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Molecular docking studies of chlorthalidone and Indapamide on Angiotensin-II

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ABSTRACT

A main target in the treatment of hypertension is the Angiotensin-converting enzyme (ACE). This enzyme is responsible for producing Angiotensin II, a potent vasoconstrictor. Therefore, one of the targets in the treatment of hypertension is to inhibit ACE activity. Prolonged increase in blood pressure condition increases the risk of heart attacks, heart failure, and stroke kidney failure. Inhibition of ACE by Angiotensin converting enzyme inhibitors results in the decreased of formation of Angiotensin II and decreased metabolism of bradykinin leading to systematic dilation of the arteries and veins and a decrease in arterial blood pressure. The molecular docking analysis indicates that the receptor of human ACE through an interaction with the chemical bonds. All this using computer-aided drug design, and studying the systems, with the proposed compounds, through molecular recognition process and compared with the compounds already on the market for hypertension.

Keywords: Chlorthalidone, Indapamide, Angiotensin converting enzyme and Hypertension.

1. INTRODUCTION

1.1. Chlorthalidone

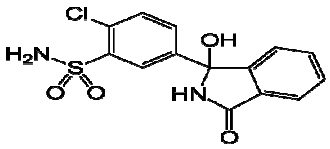
Chlorthalidone (*RS*)-2-Chloro-5-(1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindolyl) benzene-1-sulfonamide) is a diuretic (water pill) used as an antihypertensin drug. The chemical structure is shown in figure 1(a). Chlorthalidone is also known (trademarked) as Hygroton. It is the 2-chlorinated derivative of the sulfonamide and also a Benzenesulfonamideand derivative of drug. It was developed in the early 1960s by the USA drug manufacturer. Chlorthalidone has a number of uses in medicine including in the treatment of congestive heart failure, edema, kidney, liver disease and lungs problem.

Chlorthalidone is available worldwide in many dosage forms, combinations, and under various brand names [1]. Chlorthalidone is very similar to hydrochlorothiazide. They contain a actylic ring system with an alkyl amine substituent on the central ring. Chlorthalidone was still the best agent for preventing combined cardiovascular events and heart failure [2]. Hypertension also down-regulate cerebral cortical β-adrenergic receptors and sensitize post-synaptic serotonergic receptors with chronic use. Antihypertensin also block histamine-H_1 receptors, α_1-adrenergic receptors and muscarinic receptors. The useful antihypertensive α-adrenoceptors inhibitor drugs are α_1-adrenoceptors selective not blocking the α_2-adrenoceptors. The prior administration of a β-adrenoceptors blocking drugs may also increase the fall in blood pressure associated with this first dose phenomenon. β- adrenoceptors blocking drugs are often used as first choice drugs for hypertension. It is important that care is taken is patient selection.

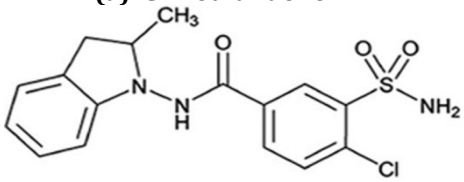
1.2. Indapamide

Indapamide4-chloro-N-(2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoyl benzamideis a diuretic (water pill) used as an antihypertensin drug. Indapamide is also known (trademarked) as Lozol. It was selected from a series of indoline and isoindoline derivatives of chlorosulfamoyl benzamide and also a sulphonamide derivative of Indapamide drug. It was developed in the early 1974s by the US and Japan drug manufacturer. Indapamide has a number of uses in medicine including in the treatment of congestive heart failure, edema. Indapamide is a Thiazide-like diuretic [3] used as an antihypertensin drug. It works by causing the kidneys to eliminate large amounts of water and salts. Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells

(80%) and, more specifically, to carbonic acid anhydrase (98%)without having any significant inhibiting activity on this enzyme. Indapamide or bendrofluazide alone, activation of the renin angiotensin system may have prevented a further fall in blood pressure. The present study has shown that Indapamide produced a significant but equivalent fall in blood pressure to that observed with Thiazide diuretics.



(a) Chlrothalidone



(b) Indapamide

Figure - 1: Molecular structure.

1.3. Computational details

Docking calculations were performed with version 1.5.2 of the program AutoDock [4]. It combines a rapid energy evaluation through pre-calculated grids of affinity potentials with a variety of search algorithms to find suitable binding positions for a ligand on a given macromolecule. Cygwin software is used to produce the protein-ligand complex. The PyMOL [5] software was used to view the protein-ligand complex. The structure of the LeuT was obtained from Brookhaven Protein Data Bank (PDB code: 4APH) [6] from that, the protein was separated for the docking study. The ligand structure was prepared using the Chemdraw software and converted into pdb format. These files are used as the input files for docking analysis.

1.4. Angiotensin-II

It is already reported that, the drug Chlorthalidone and Indapamide is used as a potent inhibitor of Angiotensin (Ang-II). Angiotensin II is a vasoconstrictor that causes blood vessels to constrict thereby causing hypertension [7]. ACE is expressed in small pulmonary arteries are normal [8]. However, during diabetes, obesity, hypertension the expression and activities of the enzyme increases in small pulmonary arteries. This led to the development of ACE inhibitors which show significant cardio protection through decreasing hypertension [9-11]. It is part of the renin angiotensin system (RAS), which is a major target for drugs that lower blood pressure. Angiotensin also stimulates the release of aldosterone, another hormone, from the adrenal cortex (AC). Aldosterone promotes sodium retention (APSR) in the distal nephron, in the kidney, which also drives blood pressure up. Angiotensin I is further cleaved in the lungs by endothelial-bound angiotensin-converting enzyme (ACE) into angiotensin II, this angiotensin II plays a role of hormone and more vasoconstriction occurs in smooth muscles. Ultimately the heart tries to overcome this excess flow and vigorously works. This mechanism leads to high blood pressure. Hence the ACE inhibitors are the more point of attraction as a target in therapeutics. Various RAS inhibitors available in market directly block the angiotensin II receptor which develops the hypotension.

1.5. Optimization structure

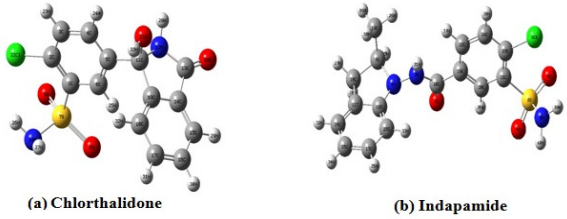


Figure - 2: Optimized structure of Chlorthalidone and Indapamide.

2. RESULTS AND DISCUSSION

2.1. Molecular docking analysis

The docking analysis predicted the lowest docked energy for Chlorthalidone and Indapamide the binding energy value is -9.86 and -8.44 Kcal/mol.

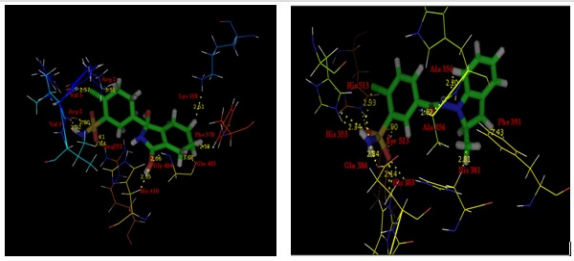
Table - 1: Lowest binding energy values in Kcal/mol

Ranking	Binding energy	
	Chlorthalidone	Indapamide
1	-9.86	-8.44
2	-9.86	-8.44
3	-9.86	-8.40
4	-9.86	-8.37
5	-9.86	-8.36
6	-9.85	-8.34
7	-9.85	-7.87
8	-9.85	-7.56
9	-9.29	-7.50
10	-9.25	-7.33

The calculated ten conformational energy values of Chlorthalidone and Indapamide in the active site of Ang-II are listed in table 1. The shortest interactions between the ligand and receptor are given in table 2.

Table - 2: Nearest neighbours and short contact distance (A°) of chlorthalidone and Indapamide with amino acid residues of Ang-II active site

Chlorthalidone···Ang-II Amino acid residues and identifier	Distance	Indapamide···Ang-II amino acid residues and identifier	Distance
Cl(22) ···Val33	2.59	Cl(1)... His 513	2.93
C(5)··· Gln403	3.28	C(9)...Phe 391	2.43
C(16)... Phe570	2.58	C(13)...His 381	2.81
C(17)... Cys 118	2.61	C(15)...Ala 356	2.20
O(8)... Arg2	2.04	O(4)...His 358	2.34
S(7)... Arg522	2.21	S(2) ...His 513	3.11
N(10)...Val3	2.93	O(5)... Glu 348	2.84



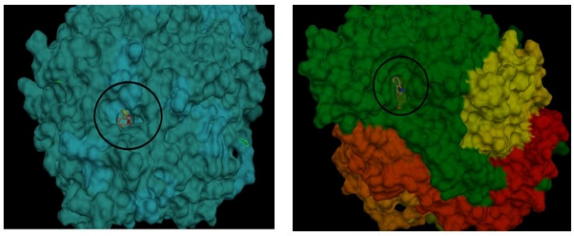
(a) Chlorthalidone-Ang-I (b) Indapamide-Ang-II

Figure - 3: complex showing some important intermolecular interactions.

2.2. Intermolecular Interaction

The chlorthalidone also bound at the inner end of the extracellular cavity in Ang-II. Figure 4(a) shows the binding cavity of the chlorthalidone in the Ang-II. The ligand has formed some hydrogen bonding and hydrophobic interactions with the nearest amino acids in active site; particularly, the halogen Cl (22) atom forms a strong interaction with the Val (33) at a distance 2.59Å. The C(15), C(16) and C(17) atoms form some strong hydrogen bonding interactions with the amino acid residues Glu403 and Phe570, Lys118 at 3.28, 2.58 and 2.61 Å respectively. Similarly the O(8), S(7) and N(10) atoms of the ligand form some strong hydrophobic interactions with the Arg2, 522 and Val3 at a distance of 2.04, 2.21 and 2.93 Å correspondingly (Table 2).

The Indapamide also bound at the inner end of the extracellular cavity in Ang-II. Figure 4(b) shows the binding cavity of the Indapamide in the Ang-II. The ligand has formed some hydrogen bonding and hydrophobic interactions with the nearest amino acids in active site; particularly, the halogen Cl(1) atom forms a strong interaction with the His 513 at a distance 2.93Å. The C(9), C(13) and C(15) atoms form some strong hydrogen bonding interactions with the amino acid residues Phe391 and His381, Ala356 at a distance 2.43, 2.81 and 2.20Å respectively. Similarly the O(4), S(2) and O(5) atoms of the ligand form some strong hydrophobic interactions with the His 358, 513 and Glu348 at a distance of 2.34, 3.11 and 2.84Å respectively (Table 2).



(a) Chlorthalidone-Ang-II (b) Indapamide-Ang-II

Figure - 4: Showing the binding cavity

Table - 3: Geometrical parameters of Optimized and Docked forms of Chlorthalidone

Bonds	Optimized	Docked
C(6)–C(1)–S(7)–O(8)	175.09	123.93
C(6)–C(1)–S(7)–O(9)	-159.32	130.94
C(6)–C(1)–S(7)–N(10)	-119.78	121.10
C(2)–C(1)–S(7)–N(10)	-61.39	-89.09

2.3. Torsion angles (°)

2.3.1. Structural accepts

The geometrical parameters like bond lengths, bond angles and torsion angles of the chlorthalidone were calculated for drug before (Optimized) and after entering into the active site (Docked). The comparison tables of the geometrical parameters of chlorthalidone were listed in table 3. By viewing the structure of the ligand, we know it has double-ring system; from

this it may assumed that the ligand is very rigid. It is reflected in comparison of the bond Length, bond angle, torsion angle. In the rings there are no much variations found. But some variations is found in the tail part of the ligand. At initial, the *trans* angles of the C(6)–C(1)–S(7)–O(8), C(6)–C(1)–S(7)–O(9) and C(6)–C(1)–S(7)–N(10) bonds are 175.09°, -159.32° and -119.78°; when the ligand enter into the active site the angles were reduced to 123.93°, 130.94° and 121.10° respectively. But in the C(2)–C(1)–S(7)–N(10) bond the *gauche* angle is increased from -61.39° to -89.09°. These variations explain the structural change of the ligand in the active site of protein.

Table - 4: Geometrical parameters of Optimized and Docked forms of Indapamide Torsion angles (°)

Bonds	Optimized	Docked
C(21)–O(4)–S(2)–N(8)	175.37	-120.08
C(21)–O(5)–S(2)–N(8)	-124.82	-119.08
O(4)–S(2)–O(5)–N(8)	152.90	117.86
C(8)–O(3)–N(6)–N(7)	-2.165	3.020

The geometrical parameters like bond Length, bond angle, torsion angle of the Indapamide were calculated for drug before **(Optimized)** and after entering into the active site **(Docked).** The comparison between the [Optimized and docked Indapamide] geometrical parameters of were listed in Table 4. Since the ligand has double-ring system; the ligand should be which very rigid is reflected in comparison of the bond lengths, bond angles and torsion angles. There is no Indapamide various observed in the ring system of the ligand. But some variations were found in the tail part of the ligand. At initial, the *trans* angles of the C(21)–O(4)–S(2)–N(8), C(21)–O(5)–S(2)–N(8) and O(4)–S(2)–O(5)–N(8) bonds are 175.37°, -124.82° and -152.90°; when the ligand enter into the active site the angles were reduced to 120.08°, -119.08° and 117.86° respectively. But in the C(18)–O(3)–N(6)–N(7) bond the *gauche* angle is increased from -2.165° to 3.020°. The change in these angles reveals that the docked ligand has rotation about its tail part, particularly the sulfonyl group only.

4. CONCLUSION

The docking analysis predicted the lowest docked energy for chlorthalidone and the binding energy value is -9.86Kcal/mol. The C(15), C(16) and C(17) atoms form some strong hydrogen bonding interactions with the amino acid residues Glu403 and Phe570, Lys118 at 3.28, 2.58 and 2.61Å respectively. The docking analysis predicted the highest docked energy for Indapamide and the binding energy value is -8.44Kcal/mol. The C(9), C(13) and C(15) atoms form some strong hydrogen bonding interactions with the amino acid residues Phe391 and His381, Ala356 at a distance 2.43, 2.81 and 2.20 Å respectively. Chlorthalidone and Indapamide both molecules were docked with Ang-II effectively. Comparing the binding energy values, chlorthalidone has low binding energy value in the docking structure which reveals chlorthalidone interacts strongly with the ligand. This is also supported by number of hydrogen bonds interactions and the changes in the docked molecular structural parameters. Whereas, the Indapamide has more rigid in the docked structure and binded with high binding energy compare to chlorthalidone which reveals the Indapamide drug will go to active site very easily. Hence Indapamide drug will be more useful for fast remedy in reducing hypertension and chlorthalidone will be strong and effective in curing hypertension.

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