Quantitative Studies on Structure−Activity Relationship of Sulfonylurea and Benzoylphenylurea Type Pesticides and Their Substituents' Bioisosterism Using Synthons' Activity Contribution

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With the Free−Wilson mathematical model method in its Fujita−Ban variant, the quantitative structure−activity relationships of some famous pesticides, their substituents' quantitative bioisosterism sequence, and their physicochemical meaning analysis are studied. In the case of sulfonylurea herbicides, the heterocycle connected with the amino group of the urea part was found to play an important role in inhibition of rape rooting, which showed positive activity contribution accounted for by the highest occupied orbital energy E_{HOMO} and the lowest unoccupied orbital energy E_{LUMO} compared with the negative contribution of the substituents on the sulfonylphenyl ring. In the case of benzoylphenylurea type insect-growth regulators, the substituent X_1, at the benzoyl moiety, was found to play an important role in the inhibition of insects' chitin synthesis, which gave strong positive activity contribution mainly accounted for by electronic σ and steric Es parameters, whereas the substituent X_2 gave a negative to weakly positive activity contribution mainly resulting from hydrophobic π.

Keywords: *QSAR; bioisosterism; sulfonylurea herbicides; benzoylphenylurea insect-growth regulators*

INTRODUCTION

The Free−Wilson method and its widely applied Fujita−Ban variant can be used for the analysis of quantitative structure−activity relationships of pharmaceuticals (Free and Wilson, 1964; Fujita and Ban, 1971; Martin et al., 1972; Craig and Hansch, 1973; Dove et al., 1997; Paleti et al., 1997). It is a simplified mathematical model method without any assumptions, does not require any empirical or semiempirical parameters, for example, hydrophobicity, electronic, and steric parameters, and does not deal with several complicated in vivo factors either, for example, the changes of the active conformation during action and transit over biomembranes; it deals only with an elementary case of "alignment", and its output results depend only on molecular bioactivities and structure input. In this paper, we report a quantitative study on structure−activity relationship and the group's bioisosterism of sulfonylurea and benzoylphenylurea pesticides using the Free−Wilson method in its Fujita−Ban variant based on synthons' activity contribution.

MATERIALS AND METHOD

Inhibition activity (pI_{50}) of benzoylphenylurea to new cuticle formation from *C. suppressali* and inhibition activity (log 1/*C*) of sulfonylureas to rape rooting length shown in Tables 1 and 3 were taken from the literature (Nakagawa et al., 1987; Jia and Li, 1996), respectively.

The molecular modeling method used is PCMODEL (Qian, 1996), and the quantum chemical procedure used is MINDO.

RESULTS AND DISCUSSION

The additivity approach is a very important method for estimating or predicting molecular physicochemical properties, of which the common feature was that a structural fragment has its independent function. For example, in the synthon approach (Corey et al., 1967), a molecule consists of fragments called "synthons" in the sense of synthesis, In hydrophobic fragment constants approach (Nys et al., 1974), a molecular hydrophobicity is the mathematical sum of hydrophobic constants of fragments.

Table 1. Inhibition Activity of Sulfonylureas to Rape Rooting Length

R	a	b	a	b	a	b	a	b	a
Y	e	e	f	f	g	g	h	h	i
log 1/*C*	3.97	4.29	3.83	4.07	3.95	3.84	3.47	3.77	4.28
calcd	4.06	4.20	3.89	4.02	3.83	3.97	3.55	3.74	4.33
R	c	a	c	d	d	a	c	b	
Y	i	j	j	j	k	k	k	k	
log 1/*C*	3.97	6.10	5.39	6.42	3.43	3.44	3.13	3.39	
calcd	3.92	6.03	5.62	6.26	3.59	3.36	2.95	3.56	

Similarly, in the Free−Wilson method in its Fujita−Ban variant, the logarithm of the

$$\log 1/C = A + \sum_i \sum_r G_{ir} X_{ir}$$

activity (log 1/*C*) is correlated with the mathematical sum of contributions (*G*) at each position of structural fragment (*X*) to the total activity of the molecule. Here, *A* is the activity of the unsubstituted compound, X_{ir} is *i*th fragment at the *r*th position ($X_{ir} = 1$, present; 0, absent), and G_{ir} is the activity contribution of X_{ir} relative to H (Free et al., 1964; Fujita et al., 1971).

However, strictly speaking, one does not always know the activity of the unsubstituted precusor; therefore, we adopt synthons' concept to structure−activity relation-

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Table 2. Synthons' Contributions of Sulfonylurea (r = 98.4%, S = 0.1813, F = 46.84)

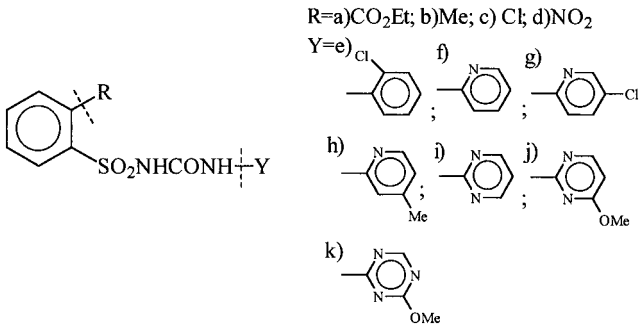
synthon	q	a	b	c	d	e	f	g	h	i	j	k
Q	3.59	−0.23	−0.094	−0.64	0.0	0.703	0.526	0.474	0.193	0.968	2.67	0.0

Table 3. Physicochemical Parameters and Synthon's Activity Contribution of R Synthons of Sulfonylureas[a]

No.	H_2N-R	E_{HOMO}(ev)	E_{LUMO}(ev)	W_{SS}(Å^2)	MMX-E(kcal/mol)	Q
e		-8.2135	-2.5575	269	12.41	0.703
f		-7.4586	-0.7840	238	-4.07	0.526
g		-7.2486	-0.7053	252	-0.18	0.474
h		-7.4279	-0.8985	265	-2.31	0.193
i		-7.4290	-1.2844	233	-4.02	0.968
j		-6.3937	-2.0299	281	1.84	2.67
k		-9.1083	-1.4526	274	-8.90	0.00

[a] Here, E_{HOMO}, E_{LUMO}, Wss, and MMX-minimize were calculated on the basis of the corresponding amine of R.

Chart 1



ship study with the activity contribution (Q) of the synthon (S_{ir}) relative to a specified

$$\log 1/C = q + \sum_i \sum_r Q_{ir} S_{ir} \qquad (1)$$

common synthon instead of the activity contribution (G) of X_{ir} relative to H; that is, the activity of a molecule, which consists of several synthons, might be as the mathematical sum of these synthons' activity contributions. Here, q is the activity contribution of a specified common parent synthon. Because of the incorporation of the synthon concept, the Free−Wilson method in its Fujita−Ban variant becomes simpler and convenient for application.

In addition, we know that bioisosterism are groups or molecules which have chemical and physical similarities producing broadly similar biological properties (Thornber, 1979), a concept widely used for drug and pesticide design; the Free−Wilson method in its Fujita−Ban variant based on synthons' activity contribution might serve as an alternative tool for quantitative analysis of bioisosterism.

Sulfonylurea Herbicides. Sulfonylureas are highly efficient herbicides. Sulfonylureas with favorable herbicidal activity are compounds having an aryl group with a substituent, such as chloro- or methoxylcarbonyl ortho to an unmodified sulfonylurea bridge and with the heterocycle as pyridine or triazine (Chart 1). The relationship between sulfonylurea structures and their

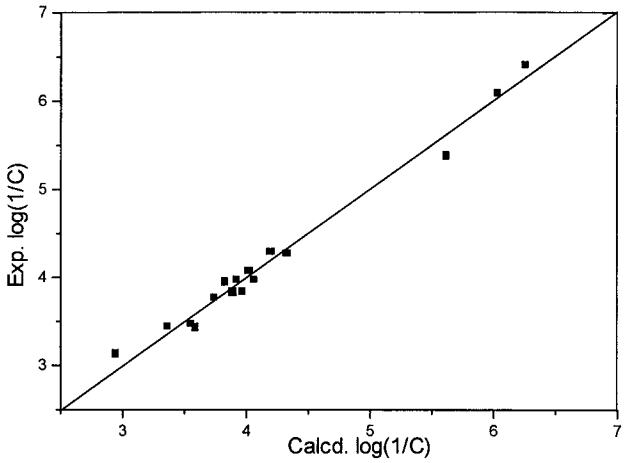


Figure 1. Correlation between experimental and calculated values of inhibition activity of sulfonylureas.

Table 4. Inhibition Activity of Benzoylphenylurea to New Cuticle of *C. suppressalis*

X_1	F	Cl	Cl	H	Cl	Br	NO_2	Br	Br	Br
X_2	F	Cl	H	F	F	H	Me	Br	Cl	F
pI_{50}	7.95	6.50	7.55	6.52	7.32	6.78	6.07	5.98	6.53	7.18
calcd	7.94	6.73	7.25	6.52	7.40	6.93	6.08	6.05	6.41	7.08

Cl	Me	Me	NO_2	NO_2	Cl	NO_2	NO_2	NMe_2	NMe_2
Me	Me	H	Cl	OMe	OMe	Br	H	F	Cl
6.75	6.05	6.87	6.27	6.89	7.29	5.88	6.45	6.39	5.75
6.64	6.15	6.88	6.17	6.81	7.37	5.82	6.69	6.40	5.73

Table 5. Synthon's Contributions of Benzoylphenylurea (r^2 = 95.2%, S = 0.2003, F = 14.29)

synthon	q	2-H	6-H	2-Cl	6-Cl	2-F	6-F
Q	6.37	0.115	−0.115	1.00	−0.637	1.54	0.033
synthon	2-Br	6-Br	2-Me	6-Me	2-NO_2	6-OMe	2-NMe_2
Q	0.675	−0.997	0.511	−0.731	0.436	0.0	0.0

activity has been well reviewed by Levitt (1991). Here we will analyze the role of the substituent R and the heterocycle Y using synthons' activity contribution.

For the following sulfonylurea derivatives, R and Y could be treated as synthons, according to eq 1, the calculated results of which are shown in Table 2, the correlation relationship between experimental value and calculated value of inhibition activity is shown in Figure 1.

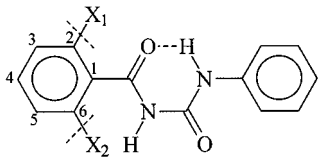
Here, a regression analysis with explained variance (r^2), standard deviation (S), and the F statistic (F) is shown in Table 2.

It is found that the R synthon has negative activity contribution, whereas the Y synthon has positive activity contribution. The bioisosterism sequence for R in the bioactivity contribution from weak to strong is c, a, b, d and that for Y is k, h, g, f, i, j. We also studied the physicochemical meaning of the group's bioisosterism of sulfonylureas on the basis of the relationship between the synthon's contribution and some physicochemical parameters (shown in Table 3), such as the energy of the highest occupied orbital (E_{HOMO}) and the lowest unoccupied orbital (E_{LUMO}) calculated by using the MINDO method and the water solvation shell surface area (W_{SS}) calculated by using the iterative energy minimization of molecular structure (MMX-minimize) method. The correlated results are shown in eq 2.

Table 6. Synthon's Contributions and Physicochemical Parameters of Benzoylphenylurea

	X_1					X_2			
2-synthon	Q	$\sigma 1$	Es	π	6-synthon	Q	$\sigma 1$	Es	π
H	0.115	0.00	0.00	0.23	H	−0.115	0.00	0.00	0.23
F	1.54	0.54	−0.30	0.37	F	0.033	0.54	−0.30	0.37
Cl	1.00	0.47	−0.94	0.94	Cl	−0.637	0.47	−0.94	0.94
Br	0.675	0.47	−1.08	1.09	Br	−0.997	0.47	−1.08	1.09
Me	0.511	−0.02	−1.11	0.89	Me	−0.731	−0.02	−1.11	0.89
NO_2	0.436	0.68	−1.58	−0.05	OMe	0.0	0.30	−0.38	0.32
NMe_2	0.0	0.17	−1.60	0.61					

Chart 2



$$Q = 6.20 + 0.844E_{\mathrm{HOMO}} - 0.732E_{\mathrm{LUMO}} \qquad (2)$$

$$N = 7 \quad S = 0.4181 \quad r^2 = 85.2\% \quad F = 11.51$$

The above analysis showed that the synthon's activity contribution and bioisosterism mainly result from molecular electronic properties, that is, the molecular electronic highest occupied orbital energy (correlation: $Q - E_{\mathrm{HOMO}}$ 53.3%; $Q - E_{\mathrm{LUMO}} = 21.4\%$; $Q - W_{\mathrm{ss}} = 8.4\%$) as well as the lowest unoccupied orbital energy.

Benzoylphenylurea Insect-Growth Regulators. Benzoylphenylurea is a well-known insecticide that mainly controls the biosynthesis of insect chitin (Nakagawa et al., 1987). The X-ray structure of benzoylphenylurea with a flexible C(O)NHC(O)NH two-amide bond is known by us (Li and Qian, 1998) and is shown in Chart 2. On the basis of this X-ray structure, the relative positions of substituents X_1 and X_2 in the minimized energy structure of the following derivatives are confirmed by using MMX-minimize of Pcmodel molecular modeling mode and are shown in Table 4, which shows that substituent X_1 usually was the group with large steric hindrance and X_2 was the group with less steric hindrance and sometimes having a tendency to form hydrogen bonding with neighbor N−H.

If X_1 and X_2 were treated as synthons, therefore, the various synthons' activity contribution could be easily obtained by using eq 1, and the results are listed in Table 5. The correlation relationship between experimental value and calculated value of inhibition activity is shown in Figure 2.

Such simple analysis gave good correlated results. It revealed that the substituent X_2 at the 6-position (except fluorine having a weak positive contribution) gave only negative contributions. The subsitutent X_1 at the 2-position gave positive contributions. The quantitative bioisosterism sequence in bioactivity contribution from weak to strong for X_1 is NMe_2, H, NO_2, Me, Br, Cl, F and that for X_2 is Br, Me, Cl, H, OMe, F.

When the synthons' activity contributions of benzoylphenylureas were analyzed with the corresponding electronic (σ), steric (Es), and hydrophobic (π) parameters listed in Table 6, it could be found that there was a correlated relationship as shown in eq 3 between the synthons' activity contributions and their hydrophobic prarameters.

$$\text{for } X_2,\ Q = -0.0058 + 0.203\pi - 1.02\pi^2 \qquad (3)$$

$$N = 6 \quad S = 0.1115, \quad r^2 = 96.1\%, \quad F = 36.74$$

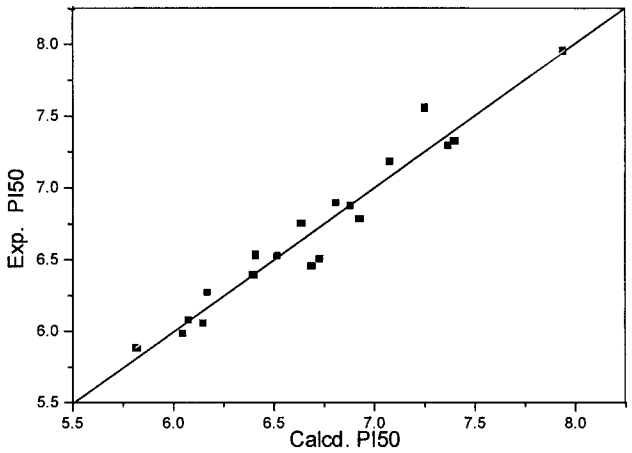


Figure 2. Correlation between experimental and calculated values of inhibition activity of benzoylphenylurea.

The analysis showed that the synthons' activity contributions and bioisosterism for X_2 were mainly dependent on the hydrophobicity parameter π (correlation $Q-\pi$ 87.7%, $Q-$Es 11.7%, $Q-\sigma$ 4.6%), and there is an optimum π value corresponding bioactivity. However, those for X_1 were mainly dependent on the electronic parameter σ as well as the steric parameter Es, and σ is the key one (correlation $Q-\sigma$ 31.3%, $Q-$Es 7.9%, $Q-\pi$ 2.2%).

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