Preparation and Root Growth-Modulatory Activity of *N*-Substituted 2-Acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides

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***N*-Substituted 2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides (8) were synthesized through the reaction of amines (13) with 2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanoic acid (3b), which was prepared *via* condensation of 2-(bromomethyl)furan (10b) with diethyl acetamidomalonate, followed by partial hydrolysis of the resultant diethyl ester (3a) in the presence of barium hydroxide. However, bulky amines such as *tert*-butylamine or 2-trifluoromethylaniline did not afford the corresponding diamides (8).**

The biological activity of the prepared diamides (8) as root growth modulators was examined by germination assay using rape and leek seeds. *N*-(5-Bromo-2-thiazolyl)- and *N*-(4-chloro-2-benzothiazolyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides (8h, i) both potently inhibited the root growth of rape seedlings, but were less effective in the case of leek seeds. The herbicide 2,4-dichlorophenoxyacetic acid completely inhibited root growth in both cases.

Key words furan derivative; plant growth regulator; herbicidal activity; rooting; propanamide; amidation

Herbicides and plant growth regulators are widely used in crop production to improve productivity.[1)] Repeated use of the same herbicide or herbicides with the same mechanism of action, however, can lead to the appearance of weed species with tolerance to the applied agrochemicals, such as sulfonylurea-resistant paddy weeds or triazine-resistant weeds.[2)] Therefore, the continued development of novel herbicides and plant growth regulators is essential to supplement the current limited treatment options for resistant weeds.[1)] We are interested in furan-containing structures, since it has been reported that L-3-(2-furyl)alanine (**1**)[3)] used as a 500 mg/l spray on tomatoes completely prevented infection by *Phytophthora infestansa*,[3a)] and L-3-(3-furyl)alanine (**2**) has fungicidal activity.[4)] These compounds (**1**, **2**) were prepared from 2-(2-furylmethyl)- and 2-(3-furylmethyl)-2-acetylaminopropanedioic acid diethyl esters (**3a**, **4**), respectively.

In addition, 3-(2-furyl)propionic acid (**5**) was proven to be a weak growth accelerator by Tamari.[5)] On the basis of this report, Kato *et al*. examined the phytogrowth-inhibitory activity of 3-(2-furyl)propionates (**6**) and 3-(2-furyl)propionamides (**7**). However, they did not show a remarkable herbicidal activity.[6)]

In this study, we examined the possibility that 2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides (**8**)[7)] having one ester group and two amide groups at the same carbon, might have plant growth-regulatory activity. We report herein the preparation of the diamides (**8**), and their testing in germination assays using rape and leek seeds.

Preparation of *N*-substituted 2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides (8) The synthetic route reported here was designed to prepare a series of test diamides (**8**) from the half acid (**3b**) obtained *via* the diester (**3a**),[8)] as shown in Chart 2. Compound **3a** has been synthesized from the reaction of diethyl acetamidomalonate with 2-(chloromethyl)furan (**10a**), itself obtained from the reaction of 2-furylmethanol (**9**) with thionyl chloride in the presence of pyridine.[9)] However, **10a** is extremely unstable and decomposes during purification by distillation to give hydrogen chloride, which catalyzes polymerization of the furan ring with explosive violence.[10)] To avoid this difficulty, we used 3-(bromomethyl)furan (**10b**)[11)] as an equivalent of **10a**. An important consideration is that the procedure for the preparation of **10b** does not require a base such as pyridine as a scavenger of hydrogen chloride.[11a)]

First, 2-furylmethanol (**9**) in THF was allowed to react with phosphorus tribromide at 0 °C for 1.5 h to yield the corresponding bromo compound (**10b**), which could be extracted from the reaction mixture with ether, and used without further purification. Then, **10b** was directly treated with diethyl acetamidomalonate at 70 °C in the presence of sodium ethoxide as a base to afford the corresponding diethyl ester (**3a**) in 81% yield. The success of this reaction using the bromo compound (**10b**) in place of the chloro compound (**10a**) allowed us to develop a convenient method of preparation of the title compounds (**8**).

Attempted partial hydrolysis of the diethyl ester (**3a**) according to the reported procedure, using 10% sodium hydroxide[3c,12)] for 1 h at room temperature, gave a mixture of

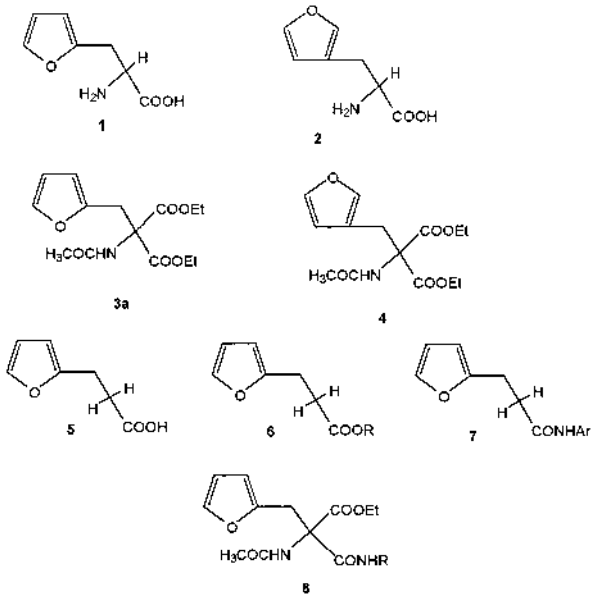

Chart 1

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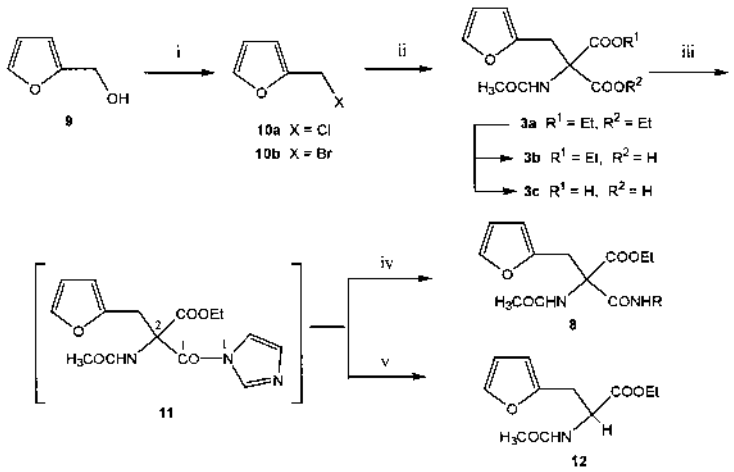

(i) $SOCl_2$, pyridine for **10a**; PBr_3 for **10b**, (ii) condensation with diethyl acetamidomalonate using ODI to give the diester (**3a**), and partial hydrolysis using $Ba(OH)_2$ to form the half acid (**3b**), (iii) activation using ODI (iv) amines (**13**), (v) decarboxylation using ODI in acetonitrile.

Chart 2

the half acid (**3b**) and full hydrolysate, the dicarboxylic acid (**3c**). These products are difficult to separate from each other by chromatography or recrystallization. However, we could obtain the half acid (**3b**) in 87% yield when the partial hydrolysis of the diethyl ester (**3a**) was carried out with barium hydroxide[13] instead of sodium hydroxide. This may be because the diethyl ester (**3a**) is hydrolyzed to afford the barium salt of the half acid (**3b**), which is sparingly soluble and precipitates from the solution.

Next, the carboxyl group of the half acid (**3b**) was activated with 1,1′-oxalyldiimidazole (ODI)[14] to form an imidazolide intermediate (**11**), which reacted with amines (**13**) to afford the corresponding diamides (**8**) in 51—71% yield. Since the average yield of **8** is about 60%, it seems that the carbonyl group of the imidazolide intermediate (**11**) is not readily amidated, presumably because of steric crowding by the nearby quaternary carbon atom and imidazole ring. Application of the activation–amidation methodology for the reaction of the half acid (**3b**) with *tert*-butylamine or 2-(trifluoromethyl)aniline, having a bulky alkyl group around the amino group, did not afford the desired diamides (**8**), but provided 2-acetylamino-3-(2-furyl)propanoic acid ethyl ester (**12**) instead. In addition, decarboxylation of the half acid (**3b**) occurred to form **12** in 66% yield accompanied with the formation of tarry matter when a mixture of **3b** and ODI was heated without any amine (**13**) at 60 °C for 1.5 h. The mechanism of the formation of **12** is unclear, but we speculate that, as the reaction to afford the diamides (**8**) does not proceed readily, prolonged heating of the imidazolide intermediate (**11**) results in C^1–C^2 (quaternary carbon) bond and C^1–N^1 (imidazole) bond cleavages accompanied with the transfer of a proton from an unidentified source to the C^2 carbon to form **12**.

All nine of the prepared diamides (**8a**—**i**), as well as the diethyl ester (**3a**) and the half acid (**3b**), were tested for plant growth-modulating activity.

Root Growth-Modulating Activity This activity was assayed according to the reported procedure[15] using seeds of rape, *Brassica campestris* L. (Brassicaceae), as a dicotyledon and leek, *Allium tuberosum* ROTTLER (Lilliacea), as a monocotyledon. The root length (in millimeters) of the seedlings was measured and averaged in each group. The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D; **14**) was used as a positive control. The results are summarized in Tables 1 and 2.

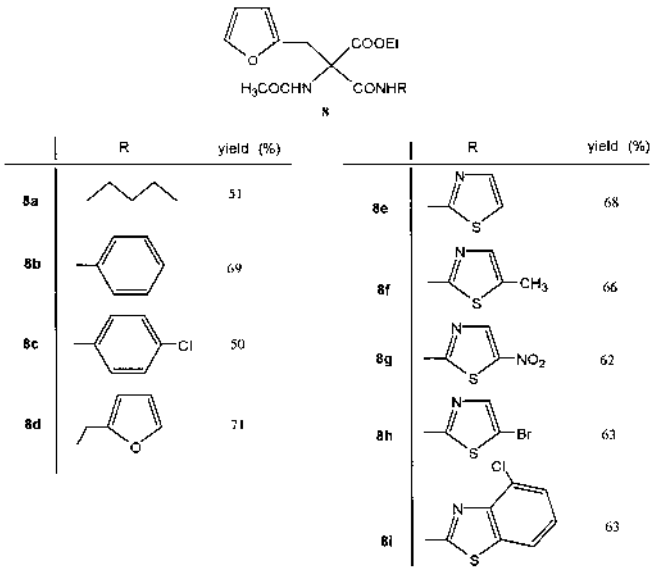

Chart 3

The half acid (**3b**) showed 66% inhibition for rape and 47% inhibition for leek at the concentration of 1.0×10^{-3} M, whereas the diethyl ester (**3a**) showed little activity. Among the *N*-substituted amides (**8**), neither the *N*-butyl derivative (**8a**) nor the *N*-phenyl derivative (**8b**) was inhibitory. However, the *N*-(4-chlorophenyl) derivative (**8c**) showed 49% inhibition for rape, and 29% inhibition for leek. Interestingly, we found that the *N*-(2-furylmethyl) derivative (**8d**) and *N*-(2-thiazolyl) derivative (**8e**) inhibited root growth of rape, but promoted that of leek. We therefore examined the effect of substituent groups on the heterocycles. The (5-nitro-2-thiazolyl) derivative (**8g**) showed 94% inhibition activity for rape, and 54% inhibition for leek. Thus, the nitro group on

Table 1. Plant Growth-Modulating Activities of 2-Acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides (**8**)

Compd.	N'-Subs. groups	Dicotyledoneae Rape; *Brassica campestris* L.			Monocotyledoneae Leek; *Allium tuberosum* Rottler			
		Growth (mm)[a]		Inhibition (%)[b]	Growth (mm)[a]		Inhibition (%)	Promotion (%)[b]
		Control	1.0×10^{-3} (M)		Control	1.0×10^{-3} (M)		
3a	Diethyl ester	57±10.5	42±8.2**	26	23±3.3	22±4.5	4	
3b	Half acid	60±11.3	20±1.4**	66	21±3.7	11±1.0**	47	
8a	*n*-Butyl	51±14.5	46±15.4	9	24±6.0	23±4.0	4	
8b	Phenyl	57±8.8	55±10.6	3	39±4.7	36±4.1	7	
8c	4-Chlorophenyl	61±13.3	31±10.5**	49	31±5.8	22±5.6**	29	
8d	2-Furylmethyl	59±9.0	51±8.6*	13	21±5.5	24±6.3		14
8e	2-Thiazolyl	49±5.3	23±9.2**	53	25±2.6	34±1.8*		36
8f	2-(5-Methylthiazolyl)	47±9.4	18±5.0**	61	26±5.3	15±3.5**	42	
8g	5-Nitro-2-thiazolyl	53±8.8	3±3.3**	94	33±4.4	15±1.2**	54	
8h	5-Bromo-2-thiazolyl	48±5.1	0**	100	30±3.7	13±1.1**	56	
8i	4-Chloro-2-benzothiazolyl	56±5.2	0**	100	30±5.2	9±1.5**	70	
14	2,4-D[c]	64±25.7	0**	100	24±6.2	0**	100	

a) The values represent mean±S.D. of 40 seeds after seven days (*A. tuberosum*; 10 d). Significant differences from the corresponding control level are indicated, * and ** indicate significant differences with $p<0.05$ and $p<0.01$, respectively. Quantity of light: 127 μmol·m^{-2}·s^{-1}. Temperature 25 °C. Relative humidity of 60%. Experimental size: 20 seeds/group. 2 groups. *b*) [(mean value of control−mean value at the concentration (M) of 1.0×10^{-3})/mean value of control]×100=*P* (%); when *P* has a positive value, this represents a promotion effect, and when *P* has a negative value, this corresponds to inhibition. *c*) 2,4-Dichlorophenoxyacetic acid (2,4-D; **14**) was used as a positive control.

Table 2. Concentration Dependence of Plant Growth-Modulating Activities of Compounds **8h**, **8i** and **14**

Compd.	N'-Subs. groups	Dicotyledoneae Rape; *Brassica campestris* L. Inhibition (%)[a]				Monocotyledoneae Leek; *Allium tuberosum* Rottler Inhibition (%)[a]			
		1.0×10^{-3} (M)	5.0×10^{-4} (M)	1.0×10^{-4} (M)	5.0×10^{-5} (M)	1.0×10^{-3} (M)	5.0×10^{-4} (M)	1.0×10^{-4} (M)	5.0×10^{-5} (M)
8h	2-(5-Bromothiazolyl)	100	98	80	21	56	53	50	30
8i	4-Chloro-2-benzothiazolyl	100	91	50	41	70	50	10	10
14	2,4-D[b]	100	99	98	98	100	100	99	97

a) See footnotes *a*) and *b*) of Table 1. *b*) 2,4-Dichlorophenoxyacetic acid (2,4-D; **14**) was used as a positive control.

the thiazole ring markedly enhanced the inhibitory activity. Similarly, the bromo derivative (**8h**) and the chloro derivative (**8i**) showed complete inhibition of rape root growth and substantial inhibition of leek root growth. The positive control (2,4-D; **14**) completely inhibited root growth of both species.

In conclusion, the condensation reaction of (2-bromomethyl)furan (**10b**) with diethyl acetamidomalonate, with subsequent partial hydrolysis of the adduct (**3a**) with barium hydroxide, has been shown to be a convenient general method for the preparation of the half acid (**3b**), and application of traditional activation–amidation methodology to **3b** smoothly afforded *N*-substituted 2-acetylamino-2-ethoxycarbonyl-3- (2-furyl)propanamides (**8**). Evaluation of **8** for plant growth-modulating activity revealed that the *N*-(5-bromo-2-thiazolyl) and *N*-(4-chloro-2-benzothiazolyl) derivatives (**8h**, **i**) completely inhibited root growth of rape seedlings and partially inhibited that of leek seedlings. These findings suggest that the compounds (**8h**, **i**) show selective phytotoxicity towards germination of dicotyledons. A halogen group such as bromine or chlorine on the heterocycles seems to play an important role in the appearance of the selective toxicity.

Experimental

Diethyl acetamidomalonate, oxalyl chloride, imidazole, dimethyl sulfoxide (DMSO) and amines (**13a**—**i**) were purchased from commercial sources and used as received. 2-(Bromomethyl)furan (**10b**) was prepared by the reported procedure.[11a)]

Melting points were taken on a Yanagimoto melting point apparatus. All melting points are uncorrected. IR spectra were measured on a Hitachi model 270-30 IR spectrophotometer. NMR spectra were measured on a Bruker DPX-400 spectrometer (400 MHz) using tetramethylsilane as an internal reference, and chemical shifts were recorded as δ-values.

2-Acetylamino-2-(2-furylmethyl)propanedioic Acid Diethyl Ester (3a) Diethyl acetamidomalonate (8.2 g, 38 mmol) was dissolved in a sodium ethoxide solution [prepared from 0.85 g of sodium (0.037 g-atm) and 100 ml of absolute ethanol]. To this stirred solution, the ether solution (*ca*. 200 ml) containing crude 2-(bromomethyl)furan (**10b**) prepared from the reaction of 2-furylmethanol (**9**) (4.9 g, 50 mmol) with phosphorus tribromide (4.9 g, 18 mmol), was added in a single portion. The mixture was distilled rapidly at atmospheric pressure until about 160 ml of ether had been collected, and the remaining reaction mixture was refluxed at 68—72 °C for 2 h. The ethanolic solution was concentrated *in vacuo*, the residue was poured into ethyl acetate (50 ml), and the resultant mixture was filtered to remove insoluble materials. The filtrate was washed with 3% HCl and water, then the ethyl acetate layer was dried over anhydrous Na_2SO_4. The organic solvent was evaporated *in vacuo* to give crude **3a**, which was chromatographed on a silica gel column (50 g, 70—230 mesh) with ethyl acetate/toluene=3/7 to give the product (**3a**) (9.1 g, 81%). Recrystallization from ether/petroleum ether gave an analytical sample of **3a**, mp 80—83 °C (lit., 81—82 °C).[8a)]

2-Acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanoic Acid (3b) A mixture of an ethanol solution (5 ml) of 2-acetylamino-2-(2-furylmethyl)-propanedioic acid diethyl ester (**3a**) (5.9 g, 20 mmol) was added to 50 ml of 4% $Ba(OH)_2$ solution. The resulting mixture was stirred at room temperature for 24 h. The precipitated product was collected by filtration. The precipitate was suspended in water (50 ml). The aqueous mixture was acidified with 5% HCl, and extracted with ethyl acetate. The organic solution was washed with brine, followed by drying under Na_2SO_4 and evaporation of the solvent to afford 4.7 g (87%) of the crude product (**3b**). Recrystallization from

toluene/ethanol gave **3b** of mp 141—144 °C (lit., 120—121 °C).[6a] IR (KBr) cm^{-1}: 3324 (N–H), 1730 (ester CO), 1609 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.92 (3H, s, –$COCH_3$), 3.52 (2H, q, J=15 Hz, furan-CH_2), 4.14 (2H, q, J=7 Hz, –<u>CH_2</u>CH_3), 6.0—6.1 (1H, m, furan-4H), 6.2—6.3 (1H, m, furan-3H), 4.7—7.5 (1H, m, furan-5H), 7.98 (1H, s, NH). *Anal.* Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.57; N, 5.20. Found: C, 53.67; H, 5.64; N, 5.37.

Decarboxylation of the Half Acid (3b) Leading to 2-Acetylamino-3-(2-furyl)propanoic Acid Ethyl Ester (12) A solution of oxalyl chloride (1.1 g, 8.6 mmol) in acetonitrile (5 ml) was added dropwise to an ice-cold, stirred solution of imidazole (2.4 g, 35 mmol) in acetonitrile (50 ml). The mixture was stirred at room temperature for 15 min, then 2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanoic acid (**3b**) (2.1 g, 8 mmol) was added rapidly in a single portion. The mixture was stirred at 60 °C for 1.5 h. The solvent was removed *in vacuo*, and the residue was poured onto ice-water and extracted with ethyl acetate. Washing of the ethyl acetate extract with 5% hydrochloric acid and water, followed by drying over Na_2SO_4 and evaporation of the solvent left 1.2 g (66%) of crude product (**12**). Distillation using the Kugelrohr apparatus gave 1.0 g of pure product (**12**) of bp 210—215° at 1 mmHg. IR (KBr) cm^{-1}: 3296 (N–H), 1740 (ester CO), 1660 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7.1 Hz, –CH_2<u>CH_3</u>), 2.01 (3H, s, –$COCH_3$), 3.46—3.57 (two 1H, each d, J=15 Hz, furan-CH_2), 4.11—4.17 (2H, q, J=7 Hz, –<u>CH_2</u>CH_3), 4.79—4.86 (1H, m, –CH_2–<u>CH</u>=), 6.04 (1H, m, furan-4H), 6.27 (1H, m, furan-3H), 7.31 (1H, m, furan-5H), 7.98 (1H, s, NH). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.66; N, 6.22. Found: C, 58.53; H, 6.78; N, 6.20.

Preparation of *N*-Substituted 2-Acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamides (8) General Procedure A solution of oxalyl chloride (1.1 g, 8.6 mmol) in acetonitrile (5 ml) was added dropwise to an ice-cold, stirred solution of imidazole (2.4 g, 35 mmol) in acetonitrile (50 ml). The mixture was stirred at room temperature for 15 min, then 2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanoic acid (**3b**) (2.1 g, 8 mmol) was added rapidly in a single portion. The mixture was stirred at 45 °C for 40 min, and then a solution of an appropriate amine (**13a**—**i**) (8.8 mmol) in acetonitrile (2 ml) was added dropwise at room temperature. The resultant mixture was stirred for 1.5 h at 55 °C. The solvent was removed *in vacuo*, and the residue was poured onto ice-water and extracted with ethyl acetate. Washing of the ethyl acetate extract with 5% hydrochloric acid and water, followed by drying over Na_2SO_4 and evaporation of the solvent, left the crude product (**8**), which was chromatographed on a silica gel column (50 g, 70—230 mesh) with ethyl acetate/toluene=3/7 to give the product (**8**).

***N*-Butyl-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamide (8a)** **8a** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with *n*-butylamine (**13a**) (0.6 g, 8.8 mmol) in 51% yield. mp 74—77 °C (cyclohexane/ethyl acetate). IR (KBr) cm^{-1}: 3350 (N–H), 1742 (ester CO), 1690 (amido CO), 1642 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 0.83 (3H, t, J=7 Hz, –$(CH_2)_3$<u>CH_3</u>), 1.14 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.13—3.10 (6H, m, –<u>$(CH_2)_3$</u>CH_3), 1.90 (3H, s, –$COCH_3$), 3.54—3.64 (two 1H, each d, J=15 Hz, furan-CH_2), 4.04—4.16 (2H, m, –<u>CH_2</u>CH_3), 6.05—6.10 (1H, m, furan-4H), 6.2—6.3 (1H, m, furan-3H) 7.4—7.5 (1H,m, furan-5H), 7.75 (1H, s, NH), 8.05 (1H, t, J=5.7 Hz, NH). *Anal.* Calcd for $C_{16}H_{24}N_2O_5$: C, 59.25; H, 7.46; N, 8.64. Found: C, 59.01; H, 7.25; N, 8.57.

***N*-Phenyl-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamide (8b)** **8b** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with aniline (**13b**) (0.8 g, 8.8 mmol) in 69% yield. mp 163—165 °C (toluene). IR (KBr) cm^{-1}: 3412 (N–H), 1740 (ester CO), 1714 (amido CO), 1652 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.96 (3H, s, –$COCH_3$), 3.60—3.82 (two 1H, each d, J=15 Hz, furan-CH_2), 4.11—4.24 (2H, m, –<u>CH_2</u>CH_3), 6.0—6.1 (1H, m, furan-4H), 6.3—6.4 (1H, m, furan-3H), 7.5 (1H, m, furan-5H), 7.10 (1H, bt, J=7.4 Hz, phenyl-4H), 7.34 (2H, d, J=7.4 Hz, phenyl-3, 5H), 7.54 (2H, d, J=7.4 Hz, phenyl-2, 6H), 7.96 (1H, s, NH), 9.79 (1H, s, NH). *Anal.* Calcd for $C_{18}H_{20}N_2O_5$: C, 62.79; H, 5.81; N, 8.14. Found: C, 63.06; H, 5.88; N, 8.11.

***N*-(4-Chlorophenyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)-propanamide (8c)** **8c** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 4-chloroaniline (**13c**) (1.1 g, 8.8 mmol) in 50% yield. mp 225—229 °C (toluene/AcOEt). IR (KBr) cm^{-1}: 3443 (N–H), 1738 (ester CO), 174 (amido CO), 1652 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.96 (3H, s, –$COCH_3$), 3.58—3.78 (two 1H, each d, J=15 Hz, furan-CH_2), 4.11—4.23 (2H, m, –<u>CH_2</u>CH_3), 6.07—6.10 (1H, m, furan-4H), 6.33—6.36 (1H, m, furan-3H), 7.50—7.52 (1H, m, furan-5H), 7.37—7.61 (two 2H, each d, J=7.4 Hz, phenyl-2H, -6H and phenyl-3H, 5H), 7.99 (1H, s, NH), 9.95 (1H, s, NH). *Anal.* Calcd for $C_{18}H_{19}ClN_2O_5$: C, 57.07; H, 5.06; N, 7.39. Found: C, 56.88; H, 4.89; N, 7.35.

***N*-(2-Furylmethyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)-propanamide (8d)** **8d** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 2-furylmethylamine (**13d**) (0.9 g, 8.8 mmol) in 71% yield. mp 75—78 °C (toluene/AcOEt). IR (KBr) cm^{-1}: 3388 (N–H), 1738 (ester CO), 1690 (amido CO), 1652 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 2.00 (3H, s, –$COCH_3$), 3.6—3.7 (two H, each d, J=15 Hz, furan-CH_2), 4.15—4.26 (2H, m, –<u>CH_2</u>CH_3), 5.18 (2H, d, J=5 Hz, furan-CH_2), 6.0—7.2 (three m, each 1H, furan-3H, 4H and 5H), 6.2—6.6 (three m, each 1H, furan-3H, 4H and 5H), 6.64 (1H, t, J=5 Hz, NH), 8.01 (1H, s, NH). *Anal.* Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.54; H, 5.79; N, 8.00.

***N*-(2-Thiazolyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamide (8e)** **8e** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 2-aminothiazole (**13e**) (0.9 g, 8.8 mmol) in 68% yield, mp 228—231 °C (EtOH/toluene). IR (KBr) cm^{-1}: 3256 (N–H), 1746 (ester CO), 1698 (amido CO), 1652 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.96 (3H, s, –$COCH_3$), 3.59—3.81 (two 1H, each d, J=15 Hz, furan-CH_2), 4.13—4.25 (2H, m, –<u>CH_2</u>CH_3), 6.08 (1H, m, furan-4H), 6.34 (1H, m, furan-3H), 7.50 (1H, m, furan-5H), 7.10 (1H, d, J=3 Hz, thiazole-5H), 7.32 (1H, d, J=3 Hz, thiazole-4H), 7.54 (1H, s, NH), 7.96 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{17}N_3O_5S$: C, 51.28; H, 4.84; N, 11.96. Found: C, 51.20; H, 5.05; N, 11.83.

***N*-(5-Methyl-2-thiazolyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)-propanamide (8f)** **8f** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 2-amino-5-methylthiazole (**13f**) (1.3 g, 8.8 mmol) in 66% yield. mp 176—179 °C (EtOH/toluene). IR (KBr) cm^{-1}: 3304 (N–H), 1746 (ester CO), 1700 (amido CO), 1664 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.93 (3H, s, thiazole-CH_3), 2.31 (3H, s, –$COCH_3$), 3.59—3.72 (two 1H, each d, J=15 Hz, furan-CH_2), 4.12—4.09 (2H, q, J=7 Hz, –<u>CH_2</u>CH_3), 6.02 (1H, m, furan-4H), 6.32 (1H, m, furan-3H), 7.10 (1H, m, furan-5H), 7.45 (1H, s, thiazole-4H), 8.05 (1H, s, NH), 12.3 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{19}N_3O_5S$: C, 52.50; H, 5.20; N, 11.50. Found: C, 52.48; H, 5.12; N, 11.52.

***N*-(5-Nitro-2-thiazolyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)-propanamide (8g)** **8g** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 2-amino-5-nitrothiazole (**13g**) (1.3 g, 8.8 mmol) in 62% yield. mp 182—185 °C (ether/AcOEt). IR (KBr) cm^{-1}: 3408 (N–H), 1738 (ester CO), 1706 (amido CO), 1640 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.97 (3H, s, –$COCH_3$), 3.58—3.73 (two 1H, each d, J=15 Hz, furan-CH_2), 4.14—4.23 (2H, m, –<u>CH_2</u>CH_3), 6.15 (1H, m, furan-4H), 6.35 (1H, m, furan-3H), 7.53 (1H, m, furan-5H), 8.17 (1H, s, thiazole-4H), 8.65 (1H, s, NH), 13.33 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{16}N_4O_7S$: C, 45.45; H, 4.04; N, 14.14. Found: C, 45.65; H, 4.24; N, 13.88.

***N*-(5-Bromo-2-thiazolyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)-propanamide (8h)** **8h** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 2-amino-5-bromothiazole (**13h**) [2-amino-5-bromothiazole monohydrobromide (2.3 g, 8.8 mmol) was neutralized with triethylamine (0.9 g, 8.8 mmol) in acetonitrile (5 ml)] in 63% yield. mp 198—200 °C (ether/toluene). IR (KBr) cm^{-1}: 3402 (N–H), 1750 (ester CO), 1696 (amido CO), 1686 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.95 (3H, s, –$COCH_3$), 3.57—3.75 (two 1H, each d, J=15 Hz, furan-CH_2), 4.18—4.14 (2H, m, –<u>CH_2</u>CH_3), 6.10 (1H, m, furan-4H), 6.33 (1H, m, furan-3H), 7.50 (1H, m, furan-5H), 7.60 (1H, s, thiazole-4H), 8.05 (1H, s, NH), 12.52 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{16}BrN_3O_5S$: C, 41.87; H, 3.75; N, 9.77. Found: C, 42.09; H, 3.71; N, 9.76.

***N*-(4-Chloro-2-benzothiazolyl)-2-acetylamino-2-ethoxycarbonyl-3-(2-furyl)propanamide (8i)** **8i** was prepared as above through the reaction of the half acid (**3b**) (2.1 g, 8 mmol) with 2-amino-4-chlorobenzothiazole (**13i**) (1.63 g, 8.8 mmol) in 63% yield. mp 154—157 °C (ether/AcOEt). IR (KBr) cm^{-1}: 3420 (N–H), 1780 (ester CO), 1720 (amido CO), 1660 (amido CO). ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7 Hz, –CH_2<u>CH_3</u>), 1.99 (3H, s, –$COCH_3$), 3.60—3.82 (two 1H, each d, J=15 Hz, furan-CH_2), 4.15—4.24 (2H, m, –CH_2CH_3), 6.15 (1H, m, furan-4H), 6.36 (1H, m, furan-3H), 7.53 (1H, m, furan-5H), 7.55 and 8.00 (each 1H, each d, J=8 Hz, benzothiazole-5H, 7H) 7.33 (1H, t, J=8 Hz, benzothiazole-6H), 8.05 (1H, s, NH), 12.85 (1H, s, NH). *Anal.* Calcd for $C_{19}H_{18}ClN_3O_5S$: C, 52.35; H, 4.13; N, 9.64. Found: C, 52.32; H, 4.12; N, 9.52.

Plant Growth-modulating Activity Test This test was carried out according to the method reported by Inamori *et al.*[15] A DMSO solution (1.0 ml) containing an amide derivative (**8a**—**i**) or DMSO alone (1.0 ml) as a

control was diluted in 100 ml of sterilized agar (0.8%, Nacalai Tesque, Inc.) to give concentrations of 5×10^{-5} M, 1.0×10^{-4} M, 5×10^{-4} M and 1.0×10^{-3} M. Agar containing a test chemical or DMSO as a control was poured into a sterilized 500 ml culture jar. Then 20 seeds of each plant species, sterilized with 70% ethanol and 1% NaClO, were put on the agar and left for seven days (*A. tuberosum*; ten days) at 25 °C under a relative humidity of 60% and a light intensity of 127 μmol$\cdot$m$^{-2}\cdot$s^{-1}. The plant growth-inhibitory activity was expressed as the root length of the seedlings in millimeters. The results are summarized in Tables 1 and 2.

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