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Research Article

Synthesis, Characterization and Antimiccrobial Screening of Some Thiadiazole Derivatives

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ABSTRACT

Heterocycles like thiadiazole plays a vital role owing to its wide range of therapeutic activities like antibacterial, anti-fungal, anti-inflammatory, anti-convulsant, antiviral, anticancer and antihistaminic. In the present project, an attempt was made to synthesize some of newer 1,3,4-thiadiazoe derivatives and evaluate their antimicrobial activity quantitatively and qualitatively. The Synthesized compounds were characterized by TLC, melting point and spectral data. Melting points were determined by using precision melting point apparatus in open capillaries and are uncorrected. The Purity of the compounds was checked by TLC on silica gel G plates using methanol: chloroform (1:9) solvent system iodine chambers used as a visualizing agent. The structures of these compounds are supported by IR, H-NMR and mass analysis. The antibacterial and antifungal activities of thiadiazole derivatives also reported.

INTRODUCTION

Illness has been man's heritage from the beginning of his existence, and the search for remedies combat it perhaps equally old. The sincere attempt by man to control and cure diseases has led to search of new drugs or suitable derivatives of existing drugs. The earlier sources of drugs were from plant, animal and mineral sources, but due to the lack of potential action and definitive cure and sometimes more toxicity, discovery of new drugs that are more potential and less toxic is essential. The synthesis of derivatives has been important part and is aimed at modifying the action of drugs , particularly to reduce the side effects and potentiate the drug action.[1] Antimicrobial drugs are the greatest contribution of 20thcentury to

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therapeutics. Their advent changed the outlook of diseases. They are one of the few curative drugs. Their importance is magnified in the developing countries , where infective diseases predominate. The clinical value of antimicrobial agent can not be assumed simply because they inhibit or kill microbial pathogens in-vitro. Pharmacodynamic studies, which show pharmaceutical agents interact with their therapeutics targets. During recent years there has been a large investigation on different classes of thiadiazole compounds many of which were found to posses an extensive spectrum of pharmacological activity such as antifungal, antibacterial, anti-mycobacterium, anti-convulsant,CNS depressant , herbicidal and antiinflammatory activity.[2,3] Five memebered heterocyclic compounds show various types of biological activity among them 2,5 - disubstituted 1,3,4-thaidiazoles are associated with diverse biological activity probably virtue. Antimicrobial are very important category of drugs these classes of drugs prescribed right from simple infection to the serious diseases like cancer and also in life threatning infection like meningitis. So it is quite clear from the spectrum of use that thes categories of drugs very important from medicinal point of view. We considered it of interest to synthesize some novel 2,5- disubstituted-1,3,4-thaidiazole derivatives for their anti-microbial properties. Several five membered aromatic system having three hetero atoms at symmentrical positions have been studied because of their interesting physiological properties.

Objectives

Research in field of anti-microbial therapy is continuous ongoing &demanding study. Among the several reasons the major ones are the resistance developed by microbes and the emergance and occurrence of newer infections. Hence the search for newer effective anti-microbial agents is imperative. It focuses on the problems of cross resistance & bettert activity against variety of infections.[1,4]

Hence, we planned in the present objectives of the study will be as below.

1. Development of the synthetic method for the synthesis of the titled 1,3,4-thaidiazole compounds
2. Chemical Charecterization of the newly synthesized compound by IR, H-NMR and Mass spectral data.
3. Screening for antibacterial and antifungal activity.
4. Screening for Antimicrobial activity.

METHODOLOGY

Chemicals and Reagents

The chemicals and reagents used in the present project were of AR grade and LR grade, purchased from Lancaster, sigma, Qualigens, NR chem , Rolex, S.D fine chem Ltd, Merck , Loba and Hi-media.

Anilne	Methanol
4-methylaniline	Etahnol
4-Chloroaniline	Chloroform
4-bromoaniline	Concentrated Ammonia
4-methoxyaniline	Carbon disulphide
Sodium chloroacetate	Hydrazine hydrate

Analytical Techniques

Physical data

Melting points of the synthesized compounds determined using melting point apparatus and were found uncorrected.

Thin layer Chromatography

Purity of the compounds was checked by thin layer chromatography using silica gel G as stationary phase and various combinations of chloroform and methanol are used as mobile phase. The spots

resolved were visualized as brown coloured spots by using iodine chamber**.**

Instrumentation

The techniques employed for the charecterization of the synthesized compounds were IR spectra

H- NMR and Mass Spectra

1. Infrared spectra

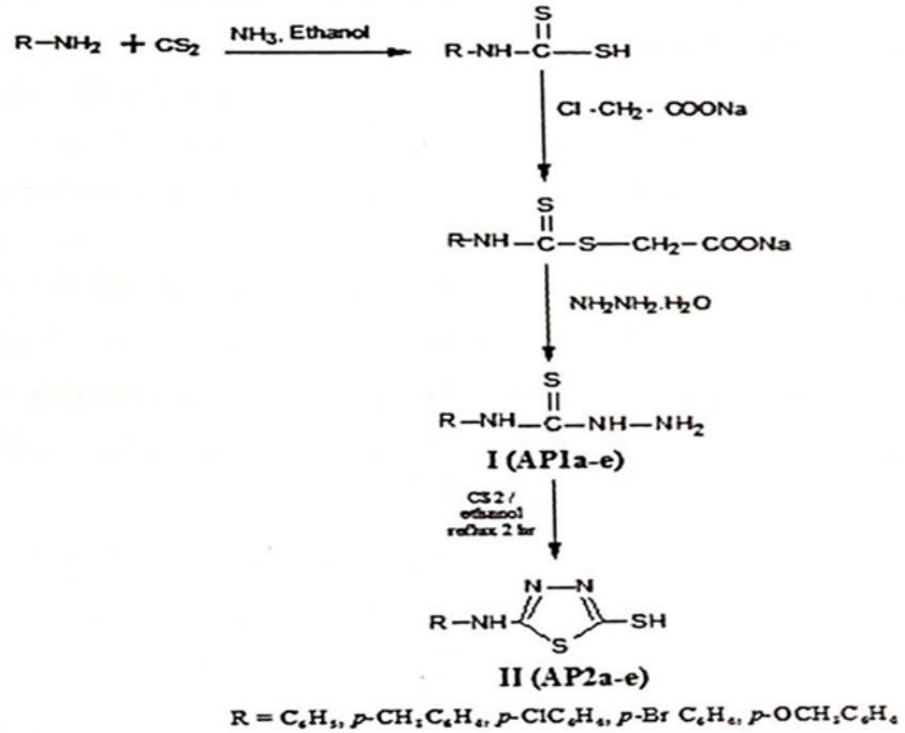
The IR spectra of the synthesized compounds were recorded using dry KBr pellets in range of 4000-400cm^{-1}on a bruker Fourier transform IR spectrometer. ^{1}H-NMR magnetic resonance spectra. ^{1}H-NMR spectra were recorded in BRUKER (200MHz) using DMSO as Solvent.

Mass spectra

Mass spectra were done by LC-MS technique.

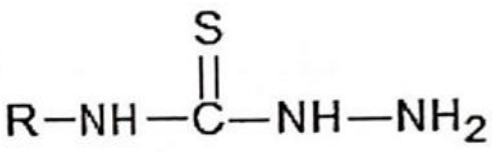
EXPERIMENTAL

SCHEME-I

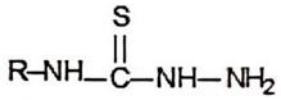


R = C_6H_5, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4, *p*-Br C_6H_4, *p*-$OCH_3C_6H_4$

Step-1: Synthesis of *N*-phenylhydrazinecarbothioamide (AP1a-e):

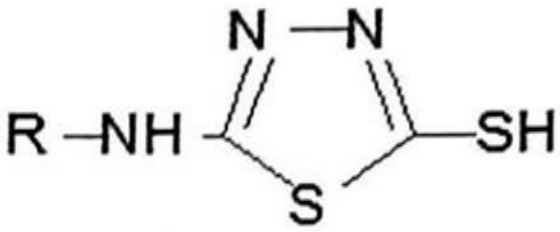


Physicochemical data of *N*- phenyl hydrazinecarbothioamide (AP1a- e):



Sl. NO	Compound Code	R	Molecular Formula	Molecular Weight	M.P (°C)	Yield (%)
1	AP1-a	$-C_6H_5$	$C_7H_9N_3S$	167.23	140-142	80%
2	AP1-b	p-$CH_3C_6H_4$	$C_8H_{11}N_3S$	181.25	135-137	75%
3	AP1-c	p-ClC_6H_4	$C_7H_8ClN_3S$	201.67	148-150	65%
4	AP1-d	p-BrC_6H_4	$C_7H_8BrN_3S$	246.12	190-192	70%
5	AP1-e	p-$OCH_3C_6H_4$	$C_8H_{11}N_3OS$	197.26	159-161	85%

Step-2: Synthesis of 5-(phenyl amino)-1, 3, 4-thiadiazole-2-thiol (AP2a-e):

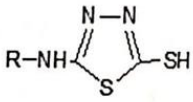


a) From solid arylamines

Aromatic amines (0.1M) were diolved in 25 ml ethanol concentrated ammonia solution (30ml) was added drop by drop followed by addition of carbon disulphide (0.1M) with constant stirring. After complete dissolution of carbon disulphide the reaction mixture was allowed to stand for two hours. A solution of sodium chloroacetate (0.1M) was added followed byhydrazine hydrate (0.1M). The reaction mixture was then warmed on a water bath and filtered while hot.The filtrate was concentrated to half of its initial volume amd allows standing overnight to give the product, which was collected, filtered, dried and recrystallised from ethanol.[5] A mixture of N-Phenylhydrazinecarbothiamide (0.06M), Carbon disulphide (0.06M) and absolute ethanol (25ml) was refluxed in 250ml RBF on water bath at 60-70^{0c} for two hours Excess alcohol was distilled of

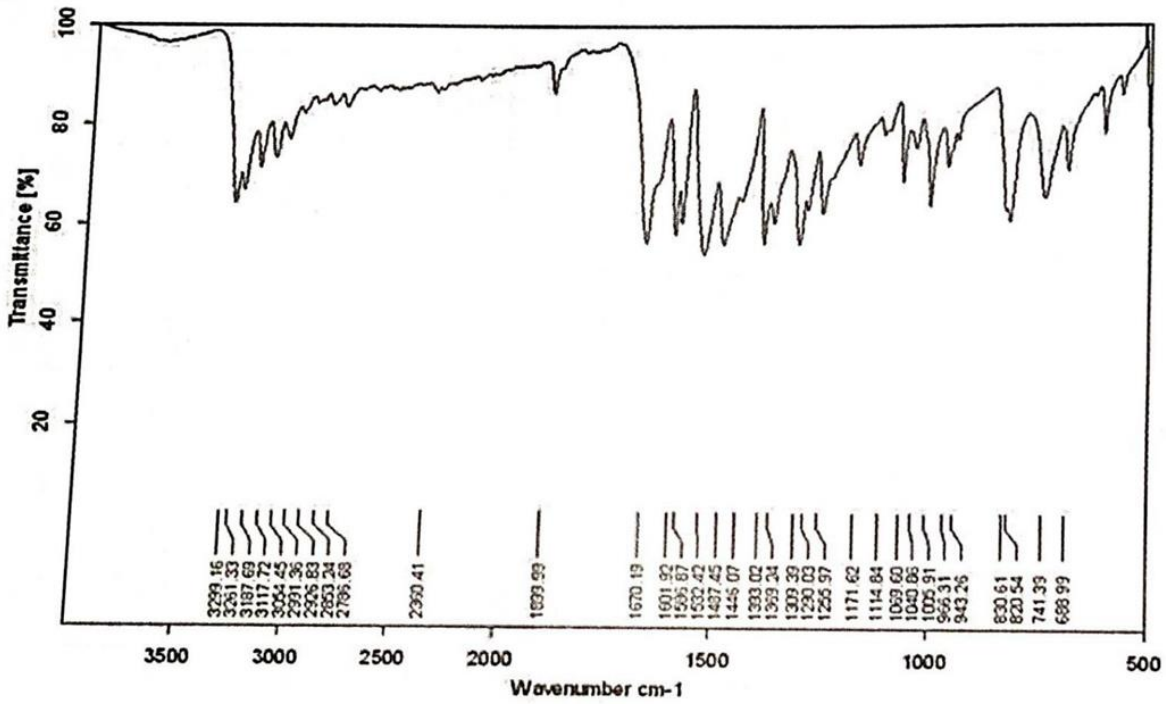
under reduced pressure and residue after cooling the reaction mixture was poured in ice cold water. The solid was seperated, filtered, washed well with water, dried and recrystalized from ethanol.[5]

Physicochemical data of 5- (phenyl amino)- 1, 3, 4- thiadiazole- 2- thiol (AP2a- e):

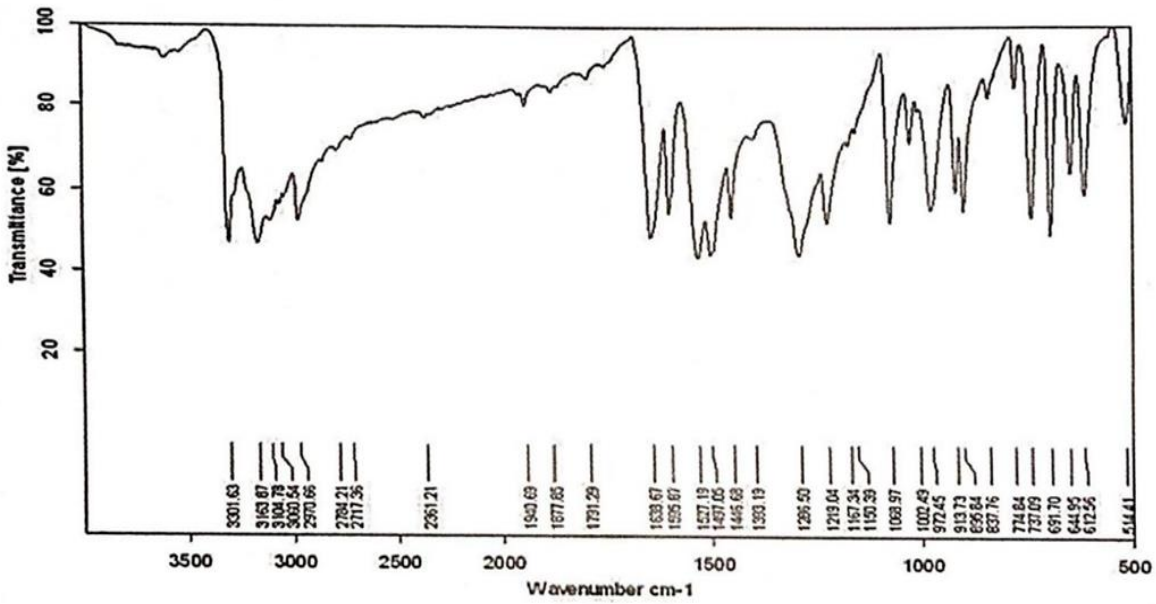


Sl. NO	Compound Code	R	Molecular Formula	Molecular Weight	M.P (°C)	Yield (%)
1	AP2-a	-C_6H_5	$C_8H_7N_3S_2$	209.29	160-162	75%
2	AP2-b	*p*-$CH_3C_6H_4$	$C_9H_9N_3S_2$	223.31	216-218	85%
3	AP2-c	*p*-ClC_6H_4	$C_8H_6ClN_3S_2$	243.73	232-234	70%
4	AP2-d	*p*-BrC_6H_4	$C_8H_6BrN_3S_2$	288.18	198-200	80%
5	AP2-e	*p*-$OCH_3C_6H_4$	$C_9H_9N_3OS_2$	239.31	174-176	90%

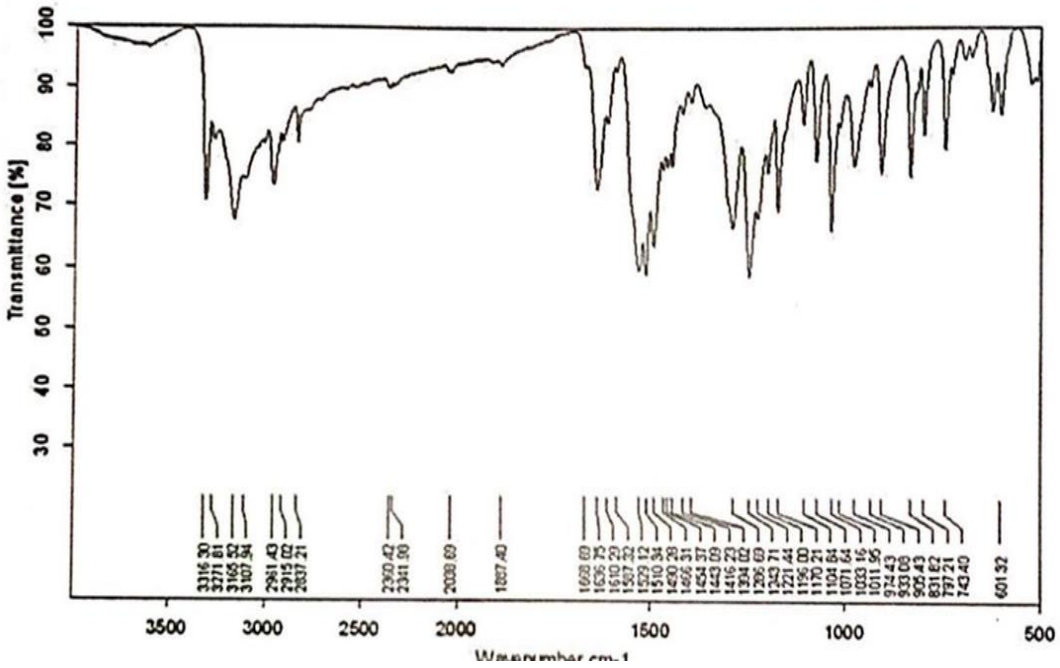
IR Spectra of AP1d

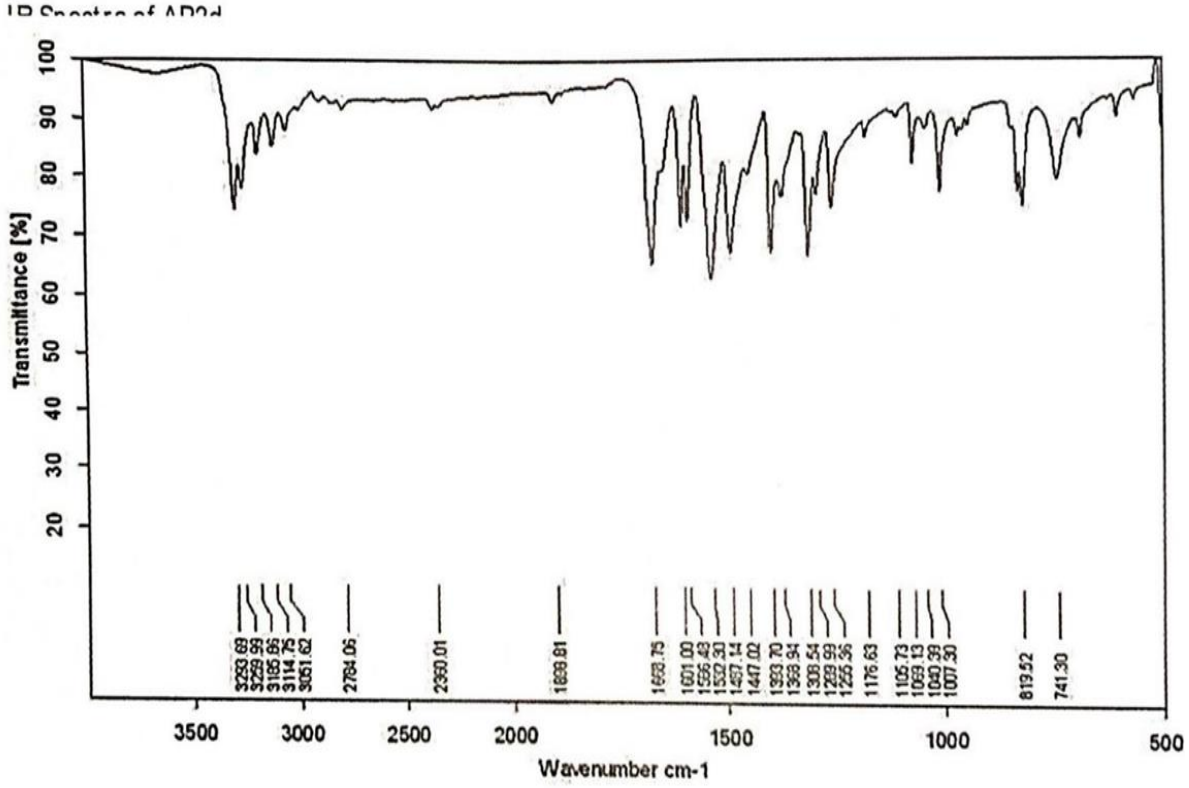


IR Spectra of AP1a

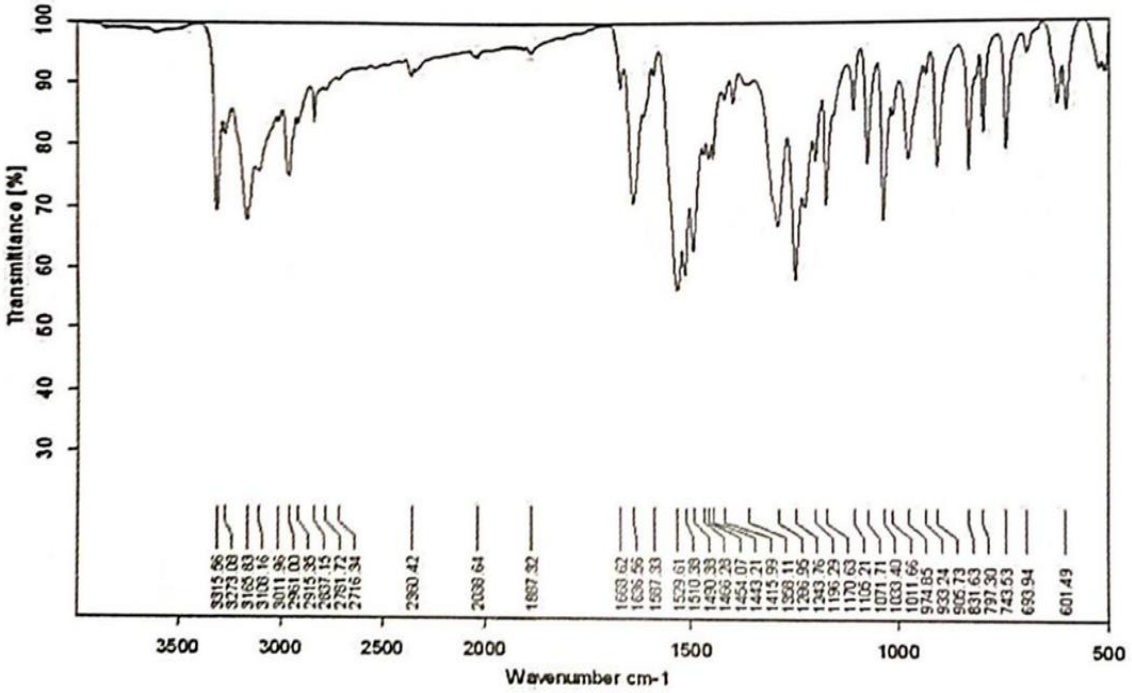


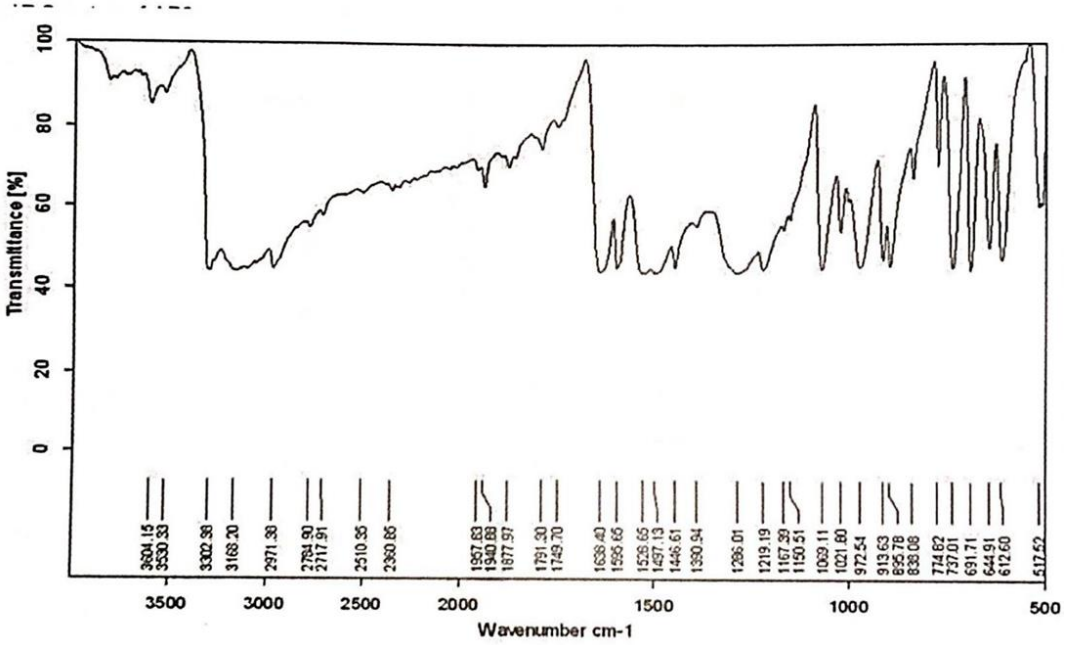
IR Spectra of AP1e





IR Spectra of AP2e

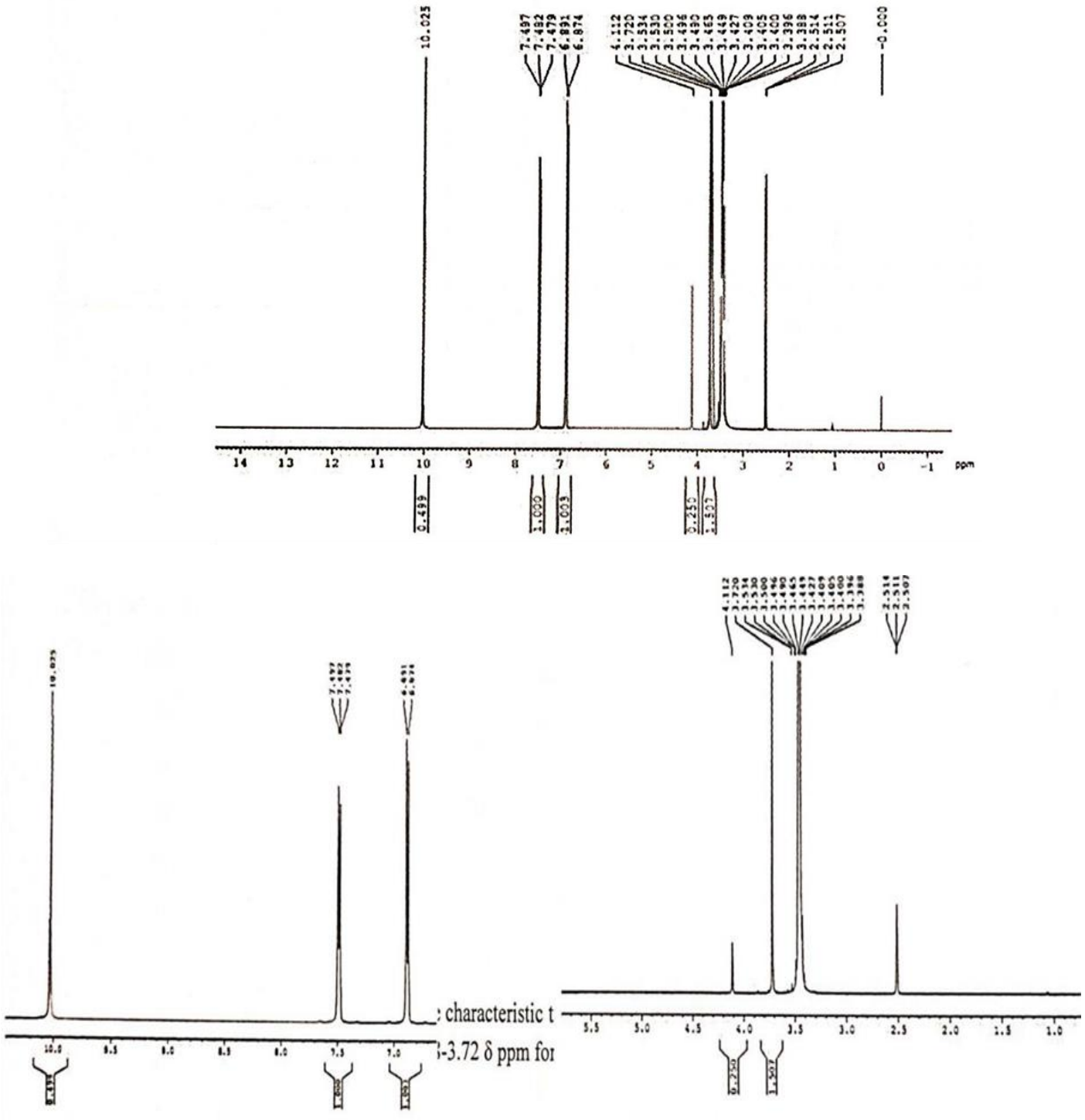




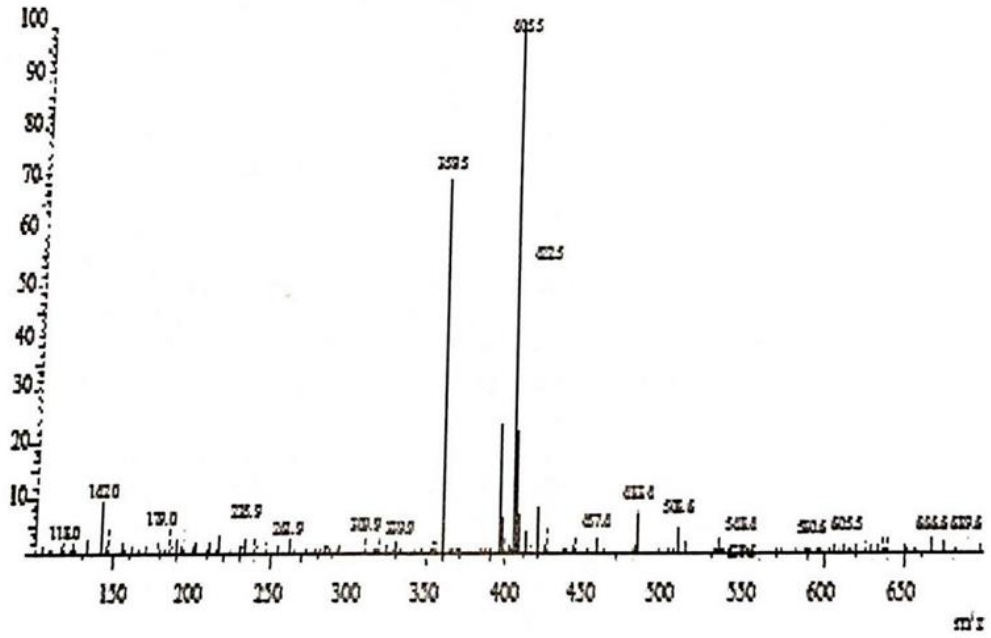
Spectral data of Synthesized compounds

Compound No.	IR (cm^{-1})	^{1}H-NMR (δ ppm)	Mass spectra (m/z)
AP1A	3301-3163 (NH,NH_2), 1068 (C=S) 2970 (Ar-H), 1638 (C=N), 1595-1446 (C=C), 895 (C-C)	—	—
AP1D	3299-3187 (NH,NH_2), 1069 (C=S) 3187-3054 (Ar-H), 1670 (C=N), 1601-1446 (C=C), 830 (C-C)	—	—
AP1E	3316-3165 (NH,NH_2), 1071 (C=S), 2961 (Ar-H), 1668 (C=N), 1490-1587 (C=C), 905 (C-C), 2837 ($O-CH_3$)	—	—
AP2A	3302 (NH), 2971 (Ar-H), 2510 (SH), 1638 (C=N), 1595-1497 (C=C), 612 (C-S)	—	—
AP2D	3293 (NH), 3051 (Ar-H), 2784 (SH), 1668 (C=N), 1586-1447 (C=C), 741 (C-S), 1898 (C-Br)	—	—
AP2E	3315-3165 (NH), 2915 (Ar-H), 2360 (SH), 1668 (C=N), 1529-1490 (C=C), 693 (C-S), 2837 ($C-OCH_3$)	—	—

^{1}H- NMR Spectra of AP2e



The mass spectra



The mass spectra showed an accurate molecular ion peak data at 361.3 *m/z* [M+1] for compound [**AP2E**].

RESULTS AND DISCUSSION

A series of (AP1a-e) and (AP2a-e) where synthesized in good yield using the synthetic route outlined in skin. Starting material 5- (Phenyl amino) -1,3,4- thiadiazole -2-thiol was prepared according to the literature procedure. Structure of the synthesized compounds was stabilized on the basis of IR,H^1-NMR and Mass spectral data. The IR spectrum of the intermediate AP2A,AP2D and AP2E showed absorption band around 3293-3315 cm^{-1} for NH and NH2, 1668-1638 cm^{-1} for C=N and several peaks around 1587-1490 cm^{-1} for C=C. The title compound displayed absorption bands ranging from 3286-3269 cm^{-1} for several peaks in between 1670-1640 cm^{-1} for C=C in their respective IR spectra. These compounds also exhibited appropriate peaks at corresponding delta ppm in their ^{1}H-NMR spectra which were in conformity with their assigned structures. H-NMR spectrum of compound (AP2E) showed the charecterestic triplet around 7.47-7.49 delta ppm for aryl CH3 Proton, a singlet at 10.2 delta ppm for NH prton and multiplet around 3.38-3.72 delta ppm for aryl proton and two doublets are observed at 6.87-6.89 delta due to methyl proton molecule attach to phenyl ring.

CONCLUSION

From the data of antibacterial and anti-fungal activity is clearly concluded that the synthesized compounds are significant and moderate antibacterial and anti-fungal agents. The substituted 1,3,4-thiadiazole moeities are already known for different biological activities. Here we have synthesized some novel 1,3,4-thiadiazole analogues combining with different substituted aromatic and aliphatic system with view to get good anti-bacterial and anti-fungal agents with less toxic and side effects. As per results screening it is clearly indicated that the compounds AP2A,AP2B,AP2C,AP2D and AP2E have shown significant antibacterial and anti-fungal activity

with the standard drugs. This is because of the presence of different groups like -CH3,-Cl,-Br at the 4th positions of phenyl nucleus which is attached to 1,3,4-thiadiazole molecule. From the above results one can establish that the synthesized substituted 1,3,4-thiadiazole can be rich source for the the exploitation. Therefore in search of new generation of the active compounds, it may be worthwhile to explore the possibility in this area by introducing different functional group or by cyclization as substitutions. Which may results into better pharmacological agents.

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