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Synthesis and Therapeutic Potential of Oxadiazole Scaffolds: A Comprehensive Review of Recent Advancements

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ABSTRACT

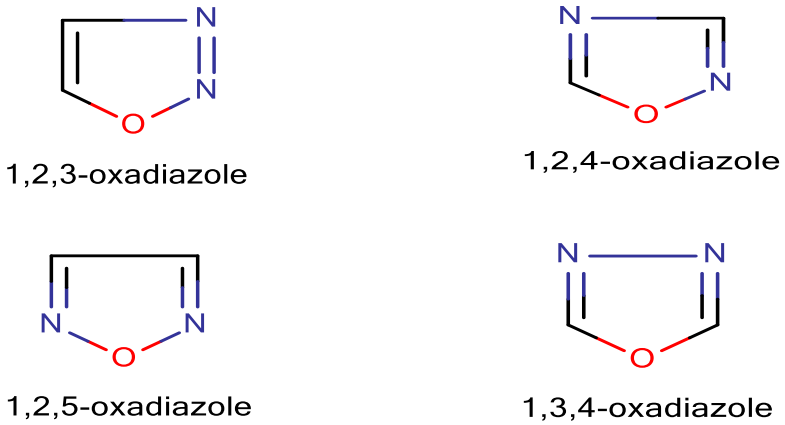
Oxadiazole is a versatile heterocyclic compound with a five-membered ring containing both oxygen and nitrogen, which has sparked significant interest in medicinal chemistry. The synthesis of oxadiazole derivatives typically involves the condensation of hydrazides with carbonyl compounds or other reactive intermediates under acidic or basic conditions. Common methods to form these compounds include cyclization reactions, Minnich-type reactions, and the use of catalysts such as phosphorous oxychloride and carbon disulfide (CS_2). Biologically, oxadiazole derivatives exhibit a broad range of pharmacological activities, including antimicrobial, anti-inflammatory, anticancer, and antidiabetic effects. They show strong antimicrobial activity against both Gram-positive and Gram-negative bacteria, as well as fungi, often exceeding the potency of standard antibiotics. In cancer research, oxadiazole derivatives inhibit tumour progression by targeting enzymes like telomerase and disrupting cell division mechanisms. Additionally, many of these compounds display significant anti-inflammatory properties, making them potential candidates for treating chronic inflammatory diseases like arthritis.

Keywords: *Heterocyclic compound, condensation, cyclization reaction, telomerase and inflammatory diseases etc*

1. INTRODUCTION

1, 3, 4-Oxadiazole is a five-membered heterocyclic aromatic compound containing two nitrogen atoms at positions three and four and one oxygen atom at position one. It is more thermally stable than other oxadiazoles and has gained importance in medicinal chemistry due to its diverse biological activities. The structure of oxadiazole exhibits a weak base characteristic due to the inductive effect of the heteroatoms. Replacing the two -CH= groups in furan with pyridine-like (-N=) groups reduces the aromaticity, making the ring behave like a conjugated diene. The oxadiazole ring is resistant to electrophilic substitution and nucleophilic attack, with substitutions occurring mainly at nitrogen if electron-releasing groups are present. Furazan (1, 2, 5-oxadiazole), with its oxygen and nitrogen atoms, is a related compound, often used in steroid derivatives like furazabol [1].

Table 1: Oxadiazole



SYNTHESIS AND BIOLOGICAL ASPECTS OF OXADIAZOLE SCAFFOLDS

1. ANTI INFLAMMATORY ACTIVITY

(i) Milda Malvina Burbuliene et al. synthesized 5-[(6-methyl-2-piperidine-1-yl-pyrimidine-4-yl)-sulfanyl methyl]-3H-1,3,4-oxadiazole-2-thione derivatives, including S-alkyl, N-acyl, and N3-amino ethyl, and evaluated them for anti-inflammatory activity [2].

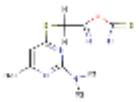


Fig-1

(ii) Asif Hussain et al. synthesized 2-[3-(4-bromo-phenyl) propane-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles from 3-(4-bromobenzoyl) propionic acid, demonstrating that 5-substituted phenyl groups with halogen or electron-withdrawing groups exhibited potent anti-inflammatory activity [3].

Fig-2

(iii) Mymoona Akhter et al. synthesized 2-[4-substituted phenyl)propane-3-one]-5-(4-substituted phenyl)-1,3,4-oxadiazole derivatives, screening them for anti-inflammatory, analgesic, ulcerogenic potential, and lipid peroxidation. Some derivatives showed better safety and efficacy than ibuprofen [4].

Fig-3

(iv) Harish Kumar et al. synthesized 5-[(biphenyl-4-yloxy)-methyl]-2-alkyl/aryl amino-1,3,4-oxadiazole derivatives, screening them for anti-inflammatory activity. Derivatives with specific substituted phenyl groups showed significantly increased anti-inflammatory activity [5].

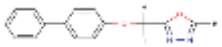


Fig-4

(v) Dhansay Dewangan et al. synthesized 1-[2-substituted-5-(pyridine-4-yl)-2,3-dihydro-1,3,4-oxadiazole-3-yl]-1-one using pyridine-4-carbohydrazide, evaluating the compounds for anti-inflammatory activity and establishing their structure-activity relationship (SAR) [6].

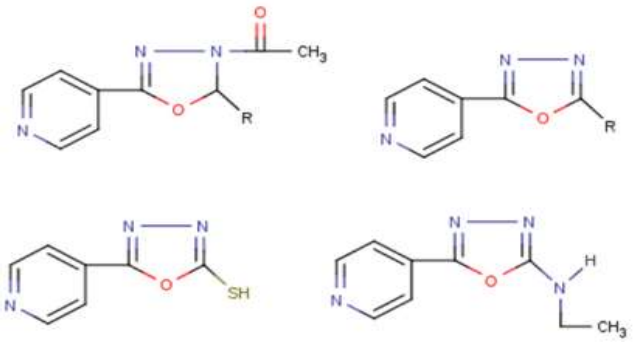


Fig-5

(vi) Virginija Jakubkiene et al. synthesized 5-(6-methyl-2-substituted-4-pyrimidinyloxymethyl)-2,3-dihydro-1, 3, 4-oxadiazole-2-thiones and their morpholinomethyl derivatives. Most derivatives showed good anti-inflammatory activity, with some being more effective than acetylsalicylic acid [7].

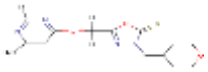


Fig-6

(vii) Erhan Palaska et al. reported sixteen novel derivatives of 1-(2-naphthyloxyacetyl)-4-substituted-3-thiosemicarbazide-2-(2-naphthyloxymethyl)-5-substituted amino-1,3,4-oxadiazole, thiadiazole, and triazole, evaluating them as orally active anti-inflammatory agents with low side effects [8].

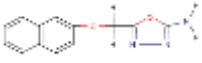


Fig-7

(viii) Shashikant V. Bhandari et al reported a series of S-substituted phenyl-1, 3, 4 oxadiazole and Schiff bases. Total eighteen derivatives were synthesized from 2-[2, 6-dichloro aniline) phenyl] acetic acid and out of those only eight were found to have significant anti-inflammatory activity along with analgesic activity. It was also found that synthesized compounds did not show any ulcerogenic potentiality [9].

Fig-8

(ix) Jaya Shankar et al reported a series of novel ether linked bis heterocyclic derivatives and evaluated their anti-inflammatory and analgesic activities. The experimental results showed very good activity against ibuprofen and aspirin [10].

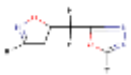


Fig-9

(x) Manjunatha et al reported a wide variety of oxadiazole mannich base and screened for their anti-inflammatory activity. A few of them found to be a potential anti-inflammatory agent than diclofenac sodium at 10 mg/kg [11].

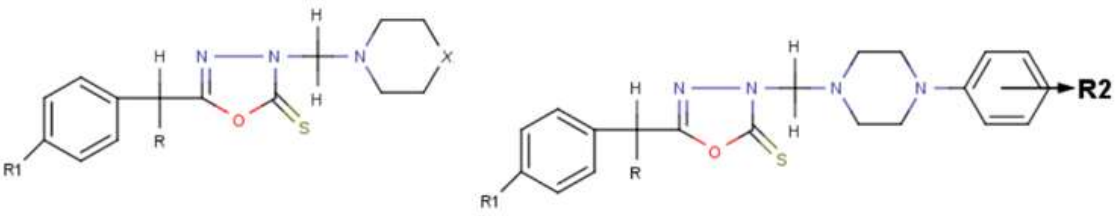


Fig-10

(xi) Gilani et al proposed a series of 6-substituted-1, 2, 4-triazolo [3, 4-b]-1, 3, 4-thiadiazole and 1, 3, 4-oxadiazoles of isonizid. These derivatives are evaluated for their anti-inflammatory activity and it was revealed that triazolothiadiazole and 1, 3, 4-oxadiazole derivatives of isonizid may be safer alternative to isoniazid for the treatment of inflammatory disease [12].

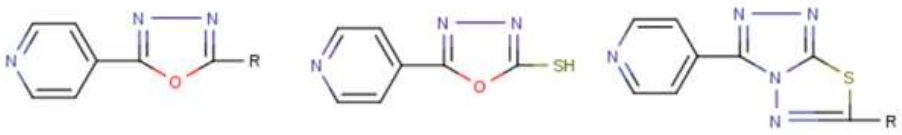


Fig-11

(xii) A series of novel derivatives, including 3-[5-(1H-indol-3-yl-methyl)-2-oxo-[1,3,4]-oxadiazol-3-yl] propionitrile and others, synthesized from (1H-indol-3-yl)-acetic acid N0-(2-cyanoethyl) hydrazide, were tested for in vivo anti-inflammatory activity [13].

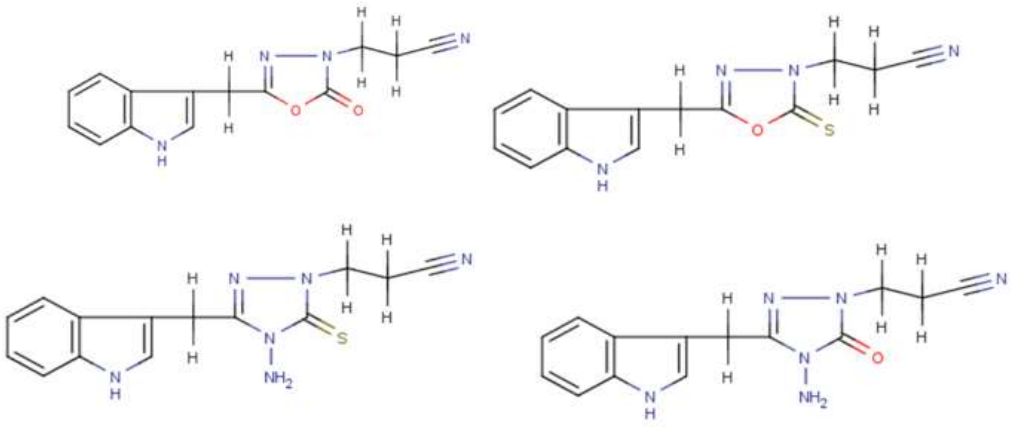


Fig-12

(xiii) MD. Amir et al reported the synthesis of aryl oxadiazole derivatives having anti-inflammatory activity in 2007 [14].

Fig-13

(xiv) F. A. Omar et al synthesized some novel derivatives of 1, 3, 4-oxadiazole and evaluated for their anti-inflammatory activity in 1996 [15].

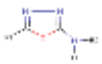
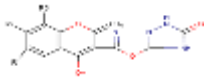


Fig-14

(xv) Airody V. Adhikari et al reported the synthesis of triazolooxadiazole having analgesic and anti-inflammatory activity in 2008 [16].



4-hydroxy-6,7,8-trimethyl-3-(6-thioxo-5,6,7,7a-tetrahydro-[1,2,4] triazolo[5,1-b][1,3,4]oxadiazol-2-yl)- 2H-chromen-2-one

Fig-15

2. ANTICANCER/ANTITUMOUR ACTIVITY

(i) A novel series of 2-Naphthalen-1-ylmethyl-1-(5-substituted phenyl-[1,3,4] oxadiazol-2-ylmethyl)-1H-benzimidazole derivatives were synthesized using chloramines T and phosphorous oxychloride, then evaluated for anticancer activity against various NCI 60 cell lines [17].

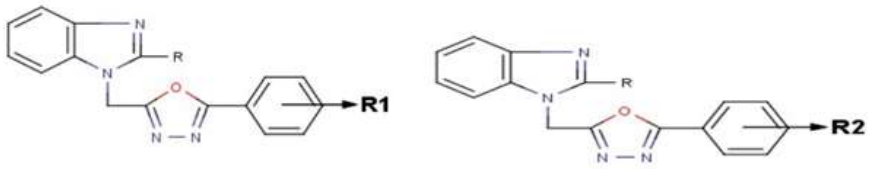


Fig-16

(ii) Sun et al designed and prepared various 1, 3, 4-oxadiazoles having 1, 4-benzodioxan and evaluated their antitumour activity. The results showed that most of the synthesized derivatives have good antitumour activity with low toxicity [18].

Fig-17

(iii) Shamsuzzaman et al. synthesized 3β-[5'-mercapto-1',3',4'-oxadiazole-2-yl]methoxycholest-5-ene from cholest-5-en-3b-O-acetyl hydrazide, showing moderate anticancer activity against HL-60 with IC_{50} values of 17.33 and 18.57 [19].

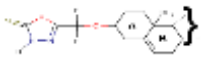


Fig-18

(iv) Ashan et al prepared ten oxadiazole analogues. Among these compounds 2-(4-chlorophenyl)-5-(4-flurophenyl)-1, 3, 4-oxadiazole and 2-(4-chlorophenyl)-5-(4-methoxy phenyl)-1, 3, 4-oxadiazole was screened for anticancer activity against various cancer cell lines (NCI 60 cell lines) [20].

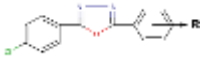


Fig-19

R= Substituted aryl ring

(v) Zhang et al. designed and synthesized 1,3,4-oxadiazole analogues containing pyridine and acylhydrazone moieties as potential telomerase inhibitors. The compounds showed significant anti-tumor activity against HEPG2, MCF, and BGC823 cell lines [21].

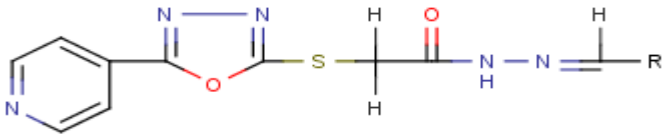


Fig-20

(vi) Novel 1, 3, 4-oxadiazoles were synthesized by Bondock et al and their anticancer activity was carried out by using NCI protocol. The data revealed that five compounds were found to exhibit variable degrees of anticancer potentiality against HEPG2, WI38 (lung fibroblast), African green monkey VERO and MCF-7 and 5-FU was used as standard drug [22].

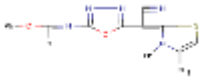


Fig-21

(vii) A series of 1,3,4-oxadiazole thioether analogues were synthesized and evaluated for in vitro anticancer activity using MTT assay on HEPG2, SGC-7901, and MCF-7 cell lines. Compounds with a nitro group showed the most potent activity [23].

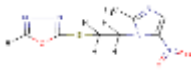


Fig-22

(viii) Rashid et al. synthesized twenty-five new benzimidazole-containing 1,3,4-oxadiazole derivatives from 4-(1H-benzimidazol-2-yl)-4-oxobutanehydrazide under microwave irradiation. The compounds were tested for in vitro anticancer activity against NCI 60 cell lines, showing significant anti-cancer effects. [24].

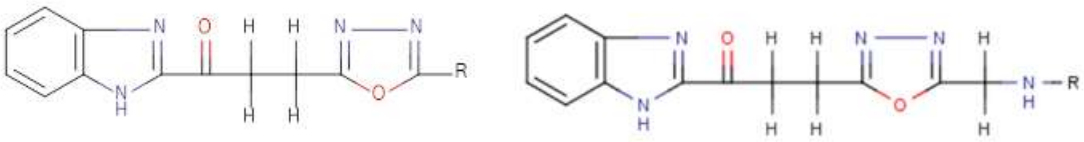


Fig-23

(ix) Zhang et al reported a series of new 1, 3, 4-oxadiazole containing 1, 4-benzodioxan nucleus. The new derivatives were synthesized from 5-(2, 3-dihydrobenzo [1, 4] dioxin-6-yl)-1, 3, 4-oxadiazole-2-thiole and screened for their anti-proliferative activity toward HEPG2, HELA (human cervical cancer cell), SW1116 (human colorectal carcinoma cell) and BGC823 [25].

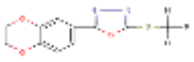


Fig-24

(x) A series of heterocyclic azoles were designed and synthesized by Liu W et al and screening was carried out for their anti-proliferative activity toward the HEPG2, SW1116, HELA and BGC823 [26].

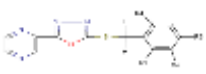


Fig-25

(xi) A number of different derivatives of substituted 2-(piparazin-1-yl) benzothiazole or benzoxazole were prepared by coupling with 1, 3, 4-oxadiazole-2-thiol pharmacophore. All the derivatives tested for their cytotoxic profile towards five

human cancer cell lines of different origins such as MCF-7, HELA, HEPG2, A431 (skin), and A549 (lung) [27].

Fig-26

(xii) A series of 3-(4-[5-mercapto-1,3,4-oxadiazole-2-yl]phenyl imino)-indolin-2-one analogues were synthesized and evaluated for anticancer activity against HELA, IMR-32, and MCF-7 cell lines. Halogen-substituted compounds showed excellent activity [28].

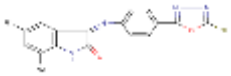


Fig-27

3. ANTIMICROBIAL ACTIVITY

(i) Li et al. synthesized two secnidazole analogues based on an oxadiazole scaffold and tested them against Gram-negative bacteria like Escherichia coli and Pseudomonas aeruginosa. Both compounds inhibited E. coli FabH effectively [29].

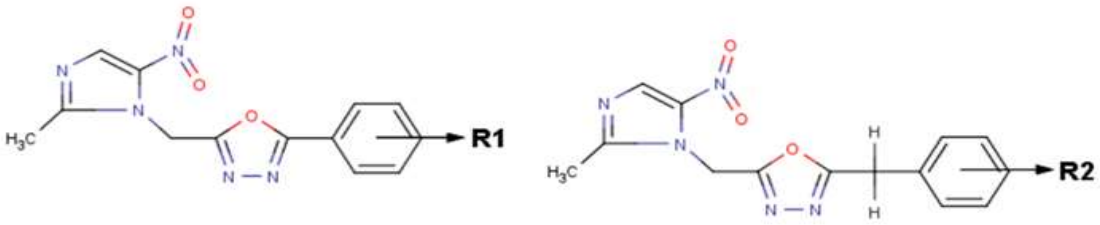


Fig-28

(ii) Zhang MZ et al. synthesized a series of 2-(indole)-substituted-1,3,4-oxadiazoles and evaluated their antifungal activity against various pathogens. Several compounds exhibited higher antifungal activity than pimprinine, with pimprinine and streptochlorin as standards [30].

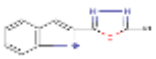


Fig-29

(iii) Desai et al. synthesized 2-(5-[4-(1-aza-2-[2-thienyl] vinyl) phenyl] (1,3,4-oxadiazole-2-yl-thio]-D-N-aryl-acetamides and evaluated their antimicrobial activity, showing effectiveness against S. aureus, E. coli, P. aeruginosa, and fungal strains [31].

Fig-30

(iv) Jha KK et al. synthesized novel 2,5-disubstituted oxadiazole derivatives through cyclization of acylhydrazides and aromatic acids with CS2 and POCl3. The compounds were evaluated for antibacterial activity against E. coli, S. epidermidis, and S. aureus [32].

Fig-31

(v) Chandrakantha B et al. synthesized 2-(2-fluoro-4-methoxyphenyl)-5-substituted-1,3,4-oxadiazoles and evaluated their antibacterial activity against Gram-positive and Gram-negative strains, as well as antifungal activity against Candida albicans, using MIC determination [33].

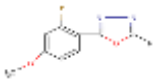


Fig-32

(vi) Khalilullah et al. synthesized 1,3,4-oxadiazole derivatives with a 1,4-benzodioxane nucleus and tested their antibacterial activity against S. aureus, B. subtilis, E. coli, and antifungal activity against A. niger, A. flavus, C. albicans [34].

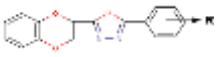


Fig-33

(vii) Desai et al. synthesized thiazole-based 1,3,4-oxadiazole derivatives and evaluated their antibacterial activity against S. aureus, S. pyogenes, E. coli, P. aeruginosa, and antifungal activity against C. albicans, A. niger, A. clavatus.[35].

Fig-34

(viii) Salimon et al. reported new acridone derivatives, evaluated for antibacterial activity against S. aureus, Strept. viridians, E. coli, and antifungal activity against various fungi. MIC testing showed mild to moderate effectiveness compared to standard drugs [36].

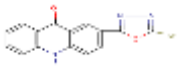


Fig-35

(ix) Ramaprasad GC et al. synthesized twenty 2-(4,5-dibromopyrrol-2-yl)-5-substituted-1,3,4-oxadiazoles and evaluated

their bactericidal, bacteriostatic, and antifungal activities against E. coli, S. aureus, P. aeruginosa, Klebsiella pneumonia, A. niger, and C. albicans [37].

Fig-36

[x] Ishii M et al reported 3-acetyl-2, 5-disubstituted-2, 3-dihydro-1, 3, 4-oxadiazole derivatives and developed as potential antimicrobial agents against *S. aureus*, *Trypanosoma cruzi* and *C. albicans* [38].

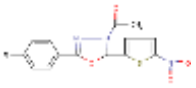


Fig-37

(ix) Desai NC et al. synthesized 1-(2-[1H-benzo(d)imidazol-2-yl]-2-methyl-5-aryl-1,3,4-oxadiazole-3-(2H)-yl)-3-(4-chlorophenyl) prop-2-en-ones using microwave irradiation, screening them for antimicrobial activity against various bacterial and fungal strains [39].

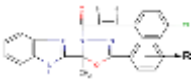


Fig-38

(xii) A series of 3-{5-[(E)-(substituted benzylidine) amino]-1,3,4-oxadiazol-2-yl}-2H-chromen-2-ones were synthesized and evaluated for antimicrobial activity against S. aureus, E. coli, and C. albicans, using ciprofloxacin and ketoconazole as standards [40].

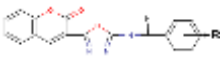


Fig-39

[xiii] Gul S et al. synthesized 2-[5-alkyl or arylalkyl-1,3,4-oxadiazole-2-yl] thio)-N-(4-[4-morpholinyl] phenyl) acetamides and evaluated their antimicrobial activity against S. aureus, B. subtilis, P. multocida, E. coli, and pathogenic fungi [41]

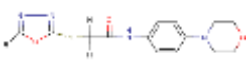


Fig-40

(xiv) Vishal and Prabha synthesized a novel chiral and chiral amide incorporating 1, 3, 4-oxadiazole derivatives and screened

for the antimicrobial activity against *E. coli*, *S. aureus*, *A. oryzae* and *A. niger* by cup plate method [42].

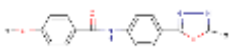


Fig-41

(xv) Vazquez, G. N et al. synthesized novel 4-(5-substituted-1,3,4-oxadiazole-2-yl) pyridine derivatives and evaluated their anti-tubercular activity. The compounds showed greater potency than isoniazid, streptomycin, and ethambutol against M. TB at 62.5µg/ml [43].

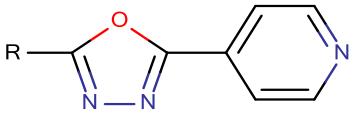


Fig-A42

(xvi) Hajimahdi et al. synthesized 4-oxo-4H-pyrido(1,2-a) pyrimidine derivatives containing 1,3,4-oxadiazole and 1,3,4-thiadiazole, and evaluated them for in vitro anti-HIV activity, showing moderate efficacy against HIV-1 virus in Hela cell cultures [44].

Fig-43

3. ANTIOXIDANT ACTIVITY

(i) Maa et al. synthesized a new series of Mannich base 1,3,4-oxadiazole derivatives containing 1,4-benzodioxane and evaluated their in vitro antioxidant activity using DPPH, ABTS, and ferric reducing assays [45].

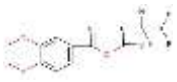


Fig-44

(ii) Kerimove I et al. reported a new series of 2-amino-1,3,4-oxadiazoles and 5-aryl-1,3,4-oxadiazoles containing a benzimidazole ring, evaluating their antioxidant properties using lipid peroxidation, ethoxyresorufin O-deethylase, and DPPH assays [46].

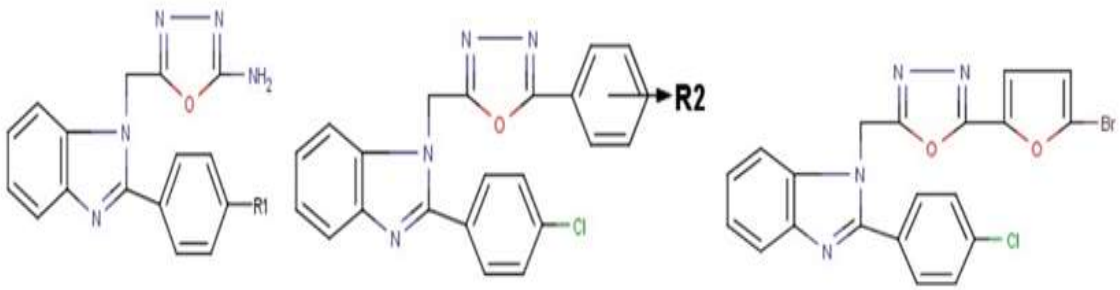


Fig-45

4. ANTHELMENTIC ACTIVITY

(i) Patel et al. synthesized 3-amino-1-(2,4-dinitrophenyl)-5-[5-substituted-1,3,4-oxadiazole-2-yl] amino-1H-pyrazole-4-carboxamide and screened for anthelmintic activity, showing good activity against Pherituma posthuma compared to albendazole [47].

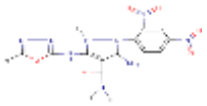


Fig-46

R= Substituted aryl ring.

(ii**)** Srinivas et al reported new compounds of 1-[(5-substituted-1, 3, 4-oxadiazole-2-yl)-methyl]-4-propylpiperazine derivatives and evaluated for their anthelmentic activity and results showed that some of them found to be possessed good to moderate activity [48].

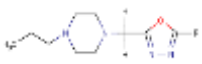


Fig-47

5. RECENT ADVANCEMENTS

Several 2, 5-disubstituted oxadiazole derivatives have recently synthesized and demonstrated significant anticancer effects by inhibiting the growth and proliferation of various cancer cell lines. Studies showed that these derivatives can induce apoptosis and suppress tumor growth in vitro and in vivo models. Molecular docking studies have indicated their interaction with proteins such as topoisomerase and cyclooxygenase, which play key roles in cancer progression [49].

2, 5-Disubstituted oxadiazoles have also shown remarkable antimicrobial properties against various bacterial and fungal strains. These compounds have been found to inhibit bacterial growth by interacting with bacterial DNA gyrase and other critical enzymes, making them promising candidates for treating infections caused by resistant strains [50].

Anti-inflammatory studies revealed that 2, 5-disubstituted oxadiazoles can act as inhibitors of COX-II, a key enzyme involved in inflammatory processes. In vivo studies demonstrated that these derivatives reduced inflammation and showed hepatoprotective effects by inhibiting portal tract inflammation and necrosis, especially against liver damage models induced by toxins like CCl_4 [51].

2, 5-Disubstituted oxadiazole derivatives have shown significant hepatoprotective properties. In in vivo studies, these

derivatives were found to reduce liver damage induced by toxins (such as CCl_4), significantly preventing liver fibrosis and necrosis. These compounds may act through mechanisms such as inhibition of NF-κB signaling and anti-inflammatory activity [52, 53].

2, 5-Disubstituted oxadiazoles have displayed promising anticancer activity against several cancer cell lines (e.g., HepG2, MCF-7, and A549). These compounds have been found to inhibit cell proliferation, induce apoptosis, and suppress tumor growth. Molecular docking studies have shown that these derivatives interact with key proteins involved in cell cycle regulation and apoptosis induction, such as Bcl-2 and p53 [54].

2, 5-Disubstituted oxadiazoles have shown substantial antimicrobial activity against gram-positive and gram-negative bacteria as well as fungi. These compounds inhibit bacterial DNA gyrase, which plays a crucial role in bacterial DNA replication, and their action extends to fungal pathogens such as Candida species [55].

2. CONCLUSION

The synthesis of 2,5-disubstituted oxadiazole derivatives resulted in satisfactory yields, confirmed by spectral analysis. Molecular docking studies revealed interactions with targeted proteins, indicating promising biological activity. In vivo hepatoprotective studies showed that these novel compounds effectively inhibited portal tract inflammation and necrosis. Anti-inflammatory studies demonstrated their potential as COX-II inhibitors. In vitro anticancer studies revealed that these compounds significantly inhibited HepG2 cell growth. Additionally, antimicrobial studies highlighted the significant antimicrobial activity of these derivatives against various bacterial and fungal strains. These findings suggest that the synthesized oxadiazoles possess broad therapeutic potential in multiple areas.

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