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QSAR study of chalcone derivatives as anti-*Leishmania* agents

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Abstract: Quantitative structure activity relationship analyses were used to identify the ideal physicochemical characteristics of potential chalcone derivatives as anti-*Leishmania* agents. The HyperChem program was used to build chalcone structures and to perform conformational analyses through the semiempirical method followed by the PM3 force field. Dragon calculated a large number of molecular descriptors. Multilinear regression was used for quantitative structure activity relationship modeling. Based on our computational studies, 4 descriptors, SEigv, RDF125v, RDF055u, and O-058, can affect the activity of chalcone derivatives.

Key words: Amastigote, chalcones, leishmaniasis, QSAR, promastigote

1. Introduction

Leishmaniasis is a parasitic disease with a broad range of clinical manifestations.[1] The most serious fetal form is visceral leishmaniasis (VL). VL is a systemic disease that is fatal if left untreated and is caused by *L. donovani* and *L. infantum* (*L. chagasi* generally is considered synonymous with *L. infantum*).[2] *L. amazonensis* has been identified as a cause of VL in HIV-positive patients;[3,4] it is also a causative agent of mucosal and cutaneous leishmaniasis.

In previous studies, it was reported that available drugs for leishmaniasis treatment are either expensive or accompanied by side effects.[5–7] Moreover, resistance to the available drugs has become a serious problem justifying the search for new synthetic and natural origin antileishmanial agents.[8–10] These facts call for safer, cheaper, and more effective new antileishmanial drugs such as synthetic chalcones; it has been reported that they are effective in both promastigote and amastigote anti-*Leishmania* activities against *L. amazonensis*.[11] Chalcones are compounds from the flavonoid family and are present in a variety of plant species with a broad spectrum of pharmacological activities. Boeck et al.[11] synthesized chalcone analogues to develop compounds with improved antileishmanial activity. In previous studies, we used a quantitative structure activity relationship (QSAR) to improve the therapeutic index of some antileishmanial agents.[5,6] QSAR is used to discern the relationship between molecular descriptors that describe the unique physicochemical properties of the set of compounds of interest with their respective biological activity.[12–16] Briefly, a wide range of descriptors (approximately 3224) have been used in QSAR modeling, such as constitutional, geometrical, topological, quantum, and chemical.[17,18] A large number of statistical models such as multilinear regression (MLR) and partial least squares (PLS) are used to calculate mathematical QSAR equations.[19–21] Our QSAR models are

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based on the anti-*Leishmania* activity of a set of 18 chalcone derivatives synthesized in a previous experiment [11] and many of the descriptors were calculated using the Dragon [17,18] and HyperChem software for all of the compounds. To select the set of descriptors most relevant to the IC_{50} of the compounds, MLR models were built and QSAR equations with stepwise selection and elimination of variables were established using SPSS and Matlab software.

In the present research, we describe the QSAR studies that have been done in order to investigate the quantitative effect of the various physicochemical parameters of chalcone on anti-*Leishmania* activity (promastigote and amastigote) and to define which physicochemical parameters may increase these anti-*Leishmania* activities.

2. Results and discussion

The leishmanicidal activities of the chalcone derivatives (Table 1) were tested against both the extracellular (promastigote) and the intracellular (amastigote) forms of the parasite. We explain the QSAR model for antileishmanial activity against promastigote and amastigote assay in Eqs. (1) and (2), respectively. In the promastigote modeling, as the QSAR model was built, it was observed that compounds 5 and 13 had a significant deviation from the regression line; therefore, they were considered outliers and deleted from the modeling procedure.

2.1. QSAR model for promastigote assay

Based on the Experimental section procedure, using a stepwise multiple linear regression method, the following 2-parametric equation (Eq. (1)) was derived for chalcones 1–18 for the leishmanicidal activity in the promastigote assay:

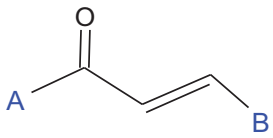
$$\begin{aligned} pIC_{50} &= -(1.698 \pm 0.338) - (0.891 \pm 0.072)SEigv - (1.63 \pm 0.297)RDF125v \\ n &= 15, F = 79.9, R^2 = 0.95, S = 0.22, P < 0.000, q^2 = 0.96 \end{aligned} \quad (1)$$

Eq. (1) explains 95% of the variance in pIC_{50} (nM) data wherein the relative error prediction (REP) of the equation is shown in Table 2, which describes the effect of SEigv and RDF125v indices on promastigote anti-*Leishmania* activity.

SEigv is among the eigenvalue-based indices that correspond to the Eigenvalue sum from the van der Waals weighted distance matrix and RDF125v is among the RDF indices weighted by atomic van der Waals volumes. Eq. (1) indicates that SEigv and RDF125v demonstrate negative contributions based on the concept of these descriptors that have negative and positive quantities, respectively, and so they demonstrate positive and negative contributions towards the promastigote anti-*Leishmania* activity. Comparison of the coefficient and quantity of SEigv and RDF125v descriptors reveals that promastigote anti-*Leishmania* activity might be affected mainly by SEigv. The calculated pIC_{50} values using Eq. (1) are presented in Table 2 and the graphical representation of cross validated calculated activity and the experimental values using Eq. (1) are presented in Figure 1. The correlation coefficient matrix for the descriptors used in the MLR Eq. (1) is shown in Table 3.

Based on this model (Eq. (1)) to design new and potent ligands, in the positions A and B (Table 1) of chalcone, moieties with high values of SEigv and low values of RDF125v should be inserted.

Table 1. The chemical structure of chalcone analogues.



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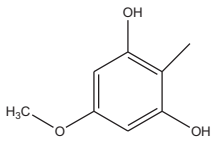
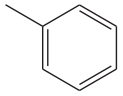
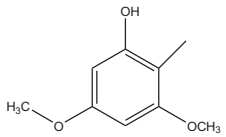
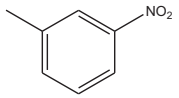
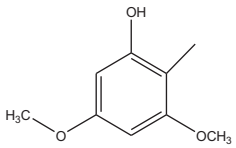
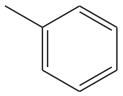
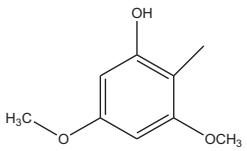
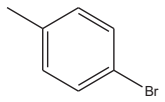
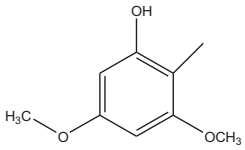
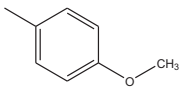
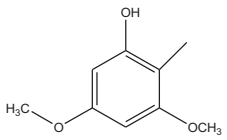
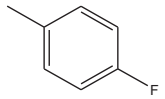
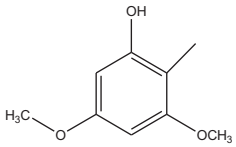
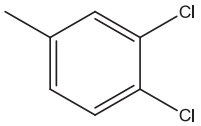
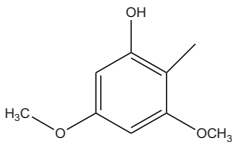
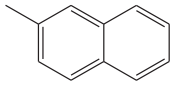
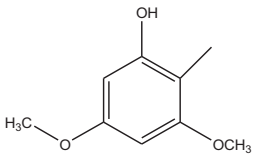
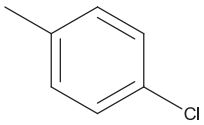
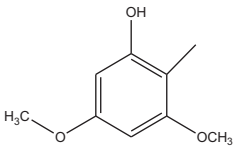
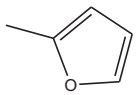
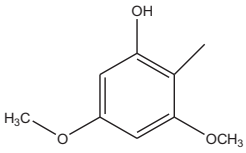
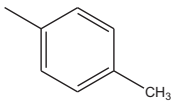
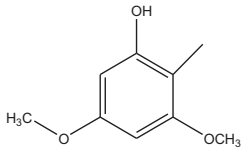
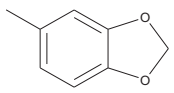
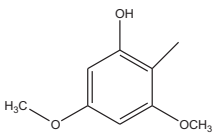
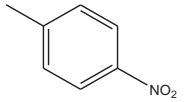
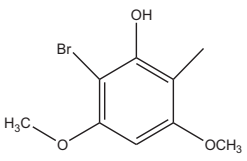
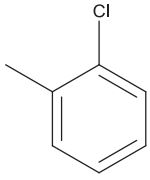
1			10		
2			11		
3			12		
4			13		
5			14		
6			15		
7			16		

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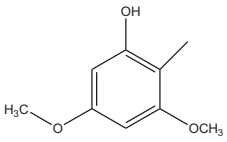
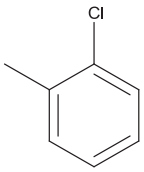
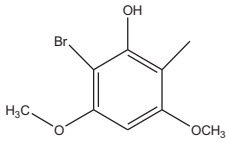
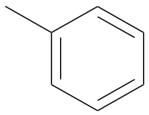
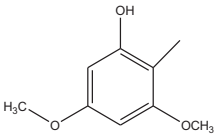
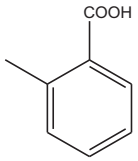
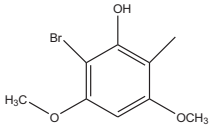
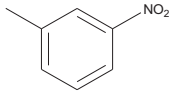
8			17		
9			18		

Table 2. Antileishmanial activity against promastigote of chalcone in terms of pIC_{50} (nM).

Compound	[a]pIC_{50} Exp.	[b]pIC_{50} Calc.	[c]|REP|%
1	1.602059991	1.702056	0.058750128
2	1.669586227	1.702056	0.019076795
3	1.139063379	1.450929	0.214942027
4	1.924453039	1.702056	0.130663761
8	2.292429824	0.710232	2.227719708
9	3.096910013	3.401193	0.089463605
10	3.15490196	2.921922	0.079735174
11	1.223298816	1.206598	0.013841243
12	3.096910013	2.981836	0.038591664
13	1.420216403	1.177196	0.206440052
14	2.301029996	2.515319	0.08519357
15	3.397940009	3.378373	0.005791844
16	3.045757491	1.454358	1.094228168
17	1.330683119	1.454358	0.08503744
18	3.301029996	3.248875	0.016053248

[a] The experimentally activity (pIC_{50}) in *Leishmania amazonensis*. [b] The calculated pIC_{50} using multilinear regression Eq. (1). [c] The absolute value of percent of the relative error of prediction.

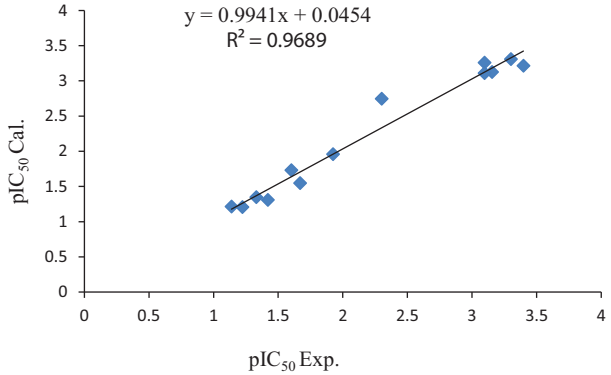


Figure 1. Plot of cross-validated calculated activity of *L. amazonensis* obtained by QSAR Eq. (1).

Table 3. Pearson correlation coefficient matrix for the descriptors of chalcones was used in the MLR activity Eq. (1).

Correlations				
		BR EXP.	SEigv	RDF125v
Pearson correlation	BR EXP.	1.000	–0.673	–0.200
	SEigv	–0.673	1.000	–0.283
	RDF125v	–0.200	–0.283	1.000
Sig. (1-tailed)	BR EXP.	.	0.003	0.237
	SEigv	0.003	.	0.154
	RDF125v	0.237	0.154	.
N	BR EXP.	15	15	15
	SEigv	15	15	15
	RDF125v	15	15	15

2.2. QSAR model for amastigote assay

Eq. (2) was derived for the amastigote anti-*Leishmania* activity of chalcones 1–18.

$$\begin{aligned} pIC_{50} &= (3.656 \pm 0.182) - (0.067 \pm 0.009)RDF055u - (0.443 \pm 0.135)O - 058 \\ n &= 14, F = 91.38, R^2 = 0.973, S = 0.047, P < 0.000, q^2 = 0.6 \end{aligned} \quad (2)$$

Eq. (2) explains 97.3% of the variance in pIC_{50} (nM) data and the REP of this equation is shown in Table 4, which describes the effect of RDF055u and O-058 indices on amastigote anti-*Leishmania* activity.

Table 4. Antileishmanial activity against amastigote of chalcone in term of pIC_{50} (nM).

Compound	[a] pIC_{50} Exp.	[b] pIC_{50} Calc.	[c]|REP|%
1	2.397940009	2.537372	0.05495134
2	2.075720714	2.166125	0.041735489
3	1.554395797	1.601985	0.029706398
4	2.420216403	2.408196	0.004991456
8	2.443697499	2.533415	0.035413661
9	1.54515514	1.538473	0.004343359
10	1.801342913	2.296775	0.215707715
12	2.366531544	1.982009	0.194006457
13	2.468521083	2.391714	0.032113824
14	2.468521083	2.411144	0.023796622
15	2.443697499	2.326791	0.050243661
16	1.847711656	1.940804	0.047965866
17	2.387216143	2.436537	0.020242195
18	2.200659451	1.988173	0.106875232

[a] The experimentally activity (pIC_{50}) in *L. amazonensis*. [b] The calculated pIC_{50} using multilinear regression Eq. (2). [c] The absolute value of percent of the relative error of prediction.

RDF055u is among the RDF descriptors and corresponds to a radial distribution function, and O-058 is among the atom-centered fragments. Eq. (2) indicates that RDF055u and O-058 demonstrate negative contributions towards the amastigote anti-*Leishmania* activity. Comparison of the coefficient and amount of descriptors RDF055u and O-058 reveals that amastigote anti-*Leishmania* activity might be affected mainly by RDF055u. The calculated pIC_{50} values using Eq. (2) are presented in Table 4 and the graphical representation

of cross-validated calculated activity and the experimental values using Eq. (2) are presented in Figure 2. The correlation coefficient matrix for the descriptors that were used in the MLR Eq. (2) is shown in Table 5.

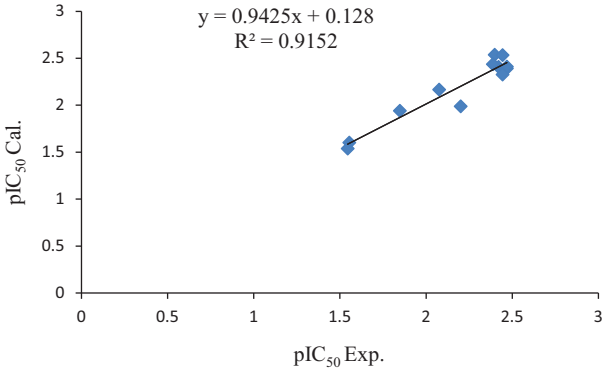


Figure 2. Plot of cross-validated calculated activity of *L. amazonensis* obtained by QSAR Eq. (2).

Table 5. Pearson correlation coefficient matrix for the descriptors of chalcones was used in the MLR activity Eq. (2).

Correlations				
		BR EXP.	RDF055u	o-058
Pearson correlation	BR EXP.	1.000	–0.691	–0.511
	RDF055u	–0.691	1.000	0.081
	o-058	–0.511	0.081	1.000
Sig. (1-tailed)	BR EXP.	.	0.003	0.031
	RDF055u	0.003	.	0.391
	o-058	0.031	0.391	.
N	BR EXP.	14	14	14
	RDF055u	14	14	14
	o-058	14	14	14

Based on this model (Eq. (2)) to design new and potent ligands, in positions A and B (Table 1) of chalcone, moieties with low values of RDF055u and O-058 should be inserted.

Since the promastigote and amastigote assays refer to extracellular and intracellular forms of parasite and penetration of drug into the cells can be affected by different physicochemical properties, comparison of Eqs. (1) and (2) confirmed this and revealed the different descriptors that may affect the activity.

3. Experimental

3.1. Molecular modeling and software

HyperChem software (version 7, Hypercube Inc.) was used to build the structures of chalcone compounds 1–18 (Table 1) and the semiempirical molecular orbital calculation (PM3) method was performed, in order to proceed with conformational analyses of all compounds. The Polak–Ribiere (conjugate gradient) algorithm (RMS gradient = 0.01 kcal mol^{-1}) was used tooptimize the molecular structures. Then the Dragon program was used for the resulting geometry.[17,18] As described previously, SPSS (version 19) and Matlab (version 7.13.0.564, R2011b) software were used for the MLR.[5,6] MLR is one of the best linear statistical methods used in QSAR investigations in which the investigated property is represented as a linear function of calculated descriptors.

3.2. Data set and descriptor generation

The biological data used in this study comprised anti-*Leishmania* activity (IC_{50}, nM) against promastigote and amastigote *L. amazonensis* of chalcone derivatives,[11] which were used for subsequent QSAR analysis as dependent variables. *Leishmania* cells have 2 morphological forms, promastigote and amastigote. In mammalian hosts, *Leishmania* parasites are named amastigotes. Amastigotes adapt to living within the confines of the phagolysosomal apparatus of the host cells and initiate infection. In the insect host, *Leishmania* parasites are named promastigotes. They are the elongated, flagellated, extracellular, and motile form of this parasite and are easily grown in appropriate culture media.[22]

A large number of molecular descriptors (3233 descriptors) were calculated using HyperChem (Table 6; 9 descriptors) and Dragon (Table 7; 3224 descriptors). Dragon was used to calculate 22 different types of descriptors like functional groups, topological, geometrical, and constitutional descriptors for each molecule. The calculated descriptors were collected in a data matrix whose numbers of rows and columns were the numbers of molecules and descriptors, respectively.

Table 6. Calculated properties of chalcone analogues using the Hyperchem software.

Compound	Surface area (approx) [a]	Surface area (grid) [a]	volume	Hydration energy	Logp	refractivity	polarizability	Dipole moment	HOMO[b]
1	429.06	497.71	804.23	13.22	2.85	76.63	29.24	4.269	–9.224
2	470.9	530.32	857.66	–9.39	2.89	81.5	31.07	4.761	–9.078
3	535.38	580.12	940.71	–11.28	2.63	87.96	33.55	5.187	–8.781
4	456.4	501.81	831.97	–9.61	3.51	80.86	31.45	2.274	–9.364
5	501.69	546.37	899.83	–9.18	3.4	86.3	33	3.744	–9.065
6	499.43	525.54	884.63	–9.68	3.35	86.54	32.91	5.402	–9.227
7	526.92	564.35	924.58	–14.76	2.99	87.19	32.91	6.761	–9.431
8	502.86	563.5	925.44	–8.69	4.33	89.87	34.56	3.087	–8.719
9	521.15	577.7	936.57	–14.6	2.58	88.26	33.63	5.575	–9.314
10	634.75	660.26	1013.46	–36.17	2.84	88.82	32.91	8.859	–9.425
11	497.72	539.63	897.89	–9.6	3.68	89.12	33.7	4.656	–9.328
12	470.24	513.49	853.21	–10.05	3.03	81.71	30.98	3.845	–9.363
13	495.6	577.77	967.84	–10.69	3.89	97.95	38.34	4.675	–8.891
14	458.05	507.15	814.08	4.29	1.83	73.98	27. 87	3.371	–8.926
15	489.01	561.22	921.4	–12.49	2.72	85.63	33.41	4.414	–8.774
16	535.37	579.88	935.24	–8.56	4.2	93.93	35.63	4.22	–9.230
17	497.23	544.73	907.01	–8.83	3.68	89.12	33.7	4.794	–9.158
18	543.25	578.48	966.03	–14.02	3.63	96.44	35.54	8.722	–9.642

[a] The van der Waals and solvent-accessible surface areas of a given set of atomic radii can be computed by 2 methods, approximate and grid. Approximate method is fast and generally accurate to within 10% for a given set of atomic radii. The grid calculation of surface area is much slower than the approximate calculation, but is more accurate. [b] highest occupied molecular orbital

3.3. Data screening and model building

As previously mentioned, constant or near-constant variables were detected and were removed; then the correlations of descriptors with each other and with the activity (pIC_{50}) of the molecules were examined

and collinear descriptors (i.e. r > 0.8) were detected. Among the collinear descriptors, the descriptor with the highest correlation with activity was retained and the others were removed from the data matrix. MLR is one of the best linear statistical methods used in QSAR investigations in which the investigated property is represented as a linear function of calculated descriptors. The MLR models were built and the QSAR equations with stepwise selection and elimination of variables were established to select the set of descriptors that were most relevant to the anti-*Leishmania* activity (pIC_{50}).[5,6]

Table 7. List of descriptors used in this study that calculated using Dragon.

No.	Descriptor group	Number of descriptors
1	Constitutional descriptors	48
2	Topological descriptors	119
3	Walk and path counts	47
4	Connectivity indices	33
5	Information indices	47
6	2D autocorrelations	96
7	Edge adjacency indices	107
8	Burden eigenvalues	64
9	Topological charge indices	21
10	Eigenvalue-based indices	44
11	Randic molecular profiles	41
12	Geometrical descriptors	74
13	RDF descriptors	150
14	3D-MoRSE descriptors	160
15	WHIM descriptors	99
16	GETWAY descriptors	197
17	Functional group counts	154
18	Atom-centered fragments	120
19	Charge descriptors	14
20	Molecular properties	29
21	2D binary fingerprints	780
22	2D frequency fingerprints	780

4. Conclusions

Eighteen analogues of chalcones with anti-*Leishmania* activity, using the MLR method, were subjected to QSAR studies in order to identify the ideal physicochemical characteristics of potential anti-*Leishmania* activity to design a new ligand with an improved therapeutic index. Based on our present computational studies, mainly 4 descriptors, SEigv, RDF125v, RDF055u, and O-058, can affect the activity of this series of ligands.

These observations and experimental results provide a suitable process to explain the potent inhibitory activities of these compounds. These computational studies may offer some useful references in order to understand the action mechanism and for molecular design or modification of this series of anti-*Leishmania* agents.

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References

1. Croft, S. L.; Coombs, G. H. *Trends Parasitol.* **2003**, *19*, 502–508.
2. Centers for Disease Control and Prevention, USA. http://www.cdc.gov/parasites/leishmaniasis/index.html.
3. Alvar, J.; Aparicio, P.; Aseffa, A.; Den Boer, M.; Canavate, C.; Dedet, J. P.; Gradoni, L.; Ter Horst, R.; López-Vélez, R.; Moreno, J. *Clin. Microbiol. Rev.* **2008**, *21*, 334–359.
4. Monzote, L. *Open. Antimicrob. Agents.* **2009**, *1*, 9–19.
5. Iman, M.; Davood, A. *Med. Chem. Res.* **2013**, *22*, 5029–5035.
6. Davood, A.; Iman, M. *Turk. J. Chem.* **2013**, *37*, 119–133.
7. Croft, S. L.; Yardley, V. *Curr. Pharm. Des.* **2002**, *8*, 319–342.
8. Agarwal, A.; Ramesh; Ashutosh; Goyal, N.; Chauhan, P. M. S.; Gupta, S. *Bioorg. Med. Chem.* **2005**, *13*, 6678–6684.
9. Hadighi, R.; Boucher, P.; Khamesipour, A.; Meamar, A. R.; Roy, G.; Ouellette, M.; Mohebali, M. *Parasitol. Res.* **2007**, *101*, 1319–1322.
10. Hadighi, R.; Mohebali, M.; Boucher, P.; Hajjaran, H.; Khamesipour, A.; Ouellette, M. *PLOS Med.* **2006**, *3*, e162.
11. Boeck, P.; Bandeira Falcão, C. A.; César Leal, P.; Yunes, R. A.; Filho, V. C.; Torres-Santos, E. C.; Rossi-Bergmann, B. *Bioorg. Med. Chem.* **2006**, *14*, 1538–1545.
12. Davood, A.; Iman, M.; Nematollahi, A.; Shafiee, A. *Med. Chem. Res.* **2012**, *21*, 325–332.
13. Davood, A.; Nematollahi, A.; Iman, M.; Shafiee, A. *Arch. Pharm. Res.* **2009**, *32*, 481–487.
14. Kubinyi, H. *Drug Discov. Today* **1997**, *2*, 457–467.
15. Akgül, Ö.; Tarikoğulları, A. H.; Aydın Köse, F.; Ballar Kırmızıbayrak, P.; Pabuççuoğlu, M. V. *Turk. J. Chem.* **2013**, *37*, 204–212.
16. Tatar, G. B.; Tokluman, T. D.; Yelekçi, K.; Yurter, H. *Turk. J. Chem.* **2011**, *35*, 861–870.
17. Todeschini, R.; Consonni, V. *Molecular Descriptors for Chemoinformatics: Volume I: Alphabetical Listing/Volume II: Appendices, References*. Wiley-VCH: Weinheim, Germany; 2009, Vol. 110.
18. Todeschini, R.; Consonni, V.; Mauri, A.; Ballabio, D.; Manganaro, A. Milano chemometrics and QSAR research group. Vol. 30. University of Milano, Milano Italy, http://michem.disat.unimib.it/chm/index.htm. 2007.
19. Gramatica, P.; Papa, E. *QSAR Comb. Sci.* **2003**, *22*, 374–385.
20. Hansch, C.; Kurup, A.; Garg, R.; Gao, H. *Chem. Rev.* **2001**, *101*, 619–672.
21. Cramer, R. D.; Patterson, D. E.; Bunce, J. D. *J. Am. Chem. Soc.* **1988**, *110*, 5959–5967.
22. Handman, E.; Noormohammadi, A. H.; Curtis, J. M.; Baldwin, T.; Sjolander, A. *Vaccine* **2000**, *18*, 3011–3017.