American Journal of Pharmacological Sciences, 2014, Vol. 2, No. 2, 42-46
Available online at http://pubs.sciepub.com/ajps/2/2/3

DOI:10.12691/ajps-2-2-3

Designing of Sulfanilamide/Sulfacetamide Derivatives as Human Topoisomerase II Inhibitor: A Docking Approach

Sapna Rani, Ajeet*, Arvind Kumar

Department of Pharmaceutical Chemistry and Drug Design, S. D. College of Pharmacy and Vocational Studies, Muzaffarnagar, India
*Corresponding author: ajeet_pharma111@rediffmail.com

Received May 05, 2014; Revised May 08, 2014; Accepted May 08, 2014

Abstract Diseases characterized by out-of-control cell growth are known as cancer. One of the most important mechanisms for handling it is the inhibition of the human topoisomerase II receptor. In same context while studying the treatment of cancer we found the significant effects of the derivatives of the sulfonamides, this promotes us to design novel derivatives by the means of *in-silico* resources with anticancer effects. Molecular docking approaches are routinely used in modern drug design to help understand drug–receptor interaction. This study has been performed with the help of Chemdraw Ultra 7.0, AutoDock Vina (Python Prescription 0.8), and PaDEL software. Results revealed that ligand-protein interaction affinity of all 12 designed molecules ranges from -6.8 Kcal/mol to -8.6 Kcal/mol which is approximately comparable to pre-existing human topoisomerase II inhibitor i.e. etoposide (CID: 36462, ligand-protein interaction affinity is -9.7 Kcal/mol).

Keywords: *sulfonamide, docking, human topoisomerase II inhibitors, etoposide, protein-ligand interaction affinity*

Cite This Article: Sapna Rani, Ajeet, and Arvind Kumar, "Designing of Sulfanilamide/Sulfacetamide Derivatives as Human Topoisomerase II Inhibitor: A Docking Approach." *American Journal of Pharmacological Sciences*, vol. 2, no. 2 (2014): 42-46. doi: 10.12691/ajps-2-2-3.

1. Introduction

Cancer is medically known as malignant neoplasia which involves unregulated/uncontrolled cell growth forming malignant tumors. Cancer may spreads through lymphatic system or bloodstream. There are about 2000 different known cancers which deliberately affects the human beings [1]. The cause of cancer is partially known with its diversity and complexity. The chances of cancer increases with the tobacco use, dietary factors, lack of physical activity, certain infections, obesity, exposure to radiation and environmental pollutants [2]. These factors cause cancerous mutations by damaging genes or combining with existing genetic faults.

Generally, cancer is treated with radiation therapy, chemotherapy and surgery. Cancer can affect people of all ages, and few are more common in children [3].

Six characters of malignancy have been found in different researches, such as [4]

Sustaining proliferative signaling.
Evading growth suppressors.
Resisting cell death.
Enabling replicative immortality .
Angiogenesis.
Activating invasion and metastasis.

When a tumor successfully spreads to other parts of the body and grows, invading and destroying other healthy tissues, it is said to have metastasized. This process itself is called metastasis, and the result is a serious condition that is very difficult to treat. Scientists reported that they have discovered an important clue as to why cancer cells spread. It has something to do with their adhesion properties. Certain molecular interactions between cells and the scaffolding that holds them in place cause them to become unstuck at the original tumor site, they become dislodged, move on and then reattach themselves at a new site.

Topoisomerase II enzymes are capable of transferring one DNA double helix through a transient break in another DNA double helix. It plays role in DNA metabolic processes where they involve in DNA replication, transcription, chromosome condensation and de-condensation, recombination etc [5,6].

It is also the cellular target for so many widely used anticancer agents currently in clinical use, such as anthracyclines, epipodophyllotoxins. They stimulate the topoisomerase II cleavable complex, which is a transient configuration of topoisomerase II on DNA in which topoisomerase II is covalently attached to DNA [5,6].

Topoisomerase II makes double strand breaks and passes double strand DNA through the nick to allow relaxation of over coiled DNA [7].

Candidates from amino-sulfonamide for designing novel anticancer agents emerge with promising effects. The derivatives with aromatic ring and aliphatic chain present in the nucleus have been shown to be critical for anticancer activity. D. Guianvarch and co-workers confirmed by the preliminary pharmacological *in-vivo* models that sulphonamides emerge with a novel anticancer series. [8]

On studying the above mentioned literature about the anticancer behavior of sulfonamide promoted us to theoretically develop moieties by the means of *in-silico* resources.

Rational drug design helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compound, out of them one method is the docking of the drug molecule with the receptor. The therapeutic action of the clinical drug will be effective when the biochemical pathway of the enzyme can be exploited. [9,10,11,12]

Docking procedures allows virtually screening a database of compounds and predict the strongest binder based on various scoring functions. It gives way in which two molecules such as drugs and an enzyme receptor fit together and dock to each other well. [9,10,11,12]

Molecular docking techniques are used in modern drug design to help understand drug–receptor interaction. It has been shown in the literature that these computational procedures can strongly support and help the design of new, more potent drugs by revealing the mechanism of drug–receptor interaction. [9,10,11,12]

2. Materials and Method

2.1. Database and Tools

For carrying out the study, National Center for Biotechnology Information's (NCBI.) website and Protein Data Bank's (PDB) website were used as receptor sources. For designing and optimizing the geometry of the derivatives, Chemdraw Ultra 7.0 [13] was used. For docking studies of derivatives, AutoDock Vina [10,11,12] molecular docking software has been employed and for descriptor calculations PaDEL software has been used [14].

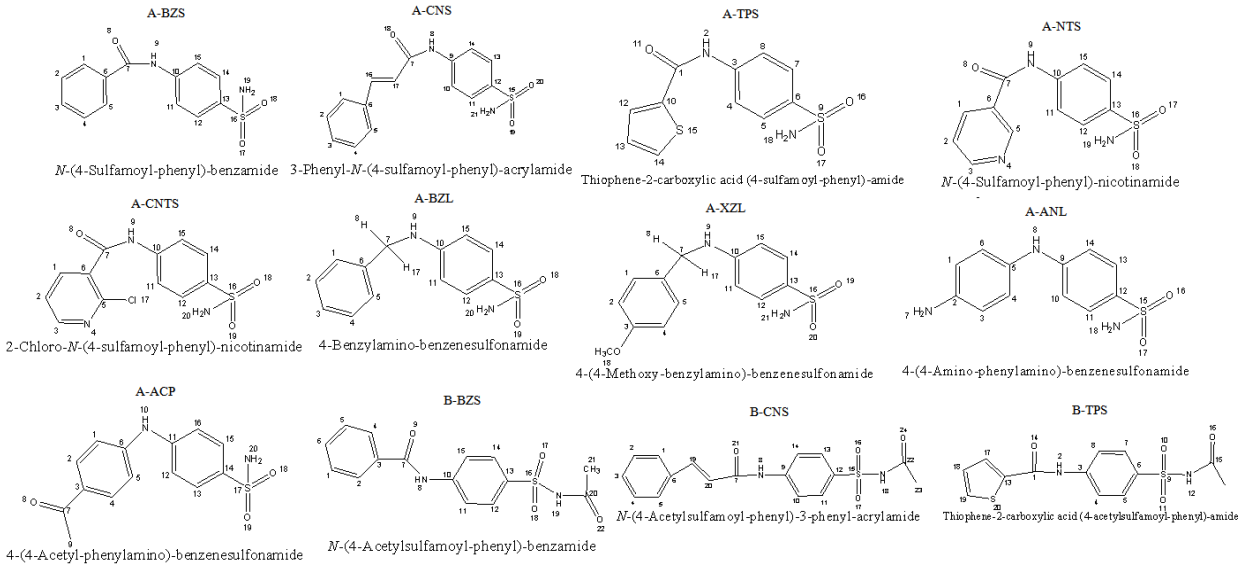

Figure 1. Chemical structures of the designed derivatives

2.2. Molecule Designing and Optimization

The chemical structures of the derivatives (Figure 1) were drawn using ChemDraw Ultra 7.0 and energy minimization of derivatives was achieved with Chem3D Pro of ChemOffice suit for taking energy of each molecule up to its lowest energy state (highest stability). 3D structure of etoposide (CID: 36462) was retrieved from PubChem compound database at NCBI.

2.3.Docking Studies

The docking analysis of hybrid derivatives with Human topoisomerase II was carried out by AutoDock Vina. The incorporation of various algorithms makes it a very good tool, as docking search algorithm is based on evolutionary algorithm. It is an iterative optimization technique inspired by Darwinian evolution theory. Evolutionary algorithm consists of population of individuals, which is exposed to random variation by means of variation operators, like mutation and recombination.

The designed sulfonamide derivatives were docked into binding site of human topoisomerase II receptor. For this study, X-ray crystal structure of human topoisomerase II receptor was retrieved from protein data bank with PDB ID 4FM9.

3. Results and Discussion

3.1. Docking Results

3.1.1. Binding Site analysis

The experimental analysis of binding site shows that ARG 727, ARG 672, ARG 673, ARG 929, GLY 1007, GLY 852 and GLY 777could be the catalytic site residue present in the structure of human topoisomerase II receptor.

3.1.2. Docking Studies of Sulfonamide Derivatives with Human Topoisomerase II Receptor

The protein-ligand interaction affinity of designed inhibitors was given by AutoDock Vina for best pose of novel inhibitors. The best pose ligand-protein interaction affinity of 12 molecules was found to be as -8 Kcal/mol, -7.5 Kcal/mol, -6.8 Kcal/mol, -7.5 Kcal/mol, -7.1 Kcal/mol, -7.2 Kcal/mol, -6.8 Kcal/mol, -7.2 Kcal/mol, -8.1 Kcal/mol, -8 Kcal/mol, -8.6 Kcal/mol and -7 Kcal/mol

respectively. Here, negative values for interaction energy would reflect the positive docking approach. Number of hydrogen bonds and other binding details are given in Table 1 and docking images are given in Figure 2.

Table 1. Docking results of sulfonamide derivatives and etoposide (CID: 36462)

Ligand	Receptor	Affinity Kcal/mol	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
A-BZS	4FM9	-8	02	O	08	Acceptor	SER 717	O	2327	Both
				O	17	Acceptor	LYS 676	N	1991	Donor
A-CNS		-7.5	03	O	08	Acceptor	ARG 727	N	2402	Donor
				O	20	Acceptor	ARG 672	N	1950	Donor
				O	19	Acceptor	ARG 673	N	1962	Donor
A-TPS		-6.8	05	O	08	Acceptor	ARG 727	N	2401	Donor
				O	08	Acceptor	ARG 727	N	2402	Donor
				N	18	Donor	GLY 1007	O	4634	Acceptor
				O	17	Acceptor	ARG 672	N	1950	Donor
				O	16	Acceptor	ARG 673	N	1962	Donor
A-NTS		-7.5	06	N	14	Donor	ASN 851	O	3391	Acceptor
				N	14	Donor	GLY 852	O	3399	Acceptor
				O	18	Acceptor	ARG 929	N	3999	Donor
				N	20	Donor	GLY 777	O	2793	Acceptor
				O	08	Acceptor	ASN 779	N	2807	Donor
				N	06	Donor	ASN 770	O	2737	Acceptor
A-CNTS		-7.1	06	N	21	Donor	GLU 854	O	3408	Acceptor
				O	20	Acceptor	GLN 726	N	2391	Donor
				O	20	Acceptor	LYS 723	N	2371	Donor
				N	06	Donor	ASN 770	O	2740	Acceptor
				N	06	Donor	GLN 773	O	2762	Acceptor
				O	08	Acceptor	GLN 773	N	2763	Donor
A-BZL		-7.2	03	O	17	Acceptor	ARG 727	N	2401	Donor
				O	17	Acceptor	ARG 727	N	2402	Donor
				N	18	Donor	GLU 839	O	3287	Acceptor
A-XZL		-6.8	04	N	20	Donor	GLY 1007	O	4634	Acceptor
				N	20	Donor	GLU 712	O	2289	Acceptor
				O	18	Acceptor	ARG 673	N	1962	Donor
				O	19	Acceptor	ARG 672	N	1950	Donor
A-ANL		-7.2	03	N	14	Donor	ILE 715	O	2310	Acceptor
				N	14	Donor	LEU 722	O	2358	Acceptor
				O	19	Acceptor	ARG 672	N	1950	Donor
A-ACP		-8.1	02	N	20	Donor	GLU 839	O	3287	Acceptor
				O	19	Acceptor	ARG 727	N	2401	Donor
B-BZS		-8	03	O	22	Acceptor	ARG 929	N	3999	Donor
				O	08	Acceptor	GLN 726	N	2391	Donor
				N	06	Donor	ASN 779	O	2806	Acceptor
B-CNS		-8.6	04	N	06	Donor	GLY 1007	O	4634	Acceptor
				O	24	Acceptor	ARG 727	N	2401	Donor
				O	24	Acceptor	ARG 727	N	2402	Donor
				O	08	Acceptor	ARG 673	N	1962	Donor
B-TPS		-7	04	O	17	Acceptor	LYS 676	N	1991	Donor
				O	17	Acceptor	ARG 673	N	1962	Donor
				O	16	Acceptor	ARG 673	N	1962	Donor
				O	08	Acceptor	ARG 727	N	2402	Donor
CID_36462		-9.7	07	O	29	Both	ARG 727	N	2401	Donor
				O	29	Both	PRO 838	O	3280	Acceptor
				O	29	Both	GLU 837	O	3276	Acceptor
				O	31	Both	GLU 837	O	3276	Acceptor
				O	02	Acceptor	GLU 837	O	3271	Acceptor
				O	43	Acceptor	GLN 544	N	868	Donor
				O	41	Both	GLN 544	N	868	Donor

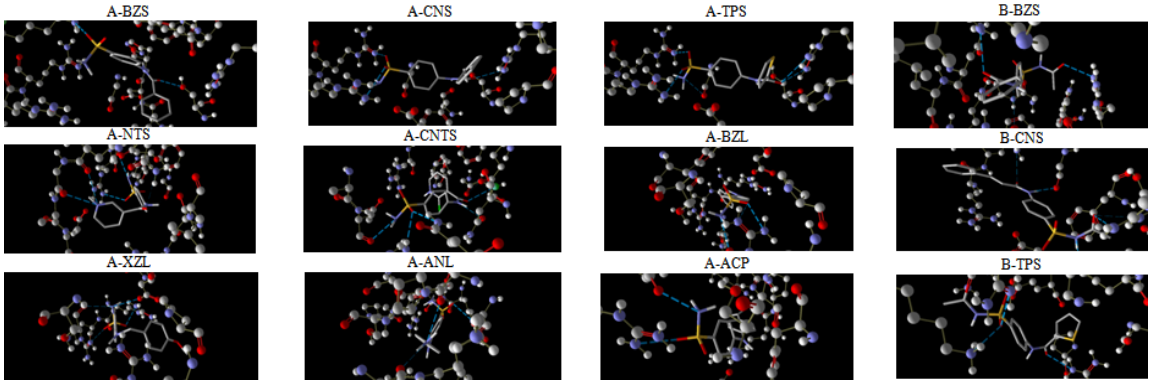

Figure 2. Docked photographs of sulfonamide derivatives with human topoisomerase II receptor

3.2. Comparison of Docking Results with Pre-existing (Standard) Human Topoisomerase II Inhibitor- Etoposide (CID: 36462)

On docking studies and docking analysis of etoposide with the human topoisomerase II, interacting residues (amino acids) are found as ARG 727, GLU 837, GLN 544 (Figure 3).

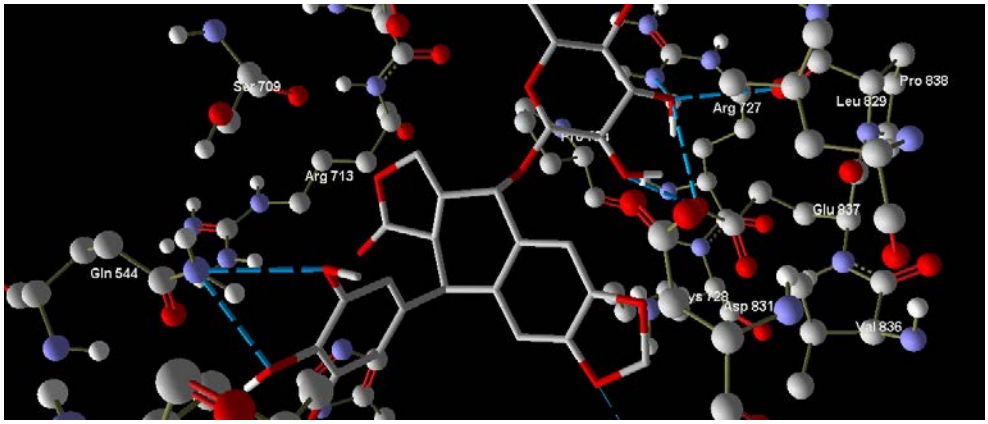

Figure 3. Docking photograph of etoposide with the human topoisomerase II showing interacting aminoacids

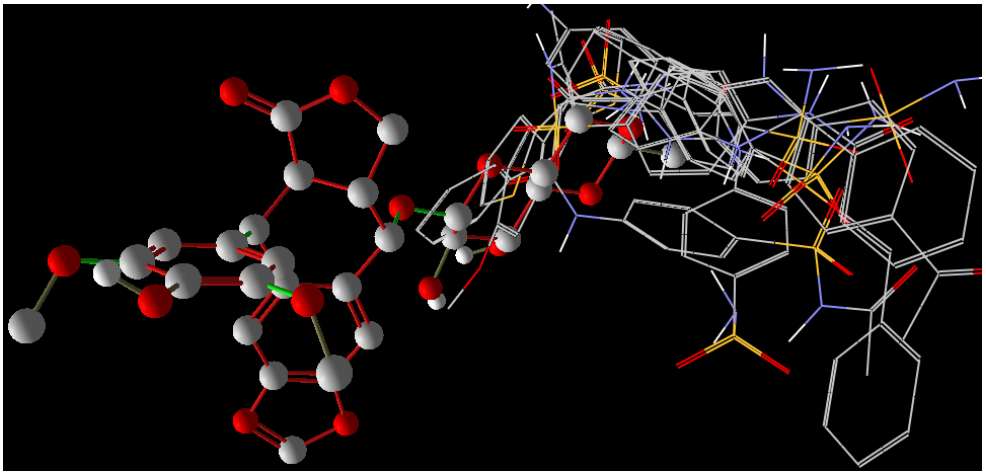

Figure 4. Superimposed (intercalated) docking poses of designed sulfonamide derivatives (showing with wireframe model) with the pre-existing ligand etoposide (showing with ball and stick model)

Table 2. Descriptor studies of the designed sulfonamide derivatives

Compound S. No.	AlogP	Eccentric Connectivity Index	Lipo-Affinity Index
A-BZS	-4.1763	341	0
A-CNS	-4.2087	445	0
A-TPS	-3.5416	298	-0.68119
A-NTS	-4.2531	341	0
A-CNTS	-3.5988	360	0.147473
A-BZL	-3.8366	326	0.338429
A-XZL	-3.6508	418	1.016806
A-ANL	-5.192	320	0
A-ACP	-4.07	387	0.653385
B-BZS	-3.9882	455	0.498572
B-CNS	-4.0206	574	0.498234
B-TPS	-3.3535	405	-0.20488

On docking analysis, the docked poses of all designed sulfonamide derivatives superimposes the etoposide, a pre-existing human topoisomerase II inhibitor which can be clearly seen in Figure4 , and the docking analysis shows that it nicely docked with protein in the catalytic domain for the human topoisomerase II, so, there are possibilities of making it with anticancer profile.

3.3. Descriptor Studies

All the 12 designed sulfonamide derivatives have been gone through some descriptor calculation, which are listed in Table 2.

4. Conclusion

Docking study of designed sulfonamide derivatives proved them potential human topoisomerase II inhibitors. Although a systemic biochemical study is necessary to confirm the findings. When designed sulfonamide derivatives were docked with human topoisomerase II then few among 12 designed molecules were found with approximately same as compared to the etoposide, so it could be concluded that these derivatives may be proved the good inhibitors of human topoisomerase II for the

anticancer activity. On comparing the chemical structure of designed derivatives with etoposide, a pre-existing human topoisomerase II inhibitor; there is no structural similarity found, so it is concluded that this system may proved a novel class of this category.

References

[1] Available: http://en.wikipedia.org/wiki/cancer. [Accessed March, 22, 2014]

[2] Anand P., et.al. "Cancer is a preventable disease that requires major lifestyle changes". *Pharm. Res.*, 25 (9), 2097-2016, 2008.

[3] Jemal A., et.al. "Global cancer statistics". *A cancer journal for clinicians*, 61 (2), 69-90, 2011.

[4] Hanahan et.al. "The hallmarks of cancer". *Cell*, 100 (1), 57-70, 2000.

[5] Liu L.F., "DNA topoisomerase poison as antitumor agents". *Annu. Rev. Biochem*, 58, 351-375, 1989.

[6] Thakur D.S., "Topoisomerase II inhibitors in cancer treatment". *International journal of pharmaceutical sciences and nanotechnology*, 3 (4), 1173-1181, 2011.

[7] Kellner U., et.al. "Culprit and victim-DNA topoisomerase II". *Lancet Oncol.* 3, 235-243, 2002.

[8] Guianvarch D., et.al. "Synthesis and biological activity of sulfonamide derivatives of epipodophyllotoxin". *J. Med. Chem.* 47 (9), 2365-2374, 2004.

[9] Siva Kumar R., Nafeez Basha S.K., Kumarnallasivan P., Vijaianand P.R., Pradeepchandran R., "A computational design and docking studies on Escherichia coli b-Ketoacyl-Acyl carrier protein synthese III using auto dock", *J Pharm Res*, 3 (7), 1460-1462, 2010.

[10] Ajeet, "In silico designing and characterization of Amiloride derivatives as ion channel modulator", *Med Chem Res*, 22 (2), 1004-1010, 2013.

[11] Ajeet, "Trans-disciplinary receptor binding of acyclovir to human phenylalanine hydroxylase: docking approach", *International Journal of Pharmacy and Pharmaceutical Sciences*, 4 (suppl 2), 182-184, 2012.

[12] Ajeet, Tripathi L., Kumar P., "Designing of Novel 6 (H)-1,3,4-Thiadiazine Derivatives as MMP12 Inhibitors: A MLR and Docking Approach", *American Journal of Pharmacological Sciences*,1 (2), 29-34, 2013.

[13] Mills N., "ChemDraw Ultra 10.0.", *J. Am. Chem. Soc.*, 128 (41), 13649-13650, 2006.

[14] Yap, C.W., "PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints," *J. Comput. Chem.* 32 (7), 1466-1474, 2011.