JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

The Biological Potential and Synthetic Diversity of 1,3,4-Oxadiazole Multiplexed with Various Heterocyclic Compounds

Rahul K[1], Deevan Paul A[1]*, Hariraj N[2], and Adhya Das[2]

[1]Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam- 603103, Tamil Nadu, India.
[2]Department of Pharmaceutical Sciences, Government Medical College Kannur, 670503, Kerala, India
* E-mail address: deevan4@gmail.com Tel: + 919000105599

Abstract: Countless bioactive compounds are having the oxadiazole nucleus showing clinical and biological applications. Oxadiazole is a heterocyclic compound of the azole family that has gained increasing attention due to its wide therapeutic potential. Many significant synthetic medicinal compounds have the oxadiazole scaffold, which provided a good treatment idea and binds with high affinity to a variety of receptors to aid in the development of novel beneficial derivatives. Numerous researchers have worked to create novel oxadiazole compounds and evaluate them for how they affect inflammation, tumor, epilepsy, microbial infections, and analgesic properties. The present review article summarizes some of the oxadiazole derivatives synthesized and their biological activities and can be a useful guide for researchers working on this scaffold.

Keywords: Heterocyclic scaffolds, 1,3,4-oxadiazole, anticonvulsant, anti-inflammatory, antimicrobial, anticholinesterase.

Submitted: November 11, 2022. **Accepted:** January 10, 2023.

Cite this: Rahul K, Deevan Paul A, Hariraj N, Adhya D. The Biological Potential and Synthetic Diversity of 1,3,4-Oxadiazole Multiplexed with Various Heterocyclic Compounds. JOTCSA. 2023;10(2):267–76.

DOI: https://doi.org/10.18596/jotcsa.1202640.

***Corresponding author. E-mail:** rahulkcpspariyaram@gmail.com.

1. INTRODUCTION

Heterocyclic compounds are a class of organic substance that has a closed ring structure and contains heteroatom. These substances have numerous medical, veterinary, and agrochemical applications. Modern drug design now places a greater emphasis on these compounds' physiological and pharmacological activity(1). Oxadiazole has a chemical formula of $C_2H_2ON_2$, an aromatic heterocyclic molecule, unsaturated, unstable, nonbenzenoid, heteroaromatic with oxygen and a couple of nitrogens in a closed cyclopentane ring and has 12 electrons (eight from lone pairs and four electrons from double bonds) (2). Because of the electronegativities of nitrogen and oxygen, Oxadiazoles show hydrogen bond acceptor properties, in this, nitrogen is a stronger hydrogen bond acceptor than oxygen(3). Additional names for the ring system include azoximes, oxybiazole, biazole, diazoxole, furadiazole, and furoxans. In 1965, Ainsworth created oxadiazole for the first time by thermolyzing hydrazine(2). Oxadiazole has the characteristics of a conjugated diene since it contains two nitrogens of the pyridine type. Depending on where the two nitrogens are situated, oxadiazole can take one of four possible isomers (Figure 1)(2).

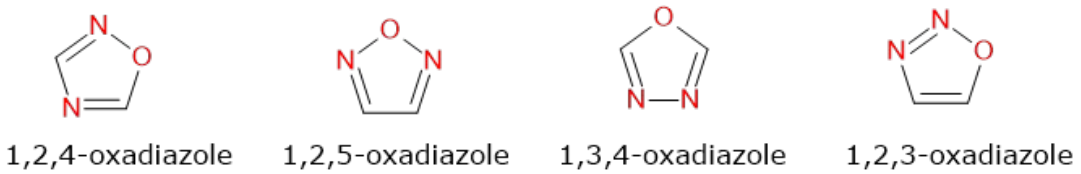


Figure 1: Four possible isomers of Oxadiazoles.

The isomer 1,3,4-oxadiazole exhibits an extensive range of therapeutic effects. The antiviral drug Raltegravir, the anti-arrhythmic medication Nesapidil, the antihypertensive medication Tiodazosin, and others are some of the 1,3,4-oxadiazole-ringed medications (Figure 2) that are commercially accessible(3). 1,3,4-oxadiazole ring changes the kinetic properties of the compounds(4). It is additionally utilized as a key component of pharmacophore that can bind to the ligand. It can also act as a linker in other circumstances to ensure optimal structural orientation. Here, we have made an effort to condense the significant pharmacological actions of oxadiazole derivatives.

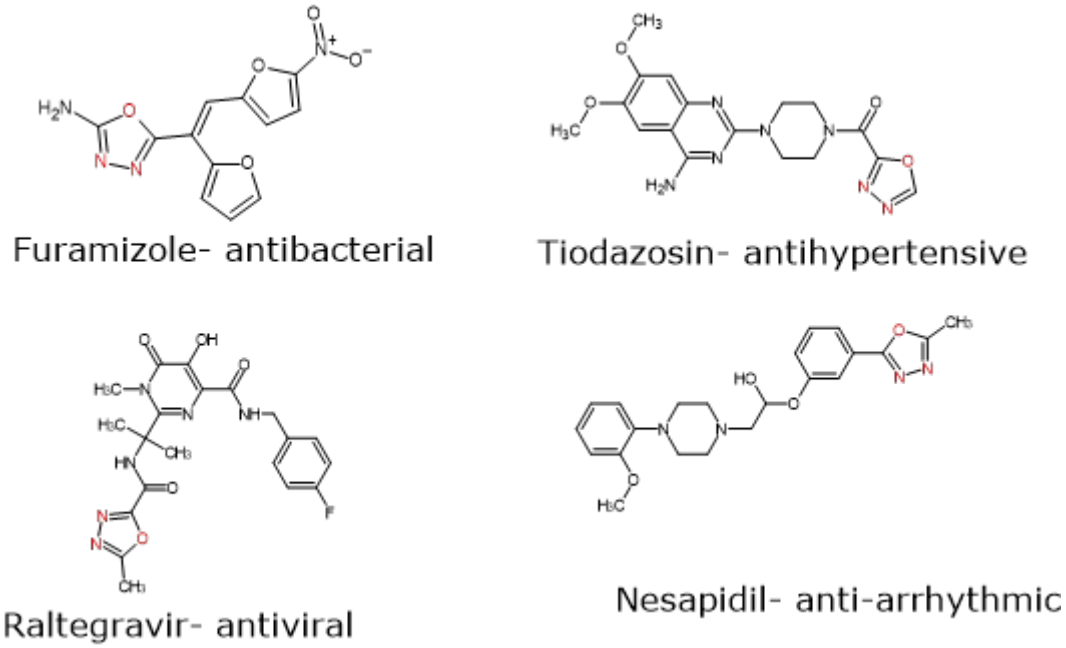


Figure 2: Chemical structure of commercial drugs.

2. BIOLOGICAL ACTIVITIES OF OXADIAZOLES

1,3,4-oxadiazole is recognized as a valuable pharmacophore for anti-infective including "antifungal, anti-bacterial, anti-trypanosomal, anti-malarial, anti-tubercular and anti-viral activities"(6,7,8).

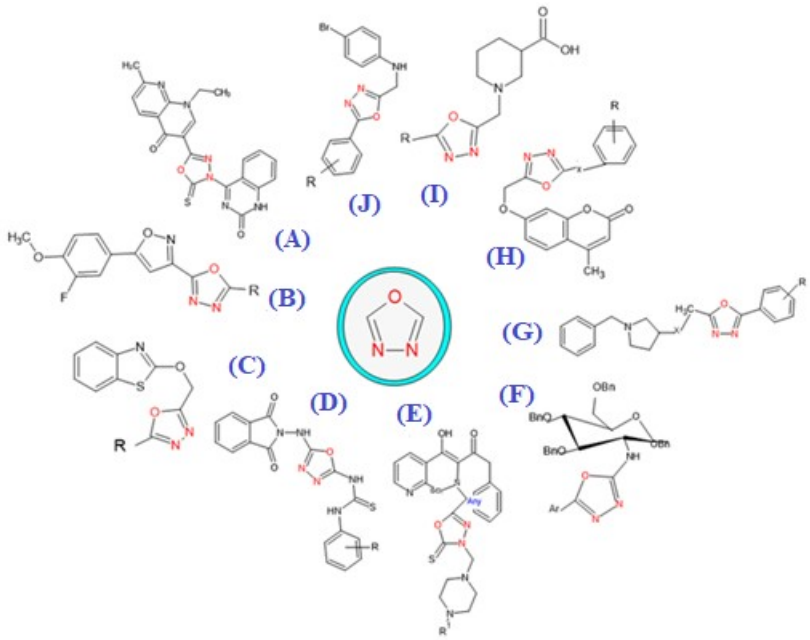


Figure 3: Structures of 1,3,4-oxadiazole with other scaffolds.

2.1. Antimicrobial Activity

Newer variants of nalidixic acid (Figure 4) were developed by Ramalingam Peraman, Reghu Veer Varma, and Y. Padmanabha Reddy. Designing novel compounds with anti-bacterial and anti-tubercular activity has made use of the COOH group of nalidixic acid. Agar plate disk diffusion and microdilution method were performed against various species for anti-bacterial screening. The compound 1-ethyl-7-methyl-3-(4-(3-oxo-3,4-dihydro quinoxaline-2-yl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1,8-naphthyridin-4(1H)-one(6) was found to potent (<6.25 µg/mL) than the reference drug ciprofloxacin against *S. aureus.* Student t-test showed 5% critical difference proves the activity significantly(6).

4-Bromo [(N-5-substituted [1,3,4-oxadiazole-2yl) methyl] aniline derivatives (Figure 5)(7) were synthesized and reported as anti-inflammatory and anti-microbial agent by KI Bhat *et al*. In all these screened compound 4-methoxy substituted one showed better antibacterial activity (zone of inhibition: 18mmin *S.aureus* and *B.subtilis*,19mm in *E.coli*, 15mm in *P.aeruginosa*) using amoxicillin as standard. Additionally, they were tested against various organism like *Candida albicans* and *Aspergillus niger* for anti-fungal activity (using ketoconazole standard)(7).

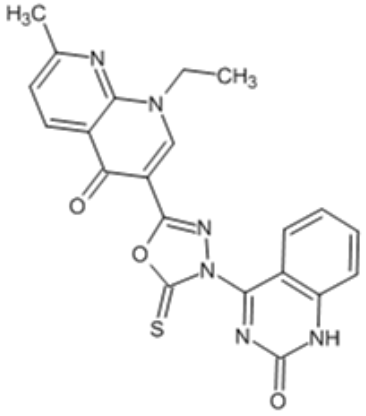


Figure 4: Oxadiazole with Nalidixic acid .

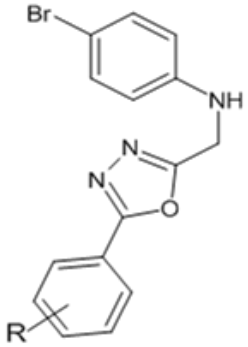


Figure 5: 1,3,4- oxadiazol with aniline derivatives.

By reacting 5-(3-fluoro-4-methoxyphenyl) isoxazole-3-carbohydrazide with pyridinyl /indoyl/benzoic acid derivatives using $POCl_3$, Ramesh Shingare, Yogesh Patil, and others were able to synthesize and assess a variety of 1,3,4-oxadiazole derivatives (Figure 6). Ampicillin was used as the reference medicine to test the antibacterial activity of this oxadiazole series(8). The results of the investigation indicated that the halogenated phenyl ring is essential for antibacterial action. Comparatively to the standard, the compounds having 4-chlorophenyl, 3,4-dichlorophenyl, 4-pyridinyl and 2-fluorophenyl groups were found to be good antibacterial activity. These compounds were also try out for anti-TB activity using isoniazid as the reference(8). It was discovered that compounds 2-methoxyphenyl and 4-fluorophenyl were effective against *M. tuberculosis*. The inhibition of the MurD ligase enzyme was also studied and was supported by molecular docking studies(8).Alghamdi, *et al*. synthesized fifteen 2- hydroxyl benzthiazole-linked 1,3,4- oxadoazoles and confirmed their anti-bacterial properties using an in-vitro susceptibility test (disc diffusion method) (Figure 7). Compounds with 2-chlorophenyl, p-methylphenyl, m-chlorophenyl, 2-methylphenyl, p-nitrophenyl and 2,4-dichlorophenyl are the best active derivatives against the bacterial strains(9). Compounds having –SH group(10) showed equivalent MIC 6.25 ±0.2 µg/disc to the amoxicillin (standard drug) against the Gram-positive bacteria and these have potent antiviral properties. The IC_{50} ranges from 0.4 to 2.1 µg/mL.(9). Insilico pharmacokinetic and drug-likeness properties of these derivatives were studied and were found to be excellent.

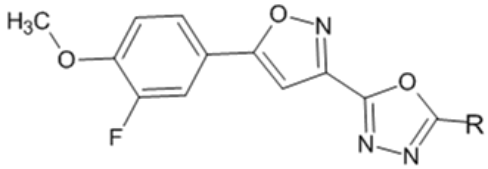


Figure 6: Isoxazole with 1,3,4-oxadiazole.

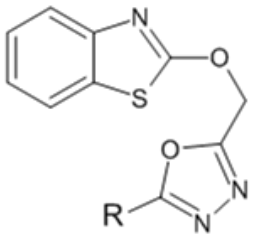


Figure 7: Benzothiazole-linked oxadiazole.

2.2. Anti-Alzheimer Activity As a potential multi-target directed ligand, George *et al*. developed and synthesized two series of ligands containing Coumarin with oxadiazole (Figure 8) and in-vitro anti-cholinesterase activity, anti-oxidant, and anti-inflammatory effects are evaluated. To ascertain the AChE and BuChE binding mechanism, molecular docking studies, as well as colorimetric assay (modified Ellman's method) were conducted,

and galantamine was used as standard. Cheminformatics software was also used to analyze the pharmacokinetic profile of all produced compounds. Based on the results they conclude that the methoxy linker between these two scaffolds has a very important role in AChE inhibition. The synthesized compounds' IC_{50} value ranges from 28.7 to 159.7 µM. Among these, three hydroxyl groups containing phenyl substitution at the 3,4,5 position of 1,3,4-oxadiazole were reported as the best AChE inhibitor(11). Docking results show that derivatives with three hydroxyl groups have dock scores of 9.7 Kcal/mol. Decreasing the -OH groups from 3,4,5 trihydroxy to 3,4 dihydroxy showed a better binding score (10.1 Kcal/Mol) but showed a slight decrease in in-vitro activity. DPPH free radical assay was performed to determine in-vitro antioxidant potential, and the compounds with phenolic hydroxyl group exhibited better performance. Based on these invitro and insilico studies it was concluded that Coumarin-1,3,4-oxadiazole scaffolds act as a multi-targeted hybrid for anti-Alzheimer's drugs(11).

Choubey *et al*. Synthesized and evaluated N-benzylpyrrolidine and 1,3,4-oxadiazole hybrid (Figure 9) for Alzheimer's treatment. All the hybrids were tested with different in-vitro parameters such as Cholinesterase and BACE-1 inhibition assay, enzyme kinetics study, PI displacement assay, BBB penetration assay, Thioflavin T assay, and neuroprotective assay(12). Invivo behavioral studies were also performed on the Scopolamine-induced amnesia model. In these, compounds having fluoro substitution on the phenyl ring showed potential inhibition against hAChE, BuChE, and BACE-1. Among these trifluoromethyl substituted derivatives showed significant permeability and prominently disaggregate Aβ fibrils. The compound was also found to reverse scopolamine-induced connective dysfunction and ameliorate cognitive dysfunction. An Ex-vivo study was also conducted to ascertain AChE inhibitory and antioxidant potential. The binding affinity was predicted by docking studies. The study concluded that the compounds with CF_3 on phenyl and amino or methyl amino spacer can be potential candidates [IC_{50}=0.091 ± 0.008 (AChE), 0.106 ± 0.013(hBChE) for amino spacer and 0.064 ± 0.006(AChE), 0.074 ± 0.016(hBChE) for methylamino spacer] for the treatment of Alzheimer's disease(13).

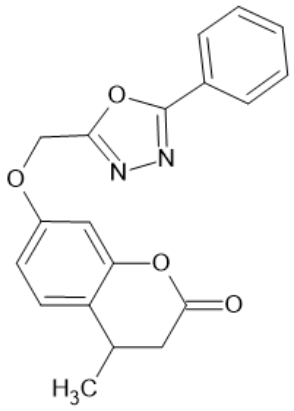


Figure 8: Coumarin-linked oxadiazole.

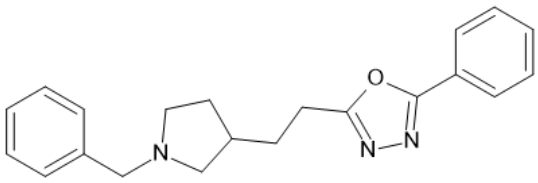


Figure 9: Oxadiazole with pyrrolidine.

A variety of C2-Glycosyl oxadiazole compounds were produced by base-catalyzed reactions by Wang *et al*. (Figure 10)**.** For acetylcholinesterase inhibition assay Ellman's method (reference: galantamine and tacrine) were used(14). Among the synthesized compound methoxy group in the fifth position possess the best one (IC_{50}2.03 ± 0.26) (13).

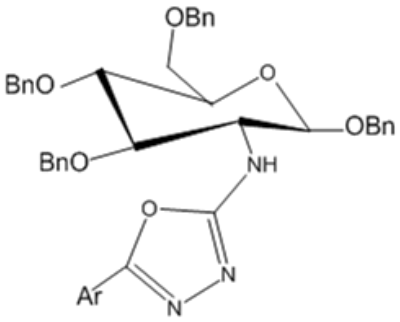


Figure 10: Glycosyloxadiazole.

Pyridine containing oxadiazole derivatives as (Figure 11) potential acetylcholinesterase inhibitory agents narrated by Puja Mishra *et al*. 4-hydroxyl substituted compound showed maximum inhibition with the IC_{50} value 1.098 µM and value of K_i = 0.960 µM. This derivative also inhibited acetylcholinesterase-induced Aβ aggregation (38.2–65.9%) determined by thioflavin T assay(15). 4-hydroxyl substituted compound and donepezil (standard) produced similar interaction (glide score reported as -10.6 kcal/mol) at the same binding site of acetylcholine esterase.

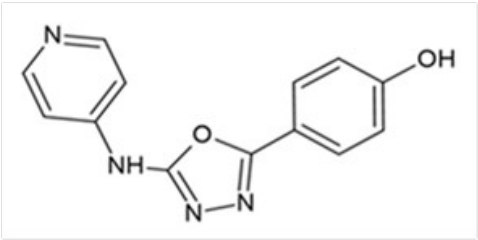


Figure 11: Oxadiazole with Pyridine.

2.3. Anti-inflammatory Activity

By reacting benzoyl chloride with different chloro-nitro-benzoyl chlorides and semi-carbazides, Singh *et al*. were able to create a variety of five-membered heterocyclic rings (Figure 12). The NMR, IR, and mass spectra were used to characterize and identify each of the synthesized oxadiazole derivatives. The anti-inflammatory activities were determined by the edema model (Carrageenan-induced rat- paw) using standard indomethacin(16). It was concluded that the entire compound has good anti-inflammatory activity. The compounds with 4-chloro-benzoic acid substitution on 2, 5-position showed improved activity than that of 3-chloro and 2-chloro substitution(16).

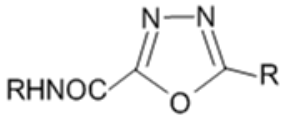


Figure 12: Oxadiazole derivatives(16).

Novel 1,3,4-oxadiazole with pyridothiazine-1,1-dioxide derived compounds (Figure 13) as inhibitors of COX-1 and 2 reported by Glomb *et al*. The final product was designed as an N-Mannich base, to obtain a synergistic effect on anti-inflammatory activity. These abilities were tested by a colorimetric inhibitor screening technique(17). On typical NHDF fibroblasts, the antioxidant and cytotoxic effects were also investigated. Multiple-criteria decision analysis discloses that 4-nitro phenyl, 2-pyridyl, and 2-pyramidal substituted compounds showed better activity (reference-Meloxicam)(17).

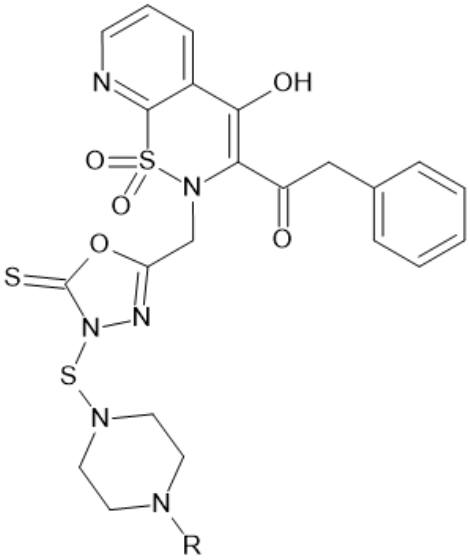


Figure 13: Oxadiazole with pyridothiazine-1,1-dioxide(17).

A new set of 2,5-biaryl-1,3,4-oxadiazoles (Figure 14) were synthesized and analyzed as possible cyclooxygenase-2 inhibitors by J. Grover *et al*. Chloro and nitro group on one of the aryl ring as well as the acetyl substitution at one of the nitrogen of oxadiazole found to be best inhibitors of COX-2 (IC_{50} = 0.48-0.89 μM)(18). Such derivatives showed superior inhibitory activity than the standard-celecoxib (carrageenan-induced model). Compounds having methylsulfonyl moieties show more selective cyclooxygenase-2 inhibition, confirmed through computational study(18).

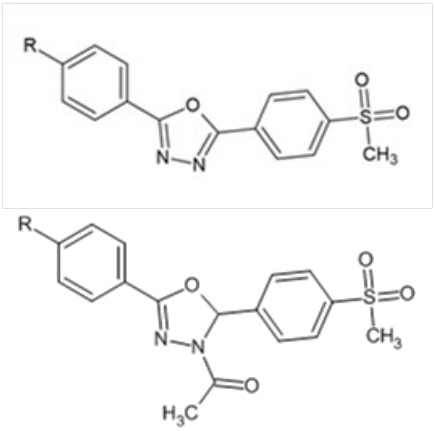


Figure 14: 1,3,4-Oxadiazole with different phenyl scaffolds.

"2,5-disubstitution at 1,3,4-oxadiazoles becomes an important strategy to generate novel heterocyclic compounds with a wide range of pharmacological activities"(19). Sudhir Bhardwaj *et al*. reported a new structural sequence of 2,5-disubstituted oxadiazoles (Figure 15) which has anti-inflammatory activity. The derivatives with hydroxyl, methoxy and tri-methyl amino group exhibited good anti-inflammatory (carrageenan-

induced paw edema, standard- diclofenac sodium; 44.45– 83.34 %) and analgesic activity (52 to 82 %)(19).

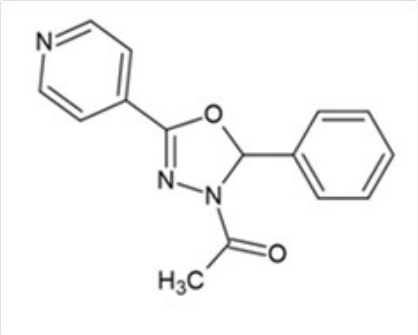


Figure 15: 1,3,4-Oxadiazole with pyridine.

Various Schiff bases of 1,3,4-oxadiazole (Figure 16) were introduced by Sahoo *et al*. microwave heating technology was applied for the synthesis. The anti-inflammatory activity is mainly influenced by substituents on the aromatic ring. In these, the compound with para substitution showed more activity than ortho and meta-substituted compounds. The para-hydroxy substitution showed maximum activity than halogens, $-OCH_3$, $-NO_2$ group(20).

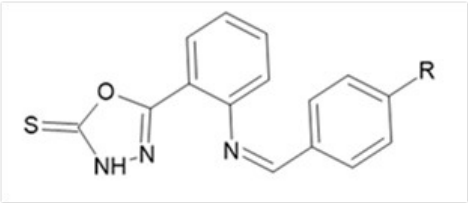


Figure 16: 1,3,4-Oxadiazole with Schiff base.

2.4. Anti-convulsant activity

For their anti-convulsant and neurotoxicity activity, Bhat *et al*. produced and assessed some phthalimide derivatives of 1,3,4-oxadiazole (Figure 17). The maximal electric shock method was used to test all of the compounds. The compound's neurotoxicity was also tested using the rotarod method, and it was discovered to be lower than phenytoin. Actophotometer was used to conduct a behavioral test, and all of the compounds except 13d displayed increased motor activity. The basic structure of the compounds had all the pharmacophoric structural requirements. The presence of constituents like $-OCH_3$ at the para position of the phenyl ring and the alkyl group at the distant aryl ring has potent activity(21). To increase the lipophilicity of the molecule, thioureido moiety was introduced into the structure. The study concluded by revealing that the phthalimide derivatives exhibit anticonvulsant activity comparable to phenytoin(7).

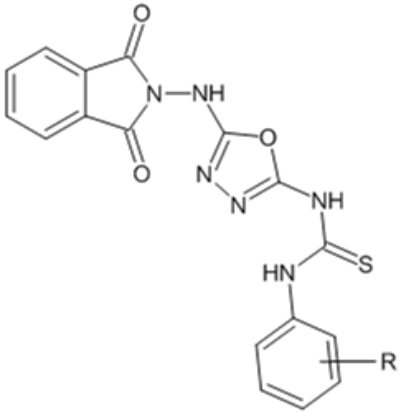


Figure 17: Phthalimide-1,3,4-Oxadiazole derivative(7).

The anticonvulsant activity of oxadiazole with nipecotic acid (Figure 18) was elaborated by Singh *et al*. Oxadiazole was attached to the secondary amine of nipecotic acid through a methylene bridge. The hybridized molecule was tested for its ability to treat epilepsy (PTZ-induced model) and depression (standard: Tiagabine (dose: 100 mg/kg), imipramine (dose: 50 mg/kg)). The homology model of the GAT_1 GABA transporter was developed and docking studies are also conducted(22). The 2,4-Dihydroxyphenyl derivative showed hydrogen bond interactions with Glycine65, Tyrosine140, and Aspartic acid451 residues (glide score -6.2) which is similar to the standard Tiagabin(22). It was concluded that the compounds 14d, 14e, 14g, 14m, and 14o showed an anti-epileptic effect comparable to Tiagabine. All the potential compounds were found to be devoid of toxicity and have a good safety profile. They concluded that derivatives with 3-Cyanophenyl, 2,4-Dihydroxyphenyl, 3-Methoxyphenyl, 3,5-Dinitrophenyl, and 2-Amino-4,5-dimethoxy phenyl substitution can be used as a lead for safer anti-epileptic agents (22).

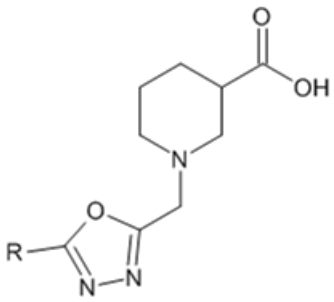


Figure 18: Nipecotic acid with oxadiazole.

Oxadiazole derivatives with dihydroquinolin and 1,2,4-triazole (Figure 19) were designed and synthesized by Shiben Wang *et al*. The anticonvulsant activity of these was tested by subcutaneous pentylenetetrazole and maximal electroshock models. In that, 4-dihydroquinolin-2-one derivative showed the best activity (maximal electroshock seizure model- ED_{50} = 8.9 mg/kg;

subcutaneous Pentylenetetrazole model- ED_{50} = 10.2 mg/kg), which showed greater activities than the ethosuximide and carbamazepine(23). Elevated plus maze experiments results conclude that these derivatives showed similar activity to that of diazepam. The radioreceptor binding assay of 4- dihydroquinolin-2-one divulges that it has a high binding affinity toward GABAA receptors (IC_{50} of 0.11 µM)(23).

Harish Rajak *et al*. designed and synthesized a set of semicarbazones containing 2, 5- disubstituted 1,3,4-oxadiazoles (Figure 20). All of them were screened for anticonvulsant activity through maximal electroshock seizure and subcutaneous Pentylenetetrazole models. Compounds having nitro or hydroxy on the phenyl ring possess high potency, but they can be replaced with methoxy and chloro substitution showed a decrease in activity(24). This study reveals that the hydroxyl-substituted compounds are more active than nitro, chloro and methoxy substituted ones.

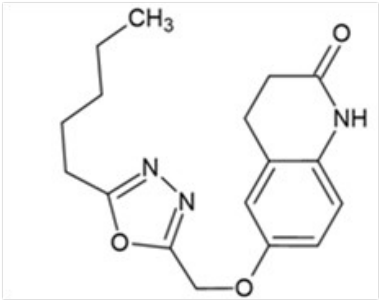


Figure 19: Dihydroquinolin with oxadiazole.

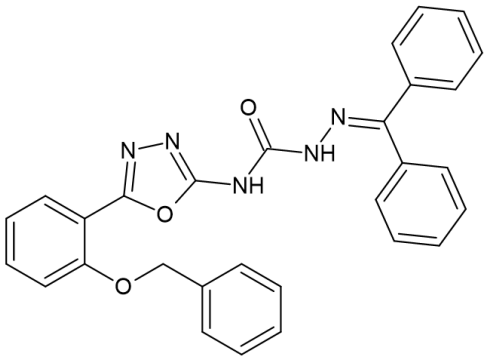


Figure 20: Oxadiazole with semicarbazone.

2.5. Commonly used synthetic strategies of 1,3,4-oxadizoles.

The 1,3,4-oxadiazole scaffolds were synthesized by various strategies (Figure 21) including the use of different hydrazides with carbon disulfide in DMF(Route A)(25), aromatic acids with POCl3(Route B)(26), and cyanogens bromide in ethanol (Route C)(27). The current review paper also focuses on synthetic methods that use all of these approaches A through C.

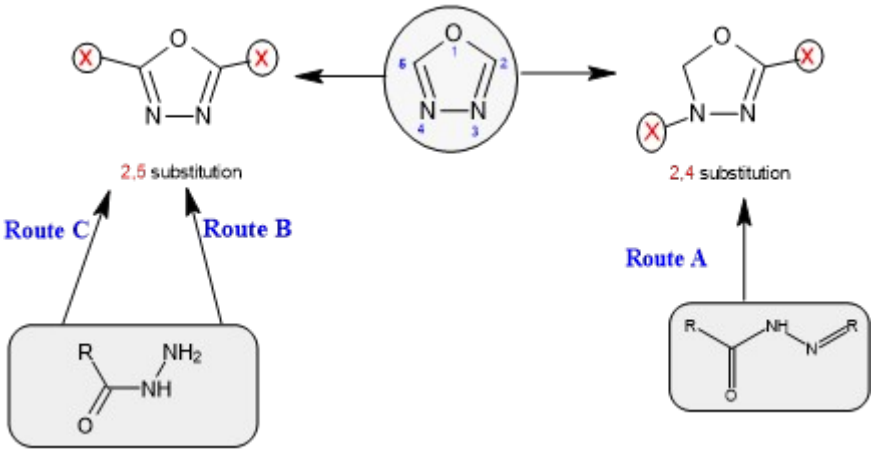
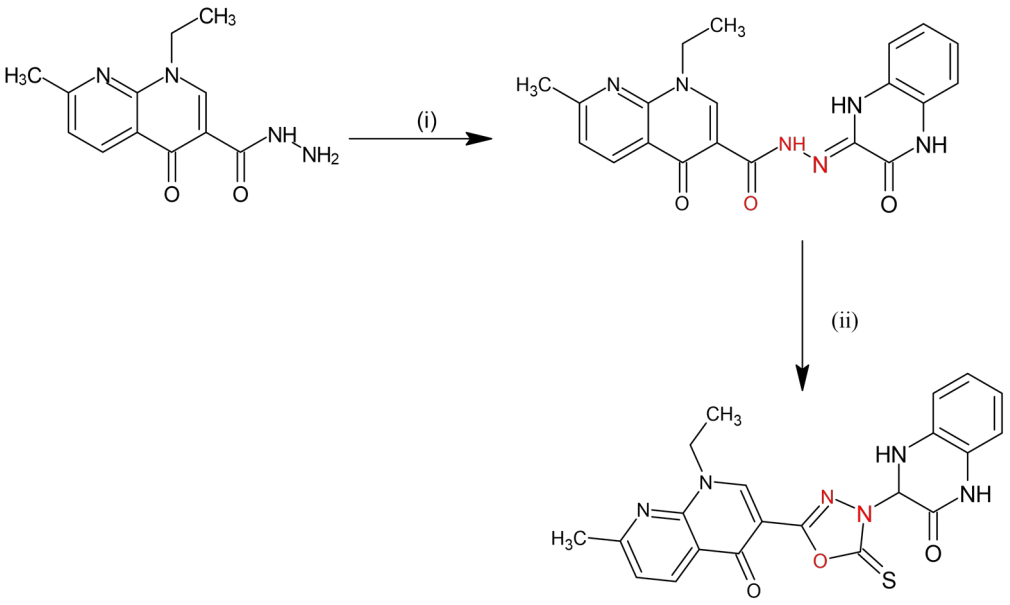


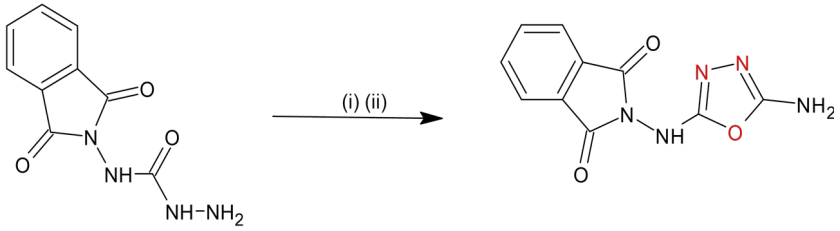
Figure 21: General strategy for the synthesis of 1,3,4-oxadiazoles.

Peraman *et al*. reported carbon disulfide-mediated synthesis of oxadiazole was achieved by cyclization in DMF. This was achieved by equimolar carbohydrazide treated with Quinoxalin-2,3(1H,4H)–dione (reflux) to give the corresponding carbohydrazide (Route A)(28). Then it was subjected to cyclization by using carbon disulfide in dimethyl formamide(Scheme 1)(6).

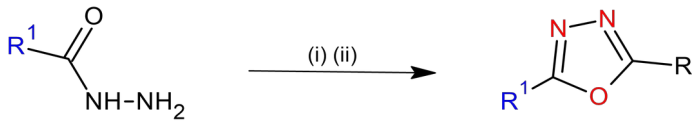


Scheme 1: Synthesis of 1,3,4-oxadiazole derivatives (i) Quinoxaline-2,3(1H, 4H)-dione, (ii) CS_2/DM.

M.A.Bhat *et al*. Reported the synthesis of 1,3,4-oxadiazole containing phthalimide by phosphorous oxychloridemediated reaction of hydrazinecarboxamide derivatives (Route B). This can be done by adding an ethanolic solution of an equimolar amount of hydrazine carboxamide (0.01 mol) to cyanogen bromide (0.01 mol) and warming at 55-60°C for one and half hours (7)(29). Then the solution was neutralized using $NaHCO_3$ (Scheme 2) (30). The same type of reaction is followed by Shingare *et al*. synthesized 1,3,4-oxadiazoles with the help of Phosphorus oxychloride and aromatic carboxylic acid by refluxing at 70ºC for 6-8 hours (Route C; Scheme 3)(8).

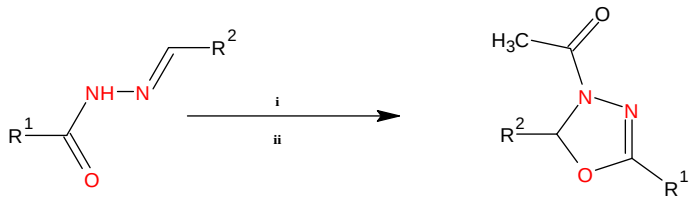


Scheme 2: Synthesis of 1,3,4-oxadiazole derivatives. (i): ethanolic solution of cyanogen bromide, (ii) $NaHCO_3$.



Scheme 3: Synthesis of 1,3,4-oxadiazole derivatives. (i): $POCl_3$, (ii): RCOOH, reflux, 6-8 h.

Sudhir Bhardwaj *et al*. applied a green chemistry approach for the synthesis (microwave-assisted) of Oxadiazoles (Scheme 4). This synthesis can be done by adding Silica gel to the different isonicotinohydrazide (0.01 mol) and acetic anhydride (10 mL) at room temperature(31). This mixture was mixed thoroughly and dried in air and irradiated in the microwave at 400W at 30s intervals. Methanol was used for extraction, and diluting the methanol solution with ice water gave the crude product(19).



Scheme 4: Synthesis of 1,3,4-oxadiazole derivatives. (i): Acetic anhydride, (ii): silica gel, M.W.

4. CONCLUSION

Derivatives with a 1,3,4-oxadiazole core exhibit different biological activities. Various synthetic leads contain an oxadiazole core as part of the pharmacophore structure, facilitating the binding of these leads to binding site residues of the desired target. These initiatives have made oxadiazole a focus of research for the identification of new chemical entities.

As a summary of the literature findings mentioned above, we can state that 1,3,4-oxadiazole exhibits a wide range of biological activities. These are generally synthesized from different hydrazides with carbon disulfide, aromatic acids with $POCl_3$, cyanogens bromide in ethanol, or by green chemistry approach like microwave irradiation. The chemistry of the 1,3,4-oxadiazole derivatives discussed in this study will aid researchers all around the world in the design and synthesis of innovative pharmaceuticals that will be helpful in the mitigation of a variety of illnesses.

5. CONFLICT OF INTEREST

No potential conflicts of interest exist between the authors' authorship and the publishing, they disclose.

6. ACKNOWLEDGMENTS

Authors are thankful to Chettinad Academy of Research and Education for infrastructure support and CARE seed money research grant (Ref.No.004/Regr./AR-Research/2022-02)

7. REFERENCES

1. Qadir T, Amin A, Sharma PK, Jeelani I, Abe H. A Review on Medicinally Important Heterocyclic Compounds. Open Med Chem J. 2022;16(1):1–34.

2. Siwach A, Verma PK. Therapeutic potential of oxadiazole or furadiazole containing compounds. BMC Chem [Internet]. 2020;14(1):1–40. Available from: https://doi.org/10.1186/s13065-020-00721-2

3. Shukla C, Srivastav S. Biologically Active Oxadiazole. Asian J Res Pharm Sci. 2015;5(4):227.

4. Khalilullah H, J. Ahsan M, Hedaitullah M, Khan S, Ahmed B. 1,3,4-Oxadiazole: A Biologically Active Scaffold. Mini-Reviews Med Chem. 2012;12(8):789–801.

5. Xie Y, Yang W, Chen X, Xiao J. Inhibition of flavonoids on acetylcholine esterase: Binding and structure–activity relationship. Food Funct. 2014 Sep 24;5(10):2582–9.

6. Chawla G, Naaz B, Siddiqui AA. Exploring 1,3,4-Oxadiazole Scaffold for Anti-inflammatory and Analgesic Activities: A Review of Literature From 2005-2016. Mini-Reviews Med Chem. 2017 Feb 23;18(3).

7. Peraman R, Varma RV, Reddy YP. Re-engineering nalidixic acid's chemical scaffold: A step towards the development of novel anti-tubercular and anti-bacterial leads for resistant pathogens. Bioorganic Med Chem Lett. 2015 Oct 1;25(19):4314–9.

8. Jang C, Yadav DK, Subedi L, Venkatesan R, Venkanna A, Afzal S, *et al*. Identification of novel acetylcholinesterase inhibitors designed by pharmacophore-based virtual screening, molecular docking and bioassay. Sci Rep. 2018 Dec 1;8(1).

9. Bhat MA, Al-Omar MA, Siddiqui N. Synthesis, anticonvulsant and neurotoxicity of some novel 1,3,4-oxadiazole derivatives of phthalimide. Der Pharma Chem [Internet]. 2010;2(2):1–10. Available from: www.derpharmachemica.com

10. Shingare RM, Patil YS, Sangshetti JN, Patil RB, Rajani DP, Madje BR. Synthesis, biological evaluation and docking study of some novel isoxazole clubbed 1,3,4-oxadiazoles derivatives. Med Chem Res [Internet]. 2018;27(4):1283–91. Available from: http://dx.doi.org/10.1007/s00044-018-2148-2

11. Alghamdi AA, Alam MM, Nazreen S. In silico ADME predictions and in vitro antibacterial evaluation of 2-hydroxy benzothiazole-based 1,3,4-oxadiazole derivatives. Turkish J Chem. 2020;44(4):1068–84.

12. George N, Sabahi B Al, AbuKhader M, Balushi K Al, Akhtar MJ, Khan SA. Design, synthesis and in vitro biological activities of coumarin linked 1,3,4-oxadiazole hybrids as potential multi-target directed anti-Alzheimer agents. J King Saud Univ - Sci. 2022 Jun 1;34(4).

13. Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. Curr Neuropharmacol. 2013;11(3):315–35.

14. Kumari P, Tripathi A, Kumar M, Seth A, Kumar S. Bioorganic Chemistry diazole as multitargeted hybrids for the treatment of Alzheimer ' s disease. 2021;111(April).

15. Dhanjal JK, Sharma S, Grover A, Das A. Use of ligand-based pharmacophore modeling and docking approach to find novel acetylcholinesterase inhibitors for treating Alzheimer's. Biomed Pharmacother. 2015 Apr 1;71:146–52.

16. Mishra P, Sharma P, Tripathi PN, Gupta SK, Srivastava P, Seth A, *et al*. Design and development of 1,3,4-oxadiazole derivatives as potential inhibitors of acetylcholinesterase to ameliorate scopolamine-induced

cognitive dysfunctions. Bioorg Chem [Internet]. 2019;89:103025. Available from: https://doi.org/10.1016/j.bioorg.2019.103025

17. Kumar Singh A, Lohani M, Parthsarthy R. Synthesis , Characterization and Anti-Inflammatory Activity of Various Isatin Derivatives. Iran J Pharm Res [Internet]. 2013;12(2):319–23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3813233/

18. Tomasz G. New 1 , 3 , 4-Oxadiazole Derivatives of Pyridothiazine- 1 , 1-Dioxide with Anti-Inflammatory Activity. Int J Mol Sci. 2020;21:1–22.

19. Grover J, Bhatt N, Kumar V, Patel NK, Gondaliya BJ, Elizabeth Sobhia M, *et al*. 2,5-Diaryl-1,3,4-oxadiazoles as selective COX-2 inhibitors and anti-inflammatory agents. RSC Adv [Internet]. 2015;5(56):45535–44. Available from: http://dx.doi.org/10.1039/C5RA01428J

20. Bhardwaj S, Parashar B, Parashar N, Sharma VK. Microwave assisted synthesis and pharmacological evaluation of. Arch Appl Sci Res [Internet]. 2011;3(2):558–67. Available from: www.scholarsresearchlibrary.com

21. Banik BK, Sahoo BM, Kumar BVVR, Panda KC, Jena J, Mahapatra MK, *et al*. Green synthetic approach: An efficient eco-friendly tool for synthesis of biologically active oxadiazole derivatives. Molecules. 2021;26(4).

22. Singh RB, Singh GK, Chaturvedi K, Kumar D, Singh SK, Zaman MK. Design, synthesis, characterization, and molecular modeling studies of novel oxadiazole derivatives of nipecotic acid as potential anticonvulsant and antidepressant agents. Med Chem Res [Internet]. 2018;27(1):137–52. Available from: http://dx.doi.org/10.1007/s00044-017-2047-y

23. Wang S, Liu H, Wang X, Lei K, Li G, Li J, *et al*. Synthesis of 1,3,4-oxadiazole derivatives with anticonvulsant activity and their binding to the GABAA receptor. Eur J Med Chem [Internet]. 2020;206:112672. Available from: https://doi.org/10.1016/j.ejmech.2020.112672

24. Rajak H, Singour P, Kharya MD, Mishra P. A Novel Series of 2,5-Disubstituted 1,3,4-oxadiazoles: Synthesis and SAR Study for their Anticonvulsant Activity. Vol. 77, Chemical Biology and Drug Design. 2011. p. 152–8.

25. Mickevičius V, Vaickelionienė R, Sapijanskaitė B. Synthesis of substituted 1,3,4-oxadiazole derivatives. Chem Heterocycl Compd. 2009;45(2):215–8.

26. Nazari M, Rezaee E, Hariri R, Akbarzadeh T, Tabatabai SA. Novel 1,2,4-oxadiazole derivatives as selective butyrylcholinesterase inhibitors: Design, synthesis, and biological evaluation. EXCLI J. 2021;20:907–21.

27. Pflégr V, Štěpánková Š, Svrčková K, Švarcová M, Vinšová J, Krátký M. 5-Aryl-1,3,4-Oxadiazol-2-Amines Decorated with Long Alkyl and Their Analogues: Synthesis, Acetyl-and Butyrylcholinesterase Inhibition and Docking Study. Pharmaceuticals. 2022;15(4):1–21.

28. Ergenç N, Çapan G, Demirdamar R. Synthesis, characterization and analgesic activity of new 4-arylhydrazono-3-methoxymethyl-2-pyrazolin-5-ones. Arzneimittel-Forschung/Drug Res. 2001;51(2):118–24.

29. Vaidya A, Pathak D, Shah K. 1,3,4-oxadiazole and its derivatives: A review on recent progress in anticancer activities. Chem Biol Drug Des. 2021 Mar 1;97(3):572–91.

30. Parikh PK, Marvaniya HM, Sen DJ. Synthesis and biological evaluation of 1,3,4-oxadiazole derivatives as potential antibacterial and antifungal agents. Int J Drug Dev Res [Internet]. 2011;3(2):248–55. Available from: http://www.ijddr.in

31. Misra HK. Synthesis of Some New Substituted 1,3,4-Oxadiazoles as Potential Insecticidal, Antibacterial and Anti-acetylcholine Esterase Agents. Arch Pharm (Weinheim). 1983;316(6):487–93.