), 2.07-2.00 (m, 8H), 1.50-1.41 (m, 17H), 1.28 (s, 3H), 1.01 (t, 12 H), 1.41-1.52 (m, 10 H).

Step 5: *trans*-sulfuric acid mono-{2-[5-(2-methylamino-ethyl)-[1,3,4]-oxadiazol-2-yl]-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl} ester:

trans-Tetrabutyl ammonium salt-methyl-{2-[5-(7-oxo-6-sulphooxy-1,6-diaza-bicyclo[3.2.1]oct-2-yl)-[1,3,4]oxadiazol-2-yl]-ethyl}-carbamic acid *tert*-butyl ester (VII) (2.0 g, 2.9 mmol) was dissolved in dichloromethane (5 ml) and to the clear solution was slowly added trifluoroacetic acid (5 ml) at 0 to -10 °C. The reaction mixture was stirred at 0 to -10 °C for 1 hour. The solvent and excess trifluoroacetic acid was evaporated under vacuum below 40°C to approximately 1/3 of its original volume to provide pale yellow oily residue. The oily residue was stirred with diethyl ether (100 ml) for 10-15 minutes. The suspension formed was filtered under suction to provide a solid. This process was repeated twice. The solid was charged in a round bottom flask and to it was added dichloromethane (100 ml). The suspension was stirred for 15 minutes and filtered under suction to provide a solid. The obtained solid was dried under vacuum below 40°C to furnish 850 mg of *trans*-sulfuric acid mono-{2-[5-(2-methylamino-ethyl)-[1,3,4]-oxadiazol-2-yl]-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl} ester as white solid in 85% yield.

Analysis:

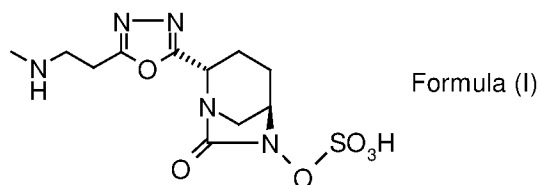
Mass: 346.3 (M-1) as a free sulfonic acid; for Molecular Formula: $C_{11}H_{17}N_5O_6S$ and Molecular Weight: 347.35;

NMR (D_2O): δ 4.74 (d, 1H), 4.16 (br s, 1H), 3.45 (t, 2H), 3.31 (t, 2H), 3.15 (d, 1H), 2.91 (d, 1H), 2.98 (s, 3H), 2.27-2.22 (m, 1H), 2.16-2.11 (m, 2H), 1.94-1.91 (m, 1H);

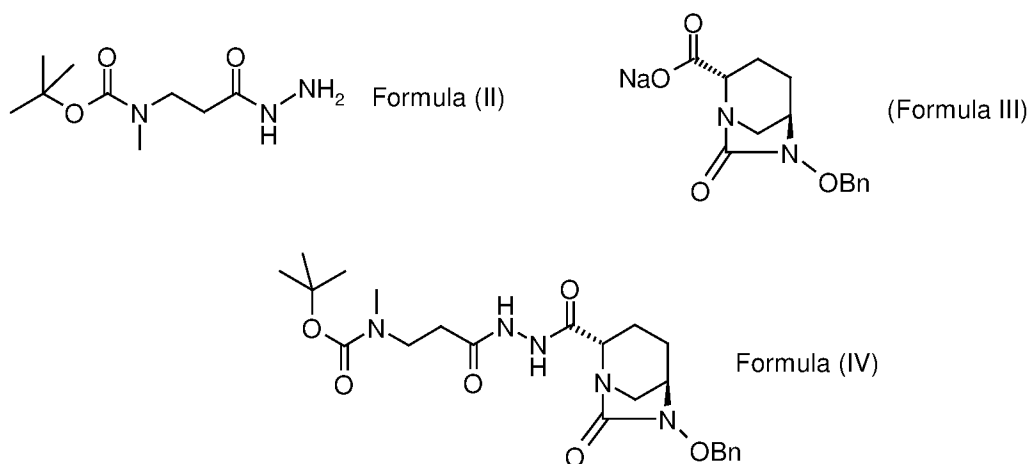
Purity as determined by HPLC: 95.56%.

CLAIMS

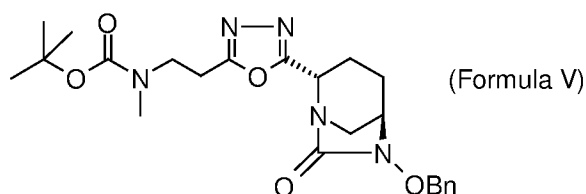
1. A process for preparation of a compound of Formula (I), comprising:



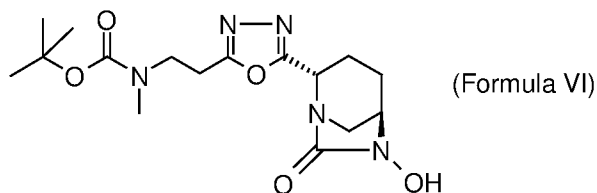
- (a) reacting a compound of Formula (II) with a compound of Formula (III) to obtain a compound of Formula (IV);



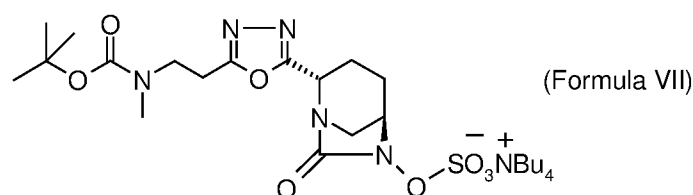
- (b) cyclizing a compound of Formula (IV) to obtain a compound of Formula (V);



- (c) hydrogenolysis of a compound of Formula (V) to obtain a compound of Formula (VI);



(d) sulfonating a compound of Formula (VI), followed by tetrabutylammonium salt formation to obtain a compound of Formula (VII); and



(e) deprotecting a compound of Formula (VII) to obtain a compound of Formula (I).

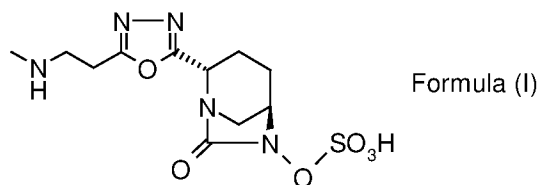
2. A process according to Claim 1, wherein a compound of Formula (IV) is obtained by reacting a compound of Formula (II) with a compound of Formula (III) in presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride.

3. A process according to Claim 1, wherein a compound of Formula (V) is obtained by cyclizing a compound of Formula (IV) in presence of triphenylphosphine, iodine and triethylamine.

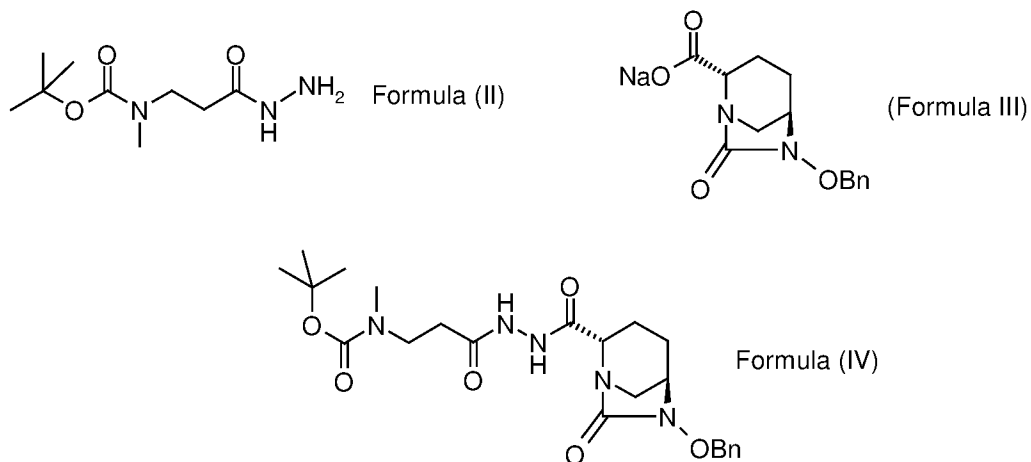
4. A process according to Claim 1, wherein hydrogenolysis of a compound of Formula (V) is carried out in presence of transition metal catalyst and a hydrogen source.

5. A process according to Claim 4, wherein the transition metal catalyst is palladium on carbon.

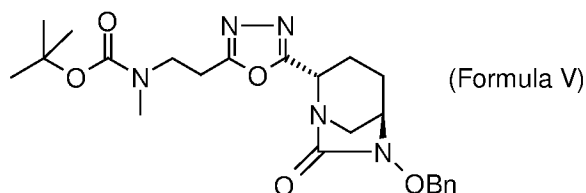
6. A process according to Claim 4, wherein the hydrogen source is hydrogen gas.
7. A process according to Claim 1, wherein sulfonation of a compound of Formula (VI) is carried out in presence of a sulfonating agent selected from the group consisting of sulfur trioxide-pyridine complex, sulfur trioxide-trimethylamine 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.
8. A process according to Claim 7, wherein a sulfonating agent is sulfur trioxide-pyridine complex.
9. A process according to Claim 1, wherein deprotection of a compound of Formula (VII) is carried out in presence of trifluoroacetic acid.
10. A compound of Formula (I) having purity of at least about 95% as determined by HPLC.
11. A pharmaceutical composition comprising a compound of Formula (I) according to Claim 10.
12. A process for preparation of a compound of Formula (I), comprising:



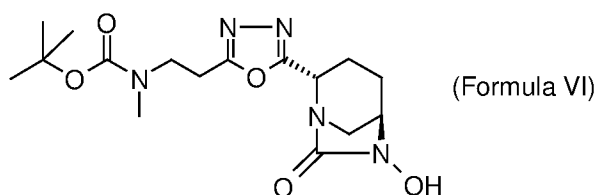
(a) reacting a compound of Formula (II) with a compound of Formula (III) in presence of 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride to obtain a compound of Formula (IV);



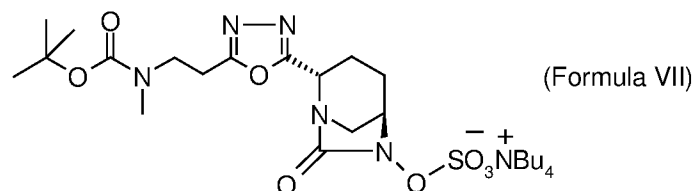
(b) cyclizing a compound of Formula (IV) in presence of triphenylphosphine, iodine and triethylamine to obtain a compound of Formula (V);



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



(d) sulfonating a compound of Formula (VI) in presence of sulfur trioxide-pyridine complex, followed by treatment with tetrabutylammonium hydrogen sulfate to obtain a compound of Formula (VII); and



(e) deprotecting a compound of Formula (VII) in presence of trifluoroacetic acid to obtain a compound of Formula (I).

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/052186

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)

EPO-Internal, WPI Data, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/149121 A1 (CUBIST PHARM INC [US]) 3 October 2013 (2013-10-03) cited in the application Scheme 1, pages 58 and 59; claims 34, 40, 46; example 19; compound 722 -----	1-12



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

10 June 2015

Date of mailing of the international search report

19/06/2015

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/052186

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