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A computational study of lipophilicity of E-2-arylmethylen-1-tetralones and their heteroanalogues using QSAR and DFT Based Molecular surface Electrostatic Potential

Sharieh Hosseini[a]*, Mohammad Reza Gholami[b] and Mohammad Haghgu[c]

[a] Department of Applied Chemistry, Faculty of Pharmaceutical Chemistry, Pharmaceutical Siences Branch, Islamic Azad University, Tehran, Iran, (IAUPS)
[b] Department of Chemistry, Sharif University of Technology, Tehran, Iran
[c] Department of Chemistry, Payame Noor University, Tehran, Iran

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ABSTRACT

E-2-Arylmethylen-1- tetralones and E-3-phenylme thylene chromanone-4-ones and their derivatives closely related to flavonoids belong to the plant secondary metabolites most investigated recently.The class of flavonoids is an enormous class of plant secondary metabolites having so different pharmacological effects as inhibition of nitric oxide synthasecancer preventive effect or potential impact on the etiology of certain vascular disease.Numerous biological activity have been attributed to the tetralones mentioned. In this study B_3P_{86}/6-31^{++}G* was used to compute and map the molecular surface electrostatic potentials of a group of tetralones and chromanones to identify common features related to their lipophilicity. Several statistical properties including potentials extrema ($V_{s,min}$, $V_{s,max}$), the average of positive electrostatic potential on the surface (V_s^t), the average of $V_{(r)}$, over the surface (V_s) and the variance of $V_{(r)}$ over the surface (6^{2-}) and system lipophilicity were computed. Statistically, the most significant correlation is a three parameter equation with correlation coefficient, R value of 0.881 and R^2_{adj}=0.743. The obtained models allowed us to reveal lipophilicity activity of tetralones.

Keywords: Molecular surface potential; lipophilicity; QSAR; Biological activity

INTRODUCTION

The flavonoid nutrient families knows known to scientists and include over 6000 already identified members. Some of the best known flavonoids include quercetin, kaempferol, catechins and anthocyanids this nutrient and anti inflammatory health benefits as well as its contribution of vibrant color to the foods we eat. In addition, it should be noted that the class of flavonoids is an enormous class of plant secondary metabolites having so different pharmacological effects as inhibition of nitric oxide synthase [1], cancer preventive effect [2] or potential impact on the etiology of certain vascular disease [3]. Tetralone is one organic chemical compound with the molecular formule $C_{10}H_6O$. Tetralones and their derivatives closely related. It is a common intermediate in organic chemistry. One of the major prerequisites for pharmacological screening and drug development is prediction of absorption, transport of amolecule through cellular

*Corresponding author: shariehhosseini@yahoo.com

membranes. Which strongly depends on lipophilicity[4, 5]. Hallgas et al [6] reported the synthesis and antifungal properties of some bicyclic α, β unsaturated ketones, E-2-arylmethylene, 1- tetralone and their derivatives. As it is known to us the biological activity correlates greatly with the structures of tetralones derivative. In this respect Quantitative structure- Activity Relation ships (QSAR) has been emerged as a promising tool to quantitatively understand the relation ship between molecular structures and biological activities. QSAR studies have been success fully employed in modern chemistry and biochemistry .

THEORY AND COMPUTATIONAL DETAILS

Molecular surface electrostatics potential (MSEP) Molecular surface electrostatic potential (MSEP), which is created on the surface of a molecule by its nuclei and electrons, is a well – established guide to physical properties and molecular interactive behavior [7,8].

Unlike many of the other quantities used now and earlier, as indexes of physicochmeicalbehavior , the electrostatic potential $V_{(r)}$ is a real physical property the one that can be determined experimentally by diffraction methods as well as computationally. The electrostatic potential $V_{(r)}$ is created in the space around a molecule by its nuclei and the electrons are given rigorously by Equation (1):

$$V_{(r)} = \Sigma \frac{Z_A}{R_{A-r}} - \int \frac{p_{r'}}{r-r} \mathrm{dr}' \qquad (1)$$

where Z_A is the charge on nucleus A, located at R_A and ρ(r`) is the electronic density [9] the molecular surface was taken to be the 0.00 lμ contour of ρ(r`) as proposed by Bader et al [10]. The quantities characterizing the MSEP are as follow [11] :

1.$V_{s,max}$ and $V_{s,min}$ are the most positive and negative values of $V_{(r)}$ on the molocular surface, respectively .

2 –π, is the average deviation on the molecular surface, defined by Equation (2):

$$\pi = \frac{1}{n}\sum_{i=1}^{n}\{(V_s(r_i - \bar{V}s)\} \qquad (2)$$

where V_s is the average of $V_{(r)}$ over the surface.

3-V_s^+ and V_s^- are the average of positive and negative electrostatic potentials on the surface of the molecular respectively.

4.$\sigma_+^2$and σ_-^2 the positive and negative variances of $V_{(r)}$ over the molecules, respectively, which are included in the σ^2_{tot}. The total variances of $V_{(r)}$ over the surface of molecules, according to Equation (3):

$$\sigma^2_{tot}=\sigma^2_+ +\sigma^2_- = \frac{1}{m}\sum_{1=1}^{m}(V_S^+(r_j) - V_S^+)2 + \frac{1}{n}\sum_{k=1}^{n}(V_S^-(r_k) - V_S^-)2 \qquad (3)$$

5- VB ,the balance between the positive and negative surface potentials , is defined by Equation(4):

$$V = \frac{\sigma^2+\sigma^2-}{(\sigma^2_{tot})2} \qquad (4)$$

The multilinear correlation regression (MLR) method was used to obtain the optimum correlation.

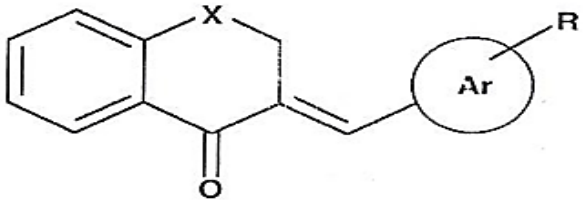
Calculation methods:

All the structures of tetralones are shown in figure 1. Based on their structural features the library could be further divided in to two subgroups:

Group1(table1) is consisting of substituted arylmethylene – tetralones (1-20) .Groupп contains the chromanones and their analogues (21-24).

The fall geometry optimizations were perfume by DFT method and 6-$31^{++}G^*$

basis set. All the calculations mentioned above were performed with the Gaussian 03 program package.



X=CH_2.$(CH_2)_2$, O, S, So_2
Ar= phenyl, substituted (R) phenyl, hetero aryl

Fig. 1 . structures of tetralones.

Table 1. The structures of 24 compounds :a-tetralones and its analogues (1-20) b-chromanones (21-24)

Comp	X	Ar	R
1	CH_2	Phenyl	H
2	CH_2	Phenyl	4'-Me
3	CH_2	Phenyl	4'-OMe
4	CH_2	Phenyl	4'-fluor
5	CH_2	Phenyl	2'-chlor
6	CH_2	Phenyl	4'-chlor
7	CH_2	Phenyl	3',4'-chlor
8	CH_2	Phenyl	2',4'-chlor
9	CH_2	Phenyl	2',6'-chlor
10	CH_2	Phenyl	4'-brom
11	CH_2	2-Furul	H
12	CH_2	2-Prroliyl	H
13	CH_2	N-Methyl-2-pyrrolyl	H
14	CH_2	2-thienyl	H
15	CH_2	2-pyridyl	H
16	CH_2	3-pyridyl	H
17	CH_2	4-pyridyl	H
18	CH_2	3-indolyl	H
19	$(CH_2)_2$	Phenyl	H
20	-	Phenyl	H
21	O	Phenyl	H
22	S	Phenyl	H
23	SO	Phenyl	H
24	SO_2	Phenyl	H

Molecular descriptors

We derived some quantum descriptors from DFT calulations , such as the v_s, A_s , V_s^+,6^{-2} and the lowest Unoccupied molecular orbital (LUMO).

Stepwise multiple Linear regression

In order to select the predominant parameters the significantly affect the lag k of the compounds, we employed the statistic software SPSS, taking log k as the dependent variable and every candidate descriptor calculated above as an independent variable to perform.

The stepwise multiple Linear regression

In the next step QSAR equations were made through the multiple linear regression (MLR) method utilizing the three calculated descriptors.

Results and discussionQSAR equation analysis and model validation the QSAR equation is demonstrated in equations (5)

logk= -0.737 (±0.788) - 0.011±0.002)σ^2-

+0.016(±0.003)As -0.230 (±0.063)<Vs^+> (5)

n= 24 R^2=0.776 R_{adg}^2 = 0.743 Se= 0.240

in which , n , SE and R^2 are the number of the compound analyzed , the correlation coefficient and the standard deviation respectively.

The mentioned indicators are usually used in QSAR analysis to judge how much the model is reliable. In order to check the reliability of predicted equation , the observed versus predicted actives logk values according to the QSAR equation are plotted in figure 2. AS it can be seen , the experimental values are in good agreement with the predicted value , indicating the reliability of the equation.

Descriptor of the QSAR equation

According to the equation increasing <V_s^+> and σ^{-2} caused an decrease in the drug lipophilicity.

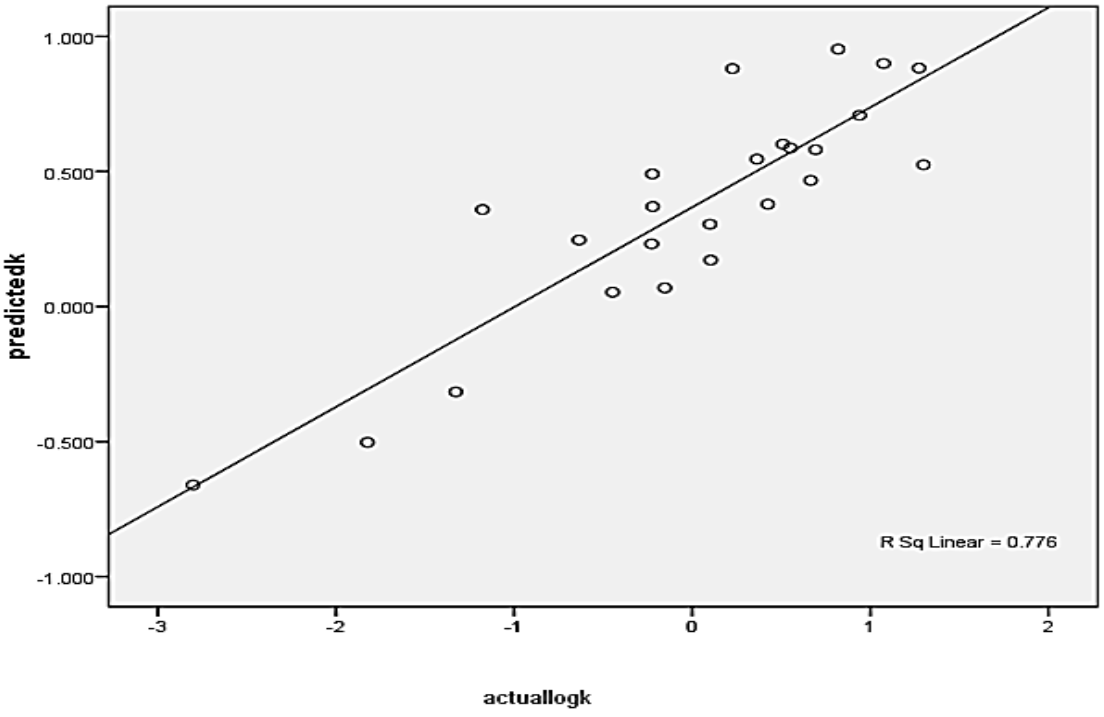


Fig. 2. The plot of predicted vs experimental activity of tetralones.

$<Vs^{+}>$ is the average positive electrostatic potential on the surface. Hogelin et al [12] showed an increase in $Vs_{, min}$or $Vs_{,max}$ caused an increase in accepting and donating power of hydrogen bond thus it could be predicted that an increase in two quantities , interaction of drug molecule with solven molecules will increase and lead to a decrease in the activity of the drug. The $Vs_{,max}$ is parameter that is related to the solvent accessible surface of the compounds [13]. The positive region of the surface electrostatic potentials. AS mentioned above the strongest positive potentials. AS mentioned above the strongest positive potential with $Vs_{,max}$ between 8.105 and 11.779 kcal/mol are produced by hydrogen of the X group or ring hydrogens. However, there is no correlation between the number of available hydrogens and their molecule subsequent.

$Vs_{,max}$ indicating that the positive region of their surface is relatively weak.the results of our study was consistent with the finding of fakhr [14]. The studied compounds are dividedtwo group according their structures. The first group including substituted arylmethylene-tetralones and the second group including chromanones and their analogues. The highest predicted logk is related to 7 ,8 and 9 compounds, that are dichloride derivative. The lowest logk is related to 15 and16 compounds specially 15 compound pyrydy1-one that negative value is obtained for it.The 8 compound has a higher log k compare to 9 compound. The 8 and 9 compounds are structure isomers with each other which the choloroposition are different in them. The Cholores are at ortho and para positions in 8 compound, but in ortho position in 9 compound. The 7 and 8 compounds which have substituated para position have higher logkcompairedto 9 compound which cholores are ortho position thus not only nature of substituate but also their position can effect on lipophilicity of molecules.The results of our study were consistent with the finding of hallgas et al[6].

In considering those aspect we can draw a conclusion that lipophilicity of the investigated compounds are influenced by the structural an electronic properties. therefore, the electronic and structural properties are important factors in the interaction between tetralone derivatives that present lipophilicity and the biological receptor.As Hosseinietal[15] study was consistent with our results.She reported a relationship between cytotoxicity activity of substituted of Pyrazine-2-Carboxylic acides, electronic and structural descriptors.

Table 2 shows the experimentally determined and actual activity.Some of the key features of the molecular surface electrostatic potentials on the basis of our calculation are also listed in Table 2.The best correlation was obtained by equation 5.Although this equation does not reproduce the absolute values of the experimental data, it can predict the activity of the drug.

The above data was used to find a regression analysis of the correlation between the descriptors(Table 3).

CONCLUSIONS

In This study,we understand that ,the QSAR model could be helpful to estimate the biological activity of drugs, by calculating the descriptors involved in the QSAR equation .The electronic and structural descriptors are the main factors which influence the lipophilicity of tetralone and their analogues. The position and the kind of substituate could be effective on the activity of drugs. Thus studying their applicability could lead to a vital improvement in QSAR.

Table 2. Actual and predicted activity and molecular descriptors used in this study

Compd	Actual logk	$\sigma -^2$	$< Vs^+ >$	As	Predicted logk
1	0.656	71.892	8.467	236.426	0.379
2	0.770	89.139	8.578	254.3	0.467
3	0.562	66.0907	8.544	265.239	0.881
4	0.627	60.341	8.896	245.812	0.546
5	0.783	57.249	9.714	257.798	0.581
6	0.843	79.096	10.367	277.336	0.525
7	1.070	49.307	10.122	277.58	0.883
8	1.058	34.263	10.497	274.627	0.900
9	0.964	90.715	8.105	263.531	0.708
10	0.900	51.056	9.736	223.202	0.068
11	0.382	62.457	8.628	236.426	0.246
12	0.154	74.887	9.288	224.475	0.232
13	0.347	81.182	8.727	240.919	0.172
14	0.504	59.846	8.978	233.975	0.359
15	-0.103	108.982	10.599	235.123	-0.503
16	-0.409	88.765	9.063	0.0531	0.053
17	-0.243	79.623	9.554	0.491	0.491
18	0.349	52.741	9.394	0.587	0.587
19	0716	60.052	8.220	0.370	0.370
20	0.350	43.846	9.718	0.305	0.305
21	0.502	29.712	9.188	0.953	0.953
22	0.696	51.648	8.813	0.601	0.601
23	-0.174	157.416	8.944	-0.316	-0.316
24	-0.873	141.370	11.779	-0.661	-0.661

Table 3. Model Summary

Model	Descriptors	R	R square	Adjusted R square	Std. Error of the Estimate
1	σ^{2-}	0.665	0.443	0.417	0.361616
2	σ^{2-}, AS	0.791	0.626	0.590	0.303141
3	$\sigma^{2-}, AS, < VS^+ >$	0.881	0.776	0.743	0.240174

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