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DOCKING STUDIES OF NOVEL 1, 3, 4- OXADIAZOLE CONTAINING 1*H*-INDOLE- 2, 3-DIONE ANALOGUES AS ANTICANCER PROPERTIES

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Key Words

1*H*-Indole-2, 3-Dione, 1, 3, 4-Oxadiazole, indoleamine 2, 3-dioxygenase, EGFR tyrosine kinase, Anti-cancer properties

ABSTRACT

The treatment of disseminated cancer has become increasingly aimed at molecular targets derived from studies of the oncogenes and tumor suppressors known to be involved in the development of human cancers. 1*H*-Indole-2, 3-Dioneis an important class of heterocyclic compound which possess interesting biological activities like anti-cancer, anti-microbial, anti-fungal, anti-tubercular, anti-malarial, anti-convulsant, anthelmintic, anti-viral, analgesic and anti-inflammatory activity. The drugs containing oxadiazole groups were the first effective chemotherapeutic agents which were systematically proved for the prevention and cure of bacterial infection in human beings. For the treatment of cancer, Indoleamine 2, 3-dioxygenase (IDO) is emerging as an important new therapeutic drug target characterized by pathological immune suppression. Recent understanding of the molecular pathophysiology of cancer have highlighted that many tyrosine kinases are found upstream or downstream of epidemiologically relevant oncogenes or tumor suppressor, in particular the receptor tyrosine kinases. The present research study is focused on the design of 1*H*-Indole-2, 3-Dione analogues containing 1,3,4-oxadiazole, docking against the known anti-cancer targets like indoleamine 2, 3-dioxygenase (IDO) and EGFR tyrosine kinase. Twenty Five compounds of 1*H*-Indole-2, 3-Dione analogues were designed and docked against indoleamine 2, 3-dioxygenase (IDO) and EGFR tyrosine kinase using Auto dock (version 4.2). Among the docked compounds five compounds (Oxa1, Oxa2, Oxa3, Oxa8, and Oxa11) were showed a highest docking score against target enzyme compared to the standard. The present study concluded that 1, 3, 4 Oxadiazole derivatives of 1*H*-Indole-2, 3-Dione analogues will be a significant lead for further investigation of anti-cancer properties.

INTRODUCTION:

Synthetic organic chemistry has always been a vital part of the highly integrated and multidisciplinary process of anticancer drug development. However, the nature of its major contribution has varied over time. In recent years, efforts have been made to synthesize potential anticancer drugs. Consequently, hundreds of chemical variants of known classes of cancer therapeutic agents have been synthesized. Recent advances in biomedical sciences and combinatorial chemistry have resulted in the design and synthesis of hundreds of new antineoplastic agents with potential activity against wide range of therapeutic targets. If our understanding of the drug action and pathogenesis of different types of neoplasm becomes clearer, more rational approaches to the design of newer drugs which selectively target the tumor with no or

reduced side effects may emerge. However, the exact biology of cancer still remain senigmatous at large offering a lot of scope for the research to develop newer compounds to target the malignant cells[1].

Isatin's are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry. A literature survey identified several isatin derivatives in the development phase as potential new drugs. A variety of biological activities are associated with isatin including CNS activities as potentiation of pentobarbitone induce nercosis, analgesic, anticonvulsant, antidepressant, anti-inflammatory, antimicrobial, and effects on the central nervous system. Isatins are capable of crossing the blood–brain-barrier. Isatin, a heterocyclic compound was identified in animals as a major component of the endogenous monoamine oxidase inhibitor. The various substituents at 3rd position of the isatin which were reported various substituted phenyl ring moieties, heterocyclic rings and aliphatic system. Isatin (1*H*-Indole-2, 3-dione) is one of the most promising new class of heterocyclic molecules having many interesting activity profiles and well-tolerated in human subjects [2]. Most tumors express potentially immunogenic antigens to which the immune system can respond. In turn, the tumor-bearing host possesses high-avidity T cells that are specific to these antigens. And yet, in a phenomenon called immune tolerance, tumor cells evolve to escape immune surveillance, and the host fails to reject the tumor. Most patients with cancer achieve a favorable clinical outcome with surgery alone or with surgery plus postoperative adjuvant chemotherapy and/or radiotherapy. However, patients with advanced cancer disease or recurrence remain to show the poor long-term survival. Therefore, in addition to conventional surgery, chemotherapy and radiotherapy, novel therapeutic strategies, such as immunotherapy and molecular-targeted therapy, are needed to further improve the survival of patients with advanced disease.

Immunotherapy has demonstrated promising results in basic and preclinical animal studies, and there have been several clinical trials in gynecologic cancer using immunologic modalities. However, clinical applications have shown only limited efficacy, and this may be mainly attributed to tumor-induced immunosuppression. Therefore, much attention has been paid for understanding and overcoming the immune resistance mechanisms. Recent studies have shown that indoleamine 2, 3-dioxygenase (IDO) is one of the molecules involved in this tumor induced immunosuppression. In this review, we focus on the immunoregulatory enzyme IDO and overview the recent studies [3]. The role of tyrosine kinases in cancer molecular pathogenesis is immense and recently kinases have come in vogue as potential anticancer drug targets, as a result a couple of anticancer drugs are in the market. The complexity and the number of tyrosine kinases have greatly increased with the sequencing effort of the Human Genome Project, thus providing more opportunities for drug discovery. Recent understanding of the molecular pathophysiology of cancer have highlighted that many tyrosine kinases are found upstream or downstream of epidemiologically relevant oncogenes or tumor suppressor, in particular the receptor tyrosine kinases [4].

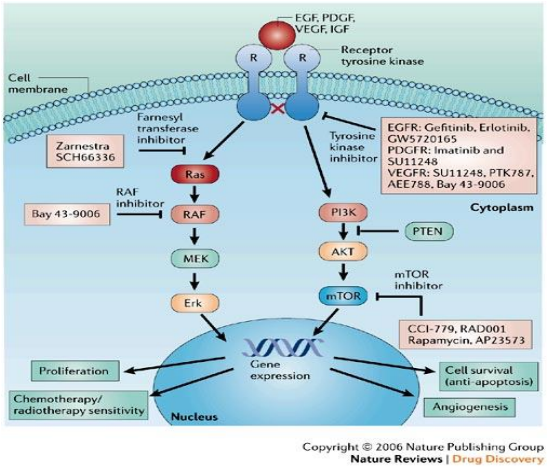

Figure 1: The role of tyrosine kinases in cancer molecular pathogenesis

Oxadiazole derived compounds are known to display wide range of biological and pharmacological activities including

anticancer, antitubercular, antibacterial, antifungal, anti-HIV, anti-inflammatory, and insecticidal activities [6-12]. There are nearly 2577 publications from 2002 to 2012 involving 1,3,4-oxadiazoles [13]. Some of the marketed oxadiazole drugs include raltegravir (antiretroviral), zibotentan (anticancer), etc. We have earlier reported the anticancer activity of some novel oxadiazole analogues [6, 14].

The Objective of the study is too carried out the docking studies of 1*H*-Indole-2, 3-Dione analogues containing 1, 3, 4-oxadiazole groups with known anti-cancer targets like indoleamine 2, 3-dioxygenase (IDO), EGFR tyrosine kinase by using Auto dock programmes.

MATERIALS AND METHODS

Preparation of protein structure

The crystal structure of the indoleamine 2, 3-dioxygenagse 1 (PDB ID: 5ETW) in complexed with NLG919 analogue and the crystal structure of EGFR tyrosine kinase (PDB ID: domain mutant "TMLR" with a imidazo pyridinyl-amino pyrimidine inhibitor analogue (Fig. 9) solved by X-ray crystallography at 2.30Å was retrieved from the Protein Data Bank (http://www.pdb.org/pdb/home/home.do).
Energy minimization of all 3D structure of proteins by Chimera 1.6.1.

Preparation of ligand structures

Marvinsketch is a tool for drawing chemical structures, adding or deleting functional group or atoms, queries and reactions.

Molecular Docking:

The twenty five ligands were drawn in Marvinsketch assigned with proper 3D orientation and the structure of each compound was analyzed for connection error in bond order. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. The docking was done by using Autodock software. Then the pre-screened ligands were validated using Autodock version 4.2 which is more efficient. In Autodock, the proteins were refined by removing water molecules and polar hydrogen's and kollmann charges were added. Grid box for docking simulations were constructed with 50 points in x, y, and z direction to be centered in the active site using Autogrid utility of the Autodock programme. The target ligand complex was subjected to 2.5 million evaluations. The binding energies are compared with the docking score of the standard ligands, Rosmarinic acid and Gefitinib.

RESULT AND DISCUSSION

Docking Analysis

The docking scores were obtained from the analogues against indoleamine 2, 3-dioxygenagse 1 and EGFR tyrosine kinase receptors. The output of all ligands was given by energy values in kcal/mol as shown in Table 1. All the compounds show good docking scores when compared to standard drugs. Docking score of the compounds targeted indoleamine 2, 3-dioxygenagse 1receptor was compared with the score of the drug **Rosmarinic** which is used as a potent drug for the tumoral immune tolerance and docking score of the compounds targeted EGFR tyrosine kinase was compared with the score of the drug **Gefitinib** which is used as drugs to treatment of cancer. In Auto dock, oxa8 shows the highest docking score than the standard drugs against the receptor IDO 1 and EGFR tyrosine kinase than the standard drugs, **Rosmarinic** and **Gefitinib.** Next comes, all the 24 analogues with high docking score against the receptor IDO 1 oxadiazole derivatives were docked with the crystallographic structures of the targets by Autodock version 4.2 screening programme as shown in Table 1.The analogues were examined for their binding energies and hydrogen bonding. The conformations with highest binding energies and greater number of hydrogen bonds of all the ligands were taken in consideration for ranking the analogues.

Table no. 1: Binding Energy and Inhibition Constant of the compounds and the standard drug

S.no	Compound code	5ETW		5HIC	
		Binding Energy (kJ mol^{-1})	Inhibition Constant (µM)	Binding Energy (kJ mol^{-1})	Inhibition Constant (µM)
	Oxa1	-10.84	11.25	-7.13	5.95
	Oxa2	-11.45	4.04	-7.31	4.35
	Oxa3	-10.66	15.99	-7.58	2.8
	Oxa4	-7.03	6.99	-6.83	9.8
	Oxa5	-10.57	17.95	-6.54	16.02
	Oxa6	-8.3	819.47	-5.91	46.81
	Oxa7	-6.88	9.04	-5.98	41.62
	Oxa8	-10.98	8.98	-7.79	1.94
	Oxa9	-7.65	2.46	-6.14	31.63
	Oxa10	-7.83	4.24	-6.1	33.87
	Oxa11	-11.59	3.2	-7.85	1.76
	Oxa12	-10.62	16.36	-6.97	7.82
	Oxa13	-8.05	1.26	-6.65	13.3
	Oxa14	-8.23	934.13	-7.12	6.0
	Oxa15	-7.29	4.51	-7.13	5.93
	Oxa16	-10.65	15.12	-5.63	74.85
	Oxa17	-10.48	20.67	-6.03	37.7
	Oxa18	-7.51	3.15	-6.13	8.25
	Oxa19	-7.99	1.39	-5.87	49.76
	Oxa20	-7.73	2.15	493.97	---
	Oxa21	-6.7	10.64	-7.12	5.23
	Oxa22	-7.46	3.38	-4.9	254.88
	Oxa23	-8.03	1.3	-6.98	7.59
	Oxa24	-7.88	1.67	-4.42	573.54
	Oxa25	-6.45	18.63	-2.67	11.01
	Rosmarinic acid	-5.14	169.43	----------	----------
	Gefitinib	----------	----------	-5.08	188.13

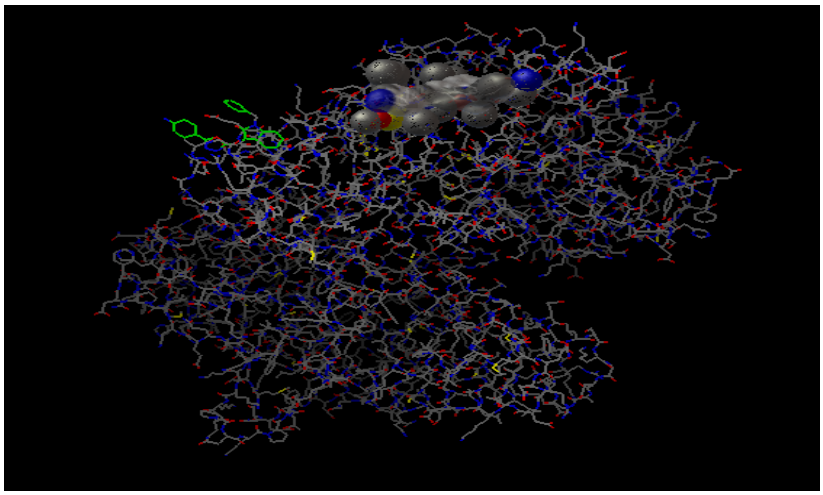

Figure 2a: Compound oxa2 docked at the receptor of indoleamine 2, 3-dioxygenagse 1

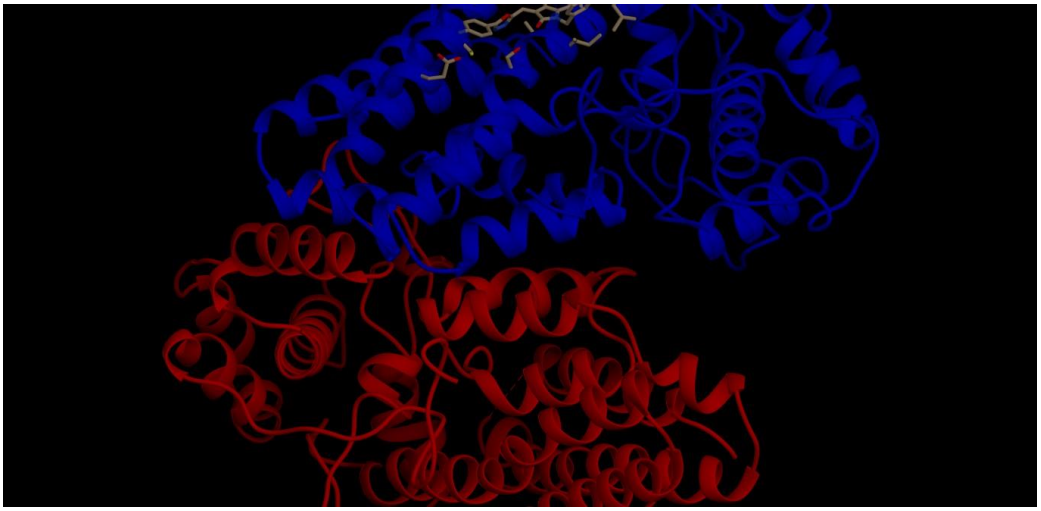

Figure 2b: Compound oxa2 docked at the receptor of indoleamine 2, 3-dioxygenagse 1 in chimera view

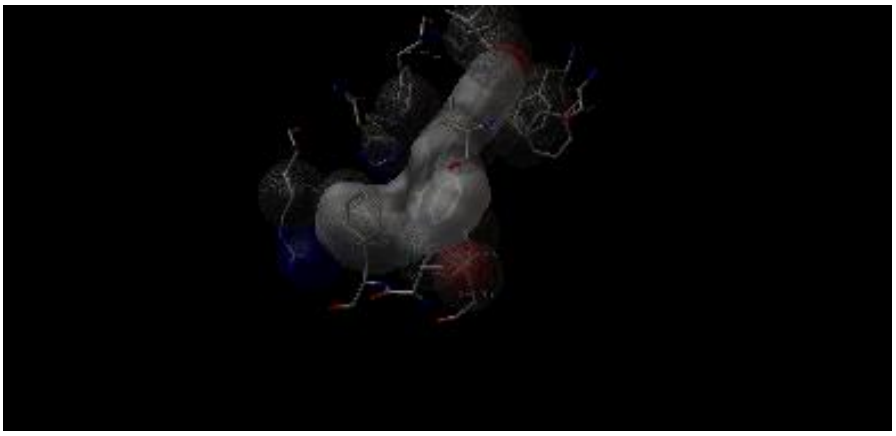

Figure 3a: Compound oxa8 docked at the receptor of indoleamine 2, 3-dioxygenagse 1

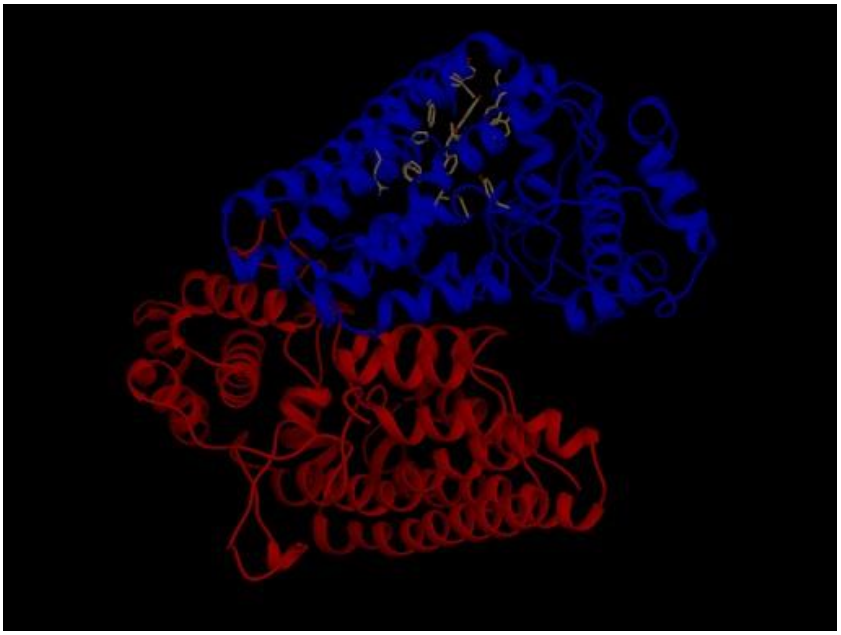

Figure 3b: Compound oxa8 docked at the receptor of indoleamine 2, 3-dioxygenagse 1 in chimera view

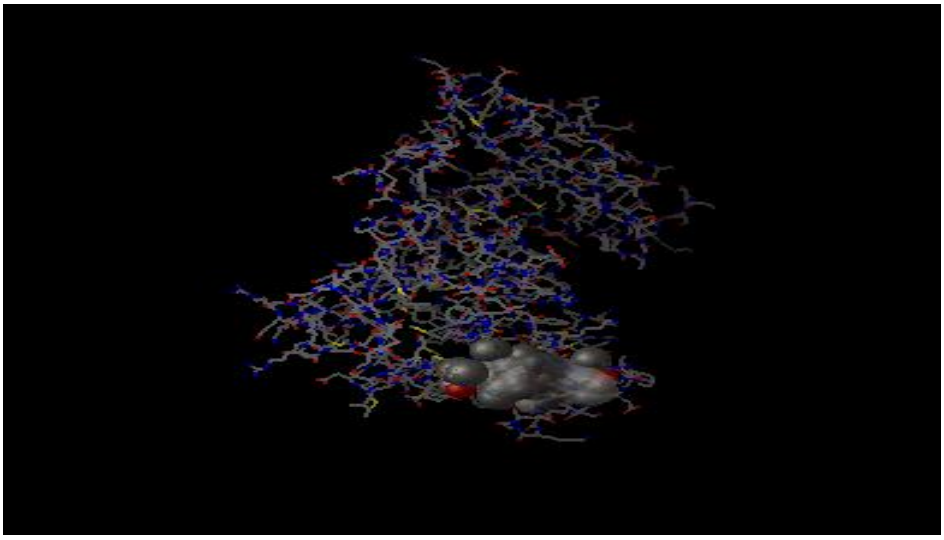

Figure No 4a: Compound oxa3 docked at the receptor of EGFR–TK

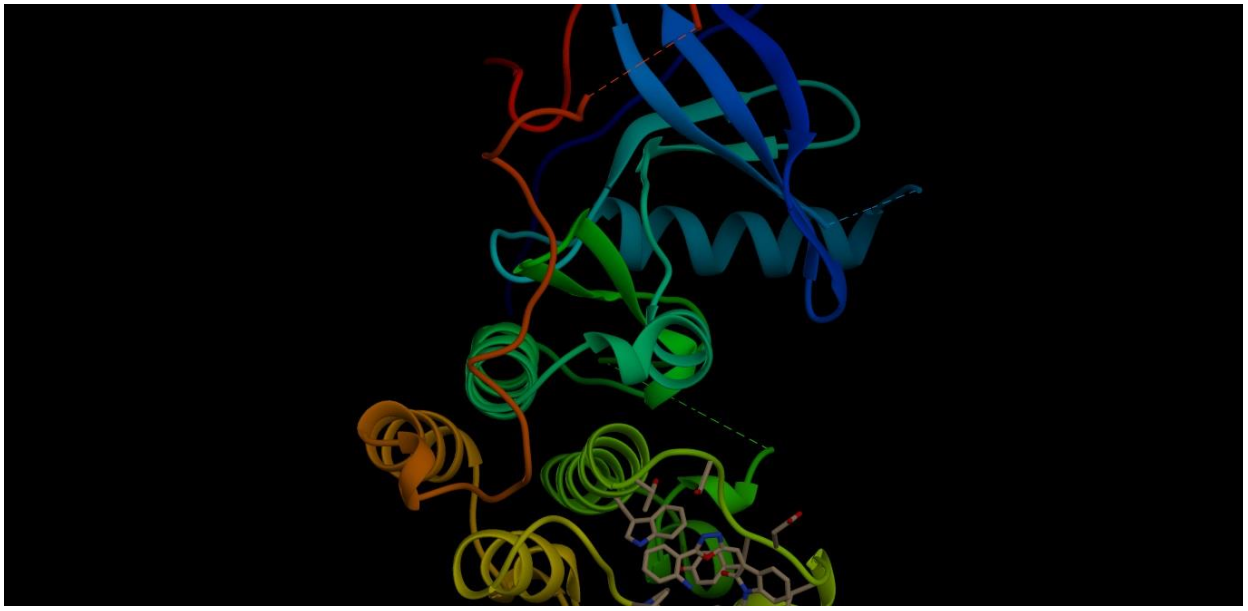

Figure No 4b: Compound oxa3 docked at the receptor of EGFR–TK in chimera view

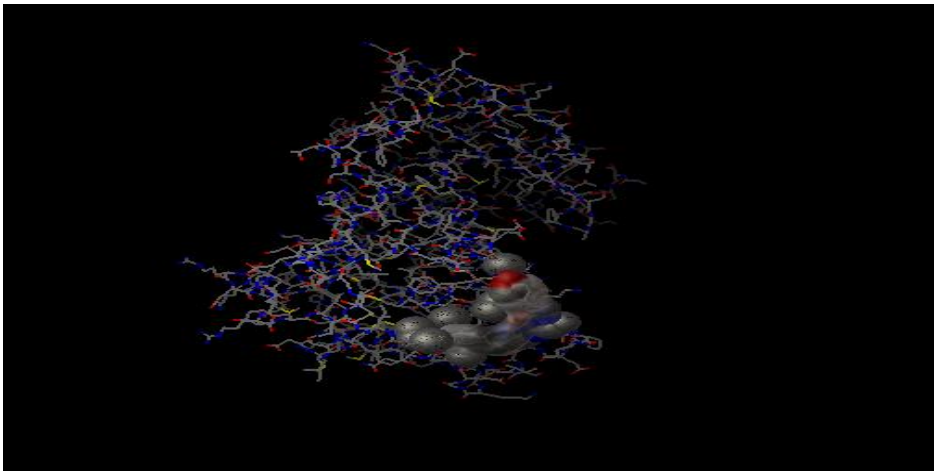

Figure No 5a: Compound oxa8 docked at the receptor of EGFR–TK

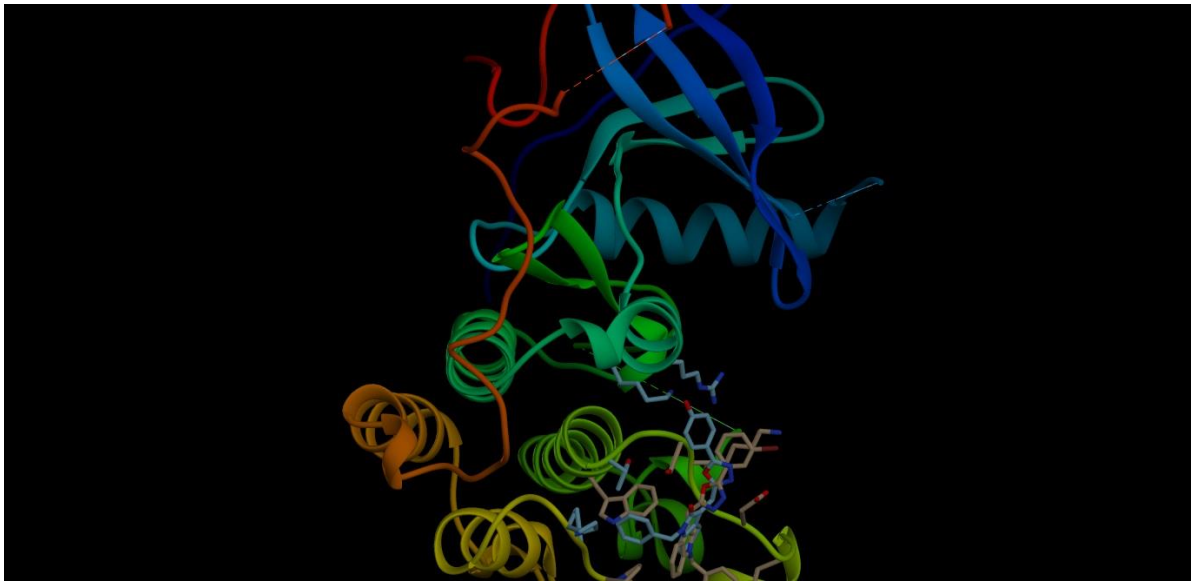

Figure No 5b: Compound oxa8 docked at the receptor of EGFR–TK in chimera view

Table 2: Analysis of Lipinski rule of 5 for the novel proposed analogues.

S.No	Compound code	Molecular weight	No. Of Hba	No. Of Hbd	ClogP	No. Of Rot.b	n violation
	Oxa1	379.41	0	2	3.604	0	0
	Oxa2	394.43	0	2	2.647	0	0
	Oxa3	394.43	2	2	2.647	2	0
	Oxa4	394.43	2	3	2.647	1	0
	Oxa5	397.4	1	2	3.7767	3	0
	Oxa6	413.86	3	4	4.3467	3	0
	Oxa7	413.86	4	4	4.3467	0	0
	Oxa8	413.86	0	5	4.0967	0	0
	Oxa9	458.31	2	5	4.4967	4	0
	Oxa10	458.31	1	5	4.4967	2	0
	Oxa11	395.41	1	2	3.2232	2	0
	Oxa12	395.41	0	2	3.2232	1	0
	Oxa13	395.41	0	1	2.7232	1	0
	Oxa14	424.41	0	1	3.41065	3	0
	Oxa15	424.41	2	3	3.41065	0	0
	Oxa16	424.41	3	3	3.41065	4	0
	Oxa17	393.44	2	3	4.103	0	0
	Oxa18	407.46	0	2	4.602	5	0
	Oxa19	422.48	0	5	3.9337	4	0
	Oxa20	425.44	1	2	3.05468	2	0
	Oxa21	439.46	1	1	2.6189	4	0
	Oxa22	448.3	2	3	4.81334	2	0
	Oxa23	448.3	2	5	4.94334	2	0
	Oxa24	469.41	3	4	3.16145	1	0
	Oxa25	469.41	1	4	3.16145	3	0

All the analogues show higher docking scores when compared to standard drugs oxa1, oxa2, oxa3, oxa8 and oxa11 shows higher docking scores with both IDO and EGFR tyrosine kinase receptors. Studies have proved that compounds showing good tumoral immune tolerance can also be considered as good agents for anti cancer therapy. The interactions were stronger (energetically lesser) for all the ligands which are used for docking simulation.

Validation of Ligands

QSAR and toxicity studies was performed to obtain the molecular properties of all ligands as shown in Table 2.QSAR studies reveals that all ligands was passed and acted as a drug molecule by their adherence to the properties such as Absorption, Distribution, Metabolism and Excretion (ADME) as per the Lipinski Rule Of 5.The results shows that all the values of analogues were relays within the optimal range. Also the compounds have molecular weight less than 500 Daltons and number of hydrogen bond donors and hydrogen bond acceptors of all the analogues is below 5 and 10 respectively. All the values of partition coefficient and number of rotatable bonds were coming under the limit of 5.All these data indicates that the analogues shows no more violations likely to be an orally active drug.

CONCLUSION:

Rigid docking of ligand to receptor molecules is an emerging approach and is extensively used to reduce cost and time in drug discovery. In this study the approach utilized is successful in finding potent inhibitors against indoleamine 2, 3-dioxygenagse 1 and EGFR tyrosine kinase receptors. All the compounds show lowest docked energy and hydrogen bonding stabilizes the interactions. The analogues of 1, 3, 4 oxadiazole showed good receptor binding with the selected targets. Heterocyclic oxadiazole ring is having tumoral immune tolerance and anti-cancer activity. The final assessment of drug-likeness and its related parameters helps to confirm the oral activity of compounds. The study concluded that all 1, 3, 4-oxadiazole derivatives will be significant lead for further investigation of anti-cancer and immunomodulater activity. Future studies are needed to elucidate the structures of synthesized compounds and finally screen for their in-vitro anti-cancer effect. This study could be utilized for the designing of effective drug for the treatment of cancer.

REFERENCES:

1. Maruthamuthu, Bharathi Dileepan A. G., Shameela Rajam, Synthesis, characterization, and anticancer activity of benzoxazole derivatives, *Journal of Chemical and Pharmaceutical Research*.7(9)(2015) 380-387
2. Bhanupriya, Search for Biological Active Isatins: A Short Review, *International Journal of Pharmaceutical Sciences and Drug Research.* 2(4) (2010) 229-235.
3. Kazuhiko Ino, Yuko Tanizaki, Aya Kobayashi, Saori Toujima, Yasushi Mabuchi and Sawako Minami, Role of the Immune Tolerance-Inducing Molecule Indoleamine 2,3-Dioxygenase in Gynecologic Cancers, *journal of Cancer Science & Therapy*. (2012) 1-5.
4. Manash and Anup K. Mukhopadhyay, Tyrosine kinase – Role and significance in Cancer, *International Journal of Medical Sciences.* 2 (2004) 101-115.
5. Moustafa T. Gabr, EGFR Tyrosine Kinase Targeted Compounds: In Vitro Antitumor Activity And Molecular Modeling Studies Of New Benzothiazole And Pyrimido[2,1-B] Benzothiazole Derivatives. *EXCLI Journal.* 13 (2014) 573-585.
6. Salahuddin, (2013) Synthesis, characterization and anticancer evaluation of 2-(Naphthalen-1-ylmethyl/ Naphthalen-2-yloxymethyl)- 1-[5-(substituted phenyl)-[1, 3, 4] oxadiazol-2-ylmethyl]-1H-benzimidazole.

Arabian Journal of Chemistry. 7 (2014) 418–424.

7. Ahsan et al. (2011) Molecular properties prediction and synthesis of novel 1,3,4-oxadiazole analogues as potent antimicrobial and antitubercular agents. *Bioorg Med Chem Lett*. 21 7246-7250.
8. Ahsan (2012) Discovery of novel antitubercular 1,5-dimethyl-2-phenyl-4-({[5-(arylamino)- 1,3,4-oxadiazol-2-yl]methyl}amino)-1,2-dihydro-3H-pyrazol-3-one analogues. Bioorg *Med Chem Lett*. 21 969-972.
9. Bakht MA, (2010) Molecular properties prediction, synthesis and antimicrobial activity of some newer oxadiazole derivatives. *Eur J Med Chem*. 45 5862-5869.
10. Akhtar (2008) In vitro antitumor and antiviral activities of new benzothiazole and 1,3,4-oxadiazole-2- thione derivatives. *Acta Pharm*. 58 135-149.
11. Ramaprasad , Kalluraya B, Kumar S, Mallaya S (2013) Synthesis of new oxadiazole derivatives as anti-inflammatory, analgesic, and antimicrobial agents. *Med Chem Res*. 22 5381-5389.
12. Li Y, et al. (2013) Synthesis, insecticidal activity, and structure-activity relationship (SAR) of anthranilic diamides analogs containing oxadiazole rings. *Org Biomol Chem*. 11 3979-3988.
13. Oliveira CS, Lira BF, Barbosa-Filho JM, Lorenzo JG, de Athayde-Filho PF Synthetic approaches and pharmacological activity of 1,3,4-oxadiazoles: *a review of the literature from 2000-2012*. *Molecules*. 17 (2012) 10192-10231.
14. Ahsan MJ, Sharma J, Bhatia S, Goyal PK, Shankhala K, et al. (2014) Synthesis of 2,5-disubstituted-1,3,4-oxadiazole analogs as novel anticancer and antimicrobial agents. *Lett Drug Des Dis*. 11(2014) 413-419
15. Nimbalkar, Molecular Docking and Antifungal Evaluation of 5-(4-(Benzyloxy)-substituted phenyl)-3-((phenylamino)methyl)-1,3,4-oxadiazole-2(3H)-thiones, *Molecules*. 5 (2016).
16. Taha M, Ismail NH, Imran S, Synthesis, molecular docking and α-glucosidase inhibition of 5-aryl-2-(6'-nitrobenzofuran-2'-yl)-1,3,4-oxadiazoles, *Bioorg Chem*. 66 (2016) 117-123.
17. Kamal A, Combretastatin linked 1,3,4-oxadiazole conjugates as a Potent Tubulin Polymerization inhibitors, *Bioorg Chem*. 65 (2016) 126-136.
18. Desai, Synthesis, biological evaluation and molecular docking study of some novel indole and pyridine based 1,3,4-oxadiazole derivatives as potential antitubercular agents, *Bioorg Med Chem Lett*. 7 (2016) 1776-1783.
19. Garcia, Novel antitumor adamantane- azole gold(I) complexes as potential inhibitors of thioredoxin reductase, *J Biol Inorg Chem*. 2 (2016) 275-292.
20. Robert M.Silverstein, Francis X.Webster, Spectrometric identification of organic compounds, John Wiley and sons, Inc. (1998) 6th edition.

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