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Semi-Empirical Based 3D-QSAR Studies Of Some Pharmacological Important Compounds with a Pathogen.

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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 pathogen viz. *streptococcus pyogenes* 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 reported on the basis of which it has been concluded that some of these quantum chemical descriptors have positive contribution towards the activity and this method has been proved to be useful tool for such type of activity relationship QSAR studies.

Keywords: Quantum chemical, 3D-QSAR, pharmacological compounds

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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 and area of interest of man since past (1-3). Some of the wonderful discoveries such as penicillin, chloromycitin, sulpha drugs and antibiotics may be treated as mile stones for these studies [4-6].

The studies involving antimicrobial activities of naturally occurring and/ or laboratory synthesized compounds which may include organic and inorganic complex compounds against various microbes were of interest of many workers since past [7-18].

A few years ago workers have started carrying out theoretical studies in this field 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 the lab.

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 or density functional studies as descriptors for QSAR studies and correlated these descriptors with activities of the compounds against micro-organisms [19-29] which has been proved as a step ahead in this 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 *streptococcus pyogenes,* are reported.

The activities of these compounds 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 $^{(™)}$ 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.

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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 stepwise statistical analysis/ regression analysis to get QSAR equations. All these statistical calculations were carried out on the same machine mentioned above using MS-Excel.

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 computer mentioned above in the heading computational details. 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 pathogen under study.

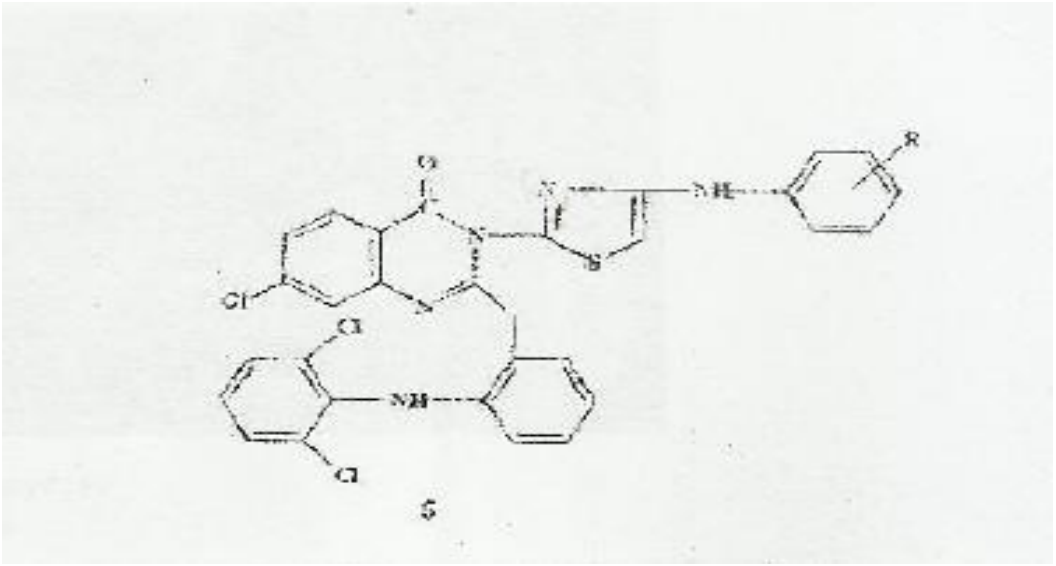

Figure -1 Compounds Under Study (J1-J15)

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

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

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

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 matrix involving all these descriptors were also obtained for all the parameters that were computed and is given in tables 4. On examination of correlation values from the correlation matrix 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. All statistical computations were carried out by MS-Excel software.

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This final equation was 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/*S.pygenes:*
p(MIC) = -0.00511 (SAA) -0.54732(LUMO) +0.175796(DM) – 0.21124
n = 15, r= 0.660166 SE = 0.278621 F= 2.832436

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.

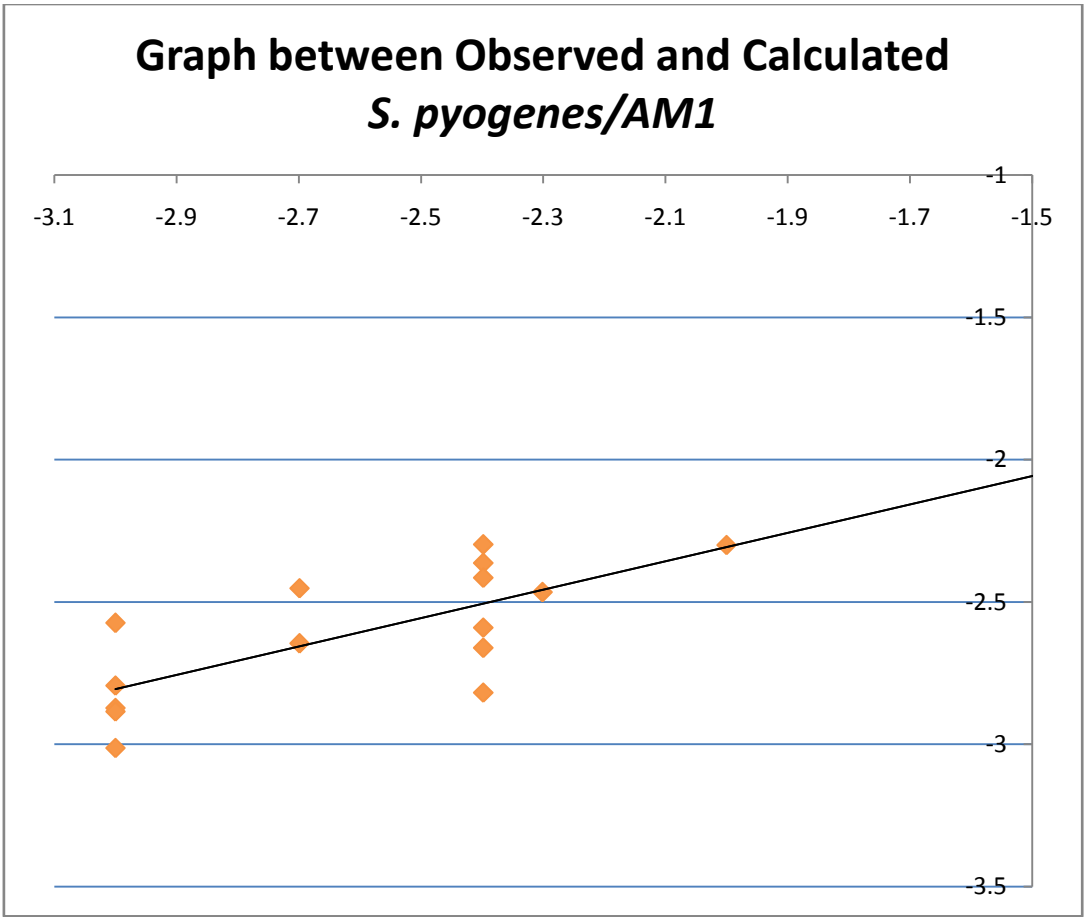

Figure 2:- AM1 Observed Vs Predicted Values /J1-J15 Compounds under Study/*S. Pyogenes*

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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

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CONCLUSIONS

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/*S.Pyogenes:* SAA, LUMO and DM

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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