2、4-Diphenyl-1、3-oxazoline類縁体のナミハダニeranychus uricaeに対する殺卵活性のQSAR

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Original Article

QSAR of 2,4-diphenyl-1,3-oxazolines for ovicidal activity against the two-spotted spider mite *Tetranychus urticae*

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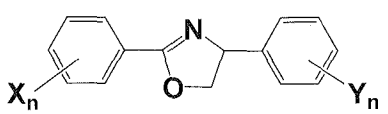
Ovicidal activity of 2,4-diphenyl-1,3-oxazoline congeners with various substituents on the 4-phenyl ring against two-spotted spider mites *Tetranychus urticae* was quantitatively analyzed using the classical QSAR (Hansch-Fujita) method. In QSAR analysis, hydrophobicity in terms of log*P* (*P*: partition coefficient between 1-octanol and water) was the most significant parameter with its square term. The optimum log*P* value for 2,4-diphenyl-1,3-oxazoline analogs was evaluated as about 7.1. The introduction of substituents with inductive electron-withdrawing properties was also favorable to activity, but the presence of substituents at the *ortho*- and *meta*-positions was not promising. © Pesticide Science Society of Japan

Keywords: 2,4-diphenyl-1,3-oxazoline, QSAR, two-spotted spider mites, *Tetranychus urticae*.

Introduction

Some phytophagous mites cause serious damage to agricultural products, and attacks by two-spotted spider mites, *Tetranychus urticae* Koch (Acari: Tetranycidae), are particularly serious. To date, a number of acaricides with various modes of action have been developed to control these mites. Among them, acaricides which inhibit the growth and molting of mites are attractive, because they are effective against strains resistant to respiration inhibitor and neurotoxic compounds, and are thought to be safe for mammals. As growth-regulatory-type acaricides, flucycloxuron,[1] flufenoxuron,[2] and hexythiazox[3] have been launched, and we recently developed a new growth inhibitor, etoxazole (X_n=2,6-F_2, Y_n=2-OEt-4-*t*-Bu in **I**).[4,5]

Etoxazole inhibits chitin synthesis in the cultured integument of the rice stem borer *Chilo suppressalis* Walker (Nakagawa, unpublished) in a similar manner to insect chitin synthesis inhibitors, benzoylphenylurea (BPU; **II**)[6,7] and 2-benzoylamino-5-phenythiadiazole (BPT; **III**) analogs.[8] With respect to BPUs such as diflubenzuron (X_n=2,6-F_2, Y_n=4-Cl in **II**) and chlorfulazuron [X_n=2,6-F_2, Y_n=3,5-Cl_2-4-*O*-2-pyridyl(3-Cl,5-CF_3) in **II**], the quantitative structure–activity relationships (QSARs) have been intensively studied for both *in vitro*[7] and *in vivo* activity.[9–16] We recently analyzed the substituent effect of the 2-phenyl moiety of 2,4-diphenyl-1,3-oxazoline analogs on the acaricidal activity against *T. urticae*. Results showed that the substituent effect on the activity is very similar to that of the benzoyl moiety of BPUs (**II**) for the inhibition of chitin synthesis,[6,7] but not of BPT (**III**),[8] in which the molecular hydrophobicity was found to be the most important physicochemical parameter.[17,18]



(**I**)

In this study we quantitatively analyzed the substituent effects of the 4-phenyl moiety of 2,4-diphenyl-1,3-oxazoline analogs on ovicidal activity against *T. urticae* to identify the essential physicochemical property for the acaricidal activity of etoxazole analogs. The accumulation of QSAR results for acaricides is very helpful to rationally design new chemistry. In addition, the QSAR results of etoxazole congeners must be useful to disclose the molecular mechanism of chitin synthesis inhibitors such as BPU (**II**) and BPT (**III**).

Materials and Methods

Ordinary substituent parameters are listed in Table 1, and are mostly cited from the references.[19] Log*P* values of com-

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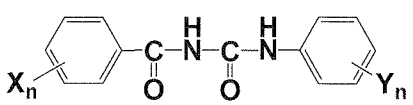
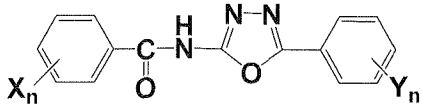


(II)



(III)

pounds were estimated from the experimentally measured log*P* values of 2-(2,6-difluorophenyl)-1,3-oxazoline congeners[17] and π values of mono-substituted benzene.[19] Log*P* values of mono-substituted benzenes have been experimentally measured or estimated using CLOGP (Ver. 4.0, BioByte Corp., Claremont, CA).[20] All parameters used in QSAR analyses are listed in Table 2. Multiple regression analysis was executed using QREG2.05.[21] In QSAR equations, *n* is the number of compounds, *s* is the standard deviation, *r* is the correlation coefficient, and *F* is the *F* ratio between regression and residual values. Values in parentheses are the confidence intervals of coefficients.

Ovicidal activity was estimated using the leaf dipping method.[22] In brief, adult females of *T. urticae* were released onto leaf disks which had been dipped into suspensions of various concentrations of test compounds, and allowed to oviposit for 24 hr. After one week, the concentrations leading to 50% mortality were evaluated as 0.01–0.1, 0.1–1, 1–10, 10–100, 100–1000, >1000 ppm. Although these values were not precisely determined, they are considered to be 0.05±0.05, 0.5±0.5, 5.0±5.0, 50±50, 500±500, and >1000 ppm, respectively. These values were converted into molar concentrations (LC_{50}, M) and their reciprocal logarithmic values (pLC_{50}) were calculated, as listed in Table 2, and submitted to the following QSAR analyses.

Results

Equation (1) was formulated for 30 *para*-substituted compounds omitting four compounds, **36** (SCH_3), **37** (S-*i*-Pr), **38** (S-*n*-C_9H_{19}), and **45** (NMe_2), because these substituents are sometimes labile to enzymatic degradation.[23,24]

$$pLC_{50}=2.712\ (\pm0.560)\log P-0.188\ (\pm0.045)\ (\log P)^2 -3.448\ (\pm1.505) \quad (1)$$
$$n=30,\quad s=0.775,\quad r=0.910,\quad F_{2,27}=65.287,\quad \log P_{opt}=7.2$$

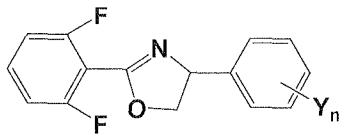
As shown in Eq. (1), a significant correlation equation was

Table 1. Substituent parameter values[a]

Substituent	π	σ_I	Substituent	π	σ_I
H	0	0	CH_3	0.56	−0.04
F	0.14	0.52	C_2H_5	1.02	−0.01
Cl	0.71	0.47	*n*-C_3H_7	1.55	−0.01
Br	0.86	0.44	*i*-C_3H_7	1.53	0.01
CF_3	0.88	0.40	*n*-C_4H_9	2.13	−0.04
OH	−0.67	0.29	*i*-C_4H_9	1.97[b]	−0.03
OCH_3	−0.02	0.27	*t*-C_4H_9	1.98	−0.07
OC_2H_5	0.38	0.28	*n*-C_5H_{11}	2.77[b]	−0.03
O-*n*-C_3H_7	1.05	0.28	*n*-C_6H_{13}	3.39[c]	−0.04
O-*i*-C_3H_7	0.77[b]	0.26	*n*-C_7H_{15}	3.69[b]	−0.04
O-*n*-C_4H_9	1.52[b]	0.28	*n*-C_8H_{17}	4.39[c]	−0.04[d]
O-*n*-C_6H_{13}	2.58[b]	0.28[e]	*n*-C_9H_{19}	4.74[b]	−0.04[d]
O-*n*-C_8H_{17}	3.63[b]	0.28[e]	*n*-$C_{10}H_{21}$	5.24[c]	−0.04[d]
O-*n*-$C_{10}H_{21}$	4.69[b]	0.28[e]	*n*-$C_{12}H_{25}$	6.33[b]	−0.04[d]
O-*n*-$C_{13}H_{27}$	6.28[b]	0.28[e]	*n*-$C_{15}H_{31}$	7.92[b]	−0.04[d]
O-*n*-$C_{14}H_{29}$	6.81[b]	0.28[e]	SCH_3	0.61	0.25
OCF_3	1.04	0.39	S-*i*-C_3H_7	1.41[b]	0.26
OCH_2CF_3	1.22[b]	0.17	S-*n*-C_9H_{19}	4.80[b]	0.23[f]
$N(CH_3)_2$	0.18	0.06	$S(=O)CH_3$	−1.58	0.49
$Si(CH_3)_3$	2.59	−0.11	SO_2CH_3	−1.63	0.59

[a] From Ref. 18 unless noted. [b] Estimated from the calculated log*P* values of mono-substituted benzenes. [c] Estimated from the measured log*P* values in CLOGP database. [d] Value of *n*-C_7H_{15}. [e] Value of O-*n*-C_4H_9. [f] Value of S-*n*-C_4H_9.

Table 2. Ovicidal activity of 2-(2,6-difluorophenyl)-4-(substituted phenyl)oxazolines and physicochemical parameters



Compounds		Parameters				Activity (pLC_{50}, M)		
No	Y_n	log $P^{a)}$	$\Sigma\sigma_I$	I^o	I^m	Obsd	Calcd$^{b)}$	Dev$^{c)}$
1	H	3.01	0.00	0	0	4.71	5.56	−0.85
2	2-CH_3	3.57	−0.04	1	0	3.74	4.64	−0.90
3	2-Et	4.03	−0.01	1	0	4.76	5.36	−0.60
4	2-OCH_3	2.99	0.27	1	0	3.76	4.24	−0.48
5	2-OEt	3.39	0.28	1	0	3.78	4.94	−1.16
6	2-F	3.15	0.52	1	0	4.74	4.98	−0.24
7	2-Cl	3.72	0.47	1	0	5.77	5.80	−0.03
8	3-CH_3	3.57	−0.04	0	1	3.74	3.70	0.04
9	3-Et	4.03	−0.01	0	1	3.76	4.42	−0.66
10	3-OCH_3	2.99	0.27	0	1	4.76	3.30	1.46
11	3-OEt	3.39	0.28	0	1	4.78	4.00	0.78
12	3-F	3.15	0.52	0	1	4.74	4.04	0.70
13	3-Cl	3.72	0.47	0	1	4.77	4.86	−0.09
14	4-CH_3	3.57	−0.04	0	0	5.74	6.42	−0.68
15	4-Et	4.03	−0.01	0	0	7.76	7.13	0.63
16	4-*i*-Pr	4.54	0.01	0	0	7.78	7.80	−0.02
17	4-*n*-Bu	5.14	−0.04	0	0	8.80	8.30	0.51
18	4-*i*-Bu	4.98	−0.03	0	0	8.80	8.17	0.63
19	4-*t*-Bu	4.99	−0.07	0	0	8.80	8.11	0.69
20	4-*n*-C_6H_{13}	6.4	−0.04	0	0	8.84	9.03	−0.19
21	4-*n*-C_8H_{17}	7.4	−0.04	0	0	8.87	9.12	−0.25
22	4-*n*-$C_{10}H_{21}$	8.25	−0.04	0	0	8.90	8.85	0.05
23	4-*n*-$C_{12}H_{25}$	9.34	−0.04	0	0	8.93	8.05	0.88
24	4-*n*-$C_{15}H_{31}$	10.93	−0.04	0	0	7.97	5.96	2.02
25	4-OH	2.34	0.29	0	0	3.74	4.80	−1.06
26	4-OCH_3	2.99	0.27	0	0	4.76	6.02	−1.26
27	4-OEt	3.39	0.28	0	0	7.78	6.72	1.06
28	4-O-*i*-Pr	3.78	0.26	0	0	7.80	7.28	0.52
29	4-O-*n*-Bu	4.53	0.28	0	0	8.82	8.28	0.54
30	4-O-*n*-C_8H_{17}	6.64	0.28	0	0	8.89	9.68	−0.79
31	4-O-*n*-$C_{10}H_{21}$	7.7	0.28	0	0	8.92	9.65	−0.73
32	4-O-*n*-$C_{13}H_{27}$	9.29	0.28	0	0	7.96	8.68	−0.72
33	4-O-*n*-$C_{14}H_{29}$	9.82	0.28	0	0	6.97	8.12	−1.15
34	4-OCF_3	4.05	0.39	0	0	7.84	7.89	−0.05
35	4-OCH_2CF_3	4.23	0.17	0	0	8.85	7.72	1.13
36	4-SCH_3	3.62	0.25	0	0	5.79$^{d)}$	7.02	−1.23
37	4-S-*i*-Pr	4.42	0.26	0	0	5.82$^{d)}$	8.12	−2.30
38	4-S-*n*-C_9H_{19}	7.81	0.23	0	0	6.92$^{d)}$	9.52	−2.60

Table 2. (Continued)

Compounds		Parameters				Activity (pLC_{50}, M)		
No	Y_n	log $P^{a)}$	$\Sigma\sigma_i$	I^o	I^m	Obsd	Calcd[b]	Dev[c]
39	4-S(=O)CH_3	1.43	0.49	0	0	3.81	3.10	0.71
40	4-SO_2CH_3	1.38	0.59	0	0	2.83	3.16	−0.33
41	4-F	3.15	0.52	0	0	5.74	6.76	−1.02
42	4-Cl	3.72	0.47	0	0	7.77	7.58	0.19
43	4-Br	3.87	0.44	0	0	7.83	7.74	0.09
44	4-CF_3	3.89	0.40	0	0	6.82	7.69	−0.87
45	4-$N(CH_3)_2$	3.19	0.06	0	0	3.78[d]	5.98	−2.20
46	4-$Si(CH_3)_3$	5.6	−0.11	0	0	8.82	8.51	0.31
47	2-CH_3-4-CH_3	4.13	−0.08	1	0	3.76	5.36	−1.60
48	2-CH_3-4-*n*-C_8H_{17}	7.96	−0.08	1	0	8.89	7.13	1.76
49	2-CH_3-4-Cl	4.28	0.43	1	0	5.79	6.49	−0.70
50	2-OCH_3-4-*t*-Bu	4.97	0.20	1	0	7.84	6.81	1.03
51	2-OCH_3-4-*n*-C_8H_{17}	7.38	0.23	1	0	6.90	7.84	−0.94
52	2-OCH_3-4-*n*-C_9H_{19}	7.73	0.23	1	0	7.92	7.77	0.15
53	2-OCH_3-4-*n*-$C_{10}H_{21}$	8.23	0.23	1	0	6.93	7.58	−0.65
54	2-OCH_3-4-F	3.13	0.79	1	0	5.79	5.44	0.35
55	2-OCH_3-4-Cl	3.7	0.74	1	0	5.81	6.27	−0.46
56	2-OEt-4-*i*-Pr	4.92	0.29	1	0	6.84	6.93	−0.09
57	2-OEt-4-*t*-Bu	5.37	0.21	1	0	7.86	7.16	0.70
58	2-OEt-4-*n*-C_5H_{11}	6.16	0.25	1	0	8.87	7.70	1.17
59	2-OEt-4-F	3.53	0.80	1	0	7.81	6.12	1.69
60	2-OEt-4-Cl	4.1	0.75	1	0	5.83	6.84	−1.01
61	2-OEt-4-Br	4.25	0.72	1	0	5.88	6.98	−1.10
62	2-O-*n*-Pr-4-*i*-Pr	5.59	0.29	1	0	8.86	7.47	1.39
63	2-O-*n*-Pr-4-*t*-Bu	6.04	0.21	1	0	7.87	7.57	0.30
64	2-O-*n*-Pr-4-*n*-C_5H_{11}	6.83	0.25	1	0	7.89	7.88	0.01
65	2-O-*n*-Bu-4-*t*-Bu	6.51	0.21	1	0	6.89	7.74	−0.85
66	2-O-*n*-Bu-4-F	4.67	0.80	1	0	8.84	7.61	1.23
67	2-O-*n*-Hex-4-*t*-Bu	7.57	0.21	1	0	5.92	7.77	−1.85
68	2-F-4-Et	4.17	0.51	1	0	5.79	6.49	−0.70
69	2-F-4-*n*-C_6H_{13}	6.54	0.48	1	0	8.86	8.24	0.62
70	2-F-4-*n*-C_7H_{15}	6.84	0.48	1	0	8.88	8.30	0.58
71	2-F-4-*n*-C_8H_{17}	7.54	0.48	1	0	8.89	8.27	0.62
72	2-F-4-*n*-$C_{10}H_{21}$	8.39	0.48	1	0	7.92	7.96	−0.04
73	2-F-4-*n*-$C_{12}H_{25}$	9.48	0.48	1	0	6.95	7.09	−0.14
74	2-F-4-F	3.29	1.04	1	0	6.77	6.17	0.60
75	2-F-4-Cl	3.86	0.99	1	0	8.79	6.96	1.83
76	2-Cl-4-Et	4.74	0.46	1	0	7.81	7.06	0.75
77	2-Cl-4-*i*-Bu	5.69	0.44	1	0	8.84	7.80	1.04
78	2-Cl-4-*n*-C_6H_{13}	7.11	0.43	1	0	8.88	8.22	0.66
79	2-Cl-4-*n*-C_8H_{17}	8.11	0.43	1	0	8.91	8.00	0.91
80	2-Cl-4-*n*-$C_{10}H_{21}$	8.96	0.43	1	0	5.94	7.47	−1.53

Table 2. (Continued)

Compounds		Parameters				Activity (pLC_{50}, M)		
No	Y_n	$\log P$[a)]	$\Sigma\sigma_I$	I^o	I^m	Obsd	Calcd[b)]	Dev[c)]
81	2-Cl-4-*n*-$C_{12}H_{25}$	10.05	0.43	1	0	5.97	6.34	−0.37
82	2-Cl-4-F	3.86	0.99	1	0	5.79	6.96	−1.17
83	2-Cl-4-Cl	4.43	0.94	1	0	6.82	7.60	−0.78
84	3-CH_3-4-CH_3	4.13	−0.08	0	1	4.76	4.42	0.34
85	3-F-4-*n*-C_6H_{13}	6.54	0.48	0	1	5.86	7.30	−1.44
86	3-F-4-F	3.29	1.04	0	1	5.77	5.23	0.54
87	3-F-4-Cl	3.86	0.99	0	1	6.79	6.01	0.78
88	3-Cl-4-*n*-C_6H_{13}	7.11	0.43	0	1	5.88	7.28	−1.40
89	3-Cl-4-F	3.86	0.99	0	1	5.79	6.01	−0.22
90	3-Cl-4-Cl	4.43	0.94	0	1	5.82	6.66	−0.84

[a)] Substituent parameter values for hydrophobicity (π) of Table 2 were added to the $\log P$ value of compound **1**. [b)] Calculated by Eq. (4). [c)] The difference between observed and calculated values. [d)] Not included in the analyses.

derived using only hydrophobicity properties, $\log P$ and $(\log P)^2$. Although a significant equation was formulated for all *para*-substituted compounds (n=34), the correlation quality was worse (s=1.006, r=0.847). The addition of steric parameters such as E_s,[25] van der Waals volume,[26] and STERIMOL parameters,[27] and electronic parameters such as Hammett constants[19] gave no significant correlation equation.

The predicted values of all *ortho*- and *meta*-substituted compounds in Eq. (1) were 10–100 times lower than their observed values. Therefore, indicator variables I^o and I^m, which take 1 as the existence of substituents at the corresponding positions (*ortho*- and *meta*-) and otherwise 0, were used to derive the significant Eq. (2) for all mono-substituted compounds excluding **36**–**38** and **45**, which were omitted to derive Eq. (1).

$$\begin{aligned} pLC_{50} = {} & 2.608\ (\pm 0.558)\log P - 0.180\ (\pm 0.045)(\log P)^2 \\ & - 2.275\ (\pm 0.748)\, I^o - 2.275\ (\pm 0.748)\, I^m \\ & - 3.165\ (\pm 1.499) \end{aligned} \quad (2)$$

$$n=42,\quad s=0.795,\quad r=0.931,\quad F_{4,37}=59.838\quad \log P_{opt}=7.2$$

Although both indicator variables can be replaced with steric parameters such as STERIMOL[27,28] or van der Waals volume[26] parameters, the correlations of new equations were worse. As shown above, the estimated optimum hydrophobicity in terms of $\log P_{opt}$ was similar between Eqs. (1) and (2).

In further analysis, 2,4- and 3,4-disubstituted compounds **47**–**90** were added to formulate Eq. (3) with decreased correlation.

$$\begin{aligned} pLC_{50} = {} & 2.746\ (\pm 0.591)\log P - 0.195\ (\pm 0.048)(\log P)^2 \\ & - 1.217\ (\pm 0.512)\, I^o - 2.196\ (\pm 0.699)\, I^m \\ & - 3.401\ (\pm 1.570) \end{aligned} \quad (3)$$

$$n=86,\quad s=1.037,\quad r=0.816,\quad F_{5,81}=40.404,\quad \log P_{opt}=7.0$$

Another significant correlation can be formulated without using indicator parameters with poorer correlation (s=1.257, r=0.697), demonstrating that about 50% of the correlation (r^2=0.486) is able to be explained by $\log P$ and $(\log P)^2$ terms. Since compounds with alkoxy and halogens were predicted to be lower than their observed values in Eq. (3), we examined the participation of another parameter. The addition of an electronic parameter, σ_I, to Eq. (3) gave better correlation in Eq. (4).

$$\begin{aligned} pLC_{50} = {} & 3.091\ (\pm 0.542)\log P - 0.218\ (\pm 0.044)(\log P)^2 \\ & + 1.832\ (\pm 0.753)\,\Sigma\sigma_I - 1.775\ (\pm 0.508)\, I^o \\ & - 2.718\ (\pm 0.655)\, I^m - 4.773\ (\pm 1.500) \end{aligned} \quad (4)$$

$$n=86,\quad s=0.918,\quad r=0.861,\quad F_{5,80}=45.954,\quad \log P_{opt}=7.1$$

In Eq. (4), Σ indicates the sum of substituent parameter values. In the final equation, the optimum hydrophobicity is calculated to be 7.1, similar to that in Eqs. (1)–(3). The presence of indicator variables I^o and I^m means that the activity decreases about 50-fold and 500-fold by introducing substituents at *ortho*- and *meta*-positions, respectively. Although these indicator variables I^o and I^m can be replaced with steric parameters, the correlation was not improved, as discussed below. The correlation matrix between parameters used to derive Eqs. (3)–(5) is shown in Table 3.

Discussion

The large standard deviations (0.775–1.037) of the equations are acceptable because the error of pLC_{50} is about 1. Throughout QSAR analyses, only four compounds (**36**–**38**, **45**) were excluded and were all predicted to be 20–100-fold more toxic. This is probably due to the fact that these substituents are susceptible to detoxification enzymes catalyzing the oxidation of the sulfur atom and *N*-demethylation. The

Table 3. Squared correlation matrix between parameters to derive Eqs. (3)–(5).

	$\log P$	$(\log P)^2$	I^o	I^m	$\Sigma\sigma_I$	E_s^o
$\log P^2$	0.965					
I^o	0.032	0.018				
I^m	0.045	0.045	0.178			
$\Sigma\sigma_I$	0.067	0.058	0.068	0.032		
E_s^o	0.022	0.013	0.770	0.137	0.017	
B_1^m	0.029	0.032	0.154	0.863	0.036	0.118

detoxication mechanisms of *S*-alkyl and *N*-alkyl groups were reviewed a quarter century ago.[23,24]

Indicator variables I^o and I^m can be substituted with steric parameters such as E_s^o and B_1^m, respectively, as shown in Eq. (5). However, the deviations between observed and predicted values for three compounds **48** (2-CH_3-4-*n*-C_8H_{17}), **67** (2-O-*n*-Hex-4-*t*-Bu) and **85** (3-F-4-*n*-C_6H_{13}) exceeded 2 in the prediction by Eq. (5). Since these compounds were predicted better in Eq. (4), this was selected as the final equation in this study. The physicochemical parameters which properly explain I^o and I^m could not be separated in this analysis.

$$\begin{aligned} pLC_{50} = {} & 2.931\ (\pm 0.542)\ \log P - 0.205\ (\pm 0.044)\ (\log P)^2 \\ & + 1.308\ (\pm 0.724)\ \Sigma\sigma_I + 1.828\ (\pm 0.579)\ E_s^o \\ & - 4.164\ (\pm 1.116)\ \Delta B_1^m - 1.465\ (\pm 1.516) \end{aligned} \quad (5)$$

$$n=86,\quad s=0.948,\quad r=0.851,\quad F_{5,80}=42.008,\quad \log P_{opt}=7.1$$

In Eq. (5), Δ means relative to the B_1 value of the H atom. The addition of another steric parameter for *ortho*-substituent, B_5^o ($r^2=0.283$ to E_s^o), in Eq. (5) gave another significant equation with slightly better correlation ($s=0.915$ $r=0.864$, $F_{6,79}=38.752$). Although E_s^o can be replaced with other steric parameters such as B_1, B_5 and V_w, the quality of their correlations was worse than that of Eq. (4). Probably the presence of large groups at *ortho*- and *meta*-positions is unfavorable to ovicidal activity, even though the *ortho*-position of the 4-phenyl ring is substituted with the OEt group for etoxazole (**57**). In fact, some compounds without *ortho*- and *meta*-substituents (**17**–**23**, **29**–**31**, **34**, **46**) are 10 times more active than etoxazole (**57**).

We previously analyzed the substituent effects at 2-phenyl moiety on ovicidal activity against *T. urticae* to derive Eq. (6).[17,18]

$$\begin{aligned} BA = {} & 1.591\ (\pm 1.187)\ \log P + 2.790\ (61.307)\ \sigma_I^o + 0.857\ (\pm 0.550)\ B_5^o \\ & - 2.153\ (\pm 1.388)\ I^{m/p} - 3.663\ (\pm 4.144) \end{aligned} \quad (6)$$

$$n=21,\quad s=0.743,\quad r=0.820,\quad F_{4,16}=8.210$$

In Eq. (6), BA is the score data such as 5, 4, 3, 2, and 1, which correspond to the respective LC_{50} value (0.01–0.1, 0.1–1, 1–10, 10–100, and 100–1000 ppm). Here, we derived a similar correlation by using pLC_{50} (M) instead of BA as shown in Eq. (7).

$$\begin{aligned} \log 1/C = {} & 1.186\ (\pm 1.152)\ \log P + 2.664\ (\pm 1.303)\ \sigma_I^o - 0.840\ (\pm 0.575)\ B_5^o \\ & - 1.873\ (\pm 1.434)\ I^{m/p} - 0.443\ (\pm 3.904) \end{aligned} \quad (7)$$

$$n=21,\quad s=0.776,\quad r=0.805,\quad F_{4,16}=7.373$$

In Eq. (7), $I^{m/p}$ takes 1 for compounds having *meta*- or *para*-substituents at 2-phenyl moiety. Alternatively, if BA is used instead of pLC_{50} of Eqs. (1)–(5), significant and similar correlations are able to be obtained. The σ_I values for SCH_3 and OC_6H_5 used to derive Eq. (7) are 0.25 and 0.4,[18,19] which are different from their previous values used in the formulation of Eq. (6). These results indicate that the use of score data is also applicable in the QSAR analysis, even though the dependent parameter in the Hansch-Fujita method must be a free-energy-related value theoretically. Of course this BA index is rather close to the logarithmic scale of concentrations, because the difference between concentrations is 10-fold (1 as log unit).

QSAR results indicated that the optimum hydrophobicity for ovicidal activity of 2,4-diphenyl-1,3-oxazoline analogs against *T. urtica* was estimated to be very high ($\log P_{opt}=7.0$), and it was higher than the $\log P$ value (5.37) of etoxazole. Here we compared $\log P$ values of various commercial acaricides with different modes of action such as neuroactive, respiration inhibitory and growth regulatory effects, as shown in Table 4. Since some reported $\log P$ values are very different from their CLOGP values, these are also listed. Interestingly most acaricides have very high $\log P$ values.

QSAR analyses of other acaricides were also executed, and it was shown that hydrophobicity is an important physicochemical property for activity[29–33]. For instance, acaricidal activities of pyrethroids[31] and alkanesulfonates[29] were parabolically correlated with hydrophobicity parameters such as π and $\log k'$. Insecticidal activities of pyrethroids toward houseflies were also correlated parabolically with the hydrophobicity of the substituent.[31] The optimum $\log P$ value (7.1) derived from the analysis of substituted 2,4-diphenyl-1,3-oxazoline analogs is not very different from that of pyrethroids. On the other hand, for systemic acaricides, chloromethanesulfonamides, activity is negatively correlated with hydrophobicity,[30] which is understandable because compounds must move through the aqueous xylem of plants.

Previously, Nakagawa and co-workers quantitatively analyzed the substituent effects of benzoylphenylureas on insecti-

Table 4. Measured and calculated log *P* values of other acaricides

Compounds	Mode[a]	Obsd[b]	Calcd[c]	Compounds	Mode[a]	Obsd[b]	Calcd[c]
Pyridaben	Mit.	6.37	5.32	Halfenprox	Neu.	—[d]	8.52
Fenpyroximate	Mit.	5.01	6.30	Bifenazate	Neu.	3.40	3.51
Fenazaquin	Mit.	5.51	4.54	Dicofol	Neu.	4.30[e]	6.06
Tebufenpyrad	Mit.	5.04[f]	4.03	Acrinathrin	Neu.	5.60	7.39
Pyrimidifen	Mit.	4.59	5.22	Flucycloxuron	GR	6.97	6.58
Chlorfenapyr	Mit.	4.83	5.42	Flufenoxuron	GR	4.0	6.39
Acequinocyl	Mit.	>6.2	8.25	Clofentezine	GR	4.10[g]	2.88
Fluacrypyrim	Mit.	4.41	4.39	Hexythiazox	GR	2.53	5.31
Diafenthiuron	Mit.	5.76	5.45	Spiromesifen	GR	4.55	7.06
Amitraz	Neu.	5.5	5.50	Spirodiclofen	GR	5.8	7.45

[a] Target sites or modes of action of acaricides: Mit.: mitochondria, Neu.: neuron, GR: growth regulator. [b] Unless noted, from Pesticide Manual (13th Edition).[34] [c] Calculated by CLOGP (ver. 4.0). [d] Not reported. [e] 4.28 in CLOGP database. [f] 4.61 in CLOGP database. [g] 3.20 in CLOGP database.

cidal activity against rice stem borers *Chilo suppressalis*,[9–12,14] common cutworms *Spodoptera litura*,[13] and silkworms *Bombyx mori*.[13] In all three insects, the substituent effects at the benzoyl moiety were similar, but those at the phenyl moiety were different. In particular, electronic effects were different among the three insects. Electron-withdrawing groups enhance insecticidal activity against *C. suppressalis*, whereas electron-donating substituents are favorable for *B. mori*.[13] The electronic effect was insignificant in QSAR for larvicidal activity against *S. litura*.[13] In their discussion, electron-donating substituents are intrinsically favored and the presence of electron-withdrawing groups at the phenyl moiety plays a role in suppressing oxidative detoxication. This hypothesis is demonstrated by analyzing the inhibition of chitin synthesis at the tissue level, which is measured with and without the inhibitor of oxidative metabolism, piperonyl butoxide (PB). In the QSAR for *in vitro* activity measured in the absence of PB, the coefficient of the electronic effect in terms of σ_I was positive, but in the QSAR for activity derived in the presence of PB it reverted to negative.[7] Thus, a significant electronic effect with a positive sign indicates that the oxidative detoxication ability in *T. urticae* is high and electron-withdrawing groups are effective to partially suppress oxidative detoxification.

In conclusion, we could derive significant QSAR equations for 86 2-(2,6-difluoro)-4-phenyl-1,3-oxazolines with various substituents at the 4-phenyl moiety. About 50% of the correlation was explained only by hydrophobicity terms $\log P$ and $(\log P)^2$, and optimum hydrophobicity was estimated to be about 7.1 in terms of $\log P$. This optimum $\log P$ value is similar to that of various acaricides on the market. The introduction of electron-withdrawing groups was favorable for ovicidal activity, but the presence of substituents at *ortho*- and *meta*-positions was unfavorable, even though the *ortho*-position of the commercialized "etoxazole" was substituted with an ethoxy group. QSAR results for 2,4-diphenyl-1,3-oxazolines were very similar to those of benzoylphenylureas with respect to both phenyl rings.

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