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Research Article

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Synthesis of some new 1,3,4-oxadiazole derivatives and evaluation of their antibacterial effects

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ABSTRACT

*In the present study, some oxadiazole derivatives have been synthesized by incorporating azetidinyl and thiazolidinyl moieties at its 2-position such as 5-(p-methoxyphenyl)-[2-substitutedbenzylidenylimino]1,3,4-oxadiazole **2-6**, 5-(p-methoxyphenyl)-[2-(3´-chloro-2´-oxo-4´-substitutedaryl-1-azetidinyl)1,3,4-oxadiazole **7-11** and 5-(p-methoxyphenyl)-[2-(2´-substitutedaryl-4´-oxo-1´,3´-thiazolidin-3´-yl)1,3,4-oxadiazole **12-16**. The structure of these compounds have been elucidated by elemental analysis (C, H, N) and IR, ^{1}H-NMR, Mass spectroscopic techniques. Further, these compounds were subjected to screening for antibacterial activities against different bacterial strains.*

Keywords Oxadiazole, azetidinone, thiazolidinone, antibacterial activity.

INTRODUCTION

Bacteria are becoming resistant to ever more antibacterial agents. Currently, bacterial resistance is combated by the discovery of new drugs. However, microorganisms are becoming resistant more quickly than new drugs are being found, thus, future research in antibacterial therapy may focus on finding ways to overcome resistance to antibacterial, or methods to treat infections with alternative means. Oxadiazole have played important role in medicinal chemistry, such as anti-inflammatory[1,2], anticonvulsant[3], antifungal[4-7], antibacterial[8-11] and many more. Also the congers of Schiff base[12,13], azetidinone[14,15] and thiazolidinone[16,17] have also been proved to exhibit promising antifungal activity. These finding prompted us to synthesize the substituted oxadiazole derivatives by the combination of azetidinone and thiazolidinone moieties in one frame may lead to compounds with interesting antibacterial activity.

EXPERIMENTAL SECTION

Chemistry

The synthetic strategies adopted to obtain the target compounds are depicted in **scheme 1**. the starting material: 2-[(p-methoxyphenyl)carbonyl]hydrazinecarboxamide was treated with concentrated sulphuric acid to give 2-amino-5-(p-methoxyphenyl)-1,3,4-oxadiazole **1**, which condensed with various aromatic aldehydes giving 5-(p-methoxyphenyl)-[2-substitutedbenzylidenylimino]-1,3,4-oxadiazole **2-6**. Compound **2-6** were reacted further with triethyl amine / chloroacetyl chloride to yield azetidinone congeners i.e. 5-(p-methoxyphenyl)-[2-(3´-chloro-2´-oxo-

4´-substituted aryl-1-azetidinyl)-1,3,4-oxadiazole **7-11**. On the other hand, reaction of compounds **2-6** with thioglycolic acid in presence of anhydrous zinc chloride led to the formation of 5-(p-methoxyphenyl)-[2-(2´-substituted aryl-4´-oxo-1´, 3´-thiazolidin-3´-yl)-1,3,4-oxadiazole **12-16.**

RESULTS AND DISCUSSION

The antibacterial screening showed that all the tested compounds (**2-16)** showed moderate to excellent inhibitory growth against gram positive bacteria *S. aureus, B. Subtilis* and *S. epidermis* and gram negative bacteria *E. Coli, K. pneumoniae* and *P. aeruginosa* at 250 µg/ml concentration using standard method.

Compound **9** having 3-methoxy-4-hydroxyphenyl group as substitutent more potent antibacterial activity against all the gram positive bacterial strains *S. aureus, B. Subtilis* and *S. epidermis* and gram negative bacteria *E. Coli* with 1.562-6.25 µg/ml. Compound **10** bearing β-lactam ring posses 4-aminodimethylphenyl group as substitutent, respectively revealed excellent antibacterial activity against *S. aureus* and *S. epidermis* with 3.125 µg/ml. Compound **14** bearing thiolactum ring also show adequate antibacterial activity against gram positive bacteria *S. aureus* and *B. Subtilis* with MIC 3.125 and 6.25 µg/ml, respectively as compared to standard drug. From the results, it is found that compound **8, 14 and 15** reflected significant antibacterial activity against gram positive bacteria and gram negative bacteria as compared to standard drug. Rest compounds of this series were least potent than reference drug.

The antibacterial result depicted in Tables 3 indicated that the conversion of compounds **2-6** into their corresponding azetidinone congeners **7-11** and thiazolidinone congeners **12-16** increases the inhibition action against the growth of different bacterial strains. However, compound 7-**11** bearing β-lactam ring exhibited better antibacterial activity as compared to thiazolidinone ring bearing compounds **12-16.** by examining the effects of different substituting group phenyl, 4-methoxyphenyl, 3-meyhoxy-4-hydroxyphenyl, 4-aminodimethylphenyl, 4-hydroxyphenyl Furthermore, among azetidinone and thiazolidinone congeners, compounds having 3-meyhoxy-4-hydroxyphenyl group (**9** and **14**) and 4-aminodimethylphenyl (**10** and **15**) showed better activity in their respective groups against different gram positive and gram negative bacterial strains.

At the end, it may be concluded that-

- Presence of 3-methoxy-4-hydroxyphenyl and 4-aminodimethylphenyl as a substituent elicits a remarkable increase in biological profile.
- Cylcylization of substituted schiff bases into their corresponding azetidinone and thiazolidinone congeners enhances the antibacterial activity
- Compounds having azetidinone moiety displayed better biological results than those containing thiazolidinone ring.

Biological evaluation:

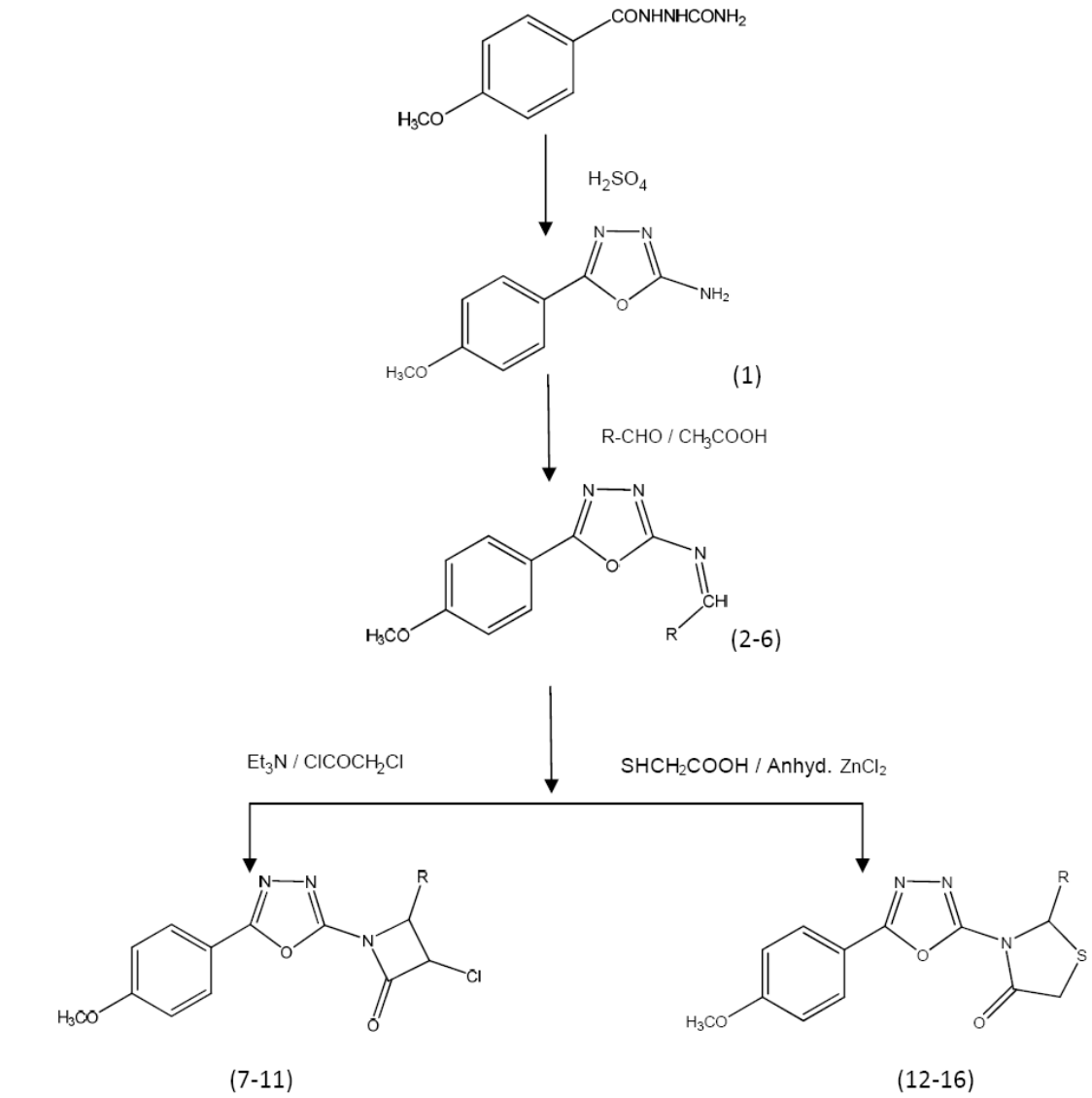
Antibacterial activity

The newly synthesized compounds and reference drug were screened for antibacterial activity against different bacterial strains (gram positive bacteria: *S. aureus, B. subtilis, and S. epidermis* and gram negative bacteria*: E. coli, K. pneumoniae* and *P. aeruginosa*) at a concentration 250 µg/mL by filter paper disc method[18]. DMSO served as control and due this there was no visible change in bacterial growth, and amphicillin was used as a standard drug. The discs of Whatmann filter paper were prepared with standard size (7 mm) and kept into 1 Oz screw capped wide mouthed containers for sterilization. These bottles are kept in to hot air oven at 150 ^{o}C. Now, solution is then put into each bottle. The discs are transferred to the inoculated plates with a pair of fine pointed tweezers. To prevent contamination tweezers may be kept with their tips in 70% alcohol and flamed off before use. Before use the test organism, which were grown on nutrient agar. They were sub cultured in nutrient broth at 37 ^{o}C for 18-20 h. Carefully each disc was applied to the surface of agar without lateral movement once the surface had been touched. Now the plates incubated for 24 h at 37 ^{o}C.

Minimal inhibitory concentration (MIC)

The antimicrobial activity was assayed *in vitro* by the two fold broth dilution [19] against different bacterial strains (gram positive bacteria: *S. aureus, B. subtilis, and S. epidermis* and gram negative bacteria*: E. coli, K. pneumoniae* and *P. aeruginosa*). The minimal inhibitory concentrations (MIC, µg/ml) were defined as the lowest concentrations of compound that completely inhibited the growth of each strain. All compounds, dissolved in dimethylsulfoxide,

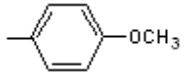
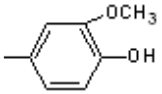
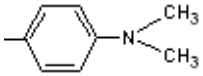
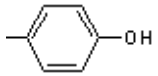
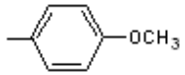
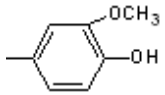
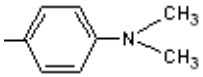
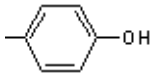
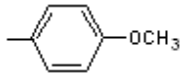
were added to culture media .Mueller Hinton Broth for bacteria to obtain final concentrations ranging from 100 µg/ml to 0.781 µg/ml. The amount of dimethylsulfoxide never exceeded 1% v/v. Inocula consisted of 5.0 x 10^4 bacteria/ml and 1.0 x10^3 fungi/ml. The MICs were read after incubation at 37 °C for 24 h. Media and media with 1% v/v dimethylsulfoxide were employed as growth controls, and amphicillin was used as a standard drug.

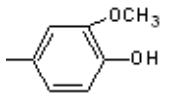
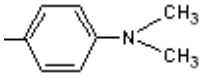
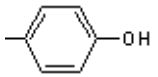


R= Substituted aryls

Scheme 1

Table 1: Characterization data of compounds 2-16.

Compound no.	R	Molecular Formula	M.P. (°C)	Yield (%)	Recryt. Solvent	Elemental Analysis [a] %					
						C		H		N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
2		$C_{16}H_{13}N_3O_2$	115	65	Methanol	68.81	68.61	4.65	4.81	15.05	14.92
3		$C_{17}H_{15}N_3O_3$	118	70	Ethanol	66.01	65.93	4.85	4.59	13.59	13.67
4		$C_{17}H_{15}N_3O_4$	131	66	Ethanol	62.76	62.57	4.61	4.57	12.92	12.81
5		$C_{18}H_{18}N_4O_2$	125	55	Acetone	67.08	67.18	5.59	5.71	17.39	17.51
6		$C_{16}H_{13}N_3O_3$	118	60	Methanol	65.08	65.22	4.40	4.54	14.23	14.42
7		$C_{18}H_{14}N_3O_3Cl$	138	58	Ethanol	60.75	60.65	3.93	3.78	11.81	11.94
8		$C_{19}H_{16}N_3O_4Cl$	102	62	Ethanol	59.14	59.23	4.15	4.27	10.89	10.68
9		$C_{19}H_{16}N_3O_5Cl$	135	55	DMF	56.78	57.62	3.98	3.81	10.46	10.62
10		$C_{20}H_{19}N_4O_3Cl$	167	53	Benzene/ pet. Ether	60.22	60.05	4.76	4.57	14.05	14.21
11		$C_{18}H_{14}N_3O_4Cl$	148	55	Methanol	58.14	58.27	3.76	3.52	11.30	11.41
12		$C_{18}H_{15}N_3O_3S$	166	40	DMF	61.18	61.02	4.24	4.37	11.89	11.97
13		$C_{19}H_{17}N_3O_4S$	109	45	Ethanol	59.53	59.71	4.43	4.56	10.93	10.71

14		$C_{19}H_{17}N_3O_5S$	162	42	Methanol	57.14	57.25	4.26	4.41	10.52	10.67
15		$C_{20}H_{20}N_4O_3S$	128	38	Acetone	60.60	60.69	5.05	5.13	14.14	14.31
16		$C_{18}H_{15}N_3O_4S$	125	45	Acetic acid	58.53	58.72	4.06	4.22	11.38	11.13

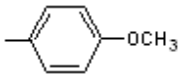
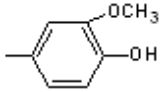
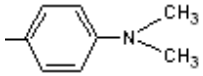
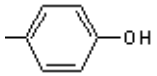
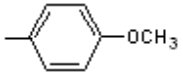
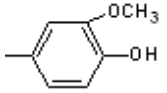
[a]C, H, N analysis were found within ±0.4 % of the theoretical values

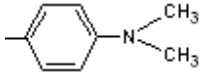
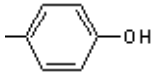
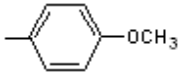
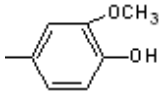
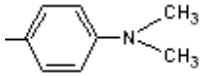
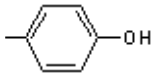
Table 2: Spectral data of newly synthesized compounds 2-16.

Compound No.	IR (KBr) ν (cm^{-1})	^{1}H-NMR δ (ppm)	MS: (m/z)
2	3064 (C-H aromatic), 2975 (C-H aliphatic), 1590 (C=N), 1585 (C------C of aromatic ring), 1080 (N-N), 1075 (C-O-C)	7.22–7.65 (m, 9H, Ar-*H*), 4.74 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.80 (s, 3H, OCH_3)	279(M^+)
3	3080 (C-H aromatic), 2970 (C-H aliphatic), 1595 (C=N), 1578 (C------C of aromatic ring), 1075 (N-N), 1070 (C-O-C)	7.29-7.71(m, 8H, Ar-*H*), 4.76 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.83 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3)	309(M^+)
4	3560 (O-H), 3077 (C-H aromatic), 2960 (C-H aliphatic), 1585 (C=N), 1570 (C------C of aromatic ring), 1075 (N-N), 1055 (C-O-C)	10.13 (s, 1H, O*H*, exchangeable with D_2O), 7.43-7.55 (m, 7H, Ar-*H*), 4.74 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.83 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3)	325(M^+)
5	3075 (C-H aromatic), 2985 (C-H aliphatic), 1588 (C=N), 1565 (C-----C of aromatic ring), 1085 (N-N),1060 (C-O-C)	7.27-7.88(m, 8H, Ar-*H*), 4.75 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.79 (s, 3H, OCH_3), 2.15(s, 6H, Ar-N(CH_3)$_2$)	322(M^+)
6	3570 (O-H), 3075 (C-H aromatic), 2965 (C-H aliphatic), 1604 (C=N), 1570 (C------C of aromatic ring), 1075 (N-N), 1065 (C-O-C)	10.14 (s, 1H, O*H*, exchangeable with D_2O), 7.25.–7.92(m, 8H, Ar-*H*), 4.74 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.81 (s, 3H, OCH_3)	295(M^+)
7	3048 (C-H aromatic), 2925 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1538 (C-----C of aromatic ring), 1085 (N-N),1154 (C-N), 1075 (C-O-C), 748 (C-Cl)	7.22–7.65 (m, 9H, Ar-*H*), 6.54 (d, 1H, C*H*-Cl, *J* = 6.5 Hz), 4.76 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.84 (s, 3H, OCH_3)	355.5(M^+), 357.5(M+2)
8	3068 (C-H aromatic), 2935 (C-H aliphatic), 1744 (C=O of β-lactum ring), 1595 (C=N), 1548 (C-----C of aromatic ring), 1095 (N-N),1164 (C-N), 1085 (C-O-C), 768 (C-Cl)	7.27-7.75 (m, 8H, Ar-*H*), 6.56 (d, 1H, C*H*-Cl, *J* = 6.5 Hz), 4.70 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.82 (s, 3H, OCH_3),, 3.31 (s, 3H, OCH_3)	385.5(M^+), 387.5(M+2)
9	3576 (O-H), 3058 (C-H aromatic), 2948 (C-H aliphatic), 1742 (C=O of β-lactum ring), 1601 (C=N), 1557 (C-----C of aromatic ring), 1075 (N-N),1164 (C-N), 1055 (C-O-C), 773 (C-Cl)	10.12 (s, 1H, O*H*, exchangeable with D_2O), 7.43-7.55 (m, 7H, Ar-*H*), 6.55 (d, 1H, C*H*-Cl, *J* = 6.5 Hz), 4.71 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.84 (s, 3H, OCH_3),, 3.29 (s, 3H, OCH_3)	401.5(M^+), 403.5(M+2)
10	3048 (C-H aromatic), 2935 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1609 (C=N), 1538 (C-----C of aromatic ring), 1085 (N-N),1154 (C-N), 1075 (C-O-C), 748 (C-Cl)	7.32-7.90 (m, 8H, Ar-*H*), 6.57 (d, 1H, C*H*-Cl, *J* = 6.5 Hz), 4.75 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.79 (s, 3H, OCH_3), , 2.18 (s, 6H, Ar-N(CH_3)$_2$)	398.5(M^+), 400.5(M+2)
11	3550 (O-H), 3078 (C-H aromatic), 2945 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1568 (C-----C of aromatic ring), 1075 (N-N), 1155 (C-N), 1065 (C-O-C), 768 (C-Cl)	10.14 (s, 1H, O*H*, exchangeable with D_2O), 7.31–7.87 (m, 8H, Ar-*H*), 6.56 (d, 1H, C*H*-Cl, *J* = 6.5 Hz), 4.71 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.81 (s, 3H, OCH_3)	371.5(M^+), 373.5(M+2)
12	3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1585 (C=N), 1538 (C-----C of aromatic ring), 1085 (N-N),1154 (C-N), 1075 (C-O-C), 645 (C-S-C)	7.22–7.65 (m, 9H, Ar-*H*), 4.72 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.81 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2 of thiazolidinone)	353(M^+)

13	3066 (C-H aromatic), 2954 (C-H aliphatic), 1730 (C=O of thiazolidinone ring), 1595 (C=N), 1548 (C-----C of aromatic ring), 1095 (N-N), 1164 (C-N), 1065 (C-O-C), 667 (C-S-C)	7.31-7.83 (m, 8H, Ar-*H*), 4.74 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.82 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2 of thiazolidinone), 3.34 (s, 3H, OCH_3),	383(M^+)
14	3570 (O-H), 3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C-----C of aromatic ring), 1085 (N-N),1154 (C-N), 1075 (C-O-C), 645 (C-S-C)	10.12 (s, 1H, O*H*, exchangeable with D_2O), 7.43-7.55 (m, 7H, Ar-*H*), 4.73 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.83 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2 of thiazolidinone), 3.31 (s, 3H, OCH_3),	399(M^+)
15	3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C-----C of aromatic ring), 1085 (N-N), 1175 (C-N), 1075 (C-O-C), 665 (C-S-C)	7.29-7.86(m, 8H, Ar-*H*), 4.76 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.81 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2 of thiazolidinone), 2.15 (s, 6H, Ar-N(CH_3)$_2$)	396(M^+)
16	3570 (O-H), 3068 (C-H aromatic), 2944 (C-H aliphatic), 1725 (C=O of thiazolidinone ring), 1605 (C=N), 1568 (C-----C of aromatic ring), 1085 (N-N), 1172 (C-N), 1063 (C-O-C), 676 (C-S-C)	10.13 (s, 1H, O*H*, exchangeable with D_2O), 7.27-7.88(m, 8H, Ar-*H*), 4.72 (d, 1H, C*H*-Ar, *J* = 11.0Hz), 3.85 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2 of thiazolidinone)	369(M^+),

Table 3: Antibacterial data of the compounds 2-16 against tested bacterial strains

Compound No.	R	*S. aureus ATCC 25923*	*B. subtilis ATCC 1633*	*S. epidermis ATCC 14940*	*E. coli ATCC 25922*	*K. pneumoniae ATCC 10031*	*P. aeruginosa ATCC 27853*
2		12 **(>100)**	-	10 **(>100)**	09 **(>100)**	07 **(>100)**	11 **(>100)**
3		16 **(50)**	14 **(>100)**	-	17 **(50)**	09 **(50)**	-
4		25 **(12.5)**	29 **(25)**	22 **(12.5)**	26 **(12.5)**	17 **(6.25)**	27 **(12.5)**
5		21 **(25)**	24 **(25)**	19 **(25)**	22 **(25)**	12 **(25)**	23 **(25)**
6		14 **(50)**	12 **(>100)**	-	15 **(>100)**	-	19 **(50)**
7		18 **(50)**	25 **(25)**	20 **(12.5)**	-	14 **(12.5)**	-
8		29 **(6.25)**	30 **(12.5)**	27 **(6.25)**	23 **(25)**	16 **(12.5)**	23 **(25)**
9		35 **(1.562)**	38 **(6.25)**	32 **(3.125)**	30 **(6.25)**	22 **(3.125)**	33 **(3.125)**

10		32 **(3.125)**	34 **(12.5)**	29 **(3.125)**	24 **(25)**	19 **(6.25)**	27 **(12.5)**
11		25 **(12.5)**	28 **(25)**	22 **(12.5)**	17 **(50)**	-	21 **(25)**
12		19 **(25)**	23 **(50)**	17 **(25)**	-	15 **(12.5)**	20 **(50)**
13		27 **(6.25)**	31 **(12.5)**	22 **(12.5)**	24 **(25)**	-	26 **(12.5)**
14		32 **(3.125)**	35 **(6.25)**	28 **(6.25)**	29 **(12.5)**	24 **(1.562)**	30 **(6.25)**
15		29 **(6.25)**	30 **(12.5)**	25 **(6.25)**	27 **(12.5)**	21 **(3.125)**	25 **(25)**
16		24 **(12.5)**	27 **(25)**	-	20 **(50)**	18 **(6.25)**	23 **(25)**
	Amphicillin	29 **(6.25)**	32 **(12.5)**	26 **(6.25)**	28 **(12.5)**	24 **(1.562)**	35 **(3.125)**

Concentration was 250 µg/mL
denotes no inhibition zone was observed.
Values in brackets of MIC

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