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QSAR Studies of 1,5-di(4-amidinophenoxy)pentane and its analogues for their anti-leishmenial activity

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Abstract

Quantitative activity relationship (QSAR) has been carried out in a series of 1,5-di(4-amidino phenoxy)pentane & its analogues against Topoisomerase II inhibitory activities. The 2D QSAR studies activity is negatively influenced by the presence of linker (O or N), contribution of hydrophobicity and substitution on para position contributed in molar refractivity. The best QSAR model with good correlation coefficient (r^2 =0.712), of high statistical significance (> 99.9%) well explained the variance in activity.

Key words: QSAR, 1,5-di(4-amidinophenoxy)pentane, antileishmanial activity

Introduction

Leishmaniasis is a collection of devastating tropical diseases caused by protozoan parasites of the Leishmania genus, affecting 12 million worldwide with 2 million new incidences occurring yearly[1]**.** The current treatment have a number of negative attributes including toxicity, expense, inconvenient/prohibitive routes of administration and loss of effectiveness due to parasite resistance, New treatment must be investigated to stay ahead of these drawback especially resistance and toxicity[2-4].

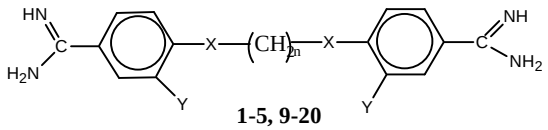
The efficacy of aromatic diamidines in treatment of protozoal disease was first recognized in the 1930s. Early clinical trials examining the activities of pentamidine, propamidine and stilbamidine against leishmaniasis[5-7].

In order to identify the influence of essential physico-chemical and structural parameter on Topoisomerase II inhibitors, QSAR studies have been carried out on a series of 36 inhibitors of Topoisomerase II using classical 2D QSAR[8-9]. To this end, we performed a quantitative structure activity relationship study on a number of 1,5-di(4-amidinophenoxy)pentane and its analogues, hope that these molecules may be further proved as powerful tool for synthesize and development of new future drug against leishmaniasis.

Materials and Methods

Experimental

The QSAR analysis was carried out on 36 compounds containing for their antileishmanial activity IC_{50} (μM) as dependent variable and different physiochemical parameters such as hydrophobic (π), electronic (σ) and molar refractivity (MR) and structural parameters like substituents x, y and some indicators (I), were used as independent variable. These independent variable were evaluated. The values for physicochemical parameters were taken from the literature.[8] The stepwise multiparameter regression (MLR) analysis by backward elimination using Systat (Version 10.2) software. Pearsion correlation matrix (Table-2) was constructed to determine the inter correlation between physico-chemical parameters used in QSAR analysis.



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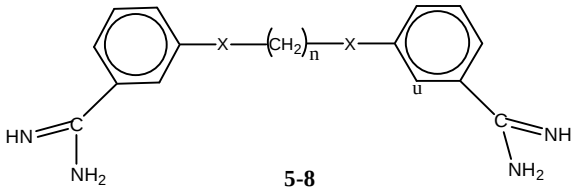

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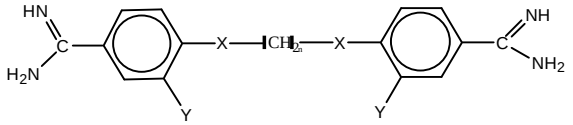

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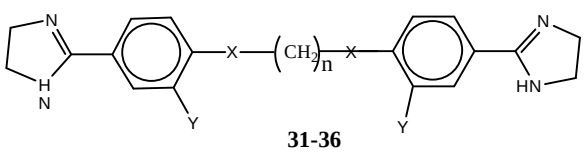

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Table-1:- topoisomerase – ii inhibitory activity (IC 50 µM) of 1,5-di(4-amidinophenoxy) pentane and its analogues along with important parameters

Comps.	Y	n	IC_{50}	pIC_{50}	pred pIC_{50}	P_4	Ion	Xmr	Xpi
1	H	2	15.822	-1.199	-0.642	1	1	1.03	0
2	H	3	0.852	0.070	-0.406	1	1	1.03	0
3	H	4	1.589	-0.201	-0.170	1	1	1.03	0
pent	H	5	0.82	0.086	0.066	1	1	1.03	0
4	H	6	0.396	0.402	0.302	1	1	1.03	0
5	H	3	6.1	-0.785	-0.818	0	1	1.03	0
6	H	4	5.435	-0.735	-0.582	0	1	1.03	0
7	H	5	2.131	-0.329	-0.346	0	1	1.03	0
8	H	6	1.034	-0.015	-0.110	0	1	1.03	0
10	NO_2	4	5.599	-0.748	-0.596	1	1	7.36	-0.28
11	NO_2	5	1.997	-0.300	-0.360	1	1	7.36	-0.28
12	NH_2	2	22.598	-1.354	-1.322	1	1	5.42	-1.23
13	NH_2	3	3.503	-0.544	-1.086	1	1	5.42	-1.23
14	NH_2	4	7.577	-0.879	-0.850	1	1	5.42	-1.23
15	OMe	3	1.785	-0.252	-0.762	1	1	7.87	-0.02
16	OMe	4	10.048	-1.002	-0.526	1	1	7.87	-0.02
17	OMe	5	3.031	-0.482	-0.290	1	1	7.87	-0.02
18	Cl	4	1.329	-0.124	-0.161	1	1	6.03	0.71
19	Cl	5	0.703	0.153	0.075	1	1	6.03	0.71
20	Br	5	0.677	0.169	-0.015	1	1	8.88	0.86
21	H	3	0.687	0.163	-0.146	1	0	1.03	0
22	H	4	0.671	0.173	0.090	1	0	1.03	0
23	H	5	0.558	0.253	0.326	1	0	1.03	0
24	H	6	0.289	0.539	0.562	1	0	1.03	0
25	NO_2	3	4.828	-0.684	-0.572	1	0	7.36	-0.28
26	NO_2	5	1.129	-0.053	-0.100	1	0	7.36	-0.28
27	NH_2	2	26.243	-1.419	-1.062	1	0	5.42	-1.23
28	NH_2	4	7.878	-0.896	-0.590	1	0	5.42	-1.23
29	NH_2	5	1.16	-0.064	-0.354	1	0	5.42	-1.23
30	NH_2	6	0.991	0.004	-0.118	1	0	5.42	-1.23
31	H	3	1.773	-0.249	-0.406	1	1	1.03	0
32	H	4	2.71	-0.433	-0.170	1	1	1.03	0
33	H	5	1.719	-0.235	0.066	1	1	1.03	0
34	OMe	3	2.258	-0.354	-0.762	1	1	7.87	-0.02
35	OMe	4	6.415	-0.807	-0.526	1	1	7.87	-0.02
36	OMe	5	4.041	-0.606	-0.290	1	1	7.87	-0.02

Table-2:- Correlation Matrix

Parameter	pIC_{50}	N	P_4	Ion	Xmr	Xpi
pIC_{50}	1					
N	0.646	1				
P_4	0.082	-0.113	1			
Ion	-0.199	-0.088	-0.219	1		
Xmr	-0.302	-0.046	0.378	0.035	1	
Xpi	0.454	0.212	-0.134	0.378	-0.129	1

Dep Var: PIC_{50} N: 36 Multiple R: 0.844 squared multiple R: 0.712
Adjusted squared multiple R: 0.664 Standard error of estimate: 0.285

Table-3:- Analysis of Variance

Effect	Coefficient	Std Error	Std Coef	Tolerance	t	P(2 Tail)
Const	-1.213	0.289	0.000		-4.193	
N	0.236	0.044	0.551	0.905	5.348	0.000
P4	0.412	0.170	0.267	0.788	2.416	0.022
ION	-0.260	0.121	-0.240	0.767	-2.148	0.040
XMR	-0.051	0.018	-0.314	0.823	-2.911	0.007
XPI	0.371	0.097	0.423	0.778	3.809	0.001

The model is of high statistical significance (>99.0%) with moderate correlation coefficient (r = 0.844). It explains 71.0 % of the variance of the Antileishmanial activity

Result and Discussion

The parameters, viz. hydrophobic (π), electronic (σ) and molar refractivity (MR) and structural parameters showed significant influence (Table 3) on Topoisomerase inhibitory activity. It has been observed that anti-leishmanial activity in this series can be explained by the spacer parameters (n) between the two aryl rings, para position of substitution and positive contribution of hydrophobicity and negative influence of molar refractivity and electronic parameters (σ) of the substituents present in the phenyl ring. The best equation, as shown below, with the above five parameters well explains the variance by about 71% and is statistically significant. This study may be useful in designing potent new chemical entities for anti-leishmanial activity.

Different combination of these parameters bearing orthogonality led to the following statistically significant equations.

$$pIC50= -1.213+0.236*N+0.412*P_4-0.26*Ion-0.051*Xmr+0.371*Xpi \quad \text{…….(Eq. 1)}$$

$$N = 36,\ r = 0.844,\ r^2 = 0.712,\ r2adj = 0.664,\ s = 0.285,\ F = 14.84$$

Where,

Xpi = Value of the hydrophobic substituents constant at position Y,

n = Spacer parameter,

P_4 = 1 for the presence of structure function C (=N) N at para position of the phenyl ring,

Ion = 1 and 0 for the presence of O and N respectively in the spacer,

Xmr = Value of the molar refractivity at position Y.

Conclusion

Among the equation 1, to be the best model with correlation coefficient (0.844) explaining 71% variance in activity. The low standard error of estimate (0.285), a significant F value and one third value of coefficient suggest that the model is statistically significant. The data showed overall statistical significance >99.9 % with F = 14.84 against tabulated value for Fischer's test as 99.9% significance. The above model eqn.1, also predicted well the inhibitory activity of the molecules of the test set as shown in fig.1, were the comparable correlation coefficient value (r = 0.844) was observed.

The present study describes important structural selection of proper substituents at benzene ring should be of the great concern while designing a potent Topoisomerase-II inhibitor. The selection should be done on the basis of their F values.The position of ring substitution have an important influence on the overall shape of the molecule for proper interaction at the active site. The substituents at amidino group should be less bulkier or it is better to keep amidino group free from any substitution. The conformational restriction of molecule enhances the Topoisomerase-II inhibitory activity. The hydrophobicity is equal considerable for *in vitro* and *in vivo* activity and toxicity to design and development of future antileishmanial agents.

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References

[1] http:/www.who.int
[2] S.L. Craft, M.P. Barrett, J.A. Urbina, *Trends Parasitol*. 21, 508-512 (**2005**)
[3] M. Grogl, A.M.J. Oduola, L.D.C. Cordero and D.E. Kyle, *Exp. Parasitol*. 69,78-90 (**1989**)
[4] M. Sands, M.A. Kron and R.B. Brown, *REV. Inect. Dis.* 7, 625 -634 (**2002**)
[5] Bell, et al. *Antimicobial. Agents Chemother*., 1381-1386 (**1990**)
[6] L.E. Napler and P.C. Sen Gupta, *Indian Med. Gaz*.,78, 177-183 (**1943**)
[7] R. Krik and M.H. Sati, *Ann. Trop. Med. Pracitol.*, 34, 181-197 (**1940**)
[8] R.R. Tidwell, S.G. Kilgore, K.A..Ohemeng, J.D. Geratz, M.Cory and J.E. Hall, *J. Med. Chem*., 33, 1252-1257 (**1990**)
[9] T. Ertan et al., *Eur. J. Med. Chem*., 20, 1-10 (**2008**)
[10] Systat Version 10.2, SPSS, Inc, 444 North Michighan Avenue, Chicago, IL, USA.