Synthesis of 2-Amino-5-Mercapto -1, 3, 4 -Thiadiazole Derivatives and Evaluation of their Biological Activity

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Abstract

In this work, new compounds, (S_1-S_{17}) were synthesized through the reaction of 5-amino-1,3,4-thiadiazole-2-thiol with different aromatic aldehyde by using fusion method. The newly synthesized compounds were confirmed by FT-IR-spectra and ^{1}H-NMR, the biological activity of some new compound tested in vitro, against some bacterial positive and negative

Key words: 5-amino-2-mercapto-1,3, 4-thiadiazole, Schiff Base, Fusion method, Biological activity.

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تحضير مشتقات 5- امينو -2- ميركبتو -1،3،4- ثايادايازول وتقييم نشاطها البايولوجي

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الخلاصة

في هذا البحث تم تحضير مركبات جديدة حيث تم تحضير (S_1-S_{17}) من تفاعل 5- امينو -2- مركبتو -1، 3،4- ثايادايازول مع ألديهايدات أروماتية مختلفة بواسطة عملية الصهر. تم تشخيص هذه المركبات المحضرة من خلال طيف أشعة تحت الحمراء(FT-IR)، وطيف الرنين النووي المغناطيسي(H^1-NMR) كما تم تقييم الفعالية الحيوية للمركبات المحضرة على بعض أنواع البكتريا حيث اظهرت بعض انواع المركبات المحضرة مقاومة لهذه البكتريا.

الكلمات المفتاحية: 5- أمينو -2- مركبتو 1,3,4 - ثايادايازول، قاعدة شف، طريقة الصهر، الفعالية البايولوجية.

Introduction

Thiadiazole are five membered rings associated with diverse biological and pharmaceutical properties [1] for example, 1,3,4-thiadiazole are interesting heterocyclic compounds due to their wide uses, which have been shown to be diverse activities against parasites and bacterial [2-4] on the other hand, Schiff bases are well known to possess promising biological activities [5,6]. In this work we synthetized some 1,3,4-thiadiazoile Schiff-base derivatives starting from 2-amino -5- mercapto-1,3,4-thiadizole compound**,** Because of their important biological activity in animal screening, antifungal and plant growth regulating properties [7].

Experimental

1. Materials

All chemicals used in this study were purchase from Aldrich Chemicals and were used without further Purification.

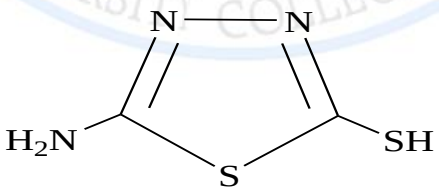
2. Instruments

All melting points are uncorrected were determined using Apparatus Electrothermal (melting point). IR spectra were recorded using spectrophotometer (Perkin Elmer) 400-4000 cm^{-1}. The ^{1}HNMR spectra were determined with NMR eady 60 Pro 60 MHz High resolution 17.7-bit spectrometer.

3. Synthetic methods

3.1. Synthesis of 2-amino-5-mercapto-1,3,4-thiadiazole

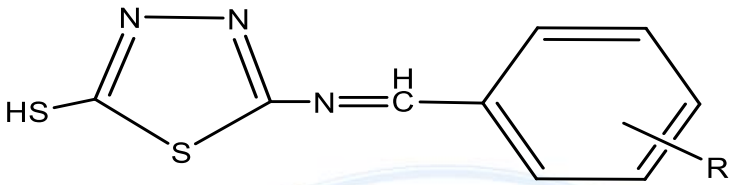
A solution of thiosemicarbazide (10 g, 0.1 mole) in 50 mL of absolute ethanol was placed in round bottom flask fitted with an efficient condenser. To this solution anhydrous sodium carbonate (6 g, 0.05 mole) and carbon disulfide (11 g, 0.14 mole) was added and the mixture was heated (40^{o}C) in a steam bath for 7 hours. The ethanol was evaporated using rotary evaporator [8] The residue was diluted by addition of 25 ml of $H_2O$and the solution was acidified by concentrated HCl and filtered. Then washing with H_2O several times, A yellow precipitate was formed which was recrystallized from ethanol. M.P (230-232^{o} C) Yield % 72, Molecular formula $C_2N_3S_2H_3$.



3.2. Synthesis of Compounds (S_2-S_7)

Mixture (0.01mole) of compound 2-amino-5-mercapto-1,3,4-thiadiazole with (0.01mole) of different aromatic aldehyde in small beaker. [9] are Heated by using fusion method for 10-15 minute with stirring until the content of the beaker was melted. It was, then washed with

water and collected by filtration. The product was recrystallized with ethanol to afford the compound **(S_2, S_3-S_4 S_5-S_6-S_7)**.



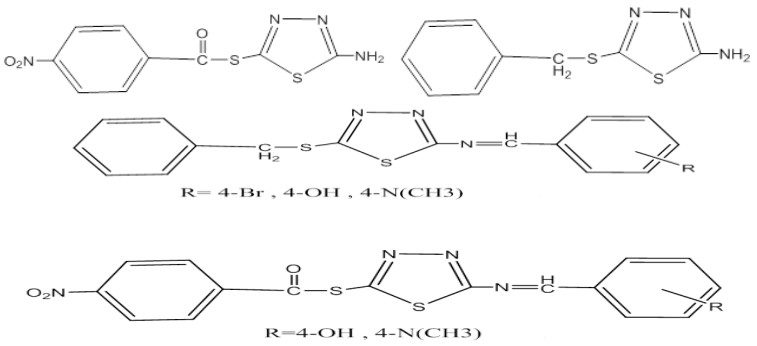
R= 4-Br, 4-OH, 4-NO2,4-Cl, 4-(CH3)2N , 2-NO2,

Table 1: Physical properties of compound **(S_2, S_3-S_4 S_5-S_6-S_7)**

Comp. No	M.P (°C)	Yield %	Colour	Recryst Solvent	Molecular formula
S2	165-167	61	Yellow	Ethanol	$C_9H_6BrN_3S_2$
S3	188-190	65	Orange	Ethanol	$C_9H_7N_3OS_2$
S4	120-123	63	Yellow	Ethanol	$C_9H_6N_4O_2S_2$
S5	175-178	71	Yellow	Ethanol	$C_9H_6ClN_3S_2$
S6	255-258	69	Red	Ethanol	$C_{11}H_{12}N_4S_2$
S7	151-154	51	Yellow	Ethanol	$C_9H_6N_4O_2S_2$

3.3. Synthesis of compounds (S_8-S_{14})

A solution of Potassium hydroxide %85 (0.003 mole) was added dropwise to a stirred solution of (0.003 mole) (S_1, S_2-S_3, S_6) in 10 mL of ethanol at room temperature (25 °C) [10]. After heating the mixture for 10-15 minutes and cooling, benzyl chloride or p-nitro benzoyl chloride (0.003 mole) was added drop wise. The solution was refluxed for 2 hours, afterwards the solvent was evaporated on rotary evaporator. Ice-water (100 mL) was added, the resulting precipitate was collected, and recrystallized from ethanol.



R= 4-Br , 4-OH , 4-N(CH3)

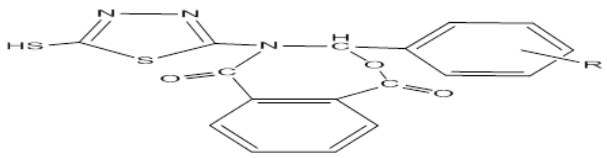
R=4-OH , 4-N(CH3)

Table 2: Physical properties of compound (S_8- S_{14})

Comp. No	M.P (°C)	Yield %	Colour	Recryst. Solvent	Molecular formula
S8	120-123	75	Yellow	Ethanol	$C_9H_9N_3S_2$
S9	145-147	50	Yellow	Ethanol	$C_{16}H_{12}BrN_3S_2$
S10	160-164	53	Orange	Ethanol	$C_{16}H_{13}N_3OS_2$
S11	140-143	45	Orange	Ethanol	$C_{16}H_{13}N_3OS_2$
S12	158-161	75	Yellow	Ethanol	$C_9H_6N_4O3S_2$
S13	151-155	59	Yellow	Ethanol	$C_{16}H_{10}N_4O_4S_2$
S14	202-205	52	Orange	Ethanol	$C_{18}H_{18}N_4S_2$

3.4. Synthesis of compounds (S_{15}-S_{17}) [9]

Mixture (0.01 mole) of compounds (S_2, S_3, S_5) with (0.01 mole) of phthalic anhydride in small beaker (10 ml) are heated using fusion method for time 10-15 minute with stirring until the content of the beaker was melted. then washed with water and collected by filtration.



R=4-Br , 4-OH , 4-Cl

Table 3: Physical properties of compound (S_{15} -S_{17})

Comp. No	M. P (°C)	Yield %	Colour	Recryst.Solvent	Molecular formula
S15	131-135	75	Yellow	Ethanol	$C_{17}H_{10}BrN_3O_3S_2$
S16	144-150	81	Yellow	Ethanol	$C_{17}H_{11}N_3O_4S_2$
S17	133-138	63	Yellow	Ethanol	$C_{17}H_{10}ClN_3O_3S_2$

4. Biological Part

The invitro antibacterial & antifungal activities of the synthesized compounds (S_2, S_3-S_8 S_{11} and S_{13}) was carried out by well diffusion method by punching template on Mullar Hinton agar well size of 6mm was made on agar with a holding capacity of 50 µl. Three standard bacterial strainsviz *E. coli, P. aeruginosa and S. aureus* were used for this purpose. In acolum size of these standard strains were matched with amoxicillin comparator [11] Lawn culture is made on mullar Hinton agar plate with standard strain. Known quantity of each sample was dissolved in. DMSO solvent in a sterile screw capped Bijou bottle. 50 ml of solvent dissolved sample was

charged into the wells of inoculated mullar Hinton Agar Incubation of plates was done for 24 hours at 36˚c & later looked for Zone of inhibition around the well [12].

The diameter of inhibitory zone was measured and recorded in millimeter and concentration [13] of test and standard were taken at 1500 and 2500 ppm. The compounds were also screened for their antifungal activity in table 6.

Result and Discussion

All the synthesized compounds were characterized by using Berkin Elmer FT-IR, and some compounds by using ^{1}HNMR spectra were determined with NMR eady 60 Pro 60 MHz [14] table 5.

S_1 IR (KBr) cm^{-1}: 3336-3253 (NH_2), 3179 (N –H), 2645(S-H),1610 (C=N),755 (C-S)

S_2 IR (KBr) cm^{-1}: 3065 aromatic C–H str, 2975 aliph C–H str, 1622 (C=N),1568 (C=C),762 (C-S), 693 (C-Br)

S_3 IR (KBr) cm^{-1}: 3157 (O-H) 3060 aromatic C–H str, 2916 aliph C–H str, 1670 (C=N),1550 (C=C),775 (C-S).

S_4 IR (KBr) cm^{-1}: 3050 aromatic C–H str, 2858 aliph C– H str, 1606 (C=N),1555 (C=C),706 (C-S), 1346 (C-N).

S_5 IR (KBr) cm^{-1}: 3103 aromatic C–H str, 2958 aliph C–H str, 1616 (C=N),1567 (C=C),706 (C-S), 768 (C-Cl)

S_6 IR (KBr) cm^{-1}: 3099 aromatic C–H str, 2954 aliph C–H str, 1599 (C= N), 1566(C=C),710 (C-S), 1265 (C-N) ^{1}HNMR: δ 11.22 (1H, S, SH) 6.84 – 7.84 (4H, m, Ar – H), δ 8.39 (1H, S, N=CH). δ 3.03 (6H, S)

S_7 IR (KBr) cm^{-1}: 3031 aromatic C–H str, 2943 aliph C–H str, 1630 (C= N),1510 (C=C),703 (C-S), 1335 (C-N).

S_8 IR (KBr) cm^{-1}: 3311-3259 (NH2) 2947 aromatic C–H str, 2850 aliph C–H str, 1535 (C=C),712 (C-S).

S_9 IR (KBr) cm^{-1}:3292(O-H), 3065 aromatic C–H str, 2925 aliph C–H str, 1666 (C=N), 1512 (C=C),742 (C-S).

S_{10} IR (KBr) cm^{-1}: 3106 aromatic C–H str, 2980 aliph C–H str, 1630 (C=N),1516 (C=C),711 (C-S), 1335 (C-N), ^{1}HNMR: δ 4.28 (2H, S, $-CH_2$) 7.11 – 7.83 (4H, m, Ar – H), δ 8.61 (1H, S, N=CH). δ 9.78 (1H, S, OH)

S_{11} IR (KBr) cm^{-1}: 3000 aromatic C–H str, 2825 aliph C–H str, 1624 (C=N),1515 (C=C),783 (C-S), 1345 (C-N), ^{1}HNMR: δ 4.50 (2H, S, $-CH_2$) 6.71 – 7.86 (4H, m, Ar – H), δ 8.57 (1H, S, N=CH). δ 3.03 (6H, S).

S_{12} IR (KBr) cm^{-1}:3311-3259 (NH_2), 2927 aromatic C–H str, 1591 (C=N),1513 (C=C),779 (C-S).

S_{13} IR (KBr) cm^{-1}:3267(O-H), 3078 aromatic C–H str, 2954 aliph C–H str, 1633 (C=N), 1501 (C=C),712 (C-S), ^{1}HNMR: δ 9.55 (O-H, S) 6.88 – 8.33 (4H, m, Ar – H), δ 8.88 (1H, S, N=CH).

S_{14} IR (KBr) cm^{-1}: 3086 aromatic C–H str, 2951 aliph C–H str, 1591 (C=N),1527 (C=C),721 (C-S), 1373 (C-N).

S_{15} IR (KBr) cm^{-1}: 3030 aromatic C–H str, 2924 aliph C–H str, 1788(C=O aster), 1730 (C=O amide), 1600 (C= N),1522 (C=C),720 (C-S), 877 (C-Br).

S_{16} IR (KBr) cm^{-1}: 3421 (O-H),3022 aromatic C–H str, 2858 aliph C–H str, ,1780 (C=O aster),1734 (C=O amide), 1599 (C= N),1539 (C=C),719 (C-S).

S_{17} IR (KBr) cm^{-1}: 3030 aromatic C–H str, 2924 aliph C–H str, 1785(C=O aster), 1732 (C=O amide), 1600 (C= N), 1512 (C=C), 733 (C-S), 879 (C-Cl).

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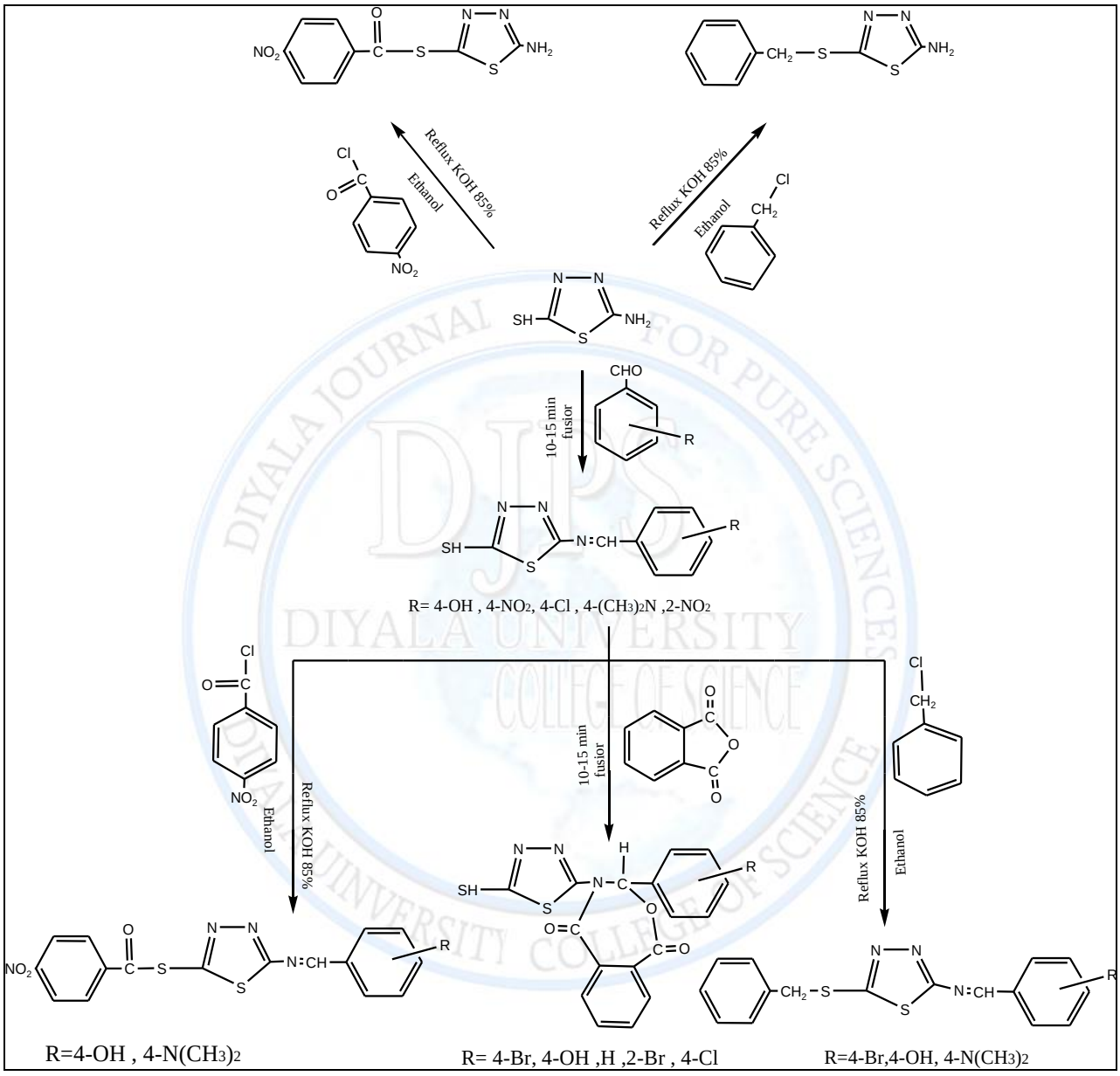

Scheme 1

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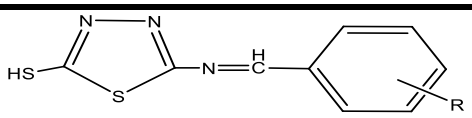
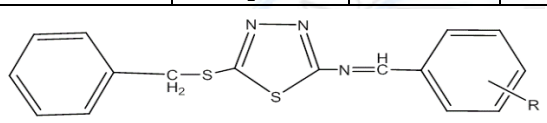
Table 4: Characteristic IR absorption Bands of the synthesised compounds

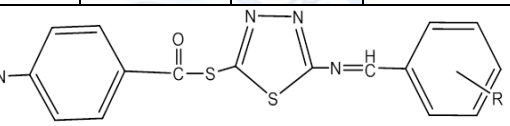


R= 4-Br, 4-OH, 4-NO2,4-Cl, 4-(CH3)2N , 2-NO2,

Compound	R	$\nu_{C-H(arom)}$	$\nu_{C-H(aliph)}$	ν C-S	$\nu_{C=N}$	ν others
S2	4-Br	3065	2975	762	1622	C-Br 693
S3	4-OH	3060	2916	775	1670	O-H 3157
S4	4-NO_2	3050	2858	779	1606	C-N 1346
S5	4-Cl	3103	2958	706	1616	C-Cl 768
S6	-$N(CH_3)_2$	3099	2954	710	1599	C-N 1265
S7	2-NO_2	3031	2943	703	1630	C-N 1335

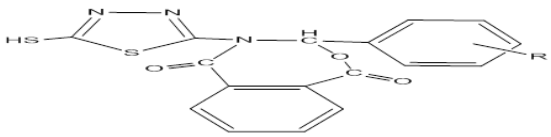


R= 4-Br , 4-OH , 4-N(CH3)



R=4-OH , 4-N(CH3)

Compound	R	$\nu_{C-H(arom)}$	$\nu_{C-H(aliph)}$	ν C-S	$\nu_{C=N}$	ν others
S8	……..	2947	2850	712	……	N-H 3311-3259
S9	4-Br	3065	2925	742	1631	C-Br 702
S10	4-OH	3106	2980	711	1666	OH 3292
S11	-$N(CH_3)_2$	3000	2825	783	1624	C- N1345
S12	……	2927	……	793	1591	N-H 3311-3259
S13	4-OH	3078	2954	712	1633	O-H 3267
S14	$N(CH_3)_2$	3086	2951	721	1591	C-N 1373



R=4-Br , 4-OH , 4-Cl

Compound	R	$\nu_{C-H(arom)}$	$\nu_{C-H(aliph)}$	ν C=O aster	ν C=O amide	ν C-S	$\nu_{C=N}$	ν others
S15	4-Br	3030	2924	1788	1730	720	1600	C-Br 877
S16	4-OH	3022	2858	1780	1734	719	1599	O-H 3421
S17	4-Cl	3030	2924	1785	1732	733	1600	C- Cl 879

Table 5: Nuclear magnetic resonance data for some of the synthesised compounds

Compounds	Chemical Shift / ppm
S_6	δ = 11.22 (-SH, 1H, s) δ = 3.03 (6H, s) δ = 8.39 (N=CH, 1H, s) δ = 7.84-6.84 (arom., 4H, m)
S_{10}	δ = 4.28 (-CH_2, 2H, s) δ = 8.61 (N=CH, 1H, s) δ = 9.78 (O-H, s) δ = 7.83-7.11 (arom., 4H, m)
S_{11}	δ = 4.50 (-CH_2, 2H, s) δ = 8.57 (N=CH, 1H, s) δ = 3.03 (6H, s) δ = 7.86-6.71 (arom., 4H, m)
S_{13}	δ = 8.88 (N=CH, 1H, s) δ = 9.55 (O-H, s) δ = 8.33-6.88 (arom., 4H, m)

s(singlet), m(multiplet)

Table 6: Inhibiting activity of synthesized compounds comparison with antibiotic amoxicillin (inhabiting diameter mm)

No.	Comp	Code	Conc (ppm)	Staph. aureues	E. coli	Pseudo. Aurogeuosa
1	13	6B	1500	22mm	18mm	14mm
		6,	2500	27mm	12mm	12mm
2	11	7B	1500	17mm	14mm	22mm
		7,	2500	18mm	10mm	19mm
3	2	8B	1500	32mm	16mm	30mm
		8,	2500	20mm	8mm	7mm
4	3	9B	1500	18mm	24mm	15mm
		9,	2500	26mm	20mm	18mm
5	8	10B	1500	30mm	16mm	12mm
		10,	2500	22mm	19mm	20mm
6	Sol	DMSO	.....	0 mm	0 mm	0 mm
7	Amox	.....	.....	30mm	24mm	0 mm

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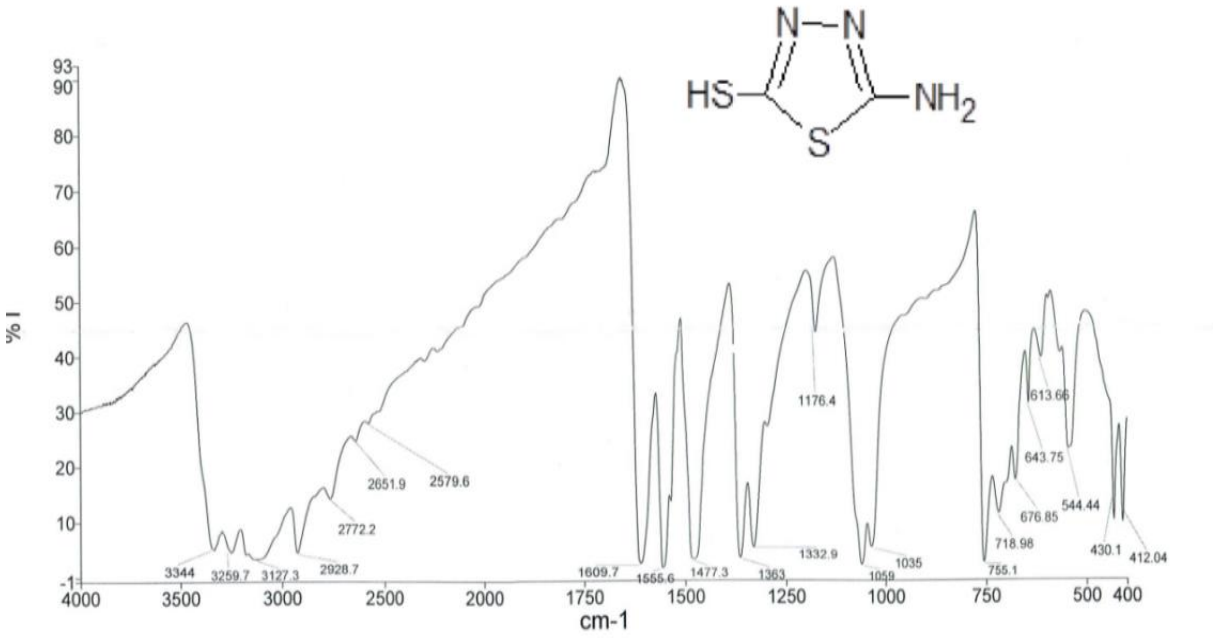

Figure 1: IR spectrum of compound 5-amino-1,3,4-thiadiazole-2-thiol (S_1)

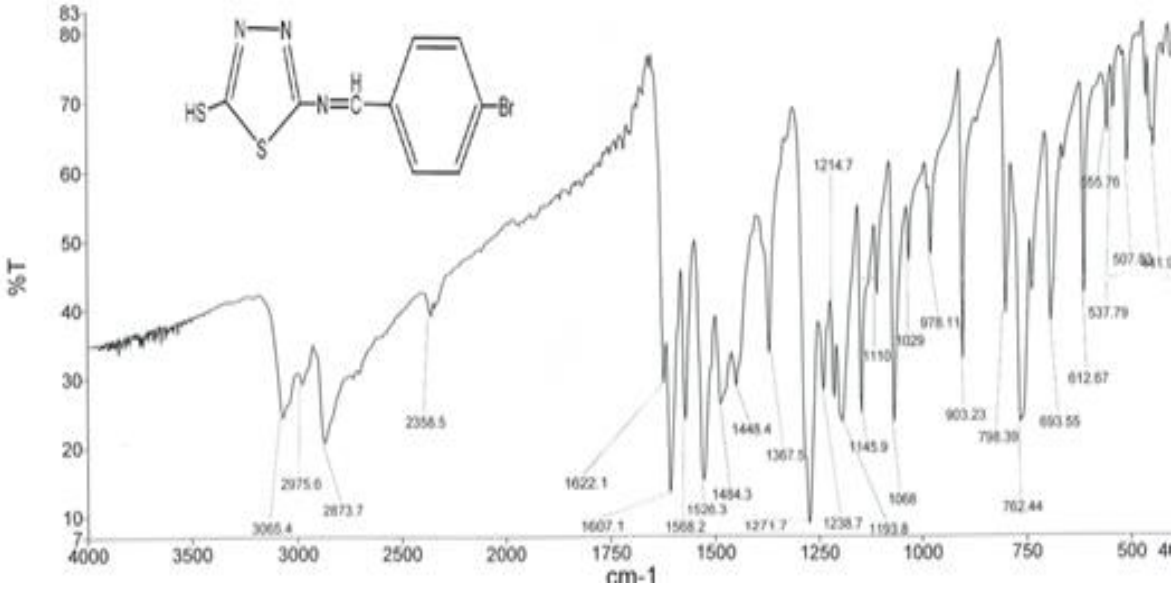

Figure 2: IR spectrum of compound 5-[(4-bromobenzylidene) amino]-1,3,4-thiadiazole-2-thiol (S_2)

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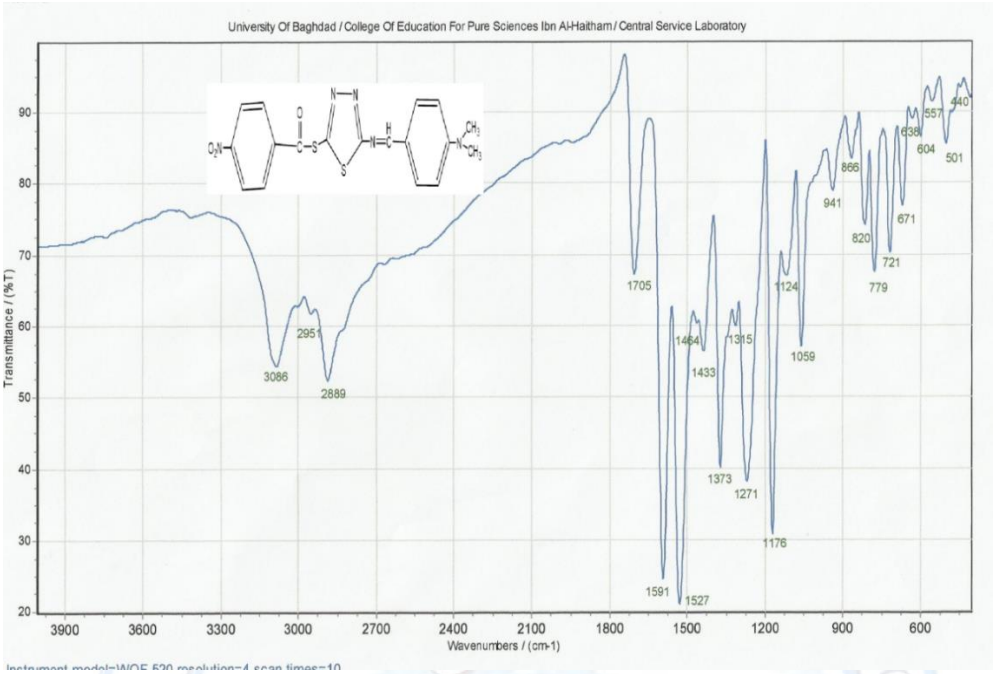

Figure 3: IR spectrum of compound S-(5-((4-(dimethylamino) benzylidene) amino)-1,3,4-thiadiazol-2-yl) 4-nitrobenzothioate (S_{14})

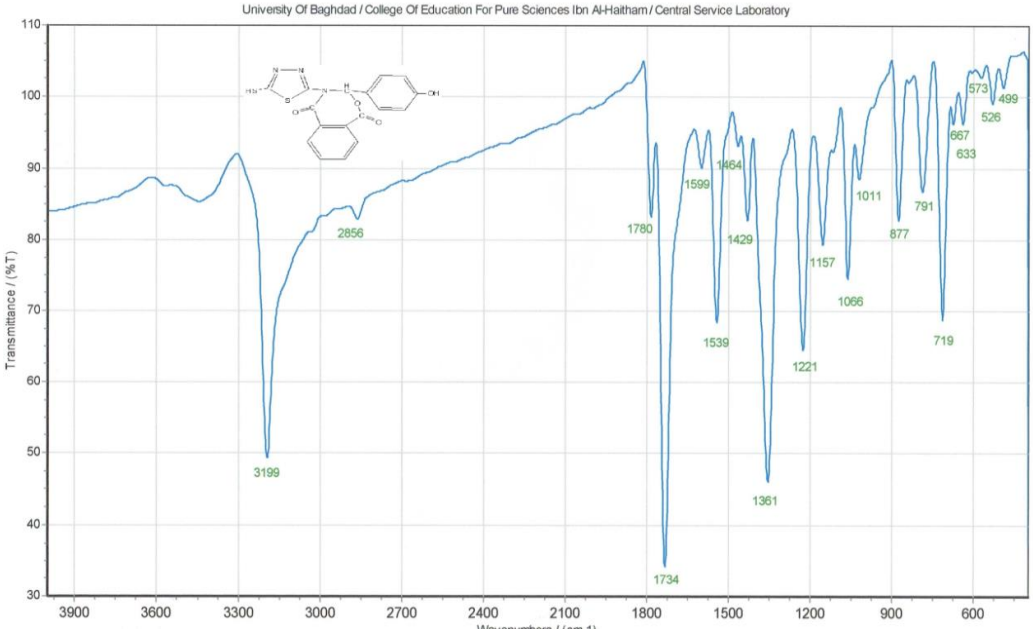

Figure 4: IR spectrum of compound 3-(4-bromophenyl)-4-(5-mercapto-1,3,4-thiadiazol-2-yl)-3,4-dihydrobenzo[e] [1,3] oxazepine-1,5-dione (S_{16})

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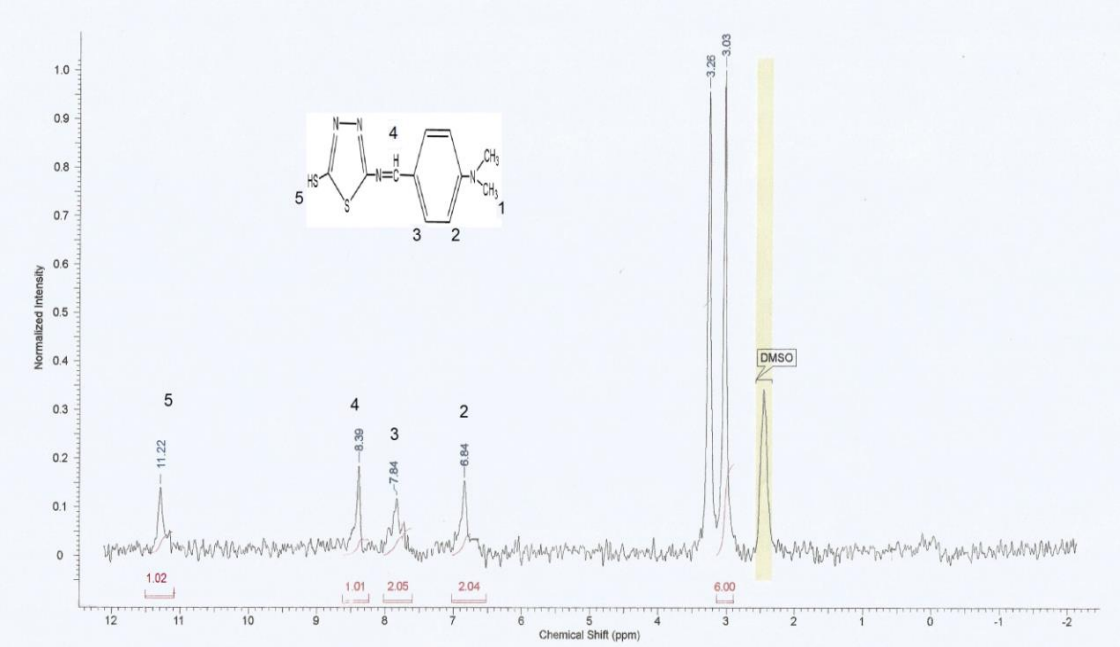

Figure 5: [1]HNMR spectrum of compound 5-{[4-(dimethylamino) benzylidene] amino}-1,3,4-thiadiazole-2-thiol (S_6)

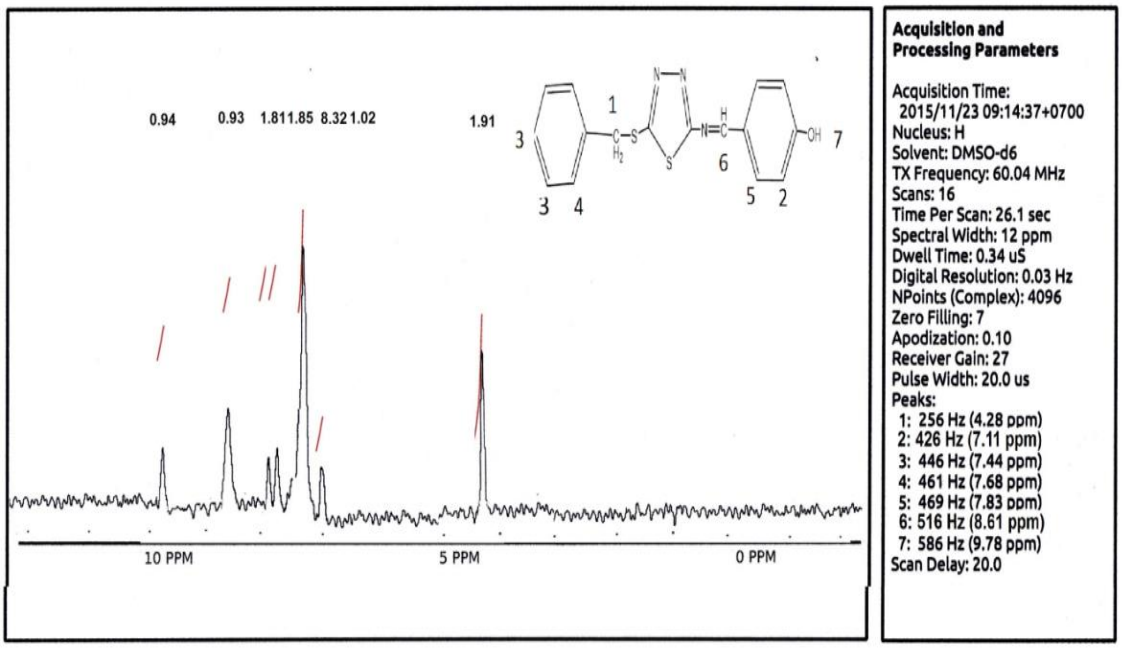

Figure 6: [1]HNMR spectrum of compound 4-(((5-(benzylthio)-1,3,4-thiadiazol-2-yl) imino) methyl) phenol (S_{10})

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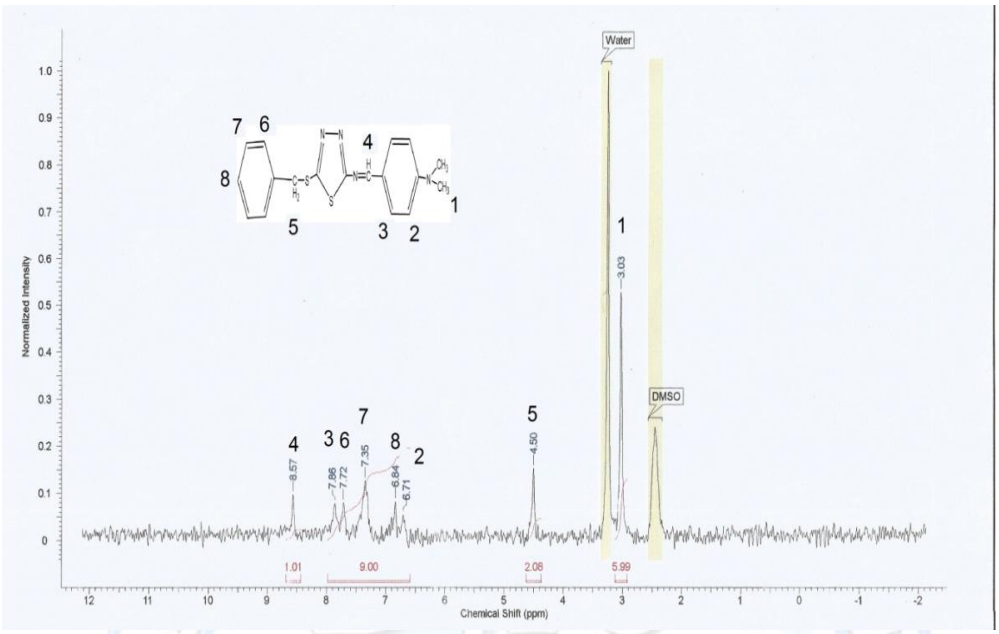

Figure 7: [1]HNMR spectrum of compound 4-(((5-(benzylthio)-1,3,4-thiadiazol-2-yl) imino) methyl)-N, N-dimethylaniline (S_{11})

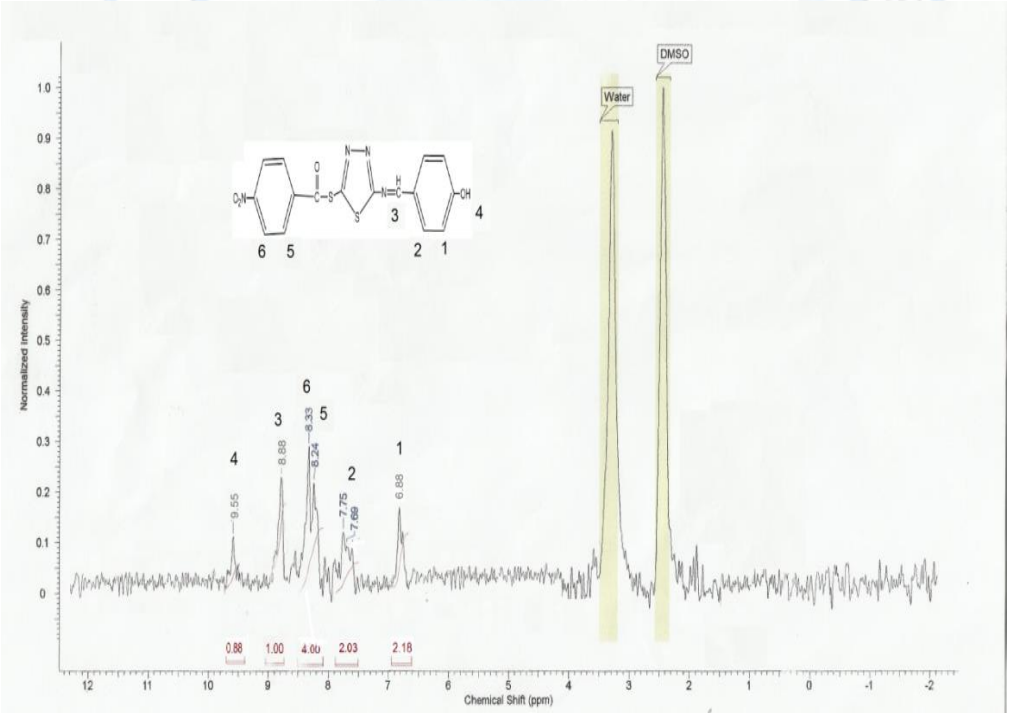

Figure 8: [1]HNMR spectrum of compound S-(5-((4-hydroxybenzylidene) amino)-1,3,4-thiadiazol-2-yl) 4-nitrobenzothioate (S_{13})

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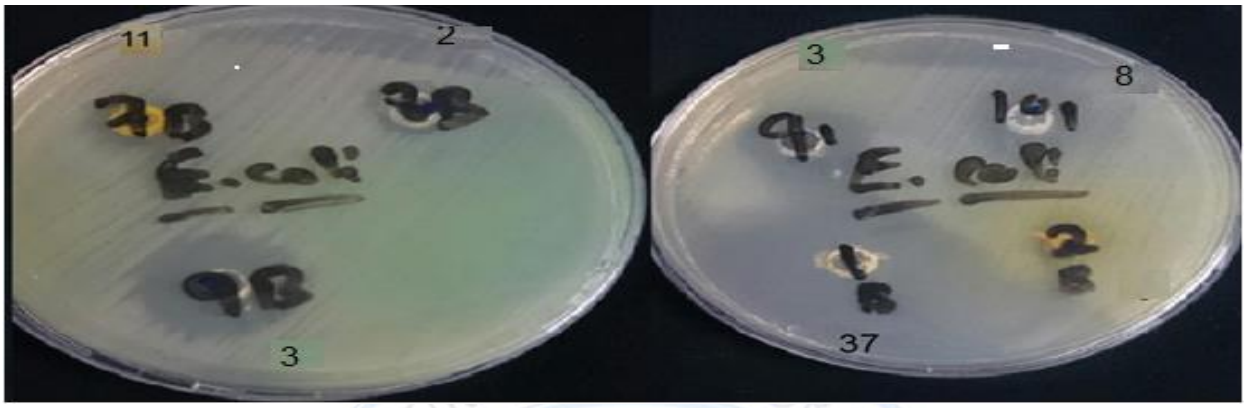

Figure 9: Biological activity for compounds trend Bacteria E. Coli.

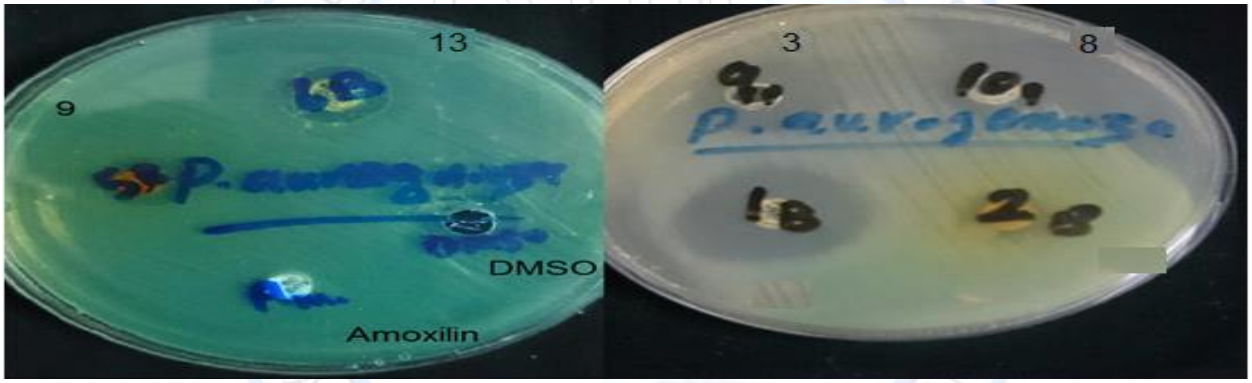

Figure 10: Biological activity for compounds trend Bacteria Pseudo aurogeuosa

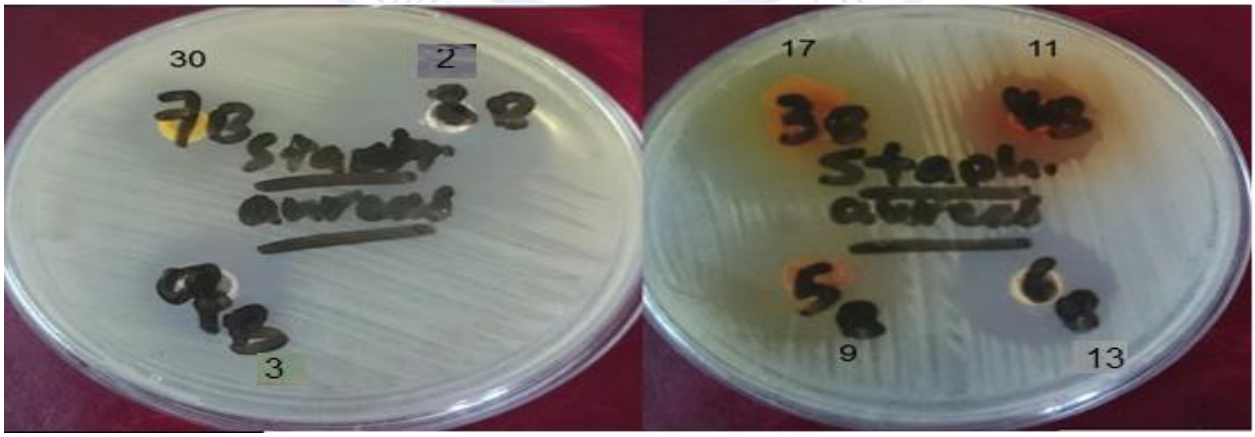

Figure 11: Biological activity for compounds trend Bacteria Staph. aureas

Conclusion

Derivatives containing 5-amino-1,3,4-thiadiazole-2-thiol were synthesized by nucleophilic reaction of 5-amino-1,3,4-thiadiazole-2-thiol with different aromatic aldehyde by using Fusion method. The pharmacological study was performed to determine the effects of substituent on the antibacterial activity, most of the derivatives showed good to moderate activity toward gram-negative (*E. coli*, *P. aeruginosa*) and gram-positive (*S. aureus*) bacteria.

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