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3D-QSAR STUDIES OF SOME PHARMACOLOGICAL IMPORTANT COMPOUNDS

KISHOR ARORA*

Department of Chemistry, Govt. P.G. Auto. College, Datia (M.P.) -475661, INDIA

ABSTRACT

3D QSAR viz. 3 descriptor quantitative structure and activity relationship studies for a series of compounds i.e. 1,3-Thiazolyl-7-Chloro-quinazolin-4-(3H) -ones involving their semi-empirical quantum chemical descriptors and their laboratory reported activities against pathogens viz. *E.coli* and *S.aureus* have been carried out and reported in the present paper. Graphs between observed and predicted activities, both in the terms of p(MIC) are also being reported on the basis of which this may be concluded that some parameters/descriptors have positive contribution towards the activity. The method has been proved to be useful tool for such type of studies.

KEY WORDS: **Semi-empirical/3dqsar/pharmacological compounds**

KISHOR ARORA
Department of Chemistry, Govt. P.G. Auto. College, Datia (M.P.) -475661, INDIA

INTRODUCTION

Micro-organism viz. fungi, bacteria and viruses etc. may be harmful to mankind(1-3). Studies of nature and properties of micro-organisms were the necessity of man since past (1-3). Some of the discoveries such as penicillin, chloromycitin, sulpha drugs and antibiotics may be treated as mile stones in this regard (4-6). The studies involving antimicrobial activities of naturally occurring and/ or synthetic compounds in the laboratory which may include organic and inorganic complex compounds were of interest of many workers since past (7-18). A few years ago workers in this field have started carrying out theoretical studies in drug discovery pertaining to QSAR studies, which may prove to be a better tool and technique to save time and labor of screening of each and every compound against microbes. In some of the recent references scientists have even utilized electronic properties or parameters of compounds computed on the basis of Quantum Chemical calculations viz. ab-initio or semi-empirical studies as descriptors for QSAR studies and correlated these descriptors with activities of the compounds against microorganisms (19-29) which has been proved as a step ahead in the related field. Keeping above discussion in mind, in this present paper QSAR precisely 3D-QSAR studies which have been carried out on a new series of compounds i.e. 1,3-Thiazolyl-7-Chloro-quinazolin-4-(3H) -ones (J1- J15 compounds shown in figure) with their activities against *E. coli* and *S. aureus,* are reported. These compounds were procured and their activities were checked and taken into consideration for the studies according to the reported references (30-31).

Computational Details

The AM1 Hamiltonia on Hyperchem 8.0 professional version were used to calculate the QSAR related descriptors such as Hydration energy (Hyd E), log P (log P), Refractivity (REF), Polarizability (POL). mass (mass), Surface area approx (SAA), Surface area Grid (SAG), volume (Vol), Heat of formation (HF) , Zero point energy (ZPE), HOMO energy (HOMO), LUMO energy (LUMO) and dipole moment (DM). All these computations were carried out on Pentium core -2 duo machine having configuration
Intel (R) core $^{(TM)}$ 2 Duo CPU
T $_{5450}$@ 1.66 GHz.
982 MHz, 896 MB RAM
150 GB HDD
with windows – Microsoft windows XP software as an operating system. These descriptors and the activities of the compounds against specified microbes, mentioned in the tables, were taken into consideration in terms of p (MIC) and were subjected to statistical analysis/ regression analysis to get QSAR equations. All these statistical calculations were carried out on the same machine mentioned above using STATISTICA 9.0 version software.

RESULTS AND DISCUSSION

In the present paper, author wishes to report the semi-empirical quantum chemically computed properties viz. Hydration energy (Hyd E), log P (log P), Refractivity (REF), Polarizability (POL). mass (mass), Surface area approx (SAA), Surface area Grid (SAG), volume (Vol), Heat of formation (HF) , Zero point energy (ZPE), HOMO energy (HOMO), LUMO energy (LUMO) and dipole moment (DM) which were used as descriptors to correlate laboratory reported activities of the compounds under studies. Structures of all the compounds were drawn on HYPERCHEM 8.0 professional version and their geometries were optimized. Their quantum chemical parameters were computed semi- empirically on Pentium core -2 duo model computer whose configuration is mentioned above in the heading computational details. Structures of the compounds under studies are shown the figure 1. The physico-chemical and analytical parameters of these compounds are taken as reported and are recorded in the tables 1-2 with their reported activities against the pathogens under studies. The computed parameters which are taken into consideration as descriptors for QSAR studies are shown in tables 3. These descriptors were

considered with activities of the compounds under studies against the mentioned pathogens. Statistical analysis of all these parameters and activities in terms of p(MIC) were carried out to get the corresponding S.D. (standard deviation), F-test , correlation (r) and square of correlation values. The QSAR equations were reported using this statistical analysis. The correlation matrices involving all these descriptors were also obtained for all the parameters that were computed using all methods viz. AM1, PM3, MNDO and ZINDO. These matrices are also given in tables 4. On examination of correlation values from the correlation matrices and adopting a cross validation process 2D- i.e. 2 Descriptor QSAR equations for various parameters and their combinations were obtained by correlating these parameters with laboratory reported activities. Out of these equations appropriate equations are selected on the basis of their statistical values. Same method was adopted for getting 3D-QSAR equations also and ultimately one most appropriate equation was selected on the basis of their statistical values computed by the software STATISTICA 9.0. These final equations were used to get predicted activities for all the series of compounds and against all microorganisms under study. The final 3D-QSAR equations are reported as under:-

AM1/J1- J15/E. Coli

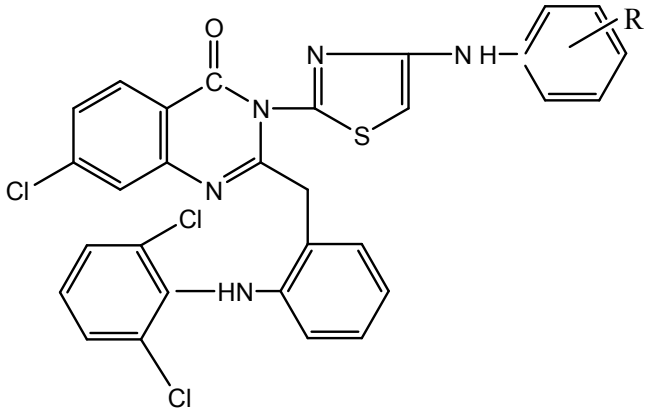
p(MIC) = -0.49 (DM) -0.73(LUMO) -0.05(HydE)
r= 0.60712734 r^2 =0.36860361 r^2(adj.) = 0.21075451
SE = 0.4706432 t= -2.588 F= 2.335165

AM1/J1- J15/S.Aureus

p(MIC) = 0.268 (HOMO)- 0.29 (LUMO) + 0.243(logP) -2.2165454
r= 0.39139 r^2 =0.15319 r^2(adj.) = 0.7775417
SE = 0.2379580 t= 1-9.315 F=0.6633251

Graphs were also drawn between observed activities and predicted activities, both in the terms of p(MIC) form 3 D-QSAR equations for this series of compounds. These trend line graphs are shown in figure 2-3.

Figure 1
Compounds Under Study (J1-J15)



R	
i	***2-Cl***
ii	***3-Cl***
iii	***4-Cl***
iv	***2-CH_3***
v	***3-CH_3***
vi	***4-CH_3***

vii	*2-NO_2*
viii	*3-NO_2*
ix	*4NO_2*
x	*4-OCH_3*
xi	*2-NO_2, 4-Cl*
xii	*2Cl, 4NO_2*
xiii	*3,4-$(Cl)_2$*
xiv	*3,5-$(Cl)_2$*
xv	*H*

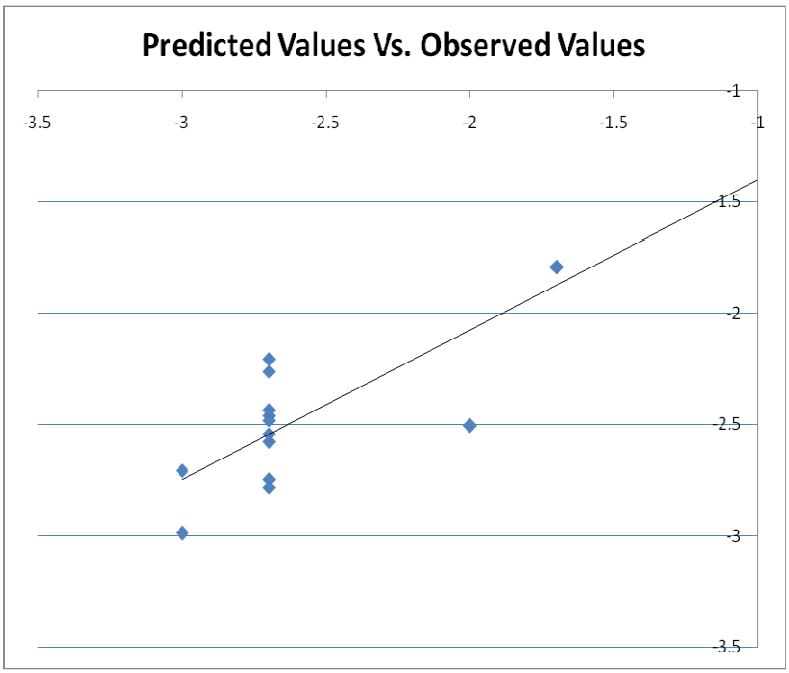


Figure 2
AM1 Observed Vs Predicted Values /J1-J15 Compounds Under Study/E. Coli

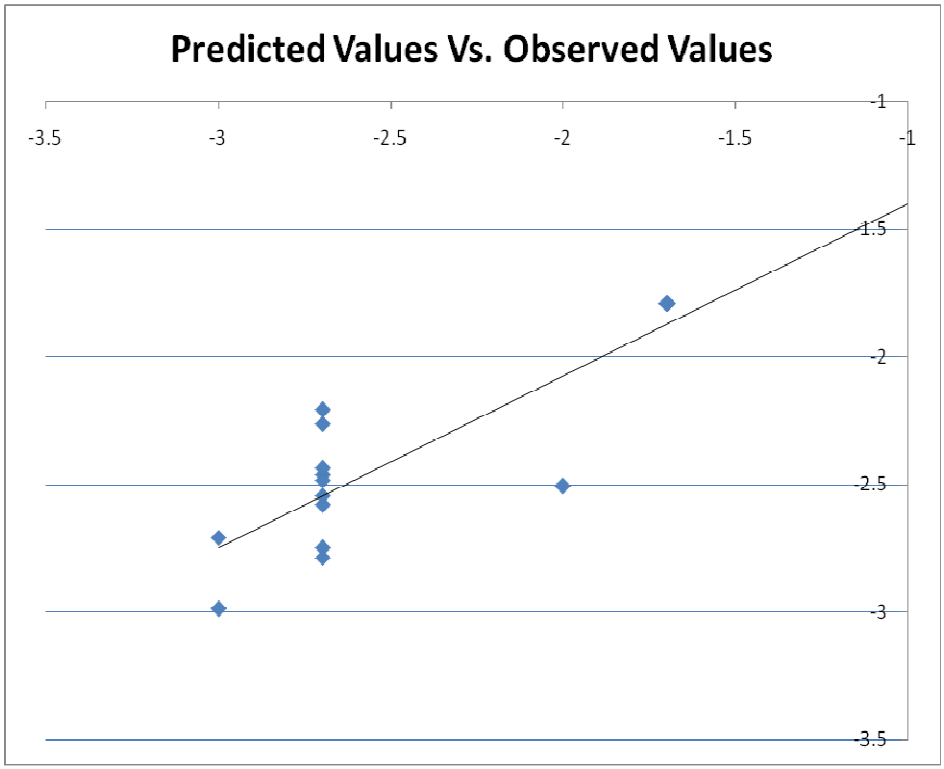


Figure 3
AM1 Observed Vs Predicted Values /J1-J15 Compounds Under Study/S.Aureus

Table 1
Physical and analytical data of the compounds under study

Compd	R-	Mol. Formula	% Yield	M.P. (^{0} C)
J1	2-Cl	$C_8H_7NOCl_2$	53	76
J2	3-Cl	$C_8H_7NOCl_2$	52	83
J3	4-Cl	$C_8H_7NOCl_2$	48	73
J4	2-CH_3	$C_9H_{10}NOCl$	56	68
J5	3-CH_3	$C_9H_{10}NOCl$	54	80
J6	4-CH_3	$C_9H_{10}NOCl$	60	78
J7	2-NO_2	$C_8H_7N_2O_3Cl$	51	64
J8	3-NO_2	$C_8H_7N_2O_3Cl$	58	69
J9	4-NO_2	$C_8H_7N_2O_3Cl$	53	73
J10	4-OCH_3	$C_9H_{10}NO_2Cl$	57	84
J11	2-NO_2,4-Cl	$C_8H_6N_2O_3Cl_2$	59	77
J12	2-Cl,4-NO_2	$C_8H_6N_2O_3Cl_2$	54	67
J13	3,4-$(Cl)_2$	$C_8H_6NOCl_3$	63	72
J14	2,5-$(Cl)_2$	$C_8H_6NOCl_3$	61	70
J15	H	C_8H_8NOCl	52	74

Table 1
Physical and analytical data of the compounds under study (Contd.)

Compd	R-	Mol. Formula	%C Found (Calcd.)	%H Found (Calcd.)	% N Found (Calcd.)
J1	2-Cl	$C_8H_7NOCl_2$	47.09 47.02	3.46 3.42	6.86 6.81
J2	3-Cl	$C_8H_7NOCl_2$	47.09 47.02	3.46 3.42	6.86 6.81
J3	4-Cl	$C_8H_7NOCl_2$	47.09 47.02	3.46 3.42	6.86 6.81
J4	2-CH_3	$C_9H_{10}NOCl$	58.86 58.81	5.49 5.46	7.63 7.59
J5	3-CH_3	$C_9H_{10}NOCl$	58.86 58.81	5.49 5.46	7.63 7.59
J6	4-CH_3	$C_9H_{10}NOCl$	58.86 58.81	5.49 5.46	7.63 7.59
J7	2-NO_2	$C_8H_7N_2O_3Cl$	44.71 44.77	3.29 3.27	13.05 13.01
J8	3-NO_2	$C_8H_7N_2O_3Cl$	44.71 44.77	3.29 3.27	13.05 13.01
J9	4-NO_2	$C_8H_7N_2O_3Cl$	44.71 44.77	3.29 3.27	13.05 13.01
J10	4-OCH_3	$C_9H_{10}NO_2Cl$	54.15 54.07	5.05 5.02	7.02 6.08
J11	2-NO_2, 4-Cl	$C_8H_6N_2O_3Cl_2$	38.58 38.52	2.43 2.41	11.25 11.21
J12	2-Cl, 4-NO_2	$C_8H_6N_2O_3Cl_2$	38.58 38.52	2.43 2.41	11.25 11.21
J13	3,4-$(Cl)_2$	$C_8H_6NOCl_3$	40.29 40.23	2.54 2.52	5.87 5.82
J14	2,5-$(Cl)_2$	$C_8H_6NOCl_3$	40.29 40.23	2.54 2.52	5.87 5.82
J15	H	C_8H_8NOCl	56.65 56.67	4.75 4.72	8.26 8.20

Table 2
Anti microbial activities of the compounds under study

Compd	R-	Mol. Formula	*E.Coli* Minimal Biocidal Concen. (µg/mL)	*S.Aureus* Minimal Biocidal Concen. (µg/mL)
J1	2-Cl	$C_8H_7NOCl_2$	500	250
J2	3-Cl	$C_8H_7NOCl_2$	**250**	500
J3	4-Cl	$C_8H_7NOCl_2$	250	250
J4	2-CH_3	$C_9H_{10}NOCl$	100	250
J5	3-CH_3	$C_9H_{10}NOCl$	100	500
J6	4-CH_3	$C_9H_{10}NOCl$	500	100
J7	2-NO_2	$C_8H_7N_2O_3Cl$	500	500
J8	3-NO_2	$C_8H_7N_2O_3Cl$	50	200
J9	4-NO_2	$C_8H_7N_2O_3Cl$	250	1000
J10	4-OCH_3	$C_9H_{10}NO_2Cl$	500	1000
J11	2-NO_2, 4-Cl	$C_8H_6N_2O_3Cl_2$	500	250
J12	2-Cl, 4-NO_2	$C_8H_6N_2O_3Cl_2$	500	500
J13	3,4-$(Cl)_2$	$C_8H_6NOCl_3$	250	500
J14	2,5-$(Cl)_2$	$C_8H_6NOCl_3$	125	100
J15	H	C_8H_8NOCl	250	250

Table 3
AM1 computed properties / QSAR descriptors of Compounds (J1-J15) under study

Compd.	HYD. E	Log P	REF	polar	Mass	SAA	SAG	VOL	HF (kCal/mol)	ZPE (kCal/mol)	HOMO	LUMO	DM (D)
J1	-7.18	0.47	184.5	65.4	639.3	548.4	789.5	1473.1	143.507	279.592	-0.0107	0.02885	2.094
J2	-7.21	0.47	184.5	65.4	639.3	557.7	793.4	1471.6	144.746	279.184	-0.0048	0.28768	1.972
J3	-7.83	0.47	184.5	65.4	639.3	569.3	807.8	1493.8	142.355	279.579	-0.0379	0.11744	4.149
J4	-6.25	0.84	184.1	65.1	618.9	546.9	789.4	1477.4	144.126	302.702	-0.0104	0.00883	3.683
J5	-6.93	0.84	184.1	65.3	618.9	567.0	797.4	1481.2	144.294	302.330	-0.1151	0.00580	3.758
J6	-6.53	0.84	184.1	65.3	618.9	563.5	798.2	1480.9	143.717	302.404	-0.1035	0.00660	3.503
J7	-19.68	-2.97	186.7	66.1	651.9	554.2	813.3	1509.8	126.256	301.974	-0.0243	0.04934	3.738
J8	-22.4	-2.97	186.7	66.1	651.9	576.1	820.4	1513.3	127.381	301.287	-0.0145	0.01763	3.978
J9	-22.8	-2.97	186.9	66.9	651.9	573.7	816.2	1514.0	125.904	301.572	-0.0464	0.00447	3.252
J10	-9.34	-0.30	186.2	65.9	634.9	577.7	812.9	1504.0	113.595	306.303	-0.0041	0.00937	2.317
J11	-19.1	-3.19	191.4	68.0	686.4	594.1	840.8	1553.7	119.882	296.056	-0.8331	0.01019	3.625
J12	-21.9	-3.19	191.4	68.0	686.4	604.3	838.9	1552.0	120.409	295.381	-0.0001	0.24576	2.398
J13	-6.93	0.24	189.2	67.33	673.8	593.7	815.1	1511.4	139.633	273.357	-0.0746	0.13243	2.464
J14	-6.86	0.24	189.2	67.33	673.8	589.2	818.0	1517.5	138.006	273.724	-0.0356	0.09127	2.581
J15	-7.65	0.69	179.8	63.48	604.9	523.5	763.7	1429.7	151.446	285.032	-0.0088	0.01056	3.379

Table 4
Correlation matrix forAM1 computed properties / QSAR descriptors of Compounds (J1-J15) under study

	HF	DM	ZPE	HOMO	LUMO	HydE	logP	REF	POL	Mass	SAA	SAG	VOL
HF	1.000												
DM	0.0719	1.000											
ZPE	0.486	0.4406	1.000										
HOMO	0.1571	0.3647	0.1257	1.000									
LUMO	0.071659	0.5500	0.5863	0.2049	1.000								
HydE	0.7292	0.22585	0.4488	0.1538	0.7684	1.000							
LogP	0.7740	0.11810	0.3661	0.1732	0.0526	0.9731	1.000						
REF	0.7209	0.23260	0.0107	0.01966	0.3345	0.5248	0.6181	1.000					
POL	0.6744	0.22336	0.0333	0.1523	0.3319	0.5410	0.6206	0.9854	1.000				
Mass	0.6001	0.26418	0.2391	0.0043	0.4494	0.5367	0.6388	0.9520	0.9498	1.000			
SAA	0.6251	0.19231	0.03384	0.2441	0.3838	0.3903	0.4329	0.9214	0.9192	0.8473	1.000		
SAG	0.8011	0.00805	0.1652	0.1339	0.2143	0.6601	0.7138	0.9475	0.9337	0.8830	0.9130	1.000	
VOL	0.7949	0.23189	0.1676	0.1186	0.1087	0.6606	0.7230	0.9637	0.9521	0.8972	0.8992	0.9929	1.000

CONCLUSION

This method has once again proved to be useful for this type of studies. The parameters/ descriptors which contribute positively to p (MIC) in final 3D QSAR equations are listed below:-
AM1/J1- J15/*E. Coli:* DM, LUMO and HydE
AM1/J1- J15/*S.Aureus:* HOMO, LUMO and log P
In conclusion this may be said that these parameters / descriptors have more impact on (MIC) over all other descriptors computed and reported.

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