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Synthesis and Antimicrobial Evaluation of Some Novel Sulfonamide Derivatives Containing Oxazole Moiety

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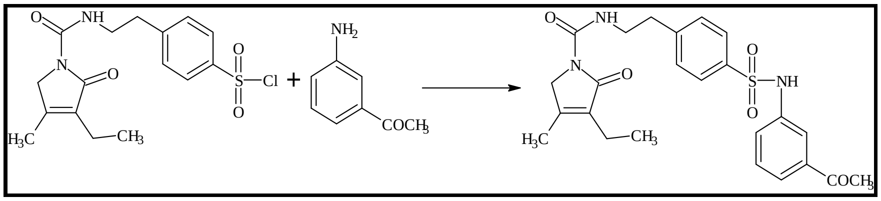
ABSTRACT

Some oxazole containing sulfonamide analogs have been synthesized by reaction of 4-(2-{[(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl) carbonyl] amino} ethyl) benzenesulfonyl chloride with 3-aminoacetophenone in acetone for 36 h, which afforded N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl} ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide. Different anilines were treated with hydrochloric acid giving aniline hydrochloride, which on further reaction with urea resulted in various phenyl ureas.N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide i.e., sulfonamide was reacted with different phenyl urea's in presence of iodine to form oxazoles, which were recrystallized from ethanol. As-synthesized oxazole derivatives were characterized by different techniques. The antimicrobial activity of as-synthesized compounds was tested against (gram-negative bacteria) Escherichia coli, and (gram-positive bacteria) Staphylococcus aureus.

Graphical Abstract



Synthesis of N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide.

Keywords: 4-(2-{[(3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl) carbonyl] amino} ethyl) benzenesulfonyl chloride, 3-aminoacetophenone, aniline hydrochloride, urea.

INTRODUCTION

Oxazoles consist of a doubly unsaturated five-membered heterocyclic ring [1, 2]. Oxazole ring is composed of three carbon atoms. They contain one oxygen atom at 1-position and one nitrogen atom at 3- positions of the ring, separated by one carbon as shown in figure1.

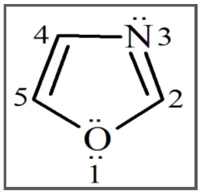


Figure 1. Oxazole structure.

They are planar molecules with conjugated electron sextets in cyclic system as it is in parent molecule. Lone pair of electrons on nitrogen, is coplanar with heterocyclic ring and it is not involved in the delocalization is confirmed by the basic properties.2,4,5-Triphenyloxazole was the first synthesized oxazole and it was reported over 140 years ago. Cornforth was the first to report the method of preparation of oxazole and also subsequently modified it [3, 4]. Oxazole chemistry has been the subject of several reviews and text books [5-9].

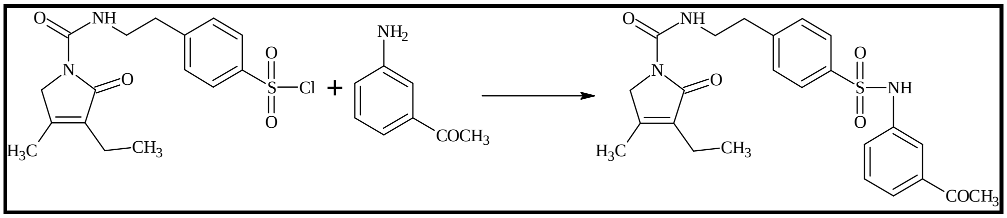
Oxazole are known to possess industrial and medicinal applications [10]. The presence of a nitrogen atom in heterocyclic ring results in perturbations of electron density frame work of the πsystem [11].They are known since 1882 [12], but the chemistry of this heterocycle gained importance during World War II. Oxazole chemistry [13-15] has been a seat of diverse biological activities [16]. The pharmacological activities of oxazole ring includes; anti-inflammatory [17], antiplatelet [18], antiproliferative [19], antibemegride [20], antiallergic [21], antibacterial [22], analgesic [23], anticancer [24], hypnotic [25] and antidiabetic [26]. Apart from these medicinal uses, oxazoles are used as luminescent material, additives to detergents and high-temperature antioxidants.

MATERIALS AND METHODS

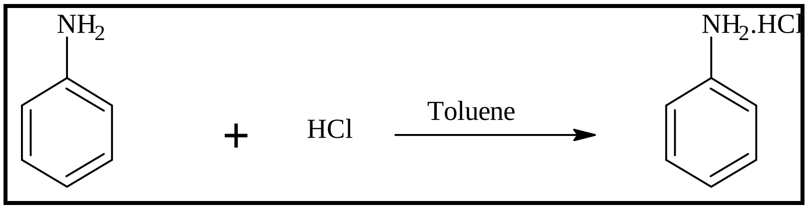
Instrumentation: Reagent-grade chemicals were purchased from Merck. All the reagents and solvents were used without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Shimadzu FTIR 8400 spectrometer. ^{1}HNMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer. The bacterial strains used were Gram positive bacteria: *Staphylococcus aureus* and Gram negative bacteria: *Escherichia coli*.

General procedure

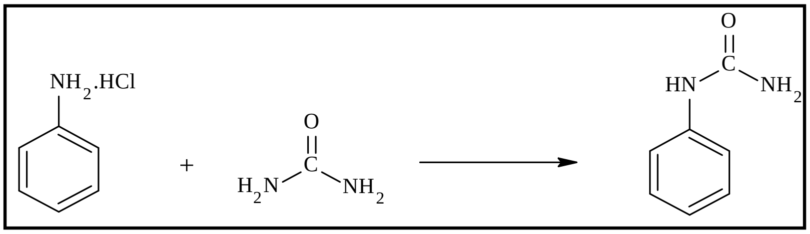
Synthesis of N-(2-{4-[(3-acetylanilino)sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide: 4-(2-{[(3-Ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]amino}ethyl) benzenesulfonyl chloride(0.1 mol, 37.06 g) was taken in acetone (345 mL) under stirring in 3 necked round bottom flask. 3-Aminoacetophenone (0.1 mol, 13.5 g) was added into it in portions and this reaction mass was stirred for 36 h at 25-30°C. After the completion of the reaction, acetone was removed and water was added for transforming it into a solid. The obtained solid was recrystallized from methyl ethyl ketone. M.P: 148-152°C, Yield: 88%.



Synthesis of phenyl urea: Aniline (2.68 mol, 250 g) and toluene 1250 mL was charged under stirring at room temperature into a 2 litre 3-necked round bottom flask. It was cooled to 15-20°C and at this temperature hydrochloric acid (35%) (4.07 mol, 465 g) was added slowly to reaction mass. Reaction mass was maintained at room temperature for 1 h. Then it was cooled to 0-5°C and reaction mass was filtered, which yielded aniline hydrochloride.



Aniline hydrochloride (2.66 mol, 345 g) and urea (2.79 mol, 168 g) was added in 2070 mL of water at room temperature into a 3 liter 3-necked round bottom flask to achieve a clear solution. Reaction mass was heated for reflux for 3 h. Then reaction mass was filtered in hot condition and the wet cake was washed by hot water (100 mL). The obtained filterate was collected and again added to round bottom flask. The filtrate was chilled, and the phenyl urea crystallized, filtered off and rinsed with a little cold water, yielding phenyl urea. M.P: 145°C, Yield: 53%

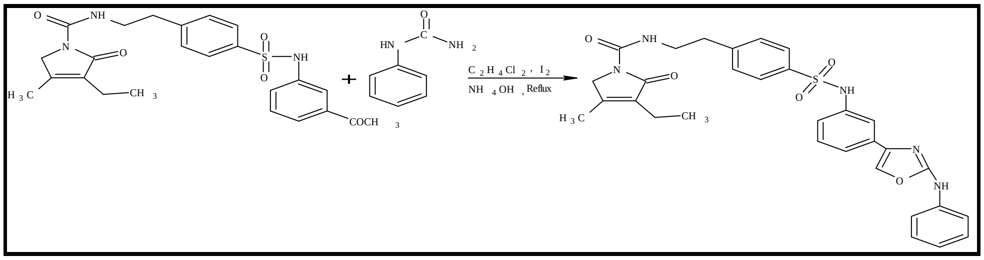


Similarly, other eleven phenyl urea's were synthesized using various anilines. The results are summarized in table 1.

Table 1. Various phenyl ureas synthesized using different anilines

S. No.	Aniline	Phenyl urea	Mol. formula of phenyl urea	Mol. weight	Yield (%)	M.P. (^{o}C)
1	2-Chloro aniline	2-Chlorophenyl urea	$C_7H_7ClN_2O$	170.51	52	150
2	4-Chloro aniline	4-Chlorophenyl urea	$C_7H_7ClN_2O$	170.51	55	201
3	2,6-Dimethyl aniline	2,6-Dimethyphenyl urea	$C_9H_{12}N_2O$	164.08	51	133
4	4-Fluoro aniline	4-Fluorophenyl urea	$C_7H_7FN_2O$	154.05	53	184
5	3-Chloro aniline	3-Chlorophenyl urea	$C_7H_7ClN_2O$	170.51	55	151
6	4-Nitro aniline	4-Nitrophenyl urea	$C_7H_7N_3O_3$	181.04	55	235
7	2,4-Dimethyl aniline	2,4-Dimethylphenyl urea	$C_9H_{12}N_2O$	164.08	52	203
8	4-Methyl aniline	4-Tolylphenyl urea	$C_8H_{10}N_2O$	150.07	54	178
9	4-Methoxy aniline	2-Methoxyphenyl urea	$C_8H_{10}N_2O_2$	166.06	51	137
10	2-Methoxy aniline	4-Methoxyphenyl urea	$C_8H_{10}N_2O_2$	166.06	50	164
11	2-Methyl aniline	2-Tolylphenyl urea	$C_8H_{10}N_2O$	150.07	52	197

Synthesis of Oxazole (N-{2-[4-({3-[2-anilino-1,3-oxazol-4-yl]aniline}sulfonyl)phenyl]ethyl}-3 ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide)(AF-108): N-(2-{4-[(3-Acetylanilino) sulfonyl]phenyl}ethyl)-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide (0.01 mol, 46.92 g) was charged to dichloroethane (50 mL) with phenyl urea (0.02 mol, 2.72 g) under stirring. Iodine crystals (0.01 mol, 2.53 g) were added into it and reaction mass was heated to reflux overnight. Water (50 mL) was added to reaction mass at 75°C and heated for 15 min, aqueous layer was separated and made alkaline with ammonium hydroxide solution at 10-15°C. Solid was separated by filtration, washed with water and dried. Finally, it was recrystallized from ethanol to give oxazole. M.P: 187-191°C, Yield: 80%.



Similarly, other eleven oxazoles were synthesized using various phenyl urea's. The results are summarized in table 2.

Table 2. Various oxazoles synthesized using different phenyl ureas

S. No.	Comp. Code	Mol. formula of Phenyl urea	Mol. formula of Oxazole	Mol. weight	Yield (%)	M.P. (°C)
1	AF-1	$C_7H_7ClN_2O$	$C_{31}H_{30}ClN_5O_5S$	619.77	76	143-145
2	AF-2	$C_7H_7ClN_2O$	$C_{31}H_{30}ClN_5O_5S$	619.77	72	158-159
3	AF-3	$C_9H_{12}N_2O$	$C_{33}H_{35}ClN_5O_5S$	613.34	71	149-152
4	AF-4	$C_7H_7FN_2O$	$C_{31}H_{30}ClN_5O_5S$	603.31	76	152-154
5	AF-5	$C_7H_7ClN_2O$	$C_{31}H_{30}ClN_5O_5S$	619.77	78	111-114
6	AF-6	$C_7H_7N_3O_3$	$C_{31}H_{30}ClN_6O_7S$	630.30	73	128-131
7	AF-7	$C_9H_{12}N_2O$	$C_{33}H_{35}ClN_5O_5S$	613.34	74	104-105
8	AF-8	$C_8H_{10}N_2O$	$C_{32}H_{33}ClN_5O_5S$	599.33	70	178-179
9	AF-9	$C_8H_{10}N_2O$	$C_{32}H_{33}ClN_5O_6S$	615.32	79	180-181
10	AF-10	$C_8H_{10}N_2O_2$	$C_{32}H_{33}ClN_5O_6S$	615.32	74	133-135
11	AF-11	$C_8H_{10}N_2O$	$C_{32}H_{33}ClN_5O_5S$	599.33	73	161-167

Elemental analysis: All the synthesized oxazoles were analyzed for their elemental composition and results are reported in table 3.

Table 3. Elemental analysis of synthesized compounds

S. No.	Comp. Code	Comp. Formula	C %		H %		N %	
			Calc.	Found	Calc.	Found	Calc.	Found
1	AF-1	$C_{31}H_{30}ClN_5O_5S$	60.04	59.99	4.88	4.85	11.29	11.28
2	AF-2	$C_{31}H_{30}ClN_5O_5S$	60.04	60.07	4.88	4.90	11.29	11.30
3	AF-3	$C_{33}H_{35}N_5O_5S$	64.58	64.54	5.75	5.74	11.41	11.40
4	AF-4	$C_{31}H_{30}FN_5O_5S$	61.68	61.67	5.01	5.00	11.60	11.58
5	AF-5	$C_{31}H_{30}ClN_5O_5S$	60.04	60.05	4.88	4.86	11.29	11.30
6	AF-6	$C_{31}H_{30}N_6O_7S$	59.04	59.01	4.79	4.77	13.33	13.32
7	AF-7	$C_{33}H_{35}N_5O_5S$	64.58	64.61	5.75	5.76	11.41	11.40
8	AF-8	$C_{32}H_{33}N_5O_5S$	64.09	64.13	5.55	5.57	11.68	11.69
9	AF-9	$C_{32}H_{33}N_5O_6S$	62.42	62.38	5.40	5.38	11.37	11.38
10	AF-10	$C_{32}H_{33}N_5O_6S$	62.42	62.37	5.40	5.37	11.37	11.36
11	AF-11	$C_{32}H_{33}N_5O_5S$	64.09	64.11	5.55	5.54	11.68	11.69
12	AF-12	$C_{31}H_{31}N_5O_5S$	63.57	63.55	5.33	5.31	11.96	11.94

Infrared Spectral Studies: Infrared spectra of two compounds (AF-3 and AF-8) were recorded in the range of 400-4000 cm^{-1} on Schimadzu FTIR 8400 with DRS. The data of the IR spectra of investigated compounds (AF-3 and AF-8)are listed in tables 4 and 5, while the infrared spectra of compounds are given in figures 2 and 3 respectively.

Table 4. Infrared spectral data of compound (AF-3)

S. No.	Functional group (vibrational mode)	Frequency (cm^{-1}) standard	Frequency (cm^{-1}) observed
1	C-O str.	1320–1000	1167.94
2	C-N str.	1335-1250	1296.21
3	C=O str. (carbonyl)	1760–1665	1697.41
4	C-H bend (ortho)	770-735	764.80
5	C–C str. (in–ring) aromatics	1600-1585	1589.40
6	N-H str.	3400–3250	3330.31

Table 5. Infrared spectral data of compound (AF-8)

S. No.	Functional group (vibrational mode)	Frequency (cm^{-1}) standard	Frequency (cm^{-1}) observed
1	C-O str.	1320–1000	1161.19
2	C-N str.	1335-1250	1288.49
3	C=O str (carbonyl)	1760–1665	1735.03
4	C-H bend (para)	850-800	808.20
5	C–C str. (in–ring) aromatics	1600-1585	1589.40
6	N-H str.	3400–3250	3311.89

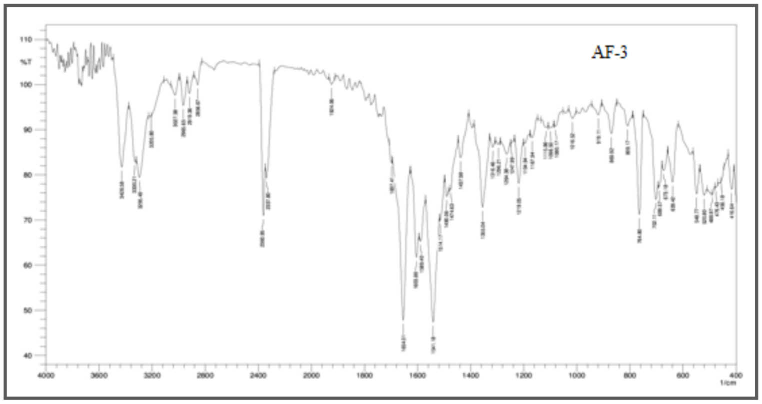


Figure 2. Infrared spectrum of compound (AF-3)

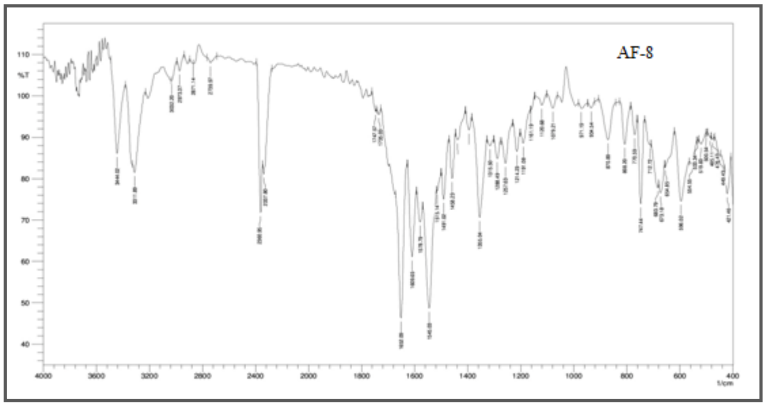


Figure 3. Infrared spectrum of compound (AF-8)

^{1}HNMR Spectral Studies: ^{1}HNMRspectrum of N-{2-[4-({3-[2-(4-Toluidino)-1,3-oxazol-4-yl] anilino} sulfonyl)phenyl]ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide (AF-8) (Figure 4) were recorded on Bruker Avance II 400 NMR spectrometer. NMR spectrum is represented in fig. 5 and data in table 6. The position of different protons were assigned on the basis of position of signal (δ value), while number of proton of a particular kind was determined on the basis of intensity of that signal.

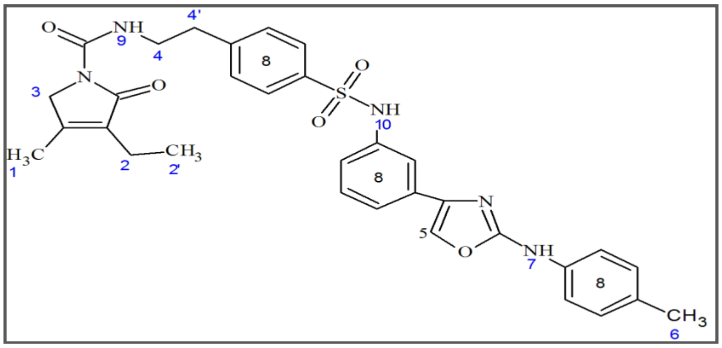


Figure 4. Structure of N-{2-[4-({3-[2-(4-Toluidino)-1,3-oxazol-4-yl]anilino}sulfonyl)phenyl]ethyl}-3-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide (AF-8)

Table 6. ^{1}HNMR spectral data of compound (AF-8)

S. No.	Signal Position	Relative No. of Proton	Multiplicity	Assignment
1	2.19	3H	singlet	-CH$_3$ [1]
2	2.00	2H	triplet	-CH$_2$ [2]
3	2.19	3H	quartet	-CH$_3$[2']
4	2.51	2H	triplet	-CH$_2$ [3]
5	2.80	2H	doublet, triplet	-CH$_2$ [4]
6	2.95	2H	quartet	-CH$_2$ [4']
7	7.82	1H	singlet	-CH [5]
8	2.09	3H	singlet	-CH$_3$ [6]
9	10.10	1H	singlet	-NH [7]
10	6.88 - 7.80	12H	multiplet	-Ar-H [8]
11	7.26	1H	doublet	-CONH [9]
12	7.21	1H	singlet	-SO$_2$NH [10]

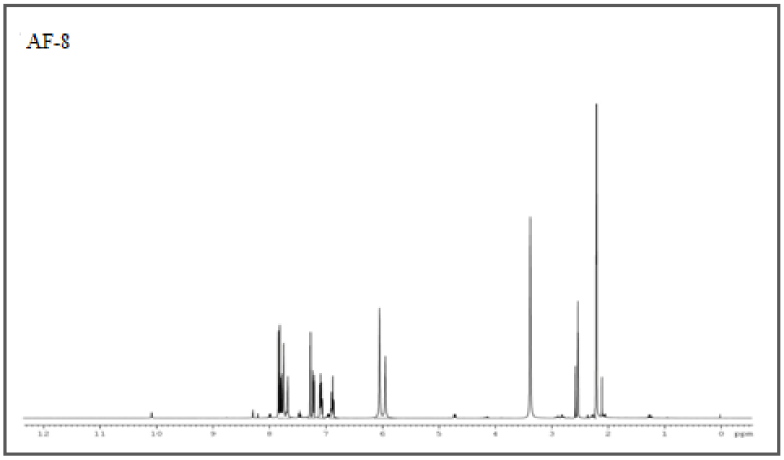


Figure 5. ^{1}HNMR spectrum of compound (AF-8)

RESULTS AND DISCUSSION

Twelve oxazoles bearing sulfonamide group have been synthesized. All the synthesized compounds are tested for their antibacterial activity against gram negative (*Escherichia coli*) and gram positive (*Staphylococcus aureus*) bacteria strains by measuring zone of inhibition in mm, revealing that all compounds have considerable antibacterial activity, Out of all these synthesized compounds, AF-7, AF-11 and AF-12, showed moderate antibacterial activity with respect to reference standard.

The substituted oxazole derivatives having sulfonamide moieties are already known for different biological activities. As per the result of the screening, it is clearly indicated that the synthesized compound of the scheme (AF-1-AF-12) are having moderate antibacterial activity equipotent with the standard drugs. From the obtained results; one can reveal that the synthesized oxazole derivatives can be a rich source for the exploitation. Therefore, in search of new compound, one can explore the possibility in this area by introducing different functional group as substituents, which may result into better pharmacological active compounds.

Synthesized compounds were purified by recrystallization using methyl ethanol. These compounds were confirmed by IR spectra, which showed the expected bands for the characteristic groups such as C–O, C–N and aromatic moiety. The presence of peaks in the region 1167.94 and 1161.19 indicates the presence of C-O, while peaks at 1296.21 and 1288.49 indicate the existence of C–N moiety in the compounds (AF-3) and (AF-8).

The structure of compound (AF-8) was confirmed by ^{1}H NMR which revealed the aromatic protons appearing as multiple peaks within the range 6.88-7.80 δ ppm, proton of CONH at 7.26 δ ppm and SO_2NH appeared at 7.21 δ ppm.

APPLICATIONS

Pharmacology: All the synthesized oxazole compounds bearing sulfonamide group were evaluated for antibacterial activity by using broth dilution method and the Minimum Inhibitory Concentration [**27**] are summarized in table 7 and Fig 6.

Antibacterial activity: The newly synthesized compounds were screened **[28]** for their antibacterial activity [**29**] against *E. coli* (MTCC-443) [**30**] and *S. aureus* (MTCC-96) [**31**] bacterial strains. The data of antibacterial screening revealed that all the tested compounds showed moderate to less bacterial inhibition against *S. aureus* and *E. coli* species. It revealed that antimicrobial activity depends on the nature of heterocyclic moieties.

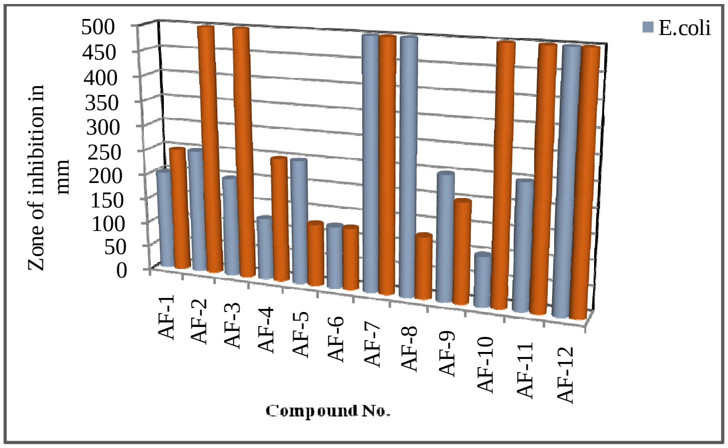


Figure 6. Antibacterial activity of synthesized compounds

Table 7. Antibacterial activity of synthesized compounds

Zone of inhibition (mm)			
S.No.	**Compound No.**	***E.coli***	***S.aureus***
		MTCC 443	**MTCC 96**
1	AF-97	200	250
2	AF-98	250	500
3	AF-99	200	500
4	AF-100	125	250
5	AF-101	250	125
6	AF-102	125	125
7	AF-103	500	500
8	AF-104	500	125
9	AF-105	250	200
10	AF-106	100	500
11	AF-107	250	500
12	AF-108	500	500
Standard Drugs			
13	Gentanmycin	0.05	0.25
14	Ampicillin	100	250
15	Chlorampheniol	50	50
16	Ciprofloxacin	25	50
17	Norfloxacin	10	10

CONCLUSION

In the present study, the antibacterial activity of the oxazole derivatives bearing sulfonamide group were investigated. The compounds (AF-2, AF-7, AF-11 and AF-12) displayed moderate antibacterial activity as compared to standard drugs. Thus, the newly synthesized compounds can be used in future by modification and designing more potent and selective antimicrobial agents.

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