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Quantitative Structure-Activity Relationships of the Trisubstitued Triazines Bearing Aminopyrimidine Group

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The quantum study of the trisubstitued triazines bearing aminopyrimidine group was calculated by Gaussian 03 program. The energies, main composition and proportion of the frontier orbitals and electron density were analyzed. The study found that there exists correlation between the antibacterial activity of the trisubstitued triazines bearing aminopyrimidine group and energy. It was found that the C(3) and C(4) atoms were the active sites. In order to get the regression equation, the correlation analysis was done between some characteristic parameters of the compound and the experiental parameters of antimicrobial activity and good parameters were selected for the linear regression. The result shows that the total energy of compound (E_{tot}), molecular weight (M), hydrophobic parameter (log P) are the main influencing factors for the antibacterial activity of the compound and when the log P is in the 0~3.881 interval.

Key Words: Triazine derivatives, Antibacterial activity, Structure-activity relationships, Quantum chemistry.

INTRODUCTION

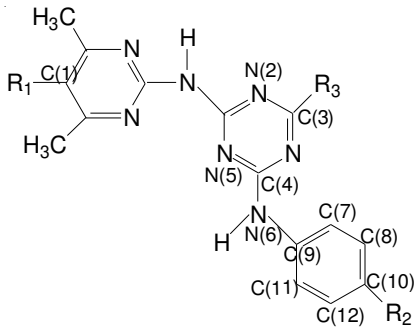
Triazine derivatives have many important uses in industry[1-4], agriculture and medicine, such as bactericide, herbicide, anti-oxidant for polymer, ultraviolet absorbers and intermediate of medicine, *et al.*, Pyrimidine is a basic nitrogen-containing heterocyclic organic compound[5-8]. Its derivatives exist in nature widely. The trisubstitued triazines bearing aminopyrimidine group have good antibacterial activity to resist apple to perish[9]. The quantum study of the trisubstitued triazines bearing aminopyrimidine group was calculated by Gaussian 03 program. The study found the correlation between the anti-bacterial activity of the trisubstitued triazines bearing aminopyrimidine group and structural parameters and filter the main factors to affect the biological activity, the influence to biological activity from the changes in the molecular structure was explained, the mechanism and sites of action of compound was discussed.

EXPERIMENTAL

Method of calculations: The geometries of all compounds were optimized using the *ab initio* HF with the 6-31G* basis set. Harmonic vibrational frequencies calculated at the same level were used for characterization of stationary points as a minimum. All quantum calculations were performed with the Gaussian 03 program.

RESULTS AND DISCUSSION

Stability configurations: The structure of compounds as follows:



R_1	R_2	R_3
2 R_1=H	a R_2=Cl	a R_3=NHCH(CH_3)$_2$
3 R_1=CH_3	b R_2=OCH_3	b R_3=OCH_3
4 R_1=Br	c R_2=CH_3	

Parameters: The result of quantum calculation was listed in Table-1.

Correlation analysis: The SPSS statistical software was used to correlation analysis. The independent variables are the parameters are given in Table-1 and the dependent variables are rate of inhibition. The correlation coefficient are given in Table-2:

TABLE-1
PARAMETERS OF COMPOUNDS

Compd.	E_{HOMO}	E_{LUMO}	E_{tot}	M	LogP	μ	R	P
2aa	-0.30804	0.11806	-1589.02718	384.87	3.22	3.1870	107.26	43.38
2ba	-0.29996	0.12324	-1244.00675	380.45	3.28	2.0194	104.77	43.92
2ca	-0.29995	0.12228	-1169.16414	364.45	4.00	0.9217	103.35	43.28
2ab	-0.30655	0.11229	-1530.77720	357.80	2.64	3.4935	94.36	38.23
2bb	-0.29591	0.11941	-1185.75650	353.38	2.84	2.6443	93.66	38.77
2cb	-0.29846	0.11822	-1110.91430	337.38	3.48	2.9432	93.05	38.14
3aa	-0.30712	0.12141	-1628.05906	398.90	4.26	3.6121	110.00	45.21
3ba	-0.29922	0.13178	-1283.03859	394.48	4.31	2.2413	107.52	45.75
3ca	-0.29917	0.12975	-1208.19600	378.48	5.03	1.3067	106.10	45.12
3ab	-0.30581	0.11403	-1569.80914	459.35	5.08	3.9869	110.39	47.09
3bb	-0.29658	0.12738	-1224.78853	367.41	3.87	4.2746	96.40	40.61
3cb	-0.29764	0.12363	-1149.94620	351.41	4.52	3.2059	95.80	39.97
4aa	-0.31187	0.11173	-4158.33075	463.77	4.74	1.8616	109.31	46.55
4ba	-0.30378	0.11834	-3813.31061	459.35	5.08	2.2322	110.39	47.09
4ca	-0.30357	0.11726	-3738.46794	443.35	5.65	1.4630	107.18	46.45
4ab	-0.31081	0.10417	-4100.08050	436.70	4.00	1.5171	99.69	40.85
4bb	-0.30050	0.11358	-3755.06026	432.28	4.20	3.6238	99.89	41.40
4cb	-0.30227	0.11114	-3680.21784	416.28	4.92	2.5572	97.56	40.76

μ-molecular dipole moment; M- relative molecular mass; R – polarizability; P-molecular molar refractive index log P - The hydrophobic parameter

TABLE-2
CORRELATION COEFFICIENT BETWEEN THE PARAMETERS AND THE RATE OF INHIBITION

	μ	E_{HOMO}	E_{LUMO}	E_{tot}	M	R	P	Log P
Y	0.437	0.389	0.496	0.859	-0.653	-0.191	-0.272	-0.618

TABLE-3
ATOM NATURAL CHARGE OF COMPOUNDS

Compd.	C(1)	N(2)	C(3)	C(4)	N(5)	N(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	R_1(Br)
2aa	-0.412	-0.751	0.806	0.807	-0.716	-0.688	-0.218	-0.224	0.185	-0.054	-0.238	-0.223	-
2ba	-0.414	-0.755	0.804	0.809	-0.718	-0.697	-0.189	-0.333	0.120	0.383	-0.181	-0.280	-
2ca	-0.413	-0.754	0.804	0.808	-0.717	-0.690	-0.213	-0.218	0.166	-0.042	-0.233	-0.219	-
2ab	-0.409	-0.715	0.952	0.806	-0.700	-0.674	-0.238	-0.215	0.194	-0.062	-0.249	-0.215	-
2bb	-0.411	-0.722	0.949	0.807	-0.703	-0.685	-0.182	-0.326	0.126	0.377	-0.205	-0.275	-
2cb	-0.410	-0.719	0.950	0.807	-0.702	-0.678	-0.225	-0.212	0.173	-0.048	-0.243	-0.213	-
3aa	-0.205	-0.751	0.806	0.807	-0.717	-0.688	-0.218	-0.223	0.186	-0.055	-0.239	-0.222	-
3ba	-0.207	-0.756	0.804	0.808	-0.719	-0.697	-0.181	-0.280	0.121	0.382	-0.190	-0.332	-
3ca	-0.207	-0.754	0.804	0.808	-0.718	-0.690	-0.213	-0.218	0.167	-0.042	-0.233	-0.219	-
3ab	-0.202	-0.716	0.952	0.806	-0.701	-0.674	-0.238	-0.215	0.195	-0.062	-0.250	-0.215	-
3bb	-0.205	-0.722	0.949	0.807	-0.705	-0.687	-0.185	-0.276	0.127	0.378	-0.201	-0.328	-
3cb	-0.204	-0.720	0.950	0.807	-0.703	-0.678	-0.225	-0.212	0.174	-0.048	-0.244	-0.213	-
4aa	-0.282	-0.749	0.806	0.807	-0.716	-0.688	-0.214	-0.226	0.180	-0.051	-0.235	-0.225	0.049
4ba	-0.283	-0.753	0.804	0.809	-0.719	-0.697	-0.181	-0.281	0.118	0.385	-0.187	-0.333	0.046
4ca	-0.283	-0.752	0.805	0.809	-0.717	-0.690	-0.213	-0.217	0.164	-0.041	-0.232	-0.218	0.047
4ab	-0.280	-0.714	0.953	0.806	-0.700	-0.675	-0.231	-0.219	0.188	-0.057	-0.245	-0.219	0.052
4bb	-0.281	-0.721	0.950	0.808	-0.704	-0.686	-0.185	-0.276	0.125	0.380	-0.199	-0.328	0.049
4cb	-0.281	-0.718	0.951	0.807	-0.702	-0.678	-0.223	-0.211	0.170	-0.046	-0.242	-0.212	0.050

Natural charge: The atom natural charge of compounds are given in Table-3. These data show that, the negative charge is mainly concentrated in the C(1) of pyrimidine ring, N(2), N(5) and N(6) of triazine ring, and C(7), C(8), C(11) and C(12) of benzene ring. These atoms make the electronegative area, they could combine with positive area of receptor. The positive charge is mainly concentrated in the C(3) and C(4) of triazine ring and C(9) of benzene ring, These atoms make the positive area, they could combine with negative area of receptor.

Energy, main composition and proportion of the frontier molecules orbitals: According to the theory of molecular orbital (MO), the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) have the greatest influence on the activity of compounds. The reaction between active molecule and receptor macromolecular operated on the frontier molecules orbitals. E_{HOMO} is the energy of HOMO, which relate to the ability of electron donor. E_{LUMO} is the energy of LUMO, which relate to the ability of acceptance of electronic. For pesticide molecules, too low-E_{LUMO} or too high-E_{HOMO} means that the molecule itself activity is too strong, it is easy to be metabolized in organism. The effect of pesticide is difficult to control, so the E_{LUMO} or E_{HOMO} of the pesticide molecule should be suitable to estimate expected value[10-12].

From Table-1, the E_{LUMO} of 2ab is low comparatively, it could accept electronic easily, on the other hand, the E_{HOMO} of

TABLE-4
MAIN COMPOSITION AND PROPORTION OF FRONTIER MOLECULES ORBITAL

Compd.	HOMO	LUMO
2aa	N(2)4.76, N(5)4.55, N(6)20.7, C(7)7.15, C(9)15.4, C(10)17.6, C(11)6.34, C(12)4.39, R_2(Cl) 12.5	N(2)8.12, C(3)20.21, C(4)19.21, N(5)5.79, N(6)7.71, R_3(N)4.66, $R_3(C_1)$3.38, $R_3(C_2)$5.38, C(9)6.61, C(10)4.68
2ba	N(6)10.1, C(7)6.71, C(8)8.92, C(9)22.6, C(10)15.9, C(11)3.39, C(12)7.91, R_2(O)14.3	N(2)9.33, C(3)21.08, C(4)23.88, N(5)6.47, N(6)7.51, R_3(N)4.85, $R_3(C_1)$4.86, $R_3(C_2)$3.61, C(9)4.15
2ca	N(2)4.61, N(5)4.26, N(6)20.1, C(7)7.23, C(8)3.89, C(9)19.3, C(10)19.5, C(11)6.84, C(12)6.11	N(2)8.33, C(3)20.86, C(4)19.85, N(5)5.94, N(6)7.67, R_3(N)4.73, $R_3(C_1)$3.85, $R_3(C_2)$5.67, C(9)6.11, C(10)3.29
2ab	N(2)3.60, N(5)4.26, N(6)21.4, C(7)7.36, C(8)3.18, C(9)15.1, C(10)18.4, C(11)7.22, C(12)3.72, R_2(Cl)12.7	N(2)7.76, C(3)18.5, C(4)16.2, N(5)5.53, C(9)9.29, C(10)8.56, C(12)5.34
2bb	N(6)14.3, C(7)7.72, C(8)5.90, C(9)20.9, C(10)15.1, C(11)3.29, C(12)9.12, R_2(O)13.0	N(2)7.75, C(3)17.95, C(4)17.06, N(5)5.50, N(6)8.53, C(9)10.51, C(10)8.17, C(11)3.70
2cb	N(2)3.77, N(5)4.15, N(6)21.4, C(7)7.35, C(8)4.03, C(9)18.8, C(10)19.9, C(11)7.60, C(12)5.38	N(2)7.44, C(3)18.3, C(4)15.6, N(5)5.43, N(6)8.76, C(9)9.74, C(10)7.27, C(12)5.32
3aa	N(2)4.92, N(5)4.50, N(6)20.8, C(7)7.16, C(9)15.3, C(10)17.5, C(11)6.37, C(12)4.34, R_2(Cl)12.4	N(2)7.62, C(3)21.1, C(4)17.9, N(5)6.17, N(6)7.23, R_3(N)4.86, $R_3(C_1)$3.61, $R_3(C_2)$5.76, C(9)6.46, C(10)4.40
3ba	N(2)2.56, N(5)2.10, N(6)10.3, C(11)6.71, C(12)8.88, C(9)22.4, C(10)15.8, C(7)3.41, C(8)7.81	N(2)4.74, C(3)21.3, C(4)23.6, N(5)6.59, N(6)7.43, R_3(N)4.90, $R_3(C_1)$4.96, $R_3(C_2)$3.70, C(9)4.10
3ca	N(2)4.74, N(5)4.24, N(6)20.3, C(7)7.24, C(8)3.85, C(9)19.1, C(10)19.5, C(11)6.85, C(12)6.06	N(2)7.91, C(3)21.8, C(4)18.8, N(5)6.36, N(6)7.26, R_3(N)4.93, $R_3(C_1)$4.13, $R_3(C_2)$5.96, C(9)5.92
3ab	N(2)3.47, N(5)4.40, N(6)21.5, C(7)7.38, C(8)3.15, C(9)15.0, C(10)18.4, C(11)7.24, C(12)3.70, R_2(Cl)12.59	N(2)7.14, C(3)20.5, C(4)14.7, N(5)6.36, N(6)8.37, C(9)8.11, C(10)7.50, C(12)4.77
3bb	N(6)14.1, C(7)3.81, C(8)6.84, C(9)21.0, C(10)15.3, C(11)7.06, C(12)8.31, R_2(O)13.0	N(2)7.60, C(3)19.8, C(4)16.9, N(5)6.40, N(6)8.07, C(9)9.61, C(10)6.92, C(11)3.16
3cb	N(2)3.71, N(5)4.24, N(6)21.5, C(7)7.37, C(8)4.00, C(9)18.7, C(10)19.9, C(11)7.64, C(12)5.35	N(2)6.82, C(3)20.3, C(4)14.1, N(5)6.30, N(6)7.94, C(9)8.96, C(10)6.33, C(12)4.74
4aa	N(2)4.92, N(5)4.28, N(6)20.2, C(7)6.99, C(8)3.01, C(9)15.7, C(10)17.4, C(11)6.10, C(12)4.60, R_2(Cl)12.9	C(1)42.0, R_1(Br)52.0
4ba	N(6)8.44, C(7)3.19, C(8)8.51, C(9)23.3, C(10)16.2, C(11)6.61, C(12)9.15, R_2(O)15.0	C(1)42.1, R_1(Br)52.0
4ca	N(2)4.62, N(5)4.03, N(6)19.5, C(7)7.19, C(8)3.99, C(9)19.6, C(10)19.8, C(11)6.67, C(12)6.30	C(1)42.0, R_1(Br)52.0
4ab	N(2)3.68, N(5)4.13, N(6)20.9, C(7)7.16, C(8)3.25, C(9)15.5, C(10)18.2, C(11)6.90, C(12)4.0, R_2(Cl)13.0	C(1)42.1, R_1(Br)52.0
4bb	N(6)13.3, C(7)3.69, C(8)7.14, C(9)21.35, C(10)15.4, C(11)6.89, C(12)8.49, R_2(O)13.5	C(1)42.0, R_1(Br)52.0
4cb	N(2)3.80, N(5)4.03, N(6)20.9, C(7)7.26, C(8)4.12, C(9)19.1, C(10)20.1, C(11)7.42, C(12)5.58	C(1)42.0, R_1(Br)52.0

2ab is low comparatively too, the ability is weak to provide electronic. The experimental results show that the biological activity of compound 2ab is higher. Therefore, the mechanism is that receptor provide electronic to pesticide molecule possibly. The E_{LUMO} of 4ab is the lowest, the activity is too strong possibly and it is easy to be metabolized in organism. The analyses of theoretical results agree with the experimental data very well.

From Table-4, the main composition and proportion of E_{LUMO} of compounds 2aa~2cb and 3aa~3cb in the N(2), C(3), C(4), N(5), N(6) and C(9), the positive charge is mainly concentrated in the C(3) and C(4), they could accept electronic from receptor; The main composition and proportion of E_{LUMO} of compounds 4aa~4cb in the C(1), the negative charge is mainly concentrated in the C(1), Its ability is weak to accept electronic. The main composition and proportion of E_{LUMO} of compounds have significant difference, it is the main factor that cause activity differences and C(3) and C(4) of these compounds are the main active site.

Regression analysis: The QSAR of the trisubstitued triazines bearing aminopyrimidine group was studied, the higher correlation parameters of Table-1 was been selected as independent variables and activity data as the dependent variable (Y) to be multiple linear regression analysis. The model (1) as follows:

$$Y = 55.171 + 0.018\ E_{tot} + 0.233M - 10.9821 \log P \quad (1)$$

n = 18, R = 0.915, Se = 0.838, F = 24.152, Q = 1.093

where n- The number of samples in the model; R- Multiple correlation coefficientl; Se- Standard deviation; F- sher's statistics; Q- Quality factor (Q=R/Se).

The model of Y and logP was discussed separately, it is a parabolic trends, the model (2) as follows:

$$Y = 90.129 + 4.758 \log P - 2.562 (\log P)^2 \quad (2)$$

The result shows that the total energy of compound (E_{tot}), molecular weight (M), hydrophobic parameter (log P) are the main influencing factors for the compound antibacterial activity and when the log P is in the 0~3.881 interval, it is an important condition that the compounds have good antibacterial activity. These would give clues for further molecular design.

Conclusions

(1) The characteristics of HOMO and LUMO are the main factors to influence antibacterial activities of these kinds of compounds.

(2) The mechanism is that receptor provide electrons to the trisubstitued triazines bearing aminopyrimidine group possibly.

(3) The results indicate that C(3) and C(4) of triazine ring might be an important active site, of which the potency of electric

charge translocation has a great influence on the antibacterial activity of this kind of compounds.

(4) When the logP is in the 0~3.881 interval, it is an important condition that the compounds have good antibacterial activity.

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