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Anticancer activity of nucleoside analogues: A density functional theory based QSAR study

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Abstract In the present work multiple linear regression analyses were performed to build QSAR models for nucleoside analogous using density functional theory (DFT) and molecular mechanics (MM+) based descriptors in both gas and solvent phases. The QSAR models for 14 carbocyclic analogues of nucleosides against murine leukemia cell line (L1210/0) and human T-lymphocyte cell lines (Molt4/C8 and CEM/0) explain more than 90% of the variances in the activity data along with higher values of $r^2_{CV}(> 0.86)$. The energy of the next lowest unoccupied molecular orbital (E_{NL}), electrophilicity (ω) and van der Waals surface area (SA) are the main independent factors contributing to the anticancer activity of nucleoside analogues. Inclusion of solvent medium increases the correlation of each descriptor with activity. Based on the key features responsible for anticancer activity, 10 new compounds with rather high anticancer activity have been theoretically designed. Cytotoxic activities of an additional set of 20 nucleoside analogues were also modeled by the same descriptors and found their predicted values to be in good agreement with the experimental values.

Keywords DFT · Nucleoside analogues · QSAR · Solvent effect

Introduction

In recent years a large number of nucleoside analogues with anticancer activity have been designed and synthesized [1, 2]. However, nucleoside anticancer drugs are commonly associated with various adverse effects [3]. Apparently, there is a need to search for nucleoside analogues that can selectively inhibit cancer cell proliferation. For instance, it has been seen that 5-substituted-2′-deoxyuridines reduces cancer cell proliferation by inhibiting thymidylate synthase, an enzyme essential in the synthesis of DNA. Carbocyclic analogues of nucleosides have attracted growing interest due to their stability *in vivo* and powerful antitumor activities of some of these compounds. Carbocyclic nucleosides are compounds in which the endocyclic oxygen of the nucleoside sugar ring is replaced by a methylene group, and 2′,3′-dideoxynucleosides. This modification makes the molecules more resistant to hydrolases than the natural nucleosides. Several derivatives of carbocyclic nucleosides Carbovir and Abacavir [4, 5], potent anticancer agents, have been recently synthesized in which the cyclopentene ring is replaced by an indane system [6] and assayed on different cancer cell lines.

The anticancer mechanism of nucleoside analogues has not been properly clarified yet. A good understanding of the chemical properties at the molecular level such as steric, lipophilic, and electronic characteristics may provide an important background for the knowledge of mutagenic and carcinogenic properties. In this respect, quantitative structure-activity relationships (QSAR) have emerged as a promising tool toward the effective screening of potential drugs. The ultimate goal of QSAR studies is to correlate the biological activity of a series of compounds with some appropriate descriptors. Among different descriptors for describing the electronic properties of molecules, the quantum chemical descriptors based on density functional theory (DFT) and semi-empirical methods have been found useful in several QSAR studies [7, 8]. In particular, net atomic charges, highest occupied molecular orbital (HOMO)-lowest unoccupied molecular orbital (LUMO) energies, frontier orbital electron densities,

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and superdelocalizabilities have shown to correlate with various biological activities [9].

In recent years, DFT based reactivity descriptors namely, global hardness (η), electronegativity (χ), chemical potential (μ), electrophilicity index (ω), Fukui functions (f(**r**)), philicity (ω^{+}) *etc*. [10–14] have attracted considerable interest to describe reactivity and site selectivity of various bio-molecules [15, 16]. The electrophilicity and philicity indices have successfully been used to determine the biological activity/toxicity/property of different organic systems [17-19]. Recently, we have reported the usefulness of DFT based reactivity descriptors in the predictions of activity and property of several *cis*-platinum complexes [20, 21]. In the present study, a series of nucleoside analogues are selected to perform QSAR analysis. Fourteen compounds are analyzed against three cancer cell lines using DFT and MM + derived parameters. In addition, we have performed QSAR analysis on a data set of 20 compounds against one cancer cell line. Based on the obtained QSAR models, 10 new compounds with high anticancer activities have been theoretically designed.

Methods

Theoretical background

In theoretical chemistry, the chemical potential (μ) is identified as the negative of the electronegativity (χ) by Iczkowski and Margrave [22] and defined as

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} \tag{1}$$

and hardness (η) [10] of an electronic system is defined as the second derivative of total energy (E) with respect to the number of electrons (N) at constant external potential, $v(\vec{r})$,

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\vec{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\vec{r})}. \tag{2}$$

According to density functional theory, the global electrophilicity index (ω) [12] is expressed in terms of chemical potential and hardness as:

$$\omega = \frac{\mu^2}{2\eta}. \tag{3}$$

In finite difference approach, global hardness (η) and chemical potential (μ) can be approximated as:

$$\eta = \frac{IP - EA}{2} \tag{4}$$

$$\mu = -\left(\frac{IP + EA}{2}\right), \tag{5}$$

where IP and EA are the first vertical ionization potential and electron affinity, respectively, of the chemical system.

Further approximation using Koopmans' theorem [23], the above parameters can be expressed by taking IP and EA as negative of the HOMO and LUMO energies:

$$\mu = \frac{E_{LUMO} + E_{HOMO}}{2} \tag{6}$$

and

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}, \tag{7}$$

where E_{LUMO} is the energy of the lowest unoccupied molecular orbital and E_{HOMO} is the energy of the highest occupied molecular orbital.

Computational details

Structures of all nucleoside analogues are presented in Fig. 1. Full geometry optimizations of these compounds without symmetry constraints were carried out using DMol^3 program [24] at BLYP/DNP level. BLYP is the most widely used exchange-correlation functional suggested exchange potential by Becke [25] with gradient corrected correlation provided by Lee, Yang, and Parr [26]. DNP is the double numerical with polarization basis set, size of which is comparable to 6–31G** basis of Hehre *et al*. [27]. However, it is believed to be much more accurate than a Gaussian basis set of the same size. Optimized geometries were verified by frequency calculations and characterized as minima (no imaginary frequency) in their potential energy surface. The reactivity descriptors electrophilicity index (ω), chemical potential (μ), and global hardness (η) were calculated for all systems using Eqs. 3, 6, and 7, respectively. The conductor-like screening model (COSMO) [28] as incorporated into the DMol^3 program with dielectric constant of 78.4 was adopted to study the solvent (water) effect. In addition, the molar refractivity (MR), Van der Waals surface area (SA), volume (V), mass (M) and lipophilicity index (logP) for whole molecule were calculated from the MM + computations with Hyperchem software [29].

QSAR modeling

The anticancer activity data of compounds (1–14) against the murine leukemia cell line (L1210/0) and human T-lymphocyte cell lines (Molt4/C8 and CEM/0) were collected from the literature [6]. All these activities calibrated to the logarithmic (log IC_{50}^{-1}) values are listed in Table 1. The

Fig. 1 Sketch of the nucleoside analogues used to build QSAR models

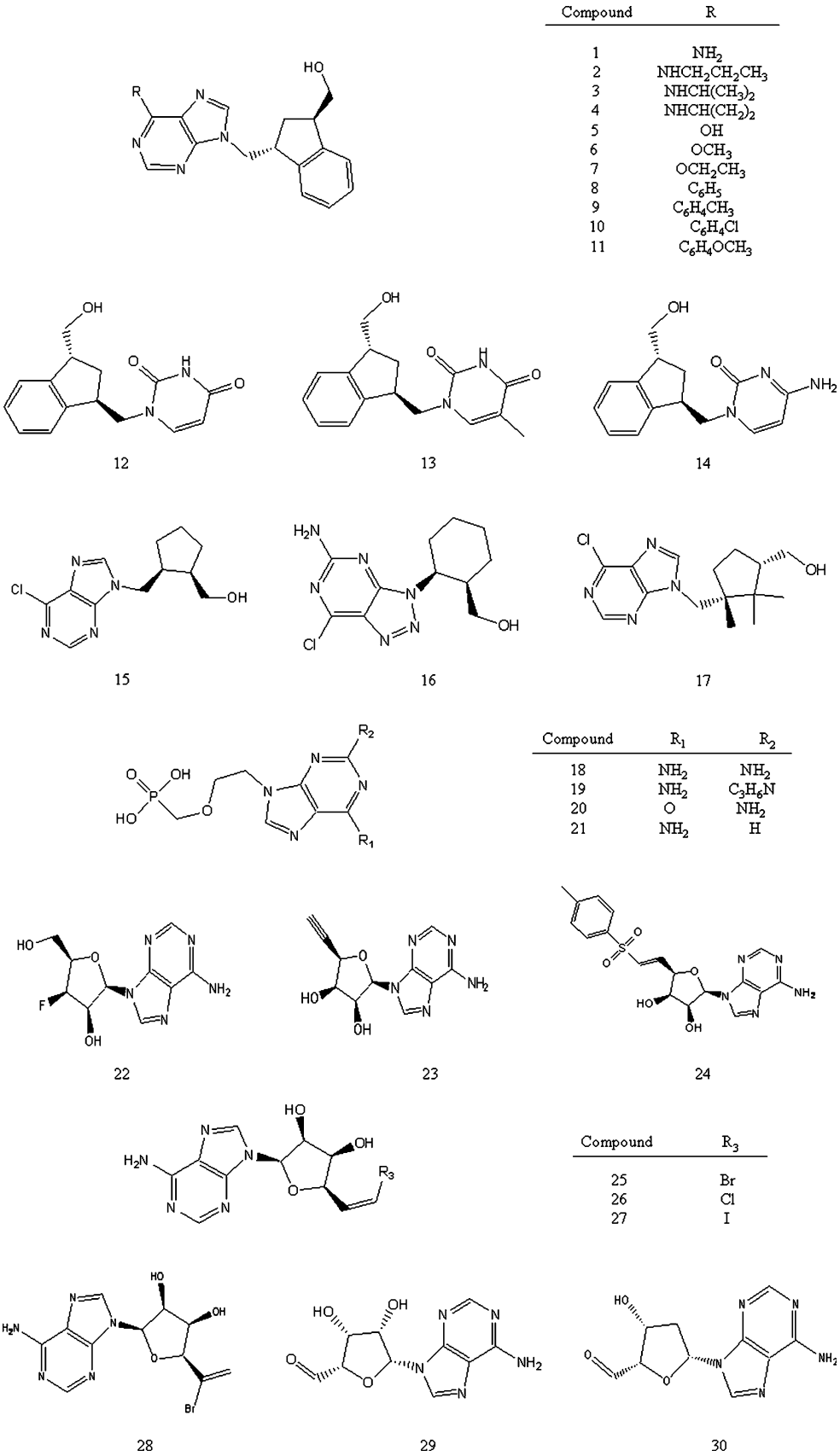

Table 1 Parameters used to build the QSAR models for 14 carbocyclic nucleosides in gas and solvent phases against three cancer cell lines

Compd	log IC_{50}^{-1}			Gas phase			Solvent phase		
	L1210/0	Molt4/C8	CEM/0	ω	E_{NL}	*SA*	ω	E_{NL}	*SA*
1	−2.53	−2.44	−2.44	3.129	−1.146	313.98	3.681	−1.167	313.69
2	−2.32	−2.04	−2.16	2.883	−1.119	375.29	3.103	−1.155	375.64
3	−2.20	−1.85	−1.93	2.884	−1.125	373.58	3.525	−1.148	374.37
4	−2.40	−2.24	−2.31	2.973	−1.129	366.61	3.202	−1.172	366.85
5	−2.42	−2.16	−2.21	3.843	−1.345	307.53	3.947	−1.387	307.49
6	−2.54	−2.33	−2.37	3.598	−1.216	330	3.848	−1.285	330.73
7	−2.33	−1.79	−1.79	3.519	−1.204	351.67	3.802	−1.27	350.04
8	−1.45	−0.980	−0.954	5.469	−1.410	376.77	5.851	−1.50	377.63
9	−1.19	−0.636	−0.578	5.271	−1.351	397.44	5.708	−1.469	397.62
10	−0.927	−0.317	−0.208	5.967	−1.576	393.70	5.906	−1.622	392.90
11	−1.25	−0.919	−0.845	5.042	−1.311	406.46	5.601	−1.477	406.46
12	−2.87	−2.87	−2.87	4.558	−1.282	288.80	4.321	−1.143	289.38
13	−2.59	−2.45	−2.45	4.259	−1.243	309.59	4.092	−1.132	309.43
14	−2.87	−2.87	−2.87	3.784	−1.042	320.46	3.680	−1.100	295.67

analyses were performed in both gas and solvent media. From the results of DFT calculations different descriptors, such as energy of highest occupied molecular orbital (E_{HOMO}), energy of lowest unoccupied molecular orbital (E_{LUMO}), energy of the next lowest unoccupied molecular orbital (E_{NL}), energy difference between LUMO and HOMO ($\Delta_{L\text{-}H}$), dipole moments, electrophilicity (ω), hardness (η), chemical potential (μ) were selected for QSAR analysis. In addition, the molecular mechanics parameters such as molar refractivity (MR), van der Waals surface area (SA), molecular volume (V), mass (M) and hydrophobicity (logP) of the compounds were also selected. The descriptors with greater correlation to log IC_{50}^{-1} with smaller autocorrelation were selected out to perform the stepwise multiple linear regression. The predictive power of the models was validated by using the "leave one out" (LOO) cross-validation method.

Results and discussion

We found electrophilicity (ω), energy of the next LUMO orbital (E_{NL}), and Van der waal surface area (SA) as the most relevant descriptors for modeling inhibitory activity of carbocyclic nucleosides (1–14, Fig. 1), values of which in both gas and solvent phases are presented in Table 1. The best fit QSAR equations with absolute values of statistical parameters for these molecules against L1210/0, Molt4/C8 and CEM/0 cell lines in both gas and solvent phases are represented in Table 2 and Table 3, respectively. The models were calculated by considering the inhibitory activity (log IC_{50}^{-1}) as a dependent variable and possible combination of other descriptors such as ω, SA, and E_{NL} as independent variables. The quality of calculated models was measured by the square of correlation coefficient, r^2, the leave-one-out (LOO) cross-validated squared correlation coefficient, r^2_{CV}, the overall F-statistics for the addition of each successive term, F and the standard deviations of regression, SD.

According to Wold [30] a good QSAR model should have statistical parameters r>0.95, SD<0.3, and $r^2_{CV} < 0.60$. Thus Eqs. (1a, 2a, and 3a) with r values 0.980, 0.982, and 0.978 and Eqs. (1b, 2b, and 3b) having r values 0.967, 0.952, and 0.955 are statistically significant. From Table 2, it can be seen that gas phase derived QSAR models for all three

Table 2 QSAR models with the statistical parameters for 14 carbocyclic nucleosides against three cancer cell lines in gas phase

	No.	Cell line	QSAR equations	r^2	r^2_{CV}	*SD*	*F*
Gas phase	1a	L1210/0	$\log(IC_{50}^{-1}) = -9.102 - 2.387\ E_{NL} + 0.011\ SA$	0.962	0.941	0.131	138.92
	1b		$\log(IC_{50}^{-1}) = -7.389 + 0.312\ \omega + 0.011\ SA$	0.935	0.899	0.170	80.24
	2a	Molt4/C8	$\log(IC_{50}^{-1}) = -10.695 - 2.996\ E_{NL} + 0.014\ SA$	0.965	0.944	0.160	149.76
	2b		$\log(IC_{50}^{-1}) = -8.520 + 0.362\ \omega + 0.014\ SA$	0.908	0.854	0.259	54.26
	3a	CEM/0	$\log(IC_{50}^{-1}) = -11.119 - 3.296\ E_{NL} + 0.015\ SA$	0.958	0.934	0.184	124.40
	3b		$\log(IC_{50}^{-1}) = -8.740 + 0.415\ \omega + 0.014\ SA$	0.912	0.860	0.264	57.55

Table 3 QSAR models with the statistical parameters for 14 carbocyclic nucleosides against three cancer cell lines in solvent phase

	No.	Cell line	QSAR equations	r^2	r^2_{CV}	*SD*	*F*
Solvent phase	1′a	L1210/0	$\log(IC_{50}^{-1}) = -7.734 - 2.239\ E_{NL} + 0.007\ SA$	0.949	0.921	0.151	103.19
	1′b		$\log(IC_{50}^{-1}) = -6.864 + 0.355\ \omega + 0.009\ SA$	0.963	0.937	0.129	143.068
	2′a	Molt4/C8	$\log(IC_{50}^{-1}) = -8.994 - 2.794\ E_{NL} + 0.010\ SA$	0.956	0.931	0.177	121.69
	2′b		$\log(IC_{50}^{-1}) = -7.914 + 0.409\ \omega + 0.012\ SA$	0.937	0.894	0.213	82.69
	3′a	CEM/0	$\log(IC_{50}^{-1}) = -9.263 - 3.109\ E_{NL} + 0.009\ SA$	0.947	0.914	0.205	98.95
	3′b		$\log(IC_{50}^{-1}) = -8.059 + 0.470\ \omega + 0.012\ SA$	0.939	0.898	0.219	85.78

cancer cell lines explain more than 90% of the variances in the activity data along with higher values of $r^2_{CV}(> 0.86)$. However, it is observed that combinations of E_{NL} and SA values can build more significant models than that obtained by ω and SA in gas phase. Descriptors E_{NL} and ω were not considered together in the regression analysis as they are highly correlated (r=0.87).

The QSAR models obtained after inclusion of solvent medium accounts for explaining 94%–96% variances of the activity data with significant values of $r^2_{CV}(> 0.89)$ (Table 3). In solvent phase, r^2 and r^2_{CV} values increase from that obtained in gas phase for Eqs. 1′b, 2′b and 3′b, where ω and SA are independent variables. It is interesting to note that when ω is singularly selected, it exhibits higher positive correlation to log (IC_{50}^{-1}) for L1210/0 cell lines in solvent phase (r=0.801) than in gas phase (r=0.730). Also for the other two cell lines, correlation coefficients calculated from ω have higher values in solvent medium. Thus solvent phase derived ω values can predict more reliable activities than gas phase. Similar results were obtained in our recent work on *cis*-platinum complexes [21]. Although, solvent medium does not show any influence for other equations containing E_{NL} and SA as independent factors, we found that solvent phase predicted E_{NL} singly can explains about 81% of variances in the activity data. We found η and E_{LUMO} (r=−0.846, −0.783, −0.798 and r=−0.67, −0.635, −0.668, respectively) are the next important parameters for the present QSAR analyses. However, the multi-linear regression analyses performed using these descriptors predict statistical parameters which are slightly less significant than that obtained in the present study. The correlation plots between experimental and calculated log IC_{50}^{-1} values of the nucleoside analogues derived from best established QSAR models (Eqs. 1a, 2a, 3a) are shown in Fig. 2 which indicates that these descriptors can be effectively used in the prediction of cytotoxicity of carbocyclic nucleoside analogues.

In general, the anticancer drug-DNA binding mechanism involves the donation of electrons from DNA and acceptance of electrons by the drug molecule. According to the frontier molecular orbital theory [31, 32], the E_{LUMO} and E_{NL} of an acceptor generally play an important role in this type of interaction by accepting electrons from the HOMO of DNA base pairs. The lower values of these parameters increase the capability of the molecules to accept electrons from DNA making the system stable. We found that

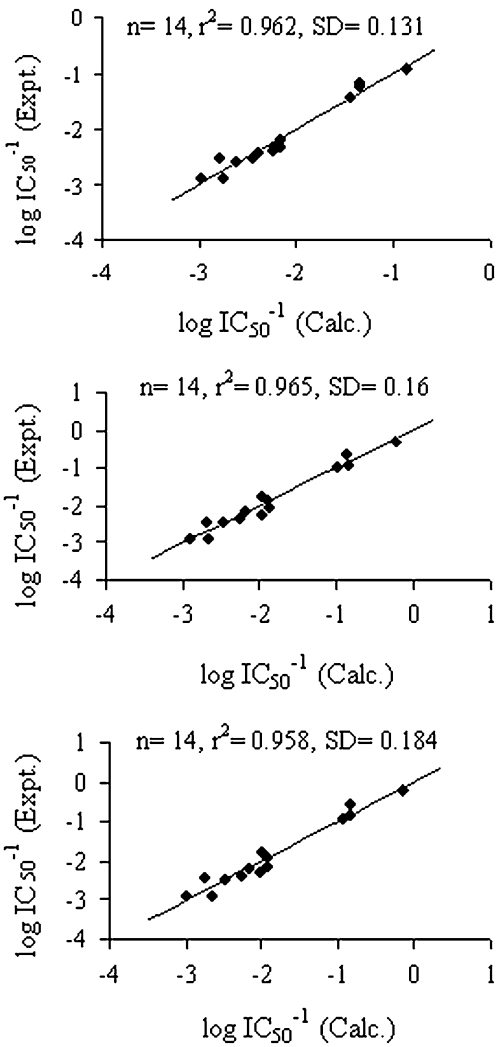

Fig. 2 Correlation plots between experimental and calculated values of cytotoxicity (log IC_{50}^{-1}) for 14 carbocyclic nucleosides using Eqs. 1a, 2a, and 3a

Table 4 Calculated activities for the 10 designed compounds against three cancer cell lines in gas phase

Compd	R*	E_{NL}	*SA*	log IC_{50}^{-1}		
				L1210/0	Molt4/C8	CEM/0
D1	C_6H_4COH	−2.054	637.45	2.812	4.383	5.212
D2	$C_6H_4COCH_3$	−1.901	417.33	0.026	0.843	1.406
D3	$C_6H_4COCH_2CH_3$	−1.873	438.65	0.194	1.057	1.634
D4	C_6H_4COOH	−1.864	645.56	2.448	3.927	4.708
D5	$C_6H_4COOCH_3$	−1.711	427.89	−0.311	0.421	0.938
D6	$C_6H_4COOCH_2CH_3$	−1.669	713.78	2.733	4.298	5.088
D7	C_6H_4COCl	−2.23	414.94	0.785	1.795	2.455
D8	$C_6H_4CF_3$	−1.738	407.25	−0.473	0.213	0.718
D9	C_6H_4CN	−1.878	397.74	−0.244	0.499	1.036
D10	$C_6H_4NO_2$	−2.639	401.71	1.616	2.835	3.604

* Substituent of compounds 1–11 in Fig. 1

coefficients of E_{NL} in the QSAR equations (Table 2 and Table 3) are negative, *i.e.*, decreasing theirs values can improve the anticancer activity. From Table 1, we can see that in both gas and solvent phases molecules 9, 10, and 11 with lower values of E_{NL} (−1.351, −1.576, −1.311 and −1.469, −1.622, −1.477) show greater activities. Also, from Table 2 and Table 3, it is seen that the coefficients of ω are positive, so decreasing the values of E_{LUMO} will increase ω (Eqs. 3, 6, and 7) and also be beneficial to improve the activity. The coefficients of SA in both gas and solvent phases are positive. Thus bigger substituent on the molecules is advantageous to the improvement of their anticancer activities. For Compounds 8, 9, and 11 with bigger substituent groups contribute to the increase in the surface area, thereby enhancing the activity. In addition, lower values of E_{NL} means more electron-withdrawing groups (e.g., halogen, -COOR, $-NO_2$ *etc.*) in the molecules. Chlorophenylpurine derivative (compound 10) with strong electron-withdrawing group is the most active one among the 14 molecules. Considering these observations, we have modified the substituent R (compounds 1–11, Fig. 1) by

Table 5 Parameters used to build the QSAR models for 20 nucleosides analogues in gas and solvent phases

Compd	log IC_{50}^{-1}	Gas phase			Solvent phase		
	L1210/0	ω	E_{NL}	*SA*	ω	E_{NL}	*SA*
8	−3.334	5.469	−1.410	376.77	5.851	−1.5	377.63
9	−2.734	5.271	−1.351	397.44	5.708	−1.469	397.62
10	−2.133	5.967	−1.576	393.70	5.906	−1.622	392.90
11	−2.868	5.042	−1.311	406.46	5.601	−1.477	406.46
15	−3.961	4.997	−1.552	278.19	5.112	−1.604	277.38
16	−4.559	5.664	−1.305	284.14	6.126	−1.331	283.60
17	−3.755	4.886	−1.516	327.25	5.110	−1.612	327.19
18	−0.548	2.375	−0.646	282.82	2.741	−0.625	282.88
19	−2.322	3.311	−0.645	333.92	3.915	−0.574	335.51
20	0.562	2.693	−1.103	276.80	2.290	−0.417	277.20
21	−2.008	3.016	−0.843	269.21	3.656	−1.084	267.72
22	−1.782	3.060	−0.963	257.29	3.458	−1.186	255.65
23	−0.182	2.041	−1.331	257.34	2.450	−0.728	255.85
24	−3.989	5.886	−1.734	407.56	5.305	−1.944	406.12
25	−4.644	5.845	−1.503	290.83	5.659	−1.486	286.68
26	−4.963	6.090	−1.505	283.29	5.470	−1.385	282.91
27	−3.761	5.071	−1.664	298.33	5.390	−1.321	295.74
28	−3.219	4.762	−1.654	282.68	4.689	−1.310	282.10
29	−3.600	5.525	−2.152	246.46	5.033	−1.301	246.16
30	−3.282	5.203	−1.752	244.95	5.060	−1.295	244.73

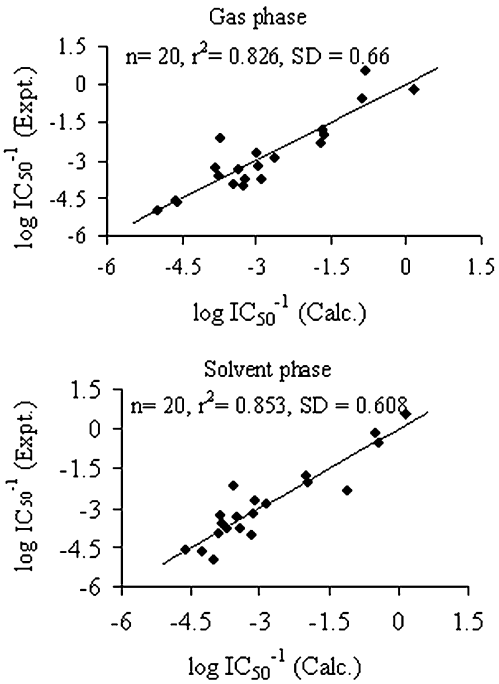

Fig. 3 Plots between experimental versus calculated values of cytotoxicity (log IC_{50}^{-1}) for 20 nucleoside analogues in both gas and solvent phases

large electron-withdrawing groups to theoretically design 10 new compounds with high anticancer activity. Table 4 lists their predicted activities against L1210/0, Molt4/C8 and CEM/0 cell lines from application of the QSAR models (Eqs. 1a, 2a, and 3a, respectively). The log IC_{50}^{-1} values of these 10 compounds are higher than those of the 14 carbocyclic nucleoside derivatives which indicate that our established models have strong predictive abilities and thus can be probably used in molecular design.

Further, we modeled the inhibitory activities of an additional set of 20 molecules (Compounds 8–11 and 15–30) against murine leukemia cells (L1210/0) with the same descriptors [33]. All the activities calibrated to the logarithmic (log IC_{50}^{-1}) values are listed in Table 5 along with the used parameters. The QSAR equations with significant values of statistical parameters in both gas and solvent phases for these 20 molecules are represented by Eqs. 3 and 4, respectively. The values were calculated using experimental activity (log IC_{50}^{-1}) as a dependent variable and combination of three descriptors, namely ω, E_{NL} and SA of the compounds with lower autocorrelation coefficients as independent variables in gas and solvent models.

$$\log\left(IC_{50}^{-1}\right) = -1.004 - 1.381\,\omega - 1.208\,E_{NL} + 0.009\,SA$$
$$n = 20,\ r^2 = 0.826,\ r^2_{CV} = 0.737,\ SD = 0.660,\ F = 25.33 \quad (3)\ \text{Gas phase}$$

$$\log\left(IC_{50}^{-1}\right) = 0.246 - 1.021\,\omega + 0.982\,E_{NL} + 0.009\,SA$$
$$n = 20,\ r^2 = 0.846,\ r^2_{CV} = 0.693,\ SD = 0.620,\ F = 29.36 \quad (4)\ \text{Solvent phase}$$

The plots between experimental and calculated values of log IC_{50}^{-1} predicted by gas and solvent phases are presented in Fig. 3. These plots suggest that the selected descriptors can be effectively used in determination of activities of nucleoside analogues.

Conclusions

In this work, 2D QSAR studies on a series of nucleoside analogues have been carried out. The QSAR equations only with two parameters calculated for 14 carbocyclic nucleosides against three cancer cell lines in gas and solvent phases show good statistical quality both in regression ($r^2 > 0.90$) and LOO cross-validation $\left(r^2_{CV} > 0.86\right)$. These regression models reveal that lower values of E_{NL} combined with higher values of ω and SA, increases inhibitory activities against three cancer cell lines. Based on the key features of the molecules that are necessary for their anticancer activity, 10 new compounds with rather high anticancer activities against L1210/0, Molt4/C8, and CEM/0 cell lines than those of 14 compounds have been theoretically designed. The QSAR models developed for an additional set of 20 nucleoside analogues with three parameters, *i.e.*, ω, E_{NL}, and SA provide significant statistical parameters in both gas and solvent media. Moreover, the presented QSAR models have a number of variables which is seven times less than the number of observations. In summary, the current work clearly shows the effectiveness of these DFT and MM + derived parameters in QSAR analysis of nucleoside analogues.

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