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Review Article

A Review on Anticancer Activity of 1, 3, 4-oxadiazole

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Abstract

In this review we are presenting the Anticancer activity of the 1, 3, 4 Oxadiazole. Designing new anti-cancer drugs with high efficiency and broad spectrum activity is a significant need of today. Drug resistance, generally caused because of long term cancer treatment is rapidly becoming a major worldwide problem. The design of new compounds to deal with the resistance problem has become one of the most important goals of anti-cancer research today. This review article describes the anticancer activity of 1, 3, 4 Oxadiazole ring being reported on various cancer cell lines and will be useful in guiding the researchers across the world working on this moiety and consequently will be instrumental in the advancement of 1, 3, 4-oxadiazole chemistry.

Keywords: 1, 3, 4-oxadiazole, Anticancer, Drug resistance

INTRODUCTION

Cancer is not a single disease, but a large group of diseases characterized by uncontrolled, rapid and pathological proliferation of abnormally transformed cells. Despite recent advances in cancer therapy, cancer is still the second leading cause of death after cardiovascular disorders throughout the world. Resistance to chemotherapeutic agents remains a key challenge in the fight against cancer. Another challenge for chemotherapy is lack of selectivity. Generally anticancer drugs destroy normal cells as well as cancer cells and often cause serious adverse effects [1-2]. The design of new compounds to deal the resistance problem has become one of the most important goals of anti-cancer research today [3]. Oxadiazole is a versatile heterocyclic nucleus, which has attracted a wide attention of the medicinal chemists for development of new drugs. Oxadiazole is a five-membered heterocyclic, aromatic chemical compound having two carbons, two nitrogens and one oxygen atom with two double bonds having general formula $C_2H_2ON_2$. 1,3,4-oxadiazole rings have been introduced into drug discovery programs for several different purposes. For example, in some cases, they have been used as an essential part of the pharmacophore, favourably contributing to ligand binding, and in other cases, oxadiazole moieties have been shown to act as a flat, aromatic linker to place substituents in the appropriate orientation, as well as modulating molecular properties by positioning them in the periphery of the molecule [4]. 1,3,4-oxadiazole is more widely studied by researchers because of their many important chemical biological activities such as Anti-inflammatory [5], Analgesic [6], Antimicrobial [7], Anti-convulsant [8], Anti-proliferative [9], Anti-mycobacterial [10], Anti-protozoal [11], Anti-diabetic [12], Anticancer [13], and pesticidal property [14].

Anticancer activity of 1,3,4-oxadiazole

B. Madhavilatha *et al*. (2018) synthesised a series of new 1,3,4-oxadiazole-linked 1,2,3-triazole/isoxazole derivatives (Figure 1). All the synthesized compounds were screened for in vitro anticancer activity against four human cancer cells: HeLa (cervical), MDA-MB-231 (breast), DU-145 (prostate), and HEPG2 (liver). Among them, 1a, 1b, and 1c showed a potent anticancer activity against all the tested cancer cell lines and inhibited tubulin polymerization. These compounds also disrupted microtubule assembly and increased the amount of insoluble tubulin fractions of cells like other potent tubulin polymerization inhibitors such as nocodazole. These results demonstrate that the series compounds are potent tubulin polymerization inhibitors,

which can serve as a useful template for the generation of a related new class of molecules as potential anticancer drugs [15].

Fatma A.F. Ragab *et al*. (2017) reported a series of dihydropyrimidine (DHPM) derivatives bearing 1, 3, 4-oxadiazole moiety as monastrol analogues. The new compounds (Figure 2) were screened for their cytotoxic activity toward 60 cancer cell lines according to NCI (USA) protocol. Seven compounds were further examined against the most sensitive cell lines, leukemia HL-60(TB) and MOLT-4. The most active compounds were1-(6 Methyl-4-Phenyl-2((5-Phenyl-1, 3, 4-oxadiazole-2-yl) methyl thio)-1,4-dihydropyrimidin-5-yl) ethanone against HL-60(TB) (IC50 = 56 nM. The pro-apoptotic activity of 2a was inferred by the significant increase in the percentage of annexin V-FITC-positive apoptotic cells. [16].

Jaroslaw Slawinski *et al*. (2017) prepared a series of novel 2-benzylthio-4-chloro-5-(5-substituted 1,3,4-oxadiazol-2-yl)benzene sulfonamides (Figure 3) as potential anticancer agents. MTT assay was carried out to determine the cytotoxic activity against three human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7 and cervical cancer HeLa as well as to determine the influence on human keratinocyte cell line HaCaT [17].

Partha Pratim Roy *et al*. (2017) synthesized compounds (Figure 4) showed significant result in different parameters of EAC bearing mice and markedly increase the average life span of experimental animals. From the present study, result indicate that the oxadiazole compounds can potentially be developed into useful anticancer agents [18].

Juan Sun *et al*. (2017) synthesized class of 1,3,4-oxadiazole-2(3H)-thione derivatives containing piperazine skeleton with improved potency toward FAK. All of the newly synthesized compounds were assayed for the anticancer activities against four cancer cells, HepG2, Hela, SW116 and BGC823. Compound (Figure 5) showed the most potent biological activities and its anti-FAK inhibitory activity was also the best. The results of FAK inhibitory assay, we could find that compound 4 exhibited the most potent FAK inhibitory activity with IC50 of 0.78 μM. In order to study the structure-activity relationships observed at the FAK, molecular docking of compound 5 into the binding site of FAK was performed on the binding model based on the FAK structure. This study showed that compound was nicely bound into active site of FAK [19].

Wael A. Elsayed *et al*. (2017) synthesised of 4-(5-(5-(1-ethyl-1H-indol-3-yl)-1-phenyl-1H-pyrazol-3-yl)-1,3,4-oxadiazol-2-yl thio)butane-1,2-diol based (indolyl)pyrazolyl ring system, their derived thioglycosides and acyclic C-nucleoside analogus. The anticancer activity of the newly synthesized compounds was studied against colorectal carcinoma (HCT116), breast adenocarcinoma (MCF7) and prostate cancer (PC3) human tumor cell lines and a number of compounds (Figure 6) showed moderate to high activities. The anticancer and docking results indicated the importance of the attachment of sugar moieties to Oxadiazole ring system in a number of most active compounds, particularly, those incorporating a thioglycosyl moiety [20].

Naveen Polkam *et al*. (2017) synthesised a series of regioisomeric (2,5-dimethoxybenzoic acid, veratric acid) analogues were prepared by swapping the carboxylic motif to its oxadiazole bioisostere and have been screened for in vitro anticancer studies by using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay. Among the screened compounds (Figure 7) (2-(2,5-dimethoxyphenyl)-5-(5-phenylthiophen-2-yl)-1,3,4-oxadiazole) demonstrated superior activity against MDA231 cells. All the compounds presented varied degree of anticancer profiles. It might be due to the synergetic effect of lipophilicity and aryl hydrophobic interactions. Comparison among the two reported series 7a and 7b, veratric acid off shoots displayed higher anticancer activity against MDA453 cell lines [21].

Francesco O. *et al*. (2016) synthesised a series of new compound 1-(2-3,4-dihydro phenyl)-5-aromatic-1,3,4-oxadiazole-3(2H)-yl) ethanone (Figure 8) potent and selective monoamine oxidase B (MAO-B) inhibitors, molecular interaction field analysis has been applied to a MAO-B complex with 3-acetyl-2, 5-diaryl-2,3-dihydro-1,3,4-oxadiazole chemical structure, known as a privileged scaffold for this target. Several compounds displayed potent in vitro activity, exhibiting IC50 values in the medium to low nano molar range [22].

Joana Darc S. Chaves *et al*. (2016) synthesized novel gold(I) complexes containing phosphine and 5-phenyl-1,3,4-oxadiazole-2-thione (Figure

9) and evaluated their anticancer and antileishmanial activities. The compound (9b) was more active murine melanoma B16F10 and colon cancer CT26.WT cell lines [23].

S. Kavitha *et al*. (2016) synthesized a series of new 2, 5-disubstitued 1,3,4 oxadiazole derivatives bearing urea, amide, sulphonamide and their anticancer activities were evaluated *in vitro*. The fifteen synthesized compounds showed moderate to good activity against anticancer activities. Among them, compound (Figure 10) was found to be effective anticancer agents. The current research is considered to synthesize 1,3,4 oxadiazole derivatives for their improves the biological activity [24].

Bereket Mochona *et al*. (2016) synthesized 1,3,4-oxadiazole derivatives and their antiproliferative properties have been studied. The in vitro screening was performed against androgen dependent (LNCaP) and androgen independent (PC-3) prostate cancer cell lines. Most of the compounds showed promising activity. Among them, compounds (Figure 11) have shown significant activities on PC-3 and LNCaP cell lines respectively but the study evidently identified the potency of compound 8d as potential anti-prostate cancer agent [25].

Vijaya Rao Pidugu *et al*. (2016) synthesized of a series of novel 2,5-disubstituted 1,3,4-oxadiazoles (Figure 12) as class I histone deacetylase (HDAC) inhibitors. 2-amino-N-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)propanamide showed substantial HDAC8 inhibitory activity and better anticancer activity which is comparable to the positive control, a FDA approved drug, vorinostat (SAHA). The study warranted further investigations to develop HDAC8-selective inhibitory molecule as a drug for neoplastic diseases. Novel 1,3,4-oxadizole substituted with glycine/alanine showed HDAC8 inhibition [26].

S. Raju D *et al*. (2015) synthesised a new compound of 1,3,4-oxadiazoles derivative. The compound were also screened for their antioxidant and anticancer activity. Three compounds (Figure 13) (13b, 13c, 13f) were found active against HepG2 cells and two compounds (13d, 13e) against Hep 2 cells. Thus promising molecules were identified for their anticancer activity [27].

D. Q Qi *et al*. (2015) synthesised a series of pyrazole-based 1, 3, 4-oxadiazole derivatives (Figure 14). The fluorescence properties of all the compounds were analysed in dimethyl sulfoxide media and were evaluated for their n vitro inhibitory activity against commercial enzyme xanthine oxidase (XO) by measuring the formation of uric acid from xanthine [28].

Rashid *et al*. (2015) synthesised a series of 3-((5-(3-(1Hbenzo[d]imidazol-2-yl)-3-oxopropyl)-1,3,4-oxadiazol-2-yl)methyl)-5-methyl pyrimidine 2,4(1H,3H)-dione (Figure 15) which exhibited significant antiproliferative activity with GI50 value of 0.09μM. The ability of oxadiazole derivatives to induce apoptosis of cancer cells. FDA has approved a number of drugs for the treatment of different types of cancer. The development of new anticancer agents due to increasing cases of drug resistance [29].

F. Zhang *et al*. (2014) synthesized a series of new (3,4-dihydroxybenzylidene)-2-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-ylthio) acetohydrazide (Figure 16) containing pyridine and acylhydrazone moieties as potential telomerase inhibitors. The compounds exhibited significant broad-spectrum anticancer activity against the four cancer cell lines (HEPG2, MCF7, SW1116 and BGC823) [30].

S. Valente *et al*. (2014) have reported 1,3,4-oxadiazole series of N-hydroxy-3-(4-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)phenyl) acrylamide (Figure 17) as anticancer agents by inhibition of HDAC. Structural activity relationship revealed that the inhibitory potency of 1,3,4-oxadiazole derivative increase by addition of 1-naphthyl ring at the C-5 position of oxadiazole and insertion of one methylene unit between the aryl ring and the C-5 position of the oxadiazole [31].

Kai Zhang *et al*. (2014) synthesised a series of novel hybrid molecules containing 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing Schiff's bases and evaluated their anti-tumour activity against human hepatoma carcinoma cell line (SMMC-7721), breast cancer cell line (MCF-7), lung cancer cell line (A549) by CCK-8 assay. Compounds (Figure 18) (18a) displayed highly effective anti-tumor activities against MCF-7 cells, with IC_{50} value of 4.56μM. Compounds (18b) exhibited significant anti-proliferative activity against A549 cells, with IC_{50} value of 4.11 μM [32].

Sohail Anjum Shahzad *et al*. (2014) reportd a series of new 3-(2-methoxyphenylaminomethyl)-5-(2bromophenyl)-1, 3, 4-oxadiazoline-2-thione derivatives has been found to possess considerable anti-tumor agents property agents. The bio-

logical assay revealed that majority of compounds displayed modest inhibitory activity against thymidine phosphorylase at low micromolar concentrations (IC50). The most active compounds were (Figure19) 19a and 19b with IC50 values [33].

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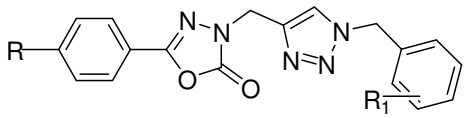
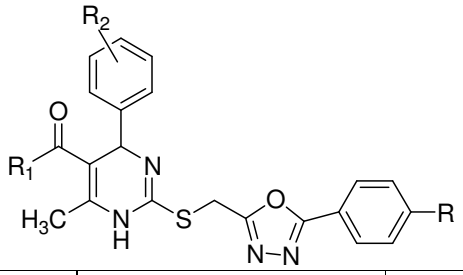


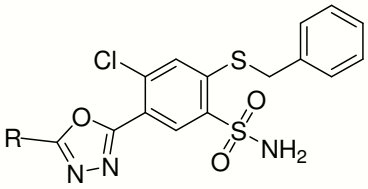
S.no.	R	R_1
1a	H	H
1b	CH_3	H
1c	CH_3	o-F

Figure. 1: 1,3,4-oxadiazole-linked 1,2,3-triazole/isoxazole derivatives



R	R_1	R_2
Cl	OC_2H_5	3-Cl

Figure. 2: 1, 3, 4-oxadiazole Dihydropyrimidine derivative



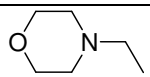
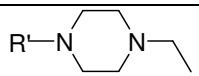
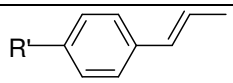
S.no	R	R′
2a		-
2b		Me Bn
2c		H 3-Cl 2,6-diCl

Figure. 3: 2-benzylthio-4-chloro-5-(5-substituted 1,3,4-oxadiazol-2-yl)benzene sulphonamides derivatives

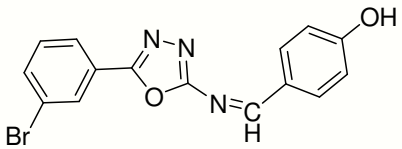


Figure. 4: 4-((5-(3-bromophenyl)-1,3,4-oxadiazol-2-ylimino)methyl)phenol

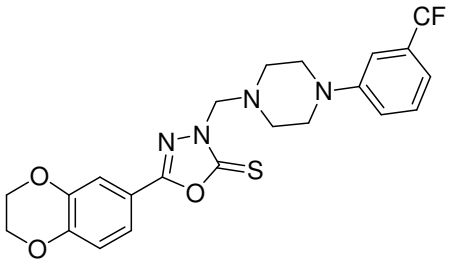


Figure. 5: 1,3,4-oxadiazole-2(3H)-thione derivative

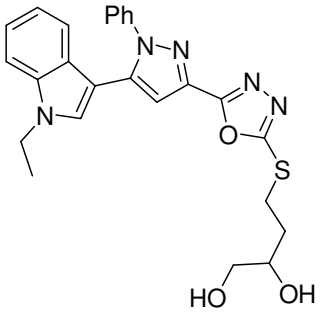
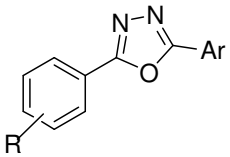
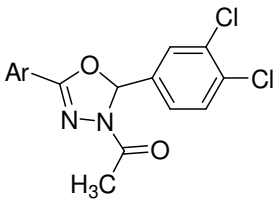


Figure. 6: 4-(5-(5-(1-ethyl-1H-indol-3-yl)-1-phenyl-1H-pyrazol-3-yl)-1,3,4-oxadiazol-2-yl thio)butane-1,2-diol



S.no.	R
7a	2,5-dimethoxy
7b	3,4-dimethoxy

Figure. 7: 2,5-disubstituted 1,3,4-oxadiazole derivatives.



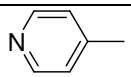
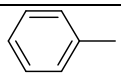
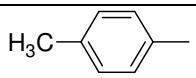
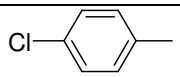
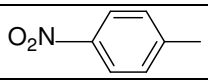
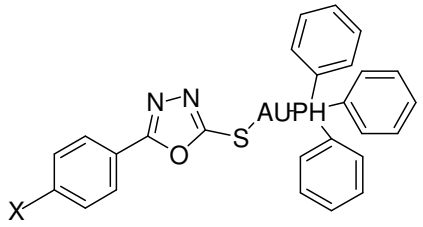
S.no	Ar
8a	
8b	
8c	
8d	
8e	

Figure. 8: 1-(2-3,4-dihydro phenyl)-5-aromatic-1,3,4-oxadiazole-3(2H)-yl) ethnone derivative



S.no.	X
9a	H
9b	Cl
9c	F
9d	NO_2
9e	OCH_3

Figure. 9: 5-phenyl-1,3,4-oxadiazole-2-thione derivative

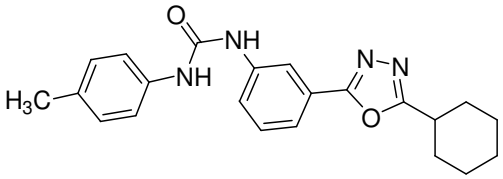


Figure. 10: 1-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-p-tolyl-urea

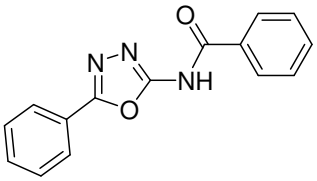


Figure. 11: 5-phenyl-1,3,4-oxadiazol-2-yl)benzamide

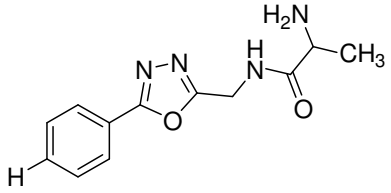
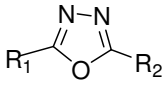


Figure. 12: 2-amino-N-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)propanamide



S.no.	R_1	R_2
13a	$C_{13}H_{12}$	C_5H_5N
13b	$C_{13}H_{12}$	$C_6H_4F_2$
13c	$C_{13}H_{12}$	C_7H_8O
13d	$C_{13}H_{12}$	$C_8H_8O_2$
13e	C_6H_6ClN	C_6H_5F
13f	C_6H_6ClN	C_6H_5Cl

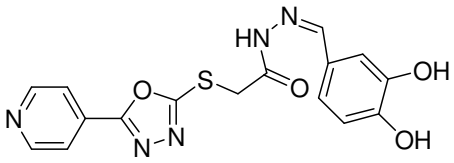
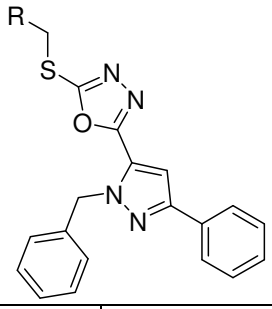


Figure. 14: (3,4-dihydroxybenzylidene)-2-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-ylthio) acetohydrazide



S.no.	R
15a	4-FC_6H_4
15b	4-CLC_6H_4
15c	4-NO_2 C_6H_4
15d	4-BrC_6H_4

Figure. 15 : pyrazole-based 1, 3, 4-oxadiazole derivatives

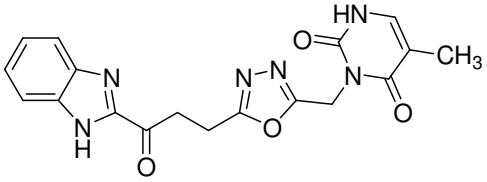
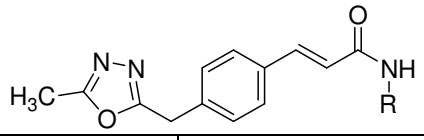
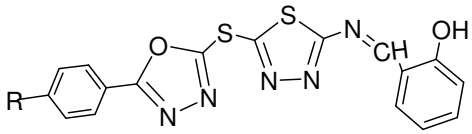


Figure .16 : 3-((5-(3-(1H-benzo[d]imidazol-2-yl)-3-oxopropyl)-1,3,4-oxadiazol-2-yl)methyl)5-methylpyrimidine2,4(1H,3H)-dione



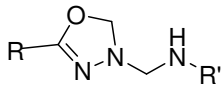
S.no.	R
17a	OH
17b	O-toluidine

Figure. 17 : N-hydroxy-3-(4-((5-methyl-1,3,4-oxadiazol-2-yl)methyl) phenyl) acrylamide derivatives



S.no.	R
18a	OCH_3
18b	H

Figure. 18 : 1,3,4-oxadiazole and 1,3,4-thiadiazole bearing Schiff's bases derivatives



S.no.	R	R′
19a	2-bromophenyl	2-methoxyphenyl
19b	4-methylphenyl	2-methoxy-5-nitrophenyl

Figure. 19 : 3-(2-methoxyphenylaminomethyl)-5-(2bromophenyl)-1, 3, 4-oxadiazoline-2-thione derivatives