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BIOLOGICAL ACTIVITIES OF 1, 3, 4-OXADIAZOLE: A REVIEW

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ABSTRACT
Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules. Out of its four possible isomers, 1, 3, 4-oxadiazole is widely exploited for various applications. 1, 3, 4-Oxadiazole derivatives have a wide range of biological activities including antibacterial, antitubercular, vasodialatory , antifungal, cytotoxic, anti-inflammatory and analgesic, hypolipidemic, anticancer and ulcerogenic activities. This Review has basic information about 1,3,4-oxadiazole and its biological activitie work for further development in this field.

KEYWORDS: 1,3,4-oxadiazole, anti-inflammatory activity, anti-tubercular activity, antitumor activity, analgesic activity.

INTRODUCTION

Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules. Out of its four possible isomers, 1, 3, 4-oxadiazole is widely exploited for various applications. Oxadiazole (Oxazole) is the parent compound for a vast class of heterocyclic compounds. These are azoles with oxygen and Nitrogen. [1]

Oxadiazole is a five-member heterocyclic aromatic chemical compound having two carbons, two nitrogen, and one oxygen atoms and two double bonds having general formula $C_2H_2ON_2$. 1,2,4-Oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer.[2]

The electrophillic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom .The present manuscript specially emphasizes on chemistry, methods of synthesis and reactivity of 1, 3, 4-oxadiazole and its derivatives.[1]

The 1, 3, 4-oxadiazole undergoes number of reactions including electrophillic substitution, nucleophilic substitution, thermal and photochemical. The present review attempts to summarize the various routes of synthesis and the reactions of 1, 3, 4-oxadiazole and its derivatives and focus on their biological potential.

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene.[1]

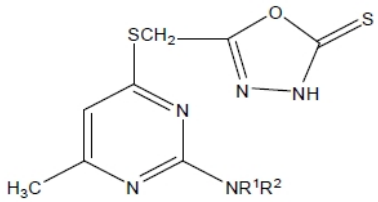
1, 3, 4-Oxadiazole derivatives exhibit a wide range of biological activities including antibacterial , antitubercular , vasodialatory, antifungal , cytotoxic , anti-inflammatory and analgesic , hypolipidemic , anticancer and ulcerogenic activities.[3]

Biological Activity

Anti-inflammatory Activity

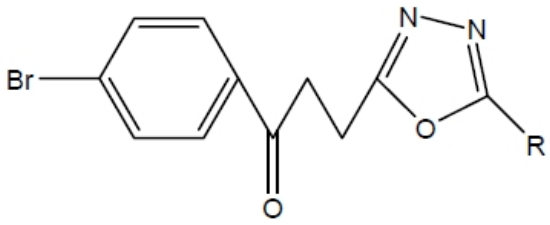
Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The two is forms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. Some evidences suggest that the hydrazones moiety present in some compounds possess a pharmacophoric character for the inhibition of COX. [4]

Milda Malvina Burbuliene *et al* 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-, *N*3-acyl- and *N*3- 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-ylpyrimidin-4-yl)-sulfanylmethyl]-3H-1, 3, 4- oxadiazole-2-thione were found to be much more active than ibuprofen. [5]



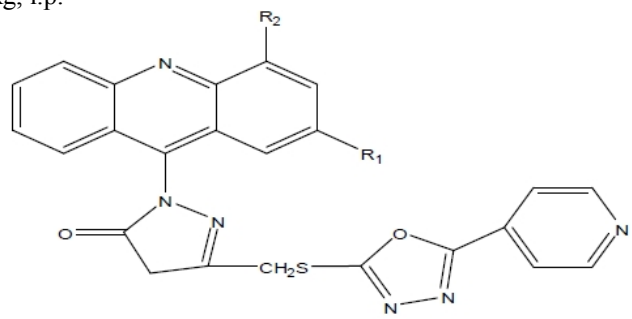
(1)

Asif Hussain *et al* reported a novel series of 2-[3-(4-bromophenyl)propan-3-one]-5- (substituted phenyl)-1,3,4-oxadiazoles and have been synthesized from 3-(4-bromobenzoyl)propionic acid with the aim to get better anti-inflammatory agents with minimum or without side effects. These were evaluated them for anti-inflammatory activity according to the method of Winter *et al*. on Wistar rats. One group was kept as a control and the animals of other groups were pretreated with test drugs (20 mg kg–1 body mass) given orally 30 minutes before carrageen an injection. The foot volume was measured before and 4 h after carrageen an injection with a plethysmograph. The mean increase in the paw volume in each group was calculated. Indomethacin used as standard drugs for comparison.[6]



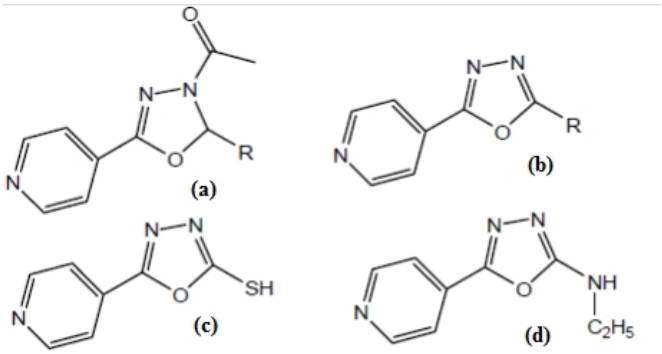
(2)

Trilok Chandra *et al* 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. [7]



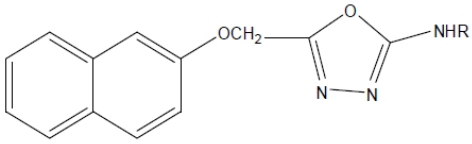
(3)

Dhansay Dewangan *et al* synthesized 4(a-d) using intermediate pyridine-4- Carbohydrazide. Schiff's base were obtained on treatment with various aromatic aldehyde, further on condensation with acetic anhydride produced the title compounds. They also synthesized derivative of 1, 3, 4 oxadiazole using same intermediate as above by different methods. They also studied SAR of these synthesized compounds .The 2-position and 5- position is an extremely important site of molecular modification, which play a dominant role in determining the pharmacological activities of 1,3,4-oxadiazole derivatives. The synthesized compounds were screened using carrageen an induced rat paw edema. Direct substitution of the 2- position with a -C_5H_4N and -2-COOH-C_6H_4, with pyridine in 5-position enhance the anti-inflammatory activity of 1, 3, 4-oxadiazole derivative. [8]



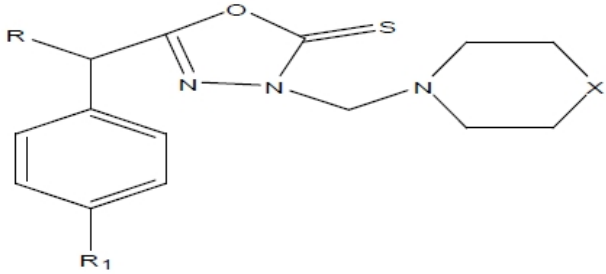
(4)

Erhan Palaska *et al* Sixteen 1-(2-naphthyloxyacetyl)-4-substituted-3- thiosemicarbazide, 2-(2-aphthyloxymethyl)-5-substitutedamino-1,3,4-oxadiazole,2-(2-naphthyloxymethyl) substituted amino-1,3,4 thiadiazole and 5-(2- naphthyloxymethyl)-4-substituted-1,2,4-triazole-3- thione derivatives have been prepared and evaluated as orally active anti-inflammatory agents with reduced side-effects.[9]



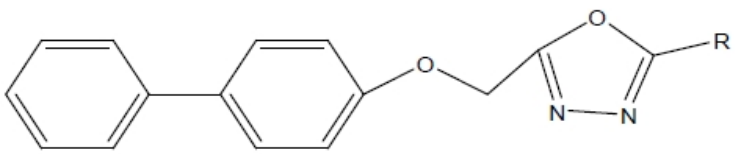
(5)

Manjunatha *et al* 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.[10]



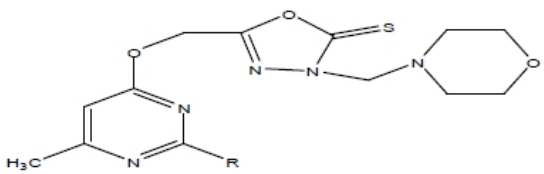
(6)

Harish Kumar *et al* 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 carrageen an 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.[11]



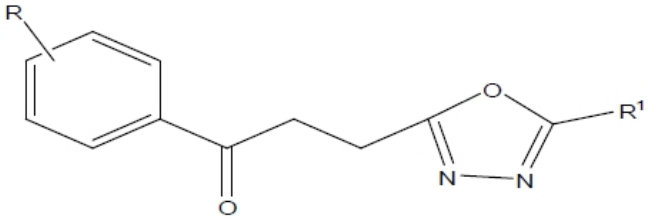
(7)

Virginija Jakubkiene *et al* The synthesis of 5-(6-methyl-2-substituted 4- pyrimidinyloxymethyl)-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. [12]



(8)

Mymoona Akhter *et al* 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]



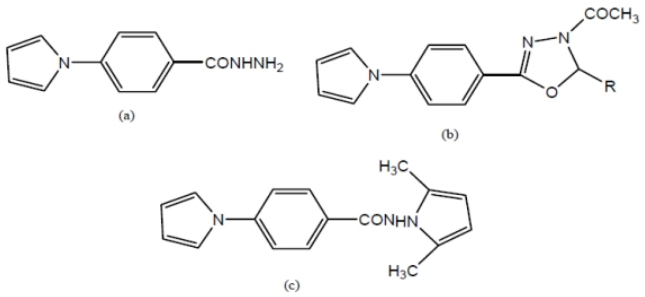
(9)

Anti-tubercular Activity

Tuberculosis, MTB, or TB (short for *tubercle bacillus*) is a common and in many cases lethal infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis*.[14] Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air when people who have an active MTB infection cough, sneeze, or otherwise transmit their saliva through the air.[15]

Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of those infected. The classic symptoms are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss (the last giving rise to the formerly prevalent colloquial term "consumption"). Infection of other organs causes a wide range of symptoms. Diagnosis relies on radiology (commonly chest X-rays), atuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. Social contacts are also screened and treated if necessary. Antibiotic resistance is a growing problem in (extensively) multi-drug-resistant tuberculosis. Prevention relies on screening programs and vaccination, usually with Bacillus Calmette-Guérin vaccine. Treatment for TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which makes many antibiotics ineffective and hinders the entry of drugs.[16,17,18,19] The two antibiotics most commonly used are isoniazid and rifampicin. However, instead of the short course of antibiotics typically used to cure other bacterial infections, TB requires much longer periods of treatment (around 6 to 24 months) to entirely eliminate mycobacteria from the body.[20] Latent TB treatment usually uses a single antibiotic, while active TB disease is best treated with combinations of several antibiotics, to reduce the risk of the bacteria developing antibiotic resistance.[21] People with latent infections are treated to prevent them from progressing to active TB disease later in life.

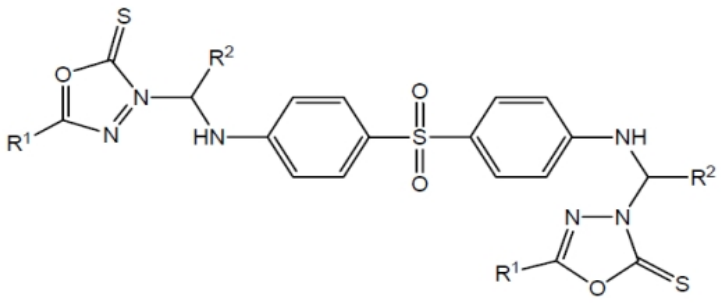
S.D. Joshi *et al* reported a novel series of 4-pyrrol-1-yl benzoic acid hydrazide (a) analogs derived 5-substituted-2-thiol-1,3,4-oxadiazoles (b), 5-substituted-4-amino-1,2,4-triazolin-3-thione and 2,5-dimethyl pyrroles (c) and these have been synthesized in good yields and characterized by IR, NMR, mass spectral and elemental analyses. These compounds were screened for antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method. compounds containing the 1,3,4-oxadiazoline ring and acetyl group, show better activity against M. tuberculosis H37Rv and compound 3 showed highest activity (MIC 16 mg/ml). They selected these compounds for further development to acquire more information about structure-activity relationships in their laboratories.[22]



(10)

Krishna Kant Jha *et al* reported 3D QSAR studies for the 41 molecules of 1,3,4-oxadiazoles by using k-Nearest Neighbor Molecular Field Analysis (kNN-MFA) combined with various selection procedures using kNN-MFA approach 3D-QSAR models were generated. This model can be used for preliminary screening of large diversified compound libraries. The model has shown that presence of sulphur is must for activity; however the larger bulky substituents reduce the activity. The presence of halogen and other non-halogen groups have also contributed to the activity. Hence the future schemes with smaller groups on sulphur and electronegative groups in the molecule would result in potentially active molecules.[23]

Mohamed Ashraf Ali *et al* have synthesized a series of oxadiazole mannich bases derivatives, dapsone and appropriate aldehyde in the presence of methanol. The reaction procedure is based on the condensation and ring closure reaction of appropriate acid hydrazide with carbondisulfide (CS_2). All the synthesized oxadiazole underwent condensation with appropriate aromatic aldehyde and dapsone in methanolic solution (reaction time varies from 8 to 22 h) affording titled mannich bases. The synthesized compounds were tested for their antimycobacterial activity in vitro against MTB and INHR-MTB by agar dilution method using double dilution technique. They reported that eleven compounds exhibited excellent antimycobacterial activity with MIC ranging from 0.1 to 5.96 lM. Among the synthesized compounds,3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1 3,4-oxadiazole-2- thione was found to be most potent compound and was 7.3-fold against MTB and 10.3-fold against INH resistant MTB more active than isoniazid. These antimycobacterial data clearly show that the presence of furfuryl with 2-naphthoxymethyl substitution at mannich bases causes remarkable improvement in Antitubercular activity against both M. tuberculosis H37Rv and INH resistant M. tuberculosis.[24]



(11)

Antitumor Activity

Tumors occur when cells divide excessively in the body. Typically, cell division is strictly controlled. New cells are created to replace older ones or to perform new functions. Cells that are damaged or no longer needed die to make room for healthy replacements. If the balance of cell division and death is disturbed, a tumor may form.

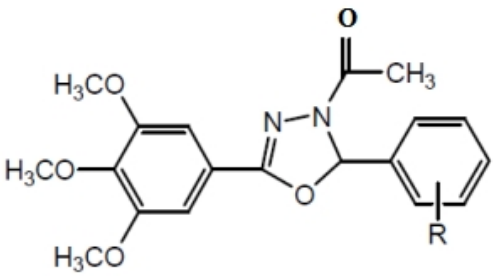
Problems with the body's immune system can lead to tumors. Treatment varies based on: The type of tumor, whether it is noncancerous or cancerous, and its location.

If the tumor is benign (meaning it has no potential to spread) and is located in a "safe" area where it will not cause symptoms or affect the function of the organ, sometimes no treatment is needed. Sometimes benign tumors may be removed for cosmetic reasons, however. Benign tumors of the brain may be removed because of their location or harmful effect on the surrounding normal brain tissue. If the cancer is in one location, the goal of treatment is usually to remove the tumor with surgery. If the tumor has spread to local lymph nodes only, sometimes these can also be removed. If all of the cancer cannot be removed with surgery, the options for treatment include radiation and chemotherapy, or both. Some patients need a combination of surgery, radiation, and chemotherapy. Lymphoma (cancer of the lymph glands) is rarely treated with surgery. Chemotherapy and radiation therapy are most often used for treating lymphoma.

A variety of antitumoral drugs are currently in clinical use. The search for antitumoral drugs led to the discovery of several 1,3,4-oxadiazol derivatives having antitumoral activity[25]

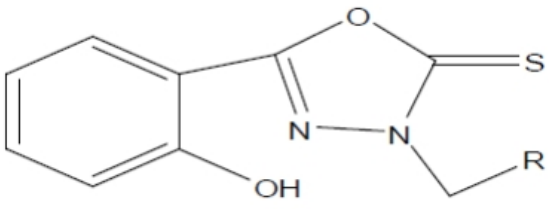
Baoan Song *et al* synthesized some 3-acetyl-2-substituted phenyl-5-(3,4,5 trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives. Among the synthesized compounds.

Maximum have highly active against PC3 cells and some are moderately active against Bcap37 and BGC823 cells. [26]



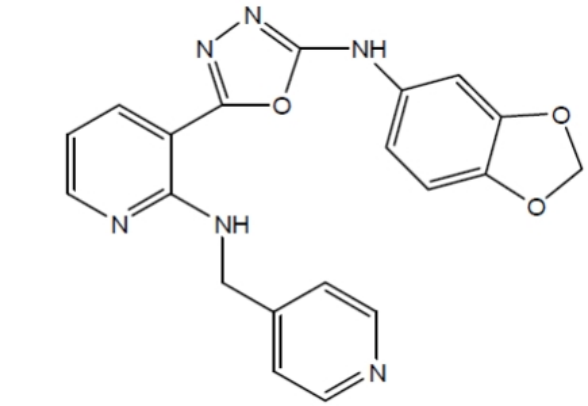
(12)

Ahmed S. Aboraia *et al* A series of 5-(2-hydroxyphenyl)-3-substituted-2,3- dihydro-1,3,4-oxadiazole-2-thione derivatives was synthesized and evaluated for their in vitro anticancer activity. These compounds have been selected for a full anticancer screening against a 60-cell panel assay where they showed non-selective broad spectrum and promising activity against all cancer cell lines. The active members in this study compared to 5- fluorouracil and cyclophosphamide as reference drugs, respectively. [27]



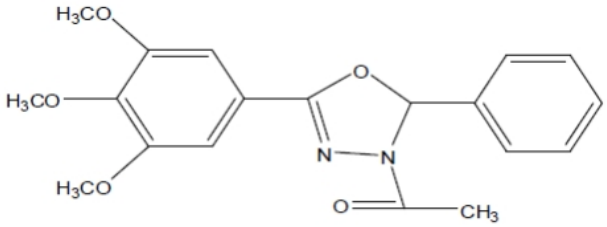
(13)

Xiaohu Ouyang *et al* synthesized derivatives of oxadiazoles and are evaluated for their ability to inhibit tubulin polymerization and to arrest mitotic division of tumor cells. Among the synthesized compounds, 14 showed potent activity [28]



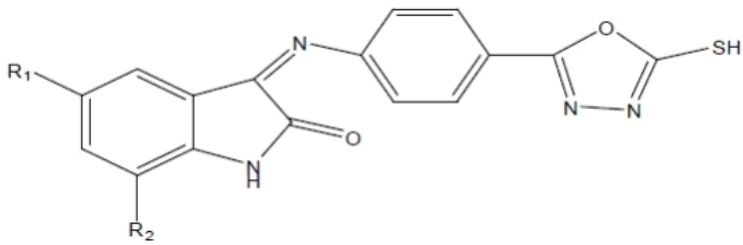
(14)

Linhong Jin *et al* Some,3-acetyl-2-substituted-phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives were synthesized by cyclization reaction of N^0-substituted benzylidene-3,4,5-trimethoxybenzo activities against some cancer cells in vitro by MTT method. [29]



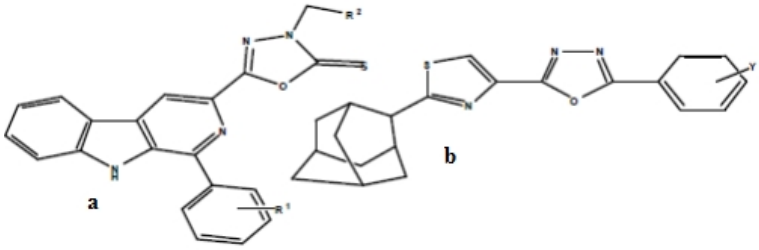
(15)

Rajyalakshmi Gudipati *et al* A series of 5-or 7-substituted 3-{4-(5-mercapto- 1, 3, 4-oxadiazol-2-yl)phenylimino}-indolin–2–one derivatives were synthesized by treating 5-(4- aminophenyl)-1,3,4-oxadiazole-2-thiol with different isatin derivatives.. All the synthesized derivatives were screened for anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependant inhibition of growth of the cells[30]



(16)

F.C. Savariz *et al* synthesized A novel series of 1-substituted phenyl-3-[3-alkylamino(methyl)-2-thioxo-1,3,4oxadiazol-5-yl] ß-carboline derivatives, 17 were found as potent antitumour agents were most promising derivatives, exhibiting a broad antitumor activity spectrum at GI50 and TGI levels, with GI50 (MG-MID) values of 5.89, 4.37 and 4.57 µ mol l-1 respectively Moreover, 1-Phenyl-3-[3-isopropylamino(methyl)-2-thioxo-1,3,4-oxadiazol- 5-yl]ß-carboline displayed cytotoxic efficacy with LC50 (MG-MID) value of60.49 µ mol l-1 .[31]

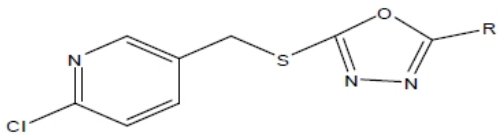


(17)

.**M.Zahid *et al*** synthesized A new series of combination of adamantanyl-1, 3-thiazole and 1,3,4-oxadiazole derivatives i.e., 2-(2-adamantyl-1,3-thiazol-4-yl)-5-(3-substituted phenyl)-1,3,4-oxadiazole, bearing various aryl groups has been synthesized and evaluated for *in-vitro* antiproliferative activity against a large panel of human tumor derived cell lines. [32]

Alex S. Kiselyov *et al* A series of novel 1, 3, 4-oxadiazole derivatives based on structural and electronic overlap with combretastatin have been designed synthesized and tested in vivo using the sea urchin embryo development assay. Monitored the effects of these agents on two specific developmental stages of the embryo, namely i) fertilized egg to assess antimitotic activity; ii) free swimming blastulae to detect behavioral changes in the embryo swimming pattern.[33]

Qing-Zhong Zheng *et al* A series of new 2-chloropyridine derivatives possessing 1, 3, 4-oxadiazole moiety were synthesized Antiproliferative assay results indicated that compounds exhibited the most potent activity against gastric cancer cell SGC-7901, which was more potent than the positive control.[34]



(18)

Analgesic Activity

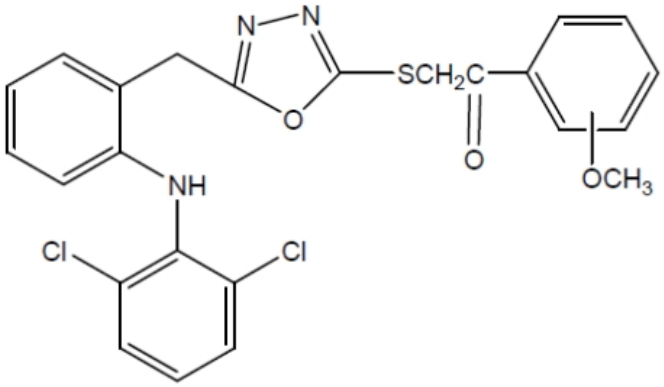
An analgesic (also known as a painkiller) is any member of the group of drugs used to relieve pain (achieve analgesia). The word *analgesic* derives from Greek *an-* ("without") and *algos* ("pain").

Analgesic drugs act in various ways on the peripheral and central nervous systems; they include paracetamol (para-acetylaminophenol, also known in the US as acetaminophen), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and opium. They are distinct from anesthetics, which reversibly eliminate sensation.

In choosing analgesics, the severity and response to other medication determines the choice of agent; the WHO pain ladder, originally developed in cancer-related pain, is widely applied to find suitable drugs in a stepwise manner.[35]

The analgesic choice is also determined by the type of pain: for neuropathic pain, traditional analgesics are less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as tricyclic antidepressants and anticonvulsants.[36]

Shashikant V. Bhandari *et al* synthesized 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 19 and 20 found to have most prominent and consistent anti-inflammatory activity. [37]



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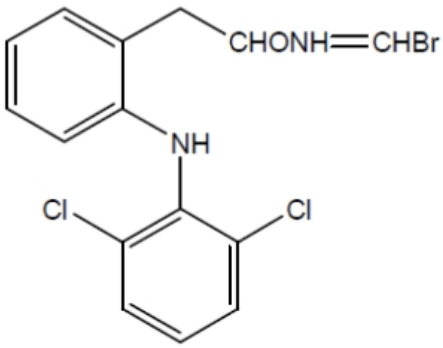
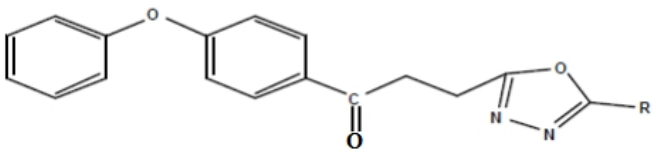


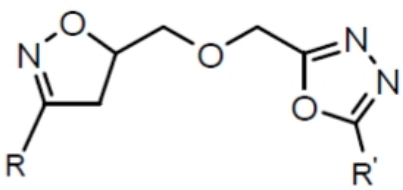
(20)

A. Husain *et al* synthesized a novel series of 1-(4-phenoxyphenyl)-3-[5-(substituted aryl)-1, 3, 4-oxadiazol- 2-yl] propan-1-ones, 21 derivatives showed significant analgesic activity in the acetic acid-induced writhing test. The 2-acetoxy phenyl derivative of this series has shown 76% protection in terms of analgesic activity which is higher even than standard drug indomethacin. [38]



(21)

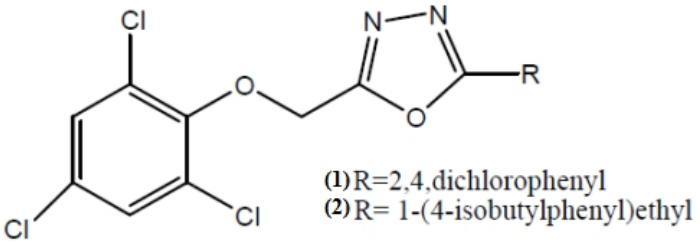
B. Jayashankar *et al* synthesized a series of novel ether-linked bis(heterocycle)s. All the synthesized compounds were screened for anti-inflammatory and analgesic activities. 22(1) and 22(2) showed excellent activity against ibuprofen and aspirin. [39]



(1) R,R'= 3-$O_2NC_6H_4$
(2) R,R'= 2,4-$Cl_2C_6H_3$

(22)

Mohd Amir *et al* synthesized a series of new 1,3,4-oxadiazole derivatives and 1,2,4-triazine-n5-one derivatives. All the compounds were screened for their Anti-inflammatory activity bynusing carrageenin-induced rat paw edema method. Compounds 22(1) and 22(2) among all thensynthesized compounds showed maximum anti-inflammatory activity. [40]



(23)

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