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SHORT *N*-ACYLDIPEPTIDES WITH ADAMANTYLBENZOYL FRAGMENT WITH POTENTIAL ANTIVIRAL ACTIVITY

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Several new short N-acyldipeptides containing the N-terminal 4-(1-adamantyl)benzoyl moiety have been synthesized using the classical peptide synthesis method in a solution based on N,N-carbonyldiimidazole. ^{1}H NMR spectroscopy monitored the stereochemical purity of the desired compounds. It has been found that in the presence of an asymmetric carbon atom, a mixture of two diastereomers of N-acyldipeptides is formed in a non-contiguous amino acid residue. It has been suggested that this is due to the formation of an optically inactive oxazole intermediate at an intermediate stage. The synthesized compounds are of interest as potential therapeutic agents with antiviral activity in combination with low toxicity.

Introduction

The medical chemistry of adamantane derivatives has developed widely in the specialized literature in recent decades [1]. Many adamantane derivatives, first introduced in the 1960s as amantadin and rimantadin, are historically known for their strong antiviral activity. The properties of these drugs are still under investigation, in particular, the affinity of rimantadine enantiomers to influenza A/M2 proteins has recently been studied [2], the influence of rimantadine homologues structure on inhibition of influenza M2 WT and S31N was demonstrated [3], and a new molecular salt of sulphometaxazole and amantadine with both effective antimicrobial and antiviral activity was obtained [4]. At the same time, there is also a lot of information about the antiviral properties of new complex adamantane derivatives. For example, the peptide-piperazine derivative adamantan has been reported as a strong inhibitor of

Ebola virus (EBOV) when binding to the major NPC1 receptor [5]. For the pyridinone and pyridisinone derivatives of adamantan, their therapeutic promise as inhibitors of hepatitis C virus p7 ion channels with low cytotoxicity has been shown [6]. An inhibitory effect on the replication of poxviruses has been found for a number of benzamide compounds with an adamantane fragment [7]. Thus, we can state that there has been a steady interest in this kind of studies over the past 20 years, especially in terms of the demand for new, effective antiviral drugs due to the ever-increasing resistance to the already known ones.

A separate and particularly interesting area of adamantane chemistry is the design, synthesis and research of compounds containing a combination of cage and peptide fragments and exhibiting antiviral activity. The adamantane fragment, being a bulk hydrocarbon fragment, increases the lipophilicity of the peptide-like drug molecule, which facilitates its better permeability through cell membranes and improves its pharmacokinetic and pharmacodynamic properties. For example, data on the activity against hepatitis C virus of amino acid derivatives of adamantanecarboxylic acid (**I**, **II**, Fig. 1) [8] and tetrapeptide derivative of 1-(1-adamantyl)ethylamine (**III**, Fig. 1) have been published [9]. An adamantan-modified dipeptide containing alanine and glutamine residues exhibited activity against influenza A virus (**IV**, Figure 1) [10]. *Wanka et al.* presented an adamantyl-containing tetrapeptide (**V**, Figure 1) with activity against HIV in their work [1].

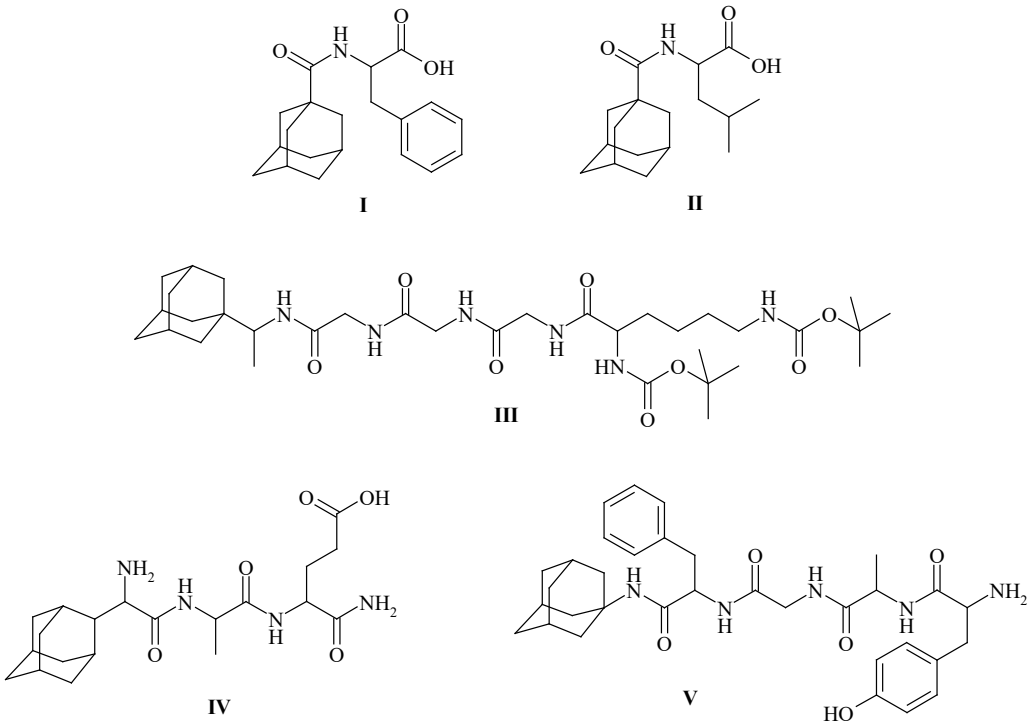


Fig. 1. Short peptides modified with an adamantane fragment with antiviral activity

Thus, reported studies mainly contains the terminal and non-terminal amino acid residues of glycine, alanine, leucine and phenylalanine, and the adamantan fragment is terminal. Therefore, the aim of this work was to synthesize short adamantane-modified dipeptides containing a combination of the above mentioned amino acids. We used 4-(1-adamantyl)benzoic acid, whose efficient synthesis was developed by us earlier [11], as an initial convenient and available reagent to introduce the cage fragment into the structure of short peptides.

Study

N-[4-(1-adamantyl)benzoyl]-amino acids synthesized according to a previously developed technique were used to obtain modified dipeptides containing the *N*-terminal 4-(1-adamantyl)benzoyl]-*α*amino acid [11]. These compounds exhibit anti-inflammatory and analgesic activity in combination with low toxicity *in vivo*. It is interesting in terms of their use as basic building blocks in the synthesis of potential therapeutic agents [12]. These acids **1.1-1.4** were individual *S*- stereoisomers as proved by ^{1}H NMR spectroscopy under shift reagent conditions [13]. We used derivatives of glycine, sarcosine, *L*-valine, and *L*-phenylalanine in our work.

Methyl esters of *N*-acyl dipeptides **3.1-3.9** were prepared by the classical peptide synthesis method in solution using *N,N*-carbonyl diamidazole (CDI) (Figure 2, Table 1). Amino acid derivatives of 4-(1-adamantyl)benzoic acid **1.1-1.4** had been reacting with 15% excess CDI for 1 hour in absolute tetrahydrofuran (THF) at solvent boiling point. As a result, the imidazolides **2.1-2.4** were formed *in situ*, which were further reacted with 20% excess methyl ester-*α*amino acid hydrochlorides and triethylamine at the same temperature for 3 hours (see Fig. 2, Table 1).

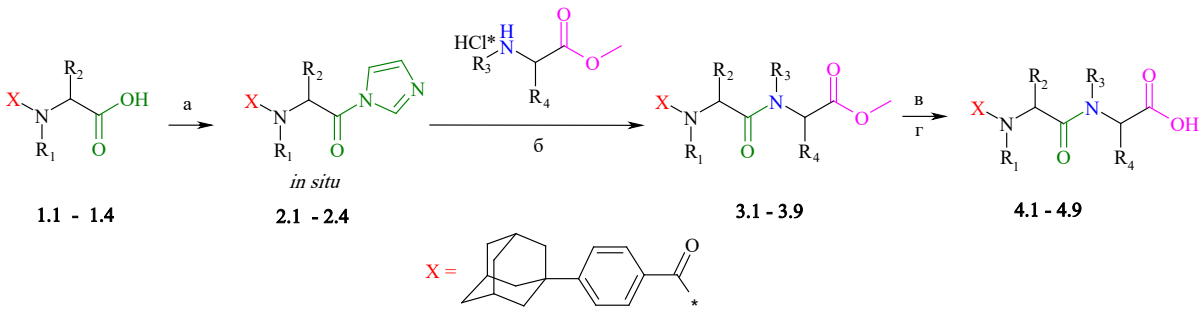


Fig. 2. Scheme for the synthesis of *N*-acyl dipeptides based on 4-(1-adamantyl)benzoic acid. Reagents and conditions: a - CDI, THF, 66 °C, 1 h; b - NEt_3, THF, 66 °C, 3 h; c - 1 n NaOH, acetone/ethanol/water = 1/1/2, *rt*, 24 h; d - 1 n. HCl, *rt*

A method for the isolation of modified dipeptide esters **3.1-3.9** was developed. It consists of concentrating the reaction mixture, further acidification with hydrochloric acid to pH 2-3, dissolution of the resulting viscous product in methylene chloride, drying of the solution and further crystallization of the final product in *n*-hexane.

Thin-layer chromatography (TLC) analysis revealed that *in situ* formed imidazolides **2.1-2.4** do not fully interact with the ester hydrochlorides of*α* -amino acids. The unreacted imidazolides are further processed into the starting *N*-[4-(1-adamantyl)benzoyl]*α*-amino acids at the product isolation step. Probably, this fact is the result of insufficient conversion due to the heterogeneity of the ester hydrochloride system into the free amine forms, which must further react with the imidazolides **2.1-2.4**.

In order to purify products **3.1-3.9** from starting compounds **1.1-1.4**, esters **3.1-3.9** were treated with a 5% $NaHCO_3$ solution when heated for two hours under stirring. As a result, methyl esters of modified dipeptides **3.1-3.9** were obtained in 40-60% yields.

The structure, purity and homogeneity of all synthesized products were confirmed by IR, ^{1}H NMR spectroscopy and TLC.

Table 1. Initial and synthesized compounds with *N*-terminal 4-(1-adamantyl)benzoyl fragment

Compound	R_1	R_2	R_3
1.1, **2.1**	H	H	-
1.2, **2.2**	H	Bn	-
1.3, **2.3**	H	*i*-Pr	-
1.4, **2.4**	Me	H	-
3.1, **4.1**	H	H	*i*-Bu
3.2, **4.2**	H	H	Bn
3.3, **4.3**	H	H	H
3.4, **4.4**	H	Bn	*i*-Bu
3.5, **4.5**	H	*i*-Pr	Bn
3.6, **4.6**	Me	H	*i*-Bu
3.7, **4.7**	Me	H	H
3.8, **4.8**	H	H	*i*-Pr
3.9, **4.9**	H	H	Me

The infrared spectra of esters **3.1-3.9** show strong absorption bands of the valence vibrations of the carbonyl groups (1740-1748 cm^{-1}) of the ester group. The valence vibrations of the N-H bond were at 3280-3296 cm^{-1}. Also, we observed strong absorption bands of 1634-1640 cm^{-1} and 1530-1535 cm^{-1}, corresponding to the valence vibrations of the carbonyl groups of the amide groups. The IR spectra did not have bands of carbonyl carboxyl groups, so it can be concluded that there are no original compounds **1.1-1.4** in products **3.1-3.9**

^{1}H NMR spectra of esters **3.1-3.9** do not contain proton signals of the carboxy groups of the initial amino acid derivatives (in the range 12.00-11.00 ppm.). NH-group proton signals of non-terminal amino acids and NH-group proton signals of terminal amino acids were observed at chemical shifts in the 8.20-8.40 and 8.00-8.20 ppm, respectively. The spectra also show three signals of the adamantane backbone protons in 1.80-2.10 ppm. The chemical shifts of 3.60-3.70 ppm show the presence of singlet signals with integral intensities corresponding to the three protons of the methyl group of the ester. It confirms the formation of modified dipeptides esters.

The specific feature of the ^{1}H NMR spectra of some of the dipeptide compounds obtained is the fermentation of protons groups signals related to asymmetric carbon atoms of non - terminal amino acid fragments. Probably, this fermentation related to the formation of *N*-acyl dipeptide esters **3.4** and **3.5** as a mixture of diastereomers and the protons of their corresponding groups are not equivalent. Thus, two duplets instead of one are observed for protons of NH-groups in the range of 8.20-8.40 ppm. Their total integral intensity equals is one (Fig. 3).

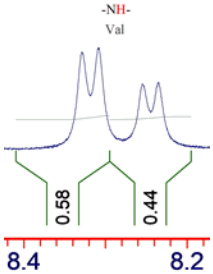
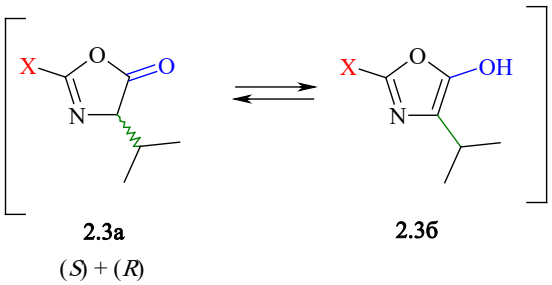


Fig. 3. Fragment of the ^{1}H NMR spectrum of **3.5** as a mixture of the methyl ester *N*-[4-(1-adamantyl)benzoyl]-*L*-valyl-*L*- phenyl alanine and the methyl ester *N*-[4-(1-adamantyl)benzoyl]-*D*-valyl-*L*-phenylalanine

The mechanism of partial racemization of compound **3.5** is assumed to be that the resulting imidazolid intermediate **2.3** undergoes a competitive intramolecular reaction to form azlactone **2.3a**, which has an optically inactive tautomeric form with the oxazole ring **2.3b** (Fig. 4).



2.3a (*S*) + (*R*) **2.3б**

Fig. 4. Formation of compounds **2.3a** and **2.3b***in situ*

There was no fermentation of NH-group proton signals in non - terminal amino acid residues by the ^{1}H NMR spectra of other products. There are no asymmetric centers in the initial amino acid derivatives.

The resulting *N*-acyl dipeptide methyl esters **3.1-3.9** were saponified with 1 n. NaOH (Fig. 2). The total yield of *N*-acyl dipeptides **4.1-4.9** for the initial amino acid derivatives was 40-50 %.

In the infrared spectra of acids **4.1-4.9** there were no signals for the valence vibrations of the carbonyl groups related to the ester, but strong absorption bands were observed for the valence vibrations of the carbonyl group in the range 1722 - 1726 cm^{-1} relating to the carboxylic group.

In the ^{1}H NMR spectra of products **4.1-4.9** there were no singlet signals in the chemical shift of 3.60-3.70 ppm with integral intensities corresponding to the three protons of the methyl group of the ester. At the same time, proton signals of carboxyl groups were observed in the 12.50-12.70 ppm, indicating the formation of modified *N*-acylipides in the form of acids. Similar to the case of *N*-acyliptytides esters, the ^{1}H NMR spectra of terminal acids **4.4** and **4.5** have seen the fermentation of proton group signals associated with asymmetric carbon atoms of non - terminal amino acid fragments.

The ^{1}H NMR spectra were measured with a Varian "VXR-400" (400 MHz) in dimethyl sulfoxide solution (DMSO-d_6). IR spectra were recorded on a Spectrum RX-1 (Perkin Elmer) for substances in suspension in vaseline oil. The melting temperatures were detected on a BUCHI Melting Point M-560. The homogeneity of the compounds obtained was controlled by TLC using Sorbfil plates. Eluent of *n*-hexane/toluene/acetone = 8 ml/8 ml/5 ml was used; the chromatograms were UV-expressed.

The methodology for the synthesis of *N*-acyldipeptide methyl esters **3.1-3.9**. To solution of 1 mmol of compound **1.1-1.4** in 10 mL tetrahydrofuran (THF) 1.15 mmol of CDI was added. The reaction mixture was stirred and heated at solvent boiling point for 1 h. Then 1.30 mmol of α-amino acid methyl ester hydrochloride and 1.3 mmol of NEt_3 were added. Stirring was continued under heat for another 3 hours. The reaction mixture was left overnight at room temperature, concentrated to half of its original volume and then 20 ml of 1 n. hydrochloric acid solution was added. Then 15 ml methylene chloride was added to the reaction mixture until the isolated product was completely dissolved, the resulting organic layer was separated,

dried, evaporated to a viscous mass, which was then crystallized in *n*-hexane. The separated crystals were filtered off and dried in the air.

General methodology for the hydrolysis of *N*-acyl dipeptide methyl esters **3.1**-**3.9** to acids **4.1**-**4.9**. To 0.68 mmol of methyl ester **3.1**-**3.9** in 10 ml acetone solution was added 75 mmol of 1 n sodium hydroxide solution. The mixture was left overnight at room temperature, after which it was evaporated to a dry residue. Thus residue was dissolved in water and acidified drop by drop with 36% hydrochloric acid solution to pH 2 when cooled to 2-6 ℃. The acid precipitate **4.1**-**4.9** was filtered off, washed with water to a neutral pH value and air-dried.

*N-[4-(1-adamantyl)benzoyl]-glycyl-L-leucine (**4.1**)*

0.226 g (78%) obtained. Melting temperatures 99-101 ℃. R_f 0.3. IR, *ν*, cm^{-1}: 3316 (N-H), 1726 (C=O), 1640 (C=O), 1610 (C_6H_4), 1544 (C=O), 1502 (C_6H_4). ^{1}H NMR, δ, ppm.: 12.60 (br.s., 1H), 8.55 (t, *J*=6.4 Hz,1H), 8.12 (d, *J*=7.0 Hz, 1H), 7.82 (d, *J*=7.8 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 4.25 (m, 1H), 3.90 (d, *J*=6.4 Hz, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80 (m, 6H), 1.65 (m, 1H), 1.52 (m, 2H), 0.90 (d, *J* = 9.3 Hz, 3H), 0.85 (m, *J* = 9.3 Hz, 3H).

*N-[4-(1-(1-adamantyl)benzoyl]-glycyl-L-phenylalanine (**4.2**)*

0,275 g (81%) obtained. Melting temperatures 95-97 ℃. R_f 0,45. IR *ν*, cm^{-1}: 3290 (N-H), 1729 (C=O), 1645 (C=O), 1610 (C_6H_4), 1541 (C=O), 1517 (C_6H_4).^{1}H NMR, δ, ppm.: 12.65 (br.s., 1H), 8.59 (t, *J*=6.4 Hz, 1H), 8.11 (d, *J*=7.0 Hz, 1H), 7.82 (d, *J*=7.8 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 7.31 (d, *J*=7.0 Hz, 2H), 7.22 (d, *J*=7.0 Hz, 2H), 7.15 (t, *J*=7.0 Hz, 1H), 4.45 (m, 1H), 3.85 (d, *J*=6.4 Hz, 2H), 2.05 (m, 3H), 1.90 (m, 6H), 1.75 (m, 6H).

*N-[4-(1-adamantyl)benzoyl]-glycyl-glycine (**4.3**)*

0.232 g (76%) obtained. Melting temperatures 90-92 ℃. R_f 0.41. IR, *ν*, cm^{-1}: 3291 (N-H), 1735 (C=O), 1644 (C=O), 1615 (C_6H_4), 1535 (C=O), 1514 (C_6H_4). ^{1}H NMR, δ, ppm.: 12.70 (br.s., 1H), 8.70 (t, *J*=7.5 Hz, 1H), 8.28 (t, *J*=6.2 Hz, 1H), 7.84 (d, *J*=7.8 Hz, 2H), 7.46 (d, *J*=7.8 Hz, 2H), 3.90 (d, *J*=6.2 Hz, 2H), 3.80 (d, *J*=7.5 Hz, 2H), 2.06 (m, 3H), 1.90 (m, 6H), 1.82 (m, 6H).

*Mixture of N-[4-(1-(1-adamantyl)benzoyl]-L-phenylalanyl-L-leucine and N-[4-(1-adamantyl)benzoyl]-D-phenylalanyl-L-leucine (**4.4**)*

0.182 g (75%) obtained. Melting temperatures 96-98 ℃. R_f 0.18. IR, *ν*, cm^{-1}: 3213 (N-H), 1720 (C=O), 1633 (C=O), 1611 (C_6H_4), 1542 (C=O), 1524 (C_6H_4). ^{1}H NMR, DMSO-d_6, δ, ppm.: 12.65 (br.s., 1H), 8.42 (d, *J*=6.4 Hz, 0.6H, *L-L*), 8.35 (d, *J*=6.4 Hz, 0.4H, *D-L*), 8.26 (d, *J*=7.0 Hz, 1H), 7.82 (d, *J*=7.8 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 7.34 (d, *J*=7.0 Hz, 2H), 7.20 (d, *J*=7.0 Hz, 2H), 7.16 (t, *J*=7.0 Hz, 1H), 4.75 (m, 0.6H, *L-L*), 4.70 (m, 0.4H, *D-L*), 4.3 (m, 1H), 3.2 (m, 1H), 3.1 (m, 1H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80 (m, 6H), 1.65 (m, 1H), 1.52 (m, 2H), 0.90 (d, *J* = 9.3 Hz, 3H), 0.85 (d, *J* = 9.3 Hz, 3H).

*Mixture of N-[4-(1-adamantyl)benzoyl]-L-valyl-L-phenylalanine and N-[4-(1-adamantyl)benzoyl]-D-valyl-L-phenylalanine (**4.5**)*

0.34 g (80%) obtained. Melting temperatures 105-107 °C. R_f 0.16. IR, *ν*, cm^{-1}: 3199 (N-H), 1718 (C=O), 1623 (C=O), 1611 (C_6H_4), 1541 (C=O), 1514 (C_6H_4). ^1H NMR, δ, ppm: 12.65 (br.s., 1H), 8.32 (d *J*=6.4 Hz, 0.6H, *L-L*), 8.24 (d, *J*=6.4 Hz, 0.4H, *D-L*), 8.06 (d, *J*=7.0 Hz, 1H), 7.82 (d, *J*=7.8 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 7.31 (d, *J*=7.0 Hz, 2H), 7.22 (d, *J*=7.0 Hz, 2H), 7.15 (t, *J*=7.0 Hz, 1H), 4.45 (m, 1H), 4.3 (m, 0.6H, *L-L*), 4.25 (m, 0.4H, *D-L*), 3.2 (m, 1H), 3.1 (m, 1H), 2.30 (m, 1H), 2.05 (m, 3H), 1.90 (m, 6H), 1.75 (m, 6H), 0.86 (d, *J* = 9.1 Hz, 3H), 0.82 (d, *J* = 9.1 Hz, 3H).

*N-[4-(1-adamantyl)benzoyl]-sarcosyl-L-leucine (**4.6**)*

0.224 g (77%) obtained. Melting temperatures 129-131 °C. R_f 0.19. IR, *ν*, cm^{-1}: 3201 (N-H), 1715 (C=O), 1633 (C=O), 1620 (C_6H_4), 1551 (C=O), 1514 (C_6H_4). ^1H NMR, δ, ppm: 12.45 (br.s., 1H), 8.10 (d, *J*=7.0 Hz, 1H), 7.82 (d, *J*=7.8 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 4.20 (m, 1H), 3.70 (c, 2H), 3.10 (c, 3H), 2.05 (m, 3H), 1.90 (m, 6H), 1.80 (m, 6H), 1.65 (m, 1H), 1.52 (m, 2H), 0.94 (d, *J* = 9.0 Hz, 3H), 0.88 (d, *J* = 9.0 Hz, 3H).

*N-[4-(1-adamantyl)benzoyl]-sarcosylglycine (**4.7**)*

0.195 g (81%) obtained. Melting temperatures 121-123 °C. R_f 0.26. IR, *ν*, cm^{-1}: 3215 (N-H), 1714 (C=O), 1633 (C=O), 1610 (C_6H_4), 1548 (C=O), 1524 (C_6H_4).^1H NMR, δ, ppm: 12.55 (br.s., 1H), 8.26 (t, *J*=6.2 Hz, 1H), 7.80 (d, *J*=7.8 Hz, 2H), 7.40 (d, *J*=7.8 Hz, 2H), 3.90 (t, *J*=6.2 Hz, 2H), 3.80 (c, 2H), 3.10 (c, 3H), 2.04 (m, 3H), 1.88 (m, 6H), 1.78 (m, 6H).

*N-[4-(1-adamantyl)benzoyl]-glycyl-L-valine (**4.8**)*

0.219 g (76%) obtained. Melting temperatures 135-137 °C. R_f 0.24. IR, *ν*, cm^{-1}: 3214 (N-H), 1715 (C=O), 1628 (C=O), 1610 (C_6H_4), 1539 (C=O), 1524 (C_6H_4). ^1H NMR, δ, ppm: 12.65 (br.s., 1H), 8.55 (t, *J*=6.4 Hz, 1H), 8.10 (d, *J*=7.0 Hz, 1H), 7.82 (d, *J*=7.8 Hz, 2H), 7.45 (d, *J*=7.8 Hz, 2H), 4.33 (m, 1H), 3.90 (d, *J*=6.4 Hz, 2H), 2.20 (m, 1H), 2.06 (м, 3H), 1.92 (m, 6H), 1.84 (m, 6H), 0.86 (d, *J* = 9.2 Hz, 3H), 0.82 (d, *J* = 9.2 Hz, 3H).

*N-[4-(1-adamantyl)benzoyl]-glycyl-L-alanine (**4.9**)*

0.194 g (80%) obtained. Melting temperatures 117-119 °C. R_f 0.20. IR, *ν*, $см^{-1}$: 3216 (N-H), 1715 (C=O), 1627 (C=O), 1610 (C_6H_4), 1542 (C=O), 1520 (C_6H_4). ^1H NMR, δ, ppm: 12.65 (br.s., 1H), 8.58 (т, *J*=6.4 Hz, 1H), 8.05 (d, *J*=7.0 Hz, 1H), 7.80 (d, *J*=7.8 Hz, 2H), 7.40 (d, *J*=7.8 Hz, 2H), 4.40 (m, 1H), 3.92 (d, *J*=6.4 Hz, 2H), 2.08 (m, 3H), 1.90 (m, 6H), 1.80 (m, 6H), 1.40 (d, *J* = 8.0 Hz, 3H).

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