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QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPSOFSOME ATENOLOL AND PROPRANOLOLDERIVATIVES

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ABSTRACT

Objective: five derivatives of atenolol and Propranolol (ATN and PPL) with different activities was studied in order to suggest unprepared derivative of atenolol and Propranolol and suggestion a general equation to calculate the activity for any ATN and PPL derivative. GAUSSIAN 03 software employed to calculate physicochemical and geometrical properties of the derivatives, the calculated quantum chemical parameters were : the energy gap between HOMO-LUMO , dipole moment (μ), electronegativity (χ), electron affinity (A), global hardness (η), ionization potential (I), the global electrophilicity (ω). the results properties used in QSAR equation, as a result a new unprepared ATN and PPL derivatives was suggested with an activity of 3.6721719 mg and 1.935597 mg respectively , as well as Development of a general equation ,specific for calculate activity of atenolol and Propranolol derivatives ,this process may be considered as cost and time consuming process, due to the ability of suggestions a new structures to be synthesized using a computational chemistry methods

Keywords: atenolol , Propranolol,QSAR ,physicochemical properties,DFT**,**dipole moment,electronegativity,electron affinity,global hardness, ionization potential, global electrophilicity.

INTRODUCTION

The continues attempts in the pharmaceutical industry to discover and improve a new biologically active compounds, stimulate the computational medicinal chemist to discover all the possibilities that been provided by what is known as Computer-aided drug design (CADD), which play a vital role in drug discovery and development[1].

Atenolol and Propranolol classified as Beta blocker compounds which are chemical substance having the ability to block the action of endogenous catecholamine such as adrenaline and noradrenalin upon β-adrenergic receptor, resulting in modifying the sympathetic nervous system activity[2].

QSAR are statistical empirical models that relate to quantitative description of chemical structure features of a series of molecules to the responses those molecules show in an experimental system .QSARs are empirical models, that is, they are based on observed trends and correlation between the chemical descriptors and response variables .medicinal chemistry approach to structure activity relationships is based on serial pair-wise comparisons of structural changes with activity changes. QSAR takes a complementary approach and tries to identify how structural changes across a series of molecules related to their activity [3].

EXPERIMENTAL

DFT theory is based on the electron density by using electron density associated with the correct Hamiltonian operator the energy of the system can be completely described. Density Functional Theory is emanating from solving the time independent Schrodinger Equation for the electrons of molecular

systems as a function of the positions of the nuclei. The premise behind the density functional theory is that the energy of a molecule can be determined from the electron density instead of a wave function [4].
Quantum Chemical Parameters that calculated in this study were:

1. Molecular orbital Energies: Highest occupied molecular orbital energy (EHOMO) and lowest unoccupied molecular orbital energy (ELUMO) are very popular quantum chemical parameters. These orbitals determine the way the molecule interacts with other species[5].The energy of the HOMO is directly related to the ionization potential and the energy of the LUMO is directly related to the electron affinity. The HOMO–LUMO gap, i.e. the difference in energy between the HOMO and LUMO, is an important stability index[6] .A large HOMO–LUMO gap implies high stability for the molecule in chemical reactions[7]. The concept of ''activation hardness" has been also defined on the basis of the HOMO–LUMO energy gap. The qualitative definition of hardness is closely related to the polarizability, since a decrease of the energy gap usually leads to easier polarization of the molecule[8].

2. Dipole moment: The most widely used quantity to describe the polarity is the dipole moment of the molecule. Dipole moment is the measure of polarity of a polar covalent bond. It is defined as the product of charge on the atoms and the distance between the two bonded atoms. The total dipole moment, however, reflects only the global polarity of a molecule. For a complete molecule the total molecular dipole moment may be approximated as the vector sum of individual bond dipole moments[9].

3 .The ionization potential (IE): The ionization potential (IE) is defined as the amount of energy required to remove an electron from a molecule. It is related to the energy of the EHOMO through the equation:

$$\mathrm{IE\ (Ionizationpotential)} = -\mathrm{E_{HOMO}}$$

Ionization energy is a fundamental descriptor of the chemical reactivity of atoms and molecules. High ionization energy indicates high stability and chemical inertness and small ionization energy indicates high reactivity of the atoms and molecules .The low ionization energy indicates the high inhibition efficiency[10].

4. Electron affinity (EA): Electron affinity (EA) is defined as the energy released when an electron is added to a system. It is related to E_{LUMO} through the equation:

$$\mathrm{EA\ (Electronaffinity)} = -\mathrm{E_{LUMO}}$$

The higher HOMO energy corresponds to the more reactive molecule in the reactions with electrophiles, while lower LUMO energy is essential for molecular reactions with nucleophiles [10].

5. Chemical Hardness (η): Chemical hardness (η) measures the resistance of an atom to a charge transfer, it is estimated by using the equation:

$$\eta(\mathrm{Hardness}) = (\mathrm{IE} - \mathrm{EA})/2$$

Absolute hardness is important property to measure the molecular stability and reactivity. It is apparent that the chemical hardness fundamentally signifies the resistance towards the deformation or polarization of the electron cloud of the atoms, ions or molecules under small perturbation of chemical reaction. A hard molecule has a large energy gap and a soft molecule has a small energy gap [11].

6. The electronegativity: The electronegativity is the measure of the power of an atom or group of atoms to attract electrons towards itself, it can be estimated by using the following equation:

$$\chi(\mathrm{electronegativity}) = (\mathrm{IE} + \mathrm{EA})/2$$

Electronegativity, hardness and softness have proved to be very useful quantities in the chemical reactivity theory. For a reaction of two systems with different electronegativities the electronic flow will occur from the molecule with the lower electronegativity towards that of higher value, until the chemical potentials are equal [12].

7. Global electrophilicity index (ω): The electrophilicity index (ω), shows the ability of the molecules to accept electrons. It is a measure of the stabilization in energy after a system accepts additional amount of electron charge from the environment. They defined Global electrophilicity index (***ω***) :

$$(\omega) = -x^2 / 2\eta$$

According to the definition, this index measures the propensity of chemical species to accept electrons. A good, more reactive, nucleophile is characterized by lower value of μ, ω; and conversely a good electrophile is characterized by a high value of μ, ω[13].

RESULTS AND DISCUSSION

DFT with a hybrid functional B3LYP is widely used to study biological and pharmacological system[14], so it will be depends. As propranolol and atenolol have the same core ,so general formula was suggested for beta blocker compound fig.1, in order to Facilitate reviewing of results, where:X=naphthalene in propranolol and phenyl acetamide in atenolol (or one of there deravitives) , Y= an isopropyl group in propranololand atenolol

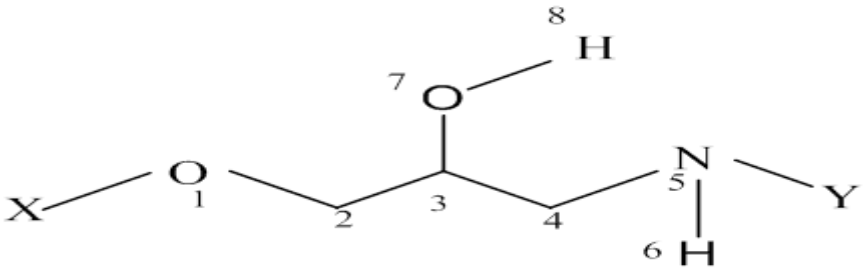

Fig.-1: General structure of beta blockers

The physicochemical properties and geometric properties for a series of ATN and PPL derivatives with different activities, was determined, presented in Table-1, 2 and 3and shown in Figures- 2, 3, 4, 5 and 6.

Table-1: Carvedilol derivatives

No	Abbreviation	Compound name	Activity / mg
1	PPL1	4-methoxy Propranolol	5
2	PPL2	7-hydroxy Propranolol	10
3	ATN1	S-atenolol	25
4	ATN2	2-Hydroxy atenolol	50
5	ATN3	Atenolol Impurity H	100

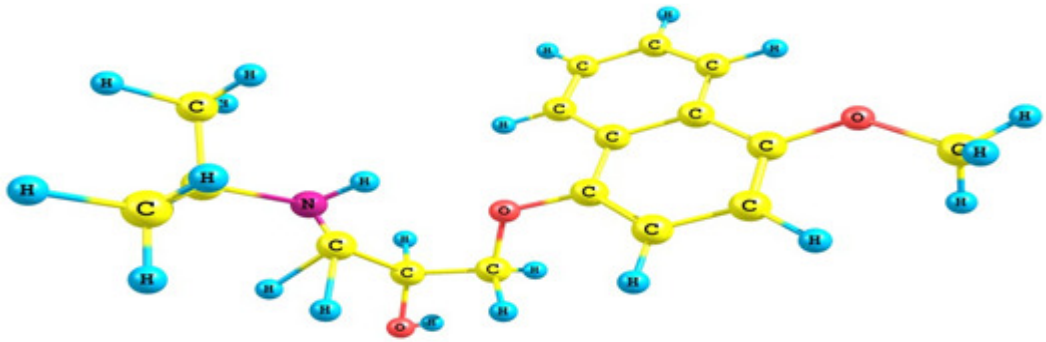

Fig. -2: Geometric structure of PPL1

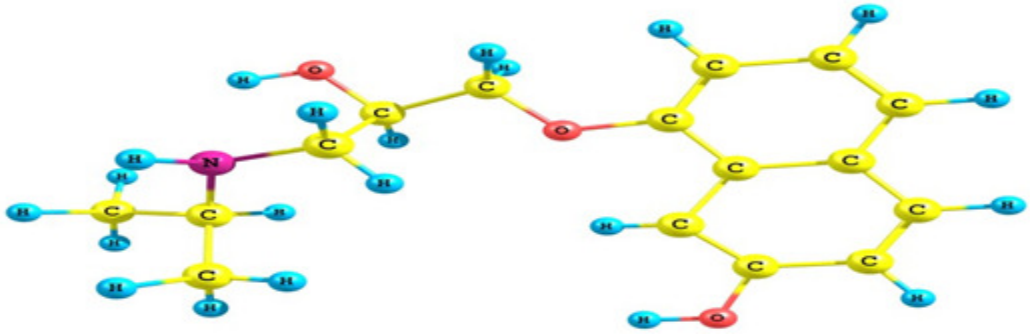

Fig. -3: Geometric structure of PPL2

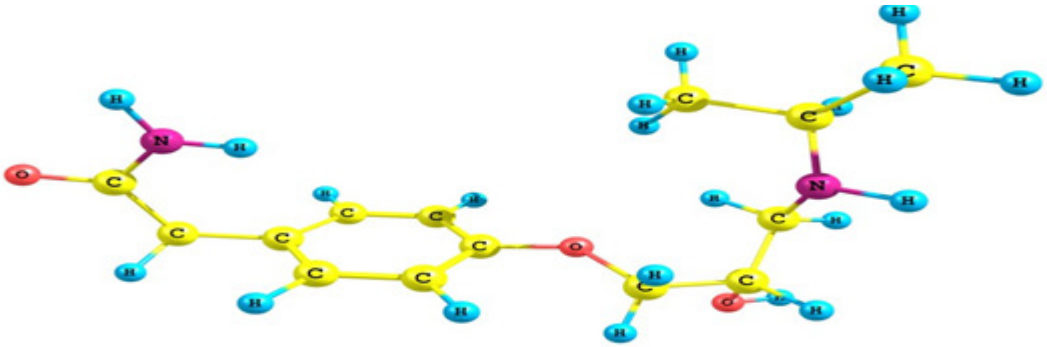

Fig.-4: Geometric structure of ATN1

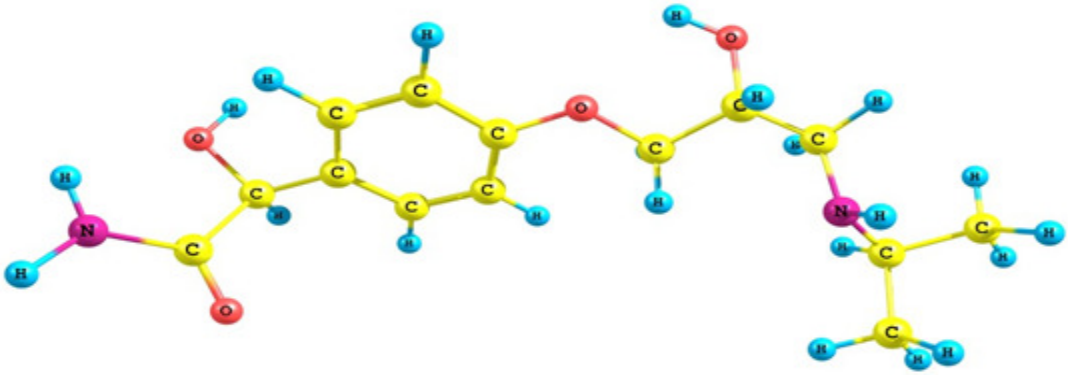

Fig.-5: Geometric structure of ATN2

Fig.-6: Geometric structure of ATN3

Table -2: Physicochemical properties of ATN and PPL derivatives

Compound / Property	PPL 1	PPL2	ATN1	ATN2	ATN3
ΔHf^{o}/ KJ mol^{-1}	-363.31	-376.29	-427.56	-485.07	-393.89
Log P	2.842	2.22	0.22	0.13	1.627
ΔE HOMO-LUMO /eV	7.976	8.04	8.437	8.707	8.722
μ /debye	2.4084	2.9217	8.0405	6.692	5.731
IE /eV	10.554	10.19	9.913	9.882	9.79
EA /eV	2.578	2.15	1.476	1.175	1.068
η /eV	3.988	4.02	4.2185	4.3535	4.361
χ /eV	6.566	6.17	5.6945	5.5285	5.429
ω	-5.40526	-4.734938	-3.843467	-3.510315	-3.379276
Log 1/C	-0.69897	-1	-1.39794	-1.69897	-2

Table -3: Geometrical Properties of ATN and PPL derivatives

Compound		PPL 1	PPL2	ATN1	ATN2	ATN3	Optimal
Property		Actual	Actual	Actual	Actual	Actual	
B.L/A^{o}	O(1)-C(2)	1.4026	1.4322	1.4594	1.4668	1.4327	1.389
	C(2)-C(3)	1.5235	1.5109	1.5161	1.5181	1.5109	1.505
	C(3)-O(7)	1.4102	1.4265	1.459	1.4557	1.4264	1.401
	O(7)-H(8)	0.9493	0.9493	0.9733	0.9744	0.9604	0.961
	C(3)-C(4)	1.5305	1.5245	1.5359	1.5267	1.5227	1.514
	C(4)-N(5)	1.4632	1.4636	1.4668	1.4695	1.4642	1.453
	N(5)-H(6)	1.0504	0.9962	1.0144	1.0166	0.9983	1.05
B.A/A^{o}	X-O(1)-C(2)	119.53	120.5	119.77	119.96	121.79	110.8
	O(1)-C(2)-C(3)	109.78	112.2	107.88	105.22	107.22	107.4
	C(2)-C(3)-O(7)	108.1	105.19	106.87	109.96	102.64	107.7
	C(3)-O(7)-H(8)	110.06	110.4	110.38	109.39	108.19	106.9
	C(3)-C(4)-N(5)	110.89	111.5	110.89	110.72	108.71	109.5
	C(4)-N(5)-H(6)	109.10	111.6	111.37	112.04	112.23	109.47
	H(6)-N(5)-Y	111.04	113.4	111.44	111.36	108.75	109.47
e^{-}	O(1)	8.80173	8.83119	8.74523	8.79723	8.8145	-
	C(2)	5.02481	5.02444	5.02564	5.08010	5.0779	-

density	C(3)	5.13554	5.11947	5.10987	5.09733	5.0688	-
	C(4)	5.17705	5.14463	5.15561	5.12777	5.0709	-
	N(5)	7.49108	7.49082	7.48742	7.4804	7.4793	-
	H(6)	0.42783	0.42338	0.41226	0.4059	0.3827	-
	O(7)	8.53175	8.5304	8.50404	8.50495	8.4899	-
	H(8)	0.37212	0.37046	0.34186	0.32507	0.3212	-
Molecular volume/ $bohr^3mol^{-1}$		2468.8	2530.58	2625.6	2669.1	2748.9	-
Molecular length/A^o		13.20	12.07	12.038	11.26	11.27	-
Molecular width/A^o		7.05	6.76	6.32	6.02	4.69	-
L/W %		1.87234	1.7855	1.90474	1.8704	2.4029	-

For each properties, select a sharing percent to the activity depending on the slope (S) of properties linearity behavior to activity, Tables-2 to 5. By solving set of mathematical equations using wolfram mathematics 7 program[15] , to found final activity equation-1:

Activity = f (Physicochemical or Geometrical Properties) + Constant (1)

Equation-1 is a simple statement of QSAR relationship. In quantitative structure activity relationship (QSAR), the calculated properties of molecules and their experimentally determined biological activity are correlated. QSAR relationships in turn may be used to predict the activity of new analogs. QSAR modeling produces predictive models derived from application of statistical tools correlating biological activity that includes desirable therapeutic effect with descriptors representative of molecular structure or properties.

Acquiring a good quality QSAR model depends on many factors, such as the quality of input data, the choice of descriptors and statistical methods for modeling and for validation. Any QSAR modeling should ultimately lead to statistically robust and predictive models capable of making accurate and reliable predictions of the modeled response of newcompounds[16].

Table -4: Linear Regression and correlation coefficient for physicochemical Properties of ATN and PPL derivatives

X=Physicochemical property	Drugs	PPL1	PPL2	ATN1	ATN2	ATN3
	Y= Log 1/C	-0.699	-1	-1.398	-1.699	-2
	R^2		Linear Regression			
ΔHf^o/ KJ mol^{-1}	0.332		y= 0.006 x + 1.169			
Log P	0.392		y= 0.271x – 1.741			
ΔE HOMO-LUMO /eV	0.941		y= -1.425x+10.85			
μ /debye	0.508		y= -0.153 x – 0.566			
IE /eV	0.886		y= 1.581x-17.28			
EA /eV	0.958		y = 0.785x - 2.685			
η /eV	0.941		y= -2.851x + 10.85			

χ /eV	0.945	y= 1.061x – 7.600
ω	0.943	y= -0.585 x – 3.801

By plotting the relation of each physicochemical and geometrical property against activity (Log 1/C) and calculate the equation of linear regression and correlation coefficient of each one ,then chosen the best properties that have the highest value of correlation coefficient which was: partition coefficient Log P , ΔE HOMO-LUMO /eV, dipole momentum and hardness η /eV.

In geometrical properties it is clearly noted that the length and the angle of bonds was not a paramount factors on the activity with a significant effect of density of electron on each atom on the activity of the compound, which explain the variation of activity values with replacement of different donating groups on the core or side group of selected compounds

Molecular length, width and volume was another effective properties on the activity of compounds this is may be due to taking a suitable shape in drug-receptor interaction, the chosen one was a molecular length with a higher value of correlation coefficient.

Table -5: Linear Regression and correlation coefficient for Geometrical Properties of ATN and PPL derivatives

X=Geometrical properties		Drugs	PPL1	PPL2	ATN1	ATN2	ATN3
		Y= Log 1/C	-0.699	-1	-1.398	-1.699	-2
		R^2		Linear Regression			
B.L/A°	O(1)-C(2)	0.375		y= -12.56 x +16.72			
	C(2)-C(3)	0.261		y= 50.34 x-77.67			
	C(3)-O(7)	0.248		y= -12.40 x +16.44			
	O(7)-H(8)	0.415		y= -27.41 x+ 25			
	C(3)-C(4)	0.127		y= 35.46 x –55.55			
	C(4)-N(5)	0.249		y= -98.23 x+142.6			
	N(5)-H(6)	0.348		y= 14.19 x- 15.76			
B.A/A°	X-O(1)-C(2)	0.443		y= -0.386 x +45.12			
	O(1)-C(2)-C(3)	0.556		y= 0.147 x – 17.31			
	C(2)-C(3)-O(7)	0.102		y= 0.059 x – 7.728			
	C(3)-O(7)-H(8)	0.624		y= 0.444 x – 50.08			
	C(3)-C(4)-N(5)	0.563		y= 0.368 x – 42.04			
	C(4)-N(5)-H(6)	0.695		y=- 0.346 x + 37.14			
	H(6)-N(5)-Y	0.401		y= 0.200 x – 23.60			
e^- density	O(1)	0.008		y= 1.465 x – 14.25			
	C(2)	0.732		y= -15.1x + 74.84			
	C(3)	0.940		y= 20.16 x – 104.3			
	C(4)	0.776		y= 11.47 x - 60.3			
	N(5)	0.907		y= 88.31x – 662.4			

	H(6)	0.975	y= 37.20 x -16.69
	O(7)	0.958	y= 27.80 x – 238.0
	H(8)	0.942	y= 20.92 x – 8.603
Molecular volume/bohr^{3}mol^{-1}		0.995	y= -0.004 x +10.89
Molecular length/A^o		0.855	y= 0.608 x – 8.645
Molecular width/A^o		0.870	y= 0.532 x – 4.640
L/W %		0.516	y= -1.516 x+1.624

The best physicochemical properties that have the highest value of correlation coefficient was: ΔE HOMO-LUMO /eV, electron affinity EA, electronegativity χ and electrophilicity index (ω)

In geometrical properties ,the length and the angle of bonds has a greater effected on activity than those noted in carvedilol compounds this is may be attributed to the small volume of side group compare with carvedilol derivatives ,which may be influence the core of molecule by any donating group on the side group with a large number of magnitude, nevertheless, it is also not a paramount factors on the activity with a significant effect of density of electron on each atom on the activity of the compound.
Molecular length, width and volume were also effective properties on the activity of compounds this is may be due to taking a suitable shape in drug-receptor interaction, the chosen one was a molecular volume length with a higher value of correlation coefficient.

Table -6: Sharing of selected physicochemical Properties to the activity of ATN and PPL derivatives as a function of slop

Property / Drug	Log 1/C	ΔE HOMO-LUMO *S	EA * S	χ * S	**ω*** S
PPL1	-0.69897	-11.3658	2.02373	6.966526	-3.162077
PPL2	-1	-11.457	1.68775	6.54637	-2.769939
ATN1	-1.39794	-12.0227	1.15866	6.041865	-2.248428
ATN2	-1.69897	-12.4075	0.922375	5.865739	-2.053534
ATN3	-2	-12.4289	0.83838	5.760169	-1.976876

y= a0 + a1D1 + a2 D2 + ……..+ a D (Hanschmodel)[17]
y :practical activity
a: regression coefficient
D: descriptors (b * property)
The general equation will be:

$Y=a_0 \pm a_1 * slope * x_1 \pm a_2 * slope * x_2 \pm a_3 * slope * x_3 \pm a_4 * slope * x_4$
Where:
X_1= S*ΔE HOMO-LUMO
X_2=S*EA
X_3=S*χ
ωX_4=S*
So:
$-0.69897=a_0-a_1*11.3658+a_2*2.02373+a_3*6.966526-a_4*3.162077$,
$-1=a_0-a_1*11.457+a_2*1.68775+a_3*6.54637-a_4*2.769939$,

$-1.39794=a_0-a_1*12.0227+a_2*1.15866+a_3*6.041865-a_4*2.248428$,
$-1.69897=a_0-a_1*12.4075+a_2*0.922375+a_3*5.865739-a_4*2.053534$,
$-2=a_0-a_1*12.4289+a_2*0.83838+a_3*5.760169-a_4*1.976876$

Results
a0→ -21.2513
a1→ 1067.25
a2→ -3870.55
a3→ 2872.65
a4→ 9.10079
Then it could conclude the final equation:

$\text{Log } 1/C = -21.2513+1067.25*\text{slope}*x_1-3870.55*\text{slope}*x_2+2872.65*\text{slope}*x_3+9.10079*\text{slope}*x_4$

By applying the amount of properties:

PPL1:
Log 1/C =-21.2513+1067.25*-11.3658-3870.55*2.02373+2872.65*6.966526+9.10079*-3.162077= -0.735986

PPL2:
Log 1/C =-21.2513+1067.25*-11.457-3870.55*1.68775+2872.65*6.54637+9.10079*-2.769939= -1.03417

ATN1:
Log 1/C =-21.2513+1067.25*-12.0227-3870.55*1.15866+2872.65*6.041865+9.10079*-2.248428= -1.42832

ATN2:
Log 1/C =-21.2513+1067.25*-12.4075-3870.55*0.922375+2872.65*5.865739+9.10079*-2.053534= -1.72787

ATN3:
Log 1/C =-21.2513+1067.25*-12.4289-3870.55*0.83838+2872.65*5.760169+9.10079*-1.976876= -2.02819

According to these results a curve was drawing between Theoretical and practical activities:

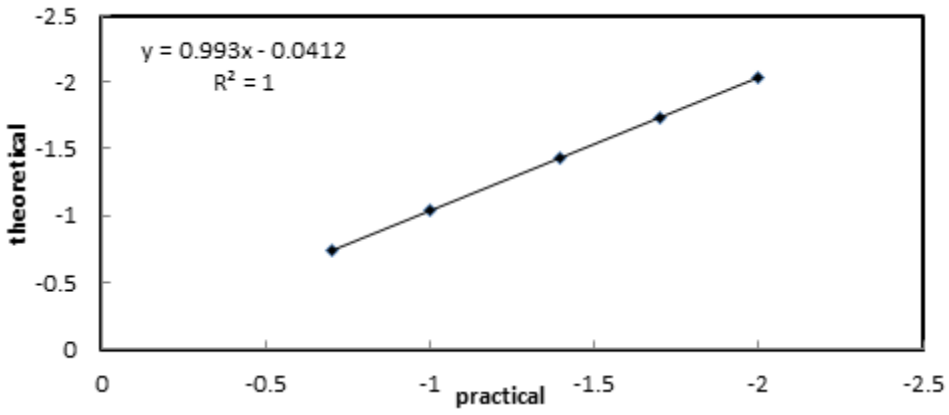

Fig. -7: The relation between practical and theoretical (physicochemical) activity values for PPL and ATN derivatives

High correspond observed with R^2=1 between practical and theoretical activity measured according to physicochemical properties, indicated a high accuracy of input data and the calculated output of program.

Table -7: Sharing of selected geometrical Properties to the activity of PPL and ATN derivatives as a function of slop

Property / Drug	Log 1/C	Density			Molecular Volume *S
		H(6) *S	O(7) *S	H(8) * S	
PPL1	-0.69897	15.91528	237.2383	7.78475	-9.8752
PPL2	-1	15.71254	237.1451	7.750023	-10.1223
ATN1	-1.39794	15.33607	236.5235	7.151711	-10.5024
ATN2	-1.69897	15.09948	236.4376	6.800464	-10.6763
ATN3	-2	14.60658	236.0195	6.7219504	-10.996

The general equation will be:

$$\mathbf{Y=a_0\pm a_1*slope*x_1\pm a_2*slope*x_2\pm a_3*slope*x_3\pm a_4*slope*x_4}$$

Where:

X_1= S* H (6)
X_2=S*O (7)
X_3=S*H (8) ⟶ e^- Density on each atom
X_4=S*Molecular volume

So:

$-0.69897=a_0+a_1*15.91528+a_2*237.2383+a_3*7.78475-a_4*9.8752$,
$-1=a_0+a_1*15.71254+a_2*237.1451+a_3*7.750023-a_4*10.1223$,
$-1.39794=a_0+a_1*15.33607+a_2*236.5235+a_3*7.151711-a_4*10.5024$,
$-1.69897=a_0+a_1*15.09948+a_2*236.4376+a_3*6.800464-a_4*10.6763$,
$-2=a_0+a_1*14.60658+a_2*236.0195+a_3*6.719504-a_4*10.996$

Results

a0→113.418
a1→0.155646
a2→-0.448919
a3→0.256043
a4→1.22389

Then it could be conclude the final equation:

Log 1/C =113.418+0.155646*slope*x_1-0.448919*slope*x_2 +0.256043*slope*x_3+1.22389*slope*x_4

By applying the amount of properties:

PPL1:

Log 1/C =113.418+0.155646*15.91528-0.448919*237.2383 +0.256043*7.78475+1.22389*-9.8752= -0.698559

PPL2:

Log 1/C =113.418+0.155646*15.71254-0.448919*237.1451+0.256043*7.750023+1.22389*-10.1223= -0.99959

ATN1:

Log 1/C =113.418+0.155646*15.33607-0.448919*236.5235+0.256043*7.151711+1.22389*-10.5024= -1.39753

ATN2:

Log 1/C =113.418+0.155646*15.09948-0.448919*236.4376+0.256043*6.800464+1.22389*-10.6763= -1.69856

ATN3:

Log 1/C =113.418+0.155646*14.60658-0.448919*236.0195 +0.256043*6.7219504+1.22389*-10.996= -1.99897

According to these results a curve was drawing between Theoretical and practical activity.

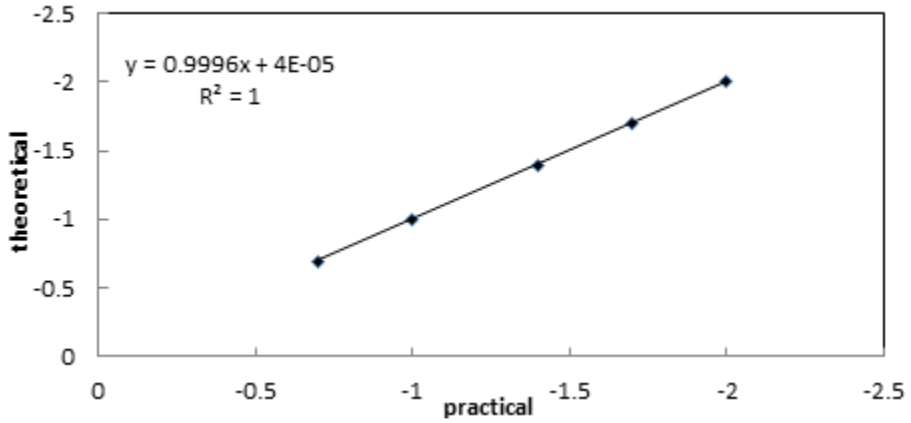

Fig.-8: The relation between practical and theoretical (geometrical) activity values for PPL and ATN derivatives

From figures-4 to 10 and Tables- 4 to 10, it had been noted that the geometrical properties given the most approach value of activity to the experimental.

Table-8: The relation between practical and theoretical activity For ATN and PPL derivatives

Compound	Experimental		Physicochemical		Geometrical	
	Log 1/C	C	Log 1/C	C	Log 1/C	C
PPL1	-0.69897	5	-0.73599	5.444851	-0.69856	4.9952704
PPL2	-1	10	-1.03417	10.818574	-0.99959	9.9905639
ATN1	-1.39794	25	-1.42832	26.811431	-1.39753	24.976409
ATN2	-1.69897	50	-1.72787	53.440437	-1.69856	49.952819
ATN3	-2	100	-2.02819	106.70628	-1.99897	99.763115

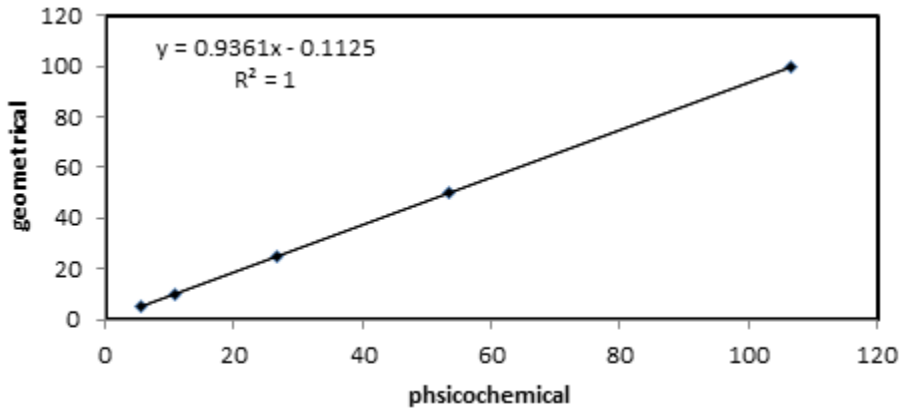

Fig.-9: Relation between activity values calculated according to physicochemical and geometrical properties

From figures-7 and 8 and Table-8, it had been noted that the geometrical properties given the most approach value of activity to the experimental.

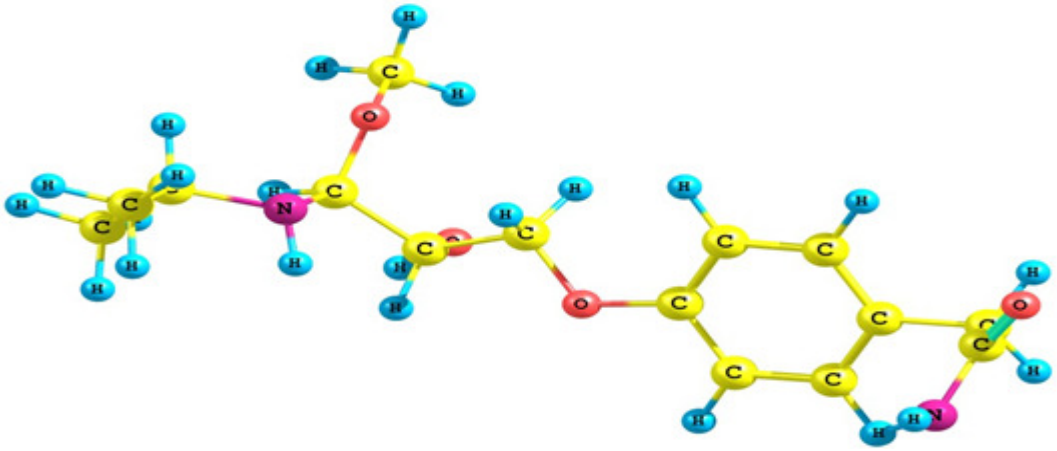

Fig.-10: Geometric structure of ATN4

Suggested unprepared ATN and PPL Compounds

According to all previous study, a new derivative of ATN and PPL was suggested .The new derivative of atenolol include replacing one of hydrogen atom on C4 by methoxy group, which is known as a strong donating group, the resulting derivatives given a name ATN4 has M.Wt= 296.17361 g/mol and a structure shown in Figure-10, The physicochemical and geometrical properties of ATN4 was determined Table-9 and 10.

Table -9: Physicochemical and geometrical properties of ATN4

Physicochemical properties		Geometrical properties	
ΔE HOMO-LUMO	9.456	Density H(6)	0.58041
EA	1.085	Density O(7)	8.688103
χ/ev	5.813	Density H(8)	0.50759
ω	-3.5735	Molecular volume	2376.985

Table-10: Sharing of selected physicochemical and geometrical properties to the activity of ATN4 as a function of slop

Physicochemical properties		Geometrical properties	
S*ΔE HOMO-LUMO	-13.4748	S* Density H(6)	21.59125
S* EA	0.851725	S* Density O(7)	241.5293
S* χ/ev	6.167593	S* Density H(8)	10.61878
S***ω**	-2.090495	S* Molecular volume	-9.50794

So: by Appling the general equation of physicochemical properties-

Log 1/C =-21.2513+1067.25*slope*x_1-3870.55*slope*x_2 +2872.65*slope*x_3+9.10079*slope*x_4

It could be calculated the activity of suggested compound ATN4:

Log 1/C =-21.2513+1067.25*-13.4748-3870.55*0.851725+2872.65*6.167593+9.10079*-2.090495 = -0.564923

Activity of ATN4 = 3.6721719mg

According to general equation of geometrical properties the activity of ATN4 calculated as above:
Log 1/C =113.418+0.155646*slope*x_1-0.448919*slope*x_2 +0.256043*slope*x_3+1.22389*slope*x_4
So:
Log 1/C =113.418+0.155646* 21.591252-0.448919*241.5293 +0.256043 *10.6187828+1.22389*-9.50794 =-0.566308
Activity of ATN4 = 3.6839014mg

Also A new derivative of Propranolol was suggested by replacing two methyl group in the side chain by tow methoxy group , which is known as a strong donating group, the resulting derivatives given a name PPL3 has M.Wt= 291.34224 and a structure shown in Figure-11.

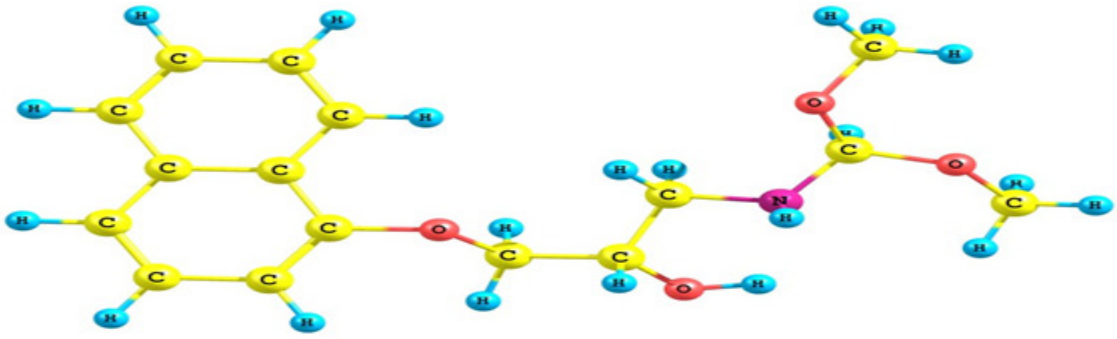

Fig.-11: Geometric structure of PPL3

The physicochemical and geometrical properties of ATN4 was determined Table-11.

Table -11: Physicochemical and geometrical properties of PPL3

Physicochemical properties		Geometrical properties	
ΔE HOMO-LUMO	9.6478	Density H(6)	0.43072
EA	1.0362	Density O(7)	8.53448
χ/ev	5.8601	Density H(8)	0.478176
ω	-3.55944	Molecular volume	2502.3

Table -12: Sharing of selected physicochemical and geometrical properties to the activity of PPL3 derivative as a function of slop

Physicochemical properties		geometrical properties	
S*ΔE HOMO-LUMO	-13.7481	S* Density H(6)	16.02278
S* EA	0.813417	S* Density O(7)	237.2585
S* χ/ev	6.217566	S* Density H(8)	10.00344
S***ω**	-2.08227	S* Molecular volume	-10.0092

So, by applied the general equation of physicochemical properties,
Log 1/C =-21.2513+1067.25*slope*x_1-3870.55*slope*x_2 +2872.65*slope*x_3+9.10079*slope*x_4
It could be calculated the activity of suggested compound PPL3

Log 1/C =-21.2513+1067.25* -13.7481-3870.55* 0.813417+2872.65* 6.217566+9.10079* -2.08227= -0.341526
Activity of PPL3 = 2.1954624≈2 mg

According to general equation of geometrical properties the activity of ATN4 calculated as above:
Log 1/C =113.418+0.155646*slope*x_1-0.448919*slope*x_2 +0.256043*slope*x_3+1.22389*slope*x_4
So: Log 1/C =113.418+0.155646* 16.02278-0.448919*237.2585+0.256043 *10.00344+1.22389*-10.0092= -0.286816
Activity of PPL3 =1.935597 ≈2mg

CONCLUSION

1. The physicochemical and geometric properties, share the same behaviour in general equation description of activity calculation, and gives a good results as shown in figures- 8 and 9.
2. The new suggested compound ATN4andPPL3 has a good activity compare with Atenolol and Propranolol Derivatives.

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