Original Article

DFT and Molecular Docking Studies on Biological Active Acridines: the Interaction with Bovine Serum Albumin

Ali Mohammad Amani[1,2,3 *], Saeed Gholamzadeh[4], Mohammad Zarenezhad[4], Abdorrasoul Malekpour[4], Ehsan Javidnezhad[4]

[1]Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Medical Nanotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Chemistry Shiraz University of Technology Shiraz, Iran
[4]Legal Medicine Research Center, Legal Medicine Organization of Iran, Tehran, Iran

Use your device to scan and read the article online

*Corresponding author:
Ali Mohammad Amani
Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
amani_a@sums.ac.ir

Received: 27.11.2015
Revised: 05.12.2015
Accepted: 15.12.2015

Abstract

Acridine derivatives, especially 1,8-dioxo-9-aryl-decahydroacridine represent significant scaffolds in medicinal chemistry. Given the biological properties of such products which are used in drug development, they need to have appropriate carrier. Proteins are generally used as helpful tools in drug delivery. Consequently, molecular docking between these compounds and bovine serum albumin (BSA) has been taken into account. Furthermore, in order to achieve better results, the suggested compounds have been optimized using Gaussian 03 software.

Keywords: DFT study, Molecular Docking, Biological active, Anti-tumor properties, BSA

https://doi.org/10.18869/nrip.jamsat.1.2.78

Introduction

Heterocyclic compounds containing one or more nitrogen atoms in their ring have a great importance in pharmaceutical research (1). Acridine derivatives, especially 1,8-dioxo-9-aryl-decahydroacridine represent significant scaffolds in the medicinal chemistry (2, 3). In spite of their popular properties as effective treatments for cardiovascular diseases like angina pectoris(4)and hypertension(5), they have been used to synthesize labeled conjugates with medicinal drugs, peptides, proteins, and nucleic acids which exhibit antitumor and DNA-binding properties(6-8).

Therefore, the molecular docking study between these compounds and DNA and proteins is considered as useful. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure. Successful docking methods search high-dimensional spaces effectively and use a scoring function which correctly rank candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in

lead optimization. Computational chemistry can also be used to achieve better results (9).

Computational study

Density functional theory (DFT) calculations have been performed using the gaussian03 program (10). In these calculations, Becke's three-parameter hybrid exchange functional has been used and combined with the gradient-corrected correlation functional of Lee, Yang, and Parr at B3LYP level of theory and with 6-311g* standard basis set for all atoms(11, 12). The geometry optimization and vibrational frequencies of all chosen compounds have also been calculated.

Molecular docking investigation

Docking calculations between our synthesized compounds and Bovine serum albumin have been performed using Auto Dock 4.2.(13). Using the Gaussian 03 program, the structures of the prepared compounds have been optimized. BSA crystal structure (PDB ID: 3V03) has been obtained from Protein Data Bank (www.pdb.org)(14). The docking calculations have then been done using the lamarckian genetic algorithm (LGA) for ligand conformational searching(15). in order to recognize the binding sites in BSA, blind docking has been performed, with the grid size set to 110, 110, and 110 along the X-, Y- and Z-axes with 0.375 ˚ A grid spacing. The conformation with the lowest binding free energy was applied for further analysis.

Results and discussions

DFT studies

Using the density functional theory (DFT) at B3LYP level of theory with the 6-311G (d) basis set, geometries of all compounds were optimized in gas phase. Besides, through the calculation of their vibrational frequencies, the considered structures were all characterized. A comparison was made between the IR spectra of the calculated structures and the spectra of the synthesized compounds, confirming they were in a good agreement. Optimized structures of the compounds 1-13 are shown in Figure 1.

Furthermore, Figure 2 depicts a comparison between experimental FT-IR spectra and calculated FT-IR spectra for compound 1.

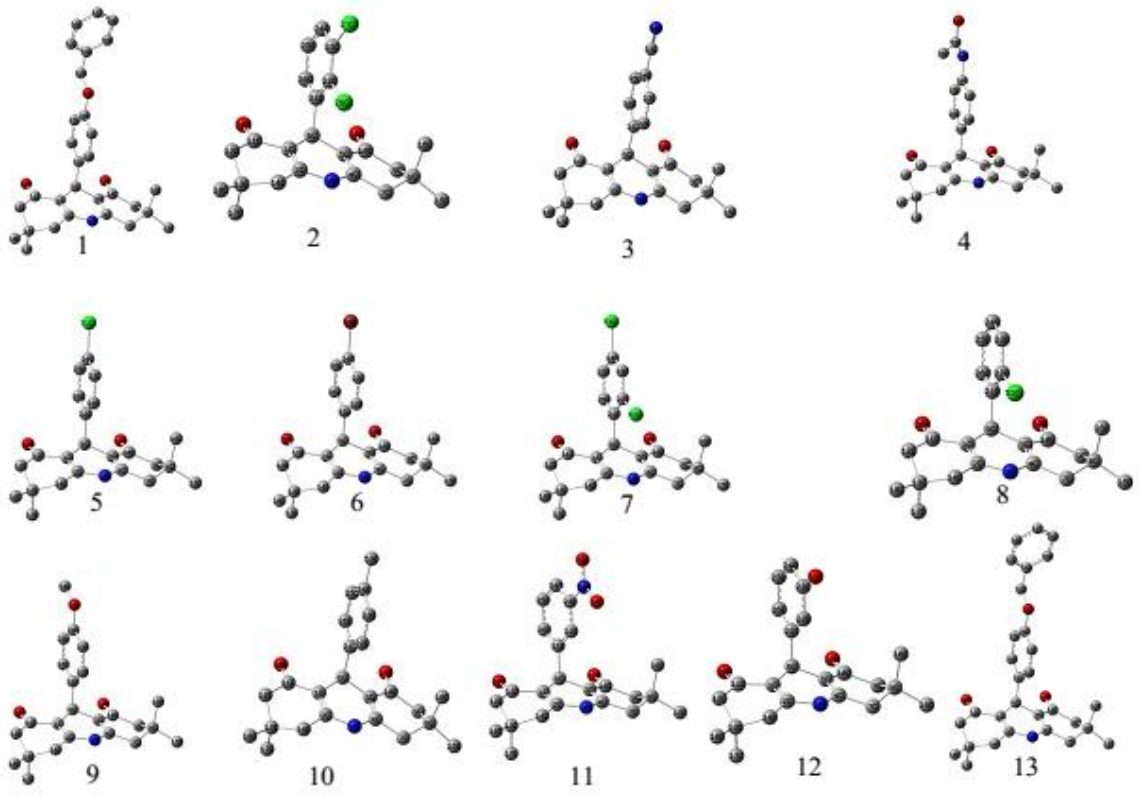


Figure 1. The optimized structure of compounds 1-13

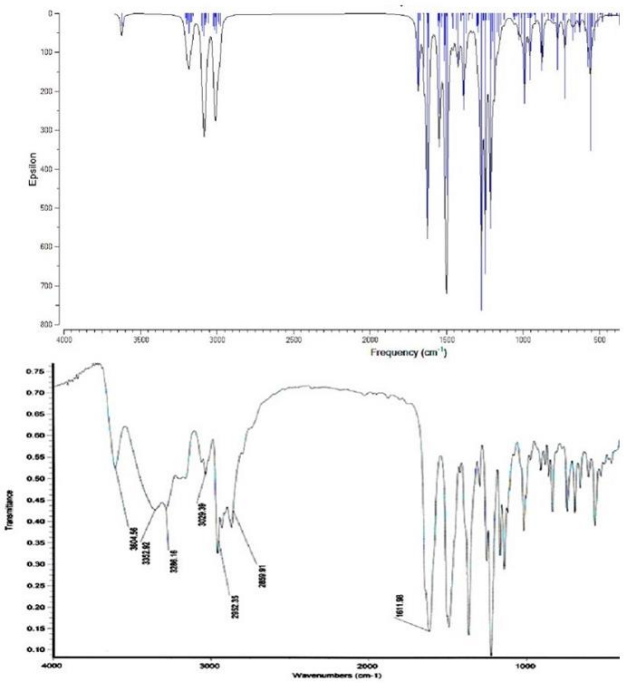


Figure 2. The comparison of the experiments and calculation of the F-TIR spectroscopic of compound 1

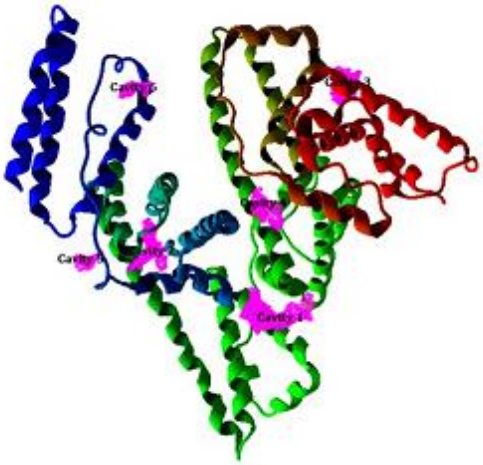
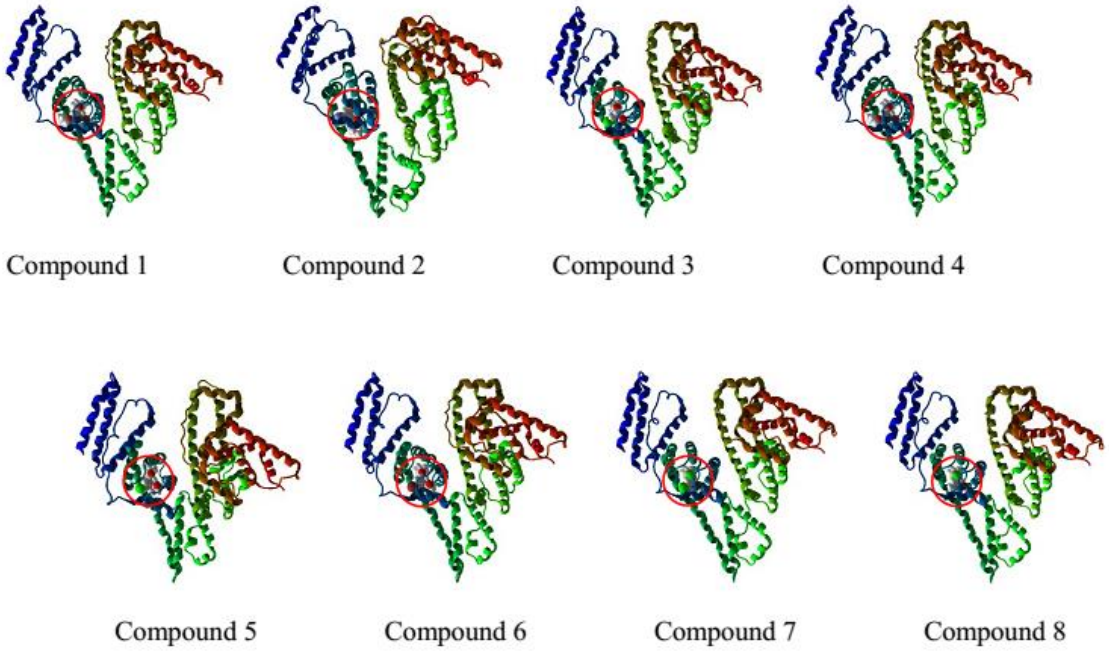


Figure 3. The structure of BSA and its main cavities



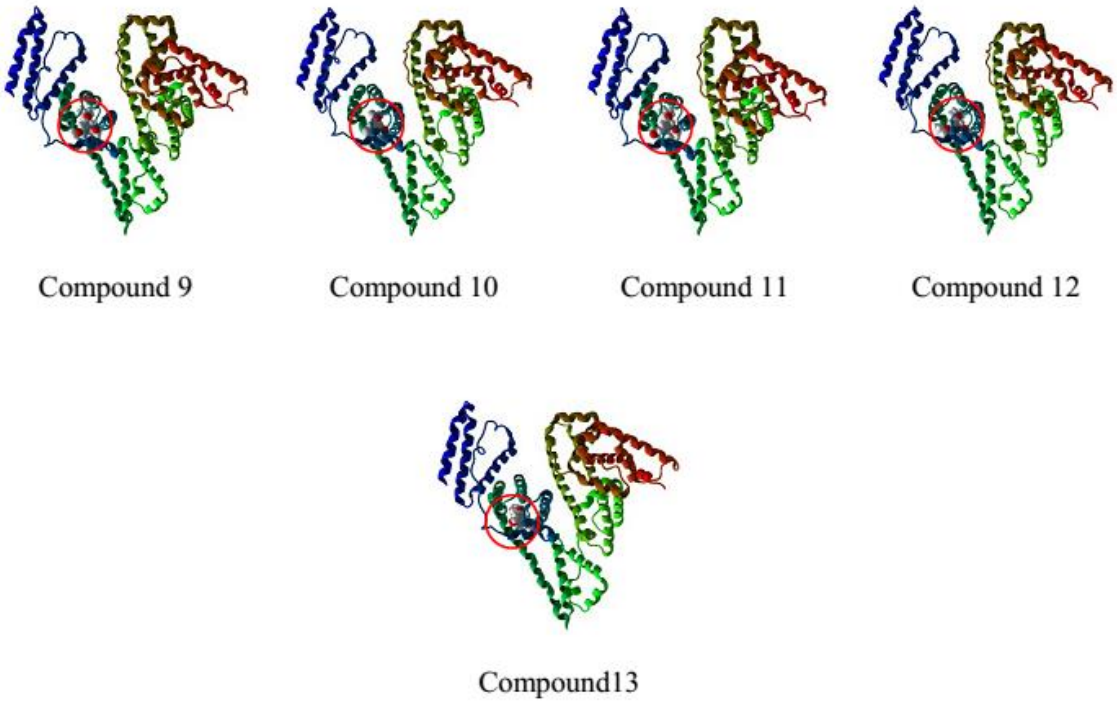


Figure 4. Compounds 1-13 docked in their binding sites

Tables 1-13. Best result in molecular docking for all cavities in BSA
Structure of all compounds

Compound 1	
Number of Cavity	Energies
Cavity 1	-137.219
Cavity 2	-150.796
Cavity 3	-114.425
Cavity 4	-126.88
Cavity 5	-121.324
Cavity 6	-113.828

Compound 2	
Number of Cavity	Energies
Cavity 1	-109.985
Cavity 2	-117.909
Cavity 3	-109.987
Cavity 4	-117.466
Cavity 5	-112.329
Cavity 6	-89.5295

Compound 3	
Number of Cavity	Energies
Cavity 1	-116.29
Cavity 2	-133.798
Cavity 3	-100.518
Cavity 4	-114.399
Cavity 5	-115.235
Cavity 6	-92.9927

Compound 4	
Number of Cavity	Energies
Cavity 1	-118.938
Cavity 2	-141.774
Cavity 3	-108.897
Cavity 4	-122.451
Cavity 5	-119.683
Cavity 6	-105.089

Compound 5	
Number of Cavity	Energies
Cavity 1	-116.361
Cavity 2	-128.294
Cavity 3	-100.248
Cavity 4	-109.988
Cavity 5	-111.989
Cavity 6	-86.7133

Compound 6	
Number of Cavity	Energies
Cavity 1	-115.672
Cavity 2	-127.896
Cavity 3	-99.0471
Cavity 4	-109.841
Cavity 5	-112.143
Cavity 6	-86.3881

Compound 7	
Number of Cavity	Energies
Cavity 1	-121.324
Cavity 2	-124.741
Cavity 3	-111.129
Cavity 4	-120.228
Cavity 5	-117.152
Cavity 6	-94.6177

Compound 8	
Number of Cavity	Energies
Cavity 1	-117.644
Cavity 2	-119.396
Cavity 3	-118.83
Cavity 4	-116.092
Cavity 5	-113.531
Cavity 6	-85.2499

Compound 9	
Number of Cavity	Energies
Cavity 1	-121.223
Cavity 2	-131.995
Cavity 3	-101.181
Cavity 4	-113.978
Cavity 5	-116.453
Cavity 6	-92.7991

Compound 10	
Number of Cavity	Energies
Cavity 1	-117.32
Cavity 2	-129.113
Cavity 3	-101.723
Cavity 4	-110.014
Cavity 5	-112.815
Cavity 6	-87.593

Compound 11	
Number of Cavity	Energies
Cavity 1	-110.505
Cavity 2	-131.468
Cavity 3	-107.152
Cavity 4	-117.085
Cavity 5	-116.54
Cavity 6	-93.885

Compound 12	
Number of Cavity	Energies
Cavity 1	-118.938
Cavity 2	-141.774
Cavity 3	-108.897
Cavity 4	-122.451
Cavity 5	-119.683
Cavity 6	-105.089

Compound 13	Number of Cavity	Cavity 1	Cavity 2	Cavity 3	Cavity 4	Cavity 5	Cavity 6
	Energies	-119.025	-128.447	-100.748	-109.451	-111.184	-87.20

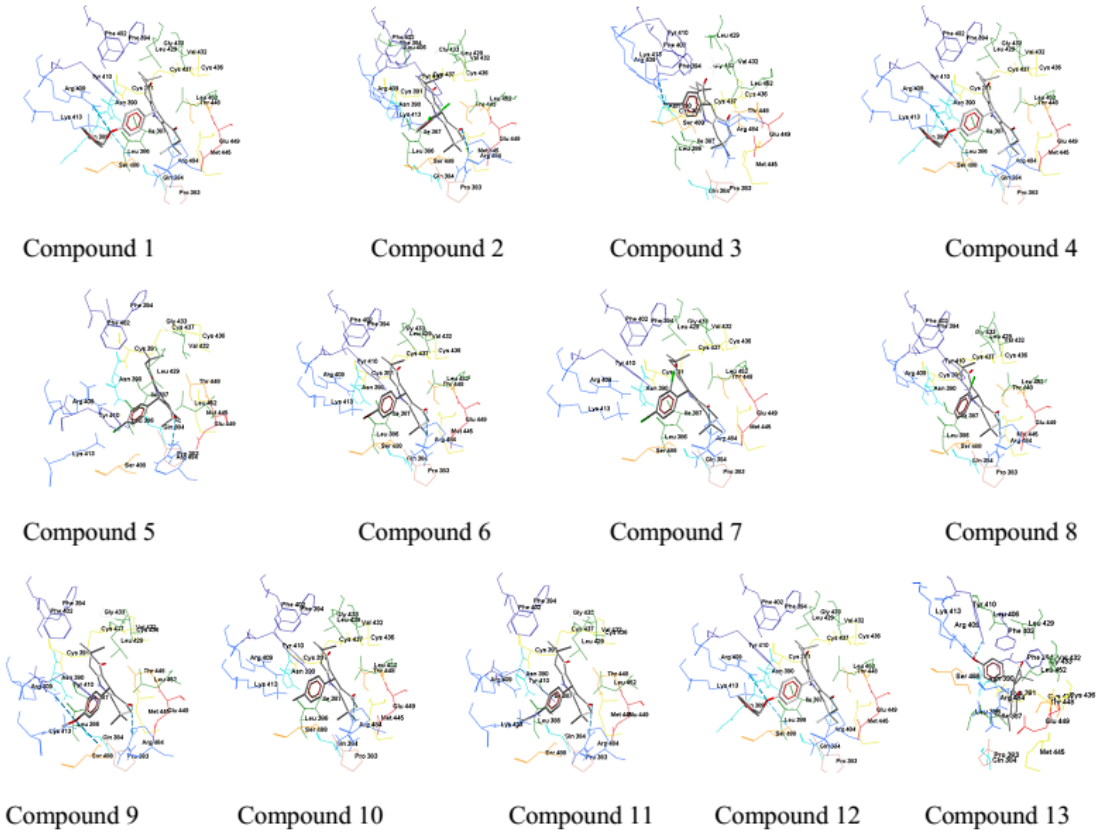


Figure 5. The hydrogen bond interactions and amino acid residues between compounds 1-13 and BSA

Molecular docking

First, for preliminary estimation of the possible connection sites, a series of seven cavities on the BSA structure have been characterized and shown in Figure 3. In fact, these cavities are the sites with spatial capability to involve ligands and permit them to penetrate. Molecular dockings of all compounds for all seven cavities have also been investigated.

According to the molecular docking results, the most powerful connection was suggested to be in cavity 2. The results for all compounds are listed in Tables 1-13 and Figure 4 showing the schematic view of the results in all compounds.

Therefore, in this context, further experiments have been carried out. Figure 5 demonstrates the interactions between all compounds and BSA. Besides, this figure represents the existing hydrogen bonds upon the reaction mentioned above. The surface of electrostatic interaction between ligand and BSA structure for all compounds are illustrated in Figure 6.

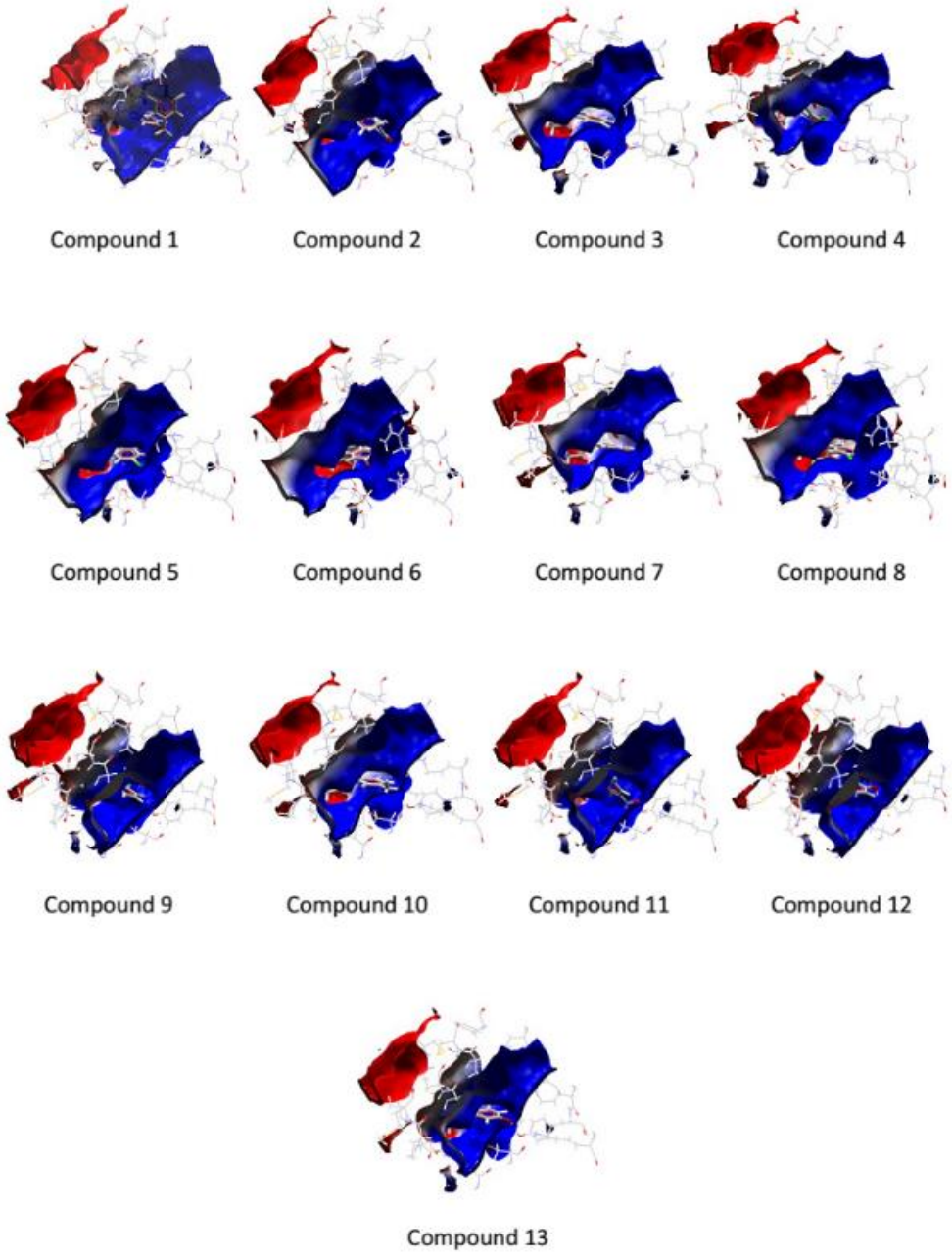


Figure 6. The electrostatic interactions between compounds 1-13 and BSA

Conclusion

For preliminary estimation of the possible connection sites as well as a series of seven cavities on the BSA structure have been characterized. These cavities are the sites spatially capable of absorbing the ligands, allowing them to penetrate. Additionally, the present study has investigated the molecular dockings of all synthesized compounds in the seven mentioned cavities. According to the results of the molecular docking, the most stable interaction among the selected compounds was in cavity 2 where the value of interaction energy was more negative compared to others.

References

1. Sharma O, Singla RK, Shrivastava B. Scientific Assessment of Antioxidant potential of Pyrimidine-2, 4 (1H, 3H)-diones. Indo Glob J Pharm Sci. 2012;2(2):142-6.
2. Girault S, Grellier P, Berecibar A, Maes L, Mouray E, Lemière P, et al. Antimalarial, Antitrypanosomal, and Antileishmanial Activities and Cytotoxicity of Bis (9-amino-6-chloro-2-methoxyacridine): Influence of the Linker#. J med chem. 2000;43(14):2646-54.
3. Cholody WM, Horowska B, Paradziej-Lukowicz J, Martelli S, Konopa J. Structure-activity relationship for antineoplastic imidazoacridinones: synthesis and antileukemic activity in vivo. J med chem. 1996;39(5):1028-32.
4. Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznik B, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. N Engl J Med. 1980;302(23):1269-73.
5. Guazzi M, Olivari MT, Polese A, Fiorentini C, Magrini F, Moruzzi P. Nifedipine, a new antihypertensive with rapid action. Am J Cardiol. 1977;22(5 Pt 1):528-32.
6. Sandjo LP, Kuete V, Biavatti MW. Pyridinoacridine alkaloids of marine origin: NMR and MS spectral data, synthesis, biosynthesis and biological activity. J Org Chem. 2015;11(1):1667-99.
7. Antonini I, Polucci P, Magnano A, Martelli S. Synthesis, Antitumor Cytotoxicity, and DNA-Binding of Novel N-5, 2-Di (ω-aminoalkyl)-2, 6-dihydropyrazolo [3, 4, 5-kl] acridine-5-carboxamides. J Med Chem. 2001;44(20):3329-33.
8. Vignesh G, Arunachalam S, Vignesh S, James RA. BSA binding and antimicrobial studies of branched polyethyleneimine–copper (II) bipyridine/phenanthroline complexes. Spectrochim. Acta. A. 2012;96:108-16.
9. Morris GM, Lim-Wilby M. Molecular docking. Molecular Modeling of Proteins: Springer; 2008. p. 365-82.
10. Anbazhagan R, Sankaran K. Syntheses, spectral characterization, single crystal X-ray diffraction and DFT computational studies of novel thiazole derivatives. J Mol Struct. 2013;1050:73-80.
11. İnkaya E, Dinçer M, Ekici Ö, Cukurovali A. N′-(2-methoxy-benzylidene)-N-[4-(3-methyl-3-phenyl-cyclobutyl)-thiazol-2-yl]-chloro-acetic hydrazide: X-ray structure, spectroscopic characterization and DFT studies. J Mol Struct. 2012;1026:117-26.
12. Güntepe F, Saraçoğlu H, Çalışkan N, Yüksektepe Ç, Cukurovali A. Synthesis, molecular and crystal structure analysis of 2-bromo-4-chloro-6-{[4-(3-methyl-3-phenyl-cyclobutyl)-thiazol-2-yl]-hydrazonomethyl}-phenol by experimental methods and theoretical calculations. J MolStruct. 2012;1022:204-10.
13. Teng Y, Liu R, Li C, Xia Q, Zhang P. The interaction between 4-aminoantipyrine and bovine serum albumin: multiple spectroscopic and molecular docking investigations. J. Hazard. Mater. 2011;190(1):574-81.
14. Shahabadi N, Hadidi S. Molecular modeling and spectroscopic studies on the interaction of the chiral drug venlafaxine hydrochloride with bovine serum albumin. Spectrochim. Acta. A. 2014;122:100-6.
15. Kumari M, Maurya JK, Singh UK, Khan AB, Ali M, Singh P, et al. Spectroscopic and docking studies on the interaction between pyrrolidinium based ionic liquid and bovine serum albumin. Spectrochim. Acta. A. 2014;124:349-56.