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REVIEW ARTICLE

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Research progress on the synthesis and pharmacology of 1,3,4-oxadiazole and 1,2,4-oxadiazole derivatives: a mini review

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ABSTRACT

Oxadiazole is a five-membered heterocyclic compound containing two nitrogen atoms and one oxygen atom. The 1,3,4-oxadiazole and 1,2,4-oxadiazole have favourable physical, chemical, and pharmacokinetic properties, which significantly increase their pharmacological activity *via* hydrogen bond interactions with biomacromolecules. In recent years, oxadiazole has been demonstrated to be the biologically active unit in a number of compounds. Oxadiazole derivatives exhibit antibacterial, anti-inflammatory, anti-tubercu-lous, anti-fungal, anti-diabetic and anticancer activities. In this paper, we report a series of compounds containing oxadiazole rings that have been published in the last three years only (2020–2022) as there was no report or their activities described in any article in 2019, which will be useful to scientists in research fields of organic synthesis, medicinal chemistry, and pharmacology.

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1. Introduction

Oxadiazole is a critical component of pharmacophores and ligand binding[1]. It is a heterocyclic aromatic linking group capable of connecting a variety of substituents and exhibits the same biological activity as esters, amides and carbamates[2]. While 1,2,3-oxadiazole is unstable, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole are all common and have been commercialised. Among them, 1,3,4-oxadiazole and 1,2,4-oxadiazole are important heterocyclic compounds with significant biological activity. Their synthesis has been the focus of our attention for a long time[3–5]. It has been reported that 1,3,4-oxadiazole and 1,2,4-oxadiazole derivatives possess antibacterial, anti-inflammatory, anti-tubercular, anti-HIV, antifungal, cathepsin K (Cat K) inhibitory, monoamine oxidase inhibitory, anti-diabetic, tyrosinase inhibitory, antioxidant and anticancer activities[6–8]. The majority of commercially available antihypertensive agents such as Tiodazosin and Nesapidil, as well as antibiotics such as Furamizole, contain the oxadiazole nucleus[9–10]. This article aims to describe the different derivatives of oxadiazole and their activities.

2. Oxadiazole

2.1. 1,3,4-Oxadiazole

2.1.1. Binding of triazoles to 1,3,4-oxadiazoles

Ustabas et al. synthesised a novel hybrid molecule containing 1,2,4-triazole and 1,3,4-oxadiazole, which exhibited stronger antibacterial and antiparasitic effects *in vitro*. The bacteriostatic and antiparasitic activities of the newly synthesised compounds were investigated using the microdilution broth method with Alamar blue. According to the test results, compound 1 (Figure 1) exhibited superior bacteriostatic activity (MIC = 5000 μg/mL) against *Citrobacter freundii*, *Haemophilus influenzae* and *S. pneumoniae isolates* and antileishmanial activity (MIC = 1250 μg/mL) against *Leishmania* major promastigotes compared to standard drug Amphotericin B (MIC < 312 μg/mL), indicating that the compound is suitable for further investigation[11].

Kashid et al. synthesised a series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives. The preliminary anti-oxidation and anti-inflammatory *in vitro* screening results indicated that compound 2 (Figure 1) had a strong antioxidant activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH) with an IC_{50} value of 23.07 ± 0.27 μM when compared it with synthetic antioxidant Diclofenac sodium (IC_{50} = 90.21 ± 0.77 μM), but the nitric oxide free radical scavenging activity was poor (IC_{50} = 88.04 ± 0.71 μM). Additionally, molecular docking studies revealed that all compounds have a high affinity for the COX-2 enzyme, providing an important starting point for structure-based drug design, resulting in the development of a series of novel derivatives with strong anti-inflammatory activity compared with synthetic antioxidant Diclofenac sodium[12].

Alam et al. synthesised nine compounds containing 1,2,3-triazole and 1,3,4-oxadiazole and evaluated their anticancer and *in vitro* thymidylate synthase activities. The results showed that compounds **3a** and **3b** (Figure 1) exhibited significant inhibitory effects on MCF-7 and HCT-116 cells. The inhibitory activity of compound **3a** on MCF-7 cells was 4-fold than that of the standard drug 5-Fluorouracil (IC_{50} = 24.74 μM) which was comparable to that of Tamoxifen (IC_{50} = 5.12 μM), while compound 13 was 5-fold than that of Tamoxifen and 24-fold than that of 5-Fluorouracil on MCF-7 cells. Compounds **3a** and **3b** inhibited thymidylate synthase (TS) with IC_{50} values of 2.52 μM and 4.38 μM compared to

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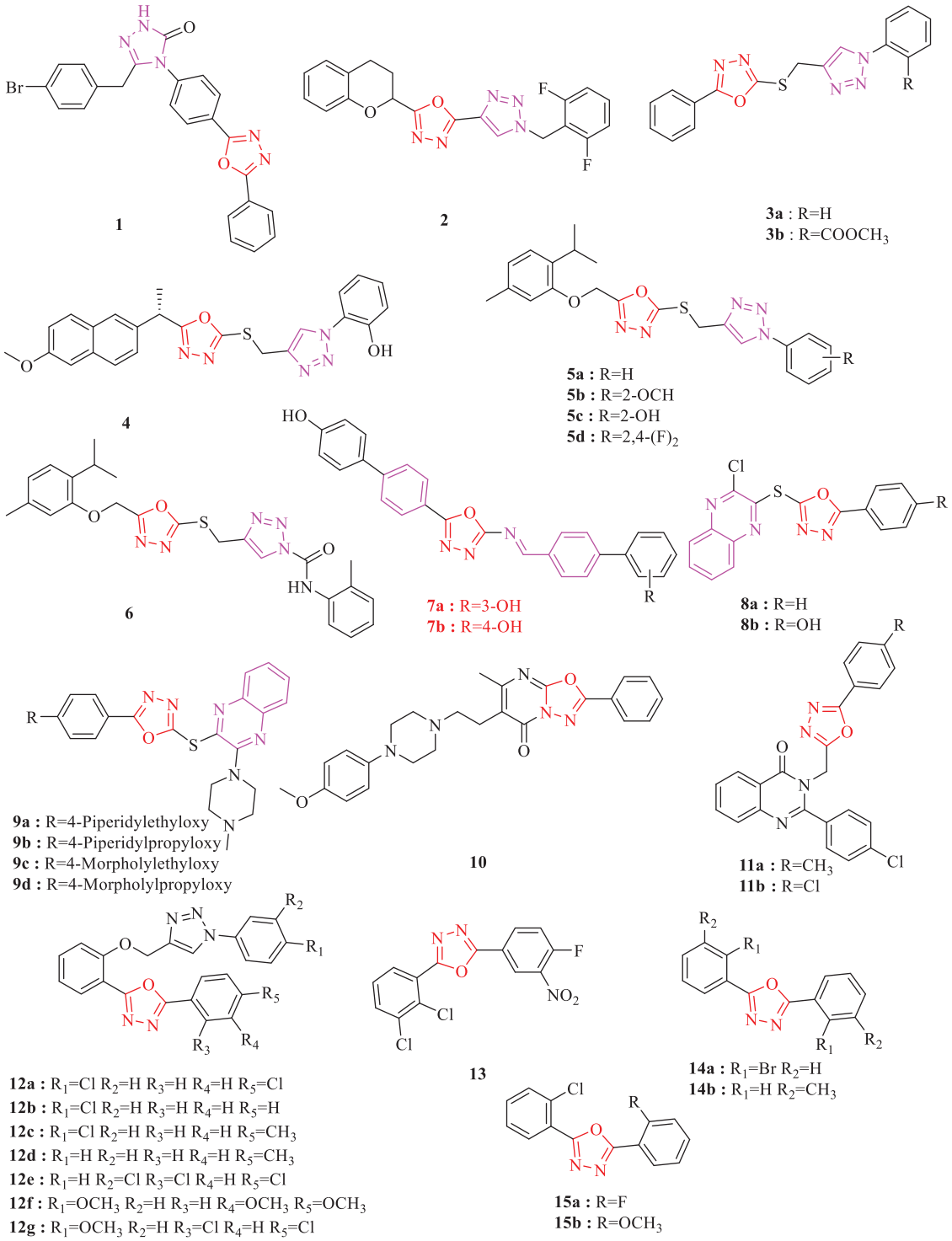

Figure 1. Derivatives of 1,3,4-oxadiazole ring.

the standard drug Pemetrexed (IC_{50} = 6.75 μM). In conclusion, compounds **3a** and **3b** can serve as candidate lead compounds[13].

Alam et al. synthesised a series of novel naproxen based 1,3,4-oxadiazole derivatives and screened their cytotoxicity as EGFR inhibitors. Among them, compound **4** (Figure 1) was the most potent compound against MCF-7 and HepG2 cells with IC_{50} values of 2.13 and 1.63 μg/mL, respectively, which was comparable to Doxorubicin (MCF-7: IC_{50} = 1.62 μg/mL, HepG2: IC_{50} = 1.62 μg/mL). In addition, compound 4 inhibited EGFR kinase with an IC_{50} value of 0.41 μM compared to the standard drug Erlotinib (IC_{50} = 0.30 μM). The results showed that these synthetic naproxen hybrids have EGFR inhibition and can serve as leads for cancer therapy[14].

Almalki et al. synthesised a series of 1,2,3-triazole-incorporated thymol-1,3,4-oxadiazole derivatives and tested their anticancer and antibacterial activities. The results showed that compound **5c** (Figure 1) exhibited significant antiproliferative activity against MCF-7, HCT-116 and HepG2 cell lines, with IC_{50} values of 1.1, 2.6 and 1.4 μM, respectively, which were superior to Doxorubicin (MCF-7: IC_{50} = 1.2 μM, HCT-116: IC_{50} = 2.5 μM, HepG2: IC_{50} = 1.8 μM) and 5-Fluorouracil (MCF-7: IC_{50} = 18.74 μM, HCT-116: IC_{50} = 30.68 μM, HepG2: IC_{50} = 28.65 μM). These compounds showed

anticancer activity by inhibiting TS, as they showed significant TS inhibitory activity with IC_{50} values in the range of 1.95–4.24 μM, compared with the standard drug Pemetrexed (IC_{50} = 7.6 μM). The antibacterial results showed that some compounds **5a**, **5b**, **5c**, **5d** and **6** (Figure 1) exhibited good inhibitory effects on *Escherichia coli* and *Staphylococcus aureus*[15].

2.1.2. Aryl-1,3,4-oxadiazole schiff bases

Ullah et al. synthesised eighteen aryl-1,3,4-oxadiazole derivatives bearing Schiff bases and assessed their inhibitory effect against α-glucosidase. All of the synthesised derivatives exhibited good inhibitory activity against α-glucosidase. They discovered that two of these compounds had a significantly greater inhibitory effect against α-glucosidase than that of the standard drug Acarbose, and compounds **7a** (IC_{50} = 0.6 ± 0.05 μM) and **7b** (IC_{50} = 0.30 ± 0.2 μM, Figure 1) had more than hundredfold inhibitory activity against α-glucosidase compared with the standard inhibitor Acarbose (IC_{50} = 38.45 ± 0.80 μM). SAR analysis revealed that compounds with *ortho*- and *para*-hydroxyl groups were more active than those with nitro and chloro groups. Molecular docking studies confirmed the binding sites and interactions between ligands and enzymes. Therefore, structural modification of active compounds may facilitate the discovery of promising antidiabetic lead compounds[16].

2.1.3. Quinoxaline-1,3,4-oxadiazole hybrid derivatives

Ono et al. synthesised a series of quinoxaline-1,3,4-oxadiazole hybrid derivatives and evaluated their anticancer activity against human leukaemia HL-60 cells. While these compounds have a significant inhibitory effect on HL-60 cell proliferation, they are highly cytotoxic to normal human cells. Compounds **8a** and **8b** (Figure 1) can significantly inhibit cell proliferation when compared to the positive control XK469. Even at a concentration of 10 μM, compounds **8a** and **8b** exhibited strong anti-proliferative effects, with cell viability less than 10% of that of the control drug. They are, however, toxic to normal human fibroblast WI-38 cells (cell viability **8a**: 1.8 ± 0.2%; **8b**: 2.9 ± 0.2%). Therefore, the quinoxaline-1,3,4-oxadiazole compounds must be further optimised. To better identify the optimised molecules, compounds **9a**, **9b**, **9c** and **9d** (Figure 1) had obtained by linking the quinoxaline frameworks to phenyl, piperazine, piperidine, and morpholine. The optimised compound successfully induced apoptosis in HL-60 cells and had low toxicity on WI-38 cells. Additionally, RT-PCR analysis revealed that these compounds mainly inhibited Bcl-2expression, with Bcl-2 relative mRNA expression levels less than 10% of the untreated level. Compounds **9a**, **9b**, **9c** and **9d** had inhibition rates of 98.3%, 97.9%, 98.2% and 98.0% on HL-60 cell, respectively. The results of the study indicated that compounds **9a–d** had great potential as proapoptotic anticancer agents[17].

2.1.4. 1,3,4-Oxadiazole conjugated pyrmidinones

Said et al. synthesised a series of new oxadiazole conjugated pyrmidinones compounds and tested their analgesic activity. All compounds showed good analgesic activity when compared to the standard Indomethacin. Among all of them, compound 10 (Figure 1) had the highest analgesic activity with 100% protection surpassing that of Indomethacin (83.33%protection). Moreover, compound 10 was evaluated for anti-inflammatory activity, ulcerative, and *in vitro* COX-1 and COX-2 enzyme inhibition tests. The results showed that compound 10 had good anti-inflammatory activity, relatively low ulcer index (ulcer index = 3.8), and strong inhibitory activity on COX-1 and COX-2 (COX-1: IC_{50} = 0.140 ± 2.38 μM, COX-2: IC_{50} = 0.007 ± 0.11 μM) compared with the standard drug Indomethacin[18].

2.1.5. 1,3,4-Oxadiazole linked benzopyrimidinones conjugates

Chortani et al. synthesised new 1,3,4-oxadiazole bibenzopyrimidine compounds and evaluated their antibacterial properties. Compounds **11a** and **11b** (Figure 1) had MIC values of between 111.3 and 10.8 μM against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Their MIC values against *Candida albicans* were 10.8 and 27.8 μM, respectively, indicating good antibacterial activity[19].

2.1.6. 2,5-Substituted 1,3,4-oxadiazoles

Bitla et al. successfully synthesised a series of novel 2,5-diaryl substituted 1,3,4-oxadiazole derivatives using methyl salicylate as the starting material. All compounds had antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis*, and antifungal activity against *Aspergillus niger* and *Saccharomyces cerevisiae*. Compared with standard antibacterial drugs, it was worth noting that the compounds effectively inhibited the growth of microorganisms. Among the compounds tested, compounds **12a–e** (Figure 1) showed the strongest antifungal activity with MIC values between 5 and 8.9 μg/mL against *Bacillus subtilis* (*MTCC 441*) and *Staphylococcus aureus* (*MTCC 96*), while compounds 12f (*MTCC 441*: MIC = 5.7 μg/mL, *MTCC 96*: MIC = 8.8 μg/mL) and 12 g (*MTCC 441*: MIC = 5.5 μg/mL, *MTCC 96*: MIC = 7.9 μg/mL, Figure 1) were also found to be effective against the growth of gram-positive bacteria compared with standard antibacterial agents Ampicillin[20].

Ningegowda et al. synthesised a series of 2–(2,3-dichlorophenyl)-5-aryl- 1,3,4-oxadiazole derivatives and assessed their antimycobacterial activity against Mycobacterium tuberculosis H37RvMa strain. Compound **13** (Figure 1) exhibited good antituberculosis activity at a concentration of 62.5 μg/mL, and its pharmacophore can be optimised to generate a series of improved anti-tuberculosis lead compounds containing the 1,3,4-oxadiazole ring[21].

Zabiulla et al. synthesised a series of 2,5-disubstituted 1,3,4-oxadiazole derivatives with biological activity and screened their antibacterial, antifungal and antioxidant activities. Compound **14a** and **14b** (Figure 1) showed significant antibacterial activity against both gram-positive bacteria and gram-negative bacteria, as well as good antifungal activity. Additionally, all compounds were evaluated *in vitro* for antioxidant activity using DPPH, NO, H_2O_2, LPO and other methods. Among them, compound **14b** (Figure 1) has strong antioxidant activity with an IC_{50} value of 15.15 μg/mL compared with the standard drug Ascorbic acid[22].

Bajaj et al. designed and synthesised a novel 1,3,4-oxadiazole derivative with a substituted benzene ring, and determined the cytotoxicity of the compound against two breast cancer cell lines MCF-7 and MDA-MB-231 using the MTT method. Compounds **15a** and **15b** (Figure 1) showed potential anti-cancer activity against MCF-7 with IC_{50} values of 2.5 ± 0.35 and 1.85 ± 0.28 μM compared with the standard Doxorubicin. Compounds **15a** and **15b** (Figure 1) showed potential anti-cancer activity against MDA-MB-231 with IC_{50} values of 4.88 ± 1.74 and 2.27 ± 0.73 μM compared with the standard drug Doxorubicin[23].

Fang et al. designed and synthesised a series of new 1,3,4-oxadiazole derivatives. The TR-FRET test revealed that these new small molecule inhibitors are effective against programmed cell death-1 (PD-1)/Programmed cell death-ligand 1 (PD-L1) blockade.

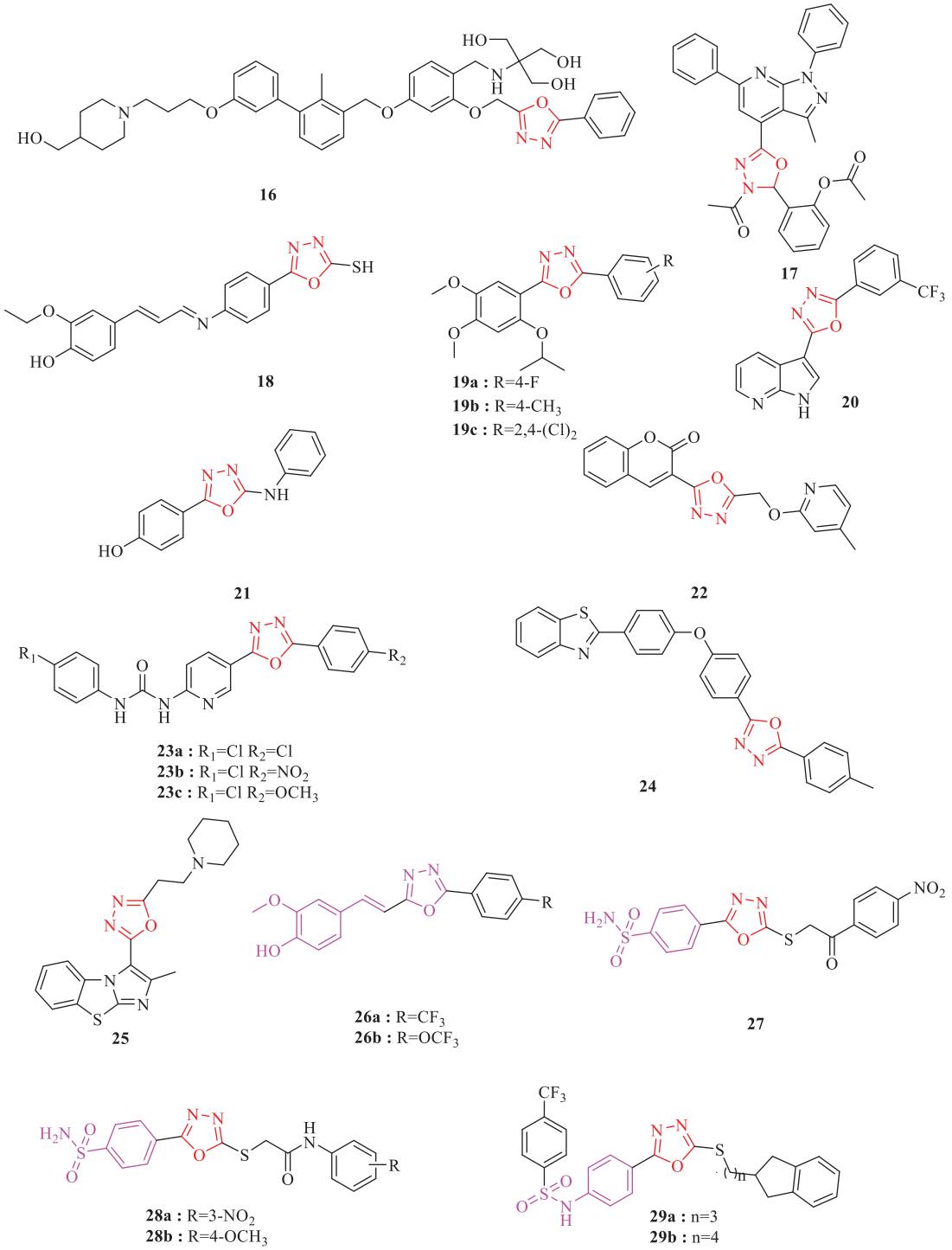

Figure 2. Derivatives of 1,3,4-oxadiazole ring.

Compound **16** (Figure 2) showed the best biochemical activity, with an IC_{50} of 0.0380 μM. Importantly, compound **16** had a TGI score of 35.74%. In addition, the TGI value of compound **16** in combination with 5-FU was 64.59% in a mouse tumour model, indicating a potential synergistic anti-tumour effect[24].

Ribeiro et al. synthesised compounds containing 2,3-dihydro-1,3,4-oxadiazole groups. Among them, compound **17** (Figure 2) showed significant *in vitro* activity against *Trypanosoma cruzi* amastigotes, and was tested in male BALB/c mice infected with the *Trypanosoma cruzi* Y strain. Research results showed that compounds containing 2,3-dihydro-1,3,4-oxadiazole groups had good active structures in the body. Compound 17 showed potential trypanocidal activity against *Trypanosoma cruzi* amastigotes with IC_{50} value of 1.11 ± 0.29 μM compared with the standard drug Benznidazole (IC_{50} = 3.98 ± 0.28 μM) [25].

Mehandi et al. synthesised a series of new oxadiazole heterocyclic derivatives and determined the antibacterial activity on *Candida albicans* using the broth dilution method. The results indicated that compound **18** (Figure 2) had significant antifungal activity, with a MIC value of 200 μg/mL, comparable to that of the standard drug Fluconazole[26].

Dhonnar et al. synthesised a series of 1,3,4-oxadiazole derivatives and screened the *in vitro* antibacterial activities of all compounds against two Gram-negative strains, namely *Escherichia coli*

and *Salmonella typhi* and two Gram-positive strains, namely *Bacillus subtilis* and *Bacillus megaterium* and antifungal activity against fungal strains such as *Aspergillus niger*, *Rhizopus oryzae*, *Penicillium chrysogenum* and *Candida albicans*. The synthesised compounds exhibited significant broad-spectrum of antibacterial and antifungal potential. Compared with standard drug Streptomycin, compounds **19a–c** (Figure 2) showed high antibacterial activity with very low MIC values between 3.9 and 31.25 μM. The synthesised compounds were also screened for free radical scavenging activity by OH and DPPH assays, which showed that they are good antioxidants. Furthermore, haemolysis studies showed that the series of 1,3,4-oxadiazole derivatives had little cytotoxicity compared to streptomycin[27].

Izgi et al. synthesised novel 1,3,4-oxadiazole derivatives and tested the *in vitro* inhibitory potential on α-glucosidase. The results showed that compound **20** (Figure 2) has an IC_{50} value of 0.46 ± 0.15 mM for GAA inhibition, which is still too low to compete with AC1[28].

Gond et al. synthesised a 5–(4-hydroxyphenyl)-2-(N-phenylamino)-1,3,4- oxadiazole (compound **21**, Figure 2) and determined the cytotoxic activity against Dalton's lymphoma cells using an MTT assay. Compound **21** showed good anticancer activity (IC_{50} = 50 μg/mL), superior to many reported compounds[29].

Jyothi et al. synthesised a series of novel 1,3,4-oxadiazole-containing coumarin analogs and screened the newly synthesised molecules on various cell lines such as ACHN, A375, SIHA, Skov3 and EAC by MTT and trypan blue assays. **T**he results showed that compound 22 (Figure 2) exhibited antiproliferative effects on EAC and Skov3 cell lines with IC_{50} values of 10.2 and 9.5 μM compared with the standard 5-Fluorouracil. In addition, studies have shown that compound 22 has a targeting effect on VEGF and can significantly inhibit the growth of ascites tumours, so it is a promising anticancer molecule[30].

Tok et al. designed and synthesised a series of 2,5-disubstituted-1,3,4- oxadiazole derivatives and determined their monoamine oxidase (MAO) inhibitory activity. The results showed these compounds had no MAO-A inhibitory activity, but exhibited potent MAO-B inhibitory activity in the range of 62% to 98%. Among them, compounds **23a–c** (Figure 2) showed potent MAO-B inhibitory activity with IC_{50} values of 0.039, 0.066, 0.045 μM, respectively[31].

Duhan et al. synthesised 1,3,4-oxadiazole derivatives and evaluated their *in vitro* inhibitory potential against α-amylase. Compound **24** (77.96 ± 2.06% at 50 μg/mL, 71.17 ± 0.60% at 25 μg/mL, 67.24 ± 1.16% at 12.5 μg/mL, Figure 2) was found to have the most potent inhibition compared to the positive control Acarbose (87.5 ± 0.74% at 50 μg/mL, 82.27 ± 1.85% at 25 μg/mL and 79.94 ± 1.88% at 12.5 μg/mL)[32].

Based on the structure of the Twist1 inhibitor harmine, Zhao et al. designed a series of 1,3,4-oxadiazole derivatives. The results showed that compound **25** (Figure 2) exhibited significant antiproliferative activity against A549 and H2228 cell lines, with IC_{50} values of 2.03 μM and 9.80 μM, respectively, which were superior to Harmine (A549: IC_{50} = 17.12 μM, H2228: IC_{50} = 31.06 μM). Overall, compound **25** was identified as a potential lead drug against advanced non-small cell lung cancer[33].

2.1.7. Ferulic acid based 1,3,4-oxadiazole hybrids

Tripathi et al. designed and synthesised thirty 1,3,4-oxadiazole derivatives based on ferulic acid, and evaluated them for their multifunctional inhibitory activity against acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and beta-secretase-1 (BACE-1). Compound **26a** (Figure 2) was the most effective AChE inhibitor (IC_{50} = 0.068 μM). The IC_{50} values of equipotent inhibition against BChE and BACE-1 were 0.218 μM and 0.255 μM, respectively. Compound **26b** (Figure 2) showed the strongest inhibitory effect on BChE and BACE-1 with IC_{50} values of 0.163 μM and 0.211 μM, respectively. Compounds **26a** and **26b** can be used in place of propidium iodide in PAS-AChEsince as they had good blood-brain barrier permeability in PAMPA experiment, and their anti-Aβ aggregation activity in the self and AChE induction experiments showed neuroprotective activity on neuroblastoma SH-SY5Y cells. *In vitro* studies had shown that these compounds have inhibitory AChE and antioxidant activity. In addition, the strongest activity of compound **26a** may be attributed to the presence of a strong electron-withdrawing group on the terminal phenyl group, which is capable of penetrating the CAS-AChE. Compound **26a** exhibited a constant binding affinity for PAS-AChE and aspartate dyads of BACE-1. Furthermore, compound **26a** improved the learning and memory behaviour of the Aβ-induced Alzheimer's disease-like-phenotypic ICV rat model in the Morris water maze experiment, and pharmacokinetic studies confirmed the good oral absorption characteristics of the compounds. The overall findings suggest that compound **26a** may be a promising multifunctional lead drug candidate for the treatment of Alzheimer's disease[34].

2.1.8. Benzenesulfonamides incorporating 1,3,4-oxadiazole hybrids

Sharma et al. designed and synthesised benzenesulfonamides containing 1,3,4-oxadiazole hybrids as a novel selective inhibitor of carbonic anhydrase (hCA) I, II, IX and XII isoenzymes. Researchers determined the inhibitory activity of these compounds against the two dominant cytosolic isoforms hCA I/II and the tumour-associated isoforms hCA IX/XII. Compared with the positive control drug Acetazolamide (AAZ), the majority of the compounds had relatively weak inhibitory effects, with Ki values ranging from 469.6 nM to 3.89 mM, but compounds **27** (Ki = 70.7 nM, Figure 2) and **28a** (Ki = 73.2 nM, Figure 2) showed a stronger inhibitory effect on hCA I than on AAZ (Ki = 250 nM). Compound **28a** exhibited strong inhibitory activity against hCA II and hCA IX, and most of the compounds were moderately effective hCA XII inhibitors, with Ki values ranging from 230.6 to 3.62 mM. CA inhibition results indicated that 1,3,4-oxadiazole containing benzenesulfonamide with an amide tail/linker was a potent inhibitor of hCA IX. Therefore, compound **28b** (Ki = 29.0 nM, Figure 2) acts as a selective inhibitor of tumour-associated isoforms hCA IX[35].

Hamdani et al. synthesised new s-benzylation hybrids by combining 1,3,4-oxadiazole, and benzenesulfonamide in two distinct series and evaluating their efficacy against DENV2 NS2B/NS3pro. Preliminary studies found that compounds **29a** and **29b** (Figure 2) were dengue protease inhibitors, with IC_{50} values of 13.9 and 15.1 μM, respectively[36].

2.1.9. S-Alkylated-1,3,4-oxadiazole-sulphonamide hybrids

Javid et al. designed and synthesised a series of 10 different oxadiazole-sulphonamide hybrid compounds through a facile method. The synthesised products were evaluated for their potential inhibitory activity against two aldo-keto reductase family enzymes: ALR1 and ALR2. The majority of the compounds showed good activity, particularly **30a**, **30b**, **30c and 30d** (Figure 3). Compound **30a** inhibited ALR1 selectively with an IC_{50} value of 4.77 ± 0.47 μM, whereas compound **30c** inhibited ALR2 selectively with an IC_{50} value of 2.21 ± 0.73 μM. The remaining analogs inhibited both enzymes in tandem[37].

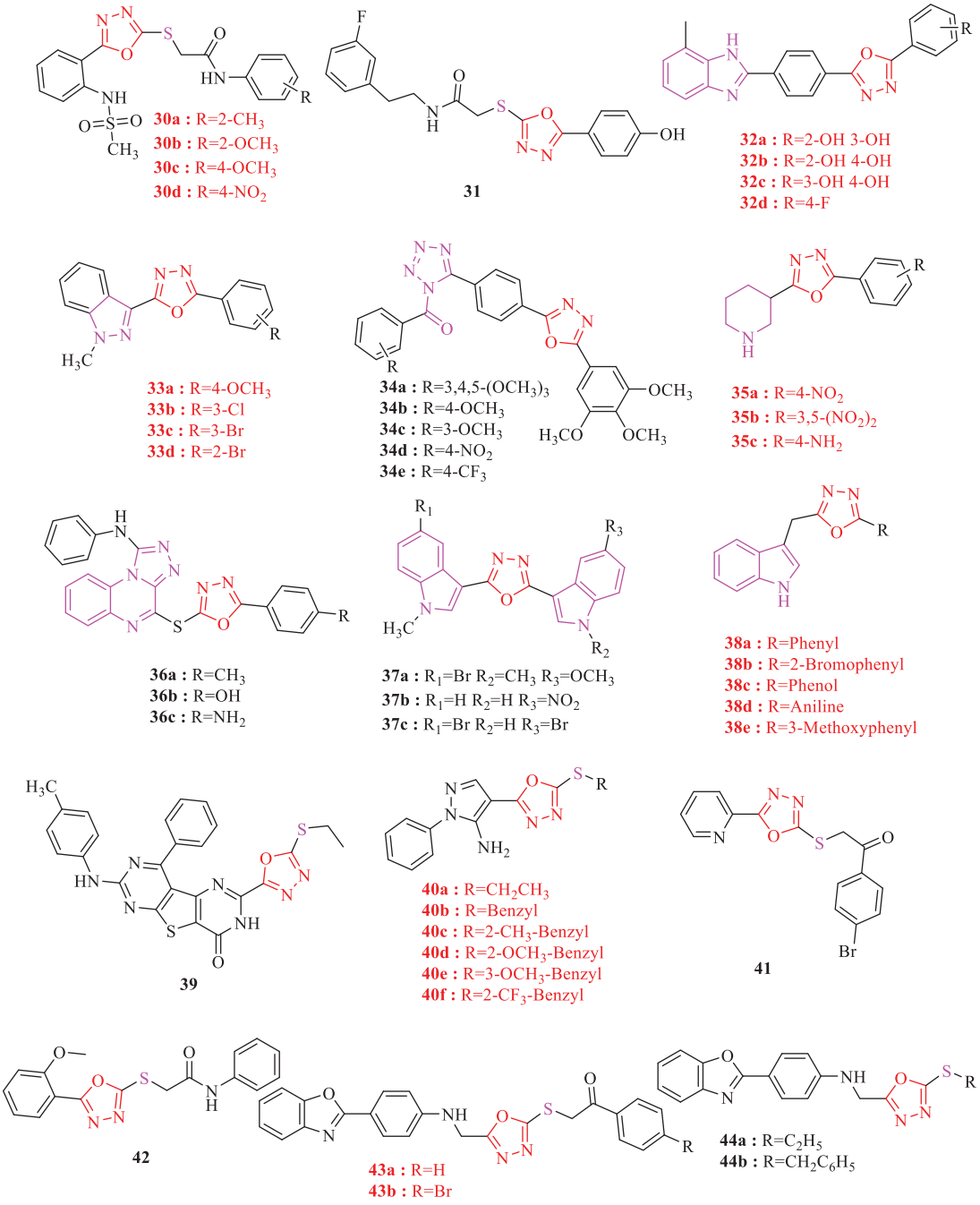

Figure 3. Derivatives of 1,3,4-oxadiazole ring.

Yu et al. designed and synthesised a series of novel 1,3,4-oxadiazole neuraminidase inhibitors, and tested their inhibitory activity against neuraminidase *in vitro*. The results showed that compound **31** (Figure 3) had the best inhibitory activity (IC_{50} = 0.027 μM), significantly 3.04-fold lower than Oseltamivir carboxylate (IC_{50} = 0.082 μM). Compound **31** also showed stronger inhibitory potency against H5N1-H274Y mutant relative to Oseltamivir carboxylate[38].

2.1.10. Benzimidazole based 1,3,4-oxadiazole derivatives

Taha et al. synthesised a series of 26 analogs of benzimidazole-based 1,3,4-oxadiazole derivatives and evaluated their α-glycosidase inhibitory effects. Most of the compounds exhibited good inhibitory activity. The inhibitory activity of the compounds was determined using an IC_{50} range of 2.6 ± 0.1 to 140 ± 0.30 μM in the presence of positive control, Acarbose (IC_{50} = 38.45 ± 0.80 μM). Compounds **32a**, **32b**, **32c and 32d** (Figure 3) had IC_{50} values of 4.6 ± 0.1, 9.50 ± 0.3, 2.6 ± 0.1 and 9.30 ± 0.4 μM, respectively. Additionally, due to the role of different substituents on the phenyl ring in biological evaluation, SAR analyses were performed on all compounds. The findings of the experiment indicated that the presence of electron-adsorbing groups aided in the formation of hydrogen bonds with Lys1460. Additionally, the methoxy group on the phenyl ring reduced the activity of some compounds[39].

2.1.11. Indazole-tethered oxadiazoles

Dukanya et al. synthesised a series of novel indazole tethered oxadiazole (OTDs) derivatives, characterised and screened them

against human liver cancer cell lines (HepG2 and HCCLM3) to determine their anti-proliferation ability. The OTDs compounds **33a**, **33b**, **33c and 33d** (Figure 3) all showed significant cytotoxicity, with IC_{50} values of 19.5, 21.4, 24.5 and 22.3 μM, respectively. Additionally, the toxicity of these compounds was determined in normal liver LO2 cell lines. All of these compounds, particularly **33a** and **33b**, showed no toxicity in LO2 cells, indicating that compounds **33a** and **33b** are more selective for cancer cells. *In vitro*, western blot, flow cytometry and molecular docking analysis and other studies revealed that compound **33a** induced apoptosis in HepG2 cells by inhibiting the expression of SIRT2[40].

2.1.12. 1,3,4-Oxadiazole fused tetrazole amide derivatives

Kotla et al. designed and synthesised a series of novel 1,3,4-oxadiazole fused tetrazol amide derivatives and investigated their anticancer activity against A549, MDA-MB-231 and MCF-7 cells. The majority of the compounds demonstrated good anticancer activity and safety compared to the standard drug Doxorubicin. The antitumor activity of compounds **34a**, **34b**, **34c**, **34d** and **34e** (Figure 3) was significantly greater than that of the positive control. Compound **34b** exhibited significant anticancer activity against A549, MDA-MB-231 and MCF-7 cells, with IC_{50} values of 1.02, 1.34 and 0.31 μM, respectively. Compound **34b** can be used as a lead drug *in vivo* and clinical studies[41].

2.1.13. Nipecotic acid 1,3,4-oxadiazole based hybrids

Singh et al. synthesised a series of 15 nipecotic acid 1,3,4-oxadiazole based hybrids. Among the synthesised compounds, compounds **35a**, **35b** and **35c** (Figure 3) showed good antiepileptic activity with the percentage of protection of 83.3% (**35a**), 100% (**35b**) and 66.66% (**35c**) compared with the standard Tiagabine, and compound **35b** exhibited the highest activity. These compounds had also been found to have good antidepressant activity. At the same time, none of the compounds was neurotoxic and they were safe for the kidneys and liver[42].

2.1.14. [1,2,4]Triazolo[4,3-a]quinoxaline-1,3,4-oxadiazole derivatives

Kaneko et al. synthesised a series of [1,2,4]triazole[4,3-a]quinoxaline-1,3,4- oxadiazole derivatives and assessed their anti-proliferative effects against a variety of cancer cell lines including histiocytic lymphoma (U937), melanoma (B16), HepG2 and HL-60. Compounds **36a–c** (Figure 3) showed a similar anti-proliferative effect on HL-60 and U937 cells as EAPB0203. Compounds **36a–c** showed significant effects on HepG2 cells with IC_{50} values of 5.35 ± 0.22, 4.86 ± 0.25 and 3.84 ± 0.13 μM, respectively, compared with EAPB0203 and Imiquimod. Compounds **36a–c** exhibited moderate effects on the B16 cells. In summary, this structure is important for anticancer drug development[43].

2.1.15. Indolyl-1,3,4-oxadiazoles

Sreenivasulu et al. designed and synthesised 10 new 2,5-bis(indolyl) −1,3,4-oxadiazoles. The cytotoxicity of these compounds was determined using the MTT reduction method in four cancer cell lines: A549, MDA-MB-231, MCF-7 and cervical cancer (HeLa). Compound **37a** (Figure 3) showed good cytotoxicity against MCF-7 and HeLa cells with IC_{50} values of 1.8 and 9.23 μM, respectively. Compound **37b** (Figure 3) showed good anti-tumour activity against A549, MCF-7 and HeLa cells, with IC_{50} values of 3.3, 2.6 and 6.34 mM, respectively. Compounds **37a** and **37b** showed moderate cytotoxicity, with IC_{50} values of 12.17 and 10.23 μM, respectively, and strong cytotoxicity to MDA-MB-231 cells. Compound **37c** (Figure 3) exhibited no cytotoxicity to the four cancer cell lines. Interestingly, none of the compounds was cytotoxic to normal human embryonic kidney cells HEK-293. It was worth noting that compound **37a** is a promising lead drug[44].

Kumar et al. designed and synthesised indole-oxadiazole derivatives **38a–e** (Figure 3) and assessed their anti-inflammatory and analgesic activity *in vivo*. As demonstrated by the results, the majority of the compounds exhibited COX-2 selectivity. Compounds **38d** and **38e** were particularly selective for COX-1. With a selectivity index (SI) of 2.19, compound **38c** was the most selective COX-2 inhibitor, followed by compound **38a** (SI = 1.95). At a concentration of 10 μM, compound **38b** inhibited COX-2 at a rate of 63.23% and a SI of 1.49[45].

2.1.16. S-Alkylation-1,3,4-oxadiazole hybrids

Tolba et al. synthesised a new compound by combining thienopyrimidine and 1,3,4-oxadiazole and evaluated the anti-inflammatory activity of carrageenan-induced acute foot swelling in rats using standard procedures. Compound **39** (Paw edoema inhibition: 52% and 60%, Figure 3) showed obvious anti-inflammatory results ranging from good to medium at 2 and 4 h compared with the standard Indomethacin (Paw edoema inhibition: 60% and 67%) [46].

Wu et al. designed and synthesised a series of 1-phenyl-5-amine-4-pyrazole sulphide derivatives containing 1,3,4-oxadiazole groups, and tested them *in vivo* for antiviral activity. The findings of the tests indicated that the majority of the target compounds had good inactivation activity against tobacco mosaic virus (TMV). Compounds **40a–f** (Figure 3) had EC_{50} values of 15.7, 15.7, 15.5, 11.9, 12.5 and 16.5 μg/mL, respectively[47].

Abbas et al. synthesised new compounds and evaluated their anti-tumour activity against MCF-7, A549 and their cytotoxicity against normal cells (MCF10A and WBC). Compound **41** (Figure 3) exhibited anti-tumour activity against MCF-7 cells (GI_{50} = 86.8 μg/mL), but not against A549, MCF10A and WBC cells[48].

Vanjare et al. synthesised a new type of 1,3,4-oxadiazole compound **42** (Figure 3) and evaluated its activity against tyrosinase. The results showed that the IC_{50} value for compound **42** was 0.003 ± 0.00 μM compared with standard drug Kojic acid (IC_{50} = 16.83 ± 1.16 μM), and was non-toxic even at high concentrations (0–50 μM)[49].

Omar et al. synthesised 1,3,4-oxadiazole derivatives and screened their anti-proliferative activity against MCF-7 and MDA-MB-231 cells *in vitro*. The results indicated that compounds **43a** and **43b** (Figure 3) had greater inhibitory effects on MCF-7 cells than that of Doxorubicin, with IC_{50} values of 1.76 ± 0.08 and 1.18 ± 0.04 μM, respectively. Compounds **43a**, **43b**, **44b** and **44d** (Figure 3) had an inhibitory effect on MDA-MB-231 cells. The inhibitory effect was stronger than that of Doxorubicin, with IC_{50} values of 0.59 ± 0.02, 3.59 ± 0.2, 1.24 ± 0.06 and 1.16 ± 0.04 μM, respectively[50].

Çevik et al. synthesised a series of 1,3,4-oxadiazole derivatives and screened the synthesised compounds for their antifungal activity against *Candida glabrata*, *Candida cruzi*, *Candida parapsilosis* and *Candida albicans*. The results showed that compounds **45a** (MIC_{50} = 0.78 μg/mL, Figure 4) and **45b** (MIC_{50} = 0.78 μg/mL, Figure 4) had better inhibitory activity against *Candida albicans* than that of Ketoconazole (MIC_{50} = 1.56 μg/mL)[51].

Alfayomy et al. synthesised a series of 1,3,4-oxadiazole derivatives and evaluated their inhibitory activities against COX-1/COX-2. Compounds **46a, 46b, 46c, 46d** and **46e** (Figure 4) were potent

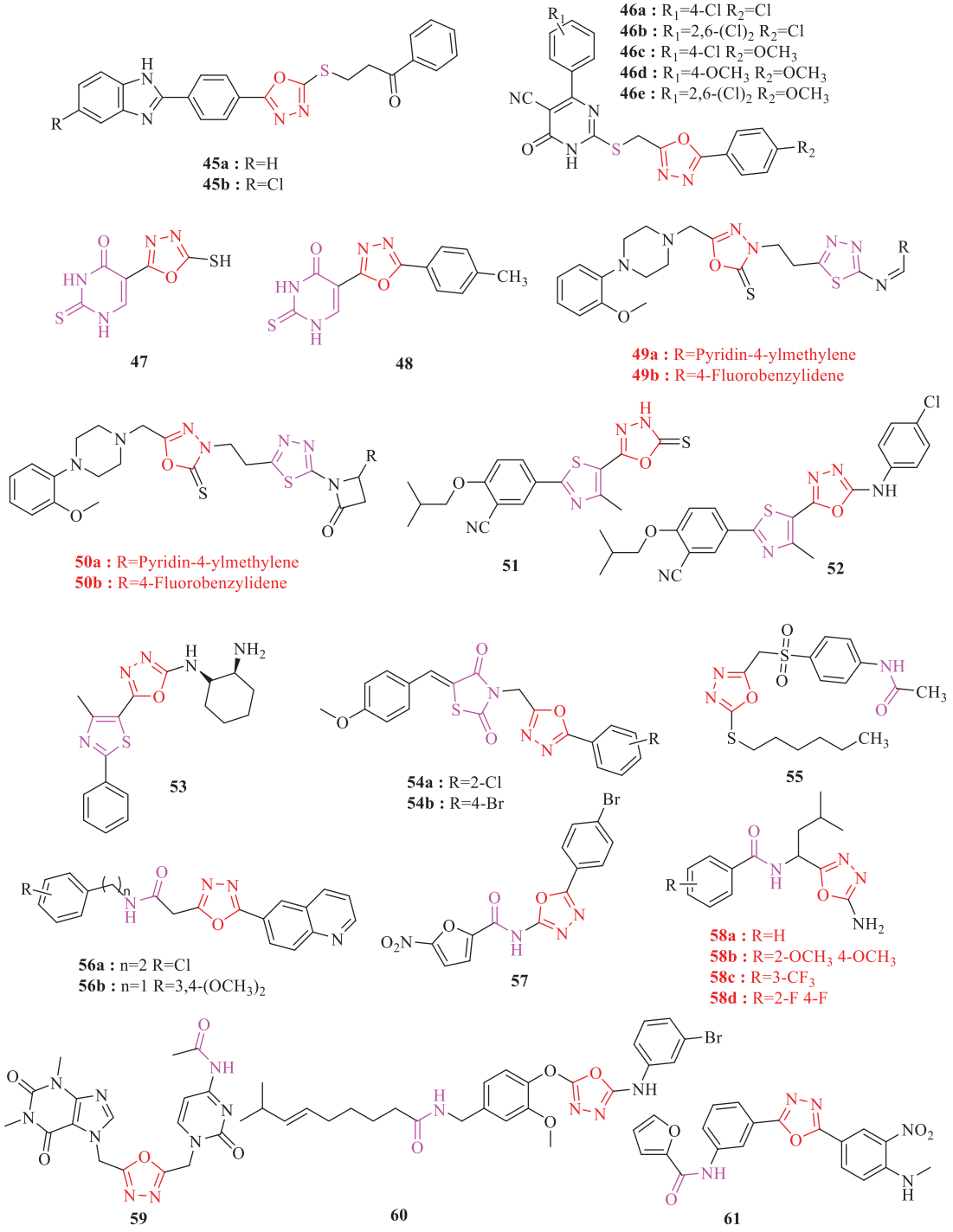

Figure 4. Derivatives of 1,3,4-oxadiazole ring.

and selective COX-2 inhibitors (IC_{50}: 0.04–0.081 μM; SI: 139.74–321.95). *In vivo* anti-inflammatory activity of the compounds was further investigated. Compounds **46a** and **46e** showed superior anti-inflammatory activity than that of the positive drug celecoxib *in vivo*. These derivatives were also tested for their ulcerogenic potential, with compound **46e** showing a better safety profile compared to Celecoxib, and compound **46a** showed minor damage[52].

2.1.17. New 2-thioxo-2,3-dihydropyrimidin-4(1H)-ones

El-Etrawy and Sherbiny synthesised a new thiouracil derivative and evaluated its activity against MCF-7 cells *in vitro*. The results showed that compared with Doxorubicin (IC_{50} = 2.97 μg/mL), compound **47** (Figure 4) had an IC_{50} value of 3.80 μg/mL for MCF-7 cells[53].

Following the preceding research, El-Etrawy and Sherbiny designed a series of new thiouracil derivatives and determined their activity *in vitro* on MCF-7 cells using the MTT method. The IC_{50} value of compound **48** (Figure 4) on MCF-7 cells was 3.50 μg/mL when Doxorubicin (IC_{50} = 2.97 μg/mL) was used as a control[54].

2.1.18. Combination of 1,3,4-oxadiazole and 1,3,4-thiadiazole

Fahim et al. designed and synthesised several new compounds containing oxadiazole rings. The activity of the synthesised compounds as acetylcholinesterase inhibitors was determined. The

IC_{50} values for compounds **49a**, **49b**, **50a** and **50b** (Figure 4) were 2.32 ± 0.03, 6.48 ± 0.10, 2.01 ± 0.00, 1.96 ± 0.01 μg/mL, respectively, when Donepezile (IC_{50} = 0.03 ± 0.00 μg/mL) was used as a control[55].

2.1.19. Combination of 1,3,4-oxadiazole and thiazole

Rashad et al. synthesised a febuxostat derivative with carboxamide and 1,3,4-oxadiazole functionalities. Compounds **51** and **52** (Figure 4) were tested for their inhibitory activity against xanthine oxidase (XO) and COX. The results showed that compounds **51** and **52** had a significant inhibitory effect on XO and COX *in vitro*. To further evaluate the anti-inflammatory activity (AI%) of compound **52** *in vivo*, Celecoxib was used as a reference standard. The results showed that after 8 h, compound **52** (AI% = 89.29%) showed higher activity than Celecoxib (AI% = 83.57%)[56].

Hagras et al. synthesised a series of oxadiazolethiazoles derivatives and tested their antibacterial activity. The results indicated that compound **53** (Figure 4) inhibits pathogenic strains of *C. albicans* and non-albicans species, including fluconazole-resistant strains. In addition, compound **53** was able to inhibit clinically important strains of *Cryptococcus* and *Aspergillus*. Furthermore, compound **53** did not affect the human microbiota and showed excellent tolerance to mammalian cells. Meanwhile, compound **53** outperformed fluconazole in disrupting mature *Candida biofilms*, except for mostly low MIC values between 0.125 and 2.0 μg/mL[57].

Alzhrani et al. synthesised a library of thiazolidine-dione-1,3,4-oxadiazole hybrids as TS inhibitors. All synthesised compounds followed Lipinski and Veber's rule, indicating good drug similarity after oral administration. Compared with the positive control drug 5-Fluorouracil (MCF-7: IC_{50} = 34.82 μM, HCT-116: IC_{50} = 40.51 μM), the inhibitory activities of compounds **54a** and **54b** (Figure 4) on MCF-7 cells were 4.5 and 4.4 folds, respectively, while the inhibitory activity of the HCT-116 cells was 3.1 and 2.5 folds. In addition, compounds **54a** and **54b** also inhibited TS enzymes with IC_{50} values of 1.67 and 2.21 μM, respectively. In conclusion, compounds **54a** and **54b** have the potential to be developed as TS inhibitors[58].

2.1.20. 1,3,4-Oxadiazole derivatives with amide structure

Wang et al. designed and synthesised a new class of p-aminobenzenesulfonyl oxadiazole antibacterial drugs. Notably, compound **55** (MIC = 1 μg/mL, Figure 4) was more active against *methicillin-resistant Staphylococcus aureus* and did not exhibit drug resistance[59].

Gu et al. synthesised 2–(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl) derivatives **56a** and **56b** (Figure 4), and evaluated their inhibitory activity against PI3Kα *in vitro*, with IC_{50} values of 6.6 ± 2.1 and 7.6 ± 4.2 μM, respectively[60].

Wang et al. designed and synthesised a series of novel nitrofuranamide based-1,3,4-oxadiazole hybrids as new anti-tuberculosis drugs. Some of them showed considerable activity against *MTB H37Rv* and *MDR-MTB 16883* strains (MIC = 0.007 ~ 3.584 μg/mL). Among them, the most active compound **57** (MIC = 0.795 μg/mL, Figure 4) had lower cytotoxicity (CC_{50} = 57.34 μg/mL), especially the inhibition on hERG (IR = 11.3 ± 1.7% at 10 μM). It has a better oral PK profile than the anti-TB drug candidate PBTZ169 (currently in Phase II clinical trials)[61].

Gontijo et al. synthesised a series of 1,3,4-oxadiazole derivatives and evaluated their inhibitory activity against Cat K *in vitro*. The results showed that compounds **58a**, **58b**, **58c** and **58d** (Figure 4) acted as competitive inhibitors of Cat K with Ki values of 2.1 ± 0.2, 4.6 ± 0.3, 7.3 ± 0.6, 6.7 ± 0.4 μM, respectively[62].

El Mansouri et al. synthesised a series of 1,3,4-oxadiazole derivatives, and the cytotoxic activity of all prepared compounds was screened *in vitro* against four cell lines, including fibrosarcoma (HT-1080), MCF-7, MDA-MB-231 and A549. Compound **59** (Figure 4) showed a significant growth inhibitory effect on all cell lines tested, especially in HT-1080 with an IC_{50} value of 17.08 ± 0.97 μM. Compound **59** induced apoptosis through caspase-3/7 activation and cell cycle arrested in HT-1080 and A-549 cells[63].

Considering the NorA efflux pump inhibitory potential of capsaicin, Naaz et al. designed a series of capsaicin-based 1,3,4 oxadiazole derivatives and evaluated the activity-enhancing effect of ciprofloxacin. Of the compounds tested, the minimum effective concentration (MEC) of compound **60** (Figure 4) against a NorA overexpressing *S. aureus* strain was 12.5 μg/mL, while the MEC of capsaicin was 50 μg/mL[64].

Meng et al. synthesised a series of 2,5-diaryl-1,3,4-oxadiazole derivatives and identified them as a novel SHP2 inhibitor. Compound **61** (Figure 4) exhibited SHP2 inhibitory activity with an IC_{50} value of 2.73 ± 0.20 μM, with approximately 1.56-fold, 5.26-fold and 7.36-fold selectivity for SHP2 over SHP1, PTP1B and TCPTP, respectively. Further studies confirmed that compound **61** induced apoptosis and inhibited the proliferation of TF-1 cells *in vitro* by blocking the SHP2/p-STAT3 pathway[65].

2.1.21. 1,3,4-Oxadiazolethione-benzimidazole derivatives

Ergül et al. synthesised a series of 1,3,4-oxadiazolethione-benzimidazole derivatives, and in this study, it has been reported that human mPGES-1 inhibitors were identified in a cell-free assay of PGE2 production. Among them, the results showed that the IC_{50} values of compounds **62a**, **62b** and **63** (Figure 5) were 0.03 ± 0.02, 0.03 ± 0.01, 0.09 ± 0.02 μM, respectively. While compounds **62a** and **63** also inhibited leukotriene C_4 synthase at sub-μM concentrations with IC_{50} values of 0.7 ± 0.19 and 0.4 ± 0.17 μM, respectively. These derivatives are worthy of further exploration for novel derivatives with potent anti-inflammatory properties[66].

2.2. 1,2,4-Oxadiazole

2.2.1. 3,5-Substituted 1,2,4-oxadiazole

Loboda et al. designed and synthesised a series of 3,5-substituted 1,2,4-oxadiazole derivatives as catalytic inhibitors of human DNA topoisomerase IIα. The selected compound also demonstrated *in vitro* cytotoxicity against the MCF-7 cell line but did not induce double-strand breaks, indicating a distinct mechanism of action at the cellular level from the topology II toxicant. Compound **64** (IC_{50} = 147.7 μM, Figure 5) had an inhibitory effect on topology IIα in the micromolar range, as demonstrated by the HTS topology IIα relaxation experiment. SPR binding experiments confirmed that these oxadiazole compounds may bind to the truncated ATPase domain, which is consistent with their targeted mode of action[67].

Zhang et al. designed and prepared twenty nine 1,2,4-oxadiazole derivatives. Western blotting and immunofluorescence analysis revealed that compound **65** (Figure 5) can significantly inhibit NO production (IC_{50} = 12.84 ± 0.21 μM) and LPS-induced NF-κB activation (IC_{50} = 1.35 ± 0.39 μM) in RAW264.7 cells. At the same time, it blocked the phosphorylation of p65. The findings indicated that compound **65** can be a promising anti-inflammatory drug[68].

Gao et al. used allopurinol as a prototype drug and synthesised a series of novel 1-alkyl-5/6–(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1*H*-indole-3-carbonitriles as a potent XO inhibitor. Compound **66** (IC_{50} = 0.36 μM, Figure 5) was shown to be the most potent

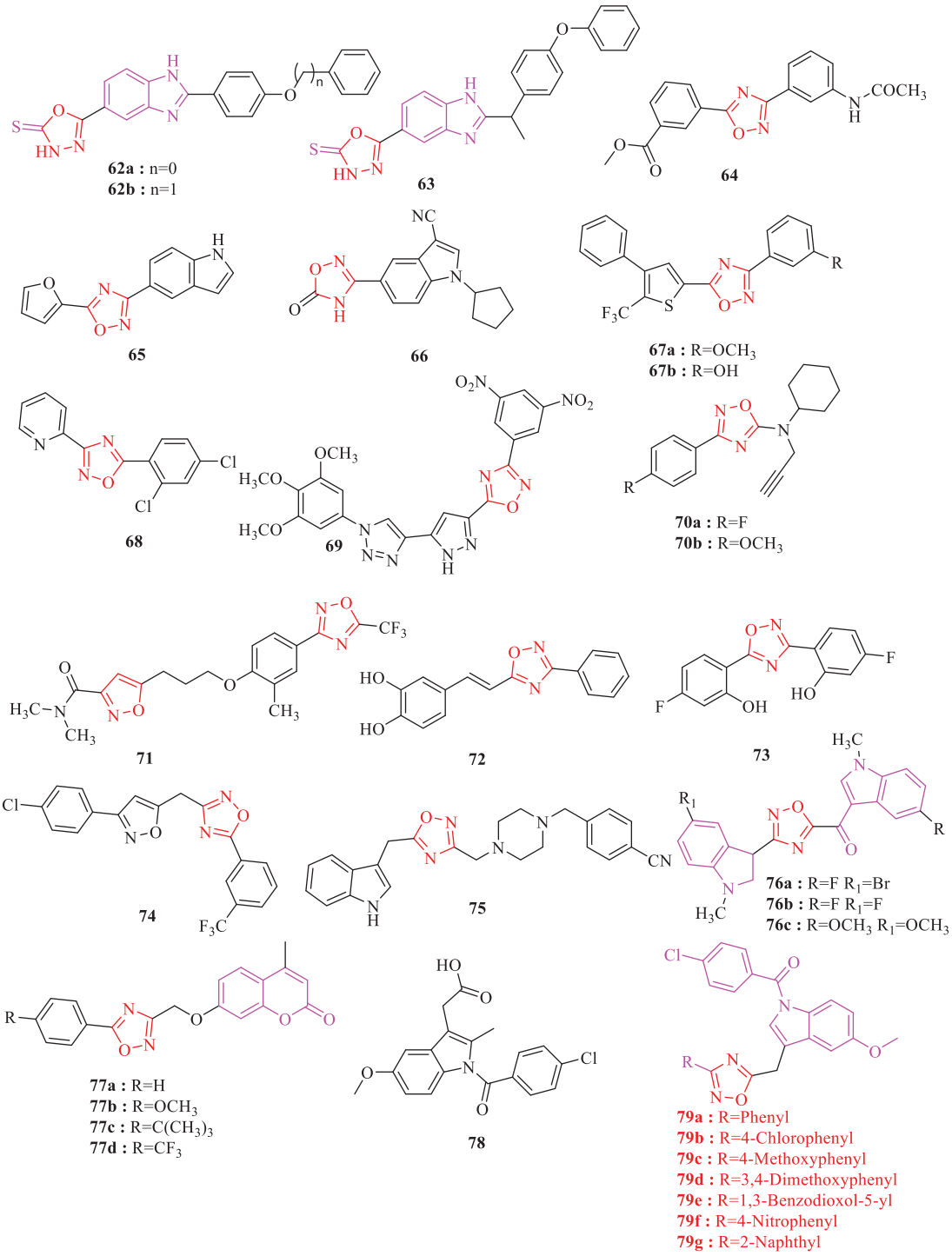

Figure 5. Derivatives of 1,2,4-oxadiazole ring.

XO inhibitor *in vitro*. The structure-activity relationship analysis revealed that the 3-cyano group was an indispensable group for the compound to exhibit inhibitory activity on XO and that the 5-carbonyl-4,5-dihydro-1,2,4-oxadiazole group was preferable at the 5-position of the indole group[69].

Chen et al. modified compound **67a** (SEW2871, Figure 5) to obtain compound **67b** (ASR396, Figure 5), allowing the new compound to be loaded into nanoliposomes (nanoASR396). NanoASR396 was capable of greatly inhibiting the permeability increase and gap formation of vascular endothelium and EC monolayer models induced by inflammatory cytokines. NanoASR396 strengthened the integrity of the endothelial cell layer by inhibiting the phosphorylation of MLC, hence inhibiting the metastasis and spread of cancer cells[70].

Choi et al. reported a new compound **68** (JY-2, Figure 5). The compound had an inhibitory effect on FoxO1 (IC_{50} = 22 μM). JY-2 was shown to protect hepatocytes and pancreatic β-cells from lipotoxicity induced by pa, and improved glucose tolerance *in vivo*, and associated with the corresponding liver gluconeogenesis and β-cell newborn mRNA expression[71].

Mohan et al. designed and synthesised 1,2,4-oxadiazole-1,2,3-triazole-pyrazole derivatives, and evaluated their anti-cancer activity against PC3, DU-145 (prostate cancer), A549 and MCF-7 cells. Among them, compound **69** (Figure 5) showed good anticancer

activity against PC3, A549, MCF-7 and DU-145 cells, with IC_{50} values of 0.01 ± 0.008, 0.45 ± 0.023, 0.081 ± 0.0012 and 1.77 ± 0.33 μM, respectively[72].

Melo de Oliveira et al. synthesised a new 1,2,4-oxadiazole derivative and evaluated it on lung cancer (NCIH-460). Compounds **70a** and **70b** (Figure 5) had the highest antiproliferative activity against NCIH-460 *in vitro*, with IC_{50} values of 3.87 ± 0.40 and 3.21 ± 0.70 μM, respectively[73].

Egorova et al. synthesised a series of novel beconazole derivatives incorporating isoxazole and 1,2,4-oxadiazole moieties and evaluated their antiviral activity against beconazole-sensitive and resistant enteroviruses. Compound **71** (Figure 5) was found to be one of the most active compounds against resistant or susceptible enterovirus, with IC_{50} values of $0.02 \sim 5.25$ μM[74].

Sucu et al. synthesised several novel CAPE-like 1,2,4-oxadiazole derivatives and subsequently evaluated their *in vitro* therapeutic efficacy in GBM cell lines (T98G and LN229). The results showed that compared with CAPE, compound **72** (Figure 5) up to 50 μM significantly reduced the viability of T98G and LN229 cells with IC_{50} values of 46.42 and 14.23 μM, respectively. Furthermore, the same concentration of compound **72** was not cytotoxic to healthy human cells (fibroblast-like mesenchymal stem cells)[75].

Shi et al. designed and synthesised a series of 1,2,4-oxadiazole compounds and tested their neuroprotective ability. Compound **73** (Figure 5) had a significant neuroprotective effect on SNP-induced apoptosis at 5 μM (cell viability: $77.02 \pm 2.00\%$) and 10 μM (cell viability: $96.85 \pm 0.33\%$), and was non-toxic to PC12 and LO2 cells, with IC_{50} values of 105.6 ± 2.90 μM, 188.7 ± 16.33 μM, respectively. Compound **73** attenuated SNP-induced apoptosis by inhibiting reactive oxygen species (ROS) accumulation and restoring mitochondrial membrane potential. *In vivo* experiments showed that compound **73** improved neurological function and reduced cerebral infarct size in the MCAO model. Overall, compound **73** may represent a promising compound for the treatment of stroke[76].

Kumar Kushwaha et al. synthesised a series of isoxazole-1,2,4-oxadiazole derivatives and tested the highest non-cytotoxic concentration (HNC) of the synthesised derivatives using the MTT cell viability assay in TZM-bl reporter cells. None of the compounds appeared to be cytotoxic at the 100 nM concentration. The antiviral activity of HNC was then tested using a luciferase reporter gene assay in HIV-1 NL4.3 virus-infected TZM-bl cells at a concentration of 100 nM. The results showed that compound **74** ($IC_{50} = 85.7 \pm 1.91$ μM, Figure 5) showed significant inhibition on luciferase activity, which indicated that viral gene expression and replication were inhibited, and the HIV-1 inhibitor AUY922 ($IC_{50} = 66.25 \pm 1.38$ μM) was used as a positive control for comparison[77].

Xie et al. designed and synthesised a series of novel indole-1,2,4-oxadiazole derivatives and evaluated their effects on oxidised low-density lipoprotein (oxLDL) -induced vascular endothelial cell (VEC) damage. Among them, compound **75** (Figure 5) exhibited the most potent protective activity and it was found to inhibit oxLDL-induced apoptosis and the expression of ICAM-1 and VCAM-1 in VECs[78].

2.2.2. 1,2,4-Oxadiazole topsentin analogs

Parrino et al. synthesised a series of new 1,2,4-oxadiazole derivatives and evaluated their inhibitory activity against *Staphylococcus aureus* ATCC 25923 biofilm formation. Compounds **76a**, **76b** and **76c** (Figure 5) significantly inhibited the formation of ATCC 25923 biofilms, with BIC_{50} values of 9.7, 0.7 and 2.2 μM, respectively. Furthermore, no cytotoxicity was observed in normal human cells[79].

2.2.3. Coumarin linked 1,2,4-oxadiazoles

Thacker et al. synthesised a series of 1,2,4-oxadiazole derivatives linked to coumarin, and evaluated them against four physiologically and pharmacologically related subtypes, namely the cytosolic subtypes hCA I and II and the transmembrane tumour-related subtypes hCA IX and XII. The results indicated that all compounds selectively inhibited hCA IX and XII, but not hCA I or II. The Ki range for hCA IX was $23.6 \sim 315.6$ nM, and compound **77b** exhibited the best inhibitory activity. The Ki value of hCA XII ranged from 1.0 to 752.6 nM, and the inhibitory effects of compounds **77a–d** (Figure 5) were 1.58, 1.26, 5.7 and 1.29 times than that of standard AAZ, respectively. It is worth noting that compound **77c** had a Ki value of 1 nM, making it a promising lead drug candidate for the design of new hCA XII inhibitors. Compound **77b** showed the strongest inhibitory effect on hCA IX, with a Ki value of 23.6 nM. Therefore, compound **77b** can be used as a lead compound for the design of dual hCA IX and XII inhibitors[80].

2.2.4. 3-Aryl-1,2,4-oxadiazoles derived from indomethacin

Marzouk et al. designed and synthesised a series of 3-aryl-1,2,4-oxadiazole compounds **79a–g** (Figure 5) derived from indomethacin (compound **78**, Figure 5). At 5 μM, all the compounds showed no obvious cytotoxicity. The anti-inflammatory effect of compounds **79a–g** containing 3-aryl-1,2,4-oxadiazole was found to be weak to moderate. Compounds **79d** and **79f** demonstrated the highest anti-inflammatory activity (strongest inhibitory effect on NO production), with inhibition rates of 37.2% and 33.7%, respectively. The anti-inflammatory activity of compounds **79b**, **79c** and **79e** were moderate (25.5%, 29.3% and 26.9%, respectively), while compounds **79a** and **79g** showed the least anti-inflammatory activity (9.6% and 17.3%, respectively). After 3 h, the anti-inflammatory activity of compounds **79a**, **79b**, **79d** and **79g** were 60.9%, 69.9%, 53.8% and 57.9%, respectively, which was significantly higher than Celecoxib (46.56%) and Indomethacin (55.63%). Compound **79b** exhibited the strongest anti-inflammatory activity of all the compounds. Compound **79c** had a moderate anti-inflammatory activity (48.5%), while compounds **79e** and **79f** exhibited the least anti-inflammatory activity (29.4% and 21.3%, respectively). After 4 h, compound **79g** showed prolonged anti-inflammatory activity (42.78%), which was comparable to that of Indomethacin (43.9%). Compound **79b**, which had the strongest anti-inflammatory activity, was orally administered to male mice to determine acute toxicity. The study demonstrated that when the compound was administered at a dose of less than 400 mg/kg, no evidence of acute toxicity or death was observed. The tested compounds in the study were non-toxic and well-tolerated. However, Indomethacin has a higher ulcerogenic potential, with an injury index of 78.7%, whereas the tested compound had a lower ulcerogenic potential, with an injury index of $35 \sim 61\%$. Among these, compound **79b** demonstrated potent anti-inflammatory activity *in vivo* and, when compared to Indomethacin, it showed a lower ulcerogenic, with an injury index of 38%. In contrast, all compounds studied were shown to be more ulcerogenic than Celecoxib[81].

2.2.5. Uracil analogs-1,2,4-oxadiazole hybrids

El Mansouri et al. Synthesised a novel uracil analogs-1,2,4-oxadiazole hybrid derivative for the first time using HAP-SO_3H as a

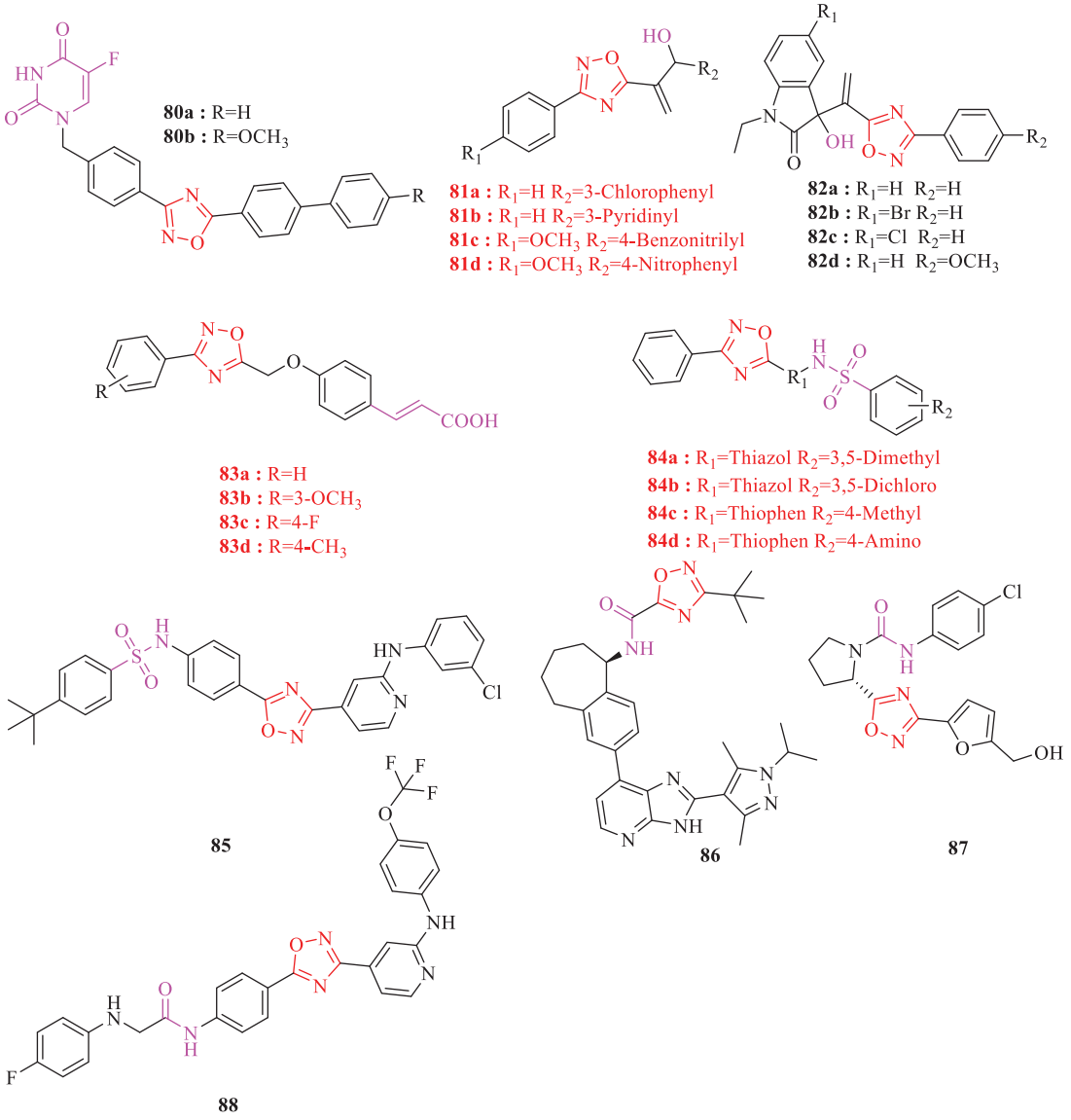

Figure 6. Derivatives of 1,2,4-oxadiazole ring.

heterogeneous acid catalyst. This was a new, simple and effective method. A series of compounds were synthesised and their anticancer activity against A-375, HT-1080, A-549, MCF-7 and MDAMB-231 cells was determined. Among these, compounds **80a** and **80b** (Figure 6) exhibited the highest levels of cytotoxicity with IC_{50} values of 0.88–8.37 μM. Additionally, these compounds were more active against HT-1080 and MCF-7 cells than that of the positive control drug Doxorubicin[82].

2.2.6. Oxadiazole-hydroxy small molecule hybrids

Fernandes et al. used molecular hybridisation methods to design and synthesise a series of vinyl-1,2,4-oxadiazole and oxadiazole-hydroxy hybrid derivatives as antiparasitic agents. The obtained compounds showed *in vitro* inhibitory activity against intracellular amastigotes of two protozoan parasites, *Trypanosoma cruzi* and *Leishmania infantum*. HFF-1 fibroblasts and HepG2 hepatocytes were used to evaluate cytotoxic activity. The majority of the compounds were not cytotoxic to HFF-1 fibroblasts, but moderate cytotoxic to the liver HepG2 cell line. It was worth noting that compounds **81a–d** had lower toxicity than that of the positive control drug Doxorubicin. The IC_{50} values for compounds **81a**, **81b**, **82a** and **82b** (Figure 6) were 6.20, 2.20, 2.30 and 2.20 μM, respectively, against *Trypanosoma cruzi*. Compounds **81c**, **81d**, **82c** and **82d** (Figure 6) were highly selective for *Leishmania infantum* (IC_{50} values of 3.89, 2.38, 2.50 and 2.85 μM, respectively)[83].

2.2.7. 1,2,4-Oxadiazole based trans- acrylic acid derivatives

The alpha and gamma nuclear receptors of peroxisome proliferator-activated receptors (PPARs) are considered to be a promising target for diabetes treatment. Activating PPAR-γ can result in an increase in insulin resistance, while activating PPAR-α can result in a decrease intriglycerides, thus reducing the complications of diabetes, particularly cardiovascular disease. Therefore, Kaur et al. designed 3,5-substituted 1,2,4-oxadiazole derivatives and screened them using molecular docking. Simultaneously, toxicity analysis of selected compounds revealed that most of the compounds were not carcinogenic or mutagenic. Additionally, *in vitro* analysis of PPAR-γ and PPAR-α demonstrated that compounds **83a–d** (Figure 6) had a more favourable effect on both receptors. Compound **83a** and **83c** were found to be the most potent on both PPAR-α and PPAR-γ receptors with EC_{50} of 0.781 ± 0.008 μM, 3.29 ± 0.03 μM and 0.07 ± 0.0006 μM, 0.06 ± 0.0005 μM respectively than the

positive control drug Pioglitazone having EC_{50} of 32.38 ± 0.2 and 38.03 ± 0.13 μM for both receptors. Compared to the standard drug pioglitazone (5 mg/kg/day), the evaluation of compounds **83a** and **83c** on a diabetic rat model revealed that two compounds significantly lowered the blood glucose level of diabetic rats. The liver and kidney biochemical indicators TBARS, GSH, CAT were normal following treatment with compounds **83a** and **83c** when being compared to the negative control group (diabetes group). Furthermore, histological examinations of the kidney and pancreas confirmed that compounds **83a** and **83c** were effective at reversing tissue regeneration. Therefore, compounds **83a** and **83c** acted as PPAR-α and PPAR-γ agonists[84].

2.2.8. 1,2,4-Oxadiazole-sulphonamide based compounds

Shamsi et al. synthesised an active scaffold against HCT-116 cells by combining three important pharmacophores: 1,2,4-oxadiazole, thiophene and sulphonamide. In summary, a series of different 3,5-disubstituted 1,2,4-oxadiazoles was synthesised and their anticancer activity was assessed in HCT-116 cells. Among them, compounds **84a**, **84b and 84c** (Figure 6) inhibited the proliferation of HCT-116 cells at concentrations of 21.4, 50.6, 11.1 μM, respectively. Compound **84c** demonstrated higher anti-proliferative activity and was also found to be active against the tumour-associated carbonic anhydrase IX (hCAIX) isoform, with an IC_{50} value of 4.23 μM. As a result of further optimisation, compound **84c** was transformed into **84d**, which doubled its anti-proliferative effect in HCT-116 cells (IC_{50} = 6.0 μM) and demonstrated significant hCAIX inhibitory potential (IC_{50} = 0.74 μM). Compound **84d** treatment decreased CAIX expression, induced apoptosis and reactive oxygen species (ROS) production, and inhibited colon cancer cellcolony formation and migration. Additionally, this result establishes a reasonable preclinical basis for further optimising compound **84d** as a potential lead for the treatment of colorectal cancer[85].

Wang et al. designed and synthesised a series of new 1,2,4-oxadiazole derivatives according to the strategy of multi-target directed ligands. All compounds were evaluated for glycogen synthase kinase 3β (GSK-3β) inhibition, anti-neurin-inflammatory, neuroprotective activity, and effects on glucose consumption in HepG2 cells. The results showed that compound **85** (Figure 6) had GSK-3β inhibition (IC_{50} = 0.19 μM) and anti-neuroinflammatory potency (IC_{50} = 6.94 ± 2.33 μM). The effect of compound **85** on glucose consumption was higher than that of the positive drug Metformin. Compound **85** significantly reduced Aβ-induced Tau hyperphosphorylation, thereby inhibiting GSK-3β at the cellular level. Notably, compound **85** exhibited a good inhibitory effect on the formation of intracellular ROS. Furthermore, these compounds cross the blood-brain barrier and are not neurotoxic at a concentration of 50 μM. Finally, *in vivo* experiments showed that compound **85** ameliorated cognitive impairment in a scopolamine-induced mouse model. The results indicated that compound **85** deserves further study as a multifunctional lead compound[86].

2.2.9. 1,2,4-Oxadiazole-amide based compounds

Qiu et al. found a potent and selective reversible BTK inhibitor. Compound **86** (Figure 6) exhibited 58 nM BTK inhibitory potency and high kinome selectivity in human whole blood. It inhibited only two off-target kinases, FGR (IC_{50} = 5.36 μM) and Src (IC_{50} = 27.12 μM), and its inhibitory activity was closest to that of BTK. In addition, the compound exhibited favourable pharmacokinetics and showed potent dose-dependent efficacy in a rat CIA model[87].

Frejat et al. synthesised a series of 1,2,4-oxadiazole derivatives to evaluate the activity of the compounds against DNA gyrase and topoisomerase IV as well as many Gram-negative and Gram-positive strains. The results showed that compound **87** (Figure 6) had an IC_{50} of 0.21 μM against *Staphylococcus aureus* DNA gyrase and an IC_{50} value of 120 nM against *Escherichia coli* DNA gyrase, which was more active than novobiocin (170 nM). Furthermore, it showed activity against *Staphylococcus aureus* topoisomerase IV (IC_{50} = 5.2 μM) and *Escherichia coli* topoisomerase IV (IC_{50} = 3.07 μM). Compared to Ciprofloxacin (30 and 60 ng/mL, respectively), compound **87** exhibited excellent antibacterial activity against Gram-positive bacteria, with MIC values of 62 and 24 ng/mL against *Escherichia coli* and *Staphylococcus aureus*, respectively. Moreover, the cytotoxicity of compound **87** was very low[88].

Liu et al. designed and synthesised a series of 1,2,4-oxadiazole derivatives, which can be used as anti-AD drugs. According to biological evaluation, compound **88** (Figure 6) had the activity of inhibiting butyrylcholinesterase (IC_{50} = 1.28 ± 0.18 μM), neuroinflammation (NO: IC_{50} = 0.67 ± 0.14 μM; IL-1β: IC_{50} = 1.61 ± 0.21 μM; TNF-α: IC_{50} = 4.15 ± 0.44 μM) and Aβ self-aggregation (51.91 ± 3.90%). Preliminary anti-inflammatory mechanism studies showed that compound **88** blocked the activation of NF-kB signalling pathway. In addition, compound **88** exhibited DPPH free radical scavenging effect and inhibition of intracellular ROS production. Compound **88** also showed adequate blood-brain barrier permeability[89].

3. Summary

In this paper, 79 articles containing 1,3,4-oxadiazole and 1,2,4-oxadiazole derivatives with good activities were screened and reviewed since 2020. According to statistics, compounds from 15 articles have good antibacterial and antiparasitic activities. Compounds from 13 articles have good anti-inflammatory and antioxidant activities. Compounds from 29 articles have good anticancer activity. Compounds from 6 articles have compounds with antiglycemic activity. Compounds from 5 articles have antiviral activity. Compounds from 2 articles may be lead compounds for Alzheimer's disease. Compounds from the remaining articles have anti-influenza (compound **31**), anti-epileptic (compounds **35a–c**), anti-tuberculosis (compound **57**), neuroprotective (compound **73**) activities and the inhibition activities on tyrosinase (compound **42**), acetylcholinesterase (compounds **49a**, **49b**, **50a** and **50b**), Cat K (compounds **58a–d**), XO (compound **66**), hcA (compounds **77a–d**) and BTK (compounds **86**).

The 1,3,4-oxadiazole and 1,2,4-oxadiazole show bioisosteric equivalency with ester and amide moieties. The presence of 1,3,4-oxadiazole or 1,2,4-oxadiazole moiety in medicinal agents can modify their polarity and flexibility, hence the biological activities are significantly improved due to various bonded and non-bonded interactions, such as hydrogen bond, steric, electrostatic, and hydrophobic with target sites. 1,3,4-oxadiazole and 1,2,4-oxadiazole can therefore be deemed as potential framework for the novel drug development. In summary, we believe that the search for promising new modifications of 1,3,4-oxadiazole and 1,2,4-oxadiazole will contribute to the development of specific, low toxic and high potent drugs, still worthy of long-term efforts by chemical researchers.

Disclosure statement

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

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