Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2019, 10(1):829-840

ISSN : 0976-8505
CODEN (USA): CSHIA5

In silico Studies of 2, 5-Disubstituted-1, 3, 4 – Oxadiazole Analogs as Anti-cancer Agents

Zonunsiami[1*], Rajasekaran S[2]

[1]*Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Bangalore, India*
[2]*Department of Pharmaceutical Chemistry, Ikon Pharmacy College, Bheemanahalli, Bidadi, Hobli, Ramanagara, Karnataka, India*

ABSTRACT

Molecular modeling study was performed on Oxadiazole derivatives as anti-cancer targets. The oxadiazole derivatives having reported for anticancer molecules were subjected for fragmentation based QSAR to explore the relationship between the chemical, physical and biological properties. MLR and PLS using stepwise forward backward methods were used for model generation. The statistically significant and effective models were developed, in order to aid in further optimization and development of newer anticancer agents. Further, the compounds were subjected to molecular docking to understand the binding and interaction with the proteins at the active sites. The molecules were also screened for in silico toxicity to gather the safety measures.

Keywords: Oxadiazole, Anticancer, G-QSAR, Molecular docking, Toxicity

INTRODUCTION

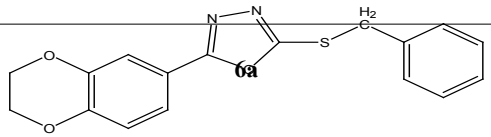
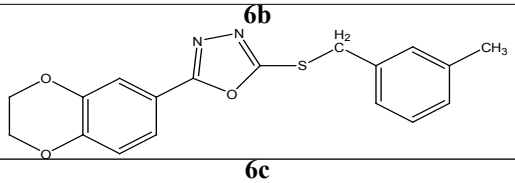
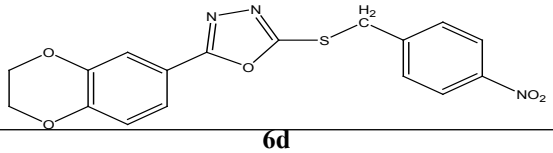
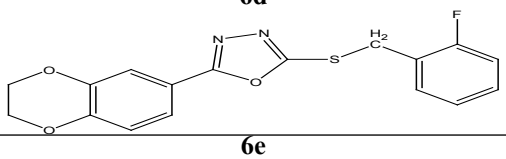
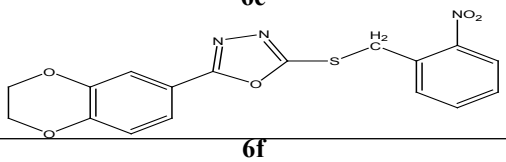
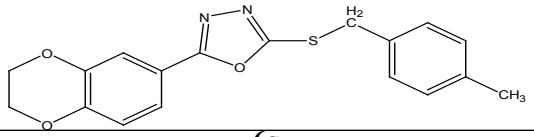
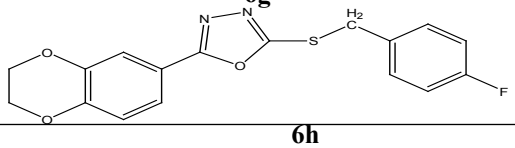
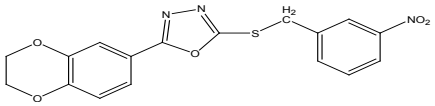
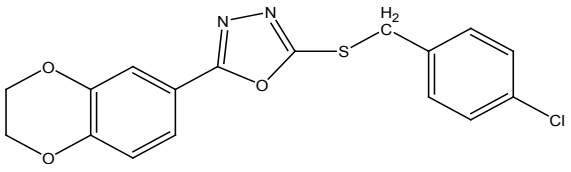
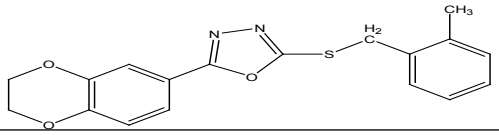
Cancers are the major cause of death worldwide despite of the availability of several drugs and treatments [1], due to which enormous research is in progress around the globe to discover new anticancer drugs with better efficacy and lesser toxicity [2]. Hepatocellular carcinoma (HCC) is the major form of liver cancer which originates from hepatocytes [3] and there is relatively uncommon liver cancer as well such as heptatoblastoma and intrehepatic cholangiocarcinoma [4]. Liver cancer is the third most common cause of cancer death globally [5] and is caused due to imbalance between the activation and inactivation of the proto-oncogenes and anti-oncogenes as well as the environmental factor such as ionizing radiation, physical damage, and specific chemicals leads to mutation of the genes, thereby activating the proto-oncogenes into oncogenes and viral infection N-ras, hepatitis B, human papillomaviruses [6]. It is also believed to be caused by abnormal activation of different molecules in various signaling pathways [7].

Oxadiazole is a heterocyclic compounds consisting of five-member ring of the azole group nucleus [8]. There is an increasing number of biochemical targets for oxadiazole compounds and has a wide range of biological activities such as anticancer [9,10], antiangiogenic [11], antimycobacterial [12,13], antibacterial [14], anthelmintic [15], antifungal [16,17], anticonvulsant [18,19], hypoglycemic [20], analgesic [21,22] and antidepressant [23]. There are several oxadiazole derivatives available in the market for various treatments such as Zibotentan (anticancer) [24], Raltegravir (antiretroviral) [25], Tiodazosin, Nesapidil (antihypertensives) [26,27], Furamizole (antibiotic) [28], Fasiplon (anti-anxiety) [29].

In the present study, a series of eighteen quinazoline derivatives reported by Zhang XM and co-workers [30] have been taken to understand the SAR by carrying out G-QSAR and docking study. Further, the molecules have been docked on three proteins (4CQ0, 5A1G and 3UG2- Breast, Liver and Lung cancer target) to evaluate their binding interaction.

EXPERIMENTAL

The molecular modeling study was carried out on four different modes, the determination of physicochemical parameters and bioactivity, fragmentation based QSAR, toxicity screening and molecular docking study. The reported

Compound	Activity	
	Liver	
	IC_{50} (µM)	pIC_{50} (M)
 **6a**	32.14	-1.507
6b 	33.37	-1.523
6c 	35.44	-1.545
6d 	23.98	-1.379
6e 	38.05	-1.58
6f 	41.90	-1.622
6g 	37.99	-1.579
6h 	38.30	-1.583
6i 	28.83	-1.459
6j 	22.02	-1.342

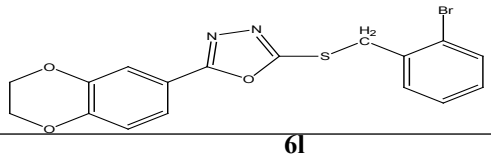
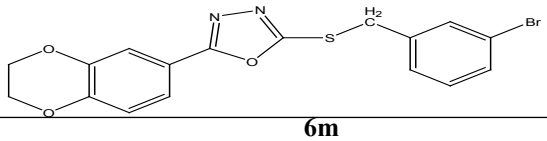
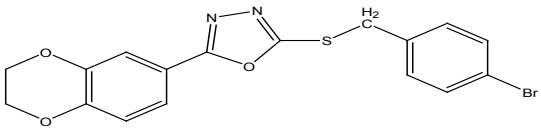
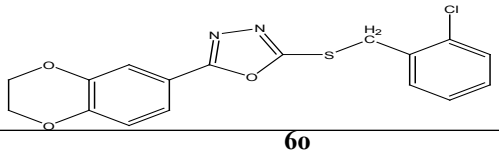
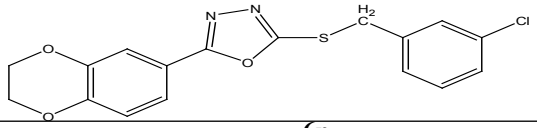
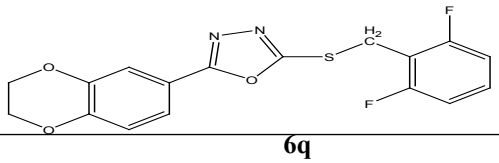
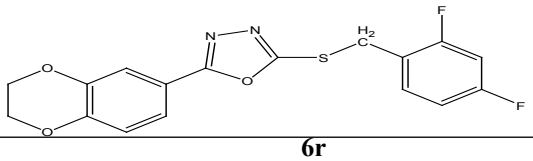
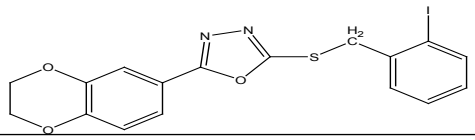
6k 	19.95	-1.299
6l 	24.95	-1.397
6m 	8.54	-0.931
6n 	22.64	-1.354
6o 	33.36	-1.523
6p 	41.60	-1.619
6q 	38.70	-1.587
6r 	7.21	-0.857

Table 1: 2, 5-disubstituted-1, 3, 4 – oxadiazole derivatives with biological activity

data set consists of oxadiazole were taken and the IC50 (μM) values of the dataset were taken and further converted to pIC50 (M) for the evaluation of their SAR (Table 1).

Physicochemical and bioactivity score screening

The drug likeness and bioactivity score of the compounds were screened using online tool Molinspiration cheminformatics (https://www.molinspiration.com/) [31-33]. The structures of the molecules were developed by JSME molecular editor provided by the online tool. It was performed to predict whether, the molecules were likely to be a bioactive according to some important parameters such as molecular weight, LogP, number of HBA and HBD

along with bioactivity score towards GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor, ligand, protease inhibitor and enzyme inhibitor.

Molecular docking

The structure of the ligands was constructed using ChemDraw Ultra ver 7.0 and the energy minimization was performed by "The PRODRG Server" (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg/submit.html). AutoDock ver 4.2 was used as the primary docking program. AutoDock Tools were used to prepare the input pdbqt file and to map the grid box. Gasteiger charges and polar hydrogen atoms were applied to the prepared protein structure (PDB id: 4CQ0, 5A1G and 3UG2) [34-36]. The protein grid center was predicted at 70 × 70 × 70 in the dimensions of x, y and z using 0.375Å spacing. Lamarckian genetic algorithm was used for the conformational search; each docking simulation was run for 50 independent runs with a population size of 150 and 25x105 energy evaluations. The pose with lowest energy of binding or binding affinity was extracted and aligned with receptor structure for further analysis. The two-dimensional interaction between the protein and ligand was carried out using Discovery studio Visualizer.

Fragmentation based Quantity structure-activity relationship analysis

VlifeEngine ver 4.3 provided by Vlife Sciences, Pune was used to perform fragment based QSAR study. The biological activity (MIC) was converted into logarithm based scale and used as dependent variables (pMIC = -log MIC) in G-QSAR study (Table 1). All the 18 structures were constructed using 2D draw application provided by VlifeEngine module of VLifeMDS [37]. The 2D structures were then converted into 3D structures. The energy minimization and geometry optimization was conducted using MMFF(Merck Molecular Force Field) with the setting of distance dependent function in the dielectric properties field(constant as 1.0), convergence criteria(i.e. RMS gradient as 0.01), maximum number of cycles(1,00,000) and gradient type (analytical) by batch energy minimization method [38]. All the preparatory steps were performed by Vlife engine platform. The total pool of 632 descriptors was calculated and the descriptors with constant values among the dataset were deleted, resulting in 202 different descriptors (independent variables) which were used in the QSAR analysis. The dataset were divided by random search method into 12 molecules of training and 6 molecules of test set, 7:3 ratios. The training set was used to generate the QSAR model and test set was used to validate the generated model. The biological activity of the molecules was used as dependent variable whereas various physico-chemicals and alignment independent parameters (template structure is defined and used for the alignment of molecules) were used as independent variable. Multiple linear regressions (MLR) and Partial least square (PLS) with Stepwise forward backward (SWFB) selection methods were used with cross correlation limit as 0.7, 3.00 as variance cut-off, f test in and out as 2.00 and 1.99 respectively and term selection criteria as r2 [39-41].

Toxicity screening

The chemical data were screened for theoretical toxicity properties (mutagenicity, tumorigenicity, irritating and reproductive effects) using DS TOPKAT supplied by Accelrys Pvt. Ltd [42] to analyze the risk of toxicity and their overall drug score.

RESULTS AND DISCUSSION

Physicochemical and bioactivity score screening

The potency of the drug molecule is theoretically screened by applying Lipinski's rule of five and molecules which fulfill all the criteria are expected to be able to become drug. The results are given in Table 2. Bioactivity score screening is to examine the bioactivity contribution of the molecules. The molecule activity score should fall within the range of -3 and +3, the data set was found to be active. The Bioactivity score of the compounds are given in Table 3.

Molecular docking

Molecular docking is a computational approach to dive inside the target sites, which allows us to understand the binding mode and affinity of the molecules towards the binding cavity. The chemical data sets were docked into three different targets by rigid docking. In rigid docking, the spatial shape of the molecules was maintained rigid during the docking process. The molecules were docked; in order predict the priority for binding site and mode of protein-ligand interactions at the active sites. The best conformation for each molecule was selected based on the lowest binding energy. The molecules were found to bind in the same pocket of active site as by its co-crystallized ligand, which could be due to the presence of aromatic rings and heteroatoms, which is important for the cancer targets based on the reported literature. All the compound have shown an average binding energy with an hydrogen bond and π–cation interaction with the protein 4CQ0 whereas in case of 3HB5 protein it showed good docking score with minimal

Com pound	miLogP	TPSA	n atoms	MW	n ON	n OHNH	n violations	n rotb	Volume
6a	3.63	57.39	23	326.38	5	0	0	4	275.78
6b	4.06	57.39	24	340.40	5	0	0	4	292.34
6c	3.59	103.22	26	371.37	8	0	0	5	299.11
6d	3.75	57.39	24	344.37	5	0	0	4	280.71
6e	3.54	103.22	26	371.37	8	0	0	5	299.11
6f	4.08	57.39	24	340.40	5	0	0	4	292.34
6g	3.79	57.39	24	344.37	5	0	0	4	280.71
6h	3.57	103.22	26	371.37	8	0	0	5	299.11
6i	4.31	57.39	24	360.82	5	0	0	4	289.31
6j	4.03	57.39	24	340.40	5	0	0	4	292.34
6k	4.39	57.39	24	405.27	5	0	0	4	293.66
6l	4.42	57.39	24	405.27	5	0	0	4	293.66
6m	4.44	57.39	24	405.27	5	0	0	4	293.66
6n	4.26	57.39	24	360.82	5	0	0	4	289.31
6o	4.29	57.39	24	360.82	5	0	0	4	289.31
6p	3.86	57.39	25	362.36	5	0	0	4	285.64
6q	3.89	57.39	25	362.36	5	0	0	4	285.64
6r	4.67	57.39	24	452.27	5	0	0	4	299.77

Table 2: Physicochemical screening of molecule data set

interaction and for 5A1G protein, few of the compounds have shown not very promising binding energy whereas compounds 6f, 6h, 6i, 6j and 6k showed better binding energy than the co-crystallized ligand. The amino acids which are involved in the bond formation between the ligands and protein are Serine 142, Cysteine 185, Threonine 190, Threonine 199, Threonine 200, Proline 201, Methionine 793, Glutamine 781. The bond diantace ranges from 2.18-5.64Å.

The compounds have shown an average binding with least interaction with amino acids of the target sites. The results are shown in Table 4 and Figure 1.

Fragmentation based QSAR

Fragmentation based QSAR was performed and models were developed by MLR (Multiple linear regression method) and PLS (Partial least square) methods using SWFB (Stepwise forward backward) methods. Chemical data sets of 18 compounds were divided into training (12 molecules) and test sets (6 molecules). The best QSAR models were selected on the basis of predicted fitness plots and statistical values of the model (which must falls within the limited range). The developed model is found with coefficient of determination (r2), cross-validated r2 (q2), r2 for external test set (pred_r2), statistical significance (F test), error in Prediction (r2 se, q2 se) and the r2 for external test set (Pred r2). The statistical parameters for each model are shown in Table 5. The descriptors which contribute positively are Mol. Wt. whereas chi4, T_2_T_1 and kappa1 contribute negatively.

Model 1 (MLR_SWFB)

pMIC = +4.1240+0.0057(±0.0001) R1-Mol.Wt. -0.4576(±0.1832) R1-chi4-1.4490

Mol.Wt: This descriptor signifies molecular weight of a compound, which is directly proportional and contributes 0.06% to the biological activity.

chi4: This descriptor signifies a retention index (fourth order) derived directly from gradient retention times, and is inversely proportional to the biological activity (45%).

Model 2 (PLS_SWFB)

pMIC = + 0.0057 R1-Mol.Wt. -0.0462 R1-T_2_T_1-1.4484

Mol.Wt: This descriptor signifies molecular weight of a compound, which is directly proportional and contributes 0.6% to the biological activity.

T_2_T_1: This descriptor signifies the count of number of double bounded atoms separated from single bond, and is inversely proportional to the biological activity (0.05%).

Com pound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
6a	-0.73	-1.13	-0.13	-0.71	-0.39	-0.38
6b	-0.74	-1.17	-0.16	-0.69	-0.41	-0.42
6c	-0.80	-1.06	-0.25	-0.73	-0.46	-0.45
6d	-0.68	-1.16	-0.19	-0.75	-0.39	-0.41
6e	-0.80	-1.06	-0.31	-0.69	-0.46	-0.43
6f	-0.75	-1.16	-0.16	-0.70	-0.42	-0.42
6g	-0.69	-1.10	-0.09	-0.65	-0.38	-0.38
6h	-0.81	-1.07	-0.25	-0.73	-0.47	-0.47
6i	-0.70	-1.09	-0.14	-0.69	-0.40	-0.40
6j	-0.74	-1.23	-0.26	-0.70	-0.43	-0.43
6k	-0.87	-1.20	-0.25	-0.84	-0.57	-0.51
6l	-0.82	-1.18	-0.20	-0.81	-0.50	-0.45
6m	-0.80	-1.17	-0.17	-0.79	-0.48	-0.44
6n	-0.73	-1.17	-0.18	-0.69	-0.43	-0.46
6o	-0.70	-1.08	-0.15	-0.70	-040	-0.40
6p	-0.69	-1.06	-0.12	-0.67	-0.34	-0.41
6q	-0.65	-1.12	-0.15	-0.71	-0.34	-0.38
6r	-0.69	-1.05	-0.14	-0.63	-0.46	-0.47

Table 3: Bioactivity screening of molecule data set

Molecule Name	Docking score/ Binding Energy [4CQ0 (Breast)]	Docking score/ Binding Energy [5A1G (Liver)]	Docking score/ Binding Energy [3UG2 (Lung)]
Reference ligand	-8.1	-5.37	-6
6a	-8.36	-5.37	-6.1
6b	-8.48	-5.48	-7.1
6c	-8.28	-4.02	-6
6d	-8.31	-5.21	-6.1
6e	-7.55	-4.65	-5.9
6f	-8.41	-5.95	-7.3
6g	-7.65	-4.66	-5.7
6h	-7.79	-6.48	-5.5
6i	-8.56	-6.35	-6.9
6j	-9.18	-6.14	-7.8
6k	-8.41	-5.52	-6.3
6l	-8.60	-5.77	-6.4
6m	-8.48	-5.23	-6.9
6n	-8.76	-3.12	-6.2
6o	-7.59	-5.06	-6.1
6p	-8.00	-5.45	-5.9
6q	-7.98	-4.90	-5.4
6r	-7.54	-4.96	-5.5
6s	-8.66	-5.87	-5.2

Table 4: Docking studies of dataset

Model 3 (PLS_SWFB)

pMIC = +0.0055(±0.0001)R1-Mol.Wt. -0.5123(±0.2062)R1-chi4-1.3412

Mol.Wt: This descriptor signifies molecular weight of a compound, which is directly proportional and contributes 0.05% to the biological activity.

chi4: This descriptor signifies a retention index (fourth order) derived directly from gradient retention times, and is inversely proportional to the biological activity (0.51%).

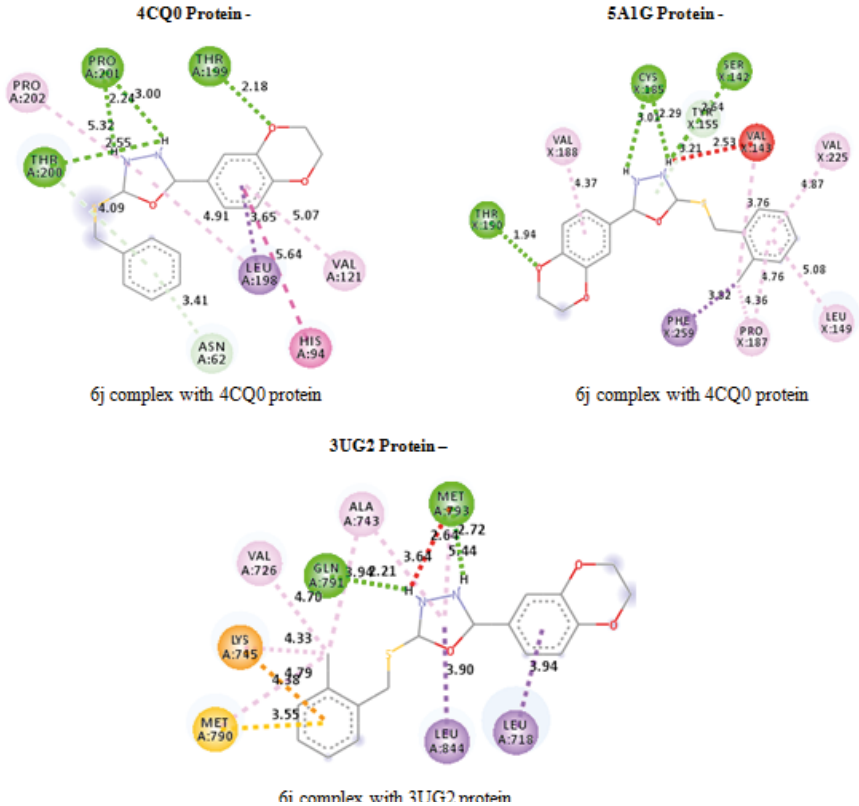


Figure 1: Interaction of 6j with 4CQ0, 5A1G and 3UG2 proteins.

Model	N	Df	r^2	r^2 se	q^2	q^2se	F test	Pred_r2	Pred_r2 se
Model_1	12	9	0.74	0.14	0.61	0.17	13	0.70	0.07
Model_2	12	10	0.71	0.13	0.57	0.17	25	0.51	0.12
Model_3	12	9	0.75	0.15	0.61	0.17	13	0.59	0.09
Model_4	12	10	0.73	0.13	0.59	0.17	28	0.58	0.1
Model_5	12	10	0.70	0.13	0.56	0.17	24	0.65	0.11
Model_6	12	9	0.75	0.13	0.63	0.16	14	0.52	0.10

Table 5: Statistical parameter for the developed G-QSAR models

Model 4 (PLS_SWFB)

pMIC = +0.0055 R1-Mol.Wt. -0.0909 R1-chi4-1.9502

Mol.Wt: This descriptor signifies molecular weight of a compound, which is directly proportional and contributes 0.06% to the biological activity.

chi4: This descriptor signifies a retention index (fourth order) derived directly from gradient retention times, and is inversely proportional to the biological activity (0.09%).

Model 5 (PLS_SWFB)

pMIC = +0.0052 R1-Mol.Wt. -0.0497 R1-T_2_T_1-1.3489

Mol.Wt: This descriptor signifies molecular weight of a compound, which is directly proportional and contributes 0.05% to the biological activity.

T_2_T_1: This descriptor signifies the count of number of double bounded atoms separated from a single bond, and is inversely proportional to the biological activity (0.5%).

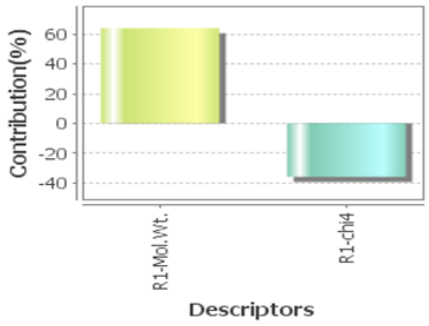
Model 6 (MLR_SWFB)

pMIC = + 0.0059(±0.0002) R1-Mol.Wt. -0.1157(±0.0493) R1-kappa1-1.4796

Mol.Wt: This descriptor signifies molecular weight of a compound, which is directly proportional and contributes 0.06% to the biological activity.

kappa1: This descriptor signifies first kappa shape index: (n-1)2 /m2, and is inversely proportional to the biological activity (0.11%).

The regression plot of predicted against actual activity and the percentage contribution plot of descriptors are displayed in Figures 2a-2f.



Graph 2a: Fitness plot of G-QSAR Model 1

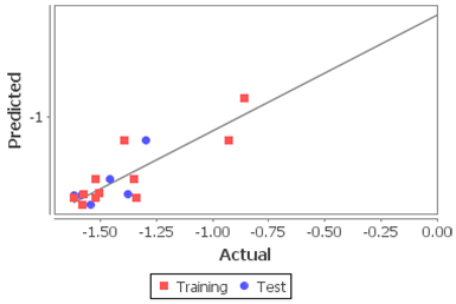
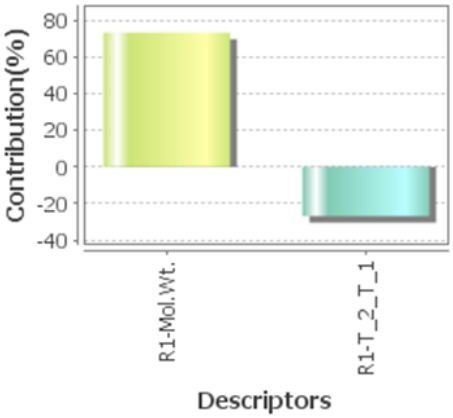


Figure 2a: Contribution plot for G-QSAR Model 1

Figure 2a: Fitness and contribution plot of Model 1.



Graph 2b: Fitness plot of G-QSAR Model 2

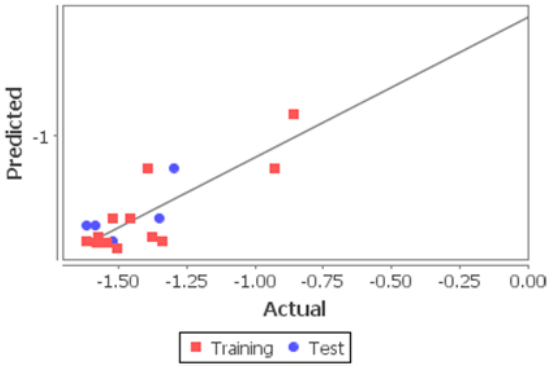
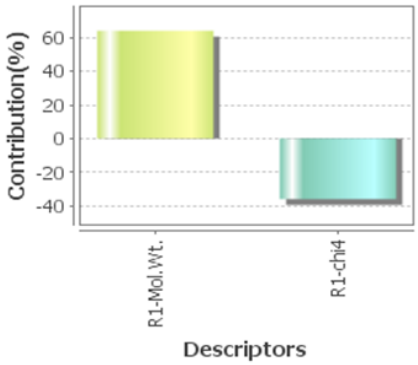


Figure 2b: Contribution plot for G-QSAR Model 2

Figure 2b: Fitness and contribution plot of Model 2.



Graph 2c: Fitness plot of G-QSAR Model 3

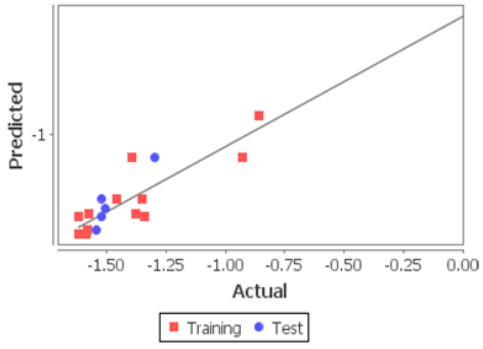
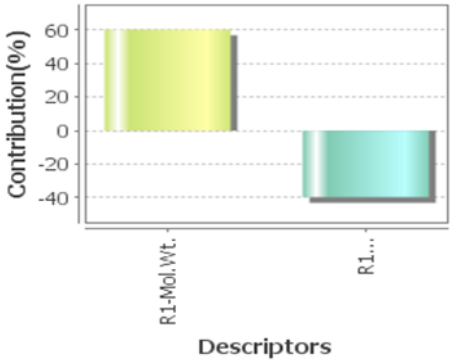


Figure 2c: Contribution plot for G-QSAR Model 3

Figure 2c: Fitness and contribution plot of Model 3.



Graph 2d: Fitness plot of G-QSAR Model 4

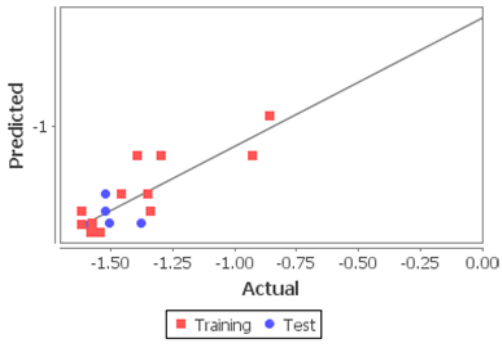
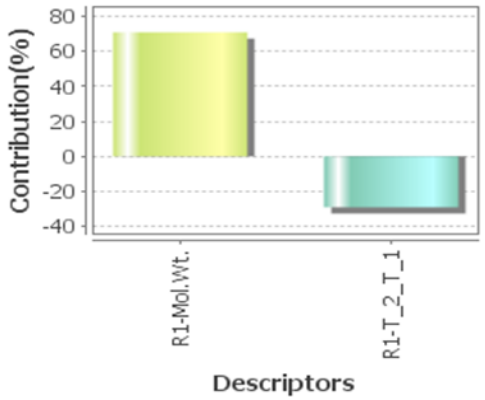


Figure 2d: Contribution plot for G-QSAR Model 4

Figure 2d: Fitness and contribution plot of Model 4.



Graph 2e: Fitness plot of G-QSAR Model 5

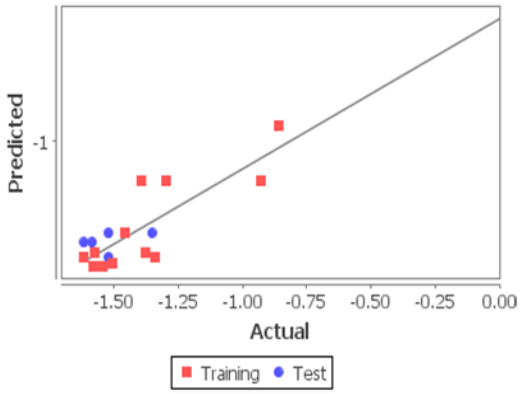
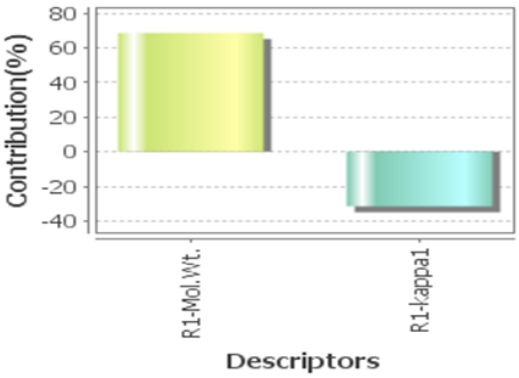


Figure 2e: Contribution plot for G-QSAR Model 5

Figure 2e: Fitness and contribution plot of Model 5.



Graph 2f: Fitness plot of G-QSAR Model 6

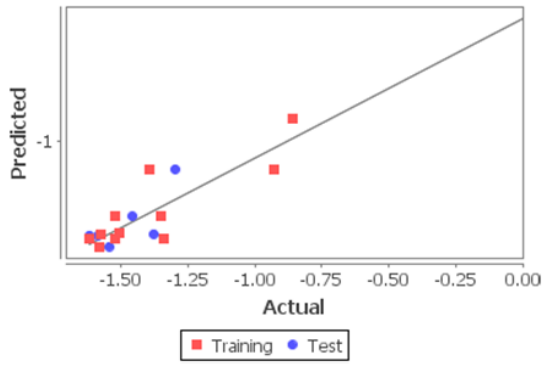


Figure 2f: Contribution plot for G-QSAR Model 6

Figure 2f: Fitness and contribution plot of Model 6.

CONCLUSION

A series of 2,5-disubstituted-1, 3, 4 – oxadiazole analogs were subjected for the different molecular modeling approaches. The drug likeness and bioactivity score performed on molinspiration software showed that the chemical data's were within the Lipinski rules. Then, fragment based qsar study was performed using random search engine algorithm for the division of the data sets and training and test sets, six models were generated by adopting the MLR and PLS method with stepwise forward backward approaches and statistically significant G-QSAR models were generated. R1- Mol. Wt at R1 position is the only descriptor which cam improved the biological activity whereas chi4, T_2_T_1 and kappa1 shown to decreased the biological activity. Furthermore, the molecular docking study was carried out against the 4CQ0, 5A1G and 3UG2 protein for different cancer targets; the data sets are showing almost similar binding patterns with the co-crystallized ligand. The compounds 6h, 6i and 6j have shown promising binding energy in all the three proteins. Finally, it is concluded that the work presented here will play an important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the molecular property, fragment based QSAR model and molecular docking one can consider and incorporate the present findings which reveals that increasing the molecular weight thereby replacing the substitution at benzyl group by other heterocyclic group. However, the aliphatic or hydrophobic groups, long chains and terminal double bond should be avoided for better achievement.

ACKNOWLEDGEMENTS

The authors are indebted to the Principal, Al-Ameen College of Pharmacy, for providing necessary facilities and support. This work was financially supported by University Grant Commission (UGC), New Delhi, India.

REFERENCES

1. Nagai H, Kim YH **(2017)** Cancer prevention from the perspective of global cancer burden patterns. *J Thorac Dis* 9:448.
2. Mustian KM, Sprod LK, Palesh OG, Peppone LJ, Janelsins MC, et al. **(2009)** Exercise for the management of side effects and quality of life among cancer survivors. *Curr Sports Med Rep* 8:325.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. **(2011)** Global cancer statistics. *CA-Cancer J Clin* 61:69-90.
4. Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, et al. **(2016)** Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. Cancer 122:1349-69.
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. **(2018)** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA-Cancer J Clin 68:394-424.
6. Zhao M, He HW, Sun HX, Ren KH, Shao RG **(2009)** Dual knockdown of N-ras and epiregulin synergistically suppressed the growth of human hepatoma cells. *Biochem Biophys Res Commun* 387:239-244.
7. Galuppo R, Ramaiah D, Ponte OM, Gedaly R **(2014)** Molecular therapies in hepatocellular carcinoma: what can we target? Digest Dis Sci 59:1688-1697.
8. Dhara D, Sunil D, Kamath PR, Ananda K, Shrilakshmi S, et al. **(2018)** New Oxadiazole Derivatives: Synthesis and Appraisal of Their Potential as Antimicrobial Agents. *Lett Drug Des Discov* 15:21-30.
9. Jin L, Chen J, Song B, Chen Z, Yang S, et al. **(2006)** Synthesis, structure, and bioactivity of N′-substituted benzylidene-3, 4, 5-trimethoxybenzohydrazide and 3-acetyl-2-substituted phenyl-5-(3, 4, 5-trimethoxyphenyl)-2, 3-dihydro-1, 3, 4-oxadiazole derivatives. *Bioorg Med Chem Lett* 16:5036-5040.
10. Shivarama HB, Narayana PK, Subrahmanya BK, Mithun A, Boja P **(2005)** Synthesis and anticancer activity studies on some 2-chloro-1,4-bis-(5-substituted-1,3,4-oxadiazol-2-ylmethyleneoxy) phenylene derivatives. *Ind J Chem* 44: 1669-1673.
11. Kumar A, D'Souza SS, Nagaraj SR, Gaonkar SL, Salimath BP, et al. **(2009)** Antiangiogenic and antiproliferative effects of substituted-1, 3, 4-oxadiazole derivatives is mediated by down regulation of VEGF and inhibition of translocation of HIF-1α in Ehrlich ascites tumor cells. Cancer Chemother. *Pharmacol* 64:1221-1233.
12. Dewangan D, Pandey A, Sivakumar T, Rajavel R, Dubey RD **(2010)** Synthesis of some novel 2, 5-disubstituted 1, 3, 4-oxadiazole and its analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activity. *Int J Chem Tech Res* 2(3):1397-1412.
13. Ali MA, Shaharyar M **(2007)** Oxadiazole mannich bases: Synthesis and antimycobacterial activity. *Bioorg Med Chem Lett* 17: 3314-3316.
14. Chawla R, Arora A, Parameswaran MK, Chan P, Sharma D, et al. **(2010)** Synthesis of novel 1,3,4-oxadiazole derivatives as potential antimicrobial agents. *Acta Pol Pharm* 67: 247-253.
15. Bharathi D, Hemalatha S, Devadass G, Kumar PR, Shanmugasundaram P, et al. **(2010)** Synthesis, characterisation and in vitro anti inflammatory and anthelmintic activities of 1, 3, 4-oxadiazole derivatives. *Int J ChemTech Res* 2:1867-1870.

16.Liu F, Luo XQ, Song BA, Bhadury PS, Yang S, et al. **(2008)** Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1, 3, 4-thiadiazole and 1, 3, 4-oxadiazole moiety. *Bioorg Med Chem* 16: 3632-3640.

17.Chen CJ, Song BA, Yang S, Xu GF, Bhadury PS, et al. **(2007)** Synthesis and antifungal activities of 5-(3, 4, 5-trimethoxyphenyl)-2-sulfonyl-1, 3, 4-thiadiazole and 5-(3, 4, 5-trimethoxyphenyl)-2-sulfonyl-1, 3, 4-oxadiazole derivatives. *Bioorg Med Chem* 15:3981-3989.

18.Almasirad A, Tabatabai SA, Faizi M, Kebriaeezadeh A, Mehrabi N, et al. **(2004)** Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy) phenyl]-1, 3, 4-oxadiazoles and 1, 2, 4-triazoles. *Bioorg Med Chem Lett* 14: 6057-6059.

19.Zarghi A, Tabatabai SA, Faizi M, Ahadian A, Navabi P, et al. **(2005)** Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1, 3, 4-oxadiazoles. *Bioorg Med Chem Lett* 15:1863-1865.

20.Shingalapur RV, Hosamani KM, Keri RS, Hugar MH **(2010)** Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. *Eur J Med Chem* 45: 1753-1759.

21.Kumar H, Javed SA, Khan SA, Amir M **(2008)** 1, 3, 4-Oxadiazole/thiadiazole and 1, 2, 4-triazole derivatives of biphenyl-4-yloxy acetic acid: synthesis and preliminary evaluation of biological properties. *Eur J Med Chem* 43: 2688-2698.

22.Bhandari SV, Bothara KG, Raut MK, Patil AA, Sarkate AP, et al. **(2008)** Design, synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel S-substituted phenacyl-1, 3, 4-oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives. *Bioorg Med Chem* 16: 1822-1831.

23.Zarghi A, Faizi M, Shafaghi B, Ahadian A, Khojastehpoor HR, et al. **(2005)** Design and synthesis of new 2-substituted-5-(2-benzylthiophenyl)-1, 3, 4-oxadiazoles as benzodiazepine receptor agonists. *Bioorg Med Chem Lett* 15:3126-3129.

24.Hatti I, Sreenivasulu R, Jadav SS, Ahsan MJ, Raju RR **(2015)** Synthesis and biological evaluation of 1, 3, 4-oxadiazole-linked bisindole derivatives as anticancer agents. *Monatsh Chem*. 146:1699-1705.

25.Temesgen Z, Siraj DS **(2008)** Raltegravir: first in class HIV integrase inhibitor. *Ther Clin Risk Manag* 4:493.

26.Vardan S, Smulyan H, Mookherjee S, Eich R **(1983)** Effects of tiodazosin, a new antihypertensive, hemodynamics and clinical variables. *Clin Pharmacol Ther.* 34: 290-296.

27.Schlecker R, Thieme PC **(1988)** The synthesis of antihypertensive 3-(1, 3, 4-oxadiazol-2-yl) phenoxypropanolahines. *Tetrahedron* 44(11): 3289-3294.

28.Ogata M, Atobe H, Kushida H, Yamamoto K **(1971)** In vitro sensitivity of mycoplasmas isolated from various animals and sewage to antibiotics and nitrofurans. *J Antibiot* 24(7): 443-451.

29.Zachariah SM, Ramkumar M, George N, Ashif MS **(2015)** A Review on Oxadiazole. Res J Pharm Biol Chem Sci 6: 205-219.

30.Zhang XM, Qiu M, Sun J, Zhang YB, Yang YS, et al. **(2011)** Synthesis, biological evaluation, and molecular docking studies of 1, 3, 4-oxadiazole derivatives possessing 1, 4-benzodioxan moiety as potential anticancer agents. *Bioorg Med Chem* 19: 6518-6524.

31.Lipinski CA, Lombardo F, Dominy BW, Feeney PJ **(2001)** Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Delivery Rev* 46: 3-26.

32.Ramalingam R, Madhavi BB, Nath AR, Duganath N, Sri EU, el al. **(2010)** In-vitro anti-denaturation and antibacterial activities of Zizyphus oenoplia. *Der Pharm Lett* 2: 87-93.

33.Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, et al. **(2002)** Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem* 45: 2615-2623.

34.Moeker J, Peat TS, Bornaghi LF, Vullo D, Supuran CT, et al. **(2014)** Cyclic secondary sulfonamides: unusually good inhibitors of cancer-related carbonic anhydrase enzymes. *J Med Chem* 57: 3522-3531.

35.Murray B, Antonyuk SV, Marina A, Lu SC, Mato JM, et al. **(2016)** Crystallography captures catalytic steps in human methionine adenosyl transferase enzymes. *PNAS* 113: 2104-2109.

36.Yoshikawa S, Kukimoto-Niino M, Parker L, Handa N, Terada T, et al. **(2013)** Structural basis for the altered drug sensitivities of non-small cell lung cancer-associated mutants of human epidermal growth factor receptor *Oncogene* 32: 27-38.

37.Abdellatif KR, Abdelall EK, Abdelgawad MA, Amin DM, Omar HA **(2015)** Design, synthesis and biological evaluation of new 4-(4-substituted-anilino) quinoline derivatives as anticancer agents. *Med Che Res* 16: 3297-3309.

38.VLife MD **(2004)**: Molecular Design Suite, 3rd edn Vlife Sciences Technologies Pvt. Ltd, Pune, India.

39.Baumann K **(2002)** An alignment-independent versatile structure descriptor for QSAR and QSPR based on the distribution of molecular features. *J Chem Inf Comput Sci* 42: 26-35.

40.Tyagi C, Gupta A, Goyal S, Dhanjal JK, Grover A **(2014)** Fragment based group QSAR and molecular dynamics mechanistic

studies on arylthioindole derivatives targeting the α-β interfacial site of human tubulin *BMC Genomics* 15: S10.

41. Ajmani S, Kulkarni SA **(2012)** Application of GQSAR for scaffold hopping and lead optimization in multitarget inhibitors. *Mol Infor* 31: 473-490.

42. Ali A, Badawy ME, Shah R, Rehman W, El kilany Y, et al. **(2017)** Synthesis, Characterization and In-Silico ADMET Screening of Mono- and Dicarbomethoxylated 6,6'-Methylenebis(2-cyclohexyl-4-methylphenol) and Their Hydrazides and Hydrazones. *Der Chem Sin* 8: 446-460.