Synthesis and Root Growth-Inhibitory Activity of 2- and 3-(Haloacetylamino)-3-(2-furyl)propanoic Acids

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A convenient synthesis of 2- and 3-(chloroacetylamino)-3-(2-furyl)propanoic acids (6a, 7a) and their fluoro analogs were developed. Both 6a and 7a showed 51—55% root growth-inhibitory activity towards rape seedlings at the concentration of 1.0×10^{-4} M.

Key words furan derivative; chloroacetamide; herbicidal activity; propanoic acid; plant growth regulator

Compounds of the chloroacetamide family are major pre-emergence herbicides for control of seedling grass in corn and soybean crops, and are among the most widely used herbicides in the world.[1,2] For example, the thiophene derivative dimethenamid [2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl)acetamide] (**1**) is used for control of annual grasses and certain broadleaf weeds, primarily in corn and soybeans and also in peanuts.[3—7] In addition, thenylchlor [2-chloro-*N*-(3-methoxy-2-thienyl)methyl-2′,6′-dimethylacetanilide] (**2**) having a chloroacetamido moiety shows high herbicidal activity for barnyard grass in paddy fields.[8—12]

In the course of work on furan derivatives as plant growth regulators, Tamari reported that 3-(2-furyl)propanoic acid (**3**) has a weak plant growth-inhibitory activity.[13] This stimulated Kato *et al.* to examine the phytogrowth-inhibitory activity of 3-(2-furyl)propanoates (**4**) and 3-(2-furyl)propanamides (**5**), though these compounds proved not to have high activity.[12]

We hoped to find a new lead compound by introducing a chloroacetylamino group into 3-(2-furyl)propanoic acid (**3**). Thus, we set out to prepare 2- and 3-(chloroacetylamino)-3-(2-furyl)propanoic acids (**6a**, **7a**)[14] and to examine their root growth-inhibitory activities in rape seedlings.

Preparation of 2-(Haloacetylamino)-3-(2-furyl)propanoic Acids (6) We initially considered the synthesis of 2-(chloroacetylamino)-3-(2-furyl)propanoic acid (**6a**) by utilizing diethyl formamidomalonate (**8**) to prepare 2-amino-3-(2-furyl)propanoic acid[15] (**12**), followed by chloroacetylation of **12** using chloroacetyl chloride. However, **8** is expensive, so we decided to employ the (chloroacetylamino)propanedioic acid diethyl ester (**15a**) route shown in Chart 2.

First of all, **15a** was synthesized in 90% yield by the reaction of diethyl aminomalonate hydrochloride (**14**) with chloroacetyl chloride in the presence of triethylamine, according the procedure of Sheehan and Bose.[16] We found that the reaction of **14** with chloroacetic acid using 1,1′-oxalyldiimidazole (ODI)[17] as a condensing reagent resulted in the formation of **15a** in 58% yield accompanied with a tarry material. This result suggest that **15a** is unstable in the presence of basic reagents such as ODI or imidazole.

Next, synthesis of 2-(chloroacetylamino)-2-(2-furylmethyl)propanedioic acid diethyl ester (**16a**) was successfully achieved by means of the following reaction. Treatment of 2-bromomethylfuran[18] (**9**) derived from 2-furylmethanol (**13**) with 2-(chloroacetylamino)propanedioic acid diethyl ester (**15a**) at 70 °C for 2.5 h in the presence of sodium ethoxide as a base gave a 61% yield of **16a**. This diester (**16a**) was hydrolyzed with 10% NaOH solution for 24 h at room temperature to give 2-(chloroacetylamino)-2-(2-furylmethyl)propanedioic acid (**17a**) in 76% yield.

Concerning the experimental conditions for the decarboxylation of propanedioic acid derivatives to give the corresponding monoacid derivatives, the literature contains a variety of procedures, such as 1) refluxing for 2.5 h with 50% acetic acid,[15] 2) boiling for 39 h in dioxane,[19,20] and 3) refluxing for 2 h in toluene.[21] Decarboxylation of our compound (**17a**) for 2 h in refluxing toluene resulted in a 5% yield of 2-(chloroacetylamino)-3-(2-furyl)propanonic acid (**6a**) together with a large amount of tarry material. We speculated that toluene, which has a low solvating power, is unable to stabilize the transition state in the pyrolysis of **17a**. Considering that the decarboxylation of propandioic acid derivatives to form the corresponding monoacid is a typical example of intramolecular fragmentation, we thought that this reaction should be carried out in highly dilute solution and in a neutral hydrophilic solvent such as ethanol to minimize the intermolecular interaction. Finally, the reaction of **17a** for 3 h in boiling ethanol in place of toluene resulted in a 93% yield of **6a**.

As shown in Chart 2, 2-(fluoroacethylamino)-3-(2-furyl)-propanoic acid (**6b**) was also prepared in order to study the effect of the halogen atom on the putative biological activities.

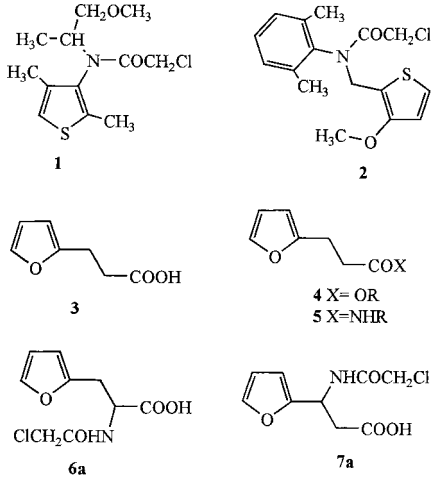

Chart 1

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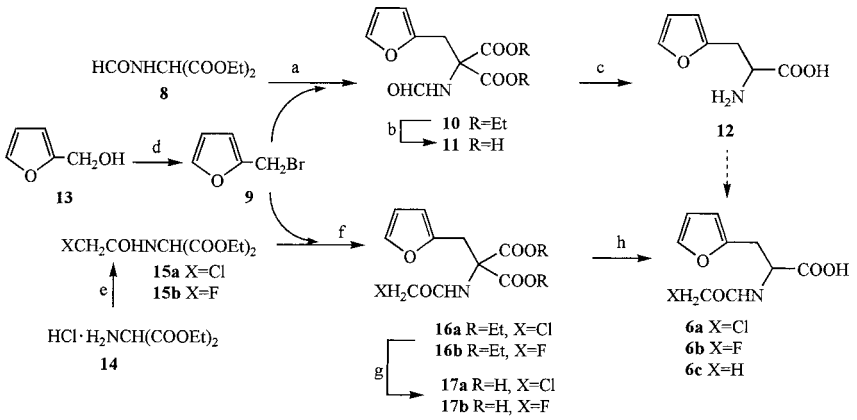
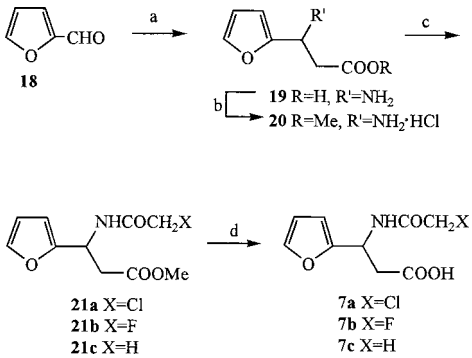


Reagents and conditions: (a) EtONa, EtOH, reflux, 2 h; (b) 10% NaOH, reflux, 6 h; (c) 50% AcOH, reflux, 2.5 h; (d) PBr_3, THF; (e) for **15a**, $ClCH_2COCl$, $ClCH_2CH_2Cl$, and for **15b**, FCH_2COOH, ODI, CH_3CN, 60 °C, 2 h; (f) EtONa, EtOH, 70 °C, 2 h; (g) 10% NaOH, r.t., 24 h; (h) EtOH, reflux, 3 h.

Chart 2



Reagents and conditions: (a) malonic acid, ammonium acetate, EtOH, reflux, 8 h; (b) $SOCl_2$, MeOH, r.t., 15 h; (c) for **21a**, $ClCH_2COCl$, $ClCH_2CH_2Cl$, and for **21b**, FCH_2COOH, ODI, CH_3CN, 60 °C, 2 h; (d) 4% NaOH, r.t., 4 h.

Chart 3

Preparation of 3-(Haloacetylamino)-3-(2-furyl)propionic Acids (7) The synthesis of 3-(chloroacetylamino)-3-(2-furyl)propanoic acid (**7a**) started with furfural (**18**), which was converted to methyl 3-amino-3-(2-furyl)propanoate hydrochloride (**20**) in 30% overall yield *via* the formation of 3-amino-3-(2-furyl)propanoic acid (**19**). As mentioned above, chloroacetylation of **20** with chloroacetyl chloride gave rise to 3-(chloroacetylamino)-3-(2-furyl)propanoic acid methyl ester (**21a**), which was subjected to hydrolytic cleavage of the methyl ester group in 4% sodium hydroxide solution to afford 3-(chloroacetylamino)-3-(2-furyl)propanoic acid (**7a**) in 95% yield (calculated on the basis of **21a**).

The fluoroacetylamino derivative (**7b**) was similarly prepared by the reaction of **20** with fluoroacetic acid using ODI to yield 3-(fluoroacetylamino)-3-(2-furyl)propanoic acid methyl ester (**21b**), followed by hydrolysis of the methyl ester group as shown in Chart 3.

These compounds (**6a**, **7a**) and related compounds (**6b**, **7b**, **c**, **12**, **19**) were tested for plant growth-regulating activities.

Root Growth-Inhibitory Activity This activity was assayed according to the reported procedure[22] using seeds of rape, *Brassica campestris* L. (Brassicaceae), as a dicotyledon. The root length (in millimeters) of the seedlings was measured and averaged for each group. The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) was used as a positive control. The results are summarized in Table 1.

All four 2- or 3-haloacetylamino derivatives (**6a**, **b**, **7a**, **b**) inhibited the root growth in rape seedlings (Table 1). Thus, the introduction of a chloroacetylamino group at the 2- or 3-position of 3-(2-furyl)propanoic acid (**3**) clearly enhances the inhibitory activity, whereas an acetylamino or amino group is ineffective.

Among the 2-substituted 3-(2-furyl)propanoic acids (**6a**—**c**, **12**), 2-(chloroacetylamino)-3-(2-furyl)propanoic acid (**6a**) showed 51% inhibitory activity at the concentration of 1×10^{-4} M. The compound obtained by replacing the chlorine atom of **6a** with fluorine, namely the 2-fluoroacetylamino derivative (**6b**) markedly enhanced the inhibitory activity, affording 90% inhibition, which is similar to that of 2,4-D used as a positive control.

Among the 3-substituted 3-(2-furyl)propanoic acids (**7a**—**c**, **19**), 3-(chloroacetylamino)-3-(2-furyl)propanoic acid (**7a**) showed 55% inhibitory activity. The inhibitory activity of the 3-substituted compounds (**7a**—**c**, **19**) was in the following order; $ClCH_2CONH$– (**7a**)>FCH_2CONH– (**7b**)>CH_3CONH– (**7c**)>H_2N– (**19**). It seems noteworthy that the inhibitory activity of the chloride derivative (**7a**) is somewhat stronger than that of the fluoride derivative (**7b**), in contrast to the finding that the inhibitory activity of the 2-chloroacetylamino derivative (**6a**) is weaker than that of the 2-fluoroacetylamino derivative (**6b**).

It is apparent that the halogen atom on the acetylamino group is critical for potent root-growth inhibition activity in rape seedling. However, the fluoroacetyl residue in **6b** or **7b** is likely to be undesirable from the viewpoint of environmental protection.[23,24] So, our interest was focused on **6a** or **7a** as candidate lead compounds for developing novel herbicides.

In conclusion, the condensation of 2-(haloacetylamino)-propanedioic acid diethyl esters (**15**) with (2-bromomethyl)-furan (**9**), followed by hydrolysis of the adduct with alkaline solution, is a convenient method for the preparation of 2-(haloacetylamino)-2-(2-furylmethyl)propanedioic acids (**17**). Thermal decomposition of **17** as a highly diluted solution in ethanol smoothly afforded 2-(haloacetylamino)-3-(2-furyl)-propanoic acids (**6a**, **b**).

Table 1. Root Growth-Inhibitory Activities of 2- and 3-Substituted 3-(2-Furyl)propanoic Acids (**6**, **7**) and Related Compounds (**12**, **19**, **2,4-D**)

2-Substituted 3-(2-furyl)propanoic acids (**6**, **12**) Dicotyledoneae Rape; *Brassica campestris* L. Growth (mm)[a]					3-Substituted 3-(2-furyl)propanoic acid (**7**, **19**) Dicotyledoneae Rape; *Brassica campestris* L. Growth (mm)[a]				
Compound	2-Substituent	Control	1.0×10^{-4} M	Inhibition (%)[c]	Compound	3-Substituent	Control	1.0×10^{-4} M	Inhibition (%)[c]
6a	$NHCOCH_2Cl$	57±11.3	28±8.1**	51	**7a**	$NHCOCH_2Cl$	62±11.4	28±8.1**	55
6b	$NHCOCH_2F$	42±13.3	4±3.4**	90	**7b**	$NHCOCH_2F$	53±7.5	30±7.9**	43
6c	$NHCOCH_3$	49±14.1	40±12.5**	19	**7c**	$NHCOCH_3$	58±12.1	45±13.1**	22
12	NH_2	45±9.5	42±13.2	7	**19**	NH_2	62±17.6	52±13.3*	16
2,4-D[b]		64±25.7	0**	100	**2,4-D**[b]		64±25.7	0**	100

a) The values represent mean±S.D. of 40 seeds after seven days. Significant differences from the corresponding control level are shown: * and ** indicate $p<0.05$ and $p<0.01$, respectively. Light intensity 127 μmol·m^{-2}·s^{-1}. Temperature 25 °C. Relative humidity 60%. Experimental size; 20 seeds/group, 2 groups. *b*) 2,4-Dichlorophenoxyacetic acid (2,4-D) was used as a positive control. *c*) % of inhibition=[(mean value of control−mean value at the concentration (M) of 1.0×10^{-4})/mean value of control]×100.

Application of traditional esterification-acetylation-hydrolysis methodology to the known 3-amino-3-(2-furyl)propanoic acid (**19**) smoothly gives the corresponding 3-(haloacetylamino)-3-(2-furyl)propanoic acids (**7a**, **b**).

Root growth-inhibitory activity assay revealed that **6a** and **7a** inhibited the root growth of rape seedlings by about 50% at the concentration of 1.0×10^{-4} M. The halogen atom on the acetylamino group appears to be critical for potent root growth-inhibition activity.

Experimental

Diethyl aminomalonate hydrochloride (**14**), diethyl formamidomalonate (**8**), chloroacetic acid, chloroacetyl chloride, 2-furylmethanol (**13**), furfural (**19**), sodium fluoroacetate, malonic acid, oxalyl chloride and imidazole were purchased from commercial sources and used as received. 2-(Bromomethyl)furan (**9**) was prepared according to the reported procedure.[18] 2-Amino-3-(2-furyl)propanoic acid[15] (**12**), 2-acetylamino-3-(2-furyl)propanoic acid (**6c**),[19,20] and 3-amino-3-(2-furyl)propanoic acid (**19**)[25] were prepared as previously described.

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 with attenuated total reflectance. NMR spectra were measured on a Bruker DPX-400 spectrometer (400 MHz) using tetramethylsilane as an internal reference, and chemical shifts were recorded as delta-values.

2-(Chloroacetylamino)propanedioic Acid Diethyl Ester (15a) Method A: The preparation of **15a** was carried out according to the method of Sheehan and Bose.[16] To a mixture of diethyl aminomalonate hydrochloride (**14**) (30 g, 140 mmol) and chloroacetyl chloride (11 g, 100 mmol) suspended in 1,2-dichloroethane (300 ml) at 0—5 °C was added slowly a solution of triethylamine (30 g, 300 mmol) in 1,2-dichloroethane (100 ml). After the addition was complete, the mixture was brought rapidly to the boiling point and then allowed to stand overnight. Triethylamine hydrochloride was removed by filtration, then the filtrate was washed with 2% hydrochloric acid and water. It was dried with sodium sulfate, the solvent was removed *in vacuo*, and the resultant residue was recrystallized from cyclohexane to give 22 g (90%) of **15a**, mp 94—96 °C (lit. 97.5—98.5 °C)[16] IR (KBr) cm^{-1}: 3316 (N–H), 1762 and 1740 (ester CO), 1656 (amido CO). ^{1}H-NMR (DMSO-d_6): 1.20 (overlapping two 3H, each t, J=7.1 Hz, $CH_3\times2$), 4.13—4.26 (overlapping two 2H, each m, $C\underline{H}_2CH_3\times2$), 4.22 (2H, s, CH_2Cl), 5.09 (1H, d, J=7.1 Hz, CH), 9.11 (1H, d, J=7.1 Hz, NH). *Anal.* Calcd for $C_9H_{14}ClNO_5$: C, 42.95; H, 5.59; N, 5.52. Found: C, 42.97; H, 5.57; N, 5.57.

Method B: This compound (**15a**) was also synthesized in 58% yield from the reaction of **14** with chloroacetic acid using ODI by the following procedure for **15b**. The mixture melting point with the compound prepared by the method A was undepressed. The IR spectrum and the NMR spectrum were identical with those of the compound prepared by the method A.

2-(Fluoroacetylamino)propanedioic Acid Diethyl Ester (15b) A solution of oxalyl chloride (2.5 g, 20 mmol) in acetonitrile (5 ml) was added dropwise to an ice-cold, stirred solution of imidazole (5.5 g, 80 mmol) in acetonitrile (50 ml). The mixture was stirred at room temperature for 15 min, and then a mixture of sodium fluoroacetate (2 g, 20 mmol) and methanesulfonic acid (3.4 g, 20 mmol) in acetonitrile (10 ml) was added rapidly in a single portion. The mixture was stirred at 45 °C for 40 min, and then diethyl aminomalonate hydrochloride (**14**) (4.2 g, 20 mmol) was added in a single portion at room temperature. The resultant mixture was stirred for 2 h at 60 °C. The solvent was removed *in vacuo*, and the residue was poured into ice-water and extracted with ethyl acetate. Washing of the ethyl acetate extract with 5% sodium hydrogencarbonate, 5% hydrochloric acid and water, followed by drying over Na_2SO_4 and evaporation of the solvent, left the crude product (**15b**), which was recrystallized from toluene to give 4.3 g (91%) of **15b**, mp 46—48 °C. IR (KBr): 3316 (N–H), 1749 (acid CO), 1656 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.20 (overlapping two 3H, each t, J=7.1 Hz, $CH_3\times2$), 4.15—4.22 (two 2H, each m, $C\underline{H}_2CH_3\times2$), 4.93 (2H, d, J=46.7 Hz, CH_2F), 5.11 (1H, d, J=7.1 Hz, CH), 8.95 (1H, br d, J=7 Hz, NH). *Anal.* Calcd for $C_9H_{14}FNO_5$: C, 45.95; H, 5.95; N, 5.95.

2-(Chloroacetylamino)-2-(2-furylmethyl)propanedioic Acid Diethyl Ester (16a) 2-(Chloroacetylamino)propanedioic acid diethyl ester (**15a**) (25 g, 100 mmol) was dissolved in a sodium ethoxide solution [prepared from 2.3 g of sodium (0.1 g-atm) and 200 ml of absolute ethanol]. To this stirred solution, an ether solution containing crude 2-(bromomethyl)furan[18] (**9**) [prepared from 2-furylmethanol (**13**) (13 g, 130 mmol)] was added in a single portion. The mixture was distilled rapidly at atmospheric pressure until about 300 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*, then 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. After removal of the solvent *in vacuo*, the resulting oily residue was chromatographed on a silica gel column (250 g, 70—230 mesh) with ethyl acetate/toluene=3/7 to give the crude product (**16a**, 24 g, 72%), which was purified by recrystallization from a mixture of ether and pet. ether; colorless needles, mp 52—53 °C. IR (KBr): 3232 (N–H), 1743 (ester CO), 1659 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.17 (overlapping 3H, each t, J=7.0 Hz, $CH_3\times2$), 3.54 (2H, s, furan-C$\underline{H}_2$), 4.16—4.22 (two 2H, each m, $C\underline{H}_2CH_3\times2$), 4.26 (2H, s, CH_2Cl), 6.14, 6.35 and 7.51 (each 1H, each m, furan-3H, 4H and 5H), 8.60 (1H, s, NH). *Anal.* Calcd for $C_{14}H_{18}ClNO_6$: C, 50.67; H, 5.42; N, 4.22. Found: C, 50.49.06; H, 5.23; N, 4.15.

2-(Fluoroacetylamino)-2-(2-furylmethyl)propanedioic Acid Diethyl Ester (16b) This compound (**16b**) was prepared as described above from the reaction of the crude 2-(bromomethyl)furan (**9**) [prepared from 2-furylmethanol (**13**) (4.9 g, 50 mmol)] with 2-(fluoroacetylamino)propanedioic acid diethyl ester (**15b**) (9 g, 38 mmol) in 85% yield, bp 225—230/5 mmHg. IR (neat): 3430 (N–H), 1746 (ester CO), 1695 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.18 (overlapping two 3H, each t, J=7.0 Hz, $CH_3\times2$), 3.56 (2H, s, furan-C$\underline{H}_2$), 4.17—4.23 (two 2H, each m, $C\underline{H}_2CH_3\times2$), 4.93 (2H, d, J=46.8 Hz, CH_2F), 6.14, 6.34 and 7.52 (each 1H, each m, furan-3H, 4H and 5H), 8.11 (1H, s, NH). *Anal.* Calcd for $C_{14}H_{18}FNO_6$: C, 53.30; H, 5.71; N, 4.44. Found: C, 53.40; H, 5.82; N, 4.44.

2-(Chloroacetylamino)-2-(2-furylmethyl)propanedioic Acid (17a) The preparation of **17a** was carried out according to the method of Watanabe *et al.*[15] A mixture of **16a** (20 g, 60 mmol) with 10% sodium hydroxide solution (100 ml) was stirred at room temperature for 24 h. Unchanged **16a** was removed by extraction with ethyl acetate, and the resulting solution was acidified with 10% HCl, and then extracted with ether. Drying and evaporation of the solvent left the crude product, **17a**, which was recrystallized from a mixture of ether and pet. ether to afford 12.7 g (76%) of **17a**, mp 135—138 °C. IR (KBr): 3376 (N–H), 1743 (acid CO), 1632 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.53 (2H, s, furan-C$\underline{H}_2$), 4.25 (2H, s, CH_2Cl), 6.08, 6.33

and 7.49 (each 1H, each m, furan-3H, 4H and 5H), 8.21 (1H, s, NH). *Anal.* Calcd for $C_{10}H_{10}ClNO_6$: C, 43.6; H, 3.62; N, 5.08. Found: C, 43.57; H, 3.89; N, 5.13.

2-(Fluoroacetylamino)-2-(2-furylmethyl)propanedioic Acid (17b) This compound **17b** was prepared according to the method described for **17a**. The hydrolysis of **16b** (18 g, 60 mmol) with 10% sodium hydroxide solution (100 ml) was carried out to give 13 g (98%) of crude product (**17b**), which was recrystallized from a mixture of ether and pet. ether to afford **17b**, mp 147—150 °C. IR (KBr): 3418 (N–H), 1740 (acid CO), 1647 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.56 (2H, s, furan-C$\underline{H}_2$), 4.91 (2H, d, J=46.8 Hz, CH_2F), 6.09, 6.34 and 7.50 (each 1H, each m, furan-3H, 4H and 5H), 7.75 (1H, s, NH). *Anal.* Calcd for $C_{10}H_{10}FNO_6$: C, 46.3; H, 3.86; N, 5.40. Found: C, 46.13; H, 3.86; N, 5.24.

2-(Chloroacetylamino)-3-(2-furyl)propanoic Acid (6a) Compound **17a** (4.5 g, 16 mmol) was refluxed in ethanol (450 ml) for 3 h. The solvent was removed *in vacuo*, and the resultant residue was recrystallized from a mixture of ether and pet. ether to give 3.4 g (93%) of **6a**, mp 88—90 °C. IR (KBr): 3364 (N–H), 1731 (acid CO), 1617 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.01 (1H, dd, J=8.3, 15.4 Hz, one proton of furan-C$\underline{H}_2$) 3.11 (1H, dd, J=5.0, 15.4 Hz, one proton of furan-C$\underline{H}_2$), 4.09 (2H, s, CH_2Cl), 4.49 (1H, m, C$\underline{H}$), 6.15, 6.35 and 7.52 (each 1H, each m, furan-3H, 4H and 5H), 8.51 (1H, d, J=7.8 Hz, NH). *Anal.* Calcd for $C_9H_{10}ClNO_4$: C, 46.6; H, 4.31; N, 6.04. Found: C, 46.32; H, 4.48; N, 5.83.

2-(Fluoroacetylamino)-3-(2-furyl)propanoic Acid (6b) The decarboxylation of **17b** (9.7 g, 40 mmol) in ethanol (1125 ml) was carried out according to the method described for **17b** to give 7.3 g (91%) of **6b**, which was recrystallized from a mixture of ether and pet. ether to afford **6b**, mp 82—84 °C. IR (KBr): 3376 (N–H), 1734 (acid CO), 1632 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 3.07 (1H, dd, J=8.8, 15.4 Hz, one proton of furan-C$\underline{H}_2$), 3.14 (1H, dd, J=5.0, 15.4 Hz, one proton of furan-C$\underline{H}_2$) 4.55 (1H, m, CH), 4.81 (2H, d, J=46.9 Hz, CH_2F), 6.14, 6.34 and 7.52 (each 1H, each m, furan-3H, 4H and 5H), 8.36 (1H, d, J=8.1 Hz, NH). *Anal.* Calcd for $C_9H_{10}FNO_4$: C, 50.23; H, 4.65; N, 6.51. Found: C, 50.46; H, 4.74; N, 6.47.

3-Amino-3-(2-furyl)propanoic Acid Methyl Ester Hydrochloride (20) Thionyl chloride (10.7 g, 90 mmol) was added dropwise to MeOH (30 ml) at −10 °C. The reaction mixture was stirred at −10 °C for 10 min, then 3-amino-3-(2-furyl)propanoic acid (**23**, 4.6 g, 30 mmol) was added rapidly in a single portion. The mixture was stirred at room temperature for 15 h. The solvent was removed *in vacuo*, and the resultant mixture was recrystallized from MeOH to give 5.8 g of the corresponding methyl ester hydrochloride (**20**) in 92% yield, mp 145—148 °C. IR (KBr) cm^{-1}: 1728 (ester CO). ^{1}H-NMR (DMSO-d_6): 3.07 (1H, dd, J=8.9, 16 Hz, one proton of CH_2), 3.19 (1H, dd, J=5.5, 16 Hz, one proton of CH_2) 3.60 (3H, s, CH_3), 4.69 (1H, dd, J=5.5, 8.9 Hz, CH), 6.48, 6.58 and 7.71 (each 1H, each m, furan-4H, 3H and 5H), 8.88 (3H, br s, NH_3^+). *Anal.* Calcd for $C_8H_{12}ClNO_3$: C, 46.73; H, 5.88; N, 6.81. Found: C, 46.69; H, 5.81; N, 6.64.

3-(Chloroacetylamino)-3-(2-furyl)propanoic Acid Methyl Ester (21a) This compound (**21a**) was prepared according to the method described above for 2-(chloroacetylamino)propanedioic acid diethyl ester (**15a**) through the reaction of chloroacetyl chloride (3 g, 27 mmol) with 3-amino-3-(2-furyl)propanoic acid methyl ester hydrochloride (**20**) (6.2 g, 30 mmol) in 33% yield, mp 82—83 °C (toluene/AcOEt). IR (KBr): 3460 (N–H), 1728 (ester CO), 1650 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.81 (1H, dd, J=7.6, 12 Hz, one proton of CH_2), 2.89 (1H, dd, J=7.0, 12 Hz, one proton of CH_2), 3.58 (3H, s, OCH_3), 4.05 (1H, d, J=14 Hz, one proton of CH_2Cl), 4.08 (1H, d, J=14 Hz, one proton of CH_2Cl), 5.31 (1H, m, CH), 6.28, 6.39 and 7.59 (each 1H, each m, furan-3H, 4H and 5H), 8.70 (1H, d, J=8.3 Hz, NH). *Anal.* Calcd for $C_{10}H_{12}ClNO_4$: C, 48.89; H, 4.92; N, 5.70.

3-(Fluoroacetylamino)-3-(2-furyl)propanoic Acid Methyl Ester (21b) This compound (**21b**) was prepared according to the method described above for 2-(fluoroacetylamino)propanedioic acid diethyl ester (**15b**) through the reaction of sodium fluoroacetate (2 g, 20 mmol) with 3-amino-3-(2-furyl)propanoic acid methyl ester hydrochloride (**20**) (4 g, 20 mmol) in 81% yield, mp 70—72 °C IR (KBr): 3484 (N–H), 1743 (acid CO), 1659 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.87 (1H, dd, J=8.0, 16 Hz, one proton of CH_2), 2.93 (1H, dd, J=7.0, 16 Hz, one proton of CH_2), 3.59 (3H, s, OCH_3), 4.81 (2H, d, J=46.9 Hz, CH_2F), 5.40 (1H, m, CH), 6.25, 6.38 and 7.56 (each 1H, each m, furan-3H, 4H and 5H), 8.62 (1H, d, J=8.6 Hz, NH). *Anal.* Calcd for $C_{10}H_{12}FNO_4$: C, 52.40; H, 5.28; N, 6.11. Found: C, 52.70; H, 5.23; N, 5.95.

3-(Acetylamino)-3-(2-furyl)propanoic Acid Methyl Ester (21c) This compound (**21c**) was prepared according to the method described above for 2-(fluoroacetylamino)propanedioic diethyl ester (**15b**) through the reaction of acetic acid (1.2 g, 20 mmol) with 3-amino-3-(2-furyl)propanoic acid methyl ester hydrochloride (**20**) (4.1 g, 20 mmol) in 95% yield, mp 63—65 °C (ether/AcoEt). IR (KBr): 3262 (N–H), 1734 (acid CO), 1644 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.81 (3H, s, –$COCH_3$), 2.74 (1H, dd, J=7.6, 15.5 Hz, one proton of CH_2), 2.82 (1H, dd, J=7.2, 15.5 Hz, one proton of CH_2), 3.57 (3H, s, $COOCH_3$), 5.30 (1H, m, CH), 6.23, 6.37 and 7.56 (each 1H, each m, furan-3H, 4H and 5H), 8.33 (1H, d, J=8.4 Hz, NH). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.61; H, 6.15; N, 6.62.

3-(Chloroacetylamino)-3-(2-furyl)propanoic Acid (7a) A 4% NaOH solution (15 ml) was added to an ice-cold, stirred solution of 3-(chloroacetylamino)-3-(2-furyl)propanoic acid methyl ester (**21a**) (2.5 g, 10 mmol) in MeOH (50 ml). The mixture was stirred at room temperature for 4 h, then the solvent was removed *in vacuo*, and the resultant residue was poured into ice-water. The cooled alkaline solution was washed with ether (20 ml), acidified with 5% HCl, and then extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over Na_2SO_4 and evaporated to afford a crude product (**7a**), which was recrystallized from ethyl acetate to give 2.2 g of **7a** in 95% yield, mp 120—122 °C. IR (KBr): 3328 (N–H), 1716 (acid CO), 1650 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.72 (1H, dd, J=7.3, 16 Hz, one proton of CH_2), 2.80 (1H, dd, J=7.1, 16 Hz, one proton of CH_2), 4.04 (1H, d, J=13 Hz, one proton of CH_2Cl), 4.08 (1H, d, J=13 Hz, one proton of CH_2Cl), 5.28 (1H, m, CH), 6.26, 6.39 and 7.58 (each 1H, each m, furan-3H, 4H and 5H), 8.68 (1H, d, J=8.4 Hz, NH), 12.4 (1H, br s, –COOH). *Anal.* Calcd for $C_9H_{10}ClNO_4$: C, 46.67; H, 4.35; N, 6.05.

3-(Fluoroacetylamino)-3-(2-furyl)propanoic Acid (7b) This compound (**7b**) was prepared according to the method described above for 3-(chloroacetylamino)-3-(2-furyl)propanoic acid (**7a**) through the hydrolysis of 3-(fluoroacetylamino)-3-(2-furyl)propanoic acid methyl ester (**21b**) (2.3 g, 10 mmol) with 4% NaOH (15 ml) in 91% yield, mp 178—180 °C (AcOEt/EtOH). IR (KBr): 3304 (N–H), 1707 (acid CO), 1662 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.77 (1H, dd, J=7.5, 16 Hz, one proton of CH_2), 2.84 (1H, dd, J=6.9, 16 Hz, one proton of CH_2), 4.81 (2H, d, J=47.0 Hz, CH_2F), 5.33 (1H, m, CH), 6.24, 6.38 and 7.56 (each 1H, each m, furan-3H, 4H and 5H), 8.61 (1H, d, J=8.6 Hz, NH), 12.4 (1H, br s, –COOH). *Anal.* Calcd for $C_9H_{10}FNO_4$: C, 50.24; H, 4.68; N, 6.51. Found: C, 50.07; H, 4.65; N, 6.27.

3-Acetylamino-3-(2-furyl)propanoic Acid (7c) This compound (**7c**) was prepared according to the method described above for 3-(chloroacetylamino)-3-(2-furyl)propanoic acid (**7a**) through the hydrolysis of 3-(acetylamino)-3-(2-furyl)propanoic acid methyl ester (**21c**) (2.1 g, 10 mmol) with 4% NaOH (15 ml) in 96% yield, 178—179 °C (AcOEt/EtOH). IR (KBr): 3346 (N–H), 1734 (acid CO), 1614 (amide CO) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 1.81 (3H, t, J=7.3 Hz, CH_3), 2.64 (1H, dd, J=7.3, 12 Hz, one proton of CH_2), 2.73 (1H, dd, J=7.3, 12 Hz, one proton of CH_2), 5.27 (1H, m, CH), 6.22, 6.37 and 7.56 (each 1H, each m, furan-3H, 4H and 5H), 8.29 (1H, d, J=8.5 Hz, NH), 12.3 (1H, br s, –COOH). *Anal.* Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.10. Found: C, 54.84; H, 5.54; N, 7.05.

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