Research Article

Computational and Polarographic study on Drug–Receptor Interaction for Atenolol

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ABSTRACT

Differential Pulse Polarographic (DPP) wave was measured for atenolol in phosphate buffer solution pH 7.4 with a concentration of 1.12 ×10^{-5} M at 37 C°, using hanging dropping mercury electrode HDME as a working electrode, the study found that atenolol is an electrical active agents and has $E_{1/2}$ 0.112 V, the important part of the polarographic study is the interaction between drug - receptors. Two amino acids cysteine and tryptophan were selected as receptors, based on literature. After formation of molecular complexes for drug-receptor, a positive displacement in the value of the half-wave potential was noted, which refers to increasing on the energy gap of HOMO-LUMO molecular orbital's of the drug. By linking to the thermodynamic K_{eq} and kinetic behavior, the rate constants of the forward k_1 and reverse k_{-1} reaction was calculated for atenolol–receptor molecular complexes and through the half-life time was calculated. Gibbs free energy was calculated which gave a negative value for all the molecular complexes under study as an indicator of the spontaneous interaction. The chemical affinity was also calculated which gave a positive result as an indicator of the high tendency of molecules to associated with each other. A computational study using Gaussian software, DFT-6311G for the formation of molecular complexes of atenolol with receptors, gave an indicated for a significant agreement between the behavior of complexes in theoretical study and polarographic study, depending on the value of the energy gap between the molecular orbitals HOMO-LUMO.

Keywords: atenolol, DFT-6311G, drug-receptor, differential pulse polarography.

INTRODUCTION

Atenolol is a cardio selective β-1 adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities and it has been used for the treatment of hypertension[1]. It is poorly absorbed from the lower gastrointestinal tract. The oral bioavailability of atenolol has been reported to be 50%[2]. The ability of drugs to exert a biochemical and/or biophysical modification in cellular activity, depend mainly on its ability to interact with cellular receptors (macromolecular structures located intracellularly or on the cell surface). This interaction could be achieved by binding of drugs to the cellular surface receptors, nucleic acids or enzymes, which will be reflected to formation of drug-receptor complex which leads to a biologic response. The selectivity of the receptor is mainly determined by the drug-receptors interaction involves the formation of chemical bonds, mainly electrostatic and hydrogen bonds, as well as weak interactions involving van der Waals forces. These bonds are important in determining the selectivity of receptors, because the strength of these noncovalent bonds is related inversely to the distance between[3]. in differential pulse Polarography (DPP) a 50 mV pulse is applied during the last 50 mS of the life time of the mercury drop. A current is measured double during the life time of each drop, firstly just before the pulse and second one just before the drop falls. The difference in the current is plotted result a peak shaped curve. The top of the peak corresponds to $E_{1/2}$ and the height of the peak depends on the concentration. The peak current in differential pulse Polarography increases linearly with the concentration of the analyte[4].

Computational chemistry has become a useful way to investigate materials that are too difficult to find or too expensive to purchase. It also helps chemists make predictions before running the actual experiments so that they can be better prepared for making observations[5].

MATERIALS AND MEASUREMENTS

All chemicals used in this investigation were obtained from commercial sources.

Device used was Polarographic analyzer model 797VA supplied from Metrohm made in Switzerland which have two electrodes Rotating disk electrode RDE & Multi-Mode Electrode MME having three modes :Dropping mercury electrode DME, Static mercury drop electrode SMDE and Hanging mercury drop electrode HMDE.

Polarographic cell Consisting of three electrodes:

1. **Working Electrode**: the dropping mercury electrode which is normally a cathode of the Polarographic cell
2. **Reference Electrode**: Silver-Silver chloride electrode immersed in a solution of potassium chloride 3M. (Ag/AgCl/KCl).

3. **Auxiliary Electrode**: it is an inert electrode consist of platinum rod

Also, there is a tube in which the nitrogen gas pass through it into the Polarographic cell.

Preparation of buffer phosphate

Preparation of aqueous solutions of phosphate buffer was occurred by mixing a given volume of Monopotassium phosphate solution 0.0667 M and then complete the volume to 100 mL with Sodium phosphate dibasic dehydrate solution 0.0667M and then it was adjusting pH values by using pH meter.

Preparation of atenolol, cysteine and tryptophan solutions

Aqueous solutions of atenolol M.Wt=266.336 g/mol, cysteine M.Wt=121.16 gm/mol and tryptophan MW.t=204.23 g/mol were prepared with concentration of 1.12×10^{-4}, 0.99×10^{-4} and 0.97×10^{-4} M of atenolol, cysteine and tryptophan respectively by weighing 0.004g, 0.0003g and 0.0005 g respectively in 100 mL as a stock solutions.

RESULTS AND DISCUSSION

Atenolol was electrochemically oxidized for example at Multi-walled carbon nanotube (MWCNT)-modified glassy carbon electrode[6]. In this study the reduction polarographic wave was determined using HMDE as a working electrode, an optimized condition was determined, which found to be: Initial purge Time 300 Sec., Drop Size 9 mm^3, Deposition Time 35 Sec., Equilibration Time 60 Sec., Voltage Step 0.006 V, Voltage Step Time 0.4 Sec, Pulse Amplitude 0.05 V, Pulse Time 0.02 Sec. Initial potential -0.4 V, Final potential +0.4V, Polarographic wave recorded before and after optimization figure 1, showed peak at $E_{1/2}$ =0.112 V and I_d= 42 µA

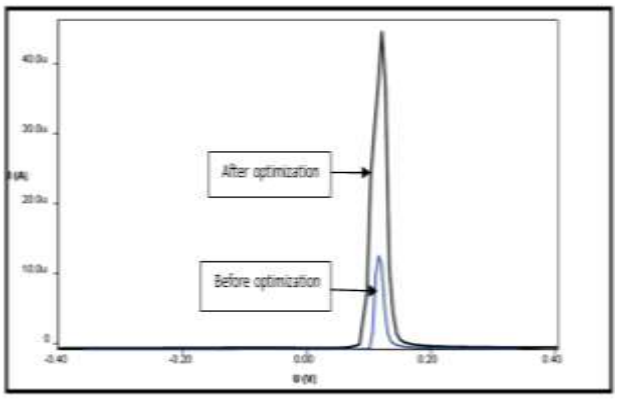

Figure 1: Atenolol DPP polarogram before and after optimization determination of drug-receptor interaction

β1-adrenoceptor (β1AR) is the site of action of beta blockers, β1-adrenoceptor having an Amino acid Side-Chain include Leu, Trp, Thr, Asp, Val, Cys, Phe, Tyr, Ala, Ser, Asn. Coupled amino acids, cysteine and tryptophan have been suggested as receptors for atenolol[7,8]

Study of polarographic behavior of receptors

From the polarographic study it had been noted that the amino acids suggested as receptors has a polarographic wave with $E_{1/2}$ value different from those of pharmaceutical compound, the polarographic behavior of amino acids have been studied by DPP in the buffer phosphate pH=7.4 with a concentration of 0.99×10^{-5} and 0.97×10^{-5} M for cysteine and tryptophan respectively, at 37°C. cysteine gave polarographic wave at $E_{1\backslash 2}$ 0.19 V and Id 16.5 µA .while tryptophan gave polarographic wave at $E_{1\backslash 2}$ 0.13V and Id 28.7 µA .the interaction between drug and receptor could be represented as:

$$\mathbf{Drug} + \mathbf{receptor} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathbf{Drug\,receptor}$$

The concentrations of reactants or product could be follow through a physical property change (as a function of concentration) during the course of the reaction, such as limiting current (Diffusion current) in a Polarography. Thus interaction kinetic equation can be written as following[9]:

$$\ln \frac{id(eq)}{id\,(eq) - id\,(x)} = (k_1 + k_{-1})t$$

$$id_{(x)} = id_{(0)} - id_{(t)}$$

where:

id $_{(t)}$: diffusion current measured in different time t

id $_{(0)}$: diffusion current at time t = 0

so, by plotting **ln[id** $_{(eq)}$**/ id** $_{(eq)}$ **– id**$_{(x)}$**]** against t and calculate the value of slop which equal to $k_1 + k_{-1}$ we could calculate the rate constants and equilibrium constant of the drug-receptor interaction.

Determination of Cys and Trp interaction with atenolol

The effect of added Cys & Trp on the half wave potential of atenolol had been studied in phosphate buffer pH 7.4 at 37C° by using a two mole ratio (1:1 & 1:2) to the drug–receptor. It has been noted that half wave potential of atenolol shifted in a different values with changing times and type of additive.

Atenolol–Cysteine interaction

Study of atenolol – Cys interaction given a clear shifting to the polarographic wave of the drug after complication, which was at $E_{1/2}$ = 0.112 V, Id = 42 µA before interaction and become at $E_{1/2}$ = 0.187 V, Id = 53.9 µA after interaction, while the polarographic wave of cysteine was $E_{1/2}$ = 0.19 V, Id = 16.5 µA, figure 2, figure 3, table 1, table 2, the interaction between Atenolol and cysteine positively shifted the polarographic peak of Atenolol in a magnitude of +0.075 V that is a proof of drug–receptor interaction, the diffusion current for both mole ratio slightly decrease from the value atenolol, In both cases the magnitude of $E_{1/2}$ shifting is the same with a difference in Id value.

Atenolol-Tryptophan interaction

The interaction study of Atenolol–tryptophan given a clear shifting to the polarographic wave of the drug after complication, which was at $E_{1/2}$ = 0.112 V, Id = 42 µA before interaction and become at $E_{1/2}$ = 0.14 V, Id = 39.9 µA after interaction, while the polarographic wave of tryptophan was $E_{1/2}$ = 0.13 V, Id = 28.7 µA, figure.2, figure.3, table 1, table 2. The interaction between Atenolol and tryptophan positively shifted the polarographic peak of Atenolol in a magnitude of +0.028 v that is a proof of drug–receptor interaction.

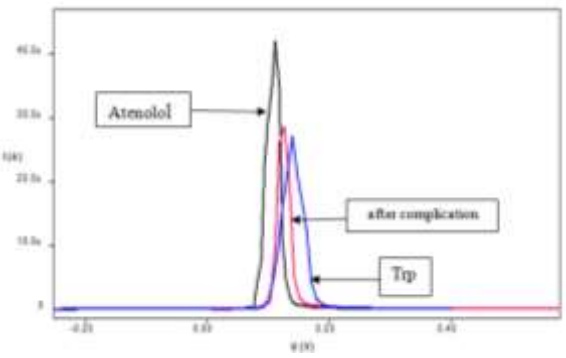

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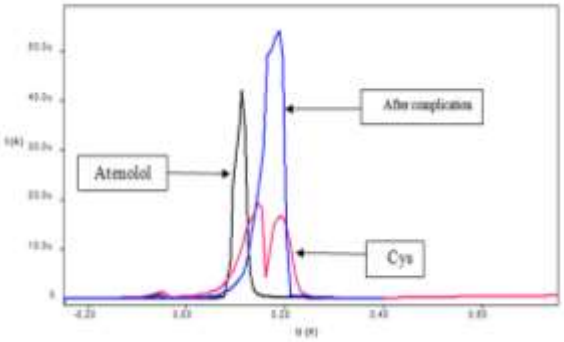
Figure 2: a-polarographic wave potential Atenolol–Cysteine interaction, b-polarographic wave potential Atenolol-Tryptophan interaction



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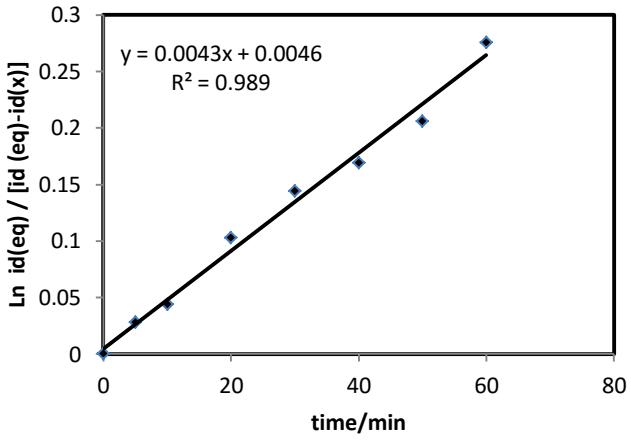

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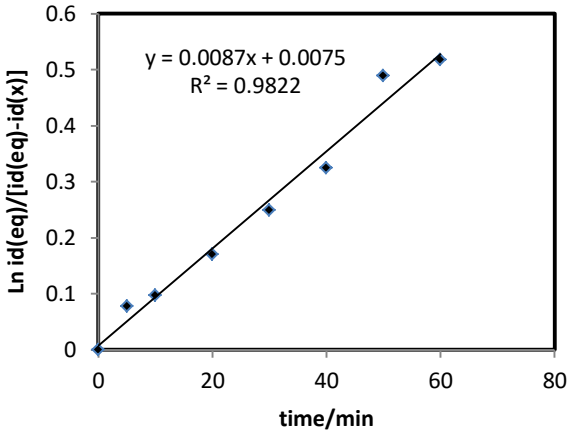

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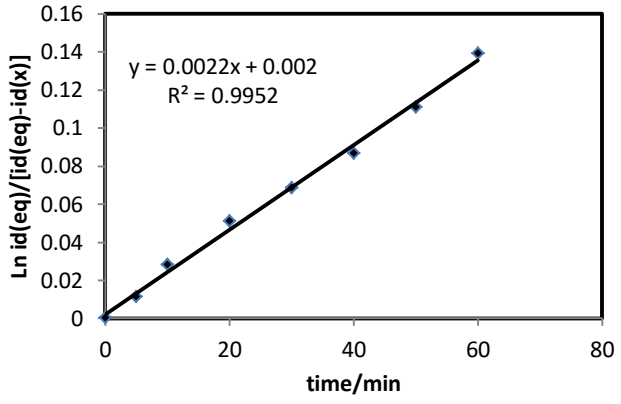

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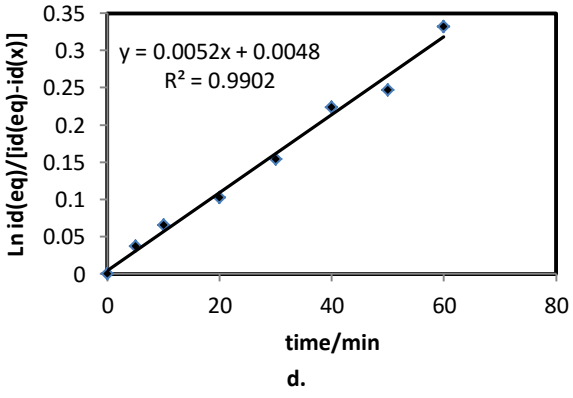

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Figure 3: a. Consequence of the rate of irreversible equilibrium interaction of ATN-Cys 1:1 vs. time, b. Consequence of the rate for irreversible equilibrium interaction of ATN-Cys 1:2 vs. time, c. Consequence of the rate for irreversible equilibrium interaction of ATN-Trp 1:1 vs. time, d. Consequence of the rate for irreversible equilibrium interaction of ATN-Trp 1:2 vs. time

Table 1: Half wave potential $E_{1/2}$ after and before complexation with time for molecular complexes

Molecular complex	Time/min	$E_{1\backslash2}$/V carvedilol	$E_{1\backslash2}$/V mixture	Δ $E_{1\backslash2}$	Id/µA
Atenolol–Cysteine 1:1	5	0.112	0.187	+0.075	41.1
	10	0.112	0.187	+0.075	40.6
	20	0.112	0.187	+0.075	38.8
	30	0.112	0.187	+0.075	37.6
	40	0.112	0.187	+0.075	36.9
	50	0.112	0.187	+0.075	35.9
	60	0.112	0.187	+0.075	34.1
	120	0.112	0.187	+0.075	33.2
	1440	0.112	0.187	+0.075	32.8
Atenolol–Cysteine 1:2	5	0.112	0.187	+0.075	41.6
	10	0.112	0.187	+0.075	41
	20	0.112	0.187	+0.075	40.2
	30	0.112	0.187	+0.075	39.6
	40	0.112	0.187	+0.075	39
	50	0.112	0.187	+0.075	38.2
	60	0.112	0.187	+0.075	37.3
	120	0.112	0.187	+0.075	36.6
	1440	0.112	0.187	+0.075	36.2
Atenolol + tryptophan 1:1	5	0.112	0.14	+0.028	39.9
	10	0.112	0.14	+0.028	39.4
	20	0.112	0.14	+0.028	37.6
	30	0.112	0.14	+0.028	35.8
	40	0.112	0.14	+0.028	34.2
	50	0.112	0.14	+0.028	31.1
	60	0.112	0.14	+0.028	30.6
	120	0.112	0.14	+0.028	29.5
	1440	0.112	0.14	+0.028	28.2
Atenolol + tryptophan 1:2	5	0.112	0.14	+0.028	40.8
	10	0.112	0.14	+0.028	39.9
	20	0.112	0.14	+0.028	38.8
	30	0.112	0.14	+0.028	37.3
	40	0.112	0.14	+0.028	35.4
	50	0.112	0.14	+0.028	34.8
	60	0.112	0.14	+0.028	32.7
	120	0.112	0.14	+0.028	31.4
	1440	0.112	0.14	+0.028	30.9

Table 2: The gradual increase in the diffusion current of molecular complexes with time

Molecular complex	*Time/min.*	$id_{(x)}$/ µA	$\frac{id\,(eq)}{id\,(eq)\,-\,id\,(x)}$	ln $\frac{id\,(eq)}{id\,(eq)-id\,(x)}$
Atenolol – Cysteine 1:1	5	0.9	1.028213	0.027823
	10	1.4	1.044586	0.043621
	20	3.2	1.108108	0.102654
	30	4.4	1.15493	0.144039
	40	5.1	1.184116	0.168996
	50	6.1	1.228464	0.205765
	60	7.9	1.317269	0.275561
	120	8.8	1.366667	0.312375
	1440	9.2	***(indeterminate)**	*
Atenolol – Cysteine 1:2	5	0.4	1.011173	0.011111
	10	1	1.028409	0.028013
	20	1.8	1.052326	0.051003
	30	2.4	1.071006	0.068598
	40	3	1.090361	0.086509
	50	3.8	1.117284	0.110901
	60	4.7	1.149206	0.139072
	120	5.4	1.175325	0.161544
	1440	5.8	* **(indeterminate)**	*
Atenolol +tryptophan 1:1	5	2.1	1.08046	0.077387
	10	2.6	1.101563	0.09673
	20	4.4	1.184874	0.169636
	30	6.2	1.281818	0.24828
	40	7.8	1.382353	0.323787
	50	10.9	1.630058	0.488615
	60	11.4	1.678571	0.517943
	120	12.5	1.796178	0.585661
	1440	13.8	* **(indeterminate)**	*
Atenolol +tryptophan 1:2	5	1.2	1.037855	0.037156
	10	2.1	1.068182	0.065958
	20	3.2	1.107744	0.102326
	30	4.7	1.166667	0.154151
	40	6.6	1.250951	0.223904
	50	7.2	1.280156	0.246982
	60	9.3	1.394068	0.332226
	120	10.6	1.475336	0.388886
	1440	11.1	* **(indeterminate)**	*

Drug-amino acid interaction is due to the formation of molecular complex between drug and receptor (amino acid), Molecular complexes are held together by hydrogen bonds or weak van der Waals attractive interaction or Dispersion Forces.

A large group of complexes formed by the weak interaction of organic substances, functioning as electron donors with other substances which act as electron acceptors.

These complexes are formed by non-covalent interaction[10].

The existence of carbonyl and NH group of amino acids play an important role in the formation of intermolecular hydrogen bonds with pharmaceutical compounds, the interaction between pharmaceutical compound and additives was an irreversible reaction therefore, it has extremely importance by linking between the kinetic behavior of the reaction and thermodynamic properties[11].

When cysteine and tryptophan add to atenolol it has been noted a positively shifted to the polarographic wave, meaning that these additives increase the energy level of the lowest unoccupied molecular orbital (LUMO) of the atenolol, which directly proportion to the half wave potential, So, the potential of atenolol will be increased because of linearity relation between the potential of unsaturated hydrocarbon compound and the lowest unoccupied molecular orbital (LUMO) of the molecule[12] also due to increasing in HOMO-LUMO energy gap.

Rate constants and equilibrium constants account for the formation of molecular complexes

The rate constants of the reaction are of great importance in various chemical reactions, because it represents the number of particles generated or consumed during a given period of time. The rate constants depend greatly on the temperature. Accordingly, increase since the higher the temperature, due to an increased number of collisions so should maintain the reaction temperature while calculation of rate constants of reaction[13]. On this basis, it can be account the rate constant of the front and reverse account depending on the value of the equilibrium constant ($K_{eq.}$). And the value of the slop (k_1 + k_{-1}) resulting from drawing the equation of equilibrium reversible reaction vs. time, shown in figure.3.

$$slop = k_1 + k_{-1}$$

$$k_{eq} = \frac{id_{eq}}{id_0 - id_{eq}} = \frac{k_1}{k_{-1}}$$

It has been noted, for all interaction, that's the rate constants of the forward molecular complex interaction are larger than those for reversible interaction, which means that the interaction moving towards products formation, the rate constant of the forward interaction became larger than those of reversible one, it is may be due to le chatelier's principle[14]. Then $t_{0.5}$ has been calculated depending on the slop value and from the below equation[13], table (3):

$$t_{0.5} = \frac{0.693147}{k_1 + k_{-1}}$$

Determination of Gibbs free energy and chemical affinity for molecular complexes

Gibbs free energy is a measure of chemical reaction Spontaneity that could be directly accounted from the equilibrium constant according to Vant-Hoff equation:

$$\Delta G^\circ = -RT\ Ln\ K_{eq}$$

The negative value of ΔG° refers to the spontaneous interaction. This had been noted in all interactions happened between atenolol and receptors. Table (3).

Chemical affinity is the tendency of a molecule to associate with another. The affinity of a drug is its ability to bind to its biological target (receptor, enzyme, transport system, etc.) For pharmacological receptors it can be thought of as the frequency with which the drug, when brought into the proximity of a receptor by diffusion, will reside at a position of minimum free energy within the force field of that receptor[15]. Chemical affinity having a positive value for the spontaneous process and vice versa:

$$A = -(\Delta G^\circ)_{T,P,n}$$

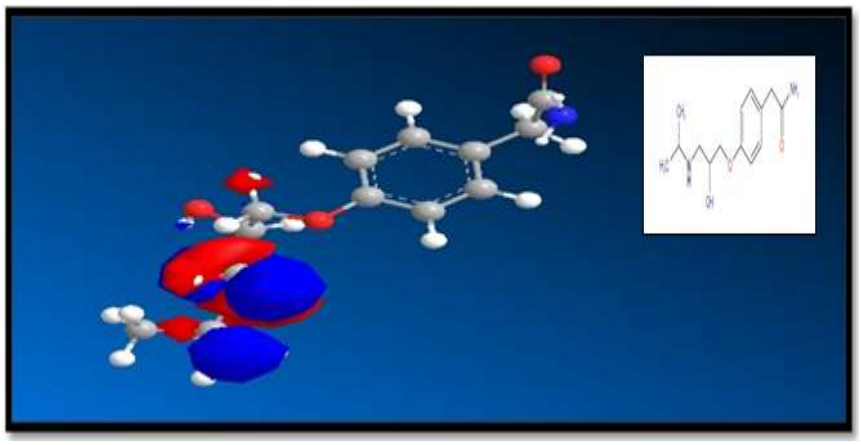
All molecular complexes had high affinity to interact

Table 3: rate constant, half time, Gibbs free energy and chemical affinity of molecular complexes

NO.	*Molecular Complex*	$K_{eq.}$	*Slop*	$t_{0.5}$/min	k_1/min^{-1}	k_{-1}/min^{-1}	ΔG° / KJ. $mole^{-1}$	A/ KJ. $mole^{-1}$
1	ATN +Cys 1:1	3.565217	0.004334	159.8985	0.0034	0.0009	-3.27654	3.27654
2	ATN +Cys 1:2	6.241379	0.002227	311.181	0.0019	0.0003	-4.71986	4.71986
3	ATN +Trp 1:1	2.043478	0.008662	80.00462	0.0058	0.0028	-1.84199	1.84199
4	ATN +Trp 1:2	2.783784	0.005231	132.4794	0.0038	0.0014	-2.63884	2.63884

Table 4: molecular orbital's energies for compounds & molecular complexes and the relation between theoretical and experimental complexation study

Compound	HOMO/eV	LUMO/eV	Δ HUMO-LUMO/eV	E 1/2 experimental	Notes
ATN	-10.579	-0.974	9.605	0.112	Increasing in Δ HOMO-LUMO energy gap that calculated theoretically, exactly agrees with Positively shifted of E1/2, the higher shifting is in wave potential for ATN-Cys complex
Trp	-10.632	1.668	12.3	0.13	
ATN +Trp	-10.645	-0.526	10.119	0.14	
Cys	-9.895	0.137	10.032	0.19	
ATN+ Cys	-10.991	-0.752	10.239	0.187	



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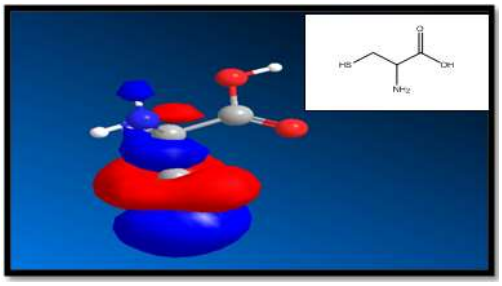

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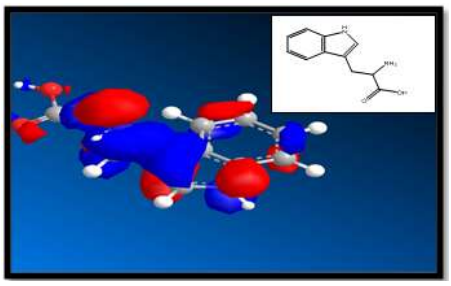

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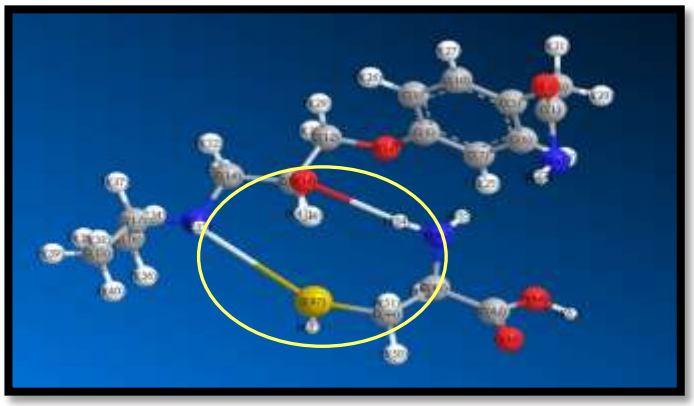

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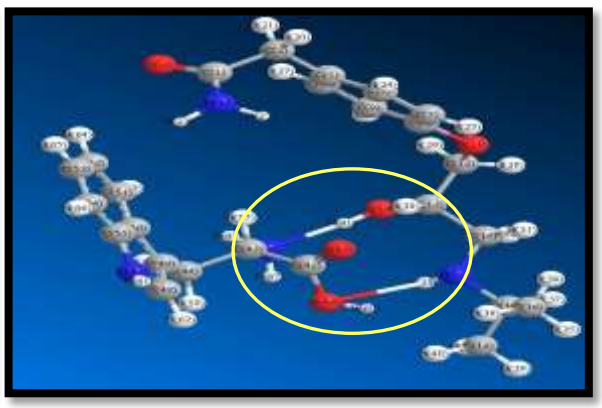

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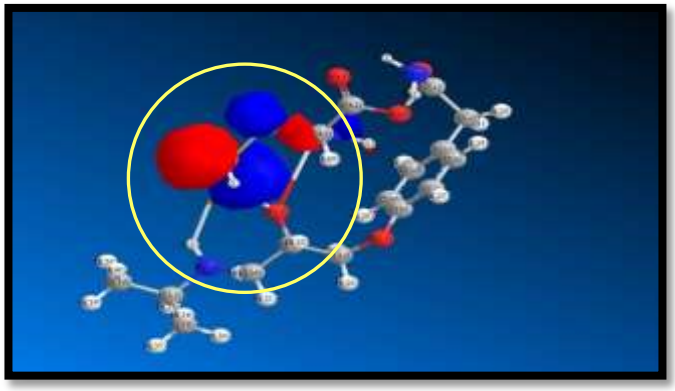

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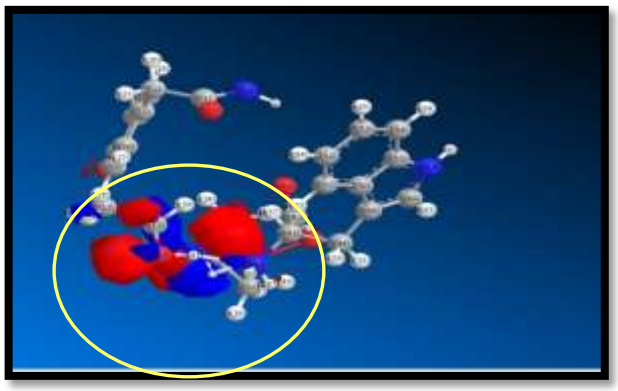

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Figure 4: a. HOMO of atenolol; b. HOMO of cysteine; c. optimized structure of ATN+ Cys molecular complex, d. HOMO of ATN+ Cys molecular complex, e. HOMO of Tryptophan, f. optimized structure of ATN + Trp molecular complex, g. HOMO of ATN + Trp molecular complex

The above results (Table 3) showed a positive value of chemical affinity for all molecular complexes meaning that, the interaction displaced towards equilibrium, formation of a stable molecular complexes between atenolol and additives. As they begin in a physical operations (move a substance towards the other) in addition to a simple equilibrium processes leading to complex systems (particles collected and interact and the formation of molecular complexes) and the occurrence of some molecular changes that characterize the chemical process such as the driving force influencing the processes (A) and standard free energy (ΔG^{o}) from which the system tends to move from any state to another, right up equilibrium state.

Complexation study

Computational modeling has become a powerful tool in understanding detailed protein-ligand interactions at molecular level and in rational drug design. To study the binding of a protein with multiple molecular species of a ligand, one must accurately determine both the relative free energies of all of the molecular species in solution and the corresponding microscopic binding free energies for all of the molecular species binding with the protein[16]. Many computational approaches, at different levels of complexity, have been developed and applied to different ligand–target systems. They essentially differ in the accuracy and resolution level of structural description and in the derived descriptors of ligand–target interactions[17].

Atenolol was studied theoretically to make a comparison between theoretical and experimental complexation study, however, atenolol have a HOMO figure (4), which indicate that HOMO is in the core of the compound. So the interaction with receptor is certainly from the core atenolol interact with both cysteine and tryptophan figure (4). The optimized structure and HOMO illustrated below, attracted attention note was about HOMO of cysteine which is focused around sulfur atom. So interaction of ATN-Cys occur with respect to this fact, hydrogen bonds were making between drug and suggested receptor to achieve the interaction.

Significant approach noted in a comparison between theoretical and experimental complexation results, this comparison depends on the value of HOMO-LUMO gap. Table (4) this may be summarized as below:

- ATN-Cys interaction increase HOMO-LUMO energy gap of atenolol from 9.605 to 10.239eV, energy of HOMO decreased after complexation with increasing of LUMO energy. Which exactly agree with experimental data, reinforce our suggested explanation
- ATN-Trp interaction increase HOMO-LUMO energy gap of atenolol from 9.605 to 10.119eV, energy of HOMO increased after complexation with decreased of LUMO energy agree with experimental data

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