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# EVALUATION OF SOME NOVEL 1,3,4-OXADIAZOLE, 1,2,4-TRIAZOLE AND 1,3,5-TRIAZIN

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**ABSTRACT**

In the basic conditions for the production of 1,3,4-oxadiazol-2-thiones (3), aminomethylation by formaldehyde and secondary amines was carried out with a series of acid-based hydrazides (2) acid derived from ibuprofen and 4-methylthiophhenylacetes (2) (4 and 5). TLC has confirmed the purity of the compounds. Based on elementary and spectral analyzes, the structures of these compounds have been established. The compounds newly synthesized for their anti-inflammatory, analgesic, ulcerogenic, antimicrobial activity were evaluated.

## 1. INTRODUCTION

### Introduction on Heterocyclic Compounds

Heterocyclic chemistry is a major branch of organic chemistry that accounts for roughly a third of all modern publications. In fact, heterocyclic compounds account for two-thirds of all organic substances. A carbocyclic compound is a cyclic organic compound with all carbon atoms arranged in a ring configuration. A heterocyclic compound is one in which at least one atom other than carbon is present in the ring structure.[1] Heterocyclic compounds are cyclic compounds that contain carbon and at least one other atom within a ring structure, such as sulphur, oxygen, or nitrogen.Simple aromatic rings or nonaromatic rings can be found in these structures. Pyridine, pyrimidine, and dioxane are other examples. Heterocyclic compounds can be used in a variety of ways. They are the most common type of chemical used in pharmaceuticals.[2]

Heterocycles are by far the most important of the classical divisions of organic chemistry, both physiologically and industrially. The bulk of medications and physiologically active agrochemicals are heterocyclic, as are a large number of additives and modifiers used in industrial applications such as cosmetics, reprography, data storage, and plastics. [3] One of the most notable structural properties of heterocycles, which the pharmaceutical industry continues to exploit to great benefit, is their ability to manifest substituents around a core scaffold in defined three-dimensional forms.The most frequent heteroatoms are nitrogen, oxygen, and sulphur, but heterocyclic rings containing additional heteroatoms are also well-known. There are a huge number of heterocyclic compounds known, and the number is continually growing. As a result, there is a large body of literature on the issue. Aliphatic and aromatic heterocyclic compounds are the two types of heterocyclic compounds. The cyclic analogues of amines, ethers, thio ethers, amides, and other aliphatic heterocyclics are known as aliphatic heterocyclics. The existence of strain in the ring has a significant impact on their qualities. Small (3 and 4 membered) and common (5 to 7 membered) ring structures are common in these compounds. [4]

Aromatic heterocyclic compounds, on the other hand, have a heteroatom in the ring and have properties that are similar to benzene in some ways. Furthermore, these compounds adhere to Huckel's proposed general rule. Heterocycles are not only abundant in natural products, but they are also important components of biological molecules like DNA and RNA. Without a question, DNA is

ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

the most crucial macromolecule in existence. The building blocks of our genes are nucleotides, which are derivatives of the pyrimidine and purine ring structures. The oxygen carriers in plants and animals, chlorophyll and heme, are both derivatives of massive porphyrin rings. [5]Many heterocyclic compounds have the ability to integrate functional groups as substituents or as part of the ring system itself, which is an essential characteristic. Basic nitrogen atoms, for example, can be used as amino substituents or as part of a ring. This means that the structures can be used to provide or imitate a functional group in a variety of ways. Because of the similarities in acidity and steric requirement, the 1H-tetrazole ring system[6] has been used as a mimic of a carboxylic acid function. Heterocyclic compounds can be found in abundance in nature.These play an important role in biological processes. Nucleic acid bases, for example, are pyrimidine and purine ring system derivatives that are essential to the replication mechanism. The components required for photosynthesis and oxygen transport in higher plants and animals, respectively, are chlorophyll and heme, both of which are derivatives of the porphyrin ring system[7-10]. Heterocyclic compounds include thiamine (vitamin B1), riboflavin (vitamin B2), pyridoxol (vitamin B6), nicotinamide (vitamin B3), and ascorbic acid (vitamin C), all of which are essential diet elements. [11]Heterocycles are a significant class of chemicals, accounting for more than half of all chemical compounds known. Antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents all contain heterocycles, as do most vitamins, many natural products, biomolecules, and biologically active compounds. [12-15]

They've also been discovered as a major structural unit in a variety of synthetic medicines and agrochemicals. Solvatochromic, photochromic, and biochemical-luminescence characteristics are all present in several of these substances.Dyestuff, fluorescent sensors, brightening agents, information storage, polymers, and analytical reagents are only a few of the heterocycles' applications in materials science. Heterocyclic compounds are a fascinating and complicated topic of chemistry. Heterocyclic compounds are the largest and most diverse group of organic chemicals. Many larger characteristics of heterocyclic compounds are acknowledged as a science with extensive implications that affect practically every element of current chemistry. Heterocyclic compounds have a wide range of structural variety and have proven to be widely and cost-effective medicinal agents. Dealing with the creation of pharmacological molecules likely gives some of the greatest hope of the succession in the present and future age as the world population grows and health problems grow in tandem. There are a large number of pharmacologically active heterocyclic compounds that are extensively distributed in nature and vital for life.

### 1.1 AIM AND OBJECTIVE

We developed this sort of chemistry and synthesised several heterocyclic scaffolds since we were interested in the design, synthesis, spectral characterization, and biological activity studies of some new [l,3,4]-oxadiazole, 1,2,4-triazole, and 1,3,5-triazin derivatives. Because of their vast applications in the pharmaceutical business, the synthesis of novel [l,3,4]-oxadiazole, 1,2,4-triazole, and 1,3,5-triazin remains of significant interest.

According to a review of the literature, [l,3,4]-oxadiazoles and their derivatives have significant biological activity. In light of these findings, several [1,3,4]-oxadiazole-2(3H)-thiones and their Mannich bases comprising 4-isobutylphenyl-1-ethyl and 4-methylthiobenzyl moieties at position 5 of the oxadiazole ring system were synthesised and their biological features studied. Antimicrobial, anti-inflammatory, analgesic, and ulcerogenic properties of the newly synthesised compounds were tested.

ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

## 2. BIOLOGICAL ACTIVITY

***Antimicrobial Activity***

Antimicrobials are chemicals that kill or prevent the growth of microorganisms including bacteria, fungus, and protozoans. Antimicrobial medications either kill or inhibit microorganisms from multiplying (microbiocidal) (microbiostatic). These medications are the most significant advance to treatments in the twentieth century, and they are meant to inhibit/kill the infected organism while having no/minimal effect on the recipient.

Antimicrobials such as penicillin and tetracycline were discovered, paving the door for better health for millions of people all over the world. Antimicrobials include antibiotics as well as synthetically produced substances. The majority of these illnesses may now be easily treated with a short course of antibiotics. Microorganisms have adapted and become resistant to prior antimicrobial agents as a result of the development of antimicrobials. For infectious disease research programs, finding and developing new antibacterial and antifungal medicines with novel mechanisms of action has become a top priority. Hence the search for new anti-microbial agents active against microorganisms has been extended.

***Antibacterial Activity***

Antibiotics are defined as chemicals produced by one microbe that kill or inhibit the growth of another bacteria. Of fact, in today's popular usage, the term antibiotic refers to nearly any medicine that is used to treat a bacterial infection in the body. In most cases, antibiotics are used to treat bacterial infections. Human pathogenic microorganisms are becoming increasingly resistant to antibacterial agents, posing a severe global health threat. The rise in antibiotic resistance necessitates a fresh effort to find antibacterial medicines that are effective against pathogenic bacteria that are resistant to conventional antibiotics. Several approaches are now being used to produce new antibiotics and increase the efficacy of existing antimicrobial drugs. The production of chemicals that target bacterial membranes is an appealing method for the development of antibacterial drugs. The structure of bacterial membranes is remarkably conserved across most gram-negative and gram-positive bacteria species. Alterations in membrane permeability can increase sensitivity to hydroprobic antibiotics194,195, hence mutations that produce major changes in bacterial membrane architecture are often not permanent. The search for new agents active against gram-positive and gram-negative bacteria has been extended.

***Procedure***

In this study, the serial plate dilution approach was used. Using phosphate buffer, serial dilutions of the medication in Muller Hinton broth were taken in tubes and their pH was adjusted to 5.0.

The test bacteria was infected with a standardised suspension and incubated at 37 °C for 16-18 hours. The minimum inhibitory concentration (MIC) was determined by observing the lowest drug concentration at which no observable growth occurred.

The main goal of placing antibacterial discs on the agar was to create zones of inhibition in the bacterial lawn. Each Petri dish was filled with 20 millilitres of agar material. The excess suspension was decanted, and the plates were dried for an hour in an incubator at 37 °C. On these seeded agar plates, wells were punched and minimum inhibitory doses of the test chemicals in dimethyl sulfoxide (DMSO) were introduced to each labelled well using a punch. In the same method, a control for the plates was made using DMSO as a solvent.

The Petri plates were made in triplicate and kept at 37 degrees Celsius for 3-4 days. The diameter of the inhibitory zone was used to determine antibacterial activity. The activity of each compound was compared to the standard ciprofloxacin.

***Antifungal activity***

ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

The antifungal activity of the produced compounds was also tested in DMSO using the serial plate dilution method200-202. Peptone was dissolved to make Sabourauds agar media (1 g). Using distilled water (100 mL) and setting the pH to 5.7, dissolve D glucose (4 g) and agar (2 g). To make a suspension of sore offungal strains for lawning, normal saline was employed. To obtain a suspension of comparable species, a loopful of a specific fungal strain was transferred to 3 mL saline. Each Petri dish was filled with 20 millilitres of agar material. The excess suspension was decanted, and the plates were dried in a 37 °C incubator for 1 hour. On these seeded agar plates, wells were punched out with a punch. Each labelled well received minimum inhibitory doses of the test chemicals in DMSO. The same solvent DMSO was used to prepare a control for the plates. The Petri dishes were made in threes and kept at 37°C for three to four days. The diameter of the inhibitory zone was used to determine antifungal activity. The activity of each chemical was compared to that of ciclopiroxolamine, which was used as a control. For all produced compounds, inhibitory zones were determined.

## 3. MATERIAL AND METHOD

### Experimental

All chemicals and reagents were used are of analytical grade. Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a Shimadzu-Fourier transform infra-red **(FTIR)-8400 Spectrophotometer** using **KBr** disc. 1H NMR spectra were recorded on a **Bruker DPX-400 MHz** spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. The mass spectral data were obtained with a **SHIMADZU-MS.**

### Synthesis of 1,3,4-oxadiazole


ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

**General Procedure for the Preparation of Aroylhydrazides (2)**

The ethyl esters were made by refluxing substituted aromatic acids in excess 100% ethanol in the presence of a few drops of cone sulfuric acid, as described in the general method. TLC had determined that the resultant esters were pure.

For 8 hours, a combination of 0.1 mol ethyl ester of substituted aromatic acids and 0.2 mol hydrazine hydrate was refluxed in absolute alcohol (50 mL). The excess solvent was then distilled out at decreased pressure before being quenched in ice cold water. Filtered, washed, and dried solids were separated. Recrystallization from ethanol refined the crude product.

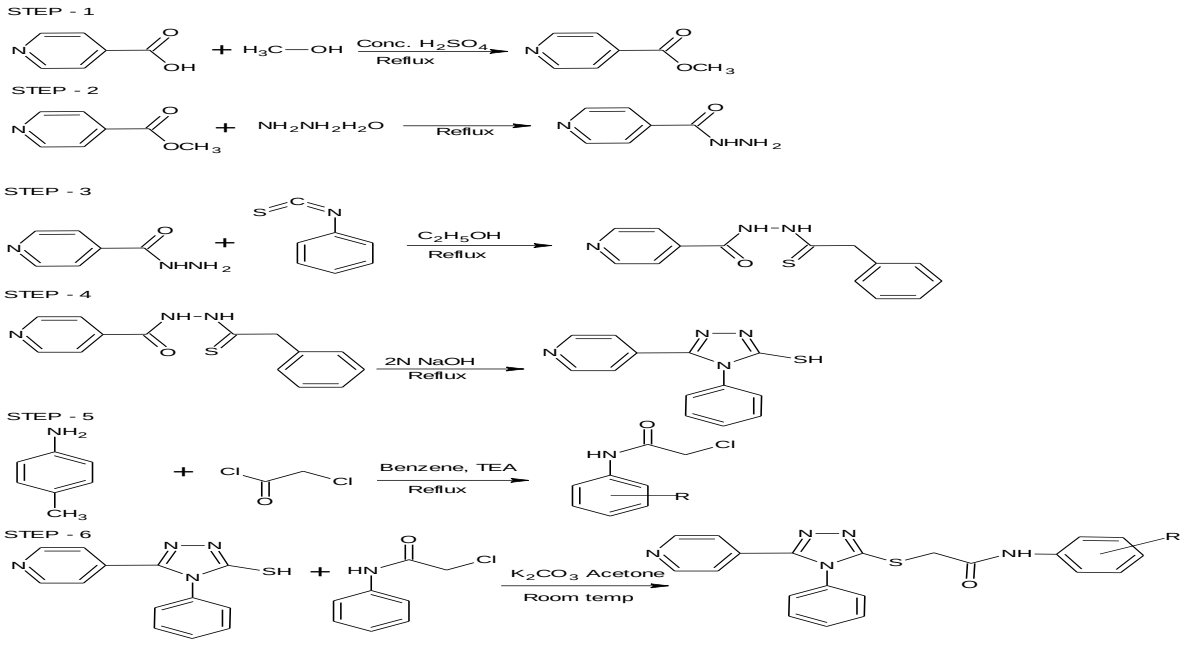
**General Procedure for the Preparation of 5-Aryl-2-mercapto-[l,3,4]-oxadiazole (3)**

In a round bottom flask, a mixture of aroyl hydarzide (2) (0.1 mol), KOH (5.6 g, 0.1 mol) in 100% alcohol (50 mL), and CS2 (15.2 g, 0.2 mol) was refluxed for roughly 4 hours until no hydrogen sulphide was produced. The reaction mixture was diluted with water after cooling to room temperature. After being acidified with dilute hydrochloric acid, the product was filtered, thoroughly rinsed with cold water, and recrystallized from ethanol.

**General Procedure for the Preparation of Mannich Bases (3a,3b and3c)**

A mixture of formaldehyde (0.45 g, 15 mmol) and a secondary amine (10 mmol) in 10 mL ethanol was added with stirring to a solution of 5-aryl-2-mercapto-[l,3,4]-oxadiazole-2-thione 3(10 mmol) in ethanol (15 mL). After all of the ingredients had been added, the stirring was continued at room temperature overnight. The solids that had precipitated were filtered, rinsed with water, and dried. Ethanol was used to recrystallize the crude product.

**Synthesis of novel 1,2,4-triazol-3-yl] sulfanyl} acetamide derivatives.**
**4 [N-(4-aryl amine)-2-{[4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl] sulfanyl} acetamide]**



ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

**General Procedure**

**4 [N-(4-aryl amine)-2-{[4-phenyl-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl] sulfanyl} acetamide]**

**Step-1: Synthesis of methyl pyridine-4-carboxylate**

Pyridine-4-carboxylic acid (0.1mole) was refluxed for 12 hours in 200 ml methanol and 6.0 ml concentrated H2SO4 before being put onto cool ice. The result was filtered and washed with cold water. Alcohol has been re-crystallized. TLC was used to track the reaction's progress, with toluene:actone(8:2) as the eluent.

**Step-2: Synthesis of pyridine-4-carbohydrazide**

In methanol, 0.1mole methyl pyridine-4-carboxylate and 0.2mole hydrazine hydrate were refluxed for 15 hours before being placed into the ice. The final product is filtered before being rinsed in cold water. From ethyl alcohol, recrystallized. TLC was used to track the reaction's progress, with toluene:acaetone(8:2) as the eluent.

**Step-3: Synthesis of N-phenyl-2-(pyridine-4-ylcarbonyl) hydrazinecarbothioamide**

The pyridine-4-carbohydrazide (0.1mole) and phenyl isothiocyanate (0.1mole) combination was refluxed for 3 hours in ethanol (220ml). The produced product was collected by filtration and recrystallization from ethanol after cooling. TLC was used to monitor the reaction's progress, with toluene:acetone(8:2) as the eluent.

**Step-4: Synthesis of 4-phenyl-5-(pyridine-4-yl)-4H-1,2,4-triazole-3-thiol**

The mixture of N-phenyl-2-(pyridine-4-ylcarbonyl) hydrazinecarbothioamide (0.05mole) and 80ml of 2N NaOH was refluxed for 4hours.The resulting solution was cooled and poured into the ice and neutralize with 2N HCl. The precipitate was filtered and washed with cold water. Dried and recrystallized from ethanol. The progress of the reaction was monitored by TLC using toluene:acetone(8:2) as eluent.

**Step-5:Synthesis of 2-chloro-N-(aryl)-acetamide**

In 30ml of Benzene, 0.02mole chloroacetyl chloride and 2-4 drops triethyl amine were added. In an ice bath, this mixture was mixed. Dropwise additions of aryl amine (0.02mole) in 30ml benzene were made, and the mixture was refluxed for 5 hours. After cooling, the resultant ppt. was filtered and washed with benzene. From ethanol, it was recrystallized. TLC was used to monitor the reaction's progress, with toluene:acetone(8:2) as the eluent.

## 4. RESULT AND DISCUSSION

**5-SUBSTITUTED-[L,3,4]-OXADIAZOLE MANNICH BASE**

**Table 1: Physical Characterization data of 5-substituted-[l,3,4]-oxadiazole Mannich bases 3a,3b and 3c.**

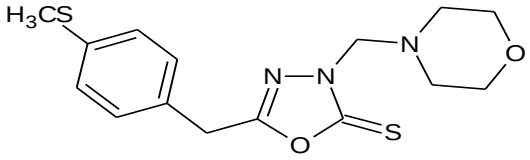
| Compd | R | R1 | R2 | R3 | X | Mol. Formula | Mol. Wt. | M.P °C | % yield |
|---|---|---|---|---|---|---|---|---|---|
| **3a** | H | $SCH_3$ | ---- | ---- | O | $C_{15}H_{19}N_3O_2S_2$ | 337 | 88–90 | 62 |
| **3b** | H | $SCH_3$ | 4-$NO_2$ | --- | --- | $C_{21}H_{23}N_5O_3S_2$ | 457 | 168-170 | 82 |
| **3c** | H | $SCH_3$ | ---- | 2,4-Cl | --- | $C_{18}H_{17}N_3OSCl_2$ | 393 | 140-142 | 85 |

ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

**Spectral Characterization Compound 3a**

***5-(4-Methylthiobenzyl)-3-[(4-methylpiperazin-l-ylmethyl)-[l,3,4]-oxadiaz0le-2(3H)' Thione***

**Structure:**




**Molecular formula:** $C_{15}H_{19}N_3O_2S_2$

**Molecular weight:**336

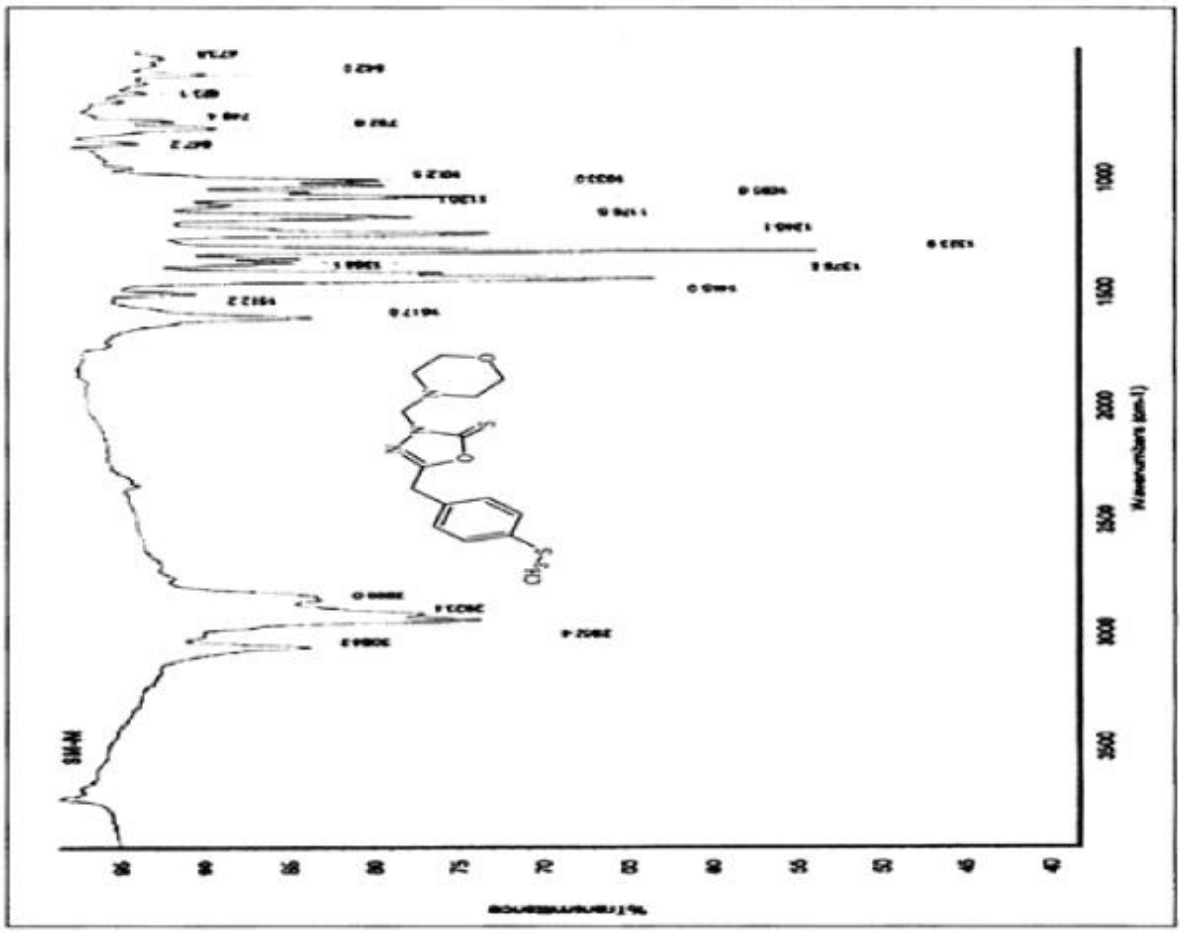


**Figure 4.1:IR Spectrum of 5-(4-Methylthiobenzyl)-3-[(4-methylpiperazin-l-ylmethyl)-[l,3,4]-oxadiaz0le-2(3H)' Thione (3a)**

ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

**Figure 4.2:[1]H NMR Spectrum of 5-(4-Methylthiobenzyl)-3-[(4-methylpiperazin-l-ylmethyl)-[l,3,4]-oxadiaz0le-2(3H)'Thione (3a)**

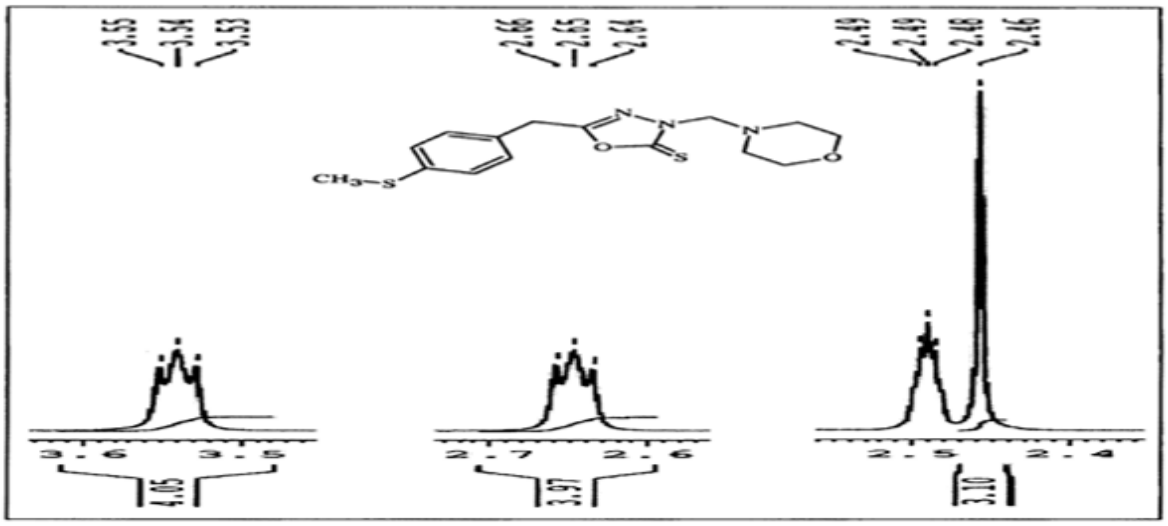
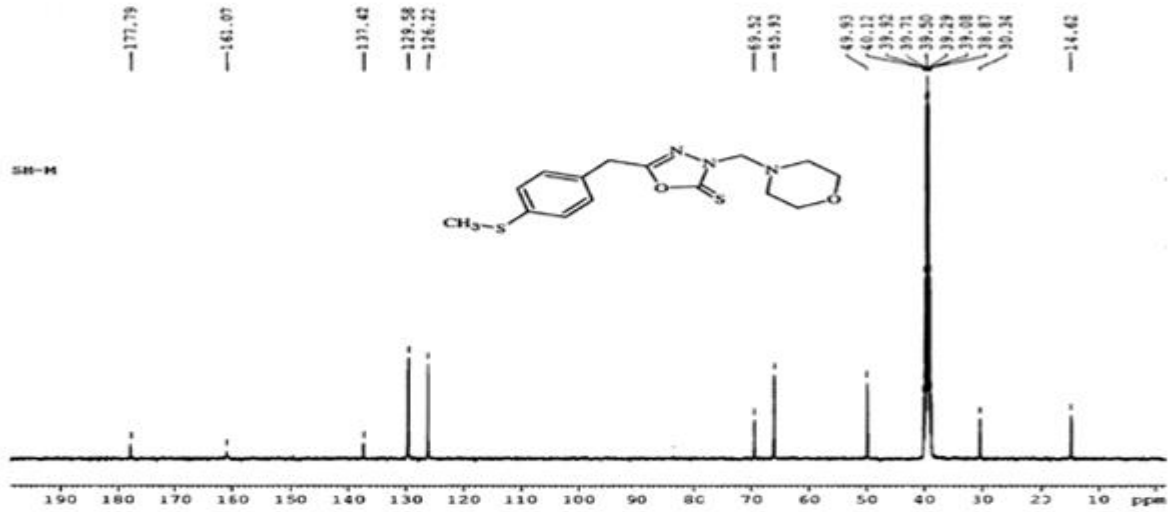


**Figure 4.3: Expanded [1]H NMR Spectrum of 5-(4-Methylthiobenzyl)-3-[(4-methylpiperazin-l-ylmethyl)-[l,3,4]-oxadiaz0le-2(3H)'Thione (3a)**



ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

**Figure 4.4: $^{13}$C NMR Spectrum of 5-(4-Methylthiobenzyl)-3-[(4-methylpiperazin-l-ylmethyl)-[l,3,4]-oxadiaz0le-2(3H)'Thione (3a)**

**CONLUSION**

Various oxadiazole Mannich bases derived from ibuprofen and 4- methylthiophenyl acetic acid were prepared with the objective of developing better anti-inflammatory molecules with minimum ulcerogenic activity and also to evaluate their antimicrobial potency. It was interesting to note that five compounds 4a, 5b, 5d, 5e and 5i were found to have anti-inflammatory activity greater than the standard drug, diclofenac at 10 mg/kg p.o. Furthermore, three compounds 4b, 5h and 5k exhibited anti-inflammatory activity equivalent to the standard drug against carrageenin induced paw oedema test in rats. When the above five more active compounds subjected to the analgesic activity against acetic acid induced writhing test in mice, compounds 4a and 5e showed increased activity than the reference drug. The presence of 4-ethoxycabonylpiperadin-1-ylmethyl, 4-chlorophenylpiperazin-4-ylmethyl, 4-nitrophenylpiperazin-4- ylmethyl, 4-fluorophenylpiperazin-4-ylmethyl groups at third and 4- isobutylphenylethyl group at fifth position in the oxadiazole nucleus increases the anti-inflammatory activity. It was further noted that 4- methylthiobenzyl group at fifth position and 3-chlorophenylpiperazin-4-ylmethyl group at third position of oxadiazole nucleus also increases the anti-inflammatory activity than the standard drug. It was very interesting to note that all the above five oxadiazole derivatives showed maximum reduction in the ulcerogenic activity

**REFERENCES**

[1] J.R. Vane, Nature New Biol. (London) (1971) 231e232.

[2] A. Robert, Adv. Prostaglandin Thromboxane Res. 2 (1976) 507.

[3] B.M. Peskar, Biochem. Biophys. Acta 487 (1977) 307.

[4] M.C. Allison, A.G. Howatson, C.J. Torrance, F.D. Lee, R.I. Russel, N. Engl. J. Med. 327 (1992) 749e754.

[5] G. Mounier, C. Guy, F. Berthoux, M.N. Beyens, M. Ratrema, M. Ollagnier, Therapie 61 (2006) 255.

[6] V. Schneider, L.E. Lévesque, B. Zhang, T. Hutchinson, J.M. Brophy, Am. J. Epidemiol. 164 (2006) 881.

[7] F.L. Lanza, Am. J. Gastroenterol. 93 (1998) 2037e2046.

[8] T. Karabasanagouda, A.V. Adhikari, M. Girisha, Indian J. Chem. 48B (2009) 430e437.

[9] D. Jagadeesh prasad, Mithun Ashok, Prakash karegoudar, Boja Poojary, B.S. Holla, N. Sucheta Kumari, Eur. J. Med. Chem. 44 (2009) 551e557.

[10] B. Mithun Ashok, Holla Shivarama, Phosphorus Sulfur Silicon Relat. Elem. 182 (2007) 1599e1608.

[11] T. Karabasanagouda, A.V. Adhikari, N. Suchetha Shetty, Phosphorus, Sulfur Silicon Relat. Elem. 182 (2007) 2925e2941.

[12] B.S. Holla, R. Gonsalves, S. Shenoy, Eur. J. Med. Chem. 35 (2000) 267e271.

ISSN: 0975-3583,0976-2833 VOL12,ISSUE04,2021

[13] F. Macaev, G. Rusu, S. Pogrebnoi, A. Gudima, E. Stingaci, L. Vlad, N. Shvets, F. Kandemirli, A. Dimoglo, R. Reynolds, Bioorg. Med. Chem. 13 (2005) 4842e4850.

[14] X.J. Zou, L.H. Lai, G.Y. Jin, Z.X. Zhang, J. Agric. Food Chem. 50 (2002) 3757e3760.

[15] E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu, G. Altinok, Il Farmaco 57 (2002) 101e107.