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QSAR Study of Calanolides against HIV-1(RP).

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ABSTRACT

We performed QSAR studies upon a series of 52 calanolide analogues, inhibitors of HIV-1 (RP). Using QSAR, that implies analysis of correlation & multi-linear regression; a significant collection of descriptors (Steric, thermodynamic and electronic) was used. The best QSAR model with good correlation coefficient (R = 0.806) of high statistical significance (>99.9 %), well explained the variance in activity. QSAR study reveal that structural features like circular molecular structure, substitution on A, B & C rings in trendy positions with lesser steric hindrance / molar volume, substituted with less electron attracting group (e.g. on position C-12) and with lesser non-1, 4 Vander Wall's forces will be helpful to deign much potent calanolide against HIV-1 (RP).

Keywords: QSAR, HIV-1(RP), Calanolides

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INTRODUCTION

Most people are familiar with divesting effects of HIV; the human immunodeficiency virus. The virus, which is transmitted by blood to blood contact, may produce no symptoms for years but typically within 10 to 15 years destroy the T4-lymphocytes, the cell that play a key role on the immune system and causes a fatal disease i.e. AIDS (acquired immunodeficiency syndrome)[1]. The resulting depletion in the level of essential immune cells leave patients vulnerable to opportunistic infection that would not normally harm a healthy person[2].

Reverse transcriptase is the key enzyme of HIV, catalysing the RNA-depending and DNA-dependant synthesis of double strand viral DNA [3]. Reverse transcriptase is an attractive target for the drug therapy of AIDS, because it is essential for HIV replication and it is not required for normal host cell replication[4].

In 1992, Kashman reported that (+) Calanolide A (Fig 1) isolated from tropical rain forest tree 'Calophyllum lanigerum'[5], represented a novel subclass of HIV-1 specific non-nucleoside reverse transcriptase inhibitor [6]. (+) Calanolide A is the first natural product identified as active against HIV-1 and has recently been investigated continuously in phase II / III clinical trials. However no final report has been evaluated since the beginning of clinical trials in 1997. The low inhibitory potency of (+) Calanolide A may be the reason accounting for such long term clinical studies.

In an attempt to understand the inhibition mechanism and obtain the compounds with high inhibitory potency, a series of calanolide analogues has been synthesized and evaluated in inhibitory activities of HIV-1 recently, and the SAR of these compounds have been discussed as well. For example, Zembower, D. E. [7] reported that the substituted group on C-10 was necessary for the anti HIV-1 activity. Galinis, G. L. [8] indicated that a heteroatom was required at C-12 probably acts as a hydrogen bond acceptor and the heteroatom must lie above the plane of the dihydropyran ring. Ma, T. [9] pointed out that the atom O_{13} was important for the anti HIV-1 activity and proper substituted group on C-4 and C-10 may increase the anti HIV-1 activity. QUI Kai-Xiong [10] concluded that calanolide analogues bearing appropriate substituted group on C-10 and appropriate distance between atoms O_{13} and X_{14} exhibit higher inhibitory for HIV-1.

However, to the best of our knowledge, QSAR studies on calanolide analogues are rare and never included so much compounds as include with this study. QSAR, which is quantitatively correlating the biological activity with the structures of compounds, has been extensively used for the studies of biological interaction mechanism and drug design [11, 12]. Recently, a number of quantum chemical descriptors calculated by quantum chemistry

calculations (such as charge, molecular orbital energy, dipole moments etc.) and a number of molecular property descriptors calculated by molecular mechanics calculations (for example steric, hydrophobic coefficients etc.) have been successfully applied to establish QSAR models for predicting the activities of compounds [13-16].

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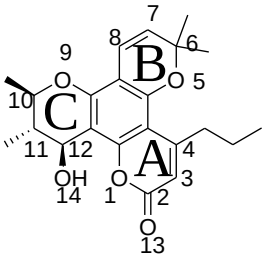
EXPERIMENTAL

Material and Methods

Set of molecules under study & corresponding IC_{50} values against HIV-1 (RP) are taken from reference [17]. The structure for all compounds is shown as figure 1 – 52. The biological activity data used in this study are *IC50*, the half maximal inhibitory concentration. Corresponding value of IC_{50} for all compounds are listed in table 1.

All computation in the present study were performed on P IV workstation. The molecular structure of training set were sketched using Chem Draw Ultra module of CS Chem Office 2004 molecular modeling software ver. 8.0, supplied by Cambridge Software company[18]. The Sketched structure were exported to Chem3D Ultra module in order to create its 3D model. Each model was cleaned up and energy minimization was performed by using semiemperical AM1 (Austin Model) Hamiltonian Method, closed shell restricted wave function available in MOPAC module by fixing Root Mean Square Gradient (RMS) to 0.1 Kcal/molÅ.



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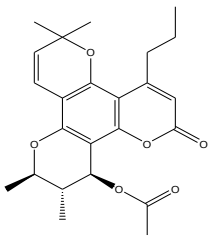

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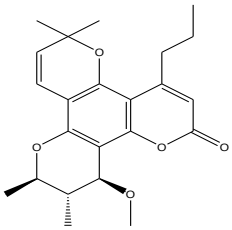

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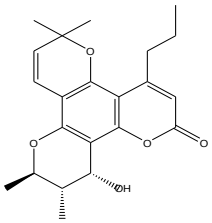

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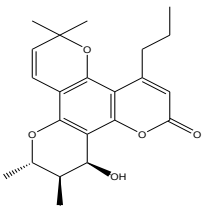

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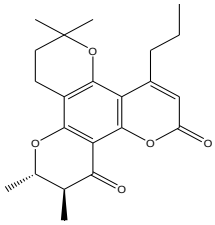

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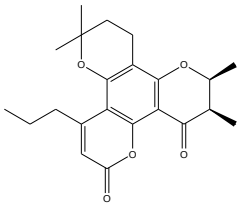

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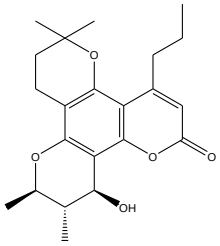

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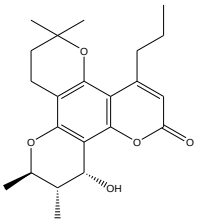

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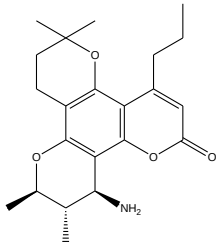

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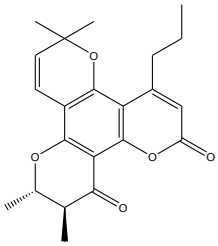

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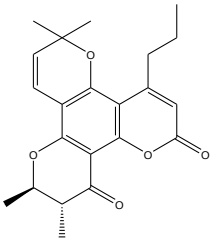

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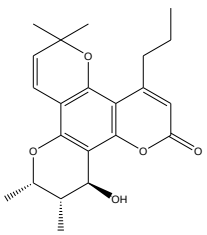

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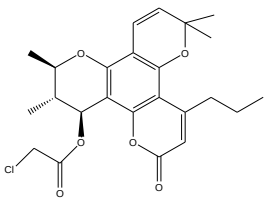

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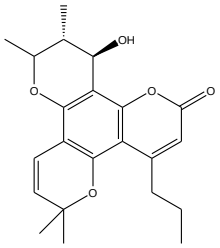

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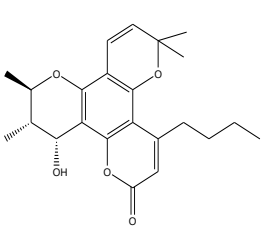

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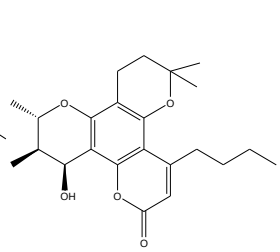

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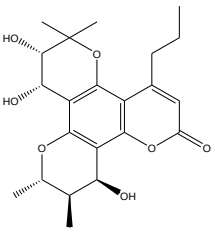

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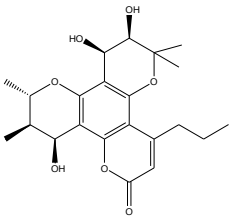

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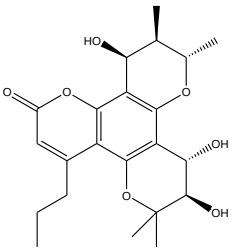

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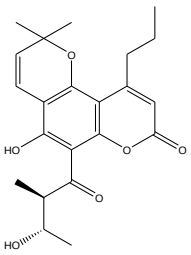

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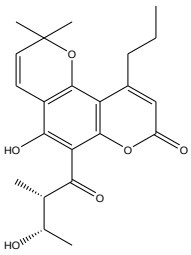

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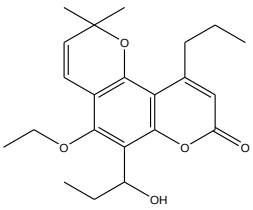

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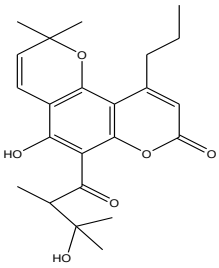

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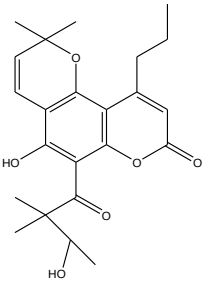

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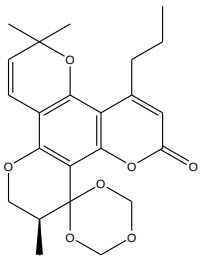

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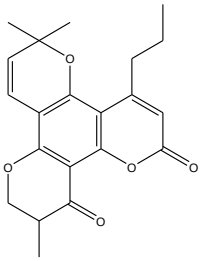

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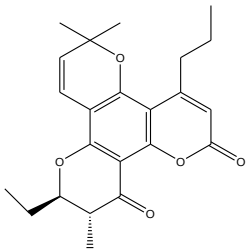

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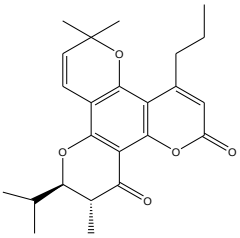

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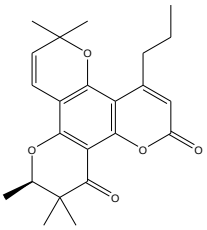

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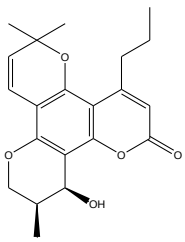

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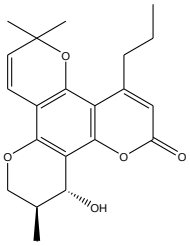

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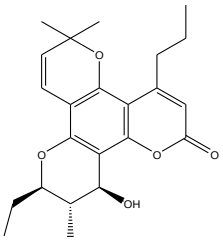

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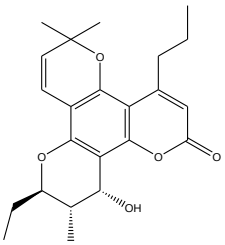

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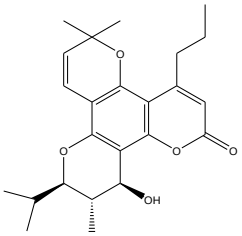

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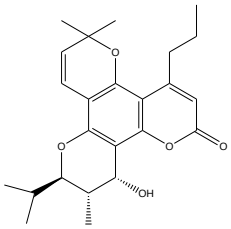

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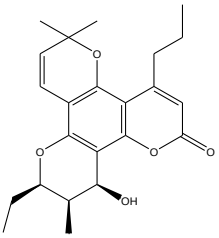

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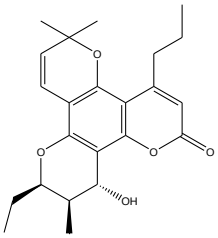

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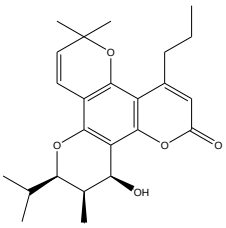

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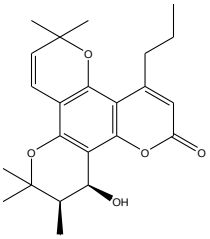

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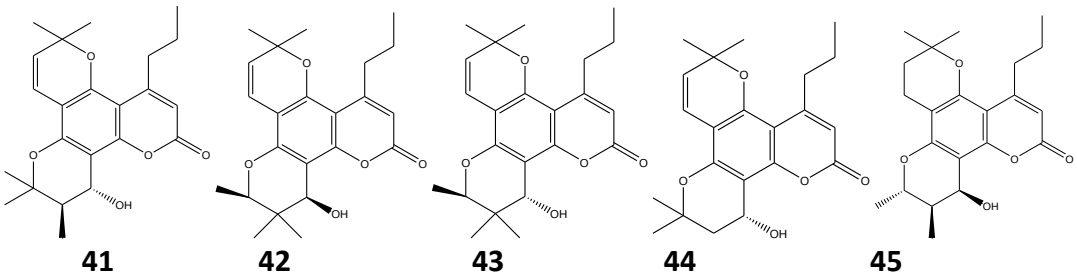

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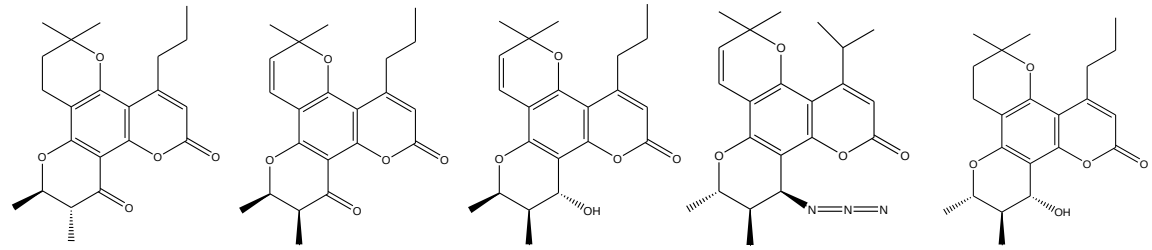

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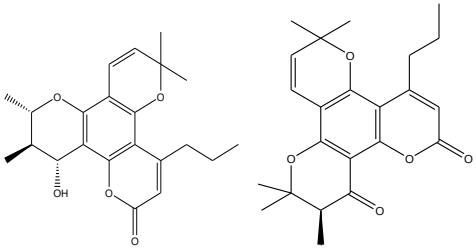

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The use of theoretical descriptors is advantageous as they are free of the uncertainty of experimental measurements and can be calculated for compounds not yet synthesized.

Multivariate Regression Analysis

The regression analysis were carried out using NCSS 2007[19]. The statistical quality of equation was judged by the parameters like correlation coefficient, standard deviation, standard error of estimation and F value. The use of more than one variable in multivariate equation was justified by autocorrelation study.

Predicted Residual Analysis

QSAR model was cross validated by predicated residual leave one out (LOO) analysis. Each compound of the list is deleted once from the data set and corresponding regression equation is found out to calculate predicted activity value and predicted residual of deleted compound. The predicted residual sum of squares provides the relation between the observed and calculated value. The stability and predictive capacity of the equation were cross validated from PRESS statistics.

Descriptors like standard gibbs free energy (G), 1,4 VDW Energy (Ev), molecular topological index (TIndx), shape coefficient (ShpC) and molecular refractivity (MR), was

expressing good accountability for anti HIV activity. The respective values for descriptors obtained from Chem3D Ultra are given in table 1 for different calanolides (Fig. 1–52).

Table 1. Descriptors value and calculated Biological Activity

S. no.	-log IC50 (BAobs)	G (KJ/mol)	Ev (Kcal/mol)	MIE	SC	MR	BAcalc (Eq. 3)	Residual (Eq. 3)
1	5.152	-213.57	1.342	11354	1	10.272	4.981	-0.171
2	4.886	-370.28	6.281	14952	1	11.235	4.715	-0.171
3*	4.678	-173.33	5.808	12526	1	10.735	5.050	0.372
4	4.914	-213.57	1.946	11354	1	10.272	4.981	0.067
5	5.229	-213.57	2.271	11354	1	10.272	4.981	-0.248
6*	5.102	-221.59	3.977	11354	1	10.18	4.968	-0.134
7	4.854	-221.59	4.621	11354	1	10.18	4.968	0.114
8	5.284	-243.53	1.208	11354	1	10.297	4.930	-0.354
9*	4.967	-243.53	1.78	11354	1	10.297	4.930	-0.037
10	5.237	-40.26	2.972	11354	1	10.513	5.276	0.039
11	5.071	-191.63	4.264	11354	1	10.154	5.019	-0.052
12*	5.032	-191.63	5.449	11354	1	10.154	5.019	-0.013
13	4.896	-213.57	1.477	11354	1	10.272	4.981	0.085
14	4.745	-382.21	4.661	15941	0.833	11.726	4.501	-0.244
15*	5.039	-213.57	1.604	11354	1	10.272	4.981	-0.058
16	4.81	-205.15	1.725	12804	0.833	10.735	4.802	-0.008
17	4.983	-235.11	1.907	12804	0.833	10.761	4.752	-0.231
18*	3.866	-532.59	-0.846	12934	0.667	10.603	4.054	0.188
19	4.053	-532.59	1.032	12934	0.667	10.603	4.054	0.001
20	3.932	-532.59	0.163	12934	0.667	10.603	4.054	0.122
21*	4.62	-439.49	1.518	12656	1	10.485	4.597	-0.023
22	4.658	-439.49	-0.614	12656	1	10.485	4.597	-0.061
23	4.796	-268.12	4.785	11554	1	10.449	4.889	0.093
24*	4.569	-425.77	0.257	13964	1	10.948	4.621	0.052
25	4.432	-425.77	-0.602	13796	1	10.948	4.621	0.189
26	5.201	-280.21	9.119	14264	1	10.864	4.868	-0.333
27*	5.167	-192.34	4.898	10238	0.8	9.69	4.786	-0.381
28	4.745	-183.21	6.011	12676	0.833	10.618	4.840	0.095
29	4.678	-177.23	5.261	14014	0.833	11.082	4.850	0.172
30*	4.721	-188.7	5.687	12464	1	10.618	5.024	0.303
31	4.658	-214.28	2.416	10238	0.8	9.808	4.749	0.091
32	4.658	-214.28	1.192	10238	0.8	9.808	4.749	0.091
33*	4.745	-205.15	1.358	12676	0.833	10.735	4.802	0.057

34	4.854	-205.15	2.089	12676	0.833	10.735	4.802	-0.052
35	5.187	-199.17	3.702	14014	0.833	11.199	4.813	-0.374
36*	5.187	-199.17	3.735	14014	0.833	11.199	4.813	-0.374
37	4.921	-205.15	3.007	12676	0.833	10.735	4.802	-0.119
38	4.678	-205.15	0.347	12676	0.833	10.735	4.802	0.124
39*	5.161	-199.17	3.238	14014	0.833	11.199	4.813	-0.348
40	4.678	-210.64	3.605	12486	1	10.735	4.986	0.308
41	4.678	-210.64	3.381	12486	1	10.735	4.986	0.308
42*	4.699	-210.64	3.506	12464	1	10.735	4.986	0.287
43	4.824	-210.64	2.933	12464	1	10.735	4.986	0.162
44	4.959	-211.35	1.004	11368	1	10.272	4.985	0.026
45*	5.086	-243.53	2.138	11354	1	10.297	4.930	-0.156
46	4.959	-221.59	5.235	11354	1	10.18	4.968	0.009
47	4.921	-191.63	4.654	11354	1	10.154	5.019	0.098
48*	4.699	-213.57	1.293	11354	1	10.272	4.981	0.282
49	5.523	57.27	1.556	11457	1	10.487	5.442	-0.081
50*	4.419	-243.53	1.915	11354	1	10.297	4.930	0.511
51*	5.491	-213.57	2.15	11354	1	10.272	4.981	-0.510
52*	5.620	-188.7	2.15	11354	1	10.272	4.981	-0.510

*molecules was taken as test set. #Biological Activity = -log IC_{50}

RESULTS AND DISCUSSION

Biological Activity (anti HIV-activity) data and various physicochemical parameter were taken as dependent and independent variables, respectively. Correlations were established using sequential multiple regression analysis. The descriptors selected for modelling anti HIV activity of calanolides are written in table 1. The best model obtained during the study is given below.

Model I

BA =0.0016(± 0.0006) G + 0.0171(± 0.0285) Ev + 1.1311(±0.6325) SC + 4.1171(± 0.6418)
(Structure No. 8 & 35, 50, 51 & 52 are outlier)
N=31, R=0.872, R^2=0.7609, R^2adj=0.7343, s=0.162, F=28.643, p<0.0001, Q^2=0.681, Spress =0.187, SDEP=0.177, C. V. = 3.4436.

Model II

BA=0.0018(±0.0006) G + 1.0790(±0.6462) SC + 0.1247(±0.1602) MR + 2.9356(±1.8375)
(Structure 8, 50, 51 & 52 are outlier)
N= 32, R=0.857, R^2=0.7374, R^2adj=0.7063, s=0.171, F=25.852, p<0.0001, Q^2=0.669, Spress =0.191, SDEP=0.182, C.V.=3.5348.

Model III

BA= 0.0017 (± 0.0006) G + 1.1574 (± 0.6842) SC + 4.1871 (± 0.7041)
N= 33, R=0.830, R^2=0.6897, R^2adj=0.669, s=0.184, F=33.343, p<0.0001, Q^2=0.637, Spress =0.199, SDEP=0.193, C.V.=3.7972.

Table 2 Pearson's Inter-correlation Matrix

	BA	G	Ev	TIndx	SC	MR
BA	1					
G	0.552	1				
Ev	0.094	0.380	1			
TIndx	-0.219	-0.416	0.108	1		
SC	0.604	0.308	0.195	-0.128	1	
MR	-0.158	-0.188	0.110	0.94	-0.071	1

In above triparametric model, higher value for squared correlation coefficient (R^2) and low value for standard error of estimates (SSE) with minimum possible descriptor makes this most acceptable. The F-value is found statistically significant at 99.9% ($F_{3,\ 32\alpha 0.001}$ = 5.53) [21]. The lower value of the coefficient of variation (C.V.), smaller the residuals relative to the predicted value. The ratio of PRESS vs. SSY is lower than 1, points out that the model predicts better chance and can be considered statistically significant. The value for Adj R^2 and R^2_{CV} >0.5 is considered as a proof of high predictive ability of the model. VIF value <3 also explains the best acceptability of model in terms of multicolinearity.

Model is the best equation found to explain the HIV-1 (RP) inhibitory activity for all 52 compounds. The equation is with Steric parameter (Molecular topological Index and Shape Coefficient) and thermodynamic parameter (Non 1,4 VDW Energy, standard Gibbs free energy & Molar refractivity). Highest value for residual (difference between BA_{obs} and BA_{calc}) is for compound no. 35.

Steric parameter

ShpC is a indicative of circular structure of moiety in 2D. Positive ShpC is indicating a restricted structural skeleton. A, B & C closed ring around a benzene ring approaches to a circular molecular structure. TIndx depends on distance metrics of compound. On addition of any new ligand or ligand modification by adding some atom / atoms, the mathematical value for TIndx is always improving.

Thermodynamic parameter

Molar refractivity (MR) is related with lipophilicity, molar volume and steric bulk. Larger the polar part in the molecule, larger is the Molar refractivity[20]. Negative molar refractivity indicates that the increase of size and polarisability of the molecule suppress the HIV-1 (RF) activity.

Standard Gibbs free energy (G) is a thermodynamic parameter, contribute positively to the activity. The reaction free energy (Gibbs function) is the magnitude that describe the spontaneity of thermic process. That is the tendency of molecular system to associate and /

or to react (Gibb's 1875). Free energy property is composed by an enthalpic and entropic contribution. Particularly, the entropic term is difficult to handle in QSAR. The gibb's free energy (ΔG), for the structures was reported in KJ/mol at 1 atm and 298.15K. Free energy perturbations techniques are used to determine relative binding energy of the molecules.

$\Delta G_{binding} = -RT \ln Ka$

Non 1, 4 VDW Energy (Ev) is the energy for the through-space interaction between pair of atoms that are separated by more than three atoms. Positive contribution of Ev suggests the ability of calanolides to interact with receptor with non-1, 4 VDW forces during drug receptor interaction. This indicates the presence of π - π interaction between molecule and active site residue.

CONCLUSION

Through the iterative QSAR, it was possible to extract a simple and highly informative model, having a high degree of predictability against HIV I (RP) of calanolides. The correlation developed was describing the effect of steric and orientation factors on the activity, but the novelty of quantitative nature could be utilize more rationally to develop more active compound. The descriptors selected by the model were standard gibb's free energy(G), non-1, 4 VDW energy (Ev), molecular topological index (TIndx), shape coefficient (SC) and molar refractivity (MR) are greately influenced by the functional group attached to parent nuclei. These descriptors can be correlated with the bulk as well as orientation of the functional group in the parent nuclei. The linear model developed in the current work is easily calculated and suitable for the rapid prediction of ant-HIV activity and cross validation of models support this claim. Thus it can be conclude that introduction of suitable functional group low G value and higher SC value may help to design potent anti-HIV 1 (RP) of calanolides series.

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