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A DFT-based QSARs of some 1,2-Dithiole-3-thione Derivatives as Inducers of Quinine Reductase.

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ABSTRACT

The DFT-based descriptors were used to derive the quantitative structure–activity relationship (QSAR) models enabling the calculated quantum chemistry parameters to be correlated to the specific activity of quinine reductase of 1,2-dithiole-3-thione derivatives. DFT/B3LYP level of theory with the 6-311G++(d,p) basis set was applied to calculate a set of quantum chemical descriptors, such as *HOMO–LUMO* energy gap, electrophilic and nucleophilic frontier electron density (f_i^E, f_i^N), and net atomic charge (*Qi*) for 19 dithiolethione derivatives. A multiple linear regression (MLR) procedure was used to obtain the QSAR models. The predictivity of the model was estimated by cross-validation with the leave-one-out method.
Keywords: QSAR, DFT, quinone reductase, MLR, 1,2-dithiole-3-thione.

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INTRODUCTION

Chemical protection against toxins and carcinogens can be successfully achieved through several different mechanisms [1]. Many phase 2 enzymes are readily inducible and are often coordinately induced in response to various stimuli. There is compelling evidence that induction of phase 2 enzymes is an effective and sufficient strategy for achieving protection against carcinogenesis [2]. While the induction of an individual phase 2 enzyme may involve multiple mechanisms, it is the Keap1–Nrf2–ARE signaling system that unites them and provides the molecular basis for their coordinate induction [3].

Dithiolethiones are a well-known class of cancer chemopreventive agents; the key mechanism of action of dithiolethiones involves activation of Nrf2 signaling and induction of phase 2 enzymes, such as glutathione S-transferases, UDP-glucuronosyl transferases, and quinone reductases [4,5].The target molecule for these enzyme inducers has been hypothesized to contain vicinal thiols, which could be modified through oxidation or alkylation [5].

Quantitative structure activity relationships (QSAR) studies are tools for predicting endpoints of interest in organic molecules acting as drugs.

The fundamental idea of QSAR consists of the possibility of a relationship between a set of descriptors, which are derived from molecular structure, and a molecular response. Within this scope, several molecular descriptors, which discretely parameterize a given molecular set, have been devised [6,7].

Quantum chemical calculations are thus an attractive source of new molecular descriptors, which can, in principle, express all of the electronic and geometric properties of molecules and their interactions [8].

In this paper, we discuss the results of our work on the quantitative structure activity relation study of 1,2-dithiole-3-thione derivatives as cancer chemopreventive agents. It is proposed that the mechanism of induction of phase 2 enzymes by the 1,2-dithiole-3-thione derivatives involves electronic interactions with receptors and therefore, we aimed to study the effect of different electronic properties of dithiolethiones on their biological activity. Therefore, we applied the DFT theory to derive quantum chemical descriptors for the QSAR study of the nineteen 1,2-dithiole-3-thione derivatives. Then MLR in conjunction was operated to model the linear relationship existed between the selected descriptors and the biological activity.

EXPERIMENTAL

Biological data

A biological parameter was used in this study is the specific activity of quinone reductase (QR) which was adopted as reported by Burgot et al [9] (Table 1).

CDQR(μM) concentrations of dithiolethiones required to double the specific activity of NAD(P)H: quinone reductase was also determined in Hepa 1c1c7 cells.

Calculated methods

All the calculations were performed with the Gaussian 09 package [10]. Full geometry optimization was carried out at the DFT [11] method by employing Becke's three-parameter hybrid functional (B3LYP) [12,13] and 6-311++G(d,p) basis set [14].

Net atomic charges were derived from ChelpG [15] method that produces charges fit to the electrostatic potential at points selected.

This work also includes calculation of 3D MESP surface map and 2D MESP contour map to reveal the information regarding charge transfer within the molecule [16].

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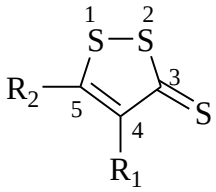
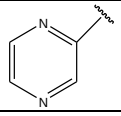
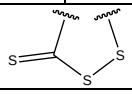
Table 1: Structure, experimental and predicted activity of 1,2-dithiole-3-thione derivatives



S. no.	R1	R2	log $(CDQR)_{exp.}$	log(CDQR)pred.
1	H	H	0.176	0.486
2	CH_3	H	1.079	1.017
3	C_2H_5	H	0.903	0.955
4	C_6H_5	H	0.301	-
5	CO_2H	H	1.380	0.891
6	$CONH_2$	H	1.662	1.322
7	H	CH_3	1.230	1.217
8	H	C_2H_5	0.903	1.069
9	H	C_6H_5	1.301	1.074
10	H	$C(CH_3)_3$	0.699	0.743
11	H	CO_2H	1.903	2.009
12	H	$CONH_2$	1.301	1.314
13	H	$C_6H_4(P)OCH_3$	1.255	1.186
14	CH_3	CH_3	1.903	1.660
15	CH_3		1.342	1.761
16	CH_3	$C_6H_4(P)OCH_3$	1.580	1.829
17			0.342	-
18	$-(CH_2)_3-$		-0.602	-0.338
19	$-(CH_2)_4-$		0.698	0.478

Quantum chemical descriptors

Quantum chemical descriptors (listed in Table 2) taken from DFT calculations were used to analyze variations in the detoxication activity of nineteen compounds of 1,2-dithiole-3-thione derivatives. The minimum energy conformations were selected as the bioactive conformations and used to calculate electronic descriptors such as ΔE is the difference between LUMO and HOMO orbital energy.

QC4, QC5 are net atomic charges of carbon atoms at position 4 and 5 respectively.

f_{S1}^{E} is the electrophilic frontier electron density of 5-position sulfur atom.

f_{S2}^{N} is the nucleophilic frontier electron density of 2-position sulfur atom.

f_{C3}^{N}, f_{C4}^{N} and f_{C5}^{N} are the nucleophilic frontier electron density of 3-, 4- and 5-position carbon atoms respectively.

Frontier orbital electron densities also involve the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), providing useful measures of donor–acceptor interactions in the molecular space [17].

The main descriptors based on molecular orbital electron densities of the any atom are the following:

Electrophilic atomic frontier electron density is defined as: $f_i^E = \sum (C_{HOMO})^2$ x 100

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Nucleophilic atomic frontier electron density is defined as: $f_i^N = \sum (C_{LUMO})^2$ x 100

Table 2: Quantum chemical descriptors of dithiolethione derivatives

Comp.	ΔE	QC4	QC5	f_{S1}^E	f_{C3}^N	f_{C4}^N	f_{C5}^N	f_{S2}^N
1	0.134	0.023	-0.213	3.308	25.155	2.628	24.048	13.634
2	0.134	0.262	-0.340	20.256	27.238	2.686	23.417	14.376
3	0.133	0.129	-0.276	18.471	48.931	12.315	41.986	14.760
4	0.126	0.198	-0.319	17.806	22.590	2.687	26.692	13.143
5	0.123	0.133	-0.242	4.808	14.809	5.422	31.444	11.063
6	0.118	0.106	-0.270	5.867	15.766	6.516	31.341	11.253
7	0.136	-0.043	0.019	18.469	27.784	2.068	29.083	13.456
8	0.135	-0.040	-0.085	17.602	36.242	18.043	37.769	14.426
9	0.120	0.104	-0.185	18.131	13.870	4.241	18.639	9.813
10	0.135	-0.022	-0.133	19.137	27.617	1.934	28.559	13.940
11	0.114	0.032	-0.151	20.504	12.368	7.126	19.259	10.452
12	0.121	0.089	-0.197	20.106	15.837	5.584	21.514	11.001
13	0.122	0.049	-0.102	15.843	15.059	3.634	19.460	10.027
14	0.136	0.189	-0.136	19.570	29.318	1.939	27.878	14.422
15	0.114	0.378	-0.357	20.949	11.368	6.337	14.977	9.443
16	0.121	0.209	-0.215	17.450	17.554	3.268	17.245	11.222
17	0.102	0.073	0.073	15.686	9.686	6.525	6.525	9.036
18	0.136	0.012	-0.098	18.979	55.931	42.317	185.214	14.958
19	0.136	0.177	-0.207	20.408	97.512	111.957	181.769	16.696

Regression analysis

The MLR analysis was employed to derive the QSAR models for some 1,2-dithiole-3-thione derivatives. MLR and correlation analysis were carried out by using statistical software SPSS version 19 for Windows [18].

RESULTS AND DISCUSSION

Variations in the induction activity on phase-2 enzyme of dithiolethione derivatives were analyzed using the quantum chemical descriptors listed in Table-1 and the obtained equations with best correlation coefficients were listed in Table-3.

Table 3: Regression models suggested by multiple linear regression analysis

No	Regression equations	n	r^2	s	F
1	log(1/CDQR)=1.641+0.015f_{C4}^N-0.013f_{C5}^N-0.024f_{S2}^N	19	0.373	0.552	2.978
2	log(1/CDQR)= 1.372+0.015f_{C4}^N-0.013f_{C5}^N	19	0.369	0.536	4.678
3	log(1/CDQR)= 1.293-0.007f_{C5}^N	19	0.283	0.554	6.715

From Table-3, we can conclude that the correlation coefficients of these equations are not satisfied and compound 4 and 17 are two outliers. After omitting compounds 4 and 17, Equation 4 with significantly improved correlation coefficients was obtained as follow:

$$\log(CDQR) = 12.476\ (\pm 2.535) - 123.792\ (\pm 29.684)\Delta E + 3.968\ (\pm 1.099)QC4 + 5.931\ (\pm 1.460)QC5 - 0.011\ (\pm 0.002) f_{C5}^N + 0.443\ (\pm .124) f_{S2}^N \quad (4)$$

n = 17, r = 0.921, s = 0.293, F = 12.252, S_{PRESS} = 0.236, q^2 = 0.848, p <0.001

In this equation, n is the number of compounds, r is the correlation coefficient, s is the standard deviation, S_{PRESS} is the root mean predictive error sum of squares, F is the Fisher's F-value, p is the p-value (calculated from F statistics), q^2 is the LOO cross-validated coefficient, which was obtained by a multiple linear regression. A good QSAR model is indicated by large F, small s and S_{PRESS}, very small p-value, as well as r^2 and q^2 values close to one. The value r^2 = 0.848 allowed us to indicate firmly the correlation between different parameters (independent variables) with specific activity of quinone reductase.

In general, the regression model is significant at p-value <0.001 using the F statistics [19], so the above QSAR model is significant. The F-value has found to be statistically significant at 95% level, since all the calculated F value is higher as compared to tabulated values.

It is generally accepted that if the cross-validated coefficient q^2>0.50, the model has good predictability [20].

Our findings of q^2 for this QSAR model have been to be 0.848. The high value of q^2 is essential criteria for the best qualification of the QSAR models.

The predicted activities by using this equation are listed in Table-1 and are plotted against the experimental values in Fig.1. Obviously, the predicted log(CDQR) values are in a good agreement with experimental ones.

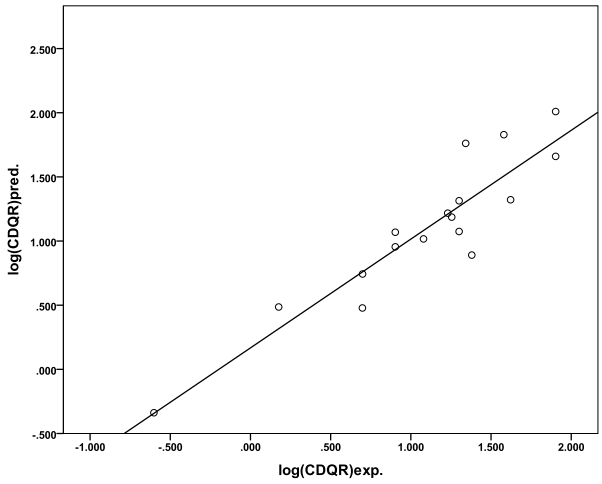

Figure 1 : Predicted plot versus experimental observed specific activity of quinone reductase (from Eq. 4)

To investigate the presence of a systematic error in developing the QSAR model, the residuals of predicted values of the biological activity log(CDQR) were plotted against the experimental values, as shown in Fig.2.

The propagation of the residuals on both sides of zero indicates that no systemic error exists, as suggested by Jalali-Heravi and Kyani [21]. It indicates that this model can be successfully applied to predict the specific activity of quinine reductase.

The above QSAR results show that quantum chemical descriptors, ΔE, QC4, QC5, f_{C5}^{N} and f_{S2}^{N}, are most likely to be responsible for the detoxication activity of 1,2-dithiole-3-thiones.

The positive coefficient of QC4 and QC5 term indicate the more positive charges of the carbon at position 4 and 5 respectively, the higher activity, which suggest that the positions 4 and 5 of the dithiolethione ring should be occupied by electro-withdrawing substituants.

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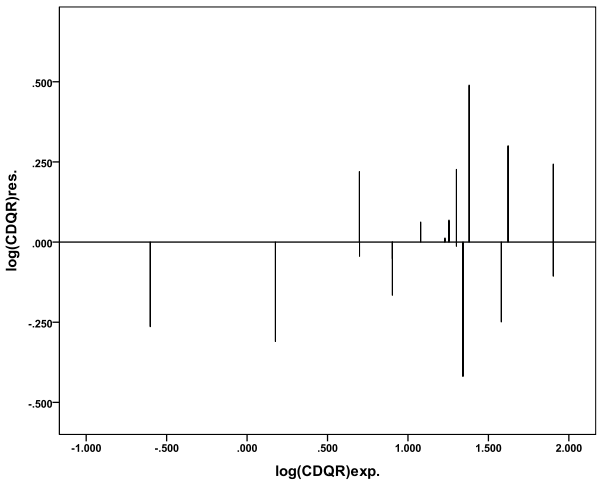
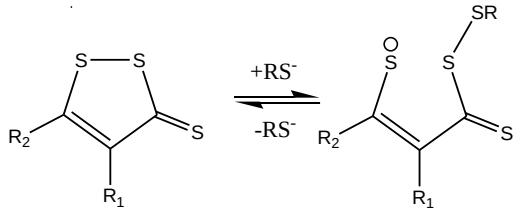


Figure 2: Pot of the residual values against the experimentally observed log(1/CDQR) (from eq. 4)

The positive coefficient of the f_{S2}^{N} shows that the higher nucleophilic frontier electron density of 2-position sulfur atom, the higher detoxication activity, which shows that the ability of sulfur atom to accept electrons has an important effect on the induction of quinine reductase.

A possible mechanism for the interaction is addition of thiolate to S-2 of the 1,2-dithiole-3-thione derivatives (Scheme 1) [5,22].The thiolate is a good nucleophile resulting from ionization of the thiol group of cysteine residue. The cysteine-151 residues in BTB domain of Keap1 may serve as molecular sensors for induction of phase 2 enzymes. Oxidation or alkylation of these sulfydryls appears to lead to dissociation of Nrf2 from Keap1, presumably allowing for its translocation to the nucleus where it can interact with the ARE to activate transcription [23].



Scheme 1

In addition, the negative sign of the coefficient of the f_{C5}^{N} indicate that the more nucleophilic frontier electron density of 5-position carbon atom, the lower detoxication activity.

The mapping of the electrostatic potential is an established technique for investigation of biologically active compounds because it plays a key role in the initial steps of ligand -receptor interactions [24].

The 3D isosurface maps of MESP were interpolated on the electron density surfaces of constant electron charge density (0.0004 e/au^3). As is well known, the electrostatic potential is defined as the interacted energy of a positively remote charge point with the nuclei and the electrons of a molecule. Electro static potential contour plot predict the substitution of electrophiles and nucleophiles.

In this part, we studied the 1,2-dithiole-3-thione (DDT). The 3D plots of the MESP for DDT is shown in Fig.3. MESP plotted onto constant electron density surface for most active compound showed the most electronegative potential region (red color) over the sulfur atom of thiocarbonyl group on the principal cycle which explain that this region is susceptible for electrophilic attacks. However, the most electropositive potential regions (blue color) were mainly distributed over the S2 and C5 atoms which explain that these regions are susceptible for nucleophilic attacks.

The 2-position sulfur atom is an electrophilic site which can be attacked by the thiolate group of cysteine residues of KEAP1 receptor, which affects the enzyme induction.

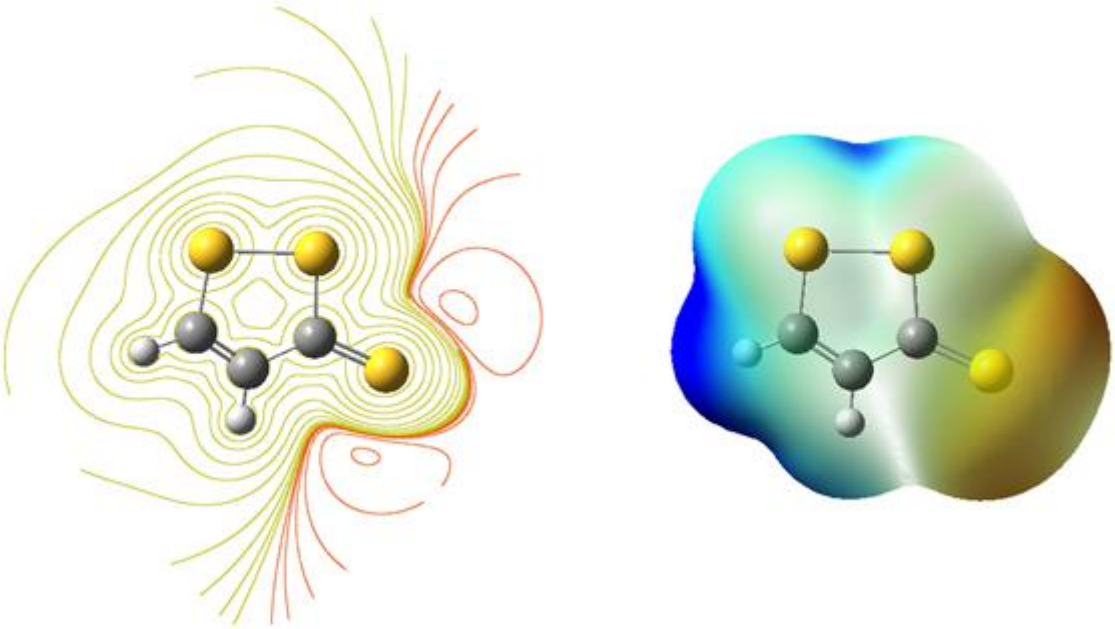


Fig. 3: 2D MESP surface map and 3D MESP contour map for 1,2-dithiole-3-thione

CONCLUSION

The present study was performed to examine the applicability of DFT-based quantum chemical descriptors in QSAR analysis for studying the biological activity of a series of 1,2-dithiole-3-thione. The DFT-based quantum chemical descriptors were obtained at the B3LYP/6-311G++(d,p) level.

It has been shown that the use of quantum chemical descriptors based-DFT indeed leads to better QSAR model which can explain the mechanism of induction of phase 2 enzymes.

The validity of the model has been established by the determination of suitable statistical parameters.

The obtained QSAR results based on the DFT-based descriptors showed the greater the ability of the 2-position sulfur atom to accept electrons, the higher the biological activity. The more the positive charge at the 4-,5-position carbon atom of dithiole ring, the higher activity.

Therefore, DFT-based QSARs could be expected to help facilitate the future design of additional substituted 1,2-dithiole-3-thione derivatives of induction of phase 2 enzymes with good biological activity.

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