1,3,4-OXADIAZOLE: A HETEROCYCLE WITH VERSATILE BIOLOGICAL ACTIVITY

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Abstract
Oxadiazole is a principal heterocyclic compound containing one oxygen and two nitrogen atoms in the five membered ring. 1,3,4-oxadiazole is a multifaceted heterocyclic moiety plays a major role in the pharmaceutical chemistry and broad range of important biological activities gain the attention of researchers to explore the new therapeutic molecule. The present review analyses the various synthetic procedures and pharmacological activities of 1,3,4-oxadiazole moiety.

Keywords: 1,3,4-oxadiazole, Synthesis, Pharmacological activities

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INTRODUCTION

Oxadiazole is one of the dominant heterocyclic compounds containing one oxygen and two nitrogen atoms in five membered ring that is derived from furan by replacing the two methane (-CH=) group by two pyridine type nitrogen (-N=). Depending upon the position of N- atom in the heterocyclic ring, oxadiazoles are further grouped in to four isomers. They are 1,2,3 oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole [1].

Among the four isomers, 1,3,4-oxadiazole and 1,2,4-oxadiazole are well known for their several notable chemical and biological properties, for example Nesapidil, a 1,3,4-oxadiazole has anti-hypertensive property. Furamizole, another one 1,3,4-oxadiazole is an effective antimicrobial agent.

Raltegravir, a 1,2,4-oxadiazole is known for its anti-retroviral property [2] (Fig. 1).

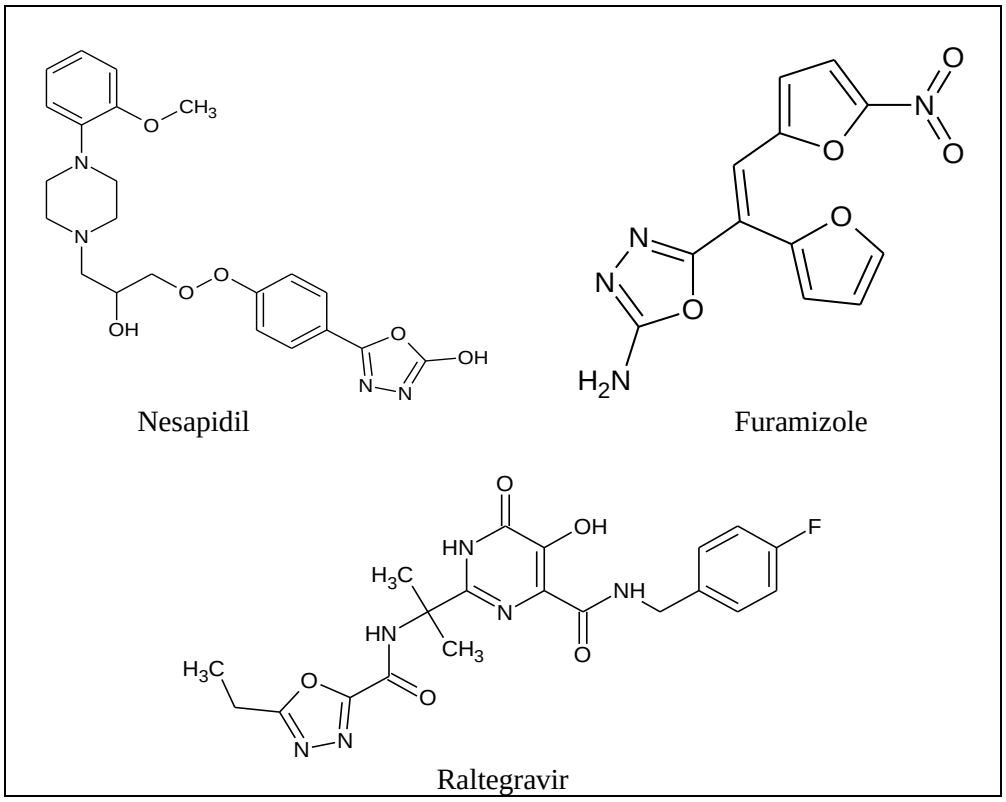


Fig. 1: Drugs contain oxadiazole nucleus

1,3,4-oxadiazole has become an important construction element for the development of novel drugs. Literature survey revealed that a slight modification in the structure can result in qualitative as well as quantitative changes in the activity that gives a hope to synthesis a wide range of new 1,3,4-oxadiazole derivatives with the aim of better activity with lesser toxicity. As a result, in the last two decades, the synthesis of novel 1,3,4-oxadiazole derivatives and the analysis of their chemical properties and biological activities has accelerated and in the recent years, it has increased considerably [1].

Thus, 1,3,4-oxadiazole derivatives is an prime pharmacophore, play a significant role in the pharmaceutical chemistry and a wide range of important biological activities. This review describes the main synthesis approaches as well as the broad spectrum pharmacological activities of 1,3,4-oxadiazole as reported in the literature.

Chemistry of Oxadiazole

Oxadiazole is a heterocyclic aromatic chemical compounds having the molecular formula of $C_2H_2N_2O$. Among the four isomers of oxadiazole, the 1,2,3-isomer is unbalanced and reverts to the diazoketone tautomer [1, 3]. Due to the inductive effect of the extra heteroatom, oxadiazole exist as very weak base. The oxadiazole ring exhibit the character of conjugated diene due to the lowering of aromaticity because of the replacement of two –CH=groups in furan by two pyridine type nitrogen (-N=). Due to the low electron density, the electrophilic substitution in the carbon atom of oxadiazole ring is extremely difficulty. However, the electrophiles attack occurs at nitrogen, if the oxadiazole ring is substituted with the electron-releasing groups. Generally, oxadiazole ring is

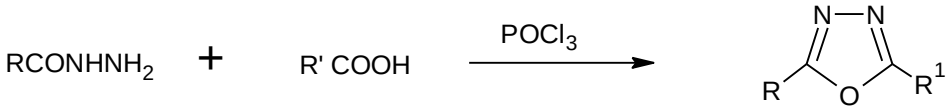
resistant to nucleophilic attack. Literature survey reveals that the oxadiazoles undergoes number of reactions such as thermal, photochemical reactions electrophilic and nucleophilic substitution[1, 4] .

Synthesis of 1,3,4-Oxadiazole

In view of the great medicinal significance and material applications a number of synthetic routes have been developed for 1, 3, 4-oxadiazoles. Most of the 1, 3, 4-oxadiazoles are usually obtained by synthesis from acyclic precursors but also by ring transformation reactions [5].

Method 1

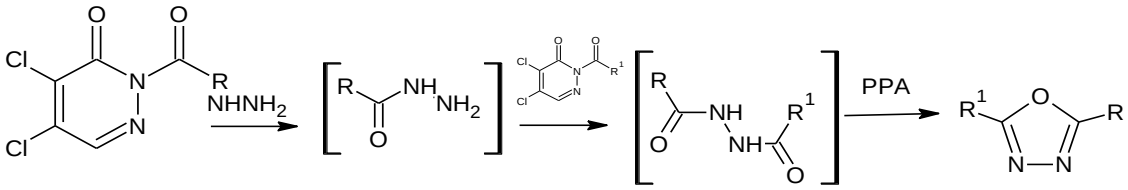
Acid hydrazides when treated with carboxylic acids in presence of phosphorous oxychloride undergo oxidative cyclization to give 2, 5-disubstituted-1, 3, 4-oxadiazoles. Cyclization refers to the ring-forming step of a reaction sequence leading to the oxidized structure. Suitably disposed reacting sites on the substrate, other functionalities elsewhere on the structure able to survive the oxidation conditions and the nature of the oxidizing agent are the fundamental requisites for the success of the reaction.



Scheme 1: Synthesis of 1,3,4-Oxadiazole from Acid hydrazide

Method 2

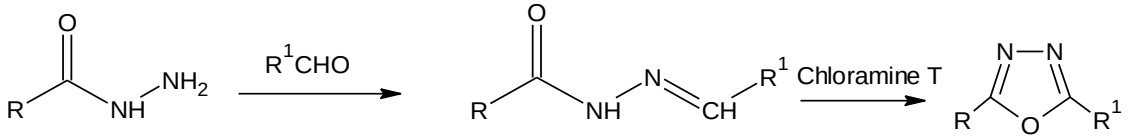
Symmetric and asymmetric 1,3,4-oxadiazoles were synthesized *in situ* from hydrazine hydrate and the corresponding 2-acyl-4,5-dichloropyridazin-3-ones as acylating agent in polyphosphoric acid (PPA) in excellent yields.



Scheme 2: Synthesis of 1,3,4-Oxadiazole from hydrazine hydrate

Method 3

Aldehyde or ketone arylhydrazides also undergo oxidative cyclization to give the 2,5-disubstituted oxadiazoles in presence of oxidizing agents such as lead tetra acetate or chloramine T.



Scheme 2: Synthesis of 1,3,4-Oxadiazole from aryl hydrazide

The Percentage of C,H,N and the bond angle existing in the 1, 3, 4-oxadiazole [1, 6]. is shown in Table 1.

Table 1: Physical properties of 1, 3, 4-oxadiazole

Atom	**Calculated Percentage**	**Found Percentage**
C	34.29	34.56
H	2.88	3.19
N	40.00	39.71
Bond/Angle	**Bond angle (°)**	**Bond length (pm)**
A	105.6	139.7
B	113.4	129.9
C	102.0	134.8
D	113.4	134.8
E	105.6	19.7

Reactivity of 1,3,4-Oxadiazole

Generally, the major reactions of 1,3,4-oxadiazole are nucleophilic at carbon followed by the cleavage of ring and electrophilic attack at nitrogen due to relatively a low electron density at 2nd and 5th position carbon and relatively a high electron density at 3rd and 4th position nitrogen. This reactivity towards the nucleophiles can also be catalysed by acid, cause difficulties to carry out the reactions involving basic or acidic conditions. This

ring is shows stability when it is substituted by one or more aryl groups. Tautomeric oxadiazole react with electrophile either at ring nitrogen or at the exocyclic heteroatom or at the both centre. In alkyl or aryl 1,3,4-oxadiazole, the reactions in the substituent groups are possible but they are limited by the sensitivity of the ring to the reagents used [1, 3].

Anti-inflammatory activity

Singh *et al.* [7] synthesized different 1,3,4-oxadiazole compounds, characterized by ^{1}HNMR, IR and Mass spectrometry methods and evaluated for anti-inflammatory activity by carrageenan-induced rat-paw-oedema method. Form the evaluation, two among the five compounds namely [3-Chloro-*N*-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide, and [4-Nitro-*N*-[5-(4-Nitro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide showed a significant anti-inflammatory activity.

Bala *et al.* [8] synthesized a series of novel n-phenyl anthranilic acid-based 1,3,4-oxadiazoles (Fig. 2) and subjected to the evaluation of anti-inflammatory activity by carrageenan-induced rat-paw-oedema method, analgesic activity by tail immersion method and molecular docking studies to target cyclooxygenase-2 enzyme. Among the evaluated, the compounds 4e and 4f showed a significant anti-inflammatory, analgesic activity and good interaction with COX-2.

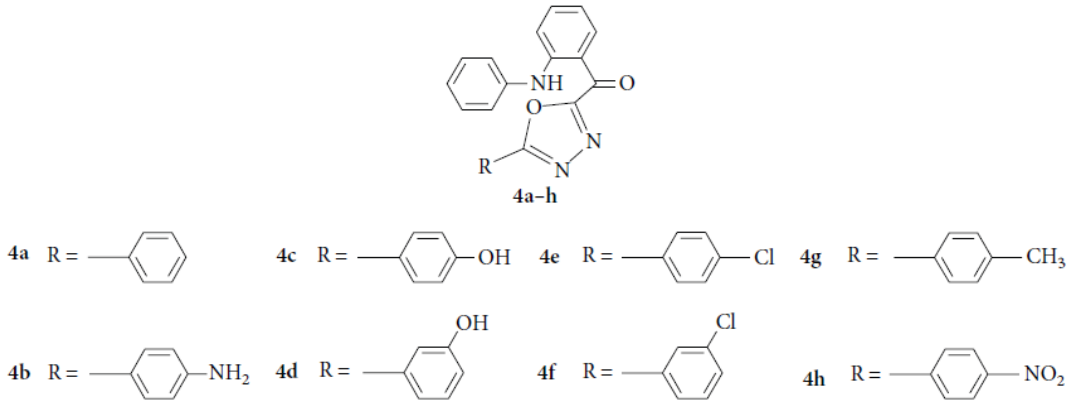


Fig. 2: The synthesized N-Phenyl anthranilic acid-based 1,3,4-oxadiazoles

Glomb *et al.* [9] synthesized Mannich base type hybrid compounds containing an aryl piperazine residue, 1,3,4-oxadiazole ring and pyridothiazine-1,1dioxide core and evaluated for anti-inflammatory activity by colorimetric inhibitor screening assay and identified four compounds among 12 synthesized have strong anti-inflammatory activity.

Vishal kumar *et al.* [10] 2020 reported anti-inflammatory and analgesic activity of 5-(2-(2,3-dimethylphenyl)phenyl-2-(aryl)-1,3,4-oxadiazole derivatives.

Bender *et al.* [11] synthesized novel 1,3,4-oxadiazole derivatives of pyrrolo[3,4-*d*]pyridazinone and identified their anti-inflammatory activity by carrageenan-induced rat-paw-oedema method.

Antimicrobial activity

Dewangan *et al.* [12] synthesized few novel 2,5-disubstituted 1,3,4-oxadizole and found a significant analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activities in two synthesized compounds viz., 3-[5-pyridine-5-yl] 1, 3, 4-oxadiazole-2-yl] pyridine; and 4-[5-{(E)-2-phenylethyl}-1, 3, 4-oxadiaziole-2-yl]pyridine.

Prasanna Kumar *et al.* [13] synthesized a series of novel 1,3,4-oxadiazole derivatives containing 5-chloro-2-methoxy benzo hydrazide moiety by reaction of 5-chloro-2-methoxy benzoate with different aromatic carboxylic acids and characterized by FT-IR, ^{1}H NMR and mass spectral methods as well as elemental analysis. Among all the synthesized, three compounds namely, 2-(5-Chloro-2-methoxyphenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole; 2-(5-Chloro-2 methoxyphenyl)-5-(2-fluoro-3-methoxyphenyl)-1,3,4-oxadiazole; and 2-(5-Chloro-2-methoxyphenyl)-5-(2-fluoro-5-methoxyphenyl)-1,3,4-oxadiazole revealed a significant antimicrobial activity against the tested bacterial organisms viz., *B. subtilis, S. aureus, E.coli, X. campestris* and fungal organism *F. oxysporum*.

Somani *et al.* [14] synthesized a series of novel Mannich bases of substituted 1,3,4-oxadiazole and evaluated for the antibacterial activity against *E. coli* and *S. aureus*. Anti-tubercular activity was carried out against *Mycobacterium tuberculosis* H37Rv strain. In the evaluation, the synthesized compounds, 3-{[(2,6-Dimethylphenyl) amino]methyl}-5-pyridin-4-yl-1,3,4-oxadiazole-2(3*H*)-thione

and 3-{[(2-Nitrophenyl) amino] methyl}-5-pyridin-4-yl-1,3,4-oxadiazole-2(3*H*)-thione exhibited a promising antibacterial and antitubercular activities even at lower concentrations.

Bala *et al.* [15] synthesized 1-(4-Methoxyphenyl)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)propan-1-one derivatives and [2-(5-Substitutedphenyl-[1,3,4] oxadiazol-2-yl)-phenyl]-phenyl-methanone derivatives and characterized the synthesized derivatives by UV, IR, ^{1}H NMR, ^{13}C NMR and mass spectral methods. In the antibacterial evaluation, *p*-chloro, *m*-methoxy and *p*-hydroxyl substitutions were found to be the most active among all the derivatives. Six physicochemical parameters viz., Log P, SAS, MR, ovality, MSA and MW were instituted to be important for the antibacterial activity.

Grewal *et al.* [16] synthesized a series of novel 2,5 disubstituted-1,3,4-oxadiazole derivatives and characterized by IR, NMR and mass spectral methods. In the antimicrobial evaluation, the synthesized compounds, namely 2-Chloro-3-(5-pyridin-4-yl)-1,3,4-oxadiazol-2-yl) quinolone and 2-Chloro-3-(5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl) quinolone showed an excellent activity against *E. coli* and the fungal strains *Penicillium marneffei, Aspergilus niger, Colletotrichum capsici.*

Das *et al.*[17] synthesized various fused 1,3,4-oxadiazole compounds and in the antimicrobial evaluation against various strains of bacteria such as *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and fungi such as *Aspergillus niger* and *Candida albicans* and in the anti-tubercular evaluation against *M. tuberculosis* H37Rv strain, the synthesized compound, 2-hydrazino-5-pyrazyl-1, 3, 4-oxadiazole showed a promising antimicrobial and anti-tubercular activity.

Khalilullah *et al.*[18] synthesized a series of novel 1,3,4-oxadiazole derivatives containing 1,4-benzo dioxane ring system and characterized by IR, mass and ^{1}HNMR spectral methods. Antimicrobial activity data of the synthesized compounds revealed that the presence of electron withdrawing group in aromatic ring of 1,3,4-oxadiazole ring improved the activity; however, a more lipophilic group at the same position greatly enhanced the antifungal activity.

Martinez *et al.* [19] synthesized novel *N*-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]- (nitro heteroaryl) carboxamides and tested against three *Mycobacterium tuberculosis* cell lines viz., H37Rv, H37Ra and 209 strain. In this study, it was found that the compounds, *N*-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-5-nitro-1*H*-pyrrole-2-carboxamide; *N*-(5-(4Chlorophenyl)-1,3,4-oxadiazol-2-yl)-3-nitro benzamide; *N*-(5-(4-Chlorophenyl)-1,3,4oxadiazol-2-yl)benzamide were suitable candidare for the development of novel anti-tubercular agents.

Yu *et al.* [20] synthesized a series of novel trifluromethyl pyridine 1,3,4-oxadiazole derivatives, evaluated for antibacterial activity against *Ralstonia solanacearum* and *Xanthomonas axonopodis* pv. citri (Xac), that affects tobacco and citrus fruits and documented a positive report viz, the novel trifluoromethyl pyridine containins1,3,4-oxadiazoles can be considered as new antibacterial agents and laid a foundation for controlling plant bacterial diseases.

Anticancer activity

Megally Abdo *et al.* [21] synthesized a series of 5-(pyridin-4-yl)-*N*-substituted-1,3,4-oxadiazol-2amine and subjected to *in vitro* anticancer evaluation against the cell lines viz., human gastric cancer (NUGC), human colon cancer (DLD1), human liver cancer (HA22T and HEPG2), nasopharyngeal carcinoma (HONE1), human breast cancer (MCF) and normal fibroblast cells (WI38) and found that the presence of 4-chlorophenyl and 4-bromophenyl substituents was essential for the activity.

Roy *et al.* 2017 [22] synthesized a series of novel 2,5-disubstituted 1,3,4-oxadiazole by using different aromatic benzaldehyde and characterized by FTIR, 1H NMR and mass spectroscopy. In the anti-cancer evaluation on Ehrlich Ascites carcinoma bearing albino mice, all the synthesized compounds showed significant anticancer activity.

Amer *et al.* [23] synthesized a sequence of acyclic nucleoside derivatives, arylidines, oxadiazole, and α-amino phosphonates derived from 1,3,4-oxadiazole moiety and the anticancer activity of synthesized was evaluated against HepG-2 cell line and reported moderate to high anticancer activity.

Mamatha *et al.* 2020 [24] synthesized a unique series of oxadiazoles by cyclization of benzophenone hydrazide followed by nucleophilic alkylation of heterocyclic scaffold. The synthesized compounds were characterized by FT-IR, LCMS and NMR spectral techniques. In the *in vitro* anticancer evaluation, the compound, (2-chlorophenyl) {3-methyl-4-[(5-((2-morpholinoethyl)thio)-1,3,4-oxadiazol-2-yl)methoxy]phenyl}methanone was found as the potent molecule.

Stecoza *et al.* 2021 [25] synthesized a set of novel 2,5-diaryl/heteroaryl-1,3,4-oxadiazole, characterized by elemental analysis, IR and NMR spectral methods. In the anticancer evaluation on HT-29 (colon adenocarcinoma) and MDA-MB-231 (breast adenocarcinoma) cell lines, the synthesized compound 2-[2-(phenylsulfanylmethyl)phenyl]-5-(4-pyridyl)-1,3,4-oxadiazole showed a promising effect on MDA-MB-231 cell line. This compound showed a less toxic effect in the *D. magna* 24h assay.

Antiviral activity

Akhtar *et al.* [26] synthesized a series of new benzo thiazole derivatives from substituted phenols via the 1,3,4-oxadizole -2-thiones and screened for antitumor and antiviral activity and reported that the compound, (*N*-(benzothiazol-2-yl)-2-{5-[1-(3,4-dichlorophenoxy)ethyl]-1,3,4-oxadiazole-2-yl thio}acetamide) being the promising agent for further structural modification and pharmacological evaluation.

A series of novel 5-[(naphthalen-5-yloxy)methyl]-1,3,4-oxadiazole derivatives and 2-{5-[(naphthalen -5-yloxy) methyl]-1,3,4-oxadiazol-2-ylthio} aceto hydrazones were synthesized by El-Sayed *et al.* [27] and found a moderates to high activity of the synthesized compounds against HIV-1.

Dong *et al.* 2016 [28] designed and synthesized a series of novel thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties and found a moderate to good antiviral activity against tobacco mosaic virus.

1,3,4-oxadiazoles containing thiophene, thiazole, coumarin, pyridine and pyridazine moieties were synthesized by Albratty *et al.* [29] and subjected to antiviral and cytotoxic investigations in which the synthesized compounds 5-(4-amino-3-ethyl-2-thioxo-2,3-dihydrothiazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione; and 5-(4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazol-5-yl)-1,3,4-oxadiazole-2(3*H*)-thione showed a significant activity against *Feline herpes virus, Feline corona virus, Herpes simplex virus*-1 and *Herpes simplex virus*-2, whereas the compound 2-(5-(2-phenylhydrazono)-4,5-dihydro-1,3,4-oxadiazol-2-yl) acetonitrile was found as most effective against *Vaccinia virus*, *Herpes simplex virus* (TK-KOS-ACVr), *Coxsackie virus* B4 and *Vesicular stomatitis virus*.

Anticonvulsant activity

Zarghi *et al.* [30] reported that the introduction of an amino group at 2nd position 1,3,4-oxadiazole ring and a fluoro substituent at *ortho* position of benzyloxy moiety had the best anticonvulsant activity in their effort of synthesize and anticonvulsant screening of 2 substituted-5-[2-(2-halobenzyloxy)phenyl]-1,3,4-oxadiazole derivatives.

Tabatabai *et al.* [31] synthesized 2-(2-phenoxy) phenyl-1,3,4-oxadiazole derivatives and evaluated for anticonvulsant activity by pentylenetetrazole induced lethal convulsion test and reported that the introduction of an amino substituent in 5th position of 1,3,4-oxadiazole has a respectable effect.

Prasannakumar *et al.* [32] synthesized a series of novel 2,5-disubstituted-1,3,4-oxadiazoles by intra molecular oxidative cyclization, screened for anticonvulsant activity by maximal electroshock seizure method and reported that the compounds, 4-Methoxy-N-[{5-(4-trifluoromethyl)phenyl}-1,3,4-oxadiazole-2-yl]methyl]aniline; N-[{5-(3-Chloro phenyl)-1,3,4-oxadiazole-2-yl}methyl]-4-methoxy aniline; and N-[{5-(4-Chlorophenyl)-1,3,4-oxadia zole-2-yl}methyl]-4-methoxyaniline were most potent of this series without any neurotoxicity.

Singh *et al.* [33] reported that the compounds having electron withdrawing substituent were found to be more potent than the electron releasing group in their effort to synthesize and the evaluation of antiepiteptic and antidepressant activity of a series of nipecotic acid 1,3,4-oxadiazole based hybrids. Based on the *in vivo* and computational study, they also added that the antiepileptic effects of the synthesized compounds may be due to the inhibition of the GAT1 GABA Transporter protein. Gatphoh *et al.* [34] synthesized the oxadiazole derivatives by the cyclization of 4-hydroxy benz hydrazide with various substituted aromatic aldehydes in the presence of ceric ammonium nitrate. In the anticonvulsant evaluation by maximal electro shock test and pentylenetetrazole induced seizure method and in the *in-silico* analysis, the compounds 4-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl) phenol and 3-(5-(2-hydroxy phenyl)-1,3,4-oxadiazol-2-yl)phenol showed the highest affinity and binding energy as well as the highest anticonvulsant activity in both electroshock and pentylenetetrazole induced lethal convulsion tests.

Chauhan *et al.* [35] synthesized a series of 2-[4-methoxy-3-(5-substitued phenyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-benzothiazoles and screened for *in vivo* anticonvulsant activity by maximum electroshocks and subcutaneous pentylenetetrazol models and *in-silico* screening by Auto Dock 4.2 software. In these screening, the synthesized

compounds, (E)-N-[1-(1H-Benzimidazol-2-yl)-2-phenylethyl]-1-(2-chloroquinolin-3-yl)-methena mine; 2-{4-Methoxy-3-[5-(4-nitro-phenyl)-[1,3,4] oxadiazol-2-ylmethoxy]-phenyl}-benzothiazole; 2-[5-(5-Benzothiazol-2-yl-2-methoxyphenoxymet hyl)-[1,3,4]oxadiazol-2-yl]-4,6-dinitro-phenol; and 4-[5-(5-Benzothiazol-2-yl-2-methoxyphenoxymet hyl)-[1,3,4]oxadiazol-2-yl]-phenol were the most potent with no neurotoxicity.

Thrombolytic activity

Vishwanathan *et al.* [36] synthesized a series of benzofuran derived 1,3,4-oxadiazole derivatives and evaluated for *in vitro* thrombolytic activity and reported the compounds 2-(4-hydrox yphenyl)-5-(5-nitrobenzofuran-2-yl)-1,3,4-oxadiazole; 2-(2-hydrox yphenyl)-5-(5-nitrobenzofuran-2-yl)-1,3,4-oxadiazole; and 2-(4-aminop henyl)-5-(5-nitro benzofuran-2-yl)-1,3,4-oxadiazole have potent thrombolytic activity among all the tested compounds.

A series of 1,3,4-oxadiazole derivatives derived from benzimdazole were subjected to *in silico* and antithrombotic screening by Vishwanathan *et al.* [37] and found the compounds, (1*H*-benzo[*d*]imidazol-2-yl)-*N*-[{5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl} methyl] methanamine; 4-(5-[{(1*H*-benzo[*d*] imida zol-2-yl) methylamino}methyl]-1,3,4-oxadiazol-2-yl) benzenamine; and 2-(5-[{(1*H*-benzo[*d*] imidazol-2-yl) methylamino}methyl]-1,3,4-oxadiazol-2-yl) phenol exhibited potent thrombolytic activity.

Batool *et al.* [38] reported that a novel 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-thiol derivatives showed a good antithrombotic activity in their *in silico*, *in vitro* and *in vivo* evaluation.

Aziz-ur-Rehman *et al.* [39] synthesized a series of novel 5-(3-chlorophenyl)-2-((N-(substituted)-2-acetamoyl)sulfanyl)-1,3,4-oxadiazole derivatives and screened for antibacterial, hemolytic and thrombolytic activities. It was reported that among the synthesized compounds, the compound, 5-(3-chlorophenyl)-2-((N-phenyl-2-acetamoyl) sulfanyl)-1,3,4-oxadiazole showed good antibacterial activity.

The compounds, 5-(3-chlorophenyl)-2-((N-(2-(methoxycarbonyl)phenyl)-2-acetamoyl) sulfanyl) -1,3,4-oxadiazole; 5-(3-chlorophenyl)-2-((N-cycloh exyl-2-acetamoyl)sulfanyl)-1,3,4-oxadiazole; and 5-(3-chlorophenyl)-2-((N-(2,5-dimethylphenyl)-2-acetamoyl)sulfanyl)-1,3,4-oxadiazole showed a very good thrombolytic activity

CONCLUSION

The present review summarizes the synthetic procedure and various pharmacological activities of 1,3,4-oxadiazole moiety. Oxadiazole is a significant heterocyclic compound containing one oxygen and two nitrogen atoms in five membered ring in which 1,3,4-oxadiazole heterocyclic nucleus is a new chemical entity which play a major role in the pharmaceutical chemistry and broad range of important biological activities.

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CONFLICTS OF INTERESTS

Conflict of interest declared none

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