Review Article

REVIEW EXPLORING ANTIINFLAMMATORY POTENTIAL OF 1,3,4-OXADIAZOLE DERIVATIVES AS PROMISING LEAD

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ABSTRACT

Steroids and non-steroidal antiinflammatory drugs are globally used for reducing inflammation in the body. 1,3,4-Oxadiazoles are five membered heterocyclic compounds, containing one oxygen and two nitrogen atoms. Literature indicates that compounds containing this nucleus have wide range of pharmacological activities include anti-inflammatory, antimicrobial, analgesic, anti-HIV, antiparkinsonian, antiproliferative, anticonvulsant, antimalarial, antihypertensive, antioxidant, antitubercular, sedative, hypnotic, hypoglycemic etc. Researchers have designed a variety of novel compounds with a means of preventing or minimizing the adverse effects of drugs which cause some serious gastric problems, and risks of complications regarding potential cardiovascular hazards of cyclooxygenase inhibitors. The review represents a broad view on the antiinflammatory activity possessed by compounds having 1,3,4-oxadiazole nucleus.

Keywords: Oxadiazole, Antiinflammatory, Ulcerogenic, NSAIDs.

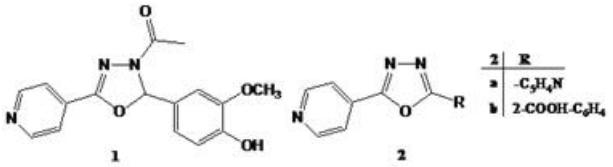
INTRODUCTION

Oxadiazoles are five-membered heterocyclic systems containing one oxygen and two nitrogen atoms, in literature also known as furadiazoles[1,2]. 1,3,4-Oxadiazole and their synthetic derivatives have diverse pharmacological activities such as, antiinflammatory[3-6], antimicrobial[7-16], analgesic, antiparkinsonian, anti-HIV[18], antiproliferative[19], anticonvulsant[20,21], antimalarial, antihypertensive[22], antioxidant[17,23,24], antitubercular[25-28], antihepatitis B[29,30] activities etc. Oxadiazoles are also used as photosenstizers, brighteners [31], lipid peroxidation inhibitor, genotoxic[32], spasmolytic, diuretic, antiemetic, hypnotic, sedative, hypotensive, hypoglycemic[33], herbicidal[14,34], pesticidal, insecticidal, nematocidal[35], amoebicidal agents[36,37] and plays a important role in agricultural chemistry[38-40]. NSAIDs are found for clinical use globally, due to their good anti-inflammatory, analgesic and antipyretic effects[37,41]. NSAIDs in comparison to analgesic and antiinflammatory drugs are used as an important tool for the clinician[42]. Antiinflammatory drugs inhibit both COX-1 and COX-2, but COX-1 is inhibited more eagerly than COX-2. COX-1 inhibition causes side effects (related to gastrointestinal and cardiovascular)[43,44] and COX-2 inhibition is responsible for therapeutic effects[45]. NSAIDs are particularly used for reducing pain and inflammation[46] in osteoarthritis, rheumatoid arthritis, and arthritis of systemic lupus erythematosus, psoriasis and other seronegative spondyloarthropathies. These agents block metabolism of arachidonic acid through the enzyme cyclooxygenase, and therefore, the production of prostaglandins[2,45]. NSAIDs are associated with side effects such as; formation of gastric ulcers, including lesions of the gastric, duodenal, intestinal mucosa and dyspepsia[47,48], due to the presence of free carboxylic acid. The chronic use of NSAIDs for a long time induces ulcer in the range of 15-30%[42]. Some marketed drugs such as; sulindac and fenbufen cause minimal risk of acute injury to the stomach. 1,3,4-Oxadiazoles have been designed for reducing the gastric ulcer[49,50] formation because of their enzyme inhibiting properties for both cyclooxygenase and 5-lipooxygenase[1,33,51]. Some novel compounds have designed by replacement of the carboxylic acid group with 1,3,4-oxadiazole nucleus have resulted in a significant antiinflammatory activity. In oxadiazoles, substitution at C-2 and C-5 positions with acetoxyphenyl, dimethoxyphenyl, methoxyphenyl, chlorophenyl has resulted in significant improvement in the antiinflammatory activity[52,53]. The most common method used for the synthesis of 1,3,4-oxadiazoles nucleus involves the cyclization of hydrazides with a variety of anhydrous reagents, such as thionyl chloride, phosphorus oxychloride, boron trifluoride etherate, 1,1,1,3,3,3-hexamethyldisilazane[23], phosphorous pentoxide, triphenylphosphine and triflic anhydride giving good yield under harsh or neutral reaction conditions[22,38,40]. Antiinflammatory activity of the synthesized compounds evaluated by carrageenan induced rat paw oedema method [37,53].

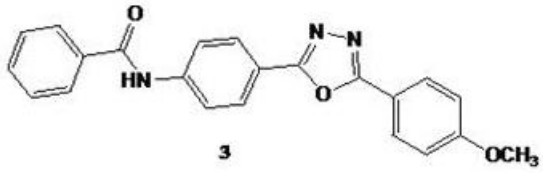
ANTIINFLAMMATORY ACTIVITY

Dhansay Dewangan *et al* synthesized 1,3,4-oxadiazole derivatives and screened them for their biological activity. They prepared 1-[2-(4-hydroxy-3-methoxy-phenyl)-5-pyridin-4-yl-[1,3,4]oxadiazol-3-yl]-ethanone **1** from pyridine-4-carbohydrazide in the presence of appropriate acids and aldehydes, via Schiff's base, on condensation with acetic anhydride. 2-Aryl-5-pyridine-1,3,4-oxadiazoles 2 were prepared from pyridine-4-carbohydrazide using phosphoryl chloride as a catalyst. Amongst all the

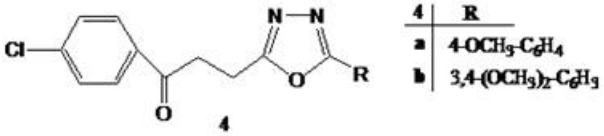
synthesized compounds, they found that, compounds **1** and **2** showed better antiinflammatory activity against the standard (indomethacin). Antiinflammatory activity of 1,3,4-oxadiazole derivatives was enhanced by the direct substitution at C-2 position with pyridinyl and benzoic acid, and also at C-5 position with pyridine[19].



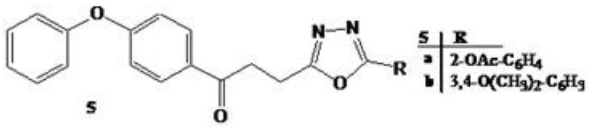
G Nagalakshmi synthesized novel derivatives of 1,3,4-oxadiazole, and tested them for their antiinflammatory activity, using carrageenan-induced rat paw oedema method. They prepared 2,5-disubstituted-1,3,4-oxadiazoles, by the condensation reactions of 4-methoxybenzohydrazide, with different aromatic acids in the presence of phosphoryl chloride. It was found that compound **3** *N*-{4-[5-(4-methoxy-phenyl)-1,3,4-oxadiazol-2-yl]-phenyl}benzamide exhibited potent antiinflammatory activity with 50 %, as compared to the standard drug phenylbutazone, with 53.57 % [32].



Asif Husain *et al* synthesized 2-[3-(4-chlorophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole and 2-[3-(4-ethylphenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazole 3-(4-chlorobenzoyl) propionic acid derivatives. They screened them for their good antiinflammatory activity using carrageenan induced rat paw oedema method. They found that compounds, 2-[3-(4-chlorophenyl)propan-3-one]-5-(4-methoxyphenyl)-1,3,4-oxadiazole **4a** and 2-[3-(4-chlorophenyl)propan-3-one]-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole **4b** showed significant antiinflammatory activity, with 58.38 % and 59.52 %, respectively, when compared to the activity of indomethacin, with 64.28 % inhibition. They indicated that the presence of 4-methoxyphenyl or 3,4-dimethoxyphenyl substitution at C-5 position of oxadiazole ring causes remarkable improvement in antiinflammatory activity [37].

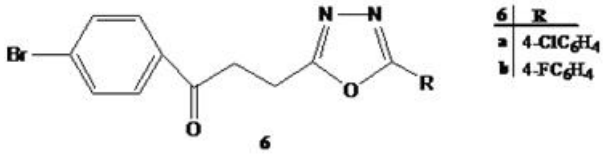


Asif Husain *et al* synthesized a novel series of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-one by condensation reaction of diphenyl ether with succinic anhydride, in the presence of anhydrous aluminium chloride, followed by the Friedel–Crafts acylation reaction, via an intermediate compound 3-(4-phenoxybenzoyl)propionic acid, using different aryl acid hydrazides, in the presence of phosphorus oxychloride. Amongst of these compounds, 3-[5-(2-acetoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one **5a** and 3-[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-phenoxyphenyl)propan-1-one **5b** showed excellent antiinflammatory activity, with 65.63 % and 62.50 %, respectively, when compared to the activity of indomethacin with 68.75 %, and greater than that of 3-(4-phenoxybenzoyl)propionic acid (parent compound) with 43.75 % [52].

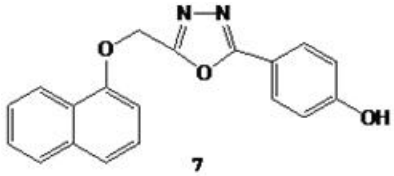


Asif Husain *et al* synthesized a novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles **6** by the condensation reaction of bromobenzene with succinic anhydride, in the presence of anhydrous aluminium chloride, following Friedel-Craft's acylation reaction, via an intermediate compound 3-(4-bromobenzoyl)propionic acid. All of these compounds were evaluated for their *in vivo* antiinflammatory activity by the carrageenan induced rat paw oedema method, with minimum or without ulcerogenic activity.

Biological evaluation of these compounds showed that compounds 2-[3-(4-bromophenyl)-propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole **6a** and 2-[3-(4-bromophenyl)propan-3-one]-5-(3,4-dimethoxy phenyl)-1,3,4-oxadiazole **6b** exhibited good antiinflammatory activity, with 59.5 % and 61.9 % respectively, compared to that of indomethacin, with 64.3 % activity[53].

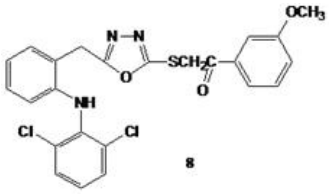


Harish Rajak *et al* synthesized a new series of oxadiazoles and evaluated their antiinflammatory activity. Compound **7** was found to be the most active compound of this series due to the presence of 4-hydroxy group on the benzene ring attached to C-2 position of the oxadiazole. They indicated that at doses of 100 mg/kg, the compound exhibited 55.93 %, 36.64 % and 49.33 % protection against carrageenan induced rat paw oedema, moist cotton pellet-induced granuloma and dry cotton pellet-induced granuloma, respectively[54].

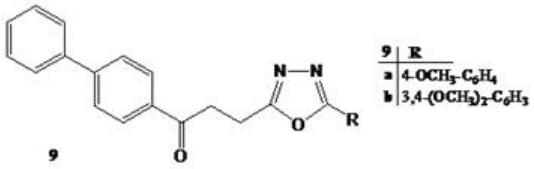


Shashikant V. Bhandari *et al* synthesized eight compounds, a series of S-substituted phenacyl 1,3,4-

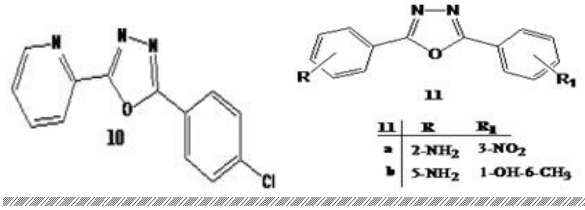
oxadiazoles **8** derived from 2-[(2,6-dichloroanilino)phenyl] acetic acid (diclofenac acid). They indicated their better antiinflammatory activity in the carrageenan induced rat paw oedema model, with no GI toxicities, compared to the standard drug diclofenac sodium. Esterification of 2-[(2,6-dichloroanilino) phenyl]acetic acid (diclofenac acid) followed by treatment with hydrazine hydrate in absolute ethanol, afforded 5-[2-(2,6-dichloroanilino) benzyl] 2-mercapto-1,3,4-oxadiazole **8**[55].



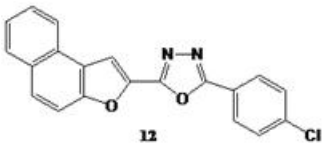
Asif Husain *et al* synthesized a new series of oxadiazole derivatives and evaluated them for their potent antiinflammatory activity using carrageenan induced rat paw oedema method. The synthesis of 3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-ones **9** by condensation reaction of biphenyl with succinic anhydride, in the presence of anhydrous aluminium chloride, followed by the Friedel-Craft's acylation reaction conditions, via an intermediate compound 4-oxo-4-(biphenyl-4-yl)butanoic acid. Biological evaluation of these compounds indicated that antiinflammatory activity of compounds **9a** and **9b** were more selective towards COX-2, as indicated by COX-2 selectivity index of 36.06 and 29.05 (COX-2 IC_{50}=1.5 µM and 1.8 µM), respectively, due to the presence of 4-methoxyphenyl or 3,4-dimethoxy phenyl substitution at the C-5 position of the oxadiazole ring. They found that compound **9b** was the most potent compound of this series, more potent than parent compound fenbufen, when compared to diclofenac[56].



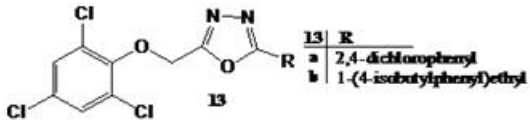
Pooja Chawla *et al* synthesized a novel series of [5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-pyridine **10** and 2-(4-substituted phenyl)-5-(2-aminophenyl)-1,3,4-oxadiazole **11**. The treatment of esters and hydrazine hydrate in the presence of ethanol, via intermediate steps isonicotinic acid hydrazide and 2-aminobenzohydrazide respectively, followed by reaction with phosphorus oxychloride and various aromatic acids, afforded different 1,3,4-oxadiazoles. From all the synthesized compounds, they found that compounds **10** and **11** exhibited significant antiinflammatory activity[57].



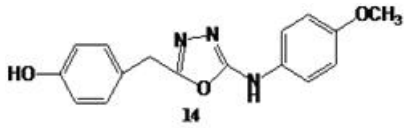
K C Ravindra *et al* synthesized 2-naphtho[2,1-b]furan-2-yl-5-aryl-1,3,4-oxadiazoles by the condensation reaction of naphtho[2,1-b]furan-2-carboxyhydrazides with different aldehydes, via an intermediate N-[(1E)-arylmethylene]-naphtho[2,1-b]furan-2-carboxyhydrazides. Of all the synthesized compounds, they found that compound **12** exhibited significant antiinflammatory activity[58].



Mohammad Amir *et al* synthesized 2-substituted aryl-5-(2,4,6-trichlorophenoxymethyl)-1,3,4-oxadiazoles **13** by the reaction of 2,4,6-trichlorophenol and ethylchloroacetate, in the presence of potassium carbonate, via an intermediate compound 2,4,6-trichlorophenoxy acetic acid, using different aromatic acids or arylalkanoic acids, in the presence of phosphorus oxychloride. They evaluated them for their biological activity by carrageenan induced rat paw oedema method. These study revealed that **13a** and **13b** possessed moderate antiinflammatory activity[59].

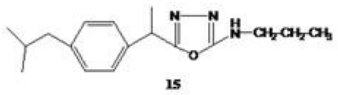


Mohammad Amir *et al* synthesized 5-(4-hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazoles and evaluated them for their biological activity. The treatment of 4-hydroxyphenylacetic acid with hydrazine hydrate in absolute ethanol gave 4-hydroxyphenyl acetic acid hydrazide. Further treatment with various aryl/alkyl isothiocyanates produce *N*-[2-(4-hydroxyphenyl)acetyl] *N*-aryl/alkyl-3-thiosemicarbazides, which were then and cyclized to form oxadiazole **14** in the presence of iodine and potassium iodide. Of all the synthesized compounds, 5-(4-hydroxyphenyl)methyl-2-aryl/alkylamino-1,3,4-oxadiazole **14** exhibited significant antiinflammatory activity with 77.77 %, due to the presence of a 4-methoxyphenylamino group at the second position of the oxadiazole ring[60].



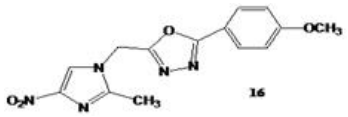
Mohammad Amir *et al* synthesized novel derivatives of ibuprofen 1,3,4-oxadiazoles by cyclization of 2-(4-*i*-butylphenyl) propionic acid hydrazide and *N*-[2-(4-*i*-butylphenyl)-propionyl]-*N*-alkyl/aryl-thiosemicarbazides. All these compounds evaluated for antiinflammatory activity and less ulcerogenic activity, compared to ibuprofen, through the severity index 0.5 to 0.8, *vs.* ibuprofen 1.8. They found that compound **15** {5-[1-(4-isobutyl-phenyl)-ethyl]-[1,3,4]oxadiazol-2-yl}-propyl-amine showed significant antiinflammatory activity which

is comparable to standard drug ibuprofen. The significant activity is due to the presence of *n*-propyl amine[61].



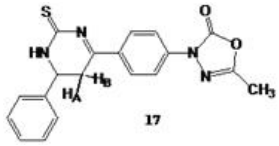
15

Priya V Frank *et al* synthesized a series of 1,3,4-oxadiazole derivatives containing nitroimidazole, moiety and evaluated them for their antiinflammatory activity, using formalin-induced rat paw oedema method. Microwave irradiation of 2-methyl-4-nitro-1-imidazo-acethydrazide with suitable carboxylic acids, in the presence of phosphorous oxychloride, afforded 5-aryl-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles. They found that 2-(4-methoxy-phenyl)-5-(2-methyl-4-nitro-imidazol-1-ylmethyl)-[1,3,4]oxadiazole **16** was the most potent compound of this series, with good yield[62].



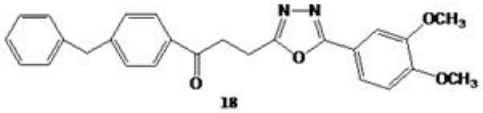
16

R. R. Kamble *et al* synthesized novel 1,3,4-oxadiazole derivatives, and tested them for their antiinflammatory activity. Bromination of *P*-acetylphenylsydnone, in presence of acetic acid, gave 4-bromo-3-(p-acetyl)-phenylsydnone at room temperature. Further treatment with aromatic aldehydes gave 4-bromo-3-[*P*-(3'-aryl-acryl-1'-oyl)] phenylsydnone, in presence of acetic anhydride. 1,3-Dipolar cycloaddition, by the elimination of bromine, afforded 5-methyl-3-[*P*-(3'aryl-acryl-1'-oyl)-phenyl]-3*H*-Δ^4-2-oxo-1,3,4-oxadiazole. By the nucleophilic addition of amino group and intermolecular dehydrative cyclization, they synthesized the final compound 5-methyl-3-[*P*-(6'-aryl-2'-thioxo-1',2',5',6'-tetrahydropyrimidin-4'-yl)-phenyl]-3*H*-2-oxo-Δ^4-1,3,4-oxadiazole. Compound **17** was to found have an excellent antiinflammatory activity[63].



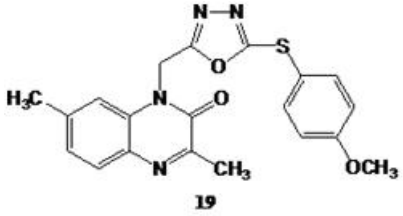
17

Asif Husain *et al* synthesized novel derivatives of 1,3,4-oxadiazole. The condensation reaction of diphenylmethane and succinic anhydride, in the presence of aluminium chloride, gave ß-(4-benzylbenzoylpropionic acid), followed by Friedel-Craft's acylation reaction. On further treatment with aryl acid hydrazides, in the presence of phosphorus oxychloride, 1-(4-bezylphenyl)-3-(5-substituted-1,3,4-oxadiazole-2-yl)-1-propanone was obtained. From biological evaluation of all the synthesized compounds, it was concluded that compound **18** possessed good antiinflammatory activity[64].



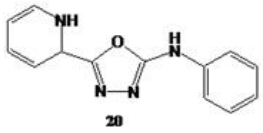
18

Shivananda Wagle *et al* synthesized novel 2-(3-methyl-7-substituted-2-oxoquinoxalin-yl)-5-(aryl)-1,3,4-oxadiazole compounds, and evaluated them for their potent antiinflammatory activity. Of all the synthesized compounds, 1-[5-(4-methoxy-phenylsulfanyl)-[1,3,4] oxadiazol-2-ylmethyl]-3,7-dimethyl-1H-quinoxalin-2-one **19** showed maximum antiinflammatory activity[65].



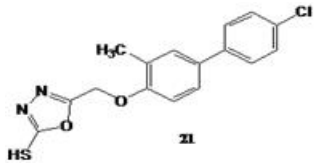
19

F. A. Omar *et al* synthesized novel substituted 1,3,4-oxadiazole derivatives, and evaluated them for their potent antiinflammatory activity. They found that compound [5-(1,2-dihydro- pyridin-2-yl)-[1,3,4]oxadiazol-2-yl]-phenyl-amine **20** exhibited good antiinflammatory activity[66].



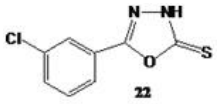
20

Sudha *et al* synthesized 5-(4-aroyl)-aryloxy-methyl-2-thiol-1,3,4-oxadiazole derivatives, and evaluated for their antiinflammatory activity. Biological evaluation of the synthesized compounds showed that 5-(4'-chloro-3-methyl-biphenyl-4-yloxymethyl)-[1,3,4]oxadiazole-2-thiol **21** was the most potent compound, as compared to other synthesized drugs. These compounds also showed good antibacterial, antifungal and diuretic activity[67].



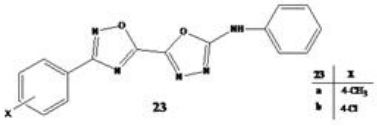
21

Saxena *et al* synthesized novel series of 1,3,4-oxadiazole derivatives and screened them for their antiinflammatory activity. They found that the compound 5-(3-chloro-phenyl)-3H-[1,3,4] oxadiazole-2-thione **22**, containing 3-chloro group showed potent antiinflammatory activity[68].



22

Jose M. dos Santos Filho *et al* synthesized novel oxadiazole derivatives containing two oxadiazole rings (1,2,4 and 1,3,4 oxadiazoles). The treatment of 1,2,4-oxadiazole carbohydrazides with phenyl isothiocyanate led to the formation of compound **23**, via an intermediate thiosemicarbazide derivative. Compounds **23a** and **23b** showed good antiinflammatory activity amongst all the synthesized compounds[69].



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CONCLUSION

This review article mainly focused on potent antiinflammatory activity of 1,3,4-oxadiazoles with lesser side-effects, which has global therapeutic and clinical importance. 1,3,4-Oxadiazole derivatives also show various important pharmacological activities and are widely used for preparation of medicinal active compounds. This activity is exploited for awaking the safe use of this important chemical moiety with minimal or no ulcerogenic activity in future. This summarized study would be useful for the researchers working in this field.

REFERENCES

1. Rajak H., Kharya M.D. and Mishra P., Biologically active 2,5-disubstituted-1,3,4-oxadiazoles, Inter. J. Pharm. Sci. and Nanotech. 2, 2009, 21.
2. Sharma S., Sharma P.K., Kumar N. and Dudhe R., A Review: oxadiazole their chemistry and pharmacological potentials, Der Pharma Chemica. 2, 2010, 253.
3. Kumar A., Singh S., Verma M., Saxena A.K. and Shanker K., Potent anti-inflammatory 2-(o-hydroxyphenyl)-5-(p-dimethylamino phenyl)-1,3,4-oxadiazoles. Ind. J. Pharm. Sci. 49, 1987, 201.
4. Mullican M.D., Wilson M.W., Connor D.T., Kostlan C.R., Schrier D.J. and Dyer R.D., Design of 5-(3,5-di-tert-butyl-4-hydroxyphenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, nonulcerogenic antiinflammatory agents, J. Med. Chem. 36, 1993, 1090.
5. Nargund L.V.G., Reddy G.R.N. and Hariprasad V., Anti-inflammatory activity of substituted 1,3,4-Oxadiazoles, J. Pharm. Sci. 83, 1994, 246.
6. Burbuliene M.M., Jakubkiene V., Mekuskiene G., Udrenaite E, Smicius R. and Vainilavicius P., Synthesis and anti-inflammatory activity of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones, IL Farmaco. 59, 2004, 767.
7. Bhardwaj N., Saraf S.K., Sharma P. and Kumar P., Syntheses, Evaluation and characterization of some 1, 3, 4-oxadiazoles as antimicrobial agents, Eur. J. Chem. 6, 2009, 1133.
8. Toliwal S.D., Jadav K., Gupte A. and Banu A., Synthesis and biological evaluation of phenyl hydrazides and their derivatives from Rice bran oil, Der Pharma Chemica. 1, 2009, 185.
9. Chawla R., Arora, Parameswaran M.K., Sharma P.C., Michael S. and Ravi T.K., Synthesis of novel 1,3,4-oxadiazole derivatives as potential antimicrobial agents, Acta Poloniae Pharm. Drug Res., 67, 2010, 247.
10. Fuloria N.K., Singh V., Shaharyar M. and Ali M., Synthesis and antimicrobial evaluation of some new oxadiazoles derived from phenylpropionohydrazides, Molecules. 14, 2009, 1898.
11. Islam M., Siddiqui A.A., Rajesh R., Bakht A. and Goyal S., Synthesis and antimicrobial activity of some novel oxadiazole derivatives, Acta Poloniae Pharm. Drug Res. 65, 2008, 441.
12. Mayekar A.N., Synthesis and antimicrobial studies on new substituted 1,3,4-oxadiazole derivatives bearing 6-bromonaphthalene moiety, Inter. J. Chem. 2, 2010, 38.
13. Omar M.A.A., Synthesis and antimicrobial activity of new 5-(2-thienyl)-1,2,4-triazoles and 5-(2-thienyl)-1,3,4-oxadiazoles and related derivatives, Molecules. 15, 2010, 502.
14. Yang G.F, Liu Z.M. and Qing X.H., Synthesis of 5,7-dimethyl-2-(5-substituted-1,3,4-oxadiazole-2-yl)-methylenethio-1,2,4-triazolo[1,5-a]pyrimidines as potential fungicides, Chin. Chemi. Lett. 12, 2001, 877.
15. Kaur H., Kumar S., Singh I. and Kumar A., Synthesis, characterization and antibacterial activity of various substituted oxadiazolylpyrazolinyl/isoxazolinylcoumarin derivatives, Inter. J. Pharm. Sci. and Res. 1, 2010, 58.
16. Shailaja M., Anitha M., Manjula A. and Rao B.V., Synthesis and biological activity of novel 2,5-disubstituted-1,3,4-oxadiazoles, Ind. J. Chem. 49B, 2010, 1088.
17. Parameswaran M.K., Ravi T.K., Subbuchettiar G., Synthesis of coumarin heterocyclic derivatives with antioxidant activity and *in vitro* cytotoxic activity against tumour cells, Acta Pharm. 59, 2009, 159.
18. El-Sayed W.A., El-Essawy F.A., Ali O.M., Nasr B.S., Abdalla M.M. and Abdel-Rahman A.A., Anti-HIV activity of new substituted 1,3,4-oxadiazole derivatives and their acyclic nucleoside analogues, Z. Naturforsch. 6, 2009, 773.
19. Dewangan D., Pandey A., Sivakumar T., Rajavel R. and Dubey R.D., Synthesis of some novel 2, 5- disubstituted 1, 3, 4-oxadiazole and its analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activity, Inter. J. Chem. Tech. Res. 2, 2010, 1397.
20. Yar M.S. and Akhter W.M., Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives, Acta Poloniae Pharm. Drug Res. 66, 2009, 393.
21. Zarghi A., Hamedi S., Tootooni F., Amini B., Sharifi B., Faizi M., Tabatabai S.A. and Shafiee A., Synthesis and Pharmacological Evaluation of New 2-Substituted-5-{2-[(2-halobenzyl)thio)phenyl}-1,3,4-oxadiazoles as Anticonvulsant Agents, Sci. Pharm. 76, 2008, 185.
22. Ramazani A. and Souldozi A., Iminophosphorane-mediated one-pot synthesis of 1,3,4-oxadiazole derivatives, ARKIVOC (xvi), 2008, 235.
23. Padmavathi V., Reddy S.N. and Mahesh K., Synthesis, antimicrobial and antioxidant activities of sulfone linked bis heterocycles—pyrazolyl oxadiazoles and pyrazolyl thiadiazole, Chem. Pharm. Bull. 57, 2009, 1376.
24. Rajasekaran S., Rao G.K., Sanjay Pai. S. and Vedavathy J., Microwave assisted synthesis of some 5-pyridyl-2-[(N-substituted phenyl) thioacetamido]-1,3,4-oxadiazoles as antibacterial and antioxidant agents, J. Chem. Pharm. Res. 2, 2010, 101.
25. Pattan S.R., Rabara P.A., Pattan J.S., Bukitagar A.A., Wakale V.S. and Musmade D.S., Synthesis and evaluation of some novel substituted 1,3,4-oxadiazole and pyrazole derivatives for antitubercular activity, Ind. J. Chem. 48B, 2009, 1453.
26. Siddiqui A.A., Islam M. and Kumar S., Synthesis and antituberculostic activity of 5-{3'-oxo-6'-(substituted phenyl)-2',3',4',5'-tetrahydropyridazin-2'-yl}methyl-2-substituted 1,3,4-oxadiazole, Der Pharmacia Lettre. 2, 2010, 319.
27. Aydogan F., Turgut Z. and Ocal N., Synthesis and electronic structure of new aryl- and alkyl-substituted 1,3,4-oxadiazole-2-thione derivatives, Turk. J. Chem. 26, 2002, 159.
28. Joshi S.D., Vagdevi H.M., Vaidya V.P. and Gadaginamath G.S., 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. 43, 2008, 1989.
29. Muthumani P., Meera R., Agarwal S.B., Devi P., Kameswaric B. and Muthuppandi R., Synthesis of some derivatives of pyrimidine, oxadiazole and indole in combination by conventional and microwave method, Der Pharma Chemica. 1, 2009, 167.
30. Jagrut V.B., Netankar P.D., Jawale D.V., Mane R.A. and Jadhav W.N., An efficient synthetic route for new 1,3,4-oxadiazoles having sulphonamido pharmacophore, Bull. Korean Chem. Soc. 30, 2009, 2812.
31. Shetgiri N.P. and Nayak B.K., Synthesis and antimicrobial activities of oxadiazoles, phthalazines and indolinones, Ind. J. Chem. 44B, 2005, 1267.
32. Nagalakshmi G., Synthesis, antimicrobial and antiinflammatory activity of 2,5-disubstituted-1,3,4-oxadiazoles, Ind. J. Pharm. Sci. 70, 2008, 49.
33. Roman G., Agache C., Manciulea I., Comanita E. and Dumitrescu L., Synthesis of new mannich bases derived from 5-phenyl-1,3,4-oxadiazole-2-thione and investigation of the conformational isomers of dimethyl 5-(5-phenyl-2-thioxo-1,3,4-oxadiazole-3-methylamino) isophthalate Revue Roumaine de Chimie. 52, 2007, 1103.

34. Kulkarni V.S., Lele M.D., Gavitre B.B., Patil M.D., Bobe K.R., Gaikwad D.T., Oxadiazole: a new profile of biological activities, Inter. J. Drug Formul. & Res. 1, 2010, 134.
35. Shaban M.A.E., Nasr A.Z. and El-Badry S.M., Synthesis and biological activities of some 1,3,4-oxadiazoles and bis (1,3,4-oxadiazoles), J. Islam. Acad. Sci. 4, 1991,184.
36. Gudasi K., Patil M., Vadavi R., Shenoy R. and Patil S., 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, J. Serb. Chem. Soc. 72, 2007, 357.
37. Husain A., Sarafroz M. and Ahuja P., 2-[3-(4-chloro/ethyl phenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles: synthesis and biological evaluation, Acta Poloniae Pharm. Drug Res. 65, 2008, 527.
38. Lee C.H., Cho H.I. and Lee K.J., Synthesis of 1,3,4-oxadiazoles having phenol or thiophenol group, Bull. Korean Chem. Soc. 22, 2001, 1153.
39. Khan K.M., Ullah Z., Rani M., Perveen S., Haider S.M., Choudhary M.I., Rahman A. and Voelter W., Microwave-assisted synthesis of 2,5-disubstituted-1,3,4-oxadiazoles, Letters in Org. Chem. 1, 2004, 50.
40. Bhattacharya J., Patel K., Tailor P., Karthikeyan, Moorthy, N S H N and Trivedi P., Design, synthesis and characterization of novel 1 ,3,4-oxadiazole dimers from benzoic acids, Int. J. ChemTech Res. 2, 2010, 2055.
41. Rigas B., The use of nitric oxide-donating nonsteroidal anti-inflammatory drugs in the chemoprevention of colorectal neoplasia, Current Opinion in Gastroenter. 23, 2007, 55.
42. Agrawal N.M., Epidemiology and prevention of non-steroidal anti-inflammatory drug effects in the gastrointestinal tract, Brit. J. Rheum. 34, 1995, 5.
43. Gene E., Calvet X., Moron A. and Iglesias M.L., Recommendations for the use of anti-inflammatory drugs and indications for gastrointestinal protection in emergency departments, Emergencias. 21, 2009, 295.
44. Rostom A., Dube C., Lewin G., Tsertsvadze A., Barrowman N., Code C., Sampson M. and Moher D., Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. preventive services task force, Annal. Inter. Med, 146, 2007, 376.
45. Dhikav V., Singh S. and Anand K.S., Newer non-steroidal anti-inflammatory drugs – a review of their therapeutic potential and adverse drug reactions, J. Ind. Acad. Clinic. Med. 3, 2002, 332.
46. Graham D.Y., Agrawal N.M., Campbell D.R., Haber M.M., Collis C., Lukasik N.L. and Huang B., Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs, Archiv. Inter. Med., 162, 2002, 169.
47. Venerito M., Wex T. and Malfertheiner P., Nonsteroidal anti-inflammatory drug-induced gastroduodenal bleeding: risk factors and prevention strategies, Pharmaceutic. 3, 2010, 2225.
48. Lanas A., Garcia-Rodriguez L.A., Arroyo M.T., Bujanda L., Gomollon F., Forne M., Aleman S., Nicolas D., Feu F., Gonzalez-Perez A., Borda A., Castro M., Poveda M.J. and Arenas J., Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants, Am. J. Gastroenterol. 102, 2007, 507.
49. Lanza F.L., Chan F.K.L. and Quigley E.M.M., Guidelines for prevention of NSAID-related ulcer complications, Am. J. Gastroenterol. 104, 2009, 728.
50. Rainsford K.D., Comparative studies of gastric ulcerogenesis by non-steroid anti-inflammatory drugs: effects of fenclofenac, Proc. roy. Soc. Med. 70, 1977, 4.
51. Kramer J.B., Boschelli D.H., Connor D.T., Kostlan C.R., Kuipers P.J., Kennedy J.A., Wright C.D., Bornemeier D.A. and Dyer R.D., Cyclooxygenase and 5-lipoxygenase inhibitory activity of 2,6 di-*t*-butylphenols linked by a sulfur atom to 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, Bioorg. & Med. Chem. Lett. 3, 1993, 2827.
52. Husain A., Ahmad F.J., Ajmal M. and Ahuja P., Synthesis of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]propan-1-ones as safer anti-inflammatory and analgesic agents, J. Serb. Chem. Soc. 73, 2008, 781.
53. Husain A. and Ajmal M., Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties, Acta Pharm. 59, 2009, 223.
54. Rajak H., Kharya M.D. and Mishra P., Synthesis of some Novel 2, 5-Disubstituted 1, 3, 4-Oxadiazole and its Analgesic, Anti-Inflammatory, Anti-Bacterial and Anti-Tubercular Activity, Yakugaku Zasshi. 127, 2007, 1757.
55. Bhandari S.V., Bothara K.G., Raut M.K., Patil A.A., Sarkate A.P. and Mokale V.J., Design, synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel s-substituted phenacyl-1,3,4-oxadiazole-2-thiol and schiff bases of diclofenac acid as nonulcerogenic derivatives, Bioorg. & Med. Chem. 16, 2008, 1822.
56. Husain A., Ahmad A., M.M. Alam M.M., Ajmal M. and Ahuja P., Fenbufen based 3-[5-(substituted aryl)-1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-ones as safer antiinflammatory and analgesic agents, Eur. J. Med. Chem., 44, 2009, 3798.
57. Chawla P., Maheshwari R. and Saraf S.A., Synthesis and evaluation of anti-inflammatory and antimicrobial activity of 2,5-disubstituted-1,3,4-oxadiazoles, Der Pharma Chemica. 2, 2010, 38.
58. Ravindra K.C., Vagdevi H.M., Vaidya V.P. and Padmashali B., Synthesis, anti-inflammatory and antimicrobial activities of 1,3,4-oxadiazoles linked to naptho[2,1-*b*]furan, Ind. J. Chem. 45B, 2006, 2506..
59. Amir M., Javed S.A. and kumar H., Synthesis of some 1,3,4-oxadiazoles derivatives as potential anti-inflammatory agents, Ind. J. Chem. 46B, 2007, 1014.
60. Amir M., Javed S.A. and Kumar H., Synthesis of some newer analogues of 4-hydroxyphenyl acetic acid as potent anti-inflammatory agents, J. Chine. Chem. Soc. 55, 2008, 201.
61. Amir M. and Kumar S., Synthesis and evaluation of anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation properties of ibuprofen derivatives, Acta Pharm. 57, 2007, 31.
62. Frank P.V., Girish K.S. and Kalluraya B., Solvent-free microwave-assisted synthesis of oxadiazoles containing imidazole moiety, J. Chem. Sci. 119, 2007, 41.
63. Kamble R.R. and Sudha B.S., Synthesis and pharmacological screening of 5-methyl-3-[*p*-(6'aryl-2'-thioxo-1',2',5',6'-tetrahydro-pyrimidin-4'-yl)-phenyl]-3*H*-2-oxo-δ^4-1,3,4-oxadiazoles, Ind. J. Pharm. Sci. 68, 2006, 249.
64. Husain A., Ahuja P. and Sarafroz M., Synthesis and biological evaluation of ß-aroyl propionicacid based 1,3,4-oxadiazoles, Ind. J. Pharm. Sci. 71, 2009, 62.
65. Wagle S., Adhikari A.V. and Kumari N.S., Synthesis of some new 2-(3-methyl-7-substituted-2-oxoquinoxalinyl)-5-(aryl)-1,3,4-oxadiazoles as potential nonsteroidal antiinflammatory and analgesic agents, I. J. Chem. 47B, 2008, 439.
66. Omar F.A., Mahfouz N.M. and Rahman M.A., Synthesis of substituted 1,3,4-oxadiazole derivatives and screened them for anti-inflammatory activity, Eur. J. Med. Chem. 31, 1996, 819.
67. Sudha B.S., Shashikanth S., Khanum S.A. and Sriharsha S.N., Synthesis and pharmacological screening of 5-(4-aroyl)-aryloxy-methyl-2-thio-1,3,4-oxadiazole, Ind. J. Pharm. Sci. 65, 2003, 465.
68. Saxena S., Verma M., Saxena A.K. and Shanker K., 1,3,4-oxadiazole thiones as inflammation inhibitors, Ind. J. Pharm. Sci. 54, 1, 199).
69. Filho J.M., Lima J.G., Leite Lucia F.C.C., Synthesis, characterization, and anti-inflammatory evaluation of 1,2,4-oxadiazoles combined with thiosemicarbazide and 1,3,4-oxadiazole moieties, J. Heterocy. Chem. 46, 2009, 722.

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