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Short Communication

Relationships between Electron Densities of Stilbene Moieties and Leukotriene D4 Antagonism

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Through a series of *in vitro* analysis with passive cutaneous anaphylaxis on MeOH, methylene chloride, and ethylacetate extracts from 50 higher plants, effective substances were identified.[1] The activities of these extracts were confirmed through the LTD4 antagonism in guinea pig ileum. After the separation of active extracts, the structures of the single compounds were determined. As a lead compound, resveratrol, one of the stilbene derivatives isolated from *Morus alba* was selected.[1] Because of its known structure and low activity, several classes of analogues were synthesized to improve its activity with the aid of QSARs calculations.

The first training set used for QSARs calculation was composed of 20 stilbene derivatives.[2] Based on the above QSARs calculation, relationships between structural parameters of stilbene derivatives and LTD4 antagonism were established. From the relationships, 13 candidates were predicted and synthesized.[3] The average of LTD4 antagonisms of those compounds was EC_{50} of 17.68 μg/m*l*.[3] These 13 compounds used for the second training set included ethenyl group. Even though 4-benzyloxyphenol used for the first training set did not include ethenyl group, it showed the best activity of 0.1 μg/m*l* among the compounds tested.[2] Therefore, by modifying the ethenyl group of the second training set into methylene oxide similar to 4-benzyloxyphenol, 4-benzyloxyphenyl butyrate, named DK-II-22, was put up as a candidate. While its predicted activity was 0.71 μg/m*l* (EC_{50}), the experimental value was 1.60 μg/m*l* (EC_{50}). Although there is a small difference between the experimental value and the calculated value, the activity was improved tenfold that of the second training set. This study was done to investigate the substitution of ethenyl group with methylene oxide which resulted in an increment of the activity.

Synthesis of 4-benzyloxyphenyl butyrate (DK-II-22). Monobenzylhydroquinone (1 g, 5 mmol) was dissolved in 40 mL of CH_2Cl_2 at 10°C. To the above clear solution, butyryl chloride (623 mg, 6 mmol) was added slowly, stirred for 2 h at room temperature, and quenched with 40 mL of water. The mixture was extracted with CH_2Cl_2 (40 mL × 2), and the combined organic layers were washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. Filtration and evaporation gave a residue which was separated with flash chromatography to give DK-II-22 (1.46 g, 92% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5 H), 6.96 (m, 4 H), 5.03 (s, 2 H), 2.50 (t, 2 H, J = 9.6 Hz), 1.76 (m, 2 H), 1.03 (t, 3 H, J = 7.4 Hz) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.52, 156.38, 144.43, 136.84, 128.62 (double intensity), 128.02, 127.47 (double intensity), 122.36 (double intensity), 115.42 (double intensity), 106.38, 70.40, 36.18, 18.49, 13.65.

While 13 compounds with ethenyl group were synthesized and their activities were measured, only one compound with methylene oxide, DK-II-22, was synthesized. Therefore 15 compounds with methylene oxide were predicted based on the QSARs equation ($r^2 = 0.95$) obtained from the first and second training sets as follows:

$$\text{Log}(EC_{50}) = -1.84 \times (\text{Hbond donor}) - 0.014 \times (\text{Area}) - 2.43 \times (\text{LUMO}) + 0.013 \times (PMI_x) - 0.068 \times (\text{Dipole}_x) + 12.49$$

Hbond donor: hydrogen bond donor
Area: surface area of the molecule
LUMO: lowest unoccupied molecular orbital energy
PMI: principal moment of inertia
Dipole: dipole moment
EC_{50}: the 50% inhibitory concentration of the test compounds on LTD4 (μg/ml)

The structures of the 15 compounds are listed in Table 1, and their calculated activities of LTD4 antagonism are listed in Table 2.

The difference between ethenyl group and methylene oxide can be caused by their electron densities. In order to obtain the electron densities of the compounds, MOPAC[4] was applied. The hardware and software used for MOPAC

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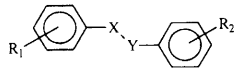
Abbreviations: LTD4, leukotriene D4; MOPAC, molecular orbital package; QSARs, quantitatively structure-activity relationships.

Table 1. Structures of compounds calculated based on the QSARs equation.



name	X-Y	R_1	R_2
CH-I-21A	CH = CH (*trans*)	3,4-OH	H
CH-II-1A	CH = CH (*trans*)	3-OH	3-OH
CH-II-5A	CH = CH (*trans*)	4-OH	3-OH
CH-II-6A	CH = CH (*trans*)	2-OH	3-OH
CH-II-10B	CH = CH (*cis*)	3,5-OH	3-OH
CH-II-12B	CH = CH (*trans*)	3,5-OH	2-OH
CH-II-13B	CH = CH (*trans*)	3,5-OH	3-OH
CH-II-15B	CH = CH (*trans*)	3,5-OH	4-OH
CH-II-16A	CH = CH (*trans*)	4-OH	2-OH
CH-II-18A	CH = CH (*trans*)	2-OH	2-OH
CH-II-20A	CH = CH (*trans*)	4-OH	4-OH
HJ-V-11A	CH = CH (*cis*)	H	3-OH
HJ-V-11B	CH = CH (*trans*)	H	3-OH
DK-II-22	CH_2 - O	H	$O_2C(CH_2)_2CH_3$
CH-IV-14	CH_2 - O	4-OMe	4-OH
CH-IV-15	CH_2 - O	4-OMe	3-OH
CH-IV-16	CH_2 - O	4-OMe	2-OH
CH-IV-17	CH_2 - O	3-OMe	4-OH
CH-IV-18	CH_2 - O	3-OMe	3-OH
CH-IV-19	CH_2 - O	3-OMe	2-OH
CH-IV-20	CH_2 - O	2-OMe	4-OH
CH-IV-21	CH_2 - O	2-OMe	3-OH
CH-IV-22	CH_2 - O	2-OMe	2-OH
KM-I-12B	CH_2 - O	3,4-Methylenedioxy	3-OH
KM-I-13	CH_2 - O	3,4-Methylenedioxy	2-OH
KM-I-16	CH_2 - O	2,3-di-OMe	4-OH
KM-I-18	CH_2 - O	2,3-di-OMe	2-OH
KM-I-21	CH_2 - O	3,5-di-OMe	4-OH
KM-I-23	CH_2 - O	3,5-di-OMe	2-OH
CH-IV-14-NN	N = N	4-OMe	4-OH
CH-IV-15-NN	N = N	4-OMe	3-OH
CH-IV-16-NN	N = N	4-OMe	2-OH
CH-IV-17-NN	N = N	3-OMe	4-OH
CH-IV-18-NN	N = N	3-OMe	3-OH
CH-IV-19-NN	N = N	3-OMe	2-OH
CH-IV-20-NN	N = N	2-OMe	4-OH
CH-IV-21-NN	N = N	2-OMe	3-OH
CH-IV-22-NN	N = N	2-OMe	2-OH
KM-I-12B-NN	N = N	3,4-Methylenedioxy	3-OH
KM-I-13-NN	N = N	3,4-Methylenedioxy	2-OH
KM-I-16-NN	N = N	2,3-di-OMe	4-OH
KM-I-18-NN	N = N	2,3-di-OMe	2-OH
KM-I-21-NN	N = N	3,5-di-OMe	4-OH
KM-I-23-NN	N = N	3,5-di-OMe	2-OH

calculation were SGI INDI R4400 and IsightII/MOPAC (MSI, SanDiego, USA), respectively. The electron densities of each atom at positions X and Y of the 13 compounds with ethenyl group and the 16 compounds with methylene oxide obtained from MOPAC calculation are listed in Table 2. While the average values of electron densities of the two carbons of ethenyl group are 4.04 and 4.04, methylene group and oxygen atom of methylene oxide are 3.76 and 6.29, respectively. In the case of stilbene derivatives connected with ethenyl group, the average value of their biological

Table 2. Activities of LTD4 antagonism and electron densities at positions X and Y calculated using MOPAC.

name	Electron density		EC_{50}(μg/ml)
	Positions X[c]	Positions Y[c]	
CH-I-21A	4.04	4.04	1.07[b] /1.40[a]
CH-II-1A	4.04	4.04	15.11[b] /11.59[a]
CH-II-5A	4.03	4.05	8.60[b] /13.00[a]
CH-II-6A	4.02	4.05	1.11[b] /1.40[a]
CH-II-10B	4.05	4.04	1.32[b] /6.30[a]
CH-II-12B	4.05	4.02	14.40[b] /31.19[a]
CH-II-13B	4.05	4.04	15.30[b] /95.72[a]
CH-II-15B	4.05	4.03	8.90[b] /5.11[a]
CH-II-16A	4.04	4.02	9.30[b] /18.28[a]
CH-II-18A	4.04	4.04	13.20[b] /15.60[a]
CH-II-20A	4.04	4.04	5.20[b] /2.90[a]
HJ-V-11A	4.04	4.05	22.88[b] /15.42[a]
HJ-V-11B	4.04	4.05	12.91[b] /17.91[a]
DK-II-22	3.76	6.28	0.71[b] /1.60[a]
CH-IV-14	3.75	6.30	0.15[b]
CH-IV-15	3.75	6.28	0.11[b]
CH-IV-16	3.78	6.28	0.13[b]
CH-IV-17	3.76	6.29	0.30[b]
CH-IV-18	3.76	6.29	0.11[b]
CH-IV-19	3.76	6.29	0.26[b]
CH-IV-20	3.76	6.29	0.21[b]
CH-IV-21	3.75	6.30	0.21[b]
CH-IV-22	3.76	6.30	0.30[b]
KM-I-12B	3.77	6.30	0.30[b]
KM-I-13	3.77	6.30	0.32[b]
KM-I-16	3.77	6.28	0.40[b]
KM-I-18	3.76	6.29	0.56[b]
KM-I-21	3.76	6.29	3.65[b]
KM-I-23	3.77	6.30	0.56[b]
CH-IV-14-NN	5.02	5.04	11.43[b]
CH-IV-15-NN	5.01	5.02	11.43[b]
CH-IV-16-NN	5.03	5.02	11.43[b]
CH-IV-17-NN	5.02	5.02	11.43[b]
CH-IV-18-NN	5.02	5.03	11.43[b]
CH-IV-19-NN	5.02	5.03	11.43[b]
CH-IV-20-NN	5.01	5.02	11.43[b]
CH-IV-21-NN	5.01	5.04	11.43[b]
CH-IV-22-NN	5.02	5.04	11.43[b]
KM-I-12B-NN	5.01	5.04	11.43[b]
KM-I-13-NN	5.09	5.10	11.43[b]
KM-I-16-NN	5.03	5.01	11.43[b]
KM-I-18-NN	5.02	4.01	9.98[b]
KM-I-21-NN	5.02	5.02	11.43[b]
KM-I-23-NN	5.09	5.11	11.43[b]

[a]experimental data
[b]calculated data
[c]Positions X and Y of the stilbene derivatives are shown in Table 1.

activities is 17.68 μg/ml. In the case of methylene oxide, the average value of the calculated activities is 0.57 μg/ml. In order to find a relationship between the electron densities at positions X and Y and the biological activities, diazene group was considerable instead of ethenyl group or methylene oxide. Another 15 stilbene derivatives connected with diazene group were put up as candidates based on the QSARs equation mentioned above. Their structures are listed in Table 1, and their activities calculated by the QSARs equation and electron densities obtained from MOPAC calculation are listed in Table 2. The average calculated activities is 11.33 μg/ml, and the averages of electron densities of the two nitrogens of diazene group are 5.03 and 4.97.

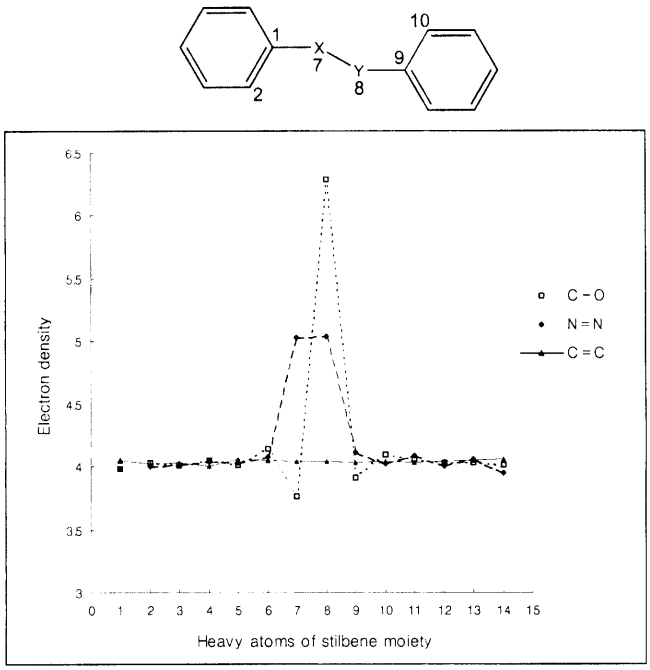


Fig. 1. Plots of electron densities calculated using MOPAC against each heavy atom of stilbene derivatives connected by (a) ethenyl, (b) methylene oxide, and (c) diazene groups.

As shown in plots of electron densities calculated by MOPAC against each heavy atom of stilebene derivatives connected by (a) ethenyl, (b) methylene oxide, and (c) diazene groups (Fig. 1), electron densities at the heavy atom number 8 (position Y in Table 1) show different values. As a result, it can be concluded that the higher the electron density at the position Y, the higher the activity of LTD4 antagonism (EC_{50}). In addition, activities of stilebene derivatives connected by diazene group do not depend on the substitution of R_1 or R_2 group shown in Table 1, because different substituents do not cause any changes in the activity. Therefore, the 15 stilbene derivatives with methylene oxide were found to be valuable and should be synthesized in future works, while the other 15 compounds with diazene group do not merit further studies.

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