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1,3,4-Oxadiazole as a Potential Anti-Cancer Scaffold: A Review

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Abstract: 1,3,4-oxadiazole is an aromatic heterocycle with –N=C=O- linkage. 1,3,4-oxadiazole derivatives possess remarkable biological properties; antimicrobial anti-inflammatory, anti-cancer, antitubercular, antioxidant, antiviral, and anti-diabetic. This scaffold is present in many marketed drugs, such as Raltegravir, Tiodazosin, Nesapidil, and Zibotentan. 1,3,4-oxadiazole derivatives have displayed significant anti-cancer potential with a diverse mode of actions *viz*. growth factors, enzymes, kinases, etc. The present review gives an overview of the anti-cancer potential of 1,3,4-oxadiazoles derivatives in cancer drug discovery and development from the last ten years.

Keywords: 1,3,4-oxadiazole; anti-cancer; heterocycle.

1. Introduction

Heterocycles play a very important role in medicinal chemistry. The heterocycles have significant biological activity, due to which they are continued explored [1-5]. 1,3,4-oxadiazole is an aromatic heterocycle with –N=C=O- linkage. It contains one oxygen and two nitrogen atoms and is found in different isomeric forms (Figure 1).

Figure 1. Different isomers of oxadiazole.

1,3,4-oxadiazole derivatives possess remarkable biological properties. It can be used as antimicrobial [6-11], anti-inflammatory [12-14], anticancer [15-18], antioxidant [19], antiviral [20, 21], antidiabetic [22, 23]. Oxadiazole derivatives can be found in marketed drugs such as Raltegravir - an antiretroviral drug against HIV, Ataluren - in treating cystic fibrosis, Tiodazosin, and Nesapidil used as antihypertensive drugs, Zabotentan - in the final stage of clinical trials as anti-cancer agents (Figure 2). Besides these, 1,3,4-oxadiazole also finds applications in material science [24-26].

1,3,4-oxadiazole derivatives have displayed significant anti-cancer potential with the diverse mode of actions such as growth factors, enzymes, kinases, etc. [27]. This review article gives an overview of the anti-cancer potential of 1,3,4-oxadiazoles in cancer drug discovery and development from the last ten years.

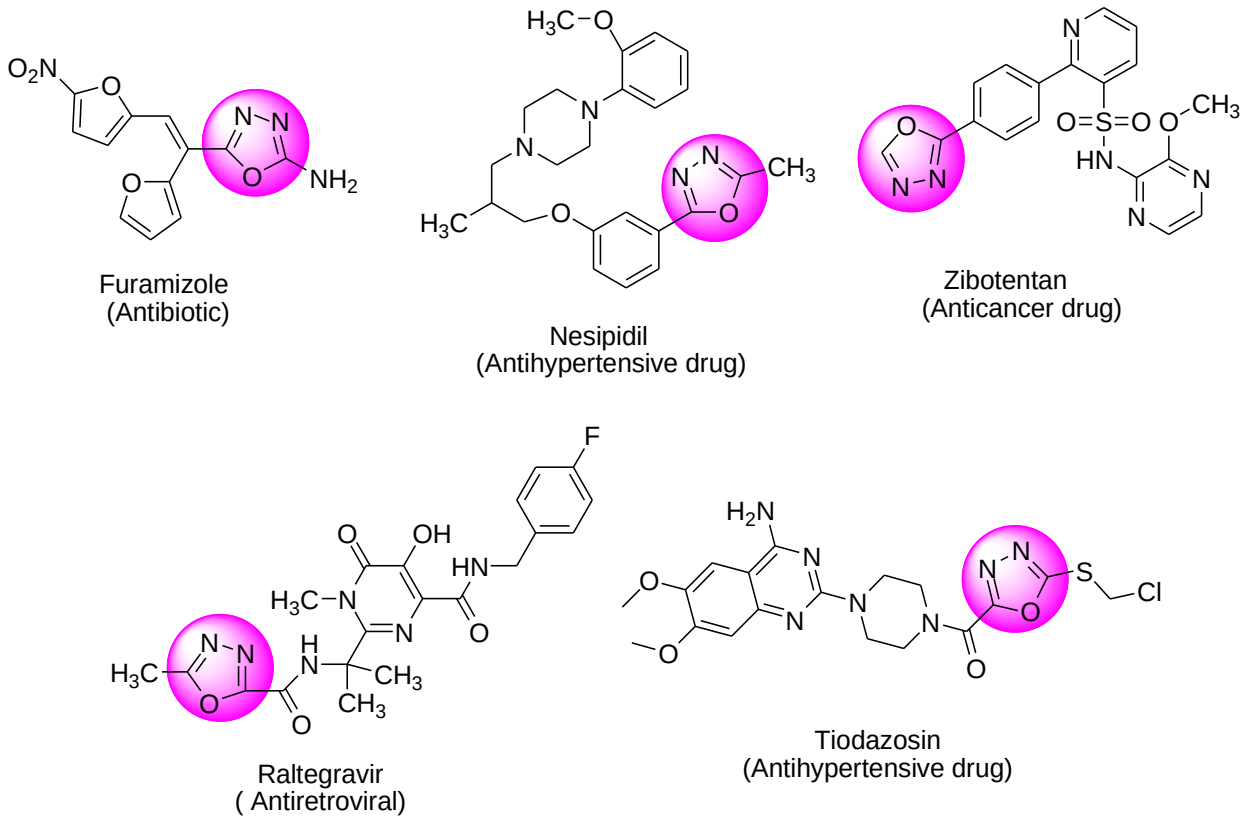
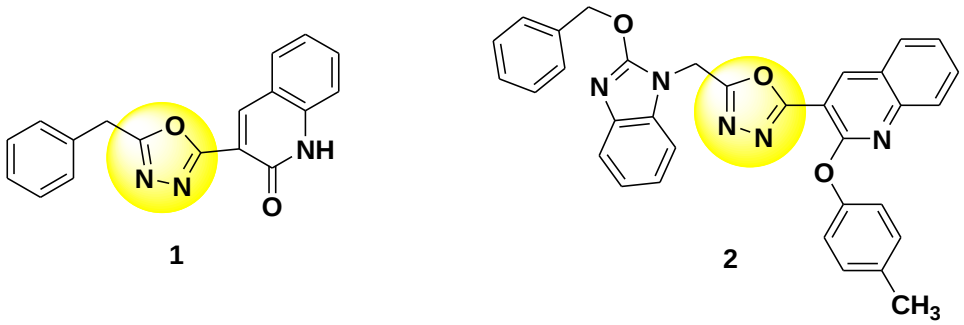


Figure 2. 1,3,4-oxadiazole based drugs in the market.

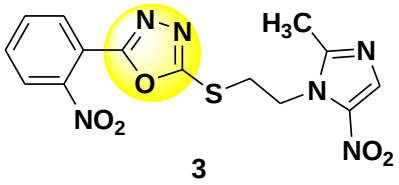
2. Anti-cancer activity of 1,3,4-oxadiazole derivatives

Quinoline based 1,3,4-oxadiazole, 3-(5-benzyl-1,3,4-oxadiazol-2-yl)quinolin-2(1H)-one (1) and 3-[5-(2-phenoxymethyl-benzoimidazol-1-ylmethyl)-[1,3,4]oxadiazol-2-yl]-2-p-tolyloxy-quinoline (2) displayed GI_{50} values in the range 1.41–15.8 μM and 0.40–14.9 μM, respectively against a panel of NCI 60 cancer cell lines [28] (Scheme 1).



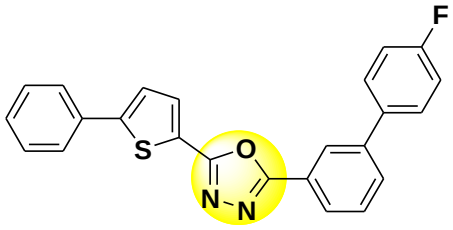
Scheme 1. Quinoline based 1,3,4-oxadiazole.

Du *et al*. reported 1,3,4-oxadiazole-thioether derivatives as anti-cancer agents targeting thymidylate synthase enzyme. Compound (3) was the best compound with IC_{50} 0.7 µM, 18.3 µM, and 30.0 µM against HepG2, MCF-7, and SGC-7901 cancer cells, respectively [29] (Scheme 2).



Scheme 2. 1,3,4-oxadiazole-thioether derivative.

Adimule and his coworkers reported 2- (4'-fluorobiphenyl-3-yl)-5-(5-phenylthiophen-2-yl)-1,3,4-oxadiazole (4) as potent cytotoxic agent with IC_{50} 5.3 µM, comparable to 5-fluorouracil (IC_{50} 8.6 µM) against Caco-2cell line [30] (Scheme 3).



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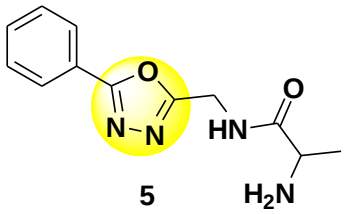
Scheme 3. Thiophene based 1,3,4-oxadiazole derivative.

Oxadiazole-based propanamide derivatives, (R)-2-amino-N-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl) propanamide (5) synthesized by Pidugu *et al*. has shown significant anti-cancer activity through the inhibition of Histone deacetylase (HDAC8) enzyme [31] (Scheme 4).



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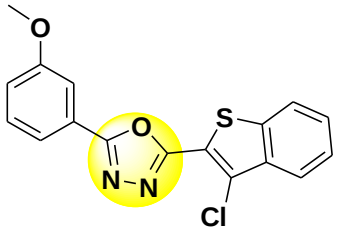
Scheme 4. Propanamide based 1,3,4-oxadiazole derivative.

Mohan *et al*. discovered 2-(3-chlorobenzo[b]thiophen-2-yl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (6) as a potent anti-cancer agent by studying apoptosis (annexin V-propidium iodide-FITC staining) and phosphorylation of NF-κB signaling pathway proteins (IκB and p65) in hepatocellular carcinoma cells (HCC) [32] (Scheme 5).



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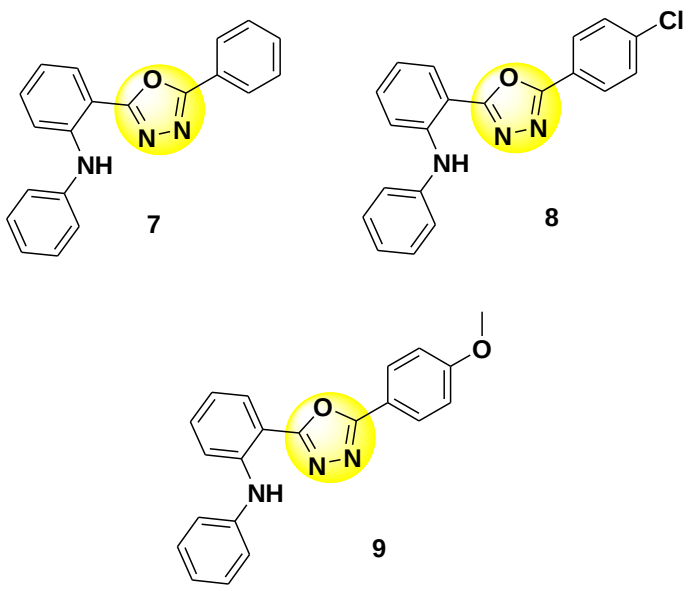
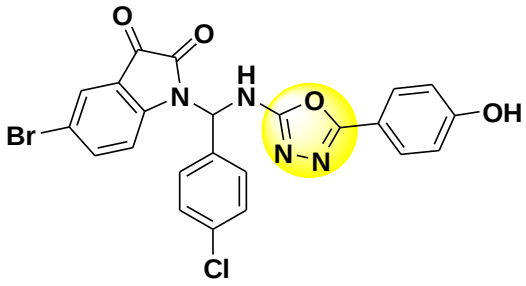
Scheme 5. Benzothiophene-based 1,3,4-oxadiazole derivative.

Rahman synthesized 1,3,4-oxadiazole incorporated diphenylamine derivatives and screened for anti-cancer activity. These compounds (7-9) have revealed significant cytotoxicity against HT29 cell line with IC_{50} in the range 1.3–2.0 Mm [33] (Scheme 6).

Recently, 5-bromo-1-((4-chlorophenyl)((5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)amino)methyl) indoline-2,3-dione (10) reported by Bhat *et al.* exhibited remarkable cytotoxicity with IC_{50} 0.78 µM and 0.26 µM against HT-29 and HepG2, respectively by inhibiting EGFR and CDK2 kinases [34] (Scheme 7).



Scheme 6. Diphenylamine incorporated 1,3,4-oxadiazole derivative.



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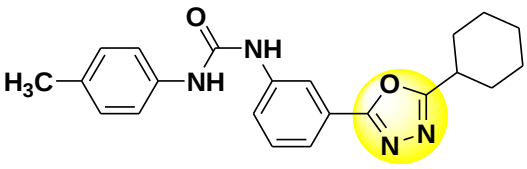
Scheme 7. Indolinedione incorporated 1,3,4-oxadiazole derivative.

Kavitha and coworkers reported 1-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-p-tolyl-urea (11) as a promising anticancer agent [35] (Scheme 8).



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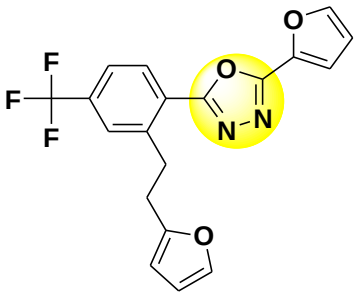
Scheme 8. Urea based 1,3,4-oxadiazole derivative.

Compound *N*-(furan-2-ylmethyl)-3-[5-(furan-2-yl)-1,3,4-oxadiazol-2-yl]-6-(trifluoromethyl)pyridin-2-amine (12) revealed promising anticancer activity against DU145 and HepG2 cell lines in comparison to 5-fluorouracil [36] (Scheme 9).



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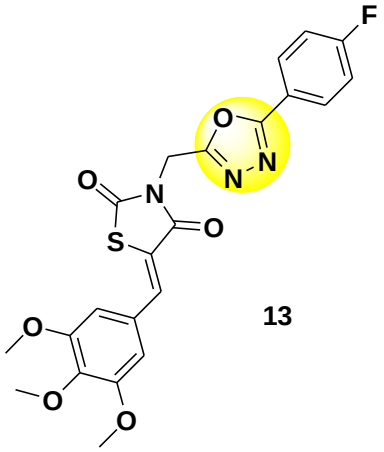
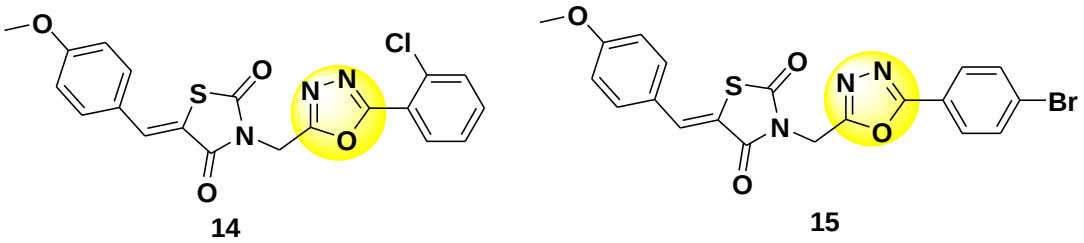
Scheme 9. Furan based 1,3,4-oxadiazole derivative.

1,3,4-oxadiazole and thiazolidine-2,4-dione based derivatives, (*E*)-3-{[5-(4-florophenyl)-1,3,4-oxadiazol-2-yl]methyl}-5-(3,4,5-trimethoxybenzylidene) thiazolidine-2,4-diones (13) exhibited promising cytotoxicity with IC_{50} 0.81 to 11.9 μM against A549, A375, MCF-7, and HT-29 cancer cell lines[37] (Scheme 10).



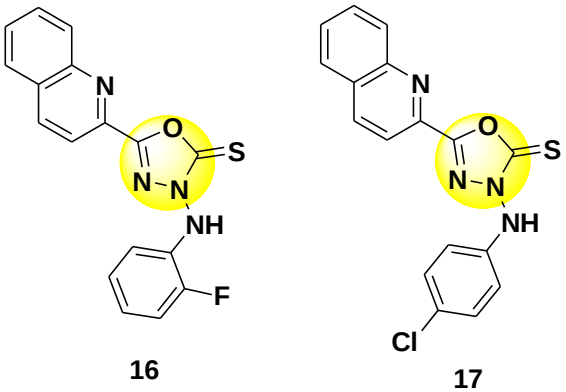
Scheme 10. Thiazolidinedione incorporated 1,3,4-oxadiazole derivative.

Zohor *et al* reported 1,3,4-oxadiazole–thiazolidinedione hybrids, 5-(4-methoxybenzylidene)-3-((5-(2-chlorophenyl)-1,3,4-oxadiazol-2-l)methyl) thiazolidinedione (14) and 5-(4-methoxybenzylidene)-3-((5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl)methyl)thiazolidinedione (15) which displayed cytotoxicity with IC_{50} 7.74 and 7.87, respectively against MCF-7 cell line through the inhibition of thymidylate synthase enzyme [38] (Scheme 11).



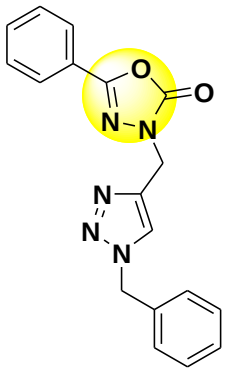
Scheme 11. Thiazolidinedione incorporated 1,3,4-oxadiazole derivative.

Quinoline incorporated 1,3,4-oxadiazole, 3-((2-Fluorophenyl)amino)methyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3H)-thione; (16) and 3-(((4-Chlorophenyl)amino)methyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3H)-thione (17) reported by Sun *et al* exhibited anticancer activity by inhibiting telomerase enzyme [39] (Scheme 12).



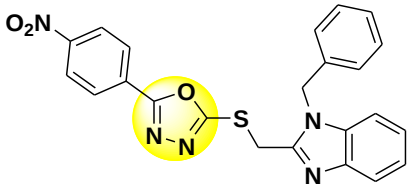
Scheme 12. Quinoline incorporated 1,3,4-oxadiazole derivative

Madhavilatha *et al*. reported 1,3,4-oxadiazole-linked 1,2,3-triazole derivative, 3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-phenyl-1,3,4-oxadiazol-2(3H)-one (18) as promising anticancer agent against HeLa, MDA-MB-231, DU-145 and HEPG2 cancer cell lines. Compound 18 arrests cell cycle at G2/M stage and acts as a tubulin polymerization inhibitor [40] (Scheme 13).



Scheme 13. 1,2,3-triazole linked 1,3,4-oxadiazole derivative.

2-((5-(4-Nitrophenyl)-1,3,4-oxadiazol-2-yl)thiomethyl)-1-benzylbenzimidazole (19) displayed moderate cytotoxicity (IC_{50} 17.5 μM) [41] (Scheme 14).



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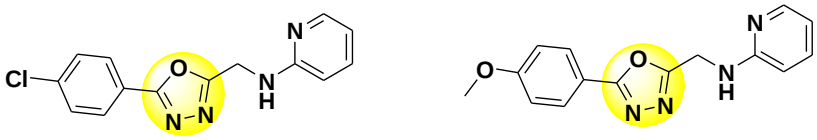
Scheme 14. Benzimidazole based 1,3,4-oxadiazole derivative.

Ahsan and Shastri synthesized *N*-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}pyridin-2-amine (20) and *N*-{[5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}pyridin-2-amine (21) which revealed mean growth percent inhibition (GP) of 96.37,and 95.12, respectively against NCI 60 cancer cell lines at 10 μM concentration [42] (Scheme 15).



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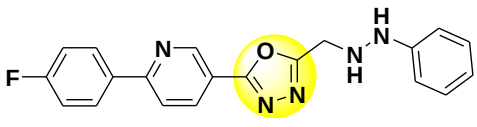
Scheme 15. Pyridine based 1,3,4-oxadiazole derivative.

Vinayak *et al* reported {5-[6-(4-Fluorophenyl)-pyridin-3-yl]-[1,3,4] oxadiazol-2-yl-methyl}-phenyl-amine (22) as a potent cytotoxic agent with IC_{50} 2.3 μM against Caco-2 cell lines [43] (Scheme 16).



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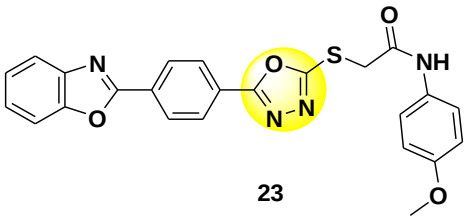
Scheme 16. Pyridine based 1,3,4-oxadiazole derivative.

Novel 1,3,4–oxadiazole linked benzoxazole analogues, *N*1-(4-Methoxyphenyl)-2-{5-[4-(1,3-benzoxazol-2-yl)phenyl]-1,3,4-oxadiazol-2-ylsulfanyl}acetamide (23) has shown potent antiproliferative effect with IC_{50} of 0.018 against HT-29cancer cell line [44] (Scheme 17).



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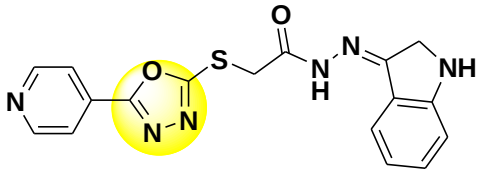
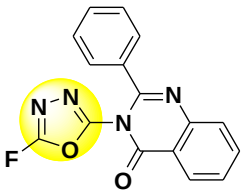
Scheme 17. Benzoxazole based 1,3,4-oxadiazole derivative.

Khalil and colleagues reported N′-[(Z/E)-(3-Indolyl)methylidene]-2-{[5-(pyridin-4-yl)-1,3,4- oxadiazol-2-yl]sulfanyl}acetohydrazide (24) which has shown significant anti-cancer effect (IC_{50}: 0.010 µM) through the inhibition of EGFR [45] (Scheme 18).



Scheme 18. Indole based 1,3,4-oxadiazole derivative.

Quinazoline based 1,3,4-oxadiazole, 3-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]-2-phenylquinazolin-4(3*H*)-one (25) exhibited cytoxicity with IC_{50} 17.7 µM against K562 cell lines, compared to doxorubicin [46] (Scheme 19).



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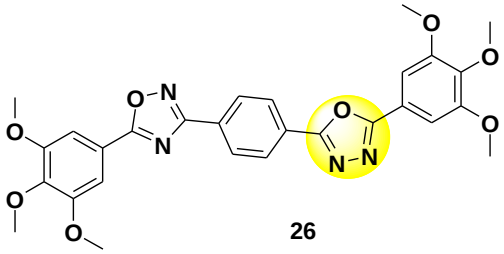
Scheme 19. Quinazoline based 1,3,4-oxadiazole derivative.

2-(3,4,5-trimethoxyphenyl)-5-(4-(5-(3,4,5- trimethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)-1,3,4-oxadiazole (26) containing 1,3,4-oxadiazole and 1,2,4-oxadiazole moieties displayed potent anticancer effect with IC_{50} 0.34 to 2.45 µM against all the tested MCF-7, A549 and MDA-MB-231 cancer cells by inhibiting EGFR (epidermal growth factor receptor) [47] (Scheme 20).



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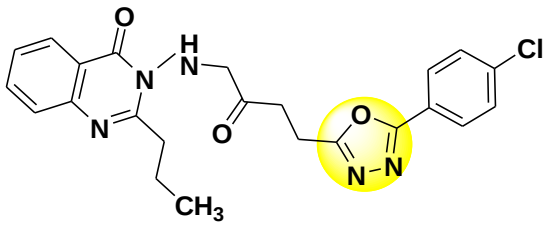
Scheme 20. 1,2,4-oxadiazole linked 1,3,4-oxadiazole derivative.

2-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylthio) N-(4-oxo-2-propylquinazolin)-3-(4H) acatamide (27) synthesized by Hassanzadeh *et al*. displayed promising anti-cancer effect with IC_{50} of 7.52 µM against the HeLa cell line [48] (Scheme 21).



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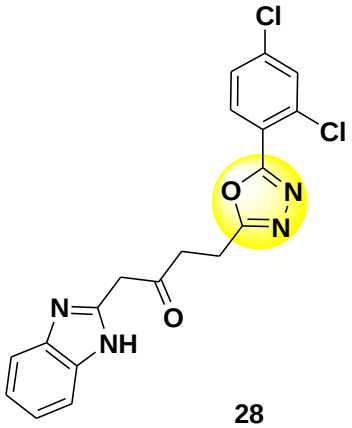
Scheme 21. Quinazoline based 1,3,4-oxadiazole derivative.

1,3,4-oxadiazole tethered benzimidazoles, 1-(1Hbenzo[d]imidazol-2-yl)-3-(5-(2,4-dichlorophenyl)-1,3,4- oxadiazol-2-yl)propan-1-one (28), was found to be a hit compound against NCI 60 cancer cell line [49] (Scheme 22).



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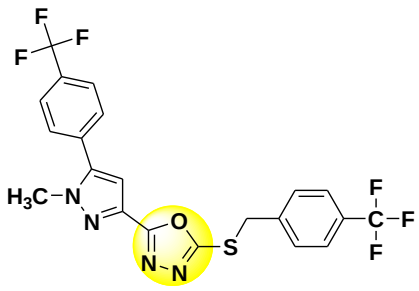
Scheme 22. Benzimidazole based 1,3,4-oxadiazole derivative.

Pyrazole-based 1,3,4-oxadiazole, N-methyl- 4-(trifluoromethyl) phenyl pyrazole (29) exerted an antiproliferative effect with IC_{50} of 15.54 μM, compared to doxorubicin [50] (Scheme 23).



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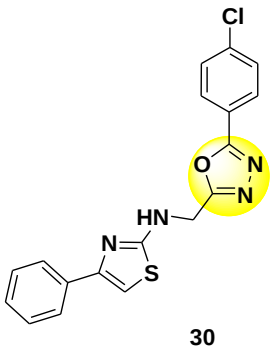
Scheme 23. Pyrazole based 1,3,4-oxadiazole derivative.



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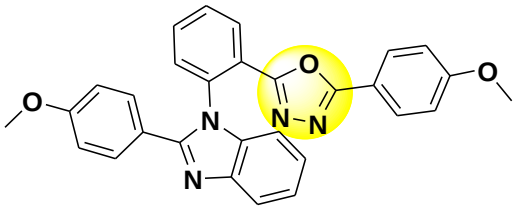
Scheme 24. Thiazole based 1,3,4-oxadiazole derivative.

Jisha *et al.* synthesized *N*-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl] methyl}-4-phenyl-1,3-thiazol-2-amine (30) which revealed promising cytotoxicity against both DLA and MCF-7 with LD_{50} 136 µg/ml and 132 µg/ml, respectively [51] (Scheme 24).

Kapoor and Dhiman reported 2-(4-dimethoxyphenyl)-1-{2-[5-(2-methoxyphenyl-1,3,4-oxadiazole-2-yl]phenyl}-1*H*benzimidazole (31) with potent cytoxicity against MCF-7 cells [52] (Scheme 25).



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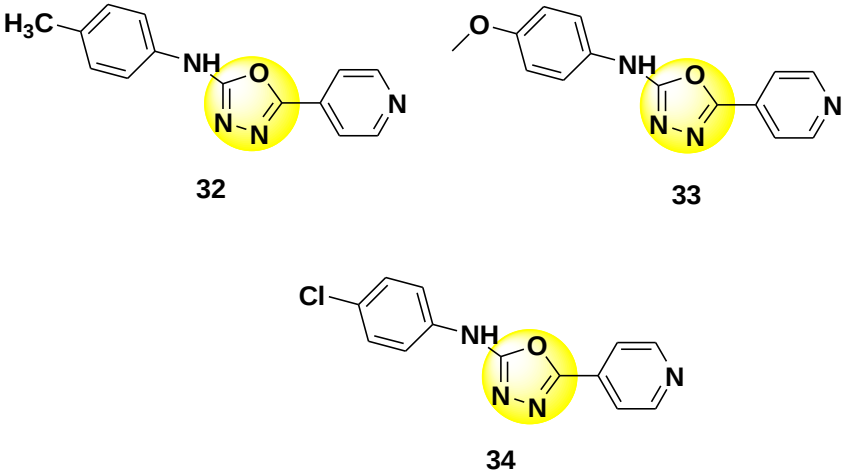
Scheme 25. Benzimidazole based 1,3,4-oxadiazole derivative.

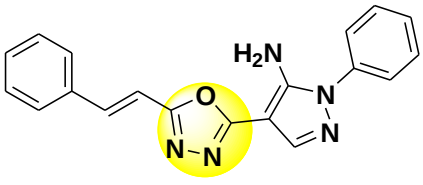
Abdo and Kamel *et al.* reported a series of 5-(pyridin-4-yl)-*N*-substituted-1,3,4-oxadiazol-2-amines (32-34) which exhibited cytotoxicity in the range of 0.725-3.274 µm against all six human cancer cell lines, NUGC, DLD1, HA22T, HEPG2, HONE1 MCF cells [53] (Scheme 26).



32 33 34

Scheme 26. Pyridine based 1,3,4-oxadiazole derivative.

Ghag and Kamath reported (E)-1-phenyl-4-(5-styryl-1,3,4-oxadiazol-2-yl)-1*H*pyrazol-5-amine (35) with excellent activity than standard drug cisplatin on breast cell lines DU145 [54] (Scheme 27).



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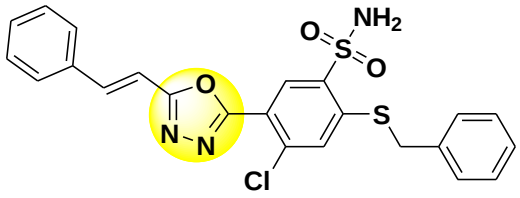
Scheme 27. Pyrazole based 1,3,4-oxadiazole derivative.

Benzenesulfonamide linked 1,3,4-oxadiazole, (E)-2-benzylthio-4-chloro-5- (5-styryl-1,3,4-oxadiazol-2-yl)benzenesulfonamide (36) reported by Sławinski*et al*. has displayed promising anti-cancer activity against HCT-116, MCF-7 and HeLa cancer cell lines with IC_{50}: 11-29 µM [55] (Scheme 28).



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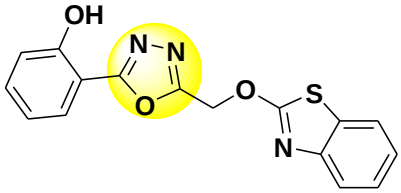
Scheme 28. Benzenesulfonamide based 1,3,4-oxadiazole derivative.

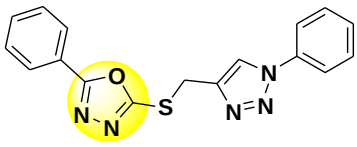
Benzothiazole clubbed 1,3,4-oxadiazole, 2-(5-((benzo[d]thiazol-2-yloxy)-methyl)-1,3,4-oxadiazol-2-yl)phenol (37) reported by Alghamdi *et al* showed cytotoxicity effect with IC_{50} 1.8 µM/mL, which was comparable to the standard drug, Doxirubicin (IC_{50} 1.2 µM/mL) [56] (Scheme 29).



37

Scheme 29. Benzothiazole linked 1,3,4-oxadiazole derivative.

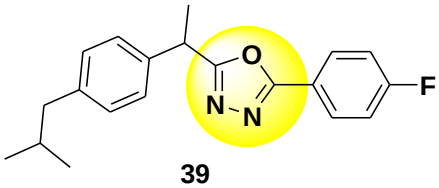
Alam *et al*. reported 4-((5-phenyl–1,3,4-oxadiazol–2-ylthio)methyl)-1-phenyl-1H–1,2,3-triazole (38) as the potent cytotoxic agent which showed significant inhibitory effects on the viability of MCF-7 and HCT-116 cells with IC_{50} 5.80 and 14.80 µM, respectively [57] (Scheme 30).



38

Scheme 30. 1,2,3-triazole linked 1,3,4-oxadiazole derivative.

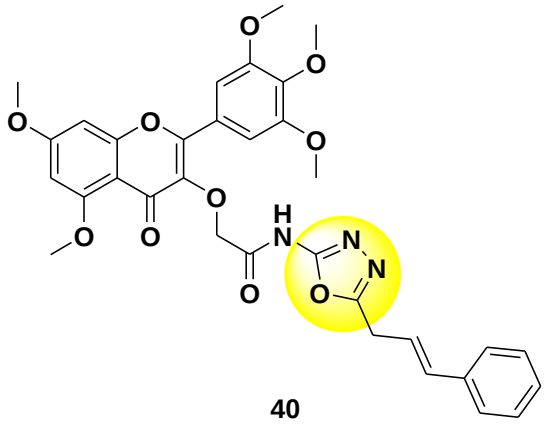
Ibuprofen-N-acyl-1,3,4-oxadiazole derivatives (39) reported by Alderawi *et al*. has shown significant cytotoxicity with 85.1% inhibition against MCF-7 cells [58] (Scheme 31).



39

Scheme 31. Ibuprofen based 1,3,4-oxadiazole derivative.

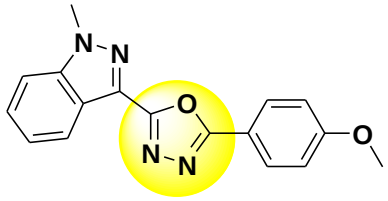
Han *et al*. reported 2-phenyl-4H-chromone derivatives containing amide and 1,3,4-oxadiazole moiety (40) as potential telomerase inhibitors with IC_{50} 0.44µM, compared to the standard drug, Staurosporine (IC_{50} 6.41 µM). Compound 40 also arrests MGC-803 cell cycle at G2/M phase and induce apoptosis [59] (Scheme 32).



40

Scheme 32. Chromone based 1,3,4-oxadiazole derivative.

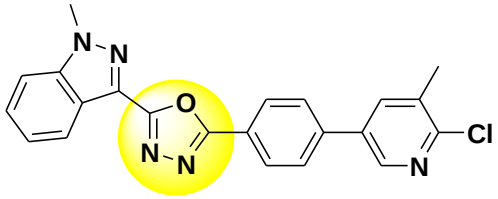
Indazole tethered oxadiazoles derivatives, 2-(4-methoxyphenyl)-5-(1-methyl- 1H-indazol-3-yl)-1,3,4-oxadiazole (41) was found to exhibit anti-cancer activity by inhibiting the catalytical activity of SIRT2 with IC_{50} 19.5 μM against HepG2 cancer cells [60] (Scheme 33).



41

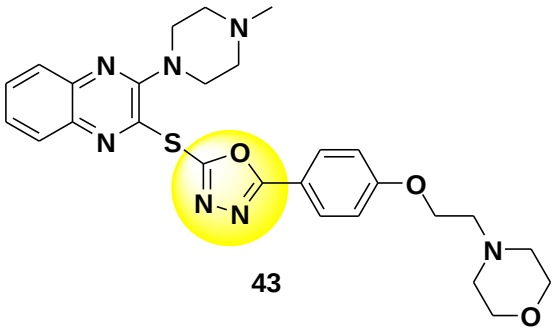
Scheme 33. Indazole based 1,3,4-oxadiazole derivative.

Malojirao discovered 2-(3-(6-chloro-5-methylpyridin-3-yl)phenyl)-5-(1-methyl-1H-indazol-3-yl)-1,3,4-oxadiazole (CHK9) (42) as a potent cytotoxic agent with IC_{50} values ranging between 4.8–5.1 μM against A549, MCf-7, A375, HepG2, Huh-7.ACHN, A498, and LLC cells [61] (Scheme 34).



42

Scheme 34. Indazole based 1,3,4-oxadiazole derivative.

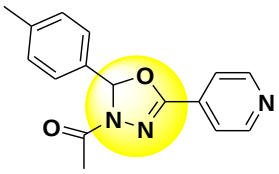


43

Scheme 35. Benzopyran based 1,3,4-oxadiazole derivative.

New benzopyran 1,3,4-oxadiazole, derivatives designed by Kumar *et al*., displayed potent anti-cancer activity on the MCF-7 cell line [62]. Quinoxaline-1,3,4-oxadiazole hybrid (43) displayed noteworthy cytotoxicity with 90% cell viability against cancer cells by inducing apoptosis through downregulation of Bcl-2 expression [63] (Scheme 35).

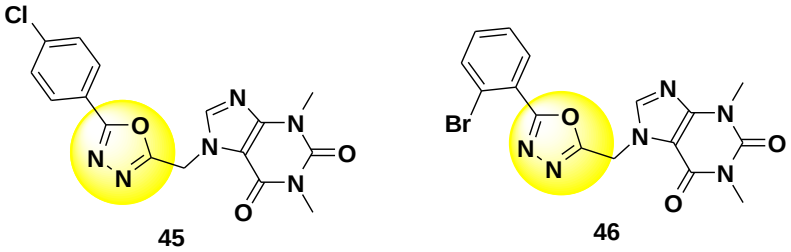
Compound 1-(5-(Pyridin-4-yl)-2-p-tolyl-1,3,4-oxadiazol-3(2H)-yl)ethanone (44) exhibited equipotent cytotoxic activity with an IC_{50} value of 8.04 µM when compared with that of standard drug doxorubicin (IC50= 8.02 µM) [64] (Scheme 36).



44

Scheme 36. Pyridine based 1,3,4-oxadiazole derivative.

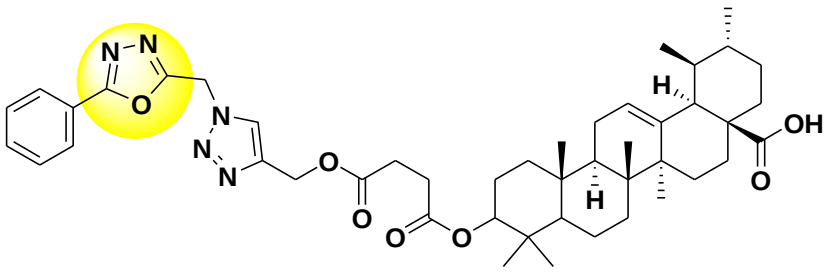
Novel theophylline-based 1,3,4-oxadiazole derivatives, (45) and (46) reported by Gopinatha *et al*.showed 6.25–8.6 fold better cytotoxicity than SCR7 in leukemic cell lines, CEM [65] (Scheme 37).



45 **46**

Scheme 37. Theophylline based 1,3,4-oxadiazole derivative.

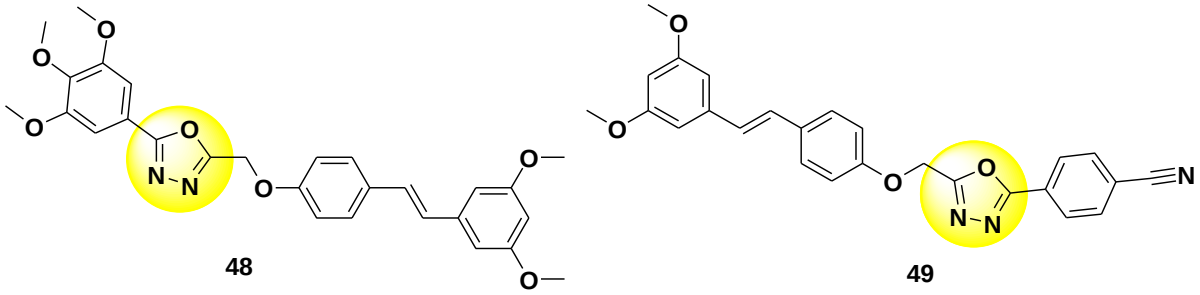
Novel Ursane 1,3,4-oxadiazole derivatives, β-(4-Oxo-4-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-1,2,3-triazol-4-yl)-methoxy)-butanoyloxy)-urs-12-en-28-oic acid (47) was found to be toxic with IC_{50} 40.26 µM towards A549 lung cancer cell line [66] (Scheme 38).



47

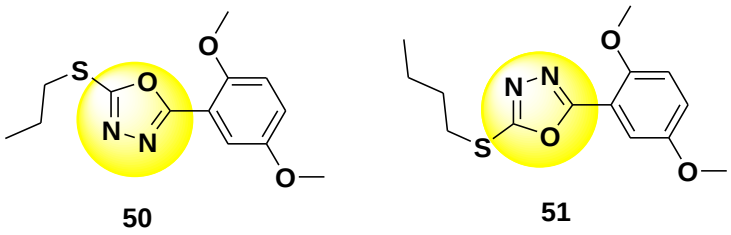
Scheme 38. Ursane based 1,3,4-oxadiazole derivative.

Resveratrol fused 1,3,4-oxadiaozle derivatives, (48) and (49) revealed better anti-cancer activity with IC_{50} in the range 0.11 µM – 1.56 µM and IC_{50} 0.45µM -1.98 µM, respectively standard drug Adriamycin showed IC_{50} in the range 2.10 µM -3.41 µM against MCF-7, A549 and MDA-MB-231 cells [67] (Scheme 39).



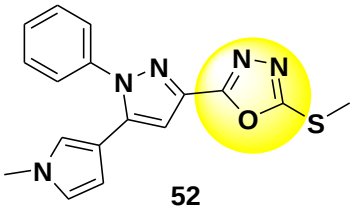
Scheme 39. Resveratrol based 1,3,4-oxadiazole derivative.

Polkam *et al*. reporetd 2-(2,5-dimethoxyphenyl)-5-propylthio-1,3,4-oxadiazole (50) and 2-(2,5-Dimethoxyphenyl)-5-butylthio-1,3,4-oxadiazole (51) as promising anticancer agents with IC_{50} 16.66 µM and 8.26 µM, respectively against prostate cancer cell line, DU145 [68] (Scheme 40).



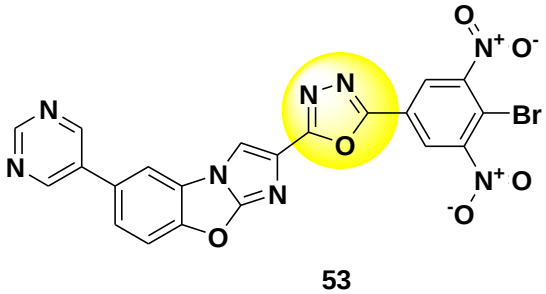
Scheme 40. Thioether based 1,3,4-oxadiazole derivative.

Abdelrehim reported 2-[5-(1-Methyl-1H-pyrrol-3-yl)-1-phenyl-1H-pyrazol-3-yl]-5-methylsulfanyl-[1,3,4]oxadiazole (52) which showed mild cytotoxicity on colon cancer cell, HCT-116 [69] (Scheme 41).



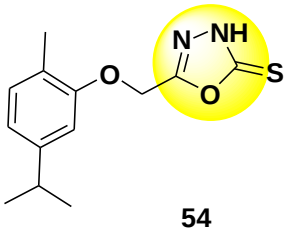
Scheme 41. Pyrazole based 1,3,4-oxadiazole derivative.

Novel pyrimidine-oxazole based 1,3,4-xadiaozle hybrids (53) demonstrated significant anti-cancer activity with IC_{50} values in the range 0.011 µM to 19.4 µM in comparison to reference drug, etoposide (IC_{50} 0.13 µM to 3.08 µM) towards MCF-7, A549, Colo-205 and A2780 cell lines [70] (Scheme 42).



Scheme 42. Benzoxazole based 1,3,4-oxadiazole derivative.

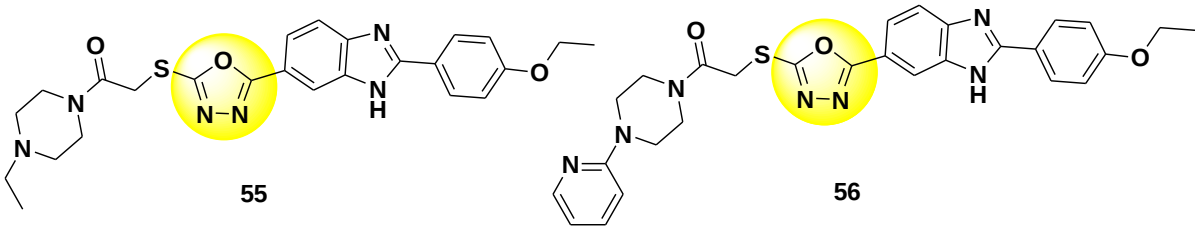
Erensoy and coworkers reported 2-[5-{[2-methyl-5-(propan-2-yl)phenoxy]methyl}-1,3,4-oxadiazol-2-yl)sulphanyl]-1-(phenyl)ethan-1-one (54) which showed inhibitory activity against mPGES-1 with an IC_{50} of 4.95 µM [71] (Scheme 43).



54

Scheme 43. Cravacrol- 1,3,4-oxadiazole hybrid.

Novel benzimidazole-1,3,4-oxadiazole hybrids (55) and (56) exhibited the potent antiproliferative activity than Hoechst 33342 and doxorubicin against HeLa cell line, with IC_{50} of 0.224 μM and 0.205 μM, respectively by inhibiting topoisomerase I enzyme [72] (Scheme 44).



55 56

Scheme 44. Benzimidazole fused 1,3,4-oxadiazole hybrid.

3. Conclusions

The article reports the different oxadiazole derivatives, which have shown significant anti-cancer potential. 1,3,4-oxadiazole is a privileged heterocycle with remarkable potential to discover new leads for cancer treatment. Furthermore, it has the potential to inhibit different enzymes which are involved in cell proliferation. The present review will give a platform to the medicinal chemists to develop new and potent 1,3,4-oxadiazole derivatives with better efficacy and reduced side effects.

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Conflicts of Interest

The authors declare no conflict of interest.

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