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2D QSAR Studies of some novel quinazolinone derivatives as selective phosphodiesterase i inhibitors

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ABSTRACT

In the present study, quantitative structure activity relationship study was performed on a series of novel quinazolinone derivatives as inhibitors of phosphodiesterase using chem. office ultra 7.0. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally as well as externally for the production of activity. The quantitative structure activity relationship evaluation involved a study on ten different models, most of them have shown F value above 50. This study indicates that steric descriptors (logP, bend energy, molar refractivity, heat of formation and Henry's law) play important role for the activity. The data obtained from this present quantitative structure activity relationship study may be useful in the design of more potent substituted quinazolinone derivatives.

Key words: 2D-QSAR, quinazolinone, phosphordiesterase I inhibitor.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a myriad of symptoms that gradually decrease the quality of life of the patient. The first line of treatment is a dopamine replacement therapy with Levodopa[1]. Among other therapeutic strategies monoamine oxidase B (MAO-B) inhibitors have also been extensively used in PD[2]. In fact, selective MAO-B inhibitors (i.e., deprenyl and rasagiline) are currently used, alone or in combination with Levodopa, in the symptomatic treatment of Parkinson's disease. The side effects associated with the use of Deprenyl and, to a lesser extent, Rasagiline, likely due to their irreversible mechanism of inhibition, and the potential application of MAO-B inhibitors as anti-Alzheimer's agents are at

the moment the driving forces for the discovery of novel potent and selective MAO-B inhibitors[3,4].

Parkinson's disease (PD) is a chronic and progressive degenerative disease of the brain that impairs motor control, speech, and other functions. The risk of developing PD is dramatically increased with age, and symptoms often appear after the age of 50. Current research indicating that 1 in 100 individuals over 60 has PD.

The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids and drugs[5]. The natural quinazolinones and their synthetic analogs possess a variety of biological activities, including PDE inhibitory activity, anticonvulsant, bronchodilator, anti-inflammatory, antimalarial, antituberculous, anti-HIV, narcotic antagonist, anti-tumor, tyrosine kinase inhibitor, adenosine antagonist, antimicrobial etc. Along with these activities, quinazoline derivatives showed a very prominent activity in PD.

QSAR studies have been widely used to understand the relationship between the structure of the molecule and biological activity. In the present study, QSAR analysis of some substituted quinazolinone derivatives with phosphodiesterase inhibitory property was performed by using multiple linear regression analysis. QSAR studies of these molecules have not been performed earlier. It was interesting to perform QSAR analysis using Chem Office 7.0 and correlate various physiochemical parameters to the activity for the design of some quinazolinone derivatives [Fig 1].

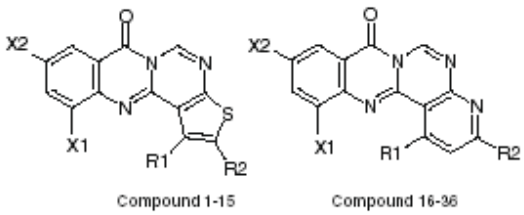


Fig 1

MATERIALS AND METHODS

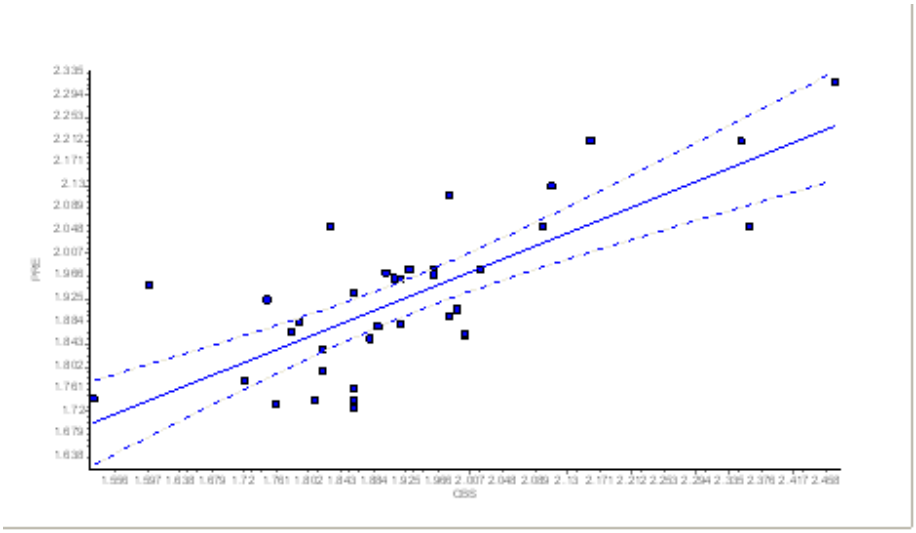
Experiments:

A data set of 36 compounds has been taken from published article[6] (*Laddha S.S and Bhatnagar S.P*). The various descriptors studied are shown in **Table 1**. The values of PIC_{50} have been considered for computational work. All structure of these quinazolinone derivatives were constructed using ChemDraw and transferred to Chem 3D to convert them in to 3D structures. The energy minimization of the molecules was done using MM2 force field followed by semi empirical AMI (Austin model) Hamiltonian method available in MOPAC module by fixing root mean square gradient as 0.1 and 0.0001 kcal/mol. Most stable structure for all the compounds was generated and used for calculating various thermodynamic, steric and electronic descriptors. Values of descriptors with their equation are shown and the values of observed and predicted activity are shown in **Table II**. All the calculated descriptor values were considered as independent variable and biological activity as dependent variable. INSTAT software was used

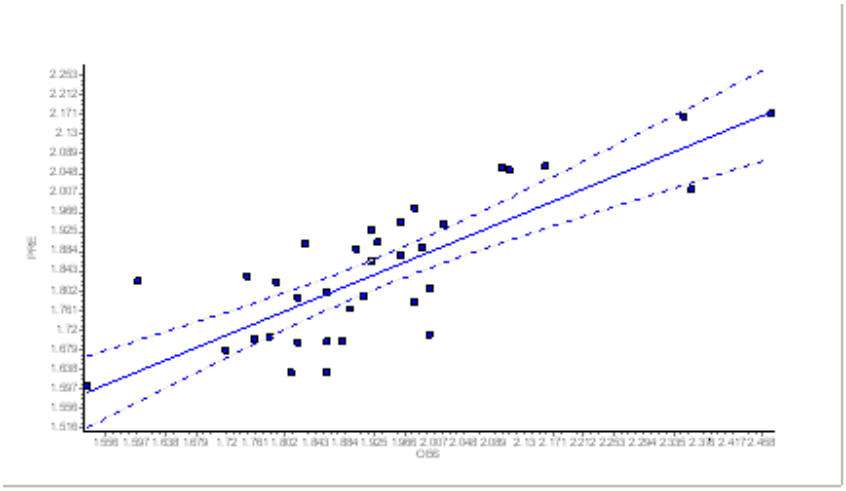
to generate QSAR models by multiple linear regression analysis. Cross validation was performed using leave-one method. Statistical measures used were: n-number of moles in regression, r^2–correlation-coefficient, F-test (Fischer's value) for statistical significance, S-standard deviation.

Table 1: Descriptors considered for the QSAR study:

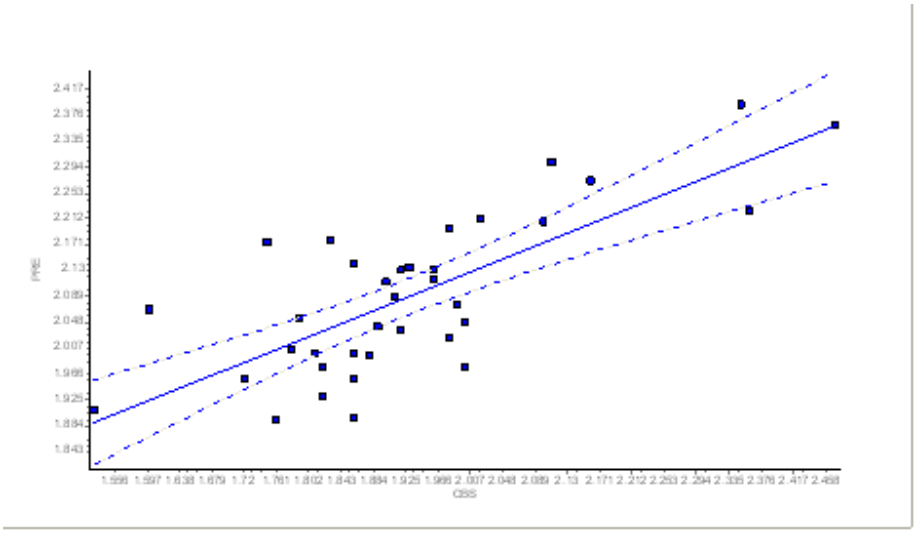
S.No	Descriptor	Type
1	Heat of formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
4	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
6	Henry's Law constant (H)	Thermodynamic
7	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
8	LogP	Thermodynamic
9	Melting Point (MP)	Thermodynamic
10	Molar Refractivity (MR)	Thermodynamic
11	Standard Gibbs Free Energy (SGFE)	Thermodynamic
12	Connolly Accessible Area (SAS)	Steric
13	Connolly Molecular Area (CMA)	Steric
14	Connolly Solvent-Excluded Volume (SEV)	Steric
15	Ovality (OVA)	Steric
16	Principal Moment of Inertia – X (PMI-X)	Steric
17	Principal Moment of Inertia – Y (PMI-Y)	Steric
18	Principal Moment of Inertia – Z(PMI-Z)	Steric
19	Dipole Moment (D)	Electronic
20	Dipole Moment – X Axis (DX)	Electronic
21	Dipole Moment – Y Axis (DY)	Electronic
22	Dipole Moment – Z Axis (DZ)	Electronic
23	Electronic Energy (EE)	Electronic
24	HOMO Energy (HOMO)	Electronic
25	LUMO Energy (LUMO)	Electronic
26	Repulsion Energy (RE)	Electronic
27	Bend Energy (E_b)	Thermodynamic
28	Charge - Charge Energy (CCE)	Thermodynamic
29	Charge - Dipole Energy (CDE)	Thermodynamic
30	Dipole - Dipole Energy (DDE)	Thermodynamic
31	Non-1,4 VDW Energy (E_v)	Thermodynamic
32	Stretch Energy (SE)	Thermodynamic
33	Stretch-Bend Energy (SEE)	Thermodynamic
34	Torsion Energy (E_t)	Thermodynamic
35	Total Energy (E)	Thermodynamic
36	Van der Waals 1,4 Energy (VDWE)	Thermodynamic



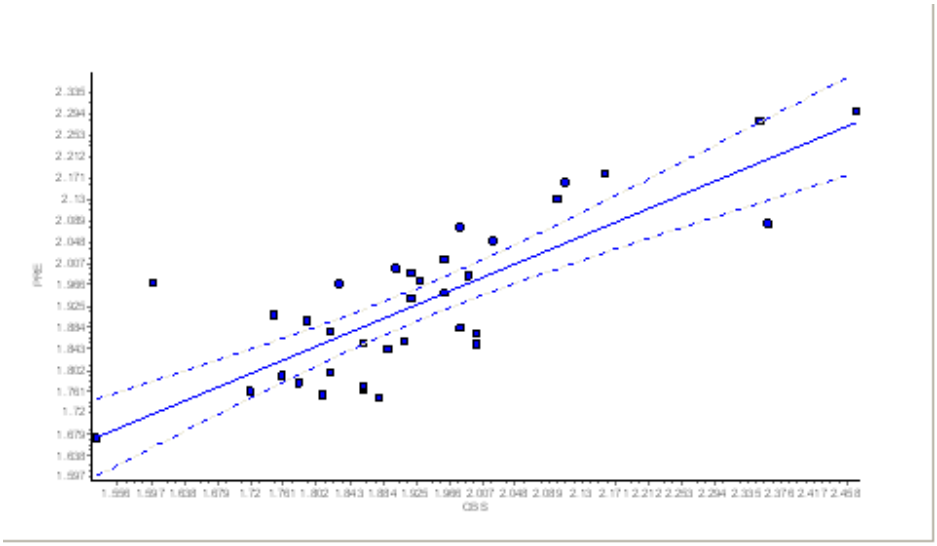
MODEL 1: [A:PIc50]=3.167-0.009981*[B:eb]+0.007234*[C:diam]+0.05935*[D:H]-0.001271*[E:log P] - 0.1262*[F:mr2]+ 0.01259*[G:rad] - 0.003204*[H:e]
Standard deviation: 0.1272, correlation coefficient (r): 0.7565, R squared:0.5723,
P Value: <0.0001, F: 45.493.



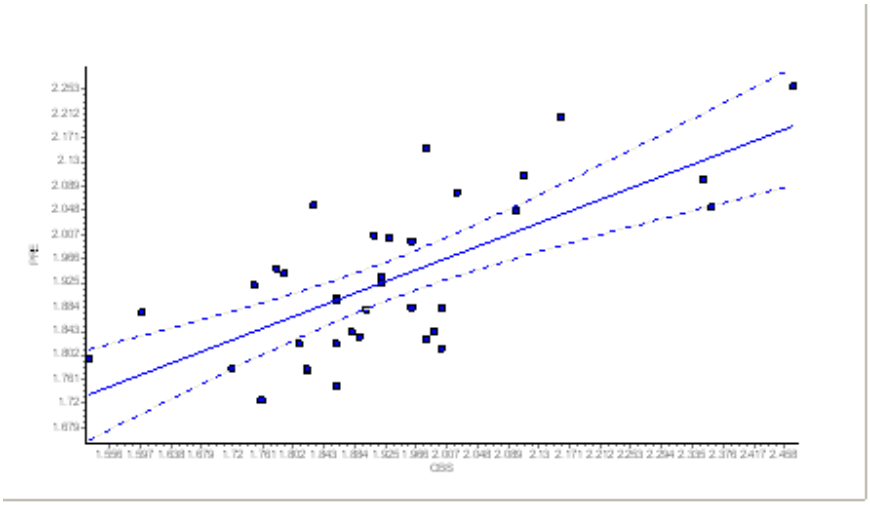
MODEL 11: [A:PIc50]=3.542+0.1587*[B:clsc]+0.0007628*[C:pc]-0.004646*[D:eb]-0.02583*[E:diam] - 0.6126*[F:mv2] + 0.2678*[G:parco] - 0.002343*[H:e]
Standard deviation: 0.09420, correlation coefficient (r): 0.7891, R squared: 0.6227,
P Value: <0.0001, F: 56.117.



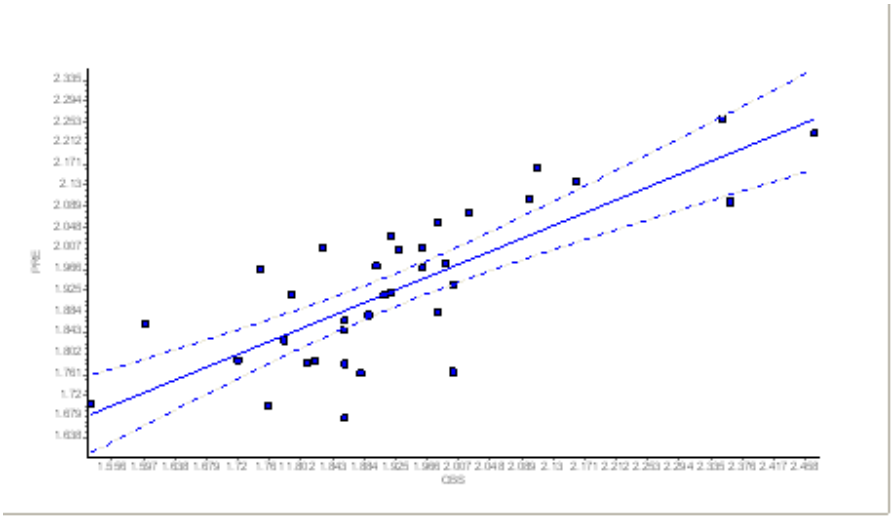
MODEL 111: [A:PIc50]=2.795-0.0002762*[B:SAS] + 0.001380*[C:CSEV]- 0.002484*[D:HF] - 0.005813*[E:CP] + 0.002847*[F:G]
Standard deviation: 0.08487, correlation coefficient (r): 0.7524, R squared: 0.5662,
P Value: <0.0001, F: 44.638.



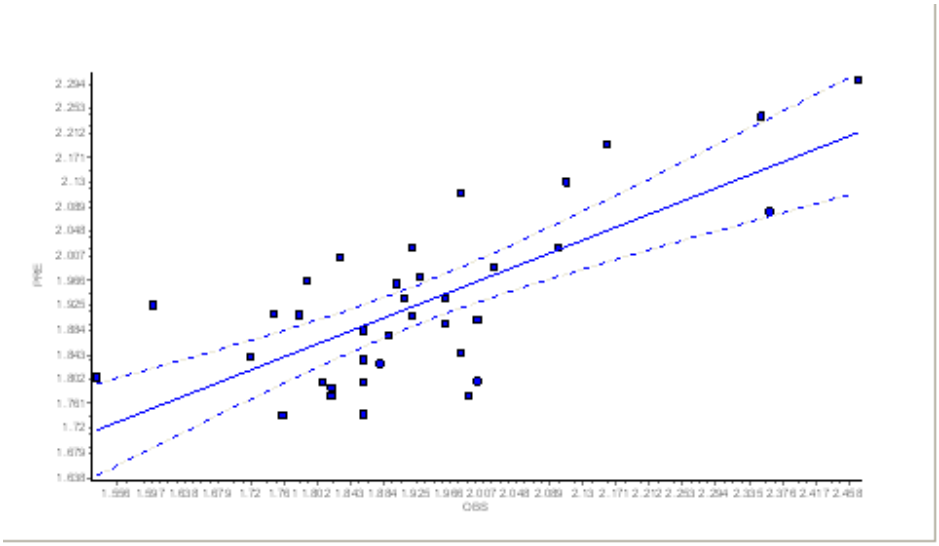
MODEL IV: [A:PIc50]=5.002+0.05274*[B:H]-0.07993*[C:logP]-0.5332*[D:Mr2]-0.6287*[E:ovality] + 0.3317*[F:parco]+ 0.1083*[G:ShPa] - 0.007709*[H:PC]
Standard deviation: 0.09310, correlation coefficient (r): 0.8018, R squared: 0.6429,
P Value: <0.0001, F: 61.201.



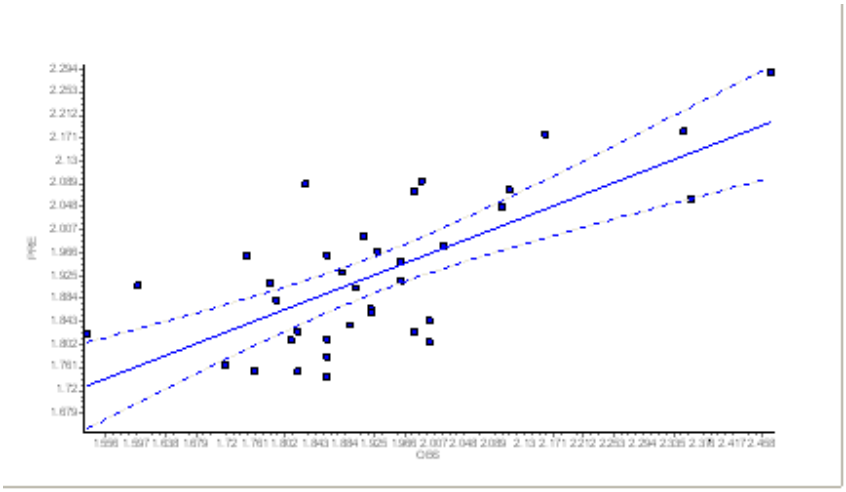
MODEL V:[A:PIc50]=2.926-0.03817*[B:sdeg]+0.01388*[C:svde]+0.006213*[D:tcon]+ 0.006289*[E:e]
Standard deviation: 0.09720, correlation coefficient (r): 0.6958, R squared: 0.4842,
P Value: <0.0001, F: 31.918.



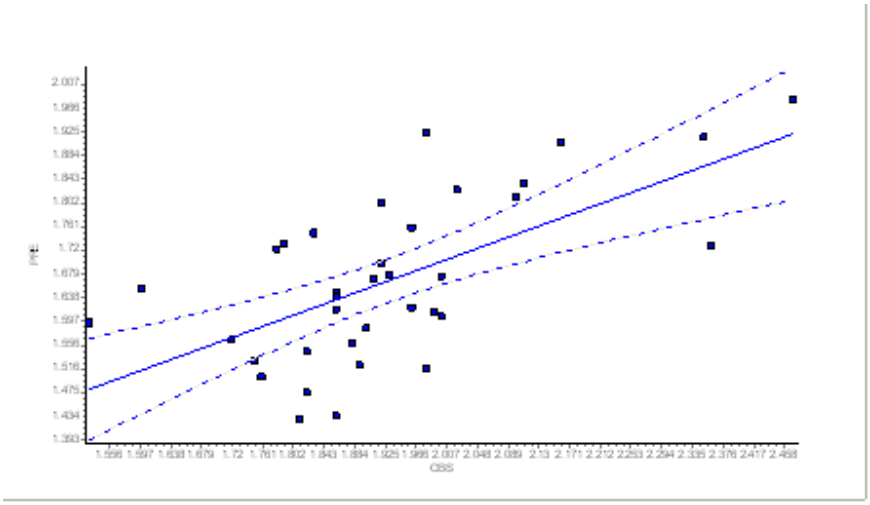
MODEL VI: [A:PIc50]=1.780+0.002223*[B:bp]-0.0003176*[C:sas]-0.0003964*[D:csev]- 0.0007705*[E:vc] - 0.002063*[F:hf]- 0.004874*[G:cp] + 0.002782*[H:g]
Standard deviation: 0.09484, correlation coefficient (r): 0.7815, R squared: 0.6107,
P Value: <0.0001, F: 53.346.



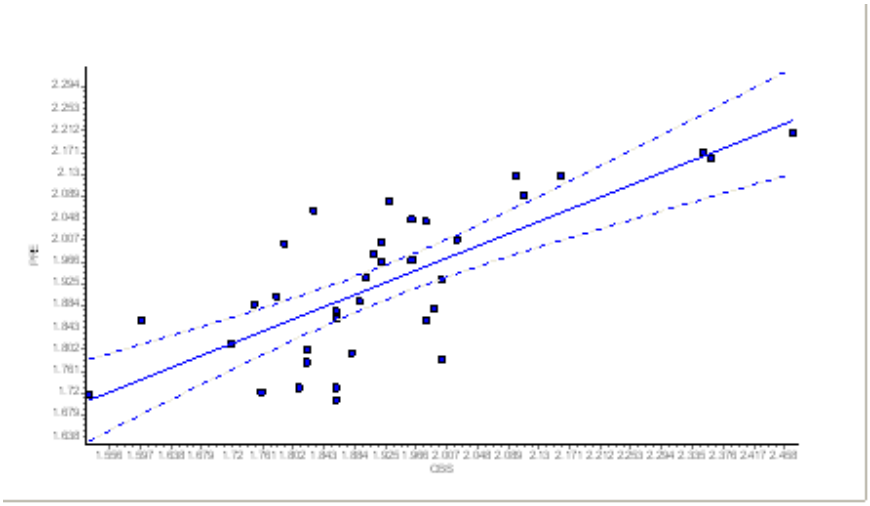
MODEL VII: [A:PIc50]=4.819+0.05090*[B:dpll]+0.02806*[C:h]-0.001012*[D:logP]-1.770*[E:ovality] - 0.04184*[F:parco]- 0.002092*[G:tcon] - 0.006702*[H:e]
Standard deviation: 0.09709, correlation coefficient (r): 0.7261, R squared: 0.5272,
P Value: <0.0001, F: 37.914.



MODEL VIII: [A:PIc50]=5.381+0.0002362*[B:WINDX]-0.0003668*[C:G]-0.003719*[D:BP] - 0.0006560*[E:SAS]
Standard deviation: 0.09724, correlation coefficient (r): 0.7083, R squared: 0.5017,
P Value: <0.0001, F: 34.233.



MODEL IX: [A:PIc50]=4.230-0.03400*[B:diam]+0.03956*[C:dpll]-0.004296*[D:eb]-0.03395*[E:logP] - 1.096*[F:ovality]
Standard deviation: 0.1109, correlation coefficient (r): 0.6354, R squared: 0.4037,
P Value: <0.0001, F: 23.022.



MODEL X: [A:PIc50]=1.975+0.0005827*[B:tc]-0.003798*[C:vc]+0.001121*[D:hf]+0.007567*[E:cp]
Standard deviation: 0.09656, correlation coefficient (r): 0.7461, R squared: 0.5566,
P Value: <0.0001, F: 42.688.

Table II: Comparison of observed activity with predicted activity

Compd	OBSERVED ACTIVITY	PREDICTED ACTIVITY									
		MODEL I	MODEL II	MODEL III	MODEL IV	MODEL V	MODEL VI	MODEL VII	MODEL VIII	MODEL IX	MODEL X
1	2.35	2.21	2.16	2.39	2.27	2.10	2.25	2.23	2.18	1.91	2.16
2	2.10	2.05	2.05	2.20	2.13	2.04	2.10	2.02	2.04	1.81	2.12
3	2.36	2.05	2.01	2.22	2.08	2.05	2.09	2.08	2.06	1.72	2.15
4	1.83	2.05	1.90	2.17	1.96	2.05	2.00	2.00	2.08	1.74	2.06
5	2.47	2.31	2.17	2.36	2.29	2.25	2.23	2.29	2.28	1.98	2.20
6	2.02	1.97	1.94	2.21	2.04	2.07	2.07	1.98	1.97	1.82	2.00
7	1.98	2.11	1.97	2.19	2.07	2.15	2.05	2.11	2.07	1.92	2.04
8	1.92	1.87	1.86	2.03	1.93	1.93	1.92	1.90	1.86	1.80	1.96
9	1.79	1.88	1.82	2.05	1.89	1.94	1.91	1.96	1.88	1.72	1.99
10	1.78	1.86	1.70	2.00	1.77	1.94	1.82	1.90	1.91	1.72	1.90
11	2.11	2.12	2.05	2.30	2.16	2.10	2.16	2.12	2.07	1.83	2.08
12	2.16	2.21	2.06	2.27	2.17	2.20	2.13	2.19	2.17	1.90	2.12
13	1.96	1.97	1.94	2.11	2.01	1.99	2.00	1.89	1.95	1.75	2.04
14	1.93	1.97	1.90	2.13	1.97	1.99	2.00	1.97	1.96	1.67	2.07
15	1.91	1.96	1.78	2.08	1.85	2.00	1.91	1.93	1.99	1.67	1.98
16	1.75	1.92	1.83	2.17	1.90	1.92	1.96	1.91	1.95	1.52	1.88
17	1.86	1.93	1.79	2.14	1.85	1.89	1.86	1.88	1.96	1.64	1.87
18	1.90	1.97	1.88	2.11	1.99	1.87	1.97	1.95	1.90	1.58	1.93
19	1.60	1.94	1.82	2.06	1.96	1.87	1.85	1.92	1.90	1.65	1.85
20	1.92	1.96	1.92	2.13	1.98	1.92	2.02	2.01	1.85	1.69	2.00
21	1.96	1.96	1.87	2.13	1.94	1.88	1.96	1.93	1.91	1.62	1.96
22	1.99	1.90	1.89	2.07	1.98	1.84	1.97	1.77	2.09	1.61	1.87
23	1.81	1.73	1.63	1.99	1.75	1.82	1.78	1.79	1.80	1.42	1.72
24	1.53	1.74	1.60	1.90	1.67	1.79	1.70	1.80	1.82	1.59	1.71
25	1.82	1.79	1.69	1.93	1.79	1.77	1.78	1.78	1.75	1.54	1.77
26	1.86	1.76	1.63	1.89	1.76	1.74	1.67	1.74	1.78	1.64	1.70
27	1.86	1.72	1.69	1.95	1.76	1.89	1.84	1.83	1.74	1.61	1.85
28	1.72	1.77	1.67	1.95	1.76	1.77	1.78	1.83	1.76	1.56	1.81
29	1.76	1.73	1.70	1.89	1.79	1.72	1.69	1.74	1.75	1.50	1.72
30	1.86	1.74	1.63	1.99	1.77	1.82	1.78	1.79	1.81	1.43	1.72
31	1.88	1.85	1.69	1.99	1.74	1.84	1.76	1.82	1.93	1.55	1.79
32	1.98	1.89	1.77	2.02	1.88	1.82	1.88	1.84	1.82	1.51	1.85
33	2.00	1.85	1.71	1.97	1.85	1.81	1.76	1.79	1.84	1.60	1.78
34	2.00	1.86	1.80	2.04	1.87	1.88	1.93	1.90	1.80	1.67	1.93
35	1.89	1.87	1.76	2.04	1.84	1.83	1.87	1.87	1.83	1.52	1.89
36	1.82	1.83	1.78	1.97	1.87	1.77	1.78	1.77	1.82	1.47	1.80

RESULTS AND DISCUSSION

The QSAR model was performed on ten different models and the results have been verified. Out of all the models studied Models IV comprising of Henry's law constant, log P, molar refractivity, ovality, partition co-efficient, shape attribute and critical pressure has been found to be extremely significant showing the importance of these descriptors in the designing of novel quinazolinone analogs for phosphodiesterase inhibitory activity, all other models were also found to be very significant emphasizing the importance of understanding various physicochemical parameters while designing a molecule to be potentially effective.

CONCLUSION

This QSAR study has shown that the descriptors Henry's law constant, log P, molar refractivity, ovality, partition co-efficient, shape attribute and critical pressure play a vital role in imparting the biological property. This study has also shown that the biological activity is governed by various thermodynamic, steric and electronic descriptors. The models provide a brief insight in to the mechanism of action of these compounds. All these parameters can be considered for further designing of newer molecules for phosphodiesterase inhibitory activity.

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