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Original Article

Quantitative Structure-Activity Relationships of Larvicidal *N*-[5-(Substituted phenyl)-1,3,4-thiadiazol-2-yl]-benzamides in the Inhibition of *N*-Acetylglucosamine Incorporation into a Cultured Integument System*

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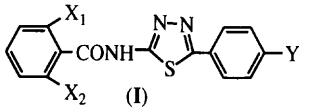
Twenty-nine *N*-[5-(substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamides with various substituents on both benzene rings were synthesized. Most of them inhibited the incorporation of *N*-acetyl-[1-^{14}C]-glucosamine into cultured rice stem borer (*Chilo suppresssalis* WALKER) integument in the presence and absence of a metabolic inhibitor for oxidative degradation, piperonyl butoxide. Variations in the activity under each experimental condition were quantitatively analyzed with physicochemical substituent parameters and regression analyses. After the separation of the hydrophobic effect, *para* substituents on the benzene ring at the 5-position of the thiadiazole ring showed peculiar electronic and steric effects on the inhibitory activity. The greater the inductive component of the electron-withdrawing property and the molecular hydrophobicity, the higher the activity. Introduction of electron-donating groups such as OMe and Me at the *ortho* position of the benzoyl moiety seemed to be favorable to the activity. A limited number of compounds showed larvicidal activity against the insects *via* topical application.

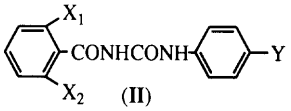
INTRODUCTION

Among various insect growth regulators, the chitin synthesis inhibiting benzoylphenylureas such as diflubenzuron,[1] triflumuron,[2] chlorfluazuron,[3,4] and teflubenzuron[4] are well known. Isoprothiolane[5] and buprofezine[6] are also chitin synthesis inhibitors, even though their mode of action is different from that of the benzoylphenylureas. Dibenzoylhydrazines, including tebufenozide, mimic molting hormone[7–10] and inhibit chitin synthesis at high concentrations.[11] These insect growth regulators are commercially available.

We have established an *in vitro* system to measure the activity of chitin synthesis inhibitors[12,13] and molting hormone-like compounds[11,14] in which the incorporation of *N*-acetylglucosamine (GluNAc) into cultured rice stem borer (*Chilo suppressalis* WALKER) integument was measured. For chitin synthesis inhibitors, integument fragments were first treated with 20-hydroxyecdysone (20-HE) to induce cuticle formation and cultured in a medium containing test compounds and radio-labeled GluNAc.[12] They inhibited the incorporation in a dose dependent manner.[12,13] For molting hormone-like compounds, including dibenzoylhydrazines, integument fragments were treated with test compounds for 24 hr, then cultured in a medium containing radio-labeled GluNAc.[11] Generally, they enhanced the incorporation of the radio-labeled GluNAc at certain lower concentrations, whereas they inhibited it at higher concentrations.



(I)



(II)

N-[5-(Substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamide derivatives (**I**) show the insecticidal effect as benzoylphenylureas (**II**) by preventing molting.[15] One of the compounds LY-131215 (**I**: $X_1=X_2=$OMe, Y=OC_2F_5) was a more potent larvicide than diflubenzuron (**II**: $X_1=X_2=$F, Y=Cl) against spruce budworms (*Choristoneura fumiferana* CLEMENS)[16] and beet armyworms (*Spodoptera exigua* HÜBNER).[17] Even though no quantitative analysis has been done for *N*-[5-

* Quantitative Structure-Activity Studies of Insect Growth Regulators (Part XII). For the previous paper, see Ref. 14).

(substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamide derivatives, the favorable substitution patterns required for optimal insecticidal activity for these two classes of compounds seemed to be much different from each other.[15,18]

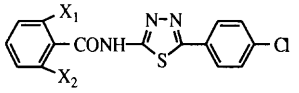
In this study, we synthesized a set of compounds with various substituents at both benzene rings of structure **I** and measured their chitin synthesis inhibiting activity in our cultured integument system. We here report the effects of Y on the activity quantitatively. We also show that the potency was varied drastically by changing the substituents X_1 and X_2.

MATERIALS AND METHODS

1. *Compounds*

2-(2,6-Disubstituted benzoylamino)-5-(4-substituted phenyl)-1,3,4-thiadiazoles (**I**) listed in Tables 1 and 2 were synthesized from substituted benzoyl chlorides and 2-amino-5-(4-substituted phenyl)-1,3,4-thiadiazoles by stirring at 0–25°C in the presence of NaH in dry tetrahydrofuran.[15] In this study, we defined the benzene ring attached to the 2- and 5-positions of the thiadiazole ring as the "phenyl" and "benzoyl" moieties, respectively. The 2-aminothiadiazoles were prepared either by dehydrative cyclization of the corresponding 1-(4-substituted benzoyl)thiosemicarbazides in phosphoric acid at 20 to 50°C or by oxidative cyclization of 4-substituted benzaldehyde thiosemicarbazones at 100°C in the presence of ferric chloride. 1-(4-Substituted benzoyl)thiosemicarbazides were prepared by treatment of thiosemicarbazide with appropriate benzoyl chlorides in dry pyridine at room temperature. Substituted benzaldehyde thiosemicarbazones were prepared from thiosemicarbazide and substituted benzaldehydes by refluxing in methanol. The prepared test compounds are listed in Tables 1 and 2 with uncorrected melting points. Chemical structures of the test compounds and their intermediates were analyzed by infrared and proton magnetic resonance spectra. The final compounds were also confirmed by the elemental analyses. The analytical values for C, H, and N agreed with the calculated values within 0.3%. Piperonyl butoxide (PB) and 20-HE were purchased from Tokyo Kasei Co., Tokyo, Japan and Rohto Pharmaceutical Co., Osaka, Japan, respectively. *N*-Acetyl-D-[1-^{14}C]glucosamine ([^{14}C]-GluNAc; 2.17×10^9 Bq/mmol) and NCS, a tissue solubilizer, were purchased from Amersham International plc., Buckinghamshire, England. [^{14}C]GluNAc was diluted with 70% aqueous ethanol to about 6000 dpm/μl. Aquasol II, a cocktail for liquid scintillation counting, was purchased from DuPont-NEM (Boston, MA, U.S.A.).

Table 1 Inhibition of 1,3,4-thiadiazoles in GluNAc incorporation into the cultured integument (pI_{50}) and their larvicidal activity against *Chilo suppressalis* (pLD_{50})



No.	Substituents X_1	Substituents X_2	pI_{50}(M)[a] PB	pLD_{50}[b] (mmol/insect) PB	mp (°C)
1	H	H	<5.30 (10%)	<5.60 (0%)	238
2	F	F	<5.30 (42%)	<4.60 (0%)	277–279
3	Cl	Cl	6.42	<5.00 (5%)	295
4	Me	Me	7.16	5.48	263–265
5	OMe	OMe	7.23	5.96	252–253
6	F	H	6.14	<4.60 (0%)	257–261
7	Cl	H	<5.30 (37%)	<4.60 (41%)	280
8	Br	H	<5.30 (32%)	<4.60 (0%)	268
9	I	H	<5.30 (17%)	<4.60 (5%)	263–265
10	CF_3	H	<4.78 (7%)	<4.60 (0%)	255–258
11	NO_2	H	<5.30 (0%)	<4.60 (0%)	>300
12	Me	H	6.80	<4.60 (0%)	252
13	OMe	H	7.27	5.96	227–230
14	OEt	H	<5.30 (23%)	<5.60 (10%)	222–223
15	NEt_2	H	<4.70 (8%)	<5.00 (0%)	172–174
Diflubenzuron			7.72[c]	6.64[d]	232–233[d]

[a] Values in parentheses are means of inhibition (%) of the incorporation of GluNAc at the maximum concentration indicated. See the text for details.

[b] Measured against the rice stem borer larvae in the presence of PB. The value in parentheses is the mortality (%) at the maximum dose indicated.

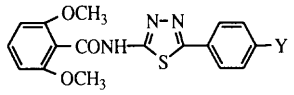
[c] From Ref. 13).

[d] From Ref. 20).

2. *Incorporation of [^{14}C]GluNAc into Cultured Integument Fragments*

Procedures for the culture of integument fragments of the insects and measurements of incorporated [^{14}C]-GluNAc were essentially the same as those described previously.[11,12] Diapause larvae of the rice stem borer were obtained by aseptic rearing on an artificial diet under short-day photoperiods (8L : 16D) at 25°C. Each of six pieces of integument excised from the dorsal part of the larvae was cultured first at 28±3°C in 1 ml of Grace's medium containing 2.2 nmol of 20-HE. After 24 hr, each fragment was transferred to another culture well containing 1 ml of medium with 3 μl of 70% aqueous ethanol solution containing [^{14}C]GluNAc (1.0×10^{-10} mol) and 1 μl of a test compound in dimethyl sulfoxide (DMSO) at various concentrations. The fragments were incubated at 28±3°C for another 72 hr. In some experiments, incubation with [^{14}C]GluNAc was performed in the presence of 20 μM PB. After the incubation with [^{14}C]GluNAc, the cultured medium was removed and the integument fragments were washed three times with 0.5 ml of water. After keeping the fragments in 0.5 ml of NCS, the radioactivity incorporated into the integument fragments was measured in Aquasol II with a liquid

Table 2 Inhibition of 1,3,4-thiadiazoles in GluNAc incorporation into the cultured integument (pI_{50}) and their larvicidal activity against *Chilo suppressalis* (pLD_{50}).



No.	Y	pI_{50}(M) None Obsd.	pI_{50}(M) None Calcd.[a]	pI_{50}(M) PB Obsd.	pI_{50}(M) PB Calcd.[b]	pLD_{50}[c] (mmol/insect) PB	mp (°C)
16	H	5.53	5.31	6.55	6.86	<5.00 (0%)	265-267
17	Me	5.91	5.59	7.07	6.85	5.00	238
18	*i*-Pr	6.40	6.13	6.74	6.76	[d]	278-280
19	*t*-Bu	6.04	6.31	6.28	6.56	[d]	251
20	F	7.01	6.93	7.05	6.90	<5.00 (14%)	253
5	Cl	7.27	7.13	7.23	7.13	5.96	252-253
21	Br	7.18	7.10	7.34	7.13	5.57	233
22	I	7.05	7.09	7.01	7.08	[d]	249
23	CF_3	7.31	6.97	7.25	7.35	[d]	233
24	NO_2	6.45	6.47	6.57	6.42	<5.00 (0%)	255
25	CN	6.68	6.70	6.70	7.08	[d]	270
26	OMe	5.65	6.27	6.78	6.70	<5.00 (0%)	257
27	OEt	6.19	6.37	7.02	6.78	<5.00 (6%)	227-231
28	Ph	6.71	6.68	6.93	6.71	[d]	245
29	NEt_2	6.13	6.20	6.17	6.39	[d]	242-243
Diflubenzuron		7.69[e]		7.72[e]		6.64[f]	232-233[f]

[a] Calculated using Eq. (3).
[b] Calculated using Eq. (4).
[c] Measured against the rice stem borer larvae in the presence of PB. The value in parentheses is the mortality (%) at the maximum dose indicated.
[d] Not determined.
[e] From Ref. 13).
[f] From Ref. 20).

scintillation counter. Radioactivity was expressed as mean disintegrations per minute (dpm) from three experimental runs.

3. *Larvicidal Tests*

The rice stem borer larvicidal tests were performed as previously described.[19,20] The third-instar, non-diapause larvae were reared on an artificial diet under long-day photoperiods (16L : 8D) for approximately 10 days after hatching. They were initially kept on a diet containing PB at 100 μM at least for 1 hr, then each larva was topically exposed to a 0.5 μl aliquot of DMSO containing various amounts of each compound. For each concentration of each test chemical, 20 larvae were used. After five days rearing at 28°C on the PB-containing diet under the long-day photoperiod condition, the pLD_{50} value, the log of the reciprocal of the median lethal dose (mmol/larva), was calculated by use of the probit transformation method.[21,22] The pLD_{50} values for each compound are listed in Tables 1 and 2.

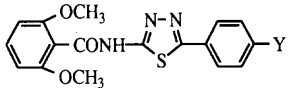
4. *Substituent Parameters*

The substituent parameters for 2,6-dimethoxy-*N*-[5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamides (**I**; $X_1=X_2=$OMe) used here are listed in Table 3. The σ_I is Charton's electronic parameter.[23] As the steric parameter, the van der Waals volume, V_W, calculated according to Bondi was used.[24] In the analyses, the value relative to that of H, ΔV_W, was scaled by 0.1 to make it comparable to that of the other parameters. The molecular hydrophobicity values, log *P*, of compounds **5**, **16**, **17**, **20**, **21** and **24**-**27** were measured using the 1-octanol/water partitioning system (Table 3). The π value was calculated by subtracting the log *P* value for each compound by the log *P* value for compound **16** (Table 3). Excluding the value for compound **24**, π values were correlated very well with ordinal hydrophobic substituent constants ($\pi_{Y/PhH}$) taken from monosubstituted benzenes[25,26] as shown in Eq. (1), even though the slope of the $\pi_{Y/PhH}$ term is much smaller than unity.

$$\pi = 0.580\ (\pm 0.122)\ \pi_{Y/PhH} - 0.002\ (\pm 0.062) \quad (1)$$
$$n=8,\ s=0.061,\ r=0.979,\ F=135.3$$

The constant term in Eq. (1) was reasonably close to zero. When compound **24** is included in the above

Table 3 Molecular hydrophobicity and substituent parameters for *N*-[5-(*para*-substituted phenyl)-1,3,4-thiadiazol-2-yl]-benzamides.



No.	Y	Hydrophobicity			$\pi_{Y/PhH}$[b]	σ_I[c]	ΔV_W
		log *P*	π				
			Obsd.	Calcd.[a]			
16	H	3.50	0.00	0.00	0.00	0.00	0.00
17	Me	3.85	0.35	0.32	0.56	−0.01	1.12
18	*i*-Pr	[d]	[d]	0.89	1.53	0.01	3.16
19	*t*-Bu	[d]	[d]	1.15	1.98	−0.01	4.18
20	F	3.50	0.00	0.08	0.14	0.54	0.33
5	Cl	3.96	0.46	0.41	0.71	0.47	0.95
21	Br	3.92	0.42	0.50	0.86	0.47	1.26
22	I	[d]	[d]	0.65	1.12	0.40	1.71
23	CF_3	[d]	[d]	0.51	0.88	0.40	1.94
24	NO_2	2.54	−0.96[e]	−0.16	−0.28	0.67	1.43
25	CN	3.14	−0.36	−0.33	−0.57	0.57	1.22
26	OMe	3.56	0.06	−0.01	−0.02	0.30	1.44
27	OEt	3.75	0.25	0.22	0.38	0.28	2.46
28	Ph	[d]	[d]	1.13	1.96	0.12	4.33
29	NEt_2	[d]	[d]	0.42	0.73	0.17	4.96

[a] Calculated using Eq. (1).
[b] Taken from Ref. 26).
[c] Taken from Ref. 23).
[d] Not measured.
[e] Not used to derive Eq. (1).

correlation analysis, the correlation equation was poor ($s=0.268$, $r=0.830$). In this and the following equations, n is the number of compounds, 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 are 95% confidence intervals of the regression coefficient. Experimental measurement of the log *P* value was difficult for some compounds because of their extremely high hydrophobicity, so we estimated their π values *via* Eq. (1) (Table 3). In the following analyses, the calculated π values were used for compounds without the experimentally measured value.

RESULTS AND DISCUSSION

1. *Inhibitory Activity for GluNAc Incorporation into Cultured Integument*

Compound **22** inhibited the incorporation of GluNAc into the rice stem borer cultured integument in a concentration-dependent manner where the radioactivity at each concentration is an average for three runs (Fig. 1). The background in this system was about 3000–4000 dpm. We have shown that this amount of radioactivity corresponds to the non-chitinous components that do not participate in the growth of the new cuticle.[11,12] By taking the difference of radioactivity counted without test compounds from the background counts as the full scale, we determined the median inhibitory concentration (I_{50} (M)) by use of the probit transformation method.[21,22] The inhibitory activity of compounds was expressed as pI_{50} values, which is the log of the reciprocal of I_{50}. The pI_{50} values for the test compounds are listed in Tables 1 and 2. The most potent compound was compound **23** and weaker than diflubenzuron by a factor of 2.3.

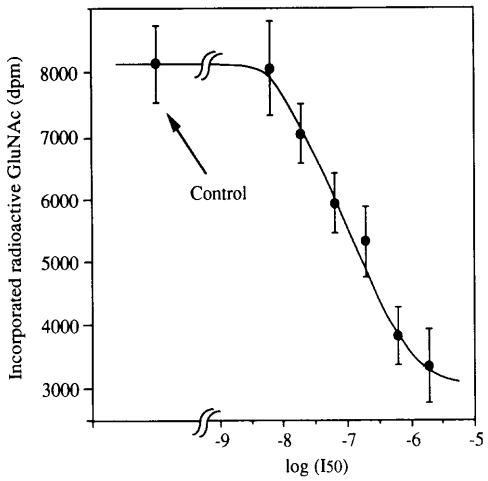


Fig. 1 Concentration-response relationship for compound **22** in the GluNAc incorporation assay.
The integument pieces were first incubated with 2.2 μM 20-HE for 24 hr. They were incubated for another 72 hr in a culture medium containing the test compound.

2. *Effects of Substituents X_1 and X_2 on the Inhibitory Activity for GluNAc Incorporation*

Among compounds listed in Table 1, the inhibitory activity in terms of pI_{50} was determinable only for six compounds **3**–**6**, **12** and **13**. Other compounds gave unmeasurably low activity. When the definitive value was not determinable because of limited solubility, the activity was expressed with the "less than" sign along with the maximum inhibition percentage at the highest concentration tested, as listed in Table 1. To calculate the value, the dpm value measured with 2 μM diflubenzuron, which was included in each series of experiments as a positive control, was taken as the background level based on our previous results.[12] Interestingly, *ortho*-monomethoxy compound **13** was equipotent to that of 2,6-dimethoxy compound **5**. In contrast, the *ortho*-monomethoxy derivative of benzoylphenylureas (**II**: X_1=H, X_2=OMe, Y=Cl; pI_{50}=6.07) had much weaker inhibitory potency than the dimethoxy derivative (**II**: $X_1=X_2$=OMe, Y=Cl; pI_{50}=7.22) in our cultured integument system.[13] For the present series of compounds, no significant correlation equation could be formulated, because the number of compounds with a definitive pI_{50} value was too small.

3. *Effects of Substituents Y on the Inhibitory Activity for GluNAc Incorporation*

Compound **5** was one of the most potent compounds tested (Table 1), so we decided to analyze the effect of substituent Y of the compound and its derivatives. In the series of compounds listed in Table 2, compounds **5**, **21**, and **23** showed the highest level of inhibitory activity in the absence of PB, although they were about three times less active than diflubenzuron (**II**: $X_1=X_2$=F, Y=Cl). Their inhibitory activity values were not much increased by PB. The inhibitory activity values of compounds **16**, **17**, **26** and **27** were, however, significantly enhanced by the addition of PB. Except for compounds **19** and **29**, introduction of substituents at the *para* position of the benzene ring was favorable to the inhibitory activity in the presence of PB.

Substituent effects on the inhibitory activity measured without PB was, first, analyzed for nine compounds, where π values were calculated from the experimentally measured log P (Table 3), to give Eq. (2).

$$pI_{50}\,(\text{none}) = 0.928\,(\pm 0.676)\pi + 2.791\,(\pm 1.252)\sigma_I + 5.387\,(\pm 0.529) \quad (2)$$
$$n=9,\ s=0.307,\ r=0.914,\ F_{2,6}=15.17$$

By the addition of the remaining six compounds, Eq. (3) was formulated, where the π values determined by Eq. (1) were used for these six compounds.

$$pI_{50}\,(\text{none}) = 0.906\,(\pm 0.363)\pi + 2.925\,(\pm 0.857)\sigma_I + 5.346\,(\pm 0.371) \quad (3)$$
$$n=15,\ s=0.266,\ r=0.908,\ F_{2,12}=28.12$$

The correlation did not change very much from Eqs. (2) and (3). Equations (2) and (3) show that as hydrophobicity is increased, inhibitory activity also is increased. The σ_I represents the inductive component of the total electronic effect. These equations show that as the electron-withdrawing property of substituents is increased, the inhibitory activity increases as well. Replacement of the σ_I term in Eq. (3) by the regular Hammett σ term or σ_R and addition of the σ_R term to Eq. (3) resulted in equations of less significance. The pI_{50} values calculated with Eq. (3) are listed in Table 2.

The substituent effects on the inhibitory activity measured in the presence of PB was analyzed as shown in Eq. (4).

$$pI_{50}\,(\text{PB}) = 0.581\,(\pm 0.351)\pi + 0.899\,(\pm 0.737)\sigma_I - 0.182\,(\pm 0.112)\Delta V_W + 6.760\,(\pm 0.372) \quad (4)$$
$$n=15,\ s=0.226,\ r=0.818,\ F_{3,11}=7.40$$

Equation (4) was highly statistically significant, although the correlation coefficient was not as great as desired. This was probably due to the narrow range of variations in the pI_{50} (PB) value. The greater the hydrophobicity and the greater the electron-withdrawing property of the substituents, the greater the inhibitory activity. As steric bulkiness decreased, inhibitory activity increased. Replacement of the σ_I term in Eq. (4) by the regular Hammett σ term or σ_R and addition of the σ_R term to Eq. (4) resulted in equations of less significance. The pI_{50} values calculated with Eq. (4) are listed in Table 2. No significant correlation between inhibitory activity and any single parameter or combinations of parameters was observed, so the development of Eq. (4) was not presented. The degree of collinearity of independent variables for Eqs. (3) and (4) is shown in Table 4.

Previously, we quantitatively analyzed the substituent effects of 15 benzoylphenylureas (**II**: $X_1=X_2$=F) possessing various substituents (Y) on the inhibitory activity in the GluNAc incorporation system.[13] As the electron-withdrawing effect of substituent Y increased, the inhibitory activity also increased. The electronic effect in terms of σ_I, however, was decreased in the presence of PB. Since oxidation is a type of electron abstraction, we felt that an introduction of an electron-withdrawing substituent would be unfavorable for oxidative metabolic degradation, yielding a compound with increased inhibi-

Table 4 Squared correlation (r^2) matrix for the variables used to derive Eqs. (3) and (4).

	π	σ_I
σ_I	0.399	
ΔV_W	0.356	0.189

tory activity. When the oxidative metabolic detoxication mechanism was blocked by use of PB, the significance of the electronic effect was diminished and ultimately reversed.[13] The decreased significance of this electronic effect in Eq. (4) compared to Eq. (3) may be rationalized similarly.

4. Larvicidal Activity against Rice Stem Borer

The treated larvae became brown and dark, and were immobilized after days. Thus, development of the symptoms was very slow. These symptoms were similar to those observed with diflubenzuron.

The larvicidal activity of the thiadiazoles for the rice stem borer in terms of pLD_{50} is listed in Tables 1 and 2. None of our test compounds were as potent as a representative chitin synthesis inhibitor, diflubenzuron (**II**: $X_1 = X_2 = F$, $Y = Cl$). The larvicidal activity of the thiadiazoles was much lower than that expected from the inhibitory activity in the GluNAc incorporation. One of the reasonings may be their poor ability to penetrate through cuticle. Among compounds having various substituents at the benzoyl moiety, only three compounds **4**, **5** and **13** yielded definitive pLD_{50} values (Table 1). For 2,6-disubstituted compounds (**I**), the order of the larvicidal activity against the Mexican bean beetle (*Epilachna varivestis*) and the southern armyworm (*Spodoptera eridania*) is as follows: $2,6\text{-}(OMe)_2 > \text{-}Me_2 > \text{-}Cl_2 > \text{-}F_2$.[15] Our findings for the rice stem borer are compatible with these results. Removal of one of the *ortho*-methoxy groups of compound **5** to give compound **13** did not affect inhibitory activity, whereas replacement of both *ortho*-methoxy groups by methyl groups (compound **4**) reduced the activity slightly. Among the tested compounds in Table 2, the activity of the *para*-bromo derivative (compound **21**) was closest to that of compound **5**.

In conclusion, most of the *N*-[5-(substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamides inhibited the incorporation of GluNAc into the rice stem borer cultured integument. A limited number of compounds showed the larvicidal activity against these insects. Although the two activities of all of the compounds tested were lower than those of diflubenzuron, the primary toxic mechanism of this class of compounds was assumed to be due to inhibition of new cuticle formation. Structural conversion of a -CONH- group of benzoylphenylureas to a thiadiazole ring has been successfully carried out to yield pharmaceuticals.[27] Three-dimensional comparative molecular field analysis (CoMFA)[28] is now in progress in our laboratory for a group of *N*-(5-aryl-1,3,4-thiadiazol-2-yl)benzamides and benzoylphenylureas.

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要　　約

殺幼虫性 *N*-[5-(substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamide 類の培養表皮への *N*-アセチルグルコサミンの取込み阻害における定量的構造活性相関

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二つのベンゼン環上にさまざまな置換基をもつ *N*-[5-(substituted phenyl)-1,3,4-thiadiazol-2-yl]benzamide 類を29種類合成し，ニカメイチュウの培養表皮系を用いて *N*-アセチルグルコサミンの取込み阻害活性を求め，活性に及ぼすベンゼン環置換基の効果を定量的に解析した．その結果，チアジアゾールの5位に結合したベンゼン環上の置換基の電子求引性および疎水性が高いほど活性は上昇することが明らかとなった．一方，ベンズアミド部を置換したものについては阻害活性を示す化合物が少なかったため，有意な相関式を得ることができなかった．この場合，ベンゾイルフェニルウレア類のベンズアミド部で得られた結果とは異なり，定性的ではあるが，活性上昇にとってメチル基やメトキシ基などの電子供与性置換基の導入が好ましいことが明らかになった．また，酸化代謝阻害剤であるピペロニルブトキシドを併用することによって，アルキル置換体の活性が顕著に上昇した．局所投与法によってニカメイチュウに対する殺虫活性を測定したところ，*N*-アセチルグルコサミンの取込み阻害活性の高いものは殺虫活性を示したが，ベンゾイルフェニルウレア類に比べると，殺虫活性はそれほど高いものではなかった．