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Synthesis of bioactive aminoacid derivatives of *trans*-5-aminomethyl-1-benzyl-6-phenylpiperidin-2-one

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Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

trans-5-Aminomethyl-1-benzyl-6-phenylpiperidin-2-one (**2**) was prepared in high yield *via* Mitsunobu methodology and acylated by means of *N*-protected α-amino acids glycine, L-tryptophan, L-phenylalanine and L-alanine to give new piperidinones with a peptide bond in the side chain to the piperidinone cycle. *N*-Deprotection was carried out and the side chain of the tryptophan derivative **4** was elongated to yield products containing two peptide bonds in it. Mass spectra (EI and/or ESI) of most of the derivatives were taken and some fragmentation patterns were suggested. Tryptophan derivatives **3**-**5** have been described in a previous paper to possess antihistamine activity. In the present study four peptide derivatives have been tested for ACE inhibitory activity and compounds **13a**,**b** and **14** have shown a weak ACE inhibitory activity.

Key words: piperidinones; pseudopeptides; ACE inhibition; *N*-deprotection; mass spectrometry

INTRODUCTION

Piperidin-2-ones (δ-lactams) containing amino groups as substituents are intensively investigated because they are regarded as constrained surrogates of dipeptides and are peptidomimetics of the β-turn of the polypeptide chain [1–6]. These peptidomimetics, the so-called Freidinger lactams [7] have shown numerous biological activities, such as ACE- [3] and renin- inhibiting activity [8], serine protease inhibition [9] *etc.* Thus, aminolactams attracted the intensive investigations of different research groups, aiming at both new applications of the compounds as pharmaceuticals and synthons for further synthetic elaboration [10]. 2-Aryl-5-oxopiperidine-3-carboxylic acids and their derivatives have shown antihistaminic and analgesic activity [11, 12]; 2-aryl-3-amino-piperidines such as CP-99,994 (**1**) have shown antagonism against the human neurokinin undecapeptide Substance P (SP) and exhibit effective antiemetic activity [13]. As a neuromediator, SP is responsible for a variety of disorders such as migraine, rheumatoid arthritis and pain [12, 13]. Having in mind the diverse biological activities of amino piperidines [1], we started a synthetic program on transformation of the carboxylic group of the easily accessible *trans*-1-benzyl-2-phenyl-5-oxopiperidine-3-carboxylic acid **1** [11, 12, 14–17] into amino group [15]. Thus, we published recently on the preparation of piperidines containing a peptide bond in the side chain, *i.e.* *trans*-5-(*N*-acylated amino)-2-oxopiperidines [15]. The present paper is a part of our on-going research program on the introduction of amino substituent onto a lactam ring and it deals with the synthesis of (±)-*trans*-5-aminomethyl-1-benzyl-6-phenyl-piperidin-2-one **2** from the acid **1**. Amino compound **2** and similarly substituted derivatives can be regarded as reversed analogs of GABA amide [14, 18]. Our purpose is to use the amino group of 5-aminomethyl compound **2** for the introduction of a peptide bond and to obtain new building blocks for biologically active molecules of pseudopeptide type. The α-amino acid residues of glycine, L-tryptophan, L-phenylalanine and L-alanine were selected to be introduced because they are components of the structure of SP. The preliminary biological tests of the newly prepared tryptophan containing pseudopeptide derivatives **3, 4** and **5** have shown that the compounds exhibit antihistamine activity [17], which is in agreement with literature data [19]. (Fig. 1) From the other

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hand, other aminopiperidinones, incorporating residues of alanine and glycine [3], or phenylalanine [8] have shown moderate to strong ACE inhibiting activity. Below the synthesis and structural characteristics of amine **2**, its peptide derivatives **3**-**5** as well as of a series of their peptide analogs **8**-**15** are described. Some of the peptides were tested for ACE inhibitory activity.

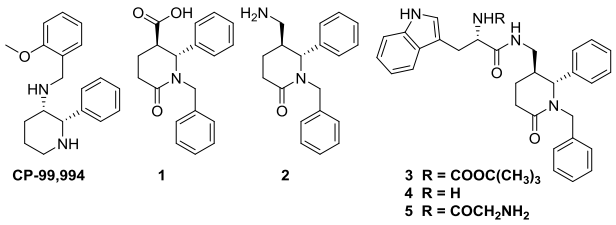


Fig. 1. CP-99,994 and compounds **1**-**5**; only one diastereomer of compounds **1**-**5** is shown for the sake of shortness.

EXPERIMENTAL

Synthesis

Melting points were taken on a microhot stage apparatus Boetius PHMK 05 and are uncorrected. IR spectra were recorded on a Specord 75 instrument. ^{1}H NMR spectra were obtained on Bruker Avance DRX-250 (250.13 MHz) and Bruker Avance III HD (500.13 MHz) spectrometers. The chemical shifts are given in parts per million (ppm; in δ-scale) relative to tetramethylsilane as internal standard. Electron impact mass spectra (EI-MS) were recorded by flow injection of acetonitrile solution into an Agilent 6890 gas chromatograph attached to a mass detector Agilent 5973 at 70 eV. ESI–MS spectra were measured on TCQ Quantum Access MAX, capillary temperature 270 °C and N_2 as a sheath gas. HPLC was performed using apparatus Waters 3000 HPLC with integrator HP 3598, column RP C18 Waters and detector RI. The microanalyses were done with Vario EL III Elemental analyzer in the Faculty of Chemistry and Pharmacy. Thin layer chromatography (TLC) was performed on Merck 1.05554 silica gel 60 F_{254} aluminum plates. Chromatographic filtration and column chromatography were carried out using Fluka 100 silica gel (0.060–0.200 mm), Riedel-de Haën Kieselgel S (0.063–0.200 mm) or Macherey-Nagel Kieselgel 60 (0.063-0.200 mm).

Preparation of (±)-trans-2-(1-benzyl-6-oxo-2-phenyl-piperidine-3-yl-methyl)-2H-isoindol-1,3-dione (7)

To a stirred solution of alcohol **6** [14] (0.886 g, 3.00 mmol), triphenylphosphine (0.984 g, 3.75 mmol) and phthalimide (0.463 g, 3.15 mmol) in 11.4 mL dry THF under argon, a 40% solution of diethylazodicarboxylate (DEAD) in toluene (1.65 mL, 3.60 mmol) was added dropwise at room temperature. The reaction mixture was irradiated in an ultrasonic bath for 90 min. The completion of the reaction was determined by TLC (hexane/ethyl acetate = 1:1). The solvent was removed *in vacuo* and ethyl acetate was added to the oily residue. The crystals of diethyl 1,2-hydrazinodicarboxylate were filtered off. From the filtrate after column chromatography (hexane/ethyl acetate = 1:1) and recrystallization from ethyl acetate white solid was obtained (75%). Mp 152-154 ºC. IR (Nujol): 1700 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.39-1.56 (1H, m, *H*-4); 1.72-1.90 (1H, m, *H*-4); 2.36-2.50 (1H, m, *H*-3); 2.58 (1H, dt, *J* = 6.3, 18.2 Hz, *H*-5); 2.90 (1H, ddd, *J* = 6.3, 8.2, 18.2 Hz, *H*-5); 3.33 (1H, d, *J* = 14.7 Hz, NC*H*$_2$Ph); 3.45 (1H, dd, *J* = 4.9, 13.9 Hz, C*H*$_2$N); 3.74 (1H, dd, *J* = 9.7, 13.9 Hz, C*H*$_2$N); 4.27 (1H, d, *J* = 5.2 Hz, *H*-2); 5.60 (1H, d, *J* = 14.7 Hz, NC*H*$_2$Ph); 7.09-7.39 (10H, m, Ph*H*); 7.65-7.82 (4H, m, Ar*H*). EI-MS: m/z 424 ($M^{+\bullet}$, 14), 333 (31), 186 (42), 172 (26), 160 (65), 159 (78), 117 (22), 106 (82), 104 (24), 91 (100). Anal. Calcd for $C_{27}H_{24}N_2O_3$ (424.50): C 76.40%, H 5.70%; found C 76.11%, H 5.99%.

Preparation of (±)-trans-5-aminomethyl-1-benzyl-6-phenyl-piperidine-2-one (2)

A mixture of phthalimide **7** (1.050 g, 2.5 mmol) and 40% aqueous solution of methylamine (28.9 mL, 10.400 g, 33.5 mmol) was refluxed until clear solution was formed (2 h). The completion of the reaction was determined by TLC (hexane/ethyl acetate = 1:1). After cooling down to room temperature, the solution was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the amine **2** as yellowish oil (85%). IR ($CHCl_3$): 3350 (NH_2); 3250 (NH_2); 1620 (CON) cm^{-1}.^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.33 (2H, br. s, NH_2) 1.46-1.69 (1H, m, H-4); 1.73-1.99 (2H, m, H-4, H-5); 2.50-2.66 (4H, m, H-3, C*H*$_2$N); 3.29 (1H, d, *J* = 14.6 Hz, NC*H*$_2$Ph); 4.31 (1H, d, *J* = 4.5 Hz, H-6); 5.63 (1H, d, *J* = 14.6 Hz, NC*H*$_2$Ph); 7.12-7.42 (10H, m, Ph*H*). EI-MS: m/z 294 ($M^{+\bullet}$, 7); 277 (42); 276 (26); 264 (13); 249 (17); 186 (13); 174 (66); 117 (15); 106 (60); 91 (100). Anal. Calcd for $C_{19}H_{22}N_2O$ (294.40): C

77.52%, H 7.53%, N 9.52%; found: C 77.60%, H 7.54%, N 9.49%.

Amino acid derivatives of (±)-trans-5-aminomethyl-1-benzyl-6-phenyl-piperidine-2-one ***3a,b, 8a,b, 13a,b, 10, 11, 15a,b*** *(General procedure)*

To a magnetically stirred solution of amine **2** (0.147 g, 0.5 mmol) and corresponding *N*-protected L-amino acid (0.5 mmol) in dichloromethane (2 mL) cooled to -20 °C, a solution of diisopropylcarbodiimide (DIC, 0.65 mmol) in dichloromethane (2 mL) was added dropwise. The mixture was stirred for 2 h at -10 °C and then 12 h at room temperature. The precipitated urea derivative was filtered and discarded. The filtrate was evaporated under reduced pressure and the resulting oil was dissolved in dicloromethane (10 mL). The solution was successively washed with 10% HCl, water, 10% Na_2CO_3 and brine. Organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by means of column chromatography. The following compounds were prepared in this way:

*tert-Butyl (S)-(1-(((2R,3S and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-ylcarbamate (**3a,b**):* From amine **2** and *N*-Boc-L-tryptophan. Column chromatography (hexane/ethyl acetate/25% aq. NH_3 = 1:2:0.015) and a subsequent recrystallization from ethyl acetate yielded a white solid of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**3a,b** (73%). Mp 138-140 ºC. IR (Nujol): 3200-3400 (NH); 1730 ($COOC(CH_3)_3$); 1680 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.41 (9H, s, $COOC(CH_3)_3$); 1.44 (9H, s, $COOC(CH_3)_3$*); 1.50-1.60 (2H, m, H-4, H-4*); 1.75-2.00 (4H, m, H-3, H-3*, H-4, H-4*); 2.40-2.50 (4H, m, H-5, H-5*); 2.67-2.81 (2H, m, CH_2NH, CH_2*NH); 2.98-3.30 (8H, m, NCH_2Ph, NCH_2*Ph, CH_2Ind, CH*$_2$Ind, CH_2NH, CH_2*NH); 3.97 (1H, d, *J* = 5.1 Hz, H-2); 4.02 (1H, d, *J* = 4.9 Hz, H-2*); 4.18 (1H, dt, *J* = 5.8, 7.6 Hz, COC*H*); 4.29 (1H, dt, *J* = 5.7, 7.7 Hz, COC*H**); 4.97 (2H, br.s, N*H*CO, N*H*CO*); 5.27 (1H, t, *J* = 6.0 Hz, N*H*CO); 5.38 (1H, t, *J* = 6.0 Hz, N*H*CO*); 5.55 (1H, d, *J* = 14.6 Hz, NCH_2Ph);), 5.56 (1H, d, *J* = 14.6 Hz, NCH_2*Ph); 6.87-7.41 (28H, m, Ph*H*, Ph*H**, *H*-ind, *H*-ind*); 7.60 (2H, d, *J* = 7.7 Hz, *H*-ind, *H*-ind*); 8.18 (2H, br.s, N*H*-ind, N*H*-ind*). EI-MS: m/z: no M^+; 355 (9); 341 (16); 281 (43); 253 (27); 207 (100); 191 (13); 147 (19); 135 (25); 91 (13); 73 (53). ESI-MS: m/z 603 (5, $(M+Na)^+$); 582 (22); 581 (64, $(M + H)^+$); 525 (15); 482 (29); 481 (100); 465 (6). Anal Calcd for $C_{35}H_{40}N_4O_4$ (580.73): C 72.39%; H 6.94%; N 9.65%; found: C 72.23%; H 7.04%; N 9.29%.

*tert-Butyl (S)-(1-((((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)amino)-1-oxopropan-2-yl)carbamate (**8a,b**):* From amine **2** and *N*-Boc-L-alanine. Column chromatography (hexane/ethyl acetate/25% aq. NH_3 = 1:1:0.015) yielded a pale yellow oil (72%) of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**8a,b**. IR ($CHCl_3$): 3420 (NH); 3410 (NH); 1710 ($COOC(CH_3)_3$); 1680 (CON);1630 (CON) cm^{-1}.^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.19 (6H, d, *J* = 7.1 Hz, CH_3, CH_3*); 1.42 (9H, s, $COOC(CH_3)_3$); 1.45 (9H, s, $COOC(CH_3)_3$*); 1.47-1.60 (2H, m, H-4, H-4*); 1.72-1.91 (2H, m, H-4, H-4*); 2.06-2.20 (2H, m, H-3, H-3*); 2.52-2.66 (4H, m, H-5, H-5*); 2.75-2.95 (2H, m, CH_2NH, CH_2NH*); 3.26 (1H, d, *J* = 14.4 Hz, NCH_2Ph); 3.27 (1H, d, *J* = 14.4 Hz, NCH_2Ph*); 3.31-3.45 (2H, m, CH_2NH, CH_2NH*); 3.79-3.96 (2H, m, COC*H*, COC*H**); 4.16 (1H, d, *J* = 4.2 Hz, H-2); 4.20 (1H, d, *J* = 4.6 Hz, H-2*); 4.76 (1H, d, *J* = 7.0 Hz, N*H*CO); 4.86 (1H, d, *J* = 7.0 Hz, N*H*CO*); 5.63 (2H, br. s, CON*H*, CON*H**); 5.68 (2H, d, *J* = 14.4 Hz, NCH_2Ph, NCH_2Ph*); 7.08-7.23 (8H, m, Ph*H*, Ph*H**); 7.28-7.43 (12H, m, Ph*H*, Ph*H**);. Anal. Calcd for $C_{27}H_{35}N_3O_4$ (465.59): C 69.65%; H 7.58%; N 9.02%; found: C 70.00%, H 7.83%, N 8.54%.

*(S)-N-(((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)-3-phenyl-2-(2,2,2-trifluoro-acetamido)-propanamide (**9a,b**):* From amine **2** and *N*-trifluoroacetyl-L-phenylalanine. Column chromatography (hexane/ethyl acetate = 1:3) yielded a pale yellow oil (69%) of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**9a,b**. IR ($CHCl_3$): 3410 (NH); 3400 (NH); 1720 ($COOC(CH_3)_3$); 1680 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (500 MHz, $CDCl_3$): 1.27-1.36 (2H, m, *H*-4, *H*-4*); 1.62-1.73 (2H, m, *H*-4, *H*-4*); 1.85-1.93 (1H, m, H-3); 2.00-2.08 (1H, m, H-3*); 2.45-2.58 (4H, m, *H*-5, *H*-5*); 2.65-2.72 (1H, m, CH_2NH); 2.77-2.84 (1H, m, CH_2NH*); 2.86-2.95 (2H, m, CH_2Ph, CH_2Ph*); 2.96-3.04 (2H, m, CH_2Ph, CH_2Ph*); 3.18-3.25 (3H, m, CH_2NH, NC*H*Ph, NC*H*Ph*); 3.29 (1H, dt, *J* = 7.0, 13.9 Hz, CH_2NH*); 3.99 (1H, d, *J* = 4.8 Hz, *H*-2); 4.11 (1H, d, *J* = 4.2 Hz, *H*-2*); 4.15 (1H, dt, *J* = 5.8, 8.2 Hz, COC*H*); 4.30 (1H, dt, *J* = 5.8, 8.2 Hz, COC*H**); 4.63 (1H, t, *J* = 6.0 Hz, CH_2N*H*); 4.88 (t, 1H, *J* = 6.0 Hz, CH_2N*H**); 5.65 (1H, d, *J* = 14.3 Hz, NC*H*Ph), 5.68 (1H, d, *J* = 14.3 Hz, NC*H*Ph*); 7.00-7.20 (15H, m, N*H*COCF_3, N*H*COCF_3*, Ph*H*, Ph*H**); 7.27-7.40 (17H, m, Ph*H*, Ph*H**). EI-MS: m/z 537 ($M^{+\bullet}$, 6); 264 (12); 187 (11); 186 (83); 172

(40); 159 (15); 117 (18); 106 (75); 103 (14); 91 (100). Anal. Calcd for $C_{30}H_{30}F_3N_3O_3$ (537.58): C 67.03%, H 5.62%, N 7.82%; found: C 67.02%, H 5.82%, N 8.08%.

*Benzyl 2-((((±)-trans-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)amino)-2-oxoethylcarbamate **(10)*** From amine **2** and Z-glycine. Column chromatography purification (ethyl acetate) yielded **10** as a colourless oil (66%). IR ($CHCl_3$): 3420(NH); 3410 (NH); 1720 ($COOCH_2Ph$); 1680 (CON); 1630 (CON) cm^{-1}. ^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.40-1.55 (1H, m, H-4); 1.70-1.88 (1H, m, H-4); 2.00-2.20 (1H, m, H-3); 2.46-2.68 (2H, m, H-5); 2.75-2.95 (1H, m, C*H*$_2$NH); 3.24 (1H, d, *J* = 14.5 Hz, NC*H*$_2$Ph); 3.29-3.44 (1H, m, C*H*$_2$NH); 3.61 (2H, d, *J* = 5.6 Hz, C*H*$_2$CO); 4.16 (1H, d, *J* = 4.0 Hz, H-2); 5.11 (2H, s, OC*H*$_2$Ph); 5.32 (1H, t, *J* = 5.6 Hz, N*H*CO); 5.56 (1H, br.s, CH_2N*H*); 5.66 (1H, d, *J* = 14.5 Hz, NC*H*$_2$Ph); 7.07-7.45 (15H, m, Ph*H*). EI-MS: m/z No $M^{+\bullet}$; 377 (12); 286 (23); 186 (42); 172 (51); 159 (49); 129 (15); 117 (19); 115 (17); 106 (87); 91 (100). Anal. Calcd for $C_{29}H_{31}N_3O_4$ (485.58): C 71.73%, H 6.43%, N 8.65%; found: C 72.03%, H 6.80, N 8.45%.

*tert-Butyl (2-((((±)-trans-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)amino)-2-oxoethyl) carbamate **(11)**:* From amine **2** and *N*-Boc-glycine. Column chromatography (hexane/ethyl acetate/25% aq. NH_3 = 1:2:0.015) yielded **11** as a pale yellow oil (83%). IR (Nujol): 3200-3400 (NH); 1710 ($COOC(CH_3)_3$); 1660 (CON) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.49 (9H, s, $COOC(CH_3)_3$); 1.46-1.60 (1H, m, H-4); 1.77-1.91 (1H, m, H-4); 2.07-2.20 (1H, m, H-3); 2.53-2.66 (2H, m, H-5); 2.80-2.95 (1H, m, C*H*$_2$NH); 3.26 (1H, d, *J* = 14.4 Hz, NC*H*$_2$Ph); 3.38 (1H, td, *J* = 6.9 Hz, *J* = 13.5 Hz, C*H*$_2$NH); 3.56 (2H, d, *J* = 5.8 Hz, C*H*$_2$CO), 4.17 (1H, d, *J* = 4.3Hz, H-2); 4.96 (1H, br.s, CON*H*); 5.55 (1H, t, *J* = 5.8 Hz, N*H*CO); 5.68 (1H, d, *J* = 14.4 Hz, NC*H*$_2$Ph); 7.10-7.23 (4H, m, Ph*H*); 7.26-7.43 (6H, m, Ph*H*). EI-MS: m/z No $M^{+\bullet}$; 377 (11); 286 (19); 186 (42); 172 (47); 159 (41); 129 (14); 117 (17); 115 (16); 106 (80); 91 (100). Anal. Calcd for $C_{26}H_{33}N_3O_4$ (451.57): C 69.16%, H 7.37%, N 9.31%; found: C 69.12%, H 7.32%, N 9.14%.

*tert-Butyl (2-(((S)-1-((((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl) amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl) amino)-2-oxoethyl)carbamate **(15a,b)**:* From **4a,b** and *N*-Boc-glycine. Column chromatography purification (hexane/ethyl acetate/25% NH_3 = 1:2:0.015) afforded **15a,b** as uncrystallizable oil of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**15a,b** (73%). **IR** (Nujol): 3150-3500(NH); 1660 ($COOC(CH_3)_3$); 1640 (CON); 1630 (CON); 1620 (CON) cm^{-1}. **^{1}H-NMR** δ (250 MHz, $CDCl_3$): 1.30 (18H, s, $C(CH_3)_3$, $C(CH_3)_3$*); 1.40-1.62 (2H, m, H-4, H-4*); 1.70-1.96 (4H, m, H-3, H-3*, H-4, H-4*); 2.30-2.63 (4H, m, H-5, H-5*); 2.72-2.97 (2H, m, C*H*$_2$NH, C*H*$_2$NH*); 3.00-3.18 (4H, m, CH_2-Ind, CH_2-Ind*); 3.20-3,37 (4H, m, NC*H*$_2$Ph, NC*H*$_2$Ph*, C*H*$_2$NH, C*H*$_2$NH*); 3.60-3.72 (4H, m, CH_2CO, CH_2CO*); 3.97 (1H, d, *J* = 5.4 Hz, H-2); 4.05 (1H, d, *J* = 4.6 Hz, H-2*); 4.49-4.67 (2H, m, COC*H*, COC*H**); 5.14 (2H, dd, *J* = 5.7 Hz, CON*H*, CON*H**); 5.50 (1H, d, *J* = 14,7 Hz, NC*H*$_2$Ph); 5.53 (1H, d, *J* = 14.7 Hz, NC*H*$_2$Ph*); 5.95-6.17 (2H, m, N*H*CO, N*H*CO*); 6.71 (2H, t, *J* = 8.6 Hz, N*H*CO, N*H*CO*); 6.90 (2H, s, *H*-Ind, *H*-Ind*); 6.98-7.38 (26H, m, Ph*H*, Ph*H**, *H*-Ind, *H*-Ind*); 7.58 (2H, d, *J* = 7.7 Hz, *H*-Ind, *H*-Ind*); 8.38 (1H, s, N*H*-Ind); 8.42 (1H, s, N*H*-Ind*). ESI-MS: m/z 660 (40, $(M+Na)^+$); 638 (7, $(M+H)^+$); 425 (100); 403 (43). Anal Calcd for $C_{37}H_{43}N_5O_5$ (637.79): C 69.68%, H 6.80%, N 10.98%; found: C 69.29%; H 6.81%, N 11.05.

*N-Boc-deprotection of the amides to **4a,b**; **5a,b**, **12a,b** and **14** (General procedure)*

A solution of *N*-Boc-protected amide **3a,b**; **8a,b**; **11; 15a,b** (1 mmol) and trifluoroacetic acid (1.07 mL, 14 mmol) was irradiated in an ultrasonic bath for 15 min. The completion of the reaction was determined by TLC. The reaction mixture was diluted with dichloromethane and the resulting solution was washed with 10% NaOH (2 x 5 mL). The organic layer was dried (Na_2SO_4) and the crude material was purified by column chromatography. The following compounds were prepared in this way:

*(S)-2-amino-N-(((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)-3-(1H-indol-3-yl)propanamide **(4a,b)**:* From amide **3a,b.** Column chromatography purification (hexane/isopropanol = 3.5:1) gave a pale yellow oil (78%) of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**4a,b**. IR (Nujol): 3150-3430 (NH_2, NH); 1630 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.35-1.55 (2H, m, H-4, H-4*); 1.66-1.84 (2H, m, H-4, H-4*); 1.94-2.24 (6H, m, NH_2, NH_2*, H-3, H-3*); 2.44-2.68 (4H, m, H-5, H-5*); 2.73-2.90 (2H, m, CH_2-Ind, CH_2-Ind*); 2.91-3.03 (2H, m, C*H*$_2$NH, C*H*$_2$NH*); 3.18-3.40 (6H, m, NC*H*$_2$Ph, NC*H*$_2$Ph*, CH_2-Ind, CH_2-Ind*, C*H*$_2$NH, C*H*$_2$NH*); 3.54-3.64 (2H, m, COC*H*, COC*H**); 4.10 (1H, d, *J* = 4.5 Hz, H-2); 4.11 (1H, d, *J* = 4.7 Hz, H-2*); 5.60 (1H, d, *J* =

14.7 Hz, NC*H*$_2$Ph); 5.61 (1H, d, *J* = 14.7 Hz, NC*H*$_2$Ph*); 6.95-7.42 (30H, m, Ph*H*, Ph*H**, *H*-ind, *H*-ind*, N*H*CO, N*H*CO*); 7.62 (1H, d, *J* = 7.8 Hz, *H*-ind); 7.63 (1H, d, *J* = 7.8 Hz, *H*-ind*); 8.24 (1H, br.s, N*H*-ind), 8.28 (1H, br.s, N*H*-ind*). ESI-MS: m/z 503 (5, $(M+Na)^+$); 482 (27); 481 (100, $(M+H)^+$). Anal. Calcd for $C_{30}H_{32}N_4O_2$ (480.61): C 74.97%; H 6.71%; N 11.66%; found: C 74.95%; H 6.90%; N 11.48%.

*(S)-2-(2-aminoacetylamino)-N-[((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl) methyl]-3-(1H-indol-3-yl)propanamide (**5a,b**):* From amide **15a,b.** Column chromatography purification (hexane/isopropanol/ 25% aq. NH_3 = 1:1:0,02) gave a pale yellow oil (64%) of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**5a,b**. IR (Nujol): 3100-3450(NH); 1640 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.20-1.48 (2H, m, H-4, H-4*); 1.44-1.76 (10H, m, H-4, H-4*, NH_2, NH_2*, C*H*$_2$Ind, C*H*$_2$Ind*); 1.77-1.95 (2H, br. s, H-3, H-3*); 2.35-2.58 (4H, m, H-5, H-5*); 2.74-2.93 (2H, m, C*H*$_2$NH, C*H*$_2$NH*); 3.00-3.35 (8H, m, NC*H*$_2$Ph, NC*H*$_2$Ph*, C*H*$_2$NH, C*H*$_2$NH*, CH_2CO, CH_2CO*); 3.98 (1H, d, *J* = 5,2 Hz, H-2); 4,03 (1H, d, *J* = 4,9 Hz, H-2*); 4.38-4.61 (2H, m, C*H*CO, C*H*CO*); 5.44 (1H, br. s, CON*H*); 5.54 (1H, d, *J* = 14,7 Hz, NC*H*$_2$Ph); 5.55 (1H, d, *J* = 14,7 Hz, NC*H*$_2$Ph*); 5.62 (1H, br. s, CON*H**); 6.88-7.40 (28H, m, Ph*H*, Ph*H**, *H*-Ind, *H*-Ind*); 7.59-7.77 (4H, CON*H*, CON*H**, *H*-Ind, *H*-Ind*); 8.03 (2H, br. s, N*H*-Ind, N*H*-Ind*). ESI-MS: m/z 560 (20, $(M+Na)^+$); 554 (21); 539 (42); 538 (100, $(M+H)^+$); 443 (32); 279 (51). Anal. Calcd for $C_{32}H_{35}N_5O_3$ (537.67): C 71.49%; H 6.56%; N 13.03%; found: C 71.42%; H 6.90%; N 12.79%.

*(S)-2-amino-N-(((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)propanamide (**12a,b**):* From amide **8a,b.** Column chromatography purification (hexane/isopropanol/ 25% aq. NH_3 = 1:1:0.015) gave a pale yellow oil (78%) of 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**12a,b** was obtained. IR ($CHCl_3$): 3410 (NH_2); 3360 (NH); 3340(NH_2); 1660 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (250 MHz, $CDCl_3$): 1.22 (3H, d, *J* = 6.9 Hz, CH_3); 1.24 (3H, d, *J* = 6.9 Hz, CH_3*); 1.46-1.63 (2H, m, H-4, H-4*); 1.75-1.92 (2H, m, H-4, H-4*); 2.00-2.20 (6H, m, H-3, H-3*, NH_2, NH_2*); 2.46-2.77 (4H, m, H-5, H-5*); 2.87-3.06 (2H, m, C*H*$_2$NH, C*H*$_2$NH*); 3.27 (2H, d, *J* = 14.6 Hz, NC*H*$_2$Ph, NC*H*$_2$Ph*); 3.32-3.48 (4H, m, C*H*$_2$NH, C*H*$_2$NH*, C*H*CO, C*H*CO*); 4.15 (1H, d, *J* = 4.8 Hz, H-2); 4.16 (1H, d, *J* = 4.7 Hz, H-2*); 5.63 (2H, d, *J* = 14.6 Hz, NC*H*$_2$Ph, NC*H*$_2$Ph*); 7.04-7.44 (22H, m, Ph*H*, Ph*H**, N*H*CO, N*H*CO*). EI-MS: m/z 365 ($M^{+\bullet}$, 8); 322 (15); 264 (16); 196 (22); 187 (15); 186 (100); 174 (12); 117 (17); 106 (41); 91 (96). Anal. Calcd for $C_{22}H_{27}N_3O_2$ (365.47): C 72.30%; H 7.45%; N 11.50%; found: C 71.51%; H 7.50%; N 10.76%.

*2-amino-N-(((±)-trans-1-benzyl-6-oxo-2-phenyl-piperidin-3-yl)methyl)acetamide (**14**):* From amide **11.** Column chromatography purification (hexane/ isopropanol/25% aq. NH_3 = 2:1:0.015) gave a pale yellow oil of **14** (91%). IR (neat): 3150-3550 (NH, NH_2); 1640 (CON); 1620 (CON) cm^{-1}. ^{1}H-ЯМР δ (250 MHz, $CDCl_3$): 1.45-1.65 (1H, m, H-4); 1.78-1.94 (1H, m, H-4); 1.96-2.20 (3H, m, H-3, NH_2); 2.50-2.77 (2H, m, H-5); 3.00 (1H, dt, *J* = 6.3 Hz, *J* = 13.9 Hz, C*H*$_2$NH); 3.19 (2H, s, C*H*$_2$CO); 3.30 (1H, d, *J* = 14.4 Hz, NC*H*$_2$Ph); 3.39 (1H, dt, *J* = 7.1 Hz, *J* = 13.9 Hz, C*H*$_2$NH); 4.17 (1H, d, *J* = 4.9 Hz, H-2); 5.64 (1H, d, *J* = 14.4 Hz, NC*H*$_2$Ph); 6.97 (1H, t, *J* = 6.3 Hz, N*H*CO); 7.07-7.44 (10H, m, Ph*H*). EI-MS: m/z 351 ($M^{+\bullet}$, 8); 264 (12); 187 (14); 186 (100); 174 (8); 172 (12); 117 (11); 115 (8); 106 (38); 91 (83). Anal. Calcd for $C_{21}H_{25}N_3O_2$ (351.45): C 71.77%; H 7.17%; N 11.96%; found: C 71.39%; H 7.16%; N 11.64%.

*Preparation of (S)-2-amino-N-(((2S,3R and 2R,3S)-1-benzyl-6-oxo-2-phenylpiperidin-3-yl)methyl)-3-phenylpropanamide (**13a,b**)*

A solution of amide **9a,b** (0.100 g, 0.2 mmol), potassium hydroxide (0.112 g, 1.8 mmol), water (1 mL) and methanol (2 mL) was stirred at room temperature for 24 h, then methanol was removed under reduced pressure. The aqueous residue was extracted with dichloromethane and the combined organic layers were dried (Na_2SO_4). Column chromatography (hexane/ethyl acetate/25% aq. NH_3 = 3:1:0.02) yielded a pale yellow oil (86%) as a 1:1 mixture of 2*S*,3*R*,α*S*- and 2*R*,3*S*,α*S*-**13a,b**. IR (CHCl3): 3150–3450 (NH, NH2); 1640 (CON); 1620 (CON) cm^{-1}. ^{1}H-NMR δ (500 MHz, $CDCl_3$): 1.40-1.51 (2H, m, *H*-4, *H*-4*); 1.67-1.81 (2H, m, *H*-4, *H*-4*); 1.99-2.11 (2H, m, H-3, H-3*); 2.46-2.58 (2H, m, *H*-5, *H*-5*); 2.59-2.68 (2H, m, *H*-5, *H*-5*); 2.68-2.77 (2H, m, C*H*$_2$Ph, C*H*$_2$Ph*); 2.90-3.02 (2H, m, C*H*$_2$NH, C*H*$_2$NH*); 3.08-3.18 (2H, m, C*H*$_2$Ph, C*H*$_2$Ph*); 3.22-3.37 (4H, m, C*H*$_2$NH, C*H*$_2$NH*, NC*H*Ph, NC*H*Ph*), 3.60-3.77 (2H, m, COC*H*, COC*H**); 4.09 (1H, d, *J* = 5.1 Hz, H-2); 4.11 (1H, d, *J* = 4.8 Hz, H-2*); 5.55 (1H, d, NC*H*Ph, *J* = 14.7 Hz); 5.56 (1H, d, NC*H*Ph*, *J* = 14.8 Hz); 7.06-7.40 (32H, m, Ph*H*, Ph*H**, N*H*CO, N*H*CO*). EI-MS: m/z 441 ($M^{+\bullet}$, 6); 350 (18); 322 (13); 264 (12); 196 (17); 187 (11); 186 (66); 120 (89); 106 (30); 91

(100). Anal. Calcd for $C_{28}H_{31}N_3O_2$ (441,57): C 76.16%, H 7.08%, N 9.52%; found:C 75.61%, H 7.08%, N 9.38%

Angiotensin-converting enzyme activity assay

Rabbit serum aliquot was incubated in buffered medium with the ACE substrate analogue Hippuryl-Histidyl-Leucine (HHL). Hippuric acid (HA) as a product of the reaction was extracted with ethyl acetate and then measured by HPLC in isocratic mode at 228 nm. The HPLC was carried out on a Polar-RP 80Å Synergi column (150x4,6 mm, 4 μm, Phenomenex) at flow rate of 1.4 mL/min and mobile phase buffer (0.02 M ammonium acetate adjusted to pH 4.3 with acetic acid)/methanol (95/5). The amount of hippuric acid formed reflects the ACE activity.

Solutions of the piperidinone derivatives **10**, **12a**,**b**, **13a**,**b** and **14** in 0.1 M acetic acid were tested for the inhibitory potency in comparison to the inhibitors of ACE Lisinopril and Quinaprilat. The IC_{50} values were determined by non-linear regression analysis of enzyme activity/inhibitor concentrations curves using software package GraphPad Prism 5.0.

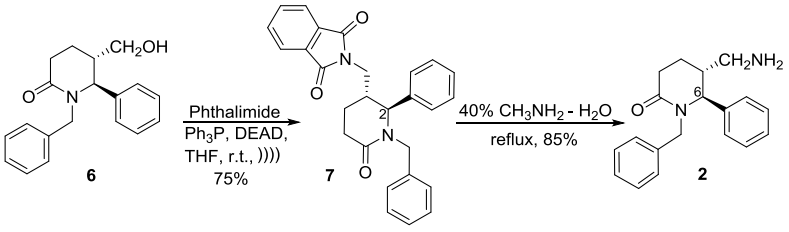
RESULTS AND DISCUSSION

(±)-*trans*-5-Aminomethyl-1-benzyl-6-phenylpiperidine-2-one (**2**) was prepared from the previously synthesized by us alcohol **6** [14] obtained in two steps from (±)-*trans*-1-benzyl-6-oxo-2-phenylpiperidine-3-carboxylic acid **1** [11, 14]. The replacement of the hydroxyl group in **6** for amino group in **2** includes the intermediate formation of phthalimido derivative **7** by means of Mitsunobu methodology [18], followed by cleavage of the phthalimido group (Scheme 1).

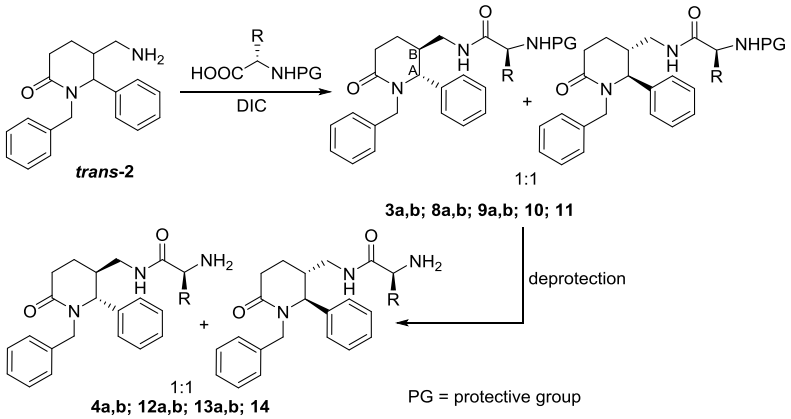
The treatment of the alcohol **6** by means of phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD; Mitsunobu step) was carried out overnight at room temperature in analogy to a literature procedure [18]. Alternatively, it was shown that the sonication of the reaction mixture accelerated the reaction, which was completed within 1.5 hours to give the phthalimido derivative **7**. The latter compound was separated from the by-products by means of column chromatography and recrystallization in 75% yield. Several reagents were tested for the cleavage of the phthalimido group in **7**. The yields of amine **2** obtained after reflux of the phthalimide **7** in the presence either of ethylenediamine [18] or hydrazine hydrate [20] varied within a broad range in different runs. When **7** was refluxed in an aqueous ethanol solution of CH_3NH_2 [21] the obtained amine **2** tended to retain ethanol, which could not be removed. Best reproducible yield of **2** (85%) was obtained by reflux of phthalimide**7** in 40% aqueous solution of CH_3NH_2, moreover the product of this reaction showed to be enough pure for the further transformations. This was important since amine **2** is highly polar oil and could not be purified by means of chromatography.

Trans relative configuration of phthalimide **7** and amine **2** was established by comparison of their ^{1}H NMR spectra with the spectra of the starting alcohol **6** [14]. Taking into account the shift of the doublet signal of the proton next to cyclic nitrogen and its ^3J, the spectra of compounds **2** and **7** showed similarity to the spectrum of **6**. The doublets of H-2, resp. H-6, in the spectra of **2** and **7** appear in the range of δ 4.27–4.31 ppm with ^3J 4.5–5.2 Hz, similarly to the values previously reported [14]. Analogous data of ^3J were recently published for *trans*-6-phenyl-5-hydroxypiperidine–2-one, for which the *trans* configuration was confirmed by means of X-ray diffraction analysis [22]. From the other hand, the transformations of the alcohol **6** to the phthalimide **7** and amine **2** do not affect the chiral carbon atoms. On this ground we accepted same *trans* configuration for the newly prepared compounds **2** and **7**. On Scheme 1 we present for shortness only one enantiomer of the racemic compounds **2**, **6** and **7**.

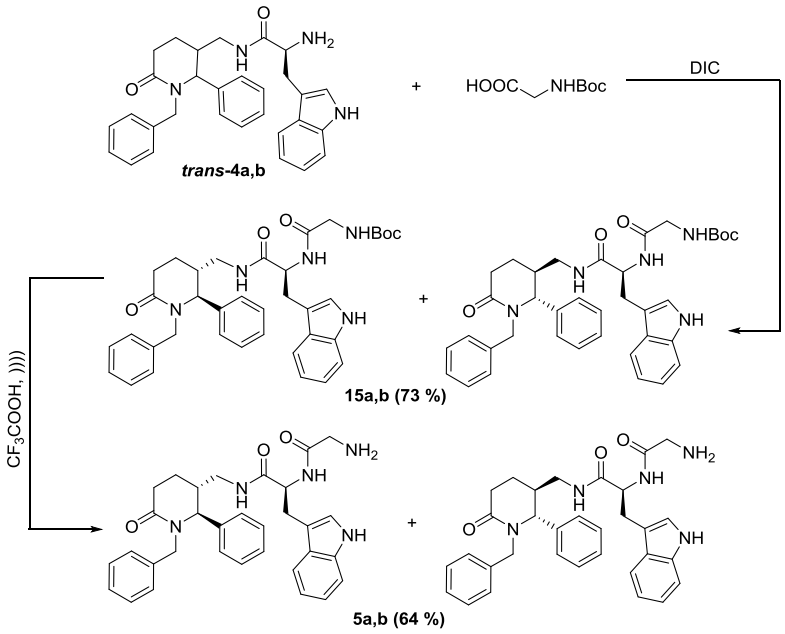
The aminomethyl derivative **2** was converted into the pseudodipeptides **3a**,**b**, **8a**,**b**, **9a**,**b**, **10** and **11** by reaction with the following *N*-protected α-amino acids: *N*-Boc-L-tryptophan, *N*-Boc-L-alanine, *N*-trifluoroacetyl-L-phenylalanine, *N*-Boc-



Scheme 1. Preparation of (±)-*trans*-5-aminomethyl-1-benzyl-6-phenylpiperidine-2-one (**2**) (one enantiomer is shown).



Scheme 2. Synthesis of pseudodipeptides.



Scheme 3. Preparation of pseudotripeptides **5a,b** and **15a,b**.

glycine and Z-glycine, resp., in the presence of diisopropylcarbodiimide (DIC) in 69–83% yields after column chromatography purification. (Table 1). *L*-Tryptophan derived *N*-Boc dipeptides **3a**,**b** were obtained as crystalline product. All the other pseudopeptide derivatives described throughout the paper were obtained as oily products. Gas chromatography analysis of the reaction products **3a**,**b**, **8a**,**b** and **9a**,**b** showed two peaks in 1:1 ratio. Similarly, ^{1}H NMR spectra of the compounds showed that they are 1:1 mixtures of diastereomers, which could not be separated by means of column chromatography. The diastereomers are designated as "a" and "b".

The deprotection gave pseudodipeptides with free *N*-terminal group. *N*-Boc-protected pseudodipeptides **3a**,**b**; **8a**,**b** and **11** were deprotected by CF_3COOH under sonication [14] to give pseudopeptides **4a**,**b**; **12a**,**b** and **14**, resp. (Scheme 2).

Table 1. Peptide derivatives **3**, **4**, **8**–**14**.

Compound (Yield, %)	R	PG
3a,b (73)	CH_2(Indol-3-yl)	Boc
4a,b (78)	CH_2(Indol-3-yl)	H
8a,b (72)	CH_3	Boc
9a,b (69)	$CH_2C_6H_5$	$COCF_3$
10 (66)	H	Z
11 (83)	H	Boc
12a,b (78)	CH_3	H
13a,b (86)	$CH_2C_6H_5$	H
14 (91)	H	H

N-Trifluoroacetyl group in **9a**,**b** was cleaved by hydrolysis with potassium hydroxide in methanol-water at room temperature [21] to give pseudopeptide **13a**,**b**. Yields are given in Table 1.

The tryptophan derivative *trans*-**4a**,**b** was used for elongation of the peptide chain – it was *N*-acylated by means of *N*-Boc-glycine to give pseudotripeptide *trans*-**15a**,**b**. Further deprotection of the Boc group as above gave pseudotripeptide *trans*-**5a**,**b**. (Scheme 3).

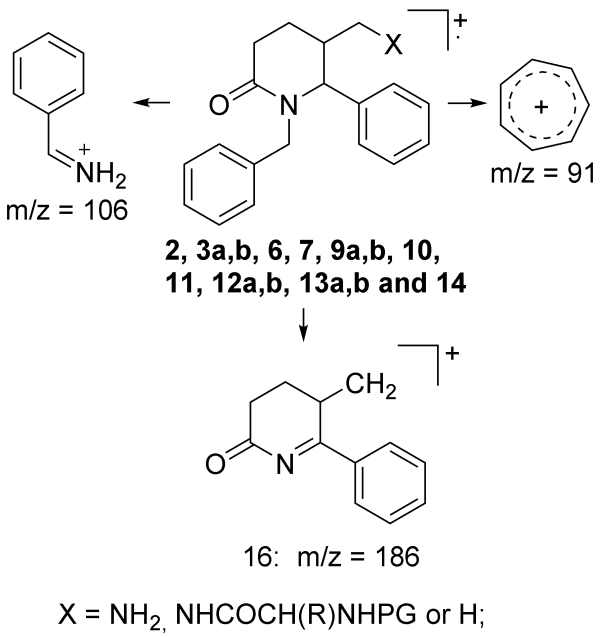
Compounds **3**, **4**, **5**, **8**, **9**, **12**, **13** and **15** incorporating amino acid moieties were 1:1 mixtures of α-*S*, (±)-*trans*-diastereomers according to their ^{1}H NMR spectra. In spite of our efforts we could not separate the diastereomeric couples by means of column chromatography. This made difficult the description of ^{1}H NMR spectral data in the Experimental part, because the signals for the same protons in the different diastereomers are not shifted in one and the same direction. Similar problem was encountered in the course of synthesis of (±)-*trans*-5-*N*-acylamino-1-benzyl-6-phenylpiperidin-2-one derivatives published recently by us [15]. For this reason in the Experimental part the signals for the same protons with higher chemical shift are noted with "*" symbol, in analogy to our previous paper [15]. Peptide bond formation did not affect the chiral centers of the piperidinone cycle, as well as the one originating from the L-amino acid. ^{1}H NMR spectra of the compounds exhibit doublet signals for 2-H in the range of δ 3.97–4.20 ppm with $J_{A,B}$ 4.0–5.4 Hz. These data are in agreement with *trans* relative configuration of the substituents with respect to the piperidinone cycle, as it was already discussed above.

EI-mass spectra (EI-MS) of compounds **2**, **3a,b**, **6**, **7**, **9a**,**b**, **10**, **11**, **12a**,**b**, **13a**,**b,** and **14** were taken. All compounds except for Z and Boc protected derivatives **3a**,**b**, **10** and **11,** showed $M^{+\cdot}$ with low intensity. The molecular ions of **3a**,**b**, **10** and **11** were not observed. The most typical fragmentation in EI-MS of the compounds studied was the formation of three fragments: tropylium ion ($C_7H_7^+$ m/z = 91), $PhCHNH_2^+$ (m/z = 106) as well as m/z =186. The latter is probably a result of α-cleavage. [23] (Scheme 4) ESI mass spectra of compounds **3a**,**b**, **4a**,**b**, **5a**,**b** and **15a**,**b** allowed us to observe the molecular ions $(M+H)^+$ and $(M+Na)^+$.

Biological assay

The compounds tested for ACE inhibitory activity were **10**, **12a**,**b**, **13a**,**b** and **14**. The significantly modified method of Chiknas [24] was applied for ACE activity determination. Enzyme sources were rabbit serum and a purified enzyme [24]. As referent compounds two well-known inhibitors of ACE with wide therapeutic application were used – Lisinopril (which does not metabolize and is excreted unchanged in the urine) and Quinaprilat (active metabolite of Quinapril).

Compounds **13a**,**b** with IC_{50} around 590 ng/ml and **14** with IC_{50} around 530 ng/ml showed a weak ACE inhibitory potency when compared with the inhibitors lisinopril or quinaprilat (with IC_{100} around 20 ng/ml).



Scheme 4. Most typical mass spectral fragmentations in EI-MS

CONCLUSION

A series of new piperidinones with a peptide bond in the side chain to the heterocycle was prepared *via* Mitsunobu methodology and subsequent acylation of the amine **2** by means of selected *N*-protected α-amino acids. Boc deprotection of tryptophan derivatives **3a**,**b** was carried out and a second peptide bond was introduced via protected glycine coupling. Mass spectra of most of the derivatives were taken and fragmentation patterns were suggested for the most abundant ions. The ACE inhibitory activity of four peptide derivatives has been assayed. Compounds **13a**,**b** and **14** have shown a weak ACE inhibitory activity.

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СИНТЕЗ НА БИОАКТИВНИ АМИНОКИСЕЛИННИ ПРОИЗВОДНИ НА *ТРАНС*-5-АМИНОМЕТИЛ-1-БЕНЗИЛ-6-ФЕНИЛПИПЕРИДИН-2-ОН

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(Резюме)

Транс-5-аминометил-1-бензил-6-фенилпиперидин-2-он (**2**) е синтезиран с висок добив по метода на Мицунобу и ацилиран под действието на *N*-защитените α-аминокиселини глицин, L-триптофан, L-фенилаланин и L-аланин до нови пиперидинони с пептидна връзка в страничната верига към пиперидиноновия пръстен. Проведено е отстраняване на *N*-защитните групи, като страничната верига в производното на триптофана **4** е удължена с оглед получаване на съединения съдържащи две пептидни връзки. Снети са мас-спектри (EI и/или ESI) на повечето съединения и са предложени схеми на фрагментация. В предишно съобщение е описана антихистаминовата активност на производните на триптофана **3**–**5**. В настоящето съобщение е изследвана ACE инхибиторната активност на четири пептидни производни. Съединенията **13a**,**b** и **14** показват слаба ACE инхибиторна активност.