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Unveiling the therapeutic potential of 1,2,4-oxadiazole derivatives: An updated review

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ABSTRACT

1,2,4-Oxadiazole derivatives, a prominent class of nitrogen-containing heterocycles, have gained considerable attention recently due to their broad spectrum of biological activities. This review focuses on the most recent developments (2018–2024) in the exploration of their therapeutic potential. Studies have highlighted the efficacy of 1,2,4-oxadiazole derivatives in multiple domains, including anticancer, antimicrobial, antidiabetic, anti-inflammatory, and neuroprotective applications. These compounds have demonstrated promising results, particularly in combating drug-resistant pathogens, managing metabolic disorders, and offering potential treatments for neurodegenerative diseases. With a growing body of research supporting their diverse biological roles, 1,2,4-oxadiazole derivatives continue to be a significant focus in drug discovery and development. This review compiles key findings from recent studies, offering insights into their therapeutic applications and potential future directions for research.

1. Introduction

Heterocyclic compounds represent a cornerstone of medicinal chemistry [1], offering diverse chemical frameworks that contribute to the development of bioactive molecules [2–4]. Among these, oxadiazoles have garnered significant interest [5,6] due to their versatile structural and electronic properties. Oxadiazoles exist in four isomeric forms—1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, and 1,2,5-oxadiazole (Fig. 1)—each differing in the positioning of nitrogen and oxygen atoms within the five-membered ring [7]. Among these isomers, 1,2,4-oxadiazole has emerged as a privileged scaffold in drug discovery due to its ability to modulate physicochemical and pharmacokinetic properties. This heterocycle functions as a bioisostere for amide, ester, and carbamate groups, enhancing metabolic stability and target binding affinity [8]. Consequently, 1,2,4-oxadiazole derivatives have been extensively explored for their potential pharmacological applications, including antimicrobial [9–11], anticancer [12,13], anti-inflammatory [14], and neuroprotective [15] activities. The wide-ranging biological significance of this heterocycle underscores its importance in the continuous pursuit of novel therapeutic agents.

While synthetic derivatives of 1,2,4-oxadiazole have been extensively investigated, naturally occurring compounds containing this scaffold are relatively rare. Nevertheless, a few notable examples highlight the biological relevance of this heterocycle in nature. One of the most well-known naturally occurring 1,2,4-oxadiazoles is **Quisqualic Acid**, which is isolated from the seeds of *Quisqualis indica* and *Quisqualis fructus*. This compound is a potent agonist for AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and group I metabotropic glutamate receptors, making it significant in neuropharmacology [16,17]. Similarly, **Phidianidines A and B,** 3-substituted

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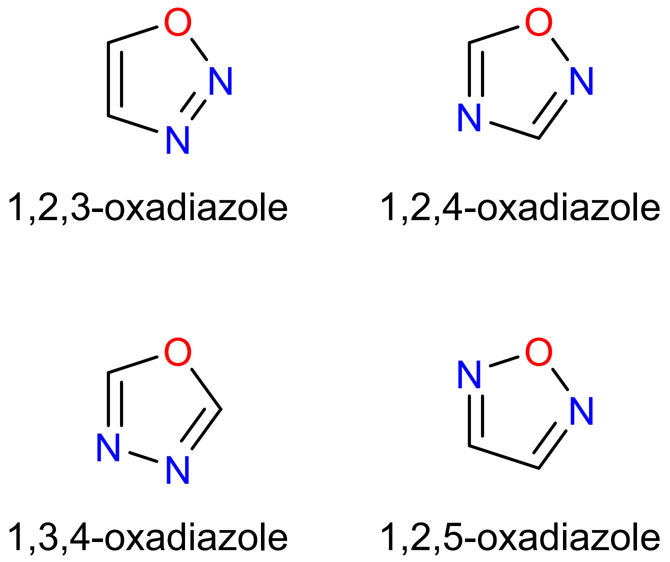


Fig. 1. The four isomeric forms of oxadiazole.

indole alkaloids derived from the marine aeolid opisthobranch *Phidiana militaris*, have demonstrated selective inhibition of the dopamine transporter (DAT) and partial agonism of the μ-opioid receptor [18,19]. These findings not only highlight the therapeutic potential of naturally occurring 1,2,4-oxadiazoles but also serve as a source of inspiration for the design and synthesis of novel analogs with enhanced pharmacological profiles.

Building on this foundation, several synthetic 1,2,4-oxadiazole-containing compounds have successfully transitioned into clinical applications, further validating the pharmacological relevance of this scaffold. For instance, **Azilsartan**, an angiotensin II receptor blocker, is widely used in the management of hypertension due to its potent antihypertensive effects and favorable pharmacokinetic profile [20]. Another clinically approved example is **Ataluren**, a small-molecule drug that facilitates translational readthrough of premature stop codons, offering a novel treatment approach for genetic disorders such as Duchenne muscular dystrophy [21,22]. Additionally, **Ozanimod**, a sphingosine-1-phosphate receptor modulator, has been approved for the treatment of multiple sclerosis [23] and ulcerative colitis [24], demonstrating the immunomodulatory potential of the oxadiazole core. These approved drugs exemplify the clinical success of 1,2,4-oxadiazole derivatives, providing a strong foundation for further drug development efforts. A summary of these approved drugs is presented in Table 1.

Despite these successes, the development of 1,2,4-oxadiazole-based drugs is not without challenges. Synthetic accessibility, structural optimization, and metabolic stability remain key considerations in lead optimization. Furthermore, potential off-target effects and toxicity profiles necessitate comprehensive preclinical and clinical evaluations to ensure both efficacy and safety. Addressing these challenges requires an integrated approach that combines rational drug design, structure-activity relationship studies, and advanced screening methodologies. By refining these strategies, researchers can maximize therapeutic efficacy while minimizing adverse effects, further advancing the potential of 1,2,4-oxadiazole derivatives in drug discovery.

Given their established clinical applications and emerging therapeutic potential, this review aims to provide a comprehensive overview of the recent biological activities of 1,2,4-oxadiazole derivatives. By examining their diverse pharmacological applications—including anticancer, antimicrobial, anti-inflammatory, and enzyme-inhibitory properties—this work seeks to highlight their broad therapeutic relevance and guide future research in medicinal chemistry. These activities are illustrated in Fig. 2. The continued exploration of 1,2,4-oxadiazole derivatives, supported by advances in medicinal chemistry and drug design, holds great promise for the discovery of novel therapeutic agents with improved efficacy and safety.

Scope of This Review versus Previous Reviews.

Several reviews have previously summarized the chemistry and biology of 1,2,4-oxadiazoles, each with a different emphasis. Kayukova (2005) [25] provided an early review focusing almost exclusively on synthetic routes to 1,2,4-oxadiazole rings (amidoxime acylation, cycloaddition strategies, etc.), with little discussion of biological activity. Biernacki et al. (2020) [6] offered a comprehensive overview of both synthesis and medicinal applications up to 2020, but this work preceded the surge of recent reports and did not highlight very new therapeutic directions. More recently, Hendawy (2022) [26] compiled the diverse biological activities of 1,2,4-oxadiazole derivatives (anticancer, antimicrobial, anti-inflammatory, neuroprotective, antidiabetic, etc.), including some structure–activity relationship (SAR) discussions. However, Hendawy's review covered literature mainly up to 2021 and did not encompass the latest compounds and emerging targets reported in the last few years. Another specialized review by Dhameliya et al. (2022) [27] centered on anti-infective 1,2,4-oxadiazoles, detailing synthetic strategies and SAR against bacterial and fungal pathogens. Table 2 compares the scope and focus of these prior works with the present review.

In contrast to those publications, the present review specifically focuses on the most recent developments (2018–2024) and emerging trends in the therapeutic potential of 1,2,4-oxadiazole derivatives. We address key gaps by covering very recent compounds and highlighting new insights that were not emphasized in earlier reviews – for example, the discovery of oxadiazole derivatives that overcome drug resistance mechanisms (in cancer and infectious diseases) and the exploration of this scaffold in metabolic and neurodegenerative disorders. Moreover, while previous reviews often treated synthesis and bioactivity separately or emphasized one over the other, our review integrates both aspects where relevant, linking synthetic modifications to biological outcomes. This work therefore updates the knowledge base and provides a broader perspective on how 1,2,4-oxadiazoles are being leveraged across multiple therapeutic areas in the last six years.

2. Biological activities of 1,2,4-oxadiazole derivatives

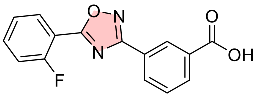
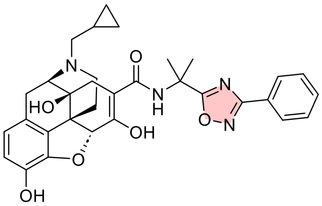
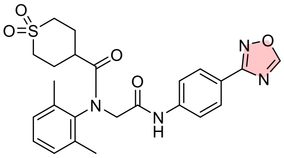
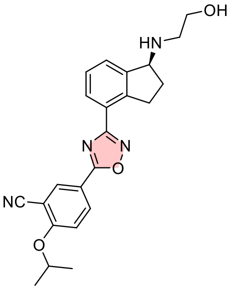
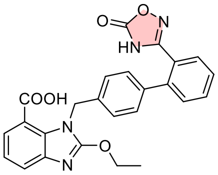
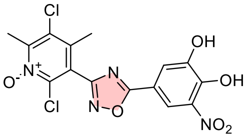
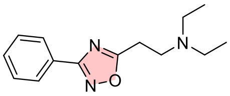
2.1. Anticancer activity

Cancer remains one of the leading causes of death worldwide, with its high incidence and complex nature posing significant challenges to current therapeutic strategies [28]. The development of resistance to conventional treatments such as chemotherapy and targeted therapy further complicates effective management, highlighting the urgent need for novel and more efficacious therapeutic agents [29–31]. Recent research has shifted focus toward identifying new classes of compounds that can overcome these limitations. Among these, 1,2,4-oxadiazole derivatives have garnered attention for their promising anticancer properties. These compounds have shown the potential to modulate various molecular targets involved in tumor growth, survival, and drug resistance, offering a multifaceted approach to cancer treatment. This section will discuss the distinct mechanisms of action of 1,2,4-oxadiazole derivatives, including kinase inhibition, carbonic anhydrase inhibition, HDAC inhibition, and other mechanisms (Fig. 3), shedding light on their diverse pharmacological profiles and potential for clinical application.

2.1.1. Kinase inhibitors

Kinase inhibitors have emerged as a key strategy in cancer therapy, given their ability to disrupt critical signaling pathways involved in tumor cell proliferation, survival, and metastasis [32,33]. Notable examples include inhibitors targeting the epidermal growth factor receptor (EGFR) and c-MET, both of which are frequently overexpressed or mutated in various cancers, making them attractive targets for selective

Table 1
Clinically approved 1,2,4-oxadiazole-containing drugs and their therapeutic applications.

Drug name	Chemical structure	Indication	Mechanism of action
Ataluren		Duchenne muscular dystrophy, Cystic fibrosis	Promotes translational readthrough of premature stop codons
Naldemedine		Opioid-induced constipation	Peripheral opioid receptor antagonist, reducing opioid-induced constipation
Amenamevir		Herpes zoster (Shingles)	Helicase-primase inhibitor, blocking viral DNA replication
Ozanimod		Multiple sclerosis, Ulcerative colitis	Sphingosine-1-phosphate (S1P) receptor modulator, regulating immune response
Azilsartan		Hypertension	Angiotensin II receptor blocker (ARB), lowering blood pressure
Opicapone		Parkinson's disease	Catechol-*O*-methyltransferase (COMT) inhibitor, prolonging dopamine activity
Oxolamine		Dry cough	Antitussive agent, acting as a local anesthetic and cough suppressant

inhibition. EGFR is particularly critical in promoting cell growth and differentiation [34], while c-MET plays a crucial role in tumor invasion and metastasis [35]. However, despite their potential, resistance to EGFR-targeted therapies remains a major challenge. In this context, recent research by Dokla et al. has highlighted a series of 1,2,4-oxadiazole derivatives capable of inducing the degradation of EGFR and c-Met, even in cases of resistance to traditional tyrosine kinase inhibitors (TKIs) [36]. Within this series, compound **1** proved to be the most potent (Fig. 4), exhibiting comparable antiproliferative activity across five NSCLC cell lines with different EGFR mutations ($IC_{50} = 0.2–0.6\ \mu M$). Unlike conventional EGFR tyrosine kinase inhibitors, **1** exerted its antitumor effect through the post-translational downregulation of EGFR and c-Met, confirmed by Western blot and RT-PCR analyses. Flow cytometry revealed that **1** induced G_2/M cell cycle arrest, with a modest contribution from apoptosis. In vivo, oral administration of **1** significantly suppressed the growth of gefitinib-resistant H1975 xenograft tumors in nude mice, achieving a dose-dependent tumor inhibition of up to 60 %. Additionally, at a suboptimal dose, **1** sensitized H1975 tumors to gefitinib, further enhancing tumor regression. Altogether, this study positions **1** as a promising candidate for overcoming EGFR TKI resistance through dual EGFR/c-Met degradation rather than direct kinase inhibition.

Building upon this, Mohamed et al. designed and synthesized a novel series of 1,2,4-oxadiazole-quinazoline-4-one hybrids as multitargeted inhibitors with potent antiproliferative activity [37]. The most active compounds, **2**, **3**, and **4** (Fig. 4), exhibited IC_{50} values of 24 nM, 26 nM, and 30 nM, respectively, against four cancer cell lines. These compounds also strongly inhibited EGFR, $BRAF^{V600E}$, and the mutant $EGFR^{T790M}$,

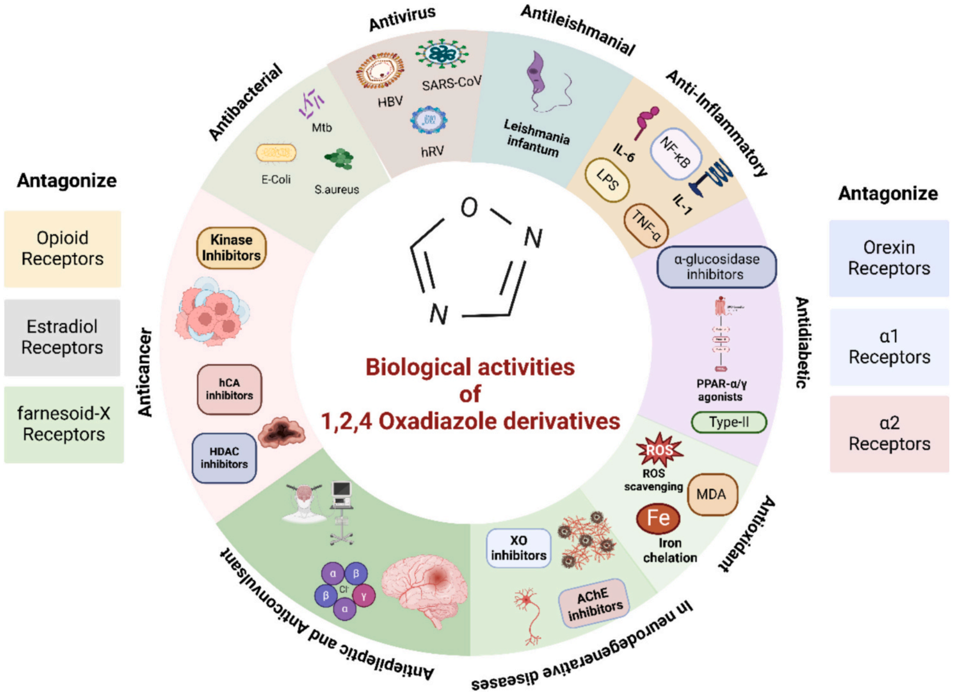


Fig. 2. Visual summary of the biological activities of 1,2,4-oxadiazole derivatives.

with **2** being the most potent (EGFR $IC_{50} = 57$ nM, $BRAF^{V600E}$ $IC_{50} = 48$ nM, and $EGFR^{T790M}$ $IC_{50} = 10$ nM), surpassing erlotinib and vemurafenib. Flow cytometry revealed that **2** induced G_2/M cell cycle arrest and apoptosis in A-549 cells. Molecular docking confirmed their strong binding to EGFR, $EGFR^{T790M}$, and $BRAF^{V600E}$, correlating with their inhibitory activity. Collectively, these results underscore the potential of **2**, **3**, and **4** as multitargeted anticancer agents capable of overcoming resistance associated with EGFR and $BRAF^{V600E}$ mutations.

In a similar vein, Kannekanti et al. synthesized a series of imidazole-morpholine-1,2,4-oxadiazole hybrids and evaluated their in vitro antiproliferative activity against MCF-7, MDA-MB-231, and MDA-MB-468 breast cancer cell lines [38]. Compound **5** (Fig. 4) was found to be the most potent ($IC_{50} = 3.7$–8.9 μM), surpassing the standard drug 5-FU ($IC_{50} = 7.5$–12.7 μM). Compounds **6**, **7**, and **8** (Fig. 4) also showed superior activity against MCF-7 ($IC_{50} = 7.1$–10.2 μM). Further, **5** demonstrated potent EGFR tyrosine kinase inhibition ($IC_{50} = 0.47$ μM), comparable to erlotinib ($IC_{50} = 0.43$ μM), while **7** and **8** also displayed promising inhibition ($IC_{50} = 0.81$ and 0.72 μM, respectively). Molecular docking studies confirmed strong interactions of **5**, **6**, **7**, and **8** with EGFR (PDB ID: 4HJO), with **7** exhibiting the highest binding affinity (binding energy = −9.67 kcal/mol, inhibition constant = 81.06 nM). These findings suggest that **5**, **7**, and **8** are promising EGFR-targeting anti-breast cancer agents with potential for further development.

Unadkat et al. also designed a series of 1,2,4-oxadiazole derivatives as potential EGFR inhibitors using a rational design approach involving molecular dynamics simulations and docking studies [39]. Among the synthesized compounds, **9** and **10** (Fig. 4) exhibited the highest antiproliferative activity against EGFR-overexpressing A549, HCT-116, HepG2, and MCF-7 cell lines, with IC_{50} values ranging from 2.9 to 12.79 μM for **9** and 8.99 to 41.87 μM for **10**. These compounds showed no cytotoxicity against EGFR-negative SW620 cells, confirming their selective EGFR inhibition. Molecular docking revealed that **9** and **10** formed strong hydrogen bonds with Met793 and Thr790 in the ATP-binding site of EGFR, with docking scores of −15.09 and − formed strong hydrogen bonds with Met793 and Thr790 in the ATP-binding site of EGFR, with docking scores of −15.09 and Molecular docking reeCollectively, these data position **9** and **10** as promising EGFR inhibitors, encouraging further optimization to improve their potency and selectivity.

Moreover, Dubba et al. synthesized a series of indole-based 1,3,4-oxadiazole-linked sulfonyl 1,2,4-oxadiazole derivatives and evaluated their anticancer activity against MCF-7 and A-549 cells [40]. Among the newly synthesized compounds, **11** and **12** (Fig. 4) displayed the highest cytotoxicity, with IC_{50} values of 3.88 μM and 4.06 μM against MCF-7 and 8.98 μM and 7.98 μM against A-549, respectively, surpassing erlotinib ($IC_{50} = 4.12$ μM for MCF-7 and 10.39 μM for A-549). EGFR tyrosine kinase inhibition assays confirmed **11** as the most potent inhibitor ($IC_{50} = 0.214$ μM), exhibiting nearly two-fold greater activity than erlotinib ($IC_{50} = 0.423$ μM), while **12** ($IC_{50} = 0.311$ μM) also outperformed the standard drug. Molecular docking revealed strong interactions of these compounds with EGFR, supporting their inhibitory activity.

Continuing this trend, Khedkar et al. explored the development of novel EGFR inhibitors for anticancer therapy, synthesizing a series of 3-(4-(4-(1,3,4-oxadiazol-2-yl)-1H-imidazol-2-yl)phenyl)-1,2,4-oxadiazoles [41]. The in vitro anticancer evaluation against PC3, DU-145, A549, and HEPG2 cell lines identified **13, 14, 15, 16,** and **17** (Fig. 4) as highly potent, surpassing Etoposide in efficacy. Compound **13** emerged as the most potent, displaying remarkable cytotoxicity with excellent selectivity and no toxicity toward normal Vero cells. EGFR enzyme assays demonstrated strong inhibition of the wild-type EGFR, with significantly lower potency against its mutant form, reinforcing their potential as EGFRWT inhibitors. Further investigations on HEPG2 cells revealed cell cycle arrest at G1/G0 and G2 phases, while western blot analysis confirmed that **13** effectively inhibited EGFR autophosphorylation. These results establish this series as a compelling foundation for the development of next-generation EGFR-targeting anticancer agents.

Inhibitors of vascular endothelial growth factor receptor 2 (VEGFR-2) have also gained significant attention for their role in inhibiting tumor angiogenesis, a critical process in tumor growth and metastasis [42]. In this regard, Boda et al. synthesized a series of isatin-1,2,4-oxadiazole hybrids as VEGFR-2-targeting anticancer agents [43]. The most potent compounds, **18**, **19**, and **20** (Fig. 4), exhibited superior cytotoxicity against A549, PC3, DU145, and MCF-7 cancer cell lines, with **18** showing the highest potency ($IC_{50} = 6.46$ μM for A549, 25.86 μM for PC3, 20.41 μM for DU145, and 10.85 μM for MCF-7),

Table 2
Comparison of previous key reviews on 1,2,4-oxadiazole derivatives with the present review.

Review (Year)	Scope & Focus	Gaps Addressed by Present Review
Kayukova (2005)	Synthetic routes to 1,2,4-oxadiazoles; methods of ring construction (amidoxime acylation, cycloadditions). Little to no discussion of biological activities. Covered literature up to ~2003–2005.	Outdated coverage; no biology. Our review updates synthetic approaches (2018–2024) *and* emphasizes biological evaluations, linking newer syntheses to pharmacological findings.
Biernacki et al. (2020)	Comprehensive review of 1,2,4-oxadiazole chemistry and pharmacology. Discussed various synthetic strategies and a broad range of bioactivities (anticancer, antimicrobial, etc.) up to early 2020.	Does not include the last ~4–5 years of research. Our review extends the timeline, covering 2020–2024 developments, and highlights recent novel targets and resistance-fighting strategies not covered by Biernacki et al.
Hendawy (2022)	Focused on biological activities of 1,2,4-oxadiazoles as therapeutic agents. Summarized antimicrobial, anticancer, anti-inflammatory, neuroprotective, and antidiabetic effects (with some SAR and mechanism insights). Literature mainly through 2021.	Lacks the very latest compounds and trends post-2021. Our review incorporates 2022–2024 studies, including newly reported activities (e.g. dual-action compounds, novel mechanisms like Hippo/YAP pathway modulation, etc.) and up-to-date SAR analyses.
Dhameliya et al. (2022)	Specialized review on anti-infective 1,2,4-oxadiazoles. Emphasized synthetic routes for antimicrobial analogues and their SAR against bacteria, fungi, etc.	Narrow scope (only anti-infectives). Our review covers anti-infectives *and* other therapeutic areas (cancer, metabolic, neurological) to provide a more comprehensive picture. It also discusses how 1,2,4-oxadiazoles perform in multi-target or multitier disease contexts (e.g. anti-biofilm activity, immune modulation) beyond what Dhameliya et al. examined.
Present Review (2024)	Updates 2018–2024 advances in 1,2,4-oxadiazole therapeutics. Broad scope: anticancer (kinase inhibitors, HDAC/CA inhibitors, etc.), antimicrobial (incl. Anti-TB and anti-biofilm agents), antidiabetic (enzyme inhibitors and PPAR agonists), anti-inflammatory, neuroprotective, and more. Integrates synthetic insights with biological outcomes, and highlights *emerging trends* (e.g. compounds overcoming drug resistance, dual-function drug designs, new molecular targets).	Addresses gaps of earlier reviews by providing: (1) the most recent data and examples post-2021; (2) emphasis on *specific new trends* (such as oxadiazoles targeting resistant cancers and pathogens, and those achieving nanomolar potencies or in vivo efficacy); (3) a multi-disciplinary outlook that links chemistry innovations to therapeutic implications across various disease areas.

outperforming 5-fluorouracil. In VEGFR-2 tyrosine kinase inhibition assays, **18** demonstrated nearly twice the potency of sorafenib (IC_{50} = 17.58 nM vs. 35.64 nM), while **19** (IC_{50} = 30.82 nM) and **20** (IC_{50} = 42.75 nM) also displayed significant inhibition. Molecular docking confirmed strong interactions of **18** with VEGFR-2 (binding energy = −10.85 kcal/mol), forming key hydrogen bonds with LYS868, CYS919, and ASP1046. The strong VEGFR-2 inhibition and superior cytotoxicity of **18**, **19**, and **20** underscore their potential as selective antiangiogenic agents with promising therapeutic applications in cancer treatment.

Expanding the scope of kinase inhibitors, cyclin-dependent kinase 1 (CDK1) has emerged as a key target in various cancers, including pancreatic ductal adenocarcinoma (PDAC), where its dysregulation contributes to uncontrolled cell proliferation [44]. In this context, Pecoraro et al. synthesized a new oxadiazole-based topsentin derivative and evaluated its cytotoxic effects on PDAC cells by targeting CDK1 [45]. Among the tested compounds, **21** (Fig. 4) displayed the highest antiproliferative activity, with IC_{50} values ranging from 5.7 to 10.7 μM against PATU-T, Hs766T, HPAF-II, and PDAC3 cell lines. Molecular docking confirmed that **21** effectively binds to the ATP-binding site of CDK1, with a docking score of −6.999 kcal/mol. Mechanistic studies revealed that **21** significantly reduced CDK1 expression by 45 % in Hs766T cells and induced apoptosis, increasing apoptotic cell populations by 1.5- and 2-fold in PATU-T and PDAC3 cells, respectively. Additionally, ADME predictions indicated favorable pharmacokinetic properties, including high gastrointestinal absorption and compliance with Lipinski's rule of five. With its potent CDK1 inhibition, pro-apoptotic effects, and favorable pharmacokinetics, **21** represents a strong candidate for further development as a targeted therapy for PDAC.

Given the critical role of p38 MAPK in cancer progression, particularly in modulating inflammatory responses and cellular stress, the development of targeted inhibitors has become an area of active research [46]. To address this, Romeo et al. synthesized a series of 2,3,4-triaryl-1,2,4-oxadiazol-5-ones as p38 MAPK inhibitors and evaluated their biological activity [47]. It was found that compounds **22** and **23** (Fig. 4) exhibited the most potent inhibition of p38α MAPK, with IC_{50} values of 80 nM and 150 nM, respectively, comparable to the reference inhibitor SB203580 (IC_{50} = 300 nM). Molecular docking confirmed that **22** binds favorably to the ATP-binding pocket of p38α MAPK, forming key hydrogen bonds with Met109 and Lys53, while the aryl groups at N-2 interact with the hydrophobic region II, contributing to enhanced affinity. Structural optimization of these azastilbenes suggests that their unique C—N bond replacement for the stilbene C=C double bond retains strong inhibitory activity. These findings highlight **22** and **23** as promising p38α MAPK inhibitors with potential applications in cancer therapy.

Another kinase of interest in cancer therapy is GSK3β, which plays a pivotal role in regulating cell survival, proliferation, and migration [48]. In this regard, Carbone et al. synthesized a series of 1,2,4-oxadiazole-based topsentin analogs and evaluated their antiproliferative activity against PDAC cells, targeting GSK3β kinase [49]. With the strongest potency observed in this series, **24** (Fig. 4) exhibited EC_{50} values of 0.40 μM, 0.80 μM, and 1.2 μM for SUIT-2, Panc-1, and Capan-1 cells, respectively. A kinase activity assay confirmed that **24** inhibited GSK3β with an IC_{50} of 0.62 μM, while **25** (Fig. 4) also showed significant inhibition (IC_{50} = 0.81 μM). Flow cytometry analysis demonstrated that **24** induced apoptosis in PDAC cells, associated with cleavage of caspase-3 and PARP, while wound healing assays showed a remarkable reduction in Capan-1 cell migration. Further mechanistic studies revealed that **24** significantly inhibited GSK3β phosphorylation at both Ser9 and Tyr216 residues, suggesting a direct effect on kinase activity. Molecular docking studies confirmed strong binding interactions between **24** and the ATP-binding site of GSK3β.

2.1.2. Carbonic anhydrase inhibitors

Carbonic anhydrase (CA) enzymes, particularly the isoforms hCA II and the tumor-associated hCA IX, have garnered significant interest in cancer therapy due to their role in maintaining tumor pH balance and facilitating the adaptation of cancer cells to hypoxic conditions [50]. These isoforms are overexpressed in many cancers and are associated with tumor progression, metastasis, and resistance to therapies, making them promising targets for anticancer agents. In line with this, Krasavin et al. synthesized a series of 1,2,4-oxadiazol-5-yl benzenesulfonamides as potent and selective inhibitors of cytosolic hCA II and membrane-bound hCA IX isoforms [51]. Compounds **26**, **27**, and **28** (Fig. 5) emerged as the most potent, with **26** showing subnanomolar inhibition of hCA II (K_i = 0.48 nM) and low nanomolar inhibition of hCA IX (K_i = 11.1 nM), outperforming acetazolamide (K_i = 12.1 nM for hCA II and 25.8 nM for hCA IX). Selectivity profiling revealed that these compounds

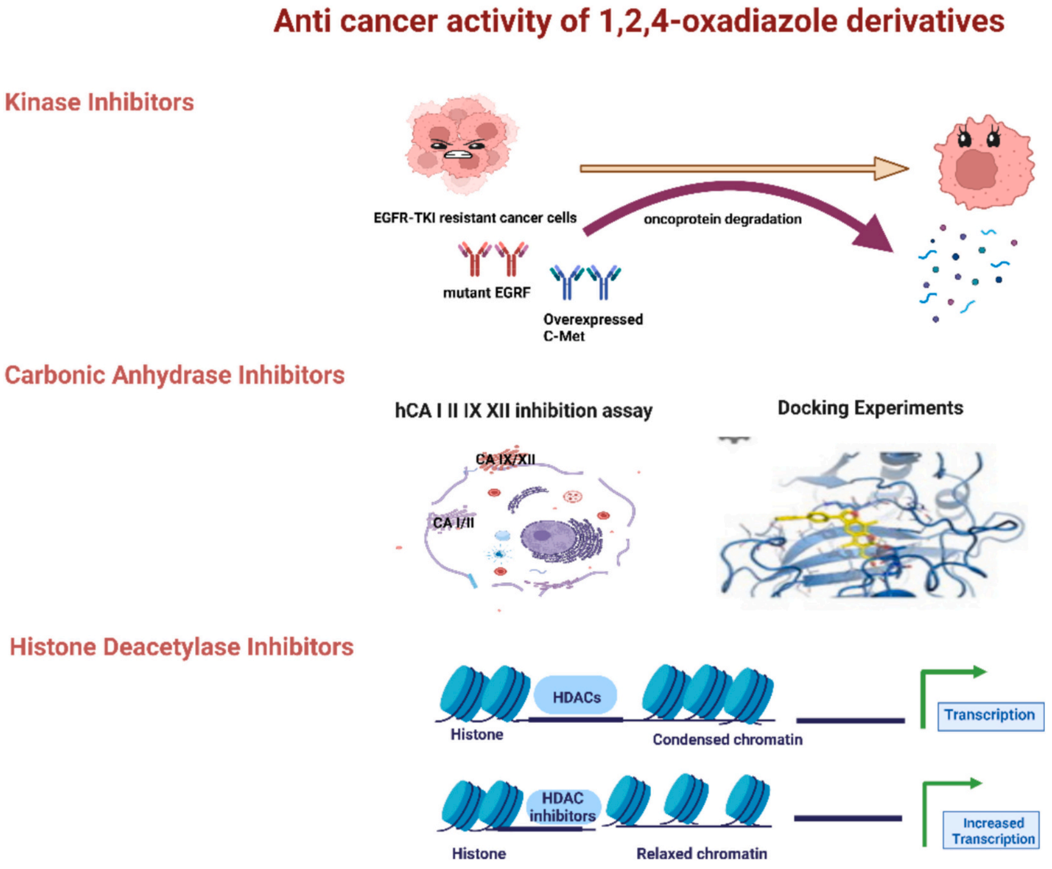
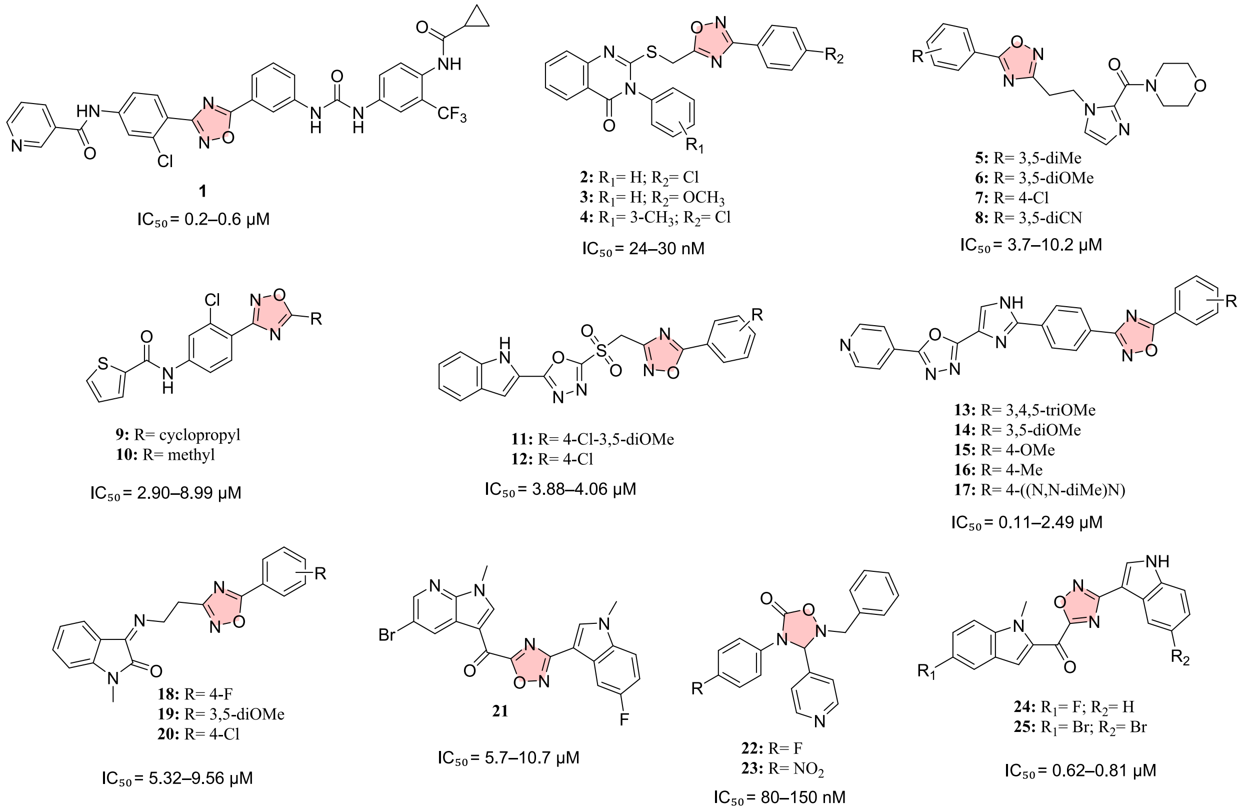


Fig. 3. Overview of the anticancer mechanisms of 1,2,4-oxadiazole derivatives.



1
IC_{50} = 0.2–0.6 μM

2: R_1= H; R_2= Cl
3: R_1= H; R_2= OCH_3
4: R_1= 3-CH_3; R_2= Cl
IC_{50} = 24–30 nM

5: R= 3,5-diMe
6: R= 3,5-diOMe
7: R= 4-Cl
8: R= 3,5-diCN
IC_{50} = 3.7–10.2 μM

9: R= cyclopropyl
10: R= methyl
IC_{50} = 2.90–8.99 μM

11: R= 4-Cl-3,5-diOMe
12: R= 4-Cl
IC_{50} = 3.88–4.06 μM

13: R= 3,4,5-triOMe
14: R= 3,5-diOMe
15: R= 4-OMe
16: R= 4-Me
17: R= 4-((N,N-diMe)N)
IC_{50} = 0.11–2.49 μM

18: R= 4-F
19: R= 3,5-diOMe
20: R= 4-Cl
IC_{50} = 5.32–9.56 μM

21
IC_{50} = 5.7–10.7 μM

22: R= F
23: R= NO_2
IC_{50} = 80–150 nM

24: R_1= F; R_2= H
25: R_1= Br; R_2= Br
IC_{50} = 0.62–0.81 μM

Fig. 4. Structures of compounds **1–25** as kinase inhibitors.

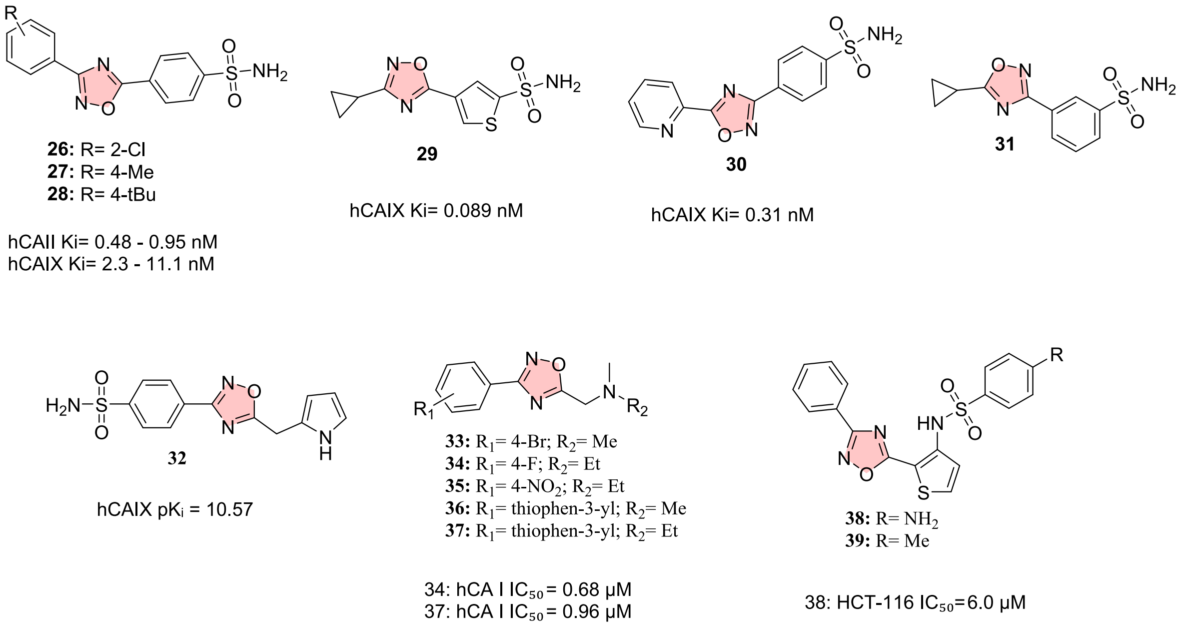


Fig. 5. Structures of compounds **26–39** as carbonic anhydrase inhibitors.

weakly inhibited hCA I and IV, demonstrating a strong preference for hCA II and IX. Molecular docking studies confirmed that **26** forms key hydrogen bonds with the catalytic zinc ion and active site residues of hCA II and IX, supporting its high potency. These findings highlight **26**, **27**, and **28** as promising isoform-selective hCA inhibitors with potential applications in cancer therapy.

Building on their work, Krasavin et al. conducted a subsequent study in which they synthesized a series of 1,2,4-oxadiazole-containing primary arene sulfonamides and evaluated their inhibition of human carbonic anhydrase (hCA) isoforms, particularly the tumor-associated hCA IX and XII [52]. Among the tested compounds, **29** (Fig. 5) exhibited the highest potency, with a Ki of 0.089 nM against hCA IX, significantly outperforming acetazolamide (Ki = 25.0 nM). Compound **30** (Fig. 5) also demonstrated strong inhibition (Ki = 0.31 nM for hCA IX), while both compounds maintained selectivity over off-target hCA I and II. Antiproliferative assays under hypoxic conditions revealed that **29** selectively inhibited the growth of SK-MEL-2 melanoma cells, whereas **31** (Fig. 5) showed cytotoxicity toward PANC-1 pancreatic cancer cells. Molecular docking confirmed that **29** forms strong interactions with the catalytic site of hCA IX, contributing to its high potency. Given their potent and selective inhibition of hCA IX and promising anticancer activity in hypoxic environments, **29** and **30** hold strong potential as targeted therapies for tumors reliant on hypoxia-driven survival mechanisms.

Further investigations by Gopinath et al. expanded on these findings, employing molecular docking, molecular dynamics simulations, and 3D QSAR studies to design oxadiazole benzene sulfonamides as selective inhibitors of hCA IX [53]. Among the designed compounds, **32** (Fig. 5) exhibited the highest predicted inhibitory activity (pK_i = 10.57) against hCA IX, outperforming reference inhibitors. Molecular docking revealed strong interactions between **32** and key active site residues, including hydrogen bonding with Gln92 and Thr200 and π-π stacking with His94, contributing to its high affinity (binding energy = −10.51 kcal/mol). Molecular dynamics simulations confirmed the stability of the **32**-hCA IX complex, showing minimal fluctuations and sustained hydrogen bonding throughout a 100 ns trajectory. MM-PBSA and MM-GBSA calculations further validated the docking results, indicating strong binding free energy. Taken together, these computational insights position **32** as a highly promising hCA IX inhibitor, warranting further experimental studies to translate its potential into viable therapeutic applications.

In a similar vein, Kucukoglu et al. synthesized a series of 3,5-disubstituted-1,2,4-oxadiazole derivatives and evaluated their inhibitory effects on human carbonic anhydrases (hCA) I and II, along with their cytotoxic activity against DU145 prostate and MDA-MB-231 breast cancer cells [54]. Compounds **34** and **37** (Fig. 5) exhibited the highest potency against hCA I (IC_{50} = 0.68 μM and 0.96 μM, respectively) and hCA II (IC_{50} = 0.65 μM and 0.40 μM, respectively), outperforming acetazolamide (IC_{50} = 6.523 μM for hCA I and 7.85 μM for hCA II). Molecular docking revealed that **34** and **37** formed π-π stacking interactions with His94 and Phe91 in hCA I and engaged in crucial hydrogen bonding with active site residues of hCA II. Cytotoxicity studies showed that **33** (Fig. 5) was the most effective compound against DU145 cells, reducing viability to 22.84 % at 50 μM, while **35–37** (Fig. 5) displayed significant cytotoxicity against MDA-MB-231 cells. ADME predictions confirmed favorable pharmacokinetic properties, supporting the potential of **34** and **37** as hCA inhibitors and **33** as a promising anticancer lead.

In a subsequent study, Shamsi et al. synthesized a series of 1,2,4-oxadiazole-sulfonamide derivatives as potential anticancer agents for colorectal cancer therapy, targeting carbonic anhydrase IX (CAIX) [55]. One particular derivative, compound **38** (Fig. 5), exhibited the highest potency, with an IC_{50} of 6.0 μM against HCT-116 colorectal cancer cells, showing a nearly two-fold improvement over **39** (Fig. 5) (IC_{50} = 11.1 μM). Additionally, **38** demonstrated significant inhibition of CAIX (IC_{50} = 0.74 μM), with a high selectivity ratio over hCA II (IC_{50} = 10.78 μM). Mechanistic studies revealed that **38** downregulated CAIX expression, induced apoptosis via caspase-3 activation and PARP cleavage, increased reactive oxygen species (ROS) levels, and suppressed colony formation and migration of HCT-116 cells. Molecular docking confirmed strong binding interactions of **38** with the CAIX active site, including key hydrogen bonds with His64, Gln92, and Thr200. All these findings suggest **38** as a promising lead for colorectal cancer treatment, with potential for further optimization.

2.1.3. *Histone deacetylase (HDAC) inhibitors*

Histone deacetylases (HDACs) are critical regulators of gene expression and have been implicated in the progression of various cancers. Inhibiting HDAC activity can induce apoptosis, arrest cell cycle progression, and enhance the expression of tumor-suppressor genes, making HDAC inhibitors promising candidates in cancer therapy [56].

Several studies have explored the development of HDAC inhibitors containing a 1,2,4-oxadiazole core, revealing their potent anticancer activity and potential for clinical application. Yang et al. designed and synthesized a series of hydroxamate-based histone deacetylase (HDAC) inhibitors containing a 1,2,4-oxadiazole core and evaluated their antitumor activity [57]. Compound **40** (Fig. 6) exhibited the highest HDAC1 inhibitory potency ($IC_{50} = 8.2$ nM), nearly twice as potent as the reference inhibitor SAHA ($IC_{50} = 15.0$ nM), while **41** and **42** (Fig. 6) also showed strong inhibition ($IC_{50} = 10.5$ nM and 12.1 nM, respectively). In cell-based assays, **40** demonstrated the most potent antiproliferative activity against HepG2 liver cancer cells ($IC_{50} = 1.07$ μM), significantly outperforming SAHA ($IC_{50} = 4.50$ μM). Western blot analysis confirmed that **40** and **41** increased histone H3 and H4 acetylation dose-dependently, validating their HDAC inhibition mechanism. Furthermore, flow cytometry analysis showed that both compounds induced apoptosis in HepG2 cells. Molecular docking studies revealed strong interactions between **40** and the HDAC1 active site, rationalizing its high potency. With their robust HDAC inhibition and potent anticancer effects, **40**, **41**, and **42** hold considerable promise as candidates for liver cancer therapy.

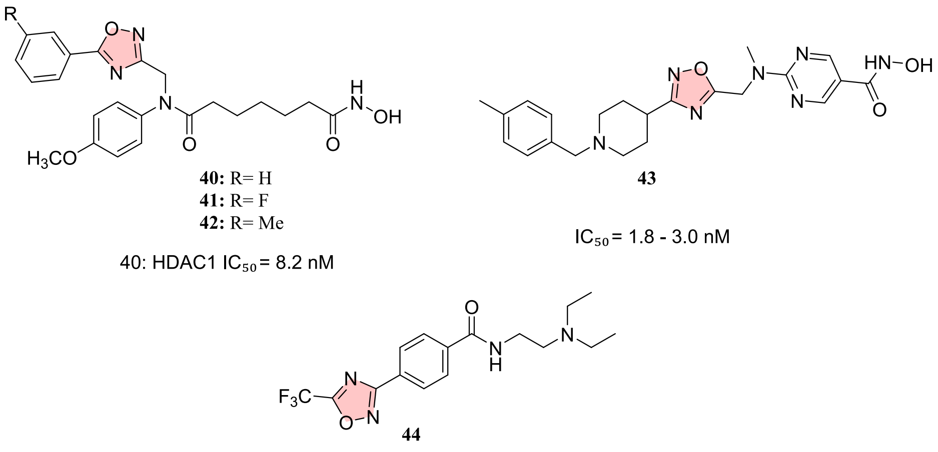
Additionally, Yang et al. synthesized a series of 1,2,4-oxadiazole-containing hydroxamic acid derivatives as histone deacetylase (HDAC) inhibitors and evaluated their potential for cancer therapy [58]. Of the compounds tested, **43** (Fig. 6) exhibited the most potent HDAC inhibition, particularly against HDAC1, 2, and 3, with IC_{50} values of 1.8, 3.6, and 3.0 nM, respectively, surpassing SAHA. In vitro antiproliferative assays confirmed its superior activity across 12 cancer cell lines, with IC_{50} values ranging from 9.8 to 44.9 nM. Western blot analysis demonstrated that **43** significantly upregulated histone H3 acetylation, while flow cytometry revealed G_1 cell cycle arrest and apoptosis induction. Notably, **43** exhibited strong activity against primary acute myeloid leukemia (AML) cells ($IC_{50} = 21.3$–77.4 nM) and showed excellent oral bioavailability (53.52 %). In vivo studies demonstrated significant tumor growth inhibition in a Daudi Burkitt's lymphoma xenograft model, with tumor inhibition rates of 53.8 % (20 mg/kg, p.o.) and 46.1 % (10 mg/kg, i.v.). These results highlight **43** as a promising HDAC inhibitor with potential for further development as an anticancer agent.

In another study, Asfaha et al. synthesized a series of 5-(trifluoromethyl)-1,2,4-oxadiazole (TFMO)-based amides and alkoxyamides as highly selective class IIa HDAC inhibitors, exhibiting potent anticancer activity [59]. The most active compound, **44** (Fig. 6), displayed strong inhibition of HDAC4 ($IC_{50} = 12$ nM) with exceptional selectivity (selectivity index >318) over non-class IIa HDACs. Unlike hydroxamate-based inhibitors, **44** utilized a TFMO moiety as a non-chelating zinc-binding group. In combination with bortezomib, **44** exhibited a strong synergistic cytotoxic effect in THP-1 leukemia cells, significantly enhancing p21 expression and caspase-mediated apoptosis. Additionally, **44** effectively inhibited tumor growth in a Cal27 head and neck cancer xenograft model, particularly in HDAC4-overexpressing cells. The unique mechanism of **44**, coupled with its synergy in combination therapy and in vivo efficacy, positions it as a compelling candidate for further preclinical investigation in targeted cancer treatment.

2.1.4. *Other mechanisms*

Several studies have explored other diverse mechanisms for anticancer activity involving 1,2,4-oxadiazole derivatives. El Mansouri et al. synthesized a new series of uracil analog-1,2,4-oxadiazole hybrids and evaluated their anticancer activity [60]. The screening results identified **45** and **46** (Fig. 7) as the most potent compounds, displaying IC_{50} values of 0.88 μM and 0.98 μM against HT-1080 fibrosarcoma cells and 1.19 μM and 0.89 μM against MCF-7 breast cancer cells, respectively, outperforming doxorubicin. Mechanistic studies revealed that **45** induced apoptosis through caspase-3/7 activation and caused S-phase cell cycle arrest in HT-1080 and A549 lung cancer cells. Annexin V staining confirmed a 10-fold increase in apoptosis for HT-1080 and a 3-fold increase for A549 cells. Molecular docking studies showed that **45** forms a stable complex with caspase-3 through key hydrogen bonds and hydrophobic interactions, supporting its pro-apoptotic mechanism. By effectively triggering caspase-mediated apoptosis and disrupting cell cycle progression, **45** and **46** emerge as strong candidates for further development in targeted cancer therapies.

In another study, Zhou et al. investigated the anticancer activity and mechanism of action of a novel 1,2,4-oxadiazole derivative, **47** (Fig. 7), as a c-MYC inhibitor in leukemia and triple-negative breast cancer cells [61]. Compound **47** exhibited potent cytotoxicity, with IC_{50} values of 0.008 μM against CCRF-CEM leukemia cells and 0.08 μM against MDA-MB-231-pcDNA3 breast cancer cells. Molecular docking and microscale thermophoresis confirmed strong binding of **47** to c-MYC at the MYC-MAX interface (binding energy = −9.91 kcal/mol, predicted inhibition constant = 0.055 μM). A c-MYC reporter assay demonstrated significant inhibition of c-MYC transcriptional activity, while western blot and qRT-PCR confirmed c-MYC downregulation at both protein and mRNA levels. Functional studies revealed that **47** induced DNA damage (alkaline comet assay), cell cycle arrest at G_2/M in leukemia cells and S phase in breast cancer cells, and apoptosis in both cell lines. Additionally, microarray-based gene expression analysis suggested that **47** may promote c-MYC ubiquitination through upregulation of ELL2, a novel ubiquitin ligase. Rather than simply inhibiting c-MYC, **47** forces its destruction, making it a potential game-changer in targeting MYC-driven cancers.



40: R= H
41: R= F
42: R= Me

40: HDAC1 IC_{50} = 8.2 nM

43

IC_{50} = 1.8 - 3.0 nM

44

44: HDAC4 IC_{50} = 12 nM

Fig. 6. Structures of compounds **40–44** as HDAC inhibitors.

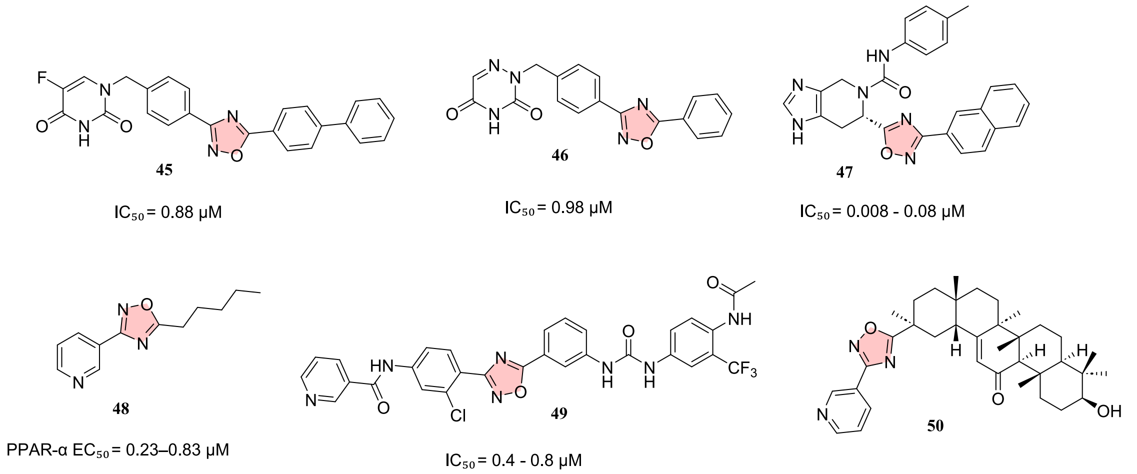


Fig. 7. Structures of compounds **45–50** with anticancer activities.

Meanwhile, Ticona et al. investigated the modulation of PPAR-α as a novel anticancer strategy, designing and synthesizing new derivatives of 3-(pyridin-3-yl)-5-(thiophen-3-yl)-1,2,4-oxadiazole with potential antitumor activity [62]. Cytotoxicity and PPAR-α agonist activity were assessed in A-498 and DU-145 tumor cell lines, revealing that most compounds were less cytotoxic than the reference WY-14643. Among them, **48** (Fig. 7) emerged as the most potent PPAR-α agonist (EC_{50} = 0.23–0.83 μM), comparable to the natural compound (EC_{50} = 0.18–0.77 μM), while displaying lower toxicity in RPTEC and WPMY-1 non-tumor cell lines (CC_{50} = 81.66–92.67 μM). Structure-activity analysis highlighted that modifications at the thiophenyl residue influence PPAR-α activity, suggesting these derivatives as promising anticancer agents.

Continuing the exploration of new anticancer strategies, Dokla et al. identified a novel 1,2,4-oxadiazole derivative, compound **49** (Fig. 7), that promotes YAP degradation by restoring Hippo pathway function, demonstrating potent anticancer activity [63]. **49** selectively activated LATS1, leading to increased YAP phosphorylation at Ser397 and subsequent proteasomal degradation without affecting MST1/2 activity. It exhibited strong antiproliferative effects across multiple cancer cell lines, with IC_{50} values ranging from 0.4 to 0.8 μM, while MCF-7 cells, with low YAP expression, were resistant. In vivo, oral administration of **49** (200 mg/kg) significantly suppressed MDA-MB-231 xenograft tumor growth by 65 % over 40 days without inducing toxicity. Western blot analysis confirmed reduced YAP, c-MYC, and Cyclin D1 levels in tumor lysates. By effectively destabilizing YAP and curbing tumor growth, **49** introduces a compelling new approach for exploiting the Hippo pathway in cancer therapy.

In a different approach to overcoming drug resistance, Moralev et al. developed a novel 3-meta-pyridine-1,2,4-oxadiazole derivative of glycyrrhetinic acid, **50** (Fig. 7), as a potent P-glycoprotein (P-gp) inhibitor to overcome multidrug resistance (MDR) in tumor cells [64]. Molecular docking revealed that **50** interacts with the transmembrane domain of P-gp with a low binding energy (−10.2 kcal/mol), forming hydrogen bonds with key residues involved in ATP hydrolysis. In vitro studies using KB-8-5 cervical carcinoma and RLS40 lymphosarcoma cells confirmed that **50**, at non-toxic concentrations, significantly increased intracellular accumulation of fluorescent P-gp substrates, including rhodamine 123 and doxorubicin. Flow cytometry analysis showed that **50** enhanced doxorubicin uptake by 8-fold in KB-8-5 cells and 11.5-fold in RLS40 cells. Furthermore, **50** sensitized MDR cells to doxorubicin cytotoxicity with a strong synergistic effect (Bliss synergy score = 24.8). Unlike verapamil, **50** exerted its inhibitory effect without altering P-gp protein expression. By selectively enhancing intracellular drug retention and sensitizing MDR cells to chemotherapy, **50** represents a valuable lead for the development of non-toxic P-gp inhibitors aimed at overcoming multidrug resistance in cancer.

Focusing on novel DNA interactions, Doria et al. synthesized a series of oxadiazole-pyridine-based ligands and evaluated their ability to stabilize G-quadruplex (G4) DNA structures, which are involved in cancer-related processes [65]. Among them, **51** and **52** (Fig. 8) exhibited the highest G4 stabilization, with ΔT_m values of 16.6 °C and 13.8 °C for the human telomeric G4 sequence (22AG) in Na^+-rich buffer, outperforming previously studied ligands. Competition assays demonstrated that these compounds selectively stabilized G4 structures over duplex DNA, with TOxAzaPhen showing superior selectivity. Circular dichroism titrations revealed that both ligands induced structural transitions in G4 DNA, favoring an antiparallel topology. Further fluorescence displacement studies suggested a mixed binding mode involving groove interactions. The pronounced G4-stabilizing effects and selective binding profile of **51** and **52** underscore their potential as targeted anticancer agents, paving the way for further exploration of oxadiazole-pyridine hybrids in therapeutic G-quadruplex modulation.

Shifting focus to breast cancer therapy, Chiacchio et al. synthesized a series of 2,3,4-triaryl-substituted 1,2,4-oxadiazole-5-ones as fixed-ring analogues of tamoxifen (TAM) for breast cancer therapy [66]. Several compounds, including **53**, **54**, **55**, **56**, and **57** (Fig. 8), demonstrated significant cytotoxicity against MCF-7 breast cancer cells, with IC_{50} values ranging from 15.63 to 31.82 μM. These compounds increased p53 expression levels and activated the apoptotic pathway, as confirmed by caspase-3 cleavage. Molecular docking studies revealed that they exhibited strong hydrophobic interactions within the estrogen receptor (ER) binding site, similar to TAM, with additional hydrogen bonding to Arg394. With their potent cytotoxicity, p53-mediated apoptotic activation, and ER-targeting capabilities, these fixed-ring TAM analogues emerge as promising candidates for advancing breast cancer therapeutics.

Turning to prostate cancer, Kumar et al. synthesized a series of 1,2,4-oxadiazole-based non-steroidal derivatives and evaluated their potential as androgen receptor antagonists for prostate cancer therapy [67]. Among them, **58** (Fig. 8) exhibited the highest potency, with an IC_{50} of 238.13 nM and an 89.99 % inhibition of PC-3 prostate cancer cells, surpassing bicalutamide. Flow cytometry and ROS assays confirmed that **58** significantly increased reactive oxygen species (ROS) production, leading to apoptosis. Additionally, androgen receptor inhibition assays demonstrated that **58** reduced receptor expression in a dose-dependent manner. Molecular docking studies revealed that **58** formed strong interactions with the active site of the androgen receptor, with a binding affinity of −9.5 kcal/mol. ADMET analysis indicated that **58** exhibited favorable pharmacokinetic properties and minimal toxicity. Overall, compound **58** emerges as a promising non-steroidal androgen receptor antagonist with strong therapeutic potential for prostate cancer, warranting further investigation and development.

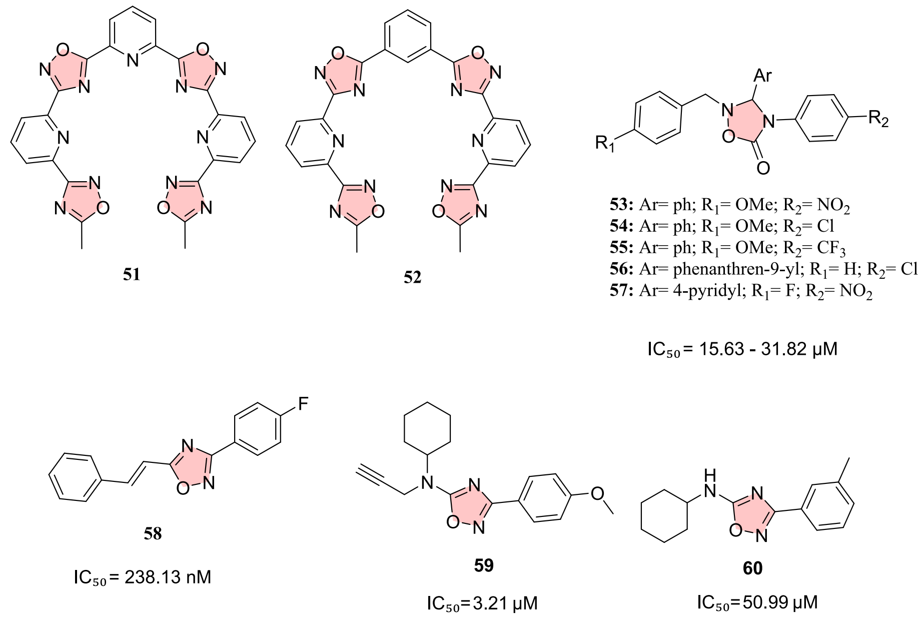


Fig. 8. Structures of compounds **51–60** with anticancer activities.

Oliveira reported a series of alkynylated 1,2,4-oxadiazole/1,2,3-triazole glycoconjugates with anticancer and antimycobacterial activities [68], among which **59** emerged as the most potent anticancer agent, showing significant inhibition of lung carcinoma cell proliferation (NCIH-460) with an IC_{50} value of 3.21 μM (1.00 μg/mL). This compound demonstrated over 69 % growth inhibition at 25 μM concentration after 72 h of exposure in the MTT assay. The enhanced potency of **59** is likely attributed to its N-propargylated 1,2,4-oxadiazole scaffold bearing a methoxy-substituted aromatic ring, which may improve cellular uptake and target interaction. Although the precise mechanism of action remains to be elucidated, the structural features of **59** align with reported apoptosis-inducing oxadiazoles, suggesting a possible caspase-mediated pathway. These findings highlight **59** as a promising lead candidate for further development in lung cancer chemotherapy.

Araújo reported the synthesis and biological evaluation of a novel compound, **60**, which exhibited potent antitumor and immunomodulatory properties [69]. This compound demonstrated significant cytotoxic activity against murine melanoma B16–F10 cells with an IC_{50} value of 50.99 μM, while showing reduced toxicity toward bone marrow-derived macrophages (BMDMs) with an IC_{50} of 132.7 μM, resulting in a selectivity index of 2.6. Flow cytometry analysis confirmed that **60** induced necrosis as the primary mode of cell death in melanoma cells. Additionally, it polarized BMDMs toward the pro-inflammatory M1 phenotype, as evidenced by increased expression of CD11b and elevated secretion of TNF-α (102.75 pg/mL at 64.34 μM) and IL-12, particularly when combined with tumor supernatants or LPS. These findings highlight the dual antitumor and immunotherapeutic potential of **60**, supporting its further development as a promising candidate for melanoma treatment.

2.1.5. *Structure–activity relationship of 1,2,4-Oxadiazole derivatives with anticancer activity*

The anticancer activity of 1,2,4-oxadiazole derivatives is closely tied to their unique structural features, particularly their role as rigid, planar, and electron-deficient heterocycles that serve as bioisosteric linkers or functional pharmacophores. Structure–activity relationship analysis across diverse targets shows that the oxadiazole core contributes not only to molecular conformation and rigidity but also to favorable interactions within hydrophobic and polar binding environments.

In kinase inhibitors, the oxadiazole ring typically connects two aromatic or heteroaromatic systems, promoting optimal geometry for ATP-binding pocket insertion. Substitutions at the terminal aryl groups—especially electron-withdrawing moieties like chloro, trifluoromethyl, or nitro—were found to enhance binding to EGFR, VEGFR-2, p38 MAPK, and GSK3β by improving hydrophobic interactions and hydrogen bonding networks. Docking studies consistently showed that oxadiazole-linked scaffolds oriented the molecule to interact with key residues such as Met793 (EGFR), Cys919 (VEGFR-2), and Lys53 (p38 MAPK), enabling favorable anchoring through hydrogen bonds or π–π stacking.

For carbonic anhydrase inhibitors, the oxadiazole acts as a spacer positioning the sulfonamide zinc-binding group into the catalytic pocket of CA IX. SAR revealed that oxadiazole-sulfonamide hybrids bearing hydrophobic tails improved selectivity toward tumor-associated isoforms. Docking confirmed that the oxadiazole ring helped direct the sulfonamide toward coordination with the Zn^{2+} ion, while enabling secondary interactions with CA IX-specific residues such as Gln92 and Val131, contributing to isoform selectivity.

In HDAC inhibitors, a trifluoromethyl-substituted oxadiazole (TFMO) served as a non-chelating zinc-binding group that mimicked the interaction profile of traditional hydroxamates while avoiding their liabilities. SAR showed that amide linkers and tertiary amine capping groups enhanced selectivity for class IIa HDACs. Docking supported this, revealing that the oxadiazole ring's oxygen and fluorine oriented toward the catalytic zinc ion in HDAC4, anchoring the ligand through polar contacts.

In apoptosis-inducing compounds, the oxadiazole scaffold played a critical role in maintaining molecular rigidity and positioning electron-deficient aryl groups that promoted caspase-3/7 activation. Molecular docking revealed that the oxadiazole ring contributed to stable binding within the active site of caspase-3, forming hydrogen bonds with catalytic residues. Likewise, in c-MYC inhibition, an oxadiazole core facilitated binding at the MYC/MAX interface, disrupting dimerization and transcriptional activation.

Additional mechanisms also benefited from oxadiazole incorporation. In YAP-targeting compounds, the oxadiazole provided a conformation conducive to Hippo pathway activation via LATS1 phosphorylation. In P-gp inhibition, the nitrogen-rich, rigid oxadiazole scaffold enhanced binding to the transmembrane drug-binding domain, supported by docking showing π–π and hydrophobic interactions. Similarly, oxadiazole–pyridine conjugates targeting G-quadruplexes leveraged the electron-deficient oxadiazole to enhance π-stacking and groove-binding affinity for G4 DNA.

Finally, in androgen receptor antagonists, the oxadiazole core facilitated optimal placement of aryl substituents into the receptor's hydrophobic pocket, with docking confirming favorable interactions with Leu704 and Phe764. Across all mechanisms, the oxadiazole ring consistently acts as a pharmacologically active scaffold that imparts structural rigidity, electronic modulation, and orientation flexibility essential for target engagement.

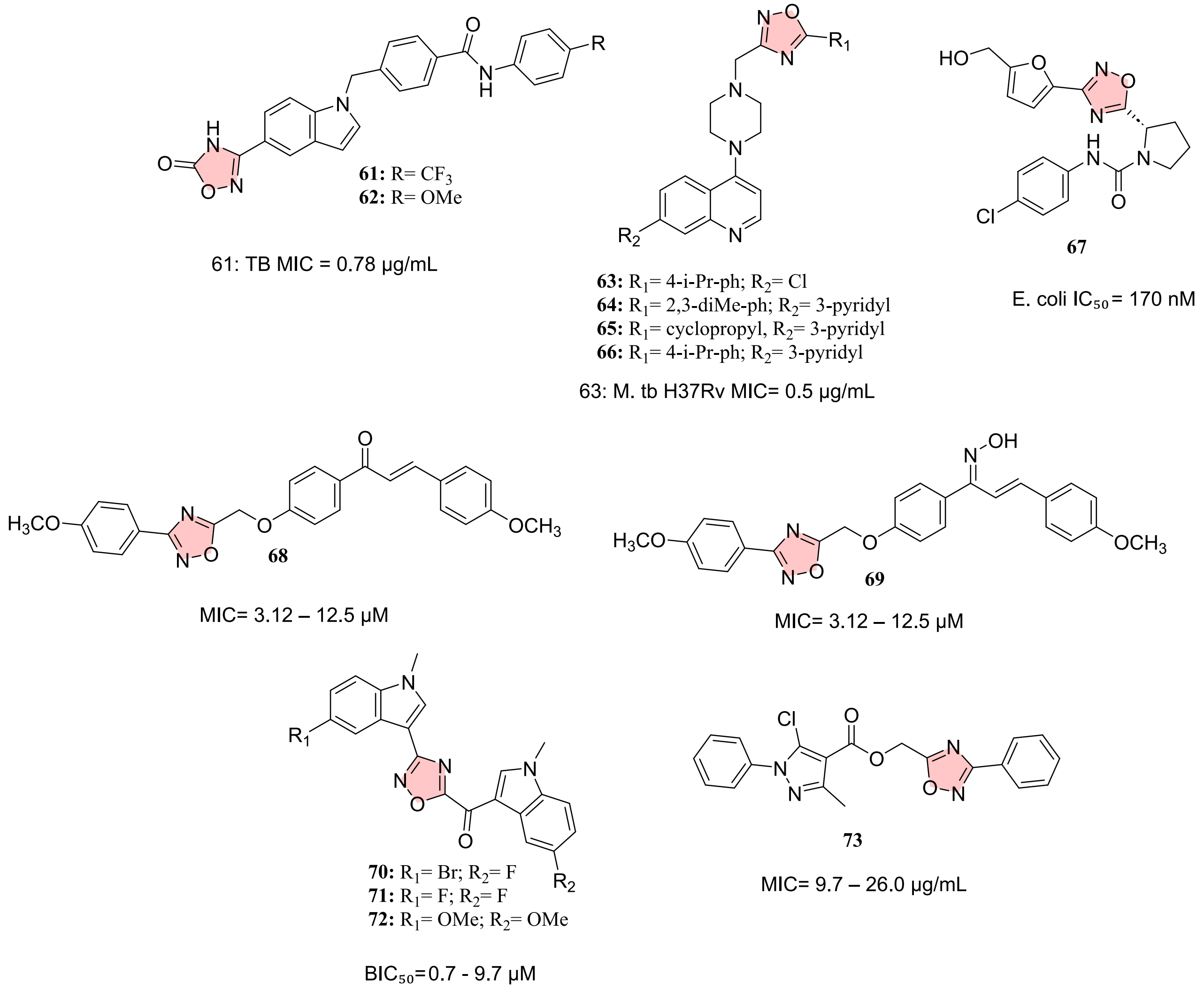
2.2. Antimicrobial activity

2.2.1. Antibacterial activity

Bacterial infections continue to pose a significant global health burden, contributing to high morbidity and mortality rates, particularly with the rise of multidrug-resistant (MDR) strains [70]. The urgent need for novel antibacterial agents has driven extensive research into heterocyclic compounds [71], including 1,2,4-oxadiazole derivatives [72], which have demonstrated diverse and potent antimicrobial properties. These five-membered heterocycles are particularly attractive due to their structural versatility and ability to interact with crucial bacterial targets, making them promising scaffolds for new antibiotic development.

Among their notable applications, 1,2,4-oxadiazoles have emerged as potential anti-tubercular agents, exhibiting significant activity against *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis (TB). Building on this, Reddy et al. synthesized a series of 3-(1-(4-(benzoyl)benzyl)-1H-indol-5-yl)-1,2,4-oxadiazol-5(4H)-ones with promising anti-tubercular activity against *M. tuberculosis* H37Rv [73]. A SAR study identified compounds with MIC values ranging from 0.78 to 25 μg/mL, comparable to Ethambutol. Notably, **61** (Fig. 9) exhibited superior potency (MIC = 0.78 μg/mL) compared to Ethambutol (MIC = 1.56 μg/mL). Molecular docking against InhA enzyme highlighted the strong binding affinities of **61** and **62** (Fig. 9), while in silico ADMET profiling confirmed favorable drug-like properties. These findings position 5-oxo-1,2,4-oxadiazoles as promising anti-TB agents, with further optimization of **61** potentially enhancing potency for future therapeutic development.

Expanding on these findings, Shruthi et al. explored another class of 1,2,4-oxadiazole derivatives by synthesizing quinoline-1,2,4-oxadiazole hybrids and evaluating their antitubercular activity against *M. tuberculosis* H37Rv [74]. Within this series, compound **63** (Fig. 9) exhibited the highest potency, with a MIC of 0.5 μg/mL, while **64**, **65**, and **66** (Fig. 9) were even more potent, with MIC values of 0.25 μg/mL for all three compounds. These compounds demonstrated excellent selectivity for Mtb, showing no significant activity against Gram-positive or Gram-negative bacterial strains. Further studies confirmed that **63** retained efficacy against drug-resistant Mtb strains, including isoniazid- and rifampicin-resistant variants. Pharmacokinetic analysis in BALB/c mice revealed that **63**, **64**, **65**, and **66** exhibited favorable oral bioavailability and metabolic stability, with plasma concentrations



61: R= CF$_3$
62: R= OMe

61: TB MIC = 0.78 μg/mL

63: R$_1$= 4-i-Pr-ph; R$_2$= Cl
64: R$_1$= 2,3-diMe-ph; R$_2$= 3-pyridyl
65: R$_1$= cyclopropyl, R$_2$= 3-pyridyl
66: R$_1$= 4-i-Pr-ph; R$_2$= 3-pyridyl

63: M. tb H37Rv MIC= 0.5 μg/mL

67

E. coli IC$_{50}$= 170 nM

68

MIC= 3.12 – 12.5 μM

69

MIC= 3.12 – 12.5 μM

70: R$_1$= Br; R$_2$= F
71: R$_1$= F; R$_2$= F
72: R$_1$= OMe; R$_2$= OMe

BIC$_{50}$=0.7 - 9.7 μM

73

MIC= 9.7 – 26.0 μg/mL

Fig. 9. Structures of compounds **61–73** with antibacterial activities.

exceeding the MIC for extended periods. Cytotoxicity studies showed that these compounds had IC_{50} values >100 μM against HepG2 cells, indicating a high therapeutic index. Collectively, these results highlight **63**, **64**, **65**, and **66** as promising lead compounds for the development of novel antitubercular agents.

Beyond tuberculosis, 1,2,4-oxadiazole derivatives have also shown potential against other bacterial pathogens through distinct mechanisms. Frejat et al. synthesized a series of 1,2,4-oxadiazole-pyrrolidine hybrids as potential antibacterial agents targeting DNA gyrase and topoisomerase IV [75]. Among the synthesized compounds, **67** (Fig. 9) exhibited the highest potency, with an IC_{50} of 120 nM against *Escherichia coli* DNA gyrase, surpassing novobiocin (IC_{50} = 170 nM). **67** also showed potent inhibition against *Staphylococcus aureus* DNA gyrase (IC_{50} = 210 nM) and *S. aureus* topoisomerase IV (IC_{50} = 5.2 μM), demonstrating its dual-target mechanism. The antibacterial activity of **67** was remarkable, with MIC values of 24 ng/mL and 62 ng/mL against *S. aureus* and *E. coli*, respectively, outperforming ciprofloxacin (MIC = 30 and 60 ng/mL). Molecular docking revealed strong binding interactions between **67** and key residues in DNA gyrase, including Arg76 and Lys103, contributing to its high potency.

Further exploring the antibacterial potential of 1,2,4-oxadiazole derivatives, Ibrahim et al. synthesized a series of 1,2,4-oxadiazole-chalcone-oxime hybrids and evaluated their antibacterial activity as DNA gyrase inhibitors [76]. Compounds **68** and **69** (Fig. 9) exhibited the highest potency against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis*, with MIC values of 3.12–12.5 μM for each of them, compared to ciprofloxacin (MIC = 6.25 μM). DNA gyrase inhibition assays confirmed that **68** and **69** inhibited *E. coli* DNA gyrase with IC_{50} values of 17.05 μM and 13.4 μM, respectively, comparable to novobiocin (IC_{50} = 12.3 μM) and ciprofloxacin (IC_{50} = 10.5 μM). Molecular docking revealed that **68** and **69** exhibited strong binding interactions with key active site residues of *E. coli* DNA gyrase, with docking scores similar to ciprofloxacin. ADMET analysis confirmed favorable pharmacokinetic properties, indicating high oral bioavailability and low toxicity positioning them as promising antibacterial agents targeting DNA gyrase.

Beyond direct antibacterial activity, 1,2,4-oxadiazole derivatives have also shown potential in targeting bacterial virulence factors. Parrino et al. synthesized a series of 1,2,4-oxadiazole topsentin analogs as staphylococcal biofilm inhibitors targeting the bacterial transpeptidase sortase A (SrtA) [77]. The most potent antibiofilm activity was observed in **70**, **71**, and **72** (Fig. 9) against *Staphylococcus aureus* ATCC 25923, with BIC_{50} values of 9.7, 0.7, and 2.2 μM, respectively. Enzymatic assays confirmed that these compounds potently inhibited SrtA, with IC_{50} values ranging from 2.2 to 10.4 μM, surpassing the activity of the reference compound deoxytopsentin (IC_{50} = 15.67 μM). The compounds displayed no significant cytotoxicity against human fibroblast Hs27 cells at active concentrations. Molecular docking studies revealed strong binding interactions of **71** with the SrtA catalytic site, supporting its mechanism of action.

Moreover, Depa et al. synthesized a series of pyrazole-1,2,4-oxadiazole conjugate ester derivatives and evaluated their antibacterial activity against Gram-positive and Gram-negative bacteria [78]. Compound **73** (Fig. 9) stood out exhibiting the highest antibacterial potency, with MIC values of 9.7 μg/mL against *Enterococcus*, 21 μg/mL against *Bacillus subtilis*, and 26 μg/mL against *Escherichia coli*, comparable to streptomycin (MIC = 10–30 μg/mL). Molecular docking studies revealed that **73** had a high LibDock score (162.751 kcal/mol), forming strong hydrogen bond interactions with Asp437 and Arg458 in bacterial DNA gyrase, supporting its inhibitory mechanism. ADMET analysis confirmed that **73** exhibited favorable pharmacokinetic properties and low toxicity. Given the aforementioned promising results, compound **73** could serve as a promising antibacterial agent targeting bacterial DNA gyrase.

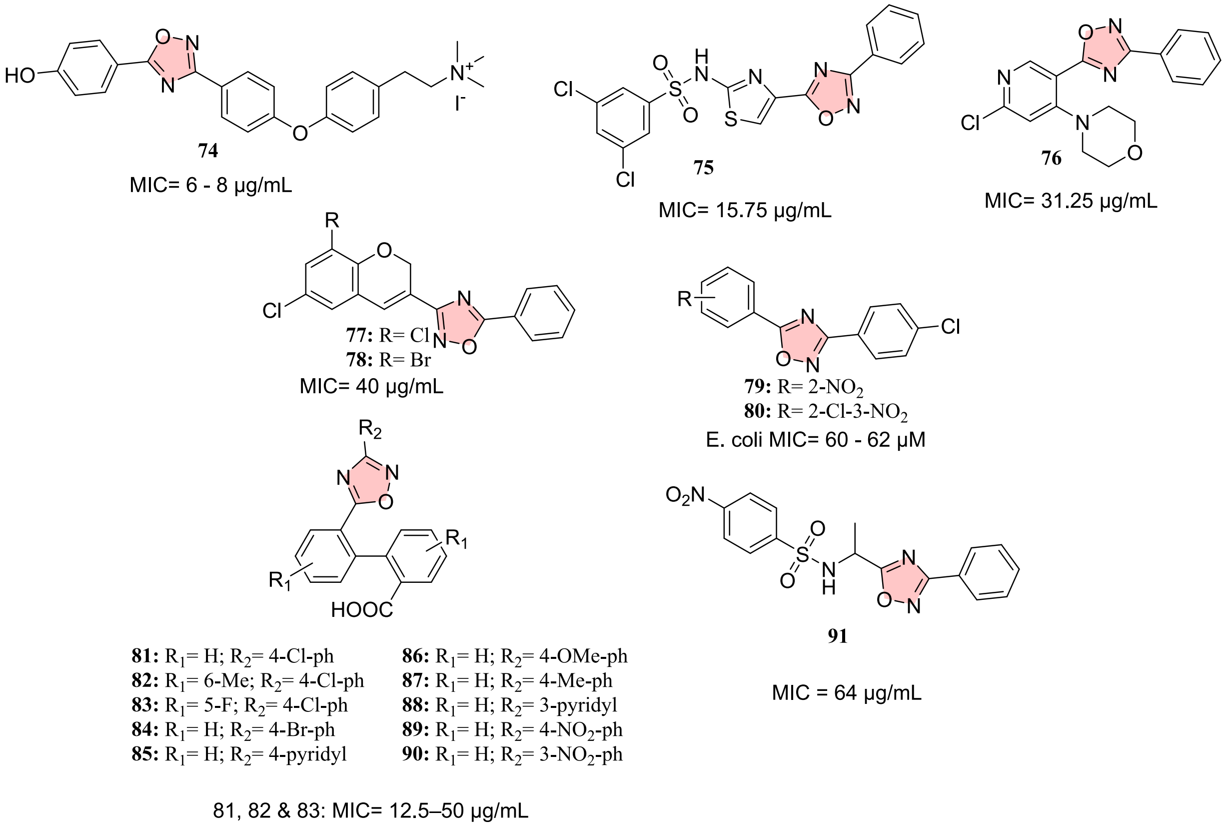
In addition to systemically active antibacterial agents, 1,2,4-oxadiazole derivatives have also been explored for targeted antimicrobial therapies. Pitcher et al. developed a series of 1,2,4-oxadiazole antimicrobial agents designed to selectively target enteric pathogens within the gastrointestinal (GI) tract while minimizing systemic absorption [79]. Compound **74** (Fig. 10) demonstrated the highest potency, exhibiting complete impermeability in Caco-2 cell monolayers while retaining strong activity against *Clostridioides difficile* (MIC = 6 μg/mL) and multidrug-resistant *Enterococcus faecium* (MIC = 8 μg/mL). Time-kill assays confirmed rapid bactericidal activity, eliminating *C. difficile* within 3 h at 4× MIC. Oral pharmacokinetic studies in rats revealed minimal systemic absorption of **74**, supporting its potential as a gut-restricted antimicrobial. However, low recovery levels in feces indicated susceptibility to metabolism, highlighting the need for further structural optimization.

Ali et al. synthesized a series of oxadiazole-sulfonamide-based compounds and evaluated their antibacterial activity [80]. The study revealed compound **75** (Fig. 10) as the most potent, with an MIC of 15.75 μg/mL against each of the 3 bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*, while **76** (Fig. 10) showed a MIC of 31.25 μg/mL against *P. aeruginosa*. Disk diffusion and time-kill assays confirmed the bactericidal nature of both compounds, with **75** effectively disrupting biofilm formation by 92–100 %. In combination studies, **75** exhibited strong synergy with ampicillin, reducing MIC values against multidrug-resistant *Klebsiella pneumoniae* and *Kluyvera georgiana*. Transmission electron microscopy revealed significant damage to bacterial cell walls upon treatment with **75**, leading to cytosolic leakage. Additionally, **75** showed no cytotoxicity against HEK293 cells and human red blood cells, and in vivo toxicity assays in *Galleria mellonella* larvae confirmed its safety.

Baral et al. synthesized a new series of chromene-based 1,2,4-oxadiazole derivatives via microwave-assisted synthesis and evaluated their antibacterial activity [81]. Of the synthesized compounds, **77** and **78** (Fig. 10) exhibited the highest potency against *Escherichia coli* (MTCC614) and *Klebsiella pneumoniae* (MTCC4031), with MIC values of 40 μg/mL for both compounds against both bacteria, comparable to the standard drug gentamicin (MIC = 60 μg/mL). Molecular docking studies confirmed strong binding interactions between **77** and **78** and the bacterial DNA gyrase of *E. coli*, with docking energies of −8.57 kcal/mol and − 8.85 kcal/mol, respectively, surpassing gentamicin (−6.71 kcal/mol). The structure-activity relationship (SAR) analysis indicated that halogen substitutions at the chromene moiety enhanced antibacterial efficacy. These findings highlight **77** and **78** as promising antibacterial agents targeting DNA gyrase, with potential for further development.

Cunha et al. synthesized a series of 3,5-diaryl-1,2,4-oxadiazole derivatives and evaluated their antibacterial activity [82]. Compounds **79** and **80** (Fig. 10) exhibited the highest potency against *Escherichia coli* (MIC = 60 μM and 62 μM, respectively) and *Proteus mirabilis* (MIC = 72 μM), while also showing moderate activity against *Enterococcus faecalis* (MIC = 95–100 μM). The antibacterial activity was attributed to a possible mechanism involving free radical formation, as these compounds contain nitro substituents that are known to undergo bioreduction, leading to oxidative stress in bacterial cells. Structure-activity relationship analysis revealed that the ortho-nitro derivative **78** displayed superior inhibition compared to meta- and para-nitro analogs, suggesting a positional effect on activity. Additionally, molecular modeling indicated that **79** and **80** interact favorably with bacterial enzymes involved in peptidoglycan biosynthesis.

Tarasenko et al. synthesized a series of 1,2,4-oxadiazole-containing biphenylcarboxylic acids and evaluated their antibacterial activity [83]. Among the synthesized compounds, **81**, **82**, and **83** (Fig. 10) exhibited the highest potency, with MIC values of 12.5–50 μg/mL against *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (C600), comparable to clinically relevant antibacterial drugs from the nitrofuran and sulfonamide classes. Structure-activity relationship analysis revealed that the presence of a 4-chlorophenyl substituent at position 3 of the oxadiazole ring enhanced activity. Compounds **84–88** (Fig. 10) showed no antibacterial effects at concentrations up to 200 μg/mL, while **89** and **89** (Fig. 10) exhibited bacteriostatic effects only at 200 μg/



74

MIC= 6 - 8 μg/mL

75

MIC= 15.75 μg/mL

76

MIC= 31.25 μg/mL

77: R= Cl
78: R= Br
MIC= 40 μg/mL

79: R= 2-NO_2
80: R= 2-Cl-3-NO_2
E. coli MIC= 60 - 62 μM

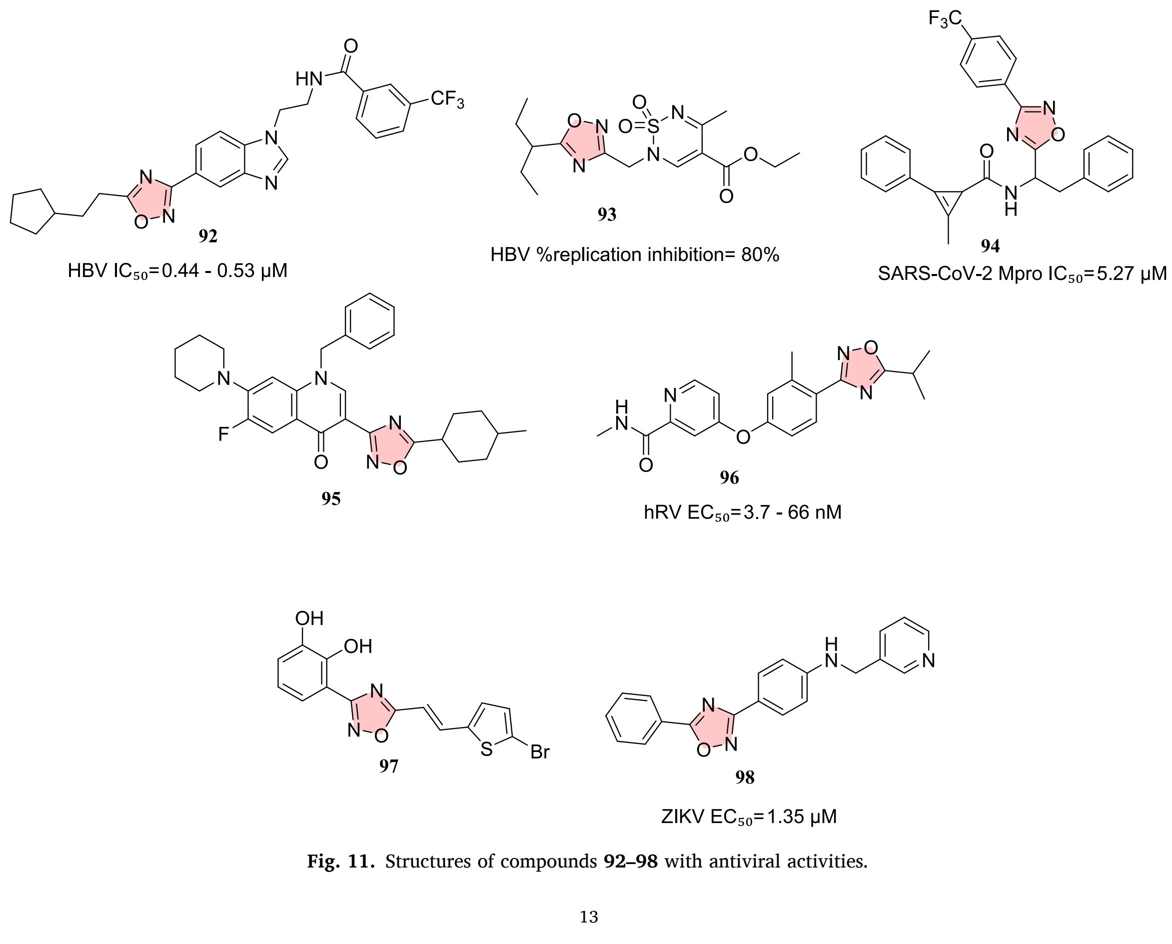
81: R_1= H; R_2= 4-Cl-ph
82: R_1= 6-Me; R_2= 4-Cl-ph
83: R_1= 5-F; R_2= 4-Cl-ph
84: R_1= H; R_2= 4-Br-ph
85: R_1= H; R_2= 4-pyridyl
86: R_1= H; R_2= 4-OMe-ph
87: R_1= H; R_2= 4-Me-ph
88: R_1= H; R_2= 3-pyridyl
89: R_1= H; R_2= 4-NO_2-ph
90: R_1= H; R_2= 3-NO_2-ph

81, 82 & 83: MIC= 12.5–50 μg/mL

91

MIC = 64 μg/mL

Fig. 10. Structures of compounds **74–91** with antibacterial activities.



92

HBV IC_{50}=0.44 - 0.53 μM

93

HBV %replication inhibition= 80%

94

SARS-CoV-2 Mpro IC_{50}=5.27 μM

95

96

hRV EC_{50}=3.7 - 66 nM

97

98

ZIKV EC_{50}=1.35 μM

Fig. 11. Structures of compounds **92–98** with antiviral activities.

mL. These findings suggest **80**, **81**, and **82** as promising lead compounds for further development as antibacterial agents.

Habib et al. synthesized a series of 1,2,4-oxadiazole-sulfonamide conjugates and evaluated their antibacterial activity against Gram-positive and Gram-negative strains [84]. Interestingly, compound **90** (Fig. 10) exhibited the strongest inhibitory effect, with MIC = 64 μg/mL against *Staphylococcus aureus* and *Enterococcus faecalis*. In the disk diffusion assay, **90** showed the highest zone of inhibition (ZOI) against *E. coli* (14 mm) and *S. aureus* (15 mm) at 2MIC. Additionally, the Fractional Inhibitory Concentration Index (FICI) confirmed its antibacterial potency, demonstrating a synergistic effect with Ampicillin against *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*. Notably, **90** exhibited no toxicity toward human red blood cells (hRBC) and displayed a favorable ADME profile, reinforcing its potential as a promising antibacterial candidate.

2.2.2. *Antiviral activity*

The antiviral potential of 1,2,4-oxadiazole derivatives has been extensively investigated, with several compounds exhibiting activity against diverse viral targets. For instance, Qiu et al. synthesized a series of benzimidazole-substituted 1,2,4-oxadiazole derivatives and evaluated their anti-HBV activity alongside their Toll-like receptor 8 (TLR8)-agonistic properties [85]. Within this series, compound **92** (Fig. 11) exhibited the highest potency, with IC_{50} values of 0.53 μM against wild-type HBV and 0.44 μM against nucleos(*t*)ide analog-resistant HBV strains, significantly outperforming the reference nucleos(*t*)ide analogue lamivudine ($IC_{50} > 100$ μM for resistant strains). Dual-luciferase reporter assays confirmed that **92** strongly induced TLR8-mediated NF-κB activity, while ELISA assays demonstrated a dose-dependent increase in TNF-α and IL-12 secretion in human PBMC cells. Molecular docking revealed that **92** binds tightly to the TLR8 dimer interface, forming key hydrogen bonds and π-π stacking interactions, rationalizing its high potency. With a selectivity index (SI) above 37 and a favorable safety profile, **92** represents a promising lead for further development as an immunomodulatory anti-HBV agent.

Building on the search for effective HBV inhibitors, Ivachtchenko et al. synthesized a novel 1,2,4-oxadiazole-thiadiazine derivative, **93** (Fig. 11), and evaluated its anti-HBV activity [86]. Molecular docking studies demonstrated that **93** effectively binds to HBV core proteins (5E0I, 5GMZ, 5WRE, 5T2P), with the highest binding affinity of −17.05 kcal/mol for 5T2P, suggesting strong capsid interaction. Hirshfeld surface analysis confirmed key hydrogen bond interactions stabilizing the molecular conformation. In an in vitro HBV replication model using HepG2-NTCP cells, **93** inhibited HBV replication by 80 % at 10 μM, showing potential to prevent resistant HBV strains. These findings highlight **93** as a promising HBV inhibitor with a well-defined structural basis for further optimization.

Beyond HBV, Guo et al. identified a new series of 3-phenyl-1,2,4-oxadiazole derivatives as SARS-CoV-2 main protease (Mpro) inhibitors [87]. The most potent compound, **94** (Fig. 11), exhibited an IC_{50} of 5.27 μM, demonstrating significant antiviral potential. Structure-activity relationship (SAR) studies revealed that modifications at the cinnamyl moiety and benzyl substitution at the S2 pocket enhanced activity. Molecular docking confirmed that **94** properly occupies the Mpro active site, forming π-alkyl interactions with Met49 and hydrogen bonds with Gln192, supporting its inhibitory mechanism. Further structural optimization is ongoing to enhance potency and pharmacokinetic properties, establishing **94** as a promising lead compound for SARS-CoV-2 antiviral drug development.

Expanding on the potential of 1,2,4-oxadiazoles as broad-spectrum antiviral agents, Vaksler et al. synthesized and characterized a novel fluoroquinolone-1,2,4-oxadiazole hybrid, **95** (Fig. 11), evaluating its potential as an antimicrobial and antiviral agent [88]. Crystallographic studies confirmed its structural arrangement, highlighting strong intermolecular interactions, including hydrogen bonding and π-π stacking. Molecular docking revealed that **95** exhibited high binding affinity for both the hepatitis B virus (HBV) capsid Y132A mutant (PDB: 5E0I, binding energy = −8.8 kcal/mol) and the SARS-CoV-2 main protease (PDB: 6LU7, binding energy = −9.1 kcal/mol), exceeding the reference inhibitors in docking score. Hirshfeld surface analysis identified critical intermolecular interactions stabilizing the crystal structure. These findings suggest **95** as a promising dual-action antimicrobial and antiviral lead compound for further biological evaluation.

The exploration of 1,2,4-oxadiazoles has also extended to picornavirus infections. Kim et al. synthesized a series of 3-aryl-1,2,4-oxadiazole derivatives and evaluated their antiviral activity against human rhinovirus (hRV) [89]. Among them, **96** (Fig. 11) exhibited the highest potency, with EC_{50} values of 66.0 nM against hRV—B14, 22.0 nM against hRV-A21, and 3.7 nM against hRV-A71, outperforming pleconaril. Pharmacokinetic studies in rats revealed that **96** had a low systemic clearance ($0.158\ L\cdot h^{-1}\cdot kg^{-1}$) and moderate oral bioavailability (27.8 %). Metabolic stability assays showed that **96** remained stable in rat liver microsomes (59.6 %) and human liver microsomes (40.7 %) after 30 min. Molecular docking confirmed that **96** binds to the viral capsid canyon, stabilizing the structure and preventing genome release. These findings establish **96** as a promising lead compound for developing novel anti-hRV agents.

Beyond rhinoviruses, 1,2,4-oxadiazole derivatives have also been explored for their potential against flaviviruses. Adawara et al. designed a series of 1,2,4-oxadiazole derivatives as potential dengue virus NS5 inhibitors using a structure-based drug design approach [90]. Among them, **97** (Fig. 11) exhibited the highest binding affinity to the DENV-2 NS5 protease, with a docking score of −29.612 kcal/mol, surpassing the lead compound (−19.10 kcal/mol) and standard inhibitors, including S-adenosyl-L-homocysteine (−16.536 kcal/mol) and Ribavirin (−12.446 kcal/mol). Molecular docking studies revealed that **97** formed strong hydrogen bonds with key amino acid residues, including ASN777, TRP833, and SER885, alongside significant hydrophobic interactions, stabilizing its binding within the active site. ADMET predictions confirmed its high oral bioavailability, good gastrointestinal absorption, and a favorable safety profile, with no AMES toxicity or significant hepatotoxicity concerns. These findings highlight **97** as a promising candidate for further development as a dengue virus NS5 inhibitor.

Nam et al. also reported the antiviral activity of 1,2,4-oxadiazole derivatives against multiple flaviviruses, including Zika virus (ZIKV), dengue virus (DENV), Japanese encephalitis virus (JEV), and classical swine fever virus (CSFV) [91]. Among them, **98** (Fig. 11) exhibited the most potent antiviral activity against ZIKV, with an EC_{50} of 1.35 μM and a selectivity index (SI) of >37. Further evaluation revealed broad-spectrum activity, with EC_{50} values of 2.0 μM for ZIKV PRVABC59, 4.3 μM for ZIKV Brazil/16321, 5.7 μM for DENV-2, 0.56 μM for JEV, and 0.65 μM for CSFV. Mechanistic studies indicated that **98** acts at an early post-entry stage, potentially targeting viral RNA replication. Pharmacokinetic studies in mice demonstrated that **98** exhibited moderate oral bioavailability (47.4 %) with a half-life of 4.6 h, suggesting its potential as a lead compound for flavivirus-targeted drug development.

2.2.3. *Antiparasitic activity*

Leishmaniasis is a neglected tropical disease with limited treatment options and increasing drug resistance, necessitating the search for new therapeutic agents [92]. Among the promising scaffolds investigated, 1,2,4-oxadiazole derivatives have emerged as potential antileishmanial agents. Barbosa et al. synthesized and evaluated a series of 1,2,4-oxadiazole derivatives for their antileishmanial activity against *Leishmania infantum*, the causative agent of visceral leishmaniasis [93]. Among them, **99** (Fig. 12) demonstrated the highest potency, with IC_{50} values of 32.9 μM against promastigotes and 10 μM against intracellular amastigotes, while maintaining a high selectivity index (SI = 18.7 and 61.7, respectively) over mammalian cells. Flow cytometry analysis revealed that **99** caused mitochondrial membrane potential disruption in promastigotes, and ultrastructural analysis confirmed severe morphological damage leading to cell death. Molecular docking and molecular

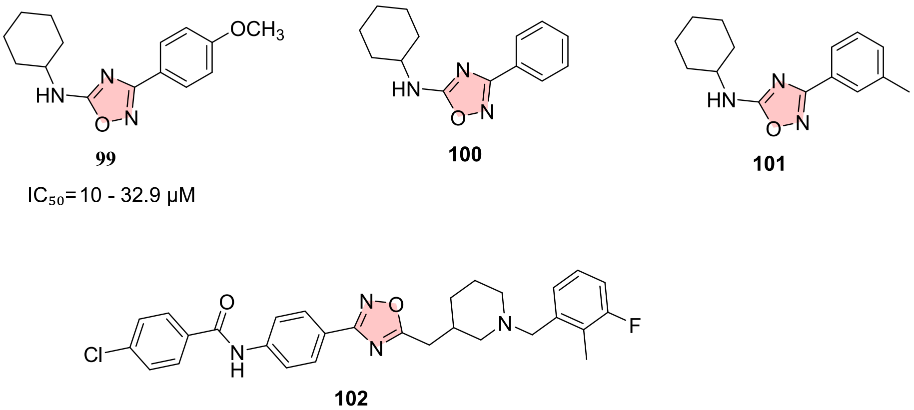


Fig. 12. Structures of compounds **99–102** with antiparasitic activities.

dynamics simulations indicated that **99** exhibited strong binding affinity for L. *infantum* CYP51, a key enzyme in sterol biosynthesis, with a docking score of 36.43 and a binding enthalpy of −50.06 kcal/mol. These findings highlight **99** as a promising lead for further development as an antileishmanial agent.

Pinheiro reported the in silico and in vitro evaluation of a novel cyclohexyl-1,2,4-oxadiazole derivative, among which **100** (Fig. 12) emerged as the most potent compound with significant leishmanicidal activity [94] against *Leishmania infantum* promastigotes, exhibiting an IC_{50} value of 30.86 μM. It showed low cytotoxicity on RAW 264.7 macrophages with a CC_{50} value of 485.5 μM, resulting in a high selectivity index (SI = 17.86), indicating a favorable safety margin. Additionally, **100** demonstrated acetylcholinesterase inhibitory activity with an IC_{50} of 11.91 μM and antioxidant activity in the DPPH assay with an IC_{50} of 12.10 μM. Molecular docking revealed a strong binding affinity to the acetylcholinesterase active site (−7.39 kcal/mol), forming π–sigma and alkyl interactions with Trp84 and His440, suggesting a potential mechanism involving membrane disruption via AChE inhibition. These results highlight **100** as a promising lead for the development of orally administered, selective, and less toxic therapeutic agents against visceral leishmaniasis.

Beyond leishmania, Rocha reported the in vitro and in silico evaluation of **101** (Fig. 12) against *Trypanosoma cruzi* strain Y, where it showed potent trypanocidal activity across all parasite stages. The compound exhibited the highest potency against epimastigote forms after 72 h [95], with an IC_{50} value of 4.43 ± 2.23 μM and a selectivity index (SI) of 21.20, calculated using a CC_{50} of 754.6 ± 196.4 μM on LLC-MK2 host cells. Additionally, it demonstrated a LC_{50} of 59.39 ± 9.08 μM against trypomastigotes and significantly reduced amastigote burden at concentrations of 30, 60, and 120 μM. Flow cytometry indicated that **101** induced parasite cell death primarily by secondary necrosis or late apoptosis, associated with mitochondrial membrane depolarization and [96] high-affinity binding to key parasite enzymes (TcGAPDH: −7.1 kcal/mol, cruzain: −6.9 kcal/mol, and trypanothione reductase: −7.3 kcal/mol), involving hydrogen bonding and π–stacking interactions with catalytic residues such as Trp337, Lys60, and Phe367. These results highlight **101** as a highly selective and mechanistically active candidate for further development as an antichagasic agent.

Colcerasa reported the development and optimization of 1,2,4-oxadiazole-based compounds as selective inhibitors of the NAD^+-dependent lysine deacylase Sirtuin 2 (Sirt2), an enzyme involved in various pathological conditions including cancer. Targeting both human Sirt2 (hSirt2) and its parasitic orthologue from *Schistosoma mansoni* (SmSirt2), the team identified these inhibitors through screening the “Kinetobox” library. Among the synthesized analogues, compound **102** (Fig. 12) was identified as the most potent, exhibiting strong inhibition of hSirt2 deacetylase activity. Mechanistic studies confirmed that the inhibition occurred via a substrate-competitive and NAD^+-noncompetitive binding mode, as supported by docking, kinetic assays, and the crystal structure of the inhibitor–enzyme complex. Furthermore, compound **102** significantly reduced prostate cancer cell viability and impaired cell migration, consistent with its potent inhibition of Sirt2 in both in vitro and cellular models.

2.2.4. Structure–activity relationship of 1,2,4-Oxadiazole derivatives with antimicrobial activity

1,2,4-Oxadiazole derivatives display broad-spectrum antimicrobial activity, with their structural features playing a central role in target engagement and biological efficacy. Across antibacterial, antiviral, and antiparasitic studies, the oxadiazole ring functions as a rigid, electron-deficient scaffold that aligns pharmacophoric groups in spatially favorable orientations for interaction with diverse biological targets. In antibacterial agents, SAR analysis reveals that substitution at the 3- and 5-positions of the oxadiazole ring with aryl, heteroaryl, or alkyl chains enhances potency, particularly when electron-withdrawing groups such as nitro, chloro, or trifluoromethyl are introduced. These modifications improve interactions with bacterial enzymes like DNA gyrase, topoisomerase IV, and sortase A. Molecular docking consistently shows that the oxadiazole core orients key substituents toward catalytic residues such as Asp437 and Tyr122, enabling hydrogen bonding, π-stacking, or metal coordination. In sulfonamide-linked derivatives, the oxadiazole acts as a conformational bridge, positioning the sulfonamide group for optimal interaction with bacterial DHPS and contributing to enhanced antibacterial profiles.

In antiviral compounds, the oxadiazole scaffold supports activity against a range of viruses, including HBV, SARS-CoV-2, dengue, Zika, and rhinovirus. SAR studies show that antiviral potency increases with hydrophobic and bulky substitutions, such as cyclohexyl or alkylated phenyl groups, which improve membrane permeability and binding within hydrophobic pockets of viral enzymes. Docking studies confirm that oxadiazole-containing compounds engage critical residues in viral proteases and polymerases, such as Cys145 and His41 in SARS-CoV-2 main protease or Ser202 in HBV reverse transcriptase, primarily via hydrogen bonding and van der Waals contacts. The oxadiazole ring itself contributes to favorable electronic distribution and molecular planarity, enhancing target binding and selectivity.

In antiparasitic agents, particularly those targeting *Leishmania* and *Trypanosoma cruzi*, SAR investigations highlight the importance of lipophilic aryl or cycloalkyl substitutions on the oxadiazole core. These substitutions enhance uptake by parasitic cells and favor interactions with essential enzymes such as trypanothione reductase and pteridine reductase. Docking and molecular dynamics simulations demonstrate that the oxadiazole ring supports stable ligand conformations and facilitates interactions through hydrogen bonding and hydrophobic contacts within the parasite’s active site clefts. In all three categories of antimicrobial activity, the oxadiazole ring acts not only as a linker or spacer but also as an active pharmacophore that governs molecular orientation, electronic properties, and target affinity. Its inclusion in drug-like scaffolds consistently improves bioactivity, stability, and cell permeability, establishing it as a privileged structure in antimicrobial drug design.

2.3. Anti-inflammatory activity

Inflammation is a key pathological process underlying various chronic diseases, including arthritis, cardiovascular disorders, and neurodegenerative conditions [97]. The search for novel anti-inflammatory agents [98] has led to growing interest in heterocyclic compounds, particularly 1,2,4-oxadiazole derivatives, due to their ability to modulate inflammatory pathways. In this regard, Kulkarni et al. synthesized a series of 1-(5-(2-fluoro-5-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-3-yl)piperazine derivatives and evaluated their anti-inflammatory activity [99]. Among them, **98** (Fig. 13) exhibited the highest potency, showing 42 % inhibition of protein denaturation at 100 µg/mL, which was comparable to diclofenac sodium (41 % inhibition). At higher concentrations (400–1600 µg/mL), **98** maintained superior inhibition (77–90 %), outperforming all other synthesized derivatives. Structure-activity relationship analysis suggested that the presence of a pyrazine moiety linked via an amide bond significantly enhanced activity. Molecular docking studies revealed that **98** strongly interacted with key anti-inflammatory targets, including IL-10, IL-13, and TGF-β, showing favorable binding energies and multiple hydrogen-bonding interactions. ADMET analysis confirmed that **98** had good oral bioavailability and low toxicity. These findings establish **98** as a promising anti-inflammatory agent for further development.

Building on their previous findings, the same research group further explored 1,2,4-oxadiazole derivatives by synthesizing a series of novel 3,5-substituted analogs using NMI-MsCl-mediated amide bond formation and evaluating their anti-inflammatory activity [100]. Among them, **99** and **100** (Fig. 13) demonstrated the highest potency, with **99** exhibiting 42 % inhibition of protein denaturation at 100 µg/mL, outperforming diclofenac sodium (40 % inhibition). At higher concentrations (400–1600 µg/mL), **99** and **100** maintained superior inhibition (77–91 %), suggesting strong anti-inflammatory effects. Structure-activity relationship (SAR) analysis indicated that electron-withdrawing groups, such as fluorine and trifluoromethoxy, significantly enhanced activity. Molecular docking studies revealed that **99** and **100** strongly interacted with key anti-inflammatory targets, including TGF-β and IL-1, forming multiple hydrogen bonds with active site residues. These findings establish **99** and **100** as promising anti-inflammatory agents with potential for further development.

Beyond these investigations, other research efforts have explored different 1,2,4-oxadiazole-based scaffolds for anti-inflammatory activity. Aziz et al. synthesized a series of pyrazolo[3,4-*d*]pyrimidine-1,2,4-oxadiazole hybrids and evaluated their anti-inflammatory activity as COX-2, 5-LOX, and nitric oxide (NO) release inhibitors [101]. Among them, **101** (Fig. 13) exhibited the highest potency as a COX-2/5-LOX dual inhibitor, with IC_{50} values of 1.837 µM for COX-2 and 2.662 µM for 5-LOX, alongside an NO release inhibition rate of 66.02 %. Additionally, **102** (Fig. 13) demonstrated the most significant in vivo anti-inflammatory effects, showing superior inhibition of carrageenan-induced paw edema with minimal gastric ulceration. Molecular docking studies revealed that **101** and **102** were favorably positioned inside the COX-2 and 5-LOX binding pockets, forming key hydrogen bonds and π-π stacking interactions with crucial residues. Molecular dynamics simulations further confirmed the stability of **101** and **102** in complex with COX-2 and 5-LOX throughout a 100 ns simulation, supporting their potential as promising anti-inflammatory candidates.

Further expanding the structural diversity of 1,2,4-oxadiazole-based anti-inflammatory agents, Ruan et al. synthesized a series of phthalide-1,2,4-oxadiazole hybrids and evaluated their anti-inflammatory activity [102]. Among them, **103** (Fig. 13) exhibited the highest potency, significantly inhibiting lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW 264.7 macrophages, with an inhibition rate exceeding 90 %. Western blot analysis confirmed that **103** down-regulated the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Further mechanistic studies revealed that **103** suppressed the TLR4/NF-κB and ERK/p38 signaling pathways, leading to reduced production of pro-inflammatory cytokines. Cytotoxicity assays confirmed that **103** had low toxicity in macrophage cells, indicating a favorable safety profile. These findings establish **103** as a promising lead compound for the development of novel anti-inflammatory agents.

In line with efforts to target inflammation via NF-κB modulation, Zhang et al. synthesized a series of 1,2,4-oxadiazole derivatives and evaluated their anti-inflammatory activity in LPS-stimulated RAW 264.7 macrophages [103]. Among them, **104** (Fig. 13) exhibited the highest potency, significantly suppressing LPS-induced nitric oxide (NO) production with an IC_{50} of 12.84 µM and inhibiting NF-κB activation with an IC_{50} of 1.35 µM. Western blot and immunofluorescence studies confirmed that **104** blocked NF-κB signaling by preventing p65 phosphorylation and nuclear translocation while reducing the expression of pro-inflammatory mediators, including TNF-α, IL-6, and IL-1β. Additionally, **104** displayed minimal cytotoxicity in RAW 264.7 cells, with a viability rate of 98.96 % at 20 µM. These findings establish **104** as a promising lead compound for further development as an anti-inflammatory agent targeting NF-κB signaling.

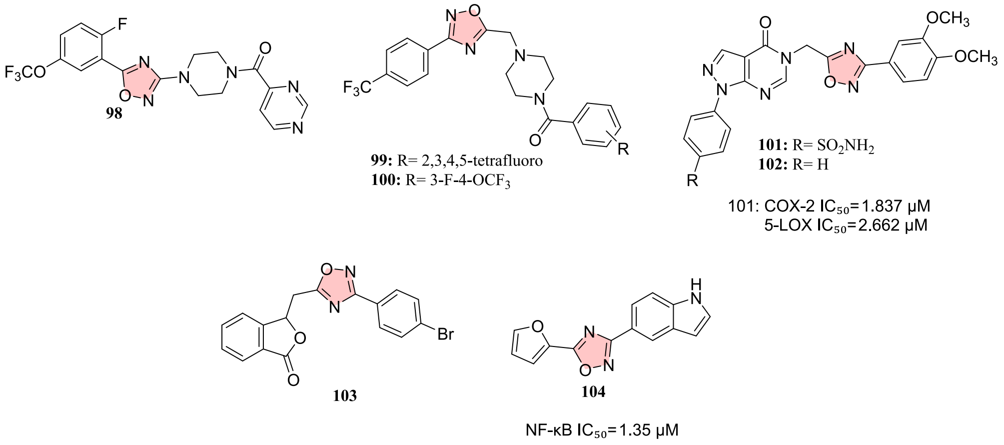


Fig. 13. Structures of compounds **98–104** with anti-inflammatory activities.

2.3.1. Structure–activity relationship of 1,2,4-Oxadiazole derivatives with anti-inflammatory activity

1,2,4-Oxadiazole derivatives have demonstrated potent antiinflammatory activity by targeting key mediators such as COX-2, 5-lipoxygenase (5-LOX), nitric oxide (NO) release, and the NF-κB signaling pathway. Structure–activity relationship studies show that substitution at the 3- and 5-positions of the oxadiazole ring with aryl or heteroaryl groups—particularly those bearing fluorinated, trifluoromethoxy, or methoxy moieties—enhances COX-2 selectivity and NO inhibition. For instance, piperazine-linked oxadiazoles with a 2-fluoro-5-trifluoromethoxyphenyl group exhibited significant COX-2 inhibition, which was supported by docking studies showing interactions with Arg120 and Tyr355 within the active site. Additionally, hybrids incorporating oxadiazole with pyrazolopyrimidine or phthalide motifs showed dual inhibition of COX-2 and 5-LOX, while sulfur-linked benzoxazole–oxadiazole conjugates effectively inhibited NO production and reactive oxygen species (ROS), likely via stabilization of interactions with NF-κB regulatory sites such as Cys62. The presence of electron-donating or polar groups improved cellular uptake and interaction with inflammatory mediators.

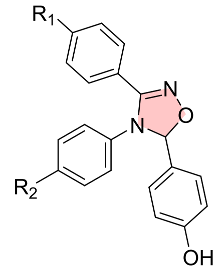
2.4. Antidiabetic activity

Diabetes mellitus remains a major global health challenge, characterized by chronic hyperglycemia due to impaired insulin secretion, insulin resistance, or both [104]. The search for novel therapeutic agents has led to increasing interest in heterocyclic compounds, including 1,2,4-oxadiazole derivatives, which have shown potential in modulating key enzymes involved in glucose metabolism. Roustaei et al. synthesized a series of ten novel triaryl-1,2,4-oxadiazole derivatives and evaluated their potential as α-glucosidase inhibitors to explore their antidiabetic properties [105]. The biological assessment demonstrated that all compounds exhibited notable inhibitory activity, with **105** and **106** (Fig. 14) emerging as the most potent, displaying IC_{50} values of 193.6 and 222.0 μM, respectively, surpassing the standard drug acarbose. Further enzyme kinetic studies were conducted to elucidate the inhibition mechanism of **105**, while molecular docking simulations provided insights into the binding interactions of the most active derivatives within the enzyme's active site. These findings highlight the triaryl-1,2,4-oxadiazole scaffold as a promising framework for developing novel antidiabetic agents.

In this context, Khan et al. synthesized a series of oxadiazole-based benzothiazole derivatives and evaluated their inhibitory activity against α-glucosidase and urease [106]. Among them, **107** (Fig. 14) exhibited the most potent α-glucosidase inhibition with an IC_{50} of 4.60 μM and urease inhibition with an IC_{50} of 8.90 μM, while **108** (Fig. 14) also demonstrated strong activity with IC_{50} values of 5.60 μM and 10.90 μM, respectively. These compounds showed significantly greater potency than the standard drugs acarbose (IC_{50} = 38.60 μM) and thiourea (IC_{50} = 58.70 μM). Structure-activity relationship analysis revealed that the presence of hydroxyl and trifluoromethyl groups enhanced enzyme inhibition, while molecular docking studies confirmed strong interactions with the active sites of α-glucosidase and urease. These findings highlight **107** and **108** as promising candidates for further development as potential anti-diabetic and anti-urease agents.

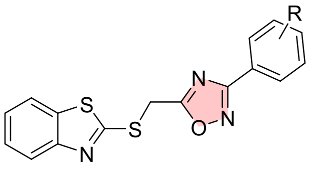
Beyond α-glucosidase inhibition, 1,2,4-oxadiazole derivatives have also been explored as potential activators of peroxisome proliferator-activated receptors (PPARs), which play a crucial role in glucose and lipid metabolism. Kaur et al. synthesized a series of 1,2,4-oxadiazole-based trans-acrylic acid derivatives as potential dual PPAR-α/γ agonists for the treatment of type 2 diabetes [107]. Among them, **109** and **110** (Fig. 14) exhibited the highest potency, with **109** showing EC_{50} values of 0.06 μM for PPAR-α and 0.07 μM for PPAR-γ, while **110** demonstrated EC_{50} values of 3.29 μM and 0.781 μM for the respective receptors. Both compounds outperformed pioglitazone, which had EC_{50} values of 38.03 μM (PPAR-α) and 32.38 μM (PPAR-γ). In vivo studies in diabetic rats confirmed their efficacy, with **109** significantly reducing plasma glucose and cholesterol levels at a 5 mg/kg/day dose, comparable to pioglitazone at 10 mg/kg/day. Histopathological analysis showed improved pancreatic islet integrity, while oxidative stress markers (TBARS, GSH, and CAT) indicated reduced oxidative damage. These findings suggest that **109** and **110** are promising lead compounds for further development as dual PPAR-α/γ agonists with improved potency and safety profiles.

In addition to targeting PPAR receptors, 1,2,4-oxadiazole derivatives have also been investigated for their ability to modulate other pathways



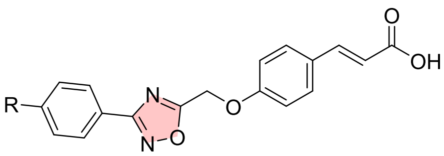
105: R_1= Cl; R_2= OMe
106: R_1= OMe; R_2= Cl

α-glucosidase IC_{50}=193.6 - 222.0 μM



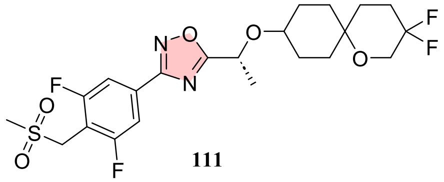
107: R= 4-F-2-OH
108: R= $4\text{-}CF_3$

107: α-glucosidase IC_{50}=4.6 μM



109: R= F
110: R= H

109: PPAR-α EC_{50}=0.06 μM
PPAR-γ EC_{50}=0.07 μM



111

GPR119 EC_{50}=6 nM

Fig. 14. Structures of compounds **105–111** with antidiabetic activities.

involved in glucose homeostasis. Harada et al. optimized a series of oxadiazole derivatives with a spirocyclic cyclohexane structure as novel GPR119 agonists for the treatment of type 2 diabetes [108]. Among them, **111** (Fig. 14) demonstrated the highest potency with an EC_{50} of 6 nM, excellent metabolic stability (98 % remaining in human liver microsomes after 1 h), and a long-acting hypoglycemic effect. Structural modifications, including the introduction of a gem-difluoro group, significantly improved both agonistic activity and metabolic stability. Pharmacokinetic studies in Sprague-Dawley rats showed **111** had a half-life of 5.1 h, low clearance (0.5 L/h/kg), and an oral bioavailability of 43 %. In intraperitoneal glucose tolerance tests, **111** effectively suppressed plasma glucose levels with insulin secretion 16 h post-administration at doses of 1 mg/kg and 3 mg/kg. These findings establish **111** as a promising GPR119 agonist with sustained in vivo activity and potential as a novel therapeutic for type 2 diabetes.

2.4.1. Structure–activity relationship of 1,2,4-Oxadiazole derivatives with antidiabetic activity

In antidiabetic studies, 1,2,4-oxadiazole-based compounds have emerged as promising agents through multiple mechanisms, including GPR119 agonism, PPARα/γ dual activation, and α-glucosidase inhibition. SAR trends reveal that introducing bulky lipophilic groups such as spirocyclic cyclohexanes or benzothiazoles at the 5-position of the oxadiazole ring enhances receptor affinity and cellular activity. For GPR119 activation, spirocyclic oxadiazoles demonstrated potent efficacy, supported by docking that revealed π–π stacking with Phe310 and hydrophobic interactions with Leu119 in the receptor's transmembrane domain. For PPAR modulation, compounds bearing trans-acrylic acid moieties exhibited dual PPARα/γ activation, facilitated by hydrogen bonding with key residues such as Tyr473 and Ser289 in their ligand-binding domains. Benzothiazole–oxadiazole hybrids showed significant α-glucosidase inhibition, attributed to hydrogen bonding interactions with Asp214 and Glu276 in the enzyme's active site. The oxadiazole scaffold's planarity and electron-deficient character were essential in maintaining the geometry necessary for multi-receptor engagement, highlighting its value as a versatile antidiabetic pharmacophore.

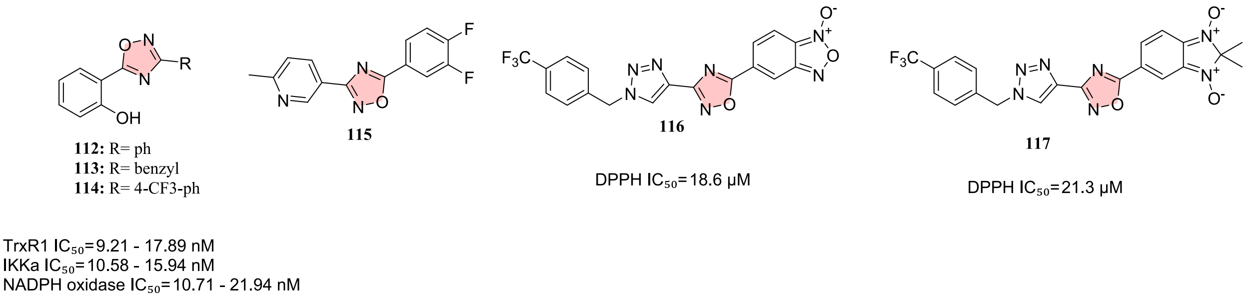
2.5. Antioxidant activity

Oxidative stress plays a crucial role in the pathogenesis of various diseases, including cancer, neurodegenerative disorders, and cardiovascular conditions [109]. Reactive oxygen species (ROS) accumulation can lead to cellular damage, while excessive oxidative stress disrupts redox homeostasis, promoting inflammation and tumor progression [110]. Consequently, antioxidant agents capable of scavenging ROS and modulating key redox pathways have gained significant attention in drug discovery [111]. Among the promising scaffolds, 1,2,4-oxadiazole derivatives have demonstrated potent antioxidant properties through multiple mechanisms.

Ayoup et al. investigated a series of rationally designed 1,2,4-oxadiazole derivatives as multitarget antioxidants for cancer therapy by activating the Nrf2 pathway through inhibition of its suppressors [112]. Among them, **112**, **113**, and **114** (Fig. 15) exhibited potent ROS scavenging (comparable to ascorbic acid) and iron chelation (similar to EDTA), effectively suppressing oxidative stress in HepG-2 cells by 3-fold. These compounds demonstrated superior cytotoxicity to doxorubicin against HepG-2, MDA-MB231, and Caco-2 cancer cells, with **114** showing the highest potency. Mechanistic studies revealed their strong inhibition of TrxR1 (IC_{50} = 9.21, 17.89, and 13.19 nM), IKKa (IC_{50} = 10.58, 15.94, and 11.00 nM), and NADPH oxidase (IC_{50} = 10.71, 21.94, and 16.40 nM), along with downregulation of NF-kB (7.6-, 1.4-, and 1.9-fold reductions, respectively). These effects led to a 2.36-, 1.78-, and 2.04-fold activation of Nrf2, suggesting their potential as multifunctional anticancer agents. Molecular docking confirmed their strong interactions with TrxR1, IKKa, and NADPH oxidase, supporting their observed biological activities. Additionally, they exhibited favorable ADMET properties and drug-like ligand efficiency metrics, highlighting their potential for further development as novel cancer therapeutics.

Xu et al. designed and synthesized a series of 1,2,4-oxadiazole derivatives as potent Nrf2 activators for the treatment of acetaminophen (APAP)-induced acute liver injury [113]. Among them, **115** (Fig. 15) exhibited the highest Nrf2 activation, inducing a 59.55-fold increase in ARE-luciferase reporter activity. In vitro, **115** effectively promoted Nrf2 nuclear translocation in hepatocyte L02 cells, significantly upregulated antioxidant enzymes (NQO1, HO-1, and GCLM), and protected against APAP-induced cytotoxicity. In vivo, **115** demonstrated strong hepatoprotective effects in an APAP-induced liver injury mouse model, reducing serum ALT and AST levels while restoring hepatic antioxidant enzyme activities (GSH, GST, and SOD). Histological analysis confirmed that **115** preserved liver architecture and mitigated hepatocellular necrosis. Further, it exhibited favorable physicochemical properties, including a fourfold increase in aqueous solubility over the parent compound. These results establish **115** as a promising Nrf2 activator with strong antioxidant and hepatoprotective potential, making it a viable candidate for the treatment of drug-induced liver injury.

Mayer et al. synthesized a series of benzofuroxan and 2H-benzimidazole 1,3-dioxide derivatives conjugated to the electron-acceptor 1,2,3-triazolyl-1,2,4-oxadiazole and evaluated their antioxidant and electrochemical properties [114]. Compounds **116** and **117** (Fig. 15) were found to exhibit the highest antioxidant activity in the DPPH assay, with IC_{50} values of 18.6 and 21.3 μM, respectively, surpassing ascorbic acid (IC_{50} = 25.4 μM). Cyclic voltammetry revealed that these compounds underwent reversible redox processes, suggesting strong electron-donating capabilities. UV–Vis spectroscopy confirmed significant intramolecular charge transfer, particularly in **117**, which displayed an ICT band around 500–650 nm. Density functional theory (DFT) calculations supported these findings, indicating that electron-withdrawing substituents enhanced redox activity. These results highlight **116** and **117** as promising redox-active antioxidants with potential applications in oxidative stress-related diseases.



112: R= ph
113: R= benzyl
114: R= 4-CF3-ph

115

116

DPPH IC_{50}=18.6 μM

117

DPPH IC_{50}=21.3 μM

TrxR1 IC_{50}=9.21 - 17.89 nM
IKKa IC_{50}=10.58 - 15.94 nM
NADPH oxidase IC_{50}=10.71 - 21.94 nM

Fig. 15. Structures of compounds **112–117** with antioxidant activities.

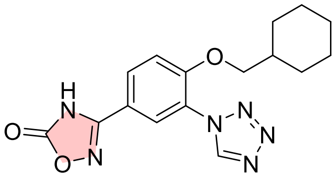
2.5.1. Structure–activity relationship of 1,2,4-Oxadiazole derivatives with antioxidant activity

Oxadiazole derivatives exert antioxidant effects primarily through Nrf2 pathway activation and direct modulation of oxidative stress markers. SAR analysis emphasizes that introducing electron-withdrawing or redox-sensitive substituents on the oxadiazole ring—such as fluorinated aryls, nitro groups, or fused aromatic systems—enhances reactivity toward electrophilic cysteine residues in Keap1, leading to Nrf2 stabilization and downstream antioxidant gene expression. Hybrid molecules containing oxadiazole–triazole or oxadiazole–benzofuroxan systems showed strong Nrf2 activation and ROS scavenging potential. Docking studies revealed key interactions with Keap1 residues such as Arg415 and Ser508, which prevent Nrf2 degradation and allow upregulation of antioxidant response element (ARE) targets. Moreover, compounds with extended conjugation and rigid scaffolding promoted better alignment within redox-sensitive protein pockets, improving efficacy in models of oxidative liver injury and cellular ROS accumulation. These findings confirm the oxadiazole scaffold's utility in fine-tuning redox modulation at both transcriptional and enzymatic levels.

2.6. Use in gout

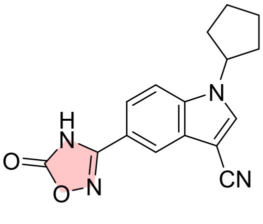
Gout is a metabolic disorder caused by excess uric acid, leading to painful joint inflammation. Xanthine oxidase (XO) inhibitors are a key treatment strategy, with increasing interest in nonpurine alternatives [115,116]. In pursuit of more potent inhibitors, Gao et al. designed and synthesized a series of 3-[4-alkoxy-3-(1H-tetrazol-1-yl)phenyl]-1,2,4-oxadiazol-5(4H)-ones as novel xanthine oxidase (XO) inhibitors for the treatment of hyperuricemia and gout [117]. Among them, **118** (Fig. 16) emerged as the most potent inhibitor, with an IC_{50} of 0.121 μM, approximately 63-fold more potent than allopurinol ($IC_{50} = 7.590$ μM). Structure-activity relationship analysis highlighted that a hydrophobic group at the 4′-position was crucial for inhibitory potency. Molecular docking studies revealed that **118** binds to the XO active site through hydrogen bonding with Arg880 and Thr1010, as well as π-π stacking interactions with Phe914 and Phe1009. Enzyme kinetic studies confirmed **118** as a mixed-type nonpurine XO inhibitor. In vivo hypouricemic studies in a rat model demonstrated that **118** significantly reduced serum uric acid levels at an oral dose of 15 mg/kg. These findings suggest **118** as a promising lead compound for developing novel nonpurine XO inhibitors with potential therapeutic applications for hyperuricemia and gout.

Building on these findings, the same research group further explored structurally distinct 1,2,4-oxadiazole derivatives as XO inhibitors. They designed a series of 1-alkyl-5/6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1H-indole-3-carbonitriles as novel xanthine oxidase (XO) inhibitors [118]. Among them, **119** (Fig. 16) emerged as the most potent compound, exhibiting an IC_{50} value of 0.36 μM, making it approximately 21-fold more potent than allopurinol ($IC_{50} = 7.59$ μM). Enzyme kinetic studies revealed that **119** functions as a mixed-type XO inhibitor, preferentially binding to the free enzyme rather than the enzyme-substrate complex. Molecular docking studies indicated that the 5-oxo-4,5-dihydro-1,2,4-oxadiazole moiety of **119** forms crucial hydrogen bonds with Arg880 and Thr1010, while its cyano group interacts with Asn768 and Lys771, explaining its high inhibitory activity. Furthermore, in a potassium oxonate-induced hyperuricemia rat model, **119** demonstrated significant hypouricemic effects, effectively reducing serum uric acid levels at an oral dose of 10 mg/kg. These findings suggest that **119** represents a promising lead compound for the development of novel nonpurine XO inhibitors for the treatment of hyperuricemia and gout.



118

IC_{50}=0.121 μM



119

IC_{50}=0.36 μM

Fig. 16. Structures of compounds **118** and **119** as xanthine oxidase inhibitors.

2.6.1. Structure–activity relationship of 1,2,4-Oxadiazole derivatives with Antigout activity

1,2,4-Oxadiazole derivatives targeting xanthine oxidase (XO) have shown significant promise in gout management by inhibiting uric acid production. SAR indicates that introducing tetrazolyl, alkoxyphenyl, or oxo-indole substituents on the oxadiazole ring enhances XO affinity and selectivity. Compounds featuring 3-(tetrazolyl-phenyl)-1,2,4-oxadiazol-5-ones or indole–oxadiazole conjugates demonstrated potent XO inhibition with low micromolar IC_{50} values. Molecular docking studies confirmed that the oxadiazole moiety facilitates key hydrogen bonding with residues such as Glu802 and Arg880 and π–π stacking with Phe914 in the XO active site. The electron-deficient nature of the oxadiazole ring appears to favor molybdenum cofactor pocket interaction, blocking substrate access. Hydrophobic side chains like alkyl or cycloalkyl groups were found to improve bioavailability and orientation within the binding site, confirming the importance of balanced hydrophobicity and polar interaction potential for effective XO inhibition.

2.7. In neurodegenerative diseases

Neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, are characterized by progressive neuronal loss and cognitive decline, often linked to oxidative stress and cholinergic dysfunction. Enzyme inhibitors targeting acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) have been widely explored as therapeutic agents for managing these conditions [119,120]. In line with these therapeutic strategies, Ölmez et al. synthesized a series of novel 1,2,4-oxadiazole thioether derivatives and evaluated their inhibitory potential against AChE and BChE [121]. Among them, **120** (Fig. 17) exhibited the most potent inhibition of AChE ($IC_{50} = 0.95$ μM) and BChE ($IC_{50} = 1.49$ μM), surpassing donepezil ($IC_{50} = 1.25$ μM for AChE and 1.71 μM for BChE). Molecular docking studies confirmed strong interactions between **120** and enzyme active sites, showing π-π stacking, hydrogen bonding, and hydrophobic interactions, particularly with key residues in AChE, and BChE. ADMET analysis identified **120**, along with **121**, **122**, **123**, and **124** (Fig. 17), as having favorable drug-like properties, including high gastrointestinal absorption and minimal CYP inhibition. These findings suggest that **120** is a promising multifunctional enzyme inhibitor with potential applications in neurodegenerative diseases.

Zhang et al. synthesized and evaluated a series of coumarin-1,2,4-oxadiazole hybrids as selective butyrylcholinesterase (BChE) inhibitors with neuroprotective activity [122]. Among them, enantiomers **125** and **126** (Fig. 17) exhibited the most potent BChE inhibitory activity, with IC_{50} values of 8.17 μM and 9.56 μM, respectively. Both compounds showed high selectivity for BChE over acetylcholinesterase (AChE), with selectivity ratios of 9.49 and 7.58, respectively. Additionally, **125** and **126** demonstrated significant neuroprotective effects in SH-SY5Y cells against $A\beta_{25-35}$-induced neurotoxicity, with cell viability recovery rates of 28.39 % and 30.68 % at 10 μM and 18.84 % and 15.91 % at 1 μM, respectively. These results suggest that **125** and **126** may serve as promising multifunctional agents for the treatment of Alzheimer's disease by combining BChE inhibition with neuroprotection.

Another study by Liu et al. in which they synthesized a novel series of (4-(1,2,4-oxadiazol-5-yl)phenyl)-2-aminoacetamide derivatives as multifunctional agents for Alzheimer's disease treatment [123]. Among them, **127** (Fig. 17) demonstrated the most potent biological activity,

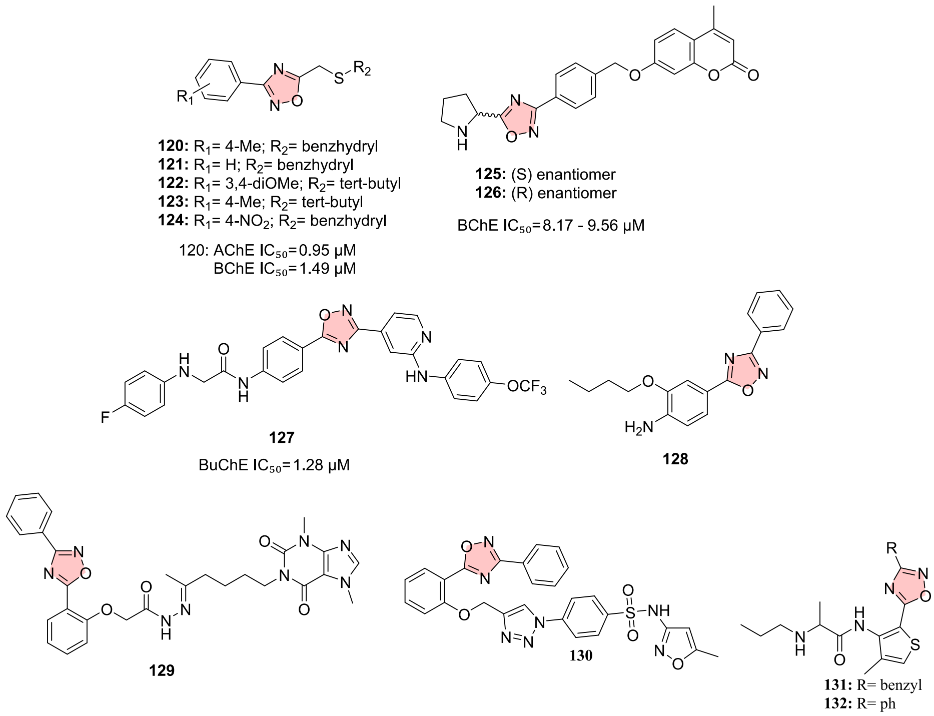


Fig. 17. Structures of compounds **120–132** with activity against Alzheimer's disease.

exhibiting a BuChE inhibitory IC_{50} of 1.28 μM and effectively inhibiting neuroinflammation by reducing NO, IL-1β, and TNF-α production with IC_{50} values of 0.67 μM, 1.61 μM, and 4.15 μM, respectively. Additionally, **127** prevented Aβ self-aggregation by 51.91 and exhibited antioxidant properties by scavenging DPPH radicals and reducing intracellular ROS production. Molecular docking and enzyme kinetic studies revealed that **127** acted as a mixed-type inhibitor of BuChE, forming key hydrogen bonds with active site residues. Furthermore, **127** displayed proper blood-brain barrier permeability and significantly improved memory and cognitive functions in a scopolamine-induced Alzheimer's mouse model at an oral dose of 10 mg/kg. These results suggest that **127** is a promising lead compound for the development of multifunctional anti-Alzheimer's agents.

Ayoup et al. synthesized a series of novel 1,2,4-oxadiazole derivatives and evaluated their potential as multitarget agents for Alzheimer's disease [124]. The biological assessment demonstrated that several compounds exhibited strong acetylcholinesterase (AChE) inhibition, with most of the compounds displaying IC_{50} values ranging from 0.0158 to 0.121 μM, making them up to 7.78 times more potent than donepezil ($IC_{50} = 0.123$ μM). While butyrylcholinesterase (BuChE) inhibition was generally weaker, **128** and **129** (Fig. 17) showed notable activity ($IC_{50} = 11.50$ and 15 μM, respectively). Additionally, **128** and **130** exhibited superior antioxidant activity compared to ascorbic acid, while **131** and **132** (Fig. 17) demonstrated monoamine oxidase-B (MAO-B) inhibition, with **130** being 3.55 times more potent than biperiden. Molecular docking studies supported the strong interactions of the most active compounds with the AChE active site.

In a subsequent study, Ayoup et al. synthesized and evaluated a series of 1,2,4-oxadiazole derivatives as potential multifunctional agents for Alzheimer's disease [125]. Among the series, **133** (Fig. 18) emerged as the most potent AChE inhibitor, exhibiting an IC_{50} of 0.00098 μM, making it 125.47 times more potent than donepezil ($IC_{50} = 0.12297$ μM). Additionally, **133** demonstrated a moderate BuChE inhibition ($IC_{50} = 35.84$ μM), a significant antioxidant effect ($IC_{50} = 991.45$ μM in the DPPH assay), and moderate MAO-B inhibition ($IC_{50} = 346.03$ μM). Molecular docking studies revealed that **133** forms crucial interactions with AChE, including hydrogen bonding with Ser203 and arene interactions with Tyr341, Phe338, and Trp86. The compound also exhibited favorable physicochemical properties and drug-likeness, supporting its potential as a promising multi-target anti-AD candidate.

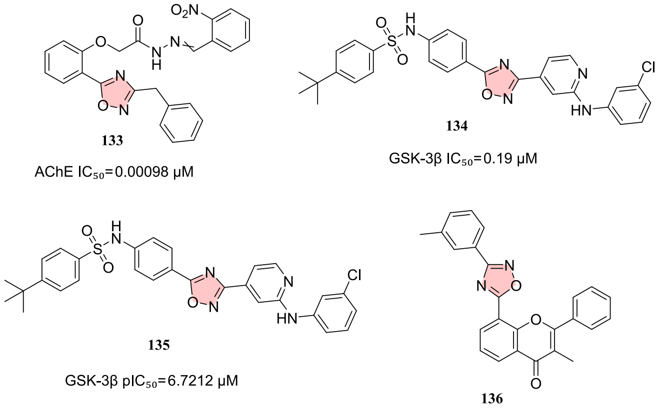


Fig. 18. Structures of compounds **133–136** with activity against Alzheimer's and Parkinson's diseases.

Expanding the therapeutic scope of 1,2,4-oxadiazole derivatives, Wang et al. investigated their potential as GSK-3β inhibitors, another emerging target in Alzheimer's disease therapy [126]. They synthesized a series of 3-(4-pyridyl)-5-(4-sulfamido-phenyl)-1,2,4-oxadiazole derivatives as novel glycogen synthase kinase-3β (GSK-3β) inhibitors and evaluated their potential as multifunctional anti-Alzheimer agents. Among them, **134** (Fig. 18) exhibited the most potent GSK-3β inhibition with an IC_{50} of 0.19 μM, significantly superior to other tested compounds. Additionally, **134** demonstrated strong anti-neuroinflammatory effects, reducing NO production in LPS-induced BV2 microglial cells ($IC_{50} = 6.94$ μM). It also enhanced glucose consumption in HepG2 cells, surpassing the positive control metformin. Further in vitro assays confirmed that **134** inhibited Aβ-induced tau hyperphosphorylation and exhibited antioxidative properties by reducing intracellular ROS levels. Molecular docking studies indicated that **134** effectively binds to the

ATP pocket of GSK-3β through hydrogen bonding with Arg141 and Tyr134. Notably, **134** displayed proper blood-brain barrier permeability and significantly improved cognitive impairment in a scopolamine-induced Alzheimer's mouse model at an oral dose of 10 mg/kg. These results suggest that **134** is a promising multifunctional candidate for the treatment of Alzheimer's disease.

To further guide the rational design of GSK-3β inhibitors, Sun et al. developed robust and predictive 3D-QSAR models for evaluating the activity of novel oxadiazole derivatives as multifunctional anti-Alzheimer agents, specifically targeting GSK-3β [127]. Among the studied compounds, **135** (Fig. 18) exhibited the highest inhibitory activity, with n pIC_{50} of 6.7212 μM, demonstrating superior potency compared to other tested derivatives. The study employed comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA), resulting in significant predictive models with cross-validated correlation coefficients ($Rcv^2 = 0.692$ for CoMFA and 0.696 for CoMSIA) and high predictive accuracy ($Rpred^2 = 0.6885$ and 0.6887, respectively). Molecular docking and molecular dynamics simulations revealed that **135** forms stable interactions with key residues of GSK-3β, including Ile62, Asn64, Val70, Tyr128, Val129, and Leu182, contributing to its inhibitory activity. The study also identified crucial structural features influencing GSK-3β inhibition, providing valuable insights for designing more potent oxadiazole-based inhibitors for Alzheimer's disease therapy.

Beyond Alzheimer's disease, 1,2,4-oxadiazole derivatives have also been investigated for their therapeutic potential in Parkinson's disease (PD). Shen et al. designed and synthesized a series of 3-methyl-8-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenyl-4H-chromen-4-one derivatives by combining flavone and 1,2,4-oxadiazole scaffolds for the treatment of PD [128]. Among them, **136** (Fig. 18) exhibited the most potent anti-inflammatory and antioxidant activities, significantly inhibiting NO and ROS production in LPS-induced BV2 microglia cells by 64.2 % and 58.3 %, respectively. Further mechanistic studies revealed that **136** modulated microglial polarization by inhibiting the NF-κB and MAPK signaling pathways, shifting M1 pro-inflammatory microglia toward the anti-inflammatory M2 phenotype. In an MPTP-induced PD mouse model, **136** ameliorated motor and behavioral deficits and increased serum dopamine levels while reducing neuronal apoptosis. Western blot analysis confirmed that **136** downregulated pro-apoptotic markers (BAX, Caspase-3) and upregulated anti-apoptotic Bcl-2 expression. These findings suggest that **136** is a promising therapeutic candidate for PD by simultaneously targeting neuroinflammation, oxidative stress, and neuronal survival.

2.8. Antiepileptic and anticonvulsant activity

Epilepsy and seizure disorders affect millions worldwide, often requiring long-term pharmacological intervention. Current treatments primarily target ion channels and neurotransmitter systems, yet drug resistance and side effects remain significant challenges [129,130]. As a result, there is growing interest in identifying novel therapeutic agents with improved efficacy and safety profiles. Among the promising scaffolds, 1,2,4-oxadiazole derivatives have emerged as potential modulators of key targets implicated in seizure control, including potassium and sodium channels, GABAergic neurotransmission, and neuroinflammation.

Qunies et al. designed and synthesized a series of 1,2,4-oxadiazole inhibitors targeting SLACK (KCNT1) potassium channels [131]. Among them, **137** (Fig. 19) was the most potent, with an IC_{50} of 0.32 μM in whole-cell electrophysiology assays and enhanced potency against the A934T SLACK mutant ($IC_{50} = 0.67$ μM). It exhibited strong selectivity, with no inhibition of SLICK ($IC_{50} > 10$ μM) or Maxi-K (inactive at 30 μM), and no hERG inhibition at 10 μM, reducing the risk of cardiotoxicity. In vitro pharmacokinetic profiling showed high plasma-protein binding ($fu < 0.01$) and moderate metabolic stability (26 % remaining after 10 min in mouse liver microsomes), though its rapid clearance may limit in vivo applications. These findings establish **137** as a valuable in vitro tool for investigating SLACK channel modulation in epilepsy research.

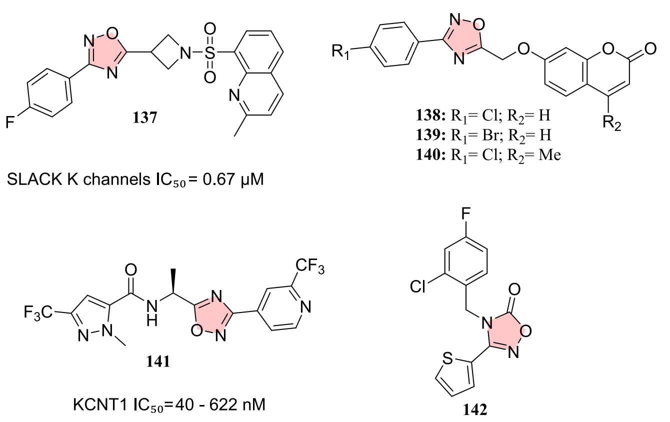


Fig. 19. Structures of compounds **137–142** with anticonvulsant activities.

Mohammadi-Khanaposhtani et al. synthesized a series of coumarin-1,2,4-oxadiazole hybrids and evaluated their anticonvulsant potential [132]. Compound **138** (Fig. 19) showed the greatest potency in the MES test, completely preventing seizures at 7 mg/kg, whereas **139** and **140** (Fig. 19) required 40 mg/kg and 20 mg/kg, respectively, to provide full protection. In contrast, most compounds showed weak or no activity in the pentylenetetrazole (PTZ) test. Mechanistic studies confirmed that the anticonvulsant activity of **138** was significantly reduced by flumazenil, indicating its interaction with benzodiazepine (BZD) receptors. Molecular docking studies further supported its binding to the BZD site of the GABA_A receptor, with key interactions including hydrogen bonds and π-π stacking with active site residues. In vivo neurotoxicity assessments revealed that **138** and **139** had lower neurological deficits than diazepam in the rotarod test.

Griffin et al. developed the first orally available, selective KNa1.1 (KCNT1) inhibitor, aiming to treat KCNT1 gain-of-function (GoF) epilepsy [133]. Among the synthesized oxadiazole derivatives, **141** (Fig. 19) was the most potent, exhibiting an IC_{50} of 40 nM against human KNa1.1-WT and 622 nM against the mouse ortholog. In vivo, **141** significantly reduced seizure frequency and interictal spikes in a KCNT1 GoF mouse model following a single 30 mg/kg subcutaneous dose. Pharmacokinetic studies revealed excellent brain penetration, high oral bioavailability, and a long half-life (>20 h). **141** demonstrated high selectivity, with minimal activity against other ion channels, including hERG ($IC_{50} = 11.9$ μM) and KNa1.2 ($IC_{50} = 16.4$ μM). Further, it did not impair locomotor activity, suggesting a favorable therapeutic window. These results establish **141** as a promising candidate for KCNT1-related epilepsy, warranting further preclinical development.

Hwang et al. identified **142**, a 1,2,4-oxadiazole derivative (Fig. 19), as a promising anti-seizure agent through phenotype-based screening in zebrafish and mouse models [134]. **142** significantly reduced seizure-like behaviors in pentylenetetrazole (PTZ)-induced zebrafish larvae and decreased seizure-specific EEG events in adult zebrafish. In PTZ-induced seizure mice, **142** reduced seizure severity based on the modified Racine's scale. Electrophysiological studies revealed that **142** preferentially binds to voltage-gated Na^+ channels, shifting V_{50} values toward hyperpolarized states and accelerating fast inactivation. Pharmacokinetic studies demonstrated that **142** effectively penetrates the blood-brain barrier, with a brain-to-plasma ratio of 1.70 in mice and 2.13 in zebrafish. These findings suggest that **142** is a strong candidate for further development as a novel anti-seizure drug.

Building on this initial characterization, Kim et al. further investigated the neurochemical and neuroprotective effects of **142** in the PTZ-induced epileptic seizure zebrafish model [135]. Their study revealed that **142** mitigates PTZ-induced epileptic behaviors by restoring neurotransmitter and neurosteroid imbalances, including upregulation of 5-hydroxytryptamine, 17-β-estradiol, dihydrotestosterone, progesterone, 5α-dihydroprogesterone, and allopregnanolone, while downregulating normetanephrine, GABA, and cortisol levels in brain tissue. Additionally, **142** exhibited neuroprotective effects by scavenging reactive oxygen species (ROS), reducing oxidative stress, and increasing zebrafish survival rates. These findings highlight the compound's dual mechanism of action, combining anti-epileptic and antioxidant properties, further reinforcing its potential as a novel anti-seizure agent.

2.9. Structure–activity relationship of 1,2,4-Oxadiazole derivatives with neuroprotective and anticonvulsant activities

1,2,4-Oxadiazole derivatives have demonstrated potent multifunctional activity in neurodegenerative and seizure-related disorders, acting as cholinesterase inhibitors, GSK-3β modulators, and KNa1.1 (SLACK) potassium channel blockers. SAR analysis revealed that aryl or heteroaryl substitution at the 3- or 5-position enhanced target affinity, particularly when combined with lipophilic or electron-donating groups. In Alzheimer's models, coumarin–oxadiazole hybrids selectively inhibited BChE, with docking showing key hydrogen bonds with Ser198 and His438 and π–π stacking within the catalytic gorge. Aminoacetamide-linked analogs targeting GSK-3β interacted with ATP-pocket residues Val135 and Asp133, while sulfonamide-bearing analogs improved polarity and orientation. In Parkinson's disease models, flavone–oxadiazole hybrids attenuated neuroinflammation, supported by predicted interactions with iNOS and COX-2 active sites. For epilepsy, halogenated oxadiazole derivatives selectively inhibited KNa1.1 channels, with docking revealing hydrophobic contacts within the S6 helix and positioning of the oxadiazole ring against key gating residues. Coumarin–oxadiazole anticonvulsants demonstrated in vivo seizure protection and docked stably within the channel vestibule, forming van der Waals interactions that blocked ion conduction. The oxadiazole scaffold played a pivotal role in maintaining planarity, ensuring precise orientation within binding pockets across all CNS targets.

2.10. Other activities

Beyond their well-established roles in anticancer, antimicrobial, and neurological applications, 1,2,4-oxadiazole derivatives have also demonstrated diverse biological activities across multiple therapeutic areas. For instance, Brotschi et al. designed and synthesized a series of 1,2,4-oxadiazole derivatives as dual orexin receptor antagonists (DORAs) with potential sleep-promoting properties [136]. The highest orexin receptor antagonistic potency was observed in **143** (Fig. 20), which recorded IC_{50} values of 27 nM (OX_1R) and 3 nM (OX_2R). **143** demonstrated high brain penetration in rats, with a brain-to-plasma ratio of 1.62 and cerebrospinal fluid exposure of 19.8 ng/mL. In EEG/EMG studies, **143** significantly reduced wakefulness (−24 %) while increasing non-REM (+14.3 %) and REM sleep (+35.2 %) over 12 h, performing comparably to suvorexant. Pharmacokinetic profiling in rats and dogs confirmed good oral bioavailability (10 % in rats, 43 % in dogs) and moderate metabolic stability.

Beyond sleep disorders, 1,2,4-oxadiazole derivatives have also been explored as modulators of immune function. Liu et al. identified a series of oxadiazole-based sphingosine-1-phosphate receptor 1 ($S1P_1$) agonists with high potency and selectivity over $S1P_3$ [137]. Among them, **144** (Fig. 20) exhibited the strongest activity, with an EC_{50} of 0.46 nM, while **145** (Fig. 20) showed similar potency (EC_{50} = 0.47 nM). Both compounds induced robust lymphocyte reduction (~90 % decrease) following oral administration in mice at 3 mg/kg, with rapid onset and full recovery within 24 h. Pharmacokinetic profiling revealed favorable bioavailability (50.31 % for **145**) and desirable physicochemical properties. Notably, neither compound significantly affected heart rate at 10 mg/kg, mitigating cardiovascular risks associated with $S1P_3$ activation. Molecular docking studies confirmed strong binding interactions with key residues, supporting their high $S1P_1$ selectivity.

1,2,4-oxadiazole derivatives have also been investigated for their role in pain management. Cao et al. synthesized a series of phenyl-1,2,4-oxadiazole derivatives as sigma-1 (σ_1) receptor ligands and evaluated their potential for neuropathic pain treatment [138]. Exhibiting the highest affinity for the σ_1 receptor, **146** (Fig. 20) recorded a K_i of 0.28 nM while maintaining a 587.1-fold selectivity over the σ_2 receptor. In vivo, **146** demonstrated dose-dependent anti-allodynic activity in a formalin-induced pain model and significantly attenuated mechanical allodynia in chronic constriction injury (CCI)-induced neuropathic rats. Moreover, **146** showed low affinity for other CNS neurotransmitter receptors, reducing potential side effects. These findings suggest that **146** is a promising σ_1 receptor antagonist with potent analgesic properties for neuropathic pain management.

1,2,4-oxadiazole derivatives have also shown potential in addressing genetic disorders. Pibiri et al. optimized a series of 1,2,4-oxadiazole-based translational readthrough-inducing drugs (TRIDs) to restore cystic fibrosis transmembrane conductance regulator (CFTR) expression and functionality in cystic fibrosis (CF) cell models [139]. The highest readthrough efficiency was observed in **147**, **148**, and **149** (Fig. 20), which surpassed ataluren at 12 μM and showed increased potency at 24 μM. In Fisher rat thyroid (FRT) cells expressing CFTR nonsense

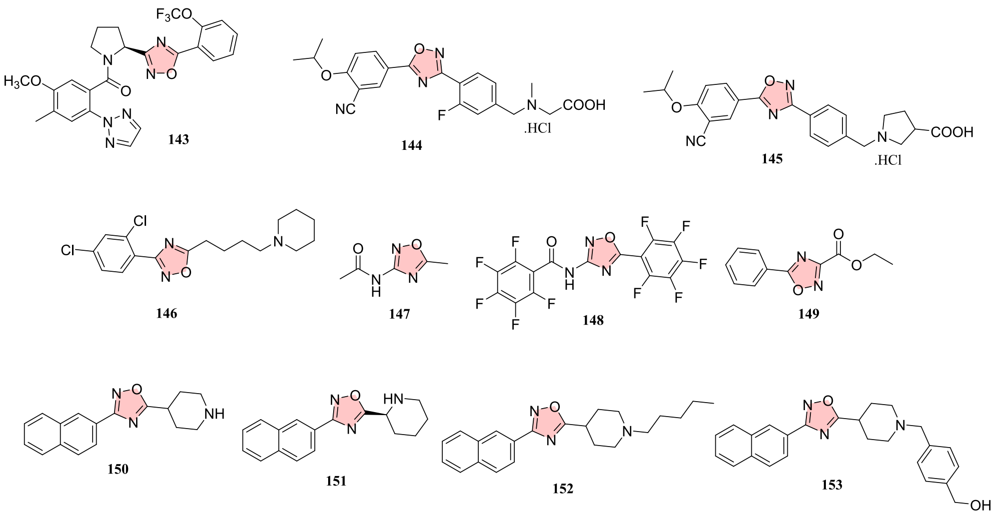


Fig. 20. Structures of compounds **143–153** with miscellaneous activities.

mutations (G542X and W1282X), these compounds restored CFTR protein expression and localization at the plasma membrane, as confirmed by immunofluorescence and Western blot analyses. Functional assays using halide-sensitive yellow fluorescent protein (YFP) demonstrated that **149** was the most effective at rescuing CFTRW1282X function, while **147** and **148** showed superior activity in CFTRG542X cells. Notably, all three compounds exhibited low cytotoxicity compared to ataluren. These findings suggest that **147**, **148**, and **149** are promising TRIDs for CF therapy, warranting further preclinical evaluation.

In addition to their role in genetic disorders, 1,2,4-oxadiazole derivatives have also been investigated for their potential in metabolic regulation. Festa et al. synthesized and evaluated a series of 3,5-disubstituted 1,2,4-oxadiazole derivatives as potent and selective farnesoid X receptor (FXR) antagonists [140]. Compounds **150** and **151** (Fig. 20), characterized by a piperidine ring, emerged as the most potent FXR antagonists, displaying IC_{50} values of 0.58 μM and 0.127 μM, respectively. Neither compound exhibited agonistic activity, and **150** was identified as the most promising due to its excellent metabolic stability (76 % remaining after 40 min of liver microsome incubation). Molecular docking studies revealed that **150** and **151** bind to the FXR ligand-binding domain, disrupting coactivator recruitment. Further, **150** effectively downregulated FXR target genes such as SHP, OSTα, PEPCK, and GC6P in HepG2 cells. These results suggest that **150** represents a promising lead for FXR-targeted therapies in metabolic disorders.

Finamore et al. expanded on the previous work in the development of 1,2,4-oxadiazole derivatives as FXR antagonists. While the earlier study identified **150** as a potent FXR antagonist (IC_{50} = 0.58 μM) with metabolic stability, the current work further modified the oxadiazole core to explore dual FXR/PXR modulation [141]. Among the newly synthesized compounds, **152** and **153** (Fig. 20) emerged as the first nonsteroidal dual FXR antagonists and pregnane X receptor (PXR) agonists, with IC_{50} values of 8.4 μM and 4.4 μM for FXR, and EC_{50} values of 6.4 μM and 7.5 μM for PXR, respectively. Both compounds modulated FXR- and PXR-regulated genes in HepG2 cells, showing potential applications in inflammatory disorders. Molecular docking studies confirmed their binding to FXR and PXR, rationalizing their dual activity. These findings build upon the previous study, further expanding the scope of oxadiazole-based nuclear receptor modulators.

3. Conclusion

Recent advances underscore the therapeutic versatility of 1,2,4-oxadiazole derivatives across multiple disease areas. In oncology, many compounds exhibit submicromolar potency, with some overcoming drug resistance through multi-target mechanisms such as EGFR degradation and kinase inhibition. In antimicrobial research, oxadiazoles show strong activity against resistant pathogens, including *Mycobacterium tuberculosis* and MRSA, and effectively inhibit bacterial virulence factors like biofilm formation. Promising developments also extend to metabolic disorders, where derivatives act as potent α-glucosidase inhibitors and dual PPAR agonists with proven in vivo efficacy. Additionally, emerging neuroprotective agents combine cholinesterase and MAO-B inhibition with anti-inflammatory and antioxidant properties, addressing complex neurodegenerative pathways. Collectively, these findings highlight the oxadiazole scaffold as a privileged structure for designing multitarget agents with novel mechanisms and strong translational potential. Continued optimization and SAR-driven design are expected to yield next-generation therapeutics across oncology, infectious diseases, metabolic syndrome, and CNS disorders.

CRediT authorship contribution statement

Hussam Elddin Nabeih Khasawneh: Writing – original draft, Resources, Methodology. **Ali Abdulrazzaq Abdulhussein Alrikabi:** Writing – original draft, Validation, Data curation. **Amran M. AL-Erjan:** Resources, Investigation. **Mustafa Jawad Kadham:** Visualization, Validation. **Raed Fanoukh Aboqader Al-Aouadi:** Software, Resources. **Natrayan Lakshmaiya:** Software, Resources, Methodology. **Roziyeva Muhayyo:** Visualization, Methodology, Data curation. **Stefan Bräse:** Writing – review & editing, Project administration, Conceptualization. **Hadeer M. Farhan:** Writing – review & editing, Visualization, Methodology.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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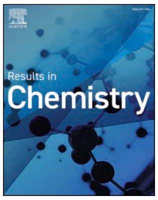

Corrigendum

Corrigendum to “Unveiling the therapeutic potential of 1,2,4-oxadiazole derivatives: An updated review” [Results Chem. 15 (2025) 102271]

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The authors regret that Mukhayya Djumaniyazova, from *Pedagogy and Psychology Department, Urganch State University, Uzbekistan*, was mistakenly omitted from the list of authors in the originally published version of the article, despite her contribution to the manuscript under the CRediT role: *Writing – review & editing*. Her inclusion was present in the initial submission metadata but was inadvertently removed during the revision process. She should be reinstated as a co-author.

The correct list of authors have been updated as above.

The authors would like to apologise for any inconvenience caused.

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