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Developing New Drug Antagonist for Alpha Adrenergic Receptors for Hypertension Diseases

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Abstract- Alpha-adrenergic receptors play a vital role in the regulation of blood pressure(BP). Hypertension referred as blood pressure above the normal range. hyper tension can cause severe complications such as stroke, coronary heart disease and kidney failure. Phentolamine is a potential antagonist for a. Alpha-adrenergic receptor. New phentolamine derivatives will be developed through FEP (Free Energy perturbation) methods.

AMBER Force fields will apply for energy Calculation. Molecular modeling includes energy minimization, molecular dynamics, mounte-carlo simulations and QSAR properties will be performed for all phentolamine analogs. The interactions studies between alpha - adrenergic Receptor and Phentolamine analogs in solvent mode and protein complex mode will be performed. The best antagonist for alpha-Adrenergic Receptor will be identified.

Keywords-*alpha adrenergic receptors, binding free energy, hyperchem, hypertension, docking, solvent, protein complex.*

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1. Introduction

1.1 PATHOGENESIS

Blood pressure is determined by the amount of blood your heart pumps and the amount of resistance to blood flow in your arteries. Your blood pressure normally varies during the day. It can even vary slightly with each beat of your heart. It increases during activity and decreases with rest. Many people may not view high blood pressure as life-threatening. But uncontrolled high blood pressure can increase your risk of serious health problems. Fortunately, high blood pressure can be detected with a simple test and once you know you have high blood pressure, you can work with your doctor to control it.

Factors affecting blood pressure: cardiac output, blood volume, resistance, flexibility of artery wall, artery diameter, blood viscosity.

Plaque: Cholesterol can combine with fat, calcium, and other substances in the blood to form plaque. Plaque then slowly builds up and hardens in the arteries, causing them to narrow. This buildup of plaque, a condition called atherosclerosis, can lead to heart disease

Clots: It is the coagulation of the blood in body, it the main factor to reduce the oozing of blood while injury and eventually it also leads to negative effects on blood diseases, lung, heart.

Blood pressure to be maintained:

Normal blood pressure is a systolic pressure which is less than 120 millimeters of mercury (mm Hg) and a diastolic pressure of less than 80 mm Hg. Having a blood pressure greater than 140/90 mm Hg is considered to be high blood pressure or hypertension.

General causes for hypertension:

you eat too much salt, you don't eat enough fruit and vegetables, you are not active enough, you are overweight, or you drink too much alcohol.

Autonomic nervous system:

It is the part of the nervous system responsible for control of the bodily functions, such as breathing, the heartbeat, and digestive processes.

Sympathetic nervous system: It part of the autonomic nervous system that contains adrenergic receptors and results in depress secretion, decrease the contractility of smooth muscle, and increase heart rate.

The **sympathetic nervous system** releases two hormones in response to stress, resulting in "adrenaline rush", or a sense that occurs during stressful conditions. Hormones released are epinephrine and norepinephrine, which help your body perform optimally high end way.

The autonomic nervous system function is to regulate the body's unconscious actions. The sympathetic nervous system's primary function is to stimulate the body's fight-or-flight response. It is, however, constantly active at a basic level to maintain homeostasis.

Parasympathetic nervous system: The parasympathetic nervous system is one among the autonomic nervous system. It is also called as the rest and digest system, the parasympathetic system conserves energy which results to slowing down of heart rate, increases intestinal and gland activity, and finally relaxes sphincter muscles which is present in the gastrointestinal tract.

1.2 TARGET RECEPTOR

The adrenergic receptors are targets of the norepinephrine (noradrenaline)
and epinephrine (adrenaline).The adrenergic receptors are targets of the catecholamine's.
Many cells possess these receptors, and the binding of a catecholamine to the receptor will stimulate the sympathetic nervous system. The sympathetic nervous system is responsible for the fight-or-flight responses, which includes dilating the pupils, increasing heart rate, mobilizing energy, and diverting blood flow from non-essential organs to skeletal muscle.

1.3 PHENTOLAMINE

Phentolaminegenerallytermed as Regitine, it is a reversible nonselective α-adrenergic antagonist. The main function of this is vasodilation which is generally due to blockage of apha receptors. Non-selective α-blockers can cause a much more pronounced reflex tachycardia than the selective α_1 blockers. Phentolamine causes a relaxation, leading to hypotension.

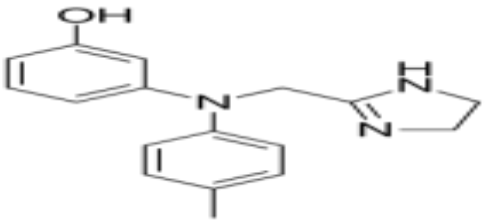

Fig. 1

2. FREE ENERGY PERTUBATION:

Free energy perturbation (FEP) is a method based on statistical mechanics.This method is used in computational chemistry. According to the free-energy perturbation method, the free energy difference from state **A** to state **B** is obtained from the following equation, known as the *Zwanzig equation*:

$$F_{AB} = F_B - F_A = -K_BT \ln(\exp(-E_B-E_A/K_BT))_A$$

where T is the temperature, k_B is Boltzmann's constant. In practice, one runs a normal simulation for state **A**, but each time a new configuration is accepted, the energy for state **B** is also computed. ΔF obtained is for "mutating" one molecule onto another. This free energy map is also known as a potential of mean force or PMF. Free energy perturbation calculations only converge properly when the difference between the two states is small enough.

FEP calculations have been used for studying host-guest binding energetics, pKa predictions, in solvent effects and protein complex. Umbrella sampling is another free-energy calculation technique that is typically used for calculating the free-energy change associated with a change in "position" coordinates as opposed to "chemical" coordinates, although Umbrella sampling can also be used for a chemical transformation when the "chemical" coordinate is treated as a dynamic variable. An alternative to free energy perturbation is thermodynamic integration. Another method which is more efficient, is the Bennett acceptance ratio method.

I. X= binding energy calculation in solvent
J. Y= binding energy calculation in protein complex
II. X – Y = binding free energy

The drug molecule is said to be best when it has minimum binding free energy.

2.1 AMBER FORCE FIELD

Assisted Model Building with Energy refinement (AMBER) is a family of force field for molecular dynamics
The term AMBER force field is the functional form used by the family of AMBER force fields. This form includes several parameters. Each member of the family of AMBER force fields provides values for these parameters and there own name.
The AMBER software provides a set of programs to apply the AMBER forcefields for simulations. Programming languages like Fortran 90 and C, with support for unix in both operating systems and compilers.

2.3 HYPERCHEM SOFTWARE:

HyperChem is the powerful computational chemistry tool than any other tools. Structure Input and Manipulation are done by this tool. Building molecules with HyperChem is simple just choose an element from the periodic table, and click to sketch a structure. Mouse can control rotations bonds, stereochemistry. Extensively selection, highlighting, and display capabilities make it easy to focus on areas of interest in complex molecules. Molecular structures can be displayed using ball and stick, van der Waals dots, and sticks with vdW dots, switching of rendering styles is easy. Display bond showing bond length and bond angles. Displays protein backbones using ribbons, with optional display of sidechains.

3. PROJECT RESULTS

Knowing the receptor and taking the reference as existing drug regitine(phentolamine) and applying conformation technique with various analogs. This all process is done in hyperchem. After drawing the analogs in the tool we need to convert them into different forms like sticks, balls, lines etc. Then select any comfortable form and find bond distance, bond angle and torsional angle. Perform geometry optimization. Perform molecular dynamics. Calculate QSAR properties.

Geometry optimization

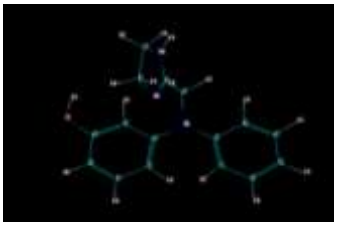

Fig. 2

3.1 DOCKING:

Docking method is which predicts the preferred bonding of one molecule to a other to attain stable complex.

Molecular docking is used methods in structure-based drug design, due to its ability to predict the binding-conformation.

There are two approaches for molecular docking. One approach is using matching technique. And other is the actual docking process in which the ligand-protein pairwise interaction energies are calculated. Here we used gold docking software.

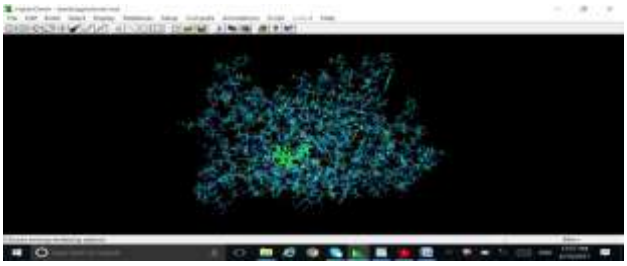

fig. 3

3.2 RESULT TABLES:

Table. 1

Comparison of energies in protein complex and without protein complex (intra molecular energy)

Analogs	With protein complex	Without protein complex
Parent molecule	9.6311	19.1145
Ch3	480.7297	1278.7110
Cl	18.5863	18.5863
Ch2oh	54.0488	18.9880
F	49.4137	18.6812
Oh	40.0320	19.3875
Br	42.6766	18.5635

Table. 2

Fittness: hydrogen bonding + vanderwaals forces(inter molecular energy)

Analogs	Hydergen bonding	vanderwaals	Total evergy
Parent molecule	0.00	38.95	37.95
Ch3	0.00	42.28	37.95
Cl	0.00	37.13	37.13
Ch2oh	1.99	27.11	29.10
F	0.00	37.80	37.80
Oh	0.00	32.99	32.99
Br	0.00	37.95	37.95

Calculation of free energy binding

- Energies with respect to solevnt: X
- Energies with respect to protein complex (intra molecular energy): A
- Fitness of the molecule (inter molecular energy) : hydrogen energy + vanderwaals energy : B
- Inter molecular energy + intra molecular energy: A+B =Y

Binding free energy

- Binding free energy (Z) = Y – X
- with respect to analogs:

  Parent molecule binding free energy

  $Z_1 = Y_1 – X$

Table. 3

Binding free energy calculations

Analog	Y(protein complex)	X(solvent)	Binding free energy
Parent molecule	58.0645	7.4325	50.632
Ch3	1320.991	7.4325	1313.7048
Cl	55.7163	7.784	47.9323
Ch2oh	48.088	12.3922	35.6958
F	56.4218	4.6485	51.7733
Oh	52.3775	7.5072	44.8703
Br	56.5135	5.0010	51.5125

Relative binding free energy

- By subtracting binding free energy of every analog from binding free energy of parent molecule we get relative binding free energy
- $Z_2 – Z_1$ = relative binding free energy of 1st analog similarly we obtain all relative binding free energies

The analog which has least relative binding free energy is termed to be best drug for hypertension

Table. 4

Relative binding free energy calculation

Analogs	Binding free energy of analogs	Binding free energy of parent molecule	Relative binding free energy
Parent molecule	50.632	50.632	Null
Ch3	1313.7048	50.632	1263.0728
Cl	47.9323	50.632	-2.6997
Ch2oh	35.6958	50.632	-14.9362
F	51.7733	50.632	1.1413
Oh	44.8703	50.632	-5.7617
Br	51.5125	50.632	0.8805

4. CONCLUSION

Therefore, by performing the above operations based relative binding free energy calculations, I had developed a new drug for hypertension.

- When hydroxy methyl is added to phentolamine forming methyl 4-(1,2,3,4-tetrahydro-1,5-benzodiazepin-5-ylmethyl) benzoate i.e., i.e., $\mathbf{C_{18}H_{20}N_2O_2}$

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