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Heterocyclic 1, 3, 4-oxadiazole compounds with diverse biological activities: A comprehensive review

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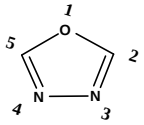
ABSTRACT

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Heterocyclic nucleus 1,3,4-oxadiazole constitutes an important class of compounds for new drug development. The synthesis of novel oxadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades. Oxadiazole compounds possess an extensive spectrum of pharmacological activities. In particular, compounds bearing 1,3,4-oxadiazole nucleus are known to exhibit unique antiinflammatory, analgesic, antimicrobial, antitumor, anticonvulsant, anthelmintic, antimycobacterial, herbicidal, antioxidant and antiviral activities. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. These observations have been guiding for the development of new oxadiazole derivatives that possess varied biological activities and can be a lead nucleus for future developments to get safer and effective compounds. References of the most relevant literature published by various research groups around the world are provided.

Key words: Heterocycles, 1,3,4-oxadiazole, biological activity

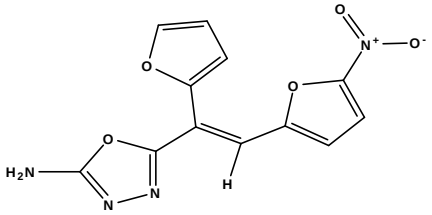
INTRODUCTION

Heterocyclic compounds containing the five membered oxadiazole nucleus possess a diversity of useful biological effects [1]. Oxadiazole is considered to be derived from furan by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=). Oxadiazoles are cyclic compounds containing one oxygen and two nitrogen atoms in a five membered ring [2-3]. In particular, compounds bearing the 1,3,4-oxadiazole nucleus are known to have unique antiinflammatory, analgesic, antimicrobial, antitumour, anticonvulsant, anthelmintic, herbicidal, antimycobacterial, antioxidant and anti-hepatitis B viral activities.



1,3,4-oxadiazole heterocyclic nucleus

Some examples which illustrate the diverse biological activities of heterocyclic nucleus 1,3,4-oxadiazole are: Furamizole, **1**, 2-amino-5-[2-(5-nitro-2-furyl)-l-(2-furyl)-vinyl]l,3,4-oxadiazole, a nitrofuran derivative possesses a strong antibacterial activity [4-5].



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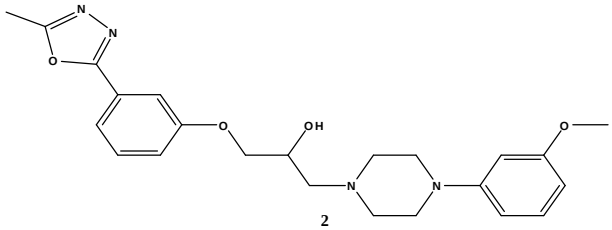
Nesapidil, **2**, 1-[4-(2-methoxyphenyl)piperazin-1-yl]-3-[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy]propan-2-ol, a well established vasodilating agent also contains 1,3,4-oxadiazle nucleus. It is calcium channel blocker. Its major effect is to slow down Ca^{+2} channels [6].



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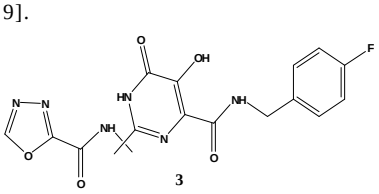
Raltegravir, **3,** an antiretroviral drug by Merck & Co having 1,3,4-oxadiazole nucleus is used to treat HIV infection. HIV replication involves the conversion of viral RNA into DNA, which is then incorporated into the host cell genome through a process catalyzed by the HIV integrase enzyme. By blocking HIV integrase, raltegravir inhibits HIV replication [7]. Another example having an oxadiazole nucleus, Tiodazosin, **4**, is an antihypertensive drug. It produced a noncompetitive antagonism of alpha adrenergic receptors in the portal vein [8-9].



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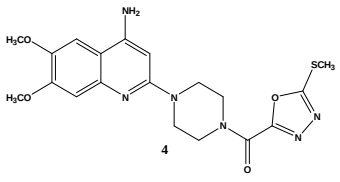

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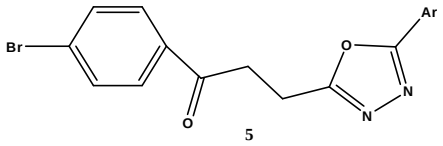
BIOLOGICAL ACTIVITIES

1.Antiinflammatory Activity

NSAIDs have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthritis, respiratory tract infections and fever [10-11]. These agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA_2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal upset and irritation [12-15]. Some evidences suggest that the oxadiazole moiety present in some compounds possess an antiinflammatory activity by virtue of dual mechanism ie, inhibiting both COX/LOs to reduce gastric

acid formation. The reported literature confirms that gastrointestinal side effects of aroylpropionic acids are due to the presence of a free carboxylic group in the parent drug [16-23]. Thus, developing new agents with minimum or without side effects is an extensive research area at present by replacing of the terminal carboxylic function of propionic acid by oxadiazole ring may enhance the antiinflammatory activity of such compounds with reduced ulcerogenic effects [24].

Few good examples of substituted 1,3.4-oxadiazole derivatives belonging to series1-(4-bromo-phenyl)-3-(5-substituted phenyl-[1, 3, 4] oxadiazole-2-yl]-propan-1-one, **5,** were synthesized and evaluated for antiinflammatory activity. Derivative 1-(4-bromo-phenyl)-3-(5-(3,4-dimethoxy-phenyl-[1,3,4]oxadiazole-2-yl]- propan-1-one presented better antiinflammatory activity and shown, 61.9 percentage inhibition response of pleurisy at a dose of 20 mg/kg against carrageenan induced rat paw edema [25].



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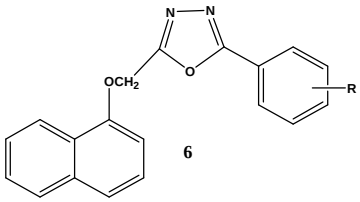
A novel series of 2-(4-substituted phenyl)-5-(napthlene-1-yloxymethyl)-[1,3,4]oxadiazole, **6** derivatives were prepared and evaluated for antiinflammatory activity. From the series 2-(4-hydroxyphenyl)-5-(napthlene-1-yloxymethyl)-[1,3,4]oxadiazole and 2-(4-methoxy-phenyl)-5-(napthlene-1-yloxymethyl)-[1,3,4]oxadiazole, presented significant antiinflammatory activity . The higher activity of compound 2-(4-hydroxyphenyl)-5-(napthlene-1-yloxymethyl)-[1,3,4]oxadiazole may be attributed to the electronegativity of the hydroxyl group, which can withdraw electron more strongly than chloro, nitro and other groups [26].

Another series of 3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-ones, **7** were synthesized and tested for their antiinflammatory activity. The 4-methoxy phenyl and 3,4-dimethoxy phenyl derivatives were showed significant antiinflammatory activity [27].



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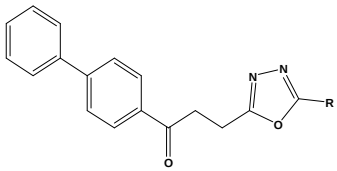

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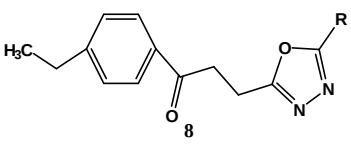
Two novel series of 1-(4-benzylphenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one, **8**, and 1-(4-ethylphenyl)-3-(5-substituted phenyl-[1,3,4]oxadiazole-2-yl]-propan-1-one**, 9** were evaluated for antiinflammatory activity. The 4-methoxy and 3,4-dimethoxy phenyl presented better antiinflammatory activity and shown 52.6, 56.2 percentage inhibition response against indomethacin, (61%) [28].



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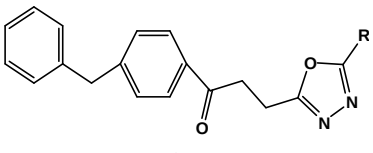

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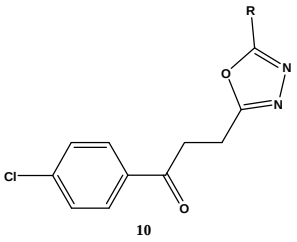
Two novel series 2-[3-(4-chlorophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole, **10** and 2-[3-(4-ethylphenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole, **11** were tested for antiinflammatory activity. The 4-methoxy phenyl and 3,4-dimethoxy phenyl derivatives were showed significant antiinflammatory activity 58.38% and 59.52% respectively against indomethacin (64.28%) [29].



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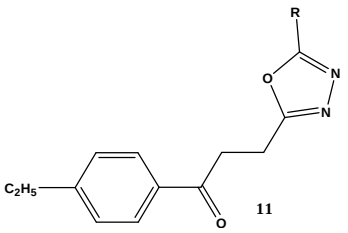

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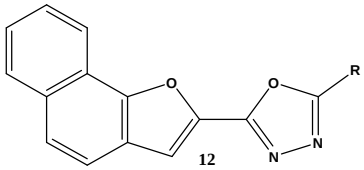
Several 2-naptho[2,1-b]furan-2-yl-5-aryl-1,3,4-oxadiazoles, **12**, derivatives were shown potent antiinflammatory activities. The 4-chloro phenyl substituted derivative shown promising activity against carrageenan induced rat paw edema [30].

Some new 2-Substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4oxadiazoles, **13**, were shown potent antiinflammatory activities. 2,4-dichlorophenyl, 1-(4-isobutylphenyl)ethyl against carrageenan induced rat paw edema and percentage inhibition was found to be 72.72 against standard drug ibuprofen (86.36) [31].



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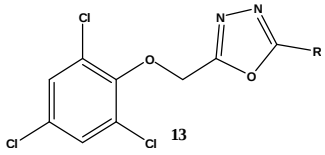

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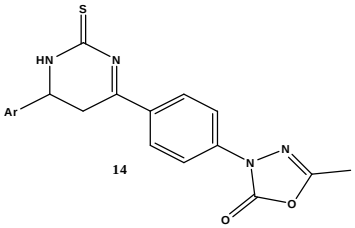
A new series of 5-methyl-3-[P-(6'-aryl-2'-thioxo-1',2',5',6'-tetrahydropyrimidin-4'-yl)-phenyl]-3H-2- oxo-△⁴-1,3,4-oxadiazole, **14** and derivatives were synthesized and evaluated for antiinflammatory activity. 5-methyl-3-[P-(6'-phe nyl-2'-thioxo-1',2',5',6'-tetrahydropyrimidin-4'-yl)-phenyl]-3H-2- oxo-△⁴-1,3,4-oxadiazole showed 55.6% inhibition even more than the standard drug (ibuprofen) in carrageenan-induced paw edema [32].



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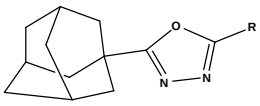

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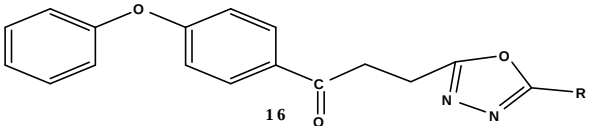
2-(1-Adamantyl)-5-substituted-1,3,4-oxadiazoles, **15**, derivatives were synthesized and evaluated for antiinflammatory activity, The best activity was observed with the oxadiazole derivatives p-chloro phenyl, 3,4-dimethoxy phenyl, 2-thienyl and 1-adamantyl which displayed strong dose-dependent inhibition of carrageenan-induced oedema producing >50% inhibition at 60 mg/kg dose [33].

2. Analgesic Activity

A novel series of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-ones, **16**, derivatives showed significant analgesic activity in the acetic acid-induced writhing test. The 2-acetoxy phenyl derivative of this series has shown 76% protection in terms of analgesic activity which is higher even than standard drug indomethacin [34].



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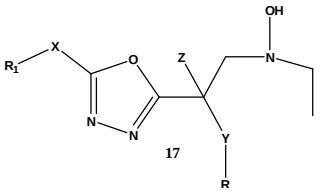
3.Antimicrobial Activity

The search for new antimicrobial agents will consequently always remain as an important and challenging task for medicinal chemists. BB-83698, **17**, is an antibacterial agent. It is an inhibitor of metallo enzyme PDF (Peptide Deformylase). PDF is considered as the most promising bacterial targets in the search for novel mode of action of antibiotics that lacks cross-resistance to existing drugs [2].

Another series of substituted 5-indole-1, 3, 4-oxadiazole were prepared and evaluated for antimicrobial activity. The antimicrobial activity was observed in compound 5-indole-1, 3, 4-oxadiazole against *B. subtilis* and *P. aeruginosa*, 2-(3-chlorophenyl)-5-indole-1, 3, 4-oxadiazole against *S. aureus*, *E.coli* and *B. subtilis* and 2-phenyl-5-indole-1, 3, 4-oxadiazole against *S. aureus* [35].

A compound 2-naptho [2,1-b] furan-2-yl-5-(4-methoxy phenyl)l-1,3,4-oxadiazole, **19**, exhibited promising activity against *E. coli, M. luteus, S. aureus a*nd zone of inhibitions for this compound were found to be 40, 36 and 35 respectively [30].



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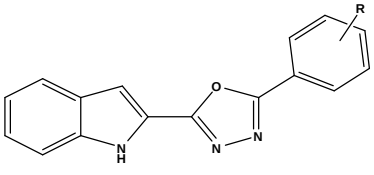

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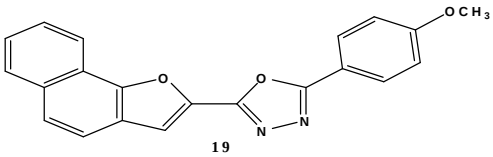

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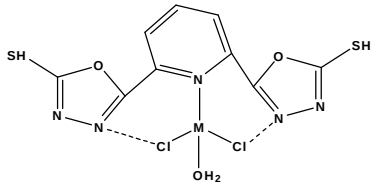
Transition metal complexes with a new tridentate ligand, 5-[6-(5-mercapto-1,3,4-oxadiazol-2-yl)pyridin-2-yl]-1,3,4-oxadiazole-2-thiol, **20** were shown good antimicrobial activity.The antibacterial and antifungal activity of the ligand transition metal salts and the corresponding complexes were assayed against bacteria, fungi by the cup plate method. The results were compared against the norfloxacin and griseofulvin [36].



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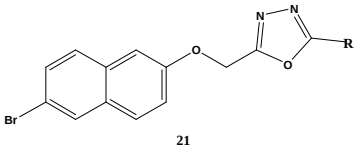
Where M = Mn(II), Co(II), Ni(II), Cu(II) and Zn(II).

The Cu(II) and Zn(II) complexes were found to be more active, while the Mn(II), Co(II) and Ni(II) complexes were moderately active.

1,3,4-oxadiazole derivatives bearing 6-bromonaphthalene moiety, 2-{[(6-bromo -2-naphthyl)oxy] methyl} -5-aryl-1,3,4-oxadiazole, **21** and 2-{[(6-bromo-2-naphthyl) oxy] methyl} -5-[(alkyl/ aryl) thio]-1,3,4-oxadiazole, **22** exhibited promising antibacterial and antifungal activity [37].



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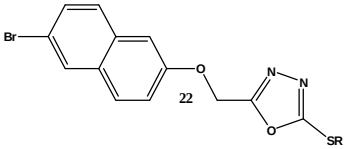

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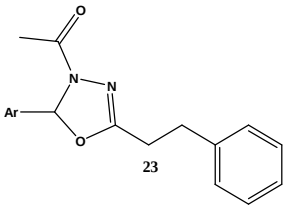
A series of new 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanones, **23** derivatives were synthesized and evaluated for anti-bacterial and anti-fungal activity against cultured strains of *S. aureus and P. aeruginosa, C. albicans* and *A. flavus* against the standards ampicillin (antibacterial) and fluconazole (anti-fungal) at a concentration of 1 mg/ml as standards. 1-(2-(4-(dimethylamino) phenyl)-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanone and 1-(2-(4-chlorophenyl)-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanone were found to possess maximum antimicrobial activity [38].



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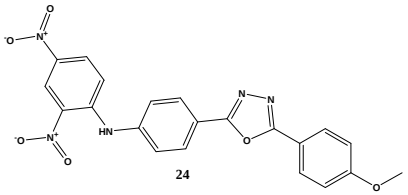

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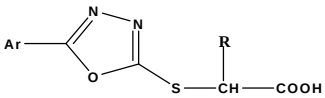
A new series of N-{4-[5-(4-substituted phenyl)-1, 3, 4-oxadiazol-2-yl]phenyl}-2,4-dinitroaniline, **24** compounds were shown *in-vitro* growth inhibiting activity against different strains of bacteria and fungi were compared with the standard antibiotics such as chloramphenicol and griseofulvin. N-{4-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2-nitroaniline exhibited very good antimicrobial activity [39].

2-[5-(Aryl)-[1,3,4]oxadiazole-2-ylsulfanyl]alkanoic acids, **25**, were synthesized and screened for antibacterial activity against standard ciprofloxacin which inhibited gram negative bacteria *E. coli* and *P. aeruginosa* at a MIC of 0.01µg ml^{-1} and 0.25 µg ml^{-1} respectively whereas against gram positive bacteria *S. aureus* and *Bacillus subtilis* MIC was found to be 0.15 µg ml^{-1} and 0.12 µg ml^{-1} respectively. Compounds containing 2,4-dichloro moiety were found to be most active (MIC-0.35-0.40 µg ml^{-1}) [40].



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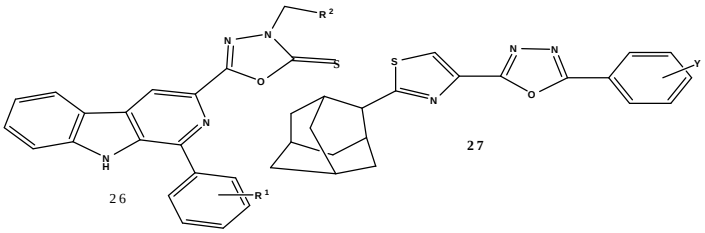
4.Antitumour Activity

A variety of antitumoral drugs are currently in clinical use. The search for antitumoral drugs led to the discovery of several 1,3,4-oxadiazol derivatives having antitumoral activity.

A novel series of 1-substituted phenyl-3-[3-alkylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl] ß-carboline derivatives, **26** were found as potent antitumour agents were most promising derivatives, exhibiting a broad antitumor activity spectrum at GI_{50} and TGI levels, with GI_{50} (MG-MID) values of 5.89, 4.37 and 4.57 µmol l^{-1} respectively [41].



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Moreover, 1-Phenyl-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol-5-yl]ß-carboline displayed cytotoxic efficacy with LC_{50} (MG-MID) value of 60.49 µ mol l^{-1}.

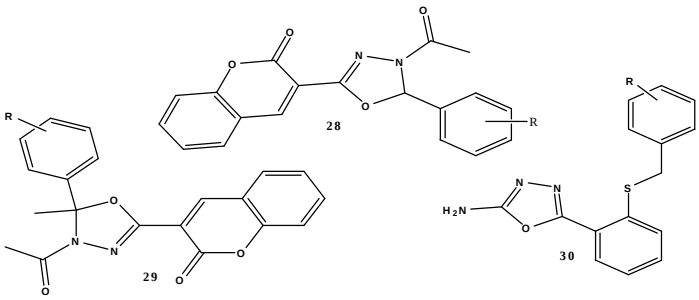
A new series of combination of adamantanyl-1,3-thiazole and 1,3,4-oxadiazole derivatives i.e., 2-(2-adamantyl-1,3-thiazol-4-yl)-5-(3-substituted phenyl)-1,3,4-oxadiazole, **27** bearing various aryl groups has been synthesized and evaluated for *in-vitro* antiproliferative activity against a large panel of human tumor-derived cell lines [42].

5.Anticonvulsant Activity

Epilepsy is a neurological disorder and involves spontaneous, intermittent,

abnormal electrical activity in the brain. Although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used models of epilepsy to characterize the anticonvulsant activity.

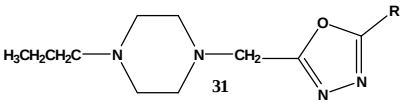
A series of 3-(4-acetyl-5-methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2Hchromene-2-ones, **28,** 3-(4-acetyl-5H-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2Hchromene-2-ones, **29**, were synthesized and evaluated for anticonvulsant activity and neurotoxicity. 3-(4-Acetyl-5-methyl-5-p-nitrophenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one was found to be potent activity at lower dose of 30 mg/kg in MES-test and less toxic as compared with the standard drug phenytoin [43].



A new series of 2-substituted-5-{2-[(2-halobenzyl)thio)phenyl}-1,3,4-oxadiazoles, **30**, were designed, synthesized and investigated for anticonvulsant activities. The designed compounds contain the main essential pharmacophore for binding to the benzodiazepine receptors. Electroshock and pentylenetetrazole induced lethal convulsion tests showed 5-{2-[(2-fluorobenzyl)thio]phenyl}-1,3,4-oxadiazol-2-amine had significant anticonvulsant activity in PTZ and MES models [44].

6.Anthelmintic Activity

A novel series of 1-[(5-substituted-1,3,4-oxadiazol-2-yl)-methyl]-4-propylpiperazines, **31** derivatives was synthesized and evaluated for anthelmintic activity.



The 2-furyl, 3-pyridyl, p-methyl phenoxy derivatives were found to be more potent against earth worms *Eudrilus* species, *Megascoplex konkanensis*, *Pontoscotex corethruses* at a dose of 2mg/ml [45].

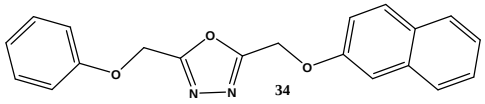
7.Herbicidal activity

Oxadiazon, 3-[2,4-dichloro-5-(1-methylethoxy)phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one, **32** is a member of the oxadiazole group of herbicide. For weed resistance management, the product is a group G herbicide [46]. Oxadiargyl (TOPSTAR 80 WP), 3-[2,4-dichloro-5-(2- propynyloxy) phenyl]-5-(1,1-dimethylethyl)-1,3,4-oxadiazol-2(3H)-one, **33** is a broad spectrum weed control (international registrations approved) [47].

8.Antimycobacterial Activity

Tuberculosis is a serious health problem that causes the death of approximately 2-3 million of people every year worldwide. A literature survey also reveals that several 1,3,4-oxadiazole derivatives possess antimycobacterial activity against *M. tuberculosis* H37Rv.

A series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives were synthesized and tested for their *in vitro* antimycobacterial activity. Some compounds showed interesting activity against a strain of *Mycobacterium tuberculosis* H37Rv. The result of the antimycobacterial activity tests revealed that 2-(2-naphthyloxymethyl)-5-phenoxymethyl-1,3,4-oxadiazole, **34** exhibited > 90% inhibition at MIC ~6.25 using the BACTEC-460 radiometric system [48].

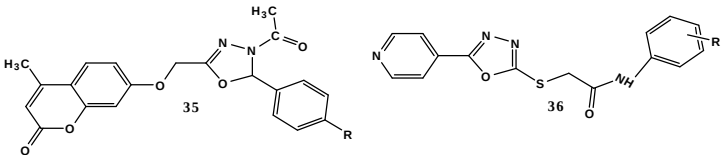


9.Antioxidant Activity

1,3,4-oxadiazole nucleus are known to exhibit potential antioxidant activity. The search for antioxidant drugs led to the discovery of several 1,3,4-oxadiazol derivatives having antioxidant activity.

A series of some 5-pyridyl-2-[(N-substituted phenyl)thioacetamido]-1,3,4-oxadiazoles, **35** were synthesized by both conventional and microwave methods and evaluated for *in-vitro* antioxidant activity by 1,1-diphenyl-2,2-picryl hydrazyl free radical method. The compound possessing 2-chloro substitution has inhibited the DPPH radical at a lower concentration [49].

A novel series of 3-acetyl-2-(substituted phenyl)-5-(4-methylcoumarinyl-7-oxymethyl)-2,3-dihydro 1,3,4-oxadiazoles, **36** were evaluated for antioxidant activity. The derivatives bearing H, CH_3 group showed more than 50 % antioxidant activity by the diphenylpicryl hydrazyl assay [50].



10.Antiviral Activity

HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Novel 2-{5-[(naphthalen-5-yloxy)methyl]-1,3,4-oxadiazol-2-ylthio} acetohydrazones **37** were evaluated for their antiviral activity against, the human immunodeficiency virus (HIV-1) and some of these compounds showed moderate to high antiviral activity [51].

CONCLUSION

This review thus gives an overview of therapeutic and diverse biological properties of the 1,3,4- oxadiazole ring and the availability of varied drugs in the market containing the heterocyclic ring. Therefore, These observations have been guiding for the development of 1,3,4-oxadiazole nucleus, which can be a lead nucleus for future developments to get safer and effective compounds. Thus this paper proves to be significant for further research work on the bioactive oxadiazole ring.

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