SYNTHESIS AND SPECTRAL CHARACTERIZATION OF 1,3,4-THIADIAZOLE DERIVATIVES

Thesis submitted in partial fulfilment for the requirement of the
Degree of Master of Pharmacy in Pharmaceutical Chemistry
Faculty of Engineering and Technology

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Certificate of Approval

This is to certify that **Sourin Nahar** (**Examination Roll No: M4PHC23027, Registration No:160240 of 2021-2022)** has carried out the project work on the subject entitled, **“Synthesis and Spectral Characterization of 1,3,4-Thiadiazole Derivatives"** under the supervision of **Prof. (Dr.) Tapan Kumar Maity**, Department of Pharmaceutical Technology, Jadavpur University. This project work is submitted by her in partial fulfilment of the requirements for the degree of **Master of Pharmacy (Pharmaceutical Chemistry)** of Jadavpur University. She has carried out her work independently and with proper care and attention to our entire satisfaction.

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DECLARATION OF THE ORIGINALITY AND COMPLIANCE OF ACADEMIC ETHICS

I hereby declare that this thesis contains literature survey and original research as part of my work on **"Synthesis and Spectral Characterization of 1,3,4-Thiadiazole Derivatives"**.

All the informations in this document have been obtained and presented in accordance with academic rules and ethical conduct.

I also declare that as required by these rules and conduct, I have fully cited and refered all the informations and results that are not original to this work.

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PREFACE

Research is carried out to design and develop newer drugs in academic institutions and pharmaceutical industry. The new drug design involves in modifying the existing bioactive drugs to change their therapeutic effects along with developing new bioactive chemical molecules.

Antibacterial resistance is now well documented for many pathogens, and studies with a variety of bacteria indicate that resistance can develop within just a few years. Resistance against many members of fluoroquinolones, particularly older ones, such as ciprofloxacin is increasing. Further advances in quinolone field are likely to provide better compounds capable of dealing with the resistant strains. So, there is ongoing research for the synthesis of less resistance antimicrobial agents with better efficacy.

The heterocyclic compounds display various biological activity. Among the heterocyclic compounds, 1,3,4-Thiadiazole molecule exhibits versatile biological activities including antibacterial and antifungal activity and the compounds with urea functional group were found to have cytotoxic activity.

The present work entitled **"Synthesis and Spectral Characterization of 1,3,4-Thiadiazole Derivatives"** undertaken with an aim to synthesize a suitable lead compound which can be exploited to develop novel antimicrobial agents.

Dedicated to

my guide, family and well wishers

INDEX

CHAPTER 1

INTRODUCTION

INTRODUCTION:

Heterocyclic compounds and their numerous analogues, as well as their uses in the medicinal and chemical area, have attracted chemists' attention over the years. Multiple recent reviews have focused on research on heterocyclic compounds such as pyrazole, tetrahydroquinolines, benzotriazole, 1,2,3,4-tetrazine, thiazole, 2-thiazoline, pyrimidine, and so on. **Thiadiazole** is a 5-membered ring system containing hydrogen binding domain, Sulphur atom and two-electron donor nitrogen system that exhibit a wide variety of biological activity. Due to the inductive effect of sulfur atom this thiadiazole ring is very weak base. Thiadiazole has four isomeric form which are 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, among them 1,3,4-thiadiazole is most pharmacologically active [1] (**Figure 1**).

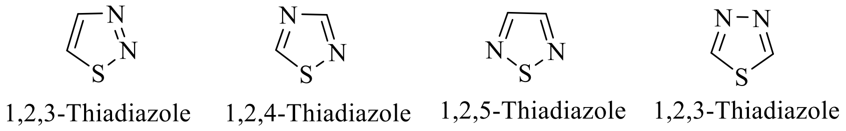

Figure 1: Isomers of Thiadiazole

Thiadiazoles are nitrogen–sulphur heterocycles that have a wide range of applications as structural units in physiologically active compounds and as valuable intermediates in medicinal chemistry. Because of their broad range of pharmacological characteristics, substituted 1,3,4-thiadiazole derivatives have received a lot of attention and have been explored a lot in recent years. Because of the presence of the =N-C-S- moiety, 1,3,4-thiadiazole derivatives are likely to have a variety of biological effects. [2]. Other researchers believe that the biological activities of 1,3,4-thiadiazole derivatives are related to the ring's strong aromaticity, which gives the five-membered ring structure exceptional in vivo stability and lesser side effects in higher vertebrates, including humans [3]. Some investigations have demonstrated the significance of isosterism for a compound's pharmacological profile. According to these findings, the bioisostere of pyrimidine is 1,2,4-thiadiazole, while the bioisostere of pyridazine is 1,3,4-thiadiazole due to the displacement of -CH=CH- by -S-[4, 5]. The benzene ring, oxadiazole, oxazole, and thiazole rings are all bioisosteres of the thiadiazole ring. [1,4]. Compounds with greater lipophilicity and improved biological characteristics may result from the bioisosteric substitution of one ring with another. Because of the sulphur atom in thiadiazole derivatives which provides high liposolubility, slow oral absorption and cell permeability, resulting in high bioavailability. Furthermore, replacing a homocyclic ring with a heterocyclic ring enables the production of certain other compounds that interact more with receptors. [4, 6, 7]. The high prevalence of pyrimidine derivatives in nature and the presence of the pyridazine ring in substances with pharmacological effects (such as the antidepressant minaprine, the GABA-A antagonist gabazine, the nonsteroidal anti-inflammatory drug emorfazone, and the antibacterial cephalosporin cefozopran), it is highly likely that 1,3,4-thiadiazole derivatives will demonstrate biological effects [8, 9, 10]. Moreover, 1,3,4-thiadiazole derivatives can produce mesoionic salts (**Figure 2**). Mesoionic system contains a pentatomic heterocyclic ring which possesses a sextet of *p* and *π* electrons and positive charge counterbalanced by formal negative charge. Despite their internal charges, the mesoionic compounds are neutral and able to cross cellular membranes, and this contributes to the good cell permeability of 1,3,4-thiadiazole derivatives. The mesoionic nature of 1,3,4-thiadiazoles enables these compounds to interact strongly with biomolecules (eg, DNA and proteins) [4, 11].

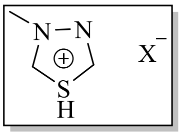

Figure 2: mesoionic salt derivatives of 1,3,4-thiadiazole

1,3,4-Thiadiazole ring is an important scaffold known to be associated with several biological activities including antimicrobial,antituberculosis,antiviral,analgesic,antidepressant and anxiolytic ,antihypertensive ,anticonvulsant, anti-inflammatory, local anesthetic and kinesin inhibitors [12].The biological importance of 1,3,4-thiadiazole derivatives has been reported following the discovery of heterocyclic sulfonamides as reasonable antimicrobial agents (eg, sulfathiazole **1**; Winthrop Chemical Company, NY, USA, 1940) [13, 14]. In analogy to sulfathiazole, other sulfonamides showing similar activity such as "sulfamethizole" **2** (4-amino-*N*-(5-methyl-1,3,4-thiadiazol-2-yl) benzene sulfonamide, Rufol [Urgo Laboratories, Chenove, France]) [15,16] or "sulfaethidole" **3** (4-amino-*N*-[5-ethyl-1,3,4-thiadiazol-2-yl] benzene sulfonamide, Globucid [Schering, Berlin, Germany]) [17] were prepared. Except sulfathiazole that is still used in the treatment of *Haemophilus vaginalis* vaginitis [18], sulfamethizole and sulfaethidole currently possess only historical importance. The synthesis of "acetazolamide" **4** (5-acetylamino-1,3,4-thiadiazol-2-sulfonamide) by Roblin and Clapp [19] (Lederle Laboratories, Pearl River, NY, USA) as carbonic anhydrase inhibitor reoriented the researchers to sulfonamides bearing 1,3,4-thiadiazole ring. The synthetic studies concerning the therapy of parasitic infections gave "megazol" **6** (2-amino-5-[1-methyl-5-nitro-1*H*-2-imidazolyl]-1,3,4-thiadiazole, CL 64855) [20]a nitroimidazole extremely active in experimental infections caused by *Trypanosoma cruzi* and *Trypanosoma brucei* as well as drug-resistant forms of trypanosomiasis.1,3,4-Thiadiazole ring is the constitutive part of some cephalosporins and cephamycins that showed high in vitro activity against both Gram-positive and Gram-negative bacteria. A good example is “cefazolin” **7**, a first-generation cephalosporin which has been used worldwide since the early 1970s (GlaxoSmithKline plc, London, UK; Ancef) [21, 22].

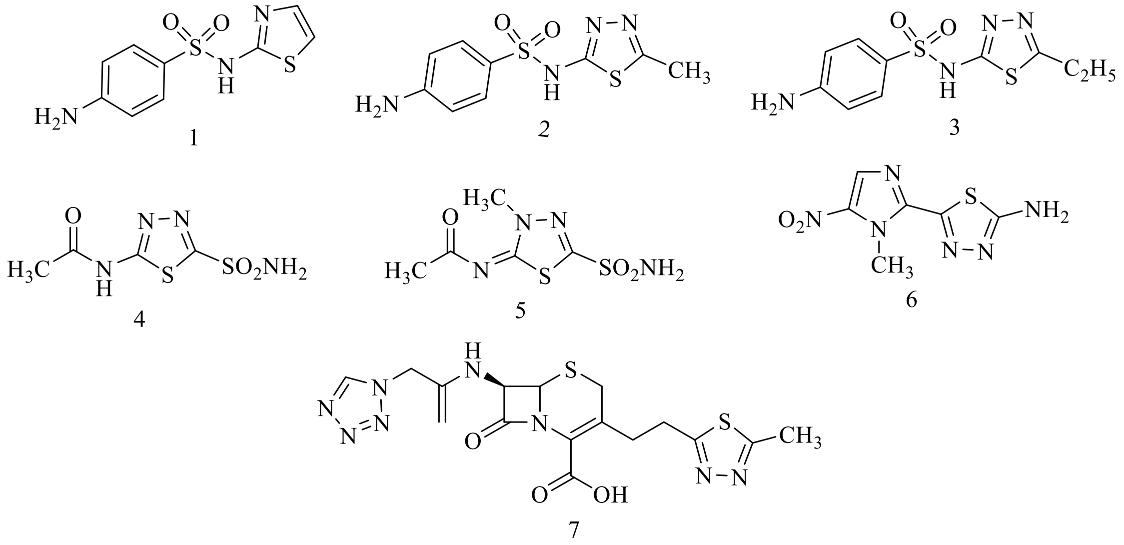

Figure 3:Structure of established molecules bearing 1,3,4-thiadiazole

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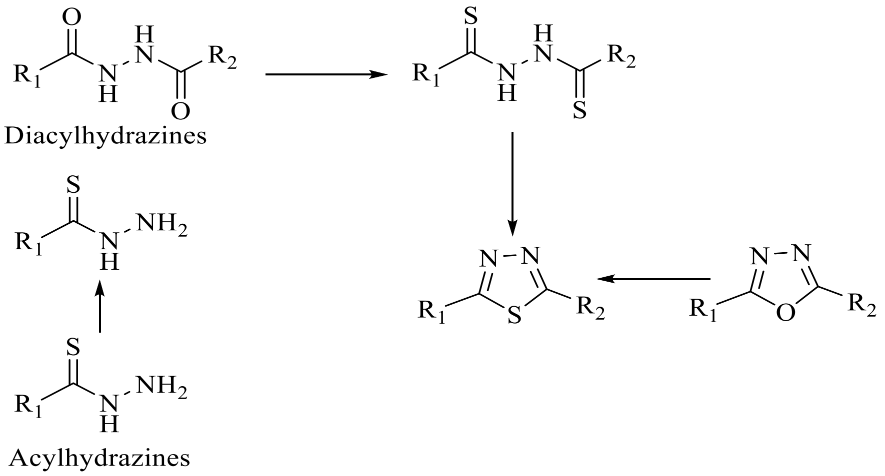
CHAPTER 2
LITERATURE REVIEW

2. LITERATURE REVIEW

2.1. Synthetic Procedures of 1,3,4-Thiadiazoles:

Development of 1,3,4-thiadiazole chemistry is linked to the discovery of phenylhydrazines and hydrazine in the late 19th century. Commonly, 1,3,4-thiadiazoles can be available via general routes from cyclization of acylhydrazines including N, N′-diacylhydrazines and monoacylhydrazines or transformation from 1,3,4-oxadiazoles (Scheme 1). We can also synthesize 1,3,4-thiadiazoles from thiohydrazines including thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines and bithioureas. Herein, summarized some recent strategies on the synthesis of 1,3,4-thiadiazolederivatives hoping that this classification can aid chemists in their preparation.

Scheme 1. General Preparation of 1,3,4-Thiadiazoles from Acylhydrazines or 1,3,4-Oxadiazoles



2.1.1. From Acylhydrazines:

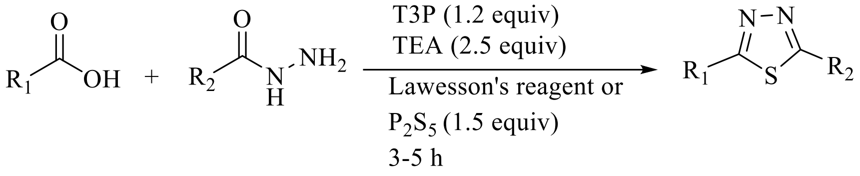
As summarized in Scheme 1, 1,3,4-thiadiazoles can be prepared via sulfuration of the corresponding 1,4-dicarbonyl or acyl precursors using phosphorus sulfide reagents such as P_2S_5 and Lawesson's reagent [1]. However, the common methods reported always suffer from harsh conditions or stoichiometric formation of an intractable byproduct.

2.1.1.1. From Acid Hydrazides:

In the past decades, several kinds of one-pot syntheses of 1,3,4-thiadiazoles have been reported, which can avoid the tedious work of multistep syntheses. Among these methods, some are still conducted under harsh conditions whereas others have been improved. Augustine *et al.* reported a one-pot synthesis of 1,3,4-thiadiazoles directly from carboxylic acids using propylphosphonic anhydride (T3P) (Scheme 2) [2].

2.1.1.2. From Diacylhydrazines:

Cyclization of N, N′-diacylhydrazines is a very common and convenient way to synthesize 1,3,4-thiadiazoles. This method has been well studied by many chemists employing phosphorus sulphides (i.e., P_2S_5 and Lawesson's reagent) in solvents, such as DMF, CH_2Cl_2, THF, dioxane, and PhMe (Scheme.3) [3].



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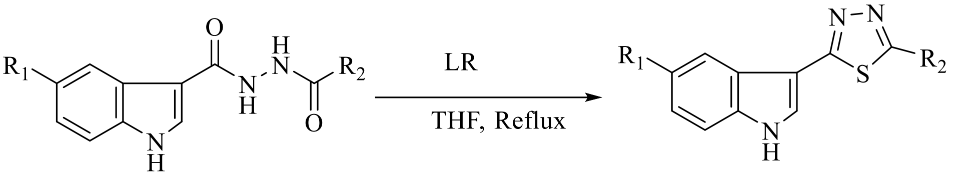


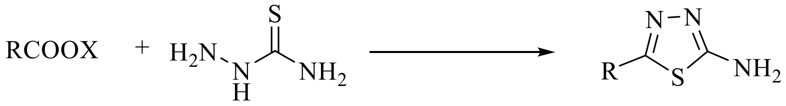
Scheme 3

2.1.2. From Thiohydrazines:

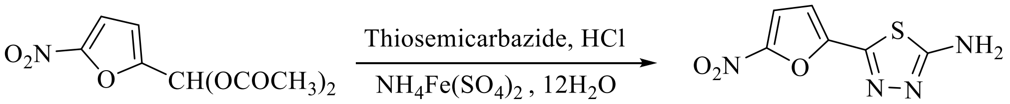
1,3,4-Thiadiazoles can also be prepared by cyclizing thiohydrazines or its equivalents. Each derivative of thiohydrazines can introduce special kinds of substituents to the thiadiazole ring, which allows for 1,3,4-thiadiazoles with a broad spectrum of reactivity and bioactivity. We herein classify thiohydrazines into thiosemicarbazides, thiocarbazides, dithiocarbazates, thioacylhydrazines, bithioureas, and other miscellaneous. The strategies on the synthesis of 1,3,4-thiadiazole derivatives have been summarized below.

2.1.2.1. From Thiosemicarbazides:

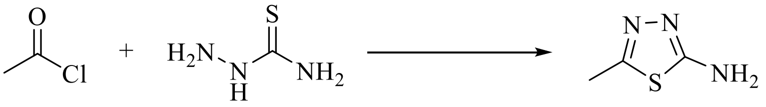
Many syntheses of 1,3,4-thiadiazoles proceed from thiosemicarbazides, substituted thiosemicarbazides, or thiosemicarbazones. Cyclization of thiosemicarbazides or substituted thiosemicarbazides efficiently lead to 2-amino-1,3,4-thiadiazoles, which have been widely studied as crucial intermediates when preparing 1,3,4- thiadiazole derivatives. In this reaction, acylation (Scheme 4) or Schiff base formation on the α-amino group initiates cyclization of thiosemicarbazides and upon the action of a dehydrating agent such as EDCI, DCC, TMSCl, TsCl, PPh3, SOCl2, PCl5, and diphenyl chlorophosphate to obtain thiadiazoles. Many common acylating agents such as carboxylic acid [4, 5] acid halides [6], and acid anhydride (Scheme 5a and 5b) have been used [7].



Scheme 4



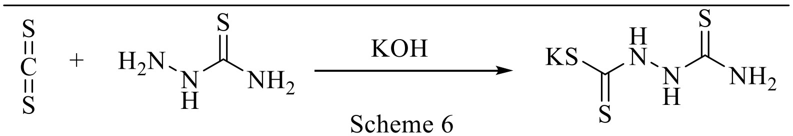
Scheme 5a



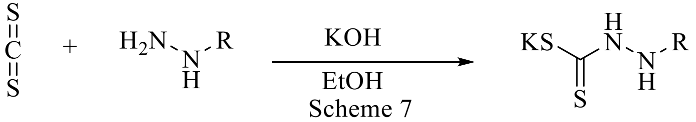
Scheme 5b

2.1.2.2. From Dithiocarbazates:

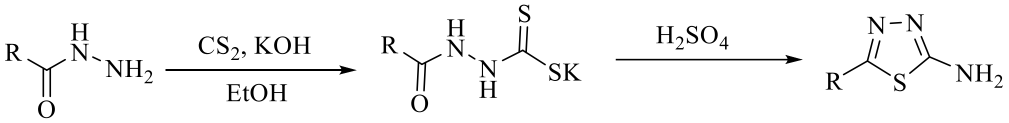
As mentioned above, dithiocarbazates are synthesized by carbon disulfide as the sulfur source reagent reacting with hydrazine, hydrazides, hydrazone, thiosemicarbazide (mentioned in Scheme 6), or thioacylhydrazine usually under basic conditions (Scheme 7). In the same step, dithiocarbazates were always acylated followed by cyclodehydration (concentrated sulfuric acid always being the dehydrant, occasionally CF_3COOH) to generate 2-thiol/thione 1,3,4-thiadiazoles. Wei *et al.* and Kadi *et al.* reported a general method to synthesize dithiocarbazate and 1,3,4-thiadiazole with acylhydrazide (Scheme 8) [8].



Scheme 6



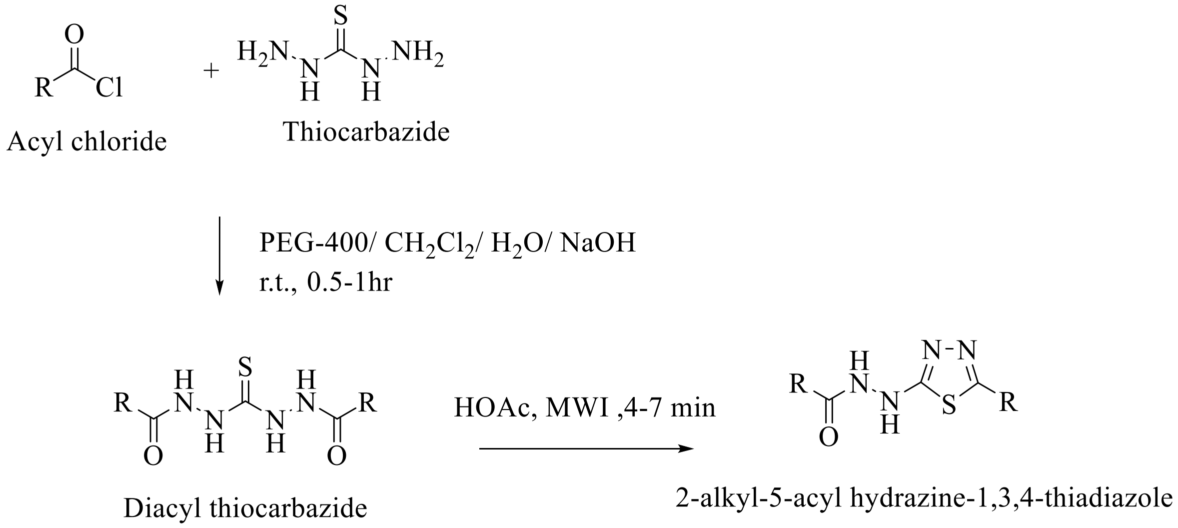
Scheme 7



Scheme 8

2.1.2.3. From Thiocarbazides:

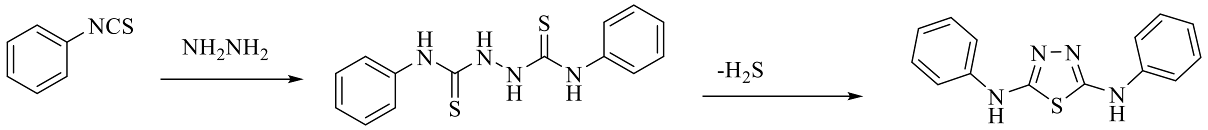
In reaction between Acyl chloride with thiocarbazide in presence of polyethylene glycol 400, dichloromethane, water, sodium hydroxide at room temperature for .5-1 hr, produces diacyl thiocarbazide. This compound then treated with acetic acid in presence of microwave irridation for 4 to 7 min and produces 2-alkyl-5-acyl hydrazine-1,3,4-thiadiazine (Scheme- 9) [1].



Scheme 9

2.1.2.4. From bithioureas:

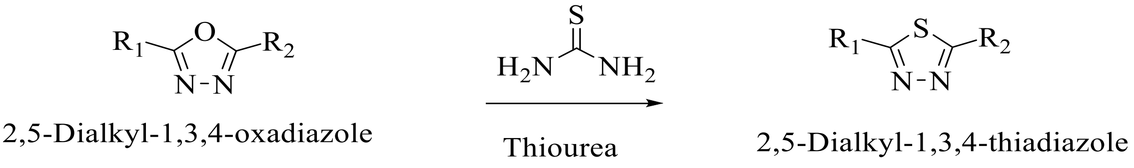
Thiadiazole was prepared by reaction of an alpha amino group on each end of hydrazines or thiosemicarbazides with isothiocyanates and followed by loss of hydrogen sulfide to get 2,5-diamino-1,3,4-thiadiazoles [9].3



Scheme-10

2.1.3. From 1,3,4-oxadiazole:

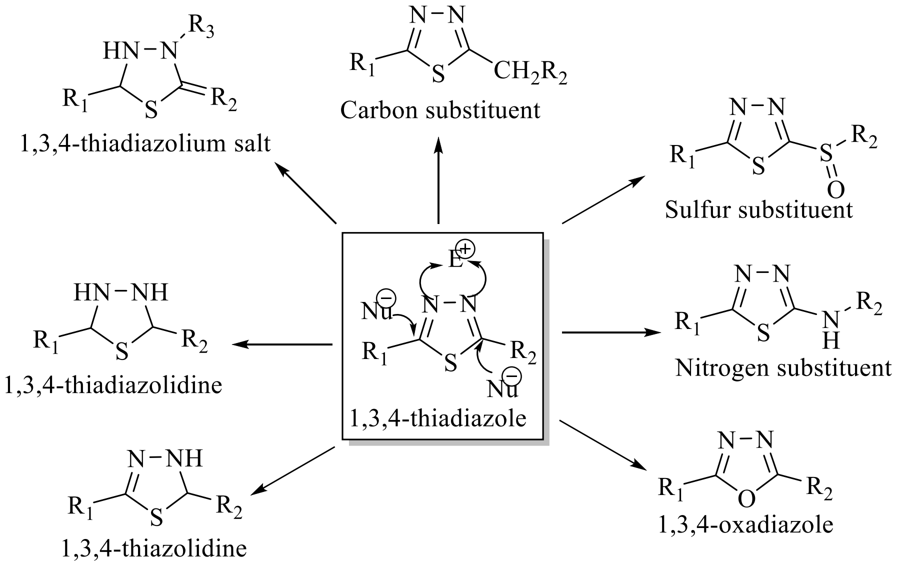
The 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. When 2,5-dialkyl-1,3,4-oxadiazole treated with thiourea, which produces 2,5-dialkyl-1,3,4-thiadiazole yields of 55–69 %, but the reaction time was long (24-30 h) (Scheme- 10) [1].



Scheme-11

2.2. REACTIVITY OF 1,3,4-THIADIAZOLE:

As with most azoles, thiadiazoles are very weak bases due to the inductive effects of the extra heteroatoms. Unsubstituted 1,3,4-thiadiazole ring (first achieved by Goerdeler and Ohm in 1956) with obvious aromaticity cannot easily be substituted nucleophilic, and electrophilic substitutions on carbon are practically unknown, apart from a few halogenations and mercurations [1], while substituted thiadiazoles are susceptible to nucleophilic attack on a carbon atom with leaving groups generally displaced easily [10]. The ring nitrogen atoms suffer electrophilic attack depending on the tautomerizability of the substituents on the C-2 or C-5 position and 1,3,4-thiadiazolium salts or 1,3,4-thiadiazol-2(3H)-ones that can be prepared. Electrophilic attack on ring sulfur atoms is rarely found; as a result, the reactivity of 1,3,4-thiadiazoles arises from the nucleophilic center localized on the ring nitrogen atoms and from the electrophilic center on the carbon of the C=N bond. A supplementary reactivity can arise from conversions of substituents attached to C2/5. Thus, 1,3,4-thiadiazoles are versatile reagents for synthesis of various compounds (Scheme 9). The tautomerism of 1,3,4-thiadiazole is primarily presented by thione−thiol or amino−imino transformation on the C-2 or C-5 position.



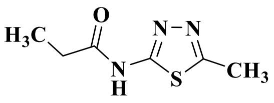
Scheme 9: General reactions of 1,3,4-thiadiazoles

2.3. PHARMACOLOGICAL ACTIVITY:

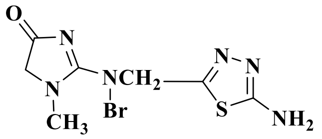
After the discovery of the carbonic anhydrases inhibitor acetazolamide AAZ, the synthesis and biological activities of many 1,3,4-thiadiazoles were reported. A large number of these derivatives have been reported to possess diverse pharmacological properties such as herbicidal, antiviral, antiparasitic, antitubercular, anticonvulsant, analgesic, and antisecretory activities. Moreover, much interest has also been focused on the antibiotic (including antibacterial and antifungal), anti-inflammatory, and anticancer activities displayed by compounds incorporating other heterocyclic systems. Owing to the different activities 1,3,4-thiadiazoles possess, we classify them as follows.

2.3.1. ANTICANCER ACTIVITY:

Thiadiazoles are advantageous frameworks in pharmaceutical chemistry due to their distinctive characteristics. Here, Finiuk *et al.,* concentrated on researching the N-(5-methyl-[1,3,4] thiadiazol-2-yl)-propionamide's anticancer properties. The synthesised thiadiazole derivative **N-(5-methyl-[1,3,4] thiadiazol-2-yl)-propionamide (compound 1, fig.1)** revealed the expansion of its inhibitory activity towards the tumour cells of the HepG2 (liver), HL-60 (leukaemia), and MCF-7 (breast) cancer cell lines with the IC_{50} values in the range of 9.4-97.6 µg/mL. The anti-proliferative efficacy of **Compound 1** declined in the following order: hepatocellular carcinoma > leukaemia > breast carcinoma cells. However, the compound exhibit very little effect on pseudo-normal HEK293 and NIH3T3 cells. This research finding is significant since the compound is a strong anticancer drug [11]. Creatinine is one of the most important basic substances. Numerous studies have shown that heterocyclic compounds made from creatinine have a variety of uses, such as antioxidant, anticancer, and antibacterial characteristics. In this work, 2-substituted-1,3,4-thiadiazole derivatives of creatinine were used to generate novel heterocyclic molecules by Ali *et al.* (2019). 1,3,4-thiadiazole was created in the first stage by cyclizing hydrazide derivatives, while schiff bases were synthesized in the second step by reacting with different aldehydes. These novel chemicals were identified using spectral data (FT-IR and ^{1}H-NMR). The synthesised compounds also showed strong antioxidant and anticancer activities when tested *in vitro* cancer cell lines . The WRL68 normal cell line was less toxic to **Compound 2,** which had a IC_{50} of 238.3 mg/mL when used as an anti-cancer agent [12]. Numerous physiologically relevant compounds have a core structure made up of the 1,3,4-thiadiazole ring system, and a variety of biological activities have been discovered for its derivatives. A novel series of N-(4-acetyl-5-aryl)4,5-dihydro-1,3,4-thiadiazol-2-yl) acetamides and N-(5-(4-(substituted phenyl)-1,3,4-thiadiazol- 2-yl)acetamides were synthesised by the reaction of 2((aryl)methylene)hydrazine-1-carbothioamides with acetic anhydride or chloroacetone. By using the MTT test against the Hela (cervical cancer), MCF-7 (breast carcinoma), and HT-29 (colorectal cancer) cell lines, the cytotoxic effects of the compounds were tested. Significant anticancer activity was shown by N-(4-acetyl-5-(naphthalen-2-yl)-4,5-dihydro-1,3,4-thiadiazol-2-yl) acetamide **(compound 3)** and N-(5-(2,6-difluorophenyl)-1,3,4-thiadiazol-2-yl) acetamide **(compound 4)** against tested cancer cell lines. Apoptotic protein levels were also used to test these active substances. The findings demonstrated that this thiazole and thiadiazole chemicals caused cancer cells to undergo apoptosis [13]. A number of 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles was synthesized by Kumar D *et al*. and evaluated for cytotoxic activity against various cancer cell lines (prostate; DU145 and LnCaP, breast; MCF-7 and MDA-MB-231, cervical; Hela and ovarian; ovcar-3). The compounds were synthesized by the treatment of some intermediate thiosemicarbazides with acetyl chloride, whereas the reaction between indolyl hydrazides and various aryl isothiocyanates afforded intermediate thiosemicarbazides. All the compounds showed selective cytotoxicity towards cell lines used. Among them the most potential cytotoxic compound is **5** with IC_{50} value 0.15-1.18 µM [14]. In continuation of research effort to develop anticancer agent Revelant *et al*. have synthesized series of 1,3,4-thiadiazole derivatives incorporating thienyl amino group. Synthesis of the targeted compounds was achieved via two step procedure, firstly conversion of thiophene isothiocyanate to thiosemicarbazide intermediate and then cyclization of intermediate thiosemicarbazides to final thiadiazole derivatives. The synthesized thiadiazoles and intermediate thiosemicarbazides subjected to anticancer evaluation on panel of six human cancer cell line. Among the compounds, **compound 6** and **7** exhibited better anticancer activity with half inhibitory concentration value lesser than 10 µM [15]. New series of 5-substituted-2-(2,4-dihydroxyphenyl)1,3,4-thiadiazole derivatives were synthesized and these compounds were evaluated for anticancer activity against various human cancer cells. Result of this study revealed that **compound 8** was most active among them. This compound 26exhibited higher inhibitory activity against T47D cells (human breast cancer cells) than cisplatin revealed by Matysiak J *et al* [16].



COMPOUND 1



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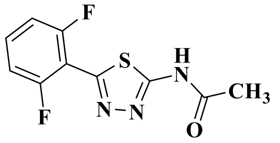

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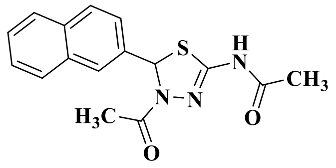

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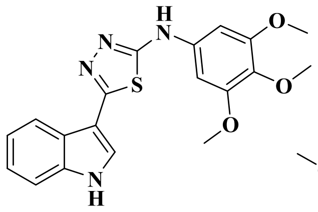

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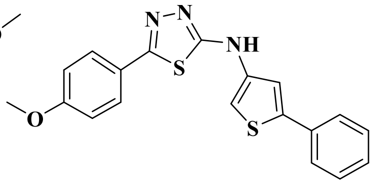

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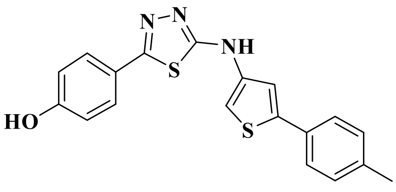

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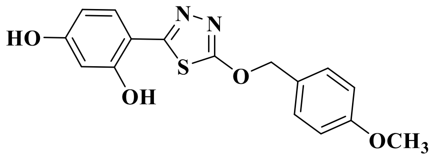
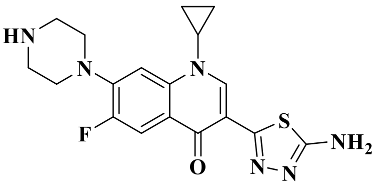


COMPOUND 8

2.3.2. ANTIMICROBIAL ACTIVITY:

2.3.2.1. ANTIBACTERIAL ACTIVITY:

VRE (Vancomycin-resistant enterococci), also known as Enterococcus faecalis and Enterococcus faecium, are high-priority drug-resistant infections that require novel therapeutic strategies. VRE are gastrointestinal tract infections that can develop into more troublesome downstream infections in a medical environment. Decolonization of VRE from carriers is one method to get rid of the downstream infections. Here, scientists provide results from a mouse model of in vivo gastrointestinal decontamination of the VRE using a group of carbonic anhydrase inhibitors containing active scaffold 1,3,4-thiadiazole. It has been demonstrated that intestinal permeability and the antibacterial effectiveness of the compounds affect the in vivo efficacy for VRE gut decontamination. Comparing carbonic anhydrase inhibitors to the current go-to medication, linezolid, they showed overall better VRE decontamination effectiveness [17]. Through [2 + 2] cycloaddition reactions specifically, the Staudinger reaction (ketene-imine) of acyl chloride and a variety of aromatic imines a convenient synthesis procedure has been established for new monocyclic bis-β-lactams that contain a 1,3,4-thiadiazole-2,5-thiol component **compound 9**. It expected that they will contribute to the area of medicine and biological activities due to the existence of a 1,3,4-thiadiazole-2,5-dithiol ring, -substituted-phenoxy groups, 1,2-dihydronaphthalene, a substituted phenyl moiety, and a bis-β-lactam moiety ring. All synthesised compounds shown effective antibacterial properties against two Gram-negative bacteria, Brucella abortus and Escherichia coli, as well as three Gram-positive bacteria, Staphylococcus aureus, Bacillus anthracis, and Clostridium perfringens. In order to establish a moderate binding contact, molecular docking experiments were conducted using the target receptor from *E. coli, S. aureus, B. anthracis, B. abortus, and C. perfringens*, with PDB IDs 3T88, 4Q7G, 3Q2O, 4WJM, and 6PV4, respectively [18]. In order to serve as antimicrobial agents, this study created new ciprofloxacin analogues containing the 2-amino-1,3,4-thiadiazole ring, tryptophan, and various sulfonamides. Then, the activities of the synthesised hybrids were tested against 18 bacterial isolates, including 14 clinical strains (2 Enterobacter cloacae and 12 Klebsiella pneumonia isolates) and 4 standard strains (*Escherichia coli* ATCC 8739, *Staphylococcus aureus* ATCC 25,923, *Acinetobacter baumannii* ATCC 19,606 and *Pseudomonas aeruginosa* PAO1). Investigations found that **compound 10** showed greater antibacterial properties than the commonly used medication, ciprofloxacin, as evidenced by its lower MIC and MBC values [19].



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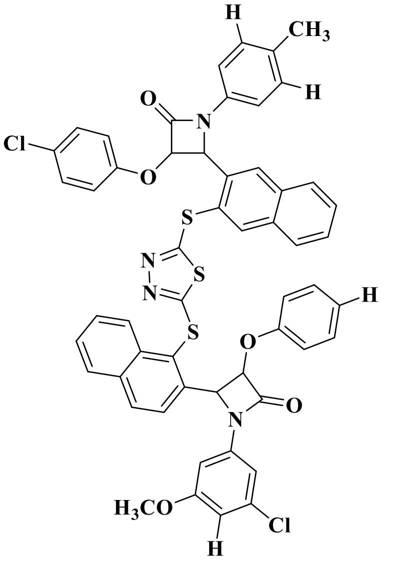

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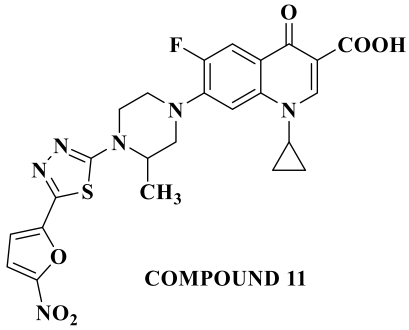

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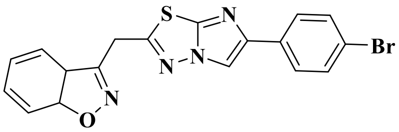
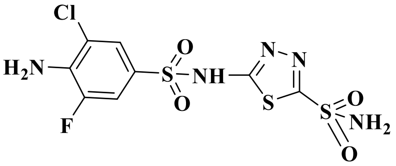


COMPOUND 13



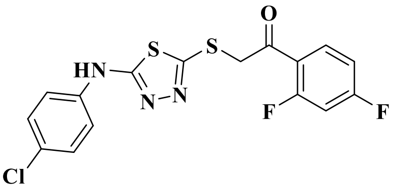
COMPOUND 12

New series of nitroaryl-1,3,4-thiadiazol derivatives were synthesized by condensing 2-chloro,5- nitroaryl-1,3,4-thiadiazol with gatifloxacin and $NaHCO_3$ in DMF by Jazayeri *et al.* Synthesized compounds were evaluated for antimicrobial activity against gram-positive bacteria including staphylococcus epidermidis (MIC = 0.0078 µg/mL), bacillus subtilis (MIC = 0.125 µg/mL), E. Faecalis (MIC = 0.0039 µg/mL) and micrococcus luteus, *escherichia coli* using agar dilution method and their zone of inhibition was compared with gatifloxacin as standard. Due to the presence of nitrofuran at C-2 of thiadiazole ring caused complete inhibition of DNA gyrase or DNA topoisomerase IV. Result of this study revealed that compound **11** was most potent compound [20]. Nishimori I *et al.* synthesized some sulfonamide containing 1,3,4-thiadiazole derivatives which acts on β-carbonic anhydrases enzyme isolated from bacterial pathogen (*Salmonella enterica*, *Salmonella typhimurium*, *Candida albicans* etc), involved in hydration of carbon dioxide to bicarbonate and protons, which is essential for many organisms, including bacteria and fungi. These synthesized compounds were evaluated for antimicrobial activity against *Salmonella enterica, Salmonella typhimurium* and their activity was compared with acetazolamide as standard drug. Result of this study revealed that **compound 12** was most potent with inhibition constant of 51nM against stCA 1 and 38 nM against stCA 2, while acetazolamide inhibited stCA 1 and stCA2 with KI of 59 and 84 nM, respectively [23]. A new series of novel methylene bridged benzisoxazolylimidazo[2,1-b][1,3,4]thiadiazole derivatives were synthesized by condensing benzisoxazolyl-3-acetic acid and thiosemicarbazide by Lazmi S. R. *et al*. Synthesized compounds were evaluated for antimicrobial activity against two Gram-positive bacteria, Staphylococcus aureus, Bacillus subtilis and Gram-negative bacteria Pseudomonas aeruginosa, Escherichia coli using Ampicillin as standard drug and antifungal activity against Candida albicans and Aspergilus fumigatus using Clotrimazole as standard drug. Result of this study revealed that **compound 13** was most potent [21].

2.3.2.2. ANTIFUNGAL ACTIVITY:

With an aim for the development of new antifungal agent, Karaburun *et al.* have synthesized some new 1,3,4-thiadiazoles via three steps and evaluated for their antifungal activity against eight candida strains. Among the synthesized compounds the derivative **14** and **15** showed potential antifungal activity. The mechanism of antifungal activity was assessed using in vitro ergosterol quantification assay via LC-MS/MS method and in silico docking study against 14-α-demethylase for investigation of inhibitory potency on ergosterol biosynthesis. Theoretical calculation of ADME profile revealed that the compounds are druggable candidates, which elevated their Pharmacologic importance. From the result of this research work it is concluded that the new thiadiazole compounds are potential antifungal agents with inhibitory activity on ergosterol biosynthesis [22]. In search of novel lead molecule having antifungal potency, Wang *et al*. has designed and synthesized a series of 1,3,4-thiadiazole based thiourea entails with thioether functionality. The targeted compounds were synthesized using commercially supplied hydrazine carbothioamide as starting material. Structure of the prepared compounds analysed by experimental data obtained from HRMS, IR, ^{1}H NMR and ^{13}C NMR. Antifungal activity evaluation on four fungal strains (*Curvularialunata, Cotton Fusarium Wilt, P. P. var nicotianae* and *Fusarium spp*) showed that some compounds exhibit significant antifungal activity against tested fungal strain, among them the best molecule is **16**. The work warrant further development of potent antifungal agent [26]. A series of 5-amino-1,3,4-Thiadiazole tethered with dihydropyrimidine **17,** was synthesised via an easy synthetic procedure by Karthic *et al*. The thiadiazole containing pyrimidine moiety synthesized from intermediate carbothioamide derivatives, and under appropriate reaction condition the pyrimidine ester was converted to carbothioamides. The structure of the synthesized compound assured by analysing the data obtained from IR, ^{1}H NMR, ^{13}C NMR and GC-MS. The result of the antifungal activity evaluation revealed that the compound exhibits notable growth inhibition of fungal strain used [23].

A series of new 2-amino-1,3,4-thiadiazole derivatives (**18 and 19**) containing acyl functionality was synthesized by Mustafa *et al.* and tested for their antifungal activity on plant pathogenic fungal strains. The result of the antifungal evaluation showed moderate to excellent activity of the compounds against fungal strain employed. Also, an in-silico study via similarity search, homology modelling, molecular dynamics and molecular docking assist in finding potential molecular target of the synthesized compound. The outcome of the study demonstrated a way for further development of antifungal agent [24].



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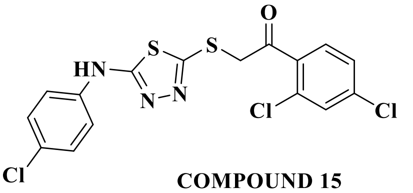

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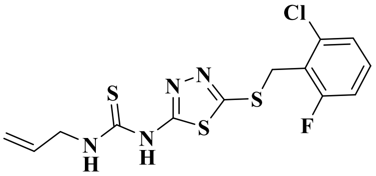

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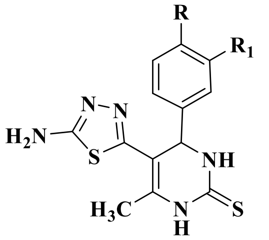

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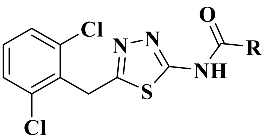

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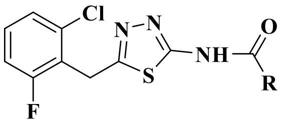


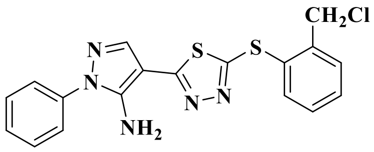
COMPOUND 19

2.3.2.3. ANTIVIRAL ACTIVITY:

The systemic tobacco mosaic virus (TMV) is a severe danger to crops all over the world. Novel 1-phenyl-4-(1,3,4-thiadiazole-5-thioether)-1H-pyrazole-5-amine derivatives were synthesised in the current studies. Results from *in vivo* antiviral bioassays showed that several of these substances have outstanding TMV protective efficacy. Compound 20 outperformed the commercial agent ningnanmycin (EC50 = 261.4 g/mL) among the compounds (EC_{50} = 203.5 g/mL). It was discovered by looking at tobacco leaves that had been infected with TMV-GFP that Compound 20 could successfully stop TMV from spreading throughout the host. The tight alignment and arrangement of the spongy mesophyll and palisade cells, together with the stomatal closure that results, formed a protective barrier to ward off viral infection in the leaves, according to further plant tissue morphological observations. MDA and H_2O_2 content measurements showed that **Compound 20** could successfully lower the peroxide concentration in the diseased plants, decreasing the oxidation-related harm to the plants. The study and development of antiviral agents for crop protection is greatly aided by this work [25]. To develop novel antiviral agents, Brai *et al*. has designed and synthesized a series of thiadiazole based molecules against viral target human helicase DDX3X. Preliminarily compounds were screened for their enzyme inhibitory activity and then the best active compounds were subjected to antiviral assay on HIV-1 cells. Cytotoxicity of the compounds were also determined on H9 cells. In vitro ADME assays of the compound revealed different metabolic stability of the compounds, however exhibit good membrane permeability and aqueous solubility. In silico computational docking study showed required binding interactions of the compounds towards enzyme. Taking in to account both the biological profile and pharmacokinetic profile it is concluded that the best compound **21** (K_i = 1.9 ± 0.4 µM) is a good antiviral agent, which may be further modified for the development of promising antiviral agents [29]. Some 1,3,4-thiadiazole derivatives synthesized by Hamad *et al.* from amino acid analogues were screened for anti-HIV-1 (strain IIIB) and anti-HIV-2 (strain ROD) activity by the inhibition of the virus-induced cytopathic effect in human MT-4 cells based on 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. 2-(Naphthalen-2-yloxy)-*N*-((5-(phenylamino)-1,3,4-thiadiazol-2-yl) methyl)acetamide **22** possessed in vitro inhibitory activity with EC_{50} values of 0.96 μg/mL (HIV-1 strain IIIB) and 2.92 μg/mL (HIV-2 strain ROD), respectively, but low selectivity (SI <1). Structure–activity relationship (SAR) studies have suggested that the substitution of the acetamide moiety with a thiadiazole ring may lead to more active derivatives compared to other compounds bearing different heterocyclic rings. Even though anti-HIV activity and selectivity of derivative **22** is limited compared to efavirenz (EC_{50} value of 0.003 μg/mL and SI ≈ 13333), it may serve as the basis for future modification in the search for new potent non-nucleoside antiviral agents [26].

A pyridine containing aryl amino 1,3,4-thiadiazole **23** was synthesized through cyclization of corresponding thiosemicarbazide. Thiadiazole **23** was evaluated for antiviral activity on hepatitis B virus (HBV) using HepG2 cells and cytotoxicity of the compound was also tested for cell safety at antiviral concentration. From the result of the work, it was seen that compound is effective toward inhibition of virus (IC_{50} = 0.3 µM) at non cytotoxic concentration (CC_{50} =

333.3 µM). The outcome of the research work warrants further optimization and development of 1,3,4-thiadiazole based antiviral agents [27].



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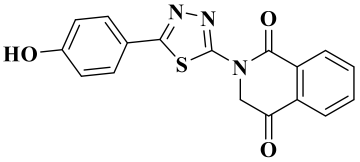

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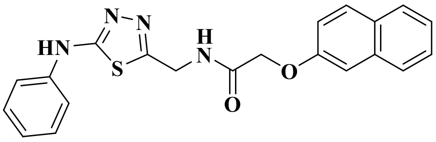

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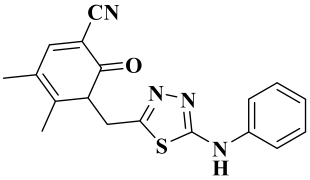
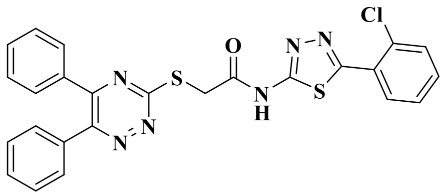


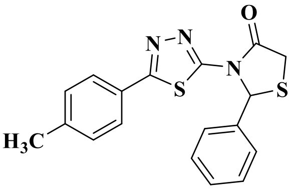
COMPOUND 23

2.3.3. ANTIDIABETIC ACTIVITY:

8) A number of 1,3,4-thiadiazole-5,6-diphenyltriazine hybrids have been synthesised and tested for their ability to inhibit α-glucosidase by Hariom *et al.* Compared to the reference drug acarbose (IC_{50}= 844.81±0.53 µM), all the synthesised compounds demonstrated improved inhibitory activity with IC_{50} values ranging between 14.36 to 743.15 µM. The most effective inhibitor in the series was discovered to be **compound 24**, which had a chloro substituent at the ortho position of the phenyl ring at the thiadiazole moiety. The binding posture and binding interactions at the enzyme site of α -glucosidase were also determined using the blind molecular docking investigations of all the hybrid compounds [28]. In a one-pot multicomponent synthesis, 5-substituted phenyl-1,3,4-thiadiazol-2-amines, substituted benzaldehydes, and 2-mercaptoacetic acid were used to create a novel library of thiazolidine-4-one molecular hybrids by Lalitha *et al.* Through the inhibition of α-glucosidase and α-amylase, as well as their antioxidant and antibacterial potentials, the synthesised compounds exhibited significant antidiabetic properties. The IC_{50} value of **compound 25**, which has a para-thiomethyl group on the phenyl ring of the thiazolidine-4-one moiety, was 2.6 µM, which is superior than the values for the standard acarbose (IC_{50} = 3.8 µM for α-glucosidase and 35.62 µM for α-amylase). Additionally, molecular docking investigations confirmed the importance of the para-thiomethyl unit for significant inhibition of α-glucosidase and α-amylase [29]. Inhibitors of α-glucosidase play a crucial role in the management of type 2 diabetes. In this regard, there is a great demand for the development of innovative and effective non-sugar-based inhibitors. Novel 5-arylisoxazole-1,3,4-thiadiazole hybrids with action against α-glucosidase were designed and synthesised by Mina *et al*. Different 5-arylisoxazole-3- carboxylic acids and ethyl 2-((5-amino-1,3,4-thiadiazol-2-yl) thio) acetate were combined to create diverse compounds. They were then tested for their ability to inhibit α-glucosidase. In comparison to reference acarbose (IC_{50} value of 750.0 µM) it was discovered that ethyl 2-((5-(5-(2-chlorophenyl) isoxazole-3-carboxamido)-1,3,4-thiadiazol- 2-yl) thio) acetate (**compound 26**) was the most effective (IC_{50} = 180.1 µM) α-glucosidase inhibitor. Additionally, the docking study findings showed desirable interactions of this molecule with amino acid residues near to the active site of α-glucosidase, and the kinetic investigation of **compound 26** suggested a competitive inhibition. The strong α-glucosidase inhibitory activity of title compounds established them as effective scaffold that should be taken into account in the development of anti-diabetic drugs [30]. Inhibition of α-glucosidase enzyme is an important aspect for the control of type-2 DM, in view of this fact Javid *et al.* have designed and synthesized a series of thiadiazole derivatives to develop molecule as a α-glucosidase inhibitor. In this study new series of thiadiazole imine derivatives were synthesized and subjected to α-glucosidase inhibition assay. Biological activity study data suggested that compounds are excellent inhibitor of the enzyme with activity in the micromolar range. The best active compound among the series are **27** and **28** having **IC_{50}** value of **2.30** µM. Docking study of the compounds against enzyme also revealed required binding interaction at the catalytic site and in good agreement with experimental results. Datar *et al*. have synthesized some thiadiazole derivatives and evaluated for their in vivo antidiabetic activity on alloxan induced diabetic rat and also subjected to in vitro α-amylase inhibitory assay. The compounds were preliminarily designed based on their docking study against PPAR-γ and synthesized thereafter. Outcome of this work revealed that compounds showed significant lowering of blood glucose level, among them the best active compound was found to be TD7 in in vivo and in vitro study. Gummidi *et al*. reported the synthesis and antidiabetic activity evaluation of 1,3,4-thiadiazole and thiazolidine hybrid molecules. The compounds were synthesized via multicomponent one pot reaction step and subjected to in vitro α-glucosidase and α-amylase inhibitory assay. Outcome of the biological study suggested that the compounds exhibit excellent enzyme inhibition property in the micromolar range. Among the compounds, derivative **29**(**IC_{50} = 2.59 µM**) showed best inhibitory potency and its potency is superior than standard drug acarbose. Furthermore, molecular docking experiment directed the significance of para thiomethyl group in phenyl moiety on thiadiazolidine ring towards enzyme inhibition. This research work provides novel lead molecule for the development of compounds active against diabetic complications [31].



COMPOUND 24



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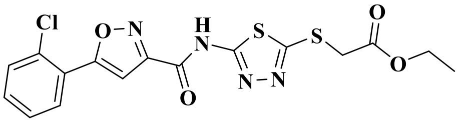
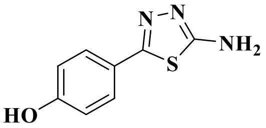


COMPOUND 26



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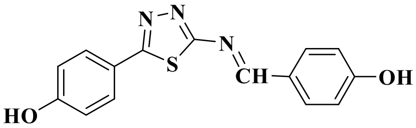

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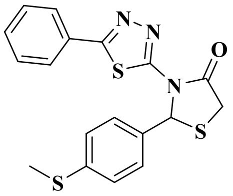
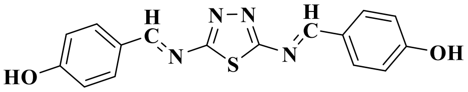


COMPOUND 29

2.3.4. ANTIHYPERLIPIDEMIC ACTIVITY:

It is of utmost importance to develop new antihyperlipidemic drugs with greater effectiveness and fewer adverse effects. As potential PPARα agonists, 1,3,4 thiadiazole Schiff base derivatives such as **compound 31**, **compound 30** and **compound 32** were developed in this study and characterised using elemental analysis, FTIR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. They were then tested for their hypolipidemic activity in a rat model of acute hyperlipidaemia caused by Triton WR-1339 and compared to Bezafibrate. Comparing the three compounds studied to the untreated control group, **compound 2** was the only one to significantly raise HDL levels while the other two compounds considerably lowered LDL levels. Genes associated in cholesterol catabolism (Cyp11a1 and Cyp7a1) and LDL receptors (Lrp12 and Lrp1b) were increased by **compound 30** in the lipoprotein signalling and cholesterol metabolism gene array. Additionally, **compound 30** increased the expression of the PPAR-δ gene (peroxisome proliferator-activated receptor-δ) by nine times [32]. The 2,5,6-trisubstituted imidazo[2,1-b] [1,3,4] thiadiazoles **4(a-d)** and **7(a-i)** were synthesised from 5-(1,3-benzodioxol-5-yl)- [1,3,4] thiadiazol-2-amine **(1)** after being rationally designed using a

QSAR-based pharmacophore method. By using the IR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques, the structures of these compounds were determined. Using a TRITON-induced hyperlipidemic animal model, the antihyperlipidemic activity of each drug was assessed *in vivo*. When compared to the conventional medicine Fenofibrate, the newly synthesised title **compounds 33, 34, and 35** demonstrated a considerable decline in serum, TCH, TG, LDL, and VLDL values as well as an increase in serum HDL levels. In addition, compared to the cholesterol-induced hyperlipidemic control group, the treated groups demonstrated a substantial decline in the atherogenic index, LDL: HDL risk ratios, and levels of SGOT, SGPT, and ALP activities [33]. Hamadneh *et al*. deals with the synthesis and hopolipidemic potential of three 1,3,4-thiadiazole derivatives. Compound **31**, **30** and **32** were prepared and evaluated for antihyperlipidemic activity in Triton WR-1339-induced acute hyperlipidaemia of rat model. Biological activity study result revealed that compound **1** and **2** causes significant reduction of TG and TC levels. All three compounds induced significant reduction of LDL level, while only compound **2** exhibited increased level of HDL. In silico docking study involving binding interaction between compounds and PPAR-α at 1KKQ binding site revealed significant bonding interaction, validated from docking score [34]. Patel *et al*. carried out the synthesis of a series of imidazo-thiadiazole with substitution at 2, 5 and 6 position and evaluated their antihyperlipidemic activity on Triton-X-100 induced hyperlipidaemia in rat model. The compounds were designed based on pharmacophore model, developed from existing compounds and synthesized via several reaction steps. The result of the biological study revealed that after treatment with compounds causes significant lowering of serum lipid profile in hyperlipidemic rat, among the compound the best active molecule is **35**. This study provides a way for the development of novel lipid lowering agent [35].



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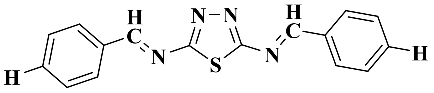

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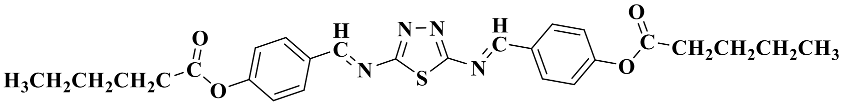

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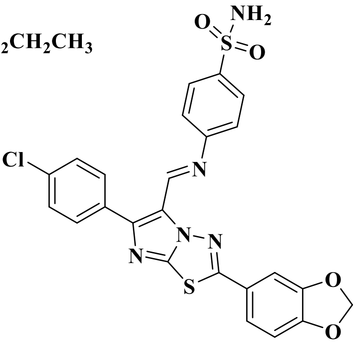

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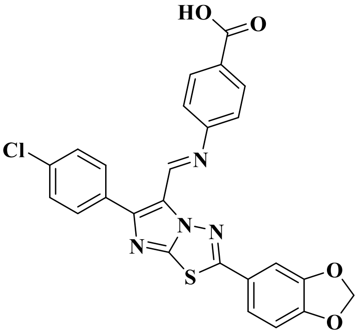

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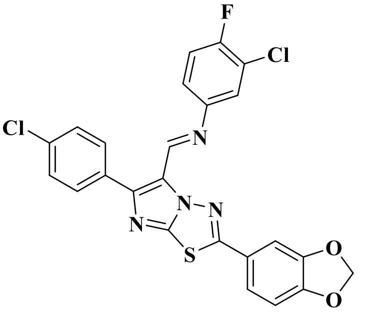


COMPOUND 35

2.3.5. ANTICONVULSANT ACTIVITY:

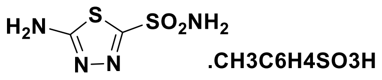
A combination of physicochemical techniques, three salts of 5-amino-2-sulfonamide-1,3,4-thiadiazole (**Hats**) were synthesised by Diaz *et al*. Since many CAIs are clinically employed as pharmacological drugs, the p-toluensulfonate **(36)**, methylsulfonate **(37)**, and chlorhydrate monohydrate **(38)** salts of Hats were examined as carbonic anhydrase inhibitors (CAIs), as well as anticonvulsants and diuretics. Eight mice per group received intraperitoneal injections of physiological saline solution (control), whereas other animals received injections of the substances Hats.tosylate, Hats.MeSO3H, Hats.HCl, and standard at doses of 20, 50, and 90 mg/kg of live animal, in volumes of 0.1mL per 30 g mouse. However, the convulsions protection was effective at larger dosage (50 and 90 mg/kg of test chemical), since none of the mice experienced convulsions. These data imply that they are successful in preventing mild convulsions. The rota-rod test and chimney test did not reveal any neurotoxic effects over the whole range of therapeutic dosages of the compounds [36]. Foroumadi *et al.* have reported the synthesis of amino thiadiazole derivatives 4a-d via simple reaction steps, and assessed their anticonvulsant property on pentylene tetrazole (PTZ) and maximal electroshock (MES) induced convulsion in animal model. Outcome of the experiment demonstrated compound **40** (MES (ED_{50}=20.11) and PTZ (ED_{50}=35.33)) is the better active compound among the tested derivatives [37].

A series of quinazoline containing 1,3,4-thiadiazole derivatives were synthesized by Jatav *et al*. and evaluated for anticonvulsant activity in PTZ and MES induced convulsion in mice model. Biological activity data displayed compound **39**, **40** and **41** are only compound exhibit anticonvulsant activity among the derivatives synthesized [38].

In another research study, Botros *et al*. carried out the synthesis of some 1,3,4-thiadiazole and phenytoid hybrid molecules (6a-e) and tested their anticonvulsant activity in maximal electroshock seizure induced mice. A moderate potency towards reduction of convulsion was observed for the prepared derivatives [39].

New series of substituted 2-hydrazino-1,3,4-thiadiazole derivatives were prepared by condensing aryl dithio esters with thiocarbonyl hydrazines. Synthesized compounds were evaluated for anticonvulsant activity by using Maximal Electroshock Seizures (MES) and Maximal Metrazol Seizures (MMS) in the Mouse and Rat and results were Compared with Phenytoin, Phenobarbital, and Carbamazepine After Oral Administration. Result of this study revealed that **compound 42** (2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole) was most potent compound among them by Stillings *et al* [40].

Dogan *et al.* synthesized new series of 2,5-disubstituted-1,3,4-thiadiazoles by dehydrative cyclization in acidic medium of the thiosemicarbazides. Synthesized compounds were evaluated for anticonvulsant activity against pentylenetetrazole-induced convulsions and results were compared with sodium valproate (150 mg/kg, ip, 80% protection) as a standard pharmacological drug. Highest protection 90 % was obtained by compound [2-Ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole] (ED_{50} 33 mg/kg) [41].



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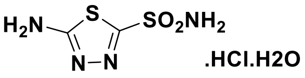

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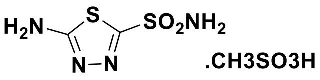

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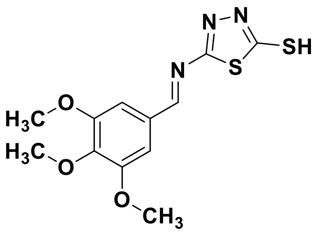

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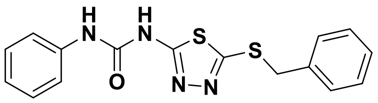

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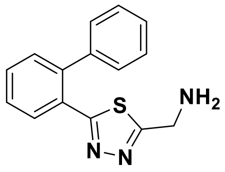

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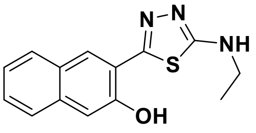
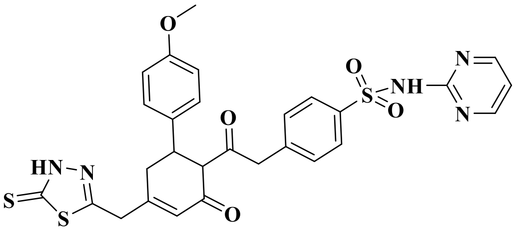


COMPOUND 42

2.3.6. ANALGEASIC AND ANTI-INFLAMMATORY ACTIVITY:

Due to cardiotoxicity of celecoxib, COX2 inhibitors with less side effects are required. Additionally, clinically, low-dose radiation (LDRT) is utilised to treat inflammatory illnesses. The goal of the current investigation was to determine if a novel series of 1,3,4 thiadiazole derivatives had analgesic and anti-inflammatory effects when used alone or in combination with LD-RT at a single dose of 0.5 Gy. The most powerful candidates were found to be the sulfonamide-containing compounds 5-10, with IC_{50} values in the range of 0.32-0.37 µM and the best selectivity indices. This was determined by in vitro COX1/COX2 inhibition experiments. Treatment with compounds 5–10 reduced oedema caused by carrageenan roughly upto 47–56%, which was virtually equal to celecoxib. Celecoxib and **compounds 43 and 44** had analgesic activity of 64.15%, 49.5%, and 84.9%, respectively, while compounds 5, 6, 9, and 10 lacked any analgesic efficacy until paired with LD-RT [42]. NSAIDs, often known as non-steroidal anti-inflammatory medicines, are a significant pharmacological family of medications used to treat inflammatory conditions. They also have serious adverse effects such gastrointestinal injury, increased cardiovascular risk, and abnormalities in renal function. A series of 2,6-diaryl-imidazo[2,1-b] [1,3,4] thiadiazole derivatives 5a-l were made, and their anti-inflammatory and analgesic activities in carrageenan-induced rat paw edema were tested in vivo. This was done in an effort to create new anti-inflammatory and analgesic substances with a safer profile of side effects. All of the compounds shown anti-inflammatory action, with

compound 45 outperforming the industry standard medication diclofenac. Compounds 5g, 5i, and 5j also demonstrated antinociceptive activity on the same level with diclofenac. Theoretical bond interactions between the chemicals and their target, the cyclooxygenases (COX-1/COX-2) were examined by molecular docking experiments [43]. Hilfiker *et al.* synthesized new series of aminothiadiazole amide derivative by condensation of semicarbathiazide with desired carboxylic acid and these synthesized compounds were evaluated for anti-inflammatory activity with cyclooxygenase-1 (COX-1), COX-2, and thromboxane synthase inhibitory activity with selective EP3 receptor antagonist. Result of this study revealed that compound **46** shows good antagonist activity for human EP3 and also against other EP subtypes like DP, FP, TP prostenoid receptor [44]. New series of 2-trifluoromethyl/ sulfonamido-5,6-diaryl substituted imidazo[2,1-b]-1,3,4thiadiazoles derivatives were synthesized by condensing 2-amino-5-trifluoromethyl/sulfonamido-1,3,4-thiadiazoles with a-bromo-1,2-(p-substituted) diaryl-1-ethanones by Gadad *et al*. Synthesized compounds were evaluated for anti-inflammatory activity and their activity was compared with celecoxib in the carrageenan-induced rat paw edema method. Among them compound **47** shown selective inhibitory activity toward COX-2 (80.6%) over COX-1 (30.6%) [45]. Some 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives were prepared by condensing 4-amino-5-substituted-3-mercapto-(4H)1,2,4-triazoles with aromatic acids through one-pot reaction. Synthesized compounds were evaluated for anti-inflammatory and analgesic activity with reduced ulcerogenic effect with compared to Ibuprofen, Flurbiprofen. Result of this study revealed that **48** showed most potent activity by Amir M *et al* [46].



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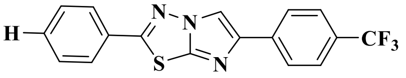

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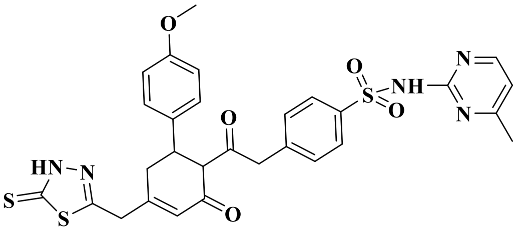

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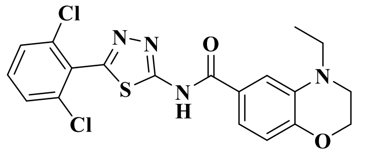

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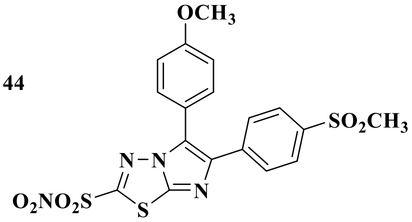

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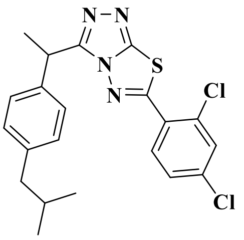
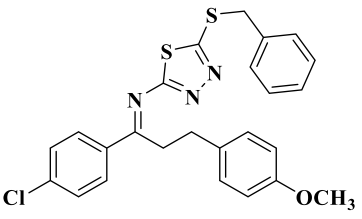


COMPOUND 48

2.3.7. ANTIDEPRESSANT ACTIVITY:

A number of new imine derivatives of 5-amino-1,3,4-thiadiazole-2-thiol synthesized by Ahmed B *et al.* by carbon disulfide addition to thiosemicarbazide under reflux and subsequent addition of different chalcones. Synthesized compounds were evaluated for their anti-depressant activity using imipramine as reference drug. compounds 5-{[1-(4-chlorophenyl)-3-(4-methoxy-phenyl) prop-2-en-1ylidene]-amino}- 5-benzylthio-1, 3,4 –thiadiazole **(49)** have shown significant anti-depressant activity, which decreased immobility time by 77.99% compared to the standard imipramine (82%). These compounds in the series have passed neurotoxicity tests also [47]. The derivatives of 5-(substituted amino)-3H-spiro(indoline-3,2-[1,3,4]thiadiazol-2-one are produced when 4-substituted thiosemicarbazides are reacted with 3-(dicyanomethylene)-2-indolone in an ethanol/piperidine solution. Using the behavioural tail suspension test, the synthesised compounds (**8a–e**) were assessed for their antidepressant efficacy. At a dosage level of 30 mg kg^{-1}, **compound 50** showed a noticeably protective effect that was superior to phenytoin sodium and roughly equivalent to phenobarbital sodium. At a dosage level of 30 mg kg^{-1}, **compound 51** has a significant protective effect that is comparable to that of phenobarbital sodium and superior to that of phenytoin sodium. As a result, these substances seem promising in terms of their antidepressant and anticonvulsant properties [48]



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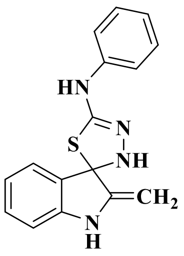

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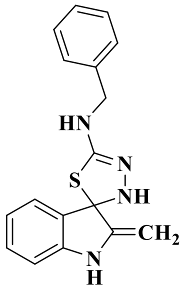
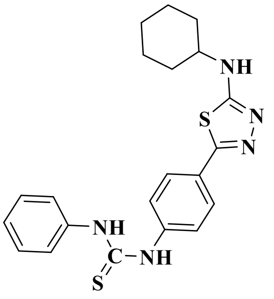


COMPOUND 51

2.3.8. ANTITUBERCULAR ACTIVITY:

Rollas S *et al.* synthesized a new series of N-phenyl-N7-[4-(5-alkyl/arylamino-1,3,4-thiadiazole-2-yl) phenyl] thiourea derivatives by condensing 4-(benzoylamino) benzoylhydrazine with isothiocyanates. Synthesized compounds were evaluated for antitubercular activity by using in vitro BACTEC 460 Radiometric System against Mycobacterium tuberculosis. Results were compared with Rifampicin using as standard. The highest inhibition observed with the synthesized compound **52** is 67% for N-phenyl-N7-[4-(5-cyclohexylamino-1,3,4-thiadiazole-2-yl) phenyl]thiourea (MIC- 6.25 µg/ml) [46]. Two series of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters were synthesized by the reaction of nitroaryl aldehyde with thiosemicarbazide in refluxing ethanol. Synthesized compounds were screened for antituberculosis activity against Mycobacterium tuberculosis using the BACTEC 460 radiometric system. The MIC values for the compounds showing more than 90% inhibition were determined. The result of the study was compared with standard Rifampicin. The **compound 53** was the most active one (MIC = 1.56 µg/ml) revealed by Foroumadi A *et al* [49]. A series of 2,5-disubstituted-1,3,4-thiadiazoles were synthesized by reacting 4-substituted benzoic acid hydrazides with thiosemicarbazides by Rollas S *et al.* Synthesized compounds were elucidated and screened for the antituberculosis activity against Mycobacterium tuberculosis using the BACTEC 460 radiometric system. Among the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole (**54**) showed the highest inhibitory activity (69% inhibition) [50].



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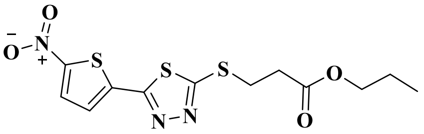

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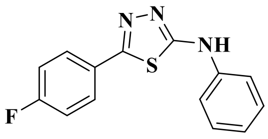
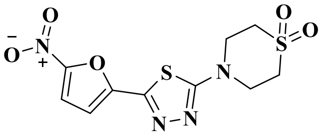


COMPOUND 54

2.3.9. ANTI-HELICOBACTER PYLORI ACTIVITY:

Foroumadi *et al*. synthesized a new series of N-[5-(5-nitro-2-heteroaryl)-1,3,4thiadiazol-2-yl] thiomorpholine derivative by refluxing 5-nitroaryl-2-carboxaldehydes with thiosemicarbazide. Synthesized compounds were evaluated in vitro Anti helicobacter pylori activity and the results were compared with Metronidazole and Amoxicillin. They found that nitrofuran analogue 4-[5-(5-Nitro-2-furyl)-1,3,4-thiadiazol2-yl] thiomorpholine 1,1-dioxide (**55**) containing thiomorpholine-S, S dioxide moiety was the most potent compound tested [51]. A series of 5-(nitroaryl)-1,3,4-thiadiazoles with sulfur containing alkyl side chain similar to tinidazole molecule were synthesized by condensing 5-nitroarylcarboxaldehyde diacetate with thiosemicarbazide by Shafiee A *et al.* synthesized compounds were evaluated against Helicobacter pylori by using disk diffusion method. Both the structure of the nitroaryl unit and the pendent group on 2-position of 1,3,4-thiadiazole ring dramatically impact the anti-H. pylori activity. Among them 2-((2-(ethylsulfonyl) ethyl) thio)-5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazole, compound **56** was the most potent compound tested against clinical isolates of Helicobacter pylori [52].



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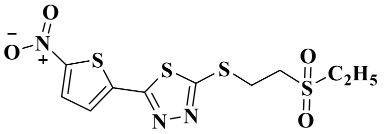

COMPOUND 56

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CHAPTER 3

EXPERIMENTAL WORK

3. EXPERIMENTAL WORKS

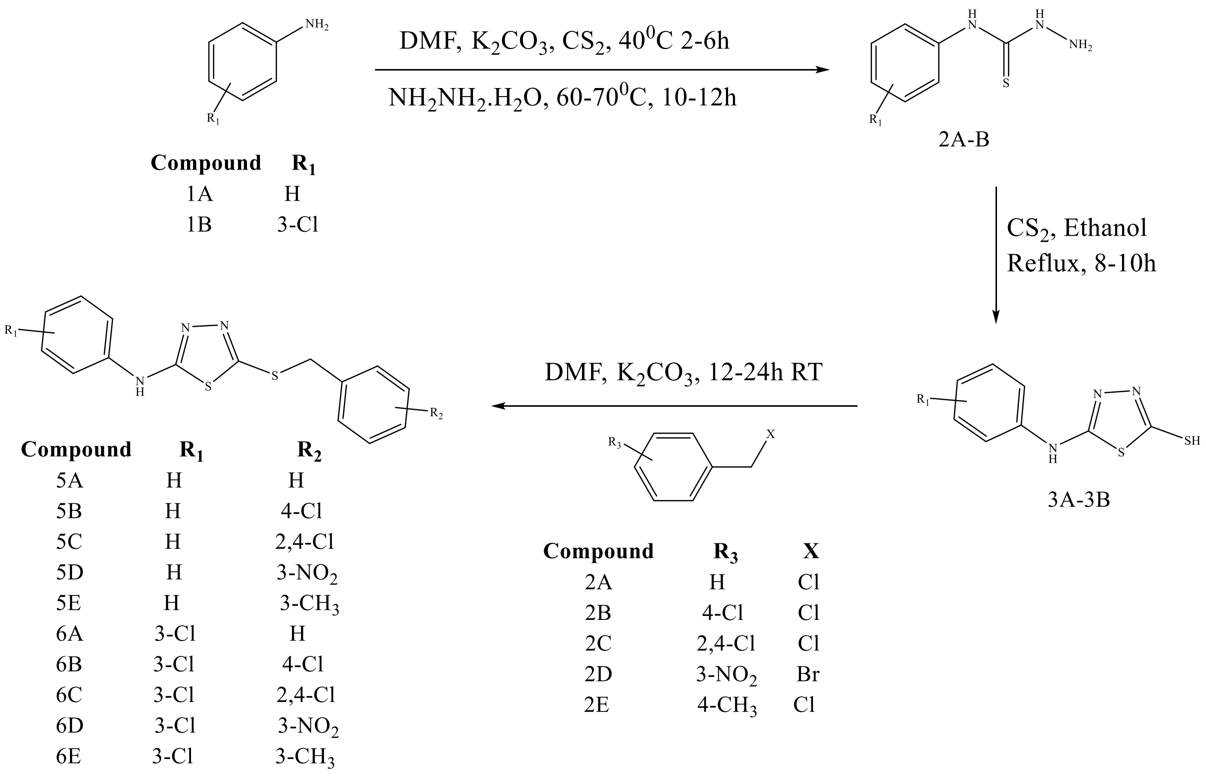
3.1. PLAN OF WORK:

In My M. Pharm work, I am planning for design and synthesis of some [1, 3, 4] Thiadiazole derivatives having suitable functional group, those will be possessed for antimicrobial activity. After synthesis the compounds will be characterised by I.R Spectroscopy, NMR Spectroscopy (1H NMR, 13C NMR), Mass Spectrometry and Elemental Analysis (CHN) for structure Elucidation.

3.2. Materials used:

All the chemicals required for this research work were reagent grade and used without further purification. KOH, NaOH, DMF, ethanol, methanol, hydrazine hydrate, DMSO was purchased from Merck, USA, aniline, 3-chloroaniline and CS_2 from Lobe chemicals, benzyl chloride, 4-chloro benzyl chloride, 2,4-dichlorobenzyl chloride, 3-nitro benzyl bromide, 4-methyl benzyl chloride from SpectroChem.

5.2. <u>Scheme for Synthesis of 1,3,4-thiadiazoles:</u>



Compound	R_1
1A	H
1B	3-Cl

Compound	R_3	X
2A	H	Cl
2B	4-Cl	Cl
2C	2,4-Cl	Cl
2D	$3\text{-}NO_2$	Br
2E	$4\text{-}CH_3$	Cl

Compound	R_1	R_2
5A	H	H
5B	H	4-Cl
5C	H	2,4-Cl
5D	H	$3\text{-}NO_2$
5E	H	$3\text{-}CH_3$
6A	3-Cl	H
6B	3-Cl	4-Cl
6C	3-Cl	2,4-Cl
6D	3-Cl	$3\text{-}NO_2$
6E	3-Cl	$3\text{-}CH_3$

3.3. PROCEDURE:

3.3.1. Synthesis of N-(substituted phenyl) hydrazine carbothioamides (2A-2B):

Potassium carbonate (0.02 mol) was dissolved in water, then this solution was added with DMF (10ml). After that substituted aniline (0.01 mol) (1A & 1B) and carbon disulphide (0.02 mol) was added in 10 min interval to that mixture and stirred well for 6-7 hour at 20-25^{o}C temperature. Hydrazine hydrate (0.03 mol) was added to the mixture, and stirring was maintained at 60-70^{o}C for 7 hours. TLC was checked whether new product is formed or not using reaction mixture and N-substituted aniline spot comparison. When crushed ice was added, a solid separated, which was recrystallized from 90% ethanol.

3.3.2. Synthesis of N-((4-substituted phenyl) amino)-1,3,4-thiadiazole-2-thiol/thione (3A-3B):

In EtOH (30ml) containing NaOH/KOH (0.02 mol), a combination of N-(substituted phenyl) hydrazine carbothioamide (0.01 mol) (2A & 2B) and carbon disulphide (0.012 mol) was added on 10 minutes of interval and refluxed for 8 hours. After the reaction was completed, the reaction mixture was acidified with 20 percent HCl to pH 4–5. The product was precipitated then filtered and rinsed with water. The residue was then dried and recrystallized using EtOH or methanol as a solvent.

3.3.3. 5-(benzylthio)-N-substituted phenyl-1,3,4-thiadiazol-2-amine (5A-E & 6A-E):

In DMF (15mL), potassium carbonate (0.01mol) was mixed and then N-((4-substituted phenyl) amino)-1,3,4-thiadiazole-2-thiol/thione and different substituted benzyl chloride (0.005 mol) (4A-E) was stirred at room temperature for 7-9hour. After the reaction was completed, crushed ice was added, and the product was recovered through filtering and crystallisation with ethanol or methanol to yield the final pure compound.

CHAPTER 4

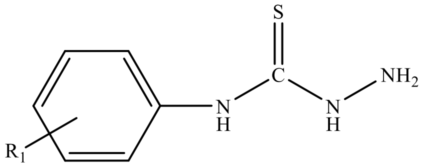
RESULT AND DISCUSSION

4. RESULTS AND DISCUSSION:

4.1 CHEMISTRY:

The reaction of aniline derivatives (**1A-B**) on reaction with carbon disulphide (CS_2) followed by addition of hydrazine hydrate afforded 4-(substituted) phenyl amino carbothioamides or 4-substituted phenyl thiosemicarbazides (**2A-B**). The thiosemicarbazides or hydrazinecarbothioamides on reflux with carbonsulfide (CS_2) in presence of base (KOH) produce dithiocarbazates and dithiocarbazades in acidic pH (2-4) addition of HCL undergo cyclization and yielded the 5-substituted phenyl-1,3,4-thiadiazole-2-thiol derivatives (**3A-B**). Reaction of 5-(substituted phenyl amino) 1,3,4-thiadiazole-2-thiol derivatives with benzyl chlorides or bromides in DMF and base (K_2CO_3) furnished final compounds 5-(substituted phenyl amino)-2-(substituted benzyl thio)-1,3,4-thiadiazoles (**5A-E & 6A-E**). The IR (ATR-FTIR) spectrum of some newly synthesized compounds have been recorded in the frequency region 4000-500 cm-1 are listed in the Table-2. The IR spectrum of the compounds (**2A, 2B**) showed absorption bands 3455.12-3446.75 cm-1 (broad str. -NH), 2980.35-2980.29 cm-1 (Aromatic - CH str.), 1487.52-1471.85 (HN-CS-NH) absorption bands in the region 1379.82.0-1379.97 cm^{-1} (-C=S str.) and 1252.41-1252.25 (-C-N str.), stretching vibrations in the region 637.8-674.0 cm^{-1} indicates the mono substitution. These results confirming the structures of compounds (2A,2B). The IR spectrum of the compounds (**3A, 3B**) shows absorption peak at 3247.50-3176.79 cm^{-1} (NH str.), 3100-2900 (Ar C-H), 1600-1550 (C=N), 1481-1480 (N=C-S), 1398-1397 (C=S) etc. Also, ^1H NMR spectrum of compound 3A display a sharp resonance peak at δ, 13.63 ppm (-SH) and δ, 10.09 ppm (-NH) confirm the structure of compounds **3A** and **3B**. ^1H NMR spectral data of final series (**5A-E and 6A-E**) of compounds displayed chemical shift position at δ, 10-10 (for NH proton) and δ, 4-4 and also ^{13}C NMR data of the derivatives confirming the final structure of the compounds.

4.1.STRUCTURE AND SPECTRAL DATA OF SYNTHESIZED COMPOUND:



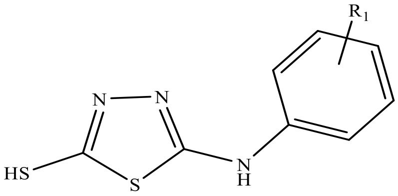
Compound	R_1	Melting Point (°C)
2A	H	181-183
2B	3-Cl	118-120

N-phenylhydrazinecarbothioamide (2A):

Off white solid; Yield 89%; Mp 181-183 ^{o}C; solubility: DMSO: FTIR (cm^{-1}); 3455.12, 3299.10, 3154.10 (-NH str.), 2980.29, 2971.40, 2888.34 (Ar CH), 1633.69, 1593.04 (NH bend), 1521.05 (C=C), 1487.52, 1473.17, 1461.89,1445.35 (NH-CS-NH), 1379.82 (C=S).

N-(3-chlorophenyl) hydrazinecarbothioamide (2B):

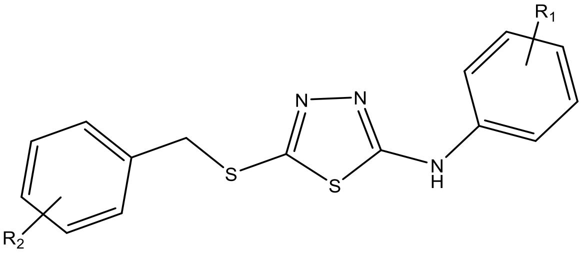
Off white solid; Yield 84%; Mp 118-120 ^{o}C; solubility: DMSO: FTIR (cm^{-1}); 3446.75 (-NH str.), 2980.35, 2971.53, 2887.91 (Ar CH), 1620.84, 1585.18 (NH bend), 1537.79 (C=C), 1471.85, 1461.96 (NH-CS-NH), 1379.97 (C=S).



Compound	R
3A	H
3B	3-Cl

5-(phenylamino)-1,3,4-thiadiazole-2-thiol (3A): Off white solid; Yield 79%; Mp ^{o}C; solubility: DMSO: FTIR (cm^{-1}); 3225.18 3178.26 (NH str), 3107.97-2913.04 ((Ar CH str.), 1600.06-1556.53 ((C=N str.), 1480.99 (N=C-S), 1397.83-1316.05 (C=S) etc;

5-((3-chlorophenyl) amino)-1,3,4-thiadiazole-2-thiol (3B): Off white solid; Yield 84%; Mp ^{o}C; solubility: DMSO: FTIR (cm^{-1}); 3225.63-3177.62 (NH str), 3108.30-2909.25 (Ar CH str.), 1600.56-1555.96 (C=N str.), 1481.33 (N=C-S), 1398.34 1316.61 (C=S) etc.



Compound	R$_1$	R$_2$	Melting Point (^{o}C)
5A	H	H	133-136
5B	H	4-Cl	165-167
5C	H	2,4-Cl	174-176
5D	H	3-NO_2	129-132
5E	H	4-CH_3	152-155
6A	3-Cl	H	165-167
6B	3-Cl	4-Cl	174-176
6C	3-Cl	2,4-Cl	149-152

6D	3-Cl	3-NO_2	144-146
6E	3-Cl	4-CH_3	180-182

5-(benzylthio)-N-phenyl-1,3,4-thiadiazol-2-amine (5A): Off white solid; Yield 75%; Mp 133-136 °C; Solubility: DMSO, Acetonitrile: FTIR (cm^{-1}); 3240.80, 3192.22, 3140.84 (NH 1str.), 3047.83, 3027.67, 2909.66 (Ar CH), 1613.70, 1599.84 (NH bend), 1455.22, 1433.15, 1411.73 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta_{H:}$ 10.37 (s, 1H), 7.62 – 7.53 (m, 2H), 7.40 (dt, *J* = 5.9, 1.6 Hz, 2H), 7.37 – 7.23 (m, 5H), 7.03 – 6.96 (m, 1H), 4.41 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 164.95, 152.11, 140.35, 136.92, 129.10, 129.05, 128.53, 127.54, 122.00, 117.38, 38.02.

5-((4-chlorobenzyl) thio)-N-phenyl-1,3,4-thiadiazol-2-amine (5B): Off white solid; Yield 80%; Mp 165-167 °C; Solubility: DMSO, sparingly soluble in Acetonitrile: FTIR (cm^{-1}); 3238.07 (NH str.), 3012.80 (Ar CH), 1667.87, 1595.92 (NH bend), 1498.38, 1440.97, 1406.46 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d_6) $\delta_{H:}$ 10.38 (s, 1H), 7.60 – 7.52 (m, 2H), 7.46 – 7.28 (m, 6H), 7.03 – 6.95 (m, 1H), 4.40 (s, 2H), ^{13}C NMR (75 MHz, DMSO) δ 165.08, 151.71, 140.31, 136.29, 132.14, 130.93, 129.12, 128.49, 122.04, 117.40, 37.15.

5-((2,4-dichlorobenzyl) thio)-N-phenyl-1,3,4-thiadiazol-2-amine (5C): Off white solid; Yield 87%; Mp 174-176°C; Solubility: DMSO: FTIR (cm^{-1}); 3200.68 (NH str.), 2917.47 (Ar CH), 1621.54, 1601.39, 1576.06 (NH bend), 1458.18, 1436.08, 1409.57 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.42 (s, 1H), 7.67 (d, *J* = 2.2 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.44 – 7.30 (m, 3H), 7.05 – 6.97 (m, 1H), 4.47 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ_C: 165.50, 150.83, 140.25, 134.27, 133.76, 133.22, 132.73, 129.13, 129.05, 127.52, 122.12, 117.44,

5-((3-nitrobenzyl) thio)-N-phenyl-1,3,4-thiadiazol-2-amine (5D): Yellow solid; Yield 69%; Mp 129-132 °C; Solubility: DMSO, Ethanol, Acetonitrile: FTIR (cm^{-1}); 3252.47, 3191.16, 3127.47 (NH str.), 3058.27, 3016.43 (Ar CH), 1616.39, 1600.15, 1576.67, 1569.35, 1558.32 (NH bend), 1480.24, 1457.86, 1442.33, 1419.20 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.38 (s, 1H), 8.30 (t, *J* = 2.0 Hz, 1H), 8.13 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H), 7.86 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.66 – 7.52 (m, 3H), 7.36 – 7.27 (m, 2H), 7.03 – 6.95 (m, 1H), 4.56 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ_C: 165.19, 151.37, 147.72, 140.28, 139.92, 135.79, 130.02, 129.12, 123.68, 122.42, 122.10, 117.43, 36.79.

5-((4-methylbenzyl) thio)-N-phenyl-1,3,4-thiadiazol-2-amine (5E): Off white solid; Yield 82%; Mp 152-155 °C; Solubility: DMSO: FTIR (cm^{-1}); 3192.01 (NH str.), 2980.44, 2887.45, 2774.47 (Ar CH), 1614.01, 1596.82, 1569.48 (NH bend), 1497.96, 1461.04, 1436.85, 1415.24 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.36 (s, 1H), 7.61 – 7.50 (m, 2H), 7.31 (dd, *J*

= 19.4, 7.8 Hz, 4H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.36 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 164.90, 152.24, 140.36, 136.80, 133.79, 129.12, 128.99, 122.00, 117.36, 37.85, 20.74.

5-(benzylthio)-N-(3-chlorophenyl)-1,3,4-thiadiazol-2-amine (6A): Off white solid; Yield 80%; Mp 165-167 ^{o}C; Solubility: DMSO: FTIR (cm^{-1}); 2980.34, 2971.43, 2887.62 (Ar CH), 1684.18, 1653.57, 1645.79, 1635.49 (NH bend), 1473.25, 1446.83 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ$_H$: 10.58 (s, 1H), 7.83 (t, *J* = 2.0 Hz, 1H), 7.44 – 7.25 (m, 7H), 7.04 (dt, *J* = 6.9, 2.0 Hz, 1H), 4.43 (s, 2H);

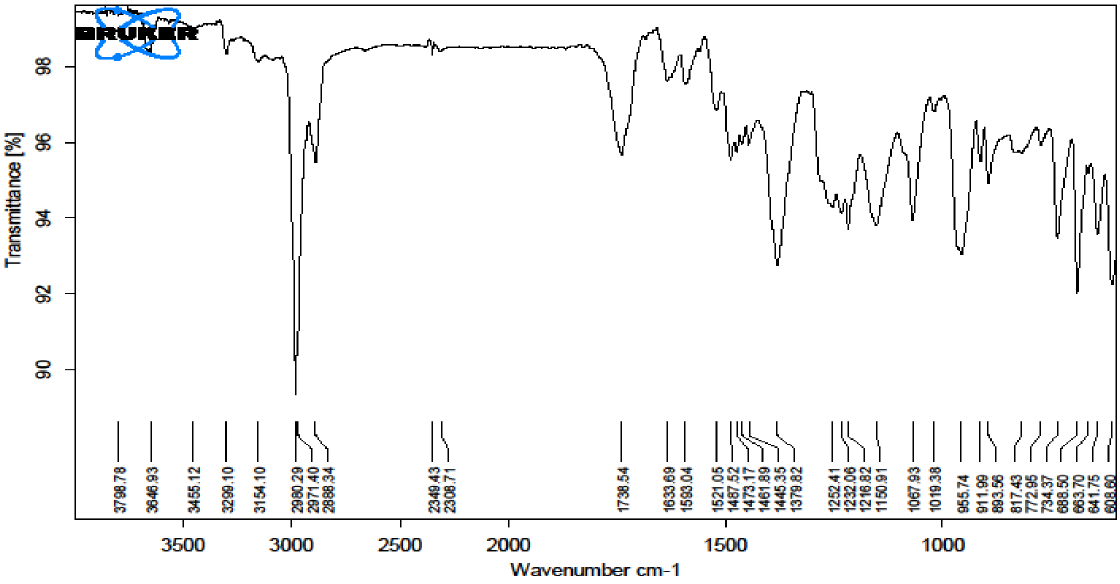
5-((3-chlorobenzyl) thio)-N-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine (6B): Off white solid; Yield 68%; Mp 174-176 ^{o}C; Solubility: FTIR (cm^{-1}); 2980.33, 2971.43, 2887.87 (Ar CH), 1669.62, 1653.51, 1623.16 (NH bend), 1486.72, 1447.75 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ$_{H:}$ 10.58 (s, 1H), 7.83 (t, *J* = 1.7 Hz, 1H), 7.47 – 7.30 (m, 6H), 7.07 – 7.00 (m, 1H), 4.42 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ$_C$: 164.49, 152.83, 141.55, 136.22, 133.51, 132.17, 130.94, 130.70, 128.51, 121.55, 116.78, 115.86, 36.98.

N-(3-chlorophenyl)-5-((2,4-dichlorobenzyl) thio)-1,3,4-thiadiazol-2-amine (6C): Off white solid; Yield 89%; Mp 149-152 ^{o}C; Solubility: DMSO; FTIR (cm^{-1}); 2980.35, 2971.46, 2888.24 (Ar CH), 1619.37, 1594.97, 1566.57 (NH bend), 1484.34, 1472.38, 1448.46 (N=C-S); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ$_H$: 10.63 (s, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.67 (q, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.08 – 7.02 (m, 1H), 4.49 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ$_C$: 164.91, 152.02, 141.50, 134.31, 133.71, 133.52, 133.28, 132.78, 130.77, 129.09, 127.58, 121.65, 116.82, 115.92, 35.40.

N-(3-chlorophenyl)-5-((3-nitrobenzyl) thio)-1,3,4-thiadiazol-2-amine (6D): Off white solid; Yield 79%; Mp 144-146 ^{o}C; Solubility: DMSO, Acetonitrile: FTIR (cm^{-1}); 2980.35, 2971.48, 2888.17 (Ar CH), 1621.79, 1599.85, 1564.33, 1526.40 (NH bend), 1484.91, 1460.94 (N=C-S); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ$_H$: 165.59, 153.44, 148.33, 141.98, 140.32, 136.42, 134.29, 131.47, 130.75, 124.15, 123.15, 122.58, 117.52, 116.60, 37.57.

N-(3-chlorophenyl)-5-((4-methylbenzyl) thio)-1,3,4-thiadiazol-2-amine (6E): Off white solid; Yield 87%; Mp 180-182 ^{o}C; Solubility: DMSO, Chloroform: FTIR (cm^{-1}); 2980.34, 2971.49, 2888.05 (Ar CH), 1649.75, 1621.03, 1592.82, 1563.49 (NH bend), 1484.91, 1460.94 (N=C-S); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ$_H$: 10.57 (s, 1H), 7.84 (t, *J* = 2.0 Hz, 1H), 7.41 – 7.25 (m, 4H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.04 (dt, *J* = 6.8, 2.0 Hz, 1H), 4.38 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ$_C$: 164.33, 153.35, 141.60, 136.84, 133.71, 133.51, 130.71, 129.13, 129.00, 121.51, 116.75, 115.85, 37.70, 20.74.

4.2.FT-IR SPECTRA OF THE SYNTHESIZED COMPOUND:



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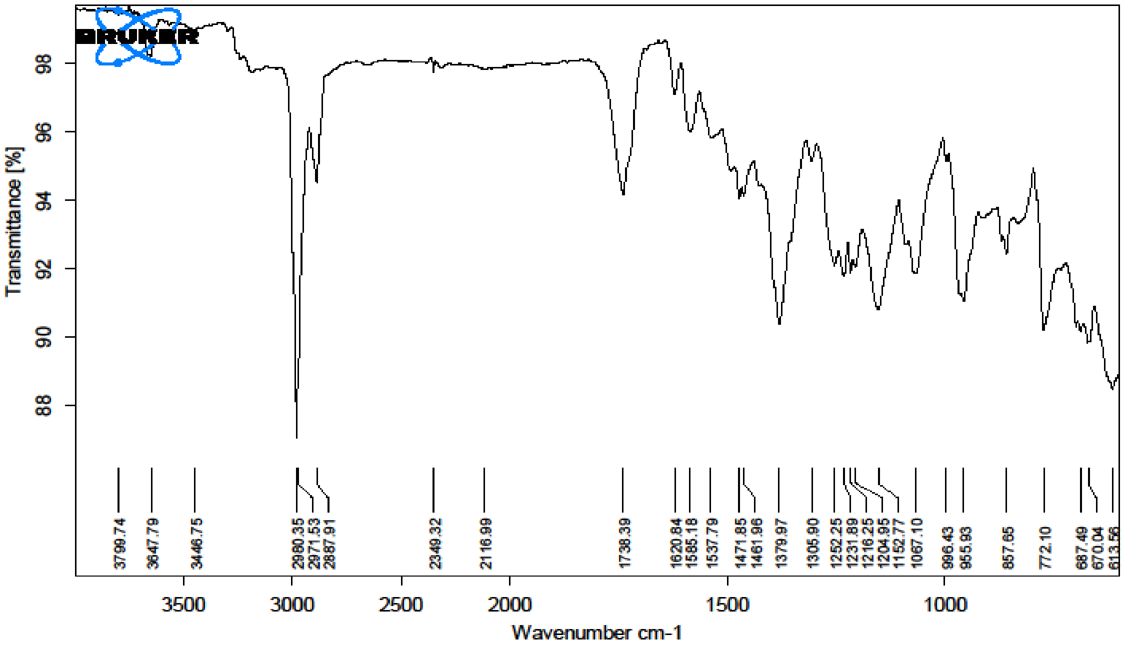
Page 1/1



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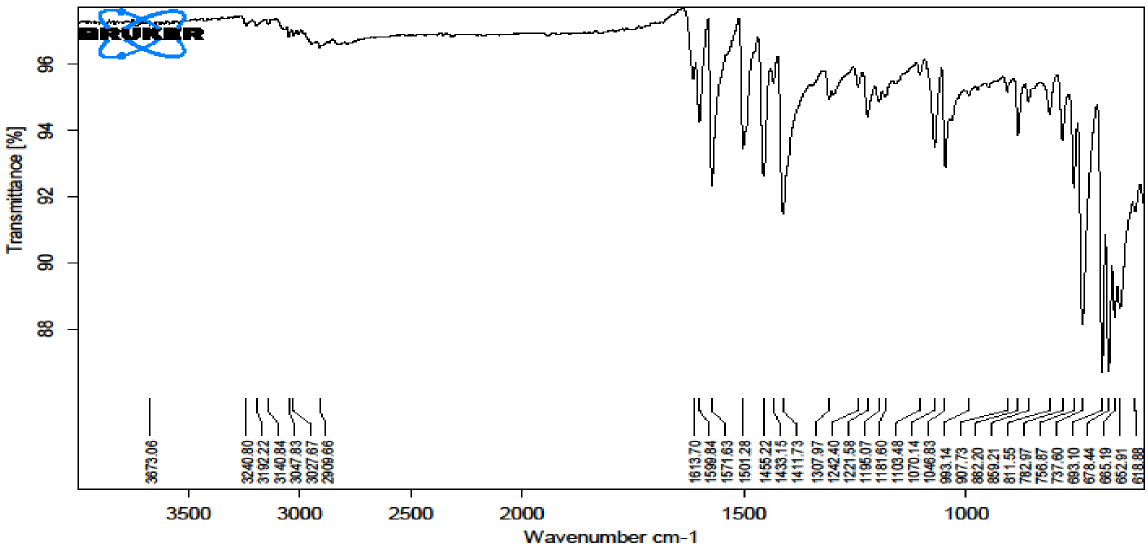
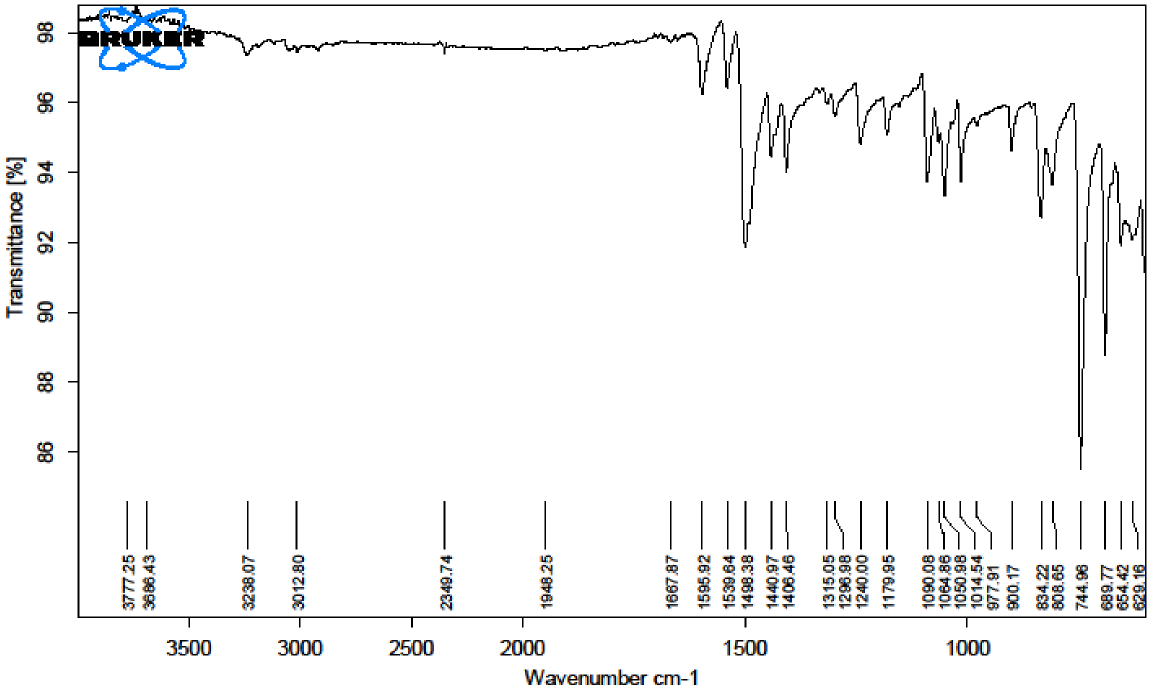
Page 1/1



D:\FTIR\AVIK\TDS 5A	TDS 5A	Instrument type and / or accessory	3/15/2022

Page 1/1



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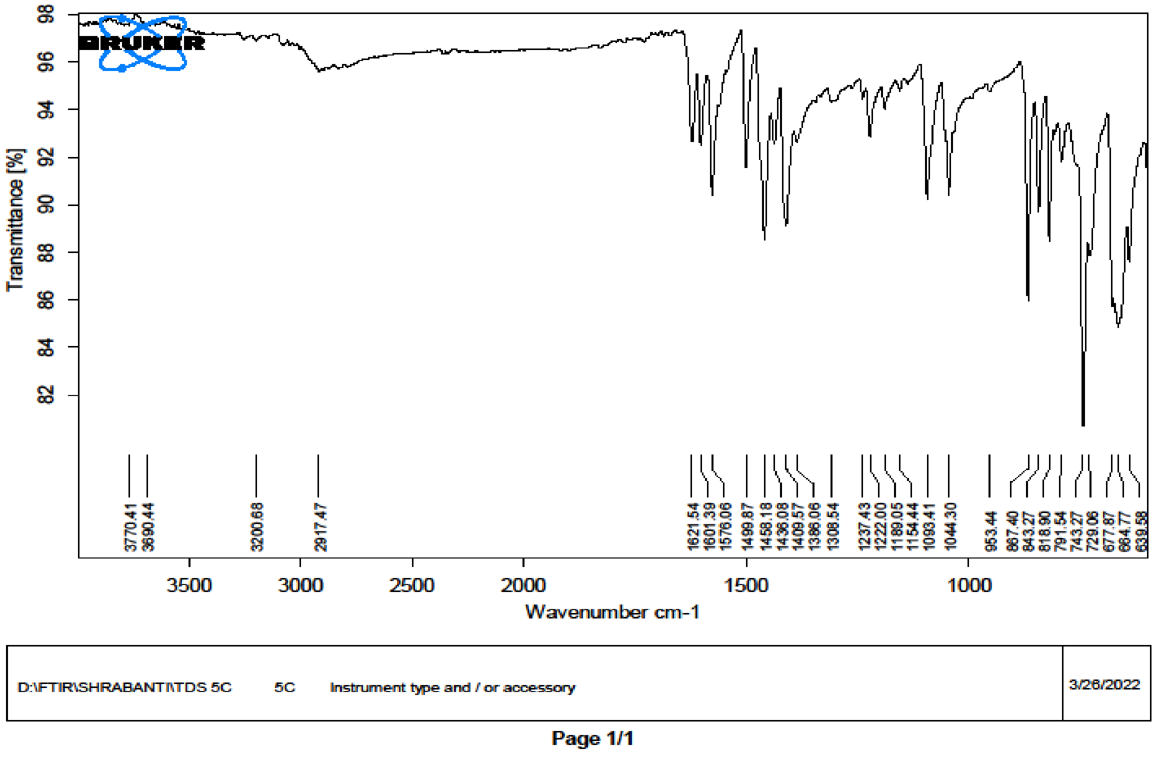
Page 1/1



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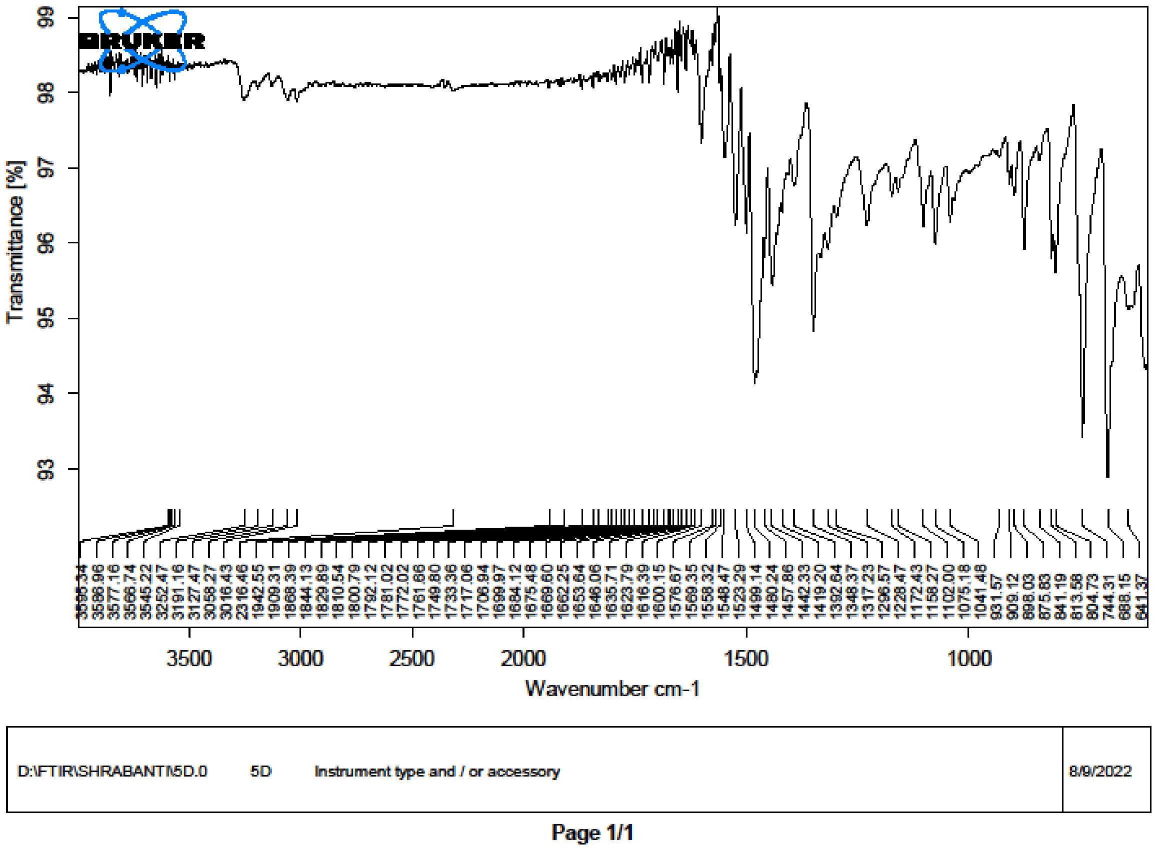
Page 1/1



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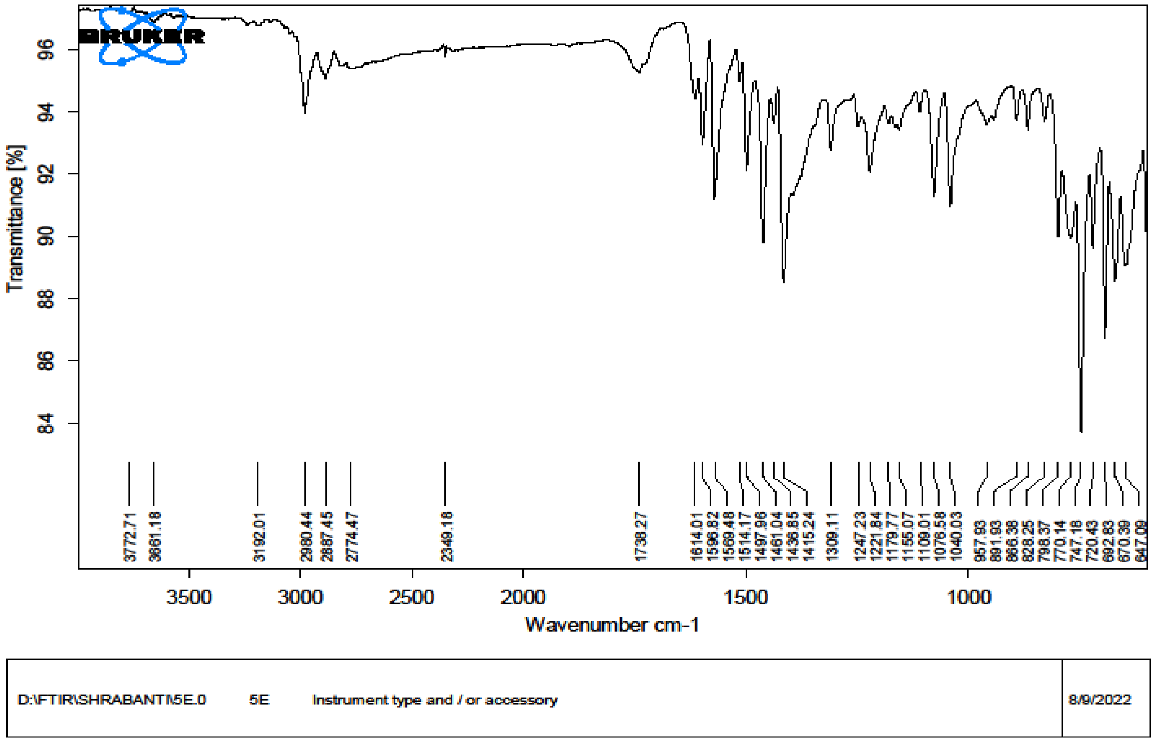
Page 1/1



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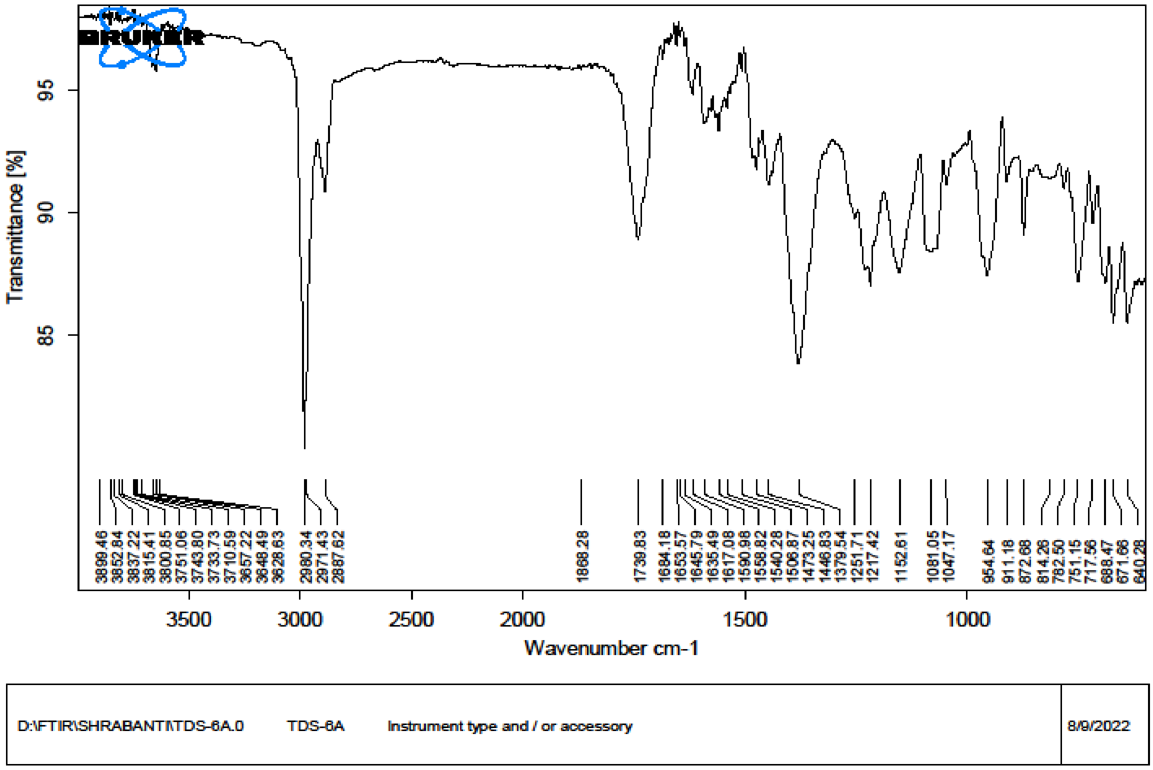
Page 1/1



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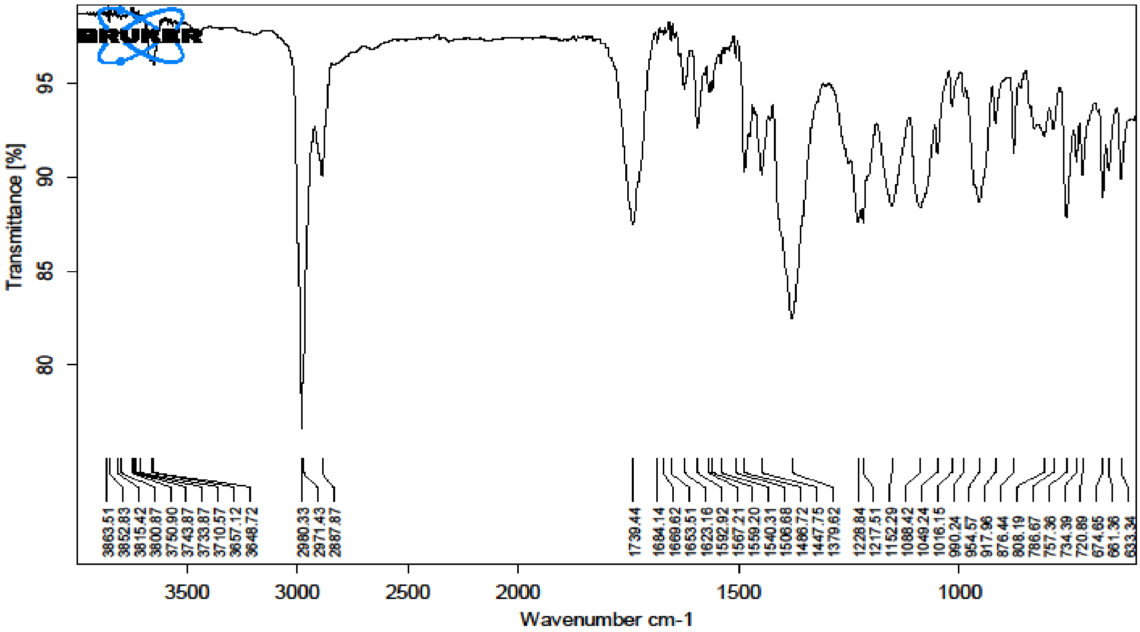
Page 1/1



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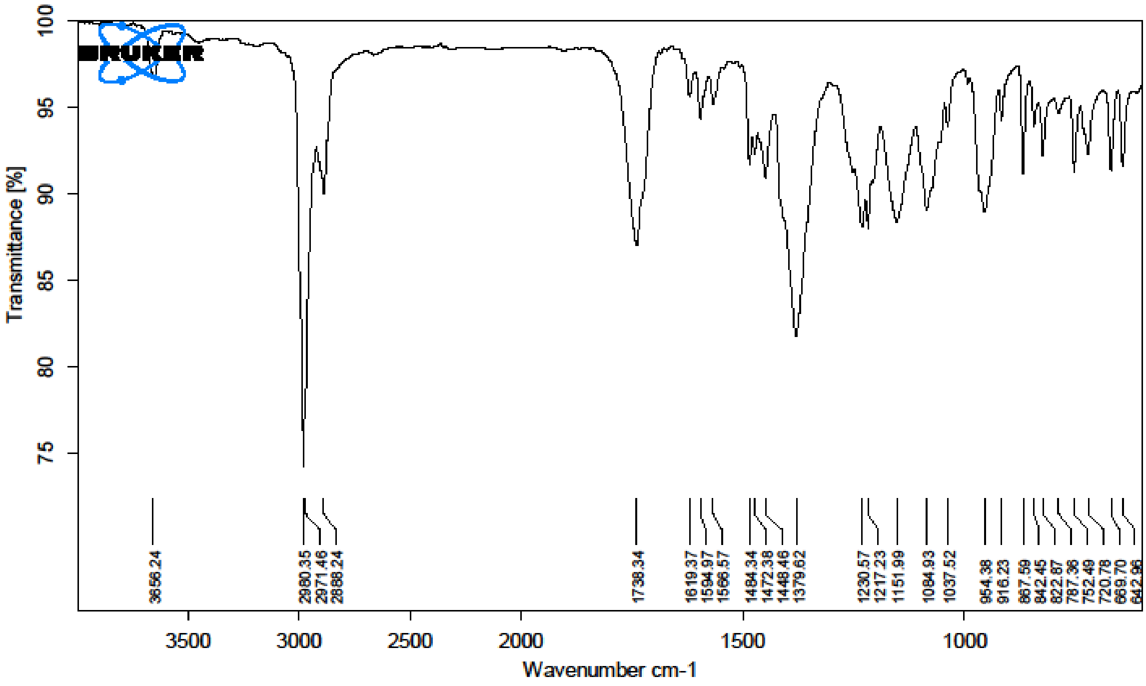
Page 1/1



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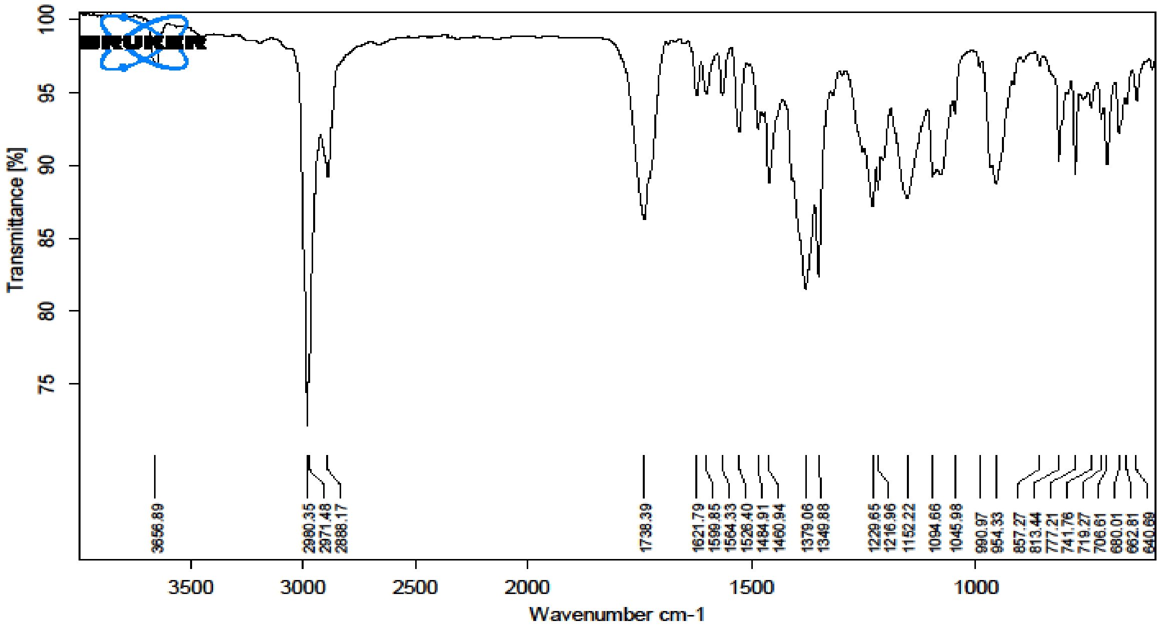
Page 1/1



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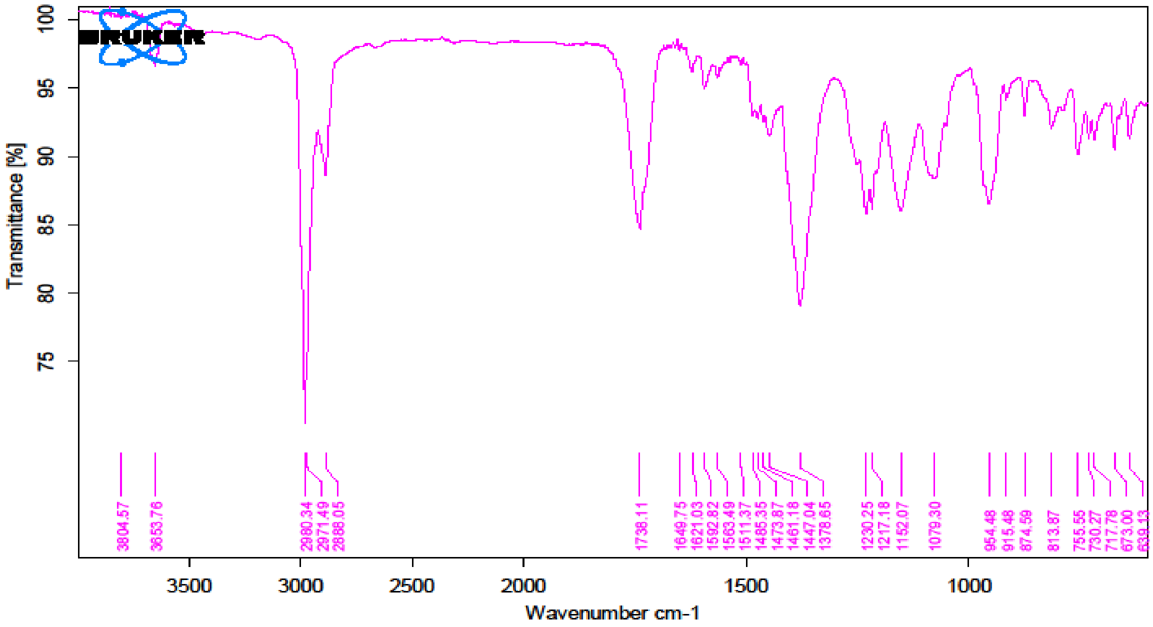
Page 1/1

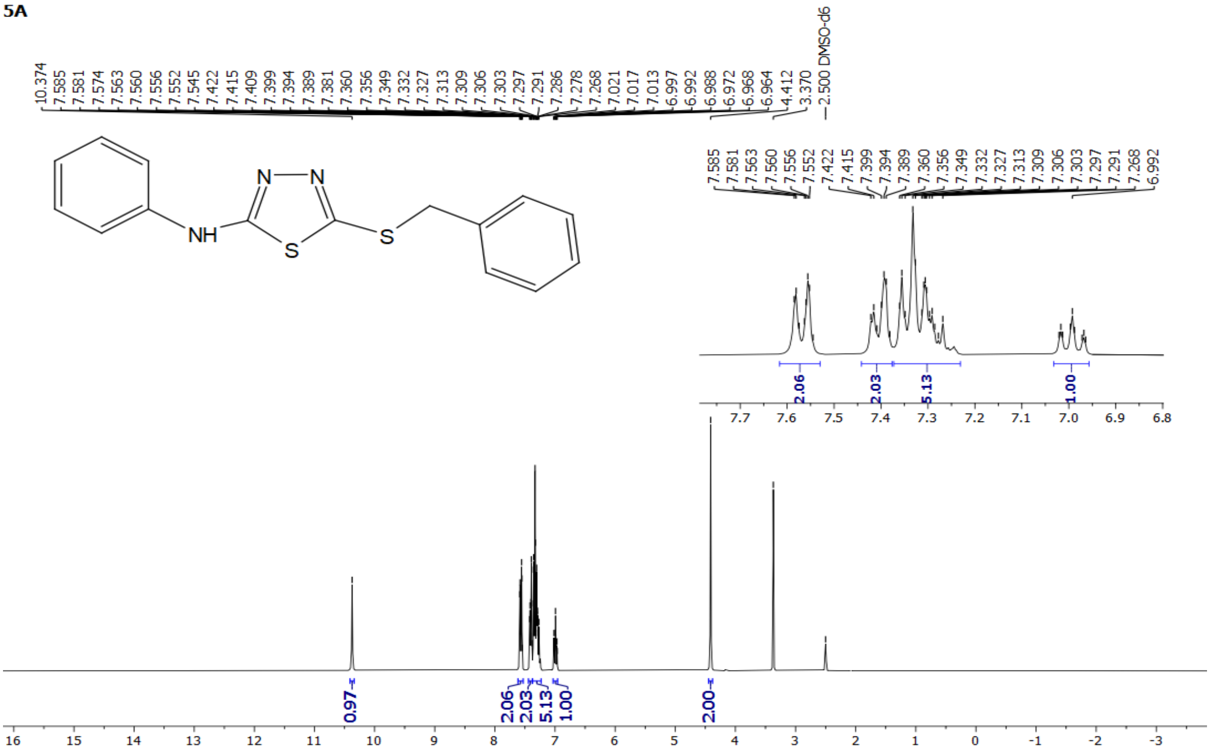


D:\FTIR\SHRABANTI\TDS-6E.0	TDS-6E	Instrument type and / or accessory	8/9/2022

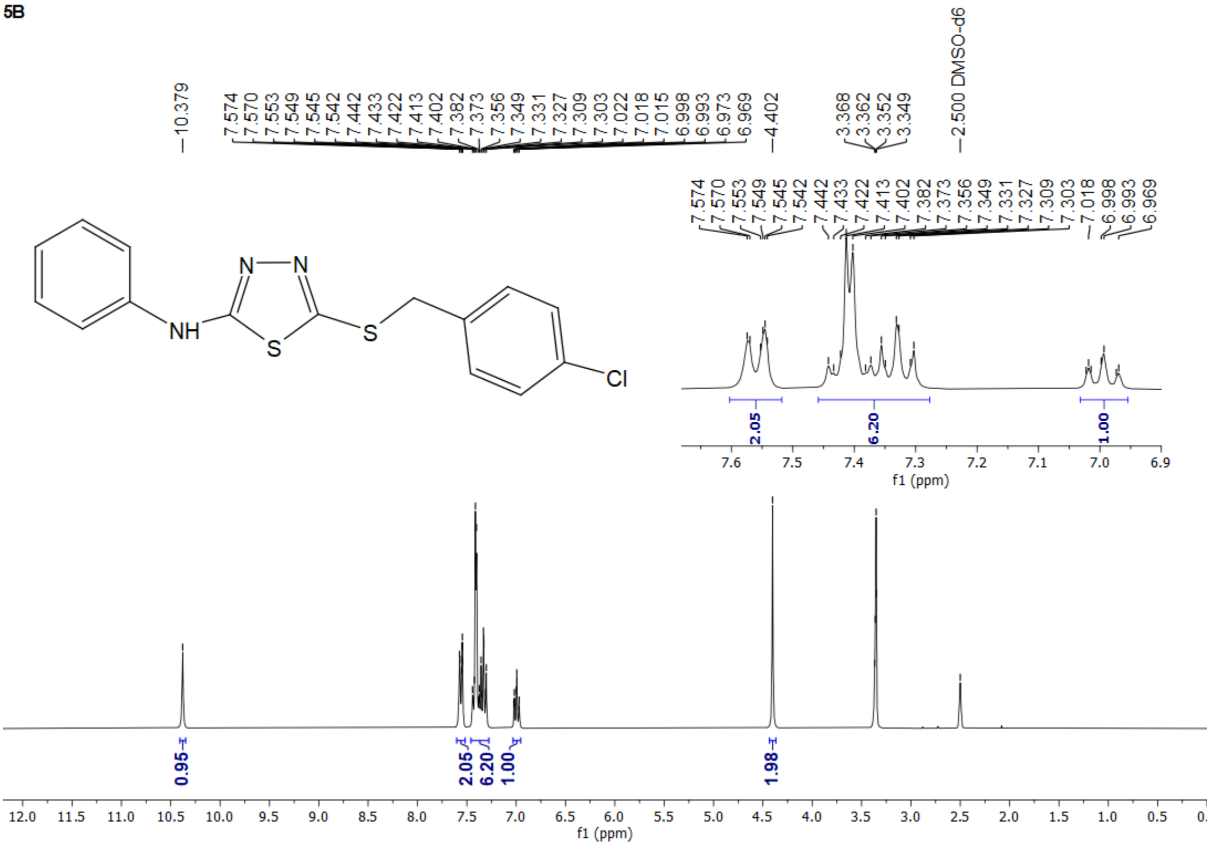
Page 1/1

4.3.^{1}H NMR SPECTRA OF THE SYNTHESIZED COMPOUND:

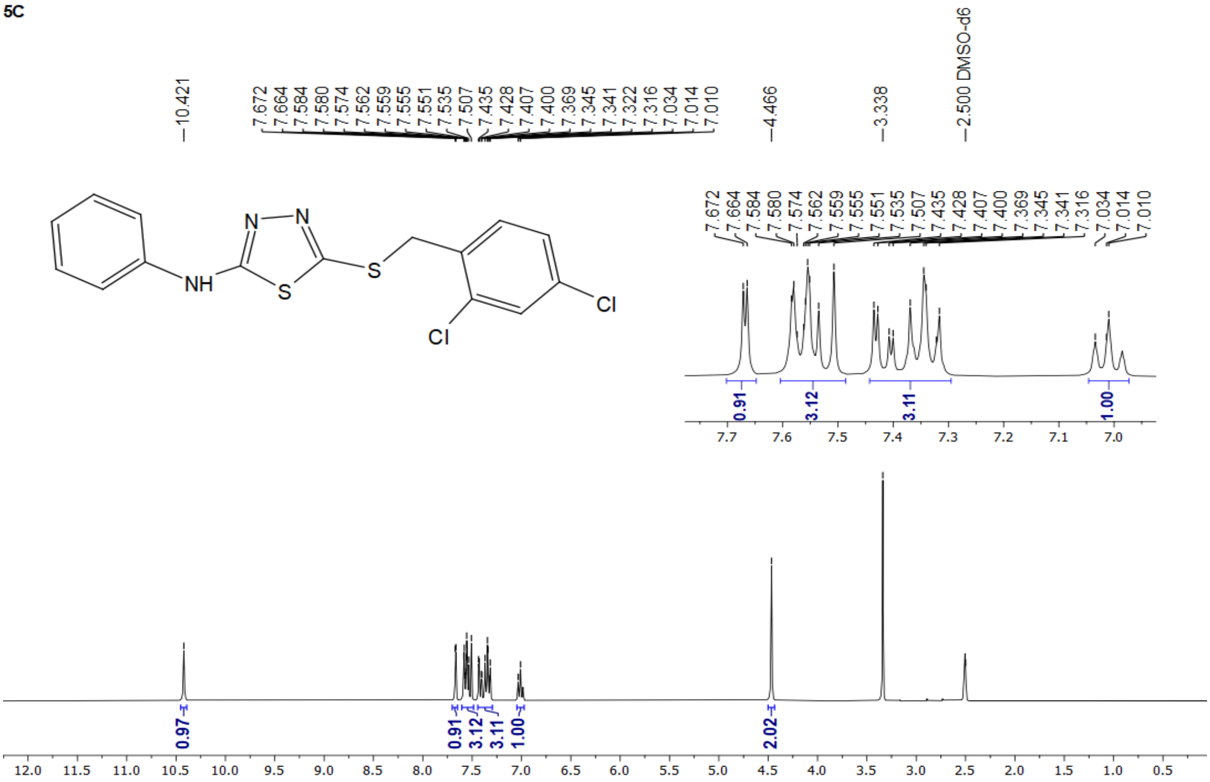
5A



5B



5C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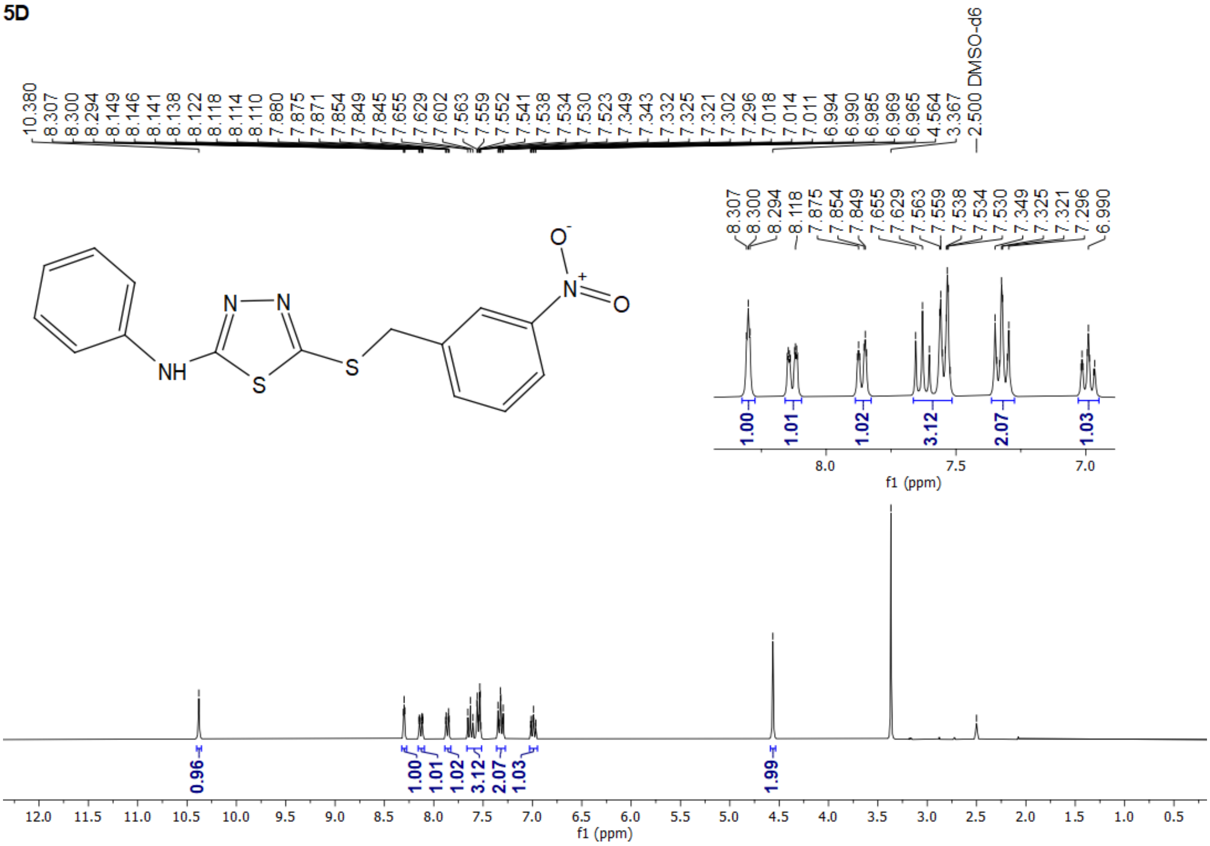
7.664
7.584
7.580
7.574
7.562
7.559
7.555
7.551
7.535
7.507
7.435
7.428
7.407
7.400
7.369
7.345
7.341
7.322
7.316
7.034
7.014
7.010
4.466
3.338
2.500 DMSO-d6
N
N
NH
S
S
Cl
Cl
0.91
3.12
3.11
1.00
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
0.97
0.91
3.12
3.11
1.00
2.02
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

5D


10.380
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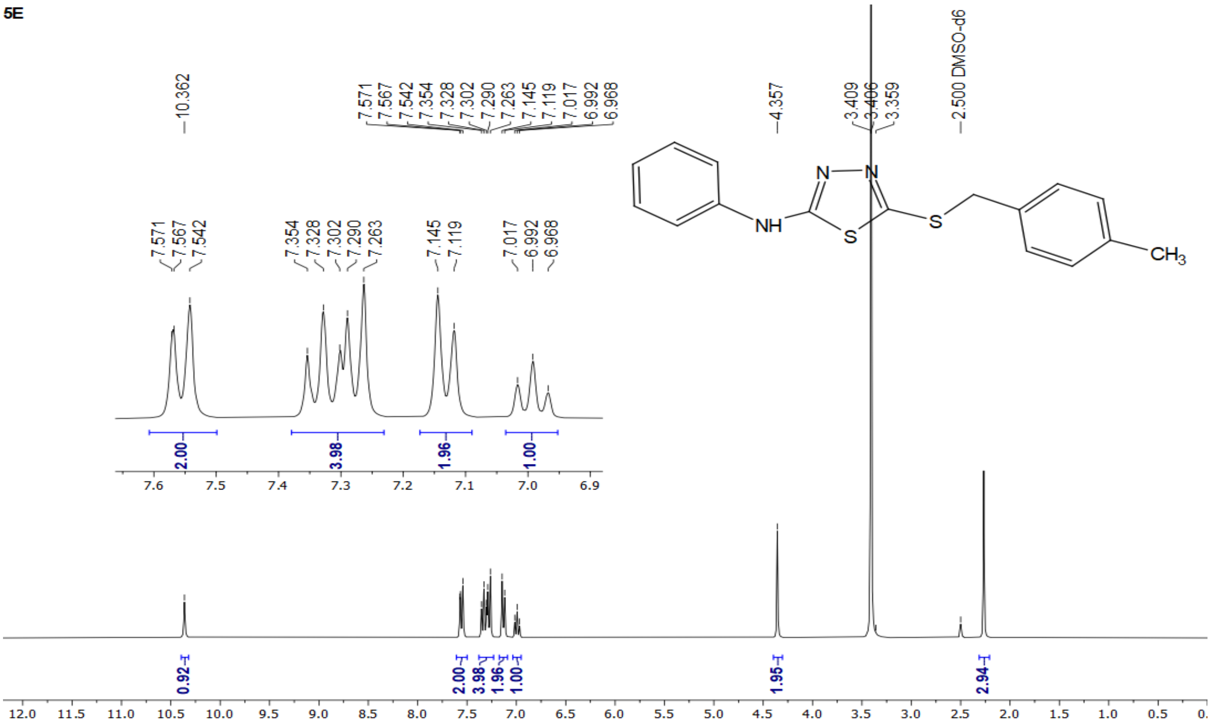
8.300
8.294
8.149
8.146
8.141
8.138
8.122
8.118
8.114
8.110
7.880
7.875
7.871
7.854
7.849
7.845
7.655
7.629
7.602
7.563
7.559
7.552
7.541
7.538
7.534
7.530
7.523
7.349
7.343
7.332
7.325
7.321
7.302
7.296
7.018
7.014
7.011
6.994
6.990
6.985
6.969
6.965
4.564
3.367
2.500 DMSO-d6
O-
N+
O
N
N
NH
S
S
1.00
1.01
1.02
3.12
2.07
1.03
8.0
7.5
7.0
f1 (ppm)
0.96
1.00
1.01
1.02
3.12
2.07
1.03
1.99
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

5E


10.362
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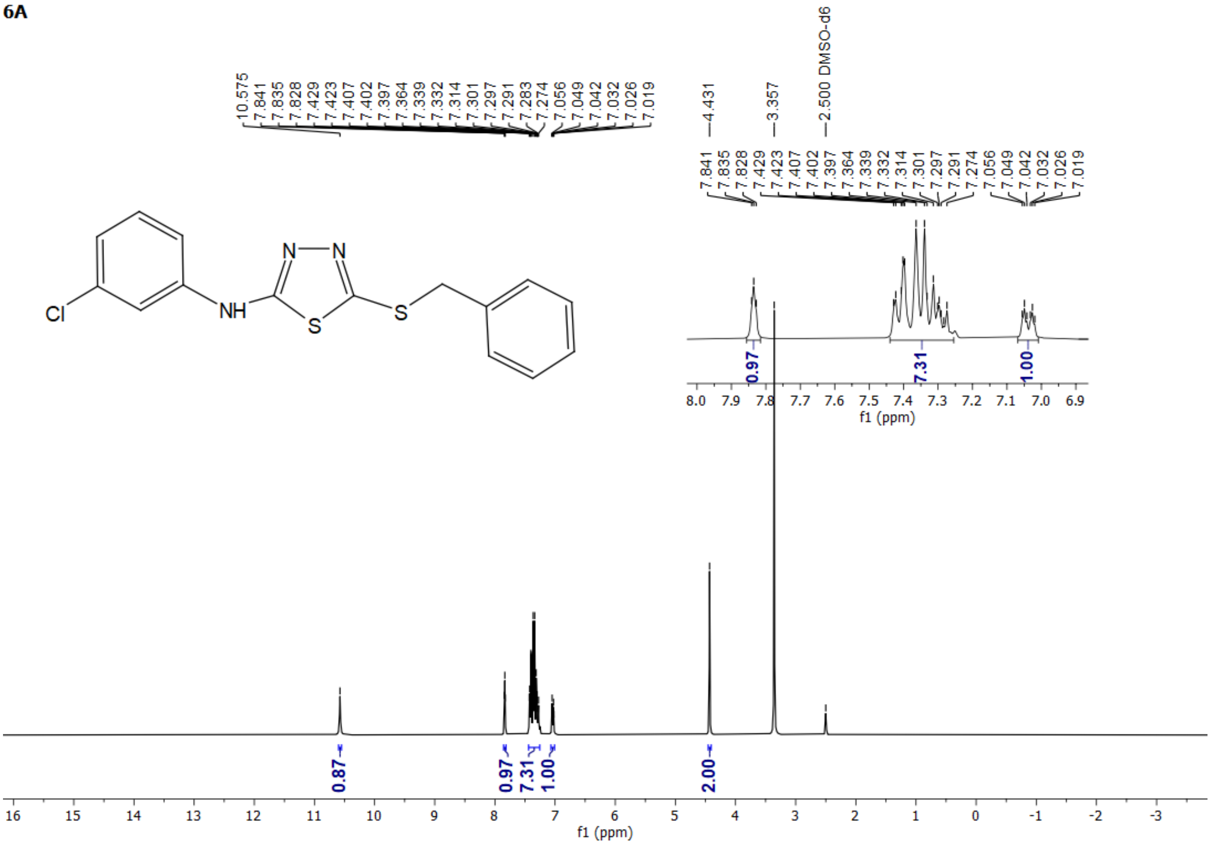
7.567
7.542
7.354
7.328
7.302
7.290
7.263
7.145
7.119
7.017
6.992
6.968
4.357
3.409
3.406
3.359
2.500 DMSO-d6
N
N
NH
S
S
CH3
2.00
3.98
1.96
1.00
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
0.92
2.00
3.98
1.96
1.00
1.95
2.94
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.

6A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7.828
7.429
7.423
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7.402
7.397
7.364
7.339
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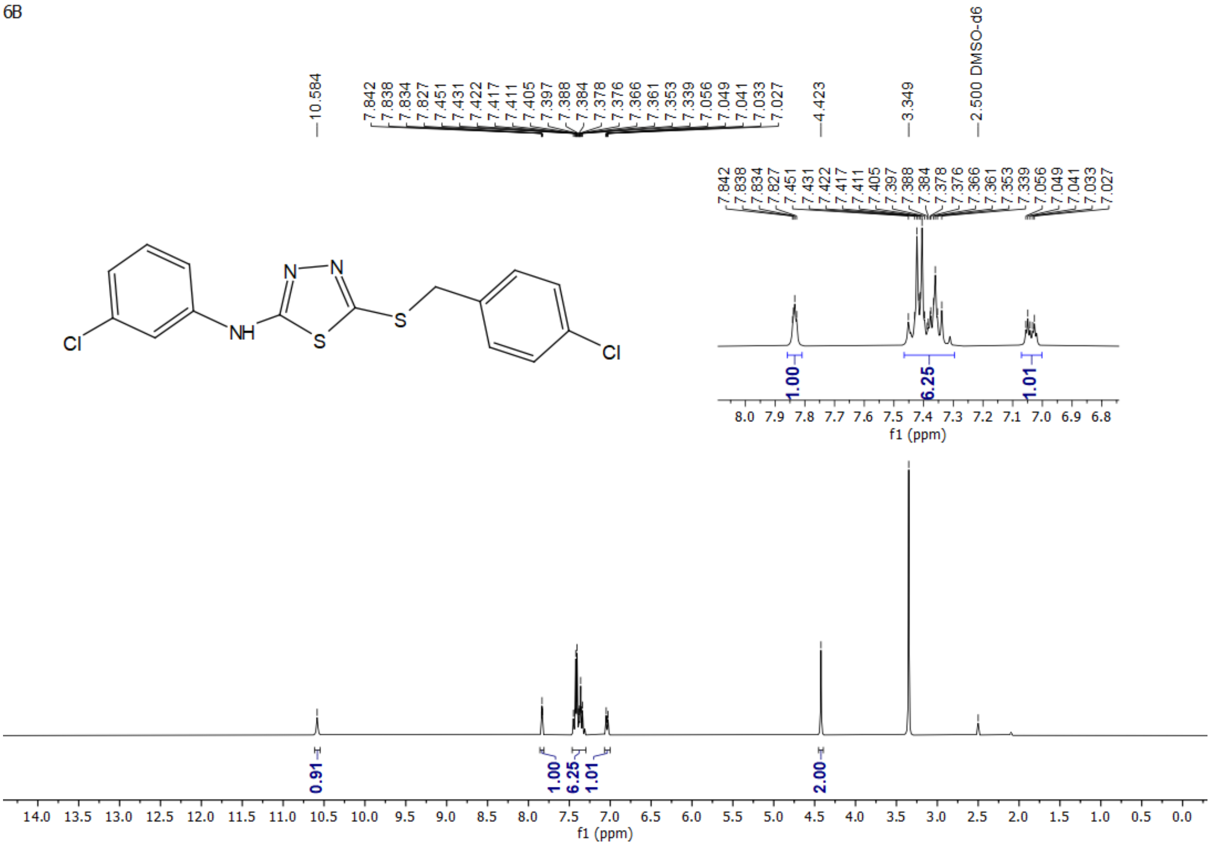
7.301
7.297
7.291
7.283
7.274
7.056
7.049
7.042
7.032
7.026
7.019
4.431
3.357
2.500 DMSO-d6
Cl
NH
N
N
S
S
0.97
7.31
1.00
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9
f1 (ppm)
0.87
0.97
7.31
1.00
2.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)

6B


10.584
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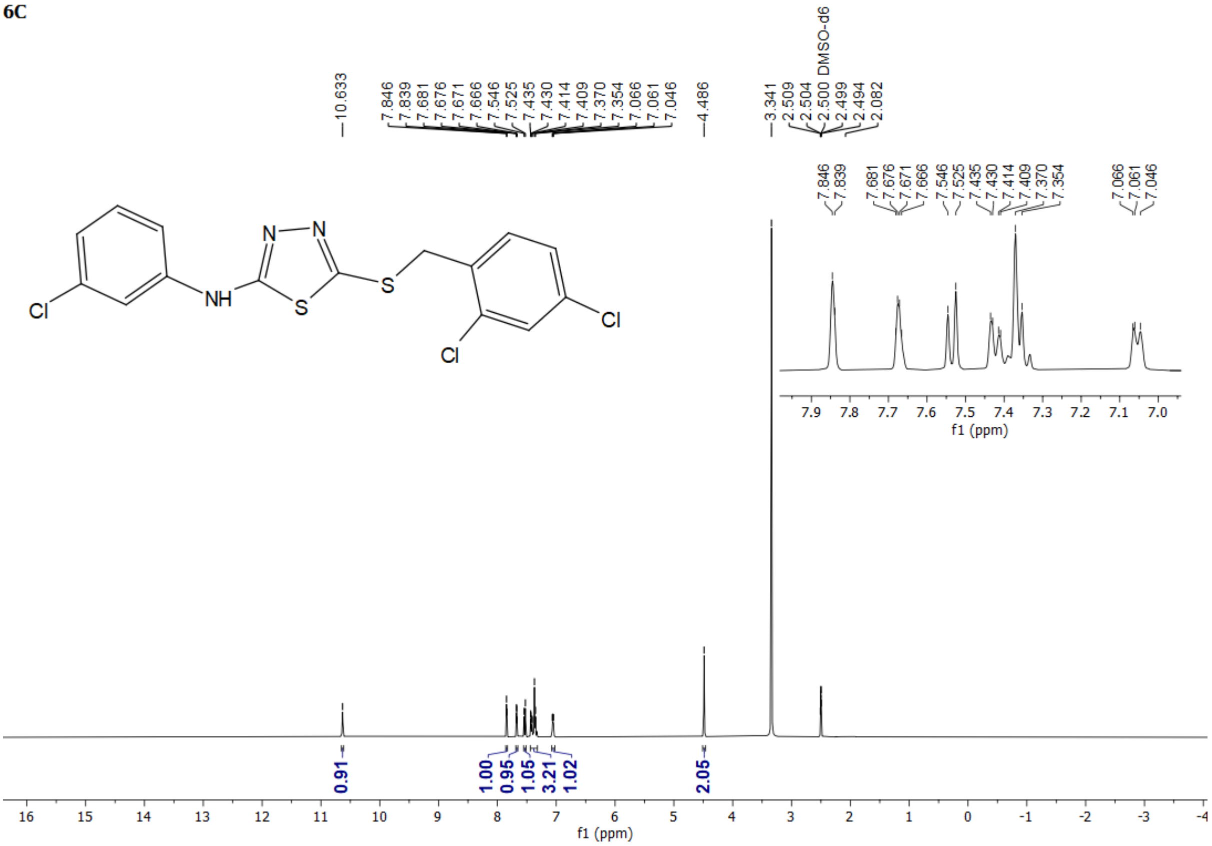
7.838
7.834
7.827
7.451
7.431
7.422
7.417
7.411
7.405
7.397
7.388
7.384
7.378
7.376
7.366
7.361
7.353
7.339
7.056
7.049
7.041
7.033
7.027
4.423
3.349
2.500 DMSO-d6
Cl
NH
N
N
S
S
Cl
1.00
6.25
1.01
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)
0.91
1.00
6.25
1.01
2.00
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

6C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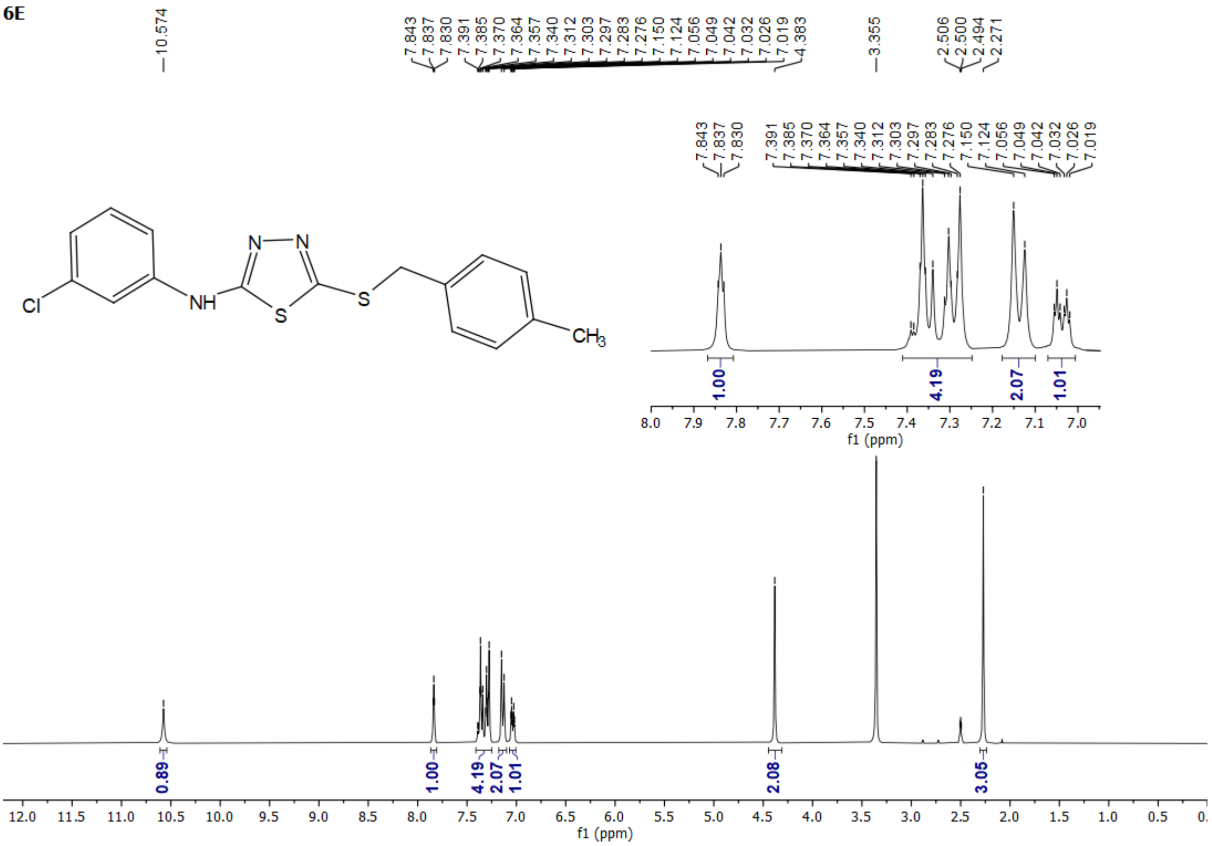
7.681
7.676
7.671
7.666
7.546
7.525
7.435
7.430
7.414
7.409
7.370
7.354
7.066
7.061
7.046
4.486
3.341
2.509
2.504
2.500 DMSO-d6
2.499
2.494
2.082
Cl
NH
N
N
S
S
Cl
Cl
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
0.91
1.00
0.95
1.05
3.21
1.02
2.05
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

6E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7.837
7.830
7.391
7.385
7.370
7.364
7.357
7.340
7.312
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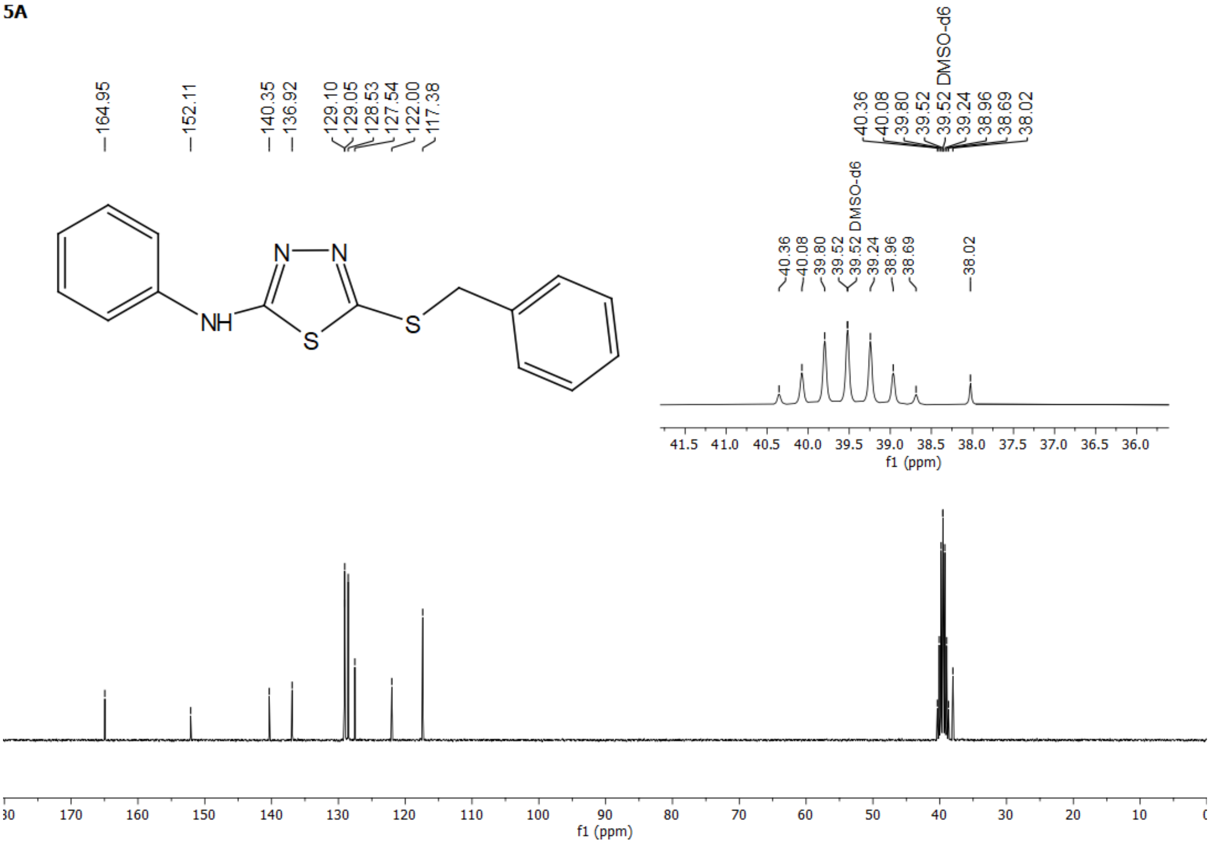
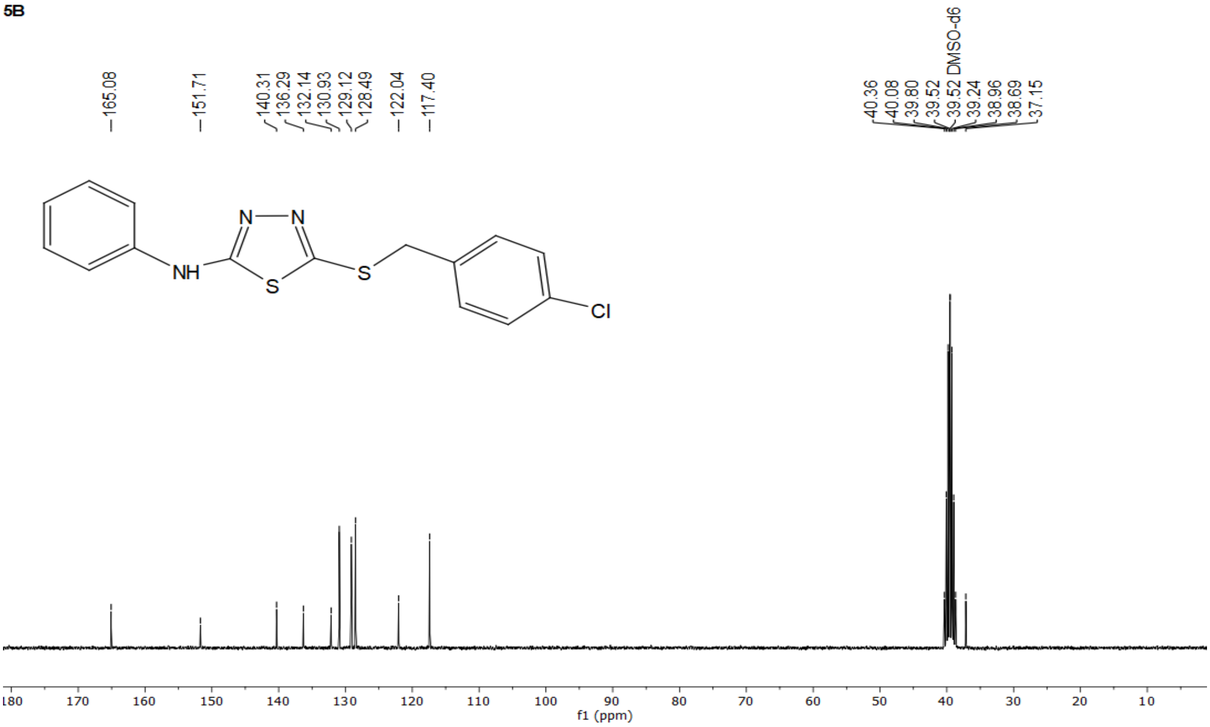
7.283
7.276
7.150
7.124
7.056
7.049
7.042
7.032
7.026
7.019
4.383
3.355
2.506
2.500
2.494
2.271
Cl
NH
N
N
S
S
CH3
1.00
4.19
2.07
1.01
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
0.89
1.00
4.19
2.07
1.01
2.08
3.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

4.4.^{13}C NMR SPECTRA OF THE SYNTHESIZED COMPOUND:

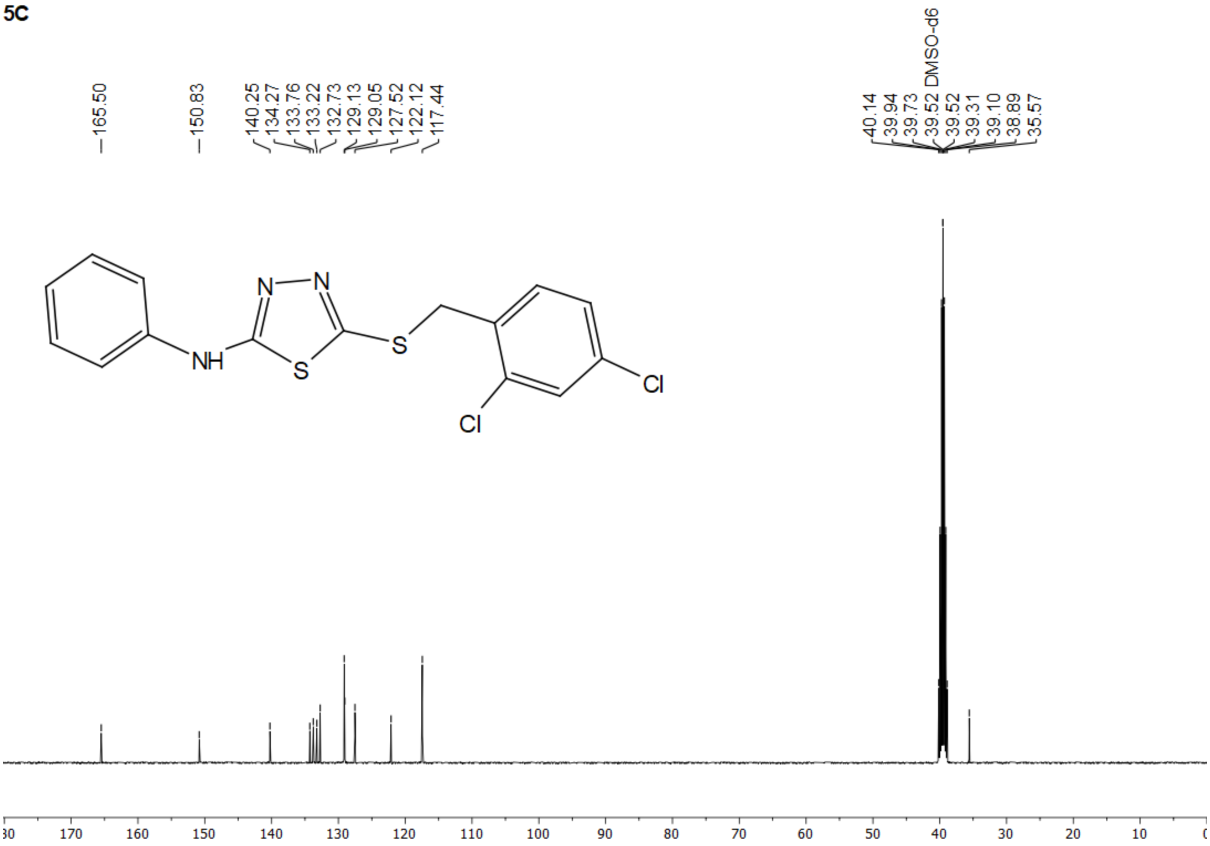
5A



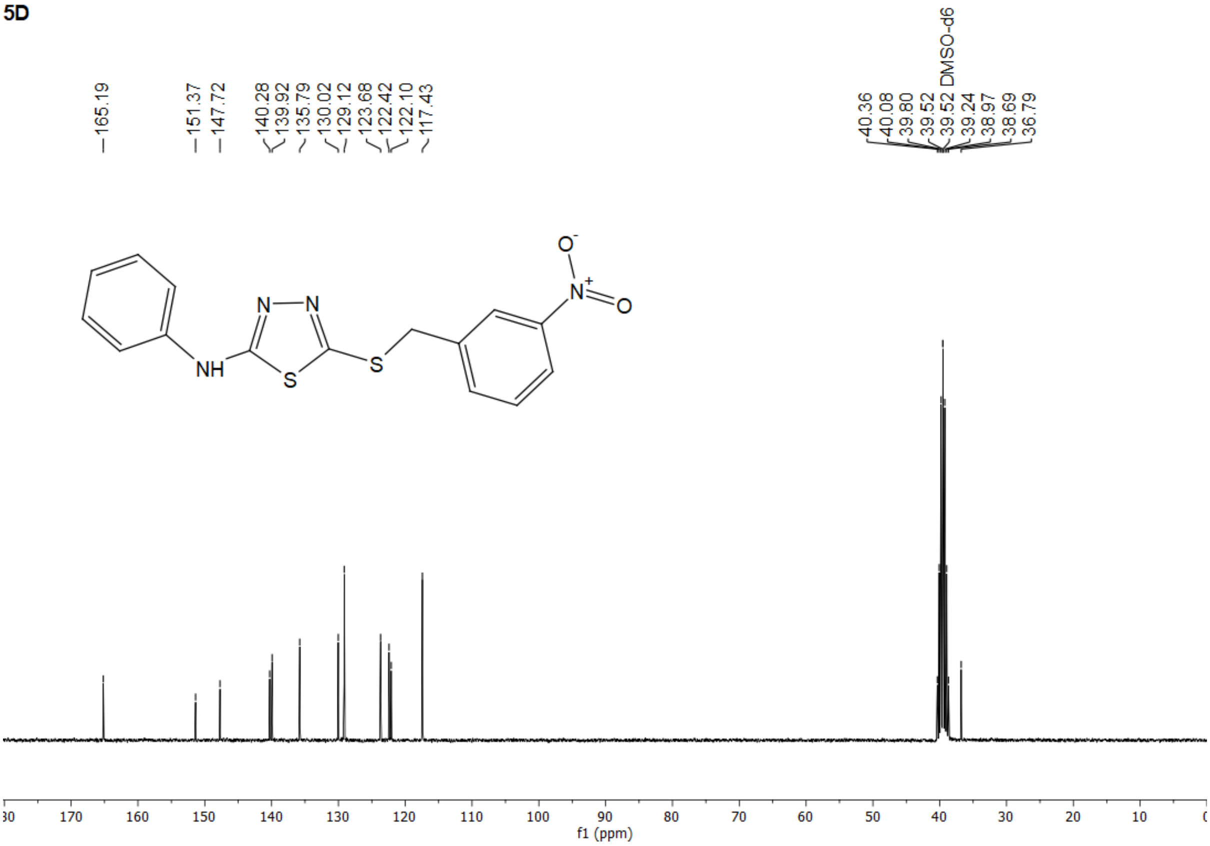
5B



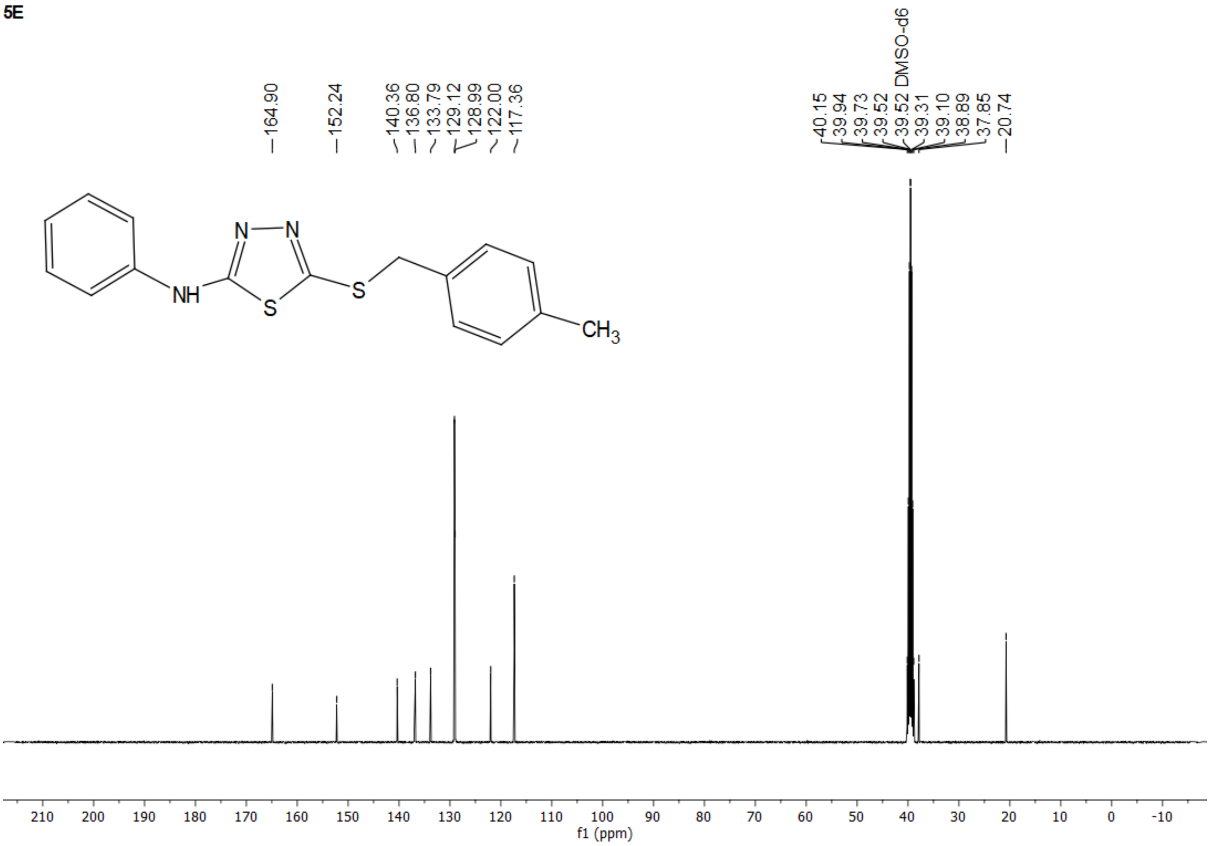
5C


165.50
150.83
140.25
134.27
133.76
133.22
132.73
129.13
129.05
127.52
122.12
117.44
40.14
39.94
39.73
39.52 DMSO-d6
39.52
39.31
39.10
38.89
35.57
N
N
NH
S
S
Cl
Cl
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

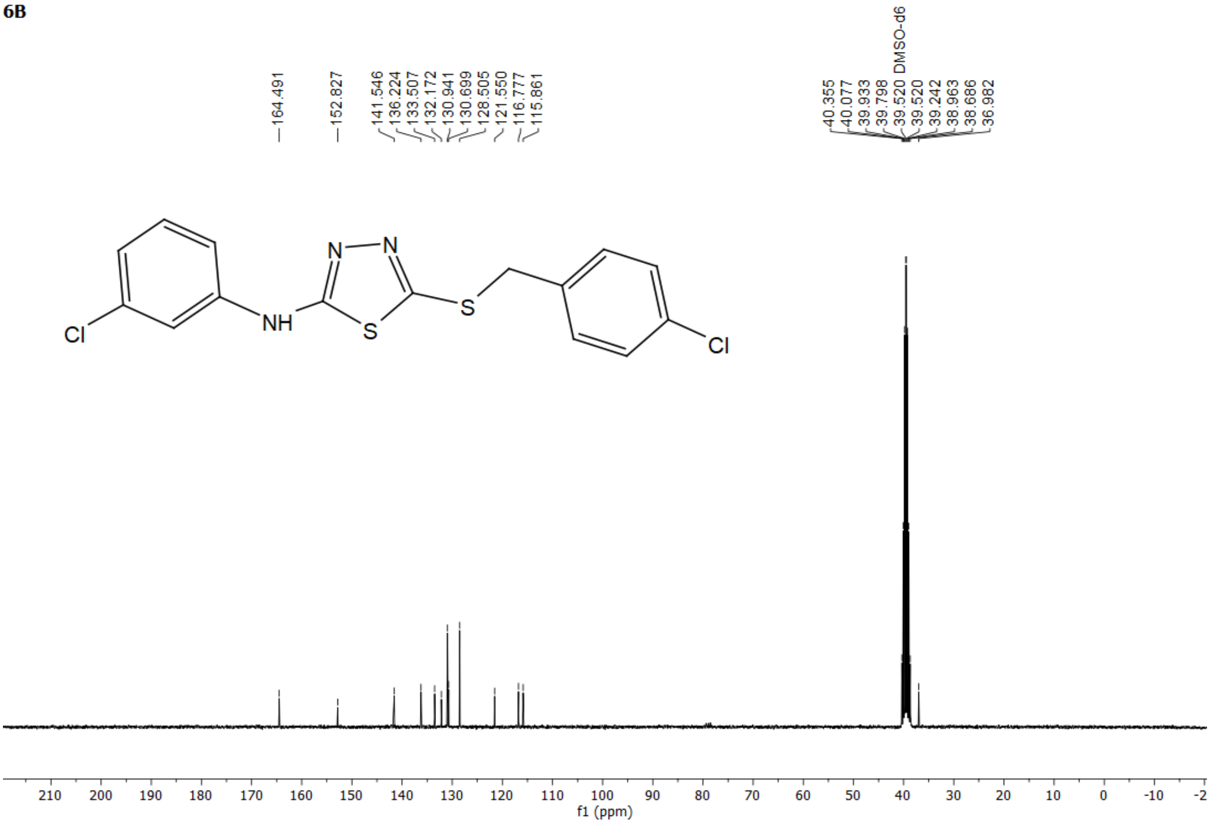
5D


165.19
151.37
147.72
140.28
139.92
135.79
130.02
129.12
123.68
122.42
122.10
117.43
40.36
40.08
39.80
39.52 DMSO-d6
39.52
39.24
38.97
38.69
36.79
O^-
N^+
O
N
N
NH
S
S
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

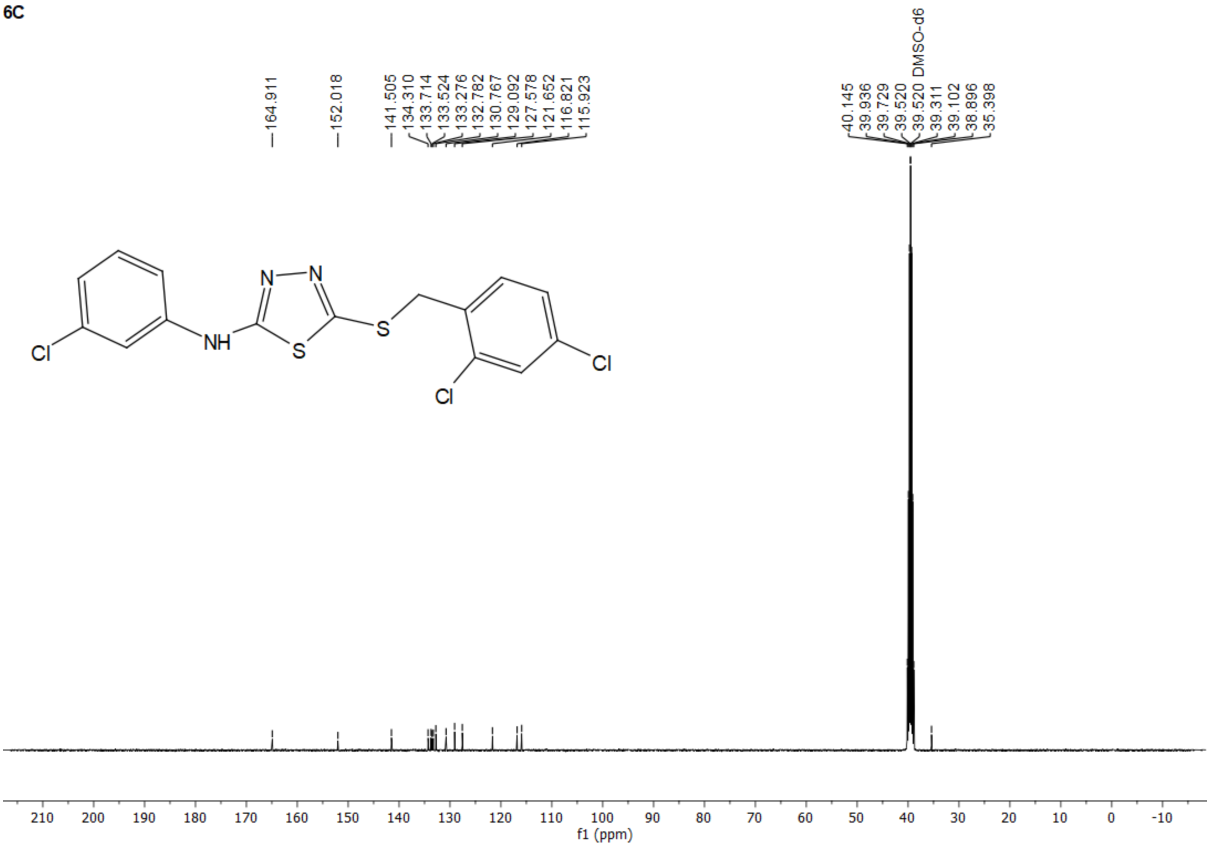
5E


164.90
152.24
140.36
136.80
133.79
129.12
128.99
122.00
117.36
DMSO-d6
40.15
39.94
39.73
39.52
39.31
39.10
38.89
37.85
20.74
N
N
NH
S
S
CH3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

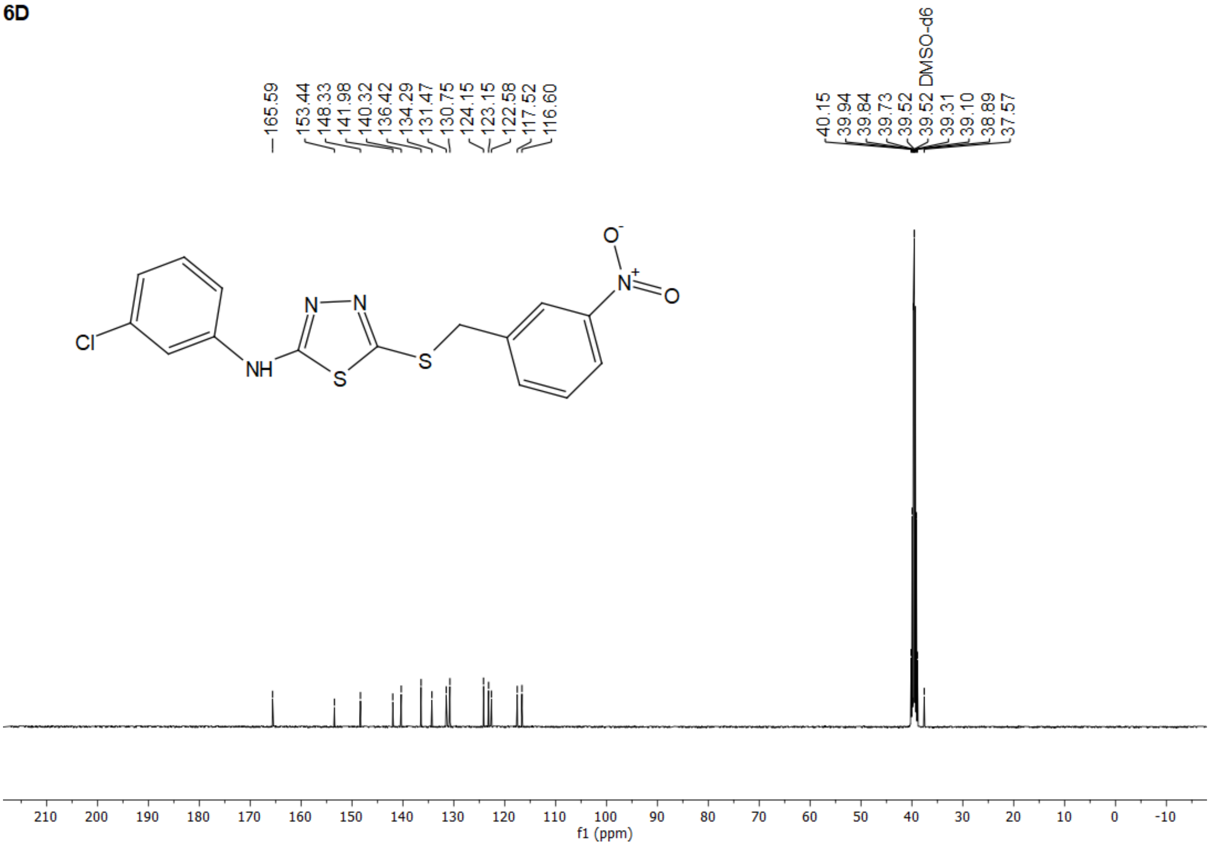
6B


164.491
152.827
141.546
136.224
133.507
132.172
130.941
130.699
128.505
121.550
116.777
115.861
DMSO-d6
40.355
40.077
39.933
39.798
39.520
39.520
39.242
38.963
38.686
36.982
Cl
NH
N
N
S
S
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2
f1 (ppm)

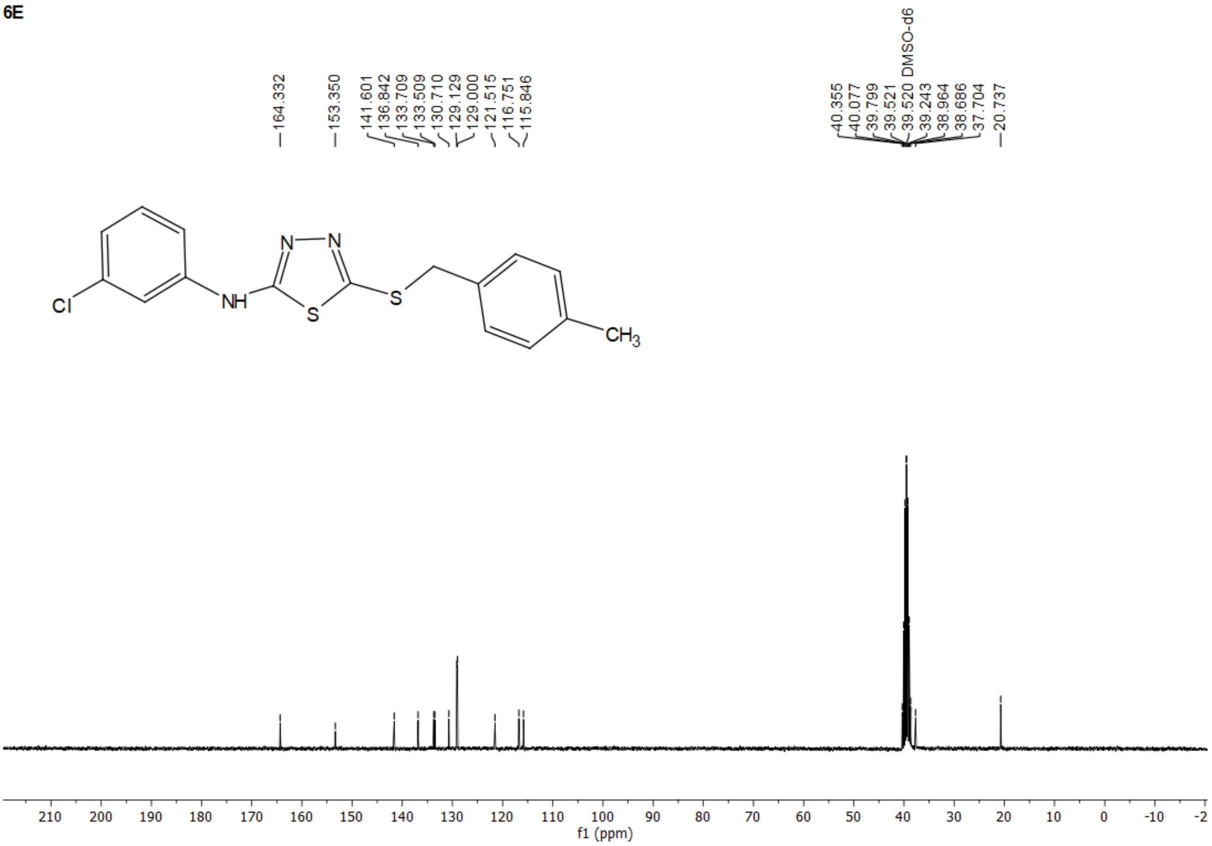
6C


164.911
152.018
141.505
134.310
133.714
133.524
133.276
132.782
130.767
129.092
127.578
121.652
116.821
115.923
40.145
39.936
39.729
39.520
39.520 DMSO-d6
39.311
39.102
38.896
35.398
Cl
NH
N
N
S
S
Cl
Cl
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

6D


165.59
153.44
148.33
141.98
140.32
136.42
134.29
131.47
130.75
124.15
123.15
122.58
117.52
116.60
40.15
39.94
39.84
39.73
39.52
39.52 DMSO-d6
39.31
39.10
38.89
37.57
O-
N+
O
Cl
NH
N
N
S
S
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

6E


164.332
153.350
141.601
136.842
133.709
133.509
130.710
129.129
129.000
121.515
116.751
115.846
40.355
40.077
39.799
39.521
39.520 DMSO-d6
39.243
38.964
38.686
37.704
20.737
Cl
NH
N
N
S
S
CH3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-2
f1 (ppm)

CONCLUSION:

As a part of my research work I have synthesized some 2,5-disubstituted 1,3,4-thiadiazole derivatives and characterized by IR, ^{1}H NMR and ^{13}C NMR Spectroscopy. 1,3,4-thiadiazole derivatives are found to be pharmacologically more potent due to their wide range of biological activities. Modification of 1,3,4-thiadiazole moiety produces valuable pharmacological activity, mostly due to their N=C-S bond and substitution at different position in heterocycle possess the potential activity with lower adverse effects and toxicity in humans.

Mesoionic character of this ring allows thiadiazole-containing compounds to cross cellular membrane and interact strongly with biological targets. Their synthesis process is not so complex. Antibacterial activity will be evaluated in terms of Zone of inhibition, MBC, and MIC value determination of established compounds. Molecular docking study will be done to identify the drug-antibacterial target (viz. Penicillin-binding protein, DNA gyrase, NAM, NAG and Sortase A, etc.) interaction along with ADME (Lipinski's rule of five) and Toxicological calculation via computational approach to determine the drug-likeness property of the molecules.