DENSITY FUNCTIONAL THEORY ANALYSIS OF ANTIHYPERTENSION COMPOUNDS

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ABSTRACT

Density Functional Theory (DFT) simulations to study the molecular causes of hypertension using PyRX software and Gaussian 4.0 software. We investigate the electronic structures, energetics, and bonding properties of important biomolecules implicated in hypertension, such as renin, angiotensin II receptor, and the angiotensin-converting enzyme (ACE), by building and optimizing molecular models of them. We obtain deeper insights into the electronic properties of these biomolecules through sophisticated analysis, such as density of states (DOS), charge density distribution, and molecular orbital analysis made possible by PyPX software. This information is crucial for the development of targeted therapeutic interventions against hypertension.

Keywords: Molecular Docking, Protein, Ligand, Antihypertension, DFT Theory, ACE Inhibitors, Gaussian 4.0, PyRX.

1. INTRODUCTION

One of the most common causes of atherosclerotic cardiovascular disease is hypertension. It has thermogenesis, resulting in a two- to three-fold elevated incidence of such occurrences, including coronary heart disease (CHD), the most prevalent and deadly after effect [1].

1.1TYPES OF HYPERENSION

1.1.1 PRIMARY HYPERTENSION

When a child's blood pressure consistently remains above the 95th percentile without a secondary cause, it is referred to as primary hypertension [2] .

1.1.2. SECONDARY HYPERTENSION

Studies have indicated that pediatric patients are more likely to get secondary hypertension, with a prevalence of 75–85% in younger children.[3]

1.2.RNA INTERFACE

RNA interference (RNAi) is an innate regulatory mechanism that suppresses gene expression. Short RNAs known as RNAis cause homologous mRNA to be targeted by ribonucleases, which silences a particular gene [4].

1.3.DENSITY FUNCTIONAL THEORY

Density Functional Theory is an alternative approach to the traditional quantum chemistry methods (ab initio and semi empirical) to study the ground-state properties of molecular systems. DFT methods are suitable for investigation of large molecular systems [5]. From Janak's theorem, the highest occupied orbital energy (HOMO) equals the chemical potential and the negative of the ionization potential [6]. The fact that is the KS method the chemical potential of electrons is equal to the energy of the highest occupied KS orbital, determining the Fermi level, suggest that the DFT methods are perfectly suitable for description of the physical and chemical properties of molecular systems [7].

2. MATERIALS AND METHODS

2.1. TARGET SELECTION

The X-ray crystal structure of 4C2R was retrieved from Protein Data Bank. The protein energy was analyzed through Ramachandran Plot. The protein energy minimized through the Swiss PDB minimizer and used for further docking studies.

2.2. RAMACHANDRA PLOT 4C2R

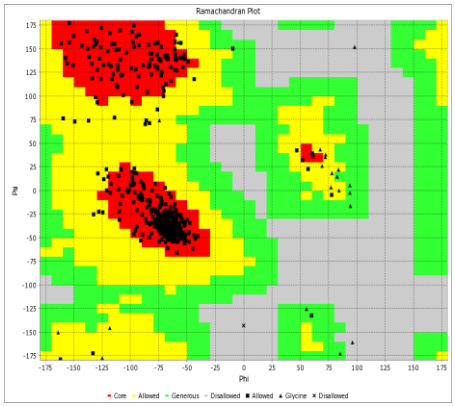


Figure 1 Ramachandra plot

2.3. BIOVIA DISCOVERY STUDIO

Discovery Studio is a complete software suite that may be used to analyze and model sequences, chemical structures, systems of small and big molecules, and other pertinent data.

2.4. PyRx DOCKING

PyRX is a Computational Drug Discovery Virtual Screening tool that allows libraries of compounds to be screened against possible therapeutic targets.

2.5. METHOD

On Windows 10 machines, ab initio calculations were carried out using Gaussian 04 software with the B3LYP method and -31G (d, p) basis sets.

2.6. MOLECULAR STRUCTURE PREDICTION

The chemical structure and vibrational wave numbers of the molecule were predicted using the computations.

2.7. FRONTIER ORBITAL ANALYSIS

The lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) analyses received a lot of attention since they are critical in evaluating the compound's stability.

2.8. CHEMICAL ACTIVITY

The determined band gaps in eV for the HOMO and LUMO energy levels were reported. The LUMO-HOMO energy gap's eigen values represent the molecule's chemical activity.

2.9. CHARGE TRANSFER INTERACTION

Because of the electron-acceptor group's potent capacity to accept electrons, there are charge transfer interactions within the molecule as seen by the decrease in the HOMO-LUMO energy gap.

2.10. HOMO AND LUMO CHARACTERISTICS

While LUMOs have an anti-bonding π^* character, HOMOs have an overall π bonding character with a considerable non-bonding character.

3. RESULTS AND DISCUSSION

3.1. TARGET SELECTION

From the Protein Data Bank, the X-ray crystal structure of 4C2R was retrieved. The Ramachandra Plot was utilized to analyze the energy of the protein. The protein energy decreased by SWISS PDB optimizer is utilized for additional docking research.

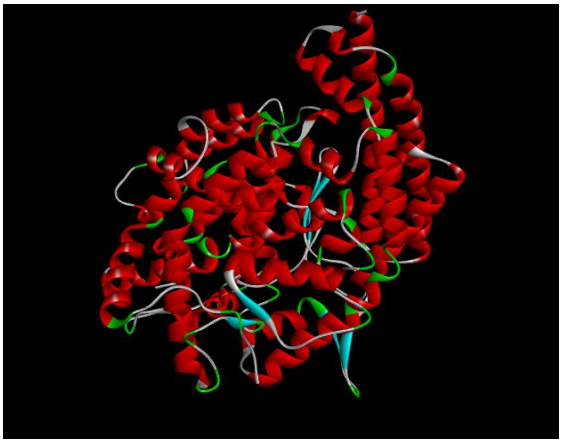


Figure 2 Crystal structure of 4c2R

3.2.HOMO-LUMO DIFFERENCES

PUMCHEM ID	HOMO	LUMO	DIFFERENCE
73442	-4.26	-1.95	-2.31
10288	-4.23	-1.95	-2.28
92729	-5.19	-2.95	-2.24
338	-5.69	-3.57	-2.12
446925	-5.69	-3.57	-2.12
101906902	-6.23	-4.35	-1.88
2520	-3.12	-1.26	-1.86
11230	-3.12	-1.26	-1.86
145068	-3.57	-1.95	-1.62
439533	-4.26	-2.85	-1.41
5317570	-4.26	-2.85	-1.41
5458646	-5.69	-4.35	-1.34
10106436	-5.69	-4.35	-1.34
2519	-4.26	-2.92	-1.34
3314	-6.45	-5.12	-1.33
12411	-3.57	-2.26	-1.31

92094	-5.26	-3.95	-1.31
5903	-3.12	-1.95	-1.17
445639	-3.12	-1.95	-1.17
3037212	-3.12	-1.95	-1.17
5281	-5.23	-4.12	-1.11
2758	-4.35	-3.26	-1.09
3639	-5.26	-4.26	-1
259846	-5.26	-4.26	-1
785	-6.23	-5.26	-0.97
5770	-6.23	-5.26	-0.97
47936	-6.23	-5.26	-0.97
174003	-6.23	-5.26	-0.97
5281516	-6.23	-5.26	-0.97
638011	-2.23	-1.26	-0.97
18818	-5.26	-4.35	-0.91
327392	-5.26	-4.35	-0.91
5281149	-2.85	-1.95	-0.9
11369949	-2.85	-1.95	-0.9
702	-4.75	-3.95	-0.8
280489	-5.69	-4.92	-0.77
3220	-3.54	-2.85	-0.69
10467	-4.26	-3.57	-0.69
5280441	-4.26	-3.57	-0.69
161192441	-4.26	-3.57	-0.69
358901	-3.57	-3.12	-0.45
525503	-3.57	-3.12	-0.45
442347	-5.69	-5.26	-0.43
9548705	-5.26	-5.26	-0.43
5564	-4.26	-3.95	-0.31
6375530	-3.23	-2.95	-0.28
131801617	-3.12	-2.85	-0.27
73568	-4.23	-4.12	-0.11

73013770	-1.95	-1.95	0
517055	-2.85	-2.92	0.07
6850743	-2.85	-2.92	0.07
16590	-4.26	-4.35	0.09
11106439	-2.23	-2.45	0.22
23662386	-5.26	-5.69	0.43
5281794	-5.69	-6.23	0.54
62351	-1.26	-1.95	0.69
398941	-1.26	-1.95	0.69
5281643	-3.57	-4.26	0.69
5318517	-3.57	-4.26	0.69
101682254	-3.57	-4.26	0.69
16133932	-2.85	-3.57	0.72
31211	-3.57	-4.35	0.78
5281647	-1.95	-2.85	0.9
6850760	-1.95	-2.85	0.9
1287	-5.23	-6.23	1
5377796	-4.26	-5.26	1
12315492	-4.26	-5.26	1
62434	-3.12	-4.26	1.14
10207	-1.95	-3.12	1.17
92158	-1.95	-3.12	1.17
5281807	-3.12	-4.35	1.23
6918391	-3.12	-4.35	1.23
3016339	-2.85	-4.26	1.41
10887728	-2.85	-4.26	1.41
6549	-1.95	-3.57	1.62
168115	-1.95	-3.57	1.62
5280666	-1.95	-3.57	1.62
6450930	-1.95	-3.57	1.62
10817	-3.57	-5.26	1.69
3776	-4.26	-6.23	1.97

8815	-4.26	-6.23	1.97
445858	-4.26	-6.23	1.97
969516	-3.12	-5.26	2.14
11617	-1.95	-4.26	2.31
94378	-1.26	-3.57	2.31
173183	-1.95	-4.26	2.31
28523	-1.95	-4.35	2.4
68111	-1.95	-4.35	2.4
1794427	-1.95	-4.35	2.4
4170585	-3.12	-5.69	2.57
12890356	-3.12	-5.69	2.57
6850762	-3.57	-6.23	2.66
91457	-2.85	-5.69	2.84
168114	-2.85	-5.69	2.84
637776	-2.85	-5.69	2.84
5281553	-2.85	-5.69	2.84
6419725	-2.85	-5.69	2.84
155381	-3.12	-6.23	3.11
10208	-1.95	-5.26	3.31
442393	-1.95	-5.26	3.31
102003051	-1.95	-5.26	3.31
5355130	-1.95	-5.69	3.74
222284	1.26	-5.69	4.4

3.3. HOMO AND LUMO ENERGY GAP IN DENSITY FUNCTIONAL THEORY

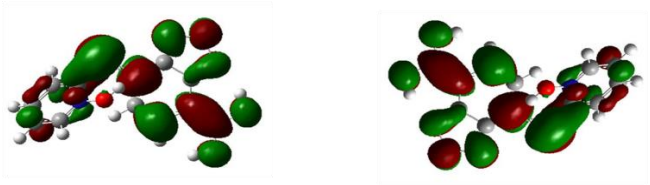
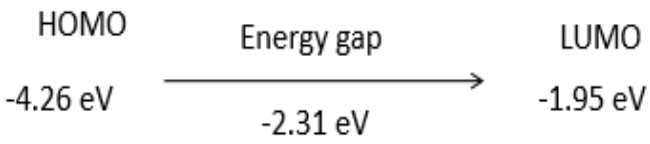


Figure 3HOMO-LUMO Energy Gap



4. CONCLUSION

One RAAS component that dramatically lowers blood pressure is called the ACE, and it is the focus of medication for hypertension. Understanding the electronic structure and reactivity of molecules depends on calculating the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) energies using Density Functional Theory (DFT) computations. These computations shed important light on a number of characteristics, including charge transport events, electron affinity, and ionization potential. It is possible to determine the HOMO-LUMO gap, a measurement of the stability and electronic transitional potential of the molecule. DFT HOMO-LUMO simulations offer important insights into the electrical characteristics of molecules, helping scientists create new materials and comprehend how they behave in various chemical setting.

5. REFERENCES

[1]William B.Kannel, MD et al., "*Blood Pressure as a Cardiovascular Risk Factor*", DOI: 10.1001/jama.1996.03530440051036, **1996**.

[2]Barbara S.Bucher et al., "*Primary Hypertension in Childhood*", **2013**.

[3]Katerina Chrysaidou et al., "*Secondary Hypertension in Children and Adolescents: Novel Insights*", DOI:http://doi.org/10.2174/1573402115666190416152820, **2019**.

[4]Agrawal N, et al., "*RNA interference: biology, mechanism, and applications*", DOI: 10.1128/mmbr.67.4.657-685, **2003**.

[5]Heran BS et al., "*Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension*", DOI: 10.1002/14651858.CD003823.pub2, **2009**.

[6] Sawsan Shanableh et al., "*Quality Of Life of Hypertensive Patients on Different Types ofAntihypertensive Medications*", **2014**.

[7]Agrawal N, et al., "*RNA interference: biology, mechanism, and applications*", DOI: 10.1128/mmbr.67.4.657-685, **2003**.