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مطالعه رابطه کمی فعالیت-ساختار براساس تئوری تابعیت چگالی مشتقات تیازولین به عنوان عاملهای ضدسرطان

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A Density Function Theory Based Quantitative Structure Activity Relationships Study of Thiazoline Derivatives as Anticancer Agents

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چکیده

مطالعه کمی فعالیت – ساختار یک سری از مشتقات جدید تیازولین با فعالیت ضد سرطانی با استفاده از روش تئوری تابعیت چگالی در سطح B3LYP/ 6-31G انجام گرفت. توصیفگرهای مکانیک کوانتومی ۲۱ مشتق تیازولین با فعالیت مشخص به‌دست آمد. رگرسیون خطی چندگانه برای تعیین رابطه میان توصیفگرهای مولکولی و فعالیت بیولوژیکی مولکول با استفاده از روش مرحله‌ای به‌کار گرفته شد. بهترین مدل، علاوه بر کیفیت آماری مناسب، توانایی پیش‌بینی مناسبی با مجذور ضریب همبستگی ۰/۹۴۵ و انحراف استاندارد ۰/۵۸۶ دارد. فعالیت ضدسرطانی که به‌صورت نصف حداکثر غلظت مهارکنندگی (IC_{50}) ارتباط نزدیکی با توصیفگرهایی مانند انرژی بالاترین اوربیتال مولکولی اشغال شده، ممان دوقطبی، نرمی، سختی، انرژی یونش و انرژی الکترونخواهی دارد. بر این اساس، می توان یک مدل مناسب پیشنهاد داد و فعالیت ترکیبات را منطبق بر آنالیز آماری چند متغیره توصیف کرد.این مطالعه نشان داد که نتایج پیش بینی شده در توافق مناسب با مقادیر تجربی هستند. نتایج می تواند ابزار مناسب و مفیدی بری فهم مکانیسم عمل و طراحی ترکیبات جدید با فعالیت ضد سرطانی باشد.

واژه‌های کلیدی

فعالیت بیولوژیکی، ضد سرطان، رابطه کمی فعالیت ساختار، تئوری تابعیت چگالی، آنالیز رگرسیون چند متغیره خطی.

Abstract

The Quantitative Structure–Activity Relationship of a series of novel Thiazoline derivatives with anticancer activity has been studied by using the density functional theory by B3LYP/ 6-31G. Descriptors of quantum mechanics of 21 thiazoline derivatives with known activity were obtained. Multiple linear regressions were employed to model the relationships between molecular descriptors and biological activity of molecules using stepwise method. The most model shows not only significant statistical quality, but also predictive ability, with the square of adjusted correlation coefficient (R2=0.945) and standard error (SE=0.586). We find that the anticancer activity expressed that as half maximal inhibitory concentration (IC50), closely relates to the highest occupied molecular orbital, dipole moment, softness, hardness, ionization energy, electron affinity. Accordingly can be offered a quantitative model, and interpret the activity of the compounds relying on the multivariate statistical analysis. This study shows that the prediction results were in excellent agreement with the experimental value. The results can offer some useful references for understanding the action mechanism and designing new compounds with anticancer activity.

Keywords

Biological activity; Anticancer; Quantitative Structure Activity Relationship; Density Function Theory; Multilinear Regression.

1. INTRODUCTION

Discovery of new drugs for treatment of cancer has been gaining a great deal of interest mainly due to a universal resistance to conventional single drug chemotherapeutic agents. Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities [1], recently found application in drug

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development for the treatment of allergies, hypertension, inflammation, bacterial, HIV infections, hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity [2-3]. Medicinal chemists have also carried out considerable research for novel antimicrobial and anti cancer agents bearing a pyrimidine moiety. A series of thiazoline derivatives bearing a hydrazone moiety (N/-(3, 4-Diarylthiazol-2(3H)-ylidene)-2-(arylthio) acetohy-drazides) have been synthesized by M.D. Altintop et al. which can act cytotoxicity and anticancer agents [4].

Quantitative structure–activity relationships (QSARs) are widely used to predict activity of chemical structure corresponding to physicochemical properties. Recently, quantum chemical descriptors have been used in QSAR studies because the quantum chemical quantities are able to provide accurate quantitative description of the molecular structures and chemical properties [5-6]. Molecular orbital energies, frontier orbital densities, dipole moments, softness, hardness and other properties have been used as descriptors within a QSAR. Density functional theory (DFT) - based descriptors have found immense usefulness in the prediction of activity of molecules [7]. Theoretically to establish the relationship between molecular property of a molecule and its activity (may be anticancer, anti-arthritis, etc.), quantitative structure activity relationship (QSAR) study is essential, which is required for novel drug design process. Mathematically QSAR models are regression models which link a set of predictor variables to the strength of the response variable. Three main components of QSAR model include the properties to be modeled, the chemical information and the algorithm/methods used to link the property and activity of the chemical [8].

Already, anticancer activity evaluation and QSAR studies of heterocyclic esters of caffeic acid [9], antioxidant/anti-inflammatory aryl-acetic and hydro-xamic acids [10], new Artemisinin Compounds [11],Novel 6-Chloro-3-(2-Arylmethylene-1-methyl-hydrazino)-1,4,2-benzodithiazine 1,1-Dioxide deriva-tives [12],3 and4-bromo benzohydrazide derivatives [13],bowsellic acid derivatives [14] and phenanthrene-based tylophorine derivatives [15] have been reported. Also, prediction of biological activity by combining DFT and QSAR results of anticancer activity of nucleoside analogues [16], 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA) derivatives [17], N-(2-chloroethyl)-N′-cyclohexyl-N-nitrosoureas [18] and substituted amides of pyrazine- 2-carboxylic acids [19] have been done. In this work we employed DFT using the B3LYP hybrid functional to explore and determine various electronic descriptors, with better accuracy, to make the necessary improvement in the QSAR models. Electronic, reactivity and quantum Descriptors were obtained for 21 thiazoline derivatives as anti-cancer and anti-microbial (Fig. 1). The multiple linear regression (MLR) method [20] was employed with the aim to obtain a correlation between these descriptors and the anticancer activity of these compounds.

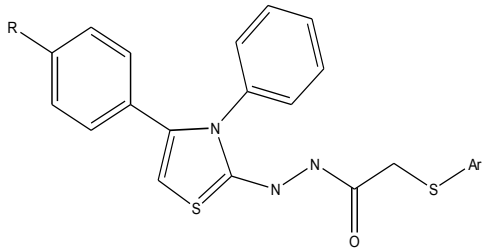

Fig. 1. Structures of thiazoline derivatives**.**

2. EXPERIMENTAL

The activity of these compounds was correlated with various physicochemical parameters by DFT. The three-dimensional structures were generated using Gauss View 3.0 and all calculations were performed with Gaussian 03W programs [21]. Geometry optimization of 21 compounds was carried out by B3LYP exchange correlation functional with the 6-31G (d) basis set [22]. This method has become very popular in recent years because it can reach similar precision to other methods in less time and less cost from the computational point of view.

Structures of the 21 thiazoline derivatives and their experimental are presented in Table 1. The geometry of the compounds was determined by optimizing all geometrical variables with no symmetry constraints. Some of quantum chemical descriptors used in this study related to the thermo chemistry of the molecules obtained from frequency calculation at the optimized geometry, such as the Gibbs free energy and entropy. The Energies of the HOMO (the highest occupied molecular orbital) and LUMO (the lowest unoccupied molecular orbital) are popular quantum mechanical descriptors which play a major role in governing many chemical reactions [23]. Based on Koopmans theorem, the ionization potential is defined as IP= $-E_{HOMO}$. The same idea applies for the electron affinity calculation. The electron affinity is obtained through Koopmans theorem as $EA=-E_{LUMO}$. The dipole moment is the most evident and most widely-used quantity to demonstrate the polarity of the molecule. The electronegativity(χ) is defined as the negative of the partial derivative of energy E of an atomic or

molecular system with respect to the number of electrons N with a constant external potential $-(\frac{\partial E}{\partial N})_V$ [24]. The lists of quantum chemical descriptors for studied compounds are summarized in Table 2. Also, values of quantum chemical descriptors for the thiazoline derivatives are presented in Table 3.

Multiple linear regression is used to study the relation between one dependent and several independent variables. MLR describes a line for which the differences between the predicted and the actual values of the dependent variable are at a minimum. Multiple linear and non-linear regression were used to predict effects on the half maximal inhibitory concentration (IC_{50}) of thiazoline derivatives. Equations were justified by the correlation coefficient(R), determination coefficient (R^2), the squared error (SE) and F-statistic the p-value associated with it [25]. In the next step, QSAR equations were made through the MLR method utilizing the calculated descriptors.

Table 1. Biological activity values (IC_{50}) and structural features of the thiazoline derivatives.

No.	R	Ar	IC_{50}	IC_{50}
1	CH_3	4-Methyl-4H-1,2,4-triazol-3-yl	130.00	85.54
2	CN	4-Methyl-4H-1,2,4-triazol-3-yl	153.30	151.49
3	H	4-Methyl-4H-1,2,4-triazol-3-yl	173.30	107.02
4	Cl	1-Methyl-1H-tetrazol-5-yl	40.00	32.69
5	NO_2	1-Methyl-1H-tetrazol-5-yl	166.70	171.36
6	Br	1-Methyl-1H-tetrazol-5-yl	19.30	20.14
7	H	1-Phenyl-1H-tetrazol-5-yl	416.70	382.99
8	CH_3	1-Phenyl-1H-tetrazol-5-yl	500.00	499.95
9	F	1-Phenyl-1H-tetrazol-5-yl	206.70	243.77
10	Br	1-Phenyl-1H-tetrazol-5-yl	433.30	395.76
11	H	5-Methyl-1,3,4-thiadiazol-2-yl	196.70	262.42
12	Br	5-Methyl-1,3,4-thiadiazol-2-yl	55.00	11.87
13	CH_3	5-Methyl-1,3,4-thiadiazol-2-yl	373.30	391.75
14	F	5-Methyl-1,3,4-thiadiazol-2-yl	383.30	365.97
15	OCH_3	5-Methyl-1,3,4-thiadiazol-2-yl	300.00	333.24
16	Cl	5-Methyl-1,3,4-thiadiazol-2-yl	253.30	258.12
17	CH_3	Pyrimidin-2-yl	500.00	488.89
18	OCH_3	Pyrimidin-2-yl	450.00	440.69
19	Cl	Pyrimidin-2-yl	396.70	383.19
20	Br	Pyrimidin-2-yl	273.30	329.17
21	F	Pyrimidin-2-yl	500.01	438.21

Table 2. Quantum Chemical Descriptors for the thiazoline derivatives.

Brief Description	Descriptor
Hartree-Fock	HF
Correction energy	Ce
Zero point energy	ZPE
Thermal energy	E_T
Change in thermal enthalpy	ΔH
Change in Gibbs free energy	ΔG
Highest Occupied Molecular Orbital The	HOMO
The Lowest Occupied Molecular Orbital	LUMO
Dipole moment	DM
Heat capacity at constant volume	Cv
Change in Entropy	ΔS
Ionization potential	IP
Electron affinity energy	EA
Softness	Ss
Hardness	η

Table 3. Values of quantum chemical descriptors for the thiazoline derivatives.

No.	HF (hartree)	Ce (hartree)	ZPE (kCal/mol)	Et (kCal/mol)	ΔH (hartree)	ΔG (hartree)	HOMO (ev)	LUMO (ev)	DM (debye)	Cv (Cal/mol-k	ΔS (Cal/ mol-k)	IP (ev)	EA (ev)	Ss (ev)	η (ev)
1	-1972.6060	0.3854	-1972.2464	241.8420	-1972.2210	-1972.3100	-0.0064	-9.20E-04	13.6060	97.1580	183.3110	0.0064	-9.20E-04	0.00366	273.2240
2	-2025.9419	0.3545	-2025.6134	222.4720	-2025.5901	-2025.6701	-0.0011	-8.10E-04	5.4311	98.1141	183.1110	0.0012	-8.10E-04	9.80E-04	1020.4081
3	-1933.6980	0.3300	-1933.3680	222.2501	-1933.3411	-1933.4311	-0.0067	-0.01546	13.1639	92.1071	173.5301	0.0067	-0.01546	0.011095	90.1306
4	-2392.8711	0.034713	-2392.5494	217.8290	-2392.5210	-2392.6101	-0.0247	-0.01414	12.5734	95.4001	182.1041	0.0247	-0.01414	0.01917	52.1648
5	-2137.7151	0.3599	-2137.3818	225.8890	-2137.3501	-2137.4401	-2.80E-04	-0.02081	4.2283	100.1411	188.4180	2.80E-04	-0.02081	0.010545	94.8316
6	-4520.2564	0.3338	-4519.9481	209.4760	-4519.9200	-4520.0112	-0.0047	-0.00684	7.9600	94.7060	186.5080	0.0047	-0.00684	0.005785	172.8608
7	-2180.2865	0.4281	-2179.8875	268.6680	-2179.8601	-2179.9601	-0.0034	-0.01273	2.7701	110.1730	205.5571	0.0034	-0.01273	0.00806	124.0694
8	-2219.5923	0.4570	-2219.1652	286.7870	-2219.1311	-2219.2311	-0.0195	-9.90E-04	10.3499	113.5211	203.5571	0.0195	-9.90E-04	0.01027	97.3709
9	-2279.4974	0.4210	-2279.1058	264.1970	-2279.0801	-2279.1710	-0.0065	-0.01591	2.7177	112.3460	202.2110	0.0065	-0.01591	0.011225	89.0868
10	-4751.2555	0.4199	-4750.8656	263.5060	-4750.8302	-4750.9300	-0.0023	-0.00231	5.6752	113.6011	208.1240	0.0023	-0.00231	0.00232	431.0344
11	-2276.0940	0.3387	-2275.7803	212.5850	-2275.7501	-2275.8401	-0.0136	-0.00337	10.7170	93.6440	182.4521	0.0136	-0.00337	0.008485	117.8550
12	-4847.0612	0.3289	-4846.7580	206.4390	-4846.7300	-4846.8202	-0.0169	-0.00444	12.2611	95.9612	187.8591	0.0169	-0.00444	0.010685	93.5891
13	-2315.4056	0.3682	-2315.0641	231.1101	-23150.0411	-2315.1311	-0.0129	-0.01073	15.5324	99.4880	192.3630	0.0129	-0.01073	0.011815	84.6381
14	2375.3066	0.3311	-2375.0014	207.7820	-2374.9710	-2375.0610	-0.01941	-0.00421	11.5118	96.7770	187.1710	0.0194	-0.00421	0.01181	84.67400
15	-2391.0334	0.3729	-2390.6883	234.0330	-2390.6600	-2390.7500	-0.0168	-0.00372	12.2977	103.1781	198.2211	0.0168	-0.00372	0.010275	97.3226
16	-2735.6644	0.3289	-2735.3611	206.4280	-2735.3301	-2735.4201	-0.0011	-0.00872	11.7691	95.8150	188.3441	0.0012	-0.00872	0.004935	202.6342
17	-1994.6915	0.4035	-1994.31471	253.2180	-1994.2900	-1994.3810	-8.20E-04	-0.0219	17.2028	100.4431	188.1320	8.20E-04	-0.0219	0.01136	88.0281
18	-2069.8625	0.4089	-2069.4815	256.6020	-2069.4510	-2069.5510	-0.0082	-0.00567	9.2947	104.4551	197.4710	0.0083	-0.00567	0.006965	143.5750
19	-2414.9534	0.3652	-2414.6146	229.2230	-2414.5910	-2414.6801	-0.0111	-0.01086	10.8924	99.0391	192.5921	0.0111	-0.01086	0.011	90.9090
20	-4526.3500	0.3652	-4526.0114	229.2210	-4525.980q	-4526.0811	-0.0163	-0.00814	9.5887	99.2071	194.7330	0.0163	-0.00814	0.012235	81.7327
21	-2055.0082	0.3646	-2054.6700	228.7570	-2054.6400	-2054.7310	-0.0173	-0.00102	7.8855	99.0581	190.8251	0.0173	-0.00102	0.009185	108.8731

3. RESULTS AND DISCUSSION

A QSAR study was carried out for a series of 21 thiazoline derivatives, in order to determine a quantitative relationship between structure and activity. To establish quantitative relationships between IC_{50} and selected descriptors, our array data were subjected to a multiple linear regression. Only variables whose coefficients are significant were retained. In the present study, we tried to develop the best QSAR model to explain the correlation between the quantum chemistry parameters and anticancer activity of thiazoline derivatives. After regression analysis with multilinear regression (MLR), the best equations obtained that have shown in Table 4.

Table 4. The best equations obtained in QSAR analysis.

No	Formula
1	IC_{50}=-530.513-0.00001572*(HF)+6996.195*(Ce)-444.017*(ZPE)-8.744*(E_T)+1263.346*(HOMO)+3.237*(DM)-2.038*(Cv)-3.296*(ΔS)+55.303*(IP) +3.709*(EA)+829.38(Ss)-0.056*(η) R=0.972 R^2=0.945 F= 11.478 SE=0.586
2	IC_{50}=-890.904-0.00001933* (HF)+5419.001*(Ce) -476.205*(ZPE)- 7.397*(E_T)+1.393*(DM) -4.959*(Cv)+ .841*(ΔS)+14.600*(IP) -14.183*(EA) -10787.096 *(Ss)+0.020*(η) R=0.967 R^2=0.936 F= 11.948 SE=0.597
3	IC_{50}=-249.157-0.00001099* (HF)+5289.544*(Ce) -306.029*(ZPE) -4.172*(E_T)+1977.935*(HOMO) -86.081*(LUMO)+3.777*(DM) -8.649*(Cv) -1.295*(ΔS)+80.722*(IP)+ 7.506*(EA) -0.140*(η) R=0.965 R^2=0.930 F= 11.421 SE=0.658
4	IC_{50}=-60.050-0.00001474* (HF)+6110.536*(Ce)-311.385*(ZPE) -6.195*(E_T)+2102.881*(HOMO) +5.075*(DM) -5.996*(ΔS)+ 85.133*(IP) +13.354*(EA) -0.183*(η) R=0.963 R^2=0.927 F= 12.722 SE=0.660
5	IC_{50}=-787.524-0.000006966* (HF)+3372.422*(Ce)- 304.242*(ZPE) -1.241*(E_T)+1457.403*(HOMO) -115.518*(LUMO)+3.835*(DM) -15.407*(Cv)+ 4.848*(ΔS)+62.328*(IP) -0.648*(EA) R=0.960 R^2=0.922 F= 9.713 SE=0.605
6	IC_{50}=-791.775+0.000007.932* (HF)+3338.801*(Ce) -284.432*(ZPE) -3.364*(E_T)+1596.506*(HOMO) +7.595*(DM)+67.689*(IP)+ 6.361*(EA)-4271.228*(Ss) -0.127*(η) R=0.959 R^2=0.919 F=10 .839 SE=0.635

The best QSAR model is said to have good predictive power in the value of the regression coefficient (R^2) is greater than 0.5. As the value of regression coefficient increases, the predictive power of QSAR model increases. Percent predictive power is achieved when the regression coefficient becomes unity. As can be seen, the equation has acceptable quality and the variables used in model 1 can explain 94.5% of the variance in the activity of thiazoline derivatives. For a good model, the standard error of estimate of dependent variable should be low. In all models, standard error (SE) is low. Also, to judge the overall significance of the regression coefficients, the F value can be defined as the ration of mean square model to deviations mean square. The p value associated with this F value is very small ($p < 0.05$). Independent variables such as HOMO and other descriptors of model can be used to reliably predict IC_{50} (the dependent variable). For overall significance of the regression coefficients, the F value should be high. Values of predicted IC_{50} of derivatives of thiazoline have been calculated by substituting the values of descriptors in MLR equations with model 1 and the plot of predicted activity versus observed activity (Fig. 2) provides an idea about how well the model was trained and how well it predicts the activity of the compounds.

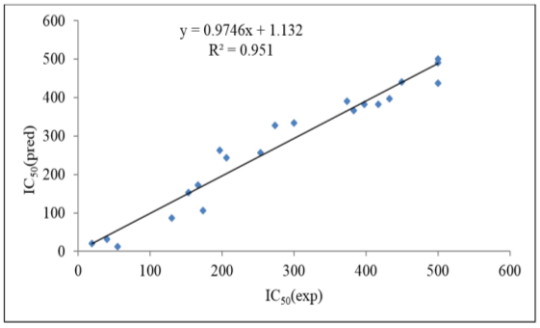

Fig. 2. The relationship between predicted and experimental IC_{50} for thiazoline derivatives.

We have developed here a useful QSAR equation derived from theoretical descriptors associated with activity of thiazoline derivatives as anticancer agents. MLR is successfully presented for activity of these compounds using a linear quantitative structure relationship. A model with high statistical quality and low prediction errors was obtained. The macroscopic (bulk) activities of thiazoline derivatives clearly depend on their microscopic (structural) characteristics. Development of QSAR on theoretical descriptors is a powerful tool not only for prediction of the chemical, physical and biological activities of compounds, but also for deeper understanding of the detailed mechanisms of interactions in complex systems that

predetermine these activities. MLR analysis provided useful equation that can be used to predict the IC_{50} of compounds based upon correction energy, highest occupied molecular orbital, dipole moment, ionization potential , electron affinity and softness parameters. Positive values of these regression coefficients indicate that the indicated descriptors contribute positively to the value of IC_{50}. Whereas negative values of regression coefficients (zero point energy, thermal energy and change in entropy) indicate that the greater value of the descriptor the lower value of IC_{50}. The results indicate that a strong correlation exists between the IC_{50} and HOMO for drug compounds. This procedure allowed us to achieve a precise and relatively fast method for determination of IC_{50} of thiazoline derivatives and to predict with sufficient accuracy the IC_{50} of new drug derivatives.

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