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QSAR and QSTR study of pyrimidine derivatives to improve their therapeutic index as antileishmanial agents

Maryam Iman · Asghar Davood

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Abstract In the treatment of leishmaniasis, chemotherapy is expensive and has various side effects. The major side effects are due to multiple injections that are required over a course of several weeks and non-selectivity of the drugs. In addition, there is no fully effective drug available against the cutaneous form of the disease. Experimental data of pyrimidine derivatives show that they are potent inhibitors of *Leishmania* growth. In the current study, a series of 2-pyridyl pyrimidine derivatives with *Plasmodium falciparum* methionine aminopeptidase 1b inhibitory activity was subjected to quantitative structure activity relationship (QSAR) and quantitative structure toxicity relationship (QSTR) analyses to identify the ideal physicochemical characteristics of potential anti *Leishmania* activity with limited cytotoxic effects. We also determined the physicochemical characteristics that affect antiparasitic activity and cytotoxicity to identify the best relationship model related to these two parameters. 2-Pyridyl pyrimidines with desirable properties were built using HyperChem program, and conformational studies were performed through the semi-empirical method followed by the PM3 force field. Different descriptors were calculated using Dragon and HyperChem software. Multilinear regression was used as a chemometric tool for QSAR and QSTR modeling and the developed models were shown to be statistically significant according to the validation parameters. Based on our computational studies, using lipophilic and electronegative moieties can improve the therapeutic index of pyrimidine derivatives.

Keywords Cytotoxicity · Leishmaniasis · 2-Pyridyl pyrimidines · QSAR · QSTR

Introduction

Leishmaniasis is a parasitic disease caused by protozoan parasites of the genus *Leishmania* (Croft and Coombs, 2003) with distinct manifestations. These manifestations vary from skin disease to its most serious form fetal visceral leishmaniasis (VL) (Dowlati *et al.*, 1996). It is a generalized infection of the reticuloendothelial system (RES) involving the spleen, liver, bone marrow and lymph nodes. The etiological agent in the old world including the Indian sub-continental, Sudan and other African countries is *L. donovani* and around the Mediterranean basin it is *L. infantum*, while *L. chagasi* is the causative agent of VL in several South American countries. VL caused by *L. donovani* is severe with very high mortality even with treatment. In addition, leishmaniasis has been reported in 98 tropical and subtropical countries, wherein 350 million people live at risk with a 1.5–2 million annual incident rate and globally 12 million people are affected (WHO report 2011). The disease is prevalent in Bangladesh, Brazil, India, Nepal, and Sudan, wherein 90 % of the annual 500,000 new cases occur (http://www.who.int/inffs/en/fact116.html).

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Available drugs are either expensive or accompanied with side effects or are not always effective (Croft and Yardley, 2002; Iman *et al.*, 2011b). Moreover, resistance to available drugs has become a serious problem which justifies the search for new synthetic and natural origin antileishmanial agents (Agarwal *et al.*, 2005; Hadighi *et al.*, 2006, 2007) such as the synthetic compound pyridyl pyrimidines, which has been reported to have antileishmania activities (Musonda *et al.*, 2009). Therefore, research and development of a potent and effective antileishmanial drug are essential to improve therapeutic strategies.

Quantitative structure activity relationships (QSAR) and quantitative structure toxicity relationships (QSTR) are widely used in the drug design process to improve the therapeutic index (TI) wherever detailed structural informations on the ligand–receptor interactions are not experimentally available (Hansch *et al.*, 2001; Hansch and Fujita, 1964; Hansch, 1969; Gaudio *et al.*, 1994; Davood *et al.*, 2009, 2012a, b; Iman *et al.*, 2011a). QSAR and QSTR models are mathematical equations relating the chemical structure to the biological activities and toxicity, respectively (Hansch and Leo, 1995; Kubinyi, 1997a, b). The first component in the definition of a QSAR and QSTR model is the computation of the structural descriptors from the 3D molecular structure, various geometrical, quantum, or molecular field descriptors are proposed in recent years to replace the Hansch substituent constants (Gaudio *et al.*, 1994; Hansch and Fujita, 1964; Hansch, 1969). Hence, a wide range of descriptors have been used in QSAR and QSTR modeling, and these descriptors have been classified into different categories such as constitutional, geometrical, topological, quantum, chemical, and so on. In this study, about 3,224 descriptors were used (Todeschini and Consonni, 2009; Todeschini *et al.*, 2007). The second component of a QSAR and QSTR model is an explicit mathematical structure activity equation to establish a statistical relationship between a dependent variable (biological activity and toxicity) and a set of independent variables (descriptors) (Gaudio *et al.*, 1994; Hansch and Fujita, 1964; Hansch, 1969). The mathematical QSAR and QSTR equations might be produced using a large number of statistical models such as multilinear regression (MLR) and partial least squares (PLS) (Gramatica and Papa, 2003; Hansch *et al.*, 2001; Cramer *et al.*, 1988).

Our QSAR and QSTR models are based on the antileishmania activity and cytotoxicity of a set of 30, 2-pyridyl pyrimidine derivatives which are synthesized in a previous experiment (Musonda *et al.*, 2009) and many descriptors were calculated using the Dragon (Todeschini and Consonni, 2009; Todeschini *et al.*, 2007) and HyperChem programs for all of the compounds. To select the set of descriptors that are most relevant to the IC_{50} of the compounds, MLR models were built and QSAR and QSTR equations with stepwise selection and elimination of variables are established using SPSS and Matlab software.

In the present research, we describe the QSAR and QSTR studies that have been done to investigate the quantitative effect of the various physicochemical parameters of 2-pyridyl pyrimidine on their antileishmania activity and cytotoxicity to define which physicochemical parameters may increase antileishmania activity while decreasing cytotoxicity.

Materials and methods

Computation of structural descriptors and QSAR equations

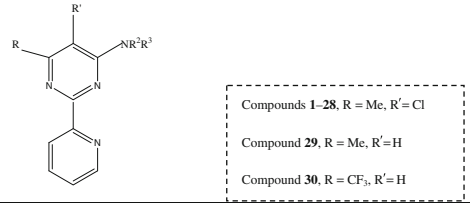
Molecular modeling and software

The 2D structures of desired compounds **1**–**30** (Table 1) were built using HyperChem software (version 7, Hypercube Inc.). Conformational analyses of all compounds were performed through the semi-empirical molecular orbital calculation (PM3) method using HyperChem software. The molecular structures were optimized using the Polak–Ribiere (conjugate gradient) algorithm until the root mean square gradient was 0.01 kcal mol^{-1}. From the energy minima conformers, the global minimum of the compounds were used in QSAR and QSTR calculations and then, the resulting geometry was transferred to the Dragon program, developed by Milano Chemometrics and QSAR Group (Todeschini and Consonni, 2009; Todeschini *et al.*, 2007). SPSS (version 18) and Matlab (version 7.6.0, R2008a) software were used for the MLR regression method.

Dataset and descriptor generation

Biological data used in this study were cytotoxicity and antileishmania activity (IC_{50}), against *L. donovani* of 2-pyridyl pyrimidines derivatives (Musonda *et al.*, 2009) which were used for subsequent QSAR and QSTR analysis as dependent variables. A large number of molecular descriptors were calculated using HyperChem (Table 2) and Dragon software. Some of the chemical parameters including molecular volume (V), molecular surface area (SA approx), surface area (SA grid) hydrophobicity (LogP), hydration energy (HE), refractivity (Rf), molecular polarizability (MP), and different quantum chemical descriptors including dipole moment (DM) and the highest occupied molecular orbital (HOMO) energies were calculated using HyperChem software (Table 2). Dragon software was used to calculate different functional groups, topological, geometrical, and constitutional descriptors for each molecule. The calculated

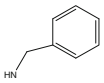
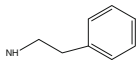
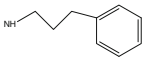
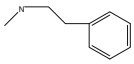
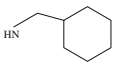
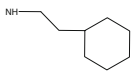
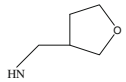
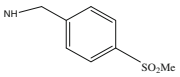
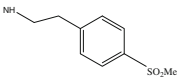
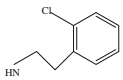
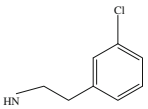
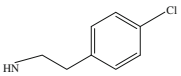
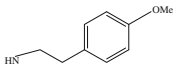
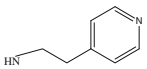
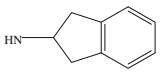
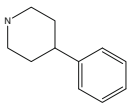
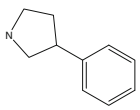
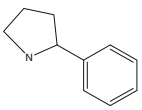
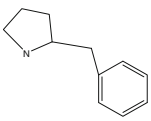
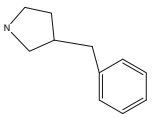
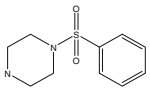
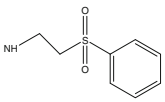
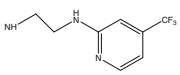
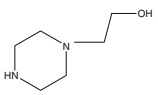
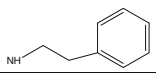
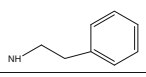
Table 1 The chemical structure of 2-pyridyl pyrimidines



Compounds **1**–**28**, R = Me, R′= Cl

Compound **29**, R = Me, R′= H

Compound **30**, R = CF_3, R′= H

Compound	NR^2R^3	Compound	NR^2R^3
1	NH_2	**2**	NMe_2
3	NEt_2	**4**	
5		**6**	
7		**8**	
9		**10**	
11		**12**	
13		**14**	
15		**16**	
17		**18**	
19		**20**	
21		**22**	
23		**24**	
25		**26**	
27		**28**	
29		**30**	

descriptors were collected in a data matrix wherein the number of rows and columns were the number of molecules and descriptors, respectively.

Data screening and model building

The calculated descriptors were first analyzed for the existence of a constant or near-constant variable and when detected they were removed. In addition to decreasing the redundancy that existed in the descriptor data matrix, the correlation 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 one that showed the highest correlation with activity was retained and the others were removed from the data matrix. To select the set of descriptors that were most relevant to the antileishmania activity and cytotoxicity (pIC_{50}), MLR models were built and the QSAR and QSTR equations with stepwise selection and elimination of variables were established using the MLR method.

In the case of each regression problem, SPSS produced many models and ranked them based on standard error of calibration and coefficient of multiple determinations, wherein some models had a large number of input variables and thus they were over-fitted. To hinder obtaining over-fitted models, the generated QSAR models were validated by the leave-one-out (LOO) cross-validation procedure to check their predictability and robustness. A balance between the high cross-validation correlation coefficient and low number of descriptors were used as the criterion for model selection. The overall prediction abilities of the final models were accessed using a prediction set containing about 25 % of the original molecules. To do so, the dataset of activity was randomly classified to calibrate and predict the sets. The model coefficients were calculated using calibration data and then they were used to calculate the antileishmania activity of the molecules in the prediction set.

Results and discussion

Quantitative structure activity relationship (QSAR) equations

Based on the procedure explained in the Materials and methods section, using a stepwise multiple linear regression method, the following two-parametric Eq. 1 was derived for 2-pyridyl pyrimidines **1**–**30**. The correlation coefficient matrix for the descriptors used in the MLR equation has been provided in Table 4. In the QSAR equations, n is the number of data points, R^2 is the correlation coefficient, S is the standard deviation, F is the Fisher's F value and q^2 is the LOO cross-validated coefficient that was obtained by a multiple linear regression

Table 2 Calculated properties of 2-pyridyl pyrimidines using the HyperChem software

Compound	Surface area (approx.)	Surface area (grid)	Volume	Hydration energy	LogP	Refractivity	Polarizability	Dipole moment	HOMO[a]
1	318.1	411.45	637.35	−6.95	3.38	57.18	23.08	2.702	−9.072
2	408.89	458.75	738.54	−1.99	4.43	66.9	26.75	2.632	−8.957
3	447.74	497.1	820.79	−0.94	5.12	76.4	30.42	0.9207	−8.723
4	398.7	485.73	801.38	−1.63	4.76	74.44	29.65	1.951	−8.959
5	436.34	551.51	901.93	−6.13	5.52	87.28	34.58	1.036	−9.117
6	483.38	580.32	952.16	−6.26	5.77	92.04	36.41	1.512	−8.992
7	523.4	612.35	1008.63	−5.99	6.17	96.64	38.25	0.8945	−8.955
8	509.03	613.88	1015.43	−5.24	5.42	94.41	38.25	2.303	−9.249
9	454.64	557.03	936.6	−3.03	5.64	88.41	35.15	1.317	−8.864
10	499.25	599.06	996.56	−3.07	5.96	93.09	36.99	2.912	−9.099
11	444.7	535.69	878.53	−5.74	3.65	81.26	32.12	2.766	−9.184
12	560.86	635.82	1047.34	−8.71	4.66	101.04	37.55	4.839	−9.336
13	603.73	668.43	1108.63	−8.27	4.91	105.79	39.38	4.58	−9.051
14	513.62	595.62	990.39	−5.93	6.29	96.84	38.34	1.485	−9.002
15	520.12	601.07	996.09	−5.86	6.29	96.84	38.34	1.497	−9.042
16	468.26	570.35	979.74	−4.94	6.29	96.84	38.34	1.635	−9.103
17	488.5	578.36	1012.41	−6.75	5.52	98.5	38.88	1.374	−8.866
18	425.92	541.42	923.81	−6.42	5.39	89.82	35.7	2.871	−9.124
19	443.42	567.96	959.88	−4.53	5.82	95.02	37.47	1.44	−8.991
20	498.56	626.32	1055.18	−3.29	6.7	103.69	41.14	2.313	−9.113
21	479.85	604.52	1010.11	−3.56	6.38	99.01	39.31	2.785	−8.649
22	461.16	583.57	997.83	−3.2	6.6	98.73	39.31	1.284	−9.05
23	461.5	601.52	1032.72	−3.01	6.86	103.48	41.14	2.701	−8.688
24	515.89	633.93	1070.21	−3.02	6.77	103.61	41.14	1.395	−9.201
25	553.83	644.05	1124.39	−6.36	5.14	110.98	41.8	2.361	−8.946
26	559.81	637.18	1053.56	−9.44	4.76	100.51	37.55	4.486	−9.102
27	547.73	647.88	1068.28	−8.8	5.92	101.05	38.62	3.532	−9.062
28	487.67	563.81	947.99	−8.12	3.79	89.25	35.31	1.814	−9.046
29	466.81	576.59	930.29	−6.79	5.25	87.23	34.48	3.31	−9.055
30	497.69	598.11	960.4	−7.13	5.88	87.93	34.21	4.646	−9.475

[a] Highest occupied molecular orbital

$$\begin{aligned} \mathrm{pIC}_{50} &= (3.654 \pm 0.481) + (0.921 \pm 0.094)\mathrm{MLOGP} \\ &\quad - (0.003 \pm 0.001)\mathrm{VOLUME} \\ n &= 23,\ F = 49.55,\ R^2 = 0.9,\ S = 0.35, \\ p &< 0.000,\ q^2 = 0.74 \end{aligned} \tag{1}$$

An appropriate QSAR model is indicated by large F, small S, small P value, as well as R^2 and q^2 values close to 1. In general, the regression model is significant at P value < 0.001 using the F statistics so the Eq. 1 is significant.

Equation 1 explains 90 % of the variance in pIC_{50} data, wherein the relative error prediction (REP) of the equation is shown in Table 3, which describes the effect of MLOGP and VOLUME indices on antileishmania activity. Equation 1 indicates that the MLOGP, partition coefficient (thermodynamic parameter) demonstrates a positive contribution and VOLUME shows a negative contribution toward the activity.

Comparison of MLOGP (0.921) and VOLUME (0.003) coefficients reveals which activity might be affected mainly by MLOGP. The calculated pIC_{50} using MLR of Eq. 1 is presented in Table 3 and the graphical representation of cross-validated calculated activity and the experimental values using Eq. 1 are presented in Fig. 1. The correlation coefficient matrix for the descriptors that were used in the MLR equation is shown in Table 4.

Based on the procedure explained in the experimental section, using a stepwise multiple linear regression method, the following four-parametric Eq. 2 was derived for cytotoxicity of 2-pyridyl pyrimidines **1**–**30**

Table 3 Antileishmanial activity of 2-pyridyl pyrimidines

Compound	pIC50 exp.[a]	pIC50 calc.[b]	|REP|%[c]
1	2.48	2.539536	0.023444
2	2.96	2.744358	0.07858
3	2.91	2.976528	0.022351
4	3.28	2.673726	0.22675
5	3.33	3.190845	0.04361
6	3.3	3.254748	0.0139
7	3.32	3.294405	0.00777
8	3.49	2.900079	0.20342
9	3.51	3.301428	0.06318
10	3.59	3.336141	0.07609
11	1.98	1.946778	0.01707
12	1.97	2.018736	0.024142
13	2.13	2.043933	0.04211
14	2.92	3.595953	0.187976
15	3.36	3.578853	0.061152
16	3.35	3.627903	0.076602
17	3.37	2.805066	0.2014
18	1.85	2.400378	0.229288
19	3.38	3.440655	0.017629
20	2.96	3.200805	0.075233
21	3.41	3.134316	0.08796
22	3.15	3.171156	0.006671
23	3.2	3.268185	0.020863
24	3.42	3.155715	0.08375
25	1.26	1.515891	0.168806
26	1.94	2.000076	0.030037
27	3.55	3.718344	0.045274
28	0.81	1.251189	0.352616
29	2.52	3.105765	0.188606
30	2.7	3.335022	0.19041

[a] The experimentally activity (pIC_{50}) in *Leishmania donovani*

[b] The calculated pIC_{50} using multilinear regression Eq. 1

[c] The absolute value of percent of the relative error of prediction

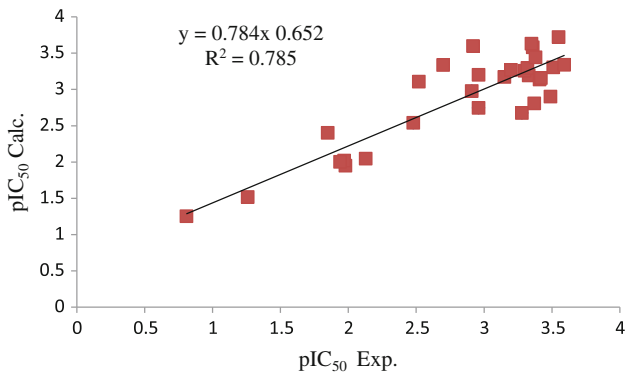


Fig. 1 *Plot* of cross-validated calculated activity of *L. donovani* obtained by QSAR Eq. 1

Table 4 Pearson correlation coefficient matrix for the descriptors of pyrimidines used in the MLR activity Eq. 1

Correlations			
	pIC_{50} exp.	MLOGP	VOLUME
Pearson correlation			
pIC_{50} exp.	1.000	0.733	−0.192
MLOGP	0.733	1.000	0.400
VOLUME	−0.192	0.400	1.000
Sig. (1-tailed)			
pIC_{50} exp.	–	0.000	0.190
MLOGP	0.000	–	0.029
VOLUME	0.190	0.029	–
N			
pIC_{50} exp.	23	23	23
MLOGP	23	23	23
Volume	23	23	23

$$\begin{aligned} pIC_{50} &= (8.955 \pm 1.6) + (0.695 \pm 0.077)\ \text{nNHRPh} \\ &\quad - (1.265 \pm 0.196)\ \text{Mor24e} - (8.167 \pm 1.6)\ \text{ATS7e} \\ &\quad - (0.763 \pm 0.224)\ \text{Mor27m} \\ n &= 23,\ F = 37.03,\ R^2 = 0.9,\ S = 0.15, \\ p &< 0.000,\ q^2 = 0.64 \end{aligned} \quad (2)$$

Equation 2 explains 90 % of the variance in pIC_{50} data, wherein the REP of this equation is shown in Table 5, which describes the effect of nNHRPh, Mor24e, ATS7e, and Mor27m indices on cytotoxicity of the compounds. nNHRPh is among the functional group fragments and corresponds to the number of secondary amines (aromatic). ATS7e is among the 2D autocorrelation descriptors and corresponds to the Broto–Moreau autocorrelation of a topological structure, which was weighted using atomic Sanderson electronegativities and Mor24e; moreover, Mor 27m are among the 3D-MoRSE descriptors that were weighted by atomic Sanderson electronegativities and atomic masses, respectively. Equation 2 indicates that nNHRPh demonstrate positive contribution, and Mor24e, Mor27m, and ATS7e demonstrate negative contribution toward the cytotoxicity but because of the negative fundamental nature of Mor27m, this descriptor has positive contribution on the cytotoxicity. Comparison of the coefficients of ATS7e (8.167), Mor24e (1.265), Mor27m (0.763), and nNHRPh (0.695) reveals which cytotoxicity can be affected mainly by ATS7e and Mor24e wherein both were weighted by atomic Sanderson electronegativities and related to electronegativity properties of the substituents. The calculated pIC_{50} using the MLR of Eq. 2 is presented in Table 5 and the graphical representation of cross-validated calculated activity and the experimental values using Eq. 1 are provided in Fig. 2. The correlation coefficient matrix for

Table 5 Cytotoxicity of 2-pyridyl pyrimidines in term of pIC_{50}

Compound	pIC_{50} exp.[a]	pIC_{50} calc.[b]	|REP|%[c]
1	1.069051	0.988379	0.00439
2	0.9393022	1.037749	0.094865
3	0.8297383	1.01616	0.183457
4	1.09691	1.092181	0.00433
5	1.154282	1.203041	0.04053
6	1.5934598	1.42308	0.11973
7	1.1337127	1.024004	0.10714
8	1.20412	1.083947	0.11087
9	1.3726341	1.006685	0.36352
10	1.3053948	1.284844	0.01599
11	0.90309	0.878885	0.02754
12	1.0287242	1.144489	0.10115
13	0.9850597	0.983995	0.00108
14	1.0381045	1.548243	0.329495
15	1.4867824	1.490239	0.002319
16	1.4867824	1.690363	0.120436
17	2.0604807	1.941819	0.06111
18	0.9586073	1.422937	0.326318
19	1.4788619	1.418594	0.04248
20	0.7375489	0.620912	0.18785
21	0.8761484	0.341036	1.56908
22	1.1163386	0.940914	0.18644
23	1.0347983	0.884562	0.16984
24	1.0555173	0.742123	0.42229
25	0.6777807	0.636426	0.06498
26	1.1378686	1.048668	0.08506
27	2.2839967	2.19681	0.03969
28	0.5686362	0.710228	0.199361
29	1.7375489	1.763743	0.014851
30	1.1295961	1.384944	0.184374

[a] The experimentally cytotoxicity pIC_{50} in rat myoblast L6

[b] The calculated pIC_{50} using multilinear regression Eq. 2

[c] The absolute value of percent of the relative error of prediction

the descriptors that were used in the MLR equation is shown in Table 6.

Based on the comparison of QSAR and QSTR equations, a new design for new ligands with an improved TI, insertion of the more lipophilic and electronegative moieties which affect activity and cytotoxicity, respectively, will produce ligand with high potency and low cytotoxicity.

Conclusion

Thirty analogs of 2-pyridyl pyrimidines with antileishmania activity using the MLR method were subjected to QSAR and QSTR studies to design new ligands with an improved TI. Based on our QSAR and QSTR equations (Eqs. 1, 2),

Table 6 Pearson correlation coefficient matrix for the descriptors of Eq. 2

Correlations					
	pIC_{50}	'nNHRPh'	'Mor24e'	'ATS7e'	'Mor27m'
Pearson correlation					
pIC_{50}	1.000	0.707	−0.339	0.292	−0.534
'nNHRPh'	0.707	1.000	0.154	0.661	−0.451
'Mor24e'	−0.339	0.154	1.000	−0.062	0.020
'ATS7e'	0.292	0.661	−0.062	1.000	−0.433
'Mor27m'	−0.534	−0.451	0.020	−0.433	1.000
Sig. (1-tailed)					
pIC_{50}	–	0.000	0.057	0.089	0.004
'nNHRPh'	0.000	–	0.241	0.000	0.015
'Mor24e'	0.057	0.241	–	0.389	0.464
'ATS7e'	0.089	0.000	0.389	–	0.019
'Mor27m'	0.004	0.015	0.464	0.019	–
N					
pIC_{50}	23	23	23	23	23
'nNHRPh'	23	23	23	23	23
'Mor24e'	23	23	23	23	23
'ATS7e'	23	23	23	23	23
'Mor27m'	23	23	23	23	23

MLOGP and VOLUME affected the activity with positive and negative contribution, respectively. Moreover, nNHRPh, Mor24e, ATS7e, and Mor27m affected the cytotoxicity wherein nNHRPh demonstrated a positive contribution, and Mor24e, Mor27m, and ATS7e demonstrated a negative contribution.

These observations and experimental results provided a suitable process to explain the potent and selective inhibitory activities of these compounds. Computational studies may offer some useful references to understand the action mechanism(s) and to perform the molecular design or modification of antileishmania agents. In addition, it seems

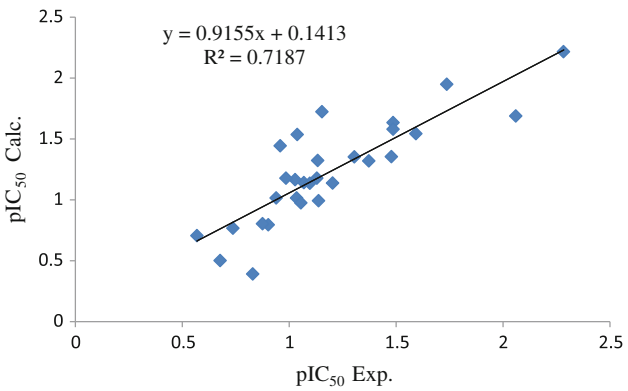


Fig. 2 *Plot* of cross-validated calculated activity of cytotoxicity obtained by QSAR Eq. 2

that using lipophilic and electronegative moieties improve the TI. Currently, our research group explores designing new compounds with more antileishmania activity.

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