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DOCKING STUDIES OF BCL2 INHIBITORS INVOLVED IN BREAST CANCER

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ABSTRACT: Cancer is one of the world's leading causes of death and occurs when the homeostatic balance between cell growth and death is disturbed. Cancer has proven to be one of the most intractable diseases to which humans are subjected, and as yet no practical and general effective drugs or methods of control. Therefore, identification of novel potent, selective, and less toxic anticancer agents remains one of the most pressing health problems. Research in cancer biology has discovered that a variety of aberrations in gene expression of anti-apoptotic, pro-apoptotic and BH3-only proteins can contribute to the many forms of the disease. Oxadiazole derivatives have many pharmacological uses i:e compounds possessing oxadiazole moiety acts as an analgesic, hypoglycemic, bactericidal and local anesthetic. Certain 1,3,4-oxadiazole derivatives were reported to possess anti-inflammatory, antitubercular, antifungal, and anticancer activities. In the present research a series of 50 oxadiazole derivatives were designed and evaluated docking studies were performed using Open eye software against cancer proteins of Breast cancer (Intraductal Carcinoma) [B-cell lymphoma 2-BCL2 (1G5M)].

Key words: Breast cancer, BCL2, Oxadiazole, Docking

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INTRODUCTION

Heterocyclic compounds are organic compounds containing at least one atom of carbon, and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. Heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are countless additives and modifiers used in industries as varied ascosmetics, reprography, information storage, and plastics.The chemistry of heterocyclic compounds has been an interesting field of study for a long time (Fink, Tobias, and Jean-Louis Reymond, 2007).

Breast cancer (malignantbreast neoplasm) is cancer originating from breast tissue, most commonly from the inner lining of milkducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas; those originating from lobules are known as lobular carcinomas (Panno, 2009).

B-cell lymphoma 2(Bcl2) is the founding member of the BCL2 family of apoptosis regulator proteins encoded by the BCL2 gene. BCL2 derives its name from B-cell lymphoma 2, as it is the second member of a range of proteins initially described in chromosomal translocations involving chromosomes 14 and 18 in follicular lymphomas. BCL2orthologs have been identified in numerous mammals for which complete genome data are available. The two isoforms of BCL2, Isoform 1, also known as 1G5M, and Isoform 2, also known as 1G5O/1GJH, exhibit similar fold.

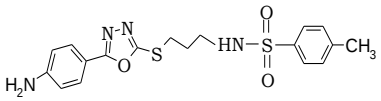
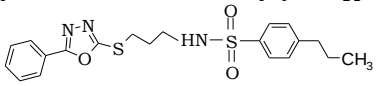
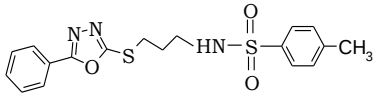
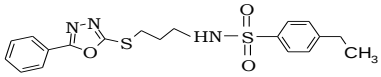
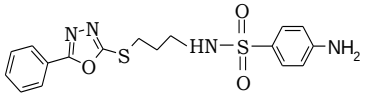
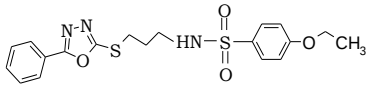
However, results in the ability of these isoforms to bind to the BAD and BAK proteins, as well as in the structural topology and electrostatic potential of the binding groove, suggest differences in antiapoptotic activity for the two isoforms (Gross et al., 1999; Souers et al., 2013). The present study was aimed at developing a new series of various 2,5 Disubstituted 1,3,4-Oxadiazoles and to perform docking studies on BCL2 (1G5M).

MATERIALS AND METHODS

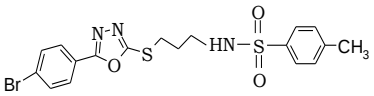
ACD/ChemSketch is an integrated software package from Advanced Chemistry Development Inc. for drawing chemical structures, reactions, schematic diagrams and designing other chemistry-related reports and presentations (Table 1). Structure mode for drawing chemical structures and calculating their properties (Mathew and Ishtiaq, 2015).

OpenEye's portfolio of molecular modeling applications is presented as a workflow involving ligand- and structure-based design strategies (Liao et al., 2011). FILTER and QUACPAC prepare the input compounds by removal of undesirables and application of a variety of charge models. OMEGA generates high quality 3D conformer ensembles. ROCS searches compound libraries for 3D shape (and chemistry) similar molecules. EON may then be used to refine the ROCS hits by electrostatic similarity. BROOD searches fragment databases for bioisosteric replacements using similar approaches to ROCS and EON. FRED is OpenEye's docking and scoring application. Hit structures may then be optimized with SZYBKI. VIDA is a powerful graphical interface for visualization and effective communication of results, which VIVANT can then export live into Power Point presentations or web pages. AFITT is a standalone application for ligand fitting to crystallographic density (Carvalho et al., 2011). Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Two approaches are particularly popular within the molecular docking community. One approach uses a matching technique that describes the protein and the ligand as complementary surfaces (Feig et al., 2004). The second approach simulates the actual docking process in which the ligand-protein pair wise interaction energies are calculated. Docking program depends on two components: the search algorithm and the scoring function (Kitchen, 2004).

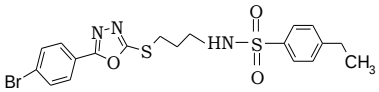
Table 1: Oxidiazole derivatives used in this study

Structures of the compounds which were designed from chemsketch (No.s 1-50):
1. N-(3-{[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide 
2. 4-methyl-N-{3-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propyl}benzenesulfonamide 
3. 4-ethyl-N-{3-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propyl}benzenesulfonamide 
4. 4-propyl-N-(3-{[5-(4-phenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)benzenesulfonamide 
5. 4-amino-N-{3-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propyl}benzenesulfonamide 
6. 4-ethoxy-N-{3-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]propyl}benzenesulfonamide 

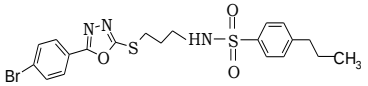
7. N-(3-{[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



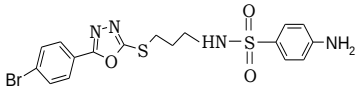
8. N-(3- {[5-(4- bromophenyl)-1,3,4- oxadiazol-2- yl]thio}propyl)-4-Ethylbenzenesulfonamide



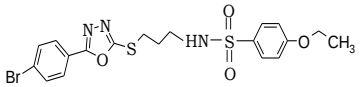
9. N-(3-{[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-propylbenzenesulfonamide



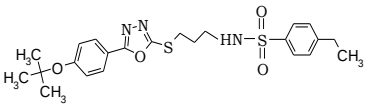
10. N-(3-{[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-aminobenzenesulfonamide



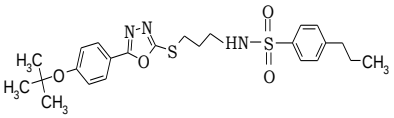
11. N-(3-{[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethoxybenzenesulfonamide



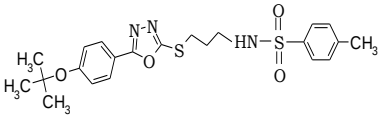
12. N-(3-{[5-(4-butoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



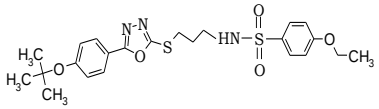
13. N-(3-{[5-(4-butaoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethylbenzenesulfonamide



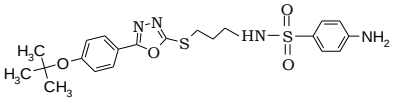
14. N-(3-{[5-(4-butoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-propylbenzenesulfonamide



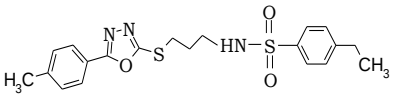
15. N-(3-{[5-(4-butoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-aminobenzenesulfonamide



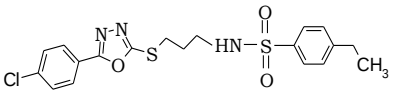
16. N-(3-{[5-(4-butoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethoxybenzenesulfonamide



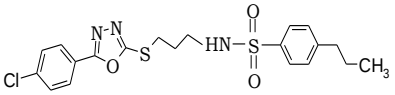
17. N-(3-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethylbenzenesulfonamide



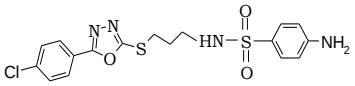
18. N-(3-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethylbenzenesulfonamide



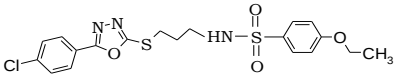
19. N-(3-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-propylbenzenesulfonamide



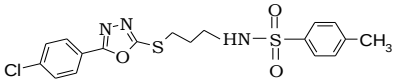
20. N-(3-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-aminebenzenesulfonamide



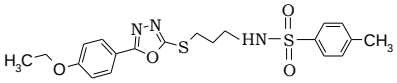
21. N-(3-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methoxybenzenesulfonamide



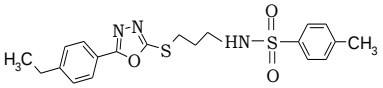
22. N-(3-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



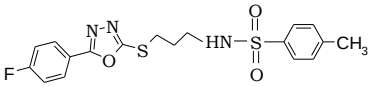
23. N-(3-{[5-(4-ethoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



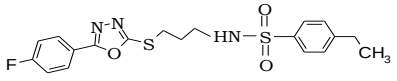
24. N-(3-{[5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



25. N-(3-{[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



26. N-(3-{[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethylbenzenesulfonamide



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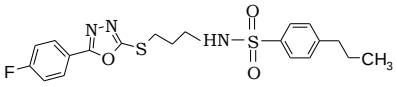

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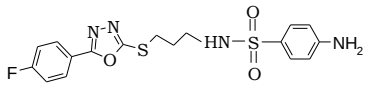

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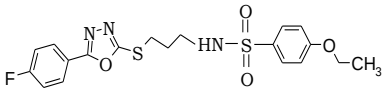
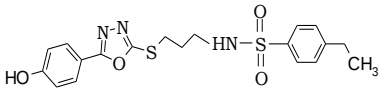
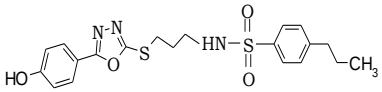


30. N-(3-{[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethylbenzenesulfonamide



31. N-(3-{[5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-propylbenzenesulfonamide



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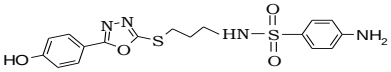

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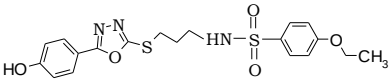

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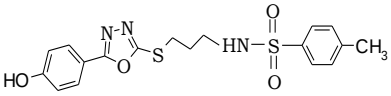
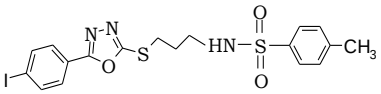


35. N-(3-{[5-(4-iodophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



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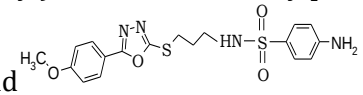

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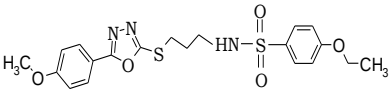
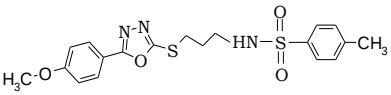
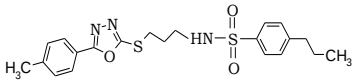


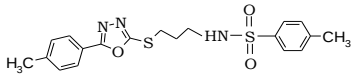
38. N-(3-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



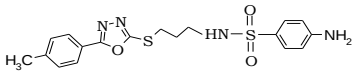
39. N-(3-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-propylbenzenesulfonamide



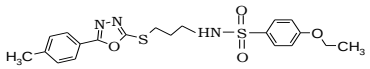
40. N-(3-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



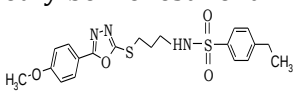
41. N-(3-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-aminobenzenesulfonamide



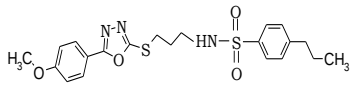
42. N-(3-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methoxybenzenesulfonamide



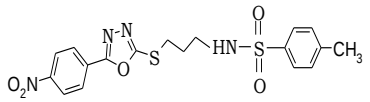
43. N-(3-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-ethylbenzenesulfonamide



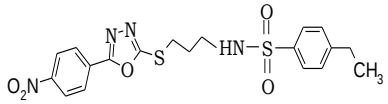
44. N-(3-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-propylylbenzenesulfonamide



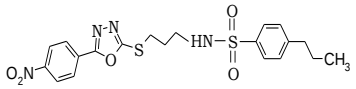
45. 4-methyl-N-(3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)benzenesulfonamide



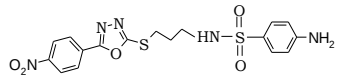
46. 4-ethyl-N-(3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)benzenesulfonamide



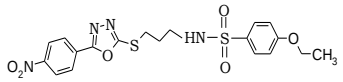
47. 4-propyl-N-(3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)benzenesulfonamide



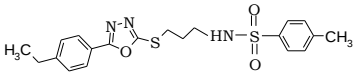
48. 4-aminol-N-(3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)benzenesulfonamide



49. 4-methoxy-N-(3-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)benzenesulfonamide



50. N-(3-{[5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl]thio}propyl)-4-methylbenzenesulfonamide



Binding-site analysis:

The Bindig-site of 18kDa antigen was identified using CASTP server (Carpena, et al, 2003). A new program, CAST, for automatically locating and measuring protein binding pockets and cavities, is based on precise computational geometry methods, including alpha shape and discrete flow theory.

Docking of derivatives:

By means of the 3D structures of 2-mercaptoethanol and 3-amino-5-methylhexanoic acid inhibitors, which were built through the Chemsketch program, the automated molecular docking was performed by using FRED (OpenEye Scientific Software, Santa Fe, NM). The relevant stereo isomers of the compounds were minimized with the MMFF force field in the Openeye package. Conformation and minimization of the compounds was performed using Omega (OpenEye Scientific Software, Santa Fe, NM). FRED requires a set of input conformers for each ligand. The conformers were generated by Omega and stored in a single binary file and the output file was used for docking. Docking calculations were performed with FRED version 1.1 for efficient handling of large compound databases.

RESULTS AND DISCUSSIONS

Active site Identification of 1G5M receptor prediction by CASTp:

After selecting receptor from PDB and isolated the A-chain in SPDBV, the possible binding sites of 1G5M receptor was searched based on the structural comparison of template and the model build and also with CASTp server and was shown in Figure ,the residues are TYR18, TYR21, LYS22, GLN25, ARG26, ARG98, GLY101, ASP102, PHE104, SER105, ARG106, TYR108, ARG109, ASP111, PHE112, ALA113, MET115, SER116, GLN118, LEU119, ARG129, THR132, VAL133, GLU136, LEU137, ARG146, VAL148, ALA149, GLU152, PHE153, GLY155, VAL156, MET157, VAL159, GLU160 (Fig.1).

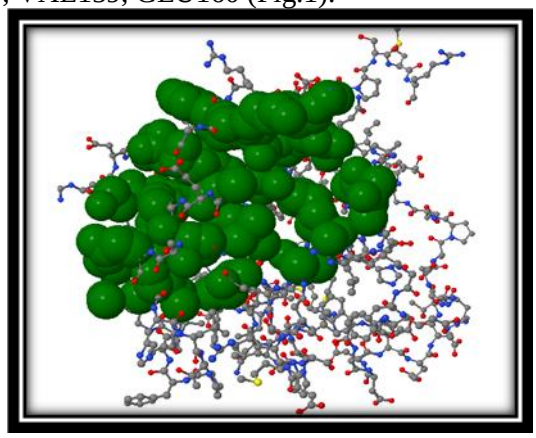


Fig 1. Showing active site Pockets of the 1G5M receptors shows highest area and volume

Homology modeling:

A high level of sequence identity should guarantee more accurate alignment between the target sequence and template structure. In the results of BLAST search only two reference proteins, 1G5M and 1GJH. In order to define SCRs of the protein family, multiple sequence alignment based on the structural conservative was used to superimpose the reference structure, and the SCRs were determined.

Docking results of ligands with 1g5m receptor:

4-methyl-N-(3-{[5-(4-substituted)-1,3,4-oxadiazol-2-yl]sulfanyl}propyl)benzene sulfonamide Derivative-1 docked with 1G5M receptor.

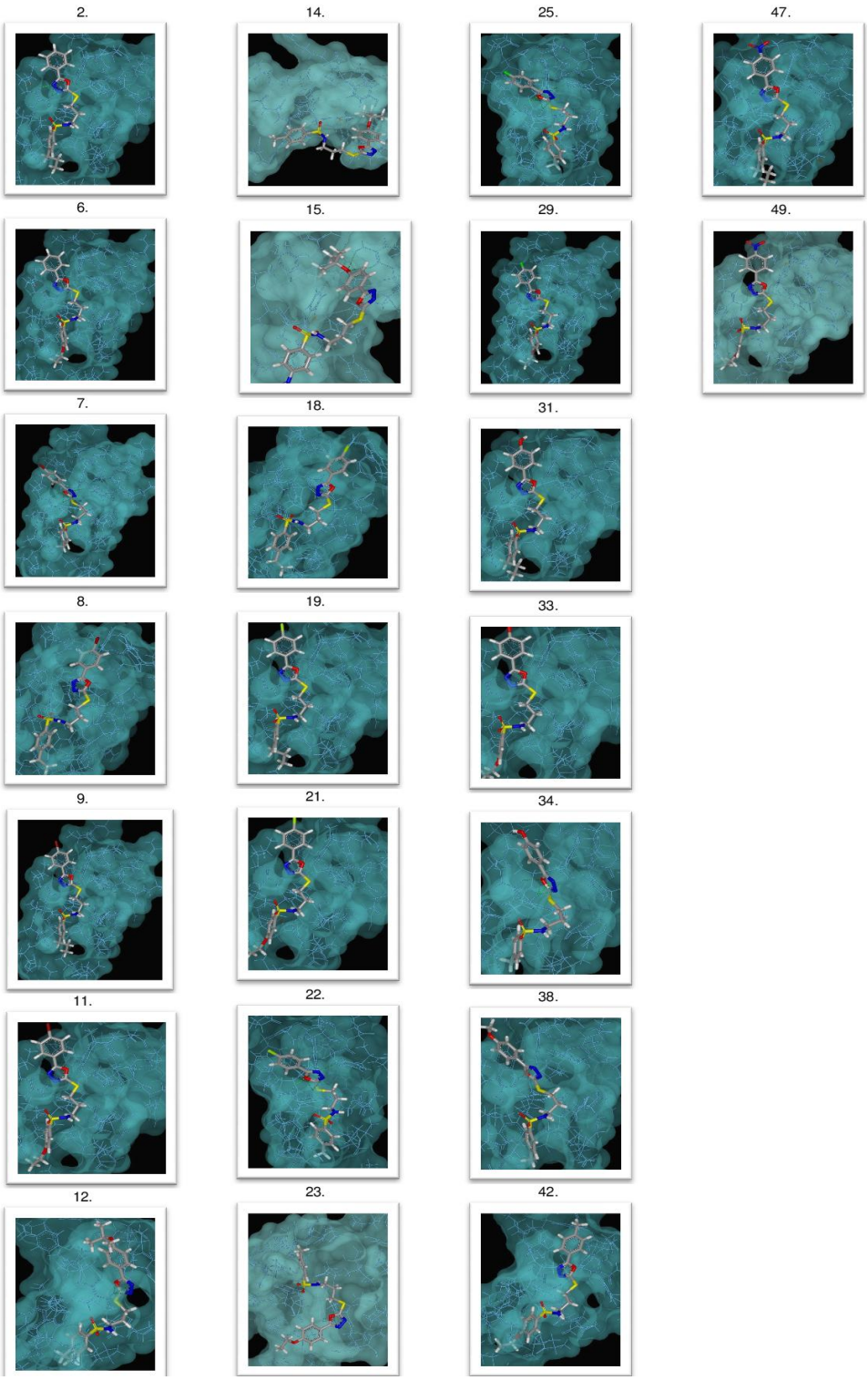


Fig. 2. Docking results of of ligands with 1g5m receptor

Table 2. The total energies of Chem scores, Docking scores

S. No	Derivatives of Primaquine	Chem scores	Chemgauss2 scores	Plp scores	Screen scores	Shapeguass Scores	Total Scores
1	Derivative-2	0.86	-51.47	-33.20	-73.25	-376.31	-157.06
2	Derivative-6	4.12	-49.99	-28.96	-79.33	-395.59	-154.16
3	Derivative-7	-12.42	-50.39	-42.20	-95.45	-383.54	-200.46
4	Derivative-8	-0.92	-53.79	-12.32	-61.16	-405.89	-128.19
5	Derivative-9	1.17	-51.51	-31.35	-76.79	-387.49	-158.48
6	Derivative-11	3.44	-51.07	-32.35	-80.99	-390.00	-160.97
7	Derivative-12	-0.86	-60.45	-32.09	-64.39	-435.50	-157.79
8	Derivative-14	2.55	-45.55	-15.63	-56.70	-380.78	-115.33
9	Derivative-15	2.29	-43.69	-24.54	-66.09	-392.23	-132.03
10	Derivative-18	0.38	-48.92	-21.45	-84.08	-398.94	-154.07
11	Derivative-19	3.47	-57.09	-29.39	-62.92	-402.50	-145.93
12	Derivative-21	4.17	-52.19	-31.62	-75.98	-392.62	-155.62
13	**Derivative-22**	-11.89	-50.67	-44.97	-94.06	-396.05	-201.59
14	Derivative-23	2.29	-45.17	-23.41	-76.69	-392.73	-142.98
15	Derivative-25	-8.67	-49.16	-43.49	-99.35	-373.32	-199.67
16	Derivative-29	4.10	-50.46	-30.24	-76.26	-399.62	-152.86
17	Derivative-31	3.92	-53.46	-32.18	-73.65	-394.58	-155.37
18	Derivative-33	4.70	-53.24	-32.35	-74.64	-398.73	-155.53
19	Derivative-34	-0.34	-54.14	-37.53	-71.88	-378.30	-163.89
20	Derivative-38	-3.86	-53.39	-28.30	-77.57	-386.75	-163.12
21	Derivative-42	4.12	-52.58	-23.42	-72.76	-403.66	-144.64
22	Derivative-47	5.88	-55.59	-32.92	-77.71	-425.75	-160.34
23	Derivative-49	3.92	-54.12	-29.54	-76.50	-410.41	-156.24

Chemguass scores, Plp scores and shapeguass scores of the best-docked conformations of 1G5M receptor. Finally, (4-methyl-N-(3-{[5-(4-substituted)-1,3,4-oxadiazol-2-yl]sulfanyl} propyl) benzene sulfonamide) was found, based on docking studies to the best of our knowledge (Table 2, Fig. 3).

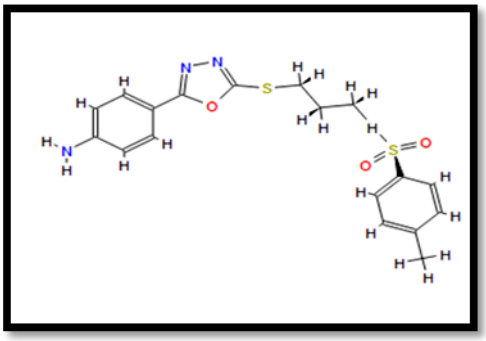


Fig.3. Chemical structure of 4-methyl-N-(3-{[5-(4-substituted)-1,3,4-oxadiazol-2-yl]sulfanyl

CONCLUSION

Oxadiazole derivatives have many pharmacological uses i:e compounds possessing oxadiazole moiety acts as an analgesic, hypoglycemic, bactericidal and local anesthetic. Certain 1,3,4-oxadiazole derivatives were reported to possess anti-inflammatory, antitubercular, antifungal, and anticancer activities.

In the present research a series of 50 oxadiazole derivatives were designed and evaluated docking studies were performed using Open eye software against cancer proteins of Breast cancer [BCL2 (1G5M)].

The designed series of 2,5 disubstitued 1,3,4,oxadiazole were docked to the bcl3 and ATAD2 protein with open eye software. Docking results shows that out of 50 ligands, randomly 23 ligands were docked to the Bcl2 protein and 23 ligands were docked to the ATAD2 protein. By this we can say that the above docked ligands may show the anti cancer activity.

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