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AN OVERVIEW OF 1,3,4- THIADIAZOLE ANALOGUES

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ABSTRACT-

A five-membered ring with two adjacent nitrogen atoms forms a pyrazole. Antipyrine, discovered by Knorr in 1883, marked the beginning of pyrazole chemistry. Since then, a large number of new derivatives have been discovered and tested for their biological potency, including their ability to perform various functions such as anticancer, anti-inflammatory, analgesic, antihypertensive, antipyretic, and antibacterial effects. Over-the-counter drugs with therapeutic potential include sildenafil, Celebrex, zometapine, fipronil, rimonabant, and lonazolac. Aspirin, ibuprofen, fenbufen, diclofenac sodium, indomethacin, and the COX-2 inhibitors celecoxib, etoricoxib, meloxicam, and other similar derivatives are examples of nonselective COX inhibitors commonly used as NSAIDs. . There are continuing reports that optimized 1,3,4-thiadiazole anti-inflammatory compounds have been synthesized or modified. Most of them are currently used clinical drugs fortified with 1,3,4-thiadiazoles. Azole compounds include thiadiazoles. These five-membered heterocycles have two nitrogen atoms and one sulfur atom. The nomenclature used by Hantzsch and Widman in which two double bonds form an aromatic ring has led to the name 'thiadiazole'. Freud and Kuhn first revealed the properties of ring systems in 1890, while Fischer introduced thiadiazoles in 1882.

Keywords- Pyrazole, Thiadiazole, Synthesis, application.

INTRODUCTION-

Thiadiazoles fall under the category of azole compounds. These five-membered heterocyclic compounds have two nitrogen atoms and one sulfur atom. Two double bonds created an aromatic ring, and the name "Thiadiazole" comes from the nomenclature used by Hantzsch and Widman. Although Freud and Kuhn first showed the nature of the ring system in 1890, Fischer first described thiadiazole in 1882. 1, 3, and 4-thiadiazole are chemical compounds that are structurally related to thiadiazole (two nitrogen and one sulfur heteroatom in a five-membered cyclic ring). This structure is displayed [1].

Thiadiazole essentially comes in four isomeric forms. A highly useful isomeric form is 1, 3, and 4, which has a variety of biological effects on the body. Thiadiazole derivatives with structural substitutions have also been discovered to possess a variety of therapeutic properties, including analgesic, antimicrobial, antitubercular, anticonvulsant, and anti-hepatitis B viral activities. More and more microbial strains that are resistant to antibiotics are being discovered in recent years. Higher mortality is being caused by multidrug-resistant microbe infections. The issue of microbial drug resistance is endangering

human health more and more. Drug resistance has slowly become an international issue over the last few decades with every antimicrobial drug that has been sold. A good strategy for combating clinical drug resistance is the development of antimicrobial drugs with distinctive chemical structures [2].

Pyrazoles are two adjacent nitrogen atoms in a five-membered ring structure. Knorr's discovery of antipyrine in 1883 sparked the chemistry of pyrazole. Since then, a large number of novel derivatives have been reported and tested for their biological potency, including their ability to perform a wide range of activities like anticancer, anti-inflammatory, analgesic, antihypertensive, antipyretic, and antimicrobial. The commercially available medications, such as Sildenafil, Celebrex, Zometapin, Fipronil, Rimonabant, and Lonazolac, among others, demonstrate their therapeutic potential [3].

A significant group of heterocycles are the 1,3,4-thiadiazoles. The "N - C- S" link found in 1,3,4-Thiadiazoles has the ability to act as the active site, have good tissue permeability, and chelate only a small number of metal ions in vivo. Thiadiazole's aromaticity has a significant impact on the compound's lower toxicity and in vivo stability. Thiadiazoles have demonstrated impressive antiviral, antimicrobial, anti-inflammatory, antitubercular, and anticancer properties thus far. Numerous medications, including cefazedone, cefazolin, cetazolamide, methazolamide, and megazol, contain the 1,3,4-thiadiazole compound [4].

The amide bond, the most prevalent chemical bond, is essential for the development of biological systems and is found in large quantities in many organic and biomolecules as well as common drugs. H2S/HCl, P2S5, P4S10, thiourea, aqueous ammonium sulphide, and Lawesson's Reagent (LR) are some of the many reagents used for the synthesis of heterocycles containing sulphur, such as thiophene, 1,3-thiazoles, and 1,3,4-thiadiazoles. LR is effectively used for the synthesis of thiadiazoles via [5].

Hybrid molecules were created by thoroughly researching various pharmacophores in the literature and framing them into one molecule to achieve synergistic chemotherapeutic activity with higher selectivity and less toxicity. This was done in an effort to develop more effective and affordable drugs for clinical use. Thus, 1,2,4-triazoles, 1,3,4-oxadiazole, 1,2,4-thiazole, and benzoxazoles were synthesised with pyrazole incorporation and were found to enhance pharmacological effect. There have also been reports of a number of biologically active analogues of pyrazolyl-1,3,4-thiadiazole. Research into the synthesis of pyrazole integrated thiadiazole derivatives is therefore crucial [6].

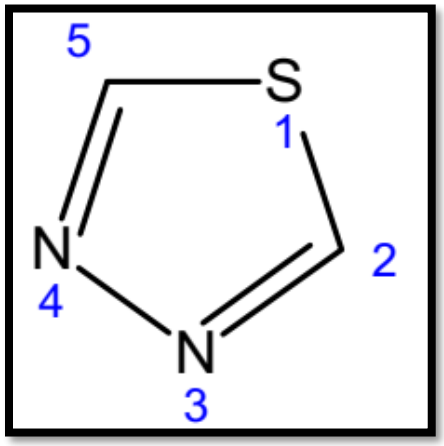


Figure Number 01- Structure of 1,3,4-thiadiazole molecule.

Chemistry-

The synthetic route of compounds (6a–s) is shown in Scheme 1. 2-(4-Formyl-2-methoxyphenoxy) acetic acid (2) was prepared by reacting vanillin with chloroacetic acid in the presence of sodium hydroxide. Various chalcone derivatives (4a–s) were synthesized by treating (2) with different derivatives of acetophenone (3a–s). Compounds (5a–s) were obtained by refluxing (4a–k) and thiosemicarbazide in the presence of glacial acetic acid and ethanol. 1,3,4-Thiadiazole derivatives (6a–s) were obtained by cyclization of (5a–s) by treating with thiosemicarbazide and POCl3 or PPA. The physical data of all the synthesized compounds is shown in Table 1 [7].

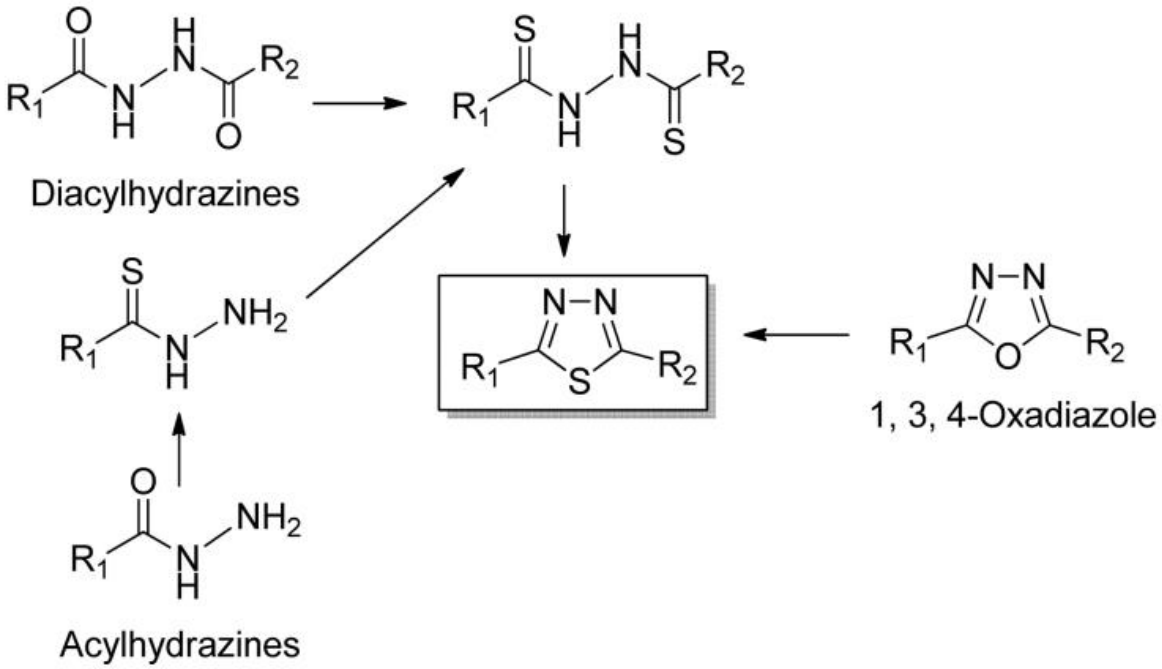
Table Number 01- Various Properties Specification of Synthesized Compounds [8-12]

Compound	R	Molecular formula	Yield (%)	Melting point (^{0}C)
6a	H	C20H20N6O2S2	42	262–267
6b	2-OCH3	C21H22N6O3S2	44	274–278
6c	2,4-di-Cl	C20H18Cl2N6O2S2	36	232–238
6d	3-NH2	C20H21N7O2S2	26	252–256
6e	3-NO2	C20H19N7O4S2	36	298–303
6f	4-OCH3	C21H22N6O3S2	42	268–272

VARIOUS METHOD OF SYNTHESIS-

5-methyl-1, 3-diphenyl-1H-pyrazole-4-carboxylic acid 2a-

Ethyl 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylate (1a, 0.306 g, 1.00 mmol) and 10% NaOH (10 mL) in MeOH (10 mL) were taken and refluxed for 4-6 hours. Once the reaction was complete (monitored by TLC), the reaction mass was reduced to half volume and then diluted with dilute HCl while stirring. The white solid thus separated was filtered, dried and dissolved in Na 2 CO 3 . A small portion of the sample was taken for analytical measurements and purified (recrystallized in hot EtOH), the remainder was used in the next step without purification. Benzhydrazides 3 were prepared by hydrazinolysis of the corresponding esters according to standard procedures. CAS Registry Numbers for Derivatives of Benzhydrazide 3 Used in the Production of 4: a) 613-94-5 b) 536-40-3 c) 636 97-5 d) 3290-99-1 e) 3619-22-5 [13, 14].



N'-benzoyl-5-methyl-1,3-diphenyl-1H-pyrazole-4-carbohydrazide 4a-

The N'-benzoyl-5-methyl-1,3-diphenyl-1H-pyrazole-4-carbohydrazide 4a was obtained when a solution of pyrazole-4-carboxylic acid (2a, 0.278 g, 1.0o mmol) in dry CH2Cl2 (5 ml) was cooled to 0 C and added ethyl-(N',N'-dimethylamino) propylcarbodiimide hydrochloride (EDC.HCl, 0.230 g, 1.2 mmol) and 1-Hydroxybenzotriazole (HOBt, 0.184 g, 1.2 mmol) under nitrogen atmosphere and stirred the reaction mixture at the same temperature for 0.5 hr. To this reaction mixture, benzohydrazide 3a (0.136 g, 1.0 mmol) was added and stirred at 0 C for 0.5 h [15, 16].

The reaction mixture was slowly brought to room temperature and stirring was continued for 8-12 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (225 ml) and the combined organic phases were washed with brine and dried over anhydrous sodium sulfate. Ethyl acetate was distilled off and the resulting residue was purified by column chromatography using hexanes: ethyl acetate (8:2) As eluent pure N'-benzoyl-5-methyl-1,3-diphenyl-1H-pyrazole-4 carbohydrazide 4a was obtained as a white solid in 72% yield (0.285 g). Single crystals suitable for X-ray analysis were obtained using the CH 3 CN solvent system [17].

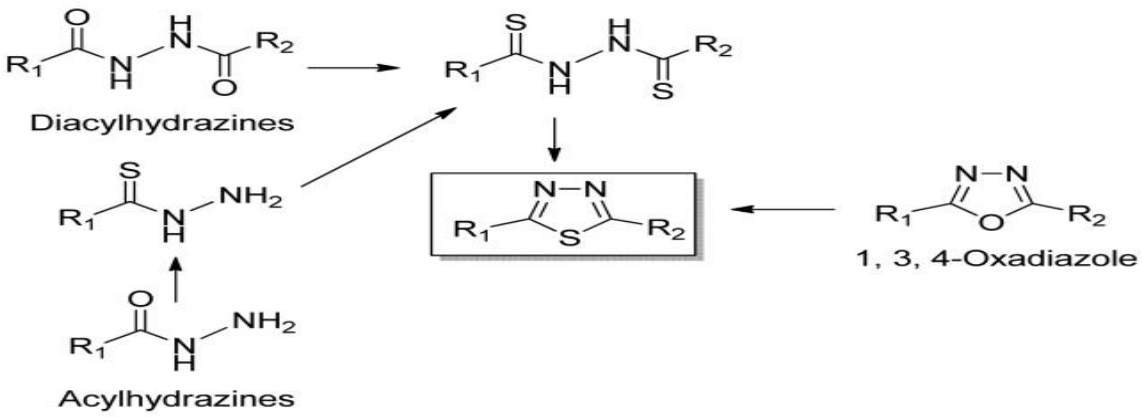
2-(5-Methyl-1,3-diphenyl-1H-pyrazol-4-yl)-5-phenyl-1,3,4-thiadiazole 5a-

A 1,4-dicarbonyl compound (4, 1.0 mmol) dissolved in THF (10 mL) was placed in a two-necked round-bottomed flask, Lawesson's reagent (0.405 g, 1.00 mmol) was slowly added, and incubated at 70 °C for 1 h. Refluxed. As the 2 h reaction progressed, the solution turned yellow or orange, indicating the progress of the reaction. After completion of the reaction (monitored by TLC), the solvent was evaporated to half the volume, then allowed to cool and the resulting viscous mixture was dissolved in CH2Cl2 and evaporated onto silica gel. Flash column chromatography on silica (200-425 mesh) gave the corresponding pyrazolyl-1,3,4-thiadiazole 5a in 86% yield. It was dried and recrystallized from chloroform to give a white amorphous solid. These reactions generate toxic H2S gas and must be performed in an efficient fume hood or well-ventilated area [18, 19].

5-Methyl-1,3-diphenyl-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-4-carboxamide 7a-

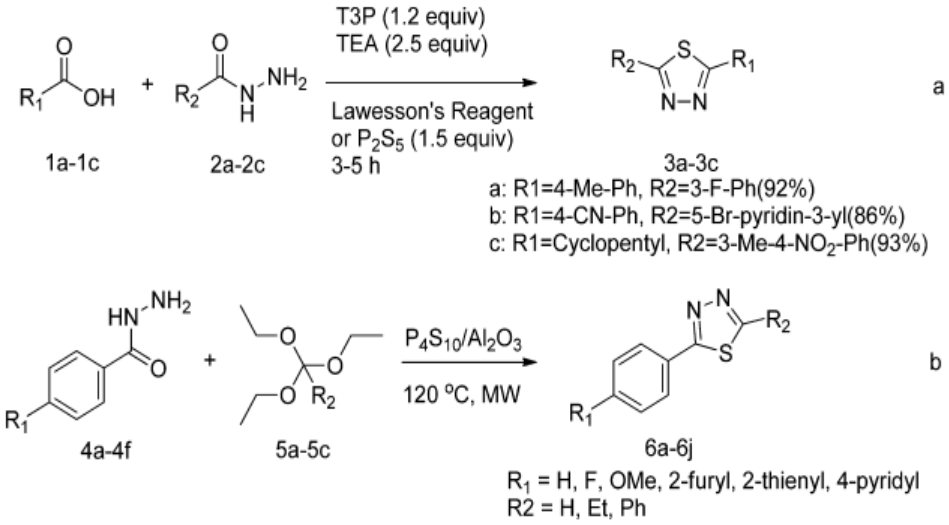
A solution of pyrazole acid (2a, 1 mmol) in dry CH2Cl2 (5 mL) was cooled to 0 C and added ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDCI) (1.2 mmol) and HOBt (1.2 mmol) under nitrogen atmosphere and stirred the reaction mixture at the same temperature for 0.5 hr. To this reaction mixture compound 2-amino-5-phenyl-1,3,4-thiadiazole (1 mmol) was added and stirred at 0 C for 0.5 h [20].

The reaction mixture was stirred for 6 to 8 hours while being gradually brought to room temperature. The reaction mixture was extracted with ethyl acetate (225 ml) after it was finished, and the combined organic phase was then washed with brine and dried over anhydrous sodium sulphate. The corresponding compound 7a was produced as a white powder with an 82% yield after ethyl acetate was distilled off and the residue resulting from this purification process was recrystallized in EtOH. With an EtOH/water (9.5:0.5) solvent system, a single crystal suitable for X-ray analysis was produced [21, 22].

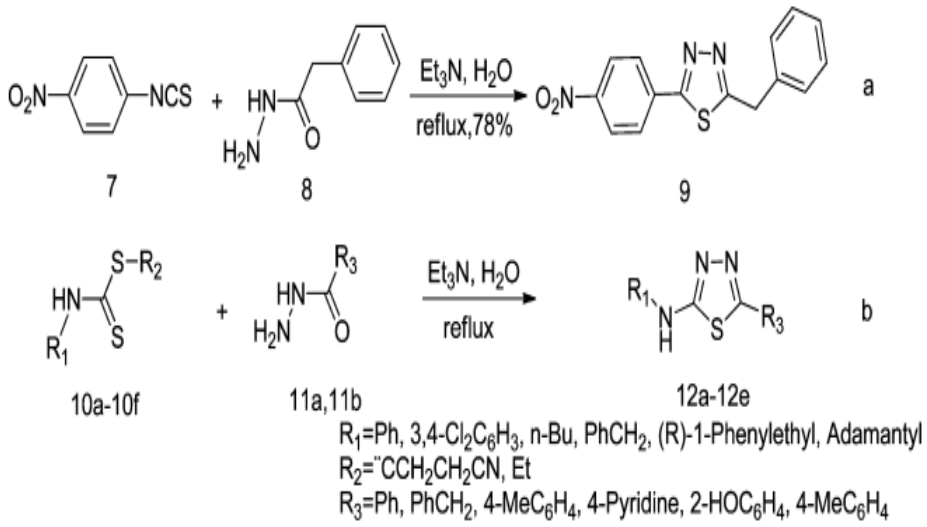


From Acid Hydrazides-

In the past decades, several kinds of one-pot syntheses of 1,3,4-thiadiazoles have been reported, which can avoid the tedious work of multistep syntheses. Among these methods, some are still conducted under harsh conditions whereas others have been improved. Augustine et al. report a one-pot synthesis of 1,3,4-thiadiazoles directly from carboxylic acids using propylphosphonic anhydride (T3P) (Scheme 3a)28 wherein it acts as both a coupling and a cyclodehydration reagent. In most cases, the reaction proceeded with high efficiency and broad functional group tolerance; however, the products were contaminated with a small percentage of byproduct 1,3,4 oxadiazole (3-5%) but could be easily purified by recrystallization or column chromatography [23, 24].



Synthesis of 1,3,4-Thiadiazoles Directly from Carboxylic Acids and Acid Hydrazides



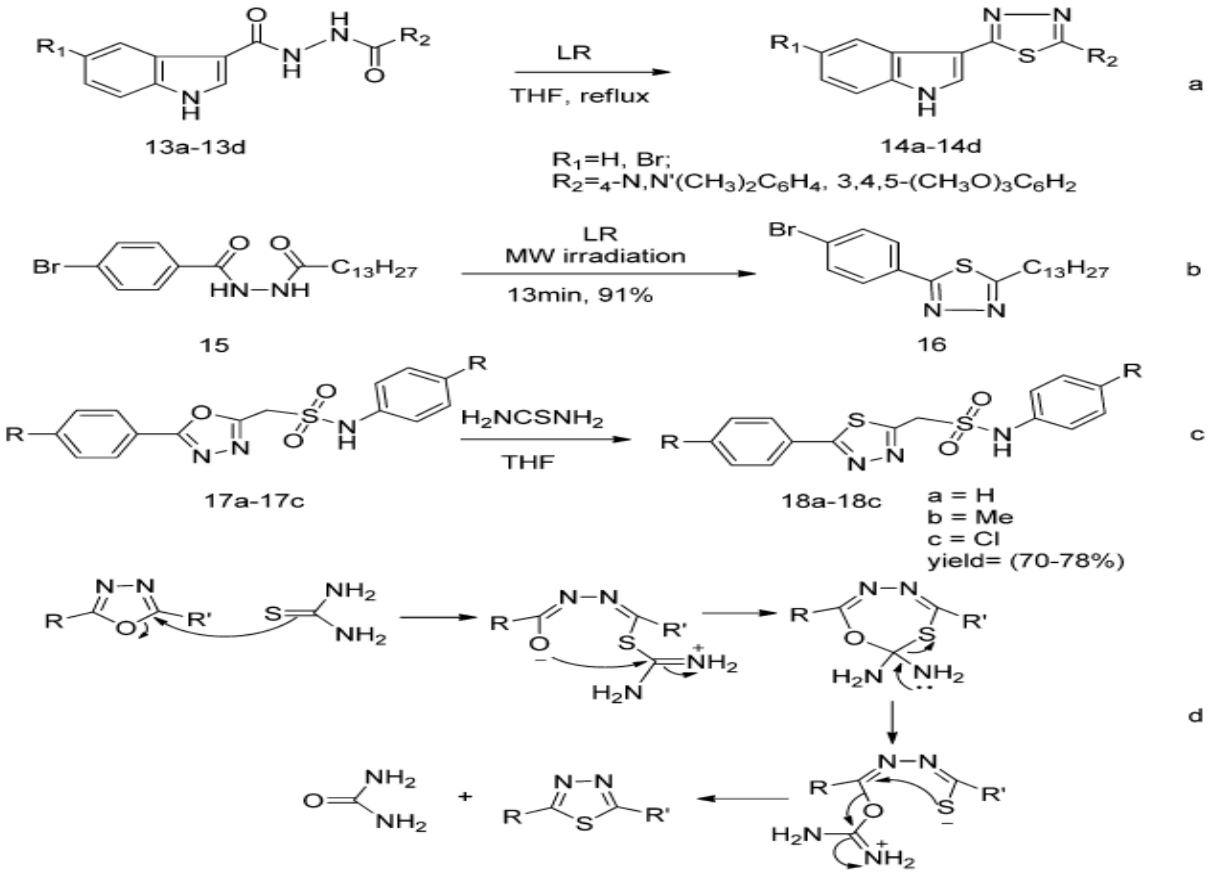
Synthesis of 1,3,4-Thiadiazoles from Acid Hydrazide and the Sulfur Reagents

From Diacylhydrazines-

The production of 1,3,4 thiadiazoles is frequently and easily accomplished through the cyclization of N,N′- diacylhydrazines. Many chemists have thoroughly studied this technique, which uses phosphorus sulfides (specifically, P2S536 and Lawesson's reagent) in solvents like DMF, CH2Cl2, THF, dioxane, and PhMe. Recent publications have frequently reported on solvent less synthesis by microwave radiation [25].

Thionation of diacylhydrazines 13a–13d by Lawesson's reagent LR followed by oxidative cyclization in different solvents (tetrahydrofuran, toluene, dioxane, xylene) afforded indolyl-1,3,4-thiadiazoles 14a–14d, and conventional methods for the synthesis of thiadiazoles in solvents are usually performed with long reaction times at high temperatures, low yields, many by-products, anhydrous hydrocarbon solvents, and sulfurizing reagents, making the process Make it environmentally friendly and Unsafe [26].

In contrast, solvent-free reactions under microwave irradiation could possibly overcome these shortcomings. You can achieve less pollution, lower costs, and easier processing and handling. The use of microwave radiation as an unconventional energy source has proven to be highly advantageous in this field. N-Acylation of 4-bromobenzohydrazide with myristoyl chloride gave the asymmetric N,N'- diacylhydrazine 15, which was cyclized to the corresponding thiadiazole 16 in 91% yield in 13 minutes. However, the procedure using Lawesson's reagent under solvent-free conditions using microwave irradiation yields a mixture of by-products along with the desired thiadiazole [27].



REACTIVITY AND SYNTHETIC APPLICATION OF 1,3,4-THIADIAZOLE-

Like most azoles, thiadiazoles are very weak bases due to the inductive effect of the extra heteroatom. Unsubstituted 1,3,4-thiadiazole rings with pronounced aromaticity cannot be readily nucleophilically substituted, and electrophilic substitution at carbon is limited to Although virtually unknown, substituted thiadiazoles are susceptible to nucleophilic attacks on carbon atoms, including elimination. Depending on the tautomerism of the substituents at the C-2 or C-5 positions, the ring nitrogen atom undergoes electrophilic attack leading to 1,3,4-thiadiazolium salts or 1,3,4-thiadiazole 2(3H) [28, 29].

Those who can prepare. Electrophilic attacks on ring sulfur atoms are rarely seen. As a result, the reactivity of 1,3,4-thiadiazoles arises from a nucleophilic center at the nitrogen atom of the ring and an electrophilic center at the carbon of the CN bond. Additional reactivity may arise from the transformation of substituents attached to C2/5. Therefore, 1,3,4-thiadiazoles are versatile reagents for synthesizing various compounds. Several types of 1,3,4-thiadiazole derivatives are named as shown. Tautomerism in 1,3,4-thiadiazoles is exhibited primarily by thione-thiol or aminoimino transformations at the C-2 or C-5 positions. The thiadiazole heterocycle can be preserved or modified depending on the attack target [30].

Intramolecular rearrangements or electrophilic substituents on the N atom form 1,3,4-thiadiazolines and 1,3,4-thiadiazolidines, which are also introduced.Protonation and alkylation or acylation at ring nitrogen atoms to form thiadiazolinium salts or 1,3,4-thiadiazol-2(3H)-ones can be classified in Section 3.1. Section 3.2 contains the main reactions at ring carbon atoms, grouped by various common leaving groups. Heterocyclic substituents on the thiadiazole ring to prepare imidazothiadiazoles and other heterocyclic compounds are described in Section 3.3. Metal complexes and polymer chemistry are introduced in section 3.4.

The last two sections focus on ring-opening reactions and various other reactions. Following the discovery of the carbonic anhydrase inhibitor acetazolamide AAZ, the synthesis and biological activities of many 1,3,4-thiadiazoles have been reported. Many of these derivatives have, for example, B. herbicidal, antiviral, antiparasitic, antituberculous, anticonvulsant, analgesic and antisecretory activity. In addition, much interest has been directed to the antibiotic (including antibacterial and antifungal), anti-inflammatory and anticancer activities exhibited by other heterocyclic-containing compounds [31].

Antibiotic Activity-

1,3,4-thiadiazoles have been reported to exhibit broad antibacterial activity. The thiadiazole ring generally acted as a scaffold to bind various pharmacophore agents that also possessed similar antibacterial activity via multiple reactive sites summarized above. Known pharmacophores include quinolines, pyrazoles, triazoles, piperines and imidazolines, which have been reported to exhibit various biological activities [32].

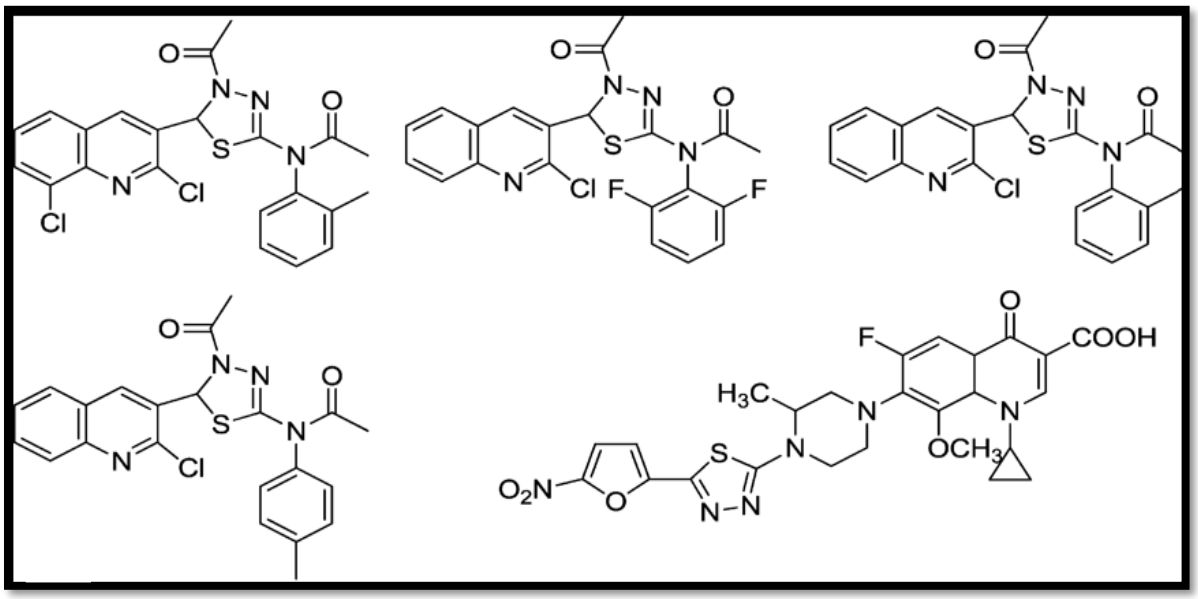


Figure Number 02 - 1, 3, 4-Thiadiazole Derivatives Having Antibiotic Activity

In addition, benzylthio and benzylsulfonyl-1,3,4-thiadiazolyl moieties attached to the N-4 hydrogen atom of the piperazinyl group of norfloxacin, ciprofloxacin, and enoxacin inhibited their respective parental Equal or more potent than drugs. 108b Furthermore, a hybrid of nitroarylthiadiazole and gatifloxacin showed potent inhibitory activity against Gram-positive bacteria compared to the reference drug gatifloxacin [33].

104h Several anti-H. pylori agents have also been synthesized. It exhibited stronger antibacterial activity against H. pylori than metronidazole 89 and several acetazolamide-AAZ derivatives mentioned, and hpCA (H. pylori, essential for acid acclimation and pathogensurvival).Unlike 92d hpCA, another β-CA from Brucella suis, Brucella suis CA, was targeted for antibacterial activity and treated with other acetazolamide sulfonamide/sulfamate derivatives. CA is a very important therapy for many diseases, so we will summarize them separately later [34].

Derivatives of 1,2,4-triazole and 1,3,4-thiadiazole have condensed nuclei, and 1,3,4-thiadiazole-oxazolidinone hybrids have been consistently reported to have beneficial antibacterial activity. Triazolo-1,3,4-thiadiazole 60e, bearing ethyl, phenyl and p-tolyl groups, showed remarkable inhibitory activity that could be attributed to the presence of electron-donating ability to condensation nuclei [35].

Moreover, 60f with substituents at the 6th and 3rd positions was more effective, probably due to electron induction effects. Compounds 69a-69h showed higher activity against Gram-positive bacteria than currently used antibiotics (ampicillin and cefuroxime), some of which may be comparable to vancomycin [36].

ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY-

Inflammation is part of a complex non-specific immune response of vascular tissue to noxious stimuli by several different types of complex triggering mechanisms. It is considered a mechanism of the immune response, playing a central role in the organism's self-defense and initiating the healing process. However, not all inflammatory responses are positive. Some inappropriate ones are even fatal. Inflammation is therefore viewed as a positive response to injury on the one hand, but an essentially pathological phenomenon on the other. Common anti-inflammatory and analgesic drugs include steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immune selective anti-inflammatory derivatives, herbs, and some diet foods [37].

In this regard, applications of 1,3,4-thiadiazole derivatives are focused on NSAIDs and steroids. NSAIDs act as a class of classical treatments for inflammation and pain by inhibiting cyclooxygenases, key enzymes in prostaglandin (PG) biosynthesis from arachidonic acid (AA). Increase. There are two types of COX enzymes, COX-1 and COX-2. COX-1 is generally thought to be a constitutive enzyme involved in the physiological production of PGs, providing maintenance functions such as gastric cytoprotection, whereas inducible COX-2 mediates inflammation [38].

Commonly used NSAIDs are non-selective COX inhibitors such as aspirin, ibuprofen, fenbufen, diclofenac sodium, indomethacin, and the COX-2 inhibitors celecoxib, etoricoxib, meloxicam, and other similar derivatives. Syntheses or modifications to generate optimized 1,3,4-thiadiazole anti-inflammatory compounds are continually being reported. Most of them are current clinical drugs modified with 1,3,4-thiadiazoles to improve their performance [39].

Modifications primarily focus on two aspects of the carboxylic acid moiety or heterocyclic nitrogen ring to reduce the potential for ulceration, a common side effect of NSAIDs, and to retain anti-inflammatory activity [40].

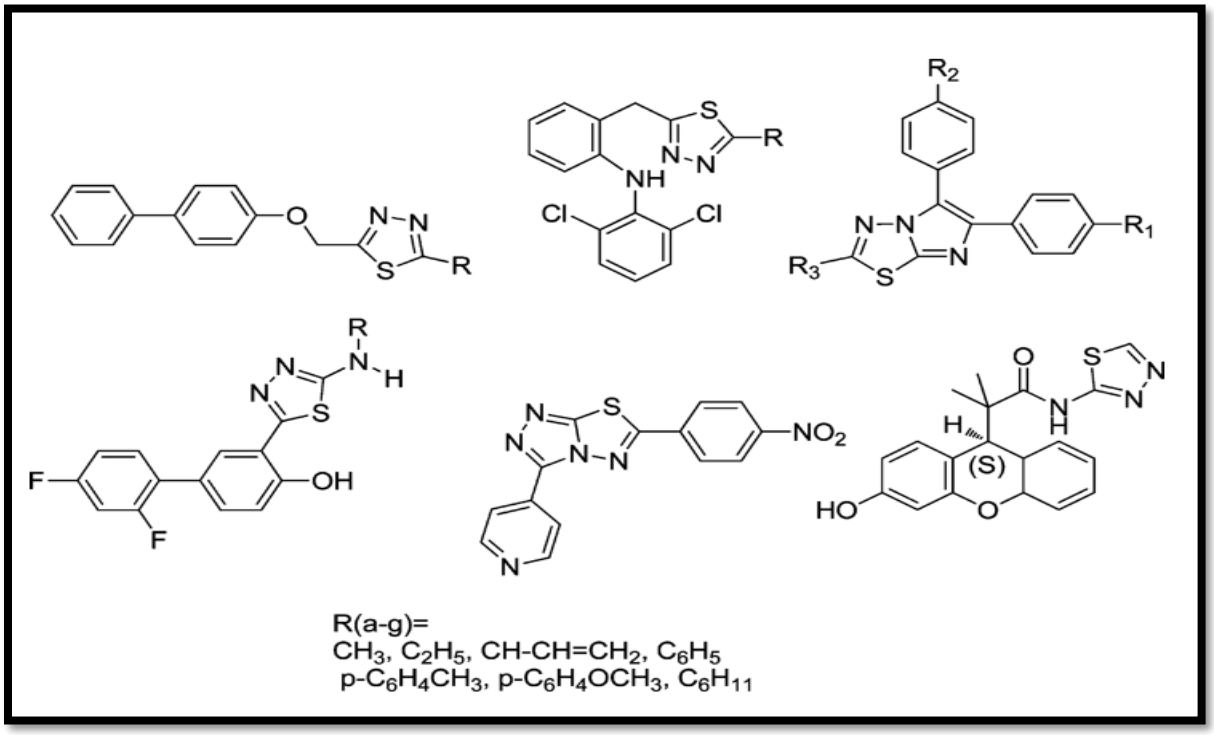


Figure Number 03- 1,3,4-Thiadiazole Derivatives Bearing Anti-Inflammatory and Analgesic Activity

Conclusion-

Thiadiazole rings are present in compounds with a variety of biological activities. Among the various isomers of thiadiazoles, 1, 3, 4-Thiadiazole derivatives have been the most studied due to their breadth of the spectrum of pharmacological activity. only one Minor pharmacological effects of 1,3,4-thiadiazoles Derivatives are currently in clinical use (e.g. antibacterial activity and carbonic anhydrase inhibitory activity), Substitution at the thiadiazole ring is a difficult approach Acquiring funds with increased efficacy and lower toxicity. Cytostatic properties of 2-amino 1, 3,4-thiadiazole and The trypanosomal properties of Megazol prove this Biological potential of 2-amino-1,3,4-thiadiazole moieties. A literature review reported the antibacterial activity of substituted 2-amino-1,3,4-thiadiazoles, 2-amino-1,3,4-thiadiazoles are unique templates with significant medical utility.

Conflicts of interest-

There are no conflicts of interest or disclosures regarding the manuscript.

Acknowledgment-

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