Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 3, Issue 4, 2011

Research Article

CHLORAMBUCIL DERIVATIVES AS ANTINEOPLASTIC AGENT: *IN-SILICO* DESIGNING AND DOCKING

AJEET*

S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar, U.P. India. Email: ajeet_pharma111@rediffmail.com

Received: 16 August 2011, Revised and Accepted: 20 September 2011

ABSTRACT

The purpose of present work was to design and characterize derivatives of Chlorambucil, an antineoplastic agent with the help of drug designing softwares and docking procedures. Docking procedures allows virtually screening a database of compounds and predict the strongest binder based on various scoring functions. This work has been performed with the help of Chemdraw Ultra 10.0, ArgusLab software, Molegro Virtual docker, Molinspiron online software, MedChem Designer, EPA DSSTox Structure Browser v2.0 by docking procedures. Result reveals that the protein-ligand interaction energy of derivatives CB1 and CB8 were -127.920 and -103.680 which is better than the original Chlorambucil molecule (CID no. 2708) as -91.779, so the derivatives which better binds with the human glutathione s-transferase may be used as antineoplastic agents.

Keywords: Chlorambucil derivatives; Antineoplastic agent; Docking; Human glutathione s-transferase *P1.*

INTRODUCTION

The anticancer drugs either kill cancer cells or modify their growth. Selectivity of majority of drugs is limited and they are one of the most toxic drugs used in therapy. Treatment of malignant diseases with drugs is a rather recent development when nitrogen mustard was used, but progress has been rapid, both in revealing pathobiology of the diseases and in discovery of new drugs. Cancer chemotherapy is now of established value and a highly specialized field. One of the classes of drugs of antineoplastic agents is an alkylating agent. These agents produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. They have Cytotoxic and radiomimetic actions. Many are cell cycle non-specific that is act on dividing as well as resting cells. Some of them have central nervous system stimulant and cholinergic properties. A agent of this class is Chlorambucil which is a very slow alkylating agent, especially active on lymphoid tissue, Myloid tissue is largely spared. It is the drug of choice for long term maintenance therapy for chronic lymphatic leukaemia; Hodgkin's disease and some solid tumours also resolve. It has some immunosuppressant property. [1]

Detoxification and xenobiotics metabolism has been the roles of human glutathione S-transferase P1 protein and by binding with c-Jun-NH_2-terminal kinase it suppresses its activity. [2]

Docking procedures permits virtually screening a database of compounds and predict the strongest binder on various scoring functions. It finds ways in which two molecules, such as drugs and an enzyme and/or protein fit together and dock to each other well [3].

Rational Drug Design helps to facilitate and fasten the drug designing process, which involves various methods to identify novel compound, out of them one method is the docking of molecule of drug with the receptor. The therapeutic action of the drug will be under consideration when the biochemical pathway of the enzyme can be exploited. [4]

Molecularly, docking techniques have been used in modern drug designing to understand drug–receptor interaction. It has been shown in the literature that computational procedures may strongly support and help the design of new, more potent drugs by revealing the mechanism of drug-receptor interaction. [5]

MATERIALS

For carrying out this work, National Center for Biotechnology Information's (NCBI) website and Protein Data Bank's (PDB) website were used as chemical data sources.

For designing the derivatives - Chemdraw Ultra 10.0 [6]

For optimizing the geometry of derivatives - ArgusLab software [7]

For docking studies - Molegro Virtual docker [8]

For characterization of the derivatives - Molinspiron online software [9], MedChem Designer and EPA DSSTox Structure Browser v2.0 online service

METHOD

Chlorambucil structure data file was downloaded from N.C.B.I. website with CID no. 2708 and protein target was downloaded from Protein Data Bank with PDB id 3CSJ.

Protocol

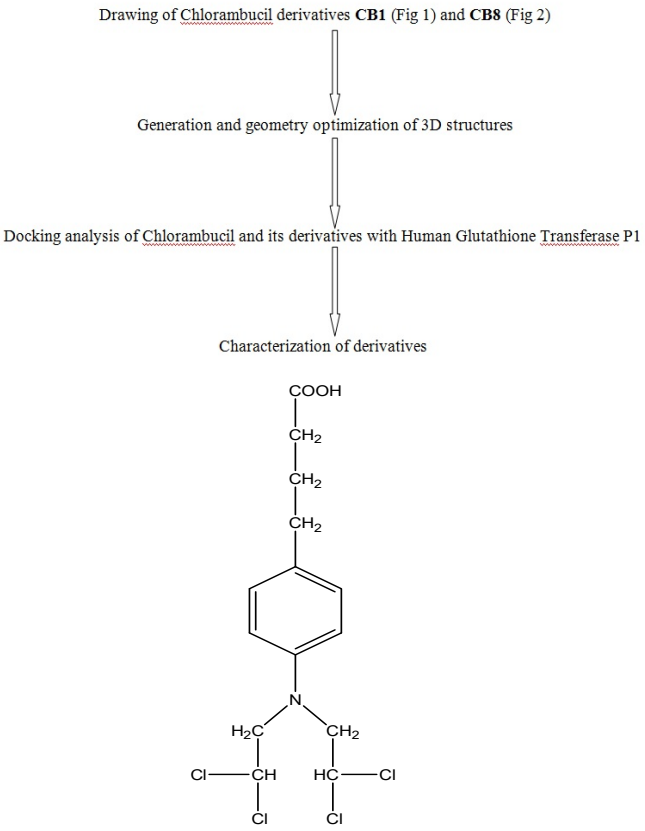

Fig.1: It shows the 2d structure of chlorambucil derivative cb1

Two dimensional structure of Chlorambucil derivative named as CB1 was drawn by ChemDraw Ultra to understand the atomic positions of different atoms in the designed molecule.

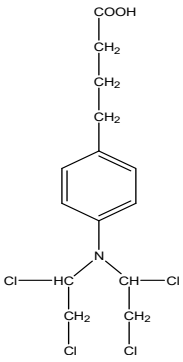

Fig. 2: It shows the 2d structure of chlorambucil derivative cb8

Two dimensional structure of Chlorambucil derivative named as CB8 was drawn by ChemDraw Ultra to understand the atomic positions of different atoms in the designed molecule.

RESULTS AND DISCUSSION

Docking results of Chlorambucil derivatives CB1 (Fig 3, Fig 4), CB8 (Fig 5, Fig 6) through Molegro Virtual Docker have been shown below.

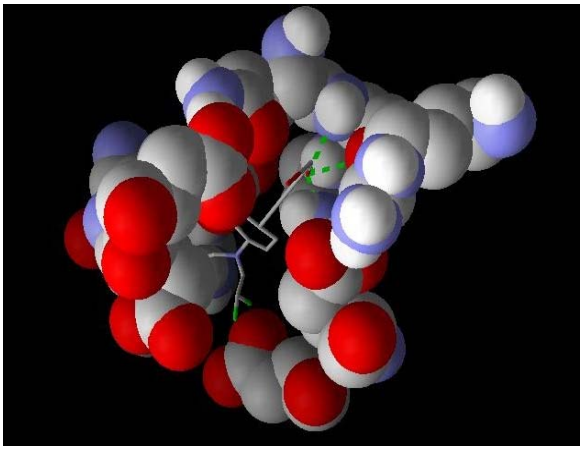

Fig. 3: It shows docking of derivative cb1 with human glutathione transferase p1

The protein has been shown with spacefill visualization and ligand molecule with stick visualization by Molegro virtual docker, which is being used for docking procedures and hydrogen bonds are described with dotted lines.

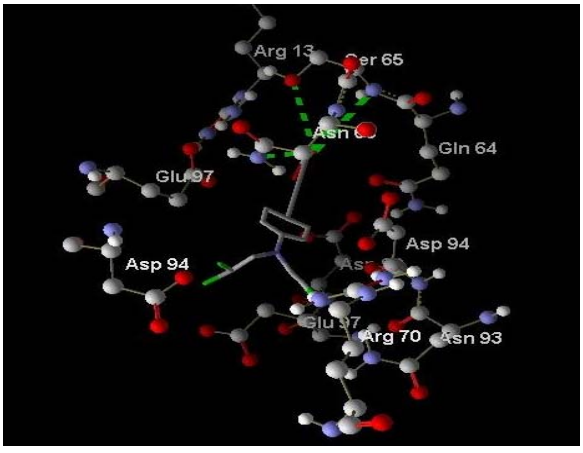

Fig. 4: It shows docking of derivative cb1 showing residues

The protein has been shown with ball and stick visualization and ligand molecule with stick visualization by Molegro virtual docker, which is being used for docking procedures and hydrogen bonds are described with dotted lines and residues are labled alongwith.

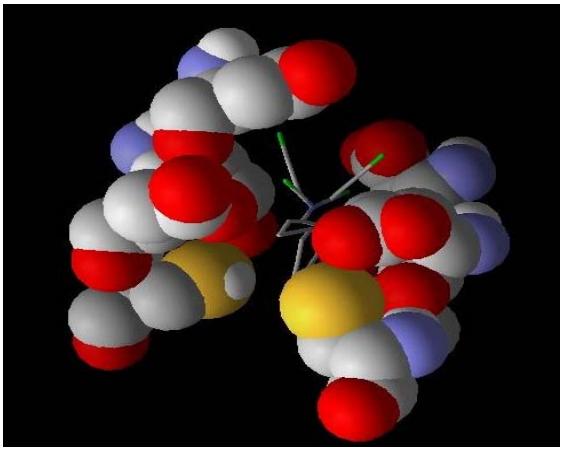

Fig. 5: It shows docking of derivative cb8 with human glutathione transferase p1

The protein has been shown with spacefill visualization and ligand molecule with stick visualization by Molegro virtual docker, which is being used for docking procedures.

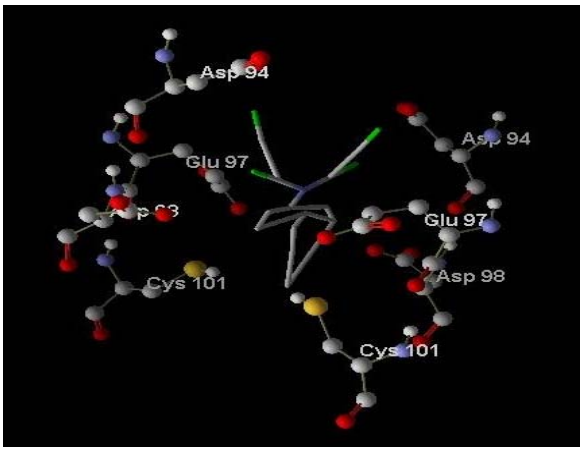

Fig. 6: It shows docking of derivative cb8 showing residues

The protein has been shown with ball and stick visualization and ligand molecule with stick visualization by Molegro virtual docker, which is being used for docking procedures and residues are labeled along with.

It reveals that the protein-ligand interaction energy of derivatives CB1 and CB8 were better than the original Chlorambucil molecule (CID no. 2708) (Table 1).

Table 1: Table Shows Protein-Ligand Interaction Energy Of Chlorambucil And Derivatives Cb1 And Cb8

Pose	Chlorambucil (CID no. 2708)	CB1	CB8
1	-91.779	-127.920	-103.680
2	-73.984	-123.070	-119.038
3	-77.874	-103.288	-111.409
4	-77.480	-126.219	-100.649
5	-77.136	-118.551	-95.955

There are different poses of same ligand which have been used during docking procedures, and further used with the comparison of protein-ligand interaction energy, much lower interaction energy is being associated with higher stability.

Bioactivity predictions were calculated by Molinspiron online software (Table 2) and ADMET properties were calculated by MedChem Designer (Table 3).

Table 2: table shows score of bioactivity prediction of chlorambucil and derivatives cb1 and cb8

	Chlorambucil (CID no. 2708)	CB1	CB8
GPCR ligand	0.03	0.07	0.08
Ion channel modulator	-0.09	-0.06	-0.11
Kinase inhibitor	-0.03	-0.11	-0.21
Nuclear receptor ligamd	0.19	0.05	0.09
Protease inhibitor	0.02	0.12	-0.03
Enzyme inhibitor	0.17	0.14	0.12

GPCR-: G-Protein coupled receptor

The designed derivatives and original drug's bioactivity predictions have been compared along with some selected activities.

Table 3: Table Shows Admet Properties Prediction Of Chlorambucil And Derivatives Cb1 And Cb8

	Chlorambucil (CID no. 2708)	CB1	CB8
S log P	3.285	3.928	3.718
S logD	0.904	1.256	1.058
M logP	3.025	3.506	3.506

The designed derivatives and original drug's ADMET properties predictions have been compared along with some selected properties.

Molecular Weight	304.218	373.108	373.108
Hydroxybutyrate dehydrogenase	1.000	1.000	1.000
Topological Polar Surface Area	40.540	40.540	40.540
Hydrogen bond acceptor	3.000	3.000	3.000
Rule of 5	0.000	0.000	0.000

Toxological comparative studies were performed through EPA DSSTox Structure Browser v2.0 online service. (Fig 7, 8)

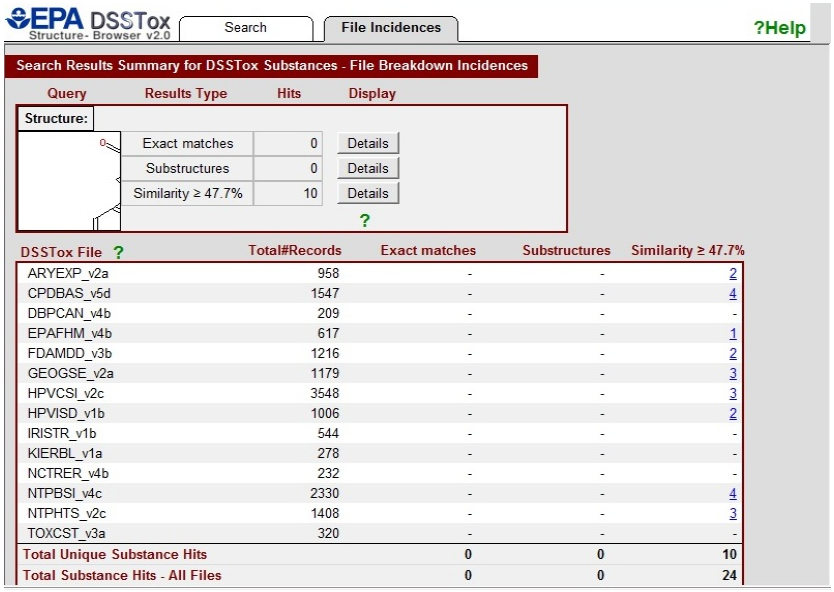

Fig. 7: It shows the toxological comparison of derivative cb1

The designed derivative CB1 has been compared for any toxicity possibility online with pre-existing similar structures, no 100% similar structures were found.

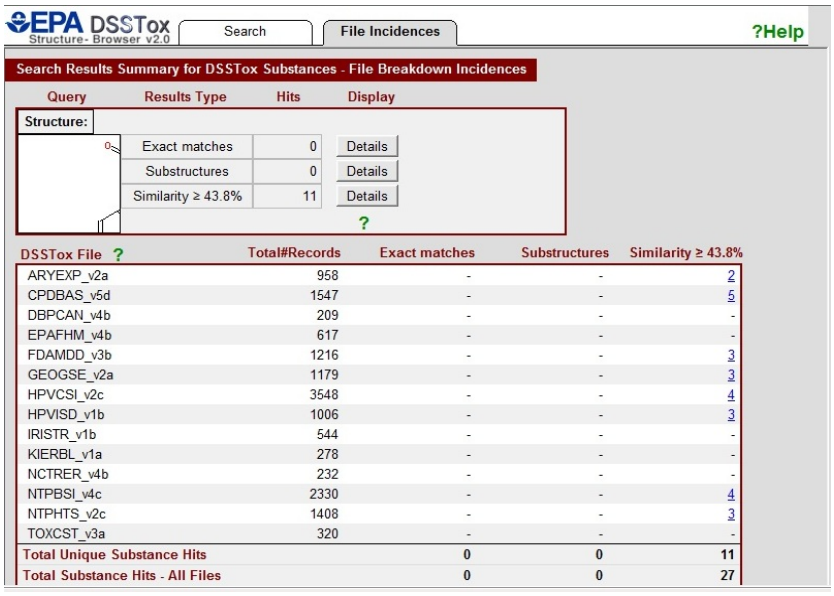

Fig. 8: It shows the toxological comparison of derivative cb8

The designed derivative CB8 has been compared for any toxicity possibility online with pre-existing similar structures, no 100% similar structures were found.

CONCLUSION

Structural based drug designing is significantly based on the protein-ligand interaction. In the present work I have taken the receptor Human Glutathione Transferase P1 and draw derivatives of Chlorambucil. When the protein 3CSJ was docked with ligand, the protein-ligand interaction energy of CB1 and CB8 were found lower than original drug which have been associated with the fact that lower interaction energy shows higher stability. From this we can conclude that some of modified ligands have better tendency to bind with the protein to which the previously existing drugs are suppose to be bind and they may be proof as better antineoplastic agents as compare to pre-existing drug molecules.

ACKNOWLEDGMENT

I am highly thankful to the institute S.D. College of Pharmacy and Vocational Studies to provide me literature and computer laboratory facilities. The moral and technical support of Mr. Om Prakash, S.R.F. Central Institute of Medicinal and Aromatic Plants, Lucknow is highly acknowledged.

REFERENCES

1. Tripathi KD. Diuretics. Essentials of Medical Pharmacology. 6th ed. New Delhi:Jaypee Brothers Medical Publishers (P) Ltd.;2008.
2. Wu Y, Fan Y, Xue B, Luo L, Shen J, Zhang S et. al. The Human glutathione *S*-transferase P1-1 interacts with TRAF2 and regulates TRAF2–ASK1 signals. Oncogene 2006;25 :5787-5800.
3. Prakash Nutan, Patel Shivani, J. Faldu Nilkanth, Ranjan Ravi, Sudheer DVN. Molecular Docking Studies of Antimalarial Drugs for Malaria. Journal of Computer Science & Systems Biology. 2010; 3(3):70-73.
4. R. Siva kumar, SK.Nafeez Basha, P. Kumarnallasivan, P.R.Vijaianand, R. Pradeepchandran. A computational design and docking studies on Escherichia coli b-Ketoacyl-Acyl carrier protein synthese III using auto dock. Journal of pharmacy research. 2010; 3(7):1460-1462.
5. Srivastava Vivek, Kumar Ashutosh, Mishra Bhartendu Nath, Siddiqi Mohammad Imran. Molecular docking studies on DMDP derivatives as human DHFR inhibitors. Bioinformation. 2008; 3(4):180-188.
6. Mills, N. ChemDraw Ultra 10.0. J. Am. Chem. Soc. 2006; 128 (41): 13649–13650.
7. Miteva MA, Violas S, Montes M, Gomez D, Tuffery P and Villoutreix BO et al. FAF-Drugs: free ADME/tox filtering of compound collections. N ucleic Acids Res. 2006; 34: 738-744.
8. Heberlé G and de Azevedo WF. Bio-Inspired Algorithms Applied to Molecular Docking Simulations. Jr. Current Medicinal Chemistry, 2011; 18(9):1339-1352.
9. Mishra, K., Raghava, PS et. al. Prediction of Specificity and Cross-Reactivity of Kinase Inhibitors. Letters in Drug Design Discovery, 2011; 8:223-228.