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The study on QSAR and relations between molecular descriptors of 5, 8-quinolinequinone derivatives

Yadigar GULSEVEN SIDIR*, Isa SIDIR

Bitlis Eren University, Faculty of Science and Arts, Department of Physics, 13000, Bitlis, Turkey

Highlights

- QSARs study was performed using some biological activity and molecular properties.
- The HL60 pIC50 values vary most with the high electrophilic index, IP, and E_{LUMO}.
- The T cell pIC50 values are most dependent on electrophilic index and electronegativity.
- The pAI_{50} value is found strongly related to the molecular hardness and softness.

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Abstract

The electronic, hydrophobic and global reactivity parameters of modeled 28 different 5,8-quinolinequinone derivatives have been calculated using DFT (B3LYP)/6-31G(d,p) method and basis set. The molecular descriptors are chosen molecular polarizability, dipole moment, frontier molecular orbital energy, molecular volume, ionization potential, electron affinity, electronegativity, molecular hardness, molecular softness, electrophilic index, molar refractivity, octanol–water partition coefficient, entropy and capacity of heat. The relations between molecular descriptors have been investigated dependent on their correlations. QSAR/QSPR models have been derived for anti-proliferative and anti-inflammatory activity of these 5, 8-quinolinequinone derivatives. The dependence of the electronegativity parameter on both electronic and thermochemical parameters is found to be the best correlated parameter.

1. INTRODUCTION

QSARs (Quantitative structure-activity relationships)/QSPRs (Quantitative structure-property relationships) is a mathematical expression showing the biological activity according to the structural definitions of the series of homologous molecules. However, QSAR/QSPR can predict the properties of a wide range of chemical compounds based on the correlation between biological activity and molecular descriptors. The main objective of QSAR is to develop new molecules with desired properties by using statistical calculation results by the computed values such as chemical, physical, topological and molecular properties. The molecules having desired properties are available when appropriate results can be found. Thus, the QSAR methodology develops and accelerates the processes in the development of novel molecules and drugs. In the QSAR and QSPR processes, descriptors related to topology, thermodynamics, quantum chemistry, shape and electronic energy are used to define these relations. In particular, the atomic charge, HOMO-LUMO energies, orbital electron densities, and super-delocalizable states are related to various biological activities [1-5].

The 5,8-quinolinequinone derivatives have some biological properties like anti-inflammatory, anti-bacterial and anti-tumor biological activities. Having more effective therapeutics properties have been effort to develop to new quinolinequinone derivatives since 5,8-quinolinequinone derivatives have a lot of therapeutics properties [6-11]. Our motivation in doing this study is to model the molecular properties of

* Corresponding author, e-mail: ygsidir@beu.edu.tr

different quinolonequinone derivatives, which have such important biological activity only theoretically. Thus, it can try to understand which feature of the molecule is effective in the therapeutic properties of these compounds, and in new molecular modeling studies, the substituent group can be added according to the desired properties in the compound. The synthetic procedure and different biological activities of studied 5,8-quinolinequinone derivatives were reported by Benjamin et al., previously [11]. Thus, in this study, we were investigated to a lot of different molecular properties with doing molecular modeling of 5,8-quinolinequinone derivatives having different biological activity. However, there are not any study in the literature on QSAR/QSPR study of twenty-eight 5,8-quinolinequinones derivatives. In this case, it has been other a source of motivation to do this study. In this present work, QSAR/QSPR between different biological activity values, such as anti-cancer and anti-inflammatory [11], and a lot of physicochemical parameters of the some 5,8-quinolinequinone derivatives have been investigated with multiple linear regression analysis. Relationships between calculated molecular descriptors were analyzed and interpreted by quantitative methods.

2. MATERIAL METHODS

2.1. Quantum Chemical Calculations

The molecular geometric energy optimization and vibrational frequency calculations (no imaginary frequency) of 5,8-quinolinequinones derivatives were performed and then molecular descriptors were calculated after making sure that each molecule was in the correct geometry. Molecule numbers and IUPAC names of 5,8-quinolinequinones derivatives are tabulated in Table 1.

Table 1. *The IUPAC names of 5,8-quinolinequinones derivatives*

Molecule Number	IUPAC Name
1	6,7-dichloroquinoline-5,8-dione
2	6,7-dichloro-2-methylquinoline-5,8-dione
3	6-amino-7-chloroquinoline-5,8-dione
4	6-(benzhydrylamino)-7-chloroquinoline-5,8-dione
5	7-chloro-6-(methylamino)quinoline-5,8-dione
6	6-chloro-7-(methylamino)quinoline-5,8-dione
7	6-(2-bromoethylamino)-7-chloroquinoline-5,8-dione
8	7-(2-bromoethylamino)-6-chloroquinoline-5,8-dione
9	7-chloro-6-(2-chloroethylamino)quinoline-5,8-dione
10	6-chloro-7-(2-chloroethylamino)quinoline-5,8-dione
11	6-(2-bromoethylamino)-7-chloro-2-methylquinoline-5,8-dione
12	7-(2-bromoethylamino)-6-chloro-2-methylquinoline-5,8-dione
13	6-amino-7-(methylthio)quinoline-5,8-dione
14	6-(methylamino)-7-(methylthio)quinoline-5,8-dione
15	7-(methylamino)-6-(methylthio)quinoline-5,8-dione
16	6-(methylamino)-7-(phenylthio)quinoline-5,8-dione
17	7-(methylamino)-6-(phenylthio)quinoline-5,8-dione
18	2,3-dihydro-1H-[1,4]thiazino[3,2-g]quinoline-5,10-dione
19	3,4-dihydro-2H-[1,4]thiazino[2,3-g]quinoline-5,10-dione
20	6-amino-7-(methylsulfinyl)quinoline-5,8-dione
21	6-(methylamino)-7-(methylsulfinyl)quinoline-5,8-dione
22	7-(methylamino)-6-(methylsulfinyl)quinoline-5,8-dione
23	6-amino-7-(methylsulfonyl)quinoline-5,8-dione
24	7-chloro-6-(toluene-4-sulfonyl)-5,8-quinolinquinone
25	6,7-bis(methylthio)quinoline-5,8-dione
26	6,7-bis(phenylthio)quinoline-5,8-dione
27	6,7-bis(phenylthio)-4a,8a-dihydroquinoline-5,8-diol
28	6,7-bis-(toluene-4-sulfonyl)-5,8-quinolinquinone

While some molecular descriptors (E_{HOMO}, E_{LUMO}, electrophilic index, molecular hardness, molecular softness, chemical potential, dipole moment, polarizability, electronegativity, ionization potential, electron affinity, molecular volume and thermochemical parameters) have been calculated by using DFT-B3LYP/6-31G(d,p) level of theory with Gaussian09W software [12-16]. The GaussView 5.0 software is used for preparation of input and reading output file. The octanol–water partition coefficient (log*P*) and molar refractivity (MR) are calculated with clog*P* driver. Then, the relationship between the calculated molecular descriptors was investigated.

2.2. Statistical Methods

The QSARs/QSPRs models between different biological activity values and molecular descriptors, and the correlations between molecular descriptors have been performed by using the statistical software SPSS 15.0 program [17].

3. RESULTS AND DISCUSSION

3.1. Molecular Definitions

The molecular descriptors calculated with using quantum chemical method belong to investigated 5,8-quinolinequinones derivatives are listed in Table 2. Relationships between molecular descriptors calculated independently from each other have been examined, and correlation graphs of the changes between them are given in Figure 1.

While the volume gives information about the size of the molecule, it changes depending on the proportion to the size of the substituent. Thus, volume of compound number 1 is calculated to be 138.40, while the volume of compound number 3 is found to be 114 as the lowest one. The volume of the quinone ring was found to be smaller than the other molecule because the amino group in the 6 position of molecule 3 is inductively attracted by the quinone ring. The volume of the molecule 28 has been found to be the largest. As can be seen from Figure 1, the relatively larger volume of this molecule is due to the toluene-4-sulfonyl substituent located at the 6,7 positions.

The dipole moment is directly related to the electronic structure of the molecules and the energy caused by the electronic structure. It is observed by Lien et al. that dipole moment is an important parameter for drug-receptor interactions. Interaction of drugs or vitamins of receptors have been occurred by the way of interaction with electronic structure, such as dipole-dipole, dipole-induced dipole and induced dipole-induced dipole interaction types [18]. In our study, the 24th compound has the largest dipole moment among investigated 5,8-quinolinequinone derivatives, which is calculated as 7.14 D, due to the electronegative atom in its 7th position, Cl and sulfonyl group substituents. This compound has the major anti-proliferative activities. On the other hand, it is seen from Table 3 that the 8th molecule with the lowest dipole moment value of 0.74 D has the lowest experimental logIC_{50} value. When we look at the dipole moments of the investigated compounds, the compounds with the smallest and largest dipole moments are compatible with the biological activity.

The log*P* value is parameter of solubility in the water/octanol system for a molecule. Less dissolution and less transport are the main reason for failure in the process of developing drugs [19-26]. Thus, we can say that the substituents added to the quinoline ring have a direct effect on the log*P* value. As seen from Table 2, while molecules 1, 20, 21, 22 and 23 have hydrophilic character, other compounds have lipophilic character. It can be said that the presence of both amino (including Cl) and sulfonyl groups in the molecule gives rise to large effect on the log*P* value. As a result, molecules with a high log*P* values have greater biological activity than those with low log*P* and can reach the receptor through the cell membrane. Negative log*P* value of the molecule in the hydrophilic properties, that is, they can interact more easily in the aqueous environment, if log*P* = 0, it has affinity both in the aqueous and in the oil environment. The molecule with a positive log*P* value can dissolve in high concentrations in its lipophilic environment. The log*P* value for molecules 16 and 17 has the highest value with a value of 3.21.

Molar refractivity (MR) (cm^3/mol) is a parameter that shows Vander Waals interaction between the atoms in the molecule and the environment of the molecule. In addition, MR shows a Lorentz-Lorentz Equation, which explains the interactions between medium and molecule as follow

$$MR=((n^2-1)/(n^2+2))(M/d)$$

where, M, n and d symbols represent to molecular weight, refractive index and density, respectively. The definition of MR is related to the polarity and size of a substituent that binds to the molecule. The larger the polar portion of a molecule, the greater the molar refractivity [27]. Molar refractivity is the size that describes the separator capacity that aids the interaction between the biological receptor and the substituent. MR also shows a measure of the molecular volume. Consequently, the MR is a measure of the capacity of the substituent that modifies the receptor conformation does not intend to interact with the substrate [28]. As seen in Table 2, the highest MR value is found in the 28th molecule, while the lowest value is calculated in the 5th molecule. It can be seen from Table 3 that experimental HL60 logIC_{50} (pIC_{50}) to 28th compound has the highest value. As seen in Table 2, the highest MR value was found for the 28th molecule, while the lowest value was found for the 5th molecule. In that, molecule 28 in biological medium has occurred to interactions via Van der Waals forces. This case can explain to biological activity of this molecule. Molecule 28 has the large surface area interaction, while surface area interaction of molecule 5 is small. As can be seen from Figure 1, the MR value was calculated to be V (R^2 = 0.683), S (R^2 = 0.8105) and C_v (R^2 = 0.7975). It is observed that molecules 10 and 5 deviate from the correlation between MR and V. Heat capacity (C_v) is related to the interactions of water-soluble compounds. The compounds having different heat capacity may behave differently against temperatures and concentrations in different solutes. They usually differ by chemical structure or electrolyte or non-electrolyte environments [29]. Among the investigated 5,8-quinolinequinones derivatives, the 28th molecule has the largest heat capacity, while the molecule with the smallest value is the 1st molecule. As can be seen from Figure 1, correlation coefficient of 0.7975 has been found between MR and C_v. It can be said that the relationship between these two parameters calculated independently from each other gives information about the solubility of molecules in biological environment.

The entropy (S_e) like molecular descriptors has demonstrated flexibility in many bioorganic and medicinal chemistry problems. Determination of whether a specific ligand-receptor interaction at equilibrium, entropy can be determined by thermodynamic analysis. The entropy of molecule is usually characterized by the displacement of ordered water molecules coupled with the formation of new hydrophobic interactions [30]. While molecules 1 and 3 have the lowest entropy value, the 28th molecule has the highest value. It is seen from Figure 1 that there is a linear correlation between S_e and MR values. Molecular polarizability has been determined as intermolecular weak interactions between closed shell species and for different molecular properties such as boiling point, melting point, vaporization enthalpy, solubility, and solvent polarity scale. In addition, it measures the response of the outer shell electrons of a molecule toward an external electric field perturbation, whereas chemical binding can be also viewed as a result of reorganization of the valence electrons of atoms due to perturbation effects [31]. The 28th molecule has the highest polarizability value, while the 3rd and 1st molecules have relatively lower value. As can be seen from Figure 1, correlation values obtained between average polarizability and volume, molar refractivity, heat capacity are R^2=0.8105, R^2=0.7905 and R^2= 0.9189, respectively.

Table 2. *Physicochemical parameters calculated with B3LYP/6-31G(d,p) of investigated 5,8-quinolinequinones derivatives*

Molecule Number	**α_{xx}**	**α_{yy}**	**α_{zz}**	**α_{mean}**	**V**	**μ**	**log*P***	**MR**	**Cv**	**S_e**	**IP**	**EA**	**χ**	**E_{HOMO}**	**E_{LUMO}**	**η**	**S**	**ω**
1	173.98	154.11	45.22	124.44	138.40	3.66	-1.02	5.03	40.79	105.75	7.61	3.70	5.65	-7.61	-3.70	1.96	0.51	31.31
2	197.00	164.82	54.66	138.83	139.45	4.07	2.92	5.50	46.96	116.22	7.48	3.58	5.53	-7.48	-3.58	1.95	0.51	29.80
3	173.76	154.29	43.34	123.80	114.00	4.75	1.70	4.91	43.11	105.71	6.38	3.19	4.78	-6.38	-3.19	1.59	0.63	18.24
4	323.16	233.57	223.79	260.17	255.07	5.04	4.87	10.40	84.28	163.85	6.07	3.09	4.58	-6.07	-3.09	1.49	0.67	15.59
5	197.15	164.73	52.62	138.17	147.13	5.12	5.37	1.74	47.40	114.08	6.07	3.11	4.59	-6.07	-3.11	1.48	0.68	15.56
6	197.85	164.06	52.62	138.18	163.20	1.51	1.74	5.37	47.27	113.40	6.11	3.10	4.60	-6.11	-3.10	1.50	0.66	15.92
7	340.78	177.76	74.93	197.82	198.18	5.54	2.47	6.61	55.20	130.12	6.36	3.30	4.83	-6.36	-3.30	1.53	0.65	17.84
8	241.50	189.87	73.51	168.29	178.58	0.74	2.47	6.61	54.98	130.14	6.26	3.15	4.70	-6.26	-3.15	1.55	0.64	17.18
9	240.99	173.38	69.40	161.26	185.72	5.64	2.33	6.33	54.73	127.41	6.37	3.31	4.84	-6.37	-3.31	1.53	0.65	17.93
10	239.87	183.74	68.03	163.88	178.26	1.58	6.33	2.33	54.97	126.31	6.45	3.31	4.88	-6.45	-3.31	1.57	0.64	18.67
11	282.34	189.40	79.90	183.88	175.11	5.31	2.97	7.08	61.56	142.85	6.16	3.12	4.64	-6.16	-3.12	1.52	0.66	16.36
12	252.89	210.80	83.45	182.38	216.67	1.03	2.70	7.08	61.16	140.41	6.18	3.05	4.62	-6.18	-3.05	1.56	0.64	16.65
13	202.01	172.84	62.76	145.87	143.13	3.55	0.64	5.69	50.17	114.58	5.87	3.04	4.45	-5.87	-3.04	1.42	0.71	14.04
14	216.58	190.70	71.54	159.61	189.79	4.12	0.67	6.15	54.71	123.61	5.63	2.97	4.30	-5.63	-2.97	1.33	0.75	12.31
15	207.62	200.39	72.48	160.16	163.39	1.45	0.67	6.15	54.69	122.31	5.80	2.93	4.36	-5.80	-2.93	1.43	0.70	13.65
16	278.11	222.70	139.83	213.54	196.03	4.16	3.21	8.20	68.21	142.17	5.69	2.98	4.34	-5.69	-2.98	1.36	0.74	12.77
17	259.85	246.30	120.48	208.88	185.83	1.58	3.21	8.20	67.97	141.85	6.06	2.98	4.52	-6.06	-2.98	1.54	0.65	15.73
18	227.86	175.73	64.59	156.06	142.25	4.87	1.19	5.97	49.00	111.46	5.55	2.94	4.24	-5.55	-2.94	1.30	0.77	11.74
19	226.28	175.18	64.65	155.37	129.30	1.86	1.19	5.97	48.87	111.06	5.57	2.93	4.25	-5.57	-2.93	1.32	0.76	11.93
20	200.09	172.40	66.62	146.37	176.86	4.13	-0.55	6.02	53.15	116.85	6.13	3.25	4.69	-6.13	-3.25	1.44	0.70	15.80
21	221.87	190.74	75.73	162.78	144.27	4.88	-0.51	6.48	58.49	127.57	5.79	3.18	4.49	-5.79	-3.18	1.30	0.77	13.12
22	211.53	197.98	75.87	161.79	176.43	2.42	-0.51	6.48	58.00	124.82	6.01	3.11	4.56	-6.01	-3.11	1.45	0.69	15.07
23	194.78	174.83	69.40	146.34	165.68	5.84	-0.55	6.17	55.79	120.12	6.88	3.44	5.16	-6.88	-3.44	1.72	0.58	22.87
24	262.56	230.66	147.67	213.63	208.74	7.14	2.69	8.81	74.39	153.41	7.17	3.76	5.46	-7.17	-3.76	1.70	0.59	25.40
25	220.78	224.96	75.56	173.77	162.56	3.04	0.69	6.59	55.75	127.50	6.04	3.19	4.61	-6.04	-3.19	1.43	0.70	15.17
26	421.14	239.34	192.37	284.28	239.76	2.40	5.77	10.68	82.65	164.31	5.82	3.17	4.50	-5.82	-3.17	1.32	0.76	13.38
27	325.27	239.34	192.37	252.33	302.39	4.17	4.17	11.28	87.38	163.29	5.33	1.52	3.43	-5.33	-1.52	1.90	0.52	11.20
28	331.75	322.26	254.39	302.80	314.55	3.58	2.56	12.58	108.28	195.08	6.87	3.69	5.28	-6.87	-3.69	1.59	0.63	22.20

α_{xx}, polarizability in the direction of x axes (esu); α_{yy}, polarizability in the direction of y axes (esu); α_{zz}, polarizability in the direction of z axes (esu); V, molecular volume ($Bohr^3$) ; μ(D), dipol moment (Debye); log*P*, water-octanol partition coefficient; MR, molar refractive index (cm^3/mol), C_v, heat capacity;S_e, entropy (joule per Kelvin); IP, ionization potential (eV); EA, electron affinity (eV); χ, electronegativity (eV); E_{HOMO}, the highest occupied molecular orbital energy (eV); E_{LUMO}, the lowest unoccupied molecular orbital energy(eV); η, molecular hardness(eV); S, molecular softness(eV); ω, electrophilic index (eV).

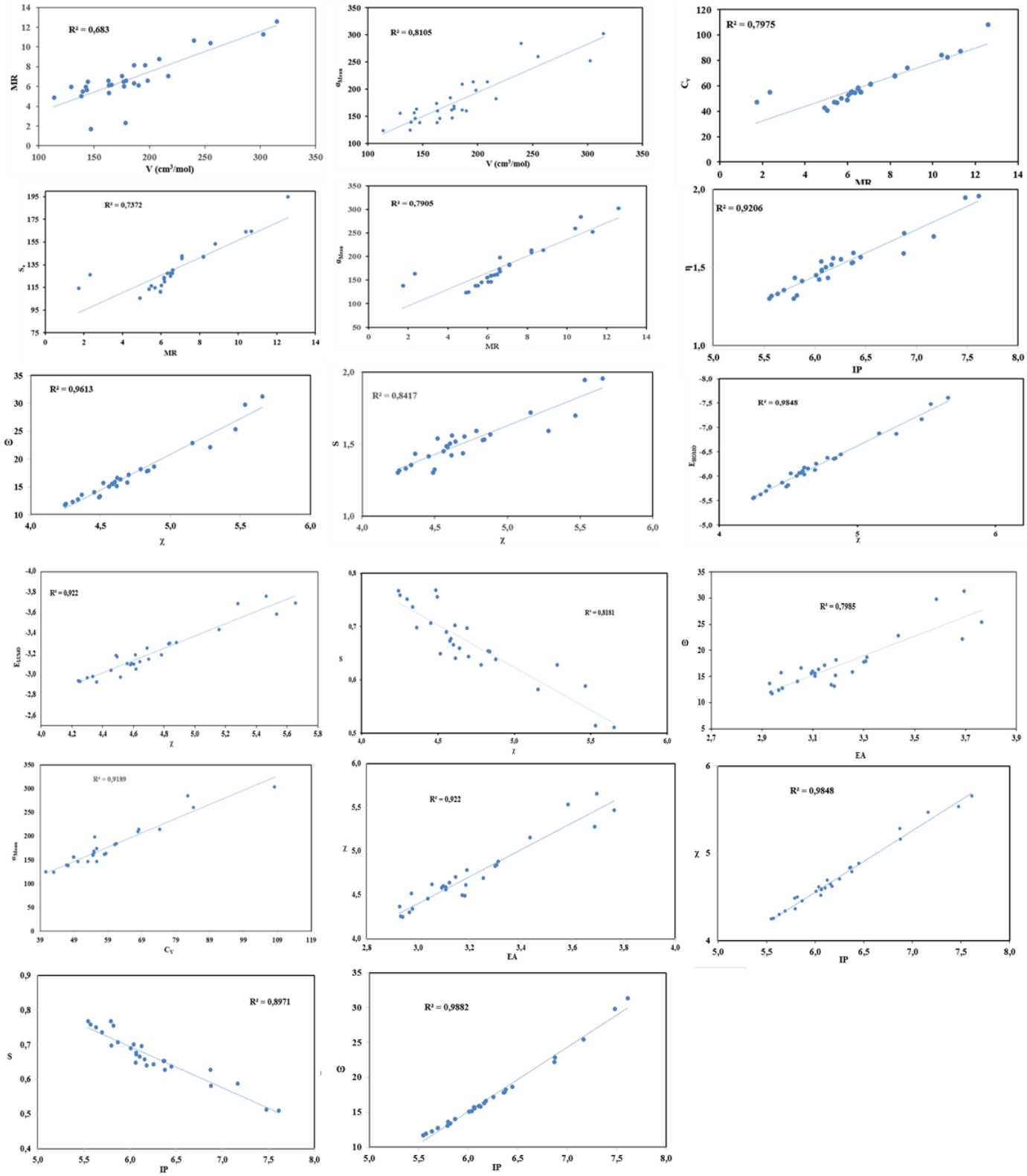

Figure 1. *The correlation graphs between physicochemical parameters*

Electronegativity (χ) according to Pauling, the molecule itself to attract electrons described as the power of an atom in the molecule [32] defined as the following Equation [33],

$$\chi_{Koopmans} = \frac{E_{HOMO} + E_{LUMO}}{2}.$$

As seen in Table 2, the order of electronegativity is 1>2>28 molecules according to high electronegativity parameter, which can react with any electron. This situation is compatible with other parameters indicating biological activity. At the same time, as can be seen from Figure 1, there are correlation graphs between χ with electrophilic index, entropy, molecular softness, E_{HOMO}, E_{LUMO}, EA and IP. The energy levels and shape of the molecular orbital arrange the HOMO (Highest Occupied Molecular Orbital) and the LUMO (Lowest Unoccupied Molecular Orbital) for molecules provide useful a lot of information on electronic transitions and structure. The HOMO and LUMO also indicate the areas having possible electrophilic and nucleophilic interaction in molecule, respectively. In this case, compound 1 has relatively bigger both electrophilic effect and nucleophilic effect, in the interaction with substrate, among the investigated compounds.

Figure 2 shows the HOMO and LUMO distribution graphs calculated with using the B3LYP/6-31G(d,p) method and basis set of the investigated compounds. So, as seen in Figure 2, green areas are positive values, when blue areas are negative values for HOMO and LUMO shape. The electrophilicity on positive charge groups or atoms gives rise to their attack to the most likely to the atomic site with a high density of orbital HOMO, while nucleophilicity on negative charge groups or atoms lead to their attack to LUMO that is correlated with atomic high density [34-36]. In Figure 2, there are changes in the HOMO and LUMO depending on the substituent.

Chemical hardness (η) is related to the stability of the molecule. It is defined as in the following Equation [22]

$$\eta \approx \frac{E_{LUMO} - E_{HOMO}}{2}.$$

Anti-chemical hardness, chemical softness (S) is a measure of the size of the chemical reactivity [23]. We can say from Table 2 that chemical hardness value of molecule 1 has the biggest one of the studied molecules, despite global softness of molecule 1 has the smallest one. In this case, the substitutions to 5,8-quinolinequinone compounds were not as effective as those on biological activity.

Global electrophilicity (ω) have described the electrophilic index as a measure of the energy falling due to the highest electron flow between the donor-acceptor molecules [24]

$$\omega = \frac{\mu^2}{2\eta}.$$

Global electrophilicity has a high (low) electrophilic index when two molecules react as one acts as an electrophile (nucleophile). The electrophilicity is the measure of the stability in the energy when the system gains an additional electronic load from the environment. Electrophilicity is the definition of reactivity that allows the quantification of a global electrophilic index of a molecule in a relative measurement scale [25-30]. The global electrophilic index of the molecule 1 is larger compared to other molecules. Thus, when the molecule 1 exchanges electrons, it becomes more stable and the total energy of the molecule is optimized. It is possible that the molecule 1 interacts with its environment in electrophilic ways.

3.2. QSAR

In Table 3, the logarithmic values of the biological activity of 28 different 5,8-quinolinequinone derivatives reported by Benjamin et al. [11] and the theoretical biological activity values found according to the QSAR models by using the multiple linear regression method using given the physicochemical values are listed in Table 2. The observed biological activity values along with the calculated biological activity values and physicochemical parameters of these molecules are listed in Table 3. The QSAR models for anti-

proliferative activity values, which is HL 60 pIC_{50} and T-cells pIC_{50}, and for anti-inflammatory activity (pAI_{50}) can be seen from Equations (1), (2) and (3), respectively.

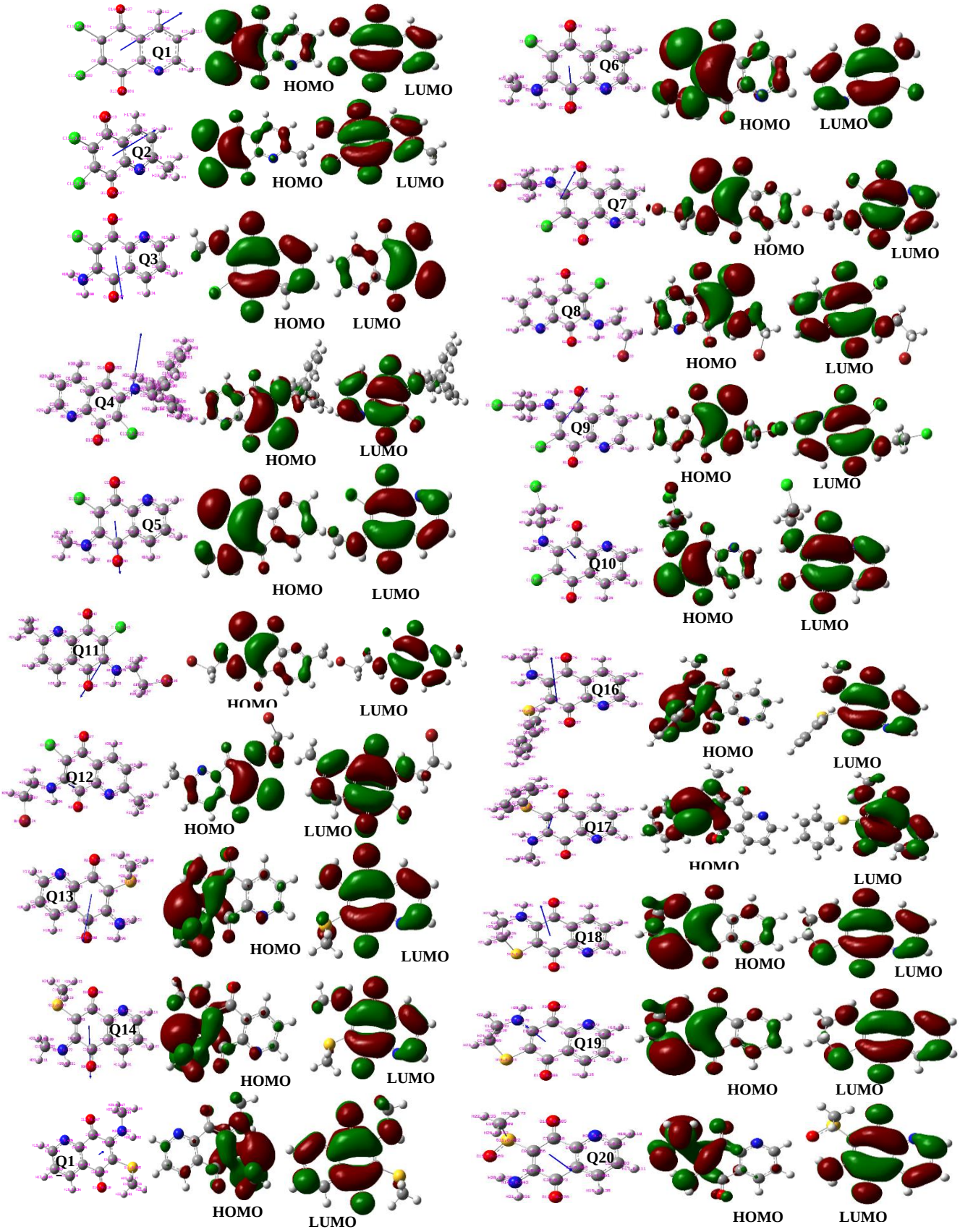

Figure 2. *The molecular structure, HOMO and LUMO shape of investigated molecules*

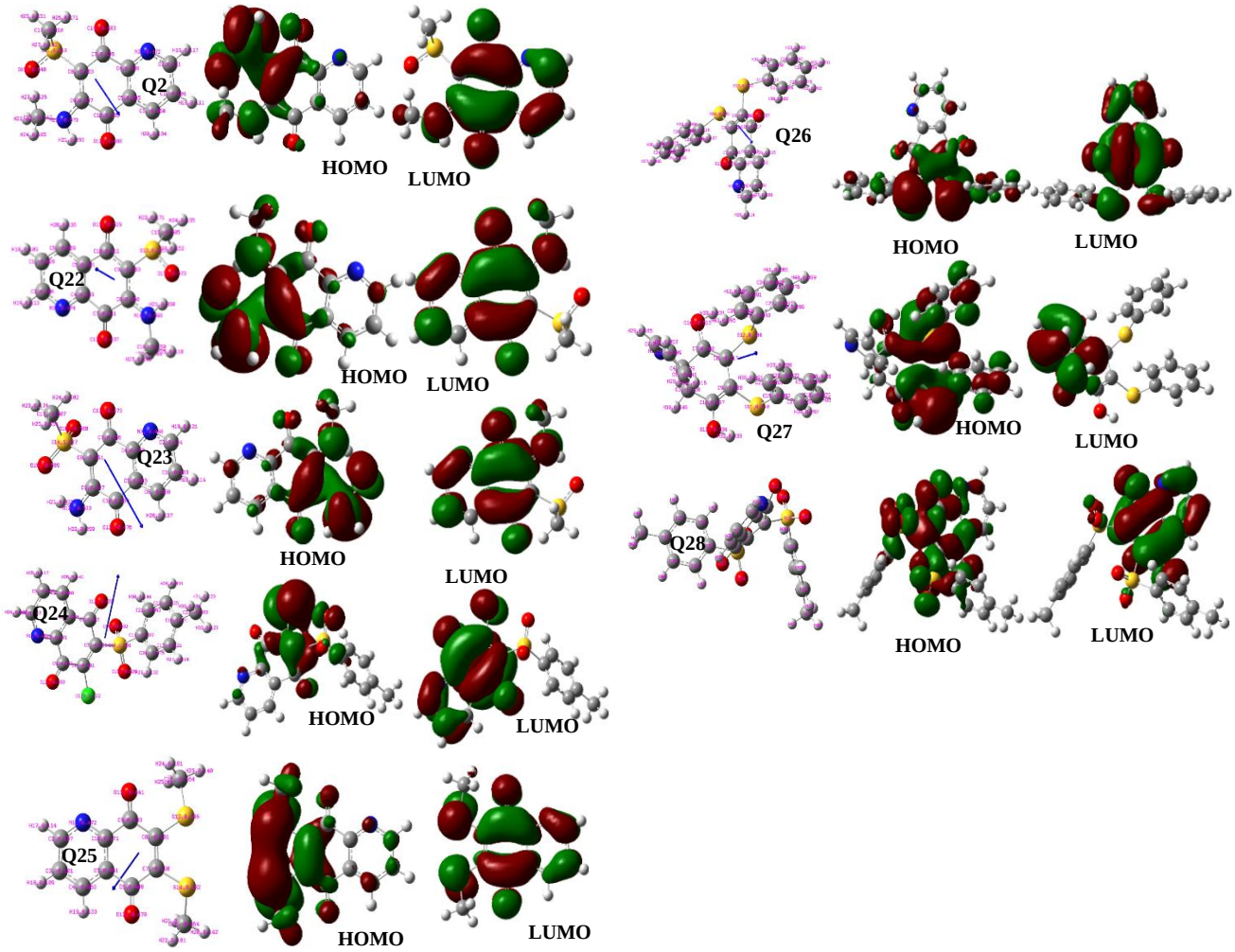

Figure 2. *The molecular structure, HOMO and LUMO shape of investigated molecules*

An ideal method derived with MLRA is one that has high correlation coefficient square ($R^2 \geq 0.7$), correlation coefficient ($R \geq 0.8$), high ability for prediction ($P \leq 0.05$) and high F statistic value. In addition, if the RMSE (Root Mean Squared Error) has a degree less than 0.5 value, it shows the accuracy of the derived linear models. The correlation graphs of calculated biological activities with experimental biological activities values have been shown in Figure 3.

As seen from Equations (1), (2) and (3) below, three linear models are applicable and correct confirmed by the statistical parameters. As can be seen from Equation (1), anti-cancer activity (HL60) depends theoretically on positive electrophilic index and heat capacity, while it depends on negatively ionization potential, LUMO energy, mean of polarizability, molecular volume and entropy.

HL60 IC_{50} (μM)

$$pIC_{50}=17.126-4.248IP-0.81E_{LUMO}+0.468\omega+0.096C-0.009\alpha_{mean}-0.005V-0.029S \quad (1)$$

$R=0.84$; $R^2=0.706$; $F=6.847$; $P=0.000$, $RMSE=0.269$

In Equation (2), it has been observed that the change of logarithmic values of T cell IC50 values has an increasing effect on polarizability, entropy and electronegativity along z, while it has a decreasing effect on electron affinity, electrophilic index and heat capacity.

T-Cell IC50 (μM)

$$pIC50=23.478-0.009\alpha_{zz}+0.086C+0.64\omega-0.032Se-11.892\chi+6.956EA \quad (2)$$

R=0.845; R^2=0.713; F=8.710; P=0.000, RMSE=0.219

As seen from Equation (3), the anti-inflammatory activity values, the dependence of molecular descriptors with multiple linear regressions below, are investigated theoretically by QSAR/QSPR models. According to the following Equation, the experimental dependent variable pAI50 is positively dependent on the energy value of LUMO, the water/octanol distribution coefficient, and the electrophilic index, while it negatively depends on molecular hardness and molecular softness.

AI50 (μM)

$$pAI_{50}=263.664+21.483E_{LUMO}-103.459\eta-125.355S+0.376\log P+2.642\omega \quad (3)$$

R=0.866; R^2=0.751; F=6.020; P=0.008, RMSE=0.403

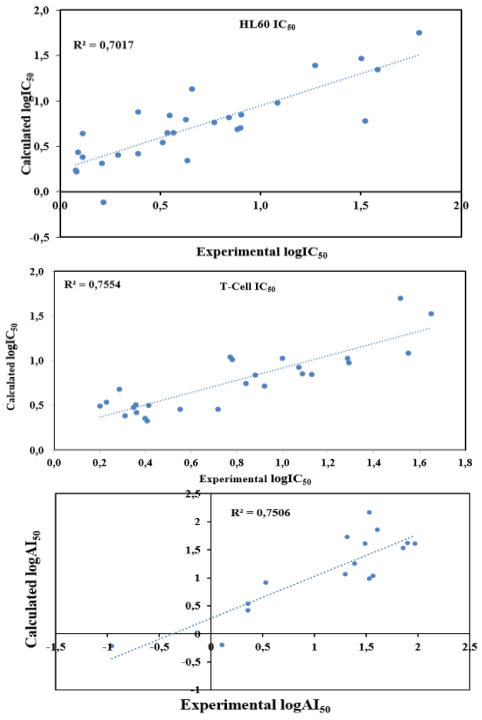

Figure 3. *The correlation graphs of calculated biological activities with experimental biological activities values*

It is satisfactory that any useful QSAR model obeys the Topliss-Costella rule in addition to having the correct statistical parameters. According to the Topliss-Costelle rule, it has been shown and reported in many studies that the ratio of molecular descriptors used in linear models created with the number of variables (experimental data) in an appropriate QSAR model is 5 and R>0.84 is provided. If greater than 5, ie M/N≥5, R>0.84 where M=molecule number and N=Molecule identifier number in the derived model [37].

While M/N=28/7=4 for Equation (1), R=0.84, for Equation (2) it was found as M/N=28/6=4.7 and R=0.845. In Equation (3), it was found that M/N=28/5=5.6. Equation (3) obeys the Topliss-Costella rule, while Equations (1) and (2) approximate this rule. We can say that the Topliss-Costello rule is valid for derived linear models.

Table 3. *The experimental and calculated biological activity data*

Molecule Number	**Experimental $logIC_{50}$ (HL60)**	**Calculated $logIC_{50}$ (HL60)**	**Experimental $logIC_{50}$ (T-Cell)**	**Calculated $logIC_{50}$ (T-cell)**	**Experimental $logAI_{50}$**	**Calculated $logAI_{50}$**
1	1.50	1.47	1.52	1.70	0.11	-0.19
2	1.27	1.39	1.65	1.52	0.53	0.90
3	0.51	0.54	0.31	0.39	-	-
4	0.39	0.88	0.41	0.50	1.53	2.15
5	0.39	0.42	0.55	0.46	1.90	1.61
6	0.63	0.34	0.72	0.46	1.61	1.85
7	0.22	-0.11	0.41	0.33	1.30	1.05
8	0.08	0.24	0.40	0.36	1.32	1.72
9	0.21	0.31	0.36	0.42	1.57	1.02
10	0.29	0.40	0.36	0.51	1.49	1.60
11	0.11	0.38	0.35	0.48	1.53	0.98
12	0.08	0.22	0.20	0.49	1.86	1.52
13	0.88	0.69	0.92	0.72	-	-
14	0.54	0.65	1.29	0.98	-	-
15	0.90	0.70	0.88	0.84	-	-
16	0.90	0.85	1.09	0.86	-	-
17	0.77	0.76	0.84	0.75	1.97	1.60
18	0.63	0.79	0.77	1.04	-	-
19	0.55	0.84	0.78	1.01	-	-
20	0.11	0.64	0.29	0.68	-	-
21	1.08	0.98	1.07	0.93	-	-
22	1.52	0.78	1.13	0.84	-	-
23	0.66	1.13	1.29	1.03	-	-
24	1.58	1.35	1.55	1.09	-	-
25	0.09	0.43	0.23	0.53	-0.96	-0.22
26	0.57	0.65	0.89	0.76	1.39	1.24
27	0.84	0.81	1.00	1.03	0.36	0.41
28	1.79	1.75	1.00	1.33	0.36	0.53

4. CONCLUSIONS

In this study, some physicochemical parameters of 28 different 5,8-quinolinequinone derivatives have been calculated by quantum chemical method, and after quantitative structure activity relationships (QSARs) have been investigated by using calculated physicochemical parameters with some biological activity values previously reported in literature. It has been observed to changing with depending on electrophilic index and polarizability of biological activity as seen from correlation among all physicochemical parameters. The relationships between calculated physicochemical parameters have determinated with correlation graphs. The best correlations were found between MR, V, α_{Mean}, ω, E_{HOMO}, E_{LUMO}, S, Se, χ, IP and η. The derived QSAR models obeying to Topliss-Costello rule has compatible with small differences.

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CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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