Journal of Computational Methods in Molecular Design, 2013, 3 (3):1-9

Scholars Research Library
(http://scholarsresearchlibrary.com/archive.html)

ISSN : 2231- 3176
CODEN (USA): JCMMDA

2D QSAR studies of some 2,3-disubstituted quinazolinone analogs as antitubercular agents

Rajasekaran Subramaniam*, Gopalkrishna Rao[1]

**Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Hosur Road, Bangalore*
[1]Goa College of Pharmacy, 18th June Road, Panaji, Goa

ABSTRACT

In the present study, quantitative structure activity relationship study was performed on a series of novel quinazolinone derivatives as antitubercular agents 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 prediction of activity. The quantitative structure activity relationship evaluation involved a study on thirty four different models; few of them have shown considerable F value. This study indicates that descriptors (logP, ovality, bend energy, partition coefficient and diameter) play an 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, antitubercular activity.

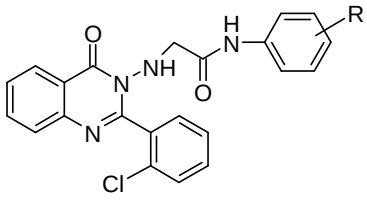
INTRODUCTION

Data from the World Organization of Health show a significant rise in drug-resistant tuberculosis [1–3]. Tuberculosis (TB) is one of the oldest and most pervasive diseases in history that probably appeared in humans about 8000 years ago [4], it is the leading infectious cause of death in the world today, with approximately three million patients deceasing every year. Nearly one-third of the world's population is infected with *Mycobacterium tuberculosis* and the World Health Organization (WHO) estimates that about 30 million people will be infected within next 20 years. Each year, 8 million people worldwide develop active TB and almost 3 million die. The computer-aided prediction of biological activity in relation to the chemical structure of a compound is now a commonly used technique in drug discovery [5–10]. Modern drug discovery also relies on the interface of chemical and biological diversity through high throughput screening [11].

Quinazolinone ring system has been consistently rewarded as a promising molecule because of its broad spectrum pharmacological activities like antitubercular, antibacterial, antifungal, anticancer, anti-HIV, anti-inflammatory and antihypertensive activities. The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids and drugs.

QSAR studies have been widely used to understand the relationship between the structure and biological activity of the molecule. We have reported the synthesis and antitubercular activity of these target compounds [12]. In the

present study, QSAR analysis of these substituted quinazolinone derivatives were performed by using multiple linear regression analysis. QSAR studies of these molecules have not been reported earlier. Hence, 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].



1-15

MATERIALS AND METHODS

Experiments:

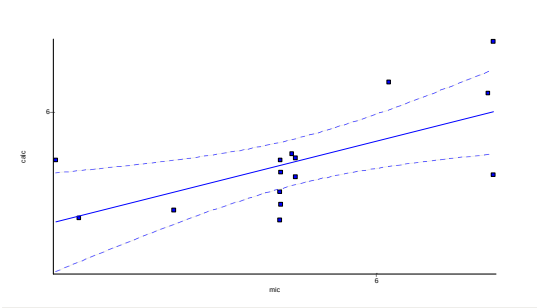
A data set of 15 compounds has been taken from published article. Various descriptors studied are shown in **Table 1**. The values of logMIC have been considered for computational work. All structure of these quinazolinone derivatives were constructed using ChemDraw and transferred to Chem 3D to convert 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.

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

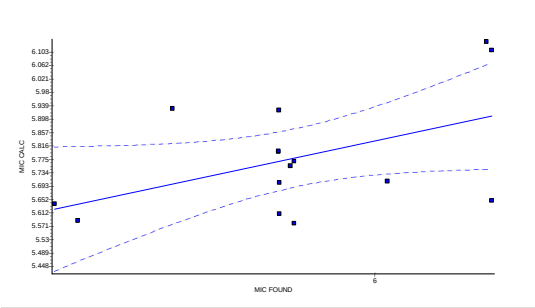
Most stable structure for all the compounds was generated and used for calculating various thermodynamic, steric and electronic descriptors. Values of descriptors with their equation are shown and the values of observed and predicted activity are shown in **Table II**. All the calculated descriptor values 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.

Model 1:



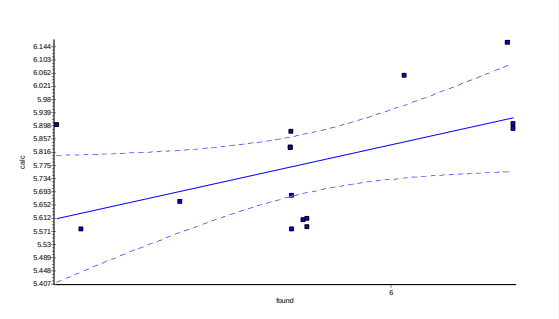
[A:MIC] = 256.49 + 0.4658*[B:BEND ENERGY] - 0.1035*[C:DPLL]
- 85.002*[D:HLC] - 1.788*[E:OVALITY] - 0.1893*[F:PARCO]
+ 0.1581*[G:TOR]

Model 2:



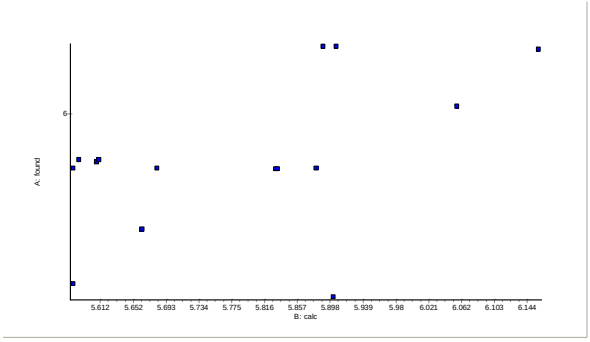
[A:MIC] = 18.001 - 0.01699*[B:SAS] + 0.0005662*[C:MS]
- 0.0008775*[D:CSEV] + 0.002645*[E:IDEAL] - 0.002649*[F:G]

Model 3:



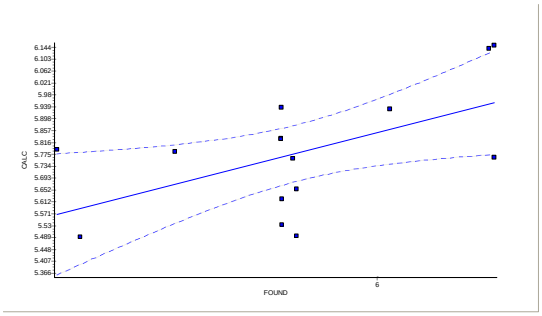
[A:MIC] = 12.303 + 0.1035*[B:CLUSTER COUNT] - 0.9384*[C:MR (LOG)]
- 0.01697*[D:TOT ENER (E)] + 0.1744*[E:VDW]

Model 4:



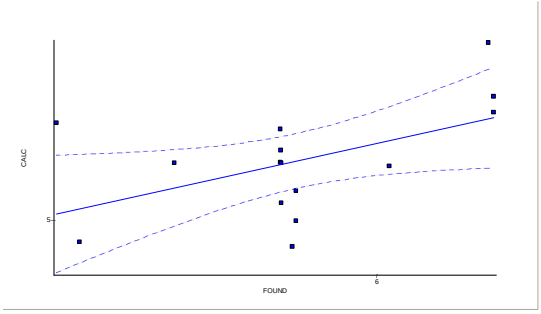
[A:MIC] = 320.87 + 0.6857*[B:BEND ENERGY] - 0.08442*[C:DPLL]
- 106.43*[D:HLC] - 3.894*[E:OVALITY] + 0.2016*[F:TOR]

Model 5:



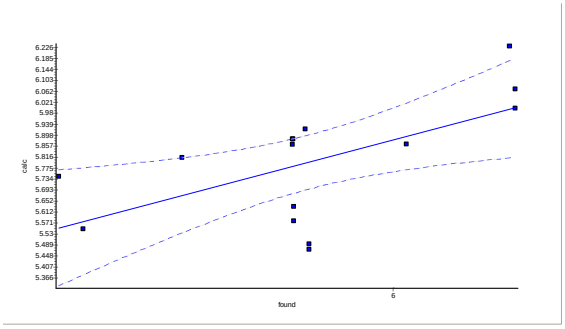
[A:MIC] = 19.919 - 0.0002038*[B:SAS] - 0.04112*[C:MS]
- 0.0005995*[D:CSEV] + 0.02342*[E:IDEAL] - 0.004799*[F:G]
- 0.04275*[G:SVDE]

Model 6:



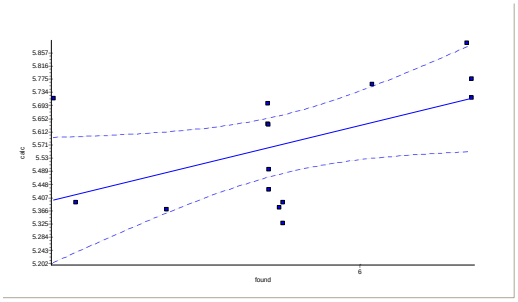
[A:MIC] = 2.548 + 0.009390*[B:TC] + 0.002485*[C:VC]
- 0.001331*[D:X] - 0.0001244*[E:Z] - 0.0004187*[F:WINDX]

Model 7:



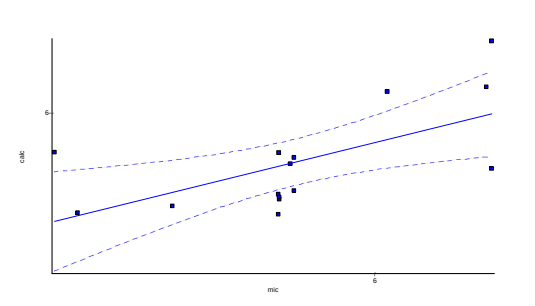
[A:mic] = 20.648 - 0.05419*[B:hf] - 0.1860*[C:ideal]
+ 0.05426*[D:SAS] - 0.1008*[E:sas] + 0.2901*[F:ms]
- 0.04506*[G:svde]

Model 8:



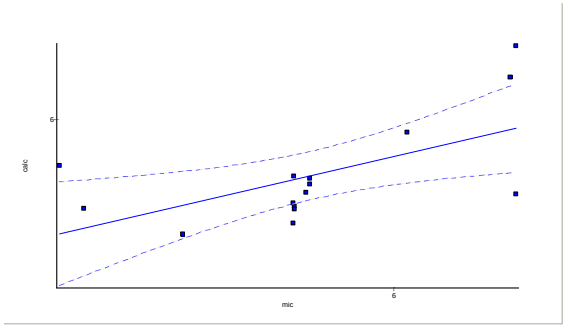
[A:mic] = 13.520 - 0.05171*[B:pc] + 0.09639*[C:diam]
- 0.003857*[D:sod] - 0.6346*[E:mr log]

Model 9:



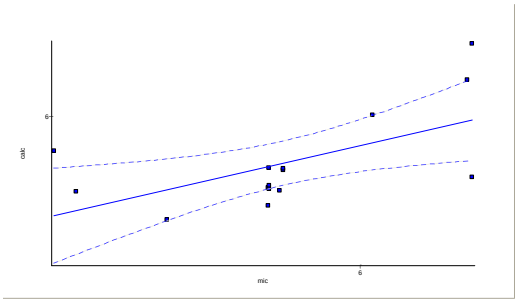
[A:MIC] = 319.05 + 0.2361*[B:BEND ENERGY] - 0.05799*[C:DPLL]
- 106.93*[D:HLC] + 0.4466*[E:OVALITY] - 0.2342*[F:PARCO]

Model 10:



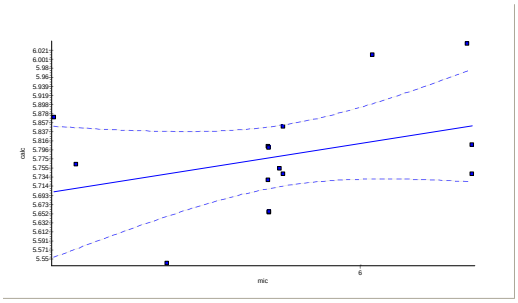
[A:MIC] = 427.04 + 0.4434*[B:BEND ENERGY] - 0.01618*[C:DPLL] - 143.28*[D:HLC] - 1.526*[E:OVALITY]

Model 11:



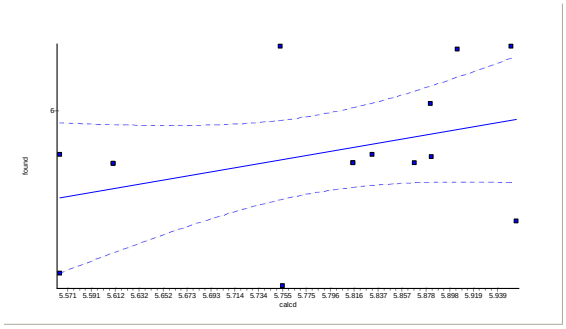
[A:MIC] = 465.44 + 0.4348*[B:BEND ENERGY] - 0.01547*[C:DPLL] - 157.21*[D:HLC]

Model 12:



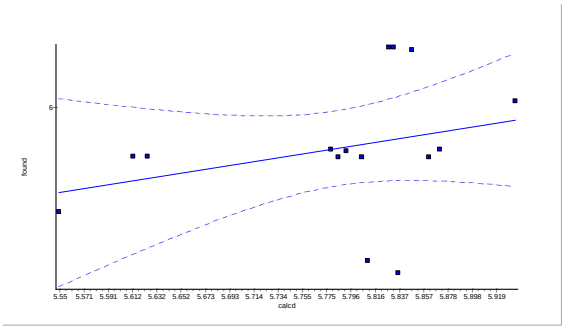
[A:MIC] = 5.082 + 0.2154*[B:BEND ENERGY] - 0.04872*[C:DPLL]

Model 13:



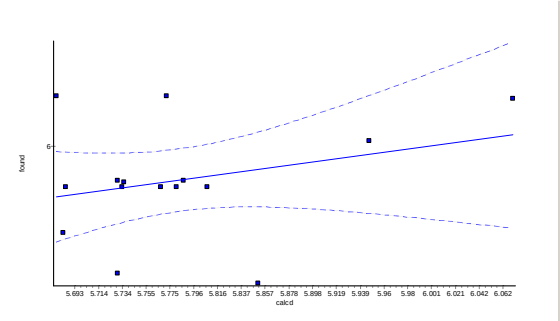
[A:mic] = 7.072 - 0.3042*[B:parco]

Model 14:



[A:MIC] = 5.981 - 0.06705*[B:DPLL]

Model 15:



[A:MIC] = 4.610 + 0.2993*[B:BEND ENERGY]

Table II: Comparison of observed activity with predicted activity

	OBSERVED ACTIVITY	PREDICTED ACTIVITY									
Compd		MODEL 1	MODEL 2	MODEL 3	MODEL 4	MODEL 5	MODEL 6	MODEL 7	MODEL 8	MODEL 9	MODEL 10
01	6.305	6.085	6.135	6.158	5.158	6.139	5.827	6.230	5.888	6.116	6.173
02	5.738	5.517	5.798	5.832	5.832	5.830	5.268	5.864	5.636	5.555	5.569
03	5.738	5.645	5.800	5.830	5.830	5.828	5.425	5.884	5.700	5.642	5.654
04	6.320	6.314	6.109	5.905	6.905	6.150	5.577	6.071	5.717	6.318	6.304
05	5.126	5.785	5.639	5.902	5.902	5.791	5.452	5.744	5.716	5.828	5.809
06	5.189	5.528	5.588	5.577	5.577	5.491	4.897	5.548	5.392	5.561	5.631
07	5.780	5.711	5.580	5.584	5.584	5.494	5.136	5.472	5.391	5.659	5.730
08	5.740	5.731	5.609	5.577	5.577	5.532	5.079	5.632	5.431	5.623	5.640
09	5.740	5.589	5.703	5.682	5.682	5.622	5.267	5.579	5.495	5.631	5.629
10	6.035	6.132	5.709	6.056	6.156	5.931	5.251	5.867	5.760	6.095	5.948
11	6.320	5.719	5.649	5.889	5.889	5.764	5.503	5.998	5.777	5.758	5.689
12	5.770	5.813	5.756	5.606	5.606	5.760	4.876	5.921	5.376	5.777	5.695
13	5.739	5.785	5.925	5.880	5.880	5.936	5.326	5.884	5.634	5.827	5.766
14	5.780	5.795	5.770	5.609	5.609	5.655	4.997	5.493	5.327	5.805	5.756
15	5.448	5.563	5.931	5.663	5.863	5.785	5.267	5.815	5.370	5.593	5.522

Table II: Comparison of observed activity with predicted activity

	OBSERVED ACTIVITY	PREDICTED ACTIVITY				
Compd		MODEL 11	MODEL 12	MODEL 13	MODEL 14	MODEL 15
01	6.305	6.166	6.035	5.904	5.847	6.070
02	5.738	5.596	5.728	5.609	5.805	5.685
03	5.738	5.680	5.803	5.609	5.861	5.733
04	6.320	6.330	5.741	5.951	5.831	5.677
05	5.126	5.845	5.869	5.754	5.835	5.851
06	5.189	5.662	5.763	5.563	5.810	5.729
07	5.780	5.760	5.849	5.563	5.870	5.787
08	5.740	5.673	5.655	5.815	5.623	5.767
09	5.740	5.690	5.656	5.815	5.611	5.780
10	6.035	6.007	6.010	5.881	5.934	5.947
11	6.320	5.728	5.807	5.753	5.827	5.772
12	5.770	5.666	5.754	5.882	5.791	5.735
13	5.739	5.769	5.801	5.868	5.785	5.807
14	5.780	5.765	5.741	5.831	5.778	5.729
15	5.448	5.533	5.540	5.955	5.549	5.683

RESULTS AND DISCUSSION

The QSAR model was performed on fifteen different models and the results have been verified. Of all the models studied, models 1 comprising of bend energy, DPLL, HLC, ovality, partition coefficient and torsion energy has been found to be very significant showing the importance of these descriptors in the designing of novel quinazolinone analogs for antitubercular activity, the models 5,6,7,8,9,10 and11 were found to be significant while the models 2,3,4,1213,14 and 15 were not significant for the biological activity. Hence the physicochemical parameters highlighted in the models 1 shall be considered while designing novel quinazolinone derivatives for antitubercular activity.

CONCLUSION

Out of 15 computational models studied, only one of them was found to be extremely significant. Therefore the parameters in this models shall provide an interesting value for the design of novel quinazolinone molecules as antitubercular agents.

Acknowledgements:
The authors are thankful to Prof. B.G.Shivananda, Principal, Al-Ameen College of Pharmacy, Bangalore for providing the facilities to carry out this research work.

REFERENCES

[1] World Health Organization. In Anti-tuberculosis Drug Resistance in the World; The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, **1997**.
[2] I Bastian; R Colebunders. *Drugs*, **1999**, 58, 633.
[3] D Butler. *Nature*, **2000**, 406, 670.
[4] Burgers Medicinal Chemistry & Drug Discovery, Vol 5, 6th edition, A john Wiley and Sons, Inc, Publication, edited by Donald J. Abraham,**2007**, 809.
[5] V V Poroikov; D A Filimonov; Y V Borodina. *J. Chem. Inf. Comput. Sci*, **2000**, 40, 1349.
[6] A V Stepanchikova; A A Lagunin; D A Filimonov, V V Poroikov, *Curr. Med. Chem*, **2003**, 10, 225.
[7] V V Poroikov; D A Filimonov; *J. Comput. Aided Mol.Des*. **2003**, 16, 819.
[8] A A Geronikaki; J C Dearden; D Filimonov; I Galaeva; T L Garibova; T Gloriozova; V Krajneva; A Lagunin; F Z Macaev; G Molodavkin; V V Poroikov; S I Pogrebnoi; F Shepeli; T A Voronina; M Tsitlakidou; L Vlad. *J. Med. Chem*, **2004**, 47, 2870.
[9] A Geronikaki; E Babaev; J Dearden; W Dehaen; D Filimonov; I Galaeva; V Krajneva; A Lagunin; F Macaev; G Molodavkin; V Poroikov; S Pogrebnoi; V Saloutin; A Stepanchikova; E Stingaci; N Tkach; L Vlad; T Voronina. *Bioorg. Med. Chem*, **2004**, 12, 6559.
[10] E E Oruc; S Rollas; F Kandemirli; N Shvets; A S Dimoglo. *J. Med. Chem*, **2004**, 47, 6760.
[11] L Collins; S G Franzblau; *Antimicrob. Agents Chemother*, **1997**, 41, 1004.
[12] Subramaniam R, Rao GK. *Chemical Sciences Journal*. **2012**, 66.