Science Publications

Online Journal of Microbiological Research, 2022, 1, 17-24
www.scipublications.org/journal/index.php/ojmr
DOI: 10.31586/ojmr.2022.360

Article

DFT-Based Prediction of Anti-Leishmanial Activity of Carboxylates and Their Antimony(III) Complexes Against Five Leishmanial Strains

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Abstract: Carboxylates and their antimony(III) complexes experimentally scanned earlier for anti-leishmanial activity (IC_{50}) against five leishmanial strains viz., *L. major, L. major (Pak), L. tropica, L. mex mex,* and *L. donovani*. These activities have been theoretically predicted by DFT method along with quantitative structure-activity relationship (QSAR) study. Molecular modeling and geometry optimization of the all the eight compounds have been performed on workspace program of CAChe Pro software of Fujitsu by opting B88-PW91 (Becke '88; Perdew & Wang '91) GGA (generalized-gradient approximation) energy functional with DZVP (double-zeta valence polarized) basis set in DFT (Density Functional Theory). For QSAR, multiple linear regression (MLR) analysis has been performed on Project Leader Program associated with CAChe. The reliability of correlation between experimental activities and predicted activities are $r^2 = 0.826$, $r^2_{CV} = 0.426$ (*L. major*); $r^2 = 0.905$, $r^2_{CV} = 0.507$ (*L. major (Pak)*); $r^2 = 0.980$, $r^2_{CV} = 0.932$ (*L. tropica*); $r^2 = 0.781$, $r^2_{CV} = 0.580$ (*L. mex mex*) and $r^2 = 0.634$, $r^2_{CV} = 0.376$ (*L. donovani*), and a comparison of the experimental values and the values obtained by theoretical calculations has been presented pictorially that shows close resemblance.

Keywords: Carboxylates and their antimony(III) complexes; anti-leishmanial activity; DFT, MLR

How to cite this paper:
Sahu, V. K., Chandra, N., & Singh, P. (2022). DFT-Based Prediction of Anti-Leishmanial Activity of Carboxylates and Their Antimony(III) Complexes Against Five Leishmanial Strains. *Online Journal of Microbiological Research*, *1*(1), 17–24. Retrieved from https://www.scipublications.com/journal/index.php/ojmr/article/view/360

Received: June 02, 2022
Accepted: July 20, 2022
Published: July 22, 2022

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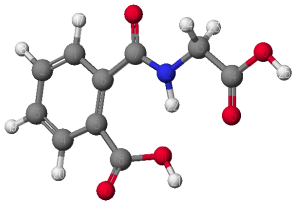
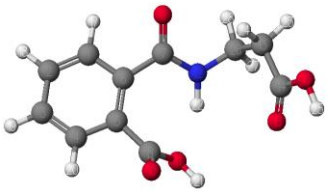
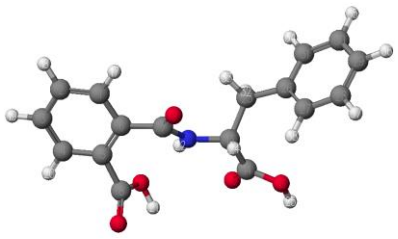
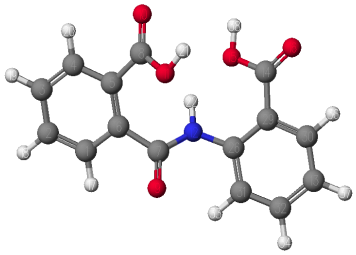
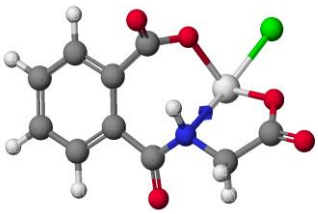
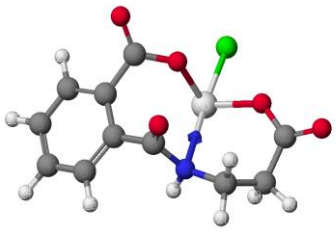
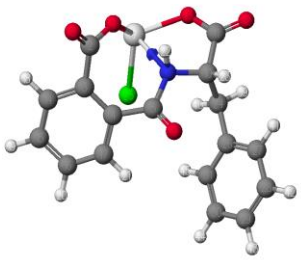
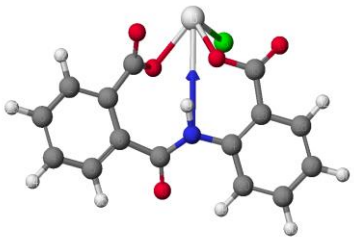
1. Introduction

Survey of literatures exposed that organoantimony compounds show diversity in their biological activity [1-8]. They show their antitumor, antimicrobial (viz., anti-fungal and anti-leishmanial) and insecticidal (viz., contact, stomach, anti-feedant and acaricidal) activities mostly in +III and +V oxidation states [1]. We know that experimental determination of various activity viz., pharmacological, toxicological, biochemical as well as human health end points of any compound are time and wealth-consuming. Hence, mathematical models were, are and will be of important use to predict these activities [9]. Gap between experimental and theoretical measurement is now bridged by computer simulation techniques [10]. In our previous work anti-fungal and insecticidal activities of perfluorophenyl antimony(III) and antimony(V) chlorides were rescaled by us using mathematical model after experimental work and the results were exciting [1]. This boost us to draw mathematical models for rescaling anti-leishmanial activities of carboxylates and their antimony(III) complexes. The quantum chemical parameters used in this study were well described in our previous publications [11-13].

Table 1. Quantum chemical properties and optimized structure of compounds

	EA = 2.716 IP = 5.952 η = 1.618 S = 0.309 μ = 1.828 E_T = -817.479 ω = 1.033 χ = 4.334		EA = 2.344 IP = 5.796 η = 1.726 S = 0.29 μ = 2.244 E_T = -856.797 ω = 1.459 χ = 4.07
Compound-1		Compound-2	
	EA = 2.18 IP = 5.911 η = 1.865 S = 0.268 μ = 3.022 E_T = -1087.84 ω = 2.448 χ = 4.045		EA = 2.833 IP = 5.885 η = 1.526 S = 0.328 μ = 2.154 E_T = -1009.23 ω = 1.52 χ = 4.359
Compound-3		Compound-4	
	EA = 3.348 IP = 6.709 η = 1.68 S = 0.298 μ = 7.208 E_T = -7592.19 ω = 15.458 χ = 5.028		EA = 24.312 IP = 22.303 η = -1.005 S = -0.498 μ = 11.329 E_T = -7564.55 ω = -63.886 χ = 23.308
Compound-5		Compound-6	
	EA = 23.136 IP = 20.499 η = -1.319 S = -0.379 μ = 5.151 E_T = -7783.44 ω = -10.062 χ = 21.817		EA = 3.435 IP = 5.853 η = 1.209 S = 0.414 μ = 4.062 E_T = -7783.96 ω = 6.824 χ = 4.644
Compound-7		Compound-8	

EA is the electron affinity in eV, IP is the ionization potential in eV, η is the absolute hardness, and S is the global softness, μ is the dipole moment in D, E_T is the total energy in hartree, ω is the electrophilicity index, and χ is the electronegativity of compounds as evaluated by DFT method

2. Materials and Methods

Carboxylates and their antimony(III) complexes listed in Table 1 are the study materials for the present study [14]. The IC_{50} of these compounds were taken from the literature against five leishmanial strains viz., *L. major*, *L. major (Pak)*, *L. tropica*, *L. mex mex*, and *L. donovani* (Table 2-5). For prediction of biological activity (IC_{50}) of these compounds, multiple linear regression analysis has been performed on Project Leader Program associated with CAChe [15-17]. The quantum chemical properties listed in Table 1 were used as independent variables and the experimental IC_{50} of the compounds listed in Table 2-6 as dependent variables. For this the molecular modeling and geometry optimization of the all the eight compounds have been performed on workspace program of CAChe Pro software of Fujitsu by opting B88-PW91GGA energy functional with DZVP basis set in DFT method [18].

3. Results and Discussion

Leishmania is a parasitic protozoan. There are more than twenty species of this. These different species are morphologically indistinguishable, but they can be differentiated by isoenzyme analysis, molecular methods, or monoclonal antibodies [19]. They are responsible for the disease leishmaniasis. Leishmaniasis is transmitted by the bite of infected female phlebotomine sand flies. Here anti-leishmanial activities are divided into five sets on the basis of their five different species.

Table 2. Anti-leishmanial activity of compounds in term of IC_{50} (μg/mL) against *L. major*

Compd. No	χ	S	IC_{50}		Δ
			Exp. [b]	Pred. [c]	
1	4.334	0.309	0.26	0.274	-0.014
2	4.070	0.290	0.28	0.307	-0.027
3	4.045	0.268	0.38	0.331	0.049
4	4.359	0.328	0.24	0.254	-0.014
5	5.028	0.298	0.24	0.255	-0.015
6	23.308	-0.498	0.25	0.249	0.001
7[a]	21.817	-0.379	0.29	0.193	0.097
8	4.644	0.414	0.17	0.150	0.020

Δ is residual, [a]data point not used in deriving the Eq.1, [b]Experimental biological activity in terms of IC_{50} against *L. major*, [c]Theoretical activity of compounds in terms of IC_{50} against *L. majo* as scanned from Eq.1

Table 3. Anti-leishmanial activity of compounds in term of IC_{50} (μg/mL) against *L. major (Pak)*

Compd. No	μ	E_T	IC_{50}		Δ
			Exp. [b]	Pred. [c]	
1	1.828	-817.479	0.33	0.316	0.014
2	2.244	-856.797	0.32	0.325	-0.005
3[a]	3.022	-1087.84	0.30	0.337	-0.037
4	2.154	-1009.23	0.31	0.318	-0.008
5	7.208	-7592.19	0.24	0.235	0.005
6	11.329	-7564.55	0.33	0.338	-0.008
7	5.151	-7783.44	0.22	0.177	0.043
8	4.062	-7783.96	0.11	0.150	-0.040

Δ is residual, [a]data point not used in deriving the Eq.2, [b]Experimental biological activity in terms of IC_{50} against *L. major (Pak)*, [c]Theoretical activity of compounds in terms of IC_{50} against *L. major (Pak)* as scanned from Eq.2

Table 4. Anti-leishmanial activity of compounds in term of IC_{50} (μg/mL) against *L. tropica*

Compd. No	I.P.	E.A.	IC_{50}		Δ
			Exp. [b]	Pred. [c]	
1	5.952	2.716	0.22	0.225	-0.005
2[a]	5.796	2.344	0.39	0.232	0.158
3	5.911	2.180	0.25	0.247	0.003
4	5.885	2.833	0.23	0.215	0.015
5	6.709	3.348	0.24	0.248	-0.008
6	22.303	24.312	0.35	0.350	0.000
7	20.499	23.136	0.28	0.280	0.000
8	5.853	3.435	0.18	0.185	-0.005

Δ is residual, [a]data point not used in deriving the Eq.3, [b]Experimental biological activity in terms of IC_{50} against *L. tropica*, [c]Theoretical activity of compounds in terms of IC_{50} against *L. tropica* as scanned from Eq.3

Table 5. Anti-leishmanial activity of compounds in term of IC_{50} (μg/mL) against *L. mex mex*

Compd. No	η	E_T	IC_{50}		Δ
			Exp. [b]	Pred. [c]	
1	1.618	-817.479	0.29	0.329	-0.039
2	1.726	-856.797	0.32	0.320	0.000
3	1.865	-1087.84	0.27	0.302	-0.032
4	1.526	-1009.23	0.40	0.329	0.071
5[a]	1.681	-7592.19	0.24	0.100	0.140
6	-1.004	-7564.55	0.31	0.289	0.021
7	-1.319	-7783.44	0.28	0.304	-0.024
8	1.209	-7783.96	0.13	0.127	0.003

Δ is residual, [a]data point not used in deriving the Eq.4, [b]Experimental biological activity in terms of IC_{50} against *L. mex mex*, [c]Theoretical activity of compounds in terms of IC_{50} against *L. mex mex* as scanned from Eq.4

Table 6. Anti-leishmanial activity of compounds in term of IC_{50} (μg/mL) against *L. donovani*

Compd. No	I.P.	S	IC_{50}		Δ
			Exp. [b]	Pred. [c]	
1	5.952	0.309	0.39	0.279	0.111
2	5.796	0.290	0.31	0.322	-0.012
3	5.911	0.268	0.32	0.347	-0.027
4	5.885	0.328	0.20	0.255	-0.055
5	6.709	0.298	0.24	0.241	-0.001
6	22.303	-0.498	0.29	0.334	-0.044
7	20.499	-0.379	0.33	0.281	0.049
8	5.853	0.414	0.10	0.121	-0.021

Δ is residual, [b]Experimental biological activity in terms of IC_{50} against *L. donovani*, [c]Theoretical activity of compounds in terms of IC_{50} against *L. donovani* as scanned from Eq.5

For sake of simplicity, the anti-leishmanial activity of each leishmanial species has been studied separately as described below.

Leishmania *major*

Prediction of anti-leishmanial of compounds listed in Table 1 against this strain in terms of 50% inhibition was scanned by using following equation:

$$IC_{50} = -0.046 \times \chi - 1.052 \times S + 0.799$$
$$r^2 = 0.826,\ r^2_{CV} = 0.426 \quad (1)$$

In this case quantum chemical properties listed in Table 1 were used as independent variables and the experimental IC_{50} of the compounds listed in Table 2 as dependent variables. Various mathematical models were developed in which above model was selected as reliable. In this model (Eq.1) molecular electronegativity is the first descriptor and global softness is the second descriptor. r^2 is the correlation coefficient (values higher than 0.5 have predictive power) and r^2_{CV} is the cross-validated correlation coefficient (values higher than 0.25 have predictive power). MLA is widely used method for building QSAR model. The coefficients of model have negative sign with respect to both χ and S. Thus, χ and S show inverse relationship with activity. A close examination of the table shows that there is little difference between the values of experimental and theoretical inhibitory activities as evident by their residual values (Δ).

Leishmania major (Pak)

Prediction of anti-leishmanial of compounds against this strain in terms of 50% inhibition was scanned by using following equation:

$$IC_{50} = 0.025 \times \mu + 3.187e - 0.005 \times E_T + 0.297$$
$$r^2 = 0.905,\ r^2_{CV} = 0.507 \quad (2)$$

In this case quantum chemical properties listed in Table 1 were used as independent variables and the experimental IC_{50} of the compounds listed in Table 3 as dependent variables. Various mathematical models were developed in which above model was selected as reliable. In this model (Eq.2) dipole moment is the first descriptor and total energy is the second descriptor. The coefficients of model have positive sign with respect to both μ and E_T. Thus, μ and E_T show direct relationship with activity.

Leishmania *tropica*

Prediction of anti-leishmanial of compounds against this strain in terms of 50% inhibition was scanned by using following equation:

$$IC_{50} = 0.069 \times I.P. - 0.046 \times E.A. - 0.058$$
$$r^2 = 0.980,\ r^2_{CV} = 0.932 \quad (3)$$

In this case quantum chemical properties listed in Table 1 were used as independent variables and the experimental IC_{50} of the compounds listed in Table 4 as dependent variables. Various mathematical models were developed in which above model was selected as reliable. In this model (Eq.3) ionization potential is the first descriptor and electron affinity is the second descriptor. The coefficients of model have positive sign with respect to I.P. and have negative sign with respect to E.A. Thus, I.P. shows direct relationship with activity, while E.A. shows inverse relationship with activity.

Leishmania *mex mex*

Prediction of anti-leishmanial of compounds against this strain in terms of 50% inhibition was scanned by using following equation:

$$IC_{50} = -0.070 \times \eta + 3.3092e - 0.005 \times E_T + 0.469$$
$$r^2 = 0.781,\ r^2_{CV} = 0.580 \quad (4)$$

In this case quantum chemical properties listed in Table 1 were used as independent variables and the experimental IC_{50} of the compounds listed in Table 5 as dependent variables. Various mathematical models were developed in which above model was selected as reliable. In this model (Eq.4) absolute hardness is the first descriptor and total energy is the second descriptor. The coefficients of model have negative sign with respect to η and have positive sign with respect to E_T. Thus, η shows inverse relationship with activity, while E_T shows direct relationship with activity.

Leishmania *donovani*

Prediction of anti-leishmanial of compounds against this strain in terms of 50% inhibition was scanned by using following equation:

$$IC_{50} = -0.075 \times I.P. - 1.587 \times S + 1.216$$
$$r^2 = 0.634,\ r^2_{CV} = 0.376 \quad (5)$$

In this case quantum chemical properties listed in Table 1 were used as independent variables and the experimental IC_{50} of the compounds listed in Table 6 as dependent variables. Various mathematical models were developed in which above model was selected as reliable. In this model (Eq.5) ionization potential is the first descriptor and global softness is the second descriptor. The coefficients of model have negative sign with respect to both I.P. and S. Thus, I.P. and S show inverse relationship with activity.

4. Conclusions

The reliability of correlation between experimental activities and predicted activities are $r^2 = 0.826$, $r^2_{CV} = 0.426$ (*L. major*, Table 2); $r^2 = 0.905$, $r^2_{CV} = 0.507$ (*L. major (Pak)*, Table 3); $r^2 = 0.980$, $r^2_{CV} = 0.932$ (*L. tropica*, Table 4); $r^2 = 0.781$, $r^2_{CV} = 0.580$ (*L. mex mex*, Table 5) and $r^2 = 0.634$, $r^2_{CV} = 0.376$ (*L. donovani*, Table 6), and a comparison of the experimental values and the values obtained by theoretical calculations has been presented pictorially (Figures 1-5) that shows close resemblance. The study reflected that descriptors derived from DFT methods have sufficient reliability to understand quantitative structure-activity relationship and also to predict the activity of new complex of this series from theoretically derived properties within limited time by QSAR models.

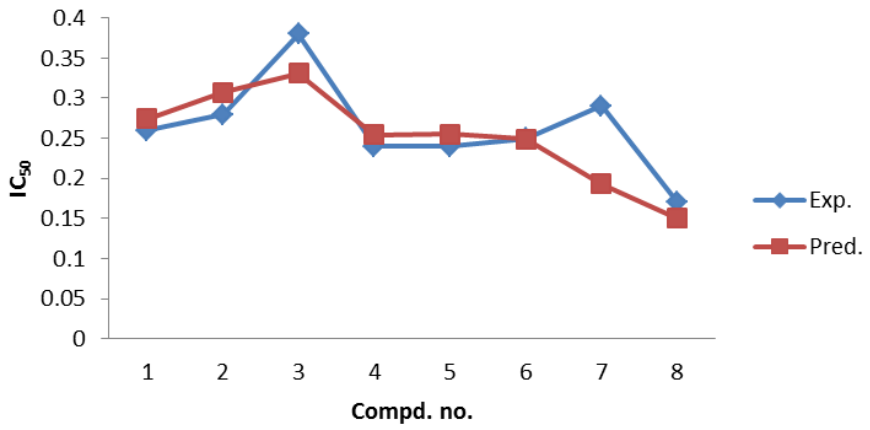


Figure 1. Graphical representation of resemblance between experimental and theoretical % inhibition of compounds against *L. major*.

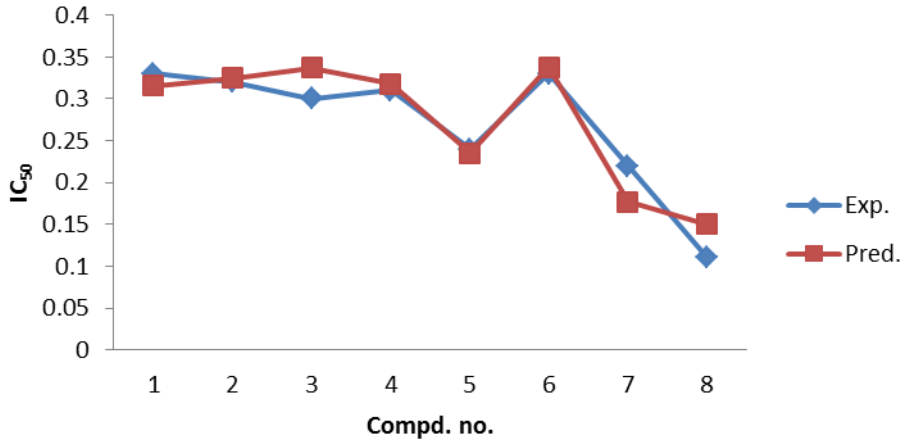


Figure 2. Graphical representation of resemblance between experimental and theoretical % inhibition of compounds against *L. major (Pak)*.

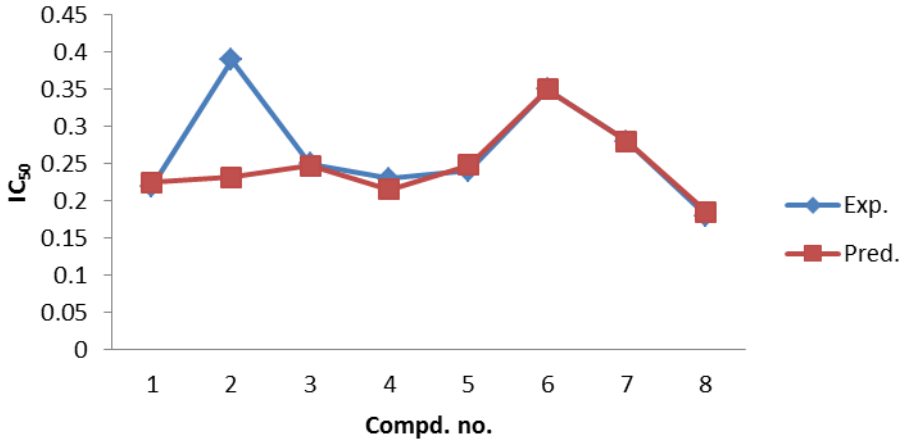


Figure 3. Graphical representation of resemblance between experimental and theoretical % inhibition of compounds against *L. tropica*.

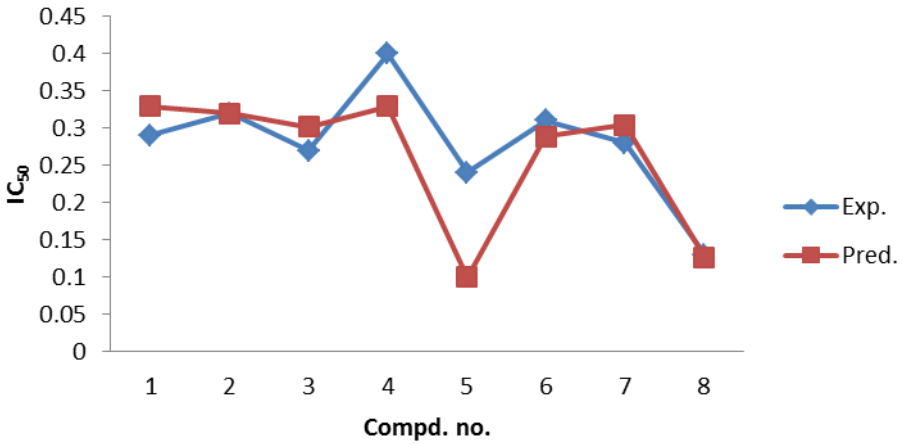


Figure 4. Graphical representation of resemblance between experimental and theoretical % inhibition of compounds against *L. mex mex*.

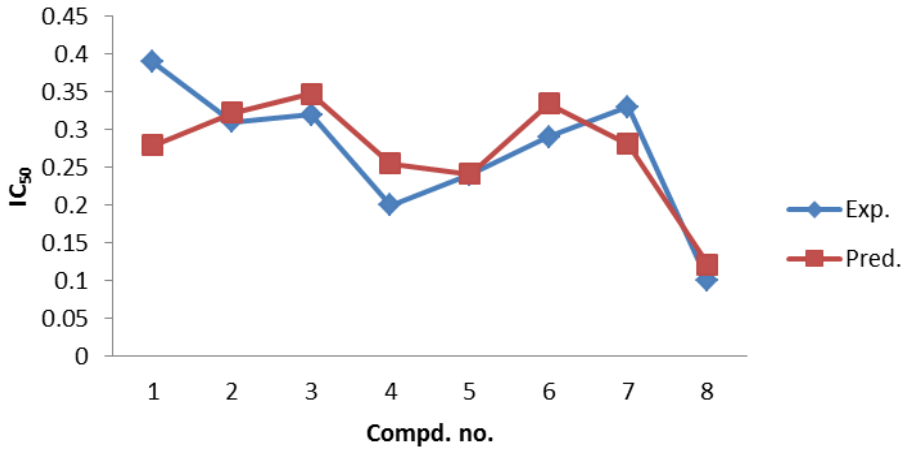


Figure 5. Graphical representation of resemblance between experimental and theoretical % inhibition of compounds against *L. donovani*.

Acknowledgement

The authors are thankful to Dr. O.P. Mishra, Ex.Principal, M.L.K. (P.G.) College, Balrampur, for providing the laboratory facilities to conduct the calculation.

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