



# Biological activity of oxadiazole and thiadiazole derivatives

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## Abstract

The 5-membered oxadiazole and thiadiazole scaffolds are the most privileged and well-known heterocycles, being a common and essential feature of a variety of natural products and medicinal agents. These scaffolds take up the center position and are the core structural components of numerous drugs that belong to different categories. These include antimicrobial, anti-tubercular, anti-inflammatory, analgesic, antiepileptic, antiviral, and anticancer agents. In this review, we mostly talk about the isomers 1,2,4-oxadiazole and 1,3,4-thiadiazole because they have important pharmacological properties. This is partly because they are chemical and heat resistant, unlike other isomers, and they can be used as bio-isosteric replacements in drug design. We are reviewing the structural modifications of different oxadiazole and thiadiazole derivatives, more specifically, the anti-tubercular and anticancer pharmacological activities reported over the last 5 years, as we have undertaken this as a core area of research. This review article desires to do a thorough study and analysis of the recent progress made in the important biological isomers 1,2,4-oxadiazole and 1,3,4-thiadiazole. This will be a great place to start for future research.

## Key points

- Five-membered heterocyclic compound chemistry and biological activity recent survey.
- Synthesis and pharmacological evolution of 1,2,4-oxadiazole and 1,3,4-thiadiazole are discussed in detail.
- The value and significance of heterocyclic compounds in the field of drug designing are highlighted.

**Keywords** Anticancer · Anti-tubercular · Heterocycles · Oxadiazole · Pharmacological activities · Thiadiazole

## Introduction

It ought to be the top priority of researchers to identify and develop new and better pharmaceuticals, pesticides, and insecticides, and to do so, they follow natural models. The pharmaceutical products with biological activity that resemble natural products are called heterocycles (Sompalle and Roopan 2017). Heterocyclic compounds are cyclic compounds in which another atom replaces one or more carbons in the ring (Ram et al. 2019). Thus, the compounds comprising heteroatoms like nitrogen, oxygen, sulfur, phosphorous, silicon, boron, and the like make the heterocyclic compounds one of the most prevalent classes of organic

compounds (Roopan and Palaniraja 2016). They are persistent in biology and do play an integral function in medicinal chemistry, particularly in drug design and synthesis. In nature, heterocycles are broadly distributed; many of them exist in the flora regarded as alkaloids, and a few of them are used in historical instances as medicinal agents (Paulo et al. 2018; Cascioferro et al. 2019).

## Importance of heterocyclic compounds in medicinal chemistry

Heterocyclic compounds possess a broad spectrum of pharmacological activities, and for this reason, it continues to yield new therapeutic agents. The biological activity exhibited by the heterocycles is owed to their potential to bind with various enzymes either to the active sites or with enzyme pocket structures through a broad range of intra-molecular interactions such as van der Waals and hydrophobic forces, hydrogen bonding, and metallic coordination bonds, making them an important scaffold in

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medicinal chemistry (Pearce 2017). A massive variety of naturally occurring substances, such as hemoglobin, chlorophyll, pyrimidines, and purine bases and enzyme co-factors, belong to the family of heterocycles, which are integral to dwelling cells (Arunachalapandi and Roopan 2021; Sompalle and Roopan 2016). They are almost critical at every step of many biochemical processes and processes that are important to life. Heterocyclic compounds, especially those containing nitrogen, sulfur, and oxygen heteroatoms, are the most important class of compounds in the pharmaceutical and agrochemical industries, in which heterocycles comprise around 60% of the drug substances. Five-membered nitrogen- and oxygen- or sulfur-containing heterocycles such as oxazolidine, isoxazolidine, oxazole, isoxazole, thiazolidine, isothiazolidine, thiazole, isothiazole, oxadiazole, and thiadiazole are important structural motifs and are present in a vast number of biologically active compounds. These heterocycles make up the core structure of numerous drugs and are therefore of great interest in the pharmaceutical industry (Manjupriya and Roopan 2021; Li et al. 2013).

The following few sections cover the review of the 5-membered oxadiazole and thiadiazole heterocycles as their derivatives continue to gain interest from researchers, being used as bio-isosteric replacements in drug designing and widely studied for their utility in agrochemical and material science (Sauer et al. 2019; Kumari et al. 2020). The main objective behind this review article was not to cover a broad spectrum of topics. Instead, this article focuses more specifically on recent advances in the anti-tubercular and anticancer pharmacological activities of isomers 1,2,4-oxadiazole and 1,3,4-thiadiazole. Because of their high chemical and thermal strength, these two isomers possess the potential to be an essential part of the pharmacological sector. During our literature review, we attempted to cover a large number of related research articles in order to make it as comprehensive as possible. We included the most recent articles to keep it up-to-date. This review article seeks to conduct an in-depth study and analysis and provide a comprehensive report in the form of detailed technical discussion and even information in the form of figures. Overall, this will serve as a great starting point for future research in this sector.

### Therapeutic targeting of the hallmarks of tuberculosis (TB)

Tuberculosis, a communicable disease caused by the bacillus *Mycobacterium tuberculosis*, is one of the top 10 causes of death. At the first-ever UN High Level Meeting in September 2018, at its headquarters in New York, heads of state came together and made strong commitments to end TB. The title of the meeting was “United to End TB: An Urgent Global Response to a Global Epidemic” (WHO, Global Tuberculosis Report 2018).

In the field of anti-TB drug discovery, although many drugs are currently in use, the developments of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) and extremely drug-resistant TB (XDRTB) are the two major challenges. Currently, the development of an effective anti-TB drug, which will have a short treatment duration, be simpler, be less toxic, be drug-resistant, and have minimal drug-drug interactions, is the current requirement in the field (Ginsberg 2010).

For TB, the main targets of choice for the researchers are mycobacterial transcriptional repressor (EthR), enoyl-ACP-reductase (InhA), enzyme decaprenylphosphoryl- $\beta$ -D-ribose 2'epimerase (DprE1), shikimate kinase, alanine racemase, etc. The hallmarks of TB are represented in Figure S1 (Zumla et al. 2014). The current anti-TB-drug pipeline contains new chemical scaffolds and a variety of targets, including the 1,2,4-oxadiazole and 1,3,4-thiadiazole, as both the nuclei are able to coordinate well with these targets.

### Therapeutic targeting of the hallmarks of cancer

Researchers have produced a vast quantity of records on proteins and muted genes towards the development of cancer cells. Recently, many environmental aspects that are associated with mutations at a genetic level have been reported. To determine the efficacy of gene expression and defective proteins, as well as to detect novel most cancers biomarkers, a one-of-a-kind molecular method has been used.

It can be beneficial to deal with most cancers and decrease associated complications. Although it appears that many aspects of epigenetic remain unknown, various studies to ascertain the mechanisms and their relationship collectively to the development and spread of quite a number of diseases, mainly most cancers, are continuing. Lack of specificity or low therapeutic index, drug resistance, and poor ADME profile are a few of the challenges in anticancer drug discovery. Hallmarks of cancer are represented in Figure S2 (Hanahan and Weinberg 2011).

### Oxadiazole

#### Introduction to 1,2,4-oxadiazole and its biological importance

As mentioned earlier, growing interest is noted among medicinal chemists for oxadiazole (**1**) due to its biological activity and being used as a privileged scaffold in drug design with various therapeutic applications (Kumar et al. 2011). While the combination of hydrophilic and electron donor properties makes the oxadiazole ring biologically active, the thermal and chemical resistance provides metabolic stability. In drug discovery and development,

1,2,4-oxadiazoles are widely used as bio-isosteric replacements for ester, amide, and acid compounds to take care of associated metabolism-related liabilities with these functional groups (Saunders et al. 1988; Patani and Voie 1996).

In a few clinical trials, 1,2,4-oxadiazole-based medicines have been found to be effective. The 1,2,4-oxadiazole scaffolds containing marketed drugs are reported in Fig. 1, which underlines their significance in the discipline of medicinal chemistry (Kleeman et al. 2001).

Oxolamine (2) majorly exhibits anti-tussive and anti-inflammatory activity. Irrigor (3) shows anesthetic and vasodilator activity, while Libexin (4) indicates anti-tussive activity. Ataluren (5) is used in the treatment of cystic fibrosis (Bora et al. 2014). The 1,2,4-oxadiazole ring binds and inhibits receptors such as 5-hydroxytryptamine1B/D (5-HT1B/D) (Selkirk et al. 1998) 1,2,4-oxadiazole exhibits an array of pharmacological activities such as anti-inflammatory (Nicolaides et al. 1998), anticancer (Matsumoto et al. 1994; Zhang et al. 2005), anti-TB, anti-tussive, and anti-tubercular (Upare et al. 2019).

Oxadiazoles have also been used within the area of material science due to their inherent characteristics to excellent

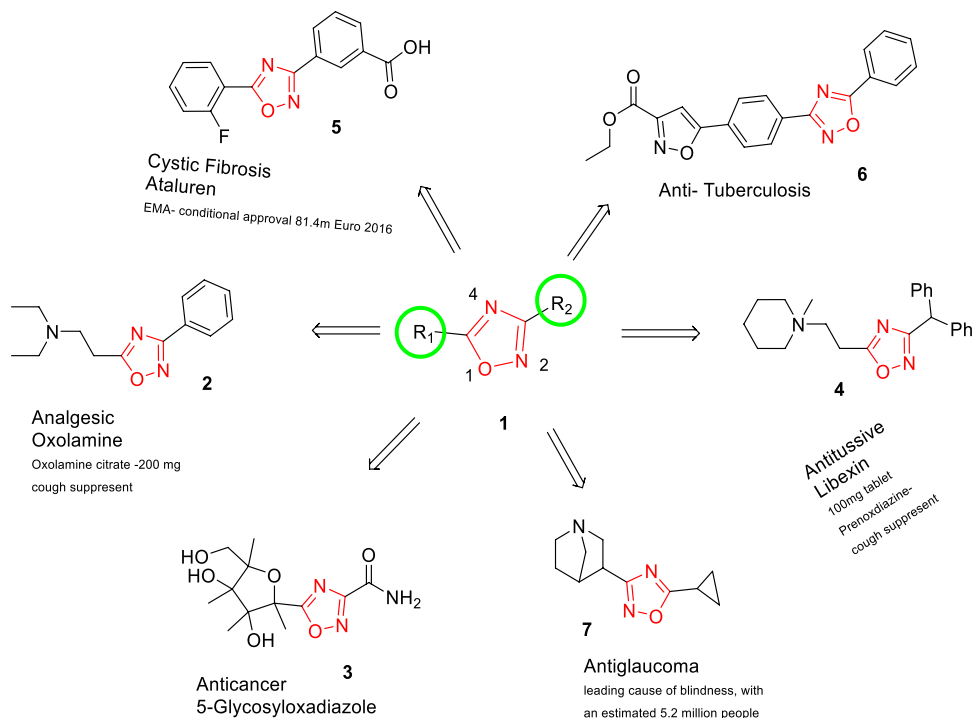
thermal and chemical stability and high photoluminescence quantum yield. The 1,2,4-oxadiazoles show useful properties in blue phosphorescent devices, solar cells, liquid crystals, fluorogenic chemosensory polymers, organic light-emitting diodes, and heat-resistant polymers (Li et al. 2014; Parra et al. 2006; Guo et al. 2014).

### Chemistry

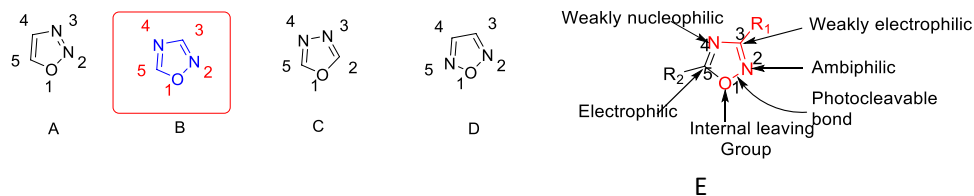
As a five-membered ring heterocycle, oxadiazole consists of oxygen and two nitrogen atoms. Based on the position of these N and O heteroatoms in the ring, it has four isomeric structures as represented in Fig. 2.

The stability of these analogues was explained using the free Gibb’s energies. Free Gibb’s energies for analogues 1,3,4; 1,2,3; 1,2,4; and 1,2,5 is 0.0, 21.28, 8.64, and 40.61 kcal/mol, respectively, making 1,3,4 analogues the most stable among them all, which has the smallest amount of free Gibb’s energy. The stability order decreases as 1,3,4 > 1,2,4 > 1,2,3 > 1,2,5; the 1,2,3-oxadiazole isomer is found solely as an unstable diazoketone tautomer due to its cyclic structure instability, making 1,3,4 and 1,2,4 isomers

**Fig. 1** Some marketed drug’s containing 1,2,4-oxadiazole



**Fig. 2** Four isomers of oxadiazole heterocycle (A–D) and oxadiazole heterocycle reactive site (E)



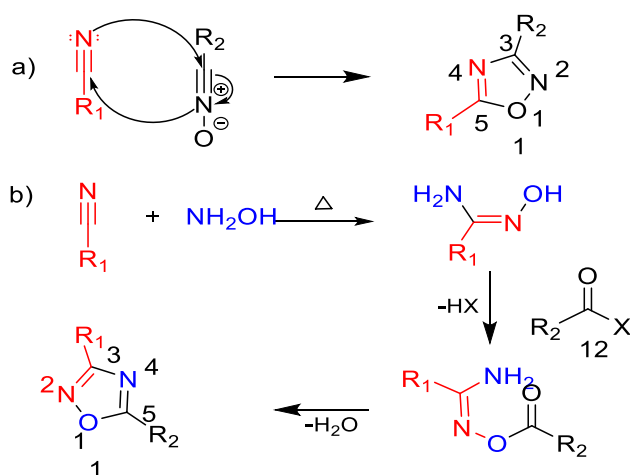
more frequent in medicinal chemistry than the other two isomers. Further UV spectral data of these isomers points out that the 1,2,4-oxadiazole heterocyclic, unlike its aromatic nature, the ring is more heterodiene in character, whilst 1,3,4-oxadiazoles have increased aromaticity, most likely due to their symmetry (Pace and Pierroa 2009). Consequently, these traits differentiate 1,2,4-oxadiazole from its 1,3,4-isomer in reactivity. The experimentally measured bond lengths in X-ray diffraction endorse the planar structure as well as its aromatic character.

It is the most electron-poor azole because it contains two pyridine-type nitrogen atoms and a furan-type oxygen atom. Mono-substituted 1,2,4-oxadiazoles are much less stable than the disubstituted. The latter can even tolerate strong acids such as concentrated sulfuric acid and strong bases. While the 3 and 5 positions are susceptible to creating 3,5-disubstituted 1,2,4-oxadiazoles via nucleophilic attack, they are almost inert towards electrophilic substitution, and, thus, disubstituted are the most commonly synthesized derivatives. The 1,2,4-oxadiazole ring electron-withdrawing effect is effectively exercised via its C-5 position rather than its C-3 position. See Fig. 2E.

## Synthesis

With time, synthetic chemists have developed many preparatory methods for 1,2,4-oxadiazole. Tiemann and Kruger report the very first synthetic method in 1884 (Tiemann et al. 1884).

**Traditional route** Worldwide, the most common and widely used two synthetic routes by chemists start with readily available nitriles, as shown in Fig. 3: (a) 1,3-dipolar cycloadditions of nitriles to nitrile N-oxides; (b) amidoxime



**Fig. 3** Traditional synthetic routes towards 1,2,4-oxadiazoles: **a** 1,3-dipolar cycloaddition of nitriles to nitrile N-oxides; **b** cyclization of amidoxime derivatives

heterocyclization. The amidoxime intermediate is formed when hydroxylamine reacts with nitrile. Acylation of the amidoxime intermediate yields O-acylamidoxime, isolable in some instances, upon cyclization as the ultimate step gives oxadiazole (Paulo et al. 2018).

It must be mentioned that when one pursues the 1,3-dipolar cycloaddition route for synthesis, the corresponding substituent (R1) of nitrile acquires the C-5 position of ultimate Oxadiazole, whilst the same acquires the C-3 position when one follows the amidoxime route (Paulo et al. 2018). Most synthetic strategies belong to either one of the two traditional routes. As a variant to the predominant route, while different acylating agents were explored to synthesize the 1,2,4-oxadiazoles, researchers additionally made use of catalyst, coupling agents, or even the preliminary O-acylation of amidoxime to tolerate the reaction conditions, assist in cyclization, and enhance the yield. They also tried some greener methods, such as microwave or ultrasound irradiation. A few of the synthetic approaches developed by researchers are summarized in Fig. 4, and various types of biologically active oxadiazole derivatives are shown in Fig. 5 and Fig. 6.

## Biological activity

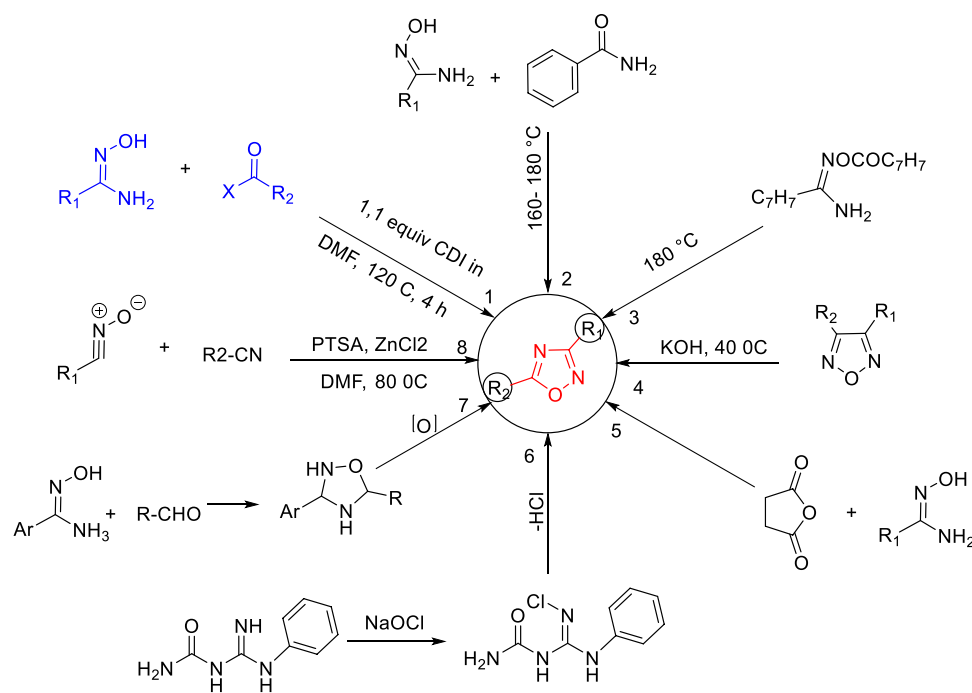
### Anti-tubercular activity

Villemagne et al. (2020) have worked on fragment-based drug-design and synthesized new oxadiazole compounds as potent EthR inhibitors (Villemagne et al. 2020). As a result of their approach, they successfully synthesized compounds with decreased metabolism and enhanced solubility. The compound 1a (BDM 71,339) showed an  $EC_{50}$  of 0.072  $\mu\text{M}$ , solubility of 9.9  $\mu\text{g}\cdot\text{mL}^{-1}$ , and an excellent pharmacokinetic profile with an elimination half-life ( $t_{1/2}$ ) of 19 min and CL of 69  $\mu\text{L}\cdot\text{min}^{-1}\cdot\text{mg}^{-1}$ .

Parikh et al. (2020) have presented the development of substituted 1,2,4-oxadiazole as a potent anti-TB agent (Parikh et al. 2020). The research group tested these compounds for their in vitro anti-tuberculosis activity towards *Mycobacterium tuberculosis* (*Mtb.*) H37Rv, anti-microbial activity, and antimalarial activity. In vitro studies performed at two different concentrations, the % inhibition observed for compound 2a against *M. tuberculosis* H37Rv is 92% at both concentrations, while the compound 2b shows 96% inhibition at a concentration of 250  $\mu\text{g}\cdot\text{mL}^{-1}$  and a 91% inhibition at 100  $\mu\text{g}\cdot\text{mL}^{-1}$ .

Shruthi et al. (2019) worked on a quinoline scaffold. The 1,2,4-oxadiazole moiety is linked to quinoline with piperazine as a linker (Shruthi et al. 2019). They have generated the structure activity relationship (SAR) via combinatorial synthesis. Among the synthesized compounds, compound

**Fig. 4** Some synthetic approaches to oxadiazole molecules: 1 Amidoxime reacted with suitably activated acid derivative; 2 amidoxime reacted with amide at high temperature; 3 pyrolysis of amidoxime and their esters; 4 ring transformations; 5 amidoxime reacted with acid anhydrides; 6 oxidation of an imino group with sodium hypochlorite; 7 oxidation of oxadiazoline; 8 addition of benzonitrile oxides to aromatic nitriles



In method 1 : X=OR, Cl, RCOO, OH i.e suitably activated acid

3a shows a minimum inhibitory concentration (MIC) of  $0.5 \mu\text{g mL}^{-1}$  towards the wild-type, *Mycobacterium tuberculosis* strain (WT H37Rv). Compound 3a has been found to be active against mono-resistant strains of Mtb. The observed activities against this strain of Mtb. are as given in Table S1.

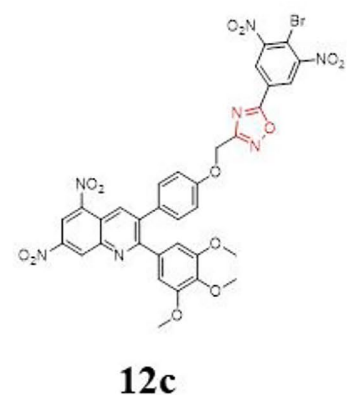
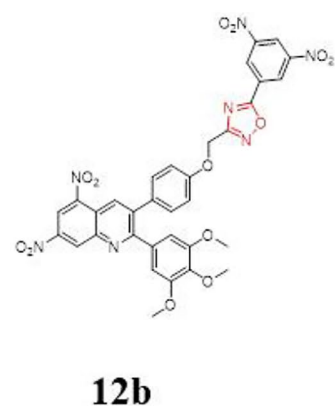
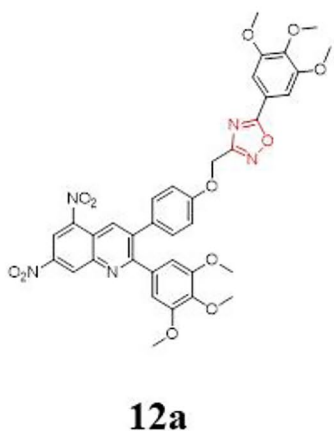
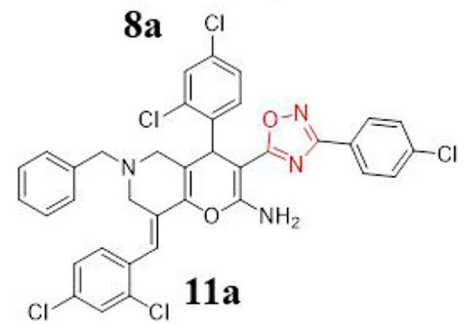
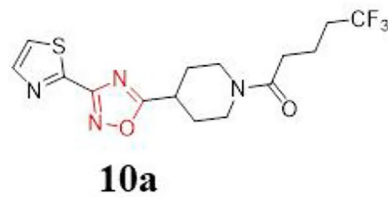
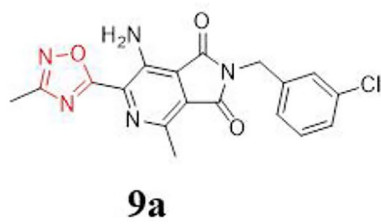
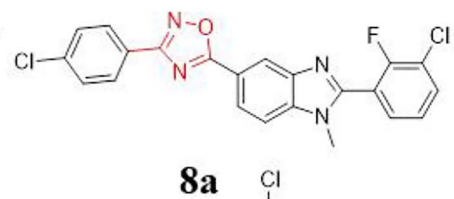
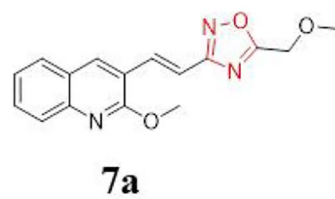
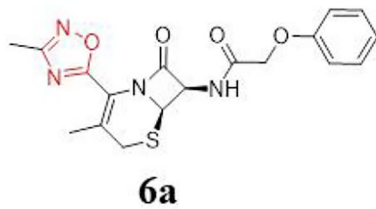
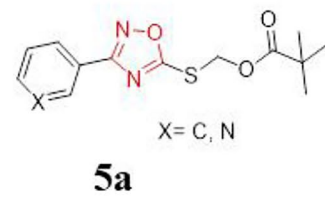
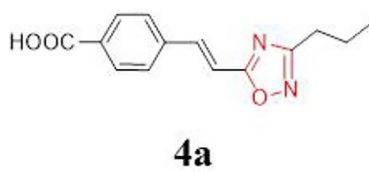
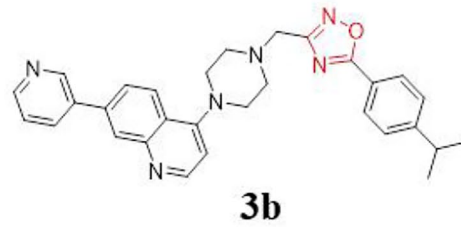
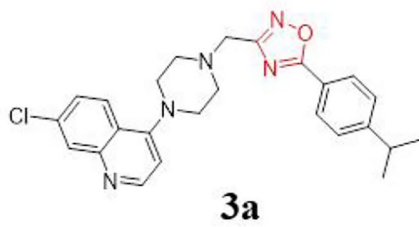
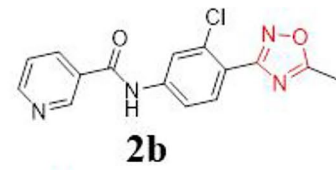
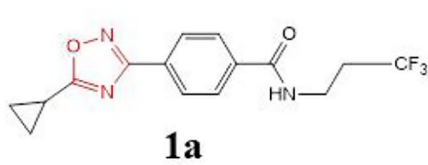
Excellent metabolic stability and bioavailability were noted for the compound 3a, with a long T<sub>1/2</sub> (h) of 1.63 h and a comparatively short concentration of a drug in the blood, cerebrospinal fluid, or target organ after a dose was given (C<sub>max</sub>) of  $2503.25 \text{ ng mL}^{-1}$ . Relatively, compound 3b showed a T<sub>1/2</sub> (h) of 1 h, with a C<sub>max</sub>  $7442.73 \text{ ng mL}^{-1}$ , owing to its less stability in human liver microsomes. Its MIC against Mtb. strain H37Rv is  $0.25 \text{ g mL}^{-1}$ . Upare et al. (2019) have synthesized the styryl oxadiazoles in good yields from cinnamic acid, wherein the terminal carboxylic group of cinnamic acid was replaced with a bio-isostere 1,2,4-oxadiazole (Upare et al. 2019). The in vitro anti-tubercular activity study against the *Mycobacterium tuberculosis* (Mtb) H37Ra strain showed varied anti-tubercular profiles. The compound 4a was reported to possess the highest anti-tubercular activity [concentration of drug required for 50% inhibition ( $IC_{50}$ ) =  $0.045 \mu\text{g/mL}$ ] among the synthesized compounds. Computational molecular docking studies on the InhA enzyme corroborated experimentally observed activities.

Desai et al. (2016) have designed molecules based on nicotinamide and pyrazinamide drugs. The synthesized 1,2,4-oxadiazole-5-ones and or -5-thiones are substituted

with pyridines and pyrazines at the C3 position. Pivaloyloxymethyl derivatives (5a) of 1,2,4-oxadiazole-5-thiones were made with improved lipophilicity and evaluated for anti-TB activity. Because these compounds have an MIC greater than  $50 \text{ mg mL}^{-1}$  against Mtb. H37Rv strain, they may not be considered potent molecules (Desai et al. 2016).

Gold et al. (2016) synthesized a novel analogue of cephalosporins which is selectively active on non-replicating Mtb (Gold et al. 2016). The compound 6a has a MIC of  $0.88 \text{ g/mL}$  for non-replicating Mtb, a MIC of  $> 100 \text{ g/mL}$  for replicating Mtb, and an LD<sub>50</sub> of  $> 100 \text{ g/mL}$  in human liver cancer cell line (HepG2). Jain et al. (2016) have reported a novel hybrid of quinoline and oxadiazole as agents for anti-TB (Jain et al. 2016). They have replaced the isoxazole ring with 1,2,4-oxadiazole as a bio-isosteric replacement. While several molecules tested against the Mtb. H37Rv strain are active, the compound 7a is shown to possess the highest activity, with a MIC of  $0.4 \mu\text{M}$  and a selectivity index of  $> 610$ .

Shruthi et al. (2016) have proposed the design strategy and synthesized benzimidazole-oxadiazole hybrid compounds as an anti-tubercular agent (Shruthi et al. 2016). Among the 20 novel compounds tested, compound 8a was found to be 546-fold selective toward *Mycobacterium tuberculosis* strain H37Rv, with an MIC of  $1.6 \text{ mg mL}^{-1}$ . Thus, it is twofold superior to the standard drug pyrazinamide and fourfold to isoniazid. Furthermore, the active compounds were tested for toxicity and found to be safe even



◀**Fig. 5** List of oxadiazole derivative 1–12 (Upare et al. 2019). Reprinted with permission from Upare et al. 2019, copyright 2019 Elsevier

at high concentrations. Westhuyzen et al. (2015) optimized a hit compound to produce a class of compounds known as pyrrolo[3,4c]pyridine-1,3(2H)diones, which target the mycobacterial respiratory cytochrome bc1 complex, a validated drug target in *Mtb* (Westhuyzen et al. 2015). The optimized compound 9a was synthesized from its hit compound wherein the ester functionality was replaced for its metabolic stability with methyl oxadiazole as a bio-isosteric replacement. This modification leads to an improved MIC of 0.065  $\mu\text{M}$  and shows improved metabolic stability, that is, human S9 (% remaining after 40 min) = 97% and good Clin < 11.6 mL/min/mg.

Flipo et al. (2012) worked on EthR inhibitors. Ethionamide is the main second-line drug used in multidrug-resistant tuberculosis (MDR-TB) (Flipo et al. 2012). This molecule has been reported to have side effects. To overcome problems associated with ethionamide, this research group came up with the most active compound, 10a, that showed an  $IC_{50}$  of 400 nM and an  $EC_{50}$  of 60 nM against *M. tuberculosis*-infected macrophages at nanomolar concentration. They also reported that this compound has good microsomal stability and suitable physicochemical properties. This compound has a solubility of 410  $\mu\text{g mL}^{-1}$  and Clint (microsomes) of 15 mL/in/mg. The bioavailability of the compound is AUC (mouse): 98.6  $\mu\text{g mL}^{-1}$  h. Besides, compound 10a (BDM41906) shows a tenfold improved activity of ethionamide and is called “ethionamide boosters.” The molecule is in a phase II clinical trial as an anti-TB agent.

Almansour and co-workers (2012) reported a 1,2,4-oxadiazoles substituted series of molecules (Almansour et al. 2012). The in vitro anti-mycobacterial behavior of this compound 11a against *Mtb*. is 0.07  $\mu\text{M}$ , and MDR-TB is 0.14  $\mu\text{M}$ .

### Anticancer activity

Kala et al. (2020) have worked on the design and synthesis of 1,2,4-oxadiazoles with quinoline derivatives and evaluated anticancer activity against etoposide (Kala et al. 2020). Etoposide is used for the treatment of non-lymphocytic leukemia, lung cancer, lymphoma, testicular cancer, and glioblastoma multiforme. In treating testicular cancer, it is usually given in combination with other drugs such as bleomycin. The compounds 12a, 12b, and 12c exhibited excellent anticancer activity when compared with etoposide (Table S2). The designed series can be considered as an extension or a modification of *M. srinivasa*, *S. satyavenia*, and *B. rambis* published work wherein the isoxazole and quinazoline heterocycles are replaced with quinolone heterocycles.

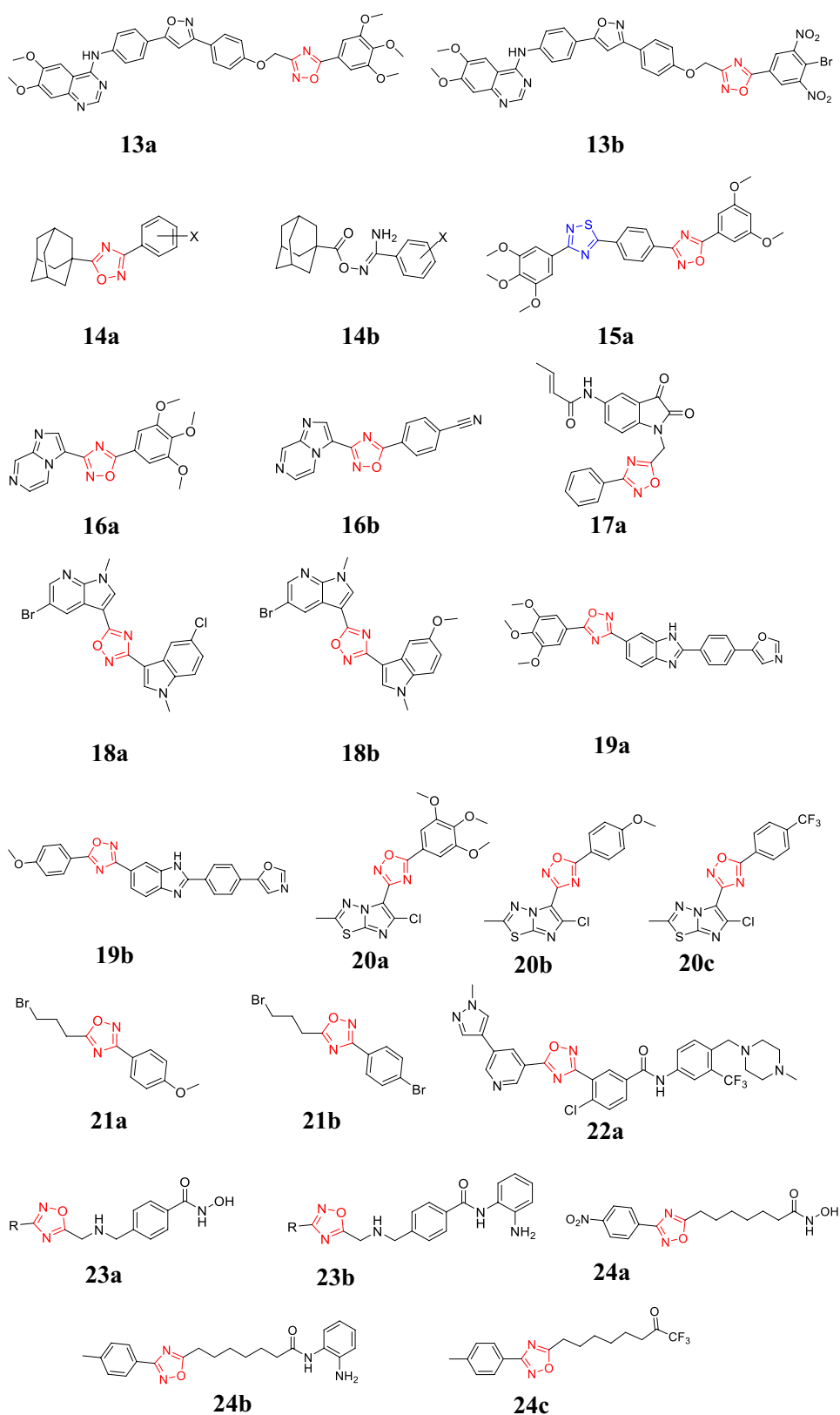
Srinivasa et al. (2019) have presented the design and synthesis of new 1,2,4-oxadiazole-isoxazole linked quinazoline derivatives as anticancer agents (Srinivasa et al. 2019). Among the tested compounds against human cell lines for breast (MCF-7, MDA MB-231), lung (A549), and prostate cancer (DU-145). Compounds 13a and 13b are the most active in the series. The compound 13a has an  $IC_{50}$  of 0.056 against MCF-7, 0.06 against MDA MB-231, 0.76 against A549, and 0.011 against DU-145. The compound 13b shows an  $IC_{50}$  0.021 against MCF-7,  $IC_{50}$  0.14 against A549,  $IC_{50}$  0.064 against DU-145,  $IC_{50}$  0.19 against MDA MB-231.

Aguiar et al. (2019) have reported the synthesis of O-acylamidoximes adamantyl and 3-Aryl-5-adamantane-1,2,4-oxadiazoles from adamantane carbonyl chloride and variously substituted arylamidoximes. Under microwave irradiation conditions, the O-acylamidoxime intermediate was cyclized (Aguiar et al. 2019). Compounds 14a and 14b were tested for cytotoxic activity against vero cells and anticancer activity against chronic myeloid leukemia (CML) cancer cells. Compound 14a showed a concentration-dependent profile for the CML human immortalized myelogenous leukemia cell line (K562) and acute pro-myelocytic leukemia for human leukemia cell line (HL60).

Sudhakara et al. (2019) worked on the design and synthesis of new derivatives that contain both the 1,2,4-isomer of oxadiazole and the thiadiazole motif as part of a molecule (Sudhakara et al. 2019). These derivatives exhibited moderate antitumor efficacy in four human cancer cell lines tested for antitumor efficacy, namely, Colo205 (colon), MCF-7 (breast), A2780 (ovarian), and A549 (lung), in a colorimetric assay for assessing cell metabolic activity (MTT assay). Among the tested compounds, 15a shows an  $IC_{50}$  of 0.10  $\mu\text{M}$ , 0.24  $\mu\text{M}$ , 0.11  $\mu\text{M}$ , and 0.32  $\mu\text{M}$  for Colo-205, MCF-7, A2780, and A549, respectively.

Reddy et al. (2019) have reported the design and synthesis of a series of 1,2,4-oxadiazole linked imidazopyrazine derivatives (Reddy et al. 2019). Compounds were tested against three human cell lines. The compounds 16a and 16b show excellent cytotoxicity activity and are more potent than adriamycin. The reported  $IC_{50}$  values for compound 16a for cell lines MCF-7, A-549, and A-375 are 0.68  $\mu\text{M}$ , 1.56  $\mu\text{M}$ , and 0.79  $\mu\text{M}$ , respectively. Similarly, for the other compounds, 16b reported  $IC_{50}$  values for cell lines MCF-7, A-549, and A-375 are 0.22  $\mu\text{M}$ , 1.09  $\mu\text{M}$ , and 1.18  $\mu\text{M}$ , respectively.

Yu et al. (2019) identified isatin as 2,3-indolinedione derivatives as a new promising class of anticancer agents (Shengping et al. 2019). They synthesized and tested 18 compounds against mantle cell lymphoma (MCL) cell lines. The most prominent active compound from the 1,2,4-oxadiazole series is compound 17a, which shows  $IC_{50}$  values of 0.4  $\mu\text{M}$ , 0.4  $\mu\text{M}$ , 0.5  $\mu\text{M}$ , 0.7  $\mu\text{M}$ , and 1.5  $\mu\text{M}$ , against MCL cell lines Mino, chronic lymphocytic leukemia

**Fig. 6** List of oxadiazole derivative 13–24



cell line (Z138), Maver-1, Jeko-R, and leukemia cell line (Granta-519) respectively.

Cascioferro et al. (2019) reported structural modifications made to nortopsentin, an alkaloid, to obtain the new derivatives wherein the 1,2,4-oxadiazole moiety replaces the central imidazole ring as the main modification and generates the SAR (Cascioferro et al. 2019). The compounds were tested on cancer cell lines such as HCT-116 (human colon cancer cell line), MCF-7 (cervical cancer cell line), and Caco-2. While compound 18a and 18b are the prominent active compounds in the series, and both induce a halt in the cell cycle resting phase (G0)–growth phase (G1) phase, the 18a is 2 to 4 times more active than the 18b, except for the HeLa cell. The SAR studies performed revealed that the halogen atom is crucial for the antiproliferative activity. Table S3 shows the cytotoxic activities measured by the MTT colorimetric assay.

Srinivas et al. (2018) have described the design and synthesis of novel 1,2,4-oxadiazole linked benzimidazoles (Srinivas et al. 2018). Preliminary evaluations of the substances' antitumor activities against A549 (lung), MCF-7 (breast), and human melanoma cell line (A375) revealed that they were more potent than the doxorubicin drug. The most active compounds, 19a and 19b, have  $IC_{50}$  values of 0.24 M, 0.31 M, 1.67 M, and 1.90 M, 0.17 M, and 1.45 M, respectively, against MCF-7, A549, and A375 cell lines. Chakrapani et al. (2018) and co-workers have described the design and synthesis of a new 1,2,4-oxadiazole linked imidazothiadiazole analogue that is structurally close to levamisole (Chakrapani et al. 2018). Anticancer activity data was generated for these compounds using the MTT assay for three human cell lines: A375, MCF-7, and human renal carcinoma cell line (ACHN) (Table S4). The compounds 20a, 20b, and 20c turned out to be the most prominent compounds with almost similar activity to that of the doxorubicin drug.

A 1,2,4-oxadiazole scaffold has been developed by S. Moniot et al. (2017) as Sirt2 inhibitors. They successfully optimized their previously reported lead compound 3-(4-chlorophenyl)-5-(piperidine-1-ylmethyl)-1,2,4-oxadiazole. For SAR studies,  $\alpha$ -tubulin-acetylLys40 peptide was used as the Sirt2 substrate (Moniot et al. 2017). The study revealed that for a molecule to possess Sirt2 inhibitory action, the 1,2,4-oxadiazole must have a para substituted phenyl ring in its 3rd position and a cyclic aminomethyl or haloalkyl chain in its 5th position as a crucial substituent. Amongst the compounds tested against leukemia cell lines, 21a and 21b emerged to be the most active in the series; 21a shows an  $IC_{50}$  of 10  $\mu$ M against Sirt2, while compound 21b shows an  $IC_{50}$  of 1.5  $\mu$ M (Table S5).

Han et al. (2016) and his co-workers have designed and synthesized a new series of 4-chloro-benzamide derivatives containing substituted 1,2,4-oxadiazole heteroaryl rings as a potent rearranged transfection kinase inhibitor (RET)

for cancer therapy (Han et al. 2016). The compound 22a strongly inhibits cell proliferation driven by RET wild-type and gatekeeper mutations. Western blotting analysis revealed that the compound 22a completely inhibits the phosphorylation of the RET enzyme at a 1- $\mu$ M concentration. The compound 22a shows an  $IC_{50}$  of 1.8 nM against RET, whereas that of Ponatinib shows an  $IC_{50}$  of 0.9 nM.

Cai et al. (2015a, b) post their successful investigation of a few derivatives of Vorinostat as an antitumor agent. The group has explored the optimization of lead compound entinostat, leading to a series of 2-aminobenzamide and hydroxamate derivatives containing 1,2,4-oxadiazole (Cai et al. 2016). The MTT-based assay performed to investigate the in vitro antiproliferative activities of these compounds revealed that the 2-aminobenzamides 23b [R = Phenyl, 4-Me-Phenyl, 4-Cl-phenyl, etc.] are predominantly active towards the histiocytic lymphoma cell line (U937) among the tested human cancer cell lines U937, NCI-H661, A549, HCT116, and MDA-MB-231. Furthermore, the compounds were tested against histone deacetylases (HDAC) 1, 2, and 8 for their inhibitory activities, while the 2-aminobenzamide derivatives 23b are active against HDAC 1, hydroxamate derivatives 23a [R = Phenyl, 4-Me-Phenyl, 4-Cl-Phenyl, etc.] are active against the HDAC 8 and exhibit lower  $IC_{50}$  values compared to suberoylanilide hydroxamic acid (SAHA) and entinostat.

Cai et al. (2015a, b) discussed how they made hydroxamate, 2-aminobenzamide, and trifluoromethyl ketone analogues of 1,2,4-oxadiazoles (Cai et al. 2015a, b). They have replaced the amide functional group of vorinostat with 1,2,4-oxadiazole as a bio-isostere to investigate the effect of replacement on activity. When these compounds were tested against three human cancer cell lines, most of the compounds showed more prominent anticancer activity against human acute myeloid leukemia cell U937 than the other two human lung cancer cell lines A549 and NCI-H661. The compound 24a shows an  $IC_{50}$  of 5.31  $\mu$ M, 3.09  $\mu$ M, and 0.29  $\mu$ M against A549, NCI-H661, and U937 cell lines. The compound 24b shows an  $IC_{50}$  of 9.17  $\mu$ M, 0.41  $\mu$ M, and 0.46  $\mu$ M against A549, NCI-H661 and U937 cell lines, respectively. The compound 24c shows an  $IC_{50}$  of > 100  $\mu$ M, 18.68  $\mu$ M, and 3.73  $\mu$ M against A549, NCI-H661, and U937 cell lines, respectively.

## Thiadiazole

### Introduction of thiadiazole and its biological importance

Thiadiazole, the most prevalent and indispensable heterocycle, is a five-membered heterocyclic compound, a scaffold that makes an important structure of several naturally

occurring as well as medicinal products (Dawood and Farhaly 2017). The thiadiazole moiety acts as a “hydrogen-binding domain” and “two-electron donor system,” which makes the thiadiazole ring biologically active, sulfur atom imparts lipo-solubility, leading to analogues with higher lipophilicity. A lot of people use 1,3,4-thiadiazoles as bio-isosteric replacements for pyrimidine, pyridine azine, oxadiazole, oxazole, thiazole, and benzene in the development of new drugs (Serban et al. 2018). A few 1,3,4-thiadiazole scaffold containing marketed drugs are reported in Fig. 7, which underlines their importance in the field of medicinal chemistry (Serban 2019). Acetazolamide (**9**) and methazolamide (**10**) are potent carbonic anhydrase inhibitors, drugs used in the treatment of glaucoma, an eye-related disorder that causes damage to optic nerves. Megazole (**11**) is an antitrypanosomal agent, a drug used to treat African trypanosomes, also called sleeping sickness. Sulfamethizole (**12**) is an anti-microbial agent. Cefazolin (**13**) and cefazedone are used as antibiotics that belong to the cephalosporin family. Azeteta (**14**) is a phosphorous-containing drug used for the treatment of cancer.

Thus, 1,3,4-thiadiazole exhibits various pharmacological activities such as anti-inflammatory (Amir and Kumar 2007), antihypertensive (Hasui et al. 2011), anti-HIV, anti-depressant, anticonvulsant, anticancer (Haider et al. 2015), anti-TB, and anti-microbial agents (Hu et al. 2014).

## Chemistry

Thiadiazole is a heterocycle ring with two nitrogen and one sulfur heteroatom. Based on the nitrogen and sulfur

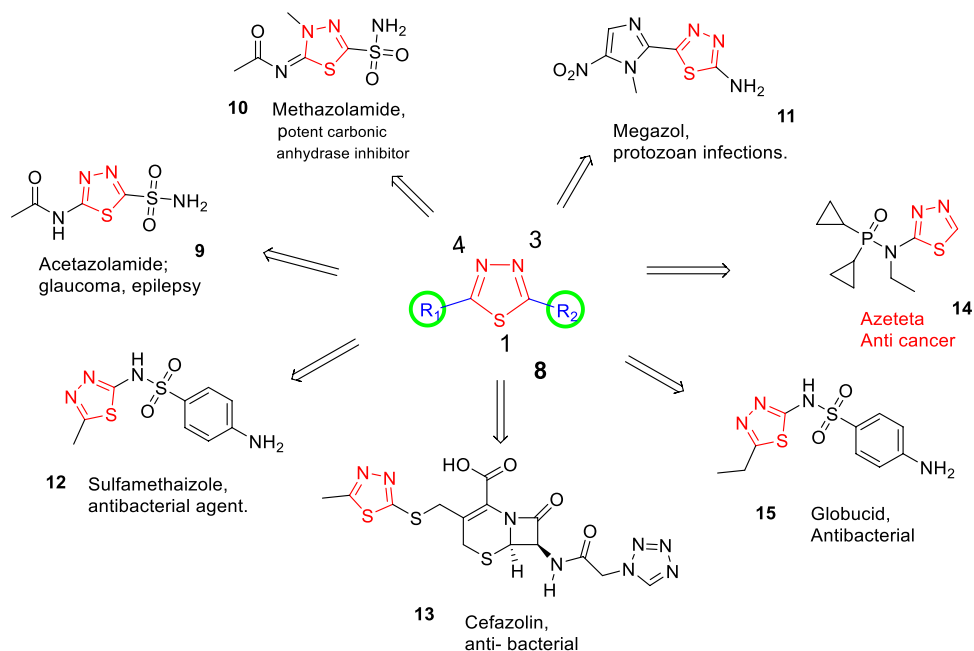
heteroatoms' positions in the ring, it has four isomers as represented in Fig. 8a.

1,3,4-Thiadiazole is a conjugated, weakly basic, planar, and electron-deficient ring system. While high aromaticity with the added +I effect of a sulfur atom makes it a weakly basic, the nitrogen atoms electron-withdrawing effect makes it electron deficient. This nature makes the carbon atoms at the C-2 and C-5 positions relatively inert towards electrophilic substitution while more reactive to nucleophilic attack. Substituents at the C-2 or C-5 positions activate the ring, favoring nucleophilic attack on carbon atoms. Although electrophilic attack on sulfur atoms is rare, the ring nitrogen atoms, dependent on the nature of the substituent on the carbon C-2 or C-5 position, do undergo electrophilic attack. See Fig. 8b. The ring is quite stable and can tolerate aqueous acidic solutions, but not the strong basic conditions under which ring cleavage is observed.

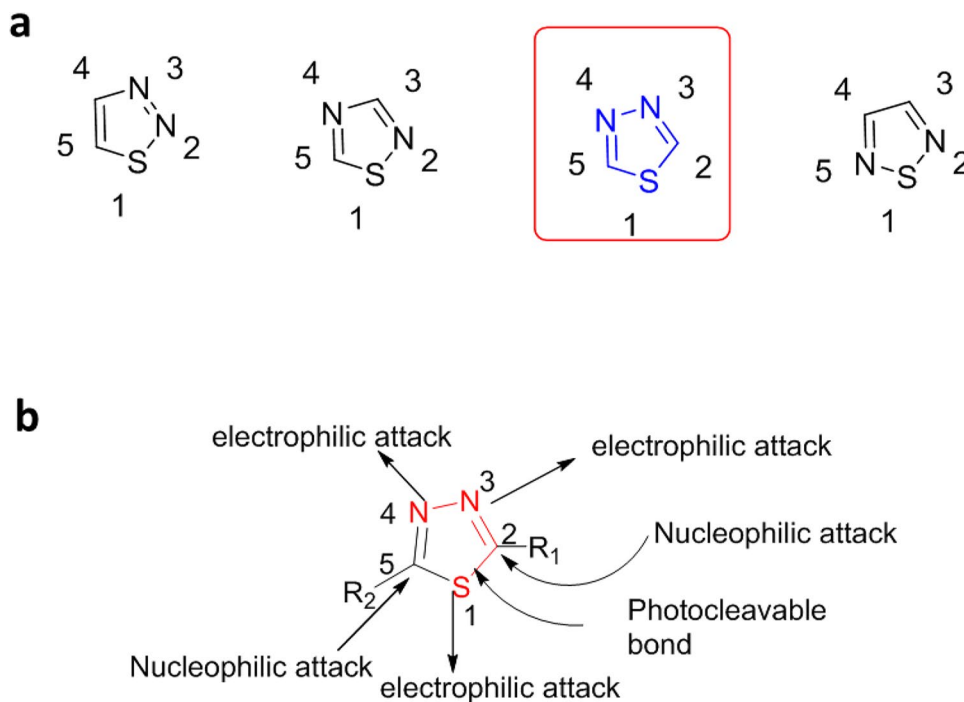
## Synthesis

Emil Fischer first synthesized 1,3,4-thiadiazole in 1882 (Goerdler et al. 1956). The most common and extensively explored synthetic route is the cyclization of acyl hydrazine, which includes diacylhydrazines and monoacylhydrazines. The other synthetic route to 1,3,4-thiadiazoles makes use of thiohydrazines. From the recent literature, we have summarized a few strategies employed by chemists for the synthesis of 1,3,4-thiadiazoles as shown in Fig. 9 (Al-Omar et al. 2011; Kristinsson and Winkler 1982). The transformation of the 1,3,4-oxadiazole ring is also a route of choice.

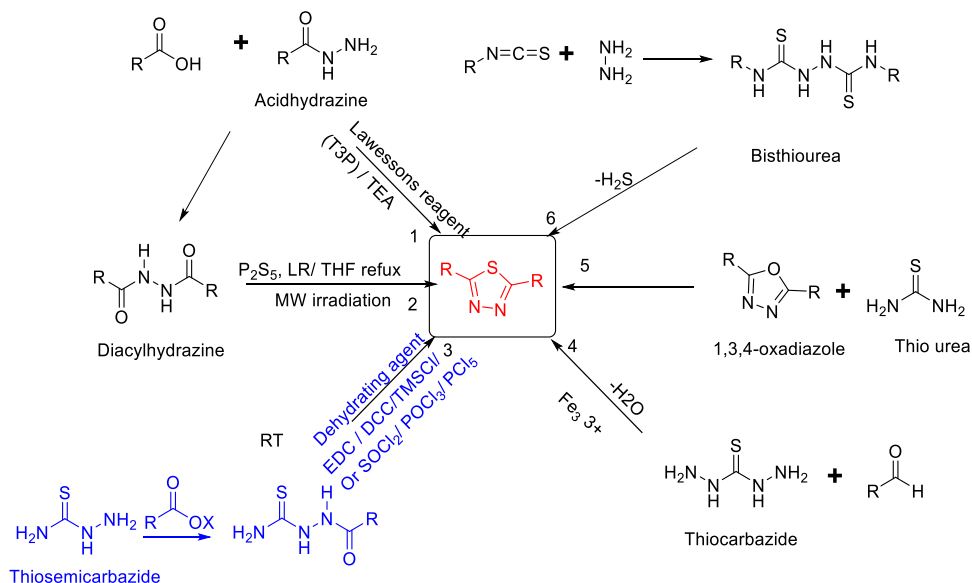
**Fig. 7** Some marketed drugs containing 1,3,4-thiadiazole (Li et al. 2013)



**Fig. 8** **a** Isomers of thiadiazole based on the position of heteroatoms. **b** Thiadiazole heterocycle reactive site



**Fig. 9** A few synthetic approaches to thiadiazole molecules with different Acyl hydrazides, diacylhydrazides, thiosemicarbazide, thiocarbazide, thiourea, bistiourea



### Biological Activity

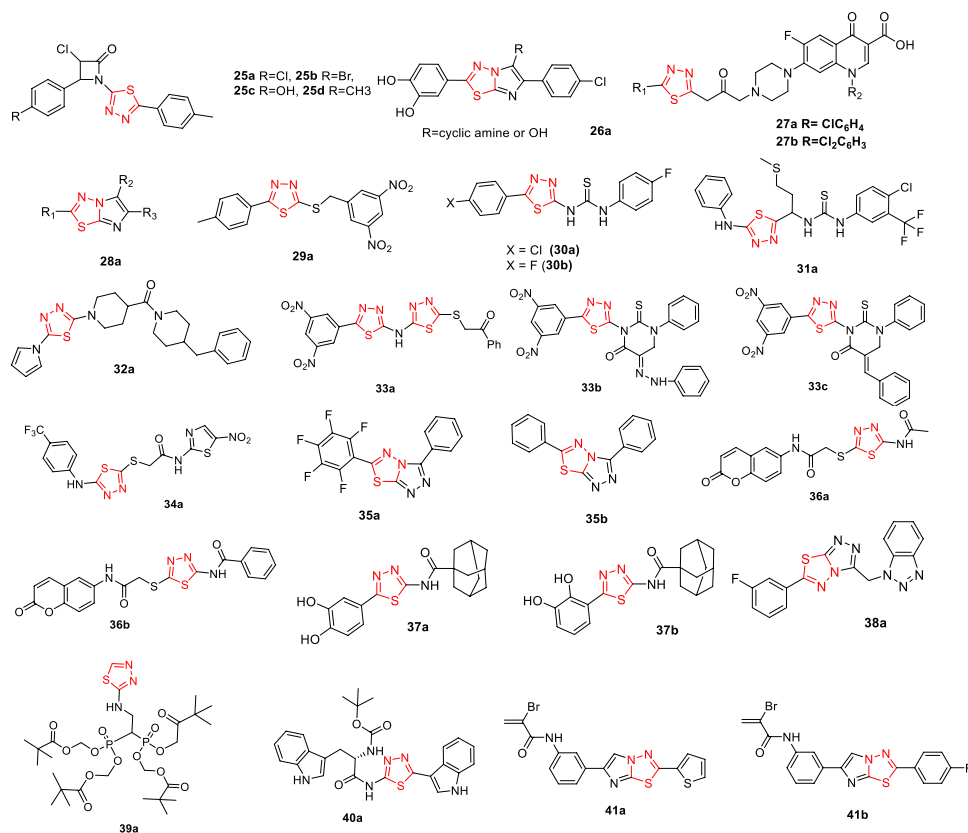
Biologically active 1,3,4-thiadiazole derivatives' structure is illustrated in Fig. 10.

#### Anti-tubercular activity

Kumar et al. (2019) have synthesized a series of azetidinone nucleus containing 1,3,4-thiadiazole derivatives from the Schiff base and are reported to exhibit good antibacterial, antifungal, and anti-tubercular activity. To obtain

anti-tubercular activity data, the microplate Alamar Blue Assay was performed. The MIC of these derivatives against the Mtb. *H37Rv* strain ranged from 6 to 25 g mL<sup>-1</sup>. The compounds 25a, 25b, 25c, and 25d with the substituent in the *para* position are active and have a MIC close to 6 μg mL<sup>-1</sup>, while the substituent in the meta position makes them inactive.

Taflan et al. (2019) reported two series of novel imidazo[2,1-b][1,3,4]thiadiazole (ITD) hybrid compounds 26a with excellent anti-tubercular profiles and MICs ranging from 0.24 to 0.49 g mL<sup>-1</sup> concentration against

**Fig. 10** List of thiadiazole derivative 25–41

*Mycobacterium smegmatis* organisms (Ebru et al. 2019). At the same time, these compounds were also found to possess antioxidant effects due to the presence of a 3,4-dihydroxy phenolic group C-2 position.

Demirci et al. (2018) have reported the synthesis of novel 1,3,4-thiadiazole-based fluoroquinolone hybrid compounds as anti-tuberculosis agents. All of the norfloxacin-derived compounds have 4-chlorophenyl 27a and 2,4-dichlorophenyl 27b substituents on the 1,3,4-thiadiazole ring and exhibit significant antimicrobial activity against the *Mtb. H37Rv* strain. MIC was measured using the Broth Microdilution method and was found in the range of 8 to 64  $\mu\text{g}\cdot\text{mL}^{-1}$ .

Wadhwa et al. (2017) presented the results of computational studies that revealed the most vital structural requirements of molecules for InhA inhibition. The molecular docking experiment performed on imidazo[2,1-*b*] [1,3,4] thiadiazole 28a revealed that PRO156, GLN100, TYR158, ALA198, LEU197, LEU218, and MET199 (active site) are the essential binding residues that are responsible for interactions between the InhA enzyme and inhibitors.

As anti-TB agents, presented 5-substituted-2-[(3,5-dinitrobenzyl)-sulfanyl]-1,3,4-oxadiazoles and 1,3,4-thiadiazole derivatives (Karabanovich et al. 2016). They assessed the anti-tubercular profile (in vitro) of the synthesized compounds as well as studied SAR deeply to conclude their earlier reported findings that the dinitrobenzylsulfanyl

substitution is crucial for anti-mycobacterial activity. The nitro-substituted 2-alkyl/aryl-5-benzylsulfanyl-1,3,4-thiadiazoles are reported to possess greater activity than the first-line anti-TB drugs, with a measured MIC as low as 0.03  $\mu\text{M}$  for the 29a compound. The compounds were also tested against nontuberculosis mycobacterial species, namely *Mycobacterium avium*, Czechoslovak National Collection of Type Cultures (CNCTC) My 331/88, *Mycobacterium kansasii* CNCTC My 235/80, the clinically isolated *M. kansasii* 6509/96, and six multidrug-resistant clinically isolated strains of *M. tuberculosis*.

Tatar et al. (2016) have synthesized and reported conjugated thiadiazole-thiourea as anti-tuberculosis agents. The 5-(4-chlorophenyl and 4-fluorophenyl)-1,3,4-thiadiazole 3-substituted thioureas were identified as the most active as well as selective compounds against the *M. tuberculosis H37Rv* strain. The MIC values measured for compounds 30a and 30b were 10.96, 11.48  $\mu\text{M}$ , respectively. Molecular docking studies performed on these compounds showed good docking scores for the enzyme InhA.

Tatar et al. (2015) reported another two series of compounds synthesized from L-methionine as anti-TB agents. The synthesized 1,3,4-thiadiazole and 1,2,4-triazole derivatives exhibited anti-tubercular activity (Batt et al. 2015). The 1,3,4-thiadiazole with (4-chloro-(3-trifluoromethyl) phenyl) substituted thiourea 31a is the most active compound against

the *M. tuberculosis H37Rv* strain, with a measured MIC of 30.88  $\mu\text{M}$ .

Batt et al. (2015) successfully used the target overexpression approach to screen the lead molecules, identifying GSK710 (32a), one of the series' analogues, as a strong receptor of enzymatic reactions, Mt-DprE1  $IC_{50} = 54 \text{ nM}$ , in *M. bovis* BCG. This compound showed an eightfold higher MIC relative to the control strain. Furthermore, spontaneous resistant mutant sequencing studies were used to conclude that DprE1 is the target of these analogues, with a single nucleotide change at both positions E221Q and G248 in the enzyme DprE1 gene molecule, in a clinical trial. SAR studies revealed that the modification could be allowable at the phenyl's terminal ring inclusive of fluorine substitution, pyridine regioisomers, and other functional groups can be substituted for the para position ensuing when solubility and distribution factors improve dramatically, while inhibitory exercise is maintained.

### Anticancer activity

Naggar et al. (2019) recently presented design, synthesis, and molecular docking experiments of antimicrobial and anticancer 5-(3,5-dinitrophenyl)-1,3,4-thiadiazole compounds. These compounds were studied in vitro and their activities were compared to those of Doxorubicin, a standard drug. The compounds 33a, 33b, and 33c are the most active compounds and show the following  $IC_{50}$  values against various tumor cell lines (Table S6).

Altintop et al. (2018) have described the design and synthesis of 1,3,4-thiadiazole derivatives and evaluated their anticancer activity towards chronic myelogenous leukemia cells. The compound 34a was screened against eight kinases and found to inhibit the Bruton's tyrosine kinase inhibitor (BTK), FYN proto-oncogene (FYNA), LCK, and C-terminal Src kinase (CSK kinases) with the highest selectivity for the Bcr-Abl-positive K562 cell line. With a measured  $IC_{50}$  value of 7.4  $\mu\text{M}$  for Abl kinase protein compound 34a, it turned out to be the most potent of all the compounds. It also had a different kinase inhibitory profile than imatinib. Compound 34a exhibited BTK activity of 30.3  $\mu\text{M}$ , whereas imatinib showed activity of > 100  $\mu\text{M}$ .

Chowrasia et al. (2017) investigated novel fused thiadiazole scaffolds as anticancer agents. The fluorinated analogue 35a is more active than the parent analogue 35b. The anti-proliferative activity observed for the most active compound 35a against different cell lines is MCF7 with an  $IC_{50}$  value of 22.1  $\mu\text{M}$ , a cell line derived from the primary osteosarcoma (SaOS-2)  $IC_{50}$  value of 19  $\mu\text{M}$  and a K562  $IC_{50}$  value of 15  $\mu\text{M}$ . The compound 35b showed significantly low activity against the same cell lines and observed are MCF7  $IC_{50}$  value of 30.2  $\mu\text{M}$ , SaOS-2,  $IC_{50}$  value of 39  $\mu\text{M}$ , and a K562  $IC_{50}$  value of 29.4  $\mu\text{M}$ .

Amin et al. (2017) presented the synthesis of various coumarin-thiadiazole-based analogues with potential anti-tumor activity. The DNA binding assay was performed to assess the antitumor activity of the synthesized compounds. These compounds were tested against a few human cancer cell lines; liver cancer (HepG-2), colorectal cancer (HCT-116), and breast cancer (MCF-7). The measured  $IC_{50}$  values for compound 36a in HepG-2, HCT-116, and MCF-7 (human cancer cell lines) are 266, 238, 398  $\mu\text{g} \cdot \text{mL}^{-1}$ , respectively. Similarly, compound 36b shows an  $IC_{50}$  of 114, 30.7, 54.9  $\mu\text{g} \cdot \text{mL}^{-1}$  in HepG-2, HCT-116, and MCF-7, cell lines.

Jakovljevic et al. (2017) developed two series of 1,3,4-thiadiazole amide derivatives containing a substituent catechol moiety as a potential antioxidant and anticancer agents. Among the two 3,4- and 2,3-dihydroxy series of derivatives, the latter showed the best activity. Moreover, the antioxidant properties of these derivatives totally depend on the substituent attached to the amide bond. Thus, adamantane-containing compounds 37a and 37b showed enhanced cytotoxic activity with  $IC_{50}$  values of 7.4 and 7.3  $\mu\text{M}$ , respectively, towards the human acute pro-myelocytic leukemia HL-60 cells and lung carcinoma A549 cells, while they showed decreased toxicity towards normal MRC-5, suggesting a selective nature in action.

Wang et al. (2017) and his group identified [1,2,4]-triazolo-[3,4-b][1,3,4]-thiadiazole a novel scaffold as a disruptor of telomeric silencing 1 (DOT1L) inhibitor that plays a crucial role in cell cycle regulation, transcriptional elongation (Wang et al. 2017). The compound 38a showed strong binding affinity to DOT1L with measured  $IC_{50}$  of 8.3  $\mu\text{M}$ . It has average selectivity over other methyl transferases and non-MLL-rearranged leukemia cell lines.

Kenji et al. (2016) have described the synthesis of nitrogen-containing bisphosphonates. These compounds show antitumor activity in particular in breast cancer and myeloma patients. Due to poor absorption, it has difficulty in cell entry and hence exhibits weak activity; it also causes bone side effects. Hence, research groups have synthesized their Pivaloyloxymethyl esters as a prodrug approach. The compound 39a shows  $IC_{50}$  of 11  $\mu\text{M}$  for U937 cell lines and 8.5  $\mu\text{M}$   $IC_{50}$  for Cancer cell lines (EJ-1).

Tingting et al. (2016), have synthesized a novel disubstituted 1,3,4-thiadiazole that includes substituted N-heterocyclic rings, mainly indole, pyridine, and quinoline, along with the aromatic rings (Tingting et al. 2016). Synthesized compounds were tested against CML cells and breast cancer cells. The compound 40a with indole as a substituent on the thiadiazole is reported to be the most potent compound among all, with a measured  $IC_{50}$  value of  $5.9 \pm 0.56 \mu\text{M/L}$  for epithelial, human breast cancer cell lines (MDA-MB231 cells), and a measured  $IC_{50}$  value of  $4.2 \pm 0.32 \mu\text{M/L}$  against K562 cell lines. Gossypol is used as the positive control.

Romagnoli et al. (2015) described the synthesis of a hybrid compound imidazo[1,2-b][1,3,4]thiadiazole as a biologically active scaffold with anticancer activity (Romagnoli et al. 2015). The compound 41a shows  $IC_{50}$ 's of 0.17, 0.37, 0.41, and 0.67  $\mu\text{M}$  against mouse lymphocytic leukemia cell line (L1210), murine breast cancer cell line (FM3A), lymphoblastic cells that happened to come from a child who had acute lymphoblastic leukemia (CEM), and HeLa cell lines, respectively. The compound 41b shows an  $IC_{50}$  of 0.25, 0.61, 0.83, and 0.87  $\mu\text{M}$  against L1210, FM3A, CEM, and HeLa cell lines, respectively.

## Conclusion

It is evident from the plethora that today, the 1,2,4-oxadiazole and 1,3,4-thiadiazole scaffolds are widely explored by researchers in medicinal chemistry, particularly as anti-tubercular and anticancer agents. The appearance of these scaffolds in the number of newly reported molecules also underlines their importance as bio-isosteres. While improving the anticancer and anti-tubercular profiles, while both the positions of these heterocycles were substituted and explored, new scaffolds in combination with other heterocycles are also reported. Although both the scaffolds are tested against various targets for their anti-tubercular and anticancer properties, other potential targets are still to be explored. SAR studies conducted helped in identifying the few structural key requirements. A few of the derivatives showed promising anti-tubercular and anticancer activity. We believe the summarized literature herein provides an overview of anti-tubercular and anticancer activities demonstrated by the 1,2,4-oxadiazoles and 1,3,4-thia diazoles, and helps researchers in rational drug design and development in this area.

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**Author contribution** A.A.U. conceived and designed the study and wrote the initial manuscript. S.M.R. conceived and designed the study and edited the manuscript. All authors read and approved the manuscript.

## Declarations

**Ethics approval** This article does not contain any studies on human volunteers or animals.

**Conflict of interest** The authors declare no competing interests.

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