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Estimation of the hydrophobicity of 2,4-diphenyl-1,3-oxazoline analogs and QSAR analysis of their ovicidal activity against *Tetranycus urticae*

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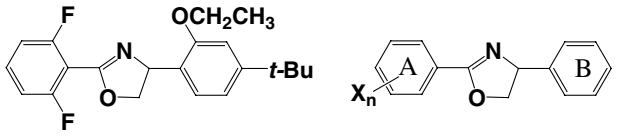
Abstract—Partition coefficients of six 2-phenyl-1,3-oxazoline congeners containing 2-I, 2-NO_2, 2-CF_3, 2,6-$(CH_3)_2$, 2,6-F_2, and 2-F-6-Cl substitutions on the phenyl moiety were measured in a 1-octanol/water system using the flask-shaking method. The effect on the hydrophobicity (Log *P*) of substituents on the phenyl moiety of 2-phenyl-1,3-oxazolines linearly correlated with that of benzamide congeners. log *P* values of other 2-(substituted phenyl)-1,3-oxazoline analogs were empirically estimated from the corresponding substituted benzamides. The ovicidal activity of 2-(substituted phenyl)-4-phenyl-1,3-oxazoline analogs against the two-spotted spider mite *Tetranycus urticae* was quantitatively analyzed using the classical QSAR (Hansch–Fujita) method. Results showed that ovicidal activity increases with hydrophobicity. The introduction of inductive electron-withdrawing groups at *ortho*-positions increased ovicidal activity, but addition of steric bulk was unfavorable. Substitution at either the *meta*- or *para*-position was detrimental to the acaricidal activity.

Etoxazole [YI-5301, 4-(4-*tert*-butyl-2-ethoxyphenyl)-2-(2,6-difluorophenyl)-1,3-oxazoline, **I** in Fig. 1] is a growth inhibitory-type acaricide discovered by Kyoyu Agri Co., Ltd (formerly Yashima Chemical Industry Co., Ltd).[1,2] This compound has an excellent activity against eggs, larvae, protonymphs, and deutonymphs of susceptible mites such as *Tetranycus kanzawai* and *Panonycus citri*, but no activity against adult mites. Etoxazole also exhibits insecticidal activity against juvenile aphids such as *Myzus persicae* and *Aphis gossypii* by inhibiting their molting process. The mode of action of this compound is thought to be via the inhibition of chitin biosynthesis in mites and insects. Similar growth inhibitory-type acaricides have also been developed, in which benzoylphenylurea (BPU) analogs are included.[3]

The discovery of a BPU-type compound, Du19111 [*N*-(2,6-dichlorobenzoyl)-*N*′-(3,4-dichlorophenyl)urea],[4,5] accelerated the study of chitin synthesis inhibitors,[6–8] as well as other insect growth regulators such as juvenile hormone mimics and molting hormone agonists.[9–11] We have been continuing the quantitative structure–activity relationship (QSAR) study of benzoylphenylurea[12–16] and thiadiazole derivatives[17] for the larvicidal activity against the rice stem borer *Chilo suppressalis* Walker and other lepidopteran insects.[18] QSAR study has also been executed for analysis of the inhibition of chitin synthesis in the cultured integuments.[19] In all QSARs, the molecular hydrophobicity is the common significant factor, whereas electronic and steric effects participate to vary the activity depending upon the insect species and experimental condition.



(**I**) (**II**)

Figure 1. Structures of etoxazole (**I**) and 2-(substituted phenyl)-4-phenyl-1,3-oxazolines (**II**).

Keywords: 2,4-Diphenyl-1,3-oxazoline; *Tetranycus urticae*; Log *P*; QSAR; Ovicidal activity.
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Previously Suzuki and co-workers reported the ovicidal activity of 2,4-diphenyl-1,3-oxazoline congeners having various substituents at both phenyl moieties against mites.[20] Introduction of halogens at *ortho*-position(s) of A-ring (**II** in Fig. 1) is favorable to the activity, but not at *meta*- and *para*-positions. Moreover, di-*ortho*-substituted compounds were more potent than the mono *ortho*-substituted. However, the physicochemical meaning of this substitution has not yet been analyzed. Since the hydrophobicity seems to be very important for the in vivo activity, we attempted to evaluate the hydrophobicity parameters for the substituents at the A-ring moiety. The hydrophobic substituent parameter, π, defined as the difference of $\log P$ (P, partition coefficient between 1-octanol and water) between mono-substituted benzene and unsubstituted benzene[21] is not valid for the QSAR of certain series of compounds,[22] particularly for *ortho*-substituted analogs.[23,24]

In this study, we synthesized 2-phenyl-1,3-oxazoline congeners containing various *ortho*-substituents and measured their $\log P$ values. Accumulation of the hydrophobicity values of such heterocyclic compounds as phenyloxazolines is very important to enhance the predictability of the $\log P$ calculation program CLOGP, which is widely used to predict the hydrophobicity of compounds.[25] In further studies the substituent effects of 2-(substituted phenyl)-4-phenyl-1,3-oxazoline analogs on the ovicidal activity against the two-spotted spider mite *Tetranycus urticae* were quantitatively analyzed using Hansch–Fujita QSAR method[21,26] to find the essential physicochemical property for the ovicidal activity.

Partition coefficient (P) values of 2-phenyl-1,3-oxazoline congeners were measured in the 1-octanol/water system using a conventional flask-shaking method[21] as listed in Table 1. Since five 2-phenyl-1,3-oxazoline congeners with H, 2-CH_3, 2-F, 2-Cl, and 2-Br were labile in the water/octanol system, their P values were not able to be determined.

Since the substructure –C(O–)(=N–) of 2-phenyl-1,3-oxazoline is somewhat similar to [–C(=O)O–] of methylbenzoate and [–C(=O)NH_2] of benzamide,[23] the experimentally measured $\log P$ values of 2-phenyl-1,3-oxazoline congeners were compared with those of corresponding methyl benzoates and benzamides as shown in Eqs. 1 and 2.

$$\log P = 1.005(\pm 0.319)\log P(\text{benzamides}) + 1.359(\pm 0.204)$$
$$n = 6,\ s = 0.107,\ r = 0.975,\ F_{1,4} = 76.54. \quad (1)$$

$$\log P = 0.809(\pm 0.152)\log P(\text{benzoate}) - 0.052(\pm 1.022)$$
$$n = 6,\ s = 0.168,\ r = 0.936,\ F_{1,4} = 28.49. \quad (2)$$

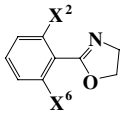
In these and the following correlation equations, n is the number of compounds included in the analysis, s is the standard deviation, r is the correlation coefficient, and F is the value of the ratio between regression and residual variances. The figures in parentheses after each coefficient are the 95% confidence intervals of the regression coefficient. Since the correlation in Eq. 1 was improved relative to Eq. 2, $\log P$ values of other substituted compounds were calculated using Eq. 1 from the corresponding benzamides.[22–24] Log P values of benzamides were either obtained from the CLOGP database, or calculated using the CLOGP program (ver. 4.0; BioByte Corp., Claremont, CA, USA).[25] $\log P$ values for 2,4-diphenyl-1,3-oxazoline analogs were calculated from the corresponding 2-phenyl-1,3-oxazoline congeners by adding 1.56 for the phenyl moiety, the difference of $\log P$ values between 2-phenyl-1,3-oxazoline and 2,4-diphenyl-1,3-oxazoline, which were calculated from the CLOGP program. All calculated $\log P$ values for 2,4-diphenyl-1,3-oxazoline analogs are listed in Table 2.

Previously we reported the ovicidal activity against *T. urticae* which is expressed in LC_{50} (ppm) values such as 0.01–0.1, 0.1–1, 1–10, 10–100, 100–1000, and >1000 ppm.[20] Although these LC_{50} 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. Since the difference between concentrations is 10-fold, they were converted to the free energy-related index, BA = 5, 4, 3, 2, 1, <0 (logarithmic scale), respectively. The activity of mono *ortho*-substituted compounds was first quantitatively analyzed to derive Eq. 3, using QREG2.05.[27] Since the substituent effect on the activity is very similar to that of BPU-type insecticides,[14] similar parameters were used in the QSAR of 2-phenyl-1,3-oxazolines.

$$\text{BA} = 1.999(\pm 1.466)\log P + 3.123(\pm 1.674)\sigma_I^o - 0.981(\pm 0.654)\Delta B_5^o - 5.134(\pm 5.180)$$
$$n = 15,\ s = 0.794,\ r = 0.831,\ F_{3,11} = 8.167. \quad (3)$$

In Eq. 3 and the following equation, σ_I is the electronic parameter representing the inductive component of the total electronic effect[28] and B_5 is the STERIMOL parameter representing the maximum width of substituents from the axis connecting an atom of substituents

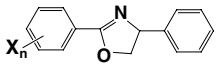
Table 1. Experimentally measured Log P values of 2-(2,6-disubstituted phenyl)-1,3-oxazolines



X^2	X^6	log P[a]	Calcd[b]
I	H	2.30 ± 0.01 (4)	2.30
NO_2	H	1.27 ± 0.02 (8)	1.22
CF_3	H	2.15 ± 0.03 (8)	1.83
CH_3	CH_3	2.21 ± 0.05 (8)	2.11
F	F	1.45 ± 0.01 (8)	1.52
F	Cl	1.89 ± 0.02 (8)	1.98

[a] Mean ± standard deviation. Numbers in parentheses are replications.
[b] Calculated by Eq. 1.

Table 2. Ovicidal activity of 2-(substituted phenyl)-4-phenyl-1,3-oxazolines against *Tetranycus urticae* and physicochemical parameters for QSAR



Compound		Activity		Physicochemical parameters			
No.	Substituents (X_n)	BA[a]	Calcd[b]	log P[c]	σ_I^o	B_5^o	$I^{m/p}$
1	H	2	2.0	3.56	0	0	0
2	2-CH_3	1	1.3	3.68	−0.01	1.04	0
3	2-OCH_3	2	1.4	3.76	0.3	2.07	0
4	2-OEt	<0	1.8	4.22	0.28	2.36	0
5	2-OPh	1	1.1	5.61	0	4.89	0
6	2-SCH_3	1	1.1	3.50	0.4	2.26	0
7	2-SEt	1	1.0	4.04	0.28	2.97	0
8	2-F	2	3.1	3.51	0.54	0.35	0
9	2-Cl	3	2.6	3.56	0.47	0.8	0
10	2-Br	4	2.7	3.69	0.47	0.95	0
11	2-I	3	2.6	3.86[d]	0.4	1.15	0
12	2-CF_3	1	2.0	3.71[d]	0.4	1.61	0
13	2-NO_2	1	1.5	2.83[d]	0.67	1.44	0
14	3-CH_3	<0	0.7	4.11	0	0	1
15	3-OCH_3	<0	0.2	3.77	0	0	1
16	3-Cl	1	1.2	4.44	0	0	1
17	4-CH_3	<0	0.7	4.11	0	0	1
18	4-OCH_3	1	0.2	3.78	0	0	1
19	4-Cl	1	1.3	4.48	0	0	1
20	2,3-Cl_2	2	1.6	4.28	0.47	0.8	1
21	2,4-Cl_2	2	1.8	4.40	0.47	0.8	1
22	2,5-Cl_2	1	1.8	4.40	0.47	0.8	1
23	2,6-F_2	3	3.5	3.01[d]	1.08	0.7	0
24	2-F-6-Cl	5	3.7	3.45[d]	1.01	1.15	0
25	2,6-Cl_2	3	3.5	3.69	0.94	1.6	0

[a] 0 = >1000 ppm; 1 = 100–1000 ppm, 2 = 10–100 ppm, 3 = 1–10 ppm, 4 = 0.1–1 ppm, 5 = 0.01–0.1 ppm.
[b] Calculated by Eq. 4.
[c] Sum of log P values of 2-phenyl-1,3-oxazolines and the fragment value (1.56) for the 4-phenyl moiety of 2,4-diphenyl-1,3-oxazoline.
[d] Calculated from their observed values listed in Table 1.

and the rest of molecules.[29] In this analysis, ΔB_5, the value relative to that of hydrogen, was utilized. The superscript '*o*' means the *ortho*-position, and values for *meta*- and *para*-positions are zero. The use of CLOGP instead of log P made the correlation poorer ($s = 0.901$, $r = 0.775$). In further analysis, six compounds containing *meta*- and *para*-substituents (**16**, **18**–**22**) were added to the compounds in Eq. 3 to formulate Eq. 4, with the addition of a new indicator parameter $I^{m/p}$ which assumes 1 for compounds having *meta*- or *para*-substituents.

$$\begin{aligned} \mathrm{BA} &= 1.591(\pm 1.187)\log P + 2.790(\pm 1.307)\sigma_I^{\mathrm{o}} \\ &\quad - 0.857(\pm 0.550)B_5^{\mathrm{o}} - 2.153(\pm 1.388)I^{m/p} \\ &\quad - 3.663(\pm 4.144) \\ n &= 21,\ s = 0.743,\ r = 0.820,\ F_{4,16} = 8.210. \end{aligned} \quad (4)$$

Eqs. 3 and 4 show that activity increases with the inductive electron-withdrawing property, whereas the introduction of the bulkier group at the *ortho*-position is unfavorable to the activity. By the introduction of substituents at either the *meta*- or *para*-position, the activity decreased 100-fold. The addition of the squared term of log P was not significant in either Eq. 3 or 4. The predicted activity values by Eq. 4 for all compounds are listed in Table 2, and the degree of collinearity of independent variables used to derive Eq. 4 is summarized in Table 3.

As shown above, significant QSAR equations were formulated for the ovicidal activity of 2-phenyl-1,3-oxazoline congeners with various substituents at the 2-phenyl moiety against *T. urticae*. The hydrophobicity parameter, π, defined for mono-substituted benzenes is generally used for the QSAR analysis of substituted benzene analogs. However, since the π value varies from one solute to another for di-substituted benzenes with hydrogen-bonders, the corrected π values are rationally used.[14,24] In the di-substituted benzenes the electronic interactions between two substituents exist for *meta*- and *para*-substitutions, and the steric interaction is also recognized for *ortho*-substitutions. Therefore, we newly determined the hydrophobicity parameter for the phenyl substituents of 2-phenyl-1,3-oxazolines.

Table 3. Squared correlation matrix between parameters

	log P	σ_I^o	B_5^o
σ_I^o	0.289		
B_5^o	0.149	0.000	
$I^{o/m}$	0.217	0.100	0.207

The log *P* value of 2-(2,6-difluorophenyl)-4-phenyl-1,3-oxazoline was calculated to be 3.01 by summing the log *P* value (1.45) of 2-(2,6-difluorophenyl)-1,3-oxazoline and the difference (1.56) of log *P* values between 2,4-diphenyl-1,3-oxazoline (X_n = H in **II**, Fig. 1) and 2-phenyl-1,3-oxazoline. According to this rule, the log *P* value of etoxazole (**I**, Fig. 1) is calculated to be 5.37 by the addition of π values of mono-substituted benzenes, OEt (0.38) and *t*-Bu (1.98), to that (3.01) of 2-(2,6-difluorophenyl)-4-phenyl-1,3-oxazoline (X_n = 2,6-F_2 in **II**, Fig. 1). This estimated log *P* value of etoxazole is not far from the reported value (5.59).[1] Moreover, the log *P* value of 2-(2,6-difluorophenyl)-4-(4-hydroxyphenyl)-1,3-oxazoline was measured to be 2.52 (unpublished data). Since the hydrophobicity parameter for OH group is −0.67, 2-(2,6-difluorophenyl)-4-phenyl-1,3-oxazoline is calculated to be 3.19, which is very close to the empirically estimated log *P* value (3.01). As a result, the log *P* value of etoxazole is estimated to be 5.55, which is very close to the reported value (5.59).

The log *P* value of etoxazole was calculated by CLOGP to be 6.56, which is 10 times more hydrophobic than the observed value. The main reason for this error is thought to be an incorrect estimation of the hydrophobicity change for the 2,6-difluoro substitution. Namely, the estimation of the hydrophobicity for 2,6-difluoro substitution is 0.29 higher than the unsubstitution, but it is lower by 0.55. Therefore, the calculated hydrophobicity of etoxazole is 10 times higher in the present CLOGP version 4.0.

A similar QSAR equation was obtained for the analysis of the larvicidal activity against *C. suppressalis* of benzoylphenylureas (**III** in Fig. 2) with various substituted benzoyl moieties as shown in Eq. 5, in which the π value is determined from various benzamide congeners.[14]

$$\begin{aligned} \mathrm{pLD}_{50} &= 0.585\pi + 0.440\sigma^{\#} + 0.774\Sigma E_s^o \\ &\quad + 6.667 \\ n &= 20,\ s = 0.257,\ r = 0.895. \end{aligned} \tag{5}$$

In Eq. (5), $\sigma^{\#}$ is the mixed electronic parameter which takes σ_I values for 2,6-diortho substituted compounds and σ for other compounds. E_s is the steric parameter which was defined by Sotomatsu and co-workers by measuring the substituent effects on the rate of hydrolysis of various substituted benzamides.[30] Although the same parameters were used to analyze the substituent effects at phenyl moiety of 2-phenyl-1,3-oxazolines, no significant correlation was derived.

Haga and co-workers also quantitatively analyzed the substituent effects of BPUs on the larvicidal activity in terms of pLC_{50} (ppm) against *Spodoptera litura*. They used chlorfluazuron congeners with various substituents at the *ortho*-, *meta*-, and *para*-positions of the benzoyl moiety (**IV** in Fig. 2).[31,32]

$$\begin{aligned} \mathrm{pLC}_{90} &= 0.233E_s^{ortho} + 3.15E_s^{meta} + 2.42E_s^{para} \\ &\quad + 0.359I + 0.593 \\ n &= 14,\ r = 0.931,\ s = 0.597. \end{aligned} \tag{6}$$

In Eq. 6, *I* is the indicator variable which takes 1 and 2 for mono- and di-*ortho* substitution, respectively, and otherwise 0. Even though the E_s parameter was used for *meta*- and *para*-substituents, the variation of substituents at *meta*- and *para*-positions is very small. The substituents at the *meta*-position are only F and Cl, and those at the *para*-position are F, Cl, and CH_3, which seems to be equivalent to the indicator variable $I^{m/p}$ in Eq. 4.

In conclusion, the molecular hydrophobicity of six 2-(substituted phenyl)-1,3-oxazoline analogs was experimentally determined. Some compounds were not able to be determined, because they were labile to the octanol/water partition system. Log *P* values of labile compounds were able to be estimated from log *P* values of corresponding substituted benzamides. Using the experimentally defined hydrophobicity parameter and other physicochemical parameters, significant QSAR equations for 2-(substituted phenyl)-1,3-oxazolines were derived. Results showed that ovicidal activity increases with molecular hydrophobicity. Introduction of inductive electron-withdrawing groups at the *ortho*-position was favorable to the activity, but the introduction of the bulky groups at the *ortho*-position and the substitution at the *meta*- and *para*-position were detrimental to the activity. Although the activity index was not as accurate as pLD_{50} and pLC_{50}, the essential physicochemical factors to vary the ovicidal activity were disclosed. Interestingly, the factors governing the ovicidal activity were similar to those found in the QSAR analysis of the larvicidal activity of BPUs. These QSAR results for 2,4-diphenyl-1,3-oxazolines will be useful in the future study regarding the mode of action of chitin synthesis inhibitors including BPUs.

Synthesis of compounds. Eleven 2-phenyl-1,3-oxazoline congeners with various substituents [H, 2-CH_3, 2-F, 2-Cl, 2-Br, 2-I, 2-CF_3, 2-NO_2, 2,6-F_2, 2-F-6-Cl, and 2,6-$(CH_3)_2$] at the benzene ring were synthesized according to the conventional method[20], from 2-aminoethanol and substituted benzoyl chloride. The structures of new-

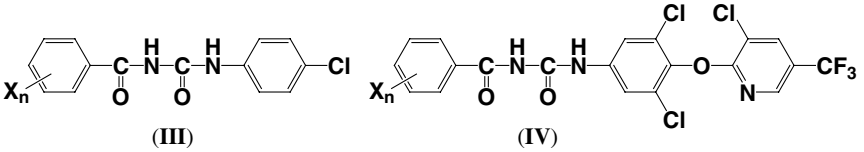


Figure 2. Structures of benzoylphenylurea (**III**) and chlorfluazuron-type compound (**IV**).

ly synthesized compounds were confirmed by ^{1}H NMR and elemental analyses. The analytical values for C, H, and N of all compounds agreed within ±0.3%. ^{1}H NMR δ_H (300 MHz, $CDCl_3$) for 2-phenyl-1,3-oxazoline: 4.06 (2H, t, $J = 9.5$ Hz, N–CH_2), 4.43 (2H, t, $J = 9.5$ Hz, O–CH_2), 7.37–7.50 (3H, m, Ar-H), 7.93–7.97 (2H, m, Ar-H); Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.68; H, 6.20; N, 9.50.

Acknowledgments

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