Review Article

Recent Developments on Pharmacological Potential of 1,3,4-Oxadiazole Scaffold

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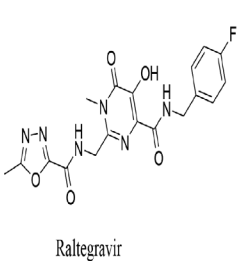
ABSTRACT

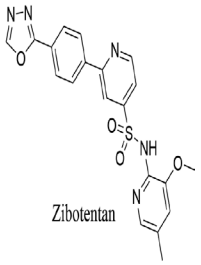
Heterocyclic compounds represent the important structural key in pharmaceutical medicinal chemistry. In literature, five-membered heterocycles are reported to be a core moiety of various pharmaceutical drugs. 1,3,4-oxadiazole scaffold, among various five-membered heterocycles is an important molecule which attracts various medicinal chemist to develop a novel biologically active molecule. 1,3,4-Oxadiazole is found to bear important pharmacological activities such as anti-diabetic, antimicrobial, anti-cancer, anticonvulsant, antioxidant, anti-Alzheimer's, anti-inflammatory, antiviral, cardiovascular, anti-tuberculosis, anti-pyretic, insecticidal. This review compiles the biological updates on various compounds containing 1,3,4-oxadiazole as a core moiety from the recent years.

Key words: Anti-diabetic, Anti-cancer, Heterocycle, Oxadiazole, Pharmacological activity.
Key messages: Five membered heterocyclic compounds are important in pharmaceutical chemistry. 1,3,4-oxadiazole scaffold possess diverse biological activities. Pharmacological activities shown by 1,3,4-oxadiazole derivatives include anti-diabetic, anticancer, anti-inflammatory, antiviral, antimicrobial etc. It can be further explored as a lead molecule because of its role in various biological activities.

INTRODUCTION

Heterocyclic ring containing compounds are of great value both medicinally and industrially.[1] Five-membered heterocycles demonstrated their efficacy in medicinal chemistry. Oxadiazole scaffold containing one oxygen and two nitrogen atoms in the five membered ring is a heterocyclic compound of great significance. Oxadiazole ring act as a pharmacophore in various clinically used number of drugs such as Raltegravir, Zibotentan, Furamizole.[2,3] It is derived by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=) from furan. Depending on the position of nitrogen atom in the ring, oxadiazole exists in four possible isomers. 1, 3, 4-oxadiazole is widely exploited isomer in the area of drug discovery because of their broad range of biological activities. Literature survey revealed that the 1,3,4-oxadiazole derivatives is found to bear tremendous activities such as anti-diabetic, antimicrobial, anti-cancer, anticonvulsant, antioxidant, anti-Alzheimer's, anti-inflammatory, antiviral, cardiovascular, anti-tuberculosis, anti-pyretic, insecticidal, making it an important pharmacophore for follow up further drug research. This review emphasizes





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on the compilation of latest update on biological profile of 1,3,4-oxadiazole derived compounds.

PHARMACOLOGICAL ACTIVITY

Anti-Diabetic Activity

Oxadiazole derivatives have been extensively studied for their anti-diabetic effect. A small series of novel benzothiazole clubbed oxadiazole mannich bases were synthesized and evaluated for their anti-hyperglycemic activity in STZ-induced model by R. Bhutani *et al.*[4] All the compounds exhibited good to moderate activity and the compound 1 (Figure 1) showed highest anti-diabetic activity.

A novel series of derivatives of 3-[2-(methylamino)methyl]-5-{[(2-phenylquinazolin-4-yl)oxy]methyl}-1,3,4-oxadiazole-2(3H)-thione were prepared by Srinivas S *et al.* and were screened for GSK-3B inhibition activity.[5] Three of the compounds 2, 3 and 4 of oxadiazolo-quinazoline series (Figure 2) exhibited good hypoglycemic activity.

A new series of fifteen 3-(5-cyclohexyl-1,3,4-oxadiazo-2-yl)N-substituted aniline analogs were prepared by S. Kavitha *et al.* and were screened for *in vitro* alpha-amylase inhibition activity.[6] Among all the synthesized hits, compound 5 (Figure 3) and 6 (Figure 4) showed good α amylase inhibition activity than other compounds.

A.K. Iqbal *et al.* synthesized some novel thiazolidinone derivatives incorporating oxadiazole moiety and the compounds were evaluated for *in vivo* hypoglycemic activity in wistar rats.[7] Compound 7 (Figure 5) showed comparable hypoglycemic activity to Pioglitazone.

Derivatives of oxadiazole containing 2-mercapto benzimidazole derivatives were synthesized and investigated for anti-diabetic activity using Oral Glucose Tolerance Test (OGTT) by R.V. Shingalapur *et al.*[8] Compounds 8(a-d) (Figure 6) were found to have outstanding activity against standard.

S. Kun *et al.* synthesized a series of 2-(β-D-Glucopyranosyl)-5-(4,hydroxymethyl-1,2,3-triazol-1,-ylmethyl)-1,3,4-oxadiazole derivatives.[9]Analogs were assayed against rabbit muscle glycogen phosphorylase b. Compound 9 (2-phenyl-5-[1-(β-D-glucopyranosyl)-1,2,3-triazol-4-yl]-1,3,4-oxadiazole (Figure 7) was found to had best inhibition.

Antimicrobial activity

Synthesis of novel benzothiazole based 1,3,4-oxadiazole derivatives containing benzothiazole were reported by Taher P. *et al.*[10] Compounds 10(a-d) (Figure 8) synthesized were evaluated for antimicrobial active and they demonstrated good activity against *Staphylococcus aureus, Escherichia coli.*

Jignesh P.R. *et al.* have reported synthesis of novel oxoethylthio-1,3,4-oxadiazole derivatives synthesized using isonicotinohydrazide and were found active against *Staphylococcus aureus, Escherichia coli, Bacillus cereus.*[11] Compounds (11a), (11d) having 2-chloro and 2-methyl-substitution respectively to the phenyl nucleus exhibited moderate to good activity against gram-negative bacteria and compounds (11b), (11c) having 3-chloro and 4-chloro substitution respectively to the phenyl nucleus exhibited moderate to good activity against gram positive bacteria only. (Figure 9)

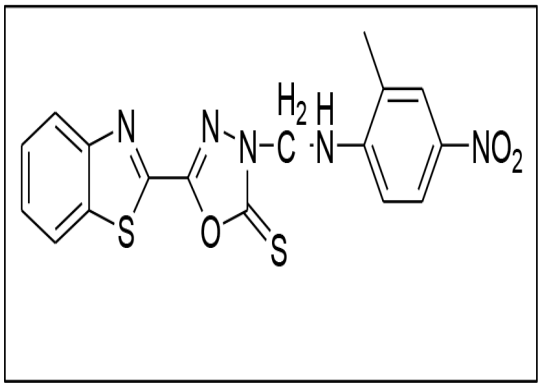

Figure 1: Chemical Structure of compound-1.

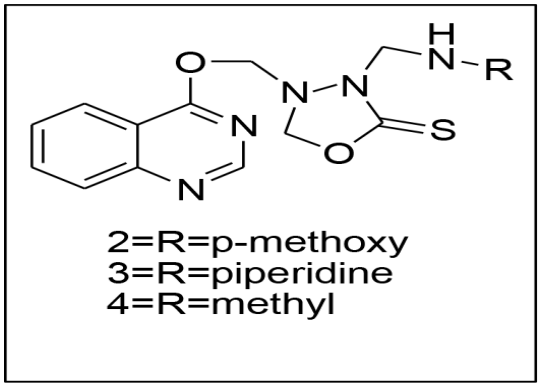

Figure 2: Chemical Structure of compounds2,3 and 4.

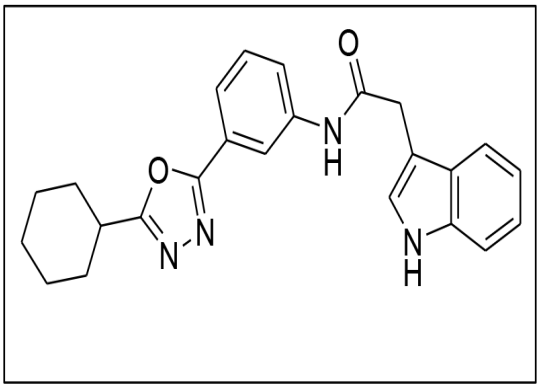

Figure 3: Chemical structure of compound 5.

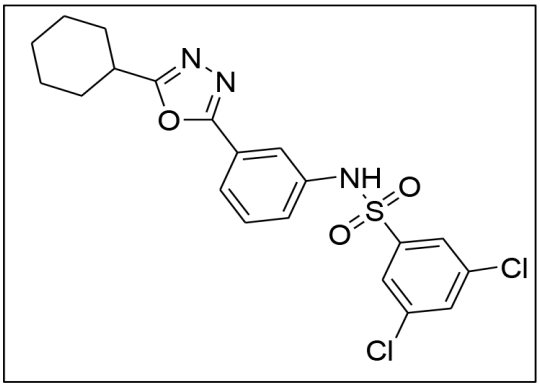

Figure 4: Chemical structure of compound 6.

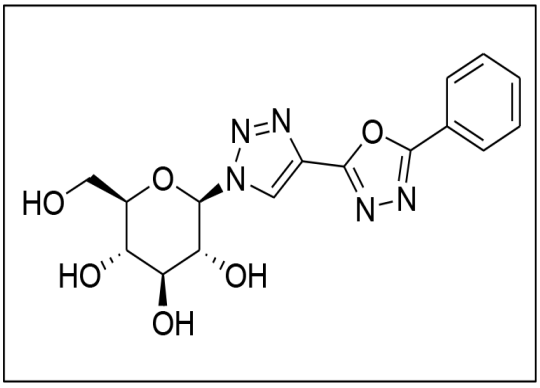

Figure 7: Chemical structure of compound 9.

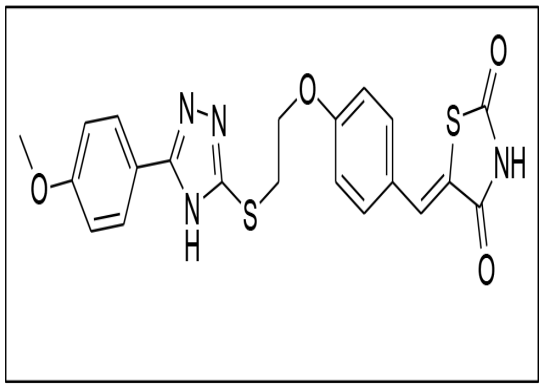

Figure 5: Chemical structure of compound 7

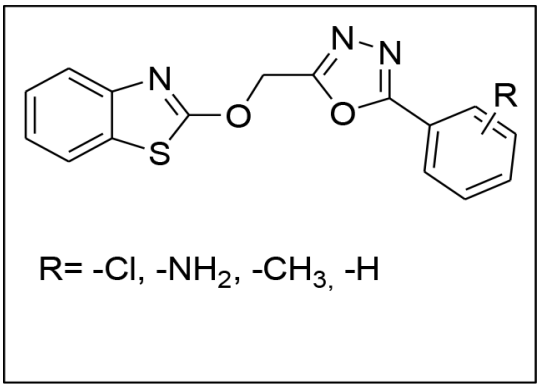

Figure 8: Chemical structure of compounds 10(a-d).

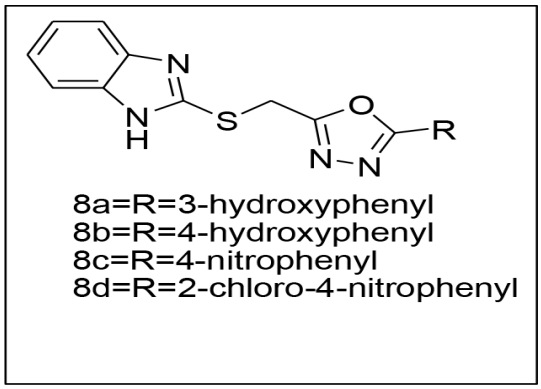

Figure 6: Chemical structure of compounds 8(a-d)

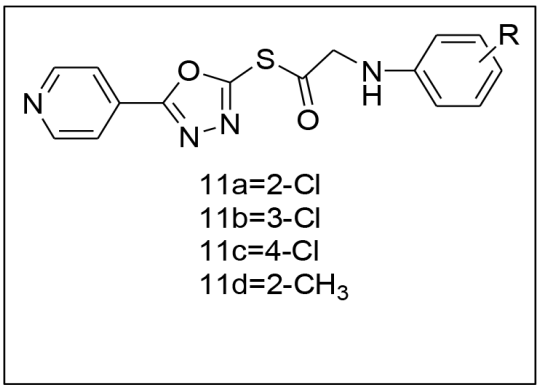

Figure 9: Chemical structure of compounds 11(a-d).

A novel series of substituted 1,3,4-oxadiazole derivatives 12(a-d) (Figure 10) were synthesized by Maryam Kouhkan *et al.* and investigated for their antimicrobial activity.[12] All of the synthesized hits showed excellent antibacterial activity against *Staphylococcus aureus* and Staphylococcus epidermidis.

A small library of 1,4-benzodioxane based oxadiazole derivatives were synthesized by H. Khalilullah *et al.* using an efficient synthetic route and were investigated for antibacterial activity.[13] Compounds 13a, 13b and 13c (Figure 11) showed magnificent activity against both gram positive and gram negative bacteria.

Salahuddin *et al.* developed a new series of oxadiazole bearing benzimidazole system as potent antibacterial and antifungal agents.[14] It was indicated that that the compounds possessing electron withdrawing group and weakly activating group showed excellent activity against *E. coli* and *S. aureus*. The derivatives with Cl, NO_2, Br and methyl group in the oxadiazole system, compounds 14(a-d) were most potent against fungal strains. (Figure 12)

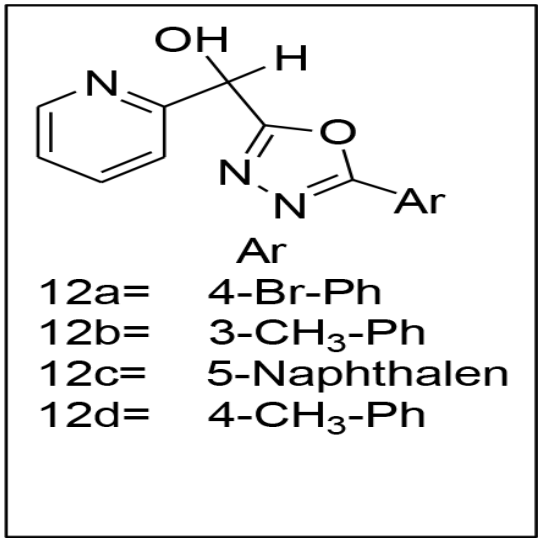

Figure 10: Chemical structure of compounds 12(a-d).

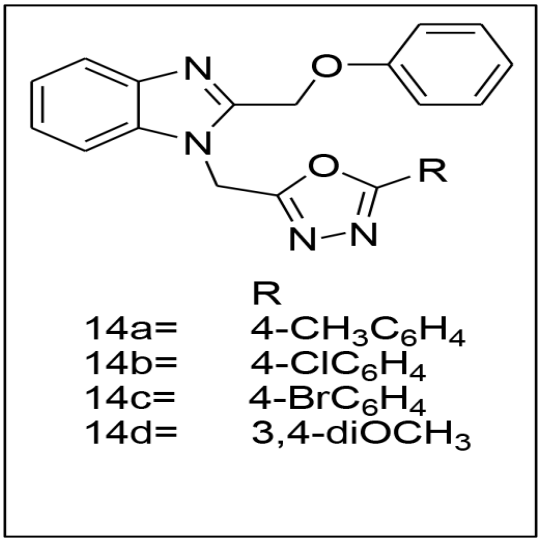

Figure 12: Chemical structure of compounds 14(a-d).

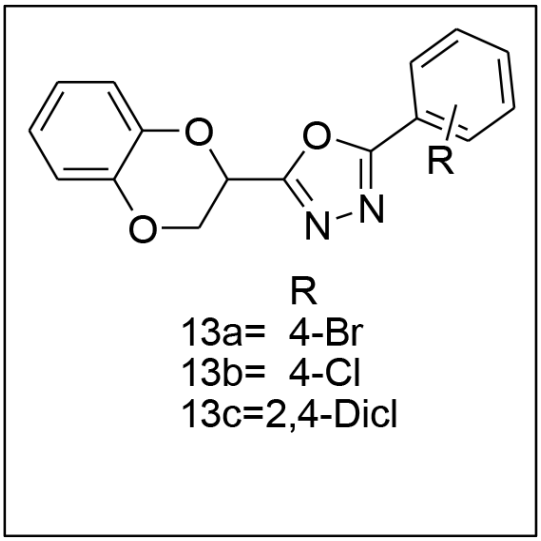

Figure 11: Chemical structure of compounds 13(a-c).

A series of ten new 1,3,4- oxadiazole derivatives bearing benzothiazole moiety were synthesized and screened for their antimicrobial potential by Gollapalli Naga Raju *et al.*[15] Compounds 15a, 15b, 15d and 15e showed significant antibacterial activity while 15c and 15e (Figure 13) showed good antifungal activity.

Anti-inflammatory activity

G. Chawla *et al.* reported the syntheses and evaluation of 2-(3-bromo4-fluorophenyl)-5-substituted-1,3,4-oxadiazoles as anti-inflammatory agent.[16] The pharmacological results revealed that, compound 16 (Figure 14) in which aryl ring was replaced by naphthyl ring, showed highest anti-inflammatory activity.

Durgashivaprasad *et al.* had explored the anti-inflammatory activity in acute and chronic models of two novel 2,5-disubstituted-1,3,4-oxadiazoles.[17] Compound OSD (compound 17) (Figure 15) was found to be better of the two compounds anti-inflammatory activity which may be due to the presence of o-phenol substitution at position 2 of oxadiazole ring.

Almasirad *et al.* designed and synthesized a new series of methyl-imidazolyl-1,3,4-oxadiazoles and were screened for anti-inflammatory activity.[18] Analogs18 and 19 (Figure 16) showed good anti-inflammatory effect in wistar rats.

Kumar *et al.* evaluated the anti-inflammatory and analgesic potential of novel 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzathiazole nine derivatives.[19] Compounds 20(a-d) (Figure 17), displayed good anti-inflammatory activity than other compounds.

H.S. Abd-Ellah *et al.* synthesized a novel library of 1,3,4-oxadiazoles which is hybridized with oxime.[20] The synthesized hits were screened for their anti-inflammatory, analgesic, antioxidant and ulcerogenic activities. Most of the tested compounds showed very good anti-inflammatory activity with compound 21 (Figure 18) being more active than standard indomethacin. Docking studies of all the compounds were also performed.

M. Akhter *et al.* reported the synthesis and pharmacological screening of various aroylpropionic acid derivatives bearing 1,3,4-Oxadiazole nucleus.[21] Compounds were evaluated for anti-inflammatory, analgesic, ulcerogenic activities and lipid peroxidation studies. 2-[3-(4 methylphenyl)-propane-3-one]-5-(4-methoxyphenyl)-1,3,4-oxadiazoles (22a) and 2-[3-(2,4-dimethylphenyl)-propane-3-one]-5-(4-methoxyphenyl)-1,3,4-oxadiazoles (22b) (Figure 19)

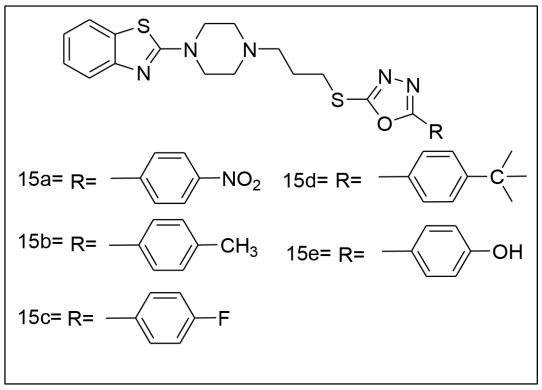

Figure 13: Chemical structure of compounds 15 (a-e).

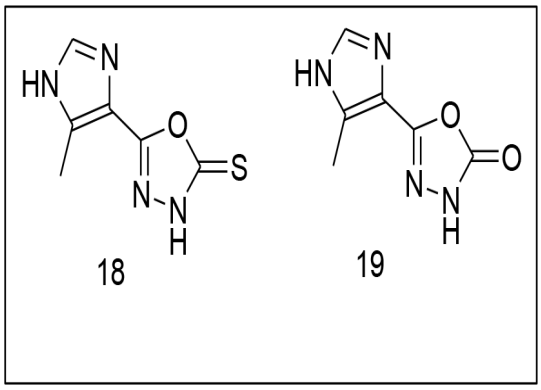

Figure 16: Chemical structure of compounds 18, 19.

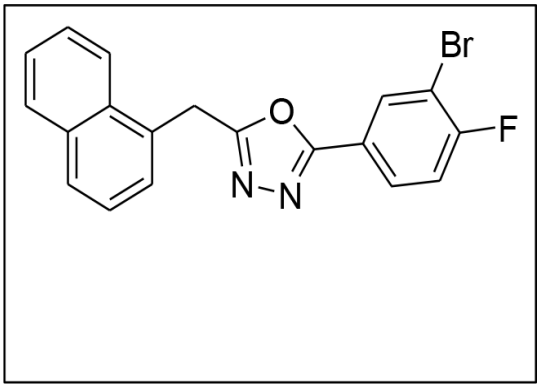

Figure 14: Chemical structure of compound 16.

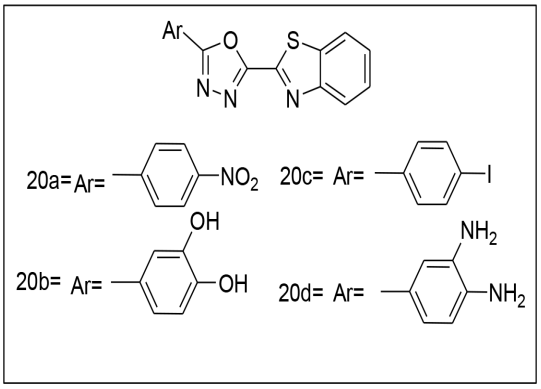

Figure 17: Chemical structure of compounds 20(a-d).

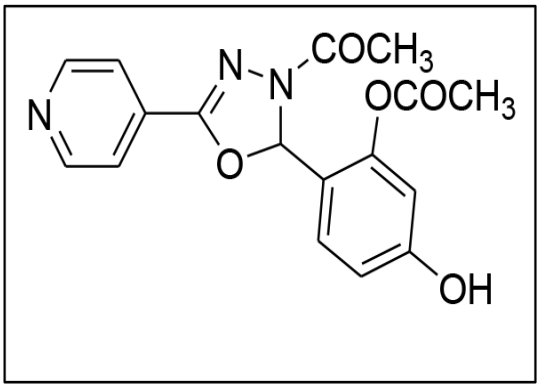

Figure 15: Chemical structure of compound 17.

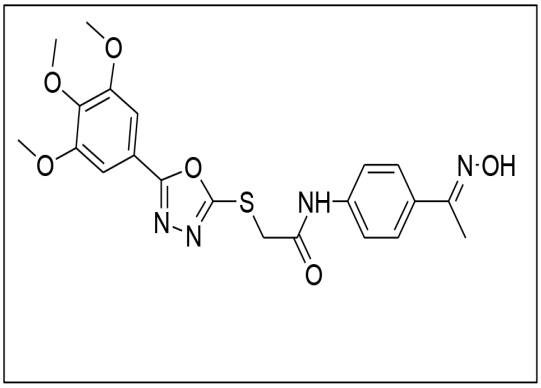

Figure 18: Chemical structure of compound 21.

were found equipotent to standard in inhibiting the rat paw edema.

Anti-tubercular activity

M. J. Ahsan *et al.* synthesized a new series of 1,5-dimethyl-2-phenyl-4-{[(5-aryl-1,3,4-oxadiazol-2-yl) methyl]amino}-1,2-dihydro-3H-pyrazol-3-one and all the derivatives were screened for anti-tubercular activity.[22] Among the synthesized derivatives, compound 23 (Figure 20) showed marked activity against Mycobacterium tuberculosis H37Rv and isoniazid resistant M. tuberculosis.

Chandrasekera *et al.* tested the potential of newly synthesized 3-substituted benzothiophene-1,1-dioxide derivatives as inhibitors of virulent Mycobacterium tuberculosis.[23] The results revealed that the substitution at the C-3 position of the benzothiophene-1,1dioxide series influenced the anti-tubercular activity. Oxadiazoles 24(a-d) (Figure 21) showed good anti-tubercular

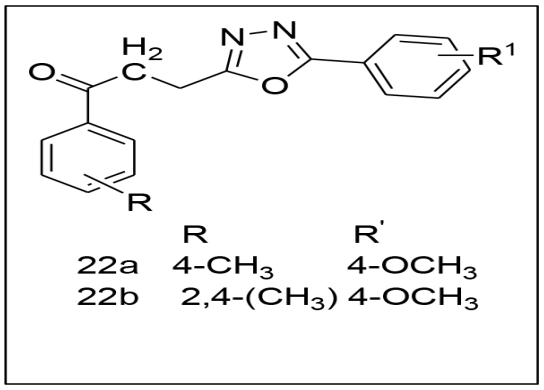

Figure 19: Chemical structure of compounds 22(a-b).

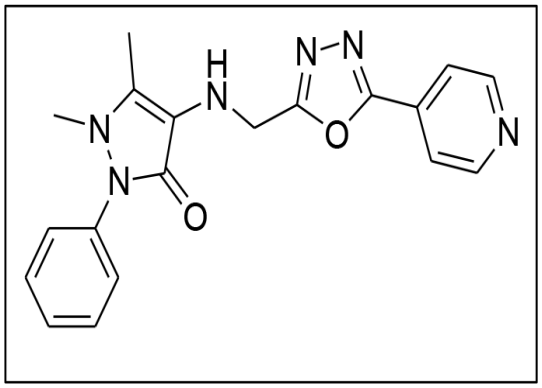

Figure 20: Chemical structure of compound 23.

activity while thiazoles, imidazoles and thiadiazoles had little activity.

Galina Karabanovich *et al.* investigated the novel synthesized 5-substituted-2-[(3,5-dinitrobenzyl)sulfanyl]-1,3,4-oxadiazoles and 1,3,4-thiadiazoles as a new class of anti-tubercular agents.[24] Most of the compounds 25(a-p) Figure 22 showed excellent *in vitro* activity against Mycobacterium tuberculosis.

G.V. Suresh Kumar *et al.* performed the preliminary antitubercular screening for 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4- oxadiazole derivatives against Mycobacterium tuberculosis H37Rv.[25] Results of anti-tubercular activity against M. tuberculosis revealed that compound26 (Figure 23) showed two fold enhanced potency than parent compound.

Ladania GG *et al.* synthesized new series of hits by coupling 1,3,4-oxadiazole with substituted quinoline moiety using molecular hybridization using different catalyst and solvents.[26] Primary screening of obtained compounds were performed against Mycobacterium tuberculosis H37Rv strain using Lowenstein-Jensen medium. The result showed that compounds 27(a-d) (Figure 24) were found to possess excellent activity.

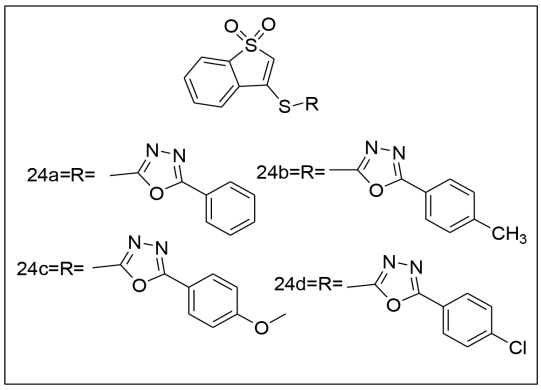

Figure 21: Chemical structure of compounds 24(a-d).

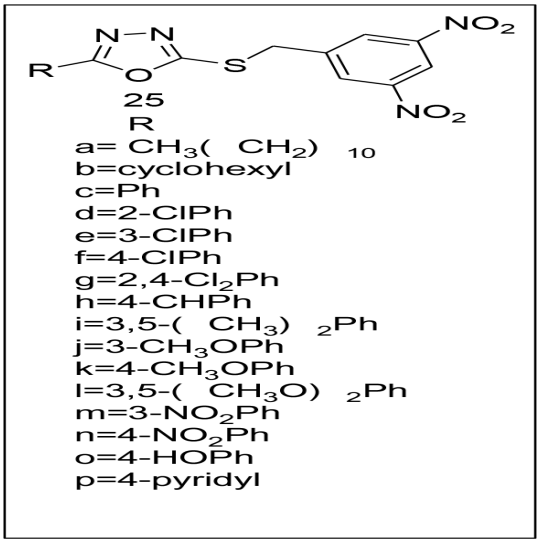

Figure 22: Chemical structure of compounds 25(a-p).

Anti-alzheimer Activity

Attaby *et al.* synthesized a number of new heterocyclic compounds, some having 1,3,4- oxadiazole derivatives and all were tested for anti-alzheimer activity.[27] Many compounds showed good activity and compound 28 (Figure 25) having oxadiazole moiety found to have high potency as anti-alzheimer agents relative to Flurbiprofen.

New chemical entities having 1,3,4-oxadiazole moiety of were synthesized and tested for their *in vitro* acetylcholinesterase (AChE) inhibitory potency by Kamal *et al.*[28] All compounds derived exhibited good inhibitory activity against AChE enzyme. Derivative 29 (Figure 26) showed IC_{50} value of 37.65 IM and resulted as a promising anti-alzheimer agent

Saitoh *et al.* designed, synthesized and reported SAR of a new library of oxadiazole derivatives as GSK-3β inhibitors which is promising agent for treating alzheimer's disease.[29] Among all derivatives compound 30 (Figure 27)

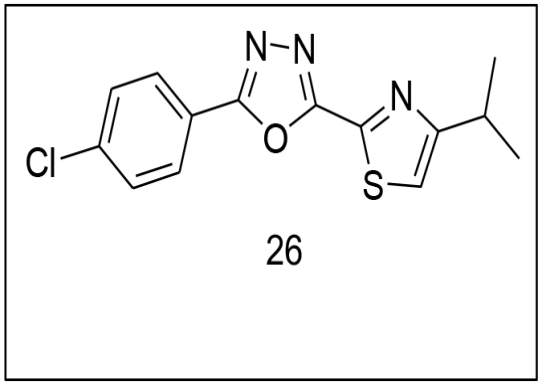

Figure 23: Chemical structure of compound 26.

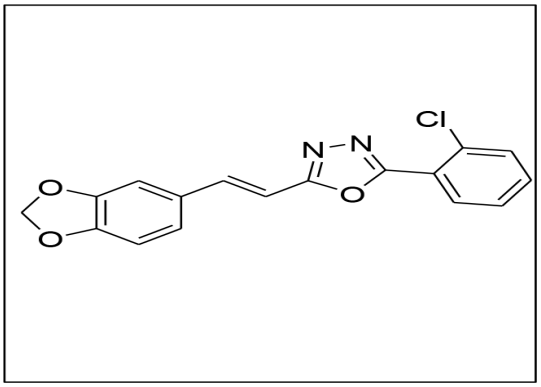

Figure 26: Chemical structure of compound 29.

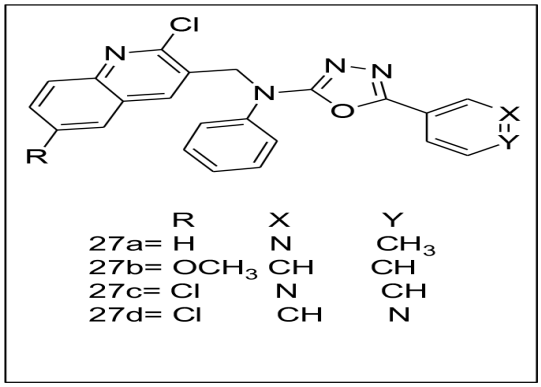

Figure 24: Chemical structure of compounds 27(a-d).

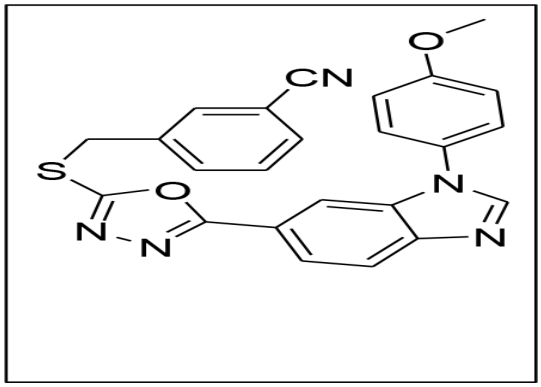

Figure 27: Chemical structure of compound 30.

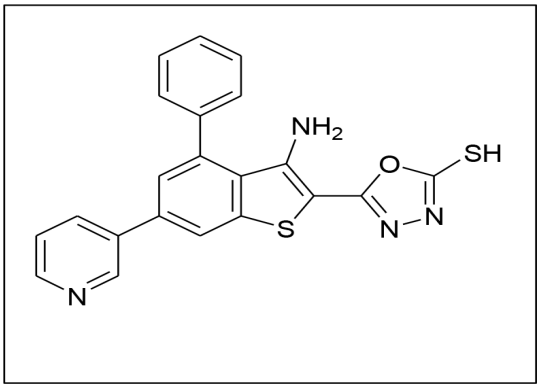

Figure 25: Chemical structure of compound 28.

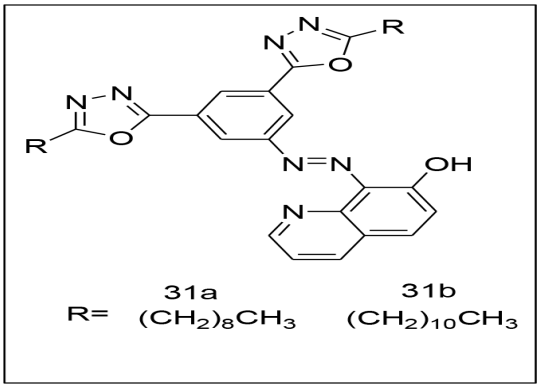

Figure 28: Chemical structure of compounds 31(a-b).

was found to show high selectivity and potency for GSK-3β inhibition *in vitro*.

Antioxidant Activity

Shridhar *et al.* synthesized novel 3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl azo dyes 4(a-f) and tested for *in vitro* antioxidant properties.[30] Results showed that all compounds have significant antimicrobial and antioxidant activities. DPPH assay was done on 4a-f at different concentrations and 31a and 31b (Figure 28) showed significant DPPH scavenging activity (>70%) due to best substitutions.

Abdelmonem *et al.* synthesized some novel oxadiazole derivatives and tested for antioxidant activity.[31] All derivatives, compound 32 (Figure 29) were found to be potent antioxidant agents.

Patrao *et al.* synthesized a new entities of 1-(substituted)-2-({5-[(naphthalen-1/2 yloxy) methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone. They were tested for antioxidant activities and showed promising results.[32] Compound 33 (Figure 30) exhibited good antioxidant activity.

A library of new 5-(2-amino-5-methylthiazol-4-yl)-1,3,4-oxadiazole-2-thiol derivatives was prepared and evaluated

for antioxidant potential by Kikkeri *et al.*[33] Compounds 34a, 34b and 34c (Figure 31) gives best scavenging effect against the free radicals.

Novel series of 2,5-disubstituted-1,3,4-oxadiazole derivatives synthesized and screening for their antimicrobial and antioxidant activities were done by Sindhe *et al.*[34] The results showed that 35(a-c)(Figure 32) displayed best antioxidant activity.

Mihailovic *et al.* synthesized some 1,3,4-oxadiazole derivatives having phenolic acid moieties and examined for their scavenging potential ie.anti-oxidant activity by scavenging stable DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals.[35] Compounds 36(a-d) (Figure 33) exhibited best DPPH scavenging activity.

Bharatiya *et al.* synthesized a novel set of 2-N- phenyl piperazino methylene-4- (4'-amino, 2'-nitro phenyl)-5-mercapto-1,3,4-oxadiazole analogs which were tested for their antioxidant potential.[36] Compounds 37a and 37b (Figure 34) showed good antioxidant activity.

Anticonvulsant activity

Vaishali and Bahar Ahmed synthesized 2-(substituted-phenyl)-2-methyl-5styryl-2,3-dihydro-[1,3,4]oxadiazole derivatives as anticonvulsant agents.[37] Among the synthesized hits 38 and 39 (Figure 35) possess good significant activity. Docking study was also done of all the prepared compounds on PDB ID: 4COF.

A new series of 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-oxadiazole derivatives was synthesized from isoniazid and various substituted isothiocyanates by M Shaharyar *et al.*[38] Synthesized compounds were screened for their anticonvulsant activity. Compound 2-(4-chlorophenyl) amino-5-(4-pyridyl)1,3,4-oxadiazole (40) (Figure 36) found to have extremely good anticonvulsant activity.

Harish Rajak *et al.* designed and synthesized a series of new substituted semicarbazones containing 1,3,4oxadiazole nucleus, 41(a-n) (Figure 37) and tested for their anticonvulsant potential through MES and scPTZ models.[39] Results demonstrated that hits bearing the groups like hydroxy or nitro on phenyl possess high potency in MES and scPTZ models.

Tabatabai A *et al.* synthesized some phenoxyphenyl-1,3,4-oxadiazole derivatives and evaluated them for anticonvulsant activity using pentylene tetrazole induced lethal convulsion test.[40] It was indicated that compound 42 (Figure 38) with an amino substituent on 5 position of 1,3,4-oxadiazole ring has a good effect whereas

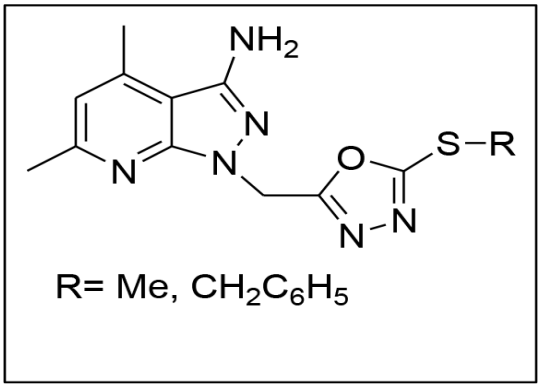

Figure 29: Chemical structure of compound 32.

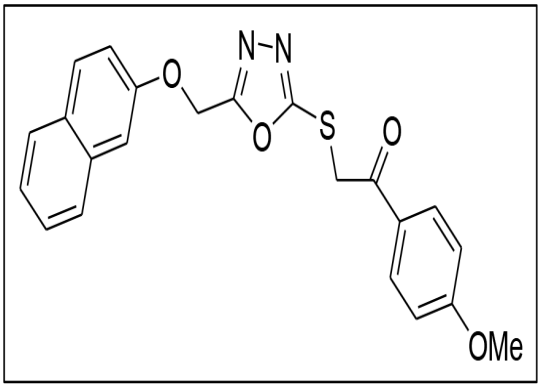

Figure 30: Chemical structure of compound 33.

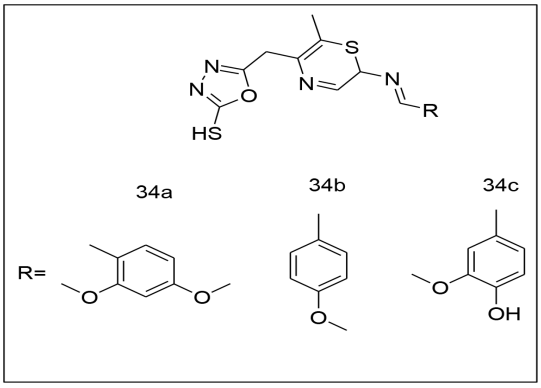

Figure 31: Chemical structure of compounds 34(a-c).

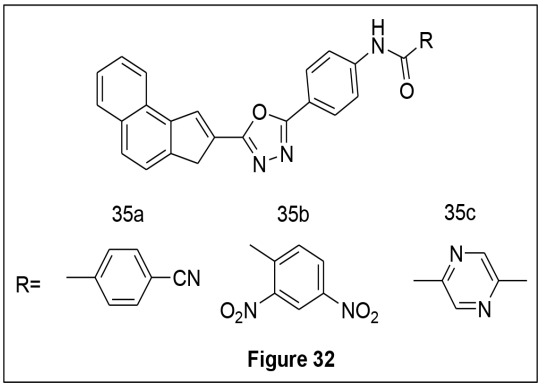

Figure 32: Chemical structure of compounds 35(a-c).

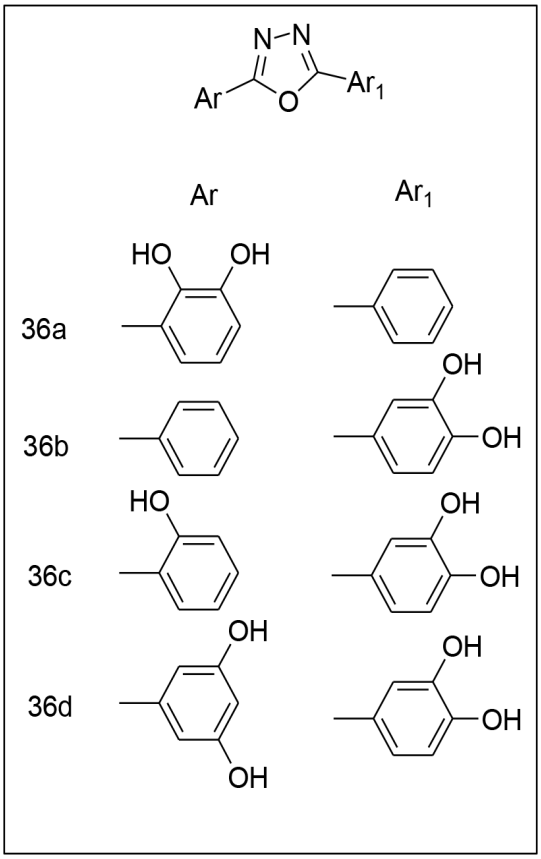

Figure 33: Chemical structure of compounds 36 (a-d).

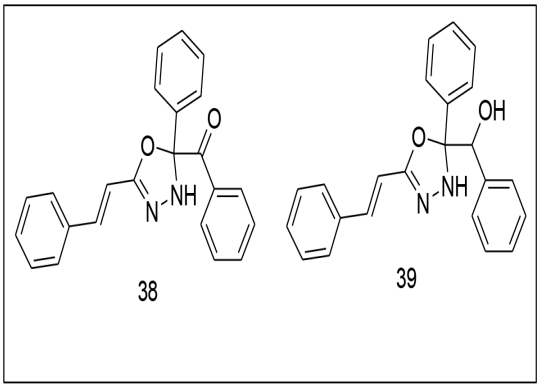

Figure 35: Chemical structure of compounds 38, 39.

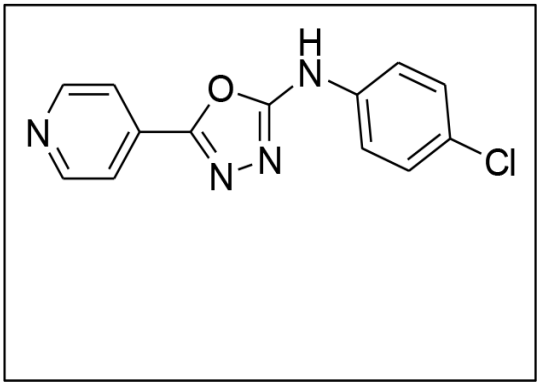

Figure 36: Chemical structure of compound 40.

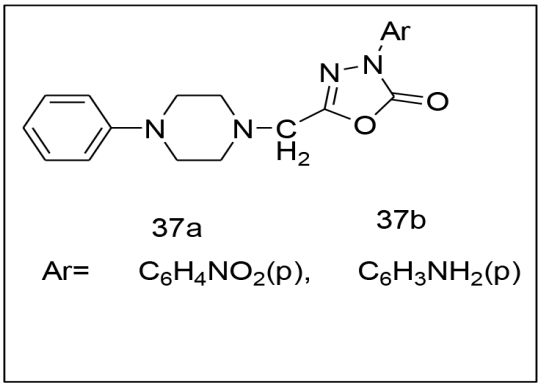

Figure 34: Chemical structure of compounds 37 (a-b).

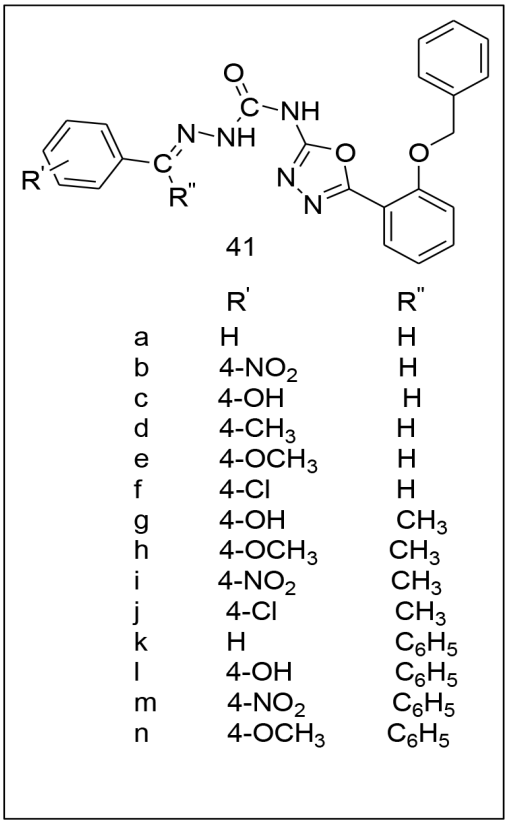

Figure 37: Chemical structure of compounds 41 (a-n).

replacement of amino group with H, OH, SH or SCH_3 diminish the anticonvulsant effect.

A library of novel phthalimide derivatives of 1,3,4-oxadiazole were synthesized and screened for their anticonvulsant activity by Mashooq A. Bhat *et al.*[41] Results showed that a number of synthesized title compounds demonstrated good activity with compound 43 (Figure 39) showing excellent anti convulsant activity comparable to standard i.e. phenytoin.

S J Gilani *et al.* synthesized a novel series of Isoniniconitic acid hydrazide incorporated derivatives of

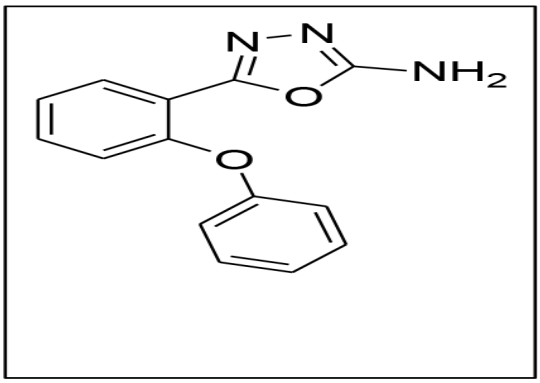

Figure 38: Chemical structure of compound 42.

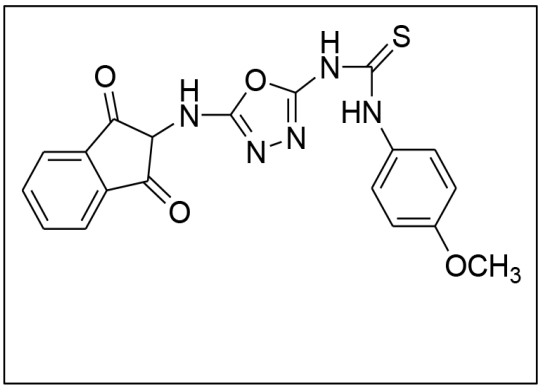

Figure 39: Chemical structure of compound 43.

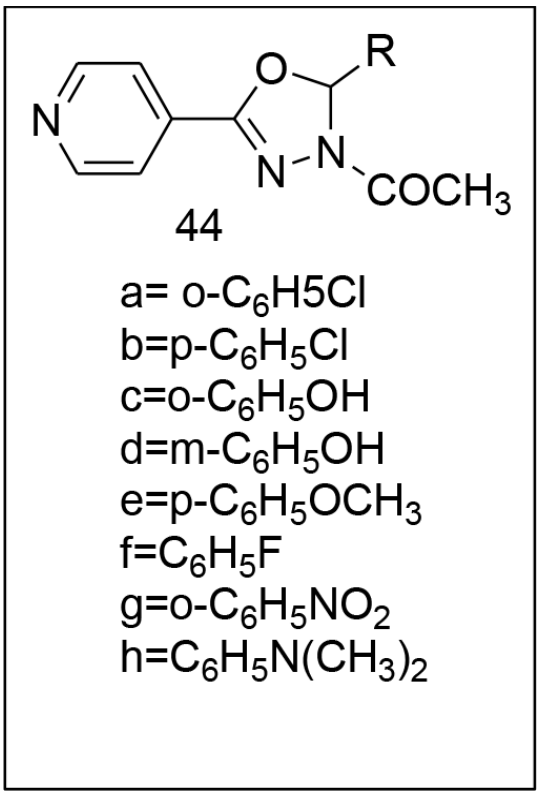

Figure 40: Chemical structure of compounds 44(a-h).

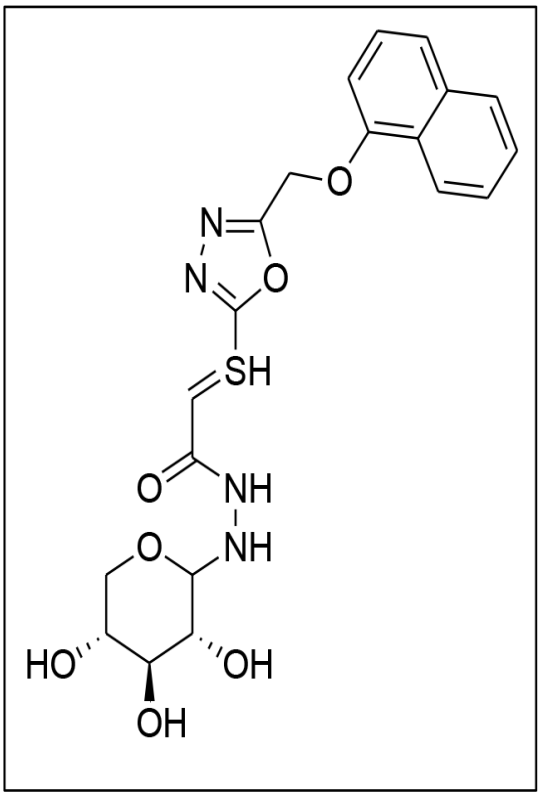

Figure 41: Chemical structure of compound 45.

1,3,4-oxadiazole and were screened for anticonvulsant activity against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (scPTZ) induced models.[42] All the synthesized compounds 44 (a-h) (Figure 40) were found to be active in MES and most of compounds were found active in scPTZ model.

Antiviral

W. A. El-Sayed *et al.* prepared a series of new 5-[(naphthalen-1-yloxy)methyl]-1,3,4-oxadiazole derivatives and were screened for their anti-HIV activity.[43] Results indicated that compound 45 (Figure 41) showed the excellent antiviral activity. Results revealed that the substitution of a free hydroxyl sugar moiety increases the antiviral activity compared to O-acetylated substituted derivatives.

A new library of novel 1,3,4-oxadiazole thioether derivatives bearing 2-methylpyrimidin-4-amine group were synthesized by W. Wu *et al.* and evaluated for their antiviral activity against TMV.[44] Antiviral results demonstrated that compound 46 (Figure 42)showed the best effect against TMV, even better than standard.

Liangrun Dong *et al.* performed the synthesis of novel thioether derivatives containing 1,3,4-oxadiazole/thiadiazole and emodin moieties.[45] The derivatives were evaluated for antiviral activity against TMV using the

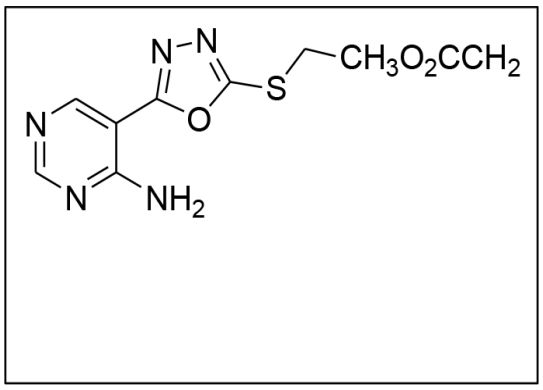

Figure 42: Chemical structure of compound 46.

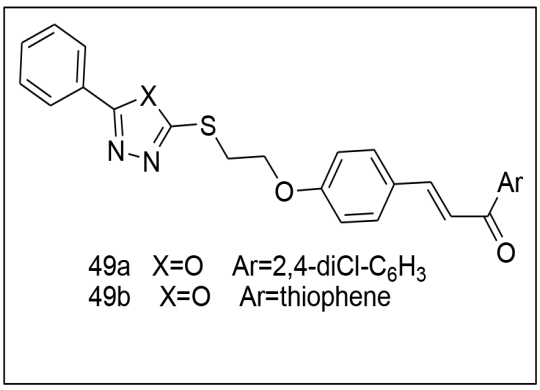

Figure 45: Chemical structure of compounds 49(a-b).

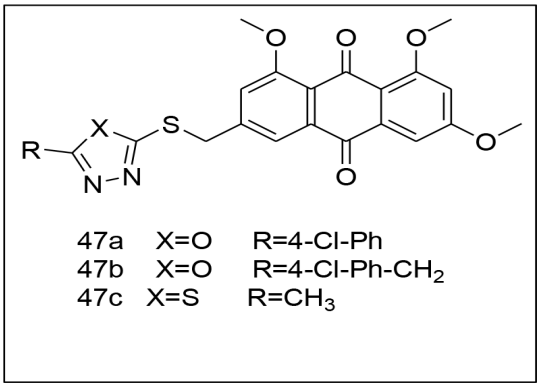

Figure 43: Chemical structure of compounds 47(a-c).

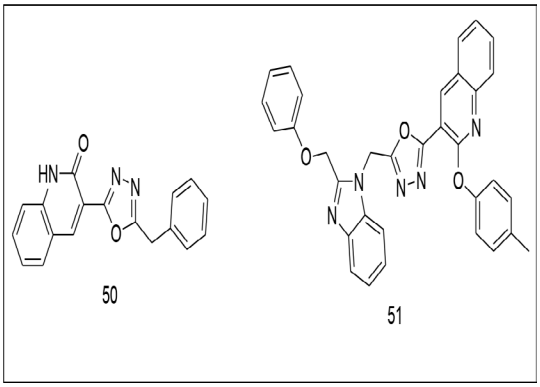

Figure 46: Chemical structure of compounds 50, 51.

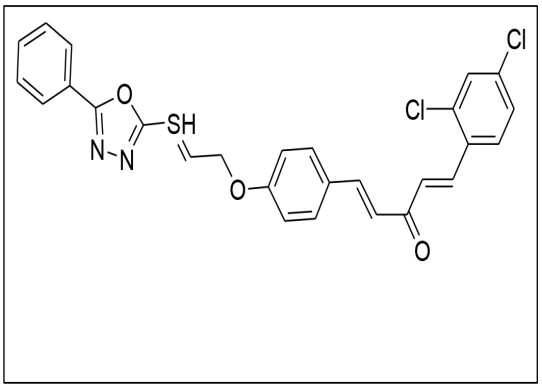

Figure 44: Chemical structure of compound 48.

half-leaf method. The results demonstrated that among the prepared compounds, 47a, 47b and 47c (Figure 43)possessed significant antiviral activity with inhibition rates of 50.51%, 52.08% and 54.62%, respectively, which were comparable to that of reference (53.40%).

Xiuhai Gan *et al.* designed and synthesized a novel series of 1,4-pentadien-3-one derivatives containing the 1,3,4-oxadiazole moiety and screened for their anti-viral activity.[46] It was indicated that some of the synthesized compounds showed moderate to good antiviral activities at 500 mg L^{-1}. Compound 48 (Figure 44) was found to demonstrate the excellent protective activity, with EC_{50} value of 135.56 mg L^{-1}, which were better to ribavirin.

A small library of twenty six new 1,3,4-oxadiazole/thiadiazole–chalcone analogs were prepared and tested for antiviral activity.[47] Compounds 49(a-b) (Figure 45) showed outstanding anti-viral activity with the EC_{50} values of 33.66, 33.97, 33.87 and 30.57 mg/mL, respectively, with reference to standard. SAR study was also done which indicated that smaller aromatic ring and electron-with drawing groups will increase the anti-TMV effect.

Anti-cancer

Salahuddin *et al.* synthesised new 2,5-disubstituted 1,3,4-oxadiazole analogs and were evaluated for anticancer activity.[48] Compound 50(NSC-776965) and compound 51 (NSC 776971) (Figure 46) showed the best results against cancer among the synthesized hits.

Mohamed Jawed Ahsan *et al.* reported the synthesis of some oxadiazole as antiproliferative agents.[49] Compound 52 (Figure 47) expressed highest antiproliferative activity towards HOP-92 human cancer cell lines at 10 μM concentration.

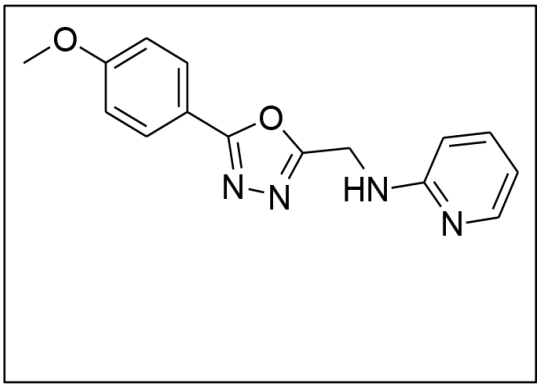

Figure 47: Chemical structure of compound 52.

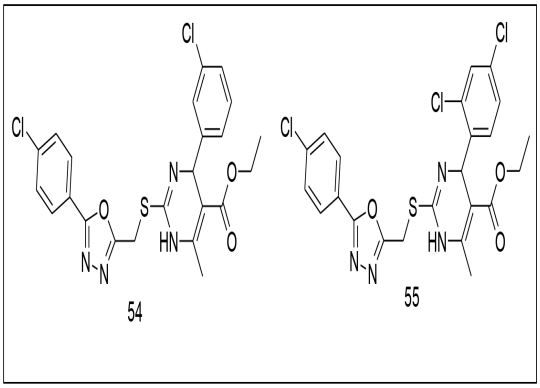

Figure 49: Chemical structure of compounds 54, 55.

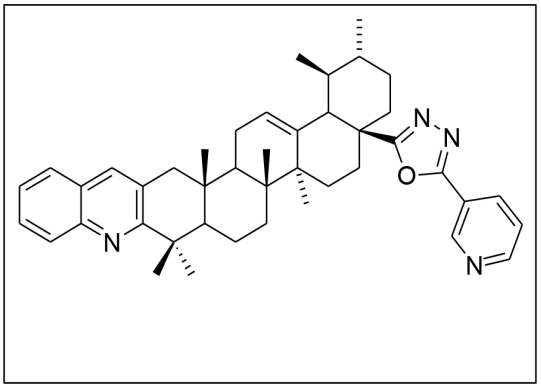

Figure 48: Chemical structure of compound 53.

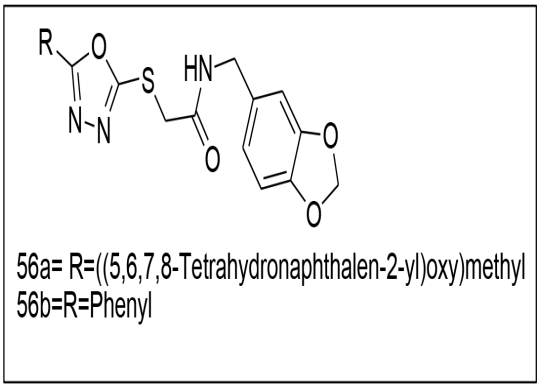

Figure 50: Chemical structure of compounds 56(a-b).

Gu W *et al.* designed and synthesized new series quinoline derivatives of ursolic acid and were tested for *in vitro* anti-cancer activity against MDA-MB-231, HeLa and SMMC-7721 cell lines.[50]

Compound53 (Figure 48) showed remarkable anticancer activity against MDA-MB-231, HeLa and SMMC-7721 cells comparable to etoposide.

F.A.F. Ragab *et al.* designed and synthesized a new series of DHPMs containing 1,3,4-oxadiazole moiety as monastrol analogues.[51] The prepared derivatives were evaluated for their cytotoxic activity against 60 cancer cell lines at one dose (10 μM). Compounds 54 against HL-60 (TB) and 55 (Figure 49) against MOLT-4, were found to be more active than monastrol.

Ahmet Özdemir *et al.* synthesized some novel oxadiazole, thiadiazole and triazole analogs and were tested for their inhibitory effects on MMPs.[52] Compounds 56 (a-b) (Figure 50) showed most promising anticancer effects on A549 and C6 cell lines similar to standard cisplatin. These analogs were also the most active MMP-9 inhibitors. Docking study has also been performed.

A. Husain *et al.* designed and synthesized two novel series of benzimidazole bearing oxadiazole and triazolothiadiazoles as a potential anticancer agents.[53] Anticancer evaluation was done at the NCI, USA. It was indicated by the results that compound 57 (Figure 51) as potent compound with broad spectrum of activities on cell lines.

Calcium channel blocker

Girish R. Bankara *et al.* tested whether the correction of endothelial dysfunction is dependent on the normalization of high blood pressure levels by synthesized 1,3,4-oxadiazole derivative (compound 58) (Figure 52) (NOX-1) in deoxycorticosterone acetate and NG-nitro-l-arginine hypertensive rats.[54] In DOCA-salt and L-NNA hypertensive rats, the mean systolic blood pressure was 185.3±4.7 and 170.2±4.1 mmHg, whereas after administration of NOX-1 to hypertensive rats, MSBB was 127.8±4.5 and 120.2±5.1mmHg, respectively.

Insecticidal activity

Cao S *et al.* performed the synthesis of 2-(5-(Trifluoromethyl)pyridyloxylmethyl)-5-aryl-1,3,4-oxadiazole derivatives.[55] All derivatives showed good insecticidal activity especially those bearing fluorine on the benzene ring, 59 (a-b) (Figure 53) demonstrated better insecticidal activity.

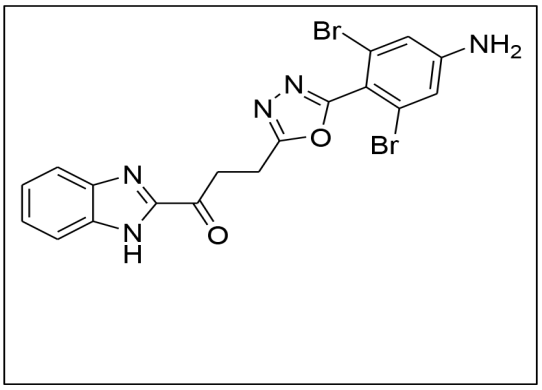

Figure 51: Chemical structure of compound 57.

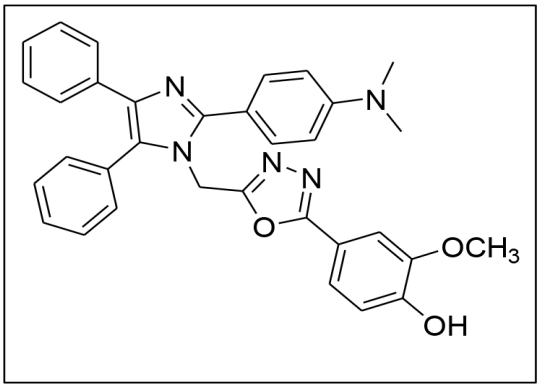

Figure 54: Chemical structure of compound 60.

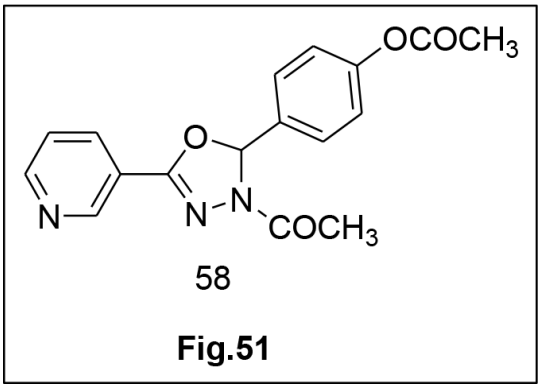

Figure 52: Chemical structure of compound 58.

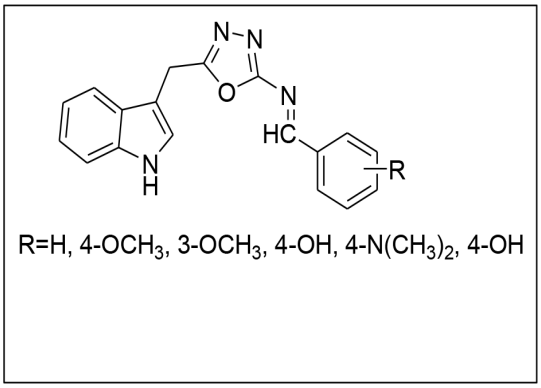

Figure 55: Chemical structure of compound 61.

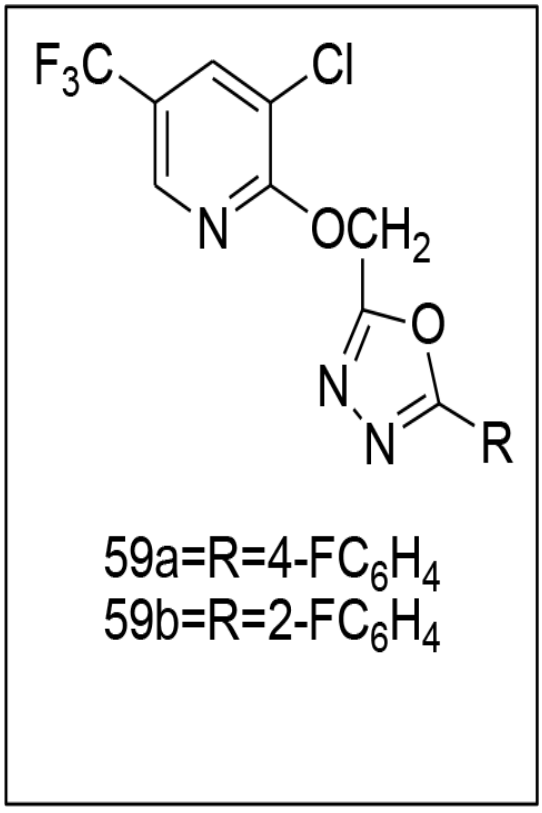

Figure 53: Chemical structure of compounds 59(a-b).

Cardiovascular activity

Vineet Malhotra *et al.* synthesized a new series of novel substituted imidazole analogs and tested it for their hypotensive and acute toxicity activities.[56] Eight compounds among the synthesized hits have shown good hypotensive and bradycardiac responses. Compound 60 (Figure 54) have shown potent activity than standard drug clonidine.

Navneet Singh *et al.* have presented the review showing the cardiovascular activity of Indole derivatives by incorporating Oxadiazole motif at 3- position of Indole, compound 61 (Figure 55).[57] Various factors i.e. the change in blood pressure, heart rate, effect on Carotid Occlusion and Nordaniline pressor responses were observed for the cardiovascular study.

MAO-Inhibitors

Elias Maccioni *et al.* designed and synthesized 3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles derivatives 62 (a-f) (Figure 56) and evaluated as inhibitors of human monoamine oxidase A and B isoform.[58] It was concluded that these prepared analogs were promising reversible and selective MAO-B inhibitors. Docking study was also performed.

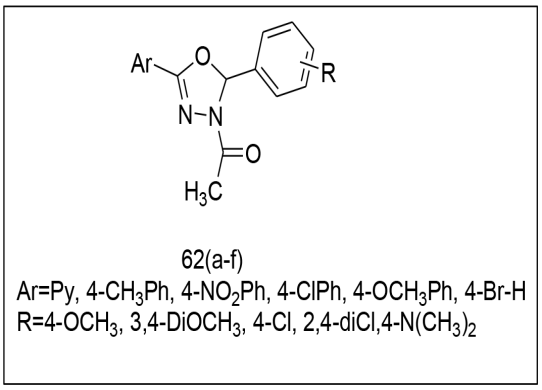

Figure 56: Chemical structure of compound 62(a-f).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

MAO: Monoamine Oxidase; **NCI:** National Cancer Institute; **DST:** Department of Science and Technology; **GSK:** Glycogen Synthase Kinase; **µM:** Micromolar; **µ:** Alpha; **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **PTZ:** Pentylene Tetrazole; **MES:** Maximal Electric Seizure; **TMV:** Tobacco Mosaic Virus; **SAR:** Structure Activity Relationship; **DST:** Department of Science and Technology.

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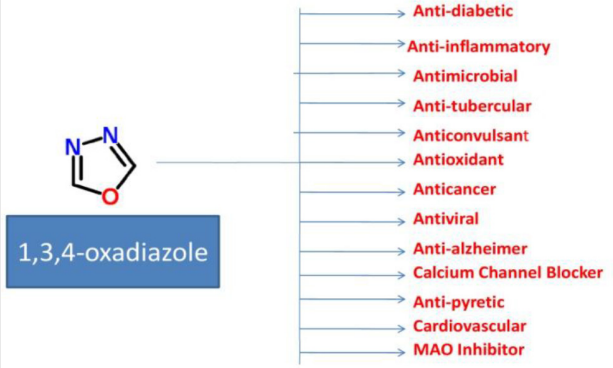
PICTORIAL ABSTRACT



SUMMARY

- Five membered nitrogen-oxygen containing hetero-cyclic core, Oxadiazole is a vital scaffold in medicinal chemistry.
- 1,3,4-oxadiazole and its derivatives showed wide range of biological potential such as anti-diabetic, anti-cancer, anti-bacterial etc.
- This review emphasizes on current updates on biological profile of 1,3,4-oxadiazole based compounds.
- Thus 1,3,4-oxadiazole scaffold can be further explored for development of potent medicinal agents.

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