Review Article

REVIEW ON ANTI-INFLAMMATORY POTENTIAL OF 1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT

Anti-inflammatory agents act by inhibiting inflammatory mediators such as prostaglandins, prostacyclins, cytokines, thromboxane, histamine, bradykinins, cyclooxygenases (COX-I and COX-II). These inflammatory agents are involved in producing inflammatory responses upon tissue injuries caused by trauma, bacteria, heat, toxins and which may lead to leakage of fluid from the blood vessels into tissues causing swelling. Chronic inflammation may also arise from imbalance between production and elimination of reactive oxygen species. 1,3,4-oxadiazoles possesses potent anti-inflammatory activity. To improve safety profile of these anti-inflammatory drugs derivatization is necessary. So that they can be tagged or derived to synergise the anti-inflammatory property.

Keywords: 1,3,4-Oxadiazoles, anti-inflammatory, COX, prostaglandins, cytokines, thromboxane.

INTRODUCTION

The inflammatory response occurs when tissues are injured by bacteria, trauma, toxins, heat *etc.,* The damaged cells release chemicals including histamine, bradykinin and prostaglandins. These chemicals cause blood vessels to leak fluid into the tissues causing swelling. When there is an oxidative stress due to imbalance between production and elimination of reactive oxygen species chronic inflammation is observed.[1]

Inflammation can be treated most commonly by non-steroid anti-inflammatory drugs through inhibition of cyclooxygenases. These are also used to treat analgesia and pyrexia. some of inflammatory mediators are prostaglandins, prostacyclins, cytokines, thromboxane *etc*., Cyclooxygenases (COXs) are involved in the biosynthesis of prostaglandins. There are two isoforms of COX such as COX-1 and COX-2. COX-1 plays a vital role in physiological homeostasis whereas COX-2 in inflammatory response and which resides in the site of inflammation.[4,11]

Pathogenesis of different human diseases such as diabetes, cancer, atherosclerosis, diabetic nephropathy *etc.,* are very closely related to oxidative stress and inflammation and are found to be life threatening. Heterocyclic compounds like oxadiazoles with five membered nuclei are known to possess many useful biological activities such as anti-tubercular, anticancer, antiparkinsonian, antihyperlipidemic, antihypertensive, hypoglycemic, anticonvulsant and these compounds possess unique anti-inflammatory activity and anti-edema action indicating that oxadiazole pharmacophore possess potential scavenging activity.[5,2,3,12]

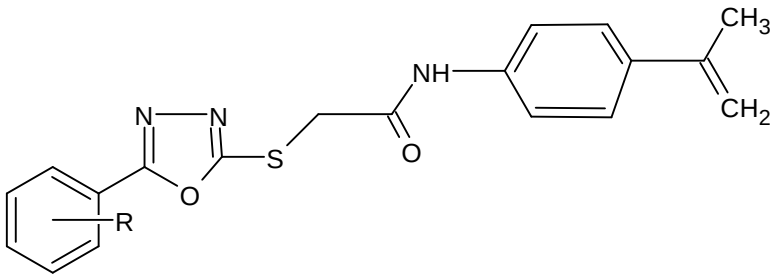
In view of the biological importance of 1,3,4-oxadiazole pharmacophore in inflammatory diseases, the present study summarizes the anti-inflammatory potential of 1,3,4-oxadiazole derivatives.

- Husain A, Ajmal M synthesised novel 1,3,4-oxadiazole derivatives and evaluated for their biological activity of anti-inflammatory using carrageenan induced paw oedema method on wistar rats. Indomethacin was used as standard drug. The test 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-dimethoxy phenyl)-1,3,4-oxadiazole have showed comparable anti-inflammatory activity of 59.5% and 61.9% respectively with indomethacin as it showed 64.3% of activity at the same oral dose of 20mg kg^{-1}. There was improved anti-inflammatory activity remarkably due to presence of 3,4--dimethoxyphenyl or 4-chlorophenyl or with the substitution of these groups at the 5^{th} position of 1,3,4-oxadiazole ring. They conclude

that further studies are required on quantitative structure activity relationship to get more information.[2]

- Mohan Sahoo B, Chandra Dinda S, Ravi Kumar BV, Panda J, S Brahmkshatriya P have carried out green synthesis of Schiff base of 1,3,4-oxadiazole and their analogues and evaluated for anti-inflammatory activity. While designing these compounds they selected cyclooxygenase-2(COX-2) from the protein data bank, with the use of UCSF DOCK 6.5 program and carried out the docking study. They concluded that better binding of drug is observed with the protein target at high score. QSAR studies revealed that there was an influenced anti-inflammatory activity greatly on positioning substituents on phenyl ring. Anti-inflammatory activity was carried out using carrageenan induced paw oedema method and indomethacin as standard drug.[3]

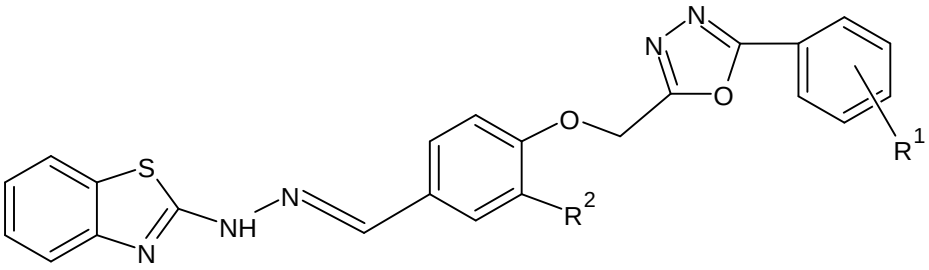
- Abd-Ellah HS, Abdel-Aziz M, Shoman ME, Beshr EA, Kaoud TS, Ahmed AS synthesized novel 1,3,4-oxadiazole hybrids and investigated for anti-inflammatory activity. The activity is carried out by carrageenan induced paw oedema method and indomethacin as a standard drug. The synthesized different compounds they exhibited significant anti-inflammatory activity when compared with the indomethacin. Compound 7d had shown 70% reduction of inflammation whereas compound 7a exhibited anti-inflammatory activity of 120% compared to indomethacin at 4th hour. Among the different test compounds of 1,3,4-oxadiazole hybrids, anti-inflammatory activity was decreased from 100% to 86% by the addition of electron withdrawing groups and upon addition of electron releasing groups also decreased activity from 100% to 78%.[4]



7a-e

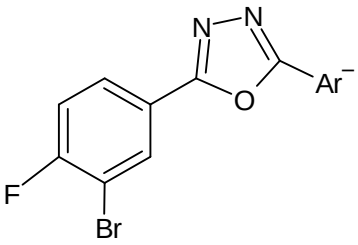
R= a:H; b:4-cl; c:4-methoxy; d:3,4-dimethoxy; e:3,4,5-trimethoxy

- Zheng XJ, Li CS, Cui MY, Song ZW, Bai XQ, Liang CW, Wang HY, Zhang TY synthesized benzothiazole derivatives containing 1,3,4-oxadiazole nucleus and evaluated for their biological activities in which anti-inflammatory activity is one. They synthesized two different series of benzothiazole derivatives linked with 1,3,4-oxadiazole moiety in which a compound **8h** had shown better inhibition of inflammation than indomethacin at the same dose. They rationalised the compound **8h** by molecular docking as it was exhibited COX-2 inhibition, in which its magnitude of inhibition is more similar to COX-2 inhibitors than the reference drug celecoxib. Therefore, their results had shown the compound **8h** is promising potent anti-inflammatory agent in the prevention of inflammatory diseases.[5]

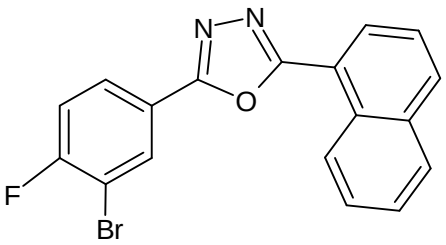


8h

- Chawla G, Kumar U, Bawa S, Kumar J synthesized 1,3,4-oxadiazole derivatives and evaluated for anti-inflammatory activity by carrageenan induced paw oedema method and ibuprofen as a standard drug. The study showed that anti-inflammatory activity can be increased by introducing halogen atoms to the aryl ring system. When the aryl system was introduced with the fluorine at para position of aryl ring which is at 5th position of 1,3,4-oxadiazole nucleus, the obtained compound **4a** exhibited increased anti-inflammatory activity from 23.75% to 34.66% and when the aryl ring was replaced with naphthyl ring, the compound obtained **4b** had shown highest anti-inflammatory activity of 35.36%.[6]

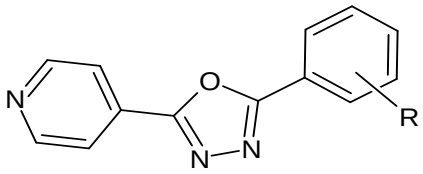


4a



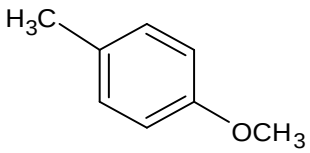
4b

- Biju CR, Ilango K, Prathap M, Rekha K synthesized 1,3,4-oxadiazole derivatives by microwave-assisted methods and evaluated for anti-inflammatory activity. By selecting the compounds which obeyed the Lipinski rule of five into the wet lab, they synthesized nine different analogues and characterised these analogues of 1,3,4-oxadiazole using spectrometric analysis such as UV, IR, ^{1}H NMR. They screened five analogues among nine different analogues for anti-inflammatory activity by carrageenan-induced rat paw oedema method and indomethacin as a standard drug. In which, the compounds 2a, 2c and 2i had shown good anti-inflammatory activity of 67.71%, 68.60% and 61.43% respectively.[7]

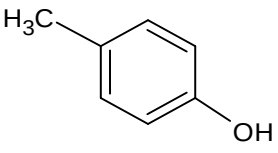


1,3,4-oxadiazole analogues

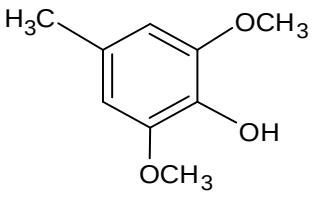
Where, R= 2a,2c,2i



2a



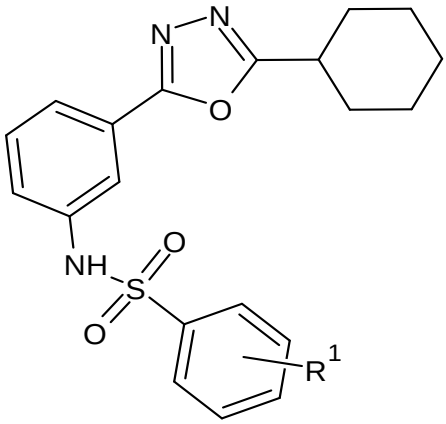
2c



2i

- Kavitha S, Kannan K, Gnanavel S synthesized 2,5-substituted-1,3,4-oxadiazole derivatives. These derivatives were characterized and evaluated for *in-vitro* anti-inflammatory activity by albumin denaturation method. There were fifteen compounds (6a-c, 7a-i, 8a-c) synthesized and screened for anti-inflammatory activity. In these, compounds 6a, 6c and 8b had shown good

anti-inflammatory activity, whereas 6b, 7a, 7c,7g and 7i had shown moderate anti-inflammatory activity. Other than these compounds possessed mild anti-inflammatory activity. Based on structure activity relationship, sulphonamide upon substitution in the 1,3,4-oxadiazole ring enhanced the anti-inflammatory activity.[9]



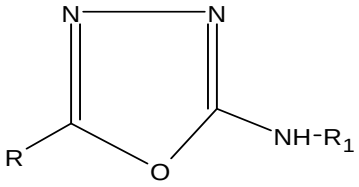
- Jayashankar B, Rai KL, Baskaran N, Sathish HS synthesized 1,3,4-oxadiazole which bears bis(heterocycle) derivatives and evaluated for anti-inflammatory activity by carrageenan-induced paw oedema method and ibuprofen as a standard.[10]

- Abd-Ellah HS, Abdel-Aziz M, Shoman ME, Beshr EA, Kaoud T, Ahmed AS designed and synthesized 1,3,4-oxadiazole hybrids and evaluated for anti-inflammatory activity by carrageenan-induced paw oedema method and indomethacin as standard. Most of the compounds which have been synthesized had shown significant reduction in the inflammation.[11]

- Durgashivaprasad E, Mathew G, Sebastian S, Reddy SM, Mudgal J, Nampurath GK synthesized and evaluated 2,5-disubstituted-1,3,4-oxadiazoles for anti-inflammatory activity by carrageenan-induced paw oedema method. They were synthesized two derivatives OSD and OPD as they produced significant effect of inhibition of oedema compared to control. OSD had shown activity comparable to ibuprofen at 100mg/kg as OSD has shown 60% of inhibition of oedema and OPD produced 32.5% of reduction in oedema. They also performed CAF(complete Freund's adjuvant) -induced arthritis in rats for chronic inflammation. In that, both paw oedema and NO levels were reduced by OSD and OPD at the concentration of 200mg/kg for 14 days. They suggested that they need pharmacokinetics for in-depth evaluation of these oxadiazoles.[12]

- Manjunatha K, Poojary B, Lobo PL, Fernandes J, Kumari NS synthesized some 1,3,4-oxadiazole derivatives and evaluated for biological activities in which anti-inflammatory is one. Anti-inflammatory activity was performed by carrageenan-induced paw oedema method and diclofenac as a standard. Their objective was to develop better anti-inflammatory compounds, therefore, 1,3,4-oxadiazole mannich bases were synthesized.[13]

- Omar FA, Mahfouz NM, Rahman MA synthesized some anti-inflammatory agents with a series of substituted 1,3,4-oxadiazole derivatives. They performed and evaluated anti-inflammatory activity by the use of Golikov's method and standard drug ibuprofen and injected histamine intradermally as phlogogenic substance with trypan blue (iv) as indicator. Anti-inflammatory activity of 1,3,4-oxadiazole derivatives by histamine induced oedema in the abdomen of rats was determined. The histamine induced oedema was significantly inhibited by 13 compounds of the oxadiazole derivatives as compared to ibuprofen. Some of the compounds such as 19a, 21a, 23b, 28c and 32d had shown potent and improved anti-inflammatory activity compared to ibuprofen and some of other derivatives of 1,3,4-oxadiazole with a substituent of *p*-tolyl group such as 22a, 26b, 30c and 34d were inactive under test conditions.[14]



19-34

- Bala S, Kamboj S, Saini V, Prasad DN studied molecular docking of N-phenyl anthranilic acid based 1,3,4-oxadiazole analogues using Molegro virtual docker and evaluated for anti-inflammatory activity by carrageenan induced paw oedema in rats and diclofenac as standard. Analogues of 1,3,4-oxadiazole (4e and 4f) had shown optimal anti-inflammatory activity.[15]

- Amir M, Saifullah K, Akhter W synthesized 1,3,4-oxadiazole derivatives of aryl acetic acid and evaluated for anti-inflammatory action by carrageenan induced paw oedema method and ibuprofen as standard drug. Some of which exhibited significant anti-inflammatory action are 5-(diphenyl-methyl)-2-(substituted phenyl)-1,3,4-oxadiazoles and 2-[(5-diphenyl-methyl-1,3,4-oxadiazol-2-yl)sulfanyl]-*N*-(substituted phenyl)-acetamides.[16]

- Palusa SK, HUdupi R, Sridhara AM synthesized a series of pyrimidine substituted 1,3,4-oxadiazole derivatives and evaluated for anti-inflammatory activity by carrageenan induced paw oedema method and ibuprofen as a standard.[17]

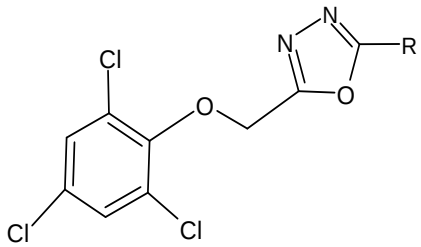
- El-Samii ZA synthesized some of novel 1,3,4-oxadiazole derivatives and evaluated for anti-inflammatory activity by carrageenan induced paw oedema method and phenylbutazone as standard.[18]

- Kashid BB, Salunkhe PH, Dongare BB, More KR, Khedkar VM, Ghanwat AA performed molecular docking studies and synthesized 2,5-disubstituted 1,3,4-oxadiazole derivatives. Further evaluated for anti-inflammatory activity by *invitro* method and diclofenac sodium as standard. 2,5-disubstituted 1,3,4-oxadiazole derivatives such as BK-12 to BK-23 had shown good to moderate anti-inflammatory activity when compared with standard diclofenac sodium.[19]

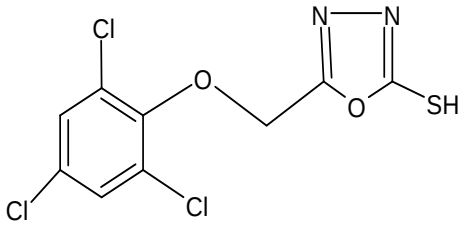
- Ujjwal S, Seth AK, Balaraman R designed and synthesized novel 1,3,4-oxadiazole derivatives with benzimidazole nucleus and evaluated for anti-inflammatory activity by *in-vitro* model i.e., inhibition of protein denaturation method and diclofenac sodium as a standard drug. Their results suggest that the derivatives 4-{1-[(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl) methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile, 4-{1-[(5-(3, 5-dichlorophenyl)-1,3,4-oxadiazol-2-yl) methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile, 4-{1-[(5-(2-bromo-4-trifluoromethyl) phenyl)-1,3,4-oxadiazol-2-yl) methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile and 4-{1-[(5-[2,3-dimethoxy-6-(1,3,4-oxadiazol-2-yl)phenol]methyl]-5-nitro-1*H*-benzimidazol-2-yl}benzonitrile had shown high activity of 64.98±1.154701 µg/ml, 67.59±0.8819171 µg/ml, 61.02±1.20185 µg/ml and 67.5±0.9865 µg/ml respectively at low concentrations compared to diclofenac sodium which was having standard activity at a concentration of 57.08±0.8819 µg/ml. The derivatives such as 4-{1-[(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile, 4-{1-[(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl) methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile, 4-{1-[(5-(3, 4-dichlorophenyl)-1,3,4-oxadiazol-2-yl) methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile, 4-{1-[(5-(4,5-difluoro-2-(1,3,4-oxadiazol-2-yl)phenol)methyl]-5-nitro-1*H*-benzimidazol-2-yl} benzonitrile, 4-{1-[(5-(2-chloro-4, 5-dimethoxyphenyl)-1, 3, 4-oxadiazol-2-yl) methyl]-5-nitro-1*H*-benzimidazol-2-yl}benzonitrile, 4-{1-[(5-(2-ethoxy-4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)methyl]-5-nitro-1*H*-benzimidazol-2-yl}benzonitrile and 4-{1-[(5-[3-ethoxy-4-(prop-2-yn-1-yloxy) phenyl]-1, 3, 4-oxadiazol-2-yl) methyl]-5-nitro-1*H*benzimidazol-2-yl}benzonitrile had shown moderate activity of 137.4±0.881917 µg/ml, 119.8±1.527525 µg/ml, 76.77±0.5773503 µg/ml, 86.48±0.5773503 µg/ml, 99.56±1.154701 µg/ml, 99.16±0.8819171 µg/ml and 100±0.5773503 µg/ml respectively at higher concentrations when compared with diclofenac sodium (57.08±0.8819) µg/ml.[20]

- Kumar H, Javed SA, Khan SA, Amir M synthesized 1,3,4-oxadiazole derivatives of biphenyl-4-yloxy acetic acid and evaluated for anti-inflammatory activity by carrageenan induced paw oedema method and standard drug flurbiprofen. The synthesized derivatives 2-8 *i.e.*, 5-[(biphenyl-4-yloxy)methyl]-2-substituted-1,3,4-oxadiazoles and the derivatives 15, 16 i.e., 5-[(biphenyl-4-yloxy)methyl]-2-alkyl/arylamino-1,3,4-oxadiazoles had shown percentage inhibition of oedema in the range of 15.90% to 79.54%. The derivative 7 i.e., 5-[(Biphenyl-4-yloxy)methyl]-2-[1-(4-isobutylphenyl)ethyl]-1,3,4-oxadiazole had shown anti-inflammatory activity with inhibition of oedema 77.27% which is similar to the standard drug flurbiprofen (79.54%).[21]

- Amir M, Javed SA, Kumar H synthesized some of new 1,3,4-oxadiazole derivatives and evaluated for anti-inflammatory activity by *in-vivo* model i.e., carrageenan induced rat paw oedema method by using ibuprofen as a standard. Ibuprofen have been showed inhibition of oedema about 86.36% and newly synthesized derivatives of 1,3,4-oxadiazole such 2a-n, 3 and 4 were compared with the standard ibuprofen at the same oral dose. After 4 hours, they have showed inhibition ranging from 50% to 72.72%. The derivatives 2d and 2j have shown optimum anti-inflammatory activity and introducing mercapto group(-SH) at the 5th position of the oxadiazole ring have shown significant activity of about 69.55% and rest of the derivatives with moderate activity.[22]



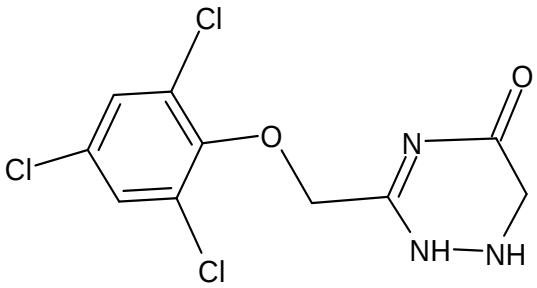
2a, 2j



3

Where, R= 2,4-dichlorophenyl → **2a**

R= 1-(4-isobutylphenyl) ethyl →**2j**



4

- Palaska E, Şahin G, Kelicen P, Durlu NT, Altinok G evaluated anti-inflammatory activity of synthesized 1,3,4-oxadiazole derivatives. They have performed air pouch test for 1,3,4-oxadiazole derivatives and it has shown significant inhibition of prostaglandin production as they reduced total number of exudates containing leukocytes.[23]

CONCLUSION

The present review reveals the fact of anti-inflammatory potential in various 1,3,4-oxadiazole derivatives as they inhibited carrageenan induced paw oedema and also significant inhibition of prostaglandins which are mediators of inflammation. From the observations of the above research work conducted it can be concluded that 1,3,4-oxadiazole moiety is showing the inhibition of various inflammatory reactions induced by histamine, bradykinin and other chemical mediators. Currently the drugs used to combat inflammatory diseases are associated with enormous side effects and these can be overcome by using 1,3,4-oxadiazole moiety bearing drugs after a thorough preclinical and clinical investigations of the reviewed compounds.

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