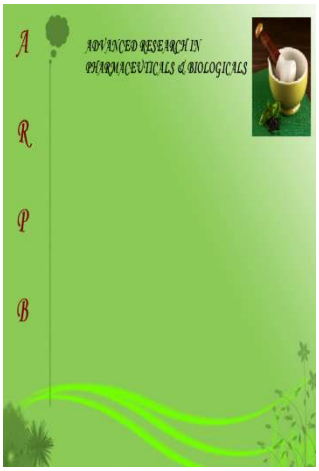
Advance Research in Pharmaceuticals and Biologicals
(A peer reviewed International journal for Pharmaceutical and allied research)

Vol -2 (1)
JAN- MARCH 2012



Received on 01/02/2012
Revised on 16/03/2012
Accepted on 22/03/2012

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2D QSAR ANALYSIS Of INOSITOL DERIVATIVES AS INOSITOL MONOPHOSPHATASE INHIBITORS

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ABSTRACT:

Inositol monophosphate plays an important role in treatment of bipolar disorders. Analogues with deleted or substituted 6-OH group and 1-phosphate group produce good inhibitors of Inositol Monophosphatase (IMPase) enzyme. Twenty two analogues displaying variable inhibition of IMPase were subjected to quantitative structure activity relationship analysis. Various thermodynamic, electronic and steric parameters were calculated using Chem 3D package of molecular modeling Software Chemoffice 8.0. Stepwise multiple linear regression analysis was performed to derive QSAR model which were further evaluated for stastical significance and prediction power by internal and external validation. The resulting model exhibited good q2 and r2 values up to 0.943 and 0.985 respectively. The QSAR model indicates that thermodynamic descriptors play an important role in the IMPase inhibitors activity. The result of the present study may be useful in the designing of more potent 6 aminoalkyl substituted inositol derivative as IMPase enzyme inhibitors.

Keywords: Inositol monophosphate, Inhibitors, QSAR, Validation, IMPase enzyme.

INTRODUCTION

Manic depressive illness is a serious psychiatric disorder due to abrupt phosphatidyl inositol pathway. In this pathway Inositol monophosphatase (IMPase) is a key enzyme which provides free Inositol for the biosynthesis of second messenger precursor phosphatidyl Inositol 4-5 bisphosphate. Hydrolysis of this precursor gives rise to second messengers which are responsible for intracellular calcium release through protein kinase C activity. Over activity of this cellular response mechanism leads to violent mood swings characteristics of manic depressive illness. Catalytic analysis explain that in hydrolysis process functional groups present at 1st and 6th position of Inositol monophosphate ring play critical role in binding with enzyme. Hence deletion or modifying groups at these positions may impart inhibitory activity to molecule[1,2,3]. QSAR methods can provide mechanistic insights to develop the properties of interest in molecules and help to to predict the activity of novel molecules prior to their synthesis.

Here an attempt has been made to describe the QSAR analysis of Inositol derivative to study and deduce a establish a reliable structure property relationship to derive an Insilico model correlation between structure and inhibitory activity of these derivatives. Once a correlation between structure and activity/property is found, any number of compounds, including those not synthesized yet, can readily be screened Insilco for selection of structure with desired properties[4,5].

MATERIALS AND METHODS

A set of 22 analogues of cyclohexane-1, 2, 3, 4, 5, 6-hexol from reported work were shown in Table-1 and fig-1[1,2] [Org. Biomol. Chem (2004) 2, 671-688]. The biological activity values [IC_{50} (µM)] reported in the literature were converted to molar units and then further to –log scale and subsequently used as the response variable for the QSAR analysis. The log values of IC_{50} along with the structure of compounds in the series are presented in Table 1.

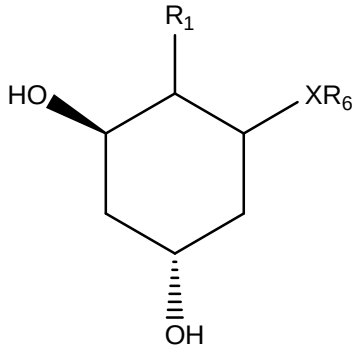

Fig 1. General structure of Inositol

Table 1. Structures and biological activity data of compounds in the series

Compound No.	**R_1**	**XR_6**	**-log IC_{50}**
1	OH	$H_2N(CH_2)_2N(CH_2)_4C_6H_5$	3.954
2	OH	$NH(CH_2)_5CH_3$	2.699
3	OH	$NH(CH_2)_2C_6H_5$	3.778
4	OH	$O(CH_2)_2CH_3$	5.176
5	OH	$O(CH_2)_5CH_3$	4.000
6	OH	$O(CH_2)_2NH_2$	3.699
7	OH	$O(CH_2)_3NH_2$	4.000
8	OH	NH_2	4.699
9	OH	$NHCH_2CH_3$	4.699
10	OH	$NH(CH_2)_3CH_3$	2.699
11	OH	$NH(CH_2)_7CH_3$	3.602
12	OH	$NH(CH_2)_4C_6H_5$	4.000
13	OH	$O(CH_2)_4O$-[(2-OH)C_6H_4]	3.602
14	$OPO(OH)CH_3$	OH	2.415
15	$OPO(OH)CH_3$	$NHCH_3$	3.903
16	$OPO(OH)CH_3$	$NH(CH_2)_5CH_3$	3.114
17	$OPO(OH)CH_3$	$NH(CH_2)_2C_6H_5$	4.732
18	$OPO(OH)_2$	--	0.477
19	$OPO(OH)_2$	OH	0.845
20	$OCH_2(PO(OH)_2)_2$	--	1.079
21	$OCH(PO(OH)_2)_2CH_3$	--	0.602
22	$OPO(OH)_2$	$O(CH_2)_4$[2-OH]C_6H_5	0.04

The QSAR analysis of an Inositol derivatives has been carried out using CS Chemoffice software 2004 version 8.0 (Cambridge Soft)[3,6]. All structure of Inositol analogues were constructed using Chem draw and transferred to chem 3D to convert them into 3D structures. The energy minimization of the molecules was done using MM2 force field followed by semi empirical AM1 (Austin model) Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001 kcal/Mol respectively for calculating partial atomic charges and electron density on various atoms. The low energy conformers obtained were used for the calculation of the ChemSAR

descriptors. The ChemSAR descriptors include physicochemical, thermodynamic, electronic and spatial descriptors available in the 'Analyze' option of the Chem3D package. All calculated descriptors are listed in Table-2. These descriptors were considered as independent variable and biological activity as dependent variable. The descriptors calculated for the present study accounts two important properties of the molecules: thermodynamic and steric, as they present the possible molecular interaction between the receptor and inositol derivatives[7,8].

Table 2. Descriptors calculated for the QSAR study

S. No.	Descriptor	Type	S. No.	Descriptor	Type
1	Henry's Law Constant (H)	T	18	Molecular Topological Index (TIndx)	S
2	Molar Refractivity (MR)	T	19	Radius (Rad)	S
3	Partition Coefficient (Octanol/Water)	T	20	Shape Attribute (ShpA)	S
4	Non-1,4 VDW Energy (Ev)	T	21	Shape Coefficient (ShpC)	S
5	VDW 1,4 Energy (E14)	T	22	Sum Of Degrees (SDeg)	S
6	Stretch Energy (Es)	T	23	Sum Of Valence Degrees (SVDe)	S
7	Stretch-Bend Energy (Esb)	T	24	Connolly Molecular Area (MS)	S
8	Torsion Energy (Et)	T	25	Connolly Solvent-Excluded Volume (SEV)	S
9	TotalEnergy (E)	T	26	Molecular Weight (MW)	S
10	Balaban Index (BIndx)	T	27	Ovality	S
11	Bend Energy (Eb)	T	28	Principal Moment of Inertia – X (PMIX)	S
12	Dipole-Dipole Energy (Ed)	T	29	Principal Moment of Inertia – Y (PMIY)	S
13	HOMOEnergy (Homo)	E	30	Principal Moment of Inertia – Z (PMIZ)	S
14	LUMOEnergy (Lumo)	E	31	Cluster Count (ClsC)	S
15	RepulsionEnergy (NRE)	E	32	Diameter (Diam)	S
16	DipoleLength (DPLL)	E	33	Total Connectivity (TCon)	S
17	Electronic Energy (ElcE)	E	34	Total Valence Connectivity (TVCon)	S

T= Thermodynamic, E= Electronic, S= Steric

Sequential multiple regression analysis was performed using in-house program VALSTAT in order to generate QSAR models[4]. This program search for all permutation and combination sequentially for the given data set and provides best model based on squared correlation coefficient (r^2). Other important parameters like correlation coefficient (r), standard deviation (std), and Fisher ratio values (F-values) for each parameter in the QSAR. Quality of the each model was estimated from cross-validated squared correlation coefficient (q^2), Standard error of predictivity (S_{DEP}), chance value and

predictive residual sum of error (S_{PRESS}). The descriptors selected for inhibitory activity of inositol derivatives are summarized in Table 3.

Table 3. Calculated values of descriptors for given series of compounds

Comp. No.	Stretch energy(Es)	Total energy (E)	VDW 1,4 Energy (E14)
1	3.84939	41.325	20.3441
2	2.56473	31.5323	14.036
3	2.39079	27.1241	14.3423
4	2.49171	29.4031	12.1179
5	2.72752	32.7143	15.5654
6	3.22999	29.3546	11.0676
7	3.18712	30.6514	12.0825
8	2.21756	20.3038	7.18124
9	2.1594	27.1121	9.44711
10	2.3993	29.3299	11.7459
11	2.7259	33.7536	16.3301
12	2.45412	28.9521	16.3046
13	3.08901	43.8209	18.106
14	34.0164	83.0667	9.45441
15	68.2614	192.446	11.7768
16	70.7811	202.7	17.2363
17	73.1719	206.066	16.1507
18	209.304	257.05	7.04373
19	205.693	251.808	7.04306
20	1.18995	-10.636	9.78053
21	1.6811	-1.1338	9.67326
22	1.44373	-13.679	8.05828

RESULTS AND DISCUSSION

Data set was subjected to stepwise multiple linear regression analysis, in order to develop 2D-QSAR between biological activity as dependent variable and substituent constants as independent variables.

Among the many correlations generated, only one best triparametric model was selected on the basis of statistical significance. The best model obtained is given below along with their statistical measures.

pIC_{50} = [-5.21769(± 0.663533)] +Es [0.00848718(± 0.00285827)] +E14 [-0.247485(± 0.0404395)] +E [-0.00153165(± 0.00014666)]

Contribution of parameters to model is Es: E14: E:1:14.8514:25.7519 n=14, r=0.992512, r^2=0.985079, variance=0.0550236, std= 0.234571, F=220.07, FIT=3423.31

The equation indicates that thermodynamic parameter; stretch energy contributes positively and vander waal energy contributes negatively towards the activity. Model has good correlation coefficient between biological activity and parameters (r = 0.993) and square correlation coefficient r^2 = 0.985 with a low standard deviation Std = 0.235. These values demonstrate accuracy of model. The robustness of the model was shown by the magnitude of the bootstrapping r^2 (r^2 = 0.985), which was near to conventional r^2. The internal predictivity of model was also good (q^2 = 0.943). The low values of S_{PRESS} and S_{DEP} also supported good predictivity of relation. The observed, calculated and predicted activity (pIC_{50}) for training set model 1 is presented in **Table 4**.

Table 4. Training set activity

Comp. No.	Observed values	Predicted values	Calculated values
1	4.00000	4.25478	4.2194
2	3.60206	3.56639	3.57166
3	1.07918	1.11592	1.10620
4	3.77815	3.76530	3.76672
5	0.47712	1.55676	0.58843
6	3.11394	2.66055	2.76764
7	4.00000	3.74500	3.77437
8	1.09691	0.69409	1.01592
9	2.41497	2.43979	2.43578
10	3.60206	4.15838	4.08399
11	0.64345	0.52272	0.57121
12	3.69897	3.72308	3.71858
13	3.95424	3.94571	3.94790
14	4.00000	3.68348	3.73130

The **figure 2** shows plot of observed versus calculated pIC_{50} values for training set compounds and **figure 3** is plot of observed versus predicted pIC_{50} values for same set.

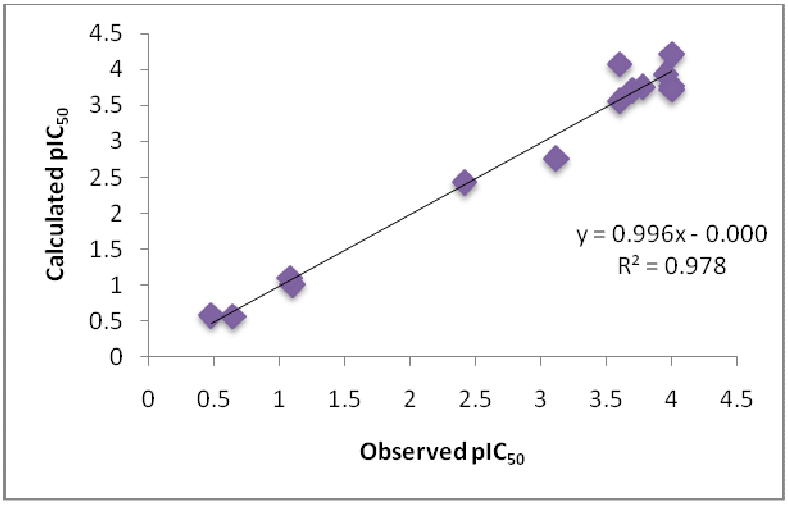

Fig. 2. Observed and calculated activities of Training set compounds for model (Scattered plot)

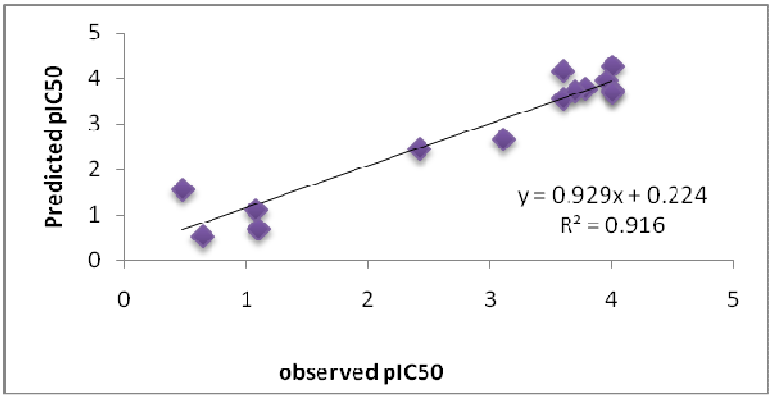

Fig. 3. Observed and predicted activities of Training set compounds for model (Scattered plot)

Figure 4 shows discrete plot between predicted and observed activities. The predicted activities for test set molecules are presented in **Table 5**.

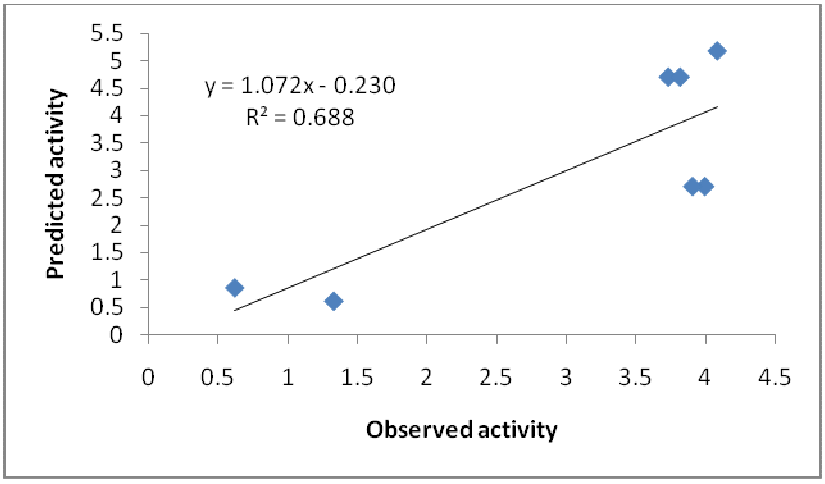

Fig. 4. Observed and Predicted activities of test set compounds for model 1 (Scattered plot)

Table 5. Test set activity for Model

Compound	pIC50 exp	Predicted Activities
1	3.99497	2.69897
2	4.08424	5.17609
3	3.73293	4.69897
4	3.90698	2.69897
5	3.81746	4.69897
6	0.618846	0.8451
7	1.3294	0.60206

The Van der waals energy is a thermodynamics parameter which can be separated by exactly 3 chemical bonds, related to the structure of the molecule itself. The coefficient of the descriptor E14 bears a negative sign which indicates that decrease in Van der Waal energy between atoms separated by three chemical bonds may increase inhibitory activity. Analysis of descriptor table shows that substituent like alkyl amine may increase the inhibitory activity and substitution with aryl amine or with any aryl and bulky chain group may decrease the inhibitory activity of inositol derivative at 6^{th} position.

Stretch energy, a thermodynamic parameter, deals with conformational flexibility of the molecule. The descriptor Es bears positive sign, indicating, substituent that increase the flexibility of inositol will enhance the inhibitory activity. Negative contribution of total energy (electron density in the defined as the sum of pair wise interaction energy terms for atoms enzyme cavity) to the biological activity indicates that minimizing the total energy of the molecule increase the activity[9,10].

CONCLUSION

QSAR analysis was performed on the series of inositol derivatives as IMPase inhibitory activity using molecular modeling program Chem Office ultra 8.0. Statistical significant QSAR model analysis suggested that thermodynamic descriptors like Van der waal energy and stretch energy play important role(s) in biological activity. Analysis of calculated descriptors values indicated that deletion of 6-OH group or substitution with aliphatic amine or any other bioisostere may improve the inhibitory activity of compound. These findings are useful in designing more potent 6- amino alkyl substituted inositol derivatives as IMPase inhibitors.

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