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(71) Applicant: **WOCKHARDT LIMITED** [IN/IN]; D-4, MIDC Area, Chikalthana, Aurangabad 431006 (IN).

(72) Inventors: **PAVASE, Laxmikant**; 15 August Colony, R.No. 09, Datta Chowk, Bhushannagar, Post Kedgaon, District : Ahmednagar 414005, Maharashtra (IN). **DESHPANDE, Prasad Keshav**; B-3, Saraswati Bhuvan Colony (W), Aurangpura, Aurangabad 431003, Maharashtra (IN). **RAIKAR, Sanjay**; Wockhardt Research Centre, D-4, MIDC Area, Chikalthana, Aurangabad 431006 (IN). **YEOLE, Ravindra Dattatraya**; 13, Pal Apartment, Plot No.6, N-2, CIDCO, 431003 Aurangabad, Maharashtra (IN). **PATEL, Mahesh Vithalbhai**; Plot No. 157, Opp. Saint Meera School, N-3, CIDCO, 431003 Aurangabad, Maharashtra (IN).

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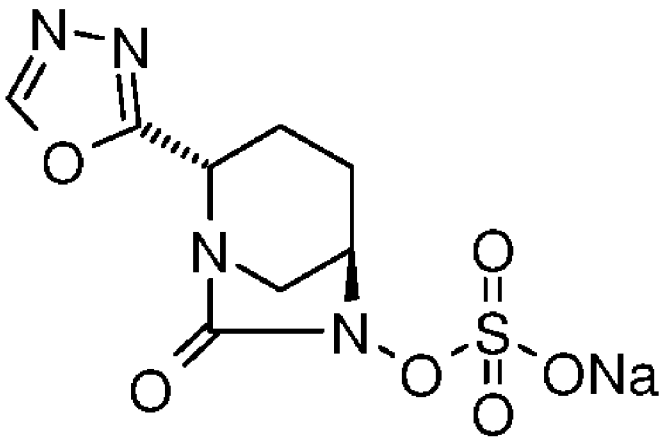
(54) **Title**: A PROCESS FOR PREPARATION OF SODIUM SALT OF (2S, 5R) SULFURIC ACID MONO-(2-[1,3,4]OXADIAZOL-2-YL-7-OXO-1,6-DIAZABICYCLO[3.2.1]OCT-6-YL)ESTER



(I)

(57) **Abstract**: A process for preparation of sodium salt of (2*S*, 5*R*)-sulfuric acid mono-(2-[1,3,4] oxadiazol-2- yl-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl) ester is disclosed.

WO 2016/157057 A1

A PROCESS FOR PREPARATION OF SODIUM SALT OF (2S, 5R) SULFURIC ACID MONO-(2-[1 ,3,4]OXADIAZOL-2-YL-7-OXO-1 ,6-DIAZABICYCLO[3.2.1]OCT-6-YL)ESTER

PRIORITY APPLICATION

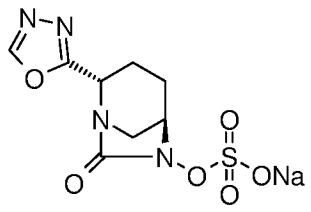
This application claims priority to Indian Patent Application No. 1077/MUM/2015 filed on March 27, 2015, the disclosures of which are incorporated herein by reference in its entirety as if fully rewritten herein.

FIELD OF THE INVENTION

The invention relates to a process for preparation of sodium salt of (2*S*, 5*R*) mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl)ester

BACKGROUND OF THE INVENTION

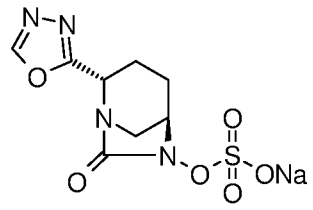
A compound of Formula (I), chemically known as sodium salt of (2*S*, 5*R*) mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl)ester has antibacterial properties and is disclosed in PCT International Patent Application No. PCT/US2013/034562. The compound of Formula (I) is also generically disclosed in PCT International Patent Application No. PCT/IB2012/054296. The present invention discloses a process for preparation of a compound of Formula (I).



Formula (I)

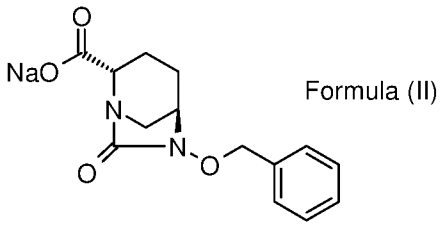
SUMMARY OF THE INVENTION

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

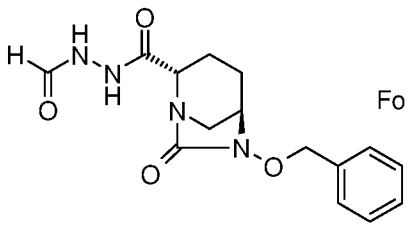


Formula (I)

(a) converting a compound of Formula (II) to a compound of Formula (III);

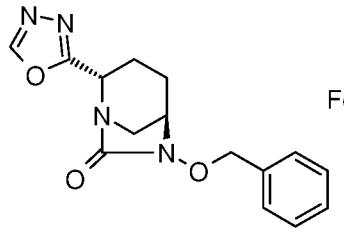


Formula (II)



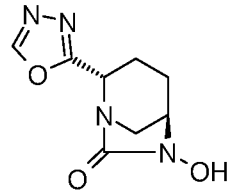
Formula (III)

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



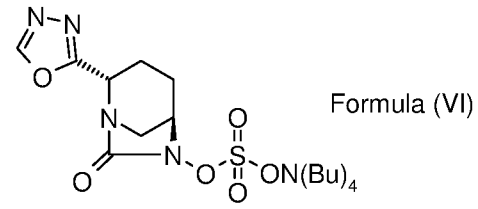
Formula (IV)

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



Formula (V)

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



(e) 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 is an X-ray powder diffraction pattern of a compound of Formula (I) in crystalline form.

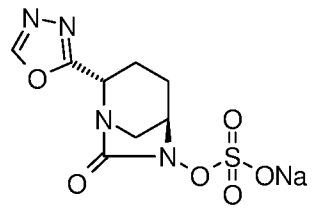
DETAILED DESCRIPTION OF THE INVENTION

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.

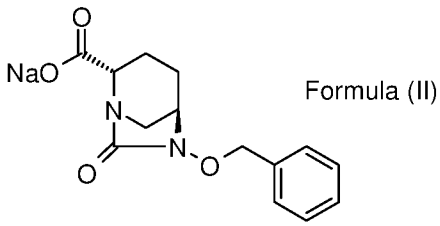
The term "HOBt" as used herein refers to 1-hydroxybenzotriazole.

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

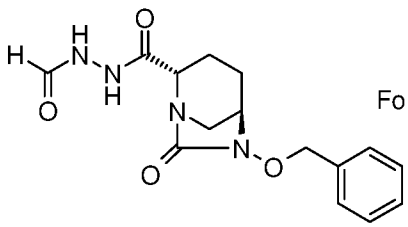


Formula (I)

(a) converting a compound of Formula (II) to a compound of Formula (III);

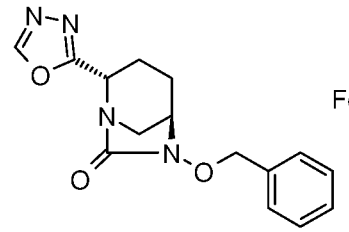


Formula (II)



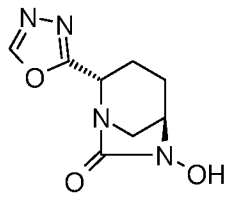
Formula (III)

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



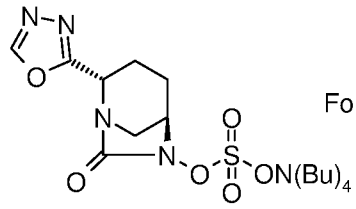
Formula (IV)

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



Formula (V)

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



Formula (VI)

(e) 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-diazabicyclo[3.2.1]octane-2-carboxylic acid (II) was coupled with formyl hydrazide in the presence of coupling agent, suitable base and suitable solvent at a temperature ranging from -5°C to 60°C to obtain a compound of Formula (III). Typical, non-limiting examples of suitable coupling agent include EDC.HCl, HOBt, *N,N'*-dicyclohexyldiimde, (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) or a mixture thereof. Typical non-limiting examples of a suitable base include triethylamine, diisopropylethylamine, pyridine, *N,N*-dimethylaminopyridine, morpholine, *N*-methylmorpholine or a mixture thereof. Typical non-limiting examples of suitable solvent include water, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or a mixture thereof. In some embodiments, compound of Formula (II) is treated with formyl hydrazide in presence of EDC.HCl, HOBt and diisopropylethylamine at a temperature of about 20°C to 35°C to provide a coupled intermediate compound of Formula (III).

The coupled intermediate (III) was subjected to ring formation by treating it with a suitable cyclizing agent in presence of a suitable base and a solvent at a temperature ranging from 0°C to 80°C to provide 1,3,4-oxadiazole ring intermediate compound of Formula (IV). Typical, non-limiting examples of cyclizing agent include methanesulfonic acid chloride, p-nitrophenylsulphonic acid chloride, p-tolylsulfonylchloride, iodine/triphenylphosphine/triethylamine combination and the like. Typical, non-limiting examples of suitable base include triethylamine, diisopropylethylamine, pyridine, N,N-diemthylaminopyridine, morpholine, *N*-methyl morpholine and the like. Typical, non-limiting examples of suitable solvent include dichloromethane, chloroform, ethylenedichloride and the like. In some embodiments, compound of Formula (III) is cyclized by the action of p-tolylsulfonylchloride in the presence of diisopropylethylamine and chloroform at a temperature of about 50°C to 70°C to provide a compound of Formula (IV).

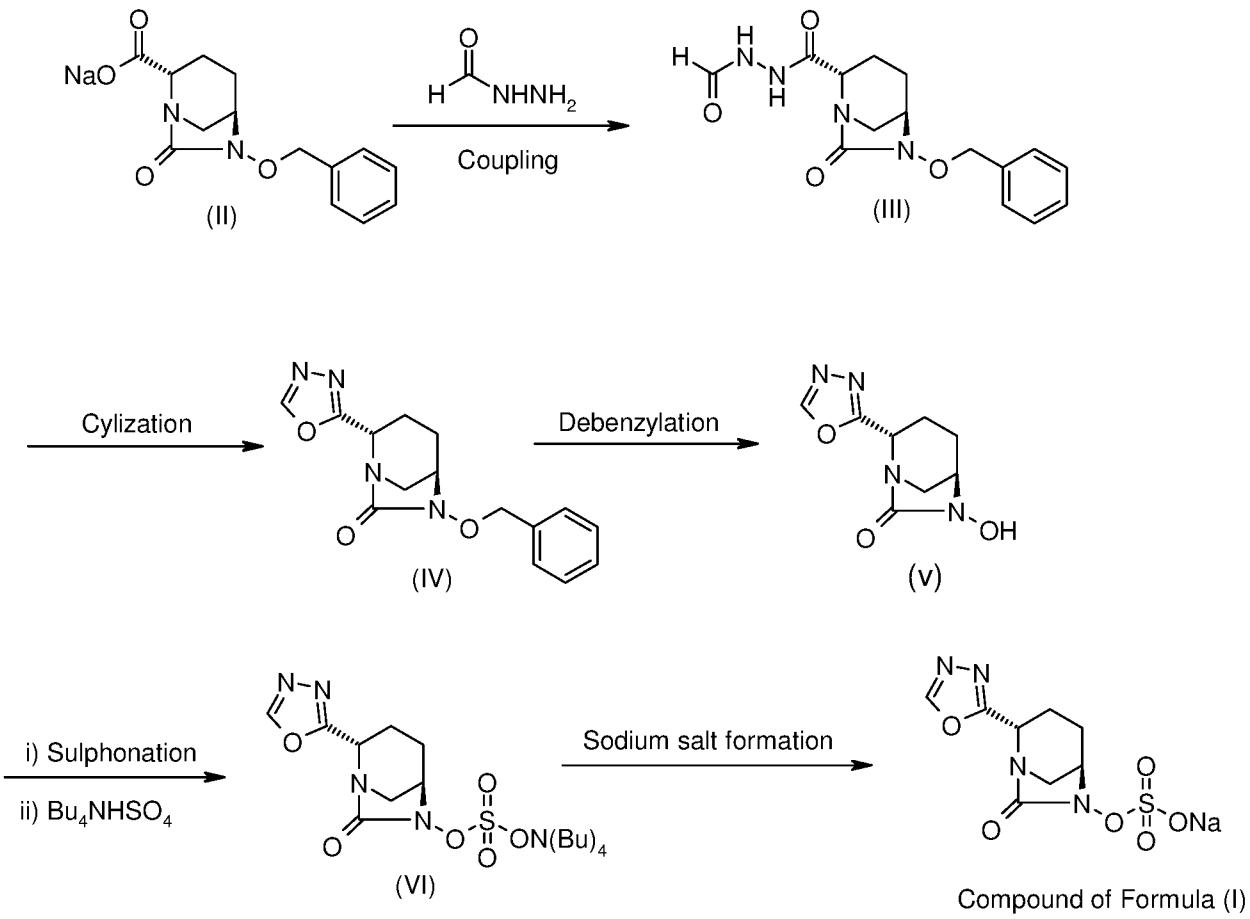
The compound of Formula (IV) is debenzylated by catalytic hydrogenolysis to obtain a compound of Formula (V). The compound of Formula (IV) is subjected to catalytic hydrogenolysis in presence of a suitable catalyst, a suitable hydrogen source and a suitable solvent at a temperature ranging from about 0°C to 40°C to obtain the hydroxyl compound of Formula (V). Typical, non-limiting examples of suitable catalyst include 5% palladium on carbon, 10% palladium on carbon, 20% palladium hydroxide and the like. Typical, non-limiting examples of suitable hydrogen source include hydrogen gas, cyclohexene, ammonium formate, hydrazinehydrate and the like. Typical, non-limiting examples of suitable solvent include methanol, ethanol, ethylacetate, tetrahydrofuran or a mixture thereof. In some embodiments, a compound of Formula (IV) is treated with 10% palladium on carbon and hydrogen gas in presence of methanol a temperature of about 25°C to 30°C to obtain a compound of Formula (V).

The compound of Formula (V) is reacted with a suitable sulphonating reagent in presence of a suitable base and a solvent at a temperature of about 0°C to 60°C to provide a sulphonated compound. Typical, non-limiting examples of sulphonating reagent include sulfur trioxide pyridine complex, sulfur trioxide dimethylformamide complex, sulfur trioxide triethylamine complex and the like. Typical, non-limiting examples of suitable base include triethylamine, pyridine, disiopropylethylamine, morpholine, *N*-methylmorpholine ant the like. Typical, non-limiting examples of suitable solvent include dichloromethane, chloroform, ethylene dichloride, pyridine or a mixture thereof. In some embodiments, a compound of Formula (V) is treated with sulfur trioxide pyridine

complex in presence of triethylamine and dichloromethane at a temperature of about 25°C to 35°C to obtain the sulphonated compound. The so obtained sulfonated compound is further converted to its corresponding tetrabutylammonium salt. In some embodiments, the sulfonated compound is treated with tetrabutylammonium hydrogen sulfate or tetrabutylammnoium acetate to provide tetrabutylammonium salt compound of Formula (VI).

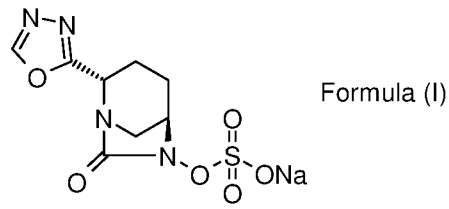
The intermediate tetrabutylammonium salt compound of Formula (VI) is converted to compound of Formula (I) by exchanging tetrabutylammonium group by sodium. In some embodiments, compound of Formula (VI) is treated with sodium-2-ethylhexanoate in a suitable solvent selected from dimethylfomamide, ethanol, acetone or a mixture thereof to obtain a compound of Formula (I). In some embodiments, compound of Formula (VI) is contacted with sodium exchange resin and eluted with a suitable solvent to obtain a compound of Formula (I). Typical, non-limiting examples of sodium exchange resin include Amberlite IR 120, DOWEX and then like. Typical, non-limiting examples of suitable solvent include mixture of tetrahydrofuran and water.

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

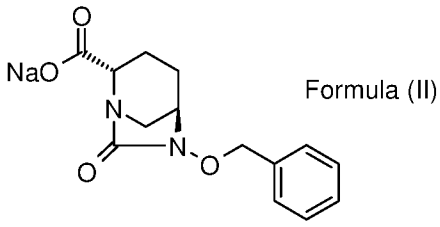


SCHEME-1

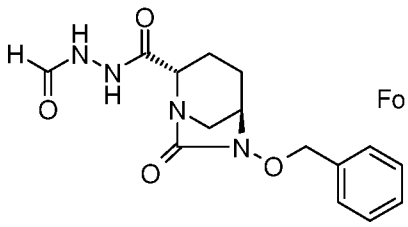
In some embodiments, there is provided a process for preparation of a compound of Formula (I), comprising:



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

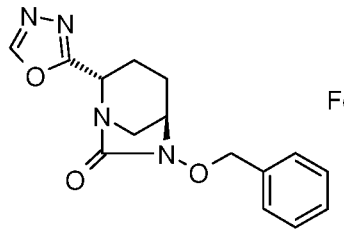


Formula (II)



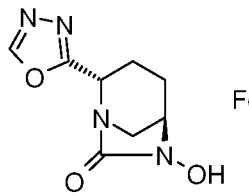
Formula (III)

(b) cyclizing a compound of Formula (III) in presence of p-tolylsulfonylchloride to obtain a compound of Formula (IV);



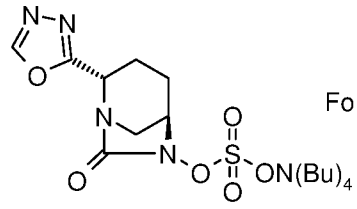
Formula (IV)

(c) hydrogenolysis of a compound of Formula (IV) in presence of 10% palladium over carbon and hydrogen gas to obtain a compound of Formula (V);



Formula (V)

(d) reacting a compound of Formula (V) with a suphonating reagent, followed by the treatment with tetrabutylammonium hydrogen sulphate to obtain a compound of Formula (VI); and



Formula (VI)

(e) contacting a compound of Formula (VI) with a sodium exchange resin 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 11.30 (± 0.2), 13.01 (± 0.2), 13.67 (± 0.2), 14.19 (± 0.2), 15.16 (± 0.2), 16.85 (± 0.2), 17.77 (± 0.2), 18.13 (± 0.2), 18.93 (± 0.2), 19.18 (± 0.2), 20.37 (± 0.2), 21.35 (± 0.2), 22.12 (± 0.2), 22.65 (± 0.2), 23.97 (± 0.2), 25.09 (± 0.2), 25.33 (± 0.2), 26.03 (± 0.2), 26.38 (± 0.2), 26.84 (± 0.2), 28.37 (± 0.2), 28.63 (± 0.2), 29.15 (± 0.2), 29.65 (± 0.2), 30.61 (± 0.2), 31.95 (± 0.2), 33.41 (± 0.2) and 33.96 (± 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 11.30 (± 0.2), 13.01 (± 0.2), 13.67 (± 0.2), 14.19 (± 0.2), 15.16 (± 0.2), 16.85 (± 0.2), 17.77 (± 0.2), 20.37 (± 0.2), 21.35 (± 0.2), 22.12 (± 0.2), 23.97 (± 0.2), 26.03 (± 0.2), 26.84 (± 0.2), 28.63 (± 0.2), 30.61 (± 0.2), 31.95 (± 0.2) and 33.96 (± 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 13.01 (± 0.2), 13.67 (± 0.2), 14.19 (± 0.2), 16.85 (± 0.2), 20.37 (± 0.2), 21.35 (± 0.2), 22.12 (± 0.2), 26.03 (± 0.2), 26.84 (± 0.2) and 31.95 (± 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 89% 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 89% as determined by HPLC. In some embodiments, the said pharmaceutical compositions 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

Sodium salt of (2*S*, 5*R*) sulfuric acid mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl) ester

Step I: Synthesis of (2*S*,5*R*)-2-(*N*'-formyl-hydrazinocarbonyl)-6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane (III):

To a turbid solution of sodium salt of (2*S*,5*R*)-6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane-2-carboxylic acid (II, 20 g, 0.067 mol) (prepared according to process disclosed in PCT/IB2013/059264) in dimethylformamide (200 ml) was added EDC hydrochloride (19.44 g, 0.10 mol) followed by formyl hydrazide (4.02 g, 0.067 mol) and N-hydroxybenzotriazole (9 g, 0.67 mol) at about 25°C under stirring. Diisopropylethylamine (35.62 ml, 0.20 mol) was added to the reaction mixture and stirred at 25°C temperature for 18 hours. The reaction mixture was evaporated under vacuum to provide a residue. The residue was dissolved in ethyl acetate (500 ml) and washed with water (500 ml × 2), followed by saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum to provide a crude intermediate, which was purified by silica gel column chromatography to provide 11 g of the titled compound as solid in 52% yield.

Analysis:

Mass: 319.1 (M+1); for Molecular Formula of $C_{15}H_{18}N_4O_4$ and Molecular Weight of 318.34;

H^1 NMR (DMSO-d6): δ 9.93 (s, 1H), 9.87 (s, 1H), 8.01 (s, 1H), 7.36-7.46 (m, 5H), 4.91-4.97 (dd, 2H), 3.83-3.84 (br s, 1H), 3.70 (s, 1H), 3.15-3.18 (br s, 1H), 2.90-2.95 (m, 1H), 1.99-2.03(m, 1H), 1.86(br s, 1H), 1.73-1.75 (m, 1H), 1.66 (m, 1H).

Step II: Synthesis of (2*S*,5*R*)-2-([1,3,4]-oxadiazol-2-yl)-6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane (IV):

To a clear solution of (2*S*,5*R*)-2-(N'-formyl-hydrazinocarbonyl)-6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane (III, 11 g, 0.0345 mol) in chloroform (120 ml) was added diisopropylethylamine (18.31 ml, 0.1035 mol) and p-tolylsulfonylchloride (9.83 g, 0.0517 mol). The solution was stirred at 60°C for 15 hours. Reaction mixture was cooled to room temperature and water (100 ml) was added. Organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum to provide a crude residue, which was purified by silica gel column chromatography to provide 7 g of the titled compound as a solid in 68% yield.

Analysis:

Mass: 301.3 (M+1); for Molecular Formula of $C_{15}H_{16}N_4O_3$ and Molecular Weight of 300.32;

H^1 NMR ($CDCl_3$): δ 8.45 (s, 1H), 7.25-7.44 (m, 5H), 5.07-5.10 (dd, 1H), 4.92-4.95 (dd, 1H), 4.76-4.78 (br s, 1H), 3.37 (br s, 1H), 2.93-.95 (br s, 1H), 2.75-2.77 (m, 1H), 2.32-2.33 (m, 2H), 2.13-2.16 (m, 1H), 1.93-2.01 (m, 1H).

Step III: Synthesis of (2*S*,5*R*)-2-([1,3,4]-oxadiazol-2-yl)-6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane (V):

To a clear solution of (2*S*,5*R*)-2-([1,3,4]-oxadiazol-2-yl)-6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane (IV, 7.0 g, 0.0233 mmol) in methanol (70 ml) was added 10% palladium on carbon (2.5 g). The suspension was stirred under atmospheric hydrogen pressure at a temperature 25^0 C for 2 hrs. The catalyst was filtered over a celite bed and the bed was washed with methanol (30 ml). The filtrate was concentrated under vacuum to provide an oily residue. The residue was triturated with cyclohexane (100 ml) to effect solid formation. The suspension was filtered under suction and the wet cake was washed with additional cyclohexane (50 ml). The soild was dried under vacuum to provide 4.5 g of the titled compound as a whitish solid in 92% yield, which was used for the next reaction immediately.

Analysis:

Mass: 211.2 (M+1); for Molecular Formula of $C_8H_{10}N_4O_3$ and Molecular Weight of 210.19;

^{1}H NMR (DMSO-d6): δ 9.88 (br s, 1H), 9.29 (s, 1H), 4.65 (d, 1H), 4.64 (br s, 1H), 2.94-2.97 (br d, 1H), 2.63-2.66 (d, 1H), 1.89-2.09 (m,3H), 1.82-1.86 (m, 1H).

Step IV: Synthesis of tetrabutylammonium salt of (2*S*, 5*R*)-sulfuric acid mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl) ester (VI):

To a clear solution of (2*S*,5*R*)-2-([1,3,4]-oxadiazol-2-yl)-6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1] octane (V, 4.5 g, 0.0214 mol) in dichloromethane (50 ml) was added triethylamine (9 ml, 0.642 mol), followed by the addition of sulfur trioxide pyridine complex (6.83 g, 0.428 mol). The resulting reaction mixture was stirred for 2 hours. Tetrabutylammonium hydrogen sulfate (7.26 g,

0.0214 mol) was added to the reaction mixture and it was stirred for 1.5 hours. A solution of aqueous 0.5 N KH_2PO_4 (100 ml) was added to the reaction mixture. Layers were separated and the aqueous layer was washed with dichloromethane (125 ml). Combined organic layer was dried over Na2SO4, and was evaporated under vacuum to yield crude foam, which was purified on silica gel column chromatography to give 7 g of the titled compound as white foam in 98% yield.

Analysis:

Mass: 289.1 (M-1); for Molecular Formula $C_8H_9N_4O_6S.(C_4H_9)_4N$ and Molecular Weight of 517.26;

^{1}H NMR (DMSO-d6): δ 9.30 (s, 1H), 4.69 (d, 1H), 4.06 (br s, 1H), 3.14-3.18 (m, 8H), 2.94-2.97 (br d, 1H), 2.67-2.70 (d, 1H), 1.98-2.05 (m,1H), 2.85-2.92 (m, 1H), 1.53-1.60 (m, 8H), 1.27-1.36 (m, 8H), 0.91-0.95 (m, 12H).

Step V: Sodium salt of (2*S*, 5*R*)-sulfuric acid mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl) ester (I):

The compound sodium salt of (2*S*, 5*R*)-sulfuric acid mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl) ester of Formula (I) was prepared by loading tetrabutylammonium salt of sulfuric acid mono-(2-[1,3,4]oxadiazol-2-yl-7-oxo-1,6-diaza-bicyclo[3.2.1]oct-6-yl) ester (VI, 7 g) on a column packed with Amberlite IR 120 Na form of resin, and by eluting the column with methanol water mixture (9:1). Fractions containing compound were collected and solvent was evaporated under vacuum below 40°C, to provide formula-1 compound in 4 gm (62%) quantity as a white solid.

Analysis:

Mass: 289.3 (M-1) as free acid; for Molecular Formula $C_8H_9N_4O_6S.Na$ and Molecular Weight 290.26;

H^1 NMR (DMSO-d6): δ 9.29 (s, 1H), 4.70(d, 1H), 4.061 (d, 1H), 2.95 (d, 1H), 2.69 (d, 1H), 2.19 (m, 1H), 2.07 (m, 2H), 1.90 (m, 1H);

Purity as determined by HPLC: 89.86%;

X-ray powder diffraction pattern (2 Theta Values): 11.30 (± 0.2), 13.01 (± 0.2), 13.67 (± 0.2), 14.19 (± 0.2), 15.16 (± 0.2), 16.85 (± 0.2), 17.77 (± 0.2), 18.13 (± 0.2), 18.93 (± 0.2), 19.18 (± 0.2),

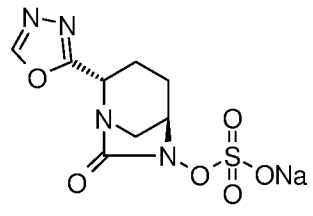
20.37 (± 0.2), 21.35 (± 0.2), 22.12 (± 0.2), 22.65 (± 0.2), 23.97 (± 0.2), 25.09 (± 0.2), 25.33 (± 0.2), 26.03 (± 0.2), 26.38 (± 0.2), 26.84 (± 0.2), 28.37 (± 0.2), 28.63 (± 0.2), 29.15 (± 0.2), 29.65 (± 0.2), 30.61 (± 0.2), 31.95 (± 0.2), 33.41 (± 0.2) and 33.96 (± 0.2).

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°

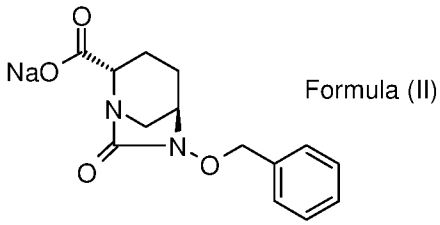
CLAIMS

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

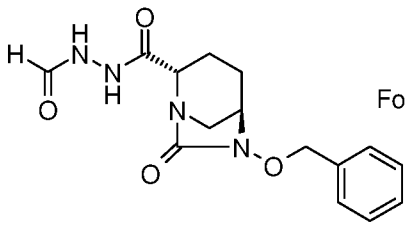


Formula (I)

(a) converting a compound of Formula (II) to a compound of Formula (III);

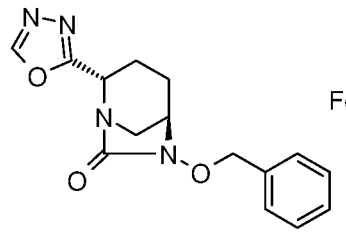


Formula (II)



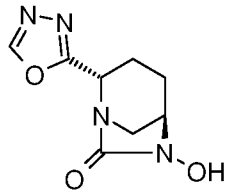
Formula (III)

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



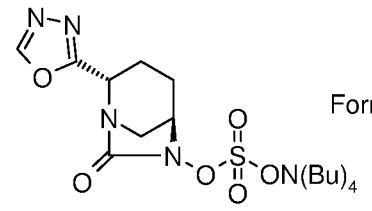
Formula (IV)

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



Formula (V)

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



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

2. The process according to Claim 1, wherein the compound of Formula (III) is obtained by reacting the compound of Formula (II) with formyl hydrazine in presence of the coupling agent.

3. The process according to Claim 2, wherein the coupling agent is 1-hydroxybenzotriazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, *N,N'*-dicyclohexyldiimde, (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) or a mixture thereof.

4. The process according to Claim 1, wherein the compound of Formula (IV) is obtained by cyclizing a compound of Formula (III) in presence of a cyclizing agent selected from methanesulfonic acid chloride, p-nitrophenylsulphonic acid chloride, p-tolylsulfonylchloride, or iodine/triphenylphosphine/triethylamine combination.

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

6. The process according to Claim 5, wherein the transition metal catalyst is palladium on carbon and hydrogen source is hydrogen gas.

7. The process according to Claim 1, wherein the compound of Formula (VI) is obtained by sulphonating the compound of Formula (V), followed by the formation of tetrabutylammonium salt.

8. The process according to Claim 7, wherein sulphonation is carried out in the presence of the sulfonating reagent selected from sulphur trioxide pyridine complex, sulfur trioxide dimethylformamide complex, sulfur trioxide triethylamine complex or a mixture thereof.

9. The process according to Claim 1, wherein the compound of Formula (VI) is converted to the compound of Formula (I) by contacting with a sodium exchange resin.

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

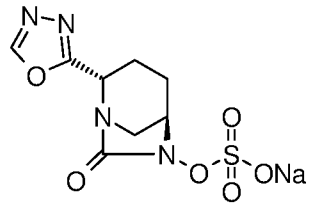
11. The compound of Formula (I) according to Claim 10, having an X-ray powder diffraction pattern comprising a peak selected from the group consisting of 11.30 (± 0.2), 13.01 (± 0.2), 13.67 (± 0.2), 14.19 (± 0.2), 15.16 (± 0.2), 16.85 (± 0.2), 17.77 (± 0.2), 20.37 (± 0.2), 21.35 (± 0.2), 22.12 (± 0.2), 23.97 (± 0.2), 26.03 (± 0.2), 26.84 (± 0.2), 28.63 (± 0.2), 30.61 (± 0.2), 31.95 (± 0.2) and 33.96 (± 0.2) degrees 2 theta.

12. The compound of Formula (I) according to Claim 10, having an X-ray powder diffraction pattern comprising a peak selected from the group consisting 11.30 (± 0.2), 13.01 (± 0.2), 13.67 (± 0.2), 14.19 (± 0.2), 15.16 (± 0.2), 16.85 (± 0.2), 17.77 (± 0.2), 18.13 (± 0.2), 18.93 (± 0.2), 19.18 (± 0.2), 20.37 (± 0.2), 21.35 (± 0.2), 22.12 (± 0.2), 22.65 (± 0.2), 23.97 (± 0.2), 25.09 (± 0.2), 25.33 (± 0.2), 26.03 (± 0.2), 26.38 (± 0.2), 26.84 (± 0.2), 28.37 (± 0.2), 28.63 (± 0.2), 29.15 (± 0.2), 29.65 (± 0.2), 30.61 (± 0.2), 31.95 (± 0.2), 33.41 (± 0.2) and 33.96 (± 0.2) degrees 2 theta.

13. A compound of Formula (I) having purity of at least 89% as determined by HPLC.

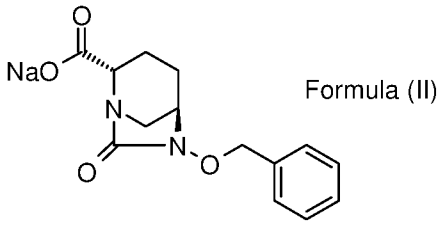
14. A pharmaceutical composition comprising a compound of Formula (I) according to any one of the Claims 10 to 13.

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

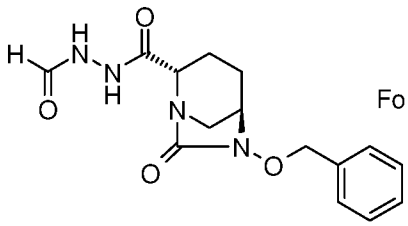


Formula (I)

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

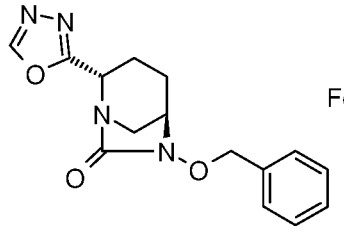


Formula (II)



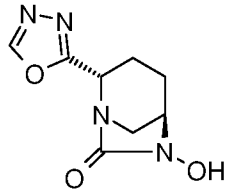
Formula (III)

(b) cyclizing a compound of Formula (III) in presence of p-tolylsulfonylchloride to obtain a compound of Formula (IV);



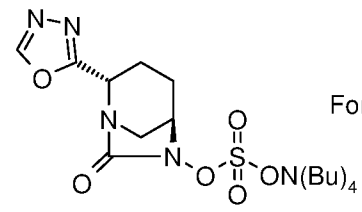
Formula (IV)

(c) hydrogenolysis of a compound of Formula (IV) in presence of 10% palladium over carbon and hydrogen gas to obtain a compound of Formula (V);



Formula (V)

(d) reacting a compound of Formula (V) with a suphonating reagent, followed by the treatment with tetrabutylammonium hydrogen sulphate to obtain a compound of Formula (VI); and



Formula (VI)

(e) contacting a compound of Formula (VI) with a sodium exchange resin to obtain a compound of Formula (I).

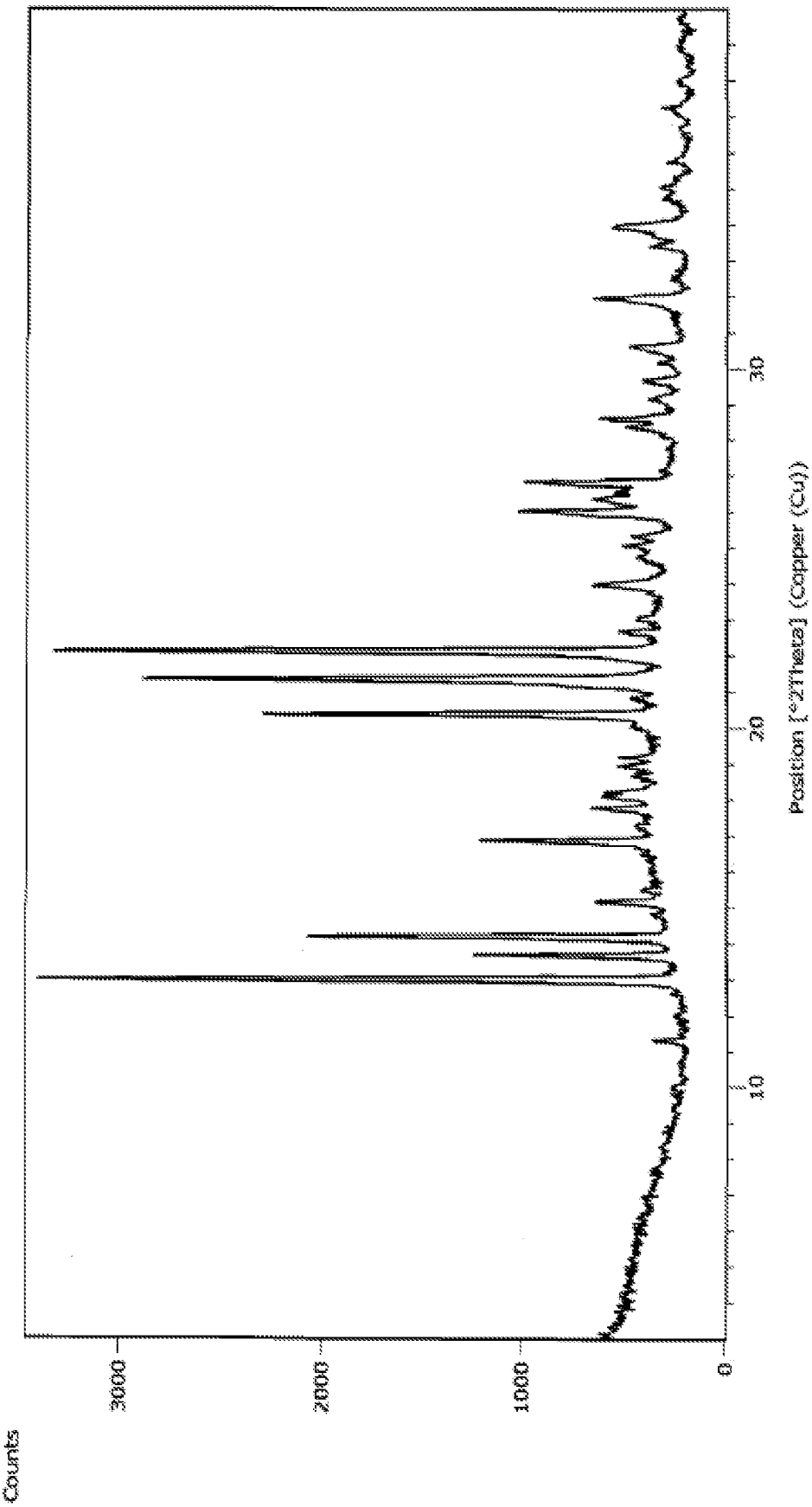


Figure 1: X-ray powder diffraction pattern of a compound of Formula (I) in crystalline form

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/051719

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08 A61K31/439 A61P31/04
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 A61K A61P

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/149121 A1 (CUBIST PHARM INC [US]) 3 October 2013 (2013-10-03) page 59; claims; example 3; compound 701	1-9,15
X	WO 2013/030735 A1 (WOCKHARDT LTD [IN]; BHAGWAT SACHIN [IN]; DESHPANDE PRASAD KESHAV [IN];) 7 March 2013 (2013-03-07) page 18 - page 19; claim 1 page 13, paragraph 3	1-9,15
Y	WO 2014/135929 A1 (WOCKHARDT LTD [IN]) 12 September 2014 (2014-09-12) cited in the application *Scheme 1*; page 1 - page 2; claim 1	1-9,15

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
25 May 2016	09/08/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Härtinger, Stefan

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/051719

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/135930 A1 (WOCKHARDT LTD [IN]) 12 September 2014 (2014-09-12) claims 1-9 -----	1-9,15
A	LAWRENCE X. YU ET AL: "Scientific considerations of pharmaceutical solid polymorphism in abbreviated new drug applications", PHARMACEUTICAL RESEARCH, vol. 20, no. 4, 1 January 2003 (2003-01-01), pages 531-536, XP055077459, ISSN: 0724-8741, DOI: 10.1023/A:1023285627778 page 531; figure 1 -----	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/051719

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013149121 A1	03-10-2013	AR 090590 A1	26-11-2014
		AU 2013237939 A1	30-10-2014
		CA 2868553 A1	03-10-2013
		CN 104334558 A	04-02-2015
		CO 7091178 A2	21-10-2014
		EP 2831075 A1	04-02-2015
		JP 2015514095 A	18-05-2015
		KR 20140144254 A	18-12-2014
		PH 12014502196 A1	10-12-2014
		RU 2014143821 A	27-05-2016
		SG 11201406123T A	30-10-2014
		TW 201343645 A	01-11-2013
		US 2013296290 A1	07-11-2013
		US 2013296291 A1	07-11-2013
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		US 2015031665 A1	29-01-2015
		WO 2013149121 A1	03-10-2013
WO 2013030735 A1	07-03-2013	AU 2012303693 A1	07-11-2013
		CA 2845108 A1	07-03-2013
		CN 103649088 A	19-03-2014
		EP 2872510 A1	20-05-2015
		JP 5677634 B2	25-02-2015
		JP 2014525434 A	29-09-2014
		KR 20140025526 A	04-03-2014
		NZ 616959 A	30-01-2015
		RU 2014107902 A	10-10-2015
		US 2014088068 A1	27-03-2014
		US 2014288064 A1	25-09-2014
		US 2015336957 A1	26-11-2015
		WO 2013030735 A1	07-03-2013
		ZA 201307963 B	28-01-2015
WO 2014135929 A1	12-09-2014	AU 2013380572 A1	10-09-2015
		CA 2902422 A1	12-09-2014
		CN 105164132 A	16-12-2015
		JP 2016511269 A	14-04-2016
		NZ 711343 A	29-07-2016
		US 2016002236 A1	07-01-2016
		WO 2014135929 A1	12-09-2014
WO 2014135930 A1	12-09-2014	AU 2013380573 A1	10-09-2015
		WO 2014135930 A1	12-09-2014

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/051719

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.:

1-9, 15

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: 1-9, 15

   Process for preparing compound (I)

   ---

2. claims: 10-14

   Compound (I) in pure or crystalline form
