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Discovering 1,3,4-oxadiazole Nucleus for EGFR Inhibitory Anti-cancer Activity

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Abstract: The chemistry of heteroatoms containing cyclic compounds which are very interesting and has a larger occupancy in the field of medicinal chemistry because of their presence in a wide variety of antibiotic, anti-inflammatory, herbicidal and insecticidal, antidepressant, anti-HIV, antimicrobial, anti-tumor, antiviral, and anti-diabetic agents. In this review, the results of different researchers who have worked on 1,3,4-oxadiazole have been reviewed, and their computational and structure-activity relationship data of the various heterocyclic nucleus-1,3,4-oxadiazole hybrid derivatives have been compiled for their EGFR inhibition. 1,3,4-oxadiazole has been taken, and its role in the inhibition of cancer targets the EGFR receptor, which has been found to be expressed in almost all types of cancers. This review covers the research from 2010 to 2023. The study shows that many researchers are working on this molecule and have proved that it possesses huge potential and can be established as an anti-cancer molecule.

Keywords: 1,3,4-oxadiazole; EGFR antagonists; analogs; tyrosine kinase receptors.

1. Introduction

Cancer is a genetic disease that is caused by a change in the gene that is responsible for controlling the function of our cells. It is the second leading cause of death that is reported in the United States [1]. Cancer causes some of the body's cells to divide uncontrollably, followed by metastasis [2]. Till now, more than 100 different types of cancer have been studied, and many new cases and cancer-related deaths have also been reported [3,4]. There are reports that the new number of cancer cases can jump to 28.4 million by the year 2040 all over the world [5-7]. There are many targets on which the researchers are going to find an effective cure for cancer [8-9]. Amongst the targets, one of the most expressed targets in different types of cancers is EGFR, which stands for Epidermal Growth Factor Receptor.

EGFR is a cellular tyrosine kinase receptor that has been observed to be expressed in almost all types of cancers [10]. The inhibition of tyrosine kinases has emerged as one of the most clinically advanced techniques for anti-cancer therapy [11-13]. The tyrosine kinases (TKs) receptors are considered an attractive target for cancer therapy. Of all the receptors tyrosine kinases, the EGFR, also known as ErbB or HER receptors, is one of the important targets in many cancers like breast cancer [14], lung cancer, etc [15-16]. The EGFR is a part of the ErbB family of receptors, and the subfamily includes four closely related receptors, namely EGFR (ErbB-1), HER2/neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4) [17]. EGFR is a key

regulator of many complex human biological activities, including motility, cell adhesion, and their regulation, along with cell adhesion, angiogenesis, apoptosis, and metastasis [18-19]. It is over-expressed in some human tumors like breast, ovarian, colon, renal, and prostate tumors, and the dysregulation of EGFR signaling is invariably associated with poor clinical outcomes. There are reports that due to drug resistance and toxicity that are involved with the existing EGFR inhibitors available in the market, there is a need to develop a new molecule [20-21]. It is proposed that compounds that can inhibit tyrosine kinase activity may have an important role in cancer treatment [22].

The compounds containing heteroatoms, also known as heterocyclic, occupy the heart of many established drugs and have shown their presence in a wide variety of drugs like antibacterial, antifungal, anthelmintic, NSAIDs, Steroidal drugs, antiprotozoal agents, hypoglycaemic agents, antidepressants and many more classes of drugs [23]. In fact, a considerable number of heterocycles have already been discovered as potent anti-cancer agents in discoveries made by different scientists [24].

This article focuses on the chemistry of oxadiazole, a five-membered azole family compound with one oxygen and two nitrogen atoms, and the chemical formula $C_2H_2N_2O$ [25]. According to the position, oxygen and two nitrogens in the oxadiazole ring have given four types of isomers, namely 1,2,4-oxadiazole, 1,2,3-oxadiazole, 1,3,4-oxadiazole and 1,3,5-oxadiazole as shown in Figure 1 [26].

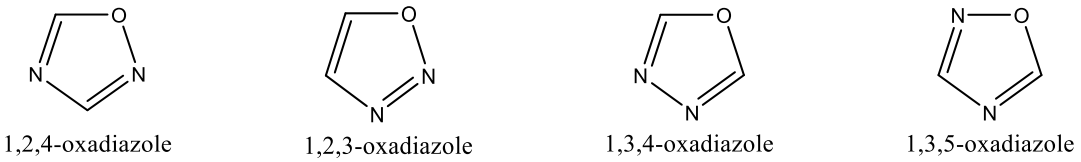


Figure 1. Isomeric forms of oxadiazoles [25-26].

This review mainly covers the 1,3,4-oxadiazole nucleus, which has shown good lipophilicity. Various reports show that it has a good binding interaction with receptors and thus inhibits different enzymes [27-28]. It is also a very good bioisostere of esters and amide groups, enhancing its pharmacological activity [29-30]. It has anti-inflammatory, analgesic, antibacterial [31], anti-cancer [32], antifungal, anti-convulsion, anti-hypertensive, muscle relaxant, and mono amino oxidase inhibitory activities [33-34]. The 1,3,4-oxadiazole rings are not only reported in many research papers but there are established drugs like raltegravir [35-36] and zibotentan [37] (Figure 2) that contain the oxadiazoles ring and are widely used for the treatment of cancer. These characteristics make the ring ideal for research purposes, and they can be used to generate new anti-cancer drugs.

According to literature reviews, substituted 1,3,4-oxadiazole derivatives can exert anticancerous activity through a variety of enzymes and growth factors and multiple mechanisms that may include tyro-sine kinase [38], telomerase [39], thymidylate synthase [40], mesenchymal-epithelial transition factor receptor (c-MET) [41], epidermal growth factor receptors (EGFR, HER2), focal-adhesion kinase (FAK) [42] and tubulin polymerase [43-44], or the thymidine phosphorylase during the DNA structure formation [45]. 1,3,4-Oxadiazole rings are used as bioisosteres for carbonyl-containing compounds, offering increased water solubility and improved metabolic stability [46].

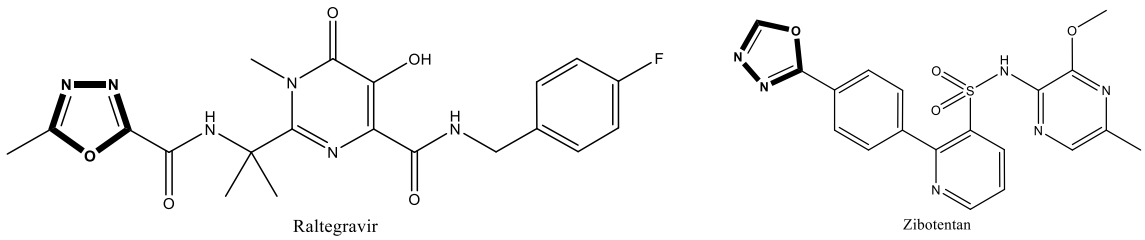


Figure 2. Examples of known drugs containing 1,3,4-oxadiazole as anti-cancer agents [35-37].

The oxadiazole ring has proven to be a good pharmacophore for the development of anti-cancer agents. Many researchers have developed hybrid molecules combining two or more different pharmacophores to develop a distinct pharmacophore, which has shown enhanced biological and novel pharmacological results. These hybrid molecules showed enhanced pharmacological and biological activity, potency, and selectivity towards the receptors and the half-life, which is quite different from their structural components. These hybrid molecules, when formulated, are found to be cost-effective with enhanced activity [47-48]. Many 2,5 di-substituted 1,3,4-oxadiazole compounds have been found to have promising anti-cancer activity [49]. Due to the extensive anti-cancer activity of 1,3,4-oxadiazole nucleus derivative, in this review, we want to summarize the various work done over the last decade from 2010 to 2023 using the Google Scholar database. We strongly believe that this review will provide a platform for researchers and biologists to design and synthesize new and potent compounds that inhibit EGFR and ErbB-2 for the treatment and management of cancer.

2. Material and Methods

For this review, the Google Scholar search engine has been widely searched from 2010 to 2023. All the research papers have been carefully studied and, according to the reporting of the heterocyclic nucleus that has shown good pharmacological activity against the EGFR receptors, have been incorporated with sufficient details and appropriate citations in the paper for the research work.

3. Anticancerous Activity of 1,3,4-oxadiazole Analogues as EGFR Antagonists

3.1. 1,3,4-oxadiazole hybrids of pyridine anticancerous drugs.

Many researchers have studied the anticancerous activity of the pyridine nucleus, and numerous modifications and derivatization have also been carried out [50].

In context, Khalil *et al*. designed a number of five substituted-1,3,4-oxadiazole and pyridine derivatives for developing potential anti-tumor agents. The molecular docking studies in the structure of the active site showed good interaction with the target molecule EGFR, and amongst all two of the compounds, 1 and 2 that have substituted indole at position 3 and ethyl phenyl at position 4 showed IC_{50} value of 0.010 μM and 0.012 μM respectively compared to the standard drug erlotinib with IC_{50} value of 0.020 μM which is almost double the potency of the standard drug [51].

Moreover, Ahsan *et al*. synthesized pyridine-2-amines incorporated oxadiazoles and evaluated the antiproliferative activity of HeLa and MDA-MB-435, compounds 3, 4, and 5, which showed the percent growth inhibitions of 34.14, 35.29, and 31.59 respectively. The SAR studies suggested that the 4-methoxyphenyl substitution at the 5^{th} position in oxadiazoles showed more significant results than the 4-chlorophenyl and 3,4-dimethoxyphenyl group at the

same position. The binding interaction was also studied, and it was found that the compounds were efficiently binding to the active site of EGFRTK [52].

In addition, El-Sayed *et al*. synthesized three and four substituted pyridines and 1,3,4-oxadiazole hybrid compounds and studied the inhibitory activity on isoforms of the COX receptors. Compounds 6, 7, and 8 showed good and selective COX-2 inhibition with IC_{50} values of 0.041 μM, 0.17 μM, and 0.081 μM taking celecoxib reference with IC_{50} value of 0.049 μM. All these compounds were studied for their EGFR kinase inhibitory activity, and compound 7, containing no substituent on the phenyl group, showed nearly double potency with IC_{50} value 0.2757 μM than the reference compound erlotinib with IC_{50} value 0.4178 μM [53].

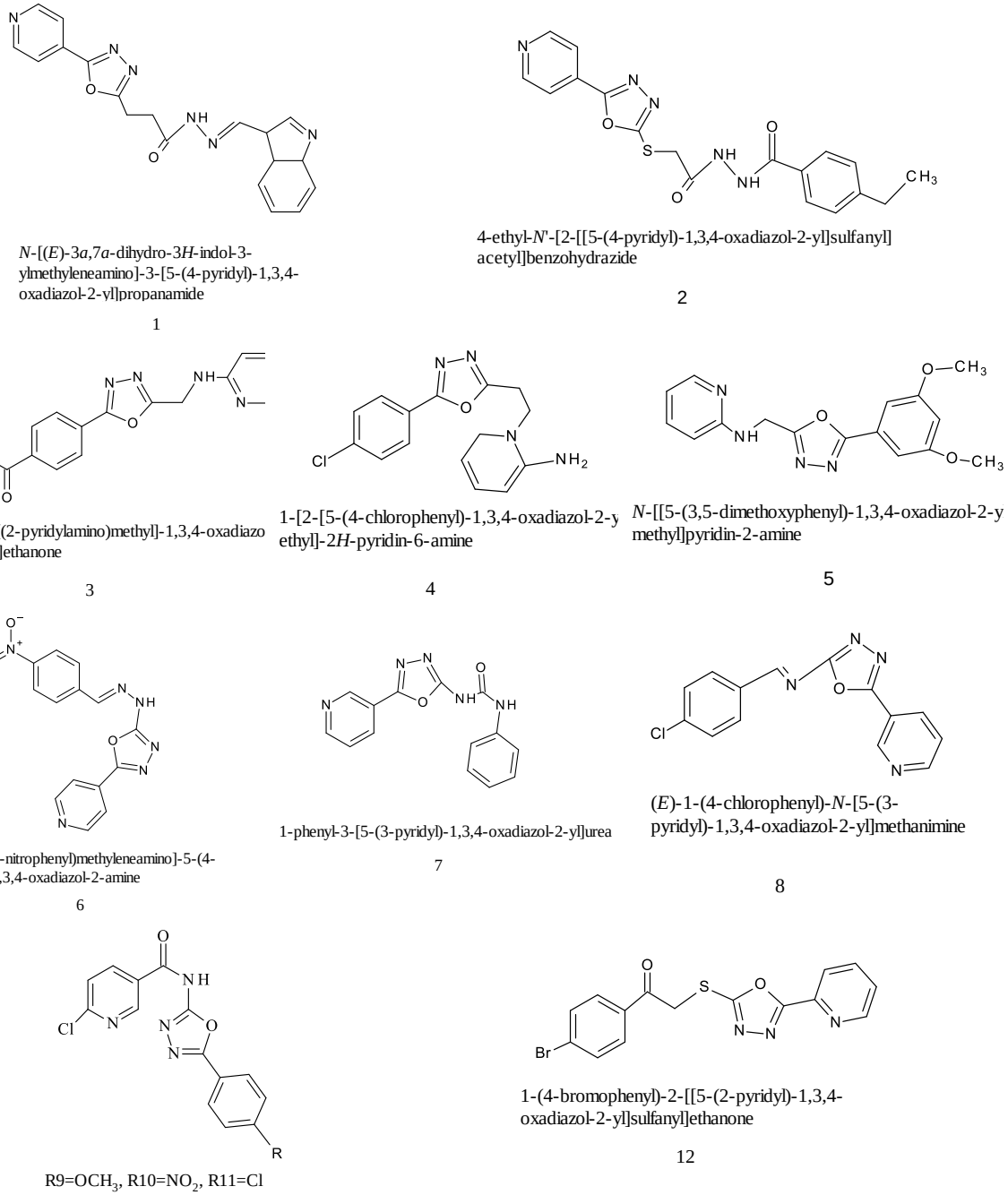


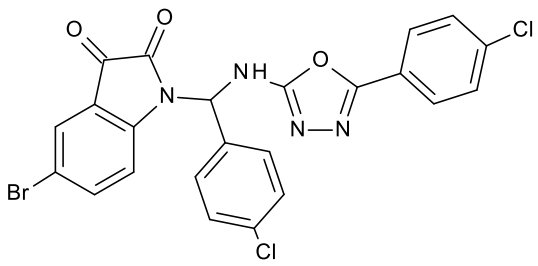
Figure 3. 1,3,4-oxadiazole hybrids of pyridine with antiproliferative activity [51-55].

Hassanzadeh *et al*. synthesized a new series of 2, 5-disubstituted 1, 3, 4-oxadiazole incorporated pyridine compounds and evaluated their cytotoxic activity against MCF-7 and HeLa cell lines. The compounds were studied for their molecular interaction with the binding sites of the EGFR crystal structure by the molecular docking study. Compounds 9-11

containing methoxy, nitro, and chloro group, respectively, at the second position in the pyridine ring showed cytotoxic activity with IC_{50} values of 19.9, 35, and 25.1 µM, respectively, against HeLa cell lines with a good docking score of -7.89 kcal/mol for compound 11 [54]. Moreover, Abbas *et al*. designed and synthesized Pyridine-2-carboxylic acid incorporated 1,3,4-oxadiazole hybrids and evaluated the compounds' anti-tumor activity against the MCF-7 breast cancer cell line. The designed compounds were also subjected to molecular docking studies against EGFR kinase, which revealed that amongst the designed compounds, compound 12 occupies the vital site of the EGFR kinase pocket and has a good binding score of -4.98 kcal/mol using erlotinib as a standard drug with the binding score of -5.90 kcal/mol [55]. The structures of pyridine-containing compounds are depicted in Figure 3.

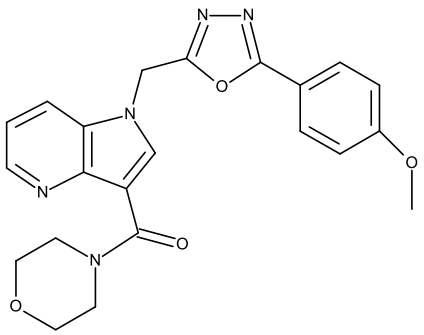
3.2. Indole incorporated 1,3,4-oxadiazole.

Indole is a six-membered benzene ring fused with a five-membered pyrrole ring, which shares a promising history as an anti-cancer drug [56]. The most prominent among them have been vincristine vinblastine.



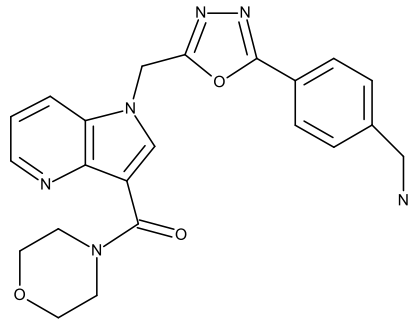
5-bromo-1-[(4-chlorophenyl)-[[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]amino]methyl] indoline-2,3-dione

13



[1-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl] pyrrolo[3,2-b]pyridin-3-yl]-morpholino-methanone

14



[1-[[5-[4-(aminomethyl)phenyl]-1,3,4-oxadiazol-2-yl] methyl]pyrrolo[3,2-b]pyridin-3-yl]-morpholino-methanone

15

Figure 4. Indole-containing anti-cancer drugs reported in the literature [57-58].

Priyanka Bhatt *et al*. synthesized isatin, phthalimide, and benzoxazoles as N-heterocycles compounds fused with the 1,3,4-oxadiazole nucleus and investigated the cytotoxicity results of the compounds against human breast cancer cell line, colorectal adenocarcinoma cell line, and liver adenocarcinoma cell line using standard drug doxorubicin and 5-fluorouracil. Among all the analogs, compound 13 containing indoline-2,3-dione and p-chlorophenyl and phenol group as the substituent exhibited the highest activity against the breast and colorectal cell lines with an IC_{50} value of 0.78 µM/mL and 0.26 µM/mL respectively. The in-silico studies also suggested that the compound showing the highest activity binds

effectively to the EGFR kinases with a binding energy of -9.9 kcal/mol [57]. Moreover, Gangadhar *et al*. designed4-azaindole and 1,3,4-oxadiazole conjugates and studied them for the antiproliferative activity towards the three cell lines, that is, MCF-7, A549, and HepG2 using MTT assay. Compounds 14 and 15 containing 4-methoxyphenyl and benzo nitrile as substituents showed superior antiproliferative activity against all the cell lines with IC_{50} values between 1.12 to 14.15 µM and erlotinib was taken as the reference drug. Compound 14 also showed highest binding energy of -10.37 kcal/mol in the pockets of EGFR [58].

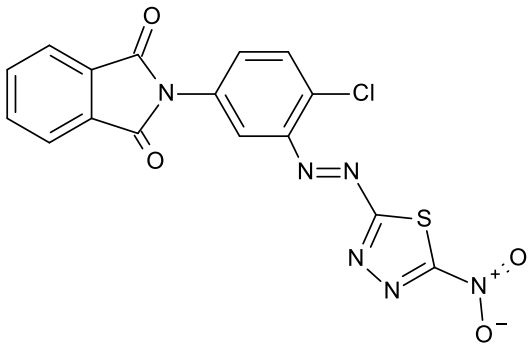
3.3. Thiazole incorporated 1,3,4-oxadiazole.

Thiazole is a heterocyclic compound containing sulfur and nitrogen in the first and third positions. It has quite promising activity and is anticancerous [59].

In context to this, Gaddam *et al*. synthesized a series of 1,3,4-oxadiazole and thiazolan-4-ones fused heterocycles and studied the compounds for their antimicrobial, nematicidal, and anti-cancer activities. The *in vitro* studies suggested that the compounds containing electron-withdrawing groups like chloro, nitro, and fluoro groups have significant activity than the standard compound. In contrast, compounds with electron-donating groups like methyl, hydroxy, amino methyl, and methoxy groups have superior or comparable activity against the standard compound. The molecular docking study also showed the same correlation in the docking score results [60].

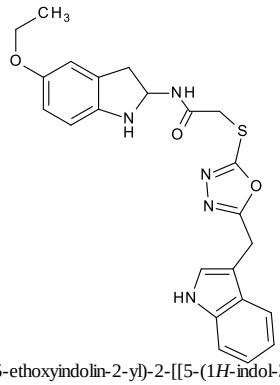
Priyanka Bhatt *et al*. designed, synthesized, and investigated azo-linked 1,3,4-thia/oxadiazole with cyclic imides derivatives. The compounds were evaluated for their cytotoxicity against human cancer cells using an MTT assay and a reference drug, doxorubicin. Compound 16 containing 1,3,4-thiadiazole with isoindole-2,3-dione showed good binding interaction with the EGFR receptors with the IC_{50} value of 0.09 ± 0.50 µM compared to the oxadiazole derivative that showed lesser binding interaction [61].

Furthermore, Belgin Sever *et al*. developed and synthesized a range of indole, 1,3,4-oxadiazole, and thiazole/benzothiazole-based analogs, then tested their cytotoxicity using the standard drug erlotinib. Compound 17 was the only one of the produced compounds that demonstrated a strong inhibitory effect on EGFR with an IC_{50} value of 2.80 ± 0.52 µM compared to the standard drug erlotinib having an IC_{50} value of 0.04 ± 0.01 µM. The promising EGFR inhibitory effect is attributable to the 6-ethoxybenzothiazole, according to an in silico molecular docking analysis [62]. The structures of pyridine-containing compounds are depicted in Figure 5.



2-[4-chloro-3-[(*E*)-(5-nitro-1,3,4-thiadiazol-2-yl)azo] phenyl]isoindoline-1,3-dione

16



N-(5-ethoxyindolin-2-yl)-2-[[5-(1*H*-indol-3-ylmethyl)-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide

17

Figure 5. Thiazole-containing anti-cancer drugs are reported in the literature [60-62]

3.4. Diphenylamine incorporated 1,3,4-oxadiazole.

Various researchers have reported that diphenylamine possesses EGFR-inhibiting activity and acts as a promising scaffold for developing novel anti-cancer agents [63]. Abou-Seri *et al.* (2010) synthesized a series of bis-substituted-diphenylamine incorporating isostere 1,3,4-oxadiazole rings as substituents. He synthesized four analogs of 1,3,4-oxadiazole, and it was found that mercapto group containing 1,3,4-oxadiazole series showed a 48 percent inhibition, for which the researcher reasoned it might be due to the free SH group, which causes decreased cellular penetration. In the other three oxadiazole derivatives, he modified the 5-mercapto with an allyl group, which increased the activity. The substitution of the ethyl group resulted in decreased inhibitory potency against EGFR. The addition of the benzyl group yielded compound 18, which had the most potent EGFR inhibitory action on the human breast cancer cell line, with an IC_{50} of 0.73 mM for anti-cancer activity [64].

Ezzat *et al*. designed and synthesized a series of compounds, including 2,5-disubstituted-1,3,4-oxadiazoles, 2-substituted thio-5-substituted-1,3,4-oxadiazoles, and Mannich bases of 5-substituted-1,3,4-oxadiazole-2(3H)-thiones, all containing a diphenylamine moiety. The compounds were then tested for their anti-tumor activity against the human tumor cell lines HT29 and MCF7. The results of the anti-tumor activity study revealed that most of the synthesized compounds displayed significant activity against the HT29 cell line, in contrast to the MCF7 cell line. Out of the all-synthesized compounds, four compounds 19-22 showed only a good percent of resistant fraction with (IC_{50}=3.6, 9.0, 9.5, and 6.6 µM, respectively [65]. The structures of Diphenylamine-containing compounds are depicted in Figure 6.

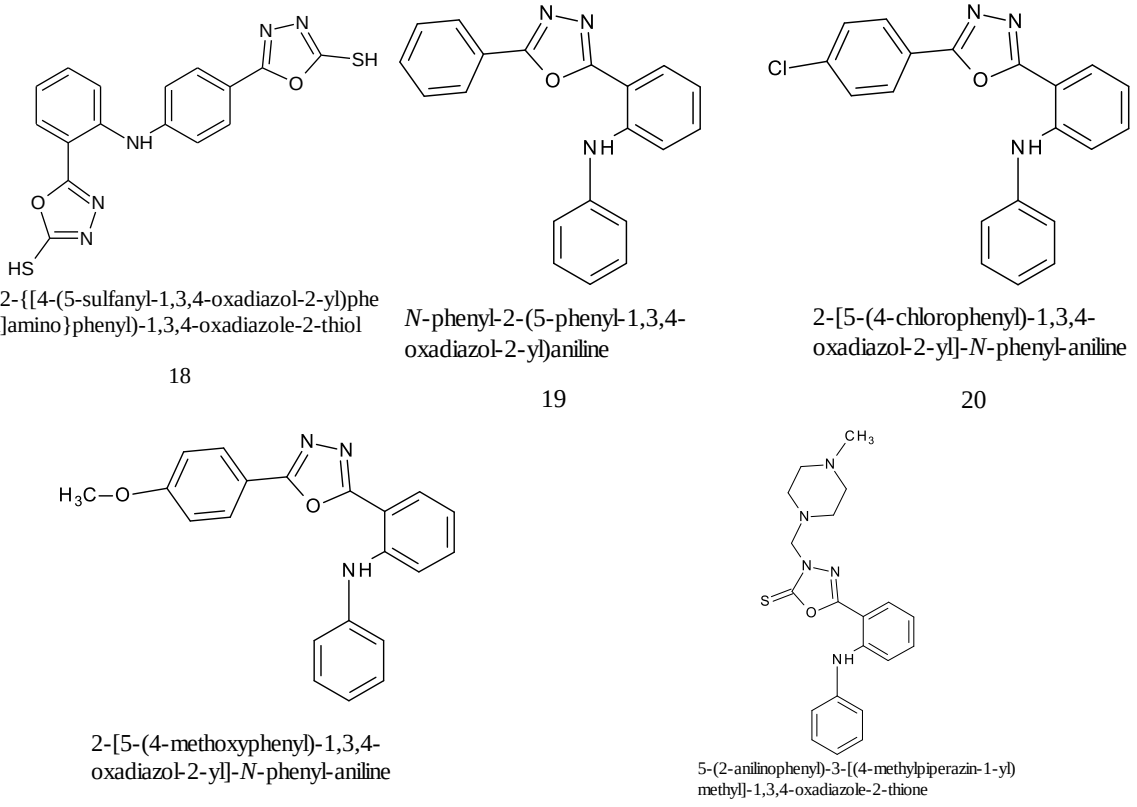
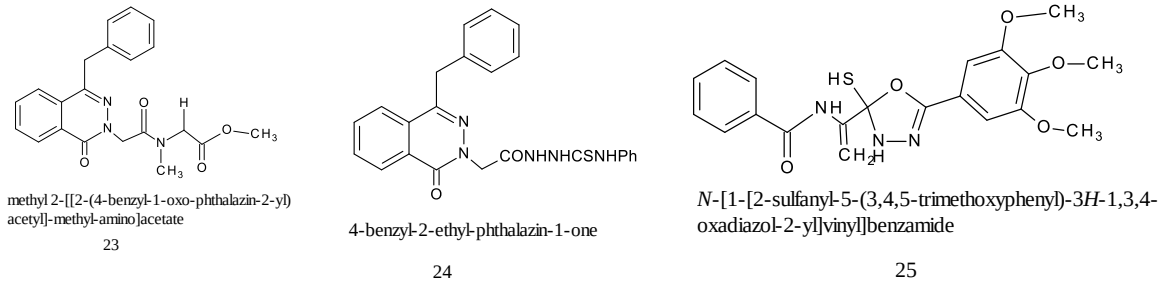


Figure 6. Diphenylamine containing anti-cancer drugs reported in the literature [64-65].

3.5. Styryl incorporated 1,3,4-oxadiazole.

Several published reports prove that styryl moiety containing 1,3,4-oxadiazoles has better potency and efficacy as an anti-cancer agent [66]. Boraei *et al*. designed and synthesized a series of analogs combining the phthalazines and 1,3,4-oxadiazoles. The anti-tumor activity of the synthesized compounds was investigated using doxorubicin as the reference medication against the human hepatocellular carcinoma cell line HepG2. The compounds were found to exhibit promising activity ranging against hepatocellular carcinoma. The compounds showed promising activity in the *in vitro* as well as in vivo experiments. The compounds were docked against the EGFR crystal structure and shown to have a high affinity for the EGFR receptors. Two compounds 23 and 24 were found to show good activity and binding affinity with EGFR and showed good interaction with the binding sites with IC_{50} values of 5.7 µg/mL and 7.09 µg/mL, respectively, compared to the reference drug doxorubicin with IC_{50} value of 4.0 µg/ml [67].

Vinjavarapu *et al*. synthesized a series of compounds incorporating the 1,3,4-oxadiazole nucleus of 1,3,4-oxadiazole with styryl moiety at position five and a thiol group at position two. She also substituted various groups on the phenyl ring and replaced the styryl moiety with a benzoyl amino group on the alpha-carbon. All the compounds were tested for cytotoxic activity using different cell lines like MCF-7, HeLa, and A549 and were docked using molecular docking simulations with human EGFR 2 (HER2), which are supposed to play a key role in the breast tumor. Compound 25, which includes 3,4,5-trimethoxy phenyl, demonstrated promising cytotoxicity against MCF-7 cell lines with an IC_{50} value of 17.12 M, compared to the standard medication cisplatin, which has an IC_{50} value of 12.06 M. According to the literature, the compound has good activity because it occupies a favorable area in the colchicine binding site [68]. The structures of styryl-containing compounds are depicted in Figure 7.



methyl 2-[[2-(4-benzyl-1-oxo-phthalazin-2-yl) acetyl]-methyl-amino]acetate
23

4-benzyl-2-ethyl-phthalazin-1-one
24

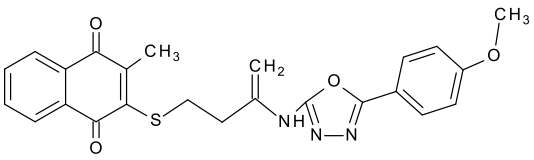
N-[1-[2-sulfanyl-5-(3,4,5-trimethoxyphenyl)-3*H*-1,3,4-oxadiazol-2-yl]vinyl]benzamide
25

Figure 7. Styryl-containing anti-cancer drugs are reported in the literature [67-68].

3.6. Naphthoquinone incorporated 1,3,4-oxadiazole.

Naphthoquinones are obtained from natural sources, and due to undergoing easy addition reaction on the aromatic ring, it has been found to be used as a promising pharmacophore for anticancerous drug development [69].

Besan *et al*. designed a set of compounds combining two different heterocycles, 1,3,4-oxadiazole with 1,4-naphthoquinone. The synthesized compounds were assessed for cytotoxicity activity using an MTT Assay. The compounds were docked using the EGFR protein's crystal structure, and the results showed that they exhibited good binding affinity for the protein, with docking scores ranging from -50.71 to -67.04. Amongst the compounds that were docked, one of the compounds 26 showed the highest binding core for EGFR with a docking score of 67.04 [70]. The structures of naphthoquinone-containing compounds are depicted in Figure 8.



2-[3-[[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]amino]but-3-enylsulfanyl]-3-methyl-naphthalene-1,4-dione

26

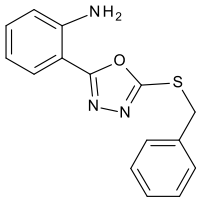
Figure 8. Naphthoquinone containing anti-cancer drugs reported in the literature [70].

3.7. Chalcone incorporated 1,3,4-oxadiazole.

Chalcones, chemically known as 1,3-diaryl-2-propen-1-one, is a secondary metabolite of flavonoids and has been widely used to develop potent anti-cancer agents [71].

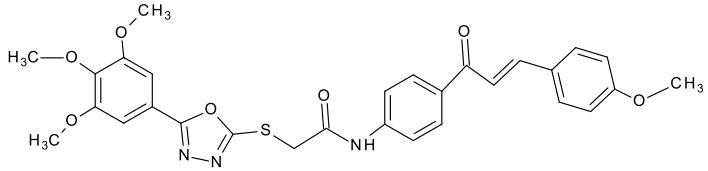
Liu *et al*. synthesized a series of 2-(benzylthio)-5-aryloxadiazole derivatives and evaluated the inhibitory effect on EGFR receptors. They selected ten compounds that had previously shown good biological activity against the MCF cell line and tested their proliferative inhibitory potency against the EGFR receptors. Compound 27 had the strongest inhibitory action against EGFR receptors, with an IC_{50} value of 1.51 mM compared to Gefitinib, which had an IC_{50} of 0.02. The docking study showed good binding affinity and was in accordance with the biological activity [72].

Fathia *et al*. synthesized a new hybrid series of 1,3,4-oxadiazole and chalcone and investigated their EGFR-inhibiting activity. Compound 28 was found to be the most potent among the series, with an IC_{50} value of 0.24 ± 0.035 μM against the standard drug Gefitinib, with an IC_{50} value of 0.023 ± 0.004. The 1,3,4-oxadiazole nucleus with substitutions like hydroxy, para-methoxy, or ortho, meta, para-trimethoxy group demonstrated greater biological activity against the malignant cell in structure-activity relationship investigations [73]. The structures of chalcone-containing compounds are depicted in Figure 9.



2-(5-benzylsulfanyl-1,3,4-oxadiazol-2-yl)aniline

27



N-[4-[(*E*)-3-(4-methoxyphenyl)prop-2-enoyl]phenyl]-2-[[5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide

28

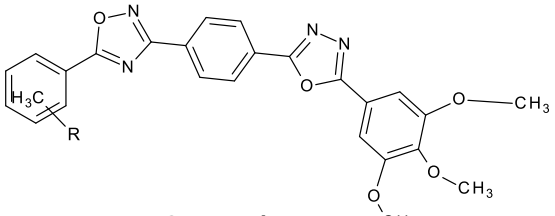
Figure 9. Chalcone-containing anti-cancer drugs reported in the literature [72-73].

3.8. 1,2,4-. Oxadiazole incorporated 1,3,4-oxadiazole.

Derivatives of 1,2,4-oxadiazole have been shown to exhibit some structural similarity between some known EGFR inhibitors that are available in the market, like 5-glycosyloxadiazole reported by some researchers [74].

In quest of promising new leads with potential anti-cancer action, Polothia *et al*. synthesized a series of 1,2,4-oxadiazole and 1,3,4-oxadiazole coupled with 3-substituted indole. The compounds were tested for their *in vitro* anti-cancer activity on MCF-7 cell lines using the MTT assay with doxorubicin as the reference drug. With IC_{50} values ranging from 0.3± 0.025 to 2.45 ± 0.023 M, the compounds demonstrated promising anti-cancer action. The structure-activity relationship revealed that compounds 29-32 containing R as the nitro substituent had the highest anti-cancer activity with an IC_{50} value of 0.34 ± 0.025 on MCF cell lines when compared to the other substituents, which is also consistent with the molecular

docking study, which revealed the highest docking score of -7.028 and glide energy was also less [75]. The structures of 1,2,4-oxadiazole-containing compounds are depicted in Figure 10.



R=3,4,5-trimethoxy
R=4-nitro
R=3-nitro
R=4-cyano

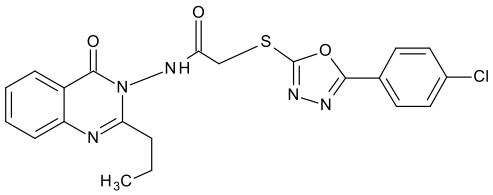
29-32

Figure 10. 1,2,4-Oxadiazole containing anti-cancer drugs reported in the literature [75].

3.9. Quinazoline incorporated 1,3,4-oxadiazole.

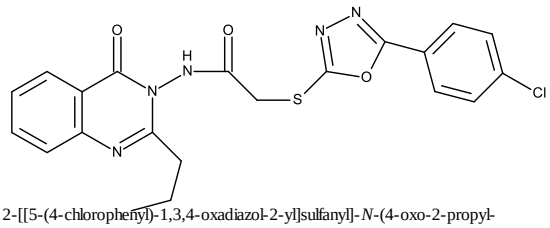
Quinazoline, a benzene ring fused with pyrimidine, has been found to act as a promising scaffold for developing anti-cancer agents with EGFR inhibition [76].

Qiao *et al*. designed and synthesized a number of derivatives comprising the 4-alkoxyquinazoline and 1,3,4-oxadiazole moiety and tested their antiproliferative ability against MCF-7 cell lines. The interactions of these analogs with VEGFR receptors were investigated using molecular docking. The molecular docking analysis revealed that compound 33 had a minimum interaction energy of -50.5831 kcal/mol, with Tivozanib as the reference medication having an interaction energy of -47.6633 kcal/mol [77].



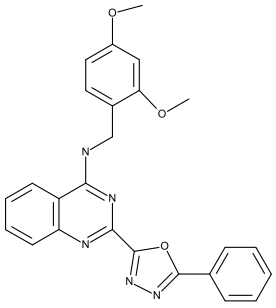
2-[[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]-*N*-(4-oxo-2-propyl-quinazolin-3-yl)acetamide

33



2-[[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]-*N*-(4-oxo-2-propyl-quinazolin-3-yl)acetamide;molecular hydrogen

34



N-[(2,4-dimethoxyphenyl)methyl]-2-(5-phenyl-1,3,4-oxadiazol-2-yl)quinazolin-4-amine

35

Figure 11. Quinazoline contains anti-cancer drugs, as reported in the literature [77-78].

Hassanzadeh *et al*. studied the synergistic response of quinazolinone and 1,3,4-oxadiazole nuclei for their cytotoxic studies. The cytotoxic studies of the compounds against HeLa and MCF-7 cell lines using MTT assay showed that the compound 34 showed promising cytotoxic effect with IC_{50} value of 82.18 ± 3 µM (MCF-7) (7.52 ± 0.6 µM (HeLa) [78]. Sangande *et al*. synthesized amino-quinazoline incorporated 1,3,4-oxadiazole hybrids and were studied for *in vitro* and *In silco* activity against EGFR and HER2 receptors. Compound 35,

containing the methoxy phenyl group as a substituent on the second position of the oxadiazole ring, showed the most promising activity with an IC_{50} value of 5.02 µM in the molecular docking studies [79]. The structures of quinazoline-containing compounds are depicted in Figure 11.

3.10. Quinoline incorporated 1,3,4-oxadiazole.

Quinoline is a bicyclic heterocyclic ring in which the benzene ring is fused with the pyridine ring and has been widely researched for the development of anti-cancer drugs [80]. This ring is a very important quinolone alkaloid and has been incorporated in various heterocyclic nuclei to develop anti-cancer agents. Some marketed drugs containing quinoline rings are tipifarnib, Bosutinib, Topotecan, etc. [81].

In search of some potent anti-cancer compounds, Salahuddin *et al*. designed and synthesized 1,3,4-oxadiazole, incorporating quinoline in its structure, and evaluated the compounds for their anti-cancer activity. Two of the compounds 36, 37 showed marked antiproliferative activity in the growth percent in one dose assay procedure against the cell lines MCF7, MDA-MB-231/ATCC with GI_{50} values ranging from 1.41 to 15.8 µM and 0.40 to 14.9 µM respectively [82].

Further, Vismaya *et al*. designed a novel series of 2-(4-chlorophenyl)-5-aryl-1,3,4-oxadiazoles and studied their binding interaction with the EGFR tyrosine kinase active site. Compound 38 showed a good binding score with the critical amino acid residue Lys 745 of EGFR and proved a promising molecule that can be considered for future studies [83].

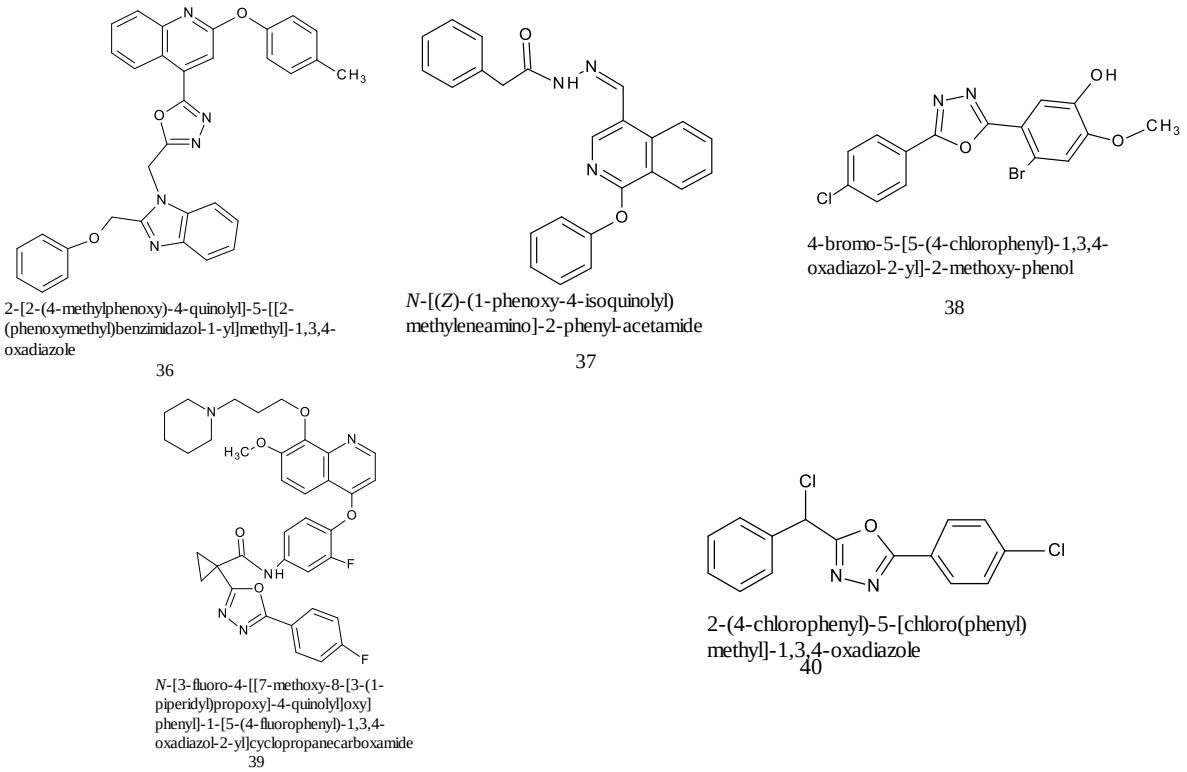


Figure 12. Quinoline-containing anti-cancer drugs reported in the literature [82-85].

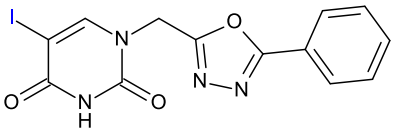
Moreover, Congjun Xu *et al*. designed and synthesized a series of 6,7-disubstituted quinoline-1,3,4-oxadiazole derivatives in the search for potent and safer anti-cancer molecules. They carried out the experiment to see the Axl kinase inhibition activity using Cabozantinib and Foretinib as standard. The experiment showed that along with the promising Axl inhibition,

compound 39 showed good EGFT-TK inhibition with an IC_{50} value of 0.081 μM [84]. Then, Hassanzadeh *et al*. synthesized a new series of 2, 5-disubstituted 1, 3, 4-oxadiazole compounds and evaluated their cytotoxic activity against MCF-7 and HeLa cell lines. The compounds were studied for their molecular interaction with the binding sites of the EGFR crystal structure by the molecular docking study. The designed compound 40 showed good binding activity to EGFR tyrosine kinase receptors with a docking score of -7.89 kcal/mol [85]. The structures of quinoline-containing compounds are depicted in Figure 12.

3.11. Purine and pyrimidine incorporated 1,3,4-oxadiazole.

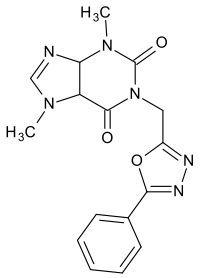
Purine and pyrimidines are the important nucleotides that constitute the RNA and DNA. Their derivatives, also known as antimetabolites, have been well-studied for developing anti-cancer agents [86].

With the goal of developing new anti-cancer and cytotoxic medicines, Mansouri *et al*. developed and synthesized a novel series of 1,3,4-oxadiazole-pyrimidines and purines ring-containing hybrids. The compounds were tested for anti-cancer action *in vitro* against breast and leukemia cancer cell lines using doxorubicin as the standard drug and compounds 41 and 42 showed good antiproliferative activity. These two compounds exhibit good binding into the active sites of EGFR in a molecular docking investigation, with inhibition constants of 1.25 for and 3.18 mM, respectively [87]. The structures of purine and pyrimidine-containing compounds are depicted in Figure 13.



5-iodo-1-[(5-phenyl-1,3,4-oxadiazol-2-yl) methyl]pyrimidine-2,4-dione

41



3,7-dimethyl-1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-4,5-dihydropurine-2,6-dione

42

Figure 13. Purine and pyrimidine-containing anti-cancer drugs are reported in the literature [87].

3.12. Benzimidazole incorporated 1,3,4-oxadiazole.

Benzimidazole has been reported to be an isostere of purine nucleotides [88] in which the benzene ring is fused with the imidazole ring and a promising scaffold for developing anti-cancer agents [89].

In the same context, Akhtar *et al*. synthesized a novel series of benzimidazoles combining 1,3,4-oxadiazole nuclei to target EGFR and erbB2 receptors. Compound 43, 44, whose para position is substituted with the chloro and methoxy group in the phenyl ring at the 5^{th} position of 1,3,4-oxadiazole found to be the most potent one with the IC_{50} value of 5.0 μM and 2.55 μM respectively. The molecular docking study was also carried out to see the binding affinity to protein kinase receptors, and the binding pattern resembled the standard drug erlotinib, an established EGFR inhibitor [90].

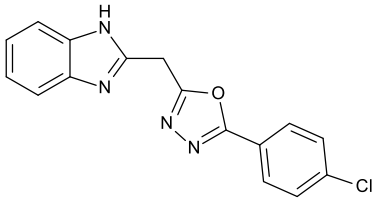
Furthermore, Katikireddy *et al*. designed and synthesized a new series of hybrid 1,3,4-oxadiazoles and benzimidazole studied the compounds for their anti-cancer activity, and conducted molecular docking studies. The compounds were tested for their *in vitro* activity

against the different cell lines like HeLa, MCF-7, and A549. One of the compounds, 45, showed promising activity with IC_{50} values of 4.68 ± 0.04, 4.16 ± 0.02, and 5.40 ± 0.08 mM against the HeLa, MCF-7, and A549 cell lines, respectively, using the reference drug doxorubicin. The docking result also matched the *in vitro* studies and showed good binding affinity into the erlotinib binding region [91].

Similarly, Alzahrani *et al*. synthesized 1, 3, and 4-oxadiazole-based benzimidazole hybrids and tested their antiproliferative activity. Compounds 46-48 showed promising activity with IC_{50} 2.39–10.98 μM, 4.57–16.35 μM, and 3.10-15.58 μM against MCF-7, HepG2, and HCT-116 cell lines. The molecular docking studies exhibited high inhibition with EGFR kinases with IC_{50} 0.91–2.1 μM and showed high binding energy of −8.34, −8.06, and −8.08 Kcal/mol, respectively [92].

Moreover, Hagar *et al*. designed the benzimidazole-incorporated oxadiazole nucleus and studied their binding interaction in the ATP binding site of EGFR using the standard drug erlotinib. The compounds 49-53 showed good binding interaction in the 7.4 kcal/mol range to - 8.7 kcal/mol compared to erlotinib, with an IC_{50} value of -9.7 kcal/mol. In silico physicochemical and pharmacokinetic properties, their prediction indicates that they have drug-like properties [93].

In addition to the above work, Hagar *et al*. designed and synthesized benzimidazole–1,3,4-oxadiazole-chalcone hybrids and evaluated the compounds for the EGFR Inhibition for cell apoptosis. Cell lines studies suggested that compound 54, carrying para methoxy phenyl group at the second position of the benzimidazole ring, had shown promising efficiency in inhibiting EGFR and inducing apoptosis [94]. The structures of benzimidazoles containing compounds are depicted in Figure 14.



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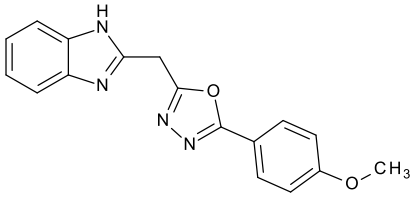
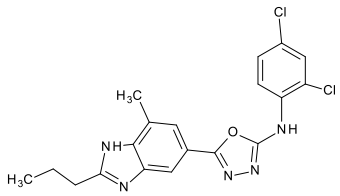


2-(1*H*-benzimidazol-2-ylmethyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole

44



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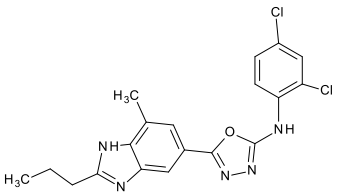
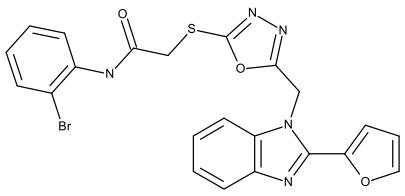


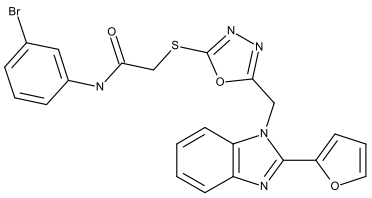
N-(2,4-dichlorophenyl)-5-(7-methyl-2-propyl-1*H*-benzimidazol-5-yl)-1,3,4-oxadiazol-2-amine

45



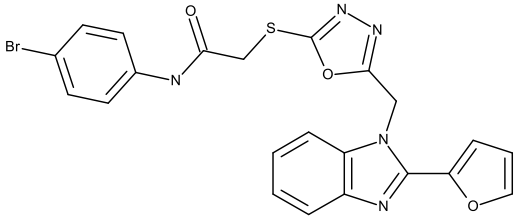
N-(2-bromophenyl)-2-[[5-[[2-(2-furyl)benzimidazol-1-yl]methyl]-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide

46



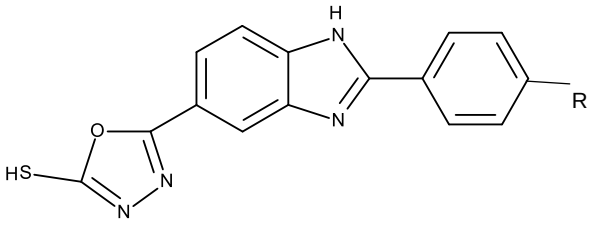
N-(3-bromophenyl)-2-[[5-[[2-(2-furyl)benzimidazol-1-yl]methyl]-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide

47

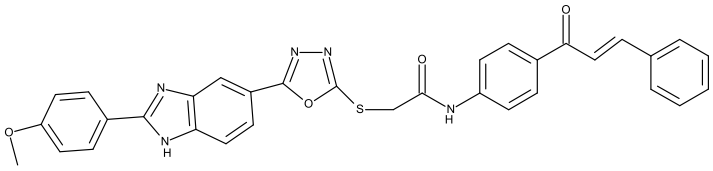


N-(4-bromophenyl)-2-[[5-[[2-(2-furyl)benzimidazol-1-yl]methyl]-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide

48



R_{49}=H, R_{50}=Cl, R_{51}=OCH_3, R_{52}=3,4-OCH_3,R_{53}=3,4,5-OCH_3



2-[[5-[2-(4-methoxyphenyl)-1*H*-benzimidazol-5-yl]-1,3,4-oxadiazol-2-yl]sulfanyl]-*N*-[4-[(*E*)-3-phenylprop-2-enoyl]phenyl]acetamide;molecular hydrogen

54

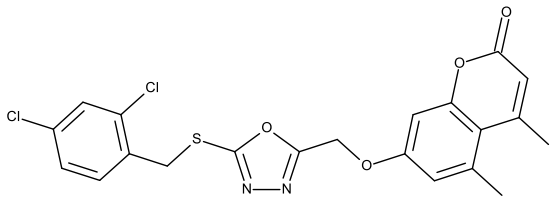
Figure 14. Benzimidazole-containing anti-cancer drugs reported in the literature [90-94].

3.13. Coumarin incorporated 1,3,4-oxadiazole.

Coumarin is chemically 2H-chromen-2-one and has been reported to interact well with the different types of enzymes and receptors expressed in cancer cells. It is also a great pharmacophore that has been reported to be researched for developing anti-cancer agents [95].

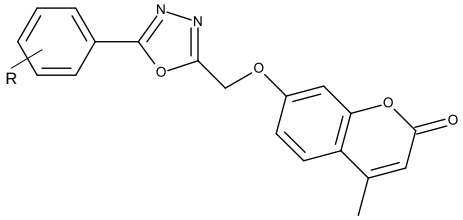
In the search for novel promising anti-cancer agents, Dhawan *et al*. synthesized a new series of compounds combining 1,3,4-oxadiazole and coumarin and tested them for antiproliferative activity using MCF-7 and MDA-MB-231 as cell lines and tamoxifen as a control. The pharmacological investigations revealed that compound 55 was the most potent, with an IC_{50} value of less than 5 M against the MCF-7 cell line, which is about 1.4 times more potent than tamoxifen. The compounds with benzyl substitution have superior activities, according to structure-activity relationship studies [96].

Furthermore, Ilango *et al*. developed and synthesized a new series of compounds combining the coumarin ring system into 1,3,4-oxadiazole with various oxadiazole replacements at the 2nd and 5th positions. The cytotoxic activity of the produced compounds was investigated. The synthesized compound 56 exhibited good cytotoxic activity in the MTT experiment. The docking investigation revealed that compound one had the highest GOLD score when docked with the EGFR receptor [97]. The structures of coumarin-containing compounds are depicted in Figure 15.



7-[[5-[(2,4-dichlorophenyl)methylsulfanyl]-1,3,4-oxadiazol-2-yl]methoxy]-4,5-dimethyl-chromen-2-one

55



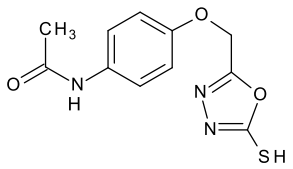
4-methyl-7-(5-phenyl-1,3,4-oxadiazol-2yl methoxy)coumarin

56

Figure 15. Coumarin-containing anti-cancer drugs reported in the literature [96-97].

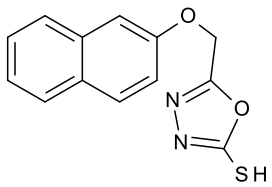
3.14. Pyrazole incorporated 1,3,4-oxadiazole.

Pyrazole is a five-membered ring containing three carbons and two nitrogens at the first and second positions. Acts as a promising scaffold for developing novel anti-cancer agents [98]. In view of studies by Faheem *et al*., pyrazole incorporated 1,3,4-oxadiazole and evaluated their computational and pharmacological activity. To understand the binding pattern, the proposed compounds 57-60 were docked against EGFR, COX-2, and 5-LOX receptors. With the EGFR and other receptors, all four drugs had a favorable binding pattern. All the drugs showed good and increased tumor suppression in the *in vitro* and *in vivo* tests with LC_{50} values of 2.47 and 5.51 µg/mL, respectively [99]. The structures of pyrazoles containing compounds are depicted in Figure 16.



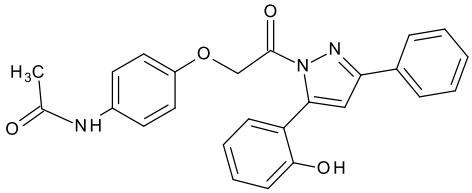
molecular hydrogen;*N*-[4-[(5-sulfanyl-1,3,4-oxadiazol-2-yl) methoxy]phenyl]acetamide

57



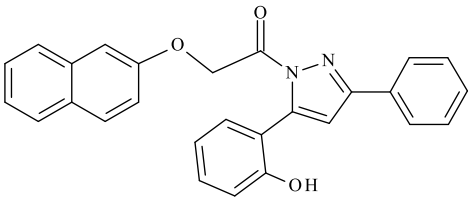
5-(2-naphthyloxymethyl)-1,3,4-oxadiazole-2-thiol

58



N-[4-[2-[5-(2-hydroxyphenyl)-3-phenyl-pyrazol-1-yl]-2-oxo-ethoxy]phenyl]acetamide

59



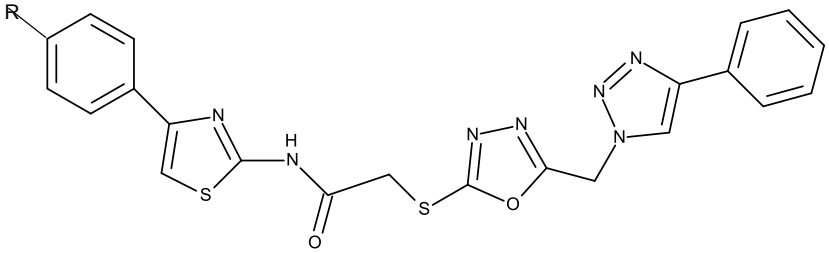
1-[5-(2-hydroxyphenyl)-3-[(*E*)-1-vinylprop-1-enyl] pyrazol-1-yl]-2-(2-naphthyloxy)ethanone

60

Figure 16. Pyrazole-containing anti-cancer drugs reported in the literature [99].

3.15. 1,2,4-. Triazole incorporated 1,3,4-oxadiazole.

Triazole is a five-membered ring containing nitrogen at the first, second, and third positions and plays an important role as a scaffold in developing anti-cancer agents [100].



molecular hydrogen;*N*-(4-phenylthiazol-2-yl)-2-[[5-[(4-phenyltriazol-1-yl)methyl]-1,3,4-oxadiazol-2-yl] sulfanyl]acetamide

R_{61}=Cl, R_{62}=Br

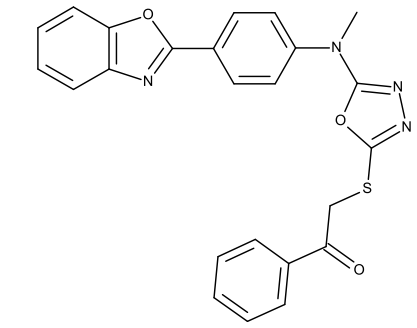
Figure 17. Triazole-containing anti-cancer drugs reported in the literature [101].

Moreover, Mahmoud *et al*. designed and synthesized 1,3,4-oxadiazole-1,2,3-triazole hybrids and evaluated the antiproliferative activity of the compounds against four cell lines, namely Panc-1, MCF-7, HT-29, and A-549 using the MTT assay using erlotinib as the

reference drug. Two compounds 61 and 62 containing chloro and bromo group showed enhanced inhibition of the EGFR at $IC_{50} = 0.11–0.73$ μM, compared to Erlotinib $IC_{50} = 0.08 \pm 0.04$ μM). The docking studies also showed that the binding pattern of the compounds is similar to that of erlotinib [101]. The structures of triazoles containing compounds are depicted in Figure 17.

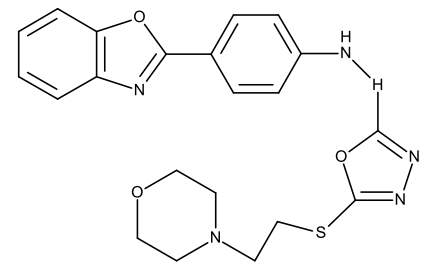
3.16. Benzoxazole incorporated 1,3,4-oxadiazole.

Benzoxazole consists of a benzene ring fused with an oxazole ring and has wide-spectrum pharmacological properties that have been widely researched for anticancerous drug development [102]. Omar *et al*. synthesized a new series of hybrid molecules containing 1,3,4-oxadiazole and benzoxazole and screened the compounds for their anticancerous activity against breast cancer cell lines using doxorubicin and cisplatin as the standard drug. Amongst the synthesized compounds, two of them, 63, 64 showed promising activity towards MCF-7 and MDA-MB-231 cell lines with an IC_{50} value of (1.76 ± 0.08 μM and 0.59 ± 0.02 μM) and (0.21 ± 0.02 μM and 214.45 ± 8.61 μM) respectively and has comparable inhibitory activity to Erlotinib towards EGFR inhibition [103]. The structures of 1,2,4-triazole-containing compounds are depicted in Figure 18.



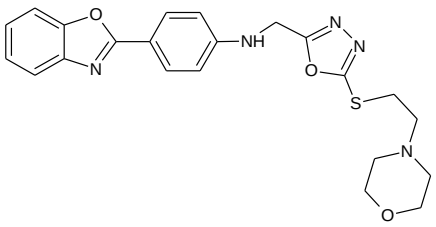
2-[[5-[4-(1,3-benzoxazol-2-yl)-*N*-methyl-anilino]-1,3,4-oxadiazol-2-yl]sulfanyl]-1-phenyl-ethanone

63

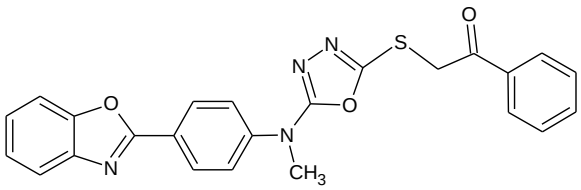


[4-(1,3-benzoxazol-2-yl)anilino]-[5-(2-morpholinoethylsulfanyl)-1,3,4-oxadiazol-2-yl] hydrogen;molecular hydrogen

64



2-(4-(N-(5-(2-(Morpholin-4-yl)ethyl)sulfanyl-1,3,4-oxadiazol-2- yl)methylamino)phenyl)benzoxazole
(XLV)



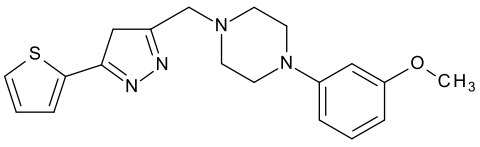
2-(4-(N-(5-(Benzoylmethylsulfanyl)-1,3,4-oxadiazol -2-yl) methyl-amino)phenyl)benzoxazole
(XLVI)

Figure 18. Triazole-containing anti-cancer drugs are reported in the literature [103].

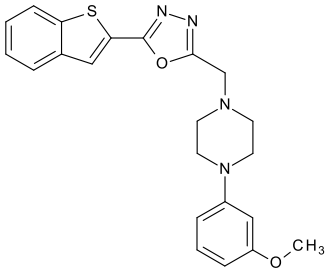
3.17. Thiophene incorporated 1,3,4-oxadiazole.

Thiophene is a five-membered azole containing one heteroatom, which is sulfur. They are reported to bind to various protein targets that can be used as treatment for cancer [104]. Kurt *et al*. designed and synthesized 1,3,4-oxadiazole derivatives incorporating benzo[b]thiophen and thiophene nucleus. The synthesized compounds were studied for their molecular properties, bioactivity, molecular docking studies, and drug-likeness scores. The results showed that the compounds obeyed Lipinski's rules with good drug-likeness scores, and two of the compounds 65 and 66, possessed the highest scores of 0.31 and 0.33,

respectively. The compounds were also studied for their binding interaction through molecular docking, and they showed hydrogen bonding interactions with Asp1046 amino acid with ΔGba score of -11.2 kcal/mol and -8.7 kcal/mol, respectively [105]. The structures of thiophene-containing compounds are depicted in Figure 19.



1-(3-methoxyphenyl)-4-{[5-(thiophen-2-yl)-4 *H*-pyrazol-3-yl]methyl}piperazine
65



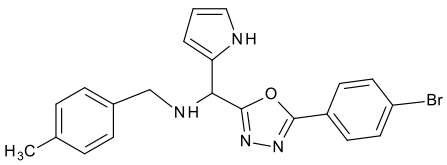
2-(Benzo[b]thiophen-2-yl)-5-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-1,3,4-oxadiazole
66

Figure 19. Thiophene-containing anti-cancer drugs reported in the literature [105].

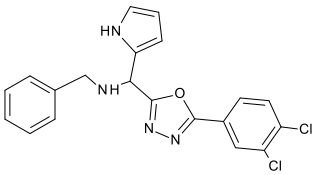
3.18. Pyrrole incorporated 1,3,4-oxadiazole.

Pyrrole is a five-membered ring containing one nitrogen atom. Various reports suggest it is pivotal in developing promising and selective cytotoxic activity [106]. In the search for potent anti-cancer agents, Ramazani *et al*. designed and synthesized 5-aryl-1,3,4-oxadiazol-2-yl combining pyrrole nucleus and evaluated the compounds for their antiproliferative activity using different cell lines with respect to the reference drug doxorubicin. The results of the studies suggested that some of the tested compounds had better cytotoxic activity against A549, HT29, or HT1080 cells when compared to the standard drug doxorubicin. One of the compounds 67 showed four times more activity than the standard reference drug with an IC_{50} value of 4.3 mM, and the reason was attributed to introducing a halogen atom on the phenyl ring at the para position [107].

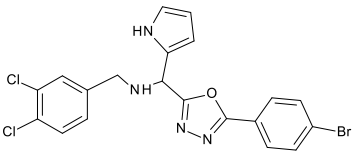
Alikhani *et al*. designed and synthesized pyrrole fused 1,3,4-oxadiazoles derivatives and studied the compounds for their cytotoxic, docking, and quantum mechanical studies against chemotherapeutic targets. The In-silico structure binding relationship studies showed that the compounds containing chlorine and bromine at the fifth position in compounds 68, 69 on the phenyl and benzyl rings had good binding energies to the target molecule EGFR with ΔGb of -10.59 kcal/mol and -11.06 kcal/mol respectively [108]. The structures of pyrrole-containing compounds are depicted in Figure 20.



1-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]- *N*-(4-methylbenzyl)-1-(1 *H*-pyrrol-2-yl)methanamine
67



N-benzyl-1-[5-(3,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]-1-(1 *H*-pyrrol-2-yl)methanamine
68



1-[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]- *N*-(3,4-dichlorobenzyl)-1-(1 *H*-pyrrol-2-yl)methanamine
69

Figure 20. Pyrrole-containing anti-cancer drugs reported in the literature [107-108].

3.19. 1,3,4-oxadiazole as Mannich base.

Mannich bases are beta-amino ketones that have been reported to have anti-cancer and cytotoxic activity and, in recent times, have been explored for the development of potent anti-

cancer molecules [109] in the view of the same Strzelecka *et al*. synthesized and evaluated *N*-Mannich base-type hybrid compounds containing 1,3,4-oxadiazoles incorporated piperazines and pyridines nucleus for their growth inhibitory activity on cancer cells. Two of the compounds 70, 71 containing 3,4-dichloro and trifluoromethyl group showed promising cytotoxicity activity in the *in vitro* study using reference drug cisplatin with IC_{50} values of 80.79 µM, 202.47 µM, and 15.98 µM respectively. The *In silco* study also showed that the compounds had similar binding affinity to the reference drug erlotinib to the EGFR receptors [110].

Further, Al-Wahaibi *et al*. synthesized a series of 1,3,4-oxadiazole-2(3H)-thione N-Mannich bases and studied the compounds for their anticancerous activity and other pharmacological activity. The antiproliferative activity of the compounds was studied using different cell lines. Four compounds 72-75 showed potent inhibitory activity in all the tested cancer cell lines [111]. The structures of 1,3,4-oxadiazole as Mannich base-containing compounds are depicted in Figure 21.

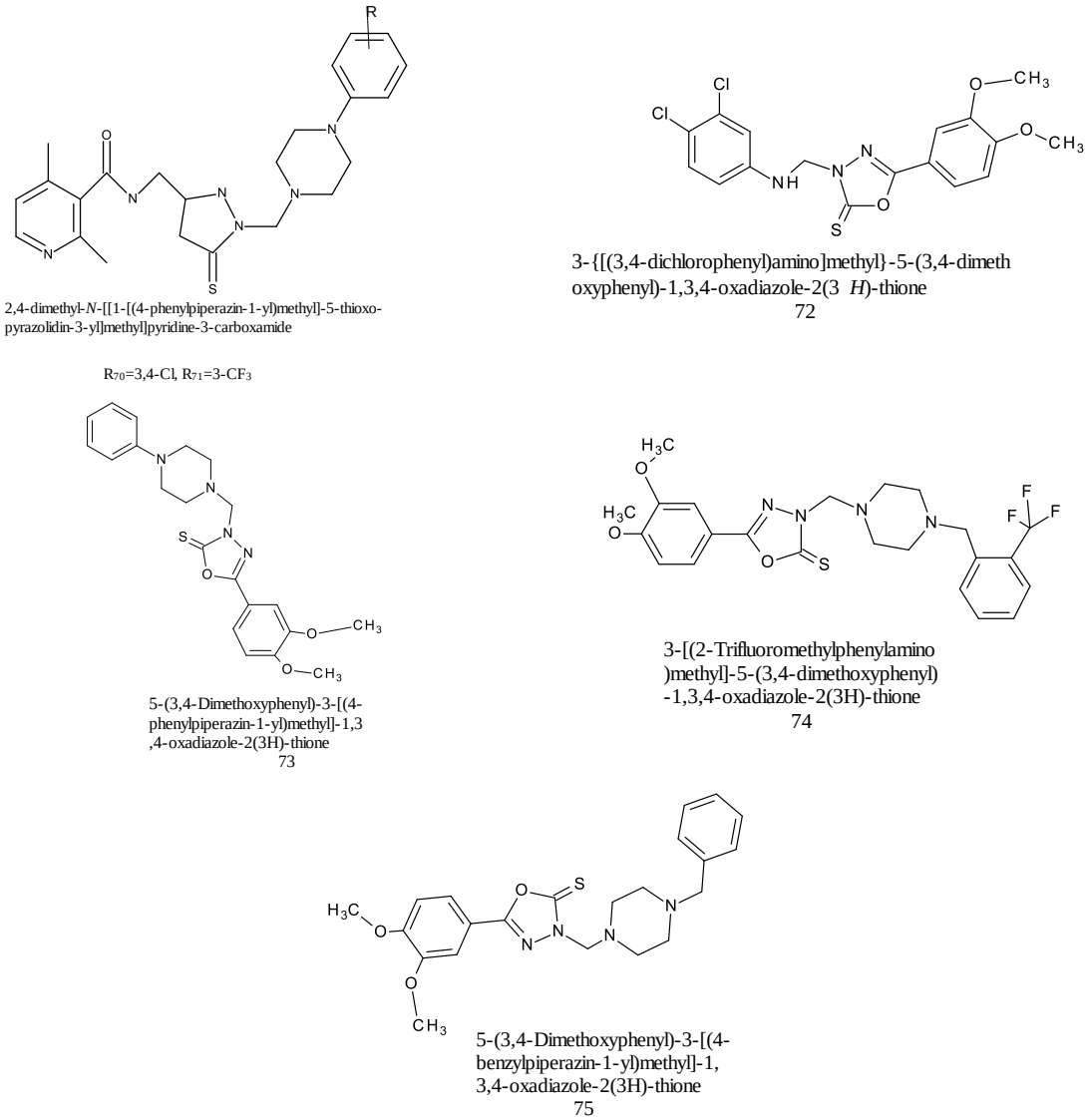
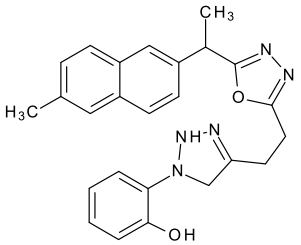


Figure 21. 1,3,4-oxadiazole as Mannich base as an anti-cancer drug reported in the literature [110-111].

3.20. Naproxen based 1,3,4-oxadiazoles.

Mahboob Alam *et al*. designed and synthesized Naproxen incorporated 1,3,4-oxadiazole derivatives and studied for cytotoxicity as EGFR inhibitors and tested the compounds on the MCF-7 and HepG2 cancer cell lines. Compound 76 showed the most potent activity comparable to standard drug doxorubicin against MCF-7 and HepG2 cancer cells with IC_{50} values of 2.13 and 1.63 g/mL, respectively. The docking studies also showed good binding interactions with the EGFR kinase with a ΔGb of -7.14 kcal/mol compared to the Erlotinib with ΔGb of -6.27 kcal/mol [112]. The structures of Naproxen-containing compounds as anti-cancer agents are depicted in Figure 22.



2-(4-((5-((S)-1-(2-methoxynaphthalen-6-yl)ethyl)-1,3,4-oxadiazol2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)phenol
76

Figure 22. A naproxen-containing compound as anti-cancer drugs reported in the literature [112].

4. Results and Discussion

This review emphasizes that 1,3,4-oxadiazole has enough reporting to prove it is the potent nucleus for antiproliferative and anti-tumor activities. The analysis of the structure relationship allows us to conclude that the most promising compounds that showed anticancerous activity were hybrids of 1,3,4-oxadiazole and another heterocyclic ring. Further, some of the compounds with an oxazole nucleus were found to be promising and are being marketed as potent anti-cancer drugs.

5. Conclusion

The study suggests that the 1,3,4-oxadiazole nucleus is a promising pharmacophore for developing antiproliferative agents. In this review, it can be seen that to enhance the antiproliferative, cytotoxic, and anticancerous activities, many heterocyclic rings are fused with oxadiazole, and the evaluation study shows that the binding with the receptors in the *in silco* study, as well as the biological activity, has significantly increased in many studies. The substituents attached with the 1,3,4 oxadiazole at positions 2 and 5 play a major role in the biological activity. The electron-withdrawing or donating nature of the substituents plays a major role in the IC_{50} value. Many studies suggest that the 1,3,4-oxadiazoles have increased binding affinity with the EGFR receptors, and the binding affinity mostly of most of the compounds has shown improved activity compared to the standard drug like erlotinib that contains 1,3,4-oxadiazole. The studies on EGFR kinase activity using 1,3,4-oxadiazole demonstrated promising results in the assays. So, it can be concluded that by adding various substituents on 1,3,4-oxadiazole or linking with different heterocycles, potent and efficient drugs can be synthesized to manage and treat cancer.

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Conflicts of Interest

The authors declare no conflict of interest.

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