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Review

Unveiling the Versatility of Thiadiazole Compounds: Synthesis, Biological Activities and Promising Applications

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ABSTRACT

Thiadiazole compounds have gathered substantial focus as a result of their adaptable uses across a variety of domains, spanning agriculture to pharmaceuticals. This mini-review offers an extensive description of the synthesis, biological activities and potential applications of 1,3,4-thiadiazole derivatives. Starting with an exploration of their structural characteristics and classifications, the review emphasizes their extensive use in herbicides, insecticides and pharmaceuticals, especially in disease treatment. It underscores the pivotal role of sulfur atoms in enhancing thiadiazoles' lipophilicity, crucial for effective interaction with biological targets. Furthermore, the review highlights key examples of medicine with 1,3,4-thiadiazole moieties that are sold commercially, underscoring its importance across therapeutic applications. The subsequent sections delve into recent advances in synthesizing thiadiazole derivatives, showcasing innovative techniques like metal-mediated cyclization. The review also examines various studies investigating the biological activities of newly synthesized thiadiazole compounds against cancer cell lines, illustrating their promising cytotoxicity and DNA-binding capabilities. Overall, this mini-review provides valuable insights into the evolving landscape of thiadiazole research, illustrating its potential to drive advancements in drug discovery and development.

Keywords: Anticancer, Cytotoxicity, DNA and BSA, IC50, *In-vitro*, In-silico, Thiadiazole

1. Introduction

Extensive research into thiadiazoles commenced years ago, yielding a diverse array of compounds with multifaceted applications[1]. Within the realm of azole compounds, thiadiazoles constitute a notable subclass characterized by heterocycles of 5-membered ring structure being composed of 2 nitrogen and 1 sulphur atom[2]. The primary categories of thiadiazoles include (1,2,3, 1,2,4, 1,3,4 and 1,2,5)-thiadiazoles (**Figure 1**)[3]. Among these, 1,2,3-thiadiazoles find widespread use as herbicides, cross-linked polymer compounds and insecticide synergists[4]. Meanwhile, the pharmaceutical sector reaps significant benefits from 1,2,4-thiadiazoles and 1,3,4-thiadiazoles, as many chemicals within these ring systems serve as crucial components in various medicinal applications, including antifungal, antiviral, antibacterial, antimigraine, anti-inflammatory and antitubercular treatments[5]. This is due to the existence of sulphur included within the ring makes the compound more lipophilic, enabling it to easily get into cellular membranes and engage in interactions

with several biological objectives[6]. The most common type is 1,3,4-thiadiazole, which can be found in drugs like acetazolamide and cefazolin (**Fig.3**)[7].

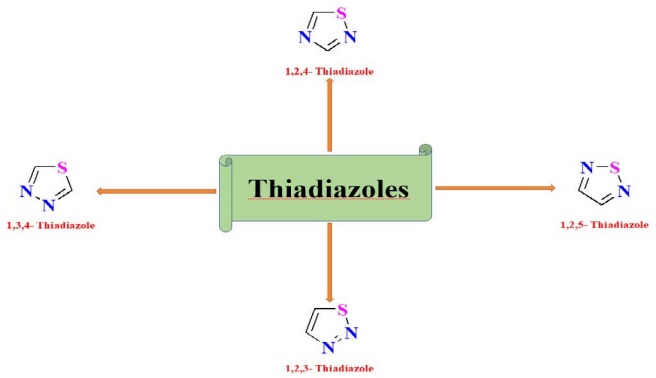


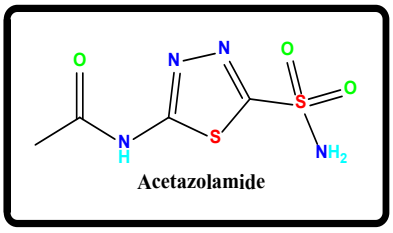
Figure1: Different forms of thiadiazoles.

Prior to the discovery of sulphonamides, 1,3,4-thiadiazole had been used as an antibacterial in the pharmaceutical industry[8]. Some of them were later employed as insecticides, lubricants, dyes, antitumor, anti-inflammatory and analytical agents (**Figure 2**)[9]. 1, 3, 4-thiadiazole family members exhibit biological activity, which is most likely brought about by the ring system's strong aromaticity, which promotes excellent in vivo consistency and typically it is non-toxic to humans and other vertebrates[10]. Different functional groups linked to the nucleus can interact with biological receptors to produce remarkable properties[11]. There are several methods for the synthesis of thiadiazoles, among them, metal-mediated cyclization thiosemicarbazones (TSCs) produce thiadiazole derivate with higher biological properties[12].

Figure 2: Various applications of 1,3,4-thiadiazoles.

Shapiro et al. conducted one of the earliest investigations in 1957, which saw the discovery of 1,3,4-thiadiazole variations' anticancer potential[13]. Their study revealed that 2-ethylamino-1,3,4-thiadiazole (EATDA) hindered the development of mammary adenocarcinomas in mice. Moreover, they observed that incorporating EATDA into a mixture of 8-azaguanine, deoxypyridoxine and testosterone augmented the anticancer effectiveness. The above discovery marked a significant milestone in thiadiazole synthesis, leading to the subsequent exploration of numerous derivative compounds in later years[14]. Importantly, many of these derivatives have become commercially available in the pharmaceutical field, serving as active drugs against various diseases. Notable examples include Cefazedone, Cefazolin, Megazol, Methazolamide, Acetazolamide and Sulphamethizole[15]. This review specifically focuses on recent innovations in the preparation and biological utilization of 1,3,4-thiadiazole compounds.

Researchers are particularly attracted to 1,3,4-thiadiazole compounds due to its remarkable biological functions and extensive range of therapeutic applications. This interest is further fueled by the substantial body of literature that underscores their potential in various medical fields **(Figure 3)**. The exceptional versatility of 1,3,4-thiadiazole derivatives has led to numerous discoveries by chemists, who have identified significant compounds with diverse uses. The following table provides a comprehensive overview of some of these notable compounds, detailing their specific applications and highlighting the breadth of ongoing research in this area. This robust exploration into 1,3,4-thiadiazole compounds demonstrates their significant promise and underscores their importance in the development of new therapeutic agents **(Table 1)**.



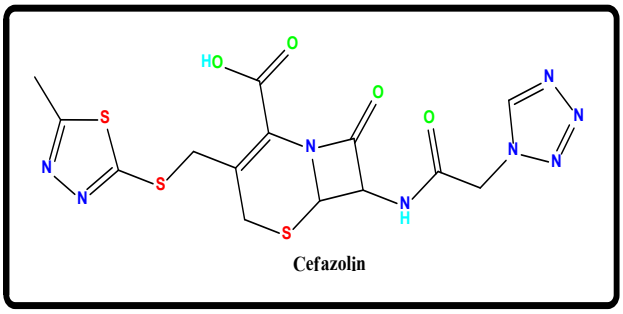
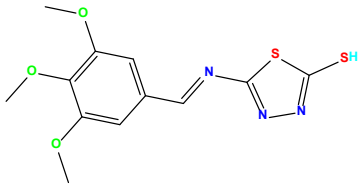
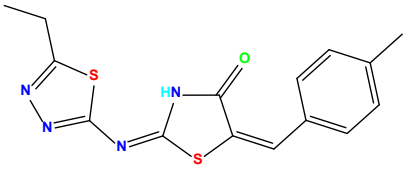
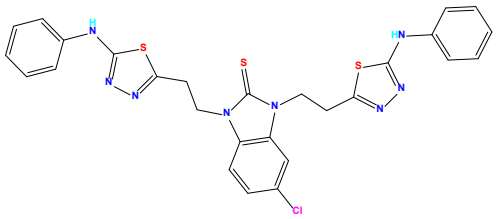
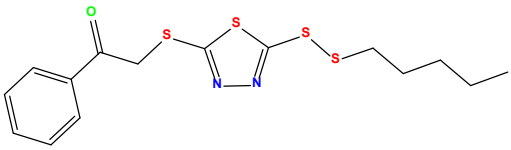
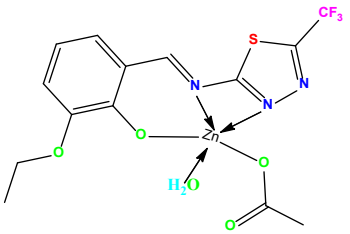
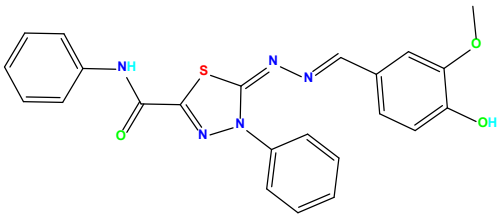
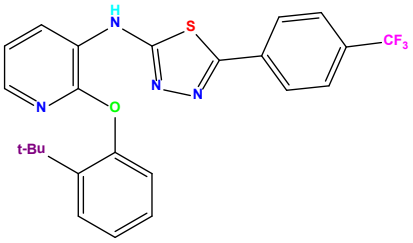
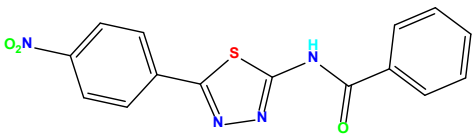
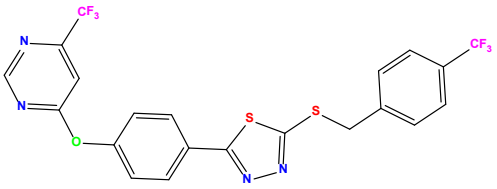


Figure 3: Structure of Acetazolamide and Cefazolin.

Table 1: Different potential applications of 1,3,4-thiadiazole.

SL.NO	Compound structure	Application	Reference
1		Anti-Convulsant Agents	Aliyu A *et al.*, 2021 https://www.researchgate.net/publication/353496797

2		Anti-Alzheimer Agents	Navidha Aggarwal *et al.*, 2022 https://doi.org/10.33263/BRIAC123.28002812
3		Anti-Tumor Agents	Neda Anastassova *et al.*, 2022 https://www.researchgate.net/publication/370220903
4		Antiproliferative Activity	Yang Liu *et al.*, 2022 https://doi.org/10.1080/17415993.2022.2071588
5		Anti-Diabetic Agents	Yogesh Deswal *et al.*, 2022 https://doi.org/10.1016/j.molstruc.2021.132266
6		Anti-Viral Agents	Huda R. M. Rashdan *et al.*, 2022 https://doi.org/10.1007/s11224-022-01985-1
7		Anti-Platelet Agents	Réjean Ruel *et al.*, 2013 http://dx.doi.org/10.1016/j.bmcl.2013.04.041
8		Anti-Tuberculosis Agents	Harun Patel *et al.*, 2019 https://doi.org/10.1016/j.ejmech.2019.01.073
9		Antifungal Activity	Nianjuan Pan *et al.*, 2022 10.3389/fchem.2022.922813

2. Discussion

The synthesis of 1,3,4-thiadiazole molecules (1–4) involved the interaction of phenyl thiosemicarbazide with methoxy cinnamic acid in the existence of phosphorus oxychloride was reported in 2022 by Hakan S. Sayiner et al[16]. With various bacteria strains, the antibacterial activity of compounds was screened and obtained to act as a inhibitor against Klebsiella pneumoniae and Staphylococcus hominis, even though substances 1, 3 and 4 acted as an inhibitors to Staphylococcus epidermidis and alpha Streptococcus haemolyticus. Additionally, UV-vis spectroscopic techniques investigated how the chemical interacted with calf thymus-DNA (CT-DNA)**(Figure 4)**.

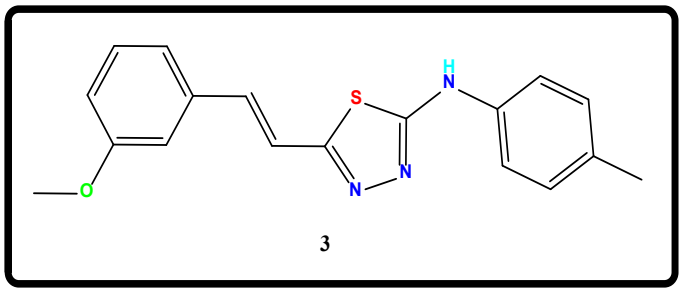


Figure 4: Structure of cinnamic acid-based 1,3,4-thiadiazole compound.

In 2023, VNV Palakkeezhillam et al developed novel heterocyclic TSCs and its cyclized forms for exploring its *in vitro* and *in silico* biological activities[17]. The compounds are 2 pyrene-based TSCs, PP1(pyrrolidine substituted) and PM1 (mopholine substituted) and their corresponding thiadiazole PP2 and PM2 picked up due to metal ($Mn(OCOCH_3)_{24}H_2O$) mediated cyclization. The cytotoxic properties of the synthesized compounds were tested against HepG-2 and T24 cancer, as well as Vero normal cell lines. The results showed that the thiadiazole compound PP2 exhibited effective cytotoxicity towards HepG-2 and T24 cells. The concentration of the compound needed to kill 50% of the HepG-2 and T24 cancer cells is 13.16 µM and 37.67 µM, respectively which is satisfactory when compared with Cisplatin (IC_{50} = 49.9 µM against HepG-2 and IC_{50} = >50 µM against T24). DNA/BSA binding studies also follow the same trend in biological activity and found that the thiadiazole compound PP2 shows significant interaction towards both DNA and BSA **(Figure 5)**.

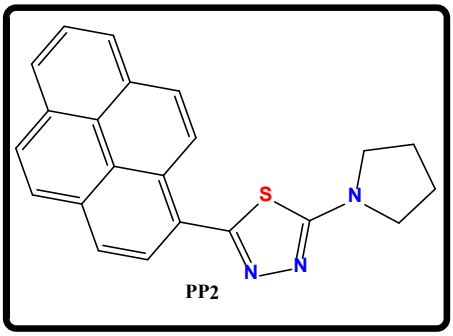


Figure 5: Structure of pyrene-based 1,3,4-thiadiazole compound.

A pair of TSCs of fluorene-2-carboxaldehyde (FM and FP) substituted with N-(4)-morpholine/pyrrolidine, along with its equivalent thiadiazoles (TDZs) (CFM and CFP), were generated in 2023 by Vishnu Narayanan Namboothiri Vadakkedath Palakkeezhillam et al[18]. The TDZs were discovered by surprise and may have been created by oxidative cyclization of the TSCs in one step using metal (copper). In the cytotoxicity assay, With half-maximal inhibitory concentration values of 12.00 and 24.80 µM, respectively, CFM exhibited the strongest efficacy against MCF-7 and T24 cancer cells. Conversely, (Vero) normal cell line showed minimal cytotoxicity (IC_{50} = 98.70 µM) when exposed to CFM. According to DNA binding experiments, CFM and CFP exhibit strong base pair intercalating interactions. From the BSA binding results, CFM binds to BSA more effectively than CFP and the molecules bind to bovine serum albumin at a distinct site of binding (n ~ 1)**(Figure 6)**.

Camelia Elena Stecoza et al reported many TDZs series and its chemical properties and possible benefits against cancer on different cells were examined in 2023[19]. By employing LoVo and MCF-7 cancer cells in both *in vitro* and in silico cell-based experiments, the anticancer potential was assessed. Viability of cells, proliferation, apoptosis and cell cycle examination were among the assays used to evaluate the chemicals' impact on the spread and lifespan of cancer cells. Several of the synthesized derivatives showed encouraging anticancer activity in the results, indicating that they could be used as lead compounds for future therapeutic development. After a 48-hour incubation, the novel amine-based 1,3,4-thiadiazol (2g) showed negligible harmful effects in the Daphnia test and superior anti-proliferative activities against LoVo and MCF-7 (IC_{50} = 2.44 and 23.29 µM respectively) **(Figure 7)**.

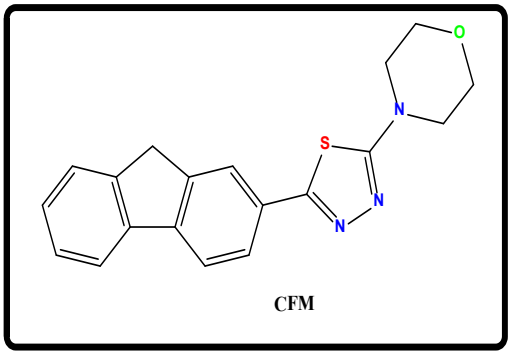


Figure 6: Structure of fluorene-based 1,3,4-thiadiazole compound.

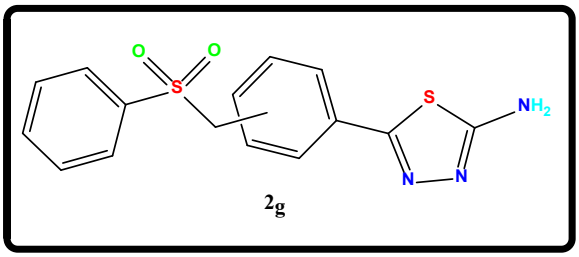


Figure 7: Structure of 5-[2-(Benzenesulfonylmethyl)phenyl]-1,3,4-thiadiazol-2-amine

From syringaldehyde, Vipin Manakkadan et al produced N(4)-substituted heterocyclic thiosemicarbazones (TSL1, TSL2) and described the cyclization of the thiosemicarbazones mediated by copper to create TDZs (TSL3, TSL4) in 2024[20]. TSL3 demonstrates the most effective cytotoxic behaviour, but not much more than cisplatin, against the A459, MCF-7 and HepG2 cancer cells. These results explore that Thiadiazoles have higher levels of cytotoxicity in comparison to TSCs. Using absorption and emission spectroscopy, the DNA binding experiment revealed that TSL3 exhibits more activity toward DNA. This is quantifiable, with values for K_b, K_q and K_{app} measuring 4.74 × 10^6 M^{-1}, 4.04 × 10^4 M^{-1} and 5 × 10^6 M^{-1}, respectively. Additionally, fluorescence spectroscopy-based investigations on BSA binding revealed that TSL3 has a higher affinity (1.64 x 10^5 M^{-1}) with bovine serum albumin **(Figure 8)**.

Likewise, several 1,3,4-thiadiazole derivatives with diverse modes of biological action are currently undergoing various stages of clinical trials, highlighting their therapeutic potential across a range of diseases (Table 2). One notable example is Megazol, a drug already available on the market for the treatment of gastrointestinal reflux disease, demonstrating the clinical relevance of this compound class. Additionally, in the Phase 1 clinical trial, the administration of litronesib in combination with

pegfilgrastim resulted in a partial response in twenty percent of patients with stable disease states and two percent of patients with advanced solid tumors. Further advancements in Phase 2 clinical trials include Telaglenastat, Filanesib, Litronesib and 2-amino-1,3,4-thiadiazole, which are being investigated for the treatment of renal cell carcinoma, myeloid leukemia, breast and lung and colon cancer, respectively. Beyond the investigational drugs, several 1,3,4-thiadiazole-based medications are already well-established in the market, such as Methazolamide, used for managing glaucoma and Sulphamethizole, employed in the treatment of urinary tract infections. These examples underscore the significant impact and broad applicability of 1,3,4-thiadiazole derivatives in modern medicine.

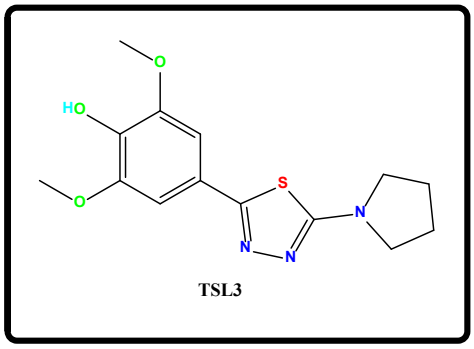
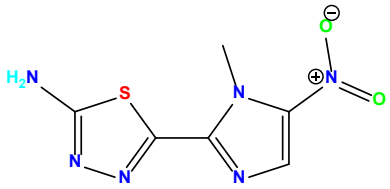
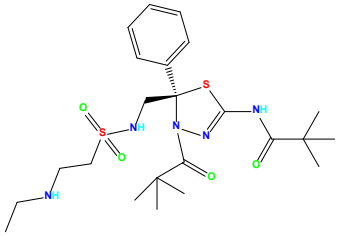
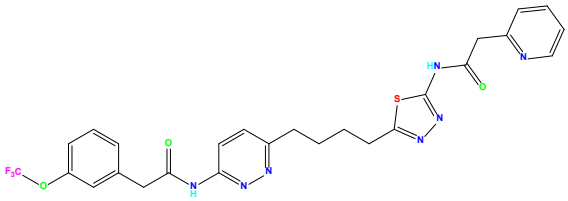
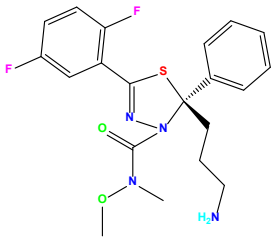
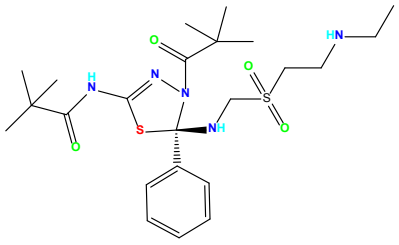
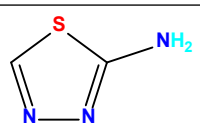
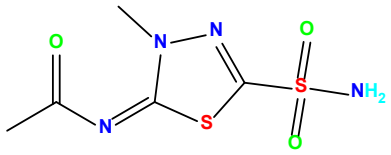
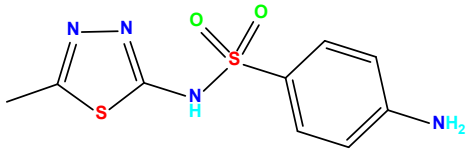


Figure 8: Structure of syringaldehyde-based 1,3,4-thiadiazole compound.

Table 2: Some 1,3,4-thiadiazole compounds and their current clinical trial status with diseases as the target.

S L . NO	Compound structure	Disease as target	Study phase
1		Gastrointestinal reflux disease	Available in market
2		Anti-tumor agent	Phase 1
3		Renal Cell Carcinoma	Phase 2
4		Myeloid Leukemia	Phase 2
5		Breast cancer Lung cancer	Phase 2
6		Colon cancer	Phase 2

7		Glaucoma	Available in market
8		Urinary tract infections	Available in market

3. Conclusions

To summarise, the investigation of thiadiazoles, specifically derivatives of 1,3,4-thiadiazole, offers a promising area of study with significant implications in various disciplines. These compounds are widely used in herbicides, insecticides and medicines and they play a crucial role in fighting diseases such as cancer. As a result, they continue to be the subject of intense scientific investigation. The unique structural features of thiadiazoles, endowed with sulfur atoms facilitating enhanced cellular permeability, underscore their therapeutic potential. Moreover, the remarkable stability and low toxicity of these compounds further bolster their appeal in medicinal contexts. Thiadiazole derivatives continue to be a primary focus in the study and development of pharmaceuticals, with a particular emphasis on their synthesis and characterization. Further research into innovative synthesis techniques and examination of their biological effects hold the potential to reveal additional therapeutic advancements, eventually promoting human health and well-being. Recent advances in understanding and using thiadiazole (especially 1,3,4-thiadiazole) molecules have been highlighted in this review.

4. Acknowledgments

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