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SYNTHESIS AND CHARACTERIZATION OF OXAZEPEN AND IMIDAZOLIN DERIVATIVES FROM 2-AMINO-5-MERCAPTO-1,3,4-THIADIAZOL AND STUDING OF THEIR BIOLOGICAL ACTIVITY

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ABSTRACT

The present study was designed to synthesize -2-amino-5-mercabto-1,3,4,-thiadiazol derivatives and their conversion to schiff bases. The synthesis of these compounds was achieved in two steps: First, by the thermal cyclization of semicarbazid with carbon disulfide in the presence of anhydrous sodium carbonate and absolute ethanol to yield 2- amino – 5 – mercapto -1,3,4-thiadiazole. Second, Schiff bases formation by reflux of aldehyde or keton with 2-amin-5-mecapto-1,3,4- thiadiazole in the presence of ethanol. The chemical structures of all the prepared compounds were confirmed by spectral data of FT IR and H-NMR. The synthesized compounds were evaluated for their antimicrobial activity against two Gram-positive bacteria (S.aureus and Enterococcus) and two Gram - negative bacteria (E.coli and K.pneumonia) and two fungi (T.harzianum and R.solani). The compound 2-amino-5-mercapto1,3,4-thiadiazol and their derivatives exhibited moderate to high antibacterial and antifungi Activity. Highest activity of the compound A5 compound to others corresponds to the presence two phenolic hydroxyl groups in compound A5.

KEYWORDS: 1,3,4- thiadiazole, imidazolidine, Schiff base, oxazepine Biological activity.

INTRODUCTION

Thiadiazole is one of the Organic heterocyclic compounds containing five member diunsaturated ring structure composed of two nitrogen atom at position (3and4) and one sulfur atom at position1.[1] In this study we synthesized the 1,3,4-thiadiazole derivatives which were investigated for antibacterial,[2] antifungal[3] antitubercular[4] anti-flammatory[5] anticonvulsant[6] antioxidant[7] anticancer[8] activity as well as for controlling blood pressure[9]

and affecting central nervous system[10] Anumber of methods have been developed for the preparation and synthesis of 1,3,4-thiadiazole from thiosemicarbazide or substituted thiosemicarbazid.[11] The derivatives of the compound 2-amino-5-mercapto 1,3,4-thiadiazol were successfully identified by FT-IR and H-NMR analysis and tested for both antibacterial and antifungi activity.

MATERIALS AND METHODS

Synthesis of compound (A1)

The synthesis was performed according to procedure described earlier.[12] A mixture of (2g,0.02mol) of thiosemicarbazide and(2.33g,0.02mol)anhydrous sodium carbonate was dissolved in 25ml ethanol. To this solution (3.2g,0.04mol)of carbon disulphide was added. The resulting mixture was heated under reflux for 7 hrs. The reaction mixture was then allowed to cool down to room temperture.Most of solvent was remoned under reduced pressure and the residue was dissolved in distilled 200ml water.Then the solution was Carefully acidified with cold concentrated hydrochloric acid to give pale yellow precipitate.The crude product was filtered and washed with cold water, recrystallized from ethanol to give the desired product as yellow colored yield. The synthesis of compound (A1) was depicted in the figure 1.

Synthesis of compound (A2)

Synthesis of schiff bases (A2)from 2-amino-5-mercapto-1,3,4-thiadiazol was carried out according to the general Proceduere[12] Amixture of compound (A1)(1mol) ethanol and appropriate ketone acetyl acetone (1mol)in acidic condition(3)drops Of glacial acetic acid was refluxed in water bath for(4-5)hrs. The reaction mixture was then allowed to cool at room temperature, and the precipitate was filtered and dried, recrystallized from 50% ethanol to give Yellow crystals of compound (A2).

Synthesis of compound (A3)

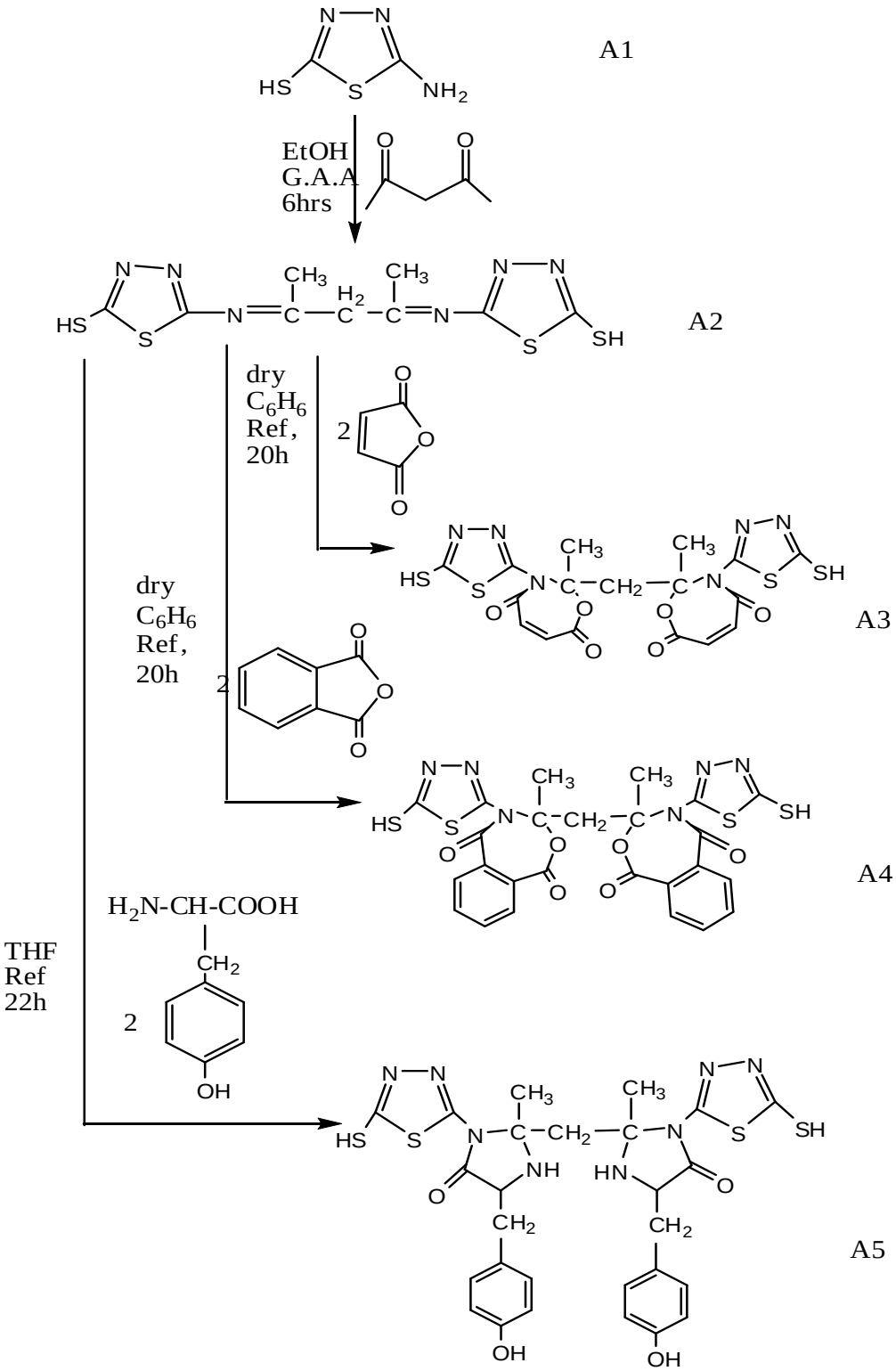
A mixture of (0.02mol) of imine compound (schiff bases) and (0.04mol) of maleic anhydride were refluxed for(7h)with stirring in presence of benzene. After cooling, the precipitate was filtered and dried, recrystallized to produce 52% of oxazepine derivative compound (A3).

Synthesis of compound (A4)

A mixture of (0.02mol)of imine comppund (schiff bases)and(0.04mol)of phthalic anhydride were refluxed for (7h) with stirring in preseuce of benzene. After cooling the precipitate filtered and dried, recrystallized to product 60% of oxazepin derivative compound (A4).

Synthesis of compound (A5)

A mixture of (0.02mol) of imine compounds (schiff bases) and (0.04mol) of amino acid tyrosin were refluxed for(8h)with stirring in presence of THF. After cooling the precipitate filtered and dried, recrystallized to product 67% of Imidazolidine compound (A5).



Scheme (1) Fragmentation of compound (A1-A5)

Analysis of compounds

Melting points were determined by capillary method on electrical melting point apparatus SMP30 Stuart, England. The identification of compounds was done using FT-IR and H-NMR

analysis. The dried powder of the reagent was used for identification.IR spectra were recorded on a FT-IR spectrophotometer Shimadzu as KBr discs.

Biological activity studies

Antibacterial activity

The antibacterial activity of the synthesized compounds were screened against serval pathogenic organisms representative two Gram-positive bacteria (*S.aureus* and *Enterococcus*) and two Gram-negativ bacteria (*E.coli* and *K .pneumonia*) by agar well duffsion method using Mueller-Hinton agar as medium (13). Wells of (6 mm in diameter) were made in the agar plates by using sterile cork borer, then agar surfaces were inoculated with each bacterium. The tested compounds were dissolved in dimethyl sulfoxide (DMSO) to obtain a solution 10^{-2}mol.L^{-1} concentrations. The plates were incubated at 37C^{o} overnight, the zones of inhibition formed were measured in mm. Each experiment was performed in triplicate and the average of the three age of the three determinations was recorded.

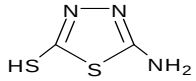
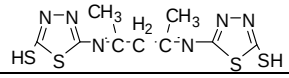
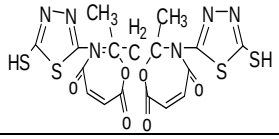
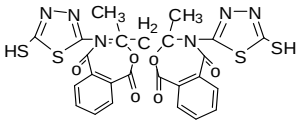
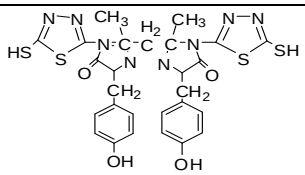
Antifungal activity

Evaluation of antifungal activity of the synthesized compounds was performed against two fungal (*T.harzianum* and *R.solani*)by agar well duffsion method.The compounds was dissolved in dimethyl sulfoxid (DMSO) and used for determination of antifungal activity using potato dextrose agar (P.D.A) as medium for 10^{-2},10^{-4} and 10^{-6} mol.L^{-1} concentrations. A disc of 5 mm of test fungal culture a specific age grown for (7 days) on solid medium was cut with a sterile cork borer and placed at the center of the solid P.D.A plates. The plates were incubated at 26C^{o} for 72h .The average percentage inhibition was calculated using the following formula.[14,15] Inhibition(%) =(C-T)100/C Were C is diameter of the colony fungus in control plates and T is diameter of the colony fungus in test plates.

RESULTS AND DISCUSSION

After synthesis the Compounds were analyzed for m.p yield and molecular weight and the results were tabulated in Table (1). Then the compounds were analyzed by FT- IR analysis and the Spectrum was presented in figure 2-6 for compounds A1-A5 respectively. Table (2-4) represents the observed bands in FT-IR spectrum.

Table 1: The yield, M.P and molecular weight of synthesized compounds

Comp No.	Formula	Molecular Formula	M.WT	m.p C°	Yield	R.F
A1		$C_2H_3N_3S_2$	133	228-230	60%	0.6
A2		$C_9H_{10}N_6S_4$	330	124-126	75%	0.7
A3		$C_{17}H_{14}N_6O_6S_4$	526	160-162	52%	0.6
A4		$C_{25}H_{18}N_6O_6S_4$	608	120-122	66%	0.50
A5		$C_{27}H_{28}N_8O_4S_4$	656	220-222	67%	0.66

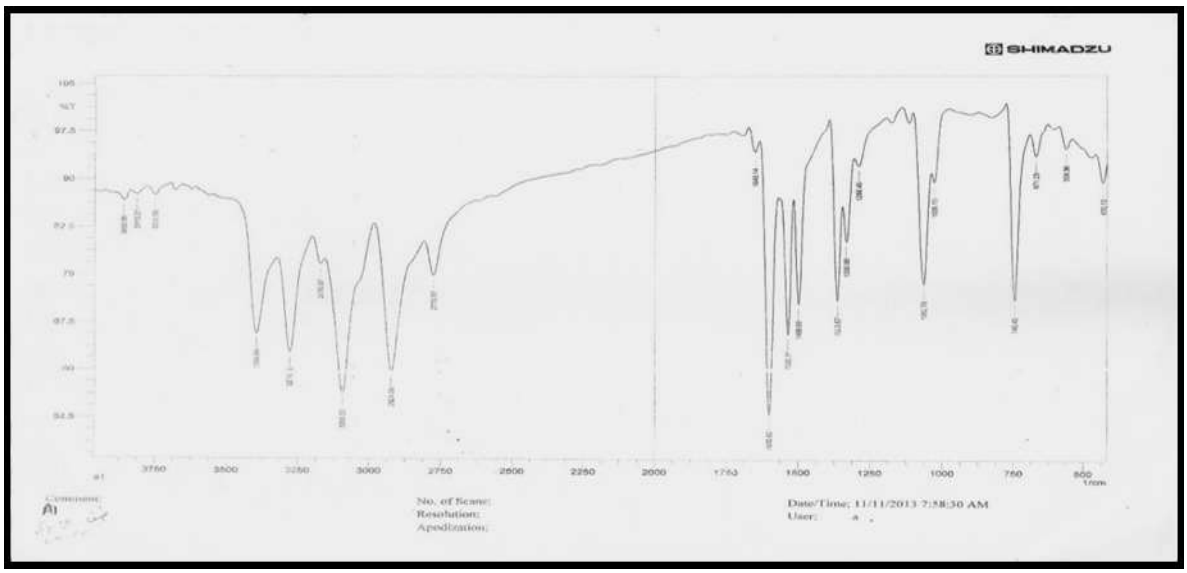


Fig (1) FT –IR Spectrum of compound A1

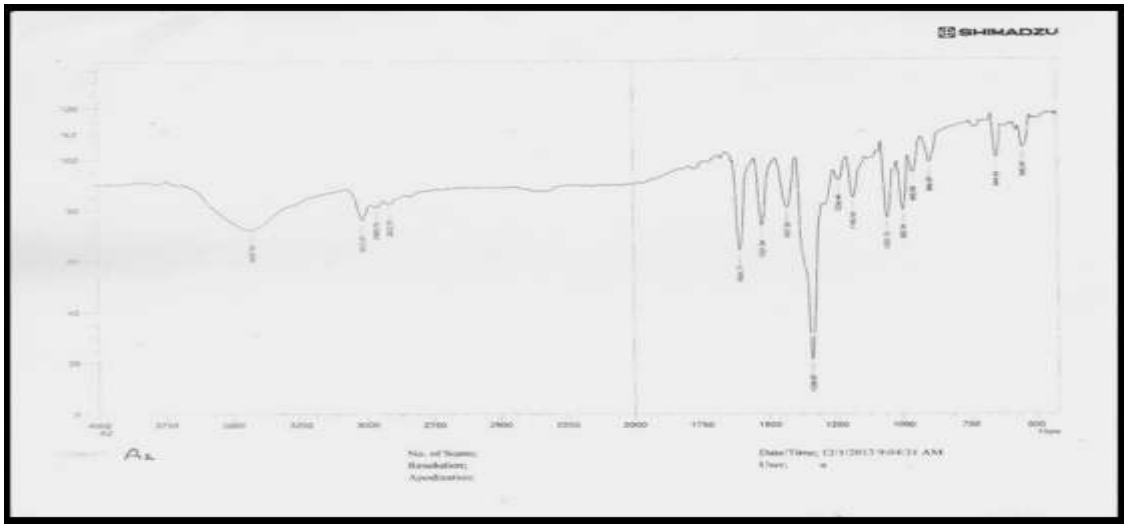
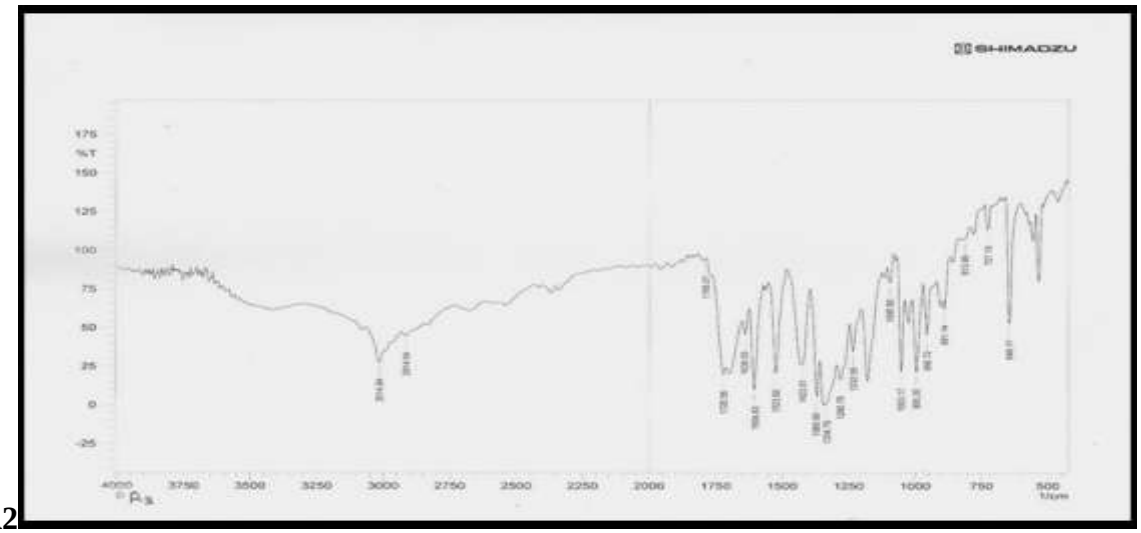
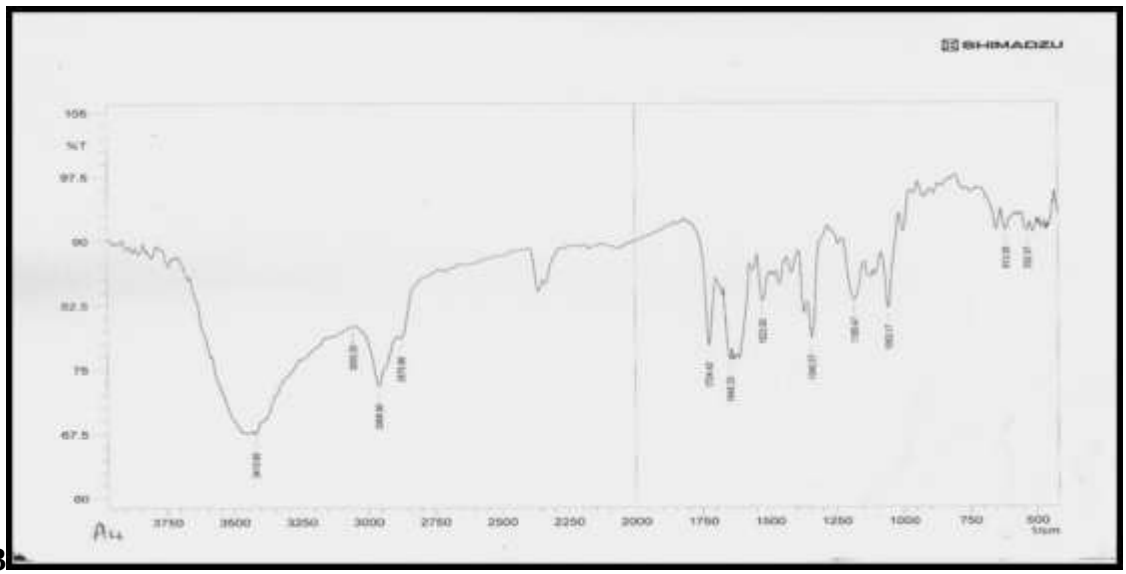


Fig (2) FT-IR S pectrum of compound (A2)



A2

Fig (3) FT-IR Spectrum of compound (A3)



A3

Fig (4) FT-IR Spectrum of compound (A4)

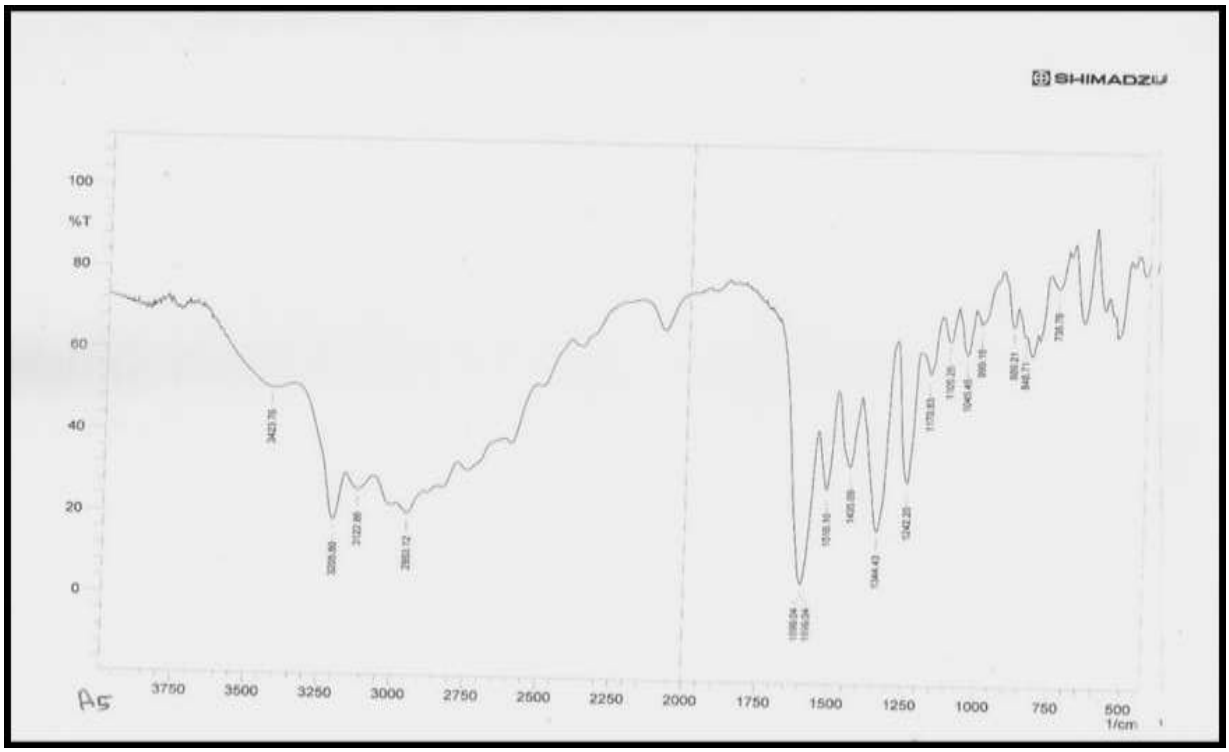


Fig (5) Spectrum of compound (A5)

Table (2) FT.IR data of compound (A2)

Comp No.	Imine υ (C=N)cm^{-1}	Thiadiazole υ (C=N)cm^{-1}	Alphatic υ (C-H)cm^{-1}	Thiadiazole υ (C-S)cm^{-1}
A2	1604	1521	2960	1053

Table (3) FT.IR data of compounds (A3-A4)

Comp No.	Lactone (C=O)cm^{-1}	Lactam (C=O)cm^{-1}	Endocyclic (C=N)cm^{-1}	Lactone (C-O)cm^{-1}	Alken (C=C)cm^{-1}
A3	1720	1639	1604	1280	1523
A4	1724	1645	1604	1253	1523

Table (4) FT.IR data of compound (A5)

Comp No.	Keton (C=O)cm^{-1}	Amine (N-H)cm^{-1}	Aliphatic (C-H)cm^{-1}	Aromatic (C-H)cm^{-1}	Thiadiazole (C=N)cm^{-1}	OH
A5	1699	3205	2953	3122	1523	3423

The FT-IR spectrum of compound (A1) shows the following characteristic bands. Two bands at 3396cm^{-1} and 3278 cm^{-1} due to asymmetric and symmetric stretching vibration of (NH_2) group respectively. An absorption band at 3093cm^{-1} due to (N-H) stretching (tautomeric) form the (-SH) stretching band found as very weak shoulder at 2775cm^{-1}. Aband at 1600cm-1 due to due to (C=N) stretching of the thiadiazole ring moiety. The sharp band at 1535cm^{-1} and 1383 cm^{-1} due to the (N-H) bending and (CN) stretching vibration respectively.Also ,the

absorption band at 1062cm^{-1} for the (C=S) group provide an evidence that compound(A1) can exist in two tautomeric forms thiol and thion form.

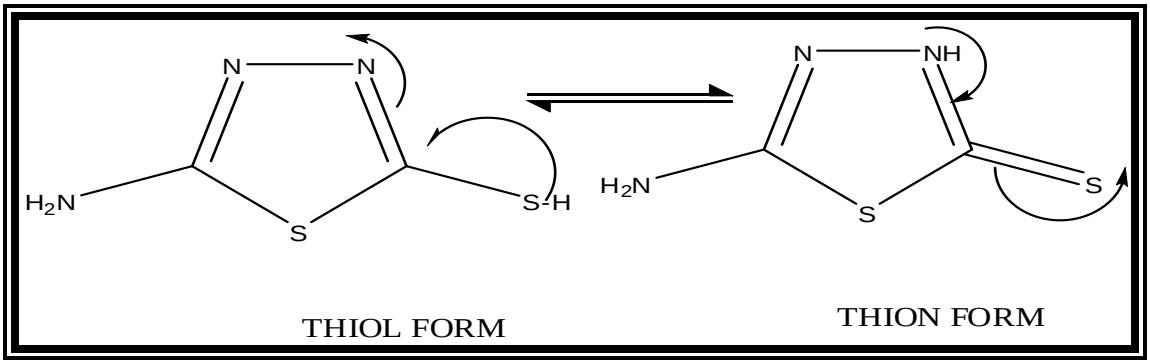
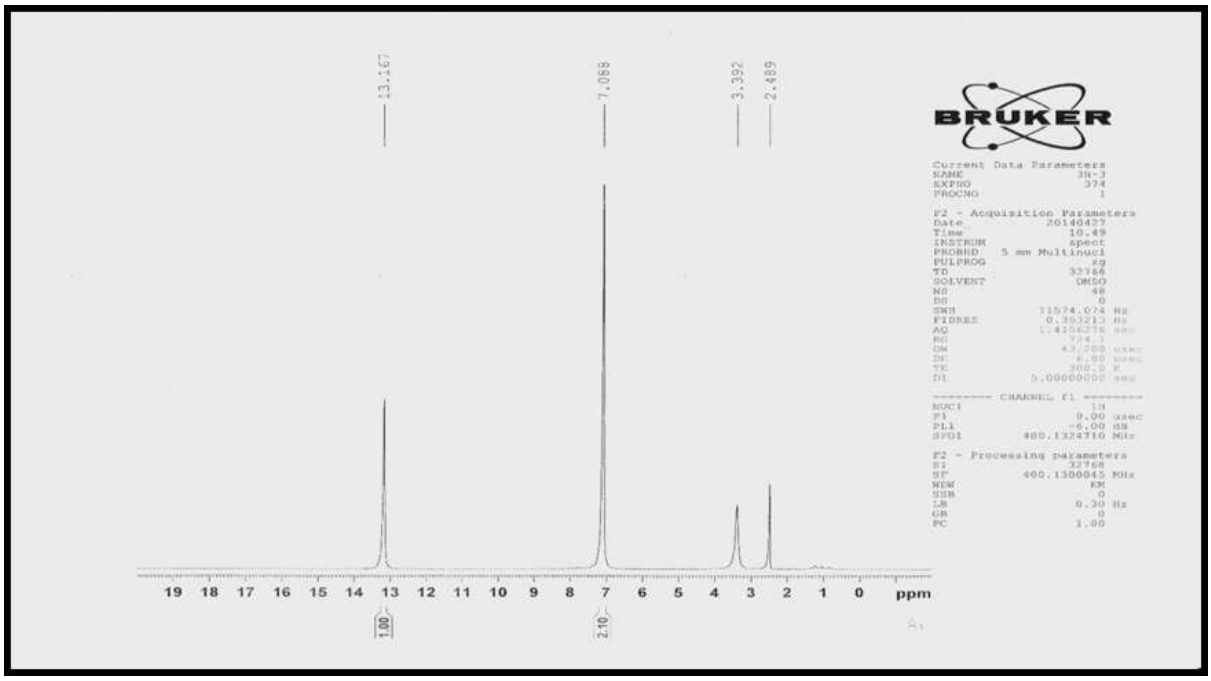


Figure 6: Two tautomeric (thiol and thion) forms of compound A1

We also performed the H.NMR analysis of compound A1 and A3 and the spectrum were presented in figure 8 and 9.Their H.NMR spectrum showed signal at 13.16 due to (NH2) amino group in compound,[1] which disappeared and other band appeared such as (-CH=CH-) at (6.02-6.08) protons of cyclic alkene in oxazepine compounds (A3) and (A4) in compound.[3] The proton of (SH) appeared at (3.39-3.58) due to protons of thiadiazol ring in compounds[1-5] and other signals.



Fig(7): NMR Spectrum of compound A1

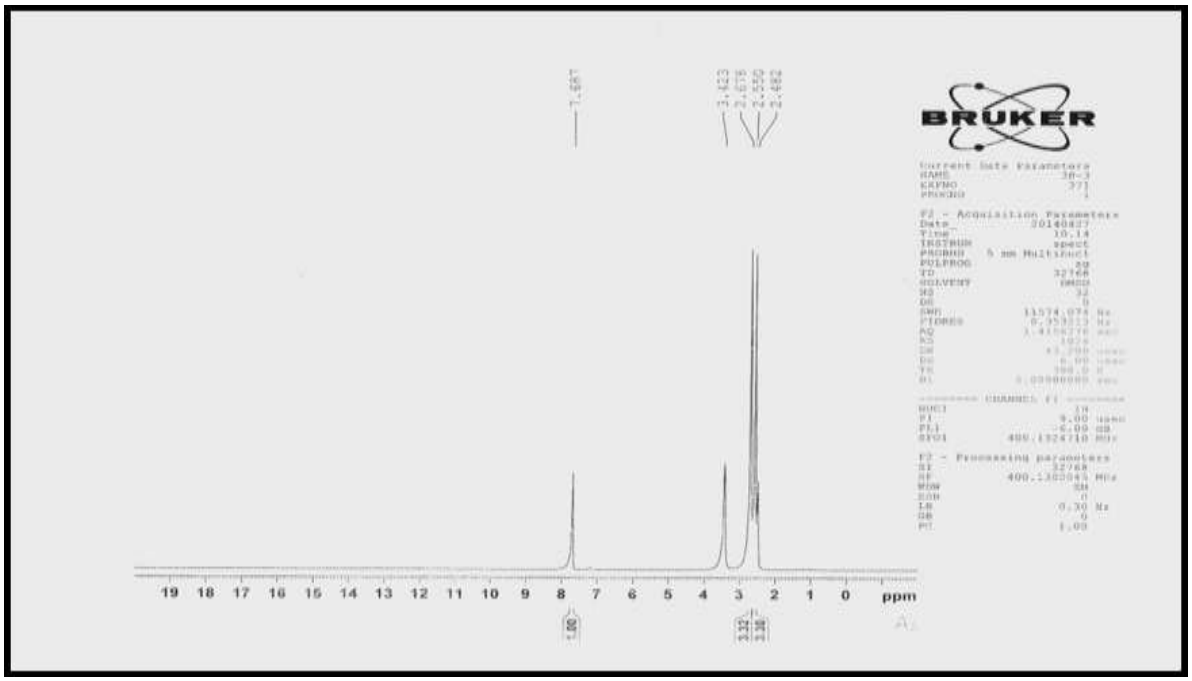


Fig (8): 1H-NMR Spectrum of compound A2

Biological activity studies

In vitro antibacterial activity of 2-amino -5-mercapto-1,3,4-thiadiazol and their newly synthesized derivatives against organisms displayed significant activity with a wide degree of variation. It is found that compounds (A5),(A4) and (A3) were shown highest activity against gram positive and gram negative bacteria except compound (A3) was exhibited moderate activity against *K.pneumonia*. Rest the compounds A (A1) and(A2)was exhibited moderate activity against the same stearin except compound (A2) was shown slight activity against *K.pneumonia*.2-amino-5-mercapto-1,3,4-thiadiazol and their derivatives were exhibited moderate to higher activity against gram positive and gram negative bacteria. S.aureus was found to be more susceptible than rest of the other strains of bacteria. The antibacterial activity results are summarized in (table 5 and Fig,9). From in vitro antifungal activity (Table.6), data reveals that all the newly synthesized derivatives indicates higher antifungal activity than the compound (A1). Substantial activity is achieved in case of compounds (A5)and(A4) against *R.solani* and the remaining compounds are significantly against the species. A comparative study of the compounds was shown significant toxicity at 10^{-2} mol.L^{-1} conc.,against all species of fungi. However, all newly synthesized derivatives are more active than the original compound (A1) and the antifungal activity decreases on dilution. Also, it was observed that compounds exhibit more significant effect *R.solani* than *T.harzianum*.

The order of increasing antimicrobial activity towards tested bacteria and fungi is as follows: (A5)>(A4)>(A3)>(A2)>(A1). Such increased activity of the compound (A5) in comparison with other compounds can be explained on The basis, compound (A5)is possessing two phenylic hydroxyl groups.It is demonstrated good electron mobility in the aromatic ring may enhance the activity increasing hydroxyl groups which are electron donating in nature on the phenyl ring in more antimicrobial activity. Furthermore,when the comparison for the compounds was made between bacteria and fungi, it was observed that the compounds found to be more active against fungi than bacteria,it was observed that the compounds are more active against gram positive bacteria than the negative bacteria. The mechanism of action of antimicrobial agents can be dissussed under five headings,(1)inhibition of cell wall synthesis,(2)inhibition of cell membranc function,(3)inhibition of protein synthesis,(4)inhibition of folate metabolism and (5) inhibition of nucleic acids thensis.[16,17]

Table (5): Antibacterial activity data (zone of inhibition in mm) of the test compounds

Compound / Bacteria	G (+ve)		G (-ve)	
	S.aureus	Entro.	E.coli	k.pneumonia
A1	10	10	12	11
A2	10	11	10	9
A3	17	17	14	13
A4	20	13	17	12
A5	20	14	16	13

Note: Highly active = inhibition zone >12 mm, Moderately = inhibition zone=9-12mm,Silightly = inhibition zone =6-8 mm.

Table (6): Antifungal activity data of the test compounds

Compound / Fungi	Average percentage inhibition (%)					
	T.herzianum			R. solani		
	10^{-2}	10^{-4}	10^{-6}	10^{-2}	10^{-4}	10^{-6}
A1	32.2	27.8	18.9	34.4	27.8	22.2
A2	36.7	30.0	23.3	42.2	32.2	24.4
A3	51.1	38.9	33.3	67.8	55.6	43.3
A4	66.7	45.6	32.2	71.1	56.7	37.8
A5	55.6	43.3	35.6	75.6	63.3	44.4

Note=Conc. in $Mol.L^{-1}$

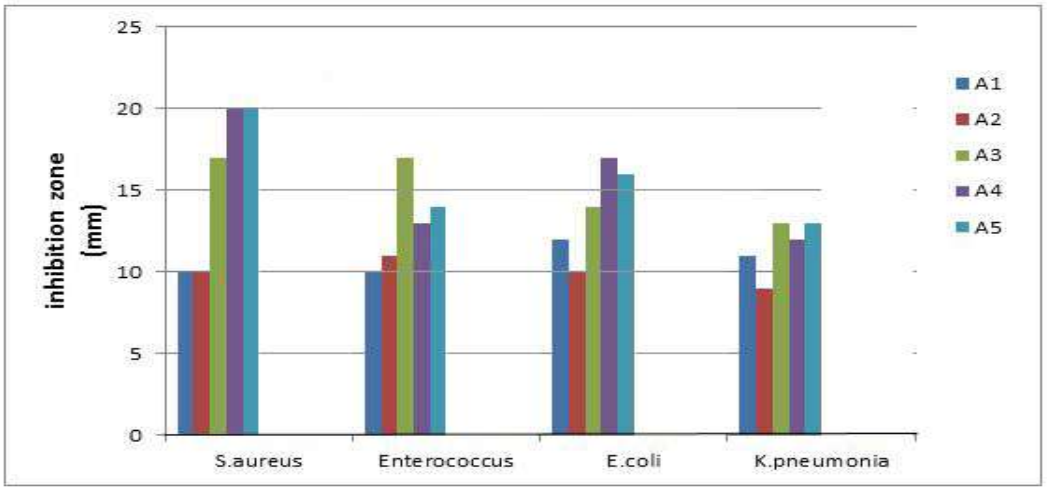


Fig (9).Statistical representation for antibacterial activity of (A1-A5)

CONCLUSION

The compound 2-amino-5-mercapto 1,3,4-thiadiazol were successfully synthesized and identified by FT-IR and H.NMR analysis. The compound 2-amino-5-mercapto 1,3,4-thiadiazol and their derivatives were tested for both antibacterial and antifungal activity and exhibited moderate to higher activity. It was observed that these compounds are more active against gram positive bacteria than the negative bacteria.

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