SYNTHESIS AND CHARACTERIZATION OF THIOUREA BASED THIADIAZOLIN DERIVATIVES

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT

FOR THE DEGREE OF MASTER OF SCIENCE (M.Sc) IN CHEMISTRY

SUBMITTED

BY

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DHAKA -1000, BANGLADESH.

December, 2016

Dedicated

To

My Mother

Bangladesh University of Engineering and Technology, Dhaka

Department of Chemistry

Certification of Thesis

A thesis on

SYNTHESIS AND CHARACTERIZATION OF THIOUREA BASED THIADIAZOLIN DERIVATIVES

BY

Md. Imrul Khalid

has been accepted as satisfactory in partial fulfillment of the requirements for the degree of Master of science (M.Sc) in Chemistry and certify that the student has demonstrated a satisfactory knowledge of the field covered by this thesis in an oral examination held on December 21, 2016.

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ACKNOWLEDGEMENT

It is a great pleasure to express my gratitude to my honorable supervisor Dr. Md. Abdur Rashid, Professor, Department of Chemistry, BUET, Dhaka to introduce me into research work. I am greatly indebted to him for his excellent supervision, inspiring guidance, enthusiastic encouragement, sagacious advice and affectionate surveillance throughout the execution of my research work.

I am highly pleased to express my best regards and sincere gratitude to Dr.**Md. Rafique Ullah ,** Professor and head , Department of Chemistry, BUET, Dhaka for his wise suggestion , sagacious advice and good wishes during this work in all respects.

I wish to express my gratitude and thanks to all other Professors and teachers of BUET for their kind help and cooperation during the entire period of my research work.

I am also like to thanks to all staff in the Department of Chemistry, BUET, Dhaka for their instant help throughout the entire period of my work.

I would like to thank the authority of BUET to give me an opportunity to purse higher studies for M.Sc Degree in this University and also give me financial support .

Finally, I would like to thanks my lab mates, my mother , relatives and friends for their inspirations, comments and suggestions during this research work.

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Chapter 3 RESULTS AND DISCUSSION

ABSTRACT

The aim of the research project is to synthesize “Thiourea based thiadiazolin derivatives” and the goal of this research was successfully performed by three different steps:

First: Thermal cyclization of thiosemicarbazide with substituted carboxylic acids to 5-phenyl 2-aminothiadiazole using catalytic amount of sulphuric acid.

Second: Various Schiff’s bases were synthesized from 5-phenyl -2-amino-1,3,4-thiadiazole and different substituted aromatic aldehydes.

Third: Addition of ammonium thiocyanate to Schiff’s bases afforded thioformimido thiadiazole derivatives.

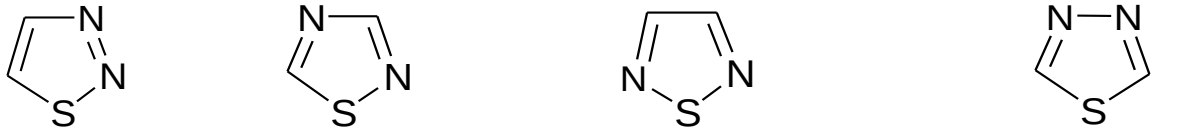
The structures of all the synthesized compounds were confirmed by spectral evidence.

Chapter 1

INTRODUCTION

INTRODUCTION

Thioureas also known as thiocarbamides, are an organo sulpher compounds with molecular formula $R_2SC(NH)_2$. It is structurally related to urea derivatives but the properties of urea derivatives differ significantly. Thiourea derivatives play an important role in many fields, of industrial chemistry [1]. Substituted thiourea are useful catalysts for organic synthesis, the phenomenon is called thioureaorgano catalysis [2]. Thiourea derivatives have also biological properties such as antioxidant, [3] antibacterial, [4,5] antimicrobial [6], ant HlV activity [7,8], anti malarial [9] and anticancer [10]. Some heterocyclic thiourea have been reported as new class of potent non-nucleoside inhibitors of human viruses type 1 reveres ariansscriptas (NNRTIS) [11,12].Thiourea based heterocyclic compounds were not only used for development the heterocyclic derivatives, but also argumentation of the application in pharmaceutical and chemical field. Till[25] to date various heterocyclic compounds had been synthesized and evaluated their biological significance. Firstly, Fischer introduced 1,3,4-thiadiazole in 1882, whereas Freund and Kuh[45] described the true nature of the ring. In addition, thiadiazole is a widespread and important five-member heterocyclic system which contains two nitrogen atoms and a sulfur atom. 1,2,3-Thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole are the isomer of thiadiazole.



1 1,2,3-Thiadiazole

2 1,2,4-Thiadiazole

3 1,2,5-Thiadiazole

4 1,3,4-Thiadiazole

Figure 1: Structural formulae of the isomers of thiadiazole.

1,3,4-Thiadiazole have been the most promised isomer than the other. Due to the inductive effect of sulfur atom of 1,3,4-thiadiazole ring. It shows very weak base property and possesses relatively high aromaticity [13-19].

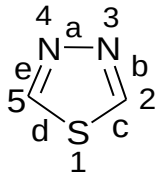


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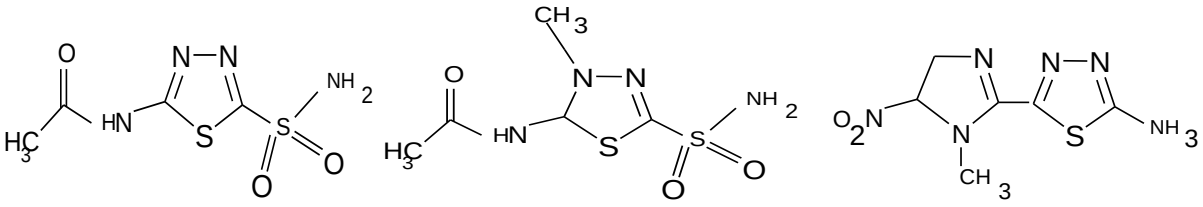
Figure 2: Numbering of the 1,3,4-thiadiazole ring system.

In addition, the nitrogen atoms of 1,3,4-thiadiazole ring is also shown to be very electron underprovided due to the electron-withdrawing effect and comparatively still toward electrophilic substitution, but susceptible to nucleophilic attack. Thus, possessing the substitution into the 2′ or a 5’ position of this ring and these substitutions involves highly activating reaction.

Till date many 1,3,4-thiadiazole nucleus containing drugs are available in the market such as acetazolamide, methazolamide, megazol and whereas 1,2,4-thiadiazole ring containing drug is the antibiotic cefozopran [20,21].



6 **7** **8**

Acetazolamide **Methazolamide** **Megazol**

Figure 3: Structural formula of 1,3,4-thiadiazole containing marketed drugs.

Among their isomers, particularly the 1,3,4-thiadiazoles possessed a broad spectrum of biological activities including antimicrobial [22] antituberculosis [23] antioxidant [24] anti-inflammatory [25] anticonvulsants [26] antidepressant and anxiolytic [27] antihypertensive [28] anticancer [29] and antifungal activity [30].

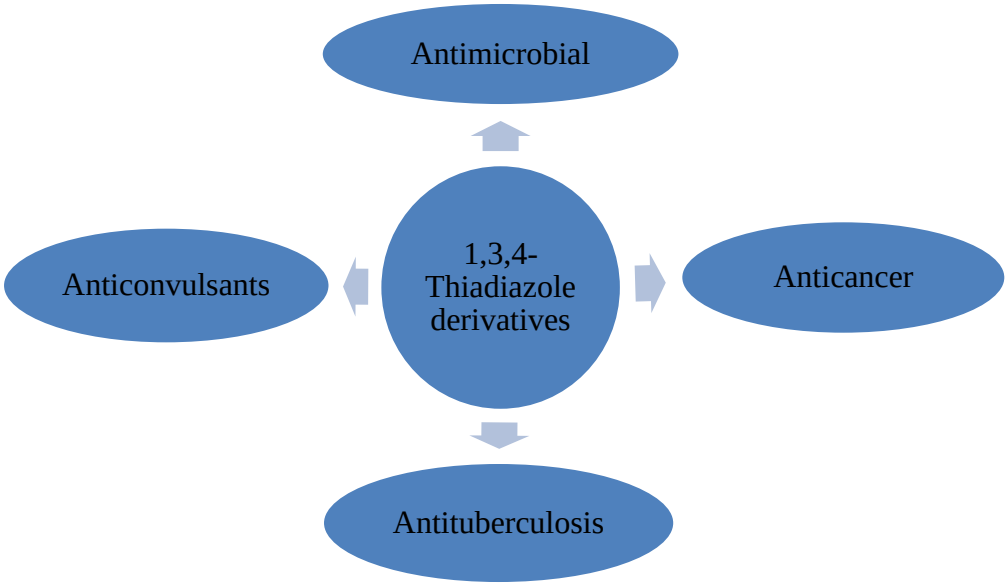
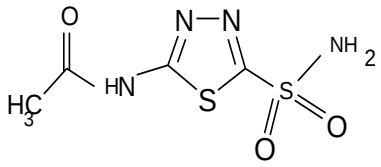


Figure 4: Biological activity of 1,3,4-thiadiazole derivatives

The 1,3,4-thiadiazole nucleus is one of the most important and well-known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and antitubercular agents. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant scaffolds.

1,3,4-Thiadazoles have become an important class of heterocycles and a great interest of researches because of their broad types of biological activity. Thiadiazole is a 5- membered ring system containing hydrogen-binding domain, sulfur atom, and two-electron donor nitrogen system that exhibit a wide variety of biological activity. They occur in four isomeric forms in the nature viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole; and 1,3,4-thiadiazole.

Many drugs containing 1,3,4-thiadiazole nucleus such as acetazolamide 1, methazolamide 2, megazol 3 are available in the market, although the only commercial 1,2,4-thiadiazole drug is the antibiotic cefozopram [31,32].



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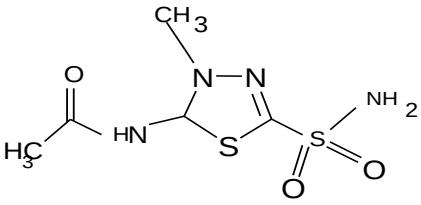

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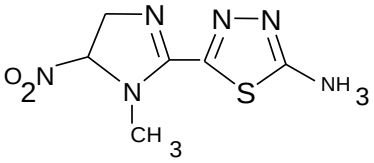

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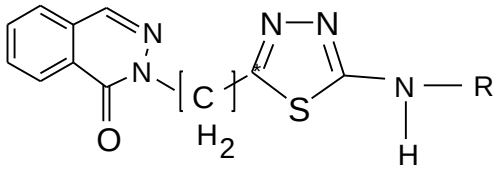
Antibacterial and Antifungal activity

1,3,4-Thiadiazole has shown a broad spectrum of activity against various pathogens, and extensive research has been performed on the synthesis of new potent antibacterial and antifungal agents. A new series of 2-[[1(2H)-phthalazinone- 2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives (**12**) have been evaluated in vitro antimicrobial activity against bacteria and fungal species. The results showed that the tested compounds possessed weak antibacterial and antifungal activity compared with standard drugs chloramphenicol and rifampicin[33]. A number of 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives (**13**) have been evaluated for antifungal activity against several clinical isolates of Candida albicans. The compounds with methyl, phenyl, 4-ethoxyphenyl, and halogenophenyl groups at C-2 of thiadiazole ring showed

higher antifungal activity [33].



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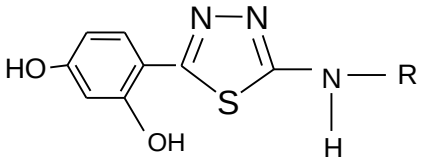

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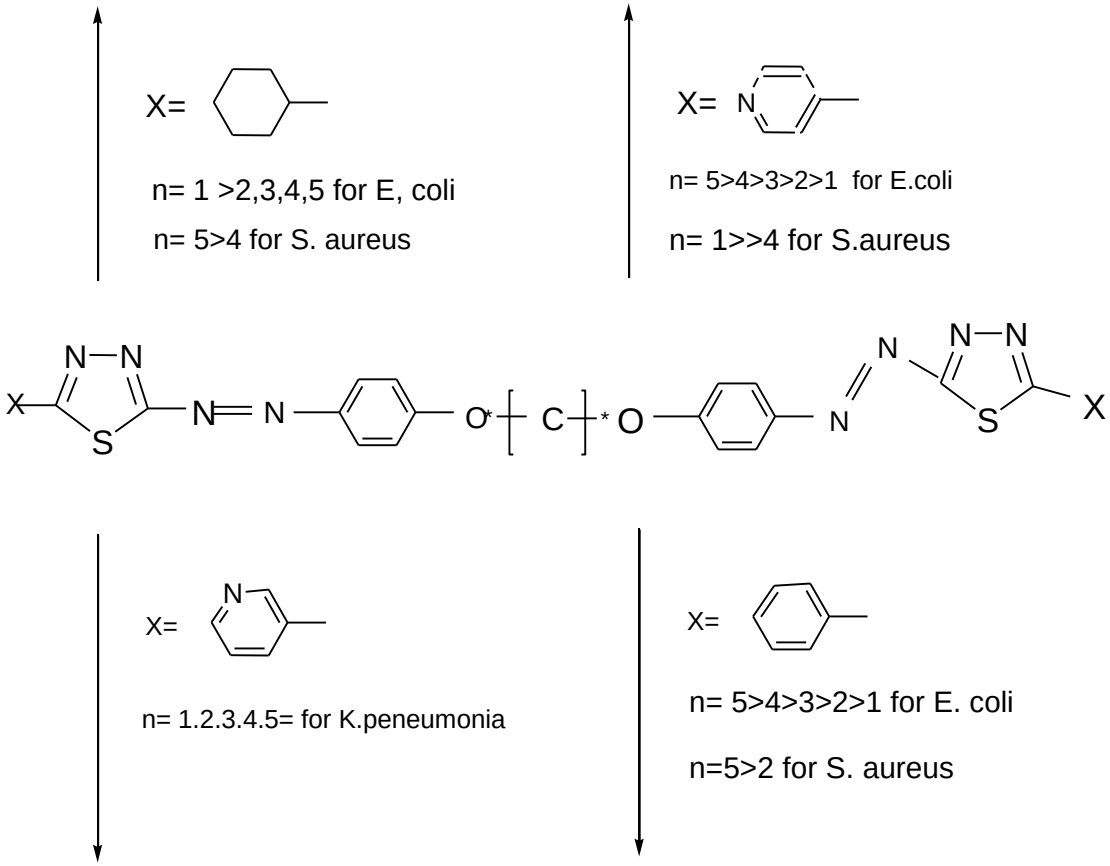
Tomi *et al*. [34] reported azo derivatives of aminothiadiazole derived from nicotinic and isonicotinic acid by cyclization, diazotization, and etherification, and evaluated them for in vitro antimicrobial activity against several microbes like: E. coli, K. pneumonia, P. aeruginosa and S. aureus. All the synthesized compounds showed good activity against E. coli. Compounds having 3-pyridyl group C-2 of thiadiazole were found to exhibit good activity against K. pneumonia (**Scheme 1**).

Active against E. coli & S. Aerous

Active against E. coli & S. Aerous

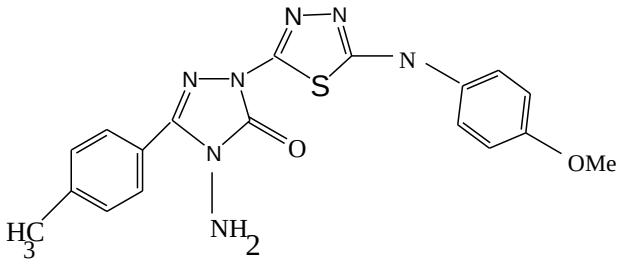


Active against K. pneumonia

Active against E. coli & S. Aerous

Scheme 1

Demirbas *et al.* [35] synthesized four different derivatives of 4-Amino-2-[(5-arylamino-4,5-dihydro-1,3,4-thiadiazol-2-yl) methyl]-5-(4-methylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-ones and investigated its antimicrobial activity. Thiadiazole (**14**) with 2-({5-[(4-methoxyphenyl) amino] group was found to possess highest antibacterial activity, whereas N-alkylation at C-5 of thiadiazole ring did not resulted in improved antibacterial activity. An attempt to prepare active compounds in the series of thiadiazolyl derivatives of antipyrine turned up unsuccessful. All the synthesized derivatives bared weak growth inhibitory activity against the tested Gram-positive bacteria (MIC 100 lg/mL) [36].



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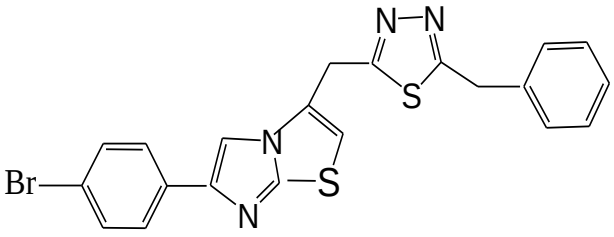
1,3,4-Thiadiazole and 2-azetidinones derivatives of 2-methyl-1H-benzimidazoles were tested for antibacterial, antifungal activity and some of the tested compounds had comparable activity against B. subtilis and E. coli with reference to amphicillin (25 lg/mL). Compounds having *o*-chloro, *o*-methyl, *p*-methoxy, *o*-hydroxy, and *p*-amino group in phenyl ring showed good antibacterial activity. Antifungal activity data indicated that some of the derivatives revealed a broad spectrum of activity against tested fungi; however, none of the derivatives showed a better spectrum of activity when compared to the reference drug [37].

A recently published article reported the antibacterial and antifungal activity of 1,3,4 thiadiazoles bearing imidazo [2,1-b]thiazole moiety (**15**) against S. aureus, P. aeruginosa, E. coli, and T. tonsurans with MIC of 64, 32, and 8lg/mL, respectively [39]. Applying QSAR study, it has been observed that positions-2 or position-3 of benzene attached with thiadiazole ring where as electron-donating and bulky group would be favorable for higher antifungal activity. On the basis of CoMFA findings, Liu et al. [38] designed a compound which was found to display a good antifungal activity (79.38%).



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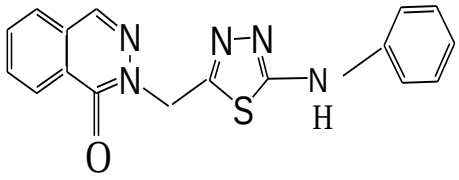
2-(*N*-acetyl-*N*-*m*-trifluoromethylphenylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazole was found to possess good activity against P. aeruginosa and equally active, comparable with the

standard drug penicillin [39]. A novel series of 2,5-disubstituted-1,3,4-thiadiazoles derivatives (**16**) have been synthesized and showed good inhibition against both Gram-(+) and Gram-(_) bacterial strains at 6.25 lg/mL concentration.The hydroxyalkenyl chain at 5th position and internal double bond in the long alkenyl substituent of synthesized thiadiazoles (**17**) were found to be more active against S. pyogenes, S. aureus, P. aeruginosa, K. pneumoniae, and E. coli [40].



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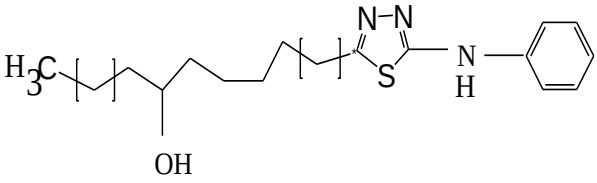

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Antibacterial activity is strongly dependent on the nature of the substituents at 5-arylamino-1,3,4-thiadiazoles in a series of 2-[[1(2H)-phthalazinone-2-yl]methyl/ethyl]-5-arylamino-1,3,4-thiadiazole derivatives. Unsubstituted compound showed 50% inhibition against B. subtilis with respect to ampicillin[41]. Compound having chloro group at para-position of

Arylsulfonylmethane moiety attached with thiadiazole ring exhibited higher antimicrobial activity [42].The antifungal activity of 1,2,4-triazolylmercaptomethyl- 1,3,4-thiadiazoles has been tested against M. gypseum (NCPF-580), M. canis, T. mentagrophytes, T. rubrum, and C. albicans. Of the five synthesized compounds screened against fungal strains, four compounds showed measurable activity against T. mentagrophytes [43].

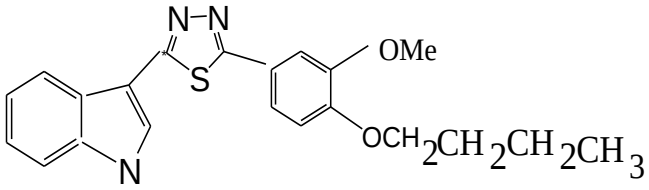
Ranjina et al. [44] synthesized a number of aminothiadiazole derivatives containing 4-pyridyl and oxothiazolidin moieties in the same molecules. All the compounds had good antimicrobial activity but the compounds having a nitro group were present at the -*m* and -*p* position of the aryl ring, respectively, possessed stronger antibacterial activity than others.

Camoutsis *et al*. [45] synthesized a series of N-{5-[2- (N-substituted sulfamoyl)-4,5-dimethoxy benzyl]-1,3,4-thiadiazole- 2-yl}-N-arylamines. All the newly sulfonamide- 1,2,4-thiadiazoles were assayed in vitro for their growth inhibitory activity against panel of selected Gram–positive bacteria, Gram-negative bacteria, and fungi and compared with reference drug ampicillin, streptomycin, bifonazole, and ketoconazole, respectively. The results of antimicrobial screening clearly indicated that the nature of substituents and their position on 1,3,4-thiadiazole nucleus

affected the in vitro activity. SAR of the compounds revealed that pyrrolidine substituted compounds were found to be more potent than piperidine-, methylpiperazine-, and dimethylamino- containing compounds. Thus, it can be said that introduction of -CF3 moiety and chloro atom in the para position of the benzene ring of pyrrolidine substituted compound is an essential part for improving antibacterial activity.

Anticancer activity

Kumar *et al*. [46] reported the synthesis of 5-(3-indolyl)- 1,3,4-thiadiazoles and evaluated for anticancer activity. Primary screening was performed at a concentration ranging from 100 nM to 1 mM. Change in cell number and cell morphology in 96-well plates was observed at 24 and 48 h had been detected. Compounds that exhibited toxicity to cancer cell lines but not to normal cells were selected for the secondary confirmation assays. For secondary screening, the same concentration which was previously used in the primary screening was used and compounds were screened in triplicate. As a result, eight compounds were identified as potent agents for inducing cytoselective toxicity. It was found that substitution on C-2 position of the 1,3,4-thiadiazole ring plays an important role in imparting the cytotoxic activity to the compound. Replacement of phenyl ring at C-2 position with benzyl, 4-(dimethylamino)phenyl, 3,4 dimethoxyphenyl and 4-benzyloxy group enhanced the antiproliferative activity, while replacement of the phenyl group with p-chlorophenyl and introduction of third methoxy group reduced the biological activity. Compound 2-(4-(Benzyloxy)-5-(5-bromo-3-indolyl)-3-methoxyphenyl)-1,3,4-thiadiazole (**18**) with 4-benzyloxy- 3-methoxyphenyl at C-2 position and 5-bromoindole at C-5 position was found to be the most potent compound of the series. Compound (4-hydroxyphenyl)[5-(2,6-dichloro)- 2-thioxo-1,3,4-thiadiazol-3-yl]methanone showed broad spectrum of growth inhibition activity against human tumor cells and remarkable cytotoxic activity on nonsmall lung cancer (HOP 92) having log GI50 value at -6.49, colon cancer (HCC-2998) at GI50 value _5.31 and significant cytotoxic activity on prostate cancer (PC-3) having GI50 value _5.48. SAR study revealed that electron withdrawing group at position C-5 of thiadiazol was favorable for activity [47].



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New derivatives of 2-arylamino-5-aryl-1,3,4-thiadiazoles were synthesized by refluxing aryl aldehydes, hydrazine hydrate, and aryl isothiocyanates in methanol followed by oxidative cyclization with ferric ammonium sulfate. Study of in vitro cytotoxic activity revealed a cytotoxic effect of individual compounds on cancer cells of prostate (PC3, DU145, and LnCaP), breast (MCF7 and MDA-MB-231), and pancrease (PaCa2). The SAR study showed that the 3,4,5-$(OCH_3)3C6H_2$ at C-5 position was responsible for binding to the Colchicine siteon tubulin and found to be favorable for activity. Further variation of C-2 arylamino group was associated with lesser degree of effect on the activity of 1,3,4-thiadiazoles. Most of the synthesized compounds were moderate in activity and compound displayed a greater potency toward pancreatic (PaCa2) cancer cell lines (IC50 = 4.3 lM) [48]. Marganakop et al. [49] synthesized quinolines derivatized with 1,3,4-thiadiazole via cyclization of quinoline thiosemicarbazones in a single step and investigated for their primary cytotoxic activity against cervical cancer cell lines (Hela). Compounds with methoxy at C- 6,7,8 of quinoline showed the potent anticancer activity and the cell lyses occurred only at 10 lg/mL. Zheng *et al*. [50] prepared several N1-acetylamino-(5-alkyl/ aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives. These compounds were evaluated for their anticancer activity onA-549 (human lung cancer cell), Bcap-37 (human breast cancer cell) by MTT assay. Compound with electron with-drawing group attached to benzene ring was found to have activity against tested cell lines and possessed more potent antitumor inhibitory activity than 5-fluorouracil. Compound (E,E)-2,5-bis[4-(3-dimethyl-aminopropoxy)styryl]- 1,3,4-thiadiazole was found to be the most potent one by the MTT assay against A549, PC-3, and HA22T [51]. A number of N-substituted 2-amino-5-(2,4 dihydroxyphenyl)- 1,3,4-thiadiazole derivatives were investigated as antiproliferative agent, their in vitro cytotoxicity against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) suggested their potential as novel anticancer agents. Compound 2-(2,4-dichlorophenylamino)- 5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole , with ID50 two times lower

(SW707, T47D) than that of cisplatin displayed the highest cytotoxicty. It was noticed that the compounds with electron donating groups at C-terminal of the phenyl ring did not increased its cytoselective toxicity and the compounds with electron withdrawing groups (Cl, F) resulted in an increased activity by inducing cell death [52]. Compound 2-(4-fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole inhibited proliferation of tumor cells derived from cancers of nervous system (medulloblastoma/rhabdosarcoma, neuroblastoma, and glioma) and peripheral cancers including colon adenocarcinoma and lung carcinoma [53]. Matysiak et al. [54] examined the effect of various substitution at 5-position of 2-(2,4 dihydroxy-phenyl)-1,3,4-thiadiazoles on antiproliferative activity against different human tumor cell lines. 2-(2,4-Dihydroxyphenyl)-5-(4-methoxybenzyloxy)-1,3,4-thiadiazole showed ID50 of 1.1 lg/mL against HCV29T bladder cancer cell line and found to be significantly lower (T47D) than that of cisplatin, used as the reference compound. In a series of chiral 2,5- disubstituted 1,3,4-thiadiazoles possessing c-butenolide moiety, compound 50 was screened against Hela cell lines by MTT assay and exhibited IC50 of 0.9 lM [55].

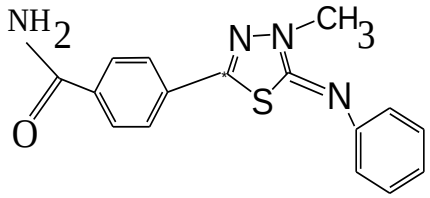
Focal adhesion kinase (FAK) is a 125 kDa protein that was involved in multiple cellular functions like cell proliferation, survival, motility, invasion, metastasis, and angiogenesis.

The inhibition of FAK plays an important role in cancer therapy through decreased cellular viability, growth inhibition, or apoptosis. Recently, FAK was proposed to be a new potential therapeutic target in cancer. Sun *et al*.[56] had designed a series of novel 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan and evaluated their activity as FAK inhibitors. The results of the inhibitory activity of the designed compounds showed that compound 51 possessed high potency against FAK (EC50 = 10.79 lM). EC50 values of 14.21–32.45 lg/mL against HEPG2, HELA, SW1116 and BGC823 cell lines. The SAR study suggested that substitution with different acids led to different antitumor activity, and the potency order was phenylpropinic acid >phenylacetic acid >benzoic acid. Compounds with substituted Cl group on benzene ring showed better antitumor activity than substitution with Br group. Replacement of -Cl with $–CH_3$ group, however, led to decrease in cytotoxic activity against all cell lines [57].

Thiadiazoles as miscellaneous agents

Vergne *et al*. [58] discussed the synthesis and SAR studies of a series of novel small thiadiazoles as inhibitors of PDE7. Out of the synthesized compounds, derivatives with 4-CONH2 on

benzene ring (**19**), 4-aminoquinazoline and 2-methyl-4-aminoquinazoline on C-5 of thiadiazole ring exhibited high PDE4 inhibitory activity with an IC50 value of 0.061, 0.027, and 0.0039 lM, respectively. From SAR studies, they concluded that the 4-aminoquinazoline derivatives along with hydrophobic steric bulk attached with nitrogen of C-2 of thiadiazole showed an increase in activity because of its structural similarity with the adenine part of cAMP. Replacement of the cyclohexyl moiety with smaller ring was not as selective and found to be detrimental to the enzymatic activity.



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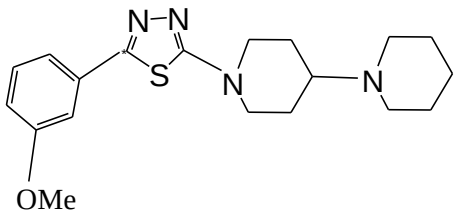
Introduction of an OH group on 3rd position of cyclohexyl group of represented IC50 of 0.088 nM toward PDE7. Modification of 4-CONH2 group with sulfonamide significantly improved the pharmacokinetic profile and binding affinity for PDE7 [59].

De *et al*. [60] reported novel small molecules thiadiazole derivatives as c-Jun N-terminal kinase inhibitors. On the basis of a lead structure from high throughput screening, they identified that substitution on 2nd-position with either 2-methoxyethyl group, sec-butyl group or n-propyl group improved the pepJIP1 displacement (DELFIA) and the kinase activity (LANTHA) assays. Out of the synthesized compounds, an IC50 of 4.8 lM in the kinase assay substrate and it displaced pepJIP1 with an IC50 of 158 nM. Modification on 4-(2,3 dihydrobenzo[b][1,4]dioxin-6-yl)-5-(5-nitrothiazol-2-ylthio)-4H-1,2,4-triazol-3-ol which showed competitive inhibition of the interactions between JNK and pepJIP1 with an IC50 of 280 nM resulted the discovery of which could bind at the JIP site with the nitrothiazol group crossing the ridge close to residues Arg127 and Cys163 of enzyme side with an IC50 of 239 nM [61].

Xiao *et al*. [62] discovered the 2-piperidinopiperidine-5-arylthiadiazoles as H_3 antagonists which lead to increase histamine levels by blocking the histaminergic neurons irreversibly

and may be useful in treating obesity, diabetes as well as other CNS disorders such as cognitive disorders like Alzheimer's and Parkinson's disease. SAR investigations revealed that o, m and p

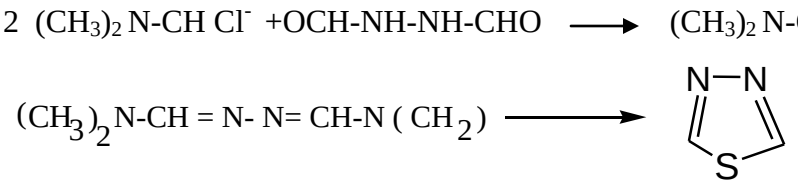
substituent such as polar groups OMe, CN, and $COCH_3$ on phenyl ring increases the H_3 receptor antagonistic activity. Further replacement of phenyl ring with 2-pyridyl was found to be favorable, while pyrimidine and pyrazole offered less activity. Compound(**20**) with 3-methoxy group at 2-pyridyl ring substituted on C-5 of thiadiazole was found to be the most active.



20

Thiadiazole contains the five-membered diunsaturated ring structure having molecular structure formula C2H3N3S containing a two carbon atom, three hydrogen, three nitrogen and one sulphur. Thiadiazole and its derivatives are used for biological activities such as antiviral, antibacterial, antifungal and antitubercular. It is a clear to yellowish liquid with a pyridine like odor. It is soluble in alcohol and ether and slightly soluble in water. It is parent material for numerous of chemical compounds including sulfur drugs, biocides, fungicides, dyes, chemical reaction accelerators. Thiadiazoles carrying mercapto, hydroxyl and amino substituent's can exist in many tautomeric forms and this property is being intensively studied using modern instrumental methods. Two azo-derivatives have been prepared containing the 1, 3, 4-thiadiazole system starting from the heterocyclic 2-amino-5-mercapto-1, 3, 4- thiadiazole system. These two azo compounds form complexes in a powder form with aluminum salts. The synthesis of the azo-derivatives gave an average yield of 50%. Heterocyclic with the molecular formula $C_2H_3S_3N_2$ present various isomers, among which may be cited bismuthiol, xanthan and perthiocyanic acid, which have many industrial applications and surprising chemical properties among which are included their capacity of forming complexes with metals. One derivative which merits special mention is 2-amino-5- mercapto-1, 3, 4-thiodiazole due to its properties in forming well-known azo dyes. These compounds will be used to evaluate their potential for coating metal surfaces in processes of corrosion inhibition. Thiadiazole and its derivatives are used for biological activities such as antiviral, antibacterial, antifungal and antitubercular 10. The antileukemic action and host toxicity of the thiadiazoles were blocked by administration of nicotinamide. 1, 3, 4 -Thiadiazole are diversified biocidal activities probably by virtue of a toxophoric – N=C-S-

Grouping. A large number of 4-thiazolidinones have been reported to be antifungal, antibacterial and antileukemic properties. These observations prompted us to synthesis the title compound with a presumption that incorporation thiadizole and thiazolidinones wound produce new compound with significant fungicidal properties. A series of 2-aryl-5-hydrizino-1,3,4-thiadiazole exemplified by the structure designed as analogue of the known vasodilator hydrazine and pyridazinyl hydrazine. Subsequent evaluation of this series showed that some analogue possessed both antihypertensive activity and anticonvulsant activity. Furthermore it found that particular substitution in the 2-position of aromatic ring to produced compound reduced with antihypertensive activity with desirable anticonvulsant activity. It was found that methylation of the α -nitrogen of the hydrazine group in the *o*-tolyl series decrease vasodilator activity without concurrent decrease in anticonvulsant activity Thus a combination of the preferred aromatic substituted units in the 2-position coupled with various alkyl and aryl substitution on the hydrazine moiety was a objective in this work. 1,3,4-thiadiazole confirmed on the corresponding thiadiazole hydrazine the best combination of potency and lack of toxicity. 1,3,4- thiadiazole was started first synthesized by Goerdereler, ohm, and Tegtmeyer who used a four stage process that started from thiosemicarbazide. Jensen and Pedersen obtained the heterocycle from hydrazine and potassium dithiformate.The synthesis which quite large number of thiadiazole can be obtained starts from N,N-dimethylormamide azine dihydrochloide which is found to good yield from dimethylfrmamidoyl and N,N-dimethyhydazine and hydrazine hydrochloride methyl azine. Sodium ethoxide converted into compound into the free dimethylazine this react with H_2S in methanol in the presence of sodium methoxide, the hydrochloride give products.



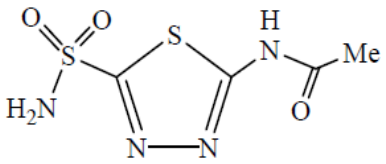
SCHIFF BASES

Compounds containing an azomethine group (-CH=N-), known as Schiff bases are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Schiff bases have number of applications viz., preparative use, identification, detection and determination of aldehydes or ketones, purification

of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions. They also form basic units in certain dyes. Schiff bases are generally bi-or tri- dentate ligands capable of forming very stable complexes with transition metals. Some are used as liquid crystals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base.

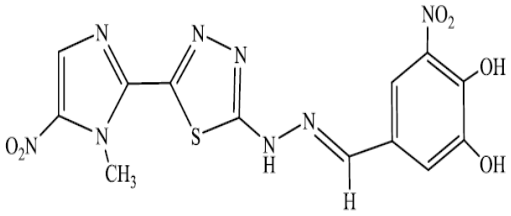
Biological activity of thiadiazole derivatives

Condensed and non-condensed 1,3,4-thiadiazoles are a class of heterocyclic compounds having an important biological activity. 2,5-Disubstituted-1,3,4-thiadiazole derivatives are known to exhibit antibacterial 199-202, antifungal 203,204, antipsychotic 205 and anti-tubercular 206,207 beside it was the best documented as anti-inflammatory 208,209 , analgesic 210, anticonvulsant 211 , antitumoral 212-214 and antidepressant activity 190,215. Also, 2,5-disubstituted-1,3,4-thiadiazole derivatives used as effective, cheap, and safe drugs for the treatment of leishmaniasis because of its in *vitro* leishmanicidal activity 167,216.2-Amino-1,3,4-thiadiazole derivatives shows anticonvulsant 217,218, analgesic 219, anti-inflammatory 220,221, antiviral 222 , antiprotozoal 44, antimicrobial 223,224 activities.Recently, condensed and non-condensed thiadiazole derivatives have proved to possess biological activity as highly anticancer 225-227, antimycotic 228, antisecretory 156, anti-trypanosomal 229, antibacterial 230 and anticonvulsant 231 activities, cardiotonic 232, diuretic 233 and Alzheimer diseases 234.Also, thiadiazole derivatives have been used as antiviral medicants against herpes virus cytomegalovirus (CMV) 235, as medicants for inflammatory disease such as hypersensivity reactions, asthma, rheumatoid, arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications 236 and for many other medical applications.One of the best known drugs based on the thiadiazole molecule is acetazolamide(**21)**, also called acetazola which is a carbonic anhydrase inhibitor. Its indication and usage are many including glaucoma, epilepsy and congestive cardiac failure. Although it is an old drug, attempts to improve its efficiency and decrease its side effects continue.



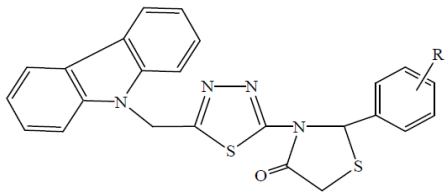
21

3,4-Dihydroxy-5-nitrobenzaldehyde [5-(1-methyl-5-nitro-1*H*-imidazol-2-yl)-1,3,4-thiadiazole-2-yl]hyrazone(**22)**, which is known as brazilizone A, showed potent in vitro trypanocidal profile. Experimental IC50 values for such compound correlate with the predicted by 3D-QSAR CoMFA model 44.



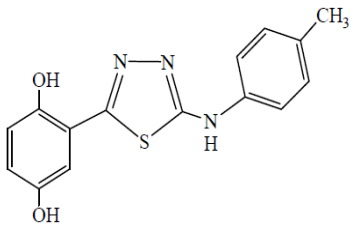
22

9-[4'-{Substitutedphenyl}-2-oxo-thiazolidin-1"-yl-1',3',4'-thiadiazol-5'-yl]methylene carbazoles (**23)**showed good antipsychotic and anticonvulsant response when compared to the reference drug, Chlorpromazine (CPZ) 205.



23

1,3,4-Thiadiazole derivatives (**24**, **25)**have been shown to possess a promising antileishmanial effect in *vitro*. The high leishmancidal activity of such compounds led for the development of effective therapeutic agents.



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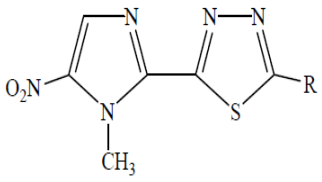
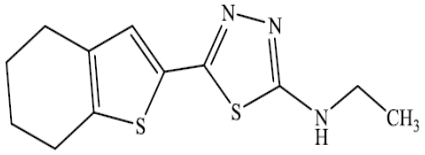


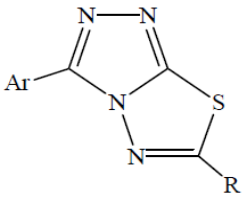
25

N-Ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazol-2-amine(**26)** was evaluated for cytotoxicity and was found to possess high cytotoxicity in vitro against thymocytes with IC50 value of 5.2 x 10-6 µ M 239.



26

3,6-Disubstituted[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives(**27)** and (**28)** were found to have dual functional properties (antiinflammatory, analgesic and antimicrobial) and represent a promising class of compounds with interesting pharmacological profile .



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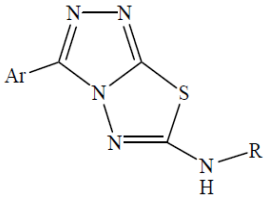
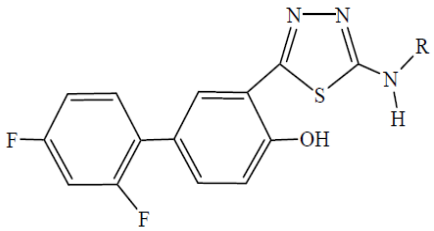


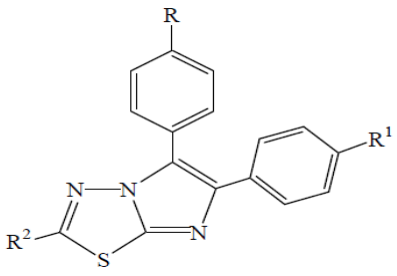
28

The anti-inflammatory activity of thiadiazole derivatives (**29)** was evaluated and compared with the reference drug diflunisal. Most of the tested compounds showed higher anti-inflammatory (23.85 to 73.03% inhibition) than the reference drug (24.16% inhibition).



29

Imidazo[2,1-b][1,3,4]thiadiazole derivatives (**30)**showed excellent in *vitro* cyclooxygenase inhibitory activity against COX-1 and COX-2 enzymes 234.



30

Further developments

Novel substituted 1,3,4-thiadiazoles were synthesized under both sonication and classical conditions. Generally, improvements in rates and yield of reactions were observed when reactions were carried out under sonication compared with classical condition.

Diabetes is a group of diseases characterized by high blood glucose level. When a person has diabetes, the body either does not produce enough insulin or is unable to use its own insulin effectively. Glucose builds up in the blood and causes a condition that, if not controlled,

can lead to serious health complications and even death. The risk of death for a person with diabetes is twice the risk of a person of similar age who does not have diabetes. Diabetes mellitus is a heterogeneous clinical disorder with numerous causes. Two main classifications of diabetes mellitus exist, idiopathic and secondary. Idiopathic diabetes is divided into two main types: Insulin dependent and Non-insulin dependent. Non insulin dependent diabetes mellitus (NIDDM or type 2 diabetes) is characterized by milder hyperglycemia and rarely leads to ketoacidosis. It leads to nephropathy, neuropathy, and retinopathy. Diabetes mellitus, long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century. The incidence of the disease currently is estimated to reach 210 million by the year 2010 and 300 million by the year 2025 [63]. Most cases will be of type 2 diabetes, which is strongly associated with a sedentary life style and obesity. Nowadays diabetes is becoming a leading cause of death in most nations. 1,3,4-thiadiazole and its derivatives

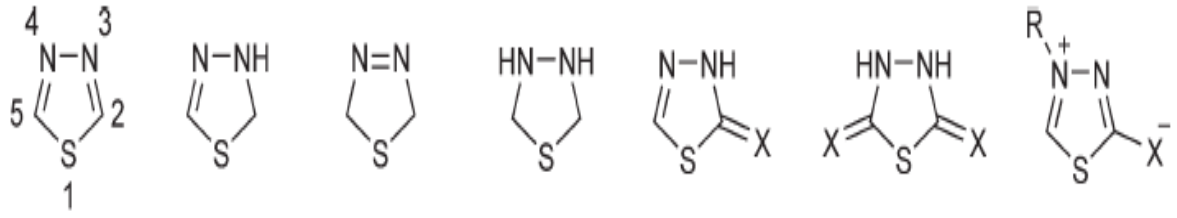
possesses wide range of therapeutic activities like activities like antimicrobial [64], antifungal, diuretics, antiulcer [65], antimycobacterial [66], antioxidant/radio-protective [67], anti inflammatory, anticonvulsant, antidepressant, anticancer, anti-leshmanial [68-69], carbonic anhydrase inhibitors [70] and antidiabetic [71]. Due to presently known limitations of liver toxicity in the use of thiazolidinediones, it is necessary to find new heterocyclic compounds with equivalent potency as that of thiazolidinedione. Thiadiazole compounds are known to bind peroxisome proliferator activating receptor (PPAR) effectively [72]. Therefore present study involves design of thiadiazole compounds on the basis of docking studies on peroxisome proliferator activating receptor (PPAR) effectively and to find important binding residues. The knowledge of binding residues would help in design of novelthiadiazole molecules as antidiabetic agents.

Designing of new molecules was done with help of docking. Virtual screening has emerged as a reliable, cost-effective and time-saving technique for the discovery of lead compounds. The virtual screening approach for docking small molecules into a known protein structure is a powerful tool for drug design that has become an integral part of the drug discovery process in recent years. Theoretically the application of virtual screening is constrained only by the chemical compounds features that can be calculated and the relation between these features and the targeted protein can be established. Practical implementation of virtual screening application requires some considerations. If the site geometry is not known, as is often the case, the design should be based on other ligand molecules that bind well to the site. If the molecules are rigid, the problem becomes one of identifying the substructures or active groups that contribute to the fit. If the site geometry is known, molecules with good affinity for the site can be built by joining the groups with alternative molecular scaffolding. In present study, thiadiazole scaffold was considered as replacement to thiazolidinedione while considering its expected interaction with PPARgamma receptor as per the previous literature reports [73]. Thiazolidinediones belongs to a chemical class that has a different pharmacological action than the sulfonylureas, biguanides, or the (alpha)-glucosidase inhibitors. Synthesized thiadiazole compounds were tested for alpha-glucosidase inhibition to verify whether these compounds work by mechanism similar to thiazolidinediones or else. In vivo study was carried out on alloxan induced diabetes rat model for all the synthesized molecules using glibenclamide, a second generation sulphonylurea as standard since it was used as a reference standard compound in the study of reference analogous

compounds [74,75]. Molecular docking studies were performed by using Glide v5.6 (Schrodinger, LLC) [76]. The X-ray crystal of peroxisome proliferator-activated receptor gamma (PPARgamma) in complex with rosiglitazone (PDB id. 1FM6) was obtained from the RCSB protein Data Bank (PDB) and utilized in order to get the detailed insights of ligand-protein structure in this study.

Protein structure was added with hydrogens and then only hydrogens were energetically optimized. In case of docking poses showing high score, some manual adjustment were done to remove large steric hindrance and final complex structures were subjected to energy minimization using OPLS force field in Schrodinger software. During the energy minimization procedure firstly whole protein structure was fixed and secondly that amino acid residues within 3.5 A from the each ligand were relaxed. Rosiglitazone was removed from the complex and the reported thiadiazole compounds were docked in PPARgamma protein and their binding interaction was validated with previously reported binding residues. These binding residues were used as reference guide. Several thiadiazole compounds have been reported for their antidiabetic effect by acting as agonist at PPAR gamma [77,78]. Docking was performed selectively on reported thiadiazole analogues for which antidiabetic activity is known to be potent and comparable to standard.

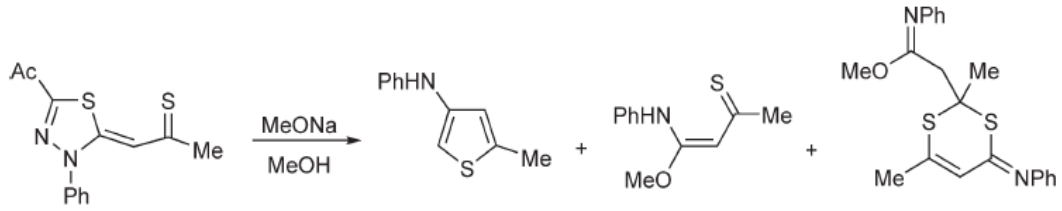
A major review which covers the synthetic chemistry of the ring system up to 2002 has also appeared [79]. Since 1991 advances in the chemistry of 1,3,4-thiadiazole have been annually reviewed in Progress in Heterocyclic Chemistry [80]. The numbering of the 1,3,4-thiadiazole ring is given below. The present chapter is intended to update the previous work on the aromatic 1,3,4-thiadiazole (**31**), the nonaromatic _2-thiadiazolines (**32**), _3-thiadiazolines(**33**), the thiadiazolidines (**34**), the tautomeric forms (**35**) and (**36**), and the mesoionic systems (**37**). Reference is made to earlier chapters of CHEC(1984) and CHEC-II(1996) where appropriate.



31 **32** **33** **34** **35** **36** **37**

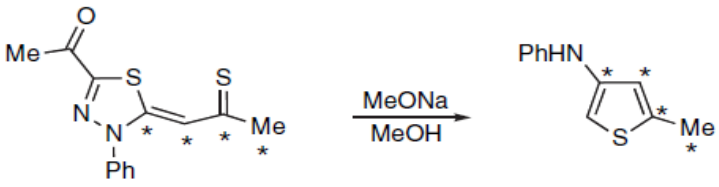
Reactivity of Thiadiazolines

The base-induced conversion of the (Z)-5-acetyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazole 40 into 3-(N-anilino)-5-methylthiophene 41 has been reported [81]. When a solution of the thiadiazole(**38)** was heated with sodium methoxide in methanol under reflux, 3-(N-anilino)-5-methylthiophene (**39**) was obtained in 25% isolated yield together with two other minor products (**40**) and (**41**).

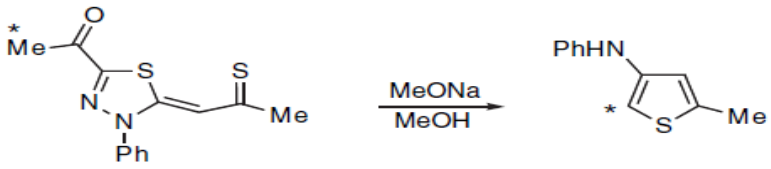


38 **39** **40** **41**

13C-labeled experiments were undertaken to establish the atom source of the thiophene ring. The methyl group and the C-3, C-4, and C-5 carbon atoms of the ring come from the (thioacyl)methylene system of **(42)**, whereas C-2 comes from the methyl group of the 5-acetyl substituent.

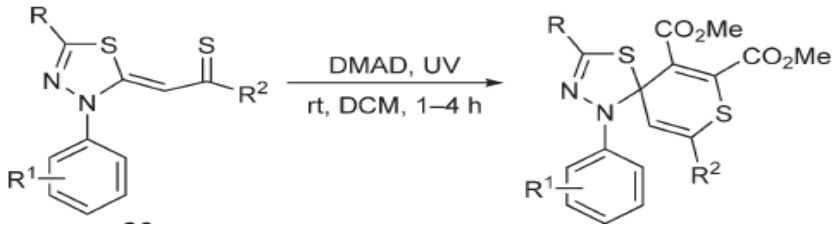


42 **43**



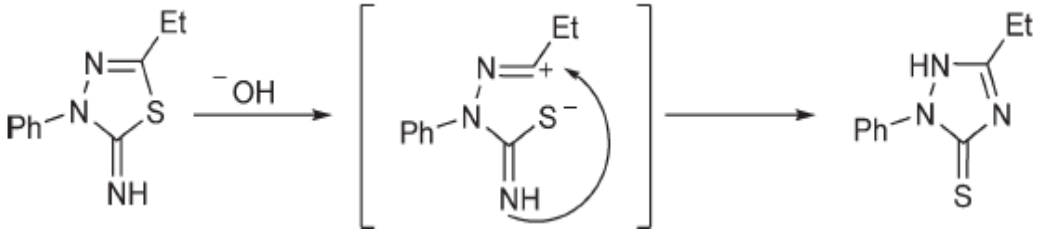
44 **45**

The cycloaddition reactions of [(thioacyl)methylene]thiadiazoles(**46**) with dimethyl acetylenedicarboxylate (DMAD) under UV irradiation at room temperature gave the spiro[3H-1,3,4-thiadiazoline-2,49-4H-thiopyrans] (**47**) in 50–60% yields [82].



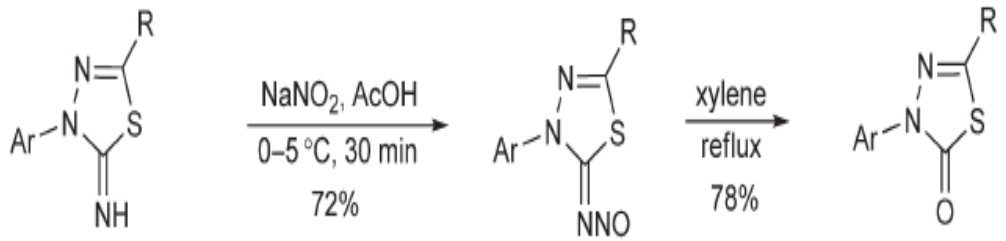
46 **47**

Heating of a solution of 5-ethyl-3-phenyl-1,3,4-thiadiazol-2(3H)-imine (**48**) in aq. NaOH to 80 _C for 5 h gave the 5-ethyl-2,3-dihydro-2-phenyl-1H-1,2,4-triazole-3-thione (**49**) via Dimroth rearrangement [83]. Nucleophilic attack of the hydroxide on the electrophilic C-5 resulted in ring opening and, after rotation around the C(2)–N(3) bond and subsequent recyclization, triazole thione formed.



48 **49**

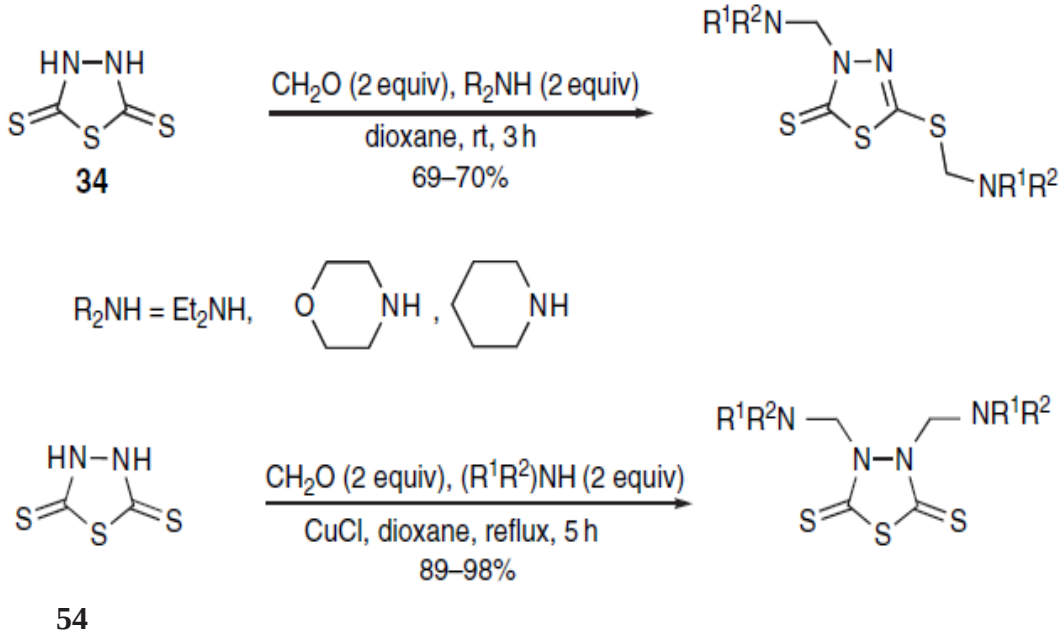
Thiadiazolin-2-imines can also be converted to thiadiazolin-2-ones in two steps [84, 85, 86]. The nitrosation of the thiadiazol-2-imines (**50**) with saturated nitrite in acetic acid at 0–5 _C gave the N-nitroso-1,3,4-thiadiazol-2(3H)imines (**51**) in 72% yield. Thermolysis of the latter in refluxing xylene gave the 1,3,4- thiadiazolin-2-one (**52**) in 78% yield [87].



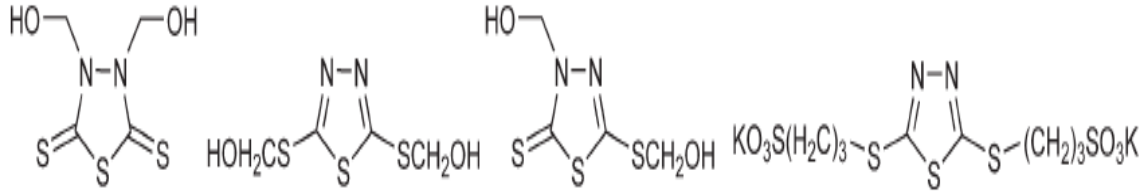
50 **51** **52**

Reactivity of Thiadiazolidines

The reaction of 2,5-dimercapto-1,3,4-thiadiazolidine (**53**) with dialkylamines under Mannich reaction conditions gave N,S-aminomethylated thiadiazoles in 69–70% yields [88]. With urea, thiourea, semicarbizide, or thiosemicarbazide, thiadiazolidine (**54**) gave N,N-aminomethylated thiadiazoles in 89–98% yields .



Depending on the pH, condensation of thiadiazolidine with formaldehyde leads to an N,N-, N,S-, or S,Sderivative. At neutral pH the 3,4-bis(hydroxymethyl)-1,3,4-thiadiazol-2,5-dithione (**55**) was formed in 87% yield while subsequent basification of the reaction mixture to pH 8.0 gave both N,N- and S,S-thiadiazoles (**56**) and (**57**) in 76% and 24% yield, respectively. In alkaline media, with subsequent acidification to pH 3.0, a mixture of N,N-, N,S-, and S,Sthiadiazole derivatives (**58**) (60%), 91 (24%), and 92 (16%) was formed. Reaction of thiadiazolidine 34 with 1,3- propanesulfone in an alkaline medium gave the dipotassium S,S-derivative of thiadiazole (61) (83%).



55 **56** **57** **58**

Synthesis of 2-Amino-5-mercapto-1,3,4-thiadiazole, Ayad S. Hameed, Nadia A . Saleh and Amar H. AlDujaily [89].Synthesis of 2-Amino-1,3,4-thiadiazole, Hussein.H.F and Khalid F. Ali. Iraq [90].

AIMS OF THE PROJECT

Thiourea based synthetic organic compounds display a broad spectrum application in the field of synthetic organic chemistry and also immence importance in medicinal chemistry. Recently, some literature reported the potential anti-microbial agents of certain thiourea derivatives. Drugs which are based on thiourea, have also been used clinically to treat patient of tuberculosis and thyroid conditions. Very recently some researcher reported that the carbonyl thiourea derivatives is the causative agent for sight-threating diseases, *Acanthamoeba keratitis*. An effective medical therapy for treating the infection is currently not available. Several antiseptics such as chlorohexidine gluconate and polyhexamethylene biguanide have been used to lessen the symptoms, but they are not specifically designed to treat the ocular diseases. The side effects are frequently reported.Since synthetic thiourea based organic compounds are being widely designed nowadays in parallel with the development of combinatorial chemistry and compound libraries, they could be exploited for the development of new drugs. Thiourea which is one of the earliest synthetic organic compound has been globally used directly and indirectly due to its ready availability. This factor has attracted researchers to evaluate thiourea based compounds for their safety point of view and potential medical properties.

Therefore, it has drawn a great interest to synthesize thiourea based thiadiazolin derivatives which might have potential biological activity such as antifungal and antibacterial properties.

The proposed research project is undertaken with the following objectives

(a) To prepare the unavailable starting materials from the available chemicals.
(b) To optimize the reaction condition for the different steps to get target compounds.
(c) To synthesize the various thiourea based thiadiazolin derivatives.
(d) To carry out the different physical, chemical and spectroscopic methods to establish the structure of the synthesized products.
(e) A facile synthetic route will be established from the available materials.
(f) Biological activities will be tested on the synthesized compound.

Chapter 2

EXPERIMENTAL

2.0 a) Purification of solvents and chemicals

All the commercial grade solvents such as n-hexane, ethyl acetate, diethyl ether, acetone, ethanol, methanol and tetrahydrofurane were purified by distillation. All the liquid samples such as benzaldehyde, *p*-hydroxy benzaldehyde, anisaldehyde , p-choloro benzaldehyde were also purified by distillation. The solid samples were purified by recrystallizing in different solvents.

b) Determination of melting points

Melting points of different synthesized compounds were determined on Gallenkamp melting point apparatus are uncorrected.

c) Infra-red (IR) spectra

The infra-red spectra were recorded on KBr pellet for films with a Shimadzu FTIR spectrophotometer from the department of chemistry, BUET, Dhaka, Bangladesh.

d) Nuclear Magnetic Resonance (NMR) spectra

The ^{1}H NMR (400MHz) and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO) and ($CDCl_3$) with a Bruker BPX- 400 spectrophotometer using tetramethylsilane (TMS) as internal standard at the Wazed Miah Science Research Center - Jahangirnagar University, Saver, Dhaka, Bangladesh.

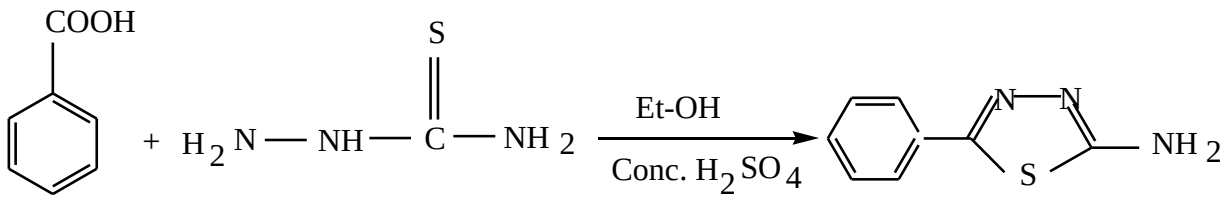
e) Drying

All the synthesized compounds were dried over anhydrous silica gel under vacuum desiccator after and before recrystallization.

f) Evaporation

The solvents were evaporated under reduced pressure in Buchi rotatory evaporator (West Germany) with a bath temperature below 40° C.

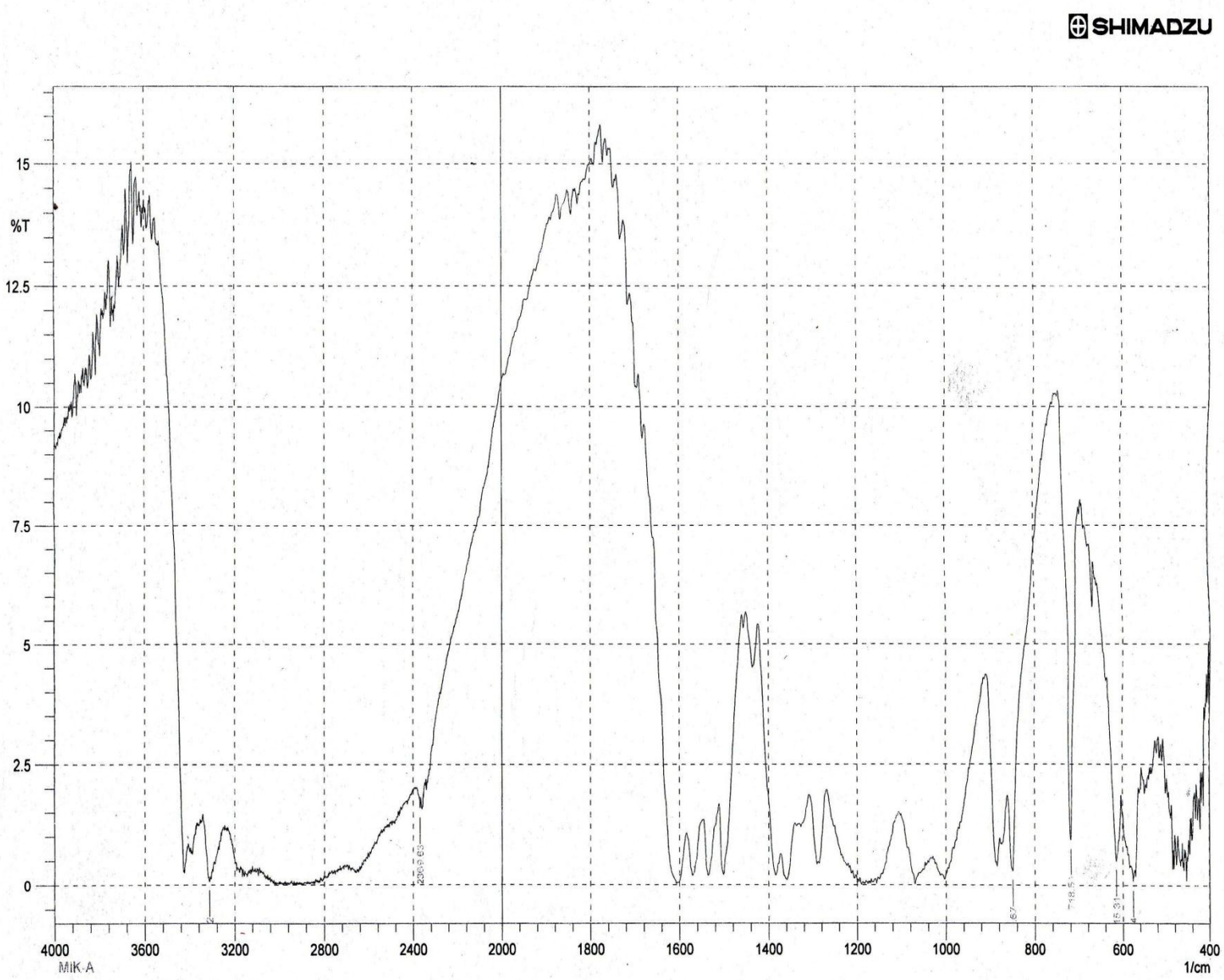
2.1 Synthesis of 5-phenyl -2-amino-1, 3, 4-thiadiazoline



1 **2** **3**

A mixture of thiosemicabazide (0.01 mol, 0.912gm), benzoic acid (0.01mol, 1.221gm) and concentrated sulfuric acid (1ml) in 5ml of ethanol was taken in a round bottomed flux. The flux was then placed on water- bath with constant stirring for one and half hour under reflux condition. The progress of the reaction was monitored by TLC. Reaction mixture was then kept on ice bath. The solid product separated out by filtration. After filtration a white crude product was obtained. The crude product was then purified by recrystallization from 10% aqueous ethanol to yield 82% as a white solid. The melting point was recorded as 223^0C - 225^0 C. The product was found to be homogeneous on TLC plate, R_f = 0.75 (Ethyl acetate: n-Hexane = 1:1).

IR (KBr, cm^{-1}) : 3394 (NH, Symmetric stretching), 3290 (NH, asymmetric stretching), 3193 (CH, aromatic), 1621 (C = N), 1600 (C=N), 1580 (C = C, aromatic), 1536 (C = C, aromatic), 1520 (C = C, aromatic), 719 (C-S-C, linkage of thiadiazole).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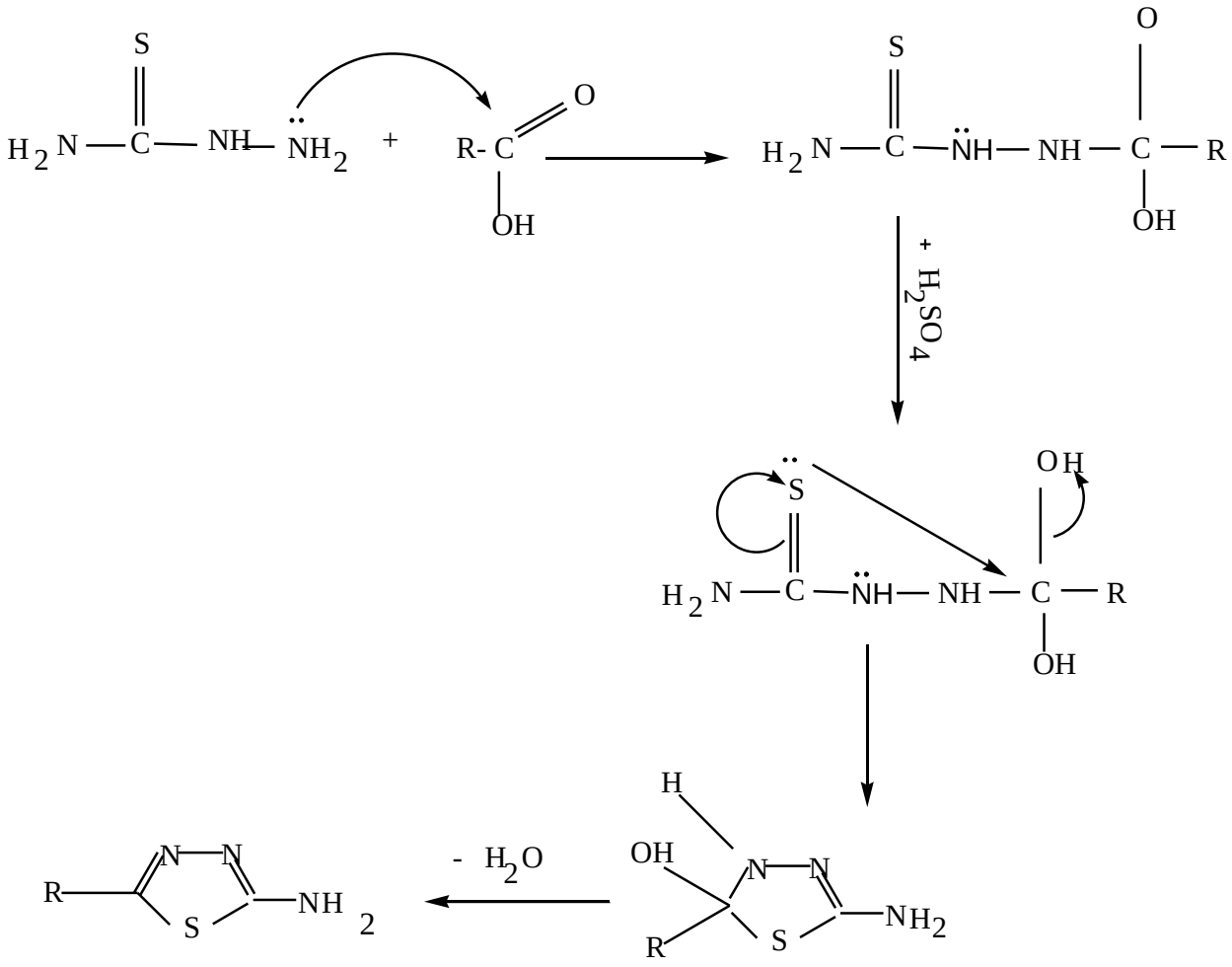
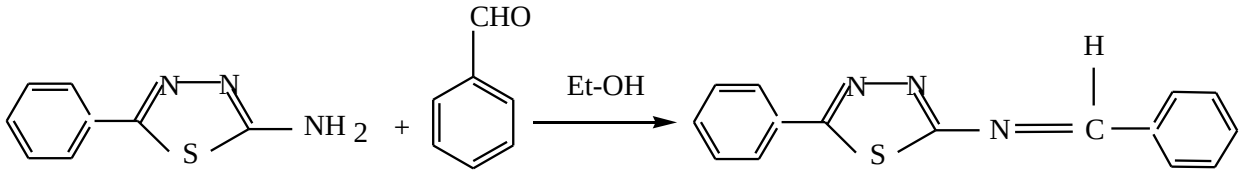
Mechanism:



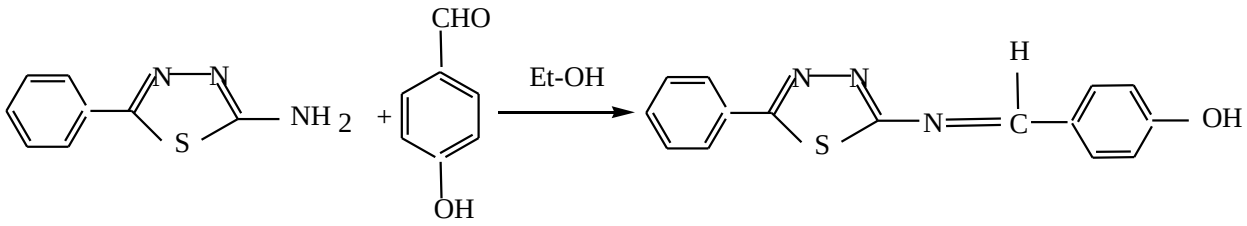
2.2 Synthesis of 5-phenyl-2-benzylidene amino- 1, 3, 4- thiadiazole.



3 **4** **5**

A solution of **3** (0.01 mol, 0.912gm) and benzaldehyde (0.01 mol, 1.06 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for one hour at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water. A yellow precipitate was separated by filtration. The crude yellow product was recrystallized from ethanol and dried in a desiccators and used for the next step reaction.

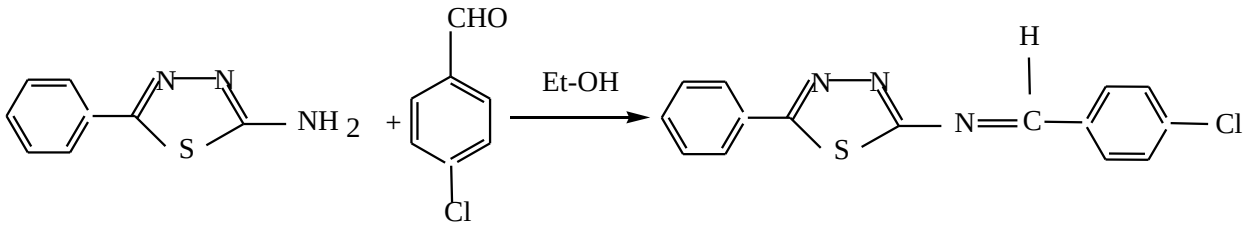
2.3 Synthesis of 5 – phenyl - 2(*p* - hydroxy benzylidene amino) - 1, 3, 4 – thiadiazole



3 **6** **7**

A solution of **3** (0.01 mol, 0.912 gm) and 4-hydroxybenzaldehyde (0.01 mol, 1.22 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for one hour at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water. An off-white precipitate was separated by filtration. The crude off-white product was recrystallied from ethanol and dried in a desiccator and used for the next step reaction.

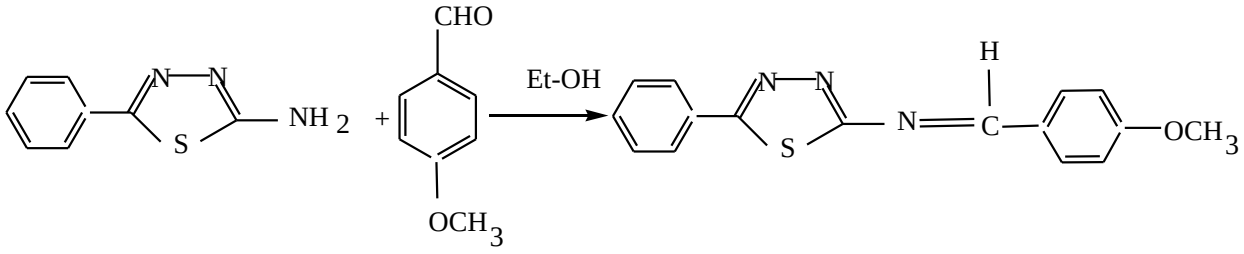
2.4 Synthesis of 5 - phenyl – 2 (*p*- chloro benzylidene amino) – 1, 3, 4 – thiadiazole.



3 **8** **9**

A solution of **3** (0.01 mol, 0.912 gm) and *p*-chlorobenzaldehyde (0.01 mol, 1.4056 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for one hour at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water. An off-white precipitate was separated by filtration. The crude off-white product was recrystallized from ethanol and dried in a desiccators and used for the preparation of thiadiazole derivative.

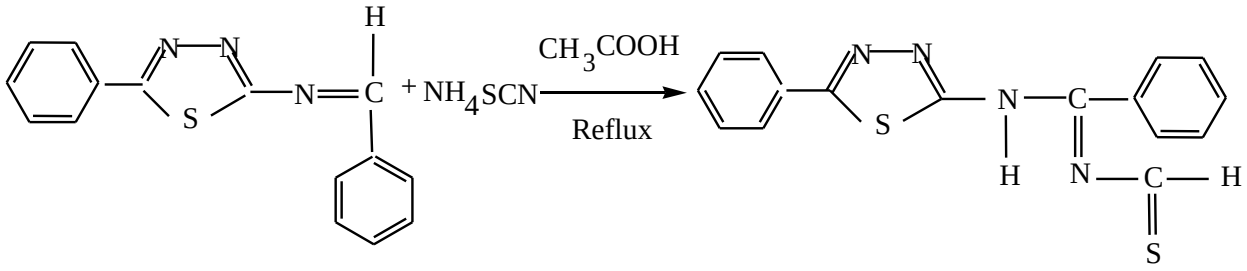
2.5 Synthesis of 5 - phenyl – 2 (*p* - methoxy benzylidene amino) – 1, 3, 4 – thiadiazole.



3 **10** **11**

A solution of **3** (0.01 mol, 0.912 gm) and *p*-methoxybenzaldehyde (0.01 mol, 1.361 gm) in ethanol was taken in a round bottomed flux and the mixture was stirred for one hour at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water. An off-white precipitate was separated by filtration. The crude product was recrystallized from ethanol and dried in a desiccators and used of the precursor of target compound.

2.6 Synthesis of 5 - phenyl - 2 (thioformimido phenyl methylamino) - 1,3,4- thiadiazole.



5 **12**

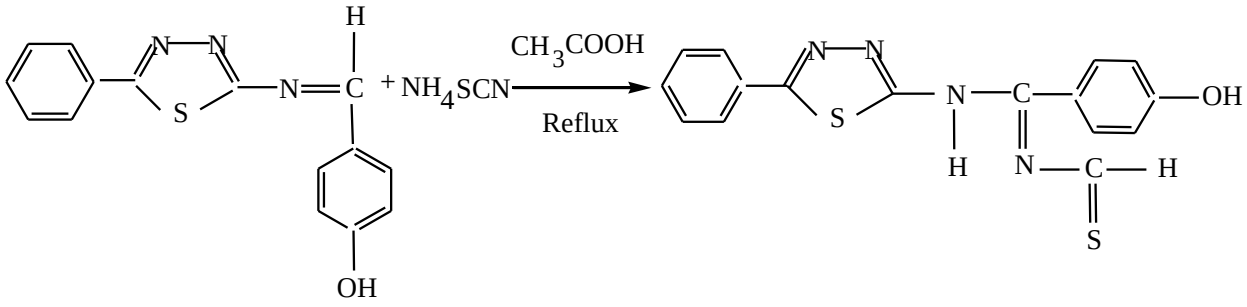
A solution of **5** (0.01 mol, 2.65 gm) in acetic acid was taken a round bottomed flux to which ammonium thiocyanate (0.01 mol, 0.0761 gm) was added with continuous as stirring. The reaction mixture was then reflux for four hours. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water and filtered. The crude product was then recrystallized by ethanol to yield 65% as yellow solid. The melting point was recorded as 153^0 C - 155^0 C.

IR (KBr, cm^{-1}) : 3405 (NH), 3236 (= C-H), 3193 (C-H , aromatic), 1600 (C = N), 1585 (C=N), 1530 (C = C, aromatic), 1520 (C = C , aromatic), 1480 (C = C, aromatic), 1286 (C = S) ,760 (C-S-C linkage of thiadiazole).

^{1}H NMR ($CDCl_3$, 400 MH_Z) : δ 10.296 **(** S, 1H, N-H),7.997 (S, 2H), 7.676 - 7.651 (m, 4H), 7.431- 7.415 (m, 4H), 6.640 (bd, S, 1H, S=C-H),

^{13}C NMR ($CDCl_3$, 400 MH_Z) : δ 178.453 (C=S), 144.185 (C′- 1, C′- 4) , 133.013 (C-1, C-4) , 130.787 (2 C=N), 128.869 (C′- 2, C′- 6, C-2, C-6 , N- C= N), 127.524 (C′- 3, C′- 5, C- 3, C- 5).

2.7 Synthesis of 5 - phenyl - 2 (*p* - hydroxy phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazole.



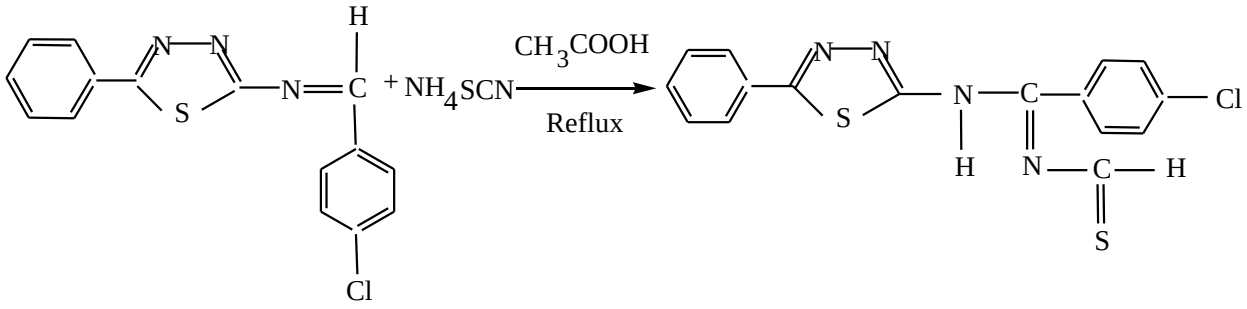
7 **13**

A solution of 7 (0.01 mol, 2.81 gm) in acetic acid was taken in a round bottomed flux. Ammonium thiocyanate (0.01 mol, 0.0761 gm) was added to it. The reaction mixture was then reflux for six hours. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water and filtered. The product was recrystallized by ethanol to yield of 75% as a white solid. The melting point was recorded as 168^0 C – 170^0 C.

IR (KBr, cm^{-1}) : 3500-3400 (bd, -OH), 3300 – 3200 (NH), 3160 (C = H), 1620 (C = N), 1550, 1547 and 1514 (C = C), 1275 (C = S), 844 (C-S-C linkage of thiadiazole).

^{1}H NMR (DMSO – d_6, 400 MH_Z) : δ 11.220 **(** S, 1H, N-H), 8.023 (bd, S, 1H, -OH), 7.945 (S, 1H, H-C=S), 7.809 (bd, S, 1H, H-C-4′), 7.612 (bd, S, 2H, H- C-3′ , H- C-5′), 7.590 (bd, S, 2H, H- C-2′ , H- C-6′), 6.784 (bd, S, 2H, H- C-3 , H- C-5), 6.763 (bd, S, 2H, H- C-2 , H- C-6).

2.8 Synthesis of 5 - phenyl - 2 (*p* - chloro phenyl thioformimido phenyl methylamino) - 1,3,4 - thiadiazole.



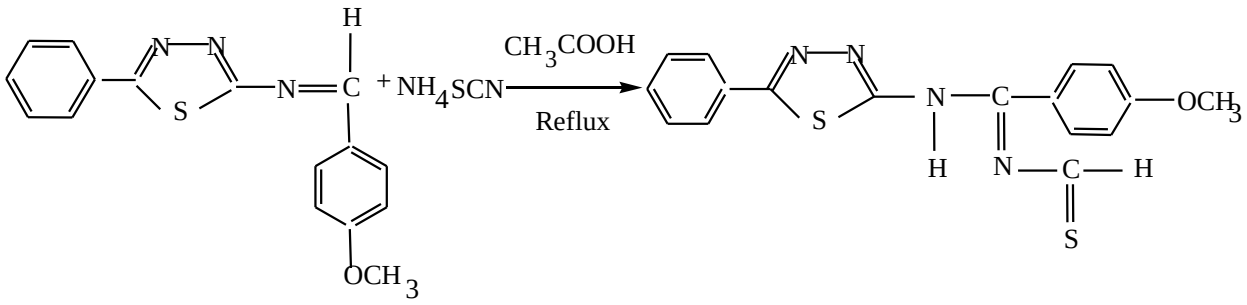
9 **14**

A solution of **9** (0.01 mol, 2.955 gm) in acetic acid was taken in a round bottomed flux. To this solution, ammonium thiocyanate (0.01 mol, 0.0761gm) was added with continuous stirring. The reaction mixture was then refluxed for four hours. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water and filtered. The product was recrystallized by ethanol to yield of 70% as a yellow solid. The melting point was recorded 208^0C - 210^0C.

IR (KBr, cm^{-1}) : 3423 (N-H), 3200 (S = C-H, stretching),
3180 (C-H, aromatic), 1600 (C=N) , 1530,1520 ,
1468(C=C , aromatic),
1282 (C=S), 815 (C-S-C linkage of thiadiazole).

^{1}H NMR ($CDCl_3$, 400 MH_Z) : δ 8.234 (N-H), δ 8.072 (S=C-H), δ 8.033 (C_4-H),
δ 7.852 (C_3-H and C_5-H), δ 7.831 (C_2-H and C_6-H),
δ 7.469 and δ 7.448 (C'_3-H, C'_5-H, of C'_2-H and C'_6-H).

2.9 Synthesis of 5 - phenyl - 2 (*p* - methoxy phenyl thioformimido phenyl methylamino)-1,3,4 - thiadiazole.



11 **15**

A solution of **11** (0.01 mol, 2.95 gm) in acetic acid was taken in a round bottomed flux. Then ammonium thiocyanate (0.01 mol, 0.0761gm) was added to it with continuous stirring. The reaction mixture was then refluxed for five hours. The progress of the reaction was monitored by TLC. The reaction mixture was then poured into ice water and filtered. The product was recrystallized by ethanol to yield 75% as yellow solid. The melting point was recorded as 114^0 C – 115^0 C.

IR (KBr, cm^{-1}) : 3390 (N-H), 3190 (S=C-H), 3020 (C-H, aromatic), 2820 (C-H, aliphatic), 1625 (C=N), 1604 (C=N), 1530 (C=C), 1512 (C= C), 1426 (C=C), 1254 (C=S), 825 (C-S-C linkage of thiadiazole).

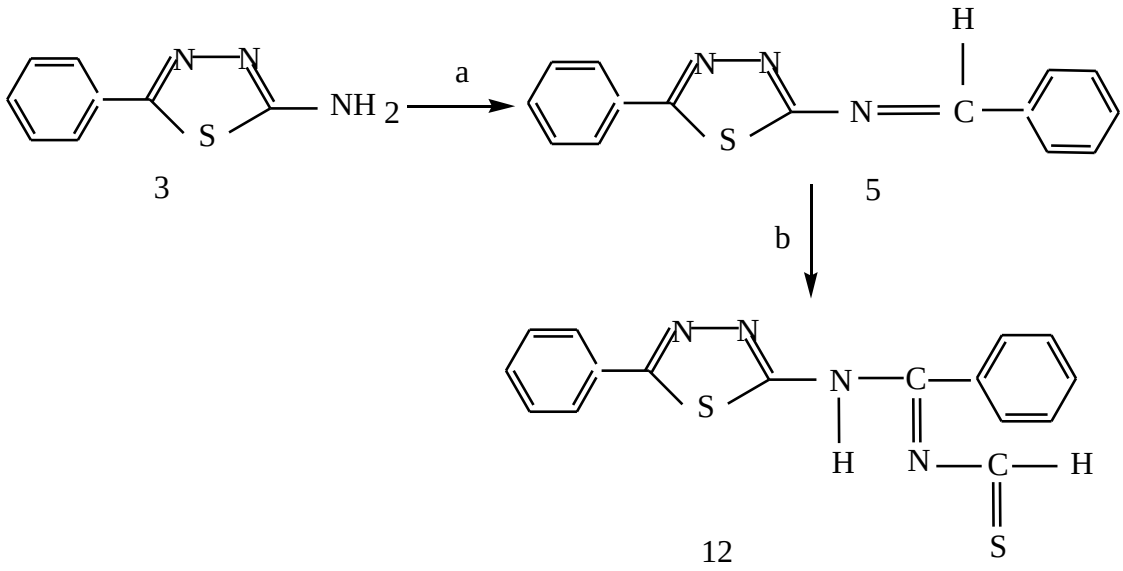
^{1}H NMR (DMSO- d_6 , 400 MH_Z) : δ 8.098 (bd, S, 1H, NH), 7.997 **(** S, 1H, H-C=S), 7.905 (bd, S, 1H, H-C-4′), 7.748 (S, 2H, H-C-3′, H-C-5′), 7.727 (bd, S, 2H, H-C-2′, H-C-6′), 6.975 (S, 2H, H- C-2, H-C-6), 6.953 (S, 2H, H-C-3 ,H-C-5), 3.797 (S, 3H, OCH_3).

Chapter 3

RESULTS AND DISCUSSION

3.1 **Characterization of 5 - phenyl - 2 (thioformimido phenyl methylamino) - 1,3,4-thiadiazole.**

The starting material **3** was prepared from benzoic acid and thiosemicarbazide by well known literature method[80]. The schiff base 5-phenyl-2-benzylidene amino- 1, 3, 4- thiadiazole **5** was synthesized from the condensation reaction of **3** and benzaldehyde using conventional method[81]. The final and expected product 5 - phenyl - 2 (thioformimido phenyl methylamino) - 1,3,4- thiadiazole **12** was synthesized by refluxing ammonia thiocyanate in presence of acetic acid as solvent as well as catalyst. The reaction sequence shown in **scheme-1.**



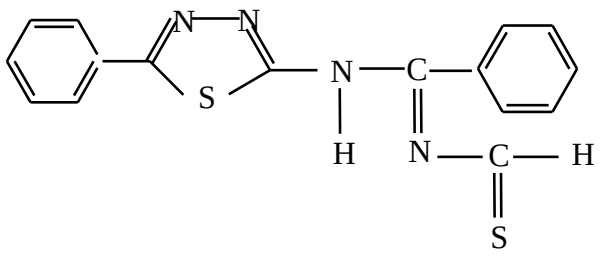
Scheme-1

a = PhCHO, EtOH

b = NH_4SCN, CH_3COOH

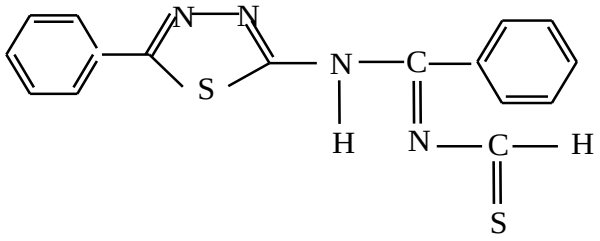
The structure of the expected product 5 - phenyl - 2 (thioformimido phenyl methylamino) - 1,3,4- thiadiazole **12** was established by IR, ^{1}H NMR and ^{13}C NMR spectral data.

The IR spectrum (Fig. 1) showed peak at 3405 cm^{-1} for N-H stretching, 3236 cm^{-1} for C-H stretching of thioformyl group , 3193 cm^{-1} for aromatic C-H stretching , 1600 cm^{-1} for C=N group, 1585 cm^{-1}, 1530 cm^{-1} , 1520 cm^{-1} for the characteristic aromatic C=C . The band at 1286 cm^{-1}, was for C=S group. The characteristic feature of C-S-C linkages was identified at 760 cm^{-1}



12

The characteristic feature of this ^{1}H NMR spectrum (Fig.2) were a singlet at δ 10.29 for N-H proton. Another singlet at δ 7.99 was assigned for two aromatic protons of C_4-H and C'_4 –H. A multiplet at δ 7.69- 7.65 was indicative for protons of C_3-H, C_5-H , C'_3 –H , C'_5 – H . Another multiplet at δ 7.43 – 7.41 was indicative for protons of C_2-H, C_6-H , C'_2 –H , C'_6 – H. The broad singlet at δ 6.64 was designated as the thioformyl proton of S=C-H group.



12

The ^{13}C NMR spectrm (Fig. 3) showed peaks of δ 178.45 for C=S , 144.18 for C'-1, C'-4 , 133.01 for C-1, C-4 , 130.78 for two carbon of C=N , 128.86 for five carbon C'-2, C'-6 , C –2 , C – 6 N-C=N , 127.52 for four carbon of C'-3, C'-5, C –3 , C – 5.

Figure:1

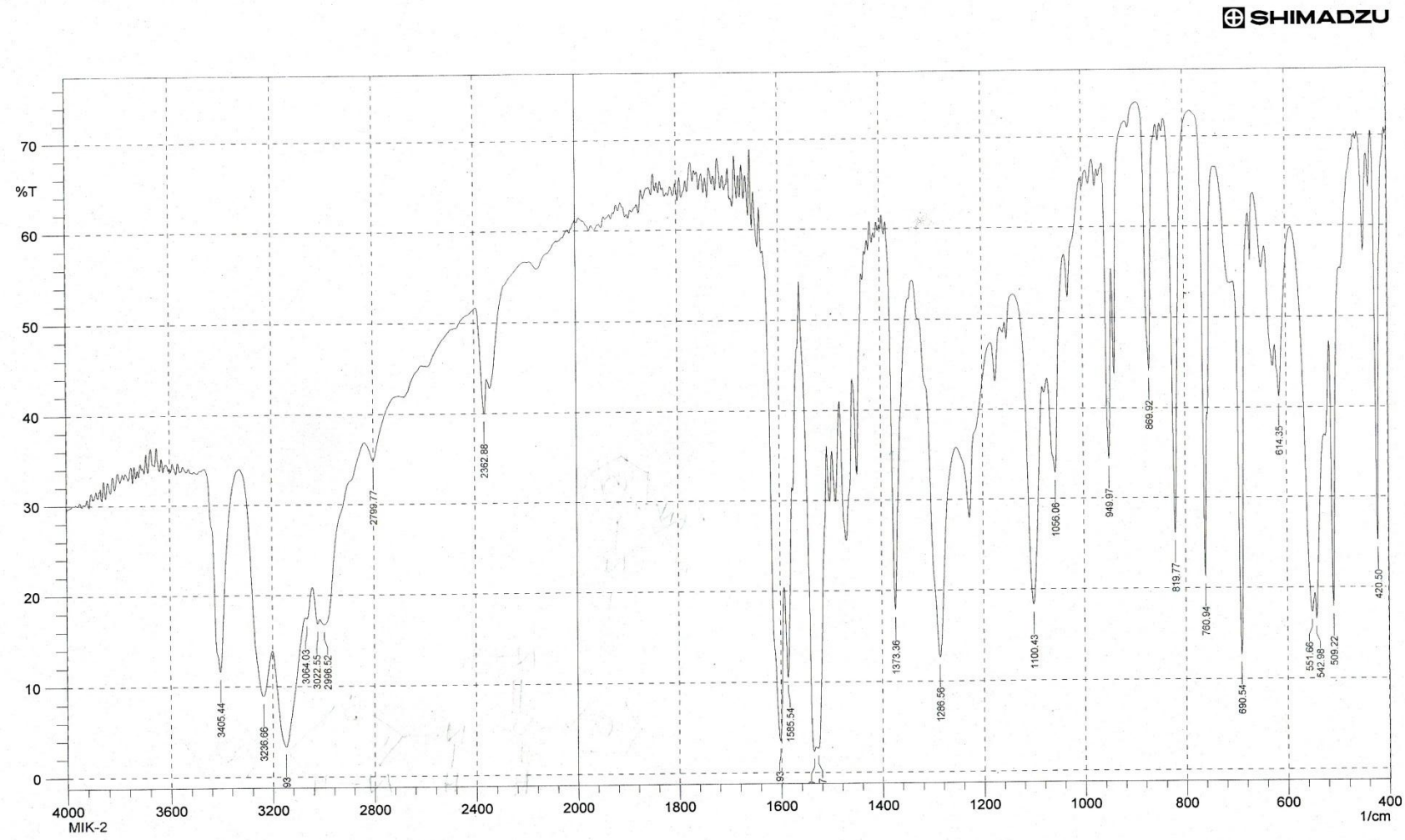


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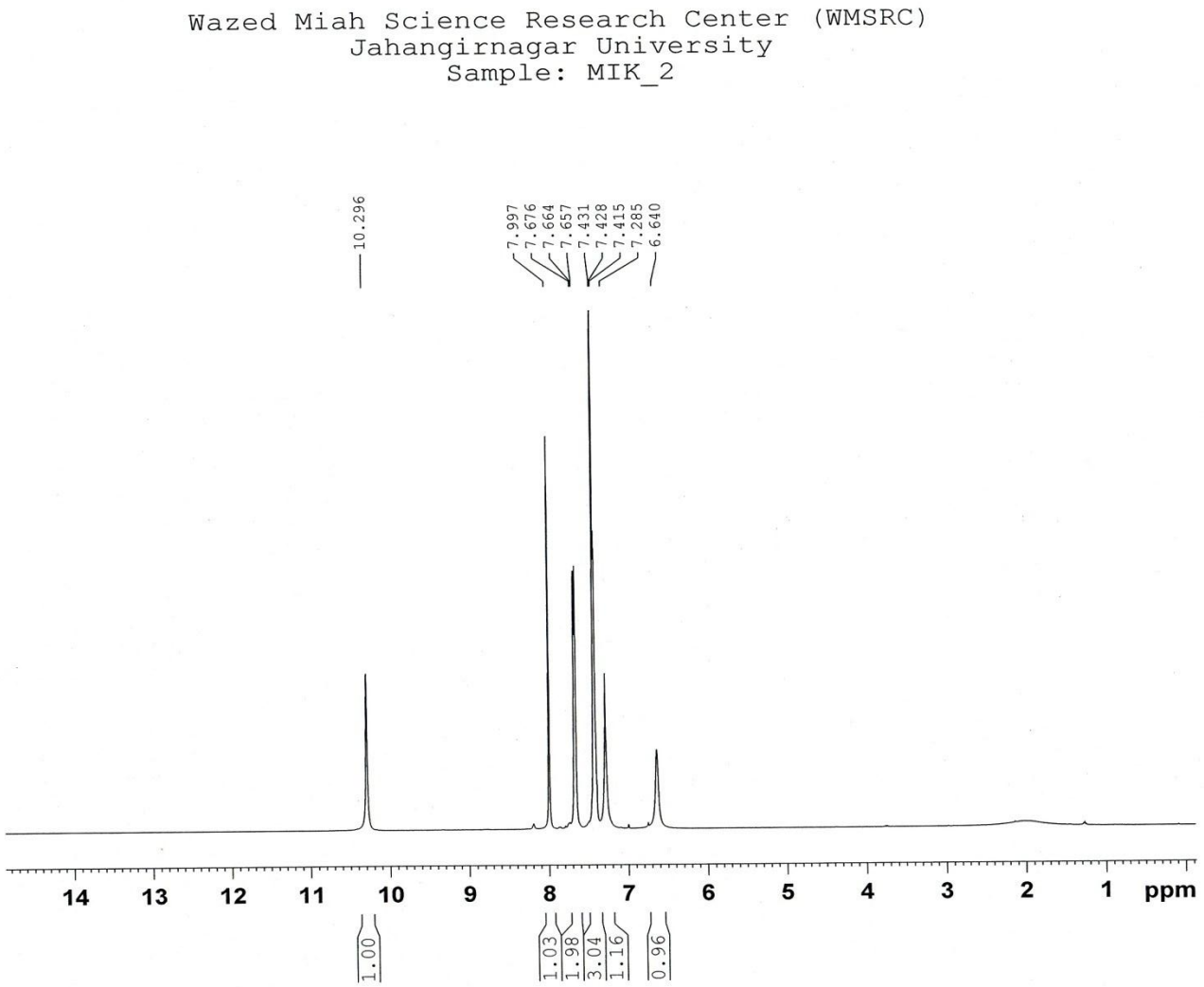
Figure:2



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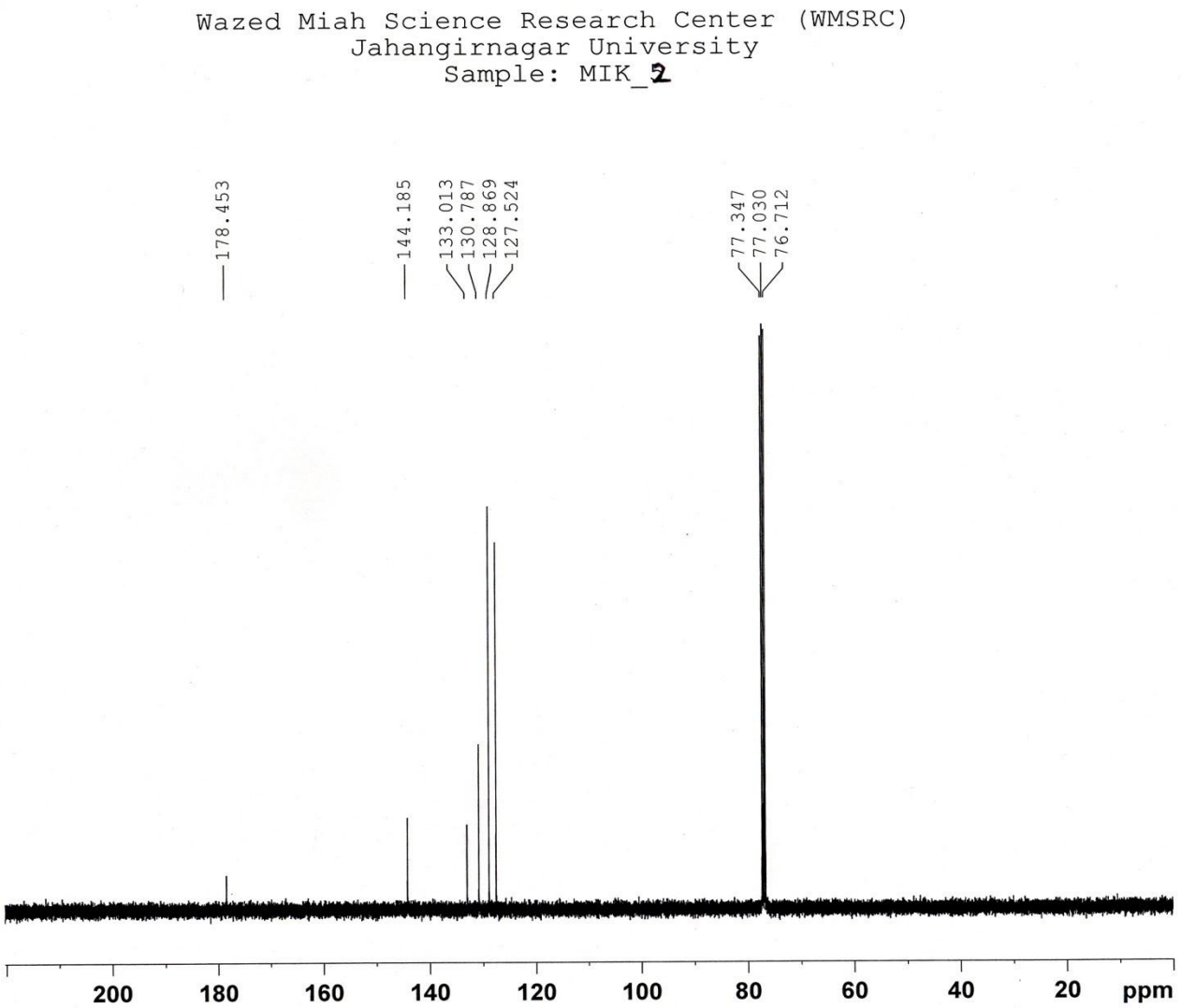

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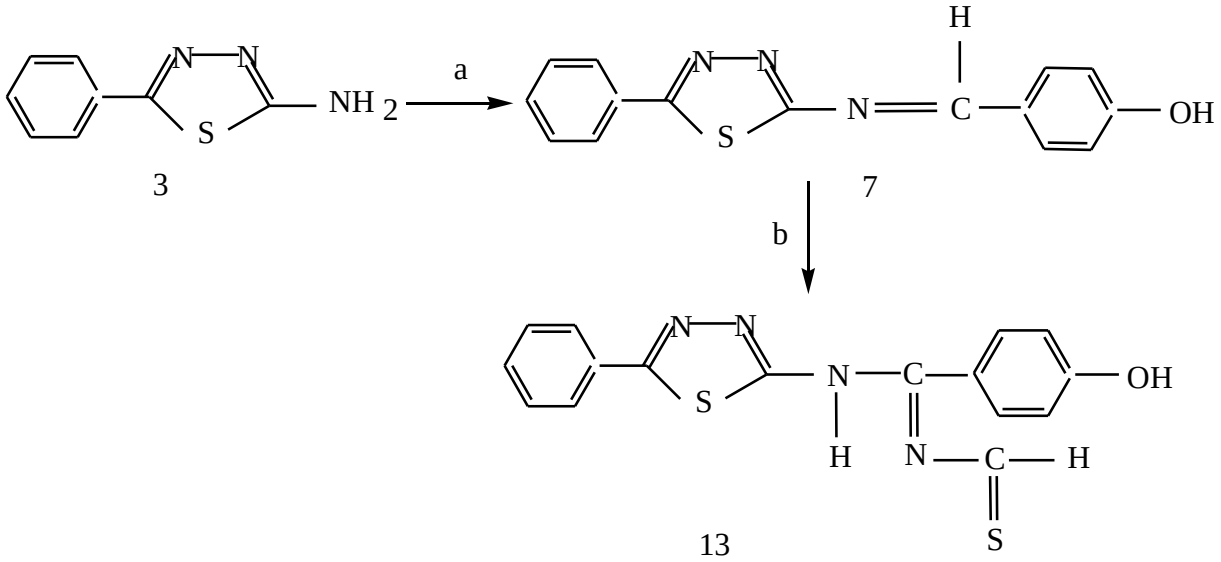
3.2 **Characterization of 5 - phenyl - 2 (*p* - hydroxy phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazole**.

The starting material **3** was prepared from benzoic acid and thiosemecarbazide by well known literature method[75]. The Schiff base 5-phenyl-2- (hydroxyl benzylidene amino)- 1, 3, 4- thiadiazole **7** was synthesized from the condensation reaction of **3** and *p*- hydroxyl benzaldehyde using conventional method. The final and expected product 5 - phenyl - 2 (*p* - hydroxy phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazole **13** was synthesized by refluxing ammonium thiocyanate in presence of acetic acid as solvent as well as catalyst. The reaction sequence shown in **scheme-2.**



a = HO C_6 H_4 CHO , Et OH **Scheme 2**

b = NH_4SCN, CH_3COOH

The structure of the expected product 5 - phenyl - 2 (*p* - hydroxy phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazole **13** was established by IR, ^{1}H NMR spectral data.

The IR spectrum (Fig. 4) showed a characteristic broad band of hydroxyl group at 3500-3400 cm^{-1}. Another broad band at 3300 – 3200 cm^{-1} was detectable for N-H group. The peak at 3160 cm^{-1} was identified for C=N. The characteristic band at 1550, 1547 and 1514 cm^{-1} were assigned for aromatic C=C. The broad band at 1275 cm^{-1} was revealed for C=S group. The C-S-C linkages was observed at 844 cm^{-1}.

Figure-4

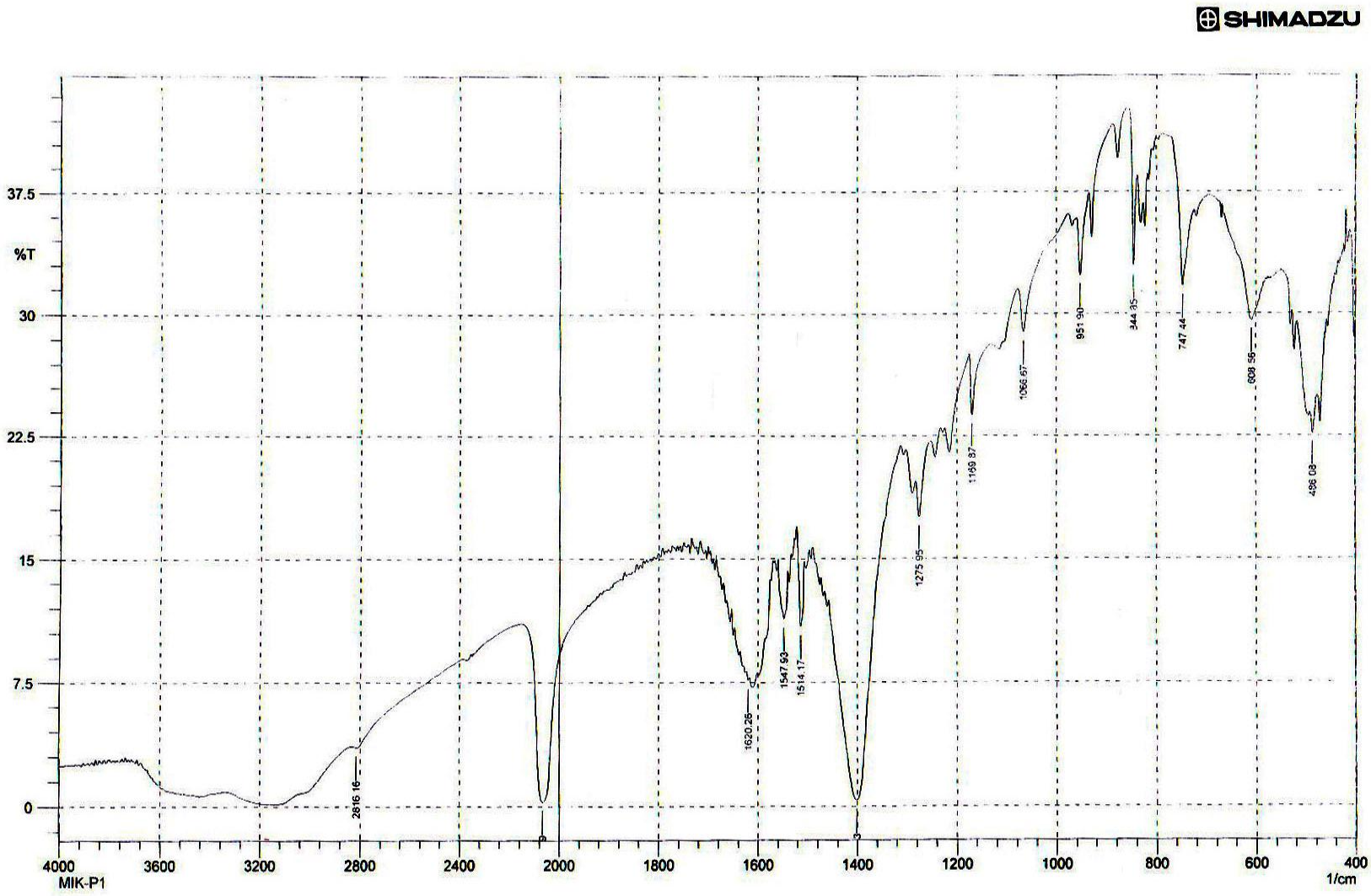

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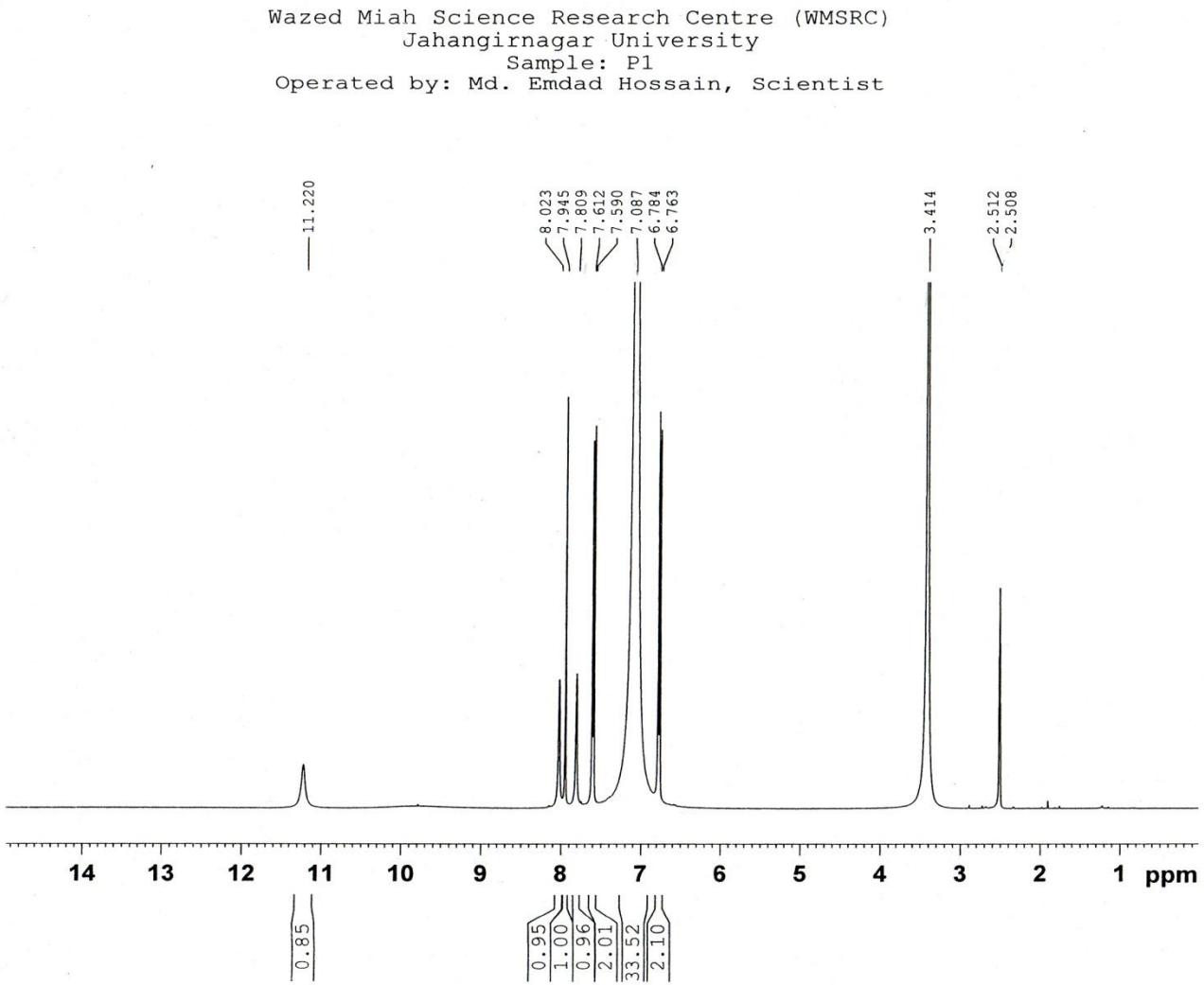
Figure-5



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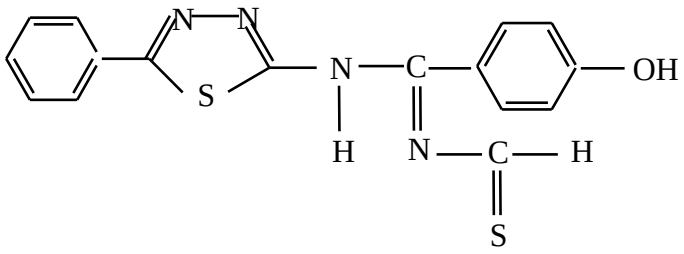
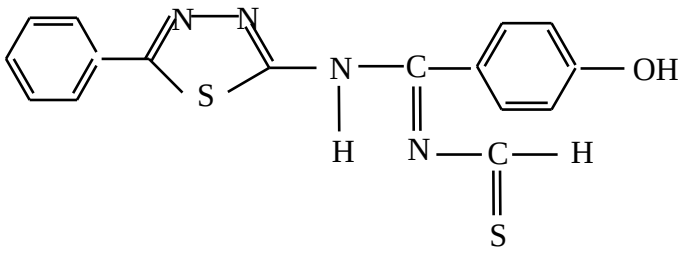


13

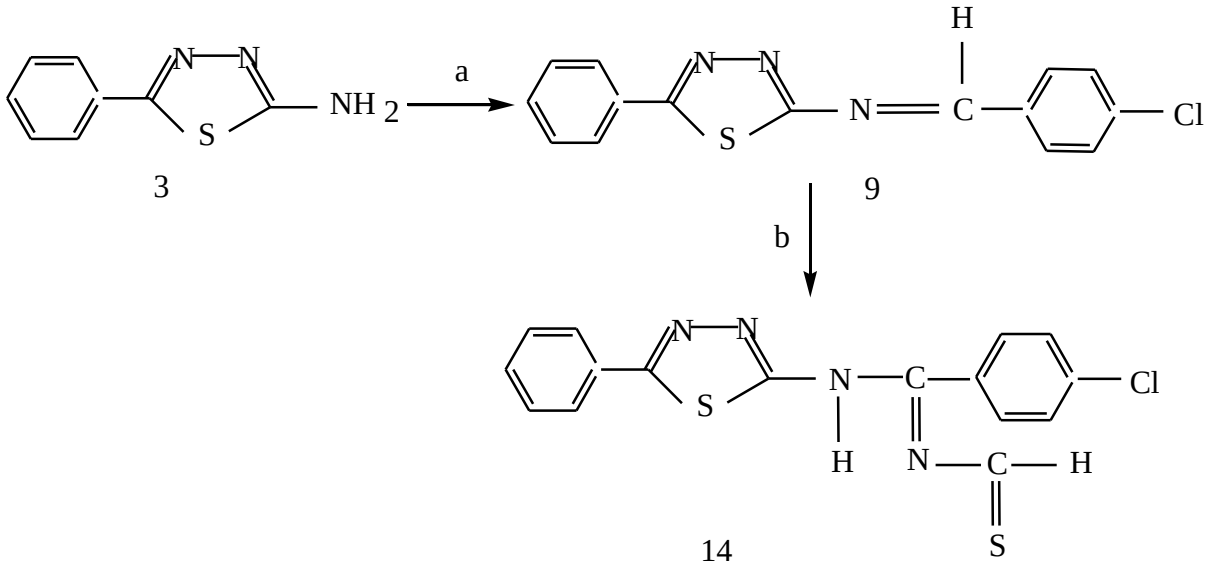
The characteristic feature of the ^{1}H NMR spectrum (Fig.5) were a singlet at δ 11.220 for N-H proton. The singlet at δ 8.023 was assigned for O-H proton. The sharp singlet was assigned for aliphatic H-C=S at δ 7.945. A broad singlet was observed for one proton of H-C$'_4$ at δ 7.809 . Another two broad singlet were identified at δ 7.612 for two protons of C$'_3$ –H , C$'_5$ –H and at 7.590 for two protons of C$'_2$ –H , C$'_6$ –H ; A broad singlet was designated at δ 6.784 for two proton of C_3 –H and C_5 –H. Another broad singlet was attributed for two protons of C_2 –H and C_6 –H at δ 6.763.



13

3.3 Characterization of 5 - phenyl - 2 (*p* - choloro phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazole.

The starting material **3** was prepared from benzoic acid and thiosemecarbazide by well known literature method[75]. The Schiff base 5-phenyl-2- (choloro benzylidene amino)- 1, 3, 4- thiadiazole **9** was synthesized from the condensation reaction of **3** and *p*- choloro benzaldehyde using conventional method[76]. The final and expected product 5 - phenyl - 2 (*p* - choloro phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazoline **14** was synthesized by refluxing with ammonium thiocyanate in presence of acetic acid as solvent as well as catalyst. The reaction sequence shown in **scheme-3**.



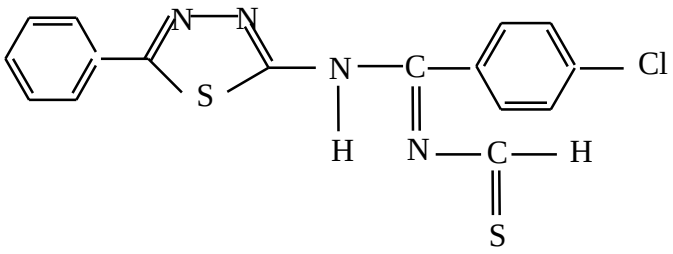
a = *p*-Cl C_6 H_4 CHO , Et OH **Scheme 3**

b = NH_4SCN, CH_3COOH

The structure of the expected product **14** was established by IR, ^{1}H NMR spectral evidences.

The IR spectrum (Fig. 6) showed a relatively sharp band at 3423 cm^{-1} for N-H. The peak ats 3200 cm^{-1} was detected as formyl C-H stretching vibration. The sharp band at 3180 cm^{-1} for aromatic C-H bond . The characteristic band at 1600 cm^{-1} was for C=N group. The peak at 1530,

1520, 1468 cm^{-1} were assigned for aromatic C=C bonds. The well known peak for C=S was detected at 1282 cm^{-1}. The characteristic C-S-C linkages was identified at 815 cm^{-1}.



14

The ^{1}H NMR spectra (Fig.7) showed broad singlet for N-H proton at δ 8.234. The singlet at δ 8.072 was assigned for thioformyal proton of S=C-H. The sharp singlet at δ 8.033 was attributable for C_4-H proton. The sharp singlet of two proton at 7.852 were assignable for C_3-H and C_5-H. Another sharp peak at 7.831 was identified for C_2-H and C_6-H . The peaks at δ 7.469 and at δ 7.448 were distinctive for two protons of C'_3-H and C'_5-H, and for two proton of C'_2-H and C'_6-H.

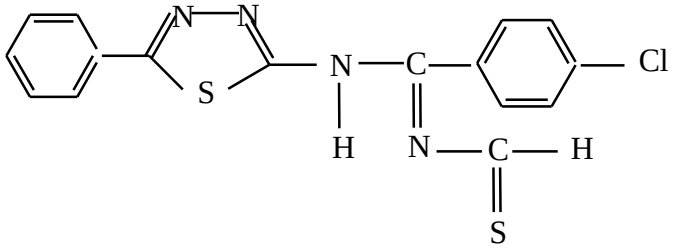


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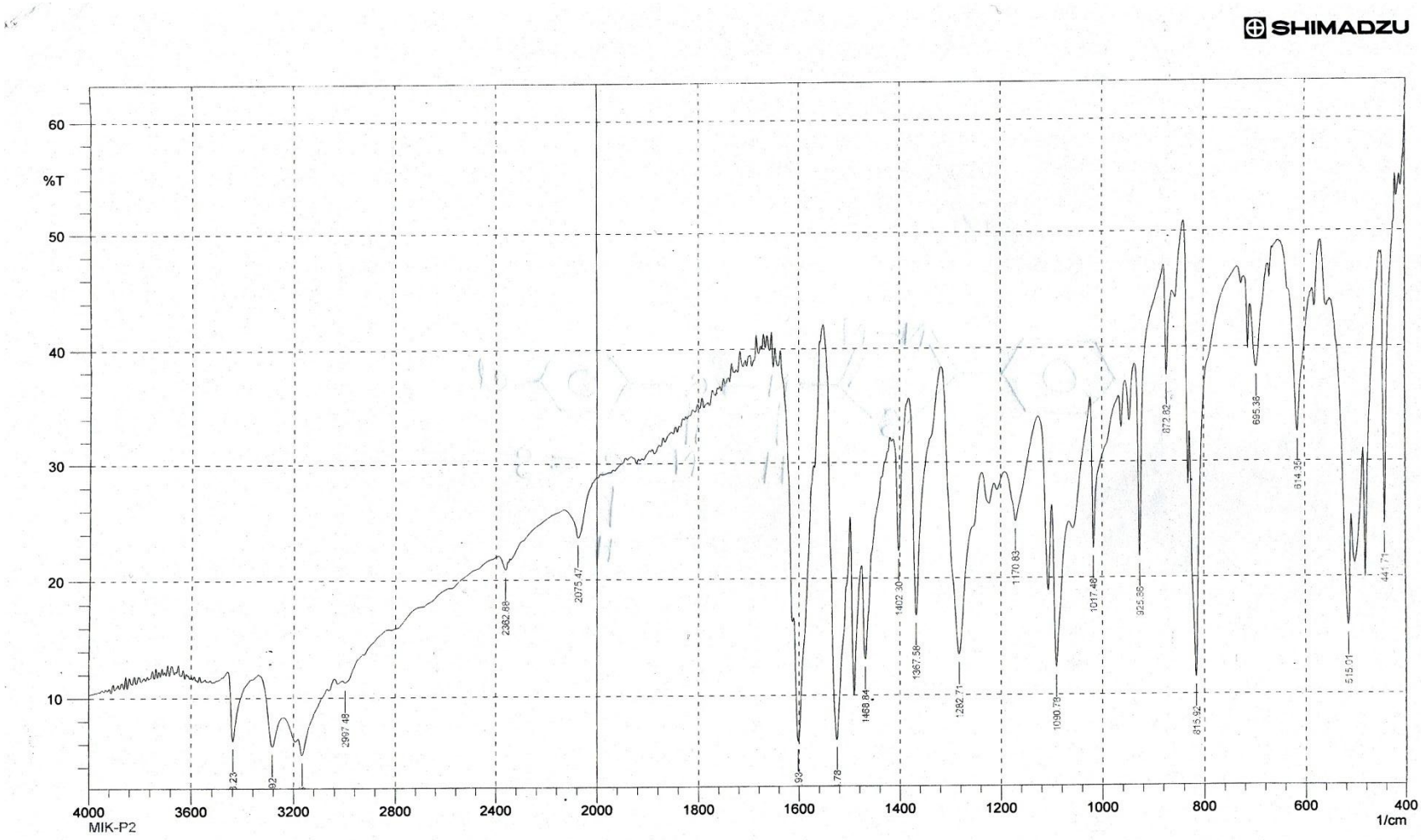
Figure-6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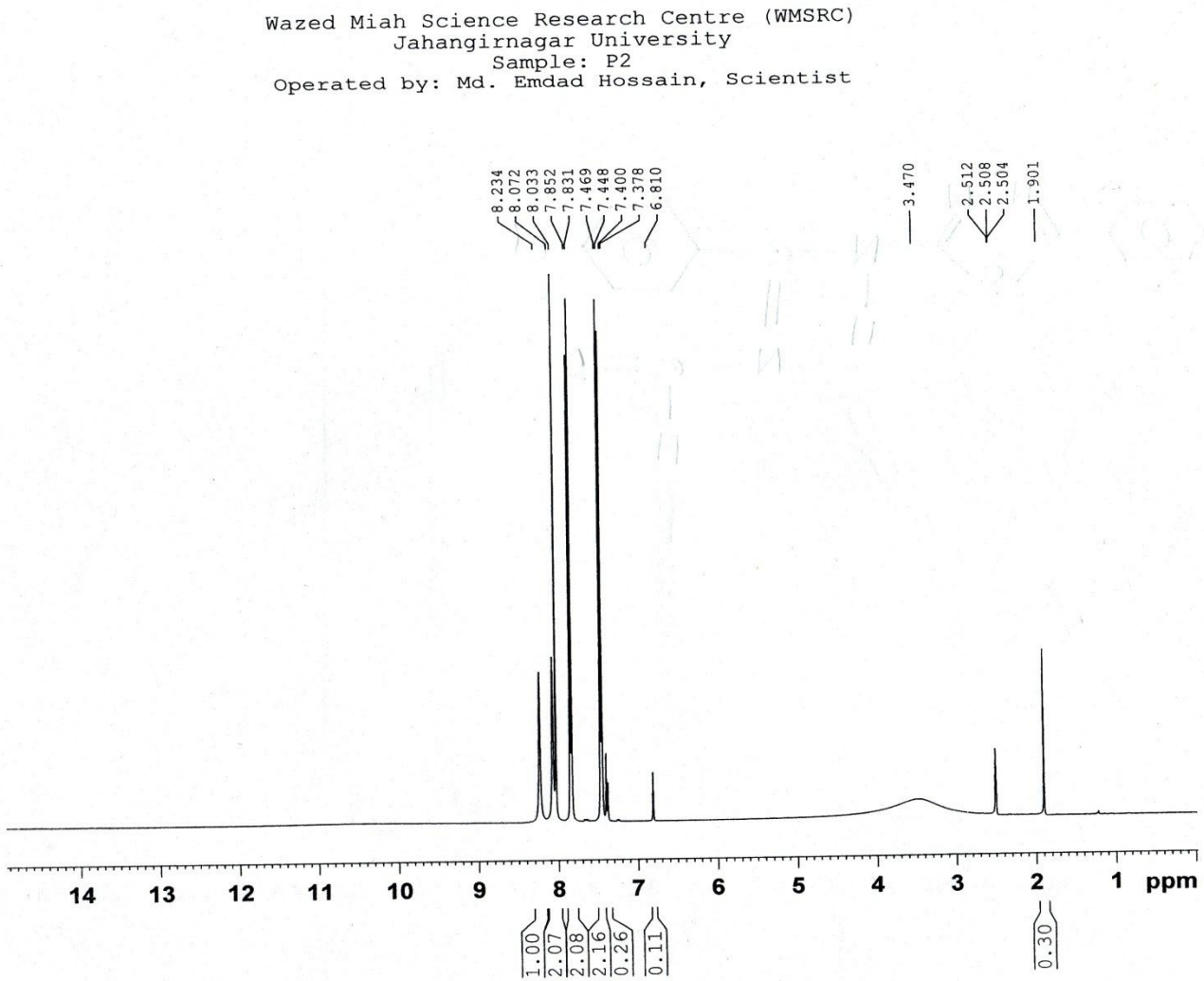

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LB 1.00 Hz
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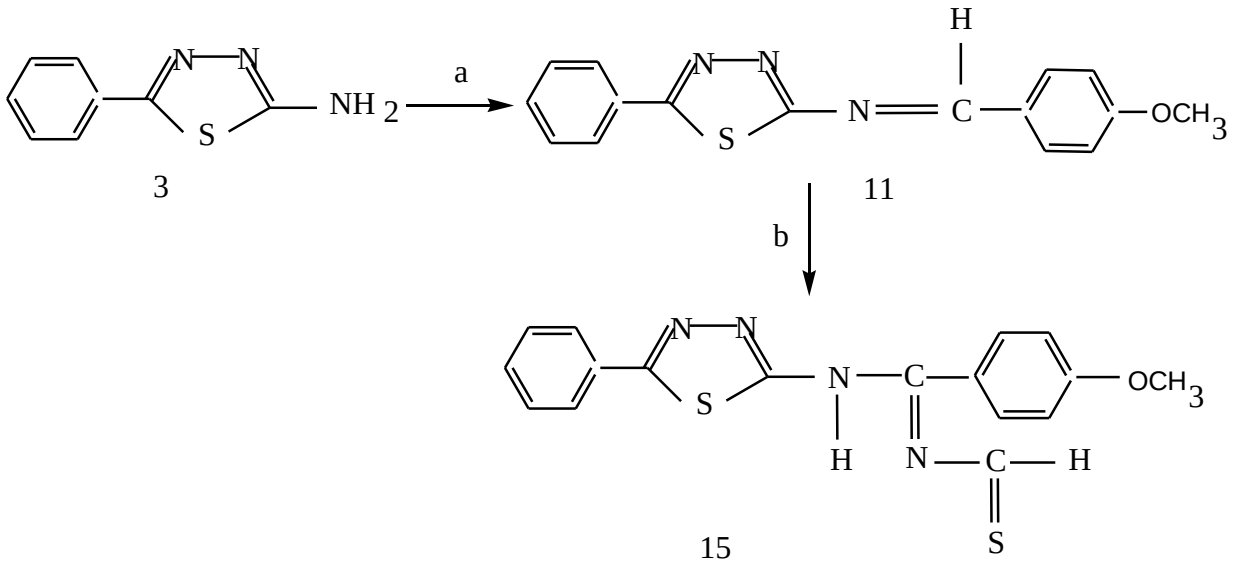
3.4 Characterization of 5 - phenyl - 2 (*p* - methoxy phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazole.

The starting material **3** was prepared from benzoic acid and thiosemicarbazide by well known literature method[75]. The schiff base 5-phenyl-2- (methoxy benzylidene amino)- 1, 3, 4- thiadiazole **11** was synthesized from the condensation reaction of **3** and *p*- methoxy benzaldehyde using conventional method[76]. The final and expected product 5 - phenyl - 2 (*p* - methoxy phenyl thioformimido phenyl methylamino) - 1,3,4- thiadiazoline **15** was synthesized by refluxing with ammonium thiocyanate in presence of acetic acid as solvent as well as catalyst. The reaction sequence shown in **scheme-4.**

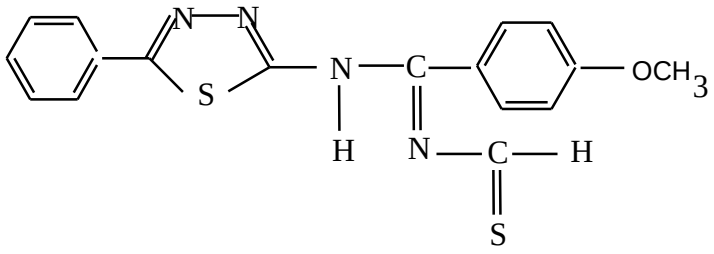


a = *p*-OCH_3 C_6 H_4 CHO, Et OH **Scheme 4**

b = NH_4SCN, CH_3COOH

The IR spectra (Fig.8) showed a peak of 3390 cm^{-1} for N-H stretching . The band at 3190 cm^{-1} was assignable for thioformamiydal C-H vibration. The peak at 3020 cm^{-1} was the characterization absorption frequency of aromatic C-H stretching. The sharp band at 2820 cm^{-1} was defected as aliphatic C-H vibration. The two bonds at 1625 cm^{-1} and 1604cm^{-1} were assignable for C=N bonds. The characteristic bands at 1530, 1512 and 1526 cm^{-1} were for

aromatic C=C bonds. The sharp peak at 1254 cm^{-1} was for the characteristic C=S group. The peak at 825 cm^{-1} was for C-S-C linkage.



15

The ^{1}H NMR spectra (Fig. 9) showed a broad singlet at δ 8.098 for one proton of N-H group. The sharp singlet at δ 7.957 was assignable for formyl S=C-H proton. The broad singlet was observed at δ 7.905 for one proton of C' $_4$-H. The singlet for two proton were designated at δ 7.748 for C' $_3$-H and C' $_5$-H. Another two proton of showed a singlet at δ 7.727 for C' $_2$-H and C' $_6$-H. The singlet peak of two protons at δ 6.975 attributable for C_2-H and C_6-H. The peak at δ 6.953 was detected for protons of C_3-H and C_5-H. The sharp singlet at δ 3.797 was identified for three protons of $–OCH_3$ group.

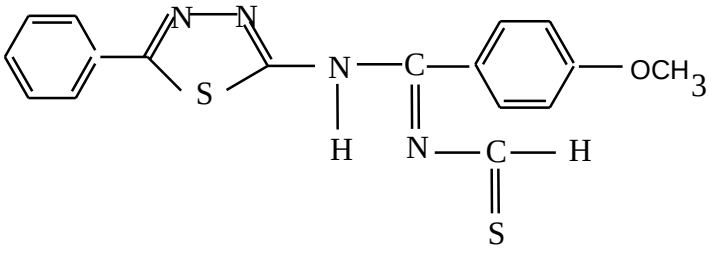


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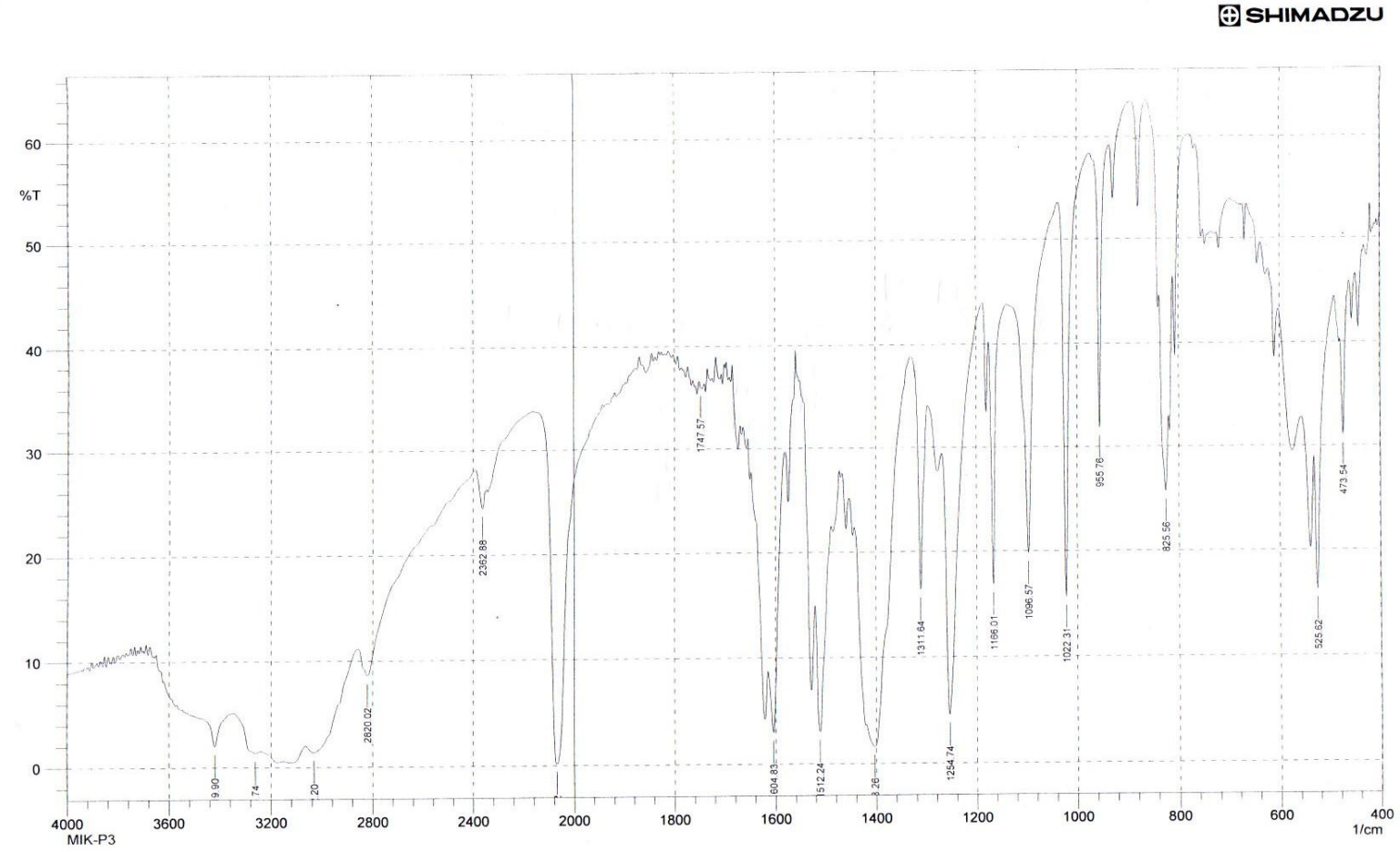
Figure -8



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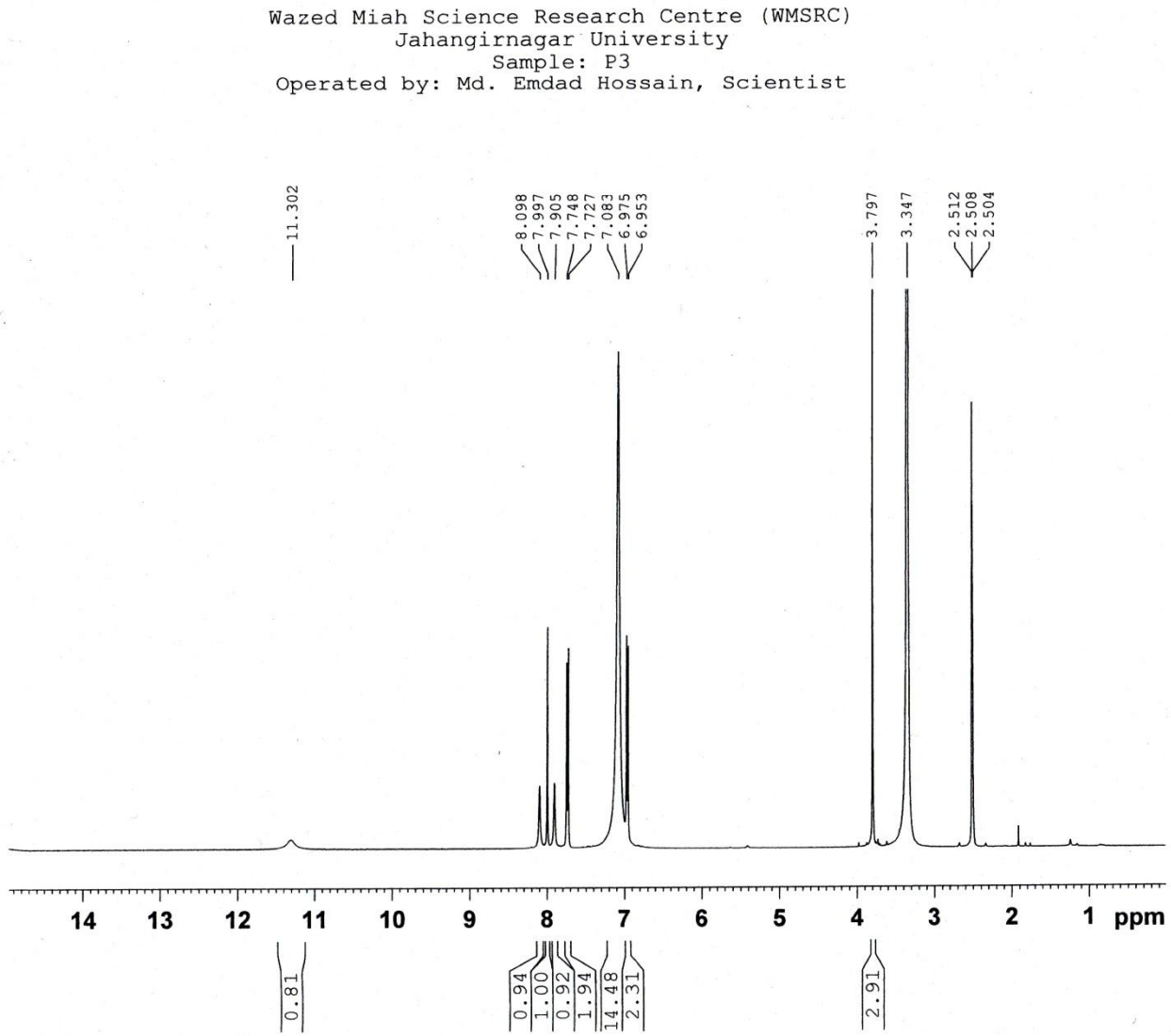

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Chapter 4

SUMMARY

Summary

The starting material 5-phenyl-2-amino-1,3,4-thiadiazole was synthesized from benzoic acid and thiosemicarbazide. The next step was to synthesize different Schiff's bases by using amine and substituted aromatic aldehydes. The addition of ammonium thiocyanate to these Schiff's bases afforded the target compounds thiofomamidal thiadiazole derivatives of moderate yield.

Synthesis of thiadiazole compound.

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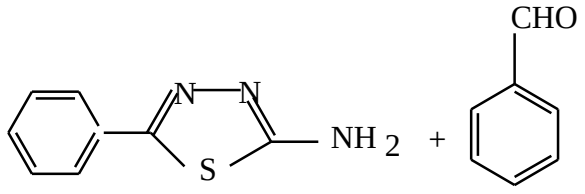	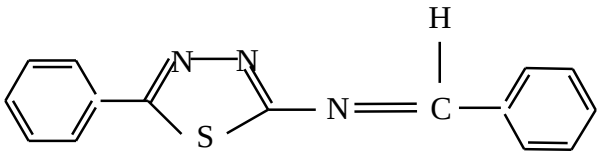
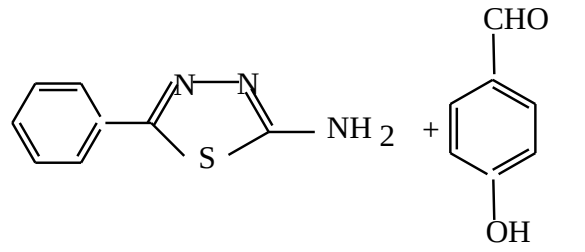	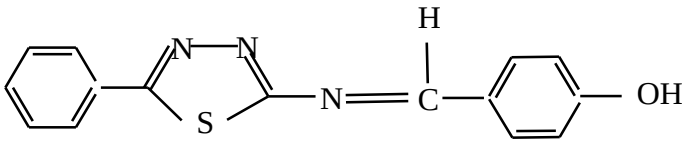
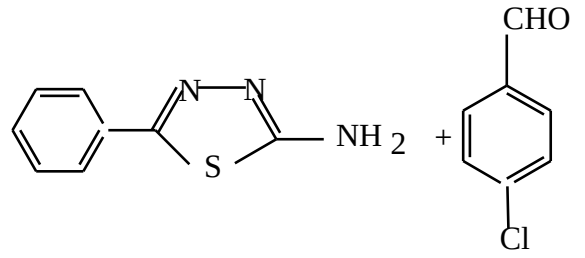	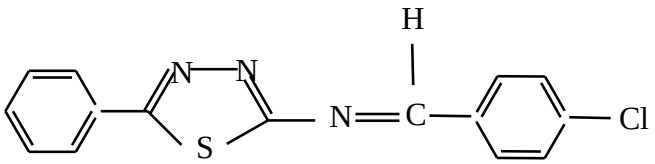
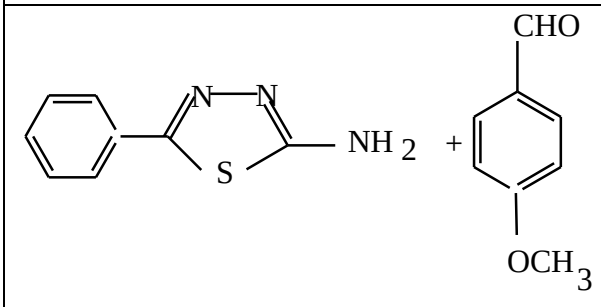	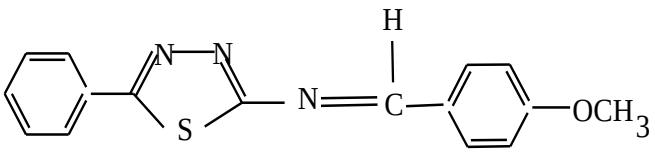

Table 2.

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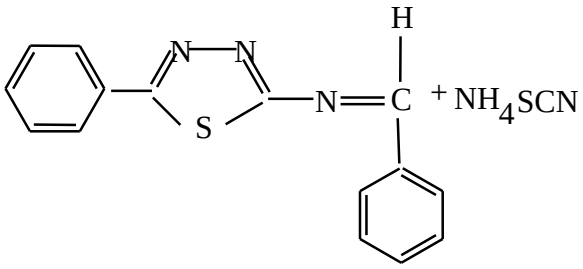
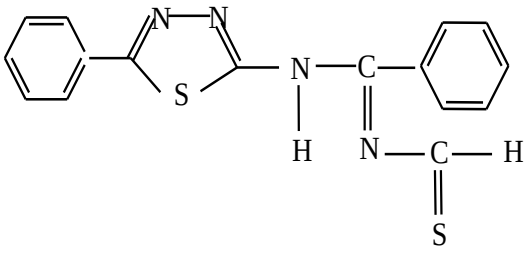
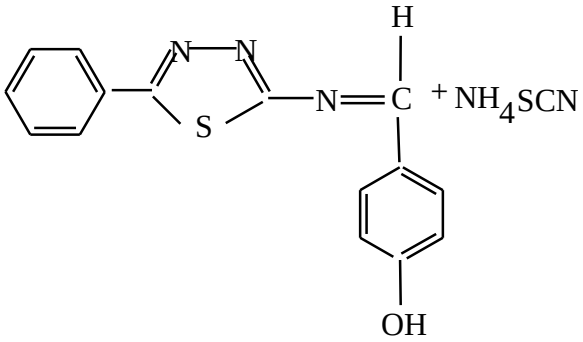
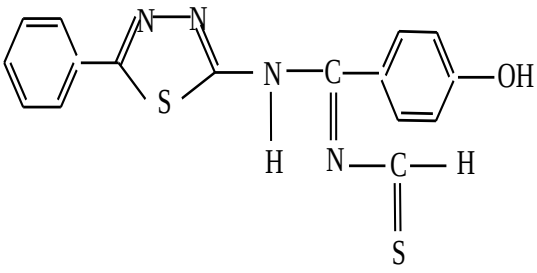
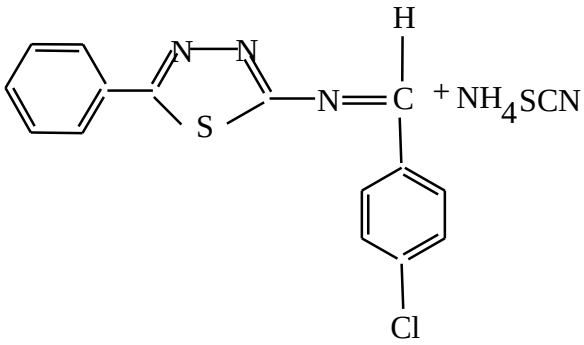
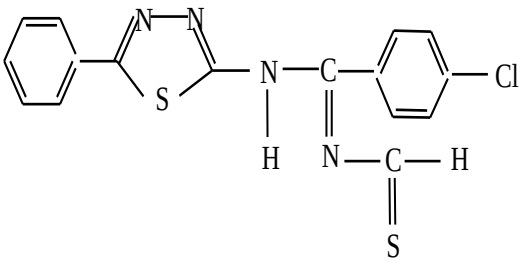
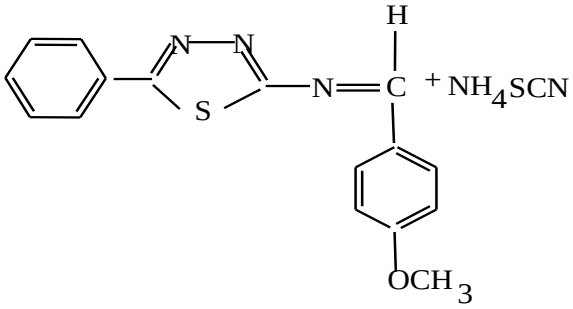
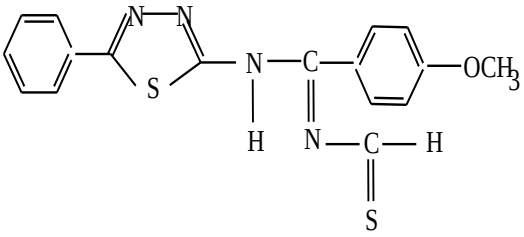
		65 m.p(^{0} C) 153-155
		75 m.p(^{0} C) 168-170
		70 m.p(^{0} C) 208-210
		75 m.p(^{0} C) 114-115

All the synthesized compounds were characterized by using analytical data obtained from m.p IR, ^{1}H NMR, ^{13}C NMR.

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REFERENCES

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