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MOLECULAR DOCKING ANALYSES OF SOME CYCLOHEXADIENE DERIVATIVES

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Abstract:

The molecular docking study was performed with aim to examine the inhibitory potency of two selected cyclohexadiene derivatives (*cis*-(1S)-3-Fluoro-3,5-cyclohexadiene-1,2-diol (**1**), and 1,1'-(3,5-Cyclohexadiene-1,3-diyl)dibenzene (**2**)). The inhibitory potency of compounds **1** and **2** was investigated toward Urokinase Type Plasminogen Activator (uPa). For this purpose AutoDock 4.0 software was used. The thermodynamic parameters achieved from molecular docking simulations, free energy of binding (ΔG_{bind}) and inhibition constant (K_i), are analyzed and discussed. The compound **2** shows better inhibitory potency through uPa, than compound **1**.

Keywords: molecular docking, cyclohexadiene derivatives

1. Introduction

Benzene and cyclohexane are important organic compounds having elevated industrial applications. Cyclohexane is a cycloaliphatic hydrocarbon possessing high thermal stability. It is colourless, volatile, non-polar and insoluble in water. Cyclohexane ring has an essential position in organic chemistry and it is found in nature, for example, terpenoids, steroids and some alkaloids. Cyclohexane has various chemical conformations, but the chair conformation is the most stable one [1]. Cyclohexane contains a hydrogen storage capacity of up to 7.2% by weight, which is an excellent medium for storing and transporting great quantities of hydrogen [2]. Substituents on cyclohexane can occupy either axial or equatorial positions and the stereochemistry of cyclohexane is broadened by substitution. Aromatic sulfonic acids possessing hydroxyl and amino functional groups are generally used as intermediates in the production of synthetic dyes, optical brightness and fluorescent whitening agents. Substituted sulphonic acid derivatives are utilized for disinfecting skin, treatment of minor wounds and refinement of drinking water in case of amoebicidal and bactericidal crises. Aromatic sulfonates

are used to monitor the lipids merging and also to manufacture the deodorants, antiseptics, disinfectants and medicines. It has antibacterial, anti-inflammatory and analgesic activities [3].

The two cyclohexadienes were selected as representers, *cis*-(1S)-3-Fluoro-3,5-cyclohexadiene-1,2-diol (**1**), and 1,1'-(3,5-Cyclohexadiene-1,3-diyl)dibenzene (**2**), of this group and they were studied in this research (Fig. 1.).

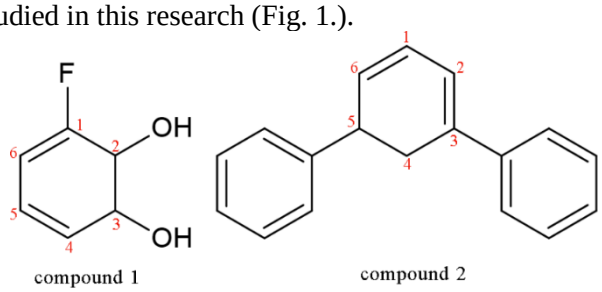

Fig. 1. Structures of two cyclohexadiene derivatives with carbon atom numbering

In our present study, the geometry optimization of investigated compounds was obtained by DFT approach which is carried out using B3LYP method in combination with 6-311++G(2df,2p) basis set. Molecular docking studies were analyzed towards Urokinase Type Plasminogen Activator (uPa) in order to examine the possible biological activities and interactions formed by the present functional groups. The study of molecular interactions will be beneficial in drug design and molecular modelling.

2. Methodology

The molecular docking simulations were carried out using the AutoDock 4.0 software [4]. The preparation of protein for docking simulations was performed in the Discovery Studio 4.0 [5]. The co-crystallized ligand, water molecules, and co-factors were removed from the protein structure. The addition of polar hydrogen atoms and calculation of Kollman charges was performed using the AutoDockTools (ADT) graphical user interface. The ligand was set to be flexible, and the bonds in the ligand were set to be rotatable. The protein remained standing as a rigid structure. For protein-ligand flexible docking simulations, the Lamarckian Genetic Algorithm (LGA) was used. The molecular docking simulation was performed at the temperature of 298.15 K.

The obtained values of the free energy of binding (ΔG_{bind}) depend on several contributions: the Final Intermolecular Energy (FIE), Final Total Internal Energy (FTIE), Torsional Free Energy (TFE), and Unbound System's Energy (USE) (Eqn. 1). The FIE is a sum of the van der Waals interaction energy, hydrogen bond energy, desolvation energy of the system, and electrostatic energy.

$$\Delta G_{bind} = (FIE) + (FTIE) + (TFE) - (USE) \quad (1)$$

The inhibition constant (K_i) can be determined based on the value of free energy of binding. Lower value of K_i signifies lower concentration of ligand required to inhibit the activity of receptor.

3. Results and Discussion

The molecular docking studies were performed towards uPa (Urokinase Type Plasminogen Activator). The experiments have proven that the presence of specific inhibitors for uPa in form of small molecules or antibodies inhibited the tumour growth in animal models [6]. The animal models without functional uPa also failed to develop invasive tumours. Therefore, specific inhibitors of this protein could possibly lead to the inhibition of tumour growth and further development of anti-tumor medicines [7]. The previously mentioned species (compounds **1** and

2) were subjected to the molecular docking study. The values of ΔG_{bind} and K_i for the most stable conformations are given in Table 1. Figure 2 and Table 1 present the most important interactions formed between the active pocket of uPa and chosen cyclohexadiene derivatives (**1** and **2**).

Table 1. The important thermodynamical parameters from docking simulations with Urokinase Type Plasminogen Activator (PDB ID: 1w11)

Compounds	ΔG_{bind} (kJmol^{-1})	K_i (μM)	FIE (kJmol^{-1})	vdW + Hbond + desolv Energy (kJmol^{-1})	Electrostatic Energy (kJmol^{-1})	FTIE (kJmol^{-1})	TFE (kJmol^{-1})	USE (kJmol^{-1})
1	-18.6	553.76	-21.1	-20.8	-0.3	-5.5	2.5	-5.5
2	-29.9	5.74	-32.4	-32.4	0.0	-2.8	2.5	-2.8

Based on the results from Table 1, the higher stability complexes were formed between uPa and compound **2**, with ΔG_{bind}=-29.9 kJmol^{-1} and Ki=5.74 μM. Although this molecule does not contain any of the polar groups responsible for the polar interactions, two of the aromatic rings could possibly form a variety of π-π interactions with the surrounding amino acids. The binding energy of compound 1 is higher, -18.6 kJmol^{-1}. As previously discussed, this result is expected due to the fact that the active positions of compound **1** include fluorine atom and two OH groups. In both cases the main contribution to this energy comes from the weak interactions, mainly van der Waals and dispersion interactions (Table 1). Electrostatic interactions account for a negligible percentage. The torsion free energies are also very low due to the rigidity of structures and extended delocalization between groups. When interactions with specific amino acids are concerned, compound **2** forms bonds with HIS57 and SER195. In the paper by Zeslawska and co-workers, these amino acids were marked as important for the inhibition of uPa by various inhibitors [8]. As suggested previously, compound **2** forms various π-interactions through aromatic rings. These include π-cation interaction with HIS57 and π-π interaction with TYR228. The halogen bonds are established between compound **1** and CYS191, as well as conventional hydrogen bonds that include OH groups of compound **1** and polar groups of CYS191, SER190, and GLY219.

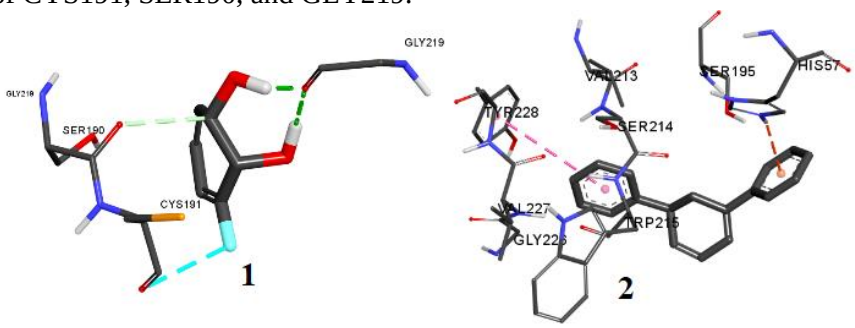

Fig. 2. Interaction of investigated compounds with Urokinase Type Plasminogen Activator (PDB ID: 1w11)

4. Conclusion

The inhibitory potency of two selected cyclohexadiene derivatives (*cis*-(1S)-3-Fluoro-3,5-cyclohexadiene-1,2-diol (**1**), and 1,1'-(3,5-Cyclohexadiene-1,3-diyl)dibenzene (**2**)) was

investigated toward Urokinase Type Plasminogen Activator (uPa). The molecular docking simulations were performed using AutoDock 4.0 software. The obtained thermodynamic parameters (ΔG_{bind} and K_i) are discussed and the accomplished interactions with uPa were carefully examined. From obtained results it can be concluded that both examined compounds can inhibit uPa, but compound **2** possess better inhibitory potency and deserves further investigation. Also, compound **2** establish interaction with HIS57 and SER195, which are proven to be crucial for inhibition of uPa.

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