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Research Article

DETERMINATION OF PHYSICOCHEMICAL AND GEOMETRICAL PROPERTIES OF SOME CARVEDILOL DEREVITIVES

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ABSTRACT

Objective: Five derivatives of Carvedilol with different activities were studied in order to suggest unprepared derivative of carvedilol and suggestion a general equation to calculate the activity foe any Carvedilol derivative..

Methods: GAUSSIAN 03 software employed to calculate physicochemical and geometrical properties of carvedilol derivatives, the calculated quantum chemical parameters are: The energy gap between the highest occupied molecular orbital and lowest unoccupied molecular orbital (HOMO-LUMO), dipole moment (μ), electronegativity (χ), electron affinity (A), global hardness (η), ionization potential (I), and the global electrophilicity (ω). The resulting properties used in quantitative structure-activity relationship equation to predict activity.

Results: Suggested unprepared carvedilol derivative with an activity of 1.99×10^{-5} mg as well as development of a general equation, two formula for calculate activity of carvedilol derivatives specifically Log 1/C = −29.5744 + 17.1334 Log p + 19603.97 Δ HOMO-LUMO + 2.7725 μ – 38902 η by mean of physicochemical properties and Log 1/C = 2828.25 + 15.01 N electron density − 308.016 O electron density + 306.97 H electron density + 0.32477 molecular length by mean of geometrical properties.

Conclusion: This process may be considered the cost- and time-consuming process, according to the ability of suggestions, new structures to be synthesized using computational chemistry methods.

Keywords: Quantitative structure-activity relationship, Density functional theory, Highest occupied molecular orbital and lowest unoccupied molecular orbital gap, Global hardness, 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, which play a key role in drug discovery and development [1].

Carvedilol (±)-1-(carbazol-4-yloxy)-3-((2-(o-methoxy-phenoxy) ethyl)o)-2-propanol is a racemic lipophilic aryloxypropanolamine. Non-cardioselective β-adrenergic blocking agent with blocking activity against blocks α1- and ß-adrenergic receptors. It is considered as an effective treatment for mild and moderate congestive heart failure [2].

Quantitative structure-activity relationship (QSAR) is a statistical-empirical model that relates to the 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].

COMPUTATIONAL METHODOLOGY

Gaussian 03 Software is employed to calculate all properties of selected compounds. Gaussian is an electronic structure modeling software application, and it is arguably the most-used computational quantum chemistry program. It does electronic-structure calculations and standard quantum chemical calculations.

Density functional theory (DFT) is based on the electron density using electron density associated with the correct Hamiltonian operator the energy of the system can be completely described. DFT 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 DFT 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 as follows:

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 EHOMO is directly related to the ionization potential, and the ELUMO is directly related to the electron affinity (EA). 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 by 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].

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].

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:

IE (Ionization potential) = $-E_{HOMO}$

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].

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

EA = $-E_{LUMO}$

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].

Chemical hardness (η)
Chemical hardness (η) measures the resistance of an atom to a charge transfer; it is estimated using the equation:

η (Hardness) = (IE−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 toward 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].

Electronegativity
The electronegativity is the measure of the power of an atom or group of atoms to attract electrons toward its self; it can be estimated using the following equation:

χ(electronegativity)=(IE + 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 (the organic inhibitor) toward that of higher value (metallic surface) until the chemical potentials are equal [12].

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):

(ω) = $-x^2/2\eta$

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].

RESULT AND DISCUSSION

Physicochemical and geometrical properties calculation
DFT with a hybrid functional P3LYP is widely used to study biological and pharmacological system [14], so it will be depend.

A general formula was suggested for carvedilol Fig. 1 to facilitate reviewing of results, Where, X = carbazole and Y = alkyl catechol (catecholamine – NH group).

The physicochemical properties and geometric properties for a series of carvedilol derivatives with different activities were determined (Tables 1-3 and Figs. 2-6).

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

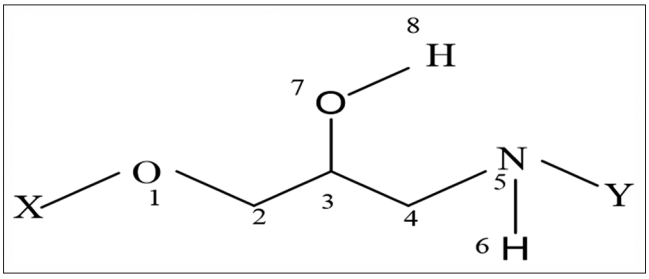

Fig. 1: General structure of beta blockers

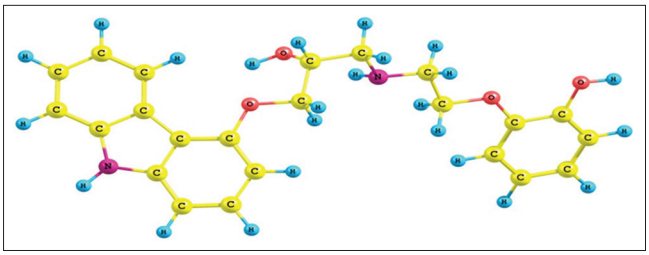

Fig. 2: Geometric structure of CRV1

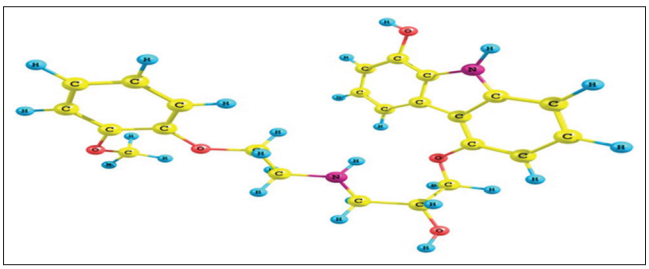

Fig. 3: Geometric structure of CRV2

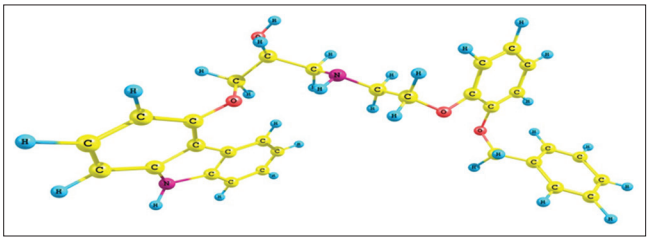

Fig. 4: Geometric structure of CRV3

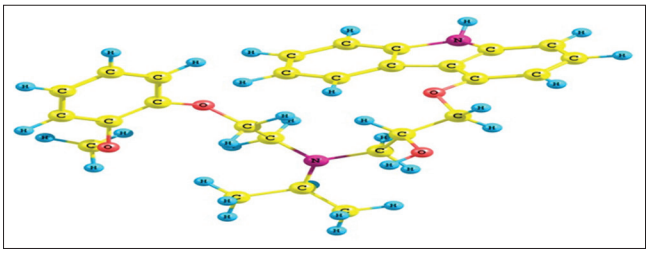

Fig. 5: Geometric structure of CRV4

Activity=ƒ (physicochemical and/or geometrical properties) + constant (1)

Equation (1) is a simple statement of QSAR relationship.

Table 1: Carvedilol derivatives

S. No.	Abbreviation	Compound name	Activity/mg
1	CRV1	R(+)-O-Desmethylcarvedilol	1
2	CRV2	8-hydroxy carvedilol	2.5
3	CRV3	2-O-benzyloxy-2-O-desmethyl carvedilol	5
4	CRV4	N-Isopropyl carvedilol	10
5	CRV5	N-Benzyl carvedilol	25

In QSAR, the calculated properties of molecules and their experimentally determined biological activity are correlated. QSARs in turn may be used to predict the activity of new analogs. QSAR modeling produces predictive models derived from the application of statistical tools

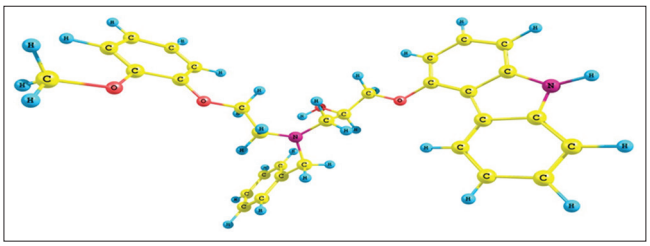

Fig. 6: Geometric structure of CRV5

Table 2: Physicochemical properties of carvedilol derivatives

Property	Compound				
	CRV5	CRV4	CRV3	CRV2	CRV1
ΔHf°/KJ/mol	−399.568	−402.93	−249.761	−208.987	−168.273
Log P	2.861	2.935	4.157	4.858	5.234
ΔE HOMO-LUMO/eV	8.323	7.69	7.533	6.366	6.299
μ/debye	3.5983	2.7081	2.3546	1.9427	1.8477
IE/eV	10.221	10.161	10.063	8.835	8.767
EA/eV	1.898	2.471	2.53	2.469	2.468
η/eV	4.1615	3.845	3.7665	3.183	3.1495
χ/eV	6.0595	6.316	6.2965	5.652	5.6175
ω	−4.411575	−5.187498	−5.262965	−5.018081	−5.009733
Log 1/C	0	−0.39794	−0.69897	−1	−1.39794

HOMO-LUMO: Highest occupied molecular orbital and lowest unoccupied molecular orbital, EA: Electron affinity

Table 3: Geometrical properties of carvedilol derivatives

Property	Compounds					
	CRV5	CRV4	CRV3	CRV2	CRV1	Optimal
	Actual	Actual	Actual	Actual	Actual	
B.L/A°						
O(1)-C(2)	1.465	1.462	1.465	1.465	1.465	1.389
C(2)-C(3)	1.524	1.529	1.524	1.524	1.524	1.514
C(3)-O(7)	1.462	1.463	1.462	1.462	1.462	1.401
O(7)-H(8)	0.975	0.972	0.975	0.975	0.975	0.961
C(3)-C(4)	1.524	1.533	1.524	1.524	1.524	1.514
C(4)-N(5)	1.467	1.464	1.467	1.467	1.467	1.453
N(5)-H(6)	1.016	1.014	1.016	1.016	1.016	1.05
B.A/°						
X-O(1)-C(2)	119.9	120.5	117.34	119.79	119.36	110.8
O(1)-C(2)-C (3)	104.92	112.2	106.27	105.61	106.57	107.4
C(2)-C (3)-O(7)	109.44	102.64	106.72	106.36	106.05	107.7
C(3)-O(7)-H(8)	108.44	110.4	105.35	106.13	104.95	106.9
C(3)-C (4)-N(5)	110.31	111.5	109.27	109.78	109.53	109.5
C(4)-N(5)-H(6)	109.25	111.6	112.05	117.58 107.7 optimal*	113.13 107.7optimal#	109.47
H(6)-N(5)-Y	112.69	113.4	111.76	113.24 107.7 optimal*	113.79 107.7 optimal#	109.47
Density						
O(1)	8.7741	8.7465	8.7393	8.7405	8.7728	-
C(2)	6.0099	6.0104	6.0243	6.0292	6.0176	-
C(3)	5.8985	5.8829	5.8812	5.8417	5.8322	-
C(4)	6.0770	6.0822	6.0997	6.1448	6.1319	-
N(5)	7.7763	7.7703	7.7643	7.7242	7.7057	-
H(6)	0.6674	0.6922	0.6959	-	-	-
O(7)	8.7519	8.7516	8.7427	8.7417	8.7392	-
H(8)	0.5951	0.5930	0.5862	0.5858	0.5819	-
Molecular volume/bohr^{3}mol^{-1}	2938.4	3307.2	4504.8	4178.8	4690.1	-
Molecular length(L)	17.51	16.56	14.64	14.38	14.94	-
Molecular width(W)	8.34	9.19	8.99	9.525	10.44	-
L/W %	2.0995	1.62568	1.84205	1.50971	1.4023	-

* and #given to those molecule that the hydrogen amine is replaced by isopropyl and benzyl group respectively. So, the value of optimal angle certainly differed

Table 4: Linear regression and correlation coefficient for physicochemical properties of carvedilol derivatives

X=Physicochemical properties	Drugs	CRV1	CRV2	CRV3	CRV4	CRV5
	Y=Log 1/C	0	−0.398	−0.699	−1	−1.397
	R^2		Linear regression			
ΔHf°/KJ mol^{-1}	0.876		y=−0.004x−2.018			
Log P	0.916		y=−0.474x+1.203			
ΔE HOMO-LUMO/eV	0.912		y=0.582x−4.920			
μ/debye	0.909		y=0.724x−2.503			
IE/eV	0.788		y=0.645x−6.900			
EA/eV	0.491		y=−1.431x+2.689			
η/eV	0.912		y=1.165x−4.920			
χ/eV	0.488		y=1.110x−7.351			
ω	0.259		y=0.818x+3.375			

HOMO-LUMO: Highest occupied molecular orbital and lowest unoccupied molecular orbital, EA: Electron affinity

Table5: Linear regression and correlation coefficient for geometrical properties of carvedilol derivatives

X=Geometrical properties	Drugs	CRV1	CRV2	CRV3	CRV4	CRV5
	Y=Log 1/C	0	−0.398	−0.699	−1	−1.397
	R^2		Linear regression			
B.L						
O(1)-C(2)	0.097		y=−125.4x+182.9			
C(2)-C(3)	0.097		y=75.25x−115.4			
C(3)-O(7)	0.097		y=376.2x−550.9			
O(7)-H(8)	0.097		y=−125.4x+121.5			
C(3)-C(4)	0.097		y=41.81x−64.49			
C(4)-N(5)	0.097		y=−125.4x+183.2			
N(5)-H(6)	0.097		y=−188.1x+190.3			
B.A						
X-O(1)-C(2)	0.051		y=0.101x−12.75			
O(1)-C(2)-C(3)	0.017		y=0.024x−3.319			
C(2)-C(3)-O(7)	0.057		y=0.053x−6.353			
C(3)-O(7)-H(8)	0.562		y=0.174x−19.14			
C(3)-C(4)-N(5)	0.312		y=0.340x−38.22			
C(4)-N(5)-H(6)	0.468		y=−0.120x+12.85			
H(6)-N(5)-Y	0.181		y=−0.291x+32.23			
Density						
O(1)	0.005		y=2.243x−20.34			
C(2)	0.365		y=−38.30x+229.8			
C(3)	0.858		y=20.00x−118.1			
C(4)	0.781		y=−15.81x+95.90			
N(5)	0.938		y=17.19x−133.9			
H(6)	0.898		y=−21.44x+14.32			
O(7)	0.910		y=92.45x−809.2			
H(8)	0.934		y=95.02x−56.61			
Molecular volume/$bohr^3mol^{-1}$	0.851		y=−0.000x+1.793			
Molecular length(L)	0.931		y=0.272x−4.824			
Molecular width(W)	0.892		y=−0.659x+5.428			
L/W %	0.759		y=1.684x−3.555			

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 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 new compounds [16].

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 were other 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.

Prediction of QSAR

$y = a_0 + a_1D_1 + a_2D_2 + \cdots\cdots + anDn$ (Hansch model) [17] (2)

y: Practical activity,

a: Regression coefficient,

D: Descriptors (b*property).

The general equation by mean of physicochemical properties will be:

$Y = a_0 \pm a_1 \times slope \times x_1 \pm a_2 \times slope \times x_2 \pm a_3 \times slope \times x_3 \pm a_4 \times slope \times x_4$

Where,

X_1 = S× Log P, X_2 = S× ΔE HOMO-LUMO, X_3 = S × μ, X_4 = S × η

So,

$0 = a_0 - a_1 \times 1.356 + a_2 \times 4.8440 + a_3 \times 2.6052 + a_4 \times 4.8482$

$-0.39794 = a_0 - a_1 \times 1.391 + a_2 \times 4.4756 + a_3 \times 1.9607 + a_4 \times 4.4794$

$-0.69897 = a_0 - a_1 \times 1.970 + a_2 \times 4.3842 + a_3 \times 1.7047 + a_4 \times 4.3880$

$-1 = a_0 - a_1 \times 2.303 + a_2 \times 3.7050 + a_3 \times 1.4065 + a_4 \times 3.7082$

$-1.39794 = a_0 - a_1 \times 2.481 + a_2 \times 3.6660 + a_3 \times 1.3377 + a_4 \times 3.6692$

Results:

$a_0 \rightarrow -29.5744$, $a_1 \rightarrow -6.14634$, $a_2 \rightarrow 33683.8$, $a_3 \rightarrow 3.82945$, $a_4 \rightarrow -33652.3$

Then, it could be conclude the final equation:

$$\text{Log } 1/C = -29.5744 - 6.14634 \times slope \times x_1 + 33683.8 \times slope \times x_2 + 3.82945 \times slope \times x_3 - 33652.3 \times slope \times x_4 \quad (4)$$

Or

$$\text{Log } 1/C = -29.5744 + 17.1334 \text{ Log p} + 19603.97 \text{ HOMO–LUMO gap} + 2.7725\ \mu - 38902\ \eta \quad (5)$$

By applying the value of properties:

CRV1:

$$\text{Log } 1/C = -29.5744 + 6.14634 \times 1.35611 + 33683.8 \times 4.8439 + 3.82945 \times 2.6052 - 33652.3 \times 4.8481 = -0.0196137$$

CRV2:

$$\text{Log } 1/C = -29.5744 + 6.14634 \times 1.391 + 33683.8 \times 4.4756 + 3.82945 \times 1.9607 - 33652.3 \times 4.4794 = -0.413778$$

CRV3:

$$\text{Log } 1/C = -29.5744 + 6.14634 \times 1.970 + 33683.8 \times 4.3842 + 3.82945 \times 1.7047 - 33652.3 \times 4.3880 = -0.714487$$

CRV4:

$$\text{Log } 1/C = -29.5744 + 6.14634 \times 2.303 + 33683.8 \times 3.7050 + 3.82945 \times 1.4065 - 33652.3 \times 3.7082 = -1.01312$$

CRV5:

$$\text{Log } 1/C = -29.5744 + 6.14634 \times 2.481 + 33683.8 \times 3.6660 + 3.82945 \times 1.3377 - 33652.3 \times 3.6692 = -1.41104$$

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

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 the program.

The general equation by mean of geometrical properties will be:

Like the formula of Equation (3)

$$Y = a_0 \pm a_1 * slope * x_1 \pm a_2 * slope * x_2 \pm a_3 * slope * x_3 \pm a_4 * slope * x_4 \quad (6)$$

Where,

X_1= S* N(50)

X_2= S* O(7) → Density on each atom

X_3= S* H(8)

X_4= S* Molecular length

So,

$0 = a_0 + a_1 \times 133.6746 + a_2 \times 809.1132 + a_3 \times 56.5464 + a_4 \times 4.76272$

$-0.39794 = a_0 + a_1 \times 133.5715 + a_2 \times 808.9467 + a_3 \times 56.34686 + a_4 \times 4.50432$

$-0.69897 = a_0 + a_1 \times 133.2964 + a_2 \times 808.2626 + a_3 \times 55.70072 + a_4 \times 3.98208$

$-1 = a_0 + a_1 \times 132.779 + a_2 \times 808.1702 + a_3 \times 55.66272 + a_4 \times 3.91136$

$-1.39794 = a_0 + a_1 \times 132.461 + a_2 \times 807.939 + a_3 \times 55.29214 + a_4 \times 4.06368$

Results:

$a_0 \rightarrow 2828.25$, $a_1 \rightarrow 0.873171$, $a_2 \rightarrow -3.87254$, $a_3 \rightarrow 3.2306$, $a_4 \rightarrow 1.19218$

The final equation by mean of geometrical properties:

$$\text{Log } 1/C = 2828.25 + 0.873171 \times slope \times x_1 - 3.87254 \times slope \times x_2 + 3.2306 \times slope \times x_3 + 1.19218 \times slope \times x_4 \quad (7)$$

Or

$$\text{Log } 1/C = 2828.25 + 15.01 \text{ N electron density} - 358.016 \text{ O electron density} + 306.97 \text{ H electron density} + 0.32427 \text{ Molecular length} \quad (8)$$

By applying the amount of properties:

CRV1:

$$\text{Log } 1/C = 2828.25 + 0.873171 \times 133.6746 - 3.87254 \times 809.1132 + 3.2306 \times 56.5464 + 1.19218 \times 4.76272 = 0.00437$$

CRV2:

$$\text{Log } 1/C = 2828.25 + 0.873171 \times 133.5715 - 3.87254 \times 808.9467 + 3.2306 \times 56.34686 + 1.19218 \times 4.50432 = -0.393567$$

CRV3:

$$\text{Log } 1/C = 2828.25 + 0.873171 \times 133.2964 - 3.87254 \times 808.2626 + 3.2306 \times 55.70072 + 1.19218 \times 3.98208 = -0.694596$$

CRV4:

$$\text{Log } 1/C = 2828.25 + 0.873171 \times 132.779 - 3.87254 \times 808.1702 + 3.2306 \times 55.66272 + 1.19218 \times 3.91136 = -0.995626$$

CRV5:

Log 1/C = 2828.25 + 0.873171 × 132.461 − 3.87254 × 807.939 + 3.2306 × 55.29214 + 1.19218 × 4.06368 = −1.39357

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

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

Suggested unprepared carvedilol compound

According to all previous study, a new derivative of carvedilol was suggested by replacing one of a hydrogen atom on C4 by donating pyrrole group. The resulting derivatives given a name CRV6 has molecular weight=471.54756 and a structure shown in Fig. 10.

The physicochemical and geometrical properties of CRV6 were determined Table 9.

So, by applied general equation of physicochemical properties

Log 1/C = −29.5744 − 6.14634 × −2.22092 + 33683.8 × 4.770654 + 3.82945 × 2.164832 − 33652.3 × 4.774753 = 4.70107

Activity of CRV6 = 1.99×10^{-5} = 0.00002 mg.

According to general equation of geometrical properties, the activity of CRV6 calculated as above:

Log 1/C = 2828.25 + 0.873171 * 136.3124197 − 3.87254 * 804.1069875 + 3.2306 * 51.2371595 + 1.19218 * 4.6855264 = 4.45034

Activity of CRV6 = 3.55×10^{-5} = 0.000036 mg.

Activity value of CRV6 was almost 100,000 time less than the value of the activity of CRV1, so it is a very active drug to prepare.

QSAR has become a tool for designing drugs. In QSAR biological activity can be related to physicochemical properties and in quantitative structure-pharmacokinetic relationship, pharmacokinetic properties can be related to physicochemical properties, relation found in terms of quantity. A number of literature and review article have been published on drug design and drug development dependence on QSAR [18,19].

Table 6: Sharing of selected physicochemical properties to the activity of carvedilol derivatives as a function of slop

Drug	Property				
	Log 1/C	Log P*S	ΔE HOMO-LUMO*S	μ*S	η*S
CRV1	0	−1.356	4.8440	2.6052	4.8482
CRV2	−0.39794	−1.391	4.4756	1.9607	4.4794
CRV3	−0.69897	−1.970	4.3842	1.7047	4.3880
CRV4	−1	−2.303	3.7050	1.4065	3.7082
CRV5	−1.39794	−2.481	3.6660	1.3377	3.6692

HOMO-LUMO: Highest occupied molecular orbital and lowest unoccupied molecular orbital, EA: Electron affinity

Table 7: Sharing of selected geometrical properties to the activity of carvedilol derivatives as a function of slop

Drug	Property				
	Log 1/C	Density			Molecular length*S
		N(5)*S	O(7)*S	H(8)*S	
CRV1	0	133.6746	809.1132	56.5464	4.76272
CRV2	−0.39794	133.5715	808.9467	56.34686	4.50432
CRV3	−0.69897	133.2964	808.2626	55.70072	3.98208
CRV4	−1	132.779	808.1702	55.66272	3.91136
CRV5	−1.39794	132.461	807.939	55.29214	4.06368

CONCLUSION

1. Substitution of a cyclocompound instead of H on C4 in general structure as in Fig. 1, give a more active compound

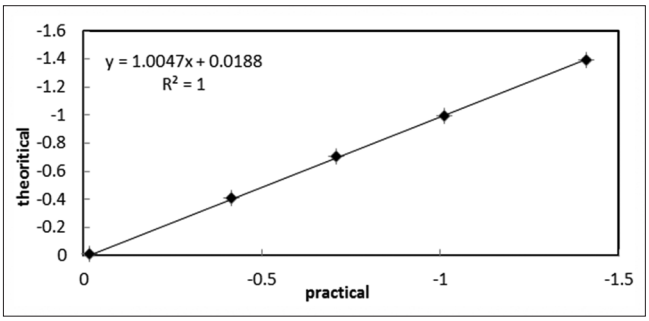

Fig. 7: The relation between practical (measured according to physicochemical properties) and theoretical activity for carvedilol derivatives

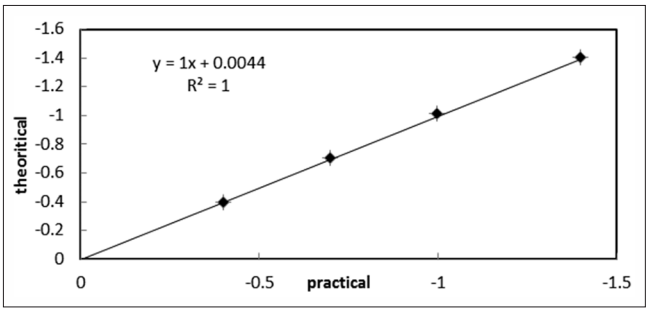

Fig. 8: The relation between practical (measured according to geometrical properties) and theoretical activity for carvedilol derivatives

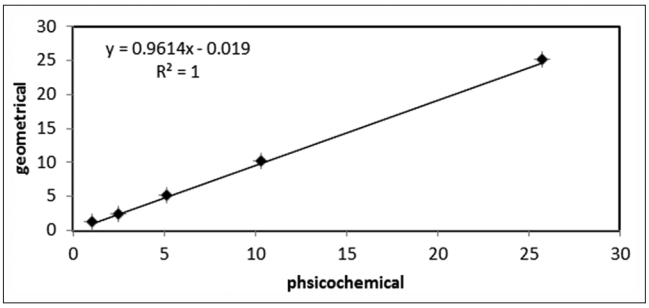

Fig. 9: Relation between activity values calculated according to physicochemical and geometrical properties

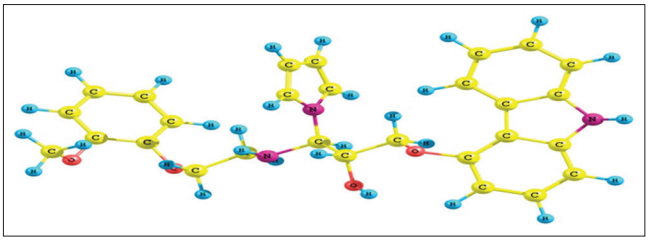

Fig. 10: Geometric structure of suggested CRV6 compound

Table 8: Experimental, physicochemical, and geometrical activity value of carvedilol derivatives

Compound	Experimental		Physicochemical		Geometrical	
	Log 1/C	C	Log 1/C	C	Log 1/C	C
CRV1	0	1	−0.019613	1.046195	0.00437	0.989988
CRV2	−0.39794	2.5	−0.413778	2.592853	−0.393567	2.474953
CRV3	−0.69897	5	−0.714487	5.181875	−0.694596	4.949895
CRV4	−1	10	−1.01312	10.30670	−0.995626	9.899790
CRV5	−1.39794	25	−1.41104	25.76558	−1.39357	24.74970

Table 9: Physicochemical and geometrical properties of CRV6

Physicochemical properties		Geometrical properties	
Log P	4.68549	Density N (5)	7.92975
ΔE HOMO-LUMO/eV	8.197	Density O (7)	8.69775
μ/debye	2.9901	Density H (8)	0.53923
η	4.0985	Molecular length	17.2262

HOMO-LUMO: Highest occupied molecular orbital and lowest unoccupied molecular orbital

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

Physicochemical properties		Geometrical properties	
S*Log P	−2.2209	S*Density N (5)	136.312
S*ΔE HOMO-LUMO	4.77065	S*Density O (7)	804.107
S*μ	2.16483	S*Density H (8)	51.2372
S*η	4.77475	S*Molecular length	4.68553

HOMO-LUMO: Highest occupied molecular orbital and lowest unoccupied molecular orbital

2. The value of activity calculated from geometric parameters is more accurate than from physicochemical parameters according to the relation in Figs. 8 and 9, but all the values obtained is less than carvedilol activity by 10^{-5} times, so CRV6 can be predict its activity before synthesized depending on computer simulation.

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