Journal of Applied Pharmaceutical Science Vol. 3 (10), pp. 023-029, October, 2013
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2013.31005
ISSN 2231-3354

In silico Analysis of 3D-QSAR and Molecular Docking for Bcl-2 Inhibitors to Potential Anticancer Drug Development

Ramachandran M[1*], Balwin Nambikkairaj[1], Kumaran K[2], Arun Kumar De[3] and G.Ramesh Kumar[4]
[1]P.G. And Research Department of Zoology, Voorhees College, Vellore-632001 (T.N), India. [2]P.G. And Research Department of Chemistry, Islamia College, vaniambadi-635752 (T.N), India. [3]Department of Animal Sciences, University of Illinois, Urbana, IL 61801, USA. [4] Bioinformatics Division, AU-KBC, M.I.T. Campus, Anna University, Chennai-600044.

ARTICLE INFO

Article history:
Received on: 10/09/2013
Revised on: 22/09/2013
Accepted on: 08/10/2013
Available online: 31/10/2013

Key words:
3D-QSAR, Pharmacophore, Docking, ligands, Bcl-2, Anti-apoptosis.

ABSTRACT

Apoptosis control is characterized by a delicate balance between homo and hetero dimerization of pro- and anti-apoptosis members of the protein family. Inhibiting this protein protein interaction is one viable approach to cancer therapy. Anti-apoptosis the prosurvival family members Bcl-2, Mcl-1, and Bcl-XL are current targets for anti-cancer drug design. The chemotherapy has aroused many researchers' interests and a great deal of current efforts has been focusing on the design and development of various anticancer drugs. Ligand-based drug designing methods approaches through pharmacophore mapping and Three Dimention- Quantitative Structure Activity Relationship (3D-QSAR) are used in drug discovery as well as molecular docking to seek potential binding sites of the Bcl-2 protein and its inhibitors interactions. Dynamically predictive 3D-QSAR model with Pearson-r value (0.74), F (62.5), Standard Deviation (0.285) of the regression and Root Mean Square Deviation RMSE (0.321), Q^2(0.514) that was obtained for binding affinity of Bcl-2 protein respectively. The bioinformatics techniques were proved that the development of good potential activity drug compound to cancer. To our knowledge the results describes anti-tumour activity of HEQ-1 drug compound promising to convey anti-tumour drug development.

INTRODUCTION

Cancer is the leading disease-related cause of death of the human population in some areas of the world, and it is predicted to continue to become the leading cause of death within the coming years (Gibbs, 2000). Chemotherapy, or the use of chemical agents to destroy cancer cells, is a mainstay in the treatment of malignancies. A major advantage of chemotherapy is its ability to treat widespread or metastatic cancers, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas. The chemotherapy has aroused many researchers' interests and a great deal of current efforts has been focusing on the design and development of varied anticancer drugs (Hayakawa et al., 2004; Hayakawa et al.,2005). The B-cell lymphoma-2 (Bcl-2) protein family plays an important role in the regulation of apoptosis in mammalian cells. Apoptosis control is characterized by a delicate balance between homo- & hetero-dimerization of pro- and anti-apoptosis members of the protein family. Inhibiting this protein–protein interaction is one viable approach to cancer therapy. Anti-apoptosis (prosurvival) family members Bcl-2, Mcl-1, and Bcl-XL are current targets for anti-cancer drug design. Disruption of the normal apoptotic process is implicated in a variety of human diseases. Interactions between 3 subgroups of the Bcl-2 protein family govern apoptosis. Bcl-2 and close relatives Bcl-xL, Bcl-w, Mcl-1, and A1 promote cell survival, whereas the essential cell death mediators Bax and Bak provoke the mitochondrial damage that leads to cell death. Their shared structural similarities include 3 Bcl-2 homology (BH) regions. Members of the proapoptotic ''BH3-only'' subgroup, such as Bid, Bim, or Bad, share only the BH3 domain, an amphipathic -helix essential for their interaction with prosurvival relatives and initiation of apoptosis (Adams, 2007; Youle, 2008). The anti-apoptotic function of Bcl-2 occurs via its heterodimerization with Bax, Bak, Bad and other pro-apoptosis Bcl-2 family members (Reed, 2005; Burger et al.,1997; Houldsworth et al, 1998; Campos *et al.*, 1996; Holinger *et al.*, 1999), hence blocking this heterodimerization represents a new avenue for anti-cancer drug

* *Corresponding Author*
M.Ramachandran, P.G. and Research Department of Zoology, Voorhees College, Vellore-632001 (T.N), India. Mobile: (0)8015015360

development (Holinger *et al.*, 1999). Bcl-2 antisense therapy has been shown to decrease cell survival in normal bone marrow progenitors and leukemia cells. BH3 peptides from Bax, Bak, and Bad have been shown to trigger apoptosis in cancer cells, which have high levels of Bcl-2 expression by inhibiting the heterodimerization of Bcl-2 with pro-apoptotic Bcl-2 family members (Holinger *et al.*, 1999; Finnegan *et al.*, 2001; Shangary, 2002).

It is possible to mimic the effects of these peptides with non-peptide small molecule inhibitors with structure-based design, aided with computer modeling. Several recent independent reports have confirmed the feasibility of designing non-peptide small molecule inhibitors that bind to the B-Cell Homology -3(BH3) binding site of Bcl-2, thereby blocking its anti-apoptotic function, thus inducing apoptosis in cancer cells, which have high levels of Bcl-2 expression (Wang *et al.*, 2000; Degterev *et al.*, 2001; Tzung *et al.*, 2001; Enyedy *et al.*, 2001; Oltersdorf *et al.*, 2005; Manion *et al.*, 2006). Ligand-based drug designing approaches like pharmacophore mapping and Three Dimention- Quantitative Structure Activity Relationship (3D-QSAR) are used in drug discovery. Database search studies for new hits and to identify important structural features for functional activity will help in identifying therapeutically stable drug without any side effects (Prashant *et al.*, 2010).

In a rational drug design approach, identification of the pharmacophore is the most important step in achieving the stipulated goal. Pharmacophore Alignment and Scoring Engine (PHASE) software was used to develop ligand-based pharmacophore model for Bcl-2 ligand. PHASE uses conformational sampling and different scoring techniques to identify common pharmacophore hypothesis, each hypothesis is accompanied by a set of aligned conformations which are necessary for the ligand to bind to the receptor (Steven *et al.*, 2006; Dixon *et al.*, 2006).

The developed model has the ability to find potential Bcl-2 inhibitor from 3D-virtual databases of drug like molecules. The conformations of active compounds obtained from the alignment of pharmacophoric points are used to derive 3D-QSAR models. Further, the binding mode of the active molecule with the active site amino acid residues was performed by XP docking using Glide. This research investigated and report herein ligand-based pharmacophore models for Bcl-2 protein.

MATERIALS AND METHODS

Dataset for analysis

The dataset contain 40 quinazoline based derivative drugs were retrieved from various literature sources with structure elucidated from marine sponge quinazolin derivative drug HEQ-1 was added in the dataset (Table-1).

All ligand chemical structures were designed and converted from 2D structure to 3D structure using Chem Draw software (Figure1-2).The dataset has been chosen by which covers the information about its biological activity. The in vitro biological activity data was reported as IC_{50}. The IC_{50} values were converted to pIC_{50}. The dataset consists of some highly active and inactive molecules, with very few molecules in between. 21 molecules were randomly chosen for training set and 19 molecules were selected for test sets according QSAR calculations.

Table. 1: 3D-QSAR predicted activity and training set and test set data of ligand molecules .

S.No	Ligand name	QSAR set	pIC_{50}	Predicted Activity	PLS factors
1	Ligand1	training	5.283	4.894	3
2	Ligand2	training	5.251	4.936	3
3	Ligand3	test	5.274	4.861	3
4	Ligand4	test	5.339	4.892	3
5	Ligand5	test	5.314	5.036	3
6	Ligand6	training	5.385	4.961	3
7	Ligand7	training	5.248	4.705	3
8	Ligand8	training	5.199	4.854	3
9	Ligand9	test	5.391	4.950	3
10	Ligand10	test	5.213	4.886	3
11	**Ligand11 (HEQ-1)**	training	6.206	5.843	3
12	Ligand12	test	5.236	5.047	3
13	Ligand13	test	5.245	4.826	3
14	Ligand14	training	5.209	4.852	3
15	Ligand15	training	5.263	5.153	3
16	Ligand16	training	5.255	4.822	3
17	Ligand17	test	5.211	4.855	3
18	Ligand18	training	5.201	4.826	3
19	Ligand19	test	5.195	4.762	3
20	Ligand20	training	5.197	4.882	3
21	Ligand21	training	5.259	4.822	3
22	Ligand22	training	5.288	4.802	3
23	Ligand23	training	5.247	4.904	3
24	Ligand24	test	5.258	5.016	3
25	Ligand25	test	5.218	4.752	3
26	Ligand26	test	5.305	4.177	3
27	Ligand27	training	5.268	4.099	3
28	Ligand28	training	5.321	4.016	3
29	Ligand29	training	5.472	5.051	3
30	Ligand30	test	5.422	4.515	3
31	Ligand31	test	4.899	4.170	3
32	Ligand32	training	5.485	5.042	3
33	Ligand33	test	5.424	4.135	3
34	Ligand34	test	4.793	4.639	3
35	Ligand35	training	5.252	4.138	3
36	Ligand36	training	5.268	4.111	3
37	Ligand37	training	4.951	3.999	3
38	Ligand38	test	5.488	4.033	3
39	Ligand39	training	5.437	4.323	3
40	Ligand40	test	5.283	4.894	3

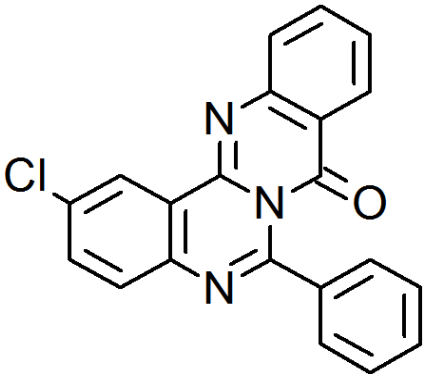

Fig. 1: The chemical structure of HEQ-1 ligand.

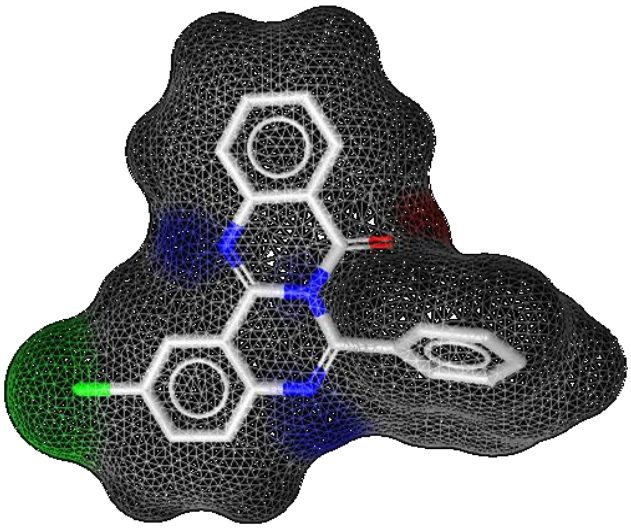

Fig. 2: 3D structure of HEQ-1 ligand molecule

Ligands preparations

Preparation of ligand was performed by using LigPrep2.4 programme. The 3D conversion and minimization was performed using LigPrep Molecular M model Force Field (MMF) incorporated in PHASE (Dixion *et al.,* 2006). Developing a pharmacophore model requires all atom 3D structures that are realistic representations of the experimental molecular structure. Most ligands are flexible, so it is important to consider a range of thermally accessible conformational states in order to increase the chances of finding something close to the putative binding mode. Purpose of pharmacophore model development, PHASE provides two built-in approaches, both of which employ the MacroModel conformational search engine. Conformers were generated using a rapid torsion angle search approach followed by minimization of each generated structure using MMFF force field, with implicit distance dependent dielectric solvent model. The ionization states in a given pH range of 7 were generated by adding or eliminate protons from the ligand using EPIK 2.1 module. A maximum of 100 conformers were generated per structure using a preprocess minimization of 100 steps and post process minimization of 50steps. Each minimized conformer was filtered through a relative energy window of 11.4 kCal/mol (50kJ/ mol) and a minimum atom deviation of 2.00 Å. Molecular properties like molecular weight, Hydrophobic component, Hydrophilic components, Total solvent accessible volume, number of hydrogen bond acceptor, Hydrogen bond donors of all ligands were studied by using QuikProp3.3 module of schrodinger package 2010.

Protein Preparation

The Bcl-2 Protein (PDB ID:1G5M) was prepared using protein preparation wizard of the Schrodinger package. Hydrogen atoms were added to Bcl-2 protein, including the protons necessary to define the correct ionization and tautomeric states of amino acids residues such as Asp, Ser, Glu, Arg, and His. The missing side chains of residues were corrected using build interface incorporated in this programme. Protein structural minimization was carried out with the impact refinement module using the OPLS-2005 force field to steric clashes that may exist in the structures. After protein preparation, receptor grid was set up which was generated by employing the receptor grid generation panel. The protein was associated with ligand, the ligand was selected to define the position and size of the active site.

Creation of pharmacophore sites

Developing pharmacophore model is to use a set of pharmacophore features to create sites for all the ligands. Each ligand structure is represented by a set of points in 3-D space, which coincide with various chemical features that may facilitate non covalent binding between the ligand and its target receptor. The pharmacophore creations was carried out for all ligands by six features, hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), negatively ionizable (N), positively ionizable (P), and aromatic ring (R). Active analogue approach was used to identify commom pharmacophore hypotheses. Common pharmacophores were identified using a treebased partitioning technique that groups together similar pharmacophores according to their intersite distances, i.e., the distances between pairs of sites in the pharmacophore.

Finding a common pharmacophore

Common pharmacophoric sites were selected from a set of variants and with the option create sites, number of acceptors were modified to 2, negatively ionizable to 0, others were kept default. This gave 6 different variant lists AAHHR, AAHRR, AARRR, AHHRR, AHRRR and HHRRR. Hypothesis generation was done by find option Pharmacophore model, which generated three maximum hypotheses with AAHRR, AARRR, AHRRR. For these hypothesis scores were calculated for both actives and inactives by score hypothesis using an overall maximum root mean square deviation (RMSD) value of 1.2 Å. The quality of alignment was measured by survival score.

Building 3D-QSAR model

3D-QSAR modeling was generated using the selected hypothesis by dividing the data set in to training set and test set data in a random manner. PHASE gives two options for alignment of 3D structure of molecules the pharmacophore based alignment and the atom-based alignment (Dixion *et al.,* 2006; Teli, 2001). In this study, atom based 3D-QSAR model, which is more useful in explaining the structure-activity relationship. In atom based 3D-QSAR, a molecule is treated as a set of overlapping van der walls spheres. Each atom is placed into one of six categories according to a simple set of rules: The hydrogens attached to polar atoms are classified D-hydrogen-bond donor, H- hydrophobic or nonpolar, N-negative ionic ,P-positive ionic ,W-electron-withdrawing includes hydrogen-bond acceptors, X-miscellaneous. For the purpose of 3D-QSAR development, van der wall's models of the aligned training set molecules were placed in a regular grid of cubes, with each cube allotted zero or more bits to account for different types of atoms in the training set that occupy the cube.

This representation gives rise to binary valued occupation patterns that can be used as independent variable to create Partial Least Square (PLS) QSAR models. Atom based 3D-QSAR models were generated for the selected hypothesis using the 21 members training set using a grid spacing of 1.0 A^o. The best 3D-QSAR models were validated by predicting activities of the 19 test set compounds.

Three components PLS factor model with good statistics was obtained for the data set whereas the maximum number of PLS factor in each model can be 1/3 of the total number of training set molecules. Moreover the increase in the number of PLS factors did not improve the model predictive ability.

Molecular docking simulations

The HEQ-1 drug and Bcl-2 protein docking studies were performed by using GLIDE (Grid –based Ligand Docking with Energetics) module in Extra precision (XP) mode of Schrodinger suite 2010. Glide docking algorithm consist of two main steps like receptor grid generation and ligand docking.

Three dimentional grid is generated by selecting a particular protein residue. Grid is constituted by receptor shape and properties by sets of fields that provide relatively better accurate scoring of the ligand poses. Extra Precision (XP) docking, a different potential segregating procedure is employed to analyse the protein ligand interations.

The scoring is identified for the energy minimized poses and the poses pass the initial screens enter the final stage of the algorithm, which involves evaluation and minimization of grid approximation to OPLS- AA nonbonded ligand protein interaction energy. The docking score from Glide Score is entirely based on ChemScore. Moreover, it includes a steric clash, term adds polar terms featured by Maestro 9.1 to correct electrostatic mismatches and modifications to other terms : GScore=0.065 * Van der waals energy + 0.130 * colomb energy + Hydrophobic interactions + H-bond + Metal binding + BuryP (Penalty for buried polargroups)+Rot(Penalty for freezing rotatable bonds) + Site(Polar interactions in the active site). Post docking calculations estimation of binding energies of the ligands protein was examines by the automated mechanism of multi ligand biomolecular associations with energetic using MacroModel module of Schrodinger package. The calculations were performed first on the protein and the ligand finally on the complex.

RESULTS AND DISCUSSION

3D-QSAR modeling was generated and select hypothesis by dividing the data set in to training set (21) and test set (19) in a random manner. Pharmacophore determinations were analyzed the arrangement of features along with their distance present in five-featured pharmacophore AAHRR hypothesis shows one hydrophobic feature, three hydrogen bond acceptors features and four ring aromatic features respectively (Figure 3). The result of pharmacophores were scored and ranked. The scoring was done to identifying the best ligand hypothesis, which provided an overall ranking of all the hypothesis. Scoring with respect to actives was conducted using default parameters for site, vector, and volume terms. Ligand activity, expressed as -log10(IC50), was incorporated into the score with a weight of 1.0, and relative conformational energy (kJ/mol) was included with a weight of 0.01. Hypotheses that emerged from this process were subsequently scored with respect to inactives, using a weight of 1.0. The inactive molecules were scored to observe the alignment of these molecules with respect to the pharmacophore hypothesis to enable making a decision on the selection of the hypothesis. Larger is the difference between the scores of active and inactives, better is the hypothesis at distinguishing the actives from inactives. 3D chemical structure alignments were done using PHASE module (Figure 4), which shows two options for alignment for 3D structure pharmacophore based alignment and the atom-based alignment. The statistical predictions was illustrated taht large value of F (62.5) indicates a statistically significant regression model, which is also supported by the small value of the variance ratio (P), an indication of a high degree of confidence. Further, small values of SD-Standard Deviation (0.285) of the regression and Root Mean Square Deviation (RMSE = 0.3211) makes an obvious implication that the data used for model generation are best for the QSAR analysis. Validity of the model can be expressed by cross-validated correlation coefficient (Q^2 = 0.5147) that was obtained for binding affinity of Bcl-2 protein respectively (Table 2).

The q2 is more reliable and robust statistical parameter than r^2 because it is obtained by external validation method by dividing the dataset into training and test set. The atoms of visualize 3D characteristics of the ligands that contribute positively or negatively to activity. The QSAR model displays 3D characteristics as cubes that represent the model and color according to the sign of their coefficient values, which by default “blue color” for positive coefficients and “red color” for negative coefficients (Figure 5). Positive coefficients indicate an increase in activity, negative coefficients a decrease. The visualization of the coefficients is useful to identify characteristics of ligand structures that tend to increase or to decrease the activity. This might give a clue to what functional groups are desirable or undesirable at certain positions in a molecule. The blue cubes of pharmacophore regions refer to ligand regions in which the specific feature is important for better activity, whereas the red cubes demonstrates that particular structural feature or functional group, which is not essential for the activity or likely the reason for decreased binding potency. Predicted activity and phase activity results were illustrated scatter plot of the selected ligand molecules activity (Figure 6). Glide docking was performed with the selected and best active compound HEQ-1 and Bcl-2 protein using Glide programme of Xtra Precision(XP) algorithm based on the lowest energy values of the best docking orientation was selected. The docking results show interaction between compound -11 (HEQ-1) and Bcl-2 protein in the active site region with ARG (98) residues (Figure 7) with docking G-Score of -6.12 kcal/mol.

Table. 2: Statistical properties of 3D-QSAR model.

ID	PLS factors	SD	R^2	F	P	RMSE	Q^2	Pearson-R
AAHRR	1	0.4122	0.566	30.1	5.744e-005	0.4188	0.3971	0.5246
	2	0.3223	0.6321	35.4	4.547e-006	0.4451	0.4651	0.6522
	3	0.2854	0.8423	62.5	7.311e-006	0.3211	0.5147	0.7458

Note: SD = Standard Deviation of the Regression, R^2= correlation coefficient, Q^2 = for the predicted activities, **RMSE** = Root-Mean-Square Error, **PEARSON-R** = correlation between the predicted and observed activity for the test set.

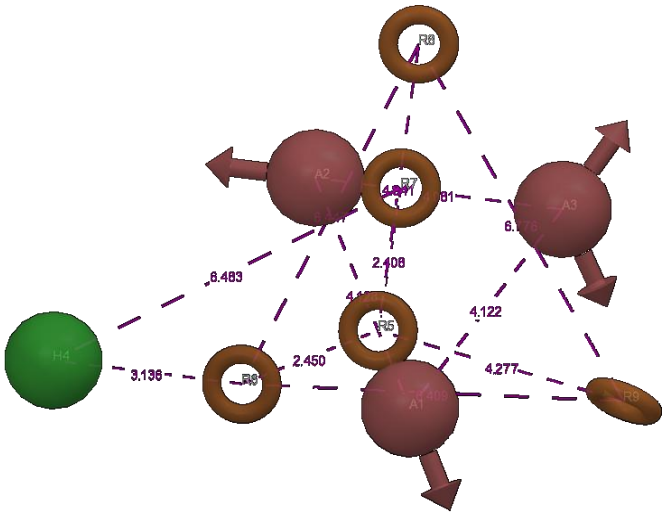

Fig. 3: Common pharmacophoric sites of active ligand with distance. All distance are in A° unit.

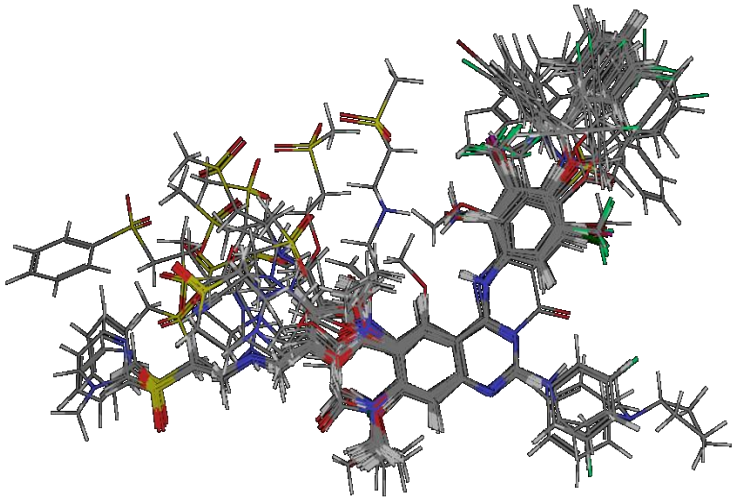

Fig. 4: Structural alignment of Bcl-2 inhibitors of 3D-QSAR models.

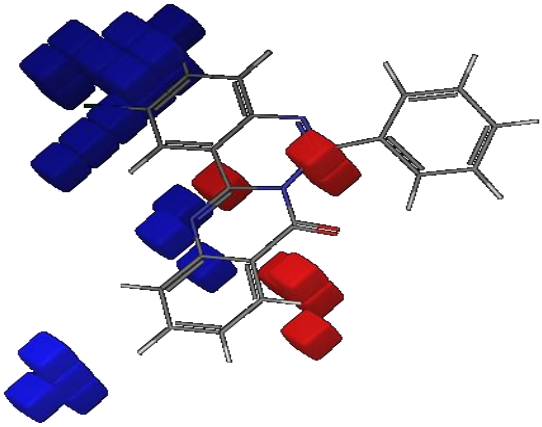

Fig. 5: Atom based 3D-QSAR model visualized context of most active compound. Blue cubes indicate favorable regions while red cubes indicate unfavorable region for the activity.

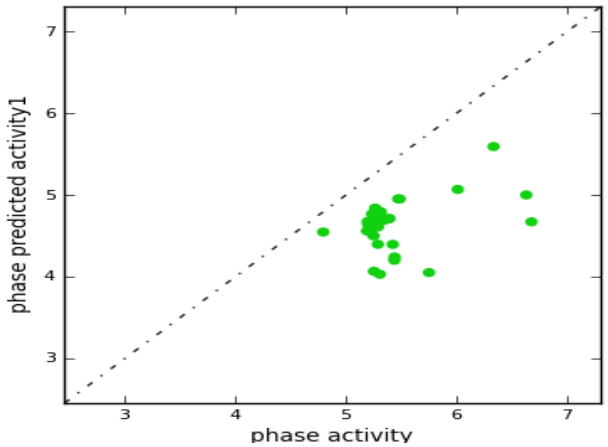

Fig. 6: Scatter plot for observed activity vs. phase-predicted activity of training and test set ligands.

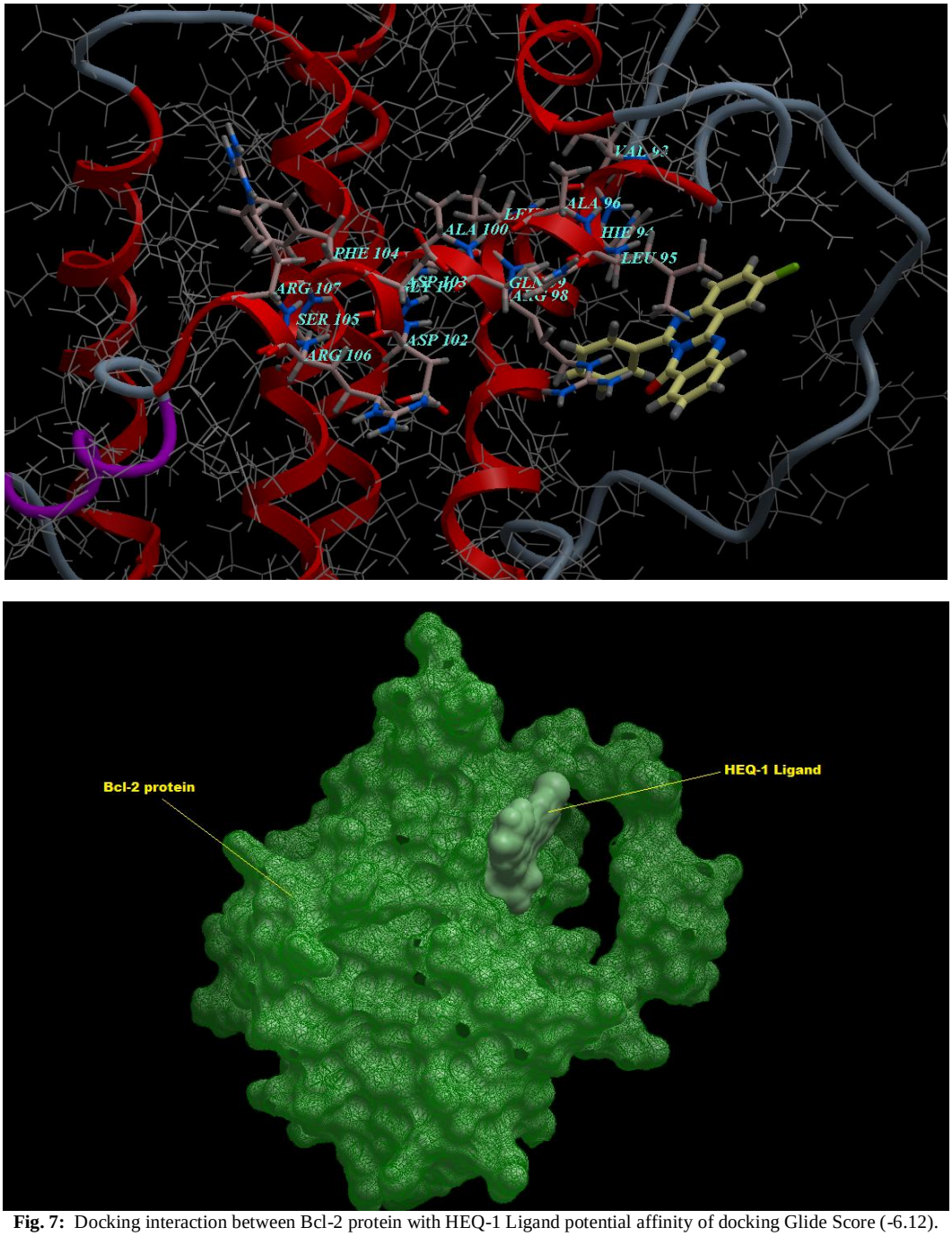

Fig. 7: Docking interaction between Bcl-2 protein with HEQ-1 Ligand potential affinity of docking Glide Score (-6.12).

CONCLUSION

Developing a pharmacophore model will help in identifying therapeutically potential compounds without any side effects. Best hypothesis obtained was AAHRRR with three hydrogen bond acceptor and four aromatic rings. Ligand11 (HEQ-1) had the best result for which a highly predictive atom based 3D-QSAR model was generated. Atom based 3D-QSAR and docking simulation understanding the relationship between drug molecule structure activity and prediction of potential affinity of protein ligand interaction, which contribute multiple path to development and design novel and potent inhibitor for Bcl-2 protein. This study can be further use for the synthesis of newer and may be more potent quinazoline derivatives against cancer.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Mr.Rahul Subra Mandal, Biomedical Informatics Centre, National Institute of Cholera and Enteric Diseases, Kolkata, India for providing access to the Schrodinger software.

REFERENCES

Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene.*2007; 26:1324-1337.

Burger H, Nooter K, Boersma AW, Kortland CJ, Stoter G. Lack of correlation between cisplatin-induced apoptosis, p53 status and expression of Bcl-2 family proteins in testicular germ cell tumour cell lines. Int J Cancer . 1997; 73:592-599.

Campos L, Sabido O, Liang H, Vasselon C, Guyotat D. Expression of human Bcl-xL, an inhibitor of programmed cell death. Nature. 1996; 33:335-341.

Degterev A, Lugovskoy A, Cardone M, Mulley B, Wagner G, Mitchison T, Yuan J. Identification of small-molecule inhibitors of interaction between the BH3 domain and Bcl-xL. Nat Cell Biol. 2001; 3:173-182.

Dixion SL, Smondyrev AM, Knoll EH, Rao SN, Shaw DE, Friesner RA. PHASE: a new engine for pharmacophore perception, 3D QSAR model development and 3D database screening:1.Methodology and preliminary results. J Computer Aided Mol Des. 2006; 20:647- 671.

Dixion SL, Smondyrev AM, Rao SN. PHASE: A novel approach to pharmacophore modeling and 3D database searching. Cem Biol Drug Des. 2006; 67: 370-372.

Dixon SL, Smondyrev AM, Knoll EH, Rao SN, Shaw DE, Friesner RA. PHASE: a new engine for pharmacophore perception, 3D QSAR model development, and 3D database screening: 1. Methodology and preliminary results. J Comput Aided Mol Des. 2006; 20:647-671.

Enyedy IJ, Ling Y, Nacro K, Tomita Y, Wu X, Cao Y, Guo R, Li B, Zhu X, Huang Y, Long YQ, Roller PP, Yang D, Wang S. Discovery of small-molecule inhibitors of Bcl-2 through structurebased computer screening. J Med Chem. 2001; 44:4313-4324.

Finnegan NM, Curtin JF, Prevost G, Morgan B, Cotter TG. Induction of apoptosis in prostate carcinoma cells by BH3 peptides which inhibit Bak/Bcl-2 interactions. Br J Cancer .2001;85: 115-121.

Gibbs J B. Mechanism-based target identification and drug discovery in cancer research. Science. 2000; 287: 1969-1973.

Hayakawa I, Shioya R, Agatsuma T, Furukawa H, Naruto S, Sugano Y. 4-Hydroxy-3-methyl-6-phenylbenzofuran-2-carboxylic acid ethyl ester derivatives as potent anti-tumor agents. Bioorg Med Chem Lett. 2004; 14: 455-458.

Hayakawa I, Shioya R, Agatsuma T, Furukawa H, Sugano Y. Thienopyridine and benzofuran derivatives as potent anti-tumor agents possessing different structure-activity relationships. Bioorg Med Chem Lett. 2004; 14: 3411-3414.

Hayakawa I, Shioya R, Agatsuma T, Sugano Y. Synthesis and evaluation of 3-methyl-4-oxo-6-phenyl-4, 5, 6, 7-tetrahydrobenzofuran- 2-carboxylic acid ethyl ester derivatives as potent antitumor agents. Chem Pharm Bull. 2005; 53(6): 638-640.

Holinger EP, Chittenden T, Lutz RJ. Bak BH3 peptides antagonize Bcl-xL function and induce apoptosis through cytochrome c-independent activation of caspases. J Biol Chem .1999; 274: 13298-13304.

Houldsworth J, Xiao H, Murty VV, Chen W, Ray B, Reuter VE, Bosl GJ, Chaganti RS. Human male germ cell tumor resistance to cisplatin is linked to TP53 gene mutation. Oncogene. 1998; 16:2345-2349.

Manion MK, Fry J, Schwartz PS, Hockenbery DM. Smallmolecule inhibitors of Bcl-2. Curr Opin Investig Drugs. 2006; 7:1077-1084 .

Oltersdorf T, Elmore SW, Shoemaker AR, Armstrong RC, Augeri DJ, Belli BA, Bruncko M, Deckwerth TL, Dinges J, Hajduk PJ, Joseph MK, Kitada S, Korsmeyer SJ, Kunzer AR, Letai A, Li C, Mitten MJ, Nettesheim DG, Ng S, Nimmer PM, O' Connor JM, Oleksijew A, Petros AM, Reed JC, Shen W, Tahir SK, Thompson CB, Tomaselli KJ, Wang B, Wendt MD, Zhang H, Fesik SW, Rosenberg SH. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature. 2005; 435:677-681 .

Prashant Revan Murumkar, Vishal Prakash Zambre and Mange RamYadav. Development of predictive pharmacophore model for in silico screening, and 3D QSAR CoMFA and CoMSIA studies for lead optimization, for designing of potent tumor necrosis factor alpha converting enzyme inhibitors. Comput Aided Mol Des. 2010;24:143-156.

Reed JC, Pellecchia M. Apoptosis-based therapies for hematologic malignancies. Blood. 2005; 106:408-418.

Shangary S, Johnson DE. Peptides derived from BH3 domains of Bcl-2 family members: a comparative analysis of inhibition of Bcl-2, Bcl-x(L) and Bax oligomerization, induction of cytochrome c release, and activation of cell death. Biochemistry. 2002; 41:9485-9495.

Steven L. Dixon, Alexander M. Smondyrev and Shashidhar N. Rao. PHASE: A Novel Approach to Pharmacophore Modeling and 3D Database Searching. Chem Biol Drug Des. 2006; 67: 370-372.

Teli MK,Rajanikant GK. Pharmacophore generation and atom based 3D- QSAR of novel quinoline-3-carbonitrile derivatives as Tpl2 kinase inhibitors.J Enzyme Inhib Med Chem. 2011; 26: 1-13.

Tzung SP, Kim KM, Basanez G, Giedt CD, Simon J, Zimmerberg J, Zhang KY, Hockenbery DM. Antimycin A mimics a celldeath- inducing Bcl-2 homology domain 3. Nat Cell Biol. 2001; 3:183-191.

Wang JL, Liu D, Zhang ZJ, Shan S, Han X, Srinivasula SM, Croce CM, Alnemri ES, Huang Z. Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells. Proc Natl Acad Sci U S A. 2000;97: 7124-7129.

Youle RJ, Strasser A. The Bcl-2 protein family: Opposing activities that mediate cell death. Nat Rev Mol Cell Biol. 2008; 9:47-59.

How to cite this article:

Ramachandran M, Balwin Nambikkairaj, Kumaran K and Arun Kumar De. *In silico* analysis of 3D-QSAR and Molecular Docking for Bcl-2 Inhibitors to Potential Anticancer Drug Development. J App Pharm Sci, 2013; 3 (10): 023-029.