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Research Paper

2D-QSAR study of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one a novel series of PDE-4 inhibitors

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ABSTRACT

A 2D-quantitative structure activity relationship (QSAR) was employed to find the correlation between the structural properties and Phosphodiestrase-4 (PDE-4) inhibitory activities of a series of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one collected from the literature. Multiple linear regression (MLR) analysis has been used to derive the QSAR models. The developed models were cross-validated by the 'leave one out' technique as well as by the calculation of statistical parameters. The present investigation indicates the importance of the quantum chemical descriptors, electronic parameters, topological parameters, hydrophobicity in contribution to studied biological activity (PDE-4).

Key Words: QSAR, MLR, PDE-4, Leave One Out Method, Molecular Descriptors.

INTRODUCTION

Bronchial asthma, a multifactorial disease related to respiratory system, is characterized by hypersensitivity of respiratory tract to external stimuli i.e. cold or warm, moist air, excertion and emotional stress. Under these conditions the airways constricts, become inflamed, and lined with excessive amount of mucous. Inflammation and narrowing of the airways are responsible for further development of severe lung diseases including asthma and chronic obstructive pulmonary disease (COPD)[1].

Inhaled β_2 receptor agonists and corticosteroids have represented the mainstay of the therapeutic management of asthma. According to the previous arguments, β_2 adrenoreceptor agonists, which inhibit bronchostriction, would provide little more than symptomatic relief, while the anti-inflammatory effect of glucocorticoides may affect disease progression.[2-3]However these agents have sever limiting side effects like tachycardia and palpitation for ß$_2$-agonosts and sever CNS effects in children for corticosteroids.

Thus the development of novel orally active anti asthmatic drugs remained much pursued area of research over the last few decades.

A PDE-4 antagonist represents one such class of orally active anti asthmatic drugs. PDE-4 a c-AMP specific PDE has attracted particular attention as a target for the treatment of asthma and COPD due to its distribution in most immune and inflammatory cells and airways smooth muscle.

The in vitro profile of PDE-4 inhibitors is thus characterized by suppression of the inflammatory and immunomodulatory responses as well as reduction of bronchial smooth muscle tone.

Rolipram, nitraqnazone and their analogous represent the drugs of this particular class. However they are known to have side effects like emesis, nausea, vomiting and increased gastric acid secretion.

Crespo et al synthesized a series of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives having PDE-4 inhibitory activity and lacking adverse effects such as emesis.

Quantitative structural activity relationship (QSAR) studies have received wide spread attention as a powerful drug design tool for the optimization of promising drug candidates.

A QSAR study defines the rate of structural features of a molecule in determining biological activity in quantitative terms.

In present work we report a QSAR study on 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives reported by Crespo, *et. al.*, **2000**[6]. Multiple linear regression analysis was used in order to find relationship between molecular descriptors and PDE-4 inhibitory activity.

EXPERIMENTAL

PDE-4 inhibitory activity

The PDE-4 inhibitory activity was taken from the reported work of Crespo et al. We have converted the biological activity values [IC50 (nM)] reported in the literature to –log scale and subsequently used as the response variable for the QSAR analysis.

Calculation of molecular descriptors and regression

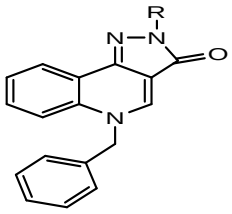
The calculation of molecular descriptors of substituted 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one as well as the regression analyses were carried out using the molecular package MDS 3.5v software for Windows.28 The details of the descriptors are available in the literature and therefore they are not described here.

Cross-validation

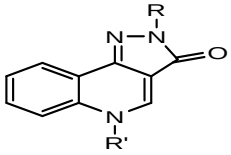
The models were cross-validated by the 'leave one out' scheme[5] where a model is built with N-1 compounds and the N^{th} compound is predicted. Each compound is left out of the model derivation and predicted in turn. An indication of the performance of the model is obtained from the cross-validated (or predictive r^2_{CV}) method which is defined as

$$r^2_{CV} = (SD\text{-}PRESS/SD)$$

Where SD is the sum of squares deviation for each activity from the mean. PRESS (or predictive sum-of-squares) is the sum of the squared difference between the actual and that of the predicted values when the compound is omitted from the fitting process. The model with high r^2 value is said to have high predictability.



[Compound (1-13)]



[Compound (14-25)]

Table 1: Chemical and biological data of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one

Compound	R	R'	IC_{50} PDE-4*	IC_{50} -log PDE-4
1	H	Benzyl	37	1.568
2	Methyl	Benzyl	14	1.146
3	Ethyl	Benzyl	3	0.477
4	Isopropyl	Benzyl	1.2	0.079
5	Butyl	Benzyl	2.1	0.322
6	tert. Butyl	Benzyl	2.1	0.322
7	Pentyl	Benzyl	6.4	0.806
8	Benzyl	Benzyl	7	0.845
9	Phenenthyl	Benzyl	10	1
10	Cyclopentyl	Benzyl	0.7	-0.154
11	Norbornyl	Benzyl	1.4	0.041
12	Cyclobutylmethyl	Benzyl	0.8	-0.096
13	Cyclohexylmethyl	Benzyl	24	1.38
14	Butyl	H	90	1.945
15	Butyl	Phenyl	18	1.832
16	Butyl	Phenenthyl	160	2.204
17	Butyl	Cyclohexylmethyl	0.7	-0.154
18	tert. Butyl	Cyclohexylmethyl	0.5	-0.3
19	Cyclopentyl	Cyclohexylmethyl	0.4	-0.39
20	Butyl	m-Nitrobenzyl	11	1.041
21	Butyl	m-Aminobenzyl	12	1.079
22	Butyl	m-Chlorobenzyl	2.3	0.361
23	Butyl	2-thienylmethyl	2.7	0.431
24	tert. Butyl	2-thienylmethyl	0.8	-0.096
25	Cyclopentyl	2-thienylmethyl	0.4	-0.39

*PDE-4 are IC_{50} values in µM

Table 2: Molecular descriptors selected for QSAR Study

S.No.	QSAR descriptors selected	Type
1	Kier'ssecond order indices (κ_2)	Topological
2	Oxygen Path count (O-Path)	Topological
3	Polarizability AHC	Hydrophobic
4	Fourth order molecular connectivity indices ($^4\chi$)	Topological
5	Valence 4th order molecular connectivity indices ($^4\chi^v$)	Topological
6	SssNE index	Electrotopological
7	Valence 1st order molecular connectivity indices ($^1\chi^v$)	Topological
8	SK Hydrophobic area	Hydrophobic
9	Quadrupole2	Electrostatic
10	Most +ve potential	Electrostatic
11	Valence 5th order molecular connectivity indices chain fregment ($^5\chi_{ch}$)	Topological
12	sd-OE index	Electrotopological

Table 3: Values of molecular descriptors used in MLR analysis (* indicates outliers)

Compound	SK hydrophobic area	$^4\chi^v$	Most +ve potential	Q-2	$^5\chi_{ch}$
1	130.831	1.833	0.056	0.745	0.096
2	134.917	1.91	0.059	2.713	0.079
3	149.171	1.935	0.044	-0.903	0.079
4*	158.977	1.96	0.043	-0.796	0.079
5*	176.307	2.016	0.044	-1.072	0.079
6	168.296	1.985	0.043	-1.287	0.079
7	214.425	2.047	0.044	-1.116	0.079
8	261.277	2.397	0.045	-1.313	0.079
9*	324.836	3.296	0.053	-0.451	0.079
10	209.827	2.306	0.042	-1.911	0.223
11	255.52	2.867	0.043	-1.86	0.271
12	182.789	2.237	0.052	7.291	0.079
13	256.994	2.375	0.044	-0.999	0.079
14	188.828	1.408	0.068	6.06	0.096
15	205.665	1.919	0.044	-1.918	0.079
16	294.662	2.906	0.053	-0.844	0.079
17*	152.928	1.985	0.044	-1.152	0.079
18	150.177	1.901	0.043	-0.026	0.079
19	196.238	2.253	0.043	-0.43	0.223
20	125.971	2.269	0.066	11.424	0.079
21	210.388	2.178	0.045	-0.548	0.079
22	258.402	2.393	0.048	6.008	0.079
23	224.276	2.393	0.041	-4.55	0.223
24	228.681	2.309	0.04	-3.865	0.223
25*	246.157	2.661	0.04	-4.241	0.367

Table 4: Correlation matrix for selected descriptors

	SK hydrophobic area	$^4\chi^v$	Most +ve potential	Quadrupole2	$^5\chi_{ch}$	IC_{50} -log PDE-4
SK hydrophobic area	1	0.7993	-0.2308	-0.3317	0.2587	0.1455
$^4\chi^v$	0.7993	1	-0.1958	-0.2271	0.3576	-0.0862
Most +ve potential	-0.2308	-0.1958	1	0.7962	-0.401	0.5997
Quadrupole2	-0.3317	-0.2271	0.7962	1	-0.4443	0.2307
$^5\chi_{ch}$	0.2587	0.3576	0.401	-0.4443	1	-0.4998
IC50 -log PDE-4	0.1455	-0.0862	0.5997	0.2307	-0.4998	1

RESULT AND DISCUSSION

In the present study we tried to develop best QSAR equation to explain the correlation between the physicochemical parameters and PDE-4 inhibitory activity of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives. Correlation between Biological data and various physicochemical parameters were established by using MLR analysis. (The complete data were taken from previously published literature.) Stepwise development of QSAR equation is summarized in **Table 5**.

In the first step, QSAR equation were developed by taking single parameters one by one showed improvement in r^2 values in parameter Most +ve potential but no one single parameter had ability to gave best r^2 value. After that we decided to select two parameters instead of single one. Model number 5 and 8 showed improvement in r^2 value but these parameters are statistically insignificant. After that by selecting three parameters, model 11 showed improved r^2 value from model 8 but not fulfill the criteria for statistically significant. The statistically significant QSAR model was obtained by using four parameters. The model clearly showed that the use of four parameters significantly improved quality of the model.

The best-fit equation in QSAR model number 14

IC_{50} (-log) PDE-4 = 115.6581 most + ve potential + (-0,1763) Q-2 + (-6.094) $^5\chi_{ch}$ + 0.0058 SK hydrophobic area – 5.1891`

N = 20, r = 0.9197, r2 = 0.8467, F = 20.6746, RMSE = 0.3473, r^2_{adj} = 0.7952, r^2_{CV} = 0.745, PRESS = 2.99, s^2 = 0.120, $\%r^2_{adj}$ = 80.5524

From the above equation we can say that the physicochemical parameters like most + ve potential, Quadrupole2, χ 5 chain and SK hydrophobic area contributes in the PDE- 4 inhibitory activity.

The correlation between the four parameters with biological activity was analyzed in terms of Coefficient of determination (r^2), Sequential Fischer's value (F), root mean square error (RMSE), Predictive Sum of squares (PRESS), and standard deviation (s^2) as shown in table 5. The equation is significant as the r = 0.9197. For better significance the r value of data should be equal to or more than 0.9 for in vitro data and 0.8 for in vivo data.

Table 5: Result of all possible-subsets regression

Model.No	Combination of descriptor(s)	Statistics					
		r^2	r^2_{cv}	F	RMSE	PRESS	s^2
1	SK hydrophobic area	.0090	-0.263	0.164	0.764	14.8	0.649
2	Most +ve potential	0.305	0.167	7.88	0.640	9.81	0.455
3	Quadrupole 2	0.022	-0.175	0.396	0.752	13.8	0.640
4	$^5\chi_{ch}$	0.282	0.161	7.071	0.650	9.89	0.470
5	SK hydrophobic area, Most +ve potential	0.424	0.246	6.266	0.632	8.89	0.399
6	SK hydrophobic area, Quadrupole 2	0.048	-0.3467	0.4350	0.812	15.8	0.659
7	SK hydrophobic area, $^5\chi_{ch}$	0.338	0.107	4.338	0.677	10.5	0.459
8	Most +ve potential, Quadrupole 2	0.542	0.416	10.074	0.563	6.89	0.317
9	Most +ve potential, $^5\chi_{ch}$	0.416	0.244	6.068	0.636	8.91	0.404
10	Quadrupole 2, $^5\chi_{ch}$	0.291	0.065	3.494	0.701	11.0	0.491
11	SK hydrophobic area, Most +ve potential, Quadrupole 2	0.626	0.504	8.936	0.524	5.84	0.275
12	SK hydrophobic area, Most +ve potential, $^5\chi_{ch}$	0.563	0.388	6.880	0.567	7.21	0.321
13	Most +ve potential, Quadrupole 2, $^5\chi_{ch}$	0.739	0.623	15.134	0.438	4.43	0.192
14	SK hydrophobic area, Most +ve potential, Quadrupole 2, $^5\chi_{ch}$	0.846	0.745	20.675	0.347	2.99	0.120

CONCLUSION

2D- QSAR study was performed on a series of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives using MDS 3.5v software. QSAR model were proposed for PDE- 4 inhibitory activity of quinoline-3-one derivatives. The selected models were checked for observed *vs.* predicted biological activity and leave one out (LOO) method. It was observed from the selected models that biological activity of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives are governed by hydrophobic, electrostatic and topological properties of molecule and also provides valuable insight into the mechanism of action of these compounds. The results of study showed that presence of groups contributing to flexibility in chain length and lipophilicity of molecule will increase PDE-4 inhibitory activity of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives. The finding of this study will be helpful in design of potent PDE-4 inhibitors analogs of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one.

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