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Amino Acids and Peptides. XLI.[1, 2] Facile Synthesis of 5-Methyl-2(1*H*)-pyrazinone Derivatives from Dipeptidyl Chloromethyl Ketones[3]

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Abstract: 5-Methyl-2(1*H*)-pyrazinone derivatives were easily synthesized by short reflux of dipeptidyl chloromethyl ketone hydrochlorides in MeOH.

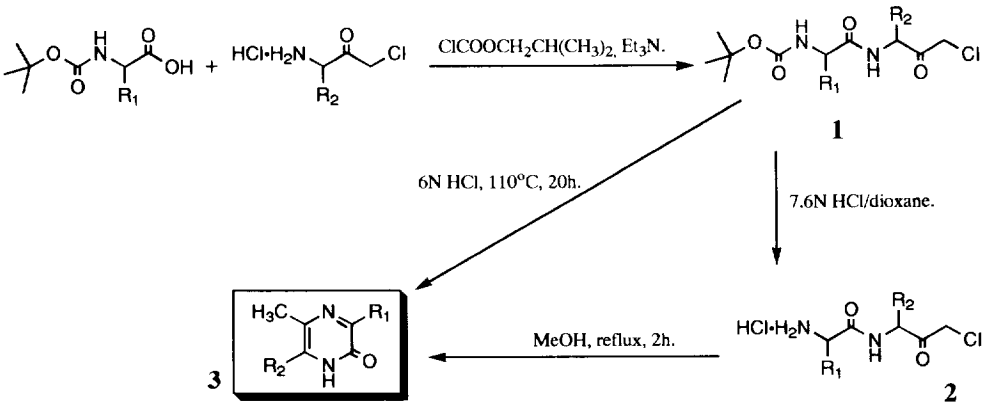
INTRODUCTION

Some naturally occurring 2(1*H*)-pyrazinone derivatives possess antibiotic and smooth muscle relaxation activities and its derivatives are key intermediates for preparing mold metabolites which exhibit antibiotic activities against gram-negative micro-organisms.[4] It is also well known that 2(1*H*)-pyrazinones can be easily converted to the corresponding pyrazinethiols by 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent).[5] Therefore, pyrazinone derivatives are useful intermediates of acyloxypyrazines[6] and acylthiopyrazines,[7] which are convenient acylating agents for amines, alcohols and phenols. Therefore, great efforts have been directed toward development of synthetic methods of 2(1*H*)-pyrazinone derivatives and various kinds of synthetic procedures were developed. Although 2(1*H*)-pyrazinone derivatives were prepared by condensation of 1,2-dicarbonyl compounds with amino acid amides[8] or by hydrolysis of the corresponding methoxypyrazine derivatives,[6, 9] which were prepared from the corresponding chloride[10, 11] and sodium methoxide, each method has some problems to be solved. For examples, cyclization reaction should be carried out under the milder condition with high yield, and the desired substituents should be introduced at position 3 and 6 easily. Therefore, the development of more convenient synthetic procedure of 2(1*H*)-pyrazinone derivatives has been required. Previously, we have reported that 5-methyl-2(1*H*)-pyrazinone derivatives were obtained from dipeptidyl chloromethyl ketones during acid hydrolysis (6N HCl, 110°C, 20h).[12] It was revealed that the above cyclized derivatives existed in pyrazinone derivatives rather than pyrazinol derivatives judging from data of NMR.[12] Therefore, we considered that this cyclization reacion might be applied to novel synthetic method of pyrazinone derivatives, and tried to optimize the reaction condition. This paper deals with a simple and convenient synthetic procedure of 5-methyl-2(1*H*)-pyrazinone derivatives.

RESULTS AND DISCUSSION

In order to assess the new synthetic procedure of 5-methyl-2(1*H*)-pyrazinone derivatives from dipeptidyl chloromethyl ketones, various kinds of Boc-NH-CH(R_1)-CONH-CH(R_2)-$COCH_2Cl$ (**1**) were prepared by the coupling of Boc-NH-CH(R_1)-COOH and H_2N-CH(R_2)-$COCH_2Cl$[13] by mixed anhydride method[14] according

to Scheme 1. First of all, Boc-Phe-Ala-CH_2Cl was converted to the corresponding 3-benzyl-5, 6-dimethyl-2(1*H*)-pyrazinone (**3a**) under the condition of acid hydrolysis (6N HCl, 110°C, 20h).[13] Although Boc-Phe-Ala-CH_2Cl was converted to **3a** with low yield of production of the corresponding amino acid residue (Phe) under



3a: R_1=Bzl, R_2=Me
3b: R_1=Et, R_2=iBu
3c: R_1=iPr, R_2=iBu
3d: R_1=Pr, R_2=iBu
3e: R_1=iBu, R_2=iBu
3f: R_1=*sec*-Bu, R_2=iBu
3g: R_1=Bu, R_2=iBu
3h: R_1=Me, R_2=Bzl
3i: R_1=Et, R_2=Bzl
3j: R_1=iPr, R_2=Bzl
3k: R_1=Pr, R_2=Bzl
3l: R_1=iBu, R_2=Bzl
3m: R_1=*sec*-Bu, R_2=Bzl
3n: R_1=Bu, R_2=Bzl
3o: R_1=H, R_2=iBu

Scheme 1

the above condition, the yield of **3a** was very low presumably due to the degradation of **3a** formed. Therefore, the rate of the decomposition of **3a** during acid hydrolysis(6N HCl, 110°C) was examined by HPLC. As shown in Fig. 1, the peak corresponding to **3a** was disappeared after 48h. In order to avoid the decomposition of 5-methyl-2(1*H*)-pyrazinone derivative formed, water as solvent was substituted with MeOH, and we further studied the yield of **3a** from Boc-Phe-Ala-CH_2Cl under various conditions such as in 6N HCl, 1N HCl and 3N HCl/MeOH and HCl•H-Phe-Ala-CH_2Cl in MeOH. The results are summarized in Table 1. From the Table 1, it can be concluded that the condition (HCl•H-Phe-Ala-CH_2Cl in MeOH) is the most favorable to cyclize dipeptidyl chloromethyl ketone to **3a**.

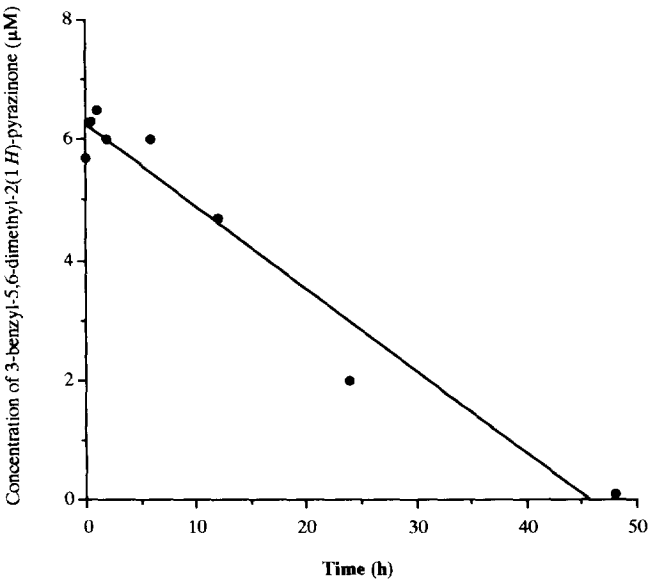


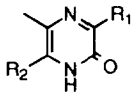
Fig. 1 Decomposition of 3-Benzyl-5,6-dimethyl-2(1*H*)-pyrazinone(**3a**) in 6N HCl

Table 1. Formation of 3-Benzyl-5,6-dimethyl-2(1*H*)-pyrazinone under Various Conditions

Starting material	Condition*	(%)Yield **
Boc-Phe-Ala-CH_2Cl	6N HCl	29.3
	1N HCl	31.0
	3N HCl/MeOH	62.9
HCl·H-Phe-Ala-CH_2Cl	MeOH	65.3

* reflux for 2h
** isolated yield

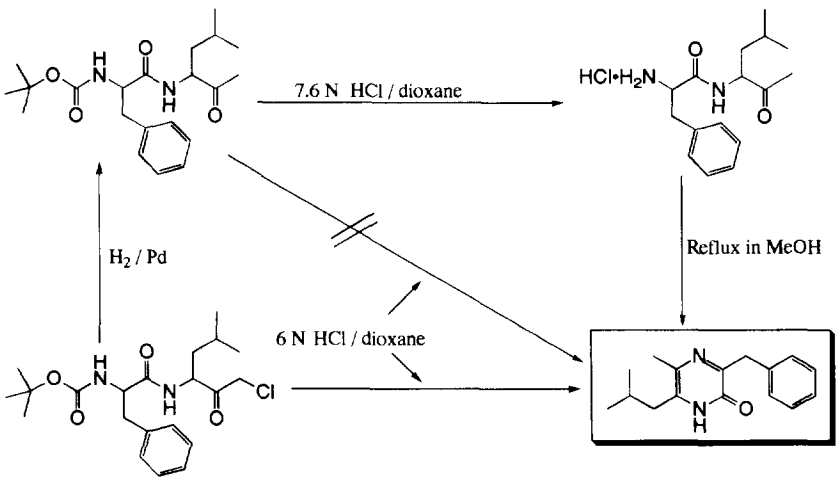
Table 2. Formation of 5-Methyl-2(1*H*)-pyrazinone Derivatives from Dipeptidyl Chloromethyl Ketones.

Products			(%)Yield *	M.p.(°C)
	R_1	R_2		
3a	Bzl	Me	65.3	161-162
3b	Et	iBu	89.9	109-100
3c	iPr	iBu	88.0	166-167
3d	Pr	iBu	78.6	88-89
3e	iBu	iBu	74.2	132-134
3f	*sec*-Bu	iBu	58.5	111-112
3g	Bu	iBu	93.4	92-93
3h	Me	Bzl	75.4	154-155
3i	Et	Bzl	56.7	169-170
3j	iPr	Bzl	67.1	214-215
3k	Pr	Bzl	60.3	152-154
3l	iBu	Bzl	67.5	161-163
3m	*sec*-Bu	Bzl	72.0	177-178
3n	Bu	Bzl	93.0	145-146
3o	H	iBu	90.6	128-130

* isolated yield

Next, in order to examine whether the distance between the amino group and carbonyl group of chloromethyl ketone moiety of dipeptidyl chloromethyl ketone affects the yield of 5-methyl-2(1*H*)-pyrazinone derivatives or not, stereoisomers of Boc-Phe-Leu-CH_2Cl (D-L, L-D, D-D) were prepared in the same manner as described for the synthesis of Boc-Phe-Leu-CH_2Cl.[13] They were converted to the corresponding 2(1*H*)-pyrazinone derivative under the same condition. The yield of 2(1*H*)-pyrazinone derivative in each case was similar to that of L-L compound,[13] indicating that the distance between the amino group and carbonyl group of chloromethyl ketone moiety of dipeptidyl chloromethyl ketone was not related to reactivity of this cyclization reaction. These results show that racemic amino acid can be employed for preparing dipeptidyl chloromethyl ketone as starting material for 2(1*H*)-pyrazinone derivative. On the basis of the above studies, 2(1*H*)-pyrazinone derivatives (**3b-3o**) were prepared by refluxing of the MeOH solution of the corresponding dipeptidyl chloromethyl ketone hydrochloride with fairly high yield. Yields and mps are summarized in Table 2.

Next, in order to examine the effect of chloride atom in dipeptidyl chloromethyl ketone on this cyclization reaction, we synthesized Boc-Phe-Leu-CH_3 from Boc-Phe-Leu-CH_2Cl by catalytic hydrogenation (Scheme 2).



Scheme 2

It was treated with 6N HCl at 110°C for 20h to afford phenylalanine residue in an yield of 75% and pyrazinone derivative was not isolated. Then, H-Phe-Leu-CH_3•HCl in MeOH was refluxed for 2h to give the corresponding pyrazinone derivative in an yield of 65%, which was identified with 3-benzyl-5-methyl-6-isobutyl-2(1*H*)-pyrazinone[12] derived from H-Phe-Leu-CH_2Cl•HCl using NMR, MS and IR. The differences in reactivity between chloromethyl ketone derivative and methyl ketone derivative might be explained as follows: 1) Electrophilicity of carbonyl group of chloromethyl ketone is higher than that of methyl ketone. 2) The formation of stable pyrazinone derivative from dipeptidyl chloromethyl ketone derivative by leaving chloride anion is much easier than that from methyl ketone derivative, in which pyrazinone derivative might be formed oxidatively in the presence of oxygen more slowly than from the corresponding chloromethyl ketone derivative.

Finally it will be concluded that this novel method can afford 2(1*H*)-pyrazinone derivatives substituted at the position 3 and 6 (R_1 and R_2, Scheme 1) with the desired alkyl groups in high yield, so far examined, therefore, this simple and convenient synthetic procedure is a recommendable one.

EXPERIMENTAL SECTION

Mps were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with an automatic polarimeter, model DIP-360 (Japan Spectroscopic Co.) and the $[\alpha]_D$ values are given in 10^{-1}deg cm^2 g^{-1}. Amino acid compositions of hydrolysates (6N HCl, 110°C, 20h) were determined with an amino acid analyzer, K-202 SN (Kyowa Seimitu Co.). ^{1}H (400, 500MHz) and ^{13}C (100, 125MHz) NMR spectra were recorded either on a Bruker AM400 or a ARX500 spectrometer. Chemical shift values are expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value). J values are given in Hz. Attribution of ^{13}C signals were made also with the aid of DEPT experiments, and multiplicities are indicated by *p* (primary), *s* (secondary), *t* (tertiary) or *q* (quaternary). Mass spectra were measured with a Hitachi M-2000 mass spectrometer using EI technique. On HPLC analysis, solvent gradient for analytical separation and coinjection was run at 1 ml/min as follows: eluent A, H_2O/0.05% TFA; eluent B, CH_3CN/0.05% TFA; isocratic 80% A for 5 min , 20 min linear gradient to 20% A, isocratic 20% A for 5min, 10 min linear gradient to initial conditions; column: Waters Nova-Pak C18 (3.9 x 150 mm); retention time was reported as t_R. TLC was conducted on precorted Kiesegel 60 F_{254} (Art. 5715; Merck) with the following solvent system: (A) $CHCl_3$-AcOEt-EtOH (30:19:1 v/v), (B) $CHCl_3$-MeOH (19:1 v/v), (C) AcOEt-hexane (1:2 v/v), (D) $CHCl_3$-MeOH-AcOH (90:8:2 v/v), (E) AcOEt-hexane (2:1 v/v) and the Rf values were reported as Rf(A), Rf(B), Rf(C), Rf(D) and Rf(E), respectively.

Optimization of cyclization reaction condition

1) Synthesis of Boc-Phe-Ala-CH_2Cl and H-Phe-Ala-CH_2Cl•HCl

Boc-Phe-Ala-CH_2Cl A mixed anhydride [prepared from Boc-Phe-OH (2.4 g, 9.0 mmol), Et_3N (1.4 ml, 9.9 mmol) and isobutyl chloroformate (1.2 ml, 9.0 mmol) as usual] in THF (100 ml) was added to an ice-cold solution of H-Ala-CH_2Cl•HCl [prepared from Boc-Ala-CH_2Cl[15] (1.0 g, 3.4 mmol) and 5.1 N HCl/dioxane (7.4 ml, 54.0 mmol) as usual] in DMF (100 ml) containing Et_3N (1.4 ml, 9.9 mmol). The reaction mixture was stirred at 0°C for 1h and then at room temperature overnight. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 2.4 g (72.4%), mp 123-127°C, $[\alpha]_D^{25}$ -34.5° (*c*=1.0, MeOH), Rf(D) 0.71, Rf(B) 0.46. *Anal.* Calcd for $C_{18}H_{25}ClN_2O_4$: C, 58.6; H, 6.83; N, 7.59. Found: C, 58.3; H, 6.85; N, 7.54.

H-Phe-Ala-CH_2Cl•HCl A solution of Boc-Phe-Ala-CH_2Cl(0.5 g, 1.4 mmol) in 5.1N HCl/dioxane(1.4 ml, 7.0 mmol) was kept at room temperature for 1h. Ether was added to the solution to form precipitate, which was collected by filtration and dried over KOH pellets *in vacuo*, yield 0.4 g (93.7%), mp 135-137°C, Rf(D) 0.1. *Anal.* Calcd for $C_{13}H_{17}ClN_2O_2$•HCl: C, 51.2; H, 5.94; N, 9.18. Found: C, 51.2; H, 5.91; N, 9.30.

2)Synthesis of 3-benzyl-5, 6-dimethyl-2(1H)-pyrazinone(3a) from Boc-Phe-Ala-CH_2Cl and H-Phe-Ala-CH_2Cl•HCl under various conditions.

i) From Boc-Phe-Ala-CH_2Cl under various acidic conditions A solution of Boc-Phe-Ala-CH_2Cl (0.6 g, 1.63 mmol) in acidic solvent (6N HCl , 3N HCl/MeOH or 1N HCl) (4 ml each) was refluxed for 2h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, mp 161-162°C, Rf(B) 0.46, MS m/z: 214 M$^+$. ^{1}H NMR ($CDCl_3$ 400MHz) δ: ppm 13.5 (1H, brs, NH), 7.40-7.12 (5H, m, 3-CH_2-ph), 4.01 (2H, s, 3-CH_2-ph), 2.24 (3H, d, J=6.0, 6-CH_3), 2.18 (3H, s, 5-CH_3), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.6 (*q*, C-2), 153.8 (*q*, C-3), 138.2 (*q*, C-1´), 131.7 (*q*, C-6), 129.9 (*q*, C-5), 129.2 (*t*, C-3´, 5´), 128.1 (*t*, C-2´, 6´), 126.2 (*t*, C-4´), 39.3 (*s*, 6-CH_2-ph), 18.7 (*p*, 5-CH_3), 15.9 (*p*, 6-CH_3). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.9 H, 6.59; N, 13.1. Found: C, 73.0; H, 6.59; N, 13.1. Yields are summarized in Table 1.

ii) From H-Phe-Ala-CH_2Cl in MeOH H-Phe-Ala-CH_2Cl•HCl (0.5 g, 1.64 mmol) was dissolved in MeOH (20ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, mp 161-162°C. Yield is shown in Table 1.

*Studies on decomposition of **3a** during acid hydrolysis*
3a (50 mg, 0.23 mmol) was dissolved in 6N HCl (2 ml). The reaction mixture was refluxed. An aliquot (0.05 ml) was taken periodically and diluted with MeOH (0.3 ml), and 0.01 ml of the diluted solution was analyzed with HPLC apparatus. The peak areas corresponding to 3-benzyl-5, 6-dimethyl-2(1*H*)-pyrazinone was plotted as a function of time (0.5, 1, 2, 6, 12, 24, 48h). The results is shown in Fig. 1.

Studies on the effect of diastereoisomer on cyclization reaction
Boc-D-Leu-CH_2Cl Diazomethane [prepared from nitrosomethyl urea (14.2 g, 0.14 mol)] in ether (100 ml) was added to a mixed anhydride [prepared from Boc-D-Leu-OH (8.0 g, 34.6 mmol), Et_3N (4.2 ml, 30 mmol) and isobutyl chloroformate (4.5 ml, 34.6 mmol) as usual] in THF (150 ml) at -15°C and the reaction mixture was stirred at 4°C overnight. Then 7.6N HCl/dioxane (18.4 ml, 0.14 mol) was added to the reaction mixture at 0°C, and the resultant solution was stirred at 0°C for 3h. After neutralization of the solution with Et_3N and removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated down. Hexane was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 5.97 g (63.3%), mp 49-50°C, $[\alpha]_D^{25}$ +50.9°(*c*=1.0, MeOH), Rf(B) 0.84. *Anal.* Calcd for $C_{12}H_{22}ClNO_3$: C, 54.6; H, 8.41; N, 5.31. Found: C, 54.3; H, 8.49; N, 5.33.

1) General procedure for the synthesis of diastereoisomers of Boc-Phe-Leu-CH_2Cl[13]
Boc-Phe-D-Leu-CH_2Cl A mixed anhydride [prepared from Boc-Phe-OH (0.64 g, 2.5 mmol), NMM (0.33 ml, 3.0 mmol) and isobutyl chloroformate (0.33 ml, 2.5 mmol) as usual] in THF (30 ml) was added to an ice-cold solution of H-D-Leu-CH_2Cl•HCl [prepared from Boc-D-Leu-CH_2Cl (0.66 g, 2.5 mmol) and 5.1N HCl/dioxane (2.9 ml, 15.0 mmol) as usual] in DMF (30 ml) containing NMM (0.33 ml, 3.0 mmol). The reaction mixture was stirred at 0°C for 1h and then at room temperature overnight. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, 0.72 g (69.6%), mp 131-134°C, $[\alpha]_D^{25}$ 64.1° (*c*=1.0, MeOH), Rf(B) 0.97, Rf(D) 0.69. *Anal.* Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.4; H, 7.60; N, 6.81. Found: C, 61.4; H, 7.73; N, 6.90.; D-L: Yield 0.7 g (67.2%), mp 126-128°C, $[\alpha]_D^{25}$ -75.2° (*c*=1.0, MeOH), Rf(B) 0.97, Rf(D) 0.71. *Anal.* Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.4; H, 7.60; N, 6.81. Found: C, 61.6; H, 7.61; N, 6.91.; D-D: Yield 0.64 g (65.2%), mp 153-155°C, $[\alpha]_D^{25}$ 51.3° (*c*=1.0, MeOH), Rf(B) 0.9, Rf(D) 0.76. *Anal.* Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.4; H, 7.60; N, 6.81. Found: C, 61.4; H, 7.46; N, 6.83.

2) Evaluation of yield of 3-benzyl-5-methyl-6-isobutyl-2(1H)-pyrazinone from diastereoisomeric dipeptidyl chloromethyl ketones
Each diastereoisomeric dipeptidyl chloromethyl ketone hydrochloride[prepared from L-L,[13] D-L, L-D or D-D,(0.82 g, 2.0 mmol) and 5.1N HCl/dioxane(1.96 ml, 10.0 mmol) as usual] was dissolved in MeOH(50 ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated down. Petroleum ether was added to the residue to afford 3-benzyl-5-methyl-6-isobutyl-2(1*H*)-pyrazinone[12] as crystals, which were collected by filtration and recrystallized from EtOH. Yields, from L-L: 65%; D-L: 70%; L-D: 62% and D-D: 73%.

General procedure for the synthesis of dipeptidyl chloromethyl ketone derivatives
A mixed anhydride [prepared from Boc protected amino acid (5.0 mmol), NMM or Et_3N (5.5 mmol) and isobutyl chloroformate (5.0 mmol) as usual] in THF (60 ml) was added to an ice-cold solution of H-Leu-CH_2Cl•HCl or H-Phe-CH_2Cl•HCl [prepared from Boc-Leu-CH_2Cl or Boc-Phe-CH_2Cl (5.0 mmol) and 5.1 N HCl/dioxane (30.0 mmol) as usual] in DMF (60 ml) containing NMM or Et_3N (5.5 mmol). The reaction mixture was stirred at 0°C for 1h and then at room temperature overnight. After removal of the solvent, the residue was extracted with AcOEt. The extract was washed with 10% citric acid, 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated down. The residue was purified by silica-gel column chromatography or recrystallization.

Boc-Gly-Leu-CH_2Cl Recrystallized from EtOH, $[\alpha]_D^{25}$ -60.0°(*c*=1.0, MeOH), Rf(D) 0.61, ^1H NMR ($CDCl_3$ 500MHz) δ: ppm 6.84 (1H, brs), 5.33 (1H, brs), 4.81 (1H, brs), 4.32 (1H, d, J=16.1), 4.26 (1H, d, J=16.1), 3.84 (1H, dd, J=5.4, 16.6), 3.77 (1H, dd, J=5.8, 16.6), 1.66 (2H, m), 1.53-1.46 (10H, m), 0.96 (3H, d, J=5.0), 0.95 (3H, d, J=6.1), ^{13}C NMR ($CDCl_3$ 125MHz) δ: ppm 201.5 (*q*), 170.0 (*q*), 156.3 (*q*), 80.6 (*q*), 54.6 (*t*), 46.7 (*s*), 44.4 (*s*), 40.0 (*s*), 28.3 (*p*), 24.9 (*s*) 23.2 (*p*) 21.5 (*p*). *Anal.* Calcd for $C_{14}H_{25}ClN_2O_4$: C, 52.4; H, 7.85; N, 8.73. Found: C, 52.3; H, 8.13; N, 8.64.

Boc-DL-Abu-Leu-CH_2Cl Work up followed by silica-gel column chromatography eluting with 1:2 v/v AcOEt-hexane, yield 0.42 g (62.5%), oil, Rf(C) 0.5.

Boc-Val-Leu-CH_2Cl Recrystallized from AcOEt, yield 0.75 g (45.8%), mp 139-141°C, $[\alpha]_D^{25}$ -67.8°(*c*=1.0, MeOH), Rf(A) 0.83. *Anal.* Calcd for $C_{17}H_{31}ClN_2O_4$: C, 56.3; H, 8.61; N, 7.72. Found: C, 56.2; H, 8.82; N, 7.65.

Boc-DL-Nva-Leu-CH_2Cl Recrystallized from EtOH, yield 1.2 g (73.7%), mp 79-81°C, Rf(A) 0.84. *Anal.* Calcd for $C_{17}H_{31}ClN_2O_4$: C, 56.3; H, 8.61; N, 7.72. Found: C, 56.3; H, 8.75; N, 7.72.

Boc-Ile-Leu-CH_2Cl Recrystallized from AcOEt, yield 0.61 g (46.4%), mp 142-143°C, $[\alpha]_D^{25}$ -70.4°(*c*=1.0, MeOH), Rf(A) 0.84. *Anal.* Calcd for $C_{18}H_{33}ClN_2O_4$: C, 57.4; H, 8.82; N, 7.43. Found: C, 57.6; H, 8.92; N, 7.54.

Boc-Leu-Leu-CH_2Cl Recrystallized from EtOH, yield 0.52 g (39.5%), mp 135-137°C, $[\alpha]_D^{25}$ -79.1°(*c*=1.0, MeOH), Rf(A) 0.76. *Anal.* Calcd for $C_{18}H_{33}ClN_2O_4$: C, 57.4; H, 8.82; N, 7.43. Found: C, 57.1; H, 8.85; N, 7.31.

Boc-DL-Nle-Leu-CH_2Cl Recrystallized from EtOH, yield 0.54 g (58.6%), mp 86-88°C, Rf(A) 0.85. *Anal.* Calcd for $C_{18}H_{33}ClN_2O_4$: C, 57.4; H, 8.82; N, 7.43. Found: C, 57.1; H, 8.66; N, 7.36.

Boc-Ala-Phe-CH_2Cl Recrystallized from EtOH, yield 0.91 g (70.5%), mp 133-134°C, $[\alpha]_D^{25}$ -101.1°(*c*=1.0, MeOH), Rf(B) 0.63, Rf(D) 0.81. *Anal.* Calcd for $C_{18}H_{25}ClN_2O_4$: C, 58.6; H, 6.83; N, 7.59. Found: C, 58.7; H, 6.98; N, 7.58.

Boc-DL-Abu-Phe-CH_2Cl Recrystallized from EtOH, yield 0.71 g (65.4%), mp 158-159°C, Rf(D) 0.59. *Anal.* Calcd for $C_{19}H_{27}ClN_2O_4$: C, 59.6; H, 7.14; N, 7.19. Found: C, 59.6; H, 7.11; N, 7.32.

Boc-Val-Phe-CH_2Cl Recrystallized from EtOH, yield 0.4 g (48.0%), mp 161-169°C, $[\alpha]_D^{25}$ -90.4° (*c*=1.0, MeOH), Rf(C) 0.41. *Anal.* Calcd for $C_{20}H_{29}ClN_2O_4$: C, 60.5; H, 7.36; N, 7.06. Found: C, 60.4; H, 7.54; N, 7.04.

Boc-DL-Nva-Phe-CH_2Cl Recrystallized from EtOH, yield 0.55 g (61.2%), mp 138-140°C, Rf(D) 0.69. *Anal.* Calcd for $C_{20}H_{29}ClN_2O_4$: C, 60.5; H, 7.36; N, 7.06. Found: C, 60.3; H, 7.42; N, 6.79.

Boc-Ile-Phe-CH_2Cl Recrystallized from EtOH, yield 0.8 g (57.4%), mp 156-157°C, $[\alpha]_D^{25}$ -87.8° (*c*=1.0, MeOH), Rf(A) 0.89. *Anal.* Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.4; H, 7.60; N, 6.82. Found: C, 61.3; H, 7.68; N, 6.58.

Boc-Leu-Phe-CH_2Cl Recrystallized from EtOH, yield 0.83 g (66.7%), mp 138-139°C, $[\alpha]_D^{25}$ -84.8°(*c*=1.0, MeOH), Rf(A) 0.85. *Anal.* Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.4; H, 7.60; N, 6.82. Found: C, 61.2; H, 7.73; N, 6.81.

Boc-DL-Nle-Phe-CH_2Cl Recrystallized from EtOH, yield 0.625 g (66.9%), mp 121-122°C, Rf(E) 0.85. *Anal.* Calcd for $C_{21}H_{31}ClN_2O_4$: C, 61.4; H, 7.60; N, 6.82. Found: C, 61.1; H, 7.58; N, 6.78.

General procedure for the synthesis of 5-methyl-2(1H)-pyrazinone derivatives (3b-3o)
Dipeptidyl chloromethyl ketone hydrochloride [prepared from Boc protected dipeptidyl chloromethyl ketone (0.5 mmol) and 5.4 N HCl/dioxane(3.0 mmol) as usual] was dissolved in MeOH (100 ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration. The crude product was purified by recrystallization from appropriate solvent as described below. Yields and mps are summarized in Table 2.

3-Ethyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3b) Recrystallized from acetone, Rf(A) 0.51, t_R 9.98 min, MS m/z: 194 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.3 (1H, brs, NH), 2.80 (2H, q, J=7.5, 3-C<u>H</u>2CH3), 2.44 (2H, d, J=7.4, 6-C<u>H</u>2CH(CH3)2), 2.29 (3H, s, 5-C<u>H</u>3), 2.04 (1H, nonet, J=6.8, 6-CH2C<u>H</u>(CH3)2), 1.26 (3H, t, J=7.5, 3-CH2C<u>H</u>3), 0.98 (6H, d, J=6.6, 6-CH2CH(C<u>H</u>3)2), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.5 (*q*, C-2), 157.0 (*q*, C-3), 134.0 (*q*, C-6), 129.6 (*q*, C-5), 38.9 (*s*, 6-<u>C</u>H2CH(CH3)2), 28.9 (*t*, 6-CH2<u>C</u>H(CH3)2), 26.2 (*s*, 3-<u>C</u>H2CH3), 22.3 (*p*, 6-CH2CH(<u>C</u>H3)2) , 18.8 (*p*, 5-CH3), 11.2 (*p*, 3-CH2<u>C</u>H3). *Anal.* Calcd for $C_{11}H_{18}N_2O \cdot H_2O$: C, 67.1; H, 9.42; N, 14.2. Found: C, 67.1; H, 9.36; N, 14.2.

3-Isopropyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3c) Recrystallized from acetone, Rf(A) 0.57 , t_R 18.83 min, MS m/z: 208 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.4 (1H, brs, NH), 3.37 (1H, heptet, J=6.9, 3-C<u>H</u>(CH3)2), 2.41 (2H, d, J=7.4, 6-C<u>H</u>2CH(CH3)2), 2.28 (3H, s, 5-CH3), 2.05 (1H, nonet, J=6.8, 6-CH2C<u>H</u>(CH3)2), 1.25 (6H, d, J=6.9, 3-CH(C<u>H</u>3)2), 0.97 (6H, d, J=6.6, 6-CH2CH(C<u>H</u>3)2), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 159.8 (*q*, C-2), 157.2 (*q*, C-3), 133.7 (*q*, C-6), 129.5 (*q*, C-5), 38.9 (*s*, 6-<u>C</u>H2CH(CH3)2), 30.6 (*t*, 3-<u>C</u>H(CH3)2), 28.8 (*t*, 6-CH2<u>C</u>H(CH3)2), 22.3 (*p*, 6-CH2CH(<u>C</u>H3)2), 20.0 (*p*, 3-CH(<u>C</u>H3)2), 18.9 (*p*, 5-CH3). *Anal.* Calcd for $C_{12}H_{20}N_2O$: C, 69.2 H, 9.68; N, 13.5. Found: C, 68.9; H, 9.95; N, 13.4.

3-Propyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3d) Recrystallized from acetone, Rf(A) 0.5 , t_R 15.67 min, MS m/z: 208 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.4 (1H, brs, NH), 2.74 (2H, t, J=7.7, 3-C<u>H</u>2CH2CH3), 2.43 (2H, d, J=7.3, 6-C<u>H</u>2CH(CH3)2), 2.29 (3H, s, 5-CH3), 2.05 (1H, nonet, J=6.8, 6-CH2C<u>H</u>(CH3)2), 1.74 (2H, hextet, J=7.7, 3-CH2C<u>H</u>2CH3), 1.03-0.97 (9H, m, 3-CH2CH2C<u>H</u>3, 6-CH2CH(C<u>H</u>3)2), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.7 (*q*, C-2), 156.1 (*q*, C-3), 134.1 (*q*, C-6), 129.6 (*q*, C-5), 38.9 (*s*, 6-<u>C</u>H2CH(CH3)2), 35.0 (*s*, 3-<u>C</u>H2CH2CH3), 28.8 (*t*, 6-CH2<u>C</u>H(CH3)2), 22.2 (*p*, 6-CH2CH(<u>C</u>H3)2), 20.6 (*s*, 3-CH2<u>C</u>H2CH3), 18.8 (*p*, 5-CH3), 14.1 (*p*, 3-CH2CH2<u>C</u>H3). *Anal.* Calcd for $C_{12}H_{20}N_2O$: C, 69.2 H, 9.68; N, 13.5. Found: C, 68.9; H, 9.95; N, 13.4.

3,6-Diisobutyl-5-methyl-2(1H)-pyrazinone(3e) Recrystallized from acetone, Rf(A) 0.58, Rf(D) 0.72, t_R 18.54 min, MS m/z: 222 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.2 (1H, brs, NH), 2.65 (2H, d, J=7.2, 3-C<u>H</u>2CH(CH3)2), 2.42 (2H, d, J=7.4, 6-C<u>H</u>2CH(CH3)2), 2.29 (3H, s, 5-CH3), 2.22 (1H, nonet, J=6.8, 3-CH2C<u>H</u>(CH3)2), 2.06 (1H, nonet, J=6.7, 6-CH2C<u>H</u>(CH3)2), 0.97 (6H, d, J=6.6, 6-CH2CH(C<u>H</u>3)2), 0.96 (6H, d, J=6.7, 3-CH2CH(C<u>H</u>3)2), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.8 (*q*, C-2), 155.7 (*q*, C-3), 134.1 (*q*, C-6), 129.5 (*q*, C-5), 41.6 (*s*, 3-<u>C</u>H2CH(CH3)2), 39.0 (*s*, 6-<u>C</u>H2CH(CH3)2), 28.8 (*t*, 6-CH2<u>C</u>H(CH3)2), 27.2 (*t*, 3-CH2<u>C</u>H(CH3)2), 22.6 (*p*, 3-CH2CH(<u>C</u>H3)2), 22.3 (*p*, 6-CH2CH(<u>C</u>H3)2), 18.7 (*p*, 5-CH3). *Anal.* Calcd for $C_{13}H_{22}N_2O$: C, 70.2; H, 9.97; N, 12.6. Found: C, 70.0; H, 10.0; N, 12.5.

3-sec-Butyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3f) Recrystallized from acetone, $[\alpha]_D^{25}$ +7.2° (c=1.0, MeOH), Rf(A) 0.67 , t_R 23.70 min, MS m/z: 222 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.3 (1H, brs, NH), 3.17 (1H, hextet, J=6.9, 3-C<u>H</u>(CH3)CH2CH3), 2.42 (2H, d, J=7.4, 6-C<u>H</u>2CH(CH3)2), 2.28 (3H, s, 5-CH3), 2.06 (1H, nonet, J=6.7, 6-CH2C<u>H</u>(CH3)2), 1.85 (1H, pentet-like, J=7.3, 3-CH(CH3)C<u>H</u>2CH3) 1.55 (1H, pentet-like, J=7.3, 3-CH(CH3)C<u>H</u>2CH3), 1.23 (3H, d, J=6.7, 3-CH(C<u>H</u>3)CH2CH3), 0.98 (6H, d, J=6.6, 6-CH2CH(C<u>H</u>3)2), 0.90 (3H, t, J=7.4, 3-CH(CH3)CH2C<u>H</u>3), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 159.3 (*q*, C-2), 157.3 (*q*, C-3), 133.6 (*q*, C-6), 129.6 (*q*, C-5), 38.9 (*s*, 6-<u>C</u>H2CH(CH3)2), 37.4 (*t*, 3-<u>C</u>H(CH3)CH2CH3), 28.8 (*t*, 6-CH2<u>C</u>H(CH3)2), 27.5 (*s*, 3-CH(CH3)<u>C</u>H2CH3), 22.3 (*p*, 6-CH2CH(<u>C</u>H3)2), 18.9 (*p*, 5-CH3), 15.3 (*p*, 3-CH(<u>C</u>H3)CH2CH), 12.2 (*p*, 3-CH(CH3)CH2<u>C</u>H3). *Anal.* Calcd for $C_{13}H_{22}N_2O$: C, 70.2; H, 9.97; N, 12.6. Found: C, 70.1; H, 9.95; N, 12.4.

3-Butyl-5-methyl-6-isobutyl-2(1H)-pyrazinone(3g) Recrystallized from hexane, Rf(A) 0.64 , t_R 19.36 min, MS m/z: 222 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.3 (1H, brs, NH), 2.77 (2H, t-like, J=7.8, 3-C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 2.43 (2H, d, J=7.4, 6-C$\underline{H}_2$CH(CH$_3$)$_2$), 2.28 (3H, s, 5-CH$_3$), 2.05 (1H, nonet, J=6.7, 6-CH$_2$C$\underline{H}$(CH$_3$)$_2$), 1.73-1.65 (2H, m, 3-CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 1.43 (2H, hextet, J=7.5, 3-CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 0.98 (6H, d, J=6.6, 6-CH$_2$CH(C$\underline{H}_3$)$_2$), 0.94 (3H, t, J=7.4, 3-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.6 (*q*, C-2), 156.4 (*q*, C-3), 134.0 (*q*, C-6), 129.5 (*q*, C-5), 39.0 (*s*, 6-$\underline{C}$H$_2$CH(CH$_3$)$_2$), 32.8 (*s*, 3-$\underline{C}$H$_2$CH$_2$CH$_2$CH$_3$), 29.4 (*s*, 3-CH$_2\underline{C}$H$_2$CH$_2$CH$_3$), 28.8 (*t*, 6-CH$_2\underline{C}$H(CH$_3$)$_2$), 22.8 (*s*, 3-CH$_2$CH$_2\underline{C}$H$_2$CH$_3$), 22.3 (*p*, 6-CH$_2$CH(C$\underline{H}_3$)$_2$), 18.8 (*p*, 5-CH$_3$), 13.9 (*p*, 3-CH$_2$CH$_2$CH$_2\underline{C}$H$_3$). *Anal.* Calcd for $C_{13}H_{22}N_2O$: C, 70.2; H, 9.97; N, 12.6. Found: C, 70.0; H, 10.27; N, 12.5.

3, 5-Dimethyl-6-benzyl-2(1H)-pyrazinone(3h) Recrystallized from EtOH, Rf(B) 0.59, t_R 8.30 min, MS m/z: 214 M^+. ^1H NMR ($CDCl_3$ 500MHz) δ: ppm 11.3 (1H, brs, NH), 7.34-7.22 (5H, m, CH$_2$-p$\underline{h}$), 3.89 (2H, s, 6-C$\underline{H}_2$-ph), 2.41 (3H, s, 3-CH$_3$), 2.34 (3H, s, 5-CH$_3$), ^{13}C NMR ($CDCl_3$ 125MHz) δ: ppm 157.0 (*q*, C-2), 154.4 (*q*, C-3), 135.8 (*q*, C-1′), 132.1 (*q*, C-6), 129.12 (*q*, C-5), 129.10 (*t*, C-3′, 5′), 128.8 (*t*, C-2′, 6′), 127.4 (*t*, C-4′), 36.2 (*s*, 6-CH$_2$-ph), 19.9 (*p*, 5-CH$_3$), 18.7 (*p*, 5-CH$_3$). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.9 H, 6.59; N, 13.1. Found: C, 73.1; H, 6.62; N, 13.1.

3-Ethyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3i) Recrystallized from EtOH, Rf(D) 0.77, t_R 14.18 min, MS m/z: 228 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 12.4 (1H, brs, NH), 7.31-7.23 (5H, m, CH$_2$-p$\underline{h}$), 3.89 (2H, s, 6-C$\underline{H}_2$-ph), 2.78 (2H, q, J=7.5, 3-C$\underline{H}_2$CH$_3$), 2.35 (3H, s, 5-CH$_3$), 1.24 (3H, t, J=7.5, 3-CH$_2$C$\underline{H}_3$), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 158.0 (*q*, C-2), 157.1 (*q*, C-3), 136.4 (*q*, C-1′), 132.4 (*q*, C-6), 129.4 (*q*, C-5), 128.9 (*t*, C-3′, 5′), 128.7 (*t*, C-2′, 6′), 127.2 (*t*, C-4′), 36.2 (*s*, 6-$\underline{C}$H$_2$-ph), 26.2 (*s*, 3-$\underline{C}$H$_2$CH$_3$), 18.8 (*p*, 5-CH$_3$), 11.2 (*p*, 3-CH$_2\underline{C}$H$_3$). *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.06; N, 12.3. Found: C, 73.4; H, 7.20; N, 12.0.

3-Isopropyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3j) Recrystallized from EtOH, Rf 0.8, t_R 19.30 min, MS m/z: 242 M^+. *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.4 H, 7.49; N, 11.6. Found: C, 74.4; H, 7.24; N, 11.6.

3-Propyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3k) Recrystallized from acetone, Rf(D) 0.78, t_R 17.15 min, MS m/z: 242 M^+. ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 12.9 (1H, brs, NH), 7.29-7.21 (5H, m, CH$_2$-p$\underline{h}$), 3.89 (2H, s, 6-C$\underline{H}_2$-ph), 2.73 (2H, t-like, J=7.6, 3-C$\underline{H}_2$CH$_2$CH$_3$), 2.35 (3H, s, 5-CH$_3$), 1.71 (2H, hexet, J=7.6, 3-CH$_2$C$\underline{H}_2$CH$_3$), 0.99 (3H, t, J=7.4, 3-CH$_2$CH$_2$C$\underline{H}_3$), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.4 (*q*, C-2), 157.0 (*q*, C-3), 136.6 (*q*, C-1′), 132.6 (*q*, C-6), 129.5 (*q*, C-5), 128.8 (*t*, C-3′, 5′), 128.7 (*t*, C-2′, 6′), 127.1 (*t*, C-4′), 36.2 (*s*, 6-$\underline{C}$H$_2$-ph), 24.9 (*s*, 3-$\underline{C}$H$_2$CH$_2$CH$_3$), 20.5 (*s*, 3-CH$_2\underline{C}$H$_2$CH$_3$), 18.9 (*p*, 5-CH$_3$), 14.1 (*p*, 3-CH$_2$CH$_2\underline{C}$H$_3$). *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.4 H, 7.49; N, 11.6. Found: C, 74.2; H, 7.39; N, 11.6.

3-Isobutyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3l) Recrystallized from EtOH, Rf(D) 0.82, t_R 20.03 min, MS m/z: 256 M^+, ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.2 (1H, brs, NH), 7.32-7.21 (5H, m, CH$_2$-p$\underline{h}$), 3.90 (2H, s, 6-C$\underline{H}_2$-ph), 2.65 (2H, d, J=7.2, 3-C$\underline{H}_2$CH(CH$_3$)$_2$), 2.36 (3H, s, 5-CH$_3$), 2.20 (1H, nonet, J=6.9, 3-CH$_2$C$\underline{H}$(CH$_3$)$_2$), 0.95 (3H, d, J=6.7, 3-CH$_2$CH(C$\underline{H}_3$)$_2$), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.7 (*q*, C-2), 156.5 (*q*, C-3), 136.6 (*q*, C-1′), 132.8 (*q*, C-6), 129.6 (*q*, C-5), 128.8 (*t*, C-3′, 5′), 128.7 (*t*, C-2′, 6′), 127.0 (*t*, C-4′), 41.6 (*s*, 3-$\underline{C}$H$_2$CH(CH$_3$)$_2$), 36.2 (*s*, 6-$\underline{C}$H$_2$-ph), 27.1 (*t*, 3-CH$_2\underline{C}$H(CH$_3$)$_2$), 22.7 (*p*, 3-CH$_2$CH(C$\underline{H}_3$)$_2$), 18.9 (*p*, 5-CH$_3$). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.2; H, 8.03; N, 10.8.

3-sec-Butyl-5-methyl-6-benzyl-2(1H)-pyrazinone(3m) Recrystallized from EtOH, $[\alpha]_D^{25}$ -13.7°(c=1.0, $CHCl_3$), Rf(D) 0.82, t_R 20.77 min, MS m/z: 256 M^+, ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 12.4 (1H, brs, NH), 7.30-7.22 (5H, m, CH$_2$-p$\underline{h}$), 3.88 (2H, s, 6-C$\underline{H}_2$-ph), 3.20 (1H, hexet, J=6.9, 3-C$\underline{H}$(CH$_3$)CH$_2$CH$_3$), 2.36 (3H, s, 5-CH$_3$), 1.82 (1H, m, 3-CH(CH$_3$)C$\underline{H}_2$CH$_3$), 1.53 (1H, m, 3-CH(CH$_3$)C$\underline{H}_2$CH$_3$), 1.20 (3H, d, J=6.9, 3-CH(C$\underline{H}_3$)CH$_2$CH$_3$), 0.89 (3H, t, J=7.4, 3-CH(CH$_3$)CH$_2$C$\underline{H}_3$), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 160.4 (*q*, C-2), 157.0 (*q*, C-3), 136.5 (*q*, C-1′), 132.0 (*q*, C-6), 129.4 (*q*, C-5), 128.9 (*t*, C-3′, 5′), 128.8 (*t*, C-2′, 6′), 127.1 (*t*, C-4′), 37.0 (*t*, 3-$\underline{C}$H(CH$_3$)CH$_2$CH$_3$), 36.1 (*s*, 6-$\underline{C}$H$_2$-ph), 27.5 (*s*, 3-CH(CH$_3$)$\underline{C}$H$_2$CH$_3$),

18.9 (*p*, 5-CH_3), 17.7 (*p*, 3-CH(CH_3)CH_2CH_3), 12.1 (*p*, 3-$CH(CH_3)CH_2$CH_3). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.1; H, 7.85; N, 11.0.

*3-butyl-5-methyl-6-benzyl-2(1H)-pyrazinone(**3n**)* Recrystallized from EtOH, Rf(D) 0.67, t_R 22.03 min, MS m/z: 256 M^+, ^1H NMR ($CDCl_3$ 400MHz) δ: ppm 13.1 (1H, brs, NH), 7.31-7.20 (5H, m, 6-CH_2-ph), 3.90 (2H, s, 6-CH_2-ph), 2.76 (2H, t, J=7.7, 3-C$H_2CH_2CH_2CH_3$), 2.35 (3H, s, 5-CH_3), 1.67 (2H, penet, J=7.4, 3-CH_2C$H_2CH_2CH_3$), 1.41 (2H, hexet, J=7.4, 3-CH_2CH_2CH_2CH_3), 0.93 (3H, t, J=7.3, 3-$CH_2CH_2CH_2$CH_3), ^{13}C NMR ($CDCl_3$ 100MHz) δ: ppm 157.4 (*q*, C-2), 157.2 (*q*, C-3), 136.6 (*q*, C-1′), 132.6 (*q*, C-6), 129.5 (*q*, C-5), 128.8 (*t*, C-3′, 5′), 128.7 (*t*, C-2′, 6′), 127.1 (*t*, C-4′), 36.2 (*s*, 6-CH_2-ph), 32.7 (*s*, 3-C$H_2CH_2CH_2CH_3$), 29.3 (*s*, 3-CH_2C$H_2CH_2CH_3$), 22.8 (*s*, 3-CH_2CH_2CH_2CH_3), 18.9 (*p*, 5-CH_3), 14.0 (*p*, 3-$CH_2CH_2CH_2$CH_3). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.86; N, 10.9. Found: C, 75.1; H, 8.05; N, 10.8.

*5-Methyl-6-isobutyl-2(1H)-pyrazinone(**3o**)* Recrystallized from EtOH, Rf(B) 0.17, t_R 4.0 min, MS m/z: 166 M^+. ^1H NMR ($CDCl_3$ 500MHz) δ: ppm 13.5(1H, brs, NH), 8.03(1H, s, 3-H), 2.48(2H, d, J=7.5, 6-CH_2CH(CH_3)2), 2.32(3H, s, 5-CH_3), 2.05(1H, nonet, 6-CH_2CH(CH_3)2), 1.00(6H, d, J=7.0, 6-CH_2CH(CH_3)2), ^{13}C NMR ($CDCl_3$ 125MHz) δ: ppm 158.4 (*q*, C-2), 144.3 (*q*, C-3), 137.0 (*q*, C-6), 131.5 (*q*, C-5), 39.2 (*s*, 6-CH_2CH(CH_3)2), 28.7 (*t*, 6-CH_2CH(CH_3)2), 22.3 (*p*, 6-CH_2CH(CH_3)2), 18.8 (*p*, 5-CH_3). *Anal.* Calcd for $C_9H_{14}N_2O$: C, 65.0 H, 8.49; N, 16.9. Found: C, 65.0; H, 8.67; N, 16.7.

Boc-Phe-Leu-CH3 The title compound was prepared from Boc-Phe-Leu-CH_2Cl (0.51 g, 1.24 mmol) by catalytic hydrogenation. After neutralization of the solution with Et_3N and removal of Pd and the solvent, hexane was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 456 mg (97.6%), mp 113-114°C, $[\alpha]_D^{25}$ -32.4°(*c*=0.1, MeOH), Rf(B) 0.46. *Anal.* Calcd for $C_{21}H_{32}N_2O_4$: C, 65.4; H, 8.63; N, 7.27. Found: C, 65.5; H, 8.50; N, 7.00, Amino acid analysis: Recovery of Phe was 79.4%.

Synthesis of 3-benzyl-5-methyl-6-isobutyl-2(1H)-pyrazinone [12] from Boc-Phe-Leu-CH3 H-Val-Leu-CH_2Cl•HCl [prepared from Boc-Phe-Leu-CH_3 (0.12 g, 0.32 mmol) and 5.0 N HCl/dioxane (0.4 ml, 2.0 mmol) as usual] was dissolved in MeOH (5 ml). The reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated down. Petroleum ether was added to the residue to afford crystals, which were collected by filtration and recrystallized from EtOH, yield 60 mg (73.2%), mp 133-135°C.

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