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A novel and expeditious synthesis of oxazolidinone drugs linezolid and eperezolid

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ABSTRACT

A concise and efficient synthesis of linezolid and eperezolid were accomplished through a convergent scheme utilizing diverse reaction conditions. The synthesis demonstrates utility of a new approach to facilitate the expeditious construction of 3-aryl-5-(substituted methyl)-2-oxazolidinones and easier insertion of *N*-acetyl group. This new approach offers the possibility of accessing related 2-oxazolidinone members easily as well as making additional analogues of Linezolid. The adopted method afforded high purity and excellent yield compared to other existing synthetic methods. The compounds were successfully characterized by known spectroscopic techniques.

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1. Introduction

Oxazolidinones represent a class of versatile compounds in antibacterial research because they represent the first members of antibiotics to enter clinical availability over the last 35 years. As the first members, linezolid **1a** and eperezolid **1b** (Figure 1) stands in the first line as antibacterial agents. Recently U.S. Food and Drug Administration (FDA) approved Linezolid for clinical use [1-2]. Linezolid was most potent *in vitro* activity against all of the major Gram-positive bacteria [3-5]. Others members of this class have entered market, such as ranbezolid (RBx 7644), rivaroxaban (Bay-59-7939) [6, 7], posizolid (AZD 2563) [8], torezolid (TR-701) [9], and radezolid (RX-1741) [10].

Numerous synthetic methods are available for the preparation of linezolid and eperezolid since these are well known drugs in the medicinal industry. One of the common synthetic strategies in the pharma industry involve conversion of 3-fluoro-4-morpholinobenzenamine (Ar-NH_2) to corresponding carbamate, which is deprotonated with *n*-butyllithium (*n*-BuLi) or lithiumdiisopropyl amide (LDA) in THF and reaction with 2-substituted oxirane at -78 °C. Other methods involve the aryl carbamate was reacted with 1-substituted 3- chloropropan-2-ol(halohydrin) using lithium *t*-butoxide (LiOtBu) or *n*-BuLi to generate (*R*)-3-aryl-5-(hydroxymethyl)-2-oxazolidinones. These 3-aryl-5-(hydroxymethyl)-2-oxazolidinone intermediates are castoff to reach final product [11-16].

Another synthetic method involves aryl isocyanate instead of aryl carbamates. But, the preparation of aryl isocyanates is cumbersome from multi-substituted aryl amines. Moreover, while preparing aryl isocyanates a major concern is the formation of corresponding urea as a significant impurity [17,18].

Few other strategies comprise the ring opening of 2-substituted oxirane using 3-fluoro-4-morpholinobenzen amine, carbonylation followed by further functional group transformations to reach linezolid [19-21] and conversion of (*R*)-1-azido-3-chloropropan-2-ol(halohydrin) to corresponding

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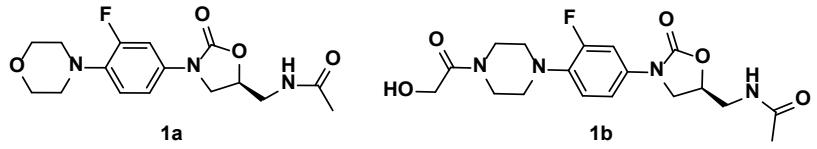
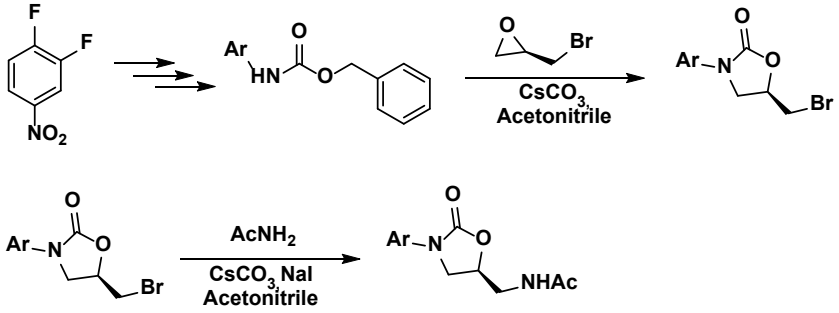


Figure 1. Molecular structure of linezolid (**1a**) and eperezolid (**1b**).



Scheme 1. Synthetic strategy for linezolid and eperezolid.

carbonate derivative followed by reaction with Ar-NH_2 to accomplish 2-oxazolidinone [22]. In addition, there are some other articles describing the construction of 5-(substituted methyl)-2-oxazolidinone followed by coupling with aryl halide using various reaction conditions and further transformations leading to Linezolid [23-26]. In all of the above mentioned methods to achieve the key intermediate 2-oxazolidinone ring highly sensitive reagents, and complex conversions were used, which limit the large-scale production in the industry.

The latest analogs have common functionalities on the C-5 aminomethyl group, such as acetamides, carbamates, ureas, thioamides, thiocarbamates, and thioureas [27,28]. During the conversion of amines to acetamides, carbamates, ureas, thioamides, thiocarbamates, and thioureas, there is a higher chance of obtaining the corresponding symmetrical derivatives. To overcome these inadequacies, we have devised a different approach (Scheme 1) for the preparation of the Linezolid and Eperezolid by using simple reagents and ordinary reaction conditions, which can be applied to the bulk scale preparation.

2. Experimental

2.1. Instrumentation

All the chemicals and solvents used were procured from Merck and Sigma Aldrich make in the appropriate grade and used without further purification; purity of the chemicals and solvents received was confirmed by thin layer chromatography. Melting points were determined in open capillary and are uncorrected. IR spectra were recorded on Bruker alpha series in KBr (ν, cm^{-1}). ^1H and ^{13}C NMR Spectra were recorded on a Bruker AV400, 400 MHz spectrometer using TMS as internal standard, LC-MS data was recorded on Agilent Waters, USA and chemical shift values are reported in δ ppm.

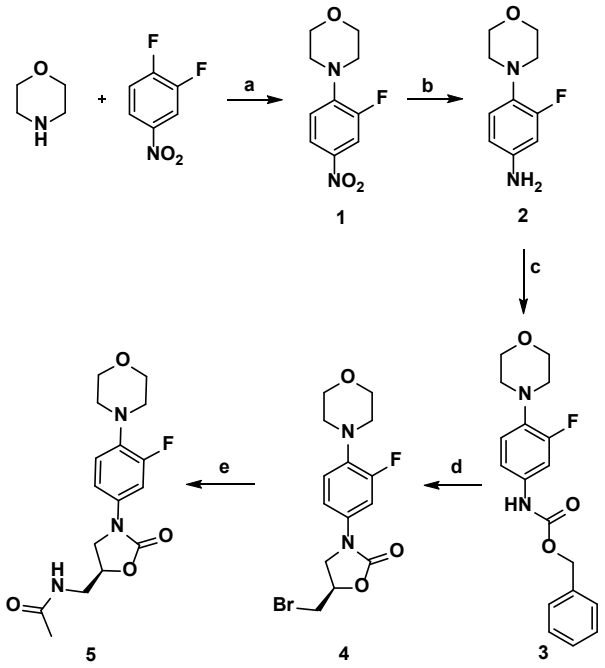
2.2. Synthesis

2.2.1. Synthesis of 4-(2-fluoro-4-nitrophenyl) morpholine (1)

3,4-Difluoronitrobenzene (25 g, 0.157 mol) was dissolved in 250 mL of dry THF (250 mL) at room temperature, added morpholine (14.37 g, 0.172 mol) and triethyl amine (26.18 mL, 0.188 mol) very slowly at room temperature and stirred at the same for 15 mins. Reaction mass was heated to 60 °C for 3 hr. Completion of the reaction was monitored by TLC. After the completion of the reaction, mass was added with 250 mL of water and 500 mL of ethyl acetate, organic layer was separated, aqueous layer was extracted with (2×250 mL), and combined organic layers were washed with water (2×100 mL), brine (1×100 mL), dried over Na_2SO_4 and concentrated to give crude product. Crude product obtained was purified by washing it with a mixture of hexane:ethyl acetate (90:10, *v*:*v*) to give pure product as yellow solid (Scheme 2). Color: Yellow. Yield: 99 %. M.p.: 125-126 °C. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.96 (dd, *J* = 3.05 Hz, 1H, Ar-H), 7.86 (dd, *J* = 3.55 Hz, 1H, Ar-H), 6.87 (dd, *J* = 4.50, 1H, Ar-H), 3.84 (t, *J* = 8 Hz, 4H, morpholine-CH_2), 3.27 (t, *J* = 8 Hz, 4H, morpholine-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 155.6 (1C, Ar-C), 150.6 (1C, Ar-C), 145.5 (1C, Ar-C), 121.0 (1C, Ar-C), 120.9 (1C, Ar-C), 112.8 (1C, Ar-C), 66.5 (2C, CH_2), 49.8 (2C, CH_2). MS (*m/z*): 227.1 (M^+). Anal. calcd. for $C_{10}H_{11}FN_2O_3$: C, 53.10; H, 4.90; N, 12.38. Found: C, 53.08; H, 4.95; N, 12.14%.

2.2.2. Synthesis 3-fluoro-4-morpholinoaniline (2)

4-(2-Fluoro-4-nitrophenyl) morpholine (25 g, 0.11 mol) was dissolved in ethanol (200 mL) in a three necked round bottom flask fitted with the condenser and cooled to -10 °C. Raney Nickel catalyst (1.25 g) was suspended in ethanol (50 mL) was introduced in to the flask at -10 °C. Hydrazine hydrate (5.73 mL, 0.184 mol) was added to the flask through the syringe by maintaining the temperature below 0 °C. Reaction was stirred at room temperature for 30 mins and the completion of the reaction was monitored by TLC. After the completion the reaction mass was filtered through the celite bed to remove Raney Nickel, washed with ethanol (2×50 mL), concentrated to give crude product as brown solid (Scheme 2). Color: Brown. Yield: 92 %. M.p.: 134-136 °C. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.85 (d, *J* = 4 Hz, 1H, Ar-H), 6.73 (dd, *J* = 4.2 Hz, 1H, Ar-H), 6.52 (dd, *J* = 6.2 Hz, 1H, Ar-H), 3.81 (t, *J* = 3 Hz, 4H, morpholine-CH_2), 3.35 (s, 2H, NH_2), 2.90 (t, *J* = 3 Hz, 4H, morpholine-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 143.01 (1C, Ar-C), 140.63 (1C, Ar-C), 129.78 (1C, Ar-C), 121.22 (1C, Ar-C), 117.09 (1C, Ar-C), 114.14 (1C, Ar-C), 67.23 (2C, CH_2), 52.18 (2C, CH_2). MS (*m/z*): 197.2 (M^+). Anal. calcd. for $C_{10}H_{13}FN_2O$: C, 61.21; H, 6.68; N, 14.28. Found: C, 61.11; H, 6.48; N, 14.12%.



Reagents and conditions: a) TEA, THF; b) Raney Ni, NH_2NH_2, EtOH; c) CBZ-Cl, THF; d) 2-(Bromomethyl)oxirane, $CsCO_3$, CH_3CN; e) Acetamide, $CsCO_3$, NaI, CH_3CN.

Scheme 2

2.2.3. Synthesis of benzyl (3-fluoro-4-morpholinophenyl) carbamate (3)

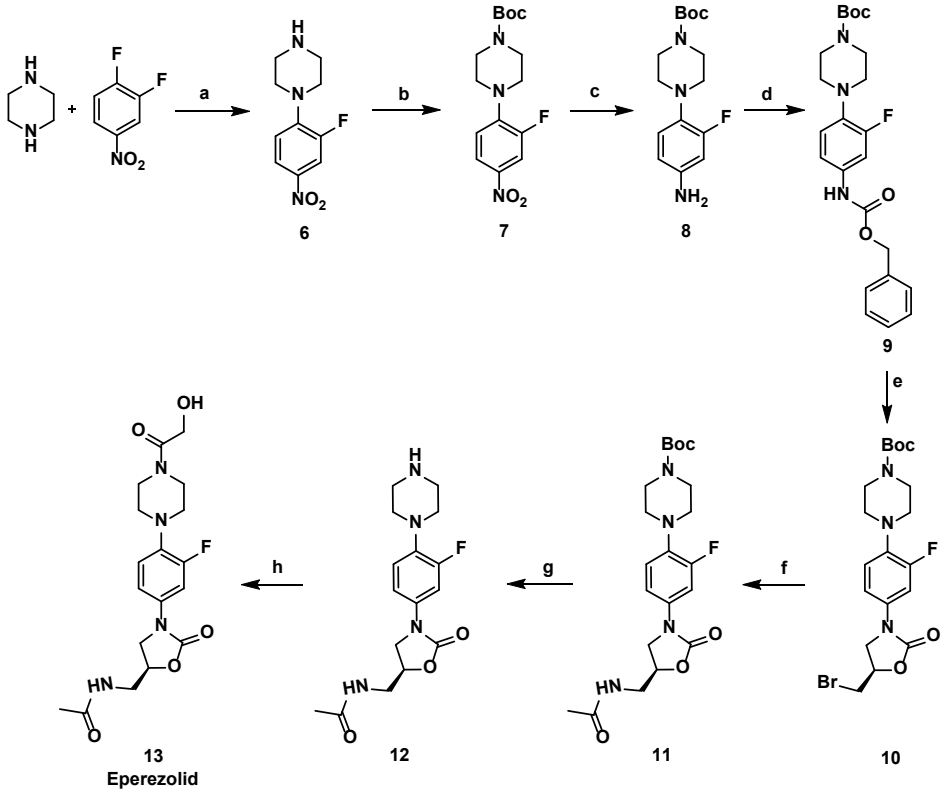
3-Fluoro-4-morpholinoaniline (22 g, 0.112 mol) was dissolved in dry THF (170 mL). Added triethyl amine (12.47 g, 0.123 mol) and cooled to -10 °C. Benzyl chloroformate (20.03 g, 0.117 mol) diluted with THF (50 mL) was slowly added in to the flask by keeping the temperature below 0 °C. After the completion of addition cooling bath is removed and reaction mixture was warmed to room temperature and stirred at the same for 1 hr. Completion of the reaction is monitored by TLC. Ethyl acetate (150 mL) and water (100 mL) were added, organic layer was separated, and aqueous layer was extracted with ethyl acetate (2×75 mL), combined organic layer was washed with water (2×70 mL), brine (75 mL), dried over Na_2SO_4, filtered and concentrated to obtain the crude product. Crude product obtained was added hexane: diethyl ether (9:1, *v*:*v*) for 10 mins. Filtered and dried to get a pure product as off white solid (Scheme 2). Color: Off white. Yield: 87%. M.p.: 126-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.27-7.33 (m, 5H, Ar-H), 7.08 (dd, *J* = 4 Hz, 1H, Ar-H) 6.93 (d, *J* = 4 Hz, 2H, Ar-H), 5.10 (s, 2H, Ar-CH_2), 3.83 (t, *J* = 2.1 Hz, 4H, morpholine-CH_2), 3.00 (t, *J* = 2.1 Hz, 4H, morpholine-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 156.1 (1C, CO), 147.4 (1C, Ar-C), 137.3 (1C, Ar-C), 136.1 (1C, Ar-C), 129.6 (1C, Ar-C), 128.4 (2C, Ar-C), 127.9 (2C, Ar-C), 127.5 (2C, Ar-C), 126.3 (1C, Ar-C), 120.21 (1C, Ar-C), 67.46 (1C, CH_2), 66.9 (2C, morpholine-C), 51.47 (2C, morpholine-C). MS (*m/z*): 331.3 (M^+). Anal. calcd. for $C_{18}H_{19}FN_2O_3$: C, 65.44; H, 5.80; N, 8.48. Found: C, 65.24; H, 5.25; N, 8.51%.

2.2.4. Synthesis of (R)-5-(bromomethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one (4)

Benzyl (3-fluoro-4-morpholinophenyl) carbamate (5 g, 0.015 mol) was dissolved in dry acetonitrile (100 mL), added cesium carbonate (5.91 g, 0.018 mol), (R)-2-(bromomethyl) oxirane (2.16 g, 0.016 mol), stirred at room temperature for 10 min and refluxed for 4.5 hours. Reaction was monitored by TLC. Reaction mixture was cooled, filtered, concentrated to obtain crude compound which was further purified by flash column chromatography using 20-30% ethyl acetate in hexane to obtain the product as yellow color solid (Scheme 2). Color: Yellow. Yield: 96%. M.p.: 145-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.41 (m, 2H, Ar-H), 6.96 (m, 1H, Ar-H), 4.71 (m, 1H, CH), 4.12 (t, *J* =4 Hz, 1H, CH_2) 3.76 (t, *J* = 4 Hz, 4H, CH_2), 3.70 (t, *J* = 4 Hz, 1H, CH_2), 3.33-3.43 (m, 2H, CH_2), 3.13 (t, J = 4 Hz, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.9 (1C, CO), 148.6 (1C, Ar-C), 131.26 (1C, Ar-C), 129.74 (1C, Ar-C), 120.62 (1C, Ar-C), 117.0 (1C, Ar-C), 109.93 (1C, Ar-C), 85.0 (1C, CH) 67.3 (2C, CH_2), 50.3 (2C, CH_2), 43.8 (1C, CH_2), 31.2 (1C, CH_2Br). MS (*m/z*): 359.1 (M^+). Anal. calcd. for $C_{14}H_{16}BrFN_2O_3$: C, 46.81; H, 4.49; N, 7.80. Found: C, 46.78; H, 4.25; N, 7.82%.

2.2.5. Synthesis of (S)-N-((3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl) methyl) acetamide (5)

(*R*)-5-(Chloromethyl)-3-(3-fluoro-4-morpholinophenyl) oxazolidin-2-one was dissolved in dry acetonitrile (50 mL), added cesium carbonate (5.91 g, 0.018 mol), acetamide (0.71 g, 0.013 mol) and sodium iodide (0.181 g, 0.0012 mol), stirred at room temperature for 10 min and refluxed for 10 hr. Reaction was monitored by TLC. Reaction mixture was cooled, filtered, concentrated to obtain crude compound which was further purified by flash column chromatography using 15-25% ethyl acetate in hexane to obtain the product as white color solid (Scheme 2). Color: White. Yield: 96%. M.p.: 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.34 (dd, *J* = 4.2 Hz, 2H, Ar-H), 6.86 (dd, *J* = 4 Hz, 2 Hz, 1H, Ar-H), 6.71 (t, *J* = 4 Hz, 1H, Ar-H), 4.69 (m, 1H , CH), 3.79 (t, *J* = 5 Hz, 4H, morpholine-H), 3.75- 3.93 (m, 2H, CH_2), 3.56 (m, 2H, CH_2), 3.07 (t, *J* = 5 Hz, 4H, morpholine-H), 1.99 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.4 (1C, $COCH_3$), 154.9 (1C, CO), 148.1 (1C, Ar-C), 135.3 (1C, Ar-C), 130.2 (1C, Ar-C), 119.3 (2C, Ar-C), 115.9 (2C, Ar-C), 71.9 (1C, CH), 66.6 (2C, CH_2), 49.3 (2C, CH_2), 47.8 (1C, CH_2), 41.73 (1C, CH_2), 22.74 (1C, CH_3). MS (*m/z*): 338.2 (M^+). Anal. calcd. for $C_{16}H_{20}FN_3O_4$: C, 56.97; H, 5.98; N, 12.46. Found: C, 56.75; H, 6.08; N, 12.01%.



Reagents and conditions: a) TEA, THF; b) Boc anhydride, TEA, DCM; c) Raney Ni, NH_2NH_2, EtOH; d) Cbz-Cl, TEA, THF; e) 2-(bromomethyl)oxirane, $CsCO_3$, CH_3CN; f) Acetamide, $CsCO_3$, NaI, CH_3CN; g) HCl in ether; h) EDCI. HoBt, TEA, DCM.

Scheme 3

2.2.6. Synthesis of 1-(2-fluoro-4-nitrophenyl) piperazine (6)

3,4-Difluoronitrobenzene (25 g, 0.157 mol) was dissolved in 250 mL of dry THF at room temperature, added piperazine (14.20 g, 0.165 mol) and triethyl amine (26.18 mL, 0.188 mol) very slowly at room temperature and stirred at the same for 15 mins. Reaction mixture was heated to 60 °C for 2 hr. Completion of the reaction was monitored by TLC. After the completion of the reaction, added 100 mL of water and 500 mL of ethyl acetate into the reaction mixture, organic layer was separated, aqueous layer was extracted with (250 mL × 2), and combined organic layers were washed with water (100 mL × 2), brine (100 mL × 1), dried over Na_2SO_4 and concentrated to give crude product. Crude product obtained was added diethyl ether (100 mL × 2) and stirred at room temperature, filtered and dried to afford a product as brown solid (Scheme 3). Color: Brown. Yield: 99%. M.p.: 68-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.01-7.98 (dd, *J* = 2.25 Hz, 1H, Ar-H), 7.90 (dd, *J* = 12.92 Hz, 1H, Ar-H), 6.94 (t, *J* = 8.72 Hz, 1H, Ar-H), 3.12 (t, *J* = 4 Hz, 4H, piperazine-H), 3.01 (t, *J* = 5 Hz, 4H, piperazine-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 155.1 (1C, Ar-C), 142.2 (1C, Ar-C), 127.7 (1C, Ar-C), 126.7 (1C, Ar-C), 123.4 (1C, Ar-C), 119.3 (1C, Ar-C), 45.82 (2C, piperazine-C), 51.81 (2C, piperazine-C). MS (m/z): 226.1 (M^+). Anal. calcd. for $C_{10}H_{12}FN_3O_2$: C, 53.33; H, 5.37; N, 18.66. Found: C, 53.32; H, 5.25; N, 18.61%.

2.2.7. Synthesis of tert-butyl 4-(2-fluoro-4-nitrophenyl) piperazine-1-carboxylate (7)

1-(2-Fluoro-4-nitrophenyl) piperazine (25 g, 0.111 mol) was dissolved in dichloromethane (250 mL), added triethyl amine (13.47 g, 0.133 mol) and the reaction mixture is cooled to -10 °C. To this di-*tert*-butyldicarbonate (Boc anhydride) (26.63 g, 0.122 mol) was added very slowly by keeping temperature between -10–0 °C, after the completion of addition of BOC anhydride reaction was warmed to room temperature and a stirred at the same for 2 hr. Added water (100 mL), organic layer was separated, aqueous layer was extracted with dichloromethane(75 mL × 3) and the combined organic layer was washed(100 mL × 2) with water (100 mL × 2), brine (100 mL × 1) , dried over Na_2SO_4, filtered and concentrated to get the crude mass, which was further purified by flash column chromatography using hexane and ethyl acetate to give a pure product as pale yellow solid (Scheme 3). Color: Pale yellow. Yield: 98%. M.p.: 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.01-7.98 (dd, *J* = 2.25 Hz, 1H, Ar-H), 7.90 (dd, *J* = 12.92 Hz, 1H, Ar-H) 6.94 (t, *J* = 8.72 Hz, 1H, Ar-H), 3.61 (t, *J* = 4.84 Hz, 4H, piperazine-H), 3.24 (t, *J* = 5.08 Hz, 4H, piperazine-H), 1.49 (s, 9H, BOC-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.6 (1C, CO), 153.7 (1C, Ar-C), 142.6 (1C, Ar-C), 128 (1C, Ar-C), 126.7 (1C, Ar-C), 123.4 (1C, Ar-C), 119.5 (1C, Ar-C), 80 (1C, C-CH_3), 50.1 (2C, piperazine-C), 50.1 (2C, piperazine-C), 28.5 (3C, CH_3). MS (m/z): 326 (M^+). Anal. calcd. for $C_{15}H_{20}FN_3O_4$: C, 55.38; H, 6.20; N, 12.92. Found: C, 55.41; H, 6.15; N, 12.82%.

2.2.8. Synthesis of tert-butyl 4-(4-amino-2-fluorophenyl) piperazine-1-carboxylate (8)

Tert-Butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate (30 g, 0.092 mol) was dissolved in ethanol (250 mL) in a three necked round bottom flask fitted with the condenser and cooled to -10 °C. Raney Nicked (1.5 g) was suspended in ethanol (50 mL) was introduced in to the flask at -10 °C. Hydrazine hydrate (5.73 mL, 0.184 mol) was added to the flask through the syringe by maintaining the temperature below 0 °C. Reaction was stirred at room temperature for 30 mins and

the completion of the reaction was monitored by TLC. After the completion the reaction mass was filtered through the celite bed to remove Raney Nickel, washed with ethanol (2×50 mL), concentrated to give crude product. It was added diethyl ether (3×100 mL) and stirred for 15 mins, filtered and dried to give pure product as light brown solid (Scheme 3). Color: yellow. Yield: 98%. M.p.: 112-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.78 (t, *J* = 8.8 Hz, 1H, Ar-H), 6.38-6.45 (m, 2H, Ar-H), 3.56 (t, *J* = 4.48 Hz, 4H, piperazine-H), 2.90 (t, *J* = 4.24 Hz, 4H, piperazine-H), 1.47 (s, 9H, BOC-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.5 (1C, CO), 144.5 (1C, Ar-C), 139.86 (1C, Ar-C), 119.2 (2C, Ar-C), 116.4 (2C, Ar-C), 79.6 (1C, C-CH_3), 50 (2C, piperazine-C), 51.2 (2C, piperazine-C), 28.5 (3C, CH_3). MS (m/z): 296.2 (M^+). Anal. calcd. for $C_{15}H_{22}FN_3O_2$: C, 61.00; H, 7.51; N, 14.23. Found: C, 61.22; H, 7.62; N, 14.21%.

2.2.9. Synthesis of tert-butyl 4-(4-(((benzyloxy) carbonyl) amino)-2-fluorophenyl) piperazine-1-carboxylate (9)

Tert-butyl 4-(4-amino-2-fluorophenyl) piperazine-1-carboxylate (20 g, 0.067 mol) was dissolved in dry THF (150 mL). Added triethyl amine (11.33 mL, 0.081 mol) and cooled to -10 °C. Benzyl chloroformate (10.55 mL, 0.074 mol) diluted with THF (50 mL) was slowly added in to the flask by keeping the temperature below 0 °C. After the completion of addition cooling bath was removed and reaction mixture was warmed to room temperature and stirred at the same for 1 hr. Completion of reaction is monitored by TLC. Ethyl acetate (100 mL) and water (100 mL) were added, organic layer was separated, and aqueous layer was extracted with ethyl acetate (2×50 mL), combined organic layer was washed with water (2×50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to obtain the crude product. Crude product obtained was added hexane: diethyl ether (9:1, *v*:*v*, 3×100 mL) and stirred for 10 mins. Filtered and dried to get a pure product as off white solid (Scheme 3). Color: Off white. Yield: 98%. M.p.: 249-250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.36 (m, 5H, Ar-H), 6.97 (d, *J* = 7.3 Hz, 1H, Ar-H), 6.87 (t, *J* = 8.9 Hz, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 5.17 (s, 2H, CH_2), 3.68 (t, *J* = 5.0 Hz, 4H, piperazine-H), 3.00 (brd, 4H, piperazine-H), 1.47 (s, 9H, BOC-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 156.0 (1C, ArNHCO), 154.3 (1C, CO), 147.6 (1C, Ar-C), 137.5 (1C, Ar-C), 136.2 (1C, Ar-C), 129.6 (1C, Ar-C),128.8 (1C, Ar-C), 128.4 (2C, Ar-C), 127.9 (2C, Ar-C), 127.7 (1C, Ar-C), 126.4 (1C, Ar-C), 120.2 (1C, Ar-C), 79.6 (1C, C-CH_3), 67.4 (1C, CH_2), 53.1 (2C, piperazine-C), 51.1 (2C, piperazine-C), 28.6 (3C, CH_3). MS (*m/z*): 431.1 (M^+). Anal. calcd. for $C_{23}H_{28}FN_3O_4$: C, 64.32; H, 6.57; N, 9.78. Found: C, 64.28; H, 6.56; N, 9.81%.

2.2.10. Synthesis of (R)-tert-butyl 4-(4-(5-(bromomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (10)

Benzyl(3-fluoro-4-morpholinophenyl)carbamate (5 g, 0.011 mol) was dissolved in dry acetonitrile (100 mL), added cesium carbonate (5.69 g, 0.017 mol), (*R*)-2-(bromomethyl) oxirane (1.74 g, 0.012 mol) through syringe, stirred at room temperature for 10 min and refluxed for 5 hr. Reaction was monitored by TLC. Reaction mixture was cooled, filtered, concentrated to obtain crude compound which was further purified by flash column chromatography using 20-35% ethyl acetate in hexane to obtain the product as pale yellow color solid (Scheme 3). Color: Pale yellow. Yield: 95%. M.p.: 196-197 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.46 (dd, *J* = 13.52 Hz, 1H, Ar-H), 7.26 (dd, *J* = 8.72 Hz, 1H, Ar-H), 6.93 (t, *J* = 9.12 Hz, 1H, Ar-H), 4.80 (m, 1H, CH), 4.07-3.83 (m, 2H, CH_2), 3.83-3.68 (m, 2H, CH_2), 3.59 (t, *J* = 4.64 Hz, 4H, piperazine-H), 3.01 (t, *J* = 4.72 Hz,4H, piperazine-H), 1.48 (s, 9H, BOC-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 154.7 (1C, CO), 154.8 (1C, CO), 145.1 (1C, Ar-C), 133.7 (1C, Ar-C), 129.2 (1C, Ar-C),120.7 (2C, Ar-C), 117.6 (1C, Ar-C), 79.8 (1C, C-CH_3), 72.9 (1C, CH), 51.2 (2C, piperazine-C), 50.9 (2C, piperazine-C), 43.8 (1C, CH_2), 33.8 (1C, CH_2Br), 28.3 (3C, CH_3). MS (*m/z*): 458.10 (M^+). Anal. calcd. for $C_{19}H_{25}BrFN_3O_4$: C, 49.79; H, 5.50; N, 9.17. Found: C, 49.65; H, 5.45; N, 9.13%.

2.2.11. Synthesis of (S)-tert-butyl 4-(4-(5-(acetamido methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazine-1-carboxylate (11)

Tert-Butyl 4-(4-(5-(chloromethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazine-1-carboxylate (5 g, 0.012 mol) was dissolved in dry acetonitrile (50 mL), added cesium carbonate (5.91 g, 0.018 mol), acetamide (0.71 g, 0.013 mol) and sodium iodide (0.181 g, 0.0012 mol), stirred at room temperature for 10 min and refluxed for 10 hr. Reaction was monitored by TLC. Reaction mixture was cooled, filtered, concentrated to obtain crude compound which was further purified by flash column chromatography using 30-40% ethyl acetate in hexane to obtain the product as pale yellow color solid (Scheme 3). Color: Pale yellow. Yield: 95%. M.p.: 211-212 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.46-7.41 (dd, *J* = 14.16 Hz, 1H, Ar-H), 7.08-7.05 (dd, *J* = 8.76 Hz, 1H, Ar-H), 6.91 (t, *J* = 9.12 Hz, 1H, Ar-H), 6.20 (t, *J* = 5.92 Hz, 1H, NH), 4.78-4.75 (m, 1H, CH), 4.07-3.73 (m, 2H, CH_2), 3.72-3.61 (m, 2H, CH_2), 3.60 (t, *J* = 4.6 Hz, 4H, piperazine-H), 3.01 (t, *J* = 4.68 Hz, 4H, piperazine-H), 2.04 (s, 3H, CH_3), 1.48 (s, 9H, BOC-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.5 (1C, NHCO), 154.8 (1C, CO), 154.51 (1C, CO), 145.5 (1C, Ar-C), 133.7 (1C, Ar-C), 129.4 (1C, Ar-C), 120.8 (2C, Ar-C),117.6 (1C, Ar-C), 72.0 (1C, C-CH_3), 51.5 (2C, piperazine-C), 51.2 (2C, piperazine-C), 47.6 (1C, CH_2), 41.8 (1C, CH_2), 29.6 (1C, C), 28.4 (3C, CH_3), 22.9 (1C, CH_3). Anal. calcd. for $C_{21}H_{29}FN_4O_5$: C, 57.79; H, 6.70; N, 12.84. Found: C, 57.85; H, 6.52; N, 12.86%.

2.2.12. Synthesis of (S)-N-((3-(3-fluoro-4-(piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl) acetamide (12)

(S)-*Tert*-Butyl 4-(4-(5-(acetamidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazine-1-carboxylate was dissolved in dichloromethane (10 mL), cooled to 0 °C, added HCl in diethyl ether and stirred at room temperature for 2 hr. Reaction was monitored by TLC. After the completion of the reaction, reaction mass was concentrated, suspended in diethyl ether (25 mL), stirred at room temperature for 10 minutes, filtered and dried under vacuum to get the pure product as white solid (Scheme 3). Color: White. Yield: 95%. M.p.: 156-157 °C. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 7.56-7.52 (dd, *J* = 14.4 Hz, 1H, Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.12 (t, *J* = 9.08 Hz, 1H, Ar-H), 4.79-4.75 (m, 1H, CH), 4.11 (t, *J* = 9 Hz, 1H, CH_2), 3.80-3.77 (m, 1H, CH_2), 3.50 (d, *J* = 5 Hz, 2H, CH_2), 3.01 (m, 8H, piperazine-H), 1.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.5 (1C, CO), 154.8 (1C, CO), 154.5 (1C, CO), 145.5 (1C, Ar-C), 133.7 (1C, Ar-C), 129.4 (1C, Ar-C), 120.8 (1C, Ar-C), 117.6 (1C, Ar-C), 51.5 (2C, piperazine-C), 51.2 (2C, piperazine-C), 47.6 (1C, CH), 41.8 (1C, CH_2), 29.6 (1C, NH-CH_2), 22.4 (1C, CO-CH_3). Anal. cald. for $C_{16}H_{21}FN_4O_3$: C, 57.13; H, 6.29; N, 16.66. Found: C, 57.21; H, 6.14; N, 16.12%.

2.2.13. Synthesis of (S)-N-((3-(3-fluoro-4-(4-(2-hydroxy acetyl) piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl) acetamide (13)

(S)-*N*-((3-(3-Fluoro-4-(piperazin-1-yl) phenyl)-2-oxooxazolidin-5-yl) methyl)acetamide (1 g, 0.0029 mol) was suspended in dichloromethane (20 mL) and cooled to 0 °C added trimethylamine (0.9030 mL, 0.0089 mol), 1-hydroxybenzotriazole (HoBt)(0.040 g, 0.0003 mol), *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (0.684 g, 0.0030 mol) and hydroxy acetic acid (0.271 g, 0.0035 mol).

Table 1. Reaction condition optimization for the conversion of compound **3** to **4** (Scheme 2).

Entry	Catalyst	Condition	Time	Yield (%) *
1	Nil	(*R*)-2-(Bromomethyl)oxirane, Na_2CO_3, Dry isopropyl alcohol:water (*v*:*v*), Reflux	10 hr	48
2	Nil	(*R*)-2-(Bromomethyl)oxirane, Na_2CO_3, Dry isopropyl alcohol, Reflux	16 hr	65
3	Nil	(*R*)-2-(Bromomethyl)oxirane, K_2CO_3, Dry isopropyl alcohol, Reflux	16 hr	72
4	Nil	(*R*)-2-(Bromomethyl)oxirane, Cs_2CO_3, Dry isopropyl alcohol, Reflux	9 hr	89
5	Nil	(*R*)-2-(Bromomethyl)oxirane, Cs_2CO_3, Acetonitrile, Reflux	8 hr	91
6	Nil	(*R*)-2-(Bromomethyl)oxirane, Cs_2CO_3, Acetonitrile, Reflux	4.5 hr	96
7	NaI	(*R*)-2-(Bromomethyl)oxirane, Cs_2CO_3, Acetonitrile, Reflux	4.5 hr	91

* Isolated yield.

Table 2. Reactions condition optimization for the conversion of compound **10** to **11** (Scheme 3).

Entry	Catalyst	Conditions	Time	Yield (%) *
1	TBAF	Acetamide, Na_2CO_3, Etanol:water (*v*:*v*), Reflux	24hr	5
2	NaI	Acetamide, Na_2CO_3, Etanol:water (*v*:*v*), Reflux	24hr	12
3	NaI	Acetamide, Na_2CO_3, Dry ethanol (20V), Reflux	24 hr	10
4	NaI	Acetamide, Na_2CO_3, Dry dimethyl formamide (20V), Reflux	24 hr	25
5	NaI	Acetamide, Na_2CO_3, Dry tetrahyhyrofuran (20V), Reflux	24 hr	26
6	NaI	Acetamide, Na_2CO_3, Dry acetonitrile (20V), Reflux	24 hr	30
7	NaI	Acetamide, K_2CO_3, Dry ethanol (20V), Room temperature	24 hr	10
8	NaI	Acetamide, K_2CO_3, Dry ethanol(20V), Reflux	24 hr	35
9	NaI	Acetamide, K_2CO_3, Dry dimethyl formamide (20V), Room temperature	24 hr	12
10	NaI	Acetamide, K_2CO_3, Dry dimethyl formamide (20V), Reflux	24 hr	41
11	NaI	Acetamide, K_2CO_3, Dry tetrahydrofuran(20V), Room temperature	24 hr	24
12	NaI	Acetamide, K_2CO_3, tetrahydrofuran (20V), Reflux	24 hr	40
13	NaI	Acetamide, K_2CO_3, Dry acetonitrile (20V), Room temperature	24 hr	18
14	NaI	Acetamide, K_2CO_3, Dry acetonitrile (20V), Reflux	24 hr	45
15	NaI	Acetamide, Cs_2CO_3, Dry ethanol (20V), Reflux	18 hr	60
16	NaI	Acetamide, Cs_2CO_3, Tetrahydrofuran (20V), Reflux	18 hr	72
17	NaI	Acetamide, Cs_2CO_3, Dry dimethyl formamide (20V), Reflux	12-14 hr	95
18	NaI	Acetamide, Cs_2CO_3, Dry acetonitrile (20V), Reflux	10 hr	95
19	TBAF	Acetamide, Cs_2CO_3, Dry acetonitrile (20V), Reflux	18 hr	91
20	TBAI	Acetamide, Cs_2CO_3, Dry acetonitrile (20V), Reflux	10 hr	95

* Isolated yield.

Reaction mixture was stirred at room temperature for 8 hr. Completion of the reaction was monitored by TLC. After the completion of the reaction, reaction mass was added water (20 mL), dichloromethane (20 mL), extracted with dichloromethane, aqueous layer was re-extracted with dichloromethane (2×10 mL), and combined organic layer was dried over Na_2SO_4, filtered and concentrated to obtain the crude product. Crude product obtained was purified by column chromatography using 20% methanol in dichloromethane to afford the pure as white solid compound (Scheme 3). Color: White. Yield: 89%. M.p.: 174-175 °C. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 7.56-7.52 (dd, *J* = 14.4 Hz, 1H, Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.12 (t, *J* = 9.08 Hz, 1H, Ar-H), 4.79-4.75 (m, 1H, CH), 4.40 (s, 2H, CH_2), 4.11 (t, *J* = 9 Hz, 1H, CH_2), 3.80-3.77 (m, 1H, CH_2), 3.5 (d, *J* = 5 Hz, 2H, CH_2), 3.01 (m, 8H, piperazine-H), 1.96 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 171.0 (1C, NHCO), 169.4 (1C, CO), 154.3 (1C, CO), 153.04 (1C, Ar-C), 147.2 (1C, Ar-C), 119.4 (1C, Ar-C), 116.2 (1C, Ar-C), 109.8 (1C, Ar-C), 105.8 (1C, Ar-C), 71.6 (1C, CH), 66.2 (1C, CH_2OH), 49.51 (2C, piperazine-C), 47.6 (2C, piperazine-C), 41.6 (1C, NCH_2), 39.7 (1C, NH-CH_2), 22.43 (1C, CO-CH_3). Anal. calcd. for $C_{18}H_{23}FN_4O_5$: C, 54.82; H, 5.88; N, 14.21. Found: C, 54.68; H, 5.843; N, 14.32%.

3. Results and discussion

In sight of the limitations associated with the previous synthetic methods of linezolid and eperezolid, herein we report the novel synthetic methodology. The synthesis of linezolid and eperezolid was achieved as per the Schemes 2 and 3. Compounds **1** to **3** in case of linezolid and compounds **6** to **9** in case of eperezolid were obtained by using known methods but the conversation of compound **3** to **5** and compound **9** to **11** were easily achieved by our new tactic.

One of the key steps in our methodology involve the conversion of compound **3** to **4** in which best results was obtained when (*R*)-2-(bromomethyl)oxirane, Cs_2CO_3, acetonitrile, were used under reflux (Table 1, Entry 6). The same method was extended for the conversion of compound **9** to **10** without any hassle since the environment around the functional groups taking part in the reaction were similar, which in turn proves the new and easier way for the construction of (*R*)-5-(bromomethyl) oxazolidin-2-one. Expeditious introduction of acetamide group was achieved by using acetamide, $CsCO_3$ with catalytic amount of sodium iodide for both Linezolid and Eperezolid (Schemes 2 and 3), which has indeed reduced the number of steps involved in the overall synthesis. Initially, we tried the reaction with different combination of solvents and catalyst (Table 2), but the ultimate result was obtained in the case of NaI: $CsCO_3$: Acetonitrile (Table 2, Entry 18). In these conditions, we achieved 95% of yield in 10 hr compared to all other conditions. In addition to these in the synthesis of eperezolid, we have avoided protection and deprotection strategy. One of the early methods in the synthesis of 2-oxazolidinones involves the reaction of phosgene and aniline with chloroethanol to produce chloroethyl-*N*-phenyl carbamate which is cyclized by boiling in potassium hydroxide solution. However, this methodology is not well utilized in synthetic organic chemistry and drug discovery probably due to the fear of low stability of 1-chloroalkan-2-yl-chloroformates. Few of the medicinal industrial methods follow the conversion of oxazolidinone methyl alcohol to methyl sulphonyl group, azide, reduction followed by acetylation of amine group. Over all by employing our new simple strategies, the cumbersome synthesis of linezolid and eperezolid have turned relaxed, inexpensive and crisp in many aspects of synthetic chemistry. In summary, we describe herein a simple, mild and facile synthesis of Linezolid and eperezolid using handy reaction conditions.

4. Conclusions

In conclusion, we have designed shortest and a simple synthetic route to reach oxazolidinone drugs linezolid and eperezolid using reagents which can be handled easily with the overall yield of 95%. This method can be versatile in the organic synthesis of linezolid and eperezolid derivatives and can be applied to large scale industrial production. By using

these conditions, an efficient method had been demonstrated for 2-oxazolidinone ring construction and express way to introduce amide functionality. The applicability of this approach was shown by the synthesis of linezolid and eperazolid. We hope this approach is not only restricted to linezolid and eperezolid, it can be extended to other oxo-zolidinone drugs available in the market.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
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Sample availability: Samples of the compounds are available from the author.

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References

[1]. Wallace, R. J. J.; Brown-Elliott, B. A.; Ward, S. C.; Crist, C. J.; Mann, L. B.; Wilson, R. W. *Antimicrob. Agents Chemother.* **2001**, *45*, 764-767.
[2]. Peters, J.; Kondo, K.; Lee, R.; Lin, C.; Inderlied, C. *J. Antimicrob. Chemother.* **1995**, *35*, 675-679.
[3]. Vardakas, K. Z.; Kioumis, I.; Falagas, M. E. *Curr. Drug Metab.* **2009**, *10*, 2-12.
[4]. Potoski, B. A.; Adams, J.; Clarke, L.; Shutt, K.; Linden, P. K.; Baxter, C.; Pasculle, A. W.; Capitano, B.; Peleg, A. Y.; Szabo, D.; Paterson, D. L. *Clin. Infect. Dis.* **2006**, *43*, 165-171.
[5]. Toh, S. M.; Xiong, L.; Arias, C. A.; Villegas, M. V.; Lolans, K.; Quinn, J.; Mankin, A. S. *Mol. Microbiol.* **2007**, *64*, 1506-1514.
[6]. Roehrig, S.; Straub, A.; Pohlmann, J.; Lampe, T.; Pernerstorfer, J.; Schlemmer, K. H. Reinemer, P.; Perzborn, E. *J. Med. Chem.* **2005**, *48*, 5900-5908.
[7]. Kalia, V.; Miglani, R.; Purnapatre, K. P.; Mathur, T.; Singhal, S.; Khan, S.; Voleti, S. R.;Upadhyay, D. J.; Saini, K. S.; Rattan, A.; Raj, V. S. *Antimicrob. Agents Chemother.* **2009**, *53*, 1427-1433.
[8]. Howe, R. A.; Wootton, M.; Noel, A. R.; Bowker, K. E.; Walsh, T. R.; MacGowan, A. P. *Antimicrob. Agents Chemother.* **2003**, *47,* 3651-3652.
[9]. Livermore, D. M.; Mushtaq, S.; Warner, M.; Woodford, N. *J. Antimicrob. Chemother.* **2009**, *63*, 713-715.
[10]. Skripkin, E.; McConnell, T. S.; DeVito, J.; Lawrence, L.; Ippolito, J. A.; Duffy, E. M.; Sutcliffe, J.; Franceschi, F. *Antimicrob. Agents Chemother.* **2008**, *52,* 3550-3557.
[11]. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.;Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673-679.
[12]. Barbachyn, M. R.; Brickner, S. J.; Hutchinson, D. K. U.S. patent 5688792; 1997; *Chem. Abstr.* **1995**, *123*, 256742.
[13]. Dhananjay, G. S.; Nandu, B. B.; Avinash, V. N.; Kamlesh, D. S.; Anindya, S. B.; Tushar, A. N. PCT Int. Appl. 063505,2009; *Chem. Abstr.* **2009**, *150*, 515152.
[14]. Imbordino, R. J.; Perrault, W. R.; Reeder, M. R. PCT Int. Appl. 116284, 2007; *Chem. Abstr.* **2007**, *147*, 469356.
[15]. Pearlman, B. A.; Perrault, W. R.; Barbachyn, M. R.; Manninen, P. R.; Toops, D. S.; Houser, D. J.; Fleck, T. J. U.S. Patent 5837870, 1998; *Chem. Abstr.* **1998**, 130, 25061.
[16]. Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jeganathan, A.;Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrinton, P.M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Greene, M. L.; Barbachyn, M. R. *Org. Proc. Res. Dev.* **2003**, *7*, 533-546.
[17]. Yu, D. S.; Huang, L.; Liang, H.; Gong, P. *Chin. Chem. Lett.* **2005**, *16*, 875-878.
[18]. Pearlman, B. A. PCT Int. Appl. 9924393, 1999; *Chem. Abstr.* **1999**, *130*, 338099.
[19]. Wang, M.; Tong, H. CN patent 101220001, 2008.
[20]. Mohan-Rao, D.; Krishna, R. P. PCT Int. Appl. 099353, 2005; *Chem. Abstr.* **2005**, *143*, 440395.
[21]. Mohan-Rao, D.; Krishna, R. P. PCT Int. Appl. 008754, 2006; *Chem. Abstr.* **2006**, *144*, 170978.
[22]. Madhusudhan, G.; Om Reddy, G.; Ramanatham, J.; Dubey, P. K. *Indian J. Chem.* **2005**, *44B*, 1236-1238.
[23]. Madhusudhan, G.; Om Reddy, G.; Rajesh, T.; Ramanatham, J.; Dubey, P. K. *Tetrahedron Lett.* **2008**, *49*, 3060-3062.
[24]. Rajesh, T.; Narayana Rao, S. P.; Suresh, K. Madhusudhan, G.; Mukkanti, K. *J. Hetercyclic Chem.* **2010**, *47*, 1392-1397.
[25]. Moran-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2008**, *10*, 1935-1938.
[26]. Mallesham, B.; Rajesh, B. M.; Rajamohan, R. P.; Srinivas, D.; Sanjay, T. *Org. Lett.* **2003**, *5*, 963-965.
[27]. Selvakumar, N.; Srinivas, D.; Manoj, K. K.; Sitaram, K. M.; Mamidi, R. N. V. S.; Hemanth, S.; Chandrashekar, C.; Srinivasa Rao, B.; Mohammed, R. A.; Jagattaran, D.; Javed, I.; Raagopalan, R. *J. Med. Chem.* **2002**, *45*, 3953-3962.
[28]. Tokuyama, R.; Takahashi, Y.; Tomita, Y.; Tsubouchi, M.; Yoshida, T.; Iwasaki, N.; Kado, N.; Okezaki, E.; Nagata, O. *Chem. Pharm. Bull.* **2001**, *49*, 361-367.