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REGULAR ARTICLE

The synthesis of sutezolid and eperezolid using proline catalyzed α-aminoxylation of an aldehyde

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Abstract. The given article describes the synthesis of 2-Oxazolidinone ring *via* proline catalyzed stereoselective α-aminoxylation of aldehyde. 2-Oxazolidinone ring is a common core structure during the synthesis of oxazolidinones class molecules. Using this simple, facile and efficient methodology, Linezolid and sutezolid were prepared using asymmetric catalysis.

Keywords. Selective α-aminoxylation; Oxazolidinone class compounds; Sutezolid; Eperezolid.

1. Introduction

Organocatalysis is a rapidly developing field that provides a discrete advantage for achieving enantioselectivity during the asymmetric synthesis of bioactive compounds. The inexpensive and environmentally friendly naturally occurring chiral catalysts that are employed under mild and simple reaction conditions have gained significant prominence in the recent past. Proline, a versatile catalyst, possesses beneficial enantiocatalytic activity in an atom economical manner towards the synthesis of chiral bioactive molecules,[1–8] Chiral α-hydroxy-carbonyl compounds are important key intermediates for the synthesis of oxazolidinones. They are synthesized using proline as a catalyst through α-functionalization of aldehydes or ketones with reducing agents that includes various compounds such as linezolid, eperezolid, sutezolid and rivaroxaban. The core structure of these chiral molecules contains a basic 2-Oxazolidinone ring (Figure 1).

The asymmetric catalytic route reported for the synthesis of Linezolid and Eperezolid involves the construction of oxazolidinone ring through intramolecular cyclization of chiral diols that are synthesized *via* proline catalyzed α- amino oxylation of corresponding aldehydes.[9] However, protection and deprotection of the intermediates is a major concern that not only increases the number of steps but ultimately hampers the yield of the product. Also, the use of hazardous reagents and the formation of azide intermediates are some of the drawbacks of the synthetic route.

To overcome these drawbacks, it is envisioned that the similar asymmetric approach[9] can be modified using a different method to introduce the amino group *via* Michael addition of phthalimide on the corresponding aldehyde to avoid protection and deprotection steps and to avoid the usage of hazardous reagent and formation azide intermediate. Accordingly, 2-oxazolidinone ring (Figure 1) can be synthesized *via* proline-directed selective α-aminoxylation of (4) with significant control over the undesired isomer. The chiral compound thus obtained is then further converted to oxazolidinone through transamination and carbonyl insertion. Based on this hypothesis and literature search, the following methodology is proposed for the synthesis of oxazolidinone core (Figure 2).

The proposed synthetic analyses for the synthesis of sutezolid and eperezolid are depicted in Figures 3 and 4, respectively.

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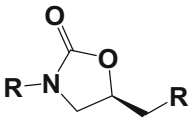

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Figure 1. Core 2-Oxazolidinone ring.

2. Experimental

2.1 *Raw materials and physical measurement*

All solvents were purified and dried by standard procedures prior to use. Reaction monitoring was monitored using thin-layer chromatography (TLC) was performed on Merck 60 F254 silica-gel plates and visualization was accomplished by ultraviolet (UV) irradiation or iodine or potassium permanganate. Crude products were purified by column chromatography on 100- to 200-mesh silica gel. The yields reported are the yields obtained after the column chromatographic separation. HRMS spectra were recorded on Waters Xevo G2 QTOF. Mass spectra were recorded on a Perkin-Elmer instrument. Infrared (IR) spectra were recorded on a Perkin spectrum 400. BX 2 Fourier transform (FT)–IR instrument as a thin film or KBr pellets and are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra are recorded on Bruker400 and 500 MHz FT-NMR spectrometer using $CDCl_3$, DMSO or D_2Oas solvent. Chemical shifts are reported in δ ppm with reference to tetramethylsilane (TMS) as an internal standard. Specific Optical rotation was carried out on Autopol IV, Sr. No. 80646. Chiral Purity was analyzed by Chiral HPLC, SHIMADZU LC-2010 CHT, CHROMELEON version 6.80, CHIRALPACK IA column, Particle size 5 µm, Dimensions 4.6 mmϕ x 250 mmL. Oven temperature 25 °C, mobile phase ethanol: n-Hexane (20:80) ratio. Flow rate 1 ml/min.

2.2 *Synthesis of 3-(1,3-dioxoisoindolin-2-yl)propanal (4)*

To a solution of phthalimide (**3**) (50.0 g; 0.3398 mol) in (200 mL) ethyl acetate, freshly distilled acryl aldehyde (**2**) (20.95 g; 0.3738 mol) was added with constant stirring and the mixture was heated to 65 °C. After stirring for 5 min, 40% solution of N-benzyl trimethylammonium hydroxide in methanol (0.42 mL; 0.020 mol) was added at 65 °C. After complete consumption of starting material, solvent was distilled out to yield crude solid mass, which was then triturated in ethyl ether to give (**4**). White Solid; Yield: 63.27 g (91%); M.p.: 123-126 °C; IR (KBr): υ_{max}; 2947, 2848, 2742, 2306, 1767, 1705, 1610, 1470, 1442, 1387, 1135, 1028, 891, 720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 9.81 (s, 1H, aldehyde H), 7.82-7.85 (m, 2H, aryl H) 7.71-7.74 (m, 2H aryl H), 4.02-4.05 (t, J = 7.0 Hz 2H, CH_2), 2.86-2.89 (m, 2H, CH_2). ^{13}C

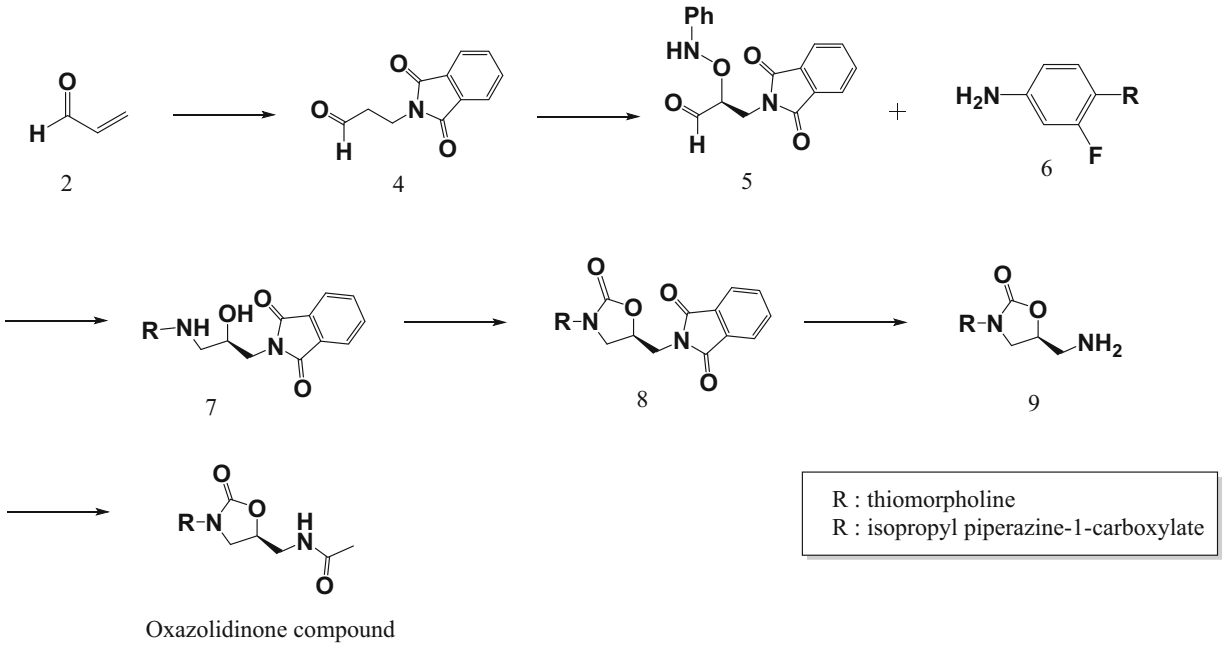

Figure 2. A general methodology for the synthesis of Oxazolidinone class compounds.

NMR (500 MHz, $CDCl_3$): δ ppm 201.45 (carbonyl C), 169.21 (carbonyl C), 134.35, 132.58 and 122.98 (Aryl CH), 41.49 (CH_2), 31.40 (CH_2); HRMS for $C_{11}H_9O_3N$: [M+1] = 204.0631.

2.3 *General method for the synthesis of amino alcohol intermediates (7)*

Solution of D-Proline (0.0615 mol) in chloroform (10 vol.) was cooled to 4 °C. To this nitrosobenzene (0.0820 mol) and 3-phthalimodo propanal (**3**) (0.2462 mol) was added. The reaction mixture was stirred and maintained at 0-4 °C until reaction mass was determined to be complete by TLC. The reaction mass then concentrated and diluted with dichloromethane (19.9 vol.). The resulting solution was then added to a solution of the corresponding amine (**6**) (0.1642 mol) in dichloromethane (71.9 vol. mL) at 0 °C. After stirring for five minutes, sodium triacetoxyborohydride (0.1642 mol) was added at 0 °C. The reaction mass was maintained at 0 °C and monitored the course of the reaction by TLC. After completion of reaction, saturated sodium bicarbonate solution was added to reaction mixture and extracted with DCM. The organic layer was concentrated and methanol (19.9 vol.) was added to residual mass followed by $CuSO_4$ (30 mmol %) and stirred for 12 h. It was concentrated under vacuum and purified by column chromatography to give amino alcohol intermediate (**7**).

2.4 *Synthesis of (R)-2-(3-((3-fluoro-4-thiomorpholinophenyl)amino) -2-hydroxypropyl)isoindoline-1,3-dione (7a)*

Intermediate (**7a**) was prepared by the method adopted for the preparation (**7**) using corresponding amine (**6a**). Brown solid; Yield: 34.1 g (79%); M.p.: 164-165 °C; [α] 11° (*c* 0.5, ACN); enantiomeric excess - 100%, IR (KBr): υ_{max}; 3511, 3343, 2819, 1773, 1698, 1523 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ ppm 2.70-2.72 (t, 4H, CH_2), 2.95-3.00 (m, 1H, CH_2), 3.06-3.07 (t, 4H, CH_2), 3.10-3.15 (m, 1H, CH_2), 3.58-3.70 (m, 2H, CH_2), 3.96-4.01 (m, 1H, CH), 5.16-5.17 (d, 1H, NH), 5.56-5.59 (t, 1H, OH), 6.35-6.37 (dd, J = 11 Hz and J = 2.5 Hz, 1H, aryl 1H), 6.41-6.44 (dd, J = 12.5 Hz and J = 2.5 Hz, 1H, aryl 1H), 6.83-6.87 (t, J = 18.5 Hz and J = 9.51 Hz, aryl H), 7.82-7.88 (m, aryl 4H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 31.40 (CH_2), 41.49 (CH_2), 122.98, 132.58 and

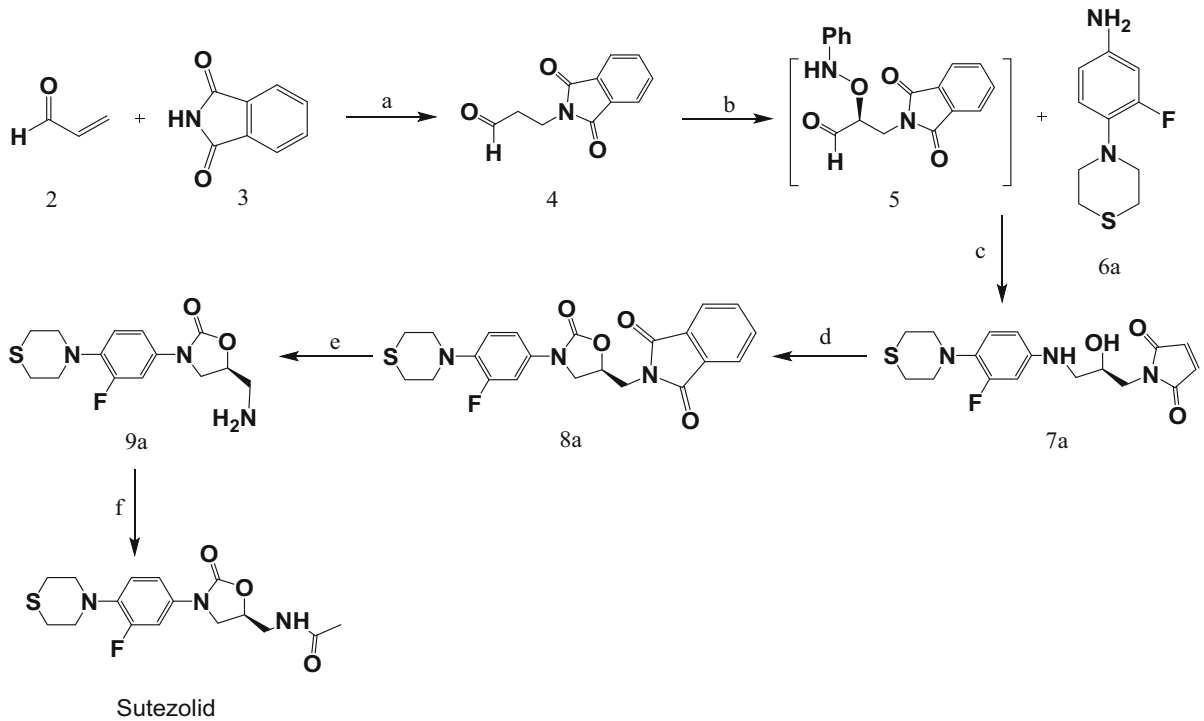

Figure 3. Reagents and conditions: (a) N-benzyltrimethylammonium hydroxide in MeOH, Ethyl acetate, 65 °C. (b) D-Proline, Nitrosobenzene, chloroform, 0-4 °C. (c) 5, sodium triacetoxyborohydride, DCM, 0-5 °C, $CuSO_4$ methanol. (d) dimethylaminopyridine, carbonyldiimidazole, DCM, 30-35 °C (e) 40% aqueous methylamine, isopropyl alcohol, 70-75 °C. (f) Acetic anhydride, dichloromethane.

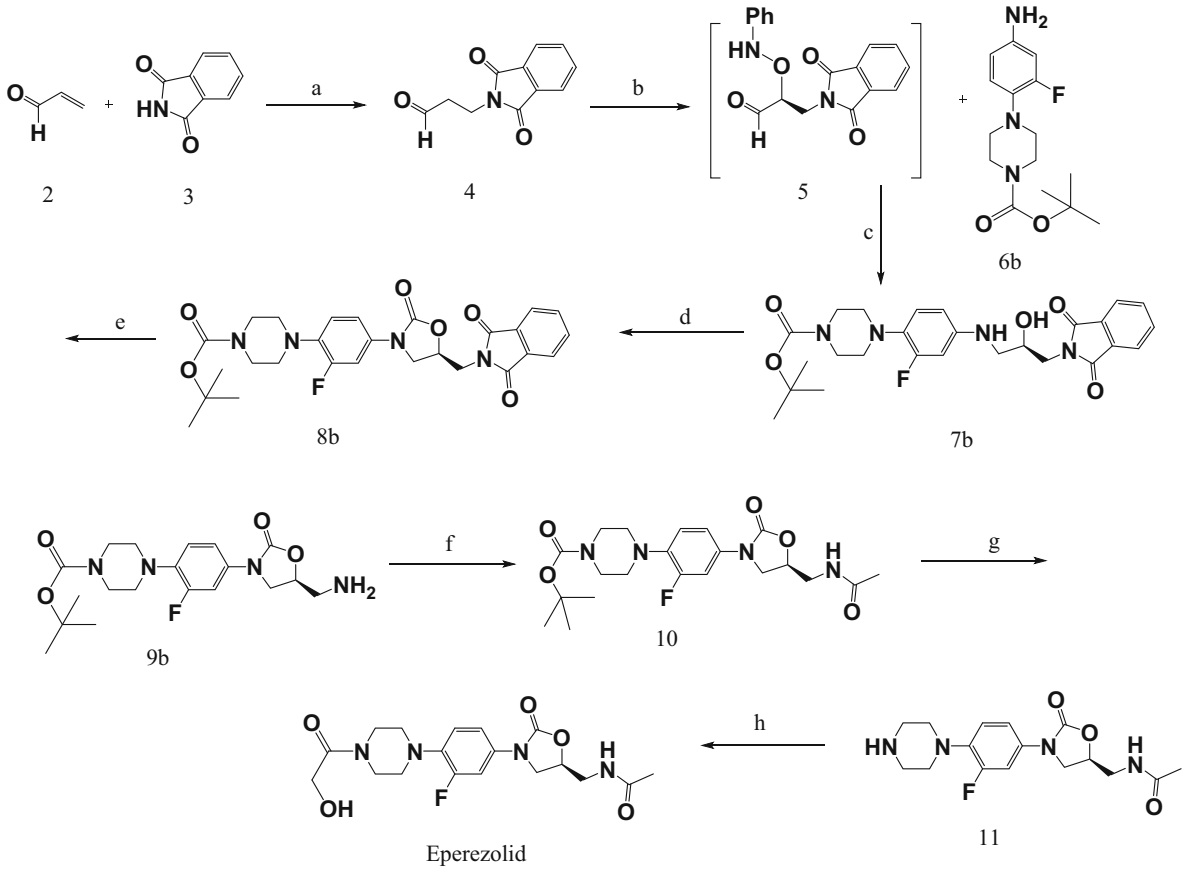

Figure 4. Reagents and conditions: (a) N-benzyltrimethylammonium hydroxide in MeOH 65 °C. (b) D-Proline, Nitrosobenzene, (c) tert-butyl 4-(4-amino-2-fluorophenyl) piperazine-1-carboxylate, sodiumtriacetoxyborohydride, 0-5 °C, $CuSO_4$ methanol. (d) N,N-dimethylaminopyridine, carbonyldiimidazole, dichloromethane, 30-35 °C (e) 40% aqueous methyl amine, isopropyl alcohol, 70-75 °C. (f) Acetic anhydride, dichloromethane. (g) Trifluoroacetic acid, dichloromethane. (h) Glycolic acid, EDC.HCl, DMF.

134.35 (Aryl C), 169.21 (carbonyl C), 201.45 (carbonyl C); HRMS for $C_{21}H_{22}FN_3O_3S$: [M+1] = 416.1460.

2.5 *Synthesis of tert-butyl (R)-4-(4-((3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)amino)-2-fluorophenyl)piperazine-1-carboxylate (7b)*

Intermediate (**7b**) was prepared by the method adopted for the preparation (**7**) using corresponding amine (**6a**). Brown solid; Yield: 33.5 (82%); M.p.: 181-187 °C; [α] 10° (*c* 0.5, ACN) IR (KBr): υ_{max}; 3474, 2930, 1747, 1716, 1668, 1520, 1424 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ ppm 1.42 (s, 9H, CH_3), 2.77-2.78 (t, 4H, CH_2), 2.95-3.00 (m, 1H, CH_2), 3.10-3.15 (m, 1H,CH_2), 3.57-3.67 (m, 2H, CH_2), 3.95-4.01 (m, 1H, CH), 5.15-5.16 (d, 1H, OH), 5.55-5.57 (t, 1H, NH), 6.35-6.37 (dd, J = 6.0 Hz and J = 2.5 Hz, 1H, aryl H), 6.40-6.46 (dd, J = 12.5 Hz and J = 2.5 Hz, 1H, aryl H), 6.81-6.85 (t, J = 10.0 Hz, 1H, aryl 2H), 7.82-7.88 (m, 4H, aryl H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 28.05 (CH_3), 42.37 (CH_2), 44.14 (CH_2), 47.57 (CH_2), 51.18 (CH_2), 66.29 (CH), 78.86 (C), 100.21, 121.02, 122.89, 128.84, 131.80, 134.23, 146.00, 153.79 (aryl C and CH), 155.53, 168.07 (carbonyl C); HRMS for $C_{26}H_{31}FN_4O_5$: [M+1] = 499.5607.

2.6 *Synthesis of (s)-2-(3-((3-fluoro-4-thiomorpholinophenyl)amino)-2-hydroxypropyl)isoindoline-1,3-dione (isomer of 7a)*

L-Proline solution (0.94 g; 0.0082 mol) in chloroform (43.5 mL) was cooled to 4 °C. To it, nitroso benzene (4.13 g; 0.0406 mol) and (**4**) (25.0 g; 0.1231 mol) was added with constant stirring. The reaction was maintained at 0-4 °C until reaction was complete which was monitored by TLC. It was then concentrated under vacuum and diluted with dichloromethane (87.5 mL). Resulting solution was added to a solution of 3-fluoro-4-thiomorpholinoaniline (**6a**) (17.42 g; 0.0821 mol) in dichloromethane (283 mL) at 0 °C. After stirring for

five minutes, sodium triacetoxy borohydride (17.4 g; 0.0821 mol) was added at 0 °C. Reaction mass was maintained at 0 °C and monitored by TLC. After completion of reaction, saturated sodium bicarbonate solution was added to reaction mixture and extracted with DCM. Organic layer was concentrated and methanol (87.5 mL) was added to residual mass followed by $CuSO_4$ (30 mmol %) and stirred for 12 h. It was then concentrated under vacuum and purified by column chromatography to yield isomer of (**7a**). Brown solid; Yield: 34.1 g (79%); M.p.: 163-164 °C; [α] −13° (*c* 0.5, ACN); enantiomeric excess - 100%, IR (KBr): υ_{max}; 3511, 3343, 2819, 1773, 1698, 1523 cm^{-1}; ^1H NMR (500 MHz, DMSO): δ ppm 2.70-2.72 (t, 4H, CH_2), 2.95-3.00 (m, 1H, CH_2), 3.06-3.07 (t, 4H, CH_2), 3.10-3.15 (m, 1H, CH_2), 3.58-3.70 (m, 2H, CH_2), 3.96-4.01 (m, 1H, CH), 5.16-5.17 (d, 1H, NH), 5.56-5.59 (t, 1H, OH), 6.35-6.37 (dd, *J* = 11 Hz and *J* = 2.5 Hz, 1H, aryl 1H), 6.41-6.44 (dd, *J* = 12.5 Hz and *J* = 2.5 Hz, 1H, aryl 1H), 6.83-6.87 (t, *J* = 18.5 Hz and *J* = 9.51H, aryl H), 7.82-7.88 (m, aryl 4H); ^{13}C NMR (500 MHz, DMSO): δ ppm 27.64 (CH_2), 42.38 (CH_2), 47.57 (CH_2), 53.90 (CH_2), 66.31 (CH) 100.26, 107.87 122.11, 122.91, 130.12, 131.81, 134.24, 146.17, 155.78 (Aryl C and CH), 168.08 (Carbonyl C); HRMS for $C_{21}H_{22}FN_3O_3S$: [M+1] = 416.1434.

2.7 *Synthesis of tert-butyl (S)-4-(4-((3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)amino)-2-fluorophenyl)piperazine-1-carboxylate (isomer of 7b)*

L-proline (0.945 g 0.0307 mol) in chloroform (43.5 mL) was cooled at 4 °C. To this solution, nitrosobenzene (5.05 g 0.0410 mol) and (**4**) (25.0 g 0.1231 mol) was added with constant stirring and the reaction was maintained at 0-4 °C. The reaction mass then concentrated and diluted with dichloromethane (87.5 mL). Resulting solution was added to a solution of tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate (**6b**) (24.2 g 0.0821 mol) in dichloromethane (283 mL) at 0 °C. After stirring for 5 min., sodium triacetoxyborohydride (17.4 g, 0.0821 mol) was added at 0 °C. Reaction mass was maintained at 0 °C and the reaction was monitored by TLC. After completion of reaction, saturated sodium bicarbonate solution was added to reaction mixture and extracted with dichloromethane. Organic layer was concentrated and methanol (87.5 mL) was added to residual mass followed by $CuSO_4$ (30 mmol %) and stirred for 12 h. Concentrated the reaction mass under vacuum and purified by column chromatography to give (**7b**). Brown solid; Yield: 16.0 (80%); [α] −8° (*c* 0.5, ACN); enantiomeric excess – 99.52%, IR (KBr): υ_{max}; 3474, 2930, 1747, 1716, 1668, 1520, 1424 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ ppm 1.42 (s, 9H, CH_3), 2.77-2.78 (t, 4H, CH_2), 2.95-3.00 (m, 1H,CH_2), 3.10-3.15 (m, 1H,CH_2), 3.57-3.67 (m, 2H, CH_2), 3.95-4.01 (m, 1H, CH), 5.15-5.16 (d, 1H, OH), 5.55-5.57 (t, 1H, NH), 6.35-6.37 (dd, *J* = 6.0 Hz and *J* = 2.5 Hz, 1H, aryl H), 6.40-6.46 (dd, *J* = 12.5 Hz and *J* = 2.5 Hz, 1H, aryl H), 6.81-6.85 (t, *J* = 10.0 Hz, 1H, aryl2H), 7.82-7.88 (m, 4H, aryl H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 28.05 (CH_3), 42.37 (CH_2), 44.14 (CH_2), 47.57 (CH_2), 51.18 (CH_2), 66.29 (CH), 78.86 (C), 100.21, 121.02, 122.89, 128.84, 131.80, 134.23, 146.00, 153.79 (aryl C and CH), 155.53, 168.07 (carbonyl C); HRMS for $C_{26}H_{31}FN_4O_5$: [M+1] = 499.5608.

2.8 *General method for the synthesis of carbamate intermediates (8)*

To a solution of compound (**7**) (0.0742 mol) in dichloromethane (10 vol.), 1,1'-carbonyldiimidazole (0.1113 mol) was added followed by the addition of the catalytic amount of dimethyl-amino-pyridine (0.0148 mol). The reaction mixture was heated to 30-35 °C under stirring and the progress of the reaction was monitored by TLC. After completion of the reaction, the crude mass was washed with DM water and 20% brine solution. The organic layer was concentrated under vacuum to yield carbamate intermediate (**8**).

2.9 *Synthesis of (S)-2-((3-(3-fluoro-4-thiomorpholinophenyl)-2-oxooxazolidin-5-yl)methyl)isoindoline-1,3-dione (8a)*

Intermediate (**8a**) was prepared from intermediate (**7a**) using general method adopted for the synthesis of (**8**). White solid; Yield: 30.3 g (95%); M.p.: 204-215 °C; [α] −64° (*c* 0.5, CH_2Cl_2) IR (KBr): υ_{max}; 2823, 1747, 1719, 1515cm^{-1}; ^1H NMR (500 MHz, DMSO): δ ppm 2.73-2.75 (t, 4H, CH_2), 3.19-3.21 (m, 4H, CH_2), 3.86-3.92 (m, 2H, CH_2), 3.97-4.01 (m, 1H, CH_2), 4.15-4.19 (t, 1H, CH_2), 4.91-4.99 (m, 1H, CH_2), 7.08-7.16 (m, aryl 2H), 7.41-7.45 (dd, *J* = 8.0 Hz and *J* = 2.5aryl 1H), 7.86-7.92 (m, aryl 4H); ^{13}C NMR (500 MHz, DMSO): δ ppm 27.1 (CH_2), 39.01(CH_2), 42.38 (CH_2), 47.56 (CH2), 53.90 (CH), 66.31 (CH) 100.06, 100.25, 107.86, 122.08, 122.11, 122.90, 130.03, 130.11,

131.81, 134.24, 146.17, 146.25, 155.71, 155.68, 167.77; HRMS for $C_{22}H_{20}FN_3O_4S$: [M+1] = 442.1266.

2.10 *Synthesis of tert-butyl (S)-4-(4-(5-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazine-1-carboxylate (8b)*

Intermediate (8a) was prepared from intermediate (**7a**) using general method adopted for the synthesis of (**8**). White solid; Yield: 29.03g (92%); M.p.: 202-204 °C; [α] −50° (*c* 0.5, $CHCl_3$) IR (KBr): υ_{max}; 2978.03, 1733, 1716, 1688, 1520, 1424 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ ppm 1.49 (s, 9H, CH_3), 2.99-3.00 (t, 4H, CH_2), 3.59-3.61 (t, 4H, CH_2), 3.86-3.89 (dd, 1H, CH_2), 3.96-4.00 (dd, 1H, CH_2), 4.10-4.17 (m, 2H, CH_2), 4.96-5.01 (m, 1H, CH), 6.91-6.95 (t, *J* = 10.0 Hz 1H, aryl H), 7.10-7.7.12 (dd, *J* = 10 Hz and *J* = 2.5 Hz, 1H, aryl H), 7.40-7.44 (dd, *J* = 10.0 Hz and *J* = 2.0 Hz, 1H, aryl H), 7.75-7.79 (m, 2H, aryl H), 7.87-7.91 (m, 2H, aryl H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 28.43 (CH_3), 40.73 (CH_2), 48.47 (CH_2), 50.68 (CH_2), 69.62 (CH), 79.91 (C), 107.46, 114.00, 119.38, 123.71, 131.68, 133.19, 134.47, 136.48, 153.81(aryl C and CH), 154.57, 156.53, 168.00 (carbonyl C); HRMS for $C_{27}H_{29}FN_4O_6$: [M+1] = 525.2161.

2.11 *Synthesis of (S)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholinophenyl)oxazolidin-2-one (9a)*

To a solution of (**8a**) (25.0 g 0.0566 mol) in isopropyl alcohol (300 mL), 40% aqueous methylamine (33.8 mL 0.4358 mol) solution was added with constant stirring. Reaction mixture was then heated and maintained at 70-75 °C and the reaction was monitored by TLC. After completion, the reaction mass was cooled and concentrated under a vacuum. Dichloromethane was added to the concentrated mass followed by the addition of aqueous hydrochloric acid and it was stirred the biphasic mass and separated organic and aqueous layers. The organic layer was discarded and the aqueous layer was treated with 5% aqueous sodium bicarbonate solution and extracted with ethyl acetate three times. Combined all the organic layers were then concentrated under vacuum to give compound (**9a**). White solid; Yield: 17.8 g (95%); M.p.: 123-126 °C; IR (KBr): υ_{max}; 3227, 2820, 1743, 1631, 1515 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ ppm 2.84-2.85 (t, 4H, CH_2), 3.28-3.30 (t, 4H, CH_2), 3.40-3.46 (m, 2H, CH2) 3.86-3.89 (m, 1H, CH_2), 4.28-4.32 (m, 1H, CH_2), 5.04-5.10 (m, 1H, CH), 7.18-7.25 (m, 2H, aryl H), 7.39-7.43 (dd, *J* = 10.0 Hz and *J* = 5.0 Hz, aryl 1H), 7.58 (s, 1H, aryl H), 9.81-9.82 (s, 1H aldehyde H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 26.02 (CH_2), 41.21 (CH_2), 47.28 (CH_2), 53.09 (CH_2), 71.44 (CH), 106.55, 114.21, 120.59, 129.35, 133.91, 154.13, (aryl C and CH), 169.24 (carbonyl C); HRMS for $C_{14}H_{18}FN_3O_2S$: [M+1] =312.1162.

2.12 *Synthesis of sutezolid*

Acetic anhydride (5.90 g; 0.0578 mol) was added to the solution of (**9a**) (15.0 g; 0.04823 mol) in dichloromethane (75 mL) under constant stirring and the progress of reaction was monitored by TLC. After completion of reaction, aqueous sodium bicarbonate was added and organic layer were separated from the aqueous layer. It was then washed with water, 20% brine solution, concentrated under vacuum and the crude mass thus obtained was recrystallized in methanol to yield sutezolid. White solid; Yield: 16.2 g (95%); M.p.: 171-173 °C; C; [α] −8° (*c* 1, $CHCl_3$); IR (KBr): υ_{max}; 3360, 2852, 1741, 1673, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ ppm 2.01 (S, 3H, CH_3) 3.04-3.05 (t, 4H, CH_2), 3.62-3.66 (m, 2H, CH_2), 3.75-3.78 (dd, 1H, CH_2), 3.85-3.87 (t, 4H, CH_2), 4.00-4.03 (t, 1H CH_2), 4.75-4.80 (m, 1H, CH), 6.73-6.76 (t, 1H, NH), 6.90-6.94 (t, 1H, aryl H), 7.05-7.07 (dd, *J* = 10.0 Hz and *J* = 5.0 Hz, aryl 2H), 7.40-7.44 (dd, *J* = 10.0 Hz and *J* = 2.0 Hz, aryl 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 23.01 (CH_2), 41.87 (CH_2), 47.62 (CH_2), 50.98 (CH_2), 66.89 (CH_2), 72.06 (CH), 107.43, 113.95, 118.89, 132.97, 136.41, 131.84, (aryl F), 154.46 (aryl CF), 161.38, 156.42 (carbamate carbonyl), 171.37 (carbonyl); HRMS for $C_{16}H_{20}FN_3O_3S$: [M+1] = 354.1280.

2.13 *Synthesis of tert-butyl (S)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazine-1-carboxylate (9b)*

To a solution of (**8b**) (25.0 g, 0.0476 mol) in (250 mL) isopropyl alcohol, 40% aqueous methylamine (27.2 ml, 0.3501 mol) was added and the reaction was heated up to 70-75 °C. After complete conversion, the reaction mass was cooled and concentrated under vacuum to give crude solid mass which was purified by column chromatography to yield (**9b**). White solid; Yield: 17.2 g (92%); M.p.: 123-126 °C; IR (KBr): υ_{max}; 3365, 3302, 2891, 1739,

1703, 1519, 1417 cm^{-1}; ^1H NMR (500 MHz, DMSO-d6): δ ppm 1.42 (s, 9H, CH_3), 2.80-2.83 (d, 2H CH_2), 3.47 (s, 4H, CH_2), 3.81-3.84 (dd, 1H, CH_2), 4.00-4.04 (t, 1H, CH_2), 4.57-4.61 (m, 1H, CH), 7.05-7.09 (t, J = 20.0 Hz and J = 10.0 Hz, aryl 2H), 7.19-7.21 (dd, J = 12.5 Hz and J =2.5 Hz, 1H, aryl H), 7.50-7.53 (dd, 1H, aryl H); ^{13}C NMR (500 MHz, DMSO-d6): δ ppm 28.04 (CH_3), 42.83 (CH_2), 44.16 (CH_2), 47.01 (CH_2), 50.34 (CH_2), 62.00 (CH_2), 73.94 (CH), 78.98(C), 106.29, 113.86, 119.77, 133.89, 135.22, 153.69 (aryl C and CH), 154.35 (carbonyl C), 155.63(carbonyl C); HRMS for $C_{29}H_{27}FN_4O_4$:[M+1] = 395.2096.

2.14 *Synthesis of tert-butyl (S)-4-(4-(5-(acetamidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazine-1-carboxylate (10)*

To a solution of (**9b**) (15.0 g, 0.0380 mol) in pyridine (75 mL), acetic anhydride (4.6 g, 0.0456 mol) was added and the mass was stirred at RT. The reaction mass was then quenched with sodium bicarbonate, the organic layer was separated and concentrated under vacuum. Crude solid obtained was purified by ethyl acetate-cyclohexane mixture (2:15) to give (**10**). White solid; Yield: 15.8 g (95%); M.p.: 170-176 °C; IR (KBr): υ_{max}; 3282, 2977, 1734, 1687, 1519, 1422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ ppm 1.49 (s, 9H, CH_3), 2.033 (s, 3H, CH_3), 3.08-3.10 (t, 4H, CH_2), 3.60-3.72 (m, 6H, CH_2), 3.75-3.78 (m, 1H, CH_2), 4.01-1.05 (t, 1H, CH_2), 4.76-4.79 (m, 1H, CH), 6.41 (broad s, 1H, NH), 6.93-6.96 (t, J = 10.0 Hz and J = 5.0 Hz, 1H, aryl H), 7.06-7.08 (dd, J = 10.0 Hz and J = 2.0 Hz, 1H, aryl H), 7.43-7.46 (dd, J = 12.0 Hz and J = 2.0 Hz, 1H, aryl H); ^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 23.08 (CH_3), 28.42 (CH_3), 41.94 (CH_2), 44.08 (CH_2), 47.63 (CH_2), 50.70 (CH_2), 71.95 (CH), 79.95(C) 107.40, 113.90, 119.45, 126.47, 133.19, 136.32, 154.37 (aryl C), 154.69 (carbonyl C), 156.53 (carbonyl C), 171.19 (carbonyl C), 201.97 (carbonyl C); HRMS for $C_{21}H_{29}FN_4O_5$: [M+1] = 437.2222.

2.15 *Synthesis of (S)-N-((3-(3-fluoro-4-(piperazin-1-yl)phenyl)-2-oxooxazolidin-5-yl)methyl)acetamide (11)*

Trifluoroaceticacid (30 mL) was added to a solution of (**9**) (15.0 g 0.0344 mol) in dichloromethane (150 mL) and it was stirred at RT. The reaction mass was concentrated under vacuum and purified by column chromatography to give (**10**). White solid; Yield: 10.4 (90%); M.p.: 198-201 °C; IR (KBr): υ_{max}; 3332, 3039, 2835, 1739, 1665, 1514, 1413 cm^{-1}; ^1H NMR (500 MHz, MeOD): δ ppm 1.98 (s, 3H, CH_3), 3.30-3.32 (t, 4H, CH_2), 3.39-3.41(m, 4H, CH_2), 3.56-3.57 (d, 2H, CH_2), 3.80-3.83 (m, 1H, CH_2), 4.12-4.15 (m, 1H, CH_2), 4.77-4.82 (m, 1H, CH), 7.11-7.15 (t, J = 9.0 Hz and J = 18.5 Hz, aryl 1H), 7.21-7.22 (m, 1H, aryl H), 7.23-7.57 (m, 1H, aryl H); ^{13}C NMR (500 MHz, MeOD): δ ppm 12.95 (CH_3), 33.64 (CH_2), 35.51 (CH_2), 39.62(CH_2), 39.4 (CH_2), 63.98 (CH_2), 98.8, 106.02, 111.70, 126.63, 146.48, 147.06, (aryl C and CH), 148.43, (carbonyl C)161.38, (carbonyl C); HRMS for $C_{16}H_{21}FN_4O_5$:[M+1] = 337.1686.

2.16 *Synthesis of Eperezolid*

To a solution of glycolic acid (2.7 g, 0.0356 mol) and triethylamine (4.5 g, 0.0447) in dimethylformamide (50 mL), EDC. HCl (6.8g, 0.0356 mol) was added with constant stirring at RT for half an hour. Compound (**10**) (10.0 g, 0.0297 mol) was added to the above solution and the progress of the reaction by TLC. The reaction mass was then quenched with water, extracted with ethyl acetate, concentrated under vacuum and the crude mass was purified by column chromatography to give eperezolid. White solid; Yield: 10.5 g (90%); M.p.: 170-175 °C; [α] −21° (*c* 1, DMSO); IR (KBr): υ_{max}; 3264, 1736, 1651, 1516, 1476, 1199 cm^{-1}; ^1H NMR (500 MHz, DMSO-d6): δ ppm 1.83 (m, 3H, CH_3), 2.96-2.97 (d, 4H, CH_2), 3.39-3.42 (t, 2H, CH_2), 3.50 (s, 2H, CH_2), 3.62 (s, 2H, CH_2), 3.69-3.72 (m, 1H, CH), 4.07-4.10 (t, 2H, CH_2) 4.63-4.65 (t, 1H OH), 4.69-4.72 (m, 1H, CH) 7.06-7.09 (t, J = 15.0 Hz and J = 5.0 Hz, aryl 1H), 7.17-7.19 (dd, J = 5.0 Hz and J = 2.0 Hz aryl 1H), 7.49-7.52 (dd, J = 2.0 Hz and J = 15 Hz aryl 1H) 8.23-8.25 (t, 1H NH); ^{13}C NMR (500 MHz, DMSO-d6): δ ppm 22.44 (CH_3), 41.36 (CH_2), 43.67 (CH_2), 47.28 (CH_2), 50.49 (CH_2), 60.12 (CH_2), 71.56 (CH), 106.48, 114.05, 114.09, 119.81, 133.69, 135.25, 153.67(aromatic C and CH), 154.05 (carbonyl C), 155.61 (carbonyl C), 170.00 (carbonyl C); HRMS for $C_{18}H_{23}FN_4O_5$:[M+1] = 394.1745.

3. Results and Discussion

Initially, the synthesis of sutezolid is undertaken as per the route outlined in Scheme 4.

During the synthesis, acryl aldehyde (**2**) and phthalimide (**3**) are condensed in presence of N-benzyltrimethylammonium hydroxide in methanol so as to

obtain (**4**) with 91% yield.[10] It is then subjected for selective α- aminoxylation. The attempts to isolate this intermediate (**5**) are unsuccessful due to its unstable nature. Also, it is reported that compounds containing α- hydroxyl aldehydes are reduced in-situ to diol intermediate.[11,12] The stereo selective α-hydroxylation of (**4**) using D-proline and nitrosobenzene results in the formation of intermediate (**5**) which undergoes *in situ* transamination with 3-fluoro-4-thio morpholinoaniline (**6a**) and sodium triacetoxy borohydride. The resulting mixture when treated with copper sulphate yields oily mass which is purified by column chromatography to give (**7a**) having enantiomeric excess of 100% with 79% yield. The enantiomeric excess is confirmed by the absence of isomer of compound (**7a**) which is synthesized through α-hydroxylation on compound (**4**) using L-proline instead of D-proline and nitrosobenzene followed by transamination with (**6a**) and sodium triacetoxy borohydride. The resulting mixture is then treated with copper sulphate to give an oily mass that on purification by column chromatography results in the formation of another isomer of (**7a**). It is then subjected to carbonyl insertion reaction using carbonyldiimidazole with catalytic amount of dimethylaminopyridine to give (**8a**) with 95% yield. This is further subjected to phthalimide deprotection using aqueous methylamine to give (**9a**) with 93% yield. Subsequent condensation of (**9a**) with acetic anhydride gives target molecule sutezolid with 94% yield. SOR of the isolated compound is in accordance with the reference.[13]

Similar strategy is adopted for the synthesis of eperezolid as outlined in Scheme 5. Compound (**4**) is converted to (**7b**) using same reaction conditions as described for the synthesis of compound (**7a**) using corresponding amine (**6b**) with 82% yield. The enantiomeric excess of (**6b**) is 100% confirmed by the isomer of compound (**7b**) synthesized using L-proline instead of D-proline. Compound (**7b**) is then subjected to carbonyl insertion reaction using carbonyl diimidazole and catalytic amount of dimethyl aminopyridine to give (**8b**) in 96% yield which is further subjected to phthalimide deprotection using aqueous methyl amine giving crude solid which is purified by column chromatography to give (**9b**) in 93% yield. Condensation of (**9b**) with acetic anhydride gives (**10**) with 95% yield. Compound (**10**) which was subjected to BOC deprotection to give (**11**) in 92%. Intermediate (**11**) condensed with glycolic acid in presence of EDC.HCl to give target molecule eperezolid in 90% yield. SOR of the isolated compound is in accordance with the reference.[14]

4. Conclusions

Present work illustrates a simple, facile and efficient methodology for the synthesis of oxazolidinone class compounds like sutezolid and eperezolid with an overall yield of 59% and 52% respectively. Induction of chirality with high enantiomeric excess is successfully achieved by addition of catalytic amount using readily available and low-cost D-proline with a simple protocol without involving non-hazardous reagents and easy workup that provides a beneficial advantage over existing methodologies. A common intermediate (**4**) can be converted to different oxazolidinone class compounds with a good overall yield.

Supplementary Information (SI)

^{1}HNMR, ^{13}CNMR, I.R. spectra, HRMS associated with this work is available in the supplementary file and can be accessed at www.ias.ac.in/chemsci.

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