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-tuberculous, 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.

1. Introduction

Oxadiazole is a critical component of pharmacophores and ligand binding. 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. 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. It has been reported that 1,3,4-oxadiazole and 1,2,4-oxadiazole derivatives possess antibacterial, anti-inflammatory, anti-tubercular, anti-HIV, antifungal, anticancer and antioxidant activities. The majority of commercially available antihypertensive agents such as Tiodazosin and Nesapidil, as well as antioxidants such as Furamizole, contain the oxadiazole nucleus. 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

Ustebas 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.

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 IC50 value of 23.07 ± 0.27 µM when compared it with synthetic antioxidant Diclofenac sodium (IC50 = 90.21 ± 0.77 µM), but the nitric oxide free radical scavenging activity was poor (IC50 = 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.

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 (IC50 = 24.74 µM) which was comparable to that of Tamoxifen (IC50 = 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 IC50 values of 2.52 µM and 4.38 µM compared to

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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$_{50}$ = 28.65 μM). These compounds showed

![Figure 1. Derivatives of 1,3,4-oxadiazole ring.](image-url)
anticancer activity by inhibiting TS, as they showed significant TS inhibitory activity with IC\textsubscript{50} values in the range of 1.95–4.24 \textmu M, compared with the standard drug Pemetrexed (IC\textsubscript{50} = 7.6 \textmu M). 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\textsuperscript{19}.

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 \textalpha-glucosidase. All of the synthesised derivatives exhibited good inhibitory activity against \textalpha-glucosidase. They discovered that two of these compounds had a significantly greater inhibitory effect against \textalpha-glucosidase than that of the standard drug Acarbose, and compounds 7a (IC\textsubscript{50} = 0.6 ± 0.05 \textmu M) and 7b (IC\textsubscript{50} = 0.30 ± 0.2 \textmu M, Figure 1) had more than hundredfold inhibitory activity against \textalpha-glucosidase compared with the standard inhibitor Acarbose (IC\textsubscript{50} = 38.45 ± 0.80 \textmu M). 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\textsuperscript{16}.

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

Oto 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 Xi-469. Even at a concentration of 10 \textmu M, 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 less than 10% of that of the control drug). They are, 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\textsuperscript{16}.

2.1.4. 1,3,4-Oxadiazole conjugated pyrimidinones

Said et al. synthesised a series of new oxadiazole conjugated pyrimidinones 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\textsubscript{50} = 0.140 ± 2.38 \textmu M, COX-2: IC\textsubscript{50} = 0.007 ± 0.11 \textmu M) compared with the standard drug Indomethacin\textsuperscript{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 \textmu M against Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa. Their MIC values against Candida albicans were 10.8 and 27.8 \textmu M, respectively, indicating good antibacterial activity\textsuperscript{19}.

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

Bita 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 \textmu g/mL against Bacillus subtilis (MTCC 441) and Staphylococcus aureus (MTCC 96), while compounds 12f (MTCC 441: MIC = 5.7 \textmu g/mL, MTCC 96: MIC = 8.8 \textmu g/mL) and 12g (MTCC 441: MIC = 5.5 \textmu g/mL, MTCC 96: MIC = 7.9 \textmu g/mL, Figure 1) were also found to be effective against the growth of gram-positive bacteria compared with standard antibacterial agents Ampicillin\textsuperscript{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 H37Rv Ma strain. Compound 13 (Figure 1) exhibited good anti-tuberculosis activity at a concentration of 62.5 \textmu g/mL, and its pharmacophore can be optimised to generate a series of improved anti-tuberculosis lead compounds containing the 1,3,4-oxadiazole ring\textsuperscript{21}.

Zabillu 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, H2O2, LPO and other methods. Among them, compound 14b (Figure 1) has strong antioxidant activity with an IC\textsubscript{50} value of 15.15 \textmu g/mL compared with the standard drug Ascorbic acid\textsuperscript{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\textsubscript{50} values of 2.5 ± 0.35 and 1.85 ± 0.28 \textmu M compared with the standard Doxorubicin. Compounds 15a and 15b (Figure 1) showed potential anti-cancer activity against MDA-MB-231 with IC\textsubscript{50} values of 4.88 ± 1.74 and 2.27 ± 0.73 \textmu M compared with the standard drug Doxorubicin\textsuperscript{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.
Compound 16 (Figure 2) showed the best biochemical activity, with an IC\textsubscript{50} of 0.0380 \textmu M. 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\textsuperscript{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 \textit{Trypanosoma cruzi} amastigotes, and was tested in male BALB/c mice infected with the \textit{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 \textit{Trypanosoma cruzi} amastigotes with IC\textsubscript{50} value of 1.11 ± 0.29 \textmu M compared with the standard drug Benznidazole (IC\textsubscript{50} = 3.98 ± 0.28 \textmu M)\textsuperscript{25}.

Mehandi et al. synthesised a series of new oxadiazole heterocyclic derivatives and determined the antibacterial activity on \textit{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 \textmu g/mL, comparable to that of the standard drug Fluconazole\textsuperscript{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 \textit{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 streptomycin27.

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 IC50 value of 0.46 ± 0.15 mM for GAA inhibition, which is still too low to compete with AC128.

Gond et al. synthesised a 5-(4-hydroxyphenyl)-2-(N-phenylal)

ligand 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. The results showed that compound 22 (Figure 2) exhibited antiproliferative effects on EAC and Skov3 cell lines with IC50 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 molecule30.

Jyothi et al. synthesised a series of novel 1,3,4-oxadiazole-con

taining coumarin analogs and screened the newly synthesised molecules in various cell lines such as ACHN, A375, SiHa, Skov3 and EAC by MTT and trypan blue assays. The results showed that compound 22 (Figure 2) exhibited antiproliferative effects on EAC and Skov3 cell lines with IC50 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 molecule30.

Tok et al. designed and synthesised a series of 2,5-disubstituted-1,3,4-oxadiazole derivatives and determined their monoo

amidase oxidase (MAO) inhibitory activity. The results showed that 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 IC50 values of 0.039, 0.066, 0.045 μM, respectively31.

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 IC50 values of 2.03 μM and 9.80 μM, respectively, which were superior to Harmine (A549: IC50 = 17.12 μM, H2228: IC50 = 31.06 μM). Overall, compound 25 was identified as a potential lead drug against advanced non-small cell lung cancer33.

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), butrylcholinesterase (BChE) and beta-secretase-1 (BACE-1). Compound 26a (Figure 2) was the most effective AChE inhibitor (IC50 = 0.068 μM). The IC50 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 IC50 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-SYSY 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 disease34.

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 isozymes hCA I/II and the tumour-associ

ated isozymes 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 nM, but compounds 27 (Ki = 70.7 nM, Figure 2) and 28 (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 μM. 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 isozymes hCA IX35.

Hamdani et al. synthesised new 1,4-benzylamination 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 IC50 values of 13.9 and 15.1 μM, respectively36.

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

Javid et al. designed and synthesised a series of 10 different oxadiazole-sulfonamide 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 IC50 value of 4.77 ± 0.47 μM, whereas compound 30c inhibited ALR2 selectively with an IC50 value of 2.21 ± 0.73 μM. The remaining analogs inhibited both enzymes in tandem37.
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 (IC₅₀ = 0.027 μM), significantly 3.04-fold lower than Oseltamivir carboxylate (IC₅₀ = 0.082 μM). Compound 31 also showed stronger inhibitory potency against H5N1-H274Y mutant relative to Oseltamivir carboxylate.

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 IC₅₀ range of 2.6 ± 0.1 to 140 ± 0.3 μM in the presence of positive control, Acarbose (IC₅₀ = 38.45 ± 0.80 μM). Compounds 32a, 32b, 32c and 32d (Figure 3) had IC₅₀ 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.

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-oxadia-
zole fused tetrazole 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 antitumour 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-oxadia-
zole based hybrids. Among the synthesised compounds, com-
ounds 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]quinazoline-1,3,4-oxadiazole derivatives
Kaneko et al. synthesised a series of [1,2,4]triazolo[4,3-a]quinaza-
line-1,3,4-oxadiazole derivatives and assessed their anti-prolifera-
tive effects against a variety of cancer cell lines including hitoicytic 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(ind-
dolyl) -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 cyto-
toxic 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 deriv-
atives 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 thieno-
pyrimidine and 1,3,4-oxadiazole and evaluated the anti-inflamma-
tory activity of carrageenan-induced acute foot swelling in rats using standard procedures. Compound 39 (Paw edema 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 edema 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 IC_{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 (IC_{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 com-
pound 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 concentra-
tions (0-50 μM).49

Omar et al. synthesised 1,3,4-oxadiazole derivatives and
cut and screened the synthesised compounds for their antifungal
activity against Candida glabrata, Candida cruzi, Candida parapsilosi-
s and Candida albicans. The results showed that compounds 45a 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. Com-
D C-6a, 6b, 6c, 6d and 6e (Figure 4) were potent
and selective COX-2 inhibitors (IC\textsubscript{50}: 0.04–0.081 \textmu M; 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.

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\textsubscript{50} = 2.97 \textmu g/mL), compound 47 (Figure 4) had an IC\textsubscript{50} value of 3.80 \textmu g/mL for MCF-7 cells.

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\textsubscript{50} value of compound 48 (Figure 4) on MCF-7 cells was 3.50 \textmu g/mL when Doxorubicin (IC\textsubscript{50} = 2.97 \textmu g/mL) was used as a control.

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
IC₅₀ 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 (IC₅₀ = 0.03 ± 0.00 μg/mL) was used as a control.15

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 oxadiazolothiazoles 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-Fluouracil (MCF-7: IC₅₀ = 34.82 μM, HCT-116: IC₅₀ = 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 IC₅₀ 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 PI3K in vitro, with IC₅₀ values of 6.6 ± 2.1 and 7.6 ± 4.2 μM, respectively.60

Wang et al. designed and synthesised a series of novel nitrofuranimide-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 (CC₅₀ = 57.34 μg/mL), especially the inhibition on hERG (IR = 11.3 ± 1.7% at 10 μM). It has a better 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 IC₅₀ 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 capsacin-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 capsain 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 IC₅₀ 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 IC₅₀ 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 C₄ synthase at sub-μM concentrations with IC₅₀ 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 I. 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 (IC₅₀ = 147.7 μM, Figure 5) had an inhibitory effect on topology II in the micromolar range, as demonstrated by the HTS topology II 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 (IC₅₀ = 12.84 ± 0.21 μM) and LPS-induced NF-κB activation (IC₅₀ = 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)-1H-indole-3-carbonitriles as a potent XO inhibitor. Compound 66 (IC₅₀ = 0.36 μM, Figure 5) was shown to be the most potent
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.

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.

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.

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.

Melo de Oliveira et al. synthesised a new 1,2,4-oxadiazole derivative and evaluated it on lung cancer (NCI-H460). Compounds 70a and 70b (Figure 5) had the highest antiproliferative activity against NCI-H460 in vitro, with IC_{50} values of 3.87 ± 0.40 and 3.21 ± 0.70 μM, respectively.

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 ± 5.25 μM.

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).

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 ± 2.00%) and 10 μM (cell viability: 96.85 ± 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.

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 ± 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 ± 1.38 μM) was used as a positive control for comparison.

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.

### 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.

### 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 value of hCA IX was 23.6 ± 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.

### 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 4 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 ulcrogenic potential, with an injury index of 78.7%, whereas the tested compound had a lower ulcrogenic potential, with an injury index of 35–61%. Among these, compound 79b demonstrated potent anti-inflammatory activity in vivo and, when compared to Indomethacin, it showed a lower ulcrogenic, with an injury index of 38%. In contrast, all compounds studied were shown to be more ulcrogenic than Celecoxib.

### 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_{2}H as a
heterogeneous acid catalyst. This was a new, simple and effective method. A series of compounds were synthesised and their anti-cancer 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 IC50 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.

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 IC50 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 (IC50 values of 3.89, 2.38, 2.50 and 2.85 μM, respectively).

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 in triglycerides, 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 EC50 of 0.781 ± 0.008 μM, 3.29 ± 0.03 μM and 0.07 ± 0.0006 μM, 0.06 ± 0.0005 μM respectively.
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.

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 anti-cancer 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) isofrom, 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 cell colony 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.

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 glycolgen 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.

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.

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 60ng/mL, respectively), compound 87 exhibited excellent antibacterial activity against Gram-positive bacteria, with MIC values of 62 and 24ng/mL against Escherichia coli and Staphylococcus aureus, respectively. Moreover, the cytotoxicity of compound 87 was very low.

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.

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), hCAIX (compounds 77a-d) and BTK (compound 86).

The 1,3,4-oxadiazole and 1,2,4-oxadiazole show biososieric 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.
References

1. Boström J, Hogner A, Llinàs A, et al. Oxadiazoles in medicinal chemistry. J Med Chem 2012;55:1817–30.
2. Patani GA, LaVoie EJ. Biosisosterism: a rational approach in drug design. Chem Rev 1996;96:3147–76.
3. Aboraia AS, Abdel-Rahman HM, Mahfouz NM, El-Gendy MA. Novel S-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives: promising anticancer agents. Bioorg Med Chem 2006;14:1236–46.
4. Adib M, Kesheh MR, Ansari S, Bijanzadeh HR. Reaction between N-isocyanamidinotri phenylmethane and Attack, and carboxylic acids: a one-pot and three-componen synthesis of S-Aryl-S-hydroxyalkyl-1,3,4-oxadiazoles. Synlett 2009; 2009;1575–8.
5. Chen Q, Zhu XL, Jiang LL, Liu ZM, et al. Synthesis, antifungal activity and CoMFA analysis of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives. Eur J Med Chem 2008;43:595–603.
6. Kadi AA, El-Brollosy NR, Al-Deeb OA, et al. Synthesis, anti-microbial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. Eur J Med Chem 2007;42:235–42.
7. Palaska E, Sahin G, Kelicen P, et al. Synthesis and anti-inflammatory activity of 1-acetylsemicarbazides, 1,3,4-oxadiazoles, 1,3,4- thiadiazoles and 1,2,4-triazole-3-thiones. Farmaco 2002;57:101–7.
8. Alisi O, Uzairu A, Abechi SE. Free radical scavenging mechanism of 1,3,4-oxadiazole derivatives: thermodynamics of OH and N–H bond cleavage. Heliyon 2020;6:e03683.
9. Zarghi A, Tabatabai SA, Faizi M, et al. Synthesis and anticongestive activity of new 2-substituted-5-(2-benzylloxypyridin-1,3,4-oxadiazoles. Bioorg Med Chem Lett 2005;15:1863–5.
10. Chandrakantha B, Shetty P, Namibyar V, et al. Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety. Eur J Med Chem 2010;45:1206–10.
11. Ustaba R, Suleymenoglu N, Uner Y, Direkel S, S-(4-Bromobenzyl)-4-(4-(5-phenyl-1,3,4-oxadiazole-2-yl)phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-one: synthesis, characterization, DFT study and antimicrobial activity. J Mol Struct 2020; 1214:128217.
12. Kashid BB, Salunkhe PH, Dongare BB, et al. Synthesis of novel of 2,5-disubstituted 1,3,4-oxadiazole derivatives and their in vitro anti-inflammatory, anti-oxidant evaluation, and molecular docking study. Bioorg Med Chem Lett 2020;30:127136.
13. Alam MM, Almalki AS, Neamatallah T, et al. Synthesis of New 1, 3, 4-Oxadiazole-incorporated 1, 2, 3-Triazole moieties as potential anticancer agents targeting thymidylate synthase and their docking studies. Pharmaceuticals 2020;13:390.
14. Alam MM, Nazreen S, Almalki ASA, et al. Naproxen based 1,3,4-oxadiazole derivatives as EGFR inhibitors: design, synthesis, anticancer, and computational studies. Pharmaceuticals 2021;14:870.
15. Almalki ASA, Nazreen S, Malebari AM, et al. Synthesis and biological evaluation of 1,2,3-triazole tethered thymol-1,3,4-oxadiazole derivatives as anticancer and antimicrobial agents. Pharmaceuticals 2021;14:866.
16. Ullah H, Rahim F, Taha M, et al. Aryl-oxadiazole Schiff bases: synthesis, S-glucosidase in vitro inhibitory activity and their in silico studies. Arabian J Chem 2020;13:4904–15.
17. Ono Y, Ninomiya M, Kaneko D, et al. Design and synthesis of quinoxaline-1,3,4-oxadiazole hybrid derivatives as potent inhibitors of the anti-apoptotic Bcl-2 protein. Bioorg Chem 2020;104:104245.
18. Said MF, Georgey HH, Mohammed ER. Synthesis and computational studies of novel fused pyrimidinones as a promising scaffold with analgesic, anti-inflammatory and COX inhibitory potential. Eur J Med Chem 2021;224:113682.
19. Chortani S, Edziri H, Manachou M, et al. Novel 1,3,4-oxadia- zole linked benzopyrimidinomides conjugates: synthesis, DFT study and antimicrobial evaluation. J Mol Struct 2020;1217:128357.
20. Bitla S, Sagurthi SR, Dhanavath R, et al. Design and synthesis of Triazole conjugated novel 2,5-diyrl substituted 1,3,4-oxadia- zoles as potential antimicrobial and anti-fungal agents. J Mol Struct 2020;1220:128705.
21. Ningeogwda R, Chandrashkeharappa S, Singh V, et al. Design, synthesis and characterization of novel 2-(2,3-dichlorophenyl)-5-aryl-1,3,4-oxadiazole derivatives for their anti-tubercular activity against Mycobacterium tuberculosis. Chem Data Collect 2020;28:100431.
22. Nagesh Khadi MJ, Bushra Begum A, Sunil MK, Kahanum SA. Synthesis, docking and biological evaluation of thiazidazole and oxadiazole derivatives as antimicrobial and antioxidant agents. Results Chem 2020;2:100045.
23. Bajaj S, Kumar MS, Tinwala H, YC M. Design, synthesis, mod-elling studies and biological evaluation of 1,3,4-oxadiazole derivatives as potent anticancer agents targeting thymidine phosphorlyase enzyme. Bioorg Chem 2021;111:104873.
24. Fang LC, Tian JP, Zhang KK, et al. Discovery of 1,3,4-oxadia- zole derivatives as potential antitumor agents inhibiting the programmed cell death-1/programmed cell death-1 ligand 1 interaction. Bioorg Med Chem 2021;46:116370.
25. Ribeiro JLS, Soares JCAV, Portapilla GB, et al. Trypanocidal activity of new 1,6-diphenyl-1H-pyrazolo[3,4-b]pyridine derivatives: synthesis, in vitro and in vivo studies. Bioorg Med Chem 2021;29:115855.
26. Mehandi R, Arif R, Rana M, et al. Synthesis, characterization, DFT calculation, anti-fungal, antioxidant, CT-DNA/pBR322 DNA interaction and molecular docking studies of heteroco-agular analogs. J Mol Struct 2021;1245:131248.
27. Dhonnar SL, More RA, Adole VA, et al. Synthesis, spectral analysis, antibacterial, anti-fungal, antioxidant and hemolytic activity studies of some new 2,5-disubstituted-1,3,4-oxadia- zoles. J Mol Struct 2022;1253:132216.
28. Izgi S, Sengul IF, Sahin E, et al. Synthesis of 7-azaindoled based carbohydradzes and 1,3,4-oxadiazoles; antioxidant activity, α-glucosidase inhibition properties and docking study. J Mol Struct 2022;1247:131343.
29. Gond MK, Shukla A, Pandey SK, et al. Mn(II) catalyzed syn-thesis of S(4-hydroxyphenyl)–(N-phenylamino)-1,3,4-oxadia- zole: crystal structure, DFT, molecular docking, Hirshfeld...
surface analysis, and in vitro anticancer activity on DL cells. J Mol Struct 2022;1249:131547.
30. Jyothi M, Sherapura A, Khamees HA, et al. Synthesis, structure analysis, DFT calculations and energy frameworks of new coumarin appended oxadiazoles, to regress ascites malignancy by targeting VEGF by diated angiogenesis. J Mol Struct 2022;1252:132173.
31. Tok F, Uğraş Z, Sağlık BN, et al. Novel 2,5-disubstituted-1,3,4-oxadiazole derivatives as MAO-B inhibitors: synthesis, biological evaluation and molecular modeling studies. Bioorg Chem 2020;112:104917.
32. Duhan M, Kumar P, Sindhu J, et al. Exploring biological efficacy of novel benzothiazole linked 2,5-disubstituted-1,3,4-oxadiazole hybrids as efficient α-amylase inhibitors: synthesis, characterization, inhibition, molecular docking, molecular dynamics and Monte Carlo based QSR studies. Comput Biol Med 2021;138:104876.
33. Zhao TM, Yang Y, Yang J, et al. Harmine-inspired design and synthesis, evaluation of ferulic acid based 1,3,4-oxadiazole hybrids as multifunctional therapeutics for the treatment of Alzheimer’s disease. Bioorg Chem 2020;95:103506.
34. Sharma V, Kumar R, Angeli A, et al. Tail approach synthesis of novel benzenesulfonamides incorporating 1,3,4-oxadiazole hybrids as potent inhibitor of carbonic anhydrase I, II, IX, and XII isoenzymes. Eur J Med Chem 2020;193:112219.
35. Hamdani SS, Khan BA, Hameed S, et al. Synthesis and evaluation of novel S-benzyl- and S-alkylphthalimide-oxadiazole-benzenesulfonamide hybrids as inhibitors of dengue virus protease. Bioorg Chem 2020;96:103567.
36. Javid N, Munir R, Chaudhry F, et al. Exploiting oxadiazole-sulfonamide hybrids as new structural leads to combat diabetic complications via aldose reductase inhibition. Bioorg Chem 2020;99:103852.
37. Yu W, Cheng LP, Pang W, Guo LL. Design, synthesis and biological evaluation of novel 1,3,4-oxadiazole derivatives as potent neuraminidase inhibitors. Bioorg Med Chem 2022;57:116647.
38. Taha M, Rahim F, Zaman K, et al. Synthesis, α-glycosidase inhibitory potential and molecular docking study of benzimidazole derivatives. Bioorg Chem 2020;95:103555.
39. Sharmugam MK, Rangappa S, Metri PK, et al. Exploring the newer oxadiazoles as real inhibitors of human SIRT2 in hepatocellular cancer cells. Bioorg Med Chem Lett 2020;30:127330.
40. Kotla R, Murugulla AC, Ruddaraju R, et al. Synthesis and biological evaluation of 1,3,4-oxadiazole fused tetrazole amide derivatives as anticancer agents. Chem Data Collect 2020;30:100548.
41. Singh RB, Das N, Singh GK, et al. Synthesis and pharmacological evaluation of 3-[5-aryl-[1,3,4]oxadiazole-2-yl]-piperidine derivatives as anticonvulsant and antidepressant agents. Arabian J Chem 2020;13:5299–5311.
42. Kaneko D, Ninomiya M, Yoshikawa R, et al. Synthesis of [1,2,4]triazolo[4,3-α]quinolinoxaline-1,3,4-oxadiazole derivatives as potent antiproliferative agents via a hybrid pharmacophore approach. Bioorg Chem 2020;104:104293.
43. Sreenivasulu R, Tej MB, Jadav SS, Sujitha P, et al. Synthesis, anticancer evaluation and molecular docking studies of 2,5-bis(indolyl)-1,3,4-oxadiazoles, Nortopsentin analogues. J Mol Struct 2020;1208:127875.
44. Kumar D, Kumar RR, Pathania S, et al. Investigation of indole functionalized pyrazoles and oxadiazoles as anti-inflammatory agents: synthesis, in-vivo, in-vitro and in-silico analysis. Bioorg Chem 2021;114:105068.
45. Tolba MS, Sayed AM, Sayed M, Ahmed M. Design, synthesis, biological evaluation, and molecular docking of some new Thieno[2,3-d] pyrimidine derivatives. J Mol Struct 2021;1246:131179.
46. Wu ZB, Yang WQ, Hou ST, et al. In vivo antiviral activity and disassembly mechanism of novel 1-phenyl-5-amino-4-pyrazole thioether derivatives against Tobacco mosaic virus. Pestic Biochem Physiol 2021;173:104771.
47. Abbas AH, Mahmood AAR, Tahtamouni LH, et al. New picolinic acid derivatives: synthesis, docking study and anti-EGFR kinase inhibitory effect. Mater Today Proc 2021;5:13–14.
48. Vanjare BD, Choi NG, Mahajan PG, et al. Novel 1,3,4-oxadiazole compounds inhibit the tyrosinase and melanin level: synthesis, in-vitro, and in-silico studies. Bioorg Med Chem 2021;41:116222.
49. Çevik UA, Celik I, Işık A, et al. Synthesis, molecular modeling, quantum mechanical calculations and ADME estimation studies of benzimidazole-oxadiazole derivatives as potent antifungal agents. J Mol Struct 2022;1252:132095.
50. Al Sayyed AH, Abdul-Aziz SA, Marzouk AA, Shyakoon MSA, et al. Design and synthesis of pyrimidine-5-carbonitrile hybrids as COX-2 inhibitors: anti-inflammatory activity, ulcerogenic liability, histopathological and docking studies. Bioorg Chem 2021;108:104555.
51. El-Etrawy AS, Sherbiny FF. Design, synthesis, biological assessment and molecular docking studies of some new 2-Thioxo-2,3-dihydropyrimidin-4(1H)-ones as potential anticancer and antibacterial agents. J Mol Struct 2021;1225:129014.
52. El-Etrawy AS, Sherbiny FF. Design, synthesis, biological evaluation and molecular modeling investigation of new N-(2-Thiocarbamoyl-5-oxy) hydrazine derivatives as potential anti-breast cancer and anti-bacterial agents. J Mol Struct 2021;1232:129993.
53. Fahim AM, Farag AM, Mermer A, et al. Synthesis of novel β-lactams: antioxidant activity, acetylcholinesterase inhibition and computational studies. J Mol Struct 2021;1233:130092.
54. Rashad AY, Kassab SE, Daabees HG, et al. Febuxostat-based thiazole hybrids as COX-2 inhibitors: anti-inflammatory activity, ulcerogenic liability, histopathological and docking studies. Bioorg Chem 2021;108:104555.
55. Al Sayyed AH, Abdul-Aziz SA, Marzouk AA, Shyakoon MSA, et al. Design and synthesis of pyrimidine-5-carbonitrile hybrids as COX-2 inhibitors: anti-inflammatory activity, ulcerogenic liability, histopathological and docking studies. Bioorg Chem 2021;108:104555.
56. Al Sayyed AH, Abdul-Aziz SA, Marzouk AA, Shyakoon MSA, et al. Design and synthesis of pyrimidine-5-carbonitrile hybrids as COX-2 inhibitors: anti-inflammatory activity, ulcerogenic liability, histopathological and docking studies. Bioorg Chem 2021;108:104555.
60. Gu DY, Cheng G, Zhang MM, et al. Discovery of 2-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)acetamide derivatives as novel PI3Kα inhibitors via docking-based virtual screening. Bioorg Med Chem 2021;29:115863.

61. Wang AP, Xu SJ, Chai Y, et al. Design, synthesis and biological evaluation of nitrofuran-1,3,4-oxadiazole hybrids as new antitubercular agents. Bioorg Med Chem 2022;53; 116529.

62. Gontjio TB, Lima PS, Icimoto MY, et al. Cathepsin K inhibitors based on 2-amino-1,3,4-oxadiazole derivatives. Bioorg Med Chem 2021;109:104662.

63. El Mansouri AE, Oubella A, Mehdi A, et al. Design, synthesis, biological evaluation and molecular docking of new 1,3,4-oxadiazole homonucleosides and their double-headed analogs as antitumor agents. Bioorg Chem 2022;108:104558.

64. Naaz F, Khan A, Kumari A, et al. 1,3,4-oxadiazole conjugates of capsaicin as potent NorA efflux pump inhibitors of Staphylococcus aureus. Bioorg Chem 2021;113:105031.

65. Meng XD, Gao LX, Wang ZJ, et al. Synthesis and biological evaluation of 2,5-diaryl-1,3,4-oxadiazole derivatives as novel Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2) inhibitors. Bioorg Chem 2021;116:105384.

66. Ergül AG, Maz TG, Kretzer C, et al. Novel potent benzimidazole-based microsomal prostaglandin E2 synthase-1 (mPGES-1) inhibitors derived from BRP-201 that also inhibit leukotriene C4 synthase. Eur J Med Chem 2022;231:114167.

67. Loboda KB, Valjavec K, Stampar M, et al. Design and synthesis of 3,5-substituted 1,2,4-oxadiazoles as catalytic inhibitors of human DNA topoisomerase IIα. Bioorg Chem 2020;99:103828.

68. Zhang YY, Zhang QQ, Zhang J, et al. Synthesis and evaluation of 1,2,4-oxadiazole derivatives as potential anti-inflammatory agents by inhibiting NF-κB signaling pathway in LPS-stimulated RAW 264.7 cells. Bioorg Med Chem Lett 2020;30:127373.

69. Gao J, Liu XG, Zhang B, et al. Design, synthesis and biological evaluation of 1-alkyl-5/6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1H-indole-3-carbonitriles as novel xanthine oxidase inhibitors. Eur J Med Chem 2020;190:112077.

70. Chen YC, Dinavahi SS, Feng QL, et al. Activating Sphingosine-1-phosphatase signaling in endothelial cells increases myosin light chain phosphorylation to decrease endothelial permeability thereby inhibiting cancer metastasis. Cancer Lett 2021;506:107–119.

71. Choi HE, Kim YS, Lee HJ, Cheon HG. Novel FoxO1 inhibitor, JY-2, ameliorates palmitic acid-induced lipotoxicity and gluconeogenesis in a murine model. Eur J Pharmacol 2021;899:174011.

72. Mohan G, Sridhar G, Laxminarayana E, Chary MT. Synthesis and biological evaluation of 1,2,4-oxadiazole incorporated 1,2,3-triazole-pyrazole derivatives as anticancer agents. Chem Data Collect 2021;34:100735.

73. Melo de Oliveira VN, Flávia do Amaral Moura C, Peixoto ADS, et al. Synthesis of alkynylated 1,2,4-oxadiazole/1,2,3-1H-triazole glycoconjugates: discovering new compounds for use in chemotheraphy against lung carcinoma and Mycobacterium tuberculosis. Eur J Med Chem 2021;220:113472.

74. Egorova A, Kazakova E, Jahn B, et al. Novel pleconaril derivatives: influence of substituents in the isoxazole and phenyl rings on the antiviral activity against enteroviruses. Eur J Med Chem 2020;188:112007.

75. Sucu BO, Koc EB, Savlug Ipek O, et al. Design and synthesis of novel caffeic acid phenethyl ester (CAPE) derivatives and their biological activity studies in glioblastoma multiforme (GBM) cancer cell lines. J Mol Graph Model 2022;113:108160.

76. Shi JG, Wang Y, Chen JW, et al. Synthesis and biological evaluation of 1,2,4-oxadiazole core derivatives as potential neuroprotectants against acute ischemic stroke. Neurochem Int 2021;148:105103.

77. Kumar Kushwaha P, Saurabh Srivastava K, Kumari N, et al. Synthesis and anti-HIV activity of a new isoxazole containing disubstituted 1,2,4-oxadiazoles analogs. Bioorg Med Chem 2022;56:116612.

78. Xie HW, Wang YH, Zhang JH, et al. Design, synthesis and biological evaluation of marine phdianidine-inspired derivatives against oxidized LDL-induced endothelial injury by activating Nr2 anti-oxidation pathway. Bioorg Chem 2022;120:105606.

79. Perrino B, Carbone D, Cascioferro S, et al. 1,2,4-Oxadiazole tosponin analogs as staphylococcal biofilm inhibitors targeting the bacterial transpeptidase Sortase A. Eur J Med Chem 2021;209:112892.

80. Thacker PS, Angeli A, Argulwar OS, et al. Design, synthesis and biological evaluation of coumarin linked 1,2,4-oxadiazoles as selective carbonic anhydrase IX and XII inhibitors. Bioorg Chem 2020;98:103739.

81. Mohamed MFA, Marzouk AA, Nafady A, et al. Design, synthesis and molecular modeling of novel aryl carboximidamides and 3-aryl-1,2,4-oxadiazoles derived from indomethacin as potent anti-inflammatory INOS/PGE2 inhibitors. Bioorg Chem 2020;105:104439.

82. El Mansouri AE, Oubella A, Maatallah M, et al. Design, synthesis, biological evaluation and molecular docking of new uracil analogs-1,2,4-oxadiazole hybrids as potential anti-cancer agents. Bioorg Med Chem Lett 2020;30:127438.

83. Fernandes FS, Santos H, Lima SR, et al. Discovery of highly potent and selective antiparasitic new oxadiazole and hydroxy-oxindole small molecule hybrids. Eur J Med Chem 2020;201:112418.

84. Kaur P, Bhat ZR, Bhat S, et al. Synthesis and evaluation of new 1,2,4-oxadiazole based trans-acrylic acid derivatives as potential PPAR-alpha/gamma dual agonist. Bioorg Chem 2020;100:103867.

85. Shamsi F, Hasan P, Queen A, et al. Synthesis and SAR studies of novel 1,2,4-oxadiazole-sulfonamide based compounds as potential anticancer agents for colorectal cancer therapy. Bioorg Chem 2020;98:103754.

86. Wang M, Liu TT, Chen SM, et al. Design and synthesis of 3-(4-pyridyl)-5-(4-sulfamido-phenyl)-1,2,4-oxadiazole derivatives as novel GSX-3β inhibitors and evaluation of their potential as multifunctional anti-Alzheimer agents. Eur J Med Chem 2021;209:112874.

87. Qiu H, Ali Z, Bender A, et al. Discovery of potent and selective reversible Bruton’s tyrosine kinase inhibitors. Bioorg Med Chem 2021;40:116163.

88. Frejat FOA, Cao YQ, Zhai HJ, et al. Novel 1,2,4-oxadiazole/ pyrrolidine hybrids as DNA gyrase and topoisomerase IV inhibitors with potential antibacterial activity. Arabian J Chem 2022;15:103538.

89. Liu TT, Chen SM, Du JY, et al. Design, synthesis, and biological evaluation of novel 4-((1,2,4-oxadiazol-5-yl)phenyl)-2-aminoacetamide derivatives as multifunctional agents for the treatment of Alzheimer’s disease. Eur J Med Chem 2022;227:113973.