

ANTI-INFLAMMATORY ACTIVITY OF 1, 3, 4-OXADIAZOLE DERIVATIVES COMPOUND

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ABSTRACT

Oxadiazole derivatives play vital role in biological field such as, Anti-microbial, Anti-viral, Anti-tubercular, Anti-inflammatory, Anti-convulsant activity and Antioedema. Therapeutic significance of these clinically useful drugs in treatment of inflammation encouraged the development of some more potent and significant compounds. Oxadiazole derivatives are remarkably effective compounds for inflammation and analgesic activity. Extensive biochemical and pharmacological studies have confirmed that these molecules are effective in inflammation. This comprehensive overview summarizes the chemistry of different derivatives of substituted oxadiazole along with their anti-inflammatory activity. Differently substituted oxadiazole moieties have also been found to have other interesting activities such as anti-hepatitis B viral activities.

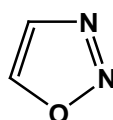
Keywords: Oxadiazole derivatives, Anti-inflammatory activity.

INTRODUCTION

Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for new therapeutic molecules. Compounds having a five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or in older furadiazoles. Oxadiazole is considered to be derived from furan by replacement of two methane group (CH=) by two pyridine type nitrogen (-N=)

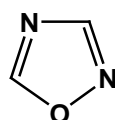
called as furadiazoles. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles. Out of these 1, 3, 4-oxadiazoles are found to be most potent biologically.

A large number of 1,3,4-oxadiazole derivatives have been found to exhibit various biological activities such as Anti-Inflammatory, Antimicrobial, Anticancerous, Anticonvulsant, antihypertensive etc^[1].



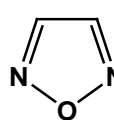
1,2,3-oxadiazole

(1)



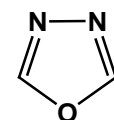
1,2,4-oxadiazole

(2)



1,2,5-oxadiazole

(3)



1,3,4-oxadiazole

(4)

Inflammation

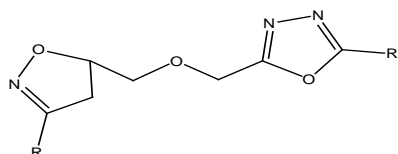
Inflammation is a response of a tissue to injury, often injury caused by invading parasites. The potent mediators of inflammation are derivatives of arachidonic acid a 20-carbon unsaturated fatty acid produced from membrane phospholipids. The principal pathways of arachidonic acid metabolism are the 5-lipoxygenase pathway, which produces a collection of leukotrienes and the cyclooxygenase (COX) pathway, which produces prostaglandin. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain, this is the method of action of non-steroidal anti-inflammatory drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat acute or chronic inflammation and offer symptomatic pain relief. Conventional NSAIDs act by non-selective inhibition of cyclooxygenase (COX) enzymes, which are involved in prostaglandins (PGs) biosynthesis from arachidonic acid. There are at least two main mammalian COX isoforms, COX-1 and COX-2.

Constitutive COX-1 has a housekeeping function; including gastro-protective and kidney function regulation PGs, whereas COX-2 is induced in inflammatory cells and generate PGs that help mediate the inflammatory response. Classical NSAIDs such as Aspirin and Ibuprofen are selective inhibitors of COX-1 isoenzyme and cause gastric failure like bleeding and ulcer. In contrast, selective COX-2 inhibitors such as Celecoxib, Rofecoxib, and Valdecoxib exert anti-inflammatory and analgesic activity with markedly less gastrointestinal toxicity than the traditional NSAIDs^[2-6].

ANTI-INFLAMMATORY ACTIVITY

(1)-Compounds were screened for their anti-inflammatory and analgesic activities. Carrageenan induced edema assay in rats was performed to test the anti-inflammatory activity of compound E (a-g), out of these two compounds (E-d, and E-g,) showed significant activity. Among these compounds, the one dichlorophenyl derivatives, E-g showed more than 50% activity. E-g exhibited the highest activity^[7].



a: R=R1= 4-MeC6H4

b: R=R1= OMeC6H4

c: R=R1= 3,4,5-(OMe)3C6H2

d: R=R1= 3-O2NC6H4

e: R=R1= 4-O2NC6H4

f: R=R1= 4-ClC6H4

g: R=R1= 2,4-Cl2C6H3

Fig. 1: Dichlorophenyl Derivatives Compound E

NMR spectroscopy further confirms the structures E (a-g) as 2-(((4,5-dihydro-3-aryl-isoxazol-5-yl)methoxy)methyl)-5-aryl-1,3,4-oxadiazole. ¹H-NMR spectra of compound E (a) showed multiplet at δ 3.88–3.98 ppm and doublet of doublet at 4.29 ppm correspond to OCH₂ group attached to the 1,3,4-oxadiazole respectively.

Another multiplet at δ 5.10 corresponds to the methine proton. The ¹³C NMR and elemental analysis data further confirm the structures of E(a-g) exhibiting excellent anti-inflammatory activity.

(2)- A novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles have been synthesized from 3-(4-bromobenzoyl) propionic acid (**3**) with the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects (ulcerogenicity). Two compounds, 2-[3-(4-bromophenyl)propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole and 2-[3-(4-bromophenyl)propan-3-one]-5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazole with anti-inflammatory activity of 59.5 and 61.9%, respectively, were found to have comparable activity with that of indomethacin which showed 64.3% activity at the same dose of 20 mg kg⁻¹[8].

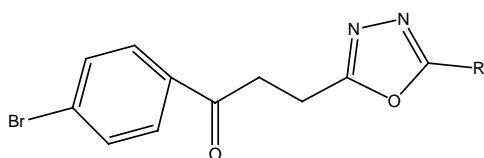


Fig. 2: 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles derivatives

(3)- Synthesis and results of anti-inflammatory activity in vivo of 5-[[2-disubstitutedamino-6-methylpyrimidin-4-yl]-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones and their S-alkyl-, N3-acyl- and N3-aminomethyl derivatives are described. All the tested compounds possess anti-inflammatory activity comparable to that of acetylsalicylic acid and some derivatives of 5-[[6-methyl-2-piperidin-1-yl pyrimidin-4-yl]-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thione were found to be much more active than ibuprofen[9].

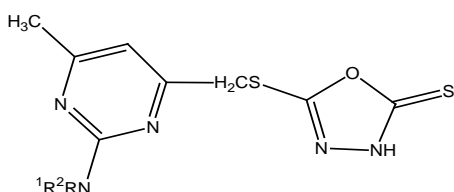


Fig. 3: 5-[[6-methyl-2-piperidin-1-yl pyrimidin-4-yl]-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thione derivatives

(4)- A series of 1,3,4-oxadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid were synthesized compounds activity, anti-inflammatory activity, analgesic activity and lower ulcerogenic potential. All compounds were evaluated for their anti-inflammatory activity by the carrageenan induced rat paw edema test method. The Compound was evaluated as the lead compound having inflammatory activity (81.81%) than the reference drug (79.54%), low ulcerogenic more anti-potential and protective effect on lipid peroxidation[10].

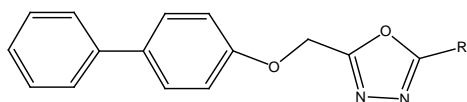


Fig. 4: 1,3,4-oxadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid derivatives

(5)- The synthesis of 5-(6-methyl-2-substituted 4-pyrimidinylloxymethyl)-2,3 dihydro-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives and the results of anti-inflammatory activity in vivo are described. Most of the tested compounds exhibited anti-inflammatory activity and some of them were more active than acetylsalicylic acid[11].

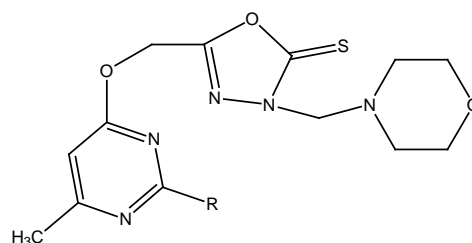


Fig. 5: 5-(6-methyl-2-substituted 4-pyrimidinylloxymethyl)-2,3 dihydro-1,3,4-oxadiazole-2-thiones Derivatives

(6)- It was observed that compounds having 4-chlorophenylpiperazin-4-ylmethyl (**5h**) and 4-fluorophenylpiperazin-4-ylmethyl also showed good activity, viz. 71.09% and 68.71%, respectively [12].

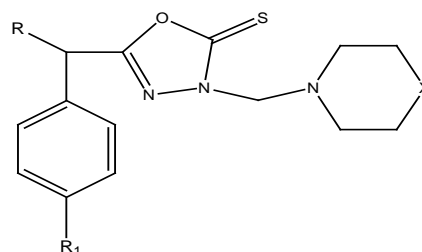


Fig. 6: 4-chlorophenylpiperazin-4-ylmethyl derivatives

(7)- Various derivatives of aroylpropanoic acid containing oxadiazole nucleus were successfully synthesized and screened for anti-inflammatory, analgesic, ulcerogenic activities and lipid peroxidation studies. Some of the synthesized compounds were very

safe with anti-inflammatory and analgesic activities comparable to ibuprofen. The results obtained support the statement that the synthesized compounds may be used as safer anti-inflammatory agents[13].

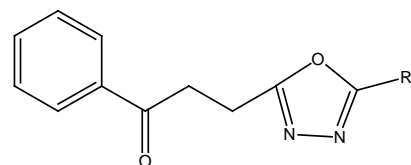


Fig. 7: Various derivatives of aroylpropanoic acid containing oxadiazole

(8)- All the newly synthesized compounds are screened for their anti-inflammatory and analgesic activities. All the compounds have shown anti-inflammatory activity ranging from 10.8 to 40.8% at the dose of 50 mg/kg, p.o. In addition of anti-inflammatory activity these compounds have also exhibited analgesic activity in the ranging from 8.6 to 33.5% at the dose of 50 mg/kg, i.p.[14].

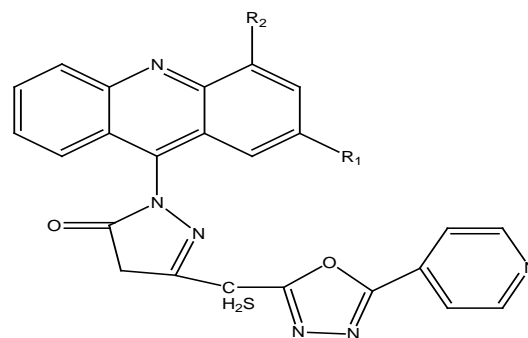


Fig. 8: Substituted acridinyl pyrazoline derivatives

(9)- Sixteen 1-(2-naphthylloxyacetyl)-4-substituted-3-thiosemicarbazide, 2-(2-naphthylloxy methyl)-5-substitutedamino-1,3,4-oxadiazole, 2-(2-naphthylloxy methyl)-5-substitutedamino-

1,3,4 thiadiazole and 5-(2-naphthylloxymethyl)-4-substituted-1,2,4-triazole-3-thione derivatives have been prepared and evaluated as orally active anti-inflammatory agents with reduced side-effects^[15].

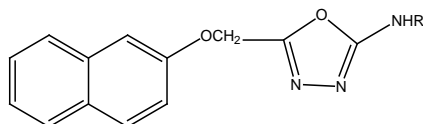
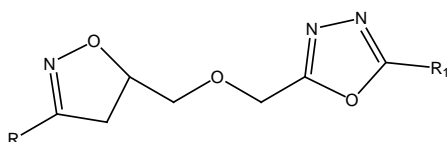


Fig.9: 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones derivatives

(10)- A series of novel ether-linked bis(heterocycle)s. All the synthesized compounds were screened for anti-inflammatory and analgesic activities. **7d** and **7g**, showed excellent activity against ibuprofen and aspirin^[16].

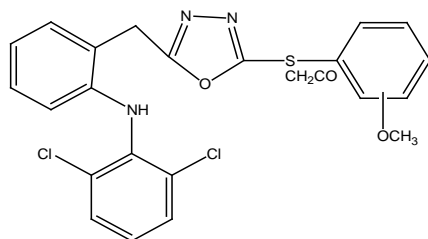


7d: R,R' = 3-O₂NC₆H₄

7g: R,R' = 2,4-Cl₂C₆H₃

Fig. 10: Ether-linked bis(heterocycle) 1,3,4-oxadiazoles derivatives

(11)- a series of S-substituted phenacryl 1,3,4-oxadiazole and Schiff bases derived from 2-[(2,6-dichloroanilino) phenyl] acetic acid (diclofenac acid). Total eighteen compounds were synthesized and out of those only eight were found to have significant anti-inflammatory activity with significant analgesic activity in acetic acid induced writhing models with no ulcerogenic activity. Among those eight active compounds **3k** and **4b** found to have most prominent and consistent anti-inflammatory activity^[17].

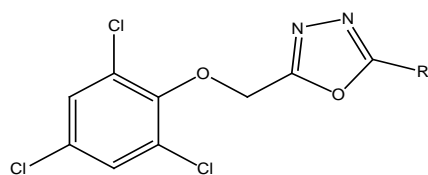


Compound 4b

Compound 3k

Fig. 11: S-substituted phenacryl 1,3,4-oxadiazole and Schiff bases derivatives

(12)- A series of new 1,3,4-oxadiazole derivatives and 1,2,4-triazine-5-one derivatives. All the compounds were screened for their Anti-inflammatory activity by using carrageenin-induced rat paw edema method. Compounds **2d** and **2j** among all the synthesized compounds showed maximum anti-inflammatory activity^[18].



2d: R = 2,4-dichlorophenyl

2j: R = 1-(4-isobutylphenyl)ethyl

Fig. 12: 1,3,4-oxadiazole derivatives and 1,2,4-triazine-5-one derivatives

(13)- The Anti-inflammatory activity of the synthesized compounds were evaluated in vivo by the carrageenan induced paw oedema method in rat. The compounds were tested at an oral dose of 100 mg/kg of body weight, and were compared with the standard drug (Indomethacin) at 1st, 2nd, 3rd and 4th hour of inflammation induction by carrageenan treatment^[19].

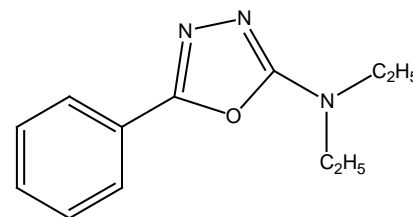
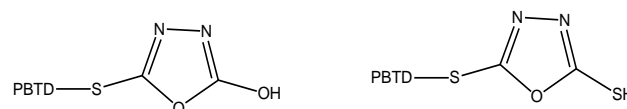


Fig.(13). Diethyl-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine

Fig. 13: Diethyl-(5-phenyl-[1,3,4]oxadiazol-2-yl)-amine

(14)- Some 1,3,4-oxadiazole derivatives has found to exert their anti-inflammatory effect via cyclooxygenase and 5-lipoxygenase inhibitory activity^[20].



DTBP = 3,5-di-tert-butyl-4-hydroxyphenyl.

Fig. 14: 1,3,4-oxadiazole derivatives

(15)- One of the important factor responsible for GI damage is local irritation by carboxylic acid moiety. On the other hand, it has been reported in literature that compounds bearing 1,3,4-oxadiazole nucleus possess significant anti-inflammatory activity. Replacement of the carboxylic acid group of diclofenac with 1,3,4-oxadiazole nucleus in novel compounds, resulted in appreciable anti-inflammatory activity in carrageenan-induced rat paw edema test^[21].

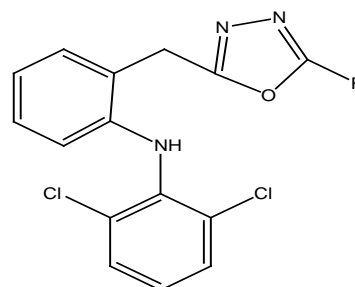


Fig. 15: 2-[(2,6-dichloroanilino)phenyl]acetic acid derivatives.

(16)- Some new 2-thio-3-(substituted-aminomethyl)-5-(3,5-dinitrophenyl)-1,3,4-oxadiazoles has been found to possess considerable anti-inflammatory property^[22].

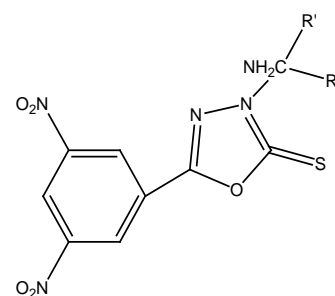


Fig. 16: 2-thio-3-(substituted-aminomethyl)-5-(3,5-dinitrophenyl)-1,3,4-oxadiazoles

(17)- With the aim of discovering dual inhibitors of 5-lipoxygenase (LO) and cyclooxygenase (CO) with improved pharmacokinetic properties, a series of 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,3,4-oxadiazoles were designed and synthesized^[23].

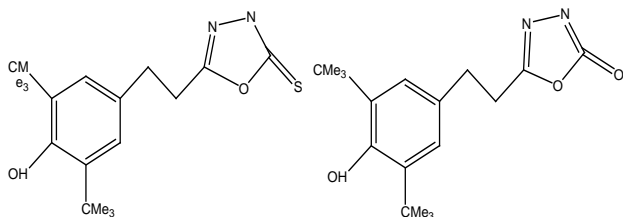
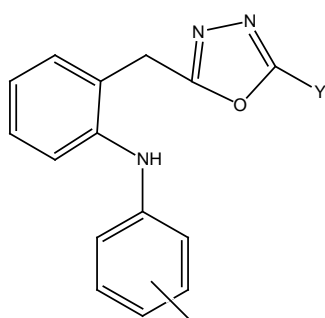


Fig. 17: 5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,3,4-oxadiazoles

(18)- The replacement of carboxylic acid functionality of several fenamates (N-arylanthranilic acid) with 1,3,4-oxadiazole nucleus resulted in dual inhibitors of CO and LO when tested in an intact rat basophilic leukemia (RBL-1) cell line. These heterocyclic analogs of flufenamic acid are also active in carrageenan-induced rat foot pad edema (CFE), a model of acute inflammation^[24].



Y = OH, SH, NH₂, NHCN

Fig. 18: 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole analogs of the fenamates

(19)- A number of 2-(2-naphthylloxymethyl)-5-substituted amino-1,3,4-oxadiazoles were synthesized for their anti-inflammatory activity^[25].

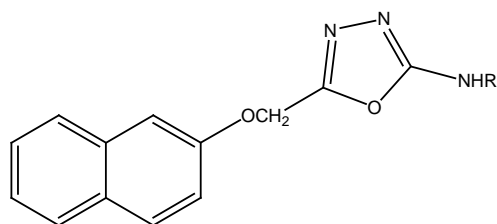


Fig. 19: 2-(2-naphthylloxymethyl)-5-substituted amino-1,3,4-oxadiazoles derivatives

(20)- The anti-inflammatory evaluation of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones found that some of these derivative were much more potent than ibuprofen^[26].

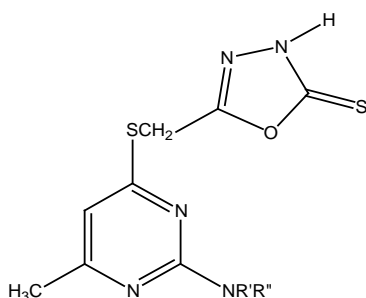


Fig. 20: 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones derivatives

(21)- Most of the compounds of series 5-(6-methyl-2-substituted-4-pyrimidyloxymethyl)-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives exhibited anti-inflammatory activity and moreover some of them were more active than acetylsalicylic acid^[27].

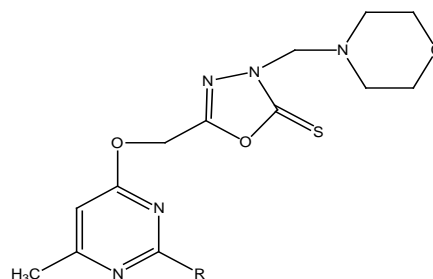


Fig. 21: 5-(6-methyl-2-substituted-4-pyrimidyloxymethyl)-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives

(22)- Some 5-(4-pyridyl)-4-(substituted methyl)-1,3,4-oxadiazoline-2-thione hydrochloride has also been found to possess anti-inflammatory activity^[28].

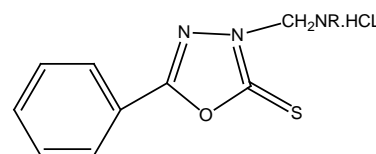


Fig. 22: 5-(4-pyridyl)-4-(substituted methyl)-1,3,4-oxadiazoline-2-thione hydrochloride

(23)- Potent anti-inflammatory activity has been reported in 2-(substituted aryl)-5-(substituted phenyl)-1,3,4-oxadiazoles^[29].

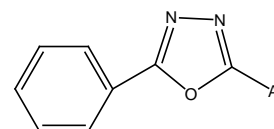


Fig. 23: 2-(substituted aryl)-5-(substituted phenyl)-1,3,4-oxadiazoles derivatives

(24)- Some 3-pentadecylphenol derivatives containing the 1,3,4-oxadiazole nucleus has been found to have good anti-inflammatory activity^[30].

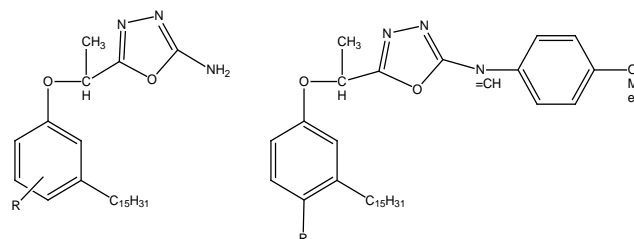


Fig. 24: α -(3-pentadecylaryloxy)-propionic acids, their hydrazides and cyclic derivatives: oxadiazoles and pyrroles

(25)- Anti-inflammatory potential of substituted oxadiazoles i.e. 2-aryl amino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles were reflected by their ability to provide 36 to 76% protection in carrageenan induced rat paw edema method^[31].

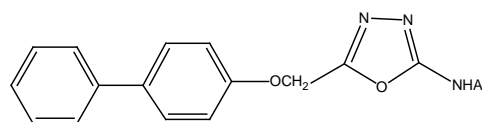


Fig. 25: 2-aryl amino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles derivatives

(26)- A series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives were also evaluated for their anti-inflammatory activity [32].

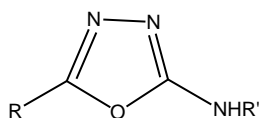


Fig. 26: 2,5-disubstituted 1,3,4-oxadiazole derivatives

(27)-2-arylamino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles on pharmacological screening as anti-inflammatory activity exhibited 10 to 76% protection in carrageenan-induced rat paw edema [33].

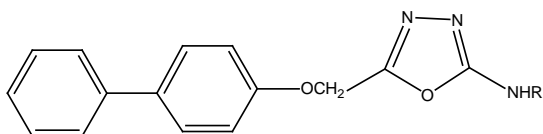


Fig. 27: 2-arylamino-5-(4-biphenoxymethyl)-1,3,4-oxadiazoles derivatives

(28)- Two novel series of compounds *i.e.*, 1,3,4-oxadiazole and oxadiazoline analogues were synthesized for their potential antiinflammatory activities, using the carrageenan-induced rat paw edema method and cotton pellet-induced granuloma method. Some compounds demonstrated marked antiinflammatory activities. They concluded that in general, all the oxadiazoles have greater antiinflammatory activity than their corresponding oxadiazoline analogues [34].

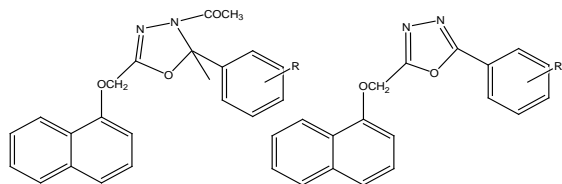


Fig. 28: 1,3,4-oxadiazole and oxadiazoline analogues derivatives

DISCUSSION

1, 3, 4-Oxadiazole are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, and as raw material for drug synthesis. The advances in the use of 1,3,4-Oxadiazole for organic synthesis during the last twenty-five years, as well as a survey of its biological and pharmacological properties are reported in this review and in the accompanying supplementary information. The survey of the literature revealed that, 1,3,4-Oxadiazole is a versatile lead molecule for designing potential bioactive agents, and its derivatives were reported to possess broad-spectrum anti-inflammatory, anticonvulsant, anxiety activities. Further we can conclude that many other derivatives of can 1,3,4-Oxadiazole be synthesized which will be expected to show potent pharmacological activities.

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