Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 7, Issue, 05, pp.15927-15936, May, 2015

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

BRACA1 GENE LOCALIZATION, STRUCTURAL ANALYSIS OF BREAST CANCER AND ITS PHYSICO CHEMICAL CHARACTERS

[1]Dr. P. Praveena, [1]Ulaganathan, [1]Jennifer Ambrose, M., [1]Jayanthi, [2]Dr Chandrasekar and [2] Dr. D. Sudarsanam

[1]School of Genomics & Bioinformatics Department of Advanced Zoology & Biotechnology, Loyola College, Chennnai-600 034
[2]Medical Science, General Surgery, Department of Bioinformatics, Bharath University, Department of Microbiology, Chennai - 600 073

ARTICLE INFO

Article History:
Received 25th February, 2015
Received in revised form
19th March, 2015
Accepted 20th April, 2015
Published online 31st May, 2015

Key words:

Chemsketch, Molsoft,
Lipinski, ADMET

ABSTRACT

Certain variations of the BRCA1 gene lead to an increased risk for breast cancer. Researchers have identified hundreds of mutations in the BRCA1 gene, many of which are associated with an increased risk of Breast cancer. The 3D structure of protein brca1 is retrieved from PDB. Then the new drug is designed by obtaining similar features from the cyclophosphamide and then that structure is chemically modified using Chemsketch. The various biochemical parameters are checked by Log p, Molsoft, Lipinski, ADMET properties etc. Finally the newly designed drug was allowed to dock with the protein and the energy score was calculated. Finally the tabular column was drawn to compare the Energy score. The lowest free Energy Binding has high Energy score. Thereby From the tabulation, the newly designed structure can also be used in the treatment of Breast cancer. Further modification of ligand molecule can increase the property of active site binding.

INTRODUCTION

Cancer is a multistep process resulting from an accumulation of genetic mutations leading to dysfunction of critical genes, including tumour suppressor genes. Epigenetic changes are now also recognised as an important alternative mechanism of gene inactivation. In particular, aberrant methylation of the promoter region of a gene can lead to silencing ultimately contributing to the initiation or malignant progression of tumours. BRCA1, a breast and ovarian cancer susceptibility gene, is a tumour suppressor gene involved in the maintenance of genome integrity. Recent evidence for BRCA1 hypermethylation corroborates the view that this epigenetic alteration may play a determinant role in tumour suppressor silencing and possibly tumorigenesis. Here, we offer a summary of the data providing evidence for BRCA1 hypermethylation in tumours, and an investigation into the associated mechanism leading to BRCA1 silencing. We also discuss the impact of BRCA1 hypermethylation, as a form of epigenetic change, versus BRCA1 genetic mutations in tumour development. (Aurélie Catteau *et al.*) Breast cancer is one of the most frequent malignancies affecting women. The human breast cancer gene 1 BRCA1 gene is mutated in a distinct proportion of hereditary breast and ovarian cancers.

Corresponding author: Dr. P. Praveena,
School of Genomics and Bioinformatics Department of Advanced Zoology and Biotechnology, Loyola College, Chennnai-600034.

Tumourigenesis in individuals with germline BRCA1 mutations requires somatic inactivation of the remaining wild-type allelle. Although, this evidence supports a role for BRCA1 as a tumour suppressor, the mechanisms through which its loss leads to tumourigenesis remain to be determined. Neither the expression pattern nor the described functions of human BRCA1 and murine breast cancer gene 1 BRCA1 can explain the specific association of mutations in this gene with the development of breast and ovarian cancer. Investigation of the role of BRCA1 in normal cell differentiation processes might provide the basis to understand the tissue-restricted properties.

MATERIALS AND METHODS

PDB

The Protein Data Bank originally developed at the brookhaven national laboratories, is now managed by the research collaboratory for structural bioinformatics. The collection contain all publically available three-dimensional structure of protein, nucleic acids, carbohydrates, and a variety of other complexes experimentally determined by x-ray crystallographers and NMR spectroscopists. The PDB at the RCSB offers a number of service for retrieving and submitting three- dimensional structure data. The structure record accessioning scheme of the protein data bank is a unique four-character alphanumeric code, called a PDB-ID or PDB code.

The PDB file format is column oriented and These files are often paradox.

Pathway constructed using yEd software

yEd can be used to automatically lay out complex graph structures. Several highly sophisticated layout algorithms have been implemented and shipped with yEd. They can be used either to automatically arrange the items or to support the user when undertaking a manual layout. yEd enables users to create groups of nodes, which can be visualized and nested to virtually any degree. Furthermore, the new layout algorithms fully support this type of visualization. Using this unique feature, complex structures can be visualized and laid out even more clearly than before. Another of yEd's excellent features is its ability to automatically assign label positions. This will enable the user to easily build improved diagrams, with each label clearly readable. Further, yEd has an intuitive user interface that complies with modern design guidelines for applications. yEd can be used to build, modify, and visualize graph structures in an effective and efficient manner. They can be loaded and saved using a variety of different file format.

Q-SiteFinder

Q-SiteFinder is a new method of ligand binding site prediction. It works by binding hydrophobic (CH3) probes to the protein, and finding clusters of probes with the most favourable binding energy. These clusters are placed in rank order of the likelihood of being a binding site according to the sum total binding energies for each cluster.

ACD CHEMSKETCH

ChemSketch is designed to be used on its own for drawing chemical structures, reactions, schematic diagrams or integrated with other ACD applications and as the front end to our software. Able to import Windows Metafile, MDL MOL, CS ChemDraw, or ISIS/Sketch BIN file. Export Bitmap, TIFF, Metafile, MOL, Paintbrush, ISIS/Sketch, GIF, and ChemDraw. Fully loaded with useful pre-drawn structures including lab equipment, DNA/RNA building kit, amino acids etc. Structures can be 2D "cleaned" as well as 3D optimized using ACD's powerful algorithm. Publish a professional quality report from within ChemSketch or drag drop structures/text into MS applications i.e. MS Word.

The ChemBasic language, which is integrated with ACD/ChemSketch chemistry drawing software, is intended to be a tool for

- Manipulating chemical structures, both 2D- and 3D;
- Customizing ACD/Labs software, through direct access to its embedded functionality;
- Developing add-ons to ACD/Labs chemistry software.
- ACD/Tautomers checks and generate the most reasonable tautomeric forms of drawn organic structures.

CORINA

CORINA is a fast and powerful 3D structure generator for small and medium sized, typically drug-like molecules. Its robustness, comprehensiveness, speed and performance makes CORINA a perfect application to convert large chemical datasets or databases.

CORINA matured through a series of versions during the past decades and has become the recognized world-wide gold standard in industry and academia to generate 3D molecular models of high quality. Currently, CORINA is used by Symyx, NCI/NIH and most major pharmaceutical and chemical companies to convert their 2D structures into 3D.

Lipinski's rule of five

Lipinski's Rule of Five is a rule of thumb to evaluate druglikeness, or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans.
Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight under 500 daltons
- An octanol-water partition coefficient log *P* of less than 5

Note that all numbers are multiples of five, which is the origin of the rule's name.

ADME PROPERTIES

ADME is an acronym in pharmacokinetics and pharmacology for absorption, distribution, metabolism, and excretion, and describes the disposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug.

Criteria

Absorption/Administration

For a compound to reach a tissue, it usually must be taken into the bloodstream - often via mucous surfaces like the digestive tract (intestinal absorption) - before being taken up by the target cells. This can be a serious problem at some natural barriers like the blood-brain barrier. Factors such as poor compound solubility, gastric emptying time, intestinal transit time, chemical instability in the stomach, and inability to permeate the intestinal wall can all reduce the extent to which a drug is absorbed after oral administration. Absorption critically determines the compound's bioavailability. Drugs that absorb poorly when taken orally must be administered in some less desirable way, like intravenously or by inhalation (e.g. zanamivir).

Distribution

The compound needs to be carried to its effector site, most often via the bloodstream. From there, the compound may

distribute into tissues and organs, usually to differing extents. After entry into the systemic circulation, either by intrascular injection or by absorption from any of the various extracellular sites the drug is subjected to a number of process called as distribution process that tend to lower its plasma concentration. Distribution is defined as the reversible transfer of a drug between one compartment to another. Some factors affecting distribution include blood flow rates and the drug binding to serum proteins forming a complex.

Metabolism

Compounds begin to break down as soon as they enter the body. The majority of small-molecule drug metabolism is carried out in the liver by redox enzymes, termed cytochrome P450 enzymes. As metabolism occurs, the initial (parent) compound is converted to new compounds called metabolites. When metabolites are pharmacologically inert, metabolism deactivates the administered dose of parent drug and this usually reduces the effects on the body. Metabolites may also be pharmacologically active, sometimes more so than the parent drug.

Excretion/Elimination

Compounds and their metabolites need to be removed from the body via excretion, usually through the kidneys (urine) or in the feces. Unless excretion is complete, accumulation of foreign substances can adversely affect normal metabolism.

Lazar toxicity prediction

In silico toxicology provides customised solutions for the computer based prediction of toxic activities.

Docking Server

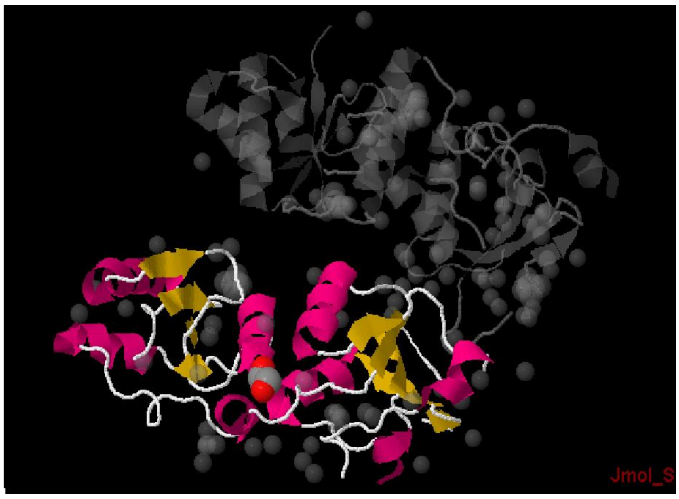
DockingServer offers a web-based, easy to use interface that handles all aspects of molecular docking from ligand and protein set-up. While its user friendly interface enables docking calculation and results evaluation carried out by researchers coming from all fields of biochemistry, DockingServer also provides full control on the setting of specific parameters of ligand and protein set up and docking calculations for more advanced users.

The application can be used for docking and analysis of single ligands as well as for high throughput docking of ligand libraries to target proteins. DockingServer integrates a number of computational chemistry software specifically aimed at correctly calculating parameters needed at different steps of the docking procedure, i.e. accurate ligand geometry optimization, energy minimization, charge calculation, docking calculation and protein-ligand complex representation.

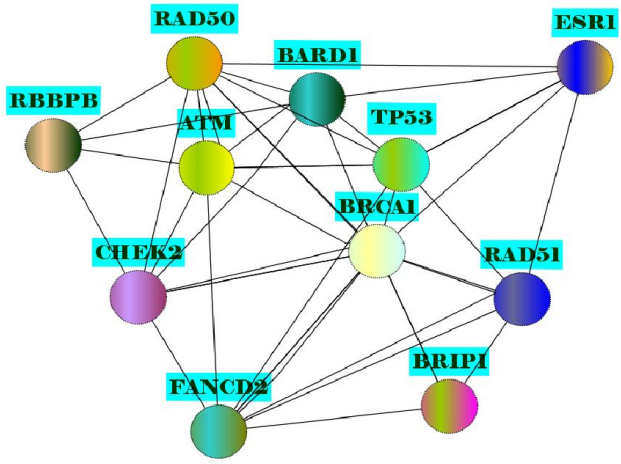
Thus, the use of DockingServer allows the user to carry out highly efficient and robust docking calculations by integrating a number of popular software used in in silico chemistry into one comprehensive web service

RESULTS

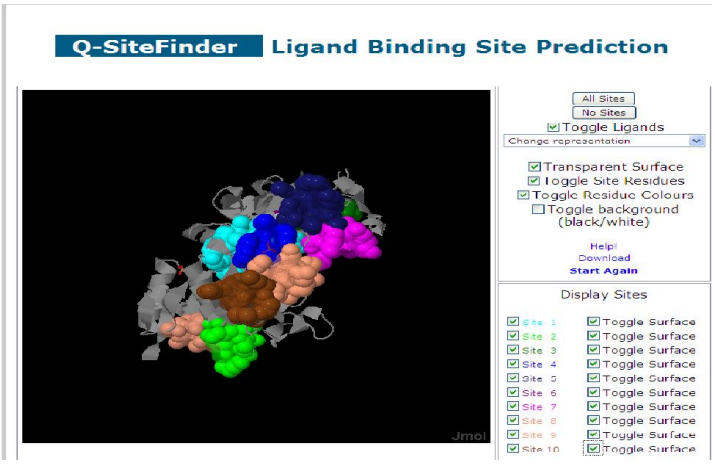
Visualization of BRCA1 protein structure using docking server



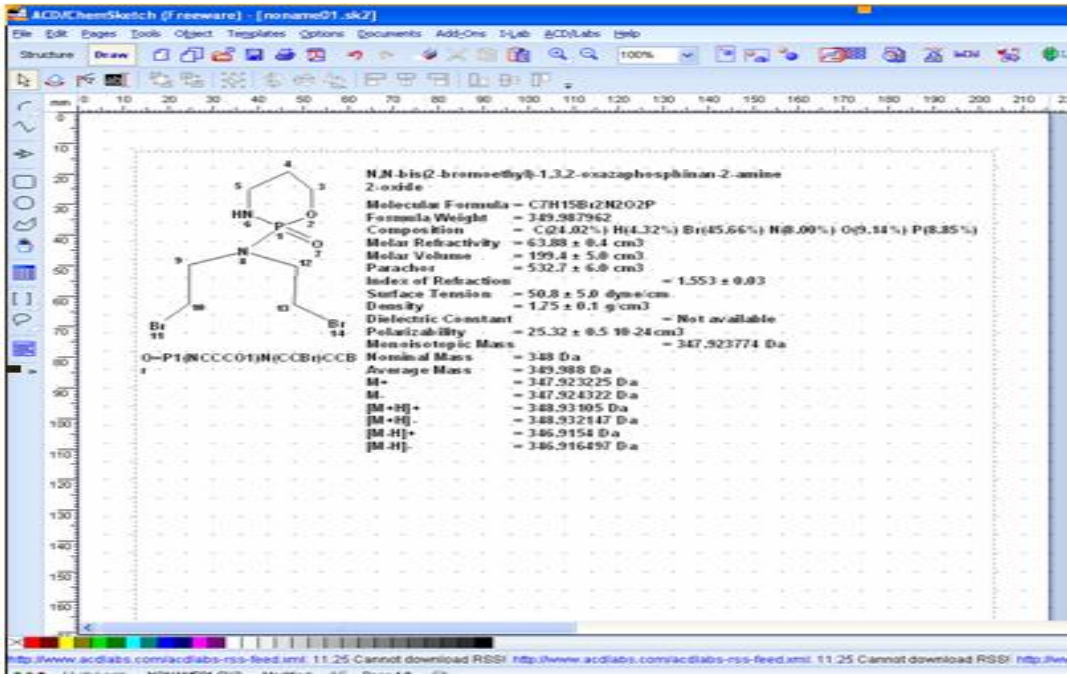
Pathway construction and its interaction of BRCA1 protein using YEd Graph Editor



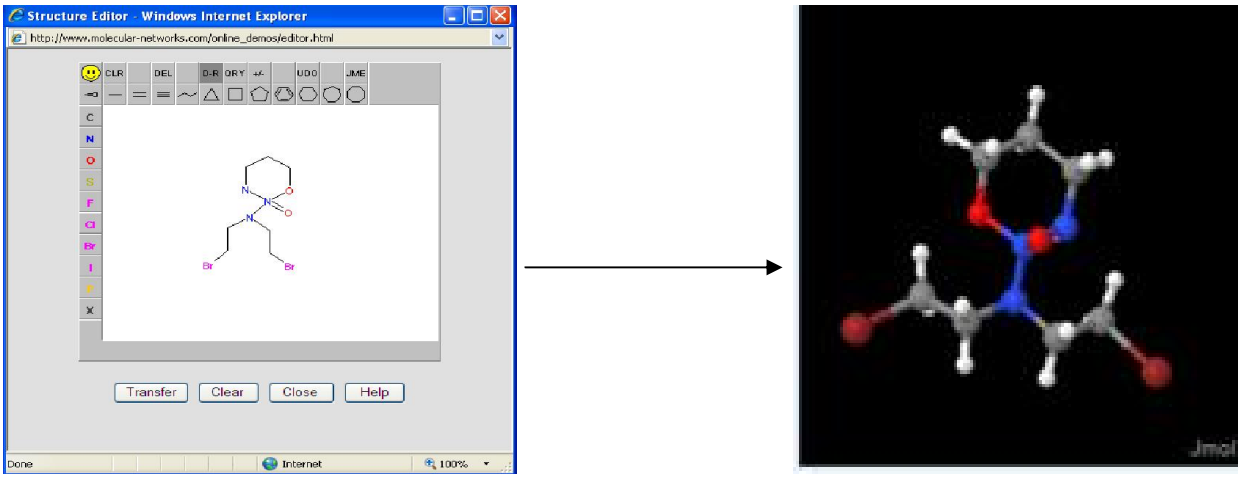
***BRCA1 protein binding site shown by* Q-SITE FINDER**



ANALOGUE STRUCTURE DRAWN BY USING ACD CHEMSKETCH



3D STRUCTURE OF ANALOG MOLECULE GENERATED BY CORINA ONLINE TOOL:



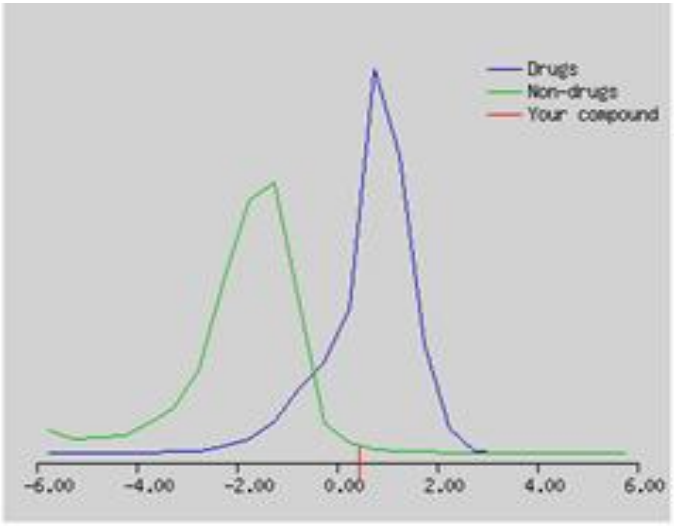
MOLECULAR PROPERTIES BY MOLSOFT

Molecular formula	C7H15BR2N2O2P
Molecular weight	347.92
Number of hba	4
Number of hbd	1
Mollogp	-0.58
Mollogs	-2.92
Molpsa	36.91 A^2
Molvol	231.17A^3
Number of stereo centers	1

MOLINSPIRATION: (Drug Likeness property)

GPCR ligand : -1.75
Ion channel modulator : -2.19
Kinase inhibitor : -1.87
Nuclear receptor ligand : -2.69

DRUG LIKENESS MODEL SCORE :0.45



LIPINSKI DRUG FILTER	
MOLECULAR WEIGHT	213
HYDROGEN BOND ACCEPTOR	3
HYDROGEN BOND DONOR	1
LOGP	2.780
MOLAR REFRACTIVITY	66.319

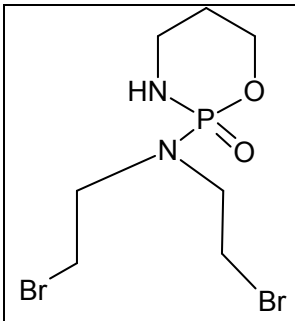
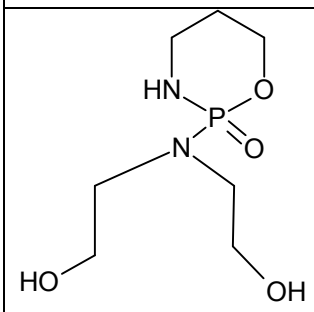
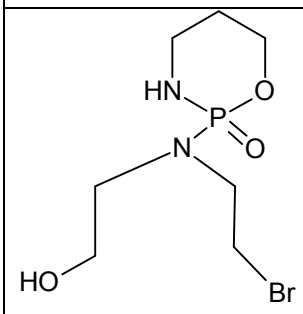
The Pharmacokinetic and the Phamacodynamic propertics of new analog from cyclophosphamide were studied using ADME/TOX WEB.The results are shown below

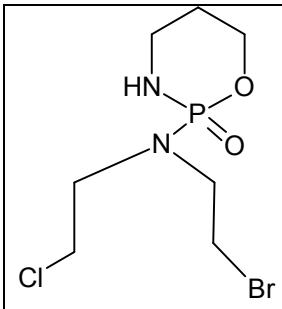
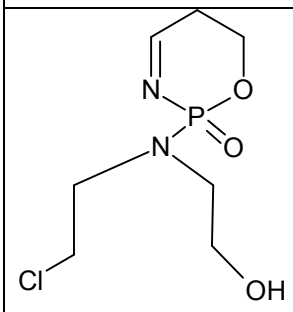
Property	**Value**
Oral Bioavailability	More than 70%
Log P	1.27
Maximum Absorption passive	100%
Active Transport	_
Plasma Protein Binding	58.04%
Volume of Distribution	1.41L/Kg
Log pKa	No Acid pKa
Solubility in pure water	LogSw: -1.38 Sw: 14.7mg/ml
Solubility in pure water	No Base pKa
PgP inhibitor specificity	_
PgP substrate specifity	_
Molecular weight	349.99
H-Bond donor	1
H-Bond Acceptors	4
TPSA	51.38
NO. of rotatable bonds	5

Result for toxicity studies

Probability of positive AMES test	0.818
Probability of effect on:	_
Blood	0.57
CVS	0.02
GI system	0.60
Kidney	0.44
Liver	0.28
Lungs	0.24
LD50(mouse):	_
Interaperitoneal	280 mg/kg
Oral	630 mg/kg
IV	150 mg/kg
Subcutaneous	5300 mg/kg
LD5o(rat):	_
Intreaperitoneal	270 mg/kg
Oral	300 mg/kg

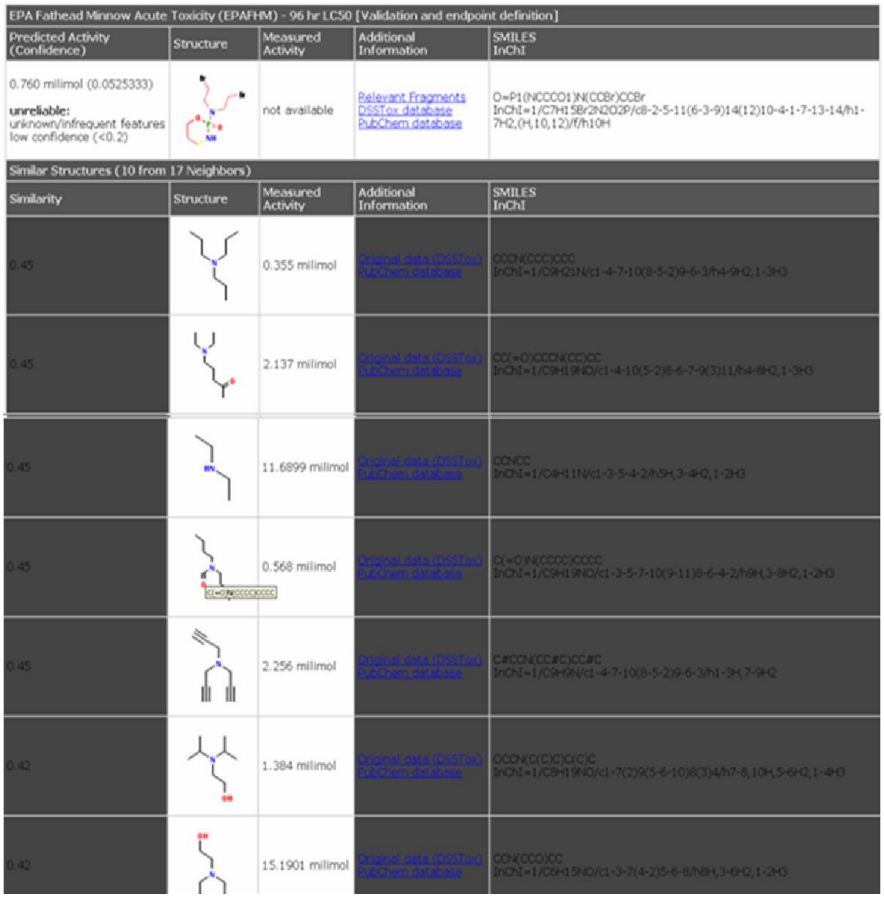
Analogues of cyclophospamide

 *N*,*N*-bis(2-bromoethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide. Log P:1.27	Molecular Formula = $C_7H_{15}Br_2N_2O_2P$ Formula Weight = 349.987962 Composition = C(24.02%) H(4.32%) Br(45.66%) N(8.00%) O(9.14%) P(8.85%) Molar Refractivity = 63.88 ± 0.4 cm^3 Molar Volume = 199.4 ± 5.0 cm^3 Parachor = 532.7 ± 6.0 cm^3 Index of Refraction = 1.553 ± 0.03 Surface Tension = 50.8 ± 5.0 dyne/cm Density = 1.75 ± 0.1 g/cm^3 Dielectric Constant = Not available Polarizability = 25.32 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 347.923774 Da Nominal Mass = 348 Da Average Mass = 349.988 Da M+ = 347.923225 Da M- = 347.924322 Da [M+H]+ = 348.93105 Da [M+H]- = 348.932147 Da [M-H]+ = 346.9154 Da [M-H]- = 346.916497 Da
 2,2'-[(2-oxido-1,3,2-oxazaphosphinan-2-yl)imino]diethanol **Log P: 2.22+/- 0.37**	Molecular Formula = $C_7H_{17}N_2O_4P$ Formula Weight = 224.194642 Composition = C(37.50%) H(7.64%) N(12.50%) O(28.55%) P(13.82%) Molar Refractivity = 51.49 ± 0.4 cm^3 Molar Volume = 167.7 ± 5.0 cm^3 Parachor = 461.0 ± 6.0 cm^3 Index of Refraction = 1.526 ± 0.03 Surface Tension = 57.1 ± 5.0 dyne/cm Density = 1.33 ± 0.1 g/cm^3 Dielectric Constant = Not available Polarizability = 20.41 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 224.092593 Da Nominal Mass = 224 Da Average Mass = 224.1946 Da M+ = 224.092044 Da M- = 224.093142 Da [M+H]+ = 225.099869 Da [M+H]- = 225.100967 Da [M-H]+ = 223.084219 Da
 2-[(2-bromoethyl)(2-oxido-1,3,2-oxazaphosphinan-2-yl)amino]ethanol **Log P: 0.62+/- 0.37**	Molecular Formula = $C_7H_{16}BrN_2O_3P$ Formula Weight = 287.091302 Composition = C(29.29%) H(5.62%) Br(27.83%) N(9.76%) O(16.72%) P(10.79%) Molar Refractivity = 57.68 ± 0.4 cm^3 Molar Volume = 183.6 ± 5.0 cm^3 Parachor = 496.9 ± 6.0 cm^3 Index of Refraction = 1.540 ± 0.03 Surface Tension = 53.6 ± 5.0 dyne/cm Density = 1.56 ± 0.1 g/cm^3 Dielectric Constant = Not available Polarizability = 22.86 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 286.008183 Da Nominal Mass = 286 Da Average Mass = 287.0913 Da M+ = 286.007635 Da M- = 286.008732 Da [M+H]+ = 287.01546 Da [M+H]- = 287.016557 Da [M-H]+ = 284.99981 Da [M-H]- = 285.000907 Da

 N-(2-bromoethyl)-N-(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide **Log p: 0.61+/- 0.36**	Molecular Formula = $C_7H_{15}BrClN_2O_2P$ Formula Weight = 305.536962 Composition = C(27.52%) H(4.95%) Br(26.15%) Cl(11.60%) N(9.17%) O(10.47%) P(10.14%) Molar Refractivity = 60.98 ± 0.4 cm^3 Molar Volume = 197.5 ± 5.0 cm^3 Parachor = 518.8 ± 6.0 cm^3 Index of Refraction = 1.529 ± 0.03 Surface Tension = 47.5 ± 5.0 dyne/cm Density = 1.54 ± 0.1 g/cm^3 Dielectric Constant = Not available Polarizability = 24.17 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 303.974296 Da Nominal Mass = 304 Da Average Mass = 305.537 Da M+ = 303.973748 Da M- = 303.974845 Da [M+H]+ = 304.981573 Da [M+H]- = 304.98267 Da [M-H]+ = 302.965923 Da [M-H]- = 302.96702 Da
 2-[(2-chloroethyl)(2-oxido-5,6-dihydro-2H-1,3,2-oxazaphosphinin-2-yl)amino]ethanol **Log P:-0.06**	Molecular Formula = $C_7H_{14}ClN_2O_3P$ Formula Weight = 240.624422 Composition = C(34.94%) H(5.86%) Cl(14.73%) N(11.64%) O(19.95%) P(12.87%) Molar Refractivity = 53.81 ± 0.5 cm^3 Molar Volume = 163.0 ± 7.0 cm^3 Parachor = 455.3 ± 8.0 cm^3 Index of Refraction = 1.573 ± 0.05 Surface Tension = 60.7 ± 7.0 dyne/cm Density = 1.47 ± 0.1 g/cm^3 Dielectric Constant = Not available Polarizability = 21.33 ± 0.5 $10^{-24}cm^3$ Monoisotopic Mass = 240.043056 Da Nominal Mass = 240 Da Average Mass = 240.6244 Da M+ = 240.042507 Da M- = 240.043605 Da [M+H]+ = 241.050332 Da [M+H]- = 241.05143 Da [M-H]+ = 239.034682 Da [M-H]- = 239.03578 Da

LAZAR TOXICITY PREDICTION

Information about toxicity and its relationship to structure lazar toxicity prediction



EPA Fathead Minnow Acute Toxicity (EPAFHM) - 96 hr LC50 [Validation and endpoint definition]

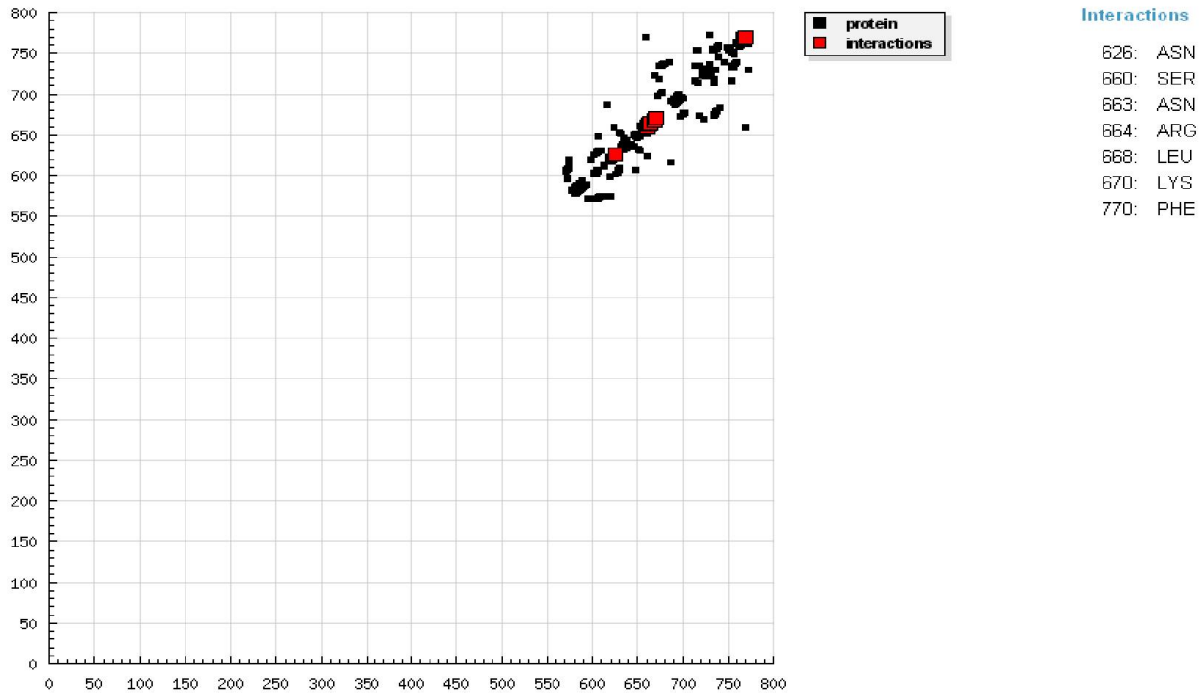
Predicted Activity (Confidence)	Structure	Measured Activity	Additional Information	SMILES InChI
0.760 millimol (0.0525333) **unreliable:** unknown/infrequent features low confidence (<0.2)		not available	Relevant Fragments DSSTox database PubChem database	O=P1(NCCCO1)N(CCBr)CCBr InChI=1/C7H15Br2N2O2P/c8-2-5-11(6-3-9)14(12)10-4-1-7-13-14/h1-7H2,(H,10,12)/f/h10H

Similar Structures (10 from 17 Neighbors)

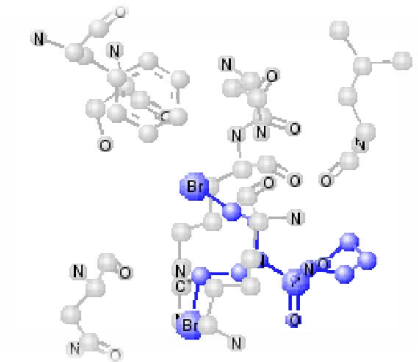
Similarity	Structure	Measured Activity	Additional Information	SMILES InChI
0.45		0.355 millimol	Original data (DSSTox) PubChem database	CCCN(CCC)CCC InChI=1/C9H21N/c1-4-7-10(8-5-2)9-6-3/h4-9H2,1-3H3
0.45		2.137 millimol	Original data (DSSTox) PubChem database	CC(=O)CCCN(CC)CC InChI=1/C9H19NO/c1-4-10(5-2)8-6-7-9(3)11/h4-8H2,1-3H3
0.45		11.6899 millimol	Original data (DSSTox) PubChem database	CCNCC InChI=1/C4H11N/c1-3-5-4-2/h5H,3-4H2,1-2H3
0.45		0.568 millimol	Original data (DSSTox) PubChem database	C(=O)N(CCCC)CCCC InChI=1/C9H19NO/c1-3-5-7-10(9-11)8-6-4-2/h9H,3-8H2,1-2H3
0.45		2.256 millimol	Original data (DSSTox) PubChem database	C#CCN(CC#C)CC#C InChI=1/C9H9N/c1-4-7-10(8-5-2)9-6-3/h1-3H,7-9H2
0.42		1.384 millimol	Original data (DSSTox) PubChem database	OCCN(C(C)C)C(C)C InChI=1/C9H19NO/c1-7(2)9(5-6-10)8(3)4/h7-8,10H,5-6H2,1-4H3
0.42		15.1901 millimol	Original data (DSSTox) PubChem database	OCCN(CCO)CC InChI=1/C6H15NO/c1-3-7(4-2)5-6-8/h8H,3-6H2,1-2H3

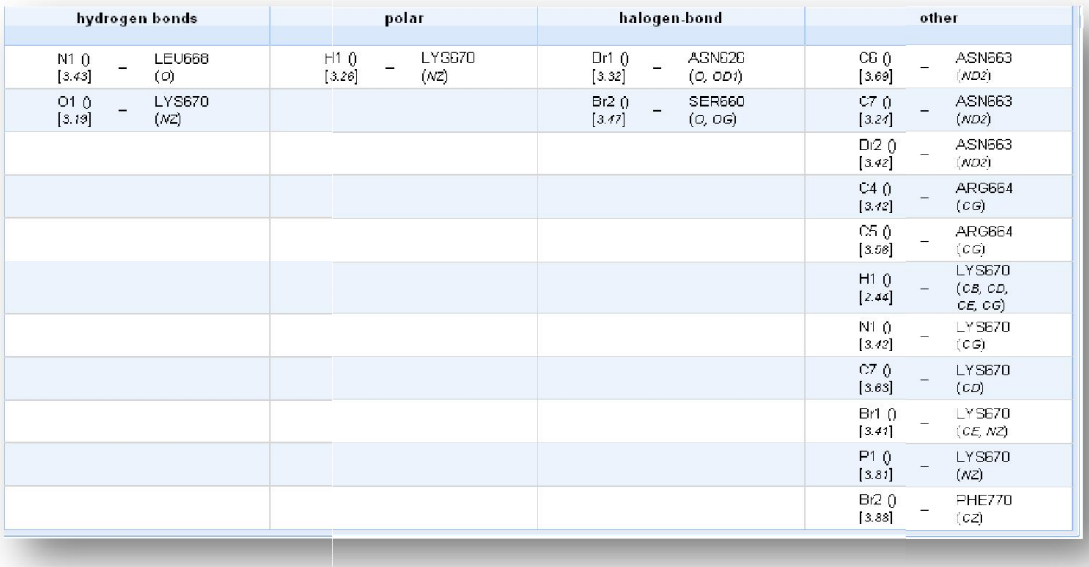
DOCKING SERVER

Hb PLOT



INTERACTION





hydrogen bonds			polar			halogen-bond			other		
N1 () [3.43]	–	LEU668 (O)	H1 () [3.26]	–	LYS670 (NZ)	Br1 () [3.32]	–	ASN626 (O, OD1)	C6 () [3.69]	–	ASN663 (ND2)
O1 () [3.19]	–	LYS670 (NZ)	Br2 () [3.47]	–	SER660 (O, OG)	C7 () [3.24]	–	ASN663 (ND2)			
						Cl2 () [3.42]	–	ASN663 (ND2)			
						C4 () [3.42]	–	ARG664 (CG)			
						C5 () [3.58]	–	ARG664 (CG)			
						H1 () [2.44]	–	LYS670 (CB, CD, CE, CG)			
						N1 () [3.42]	–	LYS670 (CG)			
						C7 () [3.63]	–	LYS670 (CD)			
						Br1 () [3.41]	–	LYS670 (CE, NZ)			
						P1 () [3.81]	–	LYS670 (NZ)			
						Br2 () [3.88]	–	PHE770 (CZ)			

RESULT TABLE

Rank	Est Free Energy of Binding	Est. Inhibition Constant,ki	Vdw+Hbond+desolEnergy	Electrostatic Energy	Total inter molecular Energy	Frequency
1	-4.10kcal/mol	994.77mM	-5.16kcal/mol	-0.13 kcal/mol	-5.28 kcal/mol	20%
2	-4.09 kcal/mol	1.00mM	-5.19 kcal/mol	-0.05 kcal/mol	-5.24 kcal/mol	60%
3	-3.72 kcal/mol	1.89mM	-4.86 kcal/mol	-0.07 kcal/mol	-4.93 kcal/mol	10%
4	-3.71 kcal/mol	1.90mM	-4.85 kcal/mol	-0.11 kcal/mol	-4.95 kcal/mol	10%

DOCK RESULT

Rank	Est Free Energy of Binding	Est. Inhibition Constant,ki	Vdw+Hbond+desol Energy	Electrostatic Energy	Total inter molecular Energy	Frequency	Interact surface
1.	-4.10 kcal/mol	994.77mM	-5.16 kcal/mol	-0.13 kcal/mol	-5.28 kcal/mol	20%	458.374

Based on docking result overall docking score and scoring function evaluate the binding affinity of the drug to the receptor. so BRCA1 with the analog molecule shows binding affinity which is -4.10 kcal/mol.

Conclusion

- The newly predicted drug which was chemically modified was allowed to dock with the target BRCA1 protein to contain the binding energy.
- The newly designed drug can be further tested for Toxicity and Lipinski rule of five and effectively can be analysed.
- The analysis of the pharmacodynamic and pharmacokinetics properties of new drug revealed that the molecule has favorable number of H-bond donors and H bond acceptors. The number of rotatable bonds, TPSA and Passive transport are also in favour of the drug molecule.
- All rotatable torsions were released during docking.
- The docking analysis was done using docking server. The binding sites were detected using Q-site finder. These results could provide useful insights into the drug-protein interactions.
- Further modification of ligand molecule can increase the property of active site binding.

REFERENCES

Blackwood M. A. and Weber, B. L. 1998. BRCA1 and BRCA2: from molecular genetics to clinical medicine, *J. Clin. Oncol.,* 16 (1998), pp. 1969–1977.

Brown E.J. and D. Baltimore, 2000. ATR disruption leads to chromosomal fragmentation and early embryonic lethality, *Genes Dev.*, 14 (2000), pp. 397–402. View Record in Scopus | Cited By in Scopus (364)

Cressman V.L., D.C. Backlund, A.V. Avrutskaya, S.A. Leadon, V. Godfrey and B.H. Koller, 1999. Growth retardation, DNA repair defects, and lack of spermatogenesis in BRCA1-deficient mice, *Mol. Cell Biol.,* 19 (1999), pp. 7061–7075. View Record in Scopus | Cited By in Scopus (59)

Easton D.F., D. Ford, D.T. 1995. Bishop and Breast Cancer Linkage Consortium, Breast and ovarian cancer incidence in BRCA1-mutation carriers, *Am. J. Hum. Genet*, 56 (1995), pp. 265–271. View Record in Scopus | Cited By in Scopus (934)

Fan S., Y.X. Ma, C. Wang, R.Q. Yuan, Q. Meng, J.A. Wang, M. Erdos, I.D. Goldberg, P. Webb and P.J. Kushner et al. 2001. Role of direct interaction in BRCA1 inhibition of estrogen receptor activity, Oncogene 20 (2001), pp. 77–87. View Record in Scopus | Cited By in Scopus (130)

Gompel A., S. Somai, M. Chaouat, A. Kazem, H.J. Kloosterboer, I. Beusman, P. Forgez, M. Mimoun and W. Rostene, 2000 . Hormonal regulation of apoptosis in breast cells and tissues, Steroids 65 (2000), pp. 593–598. Abstract

| Article | PDF (208 K) | View Record in Scopus | Cited By in Scopus (83)

Gowen L.C., B.L. Johnson, A.M. Latour, K.K. Sulik and B.H. Koller, 1996. Brca1 deficiency results in early embryonic lethality characterized by neuroepithelial abnormalities, *Nat. Genet*., 12 (1996), pp. 191–194. View Record in Scopus | Cited By in Scopus (249)

Hakem R., J.L. de la Pompa, C. Sirard, R. Mo, M. Woo, A. Hakem, A. Wakeham, J. Potter, A. Reitmair and F. Billia et al. 1996. The tumor suppressor gene Brca1 is required for embryonic cellular proliferation in the mouse, Cell 85 (1996), pp. 1009–1023. Article | PDF (3943 K) | View Record in Scopus | Cited By in Scopus (391)

Kousteni, S., T. Bellido, L.I. Plotkin, C.A. O'Brien, D.L. Bodenner, L. Han, K. Han, G.B. DiGregorio, J.A. Katzenellenbogen and B.S. Katzenellenbogen et al. 2001. Nongenotropic, sex-nonspecific signaling through the estrogen or androgen receptors: dissociation from transcriptional activity, Cell 104 (2001), pp. 719–730. Article | PDF (1497 K) | View Record in Scopus | Cited By in Scopus (581)

Liu, Q., S. Guntuku, X.-S. Cui, S. Matsuoka, D. Cortez, K. Tamai, G. Luo, S. Carattini-Rivera, F. DeMayo, A. Bradley, L.A. Donehower and S.J. Elledge, 2000. Chk1 is an essential kinase that is regulated by Atr and required for the G2/M DNA damage checkpoint, Genes Dev. 14 (2000), pp. 1448–1459. View Record in Scopus | Cited By in Scopus (655)

Ludwig, T., D.L. Chapman, V.E. Papaioannou and A. Efstratiadis, 1997. Targeted mutations of breast cancer susceptibility gene homologs in mice: lethal phenotypes of Brca1, Brca2, Brca1/Brca2, Brca1/p53, and Brca2/p53 nullizygous embryos, Genes Dev. 11 (1997), pp. 1226–1241. View Record in Scopus | Cited By in Scopus (315)

Ludwig, T., P. Fisher, S. Ganesan and A. Efstratiadis, 2001. Tumorigenesis in mice carrying a truncating Brca1 mutation, Genes Dev. 15 (2001), pp. 1188–1193. View Record in Scopus | Cited By in Scopus (60)

Moynahan, M.E., J.W. Chiu, B.H. Koller and M. Jasin, 1999. Brca1 controls homology-directed DNA repair, Mol. Cell 4 (1999), pp. 511–518. Article | PDF (214 K) | View Record in Scopus | Cited By in Scopus (451)

Neuhausen S.L. and E.A. Ostrander, 1997. Mutation testing of early-onset breast cancer genes BRCA1 and BRCA2, Genet. Test. 1 (1997), pp. 75–83. View Record in Scopus | Cited By in Scopus (6)

Rosen E.M., S. Fan and I.D. Goldberg, 2001. BRCA1 and prostate cancer, Cancer Invest. 19 (2001), pp. 396–412. View Record in Scopus | Cited By in Scopus (26)

Rutanen, E.M., 1998. Insulin-like growth factors in endometrial function, Gynecol. Endocrinol. 12 (1998), pp. 399–406. View Record in Scopus | Cited By in Scopus (46)

Sassoon D., 1999. Wnt genes and endocrine disruption of the female reproductive tract: a genetic approach, Mol. Cell. Endocrinol. 158 (1999), pp. 1–5. Abstract | Article | PDF (185 K) | View Record in Scopus | Cited By in Scopus (24)

Scully R. and D.M. Livingston, 2000. In search of the tumour-suppressor functions of BRCA1 and BRCA2, Nature 408 (2000), pp. 429–432. View Record in Scopus | Cited By in Scopus (335)

Welcsh P.L., E.L. Schubert and M.C. King, 1998. Inherited breast cancer: an emerging picture, Clin. Genet. 54 (1998), pp. 447–458. View Record in Scopus | Cited By in Scopus (20)

****