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Review Article

Various of Chemical and Pharmacological Applications of 1,3,4-Thiadiazole and It's Derivative

Dr. Jaafar Sataar Shia[1*], Marwan S. Ibrahim[1], Asmaa Safwan Al-Darraji[1]

[1]Al- Farabi University College, Department of Pharmacy, Baghdad, Iraq

***Corresponding Author:** Dr. Jaafar Sataar Shia
Al- Farabi University College, Department of Pharmacy, Baghdad, Iraq
Email- jaafar.shia@alfarabiuc.edu.iq

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Abstract: 1,3,4-Thiadiazole is a heterocyclic compound that has been widely studied for its diverse pharmacological activities. The compound is synthesized using different methods, including cyclization of linear organic derivative. The compound has been shown to exhibit various bioactivity, including its property as anticancer toward human cancers, antibacterial, diuretic, antitubercular, antifungal, and leishmanicidal agents, additionally, 1,3,4-thiadiazole derivatives have been shown to influence the central nervous system, displaying anti-inflammatory, anticonvulsant, analgesic, anxiolytic and antidepressant effects. 1,3,4-thiadiazole and its derivatives have been a subject of extensive research in the field of medicinal chemistry. These compounds exhibit a wide range of pharmacological activities, making them valuable candidates for drug development. The structural versatility of 1,3,4-thiadiazole derivatives allows for the fine-tuning of their pharmacological effects. The 1,3,4-thiadiazole moiety in a molecule enhances its bioactivity. Medicinal chemists have explored the SAR (Structure-Activity Relationship) of these derivatives to understand how different substitutions and modifications impact their pharmacological profiles. Synthesis and pharmacological activities of 1,3,4-thiadiazole and also its derivatives represent a vibrant area of research with promising implications for the progress of new therapeutic agents across various medical domains.

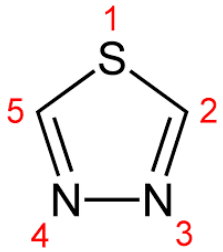
Keywords: 1,3,4-thiadiazole, synthesis, derivatives, pharmacological, bioactivity.

INTRODUCTION

Thiadiazole is a compound that can be classified as heterocyclic that contains two nitrogen atoms one sulfur atom and two carbon atoms in its five-membered ring with molecular formula ($C_2H_2N_2S$). There are different derivatives of thiadiazole, and they have diverse applications in the field of medicinal chemistry, agriculture, and materials science [1].

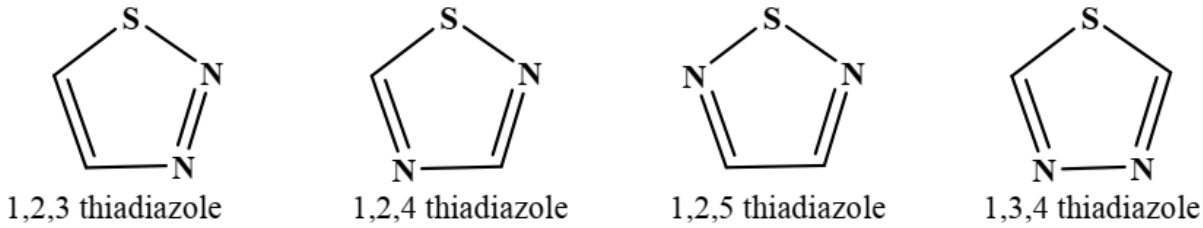
One prominent example is 1,3,4-thiadiazole, which has been investigated for its pharmacological properties. Research suggests that compounds based on 1,3,4-thiadiazole may exhibit a variety of biological actions, such as anti-inflammatory, anticancer and antimicrobial properties. Additionally, thiadiazole derivatives have been explored for their potential as agrochemicals [2].

Scheme 1 represent the five-ring structure of 1,3,4-thiadiazole [3].



Scheme 1: Chemical structure and formula of 1, 3, 4-Thiadiazole [3]

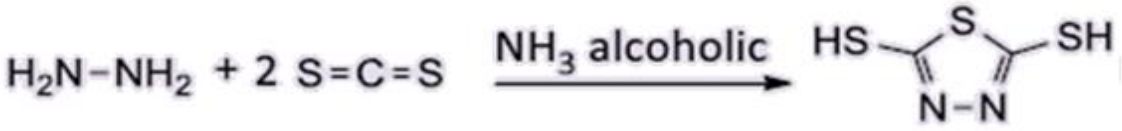
However, 1, 3, 4-Thiadiazole can be found in different isomers as depicted in scheme 2.



Scheme 2: 1, 3, 4-Thiadiazole isomers [4]

Synthesis of 1, 3, 4-Thiadiazole

The synthesis of 1,3,4-thiadiazole involves the cyclization of suitable precursors. One common method is the reaction between thiosemicarbazide and various electrophiles. Scheme 3 shows the general outlines of 1,3,4-thiadiazole synthesis [4].



Scheme 3: Common outline reaction of 1,3,4-thiadiazole synthesis [4]

However, below are the general outlines [4, 5, 6]:

Materials

1. Thiosemicarbazide
2. Electrophile (e.g., acid chlorides, isocyanates)

Procedure

Formation of Thiosemicarbazone

Reaction of thiosemicarbazide with an aldehyde or ketone is carried out to form the corresponding thiosemicarbazone.

Cyclization

Treating thiosemicarbazone with a dehydrating agent or cyclizing reagent to induce cyclization and form the 1,3,4-thiadiazole ring.

Isolation

Isolate the synthesized 1,3,4-thiadiazole through appropriate work-up procedures such as filtration or extraction.

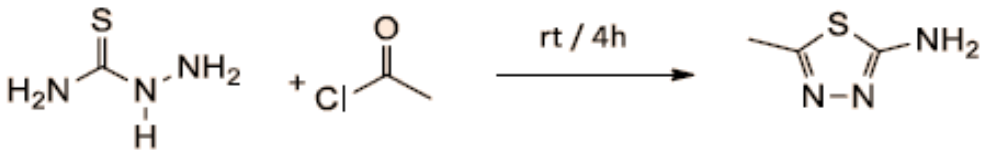
However, there are several methods for synthesizing 1,3,4-thiadiazole, including:

Cyclization of benzaldehyde derivatives

A sequence of compounds derived basically from 1,3,4-thiadiazole can be synthesized via cyclization of a variety of derivative of benzaldehyde with methoxycinnamic acid molecules and phenylthiosemicarbazide in phosphorus oxychloride [7].

Reaction of tetrazoles via hydrazonoyl chlorides:

Oligomers of 1,3,4-Thiadiazoles can be produced from hydrazonoyl chlorides and tetrazoles [8]. Scheme 4 [4].



Scheme 4: Production of 1,3,4-Thiadiazoles via acetyl chloride [4]

Full ot partial oxidation of thiadiazoles

1,3,4-Thiadiazoles can be produced by oxidation of thiadiazoles (full or partial reduction) [9].

Reaction of a carboxylic acid with thiosemicarbazide

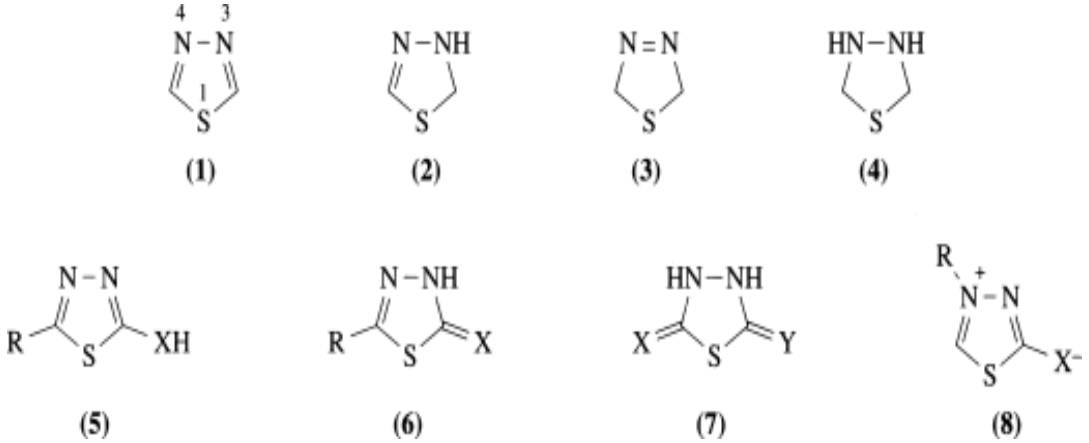
An innovative technique for 2-amino-1,3,4-thiadiazoles preparation, the reaction involves thiosemicarbazide with carboxylic acid in PPE presence [1].

Cyclization of glucosides

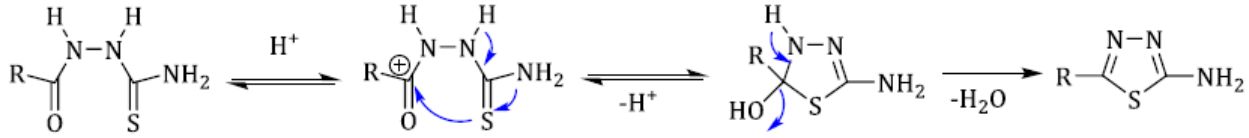
A chain of new 1,3,4-thiadiazole glucosides derivatives were produced via starting compounds (amino-1,3,4-thiadiazole and 5-d-glucose) [9, 10].

The choice of method depends on the starting materials and the desired product.

In 1996 Kornis [12] synthesize a eight of 1,3,4-thiadiazole compounds as shown in scheme 5 below, while scheme 6 shows the mechanism of the cyclization:

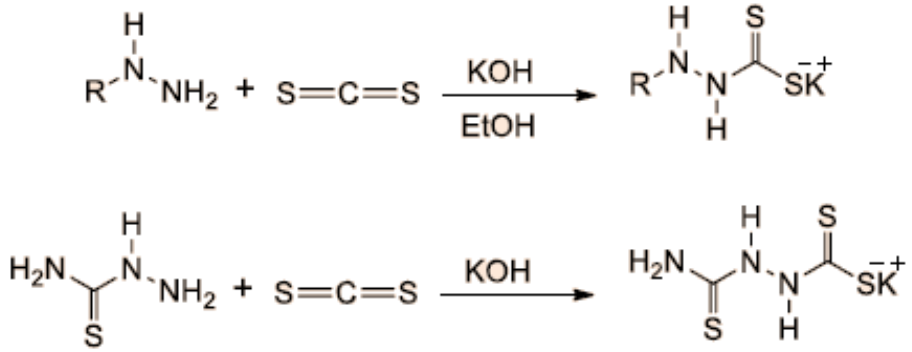


Scheme 5: Some derivatives of 1,3,4-thiadiazole [12]

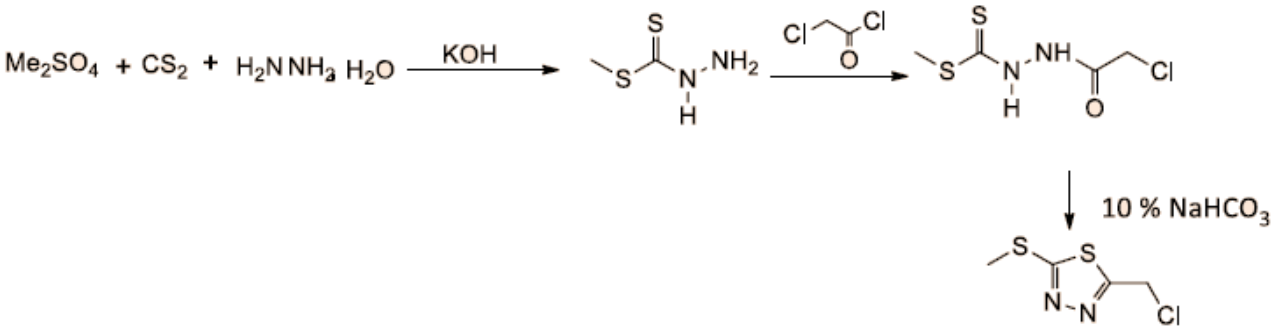


Scheme 6: Cyclization mechanism of 1,3, 4-thiadiazole [13]

1, 3, 4-thiadiazole can also be synthesized from hydrazine derivatives; scheme 7 shows the reaction scheme [4], while scheme 8 shows its synthesis from dithiocarbazates.



Scheme 7: Reaction diagram of 1, 3, 4-thiadiazole from derivatives of hydrazine [4]



Scheme 8: Synthesis diagram of 1, 3, 4-thiadiazole from dithiocarbazate [4]

Characterization of 1,3,4-thiadiazole

The heterocyclic 1,3,4-Thiadiazole compound contains two nitrogen, 2 carbon and sulfur atoms [14]. It is a adaptable pharmacophore enable the compound to display a an extensive diversity of biological behavior, including antimicrobial, anti-inflammatory, anticonvulsant, antioxidant, anticancer, and antifungal properties [15].

In recent years, there has been a growing fascination with the heterocyclic derivatives of this compound, showcasing their diverse utility in dyes, corrosion inhibition, agrochemicals, pharmaceuticals, and photographic materials [15].

The compound has been synthesized and characterized using various methods, including 13C-NMR and 1H-NMR spectroscopy, FT-IR, UV [7].

DFT calculations were conducted to explore the geometry and physiochemical properties of the structures. Additionally, the synthesis of 1,3,4-thiadiazole compounds involved the cyclization reaction between N-phenylthiosemicarbazide and 4-phenoxybutyric acid [16].

1,3,4-Thiadiazole derivatives find application as corrosion inhibitors and as agent in metal binding across various domains, including organic and analytical chemistry, as well as in industrial settings and medicine. Notably, 1,3,4-thiadiazole-2,5-dithiol compounds serve as ligands for binding transition metal cations [17].

A new chitosan variant, modified with 1,3,4-thiadiazole, has been created and examined for its antimicrobial capabilities. Additionally, its release behavior from film dressings has been thoroughly studied and characterized [18].

Properties of 1,3,4-Thiadiazole

Physical properties

3,4-thiadiazole is a colorless to light yellow solid crystalline has a melting point of 122-124°C [19], soluble in most organic solvents, while the density can be determined experimentally [19].

Chemical properties

Under generally stable conditions, 1,3,4-thiadiazole remains steady; however, exposure to strongly basic conditions may result in the fission of the ring, however 1,3,4-thiadiazole exhibits various chemical properties, and its reactivity is frequently affected with the existence of diverse functional groups. Below are some general aspects of its chemical properties [20-23]:

- **Electrophilic Substitution**: The nitrogen atoms in the thiadiazole ring can act as nucleophiles in electrophilic substitution reactions. This can involve the replacement of hydrogen atoms on the ring with other substituents.
- **Aromaticity:** The thiadiazole ring can exhibit aromatic character, and this aromaticity plays a significant role in its reactivity. Aromatic compounds often undergo different reactions compared to non-aromatic compounds.
- **Functionalization**: 1,3,4-thiadiazole can undergo various functionalization reactions, allowing for the introduction of different functional groups on the ring. This is important in the synthesis of derivatives with specific properties.
- **Metal Complex Formation**: The sulfur and nitrogen atoms in the thiadiazole ring can coordinate with metal ions, forming metal complexes. This property is often explored in the context of coordination chemistry.
- **Reduction and Oxidation Reactions**: The compound can undergo reduction or oxidation reactions depending on the reaction conditions and the substituents present. For example, the sulfur atom may be oxidized, and the nitrogen atoms may be reduced.
- **Ring Opening Reactions**: Under certain conditions, 1,3,4-thiadiazole can undergo ring-opening reactions leading to the formation of different chemical structures.

Biological properties

1,3,4-thiadiazoles display a variety of biological behaviors and were used in the fields of pharmaceuticals, such as antitumor agents, antihypertensive, and anticonvulsant agents [24],

1,3,4-thiadiazoles and their derivatives have been considered for their diverse biological activities, ranging from antimicrobial to anticancer properties. However, the specific biological properties can vary depending on the substituent's on the ring. Below are some general trends:

Antimicrobial Activity: Some 1,3,4-thiadiazoles have demonstrated significant antimicrobial activity against bacteria, fungi, and even some viruses. This makes them potential candidates for the development of antimicrobial agents [25, 26].

Anticancer Properties: Certain 1,3,4-thiadiazole derivatives have shown promising anticancer activity. They may act by inhibiting specific pathways involved in cancer cell proliferation or inducing apoptosis [27].

Anti-inflammatory Effects: Studies have suggested that some 1,3,4-thiadiazoles possess anti-inflammatory properties, which could make them interesting candidates for the development of anti-inflammatory drugs [28].

Antioxidant Activity: The presence of sulfur in the thiadiazole ring can contribute to antioxidant properties. Some derivatives have been investigated for their capability to hunt the free radicals and scavenge them [2, 29].

Antiviral Potential: Certain derivatives of 1,3,4-thiadiazole were invistigated for their antiviral activity, particularly against RNA viruses [30].

Cytotoxicity of 1,3,4-thiadiazole derivatives

1,3,4-Thiadiazole derivatives have been found to possess cytotoxic activity against cancer cells [27, 31], in particular, some studies have identified 1,3,4-thiadiazole derivatives as having cytotoxic activity towards MCF-7 cancer cell lines [32]. The mechanism of this cytotoxic activity is thought to be related to the ability of 1,3,4-thiadiazole derivatives to disrupt processes related to DNA replication [7, 33], additionally, 1,3,4-thiadiazole scaffolds have been explored as possible pharmacophore groups for antiviral activity [23, 34].

The pharmacological activities of 1,3,4 Thiadiazole

1,3,4-Thiadiazole derivatives have been found to exhibit a wide range of pharmacological activities, some of the pharmacological activities of 1,3,4-Thiadiazole derivatives include:

Antimicrobial Activity: Some 1,3,4-thiadiazole derivatives have demonstrated antimicrobial properties against bacteria and fungi, making them potential candidates for the development of antimicrobial agents [35].

Anti-inflammatory Effects: Certain derivatives of 1,3,4-thiadiazole have shown anti-inflammatory activity, suggesting their potential use in conditions involving inflammation [36].

Anticancer Properties: 1,3,4-thiadiazoles have been investigated for their anticancer potential. They may exhibit cytotoxic effects against cancer cells or interfere with pathways involved in cancer development [27, 37].

Antioxidant Activity: The presence of sulfur in the thiadiazole ring may contribute to antioxidant properties, making some derivatives potential candidates for combating oxidative stress [38].

Antiviral Potential: Some derivatives have been studied for their antiviral activity, particularly against RNA viruses [39].

Analgesic Effects: Certain 1,3,4-thiadiazole derivatives have shown analgesic (pain-relieving) effects in experimental studies [40, 41].

Anticonvulsant Activity: There is research indicating potential anticonvulsant properties of specific 1,3,4-thiadiazole derivatives [34, 42, 43].

Anti-diabetic Effects: Some studies have explored the potential of certain derivatives in managing diabetes [44, 45].

Neuroprotective Activity: Certain derivatives have shown neuroprotective effects, suggesting a potential role in conditions affecting the nervous system [46].

Hypolipidemic Activity: Some derivatives have been investigated for their ability to lower lipid levels in the blood, indicating a potential role in managing lipid-related disorders [47].

Anti-Alzheimer activity: Some studies suggest that certain derivatives of 1,3,4-thiadiazoles may exhibit neuroprotective effects, making them potential candidates for the treatment of neurodegenerative disorders like Alzheimer's disease [48, 49].

Antidepressant activity

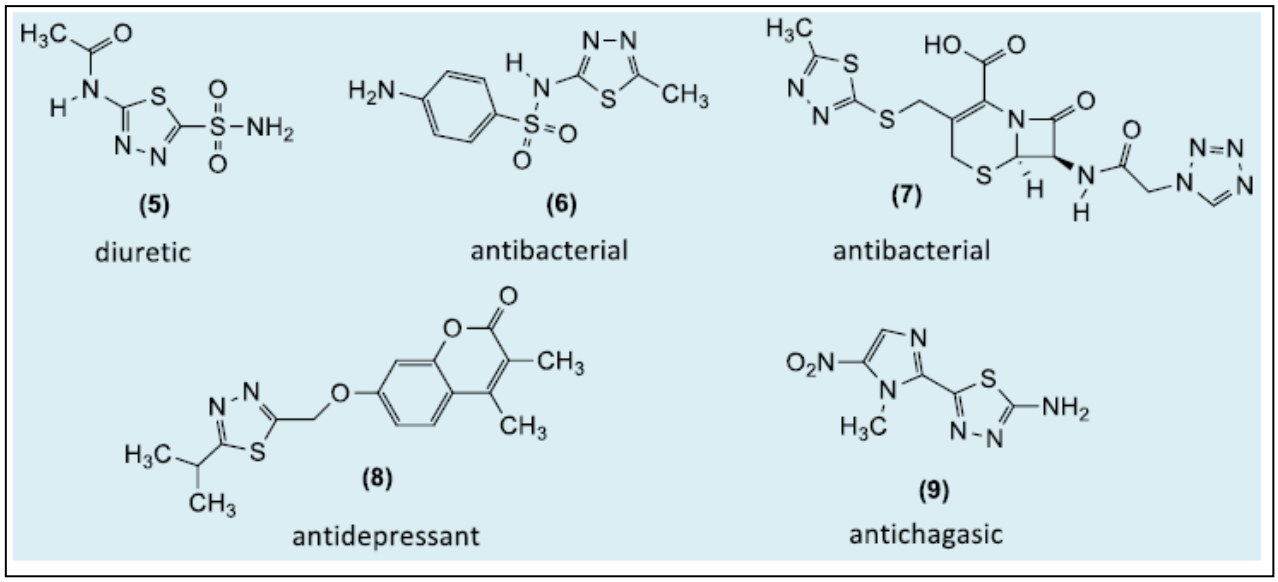
Recent studies have also shown that 1,3,4-thiadiazoles have antidepressant activity [50, 51], some key findings related to the antidepressant activity of 1,3,4-thiadiazoles:

- ✓ A study evaluated the central nervous system activity of 1,3,4-thiadiazole derivatives with varying substituent's in the thiadiazole moiety, however the findings indicates that some of the derivatives exhibited significant antidepressant activity in the tail suspension model [52].
- ✓ Another study investigated the activity as antidepressant of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives. The results showed that some of the derivatives exhibited significant antidepressant and anxiolytic activity [34].

Antitubercular Activity of 1, 3, 4

Studies have explored the anti-tubercular properties of 1,3,4-thiadiazoles. Oruc et al., in a 2004 [53, 14] research article, synthesized a range of 1,3,4-thiadiazole derivatives and analyzed their structure-activity relationship for anti-tuberculosis effects. Their findings indicated that the presence of a 5-nitrofuran-2-yl group at the C2 position and a 2,4-dichlorophenyl group at the C5 position led to the most potent anti-tubercular activity among the tested compounds. In 2016, Shkair *et al*., [41], investigated the anti-inflammatory and analgesic properties of 1,3,4-thiadiazoles through a comprehensive study that included molecular modeling, synthesis, and pharmacological evaluation.

Remarkably, some of the synthesized compounds demonstrated significant anti-tubercular activity, underscoring the potential of 1,3,4-thiadiazoles as effective agents against tuberculosis. Scheme 9 shows some of the bioactive compounds



Scheme 9: Example of some bioactive compounds of 1,3,4-thiadiazoles derivatives [4]

CONCLUSIONS

- 1,3,4-thiadiazoles is a compound that has five-membered and considered as heterocyclic which includes one sulfur atom, two atoms of nitrogen and carbon in its ring, with the molecular formula ($C_2H_2N_2S$).
- The derivatives of 1,3,4-Thiadiazole were widely studied for their diverse pharmacological activities.
- The production of 1,3,4-thiadiazole derivatives series involves different methods, including cyclization of suitable organic linear derivative, acylhydrazines, dithiocarbazates, thiosemicarbazides, and 1,3,4-thiadiazole.
- The compounds have been shown to exhibit properties as anticancer toward human cancers, antibacterial, diuretic, antifungal, leishmanicidal agents and antitubercular.
- Additionally, 1,3,4-thiadiazole derivatives have been shown to influence the central nervous system, displaying anti-inflammatory, anticonvulsant, , antidepressant, anxiolytic and analgesic effects.
- Recent studies have reported the antimicrobial activity of 1,3,4-thiadiazole isomers for potential structure.

Future Perspectives

As we venture into the future, the synthesis and pharmacological exploration of 1,3,4-thiadiazole and its series hold immense promise for the progress of new beneficial agents. The continual refinement of synthetic methodologies and the discovery of new pharmacological activities further solidify the significance of this heterocyclic scaffold in medicinal chemistry. Collaborative efforts between synthetic chemists and pharmacologists are essential to unlock the full potential of these compounds and pave the way for innovative drug development. In conclusion, the synthesis and pharmacological investigation of 1,3,4-thiadiazole derivatives stand at the forefront of cutting-edge research, providing a sneak peek into the promising potential that awaits in the realm of medicinal chemistry.

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