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SYNTHESIS OF SOME NEW 2, 5 - DISUBSTITUTED THIADIAZOLE DERIVATIVES AND THEIR SCREENING FOR ANTIMICROBIAL ACTIVITY

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ABSTRACT

Synthesis & screening of thiadiazole derivative has a great interest to numerous because of its easy accessibility and diverse biological properties. Thiadiazole derivatives have huge number of proven records of biological activities preferred in earlier discussions. So it was planned to synthesize a variety of 2,5-substituted thiadiazoles derivatives to provide an empirical approach towards, development of potent functional molecules possessing wide range of biological property, such as anti-microbial activity.

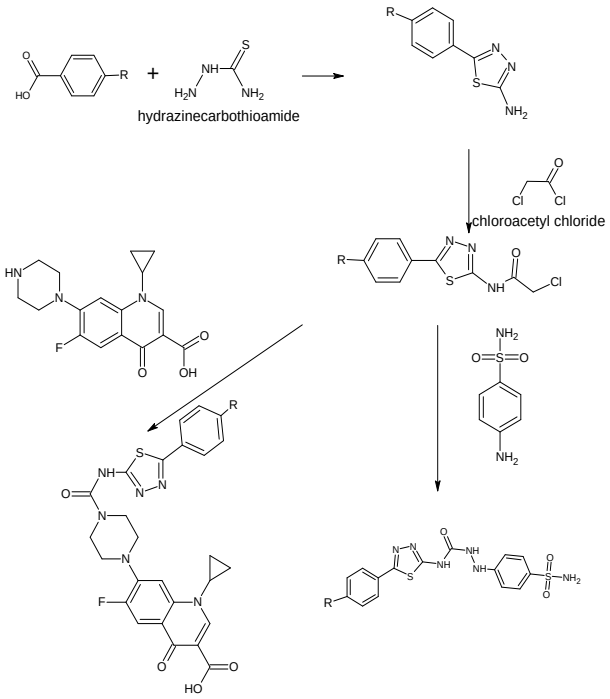
KEYWORDS: Aromatic compound, Antimicrobial, Thiadazole nucleus, Pathogens.

INTRODUCTION

Thiadiazole and substituted thiadiazole are very much popular to medicinal chemist due to their wide range of diversified biological activity e.g. antimicrobial activities. The most common uses were in the pharmaceutical area as antibacterial with known sulphonamide drugs. The resistance towards available drugs is rapidly becoming a major world-wide problem. The need to design new compounds to deal with this resistance has become one of the thrust areas of research today. Thiadiazoles continuously draws interest for development of newer drug moiety. Researchers have demonstrated a broad spectrum of biological properties of thiadiazoles in both pharmaceutical and agrochemical fields. Antimicrobial agents are employed mainly for the prevention and inhibition of bacterial infections in man. The clinical value of antimicrobial agents cannot be assumed simply because they inhibit or kill microbial pathogens *in* vitro.[1,2]

Materials: All the chemicals used are of analytical grades.

METHODS



3(P/B/T)1 3(P/B/T)2

Table 1:

Compound	R
3(T)1	CH_3
3(T)2	CH_3
3(P)1	NH_2
3(P)2	NH_2
3(B)1	H
3(B)2	H

Synthesis Procedure

Step-1: Equi-molar concentration of aromatic acid and thiosemicarbazide were mixed in a round bottom flask (100ml).Then about 10 drops of concentrated sulphuric acid &10ml of ethanol was added. It was refluxed for 2hr. The mixture was cooled and kept at room temperature overnight. Next day the excess solvent was distilled off and separated mass were poured into ice-water then separated solid was collected by filtration and dried. The crude product was recrystallized in ethanol gave the crystal, pure substances.

Step-2: Equi-molar concentration of step-1 product and sodium acetate in a beaker with 10ml of glacial acetic acid was mixed by magnetic stirrer. Then about equimolar concentration of chloro acetyl chloride was added drop wise. It was stirred for 2hr. It was kept at room temperature for overnight. Next day the excess solvent was distilled off and separated mass was poured into ice-water then separated solid mass was collected by filtration and dried. The crude product was recrystallized in ethanol gave the crystal, pure substances.

Step-3a: Step-2 product was taken in a beaker along with potassium carbonate (500mg), (0.5ml) triethyl amine in dry chloroform and ciprofloxacin in 0.0005 molar concentrations. These were mixed by using magnetic stirrer. Stirred it for half an hour then it was refluxed for 4 to 5 hour and kept at room temperature for overnight. Next day the excess solvent was distilled off and the separated mass was poured into ice-water then separated solid mass was collected by filtration and dried. The crude product was recrystallized in methanol for, pure substance.

Step-3b: Step-2 Product was taken in a beaker along with potassium carbonate (500mg),(0.5ml) triethyl amine in dry chloroform and sulphanilamide in 0.0005 molar concentrations. These were mixed by using magnetic stirrer. Stirred it for half an hour then it was refluxed for 4 to 5 hour and kept at room temperature for overnight. Next day the excess solvent was distilled off and the separated mass was poured into ice-water then separated solid mass was collected by filtration and dried. The crude product was recrystallized in methanol for, pure substance.

Interpretation

Table 2:

Compound	IR DATA (cm^{-1})
3B1	1067.36, 1092.09 (S=O stretching), 1504.33, 1548.75, 1594.21, 1626.88 (N-H Bending), 3477.41 (N-H Stretching), 1730.46 (C=0 Stretching Ketone), 704.86, 823.95, 895.78, 677.35 (C-H Bending Aromatic), 3270.33, 3376.25 (C-H Stretching Aromatic), 1626.88, 1695.00 (C=N Stretching)
3B2	1451.15, 1470.20, 1488.81,1551.14, 1597.96 (C=C Stretching aromatic) 3055.02, 3378.76 (C-H Stretching aromatic), 3378.76, 3545.00 (N-H Stretching), 1551.14, 1597.96, 1623.18, 1695.20 (N-H Bending), 705.18, 783.27, 802.75, 825.06, 609.48, 681.53, 890.45 (C-H Bending aromatic), 1020.58 (C-F Stretching), 1695.20, 1713.08 (C=O Stretching ketone), 1068.24, 1097.83, 1149.54, 1216.04, 1269.68, 12.95.19, 1379.88, 1336.09 (C-N Vibration), 3586.05 (0-H Stretching),1623.18, 1695.20 (C=O Stretching)
3P1	1071.34, 1384.88 (S=O stretching), 3456.69, 3523.69 (N-H stretching) 1549.89, 1597.50, 1626.30, 1530.58, 1694.50 (N-H Bending), 3057.43, 3397.48 (C-H stretching aromatic), 610.67, 635.21, 685.64, 702.72,, 775.36, 802.31, 825.82, 893.57 (C-H Bending Aromatic), 1626.3, 1694.46 (C=N stretching), 1726.91 (C=O stretching ketone)
3P2	1680.20, 1724.39, 1785.05 (C=O Stretching ketone), 1081.31 (C-F Stretching), 3477.79 (N-H Stretching), 1533.44, 1598.31 (N-H Bending)1626.01, 1680.20(C=N Stretching), 612.54, 686.58, 707.59, 779.89, 804.03, 828.43(C=H Bending Aromatic), 2839.56, 3058.59, 3378.93, 3477.79 (C=H Stretching Aromatic), 3586.63 (O-H Stretching).
3T1	608.83, 658.70, 681.74, 740.03, 783.07, 820.96, 896.79 (C-H Bending aromatic), 1092.75, 1337.28 (S=0 Stretching), 3260.00, 3350.43 (C-H Stretching aromatic),3475.00 (N-H Stretching),1502.08, 1591.70, 1626.45, 1679.06 (N-H Bending) ,1749.01 (Stretching ketone)

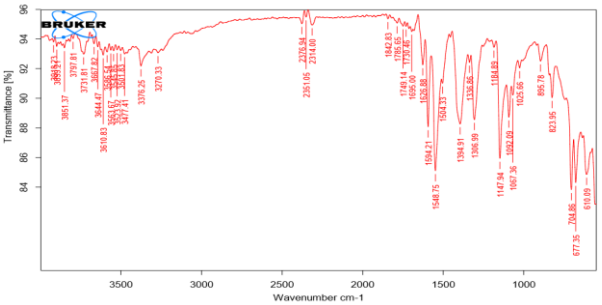


Fig 1: IR Spectra OF 3B1.

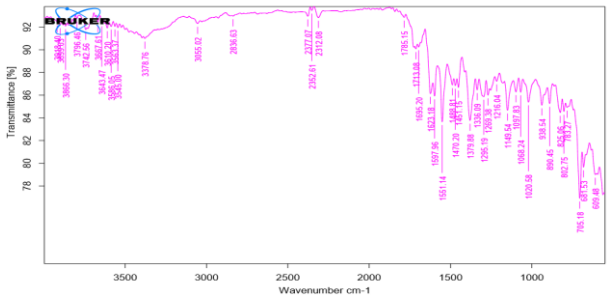


Fig 2: IR Spectra OF 3B2.

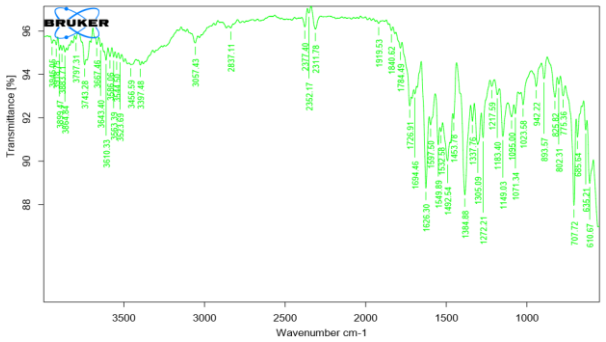


Fig 3: IR Spectra OF 3P1.

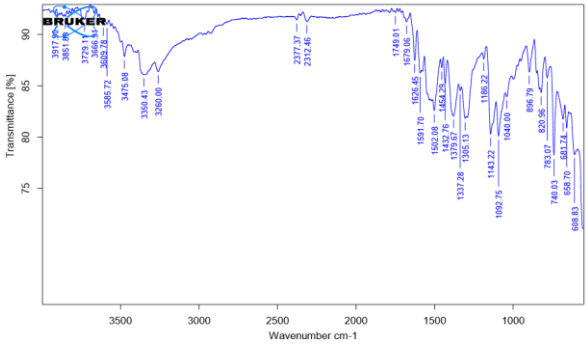


Fig 5: IR Spectra OF 3T1.

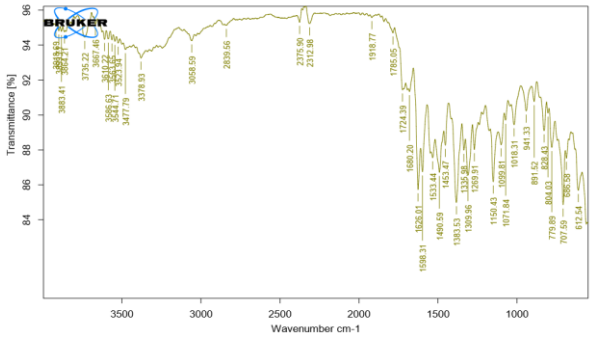


Fig 4: IR Spectra OF 3P2.

Anti-Bacterial Activity Chart
Minimum Inhibitory Concentration Chart
Table 3:

Compound code	Molecular formula	MIC *E.coli*			MIC *S. aureus*		
		Conc. (µg /ml)			Conc. (µg /ml)		
		2	5	10	2	5	10
3T1	$C_{16}H_{16}N_6O_3S_2$	+	-	-	+	-	-
3T2	$C_{27}H_{25}FN_6O_4S$	+	-	-	+	-	-
3P1	$C_{15}H_{15}N_7O_3S_2$	+	-	-	+	-	-
3P2	$C_{26}H_{24}FN_7O_4S$	+	-	-	+	-	-
3B1	$C_{15}H_{14}N_6O_3S_2$	+	-	-	+	-	-
3B2	$C_{26}H_{23}FN_6O_4S$	+	-	-	+	-	-
STD (Cipro. & Sulphonilamide		+	-	-	+	-	-
Solvent	DMF	0	0	0	0	0	0

+Ve = Turbidity observed, -Ve = Turbidity was not observed

Zone of Inhibition Chart
Table 4:

Compound code	Molecular formula	Zone of Inhibition (In mm)			Zone of Inhibition (In mm)		
		E.coli. conc. (µg /ml)			*S.aureus* conc.(µg /ml)		
		5	10	15	5	10	15
3T1	$C_{16}H_{16}N_6O_3S_2$	8	10	11	9	10	10
3T2	$C_{27}H_{25}FN_6O_4S$	9	10	14	9	9	13
3P1	$C_{15}H_{15}N_7O_3S_2$	8	9	11	9	10	11
3P2	$C_{26}H_{24}FN_7O_4S$	8	9	12	9	10	12
3B1	$C_{15}H_{14}N_6O_3S_2$	8	10	11	8	9	12
3B2	$C_{26}H_{23}FN_6O_4S$	9	10	12	9	10	13
STD	$C_{18}H_{19}FN_2O_3$	10	13	16	11	14	17
Solvent	DMF	0	0	0	0	0	0

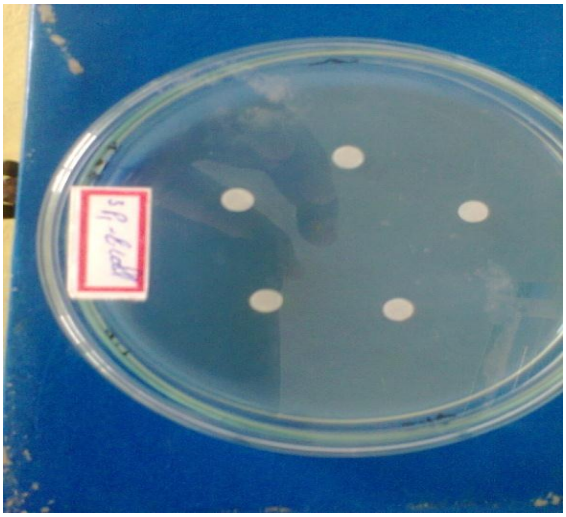


Fig. 6: Zone of inhibition of 3P1 (*E.Coli*).

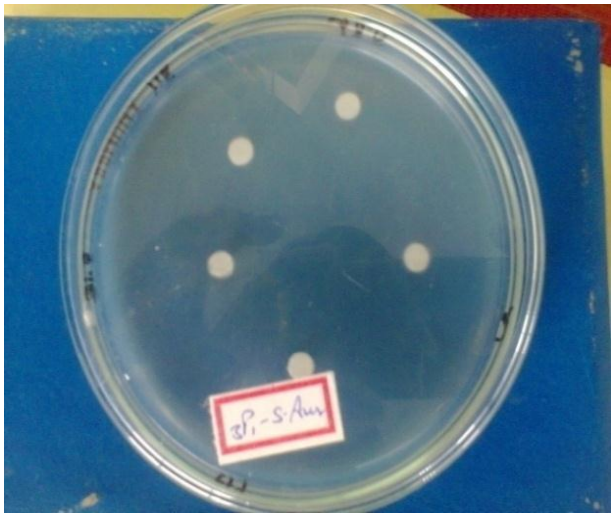


Fig. 7: Zone of inhibition of 3P1 (*S.aureus*).

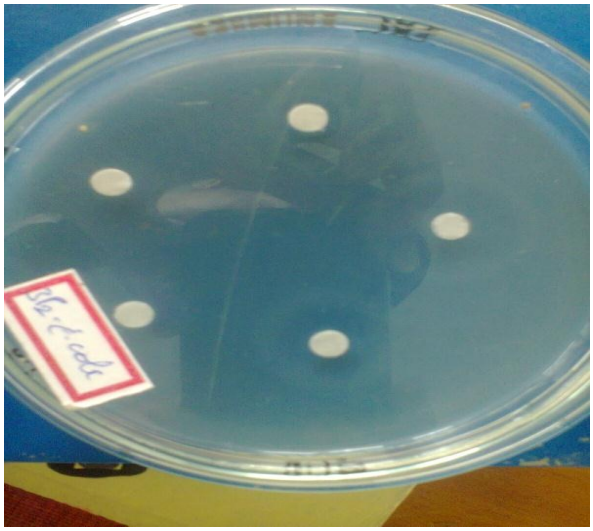


Fig. 8: Zone of inhibition of 3P2 (*E.Coli*).

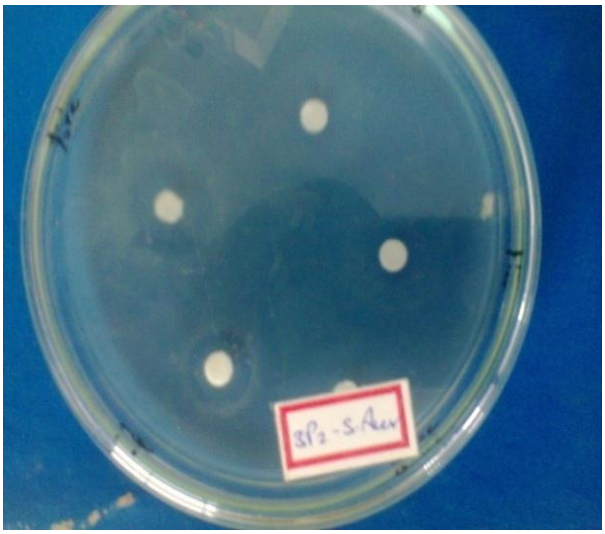


Fig. 9: Zone of inhibition of 3P2 (*S.aureus*).

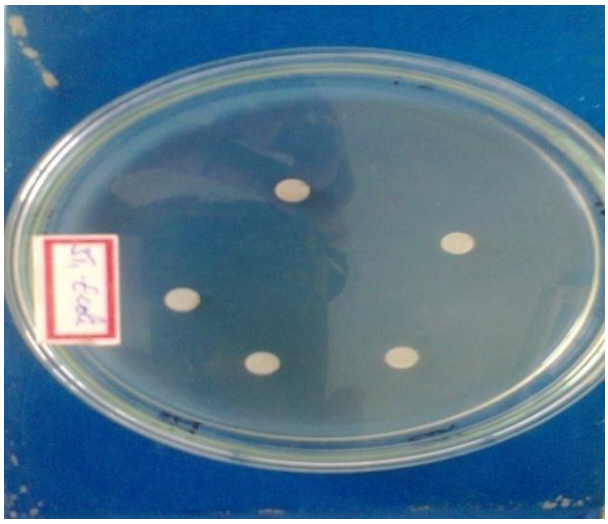


Fig. 10: Zone of inhibition of 3T1 (*E.Coli*).

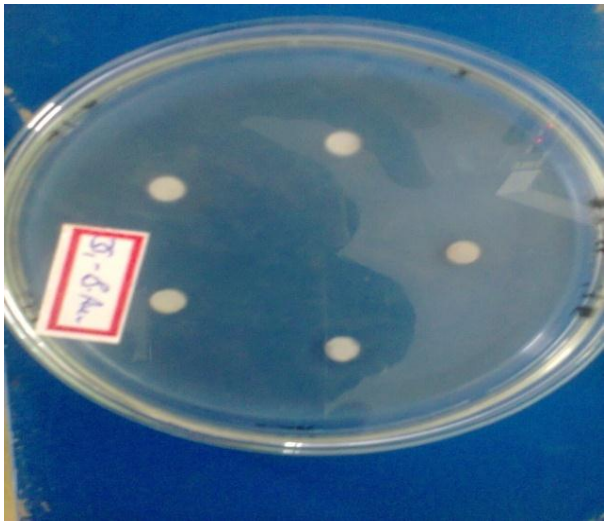


Fig. 11: Zone of inhibition of 3T1 (*S.aureus*).

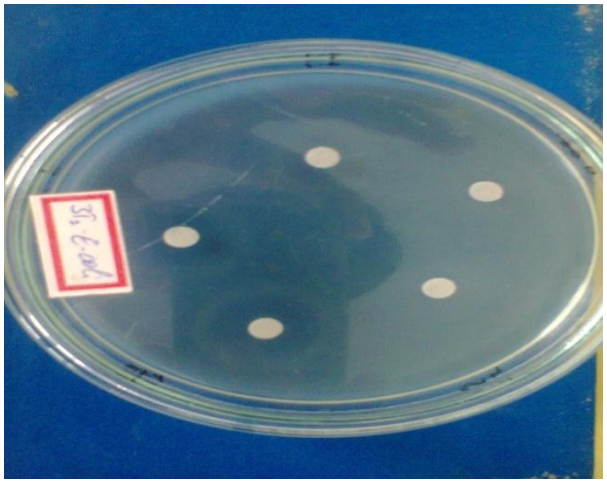


Fig. 12: Zone of inhibition of 3T2 (*E.Coli*).

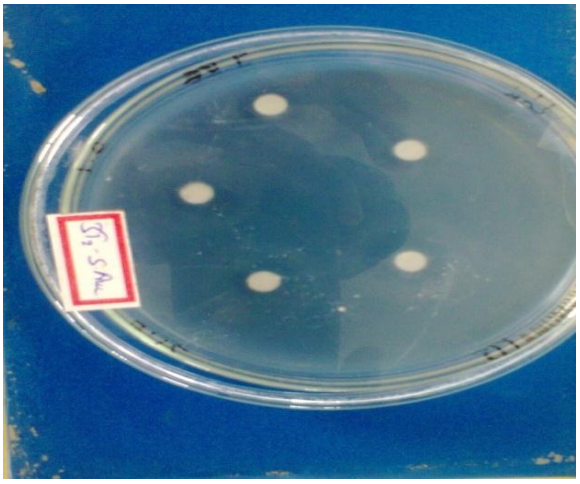


Fig. 13: Zone of inhibition of 3T2 (*S.aureus*).

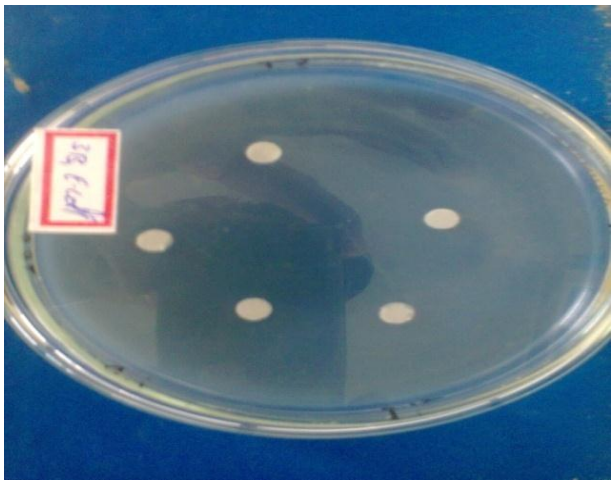


Fig. 14: Zone of inhibition of 3B1 (*E.Coli*).

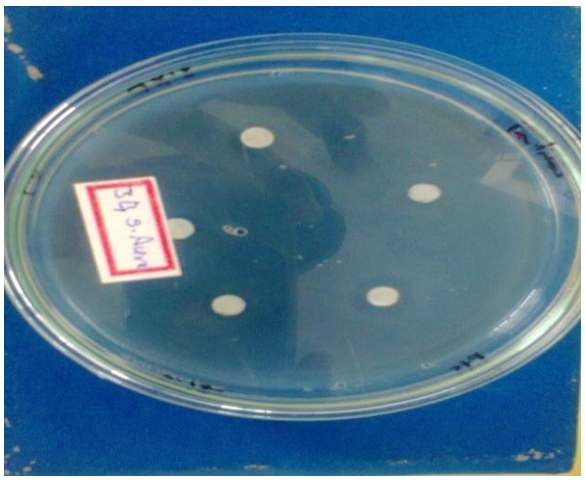


Fig. 15: Zone of inhibition of 3B1 (*S.aureus*).

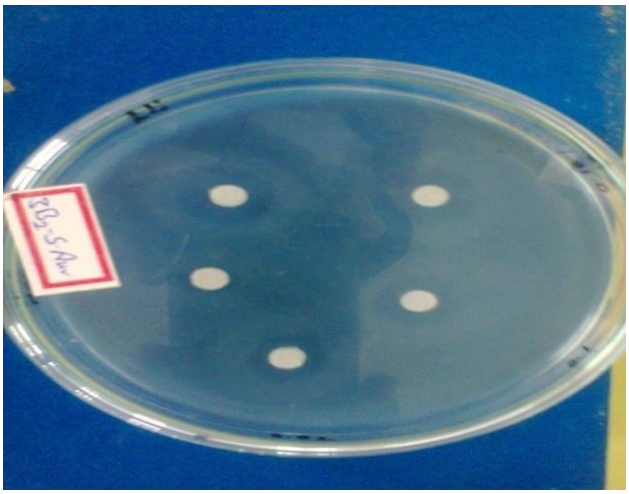


Fig. 16: Zone of inhibition of 3B2 (*E.Coli*).

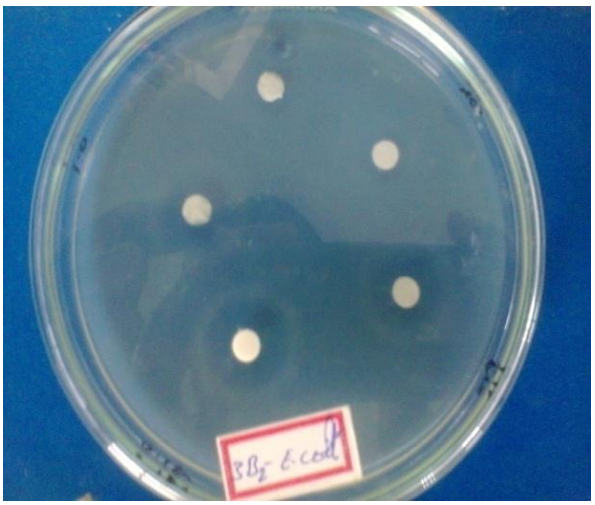


Fig. 17: Zone of inhibition of 3B2 (*S.aureus*).

RESULT AND DISCUSSION

The synthesis of thiadiazole heterocycles that have been reported in this work gave different approaches to the challenge of preparing these bioactive products and allows the synthesis of many novel thiadiazole chemical derivatives. In general, it was prepared by synthesis of thiadiazole nucleus, by the reaction between different aromatic acids with thiosemicarbazide under laboratory conditions. This was treated with chloro acetyl chloride which resulted in the formation of thidiazole derivative with chlorine molecule. This step is very much useful in condensation of ciprofloxacin & sulphanilamide to release the HCl molecule to form respective thiadiazole derivatives.

The structures of the synthesized compounds were determined on the basis of their FTIR data. The spectral data for FTIR was elaborated, which confirms the structure of synthesized compounds. Antibacterial activity data of all thiadiazole derivatives against tested organisms (*E.coli & S.aureus*) displayed significant activity. It was found that all compounds have shown significant antibacterial activity against these gram positive bacteria and gram negative bacteria.

Minimum inhibitory concentration was found using different dilutions (2 µg/ml, 5 µg/ml, 10 µg/ml) of all synthesized compounds. All dilution were transferred into the dilution tubes containing nutrient media. Later on microorganisms (both gram + ve & gram-ve bacteria) were added. The turbidity was measured. Ciprofloxacin & sulphanilamide were used as standard & DMF as control. It was found that all the synthesized compounds showed turbidity in 2 µg/ml but no one showed turbidity in 5µg/ml & 10µg/ml. So from this it concluded that the minimum inhibitory concentration (MIC) of all our synthesized compound is 5 µg/ml.

Zone of inhibition was found using agar disc diffusion methods in which different dilution of our synthesized compound (5 µg/ml, 10 µg/ml, 15 µg/ml) were prepared. Ciprofloxacin, sulphanilamide were used as standard & DMF as control. It was found that zone of inhibition was increased when I increased the concentration of the synthesized compound. Minimum zone of inhibition (8 mm) was found in case of compound, 3T1 (*E.coli*), 3P1 (*E.coli*), 3P2 (*E.coli*), 3B1 (*E.coli*) & 3B1 (*S.aureus*).

Maximum zone of inhibition (14 mm) was found in case of compound 3T2 (*E.coli)* followed by 13 mm in case of 3B2 (*S.aureus*). From above discussed matter it is confirmed that all synthesized thiadiazole derivatives have moderate antimicrobial activity.

CONCLUSION

The present study described an efficient and convenient method for the synthesis ofthiadiazole derivatives. The incorporation of two different pharamacophores in a single thiadiazole nucleus led to the development of novel derivatives with moderate activity. All the synthesized compoundsshowed moderate activity against gram +ve & gram–ve bacteria. The screening studies have demonstrated that the newly synthesized compounds exhibit promising antibacterial properties.

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