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Anti-cancer activity of 1,3,4-oxadiazole and its derivative

Kousik Maparu[1*], Ritam Mukherjee[1], Dhrita Chatterjee

[1]Department of Pharmacology, ISF College of pharmacy , Moga, Punjub-142001, India

[*]Corresponding Author:

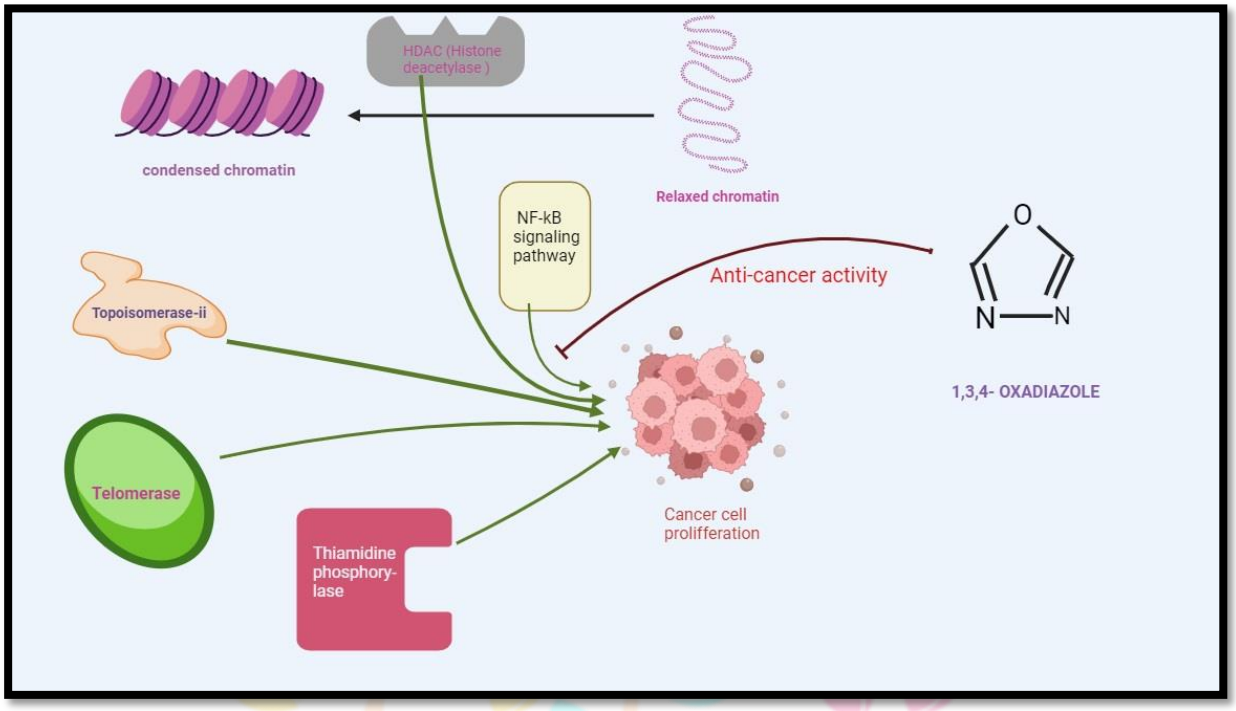
[1]Department of Pharmacology, ISF College of pharmacy , Moga, Punjub-142001, India

Author Contribution

Kousik Maparu contributed to the conceptual and framing of the article, Ritam Mukherjee and Dhrita Chatterjee were involved in writing and representation of the original manuscript. Kousik Maparu contributed to editing of the final manuscript.

Abstract

Nowadays cancer is a leading cause of death, the most common cancers worldwide are breast, colorectal, and lung cancer. Data from the International agency for Research on Cancer (IARC) says 19.3 million new cases of cancer and 10 million deaths. Oxidaizole derivatives are compounds having 5-membered rings containing one oxygen and two nitrogen atoms such as oxacillin, sulfamethoxazole, acivicin, and cycloserine have containing oxadiazole ring . 1,3,4 oxadiazole derivatives have the demand for researchers because of their various activities such as antibacterial, anti-tumor, antiviral, and antioxidant. Nowadays there are potent medicines in the market having anticancer activity, used worldwide. Some examples of anticancer agents available in the market are bleomycin and tiazofurin. There are some various mechanisms of action of 1,3,4 oxadiazole derivatives for anticancer activity, by acting on some enzymes likes thymidylate-syn-thase, HDAC(histone deacetylase), topoisomerase II, telomerase, thymidine phosphorylase to stop proliferation and also acting some pathways likes inhibiting telomerase activity, focal adhesion kinase(FAK) inhibitors, targeting thymidylate synthase, an inhibitor of the B-cell lymphoma 2, inhibitor of NF-kB signaling pathway and targeting tubulin polymerization. So,1,3,4-oxadiazole used as a promising anticancer drug in future.



Keywords

Oxadiazole ring , anticancer activity , HDAC , Proliferation , anti-tumor.

Conflict of interest statement

No potential conflicts of interest relevant to this article were reported.

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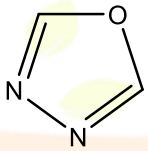
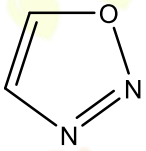
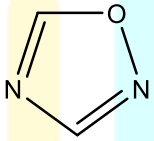
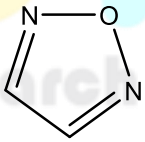
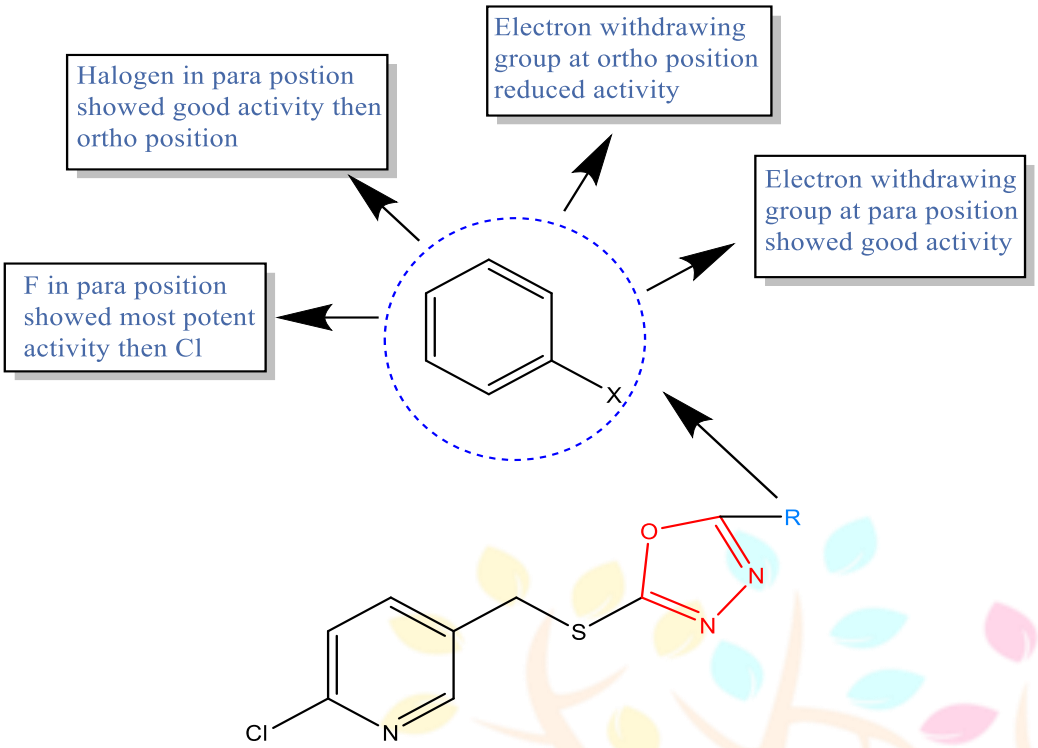
Introduction

Research is being conducted all over the world to discover new anti-cancer medications. This ongoing search for fresh compounds with a safer impact profile is driven by the increasing incidence of cancer, the numerous uncomfortable side effects of existing treatments, as well as the emergence of resistance to tumors (1). The majority of novel synthetic anti-cancer drugs are heterocyclic derivatives, with molecules with notably high cytostatic potential being those having 1,3,4-oxadiazole ring configurations (2) . The structure activity relationship of oxadiazole is given in figure no-01 . Oxidiazoleto is a five-member heterocyclic compounds having one oxygen atom and two nitrogen atoms in their structure (3) . They come in a variety of isomeric forms , somes examples are given in table-01.

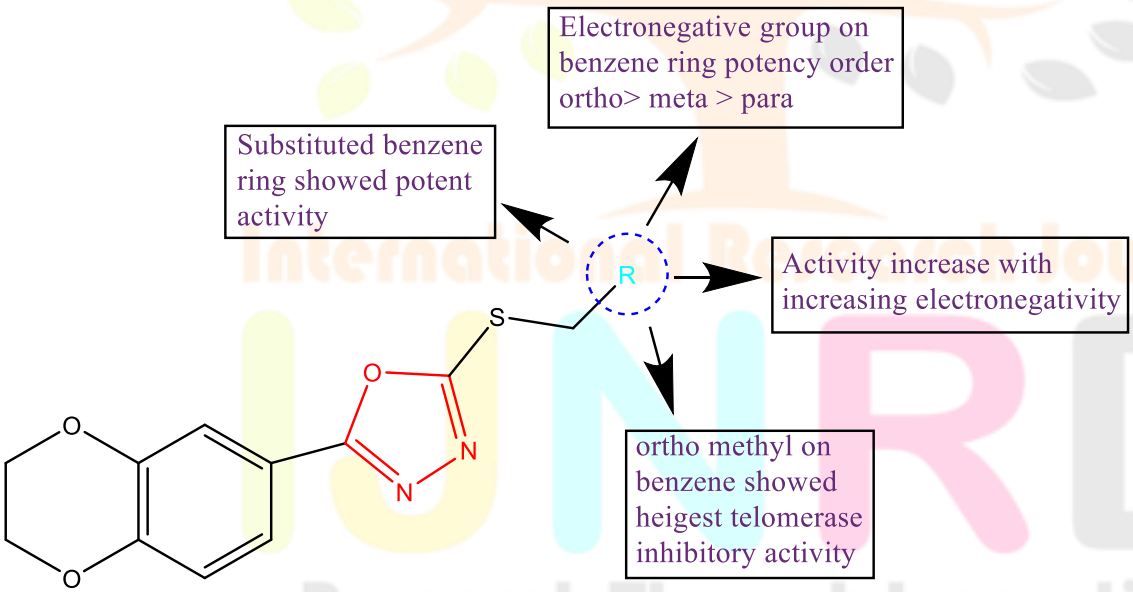
Table-01-Isomeric forms of oxadiazole and modification of unstable ring and their pharmacological effect-

SL NO	IUPAC NAME	STRUCTURE	PHARMACOLOGICAL EFFECT	REFERENCES
1	1,3,4-oxadiazole		Anticancer Antimicrobial Anti-inflammatory Antioxidant	(4)
2	1,2,3-oxadiazole		Anti-fungal Anti-convulsant Anti-bacterial Anti-tubercular Anti-inflammation	(5)
3	1,2,4-oxadiazole		Inflammation Cancer Neurodegenaration disorder Microbial infection	(6)
4	1,2,5-oxadiazole		Cancer Anti-proliferative activity Anti-inflammation	(7)

SAR of 1,3,4 oxadiazole –



SAR of 2-chloro pyridine derivatives of 1,3,4-Oxadiazole (24)



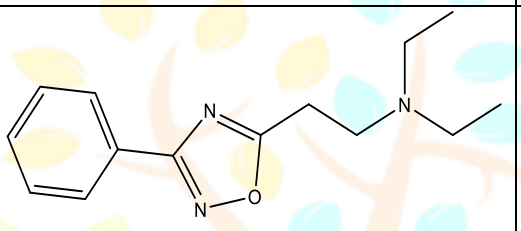
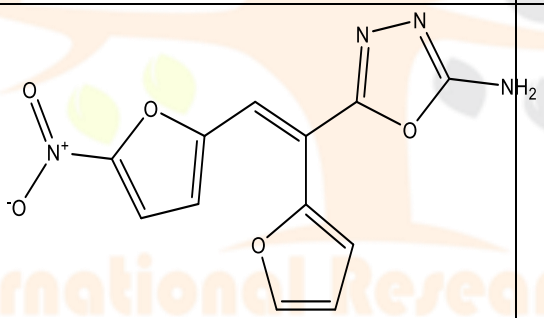
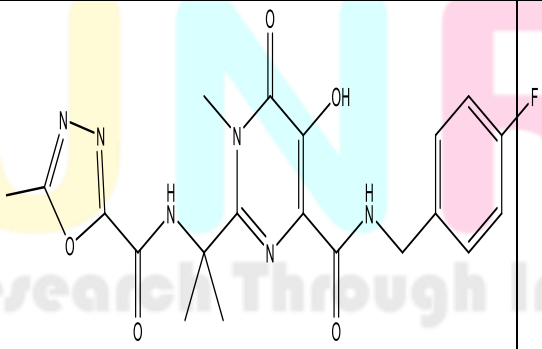
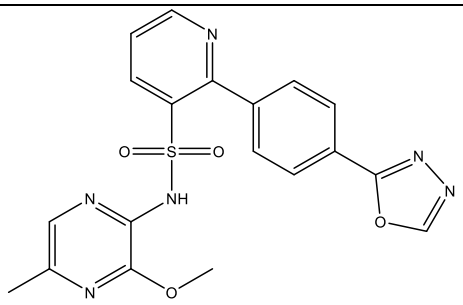
SAR of 1,3,4-Oxadiazole derivatives as telomerase inhibitors (24)**.**

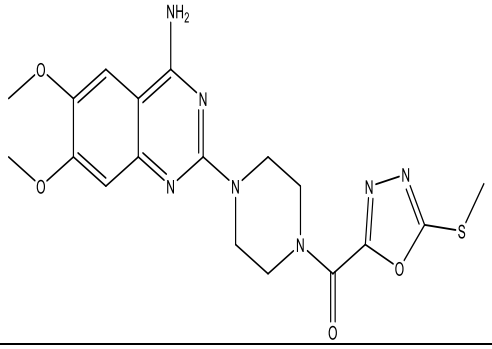
Novel substituted compound of 1,3,4-oxadiazole and its derivatives–

The 1,2,3-oxadiazole ring tautomerizes to a linear diazo-ketone form because it is unstable (8). It only occurs in extremely uncommon mesoionic forms, known as sydnones, and not in the free form (9) . The additional oxadiazole isomers are well recognised and can be found in the chemical makeup of numerous medications,

including the antiviral raltegravir , the antibiotic furamizole , and the antitussive oxolamine (2) (10) . Derivatives of 1,3,4-oxadiazole have interesting biological characteristics. It has antibacterial (11), anti-inflammatory (12), anticancer (13), antimalarial (14) , antidepressive (15), antiviral (16)(17), and analgesic (18) properties. With their numerous modes of action, including growth factors, enzymes, kinases, etc., 1,3,4-oxadiazole compounds have demonstrated substantial anti-cancer potential. An summary of the 1,3,4-oxadiazoles' anti-cancer potential in the last ten years' worth of cancer medication research is provided in this review article (19).The effect of derivatives described in table 02 .

Table-02 - Novel substituted derivatives of 1,3,4 oxadiazole and their pharmacological effect-

SL. NO	COMPOUND IUPAC NAME	STRUCTURE	PHARMACOLOGICAL EFFECT	REFERENCES
1	N,N-diethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethanamine		Antitussive activity	(10)
2	1,3,4-Oxadiazol-2-amine, 5-(1-(2-furanyl)-2-(5-nitro-2-furanyl)ethenyl)		Antibacterial activity	(20)
3	N-(4-Fluorobenzyl)-5-hydroxy-1-methyl-2-(2-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}-2-propanyl)-6-oxo-1,6-dihydro-4-pyrimidinecarboxamide		Antiviral activity	(21)
4	N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide		Anticancer activity	(22)

5	[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl][5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]methanone		Antihypertensive activity , Hemodynamic activity	(23)

Study of potent compound and its biological evaluation -

Multiple scientific studies have documented the anti-cancer properties of 1,3,4-oxadiazole derivatives when tested on various in vitro cell lines, yet the exact mechanism of action remains unclear and their effects were describe in table -03.

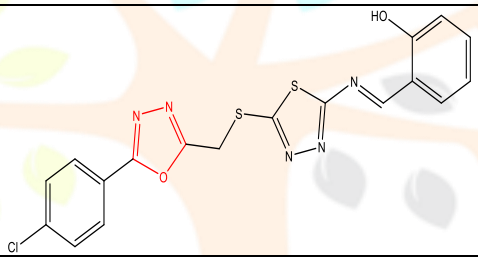
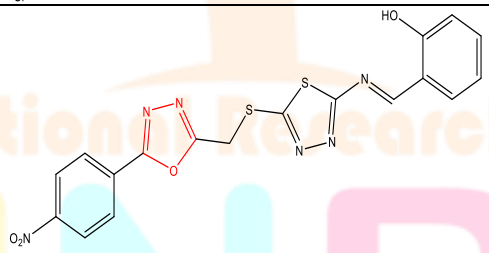
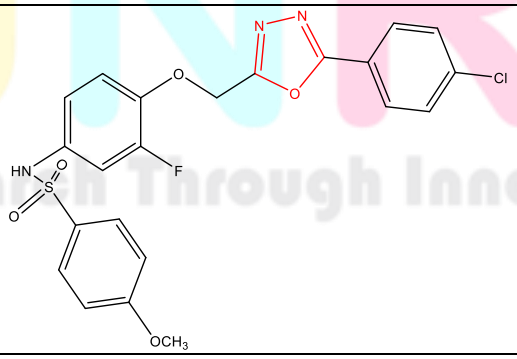
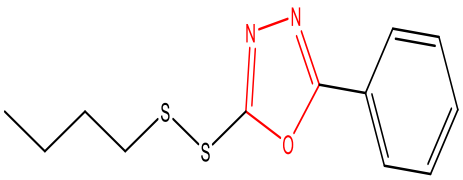
A variety of derivatives of hybrid schiff bases with 1,3,4-oxadiazole ring were studied in several cancer cell lines, including lung cancer, breast cancer, and liver cancer (SMMC-7721), were used to investigate their anti proliferative ability (A549). Derivative 1 was exhibited highest efficacy against liver cancer cells (25), while derivative 2 was demonstrated the greatest effectiveness against breast and lung cancer cells , as delineated in table -3 (25) . Both structures exhibited superior performance compared to the standard 5-fluorouracil . Derivative 3 exhibit most superior activity among all the generated derivatives against the T-47D and MDA-MB-468 breast cancer cell lines, SR leukemia, and melanoma (SK-MEL-5) ,describe in table-3. It was more potent than gefitinib as reference (26) .When asymmetric disulfides linked to the 1,3,4-oxadiazole ring it shows anti cancer properties on the lung, cervix, and liver cancer cell lines (SMMC-7721, HeLa) (A549).Among derivative 4,5,6 the most effective derivatives for inhibiting cervical cancer cells was compound 4 (HeLa) (27) , delineated in table -3 . Derivatives 4, 5, and 6 was shown more potent than 5-fluorouracil as standard .A cohort of Indian researchers developed a novel derivatives 1,3,4-oxadiazole structure , among the synthesized derivatives derivative 7 showed most promising outcomes . The findings of the experiment indicates that derivative 7 exhibited a promising effect against breast cancer cells (MCF-7) lines as compared to standard drug doxorubicin and it also proved that it less harmful and safe for normal cell lines (HEK-293) (28), shown in table -3 . It also showing promising effect to activation of apoptotic protein caspase-3 and downregulation of Bcl-2 protein (29)

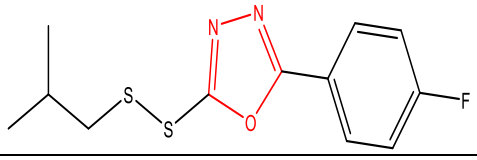
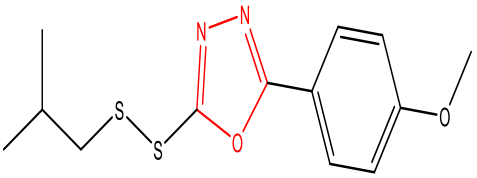
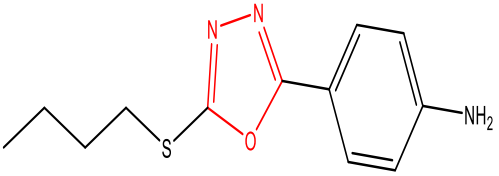
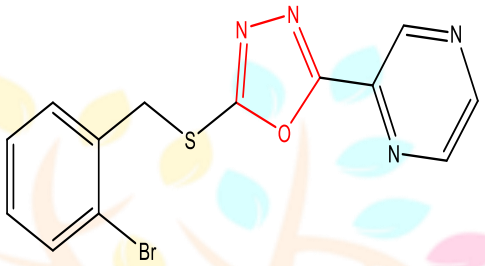
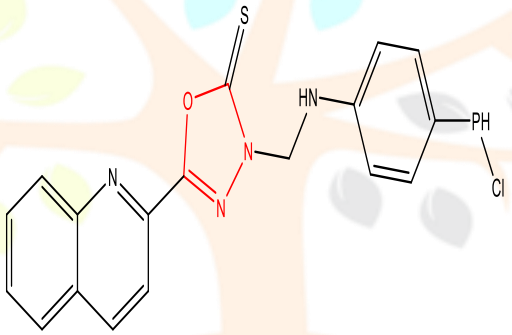
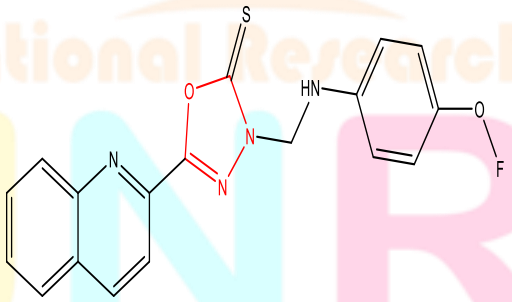
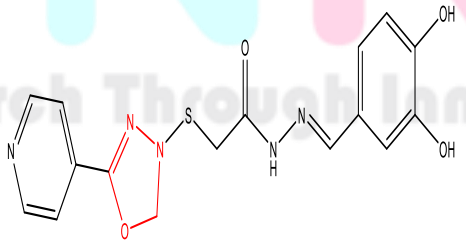
When pyrazine ring is attach with 1,3,4-oxadiazole derivatives (derivative-8) ,studied on the liver (HepG2), colorectal (SW1116), cervical (HELA), and stomach cancer cell lines (BGC823) they show promising effect as anti proliferative action against SW1116 cells as compared to 5-fluorouracil as standard it also shows telomerase inhibitor as compared to staurosporin , demonstrate in table-3 (30) .While 1,3,4-oxadiazoles attach with quinoline group (derivatives-9,10) and studied on breast cancer, stomach cancer, and liver cancer (HepG2) (MCF-7),among them derivatives 9 and 10 show promising effect as anti-proliferative effects and that were 20 times more potent than 5-fluorouracil and it also shows telomerase inhibitory effect than the standard staurosporin (31) .1,3,4-oxadiazole while combine with pyridine ring resulting derivatives (11) have

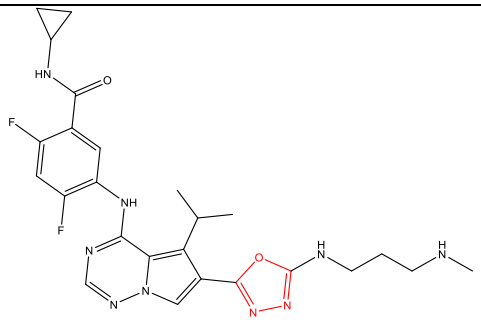
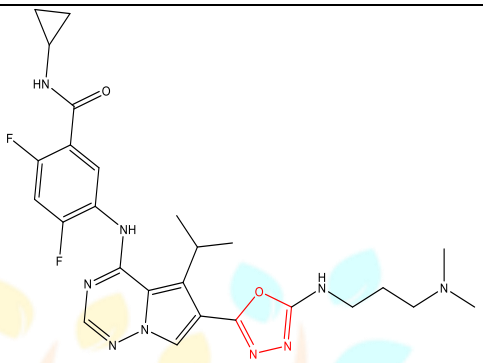
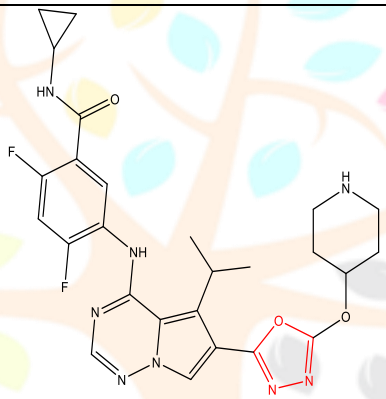
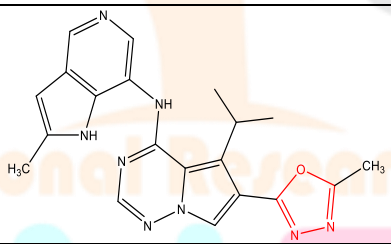
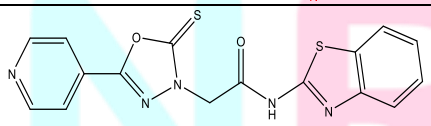
telomerase inhibitory effect and it was study on liver cancer (HEPG2), breast cancer (MCF7), colorectal cancer (SW1116), and stomach cancer (BGC823) showing anti cancer activity and gives more promising effect than 5-fluorouracil (32) .

While 1,3,4-oxadiazole combine with pyrrolotriazine gets derivatives (12,13,14 ,15) study in human umbilical vein endothelial cells (HUVEC) it gives anti-proliferative activity and showing effect against VEGFR-2 receptor reduce tumor angiogenesis . Derivative 14 also show anticancer effect in vivo using mouse transplants of human lung cancer cells (L2987) (33). Derivative 15 show most promising effect while study in human lung cancer cells (L2987) and BMS-645737 cell lines , anti-cancer activity was discovered (34). Derivatives 16 (5-pyridin-4-yl-2-thioxo-1,3,4-oxadiazol-3-yl) gives potent effect VEGFR-2 (Vascular EndotheliaL Growth Factor-2) inhibitors showing promising effect inhibition of angiogenesis in the CCM sample (Chick Chorioallantoic Membrane) compared to standard sorafenib (35) .

Table-03 : Anti-cancer activity of different potent 1,3,4-oxadiazole derivatives on various cell lines –

DERIVATIVES NO	IUPAC NAME	STRUCTURE	STUDIED IN CELL LINES	REFERENCES
1	(E)-2-(((5-(((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol		Liver Cancer Cell (SMMC-7721)	(25)
2	(E)-2-(((5-(((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methyl)thio)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol		Breast Cancer (MCF-7), Lung Cancer (A549)	(25)
3	N-(4-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)methoxy)-3-fluorophenyl)-4-methoxybenzenesulfonamide		Breast Cancer Cell Lines (T-47D and MDA-MB-468), SR Leukaemia, Melanoma (SK-MEL-5)	(26)
4	2-(butyldisulfanyl)-5-phenyl-1,3,4-oxadiazole		Cervical Cancer Cell (HeLa), Liver Cancel Cell (SMMC-7721) Lung Cancer (A549)	(27)

5	2-(4-fluorophenyl)-5-(isobutyldisulfanyl)-1,3,4-oxadiazole		Liver Cancer Cell (SMMC-7721) Lung Cancer Cell (A549)	(27)
6	2-(isobutyldisulfanyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole		Liver Cancer Cell (SMMC-7721) Lung Cancer Cell (A549)	(27)
7	4-(5-(butylthio)-1,3,4-oxadiazol-2-yl)aniline		Breast Cancer Cell (MCF-7)	(28)
8	2-((2-bromobenzyl)thio)-5-(pyrazin-2-yl)-1,3,4-oxadiazole		Colorectel Cancer Cell (SW1116) Liver Cancer Cell (HEPG2) Stomach Cancer Cell (BGC823) Cervical Cancer Cell (HELA)	(30)
9	3-(((4-(chlorophosphaneyl)phenyl)amino)methyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3H)-thione		Breast Cancer Cell (MCF7) Liver Cancer Cell (HGPT2) StomachCancer Cell (SGC-7901)	(31)
10	3-(((4-(chlorophosphaneyl)phenyl)amino)methyl)-5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3H)-thione		Breast Cancer Cell (MCF7) Liver Cancer Cell (HGPT2) Stomach Cancer Cell (SGC-7901)	(31)
11	(E)-N'-(3,4-dihydroxybenzylidene)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)thio)acetohydrazide		Liver Cancer Cell (HEPG2), Breast Cancer Cell (MCF7), Colorectal Cancer Cell (SW1116), Stomach Cancer Cell (BGC823)	(32)

12	N-cyclopropyl-2,4-difluoro-5-((5-isopropyl-6-(5-((3-(methylamino)propyl)amino)-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)benzamide		Human Umbilical Vein Endothelial Cells (HUVEC)	(33)
13	N-cyclopropyl-5-((6-(5-((3-(dimethylamino)propyl)amino)-1,3,4-oxadiazol-2-yl)-5-isopropylpyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)-2,4-difluorobenzamide		Human Umbilical Vein Endothelial Cells (HUVEC)	(33)
14	N-cyclopropyl-2,4-difluoro-5-((5-isopropyl-6-(5-(piperidin-4-yloxy)-1,3,4-oxadiazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)benzamide		Human Umbilical Vein Endothelial Cells (HUVEC) Lung Cancer Cells (L2987)	(33)
15	5-isopropyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(2-methyl-1H-pyrrolo[3,2-c]pyridin-7-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine		lung cancer cells (L2987)	(34)
16	N-(benzo[d]thiazol-2-yl)-2-(5-(pyridin-4-yl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide		VEGFR-2 (Vascular EndotheliaL Growth Factor-2) inhibitors Also Angiogenesis in CCM Cells	(35)

Future aspects –

1,3,4-oxadiazole derivatives may become a integral component of the next generation of cancer treatments and many clinical trials are going on about this compound against anti cancer activity holds significant promising effect in future .

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Table-01-Isomeric forms of oxadiazole and modification of unstable ring and their pharmacological effect .

Table-02 - Novel substituted derivatives of 1,3,4 oxadiazole and their pharmacological effect.

Table-3 Anti-cancer activity of different potent 1,3,4-oxadiazole derivatives on various cell lines .

Figure-01-SAR(Structure activity relationship) of 1,3,4-oxadiazole derivatives.