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Molecular Docking and Virtual Screening of Cefazolin as a Antibiotic Drug

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ABSTRACT

In this research paper Schrodinger software based pharmacophore features of cefazolin mapping and distance involved between 1,3,4- thiadiazole ring and other pharmacophore features of the compound is elaborated. The structure of Cefazolin is observed on Zincpharmer online server to reveal the various intermolecular features for molecular recognition, investigation of binding site (ligand-receptor complexes), characterization of unknown binding sites etc., Computer Aided Drug Design is successfully identified the flexibility of binding sites of target molecule with small ligand based on lock and key model. *In Silico* evaluation based on SBDD and MD is very useful tool to identify the pharmacofeatures and pharmacological significance of molecules before they synthesized. In the published research papers revealed on synthesized derivatives of 1, 3,4-thidiazole and their biological evaluation *in vitro* against NCIM provided Gram positive bacterial strains *Staphallococcus aureus (Sa- 2178) Bacillus subtilis (Bs-2239) Gram negative bacterial strains Eschereschia coli (Ec-25744) Klibesiella aerogenus (Ka-2249).*

Keywords: Molecular Docking, Pharmacophore, Cefazolin, Computer Aided Drug Design

I. INTRODUCTION

A key challenge in the synthesis of bimolecular containing heterocyclic component targets continues to be the development of new pathways and improvement of existing pathways [1]. Docking studies by computer graphics is easiest route rather than mechanical model construction. Macromolecular modeling by docking studies provides most possible view of drug receptor interaction and has created a new rational approach to drug design where the structure of drug is designed based on its fit to three dimensional structures of receptor site rather than by analogy to other active structure or random leads. [2] It is also important to consider that structure based drug design (SBDD) directs the discovery of a drug lead, which is not a drug product but, specifically, a compound with at least micro molar affinity for a drug target [3,4].

1, 3, 4- thiadiazole core containing drugs are currently in the market: acetazolamide®) and methazolamide® are diuretics, acting through inhibition of carbonic anhydrase; their derivatives display additional activities, including anticonvulsant and selective cerebral vasodilation, as well as the anticipated inhibition of carbonic anhydrase, cefazolin sodium® (CFZL; 3) and cefazedon® (CFZD; 4)—first-generation cephalosporins and megazol® an antiparasitic drug. The structure of cefazolin also includes a heterocyclic thiol, 2-methyl-1, 3, 4-thiadiazole-5-thiol (MTD), and this compound can also inhibit the gamma-carboxylation of glutamate. [6-11].

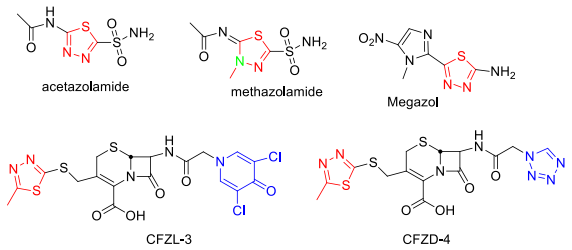

Figure 1. Structures of 1, 3, 4- thiadiazole core containing drugs available in the market

II. METHODS AND MATERIAL

Manual pharmacophore hypothesis generation module of Schrondinger maestro v9.6 was used for pharmacophore features mapping of the compounds along with location and calculation of distance between the pharmacophore features [12]. Computational docking methods, with empirical scoring functions are used to predict binding affinities and ligand orientations inside the binding sites of proteins. While the docking methods give the binding geometries; potential functions follow rules based on the binding affinity statistics. These rules are used to calculate the computer generated ligand orientations "scores" making use of the "pseudo-potentials" [13]. The macromolecule protein and ligand structures as rigid files are imported in the 3D space of the autodock software. Then, the energy scoring grid box was centered with 0.375 angstroms grid points spacing and size of the box was set to 126, 126 and 126 Å (x, y, and z) assigned with default atomic salvation parameters. The grid box was designed such that the whole macromolecule was surrounded by the three dimensional grid box centered. After the grid box fixation, all other required default parameters for grid are assigned and then the file output is saved as grid parameter file (.gpf)

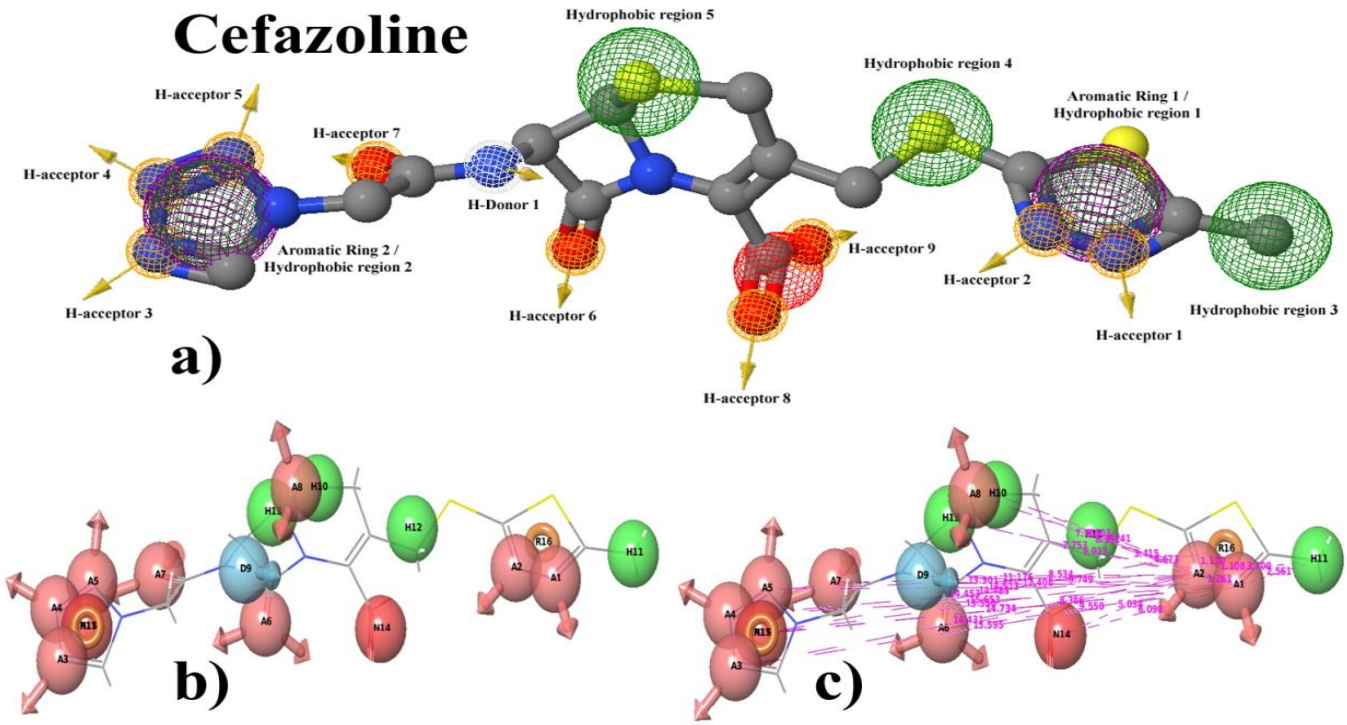

Figure 2 : Pharmacophore features of Cefazoline explained in 3D pharmacophore modeling shown in following images:

a) ZINCPharmer online server based pharmacophore features mapping showing location & direction of two aromatics rings; five hydrophobic regions; one hydrogen donor & nine hydrogen acceptors.

b) Schrodinger software based pharmacophore features mapping and

c) Distance involved between 1,3,4- thiadiazole ring and other pharmacophore features of the compound.

III. RESULTS AND DISCUSSION

Table 1 : XYZ co-ordinates and radius of each pharmacophore feature of Cefazoline

S.No	Site 1	Site 2	Distance in angstroms	Site 1	Site 2	Distance in angstroms
1.	A1	A2	1.261	A5	R16	14.187
2.	A1	A3	15.595	A5	R17	1.103
3.	A1	A4	15.653	A6	A7	3.986
4.	A1	A5	14.513	A6	A8	4.677
5.	A1	A6	9.55	A6	D9	3.77
6.	A1	A7	12.408	A6	H10	4.832
7.	A1	A8	8.392	A6	H11	11.844
8.	A1	D9	9.749	A6	H12	5.54
9.	A1	H10	7.741	A6	H13	3.364
10.	A1	H11	2.561	A6	N14	3.63
11.	A1	H12	4.673	A6	N15	6.847
12.	A1	H13	9.013	A6	R16	9.143
13.	A1	N14	6.098	A6	R17	6.847
14.	A1	N15	14.734	A7	A8	4.94
15.	A1	R16	1.108	A7	D9	3.086
16.	A1	R17	14.734	A7	H10	5.525
17.	A2	A3	14.431	A7	H11	14.826
18.	A2	A4	14.453	A7	H12	7.982
19.	A2	A5	13.301	A7	H13	3.835
20.	A2	A6	8.386	A7	N14	7.202
21.	A2	A7	11.176	A7	N15	3.285
22.	A2	A8	7.152	A7	R16	12.001
23.	A2	D9	8.534	A7	R17	3.285
24.	A2	H10	6.503	A8	D9	2.517
25.	A2	H11	3.7	A8	H10	0.678
26.	A2	H12	3.415	A8	H11	10.697
27.	A2	H13	7.753	A8	H12	3.919
28.	A2	N14	5.034	A8	H13	1.507
29.	A2	N15	13.55	A8	N14	5.158
30.	A2	R16	1.11	A8	N15	7.345
31.	A2	R17	13.55	A8	R16	7.876

32.	A3	A4	1.288	A8	R17	7.345
33.	A3	A5	2.102	D9	H10	3.006
34.	A3	A6	7.61	D9	H11	12.223
35.	A3	A7	4.236	D9	H12	5.498
36.	A3	A8	8.407	D9	H13	2.113
37.	A3	D9	6.118	D9	N14	5.472
38.	A3	H10	9.009	D9	N15	5.127
39.	A3	H11	18.125	D9	R16	9.424
40.	A3	H12	11.541	D9	R17	5.127
41.	A3	H13	7.698	H10	H11	10.028
42.	A3	N14	10.665	H10	H12	3.288
43.	A3	N15	1.112	H10	H13	1.904
44.	A3	R16	15.385	H10	N14	4.82
45.	A3	R17	1.112	H10	N15	7.961
46.	A4	A5	1.287	H10	R16	7.211
47.	A4	A6	7.524	H10	R17	7.961
48.	A4	A7	3.771	H11	H12	6.937
49.	A4	A8	8.04	H11	H13	11.328
50.	A4	D9	5.966	H11	N14	8.32
51.	A4	H10	8.679	H11	N15	17.25
52.	A4	H11	18.15	H11	R16	2.853
53.	A4	H12	11.4	H11	R17	17.25
54.	A4	H13	7.307	H12	H13	4.391
55.	A4	N14	10.697	H12	N14	3.128
56.	A4	N15	1.093	H12	N15	10.585
57.	A4	R16	15.357	H12	R16	4.084
58.	A4	R17	1.093	H12	R17	10.585
59.	A5	A6	6.621	H13	N14	4.704
60.	A5	A7	2.75	H13	N15	6.657
61.	A5	A8	6.77	H13	R16	8.475
62.	A5	D9	4.777	H13	R17	6.657
63.	A5	H10	7.415	N14	N15	9.869
64.	A5	H11	16.993	N14	R16	5.759
65.	A5	H12	10.205	N14	R17	9.869
66.	A5	H13	6.078	N15	R16	14.483
67.	A5	N14	9.681	N15	R17	0
68.	A5	N15	1.103	R16	R17	14.483

The data obtained during virtual screening of cefazoline compound is useful to identify hydrophobic surface regions of a protein structure as possible sites for intra- and intermolecular

recognition, e.g. for the association of peptide fragments during protein folding for ligand (substrate, effectors, drug) binding and for protein aggregation[14-18]. The contribution of the hydrophobic effect to globular protein stability has been estimated empirically both by measuring the thermodynamics of transfer of model compounds (e.g. blocked amino acids, cyclic peptides...) from organic solvents to water and by site directed mutagenesis studies on proteins. The number arrived at is usually given as a function of the change in the solvent accessible non-polar surface area upon going from the unfolded to the folded state [19-22]. In silico study of synthesized derivatives 1, 3,4-thidiazole sucessfully docked inside the active site of Topoisomerase IV (PDB ID: 3FV5) domain for antibacterial activity with a binding energy 4.40 to -6.84 Kcal/mole[23].

IV. CONCLUSION

The molecular docking studies help to study the detailed molecular basis of interactions and to estimate the binding affinity of the present studied FDA approved drug Cefazoline.Its important for the analysis of chemical features of designed molecule and its bioisostericity related with target molecule. Computer aided drug designing, in silco activity of planned molecule and virtual screening of molecules help to solve all future problems of synthetic chemist.

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