SYNTHESIS, CHARACTERIZATION, MOLECULAR DOCKING AND *IN SILICO* ADME STUDIES OF 1,3,4-OXADIAZOLE DERIVATIVES

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

By

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2024

Certificate of Approval

This is to certify that Rajarshi Ray (**Examination Roll No: M4PHC24008, Registration No:163661 of 2022-2023**) has carried out the project work on the subject entitled, **"Synthesis, characterization, molecular docking and *in silico* ADME studies of 1,3,4-oxadiazole Derivatives"** under the supervision of **Prof. (Dr.) Tapan Kumar Maity**, Department of Pharmaceutical Technology, Jadavpur University. This project work is submitted by him in partial fulfilment of the requirements for the degree of **Master of Pharmacy (Pharmaceutical Chemistry)** of Jadavpur University. He 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, characterization, molecular docking and *in silico* ADME studies of 1,3,4-oxadiazole Derivatives "**.

All the information 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 referred all the information 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.

Antifungal resistance is now well documented for many pathogens, and studies with a variety of fungi indicate that resistance can develop within just a few years. Resistance against many members of azoles, particularly older ones, such as miconazole is increasing. Cancer is still one of the leading cause of deaths worldwide. Adverse cytotoxicity is one of the worst outcomes of anticancer agents. So, there is ongoing research for the synthesis of less resistant antifungal agents and also anticancer agents with less cytotoxicity and better efficacy.

The heterocyclic compounds display various biological activity. Among the heterocyclic compounds, 1,3,4-oxadiazole molecule exhibits versatile biological activities including antifungal and anticancer activity.

The present work entitled **" Synthesis, characterization, molecular docking and *in silico* ADME studies of 1,3,4-oxadiazole Derivatives "** undertaken with an aim to synthesize a suitable lead compound which can be exploited to develop novel antimicrobial and/or anticancer agents.

Dedicated to

my guide, family and well wishers

INDEX

CHAPTER-1

Introduction

1.1) Introduction

Because of their biological significance, a number of physiologically significant compounds containing heteroatoms, such as those containing nitrogen, oxygen, and sulfur, have piqued the curiosity of researchers over time. These molecules that include heteroatoms have exceptional biological activities, such as antibacterial, anticancer, antidiabetic, and antiepileptic properties. An essential class of heterocyclic compounds, oxadiazoles have a five-membered ring containing two nitrogen atoms and one oxygen atom.[1] Oxadiazole has four isomers. Out of these, the 1,2,3-isomer has exhibited instability because it shows diazoketone tautomerism (ring opening). But, 1,3,4 oxadiazole is more stable than the rest of the isomers. In the realm of energetic materials, oxadiazole-based energetic compounds have garnered a lot of attention lately. Among these, 1,3,4-oxadiazole exhibits moderate energy levels and superior stability because it lacks easily cleaved N–O bonds in contrast to other oxadiazole isomers. Ainsworth *et al.* synthesized this heterocyclic ring for the first time in 1965 using the hydrazine thermal breakdown mechanism. The moiety oxadiazole has the formula C2H2ON2, a molecular weight of 70.05 g/mol, and it is soluble in water. The four isomers are shown in **Figure1**.[2][3]


1,3,4-oxadiazole 1,2,4-oxadiazole 1,2,3-oxadiazole 1,2,5-oxadiazole

Figure1; Isomers of 1,3,4-oxadiazole

1,3,4 oxadiazole is an aromatic heterocycle, having resonance energy around 167.4 kJ/mol, which is the reason of it being thermostable. It is noticed that substitution at the second position boosts its thermal stability.[4] Salts of 1,3,4-oxadiazolium are produced when electrophilic reactions at carbon atoms are difficult due to the decreased electron cloud density in the carbon centres of the oxadiazole moiety. In halogenated oxadiazole, on the other hand, nucleophilic substitution processes continue by substituting the halogen atom (**Figure 2**).[5]

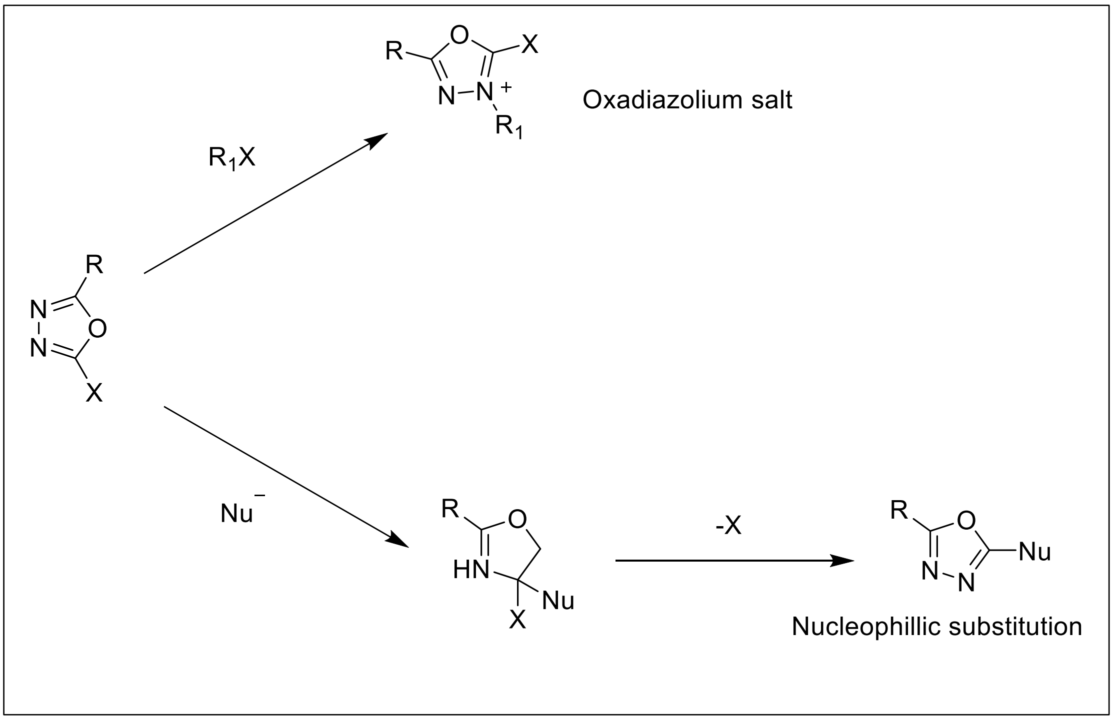


Figure2: Substitution reaction given by 1,3,4-oxadiazole

The characteristics of the 1,3,4-oxadiazole core resemble those of an aromatic heterocycle. As a result, it exhibits typical aromatic system interactions with hydrophobic amino acids like tyrosine, phenylalanine, and tryptophan, such as π-π stacking. A group of 1,3,4-oxadiazoles were created by Dhumal *et al*. with the intention of blocking the action of Mycobacterium tuberculosis's mycobacterial enoyl reductase (InhA). Dhumal *et al*.'s docking investigations on InhA revealed that the oxadiazole core interacts with Tyr158 and Phe149 via a π-π stacking(Fig 3). The authors' other 1,3,4-oxadiazoles likewise exhibit this type of interaction; the only relevant modifications occur at the level of the other structural decorations, such as a pyridine ring.[6] The cation-π interaction is another potential interaction between 1,3,4-oxadiazoles and proteins A series of α-glucosidase inhibitors was synthesized by Taha *et al*. using a 5-aryl2-(6'-nitrobenzofuran-2'-yl)-1,3,4-oxadiazole scaffold. According to docking studies, residue His279 and the 1,3,4-oxadiazole moiety interacted through a cation-π interaction.(Fig 4) [7]

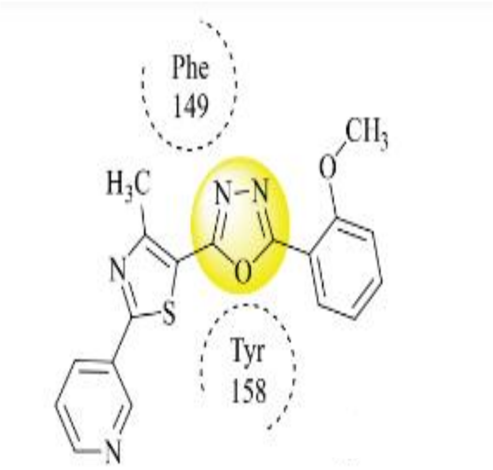


Fig3; π-π stacking of 1,3,4oxadiazole

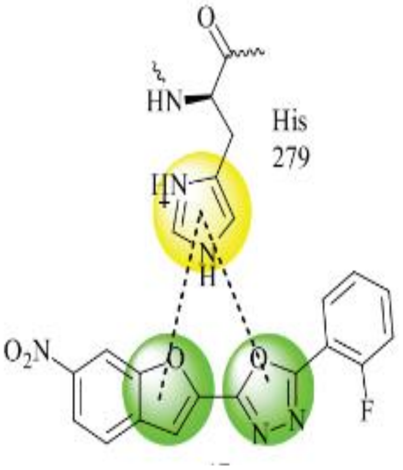


Fig4; cation-π interaction of 1,3,4-oxadiazole

Because of the diverse binding properties with proteins, 1,3,4 oxadiazole is established as a very important scaffold as a building block a pharmacophore. The hetero atoms increase hydrogen bond interactions with amino acids. Various marketed drugs have this 1,3,4 oxadiazole moiety showing diverse pharmacological significance. 1,3,4-oxadiazole is ruling in the sectors of antimicrobial, antihypertensive, anticancer, analgesics. These are depicted in figure 5. [8]

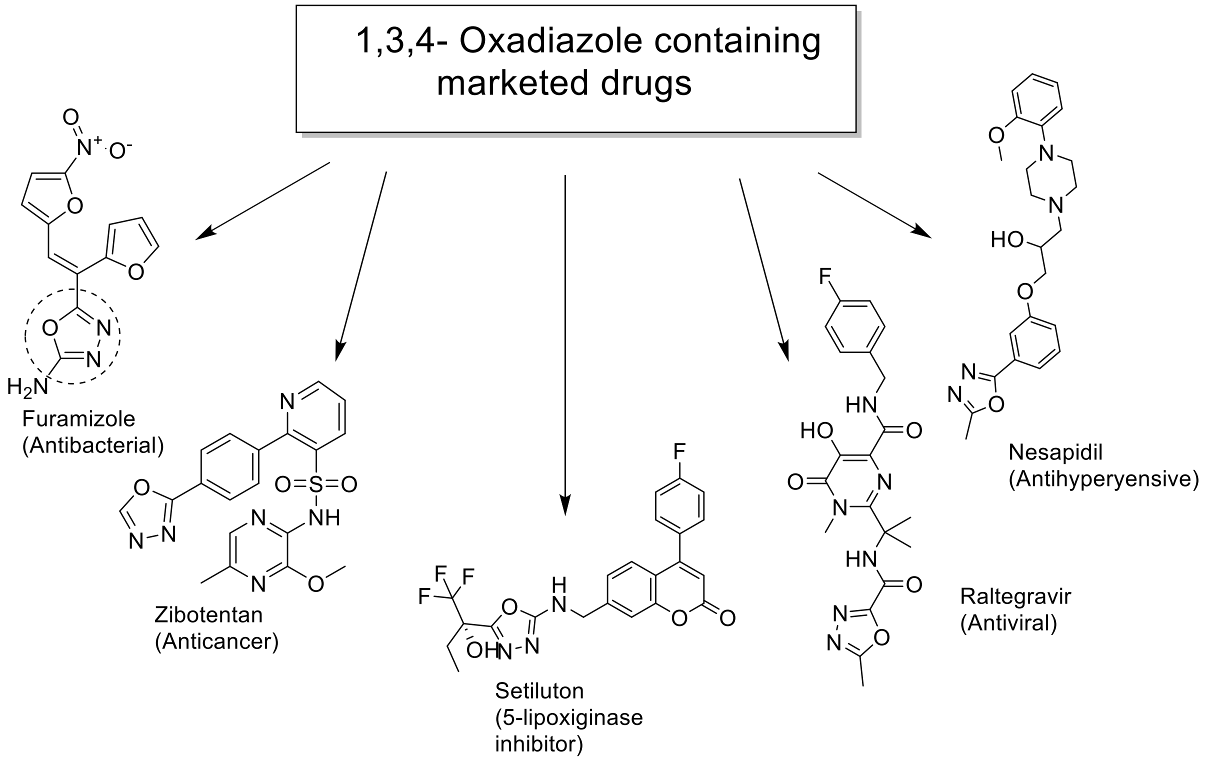


Fig5; Marketed drugs having 1,3,4-oxadiazole scaffold

There are lots of feasible synthetic pathway available for fetching this 1,3,4 oxadiazole moiety. Most widely used is cyclization of acyl hydrazides as depicted in literature.[9] Because of the stability, diverse biological properties which have gained commercialization and synthetic feasibility, 1,3,4 oxadiazole has gained lots of attention in the field of medicinal chemistry. It is already established that this scaffold has antimicrobial, anticancer, antitubercular, antiepileptic as well as analgesic properties. Researchers are working vigorously to synthesize new derivatives of 1,3,4 oxadiazole and evaluating their biological properties. My work is dedicated to synthesize 1,3,4 oxadiazol derivatives and perform their characterization.

1.2) References

1. Vaidya A, Pathak D, Shah K. 1, 3, 4-oxadiazole and its derivatives: A review on recent progress in anticancer activities. Chemical biology & drug design. 2021 Mar;97(3):572-91.

2. Kashid BB, Salunkhe PH, Dongare BB, More KR, Khedkar VM, Ghanwat AA. Synthesis of novel of 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives and their in vitro anti-inflammatory, anti-oxidant evaluation, and molecular docking study. Bioorganic & Medicinal Chemistry Letters. 2020 Jun 15;30(12):127136.

3. Du Y, Qu Z, Wang H, Cui H, Wang X. Review on the synthesis and performance for 1, 3, 4-oxadiazole-based energetic materials. Propellants, Explosives, Pyrotechnics. 2021 Jun;46(6):860-74.

4. Ainsworth C, Hackler RE. Alkyl-1, 3, 4-oxadiazoles. The Journal of Organic Chemistry. 1966 Oct;31(10):3442-4.

5. Sun J, A Makawana J, Zhu HL. 1, 3, 4-oxadiazole derivatives as potential biological agents. Mini Reviews in Medicinal Chemistry. 2013 Oct 1;13(12):1725-43.

6. Dhumal, S. T.; Deshmukh, A. R.; Bhosle, M. R.; Khedkar, V. M.; Nawale, L. U.; Sarkar, D.; Mane, R. A.; Bioorg. Med. Chem. Lett. 2016, 26, 3646.

7. Taha, M.; Ismail, N. H.; Imran, S.; Wadood, A.; Rahim, F.; Saad, S. M.; Khan, K. M.; Nasir, A.; Bioorg. Chem. 2016, 66, 117.

8. Kumar D, Aggarwal N, Deep A, Kumar H, Chopra H, Marwaha RK, Cavalu S. An understanding of mechanism-based approaches for 1, 3, 4-oxadiazole scaffolds as cytotoxic agents and enzyme inhibitors. Pharmaceuticals. 2023 Feb 7;16(2):254.9 Singh R, Chouhan A. Various approaches for synthesis of 1, 3, 4-Oxadiazole derivatives and their pharmacological activity. World J Pharm Pharm Sci. 2014 Sep 25;3(10):1474-505.

CHAPTER-2

Literature review

2.1) Pharmacological attributes of 1,3,4-oxadiazole derivatives

In medicinal chemistry, we use heterocyclic aromatic rings rather than normal aryl groups, as the lone pair of electrons on the heteroatoms(N,O,S) can act as hydrogen bond acceptors, and show higher degree of interaction with the protein. There are lot's of commercially available drugs containing 1,3,4-oxadiazole moiety like Furamizole (potent antibacterial action), Nesapidil (anti-arrhythmic action), Raltegravir (antiviral drug),Tiodazosin, (antihypertensive agent), and the most promising FDA-approved derivative, the anticancer agent Zibotentan. . The 1,3,4-oxadiazole containing compounds have showed various pharmacological significances in recent research activities by various researchers.

Owing to different activities 1,3,4-oxadiazole possess, we classify them as follows.

2.1.1) ANTIMICROBIAL ACTIVITY

2.1.1.1) Antibacterial activity

Kumar *et al.* used a serial tube dilution procedure to screen their synthesized 2,5 substituted oxadiazole derivatives for antimicrobial activities. "The erstwhile screening against Gram (+ve) and Gram-negative (-ve) bacterium strains, **compound 1[Fig 6]** displayed moderate antibacterial reaction against *S. aureus, E. faecalis, E. coli,* and *K. pneumoniae with* MIC 7.55 μM. Along the same lines, **compound 2[Fig 7]** exhibited light antimicrobial reaction against *S. aureus, E. faecalis, E. coli, K. pneumoniae,* and *T. harzianum* with MIC 7.76 μM. [1]

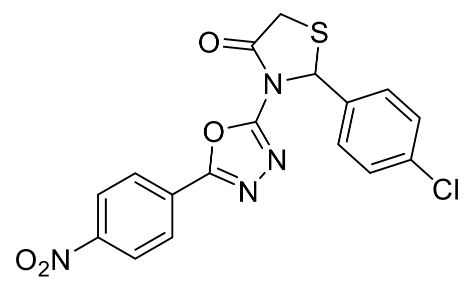


Fig 6; Compound1

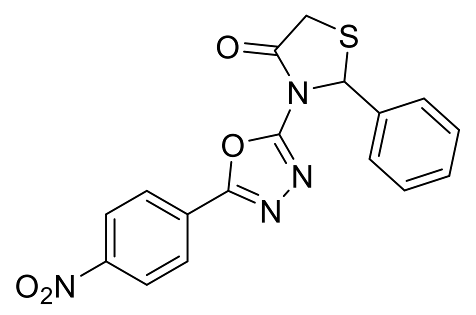


Fig7; Compound2

Kim *et al.* synthesized pyrrole ligated 1,3,4 oxadiazole compounds. They performed one-pot Maillard reaction between D-Ribose and an L-amino methyl ester in DMSO in presence of oxalic acid at 2.5 atm and 80° C to produced pyrrole-2-carbaldehyde platform chemicals, which were then utilised to. Then they took benzohydrazide, and reacted with the formyl group of the pyrrole platforms to provide the corresponding imine intermediates, which underwent Iodine-mediated oxidative cyclization to produce the pyrrole-ligated 1,3,4-oxadiazole skeleton. The MIC values of <2 µg/mL for **compound 3 (Fig 8)** and 8 µg/mL for **compound 4 (Fig 9)** against A. baumannii were much lower than those of the positive controls (>1024 µg/mL for vancomycin and 128 µg/mL for erythromycin). They also produced remarkable effects against *S.aureus* [2]

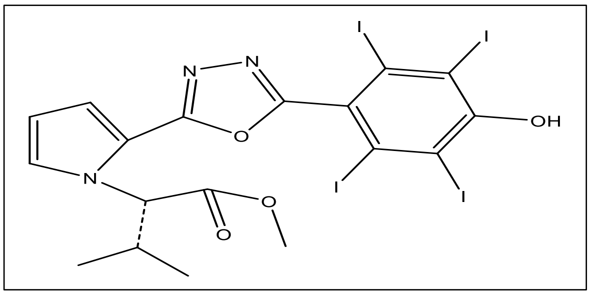


Fig8; Compound 3

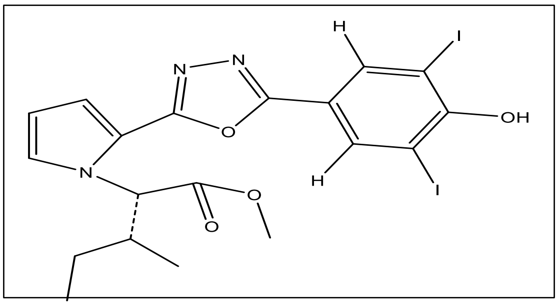


Fig9; Compound 4

In 2017, World Health Organization declared MRSA (Methicillin resistant Staphylococcus aureus) as one of the 12 deadliest antibiotic resistant bacterial strains. Guo *et al.* combined norfloxacin (2nd generation broad spectrum fluoroquinolone) with 1,3,4 oxadiazole moiety and investigated this combination against MRSA. **Compound 5 (Fig 10)** exhibited excellent antibacterial activities against *S. aureus* (MIC: 2 µg/mL) and MRSA1–3 (MIC: 0.25–1 µg/mL). The time-kill kinetics which they have used, demonstrated that **compound 5** had an advantage over commonly used antibiotics vancomycin in killing *S. aureus* and MRSA. Moreover, **compound 5** could inhibit the bacteria and destroy their membranes in a short time, and showed very low cytotoxicity to NRK-52E [3]

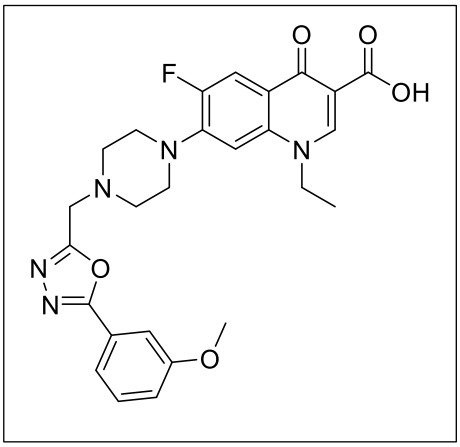


Fig10; Compound 5

2.1.1.2) Antifungal activity

Fungal infections have become a major problem worldwide, specially for immunocompromised patients. With the aim of discovering novel anti candidal agents, Karaburun *et al.* synthesized a series of benzimidazole-oxadiaazole hybrid compounds and evaluated their antifungal activities in vitro against various Candida strains including *C. albicans* (ATCC 90030), *C. krusei* (ATCC 6258) and *C. parapsilopsis* (ATCC 22019) biding by the protocol of the EUCAST. They found that Compound **6** was the most potent derivative of the series, with MIC50 values of 1.95 µg/mL, 7.8 µg/mL and 31.25 µg/mL against *C. albicans, C. krusei and C. parapsilopsis,* respectively. The cytotoxicity profiling of **compound 6** against NH/3T3 cells proved that **compound 6 (Fig 11)** is nontoxic to mammalian cells at it's active concentration.[4]

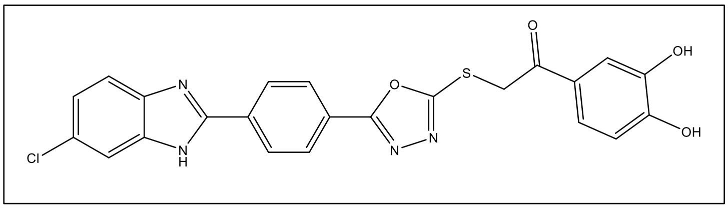


Fig11; Compound 6

Liao *et al.* designed and synthesized novel series of fluconazole based mimics incorporating 1,3,4-oxadiazole moiety and tested their antifungal activity against seven human pathogenic fungi, *Candida albican* SC5314, *Candida albican* Y0109, *Cryptococcus neoformans, Candida parapsilosis, Candida glabrata, Trichophyton rubrum,* and *Microsporum gypseum*. They kept itraconazole and fluconazole as positive controls. The MIC80 values of **compound 7 (Fig 12)** and **8 (Fig 13)** (0.125 µg/mL) against the listed fungal strains indicated that they were up to 64-fold more potent than fluconazole and itraconazole.[5]

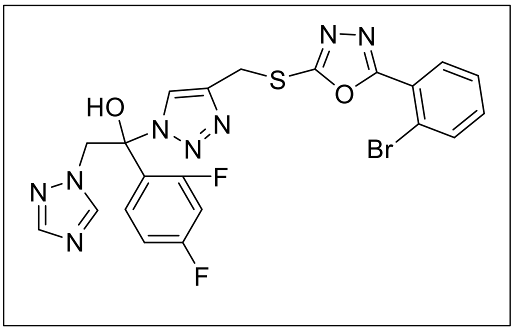


Fig12; Compound 7

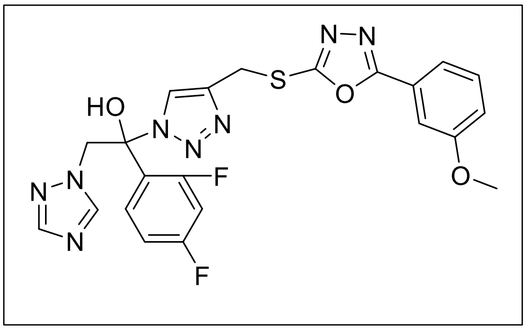


Fig13; Compound 8

2.1.1.3) Antiviral activity

Masouri *et al.* synthesized a new series of furo[2,3-d]pyrimidine–1,3,4-oxadiazole hybrid derivatives via environmentally friendly multistep synthetic tool and one pot Sonoashira-Heterocyclization. **Compounds 9-11 (Fig 14-16)** demonstrated low micromolar EC50 values and broad-spectrum action against both wild and mutant strains of the varicella-zoster virus (VZV). The **compound 11** reached three times more effective against thymidine kinase deficient VZV strains than the benchmark medication acyclovir. Significantly, derivative 9b exhibited a satisfactory selectivity index value of up to 7.8 and was not cytostatic at the highest tested concentration (CC50 > 100 µM). [6]

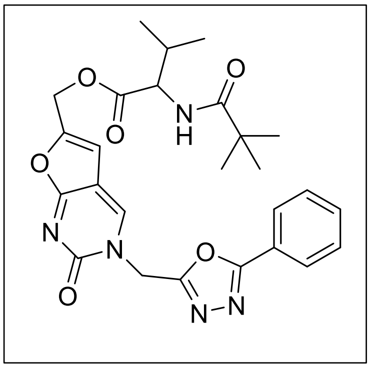


Fig14; Compound 9

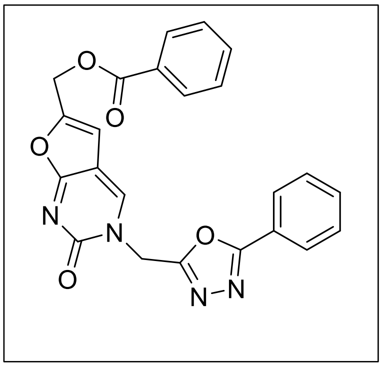


Fig15; Compound 10

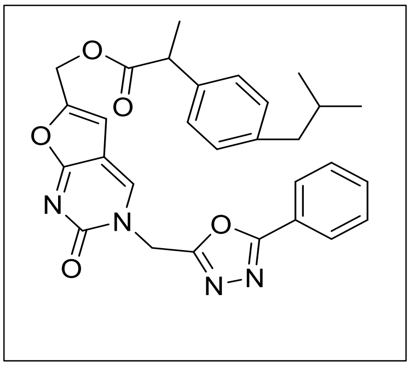


Fig16; Compound 11

A well-known plant virus called tobacco mosaic virus (TMV) can spread to at least 400 distinct species, including numerous decorative flowers, tobacco, cucumbers, and tomatoes. Gan *et al.* synthesized a number of new 1,3,4-oxadiazole/thiadiazole–chalcone conjugates. The half-leaf method and microscale thermophoresis method were used to assess each compound's antiviral activity in vivo and in vitro, respectively. According to the in vitro data, **compounds 12 (Fig 17)** and **13 (Fig 18)** had strong antiviral activity against TMV, with binding constant values of 5.93 and 6.15, respectively. These values were superior to those of ribavirin (99.25 µM) and equivalent to those of ninnanmycin (6.78 µM). With EC50 values of 33.66 and 33.97 mg/mL, respectively, **compounds 12 (Fig 17)** and **13 (Fig 18)** showed outstanding anti-TMV activity in the in vivo results. These values were equal to those of Ningnanmycin (36.85 mg/mL) and superior to ribavirin (88.52µg/ml). [7]

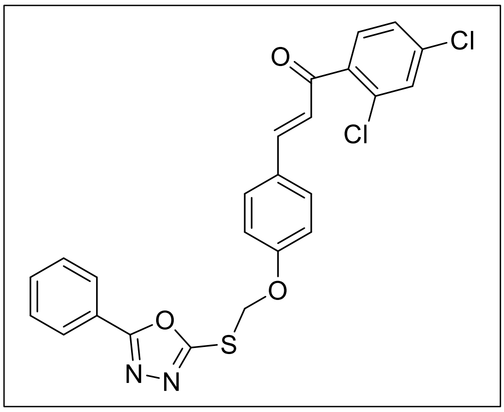


Fig17; Compound12

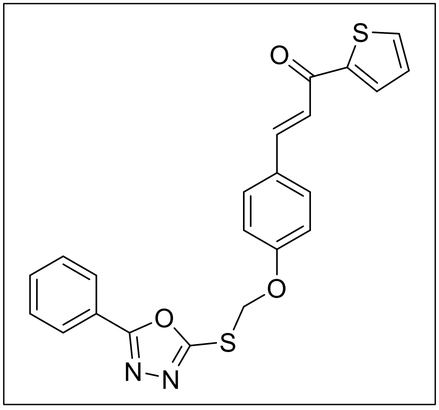


Fig18; Compound 13

2.1.2) ANTITUBERCULAR ACTIVITY:

Desai *et al.* synthesized and assessed the in vitro antitubercular activity of a series of indole- and pyridine-based 1,3,4-oxadiazole derivatives against both active and dormant forms of *Mycobacterium bovis* BCG and *Mycobacterium tuberculosis* H37Ra (MTB). **Compounds 14 (Fig 19)** and **15 (Fig 20)** demonstrated excellent antitubercular efficacy. Using a modified MTT assay, all of the newly synthesized compounds were determined to be noncytotoxic after being further assessed for their anti-proliferative efficacy against HeLa, A549, and PANC-1 cell lines. **Compound 14** came out as the most active compound against active *M. bovis* BCG with MIC of 0.94 µg/mL while, **compound 15** was most active against dormant *M. bovis* BCG with MIC of 0.85 µg/mL. [8]

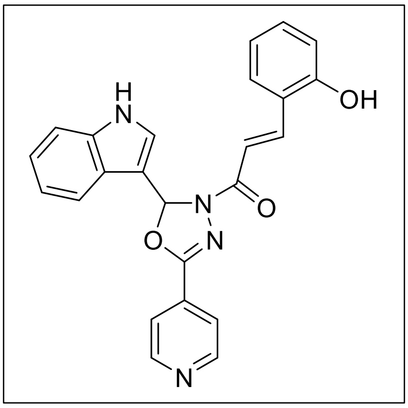


Fig 19; Compound14

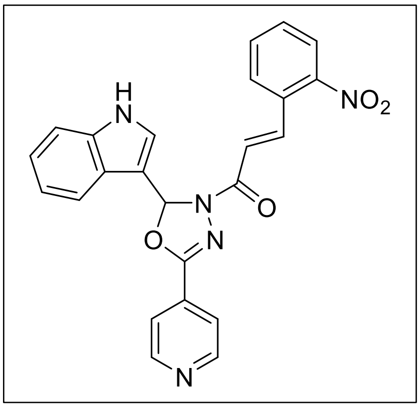


Fig 20; Compound 15

Das *et al*. performed an experiment to synthesize and assess several new compounds' for antitubercular and antibacterial properties. 3-[4-(5-pyrazin-2-yl]-3-chloro-4-aryl-1-[1,3,4]Oxadiazole: 2-ylmethoxy)-phenyl]-azetidin-2-one derivatives are made using the well-known antitubercular drug pyrazinoic acid as a precursor. Among the synthesized derivative, **16 (Fig 21)** and **17 (Fig 22)** were found to be prominent compounds which have potential antibacterial, antifungal and antitubercular activity (with near about MIC 3.12 µg/ml) [9]

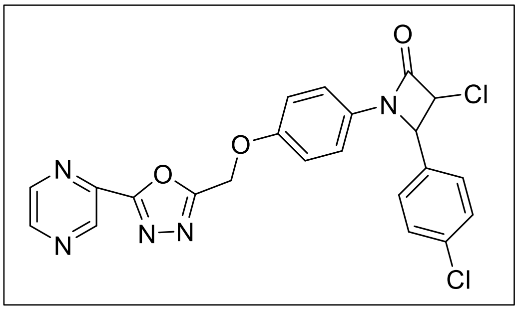


Fig 21; Compound 16

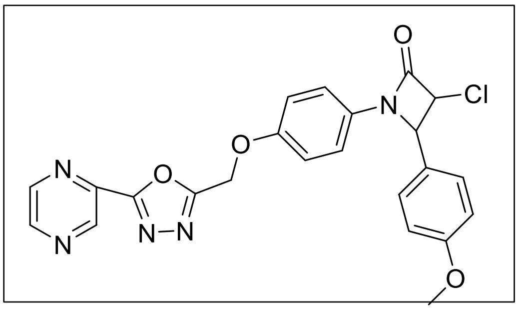


Fig 22; Compound 17

Pflegr *et al*. synthesized N-alkyl-5-(pyrimidin-5-yl)-1,3,4-oxadiazol-2-amines and their analogues by cyclizing prepared N-alkyl-2-(pyrimidine-5-carbonyl)hydrazine-1-carboxamides. Out of 48 compounds, the most effective ones at a concentration of 2 µM were oxadiazoles and C8–C12 alkyls **compound 18 (Fig 23)** against *Mycobacterium avium,* *Mycobacterium kansasii,* and *Mycobacterium TB* H37Rv. The same concentrations that inhibited the susceptible strain also inhibited the multidrug-resistant strain. The mechanism of action for the most powerful N-dodecyl-5-(pyrimidin-5-yl)-1,3,4-oxadiazol-2-amine was studied in relation to cell wall production.[10]

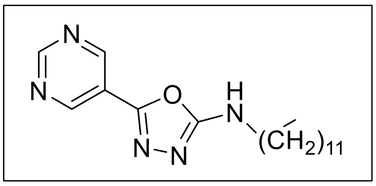


Fig 23; Compound18

Ahsan *et al.* investigated a sequence of {[(5-aryl-1,3,4-oxadiazol-2-yl)methyl] amino} 1,5-dimethyl-2-phenyl-4-{-1,2-dihydro-3H-pyrazol-3-one for lipophilicity, drug likeness using software from Molinspiration (Molinspiration, 2008) and MolSoft (MolSoft, 2007), and they did molecular properties prediction and solubility metrics with the use of the ALOGPS 2.1 software. The compounds were produced as oral bioavailable drugs/leads, adhering to the Lipinski "Rule of Five" for antibacterial and antitubercular screening. Following mass spectral, IR, and NMR analysis, all of the produced compounds were screened for microbes and mycobacteria. **Compound 19 (Fig 24)**, one of the title compounds, shown strong efficacy against isoniazid-resistant M. tuberculosis (INHR-TB) and Mycobacterium tuberculosis H37Rv, with minimum inhibitory concentrations (MICs) of 1.52 µM and 0.78 µM, respectively. [11]

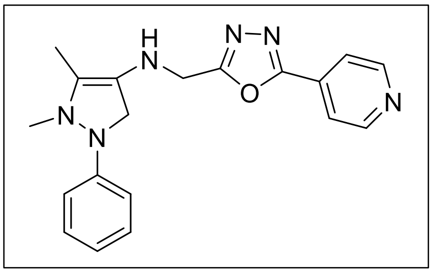


Fig 24; Compound 19

2.1.3) ANTIDIABETIC ACTIVITY:

Gani *et al.* synthesized and analysed a series of new 5-(2,5-bis(2,2,2-trifluoroethoxy)phenyl)-1,3,4-oxadiazole-2-thiol derivatives. Its bioactivity was assessed by evaluating its in vitro α-amylase and α-glycosidase inhibitory activity. Drosophila melanogaster, a genetic model, was used in an in vivo investigation to evaluate the antihyperglycemic effects. In comparison to standard acarbose (IC50 = 34.71 µg/ml), the compounds exhibited α-amylase inhibitory activity in the range of IC50 = 40.00–80.00 µg/ml and α-glucosidase inhibitory activity in the range of IC50 = 46.01–81.65 µg/ml. Out of all the produced compounds, **compounds 20 (Fig 25)** and **21 (Fig 26)** showed superior activity, according to the in vitro experiments. [12]

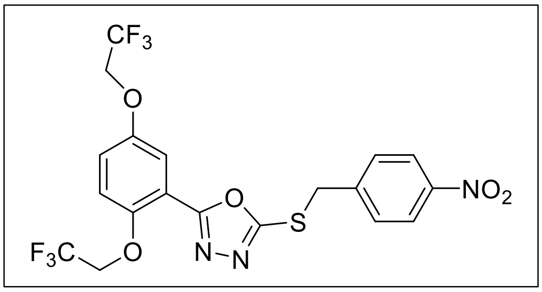


Fig 25; Compound 20

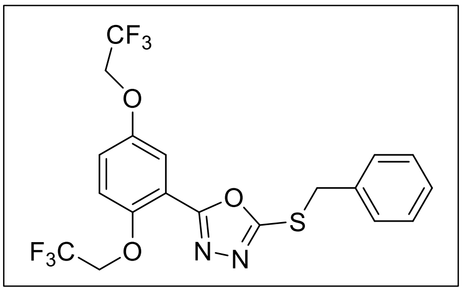


Fig 26; Compound 21

As prospective anti-α-glucosidase drugs, a series of novel benzofuran-1,3,4-oxadiazole containing 1,2,3-triazole-acetamides was designed and synthesized by Abedinifar *et al*. The α-glucosidase inhibition assay revealed that all of the synthesized compounds were more potent than the standard inhibitor acarbose (IC50 = 750.0 ± 12.5 µM), with half-maximal inhibitory concentration (IC50) values in the range of 40.7 ± 0.3–173.6 ± 1.9 µM. **Compound 22 (Fig 27)** was the most potent of them all, with an inhibitory action that was approximately 19 times greater than that of acarbose. A docking investigation of the most powerful chemical into the active site of α-glucosidase was also conducted, as it inhibited the enzyme in a competitive fashion. The title compounds' in vitro and in silico toxicity tests were also carried out.[13]

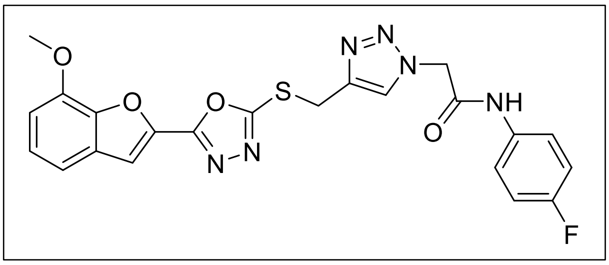


Fig 27; Compound 22

A new series of quinoxalin-1,3,4-oxadiazole derivatives was synthesized and evaluated by Mirzazadeh *et al*. against some metabolic enzymes including human α-glucosidase. Obtained data revealed that all the synthesized compounds were more potent as compared with the used standard inhibitors against studied target enzyme. Among the synthesized compounds, 3-bromo derivative **23 (Fig 28)** against α-glucosidase were the most potent compounds with inhibitory activity around 1.8- to 7.37-fold better than standard inhibitor with IC50 37.17 nM. Furthermore, docking studies of these compounds were performed at the active site of their target enzyme.[14]

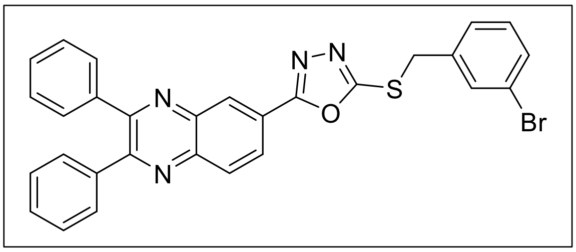


Fig 28; Compound 23

A library of brand-new bis-heterocycles based on 2-4-thiazolidinedione and 1,3,4-oxadiazole has been synthesized by Nazreen *et al.*, which demonstrated PPAR-γ transactivation and blood glucose lowering effects comparable to those of the prescription medications pioglitazone and rosiglitazone. Compounds 7m and 7r did not produce weight gain in the body and were shown to have no hepatotoxic or cardiotoxic adverse effects. PPAR-γ gene expression was elevated by **compounds 24 (Fig 29)** and **25 (Fig 30)** by 2.10 and 2.00 folds, respectively, in contrast to the conventional medication pioglitazone (1.5 fold) and rosiglitazone (1.0 fold). Thus, the molecules **24** and **25** could be taken into consideration as possible leads for the creation of novel antidiabetic drugs.[15]

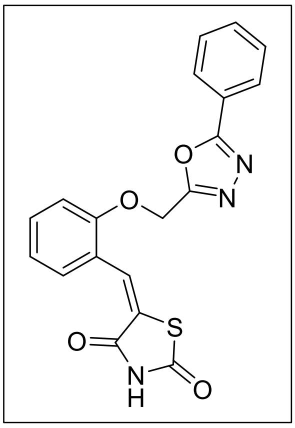


Fig 29; Compound 24

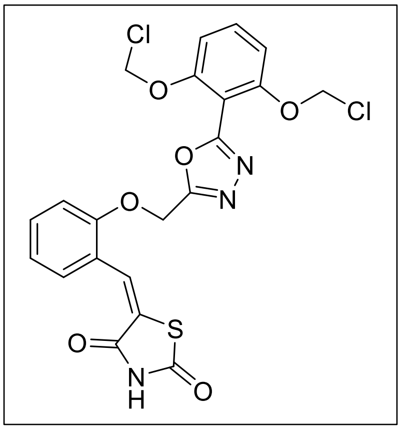


Fig 30; Compound 25

2.1.4) ANTICANCER ACTIVITY:

Despite significant progress in the development of drugs for the prevention and treatment of cancer, it remains one of the deadliest diseases in the world. Global data show that cancer is the world's biggest cause of mortality, with an estimated 10 million deaths from the disease in 2020. The lack of selectivity of anticancer medications, which causes numerous side effects, is another factor contributing to the cancer problem in addition to the disease's spreading and metastasis. Furthermore, the issue gets worse because anticancer medication targets are constantly changing and leading to resistance4. Currently, medicinal chemists are working to create novel, highly selective anticancer drugs that can circumvent the development of treatment resistance.

As VEGFR-2 inhibitors, some 1,3,4-oxadiazole-naphthalene hybrids were created and synthesized by Hagras *et al*., and were assessed in vitro for their ability to inhibit the growth of two human cancer cell lines, specifically HepG-2 and MCF-7. The potential cytotoxicity of compounds was assessed further, and their VEGFR-2 inhibitory properties were also assessed. **Compound 26 (Fig 31)** demonstrated strong inhibitory action on VEGFR-2 and antiproliferative efficacy against both cell lines. Furthermore, it caused 22.86% more apoptosis in the treated cells than in the control group (HepG2). The amount of caspase-3 increased 5.61 times more in the treated cells than in the control group, indicating an apoptotic effect. Furthermore, it primarily stopped HepG2 cell development at the Pre-G1stage. [16]

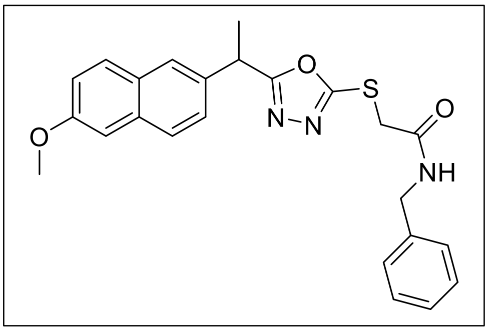


Fig 31; Compound 26

Herein, Kandukuri *et al.* synthesised some oxadiazole compounds and evaluated their potency against A549 (lung), MCF-7 (breast), HeLa (cervical) and HEK-293 (embryonic kidney) and etoposide acts as a standard drug. The most potent **compound 27 (Fig 32)** showed potency against all cell lines than the standard Etoposide with IC50 ranging from 0.93 (A549), 1.95 (MCF-7), 1.87 (HeLa) and 2.13 (HEK-293) respectively in micro molar concentration. The second most potent compound was **28 (Fig 33)** with IC_{50} (µM) 1.46 (A549), 2.45 (MCF-7), 2.45 (HeLa) and 2.67 (HEK-293). [17]

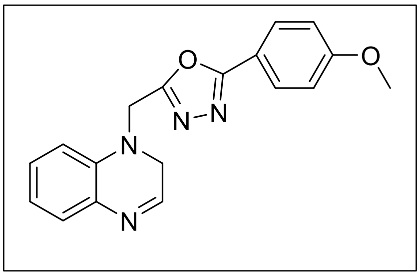


Fig 32; Compound 27

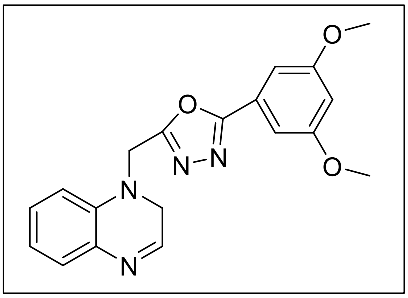


Fig 33; Compound 28

A novel class of 1,3,4-oxadiazole carrying pyrimidine-pyrazine derivatives were synthesized by Rachala *et al.*, and bio evaluated against four human cancer cell lines, including PC3 &DU-145 (prostate cancer), A549 (lung cancer) and MCF-7 (breast cancer). The popular chemotherapy drug etoposide is utilized as the positive control. The target compounds' IC50 values range from 9.44 ± 5.36 mM to 0.05 ± 0.007 mM, while the positive control showed results ranging, respectively, from 1.97 ± 0.45 mM to 3.08 ± 0.135 mM. One molecule, **29 (Fig 34),** shown better activity primarily.[18]

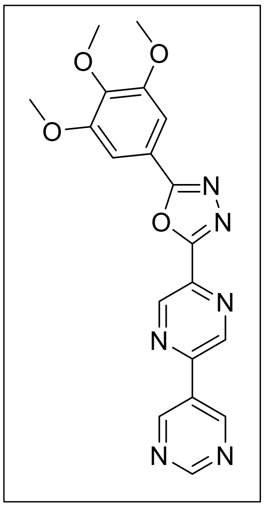


Fig 34; Compound 29

Agarwal et al. used scaffold hopping to design novel 1,3,4-oxadiaazole derivatives, synthesized them and evaluated their anticancer activity. N-(Dimethylphenyl-2,4)1-3,4-oxadiazol-2-amine and 5-(3,4,5-trifluorophenyl) **compound 30 (Fig 35)** showed moderate anticancer efficacy against HOP-92, SNB-75, ACHN, NCI/ADR-RES, 786-O, and considerable anticancer activity against SNB-19, OVCAR-8, and NCI-H40 with percent growth inhibitions (PGIs) of 86.61, 85.26, and 75.99. With PGIs of 67.55, 65.46, 59.09, 59.02, 57.88, 56.88, 56.53, 56.4, and 51.88, A549/ATCC, HCT-116, MDA-MB-231, and SF-295, correspondingly. Additionally, **compound 30** demonstrated superior anticancer activity against CNS, ovarian, renal, breast, and prostate cancers compared to imatinib with average PGIs of 56.18, 40.41, 36.36, 27.61, 22.61, and 10.33 for melanoma tumors, respectively.[19]

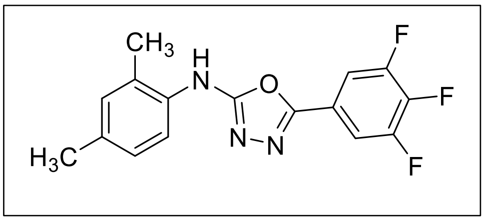


Fig 35; Compound 30

This study was done by Basappa et al. which used click chemistry to synthesize methyl-thiol-bridged oxadiazole and triazole heterocycles. It was found that the lead structure, 2-((1-(3,4-dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-5-(4-methoxybenzyl)-1,3,4-oxadiazole (4c), decreased the viability of MCF-7 cells with an IC50 value of 7.4 ~M. In addition, **compound 31** led to a concentration-dependent decrease in the viability of CML (chronic myelogenous leukemia) cells. Furthermore, nuclear translocation and DNA binding experiments revealed that **compound 31** reduced NF-B activation in human CML cells. Functionally, **compound 31** caused PARP cleavage and inhibited the production of VEGF, MMP-9, COX-2, survivin, and Bcl-2/xl, which caused CML cells to undergo apoptosis.[20]

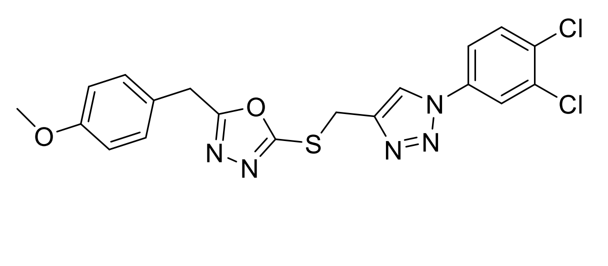


Fig 36; Compound 31

Afzal and colleagues created and produced a number of novel compounds of 1,3,4-oxadiazole. The oxadiazole-linked aryl core of tubulin inhibitors of IMC-038525 and IMC-094332 served as the basis for the creation of the novel compounds, which were made in five steps and further described using spectrum analyses.The chemicals' efficacy was evaluated against multiple cancer cell lines from nine distinct panels in accordance with National Cancer Institute (NCI US) guidelines.Against SNB-19, 4-Chloro-2-((5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)amino)phenol, **compound 32 (Fig 37)** showed strong anticancer activity at 10 µM, NCI-H460 (PGI = 55.61), SNB-75 (PGI = 54.68), and (PGI = 65.12).[21]

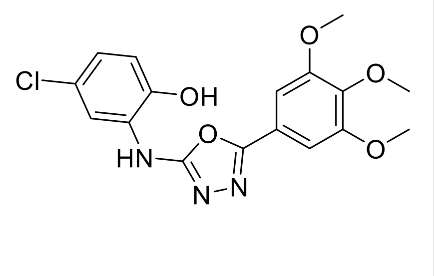


Fig 37; Compound 32

2.1.5) ANTIEPILEPTIC ACTIVITY:

In this work, Wang *et al.* developed and synthesized a series of 1,3,4-oxadiazole derivatives and tested the anticonvulsant activity of the target compounds in vivo utilizing subcutaneous pentylenetetrazole (scPTZ) and maximum electroshock (MES) models. The rotating rod (ROT) method was utilized to quantify the neurotoxicity (NT) of the target chemicals. In order to determine the 50% toxic dosage (TD50) and 50% effective dose (ED50), seven substances with possible action were chosen. Pharmacological tests demonstrated that **compound 33 (Fig 38)** had superior anticonvulsant activity (MES, ED50 ¼ 8.9 mg/kg; scPTZ, ED50 ¼ 10.2 mg/kg), surpassing the actions of ethosuximide and carbamazepine. In vitro binding tests revealed that **compound 33** had the most affinity for the GABAA receptor (IC50 ¼ 0.11 mM).[22]

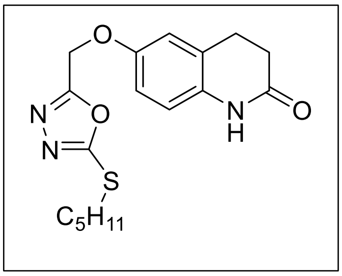
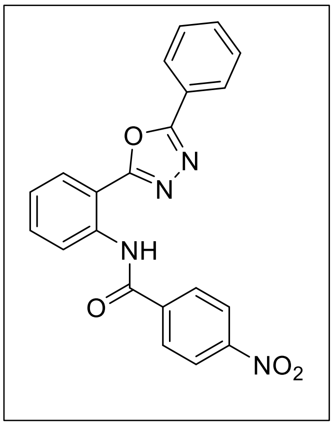


Fig 38; Compound 33

Khoramjouy *et al*. developed, produced, and assessed novel diphenyl 1,3,4-oxadiazole compounds as BZD ligands, taking into account the pharmacophore model of BZD binding to GABA-A receptor. Through in-vitro experiments, they examined the compounds' affinity for BZD receptors using the radioligand [3H]-flumazenil. In both the MES and PTZ produced seizure tests, **compounds 34 (Fig 39)** and **35 (Fig 40)** demonstrated the highest potency as anticonvulsant drugs among the synthesized compounds.[23]



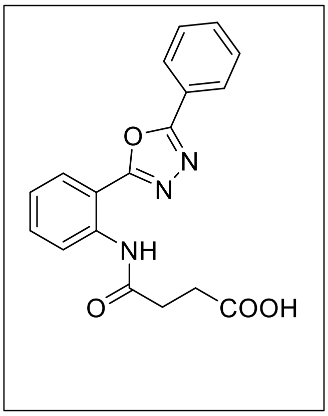


Fig 39; Compound 34

Fig 40; Compound35

Kikkheri *et al.* produced a number of novel 2-methyl-2-[3-(5-piperazin-1-yl-[1,3,4]oxadiazol-2-yl)-phenyl]-propionitrile derivatives in order to satisfy the structural conditions necessary for the anticonvulsant property. Mass spectroscopy, 1H NMR, and 13C NMR were used to confirm the structures of all the produced compounds. The anticonvulsant activity of each chemical was tested using the maximum electroshock (MES) seizure method, and the rotorod test was used to assess any neurotoxic consequences. The compounds with the highest potency in this series were discovered to be **36 (Fig 41)**, **37 (Fig 42)**, and **38 (Fig 43)**. The identical substances exhibited no neurotoxicity when given up to the maximal dosage (100 mg/kg). Additionally, an attempt was made to determine the correlations between the synthesized compounds' structures and activities.[24]

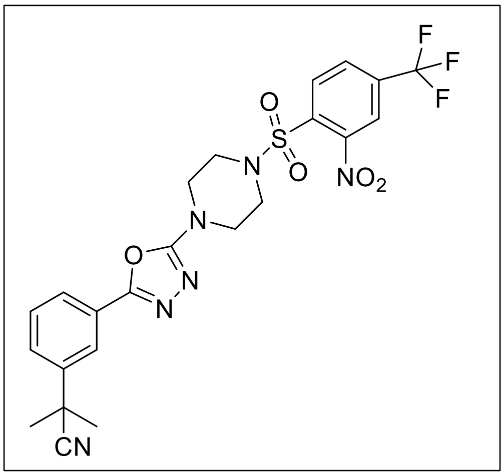


Fig 41; Compound 36

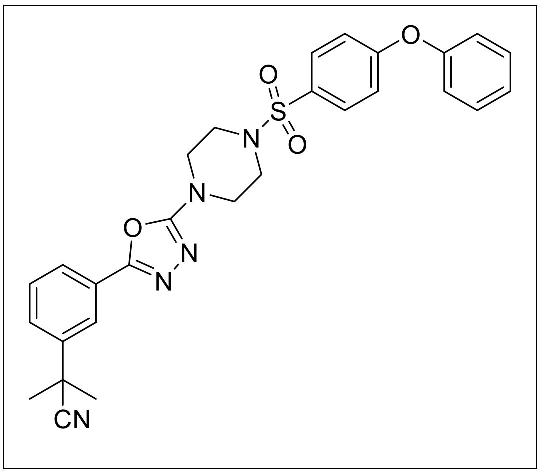


Fig 42; Compound 37

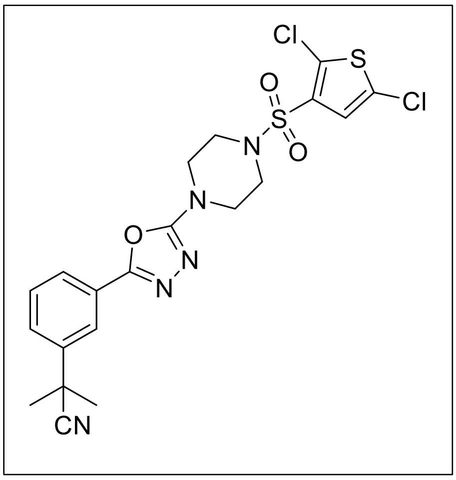


Fig 43; Compound 38

2.1.6) ANTI-INFLAMMATORY ACTIVITY:

Recent research has attempted to substitute the carboxylate functionality of nonsteroidal anti-inflammatory medications with less acidic heterocyclic bioisosteres, such as 1,3,4-oxadiazole, in order to produce novel anti-inflammatory compounds while shielding the stomach mucosa from free carboxylate moieties. Koksal *et al.* created and synthesized a series of 3,5-disubstituted 1,3,4-oxadiazole derivatives with an enhanced activity profile to decrease the formation of prostaglandin E2 (PGE2) and NO in light of these observations. The results of the biological experiments demonstrated that **compounds 39 (Fig 44)**, **40 (Fig 45),** and **41 (Fig 46)** had anti-inflammatory efficacy comparable to indomethacin and considerably suppressed NO generation with 12.61 ± 1.16, 12.61 ± 1.16, and 18.95 ± 3.57 µM, respectively, when compared to indomethacin.[25]

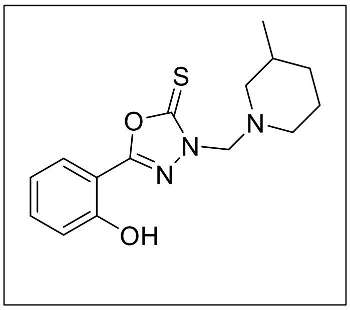


Fig 44; Compound 39

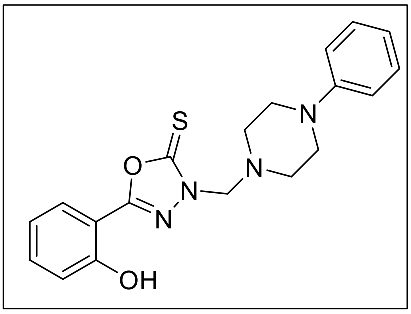


Fig 45; Compound 40

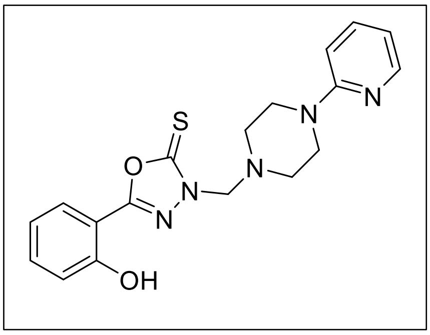


Fig 46; Compound 41

Świątek *et al*. reported the design, synthesis, and biological evaluation of a new series of Schiff base-type hybrid compounds containing 4,6-dimethylpyridine core, 1,3,4-oxadiazole ring, and differently substituted N-acyl hydrazone moieties in order to develop powerful, safe, and non-toxic chemopreventive compounds. Studies were conducted on the anti-COX-1/COX-2, antioxidant, and anticancer properties. At a lower dose than typical medications, Schiff base **42 (Fig 47)**, which contains 2-bromobenzylidene residue, inhibited the activity of both isoenzymes, COX-1 and COX-2. Its COX-2/COX-1 selectivity ratio was comparable to that of meloxicam. [26]

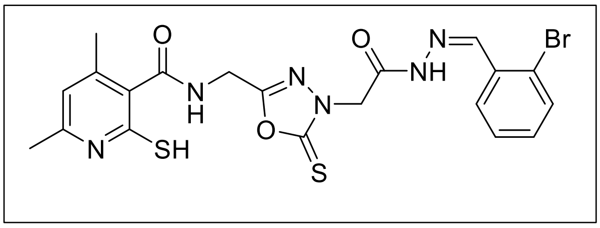


Fig 47; Compound 42

Abd-Ellah *et al*. created a number of novel 1,3,4-oxadiazole/oxime hybrids and engineered them to be highly effective COX inhibitors. The synthesized compounds' anti-inflammatory effects were evaluated. After four hours, the synthesized compounds showed impressive anti-inflammatory action, with 69.60–109.60% of indomethacin activity, according to the data. **Compounds 43 (Fig 48)** and **44 (Fig 49)** are strong COX inhibitors, as demonstrated by an in vitro COX inhibitory test, with IC50 values of 1.10–0.94 and 2.30–5.00 mM on both COX-1 and COX-2, in that order. It was discovered that compound 44 inhibited both COXs non-competitively with 89 mM and 73 mM are the Ki values. The majority of the substances that were examined had stomachs free of ulcers.[27]

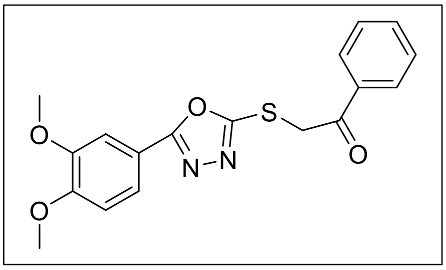


Fig 48; Compound 43

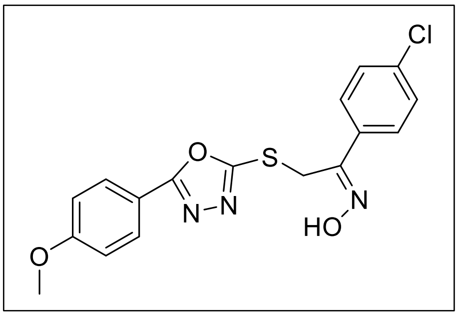
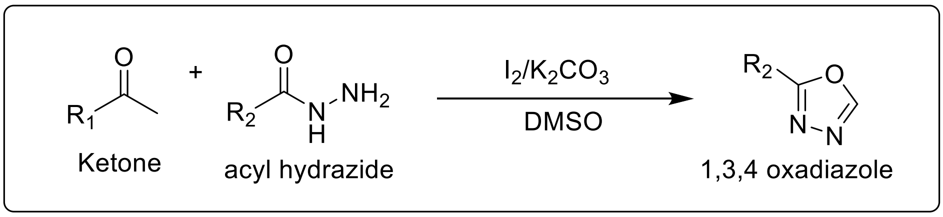


Fig 49; Compound 44

2.2) Synthesis of 1,3,4 oxadiazole derivatives

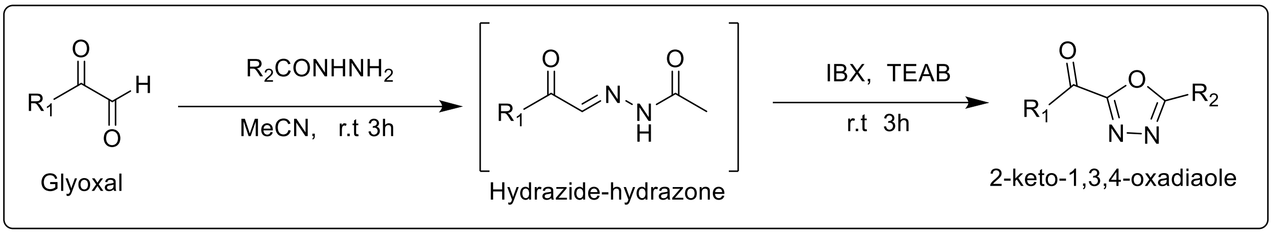
2.2.1) From Acyl hydrazides

A novel path for the synthesis of 1,3,4-oxadiazoles was designed by Gao et al, (scheme 1) through direct annulation of hydrazides with methyl ketones. Potassium Carbonate (K2CO3) was used as a base, and achieved an unexpected and highly efficient C−C bond cleavage. This reaction is proposed to go through oxidative cleavage of Csp3−H bonds, followed by cyclization and deacylation.[28]



Scheme 1; Synthesis of 1,3,4-oxadiazole by direct annulation of hydrazide

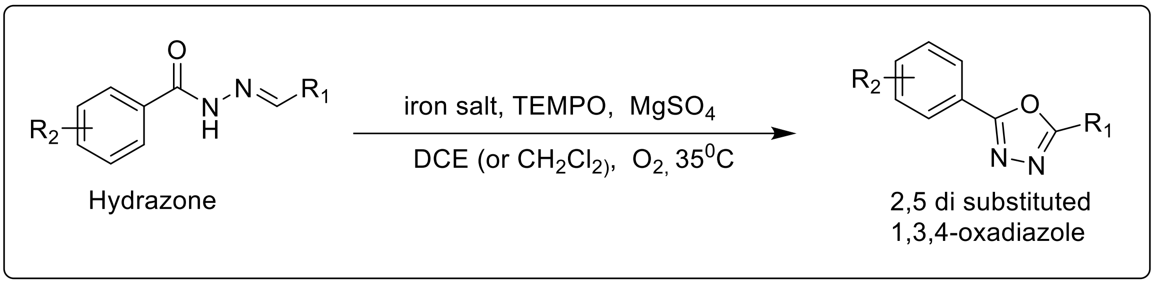
A high-yielding and efficient methodology has been established for the synthesis of α-keto-1,3,4-oxadiazoles by Kumar et al. The oxidative cyclization of hydrazide-hydrazones, which are produced in situ by the interaction of aryl glyoxal with hydrazides, is mediated by 2-iodoxybenzoic acid and tetraethylammonium bromide and results in the formation of α-keto-1,3,4-oxadiazoles (Scheme 2). This one-pot procedure is quite universal for the manufacturing of α-keto-1,3,4-oxadiazoles in moderate circumstances in rapid response times. [29]



Scheme 2; Synthesis of 1,3,4-oxadizole by oxidative cyclization of hydrazide-hydrazones

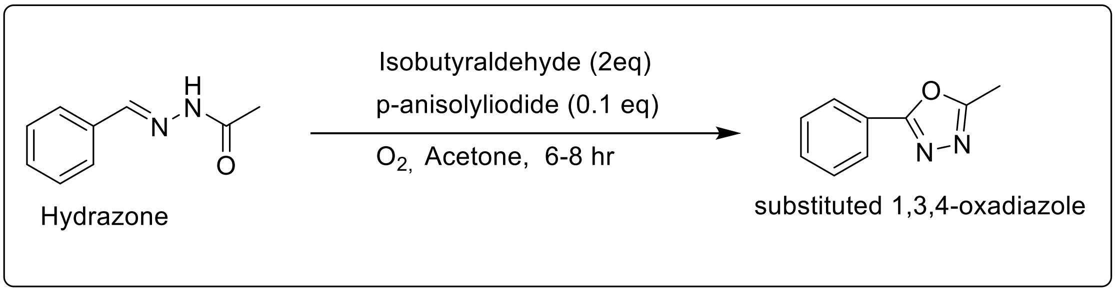
2.2.2) From hydrazones

To synthesise 2,5-disubstituted 1,3,4-oxadiazole derivatives, a facile and effective cationic Fe(III)/TEMPO-catalyzed oxidative cyclization of aroyl hydrazones has been developed by Zhang *et al.* (scheme 3). Under benign circumstances with O_2, the reaction provides a wide range, good functional-group tolerance, and high yields.[30]



Scheme 3; Synthesis of 1,3,4-oxadiazole from aroyl hydrazone

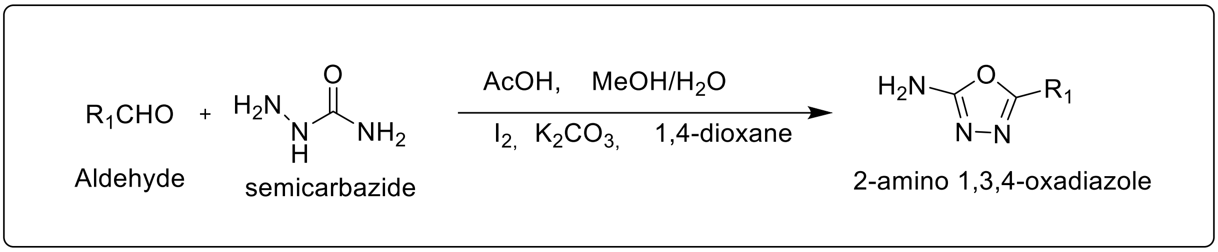
In a "metal-free" atmosphere, isobutyraldehyde underwent auto-oxidation to produce an acyloxy radical when molecular oxygen was present. They were then used on-site to produce hypervalent iodines combined with p-anisolyl iodide to produce substituted 1,3,4-oxadiazoles from N′-arylidene acetohydrazide in moderate to good yields (scheme 4) . The response plan allowed for a variety of replacement on the substrates of hydrazides.[31]



Scheme 4; Synthesis of 1,3,4-oxadiazole from hydrazone

2.2.3) From semicarbazides

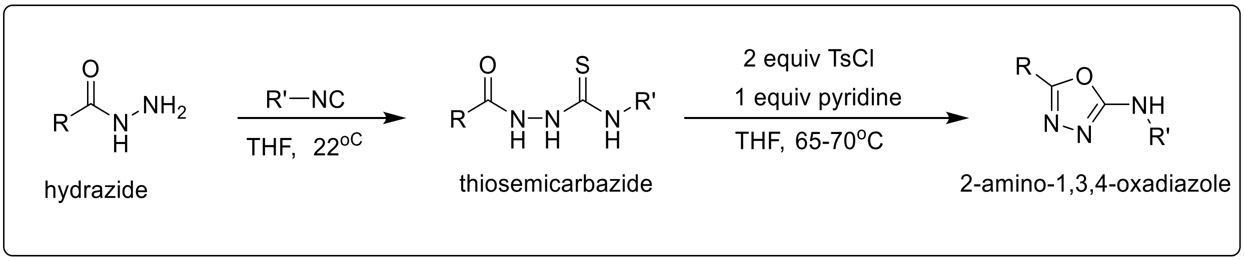
Condensation of semicarbazide and the associated aldehydes was used to create 1,3,4-oxadiazoles by Niu et al, which were then formed via I_2-mediated oxidative C–O bond synthesis (scheme 5). This rapid and scalable sequential synthesis method without the need for transition metals works with aromatic, aliphatic, and cinnamic aldehydes to yield a wide range of diazole derivatives with a 2-amino substituent.[32]



Scheme 5; Synthesis of 1,3,4-oxadiazole by condensation of semicarbazide

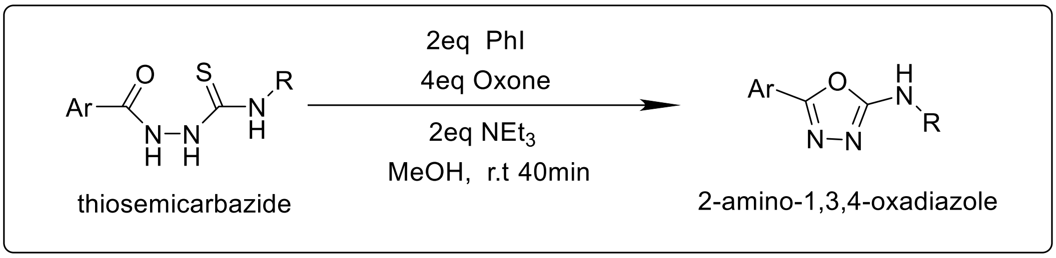
2.2.4) From Thiosemicarbazides

Dolman et al. reported a simple and universal methodology for the synthesis of 2-amino1,3,4-oxadiazoles. This technique is based on the cyclization of a thiosemicarbazide by tosyl chloride/pyridine, which can be easily synthesized by acylating a specific hydrozide with the right isothiocyanate (scheme 6). [33]



Scheme 6; Synthesis of 1,3,4-oxadiazole by cyclization of thiosemicarbazide

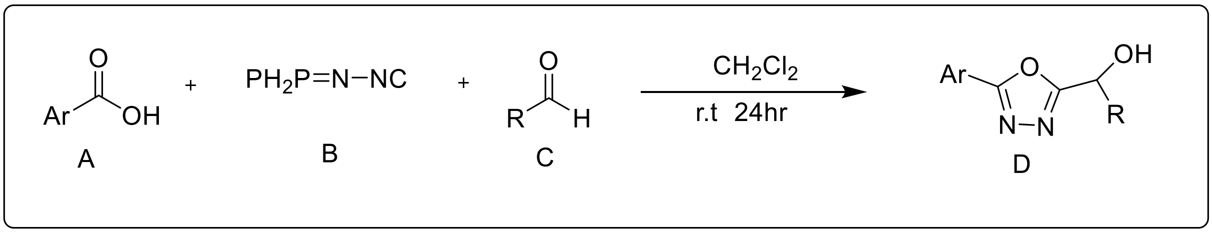
Oxone and iodobenzene have been combined to create oxadiazole heterocycles by Patel et al through the process of oxidative desulfurization. The desulfurization reaction method is made easy and adaptable by the use of iodobenzene and Oxone, which is an inexpensive and easily accessible oxidant (scheme 7).[34]



Scheme 7; Synthesis of 1,3,4-oxadiazole by oxidative desulfuration

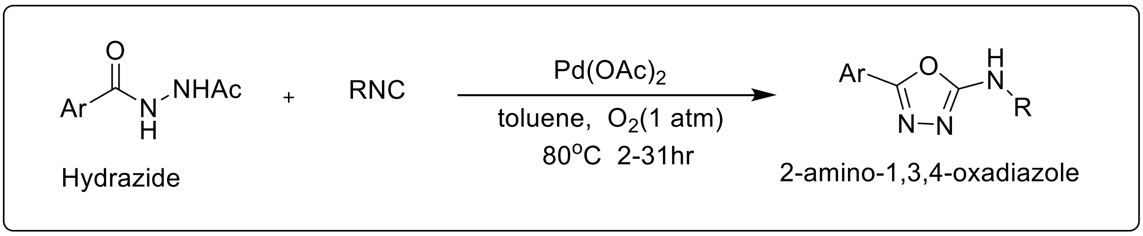
2.2.5) Miscellaneous

A one-pot and three-component synthesis of 2-aryl-5- hydroxyalkyl-1,3,4-oxadiazoles(**D**) has been reported by Adib et al. N-Isocyaniminotriphenylphosphorane(**B**), an aldehyde(**C**), and a carboxylic acid(**A**) undergo addition reaction in normal conditions to make the title compound in good yields (scheme 8). [35]



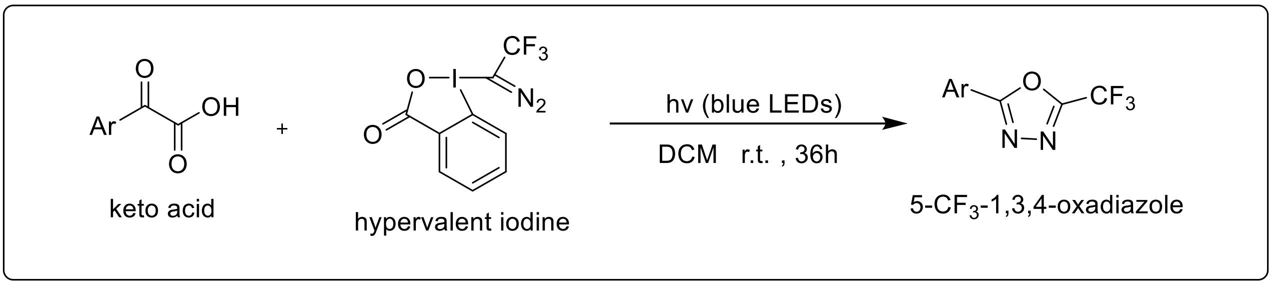
Scheme 8; A one pot three component synthesis of 1,3,4-oxadiazole

By sequentially inserting isocyanides into the N-H and O-H bonds of hydrazides, Fang et al. established an effective palladium-catalyzed oxidative annulation procedure that efficiently yields useful 2-amino-1,3,4-oxadiazoles and their derivatives (scheme 9). [36]



Scheme 9; Synthesis of 1,3,4-oxadiazole by insertion of isocyanides into hydrazide

Here, Zhao et al. describe a visible light-induced [3 + 2] cycloaddition of α-ketoacids with a hypervalent iodine(III) reagent to create 5-CF_3-1,3,4-oxadiazoles (scheme 10), which are important in medicinal chemistry. In mild conditions, the process proceeds without a photocatalyst, metal, or additive. In contrast to the well-known trifluorodiazoethane (CF 3CHN2), the current reaction system involves the diazotrifluoroethyl radical [CF3C(·)N2], a trifluoroethylcarbyne (CF3 CĊ:) equivalent, and an uncommon CF 3-containing building block.[37]



Scheme 10; Synthesis of 1,3,4-oxadiazoles via [3+2] cycloaddition

2.2.6) References

1. Kumar D, Aggarwal N, Kumar H, Kapoor G, Deep A, Bibi S, Sharma A, Chopra H, Kumar Marwaha R, Alshammari A, Alharbi M. 2-Substituted-3-(5-substituted-1, 3, 4-oxadiazol/thiadiazol-2-yl) thiazolidin-4-one derivatives: Synthesis, anticancer, antimicrobial, and antioxidant potential. Pharmaceuticals. 2023 May 29;16(6):805.

2. Kim H, Gu L, Yeo H, Choi U, Lee CR, Yu H, Koo S. Rapid Assembly of Pyrrole-Ligated 1, 3, 4-Oxadiazoles and Excellent Antibacterial Activity of Iodophenol Substituents. Molecules. 2023 Apr 21;28(8):3638.

3. Guo Y, Xu T, Bao C, Liu Z, Fan J, Yang R, Qin S. Design and synthesis of new norfloxacin-1, 3, 4-oxadiazole hybrids as antibacterial agents against methicillin-resistant Staphylococcus aureus (MRSA). European Journal of Pharmaceutical Sciences. 2019 Aug 1;136:104966.

4. Karaburun AÇ, Kaya Çavuşoğlu B, Acar Çevik U, Osmaniye D, Sağlık BN, Levent S, Özkay Y, Atlı Ö, Koparal AS, Kaplancıklı ZA. Synthesis and antifungal potential of some novel benzimidazole-1, 3, 4-oxadiazole compounds. Molecules. 2019 Jan 6;24(1):191.

5. Liao J, Yang F, Zhang L, Chai X, Zhao Q, Yu S, Zou Y, Meng Q, Wu Q. Synthesis and biological evaluation of novel fluconazole analogues bearing 1, 3, 4-oxadiazole moiety as potent antifungal agents. Archives of pharmacal research. 2015 Apr;38:470-9.

6. El Mansouri AE, Oubella A, Danoun K, Ahmad M, Neyts J, Jochmans D, Snoeck R, Andrei G, Morjani H, Zahouily M, Lazrek HB. Discovery of novel furo [2, 3-d] pyrimidin-2-one–1, 3, 4-oxadiazole hybrid derivatives as dual antiviral and anticancer agents that induce apoptosis. Archiv der Pharmazie. 2021 Oct;354(10):2100146.

7. Gan X, Hu D, Chen Z, Wang Y, Song B. Synthesis and antiviral evaluation of novel 1, 3, 4-oxadiazole/thiadiazole-chalcone conjugates. Bioorganic & medicinal chemistry letters. 2017 Sep 15;27(18):4298-301.

8. Desai NC, Somani H, Trivedi A, Bhatt K, Nawale L, Khedkar VM, Jha PC, Sarkar D. Synthesis, biological evaluation and molecular docking study of some novel indole and pyridine based 1, 3, 4-oxadiazole derivatives as potential antitubercular agents. Bioorganic & medicinal chemistry letters. 2016 Apr 1;26(7):1776-83.

9. Das R, Mehta DK. Evaluation and docking study of pyrazine containing 1, 3, 4-oxadiazoles clubbed with substituted azetidin-2-one: A new class of potential antimicrobial and antitubercular. Drug Research. 2021 Jan;71(01):26-35.

10. Pflégr V, Stolaříková J, Pál A, Korduláková J, Krátký M. Novel pyrimidine-1, 3, 4-oxadiazole hybrids and their precursors as potential antimycobacterial agents. Future Medicinal Chemistry. 2023 Jun;15(12):1049-67.

11. Ahsan MJ, Samy JG, Khalilullah H, Nomani MS, Saraswat P, Gaur R, Singh A. Molecular properties prediction and synthesis of novel 1, 3, 4-oxadiazole analogues as

potent antimicrobial and antitubercular agents. Bioorganic & medicinal chemistry letters. 2011 Dec 15;21(24):7246-50.

12. Gani RS, Kudva AK, Timanagouda K, Mujawar SB, Joshi SD, Raghu SV. Synthesis of novel 5-(2, 5-bis (2, 2, 2-trifluoroethoxy) phenyl)-1, 3, 4-oxadiazole-2-thiol derivatives as potential glucosidase inhibitors. Bioorganic Chemistry. 2021 Sep 1;114:105046.

13. Abedinifar F, Mohammadi-Khanaposhtani M, Asemanipoor N, Mojtabavi S, Faramarzi MA, Mahdavi M, Biglar M, Larijani B, Hamedifar H, Hajimiri MH. Synthesis and biological evaluation of a new series of benzofuran-1, 3, 4-oxadiazole containing 1, 2, 3-triazole-acetamides as potential α-glucosidase inhibitors. Journal of Biochemical and Molecular Toxicology. 2021 Apr;35(4):e22688.

14. Mirzazadeh R, Asgari MS, Barzegari E, Pedrood K, Mohammadi-Khanaposhtani M, Sherafati M, Larijani B, Rastegar H, Rahmani H, Mahdavi M, Taslimi P. New quinoxalin-1, 3, 4-oxadiazole derivatives: Synthesis, characterization, in vitro biological evaluations, and molecular modeling studies. Archiv der Pharmazie. 2021 Sep;354(9):2000471.

15. Nazreen S, Alam MS, Hamid H, Yar MS, Shafi S, Dhulap A, Alam P, Pasha MA, Bano S, Alam MM, Haider S. Design, synthesis, in silico molecular docking and biological evaluation of novel oxadiazole based thiazolidine-2, 4-diones bis-heterocycles as PPAR-γ agonists. European Journal of Medicinal Chemistry. 2014 Nov 24;87:175-85.

16. Hagras M, Saleh MA, Ezz Eldin RR, Abuelkhir AA, Khidr EG, El-Husseiny AA, El-Mahdy HA, Elkaeed EB, Eissa IH. 1, 3, 4-Oxadiazole-naphthalene hybrids as potential VEGFR-2 inhibitors: design, synthesis, antiproliferative activity, apoptotic effect, and in silico studies. Journal of enzyme inhibition and medicinal chemistry. 2022 Dec 31;37(1):386-402.

17. Kandukuri P, Dasari G, Nukala SK, Bandari S, Juluru B. Design and Synthesis of Some New Quinoxaline Containing 1, 3, 4-Oxadiazole Hybrids and Evaluation of Their Anti-Cancer Activity. Russian Journal of Bioorganic Chemistry. 2023 Feb;49(1):139-46.

18. Rachala MR, Maringanti TC, Syed T, Eppakayala L. Synthesis and biological evaluation of 1, 3, 4-oxadiazole bearing pyrimidine-pyrazine derivatives as anticancer agents. Synthetic Communications. 2023 Aug 3;53(15):1262-8.

19. Agarwal M, Afzal O, Salahuddin, Altamimi AS, Alamri MA, Alossaimi MA, Sharma V, Ahsan MJ. Design, Synthesis, ADME, and Anticancer Studies of Newer N-Aryl-5-(3, 4, 5-Trifluorophenyl)-1, 3, 4-Oxadiazol-2-Amines: An Insight into Experimental and Theoretical Investigations. ACS omega. 2023 Jul 20;8(30):26837-49.

20. Basappa B, Jung YY, Ravish A, Xi Z, Swamynayaka A, Madegowda M, Pandey V, Lobie PE, Sethi G, Ahn KS. Methyl-Thiol-Bridged Oxadiazole and Triazole Heterocycles as Inhibitors of NF-κB in Chronic Myelogenous Leukemia Cells. Biomedicines. 2023 Jun 8;11(6):1662.

21. Afzal O, Ali A, Ali A, Altamimi AS, Alossaimi MA, Bakht MA, Salahuddin, Alamri MA, Ahsan MF, Ahsan MJ. Synthesis and Anticancer Evaluation of 4-Chloro-2-((5-aryl-1, 3, 4-oxadiazol-2-yl) amino) phenol Analogues: An Insight into Experimental and Theoretical Studies. Molecules. 2023 Aug 16;28(16):6086.

22. Wang S, Liu H, Wang X, Lei K, Li G, Li J, Liu R, Quan Z. Synthesis of 1, 3, 4-oxadiazole derivatives with anticonvulsant activity and their binding to the GABAA receptor. European Journal of Medicinal Chemistry. 2020 Nov 15;206:112672.

23. Khoramjouy M, Zarepishe N, Rezaee E, Imani A, Mahmoudzadeh-Mandolakani R, Hashemi S, Fallah M, Hasheminasab G, Shahhosseini S, Tabatabai SA, Faizi M. Novel derivatives of diphenyl-1, 3, 4-oxadiazol as ligands of benzodiazepine receptors; synthesize, binding assay and pharmacological evaluation. Iranian Journal of Pharmaceutical Research: IJPR. 2021;20(4):47.

24. Harish KP, Mohana KN, Mallesha L, Veeresh B. Synthesis and In Vivo Anticonvulsant Activity of 2-Methyl-2-[3-(5-piperazin-1-yl-[1, 3, 4] oxadiazol-2-yl)-phenyl]-propionitrile Derivatives. Archiv der Pharmazie. 2014 Apr;347(4):256-67.

25. Koksal M, Dedeoglu-Erdogan A, Bader M, Gurdal EE, Sippl W, Reis R, Ozgurbuz M, Sipahi H, Celik T. Design, synthesis, and molecular docking of novel 3, 5-disubstituted-1, 3, 4-oxadiazole derivatives as iNOS inhibitors. Archiv der Pharmazie. 2021 Aug;354(8):2000469.

26. Świątek P, Glomb T, Dobosz A, Gębarowski T, Wojtkowiak K, Jezierska A, Panek JJ, Świątek M, Strzelecka M. Biological evaluation and molecular docking studies of novel 1, 3, 4-oxadiazole derivatives of 4, 6-dimethyl-2-sulfanylpyridine-3-carboxamide. International Journal of Molecular Sciences. 2022 Jan 4;23(1):549.

27. Abd-Ellah HS, Abdel-Aziz M, Shoman ME, Beshr EA, Kaoud T, Ahmed AS. New 1, 3, 4-oxadiazole/oxime hybrids: Design, synthesis, anti-inflammatory, COX inhibitory activities and ulcerogenic liability. Bioorganic Chemistry. 2017 Oct 1;74:15-29.

28. Gao Q, Liu S, Wu X, Zhang J, Wu A. Direct annulation of hydrazides to 1, 3, 4-oxadiazoles via oxidative C (CO)–C (methyl) bond cleavage of methyl ketones. Organic letters. 2015 Jun 19;17(12):2960-3.

29. Kumar D, Pilania M, Arun V, Mishra B. A facile and expeditious one-pot synthesis of α-Keto-1, 3, 4-oxadiazoles. Synlett. 2014 May;25(08):1137-41.

30. Zhang G, Yu Y, Zhao Y, Xie X, Ding C. Iron (III)/TEMPO-catalyzed synthesis of 2, 5-disubstituted 1, 3, 4-oxadiazoles by oxidative cyclization under mild conditions. Synlett. 2017 Jul;28(11):1373-7.

31. Chauhan J, Ravva MK, Sen S. Harnessing autoxidation of aldehydes: in situ iodoarene catalyzed synthesis of substituted 1, 3, 4-oxadiazole, in the presence of molecular oxygen. Organic letters. 2019 Aug 1;21(16):6562-5.

32. Niu P, Kang J, Tian X, Song L, Liu H, Wu J, Yu W, Chang J. Synthesis of 2-amino-1, 3, 4-oxadiazoles and 2-amino-1, 3, 4-thiadiazoles via sequential condensation and I2-mediated oxidative C–O/C–S bond formation. The Journal of organic chemistry. 2015 Jan 16;80(2):1018-24.

33. Dolman SJ, Gosselin F, O'Shea PD, Davies IW. Superior reactivity of thiosemicarbazides in the synthesis of 2-amino-1, 3, 4-oxadiazoles. The Journal of organic chemistry. 2006 Dec 8;71(25):9548-51.

34. Patel KN, Jadhav NC, Jagadhane PB, Telvekar VN. A novel strategy for the construction of azole heterocycles via an oxidative desulfurization approach using iodobenzene and oxone®. Synlett. 2012 Aug;23(13):1970-2.

35. Adib M, Kesheh MR, Ansari S, Bijanzadeh HR. Reaction between n-isocyaniminotriphenylphosphorane, aldehydes, and carboxylic acids: A one-pot and three-component synthesis of 2-aryl-5-hydroxyalkyl-1, 3, 4-oxadiazoles. Synlett. 2009 Jun;2009(10):1575-8.

36. Fang T, Tan Q, Ding Z, Liu B, Xu B. Pd-catalyzed oxidative annulation of hydrazides with isocyanides: synthesis of 2-amino-1, 3, 4-oxadiazoles. Organic letters. 2014 May 2;16(9):2342-5.

37. Zhao WW, Shao YC, Wang AN, Huang JL, He CY, Cui BD, Wan NW, Chen YZ, Han WY. Diazotrifluoroethyl Radical: A CF3-Containing Building Block in [3+ 2] Cycloaddition. Organic Letters. 2021 Nov 21;23(23):9256-61.

CHAPTER-3

Experimental Work

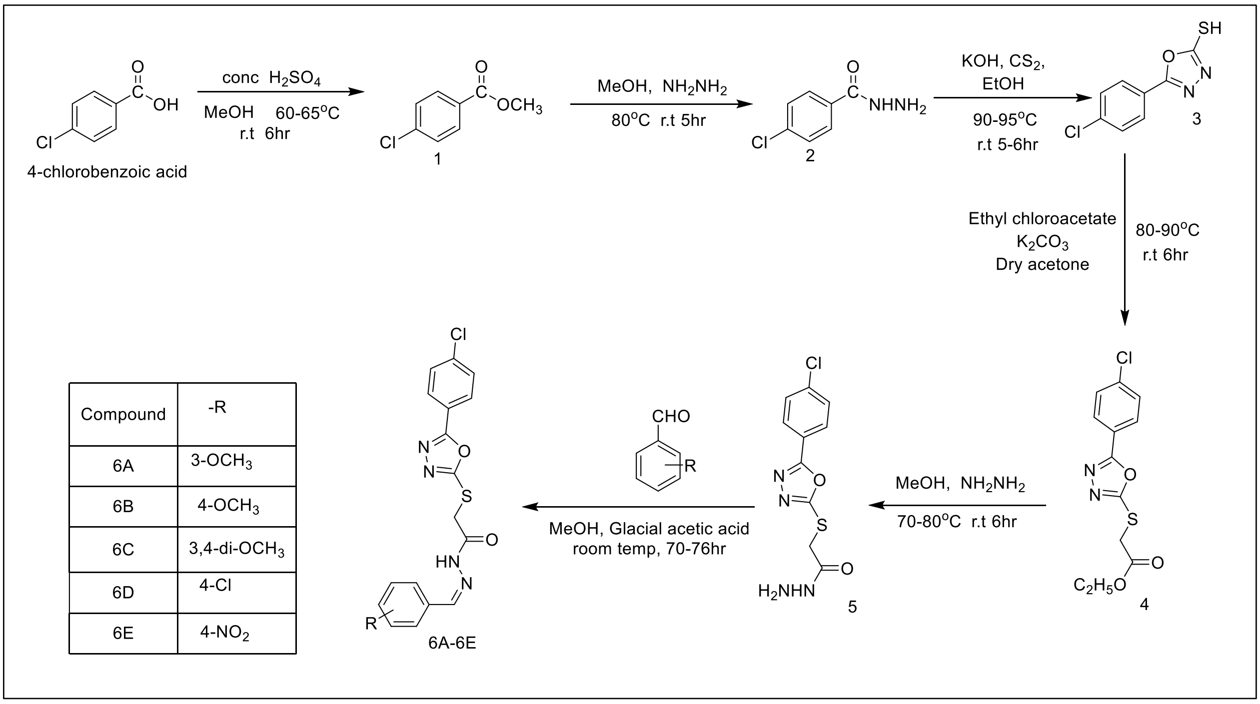
3.1) Plan of work:

In my M.Pharm work, I am planning for design and synthesis pf some 1,3,4-oxadizole derivatives having suitable functional group, which might be important for various biological activities. After synthesis will be characterised by I.R spectroscopy and NMR spectroscopy (1H NMR, 13C NMR) for structural elucidation.

3.2) Materials used:

All the chemicals required for this research work were reagent grade and used without further purification. KOH, EtOH, MeOH, hydrazine hydrate was purchased from Merck, USA. 4-chlorobenzoic acid, CS_2 was purchased from Lobe chemicals, 4-chloro benzaldehyde, 4-nitro benzaldehyde, 3-methoxy benzaldehyde, 3,4-dimethoxy benzaldehyde, 4-methoxy benzaldehyde was bought from Spectro Chem.

3.3) Scheme for synthesis of 1,3,4-oxadiazole



Compound	-R
6A	3-OCH_3
6B	4-OCH_3
6C	3,4-di-OCH_3
6D	4-Cl
6E	4-NO_2

3.4) Novelty check

For checking the novelty, the structures of the final compounds were searched in SciFinder where we found that the structures are not reported. We can conclude, that the structures are completely novel.

Task History

Initiating Search

August 20, 2024, 5:13 PM

References:

Filtered By:

Structure Match: **As Drawn**

Search Tasks

Task	Search Type	View
Exported: Returned Reference Results + Filters (0)	References	View Results

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CAS SciFinder® Page 2

References (0) View in CAS SciFinder

We couldn't find any results. Please update your search query and try again.

References with (0) results

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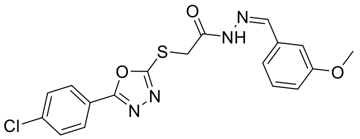
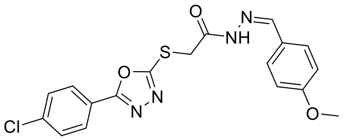
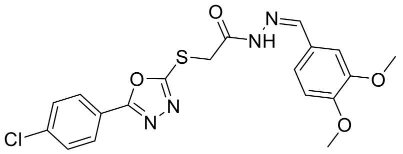
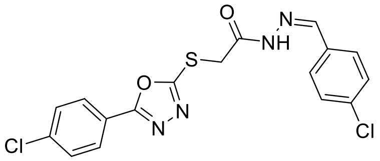
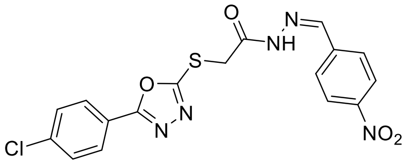
Table 1; Novelty check of synthesized compounds

Compound	Structure	SciFinder status	Biological activity
6A		**Not Reported**	**Not Reported**
6B		**Not Reported**	**Not Reported**
6C		**Not Reported**	**Not Reported**
6D		**Not Reported**	**Not Reported**
6E		**Not Reported**	**Not Reported**

3.5) Procedure:

3.5.1) Synthesis of methyl 4-chlorobenzoate(1):

4-chlorobenzoic acid (0.01mol) was reacted with methanol (15ml) in the presence of concentrated H_2SO_4 (1ml). The reaction mixture was taken in a flat bottom flask and was refluxed at 60-65°C for 5-6 hours with continuous stirring. The progress of the reaction was monitored with the help of TLC. After completion, crushed ice was poured and a solid was separated which was then filtered and dried.

3.5.2) Synthesis of 4-chlorobenzohydrazide (2):

4-chlorobenzoate (0.01 mol) was taken in a flat bottom flask and was dissolved in 20ml of methanol. Then hydrazine hydrate (4ml) was added. The whole reaction mixture was refluxed at 80°C with continuous stirring for 5 hours. The reaction was monitored through TLC and after completion, crushed ice was added. A solid product was then filtered and dried.

3.5.3) Synthesis of 5-(4-chlorophenyl)-1,3,4-oxadiazole-2-thiol (3):

4-chlorobenzohydrazide (0.005 mol) was taken in a reaction vessel where KOH (3 pellets) and carbon disulfide (2ml) were added in the presence of ethanol (10ml) as solvent. The reaction mixture was refluxed at 90-95°C for 5-6 hours with continuous stirring. TLC was used to monitor the reaction. After completion, the reaction mixture was neutralized with few drops of concentrated HCL. Then crushed ice was poured and a solid product was separated and dried.

3.5.4) Synthesis of ethyl 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate (4):5-(4-chlorophenyl)-1,3,4-oxadiazole-2-thiol (0.005 mol) was taken in a reaction vessel where 0.7ml of ethylchloroacetate and 1.4g of K_2CO_3 was added. Dry acetone (12ml) was taken as a solvent. The reaction mixture was refluxed at 80-90°C for 6 hours with continuous stirring. The reaction was monitored by TLC. After completion of the reaction, crushed ice was added and a solid product was separated which was then filtered and dried.

3.5.5) Synthesis of 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (5):

0.005 mole of 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate was taken in a reaction vessel. 15ml of methanol and 2.5ml of hydrazine hydrate was added. The reaction mixture was refluxed at 80-90°C for 6 hours with continuous stirring. The reaction was monitored by TLC. After completion of the reaction, crushed ice was added and a solid product was separated which was then filtered and dried.

3.5.6) Synthesis of substituted N'-benzylidene-2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (6A,6B,6C,6D,6E):

2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide was taken in 0.001mol and was reacted with substituted benzaldehydes (0.001 mol) in the presence of methanol(15ml) and glacial acetic acid (few drops). The reaction mixture was continuously stirred in room temperature for 70-75 hours to get the final products. The final products were recrystallized in ethanol, filtered, dried and were sent for characterization.

CHAPTER-4

Results and discussion

4.1) Chemistry:

4-chlorobenzoic acid was reacted with methanol in presence of concentrated sulfuric acid to give 4-chlorobenzoate (**1**). This was an esterification reaction. Then (1) was reacted with hydrazine in the presence of methanol. It was a substitution reaction at the carbon centre of carbonyl group to give us 4-chlorobenzohydrazide (2) which was then refluxed with carbon disulfide in ethanol, using KOH as a base in the next step. The reaction went through cyclization mechanism and yielded 5-(4-chlorophenyl)-1,3,4-oxadiazole-2-thio**l (3)**. Then in the next step, K_2CO_3 was used to abstract the proton next to sulfur of (3) which then attacks the carbon next to chlorine of ethyl chloroacetate to give us 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetate (4). Then (4) was subjected to hydrazine in presence of methanol. Again a substitution by $NHNH_2$ happens at the carbon centre of carbonyl group to yield 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide(5). In the final step, the penultimate compound (5) was reacted with various substituted benzaldehyde (3-methoxy benzaldehyde, 4-methoxy benzaldehyde, 3,4-dimethoxy benzaldehyde, 4-chloro benzaldehyde, 4-nitro benzaldehyde) to give 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(3-methoxybenzylidene)acetohydrazide(6A), 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(4-methoxybenzylidene)acetohydrazide(6B), 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(3,4-dimethoxybenzylidene)acetohydrazide(6C), N'-(4-chlorobenzylidene)-2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide(6D) and 2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(4-nitrobenzylidene)acetohydrazide (6E) respectively. The ^1H NMR spectrum of compounds 6A, 6B and 6C showed peaks near δ, 3.84 suggesting the presence of the OCH_3 protons. All the compounds showed a peak near δ, 4.64 ppm suggesting the S-CH_2- protons, the O=C-NH protons showed their presence near δ, 7.7-7.8 ppm. The aromatic peaks were found in δ, 6.5-8.0 ppm. In FTIR spectrum, all compounds showed an absorption band near 1700-1790 cm^{-1} suggesting the presence of C=O group. The physical properties of the synthesized compounds are discussed in table 2.

Table 2; Physical properties of synthesized compounds

Compound	%Yield	Melting Point (^{0}C)	Solubility	Recrystallized in
6A	72%	178-180	$CHCl_3$, DMF, THF	Ethanol
6B	68%	174-176	$CHCl_3$, DMF, THF	Ethanol
6C	75%	177-179	$CHCl_3$, DMF, THF	Ethanol
6D	72%	180-182	$CHCl_3$, DMF, THF	Ethanol
6E	62%	168-171	$CHCl_3$, DMF, THF	Ethanol

2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(3-methoxybenzylidene)acetohydrazide(6A):

Off white solid; Yield 72%, Mp 178-180 ^{0}C: Solubility: $CHCl_3$, DMF, THF ; FTIR (cm^1):3260.20, 3078.81, 2877.44, 1760.19, 16794.94, 1651.45, 1546.53, 1515.71, 696.87, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.84 (s, 3H), 4.02 (s, 1H), 4.64 (s, 2H), 6.76 (s, 1H), 6.94-6.96 (m, 1H), 7.20-7.33 (m, 2H), 7.472 (d, J = 8.4 Hz, 1H), 7.81(s, 1H), 7.94-7.90 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.8, 55.5, 112.6, 116.8, 120.6, 122.1, 128.1(2C), 129.6 (2C), 129.8, 130.0 (2C), 134.4, 136.7, 145.4, 160.0.

2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(4-methoxybenzylidene)acetohydrazide(6B)

Off white solid; Yield 68%, Mp 174-176 ^{0}C; $CHCl_3$, DMF, THF; ; FTIR (cm^{-1}):3226.60, 3078.81, 2877.44, 1760.19, 1694.94, 1651.45, 1546.53, 1515.71, 696.87 ^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 3.84 (s, 3H), 4.00 (s, 1H), 4.64(s, 2H), 6.90 (d J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.51-7.44 (m, 2H), 7.59 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 13C NMR (100 MHz, CDCl3) δ: 35.3, 55.5, 114.2, 114.4(2C), 122.1, 125.7, 128.1 (2C), 129.1 (2C), 129.5 (2C), 129.7, 129.8, 138.0 145.1, 161.7

2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(3,4-dimethoxybenzylidene)acetohydrazide(6C):

Off white solid; Yield 75%, Mp 177-179 ^{0}C; $CHCl_3$, DMF, THF; FTIR (cm^{-1}):3226.60, 3078.81, 2877.44, 1760.19, 1694.94, 1651.45, 1546.53, 1515.71, 696.87 ^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 3.90 (s, 1H), 3.92 (s, 3H), 3.95 (s, 3H), 4.54 (s, 1H), 4.64 (s, 1H), 6.86-6.82(m, 1H), 7.13-7.09 (m, 1H), 7.51-7.44(m, 3H), 7.74(s, 1H), 7.95-7.90(m, 2H), 13C NMR (100 MHz, CDCl3) δ: 35.4, 56.0, 56.1, 108.2, 110.7(2C), 122.3(2C),127.9(2C), 129.4 (2C), 129.6 (2C), 145.2, 145.3, 149.4, 156.4, 168.2

N'-(4-chlorobenzylidene)-2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide(6D):

Off white solid; Yield 72%, Mp 180-182 ^{0}C; $CHCl_3$, DMF, THF; FTIR (cm^{-1}) 3392.11, 2991.15, 2883.31, 1750.98, 1694.22, 1513.55, 695.14, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.01 (s, 1H), 4.63 (s, 2H), 7.37-7.32 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.77 (d, J = 10.4, 1H), 7.86 (d, J = 1.2 Hz), 7.925 (d, J = 8 Hz, 2H), 13C NMR (100 MHz, CDCl3) δ: 35.1, 122.0, 125.8, 127.1(2C), 128.1 (2C), 128.3 (2C), 129.6, 129.8(2C), 130.2, 130.7, 130.8, 143.9, 163.8

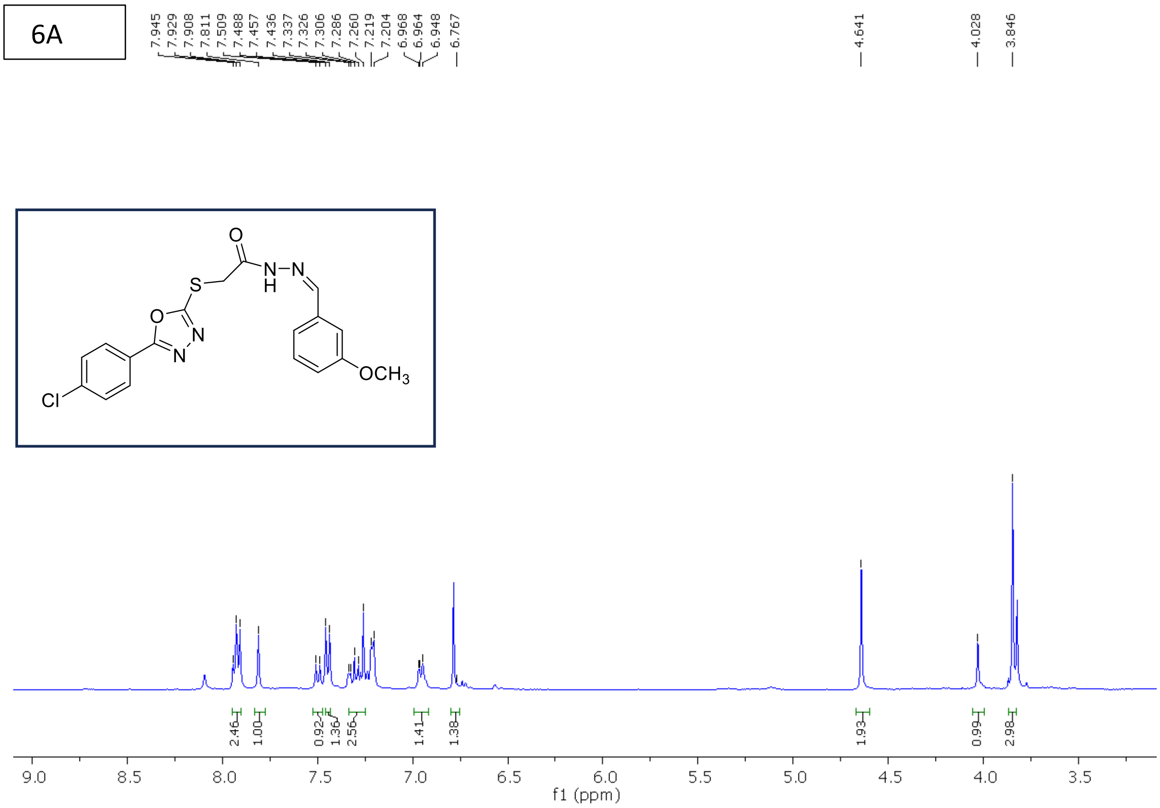
2-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)thio)-N'-(4-nitrobenzylidene)acetohydrazide (6E):

Off white solid; Yield 62%, Mp 168-171 ^{0}C; $CHCl_3$, DMF, THF; FTIR (cm^{-1}) 3390.66, 3020.65, 2878.65, 1740.71, 1694.06, 1582.39, 1518.30, 691.36, ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.11 (s, 2H), 4.99-4.91 (m, 1H), 7.49-7.46 (d, J = 8.8 Hz, 5H), 7.94 (d, J = 8.8 Hz, 4H), 13C NMR (100 MHz, CDCl3) δ: 35.0, 102.9, 122.0, 125,7 (2C), 127.1 (2C), 128.0 (2C), 128.3, 129.5 (2C), 129.7, 130.2, 130.7, 130.8, 143.9 165.3

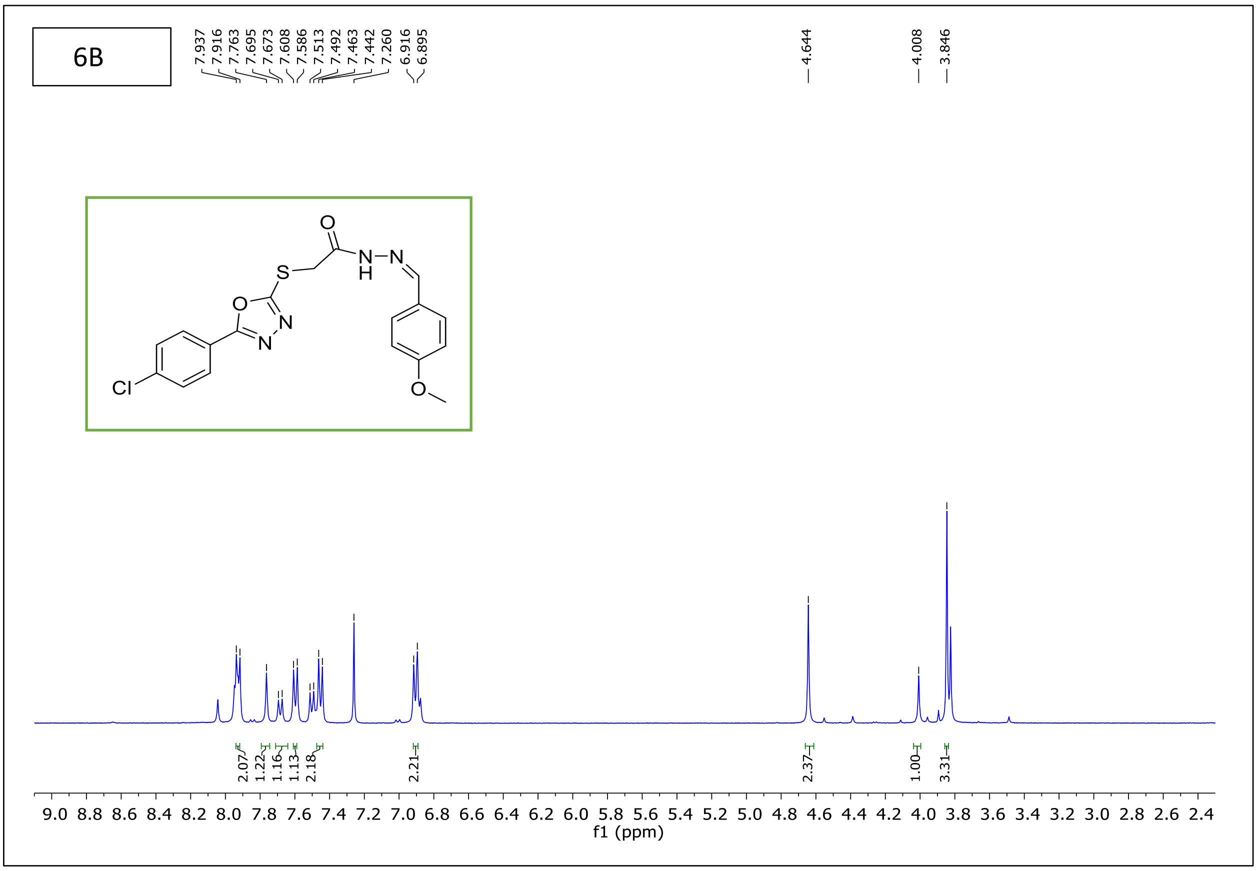
4.2) Spectral data of synthesized compounds

^{1}H NMR spectra of synthesized compounds (6A-6E):

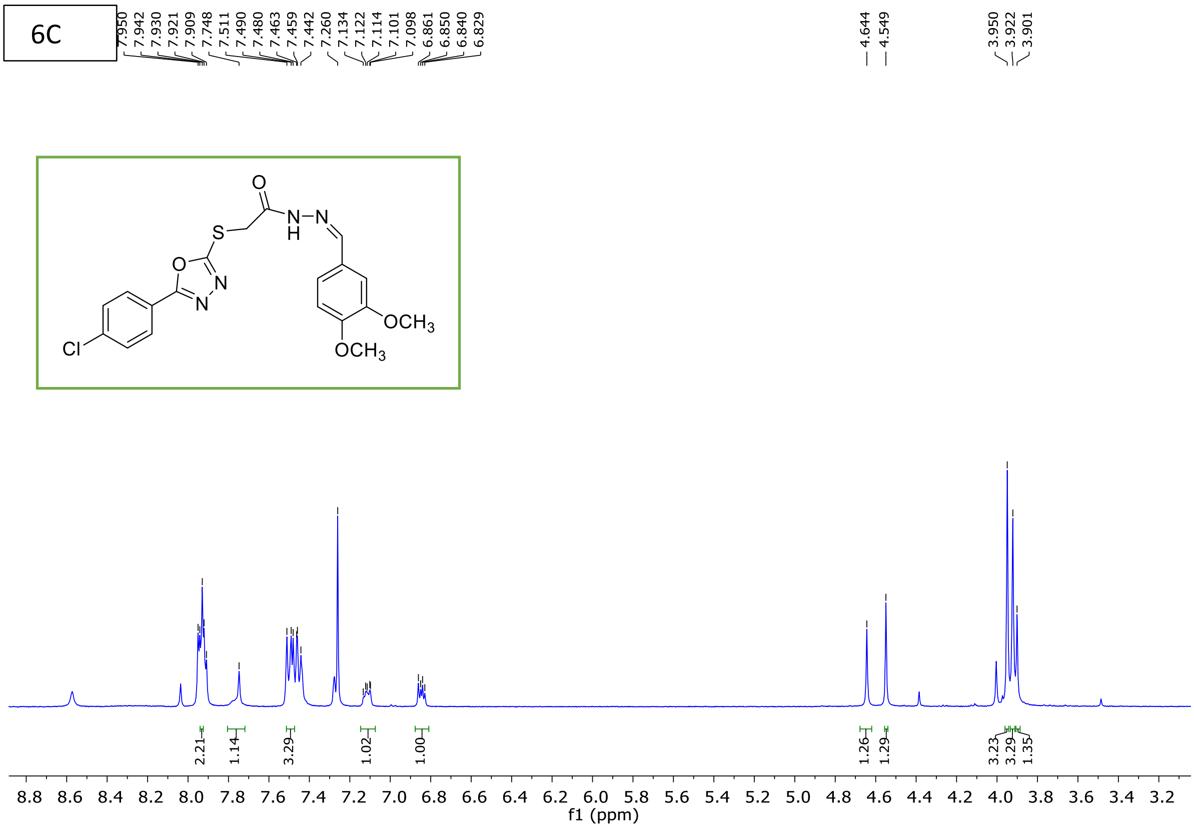
6A



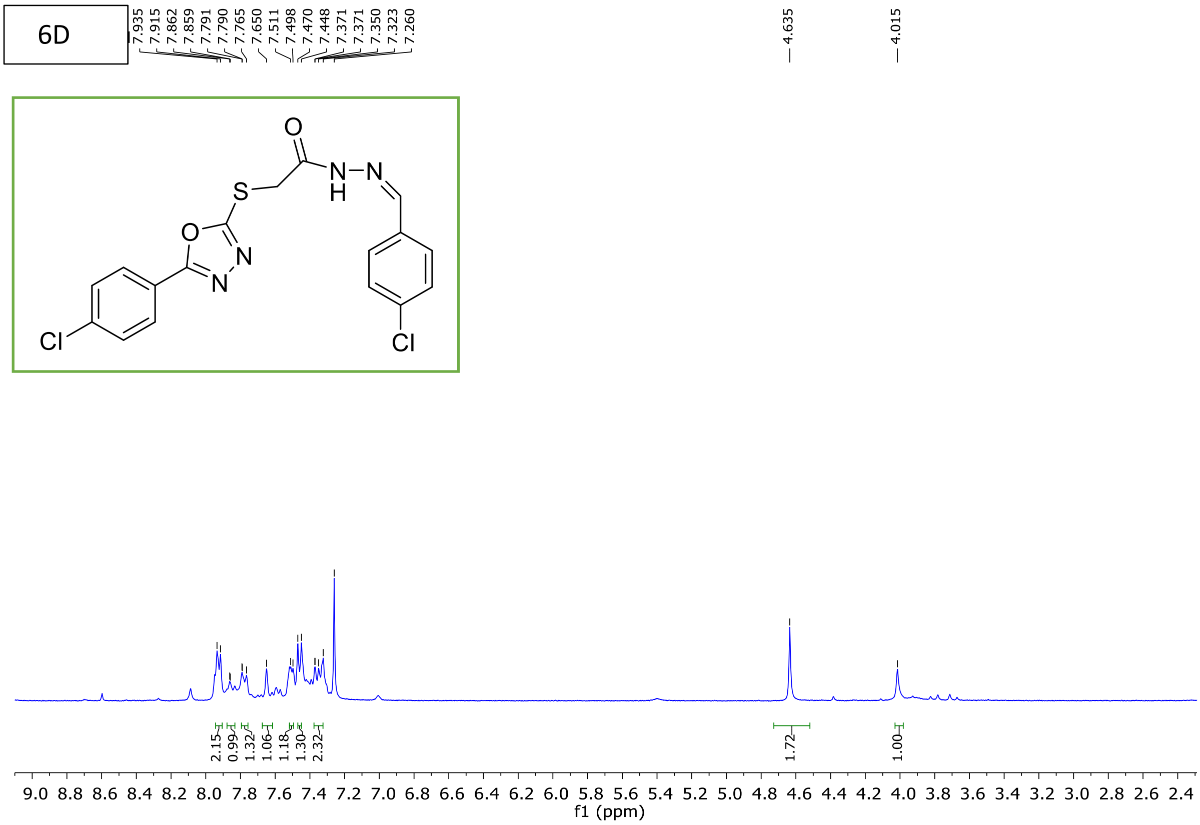
6B



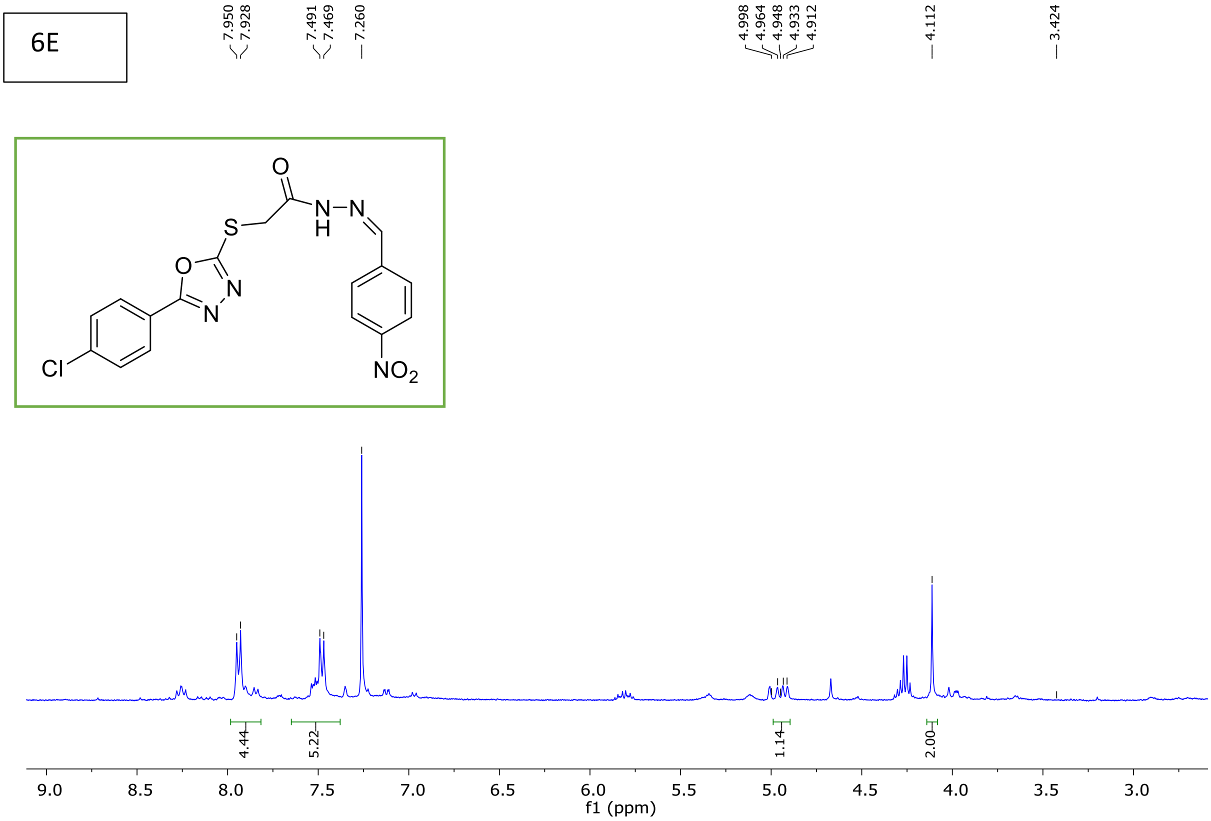
6C


7.950
7.942
7.930
7.921
7.909
7.748
7.511
7.490
7.480
7.463
7.459
7.442
7.260
7.134
7.122
7.114
7.101
7.098
6.861
6.850
6.840
6.829
4.644
4.549
3.950
3.922
3.901
O
S
N–N
H
O
N
N
Cl
OCH3
OCH3
2.21
1.14
3.29
1.02
1.00
1.26
1.29
3.23
3.29
1.35
8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2
f1 (ppm)

6D


7.935
7.915
7.862
7.859
7.791
7.790
7.765
7.650
7.511
7.498
7.470
7.448
7.371
7.371
7.350
7.323
7.260
4.635
4.015
O
S
N–N
H
O
N
N
Cl
Cl
2.15
0.99
1.32
1.06
1.18
1.30
2.32
1.72
1.00
9.0 8.8 8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4
f1 (ppm)

6E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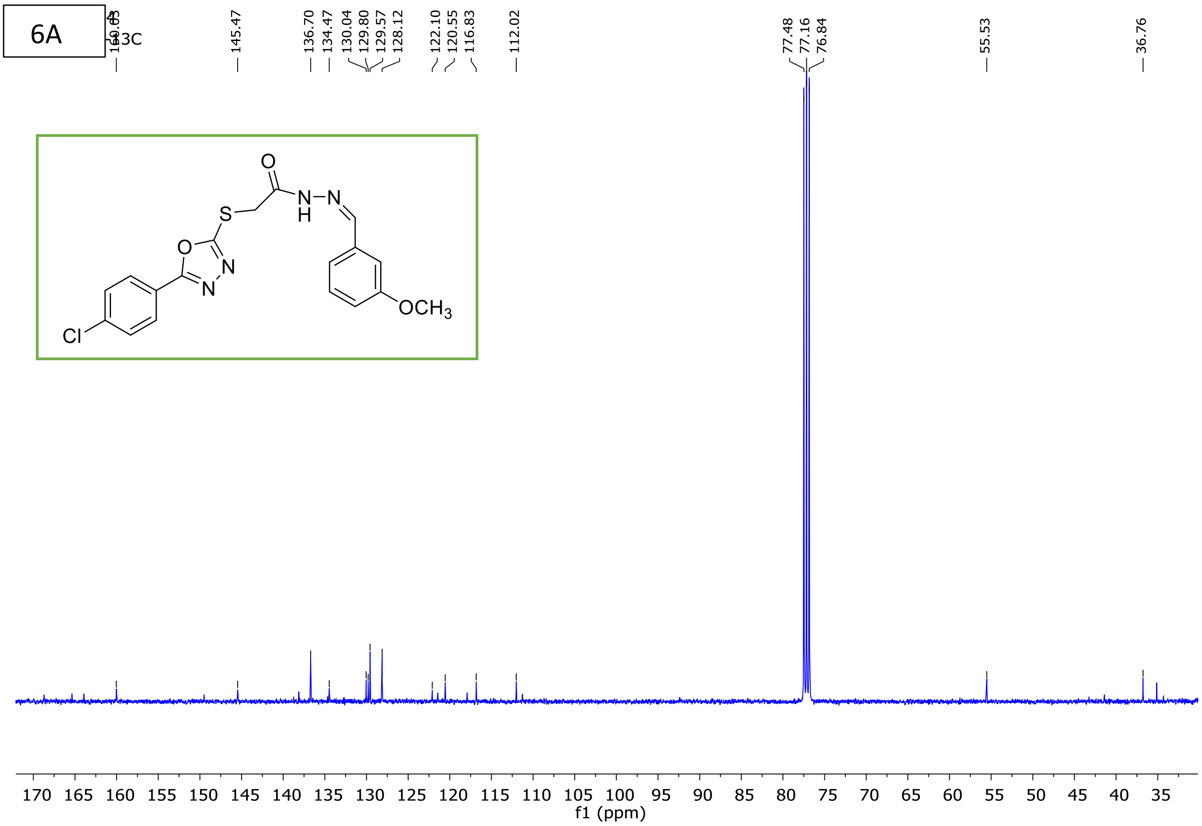
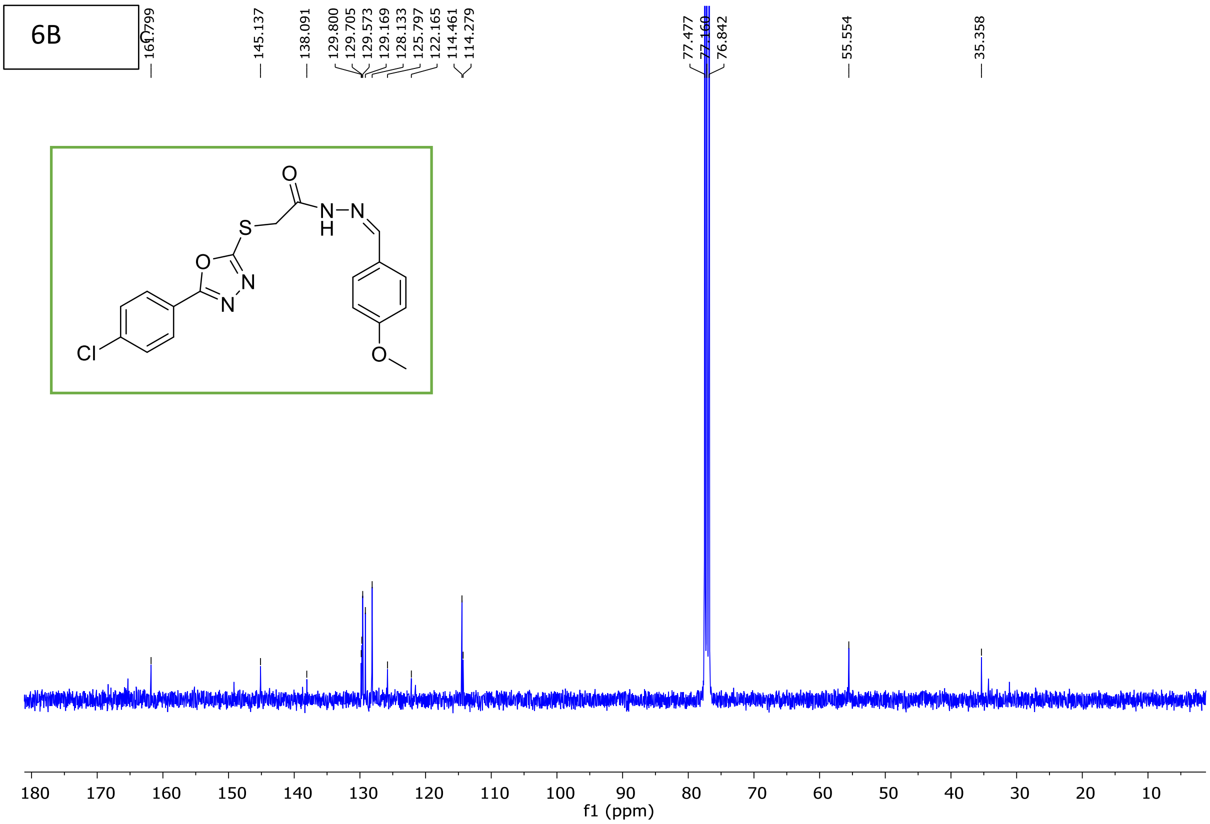
7.491
7.469
7.260
4.998
4.964
4.948
4.933
4.912
4.112
3.424
O
N
H
N
S
O
N
N
Cl
NO$_2$
4.44
5.22
1.14
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)

^{13}C NMR spectra of synthesized compounds (6A-6E) :

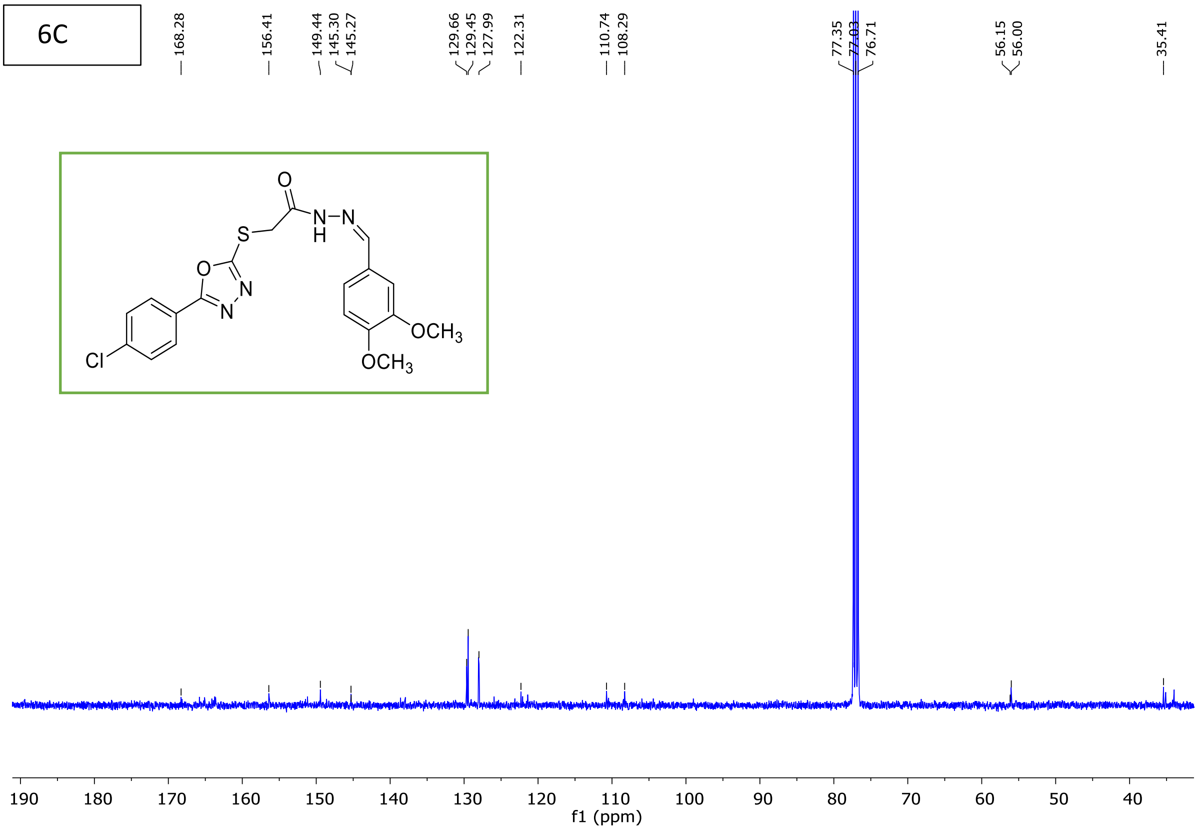
6A



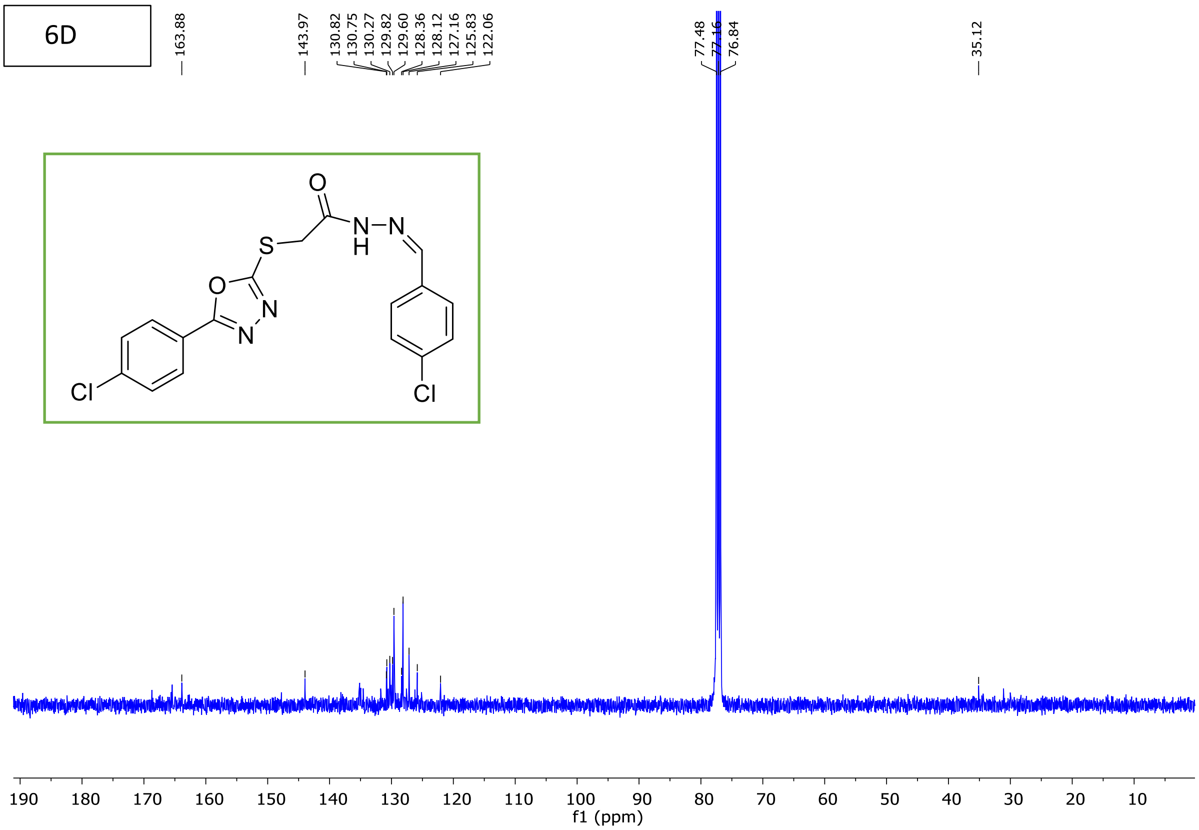
6B



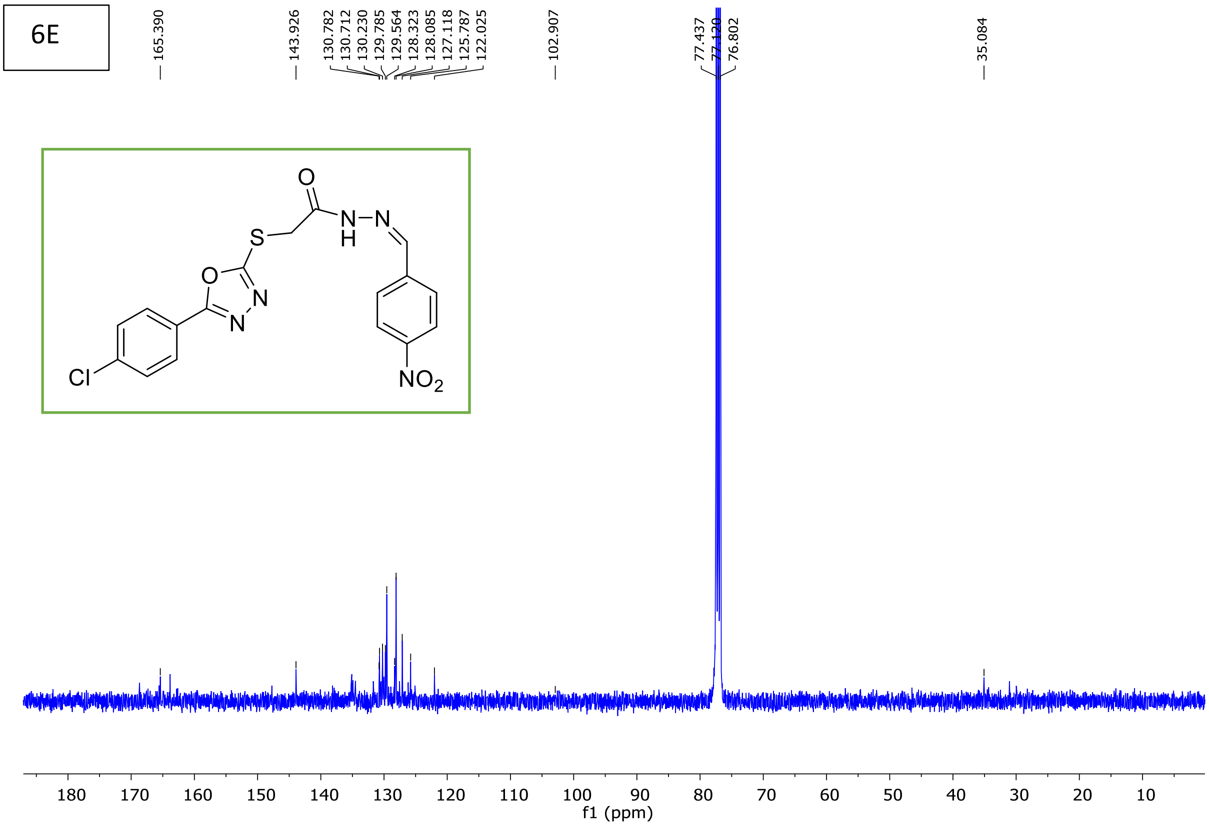
6C


168.28
156.41
149.44
145.30
145.27
129.66
129.45
127.99
122.31
110.74
108.29
77.35
77.03
76.71
56.15
56.00
35.41
O
N
H
N
S
O
N
N
Cl
OCH3
OCH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
f1 (ppm)

6D


163.88
143.97
130.82
130.75
130.27
129.82
129.60
128.36
128.12
127.16
125.83
122.06
77.48
77.16
76.84
35.12
O
N
H
N
S
O
N
N
Cl
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

6E


165.390
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130.782
130.712
130.230
129.785
129.564
128.323
128.085
127.118
125.787
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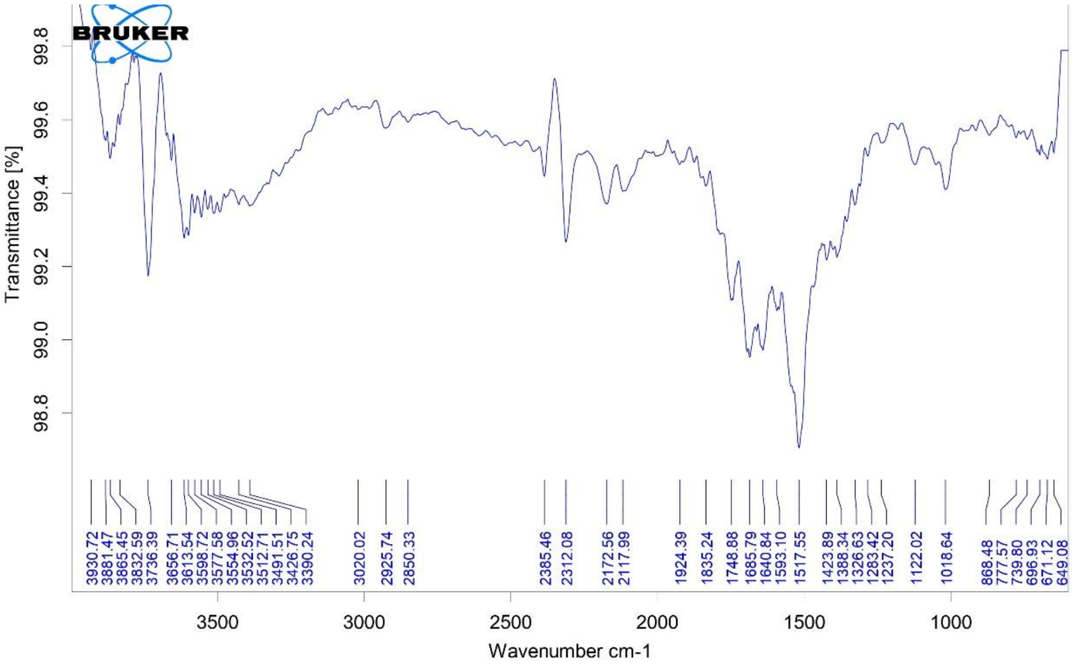
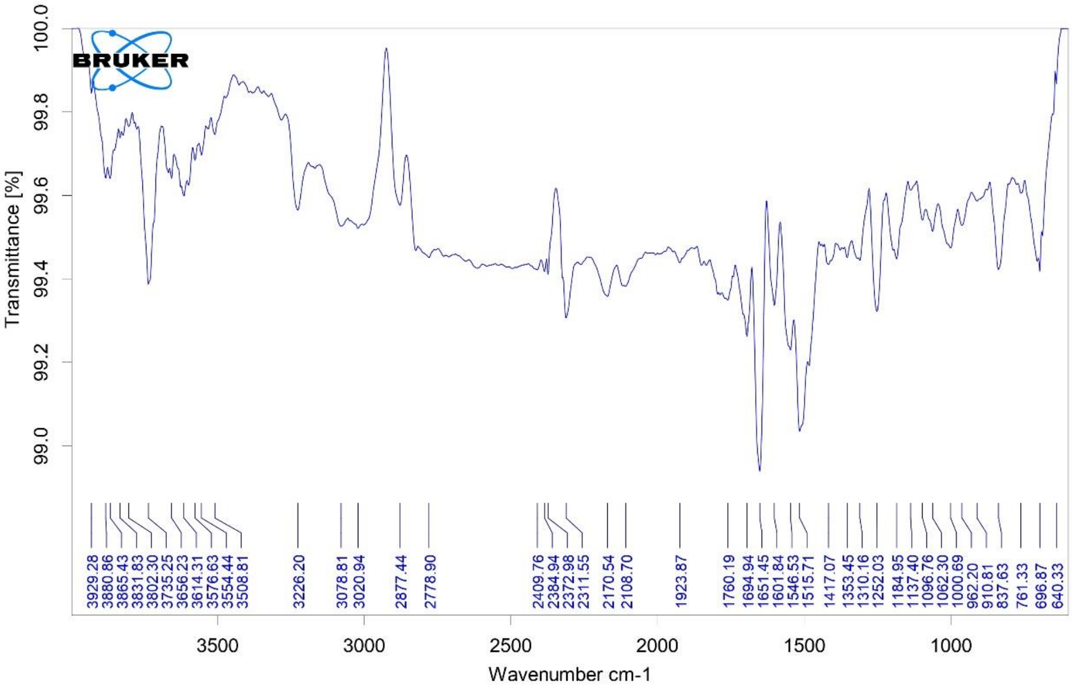
102.907
77.437
77.120
76.802
35.084
O
S
N
H
N
O
N
N
Cl
NO2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

FT-IR spectra of synthesized compounds

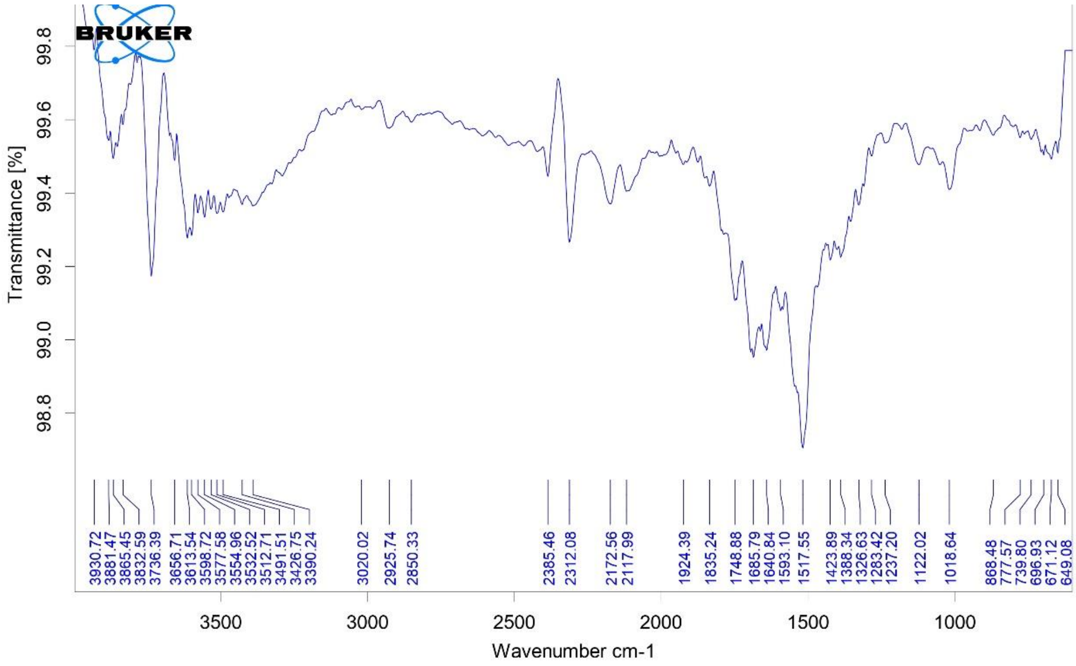
6A



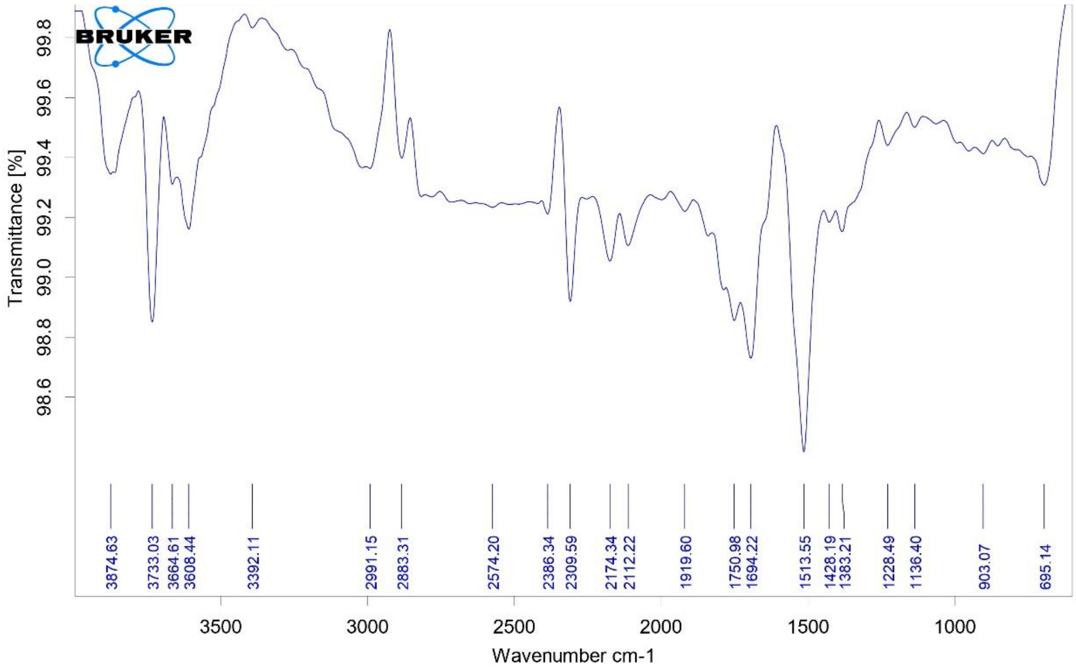
6B



6C


BRUKER
Transmittance [%]
99.8
99.6
99.4
99.2
99.0
98.8
3930.72
3881.47
3865.45
3832.59
3736.39
3656.71
3613.54
3598.72
3577.58
3554.96
3532.52
3512.71
3491.51
3426.75
3390.24
3020.02
2925.74
2850.33
2385.46
2312.08
2172.56
2117.99
1924.39
1835.24
1748.88
1685.79
1640.84
1593.10
1517.55
1423.89
1388.34
1326.63
1283.42
1237.20
1122.02
1018.64
868.48
777.57
739.80
696.93
671.12
649.08
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

6D


BRUKER
Transmittance [%]
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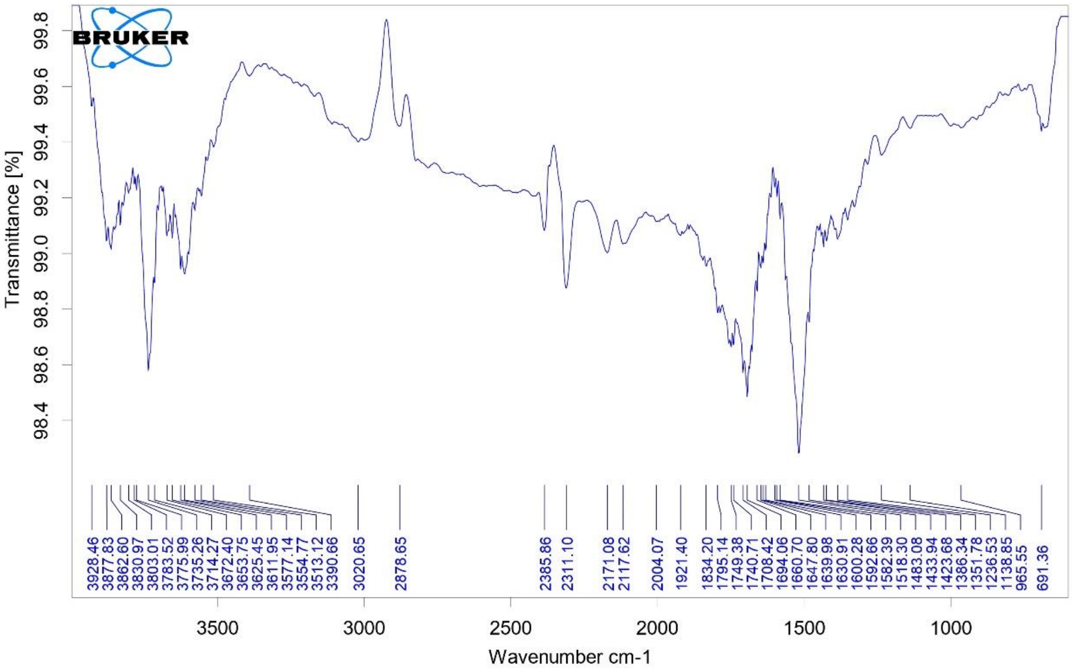
99.6
99.4
99.2
99.0
98.8
98.6
3874.63
3733.03
3664.61
3608.44
3392.11
2991.15
2883.31
2574.20
2386.34
2309.59
2174.34
2112.22
1919.60
1750.98
1694.22
1513.55
1428.19
1383.21
1228.49
1136.40
903.07
695.14
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

6E


BRUKER
Transmittance [%]
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98.6
98.8
99.0
99.2
99.4
99.6
99.8
3928.46
3877.83
3862.60
3830.97
3803.01
3783.52
3775.99
3735.26
3714.27
3672.40
3653.75
3625.45
3611.95
3577.14
3554.77
3513.12
3390.66
3020.65
2878.65
2385.86
2311.10
2171.08
2117.62
2004.07
1921.40
1834.20
1795.14
1749.38
1740.71
1708.42
1694.06
1660.70
1647.80
1639.98
1630.91
1600.28
1592.66
1582.39
1518.30
1483.08
1433.94
1423.68
1386.34
1351.78
1236.53
1138.85
965.55
691.36
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

CHAPTER-5

ADME STUDIES

5.1) *In silico* ADME studies of synthesized compounds

ADME stands for absorption, distribution, metabolism, excretion which basically explains the pharmacokinetics of the drugs. Here, we have studied the pharmacokinetics (table 3) and drug likeness studies (table 4) of our synthesized compounds with the help of a widely used webserver SwissADME. These data are fully predicted by this webserver.

Pharmacokinetic studies

Table 3; Pharmacokinetic studies of the synthesized compounds

Compounds	G.I absorption	BBB permeant	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p(cm/sec)
6A	High	No	Yes	Yes	Yes	No	Yes	-6.04
6B	High	No	Yes	Yes	Yes	No	Yes	-6.04
6C	High	No	Yes	Yes	Yes	No	Yes	-6.24
6D	High	No	Yes	Yes	Yes	No	Yes	-5.60
6E	Low	No	Yes	Yes	Yes	No	Yes	-6.23

Drug likeness studies

Table 4; Drug-likeness studies of the synthesized compounds

Compounds	Molecular Weight(g/mol)	Lipinski	Ghose	Veber	Bioavailability score	Synthetic accessibility
6A	402.85	Yes	Yes	Yes	0.55	3.39
6B	402.85	Yes	Yes	Yes	0.55	3.39
6C	432.88	Yes	Yes	Yes	0.55	3.54
6D	407.27	Yes	Yes	Yes	0.55	3.33
6E	417.83	Yes	Yes	Yes	0.55	3.35

5.2 Discussion:-

The ADME studies revealed that none of the synthesized compound are going to cross blood-brain barrier. Except 6E, every compound has high G.I absorption and none of the compounds are P-gp substrate. Drug likeness study revealed that all the synthesized compounds are following Lipinski, Ghose and Veber rules which suggests they have drug-like property with very good bioavailability score of 0.55 suggesting, they are going to be absorbed pretty well in the human body.

CHAPTER-6

Docking Studies

6) Docking studies of the final compounds with Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2)

VEGFR-2 is a key mediator of tumour angiogenesis and reported as a major therapeutic target for anticancer drug development. The synthesized compounds were docked within the receptor which gave us appreciable binding energies and interactions.

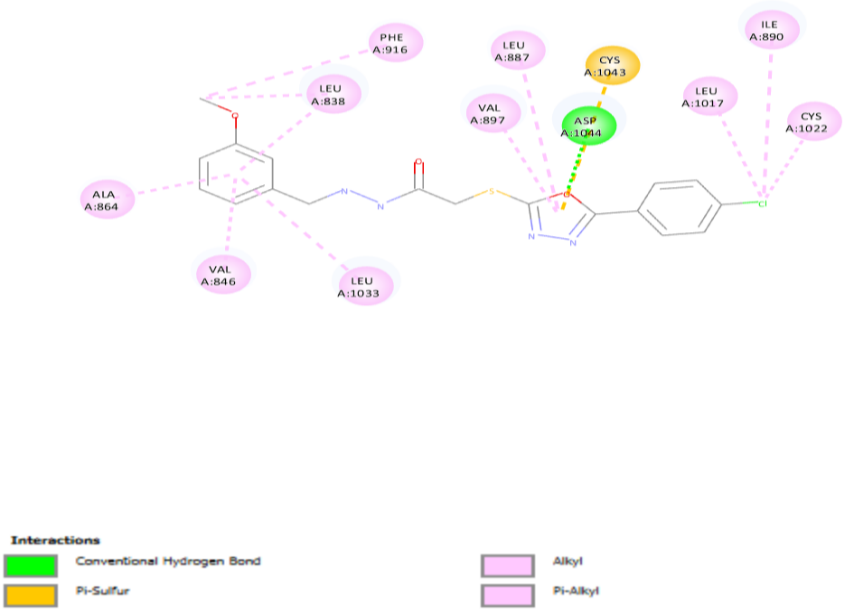
6.1) Procedure:

The receptor protein was taken from Protein Data Bank, had a co-crystallized benzimidazole ligand. This ligand directed us to the active binding site. PDB ID of the protein is 2OH4. The protein was prepared using BIOVIA Discovery Studio Visualiser. Protein preparation took few steps like water removal, addition of polar hydrogen, addition of gasteiger charges and minimization. The synthesized compounds were taken in mol2 format and energies were minimized. The docking was performed via PyRx tool.

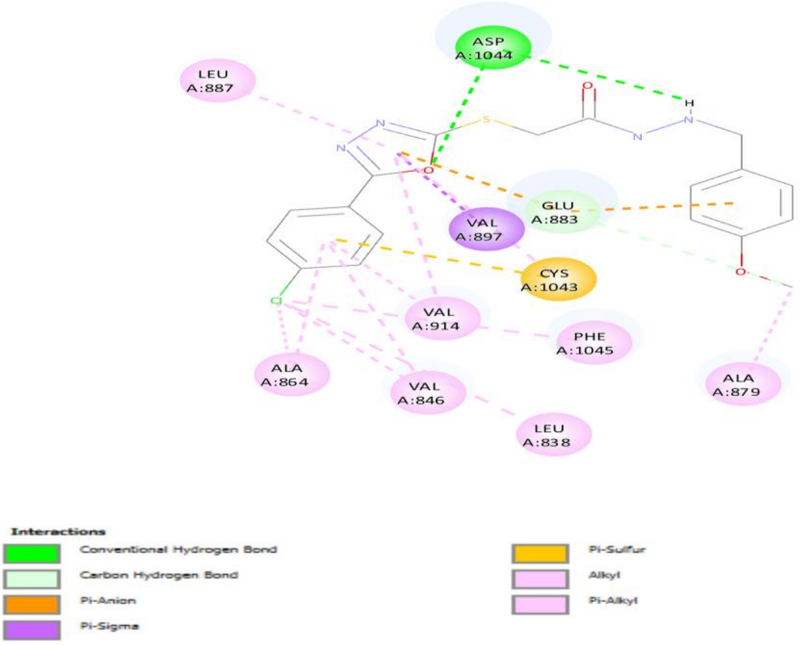
6.2) Results and discussion:

The best binding affinity was shown by 6A (-9.5 kcal/mol) followed by 6C (-9.3 kcal/mol), 6D (-9.0 kcal/mol), 6E (-8.6 kcal/mol) and 6B (-8.3 kcal/mol). As it was a localized docking, each and every compound showed interaction more or less, with the active site predicted by DS Visualizer. The active site consists of, LEU838, GLY839, ARG840, VAL846, ALA864, GLU883, VAL 896, VAL897, VAL914, GLU915, PHE916, CYS917, LYS918, GLY 920, LEU1017, HIS 1024, LEU1033, ILE1042, CYS 1043, ASP 1044, PHE1045, GLY 1046, LEU 1047, ALA1048, ARG1049. Interaction of the synthesized compounds with amino acids are listed in table 5.

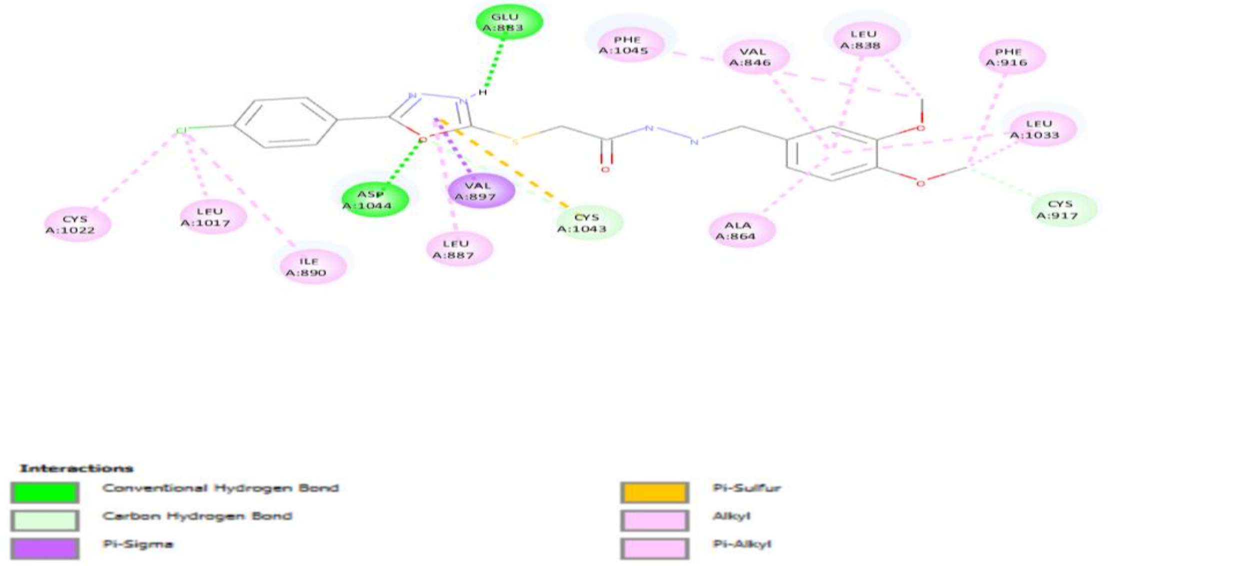
Interaction with 6A



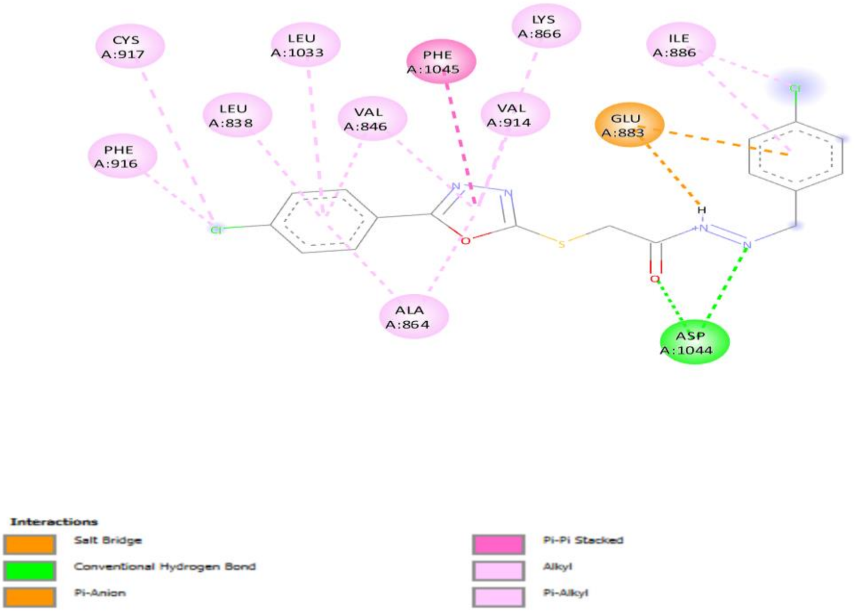
Interaction with 6B



Interaction with 6C



Interaction with 6D



Interaction with 6E

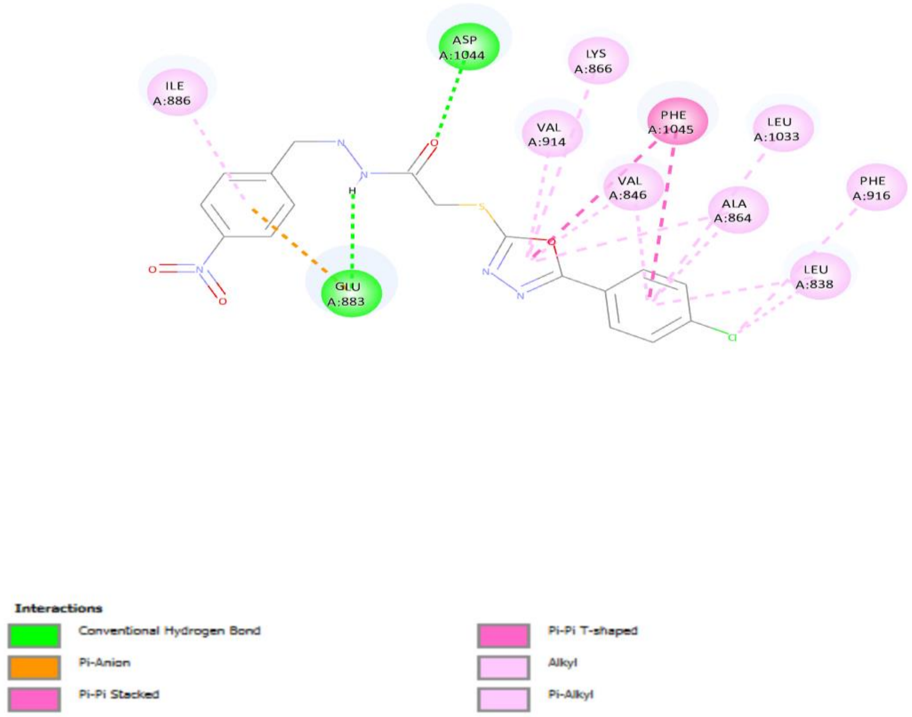


Table 5; Docking interaction of synthesized compounds with VEGFR-

Compound	Binding affinity(kcal/mol)	Interaction with amino acid
6A	-9.5	ALA864, VAL846, LEU838, LEU1033, PHE916, VAL897, LEU887, ASP1044, CYS1043, LEU1017, ILE890, CYS1022
6B	-9.3	LEU838, ALA879, VAL846, ALA864, VAL914, PHE1045, CYS1043, VAL897, GLU883, LEU887, ASP1044
6C	-9.0	CYS1022, LEU1017, ILE890, ASP1044, LEU887, VAL897, GLU883, CYS1043, PHE1045, VAL846, ALA864, LEU838, PHE916, LEU1033, CYS917
6D	-8.6	PHE916, CYS917, LEU838, LEU1033, VAL846, ALA864, PHE1045, VAL914, LYS866, GLU883, ILE886, ASP1044
6E	-8.3	ILE886, GLU883, ASP1044, VAL914, LYS866, VAL846, PHE1045, ALA864, LEU1033, LEU838, PHE916

CHAPTER-7

Conclusion and Future Perspectives

7) CONCLUSION and FUTURE PERSPECTIVES:

As a part of my research work, I have synthesized some 2,5-disubstituted 1,3,4-oxadiazole derivatives and characterized by ^{1}H NMR, ^{13}C NMR and FT-IR Spectroscopy. The in silico ADME profiling was done, along with molecular docking with VEGFR-2. According to the literature review, 1,3,4-oxadiazole derivatives are found to be pharmacologically more useful due to their wide range of biological activities and chemical stability. Modification of 1,3,4-oxadiazole moiety produces valuable pharmacological activity, mostly due to the presence of heteroatoms and substitution at different position in heterocycle. The synthesized compounds followed the parameters of being drug-like and showed appreciable bioavailability. ADME profiling showed none of the synthesized compounds are going to cross blood-brain barrier. Docking study showed good interaction with VEGFR-2. All these results indicate the compounds can be assumed as promising drug candidates.

In future, I will evaluate the antifungal and anticancer activity of these synthesized compounds. Antifungal activity will be tested against various pathogenic fungal strains like *C. albicans*, *C. krusei*, *C. parapsilopsis*, etc. in terms of MIC values or Zone of inhibition. Anticancer studies will be held against various human cancer cell lines like A549 (lung), MCF-7 (breast), HeLa (cervical) and HEK-293 (embryonic kidney) in terms of IC_{50} or percentage growth inhibition (PGI)

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