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Review article

1,2,4-Oxadiazoles in medicinal chemistry: trends of the last years

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ABSTRACT

1,2,4-Oxadiazoles have emerged as a significant class of heterocyclic compounds in medicinal chemistry due to their diverse biological activities and versatile applications in drug discovery. Herein is reported an in-depth analysis of the structural properties, synthetic methodologies, and pharmacological significance of 1,2,4-oxadiazoles. The compound's unique five-membered ring containing three heteroatoms offers remarkable stability and tunable physicochemical properties, making it an attractive scaffold for the development of novel therapeutic agents, as confirmed by already approved drugs.

The review highlights the broad spectrum of biological activities associated with 1,2,4-oxadiazoles, including antimicrobial, anti-inflammatory, anticancer, antiviral, and central nervous system related activities. These diverse effects underscore the scaffold's potential for targeting multiple disease pathways. Several studies demonstrate that structural modifications on the oxadiazole ring can significantly influence its pharmacokinetic and pharmacodynamic profiles, enabling the design of selective and potent drug candidates.

Additionally, it has explored recent advances in synthetic strategies for constructing the 1,2,4-oxadiazole core, such as cyclization reactions involving amidoximes, nitrile oxides, and other precursors. Modern approaches using transition-metal catalysis, microwave-assisted synthesis, and green chemistry techniques are also discussed, emphasizing their importance in improving efficiency and scalability for pharmaceutical applications.

Furthermore, the role of 1,2,4-oxadiazole as bioisostere replacement for esters and amides is highlighted, particularly in enhancing metabolic stability and modulating target selectivity. Application of computational methods, including molecular docking and QSAR modeling, have been also covered in understanding ligand-receptor interactions and guiding lead optimization.

This review underscores the growing prominence of 1,2,4-oxadiazoles in modern drug design and their potential to address unmet medical needs. With continued research and innovation, these scaffolds are poised to play a pivotal role in the next generation of therapeutic agents across multiple disease areas.

1. Introduction

From the medicinal chemistry perspective and target-based drug design, functional derivatives of the 1,2,4-oxadiazole ring represent a privileged class of organic compounds. In fact, molecules containing the 1,2,4-oxadiazole moiety possess a number of valuable biological activities, including antiproliferative [1–7], anti-inflammatory [8–10], antibacterial [11,12], antimycobacterial [13], antiparasitic [14–18],

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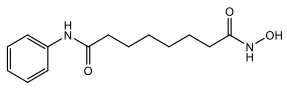
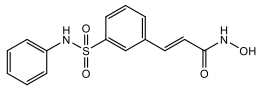
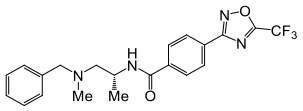
antifungal [19,20], antiviral [21], anti-infective, in general [22], and other activities. The 1,2,4-oxadiazole fragment is also known to be a building block for the synthesis of novel high-energy materials [23]. This heterocycle is of particular importance and may act as a hydrolytically stable bioisoster of either the ester fragment or the *N,N*-disubstituted carboxamide [24]. Such substitutions can result in reduced formation of toxic metabolites, the ability to form hydrogen bonds, increased stability, prolonged duration of action, increased binding affinity and increased pK_a [22]. Although disubstituted 1,2,4-oxadiazole derivatives exhibit increased stability, whereas monosubstituted and unsubstituted 1,2,4-oxadiazoles are susceptible to thermal decomposition and hydrolysis [25]. It is often observed that bioisosteric replacement with 1,2,4-oxadiazole results in modulated molecular lipophilicity. This could be used to increase the ability to cross the blood-brain barrier (BBB), as well as to improve bioavailability and duration of action, which in certain cases are of significant importance in the context of drug development and make the 1,2,4-oxadiazole moiety a game-changer scaffold in pharmacokinetics. The combination of numerous favorable physicochemical and pharmacological properties of this heterocycle led to the development of numerous active pharmaceutical ingredients, containing 1,2,4-oxadiazole, which is typically a part of the pharmacophore group (Fig. 1) (see Tables 1–11).

Pleconaril is an inhibitor of replication of picornaviruses used as part of ethiotropic therapy of some respiratory diseases [26]. Oxolamine – an antitussive agent that reduces irritation of nerve receptors of the respiratory tract [27]. Proxazole - analgesic and anti-inflammatory agent for functional gastrointestinal disorders [28]. Opicapone is a drug for the treatment of Parkinson's disease [29]. Amenamevir is an antiviral drug used to treat shingles [30]. Ozanimod is an immunomodulatory drug for the treatment of relapsing multiple sclerosis and ulcerative colitis [31]. Ataluren is an agent for the treatment of Duchenne muscular dystrophy [32]. Butalamine is a vasodilating agent and a smooth muscle relaxant [33].

Recent reviews have discussed the various biological activities of 1,2,4-oxadiazole derivatives [34,35]. One review [34] even mentions the possible use of oxadiazole-based compounds in proteolysis-targeting chimera (PROTAC) strategies based on bifunctional molecules designed to recruit E3 ubiquitin ligase to a specific target protein, which should be invaluable in the near future. These papers give a good insight into the use of 1,2,4-oxadiazoles in drug discovery. There are also several late reviews [36,37] on the biological activities of isomeric oxadiazole and thiadiazole derivatives, which are also useful. One of these papers discusses the wide application of oxadiazole isomers as therapeutic agents. 1,2,4-Oxadiazole is not the only scaffold showing a broad spectrum of biological activity. Thus, there are works showing the importance of the development and application of its isomer - 1,3,4-oxadiazole [38,39]. Its many derivatives may be of interest as pharmaceutical anti-HIV/AIDS

Table 1
The 1,2,4-oxadiazole derivative HDAC inhibitor **NT160**, compared to the approved drugs Vorinostat and Belinostat.

	Structure	IC_{50} (nM)
Approved Drugs		~10
	Vorinostat (SAHA)	
		~27
	Belinostat	
1,2,4-oxadiazole derivate		~1.0
	5, NT160	

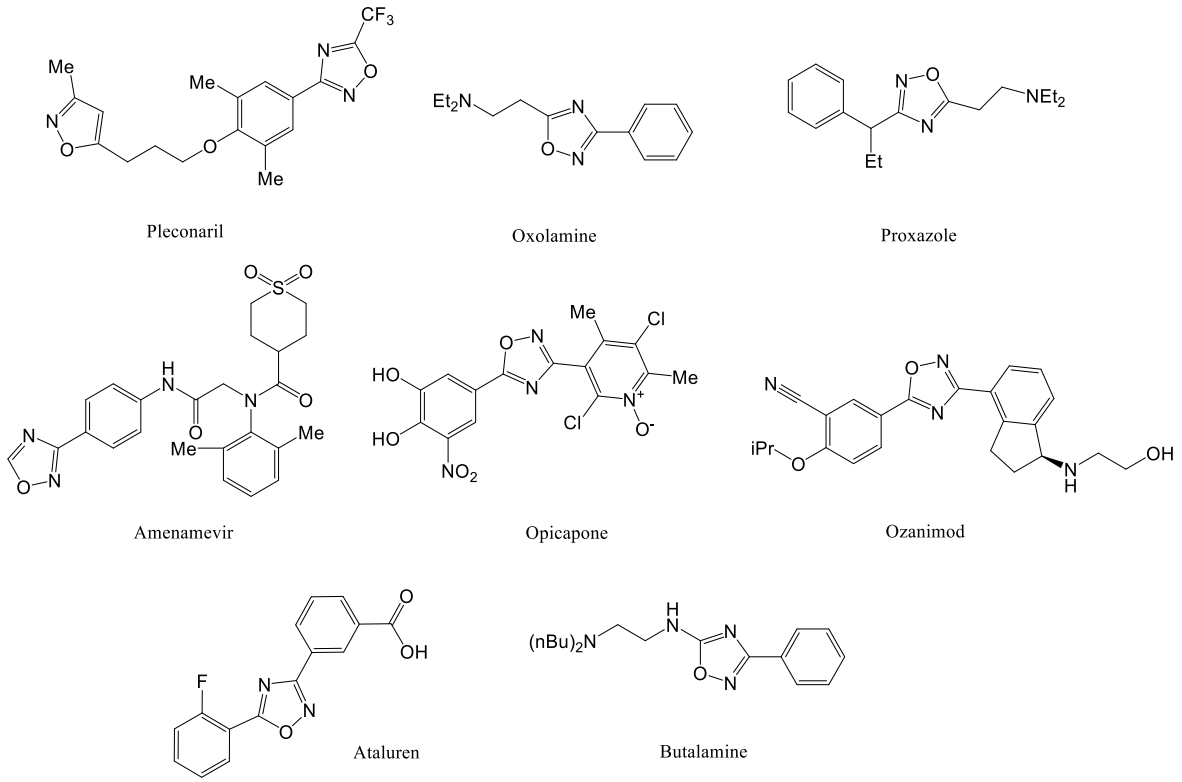


Fig. 1. Chemical structures of active pharmaceutical substances containing the 1,2,4-oxadiazole fragment.

Table 2
The tubulin inhibitors 1,2,4-oxadiazole derivatives **7** and **8** compared to the approved drug Combretastatin A4 Phosphate.

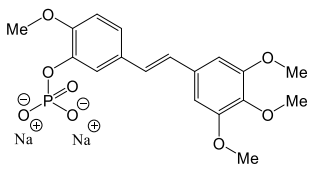
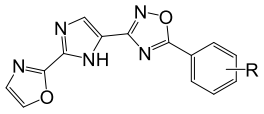
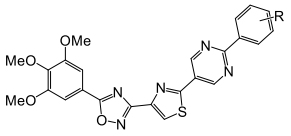
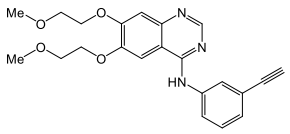
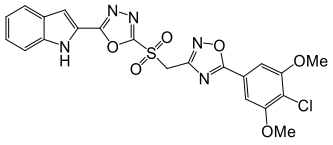
	Structure	IC_{50} (μM)
Approved Drugs (tubulin inhibitors)	 **Fosbretabulin (Combretastatin A4 Phosphate) Disodium**	~2.4
1,2,4-oxadiazole derivate	 **7**	~1.8
	 **8**	~0.06

Table 3
The EGFR inhibitor 1,2,4-oxadiazole derivatives **12** compared to the approved drug Erlotinib.

	Structure	IC_{50}, μM
Approved Drugs (EGFR inhibitors)	 **Erlotinib**	~0.42
1,2,4-oxadiazole derivate	 **12**	~0.21

drugs. However, the cited reviews are either focused on a particular type of biological activity of the corresponding 1,2,4-oxadiazole derivatives, or dealing with the biological properties of the related heterocycles, as well. The purpose of the current review is to make a focus exclusively on the derivatives of 1,2,4-oxadiazoles, as well, as to highlight the most relevant trends of their exploitation in drug discovery of the last years. For the sake of clarity, a large number of compounds containing the 1,2,4-oxadiazole motif are presented here and their broad biological activity is considered. The review helps to focus on understanding the structure-activity relationship of 1,2,4-oxadiazole derivatives with the classification of the material according to the dominant type of pharmacological action of the corresponding derivatives.

Table 4
The VGFR inhibitor 1,2,4-oxadiazole derivatives **16c** compared to the approved drug Sorafenib.

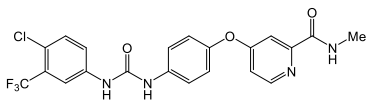
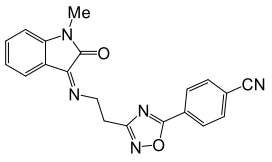
	Structure	IC_{50}, μM
Approved Drugs (VGFR inhibitors)	 **Sorafenib**	~0.09
1,2,4-oxadiazole derivate	 **16c**	~0.045

Table 5
The DNA-gyrase inhibitor 1,2,4-oxadiazole derivatives **55** compared to the approved drug **Novobiocin**.

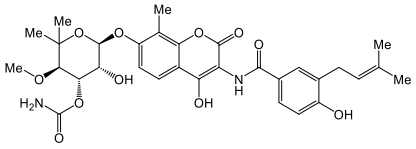
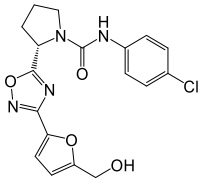
	Structure	IC_{50}, μM
Approved Drugs (DNA-gyrase inhibitors)	 **Novobiocin**	~0.17
1,2,4-oxadiazole derivate	 **55**	~0.012

Table 6
The antibacterial 1,2,4-oxadiazole derivatives **64a** compared to the approved drug **Ciprofloxacin**.

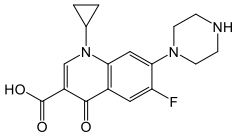
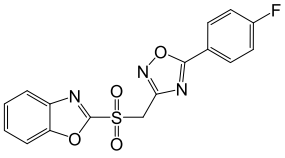
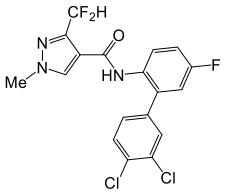
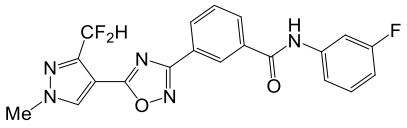
	Structure	MIC, μg/ml
Approved antibiotic	 **Ciprofloxacin**	~6.25
1,2,4-oxadiazole derivate	 **64a**	~3.12

Table 7
The antifungal 1,2,4-oxadiazole derivatives **69b** compared to the approved drug **Baxifen**.

	Structure	EC_{50}, μg/ml
Approved fungicide	 **Baxifen**	~9.15
1,2,4-oxadiazole derivate	 **69b**	~5.49

2. Methodology of literature search

The present review is based on a thorough critical analysis of the recent literature on pharmacologically active 1,2,4-oxadiazole functional derivatives. The search for relevant literature was conducted using the SciFinder, PubMed and Scopus databases. The initial step involved searching for information about these substances by their substructure. Next, the material was classified according to the predominant biological activity exhibited by the compounds under investigation.

At the subsequent stage, each literary source was subjected to a comprehensive analysis using a multitude of parameters derived from the Scopus abstract database, accompanied with the analysis of PubMed database. On the one hand, publications that were cited by sources identified through SciFinder were deemed pertinent to the scope of our review. Conversely, sources that were themselves cited in these publications also merited consideration.

Furthermore, a subset of the initial and concluding authors of the literature sources under investigation was curated, and their subsequent publication activity was meticulously analyzed using the resources of the Scopus and, when necessary, PubMed databases, concurrently identifying publications that were germane to the subject matter at hand. This process resulted in an extensive list of literary sources for each category of 1,2,4-oxadiazole derivatives, taking into account their pharmacological properties.

Following a careful evaluation and, where necessary, revision of the accumulated data, the final iteration of this review was formulated, culminating in a comprehensive and well-structured analysis.

Due to the fact that 1,2,4-oxadiazole derivatives can rightfully be considered privileged structures for the targeted search for biologically active compounds with a given type of pharmacological activity, several review papers have been devoted to these derivatives. In comparison with them, however, the present work has several fundamental distinguishing features. Thus, unlike the works of [34,35], the present work focuses on literary sources that were published after the publication of these reviews. The literature review [36] is less thematically consistent from a conceptual point of view, since it also deals with thiadiazole derivatives along with isomeric oxadiazole derivatives. In addition, this review also does not include an analysis of the literary sources of 2023 and 2024, which the present review is focused on. The same applies to the comparison of this review with the review [37], which is a little out of focus, as it is dealing with various isomeric derivatives of oxadiazole, as well as does not include the latest literature data, since it was published 3 years ago.

3. Functional derivatives of 1,2,4-oxadiazole with anticancer properties

In recent years, a number of 1,2,4-oxadiazole derivatives have been identified as potential oncolytic agents. Depending on their chemical structure, these compounds exert their biological effects by acting on a variety of different biological targets. For example, the synthesis and biological properties of 1,2,4-oxadiazole derivatives containing a chromene fragment in their structure have been described [40]. The obtained compounds were characterized by the authors as agonists of the TLR receptor. In particular, the TLR-2 receptor is a transmembrane protein that participates in the innate immune response by forming heterodimers with TLR-1 or TLR-6 receptors. TLR-2 agonists are attractive candidates for the development of immunotherapeutic agents against malignant neoplasms. The general structure of the synthesized derivatives **1** and the lead compound **2** (**WYJ-2**) is shown in Fig. 2. **WYJ-2** exhibited potent agonistic activity against TLR-2 and TLR-1 with TLR-2 EC_{50} = 18.57 nM, thereby inducing pyroptosis of cancer cells. This compound showed high efficacy against non-small-cell lung cancer (NSCLC) both *in vitro* and *in vivo*.

The combination of 1,2,4-oxadiazole and chromene skeleton led to the development of compounds with antiproliferative activity on MCF-7 and HeLa cell lines [41]. Compounds **3a**, **3b** and **3c** were found to be the most active. Compound **3a** showed activity on MCF-7 with IC_{50} = 4.12 μM. The 1,2,4-oxadiazole fragment in these compounds is a part of the pharmacophore and enhances the drug-like properties. The authors also

Table 8
The antimycobacterial 1,2,4-oxadiazole derivatives **73a** compared to the approved drug **Ethambutol**.

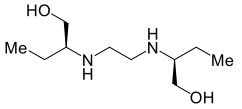
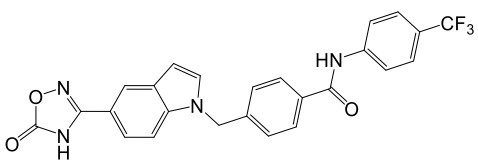
	Structure	MIC, μg/ml
Approved antimycobacterial drug	 **Ethambutol**	~1.56
1,2,4-oxadiazole derivate	 **73a**	~0.78

Table 9
The antiparasitic 1,2,4-oxadiazole derivatives **82** compared to the approved drug **Astemizole**.

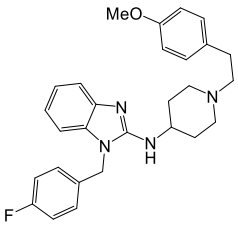
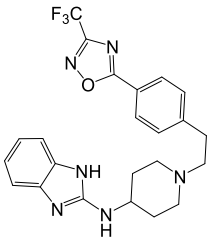
	Structure	IC_{50}, μM
Approved antiparasitic drug	 **Astemizole**	~0.63
1,2,4-oxadiazole derivate	 **82**	~0.0042

Table 10
The anti-HBV 1,2,4-oxadiazole derivatives **93** compared to the approved drug **Lamivudine**.

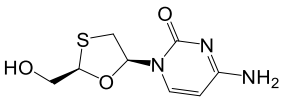
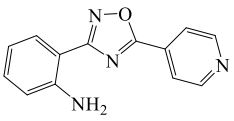
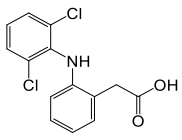
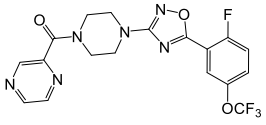
	Structure	IC_{50}, μM
Approved anti-HBV drug	 **Lamivudine**	~0.316
1,2,4-oxadiazole derivate	 **93**	~0.44

Table 11
The anti-inflammatory 1,2,4-oxadiazole derivatives **101** compared to the approved drug Lamivudine.

	Structure	MIC, μg/ml
Approved anti-inflammatory drug	 **Diclofenac**	~1.56
1,2,4-oxadiazole derivate	 **101**	~0.78

concluded that electron acceptor groups in the benzene ring increase the antiproliferative activity of the compounds.

An alternative mechanism of antitumor action is provided by derivatives of 3-aryl-5-(trifluoromethyl)-1,2,4-oxadiazole [42], which inhibit histone deacetylases (HDAC) of class IIa. The compounds contain 5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl (TFMO) group as zinc-binding moiety instead of the more classical hydroxamic acid, benzamide or thiol moiety. The most active compound **4** selectively inhibits HDAC IIa isoforms 4, 5, and 7 with IC_{50} values of = 12, 19 and 46 nM, respectively, and a selectivity factor of >300 over class I HDAC isoforms. It also showed inhibitory cytotoxic effect against Cal27 head and neck cancer cells in an assay where it was superior to the known class IIa HDAC inhibitor YAK540. In addition, the compound was shown to have the potential for synergistic anti-tumor activity with bortezomib. The TMFO binding group is also present in the structure of 1,2,4-oxadiazole derivative **5** (**NT160**), another selective HDAC IIa inhibitor with nanomolar and subnanomolar activity range of concentrations (IC_{50} = 0.08 nM vs HDAC4, 1.2 nM vs HDAC5, 1 nM vs HDAC7, 0.9 nM vs HDAC9) and similar mechanism of action [43]. It was established that the synthesized radiolabeled **[18F]-NT160** analogue could cross the blood-brain barrier and be used for diagnostic positron emission tomography, thus facilitating further targeted therapy with non-radioactive **5** (**NT160**).

Another important biological target for 1,2,4-oxadiazole derivatives with anti-tumor properties is the active tubulin binding site. A series of 1,2,4-oxadiazole derivatives **6** demonstrated the ability to inhibit the proliferation of breast (MCF-7, MDA MB-231), lung (A549), and prostate (DU-145) cancer cells and were compared to etoposide [44]. Derivatives of 1,2,4-oxadiazole **7** containing an imidazole moiety at the C-3 position showed antiproliferative activity against breast MCF-7 (IC_{50} = 0.09–3.42 μM), lung A549 (IC_{50} = 0.06–2.58 μM), prostate DU-145 (IC_{50} = 0.19–2.80 μM) and PC-3 (IC_{50} = 0.23–2.77 μM) cancer cell lines and were comparable or superior to the reference drug etoposide (IC_{50} = 2.11, 3.08, 1.97, 2.39 μM, respectively) [45]. Another series of 1,2,4-oxadiazole derivatives **8**, which demonstrated activity against the same cancer cell lines, contain thiazole and pyrimidine in their structure [46]. The derivatives showed highly selective antiproliferative activity ($IC_{50} \geq 19$ μM on Vero kidney epithelial cells) with IC_{50} values ranging from 0.02 to 10.3 μM, as compared to etoposide (IC_{50} = 1.97–3.08 μM). The 1,2,4-oxadiazole derivative (**9**, **SP04**) is endowed with high *in vitro* activity against the prostate cancer cell line PC-3 (IC_{50} = 238.13 nM and 89.99 % inhibition). Bicalutamide was used as a reference drug. Furthermore, this compound reduced the expression of the androgen receptor [47].

Given the crucial function of caseinolytic protease P (HsClpP) in maintaining homeostasis, agonists of this enzyme are considered to be potential antitumor agents. The 1,2,4-oxadiazole derivative **10** (**SL44**) was found to exhibit agonist activity on HsClpP, with an EC_{50} value of 1.3 μM. In addition, it demonstrated the ability to inhibit the growth of human hepatocellular carcinoma HCCLM3 cells (IC_{50} = 3.1 μM). Furthermore, it was determined to be a safer alternative to sorafenib [48]. Notably, this is the first reported example of an HsClpP agonist demonstrating antiproliferative activity in hepatocellular carcinoma (HCC). Further investigation of this novel class of agonists is certainly warranted.

In some studies, the antitumor activity of 1,2,4-oxadiazole derivatives has been linked to the inhibition of EGFR tyrosine kinase activity. One of the examples is the synthesis and study of the novel substituted 1,2,4-oxadiazoles [49] of the following general structure 11 (Fig. 3). The most active derivative showed efficacy against the breast cancer cell lines MCF-7, MDA-MB-231 and MDA-MB-468 (IC_{50} < 10 μM), exhibiting superior activity compared to the drug 5-fluorouracil (5-FU). Additionally, it showed greater potency against EGFR tyrosine kinase (IC_{50} = 0.47 μM), outperforming the reference drug erlotinib (IC_{50} = 0.43 μM).

Derivatives of the compounds **12** [50] and **13** [51], which

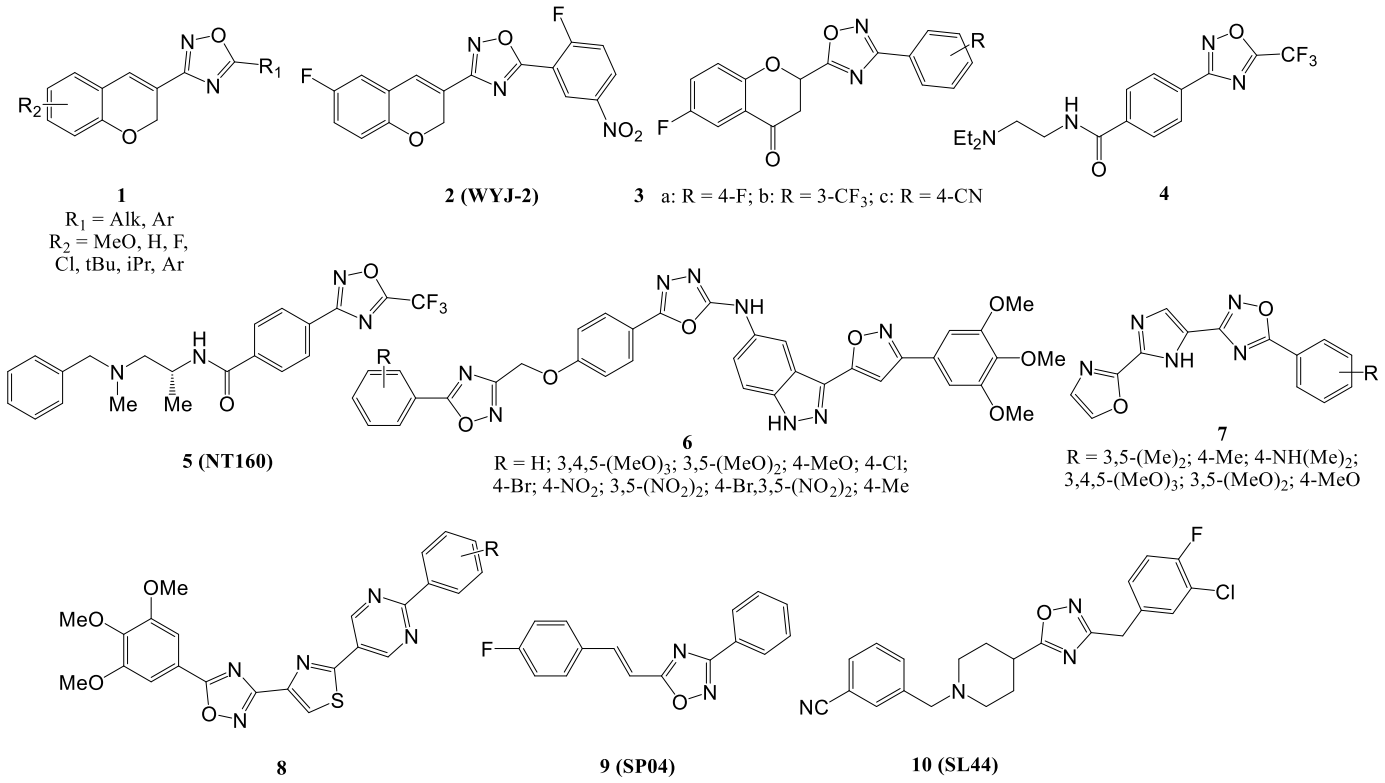


Fig. 2. The structures of compounds **1**–**10** exhibiting antiproliferative properties.

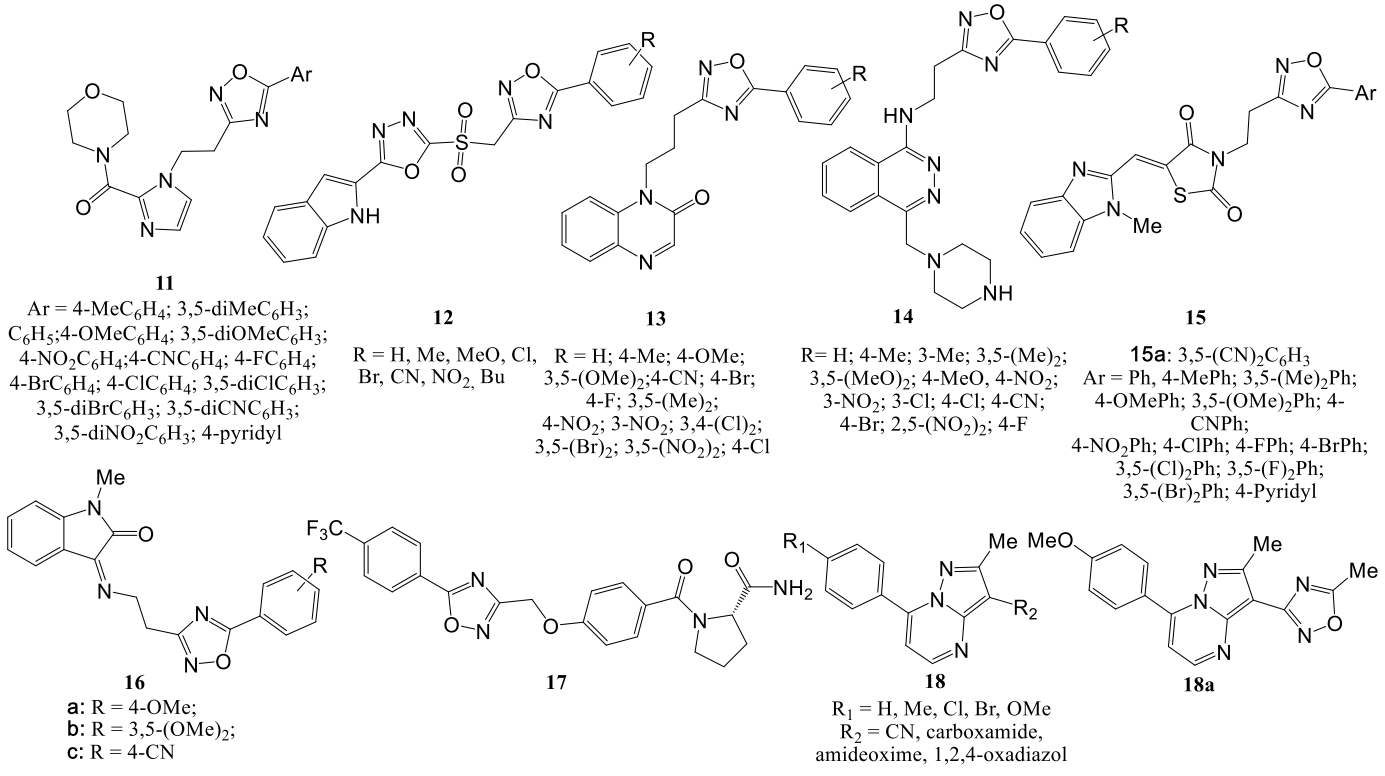


Fig. 3. The structures of compounds **11**–**18** exhibiting antiproliferative properties.

demonstrated inhibitory activity against the growth of MCF-7 (breast cancer), A-549 (lung cancer), HeLa (human cervical cancer), HCT116 (human colorectal cancer), and HepG2 (human hepatocellular carcinoma) cells, also exhibited inhibitory activity against EGFR tyrosine kinase. Erlotinib [50,51] was used as reference drugs. Similar activity was also observed for the 5-phenyl-1,2,4-oxadiazole derivatives

14 [52]. Compounds **12** and **13** were more effective than conventional Erlotinib treatment in inhibiting EGFR tyrosinekinase. The best of the series, compound 12, showed an IC_{50} value of 0.214 μM vs 0.42 μM for Erlotinib. The best compound **13** showed inhibitory activity against EGFR tyrosinekinase with an IC_{50} value of 0.31 μM vs 0.41 μM for the reference drug. In this study, etoposide (MCF-7 IC_{50} = 0.92 μM) was used as the reference drug. The most active compound exhibited carcinolytic properties against several human cancer cell lines, including MCF-7 (breast cancer) with an IC_{50} value of 0.9 μM, A549 (lung cancer) with an IC_{50} value of 1.4 μM, and DU-145 (prostate cancer) with an IC_{50} value of 2.16 μM. Other 1,2,4-oxadiazole derivatives **15**, showing inhibitory activity against EGFR tyrosine kinase contain benzimidazole and thiazolidine-2,4-dione fragments in their structure, as well. A systematic analysis of the SAR, revealed that nitro groups in the benzene ring positively contribute to the desired biological activity. The lead compound **15a** demonstrated antiproliferative activity against MCF-7 (IC_{50} = 1.32 μM), A-549 (IC_{50} = 19.72 μM) and HepG2 (IC_{50} = 11.27 μM) cell lines, and exhibited superior efficacy compared to the reference drug erlotinib in both cell lines (IC_{50} = 4.15, 20.10, and 13.30 for erlotinib, respectively) and in the enzymatic assay for EGFR (IC_{50} = 0.26 μM vs. IC_{50} = 0.40 μM for erlotinib) [53]. Overall, these findings highlight the potential of these compounds as therapeutics in cancer treatment.

1,2,4-Oxadiazole derivatives containing an isatin fragment were reported to inhibit VGFR-2, another tyrosine kinase. Compounds **16a**, **16b** and **16c** showed better antiproliferative activity on A549, PC3, DU145 and MCF-7 cell lines than 5-fluoro uracil used as reference drug, with compound **16c** being almost 2-fold more active than sorafenib when tested against VEGFR-2 [54]. For some kinase inhibitors with antitumor activity, the bioisosteric replacement of the benzene nucleus in the pharmacophore structure with a more hydrophilic 1,2,4-oxadiazole fragment appeared to be fruitful from the point of the desired pharmacological activity of the latter [55]. In particular, a number of new sphingosine kinase 2 inhibitors have been obtained, representing a promising class of potential oncolytics. The structural formula of the most active (SphK2 IC_{50} = 2.4 nM) and selective (SphK1 IC_{50} > 10 μM) compound **17** is shown in Fig. 3. Among the functional derivatives of 1,2,4-oxadiazole, compounds capable of blocking the activity of several different kinases (TrkA, ALK2, c-KIT, EGFR, PIM1, CK2α, CHK1 and CDK2) have also been found [56]. General formula of these compounds **18** and the structure of the compound, which turned out to be the most active in cellular assays **18a** (MCF7 IC_{50} = 3.36 μM, HCT116 IC_{50} = 1.4 μM, EKVX IC_{50} = 3.49 μM) are shown in Fig. 3. Compound **18a** also exhibited high inhibitory activity against a number of kinases: TrkA IC_{50}

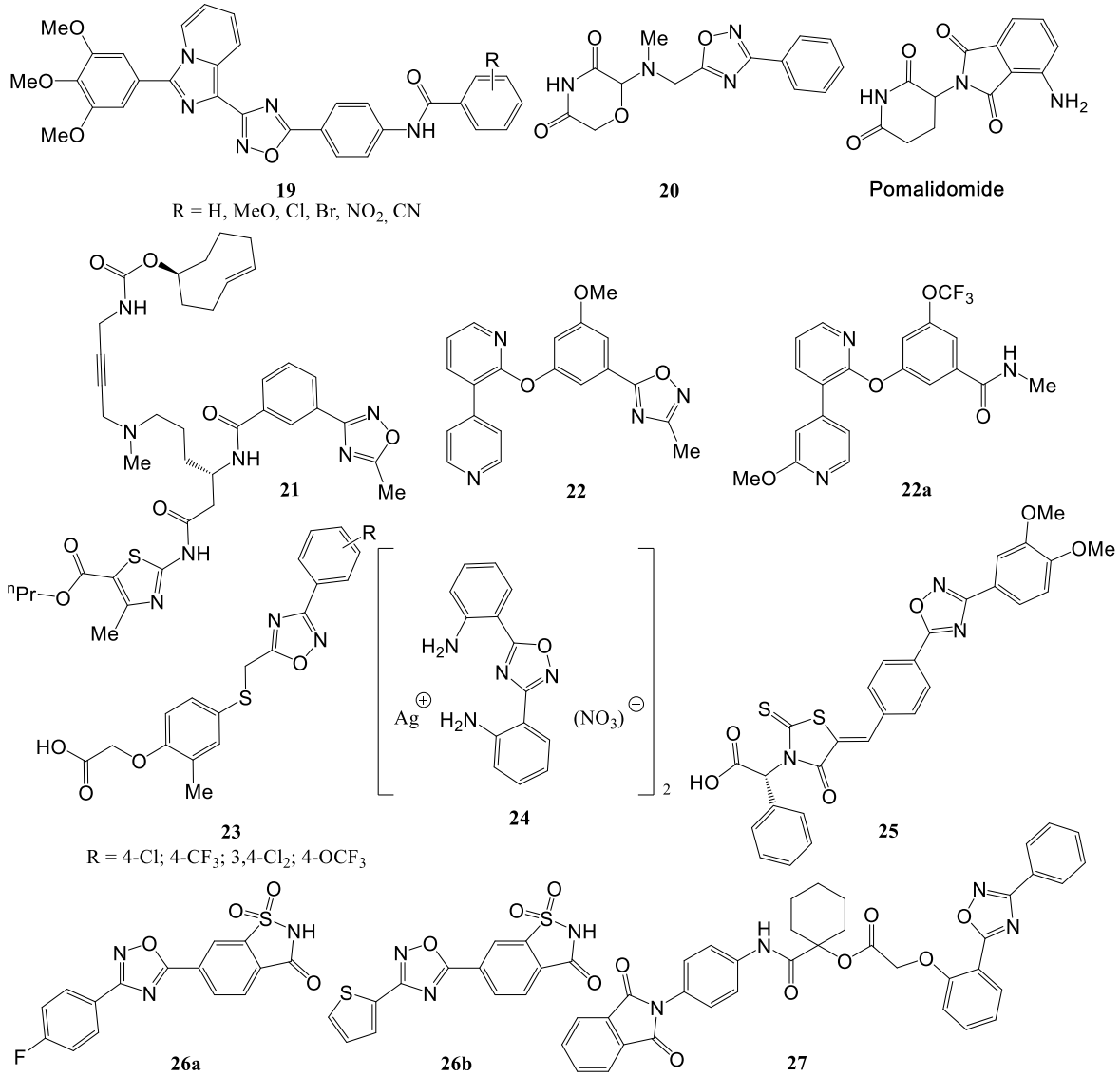


Fig. 4. The structures of compounds **19**–**27** that demonstrate anti-proliferative properties.

= 0.33 μM, ALK2 IC_{50} = 0.03 μM, c-KIT IC_{50} = 0.05 μM, EGFR IC_{50} = 0.10 μM, PIM1 IC_{50} = 0.42 μM, CK2α IC_{50} = 0.09 μM, CHK1 IC_{50} = 0.15 μM and CDK2 IC_{50} = 0.71 μM. Collectively, these results suggest that 1,2,4-oxadiazole derivatives have potential as oncolytics with multiple kinase inhibitory properties.

Some studies are dedicated to the investigation of oncolytic properties of 1,2,4-oxadiazole derivatives, based upon the phenotypic screening of the latter. However, their specific biomolecular mechanism of action remains to be elucidated. In particular, derivatives of 5-phenyl-1,2,4-oxadiazole **19** (Fig. 4) containing an imidazopyridine fragment as part of the molecule have been obtained [57]. The synthesized compounds were found to have cytotoxic properties on various human cancer cell lines, namely MCF-7, lung A549, Colo-205 and A2780 cancer cells. Some of their cyclic derivatives with antitumor properties were also investigated, and it was found that the 1,2,4-oxadiazole fragment was present outside the structure of the main pharmacophore [58]. Specifically, the derivative **20** was discovered to have cytotoxic properties against malignant MOLT-4 and KMS-12 PE cells comparable to the reference drug pomalidomide (Fig. 4). Overall, further research is needed for the complete understanding of the mechanism of action of these compounds and their anticancer potential.

Pharmacophore decoration with a 1,2,4-oxadiazole fragment in the directed design of inhibitors of HSET protein activity (KIFC1) with carcinolytic properties has yielded successful results. The introduction of the methyl-1,2,4-oxadiazole fragment in place of the methyl group resulted in a significant increase in the overall activity, as evidenced by the most active compound **21** (**CCT369834**), which exhibited a nanomolar concentration range (HSET IC_{50} = 39 nM) [59]. The carcinolytic effect of these compounds is based upon their ability to inhibit HSET (KIFC1), which is crucial for cancer cells to cluster additional centrosomes into two groups to mimic the formation of a bipolar spindle and ensure their survival.

The decoration of the structural framework of oncolytic agents with 1,2,4-oxadiazole led to the preparation of new inhibitors of aurora kinases (AURKs) [60]. In this case, the 1,2,4-oxadiazole fragment was used as a bioisostere of the amide group. The resulting derivative **22** (Fig. 4), was found to exhibit reduced activity compared to open-chain analogues, with **22a** exhibiting the most remarkable activity with an EC_{50} range of 6.5–17.5 nM across seven cancer cell lines.

Other targets for the anticancer drug development are the receptors for activators of proliferation such as peroxisome proliferator-activated receptor δ/β (PPARδ/β). The authors reported the preparation of (4-{[(3-aryl-1,2,4-oxadiazole-5-yl)methyl]thio}-2-methylphenoxy)acetic acids **23**, which exhibit pronounced agonist activity with respect to the aforementioned receptors [61].

Metal complexes with ligands capable of inhibiting tumor cells growth have also been developed. The complexes of Ag (I) and Cu (II) with 2,2'-(1,2,4-oxadiazol-3,5-diyl)dianiline showed remarkable cytotoxic activity against A549, Caco-2, and MDA-MB231 cell lines, exhibiting superior efficacy compared to the chemotherapeutic drug 5-FU [62]. Among the obtained compounds, **24** was the most active, exhibiting IC_{50} values of = 0.074, 0.085 and 0.533 μM vs A549, Caco-2, and MDA-MB231 cell lines, respectively. The MTT cytotoxicity assay demonstrated that compound **24** had a superior safety profile compared to 5-FU. Quantitative PCR analysis revealed that the synthesized complex compounds were capable of suppressing the *BCL-2* oncogene and enhancing the expression of the pro-apoptotic gene *BAX*.

The application of the 1,2,4-oxadiazole core in the design of inhibitors targeting various isoforms of human carbonic anhydrase (hCA) resulted in the synthesis of the rhodanine-bound 1,2,4-oxadiazole **25**, which demonstrated activity against hCA II and hCA IX (Ki = 5.8 and 81.8 μM, respectively) [63] (Fig. 4). The mechanism of action of this compound was investigated by molecular modeling. Derivatives of 1,2,4-oxadiazole containing a saccharin residue in their structure exhibit a similar mechanism of action [64]. The inhibitory activity of compounds **26a** and **26b** against hCA II was found to be particularly high, with a Ki value of 3 μM.

It has been demonstrated that compounds with anticancer properties may exert their effects on caspase-3/7, which represents a potential target for such action. Using the so-called scaffold hopping approach, compounds capable of inducing caspase-3/7 dependent apoptosis of cancer cells have been developed [65]. These compounds exhibited superior efficacy to 5-FU (A549 IC_{50} = 3.08 μM, Caco-2 IC_{50} = 0.28 μM, MDA-MB 231 IC_{50} = 21.84 μM) on lung A549, colon Caco-2, and breast MDA-MB 231 tumor cell lines. One of the most active compounds was the 1,2,4-oxadiazole derivative **27** (A549 IC_{50} = 0.16 μM, Caco-2 IC_{50} = 0.19 μM, MDA-MB 231 IC_{50} = 0.04 μM) (Fig. 4), but it had some limitations in terms of its molecular weight, number of rotating bonds, and low solubility for oral administration. The derivative was observed to induce apoptosis by 53.11 % with an IC_{50} = 0.04 μM and a selectivity index (SI) of 105.28. Additionally, the researchers modeled the binding of the synthesized compounds to the XIAP domain of BIR2, which is a specific receptor for caspase-3/7 activators. In general, further optimization of the structure of this series of compounds is required.

Inhibition of oxidative phosphorylation (OXPHOS) is a promising approach for the treatment of certain cancers that depend on aerobic metabolism. For instance, derivative **28a** (**DX3-235**) (Fig. 5) has been observed to inhibit the proliferation of pancreatic cancer cells by inhibiting the OXPHOS complex I (IC_{50} = 30 nM) and adenosine triphosphate (ATP) production, resulting in a notable degree of cytotoxicity on the MIA PaCa-2 cell line at nanomolar concentrations (IC_{50} = 70 nM) [66]. It is noteworthy that derivative **28b** (**DX3-234**) was observed to have a pronounced inhibitory effect on tumor growth in the Pan02 syngeneic mouse model of pancreatic cancer and is well tolerated in mice. These findings suggest the potential for the development of novel antitumor drugs targeting OXPHOS-dependent cancers. In this study, the ester group of the lead compound was replaced with a 1,2,4-oxadiazole-containing fragment, resulting in significant improvements in metabolic stability, antiproliferative activity, and enzymatic potency. In this study, the fragment containing 1,2,4-oxadiazole was employed as a bioisosteric replacement for the ester group.

Another strategy for the treatment of pancreatic cancer is the inhibition of STAT3 phosphorylation. Therefore, 3-aryl-1,2,4-oxadiazole derivatives containing a 1-methyl-1*H*-indole moiety where the 1,2,4-oxadiazole fragment is a part of the pharmacophore have been synthesized [67]. *In vitro* and *in vivo* studies demonstrated that compound **29** was the most active with a favorable ADMET profile. This compound, which acts on the SH2 domain of STAT3, was observed to inhibit the nuclear transcription and mitochondrial oxidative phosphorylation function of STAT3 at nanomolar level. Furthermore, when administered orally, this substance demonstrated a suppressive effect on the pancreatic cancer xenograft model, indicating its potential for the treatment of this disease. Replacement of the indole and pyrazine structural fragment with a benzene ring in compound **29** resulted in the construction of a novel inhibitor of STAT3 phosphorylation - compound **30** (**HP590**) [68]. This compound was found to significantly inhibit STAT3 activation, which led to the inhibition of gastric cancer growth both *in vitro* and *in vivo*. In a different study regarding the targeting of gastric cancer, a derivative of 1,2,4-oxadiazole with a pyridin-2-one fragment at the C-5 position, compound **31**, was developed and evaluated. This compound targeted the hairpin in pre-microRNA-372 (affinity 300 nM). It has been demonstrated to contribute to the inhibition of pre-microRNA-372 processing into mature microRNA in cancer cells (IC_{50} = 1 μM) [69]. Derivatives of the 1,2,4-oxadiazole heterocycle incorporating an indole moiety were synthesized as potential therapeutic agents against pancreatic adenocarcinoma [70]. The most active compound **32** demonstrated activity with IC_{50} values in the range of 5.7–10.7 μM on PATU-T, Hs766T, HPAF-II, and PDAC3 cell lines. Furthermore, this compound demonstrated favorable pharmacokinetic properties, induced apoptosis in PATU-T and PDAC3 cells, and inhibited the expression of cyclin-dependent kinase 1 (CDK1).

In another study, oxadiazole derivatives **33a** and **33b** were reported

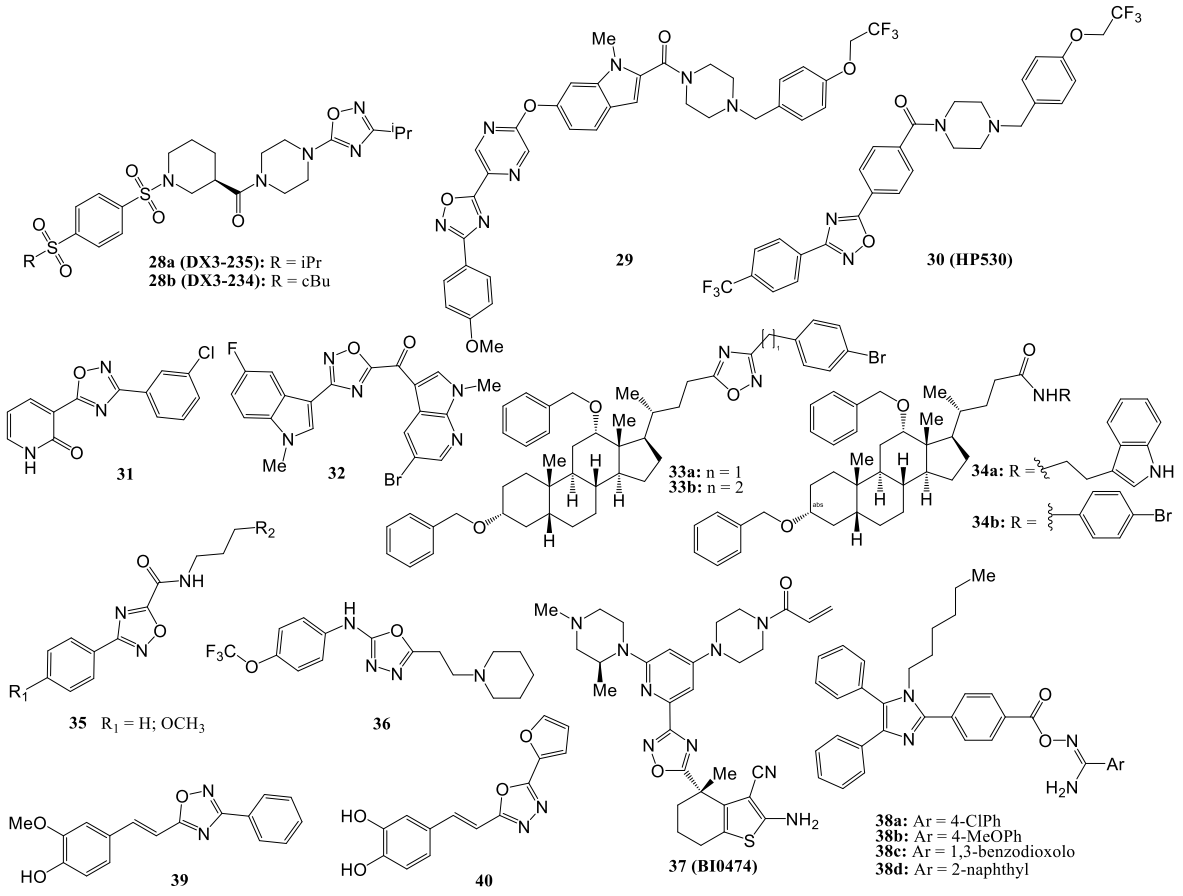


Fig. 5. The structures of compounds **28**–**40** that demonstrate anti-proliferative properties.

to be selectively active against the enzyme tyrosyl-DNA phosphodiesterase 1 (TDP1) and synthesized-with IC_{50} values of = 0.53 μM and 0.42 μM, respectively, and with IC_{50} > 50 μM *vs* tyrosyl-DNA phosphodiesterase 2 (TDP2) [71]. The analogues **34a** and **34b,** showed a much lower selectivity (TDP1 IC_{50} = 0.24 and 0.57 μM for **34a** and **34b**, respectively; TDP2 28 % and 47 % of inhibition at 1 mM for **34a** and **34b**, respectively). Furthermore, these compounds demonstrated no cytotoxicity on HeLa and HEK293 cell lines. It is noteworthy that TDP1 and TDP2 enzymes play a significant role in the development of resistance to anticancer drugs that target DNA damage in malignant cells. Consequently, they are considered an attractive target for the development of drugs that can overcome the resistance of tumor cells to chemotherapy. Through SAR analysis, it was established that the incorporation of an amide group and a 1,2,4-oxadiazole heterocycle enhances the activity against both TDP1 and TDP2 enzymes. Overall, these findings suggest the potential for developing novel TDP1 and TDP2 inhibitors as adjuncts to cancer chemotherapy, particularly in combination with topoisomerase poisons.

Another target for compounds with antiproliferative activity is the mechanistic target of rapamycin (mTOR), which plays a role in regulating growth and metabolism by modulating anabolic and catabolic processes. In order to develop inhibitors of this enzyme, 3-aryl-1,2,4-oxadiazole-5-carboxamide derivatives **35** and their isomers containing 1,3,4-oxadiazoles were developed. The latter showed higher antiproliferative activity against the breast cancer cell line MDA-MB-231 with the most active compound being **36** (mTOR IC_{50} = 0.51 μM and MDA-MB-23 IC_{50} = 3.9 μM). The derivatives obtained can be used to treat various types of cancer by inhibiting mTOR [72].

One of the most promising biological targets in the search for anticancer agents is the GTPase $KRAS^{G12C}$. In this regard, the development of inhibitors who selectively inhibit KRAS among the other RAS family proteins and specific oncogenic KRAS mutations without affecting the wild-type protein is a challenging task. Compound **37** (**BI0474**) [73] was designed as a reversible covalent inhibitor of $KRAS^{G12C}$ oncogenic mutant, trapping the protein to the inactive GDP-bound state by bindings to the switch II pocket. In this study, the 1,2,4-oxadiazole moiety was employed to impart conformational rigidity to the structure and mitigate entropic losses during the interaction of the inhibitor with the biological target. The crystal structure of a non-covalent analogue of compound **37** in complex with $KRAS^{G12V,S39C}$ (PDB ID: 8AFB) firstly revealed the importance of the oxadiazole fragment in gaining affinity with the target through an hydrogen bond with His95. Further decoration of the main oxadiazole-containing scaffold and the introduction of an acrylamide warhead to covalently bind Cys12 led to compound **37**. The antiproliferative activity of **37** was demonstrated in cell-based assays on the NCI–H358 line (non-small cell lung cancer xenograft model) with a G12C mutation and gave an IC_{50} = 26 nM. The assay was also performed on GP2D or LS513 cells carrying G12D mutation showing an antiproliferative effect was only observed above 4 μM. Additionally, the compound exhibited *in vitro* activity on $KRAS^{G12C}$ with an IC_{50} = 7 nM. The efficacy of this compound was also confirmed *in vivo*. The inhibition of cancer growth at day 19 was 98 % for mice dosed intraperitoneally with 40 mg/kg twice weekly, which is a promising result.

1,2,4-Oxadiazole derivatives containing imidazole were synthesized as inhibitors of $BRAF^{V600E}$ (a common oncogenic mutation found in many cancers) and p38α, an isoform of P38 mitogen-activated protein kinase (MAPK), which is required for the regulation of the tumor suppressor protein p53, the major mediator of apoptotic cell death. The carboxamide group was shown to play a pivotal role in conferring high biological activity. The highest activity was observed for compounds **38a**, **38b**, **38c** and **38d**, and in particular **38c** showed IC_{50} values of 0.80 μM (PC-3), 0.70 μM (MCF-7), 1.10 μM (Panc-1) and 0.90 μM (HT-

29) which additionally exhibited inhibitory effects on $BRAF^{V600E}$ and p38α, with IC_{50} = 0.33 and 0.19 μM, respectively [74].

Bioisosteric 1,2,4-oxadiazole derivatives of the fatty aromatic esters of ferulic and caffeic acids, along with their structural analogues containing 1,3,4-oxadiazole moieties, have also demonstrated the capacity to impede the proliferation of malignant cancer cells. In particular, compound **39** demonstrated inhibitory activity against glioblastoma cell lines LN229, T98G and U87 (IC_{50} = 80.4, 39.2, 60.3 μM), and against SKOV3, MCF7, A549 cells (IC_{50} = 21.1, 70.9, 62 μM) [75]. The 1,3,4-oxadiazole derivative **40** demonstrated inhibitory activity against the growth of U87, T98G, LN229, and SKOV3, MCF7, and A549 cell lines, with IC_{50} values of 35.1, 34.4, 37.9, 14.2, 30.9, and 18.3 μM, respectively. Furthermore, compounds **39** and **40** demonstrated no toxicity towards human mesenchymal stem cells (hMSC). The structures containing fragments of 1,2,4-oxadiazole and hippuric acid demonstrated inhibitory activity against breast (MCF-7), lung (A549), colon (Colo-205) and ovarian (A2780) cancer cell lines with IC_{50} values in the range of 0.018–21.5 μM [76].

1,2,4-Oxadiazole derivatives have been identified as potent and selective inhibitors of Sirtuin 2 (SIRT2), a member of the sirtuin family of NAD^+-dependent deacetylases involved in various cellular processes, including aging and cancer progression (Fig. 6).

The authors reported the development of 1,2,4-oxadiazole derivatives as potent inhibitors of SIRT2. Compounds **41a**-h (Fig. 6) demonstrated activity in the single-digit micromolar range and selectively inhibited SIRT2 while being inactive against other isoforms such as SIRT1, SIRT3, and SIRT5. Structural analysis revealed an uncompetitive inhibition mechanism, suggesting potential for further development in anticancer strategies. Compounds **41a-41c** and **41f** were selected according to their potency in inhibiting Sirt2 and/or inducing apoptosis in U937 cells and were tested against leukemia cells (U937, NB4, HL-60 and K562) and breast cancer cells MDA-MB-231 for 48h at 5, 10, 25 and 50 μM. Among the tested compounds, **41b** was highly active against NB4 cells already at 10 μM and showed >80 % apoptosis in U937 cells at 50 μM. Compound **41a** was the most effective (>80 %) as an apoptosis inducer at 25 μM in 3 out of 5 cell lines (NB4, K562, and MDA-MB-231), while **41f** showed 30–40 % apoptosis at only 50 μM against NB4 and MDA-MB-231 cells, and **41c** was less effective overall [77]. A recent study detailed structure-activity relationship (SAR) studies of 1,2,4-oxadiazoles targeting SIRT2. The work highlighted the ability of compounds **42a-k** to inhibit SIRT2 deacetylation, reduce cell viability, and inhibit prostate cancer cell migration. Molecular interactions were confirmed by docking and crystallographic studies, showcasing the therapeutic relevance of oxadiazoles as SIRT2 inhibitors [78]. The authors evaluated oxadiazole-carbonylaminothioureas **43a-d** as inhibitors of SIRT1 and SIRT2. The compound **43a** exhibited moderate selectivity and potency, with IC_{50} values of 192 μM for SIRT1 and 57 μM for SIRT2. These inhibitors demonstrated the potential to interfere with NAD $^+$ binding, a key requirement for sirtuin activity [79].

The authors synthesized a new series of **topsentin** analogues (Fig. 7) in which the central imidazole ring of natural lead was replaced by a 1,2,4-oxadiazole moiety [80]. All derivatives were preliminarily screened for antiproliferative activity against a panel of National Cancer Institute (NCI-60) cell lines. The five most potent compounds were further tested on various pancreatic ductal adenocarcinoma (PDAC) cell lines, including SUIT-2, Capan-1, and Panc-1 cells, yielding EC_{50} values in the micromolar and submicromolar range associated with a significant reduction in cell migration. The authors attributed the obtained data to the effects of the synthesized compounds on markers of epithelial-mesenchymal transition, including SNAIL-1/2 and metalloproteinase-9. Moreover, flow cytometric analysis after Annexin V-FITC and propidium iodide staining demonstrated that these 1,2,4-oxadiazole derivatives enhance PDAC cell apoptosis. The authors used the ADP-Glo™ specific activity assay to modulate GSK-3β activity by the obtained compounds. The 1,2,4-oxadiazole compounds demonstrated GSK-3β inhibition in a dose-dependent manner. The IC_{50} values for the two most active compounds (**44b** and **44l**) (Fig. 7) were 0.62 and 0.81 μM, respectively. The other compounds (**44c**, **44l**, and **44j**) inhibited GSK3β with slightly lower potency (IC_{50} values in the range of 1.2–2.5 μM). These results indicate that the obtained 1,2,4-oxadiazole derivatives are direct inhibitors of GSK-3β *in vitro*. The most active compounds were docked to the ATP binding site of GSK3β (PDB 1UV5), showing similar interactions with the co-crystallized ligand **6-bromoindirubin**, a known potent and selective bis-indolyl inhibitor of the enzyme. Compounds **44b** and **44l** are located in the same narrow hydrophobic pocket of the co-crystallized ligand, establishing a hydrogen bond through their indole nitrogen with the peptide carbonyl oxygen of residue Val135. Moreover, their carbonyl group accepts a hydrogen bond from a water molecule interacting with Lys85, a residue that has been successfully targeted by carbonyl groups of potent inhibitors

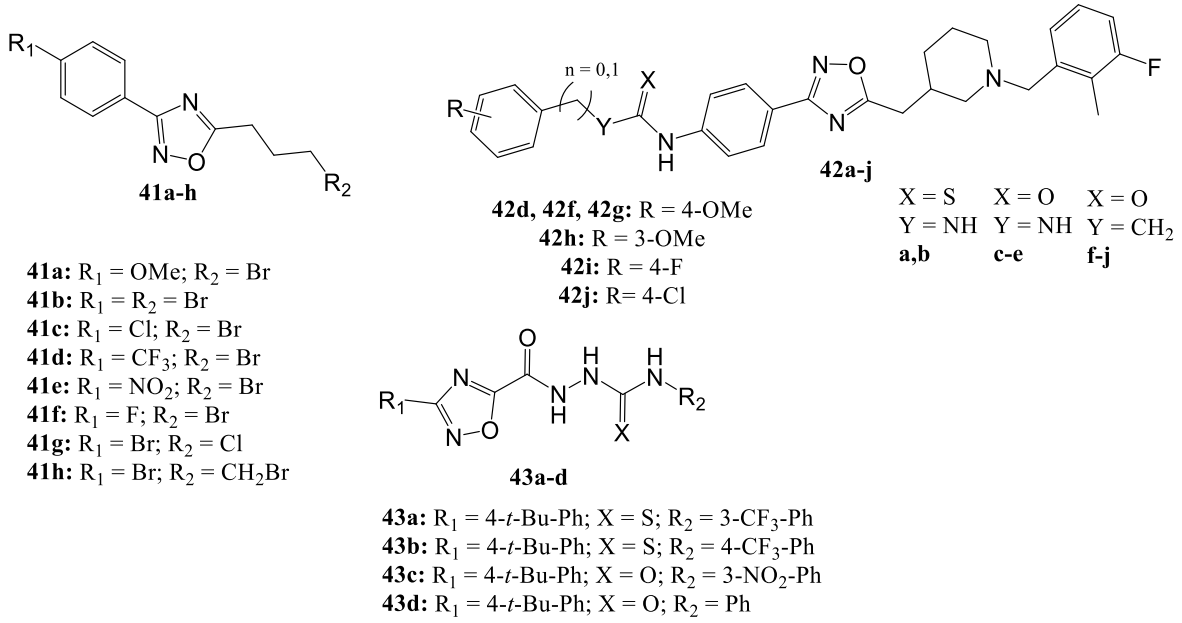
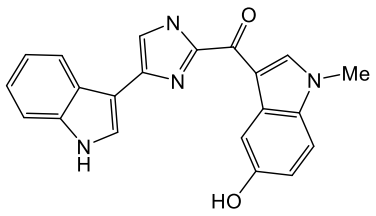
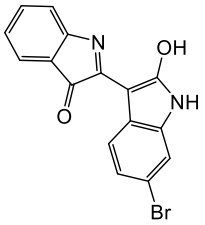


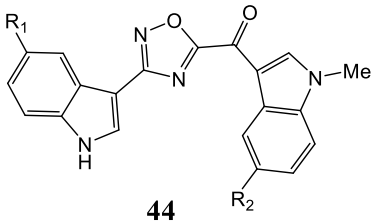
Fig. 6. Structures of compounds **41**–**43** inhibiting sirtuin.



Topsentin

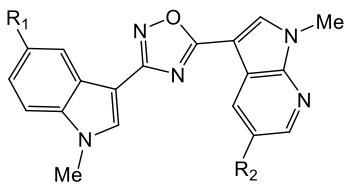


6-Bromoindirubin



44

a: R_1 = H, R_2 = Br;
b: R_1 = H, R_2 = F;
c: R_1 = R_2 = H;
d: R_1 = H, R_2 = OMe;
e: R_1 = OMe, R_2 = F;
f: R_1 = OMe, R_2 = OMe;
g: R_1 = OMe, R_2 = Br;
h: R_1 = OMe, R_2 = H;
i: R_1 = Br, R_2 = OMe;
j: R_1 = Br, R_2 = H;
k: R_1 = Br, R_2 = F;
l: R_1 = Br, R_2 = Br;
m: R_1 = F, R_2 = H;
n: R_1 = F, R_2 = F;
o: R_1 = F, R_2 = OMe;
p: R_1 = F, R_2 = Br;



45

a: R_1 = H, R_2 = Br;
b: R_1 = F, R_2 = Br;
c: R_1 = OMe, R_2 = Br;
d: R_1 = R_2 = H;
e: R_1 = F, R_2 = H;
f: R_1 = OMe, R_2 = H;

Fig. 7. Structures of **Topsentin** and its 1,2,4-oxadiazole derivatives **44,45** as inhibitors of GSK3β and CDK1.

through direct or water-mediated interactions.

The same authors synthesized a new series of 1,2,4-oxadiazole derivatives and evaluated their ability to inhibit cell growth in PATU-T, Hs766T, and HPAF-II cell lines and primary culture of pancreatic ductal adenocarcinoma PDAC (PDAC3) cells [81]. Among the tested compounds, derivative **45b** showed the highest activity, showing an IC_{50} value of 10.7 μM, while the other compounds showed minimal cytotoxic effect with $IC_{50} > 20$ μM. To extend the antiproliferative evaluation of compound **45b** to other pancreatic cells, we assessed cell growth inhibition in primary pancreatic cell lines, including both immortalized HPAF-II and Hs766T cancer cell lines and primary culture of PDAC3. Interestingly, compound **45b** was active against all these PDAC cells. The best result was observed against Hs766T with an IC_{50} value of 5.7 μM. However, compound **45b** was also able to inhibit the viability of PDAC3 and HPAF-II with IC_{50} values of 6.9 and 9.8 μM, respectively.

Molecular docking of **45b** in the active site of CDK1 revealed the ability of the compound to effectively interact with the adenosine triphosphate binding pocket. The ability of this compound to induce apoptosis (which was increased by 1.5 and 2-fold in PATU-T and PDAC3 cells, respectively) and inhibit CDK1 expression, which was reduced by 45 % in Hs766T, was assessed. Finally, compound **45b** passed the ADME prediction, showing good pharmacokinetic parameters. These data indicate that **45b** exhibits cytotoxic activity, induces apoptosis, and targets CDK1. From the structure-activity-relationship (**SAR**) analysis of compounds of type **44** and **45** (Fig. 7), it was observed that the introduction of a nitrogen atom at position 7 of the indole moiety did not result in a significant improvement in antiproliferative activity, nor did the presence of a methyl group at the nitrogen atom of the indole. In contrast, in derivatives of type **45**, the presence of a halogen atom, such as fluorine or bromine, at position 5 of the indole or 7-azaindole ring appears to be essential for the cytotoxic activity.

In conclusion, the substituted 1,2,4-oxadiazole core represents a particular example of a privileged structure in the directed design of potential anticancer agents. This heterocycle can serve as the foundation for a pharmacophore group or can be incorporated into the decoration of the main scaffold. The tropism of the compounds containing 1,2,4-oxadiazole towards specific biological targets can vary significantly depending on the heterocyclic fragments included in their composition. It is noteworthy that the antitumor activity is a prevalent characteristic of 1,2,4-oxadiazole derivatives, with the potential to affect a wide range of biological targets.

4. Functional derivatives of 1,2,4-oxadiazole with antibacterial, antifungal and antimycobacterial properties

4.1. 1,2,4-Oxadiazole derivatives with antibacterial activity

1,2,4-oxadiazole derivatives have attracted considerable attention as antibacterial agents and synergists of antibiotic drugs. Indeed, 3-aryl-1,2,4-oxadiazole derivatives demonstrated the capacity to enhance the efficacy of nalidixic acid, rifampicin, and kanamycin on *E. coli* strain *MG1655*. The most potent compounds, **46a** and **46b** (Fig. 8), demonstrated to inhibit the growth of *P. aeruginosa* in the presence of nalidixic acid and rifampicin. This resulted in a MIC-reduction of rifampicin (MIC = 4.86 μM), which was observed to decrease by a factor of 2–64 at concentrations of 25–50 μM [82].

1,2,4-Oxadiazole derivatives containing a diphenylpyrazole fragment in their structure have been described [83]. The compounds **47a-c** showed antibacterial activity against *B. subtilis* with MIC = 31.25 μg/ml (disc diffusion method) and moderate activity against *S. albus* strain (inhibition zone = 12.4–13 mm, disc diffusion method). Additionally, they exhibited antifungal activity against *A. niger* with MIC = 7.81 μg/ml, exhibiting comparable efficacy to the reference drug fluconazole. SAR analysis showed that the introduction of a chlorine atom or a methyl group into the benzene ring of the 5-phenyl-1,2,4-oxadiazole fragment enhanced the activity of the compounds. Furthermore, the cytotoxicity study on the cell line of newborn mouse skin fibroblasts (NMDF) showed that the investigated compounds did not exhibit any toxic properties at concentrations up to 25 μg/ml.

Derivatives of *N*-(4-aminophenyl)-1,2,4-oxadiazole-5(4*H*)-ones **48** were prepared through the reduction of the corresponding *N*-(4-nitrophenyl)-1,2,4-oxadiazole-5(4*H*)-ones [84]. One of the resulting

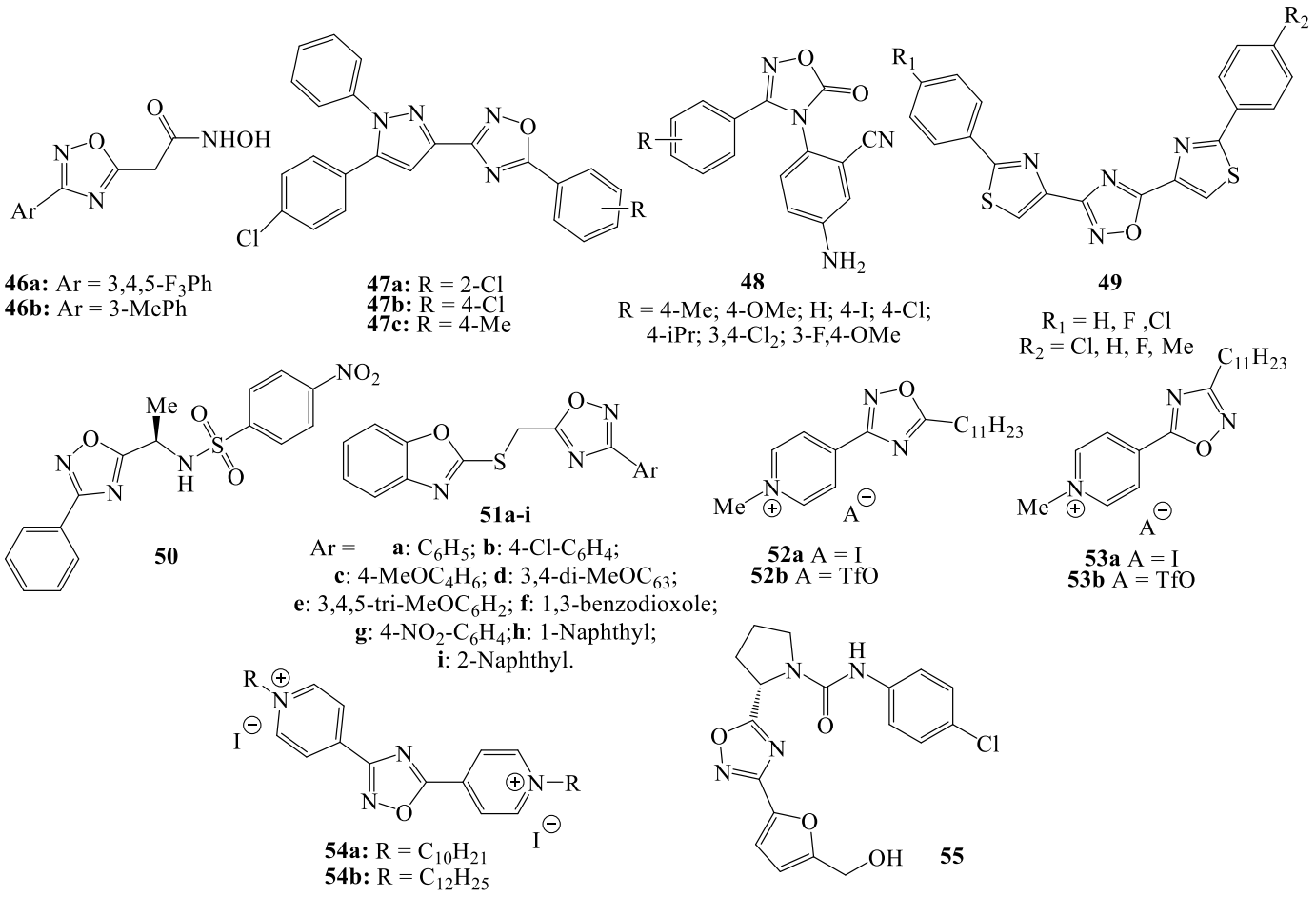


Fig. 8. 1,2,4-Oxadiazole derivatives **46**–**55** with antibacterial activity.

compounds was reported to possess antibacterial properties against both *S. aureus* and *E. coli*. A series of derivatives of 1,2,4-oxadiazoles containing two thiazole rings were also prepared [85]. The antibacterial activity of compound **49** was of moderate level against *S. albus* with MIC = 31.25–62.5 μg/ml, and demonstrated moderate activity against *P. mirabilis*.

A series of functional derivatives of 5-phenyl-1,2,4-oxadiazoles with antibacterial properties were synthesized, among which the most active compound was **50**, which showed activity against *S. aureus*, *E. faecalis* and *K. pneumoniae* with MIC = 64 μg/ml and against *E. coli* with MIC = 128 μg/ml (broth microdilution method) [86]. Furthermore, this compound demonstrated a synergistic effect in combination with ampicillin on *E. faecalis*, *E. coli*, *S. aureus*, *P. aeruginosa*, and *K. pneumoniae* strains reducing their MIC from 1 to 32 μg/ml to 0.5–4 μg/ml. The analysis of the cytotoxicity of **50** on the human red blood cell (hRBC) cell line demonstrated that this compound is safe at concentrations within the range of its antibacterial activity. Therefore, compound **50** showed potential as a prototype for further development of effective and safe antibacterial agents and antibiotic synergists.

Novel compounds **51 a-i** (Fig. 8) with antibacterial properties containing a benzoxazole fragment in their structure along with a 1,2,4-oxadiazole residue were described [87]. The most active compounds demonstrated notable antibacterial activity against *B. subtilis*, *S. aureus*, and *K. pneumoniae* with inhibition zones of 31–32 mm, 34–36 mm and 34–35 mm, respectively. Furthermore, they also inhibited the aforementioned strains with MIC = 3.9–7.81 μg/ml, 0.97–3.9 μg/ml, and 1.95–3.9 μg/ml, respectively (broth microdilution method).

The authors [88] reported the synthesis and antibacterial activity of mono- and bi-cationic pyridinium 1,2,4-oxadiazoles. They found that monopyridinium isomers **52a,b** and **53a,b** showed the highest potency against Gram-positive bacteria, specifically *S. aureus*, *S. epidermidis*, and *S. haemolyticus*, with MIC values in the range of = 2–16 μg/ml through a broth microdilution method. The introduction of a second pyridinium group, afforded compounds **54a,b** that showed activity against the same bacterial strains with MIC <2 μg/ml and also exhibited antibiofilm activity. In particular, dodecyl salt **54b** inhibited the biofilm formation of *S. haemolyticus* strain by 94.1 %, at a concentration of less than 1 μg/ml, while decyl salt **54a** inhibited the biofilm of *A. baumanni* by 97.4 %, at a concentration lower than 8 μg/ml. The authors also explored the effect of different factors such as charge, heterocyclic core, alkyl chain length, and anion on the antibacterial activity.

The hybrids of 1,2,4-oxadiazole and pyrrolidine demonstrated inhibitory effects on both DNA gyrase and topoisomerase IV [89]. The synthesized compounds demonstrated inhibitory activity (IC_{50} = 120–270 nM) against *E. coli* DNA gyrase comparable to that of novobiocin (IC_{50} = 170 nM). The compound **55** was found to be the most potent with MIC = 24 and 62 ng/ml (broth microdilution method) against *S. aureus* and *E. coli*, respectively. This was observed to be more effective than novobiocin with MICs = 30 and 60 ng/ml. Furthermore, compound **55** demonstrated activity against *B. subtilis* and *P. aeruginosa* strains with MIC = 12 and 65 ng/ml, respectively. In general, the compounds demonstrated greater inhibitory efficacy against the growth of Gram-positive than Gram-negative bacteria. The SAR suggested that the 4-chlorophenyl substituent enhanced the inhibitory activity of the compounds on *E. coli* DNA gyrase. A cytotoxicity study on a mammary epithelial cell line (MCF-10A) utilizing an MTT assay demonstrated that compound **55** was non-toxic at a concentration of 50 μM. It can be concluded that compound **55** has the potential to be developed as a new

antibiotic drug due to its high level of activity.

In a separate study, thiazolyl-1,2,4-oxadiazoles were synthesized and their antibacterial activity was evaluated on *E. coli*, *P. mirabilis, B. subtilis*, and *S. albus* strains [90]. Among the synthesized compounds, only **56a** and **56b** (Fig. 9) demonstrated antibacterial activity against *P. mirabilis* with a MIC = 62.5 μg/ml. A cytotoxicity study indicated that the compounds exhibited no toxicity towards the HEK-293 cell line at a concentration of 25 μg/ml. Compound **57**, comprising a 1,2,4-oxadiazole fragment, demonstrated selective activity against *C. difficile* (MIC_{50} on 101 strains = 0.5 μg/ml, broth microdilution method), while exhibiting minimal or no activity against bacteria of the digestive tract [91]. The mechanism of action is the inhibition of cell wall synthesis.

Another study focused on the design of antibacterial agents against intestinal pathogens, to this end compounds with general structure **58** were synthesized [92]. The potency activity against *C. difficile* was slightly lower than that of **57**, but showed interesting activity against MDR *E. faecium*. The most potent derivative, compound **59**, exhibited a MIC of 8 μg/ml (broth microdilution method) against both strains. It is noteworthy that the molecular fragments in the C-3 position of the 1,2,4-oxadiazole in compounds **57** and **59** were similar. This similarity is probably the key factor determining the specific antibacterial activity of these compounds. The primary objective was to develop antibacterial drugs that do not affect intestinal cells. This goal was achieved, as demonstrated by compound **59**, which is a quaternary ammonium salt and has been shown to be impermeable to Caco-2 cells. Nevertheless, the susceptibility of this derivative to intestinal degradation and metabolism was observed after oral administration to mice, which represents a significant motivation for the further optimization of this series of 1,2,4-oxadiazole derivatives.

A tertiary aromatic amide containing a 1,2,4-oxadiazole fragment **60** was reported as an antibacterial agent against infections caused by MRSA [93]. In this study, the replacement of the naphthalene fragment with a phenol linked to a 5-trifluoromethyl 1,2,4-oxadiazole resulted in an enhanced antibacterial activity. The 1,2,4-oxadiazole derivative **60** demonstrated notable activity against MRSA both *in vitro* and *in vivo*. It is noteworthy that this compound exhibits low cytotoxicity as well as a low propensity to develop resistance, low hemolytic activity, and the ability to destroy bacterial biofilms. The mechanism of action of this compound is the binding to cardiolipin (CL), which subsequently results in the disruption of the cell membrane and the accumulation of reactive oxygen species (ROS).

A distinct mechanism of action was exhibited by the 5-aryl-1,2,4-oxadiazole derivative **61**, which contains a 2,6-difluorobenzamide moiety in its structure [94]. The mechanism of action of this derivative is the inhibition of the filamentous temperature-sensitive mutant Z (FtsZ) protein, which is involved in bacterial fission. This results in the formation of an abnormal bacterial morphology was due to the mislocalization of the dividing septum. The research project aimed to investigate the impact of different heterocyclic fragments on the antibacterial activity against *S. aureus* strains showed that the 1,2,4-oxadiazole derivative containing the 4-*tert*-butylbenzene at the C-3 position was the most active one and was non-toxic *in vitro*. The compound demonstrated antibacterial activity against three MDR strains of *S. aureus* with MIC = 0.5–1 μg/ml (broth microdilution method).

Another 1,2,4-oxadiazole derivative that inhibited the growth of *S. aureus*, was an analogue of etrasimod. This was created by adding a fragment of 1,2,4-oxadiazole between the aromatic ring and the ether group, resulting in the formation of compound **62** [95]. Nevertheless, further optimization of the structure led to the identification of the more active compound **63** with a MIC = 2.5–5 μM against *staphylococci* (broth

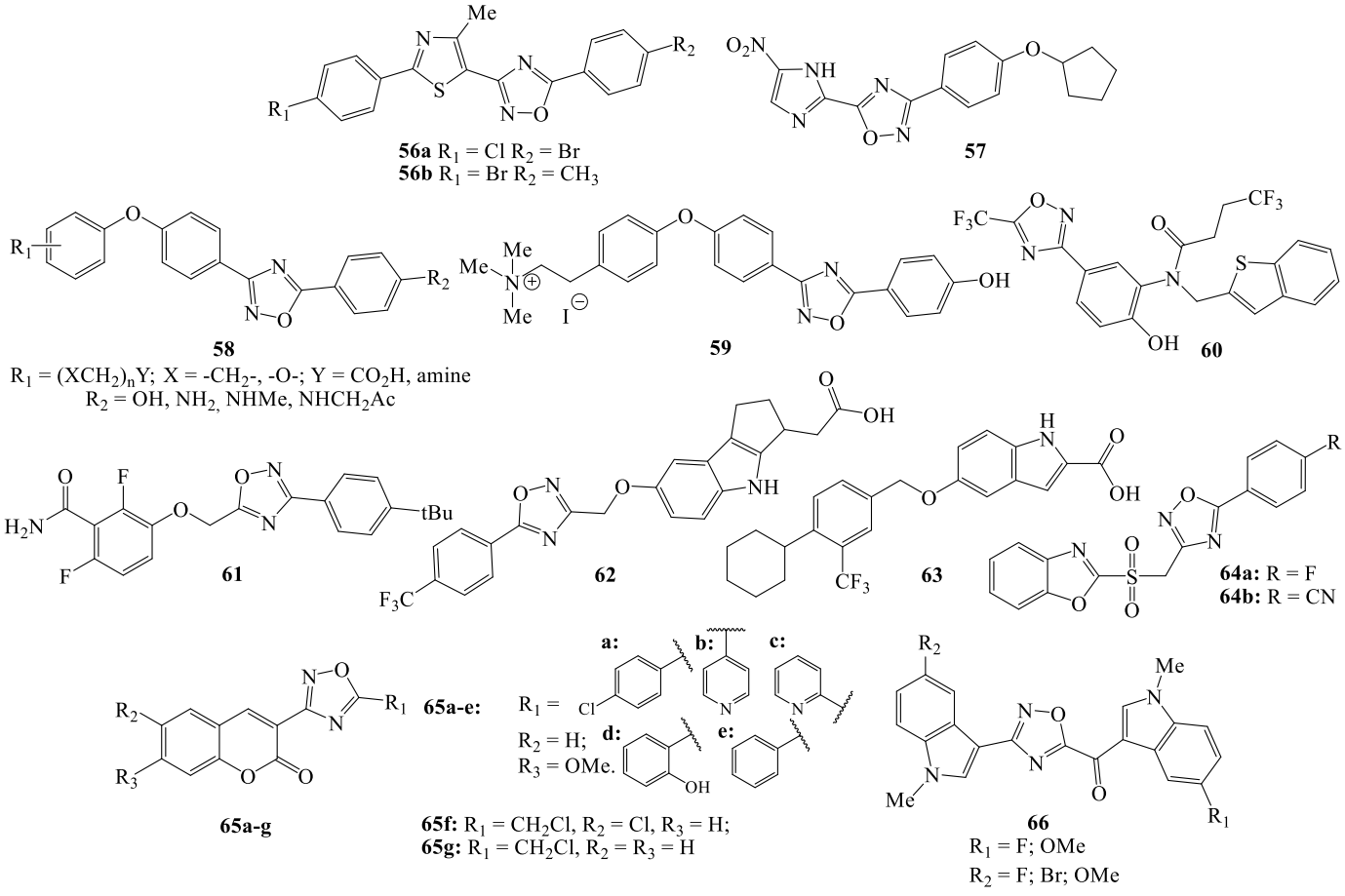


Fig. 9. 1,2,4-Oxadiazole derivatives **56**–**66** with antibacterial activity.

microdilution method).

In a separate study, the authors synthesized 1,2,4-oxadiazole derivatives containing a benzoxazole fragment [96]. The compounds demonstrated activity against Gram-positive bacterial strains, with the derivative **65a** exhibiting particularly high activity against *B. subtilis* at a level 2-fold higher than that of ciprofloxacin. Furthermore, both compounds **65a** and **65b** displayed antibiofilm activity. In this case, the 1,2,4-oxadiazole moiety is situated within the pharmacophore of the molecules, playing an essential role in the observed antibacterial activity.

Other 1,2,4-oxadiazole derivatives with antibacterial activity include compounds containing the 2H-chromen-2-one fragment [97]. The structures of the synthesized derivatives **65a-g** are illustrated in Fig. 9. Compound **65f** exhibited the highest level of potency, demonstrating an average MIC of 37.5 μg/ml against both *S. aureus* and *E. coli* strains. The authors discovered that the groups at the C-5 position of the 1,2,4-oxadiazole moiety were essential for the observed antibacterial activity. It is noteworthy that the synthesized derivatives also demonstrated antifungal activity against *A. niger* with a MIC that was generally superior or comparable to that of nystatin (MIC = 100 μg/ml).

By introduction of the carbonyl group in 1,2,4-oxadiazoles **45** (Fig. 7) the authors of the next article obtained compounds **66** which are potential novel antivirulence agents [98]. The ability to inhibit biofilm formation was assessed against both Gram-positive and Gram-negative pathogens. All compounds inhibited S. aureus and/or P. aeruginosa biofilm formation in a dose-dependent manner, with 50 % biofilm inhibitory concentrations (BIC_{50s}) below 10 μM for the most active compounds. The authors also investigated the novel 1,2,4-oxadiazole derivatives in inhibition of SrtA, as one of the possible mechanisms of action of the compounds, in the tested Gram-positive pathogen using a specific enzymatic assay for recombinant S. aureus SrtA. The three most active compounds, eliciting BIC_{50} values for S. aureus ATCC 25923 between 0.7 and 9.7 μM, showed good activity against SrtA eliciting IC_{50} values in the range of 2.2–10.4 μM.

The use of the 1,2,4-oxadiazole core for the design of antibacterial drugs has demonstrated to be very relevant in recent years. Nevertheless, it is noteworthy that a review of the scientific literature revealed that the study of the antibacterial activity of 1,3,4-oxadiazole is more prevalent than that of 1,2,4-oxadiazole. It is noteworthy that in the majority of the reviewed works on the development of antibacterial drugs, the 1,2,4-oxadiazole fragment was present in the pharmacophore and was a crucial determinant of activity. In addition to 1,2,4-oxadiazole, other five-membered aromatic heterocycles (imidazole, thiazole, furan, pyrazole), substituted aromatic rings or condensed heterocycles (coumarin, benzoxazole, indole, benzothiophene) were frequently present in the most active compounds. In rare instances, six-membered heterocycles (pyridine) or saturated heterocycles (pyrrolidine) were observed.

With regard to the biological activity of 1,2,4-oxadiazole derivatives, the compounds under consideration exhibited enhanced antibacterial activity against Gram-positive bacterial strains in comparison to Gram-negative strains. The microorganisms on which 1,2,4-oxadiazoles demonstrated activity included clinically relevant strains of *MRSA* and *VRE*, *MDR S. aureus*, *C. difficile, E. coli, P. aeruginosa, S. pneumoniae, S. pyogenes and L. monocytogenes, B. subtilis, S. albus, P. mirabilis, E. faecalis, S. aureus*, and *K. pneumoniae.* It is important to note that 1,2,4-oxadiazole derivatives predominantly exhibited antibacterial activity rather than a synergistic effect when combined with antibiotics. The most common mechanism of action observed was the disruption of bacterial membrane integrity or the inhibition of the biosynthesis of its components. It is noteworthy that some derivatives exhibited simultaneous antibacterial and antifungal activity.

4.2. 1,2,4-Oxadiazole derivatives with antifungal activity

As previously stated, 1,2,4-oxadiazole derivatives have also showed antimycotic properties. Some of these compounds have been demonstrated to possess antifungal activity against plant-pathogenic fungi. For example, compounds containing quinoline and 1,2,4-oxadiazole fragments **67a** and **67b** (Fig. 10), obtained by splicing principle of the active substructures, demonstrated inhibitory activity against *S. sclerotiorum* (a plant pathogen causing white mold and also known as cotton rot) at a concentration of 50 μg/ml by 86.1 % and 77.8 %, respectively, and were comparable or slightly better than the reference drug quinoxifene (77.8 %) [99]. The fungicidal activity (EC_{50} = 5.17 and 6.67 μg/ml, respectively) of these derivatives was superior to that of quinoxifene (EC_{50} = 14.19 μg/ml), a fungicide containing a quinoline fragment. An LC_{50} of 19.42 μg/ml was determined for compound **67b** on the zebrafish embryo. Some derivatives showed superior activity against *A. solani, G. zeae, P. capsici*, and *P. piricola* compared to quinoxifene. However, their inhibitory activity was less than 50 %. The results of the SAR analysis indicated that the inhibitory activity was enhanced by the presence of 3-CF_3 and 3,4-$(Cl)_2$ in the benzene ring, as well as by the electron-acceptor groups in general. The derivative **68a**, with an EC_{50} value of 2.9 μg/ml, also demonstrated high activity against *S. sclerotiorum in vitro*, comparable to the drugs tifluzamide (EC_{50} = 4.3 μg/ml) and fluopyram (EC_{50} = 1.2 μg/ml) [100]. The mechanism of action of this compound is the inhibition of succinate dehydrogenase (SDH) of *S. sclerotiorum* (IC_{50} = 12.5 μg/ml). Furthermore, compound **68a** demonstrated minimal toxicity towards the human liver cell line L-02. Compound **68b** demonstrated nematocidal activity against *M. incognita* at a concentration of 200 μg/ml, exhibiting a 93.2 % reduction in nematode population, which was more pronounced than the 23.9 % observed with thioxazaphene. SAR analysis revealed that compounds with a thienyl moiety at the C-3 position of the oxadiazole ring and a methylene bridge at the amide group exhibited enhanced antifungal activity.

1,2,4-Oxadiazole derivatives containing a pyrazole heterocycle have also been observed to exhibit antifungal activity. As in the previous study, the method of splicing active substructures was employed in the design of these compounds. The most active compounds, **69a** and **69b**, demonstrated efficacy against *P. oryzae*, the fungus responsible for rice pyriculariosis, the most detrimental disease affecting rice crops, with potential yield losses reaching 15–40 % [101]. The fungicidal activity of **69a** and **69b** (70.6 % and 100 % at a 50 μg/ml concentration) was superior to that of the reference drug bixafen (EC_{50} = 9.15 μg/ml) with an EC_{50} = 8.28 and 5.49 μg/ml, respectively. The activity of **69a** against *S. sclerotiorum* was EC_{50} = 14.31 μg/ml. The results of the SAR analysis indicated that the fluorine atom at the *meta*-position of the benzene ring contributed to an enhancement of fungicidal activity. However, the LC_{50} of **69c** on Zebrafish embryos was 0.39 μg/ml, suggesting that these compounds can only serve as potential fungicidal compounds and that further optimization is required to reduce the toxicity. It is noteworthy that compound **69c** also demonstrated insecticidal activity against mosquito larvae with a mortality rate of 100 % at a concentration of 5 μg/ml. Furthermore, the authors synthesized another derivative **70a** which demonstrated activity against *P. oryzae* (77.8 %) at a concentration of 50 μg/ml (EC_{50} = 16.95 μg/ml). However, in contrast, the aforementioned compounds exhibited reduced toxicity towards embryos of Zebrafish with an LC_{50} = 14.01 μg/ml. This suggests that optimizing this compound for the development of novel fungicidal agents may prove beneficial [102]. Furthermore, the synthesized compounds demonstrated notable insecticidal activity against *M. separata, H. armigera, O. nubilalis*, and *S. frugiperda* at a concentration of 500 μg/ml. In particular, compound **70b** exhibited an inhibitory effect against *M. separata* by 70 %.

The 1,2,4-oxadiazole and chromene combination also leads to the formation of compounds with antifungal activity [97,103]. In particular, the activity of these derivatives is demonstrated against a different biological target – *A. niger*. Derivatives **71** have demonstrated noteworthy activity [103]. Compounds **65 a,b,c,f,g** (Fig. 9) have exhibited exceptional antifungal efficacy with MIC = 75–87.5 μg/ml, which is superior to that of nystatin (MIC = 100 μg/ml) [97].

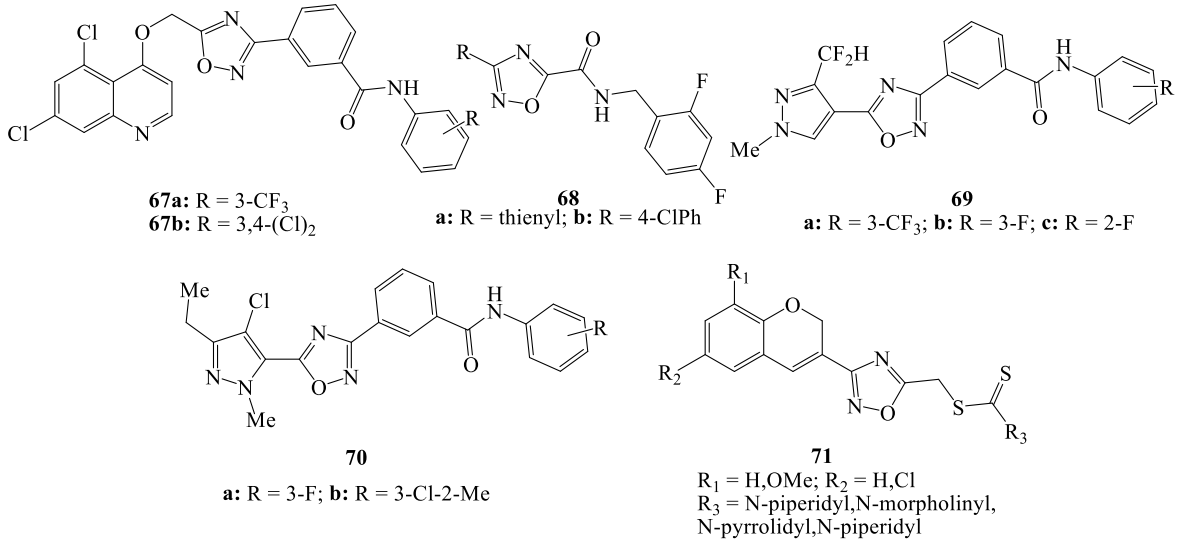


Fig. 10. Structures of 1,2,4-oxadiazole derivatives **67**–**71** with antifungal activity.

The combination of the 1,2,4-oxadiazole ring with pyrazole, chromene, thiophene and quinoline resulted in the creation of active antifungal substances. The majority of the synthesized compounds demonstrated antifungal activity against plant-pathogenic fungi, with the greatest efficacy observed against *S. sclerotiorum* and *P. oryzae*. Furthermore, numerous compounds exhibited dual biological activity, demonstrating both antifungal and insecticidal or antibacterial or nematocidal properties, with insecticidal activity being predominant. It is noteworthy that, despite the frequent use of 1,2,4-oxadiazole as a bioisostere of the amide group, the latter was present in the structures of some antifungal compounds under consideration, indicating that the 1,2,4-oxadiazole heterocycle is not only used in the composition of the compounds pharmacophores with the purpose of increasing their metabolic stability.

4.3. 1,2,4-Oxadiazole derivatives with antimycobacterial activity

As with antibacterial compounds, there is an urgent need to develop new antimycobacterial compounds, particularly antitubercular compounds, due to the increasing resistance to existing drugs and the

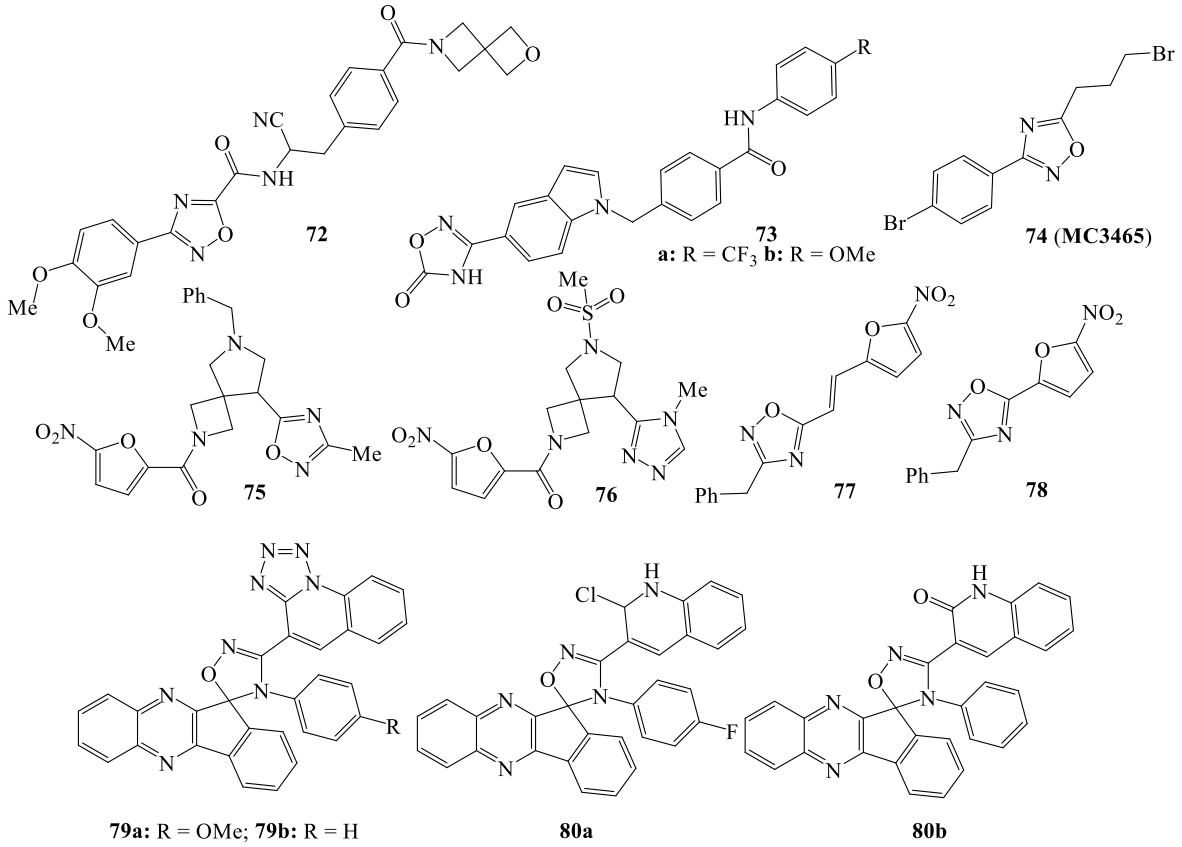


Fig. 11. Structures of 1,2,4-oxadiazole derivatives **72**–**80** with antimycobacterial activity.

consequent rise in mortality from the disease. 1,2,4-Oxadiazole derivatives are also being used in the development of active pharmaceuticals with this activity. For example, a high-throughput screening was performed to derive novel inhibitors of the polyketide synthase 13 (Pks13) thioesterase domain, which is currently a promising target for the development of antitubercular agents [104]. They identified an active substance containing the 1,2,4-oxadiazole ring in its structure, which was further optimized to yield compound **72** (Fig. 11). This compound exhibited the most favorable overall profile among the synthesized derivatives, with a *M. tuberculosis* (H37Rv) MIC = 0.7 μM, a Pks13 IC_{50} = 0.4 μM and good metabolic stability in mice. However, this compound demonstrated no effect on the development of tuberculosis infection in mice by oral *in vivo* administration, which may be attributed to its low cellular permeability as demonstrated by the PAMPA assay.

Another target for the development of antitubercular agents is the enoyl reductase (InhA), a key enzyme involved in the biosynthesis of fatty acids, including mycolic acid, which is a major component of the mycobacterial cell wall [105]. 5-Oxo-1,2,4-oxadiazole derivatives, which also contain an indole fragment, demonstrated activity against this enzyme as well as against the *M. tuberculosis* strain H37Rv, with MIC = 0.78 and 1.56 μg/ml for compounds **73a** and **73b**, respectively (Fig. 11). These values exceed those of the known anti-tuberculosis drug ethambutol (MIC = 1.56 μg/ml).

A recent study explores host-directed therapies (HDTs) as a promising addition to existing antibiotics [106]. Through high-content imaging and screening of an epigenetics-related compound library, the researchers identified **74** (**MC3465)** as a promising candidate that significantly reduces intracellular *M. tuberculosis* growth without causing toxicity to macrophages. The study reveals that **MC3465** induces zinc remobilization within macrophages. This manipulation of heavy metal homeostasis results in increased sensitivity of *M. tuberculosis* to anti-tuberculosis drugs, both *in vitro* and *in vivo* using a mouse model. **MC3465** showed selective action against *M. tuberculosis*, with no significant impact on other bacterial species tested - *L. monocytogenes*, *S. enterica*, and *E. coli*, indicating its targeted mechanism against tuberculosis. The findings underscore the potential of manipulating host immune responses and metal ion homeostasis as a viable strategy for developing new tuberculosis (TB) treatments.

In a separate study, the authors employed the 1,2,4-oxadiazole core in the modification of the heterocyclic ring, resulting in the synthesis of compound **75** (MIC = 6.2 μg/ml on *M. tuberculosis H37Rv*) [107]. It was established that the 1,2,4-oxadiazole derivative demonstrated superior activity in comparison to its triazole bioisostere. However, the most active synthesized compound was **76**, with a MIC = 0.016 μg/ml. Further *in vitro* and *in vivo* studies are planned for this compound.

1,2,4-Oxadiazole derivatives, **77** and **78** (Fig. 11), containing a nitrofuran fragment demonstrated selective activity against the *M. tuberculosis* strain HRv37 [108]. 1,2,4-Oxadiazole derivatives containing condensed heterocycles in their structure have also exhibited antimycobacterial activity. The most active compound **79a** demonstrated inhibitory activity against *M. tuberculosis H37Rv* (MIC = 0.78 μg/ml). Additionally, it exhibited a CC_{50} = 26.4 μg/ml on the RAW264.7 cell line. The compounds **79b**, **80a** and **80b** demonstrated activity against *M. tuberculosis* H37Rv with a MIC_{99} = 6.25 μg/ml. It is noteworthy that spiroquinoxaline-1,2,4-oxadiazole derivatives were synthesized via a [3 + 2] cycloaddition of quinoxaline Schiff bases and aryl nitrile oxides at room temperature, without chromatographic purification, with short reaction times and high yields [109].

The described series of derivatives represent highly promising prototypes for the development of antimycobacterial drugs, and the 1,2,4-oxadiazole fragment constitutes an important part of the pharmacophore, resulting in an enhanced activity. The furan fragment and the benzamide fragment were also present in some of the aforementioned molecules. It is noteworthy that the selectivity of the compounds against *M. tuberculosis* is important because it allows the killing of pathogenic mycobacteria without affecting the beneficial microorganisms present within the organism.

5. Functional derivatives of 1,2,4-oxadiazole with antiparasitic and insecticidal activity

The 1,2,4-oxadiazole fragment has been employed in the development of compounds with anti-parasitic activity. For example, derivative **81** (**WJM-228**) (Fig. 12) has been demonstrated to inhibit the growth of the parasite *P. falciparum* with an EC_{50} = 0.019 μM [109]. The compound was observed to inhibit the growth of *P. berghei* (a popular model organism for the study of human malaria) *in vivo* in a mouse model of malaria, with the effect being attributed to its ability to affect the Q_o site in cytochrome *b*, an essential component of the electron transport chain that is required for the synthesis of pyrimidine. In this study, the 1,2,4-oxadiazole fragment was inserted as a bioisostere of the ester group. This strategy enhanced both the metabolic stability and the potency of the compounds. In contrast, it also resulted in decreased water solubility, the improvement of which is one of the main goals of further structural optimization.

Other 1,2,4-oxadiazole derivatives showing activity against *P. berghei* contained benzimidazole [110]. The structure of the most active compound **82** (*P. falciparum NF54* IC_{50} = 0.012 μM; *P. falciparum K1* IC_{50} = 0.040 μM) is shown in Fig. 12. This compound exhibited high microsomal metabolic stability and higher selectivity than **astemizole** (AST) (hERG IC_{50} = 0.0042 μM), with less effect on the hERG K^+ channel (hERG IC_{50} = 0.63 μM; SI = 53). **Astemizole**, a second-generation antihistamine, is known to block the hERG K^+ channel, leading to cardiac arrhythmias and has been withdrawn from the market in many countries. The selectivity index in the cytotoxicity study of compound **82** on the Chinese hamster ovary (CHO) cell line was high (IC_{50} = 1.96 μM, SI = 163). The compound also showed high *in vivo* activity in a mouse model of *P. berghei* malaria (99.5 % inhibition of parasitaemia at an oral dose of 4–50 mg/g). In this work, the 1,2,4-oxadiazole ring was used as a bioisostere of the ester group to improve metabolic stability, preserve spatial geometry, and increase structural rigidity. The best substituent at the C-3 position of the 1,2,4-oxadiazole core was the trifluoromethyl group. The authors also found that the removal of the benzene ring at N-1 position of benzimidazole in **astemizole**, while retaining the C-3 substituted 1,2,4-oxadiazole in the side phenyl group, does not affect the antiplasmodial activity at the stage of asexual reproduction in humans, but provides high activity, high metabolic stability *in vitro*, low lipophilicity, and low molecular weight, contributing to improved solubility and selectivity over the hERG K^+ channel. A common feature of the two above-mentioned studies on the development of compounds active against *P.* parasites is the presence of a condensed heterocycle and a piperidine in the structures of the most active compounds, in addition to the 1,2,4-oxadiazole core. It can be concluded that compound **82** is a promising antimalarial compound with excellent *in vitro* and *in vivo* activity and a greater selectivity over the hERG K^+ channel compared to **astemizole**. Anyway, further studies are warranted to fully elucidate the potential of compound **82**.

In another work on the development of antiparasitic compounds, a 1,2,4-oxadiazole core was used by varying the heterocyclic core in the molecule [111]. One of the active compounds was found to be 1,2,4-oxadiazole derivative **83**, which showed activity against *T. cruzi* with an EC_{50} = 34.2 μM and a lethality of 46.2 % at a concentration of 50 μM. The isoxazole derivatives of structure **84a** and **84b** were slightly more active with EC_{50} = 5.1 and 9.8 μM, respectively, and synergistic activity with benznidazole (a drug used to treat Chagas' disease) was observed for compound **84b**. The compounds were found to affect the parasite mitochondria and had low toxicity to healthy cells (SI = 5–71). Good ADME properties were also predicted for the obtained compounds.

In a separate study, a 1,2,4-oxadiazole derivative with structure **85** was synthesized by modifying one of the heterocyclic units of molecules developed for the control of human filarial diseases. However, this derivative exhibited slightly reduced activity and solubility compared to

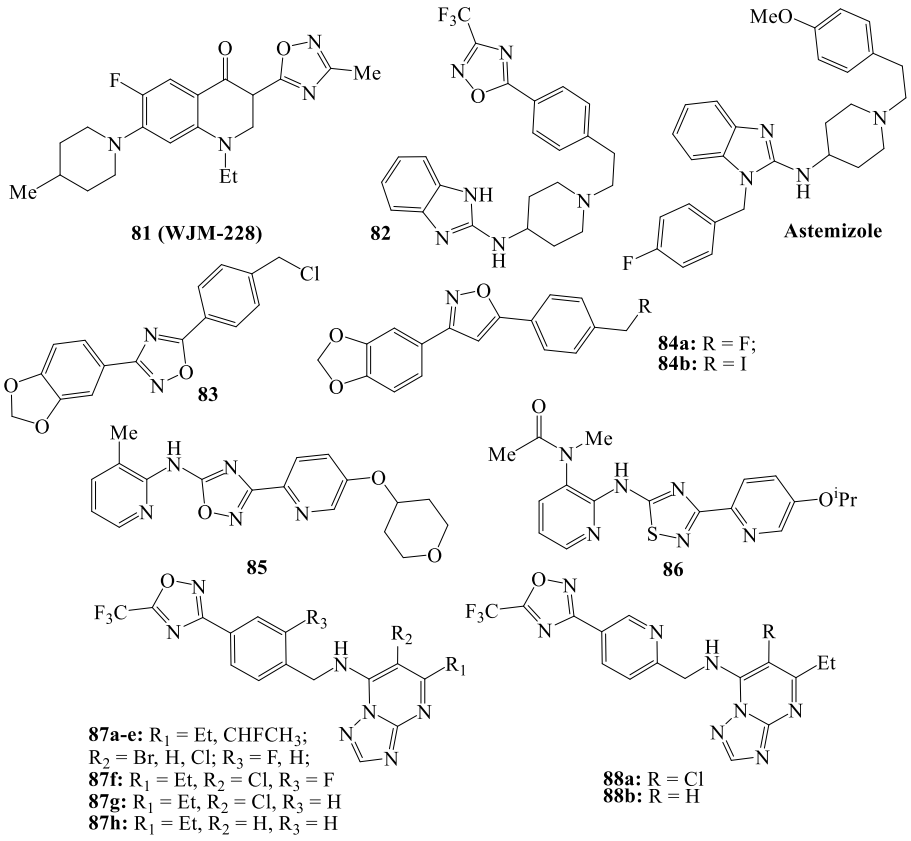


Fig. 12. Derivatives of 1,2,4-oxadiachol with antiparasitic and insecticidal activity.

thiadiazole derivatives [112] among which, compound **86** was the most effective (*O. gutturosa* EC_{50} = 1.1 μM, inhibition of *O. volvulus* L*5* motility at 1 μM = 100 %, reduction of parasitic load caused by *L. sigmodontis* worms by 59 %). It is noteworthy that filariae are the causative agents of several parasitic diseases, including onchocerciasis, elephantiasis, and lymphatic filariasis, which collectively affect approximately 145 million people. Current therapeutic strategies primarily target microfilariae, requiring prolonged and repeated treatment due to the sustained production of microfilariae by adult worms. Furthermore, the emergence of drug-resistant filarial worms underscores the urgent need for the development of novel antiparasitic compounds that effectively target filariae.

The compounds **87a-e** and **88a,b** which contain a fragment of 1,2,4-oxadiazole in their structure, demonstrated insecticidal activity against *M. separata*, a major pest of maize in Asia, at a concentration of 500 ppm. Additionally, compound **87f** exhibited efficacy against *A. medicagini*, an aphid detrimental to agricultural crops [113]. Furthermore, compounds **87g** and **87h** have been observed to exhibit antifungal activity at a concentration of 200 ppm against the fungus *P. cubensis*, a water mold that causes false powdery mildew on a range of crops, including melon, cucumber, pumpkin, courgettes, and watermelon.

Additionally, the insecticidal [102,103], and antiparasitic [100] activities of certain other 1,2,4-oxadiazole derivatives have been previously discussed in Section 3.

Thus, it was demonstrated that compounds containing the 1,2,4-oxadiazole fragment exhibited efficacy against a range of parasites, including *M. incognita, P. falciparum, P. berghei, T. cruzi, O. gutturosa, O. volvulus,* and *L. sigmodontis*. Furthermore, the compounds demonstrated efficacy against insects, including the mosquito *M. separata*, the beet armyworm *H. armigera*, the fall armyworm *O. nubilalis*, the southwestern corn rootworm *S. frugiperda*, and the cotton leafworm *A. medicagini*. It is noteworthy that during the development of compounds with the aforementioned activity, the 1,2,4-oxadiazole fragment was frequently employed to enhance the metabolic stability of the compounds. Moreover, among the substances exhibiting antiparasitic activity, the 1,2,4-oxadiazole fragment was identified as a constituent of the most active compounds synthesized for the control of the *Plasmodium* parasite.

6. Functional derivatives of 1,2,4-oxadiazole with antiviral activity

Additionally, antiviral activity was observed for 1,2,4-oxadiazole derivatives. For example, compound **89** (**11526092**) has been demonstrated to effectively inhibit the reproduction of enterovirus D68 (EV-D68) (IC_{50} = 58 nM) and other enteroviruses, including pleconaril-resistant Coxsackievirus B3-Woodruff (IC_{50} = 6–20 nM) and Coxsackievirus B5 (CVB5) (EC_{50} = 1 nM) *in vitro* (Fig. 13) [114]. The mechanism of action of this compound is the destabilization of viral proteins. Furthermore, the use of compound **89** (**11526092**) in a mouse model of EV-D68 respiratory infection resulted in a reduction in virus levels in the lungs, and in a mouse model of CVB5 infection resulted in a reduction in the viral load in the pancreas. It is noteworthy that enterovirus D68 and Coxsackievirus B5 remain without an approved treatment, and the obtained functional derivative of 1,2,4-oxadiazole represents a promising candidate for a broad-spectrum antiviral drug against enterovirus infections.

A further 1,2,4-oxadiazole derivative directed against enterovirus D68 was compound **90**. It demonstrated slightly diminished activity compared to the previously described compound **89** (**11526092**), but it remained highly active (EC_{50} = 50–100 nM) against various strains of enterovirus D68, exhibiting acceptable pharmacokinetic properties [114,115]. Furthermore, as with compound **89**, the biological target is the capsid surface protein VP1. It is noteworthy that the structures of these VP1 inhibitors exhibit a similar chemical composition, characterized by the presence of a trifluoromethyl group at the C-5 position of the 1,2,4-oxadiazole moiety. All these findings highlight the potential of

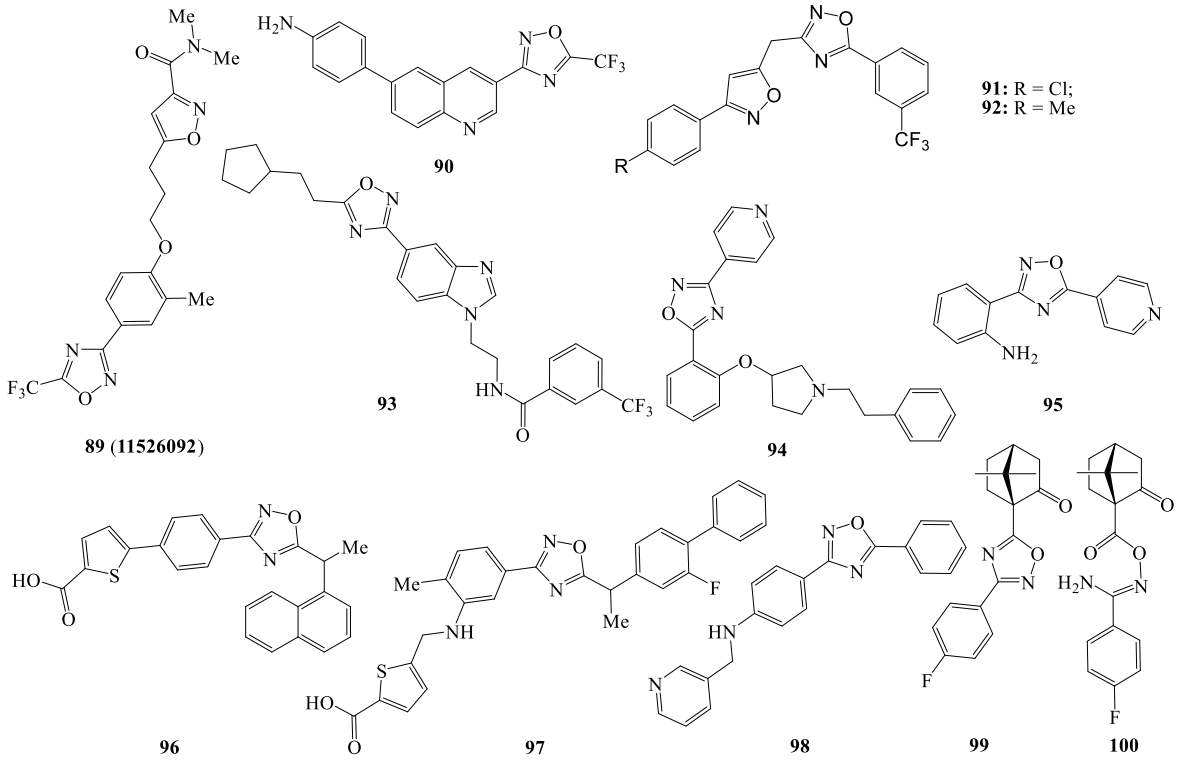


Fig. 13. 1,2,4-Oxadiazole derivatives **89**–**100** with antiviral activity.

these 1,2,4-oxadiazole derivatives as effective antiviral agents.

Additionally, functionalized 1,2,4-oxadiazole derivatives demonstrated activity against the HIV virus. Indeed, compound **91** was observed to exhibit antiviral activity, with an IC_{50} = 85.7 nM. Furthermore, both compounds **91** and **92** demonstrated activity against human $CD4^+$ reporter cell lines, TZM-bl and CEM-GFP infected with HIV [116]. The mechanism of action of these 1,2,4-oxadiazole derivatives is the inhibition of HIV-1 replication. In this study, the 1,2,4-oxadiazole fragment was employed as a non-classical bioisosteric replacement for the amide group.

The compound **93**, which is a derivative of benzimidazole functionalized with a 1,2,4-oxadiazole, has shown activity against both HBV resistant and wild-type strains [117]. It exhibited an IC_{50} = 0.44 μM and 0.53 μM for resistant and wild-type HBV, respectively. In addition to its antiviral activity, compound **93** also induced TLR8-regulated NF-κB activity in a dose-dependent manner. It was able to promote the secretion of cytokines TNF-α and IL-12 in human PBMC cell supernatants. It is worth noting that hepatitis B infection is a global public health problem due to the occurrence of dysfunctional immune responses and cerebrotoxic effects. The commonly used antiviral drug lamivudine is only effective against wild-type HBV, making compound **93** an important potential anti-HBV drug that requires further research and optimization.

The 1,2,4-oxadiazole derivative **94** demonstrated activity against SARS-CoV-2 with an EC_{50} = 4.7 μM [118]. In this study, the five-membered heterocyclic fragment was subjected to variation and differently replaced by other heterocycles, and it was established that 1,2,4-oxadiazole is not involved in significant interactions with the target, as it can be substituted without compromising the antiviral activity, only acting as linker. In order to combat the SARS-CoV-2 virus, 1,2,4-oxadiazole derivatives were developed with the objective of inhibiting the SARS-CoV-2 viral papain-like protease (PLpro) [119]. This enzyme plays a role in viral replication, making it an attractive target for the development of antiviral agents. Compound **95** was found to inhibit both the SARS-CoV-2 PLpro (IC_{50} = 7.197 μM) and the spike protein binding domain (RBD) (IC_{50} = 8.673 μM), which is responsible for viral invasion. The cytotoxic concentrations of this compound on Wi-38 and LT-A549 lung cells were found to be CC_{50} = 51.78 μM and 45.77 μM, respectively. The researchers used 1,2,4-oxadiazole as a bioisostere replacement for the amide group and found that it interacts with amino acid residues of various targets. Overall, compound **95** serves as a good prototype for future structural modifications to improve its antiviral properties while reducing cytotoxicity. The 1,2,4-oxadiazole derivatives **96** and **97** with an IC_{50} = 1.8 and 1.0 μM, respectively, act on a similar target (SARS-CoV-2 PLpro) [120]. Furthermore, they demonstrate efficacy against SARS-CoV-2 (EC_{50} = 5.4 and 4.3 μM) and exhibit favorable pharmacokinetic properties when evaluated in murine models. Given a bioavailability of 39.1 % and a CC_{50} = 124.2 μM on Vero E6 cells, compound **97** was selected as lead compound. Further *in vivo* studies are required to ascertain its potential for the development into a pharmaceutical.

A study focused on finding potential treatments for the Zika virus, which causes severe neurological effects and congenital anomalies, has led to the preparation of various 1,2,4-oxadiazole derivatives [121]. One of the most active compounds discovered was compound **98** which has also shown antiviral activity against other viruses of the *Flaviviridae* family, including dengue, Japanese encephalitis, and classical swine fever viruses. Due to these promising results, **98** can serve as a starting point for the development of 1,2,4-oxadiazole derivatives with broad-spectrum antiviral properties. This research could potentially lead to the creation of effective antiviral drugs to combat a range of viral infections.

The combination of 1,2,4-oxadiazole with (+)-ketopinic acid yielded compound **99**, which demonstrated activity against the influenza virus H1N1 (IC_{50} = 4 μM). Additionally, *O*-acylamidoxime **100** – an open-chained 1,2,4-oxadiazole analogue, exhibited activity against the influenza virus H7N9 (IC_{50} = 3 μM) [122]. The mechanism of action of these compounds is the effect on the fusion of the viral hemagglutinin (HA).Therefore, the 1,2,4-oxadiazole ring was employed in the development of antiviral pharmaceuticals as a linker, a bioisostere for amide or ester functional groups, as well as an independent pharmacophore

fragment. The functional derivatives of 1,2,4-oxadiazole have demonstrated antiviral activity against a range of viral families, including picornaviruses (genus *Enterovirus*), retroviruses (genus *Lentivirus*), hepadnaviruses (genus *Orthohepadnavirus*), coronaviruses (genus *Betacoronavirus*), and members of the *Flaviviridae* family (genus *Pestivirus* and *Flavivirus*).

7. Functional derivatives of 1,2,4-oxadiazole with anti-inflammatory activity

It has been demonstrated that 1,2,4-oxadiazole derivatives also possess anti-inflammatory activity. The synthesis of 3,5-disubstituted-1,2,4-oxadiazoles containing piperazine in their molecular structure demonstrated anti-inflammatory activity in a denaturation inhibition test using diclofenac sodium as reference drug [123]. In the study, the authors varied the substituents at the *N*-4 position of piperazine. The optimal compound **101** (Fig. 14) exhibited comparable inhibitory activity to the reference drug.

The combination of the 1,2,4-oxadiazole pharmacophore with the flavone pharmacophore, both of which have anti-inflammatory activity, led to the generation of derivatives of 3-methyl-8-(3-methyl-1,2,4-oxazol-5-yl)-2-phenyl-4*H*-chromen-4-ones with antioxidant and anti-inflammatory properties [124]. Among the synthesized compounds, **102** exhibited the most pronounced inhibitory effect on ROS and NO release in BV2 microglial cells. *In vivo* studies demonstrated that this compound inhibited the NF-κB and MAPK signaling pathways, thereby reducing neuronal apoptosis. Furthermore, compound **102** demonstrated *in vivo* efficacy in a mouse model of Parkinson's disease, by restoring dopamine levels, improving MPTP-induced motor ability, eliminating behavioral abnormalities, and promoting the transformation of M1-type macrophages into M2-type macrophages. Consequently, these findings suggest that compound **102** could be a potential treatment for Parkinson's disease.

The anti-inflammatory activity of 1,2,4-oxadiazole derivatives containing a pyridine fragment in their structure is mediated by a distinct mechanism. For example, compound **103a** is an analogue of compound **103b** (**DDO-7263**), which has been demonstrated to function as an activator of the Nrf2-ARE signaling pathway [125]. The activation of this signaling pathway has been demonstrated to affect a number of processes, including those associated with inflammation, cancer, neurodegeneration, and microbial infection. Biotin and fluorescein-based probes of **103a** were observed to activate Nrf2, as well as elicit antioxidant stress and anti-inflammatory effects. Through affinity chromatography and mass spectrometry, the Rpn6 protein was identified as a potential target that regulates the Nrf2 signaling pathway. *In vitro* affinity studies confirmed that **103b** (**DDO-7263**) binds to Rpn6, inhibiting the assembly of the 26S proteasome and the subsequent degradation of ubiquitinated Nrf2. This research highlights the unique mechanism of action of the compounds and their potential as anti-inflammatory agents.

The phidianidine derivatives **104a,b** which contain a of *N,N*-dimethyl-*N′*-phenylethane-1,2-diamine fragment, demonstrated anti-inflammatory activity and low toxicity, with IC_{50} = 5.3 μM and 7.7 μM, respectively, for IL-17A cytokine production in PMA/ionomycin-stimulated EL-4 T-cell lymphoma cells [126]. Furthermore, it was established that compound **104b** can reduce STAT3 phosphorylation, which ultimately leads to the inhibition of IL-17A production in EL-4 cells. Additionally, this compound can inhibit the differentiation of T helper 17 (Th17) cells. Consequently, further investigation of this compound series may potentially contribute to the development of novel therapeutic strategies for T-cell mediated diseases.

The 1,2,4-oxadiazol-5-one fragment was employed for the development of soluble epoxide hydrolase (sEH) inhibitors, resulting in the formation of compound **105a** (Fig. 9) [127]. However, the analogue **105b**, which contains a 1,3,4-oxadiazol-5-one moiety, was found to exhibit enhanced activity and selectivity, with an IC_{50} value of 42 nM on sEH and an IC_{50} > 10 μM on microsomal prostaglandin E2 esterase (mPGES-1). The SAR analysis revealed that the utilization of a terminal 1,3,4- oxadiazol-5-one or thione linked to the benzene ring, in conjunction with a urea group, is of significant importance with regard to sEH inhibition.

Therefore, the combination of the 1,2,4-oxadiazole core with piperazine, pyrazine, flavone, pyridine, and indole resulted in the synthesis of a series of compounds that exhibited anti-inflammatory activity. The mechanism of action was found to be the inhibition of the NF-κB and MAPK signaling pathways, the activation of the Nrf2-ARE signaling pathway by binding to Rpn6, the inhibition of IL-17A cytokine production, and the inhibition of the sEH.

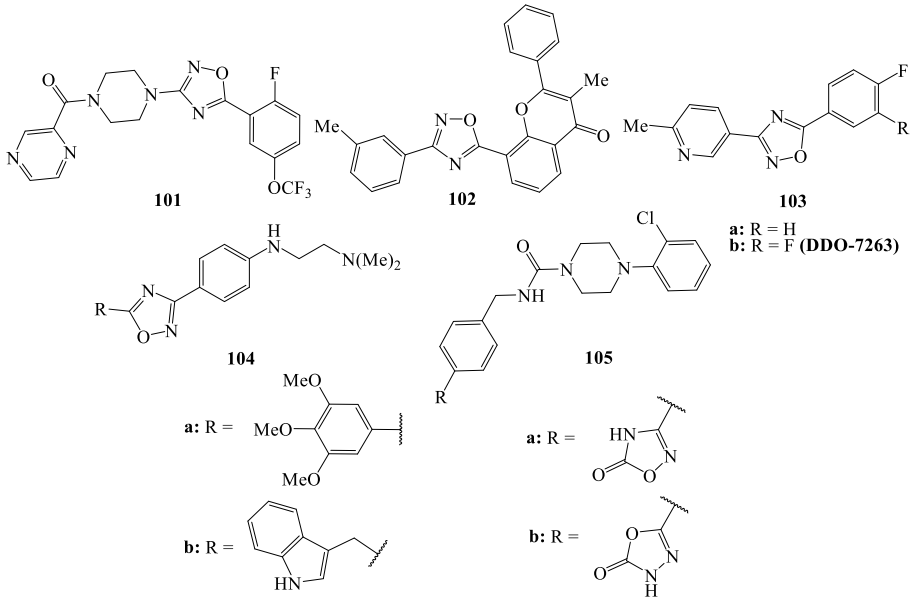


Fig. 14. 1,2,4-Oxadiazole derivatives **101**–**105** with anti-inflammatory activity.

8. Functional derivatives of 1,2,4-oxadiazole with neuroprotective activity

Alzheimer's disease (AD) represents the most prevalent form of dementia, accounting for approximately 60–70 % of cases. The majority of cases of AD occur in people between the ages of 60 and 70 years old. However, recent findings have revealed an alarming trend, with an increasing number of cases of AD being diagnosed in individuals aged 40–50. Therefore, there is an urgent need to develop an advanced drug for the treatment of this disease.

In an effort to develop multifunctional agents for the treatment of AD, 1,2,4-oxadiazole derivatives with the capacity to inhibit AChE and activate Nrf2 were synthesized [128]. Compound **106** (Fig. 15), effectively inhibited AChE (acetylcholinesterase), with an IC_{50} value of 0.07 μM for eeAChE and 0.38 μM for hAChE. It also activated the Nrf2 pathway by regulating the expression of related proteins (HO-1, NQO1, GCLM), leading to a significant increase in Nrf2 levels. Compound **106** displayed neuroprotective, antioxidant, and anti-inflammatory effects by protecting against H_2O_2 damage, Aβ1-42 aggregation, reducing ROS production, and pro-inflammatory cytokines. *In vivo* testing in a mouse brain model showed that **106** reversed cognitive impairment induced by scopolamine and $A\beta_{1\text{-}42}$, and reduced levels of pro-inflammatory factors. Interestingly, it outperformed the combination of donepezil (an AChE inhibitor) and a Nrf2 activator. These findings suggest that compound **106** has promising potential for the treatment of AD and warrants further investigation. The derivatives of 2-{[4-(1,2,4-oxadiazol-5-yl) phenyl]amino}acetamide have also been found to possess anti-AD activity [129]. Compound **107**, has demonstrated multi-targeting activity, inhibiting butyrylcholinesterase (BuChE) (IC_{50} = 1.28 μM) and neuroinflammatory processes, reducing Aβ self-aggregation by 51.91 %, and showing neuroprotective and antioxidant properties. Compound **107** also exhibited a DPPH radical scavenging effect and the ability to cross the blood-brain barrier. Additionally, it improved memory and cognitive performance in mice treated with scopolamine *in vivo*. The structural similarity of compounds **106** and **107**, both containing a 1,2,4-oxadiazole fragment with a substituted pyridine at the C-3 position, may explain their similar biological activities. Overall, these findings suggest that compound **107** and its derivatives could be potential candidates for the treatment of AD. 3,5-Disubstituted 1,2,4-oxazolidines have also demonstrated promising activity against AChE *in vitro* with IC_{50} = 0.0158–0.121 μM. These compounds may provide a promising avenue for the development of novel therapeutics for AD [130]. Of the compounds tested, **108** (AChE IC_{50} = 0.0158 μM) demonstrated the most promising activity, exhibiting superior performance compared to the reference drug donepezil (IC_{50} = 0.123 μM). Additionally, some compounds demonstrated activity against BuChE (IC_{50} = 11.5–15 μM) and monoamine oxidase B (MAO-B) (IC_{50} = 74.68–225). Furthermore, the compounds demonstrated antioxidant properties with an IC_{50} range of 59.25–56.69 μM. Ascorbic acid (IC_{50} = 74.55 μM) was used as the reference drug. The authors of the article suggest that compound **108** is the most promising for further development, as it has acceptable predicted ADME properties and the highest probability of crossing the blood-brain barrier.

Histone deacetylase 4 (HDAC4) has previously been demonstrated to interact with the product of the huntingtin gene (HTT), a CAG repeat in which is a causative factor in the development of Huntington's disease (HD). The deletion of HDAC4 in a mouse model of HD has been observed to result in an increase in lifespan. The first selective HDAC4 protein disruptors were synthesized and the structure of the most active compound **109** is presented in Fig. 10 [131]. The compounds act through the ubiquitin-proteasomal system and demonstrate efficacy in a range of cell lines, including those of the cortical neurons observed in the mouse model of HD.

1,2,4-Oxadiazole derivatives that act as reversible inhibitors of the BTK enzyme have been demonstrated to exhibit anti-multiple sclerosis activity [132]. The compound **110** contains structural elements of both the pyrimidine and pyrazole rings, in addition to the 1,2,4-oxadiazole core. It exhibited notable inhibitory activity (BTK IC_{50} < 0.5 nM, pBTK IC_{50} = 21 nM), while compound **111** (**BIIB091**), which contains a triazole heterocycle, demonstrated greater selectivity (BTK IC_{50} < 0.5 nM, with no activity on pBTK). ADME, physicochemical properties, and safety studies provided evidence that **111** (**BIIB091**) is a viable

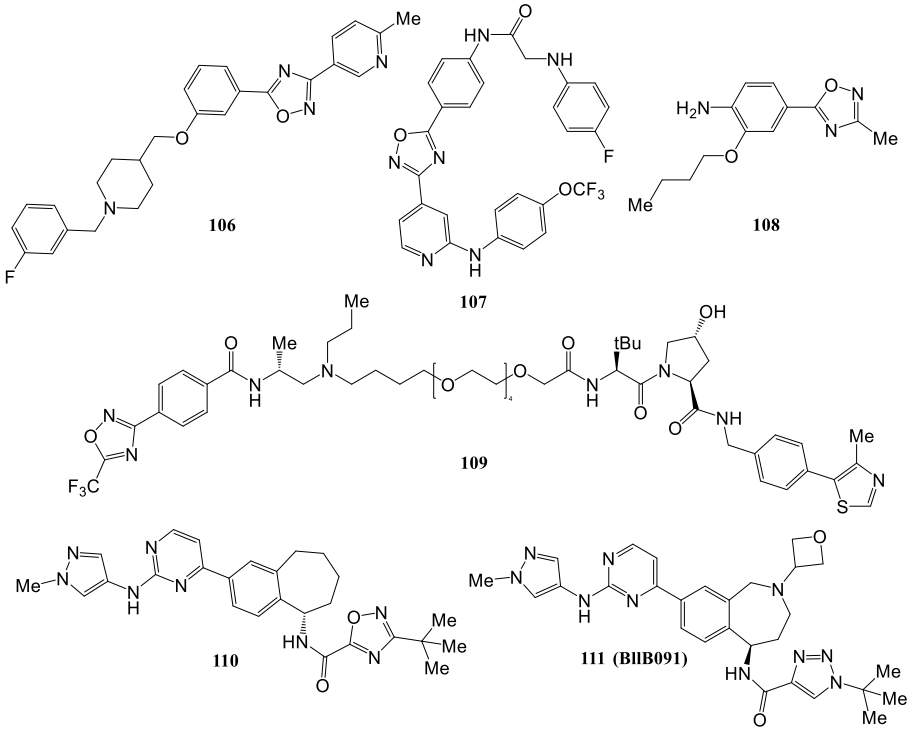


Fig. 15. Derivatives of 1,2,4-oxadiazole **106**–**111** with neuroprotective activity.

candidate for clinical trials in the treatment of autoimmune diseases such as multiple sclerosis.

Another frequently occurring neurodegenerative disease is Parkinson's disease (PD). Compounds exhibiting potential for the management of this condition, comprising the 1,2,4-oxadiazole ring system [114], have been outlined in the section pertaining to anti-inflammatory activity (Section 6).

It has been demonstrated that compounds incorporating the 1,2,4-oxadiazole fragment exhibit favorable properties and potential for the treatment of difficult-to-treat neurodegenerative diseases, including PD, HD, AD, and autoimmune diseases such as multiple sclerosis. Furthermore, most of the compounds under consideration demonstrate multi-target action with a range of activities, which represents a significant advantage in practical applications.

9. Miscellaneous

In addition to the aforementioned activity, compounds containing the 1,2,4-oxadiazole ring exhibit other significant biological activities.

Derivatives of 2-{[3-aryl-1,2,4-oxadiazole-5-yl)methyl]thio}-1*H*-benzimidazole have been demonstrated to possess anti-atherosclerotic and lipid-lowering properties [133]. The general structure **112** of these compounds is depicted in Fig. 16. The most active compound in this series was observed to exhibit antioxidant effects, with a radical scavenging capacity of 77 %. Furthermore, docking studies were conducted with the Niemann-Pick C1-Like 1 enzyme (NPC1L1). NPC1L1 is a transmembrane protein that is localized on the apical membranes of enterocytes and hepatocytes, playing a crucial role in cholesterol absorption in the intestine. This protein is responsible for transporting phytosterols and cholesterol across the intestinal epithelium, serving as a key regulator of cholesterol homeostasis throughout the body. Mutations in the gene encoding this enzyme result in the neurodegenerative disease Niemann-Pick disease type C1, characterized by the accumulation of lipids and cholesterol in late endosomes and lysosomes of cells. *In silico* studies have confirmed that (aryloxy)benzimidazole derivatives possess acceptable physicochemical properties.

The 1,2,4-oxadiazole derivatives **113**, which act as inhibitors of acid sphingomyelinase (ASM), a regulatory enzyme involved in sphingolipid metabolism, have also been observed to possess antiatherosclerotic properties. The results of the SAR analysis indicated that the presence of a five-membered heterocycle with three heteroatoms linked to a hydroxamic acid residue is a crucial determinant for activity, while the attachment of a bulky hydrophobic moiety to the scaffold also enhances the activity. The most active compound **113a** exhibited activity with an IC_{50} = 1.5 μM on ASM [134]. Furthermore, this compound demonstrated anti-inflammatory effects by reducing the levels of inflammatory factors IL-6, TNF-α, and MCP-1. It revealed acceptable pharmacokinetic properties and *in vivo* activity, regulating ceramide and sphingomyelin levels, and reducing the amount of lipid plaques in the aorta and its arch in mice with atherosclerosis. These findings support the potential of targeting ASM for the development of anti-atherosclerotic agents.

Other derivatives of 1,2,4-oxadiazole, which have been demonstrated to possess anti-atherosclerotic and anti-inflammatory activities, contain an indole fragment within their structure [135]. The inhibitory effect of compound **114** on vascular endothelial cell (VEC) apoptosis induced by oxidised low-density lipoprotein (oxLDL) – a strategy that has proven effective in the treatment of atherosclerosis – was found to be mediated by the activation of the Nrf2/HO-1 pathway. Additionally, compound **114** reduced the expression of ICAM-1 and VCAM-1 in VECs, as well as the levels of AFC (a marker of inflammation) and the nuclear translocation of NF-κB. It is noteworthy that compound **114** and other lead compounds in previous research [127] are derived from the alkaloid fidianidine. This indicates the importance of synthesizing derivatives of fidianidine for the further development of drugs targeting inflammation and atherosclerosis.

Derivatives of 1,2,4-oxadiazol-5(4*H*)-one, which contain a thiazole ring and an *N*-acylsulfonamide group, have demonstrated inhibitory activity against the ChemR23 receptor, which represents a potential target for the treatment of autoimmune diseases [136]. This G-protein-coupled receptor is located on the surface of plasmacytoid dendritic cells and contributes to their attraction to inflamed tissues through chemotaxis. Among the tested compounds, **115** demonstrated the highest activity, with an IC_{80} = 12 nM. It is noteworthy that this compound exhibited prolonged *in vivo* activity in crab-eating macaques, exceeding the activity of the known inhibitors ChemR23 based on 2-aminobenzoxazole.

A further target for the treatment of autoimmune diseases is the CXCR3 receptor. The receptor provides selective recruitment of immune cells, including T lymphocytes, to inflamed tissue which can lead to tissue damage. Therefore, the inhibition of this receptor may prove beneficial in the treatment of autoimmune diseases characterized by high concentrations of CXCR3 ligands. Compound **116** (**ACT-672125**)

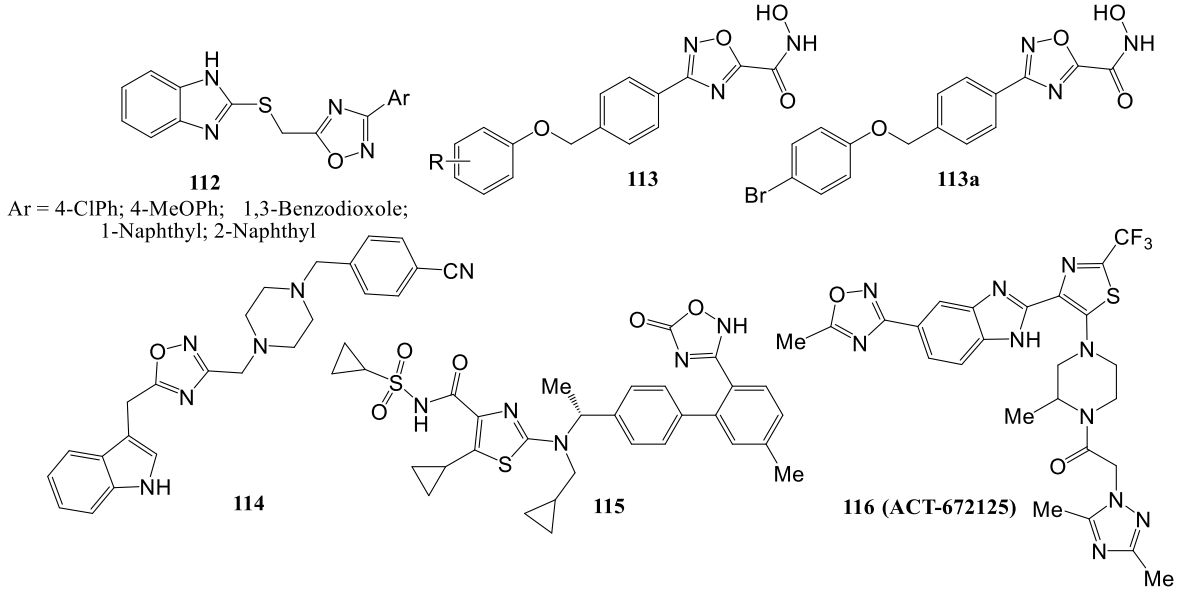


Fig. 16. 1,2,4-Oxadiazole derivatives **112**–**116** with various types of activity.

demonstrated high activity at the CXCR3 receptor with an IC_{50} = 239 nM and notable selectivity against other chemokine receptors (<50 % inhibition at 10 μM concentration). In an *in vivo* mouse model, compound **116** dose-dependently inhibited the entry of T cells expressing CXCR3 into the inflamed lung. However, its administration caused an increase in bilirubin levels in mice and macaque monkeys, leading to the cessation of further preclinical trials [137].

1,2,4-Oxadiazole derivatives have also been found to possess antidiabetic activity. Diabetes mellitus is a serious and widespread disease. As evidenced by numerous studies, the prevalence of diabetes has increased markedly in nearly all countries, thereby rendering it a significant global epidemic [138]. It is estimated that the number of people with diabetes worldwide will increase by 48 % by 2045, reaching 628.6 million [139]. In light of these findings, the development of effective antidiabetic drugs is a matter of great urgency. Compound **117** (Fig. 17) demonstrated high agonistic activity towards G-protein coupled receptor 119 (GPR119) (IC_{50} = 6.3 nM), which represents a potential target for the treatment of type 2 diabetes and obesity [140].

Furthermore, compound **117** demonstrated favorable pharmacokinetic properties and markedly reduced blood glucose levels in rodents *in vivo*. Another potential target for the treatment of type 2 diabetes is the glucagon-like peptide-1 receptor (GLP1R), which is a G-protein-coupled receptor. This receptor is located on the beta cells of the pancreas and on neurons in the brain. It plays a role in regulating blood glucose levels by enhancing insulin secretion. The activation of this receptor has been associated with weight loss and the treatment of type 2 diabetes. Compound **118** (**V-0219**) is an allosteric agonist of GLP1R, containing the 1,2,4-oxadiazole moiety as part of the pharmacophore group [141]. The compound was observed to potentiate GLP-1 Emax = 60 % at a concentration of 10 μM. Furthermore, this compound enhanced insulin secretion in the rat β-cell line INS-1 at a concentration of 1 μM and potentiated the effect of cAMP accumulation in HEK-GLP-1 cells at nanomolar concentration. Additionally, *in vivo* studies have shown that **118** (**V-0219**) reduces food intake and enhances glucose uptake in both healthy and diabetic mice following oral administration.

Another common disorder associated with diabetes mellitus is non-alcoholic steatohepatitis (NASH), a chronic liver disease that may remain asymptomatic for extended periods of time. NASH and advanced fibrosis can result from improper regulation of bile acid homeostasis. A promising therapeutic strategy involves targeting the farnesoid X receptor (FXR), a nuclear receptor that regulates genes responsible for bile acid biosynthesis and is expressed in multiple tissues.

In order to reduce adverse effects, the challenge was to design an FXR agonist with a tissue-selective activation profile and reduced activity in liver cells. To minimize adverse effects, the challenge was to design an FXR agonist with a tissue-selective activation profile and reduced activity in liver cells. To address this, extensive systematic SAR studies led to the identification of compound **119** (**BMS-986339**), which incorporates a 1,2,4-oxadiazole moiety [142]. This compound demonstrated an optimal balance of potency, metabolic stability, and CYP inhibition/induction profiles *in vitro* and showed antifibrotic activity, pharmacokinetic properties and a context-dependent activation profile *in vivo*.

The 1,2,4-oxadiazole moiety was originally introduced to replace a potentially toxic phenyl aniline group and to enhance the physicochemical properties. Some compounds in the series also feature a second oxadiazole moiety in place of the more polar hydroxy isopropyl phenyl group present in compound **119**. The oxadiazole was initially used to replace a reactive α,β-unsaturated ester with a more druglike motif, resulting in a well-balanced profile but suboptimal potency that required further optimization.

Some compounds in the series also feature a second oxadiazole moiety, initially introduced to replace a reactive α,β-unsaturated ester with a more druglike motif. While that substitution resulted in a well-balanced profile, it exhibited suboptimal potency, which was ultimately improved by the incorporation of the more polar hydroxy isopropyl phenyl group present in compound **119**.

Another pharmacologically active compound, **120** (**GDC-6599**), contains the chemical 1,2,4-oxadiazole nucleus and functions as an antagonist of the TRPA1 ankyrin receptor with an IC_{50} = 5.3 nM [143]. This receptor is capable of sensing both exogenous and endogenous signals and has been associated with the development of neuropathic pain and respiratory diseases. The developed compound **120** (**GDC-6599**) is a first-in-class drug and is currently undergoing phase 2 clinical trials for the treatment of respiratory diseases.

Compounds containing the fragments of 1,2,4-oxadiazol-5(4*H*)-one, triazole, and terminal amine have been found to have antifibrinolytic activity [144]. Among these compounds, **121** showed significantly higher activity (IC_{50} = 13.8 μM) than the reference drug tranexamic acid (IC_{50} = 33.3 μM). The compound targets the Kringle 1 domain of plasminogen activator. Analysis of the SAR and molecular docking studies confirmed that the presence of the 1,2,3-triazole heterocycle is crucial

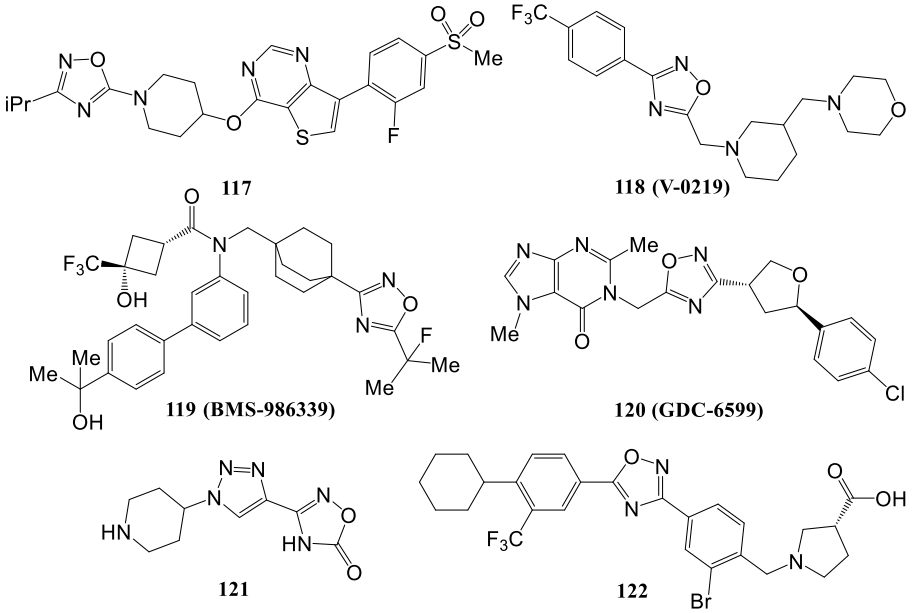


Fig. 17. 1,2,4-Oxadiazole derivatives **117**–**122** with various types of activity.

for activity, as it participates in pi-pi stacking interactions. Additionally, the presence of the piperidine ring in the molecule was found to enhance the activity compared to aliphatic amines. Furthermore, it was established that the derivative with the 1,2,4-oxadiazolone demonstrated a higher affinity, and substituting the 1,2,4-oxadiazolone with a carboxylic acid resulted in decreased activity. Overall, this study has established a new promising scaffold for the development of antifibrinolytic drugs.

The 1,2,4-oxadiazole derivative **122** showed selective agonist activity against S1PR1 involving β-arrestin (EC_{50} = 0.36 nM/L) and receptor internalization (EC_{50} = 8.09 nM/L) [145]. In addition, a bioavailability of 93.6 % and an *in vivo* activity in a mouse model of ulcerative colitis at a dose of 0.1 mg/kg have been determined for this compound.

10. In-silico studies applied to 1,2,4-oxadiazole derivatives

10.1. Application of QSAR/QSPR methods to 1,2,4-oxadiazole derivatives

The heterocyclic scaffold of 1,2,4-oxadiazoles has been extensively studied in medicinal chemistry due to its broad biological activity and favorable physicochemical properties. Quantitative Structure–Activity Relationship (QSAR) and Quantitative Structure–Property Relationship (QSPR) techniques have played a pivotal role in elucidating structure–activity correlations, guiding molecular design, and predicting the biological behavior of these compounds. Over the past two decades, multiple QSAR studies have explored the potential of 1,2,4-oxadiazole derivatives as antibacterial, antifungal, anticancer, antiviral, and insecticidal agents, among others.

The earliest QSAR study by Geban et al. (1999) focused on 3,4-disubstituted-1,2,4-oxa(thia)-diazole-5(4H)-ones(thiones) and demonstrated that quantum chemical parameters such as HOMO electron density at sulfur and oxygen atoms were strongly correlated with antimicrobial activity [146]. These heteroatoms were found to interact with SH enzymes in microbial systems, highlighting the importance of electronic distribution around the oxadiazole ring.

In 2010, Outirite et al. extended the use of computational modeling to corrosion inhibition, where DFT-based QSPR studies showed that the electron-rich nitrogen and oxygen atoms of 3,5-bis(n-pyridyl)-1,2,4-oxadiazoles enable strong donor interactions with metal surfaces, particularly in acidic environments [147]. Protonation was found to enhance adsorption through HOMO localization, reinforcing the molecule's ability to form protective layers.

Muratov et al. identified the trifluoromethyl-substituted 1,2,4-oxadiazole moiety as a critical structural feature for high antiviral activity against coxsackievirus B3 (CVB3) [148]. Other substituents like biphenyl or naphthyl groups were detrimental, emphasizing the need for precise substitution patterns.

In oncology, Belaidi et al. conducted SAR and QSAR modeling on 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amine derivatives, identifying descriptors such as logP, polarizability, molar refractivity, and frontier orbital energies (HOMO and LUMO) as significantly correlated with cytotoxic potency [149]. Electron-withdrawing groups on aryl rings enhanced activity, likely due to improved target binding and metabolic stability.

Praseetha et al. applied multiple QSAR models to Vorinostat derivatives containing 1,2,4-oxadiazole moieties for targeting histone deacetylases (HDACs) in tumor treatment [150]. Hydrogen bonding capacity and zinc-binding affinity were shown to be essential for HDAC inhibition, confirming the importance of this scaffold in epigenetic therapy.

Maciel et al. reported on a second generation of 1,2,4-oxadiazole derivatives with enhanced solubility while retaining HKT inhibitory activity [151]. QSAR-guided modifications led to improved bioavailability without compromising biological efficacy. Substituents such as polar side chains and hydrophilic groups were identified as favorable features for increasing aqueous solubility.

In 2021, Vaidya further expanded the scope of 1,2,4-oxadiazole-based therapeutics by exploring their use as caspase-3 activators for cancer treatment using Step-Wise k-Nearest Neighbour Molecular Field Analysis (SW kNN MFA) and docking simulations [152]. Electronegative substitutions at the 5th position of the oxadiazole ring were found to significantly enhance apoptotic activity. Descriptors such as ionization potential (IP), dipole moment (DM), and polar surface area (PSA) were positively correlated with caspase-3 activation, particularly through hydrogen bonding with residues Cys205 and Gly238.

Da Silva et al. (2023) investigated the larvicidal activity of new 1,2,4-oxadiazoles against Aedes aegypti mosquitoes using QSAR and molecular docking [153]. They found that larger and more hydrophobic substituents—particularly biphenyl groups attached at the 3rd position—significantly enhance larvicidal activity. Nanocapsulation of selected derivatives improved solubility and efficacy, indicating practical strategies for future pesticide development.

Yu et al. (2023) took an integrative approach in studying α-keto-[1,2,4]-oxadiazoles as inhibitors of human β-tryptase, a mediator in allergic and inflammatory diseases [154]. Combining QSAR, molecular docking, MD simulations, and pharmacophore modeling, they identified molecular volume, dipole moment, and electronic distribution as key contributors to binding affinity and selectivity.

The most recent study published in 2025 by Asad et al. explores the synthesis and evaluation of 3,5-disubstituted-1,2,4-oxadiazolyl benzamides as potential anti-breast cancer agents, both *in vitro* and in silico [155]. This work builds upon previous QSAR findings by designing new analogues based on earlier predictive models. In vitro screening revealed promising activity against MCF-7 (ER+), MDA-MB-231 (ER−), HeLa, Ishikawa, and HEK-293 cell lines, with some compounds showing comparable or superior activity to standard chemotherapeutic agents like paclitaxel and mitomycin.

Computational analysis confirmed favorable ADMET profiles and strong interactions with tumor-associated proteins, underscoring the continued relevance of the 1,2,4-oxadiazole scaffold in targeted cancer therapy. Notably, the integration of in silico modeling with experimental validation highlights the power of combining modern computational tools with traditional medicinal chemistry approaches.

Collectively, the QSARs studies illustrate the growing versatility and pharmacological significance of the 1,2,4-oxadiazole scaffold. Whether used in epigenetics, apoptosis induction, inflammation suppression, pest control, or corrosion protection, the oxadiazole moiety continues to serve as a privileged structural element that can be fine-tuned for desired biological outcomes.

10.2. 3D QSAR studies on compounds containing the 1,2,4-oxadiazole moiety

The 1,2,4-oxadiazole ring is a five-membered heterocyclic compound that has attracted significant attention in medicinal chemistry due to its broad spectrum of biological activities. These include antibacterial, anticancer, and enzyme inhibitory properties. Quantitative Structure–Activity Relationship (QSAR) studies, particularly three-dimensional (3D-QSAR), have been instrumental in understanding how structural modifications can enhance the biological activity of these compounds.

Regarding antibacterial 1,2,4-Oxadiazoles, a comprehensive 3D-QSAR analysis was conducted by Leemans et al. (2016) to design new 1,2,4-oxadiazole-based antibacterial agents. The study utilized computational docking and scoring procedures to identify this class of antibiotics as active against Gram-positive bacteria, including *Staphylococcus aureus*. The lead compound served as the basis for extensive structure–activity relationship (SAR) analysis, leading to the development of a robust 3D-QSAR model using Comparative Molecular Field Analysis (CoMFA). The model provided insights into the steric and electrostatic

requirements for enhancing antibacterial potency [156]. In another study, Shakour et al. (2021) explored 3D-QSAR investigations on 120 molecules of 1,2,4-oxadiazoles with antibacterial properties targeting Sortase A (SrtA), a key enzyme in bacterial cell wall synthesis. Using Schrödinger software suite, they performed molecular docking and developed a 3D-QSAR model based on Partial Least Squares (PLS) regression. The best model, selected based on cross-validation statistics ($q^2 = 0.610$, $r^2 = 0.743$), highlighted the importance of hydrophobic substituents in the D-ring region for enhanced SrtA inhibition. This study also emphasized the role of hydrogen bond donors (HBDs) in the A-ring for optimal antibacterial activity [157].

In the pursuit of novel anticancer agents, a series of pyrazole derivatives were synthesized and biologically validated guided by 3D-QSAR analysis [158]. Among these, compound 10, featuring a rigid 1,2,4-oxadiazole moiety, emerged as a particularly promising candidate. In the study, 3D-QSAR analysis played a pivotal role in guiding the design and synthesis of novel pyrazole derivatives with anticancer activity. By analyzing molecular properties impacting antitumor activity against lung cancer cells, researchers identified key structural modifications, such as substituting the hydrazine linker with a rigid 1,2,4-oxadiazole moiety, which led to compound 10. This compound exhibited strong cytostatic activity with minimal cytotoxic effects, underscoring the importance of 3D-QSAR in optimizing lead compounds for enhanced therapeutic potential and safety.

Another notable contribution came from Singh et al. (2017), who applied CoMFA, CoMSIA, and SW kNN MFA methods to analyze a dataset of 28 3-aryl-5-aryl-1,2,4-oxadiazole derivatives. Their models revealed that bulky groups at the 5th position of the oxadiazole ring and electronegative substituents at the 3rd position significantly enhanced caspase-3 activating activity. Docking studies further supported these findings by showing favorable interactions between the compounds and the active site of caspase-3 [159].

Building upon the insights gained from 3D-QSAR studies, several research teams have designed and synthesized new 1,2,4-oxadiazole derivatives with improved biological profiles. For instance, Kumar et al. (2020) used SW kNN MFA models to guide the substitution patterns of newly designed compounds. They introduced bulky and electronegative groups at specific positions on the oxadiazole scaffold, resulting in enhanced anticancer activity. Spectroscopic characterization confirmed the structures of the synthesized compounds, which were then tested against various cancer cell lines [160].

Similarly, Patel et al. (2021) leveraged 3D-QSAR models to develop novel 1,2,4-oxadiazole derivatives as potent caspase-3 activators. Their approach combined computational modeling with experimental validation, demonstrating that strategic substitutions could significantly boost the apoptotic potential of these compounds. Four of the synthesized derivatives showed significant anticancer activity, rivaling established chemotherapeutic agents [161].

10.3. Molecular docking applied on compounds containing the 1,2,4-oxadiazole moiety

Molecular docking is a computational technique widely used in drug discovery and development to predict the preferred orientation of small molecules when they bind to their target proteins. This approach helps researchers understand the molecular interactions that govern ligand-receptor binding affinities and specificities. In recent years, several studies have focused on the application of molecular docking to compounds containing the 1,2,4-oxadiazole scaffold, a heterocyclic ring system known for its biological activity and synthetic versatility.

The 1,2,4-oxadiazole core has been extensively explored in medicinal chemistry due to its broad spectrum of pharmacological activities, including anti-inflammatory, anticancer, antiviral, and neuroprotective properties.

These derivatives are often designed to interact with various biological targets, such as enzymes, receptors, and ion channels. The incorporation of this scaffold into novel chemical entities allows for the modulation of physicochemical properties, enhancing drug-like characteristics such as solubility, stability, and bioavailability.

From a survey on the SCOPUS database (www.scopus.com, accessed in October 2024 and also April 2025) using the key "1,2,4-oxadiazole" AND "molecular docking" revealed more than 190 articles have been published indicating that several molecular docking techniques were used and that there is no particular software to be used for compounds containing the 1,2,4-oxadiazole moiety.

Molecular docking has played a pivotal role in elucidating the binding modes and mechanisms of action of 1,2,4-oxadiazole derivatives. Several studies have employed this technique to evaluate the potential of these compounds as inhibitors or activators of specific therapeutic targets.

A study by Lingam et al. [162] reported the design and synthesis of 1,2,4-oxadiazole-incorporated indazole-isoxazole derivatives, followed by their evaluation as anticancer agents. Molecular docking was utilized to assess the binding affinity of these compounds towards cancer-related targets. The results indicated that certain derivatives exhibited strong interactions with key residues in the active sites of their respective targets, suggesting their potential as lead candidates for further development.

Another significant application of molecular docking in 1,2,4-oxadiazole research involves the identification of caspase inhibitors. Caspases are cysteine proteases involved in apoptosis regulation, making them attractive targets for the treatment of diseases characterized by excessive cell death, such as neurodegenerative disorders. A study highlighted the use of molecular docking to explore the binding orientations and conformations of 1,2,4-oxadiazole derivatives interacting with caspases. The findings demonstrated that these compounds could effectively occupy the catalytic pockets of caspases, thereby inhibiting their activity [163].

Researchers have also investigated the multifunctional capabilities of 1,2,4-oxadiazole derivatives through molecular docking. For instance, a study aimed to develop potential multifunctional agents capable of targeting multiple pathways simultaneously. The docking simulations revealed that these compounds could engage in favorable interactions with various protein targets, supporting their utility as multitarget-directed ligand [164].

For specific application, the xanthine oxidase (XO) enzyme has been targeted using 1,2,4-oxadiazole thioether derivatives. XO is implicated in oxidative stress and inflammation, making it a relevant target for the treatment of gout and other inflammatory conditions. Molecular docking studies showed that some compounds, particularly 4e and 4j, displayed potent inhibition activity against XO, with predicted binding energies indicating strong interactions within the enzyme's active site [165].

10.4. Virtual screening strategies to disclose bioactive 1,2,4-oxadiazole derivatives

Virtual screening has emerged as a pivotal computational tool in modern drug discovery, enabling the rapid identification and optimization of bioactive compounds across a wide range of therapeutic areas. Among the various molecular scaffolds explored through these methodologies, the 1,2,4-oxadiazole heterocycle has demonstrated consistent promise due to its structural versatility, metabolic stability, and ability to engage in key non-covalent interactions within target protein binding sites. Several studies have employed ligand-based and structure-based virtual screening strategies to explore novel 1,2,4-oxadiazole derivatives with potential applications in oncology, infectious diseases, inflammation, and neglected tropical diseases. In one such effort, ligand-based virtual screening was applied to identify non-acidic analogues of Ataluren for promoting readthrough of nonsense mutations. This approach led to the selection of 3,5-diaryl-1,2,4-oxadiazoles as promising leads following pharmacophore modeling and experimental

validation [166]. These findings highlight the scaffold's adaptability in targeting genetic disorders involving premature termination codons. Another study further expanded this application by exploring structure–activity relationships (SAR) around PTC124 analogues, emphasizing how variations in fluorine substitution patterns on the aromatic rings significantly influence activity profiles [166].

In oncology, pharmacophore-based virtual screening was employed to discover small-molecule inhibitors of T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), a critical immune checkpoint receptor implicated in acute myeloid leukemia (AML). The identified lead compounds featured a diphenyl-1,2,4-oxadiazole scaffold, with meta-substitution at the 5-position proving crucial for optimal binding and inhibitory activity [167]. Similarly, structure-based virtual screening was used to identify novel RIPK1 inhibitors, where compound 2—bearing a 5-(1-benzyl-1H-imidazole-4-yl)-1,2,4-oxadiazole core—was selected as a hit based on crystal structure-guided similarity searching and subsequently used for SAR-driven optimization [168]. These examples underscore the scaffold's utility in modulating protein–protein interactions and enzyme activity in cancer-related pathways.

The antiviral potential of 1,2,4-oxadiazoles has also been extensively investigated using virtual screening methods. A comprehensive study combined virtual screening, molecular docking, and supervised machine learning to identify novel compounds targeting three SARS-CoV-2 proteins: spike, nucleocapsid, and 2′-O-ribose methyltransferase. While not explicitly detailing oxadiazole hits among the top-ranked candidates, the methodology showcased the integration of computational techniques in accelerating antiviral lead discovery [169]. Earlier QSAR analyses of [(biphenyloxy)propyl]isoxazoles highlighted the importance of specific molecular fragments such as 5-trifluoromethyl- [1,2,4]oxadiazole in enhancing antiviral activity against coxsackievirus B3 (CVB3), guiding the rational design of new agents against this pathogen [148]. Additionally, a small molecule featuring a 1,2,4-oxadiazole moiety was identified via virtual screening and SPR-based assays as an inhibitor of HIV-1 matrix protein, exhibiting broad-range antiviral activity by interfering with the phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) binding site [170], reinforcing the scaffold's applicability in virology.

Antibacterial research has also benefited from virtual screening efforts focusing on 1,2,4-oxadiazoles. A 3D-QSAR study on 120 oxadiazole derivatives revealed key structural features necessary for inhibiting SrtA, an essential enzyme in Gram-positive bacterial pathogenesis. Hydrogen bond donor moieties in ring A and hydrophobic substituents were found to be particularly important for antibacterial potency. Docking simulations provided insights into binding modes, aiding the rational design of more effective antibiotics **[157]**. Parallel efforts have shown that substituted 1,2,4-oxodiazoles can serve as potent inhibitors of human 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a validated target in metabolic disorders. Virtual screening followed by molecular docking and Lipinski-like filters identified a set of 23 promising compounds with favorable physicochemical properties for further development [171].

In parasitology, virtual screening combined with molecular docking and MD simulations has been used to evaluate 1,2,4-oxadiazole derivatives as larvicidal agents targeting *Anopheles gambiae* HKT transporters. Compounds such as 2-[3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl]cyclopentane-1-carboxylic acid showed strong binding affinities (~8.5 kcal/mol), suggesting their potential use in vector control strategies for malaria prevention [172]. These results align with earlier reports showing the larvicidal activity of isoxazole and oxadiazole derivatives synthesized via 1,3-dipolar cycloaddition reactions [173], highlighting the broader utility of five-membered heterocycles in insecticidal applications.

11. ADME, pharmacokinetics profile of 1,2,4-oxadiazole derivatives

The 1,2,4-oxadiazole scaffold has consistently demonstrated favorable ADME (Absorption, Distribution, Metabolism, Excretion) and pharmacokinetic properties, making it a valuable motif in medicinal chemistry for diverse therapeutic applications. Across multiple studies published during the last decade, these heterocyclic compounds have shown improved metabolic stability, often serving as bioisosteres of esters and amides, which are prone to enzymatic hydrolysis [174–176]. In anticancer research, several 1,2,4-oxadiazole derivatives exhibited potent cytotoxic activity against breast, pancreatic, and leukemia cell lines, with IC_{50} values in the low micromolar range and excellent *in vitro* metabolic stability [70,177,178]. Notably, phthalazine-piperazine hybrids like compound 4d in Ref. [179] displayed high selectivity toward cancer cells while showing minimal toxicity to normal cells, along with compliance with Lipinski's Rule of Five, indicating strong drug-likeness [179].

In infectious diseases, oxadiazole-containing molecules showed promising antitubercular and antiviral activities, with some derivatives demonstrating low minimum inhibitory concentration (MIC) values and good cell membrane permeability [109,180,181]. For example, spiroquinoxaline-1,2,4-oxadiazole hybrids synthesized under ultrasound irradiation exhibited MIC_{99} values as low as 0.78 μg/mL against Mycobacterium tuberculosis, with acceptable cytotoxicity profiles on RAW 264.7 macrophages [182]. Similarly, 3-trifluoromethyl-1,2,4-oxadiazole analogues of astemizole showed multi-stage antiplasmodial activity and enhanced *in vivo* efficacy in murine models [183].

From a pharmacokinetic perspective, many 1,2,4-oxadiazole derivatives were predicted to have good oral bioavailability using tools like SWISS/ADME and pkCSM, with favorable logP values, solubility, and intestinal absorption profiles [184–186]. These properties were particularly evident in CNS-targeting agents, where certain derivatives demonstrated effective blood-brain barrier penetration, supporting their potential in treating neurological conditions such as Huntington's disease and Alzheimer's disease [131,186]. Additionally, DFT-based computational studies confirmed the electronic stability and reactivity of oxadiazoles, further reinforcing their utility in drug design [182].

Despite these advantages, some oxadiazole compounds showed concerns regarding genotoxicity, as indicated by AMES testing, highlighting the need for careful structural optimization to avoid mutagenic liabilities [187]. Moreover, molecular docking and molecular dynamics simulations revealed that oxadiazole derivatives can engage effectively with targets such as EGFR, HDACs, FXR, and SLACK potassium channels, offering high binding affinity and selectivity [135,188,189]. In particular, novel FXR antagonists derived from this scaffold exhibited favorable *in vitro* ADME profiles, including low CYP inhibition and good half-life, supporting chronic administration in metabolic disease models [190].

12. Conclusions

As this literature review indicates, 1,2,4-oxadiazole as a scaffold for the targeted design of biologically active compounds with specific pharmacological activity has not only retained its significance in recent years but is also gaining increasing popularity.

On the one hand, this can be attributed to the ease with which the 1,2,4-oxadiazole moiety can be constructed from acyclic precursors, which is facilitated by a variety of approaches. The diverse raw material base and ease of synthesis of these precursors represent a significant advantage for potential pharmaceutical compounds.

Moreover, 1,2,4-oxadiazole can be equally regarded as a more hydrophilic bioisostere of benzene, furan and other monocyclic aromatic descriptors [191]. This bioisosteric replacement results in a clear shift in the hydrophobic-hydrophilic balance of the resulting compounds. This allows us to achieve stronger Coulomb interactions with specific sites of

the biological target, while maintaining the geometry of the original molecule relatively intact.

Moreover, the importance of 1,2,4-oxadiazole cannot be overstated as a hydrolytically stable bioisostere of an ester moiety or N,N-disubstituted carboxamide. Based on theoretical studies [192–196], it has been shown that increasing the number of planar nuclei in a small molecule decreases the likelihood of the resulting compound being successful as an active pharmaceutical ingredient (although there exists an opposing viewpoint [197]). On the contrary, the benefit in terms of hydrolytic stability of the synthesized compounds, as well as their enhanced resistance to intramolecular solvolytic reactions, offsets the disadvantage associated with incorporating the 1,2,4-oxadiazole moiety into the target molecule's structure. Moreover, the rigidity of the 1,2,4-oxadiazole group surpasses that of the ester and N,N-disubstituted carboxamide fragments, enabling it to minimize entropy losses during ligand-receptor interaction. This factor potentially enhances the selectivity of compounds resulting from bioisosteric replacement, exemplified by the development of selective cholinergic agents based on non-selective lead compounds through the substitution of an ester linker with a 1,2,4-oxadiazole unit, as demonstrated in patents such as [198,199]. These are the key observations derived from this literature review, supported by the presented data.

Furthermore, researchers are increasingly able to predict and validate the impact of molecular modifications by leveraging modern QSAR/QSPR tools, accelerating the discovery of next-generation oxadiazole-based agents across multiple therapeutic areas. The oxadiazole ring's consistent identification as a key contributor to activity, coupled with its synthetic accessibility and tunable properties, makes it an ideal candidate for further exploration in rational drug design. As machine learning and multi-target QSAR models evolve, the future holds great promise for expanding the therapeutic potential of this remarkable heterocycle.

Indeed, the application of 3D-QSAR methodologies has greatly advanced our understanding of the structure-activity relationships of 1,2,4-oxadiazole derivatives. These studies have identified key structural features that influence biological activity and facilitated the rational design of more effective therapeutic agents.

In addition to QSAR and 3D-QSAR, molecular docking applications enable the prediction of binding affinities. Recently, molecular docking has been integrated with ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling to optimize the pharmacokinetic properties of 1,2,4-oxadiazole derivatives. One study emphasized the importance of combining docking analysis with ADMET predictions to identify compounds with improved drug-likeness and reduced toxicity risks [47].

All in silico techniques have been applied to a variety of virtual screening applications. These studies demonstrate how virtual screening methodologies, including ligand-based pharmacophore modeling, structure-based docking, and 3D-QSAR, have significantly accelerated the discovery and refinement of 1,2,4-oxadiazole-based therapeutics. The modular nature of the scaffold allows for the fine-tuning of pharmacokinetic and pharmacodynamic properties, making it a versatile platform for drug design. To the best of the author's knowledge, the use of AI-assisted prediction tools integrated with ADMET profiling has yet to be reported; therefore, it is expected that they will soon be applied in the early steps of the screening pipeline to enhance translational success.

In conclusion, the analysis of the above literature and the available ADME and pharmacokinetic data for the 1,2,4-oxadiazole scaffold indicates that it remains a robust and versatile building block in drug discovery. It offers enhanced metabolic resilience, target specificity, and drug-like characteristics across various therapeutic areas.

CRediT authorship contribution statement

Anastasia Cherkasova: Writing – review & editing, Writing – original draft, Data curation. **Roberta Astolfi:** Writing – review & editing. **Maxim Nawrozkij:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Data curation, Conceptualization. **Boris Gladkikh:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Eleonora Proia:** Writing – review & editing. **Lidia Giuliani:** Writing – review & editing. **Dante Rotili:** Writing – review & editing, Writing – original draft. **Rino Ragno:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Data curation, Conceptualization. **Roman Ivanov:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of all abbreviations and acronyms

3D QSAR	Three-dimensional Quantitative Structure-Activity Relationships
5-FU	5-Fluorouracil
A2780	Ovarian cancer cell line
A549	Lung cancer cell line
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity
ADP	Adenosine diphosphate
ADP-Glo™	Bioluminescent and homogeneous ADP monitoring assay for kinases
AIDS	Acquired immunodeficiency syndrome
ALK2	Activin receptor-like kinase-2
ARE	Antioxidant responsive element
ASM	Acid sphingomyelinase
AST	Astemizole
ATP	Adenosine triphosphate
AURKs	Aurora kinases
BBB	Blood-brain barrier
BCL-2	Protooncogene
BIC_{50s}	50 % Biofilm inhibitory concentrations

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$BRAF^{V600E}$	Mutation of the BRAF gene
BTK	Bruton's tyrosine kinase
BuChE	Butyrylcholinesterase
c-KIT	Receptor tyrosine kinase protein
Caco-2	Human colorectal adenocarcinoma cell line
cAMP	Cyclic adenosine monophosphate
Capan-1	Human pancreatic adenocarcinoma cell line
CC_{50}	50 % cytotoxic concentration
CDK1	Cyclin-dependent kinase 1
CDK2	Cyclin-dependent kinase 2
CHK1	Checkpoint kinase 1
CHO	Chinese hamster ovary cell line
CK2α	Casein Kinase II
CL	Cardiolipin
Colo-205	Colon cancer cell line
CVB5	Coxsackie virus B5
CXCR3	C-X-C chemokine receptor type 3
CYP	Cytochrome P450 enzyme
DFT	Density Functional Theory
DNA	Deoxyribonucleic acid
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DU-145	Prostate cancer cell line
EC_{50}	Half maximal effective concentration
EGFR	Epidermal growth factor receptor
EKVX	Human lung adenocarcinoma cell line
EL-4	Mouse T-cell lymphoma cell line
EV	Enterovirus
FtsZ	Filamentous temperature-sensitive mutant Z
FXR	Farnesoid X receptor
GDP	Guanosine diphosphate
GLP1R	Glucagon-like peptide-1 receptor
GPR119	G-protein coupled receptor 119
GSK-3β	Glycogen synthase kinase-3 beta
GTPase	Family of hydrolase enzymes that bind to the nucleotide guanosine triphosphate
H1N1	Influenza A virus subtype
H37Rv	*Mycobacterium tuberculosis* strain
HA	Hemagglutinin
hCA	Human carbonic anhydrase
HCC	Hepatocellular carcinoma
HCCLM3	Human hepatocellular carcinoma cell line
HCT116	Human colorectal cancer cell line
HD	Huntington's disease
HDAC	Histone deacetylase
HDTs	Host-directed therapies
HeLa	Human cervical cancer cell line
HepG2	Human hepatocellular carcinoma cell line
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HL-60	Leukemia cell line
hMSC	Human mesenchymal stem cell line
HPAF-II	Human pancreatic adenocarcinoma cell line
hRBC	Human red blood cell
Hs766T	Human pancreatic ductal adenocarcinoma cell line
HsClpP	Homo sapiens caseinolytic protease P
HSET (KIFC1)	Kinesin family member C1
HT-29	Human colorectal cancer cell line
HTT	Huntingtin gene
IC50	Half maximal inhibitory concentration
ICAM-1	Intercellular adhesion molecule 1
IL-12	Interleukin 12
IL-6	Interleukin 6
InhA	Mycobacterium enoyl-acyl carrier protein reductase
K562	Human myelogenous leukemia cell line
Ki	Inhibitory constant
KMS-12 PE	Human myeloma cell line
$KRAS^{G12C}$	Glycine-to-cysteine amino acid substitution in the Kirsten rat sarcoma virus gene
L-02	Human liver cell line
LC_{50}	Median lethal dose
LN229	Human brain glioblastoma cell line
LT-A549	A549 lung cells cultivated in Ham's F12 medium for a long term
MAO-B	Monoamineoxidase B
MAPK	Mitogen-activated proteinkinase
MCF-10A	Mammary epithelial cell line
MCF-7	Breast cancer cell line
MCP-1	Monocyte chemoattractant protein 1
MDA MB-231	Monroe Dunaway Anderson Metastatic Breast – 231 cell line
MDR	Multiple drug resistance

(*continued on next page*)

(*continued*)

MIA PaCa-2	Human pancreatic cancer cell line
MIC	Minimum inhibitory concentration
MOLT-4	Human acute T lymphoblastic leukemia cell line
mPGES-1	Microsomal prostaglandin E synthase-1
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRSA	Methicillin-resistant *Staphylococcus aureus*
mTOR	Mechanistic target of rapamycin
MTT	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NAD^+	Oxidised nicotinamide adenine dinucleotide
NASH	Non-alcoholic steatohepatitis
NB4	Acute promyelocytic leukemia cell line
NCI-60 cell panel	Group of 60 human cancer cell lines used by the National Cancer Institute
NCI–H358	Epithelial-like cell line
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMDF	Neonatal murine dermal fibroblasts
NPC1L1	Niemann-Pick C1-like1enzyme
Nrf2	Nuclear factor erythroid 2
NSCLC	Non-small-cell lung cancer
oxLDL	Oxidised low-density lipoprotein
OXPHOS	Oxidative phosphorylation
PAMPA	Parallel artificial membrane permeability assay
Panc-1	Human pancreatic cancer cell line
PATU-T	Human pancreatic cancer cell line
PBMC	Peripheral blood mononuclear cell
PC3	Human prostate cancer cell line
PCR	Polymerase chain reaction
PD	Parkinson's disease
PDAC	Pancreatic ductal adenocarcinoma cell lines
PIM1	Proto-oncogene serine/threonine-protein kinase
pKa	Logarithm of the acid dissociation constant
Pks13	Polyketidesynthase 13
PLpro	Papain-like protease
PMA	Phorbol myristate acetate
PPARδ/β	Peroxisome proliferator-activated receptor δ/β
Ppm	Parts per million
PROTACs	Proteolysis-targeting chimeras
QSAR	Quantitative Structure Activity Relationships
RAS	Rat sarcoma virus, a class of protein called small GTPase
RAW 264.7	Mouse macrophage cell line
RBD	Protein binding domain
RNA	Ribonucleic acid
ROS	Reactive oxygen species
S1PR1	Sphingosine-1-phosphate receptor 1
SAR	Structural-activity relationship
SARS-CoV-2	Severe acute respiratory syndrome-related coronavirus 2
SDH	Succinate dehydrogenase
sEH	Soluble epoxide hydrolase
SI	Selectivity index
SIRT2	Sirtuin 2
SKOV3	Ovarian cancer cell line
SrtA	Sortase A
STAT3	Signal transducer and activator of transcription 3
SUIT-2	Pancreatic ductal adenocarcinoma cell line
T98G	Glioblastoma cell line
TB	Tuberculosis
TDP1	Tyrosyl – DNA phosphodiesterase 1
TDP2	Tyrosyl – DNA phosphodiesterase 2
TFMO	5-(Trifluoromethyl)-1,2,4-oxadiazol-3-yl
TLR8	Toll-like receptor 8
TNF-α	Tumor necrosis factor-alpha
TrkA	Tropomyosin receptor kinase A
TRPA1	Transient receptor potential ankyrin 1
U87	Human astrocytoma cell line
U937	Pro-monocytic, human myeloid leukemia cell line
VCAM-1	Vascular cell adhesion protein 1
VEC	Vascular endothelial cell
Vero E6	Kidney epithelial cell line derived from an African green monkey
VGFR-2	Vascular endothelial growth factor receptor-2
VP1	Major capsid protein
VRE	Vancomycin-resistant *Enterococcus faecium*
Wi-38	Human embryonic lung fibroblast cell line

Data availability

No data was used for the research described in the article.

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