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Studies on Structure-Activity Relationship of *N*-Substituted Phenyl Cinnamide Compounds with Antitumor Activity

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The relationship of structure and antitumor activity of *N*-substituted phenyl cinnamide derivatives were studied. The main influntcing factor is LUMO orbital of molecular. When these compounds reacted with the receptors, they could accept the electrons. The C(8) atom on carbonyl is the active site. The result of QSAR showed that there is a positive correlation between the antitumor activity and the E_{LUMO} of compounds.

Keywords: Cinnamamide, Antitumor activity, Quantum chemistry, Quantitative structure-activity relationship.

INTRODUCTION

Cinnamide derivatives have many applications in medicine, they can be the protective agent to the brain nerve. Cinnamide derivatives were interested because of its good antitumor effect[1-5]. Welch *et al.*[6] extracted cinnamide derivatives from *Streptomyces griseolutens*. They can inhibit the invasion and metastasis of human malignant melanoma cell line C8161 and A375M. Cinnamide derivatives are low toxicity, can inhibit the growth and metastasis of tumor effectively. They are the lead compounds for the development of anticancer drugs.

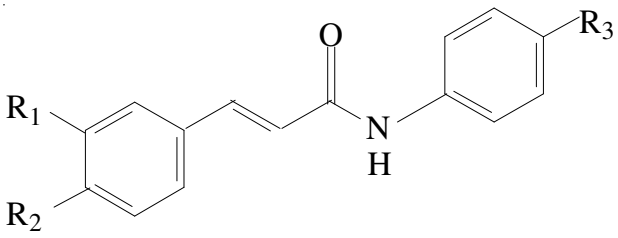
The study found the correlation between the antitumor activity of these compounds and structural parameters and filter the main factors to affect the biological activity and the influence to biological activity from the changes in the molecular structure was explained, the mechanism and sites of action of compound was discussed[7-9].

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 and natural charge: The structure of *N*-substituted phenyl cinnamide compounds[10] as follows:



B: R_1=R_2=OH, D: R_1=R_2= –OCH_2 –

1: R_3=H, 2: R_3=Cl, 3: R_3=CH_3, 4:R_3=OCH_3, 5:R_3=$COOCH_3$

The atom natural charge of compounds are given in Table-1. These data show that, the negative charge is mainly concentrated in the C(1), C(2), C(3), C(4), C(6), C(7), O(9), N(10), C(12), C(13) and C(14); and the positive charge is mainly concentrated in the C(8) and C(11), C (5) in the molecular B1-B5 is positive charge, the reason: the substituent of R_2 is -OH, are the electron donating group, so the C(1) were negative, C(5) were positive. The positive electricity of C(8) is great and the electron withdrawing effect of it is strong, so the C(8) is the active site of *N*-substituted phenyl cinnamide compounds.

Energy, main composition and proportion of the frontier molecules orbital: 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.

TABLE-1
ATOM NATURAL CHARGE OF COMPOUNDS

Compound No.	B1	B2	B3	B4	B5	D1	D2	D3	D4	D5
C(1)	-0.287	-0.288	-0.287	-0.288	-0.288	-0.185	-0.185	-0.185	-0.186	-0.185
C(2)	-0.213	-0.214	-0.213	-0.213	-0.213	-0.233	-0.235	-0.233	-0.234	-0.234
C(3)	-0.255	-0.255	-0.255	-0.255	-0.255	-0.257	-0.258	-0.257	-0.234	-0.257
C(4)	-0.106	-0.108	-0.105	-0.105	-0.110	-0.073	-0.076	-0.072	-0.072	-0.077
C(5)	0.303	0.304	0.302	0.302	0.305	-0.156	-0.155	-0.156	-0.157	-0.154
C(6)	-0.174	-0.170	-0.176	-0.176	-0.167	-0.182	-0.177	-0.183	-0.184	-0.175
C(7)	-0.308	-0.311	-0.307	-0.306	-0.314	-0.299	-0.303	-0.298	-0.297	-0.305
C(8)	0.822	0.824	0.822	0.821	0.824	0.822	0.823	0.821	0.820	0.824
O(9)	-0.710	-0.708	-0.712	-0.716	-0.702	-0.709	-0.707	-0.711	-0.715	-0.701
N(10)	-0.702	-0.703	-0.702	-0.702	-0.704	-0.702	-0.702	-0.701	-0.701	-0.703
C(11)	0.196	0.195	0.183	0.148	0.235	0.195	0.193	0.182	0.146	0.234
C(12)	-0.273	-0.257	-0.259	-0.233	-0.291	-0.272	-0.249	-0.258	-0.231	-0.286
C(13)	-0.266	-0.250	-0.252	-0.221	-0.287	-0.265	-0.256	-0.252	-0.220	-0.290
C(14)	-0.260	-0.066	-0.061	0.357	-0.237	-0.259	-0.065	-0.060	0.358	-0.235

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 molecules of medicine, 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 medicine is difficult to control, so the E_{LUMO} or E_{HOMO} of the medicine molecule should be suitable to estimate expected value[11,12].

We know from the literature[10], the antitumor activity of D2 and D1 is the highest and the antitumor activity of B3 and B4 is low comparatively. From Table-2, the E_{HOMO} of D2 and D1 is low, so the electron donating ability of D2 and D1 is very weak; The E_{LUMO} of D2 and D1 are low comparatively, it could accept electronic easily, so the antitumor activity of D2 and D1 are higher; The E_{LUMO} of B3 and B4 are high comparatively, it make the weak ability of molecular to accept electronic, so the antitumor activity of B3 and B4 are lower. We can conclude that, the lower E_{LUMO} of compound, the better antitumor activity of the compound relatively. And the conclusion is consistent with the experimental values.

The E_{LUMO} of B5 and D2 only has little difference, the activity of B5 should be similar to D2 for theoretically speaking, but the experimental data of B5 is bad. So the analysis of this theory and experimental results is not consistent, the possible reasons are the experimental data of compound B5 is singular value, so the B5 is no longer considered in the later discussion.

From Table-3, the main composition of HOMO of most compounds are in the N(10), C(11), C(12), C(13) and C(14). The main composition of LUMO of most compounds are in the C(3), C(4), C(5), C(6), C(7), C(8) and O(9). It has been discussed in the previous, that the differences of E_{LUMO} may be the main factors to the antimicrobial activity. So, the main composition of LUMO of compounds may be the active sites.

Parameters: The result of quantum calculation was listed in Table-4.

Correlation analysis: The SPSS statistical software was used to correlation analysis. The independent variables are the parameters in Table-4 and the dependent variables are antitumor activity. The correlation coefficient in Table-5:

Regression analysis: The QSAR of the *N*-substituted phenyl cinnamide compounds was studied, the higher correlation parameters of Table-4 were been selected as independent variables and anti-tumor activity as the dependent variable (Y) to be stypwise linear regression analysis. The model (1) as follows:

$$Y = -479.885 + 6040.224\ E_{LUMO} \quad (1)$$

n = 9, R = 0.740, Se = 0.935, F = 6.677, Q = 0.791

n-The number of samples in the model

R-Multiple correlation coefficient

Se-Standard deviation

F-Sher's statistics

Q-Quality factor (Q = R/Se)

The model (1) shows that, there is a positive correlation between the antitumor activity and the E_{LUMO} of compounds. The antitumor activity is batter when the E_{LUMO} of compounds is low. The conclusion of model (1) is consistent with the experimental values.

Conclusions

• The characteristics of LUMO are the main factors to influence antitumor activities of *N*-substituted phenyl cinnamide compounds. The mechanism is that receptor provide electronic to the compounds.

• The results indicate that C(8) of compounds might be the important active site.

• There is a positive correlation between the antitumor activity and the E_{LUMO} of compounds.

TABLE 2
ENERGY OF THE MOLECULAR FRONTIER ORBITALS

Compd.	B1	B2	B3	B4	B5	D1	D2	D3	D4	D5
E_{HOMO}	-8.0720	-8.2162	-7.9044	-7.6883	-8.2832	-8.1634	-8.3063	-7.9525	-7.7161	-8.4350
E_{LUMO}	2.6752	2.5026	2.7113	2.7445	2.3443	2.4381	2.2868	2.4689	2.4975	2.1949
ΔE	10.7471	10.7188	10.6157	10.4328	10.6274	10.6016	10.5931	10.4214	10.2135	10.6299

TABLE-3
MAIN COMPOSITION AND PROPORTION OF FRONTIER MOLECULES ORBITAL (%)

Compd.	HOMO	LUMO
B1	C(2)6.09, C(4)6.51, C(5)7.17, C(7)3.30, N(10)17.21, C(11)11.63, C(12)5.99, C(13)6.39, C(14)14.10, R_1(O)3.23, R_2(O)3.93	C(2)3.88, C(3)10.50, C(4)10.16, C(5)11.57, C(6)17.65, C(7)16.70, C(8)4.51, O(9)4.25
B2	C(2)6.02, C(4)6.37, C(5)7.06, C(7)3.13, N(10)14.89, C(11)10.00, C(12)5.07, C(13)5.20, C(14)12.74, R_1(O)3.29, R_2(O)3.93, R_3(Cl)8.46	C(2)3.60, C(3)9.74, C(4)9.15, C(5)10.45, C(6)17.81, C(7)15.75, C(8)5.21, O(9)4.75, C(11)3.12, C(14)3.20
B3	C(2)3.03, C(4)3.31, C(5)3.55, N(10)18.60, C(11)15.70, C(12)7.05, C(13)7.06, C(14)18.10	C(2)3.90, C(3)10.64, C(4)10.37, C(5)11.79, C(6)17.46, C(7)16.83, C(8)4.28, O(9)4.05
B4	N(10)16.54, C(11)18.32, C(12)4.46, C(13)7.93, C(14)15.13, R_3(O)11.64	C(2)4.11, C(3)10.94, C(4)10.88, C(5)12.27, C(6)17.42, C(7)17.27, C(8)3.95, O(9)3.77
B5	C(2)9.79, C(4)10.19, C(5)11.47, C(7)4.83, N(10)12.10, C(11)5.85, C(12)3.58, C(13)4.51, C(14)9.11, R_1(O)5.70, R_2(O)6.53	C(3)6.78, C(4)5.90, C(5)6.96, C(6)14.83, C(7)11.42, C(8)6.24, O(9)5.12, C(11)8.67, C(14)6.53
D1	O(9)3.71, N(10)21.65, C(11)17.56, C(12)8.40, C(13)8.84, C(14)20.64	C(1)5.38, C(3)11.47, C(4)13.01, C(5)12.76, C(6)14.28, C(7)15.37, C(8)3.12, O(9)3.18
D2	N(10)18.33, C(11)15.09, C(12)6.70, C(13)7.10, C(14)18.53, R_3(Cl)12.86	C(1)5.02, C(3)10.99, C(4)12.12, C(5)11.92, C(6)14.85, C(7)14.90, C(8)3.71, O(9)3.63
D3	O(9)3.62, N(10)19.79, C(11)18.72, C(12)7.47, C(13)8.49, C(14)21.12	C(1)5.47, C(3)11.55, C(4)13.18, C(5)12.92, C(6)14.03, C(7)15.41, O(9)3.04
D4	O(9)3.09, N(10)16.37, C(11)19.61, C(12)4.52, C(13)8.20, C(14)15.94, R_3(O)12.44	C(1)5.60, C(3)11.74, C(4)13.61, C(5)13.29, C(6)13.81, C(7)15.61
D5	C(4)3.17, C(5)4.59, N(10)19.95, C(11)13.14, C(12)7.00, C(13)8.77, C(14)19.25, R_3(O)3.11	C(1)3.86, C(3)9.02, C(4)9.46, C(5)9.47, C(6)14.16, C(7)12.76, C(8)4.80, O(9)4.52, C(11)5.37, (14)4.09

TABLE-4
PARAMETERS OF COMPOUNDS

Compd.	E_{HOMO}	E_{LUMO}	μ	P	M	V	S(G)	log P	R
B1	-0.29664	0.09831	3.7772	28.24	255.27	750.80	465.89	2.48	73.71
B2	-0.30194	0.09197	4.2066	30.17	289.72	795.30	489.00	2.18	79.24
B3	-0.29048	0.09964	3.8271	30.08	269.30	803.75	493.07	3.09	77.11
B4	-0.28254	0.10086	2.9309	30.72	285.30	825.78	502.61	2.37	78.54
B5	-0.30440	0.08615	2.8447	32.00	313.31	882.55	532.82	2.34	82.37
D1	-0.30000	0.08960	3.5151	31.14	281.31	818.40	498.25	2.73	81.19
D2	-0.30525	0.08404	4.9951	33.07	315.76	862.87	526.01	2.43	86.72
D3	-0.29225	0.09073	3.3977	32.97	295.34	871.87	531.14	3.34	84.6
D4	-0.28356	0.09178	2.2711	33.61	311.34	893.51	539.23	2.62	86.02
D5	-0.30998	0.08066	3.4401	34.90	339.35	952.30	572.21	2.58	90.21

E_{HOMO} or E_{LUMO}-The energy of HOMO or LUMO; μ-Molecular dipole moment in water; P-The molecular polarizability; M-Relative molecular mass; V-The molecular volume; S(G)-The molecular surface area; log P-The hydrophobic parameter; R-Molecular molar refractive index

TABLE-5
CORRELATION COEFFICIENT BETWEEN THE PARAMETERS AND THE ANTITUMOR ACTIVITY

	E_{HOMO}	E_{LUMO}	μ	P	M	V	S(G)	log P	R
Y	0.774	0.740	-0.546	-0.280	-0.419	-0.180	-0.184	0.398	-0.421

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