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A Novel Synthesis of Oxazolidinone Derivatives (A Key Intermediate of Linezolid)

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ABSTRACT

Oxazolidinone derivatives a very key intermediate of Linezolid 7(a-e) have been synthesized from 3-fluoro-4-morpholinyl aniline 2 in good yield.The structures of all the compounds were confirmed by IR, ^{1}H NMR,C^{13} NMR and Mass Spectral data.

Key words: Oxazolidinone, epichlorohydrin, Antibacterial, Linezolid.

INTRODUCTION

The increasing incidence of bacterial resistance to a large number of antibacterial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major issue[1-4]. For the past several years, vancomycin has been considered the last line of defence against Gram-positive infections and there is no suitable therapy available for treating diseases that have become resistant to vancomycin[5].

This growing problem has recently rekindled interest in the search for new antibiotic structural classes that inhibit or kill by novel mechanisms[6]. Clearly this encourages the scientists for discovery and development of effective agents against the emerging problematic Gram-positive pathogens MRSA, methicillin-resistant coagulase-negative staphylococci, VRE, and penicillin-resistant pneumococci, as well as the perceived looming threat of a vancomycin-resistant *staphylococcus aureus*[7-9].

The oxazolidinones are a class of totally synthetic antibacterial agents. They have a novel mechanism of action that involves the inhibition of bacterial protein synthesis at a very early stage, prior to chain initiation[10].

Linezolid (7a) is a sucessful agent of this class and has already gained the permission of the FDA and come into the market.Reffering to the structure activity relationship studies and the synthesis of Linezolid , we have reported a very simple and efficient synthesis of Linezolid (7a) and other oxazolidinone derivaitives 7(b-e) strating from 3-fluoro -4-morpholinyl aniline (2).

RESULTS AND DISCUSSION

The synthetic strategy is shown in Scheme-1. The *R*-epichlorohydrin (2) reacted with 3-fluoro-4-marpholinyl aniline (1) in methanol at 60-65 °C and the crude adduct was allowed to react with carbonyl diimidazole in dichloromethane at ambient temperature to furnish the compound (4) which upon condensation with potassium phthalimide in dimethylformamide at reflux temperature afforded oxazolidinone phthalimide (5). By the treament of (5) with hydrazinehydrate and the corresponding anhydrides and acid chlorides produced Linezolid derivatives 7(a-e).

In conclusion, we have achieved a general and very reliable synthesis of Linezolid and its derivatives via., chiral oxazolidinones starting from 3-fluoro-4-morpholinyl aniline (1) with a cheap and readily available (*R)*-epichlorohydrin (2) in good yields (Table-1).The structures of all the target compounds were confirmed by IR, ^{1}H NMR, C^{13} NMR and Mass Spectral data.

EXPERIMENTAL

Melting points were determined on Stuart SMP-30 apparatus and are uncorrected. The IR spectra were recorded in the solid state as KBr dispersion media using a Perkin-Elmer model 1600 Fourier transform infrared (FT)-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a 300-MHz Bruker Avance spectrometer. Chemical shifts values are expressed in δ (ppm) using TMS as the internal standard. The liquid chromatography-mass spectrometry (LC-MS) was performed on a 2010 EV mass spectrometer.

Procedure for N-[3-Chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinylaniline (3)

3-Fluoro-4-morpholinyl aniline (1) (1.08 g, 0.005 mol) was added to a stirred solution of *R*-epichlorohydrin (2) (0.46 g, 0.005 mol) in methanol (10 mL). The mixture was heated to reflux for 16 h and concentrated to give thick liquid (3).

I R (KBr, cm^{-1}): 3382 (O-H stretching), 3068 (aromatic C-H stretching), 2960 (aliphatic C-H stretching), 1582 (aromatic C=C stretching), 1520, 1451 (N-H, O-H bending), 1377, 1319 (aliphatic C-H bending), 1301 (C-N stretching), 1273 (C-O bending), 1259, 1225 (C-F bending), 1167, 1112 (aliphatic C-C stretching), 744 (C-Cl stretching); ^{1}H NMR (DMSO-d$_6$) δ ppm: 6.88 (m, 1H), 6.43 (m, 2H), 3.94 (m, 1H), 3.80 (m, 4H), 3.62 (m, 2H), 3.26 (m, 1H), 3.10 (m, 1H), 2.93 (m, 4H); MS: 289 *(*M$^+$ *+*H*)*.

(5R)-5-(Chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (4):

Carbonyl diimidazole (3.2 g, 0.019 mol) was added to a solution of *N*-[3-Chloro-2-(*R*)-hydroxypropyl]-3-fluoro-4-morpholinylaniline (3) (5.7g,0.019mol) in dichloromethane (60mL).The reaction mixture was then stirred at room temperature for 20 h. The solution was washed with water (60 mL) and concentrated to afford compound (5R)-5-(Chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (4). Yield: 77%.

(S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]phthalimide (5)

A solution of (5*R*)-5-(Chloromethyl)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxazolidinone (4) (6.0 g, 0.019 mol) in *N,N*-Dimethylformamide (40 mL) was added potassium phthalimide (4.0 g, 0.021 mol), and the reaction mixture was heated to reflux and stirred for 5 h. The reaction mixture was cooled to ambient temperature and diluted with water (200 mL).The precipitated solid was filtered off and dried to give compound (5). Yield: 62%. IR(KBr, cm^{-1}): 3026 (aromatic C-H stretching), 2982, 2952, 2908 (aliphatic C-H stretching), 1737, 1716 (C=O stretching), 1628, 1571, (aromatic C=C stretching), 1475, 1466 (aliphatic C-H bending), 1385, 1325 (C-N stretching), 1276, 1253 (C-O stretching), 1170, 1115 (C-F stretching), 1050,1006 (aromatic C-H bending).^{1}H NMR (DMSO-d$_6$) δ ppm: 7.88 (m, 4H), 7.43 (m, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 4.93 (m, 1H), 4.04 (m, 4H), 3.46 (m, 4H), 2.95 (m, 4H); MS: 426 *(*M$^+$ *+*H*)*.

(S)-N-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine (6)

Hydrazine hydrate (2.0g, 0.04 mol) was added to a solution of (*S*)-*N*-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] phthalimide (5) (4.0 g, 0.009 mol) in methanol (25 mL).The reaction mixture was heated to reflux and stirred for 1 h. The mass was cooled to ambient

temperature, and diluted with water (50 mL) and extracted with dichloromethane (30 mLx2). The combined organic extracts were washed with water (30 mL) and concentrated to give (6). Yield: 90%. IR (KBr, cm^{-1}): 3579, 3377, (N-H stretching), 3293 (aromatic C-H stretching), 2954, 2893, 2846, (aliphatic C-H stretching), 1734 (C=O stretching), 1625, 1572 (aromatic C=C stretching), 1519, 1480 (N-H bending), 1381, 1332 (aliphatic C-H bending), 1273, 1256, 1231 (C-N stretching), 1194, 1176 (C-O stretching), 1114 (C-F stretching), 1066, 1048 (aromatic C-H bending). ^{1}H NMR (DMSO-d_6) δ ppm: 7.51 (m, 1H), 7.20 (m, 1H), 7.05 (t, 1H), 4.59 (m, 1H), 3.92 (m, 2H), 3.73 (m, 4H), 2.95 (m, 4H), 2.80 (m, 2H), 1.63 (s, 2H); MS: 296 (M^+ +H).

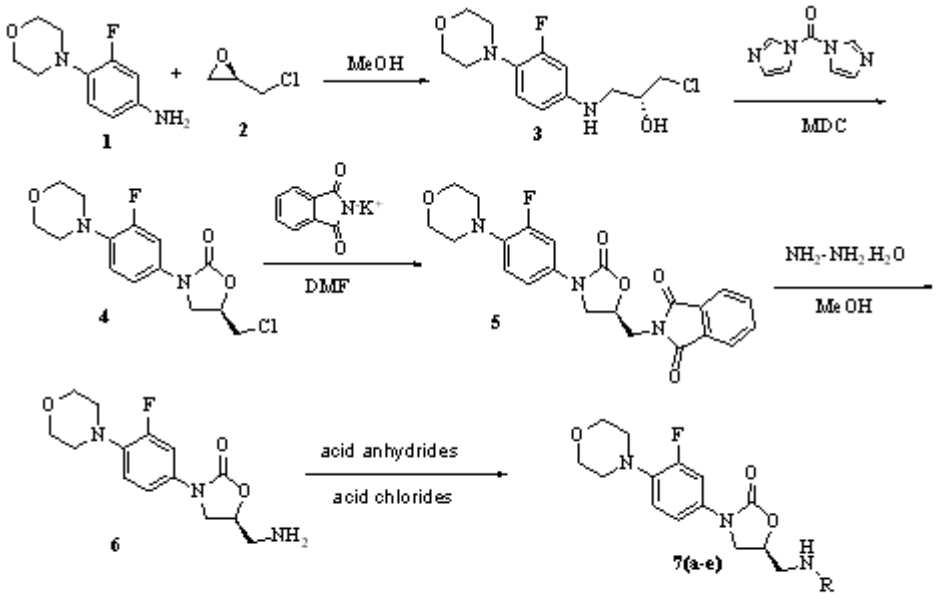
General procedure for N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl] acetamide (7a) and N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl)

-2-oxo-5-oxazolidinyl]methyl]propanamide(7b)

A solution of acetic anhydride and propionic anhydride (0.020 mol) was added dropwise to a stirred solution of *(S)*-*N*-[[3-[3-Fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine (6) (2.5 g, 0.008 mol) in ethyl acetate (20 mL) at ambient temperature and the reaction mixture was allowed to stirred for 1 h. The reaction mixture was cooled to 0-5°C. The precipitated solid was filtered off and re-crystallized from methanol (20 mL) to give the corresponding compounds (7a-b).

N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (7a)

IR (KBr, cm^{-1}): 3338 (N-H stretching), 3117, 3066 (aromatic C-H stretching), 2971, 2863, 2818 (aliphatic C-H stretching), 1738, 1662 (C=O stretching), 1545, 1516,1453 (aromatic C=C stretching), 1425 (C-N stretching), 1381 (aliphatic C-H bending), 1334 (C-F stretching), 1274 (C-O stretching), 1198, 1177 (C-N bending), 1117, 1081 (aromatic C-H bending). ^{1}H NMR ($CDCl_3$) δ ppm: 7.44 (m, 1H), 7.26 (m, 1H), 6.99 (m, 1H), 6.01 (t,1H), 4.76 (m, 1H), 4.02 (m, 2H), 3.80 (m, 4H), 3.61(m, 2H), 3.05 (m, 4H), 2.02 (t, 3H): C^{13}NMR($CDCl_3$) δ ppm: 171.33, 156.87, 154.44, 136.40, 132.84,



7a R=-CO-CH_3 7b R=-CO-CH_2-CH_3 7c R=-CO-$(CH_2)_3$-CH_3

7d R=-CO-$(CH_2)_4$-CH_3 7e R=-CO-$(CH_2)_5$-CH_3

Scheme 1:

118.67, 113.81, 107.52, 71.96, 66.76, 50.79, 47.46, 41.68, 22.81. MS: 338 (M^++H);

N-[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl)-2-oxo-5-oxazolidiny]methyl}propanami de(7b)

IR (KBr, cm^{-1}): 3342 (N-H stretching), 3073 (aromatic C-H stretching), 2896, 2857, 2824 (aliphatic C-H stretching), 1743, 1660 (C=O stretching), 1543, 1516 (aromatic C=C stretching), 1467, 1423 (NH bending), 1334 (aliphatic C-H bending), 1272, 1256 (C-N stretching), 1228 (C-F stretching), 1196 (C-O stretching), 1118 (C-C stretching). ^{1}H NMR ($CDCl_3$) δ ppm: 8.14-8.28 (m, 1H), 7.45-7.51 dd, 1H), 7.15 -7.19 (m, 1H), 7.03-7.09 (m,1H), 4.68-4.73 (m, 1H), 4.04 - 4.10 (t, 1H), 3.67-3.74 (m, 5H), 3.38-3.42 (m, 2H), 2.93-2.96 (t, 4H), 2.05-2.12 (q, 2H), 0.92-0.97 (t, 3H). C^{13} NMR ($CDCl_3$) δ ppm: 173.86, 156.23, 154.09, 135.46, 119.15, 113.99, 106.42, 71.62, 66.19, 50.13, 47.31, 41.42, 28.40, 9.91. MS: 352 (M^++H);

General procedure for (S)- N-(3-[3-fluoro-4-morpholinophenyl]-2-oxo-5-oxazolidinyl] methyl]amides 7(c-e)

To a stirred mixutre of *(S)-N*-[[3-[3-Fluoro-4-[4-morpholinyl] phenyl]-2-oxo-5-oxazolidinyl] methyl]amine (**6)** (0.001 mol) in toluene(15 mL) was added triethylamine slowly at room temperature. Added corresponding acid chlorides (valeryl chloroide, n-hexanoyl chloride and n-heptanoyl chloride) (0.001 mol) at 0-5 ^{0}C . The reaction mixture was stirred for 3 h at room temperature. The separated solid was filtered and washed with toluene (15 mL). The resulting solid was recrystallized from methanol produced the corresponding compounds **7(c-e)**.

Table 1: Characterization data of linezolid dervatives 7(a-e)

Compound	R	Mol.Formula	Mp / ^{0}C	Yield / %
7a	-CO-CH_3	$C_{16}H_{20}FN_30_4$	181-182	87
7b	-CO-CH_2CH_3	$C_{17}H_{22}FN_30_4$	174-176	67
7c	-CO-$(CH_2)_3CH_3$	$C_{19}H_{26}FN_30_4$	152-158	65
7d	-CO-$(CH_2)_4CH_3$	$C_{20}H_{28}FN_30_4$	152-154	60
7e	-CO-$(CH_2)_5CH_3$	$C_{21}H_{30}FN_30_4$	156-158	65

(S)-N-(3-[3-fluoro-4-morpholinophenyl]-2-oxo-5-oxazolidinyl]methyl]pentanamide 7(c)

IR (KBr, cm^{-1}): 3344 (N-H stretching), 3100 (aromatic C-H stretching), 2955, 2934, 2863 (aliphatic C-H stretching), 1741, 1660 (C=O stretching), 1547, 1519 (aromatic C=C stretching), 1445, 1427 (N-H bending), 1380,1334 (aliphatic C-H bending), 1273, 1256 (C-N stretching), 1228 (C-F stretching), 1195,1177(C-O stretching), 1116 (C-C stretching). ^{1}H NMR ($CDCl_3$) δ ppm: 7.41-7.46 (dd, 1H), 7.11 (s, 1H), 7.04 -7.07 (m, 1H), 6.87-6.93 (t, 1H), 4.76-4.83 (m, 1H), 4.02 - 4.06 (t, 1H), 3.84-3.87 (t, 4H), 3.69-3.81(m, 1H), 3.57-3.61 (m, 2H), 3.02-3.04 (t, 4H), 2.20-2.25 (t, 2H),1.49-1.59(m, 2H),1.20-1.32(m, 2H), 0.80-0.84 (t, 3H). C^{13} NMR ($CDCl_3$) δ ppm: 174.47, 156.78, 154.38, 136.05, 132.74, 118.50, 113.58, 106.94, 71.93, 66.66, 50.70, 47.33, 41.46, 35.83, 27.60, 22.08, 13.49: MS: 380 (M^++H);

(S)- N-(3-[3-fluoro-4-morpholinophenyl]-2-oxo-5-oxazolidinyl]methyl]hexanamide 7(d)

IR (KBr, cm^{-1}): 3339 (N-H stretching), 3061 (aromatic C-H stretching), 2950, 2934, 2861 (aliphatic C-H stretching), 1742, 1660 (C=O stretching), 1547, 1518 (aromatic C=C stretching), 1466, 1427 (N-H bending), 1381,1334 (aliphatic C-H bending), 1274, 1256 (C-N stretching), 1227 (C-F stretching), 1196,1180(C-O stretching), 1116 (C-C stretching). ^{1}H NMR ($CDCl_3$) ´ ppm: 8.19-8.23 (t, 1H), 7.46 -7.51 (m, 1H), 7.14 -7.17 (m, 1H), 7.03-7.09 (m, 1H), 4.70-4.74 (m, 1H), 4.05 - 4.11 (t, 1H), 3.66 -3.73 (m, 5H), 3.43-3.51 (m, 2H), 2.93-2.95 (m, 4H), 2.04-2.09 (t, 2H), 1.36-1.46 (m, 2H), 1.14-1.18 (m, 4H), 0.74-0.79 (t, 3H). C^{13} NMR ($CDCl_3$) δ ppm: 173.23, 156.26, 154.09, 135.41, 133.43, 119.16, 113.86, 106.30, 71.65, 66.20, 50.73, 47.15, 41.23, 35.30, 30.83, 25.08, 21.90, 13.75: MS:394 (M^++H).

(S)- N-(3-[3-fluoro-4-morpholinophenyl]-2-oxo-5-oxazolidinyl]methyl]heptanamide 7(e)

IR (KBr, cm^{-1}): 3348 (N-H stretching), 3060

(aromatic C-H stretching), 2954, 2864, 2821 (aliphatic C-H stretching), 1744, 1660 (C=O stretching), 1546, 1517 (aromatic C=C stretching), 1448, 1425 (N-H bending), 1379,1333 (aliphatic C-H bending), 1274, 1252 (C-N stretching), 1227 (C-F stretching), 1197,1177(C-O stretching), 1115 (C-C stretching). ^{1}H NMR ($CDCl_3$) δ ppm: 8.19-8.22 (t, 1H), 7.46 -7.52 (dd, 1H), 7.14 -7.17 (m, 1H), 7.02-7.08 (m,1H), 4.70-4.74 (m, 1H), 4.04 - 4.10 (t, 1H), 3.71 -3.74 (m, 4H), 3.66-3.69 (m, 1H), 3.43-3.52 (m, 2H), 2.93-2.96 (m, 4H), 2.04-2.08 (t, 2H),1.38-1.40 (m, 2H), 1.13 (m, 6H), 0.77-0.82 (t, 3H). C^{13} NMR ($CDCl_3$) δ ppm: 173.24, 156.26, 154.07, 135.39, 133.42, 119.08, 113.81, 106.27, 71.66, 66.21, 50.75, 47.13, 41.19, 35.35, 31.09, 28.33, 25.38, 21.97, 13.91: MS: 408 (M^++H).

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