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Quantitative Structure-Activity Relationships of Thiazole Amide Derivatives Containing 2-Substituted-1,3-thiazolidine Ring

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The quantum correlation between antibacterial activity of thiazole amide derivatives containing 2-substituted-1,3-thiazolidine ring and structure were studied. The quantum study of these compounds was calculated by Gaussian 03 program. Then the related parameters were calculated and quantitative structure-activity relationships were studied. The study found that correlation is existed between the antibacterial activity of compounds and hydrophobic parameter (log P) and energy of LUMO orbital. The good parameters were selected for the linear regression. The result shows that linear equations was only related to log P. By analyzing of orbital composition, it was found that R(N) atoms were the active sites.

Keywords: Thiazole amide derivatives thiazolidine ring antibacterial activity quantitative structure-activity relationships.

INTRODUCTION

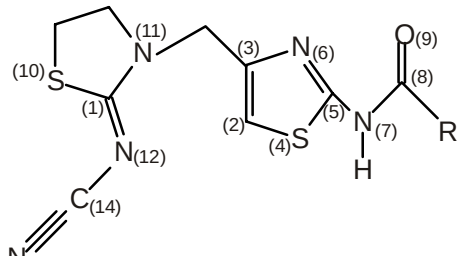
Thiazole amide derivatives containing as a chemical widely used in the field of agriculture[1-4], there are a lot of products of these pharmaceutical, such as, seedvax, metsulfovax, trifluzamide, ethaboxam, They are efficient, low toxicity, environmentally friendly compounds[5]. The thiazole amide derivatives were studied by quantum chemistry and quantitative structure-activity relationships (QSAR) in our work[6]. The study found that the correlation between antibacterial activity of the thiazole amide derivatives containing group and structural parameters and filter the main factors to affect the biological activity. The influences to biological activity from the changes in the molecular structure were explained. The mechanism and sites of action of compound were also discussed.

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[7] (**Scheme-I**):



4a R=C_6H_5	4b R=2-$CH_3C_6H_4$	4c R=4- $CH_3C_6H_4$	4d R=4-$CH_3CH_2C_6H_4$	4e R=4-$CH_3CH_2OC_6H_4$
4f R=2-FC_6H_4	4g R=3-FC_6H_4	4h R=4-FC_6H_4	4i R=2-ClC_6H_4	4j R=3-ClC_6H_4
4k R=4-ClC_6H_4	4l R=4-BrC_6H_4	4n R=3-$O_2NC_6H_4$	4o R=4-$O_2NC_6H_4$	4p R=2,4-$Cl_2C_6H_3$
4q R=3,4-$Cl_2C_6H_3$	4r R= CH_3			

Scheme-I

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

Natural charge: The atom natural charge of compounds are given in Table-2. These data show that, the negative charge is mainly concentrated in the O(9), N(6), N(7), R(O1) and R(O2) of compounds **4n** and **4o**,These atoms make the electronegative area, they could combine with positive area of receptor. the positive charge is mainly concentrated in the S(4), C(5), C(8), S(10), R(N) of compounds **4n** and **4o**, 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

TABLE-1
PARAMETERS OF COMPOUNDS

Compounds	E_{HOMO}	E_{LUMO}	ΔE	μ	R	P	log P	M
4a	-0.3280	0.0925	0.4205	6.5411	90.94	35.88	1.35	343.43
4b	-0.3231	0.1035	0.4266	7.2707	95.98	37.72	1.82	357.45
4c	-0.3267	0.0941	0.4208	6.8200	95.98	37.72	1.82	357.45
4d	-0.32652	0.0942	0.4208	6.8520	100.58	39.55	2.21	371.47
4e	-0.3268	-0.0026	0.3242	9.8550	83.83	34.27	1.82	347.38
4f	-0.3246	0.0960	0.4206	6.9829	91.15	35.79	1.49	361.41
4g	-0.3304	0.0858	0.4162	6.2891	91.15	35.79	1.49	361.41
4h	-0.3255	0.0990	0.4245	6.3782	91.15	35.79	1.49	361.41
4i	-0.3247	0.0944	0.4190	6.9938	95.74	37.81	1.87	377.87
4j	-0.3333	0.0813	0.4146	7.2662	95.74	37.81	1.87	377.87
4k	-0.3286	0.0863	0.4149	7.5033	95.74	37.81	1.87	377.81
4l	-0.3442	0.0708	0.4150	6.6342	102.96	38.63	1.87	422.32
4n	-0.3350	0.0383	0.3732	7.5037	97.26	37.72	-2.56	388.42
4o	-0.3350	0.0315	0.3666	5.5402	97.26	37.72	-2.56	388.42
4p	-0.3349	0.0733	0.4082	4.8867	100.05	39.74	2.95	412.31
4q	-0.3282	0.0872	0.4154	7.1921	100.55	39.74	2.39	412.31
4r	-0.3260	0.1021	0.4282	5.1666	70.77	28.06	-0.50	281.35

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

TABLE-2
ATOM NATURAL CHARGE OF COMPOUNDS

Compounds	S(4)	C(5)	C(8)	O(9)	S(10)	N(6)	N(7)	R(N)	R(O1)	R(O2)
4a	0.4112	0.3227	0.8710	-0.6592	0.3246	-0.5937	-0.7675			
4b	0.3976	0.3365	0.8693	-0.6642	0.3220	-0.6068	-0.7495			
4c	0.4108	0.3227	0.8720	-0.6617	0.3243	-0.5925	-0.7688			
4d	0.4106	0.3231	0.8720	-0.6617	0.3243	-0.5928	-0.7687			
4e	0.2020	0.4900	0.8669	-0.6509	0.2742	-0.6926	-0.7466			
4f	0.4032	0.3397	0.8689	-0.6514	0.3240	-0.6168	-0.7469			
4g	0.4142	0.3214	0.8686	-0.6544	0.3258	-0.5965	-0.7642			
4h	0.4007	0.3335	0.8685	-0.6585	0.3235	-0.6072	-0.7497			
4i	0.4028	0.3404	0.8665	-0.6492	0.3241	-0.6168	-0.7468			
4j	0.4223	0.3574	0.8677	-0.6370	0.3315	-0.6506	-0.7648			
4k	0.4111	0.3367	0.8679	-0.6507	0.3239	-0.6166	-0.7571			
4l	0.4010	0.3266	0.8657	-0.6683	0.3013	-0.5870	-0.7609			
4n	0.4222	0.3174	0.8661	-0.6508	0.3286	-0.6020	-0.7617	0.6482	-0.4560	-0.4584
4o	0.4166	0.3313	0.8618	-0.6466	0.3231	-0.6176	-0.7511	0.6572	-0.4573	-0.4605
4p	0.4244	0.3545	0.8646	-0.6149	0.3315	-0.6525	-0.7663			
4q	0.4035	0.3303	0.8654	-0.6543	0.3223	-0.6073	-0.7484			
4r	0.4044	0.3240	0.8506	-0.6783	0.3254	-0.6088	-0.7516			

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[8-10].

From Table-1, there is no significant changes in E_{HOMO} of compounds and the E_{LUMO} are different. Therefore, the antibacterial activity of these compounds may have some relationship with E_{LUMO}. The E_{LUMO} of compound **4e** is a negative value, 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. The E_{LUMO} of compounds **4n** and **4o** is comparatively low (closed to the 1.00 ev), it could accept electronic easily and the antibacterial activity of them is good. The E_{LUMO} of compounds **4d**, **4p** and **4q** is 1.99-2.56 ev, they have no antibacterial activity almost. So, the antibacterial activity of compounds is correspondingly better when the E_{LUMO} is closed to the 1.00 ev. the antibacterial activity of compound **4b** is good too, but the E_{LUMO} of compound **4b** is 2.82 ev, it maybe a uncommon value, or there are other factors to influence the activity.

From Table-3, the main composition and proportion of E_{LUMO} of compounds **4n** and **4o** in the R(C3), R(C4), R(N), R(O1) and R(O2), the positive charge is mainly concentrated in the R(N), which could accept electronic from receptor. The main composition and proportion of E_{LUMO} of other compounds in C(5), C(8) and S(10) and they are positive charge. The main composition and proportion of E_{LUMO} of compounds have significant difference, it is the main factor that cause activity differences and a strong electron withdrawing group (nitro

TABLE-3
MAIN COMPOSITION AND PROPORTION OF FRONTIER MOLECULES ORBITAL

Comps.	HOMO	LUMO
4a	C(2)26.64, C(3)16.82, S(4)13.37, C(5)13.14, N(6)5.89, N(7)13.36, N(11)4.02	C(2)9.60,S(4)9.59,C(5)16.83,N(6)5.26,C(8)9.69, O(9)8.05,R(C2)4.46,R(C1)6.29,R(C6)5.43,R(C4)8.93
4b	C(2)26.84, C(3)15.45, S(4)13.17, C(5)11.73, N(6)7.08, N(7)15.33, O(9)3.25, N(11)3.38	C(1)5.63,C(2)13.46,C(3)4.42,S(4)12.16,C(5)25.12, N(6)6.99,C(8)7.92,O(9)5.42
4c	C(2)25.59, C(3)15.75, S(4),12.29, C(5)12.84, N(6)6.02, N(7)12.84, N(11)3.75	C(2)10.20,C(3)3.03,S(4)10.02,C(5)17.60,N(6)5.39, C(8)9.16,O(9)7.55,R(C2)3.94,R(C1)5.26,R(C6)5.06, R(C4)7.78
4d	C(2)25.47, C(3)15.63, S(4)12.20, C(5)12.77, N(6)6.05, N(7)12.83, N(11)3.72	C(2)10.1,C(3)3.00,S(4)9.95,C(5)17.44,N(6)5.33,C(8)9.09,O(9)7.5(, R(C2)3.68, R(C1)5.26, R(C6)5.12
4e	C(2)29.35, C(3)7.88, C(5)6.43, N(6)23.83, N(7)9.43, R(C1)4.36	C(3)16.76,S(4)37.79,C(5)17.13,N(6)4.05,N(7)4.53, N(11)4.50
4f	C(2)27.05, C(3)15.74, S(4)13.68, C(5)11.64, N(6)7.07, N(7)15.49, O(9)3.06, N(11)3.27	C(2)5.53,S(4)6.33,C(5)11.11,N(6)3.44,N(7)3.13,C(8)8.42,O(9)6.8 3, R(C2)5.18,R(C1)11.52, R(C3)5.31,R(C6)6.05, R(C4)16.21
4g	C(2)26.75, C(3)17.11, S(4)13.57, C(5)13.09, N(6)5.76, N(7)13.40, N(11)4.05	C(2)6.28, S(4)6.69, C(5)11.77, N(6)4.06, C(8)10.71, O(9)8.86, R(C2)8.37, R(C1)10.35, R(C6)5.06, R(C4)12.58, R(C5)4.36
4h	C(2)27.00, C(3)15.78, S(4)13.23, C(5)11.90, N(6)6.95, N(7)15.22, O(9)3.24, N(11)3.26	C(1)3.08, C(2)7.56, S(4)8.40, C(5)18.90, N(6)5.77, C(8)7.23, O(9)4.33, R(C2)11.70, R(C3)6.93, R(C6)7.14, R(C5)10.16
4i	C(2)26.97, C(3)15.76, S(4)13.78, C(5)11.60, N(6)7.01, N(7)15.49, N(11)3.28	C(2)4.11,S(4)5.20,C(5)9.28,N(6)3.07,N(7)3.02,C(8)7.77,O(9)5.98, R(C2)12.57, R(C1)13.17,R(C5)15.20, R(C6)8.34
4j	C(2)25.54, C(3)16.19, S(4)14.12, C(5)11.08, N(6)6.43, N(7)4.59	C(2)4.51,S(4)6.17,C(5)12.55,N(6)4.73,C(8)12.06,O(9)9.76,R(C6)5 .59, R(C1)10.32, R(C5)4.64,R(C2)8.46, R(C4)13.73
4k	C(2)26.96, C(3)16.37, S(4)13.91, C(5)11.98, N(6)6.21, N(7)14.34	S(10)50.23, N(11)21.91
4l	C(2)18.63, C(3)12.33, S(4)10.88, C(5)9.32, N(6)4.26, N(7)11.43, R(C1)6.80, R(C4)5.30, R(Br)8.58	S(4)3.79, C(5)6.38, C(8)10.79, O(9)9.53, R(C1)14.20, R(C5)3.55, R(C2)8.76, R(C4)19.07
4n	C(2)26.69, C(3)17.57, S(4)13.54, C(5)13.20, N(6)5.54, N(7)13.17, N(11)4.06	R(C2)7.80, R(C3)14.14, R(C6)18.85, R(C4)12.03, R(O1)11.52, R(N)16.44, R(O2)11.31

TABLE-4
CORRELATION COEFFICIENT BETWEEN THE PARAMETERS AND THE RATE OF ANTIBACTERIAL RATE

	μ	E_{HOMO}	E_{LUMO}	ΔE	R	P	log P	M
Y	-0.112	-0.126	0.085	0.115	-0.195	-0.273	-0.513	-0.206

group) into benzene ring of these compounds are the main active site.

Correlation analysis: The independent variables are the parameters (Table-1) and the dependent variables are rate of inhibition. The correlation coefficient are given in Table-4.

Regression analysis: QSAR of thiazole amide derivatives containing group was studied, the higher correlation parameters (Table-4) has been selected as independent variables and activity data as the dependent variable (Y) for multiple linear regression analysis. The model (1) are as follows:

$$Y = 17.426 - 3.429 \log P \quad (1)$$

$$N = 17; R = 0.513; Se = 0.968; F = 5.361; Q = 0.5300$$

n-Number of samples in the model
R-Multiple correlation coefficient
Se-Standard deviation
F- Sher's statistics
Q-Quality factor (Q = R/Se)

The result shows that hydrophobic parameter (log P) is the main influencing factors for the antibacterial activities and the antibacterial activity was negatively correlated with log P.

Conclusions

• The characteristics of LUMO are the main factors to influence antibacterial activities of these kinds of compounds.

• The mechanism is that receptor provide electronic to the thiazole amide derivatives containing group possibly.

• The results indicate that R(N) of nitro group might be an important active site, of which the potency of electric charge translocation has a great influence on the antibacterial activity of compounds.

• When log P was negatively correlated with the antibacterial activity.

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