Iranian Journal of Pharmaceutical Sciences
2014: 10 (2): 69- 78
www.ijps.ir

Original Article

Novel Linezolid like Analogues: Synthesis, Characterization and Biological Evaluation

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Abstract

The synthesis of 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one was achieved in two steps, In first step, pyrazine-2-carboxamide dissolved in EtOH, 10% KOH solution with $ClCH_2COOH$ produced compound 2-(pyrazine-2-carboxamido) acetic acid (II) and in second step, compound (II) in $(CH_3CO)_2O$ with aromatic aldehyde, and catalyst potassium acetate produced title compounds 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA1-PA14). All the newly synthesized compounds structure were elucidated using various spectral techniques viz. FT-IR, ^{1}H-NMR, GC-MS spectroscopy, and CHN elemental analysis data and screened for *in vitro* antimicrobial and antifungal activity. *In vitro* anti bacterial activity was carried out against organisms *E.coli, K.pneumonia, S.aureus*, and *B. Subtilis* as well as antifungal activity were carried out against *A.niger* and *S. cerevisiae* activity by minimum inhibitory concentration method. The most promising broad spectrum compounds PA3, PA4, and PA5 were observed and study data reveals that additions of different functional groups had varying effects on activity. In addition, the greater biological activities were observed when the electron-withdrawing groups like fluorine, bromine and chlorine were incorporated at *p*-position of the phenyl ring.

Keywords: Antimicrobial, Linezolid, MIC, 1, 3-oxazolone-5-one, FT-IR, ^{1}H-NMR.

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Cite this article as: Rajurkar VG, Radhakishan Pund A, Novel Linezolid like Analogues: Synthesis, Characterization and Biological Evaluation.Iranian Journal of Pharmaceutical Sciences, 2014, 10(2): 69-78.

1. Introduction

In spite the existence of a number of antibiotics that are used for the treatment of bacterial infections, the mortality and morbidity caused by microbes have an alarming worldwide impact on the human population due to the increasing number of multidrug-resistant microbial pathogens [1].

Linezolid [Fig.1], N-[[(5S)-3-(3-fluoro-4-morpholin-4-ylphenyl)-2-oxo-1, 3-oxazolidin-5-yl] methyl] acetamide is clinically used drug in the oxazolidinone class having good *in vitro* activity against most of the major Gram-positive bacteria that are pathogenic to human beings [2]. Ranbezolid (RBX 7644; Ranbaxy Research Laboratories, India) [Fig.2] is a new oxazolidinone with enhanced activity against gram-positive organisms and some fastidious gram-negative organisms [3].Literature survey reveals SAR of oxazolone nucleus that substitution of various functional groups at C-4 and C-2 position plays a vital role in the tyrosinase inhibitory activity, substituted (*p*-NO_2) exocyclic phenyl group at C-4 greatly influences the immune suppressive activity, cinnamoyl residue at C-4, an extension of conjugation through an aliphatic double bond at C-4 and a phenyl ring at C-2 play a pivotal role in activity [4, 5, 6]. Some oxazolone are highly versatile intermediates for the synthesis of several organic molecules, amino acids, peptides and anti-inflammatory [7], antimicrobial [8,9], antitumor [10], immune modulators [11], and anti-diabetic [12] compounds. Above mentioned facts prompted us to synthesis a series of 4-(substituted benzylidene)-2-(pyrazin-2-yl)

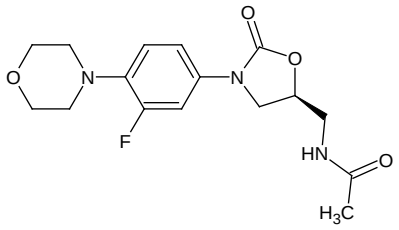


Figure 1. Linezolid.

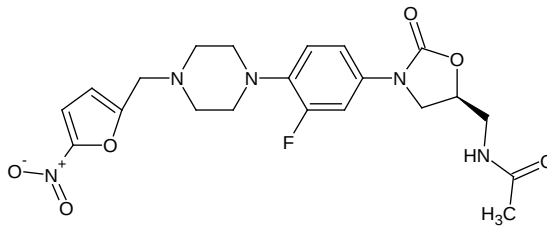


Figure 2. Ranbezolid.

oxazol-5(4*H*)-one compounds having antimicrobial activity. The structures of the compounds were confirmed by FT-IR, ^{1}H-NMR, GC-mass spectroscopy and elemental analysis data studies; their antibacterial and antifungal activities were performed by MIC (Minimum Inhibitory Concentration) method.

2. Material and Methods

2.1. Materials

All reagents and solvents used in the present study were of analytical grade and procured from Loba chemie (India).The progress of the reactions were monitored by TLC using Merck silica gel precoated plate, with appropriate mobile phase, visualization by iodine vapour and UV chamber and product are purified by recrystallization technique. All the melting points recorded on a Veego apparatus (Mumbai, India) and were uncorrected. All the synthesized compounds were characterized by their FT-IR, ^{1}H-NMR, and GC Mass spectroscopies. FT-IR spectra were recorded in KBr on Bruker FT-IR instrument (Germany),^{1}H-NMR spectra were recorded on Bruker Avance ^{1}H-NMR spectrometer (Germany), at 400 MHz in DMSO-d6, by using varian instrument using TMS as internal standard and chemical shift

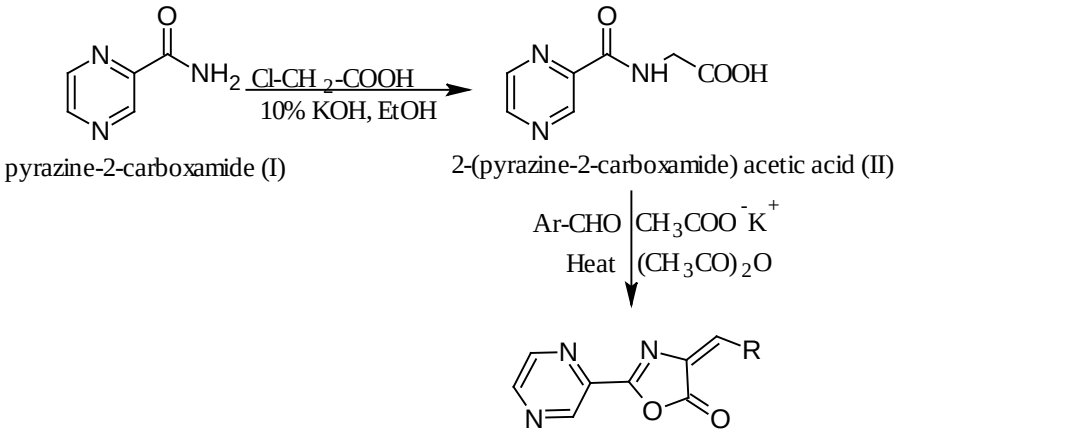
values are given in ppm downfield to TMS (tetramethylsilane) and GC Mass spectra were recorded on GCMS-QP-5050 Schimadzu (Japan). The standard drugs Norfloxacin, Ketoconazole, Ascorbic acid and Ibuprofen were obtained as gift sample from Wockhardt Ltd., Aurangabad, India.

2.2. Synthesis of 2- (Pyrazine-2-Carboxamido) Acetic Acid [II] [13]:

In a 100 ml conical flask, placed a pyrazine-2-carboxamide **I** (0.075mol, 9.23 g) in a 12 ml of 10% KOH solution, added 10 ml of EtOH to above solution to dissolve all pyrazine-2-carboxamide.Then monochloro acetic acid 0.47g (0.05mole) in small-small portion loaded in above solution with constant stirring at RT on magnetic stirrer for 3 h. The mixture was acidified with Conc. hydrochloric acid. The precipitate obtained was filtered, dried and recrystalized using ethanol to furnish white solid. m.p: 210-212^{o}C, TLC mobile phase- Ethyl acetate: Ethanol: Diethyl ether (1:1:1), Yield 75%. FT-IR ν max (KBr, cm^{-1}): 3116 (N-H $_{Str}$), 3062 (C-H $_{Str}$, aromatic), 2788 (C-H $_{Str}$, methylene), 2790-2801 (O-H $_{Str}$, carboxyl), 1702-1730 (C=O $_{Str}$, carboxyl), 1649 (C=O $_{Str}$, amide), ^{1}H-NMR (DMSO, 400 MHz) δ: 3.60 (2H, methylene), 8.10 (s, 1H, sec. amide), 8.10-9.90 (m, 3H, pyrazine), 13.10 (s,1H, hydroxyl), MS: [M] + at m/z 181. Elemental Anal. Cal. for $C_7H_7N_3O_3$: C 46.41, H 3.89, N 23.20 %. Found: C 46.38, H 3.91, N 23.22%.

2.3. 4-(Substituted Benzylidene)-2-(Pyrazin-2-yl) Oxazol-5(4H)-One [III] [13]*:*

In a 100 ml round bottom flask, placed 2-(pyrazine-2-carboxamido) acetic acid **II (**0.01 mole,1.81g) then added acetic anhydride (0.01 mole), aromatic aldehyde (0.01 mole) mixed thoroughly then added catalyst potassium acetate (0.01 mole,0.98g) liquefied the mixture on heating mental, continued heating on water bath for 4 h. Then 10 ml of



Scheme 1. Synthesis of 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one [III]: Where, R= ph, *2*-Cl-ph*; 4*-F-ph; *4*-Br-ph; *4*-Cl-ph*; 4*-CH_3-ph*; 4*-OH,*3*-OCH_3-ph; furan; *4*-OCH_3-ph; *2*- OH-ph; *4*-OH-ph; *4*-OH, 3-Br&*3*-OCH_3-ph ; *3*-OH-ph; *4*-CN-ph.

EtOH was added to reaction mixture. The product precipitated upon over night storage in refrigerator; the precipitate obtained was filtered, dried and recrystalized using ethanol (PA1-PA14). Mobile phase Ethyl acetate: Ethanol: Acetone: drop of Glacial Acetic Acid (2:1:1). Scheme I.

2.3.1. 4-(Phenylmethylidene)-2-Pyrazin-2-yl-1, 3-Oxazol-5(4H)-One (PA1)

Yield (75%), m.p.: 153-154 ^{o}C. FT-IR ν max (KBr, cm^{-1}): 2917 (C-H $_{Str,}$ aromatic), 2845(C-H $_{Str,}$ alkane), 1746(C=O $_{Str,}$ ring), 1678 (C=N $_{Str}$, ring), 1595 (C=C $_{Str}$, ring),1123(C-O-C $_{Str}$, ring), ^{1}H-NMR (DMSO, 400 MHz) δ: 6.90 (s,1H, ethylene), 7.52-8.17 (m, 5H, aromatic), 8.76-9.21 (m, 3H, pyrazine), MS:[M]+ at m/z 251.Anal. Cal. for $C_{14}H_9N_3O_2$: C 66.93, H 3.61, N16.73 %. Found: C 66.90, H 3.64,N 16.75 %.

2.3.2. 4-[(2-Chlorophenyl) Methylidene]-2-Pyrazin-2-yl-1, 3-Oxazol-5(4H)-One (PA2)

Yield (68%), m.p.: 175-176 ^{o}C. FT-IR ν max (KBr, cm^{-1}): 2917 (C-H $_{Str,}$ alkane), 1710 (C=O $_{Str,}$ ring), 1589 (C=N $_{Str}$, ring), 1552(C=C $_{Str}$, ring), 1589 (C=C $_{Str}$, ring),1160 (C-O-C $_{Str}$, ring),742 (C-Cl $_{Str}$, aromatic), ^{1}H -NMR (DMSO, 400 MHz) δ: 7.4 (s,1H, ethylene), 7.80-8.18 (m,4H, aromatic), 8.52-9.30 (m,3H, pyrazine), MS:[M+2] at m/z 287.Anal. Cal. for $C_{14}H_8ClN_3O_2$: C 58.86, H 2.82, N14.71 %. Found: C 58.81, H 2.78, N14.74%.

2.3.3. 4-[(4-Fluorophenyl) Methylidene]-2-Pyrazin-2-yl-1, 3-Oxazol-5(4H)-One (PA3)

Yield (77%), m.p.: 156-157 ^{o}C. FT-IR ν max (KBr, cm^{-1}): 3080 (C-H $_{Str}$, aromatic), 2919 (C-H $_{Str,}$ alkane), 1679(C=O $_{Str,}$ ring), 1603 (C=N $_{Str}$, ring), 1510 (C=C $_{Str}$, ring), 1156 (C-O-C $_{Str}$, ring), 1051(C-F $_{Str}$, aromatic), ^{1}H -NMR (DMSO, 400 MHz) δ: 7.18 (s,1H, ethylene), 7.65-8.26 (m,4H, aromatic), 8.33-9.26 (m,3H, pyrazine), MS:[M]+ at m/z 269.Anal. Cal. for $C_{18}H_{15}FN_3O_2$: C 63.90, H 4.47, N 16.56 %. Found: C 63.93, H 4.50, N 16.50%.

2.3.4. 4-[(4-Bromophenyl) Methylidene]-2-Pyrazin-2-yl-1, 3-oxazol-5(4H)-one (PA4)

Yield (67%), m.p.: 170-171 ^{o}C. FT-IR ν max (KBr, cm^{-1}): 2914 (C-H $_{Str}$, aromatic), 2847 (C-H $_{Str,}$ alkane), 1678(C=O $_{Str,}$ ring), 1585 (C=N $_{Str}$, ring), 1422 (C=C $_{Str}$, ring), 1067 (C-O-C $_{Str}$, ring), 680(C-Br $_{Str}$, aromatic), ^{1}H-NMR (DMSO, 400 MHz) δ: 6.92 (s,1H,ethylene), 7.28-7.80 (m,4H, aromatic), 8.52-9.37 (m,3H, pyrazine), MS:[M]+ at m/z 330.Anal. Cal. for $C_{14}H_8BrN_3O_2$: C 50.93, H 2.44, N 12.73%. Found: C 50.89, H 2.40, N 12.76%.

2.3.5. 4-[(4-Chlorophenyl) Methylidene]-2-Pyrazin-2-yl-1, 3-Oxazol-5(4H)-One (PA5)

Yield (72%), m.p.: 165-166 ^{o}C. FT-IR ν max (KBr, cm^{-1}): 2954 (C-H $_{Str}$, aromatic), 2915 (C-H $_{Str,}$ alkane), 1738 (C=O $_{Str,}$ ring), 1667 (C=N $_{Str}$, ring), 1633(C=C $_{Str}$, ring), 1059 (C-O-C $_{Str}$, ring), 784 (C-Cl $_{Str}$, aromatic), ^{1}H -NMR (DMSO, 400 MHz) δ: 7.48 (s,1H, ethylene), 7.40-7.65 (m, 4H,

aromatic), 8.30-9.14 (m, 3H, pyrazine), MS:[M+2] at m/z 287.Anal.Cal. for $C_{14}H_8ClN_3O_2$: C 58.86, H 2.82, N14.71%. Found: C 58.87, H 2.79, N14.70 %.

2.3.6. 4-[(4-Methylphenyl) Methylidene]-2-Pyrazin-2-yl-1, 3-Oxazol-5(4H)-One (PA6)

Yield (65%), m.p.: 120-122 ^oC. FT-IR ν max (KBr, cm^{-1}): 2917 (C-H $_{Str}$, aromatic), 2849 (C-H $_{Str,}$ alkane), 1676 (C=O $_{Str,}$ ring), 1606 (C=N $_{Str}$, ring), 1538(C=C $_{Str}$, ring), 1051 (C-O-C $_{Str}$, ring), ^{1}H-NMR (DMSO, 400 MHz) δ: 2.53-2.54(t,3H, methyl), 7.27 (m,1H, ethylene), 7.25-8.21 (m, 4H, aromatic), 8.87-9.30 (m, 3H, pyrazine), MS:[M]+ at m/z 265.Anal. Cal. for $C_{15}H_{11}N_3O_2$: C 67.92, H 4.18, N 15.84 %. Found: C 67.95, H 4.14, N 15.80 %.

2.3.7. 4-[(4-Hydroxy-3-Methoxyphenyl) Methylidene]-2-Pyrazin-2-yl-1, 3-Oxazol-5(4H)-One (PA7)

Yield (69%), m.p.: 163-164 ^oC. FT-IR ν max (KBr, cm^{-1}): 3405-3420 (OH $_{Str}$, hydroxyl), 3153 (C-H $_{Str}$, aromatic), 3139 (C-H $_{Str,}$ alkane), 2349 (OCH_3 $_{Str}$, aromatic),1753 (C=O $_{Str,}$ ring), 1695 (C=N $_{Str}$, ring), 1588(C=C $_{Str}$, ring), 1091 (C-O-C $_{Str}$, ring), ^{1}H-NMR (DMSO, 400 MHz) δ: 3.86-3.89 (t,3H,methoxy), 5.60 (s,1H, hydroxyl), 6.96 (s, 1H, ethylene), 6.96-7.58 (m, 3H, aromatic), 8.88-9.76 (m, 3H, pyrazine), MS:[M]+ at m/z 297.Anal. Cal. for $C_{15}H_{11}N_3O_4$: C 60.61, H 3.73, N 14.14 %. Found: C 60.58, H 3.75, N 14.16 %.

2.3.8. 4-(Furan-2-Ylmethylidene)-2-(Pyrazin-2-yl)-1, 3-Oxazol-5(4H)-One (PA8)

Yield (76%), m.p.: 180-181 ^oC. FT-IR ν max (KBr, cm^{-1}): 3062 (C-H $_{Str}$, aromatic), 2847 (C-H $_{Str,}$ alkane), 1712 (C=O $_{Str,}$ ring), 1666 (C=N $_{Str}$, ring), 1651(C=C $_{Str}$, ring), 1017 (C-O-C $_{Str}$, ring), ^{1}H-NMR (DMSO, 400 MHz) δ: 7.85 (s,1H, ethylene), 8.16-8.85 (m,3H, furan), 8.83-9.36 (m,3H, pyrazine), MS:$[M]^+$ at m/z 241; Anal. Cal. for $C_{12}H_7N_3O_3$: C 59.75, H 2.93, N 17.42 %. Found: C 59.70, H 2.96, N 17.40 %.

2.3.9. 4-(4-Methoxybenzylidene)-2-(Pyrazin-2-yl)-1,3-Oxazol-5(4H)-One (PA9)

Yield (80%), m.p.: 135-136 ^oC. FT-IR ν max (KBr, cm^{-1}): 3030 (C-H $_{Str}$, aromatic), 2842 (C-H $_{Str,}$ alkane), 2515 (OCH_3 $_{Str}$, aromatic),1742 (C=O $_{Str,}$ ring), 1680 (C=N $_{Str}$, ring), 1601(C=C $_{Str}$, ring), 1071 (C-O-C $_{Str}$, ring), ^{1}H -NMR (DMSO, 400 MHz) δ: 3.79-3.84(t, 3H,methoxy),6.94(s,1H, ethylene), 6.96-7.99 (m,4H, aromatic), 8.85-9.34 (m, 3H, pyrazine), MS:$[M]^+$ at m/z 282; Anal. Cal. for $C_{15}H_{11}N_3O_3$: C 64.05, H 3.94, N 14.94 %. Found: C 64.00, H 3.99, N 14.96 %.

2.3.10 4-(2-Hydroxybenzylidene)-2-(pyrazin-2-yl)-1,3-Oxazol-5(4H)-One (PA10)

Yield (81%), m.p.: 90-91^oC. FT-IR ν max (KBr, cm^{-1}): 3076-3082 (OH $_{Str}$, hydroxyl), 3058 (C-H $_{Str}$, aromatic), 2919 (C-H $_{Str,}$ alkane), 1678 (C=O $_{Str,}$ ring), 1656 (C=N $_{Str}$, ring), 1553(C=C $_{Str}$, ring), 1048 (C-O-C $_{Str}$, ring), ^{1}H -NMR (DMSO, 400 MHz) δ: 7.30(s,1H, ethylene), 6.71-7.55 (m, 4H, aromatic), 8.73-9.28 (m, 3H, pyrazine), 11.55

(s,1H, hydroxyl) MS:$[M]^+$ at m/z 267; Anal. Cal. for $C_{14}H_9N_3O_3$: C 62.92, H 3.39, N 15.72 %. Found: C 62.88, H 3.42, N 15.75 %.

2.3.11. 4-(4-Hydroxybenzylidene)-2-(Pyrazin-2-yl)-1,3-Oxazol-5(4H)-One (PA11)

Yield (72%), m.p.: 140-141 ^oC. FT-IR ν max (KBr, cm^{-1}): 3152-3160 (OH $_{Str}$, hydroxyl), 2917(C-H $_{Str}$, aromatic), 2849 (C-H $_{Str,}$ alkane), 1665 (C=O $_{Str,}$ ring), 1597 (C=N $_{Str}$, ring), 1552(C=C $_{Str}$, ring), 1111 (C-O-C $_{Str}$, ring), ^1H -NMR (DMSO, 400 MHz) δ: 6.89(s, 1H, ethylene), 6.90-7.74 (m, 4H, aromatic), 8.68-9.77 (m, 3H, pyrazine), 10.29 (s,1H, hydroxyl), MS:$[M]^+$ at m/z 267; Anal. Cal. for $C_{14}H_9N_3O_3$: C 62.92, H 3.39, N 15.72 %. Found: C 62.88, H 3.42, N 15.75 %.

2.3.12.4-(3-Bromo-4-Hydroxy-5-Methoxybenzylidene)-2-(Pyrazin-2-yl)-1, 3-Oxazol-5(4H)-One (PA12)

Yield (68%), m.p.: 146-147 ^oC. FT-IR ν max (KBr, cm^{-1}): 3245-3266 (OH $_{Str}$, hydroxyl), 2915 (C-H $_{Str}$, aromatic), 2847 (C-H $_{Str,}$ alkane), 2362 (OCH_3 $_{Str}$, aromatic),1668(C=O $_{Str,}$ ring), 1585 (C=N $_{Str}$, ring), 1557 (C=C $_{Str}$, ring), 1058 (C-O-C $_{Str}$, ring), 675 (Br $_{Str}$, aromatic), ^1H-NMR (DMSO, 400 MHz) δ:3.88-3.94(t, 3H, methoxy), 7.22 (s,1H, ethylene), 7.36-8.12 (m,2H, aromatic), 9.78-10.10 (m, 3H, pyrazine), 10.80 (s,1H,hyroxyl), MS:[M+2] at m/z 378; Anal. Cal. for $C_{15}H_{10}BrN_3O_4$: C 47.89, H 2.68, N 11.17 %. Found: C 47.85, H 2.69, N 11.19 %.

2.3.13. 4-(3-Hydroxybenzylidene)-2-(Pyrazin-2-yl)-1,3-Oxazol-5(4H)-One (PA13)

Yield (65%), m.p.: 105-106 ^oC. FT-IR ν max (KBr, cm^{-1}): 3340-3369 (OH $_{Str}$, hydroxyl), 3065 (C-H $_{Str}$, aromatic), 2917 (C-H $_{Str,}$ alkane), 1678 (C=O $_{Str,}$ ring), 1645 (C=N $_{Str}$, ring),1513(C=C $_{Str}$, ring), 1119 (C-O-C $_{Str}$, ring), ^1H -NMR (DMSO, 400 MHz) δ: 7.20 (s, 1H, ethylene), 6.65-7.54 (m, 4H, aromatic), 8.50-9.40 (m, 3H, pyrazine), 9.50 (s,1H, hydroxyl), MS:$[M]^+$ at m/z 267; Anal. Cal. for $C_{14}H_9N_3O_3$: C 62.92, H 3.39, N 15.72 %. Found: C 62.95, H 3.42, N 15.68 %.

2.3.14. 4-(5-Oxo-2-(Pyrazin-2-yl) Oxazol-4(5H)-Ylidene) Methyl) Benzonitrile (PA14)

Yield (72%), m.p.: 149-150 ^oC. FT-IR ν max (KBr, cm^{-1}): 2916 (C-H $_{Str}$, aromatic), 2848 (C-H $_{Str,}$ alkane), 1741(C=O $_{Str,}$ ring), 1649 (C$^{\equiv}$N $_{Str}$, ring), 1563(C=C $_{Str}$, ring), 1097 (C-O-C $_{Str}$, ring), ^1H -NMR (DMSO, 400 MHz) δ: 7.62 (s,1H, ethylene), 7.62-8.14 (m, 4H, aromatic), 8.70-9.40 (m,3H, pyrazine), MS:$[M]^+$ at m/z 276; Anal. Cal. for $C_{15}H_8N_4O_2$: C 65.22, H 2.92, N 20.28 %. Found: C 65.20, H 2.95, N 20.24 %.

2.4. Biological Evaluation

2.4.1. Antimicrobial Activity [14]

All the synthesized compounds were screened for *in vitro* antimicrobial activity against two gram positive strains *S.aureus* (*S.aureus*, NCIM 2079), *B.subtillis* (*B.subtillis*, NCIM 2711) and two gram negative strains *E.coli* (*E.coli*, NCIM 2685), *K.pneumonia* (*K.pneumoniae*, NCIM 2957) bacteria for antibacterial and two fungal

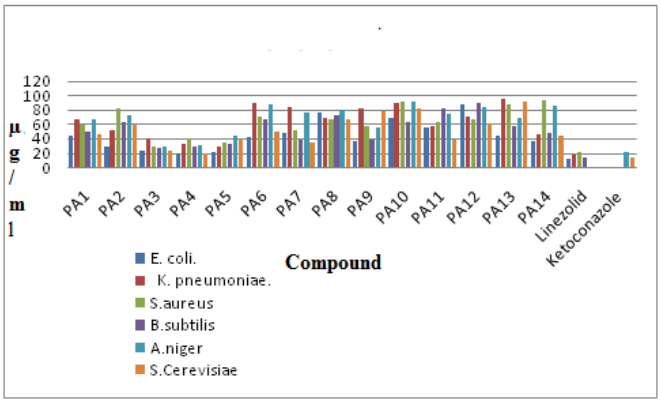


Figure 3. Minimum inhibitory concentration of compounds PA1-PA14 against different microbial strains.

Table 1. Minimum inhibitory concentration values (µg/ml) of compounds PA1-PA14 against microbes.

Comp	**R**	***E. coli***	***K. pneumoniae***	***S. aureus***	***B. subtilis***	***A. niger***	***S. cerevisiae***
PA1	ph	44	66	60	50	66	45
PA2	*2*-Cl-ph	29	51	82	62	72	59
PA3	*4*-F-ph	23	40	29	26	28	23
PA4	*4*-Br-ph	19	33	40	29	30	20
PA5	*4*-Cl-ph	21	29	35	33	44	38
PA6	*4*-CH_3-ph	41	90	71	66	88	49
PA7	*4*-OH, *3*-OCH_3-ph	48	83	52	39	77	34
PA8	Furan	77	68	67	72	80	66
PA9	*4*-OCH_3-ph	36	81	58	38	55	79
PA10	*2*-OH-ph	69	89	92	63	91	81
PA11	*4*-OH-ph	56	58	62	81	75	39
PA12	*4*-OH, *3*-Br&OCH_3-ph	87	71	66	89	83	61
PA13	*3*-OH-ph	44	96	88	57	69	92
PA14	*4*-CN-ph	37	46	94	48	86	44
Linezolid		12	18	21	14	----	----
Ketoconazole		----	----	----	----	21	13

species *A.nigar* (*A.nigar*, NCIM 596), *S.cerevisiae* (*S.cerevisiae*, NCIM 3102) for antifungal activity, using the broth micro dilution method. Minimum inhibitory concentration (MIC) was determined and compared with standard drugs linezolid for antibacterial, ketoconazole for antifungal activity (Table 1).

3. Results and Discussion

The synthesis of 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one compound were prepared by the Erlenmeyer-Polchl reaction, a cyclodehydrationcondensation of the appropriate aldehyde and 2-(pyrazine-2-carboxamido) acetic acid in dry acetic anhydride catalyzed by acetate anion are depicted in scheme I. The FT-IR spectra, reveals that functional groups present in the molecule appeared at their characteristic frequency C-H, $_{Str.}$ alkane between 2842-3139cm^{-1}, C-H, $_{Str.}$ aromatic between 2914-3153cm^{-1}, C=O $_{Str.}$ ring between 1665-1753cm^{-1}, C=N $_{Str.}$ ring between 1585-1695cm^{-1}, C=C $_{Str.}$ ring between 1422-1651cm^{-1}, C-O-C $_{Str.}$ ring between 1017-1160cm^{-1}, C-Cl $_{Str.}$ aromatic between 742-784cm^{-1}, C-Br $_{Str.}$ aromatic between 675-680 cm^{-1}, OH $_{Str.}$ hydroxyl between 3082-3420 cm^{-1}, OCH_3 $_{Str.}$ aromatic between 2349-2515 cm^{-1}, C-F $_{Str.}$ at 1051 cm^{-1}, etc. The chemical shift (δ) for ethylene hydrogen was observed in the range of 6.89-7.85 ppm, δ value for methyl three hydrogen was observed at 2.54 ppm, δ value for methoxy three hydrogen was observed in the range of 3.83-3.94 ppm, δ value for C-H, pyrazine hydrogen was observed in the range of 7.65-10.10 ppm, δ value for aromatic hydrogen was observed in the range of 6.85-8.25 ppm, δ value for hydroxyl hydrogen was observed in the range of 5.60-11.55 ppm, δ value for furan hydrogen was observed in the range of 8.16-8.85 ppm . The m/e value was observed, e.g., in case of PA1-PA14 at 241-376 $(M)^+$. So, from the physical and spectral data, we could conclude that the desired compounds synthesized successfully.

3.1. Antimicrobial Activity

From *in vitro* antibacterial activity, In case of *E. coli* ,*K. pneumonia*, *S.aureus* and *B. subtilis* compounds PA3, PA4, and PA5 (*4*-F-ph, *4*-Br-ph and *4*-Cl-ph) were found to have significant activity which is 1-2 folds less than the standard drug Linezolid, while the rest of the compounds showed moderate activity. *In vitro* antifungal activity, In case of *A.nigar* and *S.cerevisiae* compounds PA3, and PA4 (*4*-F-ph and *4*-Br-ph) were found to have significant activity which is 1-2 folds less than the standard drug Ketoconazole, while the rest of the compounds showed moderate activity Fig.3. Thus from the obtained antibacterial and antifungal activity data we could conclude that the electron-withdrawing groups substituted at specific position on phenyl ring i.e., (*4*-F-ph, *4*-Br-ph and *4*-Cl-ph) are contributing positively for activity (Table 1).

4. Conclusion

A series of 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one have been synthesized in quantitative yields with the use of conventional method and evaluated for their *in vitro* antimicrobial activity result are shown in Table 1.On the basis of observed results, we could conclude that additions of different functional groups have varying effects. In addition, the greater biological profiles were observed when the electron-

withdrawing groups were incorporated at *p*-position of the phenyl ring.

Acknowledgements

The authors thank Shri. Prashant Patil Gadakh, President, Mula Education Society and Dr .V. K. Deshmukh, Principal, MES`s College of Pharmacy, Sonai for providing all laboratory facilities, UDCT Dr. BAMU, Aurangabad for recording FT-IR Spectra , ^{1}H-NMR spectra at SAIF Punjab University, Chandigarh, GC-MS spectra at Savitribai Phule Pune University, Pune for recording spectra.

References

[1] Serap B, Meltem Y, Ahmet D, Hakan B, Rza A, Neslihan D. Synthesis of linezolid-like molecules and evaluation of their antimicrobial activities. *Turk J. Chem* (2012) 36: 37-53.

[2] Wallace R. J. J, Brown-Elliott B.A, Ward S. C, Crist C. J, Mann L. B, Wilson R. W. A. In vitro activities of linezolid against multiple *Nocardia* Species. *Antimicrob Agents Chemother (2001*) 45(4): 1295-1297.

[3] Lois M. E, Ashok R, Michael R. J, Appelbaum P. C. Anti anaerobe activity of RBX 7644 (Ranbezolid), a new oxazolidinone, compared with those of eight other agents. *Antimicrob Agents Chemother (2003)* 47(3): 1143-1147.

[4]Ahmed S. A. A. Pesticidal effects of some imidazolidine and oxazolone derivatives. *World J Agri. Sci.(2009)* 5(1): 105-113.

[5]Ahmada et al. Synthesis and immunomodulatory properties of selected oxazolone derivatives. *Bioorg. Med. Chem.(2004)*12(9):2049-2057.

[6] Khalid M.K, Uzma R. M, Mahmud T. Hassan K, Zia U, Shahnaz P, Muhammad I. C. Oxazolones: New tyrosinase inhibitors; synthesis and their structure-activity relationships. *Bioorg. Med. Chem. (2006)* 14(17):6027-6033.

[7] Hemashrilatha S, Shruthi K, Manjula A, Harinandha babu V, Vithalrao B. Synthesis and anti-inflammatory activity of imidazo [1,2-a] pyridinyl / pyrazinyl benzamides / acetamides. *Indian J. chem. (2012)* 51B: 981-987.

[8] Gadada N, Amorn P. Synthesis and antimicrobial activity of oxazolone, imidazolone and triazine derivatives containing benzothiophene. *Bull. Korean Chem. Soc. (2011)* 32(11): 3914-3922.

[9] Osman M. O. H, Hussein M. H, Evelin B. M, Ahmed El-M. Synthetic approaches and biological evaluation of some new sulfonate ester-containing imidazolone derivatives. *Ameri. J. Org. Chem. (2012)* 2(4): 79-86.

[10] Sarragiotto et al. Synthesis and evaluation of new *β*-carboline-3-(4-benzylidene)-4*H*- oxazol-5-one derivatives as antitumor agents. *Molecules (*2012) 17: 6100-6113.

[11] Pasha M. A, Jayashankara V. P, Venugopala K. N, Gopalkrishna R. Zinc oxide (ZnO):An Efficient catalyst for the synthesis of 4-arylmethylidene-2-phenyl-5-(4*H*)-oxazolone having antimicrobial activity. J. *Pharmacology and Toxicology (2007)* 2(3): 264-270**.**

[12] Mariappan G, Saha B. P, Sriparna D, Deepak K , Haldar P. K. Design, synthesis and antidiabetic evaluation of oxazolone derivatives. *J. Chem. Sci. (2011)*123(3): 335-341.

[13] Nicolaou K. C, Pfefferkorn J. A, Roecker A. J, Cao G. Q, Barluenga S, Mitchell H. J. Natural product-like combinatorial libraries based on privileged structures: General principles and solid-phase synthesis of benzopyrans. *J. Amer. Chem. Soc (2000)*122(41):9939.

[14] Poonam K, Pawan K, Arpana M, Neeraj K. A, Pawan K. S. Synthesis of some novel 4-arylidene pyrazoles as potential antimicrobial agents. *Org.Med.Chem.Lett. (2013)*3(9):1-7.

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