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New Serine Protease Inhibitors with Leukotriene B_4 (LTB_4) Receptor Binding Affinity

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Abstract—A series of new trypsin-like serine protease inhibitors, **1**, **2** and **7–23**, containing amidinobenzene moiety was found to show potent LTB_4-receptor affinity. Among them, compounds **1** and **2** were found to be LTB_4 receptor antagonists based on an inhibition assay of human polymorphonuclear neutrophil (PMN) intracellular calcium mobilization induced by LTB_4. Compounds **1** and **2**, which satisfy the reported structural requirements for good oral activity, are expected to show a balanced dual mode of action, i.e., protease inhibitory activity and LTB_4 receptor antagonist activity, in vivo. © 1997 Elsevier Science Ltd.

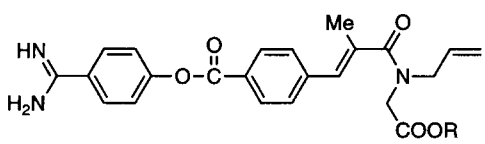
Introduction

Compounds containing amidine function in their molecules are known to possess a variety of biological activities such as leukotriene B_4 (LTB_4) receptor antagonist activity,[1] inhibitory activity of blood coagulation factor (as illustrated in thrombin inhibitor[2] and fibrinogen receptor antagonist **6**[3]), and induced nitrogen oxide synthase inhibitor,[4] among others.

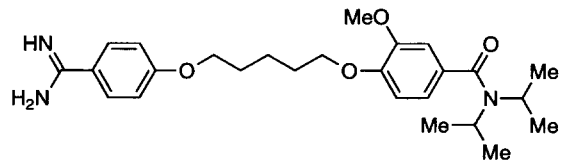
In the process of developing orally active trypsin-like serine protease inhibitors, we have prepared many phenyl ester derivatives with basic components such as amidine or guanidine. We screened novel serine protease inhibitors[5,6] including **3** and **4** to determine whether they have any additional biological activity. We found that the series of serine protease inhibitors bearing an amidinobenzene moiety possesses potent LTB_4 receptor binding affinity. Among them, **1** and **2** were shown to be potent LTB_4 antagonists when evaluated by a human polymorphonuclear neutrophil (PMN) intracellular calcium mobilization assay.[7] Here, we report the synthesis and structural requirements for LTB_4 receptor binding affinity.

Chemistry

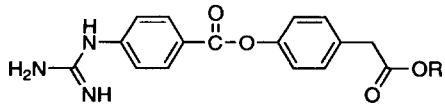
Compounds **1**, **2** and **7–24** (Table 1) were prepared by the same procedure as described previously.[5,6] The amino ester moieties in **25–29** were synthesized as shown in Scheme 1-1 and 1-2, and compounds **25–29** were prepared as shown in Scheme 1-3. The preparation of compound **30** is shown in Scheme 2-1. Compound **31** was prepared from **65** by the sequential reactions shown in Scheme 2-2. Compounds **32**, **34a,b**, **35** and **36** were synthesized from **70a–c** and **70d,e**, respectively (Scheme 2-3). The syntheses of **69a–e** and **70a–e** are shown in Scheme 2-3. As illustrated in Scheme 2-4, **33** was synthesized from **71**. Scheme 2-5 illustrates the preparation of amidine ester derivative **37**. The preparation of **38–39** is shown in Scheme 3-1. Compounds **80a,b** were prepared from methyl-4-formylbenzoate with *t*-butyl-2-diethylphosphonopropionate



1: R = H
2: R = Et



5 (CGS25019C)



3: R = H (FOY-251)
4: R = CH_2CONMe_2 (FOY-305)

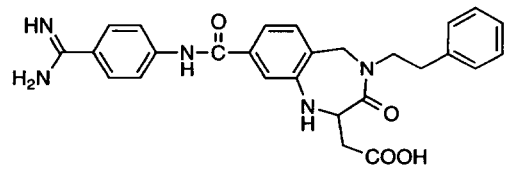


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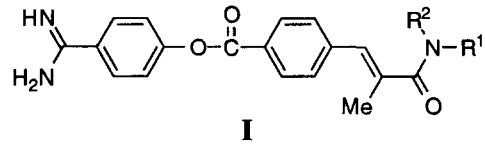
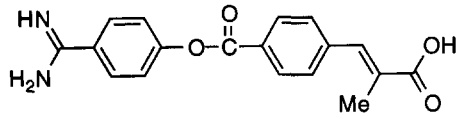
Chart 1.

Table 1. Effect of R^1 and R^2 on inhibition of [^{3}H]LTB_4 binding to human PMN



I

Compound	R^1	R^2	IC_{50} (nM)[a]
1[c]	allyl	CH_2CO_2H	201±23.1
2[c]	allyl	CH_2CO_2Et	63±7.3
7[c]	allyl	$(CH_2)_3CO_2H$	126.0±6.4
8[c]	allyl	$(CH_2)_3CO_2Et$	27.4±9.8
9	allyl	$CH_2C_6H_4$-*p*-CO_2Et	52.7±7.5
10[c]	CH_2Ph	CH_2CO_2H	23.9±3.6
11	$Me_2CH(CH_2)_2$	$(CH_2)_2CO_2Et$	29.2±7.0
12	$Me_2CH(CH_2)_2$	CH_2CO_2H	25.7±3.6
13	*i*-Pr	$(CH_2)_2CO_2H$	190.1±19.8
14	Me	$(CH_2)_2CO_2H$	3735.8±294.4
15	Cyclohexyl	$(CH_2)_2CO_2H$	25.7±2.1
16	$(CH_2)_2OMe$	CH_2CO_2Et	191.4±33.5
17	2-Tetrahydrofuranyl-CH_2	CH_2CO_2H	149.1±39.5
18	$(CH_2)_2CO_2H$	$(CH_2)_2CO_2H$	>10,000 (2.8 %)[b]
19	$(CH_2)_2CO_2Et$	CH_2CO_2Et	242.0±6.2
20	CH_2CO_2H	CH_2CONH_2	(9.4 %)[c]
21	(*E*)-CH_2CH=$CHCO_2Et$	$CH(CH_2CO_2Et)CO_2Et$	62.7±16.0
22	C_3H_7	$CH(CH_2CO_2Et)_2$	76.8±14.6
23	Cyclohexyl	$CH(CH_2CO_2Et)_2$	105.0±19.0
24			>10,000

[a]IC_{50} values are the mean ± SEM ot three separate experiments.
[b]Percentage of inhibition at 1 μM.
[c]Elemental analyses of these compounds were repeated in ref 6.

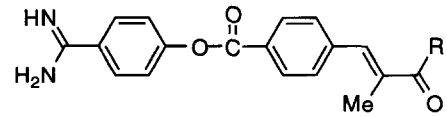
and methyl-4-acetylbenzoate with *t*-butyl-2-diethylphosphonoacetate, respectively, followed by alkaline hydrolysis under the Horner–Emmons conditions. Scheme 3-2 depicts the synthesis of **40a,b** and **41a,b**. The condensation of **47b** with ethyl-3-amidinosalicylate (**82**)[9] gave **42** (Scheme 3-3). The preparation of **43a,b** and **44a–d** is described in Scheme 4. Unsaturated nitrile **89**, which was obtained from 6-methoxy-β-tetralone *via* dehydration of its cyanohydrin derivative, was converted to amidine **90**, then to **44a** by demethylation followed by salt exchange with methanesulfonic acid. The 6-amidino-7,8-dihydro-2-naphthol was converted to **44b–d** by acylation with the corresponding carboxylic acids. The synthesis of **48** is described in Scheme 5.

Results and Discussion

The newly found synthetic serine protease inhibitors[5,6] were examined for LTB_4-receptor binding activity. The antagonist activity of these compounds toward LTB_4 receptor was evaluated by their inhibition of human PMN calcium mobilization stimulated by LTB_4.[7] Although guanidine derivatives **3** and **4** did not show any affinity toward LTB_4 receptor up to 10 μM, most of the newly found protease inhibitors which contain an amidine moiety showed strong binding affinity toward the receptor at 1 μM.

As shown in Table 1, compound **24** did not show any affinity up to 10 μM. Therefore, the tail moiety R in general formulae I, II and III is thought to play an important role in the binding to the receptor. Compound **14**, possessing less lipophilic amide moiety exhibited less affinity. The introduction of carboxylic

Table 2. Effect of R on inhibition of [^{3}H]LTB_4 binding to human PMN

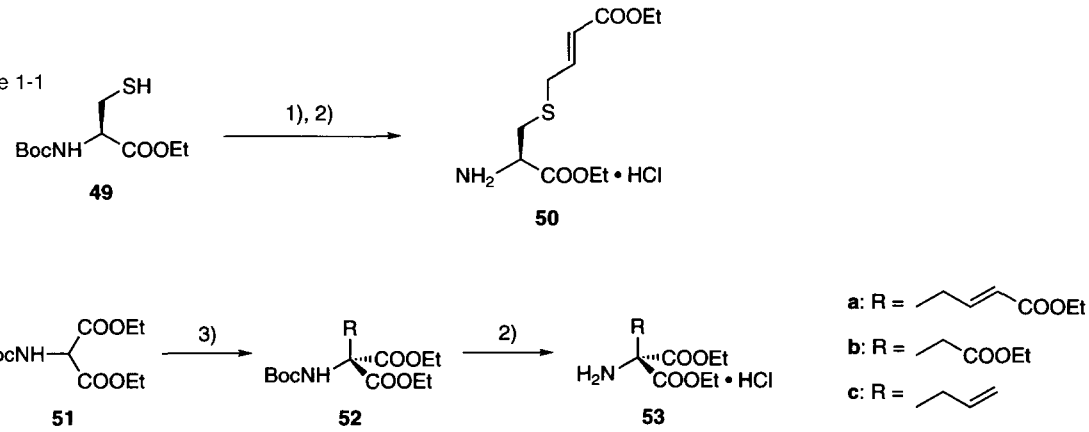


II

Compound	IC_{50} (nM)[a]
25	36.3±5.2
26	54.9±19.2
27	159.6±32.7
28	93.6±5.7
29	94.5±27.4

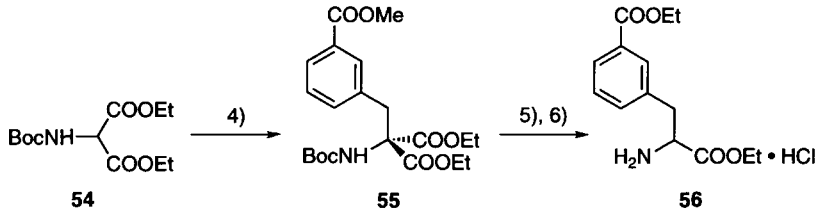
[a]IC_{50} values are the mean ± SEM of three separate experiments.

Scheme 1-1



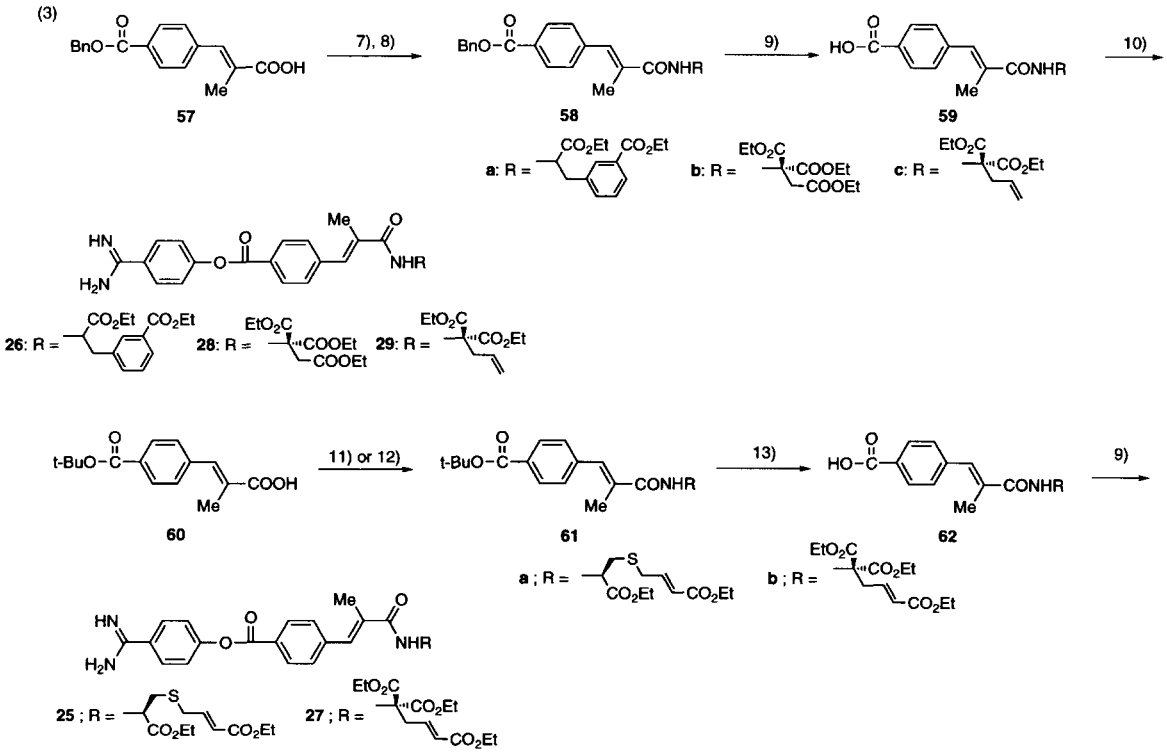
Reagents : 1) NaH, ethyl 4-bromocrotonate, CH_3CN, 25 °C, 0.5h, 55 %; 2) 4N HCl, AcOEt, 25 °C, 1h, ≥95 % (**50** and **53a-c**); 3) NaH, RBr, DMF, 25 °C, 2h, 82 % (**52a**), 86 % (**52b**) and 98 % (**52c**), respectively.

Scheme 1-2



Reagents : 4) NaH, methyl 3-bromomethylbenzoate, DMF, 25 °C, 3h, 81 %; 5) 6N HCl, reflux, 4h, 94 %; 6) HCl, EtOH, reflux, 16h, 83 %.

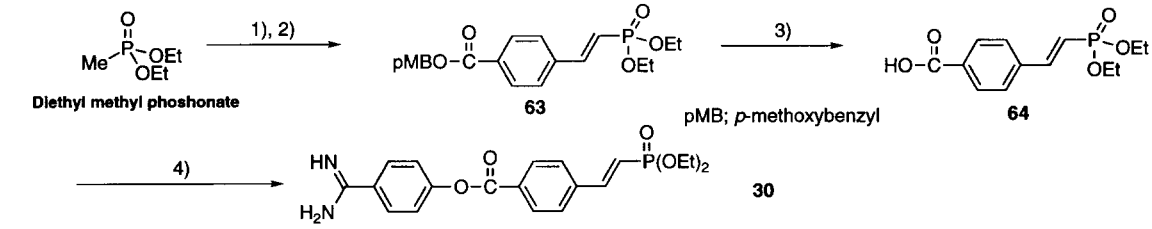
Scheme 1-3



Reagents : 7) $SOCl_2$, reflux, 0.5h; 8)RNH_2, pyridine, CH_2Cl_2, 25 °C, 2h, 76 % (**58a**), 89 % (**58b**) and 95 % (**58c**), respectively; 9) $MeSO_3H$, anisole, 25 °C, 2h, 100 % (**59a**), 96 % (**59b**) and 75 % (**59c**), respectively; 10) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 17h, 66 % (**26**), 56 % (**28**), 59 % (**29**), 68 % (**25**) and 53 % (**27**), respectively; 11) **50**, EDC•HCl, pyridine, 25 °C, 2h, 87 % (**61a**); 12) **53a**, 2-chloro-1-methylpyridinium iodide, diisopropylethylamine, DMAP (cat.), THF, reflux, 3day, 71 % (**61b**); 13) TFA, CH_2Cl_2, 25 °C, 3.5h, 68 % (**62a**) and76 % (**62b**), respectively.

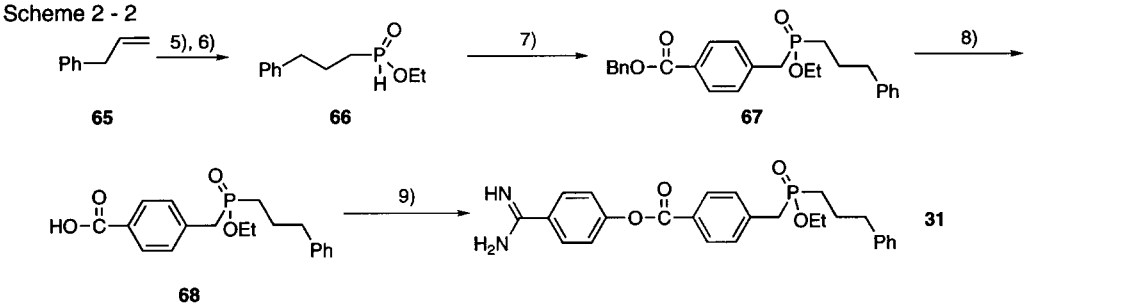
Scheme 1. Preparation of **25–29** (General formula II)

Scheme 2 - 1



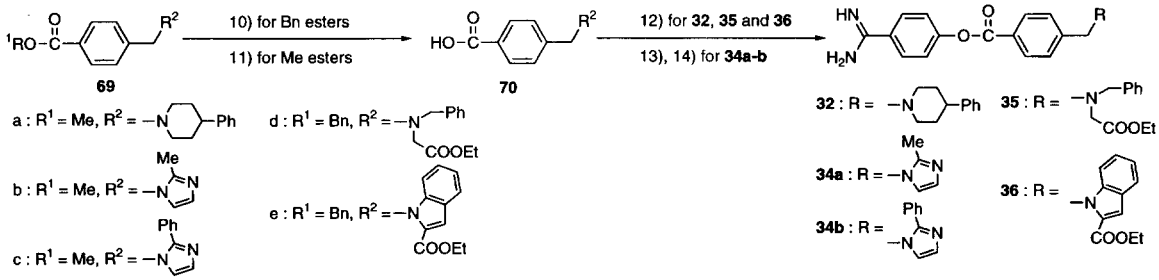
Reagents : 1) *n*-BuLi, *p*-methoxybenzyl 4-formylbenzoate, THF, -78 °C, 0.5h, 67 %; 2) MsCl, NEt_3, 25 °C, 13h, 82 %; 3) TFA, anisole, 25 °C, 1.5h, 63 %; 4) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 17h, 95 %.

Scheme 2 - 2



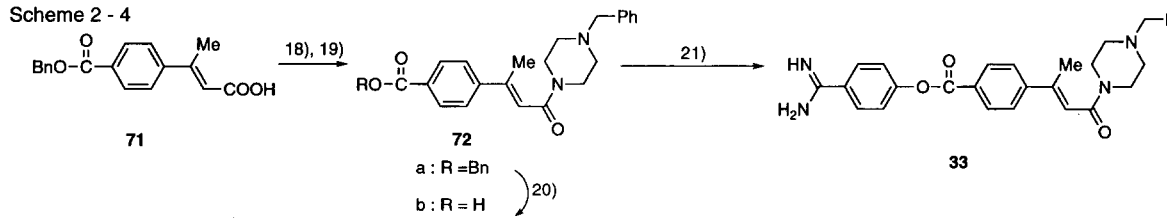
Reagents : 5) sodium hypophosphite, H_2SO_4, AIBN, EtOH, 100 °C, 72h, 97 %; 6) EtOH, DCC, DMAP, THF, 25 °C, 12h, 71 %;7) TMSCl, NEt_3, $CHCl_3$, benzyl 4-bromomethylbenzoate, 25 °C, 15 days, 37 %; 8) Pd-C, H_2, EtOH, 25 °C, 2h, 100 %; 9) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 15h, 65 %.

Scheme 2- 3



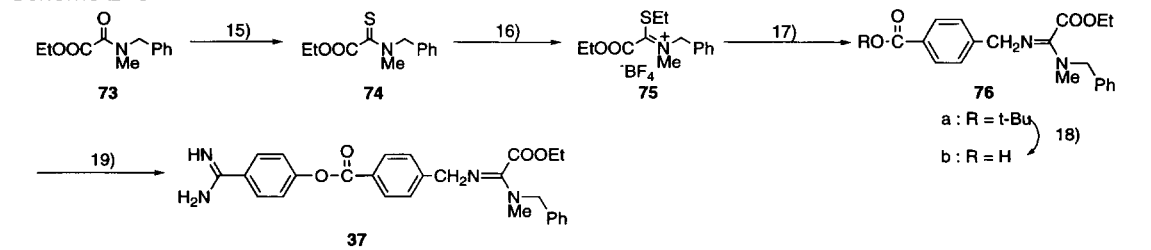
Reagents : 10) $MeSO_3H$, anisole, 25 °C, 2h, 46 and 73 %, respectively; 11) 1N NaOH, 1,4-dioxane, 25 °C, 1h, 95, 45 and 40 %, respectively; 12) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 17h, 48, 57 and 83 %, respectively; 13) $SOCl_2$, reflux, 0.5h; 14) 4-amidinophenol hydrochloride (**46**), pyridine, CH_2Cl_2, 5 °C, 2h, 37 and 50 %, respectively.

Scheme 2 - 4



Reagents : 18) $(COCl)_2$, 25 °C, 0.5h; 19) *N*-benzylpiperazine, pyridine, CH_2Cl_2, 5 °C, 2h, 86 %; 20) $MeSO_3H$, anisole, 25 °C, 5h, 59 %; 21) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 17h, 59 %.

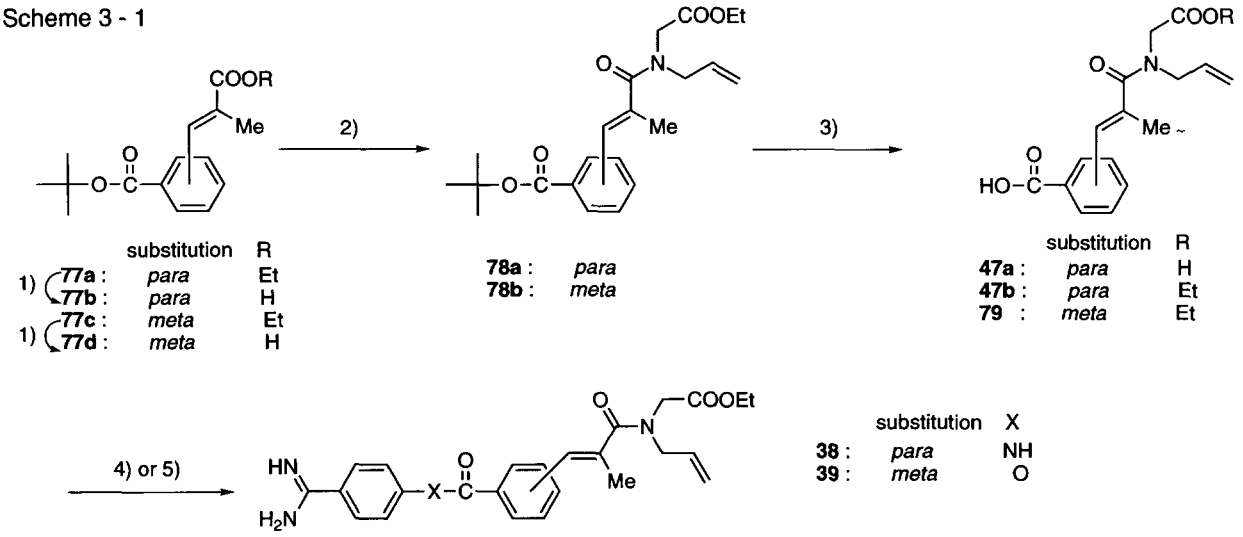
Scheme 2- 5



Reagents : 15) P_2S_5, THF, reflux, 2.5h, 80 %; 16) $Et_3O^+BF_4^-$, CH_2Cl_2, 25 °C, 0.5h; 17) *t*-butyl 4-aminomethylbenzoate, CH_2Cl_2, 25 °C, 0.5h, 39 %; 18)TFA, anisole, 25 °C, 2h, 57 %; 19) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 24h, 38 %.

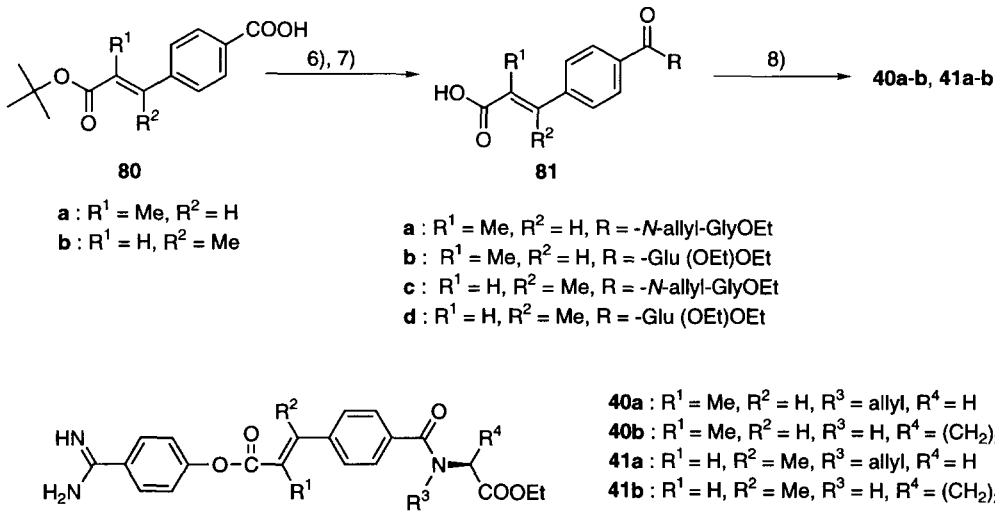
Scheme 2. Preparation of **30–37** (general formula III).

Scheme 3 - 1



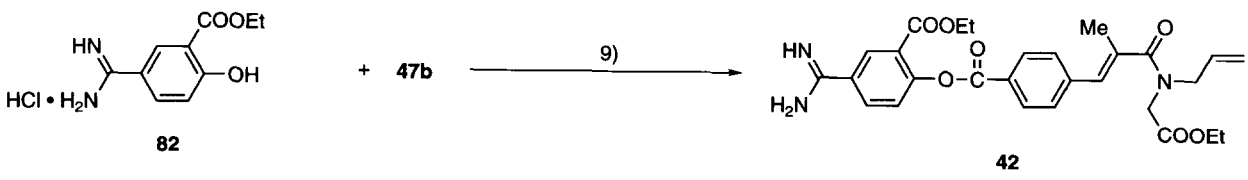
Reagents :1) NaOH, 1,4-dioxne, 25 °C, 3h, 78 % ; 2) ethyl *N*- allylglycinate, EDC•HCl, CH_2Cl_2, 25 °C, 2h, 66 %; 3) TFA, anisole, 25 °C, 2h, 100 %; 4) 4-amidinoaniline hydrochloride, DCC, pyridine, 25 °C, 12h, 21 %; 5) 4-amidinophenol hydrochloride (**46**), DCC, pyridine, 25 °C, 17h, 74 %.

Scheme 3 - 2



Reagents : 6) ethyl *N*-allylglycinate or L-glutamic acid diethylester hydrochloride, EDC•HCl, CH_2Cl_2, 25 °C, 3h, 93, 78, 85 and 80 %, respectively; 7) TFA, anisole, 25 °C, 2h, 100 %; 8) 4-amidinophenol hydrochloride, DCC, pyridine, 25 °C, 15h, 61, 67, 53 and 58 %, respectively.

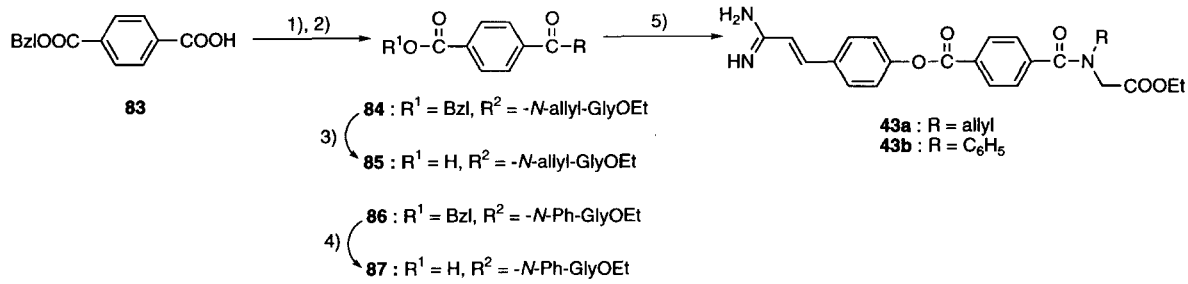
Scheme 3 - 3



Reagents : 9) DCC, pyridine, 25 °C, 17h, 54 %.

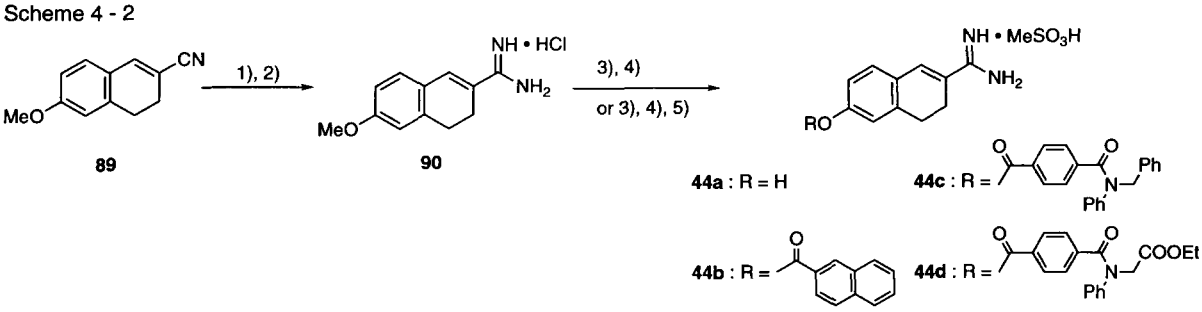
Scheme 3. Preparation of **38–42**.

Scheme 4 - 1



Reagents : 1) $SOCl_2$, reflux, 0.5 h; 2) ethyl *N*-allyl or phenyl glycinate, pyridine, CH_2Cl_2, 25 °C, 3h, 85 (**84**) and 80 % (**86**); 3) $MeSO_3H$, anisole, 25 °C, 2h, 77 %; 4) 10 % Pd-C, H_2, MeOH, 77 %; 5) 3-(4-hydroxyphenyl)-2-propenimidamide (**88**), DCC, pyridine, 25 °C, 17h, 39 % (**43a**) and 23 % (**43b**).

Scheme 4 - 2

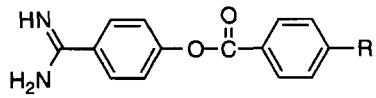


Reagents : 1) HCl, MeOH, 25 °C, 17h, 100 %; 2) NH_3, MeOH, 25 °C, 15h, 100 %; 3) BBr_3, CH_2Cl_2, 25 °C, 71 %; 4) $MeSO_3H$, MeOH, 25 °C, 0.5h, 100 %; 5) RCOOH, DCC, pyridine, 25 °C, 17h, 94 % (**44b**), 86 % (**44c**) and 62 % (**44d**), respectively.

Scheme 4. Preparation of **43** and **44**.

acid (**18**) or carboxyamide (**20**) markedly reduced the affinity. When the nitrogen in the amino acid moiety was alkylated with the lipophilic alkyl group (**1**, **7**, **10**, **12**, **13**, **15**, **22** and **23**), potent to moderate activity was maintained. Amino ester derivatives **2** and **8** possessed stronger activity compared to the corresponding carboxylic acid derivatives **1** and **7**, respectively, as expected from on the basis of lipophilicity.

Table 3. Effect of R on inhibition of [^{3}H]LTB_4 binding to human PMN



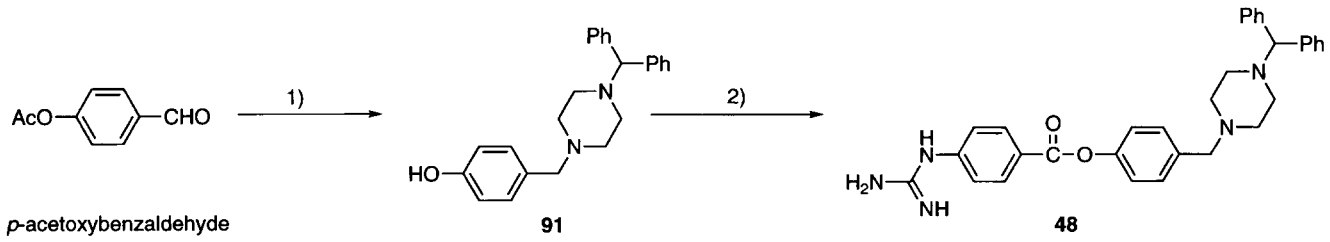
III

Compound	IC_{50} (nM)[a]
30	1954.0±186.7
31	488.4±94.2
32	156.7±16.8
33	285.2±43.4
34a	(12.4%)[b]
34b	(62.5%)[b]
35	301.7±76.5
36	96.1±9.6
37	86.4±25.6

[a]IC_{50} values are the mean ± SEM of three separate experiments. [b]Percentage of inhibition at 1 μM.

As shown in Table 2, compounds containing primary amide esters also showed moderate to potent affinity. The potent activity was retained by the introduction of an aromatic group to the amide ester moiety (**26**). Compounds **27–29** were less active than **25** and **26**. For potent activity, a lipophilic substituent (R) appears to be required.

Miscellaneous chemical modification of the tail moiety R of general formula III afforded **30–37**, as shown in Table 3. The introduction of terminal diethyl vinyl phosphonate markedly reduced the affinity. Although the presence of phosphinic acid ester was thought to cause a reduction in the activity, compound **31**, containing a phenylpropyl moiety, maintained the activity to some extent. Compounds **32**, **33**, **35** and **37** all have a hydrophilic nitrogen function and a lipophilic moiety. Reduced activity was also shown by **34a**. Activity in **34b** was recovered by the replacement of a 2-methylimidazole moiety in **34a** with a 2-phenylimidazole moiety. Compound **36**, containing an indole moiety possessing non-basic nitrogen, retained moderate activity. The maintenance of the potent binding affinity of **2** by amide analog **38** indicates that the phenol ester moiety is not a requirement for the binding affinity. Shifting the amide tail of **2** from the *para*- to the *meta*-position provided **39**, which had weaker activity than **2**, suggesting that the geometry of the amide tail moiety is important. The potent receptor affinity was maintained by shifting the trisubstituted *E*-double bond from the



Reagents :1) diphenylmethylpiperazine, $NaBH_3CN$, MeOH, 25 °C, 1h, 39 %; 2) *p*-guanidinobenzoic acid, DCC, pyridine, DMF, 25 °C, 3 days, 25 %.

Scheme 5.

tail part of the conjugated position to the phenol ester carbonyl (**40a,b** and **41a,b**).

The introduction of ethoxycarbonyl into the 4-amidinophenol moiety (**42**) caused a reduction in receptor affinity, in comparison with **2**. The insertion of the *trans*-double bond between amidine and a phenol moiety provided **43a**, which had weaker activity than **2**. Compound **43b** is considered to have stronger activity than its corresponding *N*-alkyl derivative as a result of the increased lipophilicity of *N*-phenyl glycinate. The activity of amidinodihydronaphthalene derivatives **44a–d** was similar to that of the amidinophenol derivatives. Although compounds **44a,b** showed no affinity to the LTB_4 receptor up to 1 mM, compounds **44c,d**, containing an amide tail, showed moderate to potent receptor affinity. Components **1** and **2**, 4-amidinophenol **46** and carboxylic acids **47a,b** (Scheme 3-1) were inactive up to 10 mM. Interestingly, guanidine derivatives **3**, **4** and **48** did not affect the LTB_4 receptor. Consequently, both the conjugated amidine moiety and the lipophilic tail moiety were thought to be required for the components to show LTB_4 receptor affinity. Compounds **1** and **2** were found to be potent LTB_4 receptor antagonists when tested by the LTB_4-induced human PMN intracellular calcium mobilization assay (IC_{50} 115.0±21.0 and 106.6±33.8 nM, respectively) and degranulation assay (IC_{50} 103.9±34.1 and 16.4±2.5 nM, respectively) (see Table 4).[7]

In summary, we have demonstrated that aryl amidines and vinyl amidines are a new class of LTB_4 receptor ligands structurally distinct from LTB_4 and other reported antagonists.[11] An amidine moiety at one end and a lipophilic moiety at the other end are necessary for the LTB_4 receptor affinity. The structurally closest LTB_4 antagonist to **1** and **2** seems to be **5** (CGS25019C).[1] Although these protease inhibitors were not optimized as LTB_4 antagonists, they are expected to show a balanced dual mode of action in vivo, judging from their in vitro potency.[12] In addition, compounds **1–23** may have oral activity since they satisfy the reported structural requirements for good oral activity.[5,6] These dually active compounds may be more useful than a protease inhibitor or LTB_4 antagonist alone for the treatment of inflammatory diseases, because both protease and LTB_4 are considered to play an important role in inflammatory diseases. Further structural modification studies of these protease inhibitors with the goal of maximization of the LTB_4 receptor antagonistic activity are currently underway.

Experimental

Chemistry

General directions. All ^1H and ^{13}C NMR spectra were obtained using a JEOL FX-90Q or Varian VXR-200s or 500s spectrometer. Mass spectra were obtained on a

Table 4. Inhibition of [^{3}H]LTB_4 binding to human PMN by the miscellaneous compounds **38–48**

Compd	IC_{50} (nM)[a]	Compd	IC_{50} (nM)[a]
38	65.0±9.8 (65.3%)	**44b**	(4.3%)[b]
39	119.2±20.7 (83.6%)	**44c**	99.1±4.9 (92.0%)[b]
40a	(81.0%)[b]	**44d**	30.6±5.2 (103.2%)[b]
40b	76.5±17.4 (89.6%)[b]	**45a**[10]	(−6.0%)[b]
41a	50.4±20.3	**45b**[10]	(1.4%)[b]
41b	54.1±12.6	**45c**[10]	(−6.0%)[b]
42	275.2±43.8 (78%)	**46**	>10,000
43a	289.1±68.3	**47a**	>10,000
43b	22.0±6.4	**47b**	>10,000
44a	(3.2%)[b]	**48**	(−8.5%)[b]

[a]IC_{50} values are the mean ± SEM of three separate experiments.
[b]Percentage of inhibition at 1 mM.

JEOL JMS-DX-303HF spectrometer. IR spectra were measured on a Perkin–Elmer FT-IR 1760X. Melting points were uncorrected. Column chromatography was carried out on silica gel (E. Merck; particle size 0.063–0.02 mm). Thin layer chromatography was performed on silica gel (Merck Art. No. 5715). All solvents were distilled before use.

General procedure A: preparation of diethyl 2-allyl-2-[4-(4-amidinophenoxycarbonyl)-α-methylcinnamamido]-malonate acetate (29). This procedure illustrates the general method for the preparation of **26** and **28**. To a solution of diethyl 2-(*t*-butoxycarbonyl)aminomalonate **51** (4.0 g, 15 mmol) in DMF (30 mL) were added NaH (582 mg, 15 mmol) and allyl bromide (1.51 mL) at 0 °C, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with cold water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel (9% EtOAc/hexane) gave 4.50 g (98%) of **52c**: R_f 0.53 (20% EtOAc/hexane); MS (EI, *m/e*) 315 (M^+); ^1H NMR (90 MHz, $CDCl_3$) d 5.80 (1H, m), 5.45 (1H, m), 5.10 (2H, m), 4.20 (4H, q, J = 8.0 Hz), 3.00 (2H, d, J = 8.0 Hz), 1.40 (9H, s), 1.20 (6H, t, J = 8.0 Hz). A mixture of **52c** (4.50 g, 14 mmol) and 4N-HCl in EtOAc (29 mL) was stirred at 25 °C for 1 h and the reaction mixture was concentrated. Purification by column chromatography on silica gel (5% MeOH/CH_2Cl_2) gave 3.11 g (87%) of **53c**: R_f 0.32 (33% EtOAc/hexane) ; MS (EI, *m/e*) 174 (M^+-41); ^1H NMR (90 MHz, $CDCl_3$) d 6.00 (1H, m), 5.30 (2H, m), 4.30 (4H, q, J = 8.0 Hz), 3.10 (2H, d, J = 8.0 Hz), 1.30 (6H, t, J = 8.0 Hz). A mixture of thionyl chloride (20 mL) and **57** (2.24 g, 7.57 mmol) were refluxed for 1 h. Thionyl chloride was removed azeotropically with benzene. A solution of the obtained residue in CH_2Cl_2 (10 mL) was added to a stirred mixture of **53c** (1.90 g, 7.57 mmol) and pyridine (1.84 mL, 22.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring at 25 °C for 1 h, the reaction mixture was poured into 1 N HCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$, and brine, dried over $MgSO_4$ and concentrated to give 3.54 g (95%) of the crude product **58c**: R_f 0.50 (33% EtOAc/hexane) ; MS (EI, *m/e*) 493 (M^+), 448, 420; ^1H NMR (200 MHz, $CDCl_3$) d 8.05 (2H, d, J = 8.0 Hz), 7.50–7.30 (8H, m), 5.60 (1H, m), 5.40 (2H, s), 5.15 (2H, m), 4.30 (4H, q, J = 7.0 Hz), 3.20 (2H, d, J = 7.0 Hz), 2.10 (3H, brs), 1.30 (6H, t, J = 7.0 Hz). The mixture of **58c** (3.54 g, 7.18 mmol), CH_3SO_3H (15 mL) and anisole (30 mL) was stirred at 25 °C for 1.5 h. To the reaction mixture was added cold water, and the mixture was then extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica gel (1% MeOH/$CHCl_3$) gave 2.16 g (75%) of **59c**: R_f 0.30 (hexane/EtOAc/AcOH = 12/4/1); MS (EI, *m/e*) 403 (M^+); ^1H NMR (200 MHz, $CDCl_3$) d 8.10 (2H, d, J = 8.0 Hz), 7.45 (3H, m), 5.60 (1H, m), 5.15 (2H, m), 4.30 (4H, q, J = 7.0 Hz), 3.20 (2H, d, J = 7.0 Hz), 2.15 (3H, brs), 1.30 (6H, t, J = 7.0 Hz). A mixture of 4-amidinophenol hydrochloride (925 mg, 5.36 mmol), **59c** (2.16 g, 5.36 mmol) and DCC (1.66 g, 8.04 mmol) in pyridine (20 mL) was stirred at 25 °C overnight. The resulting urea was removed by filtration and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel ($CHCl_3$/MeOH/AcOH = 20/2/1) gave 1.65 g (53%) of **29** as a white powder: R_f 0.50 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (EI, *m/e*) 504 (M^+-17); IR (KBr) 3418, 3079, 2983, 1741, 1686, 1607, 1568, 1489, 1412, 1370, 1309, 1267, 1217, 1177, 1065, 1014 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.20 (2H, d, J = 8.5 Hz), 7.90 (2H, d, J = 11.5 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.55 (2H, d, J = 11.5 Hz), 7.35 (1H, br.s), 5.70 (1H, m), 5.15 (2H, m), 4.25 (4H, q, J = 7.0 Hz), 3.10 (2H, d, J = 7.0 Hz), 2.15 (3H, s), 1.95 (3H, s), 1.25 (6H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 170.62, 168.82, 167.89, 165.50, 156.82, 143.08, 135.15, 134.40, 132.64, 131.34, 130.90, 130.74, 129.45, 127.32, 124.08, 120.44, 63.78, 38.30, 14.53, 14.35.

General procedure B: preparation of *N*-[4-(4-amidinophenoxycarbonyl)-α-methylcinnamoyl]-3-[3-ethoxycarbonyl-2-(*E*)-allylthio]-L-alanine ethyl ester methanesulfonate (25). This procedure illustrates the general method for the preparation of **27**. To a solution of **49** (4.8 g, 22 mmol) in CH_3CN (50 mL) was added sodium hydride (0.98 g, 24 mmol) at 0 °C. After stirring for 0.5 h at 0 °C, ethyl-4-bromocrotonate (75% purity, 4.1 mL, 22 mmol) was added to the resulting solution at −30 °C. After stirring for an additional 0.5 h at 25 °C, the reaction mixture was poured into ice cold water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (33% EtOAc/hexane) to give 4.5 g (55%) of *N*-*t*-butoxycarbonyl-*S*-(3-ethoxycarbonyl-2-propenyl) cysteine ethyl ester: R_f 0.32 (33% EtOAc/hexane). To a solution of *N*-*t*-butoxycarbonyl-*S*-(3-ethoxycarbonyl-2-propenyl) cysteine ethyl ester (4.5 g, 12 mmol) in AcOEt (10 mL) was added 4 N HCl in AcOEt (20 mL) at 0 °C. After 1h at 25 °C, the resulting solution was evaporated, and the residue was filtrated and washed with Et_2O to yield 2.5 g (68%) of **50**: R_f 0.13 (33% EtOAc/hexane). To a solution of **60** (2.5 g, 8.5 mmol) and **50** (2.2 g, 8.5 mmol) in pyridine was added EDC.HCl (2.8 g, 15 mmol) at 0 °C. After 2 h at 25 °C, the reaction mixture was concentrated, diluted with AcOEt, washed with 1N HCl, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (30% EtOAc/hexane) to yield 3.7 g (87%) of **61a**: R_f 0.40 (33% EtOAc/hexane). To a solution of **61a** (3.7 g, 7.5 mmol) in CH_2Cl_2 (10 mL) was added TFA (20 mL) at 0 °C. After 3.5 h at 25 °C, the reaction mixture was evaporated, and the resulting precipitate was collected by filtration and washed with Et_2O to give 2.3 g (68%) of **62a**: R_f 0.35 (EtOAc). To a solution of **62a** (2.3 g, 5.1 mmol) and 4-amidinophenol hydrochloride (0.9 g, 5.1 mmol) in pyridine (20 mL) was added DCC (2.0 g, 10 mmol) at 25 °C. After 15h, the resulting urea was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 20/2/1) to give 2.2 g (68%) of **25** as a white powder: R_f 0.69 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 568 (M^++1); IR (KBr) 3366, 1738, 1649, 1607, 1535, 1490, 1415, 1370, 1318, 1270, 1207, 1061, 1045, 1015, 885, 771,

689 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) d 8.22 (2H, d, J = 9.0 Hz), 7.92 (2H, d, J = 9.0 Hz), 7.60 (2H, d, J = 9.0 Hz), 7.52 (2H, d, J = 9.0 Hz), 7.37 (1H, s), 6.88 (1H, ddd, J = 15.0, 7.5, 7.5 Hz), 5.98 (1H, d, J = 15.0 Hz), 4.66 (1H, dd, J = 9.0, 5.0 Hz), 4.22 (2H, q, J = 7.0 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.36 (2H, d, J = 7.5 Hz), 3.08 (1H, dd, J = 14.0, 5.0 Hz), 2.88 (1H, dd, J = 14.0, 9.0 Hz), 2.15 (3H, d, J = 2.0 Hz), 1.31 (3H, t, J = 7.0 Hz), 1.27 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 172.15, 172.02, 167.70, 167.53, 165.40, 156.75, 144.72, 1143.28, 135.70, 133.86, 131.25, 130.77, 130.68, 129.21, 127.12, 124.12, 124.01, 62.76, 61.60, 53.82, 39.43, 33.33, 33.03, 14.76, 14.56, 14.51.

Diethyl-2-[4-(4-amidinophenoxycarbonyl)-α-methylcinnamamido]-2-[(*E*)-3-ethoxycarbonylallyl]malonate hydrochloride (27). R_f 0.48 ($CHCl_3$/MeOH/AcOH = 15/2/1); MS (EI) 576 (M-NH_3), 503, 474, 458, 429; IR (KBr) 3363, 2984, 1741, 1674, 1606, 1488, 1412, 1369, 1267, 1216, 1177, 1096, 1066, 1014, 858, 766, 712, 541 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.24 (2H, d, J = 8.5 Hz), 7.95 (2H, d, J = 8.5 Hz), 7.62 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 8.0 Hz), 7.35 (1H, s), 6.85 (1H, dt, J = 7.5, 15.0Hz), 5.93 (1H, d, J = 15.0 Hz), 4.28 (4H, q, J = 7.5 Hz), 4.18 (2H, d, J = 7.5 Hz), 3.23 (2H, d, J = 7.5 Hz), 2.14 (3H, s), 1.26 (6H, t, J = 7.5 Hz), 1.23 (3H, t, J = 7.5 Hz); ^{13}C NMR (50 MHz, CD_3OD) 170.79, 168.24, 167.60, 167.21, 165.26, 156.69, 142.90, 142.76, 134.98, 134.41, 131.24 (2C), 130.79 (2C), 130.63 (2C), 129.31, 127.01, 126.55, 123.96 (2C), 117.06, 67.26, 63.95 (2C), 61.59, 36.72, 14.65, 14.58, 14.40 (2C).

Preparation of 4-(4-amidinophenoxycarbonyl)styrylphosphonic acid diethyl ester acetate (30). To a solution of diethyl methyl phosphonate (14 g, 97 mmol) in THF (100 mL) was added 1.4M *n*-BuLi in hexane (60 mL) at −78 °C. After 0.5 h, the resulting solution was added dropwise to a solution of *p*-methoxybenzyl 4-formylbenzoate (24 g, 88 mmol) in THF (50 mL) at −78 °C. After 0.5 h, the reaction mixture was poured into ice cold water and extracted with EtOAc. The organic layer was washed with 1N HCl, saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (hexane/AcOEt = 1/2) to give 25 g (67%) of diethyl 2-hydroxy-2-(4-methoxybenzyloxycarbonyl)phenethyl phosponate: R_f 0.31 (EtOAc). To a solution of diethyl 2-hydroxy-2-(4-methoxybenzyloxycarbonyl)phenethyl phosponate (25 g, 59 mmol) and Et_3N (33 mL, 238 mmol) in CH_2Cl_2 (200 mL) was added methanesulfonyl chloride (6.9 mL, 89 mmol) at −20 °C. After 13 h at 25 °C, the reaction mixture was poured into ice cold water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (hexane/AcOEt = 1/1) to give 19 g (82%) of **63**: R_f 0.50 (EtOAc). To a solution of **63** (19 g, 49 mmol) in anisole (25 mL) was added trifluoroacetic acid (50 mL) at 0 °C. After 1.5 h at 25 °C, the resulting solution was evaporated, and the residue was solidified with Et_2O to give 8.8 g (63%) of **64**: R_f 0.33 (EtOAc). To a solution of **64** (1.7 g, 5.2 mmol) and 4-amidinophenol hydrochloride (1.0 g, 5.2 mmol) in pyridine (20 mL) was added DCC (1.6 g, 8 mmol) at 25 °C. After 17 h, the resulting urea was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 20/2/1) to give 2.2 g (95%) of **30**: R_f 0.60 ($CHCl_3$/MeOH/AcOH = 10/2/1); IR (KBr) 3209, 2990, 1749, 1678, 1609, 1571, 1490, 1414, 1263, 1227, 1176, 1061, 1016 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.22 (2H, d, J = 9.0 Hz), 7.93 (2H, d, J = 9.0 Hz), 7.82 (2H, d, J = 9.0 Hz), 7.56 (1H, dd, J = 23.0, 18.0 Hz), 7.54 (2H, d, J = 9.0 Hz), 6.68 (1H, t, J = 18.0 Hz), 4.15 (4H, q, J = 7.0Hz), 1.36 (6H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 167.69, 165.13, 156.59, 148.43, 141.46, 141.27, 131.73, 131.37, 131.03, 130.65, 129.23, 127.27, 123.94, 119.03, 117.51, 63.66, 16.70.

Preparation of *p*-amidinophenyl-*p*-[ethoxy(3-phenylpropyl)phosphinoyl]methylbenzoate acetate (31). A mixture of allylbenzene (23.6 g, 0.20 mol), sodium hypophosphite (63.6 g, 0.60 mol), AIBN (3.2 g, 0.019 mol) and conc. H_2SO_4 (16 mL) in ethanol (500 mL) was stirred at 100 °C for 3 days. The reaction mixture was evaporated, and 50% NaOH in water (250 mL) was poured into the residue. The aqueous layer was washed with ether (100 mL) and conc. HCl was added to the aqueous layer (pH 1.0). The mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo to give 35.8 g (97%) of 3-phenylpropylphosphinic acid: R_f 0.71 (*iso*-PrOH/aq NH_4OH/H_2O = 7/2/3); MS (EI, *m/e*) 184 (M^+); ^1H NMR (200 MHz, $CDCl_3$) 7.35–7.10 (5H, m), 2.70 (2H, t, J = 7.0 Hz), 2.00–1.65 (4H, m). A mixture of 3-phenylpropylphosphinic acid (35.8 g, 0.19 mol), ethanol (23 mL), DCC (48 g, 0.23 mol) and DMAP (4.8 g, 0.039 mol) in THF (400 mL) was stirred at 25 °C overnight. The reaction mixture was filtrated and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc) to give 29.1 g (70.5%) of **66**: MS (EI, *m/e*) 212 (M^+); ^1H NMR (200 MHz, $CDCl_3$) 7.30–7.10 (5H, m), 4.10 (2H, m), 2.75 (2H, t, J = 7.0 Hz), 2.00–1.60 (4H, m), 1.35 (3H, t, J = 7.0 Hz). To a solution of **66** (1.2 g, 5.7 mmol) and Et_3N (2.4 mL, 17 mmol) in $CHCl_3$ (30 mL) was added a solution of benzyl 4-bromomethylbenzoate (1.75 g, 5.7 mmol) and trimethylsilylchloride in $CHCl_3$ (10 mL) and the mixture was stirred at 25 °C for 1.5 day. Cold water was added to the reaction mixture and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (25% CH_2Cl_2/EtOAc) to give 900 mg (36%) of **67**: R_f 0.41 (EtOAc); MS (EI, *m/e*) 436 (M^+), 330; ^1H NMR (200 MHz, $CDCl_3$) 8.00 (2H, d, J = 8.0 Hz), 7.50–7.10 (12H, m), 5.40 (2H, s), 4.00 (2H, m), 3.15 (2H, d, J = 16.0 Hz), 2.65 (2H, t, J = 7.0 Hz), 1.90 (2H, m), 1.60 (2H, m), 1.25 (3H, t, J = 7.0 Hz). A mixture of **67** (900 mg, 2.1 mmol) and 10% Pd–C (180 mg) in EtOH (10 mL) was stirred vigorously under an atmosphere of H_2 at 25 °C for 2 h. The reaction mixture was filtrated through celite545 and concentrated to give

815 mg (100%) of **68**: R_f 0.39 (10% MeOH/$CHCl_3$); MS (EI, *m/e*) 346 (M^+); ^1H NMR (200 MHz, $CDCl_3$) 8.00 (2H, d, J = 8.0 Hz), 7.35–7.10 (7H, m), 4.00 (2H, m), 3.20 (2H, d, J = 16.0 Hz), 2.70 (2H, t, J = 7.0 Hz), 2.00–1.60 (4H, m), 1.25 (3H, t, J = 7.0 Hz). A solution of **68** (815 mg, 2.1 mmol), 4-amidinophenol hydrochloride (360 mg, 2.1 mmol) and DCC (640 mg, 3.1 mmol) in pyridine (10 mL) was stirred at 25 °C overnight. The reaction mixture was filtrated and the filtrate was concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 20/2/1) to give 805 mg (65%) of **31** as a white powder: R_f 0.62 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 465 (M+1), 329, 137; IR (KBr) 3059, 1741, 1685, 1608, 1572, 1542, 1489, 1454, 1418, 1266, 1216, 1176, 1065, 1034, 1018 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.10 (2H, d, J = 8.0 Hz), 7.95 (2H, d, J = 9.0 Hz), 7.55 (2H, d, J = 9.0 Hz), 7.60–7.40 (2H, m), 7.30–7.10 (3H, m), 7.20 (2H, d, J = 8.0 Hz), 4.00 (2H, m), 3.40 (2H, d, J = 24.0 Hz), 2.70 (2H, t, J = 6.5 Hz), 2.00–1.60 (4H, m), 1.30 (3H, t, J = 7.5 Hz); ^{13}C NMR (50 MHz, CD_3OD) 167.75, 165.51, 156.75, 142.17, 140.22, 140.16, 131.42, 131.06, 130.65, 129.55, 129.43, 128.62, 127.12, 124.01, 117.13, 62.39, 37.38, 37.25, 36.65 (d, J = 41.7 Hz), 27.51 (d, J = 46.5 Hz), 24.65, 16.90.

General procedure C: preparation of *N*-[4-(4-amidinophenoxycarbonyl)benzyl]-*N*-benzylglycine ethyl ester dihydrochloride (35). This procedure illustrates the general method for the preparation of **32**, **34a**, **34b** and **36**. A mixture of **69d** (2.26 g, 5.4 mmol), methanesulfonic acid (10.5 mL) and anisole (25 mL) was stirred at 25 °C for 1h. To the reaction mixture were added cold water and Na_2CO_3 (8.6 g), and the mixture was extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (2% MeOH/$CHCl_3$), followed by treating with 4 N HCl in dioxane (10 mL) to give 1.76 g (89%) of **70d**: MS (EI, *m/e*) 327 (M^+), 254; ^1H NMR (200 MHz, $CDCl_3$) 8.05 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 8.0 Hz), 7.40–7.20 (5H, m), 4.20 (2H, q, J = 7.0 Hz), 3.90 (2H, s), 3.80 (2H, s), 3.30 (2H, s), 1.25 (3H, t, J = 7.0 Hz). A mixture of **70d** (1.76 g, 4.84 mmol), 4-amidinophenol hydrochloride (0.84 g, 4.8 mmol) and DCC (1.5 g, 7.3 mmol) in pyridine (20 mL) was stirred at 25 °C overnight. The reaction mixture was filtrated and concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 20/2/1) to give 1.33 g (53%) of **35** as a white powder; R_f 0.42 ($CHCl_3$/MeOH/AcOH = 10/2/1): MS (EI/*m/e*) 428 (M^+-17), 355, 310, 253, 235, 192, 91; IR (KBr) 3361, 2987, 1749, 1733, 1684, 1668, 1609, 1562, 1490, 1416, 1373, 1302, 1266, 1220, 1194, 1174, 1125, 1072, 1031, 1019 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.25 (2H, d, J = 8.0 Hz), 7.90 (2H, d, J = 8.0 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.0 Hz), 7.40–7.20 (5H, m), 4.15 (2H, q, J = 7 Hz), 3.90 (2H, s), 3.80 (2H, s), 3.30 (2H, s), 1.25 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 172.65, 167.73, 165.69, 156.81, 147.67, 139.82, 131.24, 130.51, 130.25, 130.01, 129.34, 128.91, 128.34, 127.06, 124.02, 117.13, 61.46, 59.01, 58.58, 54.74, 14.61.

***p*-Amidinophenyl-*p*-(4-phenylpiperidinomethyl)benzoate dihydrochloride (32).** R_f 0.33 ($CHCl_3$/MeOH/AcOH = 5/1/1); MS (FAB, *m/e*) 414 (M^++1); IR(KBr) 3382, 2714, 1743, 1677, 1607, 1483, 1267, 1218, 1176, 1069, 1019 cm^{-1}; ^1H NMR (200 MHz, CD_3OD)8.32 (2H, d, J = 8.0 Hz), 7.95 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 8.8 Hz), 7.28 (5H, m), 4.52 (2H, s), 3.62 (2H, br), 3.25 (2H, br), 2.94 (1H, m), 2.12 (4H, m); ^{13}C NMR (50 MHz, CD_3OD) 167.57, 165.03, 156.52, 144.74, 136.41, 133.05, 131.80, 131.59, 130.70, 129.66, 127.91, 127.62, 127.13, 123.91, 60.98, 54.18, 40.78, 31.57.

***p*-Amidinophenyl-*p*-[(2-methyl-1-imidazolyl)methyl]-benzoate dihydrochloride (34a).** R_f 0.23 (EtOAc/AcOH/H_2O = 3/1/1); MS (EI, *m/e*) 334 (M^+), 317, 215, 199, 171, 135; IR (KBr) 3397, 1739, 1678, 1609, 1528, 1484, 1419, 1267, 1217, 1178, 1072, 1017 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.25 (2H, d, J = 8.0 Hz), 7.95 (2H, d, J = 8.0 Hz), 7.60 (1H, d, J = 2.0 Hz), 7.55 (4H, d, J = 8.0 Hz), 7.52 (1H, d, J = 2.0 Hz), 5.58 (2H, s), 2.67 (3H, s); ^{13}C NMR (50 MHz, CD_3OD) 167.57, 165.04, 156.56, 146.25, 141.41, 132.04 (2C), 130.68 (2C), 130.54, 129.18 (2C), 127.10, 123.92 (2C), 123.69, 119.58, 51.52, 10.96.

***p*-Amidinophenyl-*p*-[(2-phenyl-1-imidazolyl)methyl]-benzoate dimesylate (34b).** R_f 0.30 ($CHCl_3$/MeOH/AcOH = 50/10/1); MS (FAB, *m/e*) 397 (M^++1); IR (KBr) 3367, 1742, 1684, 1610, 1484, 1421, 1268, 1206, 1191, 1060, 1016 cm^{-1}; ^1H NMR (200MHz, CD_3OD) 8.20 (2H, d, J = 8.0 Hz), 7.95 (2H, d, J = 8.0 Hz), 7.81 (1H, d, J = 2.0 Hz), 7.79 (1H, d, J = 2.0 Hz), 7.69 (5H, brs), 7.55 (2H, d, J = 8.5 Hz), 7.39 (2H, d, J = 8.5 Hz), 5.63 (2H, s), 2.72 (6H, s); ^{13}C NMR (50 MHz, CD_3OD) 167.58, 165.00, 156.53, 146.93, 141.77, 133.78, 131.92 (2C), 130.77 (2C), 130.68 (2C), 130.54, 130.45, 128.90 (2C), 127.17, 125.06, 125.04, 123.91 (2C), 123.55, 121.00, 52.43, 39,49 (2C, CH_3SO_3H).

Ethyl-1-[*p*-(*p*-amidinophenoxycarbonyl)benzyl]-2-indolecarboxylate mesylate (36). R_f 0.48 ($CHCl_3$/MeOH/AcOH = 10/1/1); MS (EI, *m/e*) 441 (M^+), 322; IR (KBr) 3393, 1733, 1685, 1609, 1523, 1485, 1269, 1206, 1176, 1063 cm^{-1}; ^1H NMR (200MHz, CD_3OD+$CDCl_3$) 8.05 (2H, d, J = 8.4 Hz), 7.89 (2H, d, J = 8.8 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.46 (2H, d, J = 8.8 Hz), 7.40 (1H, s), 7.37–7.30 (2H, m), 7.17 (1H, d, J = 8.0 Hz), 7.16 (2H, d, J = 8.4 Hz), 5.95 (2H, s), 4.30 (2H, q, J = 7.4 Hz), 2.73 (3H, s), 1.33 (3H, t, J = 7.4Hz); ^{13}C NMR (50 MHz, CD_3OD+$CDCl_3$) 167.44, 165.37, 163.09, 156.57, 146.69, 140.69, 131.35, 130.48, 128.61, 127.54, 127.39, 126.82, 126.49, 123.85, 123.60, 122.03, 112.24, 111.56, 61.68, 39.75, 14.61.

Preparation of *p*-amidinophenyl-*p*-[3-(4-benzylpiperazino)-1-methyl-3-oxo-1-(*E*)-propenyl]benzoate dihydrochloride (33). A mixture of **71** (4.0 g, 0.014 mol) and oxalyl chloride (5.8 mL) in CH_2Cl_2 (10 mL) was stirred at 25 °C for 30 min, and the reaction mixture was evaporated. A solution of the residue in CH_2Cl_2 (10 mL) was added to the solution of *N*-benzylpiperazine (2.4 mL, 0.014 mol) in pyridine (40 mL) at 0 °C, and the mixture was stirred at the same temperature for 2 h.

Cold water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (33% EtOAc/hexane) to give 5.3 g (86%) of **72a** as a yellow oil: R_f 0.30. A solution of **72a** (5.3 g, 0.012mmol) and methanesulfonic acid (23 mL) in anisole (50 mL) was stirred at 25 °C for 5 h. To the reaction mixture were added cold water and 5 M NaOH (90 mL) and the aqueous layer was washed with EtOAc. To the aqueous layer was added 2 M HCl (50 mL) and the mixture was extracted with 10% MeOH/$CHCl_3$. The organic layer was washed with brine and dried through the pad of $MgSO_4$. To the filtrate was added 4 M HCl in dioxane (10 mL), and the mixture was concentrated to give 2.8 g (59%) of **72b**: R_f 0.22. A mixture of **72b** (2.75 g, 6.87 mmol), 4-amidinophenol (1.18 g, 6.87 mmol) and DCC (2.13 g, 13.8 mmol) in pyridine (20 mL) was stirred at 25 °C overnight. The reaction mixture was filtrated and the filtrate was evaporated. The residue was purified by silica gel chromatography (10% MeOH/CHCl) followed by treating with 4 M HCl in dioxane to give **33** as a white powder: R_f 0.31 (20% MeOH/$CHCl_3$); MS(FAB, *m/e*) 483 (M^++1); IR(KBr) 3387, 2586, 1748, 1678, 1607, 1485, 1412, 1303, 1264, 1245, 1182, 1083, 1018 cm^{-1}; ^1H NMR(200MHz, CD_3OD) 8.20 (2H, d, J = 8.0 Hz), 7.95 (2H, d, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 7.70–7.43 (7H,m), 6.60 (1H, d, J = 1.0 Hz), 4.80–4.60 (1H, m), 4.43 (2H, s), 4.40–4.18 (1H, m), 3.80–3.40 (3H, m), 3.40–3.05 (3H, m), 2.31 (3H, s); ^{13}C NMR(50 MHz, CD_3OD) 168.69, 167.63, 165.32, 156.70, 147.96, 147.40, 132.54 (2C), 131.45, 131.33, 130.68 (2C), 130.33 (2C), 129.91, 129.74, 127.64 (2C), 127.02, 123.98 (2C), 121.54 (2C), 61.54, 52.57, 52.24, 44.13, 39.32, 18.19.

Preparation of 2-{*N*-[*p*-(*p*-amidinophenoxycarbonyl)-benzyl]imino}-*N*-benzyl-*N*-methylglycine ethyl ester (37). To a solution of **73** (33 g, 150 mmol) in THF (200 mL) was added P_2S_5 at 25 °C. The reaction mixture was heated to reflux for 2.5 h. After cooling to 25 °C, the precipitate was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to yield 29 g (80%) of **74**: R_f 0.51 and 0.43 (33% EtOAc/hexane). To a solution of **74** (5.7 g, 24 mmol) in CH_2Cl_2 (50 mL) was added 1M $Et_3O^+BF_4^-$ in CH_2Cl_2 (72 mL) at 0 °C. After 0.5 h at 25 °C, the resulting solution was evaporated. The residue was washed with Et_2O to yield 6.0 g of crude **75**. To a solution of **75** (6.0 g) in CH_2Cl_2 (50 mL) was added dropwise a solution of *t*-butyl 4-aminomethylbenzoate (4.9 g, 24 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 0.5 h at 25 °C, the reaction mixture was poured into cold water and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (20% EtOAc/hexane) to yield 3.8 g (39%) of **76a**: R_f 0.46 (25% EtOAc/hexane). To a solution of **76a** (3.7 g, 9.1 mmol) in anisole (10 mL) was added TFA (20 mL) at 0 °C. After 2 h at 25 °C, the resulting solution was evaporated and the residue was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (25% hexane/EtOAc) to yield 1.8 g (57%) of **76b**: R_f 0.36 (33% hexane/EtOAc). To a solution of **76b** (1.8 g, 5.2 mmol) and 4-amidinophenol hydrochloride (0.9 g, 5.2 mmol) in pyridine (20 mL) was added DCC (2.0 g, 10 mmol) at 25 °C. After 24 h, the resulting urea was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$:MeOH:AcOH = 20:2:1) to give 0.9 g (38%) of **37** as a pale ivory powder: R_f 0.34 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (EI, *m/e*) 455 (M^+-17); IR (KBr) 3392, 1741, 1678, 1624, 1609, 1575, 1490, 1455, 1415, 1261, 1226, 1174, 1097, 1069, 1018 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.12 (2H, d, J = 9.0 Hz), 7.92 (2H, d, J = 9.0 Hz), 7.52 (2H, d, J = 9.0 Hz), 7.48 (2H, d, J = 9.0 Hz), 7.27–7.35 (5H, m), 4.50 (2H, s), 4.49 (2H, s), 4.36 (2H, q, J = 7.0 Hz), 2.88 (3H, s), 1.26 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 167.66, 165.71, 164.59, 157.53, 156.78, 149.30, 138.18, 131.04, 130.55, 130.19, 129.59, 128.81, 128.27, 127.00, 124.01, 63.06, 54.80, 35.22, 14.41.

General procedure D: preparation of *N*-allyl-*N*-[4-(4-amidinophenoxycarbonyl)-α-methylcinnamoyl]glycine ethyl ester acetate (39). This procedure illustrates the general method for the preparation of **38-39**. A mixture of **77c** (9.9g, 34 mmol) and 1 M NaOH (37 mL, 37 mmol) in dioxane (50 mL) was stirred at 50 °C for 2 h. To the reaction mixture was added 1 N HCl (37 mL) at 0 °C, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated to give 7.0 g (78%) of **77d**. A solution of **77d** (3.0 g, 11 mmol), *N*-allylglycine ethyl ester (1.6 g, 11 mmol) and EDC (3.3 g, 17 mmol) was stirred at 25 °C overnight. To the reaction mixture was poured cold water and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (25% EtOAc/hexane including 0.5% Et_3N) to give 2.92 g (66%) of **78b**: MS (EI, *m/e*) 387 (M^+); ^1H NMR (200 MHz, $CDCl_3$) 7.95 (2H, m), 7.40 (2H, m), 6.65 (1H, m), 5.80 (1H, m), 5.25 (2H, m), 4.20 (2H, q, J = 7.0 Hz), 4.15-4.05 (4H, m), 2.15 (3H, brs), 1.60 (9H, s), 1.25 (3H, t, J = 7.0 Hz). A solution of **78b** in CF_3CO_2H (15 mL) and CH_2Cl_2 was stirred at 25 °C for 1 h. The reaction mixture was concentrated and the residue was purified by silica gel chromatography (2% MeOH/$CHCl_3$) to give 2.69 g (100%) of **79**: MS (EI, *m/e*) 331 (M^+); ^1H NMR (200 MHz, $CDCl_3$) 8.00 (2H, m), 7.55 (2H, m), 6.70 (1H, m), 5.80 (1H, m), 5.30 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 4.20–4.00 (4H, m), 2.15 (3H, brs), 1.30 (3H, t, J = 7.0 Hz). A solution of **79** (2.7 g, 8.1 mmol), 4-amidinophenol hydrochloride (1.4 g, 8.1 mmol) and DCC (2.5 g, 12 mmol) was stirred at 25 °C overnight. The resulting urea was removed by filtration and the filtrate was concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 30/3/1) to give 3.1 g (74%) of **39** as a white powder: R_f 0.41 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (EI, *m/e*) 432

(M^+-17); IR (KBr) 3401, 1741, 1678, 1610, 1484, 1419, 1377, 1273, 1213, 1190, 1063, 1019 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.15 (2H, m), 7.95 (2H, d, J = 8.0 Hz), 7.80–7.60 (2H, m), 7.55 (2H, d, J = 8.0 Hz), 6.75 (1H, m), 5.90 (1H, m), 5.40–5.20 (2H, m), 4.30–4.10 (6H, m), 2.15 (3H, br), 1.30 (3H, m); ^{13}C NMR (50 MHz, CD_3OD) 174.50, 173.34, 172.54, 167.88, 165.63, 156.82, 138.29, 135.93, 134.86, 133.79, 131.88, 130.76, 130.54, 130.48, 130.24, 127.31, 124.10, 62.52, 62.52, 61.76, 53.81, 31.57, 27.31, 14.54, 14.50, 14.48.

***N*-Allyl-*N*-[4-(4-amidinophenoxycarbamoyl)-α-methylcinnamoyl]glycine ethyl ester methanesulfonate (38).** R_f 0.34 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 449 (M^++1); IR (KBr) 3392, 1743, 1676, 1656, 1606, 1523, 1484, 1412, 1376, 1330, 1253, 1202, 1186, 1144, 1059 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.00 (4H, m), 7.80 (2H, d, J = 8.0 Hz), 7.55 (2H, d, J = 7.0 Hz), 6.70 (1H, m), 5.90 (1H, m), 5.30 (2H, m), 4.30–4.10 (6H, m), 2.75 (3H, s), 2.15 (3H, brs), 1.30 (3H, m); ^{13}C NMR (50 MHz, CD_3OD) 176.17, 170.47, 168.44, 167.64, 145.81, 140.93, 135.59, 134.73, 134.34, 130.29, 130.03, 129.98, 129.01, 124.11, 121.70, 121.63, 118.75, 62.36, 54.08, 47.76, 39.46, 16.25, 14.48.

General procedure E: preparation of *N*-{4-[2-(4-amidinophenoxycarbonyl)-1-(*E*)-propenyl]benzoyl}-L-glutamic acid diethyl ester hydrochloride (40b). This procedure illustrates the general method for the preparation of **40a**, **41a** and **41b**. A mixture of **80a** (2.0 g, 7.6 mmol), L-glutamic acid diethylester hydrochloride (1.8 g, 7.6 mmol) and EDC (2.2 g, 11 mmol) in pyridine (15 mL) was stirred at 25 °C overnight. To the reaction mixture was added cold water and the mixture was extracted with EtOAc. The organic layer was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (2% CH_2Cl_2/EtOAc containing 0.5% Et_3N) to give 2.7 g (78%) of **81b** *t*-butyl ester: R_f 0.36 (33% EtOAc/hexane); MS (EI, *m/e*) 447 (M^+), 402; ^1H NMR (200 MHz, $CDCl_3$) 7.80 (2H, d, J = 9.0 Hz), 7.60 (1H, brs), 7.45 (2H, d, J = 9.0 Hz), 7.05 (1H, d, J = 7.0 Hz), 4.80 (1H, m), 4.25 (2H, q, J = 7.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 2.55–2.10 (4H, m), 2.05 (3H, d, J = 1.0 Hz), 1.60 (9H, s), 1.30 (3H, t, J = 7.0 Hz), 1.20 (3H, t, J = 7.0 Hz). A solution of **81b** *t*-butyl ester (2.7 g, 5.9 mmol) in CF_3CO_2H (20 mL) and anisole (10 mL) was stirred at 25 °C for 2 h and concentrated. The resulting solid was washed with diisopropyl ether to give 2.10 g (91%) of **81b**: MS (EI, *m/e*) 377 (M^+), 332; ^1H NMR (200 MHz, $CDCl_3$)7.85 (2H, d, J = 9.0 Hz), 7.80 (1H, brs), 7.50 (2H, d, J = 9.0 Hz), 7.15 (1H, d, J = 7.0 Hz), 4.80 (1H, m), 4.25 (2H, q, J = 7.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 2.60-2.20 (4H, m), 2.15 (3H, d, J = 1.0 Hz), 1.35 (3H, t, J = 7.0 Hz), 1.25 (3H, t, J = 7.0 Hz). A mixture of **81b** (2.1 g, 5.4 mmol), 4-amidinophenol hydrochloride (930 mg, 5.4 mmol) and DCC (1.7 g, 8.1 mmol) in pyridine (25 mL) was stirred at 25 °C overnight. The resulting urea was removed by filtration and the filtrate was concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 30/3/1) to give 2.0 g (67%) of **40b** as a white powder: R_f 0.46 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 510 (M^++1), 171, 137; IR (KBr) 3266, 1733, 1678, 1640, 1608, 1541, 1488, 1447, 1411, 1376, 1299, 1213, 1176, 1083, 1017 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.00–7.90 (5H, m), 7.65 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.0 Hz), 4.65 (1H, dd, J = 4.5, 4.5 Hz), 4.20 (2H, q, J = 6.5 Hz), 4.15 (2H, q, J = 6.5 Hz), 2.50 (2H, t, J = 7.5 Hz), 2.30 (1H, m), 2.25 (3H, m), 2.10 (1H, m), 1.30 (3H, t, J = 6.5 Hz), 1.25 (3H, t, J = 6.5 Hz); ^{13}C NMR (50 MHz, CD_3OD) 174.33, 173.07, 169.52, 167.69, 167.40, 156.97, 141.26, 141.23, 140.01, 135.12, 130.90, 130.65, 130.59, 130.05, 128.73, 126.92, 123.97, 117.07, 62.50, 61.73, 53.88, 31.59, 27.36, 14.52.

***N*-Allyl-*N*-{4-[2-(4-amidinophenoxycarbonyl)-1-(*E*)-propenyl]benzoyl}glycine ethyl ester acetate (40a).** R_f 0.49 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 450 (M^++1); IR (KBr) 3401, 1730, 1678, 1610, 1561, 1466, 1412, 1296, 1213, 1178, 1085, 1003 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 7.98 (1H, s), 7.90 (2H, d, J = 9.0 Hz), 7.58 (4H, m), 7.48 (2H, d, J = 9.0 Hz), 5.78–5.96 (1H, m), 5.23–5.32 (2H, m), 4.22 (2H, q, J = 7.0 Hz), 4.20 (2H, s), 3.98–4.03 (2H, m), 2.24 (3H, s), 1.30 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 174.00, 170.51, 167.89, 167.59, 157.07, 141.30, 138.72, 136.79, 134.13, 131.12, 130.66, 129.94, 128.10, 127.14, 124.05, 118.74, 62.43, 54.43, 48.20, 23.75, 14.42.

***N*-Allyl-*N*-{4-[(*E*)-2-(4-amidinophenoxycarbonyl)-1-methylvinyl]benzoyl}glycine ethyl ester acetate (41a).** R_f 0.50 ($CHCl_3$/MeOH/AcOH = 10/1/1); MS (EI, *m/e*) 449 (M^+), 434; IR (KBr) 3086, 1741, 1670, 1647, 1607, 1489, 1462, 1408, 1376, 1349, 1266, 1213, 1122, 1001 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 7.89 (2H, d, J = 8.8 Hz), 7.73 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.44 (2H, d, J = 8.8 Hz), 6.49 (1H, s), 5.88 (1H, m), 5.35–5.20 (2H, m), 4.30–4.10 (4H, m), 4.00 (2H, m), 2.65 (3H, s), 1.93 (3H, s), 1.31 (3H, t, J = 7.2 Hz); ^{13}C NMR (50 MHz, CD_3OD) 180.00, 173.95, 170.49, 167.89, 165.34, 159.99, 156.65, 144.74, 137.57, 134.11, 130.59, 128.27, 127.88, 126.97, 124.04, 118.74, 117.22, 62.43, 54.39, 48.18, 23.41, 18.36, 14.49.

***N*-{4-[(*E*)-2-(4-Amidinophenoxycarbonyl)-1-methylvinyl]benzoyl}-L-glutamic acid diethyl ester methanesulfonate (41b).** R_f 0.50 ($CHCl_3$/MeOH/AcOH = 10/1/1); MS (FAB, *m/e*) 510 (M^++1); IR (KBr) 3289, 1737, 1685, 1640, 1607, 1585, 1210, 1122, 1045, 1017, 1000 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) 7.94 (2H, d, J = 8.0 Hz), 7.89 (2H, d, J = 8.5 Hz), 7.72 (2H, d, J = 8.5 Hz), 7.44 (2H, d, J = 8.0 Hz), 6.49 (1H, s), 4.64 (1H, m), 4.23 (2H, q, J = 7.5 Hz), 4.14 (2H, q, J = 7.0 Hz), 2.74 (3H, s), 2.66 (3H, s), 2.52 (2H, t, J = 7.0 Hz), 2.32 (2H, m), 2.14 (2H, m), 1.30 (3H, t, J = 7.0 Hz), 1.25 (3H, t, J = 7.5 Hz); ^{13}C NMR (50 MHz, CD_3OD) 174.36, 173.06, 169.38, 167.50, 165.11, 159.90, 156.44, 145.93, 135.75, 130.44, 128.86, 127.59, 126.54, 123.85, 117.28, 62.44, 61.67, 53.74, 39.52, 31.50, 27.22, 18.44, 14.45.

Preparation of *N*-allyl-*N*-[4-(4-amidino-2-ethoxycarbonylphenoxycarbonyl)-α-methylcinnamoyl]glycine ethyl ester hydrochloride (42). A mixture of **82** (2.0 g, 8.0

mmol), **47b** (2.3 g, 8.0 mmol) and DCC (2.0 g, 9.6 mmol) in pyridine (16 mL) was stirred at 25 °C overnight. The resulting urea was removed by filtration and the filtrate was concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 30/2/1), followed by treating with 4 N HCl in dioxane (3 mL) to give 2.4 g (54%) of **42** as a white powder: R_f 0.57 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (EI, *m/e*) 521 (M^+), 504, 330, 314; IR (KBr) 3078, 1742, 1681, 1609, 1476, 1412, 1373, 1270, 1218, 1182, 1084, 1060, 1015 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$ + CD_3OD) 8.48 (1H, d, J = 2.5 Hz), 8.21 (2H, d, J = 8.0 Hz), 8.08 (1H, dd, J = 2.5, 9.0 Hz), 7.51 (1H, d, J = 9.0 Hz), 7.47 (2H, d, J = 8.0 Hz), 6.73 (1H, brs), 6.00–5.75 (1H, m) 5.40–5.20 (2H, m), 4.38–4.20 (4H, m), 4.20–4.05 (4H, m), 2.18 (3H, brs), 1.31 (3H, t, J = 7.5 Hz), 1.13 (3H, t, J = 7.5 Hz); ^{13}C NMR (50 MHz, CD_3OD) 176.05, 170.50, 167.24, 165.80, 164.89, 155.87, 142.97, 136.44, 134.35, 132.80, 131.56 (2C), 130.51 (2C), 129.83, 129.13, 127.85, 126.59 (2C), 118.77 (2C), 63.06, 62.34, 54.09, 47.79, 16.31, 14.48, 14.23.

General procedure F: preparation of *N*-allyl-*N*-{4-[4-((*E*)-2-amidinovinyl)phenoxycarbonyl]benzoyl}glycine ethyl ester acetate (43a). This procedure illustrates the general method for the preparation of **43b**. A solution of **83** (3.5 g, 13 mmol) in $SOCl_2$ (20 mL) was heated to reflux for 0.5 h. After cooling at 25 °C, the reaction mixture was concentrated and the crude acid chloride was added to a solution of ethyl *N*-allylglycinate (2.0 g, 13 mmol) in pyridine (10 mL) and CH_2Cl_2 (10 mL) at 0 °C. After 3 h at 25 °C, the reaction mixture was poured into cold water and extracted with EtOAc. The organic layer was washed with 1N HCl, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (25% EtOAc/hexane) to give 4.5 g (85%) of **84**: R_f 0.38 (33% EtOAc/hexane). To a solution of **84** (4.5 g, 11 mmol) in anisole (50 mL) was added dropwise methanesulfonic acid (23 mL, 355 mmol) at 0 °C. After 2 h at 25 °C, the reaction mixture was poured into cold water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (25% EtOAc/hexane) to give 2.6 g (77%) of **85**: R_f 0.15 (50% EtOAc/hexane). To a solution of **85** (2.6 g, 9.1 mmol) and 3-(4-hydroxyphenyl)-2-propenimidamide **88** (1.8 g, 9.1 mmol) in pyridine (20 mL) was added DCC (3.0 g, 15 mmol) at 25 °C. After 15 h, the resulting urea was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 20/2/1) to give 1.7 g (39%) of **43a** as a white powder: R_f 0.43 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (EI, *m/e*) 435 (M^+), 418; IR (KBr) 3372, 1741, 1685, 1646, 1509, 1466, 1418, 1376, 1265, 1206, 1169, 1073, 1003 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) 8.24 and 8.26 (2H, d, J = 9.0 Hz), 7.81 (1H, d, J = 18.0 Hz), 7.75 (2H, d, J = 9.0Hz), 7.58 and 7.66 (2H, d, J = 9.0 Hz), 7.37 (2H, d, J = 9.0 Hz), 6.73 (1H, d, J=18.0Hz), 5.77–5.96 (1H, m), 5.22–5.34 (2H, m), 4.12–4.28 (4H, m), 3.96–4.00 (2H, m), 1.20 and 1.30 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 176.49, 173.36, 170.41, 165.40, 165.16, 154.61, 144.71, 141.85, 133.90, 133.37, 132.86, 131.95, 131.48, 130.85, 128.19, 123.82, 119.07, 118.91, 115.98, 62.50, 54.32, 48.15, 14.49.

***N*-Phenyl-*N*-{4-[4-((*E*)-2-amidinovinyl)phenoxycarbonyl]benzoyl}glycine ethyl ester acetate (43b).** R_f 0.45 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 472 (M^++1), 310; IR (KBr) 3369, 1741, 1682, 1645, 1596, 1511, 1494, 1418, 1384, 1265, 1204, 1168, 1073, 1019 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) 8.00 (2H, d, J = 8.0 Hz), 7.80 (1H, d, J = 16.0 Hz), 7.75 (2H, d, J = 8.0 Hz), 7.50 (2H, d, J = 8.0 Hz), 7.35 (2H, d, J = 8.0 Hz), 7.30–7.20 (5H, m), 6.70 (1H, d, J = 16.0 Hz), 4.65 (2H, s), 4.25 (2H, q, J = 7.0 Hz), 1.30 (3H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 170.36, 165.23, 165.07, 154.55, 146.18, 144.75, 144.33, 141.99, 132.72, 131.62, 131.42, 130.77, 130.68, 130.42, 130.36, 130.00, 129.84, 129.59, 128.93, 128.85, 128.75, 128.66, 123.78, 117.16, 115.83, 62.57, 53.28, 14.51.

General procedure G: preparation of 6-amidino-7,8-dihydro-2-naphthyl-2-naphthoate methanesulfonate (44b). This procedure illustrates the general method for the preparation of **44c** and **44d**. Compound **89** (21 g, 120 mmol) was dissolved in anhydrous MeOH (600 mL), and HCl gas was introduced into the solution for 1 h at −30 °C. After 17 h at 25 °C, the resulting solution was concentrated. The residue was dissolved in anhydrous MeOH (500 mL), and NH_3 gas was introduced into the solution for 3 h at −30 °C. After 15 h at 25 °C, the resulting solution was concentrated and the resulting solid was collected by filtration and washed with Et_2O to give 28 g (100%) of **90**: R_f 0.58 ($CHCl_3$/MeOH/AcOH = 10/2/1). To a solution of **90** (14 g, 68 mmol) in CH_2Cl_2 (100 mL) was added dropwise BBr_3 (50 g, 200 mmol) at −78 °C. After 2 h at 25 °C, the resulting solution was poured into cold water and then evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 10/2/1) to give 13 g (71%) of acetic acid salt. To a solution of the acetic acid salt (13 g, 45 mmol) in MeOH (100 mL) was added methanesulfonic acid (5.0 mL, 49 mmol) at 5 °C. After 0.5 h at 25 °C, the resulting solution was evaporated, and the residue was solidified with Et_2O to give **44a** quantitatively: R_f 0.33 ($CHCl_3$/MeOH/AcOH = 10/2/1). To a solution of 2-naphthoic acid (1.0 g, 6.0 mmol) and **44a** (1.4 g, 5.0 mmol) in pyridine (10 mL) was added DCC (1.4 g, 7.0 mmol) at 25 °C. After 15 h, the resulting urea was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 20/2/1) to give 1.6 g (94%) of **44b** as a white powder: R_f 0.52 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 343 (M^++1); IR (KBr) 3349, 1735, 1665, 1629, 1574, 1509, 1429, 1330, 1267, 1212, 1154, 1130, 1090, 1076 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) 8.79 (1H, s), 8.13 (1H, dd, J = 10.0, 1.0 Hz), 8.07–7.94 (3H, m), 7.62 (2H, m), 7.48 (1H, s), 7.41 (1H, d, J = 9.0 Hz), 7.21–7.18 (2H, m), 3.02 (2H, t, J = 8.0 Hz), 2.63 (2H, t, J = 8.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 168.02, 166.35, 153.95, 139.79, 137.31, 137.08, 136.98, 133.86, 132.94, 131.30, 130.34,

129.84, 129.58, 128.85, 128.11, 127.59, 127.31, 126.05, 122.45, 121.54, 28.15, 24.07.

6-Amidino-7,8-dihydro-2-naphthyl-*p*-(*N*-benzyl-*N*-phenylcarbamoyl)benzoate mesylate (44c). R_f 0.57 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 502 (M^++1); IR (KBr) 3356, 1737, 1673, 1641, 1594, 1572, 1496, 1455, 1408, 1330, 1298, 1264, 1226, 1196, 1151, 1074, 1019 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 7.98 (2H, d, *J* = 8.0 Hz), 7.48 (2H, d, *J* = 8.0 Hz), 7.43 (1H, s), 7.38 (1H, d, *J* = 9.0 Hz), 7.30 (5H, s), 7.16–7.09 (5H, m), 7.02–6.99 (2H, m), 5.17 (2H, s), 2.98 (2H, t, *J* = 8.0 Hz), 2.60 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 171.54, 168.00, 165.29, 153.62, 143.42, 142.62, 139.74, 138.11, 136.97, 136.88, 131.18, 130.58, 130.48, 130.39, 130.21, 129.46, 128.55, 128.51, 127.39, 122.30, 121.39, 54.63, 28.09, 24.03.

Ethyl-[*p*-(6-amidino-7,8-dihydro-2-naphthyloxycarbonyl)-*N*-phenylbenzamido]acetate hydrochloride (44d). R_f 0.53 ($CHCl_3$/MeOH/AcOH = 10:2:1); MS (FAB, *m/e*) 498 (M^++1); IR (KBr) 3349, 1739, 1670, 1495, 1386, 1266, 1227, 1151, 1069, 1020 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.00 (2H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz), 7.46 (1H, s), 7.40 (1H, d, *J* = 8.0 Hz), 7.24 (5H, s), 7.12 (1H, s), 7.10 (1H, d, *J* = 8.0 Hz), 4.61 (2H, s), 4.22 (2H, q, *J* = 8.0 Hz), 3.00 (2H, t, *J* = 9.0 Hz), 2.61 (2H, t, *J* = 9.0 Hz), 1.30 (3H, t, *J* = 8.0 Hz); ^{13}C NMR (50 MHz, CD_3OD) 171.72, 170.28, 168.07, 165.31, 153.66, 144.28, 141.85, 139.78, 137.02, 136.92, 131.23, 131.14, 130.62, 130.55, 130.41 (2C), 129.85, 129.73, 128.87 (2C), 128.71 (2C), 122.33, 121.41, 62.56, 53.27, 28.10, 24.07, 14.57.

***p*-[(4-Benzhydrylpiperazino)methyl]phenyl-*p*-guanidinobenzoate acetate dihydrochloride (48).** To a solution of *p*-acetoxybenzaldehyde (3.2 g, 20 mmol) and diphenylmethylpiperazine (5.5 g, 22 mmol) in MeOH (50 mL) was added $NaBH_3CN$ (1.8 g, 30 mmol) at 0 °C. After 1 h at 25 °C, the reaction mixture was poured into cold water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel chromatography (50% EtOAc/hexane) to give 2.8 g (39%) of **91**: R_f 0.37 (33% EtOAc/hexane). To a solution of **91** (2.5 g, 6 mmol) and *p*-guanidinobenzoic acid (1.9 g, 9.0 mmol) in pyridine (10 mL) and DMF (10 mL) was added DCC (3.0 g, 15 mmol) at 25 °C. After 3 days, the resulting urea was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH = 10/2/1) to give 1.0 g (25%) of **48** as a white powder: R_f 0.51 ($CHCl_3$/MeOH/AcOH = 10/2/1); MS (FAB, *m/e*) 520 (M^++1); IR (KBr) 3446, 1733, 1673, 1637, 1604, 1572, 1513, 1453, 1268, 1206, 1171, 1077, 1018 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) 8.22 (2H, d, *J* = 9.0 Hz), 7.67 (2H, d, *J* = 9.0 Hz), 7.46 and 7.42 (6H, m), 7.32–7.13 (8H, m), 4.43 (1H, s), 4.38 (2H, s), 3.31 (4H, br), 2.73 (4H, br); ^{13}C NMR (50 MHz, CD_3OD) 165.31, 157.46, 153.42, 142.56, 141.85, 133.81, 132.87, 129.77, 128.78, 128.52, 128.20, 124.72, 123.56, 76.18, 60.52, 52.92, 49.79.

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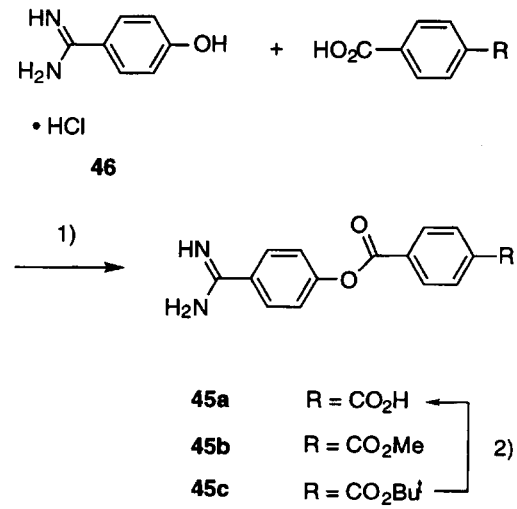

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12. All the amidine-containing protease inhibitors reported here exhibited almost the same inhibitory activities and spectrum as described in the previous reports[5,6] for **1** and **2** because they contain a common amidinophenyl function as a potency- and spectrum -determining function.

13. All of the amidine derivatives and the guanidine derivatives were isolated and evaluated as their methanesulfonates.

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