WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 15, 214-238. Review Article ISSN 2277– 7105

PHARMACEUTICAL ACTIVITY OF 1,3,4-OXADAIZOLE IN HETEROCYCLIC CHEMISTRY. A REVIEW

Vikram Panchal*[1], Hiren H. Variya[2] and G. R. Patel[3]

Department of Chemistry, Sheth M. N. Science College, NGES Campus, Patan, India.

Article Received on
04 June 2018,

Revised on 24 June 2018,
Accepted on 14 July 2018

DOI: 10.20959/wjpr201815-12964

***Corresponding Author**
Vikram Panchal
Department of Chemistry, Sheth M. N. Science College, NGES Campus, Patan, India.

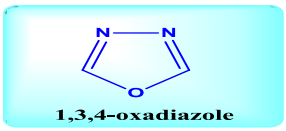
ABSTRACT

Oxadiazole and its derivatives have been focused on for their broadly chemical and biological importance in a previous couple of years. In this review, the Different Synthesis and its biological activities of 1,3,4-Oxadiazole have been summarized from 2003-2017. Oxadiazole is a useful ring in the biological active compound. This moiety has four different structures which depend on the position of nitrogen. Among these, 1,3,4-oxadiazole is a very useful ring for therapeutic interest. 1,3,4-oxadiazole have various biological activity, for example, Anti-HIV, Anticancer, Antioxidant, Antimicrobial, Anti-inflammatory etc. this article is review the literature work described by researchers on 1,3,4-oxadaizole moiety for their biological activity.

KEYWORDS: 1,3,4-oxadiazole; Various synthetic method; Biological activity.

INTRODUCTION

Aromatic compound with hetero atom is the important portion of some biologically active compound. This type of compound commonly used because it contains similarity with another biologically active molecule. For example, hormones, nucleic acid, neurotransmitters etc. molecule inside living things. Between many hetero aromatic compounds present, oxadiazoles rings are important rings of biological drugs.



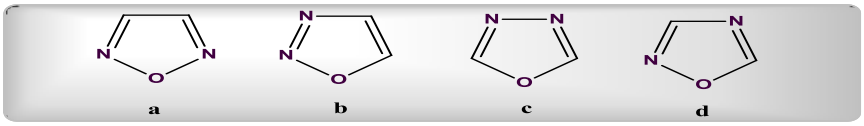


Fig. 1: The classification of Oxadiazole ring.

Depending on the position of N(Nitrogen) and O(Oxygen) atoms the oxadiazole ring categorized into four different Isomers. The classification of rings defined as 1,2,5-oxadiazole (a), 1,2,3-oxadiazole (b) and 1,3,4-oxadiazole(c) 12,4-oxadiazole (d) (fig 1).

1,3,4-oxadiazoles moieties reveal various pharmacological activity like anti-inflammatory . hypoglycemic, analgesic, anti-HIV, anti-microbial, anti-tubular etc.[1]

Some examples of pharmaceutical drug which having the 1,3,4-oxadiazole ring presently available in clinical drugs.[2] For examples: Zibotentan[3] **1**as anti-cancer drug, Raltegravir[4] **2**, as antiretroviral agent, Tidazosin **3** and Nesapidil **4**, as anti hypertensive and Furamizole **5**, as antibiotics[5] (Fig. 2).

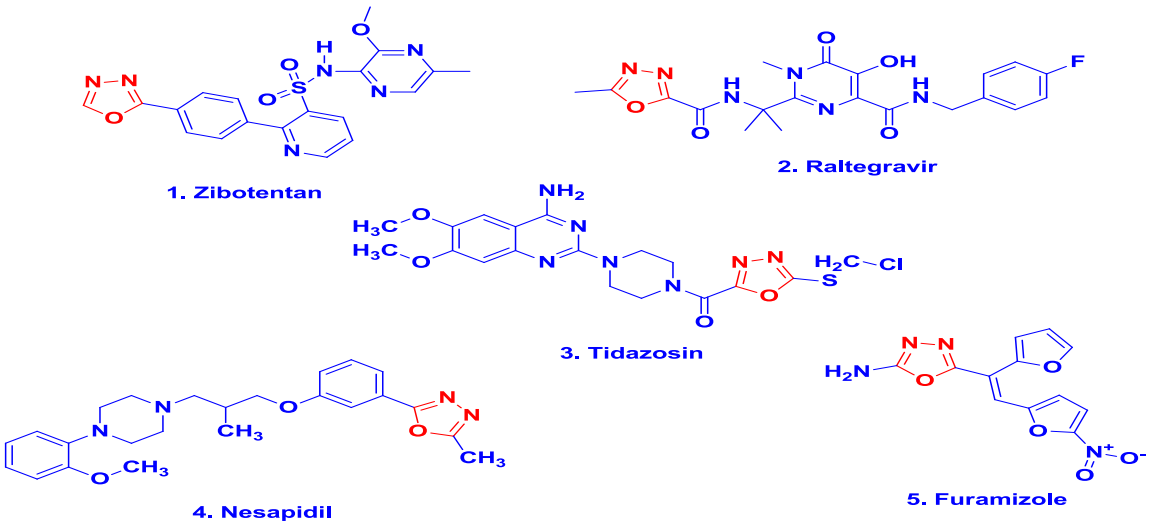


Fig. 2: Examples of pharmaceutical drug which having the 1,3,4-oxadiazole ring.

Pharmacological Activities

The 1,3,4-oxadaizole moieties have broad spectrum of biological and medicinal activity. In this review we are mostly concentrated on the following activities such like anti-inflammatory, antimicrobial, anticonvulsant, analgesic, anti-HIV, anti-oxidant etc.

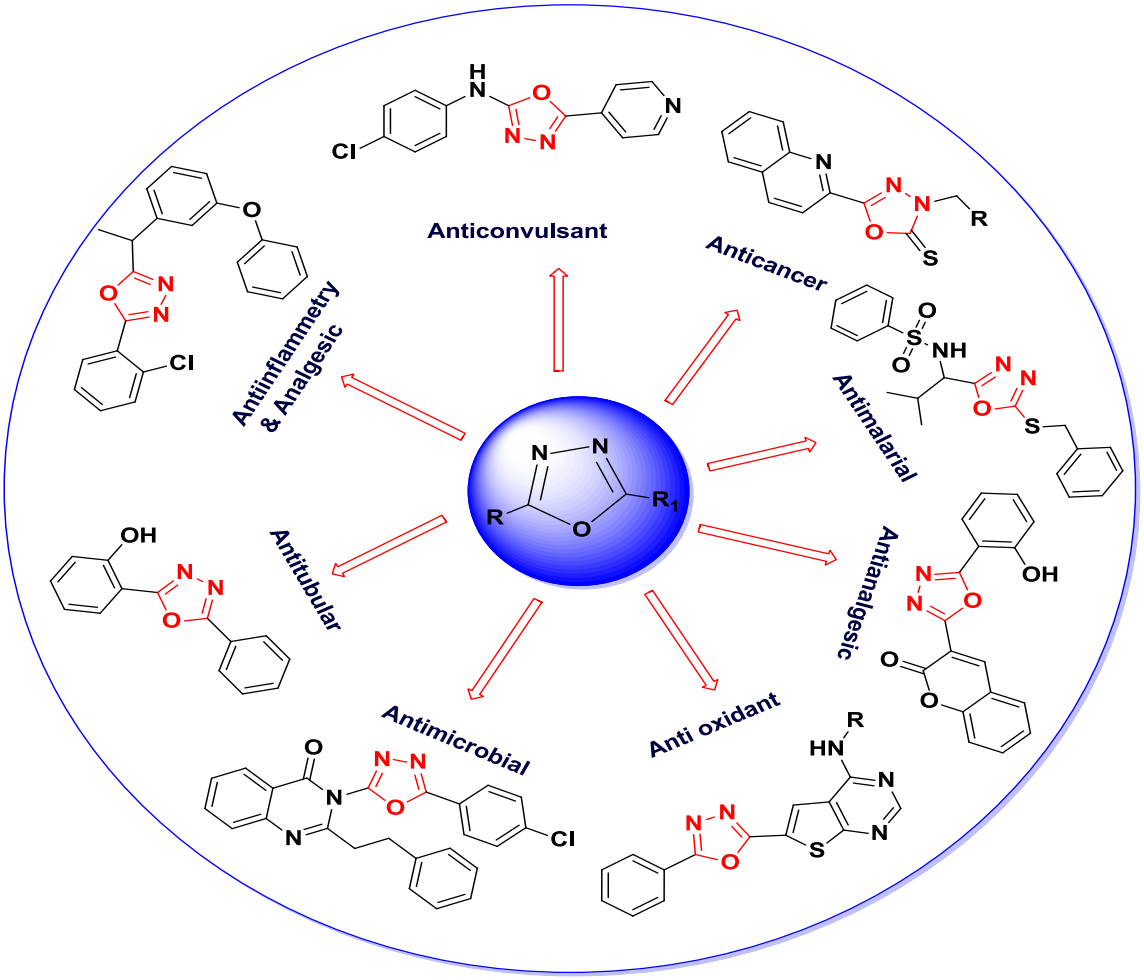


Fig. 3: Various type of biological application of 1,3,4-oxadiazole derivatives.

Anti-inflammatory Activity

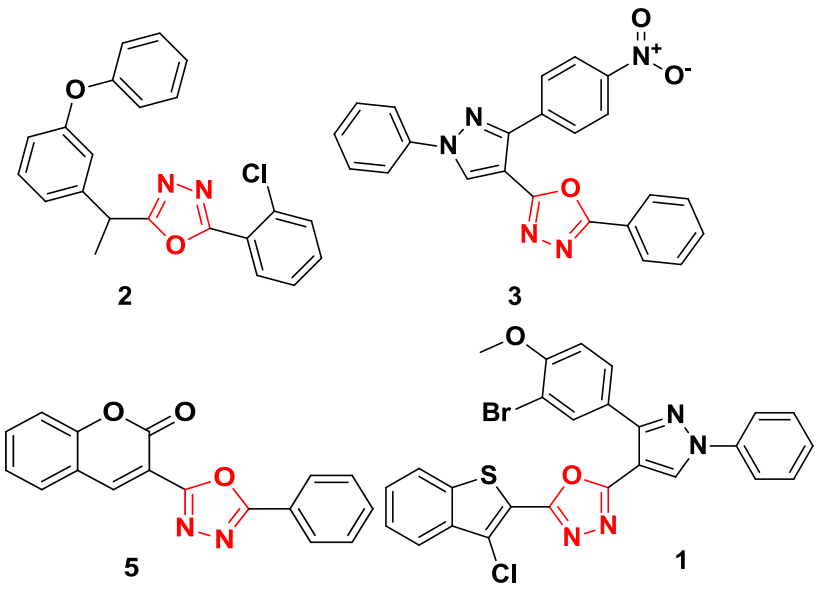
Inflammation is a biological response of vascular tissue to harmful stimuli, such as pathogens, damaged cells, or irritant. While injury the action of the tissue characterized as an inflammation. Arahidonic acid derivatives which contain unsaturated twenty carbons fatty acid produced from phospholipids membrane are the effective mediators of inflammation. An assembly of the cyclooxygenase (COX) and leukotriene‘s pathway produced by 5-lipoxygenase.[6]

A series of 3-Chloro-benzo (b) thiophene-2-carbohydrazide containing Aldehyde or Isatin derivatives synthesized by Elmiligy et al. compounds exhibited significant *in vitro*LOX inhibitory activity better than that of meclofenamate sodium. Compounds exhibited significant in vitro COX-2 inhibition more than celecoxib and *in vitro* LOX inhibitory activity two times more than that of reference. Compound **1** produced significantly in vivo anti-inflammatory activities higher than celecoxib in formalin-induced paw edema test.[7]

A new series of 2,5-disubstituted 1,3,4-oxadiazole derivatives were synthesized by Kameshwar et al. screened for anti-inflammatory activity and targets basic phospholipase A2 from *ViperaRusselli*. Some compound **2** exhibited potent activity comparable to reference Quercetin drug.[8] Sumit et al. reported a synthesis of 1,3,4-oxadiazole bearing diarylpyrazoleompound **3** and screened for anti-inflammatory activity and analgesic activity. Compounds showed a better activity against the used drug diclofenac. *In vivo* rat carrageenan-induced paw edema method was used for activity.[9]

Akhter et al reported a new synthesis of Coumarin based 1,3,4-oxadiazole derivatives **4** and estimated their anti-inflammatory activity using carrageenan-induced edema in hind pw of the rat method.[10] A novel series of 5,6,-diphenyl-1,2,4-tizazin-3(2H)-one bearing 5-substiutted 1,3,4-oxadiazole derivatives were synthesized by Banerjee et al. Compound **5** exhibited as potent anti-inflammatory and analgesic agents. Indomethacin used as reference drug for comparison.[11]

Using a 3-(4-bromobenzoyl) propionic acid Hussain et al synthesized a new series of 1,3,4-oxadiazoles. Compounds **6** evaluated as a potent analgesic and anti-inflammatory agent on Wister rats in compared to standard indomethacin drug.[12] Harish and coworkers reported a synthesis of 1,3,4-oxadiazole derivatives of biphenyl-4-yloxy acetic acid **7** and evaluated biological activity through standard method. Compounds exhibited a better activity (81.81%) than the standard drug flurbiprofen (79.54%).[13]



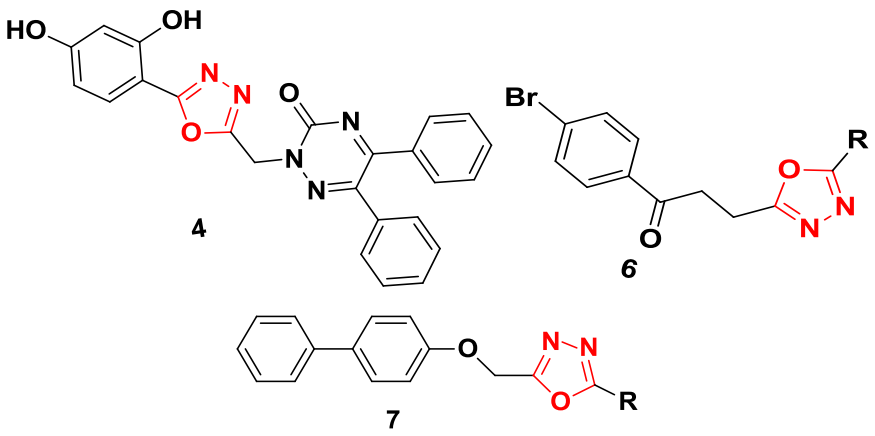


Fig. 4: Anti-inflammatory Analogues of 1,3,4-oxadiazole.

Anti-Cancer Activity

Cancer is a genetic infection which affects the cell growth and produced an abnormal cell and damaged DNA. Because of DNA damage a mutation can happen in genes and normal cell converting into an abnormal cell or cancerous cell. An infected gene increase the production of cancerous cell and departed to it daughter cell. Cancer cell has rapid and continuous cell division and able to migrate through embryonic cells. Mutations can occur from viruses, radiation and UV. Some method for anticancer activity such as membrane integrity assay, functional assay, DNA assay, Morphological assay, the reproductive assay used for evaluation of the activity.

A series of 1,3,4-oxadiazole derivatives were synthesized from pyridine and acylhydrazone molecule by Zhang et al. and evaluated for anticancer activity by TRAP-PCR-ELISHA assay. Compound **8** exhibited the higher activity against four cancer lines (MCF7,BGC823, SW1116,HEPG) and produced the best effective telomerase inhibitory activity.[14]

A new series of 1,4-benzodioxan containing 1,3,4-ocadiazole moiety **9** was synthesized by X.M. Zhang et al. and screened anticancer activity. The compound displayed broad spectrum for antitumor activity compared to the standard anticancer agent 5-fluorouracil.[15] Zheng et al. synthesized a series of 2-chloropyridine possessing 1,3,4-oxadiazole moiety for telomerase inhibitory activity. Compound with electron donating groups on *para* position of benzene ring showed less activity than another compound. Compound **10** and **11** showed potent inhibitory activity compared to telomerase enzyme.[16]

Zhang et al. described the synthesis of Focal adhesion kinase (FAK) with aim of to find potent anticancer agents. Inhibitors displayed better effective activity against HT29 and

MCF-7 cell lines. Compound **12** may be a potential anticancer agent against to MCf-7 cancer lines.[17] A new series of 1,3,4-oxadiazole derivatives were reported by Sun et al. and evaluated as telomerase inhibitors. Compound **13** showed a potent antitumor activity against the cancer cell lines.[18]

A novel series of 1,3,4-oxadiazole have reported by Valente et al. as anticancer agent by inhibition of HDAC. Compound **14** showed a potent activity compared to standard.[19] Rajak et al. synthesized a Novel series of 2-[5-4(4-substituted phenyl)-[1,3,4-oxadiazole-2-ylamino]-pyridine-5-carboxylic acid(tetrahydro-pyran-2-yloxy)-amides **15** as HDACi for treatment of cancer. The activity of compounds screened in vitro using MTT method and HDAC inhibitory assay.[20]

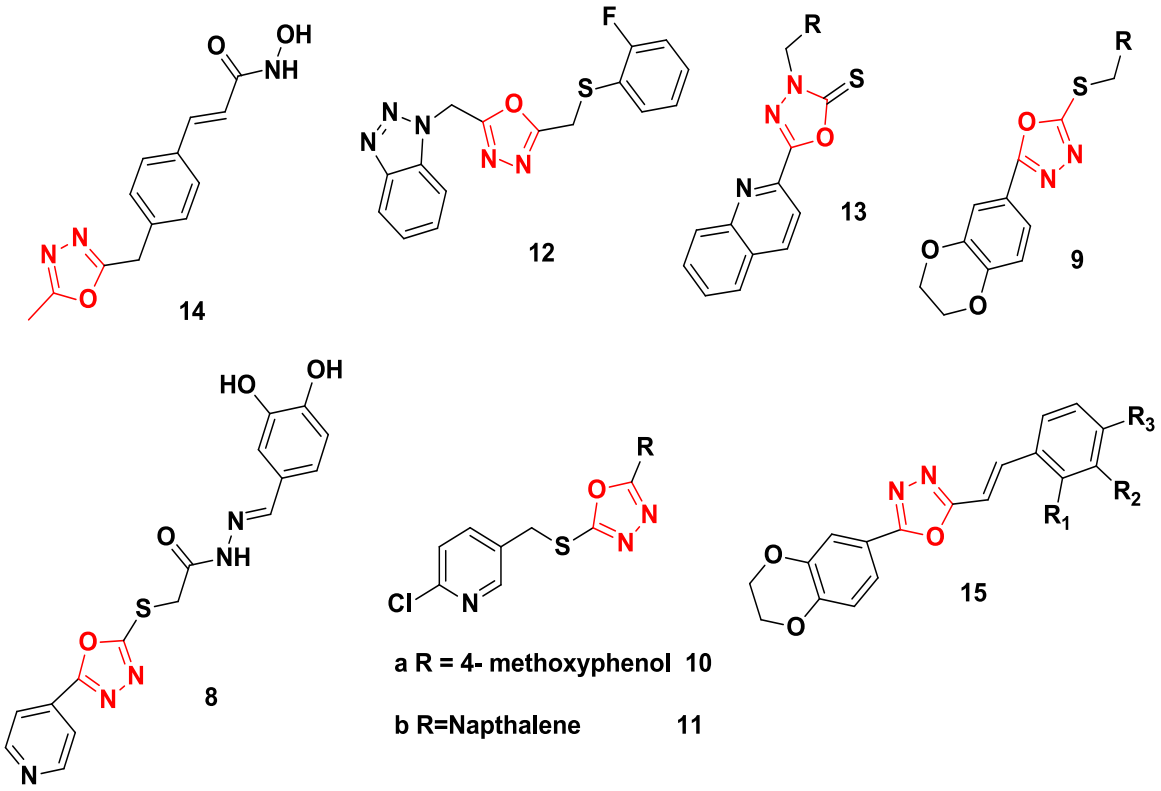


Fig. 5: Anticancer Analogues of 1,3,4-oxadaizole.

Anti-tubercular Activity

Tuberculosis is currently the foremost killer disease of the Human being throughout the world. TB spread from person to person via airborne droplets like Coughing, sneezing, speaking-disperse organism and can be inhaled. First successful drug for Tb was *para*-aminosalicylic acid (PAS) developed by Lehman in 1943. some drugs such as streptomycin rifampicin, isoniazid, ethionamide are used for TB.[21],[22]

A novel compound of 2-(5-phenyl-1,3,4-oxadiazole-2-yl)phenol **16** was synthesized by R pattan et al. and evaluated for their anti-tubular activity. The anti-tubular activity was carried by Middle Brook 7H9 agar medium against the H37Rv strain. Streptomycin was used as a standard reference.[23]

A new series of 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-ocadiazole derivatives **17** was reported by Dhumal and coworkers and screened for their *in vitro* anti-tubular activity against M. Bovis BCG and M. tuberculosis H37Ra. Rifampicin was used as standard drug.[24]

A novel series of 1,3,4-oxadiazole clubbed dihydropyrimidines was reported by Desai et al and screened for *in vitro* anti-tubercular activity with a prospect of creating new ant tubular agent. They observed that compounds with electronic withdrawing group like NO2, Cl- and F- at para position of 1,3,4-oxadiazolyl phenyl ring such as compound **18** exhibited very good antitubercular activity.[25]

A series of 2-(ethylthio)-5-(3-nitro-5-(trifluoromethyl)phenyl)-1,3,4-oxadiaozle **19** derivatives was reported by Galina et al. all compound were evaluated for their anti-tuberculosis activity.[26] Joshi et al. synthesized a new series of 4-pyrrol-1-yl-benzoic acid hydrazide analogs derived 5substituted 1,3,4-oxadiazole **20** and carried out for anti-tuberculosis activity. *Mycobacterium tuberculosis* H37Rv strain was used to evaluate activity by using broth dilution method.[27] Macaev and coworkers reported a designed synthesis of novel series of 5-aryl-2-thio-1,3,4-oxadiazole derivatives. All the compounds were screened for *in-vitro* anti-microbacterial activity against *mycobacterium tuberculosis* by the alamer blue assay (MABA) method. Compound **21** exhibited potent activity against standard drug.[28]

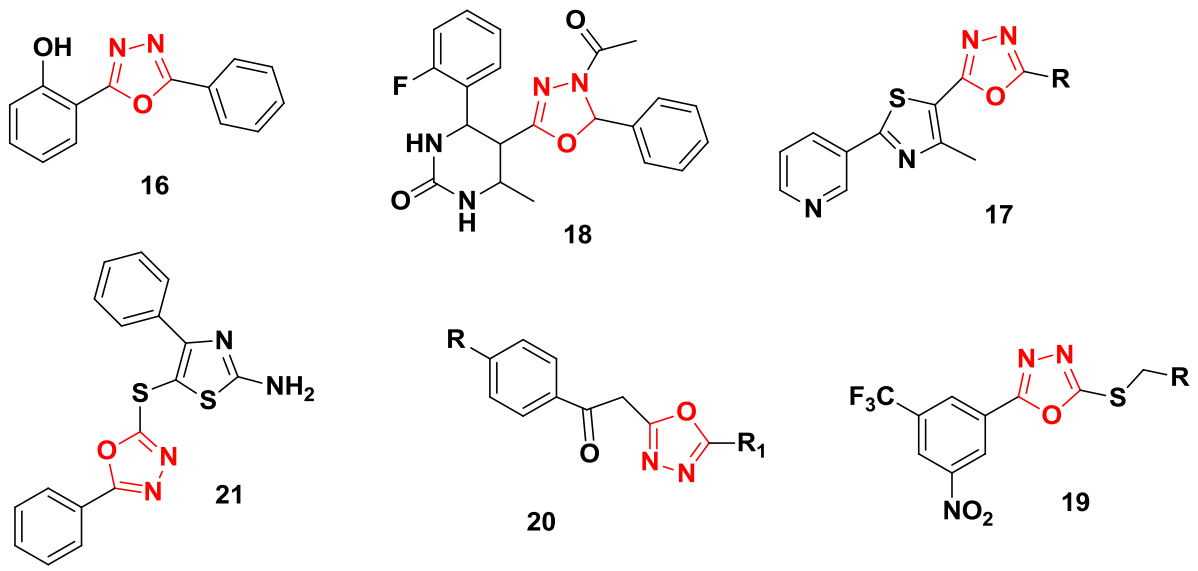


Fig. 6: Anti-tubercular Analogues of 1,3,4-oxadiazole.

Anticonvulsant Activity

Epilepsy is a very common disorder, characterized by seizures, which take various forms and results from neuronal discharge, with or without characteristic body movement. The usual approach to anticonvulsant drug testing in animals is to observe the effect of prior drug administration on seizures produced by electrical stimulation of the brain and systemic administration of a convulsant drug, animal strain with spontaneous or sensory-evoked convulsants. some useful in vivo method for anticonvulsant are electroshock seizures, chemical induced seizures, epilepsy induced by focal seizures, kindled rat seizure model electrical recording from isolated brain cells, GABA uptake in rat cerebral cortex, TBPS binding assay and genetic rat model of epilepsy. Pharmacological screening involves sequential testing of drug in isolated organ followed by tests in whole animals, mostly rats & mice but also in higher animals if indicated.[29]

A new series 2-methyl-2-[3-(5-piprazin-1yl-1,3,4-oxadazole-2-yl)-phenyl]-prppionitrile derivatives were synthesized by Harish et al. and evaluated for anticonvulsant activity against maximal electroshock seizure method and neurotoxic effects were tested by rotarod method. Such compound **113, 23, 24, 25** showed good anticonvulsant activity (75.24, 73.32 and 72.41 respectively) while compound **25** showed moderate activity (69.34 respectively) in compare to the standard control vehicle.[30]

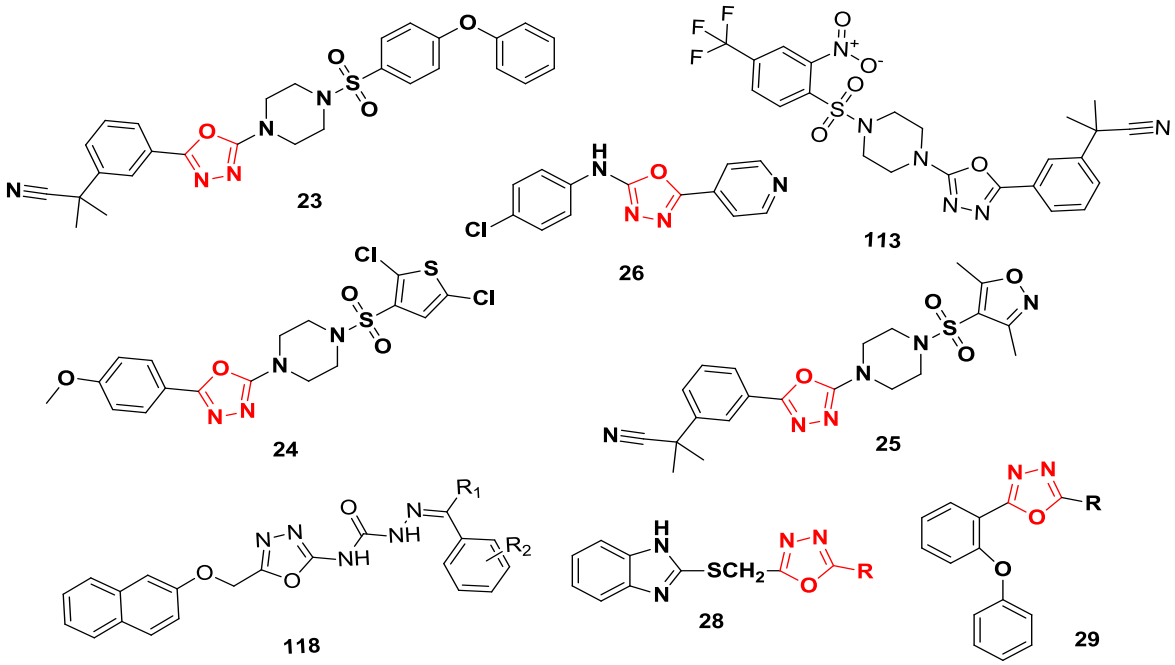
A new series of 2-(substituted phenyl) amino-5-(4-pyridil)-4H-1,3,4-oxadiazole was reported by Mohammad et al. and screened for anticonvulsant activity using MES method.

Compounds showed activity in the range of 33-100% in comparison to phenytoin using electro convulsometer in albino mice. Compound **26** gives a 100% activity in comparison to phenytoin.[31]

Harish and coworkers investigated new compound **118** as an anticonvulsant agent. aryl semicartbazones bearing 1,3,4-oxadiazoles moiety showed good activity via GABA mediation.[32] Ramya et al. reported synthesis and biological evaluation of a series of benzimidazole contain 1,3,4-oxadiazole **28**. Compounds inhibited for their anticonvulsant activity using phenytoin as a standard drug.[33]

A new series of phenoxyphenyl-1,3,4-oxadiazole derivatives **29** was synthesized by Tabatabai et al. Among oxadiazoles, Compounds 29 evaluated potent anticonvulsant activity against a lethal dose of pentylenetetrazle using PTZ induced a lethal convulsant method. Diazepam was considered as a standard drug.[34] Mashooq et al reported a synthesis a series of 3-(4-acetyl-5-methyl-5-(4-nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-ones and screened for neurotoxicity and anticonvulsant activity. Compound **30** was showed to be effective activity at lower dose 30 mg/kg in MES test using phenytoin drug.[35]

Kashaw et al reported a synthesis of novel 3-(5-(4-(substituted) phenyl)-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-one derivatives and screened for biological activity. Among oxadiazoles, compound **122** and **32** was found to shown good anticonvulsant activity in MES screen.[36]



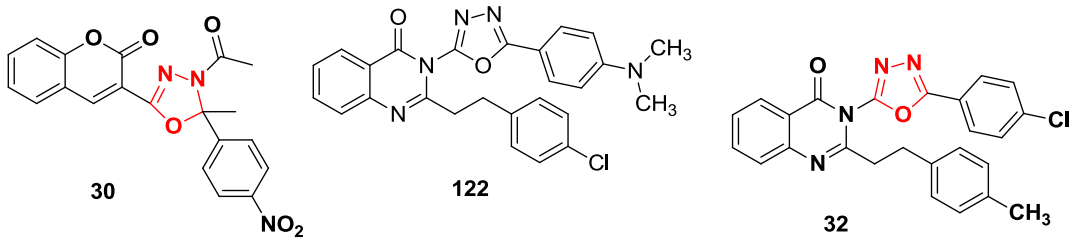


Fig. 7: Anticonvulsant analogues of 1,3,4-oxadiazole.

Antimicrobial Activity

Anti-microbial agents are the agents who are used to prevent the bacterial and fungal infections by killing or preventing the growth of *bacteria* and *fungi*. Such method are used for activity are serial dilution in fluid media, serial dilution in solid media, cup plate methods, and the ditch-plate technique.[37],[38]

A novel series of Chalcone containing 1,3,4-oxadiazolederivatives **33** were reported by Afroz et al. and evaluated for their microbial activity by using adopting the standard method. Most of them exhibited good activity against *E-coli* and *Pseudomonas aeruginosa* compared to standard Ciprofloxacin drug. Among the evaluated compounds exhibited better inhibition against both of fungal strains *Aspergillus Niger* and *Candida albicans.*[39]

Gupta et al reported a synthesis of quinazoline based oxadiazole moieties and their biological activity using sequential dilution method to estimate MIC. All the moieties exhibited antibacterial activity in the range of 95-138 in gm/ml for *P.aeruginosa*, 84-129 mg/ml for *Bacillus subtilis*, 80-120 gm/ml for *E-Coli* and 88-130 gm/ml for *S.aureus*. Compound **34** was showed to be the potent activity.[40]

A new series of 1,3,4-oxadiaole pharmacores **35** were reported by N.desai et al. evaluated as an antibacterial agent using conventional broth dilution method. Chloramphenicol used as a controlled drug for antibacterial activity. Compound **35** exhibited better antibacterial activity then antifungal activity.[41] Al-omar et al. reported a synthesis of 2-thienyl based oxadiazole derivatives **36**,**37** and screened for *in-vitro* antimicrobial activity against *Gram positive* and *Gram negative* bacteria.[42]

Novel series of 1-(2aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanone were reported by Fuloria and coworkers and evaluated as a microbial agent. Among compounds, compound **38** demonstrated a good activity against microorganism compared to ampicillin drug.[31]

A novel series of pyrazole integrated 1,3,4-oxadiazoles derivatives were synthesized by Srikantamurthy et al through an efficient single chemical transformation. Compounds studied for their antimicrobial activity. The MIC of the compounds was in the range of 25-55 µm/ml against *fungi* & 20-50 µm/ml against *bacteria*. among the synthesized compounds, compound **130** exhibited superb antimicrobial activity compared to standard Nystatin and Tetracycline drug.[43]

Navin et al reported a newer synthesis of 1,3,4-oxadiazolyl-benzodiazepines and benzothiazepines derivatives **40** and studied for *in-vitro* antibacterial, antifungal, and antiprotozoal activities against various *Gram positive* and *Gram negative fungal*, *bacteria* and *protozoa* species. Ampicillin was use as standard drug.[44]

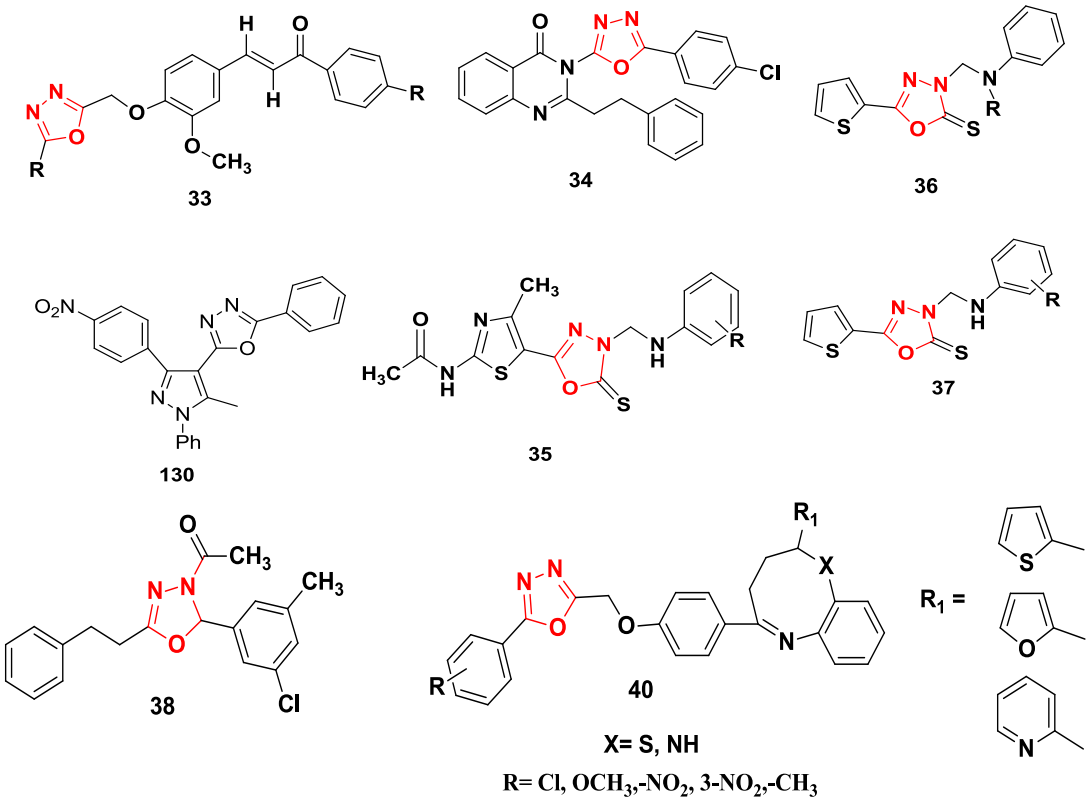


Fig. 8: Antimicrobial Analogues of 1,3,4-oxadiazole.

Analgesic Activity

Analgesic drugs relieve pain without causing loss of consciousness. Salicylates acetaminophen and combination of narcotic and non-narcotic analgesic are used as analgesic agent.[45]

A novel series of 8- {(5- aryl -1.3,4- oxadiazol- 2- yl)methoxy}quinolones derivatives **41** were synthesized from Aromatic acid and acylhydrazide by Mohammed et al. The analgesic activity was screened using tail flick method in Winstar rats. Analgesic activity was stated as reaction time of tail flicking. Compound **43** consuming analgesic activity will show more reaction time than the control. The compound exhibited enough to comparable activity against indomethacin drug.[46]

A series of 2- (substituted – phenyl_ - 5- (N. N. –diphenylaminomethl)-1,3,5-oxadiazoles were synthesized by Kataria et al and evaluated for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activity. Analgesic activity was estimated by acetic acid induce writhing method at 20 mg/kg using ibuprofen as standard drug. Compound **44** and **45** showed 56.17% and 55.17% protection against acetic acid-induced writhings. This percentage protection was similar to ibuprofen (61.03%).[47]

A novel series of N- (tetrazol- 1H- 5-yl) -6,14endoethenotetrahydrothebaine 7- substituted 1,3,4- oxadiazole was reported by Yavuz and coworkers and evaluated as analgesic agent. Analgesic activity of compounds was estimated in rat by the hot plate and tail flick method against the standard drug morphine. Compound **137** was found to be better potent than the morphine.[48] Some new compounds were synthesized by Seigmund E and Cadmus. Wister mice were used for the evolution of activity by using tail flick method. Compound **47,48,49,50,51** exhibited better activity (88.85, 76.32, 80.50, and 86.11 respectively) among compounds, compound **51** exhibited enough activity 55.5 against the standard drug pentazocine.[49]

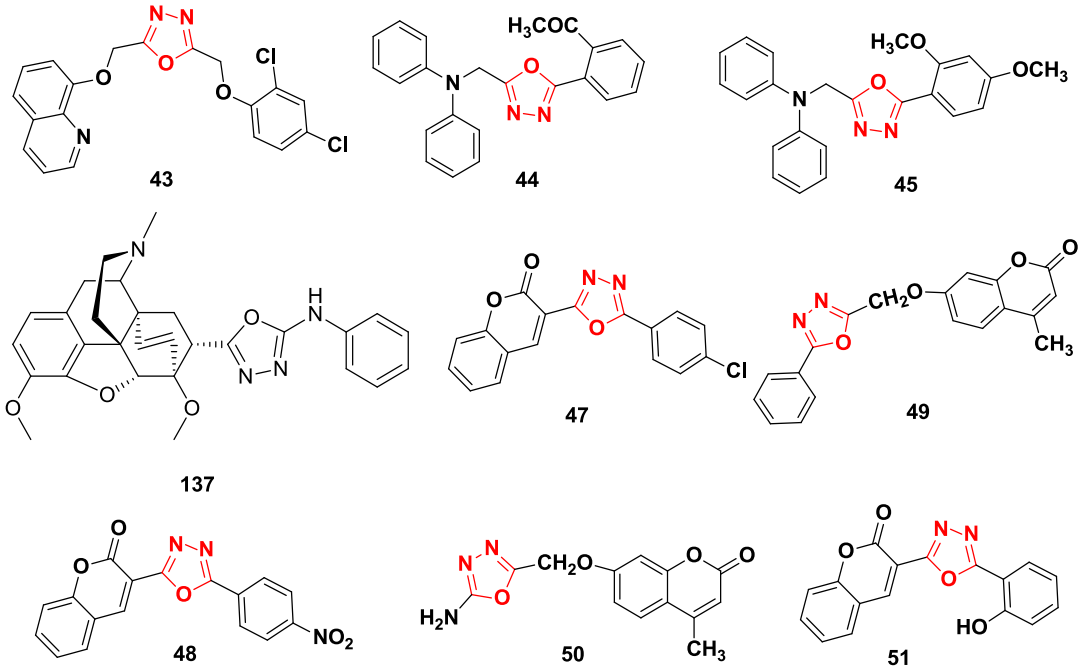


Fig. 9: Anti-analgesic analogues of 1,3,4-oxadiazole.

Anti-Alzheimer's Activity

Alzheimer's disease (AD) is an overwhelming neurodegenerative disease showed by detoriation in cognition and memory, impairment in performing activates of daily living, behavioral and neuropsychiatric disturbances. Some drugs are used for Alzeihemer's disease such as memantine, Galantamine, rivastigmine etc.

Saitoh et al reported a synthesis of heterocyclic esters and the hyrazide, bearing 1,3,4-oxadiazolederivatives. Among compounds, Compound **143** exhibited potentGSk-3β inhibitory activity. Binding mode was screened by obtaining the X-ray co-crystal structure of 20x & GSK-3β.[50] A new compound 2-methyl-5-(3-(4-(methylsulfinyl)phenyl)benzofuran-5-yl)-1,3,4-oxadiazole was reported by Onishi et al. compound **53** screened for effects of NMBO on tau phosphorylation in an Alzheimer's disease animal model.[51]

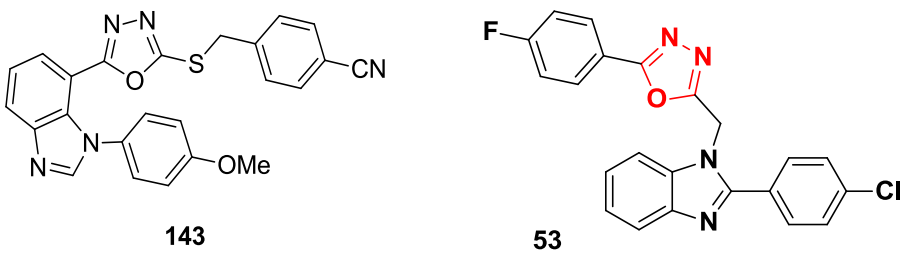


Fig. 10: Anti-Alzheimer analogues of 1,3,4-oxadiazole.

Antioxidant Activity

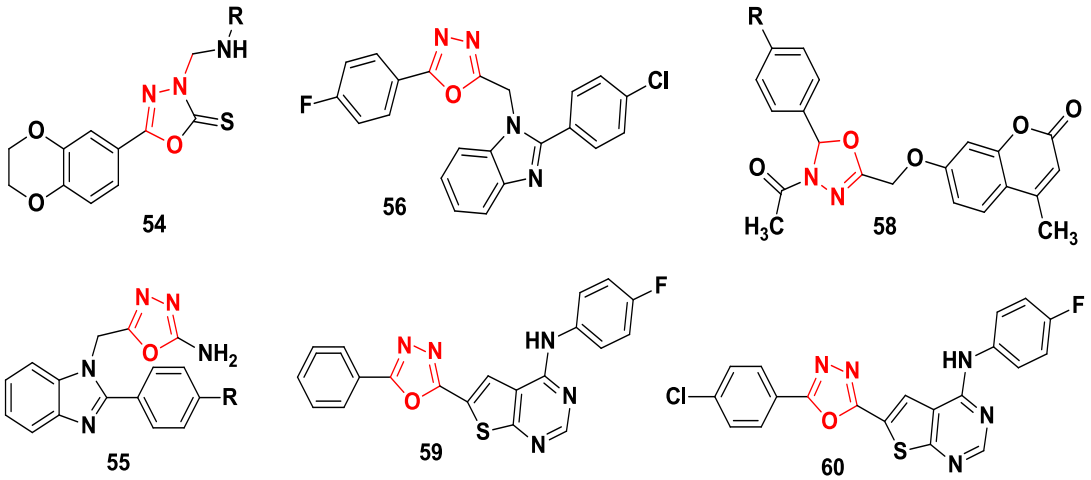
Antioxidants are a group of substance that protects cells from damage caused by free radicals, by interacting with free radicals and stabilizing them. Free radical is an atom that has at least one unpaired electron which is normally present in our body in small number. Free radicals are released by normal metabolism, as well as by stress, radiation, smoking, and pollution.

Ma and coworkers reported a synthesis of a mannich base of oxadiazole derivatives and evaluated for their antioxidant activity using DPPH, ABTS+• and Fe^{+3} reducing antioxidant assay. Among compounds, compound **54** showed potent antioxidant activity. Trolox and butylated hydroxytoluene (BHT) were used as a standard oxidizing agent.[52]

Kerimov et al synthesized a series of 2-amino-1,3,4-oxadiazole and 5-aryl-1,3,4-oxadiazole carrying benzimidazole derivatives **55,56,57** and screened for their antioxidant properties using *in-vitro* determination of the microsomal NADPH-dependent inhibition of lipid peroxidation levels among compounds, compound **56** inhibited most potent antioxidant activity.[53]

A new series of 3-acetyl-2-(substitutedphenyl)-5-(4-methylcoumarinyl-7-oxymethyl)-2,3-dihydro-1,3,4-oxadiazoles moieties **58** was reported by Manoj and coworkers and screened for the antioxidant activity. The entire compounds were screened by DPPH assay method.[54]

Kaitoh et al reported a study of 1,3,4-oxadiazole containing thieno[2,3-d]pyrimidines derivatives synthesis and evaluated for their antioxidant activity. among compound, compound **59,60,61,62** exhibited better activity then reference drug.[55]



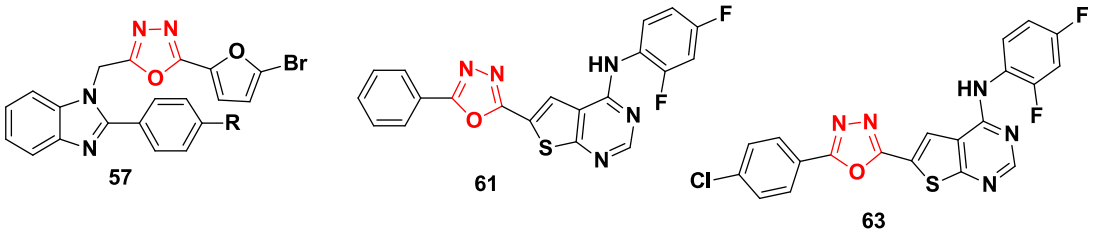


Fig. 11: Antioxidant Analogous of 1,3,4-oxadiazole.

Anti-Proliferation Activity

Proliferation means speedy growth of any stuff and in case of cells it is cell proliferation. Cell proliferation is nothing but cancer. Anti-proliferative activity is the capacity of a compound to stop the growth of cells. It means that not permitting the cells to multiply speedily. While cytotoxicity states to causing damage to cells there by killing them. The anticancer and anti-proliferative effect of medicinal plants involves the use of natural yields for the cancer treatment. Cancerous cell lines such as Hela, MCF7, CaCo2, Hep G2 and A549 are commonly used. In these kinds of assays, there should be interested the plant species with low IC50 OR LC50 as they are likely to prevent the evolution of cancer.

Luo et al. designed and synthesized a series of novel oxadiazolederivative bearing benzotriazole for FAK inhibitory estimation. Among all the compounds, compound **63** showed a better inhibitory activity for cancer cell growth with IC50 value of 11µM & 0.250µM against Hela cells and FAK.[56]

Kamal et al. synthesized pyrazole and oxadiazole derivatives and screened as an anti-proliferative agents against different Human cancer cell. Among compounds, compound **64, 65** and **66** exhibited better cytotoxicity with IC50. Value.[57]

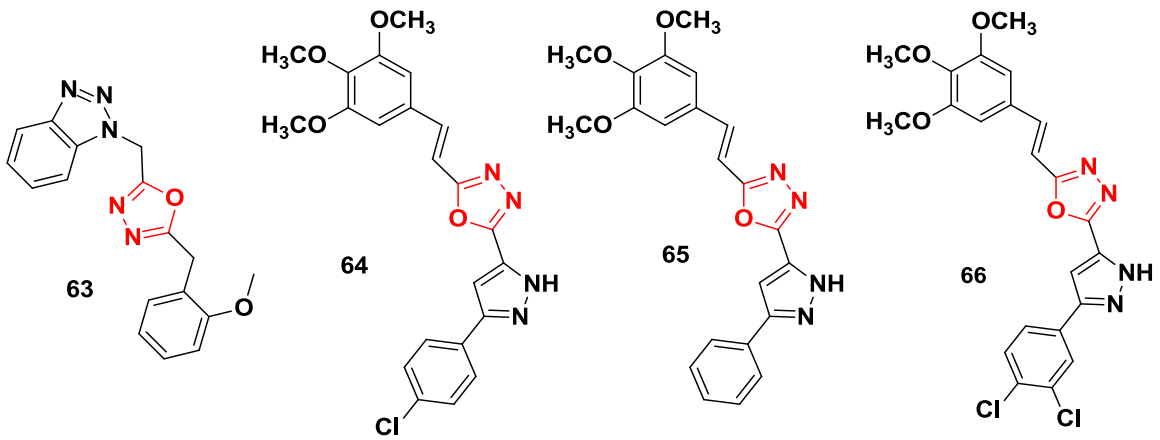


Fig. 12: Anti-Proliferation Analogous of 1,3,4-oxadiazole.

Anti-Diabetic Activity

Diabetes is defined as assembly of metabolic diseases in which there is high blood glucose (blood sugar).

A novel series of Inhibition of diacylglycerol acyl transferase-1 (DGAT-1) inhibitors was discovered from an oxadiazole amide high throughput screening (HTS) hit by Willium et al. and evaluated for anti-diabetic activity. Compound **158** demonstrated tremendous DGAT-1 potency (0.6 nM), good pharmacokinetics and pre-clinical in vivo ability that could be reorganized through a PK/PD relationship.[58] A series of 1, 3, 4-oxadiazole containing 2-mercepto benzimidazole **68** synthesized & tested a group by Shingalapur et al and synthesized compound **68** evaluated for anti-diabetic activity by oral glucose tolerance test (OGTT).[33]

A new series of oxadiazolebenzohydrazones derivatives **69** synthesized by Taha et al. Theoxadiazoles derivatives were screened for their α-glucosidase inhibitory activity. The IC50 values for inhibition activity differ in the range between 2.64 ± 0.05 to 460.14 ± 3.25 µM. The IC50 values were being compared to the standard acarbose (IC50 = 856.45 ± 5.60 µM).[59]

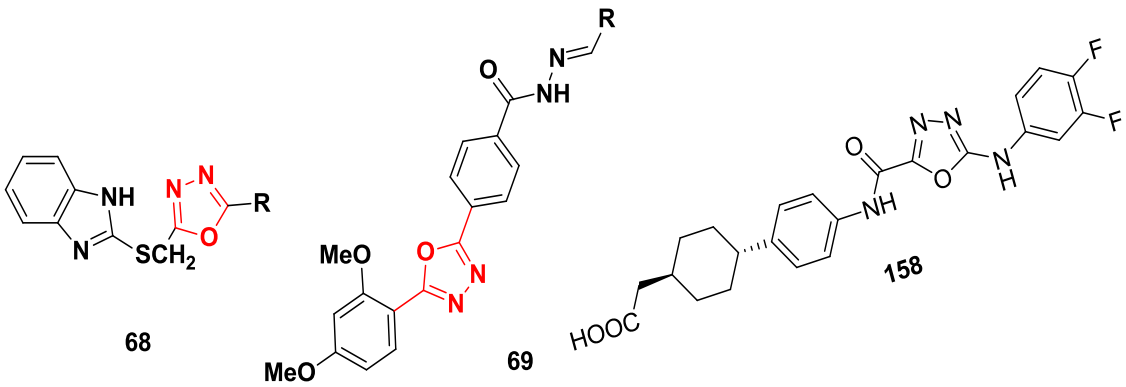


Fig. 13: Anti-Diabetic analogues of 1,3,4-oxadiazole.

Anti-HIV Activity

A new series of novel 1,3,4-oxadiazole derivatives **70** were synthesized by Syed et al. and screened for their anti HIV activity.[60] A new of series of 2-adamantan-1-ylmethyl)-5-(aryl)-1,3,4-oxadiazole were synthesized by Mehmood et al. and screened for their Anti-HIV activity. Compound **71** showed potent activity in vitro with EC50 value 10.86 µg/mL both virus types. IIIB and ROD.[61]

Hajimahdi and coworkers reported a designed synthesis of 4-oxo-4H-pyrido (1,2-a) pyrimidine derivatives containing 1,3,4-oxadiazole **72** and for in vitro anti HIV-1 activity.[62]

A new series of substituted 1,3,4-oxadiazole naphthyridines were synthesized by Ravichandran V et al. and evaluated for HIV-1 integrase inhibitors. Compound **73** showed potent inhibitory properties.[63]

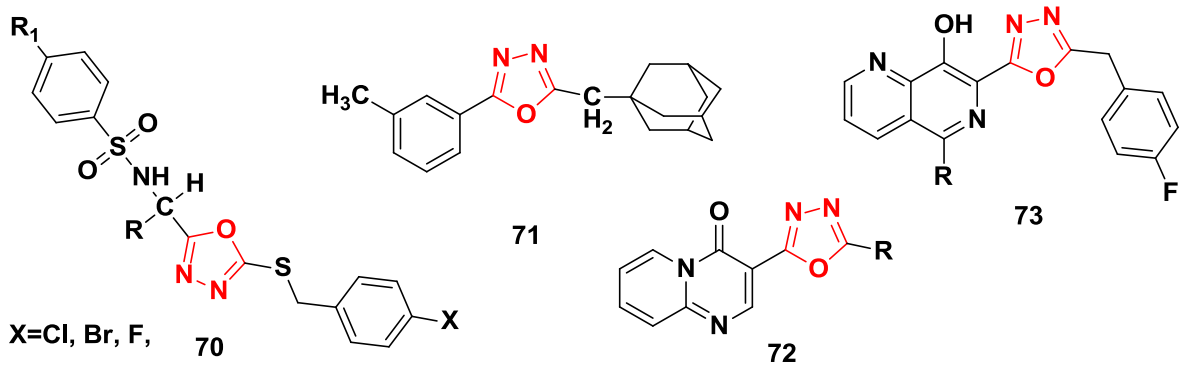


Fig. 14: Anti-HIV analoguess of 1,3,4-oxadiazole.

Anthelmintic Activity

Anthelmintic drugs are used to treat worm infection of livestock and humans with parasitic worms. It includes both round worm i.e., *nematodes* and flat worm e.g., *flukes* and *tapeworms*. Anthelmintic drug prevents infection without causing significant damage to the host. They are of huge significance for human tropical medicine and for veterinary medicine. A series of different 1,3,4-oxadiazole derivatives were reported by kalpesh and coworkers. The entire compound was evaluated for their anthelmintic activity against *Pherituma Posthuma*with the standard drug albendazole. Compound **74** showed better activity compared to standard.[64]

A new series of 3-(4-acetyl-5-phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2 H-chromen-2-one derivatives **76** were reported by Sudha and coworkers. Compounds evaluated for *in vitro* anthelmintic activity using standard method by taking albendazole as reference drug.[65]

A new series of 1-[(5-substituted-1, 3, 4-oxadiazole-2-yl) methyl]-4-propylpiperazines derivatives **77** were synthesized by Srinivas et al. and evaluated for their anthelmintic activity. Compounds exhibited anthelmintic activity compared to standard drug against earthworms *Pontoscotexcorethruses, Megascoplexkonkanensis* and *Eudrilus species*.[66]

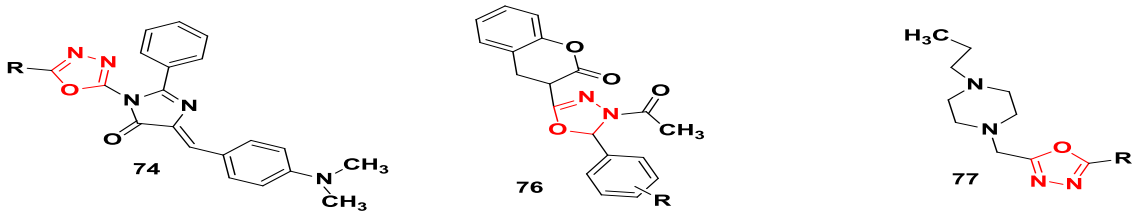
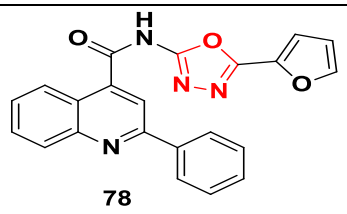


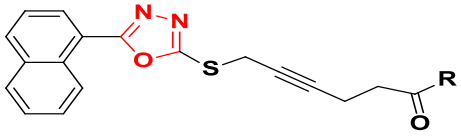
Fig. 15: Anthelmintic analogues of 1,3,4-oxadiazole.

Some other biological activity exhibited by 1,3,4-oxadiazole are given below. 78[67], 79[68], 80[69], 81[70], 82[71], 83[72], 84[73], 85[74], 86[75], 87[76], 88[77], 89[78], 90[79], 91[80], 92.[81]



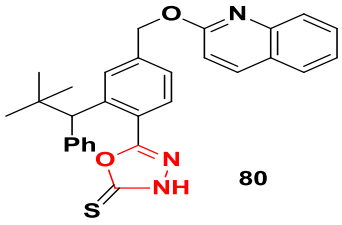
78

IC50= 74 µM
Inhibitor of signal transducer and activators of transcription (STAT3)



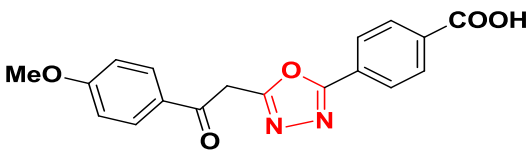
79

Inhibitor of Human Reticulocyte 15-Lipoxygenase-1



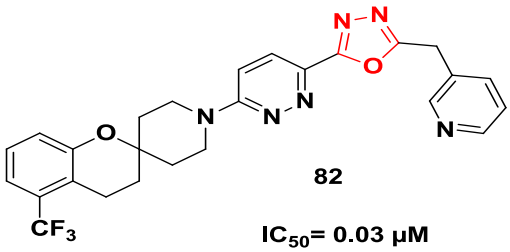
80

5-lipoxygenase inhibitor
FLAP binding IC50= 1.1 µM



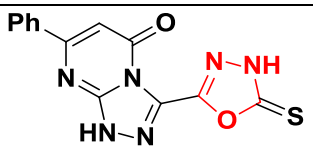
81

IC50= 74 µM
Inhibitor of protein kinase CK2a



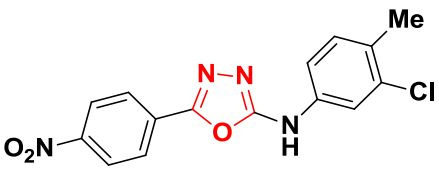
82

IC_{50}= 0.03 µM
stearoyl-CoA desaturase 1 Inhibitor



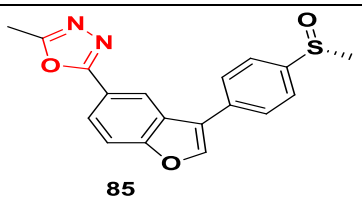
83

Antihypertensive and diuretic activities



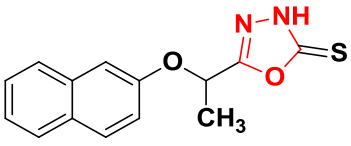
84

Inhibitor of GSK-3β



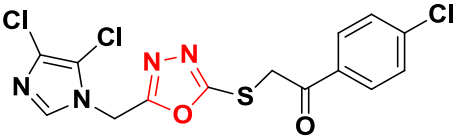
85

GSK-3 and tau phosphorylation inhibitor



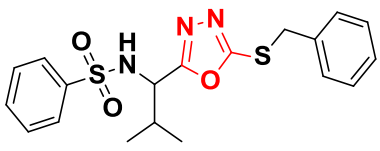
87

Antihyperlipidemic activity



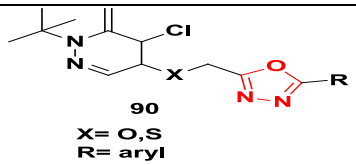
88

Antiviral activity against multiple flaviviruses



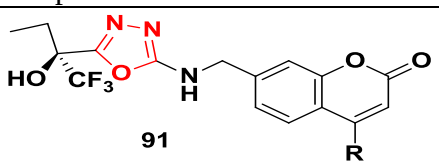
89

Antimalarial activity



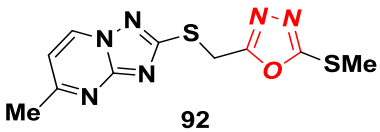
90
X= O,S
R= aryl

Antifeedant activity



91

5-lipoxygenase inhibitor



92

Herbicidal activity

CONCLUSION

The present article study showed a synthetic method of 1,3,4-oxadiazole derivatives indicate an attention grabbing class of moiety having a broad spectrum of pharmalogical activity. Different reported study showed a various activity like anti-inflammatory, anti-HIV, anticancer, analgesic, anti-tubercular etc. A new series of compounds can synthesize by reported method and evaluated as a pharmalogical agent with better activity power and low harmfulness. Many researchers can also achieve an improvement in activity by minor modification on oxadiazole ring. This has been remarked that minor modification on oxadiazole ring exhibited a potent biological activity. Future researchers can develop a new compound as novel therapeutic agent.

ACKNOWLEDGEMENT

The writers appreciatively acknowledged to SEAS, Ahmadabad University, Ahmadabad, Gujarat, India, for providing amenities and forthcoming stage for the research work to the related area.

REFERENCES

1. J. Boström, A. Hogner, A. Llinàs, E. Wellner, and A. T. Plowright, "Oxadiazoles in medicinal chemistry," *J. Med. Chem.*, 2012; 55(5): 1817–1830.
2. K. D. Patel, S. M. Prajapati, S. N. Panchal, and H. D. Patel, "Review of Synthesis of 1, 3, 4-Oxadiazole Derivatives," *Synth. Commun.*, 2014; 44(13): 1859–1875.
3. N. D. James and J. W. Growcott, "ZIBOTENTAN Endothelin ETA Receptor Antagonist Oncolytic," *Drugs Future*, 2009; 34(8): 624–633.
4. R. T. Steigbigel *et al.*, "Raltegravir with optimized background therapy for resistant HIV-1 infection," *N. Engl. J. Med.*, 2008; 359(4): 339–354.
5. S. J. Dolman, F. Gosselin, P. D. O. Shea, and I. W. Davies, "Superior Reactivity of Thiosemicarbazides in the Synthesis of 2-Amino-1, 3, 4-oxadiazoles 1, 3, 4-oxadiazoles is reported. This method relies on a tosyl zide, which is readily prepared by acylation of a given hydrazide with the appropriate isothiocy," 2006; 4: 9548–9551.
6. D. W. Gilroy, T. Lawrence, M. Perretti, and A. G. Rossi, "INFLAMMATORY RESOLUTION : NEW OPPORTUNITIES FOR DRUG DISCOVERY," May, 2004; 3.
7. M. M. M. El-Miligy, A. A. Hazzaa, H. El-Messmary, R. A. Nassra, and S. A. M. El-Hawash, "New benzothiophene derivatives as dual COX-1/2 and 5-LOX inhibitors: synthesis, biological evaluation and docking study," *Future Med. Chem.*, 2017; 0.

8. V. Hamse, K. Kumar, J. R. B. S. Priya, and S. N. Swamy, "Synthesis, characterization and bioactivity studies of novel 1, 3, 4- oxadiazole small molecule that targets basic phospholipase A 2 from Vipera russelli," *Mol. Cell. Biochem.*, 2016.
9. S. Bansal *et al.*, "European Journal of Medicinal Chemistry Design and synthesis of novel 2-phenyl-5- (1, 3-diphenyl-1 H -pyrazol- 4-yl) -1, 3, 4-oxadiazoles as selective COX-2 inhibitors with potent anti- in fl ammatory activity," *Eur. J. Med. Chem.*, 2014; 80: 167–174.
10. M. Akhter, N. Akhter, M. M. Alam, M. S. Zaman, R. Saha, and A. Kumar, "Synthesis and biological evaluation of 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives with both COX and LOX inhibitory activity," 2011, December 2010; 26: 767–776.
11. A. G. Banerjee, N. Das, S. A. Shengule, R. S. Srivastava, and S. K. Shrivastava, "SC," *Eur. J. Med. Chem.*, 2015; 3.
12. A. Husain, "Synthesis of novel 1, 3, 4-oxadiazole derivatives and their biological properties," 2009; 59: 223–233.
13. H. Kumar, S. A. Javed, S. A. Khan, and M. Amir, "biphenyl-4-yloxy acetic acid : Synthesis and preliminary evaluation of biological properties *," *Eur. J. Med. Chem.*, 2008; 43(12): 2688–2698.
14. F. Zhang *et al.*, "Bioorganic & Medicinal Chemistry Synthesis, molecular modeling and biological evaluation of acetohydrazide derivatives as potential anticancer agents," *Bioorg. Med. Chem.*, 2013; 2–11.
15. X. Zhang *et al.*, "Bioorganic & Medicinal Chemistry Synthesis, biological evaluation, and molecular docking studies moiety as potential anticancer agents," *Bioorg. Med. Chem.*, 2011; 19(21): 6518–6524.
16. Q. Zheng, X. Zhang, Y. Xu, K. Cheng, Q. Jiao, and H. Zhu, "Bioorganic & Medicinal Chemistry Synthesis, biological evaluation, and molecular docking studies of 2-chloropyridine derivatives possessing 1, 3, 4-oxadiazole moiety as potential antitumor agents," *Bioorg. Med. Chem.*, 2010; 18(22): 7836–7841.
17. S. Zhang, Y. Luo, L. He, Z. Liu, and H. Zhu, "Synthesis, biological evaluation, and molecular docking studies of novel 1,3,4-oxadiazole derivatives possessing benzotriazole moiety as FAK inhibitors with anticancer activity," *Bioorg. Med. Chem.*, 2013.
18. J. Sun *et al.*, "Bi oorganic & Medic inal Chemistry Letters Synthesis and antitumor activity of 1, 3, 4-oxadiazole possessing 1, 4-benzodioxan moiety as a novel class of potent methionine aminopeptidase type II inhibitors," *Bioorg. Med. Chem. Lett.*, 2013; 23(10): 2876–2879.

19. S. Valente *et al.*, "1,3,4-Oxadiazole-Containing Histone Deacetylase Inhibitors: Anticancer Activities in Cancer Cells," 2014; 1–7.
20. H. Rajak *et al.*, "Bioorganic & Medicinal Chemistry Letters moiety : Design and synthesis of novel hydroxamic acid based histone deacetylase inhibitors," *Bioorg. Med. Chem. Lett.*, 2011; 21(19): 5735–5738.
21. V. Kumar, A. K. Abbas, and J. C. Aster, *Robbins basic pathology*. Elsevier Health Sciences, 2013.
22. A. Konstantinos, "Testing for tuberculosis," *Aust. Prescr.*, 2010; 33(1): 12–18.
23. S. R. Pattan, P. A. Rabara, and J. S. Pattan, "derivatives for antitubercular activity," October, 2009; 48: 1453–1456.
24. A. Activity and B. Pyr-, "Synthesis and Antitubercular Activity of New 1,3,4-Oxadiazoles Bearing Pyridyl and Thiazolyl Scaffolds," *Bioorg. Med. Chem. Lett.*, 2016.
25. N. C. D. A. R. Trivedi and H. V. V. H. C. Somani, "CHEMISTRY Synthesis and biological evaluation of 1, 3, 4-oxadiazole bearing dihydropyrimidines as potential antitubercular agents," *Med. Chem. Res.*, 2015; 1–10.
26. G. Karabanovich *et al.*, "Thiadiazoles as Selective Antitubercular Agents Active Against Replicating and Nonreplicating Mycobacterium tuberculosis," 2016.
27. S. D. Joshi, H. M. Vagdevi, V. P. Vaidya, and G. S. Gadaginamath, "Synthesis of new 4-pyrrol-1-yl benzoic acid hydrazide analogs and some derived oxadiazole, triazole and pyrrole ring systems: a novel class of potential antibacterial and antitubercular agents," *Eur. J. Med. Chem.*, 2008; 43(9): 1989–1996.
28. F. Macaev *et al.*, "Synthesis of novel 5-aryl-2-thio-1, 3, 4-oxadiazoles and the study of their structure – anti-mycobacterial activities," 2005; 13: 4842–4850.
29. S. Mahendran, B. S. Thippeswamy, V. P. Veerapur, and S. Badami, "Anticonvulsant activity of embelin isolated from Embelia ribes," *Phytomedicine*, 2011; 18(2): 186–188.
30. K. P. Harish, K. N. Mohana, L. Mallesha, and B. Veeresh, "Full Paper Synthesis and In Vivo Anticonvulsant Activity of 2-Methyl-2-," 2014; 256–267.
31. N. K. Fuloria, V. Singh, M. Shaharyar, and M. Ali, "Synthesis and Antimicrobial Evaluation of Some New Oxadiazoles Derived from Phenylpropionohydrazides," 2009; 1898–1903.
32. H. Rajak, R. Deshmukh, R. Veerasamy, A. Kumar, and P. Mishra, "Bioorganic & Medicinal Chemistry Letters step towards establishing four binding site pharmacophoric model hypothesis for anticonvulsant activity," *Bioorg. Med. Chem. Lett.*, 2010; 20(14): 4168–4172.

33. R. V Shingalapur, K. M. Hosamani, R. S. Keri, and M. H. Hugar, "European Journal of Medicinal Chemistry Derivatives of benzimidazole pharmacophore : Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies," *Eur. J. Med. Chem.*, 2010; 45(5): 1753–1759.
34. A. Zarghi *et al.*, "Synthesis and anticonvulsant activity of new," 2005; 15: 1863–1865.
35. M. A. Bhat, N. Siddiqui, and S. A. Khan, "Synthesis of novel 3-(4-acetyl-5H/methyl-5-substituted phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl)-2H-chromen-2-ones as potential anticonvulsant agents," *Acta Pol Pharm*, 2008; 65(2): 235–239.
36. S. K. Kashaw, V. Gupta, V. Kashaw, P. Mishra, J. P. Stables, and N. K. Jain, "Anticonvulsant and sedative-hypnotic activity of some novel 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazoline-4 (3H)-ones," *Med. Chem. Res.*, 2010; 19(3): 250–261.
37. T. J. Chandra and P. S. Mani, "A study of 2 rapid tests to differentiate Gram positive and Gram negative aerobic bacteria," *J. Med. Allied Sci.*, 2011; 1(2): 84.
38. R. I. Amann, W. Ludwig, and K.-H. Schleifer, "Phylogenetic identification and in situ detection of individual microbial cells without cultivation.," *Microbiol. Rev.*, 1995; 59(1): 143–169.
39. M. Afroz, M. S. Yar, S. G. Abdel-hamid, S. I. Al, and A. Samad, "European Journal of Medicinal Chemistry Molecular properties prediction, synthesis and antimicrobial activity of some newer oxadiazole derivatives," *Eur. J. Med. Chem.*, 2010; 45(12): 5862–5869.
40. A. Gupta, R. Singh, P. K. Sonar, and S. K. Saraf, "Novel 4-Thiazolidinone Derivatives as Anti-Infective Agents: Synthesis, Characterization, and Antimicrobial Evaluation," *Biochem. Res. Int.*, 2016; 2016: 3–10.
41. N. C. Desai, N. Bhatt, H. Somani, and A. Trivedi, "European Journal of Medicinal Chemistry Synthesis, antimicrobial and cytotoxic activities of some novel thiazole clubbed 1, 3, 4-oxadiazoles," *Eur. J. Med. Chem.*, 2013; 67: 54–59.
42. M. A. Al-omar, "Synthesis and Antimicrobial Activity of New 5-(2-Thienyl)-1,2,4-triazoles and 5-(2-Thienyl)-1,3,4-oxadiazoles and Related Derivatives," 2010; 502–514.
43. S. Ningaiah, U. K. Bhadraiah, S. D. Doddaramappa, S. Keshavamurthy, and C. Javarasetty, "Novel pyrazole integrated 1,3,4-oxadiazoles: Synthesis, characterization and antimicrobial evaluation," *Bioorg. Med. Chem. Lett.*, 2013.
44. P. Navin *et al.*, "Synthesis and biological evaluation of newer 1, 3, 4-oxadiazoles incorporated with benzothiazepine and benzodiazepine moieties," 2017; 1–14.
45. M. Farooqui, R. Bora, and C. R. Patil, "Synthesis, analgesic and anti-inflammatory

activities of novel," *Eur. J. Med. Chem.*, 2009; 44(2): 794–799.

46. A. Activities, M. M. Alam, M. Shaharyar, H. Hamid, S. Nazreen, and S. Haider, "Synthesis of Novel 8-Hydroxy Quinolin Based 1, 3, 4-oxadiazoles and S-substituted 1, 2, 4-triazole Derivatives and Evaluation of their," 2011; 663–673.
47. A. K. Kataria *et al.*, "SYNTHESIS OF SOME NEW 2-(SUBSTITUTED-PHENYL)-5-(N, N-DIPHENYLAMINOMETHYL)-1, 3, 4-OXADIAZOLES: A SAFER ANTI-INFLAMMATORY AND ANALGESIC AGENTS," *Acta Pol. Pharm Drug Res*, 2011; 68: 381–386.
48. S. Yavuz *et al.*, "Synthesis and Pharmacological Evaluation of Some Novel Thebaine Derivatives: N-(Tetrazol-1H-5-yl)-6, 14-endoethenotetrahydrothebaine Incorporating the 1, 3, 4-Oxadiazole or the 1, 3, 4-Thiadiazole Moiety," *Arch. Pharm. (Weinheim).*, 2013; 346(6): 455–462.
49. E. Siegmund, R. Cadmus, and G. Lu, "A method for evaluating both non-narcotic and narcotic analgesics," *Proc. Soc. Exp. Biol. Med.*, 1957; 95(4): 729–731.
50. M. Saitoh *et al.*, "Bioorganic & Medicinal Chemistry Design, synthesis and structure – activity relationships of 1, 3, 4-oxadiazole derivatives as novel inhibitors of glycogen synthase kinase-3 b," *Bioorg. Med. Chem.*, 2017; 17(5): 2017–2029.
51. J. O. F. Neurochemistry, "No Title," 2011; 1330–1340.
52. L. Ma *et al.*, "Synthesis and antioxidant activity of novel Mannich base of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan," *Bioorg. Med. Chem.*, 2013.
53. B. Can-eke, "Full Paper Design and One-Pot and Microwave-Assisted Synthesis of Moiety as Antioxidants," 2012; 1–8.
54. A. Pharm and S. Ramakrishna, "Synthesis of coumarin heterocyclic derivatives with antioxidant activity and in vitro cytotoxic activity against tumour cells," 2009; 59: 159–170.
55. Y. Kotaiah, N. Harikrishna, K. Nagaraju, and C. V. Rao, "European Journal of Medicinal Chemistry pyrimidine derivatives," *Eur. J. Med. Chem.*, 2012; 58: 340–345.
56. Y. Luo, Z. Liu, G. Chen, J. Shi, J. Li, and H. Zhu, "1,3,4-Oxadiazole derivatives as potential antitumor agents: discovery, optimization and biological activity valuation," *Medchemcomm*, 2015.
57. A. Kamal *et al.*, "Pyrazole-oxadiazole conjugates: synthesis, antiproliferative activity and inhibition of tubulin polymerization.," *Org. Biomol. Chem.*, 2014; 12(40): 7993–8007.
58. W. Mccoull *et al.*, "Bioorganic & Medicinal Chemistry Letters Identification, optimisation and in vivo evaluation of oxadiazole DGAT-1 inhibitors for the treatment of

obesity and diabetes," *Bioorg. Med. Chem. Lett.*, 2012; 22(12): 3873–3878.

59. M. Taha *et al.*, "Synthesis of New Oxadiazole Derivatives as α -Glucosidase Inhibitors," *Bioorg. Med. Chem.*, 2015.
60. T. Syed, T. Akhtar, N. A. Al-masoudi, P. G. Jones, and S. Hameed, "Synthesis, QSAR and anti-HIV activity of new 5-benzylthio- 1, 3, 4-oxadiazoles derived from α -amino acids," 2011, December 2010; 26: 668–680.
61. M.-H. Khan, T. Akhtar, N. A Al-Masoudi, H. Stoeckli-Evans, and S. Hameed, "Synthesis, crystal structure and anti-HIV activity of 2-adamantyl/adamantylmethyl-5-aryl-1, 3, 4-oxadiazoles," *Med. Chem. (Los. Angeles).*, 2012; 8(6): 1190–1197.
62. Z. Hajimahdi, A. Zarghi, R. Zabihollahi, and M. R. Aghasadeghi, "CHEMISTRY Synthesis, biological evaluation, and molecular modeling studies," 2012.
63. V. Ravichandran, S. Shalini, K. Sundram, and A. D. Sokkalingam, "QSAR study of substituted 1, 3, 4-oxadiazole naphthyridines as HIV-1 integrase inhibitors," *Eur. J. Med. Chem.*, 2010; 45(7): 2791–2797.
64. K. Patel, E. Jayachandran, R. Shah, V. Javali, and G. M. Sreenivasa, "International Journal of Pharma and Bio Sciences SYNTHESIS, CHARACTERIZATION AND ANTHELMINTIC ACTIVITY (PERITUMA POSTHUMA) OF NEW OXADIAZOLE INCORPORATED WITH IMIDAZOLE AND PYRAZOLE.," 2010; 1(3): 1–13.
65. B. N. Sudha *et al.*, "Synthesis, characterisation and anthelmintic activity of 3-(4-acetyl-5-phenyl-4, 5-dihydro-1, 3, 4-oxadiazol-2-yl)-2H-chromen-2-one derivatives," 2013.
66. K. Srinivas and K. P. Kumar, "International Journal of Biopharmaceutics," 2010; 1(1): 14–19.
67. K. Matsuno *et al.*, "Identification of a new series of STAT3 inhibitors by virtual screening," *ACS Med. Chem. Lett.*, 2010; 1(8): 371–375.
68. G. Rai *et al.*, "Discovery of potent and selective inhibitors of human reticulocyte 15-lipoxygenase-1," *J. Med. Chem.*, 2010; 53(20): 7392–7404.
69. Y. Uto *et al.*, "Synthesis and evaluation of novel stearoyl-CoA desaturase 1 inhibitors: 1′-{6-[5-(pyridin-3-ylmethyl)-1, 3, 4-oxadiazol-2-yl] pyridazin-3-yl}-3, 4-dihydrospiro [chromene-2, 4′-piperidine] analogs," *Eur. J. Med. Chem.*, 2010; 45(11): 4788–4796.
70. Z. Hou *et al.*, "Structure-based design of novel potent protein kinase CK2 (CK2) inhibitors with phenyl-azole scaffolds," *J. Med. Chem.*, 2012; 55(6): 2899–2903.
71. Y. Uto *et al.*, "Novel spiropiperidine-based stearoyl-CoA desaturase-1 inhibitors: Identification of 1′-{6-[5-(pyridin-3-ylmethyl)-1, 3, 4-oxadiazol-2-yl] pyridazin-3-yl}-5-(trifluoromethyl)-3, 4-dihydrospiro [chromene-2, 4′-piperidine]," *Bioorg. Med. Chem.*

Lett., 2010; 20(2): 746–754.

72. K. A. Ali, E. A. Ragab, T. A. Farghaly, and M. M. Abdalla, "Synthesis of new functionalized 3 subsitituted [1, 2, 4] triazolo [4, 3-a] pyrimidine dreivatives: Potential antihypertensive agents," *Acta Pol. Pharm*, 2011; 68(2): 237–247.
73. M. A. Khanfar, R. A. Hill, A. Kaddoumi, and K. A. El Sayed, "Discovery of novel GSK-3β inhibitors with potent in vitro and in vivo activities and excellent brain permeability using combined ligand-and structure-based virtual screening," *J. Med. Chem.*, 2010; 53(24): 8534–8545.
74. M. Saitoh *et al.*, "2-{3-[4-(Alkylsulfinyl) phenyl]-1-benzofuran-5-yl}-5-methyl-1, 3, 4-oxadiazole derivatives as novel inhibitors of glycogen synthase kinase-3β with good brain permeability," *J. Med. Chem.*, 2009; 52(20): 6270–6286.
75. T. Onishi *et al.*, "A novel glycogen synthase kinase-3 inhibitor 2-methyl-5-(3-{4-[(S)-methylsulfinyl] phenyl}-1-benzofuran-5-yl)-1, 3, 4-oxadiazole decreases tau phosphorylation and ameliorates cognitive deficits in a transgenic model of Alzheimer's disease," *J. Neurochem.*, 2011; 119(6): 1330–1340.
76. G. A. Idrees, O. M. Aly, G. E.-D. A. A. Abuo-Rahma, and M. F. Radwan, "Design, synthesis and hypolipidemic activity of novel 2-(naphthalen-2-yloxy) propionic acid derivatives as desmethyl fibrate analogs," *Eur. J. Med. Chem.*, 2009; 44(10): 3973–3980.
77. T. Kampmann *et al.*, "In silico screening of small molecule libraries using the dengue virus envelope E protein has identified compounds with antiviral activity against multiple flaviviruses," *Antiviral Res.*, 2009; 84(3): 234–241.
78. M. Zareef *et al.*, "Synthesis and antimalarial activity of novel chiral and achiral benzenesulfonamides bearing 1, 3, 4-oxadiazole moieties," *J. Enzyme Inhib. Med. Chem.*, 2007; 22(3): 301–308.
79. S. Cao, X. Qian, G. Song, B. Chai, and Z. Jiang, "Synthesis and antifeedant activity of new oxadiazolyl 3 (2 H)-pyridazinones," *J. Agric. Food Chem.*, 2003; 51(1): 152–155.
80. C. M. Maciolek *et al.*, "Novel cytochrome P450-mediated ring opening of the 1, 3, 4-oxadiazole in setileuton, a 5-lipoxygenase inhibitor," *Drug Metab. Dispos.*, 2011; 39(5): 763–770.
81. Z. Liu, G. Yang, and X. Qin, "Syntheses and biological activities of novel diheterocyclic compounds containing 1, 2, 4-triazolo [1, 5-a] pyrimidine and 1, 3, 4-oxadiazole," *J. Chem. Technol. Biotechnol.*, 2001; 76(11): 1154–1158.