

Biological Activity and Molecular Docking Studies of Sulfasalazine

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ABSTRACT: Sulfasalazine (SSZ) is very effective anti-arthritis drug. Docking used for virtual screening for the prediction of the strongest binders based on various scoring functions. Docking studies are carried out on sulfasalazine for better activity which is important for the development of a new class of inhibitors. Protein-ligand interaction plays an important role in structural based drugs design. In our research we have selected different receptor which shows anti-HIV-1 activity. The receptors were docked with sulfasalazine and the energy value obtained using 'HEX' software. Our study reveals that the minimum energy values observed with the 13GS and energy value is -303.7. The title compound is also studied to determine the probabilities of this molecule being active or inactive against certain standard/selected activities using 'PASS' software. The analysis of which predicts the activity of SSZ against embryotoxic, carcinogenic etc.

KEYWORDS: Sulfasalazine, Docking, Protein-ligand interaction, Interaction energy, HEX, Biological activity, PASS

I. INTRODUCTION

Sulfonamides are the first chemotherapeutic agents which were employed systematically for the prevention and cure of bacterial infections in human beings [1-4]. Sulfonamides is also the very first antimicrobial agent having wide spread applications as anti bacterial, anti fungal and anti viral drugs. Sulfasalazine is mainly used for the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease [5]. It is also effective in several types of arthritis, particularly rheumatoid arthritis. Computational Biology and bioinformatics are useful for the drugs recovery process which reduces the cost of drugs. Rational Drug Design is the inventive process of finding new medications based on the knowledge of the biological target. Molecular docking predicts the strength of the binding, the energy of the ligand-receptors complex.

The biological potential of compound includes all activities, which can be discovered under some specific experimental conditions. We call such biological potential the biological activity spectrum. Biological activity spectrum of compound can be predicted on the basis of structure-activity relationship found by the known data from the training set. Based on the analysis of large training set consisting of tens of thousands of the known biological active compounds, computer program PASS [6-7] provides the means to evaluate any new compound in huge chemical-pharmacological space. 'PASS' (Prediction of Activity Spectra for Substances), predicts simultaneously several hundreds of biological activities (pharmacological main and side effects, mechanisms of action, mutagenicity, tetragenicity and embryotoxicity) with mean accuracy of prediction about 85% on the basis of the compound's structural formula. So that we can use PASS for the prediction of the biological activity spectrum for existing compounds and compounds, which are only planned to synthesize.

The title compound sulfasalazine (2-Hydroxy-5-[4-(1H-pyridin-2-ylidenesulfamoyl)-phenylazo]-benzoic acid) is procured from Sigma-Aldrich Company and docked with different sulfonamide receptors like 13GS, 2Y5S, 1OKL, 4J7X, 1AZM, 4ITO, 4LHI and also the biological activity like uric acid excretion stimulant, endothelin converting enzyme inhibitor, endothelin receptor antagonist, Beta adrenoreceptor agonist, carcinogenic, embryotoxic, uric acid excretion stimulant of title compound are reported in this paper.

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II. METHODOLOGY

Computer Aided Drug Design (CADD) is a specialized discipline for the study of simulation of ligand- receptor interactions and is strongly dependent on bioinformatics tools, applications and databases.

The structure of sulfasalazine and sulfonamide receptors were referred from different journals and retrieved from PDB data bank [8]. Sulfasalazine was procured from Sigma-Aldrich Company and three dimensional structure has been investigated by X-ray diffraction. The corresponding cif file has been converted into PDB file using OBGUI software. This PDB structure was used for the docking studies using Hex software [9]. The receptor proved to be the best inhibitor of the ligand when ligand-receptor docks each other well. The title compound was docked with the different receptors.

II.1. Molecular Docking studies

The chemical structure of ligand like sulfasalazine is shown in Fig. 1. The sulfasalazine (2-Hydroxy-5-[4-(1H-pyridin-2-ylidene-sulfamoyl)-phenylazo]-benzoic acid) is docked with few selected receptors. The parameters used for the docking process were

- Correlation type - Shape only
- FFT Mode - 3D fast lite
- Grid Dimension - 0.6
- Receptor range - 180
- Ligand range - 180
- Twist range - 360
- Distance Range - 40

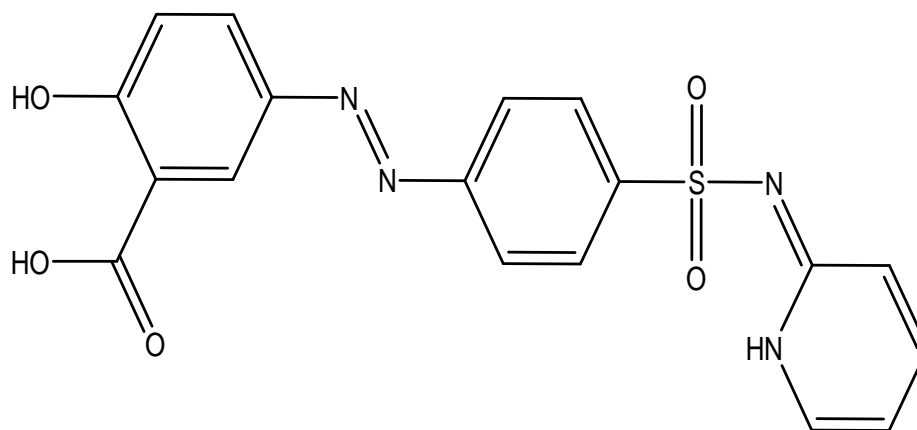


Fig. 1. Chemical structure of 2-Hydroxy-5-[4-(1H-pyridin-2-ylidene-sulfamoyl)-phenylazo]-benzoic acid

II.2. PASS activity

To correlate the structure-function relationship, the compound has been tested for its biological response. Number of biological test can be carried out to test the biological response. For PASS software, one has to prepare the file in the 'sdf' format and biological activity can be predicted as probabilities of the molecule being active or inactive against certain standard/selected activities.

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III. RESULTS AND DISCUSSION

The docking result gives the interaction energy between ligand and receptor i.e. energy of ligand within the binding site. The docking results are tabulated in Table 1.

Table 1. Docking results of Sulfasalazine with different receptors

2-Hydroxy-5-[4-(1H-pyridin-2-ylidenesulfamoyl)-phenylazo]-benzoic acid							
	Receptors						
	13GS	2Y5S	1OKL	4J7X	1AZM	4ITO	4LHI
E-Value	-303.7	-285.1	-259.0	-264.9	-248.3	-266.9	-280.17

From the table it can be clearly seen that the best ligand-receptor fitting is archived with 13GS receptor having minimum energy value -303.7. The E-values for different receptors are graphically represented in Fig.2.

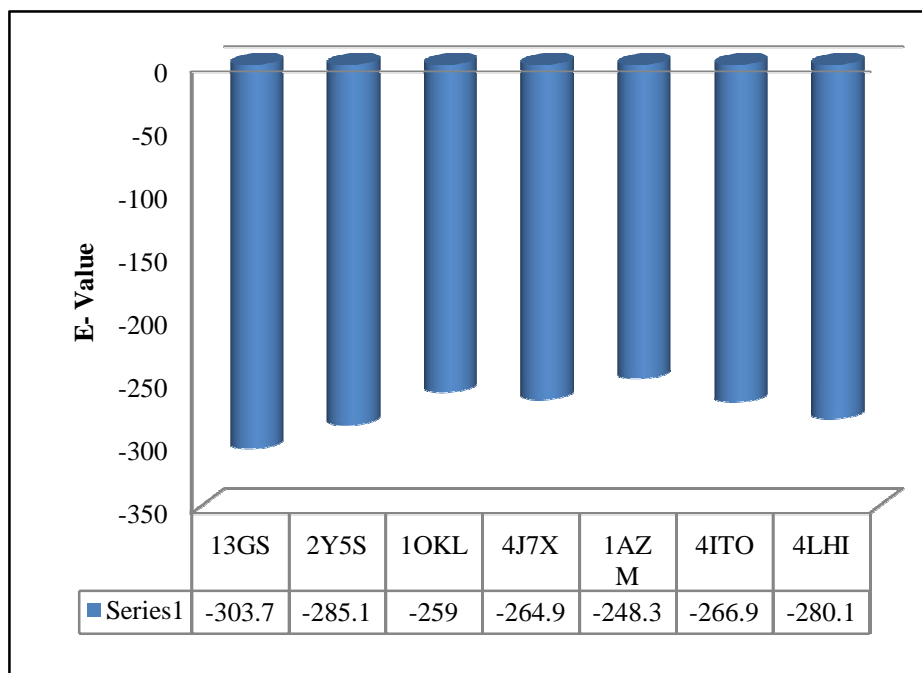


Fig. 2. Graphical representation of docking results

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The 13GS receptor gives the minimum value which indicates that the stability of the structure is more for 13GS receptor compared to other receptors. The ligand-receptor interaction for 13GS receptor is shown in Fig. 3.

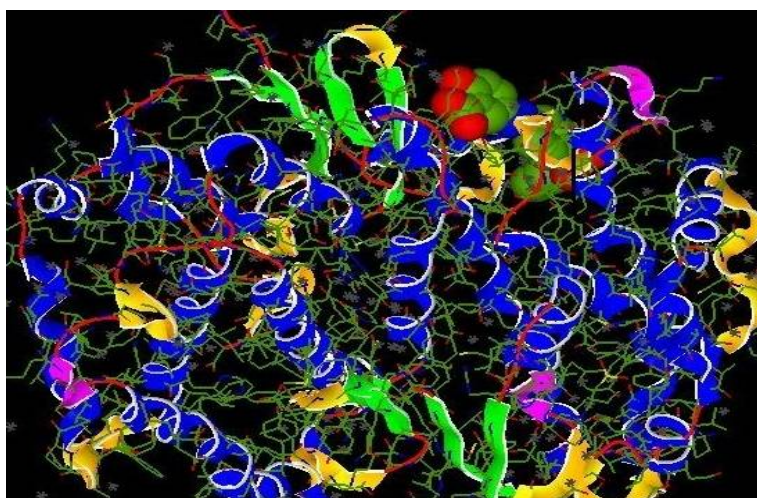


Fig. 3. Interaction of Sulfasalazine with 13GS receptor

IV. BIOLOGICAL ACTIVITY

The title compound is studied to determine the probabilities of this molecule being active or inactive against certain standard/selected activities. A software PASS is used to carry out this test. The probabilities of a given molecules to be active or inactive on a scale of 0 to 1 are generally referred to as Pa (active) to Pi (inactive). This test gives us predictions about possible drug-likeness of a given molecule. Pa and Pi are the calculated probabilities for presence and absence of each activity. PASS gives us an opportunity to evaluate the contribution of each atom of the structure to the estimation of biological activity. The activity has been carried out for the title compound. It is found that the title compound has 10 possible activities out of 51 at Pa > 0.100. Among them, all important activities are listed below in Table 2.

Table 2. Biological activity of sulfasalazine

	Sr. no.	Pa	Pi	Activity
Possible Pharmacological Effects	1	0.202	0.140	Uric acid excretion stimulant
Possible Molecular mechanisms	1	0.135	0.112	Endothelin converting enzyme inhibitor
	2	0.097	0.024	Endothelin receptor antagonist
	3	0.045	0.037	Beta adrenoreceptor agonist
Possible side effects and Toxicity	1	0.372	0.049	Carcinogenic
	2	0.346	0.096	Embryotoxic

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Short Detail of Activity

Uric acid excretion stimulant: Substance that increases the urinary excretion of uric acid, thereby reducing the concentration of uric acid in the blood.

Endothelin converting enzyme inhibitor: A substance that binds to an enzyme and decreases the enzyme's activity.

Endothelin receptor antagonist: Substance that bind to the Endothelin receptor and prevent its stimulation.

Beta adrenoreceptor agonist: A drug that has affinity for Beta adrenoreceptor and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances, thus triggering a biochemical response. It is a substance that creates the same bodily responses, but does not bind to Beta adrenoreceptor.

Carcinogenic: The term carcinogen refers to any substance, radionuclide or radiation that is an agent directly involved in the promotion of cancer or in the increase of its propagation. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes.

Embryotoxic: Any toxicity that affects an embryo is known as carcinogenic. It may result in death or abnormal development of the embryo.

V. CONCLUSION

We can conclude that the sulfasalazine having minimum interaction energy with 13GS receptors having high energy values -303.74, which means that it was more compatible with receptor 13GS compare to other analogous. It has been also observed that sulfasalazine may possess several pharmacological activities as like reducing the concentration of uric acid in the blood, carcinogenic, embryotoxic etc.

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