

Determination With QSAR of Biological Activity and Relations of Between Molecular Descriptions of 5,8-Quinolinequinones Derivatives

Yadigar GÜLSEVEN SIDIR (✉ yadigar.gulseven@gmail.com)

Bitlis Eren University <https://orcid.org/0000-0002-5329-2815>

İsa SIDIR

Bitlis Eren University

Research Article

Keywords: 5,8-Quinolinequinones, DFT, QSAR, QSPR, biological activity.

Posted Date: July 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-665038/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Determination with QSAR of Biological Activity and relations of between molecular descriptions of 5,8-Quinolinequinones derivatives

Yadigar GÜLSEVEN SIDIR*, İsa SIDIR

Bitlis Eren University, Faculty of Arts & Sciences, Department of Physics, 13000,
Bitlis, Turkey

ABSTRACT

In this study, some electronic, hydrophobic and thermochemical parameters of 28 different 5,8-quinolinequinones derivatives having diversity substituents have been calculated by using DFT (B3LYP) / 6-31G (d, p) method and basis set. Relationships between different molecular descriptives have been studied with used like molecular polarizability (α), dipole moment (μ), E_{HOMO} , E_{LUMO} , molecular volume (V_m), ionization potential (IP), electron affinity (EA), electronegativity (χ), molecular hardness (η), molecular softness (S), electrophilic index (C), molar refractivity (MR), octanol–water partition coefficient ($\log P$), thermochemical properties (entropy (S_e), capacity of heat (C)); as to investigate activity relationships with molecular structure. In addition, The QSAR/QSPR between molecular properties and biological activity (Anti-proliferative and Anti-inflammatory activity) has investigated, where R, R^2 , F and P have taken into account in order to find a statistically correct model in QSAR studies. The dependence of the electronegative parameter on both electronic and thermochemical parameters was the most correlated parameter.

Keywords: 5,8-Quinolinequinones, DFT, QSAR, QSPR, biological activity.

* Corresponding Author: Dr. Yadigar GÜLSEVEN SIDIR, ygsidir@beu.edu.tr, yadigar.gulseven@gmail.com, Bitlis Eren University, Faculty of Arts and Science, Department of Physics, +904342220020-2319

1. Introduction

The 5,8-quinolinequinones derivatives have some biological properties like anti-tumour, anti-inflammatory and anti-bacterial activities. In addition, these compounds have much effort to developing since they have more effective quinolinequinone-based therapeutics properties [1-6]. The synthesis procedure, anti-proliferative, anti-inflammatory and tuberculostatic activities of investigated 5,8-Quinolinequinones derivatives were reported by Mulchin et al., previously [6].

QSARs (Quantitative structure-effect relationships) / QSPRs (Quantitative structure-property relationships) is a mathematical expression showing the biological activity according to structural definitions of the series of homologous molecules. However, QSAR/QSPR can predict of 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 calculations results with computational values such as chemical, physical, topological and molecular properties. The molecules having desired properties are available when appropriate results can found. Thus, the QSAR methodology develops and accelerates processes in the development of novel molecules and drugs. In the QSAR and QSPR process have used to definitions related to topology, thermodynamics, quantum chemistry, shape and electronic energy. In particular, the net atomic load, HOMO-LUMO energies, orbital electron densities, and super-delocalizable diene are related to various biological activities [7-11].

The investigated 5,8-Quinolinequinones derivatives have previously been experimentally reported in the literature for their anti-proliferative and anti-inflammatory activities [6]. However, there are no studies in the literature on QSAR / QSPR study of 28 5,8-Quinolinequinones derivatives. In this case, it has been a source of motivation to do this study. In this present work, QSARs/QSPR between different biological activity values, such as anti-cancer and anti-inflammatory [6], and a lot of physicochemical parameters of the some 5,8-quinolinequinones derivatives have been investigated with remove multi linear regression analysis. Relationships between calculated molecular descriptors were analyzed and interpreted by quantitative methods.

2. Calculation Methods

2.1. Quantum Chemical Calculations

Firstly, optimization and vibration frequency calculations (no imaginary frequency) of 5,8-Quinolinequinones derivatives were done, molecular descriptors were calculated after making sure that each molecule was in the correct geometry. While some molecular descriptions (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 calculated with DFT-B3LYP/6-31G(d,p) method and basis set by using Gaussian09W software. [12-16] GaussView5.0 have used for input preparation and output reading. The octanol–water partition coefficient ($\log P$) and molar refractivity (MR) are calculated with $\text{clog}P$ driver. Then, the relationship between the calculated molecular descriptors was investigated.

2.2. Statistical Methods

Afterwards, remove multiple linear regression method is used to investigated quantitative structure-activity relationships (QSARs) between different biological activity values and different physicochemical parameters. This statistical method has been applied by using the statistical software SPSS 15.0 program [17].

3. Results and Discussion

3.1. Molecular Definitions

In table 1 have tabulated to molecule number and IUPAC names of 5,8-Quinolinequinones derivatives. Table 2 have been listed to molecular descriptions belong to investigated compounds. Relationships between molecular descriptions calculated independently from each other have been examined in Figure 2, and correlation graphs of the changes between them have given.

While the volume of a molecule gives information about the size of the molecule, it changes in proportion to the size of the substituent added. Thus, compound number 1 has been found with the smallest volume ($138.40 \text{ cm}^3/\text{mol}$), while the volume of compound number 3 has been found ($114 \text{ cm}^3/\text{mol}$). The volume of the quinone ring was found to be smaller than the other molecule because the amino group in the 6 position of 3. molecule is inductively attracted by the quinone ring. The volume of the 28. molecule has been found to be the largest. As can be seen from figure 1, this molecule is due to the toluene-4-sulfonyl substituent at the 6,7 position added large volume substituent.

The dipole moment is directly related to the electronic structure of the molecules and the energy caused by the electronic structure. It was 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 to the interaction with electronic structure. For example, dipole-dipole, dipole-induced dipole and induced dipole-induced dipole [18]. In our study, the 24th compound has the largest dipole moment among investigated 5,8-Quinolinequinones derivatives, which is founding as 7.14 D dipole moment value due to the electronegative atom in its 7th position, Cl and containing 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 really has the lowest experimental logIC50 value. When we look at the dipole moment of the investigated it is that the smallest and largest dipole moment is compatible with the biological activity.

The log P value is parameter of soluble 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]. As a result, molecules with a high logP value 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 logP value can dissolve in high concentrations in its lipophilic environment. Thus, we can say that the substituents added to the quinoline ring have a direct effect on the logP value. While 1, 20, 21, 22 and 23 molecules as seen from Table 2 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 has an effect on the logP value. The logP value for molecules 16 and 17 has the highest value with a value of 3.21.

Molar refractive (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,

$$\text{MR} = \frac{(n^2 - 1)}{(n^2 + 2)} \left(\frac{M}{d} \right)$$

In here, M, n and d symbols are representing 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 power 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 that does not want to interact with the substrate [28]. As seen in Table 2, the highest MR value have found in the 28th molecule, while the lowest value has found in the 5th molecule. It can be seen from Table 3 that experimentally HL60 logIC₅₀ (pIC₅₀) has the highest value. As seen in Table 2, the highest MR value was found in the 28th molecule, while the lowest value was found in the 5th molecule. It can be seen from Table 3 that HL60 logIC₅₀ (pIC₅₀) has experimentally the highest value. In that, 28. molecule in biological medium has occurred to interactions via Vander Waals forces. This case can explain to biological activity of this molecule. Surface area interaction of 28. molecule have wide, when surface area interaction of 5. molecule have small. As can be seen from Figure 2, the MR value was found to be V ($R^2 = 0.683$), S ($R^2 = 0.8105$) and C_v ($R^2 = 0.7975$). The 5 and 10 molecules have deviated from the correlation between MR and V.

Heat capacity (C) 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 2, correlation coefficient square of 0.7975 have been found between MR and C. It can be said that the relationship between these two sizes 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 determinate 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 1 and 3 molecules have the lowest entropy value, the 28th molecule has the highest value. It is seen from Figure 2 that there is a linear correlation between S_e and MR values.

Molecular polarizability has been determined as (1) intermolecular weak interactions between closed shell species, and (2) for different molecular properties such as boiling points, melting points, vaporization enthalpies, solubilities, and solvent polarity scales. In addition, it measures the response of the outer shell electrons of a molecule toward an external 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 molecule and the 1st molecule have the lowest value. As can be seen from Figure 2, between average polarizability and volume, molar refractivity, heat capacity, $R^2=0.8105$, $R^2=0.7905$ and $R^2=0.9189$, respectively.

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

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

As seen in Table 2, Electronegativity is the 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 2, there have correlation between χ with electrophilic index, entropy, molecular softness, E_{HOMO} , E_{LUMO} , EA and IP.

The energy levels and shape of the molecular orbital order HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) for molecules provide useful a lot of information on electronic transitions and structure. The HOMO and LUMO also indicate to areas having possible electrophilic and nucleophilic interaction in molecule, respectively. In this case, Compound 1 has both electrophilic effect and nucleophilic effect among the investigated compounds. As seen in Figure 1S in Supplementary Materials, green areas are positive value, when blue areas are negative value HOMO-LUMO shape. The electrophilic on positive charge groups or atoms their attack to the most likely to the atomic site with a high density of orbital HOMO, while nucleophilic on negative charge groups or atoms attack LUMO that is correlated with atomic high density of orbital LUMO [34-36]. There are changes in the HOMO and LUMO fields depending on the substitution added. As seen in Figure 1S, there are changes in the HOMO and LUMO fields depending on the substitution added.

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 1. molecule has the biggest t other molecule, despite global softness of molecule 1 has the smallest of stability other molecule. In this case, the substitutions added to 5,8-Quinolinequinones compounds were not as effective as effective on biological activity.

Global Electrophilicity Index (ω) have been 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) electrophilicity 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 1. molecule is large compared to other molecule. Thus, when the 1. molecule exchanges electrons, it becomes more stable and the total energy of the molecule is optimized. It is possible that the 1. molecule interacts with its environment in electrophilic ways.

3.2. QSAR

In Table 3, the logarithmic values of the biological activity values of 28 different 5,8-Quinolinequinones derivatives made by Benjamin et al. and the theoretical biological activity values found according to the QSAR models by using the removed multiple linear regression method using the physicochemical values in Table 2 are listed. The observed biological activity values, 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 pIC₅₀ and T-cells pIC₅₀, and for anti-inflammatory activity (pAI₅₀) can see from 1, 2 and 3 equations, respectively. An ideal method derived with MLRA is one that has high

correlation coefficient square ($R^2 \leq 0.7$), correlation coefficient ($R \leq 0.8$), high ability for prediction ($P \leq 0.05$) and high F statistic value. The correlation graphs of calculated biological activities with experimental biological activities values have shown in Figure 3.

As can be seen from Eq.(1) that 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 IC₅₀ (μM)

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

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

In Eq (2), it has been observed that the logarithmic values of T-cell IC₅₀ values change have been positively depending on Electron Affinity, electrophilic index and heat capacity, when it has been negatively depending on polarizability along z, entropy and electronegativity.

T-Cell IC₅₀ (μM)

$$pIC_{50} = 23.478 - 0.009\alpha_{zz} + 0.086C + 0.64\chi - 0.032S_e - 11.892\chi + 6.956EA \quad (2)$$

$$R = 0.845; R^2 = 0.713; F = 8.710; P = 0.000$$

As seen in Eq. 3, the anti-inflammatory activity is theoretically the QSAR / QSPR models found with the following removed multiple linear regressions, below. According to the following equation, the dependent variable pAI₅₀ value positively depends on the energy value of LUMO, Water/octanol partition coefficient and the electrophilic index, while pAI₅₀ value is connected negatively only on the molecular hardness and softness.

AI₅₀ (μM)

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

$$R = 0.866; R^2 = 0.751; F = 6.020; P = 0.008$$

Conclusions

In this study, some physicochemical parameters of 28 5,8-Quinolinequinones derivatives have been calculated by quantum chemical calculations, after quantitative structure-effect relationships (QSARs) have been investigated by using calculated physicochemical parameters with some biological activity values previously reported in literature. It has been observed that, among all physicochemical parameters, it changes depending on the

electrophilic index and polarizability. The relationships between calculated physicochemical parameters are studied. The correlations were found between MR, V, α_{Mean} , ω , E_{HOMO} , E_{LUMO} , S, Se, χ , IP, η .

Acknowledgements

The authors greatly acknowledge for Gaussian09W and GaussView5.0 software to Bitlis Eren University.

Supplementary Information

The data derived in this study are available in Electronic Supplementary Materials..

Code availability

Gaussian09W and GaussView5.0 software

Author contribution

This manuscript has been written by YGS and IS.

Declarations

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Not applicable

Conflict of interest

The authors declare no competing interests.

References

- [1] J.A.Valderrama, J.A. Ibacache, V. Arancibia, J. Rodriguez, C. Theoduloz, Studies on quinones. Part 45: Novel 7-aminoisoquinoline-5,8-quinone derivatives with antitumor properties on cancer cell lines, Bioorg. Med. Chem. 17 (2009) 2894-2901. <https://www.sciencedirect.com/science/article/pii/S0968089609001497>
- [2] C.K. Ryu, J.Y. Lee, S.H. Jeong, J.H. Nho, Synthesis and antifungal activity of 1*H*-pyrrolo[3,2-*g*]quinoline-4,9-diones and 4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indoles. Bioorg.

Med. Chem. Lett. 19 (2009) 146-148.

<https://www.sciencedirect.com/science/article/pii/S0960894X08013474>

[3] Y. Cheng, L.K. An, N. Wu, X.D. Wang, X.Z. Bu, Z.S. Huang, L.Q. Gu, Synthesis, cytotoxic activities and structure–activity relationships of topoisomerase I inhibitors: Indolizinoquinoline-5,12-dione derivatives. *Bioorg. Med. Chem.*, 16 (2008), 4617-4625.

<https://www.sciencedirect.com/science/article/pii/S0968089608001570>

[4] E.W. Chia, A.N. Pearce, M.V. Berridge, L. Larsen, N.B. Perry, C.E. Sansom, C.A. Godfrey, L.R. Hanton, G.L. Lu, M. Walton, W.A. Denny, V.L. Webb, B.R. Copp, J.L. Harper, Synthesis and anti-inflammatory structure-activity relationships of thiazine-quinoline-quinones: inhibitors of the neutrophil respiratory burst in a model of acute gouty arthritis.

Bioorg. Med. Chem., 16 (2008) 9432-9442. doi: 10.1016/j.bmc.2008.09.052

[5] A. Bolognese, G. Correale, M. Manfra, A. Esposito, E. Novellino, A. Lavecchia, Antitumor Agents 6. Synthesis, Structure–Activity Relationships, and Biological Evaluation of Spiro[imidazolidine-4,3'-thieno[2,3-g]quinoline]-tetraones and Spiro[thieno[2,3-g]quinoline-3,5'-[1,2,4]triazinane]-tetraones with Potent Antiproliferative Activity *J. Med. Chem.*, 51 (2008) 8148-8152. doi: 10.1021/jm8007689

[6] J.M. Benjamin, G.N. Christopher, W.B. James, H.G. Carole, J.M. William, C.W. Michaela, M.D. Emma, H.P. Catherine, V.B. Michael, L.H. Jacquie, S.M.T. Mattie, L.S. Bridget The anti-cancer, anti-inflammatory and tuberculostatic activities of a series of 6,7-substituted-5,8-quinolinequinones, *Bio. & Med.Chem.*, 18 (2010) 3238–3251.

<https://www.sciencedirect.com/journal/bioorganic-and-medicinal-chemistry/vol/18/issue/9>

[7] Y. Gülseven Sıdır, İ. Sıdır, E. Taşal, C. Öğretir A Theoretical Study on Electronic Structure and Structure-Activity Properties of Novel Drug Precursor 6-Acylbenzothiazolon Derivatives *Inter. J. of Quant. Chem.*, 111 (2011) 3616–3629. <https://doi.org/10.1002/qua.22736>

[8] C. Hansch, A. Leo, R. W. Taft, A survey of Hammett substituent constants and resonance and field parameters, *Chem. Rev.* 91 (1991) 165-195. <https://doi.org/10.1021/cr00002a004>

[9] H. Gao, J. A. Katzenellenbogen, R. Garg, C. Comparative QSAR analysis of estrogen receptor ligands, *Chem. Rev.* 99 (1999) 723-744. DOI: 10.1021/cr980018g

[10] R. Franke, *Theoretical Drug Design Methods*; Elsevier: Amsterdam, New York, 1984.

[11] S. P. Gupta, M. Singh, C. Bindal, QSAR studies on hallucinogens, *Chem. Rev.* 83 (1983) 633-649. <https://doi.org/10.1021/cr00058a003>

[12] M.T.D Cronin., Computational methods for the prediction of drug toxicity, *Current Opinion in Drug Discovery and Development* 3 (2000) 292-297. PMID: 19649861

- [13] A.D. Becke, Density functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.*, 98 (1993), pp. 5648-5652. <https://doi.org/10.1063/1.464913>
- [14] C. Lee, W. Yang, R.G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density *Phys. Rev. B*, 37 (1988), pp. 785-789. DOI: 10.1103/physrevb.37.785
- [15] M.J. Frisch, Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Petersson, G.A.; Nakatsuji, H.; et al. Gaussian 09, Revision A.02; Gaussian, Inc.: Wallingford, CT, USA, 2009
- [16] Nielsen, A.B. and Holder, A.J. (2009) Gauss View 5.0, User's Reference. GAUSSIAN Inc., Pittsburgh.
- [17] IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
- [18] E.J. Lien, Z.R. Guo, Use of Dipole moment as a Parameter in Drug-Receptor Interaction and Quantitative Structure-Activity Relationship Studies, *Journal of Pharmaceutical Sciences* (1982) 71(6) 641-655. doi: 10.1002/jps.2600710611.
- [19] J. Kujawski, H. Popielarska, A. Myka, B. Drabińska, M. K. Bernard, The log P Parameter as a Molecular Descriptor, in the Computer-aided Drug Design – an Overview, *Computational Methods In Science And Technology* 18(2) (2012) 81-88. doi: 10.12921/cmst.2012.18.02.81-88
- [20] A. Avdeef, Physicochemical profiling (solubility, permeability and charge state) *Curr. Top. Med. Chem.* 1 (2001) 277-351. doi: 10.2174/1568026013395100
- [21] M. Matoga, E. Laborde-Kummer, M.H. Langlois, P. Dallet, J.J. Bose, C. Jarry, P. Dubost, Determination of pKa values of 2-amino-2-oxazolines by capillary electrophoresis, *J. Chromatogr. A* 984 (2003) 253-260. [https://doi.org/10.1016/S0021-9673\(02\)01848-4](https://doi.org/10.1016/S0021-9673(02)01848-4)
- [22] M. Remko, K.R. Liedl, B.M. Rode, Structure, Reaction Enthalpies, Entropies, and Free Energies of Cation-Molecule Complexes. A Theoretical Study by Means of the ab Initio Complete Basis Set CBS-Q Method, *J. Phys. Chem. A* 102 (1998) 771-777. <https://doi.org/10.1021/jp9725801>
- [23] R.R. Ruffolo, Jr. W. Bondinell, J.P. Hieble, Alpha- and beta-adrenoceptors: from the gene to the clinic. 1. Molecular biology and adrenoceptor subclassification *J. Med. Chem.* 38 (1995) 3681-3761. DOI: 10.1021/jm00018a001
- [24] B. Szabo, Imidazoline antihypertensive drugs: a critical review on their mechanism of action, *Pharmacol. Ther.* 93 (2002) 1-35. doi: 10.1016/s0163-7258(01)00170-x.

- [25] M. Anastassiadou, S. Danoun, L. Crane, G. Baziard-Mouysset, M. Payard, D.H. Caignard, M.C. Rettori, P. Renard Synthesis and pharmacological evaluation of imidazoline sites I_1 and I_2 selective ligands *Bioorg. Med. Chem.* 9 (2001) 585-592. doi: 10.1016/s0968-0896(00)00280-7
- [26] F. Yoshida, J.G. Toplis Isoquinoline and Quinazoline Urea Analogues as Antagonists for the Human Adenosine A_3 Receptor *J. Med. Chem.* 43 (2000) 5272-5275.
<https://doi.org/10.1021/jm000002u>
- [27] H. Kubinyi, *QSAR: Hansch analysis and Related Approaches*, VCH, New York, 1993.
- [28] W.J. Dunn, *Eur. J. Med. Chem.-Chim. Ther.* 12 (1977) 109-112.
- [29] R. Darros-Barbosa, Temperature and Concentration Dependence of Density of Model Liquid Foods, *International journal of Food Properties* (2003), 6.2, 239-258.
<https://doi.org/10.1081/JFP-120017815>
- [30] M. Varese, S. Guardiola, J. Garcia, E. Giralt, Enthalpy- versus Entropy-Driven Molecular Recognition in the Era of Biologics, *ChemBioChem* 2019, 20,2981 –298
<https://doi.org/10.1002/cbic.201900270>
- [31] R. P. Verma, A. Kurup, C. Hansch, On the role of polarizability in QSAR, *Bioorganic & Medicinal Chemistry* 13 (2005) 237–255 <https://doi.org/10.1016/j.bmc.2004.09.039>
- [32] L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press: Ithaca, New York, 1960
- [33] R.G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, UK, 1989.
- [34] A. Kumer, N. Sarkar, S. Paul, A. Zannat, The Theoretical Prediction of Thermophysical properties, HOMO, LUMO, QSAR and Biological Indices of Cannabinoids (CBD) and Tetrahydrocannabinol (THC) by Computational Chemistry *Advanced Journal of Chemistry-Section A*, 2019, 2(3), 190-202. doi: 10.29088/SAMI/AJCA.2019.2.190202
- [35] Y. Gülseven Sıdır, İ. Sıdır, “Structure-activity relationships for novel drug precursor *N*-substituted-6-acylbenzothiazolone derivatives: A theoretical approach” *Journal of Molecular Structure*, 1045, 2013, 131-138. DOI: 10.1016/j.molstruc.2013.04.006
- [36] Y. Gülseven Sıdır, İ. Sıdır, “Quantitative structure activity relationships of cytotoxicity effect on various cancer cells of some imidazo[1,2- α]pyrazine derivatives” *Bitlis Eren University Journal of Science and Technology*, ISSN 2146–7706, 3, 2013, 9–14.
<https://doi.org/10.17678/beuscitech.47133>

Figures

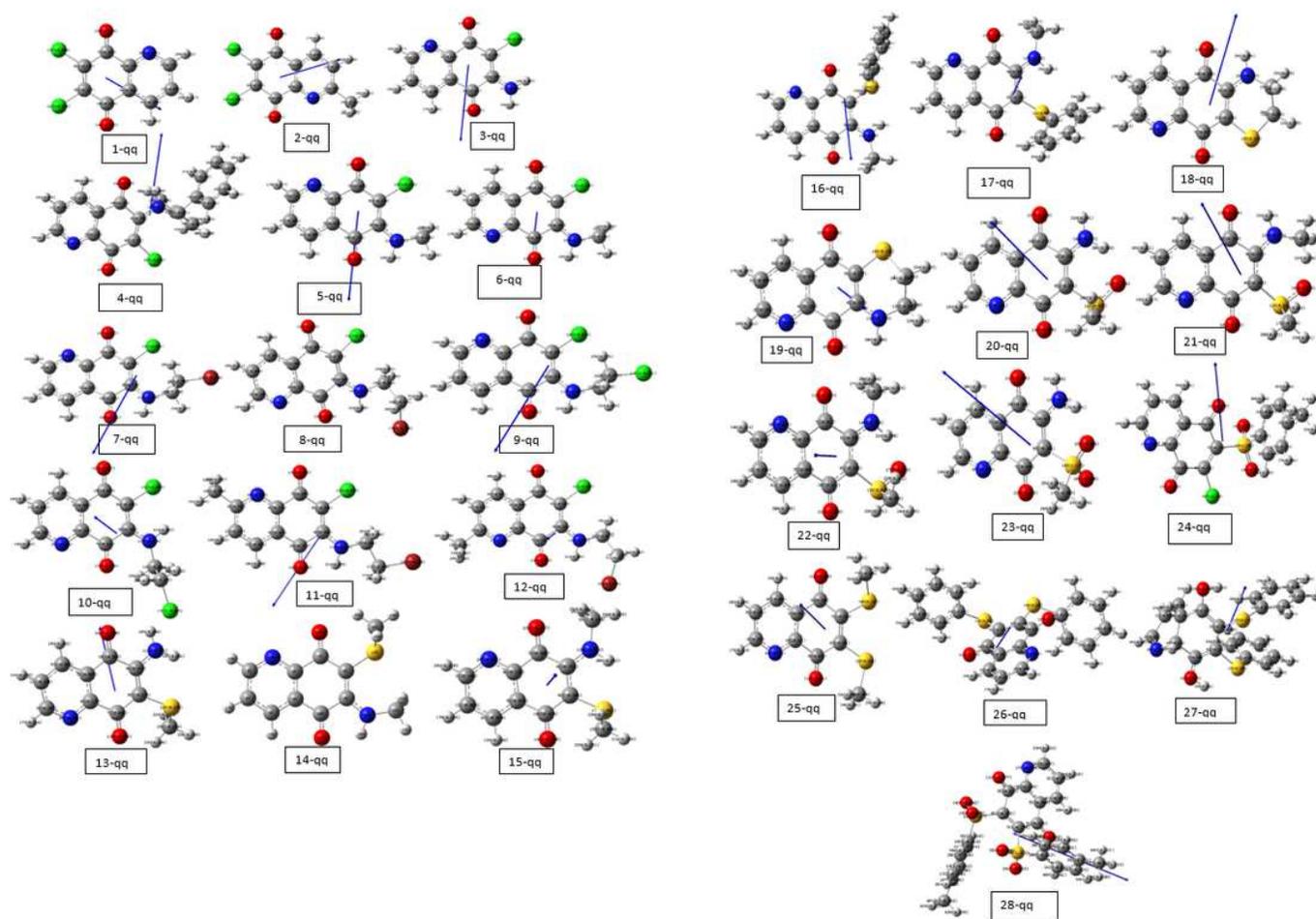


Figure 1

The molecular structure of 5,8-Quinolinequinones derivatives

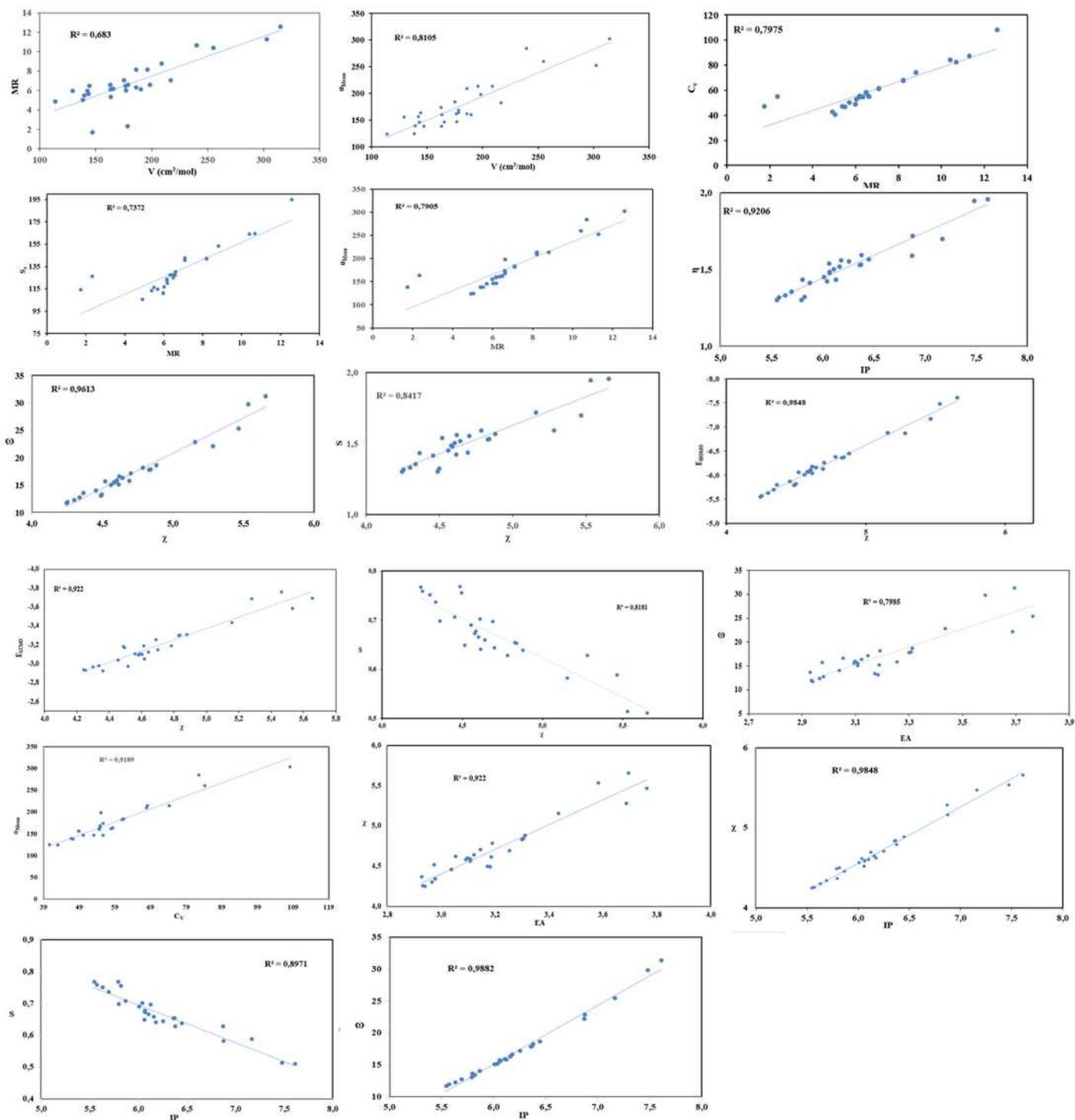


Figure 2

The correlation graphs between physicochemical with physicochemical parameters.

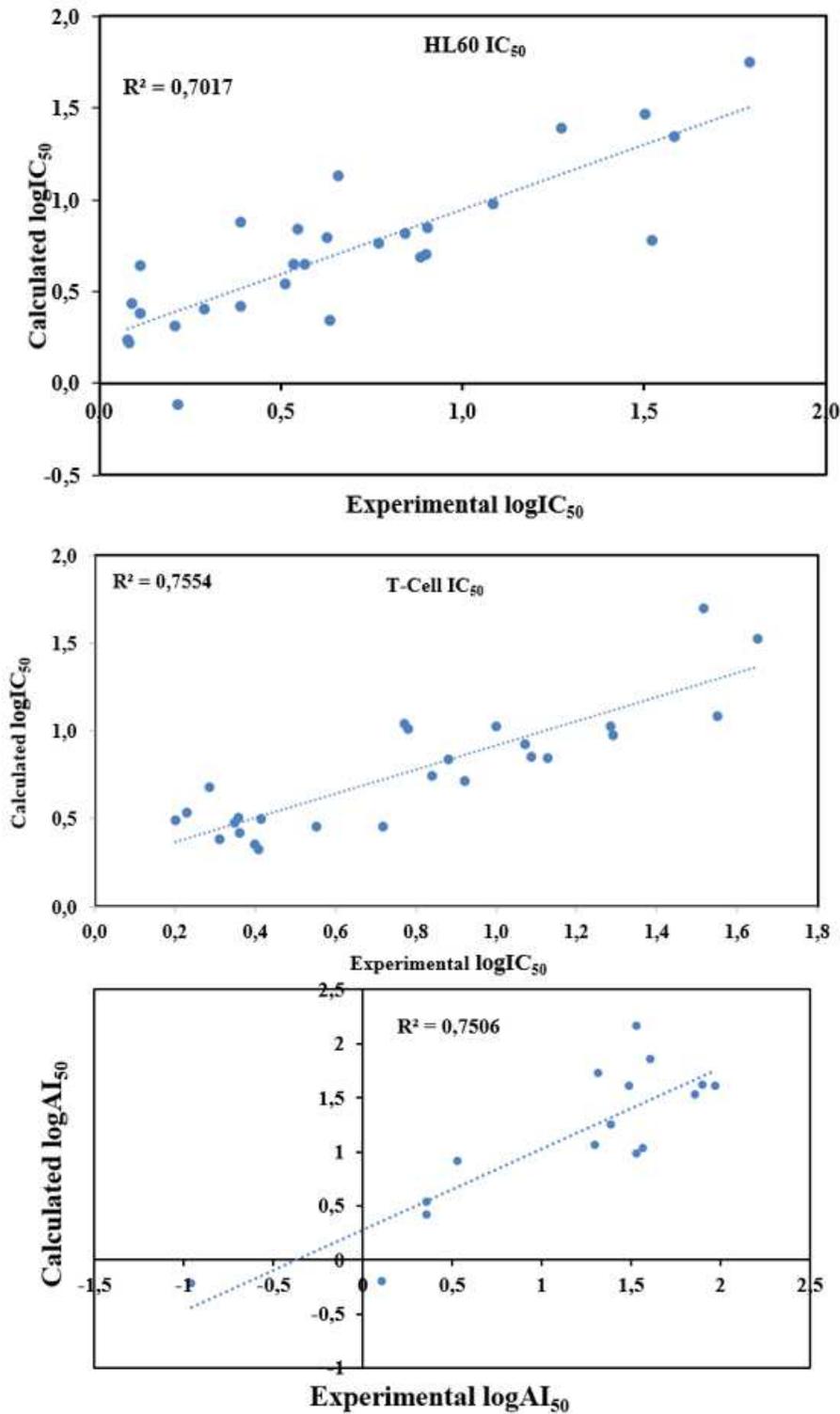


Figure 3

The correlation graphs of calculated biological activities with experimental biological activities values.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterials.docx](#)
- [Tables.pdf](#)