Synthesis of a Novel Thyrotropin Releasing Hormone (TRH) Analog Incorporating a Piperazin-2-one Ring

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The synthesis of a Thyrotropin Releasing Hormone (TRH) analog incorporating a piperazin-2-one ring is described. This conformationally restricted peptidomimetic attempts to retain the key recognition elements of the interaction between TRH and its receptor. The synthesis started from the protected dipeptide **2** and proceeded *via* the 4-nitrobenzenesulfonyl-activated intermediate **3**, which was then cyclized, *N*-acylated, and deprotected to yield the target compound **1**.

Introduction. – Thyrotropin Releasing Hormone (TRH) was the first hypothalamic hormone isolated and characterized [1]. This tripeptide ($GlpHisProNH_2$) displays dual functions, acting both as a hormone and as a neuropeptide. TRH was initially classified as a hormone that releases prolactin and thyrotropin from the pituitary, but it has also been shown to act as a neurotransmitter. This characterization is based primarily on its analeptic properties and its ability to reverse the sedation and hypothermia induced by pentobarbital, ethanol, and diazepam. TRH augments many of the neurotransmitter systems implicated in memory storage and retrieval independently of its hormonal activity, and it is effective in ameliorating many forms of memory disruption. TRH-Related alterations are associated with various diseases, including *Alzheimer*'s disease, depression, schizophrenia, epilepsy, and metabolic disorders [2].

The biological activities of TRH are brought about by the interaction of TRH with its receptor (TRH-R). This receptor is a member of a large family of transmembrane proteins (TM) that couple to G-proteins. To understand TRH signaling at the molecular level, it is important to determine the structure of the complex between TRH and its receptor. The transmembrane nature of these G-protein-coupled receptors makes it nearly impossible to determine the three-dimensional structure of the TRH receptor. Moreover, all attempts to crystallize this receptor with a bound ligand have been unsuccessful. Consequently, the only attempts to delineate the biologically active conformation of TRH have been syntheses of various conformationally restricted analogs of TRH and investigations of their activities[2]). Through these studies, it is known that there are at least three primary sites of interaction between TRH and its receptor. These include *a*) the C-terminal amide group of proline with Arg-306 in transmembrane region 7 (TM-7); *b*) the imidazole ring of histidine with Tyr-282 in TM-

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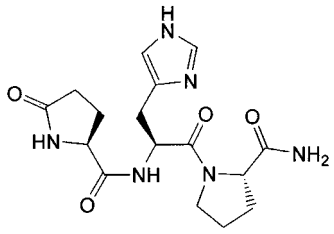
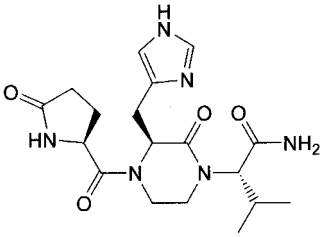
[2]) For the synthesis of various TRH analogs, which have some or all of these functional groups, see [3].

6; *c*) the carboxamide functionality of pyroglutamic acid (= 5-oxoproline, Glp) with Tyr-106 and Asn-110 in TM-3. TRH is rapidly metabolized by the body, and, hence, an analog that retains these interactions while imparting rigidity to the peptide backbone would be an ideal TRH analog.

Several peptidomimetics incorporating a piperazin-2-one ring have shown interesting biological properties [4], and therefore it was intriguing to investigate whether the target TRH analog **1** would bind to the TRH receptor. In this TRH analog, the three major sites of interaction with the TRH receptor are retained. The N-terminal pyroglutamic acid is kept intact, histidine is made a part of the piperazin-2-one ring, and valine has replaced proline. The synthesis of this analog **1** thus involves the generation of the piperazin-2-one ring with His and Val, installation of Glp on the free N-terminus of this piperazin-2-one, and converting the C-terminus of valine to amide function. We have recently described syntheses of piperazin-2-ones from amino acids [5], and our goal was to adapt these methods to the synthesis of the TRH analog **1**.



TRH



TRH Analog **1**

Results and Discussion. – The protection of the imidazole moiety of histidine is of critical importance in this synthesis. The use of tosyl, 2,4-dinitrophenyl, and benzyl protecting groups all led to premature deprotection during the cyclization step (*vide infra*). The synthesis was eventually carried out with trityl (triphenylmethyl, Tr) protection for the imidazole moiety of histidine. In the first step, *N*-(Fmoc)His(Tr)OH (Fmoc = (9*H*-fluoren-9-yl)methoxycarbonyl) was coupled with valine methyl ester hydrochloride in presence of BOP and Et_3N to give the protected dipeptide **2** in nearly quantitative yield (*Scheme*)[3]). 4-(Aminomethyl)piperidine was used to deprotect the Fmoc group [6] from the dipeptide, the reaction of which with 4-nitrobenzenesulfonyl chloride and Et_3N in $CHCl_3$ gave the 4-nitrobenzenesulfonyl-protected dipeptide **3**. On heating **3** at 60° in DMF with excess 1,2-dibromoethane and K_2CO_3, 2-oxopiperazine derivative **4** was obtained. Use of tosyl, 2,4-dinitrophenyl, or benzyl groups for protection of the imidazole ring resulted in premature cleavage of these groups to varying degrees. Trityl protection for the imidazole ring was thus suitable for our purposes. The (4-nitrophenyl)sulfonyl group on **4** was removed by $PhSH/K_2CO_3$ in DMF, and the piperazin-2-one **5** was coupled with pyroglutamic acid with BOP as the

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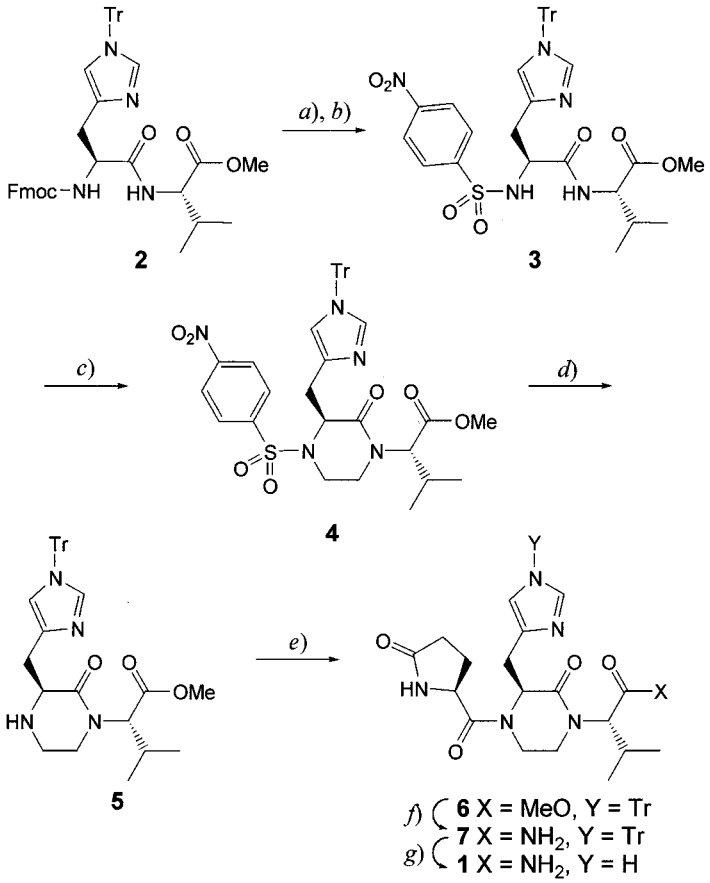
[3]) Commercially available, optically pure amino-acid derivatives were used, but no effort was made to ascertain the optical purity of the compounds prepared. ^1H- and ^{13}C-NMR spectra of the compounds did not show any evidence that racemization had occurred at any stage. So, for convenience, the formulas given represent a single possible diastereoisomer, although the optical purity has not rigorously been established.

Scheme



a) 4-(Aminomethyl)piperidine; 99%. *b*) (4-Nitrophenyl)sulfonyl chloride, CH_2Cl_2; 94%. *c*) K_2CO_3, 1,2-dibromoethane, DMF; 40%. *d*) K_2CO_3, PhSH, DMF; 88%. *e*) GlpOH, BOP, CH_2Cl_2; 79%. *f*) 1. LiOH, MeOH, H_2O; 2. C_6F_5OH, DCC, DMAP, CH_2Cl_2; 3. NH_3, EtOH; 52% (3 steps). *g*) 5% AcOH in MeOH, 81%. BOP = (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

coupling agent to give the coupled product **6**. The methyl ester was hydrolyzed with LiOH in aqueous MeOH, and the corresponding acid reacted with C_6F_5OH in the presence of DCC and DMAP to give the activated pentafluorophenyl ester. Its treatment with 2M ethanolic NH_3 solution gave the amide **7** in 52% yield with respect to **6**. The amide **7** was reacted with 5% AcOH solution in MeOH at reflux for 6 h to deprotect the Tr group. Aqueous workup resulted in the desired product partitioning into the aqueous layer, from which it was difficult to purify. Evidently, the compound was extremely polar and, therefore, could not be isolated in this manner. The solubility pattern of the peptide and the trityl acetate are very different, as was evident from previous unsuccessful attempts, and this property was then exploited to isolate the desired tripeptide derivative. The polar peptide is expected to migrate into a

MeOH/H_2O layer, whereas the non-polar trityl acetate will preferentially dissolve in a non-polar hexanes layer. Therefore, deprotection was carried out on **7** again, and, this time, the crude product was partitioned into a biphasic hexanes/aqueous MeOH system. As anticipated, the peptide **1** went into the aqueous MeOH layer, and the trityl acetate into the hexanes layer. Separation of the two phases and evaporation of the aqueous MeOH phase under vacuum gave the desired product **1**.

This piperazin-2-one derivative was tested for its affinity towards the TRH receptor. Binding studies were carried out on the TRH receptor from rat forebrain membrane with 3-[$^3H_3$]MeHis^2) TRH. Reactions were carried out in 20 mM Na_2HPO_4 (pH 7.4) at 4° for 3–4 h. The reactions were terminated by rapid vacuum filtration onto glass fibers. The radioactivity trapped onto the fibers was determined and compared to control values in order to evaluate any interactions of the analog with the TRH receptor. The binding studies showed that the K_i value for this TRH analog was $> 10^{-6}$ M, thus indicating weak binding to the receptor.

Conclusion. – This report describes the first synthesis of a novel TRH analog incorporating a piperazin-2-one structure. Altough this particular analog did not show a high affinity for the TRH receptor, there is a possibility of synthesis of better analogs by varying the amino-acid side chains or by increasing the size of the ring. These results can perhaps pave the way for analogs with greater flexibility for enhanced interaction with the TRH receptor.

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Experimental Part

General. Amino acids were purchased from *Chem-Impex International or Aldrich Chemical Company Inc*. TLC: on silica gel thin-layer sheets *60 F 254* from *Merck*. Column chromatography (CC): with silica gel (40–63 μm). ^{1}H- and ^{13}C-NMR spectra: *Varian UNITY 500* spectrometer at 500 and 125 MHz, resp. 3-NBA: 3-Nitrobenzyl alcohol. TRH Binding studies were carried out at *Novascreen* (www.novascreen.com).

*Methyl 2-(2-{[(9*H*-Fluoren-9-yl)methoxycarbonyl]amino}-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanamido}-3-methylbutanoate* (**2**). A soln. of *N*-(Fmoc)His(Tr)OH (1.510 g, 2.434 mmol) in 2.5 ml of dry CH_2Cl_2 was treated with valine methyl ester hydrochloride (0.467 g, 2.783 mmol), BOP (1.181 g, 2.670 mmol), and Et_3N (0.40 ml, 2.70 mmol). The soln. was stirred for 12 h, then washed with 1N HCl, 10% $NaHCO_3$, and H_2O, dried ($MgSO_4$), and filtered. Solvent evaporation gave the crude, which was chromatographed (hexanes/AcOEt 1:1) to yield **2** (1.348 g, 99%). White foam. R_f (hexanes/AcOEt 1:1) 0.15. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.85–0.90 (*m*, 2 Me); 2.10–2.20 (*m*, Me_2CH); 3.00–3.10 (m, CH_2–imidazole); 3.66 (*s*, MeO); 4.22–4.26 (*m*, CH); 4.30–4.40 (*m*, CH_2); 4.49 (*dd*, $J = 8.0, 4.5$, C*H*COOMe); 4.58 (*m*, CH); 6.69 (*s*, C=CH); 6.89 (*d*, $J = 6.5$, 1 NH); 7.10–7.75 (*m*, 23 arom. H); 7.83 (*d*, $J = 7.5$, NHCO). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.67; 18.89; 30.30; 30.92; 46.95; 51.82; 54.71; 57.29; 67.06; 75.18; 119.25; 119.76; 125.14; 125.08; 126.89; 126.90; 127.47; 127.88; 129.58; 138.21; 141.06; 142.15; 143.74; 143.81; 171.22; 171.84. HR-FAB-MS (3-NBA): 733.3393 ([$C_{46}H_{44}N_4O_5$ + H]$^+$; calc. 733.3390).

*Methyl 3-Methyl-2-{2-(4-nitrobenzenesulfonamido)-3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propanamido}butanoate* (**3**). A soln. of dipeptide **2** (0.450 g, 0.614 mmol) was taken in 5 ml of $CHCl_3$ and 5 ml 4-(aminomethyl)piperidine was added. The soln. was stirred for 2 h, diluted with $CHCl_3$, and washed twice with sat. NaCl soln. It was then washed with phosphate buffer (prepared by adding 90 g of $NaH_2PO_4 \cdot H_2O$ and 32.7 g of Na_2HPO_4 in 500 ml of dist. H_2O; pH 5.5), H_2O, dried ($MgSO_4$), and filtered. Partial solvent evaporation *i.v.* gave the free dipeptide as a soln. in $CHCl_3$. It was taken with 4-nitrobenzenesulfonyl chloride (0.163 g, 0.735 mmol) and Et_3N (0.10 ml, 0.717 mmol), and the soln. was stirred for 5 h. It was washed with 1N HCl, 10%

$NaHCO_3$, and H_2O, dried ($MgSO_4$), and filtered. Solvent evaporation gave **3** (0.400 g, 93.6%). M.p. 192–194°. R_f (hexanes/AcOEt 1:2) 0.32. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.72 (*d*, *J* = 7.0, Me); 0.76 (*d*, *J* = 6.5, Me); 2.00–2.10 (*m*, Me_2CH); 2.70–3.10 (*m*, CH_2); 3.69 (*s*, MeO); 4.08–4.10 (*m*, CH); 4.36 (*dd*, *J* = 9.0, 5.0, C*H*COOMe); 6.60 (*s*, C=CH); 7.00–7.36 (*m*, CH=N, 3 Ph); 7.59 (*d*, *J* = 9.0, CONH); 8.09 (*d*, *J* = 8.5, 2 H, C_6H_4); 8.30 (*d*, *J* = 8.5, 2 H, C_6H_4). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.50; 18.73; 29.81; 30.86; 51.92; 56.73; 57.28; 73.45; 119.68; 124.10; 127.96; 128.08; 128.46; 129.48; 135.55; 138.18; 141.80; 145.63; 149.87; 169.71; 171.30. HR-FAB-MS (3-NBA): 696.2490 ($[C_{37}H_{37}N_5O_7S + H]^+$; calc. 696.2492).

*Methyl 3-Methyl-2-(4-(4-nitrobenzenesulfonamido)-2-oxo-3-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-methyl]piperazin-1-yl)butanoate* (**4**). A soln. of **3** (0.093 g, 0.134 mmol) in 1 ml of dry DMF was treated with K_2CO_3 (0.143 g, 1.032 mmol), and the soln. was heated at 60° for 30 min. Then, 1,2-dibromoethane (0.11 ml, 1.277 mmol) was added. The soln. was stirred for 14 h, and then solvent was evaporated under high vacuum. AcOEt was added, and the soln. was washed with 1N HCl, H_2O, dried ($MgSO_4$), and filtered. Solvent evaporation gave the crude, which was chromatographed (AcOEt/hexanes 1:1) to give **4** (0.038 g, 40%). R_f (hexanes/AcOEt 1:2) 0.18. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.74 (*d*, *J* = 6.8, Me); 0.90 (*d*, *J* = 6.3, Me); 1.90–2.10 (*m*, Me_2CH); 3.05–3.10 (*m*, 1 H, CH_2N); 3.18 (*d*, *J* = 6.5, CH_2–imidazole); 3.25–3.50 (*m*, 1 H, CH_2N); 3.53 (*s*, MeO); 3.60–3.65 (*m*, 1 H, CH_2N); 4.69 (*t*, *J* = 6.5, CH); 4.75 (*d*, *J* = 10.5, C*H*COOMe); 6.67 (*s*, C=CHN); 7.10–7.40 (*m*, 16 H, $CHNCPh_3$); 7.95 (*d*, *J* = 9.0, 2 H, C_6H_4); 8.26 (*d*, *J* = 9.0, 2 H, C_6H_4). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.70; 19.36; 27.12; 32.03; 40.42; 41.02; 51.58; 58.81; 60.43; 75.08; 120.11; 124.31; 127.84; 127.88; 128.28; 129.59; 135.49; 138.13; 142.22; 145.11; 149.95; 166.88; 170.61. HR-FAB-MS (3-NBA): 722.2645 ($[C_{39}H_{39}N_5O_7S + H]^+$; calc. 722.2648).

*Methyl 3-Methyl-2-(2-oxo-3-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]piperazin-1-yl)butyrate* (**5**). A soln. of K_2CO_3 (0.166 g, 1.201 mmol) in 0.2 ml of dry DMF at r.t. was treated with PhSH (0.085 ml, 0.828 mmol). The soln. was stirred at r.t. for 30 min, and **4** (0.144 g, 0.200 mmol) was added as a 0.5-ml soln. in DMF. The soln. was stirred at r.t. for 12 h. The solvent was evaporated *i.v.*, and AcOEt was added. The soln. was then washed with 10% $NaHCO_3$, H_2O, dried ($MgSO_4$), and filtered. Evaporation gave the crude, which was chromatographed (AcOEt/MeOH 10:1) to yield **5** (88.3%). R_f (AcOEt) 0.05. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.80, 0.95 (2*d*, *J* = 7.0 each, Me_2CH); 2.10–2.20 (*m*, Me_2CH); 2.80–2.85 (br. *s*, NH); 2.89 (*m*, 1 H, CH_2–imidazole); 2.92–3.20 (*m*, CH_2N); 3.21 (*m*, 1 H, CH_2–imidazole); 3.25–3.50 (*m*, NCH_2); 3.68 (*s*, MeO); 3.78 (*m*, CH); 4.92 (*d*, *J* = 11.0, C*H*COOMe); 6.66 (*s*, CH); 7.10–7.40 (*m*, $CHNCPh_3$). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.74; 19.36; 26.63; 30.35; 41.95; 44.26; 51.60; 59.75; 60.58; 75.02; 119.25; 127.83; 129.57; 138.10; 138.42; 142.27; 170.07; 171.42. ES-MS: 537 ($[C_{33}H_{36}N_4O_3 + H]^+$; calc. 537).

*Methyl 3-Methyl-2-(2-oxo-4-[(5-oxopyrrolidin-2-yl)carbonyl]-3-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]-methyl]piperazin-1-yl)butanoate* (**6**). A soln. of **5** (0.096 g, 0.178 mmol) in 0.2 ml of dry CH_2Cl_2 was treated with pyroglutamic acid (0.028 g, 0.214 mmol), BOP (0.100 g, 0.226 mmol), and Et_3N (0.03 ml, 0.215 mmol). The soln. was stirred at r.t. for 48 h. The soln. was diluted with 20 ml of CH_2Cl_2 and washed with 10% $NaHCO_3$, 1N HCl, H_2O, dried ($MgSO_4$), and evaporation *i.v.* gave the crude, which was chromatographed (hexanes/AcOEt 1:4) to yield **6** (0.091 g, 79%). White solid. M.p. 186–188°. R_f (AcOEt/MeOH 10:1) 0.07. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.67, 0.91 (2*d*, *J* = 6.6 each, 2 Me); 2.00–2.30 (*m*, CH, CH_2CH_2); 3.00–3.15 (*m*, 2 CH_2–imidazole); 3.15–3.50 (*m*, NCH_2CH_2N); 3.65 (*s*, MeO); 4.36–4.46 (*m*, CH); 4.90 (*d*, *J* = 10.5, C*H*COOMe); 5.07 (*dd*, *J* = 5.9, 11.8, CH); 6.58–6.62 (*m*, NH); 6.65 (*s*, C=CH); 7.00–7.30 (*m*, C=CHNPh_3). ^{13}C-NMR (125 MHz, $CDCl_3$): 18.53; 19.32; 24.26; 26.80; 28.97; 29.29; 40.64; 42.46; 51.79; 53.35; 56.56; 60.32; 75.08; 119.71; 127.86; 129.53; 135.87; 138.41; 142.16; 167.13; 169.13; 170.72; 177.62. HR-FAB-MS (3-NBA): 648.3188 ($[C_{38}H_{41}N_5O_5 + H]^+$; calc. 648.3186).

*3-Methyl-2-(2-oxo-4-[(5-oxopyrrolidine-2-yl)-carbonyl]-3-{[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl}-piperazin-1-yl)butanamide* (**7**). A soln. of **6** (12 mg, 0.018 mmol) was dissolved in 0.2 ml of MeOH/H_2O 1:1 at r.t. and treated with 2.4 mg of LiOH. The soln. was stirred for 6 h, and then dil. HCl and AcOEt were added. The org. layer was collected, dried ($MgSO_4$), filtered, and the solvent was evaporated. The solid obtained was then treated with 5 mg of C_6F_5OH, 5 mg of DCC, 1 mg of DMAP, and 3 µl of Et_3N in 0.3 ml of dry CH_2Cl_2 at 0°. The soln. was stirred at 0° for 15 min and then at r.t. overnight. After the reaction was complete (TLC), the soln. was diluted with CH_2Cl_2 and filtered to remove DCU. The solvent was evaporated from the filtrate, and then the filtrate was treated with 1.5 ml of 2M NH_3 soln. in EtOH at r.t. for 8 h. 1N HCl was then added to the soln., which was extracted with AcOEt. The org. layer was dried ($MgSO_4$) and then filtered. Evaporation gave the crude, which was chromatographed (5% MeOH in AcOEt) to yield **7** (6.2 mg, 52.2%). Yellow oil. R_f (MeOH/AcOEt 1:10) 0.31. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.62 (*d*, *J* = 7.0, Me); 0.70 (*d*, *J* = 6.0, Me); 2.00–2.40 (*m*, CH, CH_2CH_2); 2.80–2.95 (*m*, CH_2–imidazole); 3.00–3.40 (*m*, NCH_2CH_2N); 4.24–4.34 (*m*, CH); 4.58 (*d*, *J* = 6.5, C*H*COOMe); 4.98–5.10 (*m*, CH); 5.60, 6.20 (2 br. *s*, $CONH_2$); 6.56 (br. *s*, NHCO); 6.56 (*s*, C=CH); 7.00–7.40

(*m*, N=CHNCPh$_3$). ^{13}C-NMR (125 MHz, CDCl$_3$): 18.15; 19.33; 25.25; 29.16; 29.67; 31.54; 40.42; 41.56; 51.90; 56.48; 61.42; 75.18; 119.79; 127.95; 129.53; 135.73; 138.83; 141.95; 168.04; 169.32; 170.91; 177.79. HR-FAB-MS (3-NBA): 633.3188 ([$C_{37}H_{40}N_6O_4$ + H]$^+$; calc. 633.3189).

*2-{3-[(1*H*-Imidazol-4-yl)methyl]-2-oxo-4-[(5-oxopyrrolidine-2-yl)carbonyl]piperazin-1-yl}-3-methylbutyramide* (**1**). A soln. of **7** (9 mg) in 2 ml MeOH was treated with 0.1 ml of AcOH and refluxed for 6 h. The solvent was evaporated *i.v.* to remove excess AcOH, and then MeOH and hexanes were added in equal amounts by volume. A few drops of H_2O were added to create two layers. The two layers were thoroughly mixed, and then the top hexane layer was removed. The MeOH/H_2O mixture was evaporated *i.v.* to give **1** (4.5 mg, 81%). ^{1}H-NMR (500 MHz, CDCl$_3$): 0.90–1.00 (*m*, 2 Me); 1.80–2.00 (*m*, 1 H, CH$_2$); 2.05–2.10 (*m*, Me$_2$C*H*); 2.20–2.40 (*m*, 3 H, CH$_2$CH$_2$); 3.20–3.85 (*m*, CH$_2$–imidazole, NCH$_2$CH$_2$N); 4.60–4.65 (*m*, CH); 4.90–4.95 (*m*, C*H*COOMe); 5.15–5.20 (*m*, CH); 6.95 (br. *s*, 1 H, C$_3$H$_2$N$_2$); 8.10 (br. *s*, 1 H, C$_3$H$_2$N$_2$). ^{13}C-NMR (125 MHz, CDCl$_3$): 18.73; 19.29; 21.83; 24.39; 27.17; 29.23; 40.90; 42.43; 53.68; 56.58; 60.87; 118.06; 129.90; 134.31; 167.14; 170.22; 176.34; 179.36. HR-FAB-MS (3-NBA): 391.2095 ([$C_{18}H_{26}N_6O_4$ + H]$^+$; calc. 391.2094).

REFERENCES

[1] a) J. Bler, F. Enzmann, K. Folkers, C. Y. Bowers, A. V. Schally, *Biochem. Biophys. Res. Commun.* **1969**, *37*, 705; b) R. Burgus, T. F. Dunn, D. Desiderio, W. Vale, R. C. Guillemin, *R. Acad. Sci. (Paris)* **1969**, *269*, 1870.

[2] A. A. Mazurov, S. A. Andronati, T. I. Korotenko, N. I. Sokolenko, A. I. Dyadenko, Y. E. Shapiro, V. Y. Gorbatyuk, T. A. Voronina, *Bioorg. Med. Chem. Lett.* **1997**, *5*, 2029.

[3] a) G. L. Olson, H.-C. Cheung, E. Chiang, V. S. Madison, J. Sepinwall, G. P. Vincent, A. Winkour, K. A. Gary, *J. Med. Chem.* **1995**, *38*, 2866; b) M. Bos, G. L. Olson, G. P. Vincent, *Helv. Chim. Acta* **1994**, *77*, 463; c) K. Ikeda, Y. Iwasaki, M. Kinoshita, *Neurosci. Lett.* **1998**, *250*, 9; d) K. Toide, M. Shinoda, M. Takase, K. Iwata, H. Yoshida, *Eur. J. Pharmacol.* **1993**, *233*, 21.

[4] a) Y. Tong, Y. M. Fobian, M. Wu, N. D. Boyd, K. D. Moeller, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1679; b) H. Sugihara, H. Fukushi, T. Miyaki, Y. Imai, Z. Terashita, M. Kawamura, Y. Fujisawa, S. Kita, *J. Med. Chem.* **1998**, *41*, 489; c) I. Torrini, G. Mastropietro, G. P. Zecchini, M. P. Paradishi, G. Lucente, S. Spisani, *Arch. Pharm. Med. Chem.* **1998**, *331*, 170.

[5] a) U. Bhatt, N. Mohammed, G. Just, E. Roberts, *Tetrahedron Lett.* **1997**, *38*, 3679; b) N. Mohamed, U. Bhatt, G. Just, *Tetrahedron Lett.* **1998**, *39*, 8213.

[6] L. A. Carpino, D. Sadat-Aalaee, M. Beyermann, *J. Org. Chem.* **1990**, *55*, 1673.

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