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Insilico Design and Molecular Docking Studies of Novel 2-(4-chlorophenyl)-5-aryl-1,3,4-Oxadiazole Derivatives for Anti-cancer Activity

V. Vismaya*

Department of Pharmaceutical Chemistry, Ezhuthachan College of Pharmaceutical Sciences , Marayamuttom, Neyyattinkara, Trivandrum-695124, India

Abstract:

2018 was a challenging year in cancer research, since cancer is considered as one of the feared diagnosis among patients and development of a new anticancer drug with less adverse effect is a risky matter. 1,3,4-oxadiazole is an important heterocyclic core for the development of novel anti-cancer drugs. Among its various derivatives 2-(4-chlorophenyl)-5-aryl-1,3,4-oxadiazoles shows potent anti-cancer activity. In the research work, a series of novel 2-(4-chlorophenyl)-5-aryl-1,3,4-oxadiazole analogues has been designed and are molecularly evaluated by using various softwares. The anti-proliferative effects of 1,3,4-oxadiazole is associated with various mechanisms, such as inhibition of growth factors, enzymes, kinases and others. Here the inhibition of epidermal growth factor receptor tyrosine kinase was taken and the X-ray crystal structure of tyrosine kinase (PDB:2J5F) was downloaded from the protein data bank. Ten novel derivatives of 1,3,4-oxadiazole were taken to evaluate the anti-cancer activity. Among these derivatives one of the derivative shows critical binding with high docking score can be considered for future synthesis.

Keywords: 2-(4-chlorothphenyl)-5-aryl-1,3,4-oxadiazole, ACD Lab ChemSketch, molinspiration, admetSAR, PASS, Discovery studio, EGFR tyrosine kinase inhibitor.

INTRODUCTION

In the drug discovery scenario the presence of nitrogen heterocycles play an important role in the development of newer drugs having various pharmacological activities. Oxadiazoles are heterocyclic aromatic chemical compounds containing one oxygen and two nitrogen atoms in a five membered ring of the azole family; with the molecular formula C2H2N2O[1].

Tiemann and Kruger first discovered oxadiazole ring in 1884, then named it as furo[ab]diazoles. Since it is obtained from furan by replacing of two methane (–CH=) groups by two pyridine type nitrogen atoms (–N=). Here the two nitrogen (-N=) is SP^2 hybridized that reduces their aromaticity. So their isomers are electronically comparable to conjugated diene systems. In medicinal chemistry they are used as surrogates (bioisosteres) for carboxylic acids, esters and carboxamides. 1,3,4-oxadiazole undergo various chemical reactions because of their privileged structure, which has enormous biological potential. They possess a diversity of useful biological effects such as antibacterial , antitubercular, antiviral, cytotoxic, anticancer, anti-inflammatory, analgesic etc[2].

The four isomers of oxadiazole are[2] fig.1-4

1. 1,2,3-oxadiazole
2. 1,2,4-oxadiazole
3. 1,3,4-oxadiazole
4. 1,3,5-oxadiazole

Among these isomers, 1,3,4-oxadiazole has become an important construction motif for the development of new drugs. The various activities like antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant and anti-diabetic are the characteristic feature compounds having 1,3,4-oxadiazole ring. The1,3,4-oxadiazole core can be used as a bioisosteres for carboxylic acids, esters and carboxamides. 1,3,4-oxadiazole undergo various chemical reactions, so it has enormous biological potential.[4]

The drugs available in the market having the 1,3,4-oxadiazole unit are in fig. 5-8.

1. Raltegravir {Antiretroviral}
2. Zibotentan {Anticaner}
3. Nesapidel {Antihypertensive}
4. Furamizole {Atifungal}

The presence of toxophoric –N=C–O– linkage in 1, 3, 4-oxadiazole ring might be responsible for their potent pharmacological activities[6]. Among these, substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 2,5-disubstituted-1,3,4-oxadiazole derivatives are stable, especially 2,5-diaryl-1,3,4-oxadiazoles are more stable than the corresponding 2,5-dialkyl derivatives[7].
Medicinal chemists have great perseverance in research and development (R & D) for the search of newer and safer anticancer agents. EGFR family of Tyrosine Kinases (TK) play a vital role in cancer proliferation and it is suggested that any agent which would inhibit the TK activity may have substantial role in the cancer treatment[8]. So here EGFR family of TK were selected and explore the binding mode of the my novel compounds to EGFR tyrosine kinase active site.

This research work aims the in-silico design and molecular docking studies of novel 2-(4-chlorophenyl)-5-aryl-1,3,4-oxadiazoles for anti-cancer activity.The general structure of compound is given in fig - 9.

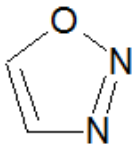

Fig. 1: Structure of 1,2,3-oxadiazole

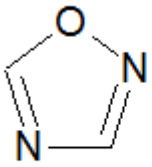

Fig. 2: Structure of 1,2,4-oxadiazole

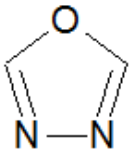

Fig. 3: Structure of 1,3,4-oxadiazole

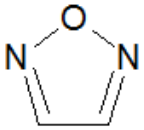

Fig. 4: Structure of 1,3,5-oxadiazole

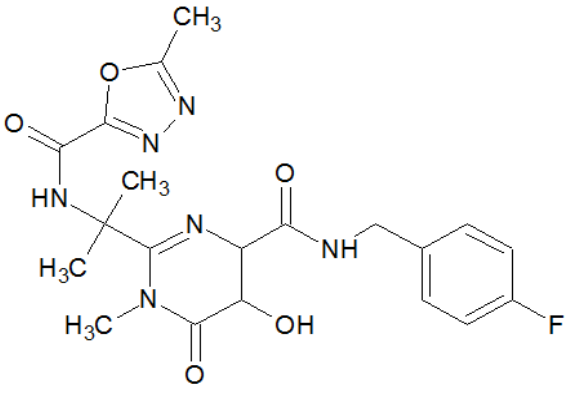

Fig. 5: Structure of Raltegravir {Antiretroviral}

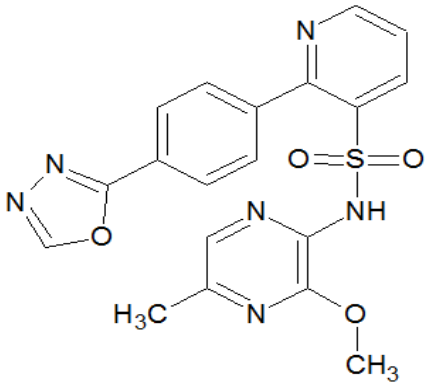

Fig. 6: Structure of Zibotentan {Anticancer}

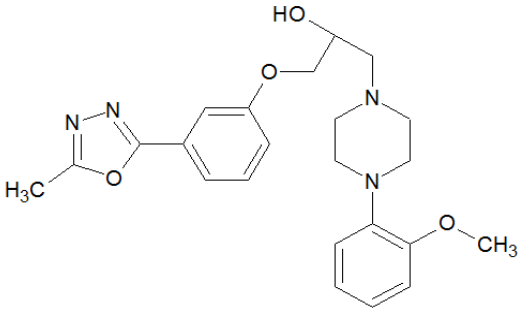

Fig. 7: Structure of Nesapidil {Antihypertensive}

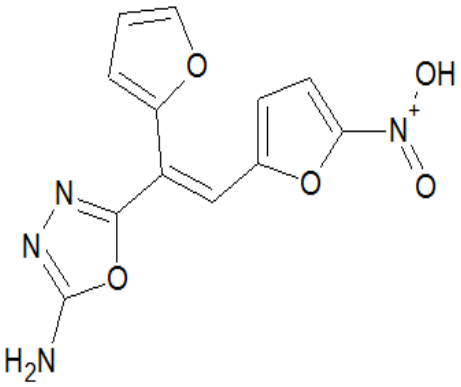

Fig. 8: Structure of Furamizole {Antibacterial}

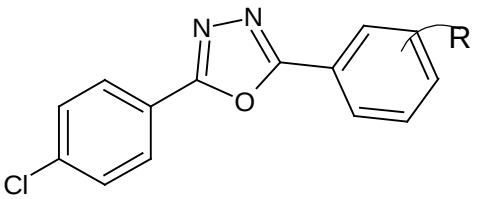

Fig. 9: Structure of 2-(4-chlorophenyl)-5-aryl-1,3,4-oxadiazole analogues

MATERIALS AND METHODS:

The various software's used for the in-silico modelling of novel derivatives include,

- ACD Lab Chemsketch 12.0
- Molinspiration
- PASS
- admetSAR
- Discovery studio

ACD Lab Chemsketch 12.0

This software is used to,

- Generate IUPAC name and SMILE notation of novel compounds.
- Determination of molecular descriptors like molar refractivity, molar volume, parachor, surface tension and polarizability.
- Construction of 3D structure of novel compounds.

Molinspiration

Lipinski Rule of Five and drug likeness can be determined through this software. For this either we can draw the structure or can copy the smile notations of various derivatives. This provides various informations like logP, molecular weight, total polar surface area, number of hydrogen bond donors, number of hydrogen bond acceptors, number of rotatables bonds, number of violations and other drug likeness properties.

PASS

It is Prediction of activity spectra for substances. This software is mainly used to predict various biological activities. It helps to find out compound with desired pharmacological activity and with less side effect. Here the SMILES of novel compounds were used to find out the pharmacological activity.

ADMET SAR

ADMETSAR provides the new and most important manually curated data for diverse chemicals associated with known absorption, distribution, metabolism, excretion and toxicity profiles. This software is mainly used to discard compounds in the drug discovery phase and to prevent the further expenses[3].

Docking by Discovery studio

A docking software used to find out the best binding orientation of ligand with the receptor. The X-ray crystal structure of EGFR tyrosine kinase (PDB: 2J5F) was downloaded from the protein data bank[8].

RESULTS AND DISCUSSION

Datas obtained from ACD Lab Chemsketch such as IUPAC name and SMILES for all the ten novel compound is included in Table1. Also the molecular descriptors computed from ACD Lab Chemsketch is included in Table 2.

TABLE 1: SUMMARY OF DATAS OBTAINED FROM ACD LAB CHEMSKETCH

Compounds	IUPAC name	SMILES
C1	2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-5-methoxyphenol	Clc1ccc(cc1)c2nnc(o2)c3ccc(cc3O)OC
C2	4-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]benzene-1,3-diol	Clc1ccc(cc1)c2nnc(o2)c3ccc(O)cc3O
C3	2-chloro-3-[5-chlorophenyl)-1,3,4-oxadiazol-2-yl] phenol	Clc1ccc(cc1)c2nnc(o2)c3cccc(O)c3Cl
C4	2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-nitrophenol	[O][N+](=O)c1ccc(O)c(c1)c2nnc(o2)c3ccc(Cl)cc3
C5	2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-methylphenol	Clc1ccc(cc1)c2nnc(o2)c3cc(C)ccc3O
C6	2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-methoxyphenol	Clc1ccc(cc1)c2nnc(o2)c3cc(ccc3O)OC
C7	4-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-methoxyphenol	Clc1ccc(cc1)c2nnc(o2)c3cc(OC)c(O)cc3
C8	4-bromo-2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl] phenol	Clc1ccc(cc1)c2nnc(o2)c3cc(Br)ccc3O
C9	2-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-5-methylphenol	Clc1ccc(cc1)c2nnc(o2)c3ccc(C)cc3O
C10	4-bromo-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-methoxyphenol	Clc1ccc(cc1)c2nnc(o2)c3cc(O)c(cc3Br)OC

TABLE 2: SUMMARY OF MOLECULAR DESCRIPTORS OBTAINED FROM ACD LAB CHEMSKETCH

Compounds	Molar refractivity (Cm^3)	Molecular volume (Cm^3)	Parachor (Cm^3)	Surface tension (dynes/cm)	Polarizability (Cm^3)
C1	77.37+/-0.3	223.6+/-3.0	603.8+/-4.0	53.1+/-3.0	$30.67+/-0.5x10^{-24}$
C2	72.57+/-0.3	198.0+/-3.0	562.1+/-4.0	64.9+/-3.0	$28.77+/-0.5x10^{-24}$
C3	75.59+/-0.3	211.5+/-3.0	583.0+/-4.0	57.6+/-3.0	$29.96+/-0.5x10^{-24}$
C4	77.24+/-0.3	211.4+/-3.0	602.6+/-4.0	65.9+/-3.0	$30.62+/-0.5x10^{-24}$
C5	75.52+/-0.3	215.9+/-3.0	584.7+/-4.0	53.8+/-3.0	$29.93+/-0.5x10^{-24}$
C6	77.37+/-0.3	223.6+/-3.0	603.8+/-4.0	53.1+/-3.0	$30.67+/-0.5x10^{-24}$
C7	77.37+/-0.3	223.6+/-3.0	603.8+/-4.0	53.1+/-3.0	$30.67+/-0.5x10^{-24}$
C8	78.38+/-0.3	215.8+/-3.0	597.6+/-4.0	58.8+/-3.0	$31.07+/-0.5x10^{-24}$
C9	75.52+/-0.3	215.9+/-3.0	584.7+/-4.0	53.8+/-3.0	$29.93+/-0.5x10^{-24}$
C10	85.06+/-0.3	239.8+/-3.0	654.3+/-4.0	55.4+/-3.0	$33.72+/-0.5x10^{-24}$

TABLE 3: SUMMARY OF DETAILS OF LIPINSKY RULE OF FIVE BY MOLINSPIRATION SOFTWARE

Sl.no	miLogp	TPSA	natoms	Molecular weight	nON	nOHNH	Nviolations	Nrotb
C1	4.17	68.39	21	302.72	5	1	0	3
C2	3.63	79.38	20	288.69	5	2	0	2
C3	4.77	59.15	20	307.14	4	1	0	2
C4	4.07	104.98	22	317.69	7	1	0	3
C5	4.56	59.19	20	286.72	4	1	0	2
C6	4.17	68.39	21	302.72	5	1	0	3
C7	3.74	68.39	21	302.72	5	1	0	3
C8	4.92	59.15	20	351.59	4	1	0	2
C9	4.56	59.15	20	286.72	4	1	0	2
C10	4.48	68.39	22	381.61	5	1	0	3

TABLE 4: SUMMARY OF DRUG LIKENESS ANALYSIS OF NOVEL MOLECULES BY MOLINSPIRATION SOFTWARE

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
C1	-0.24	-0.52	-0.22	-0.22	-0.43	-0.17
C2	-0.20	-0.44	-0.19	-0.17	-0.43	-0.10
C3	-0.12	-0.43	-0.16	-0.19	-0.37	-0.04
C4	-0.33	-0.48	-0.29	-0.28	-0.48	-0.23
C5	-0.25	-0.53	-0.25	-0.24	-0.47	-0.18
C6	-0.24	-0.50	-0.19	-0.22	-0.43	-0.16
C7	-0.20	-0.36	-0.12	-0.24	-0.41	-0.09
C8	-0.37	-0.53	-0.29	-0.40	-0.59	-0.21
C9	-0.28	-0.54	-0.30	-0.29	-0.50	-0.20
C10	-0.37	-0.52	-0.17	-0.37	-0.54	-0.27

TABLE 5: SUMMARY OF PASS VALUES OF NOVEL MOLECULES

Compounds	Anticancer activity	
	P_a	P_i
C1	0.926	0.004
C2	0.922	0.004
C3	0.845	0.012
C4	0.763	0.028
C5	0.868	0.009
C6	0.925	0.004
C7	0.921	0.004
C8	0.801	0.020
C9	0.859	0.010
C10	0.826	0.016

TABLE 6: SUMMARY OF ADMET PROPERTIES OF NOVEL MOLECULES

Compounds	ADME prediction				Toxicity prediction	
	BBB	CaCo2 cell permeability	HIA	Cytochrome p^{450} inhibitor	AMES test	Carcinogenicity
C1	0.9660	0.5270	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C2	0.9400	0.6283	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C3	0.9894	0.5359	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C4	0.8468	0.5513	0.9953	Inhibitor	AMES toxic	Non-carcinogen
C5	0.9831	0.5230	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C6	0.9660	0.5270	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C7	0.9644	0.5158	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C8	0.9865	0.5507	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C9	0.9831	0.5230	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen
C10	0.9617	0.5244	1.0000	Inhibitor	Non AMES toxic	Non-carcinogen

Details of Lipinsky Rule of Five and drug likeness analysis of novel molecules by molinspiration software is included in Table 3 and Table 4 respectively. From the result it can concluded that all the derivatives obey Lipinsky Rule of Five and have drug likeness properties.

The result obtained from PASS software is included in table 5. It shows that most of the derivatives have good anti-cancer activity.

The result obtained from admetSAR software is included in Table 6. It shows that all the derivatives pass ADMET properties instead of C4.

The crystal structure of EGFR kinase domain in complex with an irreversible inhibitor 34-jab was retrieved from Protein Data Bank with PDB ID: 2J5F with a resolution of $3A^0$.The protein was preprocessed by removing the bounded ligands and the energy of the protein is minimized to form a stable structure for molecular docking. The active side residues are Lys 745, Glu 762, Met 793, Cys 797, Thr 854 and Asp 855. The standard drug shows better binding interaction with target protein residues such as Thr 854 and Ser 720. The docking scores of the compounds is given in Table 7. The novel compound C10 docked at the critical amino acid residue Lys 745 with good docking score can be considered for future synthesis. The docked images of C10 with 2J5F is given in (fig. 10) and the binding interaction of of C10 with 2J5F is given in (fig. 11).

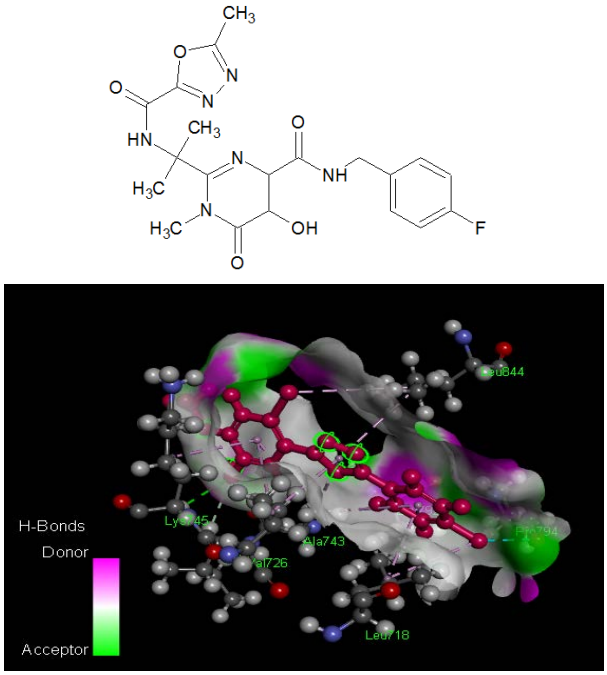

Fig. 10: Docked image of C10 with 2J5F

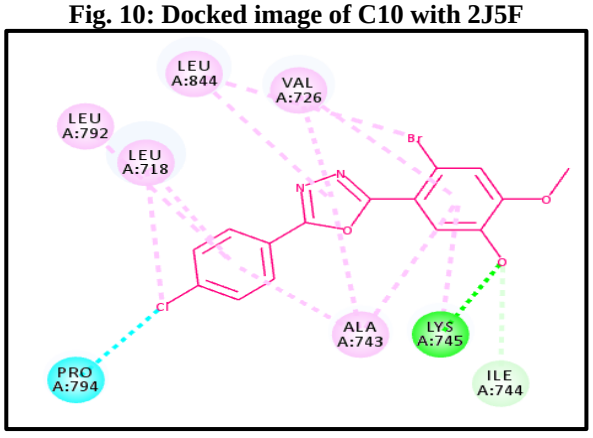

Fig. 11: Binding interaction of C10 with 2J5F

CONCLUSION

A series of ten novel oxadiazole analogues were designed by various softwares. The result obtained from various softwares shows that almost all the derivatives shows drug likeness and other molecular properties. The anti-cancer activities of these novel derivatives were confirmed by their docking scores. The C10 compound bind to the the critical amino acid residue Lys 745 with good docking score for anti-caner activity can be considered for future studies.

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REFERENCE

1. Sonia Y, Neelam V, Vinod G, Aarti R, Sushma M. Oxadiazole and their Synthetic Analogues: An Updated Review. International Journal of Pharmaceutical & Biological Archives. 2018; 9(3):4-9
2. Nagaraj, Chaluvaraju KC, Niranjan MS, Kiran S. 1, 3, 4 oxadiazole: a potent drug candidate with various pharmacological activities. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(3):9-16.
3. Feixiong C, Weihua L, Yadi Z, Jie S, Zengrui W, Guixia L, Philip WL, Yun T. AdmetSAR: a comprehensive source and free tool for evaluating chemical ADMET properties. J. Chem. Inf. Model. 2012;52(11): 3099-3105.
4. Musmade DS, Pattan SR, Manjunath SY. Oxadiazole a nucleus with versatile biological behaviour. International Journal of Pharmaceutical Chemistry. 2015;5(1):10-20.
5. Entesar O, Tamimi1 AL, Khalida, AT. Synthesis, Characterization and Polymerization of 1,3,4- Oxadiazole Derivatives of Amoxicillin and Evaluation Antibacterial Activities. International Journal of Current Microbiology and Applied Sciences. 2016; 5(2): 511-522.
6. Partha Pratim Roy, Shalini Bajaj, Tapan Kumar Maity, Jagadish Singh. Synthesis and Evaluation of Anticancer Activity of 1, 3, 4-Oxadiazole Derivatives against Ehrlich Ascites Carcinoma Bearing Mice and Their Correlation with Histopathology of Liver. Indian Journal of Pharmaceutical Education and Research. 2017; 51(2):260-269.
7. Santhanalakshmi K, Kalyanasundaram S, Jacquline PR, Muthukumar S. Synthesis, characterization, antibacterial and insilico molecular docking studies of 2,5-disubstituted-1,3,4-oxadiazole derivatives. International journal of current engineering and scientific research. 2017;11(4):99-110.
8. Mohamed JA, Vikram PS, Monika S, Ramdayal S, Sabina Y. Synthesis, anticancer and molecular docking studies of 2-(4-chlorophenyl)-5-aryl-1,3,4-oxadiazole analogue. Journal of medicinal chemistry. 2013; 3(4):294-297.
9. Irfan R, Matloob A, Zulfiqar AK, Asim M, Tahir M. Recent advancements in oxadiazole-based anticancer agents. Tropical Journal of Pharmaceutical Research. 2017; 16 (3): 723-733.
10. Nadia AK, Aliaa MK ,Soha HE. Design, synthesis, antitumor activity of novel 5-pyridyl-1,3,4-oxadiazole derivatives against the breast cancer cell line MCF-7. Biological and pharmaceutical bulletin. 2015;38(5): 763–773.
11. Rajwant K and Parminder K. Synthesis and pharmacological activities of 1,3,4-oxadiazole derivatives: a review. European journal of biomedical and pharmaceutical sciences. 2018;5(6).
12. Ahsan JA, Sharma J, Singh M. Synthesis and anti-cancer activity of N-aryl-5-substituted-1,3,4-oxadiazole-2-amine analogues. Biomed Research International. 2014; 1-9.
13. Gudipati R, Anreddy RN, Manda S. Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1,3,4-

oxadiazole-2-yl)phenylimino}indolin-2-one derivatives. Saudi Pharmaceutical Journal, 2011; 19: 153-158
14. Abdel AM, Metwally KA, Gamal AM. 1,3,4-oxadiazole-2-thione derivatives; Novel approach for anticancer and tubulin polymerization inhibitory activities. Anti-Cancer Agents Med Chem., 2016; 16(9): 269-277.
15. Roeper, Julia G, Frank. Epidermal growth factor receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer. Current Opinion in Oncology. 2019;31(1):1–7.
16. Qinlian J , Lei B , Yidan R , Shuliang S , Qin W, Yun-shan W. Advances in studies of tyrosine kinase inhibitors and their acquired resistance. Journal of Molecular Cancer.2018; 17(36):2-12.
17. Pierce B, Weng Z. A Combination of Rescoring and Refinement Significantly Improves Protein Docking Performance. Proteins, 2008;72(1):270-279.
18. Chen R, Weng Z. ZDOCK: An Initial-stage Protein-Docking Algorithm. 2003;52:80-87.
19. Pierce B, Weng Z. ZRANK: Reranking Protein Docking Predictions with an Optimized Energy Function. Proteins, 2007;67(4):1078-1086.
20. Erickson JA., Jalaie M., Robertson DH., Lewis RA., Vieth M. Lessons in Molecular Recognition: The Effects of Ligand and Protein Flexibility on Molecular Docking Accuracy. J Med Chem. 2004;47(1):45-55.