# GPIIb/IIIa Integrin Antagonists with the New Conformational Restriction Unit, Trisubstituted *β*-Amino Acid Derivatives, and a Substituted Benzamidine Structure

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*Life Science Research Center, Advanced Technology Research Laboratories, Nippon Steel Corporation, 3-35-1 Ida, Nakahara-ku, Kawasaki 211-0035, Japan, and Department of Chemistry, State University of New York at Stony Brook, New York 11794-3400*

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Ethyl *N*-[3-(2-fluoro-4-(thiazolidin-3-yl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate **40** (NSL-96184) is a highly potent and orally active fibrinogen receptor antagonist, which is characterized by the presence of the trisubstituted *β*-amino acid residue, 3-ethyl-2,2-dimethyl-*β*-alanine. This compound was developed on the basis of the SAR study of *N*-[3-(*N*-4-amidinobenzoyl)amino-2,2-dimethyl-3-phenylpropionyl]piperidine-4-acetic acid **1** (NSL-95301) with the derivatization focused on the central trisubstituted *β*-amino acid unit as well as the basic amidinobenzoyl unit, and the esterification of the carboxyl group for prodrug composition. Compound **1**, which was reported in our previous study, was discovered by the application of combinatorial chemistry. The molecular modeling study suggests that the trisubstituted *β*-amino acid unit is responsible for fixing the molecule to its active conformation. Compound **40** showed an excellent profile in the in vitro and in vivo studies for its human platelet aggregation inhibitory activity and oral availability in guinea pigs. This oral availability largely depends on the modification of the amidino group with a cyclic secondary amine, i.e., thiazolidine in **40**. In in vivo studies, the onset of the antiplatelet action of **40** is very fast after oral administration, whereas its duration of action is relatively short. These results suggest that **40** has an excellent therapeutic potential, especially for antithrombotic treatment in the acute phase. 3-Substituted-2,2-dimethyl-*β*-amino acid residues would serve as new and useful linear templates to restrict the conformational flexibility of peptidomimetics.

## Introduction

Undesired platelet aggregation and subsequent thrombosis are suspected to play an important role in various vasoocclusive diseases such as unstable angina, myocardial infarction, transient ischemic attacks and stroke.[1−3] The effective drugs to prevent such irregular platelet aggregation are in serious demand. The fibrinogen receptor, glycoprotein (GP) IIb/IIIa, has recently been one of the major targets for the development of antagonists. Since the binding of fibrinogen to GPIIb/IIIa is the final and common pathway for platelet aggregation through the cross-linking of platelets, these antagonists are likely to serve as a new class of antithrombotic agents.[4,5] In this binding process, it is known that (i) the RGD sequence(s) in fibrinogen is responsible for the recognition of GPIIb/IIIa and (ii) the guanidino group of the Arg residue and the *β*-carboxylic acid of the Asp residue in the RGD sequence are the essential functionalities in this recognition.[5−14] Therefore, most of the fibrinogen receptor antagonists have initially been designed to reproduce the three-dimensional conformation of the RGD sequence(s) in fibrinogen by adjusting the distance between these two functional groups.[15]

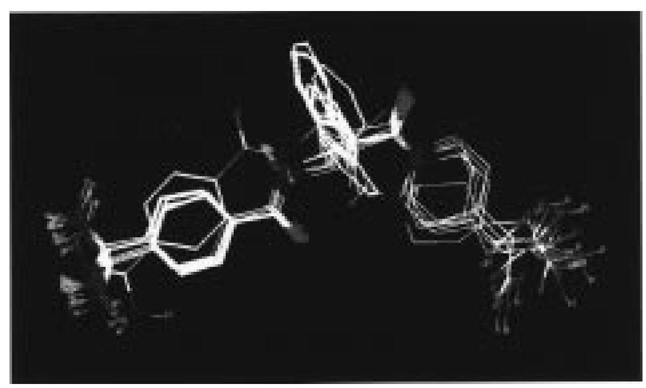

**Figure 1.** Superimpositioning study of the lower energy conformations of **1**.

Combinatorial chemistry should be an efficient tool for discovering GPIIb/IIIa antagonists,[16−18] since previous studies regarding the antagonistic effects of RGD peptides against the GPIIb/IIIa receptor provided information about the active conformation of the antagonistic molecules.[19−24] In our previous study[16] using three-component combinatorial approach, we have reported a potent non-peptide GPIIb/IIIa antagonist **1** (NSL-95301) (Figure 1), wherein the space between the basic moiety and the acidic moiety was adjusted to the

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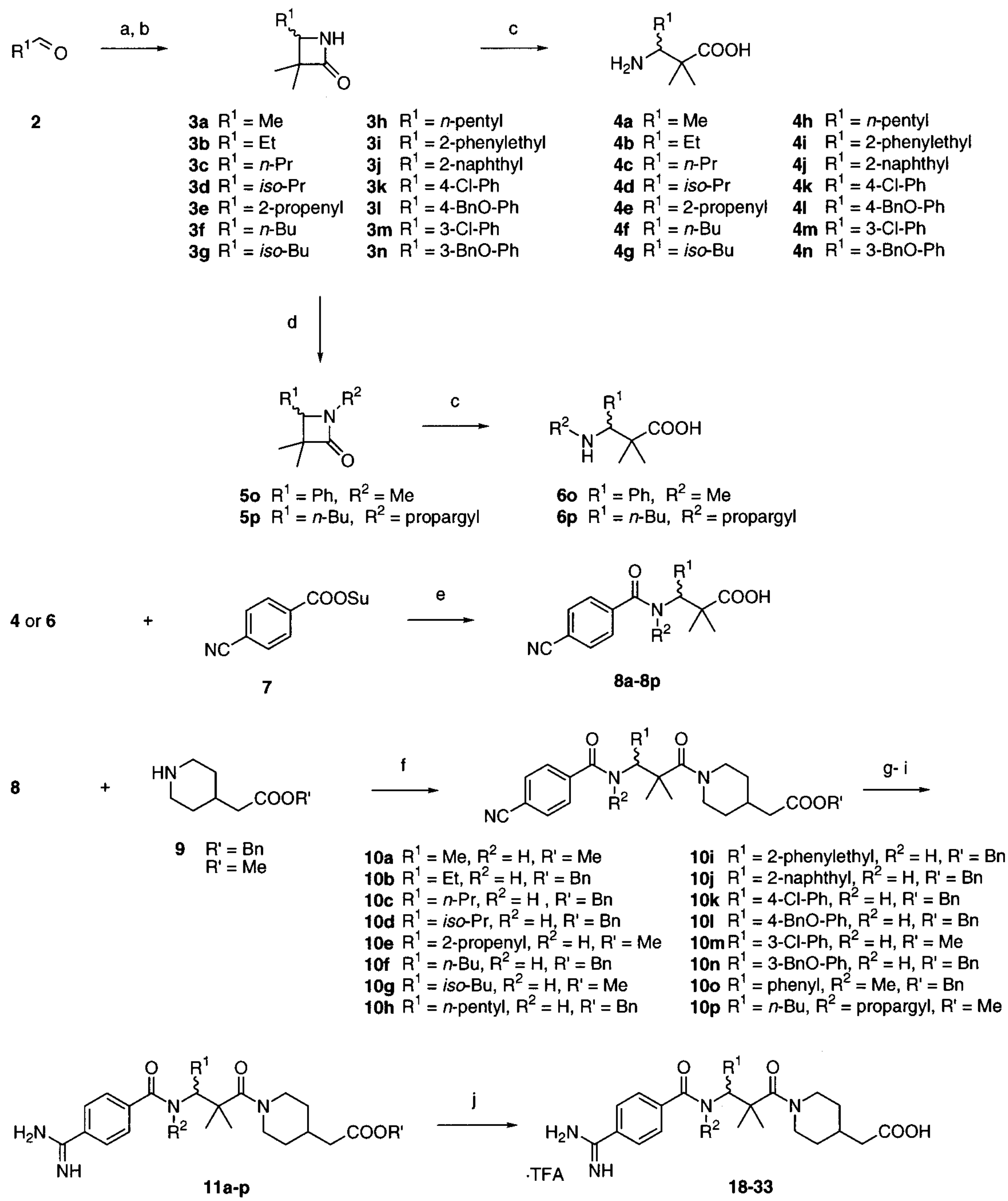
**Scheme 1**[a]



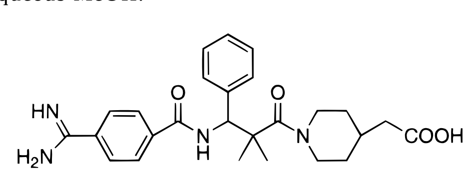

[a] (a) $LiN(SiMe_3)_2$, THF, −20 °C; (b) $(CH_3)_2C(Li)COOEt$, THF, −70 °C; (c) 6 N HCl, room temperature; or KOH, THF, reflux; (d) $R^2X$, NaH, THF; (e) $Et_3N$, DMF; (f) BOP reagent, DIEA, $CH_2Cl_2$; (g) $H_2S$, $Et_3N$, pyridine; (h) MeI, acetone, reflux; (i) $CH_3COONH_4$, MeOH, reflux; (j) $Pd(OH)_2$, 90% aqueous MeOH containing 2% AcOH; or LiOH, 80% aqueous MeOH.

proper distance. This molecule is unique for its trisubstituted $\beta$-amino acid residue serving as the central core unit.

In this paper, we describe the development of a potent and orally active GPIIb/IIIa antagonist based on the conformational analysis and the SAR study of **1** and further modification of the amidine group of the antagonist molecule.

## Chemistry

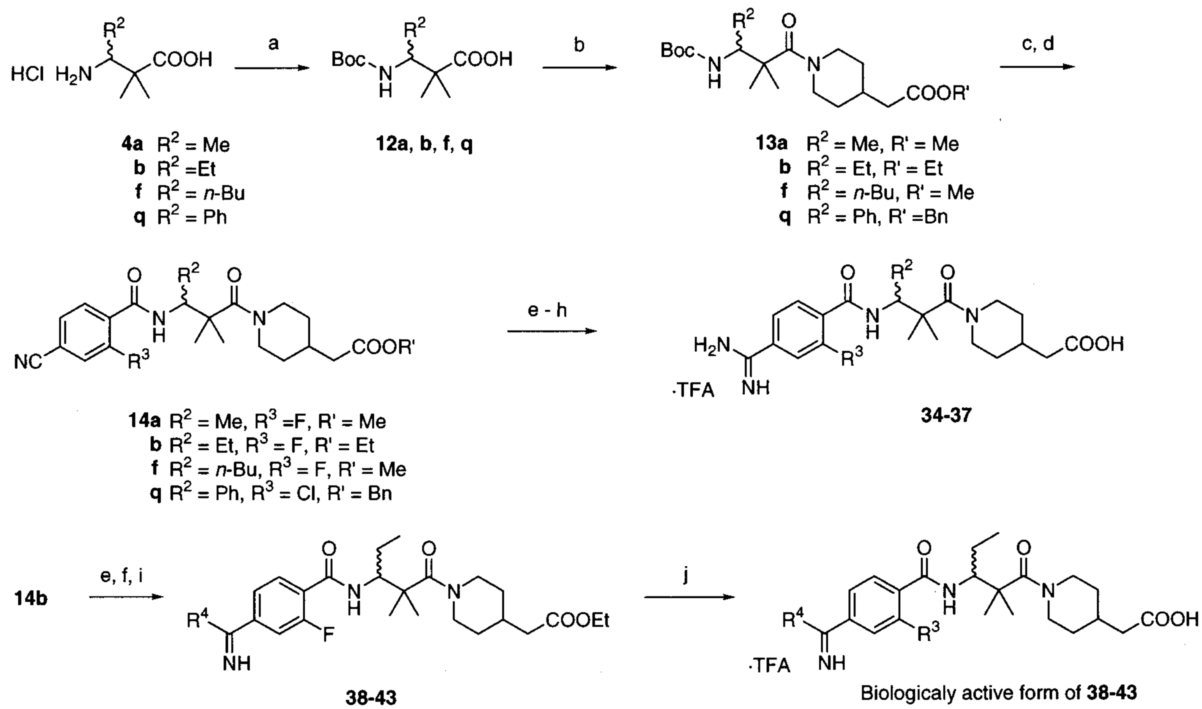
Analogues of **1**, in which the $\beta$-position of the central $\beta$-amino acid is varied, were generally synthesized by the methods shown in Schemes 1 and 2. In Scheme 1,



**1** (NSL-95301)

for the synthesis of $\beta$-substituted-α,α-dimethyl-$\beta$-alanine **4**, the corresponding lactam **3**, which was prepared by convenient ester−imine condensation[25] with *N*-(trimethylsilyl)imines of **2** and lithium enolate of ethyl isobutyrate, was hydrolyzed in 6 N HCl or with KOH in THF. Compound **4** was coupled with *N*-hydroxysuccinimide ester of 4-cyanobenzoic acid (**7**) in the presence

**Scheme 2**[a]

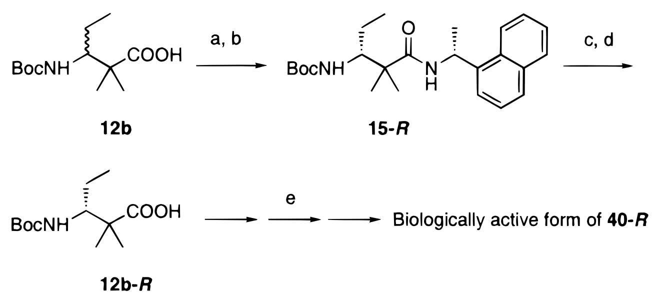



[a] (a) $(Boc)_2O$, 10% $Na_2CO_3$, dioxane; (b), benzyl, methyl, or ethyl piperidine-4-acetate, HATU, DIEA, $CH_2Cl_2$; (c) TFA, anisole; 0 °C; (d) 2-halo-4-cyanobenzoic acid, WSCD·HCl, HOBt, DMF; (e) $H_2S$, $Et_3N$, pyridine; (f) MeI, acetone, reflux; (g) $CH_3COONH_4$, MeOH, reflux; (h) $Pd(OH)_2$, 90% aqueous MeOH containing 2% AcOH; or LiOH, 80% aqueous MeOH; (i) amine, MeOH, reflux; (j) LiOH, 80% aqueous MeOH.

of triethylamine to give amide **8**, which was coupled with benzyl or methyl piperidine-4-acetate **9** using the BOP reagent[26] in the presence of *N*,*N*-diisopropylethylamine (DIEA) to give **10**. Subsequent amidination[27] of the nitrile group of **10** provided **11**. The biologically active form of compounds **18**−**33** was obtained as a trifluoroacetic acid salt by hydrogenolysis of the benzyl protecting group with 20% palladium hydroxide on carbon or saponification of methyl ester with LiOH and the subsequent reverse phase HPLC purification. In the synthesis of **29** and **31**, the phenolic hydroxyl group at the *β*-position of central *β*-alanine analogues was protected with a benzyl group and deprotected at the final step of the synthesis via hydrogenolysis with the benzyl protecting group for the terminal carboxylic acid. This benzyl protection for the phenolic hydroxyl group was introduced by preparing *β*-(3- or 4-benzyloxy)-phenyl-α,α-dimethyl-*β*-alanine (**4n** or **4l**) via hydrolysis of the corresponding *β*-lactam. In the synthesis of **32** and **33**, *β*-lactam **3** was alkylated with methyl iodide in the presence of NaH or propargyl bromide in the presence of NaH and HMPA, respectively. For the synthesis of **18**, *β*-methyl-α,α-dimethyl-*β*-alanine (**4a**) was synthesized from corresponding *β*-lactam **3a**, which was prepared from bis(trimethylsilyl)formamide on the basis of the method of Uyehara et al.[28]

In the synthesis of compound **34**−**43** (Scheme 2), *t*-Boc-protected *β*-substituted-α,α-dimethyl-*β*-alanine derivative **12** was coupled with benzyl, methyl, or ethyl piperidine-4-acetate by *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)[29] to give **13**. After the deprotection of the *t*-Boc group of **13** by TFA in the presence of anisole, coupling with 2-chloro-4-cyanobenzoic acid for **34** or 2-fluoro-4-cyanobenzoic acid[30] for **35**−**43** by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl)[31] in the presence of 1-hydroxybenzotriazole (HOBt)[32] was carried out to give **14**. In the synthesis of **34**−**37**, amidination of **14** and subsequent cleavage of the protecting group for the terminal carboxyl group were performed by the same method shown in Scheme 1. For the modification of the amidino group in **38**−**43**, corresponding secondary amine was used in the final step of the above-mentioned amidination method. The biologically active form of compounds **38**−**43** was obtained as a trifluoroacetic acid salt by saponification of ethyl ester with LiOH and the subsequent reverse phase HPLC purification.

**Scheme 3**[a]




[a] (a) (*R*)-(+)-1-(1-Naphthyl)ethylamine, HATU, DIEA, $CH_2Cl_2$; (b) $SiO_2$ chromatography; (c) 6 N HCl, reflux; (d) $(Boc)_2O$, 10% $Na_2CO_3$, dioxane; (e) see Scheme 2.

The synthesis of two individual enantiomers of the racemic **40** is outlined in Scheme 3 for the (*R*)-enantiomer. (*R*)-(+)-3-[*N*-(*t*-Boc-amino)-2,2-dimethylpentanoyl]-1-(1-naphthyl) ethylamine (**15-*R***) was obtained by the separation of diastereomers of **15** prepared from 3-(*N*-*t*-Boc)amino-2,2-dimethylpentanoic acid (**12b**) by column chromatography; the absolute configuration of **15-*R*** was

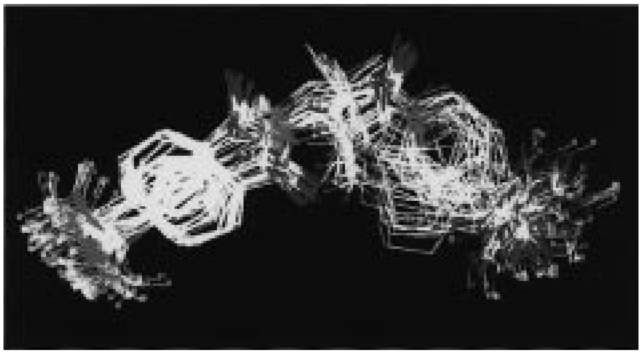
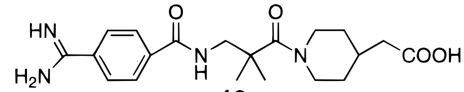


**Figure 2.** Superimpositioning study of the lower energy conformations of **16**.

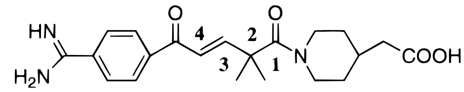
determined by X-ray crystallographic analysis. Compound **15-*R*** was hydrolyzed and converted into the corresponding *t*-Boc-protected amino acid **12b-*R***, and the biologically active form of **40-*R*** was obtained as a trifluoroacetic acid salt by the same procedure described in Scheme 2. In the same manner, the (*S*)-enantiomer **40-*S*** was prepared from **15-*S***.

## Results and Discussion

**Molecular Modeling.** Molecular modeling studies of **1** and the related compound **16** have revealed unique conformational characteristics of **1** (Figure 1). First, this molecule exhibits a cup-shaped conformation with the amidino group and the carboxyl group protruding at each end of the molecule. Second, the phenyl group at the β-position is oriented perpendicular to the pseudo plane including the amidinophenyl group and the piperidine ring. Third, this compound is quite rigid despite its linear structure, fixing the spatial distance between the amidino group and the carboxyl group. This cup-shaped conformation with considerable rigidity can be ascribed to the correlated and restricted movements of the phenyl group at the β-position, the *gem*-dimethyl group at the α-position and the piperidine ring to avoid steric repulsion among these three moieties. Especially, the existence of a substituent at the β-position appears to be very important to maintain such rigidity. In fact, compound **16**, which has no substituent at the β-position, showed much greater conformational flexibility as compared to **1** (Figure 2). Compound **1** is a potent antagonist of the GPIIb/IIIa receptor on platelets ((+)-**1** shows the $IC_{50}$ value of 0.092 μM [human PRP/collagen], but the antagonistic activity of (−)-form is more than 300 times less than that of (+)-form),[16] whereas **16** shows a weaker activity (10 times less active based on the ELISA GPIIb/IIIa binding assay, if we consider the chimeric structure of **1**) as shown in Table 1. These results suggest that the potent activity of **1** is ascribed to the fixation of the molecule to its bioactive conformation preferable for the binding to GPIIb/IIIa. This hypothesis is also supported by the fact that **17**, bearing an (*E*)-olefin moiety at the C3−C4 position to freeze the free rotation around the C3−C4 bond, shows almost the same activity as that of **1**.[33]



**16**

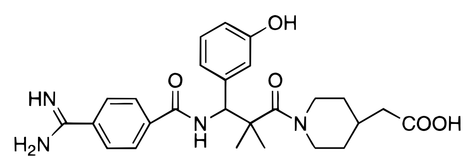


**17**

**Structure−Activity Relationships.** On the basis of these findings, we have synthesized and looked at the SAR of a series of analogues **18**−**31** in which the β-substituent of the trisubstituted β-amino acid residue is varied. Results are summarized in Table 1. As Table 1 shows, the introduction of a relatively small alkyl group such as methyl (**18**), ethyl (**19**), and *n*-propyl (**20**) increases the activity as compared to that of **1**. *n*-Butyl analogue **23** and isobutyl analogue **24** are also 3 times as active as **1**, but isopropyl analogue **21**, 2-propenyl analogue **22**, and normal pentyl analogue **25** do not show improved activity as compared to **1** in the platelet aggregation inhibitory assay.

Accordingly, this SAR study indicates that the replacement of the phenyl group of **1** with an alkyl substituent retains or improves inhibitory activity for platelet aggregation, and the bulkiness of the alkyl β-substituents has a rather small (less than a factor of 2 in the platelet aggregation assay) effect on the biological activity. Compounds with an aromatic substituent such as 4-chlorophenyl (**28**) at the β-position are less potent. However, 2-naphthyl (**27**), 3-chlorophenyl (**30**), and 2-phenylethyl (**26**) are tolerated.

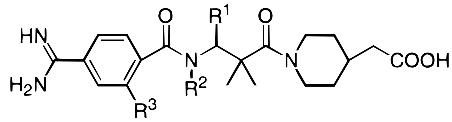
The effect of the introduction of hydroxyphenyl group as the β-substituent on the activity is worth mentioning. As Table 1 shows, while 4-hydroxyphenyl analogue **29** only possesses virtually the same activity as **1**, 3-hydroxyphenyl analogue **31** exhibits more than 3-fold better activity than **1**. This may imply that there is a basic residue in the GPIIb/IIIa binding site which can form a hydrogen bonding with the 3-hydroxyphenyl group, enhancing the binding of **31** to the receptor.



**31**

Next, we carried out further optimization of **19** in order to improve antiplatelet activity and pharmacokinetic properties. Analogue **19** was chosen based on the fact that the plasma half-life (T1/2β) of **19** was slightly longer than those of its analogues with comparable in vitro potency. Compound **19** is a hydrophilic compound containing the amidine group, carboxylic acid, and two amide bonds. This hydrophilicity may restrict wide tissue distribution and the binding to plasma proteins, resulting in high clearance rate of this compound. Hence, modification of **19** was carried out to increase hydrophobicity, especially modification of a secondary amide bond with N-alkylation and an introduction of an hydrophobic functional group such as halogen to an aromatic ring. As Table 1 shows, the modification of the amide nitrogen of the central β-amino acid residue by the introduction of an *N*-methyl group (**32**) or an *N*-propargyl group (**33**) decreases antiplatelet activity. The introduction of a fluorine atom at the meta position of the amidinobenzoyl group (**35**−**37**) not only slightly

**Table 1.** Structure−Activity Relationships of the Analogues of **1**



| compd | $R^1$ | $R^2$ | $R^3$ | platelet aggregation[a] $IC_{50}$ (μM) | GPIIb/IIIa ELISA $IC_{50}$ (nM) | T1/2β (min) |
|---|---|---|---|---|---|---|
| **1** | phenyl (NSL-95301) | H | H | 0.23 ± 0.035[b] | 25.3 ± 3.5 | 32 |
| **16**[c] | H | H | H | 0.57 ± 0.032 | 125 ± 25 | |
| **17**[c] | na[d] | na[d] | H | 0.31 ± 0.087 | 36.0 ± 7.5 | |
| **18** | Me | H | H | 0.082 ± 0.007 | 5.3 ± 0.78 | 53 |
| **19** | Et | H | H | 0.085 ± 0.005 | 5.0 ± 0.60 | 78 |
| **20** | *n*-Pr | H | H | 0.082 ± 0.007 | 5.1 ± 0.98 | 54 |
| **21** | *i*-Pr | H | H | 0.15 ± 0.036 | 8.6 ± 2.4 | 48 |
| **22** | 2-propenyl | H | H | 0.17 ± 0.061 | 13.0 ± 1.2 | 56 |
| **23** | *n*-Bu | H | H | 0.082 ± 0.011 | 3.8 ± 0.52 | 62 |
| **24** | *i*-Bu | H | H | 0.081 ± 0.009 | 2.7 ± 0.25 | 55 |
| **25** | *n*-pentyl | H | H | 0.16 ± 0.036 | 22.3 ± 7.9 | 31 |
| **26** | 2-phenylethyl | H | H | 0.16 ± 0.020 | 47.3 ± 4.0 | 46 |
| **27** | 2-naphthyl | H | H | 0.38 ± 0.219 | 21.0 ± 3.7 | 51 |
| **28** | 4-Cl-phenyl | H | H | 0.66 ± 0.163 | 34.7 ± 2.3 | 72 |
| **29** | 4-OH-phenyl | H | H | 0.22 ± 0.017 | 23.7 ± 5.2 | 63 |
| **30** | 3-Cl-phenyl | H | H | 0.25 ± 0.072 | 31.3 ± 5.0 | 150 |
| **31** | 3-OH-phenyl | H | H | 0.076 ± 0.012 | 2.6 ± 0.43 | 65 |
| **32** | phenyl | Me | H | 0.30 ± 0.038 | 21.3 ± 2.0 | 85 |
| **33** | *n*-Bu | propargyl | H | 1.4 ± 0.22 | 363 ± 55 | 90 |
| **34** | phenyl | H | Cl | 0.37 ± 0.036 | 27.3 ± 5.9 | 75 |
| **35** | Me | H | F | 0.076 ± 0.009 | 4.3 ± 0.50 | 84 |
| **36** | Et (NSL-96173) | H | F | 0.062 ± 0.023 | 2.7 ± 0.23 | 89 |
| **37** | *n*-Bu | H | F | 0.081 ± 0.012 | 5.7 ± 1.2 | 78 |

[a] Collagen (5 μg/mL)-induced platelet aggregation using human platelet-rich plasma. [b] Values are means ± SEM of three experiments. [c] See refs 16 and 33. [d] na = not applicable.

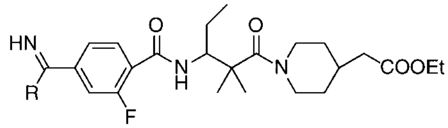
increases the activity, but also prolongs the plasma half-life, while replacement with a chlorine atom at the same position (**34**) does not improve the activity as compared to **1**. These results may be due to the strong hydrophobic effect of a fluorine atom without affecting conformation, since a fluorine atom can possess similar atom space as a hydrogen atom.

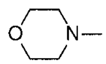
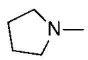
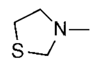
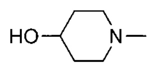
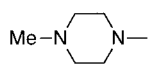
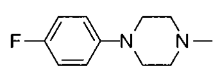
Analogue **36** (NSL-96173) is a potent platelet aggregation inhibitor in vitro, possessing the longest plasma stability in this series. However, even by the introduction of the fluorine atom, this analogue showed only a limited bioavailability after po administration in guinea pigs (data not shown). One reason for this low oral bioavailability may be due to the fact that the amidino group exists in its ionic form in the acidic condition of stomach and even in the weak basic condition of intestine due to its strong basicity, and this lasting ionic form prevents the absorption through a passive transport from the intestine, which is generally dependent on the hydrophobicity of the molecule. The terminal carboxylic acid may also have a higher rate of dissociation in intestine. However, these free basic and acidic groups are thought to be critical to induce the activity. To improve oral bioavailability, we modified the amidino group by alkylation to increase hydrophobicity. The carboxylic acid was also blocked by ester formation as prodrugs. However, the esterification of **36** to provide the corresponding methyl, ethyl, isopropyl, and benzyl esters as a prodrug brought about only slight improvement in oral bioavailability regardless of the nature of the esters (data not shown).

Since monoalkylation of the amidino group significantly decreased the antiplatelet activity in our preliminary study,[34] the effects of dialkylation (the introduction of cyclic secondary amine structure)[35] were investigated by modifying the ethyl ester of **36**. As shown in Table 2, the introduction of cyclic secondary amine structure at one of the amidino nitrogens resulted in the improved pharmacokinetic properties in most compounds tested, represented by the prolonged T1/2β values or high $C_{max}$ values, after po administration. Further, despite the modification of the amidino group, which is one of the essential pharmacophores of these compounds, their antagonistic activities were not altered. Although the mechanism underlying the improvement of pharmacokinetic properties by dialkylation is not clear, it can be attributed to the increased hydrophobicity at the amidino group which is positively charged in physiological conditions. Dialkylation at the amidino group may increase the permeability through the cell barrier such as epithelium of gastrointestinal tract and endothelium of blood vessels, probably by masking the positive charge or affecting the basicity.

As shown in Table 2, the active form, i.e., free carboxylic acid form, of **40** (NSL-96184) with a thiazolidine group at one of the amidino nitrogens not only exhibits most potent activity ($IC_{50}$ 45 nM, human PRP/collagen), but also possesses a high $C_{max}$ value (1.2 μg/mL) in rats after oral administration (10 mg/kg). The presence of a heteroatom within the ring structure such as oxygen in morpholine (**38**) and sulfur in thiazolidine (**40**) seems to be important in the increase of the $C_{max}$ value, because **39** with no heteroatom in the ring structure shows very low $C_{max}$ value compared to those of **38** and **40**. These results suggest that the modification of amidino or guanidino group by introducing cyclic secondary amines can be one of the useful approaches

**Table 2.** Modification of Amidino Group for Oral Bioavailability



| compd | R- | platelet aggregation collagen[a] $IC_{50}$ (μM)[b] | GPIIb/IIIa ELISA[a] $IC_{50}$ (nM)[b] | $T_{1/2}\beta$[a] (min) | Cmax ng/mL | Tmax (min) |
|---|---|---|---|---|---|---|
| 36-Et | $H_2N$— | 0.062 ± 0.023 | 2.7 ± 0.23 | 89 | 90 | 30 |
| 38 |  | 0.16 ± 0.062 | 4.0 ± 0.59 | 277 | 922 | 30 |
| 39 |  | 0.089 ± 0.005 | 7.0 ± 1.31 | 124 | 194 | 60 |
| 40 |  (NSL-96184) | 0.045 ± 0.004 | 2.3 ± 0.50 | 110 | 1210 | 30 |
| 41 |  | 0.048 ± 0.008 | 5.8 ± 1.08 | 210 | 290 | 60 |
| 42 |  | 0.072 ± 0.009 | 5.4 ± 0.75 | 106 | 392 | 120 |
| 43 |  | 0.079 ± 0.010 | 5.6 ± 1.25 | 25 | 232 | 60 |

[a] Data of biologically active form of each compound. [b] Values are means ± SEM of three experiments.

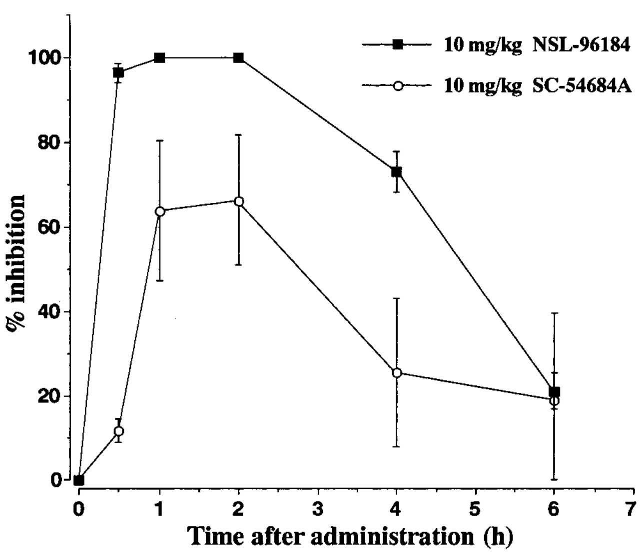
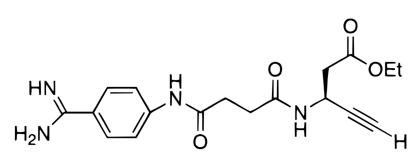



**Figure 3.** Effects of **40** and SC-54684A on ex vivo platelet aggregation in guinea pigs.

to improve pharmacokinetic properties in GPIIb/IIIa antagonists.

To evaluate pharmacological and pharmacodynamic properties of **40**, ex vivo platelet aggregation was examined by the oral administration of **40** in guinea pigs. As shown in Figure 3, the 10 mg/kg oral administration of **40** results in the complete inhibition of ex vivo platelet aggregation over 3 h. It is noteworthy that the onset of the antiplatelet activity was very rapid and almost the maximum inhibition was observed even at the 30 min period after the administration, the earliest time point of the experiment. Since SC-54684A was reported to have an oral bioavailability of more than 20% in dogs, we used SC-54684A as a reference compound for evaluation of **40**.[36] Racemic SC-54684A, when administered orally at the same dose (10 mg/kg) as that used for **40**, showed less than 70% inhibition for ex vivo platelet aggregation in the guinea pig at its maximum (Figure 3). The plasma half-life of the active form of **40** after intravenous administration to the guinea pig (1 mg/kg) was found to be relatively short with a $T1/2\beta$ value of 1.8 h. Since most sulfur containing drugs are metabolized via the S-oxidation pathway in vivo, catalyzed by cytochrome P450 or flavin-containing monooxygenase (FMO), this relatively short half-life may be due to the oxidative metabolism of the thiazolidine group in **40**.[37] However, in this experiment using HPLC analysis for the detection of the biologically active form of **40** in plasma, we could not observe any other metabolite. The other possibility is that the active form of **40** is quickly excreted from the circulation without metabolism due to its relatively hydrophilic structure.



**SC-54684A** (ref. 36)

These encouraging results prompted us to synthesize two individual enantiomers of the racemic **40**. Both synthetic enantiomers were subjected to in vitro activity assay (human PRP/collagen). We have found that only

**40-*R*** is a highly potent platelet aggregation inhibitor ($IC_{50}$ 22 nM) while **40-*S*** shows poor activity ($IC_{50}$ 3100 nM).

In conclusion, the active form of **40-*R*** is a highly potent antagonist of the platelet fibrinogen receptor GPIIb/IIIa, effectively inhibiting platelet aggregation in vitro. This compound is characterized by the presence of the trisubstituted $\beta$-amino acid residue, 3-ethyl-2,2-dimethyl-$\beta$-alanine, which is responsible for fixing the molecule to its active conformation. In vivo assay results clearly show that **40** is orally active in guinea pigs. The onset of antiplatelet action is very fast, whereas its duration of action is relatively short. These results suggest that **40** may have an excellent therapeutic potential, especially for antithrombotic treatment in the acute phase.

## Experimental Section

**Conformational Analysis.** All the conformational analyses were carried out on Macromodel ver. 5.5d. The 10000 Monte Carlo conformational search steps were performed with AMBER* force field UA minimization. Conformers whose steric energy was within 10 kJ from global minima were subjected to the superimpositioning study. The distance constraint factor has been set between center carbon atom of the amidine and center carbon atom of the carboxylic acid to be larger than 12 Å.

**In Vitro Platelet Aggregation.** Platelet aggregation studies were performed in platelet-rich plasma (PRP) obtained from human volunteers. Blood was drawn into plastic syringes containing 1/10 volume of 3.8% trisodium citrate. PRP was prepared by centrifugation of citrated whole blood at 160*g* for 15 min at room temperature. PRP was removed, and the platelet count was determined. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 2000*g* for 15 min. Saline or sample solution of various concentrations was added to PRP at 37 °C 1 min prior to the initiation of platelet aggregation. Platelet aggregation was initiated with 5 $\mu$g/mL collagen, and the aggregation was measured in an aggregometer (NBS Hematracer-601, Nikoh Bioscience Co., Ltd., Tokyo) as an increase in light transmission. Platelet aggregation is presented as the percent inhibition of the rate of platelet aggregation compared to control samples, and $IC_{50}$ values were calculated from dose−inhibition curves. Throughout the platelet aggregation assay, GRGDS peptide was used as a reference compound, and we confirmed that the $IC_{50}$ values of this peptide did not significantly vary with PRPs from different blood donors (470 ± 23 $\mu$M; mean ± SEM from five different donors).

**Solid-Phase Binding Assay.** The inhibitory effects of each compound on the interaction of fibrinogen and its receptor, GPIIb/IIIa, were evaluated using a competitive enzyme-linked immunosorbent assay. Briefly, a 96-well plate (MAXISORP, Nunc) was coated with 5 $\mu$g/mL human GPIIb/IIIa solution (Enzyme Research Lab., Inc.) overnight at 4 °C. The plate was washed with wash buffer containing 50 mM Tris, 100 mM NaCl, 2 mM $CaCl_2$, and 0.02% $NaN_3$ (pH 7.4) and was blocked with wash buffer supplemented with 35 mg/mL bovine serum albumin (Fraction V, Sigma) for 3 h at room temperature. Ninety microliters of human fibrinogen solution (30 $\mu$g/mL, Calbiochem Co., CA) and 10 $\mu$L of the inhibitor solution were added to each well, and the plate was incubated for 3 h at room temperature. After the plate was washed three times with wash buffer, bound fibrinogen was detected using alkaline phosphatase-conjugated goat anti-human fibrinogen antibody (EY Laboratories, Inc., CA).

**Measurement of Plasma Half-Life.** Male Hartley guinea pigs (400−500 g) were anesthetized with urethane (1.0 g/kg, ip), and a cannula was inserted into the left carotid artery. Each compound was dissolved in saline and administered intravenously (1 mg/kg) via a right jugular vein. Blood samples (0.3 mL) were collected through the arterial cannula with heparin as an anticoagulant at 1, 5, 10, 30, 45, 60, 120, and 180 min after the intravenous administration. These samples were centrifuged, and plasma concentrations of each compound were determined by HPLC. In most of the compounds tested here, plasma concentration declined biexponentially and T1/2$\beta$ values were calculated from the exponential curve fitted by the least-squares methods.

**Measurement of $C_{max}$ Values.** Male Sprague−Dawley rats (190−210 g) were fasted overnight with water ad libitum. Each compound was suspended in 2% arabic gum solution and was administered po (10 mg/kg). Blood samples were collected from the jugular vein at 30, 60, and 120 min after the administration, and plasma concentrations of the active form were determined by HPLC. Prodrug form was not detected in plasma. $C_{max}$ value was defined as the maximum plasma concentration of the active form achieved at these three time points.

**Ex Vivo Study in Guinea Pigs.** Male hartley guinea pigs (170−250 g), fasted for 24 h, were used for ex vivo platelet aggregation study. **40** or SC-54684A was dissolved in distilled water and administered orally at a dose of 10 mg/kg. Blood samples were collected at selected times after the administration for 6 h from the abdominal artery under anesthesia with pentobarbital, and PRP was prepared by centrifugation. Inhibition of collagen (10 mg/mL)-induced platelet aggregation was determined by comparing the responses in the samples from drug-administered animals with those of vehicle control group at each time point. Mean ± SEM ($n$ = 3).

**Chemistry.** $^1$H NMR and $^{13}$C NMR spectra were recorded on JEOL GSX270J or EX-400 spectrometer. These spectra were recorded with tetramethylsilane ($\delta$ = 0.0 for $^1$H); $CD_3OD$ ($\delta$ = 49.8 for $^{13}$C); $CDCl_3$ ($\delta$ = 77.0 for $^{13}$C); $(CD_3)_2SO$ ($\delta$ = 39.5 for $^{13}$C) as internal reference. Mass spectra (electrospray ionization, methanol as the mobile phase) were analyzed with Finnigan SSQ 7000 spectrometer. High-resolution fast atom bombardment mass spectra were analyzed with JEOL JMS-DX303 spectrometer. HPLC was carried out using a Jasco system (800 series) equipped with a UV/VIS detector and an integrator. The solvent system used for analytical HPLC was a binary system, water containing 0.1% TFA and acetonitrile containing the same TFA as the organic modifier. The column used for analytical chromatography had dimensions of 4.6 × 250 mm (Wakosil-II 5C18 HG). The analytical conditions for $K'$ values are (a) a linear gradient with 10% to 40% acetonitrile in 0.1% TFA over 60 min at a flow rate of 1.0 mL/min, (b) a linear gradient with 10% to 55% acetonitrile in 0.1% TFA over 30 min at a flow rate of 1.0 mL/min. HPLC on a semipreparative scale was performed with a reverse phase column (Waters, $\mu$Bondasphere 19 × 150 mm, 10 $\mu$m, C-18) employing the same binary solvent system used for analytical HPLC at a flow rate of 17 mL/min on a Waters system (600E series). GRGDS was purchased from the Peptide Institute Inc.

**General Procedure A for $\beta$-Lactam Preparation: 4-Ethyl-3,3-dimethyl-2-azetidinone (3b).** To 14 mL (66 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 20 mL of dry tetrahydrofuran was added 40 mL (66 mmol) of 1.65 M $n$-butyllithium in hexane at 0 °C over 10-min period. The mixture was stirred at 0 °C for 20 min, and the solvent was removed in vacuo until a white precipitate appeared. To the resulting slurry was added dropwise a solution of 4.0 mL (55 mmol) of propionaldehyde in 15 mL of tetrahydrofuran at −20 °C over 5-min period. The resulting solution of trimethylsilyl imine was used directly in the following reaction. To 9.1 mL (65 mmol) of diisopropylamine in 30 mL of tetrahydrofuran was added 36.4 mL (60 mmol) of 1.65 M $n$-butyllithium in hexane at −70 °C. The mixture was stirred at −70 °C for 20 min followed by the addition of 6.7 mL (50 mmol) of ethyl isobutyrate in 10 mL of tetrahydrofuran over a 10-min period. The solution was stirred at −70 °C for 60 min followed by addition of the solution of trimethylsilyl imine via cannula at a rate such that the temperature did not exceed −50 °C. The mixture was stirred at −70 °C for 60 min, allowed to warm to room temperature, and stirred for an additional 18 h. Then 100 mL of saturated aqueous $NH_4Cl$ was added to the reaction mixture, and the mixture was extracted three times with 50 mL of diethyl ether. The combined organic layers were washed with saturated NaCl, dried over $Na_2SO_4$, and concentrated in vacuo. The residual pale yellow oil was applied to a silica gel column (5 × 50 cm) and eluted with EtOAc−hexane (1:4) to give 3.33 g (53%) of azetidinone **3b** as a pale-yellow oil: $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.95 (t, $J$ = 8.0 Hz, 3H), 1.18 (s, 3H), 1.32 (s, 3H), 1.56 (m, 2H), 3.22 (dd, $J$ = 6.0, 9.0 Hz, 1H), 6.01 (br s, 1H); MS (ESI) $m/z$ 128 $(M + H)^+$.

Compounds **3c**−**n** were prepared according to the general procedure A described for **3b** starting from the corresponding aldehydes **2**. **3a** was prepared from bis(trimethylsilyl)formamide based on the method of Uyehara et al.[28]

**4-*n*-Propyl-3,3-dimethyl-2-azetidinone (3c):** 42% yield from *n*-butylaldehyde; mp 70−71 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.92 (t, $J$ = 7.0 Hz, 3H), 1.17 (s, 3H), 1.31 (s, 3H), 1.25−1.64 (m, 4H), 3.27 (dd, $J$ = 6.0, 8.0 Hz, 1H), 5.92 (br s, 1H); MS (ESI) $m/z$ 142 $(M + H)^+$.

**4-Isopropyl-3,3-dimethyl-2-azetidinone (3d):** 55% yield from isobutylaldehyde; mp 94−96 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.89 (d, $J$ = 6.0 Hz, 3H), 0.93 (d, $J$ = 6.0 Hz, 3H), 1.23 (s, 3H), 1.31 (s, 3H), 1.75 (m, 1H), 2.90 (d, $J$ = 10.0 Hz, 1H), 5.85 (br s, 1H); MS (ESI) $m/z$ 142 $(M + H)^+$.

**4-(2-Propenyl)-3,3-dimethyl-2-azetidinone (3e):** 82% yield from crotonaldehyde; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.10 (s, 3H), 1.32 (s, 3H), 1.75 (dd, $J$ = 1.4, 7.3 Hz, 3H), 3.77 (d, $J$ = 7.3 Hz, 1H), 5.41−5.51 (m, 1H), 5.64−5.74 (m, 1H), 5.84 (br s, 1H); MS (ESI) $m/z$ 140 $(M + H)^+$.

**4-*n*-Butyl-3,3-dimethyl-2-azetidinone (3f):** 53% yield from *n*-valeraldehyde; mp 59−60 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 6.0 Hz, 3H), 1.17 (s, 3H), 1.31 (s, 3H), 1.21−1.64 (m, 6H), 3.28 (dd, $J$ = 6.0, 8.0 Hz, 1H), 5.87 (br s, 1H); MS (ESI) $m/z$ 156 $(M + H)^+$.

**4-Isobutyl-3,3-dimethyl-2-azetidinone (3g):** 15% yield from isovaleraldehyde; mp 101−102 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93 (d, $J$ = 4.4 Hz, 3H), 0.96 (d, $J$ = 4.4 Hz, 3H), 1.16 (s, 3H), 1.31 (s, 3H), 1.37−1.50 (m, 2H), 1.54−1.68 (m, 1H), 3.39 (dd, $J$ = 3.4, 8.3 Hz, 1H), 5.80 (br s, 1H); MS (ESI) $m/z$ 156 $(M + H)^+$.

**4-*n*-Pentyl-3,3-dimethyl-2-azetidinone (3h):** 52% yield from 1-hexanal; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.90 (m, 3H), 1.17 (s, 3H), 1.31 (s, 3H), 1.22−1.40 (m, 6H), 1.43−1.62 (m, 2H), 3.29 (dd, $J$ = 5.8, 3.0 Hz, 1H), 5.96 (br s, 1H); MS (ESI) $m/z$ 170 $(M + H)^+$.

**4-(2-Phenylethyl)-3,3-dimethyl-2-azetidinone (3i):** 35% yield from 3-phenylpropionaldehyde; mp 83−85 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.17 (s, 3H), 1.30 (s, 3H), 1.71−1.98 (m, 2H), 2.53−2.75 (m, 2H), 3.29 (dd, $J$ = 4.0, 8.0 Hz, 1H), 5.52 (br s, 1H), 7.09−7.31 (m, 5H); MS (ESI) $m/z$ 204 $(M + H)^+$.

**4-(2-Naphthyl)-3,3-dimethyl-2-azetidinone (3j):** 87% yield from 2-naphthaldehyde; mp 160−162 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.79 (s, 3H), 1.53 (s, 3H), 4.66 (s, 1H), 6.36 (br s, 1H), 7.31−7.34 (m, 1H), 7.47−7.53 (m, 2H), 7.72 (s, 1H), 7.82−7.86 (m, 3H); MS (ESI) $m/z$ 226 $(M + H)^+$.

**4-(4-Chlorophenyl)-3,3-dimethyl-2-azetidinone (3k):** 67% yield from 4-chlorobenzaldehyde; mp 127−128 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.77 (s, 3H), 1.46 (s, 3H), 4.48 (s, 1H), 6.13 (br s, 1H), 7.20 (d, $J$ = 8.3 Hz, 2H), 7.36 (d, $J$ = 8.3 Hz, 2H); MS (ESI) $m/z$ 210 $(M + H)^+$.

**4-(4-Benzyloxyphenyl)-3,3-dimethyl-2-azetidinone (3l):** 94% yield from 4-benzyloxybenzaldehyde; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.70 (s, 3H), 1.39 (s, 3H), 4.45 (s, 1H), 5.07 (s, 2H), 7.00 (d, $J$ = 8.8 Hz, 2H), 7.17 (d, $J$ = 8.8 Hz, 2H), 7.26−7.43 (m, 5H); MS (ESI) $m/z$ 282 $(M + H)^+$.

**4-(3-Chlorophenyl)-3,3-dimethyl-2-azetidinone (3m):** 87% yield from 3-chlorobenzaldehyde; mp 120−121 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.80 (s, 3H), 1.47 (s, 3H), 4.48 (s, 1H), 6.41 (br s, 1H), 7.14 (dt, $J$ = 7.0, 2.0 Hz, 1H), 7.30 (s, 1H), 7.22−7.35 (m, 2H); MS (ESI) $m/z$ 210 $(M + H)^+$.

**4-(3-Benzyloxyphenyl)-3,3-dimethyl-2-azetidinone (3n):** 47% yield from 3-benzyloxybenzaldehyde; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.77 (s, 3H), 1.44 (s, 3H), 4.46 (s, 1H), 5.07 (s, 2H), 6.11 (br s, 1H), 6.80−6.95 (m, 3H), 7.25−7.46 (m, 6H); MS (ESI) $m/z$ 282 $(M + H)^+$.

***N*-Methyl-4-phenyl-3,3-dimethyl-2-azetidinone (5o).** To a solution of 4-phenyl-3,3-dimethyl-2-azetidinone[25] (1.75 g, 10 mmol) in tetrahydrofuran (40 mL) was added 0.48 g (12 mmol) of sodium hydride (60% in mineral oil) in portions, and the mixture was stirred at 0 °C for 15 min. To this mixture was added dropwise 0.74 mL (12 mmol) of MeI, and the mixture was allowed to warm to room temperature and stirred for an additional 2 h. Then, 50 mL of saturated aqueous $NH_4Cl$ was added to the reaction mixture, and the mixture was extracted two times with 50 mL of EtOAc. The combined organic layers were washed with saturated NaCl, dried over $Na_2SO_4$, and concentrated in vacuo. The residual oil (2.1 g) was chromatographed over 150 g of silica gel and eluted with EtOAc−hexane (1:2) to give 1.9 g (quant) of **5o** as an oil: $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.76 (s, 3H), 1.43 (s, 3H), 2.86 (s, 3H), 4.31 (s, 1H), 7.14−7.23 (m, 2H), 7.28−7.50 (m, 3H); MS (ESI) $m/z$ 212 $(M + Na)^+$.

***N*-(2-Propargyl)-4-*n*-butyl-3,3-dimethyl-2-azetidinone (5p).** This compound was prepared from **3f** and propargyl bromide following the procedure described for **5o**, but HMPA (3 mL) was added to the reaction mixture. The crude product (2.5 g) was chromatographed over 70 g of silica gel and eluted with EtOAc−hexane (1:5) to give 1.6 g (quantitative) of **5p** as an oil: $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 6.8 Hz, 3H), 1.17 (s, 3H), 1.27 (s, 3H), 1.20−1.78 (m, 6H), 2.26 (t, $J$ = 2.4 Hz, 1H), 3.35 (t, $J$ = 6.4 Hz, 1H), 3.76 (dd, $J$ = 2.4, 17.6 Hz, 1H), 4.21 (dd, $J$ = 2.4, 17.6 Hz, 1H); MS (ESI) $m/z$ 194 $(M + H)^+$.

**General Procedure B for the Preparation of 8: 3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethylpentanoic Acid (8b).** A mixture of 4-ethyl-3,3-dimethyl-2-azetidinone (**3b**) (2.0 g, 15.7 mmol) and 6 N HCl (100 mL) was stirred at room temperature for 24 h. The solution was condensed under reduced pressure, and then toluene (30 mL) was added to the residue and evaporated twice to give 2.3 g (81%) of a hydrochloride salt of 3-amino-2,2-dimethylpentanoic acid (**4b**) as a white solid: mp 216−218 °C; $^1$H NMR (270 MHz, $D_2O$) $\delta$ 0.84 (t, $J$ = 7.0 Hz, 3H), 1.06 (s, 3H), 1.10 (s, 3H), 1.38 (m, 1H), 1.63 (m, 1H), 3.16 (dd, $J$ = 3.0, 10.0 Hz, 1H); MS (ESI) $m/z$ 146 $(M + H)^+$. To a solution of this material (1.0 g, 5.5 mmol) in DMF (40 mL) were added triethylamine (1.7 mL, 12.1 mmol) and *N*-succinimidyl-4-cyanobenzoate (1.6 g, 6.6 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 17 h. The solvent was removed by evaporation, and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with 5% citric acid and saturated NaCl, dried over $Na_2SO_4$, and concentrated in vacuo. The resulting powder was recrystallized from EtOAc with ether−hexane (1:1): yield 1.32 g (87%); mp 157−160 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.94 (t, $J$ = 7.3 Hz, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.14 (ddq, $J$ = 10.7, 14.0, 7.3 Hz, 1H), 1.83 (ddq, $J$ = 2.0, 14.0, 7.3 Hz, 1H), 4.06 (dt, $J$ = 2.0, 10.7 Hz, 1H), 7.44 (d, $J$ = 10.7 Hz, 1H), 7.75 (d, $J$ = 8.8 Hz, 2H), 7.94 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 10.8, 23.0, 23.6, 24.1, 45.3, 57.7, 114.3, 117.8, 127.4, 132.0, 138.5, 165.2, 178.9; MS (ESI) $m/z$ 297 $(M + Na)^+$.

Compounds **4a**,**c**,**d**,**f**−**n**, **6o**,**p**, and **8a**−**p** were prepared according to the general procedure B described for **8b** starting from the appropriate intermediates (**3a**−**n** and **5o**,**p**).

**3-Amino-2,2-dimethylbutanoic acid (4a) (hydrochloride):** 88% yield from **3a**; $^1$H NMR (270 MHz, $D_2O$) $\delta$ 1.05 (s, 3H), 1.09 (s, 3H), 1.10 (d, $J$ = 6.8 Hz, 3H), 3.38 (q, $J$ = 6.8 Hz, 1H); MS (ESI) $m/z$ 132 $(M + H)^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethylbutanoic acid (8a):** 76% yield from **4a**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.28 (d, $J$ = 6.4 Hz, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 4.31 (dq, $J$ = 6.4, 9.8 Hz, 1H), 7.16 (d, $J$ = 9.8 Hz, 1H), 7.75 (d, $J$ = 8.8 Hz, 2H), 7.88 (d, $J$ = 8.8 Hz, 2H); MS (ESI) $m/z$ 259 $(M - H)^-$.

**3-Amino-2,2-dimethylhexanoic acid (4c) (hydrochloride):** 98% yield from **3c**; mp 208−210 °C; $^1$H NMR (270 MHz, $D_2O$) $\delta$ 0.74 (t, $J$ = 7.0 Hz, 3H), 1.07 (s, 3H), 1.10 (s, 3H), 1.04−1.57 (m, 4H), 3.23 (dd, $J$ = 2.0, 10.0 Hz, 1H); MS (ESI) $m/z$ 160 $(M + H)^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethylhexanoic acid (8c):** 67% yield from **4c**; mp 234−235 °C; $^1$H NMR (270 MHz,

$CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.26−1.46 (m, 3H), 1.69 (m, 1H), 4.12 (m, 1H), 7.41 (d, *J* = 9.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) δ 13.6, 19.5, 23.1, 24.2, 32.9, 45.4, 55.9, 114.3, 117.8, 127.4, 132.0, 138.5, 165.0, 179.0; MS (ESI) *m/z* 289 (M + H)$^+$.

**3-Amino-2,2-dimethyl-4-methylpentanoic acid (4d) (hydrochloride):** 97% yield from **3d**; mp 218 °C; $^1$H NMR (270 MHz, $D_2O$) δ 0.75 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 1.09 (s, 3H), 1.14 (s, 3H), 2.02 (m, 1H), 3.12 (d, *J* = 3.0 Hz, 1H); MS (ESI) *m/z* 160 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-4-methylpentanoic acid (8d):** 85% yield from **4d**; mp 148−150 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.33 (s, 3H), 1.36 (s, 3H), 2.21 (dsep, *J* = 3.4, 6.8 Hz, 1H), 4.19 (dd, *J* = 3.4, 10.3 Hz, 1H), 7.57 (d, *J* = 10.3 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) δ 16.6, 22.0, 23.0, 26.0, 29.2, 44.6, 60.8, 115.1, 117.9, 127.6, 132.5, 138.4, 166.1, 182.8; MS (ESI) *m/z* 311 (M + Na)$^+$.

**3-Amino-2,2-dimethylheptanoic acid (4f) (hydrochloride):** 99% yield from **3f**; mp 194−195 °C; $^1$H NMR (270 MHz, $D_2O$) δ 0.69 (t, *J* = 7.0 Hz, 3H) 1.07 (s, 3H), 1.10 (s, 3H), 1.12−1.32 (m, 4H), 1.37 (m, 1H), 1.55 (m, 1H), 3.22 (dd, *J* = 10.0, 2.0 Hz, 1H); MS (ESI) *m/z* 174 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethylheptanoic acid (8f):** 41% yield from **4f**; mp 204−206 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.14−1.48 (m, 4H), 1.19 (s, 3H), 1.22 (s, 3H), 1.48−1.65 (m, 2H), 4.40 (m, 1H), 7.83 (d, *J* = 10.0 Hz, 2H), 7.96 (d, *J* = 10.0 Hz, 2H); MS (ESI) *m/z* 303 (M + H)$^+$.

**3-Amino-2,2-dimethyl-5-methylhexanoic acid (4g) (hydrochloride):** quantitative yield from **3g**; mp 224−226 °C; $^1$H NMR (270 MHz, $D_2O$) δ 0.73 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 3H), 1.10 (s, 3H), 1.17−1.45 (m, 2H), 1.48 (m, 1H), 3.28 (dd, *J* = 2.0, 10.0 Hz, 1H); MS (ESI) *m/z* 174 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-5-methylhexanoic acid (8g):** 41% yield from **4g**; mp 188−190 °C; $^1$H NMR (270 MHz, $CD_3OD$) δ 0.90 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.17 (s, 3H), 1.21 (s, 3H), 1.10−1.41 (m, 3H), 4.49−4.58 (m, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H); MS (ESI) *m/z* 303 (M + H)$^+$.

**3-Amino-2,2-dimethyloctanoic acid (4h) (hydrochloride):** 90% yield from **3h**; mp 152−154 °C; $^1$H NMR (270 MHz, $D_2O$) δ 0.70−0.76 (m, 3H), 1.12 (s, 3H), 1.14 (s, 3H), 1.08−1.29 (m, 5H), 1.33−1.49 (m, 2H), 1.52−1.66 (m, 1H), 3.26 (dd, *J* = 3.8, 14.0 Hz, 1H); MS (ESI) *m/z* 188 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyloctanoic acid (8h):** 20% yield from **4h**; mp 149−150 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.4 Hz, 3H), 1.15−1.38 (m, 6H), 1.18 (s, 3H), 1.22 (s, 3H), 1.47−1.60 (m, 2H), 4.39 (dd, *J* = 4.3, 9.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H); MS (ESI) *m/z* 339 (M + Na)$^+$.

**3-Amino-2,2-dimethyl-5-phenylpentanoic acid (4i) (hydrochloride):** 99% yield from **3i**; mp 202−203 °C; $^1$H NMR (270 MHz, $D_2O$) δ 1.02 (s, 3H), 1.06 (s, 3H), 1.69 (m, 1H), 1.82 (m, 1H), 2.47 (m, 1H), 2.68 (m, 1H), 3.22 (br d, *J* = 9.0 Hz, 1H), 7.02−7.23 (m, 5H); MS (ESI) *m/z* 222 (M + H)$^+$.

**3-Amino-2,2-dimethyl-3-(2-naphthyl)propionic acid (4j) (hydrochloride):** 99% yield from **3j**; mp 254 °C; $^1$H NMR (270 MHz, $D_2O$) δ 1.09 (s, 3H), 1.22 (s, 3H), 4.59 (s, 1H), 7.33−7.37 (m, 1H), 7.46−7.51 (m, 2H) 7.79−7.87 (m, 4H); MS (ESI) *m/z* 244 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-3-(2-naphthyl)propionic acid (8j):** 83% yield from **4j**; mp 207−208 °C; $^1$H NMR (400 MHz, $CD_3OD$) δ 1.23 (s, 3H), 1.33 (s, 3H), 5.53 (s, 1H), 7.41−7.43 (m, 2H), 7.52 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.74 (t, *J* = 1.8 Hz, 1H), 7.74−7.80 (m, 4H), 7.86−7.89 (m, 3H); MS (ESI) *m/z* 373 (M + H)$^+$.

**3-Amino-2,2-dimethyl-3-(4-chlorophenyl)propionic acid (4k) (hydrochloride):** 98% yield from **3k**; mp 251−252 °C; $^1$H NMR (270 MHz, $CD_3OD$) δ 1.21 (s, 3H), 1.30 (s, 3H), 4.54 (s, 1H), 7.45 (s, 4H); MS (ESI) *m/z* 228 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-3-(4-chlorophenyl)propionic acid (8k):** 87% yield from **4k**; mp 272−273 °C; $^1$H NMR (270 MHz, DMSO-$d_6$) δ 1.09 (s, 3H), 1.13 (s, 3H), 5.48 (d, *J* = 9.8 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 8.88 (d, *J* = 9.8 Hz, 1H); MS (ESI) *m/z* 355 (M − H)$^-$.

**3-Amino-2,2-dimethyl-3-(4-benzyloxyphenyl)propionic acid (4l) (hydrochloride):** 92% yield from **3l**; mp 142−145 °C; $^1$H NMR (270 MHz, $D_2O$) δ 1.19 (s, 3H), 1.26 (s, 3H), 4.41 (s, 1H), 5.10 (s, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.29−7.44 (m, 7H); MS (ESI) *m/z* 298 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-3-(4-benzyloxyphenyl)propionic acid (8l):** 77% yield from **4l**; mp 147−149 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.47 (s, 3H), 5.01 (s, 2H), 5.11 (d, *J* = 9.3 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.22−7.42 (m, 5H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 8.44 (d, *J* = 9.3 Hz, 1H); MS (ESI) *m/z* 429 (M + H)$^+$.

**3-Amino-2,2-dimethyl-3-(3-chlorophenyl)propionic acid (4m) (hydrochloride):** 98% yield from **3m**; mp 232−233 °C; $^1$H NMR (270 MHz, $D_2O$) δ 1.12 (s, 3H), 1.31 (s, 3H), 4.50 (s, 1H), 7.33 (dt, *J* = 7.0, 2.0 Hz, 1H), 7.41−7.52 (m, 3H); MS (ESI) *m/z* 228 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-3-(3-chlorophenyl)propionic acid (8m):** 92% yield from **4m**; mp 160−163 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.28 (s, 3H), 5.34 (s, 1H), 7.27−7.34 (m, 3H), 7.44 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.90 (dt, *J* = 8.4, 1.6 Hz, 2H); MS (ESI) *m/z* 379 (M + H)$^+$.

**3-Amino-2,2-dimethyl-3-(3-benzyloxyphenyl)propionic acid (4n) (hydrochloride):** 51% yield from **3n**; $^1$H NMR (270 MHz, $CD_3OD$) δ 1.15 (s, 3H), 1.22 (s, 3H), 4.43 (s, 1H), 5.07 (s, 2H), 6.72−6.88 (m, 2H), 6.92−7.08 (m, 2H), 7.13−7.41 (m, 5H); MS (ESI) *m/z* 300 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-3-(3-benzyloxyphenyl)propionic acid (8n):** 43% yield from **4n**; mp 180−181 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.45 (s, 3H), 5.02 (s, 2H), 5.11 (d, *J* = 9.3 Hz, 1H), 6.80−6.98 (m, 2H), 7.17−7.43 (m, 6H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 8.3 Hz, 2H), 8.17 (br t, *J* = 8.0 Hz, 1H); MS (ESI) *m/z* 451 (M + Na)$^+$.

**3-(*N*-Methyl)amino-2,2-dimethyl-3-phenylpropionic acid (6o) (hydrochloride):** 96% yield from **5o**; mp 228−229 °C; $^1$H NMR (270 MHz, $D_2O$) δ 1.10 (s, 3H), 1.25 (s, 3H), 2.47 (s, 3H), 4.31 (s, 1H), 7.30−7.38 (m, 5H); MS (ESI) *m/z* 208 (M + H)$^+$.

**3-[(*N*-4-Cyanobenzoyl)-(*N*-methyl)]amino-2,2-dimethyl-3-phenylpropionic acid (8o):** 61% yield from **6o**; mp 176−177 °C; $^1$H NMR (270 MHz, $CD_3OD$) δ 1.43 (s, 3H), 1.48 (s, 3H), 2.76 (s, 3H), 5.27 (s, 1H), 7.15−7.55 (m, 5H), 7.60 (d, *J* = 7.8 Hz, 2H), 8.31 (d, *J* = 7.8 Hz, 2H); MS (ESI) *m/z* 359 (M + Na)$^+$.

**3-(*N*-Propargyl)amino-2,2-dimethylheptanoic acid (6p) (hydrochloride):** 98% yield from **5p**; $^1$H NMR (270 MHz, $CD_3OD$) δ 0.97 (t, *J* = 6.8 Hz, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.18−1.82 (m, 6H), 3.30 (t, *J* = 2.4 Hz, 1H), 3.43 (t, *J* = 5.9 Hz, 1H), 4.06 (d, *J* = 2.4 Hz, 2H); MS (ESI) *m/z* 212 (M + H)$^+$.

**3-Amino-2,2-dimethyl-4-hexenoic Acid (4e).** A mixture of 4-(2-propenyl)-3,3-dimethyl-2-azetidinone **3e** (1.5 g, 10.7 mmol) and KOH (0.67 g, 11.8 mmol) in THF (50 mL) was refluxed for 72 h. The solution was condensed under reduced pressure, toluene (30 mL) was added to the residue, and the mixture was evaporated twice to give 2.30 g (99%) of **4e** as a white solid: mp 187 °C dec; $^1$H NMR (270 MHz, $D_2O$) δ 0.98 (s, 3H), 1.10 (s, 3H), 1.65 (br d, *J* = 6.8 Hz, 3H), 3.36 (d, *J* = 7.8 Hz, 1H), 5.33−5.42 (m, 1H), 5.53−5.65 (m, 1H); MS (ESI) *m/z* 158 (M + H)$^+$.

**3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethyl-4-hexenoic acid (8e):** 38% yield from **4e**; mp 172−174 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.37 (s, 3H), 1.71 (dd, *J* = 1.4, 6.2 Hz, 3H), 4.64 (br t, *J* = 9.2 Hz, 1H), 5.38 (ddd, *J* = 1.4, 7.8, 15.1 Hz, 1H), 5.81 (dt, *J* = 6.2 Hz, 15.1 Hz, 1H), 7.29 (br d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H); MS (ESI) *m/z 285* (M − H)$^-$.

**General Procedure C for Preparation of 10: Benzyl *N*-[3-(*N*-4-Cyanobenzoyl)amino-2,2-dimethylpentanoyl]-piperidine-4-acetate (10b).** To a solution of **8b** (0.5 g, 1.82 mmol) and benzyl piperidine-4-acetate (2.2 g, 5.47 mmol) in $CH_2Cl_2$ (30 mL) were added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent, 0.9 g, 2.0 mmol) and DIEA (0.36 mL, 2.0 mmol), and the mixture was stirred at room temperature for 18 h. After the solvent was removed in vacuo, the residue was dissolved in EtOAc (50 mL), washed with 5% citric acid, 5% sodium bicarbonate, and saturated NaCl, dried over $Na_2SO_4$, and concentrated in vacuo. The residual oil (0.78 g) was applied to a silica gel column (2.2 × 25 cm) and eluted with EtOAc−hexane (1:4 to 1:1) to give 0.60 g (67%) of **10b** as an oil; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.94 (t, $J$ = 7.8 Hz, 3H), 1.07−1.30 (m, 2H), 1.33 (s, 3H), 1.41 (s, 3H), 1.63−1.86 (m, 4H), 1.98−2.17 (m, 1H), 2.31 (d, $J$ = 6.8 Hz, 2H), 2.69−2.92 (m, 2H), 3.95 (dt, $J$ = 3.9, 9.8 Hz, 1H), 4.36 (br d, $J$ = 12.7 Hz, 2H), 5.12 (s, 2H), 7.35 (m, 5H), 7.67−7.76 (m, 1H), 7.72 (d, $J$ = 8.3 Hz, 2H), 7.90 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 11.7, 23.9, 24.5, 24.6, 31.9, 32.2, 33.1, 40.7, 46.2, 62.1, 66.3, 114.7, 118.1, 127.6, 128.2, 128.3, 128.6, 132.3, 135.8, 138.8, 165.5, 171.9, 175.4; MS (ESI) $m/z$ 512 (M + Na)$^+$.

Compounds **10a**,**c**−**p** were prepared according to the general procedure C described for **10b** starting from the appropriate intermediates (**8a**−**p**) by coupling with benzyl piperidine-4-acetate for **10c**,**d**,**f**,**h**−**l**,**n**,**o** or methyl piperidine-4-acetate for **10a**,**e**,**g**,**m**,**p**.

**Methyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethylbutanoyl]piperidine-4-acetate (10a):** 98% yield from **8a**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.09−1.35 (m, 2H), 1.34 (d, $J$ = 6.2 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.73−1.87 (m, 2H), 1.96−2.13 (m, 1H), 2.26 (d, $J$ = 7.3 Hz, 2H), 2.72−2.89 (m, 2H), 3.67 (s, 3H), 4.10−4.20 (m, 1H), 4.37 (br d, $J$ = 13.5 Hz, 2H), 7.71 (d, $J$ = 8.4 Hz, 2H), 7.88 (d, $J$ = 8.4 Hz, 2H), 7.92 (d, $J$ = 9.5 Hz, 1H); MS (ESI) $m/z$ 422 (M + Na)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethylhexanoyl]piperidine-4-acetate (10c):** 25% yield from **8c**; mp 113−114 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.19 (t, $J$ = 7.3 Hz, 3H), 1.08−1.46 (m, 4H), 1.33 (s, 3H), 1.41 (s, 3H), 1.55−1.85 (m, 4H), 1.98−2.16 (m, 1H), 2.31 (d, $J$ = 7.3 Hz, 2H), 2.68−2.89 (m, 2H), 4.03 (dt, $J$ = 3.0, 10.3 Hz, 1H), 4.36 (br d, $J$ = 13.2 Hz, 2H), 5.12 (s, 2H), 7.35 (m, 5H), 7.67−7.76 (m, NH), 7.72 (d, $J$ = 8.3 Hz, 2H), 7.89 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 14.0, 20.4, 24.5, 24.7, 31.9, 32.2, 33.1, 33.3, 40.7, 46.2, 60.3, 66.3, 114.7, 118.1, 127.6, 128.2, 128.3, 128.6, 132.3, 135.8, 138.8, 165.3, 171.9, 175.5; MS (ESI) $m/z$ 526 (M + Na)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-4-methylpentanoyl]piperidine-4-acetate (10d):** 15% yield from **8d**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93 (d, $J$ = 6.4 Hz, 3H), 1.02 (d, $J$ = 6.4 Hz, 3H), 1.08−1.27 (m, 2H), 1.30 (s, 3H), 1.40 (s, 3H), 1.75−1.88 (m, 2H), 1.97−2.18 (m, 2H), 2.33 (d, $J$ = 6.8 Hz, 2H), 2.69−2.95 (m, 2H), 4.11 (dd, $J$ = 5.4, 9.8 Hz, 1H), 4.45 (br d, $J$ = 13.2 Hz, 2H), 5.12 (s, 2H), 7.35 (m, 5H), 7.75 (d, $J$ = 8.3 Hz, 2H), 7.84−7.93 (m, 1H), 7.92 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 19.3, 22.7, 24.3, 24.6, 29.9, 31.7, 32.0, 33.0, 40.6, 46.6, 62.5, 66.3, 114.6, 118.0, 127.6, 128.1, 128.2, 128.4, 132.3, 135.6, 138.6, 166.1, 172.1, 175.9; MS (ESI) $m/z$ 504 (M + H)$^+$.

**Methyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-4-hexenoyl]piperidine-4-acetate (10e):** 78% yield from **8e**; mp 105−108 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.07−1.42 (m, 2H), 1.35 (s, 3H), 1.37 (s, 3H), 1.68 (d, $J$ = 4.9 Hz, 3H), 1.73−1.87 (m, 2H), 1.98−2.14 (m, 1H), 2.27 (d, $J$ = 6.8 Hz, 2H), 2.69−2.90 (m, 2H), 3.68 (s, 3H), 4.32−4.77 (m, 3H), 5.68−5.76 (m, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.90 (d, $J$ = 8.4 Hz, 2H), 8.08 (d, $J$ = 12.6 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 17.8, 24.1, 24.5, 31.9, 32.2, 33.0, 40.5, 44.9, 45.1, 45.7, 51.5, 63.2, 114.7, 118.2, 127.7, 128.9, 130.0, 132.3, 138.8, 164.4, 172.5, 175.2; MS (ESI) $m/z$ 448 (M + Na)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethylheptanoyl]piperidine-4-acetate (10f):** 58% yield from **8f**; mp 104−107 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.86 (t, $J$ = 6.0 Hz, 3H), 1.15−1.45 (m, 6H) 1.33 (s, 3H), 1.41 (s, 3H), 1.70 (br s, 2H), 1.79 (d, $J$ = 12.8 Hz), 2.04−2.13 (m, 1H), 2.31 (d, $J$ = 7.6 Hz, 2H), 2.80 (br s, 2H), 4.04 (dt, $J$ = 2.8, 6.8 Hz, 1H), 4.38 (br d, $J$ = 11.6 Hz, 2H), 5.12 (s, 2H), 7.30−7.38 (m, 5H), 7.71 (d, $J$ = 8.0 Hz, 2H), 7.90 (d, $J$ = 8.0 Hz, 2H); MS (ESI) $m/z$ 540 (M + Na)$^+$.

**Methyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-5-methylhexanoyl]piperidine-4-acetate (10g):** 33% yield from **8g**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.90 (d, $J$ = 6.3 Hz, 3H), 0.96 (d, $J$ = 6.3 Hz, 3H), 1.07−1.29 (m, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.33−1.44 (m, 2H), 1.70−1.86 (m, 2H), 1.97−2.15 (m, 1H), 2.27 (d, $J$ = 6.8 Hz, 2H), 2.71−2.92 (m, 2H), 3.68 (s, 3H), 4.10 (dt, $J$ = 2.4, 10.3 Hz, 1H), 4.38 (br d, $J$ = 12.7 Hz, 2H), 7.66 (d, $J$ = 10.3 Hz, 1H), 7.72 (d, $J$ = 8.8 Hz, 2H), 7.89 (d, $J$ = 8.8 Hz, 2H), MS (ESI) $m/z$ 442 (M + H)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyloctanoyl]piperidine-4-acetate (10h):** 76% yield from **8h**; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.75 (t, $J$ = 7.0 Hz, 3H), 1.03−1.35 (m, 8H), 1.24 (s, 3H), 1.32 (s, 3H), 1.52−1.66 (m, 2H), 1.70 (br d, $J$ = 13.2 Hz, 2H), 1.94−2.03 (m, 1H), 2.22 (d, $J$ = 8.4 Hz, 2H), 2.71 (br s, 2H), 3.96 (dt, $J$ = 2.8, 10.4 Hz, 1H), 4.29 (d, $J$ = 12.4 Hz, 2H), 5.03 (s, 2H), 7.21−7.29 (m, 5H), 7.62 (d, $J$ = 8.4 Hz, 2H), 7.81 (d, $J$ = 8.4 Hz, 2H); MS (ESI) $m/z$ 532 (M + H)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-5-phenylpentanoyl]piperidine-4-acetate (10i):** 66% yield from all of the crude product of **8i** obtained in the previous step; mp 162−164 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.76−0.89 (m, 1H), 1.05 (br dd, $J$ = 12.0, 11.0 Hz, 2H), 1.24 (s, 3H), 1.27 (s, 3H), 1.64−1.72 (m, 2H), 1.83−2.11 (m, 3H), 2.21 (d, $J$ = 6.8 Hz, 1H), 2.47−2.57 (m, 1H), 2.57−2.69 (m, 2H), 4.03 (dt, $J$ = 9.6, 0.3 Hz), 4.18−4.29 (m, 2H), 5.04 (s, 2H), 7.05−7.12 (m, 3H), 7.15−7.19 (m, 2H), 7.25−7.29 (m, 5H), 7.64 (d, $J$ = 8.0 Hz, 2H), 7.80 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 24.3, 24.5, 24.6, 31.8, 32.2, 33.0, 33.2, 33.5, 40.6, 44.9, 46.3, 60.0, 65.2, 66.3, 125.8, 127.0, 127.7, 128.2, 128.3, 128.5, 128.6, 132.3, 135.8, 138.6, 141.8; MS (ESI) $m/z$ 588 (M + Na)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-3-(2-naphthyl)propionyl]piperidine-4-acetate (10j):** 45% yield from **8j**; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.67−0.72 (m, 0.5H), 0.72−1.35 (m, 3.5H), 1.35−1.50 (m, 3H), 1.50−1.76 (m, 1H), 1.83−1.92 (m, 1H), 2.02−2.09 (m, 1.4H), 2.14−2.24 (m, 0.6H), 2.48−2.93 (m, 2H), 2.57−2.63 (m, 2H), 4.10−4.35 (br s, 2H), 4.97−5.06 (m, 1H), 5.06−5.20 (m, 2H), 7.15−7.89 (m, 16H), $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 23.0, 24.8, 25.4, 25.5, 25.9, 26.7, 27.1, 31.7, 32.0, 32.8, 33.2, 33.9, 36.2, 36.3, 38.8, 40.2, 41.0, 45.4, 45.5, 46.3, 46.9, 47.0, 51.7, 61.3, 63.7, 66.0, 66.2, 67.1, 114.7, 118.1, 125.1, 126.0, 126.1, 126.2, 126.7, 127.1, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.05, 128.1, 128.2, 128.4, 128.5, 128.6, 132.2, 132.3, 132.7, 132.8, 133.0, 135.0, 135.7, 136.0, 136.1, 136.8, 136.9, 138.4, 164.2, 164.3, 171.8, 172.5, 175.6, 177.0; MS (ESI) $m/z$ 588 (M + H)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-3-(4-chlorophenyl)propionyl]piperidine-4-acetate (10k):** 45% yield from **8k**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.89−1.15 (m, 2H), 1.22 (s, 3H), 1.42 (s, 3H), 1.69 (br t, $J$ = 13.6 Hz, 2H), 1.88−2.07 (m, 1H), 2.20 (d, $J$ = 6.8 Hz, 2H), 2.68 (br q, $J$ = 12.0 Hz, 2H), 4.13−4.38 (m, 2H), 4.93 (d, $J$ = 8.8 Hz, 1H), 5.04 (s, 2H), 7.18 (d, $J$ = 8.4 Hz, 2H), 7.34 (d, $J$ = 8.4 Hz, 2H), 7.15−7.37 (m, 5H), 7.64 (d, $J$ = 8.0 Hz, 2H), 7.83 (d, $J$ = 8.0 Hz, 2H), 8.97 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 25.2, 26.2, 31.7, 32.2, 32.9, 40.6, 45.4, 45.5, 46.6, 63.5, 66.3, 114.9, 118.1, 127.7, 128.2, 128.3, 128.6, 130.6, 132.3, 133.4, 135.7, 138.0, 138.2, 164.4, 171.8, 175.5; MS (ESI) $m/z$ 594 (M + Na)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-3-(4-benzyloxyphenyl)propionyl]piperidine-4-acetate (10l):** 49% yield from **8l**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.97−1.37 (m, 2H), 1.31 (s, 3H), 1.48 (s, 3H), 1.63−1.84 (m, 2H), 1.94−2.18 (m, 1H), 2.26 (d, $J$ = 6.8 Hz, 2H), 2.56−2.84 (m, 2H), 4.17−4.41 (m, 2H), 5.00 (d, $J$ = 8.8 Hz, 1H), 5.02 (s, 2H), 5.11 (s, 2H), 6.89 (d, $J$ = 8.8 Hz, 2H), 7.22−7.52 (m, 12H), 7.69 (d, $J$ = 8.3 Hz, 2H), 7.91 (d, $J$ = 8.3 Hz, 2H), 8.94 (d, $J$ = 8.8 Hz, 1H); MS (ESI) $m/z$ 666 (M + Na)$^+$.

**Methyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-3-(3-chlorophenyl)propionyl]piperidine-4-acetate (10m):** 65% yield from **8m**; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.01 (br dd, $J$ = 11.1, 25.2 Hz, 1H), 1.16 (ddd, $J$ = 4.0, 12.4, 25.2 Hz, 1H), 1.33 (s, 3H), 1.51 (s, 3H), 1.70 (br d, $J$ = 16.0 Hz, 1H), 1.79 (br d, $J$ = 16.4 Hz, 1H), 1.96−2.10 (m, 1H), 2.23 (d, $J$ = 6.8 Hz, 2H), 2.71 (dd, $J$ = 10.8, 1.2 Hz, 1H), 2.67−2.86 (m, 1H), 3.67 (s, 3H), 4.33 (br s, 2H), 4.99 (d, $J$ = 9.2 Hz, 1H), 7.23−7.25 (m, 2H), 7.30−7.36 (m, 1H), 7.46 (s, 1H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.92 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 25.3, 26.5, 31.8, 32.1, 32.9, 40.4, 45.4, 46.7, 51.5, 63.5, 114.9, 118.1, 127.6, 127.75, 127.82, 129.0, 129.4, 132.4, 134.1, 138.2, 141.6, 164.4, 172.5, 175.6; MS (ESI) $m/z$ 518 (M + Na)$^+$.

**Benzyl *N*-[3-(*N*-4-cyanobenzoyl)amino-2,2-dimethyl-3-(3-benzyloxyphenyl)propionyl]piperidine-4-acetate (10n):** 60% yield from **8n**; $^{1}$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.84−1.38 (m, 2H), 1.33 (s, 3H), 1.48 (s, 3H), 1.72 (br t, $J$ = 10.7 Hz, 2H), 1.92−2.12 (m, 1H), 2.25 (d, $J$ = 6.8 Hz, 2H), 2.54−2.73 (m, 2H), 4.11−4.38 (m, 2H), 4.99 (d, $J$ = 8.8 Hz, 1H), 5.06 (s, 2H), 5.10 (s, 2H), 6.87 (dd, $J$ = 3.0, 8.5 Hz, 1H), 6.95−7.09 (m, 2H), 7.17−7.43 (m, 11H), 7.66 (d, $J$ = 8.3 Hz, 2H), 7.90 (d, $J$ = 8.3 Hz, 2H), 8.94 (d, $J$ = 8.8 Hz, 1H); MS (ESI) $m/z$ 666 (M + Na)$^+$.

**Benzyl *N*-[3-[(*N*-4-cyanobenzoyl)-(*N*-methyl)]amino-2,2-dimethyl-3-phenylpropionyl]piperidine-4-acetate (10o):** 98% yield from **8o**; $^{1}$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.53 (s, 3H), 1.57 (s, 3H), 1.53−1.82 (m, 4H), 1.94 (br s, 1H), 2.13 (d, $J$ = 6.8 Hz, 2H), 2.53−2.90 (m, 2H), 2.67 (s, 3H), 4.48 (br t, $J$ = 13.6 Hz, 2H), 5.08 (s, 2H), 5.06−5.20 (m, 1H), 7.24−7.50 (m, 10H), 7.53 (d, $J$ = 7.8 Hz, 2H), 7.74 (d, $J$ = 7.8 Hz, 2H); MS (ESI) $m/z$ 574 (M + Na)$^+$.

**Methyl *N*-[3-[(*N*-4-cyanobenzoyl)-(*N*-propargyl)]amino-2,2-dimethylheptanoyl]piperidine-4-acetate (10p):** 52% yield from all of the crude product of **8p** obtained in the previous step; $^{1}$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.80−0.98 (m, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.08−1.58 (m, 8H), 1.64−1.92 (m, 2H), 1.96−2.16 (m, 1H), 2.18−2.31 (m, 3H), 2.70−3.04 (m, 2H), 3.65 (s, 3H), 3.92−4.18 (m, 2H), 4.55−4.76 (m, 2H), 5.20 (br d, $J$ = 11.2 Hz, 1H), 7.73 (d, $J$ = 8.3 Hz, 2H), 7.93 (d, $J$ = 8.3 Hz, 2H); MS (ESI) $m/z$ 502 (M + Na)$^+$.

**General Procedure D for Preparation of Compound 1 Analogues. *N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (19).** A solution of the nitrile **10b** (245 mg, 0.5 mmol) in pyridine (40 mL) was bubbled with 10% $H_2S/N_2$ gas for 15 min in the presence of triethylamine (1 mL) and allowed to stand at room temperature for 24 h. The solvent was removed by evaporation, and then toluene (30 mL) was added to the residue and evaporated twice. The resulting yellow powder and MeI (1.2 mL) were dissolved in acetone (20 mL) and refluxed for 1 h. After evaporation, to the residual pale yellow oil was added ammonium acetate (0.6 g) in MeOH (25 mL), and the mixture was refluxed for 1.5 h. The solvent was removed by evaporation, and the residue was dissolved in $CHCl_3$. The mixture was washed with saturated NaCl, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residual oil (0.78 g) was applied to a silica gel column (1.5 × 18 cm) and eluted with $CHCl_3$−MeOH (10:1) to give 80 mg (32%) of **11b** as an oil: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.84 (t, $J$ = 7.0 Hz, 3H), 1.07−1.22 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H), 1.53−2.07 (m, 5H), 2.28 (d, $J$ = 7.2 Hz, 2H), 2.58−2.96 (m, 2H), 4.09 (t, $J$ = 6.8 Hz, 1H), 4.34 (d, $J$ = 12.0 Hz, 2H), 5.10 (s, 2H), 7.28−7.37 (m, 5H), 7.83 (d, $J$ = 8.4 Hz, 2H), 7.92 (d, $J$ = 8.4 Hz, 2H), 8.18 (br s, 3H); MS (ESI) $m/z$ 507 (M + H)$^+$. To a solution of **11b** (40 mg, 0.079 mmol) in 20 mL of 90% aqueous MeOH containing 2% AcOH was added 10 mg of 20% $Pd(OH)_2$ on carbon, and the mixture was stirred at room temperature for 15 min under atmospheric hydrogen pressure. After the catalyst was filtered off and the filtrate was concentrated under reduced pressure, the residue was dissolved in 1 N AcOH and purified over preparative reverse phased HPLC ($\mu$Bondasphere 5$C_{18}$ 100 Å, 19 × 150 mm) eluted in a linear gradient with 20% to 30% acetonitrile in 0.1% aqueous TFA over 20 min at a flow rate of 17 mL/min) to give 21 mg (64%) of **19** (TFA salt) as a white fluffy powder: $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89−0.99 (m, 3H), 1.12−1.26 (m, 2H), 1.27 (s, 3H), 1.30 (s, 3H), 1.53−1.70 (m, 2H), 1.84 (br t, $J$ = 14.8 Hz, 2H), 2.00−2.14 (m, 1H), 2.21−2.30 (m, 2H), 2.75−3.10 (br, 2H), 4.47 (m, 1H), 4.55 (br d, $J$ = 13.6 Hz, 2H), 7.89 (d, $J$ = 8.4 Hz, 2H), 7.99 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 12.7, 27.1, 24.6, 25.0, 34.0, 34.1, 35.1, 42.3, 47.5, 130.1, 133.1, 144.9, 168.8, 170.5, 176.8, 177.1; MS (ESI) $m/z$ 417 (M + H)$^+$; HRMS (FAB) calcd for $C_{22}H_{33}N_4O_4$ (M + H)$^+$ 417.2501, found 417.2473; HPLC[a] K′ 8.49. Anal. ($C_{22}H_{32}N_4O_4 \cdot CF_3COOH \cdot H_2O$) C, H, N.

Compounds **18** and **20**−**33** were prepared according to the general procedure D described for **19** starting from the appropriate intermediates (**10a**−**p**). However, in compounds **18**, **22**, **24**, **30**, and **33**, methyl ester for the protection of carboxylic acid was removed by the procedure described for **18**.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethylbutanoyl]-piperidine-4-acetic Acid (18).** All of the crude product of **11a** (0.68 g), which was prepared according to the general procedure D for **19** from **10a** (0.60 g, 1.5 mmol), was dissolved in 80% aqueous MeOH (10 mL). To the solution was added LiOH (54 mg, 2.25 mmol), and the mixture was stirred at room temperature for 30 min. After solvent was removed in vacuo, the residue was dissolved in 1 N AcOH (3 mL) and purified over preparative reverse phased HPLC ($\mu$Bondasphere 5$C_{18}$ 100 Å, 19 × 150 mm) eluted in a linear gradient with 9% to 14% acetonitrile in 0.1% TFA over 15 min at a flow rate of 17 mL/min) to give **18** (TFA salt) as a white fluffy powder (0.36 g, 46%): $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.00−1.25 (m, 2H), 1.18−1.22 (m, 3H), 1.41−1.46 (m, 3H), 1.60−1.63 (m, 3H), 1.68−1.95 (m, 2H), 2.00−2.14 (m, 1H), 2.19−2.29 (m, 2H), 2.64−2.70 (m, 1H), 3.09−3.20 (m, 1H), 3.29−3.31 (m, 3H), 3.46−3.52 (m 1H), 4.23−4.30 (m, 1H), 4.55−4.65 (m, 1H), 7.81−7.99 (m, 4H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 14.5, 14.7, 15.1, 25.7, 25.8, 26.4, 26.8, 33.6, 33.7, 34.4, 34.9, 35.0, 35.1, 42.17, 42.24, 43.3, 43.4, 44.0, 44.1, 58.1, 58.3, 129.5, 129.66, 129.71, 130.2, 133.0, 134.5, 142.8, 168.6, 168.7, 168.8, 176.8, 177.0; MS (ESI) $m/z$ 403 (M + H)$^+$; HRMS (FAB) calcd for $C_{21}H_{31}N_4O_4$ (M + H)$^+$ 403.2345, found 403.2380. Anal. ($C_{21}H_{30}N_4O_4 \cdot 2CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethylhexanoyl]piperidine-4-acetic acid (20):** 32% yield from **10c**; $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.90−0.97 (m, 3H), 1.15−1.36 (m, 3H), 1.27 (s, 3H), 1.31 (m, 3H), 1.36−1.47 (m, 2H), 1.58−1.71 (m, 1H), 1.76−1.89 (m, 2H), 1.97−2.13 (m, 1H), 2.19−2.28 (m, 2H), 4.48−4.63 (m, 3H), 7.83−7.92 (m, 2H), 7.94−8.02 (m, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 15.0, 22.0, 24.1, 24.6, 34.1, 35.2, 42.4, 56.8, 130.8, 133.1, 141.9, 168.7, 170.2, 176.8, 177.1; MS (ESI) $m/z$ 431 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{35}N_4O_4$ (M + H)$^+$ 431.2658, found 431.2652; HPLC[a] K′ 10.69. Anal. ($C_{23}H_{34}N_4O_4 \cdot CF_3COOH \cdot 1.5H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-4-methypentanoyl]piperidine-4-acetic acid (21):** 38% yield from **10d**; $^{1}$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.97 (d, $J$ = 5.6 Hz, 6H), 1.17−1.32 (m, 6H), 1.28 (m, 6H), 1.83−1.92 (m, 2H), 1.96−2.13 (m, 2H), 2.27 (d, $J$ = 6.8 Hz, 2H), 2.73−3.09 (br s, 2H), 4.45 (br t, $J$ = 8.8 Hz, 1H), 4.48−4.73 (m, 2H), 7.90 (d, $J$ = 7.2 Hz, 2H), 8.01 (d, $J$ = 7.2 Hz, 2H); MS (ESI) $m/z$ 431 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{35}N_4O_4$ (M + H)$^+$ 431.2658, found 431.2626; HPLC[a] K′ 9.72. Anal. ($C_{23}H_{34}N_4O_4 \cdot 1.5CF_3COOH \cdot H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-4-hexenoyl]piperidine-4-acetic acid (22):** 31% yield from **10e**; 1H NMR (400 MHz, $CD_3OD$) $\delta$ 1.13−1.27 (m, 2H), 1.32 (s, 6H), 1.70 (d, $J$ = 5.2 Hz, 3H), 1.82 (br d, $J$ = 12.4 Hz, 2H), 1.96−2.09 (m, 1H), 2.24 (d, $J$ = 6.8 Hz, 2H), 2.60−3.04 (m, 2H), 4.47 (br d, $J$ = 13.2 Hz, 2H), 4.87 (br d, $J$ = 7.2 Hz, 1H), 5.64 (ddd, $J$ = 1.6, 7.2, 15.2 Hz, 1H), 5.73 (dq, $J$ = 5.2, 15.2 Hz, 1H), 7.87 (d, $J$ = 8.8 Hz, 2H), 7.97 (d, $J$ = 8.8 Hz, 2H); MS (ESI) $m/z$ 429 (M + H)$^+$; HRMS (FAB) calcd for $C_{23}H_{33}N_4O_4$ (M + H)$^+$ 429.2501, found 429.2524; HPLC[a] K′ 9.89. Anal. ($C_{23}H_{32}N_4O_4 \cdot 1.5CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethylheptanoyl]piperidine-4-acetic acid (23):** 24% yield from **10f**;

$^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.89 (t, $J$ = 6.8 Hz, 3H), 1.13−1.43 (m, 6H), 1.27 (s, 3H), 1.30 (s, 3H), 1.49 (br dd, $J$ = 6.9, 13.8 Hz, 1H), 1.64 (br dd, $J$ = 11.1, 22.0 Hz, 1H), 1.86 (br t, $J$ = 12.8 Hz, 2H), 2.01−2.12 (m, 1H), 2.25 (d, $J$ = 6.8 Hz, 2H), 2.77−3.08 (br, 2H), 4.52−4.61 (m, 3H), 7.89 (d, $J$ = 8.0 Hz, 2H), 7.99 (d, $J$ = 8.0 Hz, 2H); MS (ESI) $m/z$ 445 $(M + H)^+$; HRMS (FAB) calcd for $C_{24}H_{37}N_4O_4$ $(M + H)^+$ 445.2814, found 445.2792; HPLC[a] K′ 13.31. Anal. ($C_{24}H_{36}N_4O_4$·$CF_3$-COOH·1.5$H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-5-methyhexanoyl]piperidine-4-acetic acid (24):** 23% yield from **10g**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.92 (d, $J$ = 7.2 Hz, 3H), 0.94 (d, $J$ = 6.0 Hz, 3H), 1.11−1.35 (m, 3H), 1.52−1.63 (m, 1H), 1.69 (ddd, $J$ = 3.2, 11.2, 14.4 Hz, 1H), 1.84 (br d, $J$ = 12.8 Hz, 2H), 1.97−2.11 (m, 1H), 2.25 (d, $J$ = 7.2 Hz, 2H), 2.80−3.05 (br s, 2H), 4.48−4.61 (m, 2H), 4.70 (br t, $J$ = 8.8 Hz, 1H), 7.88 (dt, $J$ = 8.8, 2.0 Hz, 2H), 7.98 (dt, $J$ = 8.8, 2.0 Hz, 2H); MS (ESI) $m/z$ 445 $(M + H)^+$; HRMS (FAB) calcd for $C_{24}H_{37}N_4O_4$ $(M + H)^+$ 445.2814, found 445.2788; HPLC[a] K′ 10.95. Anal. ($C_{24}H_{36}N_4O_4$·1.5$CF_3COOH$·0.5$H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyloctanoyl]-piperidine-4-acetic acid (25):** 39% yield from **10h**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.15−1.52 (m, 9H), 1.26 (s, 3H), 1.30 (s, 3H), 1.57−1.69 (m, 1H), 1.85 (br t, $J$ = 12.4 Hz, 2H), 2.02−2.13 (m, 1H), 2.25 (d, $J$ = 6.8 Hz, 2H), 2.70−3.09 (m, 2H), 4.52−4.61 (m, 3H), 7.89 (dt, $J$ = 6.8, 2.0 Hz, 2H), 7.99 (dt, $J$ = 6.8, 2.0 Hz, 2H); MS (ESI) $m/z$ 459 $(M + H)^+$; HRMS (FAB) calcd for $C_{25}H_{39}N_4O_4$ $(M + H)^+$ 459.2971, found 459.2991; HPLC[a] K′ 15.53. Anal. ($C_{25}H_{38}N_4O_4$·1.4$CF_3$-COOH) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-5-phenylpentanoyl]piperidine-4-acetic acid (26):** 17% yield from **10i**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.77−0.97 (br s, 1H), 0.97−1.13 (m, 1H), 1.13−1.28 (m, 6H), 1.62−1.78 (m, 2H), 1.83−1.96 (m, 1H), 1.96−2.11 (m, 1H), 2.18 (d, $J$ = 6.8 Hz, 2H), 2.41−2.57 (m, 2H), 2.68−2.87 (m, 2H), 4.38 (br t, $J$ = 14.4 Hz, 2H), 4.58 (br t, $J$ = 11.2 Hz, 1H), 7.15−7.21 (m, 3H), 7.27 (t, $J$ = 7.2 Hz, 2H), 7.92 (d, $J$ = 7.2 Hz, 2H), 8.04 (d, $J$ = 7.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 23.9, 24.4, 33.7, 33.9, 34.3, 34.6, 35.0, 42.2, 55.0, 128.1, 130.1, 130.4, 130.9, 133.1, 141.9, 143.6, 168.8, 170.5, 176.8; MS (ESI) $m/z$ 493 $(M + H)^+$; HRMS (FAB) calcd for $C_{28}H_{37}N_4O_4$ $(M + H)^+$ 493.2814, found 493.2827; HPLC[a] K′ 14.71. Anal. ($C_{28}H_{36}N_4O_4$·1.3$CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-3-(2-naphthyl)propionyl]piperidine-4-acetic acid (27):** 32% yield from **10j**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.95−1.08 (m, 1H), 1.16−1.29 (m, 1H), 1.36 (s, 3H), 1.41 (m, 3H), 1.79 (br t, $J$ = 12.8 Hz, 2H), 1.92−2.07 (m, 1H), 2.07−2.17 (m, 2H), 2.53−3.07 (br, 1H), 2.99 (br t, $J$ = 13.2 Hz, 1H), 4.55 (br d, $J$ = 13.6 Hz, 2H), 5.76 (s, 1H), 7.42−7.53 (m, 2H), 7.59 (d, $J$ = 8.4 Hz, 1H), 7.81−7.87 (m, 3H), 7.87−7.91 (m, 3H), 7.99 (d, $J$ = 6.8 Hz, 2H); MS (ESI) $m/z$ 515 $(M + H)^+$; HRMS (FAB) calcd for $C_{30}H_{35}N_4O_4$ $(M + H)^+$ 515.2658, found 515.2668; HPLC[a] K′ 18.56. Anal. ($C_{30}H_{34}N_4O_4$·1.5$CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-3-(4-chlorophenyl)propionyl]piperidine-4-acetic acid (28):** 33% yield from **10k**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.09 (q, $J$ = 12.4 Hz, 1H), 1.22 (q, $J$ = 12.4 Hz, 1H), 1.29 (s, 3H), 1.35 (s, 3H), 1.81 (br d, $J$ = 12.0 Hz, 2H), 1.94−2.07 (m, 1H), 2.14−2.25 (m, 2H), 2.75−3.00 (m, 2H), 4.51 (br d, $J$ = 12.0 Hz, 2H), 5.56 (s, 1H), 7.33 (d, $J$ = 8.4 Hz, 2H), 7.44 (d, $J$ = 8.4 Hz, 2H), 7.89 (d, $J$ = 8.8 Hz, 2H), 7.96 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 25.2, 25.7, 33.9, 34.0, 35.0, 42.3, 47.7, 61.6, 130.0, 130.2, 132.3, 133.2, 135.4, 139.6, 141.7, 169.0, 176.6, 176.8; MS (ESI) $m/z$ 499 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{32}ClN_4O_4$ $(M + H)^+$ 499.2111, found 499.2086; HPLC[a] K′ 12.29. Anal. ($C_{26}H_{31}ClN_4O_4$·1.5$CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-3-(4-hydroxyphenyl)propionyl]piperidine-4-acetic acid (29):** 33% yield from **10l**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.08 (dq, $J$ = 1.6, 10.4 Hz, 1H), 1.22 (dq, $J$ = 1.4, 10.4 Hz, 1H), 1.29 (s, 3H), 1.33 (s, 3H), 1.79 (br d, $J$ = 13.2 Hz, 2H), 1.94−2.07 (m, 1H), 2.13−2.24 (m, 2H), 2.55−3.00 (m, 2H), 4.44−4.53 (m, 2H), 5.48 (s, 1H), 6.74 (d, $J$ = 6.8 Hz, 2H), 7.25 (d, $J$ = 8.8 Hz, 2H), 7.87 (d, $J$ = 8.8 Hz, 2H), 7.95 (d, $J$ = 8.8 Hz, 2H); MS (ESI) $m/z$ 481 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{33}N_4O_5$ $(M + H)^+$ 481.2450, found 481.2448; HPLC[a] K′ 8.45. Anal. ($C_{26}H_{32}N_4O_5$·1.5$CF_3COOH$·0.5$H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-3-(3-chlorophenyl)propionyl]piperidine-4-acetic acid (30):** 20% yield from **10m**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.08 (br dd, $J$ = 22.0, 8.0 Hz, 1H), 1.22 (ddd, $J$ = 2.8, 12.4, 24.4 Hz, 1H), 1.30 (s, 3H), 1.36 (s, 3H), 1.81 (br s, 2H), 1.97−2.10 (m, 1H), 2.14−2.25 (m, 2H), 2.80−3.03 (br m, 2H), 4.51 (br d, $J$ = 13.2 Hz, 2H), 5.56 (s, 1H), 7.29−7.34 (m, 2H), 7.39 (dt, $J$ = 6.8, 1.6 Hz, 1H), 7.52 (s, 1H), 7.89 (dt, $J$ = 8.4, 2.0 Hz, 2H), 7.96 (dt, $J$ = 8.4, 2.0 Hz, 2H); MS (ESI) $m/z$ 499 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{32}ClN_4O_4$ $(M + H)^+$ 499.2111, found 499.2095; HPLC[a] K′ 17.02. Anal. ($C_{26}H_{31}ClN_4O_4$·1.5$CF_3$-COOH·0.5$H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)amino-2,2-dimethyl-3-(3-hydroxyphenyl)propionyl]piperidine-4-acetic acid (31):** 27% yield from **10n**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.05 (dq, $J$ = 1.6, 8.8 Hz, 1H), 1.23 (dq, $J$ = 1.6, 12.4 Hz, 1H), 1.32 (s, 3H), 1.36 (s, 3H), 1.79 (br t, $J$ = 11.0 Hz, 2H), 1.92−2.07 (m, 1H), 2.13−2.24 (m, 2H), 2.77−2.98 (m, 2H), 4.48 (br d, $J$ = 13.2 Hz, 2H), 5.46 (s, 1H), 6.71 (dd, $J$ = 1.2, 9.6 Hz, 1H), 6.85 (t, $J$ = 1.2 Hz, 1H), 6.89 (br d, $J$ = 7.6 Hz, 1H), 7.14 (t, $J$ = 7.6 Hz, 1H), 7.88 (d, $J$ = 8.8 Hz, 2H), 7.96 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 25.6, 26.3, 33.9, 35.1, 42.3, 47.7, 62.1, 116.4, 117.5, 121.7, 130.1, 130.9, 133.2, 141.8, 142.2, 159.2, 168.9, 176.8, 177.1; MS (ESI) $m/z$ 481 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{33}N_4O_5$ $(M + H)^+$ 481.2450, found 481.2440; HPLC[a] K′ 9.20. Anal. ($C_{26}H_{32}N_4O_5$·$CF_3COOH$·1.5$H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)-(*N*-methyl)]amino-2,2-dimethyl-3-phenylpropionyl]piperidine-4-acetic acid (32):** 17% yield from **10o**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.28−1.60 (m, 2H), 1.55 (s, 3H), 1.57 (s, 3H), 1.64−1.75 (m, 2H), 1.85−2.00 (m, 1H), 2.06 (m, 2H), 2.71 (s, 3H), 2.60−3.05 (m, 2H), 4.49 (br t, $J$ = 13.5 Hz, 2H), 5.06 (m, 1H), 7.28−7.50 (m, 5H), 7.67 (d, $J$ = 7.6 Hz, 2H), 7.90 (d, $J$ = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 26.8, 27.3, 33.7, 34.9, 38.0, 42.3, 47.5, 48.1, 62.8, 129.2, 130.0, 130.4, 130.5, 131.3, 131.7, 138.9, 144.1, 163.0, 168.8, 174.9, 176.7; MS (ESI) $m/z$ 479 $(M + H)^+$; HRMS (FAB) calcd for $C_{27}H_{35}N_4O_4$ $(M + H)^+$ 479.2658, found 479.2678; HPLC[a] K′ 13.01. Anal. ($C_{27}H_{34}N_4O_4$·1.5$CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidinobenzoyl)-(*N*-propargyl)]amino-2,2-dimethylheptanoyl]piperidine-4-acetic acid (33):** 14% yield from **10p**; $^1$H NMR (270 MHz, $CD_3OD$) $\delta$ 0.95 (t, $J$ = 6.8 Hz, 3H), 1.08−1.68 (m, 8H), 1.36 (s, 3H), 1.42 (s, 3H), 1.77−1.98 (m, 2H), 1.98−2.13 (m, 1H), 2.25 (d, $J$ = 6.8 Hz, 2H), 2.68 (t, $J$ = 2.2 Hz, 1H), 2.76−3.09 (m, 2H), 4.06 (dd, $J$ = 25.5, 2.2 Hz, 1H), 4.15 (dd, $J$ = 25.5, 2.2 Hz, 1H), 4.58−4.74 (m, 2H), 5.27 (br d, $J$ = 16.1 Hz, 1H), 7.67 (d, $J$ = 8.8 Hz, 2H), 7.90 (d, $J$ = 8.8 Hz, 2H); MS (ESI) $m/z$ 483 $(M + H)^+$; HRMS (FAB) calcd for $C_{27}H_{39}N_4O_4$ $(M + H)^+$ 483.2971, found 483.2984; HPLC[a] K′ 14.66. Anal. ($C_{27}H_{38}N_4O_4$·1.4$CF_3COOH$) C, H, N.

**General Procedure E for Preparation of Boc-Protected *β*-Alanine Analogues: 3-(*N*-Boc)amino-2,2-dimethylheptanoic acid (12f).** 3-Amino-2,2-dimethylheptanoic acid hydrochloride **4f** (3.65 g, 17.4 mmol) was dissolved in 10% $Na_2CO_3$ (18.4 mL), and di-*tert*-butyl dicarbonate (4.6 g, 20.87 mmol) in dioxane (50 mL) was added to the above ice-chilled solution. After being stirred at room temperature overnight, the solution was washed with ether (100 mL) and the aqueous phase was acidified to pH 3 with citric acid. The resulting powder was dissolved in EtOAc (70 mL), and the organic phase was washed with saturated NaCl, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was recrystallized from EtOAc with ether−hexane (1:1): yield 3.16 g (66%); mp 125−126 °C; $^1$H NMR (270 MHz, $CD_3OD$) $\delta$ 0.84−0.93 (m, 3H), 1.06 (s, 3H), 1.14 (s, 3H), 1.22−1.46 (m, 6H), 1.44 (s, 9H), 3.17−3.82 (m, 1H); MS (ESI) $m/z$ 296 $(M + Na)^+$.

Compounds **12a**,**b**,**q** were prepared according to the general procedure E described for **12f** starting from the appropriate $\beta$-alanine analogues (**4a**,**b**,**q**).

**3-(*N*-Boc)amino-2,2-dimethylbutanoic acid (12a):** 31% yield from **4a**; mp 123−124 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.15 (d, $J$ = 6.8 Hz, 3H), 1.33 (s, 3H), 1.37 (s, 3H), 1.46 (s, 9H), 3.15 (q, $J$ = 6.8 Hz, 1H); MS (ESI) $m/z$ 232 $(M + H)^+$.

**3-(*N*-Boc)amino-2,2-dimethylpentanoic acid (12b):** 98% yield from **4b**; mp 146−149 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.94 (t, $J$ = 7.3 Hz, 3H), 1.23 (s, 6H), 1.17−1.32 (m, 1H), 1.45 (s, 9H), 1.68 (ddq, $J$ = 14.2, 7.8, 2.9 Hz, 1H), 3.55 (dt, $J$ = 10.7, 2.4 Hz, 1H), 4.93 (d, $J$ = 10.7 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 11.2, 22.9, 23.3, 24.3, 28.3, 46.3, 58.6, 79.1, 156.5, 182.7; MS (ESI) $m/z$ 246 $(M + H)^+$.

**3-(*N*-Boc)amino-2,2-dimethyl-3-phenylpropionic acid (12q):** 95% yield from 3-amino-2,2-dimethyl-3-phenylpropionic acid hydrochloride;[16] mp 144−146 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.15 (s, 3H), 1.26 (br s, 3H), 1.40 (br s, 9H), 4.74 (d, $J$ = 9.2 Hz, 1H), 6.05 (d, $J$ = 9.2 Hz, 1H), 7.22−7.34 (m, 5H); MS (ESI) $m/z$ 294 $(M + H)^+$.

**General Procedure F for Preparation of 13: Methyl *N*-[3-(*N*-Boc)amino-2,2-dimethylheptanoyl]piperidine-4-acetate (13f).** To a solution of **12f** (1.68 g, 6.13 mmol) and methyl piperidine-4-acetate (1.45 g, 9.12 mmol) in $CH_2Cl_2$ (20 mL) were added *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 2.8 g, 7.37 mmol) and DIEA (6.58 mL, 36.8 mmol), and the mixture was stirred at room temperature for 18 h. After the solvent was removed by evaporation, the residue was dissolved in EtOAc (50 mL). The organic layer was washed with 5% citric acid (3 × 30 mL), 5% $NaHCO_3$ (3 × 30 mL), and saturated NaCl (3 × 30 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica (2.2 × 20 cm) using hexane−EtOAc (2:1) as an eluent to give 1.70 g (67%) of **13f** as a white powder: mp 106−108 °C; $^1$H NMR (270 MHz, $CD_3OD$) $\delta$ 0.84−0.93 (m, 3H), 1.10 (s, 3H), 1.21 (s, 3H), 1.06−1.42 (m, 8H), 1.44 (s, 9H), 1.73−1.86 (m, 2H), 1.95−2.12 (m, 1H), 2.28 (d, $J$ = 6.8 Hz, 2H), 2.74−3.02 (m, 2H), 3.65 (s, 3H), 3.88−4.01 (m, 1H), 4.42−4.57 (m, 2H), 6.55 (d, $J$ = 9.8 Hz, 1H); MS (ESI) $m/z$ 435 $(M + Na)^+$.

Compounds **13a**,**b**,**q** were prepared according to the general procedure F described for **13f** starting from the appropriate intermediates (**12a**,**b**,**q**).

**Ethyl *N*-[3-(*N*-Boc)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (13b):** 91% yield from **12b**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 7.3 Hz, 3H), 1.12−1.30 (m, 2H), 1.22 (s, 3H), 1.26 (t, $J$ = 7.3 Hz, 3H), 1.27 (s, 3H), 1.32−1.58 (m, 2H), 1.43 (s, 9H), 1.79 (br d, $J$ = 11.2 Hz, 2H), 1.93−2.14 (br m, 1H), 2.24 (d, $J$ = 6.8 Hz, 2H), 2.81 (br q, $J$ = 12.7 Hz, 2H), 3.66 (dt, $J$ = 10.3, 2.9 Hz, 1H), 4.14 (q, $J$ = 6.8 Hz, 2H), 4.37−4.54 (br m, 2H), 4.96 (d, $J$ = 10.3 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 11.5, 14.2, 23.0, 23.5, 24.3, 28.3, 32.1, 33.1, 40.9, 45.0, 45.3, 47.0, 59.3, 60.3, 77.2, 78.7, 156.6, 172.2, 174.5; MS (ESI) $m/z$ 399 $(M + H)^+$.

**Benzyl *N*-[3-(*N*-Boc)amino-2,2-dimethyl-3-phenylpropionyl]piperidine-4-acetate (13q):** 98% yield from **12q**; mp 128−131 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.19 (s, 3H), 1.32 (s, 3H), 1.37 (s, 9H), 1.02−1.28 (m, 2H), 1.68−1.79 (m, 2H), 1.94−2.11 (m, 1H), 2.27 (d, $J$ = 6.8 Hz, 2H), 2.68−2.82 (m, 2H), 4.28−4.44 (m, 2H), 4.83 (br d, $J$ = 8.8 Hz, 2H), 5.11 (s, 2H), 5.98 (br s, 1H), 7.18−7.36 (m, 10H); MS (ESI) $m/z$ 509 $(M + H)^+$.

**General Procedure G for Preparation of 14: Methyl *N*-[3-(*N*-4-Cyano-2-fluorobenzoyl)amino-2,2-dimethylheptanoyl]piperidine-4-acetate (14f).** To **13f** (0.77 g, 1.86 mmol) were added anisole (0.7 mL) and TFA (20 mL). The reaction mixture was stirred for 1 h under cooling with ice. After TFA was removed in vacuo at room temperature, the resulting residue was washed with hexane three times and dissolved in DMF (20 mL) under cooling with ice. After being neutralized by triethylamine, 2-fluoro-4-cyanobenzoic acid (0.40 g, 2.42 mmol), 1-hydroxybenzotriazole (HOBt, 0.33 g, 2.42 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl, 0.56 g, 2.91 mmol) were added, and the mixture was stirred overnight. After the solvent was removed by evaporation, the resulting residue was dissolved in EtOAc (50 mL), washed with 5% citric acid (3 × 30 mL), 5% $NaHCO_3$ (3 × 30 mL), and saturated NaCl (3 × 30 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica (1.8 × 20 cm) using hexane−EtOAc (3:1) as an eluent to give a powder of **13f** (0.37 g, 43%): mp 128−132 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.87 (m, 3H), 1.08−1.42 (m, 6H), 1.34 (s, 3H), 1.40 (s, 3H), 1.59−1.75 (m, 2H), 1.73−1.86 (m, 2H), 1.96−2.15 (m, 1H), 2.27 (d, $J$ = 6.8 Hz, 2H), 2.81 (m, 2H), 3.68 (s, 3H), 4.12 (m, 1H), 4.40 (br d, $J$ = 13.2 Hz, 2H), 7.44 (dd, $J$ = 1.5, 10.7 Hz, 1H), 7.55 (dd, $J$ = 1.5, 8.3 Hz, 1H), 7.81 (br t, $J$ = 9.3 Hz, 1H), 8.12 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 14.0, 22.5, 24.2, 24.4, 29.4, 30.8, 32.0, 32.2, 33.1, 40.6, 46.4, 51.5, 59.9, 115.8, 115.9, 116.8, 116.9, 119.8, 120.3, 126.6, 126.8, 128.3, 128.4, 132.89, 132.94, 157.8, 161.5, 161.7, 161.8, 172.6, 174.9; MS (ESI) $m/z$ 482 $(M + Na)^+$.

Compounds **14a**,**b**,**q** were prepared according to the general procedure G described for **14f** starting from the appropriate intermediates (**13a**,**b**,**q**).

**Methyl *N*-[3-(*N*-4-cyano-2-fluorobenzoyl)amino-2,2-dimethylbutanoyl]piperidine-4-acetate (14a):** 21% yield from all of the crude product of **13a** obtained in previous step; $^1$H NMR (270 MHz, $CD_3OD$) $\delta$ 1.23 (d, $J$ = 6.8 Hz, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.83 (br d, $J$ = 12.7 Hz, 2H), 1.93−2.14 (m, 1H), 2.25 (d, $J$ = 6.8 Hz, 2H), 2.80−3.05 (m, 2H), 3.30 (s, 3H), 4.49 (br d, $J$ = 13.2 Hz, 2H), 4.55−4.71 (m, 1H), 7.69 (d, $J$ = 9.3 Hz, 2H), 7.86 (t, $J$ = 7.8 Hz, 1H); MS (ESI) $m/z$ 440 $(M + Na)^+$.

**Ethyl *N*-[3-(*N*-4-cyano-2-fluorobenzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (14b):** 77% yield from **13b**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.00 (t, $J$ = 7.3 Hz, 3H), 1.13−1.40 (m, 2H), 1.31 (t, $J$ = 7.3 Hz, 3H), 1.39 (s, 3H), 1.46 (s, 3H), 1.68−1.93 (m, 4H), 2.02−2.23 (br m, 1H), 2.31 (d, $J$ = 6.8 Hz, 2H), 2.90 (br t, $J$ = 11.2 Hz, 2H), 4.10−4.25 (m, 1H), 4.18 (q, $J$ = 6.8 Hz, 2H), 4.48 (br d, $J$ = 12.7 Hz, 2H), 7.50−7.68 (m, 2H), 7.89 (br t, $J$ = 7.8 Hz, 1H), 8.11 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) 11.2, 13.6, 23.4, 23.5, 23.7, 31.5, 31.7, 32.6, 40.3, 44.5, 44.8, 45.9, 59.8, 60.5, 115.2, 115.3, 116.3, 119.4, 119.8, 126.5, 126.7, 127.8, 127.9, 132.1, 157.2, 160.9, 161.7, 161.8, 171.6, 174.2; MS (ESI) $m/z$ 469 $(M + Na)^+$.

**Benzyl *N*-[3-(*N*-4-cyano-2-chlorobenzoyl)amino-2,2-dimethyl-3-phenylpropionyl]piperidine-4-acetate (14q):** 63% yield from **13q**; mp 155−157 °C; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93−1.25 (m, 2H), 1.31 (s, 3H), 1.52 (s, 3H), 1.63−1.79 (m, 2H), 1.93−2.10 (m, 1H), 2.26 (d, $J$ = 7.3 Hz, 2H), 2.59−2.84 (m, 2H), 4.30 (br t, $J$ = 14.0 Hz, 2H), 5.11 (s, 2H), 5.12 (d, $J$ = 8.8 Hz, 1H), 7.23−7.45 (m, 10H), 7.51−7.68 (m, 3H), 8.52 (d, $J$ = 8.8 Hz, 1H); MS (ESI) $m/z$ 594 $(M + Na)^+$.

***N*-[3-(*N*-4-amidino-2-chlorobenzoyl)amino-2,2-dimethyl-3-phenylpropionyl]piperidine-4-acetic Acid (34).** **34** was prepared via the general procedure D: 24% yield from **14q**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.18−1.41 (m, 4H), 1.27 (s, 3H), 1.30 (s, 3H), 1.86 (br d, $J$ = 11.2 Hz, 2H), 1.99−2.14 (m, 1H), 2.25 (d, $J$ = 7.2 Hz, 2H), 2.87−3.14 (m, 2H), 4.57 (br d, $J$ = 12.4 Hz, 2H), 5.78 (s, 1H), 7.28−7.37 (m, 3H), 7.39−7.45 (m, 2H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.78 (dd, $J$ = 1.2, 7.8 Hz, 1H), 7.93 (d, $J$ = 2.0 Hz, 1H); MS (ESI) $m/z$ 499 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{32}ClN_4O_4$ $(M + H)^+$ 499.2111, found 499.2083; HPLC[a] K′ 12.28. Anal. ($C_{26}H_{31}ClN_4O_4 \cdot 1.5CF_3COOH \cdot 0.5H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidino-2-fluorobenzoyl)amino-2,2-dimethylbutanoyl]piperidine-4-acetic Acid (35).** **35** was prepared from **14a** via the general procedure D with the modification for the deprotection of methyl ester described for **18**: 17% yield from **14a**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 1.05 (d, $J$ = 7.5 Hz, 3H), 1.05−1.28 (m, 2H), 1.27 (s, 3H), 1.30 (s, 3H), 1.81 (m, 2H), 1.91−2.07 (m, 1H), 2.26 (d, $J$ = 7.4 Hz, 2H), 2.81−3.12 (m, 2H), 4.41 (m, 1H), 4.57 (br d, $J$ = 13.3 Hz, 2H), 7.62 (s, 1H), 7.69 (d, $J$ = 7.2 Hz, 1H), 7.79 (t, $J$ = 7.3 Hz, 1H); MS (ESI) $m/z$ 421 $(M + H)^+$; HRMS (FAB) calcd for $C_{21}H_{30}FN_4O_4$ $(M + H)^+$ 421.2250, found 421.2231; HPLC[a] K′ 6.83. Anal. ($C_{21}H_{29}FN_4O_4 \cdot 1.25CF_3COOH$) C, H, N.

***N*-[3-(*N*-4-Amidino-2-fluorobenzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (36).** **36** was prepared from **14b** via the general procedure D with the modification for the deprotection of ethyl ester described for **18**: 51% yield from **14b**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.97 (t, $J$ = 7.3 Hz, 3H), 1.10−1.28 (m, 2H), 1.25 (s, 3H), 1.34 (s, 3H), 1.56 (m, 2H), 1.84 (br t, $J$ = 8.9 Hz, 2H), 1.95−2.15 (m, 1H), 2.26 (d, $J$ = 7.3 Hz, 2H), 2.75−3.08 (m, 2H), 4.44 (m, 1H), 4.53 (br d, $J$ = 13.7 Hz, 2H), 7.68 (s, 1H), 7.70 (d, $J$ = 7.3 Hz, 1H), 7.82 (t, $J$ = 7.3 Hz, 1H); MS (ESI) $m/z$ 435 $(M + H)^+$; HRMS (FAB) calcd for $C_{22}H_{32}FN_4O_4$ $(M + H)^+$ 435.2407, found 435.2408; HPLC[a] K′ 8.36. Anal. ($C_{22}H_{31}FN_4O_4$·1.5$CF_3COOH$·$H_2O$) C, H, N.

***N*-[3-(*N*-4-Amidino-2-fluorobenzoyl)amino-2,2-dimethylheptanoyl]piperidine-4-acetic Acid (37).** **37** was prepared from **14f** via the general procedure D with the modification for the deprotection of methyl ester described for **18**: 10% yield from **14f**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.91 (br t, $J$ = 6.4 Hz, 3H), 1.15−1.65 (m, 8H), 1.25 (s, 3H), 1.34 (s, 3H), 1.80−1.88 (m, 2H), 2.00−2.13 (m, 1H), 2.25 (d, $J$ = 7.2 Hz, 2H), 2.75−3.14 (m, 2H), 4.47−4.58 (m, 3H), 7.70 (d, $J$ = 7.2 Hz, 2H), 7.81 (t, $J$ = 7.2 Hz, 1H); MS (ESI) $m/z$ 464 $(M + H)^+$; HRMS (FAB) calcd for $C_{24}H_{36}FN_4O_4$ $(M + H)^+$ 463.2720, found 463.2738; HPLC[a] K′ 11.63. Anal. ($C_{24}H_{35}FN_4O_4$·1.25$CF_3COOH$·0.25$H_2O$) C, H, N.

**Ethyl *N*-[3-(2-Fluoro-4-(morpholin-4-yl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (38).** **38** was prepared via the general procedure D. However, morpholine was used instead of ammonium acetate: 28% yield from **14b**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.93 (m, 3H), 1.12−1.41 (m, 8H), 1.26 (t, $J$ = 7.0 Hz, 3H), 1.57−1.89 (m, 4H), 1.92−2.16 (m, 1H), 2.24 (d, $J$ = 6.8 Hz, 2H), 2.82 (m, 2H), 3.41 (br s, 2H), 3.70 (br s, 2H), 3.85−3.97 (m, 4H), 4.03−4.19 (m, 1H), 4.13 (q, $J$ = 7.3 Hz, 2H), 4.27−4.47 (m, 2H), 7.32−7.43 (m, 2H), 7.68−7.82 (m, 1H), 8.00 (t, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 11.6, 14.2, 23.8, 23.9, 24.1, 32.0, 32.2, 33.0, 33.1, 40.6, 40.8, 45.1 (br), 46.5, 47.2, 50.1, 60.4, 60.7, 65.6, 66.2, 77.2, 116.4, 116.8, 124.2, 126.4, 126.6, 132.1, 132.2, 132.7, 157.9, 161.6, 162.7, 163.1, 172.3, 174.8; MS (ESI) $m/z$ 533 $(M + H)^+$; HRMS (FAB) calcd for $C_{28}H_{42}FN_4O_5$ $(M + H)^+$ 533.3139, found 533.3136. Anal. ($C_{28}H_{41}FN_4O_5$·$CF_3COOH$·$H_2O$) C, H, N.

***N*-[3-(2-Fluoro-4-(morpholin-4-yl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (Biologically Active Form of 38).** This compound was prepared according to the procedure described for **18**: 77% yield from **38**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.97 (t, $J$ = 7.6 Hz, 3H), 1.12−1.25 (m, 2H), 1.26 (s, 3H), 1.34 (s, 3H), 1.50−1.63 (m, 2H), 1.78−1.91 (m, 2H), 2.06 (br s, 1H), 2.26 (d, $J$ = 7.2 Hz, 2H), 2.78−3.08 (m, 2H), 3.39−3.50 (m, 2H), 3.65−3.76 (m, 2H), 3.76−3.84 (m, 2H), 3.86−3.95 (m, 2H), 4.37−4.45 (m, 1H), 4.52 (br d, $J$ = 12.4 Hz, 2H), 7.53 (d, $J$ = 7.6 Hz, 1H), 7.58 (d, $J$ = 10.4 Hz, 1H), 7.85 (t, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 12.7, 24.1, 24.7, 25.3, 34.0, 34.1, 35.2, 42.3, 47.3, 47.8, 48.9, 49.3, 52.2, 59.9, 67.1, 68.0, 118.5, 118.7, 126.5, 129.8, 129.9, 133.5, 134.5, 134.6, 160.4, 162.9, 165.6, 167.0, 176.8, 177.1; MS (ESI) $m/z$ 506 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{38}FN_4O_5$ $(M + H)^+$ 505.2826, found 505.2827; HPLC[b] K′ 6.00. Anal. ($C_{26}H_{37}FN_4O_5$·1.5$CF_3COOH$·0.5$H_2O$) C, H, N.

**Ethyl *N*-[3-(2-Fluoro-4-(pyrrolidinyl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (39).** **39** was prepared via the general procedure D. However, pyrrolidine was used instead of ammonium acetate: 25% yield from **14b**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.16−1.42 (m, 2H), 1.26 (t, $J$ = 7.29 Hz, 6H), 1.31 (s, 3H), 1.37 (s, 3H), 1.59−1.89 (m, 4H), 1.91−2.30 (m, 5H), 2.25 (d, $J$ = 7.3 Hz, 2H), 2.71−2.91 (m, 2H), 3.43 (br t, $J$ = 6.3 Hz, 2H), 3.76 (br s, 2H), 4.06−4.48 (m, 1H), 4.13 (q, $J$ = 6.9 Hz, 2H), 4.41 (br d, $J$ = 12.7 Hz, 2H), 7.28−7.43 (m, 2H), 7.66 (br d, $J$ = 8.2 Hz, 1H), 8.00 (m, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 11.5, 14.2, 23.8, 23.9, 24.1, 24.9, 25.0, 25.5, 29.7, 32.0, 32.2, 32.3, 33.1, 40.8, 45.1, 45.4, 46.5, 49.1, 52.1, 60.4, 60.7, 77.2, 115.7, 116.1, 123.6, 125.9, 126.1, 132.6, 133.2, 133.4, 157.8, 160.9, 161.0, 161.5, 162.7, 172.2, 174.8; MS (ESI) $m/z$ 517 $(M + H)^+$; HRMS (FAB) calcd for $C_{28}H_{42}FN_4O_4$ $(M + H)^+$ 517.3189, found 517.3207. Anal. ($C_{28}H_{41}FN_4O_4$·$CF_3COOH$·1.5$H_2O$) C, H, N.

***N*-[3-(2-Fluoro-4-(pyrrolidinyl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (Biologically Active Form of 39).** This compound was prepared according to the procedure described for **18**: 39% yield from **39**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.97 (t, $J$ = 7.2 Hz, 3H), 1.14−1.28 (m, 2H), 1.26 (s, 3H), 1.34 (s, 3H), 1.50−1.62 (m, 2H), 1.78−1.91 (m, 2H), 1.94−2.13 (m, 3H), 2.13−2.23 (m, 2H), 2.26 (d, $J$ = 7.2 Hz, 2H), 3.48 (t, $J$ = 6.8 Hz, 2H), 3.63 (t, $J$ = 7.2 Hz, 2H), 4.38−4.46 (m, 1H), 4.53 (br d, $J$ = 12.8 Hz, 2H), 7.53 (d, $J$ = 8.0 Hz, 1H), 7.57 (d, $J$ = 10.4 Hz, 1H), 7.83 (t, $J$ = 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 12.7, 24.1, 24.7, 25.2, 26.7, 27.3, 34.1, 34.2, 35.2, 42.3, 47.4, 47.8, 50.9, 54.0, 59.8, 117.8, 118.1, 125.9, 129.5, 129.7, 133.3, 135.7, 135.8, 160.2, 163.3, 167.17, 167.21, 176.8, 177.0; MS (ESI) $m/z$ 489 $(M + H)^+$; HRMS (FAB) calcd for $C_{26}H_{38}FN_4O_4$ $(M + H)^+$ 489.2876, found 489.2862; HPLC[b] K′ 6.45. Anal. ($C_{26}H_{37}FN_4O_4$·1.5$CF_3COOH$·0.5$H_2O$) C, H, N.

**Ethyl *N*-[3-(2-Fluoro-4-(thiazolidin-3-yl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (40).** **40** was prepared via the general procedure D. However, thiazolidine was used instead of ammonium acetate: 23% yield from **14b**; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (t, $J$ = 7.2 Hz, 3H), 1.16 (br q, $J$ = 12.0 Hz, 2H), 1.24 (t, $J$ = 7.2 Hz, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.59−1.73 (m, 2H), 1.78 (br d, $J$ = 12.0 Hz, 2H), 1.97−2.09 (m, 1H), 2.23 (d, $J$ = 6.8 Hz, 2H), 2.70−2.93 (m, 2H), 3.05 (t, $J$ = 6.4 Hz, 1H), 3.31 (t, $J$ = 6.0 Hz, 1H), 3.72 (t, $J$ = 5.6 Hz, 1H), 4.02−4.08 (m, 2H), 4.12 (q, $J$ = 6.8 Hz, 2H), 4.37 (br d, $J$ = 13.2 Hz, 2H), 4.41 (s, 1H), 4.79 (s, 1H), 7.34 (t, $J$ = 8.4 Hz, 1H), 7.38 (t, $J$ = 8.0 Hz, 1H), 7.98 (q, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 11.7, 14.3, 24.0, 24.1, 24.2, 30.2, 30.5, 32.1, 32.3, 33.3, 41.0, 45.2, 45.6, 46.7, 51.1, 51.8, 54.4, 55.2, 60.5, 61.06, 61.14, 114.6, 115.9, 116.0, 116.1, 116.3, 117.4, 123.6, 123.70, 123.73, 126.8, 127.0, 132.8, 132.9, 133.0, 158.6, 160.7, 161.1, 161.3, 161.6, 162.7, 162.8, 172.3, 175.1; MS (ESI) $m/z$ 535 $(M + H)^+$; HRMS (FAB) calcd for $C_{27}H_{40}FN_4O_4S$ $(M + H)^+$ 535.2754, found 535.2750. Anal. ($C_{27}H_{39}FN_4O_4S$·1.3$CF_3COOH$) C, H, N.

***N*-[3-(2-Fluoro-4-(thiazolidin-3-yl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (Biologically Active Form of 40).** This compound was prepared according to the procedure described for **18**: 71% yield from **40**; $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 0.97 (t, $J$ = 7.6 Hz, 3H), 1.12−1.28 (m, 2H), 1.26 (s, 3H), 1.34 (s, 3H), 1.49−1.62 (m, 2H), 1.84 (br t, $J$ = 11.2 Hz, 2H), 1.98−2.12 (m, 1H), 2.26 (d, $J$ = 7.6 Hz, 2H), 2.69−3.08 (m, 2H), 3.13 (t, $J$ = 6.4 Hz, 1H), 3.38 (t, $J$ = 6.4 Hz, 1H), 3.79 (t, $J$ = 6.0 Hz, 1H), 3.92 (t, $J$ = 6.0 Hz, 1H), 4.42 (dd, $J$ = 8.8, 4.8 Hz, 1H), 4.52 (br d, $J$ = 14.8 Hz, 2H), 4.56 (s, 1H), 4.71 (s, 1H), 7.57 (ddd, $J$ = 7.6, 4.0, 1.6 Hz, 1H), 7.61 (ddd, $J$ = 9.6, 4.0, 1.6 Hz, 1H), 7.85 (t, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 12.7, 24.1, 24.7, 25.2, 31.8, 34.0, 35.2, 47.3, 47.8, 52.3, 53.7, 56.0, 57.2, 59.7, 117.1, 117.3, 117.9, 118.0, 118.1, 118.2, 125.8, 126.0, 129.9, 130.1, 133.4, 135.1, 135.2, 135.7, 160.2, 162.7, 163.0, 163.4, 163.7, 167.1, 176.8, 177.0; MS (ESI) $m/z$ 507 $(M + H)^+$; HRMS (FAB) calcd for $C_{25}H_{36}FN_4O_4S$ $(M + H)^+$ 507.2441, found 507.2426; HPLC[b] K′ 6.54. Anal. ($C_{25}H_{35}FN_4O_4S$·1.5$CF_3COOH$) C, H, N.

**Ethyl *N*-[3-(2-Fluoro-4-(4-hydroxypiperidinyl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (41).** **41** was prepared via the general procedure D. However, 4-hydroxypiperidine was used instead of ammonium acetate: 30% yield from **14b**; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.92 (t, $J$ = 7.3 Hz, 3H), 1.09−1.39 (m, 2H), 1.25 (t, $J$ = 7.0 Hz, 6H), 1.29 (s, 3H), 1.35 (s, 3H), 1.55−1.92 (m, 7H), 1.92−2.13 (m, 2H), 2.24 (d, $J$ = 6.75 Hz, 2H), 2.74−2.93 (m, 2H), 3.22−3.36 (m, 1H), 3.53−3.68 (m, 1H), 3.68−3.83 (m, 1H), 3.94−4.19 (m, 3H), 4.12 (q, $J$ = 7.2 Hz, 2H), 4.37 (br d, $J$ = 11.6 Hz, 2H), 7.29−7.39 (m, 2H), 7.72 (br t, $J$ = 8.1 Hz, 1H), 7.94 (t, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) $\delta$ 11.5, 14.2, 23.8, 24.0, 31.9, 32.1, 32.5, 33.1, 33.4, 40.8, 43.8, 45.0, 45.5, 46.5, 47.3, 60.4, 60.6, 63.9, 77.2, 113.8, 116.1, 116.5, 118.1, 124.0, 126.1, 126.3, 132.4, 132.7, 132.9, 157.8, 160.3, 160.8, 161.5, 162.3, 163.0, 172.3, 174.9; MS (ESI) $m/z$ 547 $(M + H)^+$;

HRMS (FAB) calcd for $C_{29}H_{44}FN_4O_5$ (M + H)$^+$ 547.3295, found 547.3309. Anal. ($C_{29}H_{43}FN_4O_5$·$CF_3COOH$·$H_2O$) C, H, N.

***N*-[3-(2-Fluoro-4-(4-hydroxypiperidinyl(imino)methyl)-benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (Biologically Active Form of 41).** This compound was prepared according to the procedure described for **18**: 84% yield from **41**; $^1$H NMR (400 MHz, $CD_3OD$) δ 0.91−1.04 (m, 3H), 1.12−1.28 (m, 2H), 1.26 (s, 3H), 1.34 (s, 3H), 1.50−1.67 (m, 3H), 1.74−1.95 (m, 4H), 2.09 (br s, 2H), 2.26 (br d, *J* = 6.4 Hz, 2H), 2.70−3.10 (m, 2H), 3.30−3.38 (br s, 1H), 3.55−3.74 (m, 2H), 3.90−4.08 (m, 2H), 4.42 (br s, 1H), 4.53 (br d, *J* = 12.0 Hz, 2H), 7.51 (br d, *J* = 7.6 Hz, 1H), 7.57 (br d, *J* = 10.0 Hz, 1H), 7.84 (m, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 12.7, 24.0, 24.7, 25.2, 34.0, 34.2, 34.3, 35.2, 35.4, 42.3, 45.7, 47.4, 47.7, 59.7, 66.1, 118.1, 118.4, 126.1, 129.7, 129.8, 133.3, 135.1, 135.2, 160.3, 162.8, 164.8, 167.2, 176.8, 177.0; MS (ESI) *m/z* 519 (M + H)$^+$; HRMS (FAB) calcd for $C_{27}H_{40}FN_4O_5$ (M + H)$^+$ 519.2982, found 519.2981; HPLC$^b$ K′ 5.70. Anal. ($C_{27}H_{39}FN_4O_5$·1.5$CF_3COOH$·$H_2O$) C, H, N.

**Ethyl *N*-[3-(2-Fluoro-4-(4-methylpiperazinyl(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetate (42).** **42** was prepared via the general procedure D. However, 4-methylpiperazine was used instead of ammonium acetate: 28% yield from **14b**; $^1$H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.03−1.40 (m, 2H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.28 (s, 3H), 1.32 (s, 3H), 1.48−1.92 (m, 4H), 2.03 (br s, 1H), 2.23 (d, *J* = 6.5 Hz, 2H), 2.65−3.00 (m, 2H), 2.88 (s, 3H), 3.42 (br s, 2H), 3.61 (br s, 2H), 3.78 (br s, 2H), 3.95−4.17 (m, 1H), 4.11 (q, *J* = 6.8 Hz, 2H), 4.19−4.50 (m, 4H), 7.44 (m, 2H), 7.86 (m, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) δ 11.4, 14.2, 23.8, 23.9, 31.9, 32.0, 33.0, 40.8, 42.9, 43.8, 45.0, 45.5, 46.4, 46.8, 51.3, 51.9, 60.4, 60.7, 77.2, 113.9, 116.7, 117.0, 118.2, 124.4, 126.8, 127.0, 131.4, 131.5, 132.2, 157.7, 160.4, 161.0, 161.4, 161.5, 162.1, 163.0, 164.1, 172.3, 174.9; MS (ESI) *m/z* 546 (M + H)$^+$; HRMS (FAB) calcd for $C_{29}H_{45}FN_5O_4$ (M + H)$^+$ 546.3455, found 546.3443. Anal. ($C_{29}H_{44}FN_5O_4$·2$CF_3COOH$·1.5$H_2O$) C, H, N.

***N*-[3-(2-Fluoro-4-(4-methylpiperazinyl(imino)methyl)-benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (Biologically Active Form of 42).** This compound was prepared according to the procedure described for **18**: 76% yield from **42**; $^1$H NMR (400 MHz, $CD_3OD$) δ 0.97 (t, *J* = 7.6 Hz, 3H), 1.14−1.27 (m, 2H), 1.26 (s, 3H), 1.34 (s, 3H), 1.50−1.63 (m, 2H), 1.84 (br t, *J* = 10.0 Hz, 2H), 2.01−2.13 (m, 1H), 2.25 (d, *J* = 6.8 Hz, 2H), 2.78−3.02 (m, 2H), 2.93 (s, 3H), 3.36 (br s, 2H), 3.54 (br s, 2H), 3.74 (br s, 2H), 4.09 (br s, 2H), 4.40 (dd, *J* = 4.4, 10.0 Hz, 1H), 4.51 (br d, *J* = 13.6 Hz, 2H), 7.56 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.61 (dd, *J* = 1.2, 10.0 Hz, 1H), 7.88 (t, *J* = 7.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 12.7, 24.1, 24.7, 25.2, 34.0, 34.1, 35.1, 42.3, 44.6, 45.9, 47.7, 53.5, 54.4, 59.9, 118.6, 118.9, 126.6, 130.3, 133.6, 133.9, 162.8, 163.8, 166.6, 166.9, 176.8, 177.0, 186.9; MS (ESI) *m/z* 518 (M + H)$^+$; HRMS (FAB) calcd for $C_{27}H_{41}FN_5O_4$ (M + H)$^+$ 518.3142, found 518.3125; HPLC$^b$ K′ 5.00. Anal. ($C_{27}H_{40}FN_5O_4$·2.5$CF_3COOH$·1.5$H_2O$) C, H, N.

**Ethyl *N*-[3-(2-Fluoro-4-(4-(4-fluorophenyl)piperazinyl-(imino)methyl)benzoyl)amino-2,2-dimethylpentanoyl]-piperidine-4-acetate (43).** **43** was prepared via the general procedure D. However, 4-(4-fluorophenyl)piperazine was used instead of ammonium acetate: 19% yield from **14b**; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.16 (br q, *J* = 12 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.60−1.72 (m, 2H), 1.78 (br d, *J* = 11.6 Hz, 2H), 1.97−2.08 (m, 1H), 2.23 (d, *J* = 6.8 Hz, 2H), 2.82 (br s, 2H), 3.15 (m, 2H), 3.37 (m, 2H), 3.59 (m, 2H), 4.02−4.14 (m, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.35 (br d, *J* = 12.4 Hz, 2H), 6.92 (dd, *J* = 4.4, 9.6 Hz, 2H), 6.99 (t, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 10.8, 14.0 Hz, 2H), 7.96 (t, *J* = 7.2 Hz, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) δ 11.6, 14.3, 23.8, 24.0, 24.1, 32.0, 32.2, 33.1, 40.9, 45.2, 45.6, 46.5, 47.0, 49.8, 50.0, 50.8, 60.6, 61.2, 116.0, 116.3, 116.4, 116.8, 119.4, 119.5, 124.3, 126.6, 126.8, 132.1, 132.3, 132.8, 145.7, 145.8, 156.8, 158.0, 160.4, 161.0, 161.7, 162.9, 163.1, 172.4, 175.1; MS (ESI) *m/z* 626 (M + H)$^+$. Anal. ($C_{34}H_{45}F_2N_5O_4$·1.5$CF_3COOH$) C, H, N.

***N*-[3-(2-Fluoro-4-(4-(4-fluorophenyl)piperazinyl(imino)-methyl)benzoyl)amino-2,2-dimethylpentanoyl]piperidine-4-acetic Acid (Biologically Active Form of 43).** This compound was prepared according to the procedure described for **18**: 72% yield from **43**; $^1$H NMR (400 MHz, $CD_3OD$) δ 0.98 (t, *J* = 7.6 Hz, 3H), 1.15−1.28 (m, 2H), 1.26 (s, 3H), 1.35 (s, 3H), 1.51−1.62 (m, 2H), 1.84 (br t, *J* = 11.2 Hz, 2H), 1.98−2.15 (m, 1H), 2.25 (d, *J* = 7.2 Hz, 2H), 2.75−3.07 (m, 2H), 3.20 (t, *J* = 4.8 Hz, 2H), 3.40 (t, *J* = 4.8 Hz, 2H), 3.61 (t, *J* = 4.4 Hz, 2H), 3.95 (t, *J* = 4.8 Hz, 2H), 4.41 (dd, *J* = 5.2, 9.6 Hz, 1H), 4.52 (br d, *J* = 13.2 Hz, 2H), 7.01 (d, *J* = 6.8 Hz, 4H), 7.56 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.61 (d, *J* = 10.4 Hz, 1H), 7.87 (t, *J* = 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 12.7, 24.1, 24.7, 25.2, 34.0, 34.1, 35.2, 42.3, 47.3, 47.7, 50.9, 51.9, 52.0, 59.8, 117.3, 117.5, 118.5, 118.8, 120.7, 120.8, 126.5, 129.8, 129.9, 133.4, 134.7, 134.8, 149.1, 165.4, 167.1, 176.8, 177.0; MS (ESI) *m/z* 598 (M + H)$^+$; HPLC$^b$ K′ 8.83. Anal. ($C_{32}H_{41}F_2N_5O_4$·2$CF_3COOH$) C, H, N.

***N*-[(*R*)-3-(*N*-Boc)amino-2,2-dimethylpentanoyl]-(*R*)-1-(1-naphthyl)ethylamine (15-*R*).** To a solution of 3-(*N*-Boc)-amino-2,2-dimethylpentanoic acid **12b** (4 g, 16.4 mmol) and (*R*)-1-(1-naphthyl)ethylamine (5 g, 33 mmol) in $CH_2Cl_2$ (200 mL) were added HATU (8 g, 21 mmol) and $Et_3N$ (10 mL, 72 mmol) at 0 °C. After being stirred at room temperature for 5 h, the solvent was removed in vacuo and the residue was purified by the column chromatography on silica using hexane−EtOAc (1:1) as an eluent to give *N*-(3-(*N*-Boc)amino-2,2-dimethylpentanoyl)-(*R*)-1-(1-naphthyl)ethylamine **15** (4.2 g, 64%). The diastereomers of **15** were separated into two fractions by the silica gel column chromatography (LiChrosorb Si60-7, 250 × 25 mm) using hexane−EtOAc (1:4) as an eluent. Evaporation of each solvent yielded a product as a colorless powder. Recrystallization from hexane yielded the product as colorless needles. The absolute configuration of the needles from the front fraction (**15-*R***, 1.64 g, 39%) was determined as *R* by the X-ray crystallographic analysis: mp 127−128 °C; $^1$H NMR (270 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.8 Hz, 3H), 1.13 (s, 3H), 1.85 (s, 3H), 1.06−1.24 (m, 1H), 1.44 (s, 9H), 1.39−1.58 (m, 1H), 1.63 (d, *J* = 6.8 Hz, 3H), 3.41 (dt, *J* = 10.7, 2.4 Hz, 1H), 5.31 (d, *J* = 10.3 Hz, 1H), 5.88 (dq, *J* = 6.8, 6.8 Hz, 1H), 6.06 (d, *J* = 7.3 Hz, 1H), 7.40−7.58 (m, 4H), 7.72−7.92 (m, 2H), 7.97−8.08 (m, 1H); $^{13}$C NMR (67.5 MHz, $CDCl_3$) δ 11.1, 14.1, 20.4, 22.7, 23.9, 24.3, 28.4, 44.5, 45.9, 59.4, 78.8, 122.4, 123.3, 125.1, 125.8, 126.3, 128.3, 128.7, 131.0, 133.9, 138.2, 156.7, 175.8; $[\alpha]^{25}_D$ = −35.6° (*c* 1.0, EtOH); MS (ESI) *m/z* 399 (M + H)$^+$.

**(*R*)-3-(*N*-Boc)Amino-2,2-dimethylpentanoic Acid (12b-*R*).** **12b-*R*** was prepared according to the general procedure E described for **12f**: 81% yield from **15-*R***; $[\alpha]^{25}_D$ = 15.7° (*c* 1.0, EtOH); MS (ESI) *m/z* 244 (M − H)$^-$.

**Biologically Active Form of 40-*R*.** This compound was prepared according to the same procedure described for biologically active form of **40**: 14% yield (TFA salt) from **12b-*R***; $[\alpha]^{20}_D$ = −39.1° (*c* 0.1, $H_2O$); MS (ESI) *m/z* 507 (M + H)$^+$.

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**Supporting Information Available:** X-ray crystallographic data of **15-*R*** (35 pages). Ordering information is given on any current masthead page.

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