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ORIGINAL ARTICLE

QSAR models of antiproliferative activity of imidazo[2,1-b][1,3,4]thiadiazoles in various cancer cell lines

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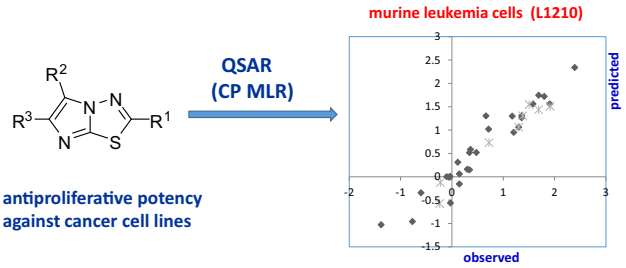
Abstract Imidazo[2,1-*b*][1,3,4]thiadiazoles have been recognized to possess antiproliferative potency towards a wide spectrum of cancer cell lines. QSAR investigations on a set of 42 di(tri)substituted imidazo[2,1-*b*][1,3,4]thiadiazoles were carried out to find the descriptors determining their biological potency. Three-variable equations were obtained by combinatorial protocols in multiple linear regression (CP MLR) for all three studied cancer cell lines. They showed that lipophilicity, electronic, and steric factors are decisive for the antiproliferative potency of compounds and indicate the important role of nitrogen atoms of imidazothiadiazole ring in the interactions with the molecular target. The best models gave high *r* squared values in the range from 0.887 to 0.924. They also have good predictive accuracy confirmed by the high value LOO cross-validation coefficient R^2_{CV} (from 0.842 to 0.904) and by the external validation quantities.

Graphical Abstract



Keywords Imidazothiadiazoles · Antiproliferative activity · QSAR · MLR

Introduction

Imidazo[2,1-*b*][1,3,4]thiadiazoles exhibit different kinds of biological activities. 2,6-Disubstituted imidazothiadiazole derivatives are described as antifungal, antibacterial, and antitubercular agents [1–3], while other analogs display anti-inflammatory activity or inhibit cyclooxygenase-2 [4, 5]. Several imidazo[2,1-*b*][1,3,4]thiadiazole analogs have been evaluated as potential anticancer agents [6–12] and some inhibited proliferation in a wide panel of cancer cell lines [7,13,14] with nM IC_{50} potency [6,8]. Molecular mechanism studies have shown that most imidazo[2,1-*b*][1,3,4]thiadiazoles induce apoptosis in cancer cell lines [8,10,15,16].

2D and 3D quantitative structure activity relationship (QSAR) models concerning anticancer agents are well known [17–28]. In many cases, they use the Hansch equation taking into account lipophilicity as well as electronic and steric parameters [21,22]. A multiple linear regression analysis of a set of indane carbocyclic nucleosides with antiproliferative potency against L1210 and CEM cell

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lines gave a QSAR model including the lowest unoccupied molecular orbital energy (E_{lumo}) and the solvent accessible-hydrophobic surface area [23].

Elucidation of the structure-antiproliferative activity of 2- and 6-substituted-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells showed that the most important factor is hydrophobicity [24]. These results were confirmed by Mekapati et al. who analyzed leukemia cells using bis(heterocyclic-carboxamides) [25]. A 3D QSAR study on the antiproliferative activity of 1,2,4,5-tetraoxane derivatives showed that hydrophobicity and hydrogen bond donor features are the main factors affecting antiproliferative activity of the studied analogs against the HeLa (cervix carcinoma) human cancer cell lines [27]. The established QSAR models were usually estimated by leave-one-out cross-validation and tested through the use of external test sets of compounds and characterized by good predictability [20,29,30].

In this paper, QSAR models for a set of imidazo[2,1-*b*][1,3,4]thiadiazoles possessing antiproliferative activity against three cancer cell lines were built and discussed. The biological data used for this study came from a set of compounds described previously [6,8]. For the building of our QSAR models lipophilicity, electronic, and steric parameters were taken into account. The obtained models could explain if cell membrane permeability has an impact on the biological potency of the compounds, provide information about critical ligand–target interactions [24], and indicate differences in the structure of compounds that are crucial to antiproliferative activity.

Results and discussion

Dataset

Two different sets of imidazo[2,1-*b*][1,3,4]thiadiazoles were the object of our QSAR studies. The first group includes 15 analogs of 2-bromo-*N*-[3-(imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)phenyl]acrylamide modified in position 2 of the heterocyclic ring described by Romagnoli and co-workers (Table 1) [6]. The second set consists of 27 compounds, 5,6-disubstituted 2-(4-chlorobenzyl)imidazo[2,1-*b*][1,3,4] thiadiazoles presented by Kumar and co-workers (Table 1) [8]. The antiproliferative potency of both groups of compounds was evaluated against the same cancer cell lines using the MTT assay. In the case of these QSAR studies, the IC_{50} values were converted to the logarithm of IC_{50} (Table 1).

Descriptors

The QSAR model construction was based on lipophilicity, electronic, and steric descriptors obtained by computational methods: the lipophilicity of compounds was expressed as log *P* values estimated according to three different approaches (Clog *P*, Mlog *P*, log *P*) [31,32] and is one of the most important QSAR model descriptors. Electronic parameters include the atomic partial charges of some atoms of heterocyclic skeleton and the Highest Occupied Molecular Orbital (E_{homo}) and the Lowest Unoccupied Molecular Orbital (E_{lumo}) were taken into account since they are associated with the nucleophilic and electrophilic properties of a molecule. Based on the energies of frontier orbitals, the hardness (η) descriptor was obtained using the equation $\eta = (E_{lumo} - E_{homo})/2$ [33]. Polar surface area (PSA) was also taken into account. Molar refractivity (MR, CMR determined according two different algorithms), volume, ovality, and the surface area of a molecule were used as steric parameters (supplementary materials). The correlation matrix between the parameters used in the QSAR model equations is presented in Table 2.

QAAR studies

To compare sensitivity of the individual cancer cell lines for the compounds under consideration, the quantitative–activity–activity relationships (QAAR) were studied and the results are presented in Table 3. They indicate that the activities of compounds against the studied cell lines are highly correlated with r^2 values in the range 0.771–0.924. The best relationship was obtained comparing the antiproliferative potency of compounds against human HeLa and CEM cells which is described by the equation

$$\log IC_{50(HeLa)} = 0.907 \log IC_{50(CEM)} + 0.085 \quad (1)$$

$n = 37$; $r^2 = 0.943$; $s = 0.161$; $F = 575.7$

The highest correlations can be explained by the same origin of both lines (human cells).

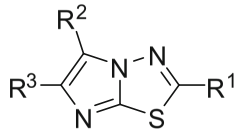
QSAR analyses

The dataset was divided into training (26–28 compounds) and test (8 compounds) sets by the Kennard Stone method. Using Multiple Linear Regression (MLR) and setting up the selection criteria for descriptors, three-variable QSAR equations were constructed. QAAR studies showed that activities of the studied compounds against the considered cell lines are highly correlated; therefore, similar QSAR models were expected to be obtained.

The best QSAR model of antiproliferative potency of imidazo[2,1-*b*][1,3,4]thiadiazoles against the L1210 cell line is described by the following equation:

$$\log IC_{50(L1210)} = 0.861(\pm 0.067) \log P + 1.409(\pm 0.227) E_{Lumo} - 0.444(\pm 0.0764) CMR + 2.149(\pm 1.065) \quad (2)$$

Table 1 Structure and antiproliferative potency (observed and calculated) of imidazo[2,1-*b*][1,3,4]thiadiazoles against murine leukemia (L1210), human T-lymphocyte (CEM), and human cervix carcinoma (HeLa) cells



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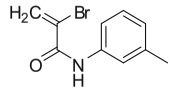
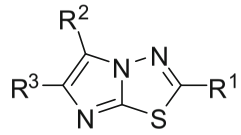


No.	R^1	R^2	R^3	L1210/log IC_{50}			CEM/log IC_{50}			HeLa/log IC_{50}		
				Obs.	Calc. Eq. (2)	Res.	Obs.	Calc. Eq. (4)	Res.	Obs.	Calc. Eq. (5)	Res.
1.	Ph-	H-	BrAAPh	−0.222[d]	−0.125	0.097	−0.018[d]	0.125	0.143	0.146[d]	0.378	0.232
2.	$PhCH_2$-	H-	BrAAPh	0.477	0.519	0.042	0.623	0.533	0.090	0.653	0.764	0.111
3.	$Ph(CH_2)_2$-	H-	BrAAPh	0.342	0.518	0.176	0.623	0.326	0.297	0.519	0.641	0.122
4.	Thien-2-yl	H-	BrAAPh	−0.770	−0.593	0.177	−0.387	−0.283	0.104	−0.174	0.044	0.218
5.	4-F-Ph-	H-	BrAAPh	−0.602	−0.343	0.259	−0.081	0.475	0.556	−0.06	0.186	0.246
6.	4-Cl-Ph-	H-	BrAAPh	0.146	−0.156	0.302	0.505	0.514	0.009	0.477	0.211	0.266
7.	4-Cl-Ph CH_2-	H-	BrAAPh	0.362	0.587	0.225	0.519	0.904	0.385	0.431	0.674	0.243
8.	4-CH_3-Ph-	H-	BrAAPh	−0.036	0.009	0.045	0.230	0.414	0.184	0.301	0.352	0.051
9.	4-C_2H_5-Ph-	H-	BrAAPh	0.342	0.147	0.195	0.531	0.557	0.026	0.505	0.339	0.166
10.	4-OCH_3-Ph-	H-	BrAAPh	−0.027	−0.560	0.533	0.079	0.021	0.058	0.362	−0.031	0.393
11.	4-OCH_3-Ph CH_2-	H-	BrAAPh	0.146	0.062	0.084	0.362	0.246	0.116	0.362	0.338	0.024
12.	3-OCH_3-Ph-	H-	BrAAPh	−0.237	−0.574	0.337	0.079	−0.297	0.376	0.041	−0.042	0.083
13.	3-OCH_3-Ph CH_2-	H-	BrAAPh	0.301	0.160	0.141	0.491	0.022	0.469	0.398	0.415	0.017
14.	2.3-$(OCH_3)_2$-$PhCH_2$-	H-	BrAAPh	−1.377	−1.027	0.350	−0.420	−0.413	0.007	−0.215	−0.464	0.249
15.	4-OC_2H_5-Ph-	H-	BrAAPh	−0.102	−0.339	0.237	0.146	0.179	0.033	0.041	0.032	0.009
16.	4-Cl-$PhCH_2$-	H-	4-Cl-Ph-	–[a]	2.039	–	–[a]	–	–	1.978	2.031	0.053
17.	4-Cl-$PhCH_2$	H-	4-OCH_3-Ph-	1.580	1.562	0.018	–[a]	–	–	–[a]	–	–
18.	4-Cl-$PhCH_2$-	H-	2.4-di-Cl-Ph-	2.393	2.338	0.055	–[a]	–	–	2.037	2.105	0.068
19.	4-Cl-$PhCH_2$	H-	4-NO_2-Ph-	2.330	–[b]	–	–[a]	–	–	–[a]	–	
20.	4-Cl-$PhCH_2$-	Br-	4-Br-Ph-	–[a]	2.286	–	2.377	2.158	0.219	2.274	1.944	0.330
21.	4-Cl-$PhCH_2$	Br-	4-OCH_3-Ph-	1.799	1.719	0.080	1.763	1.329	0.434	1.82	1.637	0.183
22.	4-Cl-$PhCH_2$-	Br-	2.4-di-Cl-Ph-	1.491	–[c]	1.027	2.025	2.038	0.013	2.072	2.059	0.013
23.	4-Cl-$PhCH_2$	Br-	4-NO_2-Ph	1.973	–[b]	–	1.863	–[b]	–	–[a]	–	–
24.	4-Cl-$PhCH_2$-	Br-	coumarin-3-yl	0.716	1.021	0.305	0.568	0.846	0.278	0.653	1.002	0.349
25.	4-Cl-$PhCH_2$	-CHO	4-F-Ph-	1.301[d]	1.064	0.237	1.230	1.372	0.142	1.301	1.333	0.032
26.	4-Cl-$PhCH_2$-	-CHO	4-Cl-Ph-	1.176	1.299	0.123	0.763	0.768	0.005	1.204	1.396	0.192
27.	4-Cl-$PhCH_2$	-CHO	4-Br-Ph-	0.663	1.304	0.641	0.602	–[c]	–	0.626	–[c]	–

Table 1 continued



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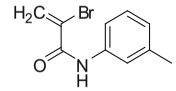

No.	R^1	R^2	R^3	L1210/log IC_{50}			CEM/log IC_{50}			HeLa/log IC_{50}		
				Obs.	Calc. Eq. (2)	Res.	Obs.	Calc. Eq. (4)	Res.	Obs.	Calc. Eq. (5)	Res.
28.	4-Cl-PhCH_2-	-CHO	4-OCH_3-Ph-	0.724[d]	0.730	0.006	0.580	0.738	0.158	0.778[d]	1.027	0.249
29.	4-Cl-PhCH_2	-CHO	4-CH_3-Ph-	1.362	1.308	0.054	1.230[d]	0.998	0.232	1.322[d]	1.417	0.095
30.	4-Cl-PhCH_2-	-CHO	2.4-di-Cl-Ph-	1.914[d]	1.507	0.407	1.898[d]	1.666	0.232	1.806	1.415	0.391
31.	4-Cl-PhCH_2	-CHO	Ph-	1.301	1.062	0.239	1.342[d]	0.991	0.351	1.653[d]	1.355	0.328
32.	4-Cl-PhCH_2-	-CHO	4-NO_2-Ph-	1.176	–[b]	–	1.114	–[b]	–	−0.046	–[b]	
33.	4-Cl-PhCH_2	-CHO	Coumarin-3-yl	−0.051	−0.010	0.041	−0.125	−0.077	0.048	–[a]	–	–
34.	4-Cl-PhCH_2-	-SCN	4-F-Ph-	1.362	1.264	0.098	1.380[d]	1.356	0.024	1.301[d]	1.245	0.056
35.	4-Cl-PhCH_2	-SCN	4-Cl-Ph-	1.690[d]	1.437	0.253	1.477[d]	1.414	0.063	1.301[d]	1.259	0.042
36.	4-Cl-PhCH_2-	-SCN	4-Br-Ph-	1.908	1.560	0.348	1.785	1.591	0.194	1.342	1.279	0.063
37.	4-Cl-PhCH_2	-SCN	4-OCH_3-Ph-	1.204	0.953	0.251	1.000	0.871	0.129	0.954	0.956	0.002
38.	4-Cl-PhCH_2-	-SCN	4-CH_3-Ph-	1.505[d]	1.545	0.040	1.342[d]	1.446	0.104	1.342[d]	1.357	0.015
39.	4-Cl-PhCH_2	-SCN	2.4-di-Cl-Ph-	1.690	1.744	0.054	1.663	1.712	0.049	1.255	1.355	0.100
40.	4-Cl-PhCH_2-	-SCN	Ph-	1.380[d]	1.304	0.076	1.146[d]	1.060	0.086	1.079[d]	1.300	0.221
41.	4-Cl-PhCH_2	-SCN	4-NO_2-Ph-	–[a]	–	–	1.301	–[b]	–	1.204	–[b]	–
42.	4-Cl-PhCH_2	-SCN	Coumarin-3-yl	0.114	0.311	0.197	0.146	0.532	0.386	0	0.365	0.365

Activity is expressed as log IC_{50}(μM)

[a] Activity not determined

[b] Not calculated (log *P* values were not calculated)

[c] Outlier compound

[d] Test set

Table 2 Correlation coefficient matrix (r^2) for the descriptors used in the QSAR models

	log *P*	Mlog *P*	E_{lumo}	$q_{(C2)}$	$q_{(N3)}$	$q_{(N7)}$	PSA	MR	CMR
log *P*	1.00								
Mlog *P*	0.048	1.00							
E_{lumo}	0.022	0.020	1.000						
$q_{(C2)}$	0.002	0.240	0.003	1.00					
$q_{(N3)}$	0.053	0.185	0.029	0.004	1.00				
$q_{(N7)}$	0.001	0.102	0.000	0.176	0.053	1.00			
PSA	0.068	0.490	0.036	0.176	0.084	0.004	1.00		
MR	0.044	0.194	0.010	0.185	0.003	0.016	0.436	1.00	
CMR	0.012	0.116	0.006	0.145	0.001	0.020	0.436	0.960	1.00

Table 3 Correlation coefficient matrix (r^2) between the antiproliferative activities of compounds against the studied cancer cell lines

	log $IC_{50(L1210)}$	log $IC_{50(CEM)}$	log $IC_{50(HeLa)}$
log $IC_{50(L1210)}$	1.000		
log $IC_{50(CEM)}$	0.924; $n = 37$	1.000	
log $IC_{50(HeLa)}$	0.867; $n = 37$	0.943; $n = 37$	1.000

$n = 27$; $r = 0.960$; $r^2_{adj} = 0.911$; $s = 0.266$; $F = 90.1$; $p < 0.0001$; $Q^2 = 0.896$; Press $= 1.63$; (compound 22 outlier)

Other statistical metrics are presented in Table 4. The calculated parameters are in the range recommended in the literature about the QSAR models validation: $R^2_{pred} > 0.6$; $Q^2 > 0.5$; $\overline{r^2_{m\,(pred)}}$ (scaled) > 0.5; $\Delta r^2_{m(pred)}$ (scaled) > 0.2; k and k' in the range of 0.85–1.15 and $|R^2_0 - R'^2_0| < 0.3$. The statistical quantities for chance correlation (R^2_r, $^{c}R^2_p$) as well as $r^2_{m\,(LOO)}$ and $r^2_{m\,(overall)}$ confirm external prediction ability of the obtained models (Table 4) [34–38].

Model Eq. (2) is the Hansch equation including lipophilicity as well as electronic and steric parameters. The equation could estimate 91 % variance in the observed activity. The model gives a leave-one-out cross-validation of 90 %. Other models were obtained similar to Eq. (2) which included E_{Lumo}, log *P*, and another steric descriptor: MR, surface area, volume, or ovality that are highly correlated with CMR. The predicted log $IC_{50(L1210)}$ values based on Eq. (2) and the residues between the observed and predicted activities are presented in Table 1 and graphically in Fig. 1.

The QSAR model similar to that in Eq. (2) was obtained for the CEM cells, expressed by the following equation:

$$\log IC_{50(CEM)} = 0.646(\pm 0.060)\log P - 0.0278(\pm 0.009)MR + 1.017(\pm 0.245)E_{Lumo} + 1.191(\pm 1.335) \quad (3)$$

($n = 25$; $r = 0.942$; $r^2_{adj} = 0.872$; $s = 0.265$; $F = 57.6$; $p < 0.0001$; $Q^2 = 0.842$; Press = 1.555 (compound 27 outlier)

A slightly better model was obtained including lipophilicity (Mlog *P*) and two electronic parameters

$$\log IC_{50(CEM)} = 2.454(\pm 0.578)q_{(C2)} - 6.855(\pm 2.346)q_{(N7)} + 0.848(\pm 0.085)\text{Mlog } P 6.996(\pm 1.404) \quad (4)$$

$n = 26$; $r = 0.942$; $r^2_{adj} = 0.872$; $s = 0.241$; $F = 58.03$; $p < 0.0001$; $Q^2 = 0.850$; Press $= 1.544$ (compound 27 outlier).

The other statistical quantities are presented in Table 4. They confirm the predictability of the obtained models. The log $IC_{50(CEM)}$ values predicted based on Eq. (4) and the residues between the calculated and observed activities are presented in Table 1.

In the case of HeLa cells, the best model also includes lipophilicity as well as electronic and steric factors and is expressed by

$$\log IC_{50(HeLa)} = 0.5378(\pm 0.048)\log P + 1.095(\pm 0.1929)E_{lumo} - 0.486(\pm 0.068)\text{CMR} + 4.345(\pm 0.954) \quad (5)$$

$n = 27$; $r = 0.961$; $r^2_{adj} = 0.917$; $s = 0.221$; $F = 97.2$; $p < 0.0001$; $Q^2 = 0.904$; Press $= 1.129$ (compound 27 is outlier).

The above equation shows that the parameters log *P*, E_{lumo}, and CMR play a significant role in explaining the variance (92 %) in the activity against the HeLa cells.

Another effective model is expressed by

$$\log IC_{50(HeLa)} = 3.050(\pm 0.562)q_{(C2)} - 7.891(\pm 3.117)q_{(N3)} - 0.033(\pm 0.005)\text{PSA} - 3.598(\pm 1.863) \quad (6)$$

$n = 29$; $r = 0.906$; $r^2_{adj} = 0.799$; $s = 0.342$; $F = 38.24$; $p < 0.0001$; $Q^2 = 0.705$; Press $= 2.921$ (compound 27 is outlier).

Table 4 Statistical metrics and validation parameters of the models

	R^2_{pred}	Q^2	$\overline{r^2_{m\,(\text{pred})}}$ (scaled)	$r^2_{m\,(\text{LOO})}$	$\Delta r^2_{\text{m(pred)}}$ (scaled)	k/k'	$\lvert R^2_0 - R'^2_0 \rvert$	R^2_r	${}^c R^2_p$	$r^2_{m\,(\text{overall})}$
Equation (2)	0.950	0.896	0.885	0.851	0.044	1.103/0.885	0.008	0.130	0.870	0.902
Equation (3)	0.830	0.842	0.690	0.784	0.159	1.116/0.873	0.064	0.156	0.821	0.805
Equation (4)	0.911	0.850	0.851	0.794	0.080	1.085/0.909	0.012	0.134	0.837	0.828
Equation (5)	0.879	0.904	0.576	0.867	0.199	0.978/0.999	0.157	0.154	0.861	0.845
Equation (6)	0.732	0.705	0.576	0.622	0.199	0.965/1.000	0.039	0.131	0.766	0.695

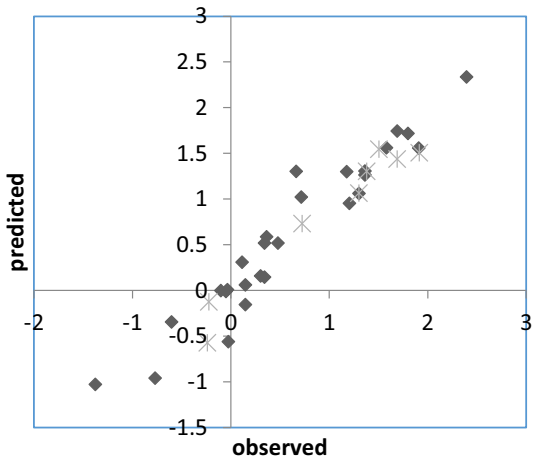

Fig. 1 Log $\text{IC}_{50(L1210)}$ observed versus predicted from. Eq. (2). Compound **22** is the outlier

The log $\text{IC}_{50(\text{HeLa})}$ values predicted from Eq. (5) and the residues between the calculated and observed activities are presented in Table 1.

The results showed that the best models, including all studied cell lines, were obtained when lipophilicity parameters were taken into account in the equations. Lipophilicity determines a compound passage through cell membranes. Biological potency of compounds is a parabolic function of lipophilicity in its wide range [39,40]. Lipophilicity of the studied compounds is limited as reflected by log *P* since values are in the 4.86–8.08 range. It can be assumed that the considered compounds represent only one ram of parabola. In that case, the antiproliferative activity is enhanced with a decrease of compound lipophilicity.

The biological potency of the compounds is also connected to the binding force of a ligand with a biomolecule which is associated to the charge distribution in a molecule. The charge of nitrogens N3 and N7 as well as that of carbon C-2 of the imidazo[2,1-*b*][1,3,4]thiadiazole ring is a statistically significant descriptor in the generated models. The obtained results showed that low negative charge of nitrogen ($q_{(\text{N3})}$, $q_{(\text{N7})}$) and low positive charge of carbon ($q_{\text{C}(2)}$) atoms contribute to antiproliferative potency. The generated models indicate the important role of the nitrogen atoms in the imidazothiadiazole ring for interactions with a potential molecular target. E_{lumo} as an electronic factor that influences biological potency and activity increased with a decreasing E_{lumo}. The antiproliferative activity of 1,3,4-thiadiazoles was also found to be a function of E_{Lumo} in a molecule [21]. The activity of the considered compounds is additionally enhanced by the high MR parameter.

Conclusions

Using combinatorial protocols in multiple linear regression (CP MLR), statistically significant QSAR models were obtained for all studied cell lines. For all systems three-variable equations were obtained. As the activities of the studied compounds against the individual cell lines were highly correlated, similar dependences were obtained. The constructed models gave high square correlation coefficient values and exhibited good predictive accuracy confirmed by internal and external validations as well as by a randomization procedure.

Taking into account the descriptors of model equations, there can be drawn some conclusions about the antiproliferative potency of imidazo[2,1-*b*][1,3,4]thiadiazoles: (1) compounds should have suitable lipophilicity–hydrophobicity character which determines cell membrane penetration; (2) models indicate a significant role of nitrogen atoms which can interact with a potential molecular target; (3) E_{lumo} influences the biological potency of the compounds; and (4) activity promotes high MR of the molecule.

These conclusions will be the guidance for the design and syntheses of novel compounds that could express significant potency against the presented cancer cells.

Experimental section

Antiproliferative activity

The compounds presented in Table 1 were analyzed. Their antiproliferative potency in vitro against the following cancer cell lines was assessed: murine leukemia (L1210), human T-lymphocyte (CEM), and human cervix carcinoma (HeLa)

cells [6,8]. Activity of compounds was expressed as IC_{50} values (μM), concentrations inducing a 50 % inhibition of cells compared to the control. The cytotoxicity was evaluated using the colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay.

Descriptors

The compounds were built with a standard bond length and angles using the PC SPARTAN Pro Ver. 1.08 molecular modeling program [41]. The energy of a molecule was minimized using molecular mechanics methods followed by the semi-empirical PM3 method and used for the electronic properties determination. Charge of atoms was determined (C, N, and S) from the potential distribution. Other descriptors were calculated from the ChemSketch 11.02 and MedChem Designer 3.0 programs [42,43].

Methodology of QSAR studies

Combinatorial protocols in multiple linear regression (CP MLR) was used to build the QSAR models [44,45]. The strategy combines the MLR procedure and properly set-up criteria for the selection of descriptors and equations: the descriptors in terms of interparameter correlation cut off limits in the subset regressions (0.79); *t* values of the regression coefficients (2.0); square-root of adjusted multiple correlation coefficient, *r* bar (0.71); the external consistency, R^2_{CV} ($0.3 \leq R^2_{CV} \leq 1.0$) [28]. There was used the outlier criterion: $|Yobs. - Ycalc.| > 2$ st. dev. The model selection and statistics were made using the BuildQSAR version 2.1.0.0 and Statistica version 7.1 software packages [46–48]. Statistical significance of the regression equation was tested by the correlation coefficient (r), the adjusted r square coefficient (r^2_{adj}), the standard error of estimate (s), and the variance ratio (F). The leave-one-out cross-validation (LOO CV) algorithm was applied to estimate the quality of the obtained equations (Q^2). The statistical quantities of external validation as well as randomization test: R^2_r, $^c R^2_p$ were calculated. Additionally, $r^2_{m\,(overall)}$ was determined [34–38].

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