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Organic Chemistry

Synthesis of Indole and Adamantane Containing some Dipeptides via Isocyanide Based Multicomponent Reaction (IMCR)

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ABSTRACT. In the present paper the synthesis of N-methyl indole and adamantane fragment containing new dipeptides via isocyanide based multicomponent reaction (IMCR) by using amino-1-adamantane with equimolar ratio of aldehydes, N-methyl-1H-indolecarboxylic acid and ethyl isocyanoacetate in the area of ethanol at 45°C is described and the preparative method and optimal conditions of the synthesis of indole and adamantane containing dipeptides via Ugi-multicomponent reaction was worked up. From the reaction mixture the dipeptides, Passerine products, indole containing amide and adamantine containing some schiff bases were isolated by using column chromatography and the structures of the obtained compounds were confirmed by IR, NMR and LC-MS spectra. Possible biological activity for the synthesized compounds was implemented on the basis of a PASS prediction program by ParmaExpert software. According to the predicted results, adamantane and indoles containing dipeptides revealed high activity as Proteasome ATPase inhibitor, Sigma 1 receptor agonist, Nootropic and anti-viral properties against influenza. © *2019 Bull. Georg. Natl. Acad. Sci.*

Key words: adamantane and indole containing dipeptides, Ugi-4MCRs

The isocyanide based multicomponent reaction (IMCR) is an efficient reaction for coupling four different functional classes. This IMCRs comprises the condensation of an amine, an oxo compound, a carboxylic acid and an isocyanide to form a dipeptidic scaffold [1,2]. The Ugi reaction is one of the most important MCRs, and it is widely used in the synthesis of bioactive compounds, in pharmaceutical industry for preparing compounds with interesting properties. This powerful reaction involves a one-pot condensation of amine, carbonyl compound, carboxylic acid and isocyanide to provide a substituted peptide-like product. The Ugi reaction is an isonitrile-based MCR that provides a rapid route for the preparation of a-aminoacyl amide derivatives [3-5].

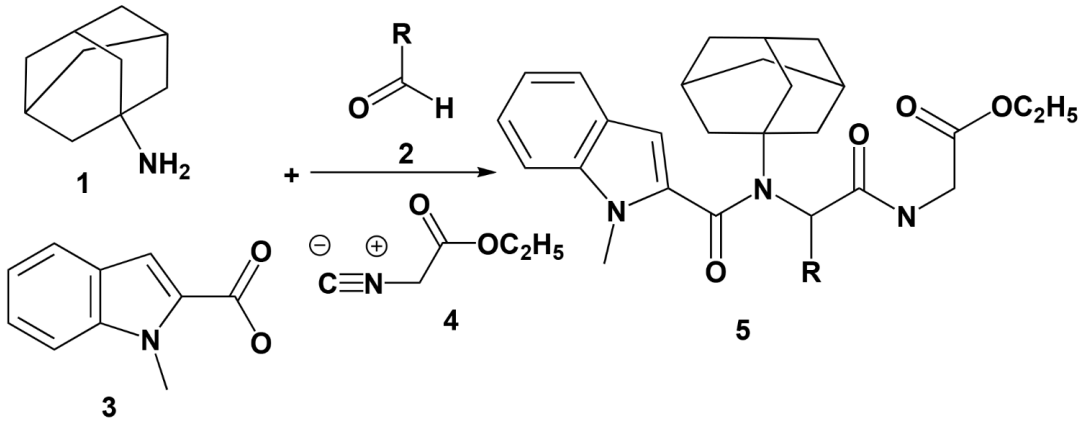
In recent years the synthesis of peptides received considerable attention. Peptides, especially of

indoles or adamantane, gained popularity as promising building blocks. It has been studied that indole derivatives are associated with various biological activities as antifungal, anti-inflammatory and analgetic, anticancer, antihypertensive, antihistaminic, antiHIV, antioxidant, antidiabetic, photochemotherapeutic, antidepressant, tranquillizing, antoconvulsant, thrombin catalytic, opioid antagonist, antitubercular, insecticidal, antiviral, antimicrobial and is a highly promising pharmaceutical agent [6-9].

Chemistry and pharmacology of adamantane derivatives are of great interest to medicinal chemistry because adamantane derivatives have wide range of pharmacological properties like antiviral, antibacterial, anticancer, anticataleptic, immunotropic, neuro-psychotropic and other properties. They amplify energy of the human body and significantly improve emotional and physical state in patients. Furthermore, it has been experimentally found that introduction of the adamantane fragment into the molecule of an active substance enhances its bioactivity and generally reduces the toxicity [10-13]. Number of molecules having adamantane moiety as a core are in market for different therapeutic category. Also number of molecules having adamantane moiety as a core are in different clinical trials.

In the present study the aim of our work was to synthesize a series of novel indole- and amino-1-adamantane moiety containing dipeptides by an Ugi-4CRs [14].

The reaction was performed at 45˚C temperature in a three-necked glass reactor equipped with a magnetic stirrer, thermometer and condenser. The procedure consisted of the following: dissolving amino-1-adamantane (1) in an ethanol area, addition of equimolar amount of aldehyde (2) and at the selected time intervals it was stirred. Then N-methyl indole carboxylic acid and ethyl isocyanoacetate was added. The reaction mixture was stirred for 30h. After finishing reaction dichloromethane was added to the reaction mixture, quaked with saturated $NaHCO_3$, then with 1M $KHSO_4$ solution and washed with brine. The organic phase was concentrated and chromatically purified on the column by standard method (SiO_2, hexane/ethyl acetate), dipeptides **5** (Scheme 1) were obtained with 26-36% yield.

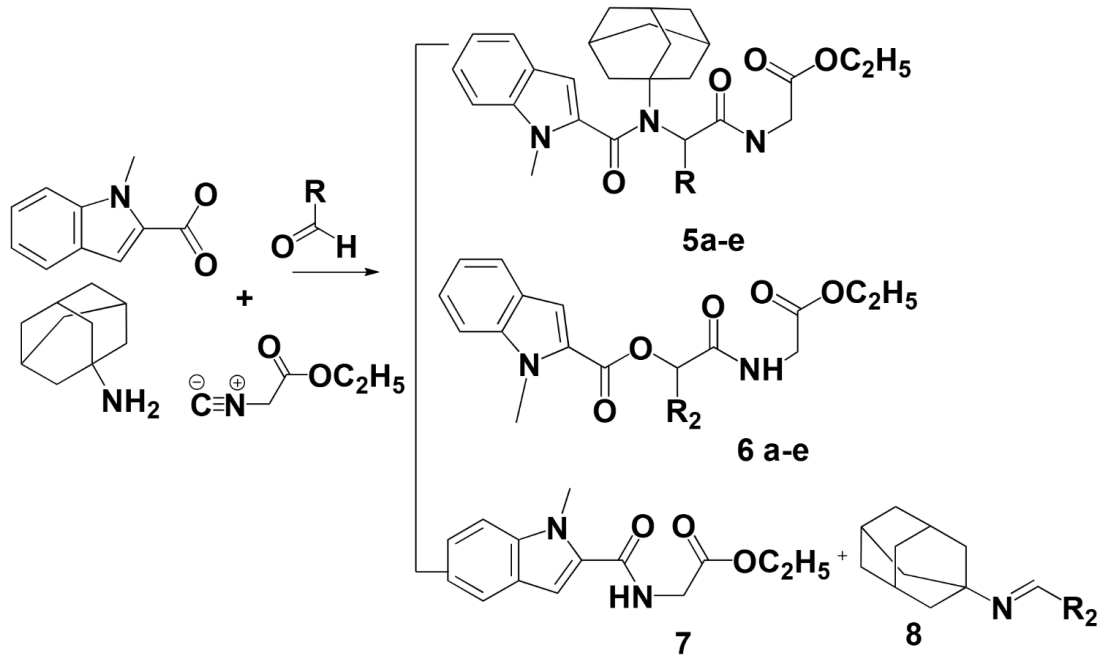


Scheme 1. Synthesis of indole and adamantane containing dipeptides via Ugi-4MCR.

It turned out that in the reaction mixture with the dipeptides (5a-e) as a side products two or three new substances are formed such as Passerini three-component products (6), aminamide (7) and Schiff base (8) (Scheme 2). The yield of side products is 35-55%. The low yield of dipeptides and otherwise high yield of Passerini products is caused

because of adamantane. The adamantane (tricyclo[3.3.1.1]decane) is a highly symmetric molecule which composed of three rigid of cyclohexane in chair-type conformation. This conformation, relatively free of conformational stress, results in a large and bulky structure.

In ^{1}H NMR spectra of synthesized compounds, NH group signals appear as singlets at 8.00– 11.92 ppm (compounds 5a-e, 6a-e and 7). In spectra of compounds 5a-e, 6a-e and 7, CH of aromatic group resonance signals appear as singlets in the 6.64- 8.57 9.25 ppm range, whereas the aromatic



(5a)R= -C(CH$_3$)$_2$, (5b)R= -C$_6$H$_5$, (5c)R= -C$_6$H$_4$OH, (5d)R= -C$_6$H$_4$NO$_2$, (5e)R=-C$_6$H$_3$NO$_2$OH;

Scheme 2. Synthesis of indole and adamantane containing dipeptides (5), Passerini product (6), indole containing amide (7) and adamantane containing imines (8).

Structures of the obtained compounds were determined by the IR, ^{1}H and ^{13}C NMR and LS-MS spectra.

The IR spectra of compounds 5a-e, 6a-e and 7 manifest the characteristic absorption bands of NH groups at 3229–3350 cm^{-1}, and the characteristic bands of aromatic CH groups of the indole ring at 3057-3060 cm^{-1}. The characteristic absorption bands of CH and CH$_2$ of adamantane tricycle at 2820-2915 cm-^{1}, respectively. The absorption bands of functional groups C=O is also observed at 1622-1670 cm-^{1}. The characteristic absorption bands of OH group of 5c, 5e and 6c and 6e 3451-3489cm-^{1} and C–NO$_2$ of 5d, 5e and 6d and 6e at 1337-1535cm-1, respectively.

proton signals appear as singlets, doublets, doublets of doublets, and multiplets. In spectra of indole N-CH$_3$ group resonance signals appear as singlets in the 3.87– 4.19 ppm range. Proton signals of the adamantane fragment in the spectra of compounds 5a-e, 6a-e and 7 appear as multiplets in the upfield region of the spectra.

In 13C NMR spectra of compounds 5a-e and 7, the carbon atom signals of the adamantane fragment appear in the 27.5-61.7 ppm upfield region. Resonance signals of functional groups C=O and C–OH appear in the 160.1-177.3 ppm regions, respectively. The carbon atom signals of the indole ring appear in the 108.6-144.3 ppm range.

Biological Activity Spectra Prediction

Estimation of possible biological activity for the synthesized compounds (5a-e and 6a-e) was implemented on the basis of a PASS (prediction of activity spectra for substances) prediction results by ParmaExpert software. It is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. *It* provides predictions of biological activity based on the structure of organic compounds and estimate the biological activity profiles for molecules. Activity spectrum of a compound is estimated as probable active (Pa) or probable inactive (Pi), and their value varies from 0.000 to 1.000. Only activities with Pa > Pi are considered as possible for a particular compound. The average accuracy of a prediction is reported to be as high as 95% [15]. According to the predicted results, adamantane and indoles containing peptides 5a-e and 6a-e revealed high activity (Pa > 0.7) as Proteasome ATPase inhibitor, Sigma 1 receptor agonist, (Pa > 0.6) Nootropic and anti-viral properties against influenza.

Experimental Section

The chemical reagents used in synthesis were obtained from Sigma-Aldrich and VWR. All solvents were purified using standard procedures. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker-400 MHz NMR. Chemical shifts δ are in parts per million (ppm) measured in DMSO-d6 as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a Thermo Nicolet-Is5 FTIR instrument. Thin layer chromatography (TLC) was performed on Merck precoated silica gel 60F254 plates and spots were visualized by ultraviolet light and iodine. The final dipeptides were purified using column chromatography.

General Procedure for Synthesis of Dipeptides

In a 50 mL three necked round bottom flask to the solution of aldehyde (2 mmol) in 4 mL of ethanol the 1-aminoadamantane (2 mmol) was added successively, and the reaction mixture was stirred at 40˚C temperature for 4 h. Then N-methyl indole carboxylic acid (2 mmol) was added and stirring was continued for 20 min, afterwards the ethyl isocyanoacetate (2 mmol) was added. The reaction mixture was heated and stirred for 30 h at 40°C. The regular control of the reaction progress was conducted by TLC. After finishing reaction the mixture was transferred to a separating funnel and was extracted with CH_2CL_2. The organic layer was separated and washed with a saturated solution of $NaHCO_3$ (90 ml) followed by brine (90 ml). The organic layer was then dried over $MgSO_4$ and solvent removed in vacuo. Dipeptides 5a-e was separated by column chromatography.

Compound 5a. Yellowish crystal, 35%**,** Rf=0.45 (ethyl acetate/hexane ½),.**IR (cm-1):** 3350 (N-H), 3050 (Ar C-H), 2908-2820 (Ad, CH_2, CH_3); 1622 (C=O); ^{1}H NMR: 9.25 (NH, s) 8.05 (1H, s) 7.70 (1H, d, j=12), 7.43(1H, d, j=12), 7.35 (1H, td, j=8, j=12), 7.16 (1H td, j=8, j=12), 5.50 (1H,m), 4.19 (3H, m), 4.10 (1H, m), 3.99 (1H, s), 2.10 (3H,s), 1.97 (8H,m), 1.77 (7H, m), 1.49 (3H,m), 1.26(3H, m),0.96 (3H, m); ^{13}CNMR: 177.3, 170.2, 169.6, 137.3, 138.5, 127.3, 126.0, 125.9, 125.7, 122.7, 121.0, 112.1, 109.6, 61.7, 41.3, 41.0, 39.3, 36.4, 34.0, 28.1, 18.1, 14.0; 13.7 ppm. LC-MS: found, *m*/*z:* 493.31, calculated, *m*/*z*: 493.29;

Compound 5b, yellowish crystal, 32% Rf=0.47 (ethyl acetate/hexane ½). IR **(cm-1):** 3337 (N-H), 3060 (Ar C-H), 2915-2857(Ad, CH_2, CH_3), 1653, 1636 (C=O); ^{1}H NMR: 11.88 (s, 1H), 8.50 (1H, s) 7.82 (1H, s), 7.70(2H, dd j=8), 7.50 (1H, dq, j=8,), 7.34-7.25(3H m), 7.10 (1H, m), 5.06 (1H, s), 4.09 (3H, m), 3.88 (3H, m), 2.27 (2H, m), 2.09 (2H,m), 1.77 (3H, m), 1.67 (2H,m), 1.58(2H, m),1.21 (6H,m) 1.07 (3H, m); ^{13}CNMR: 169,4 169.1, 160.5, 137.4, 126.6, 124.8, 122.3, 112.5, 108.6, 79.2, 78.9, 78.5, 77.5, 60.4, 50.8, 40.5, 34.9, 30.4, 28.2, 18.6, 16.9, 13.9 ppm; LC-MS: found, *m*/*z:* 527.32, calculated, *m*/*z*: 527.28;

Compound 5c. 36% Rf=0.46 (ethyl acetate/hexane ½), yellowish crystal. IR **(cm-1):** 3451 (OH), 3249 (N-H), 3057(Ar C-H), 2911–2839 (Ad, CH_2, CH_3), 1651,1638 (C=O); ^{1}H NMR: 11.53 (s, 1H), 8.52 (s, 1H), 7.73 (dt, *J* = 8.1, 1.0 Hz, 2H), 7.61 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.22 – 7.11 (m, 5H), 5.20 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 4H), 4.03 (s, 3H), 2.07 – 2.01 (m, 3H), 1.92 – 1.80 (m, 6H), 1.78 – 1.64 (m, 3H), 1.49 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}CNMR: 170.3, 169.5, 160.7, 140.1, 126.5, 125.8, 122.8, 120.9, 110.9, 110.4, 109.2, 60.3, 41.1, 39.4, 36.4, 34.1, 31.7, 28.1, 18.2, 14.1, 13.7 ppm; LC-MS: found, *m*/*z:* 543.23, calculated, *m*/*z*: 543.27;

Compound 5d. 26% Rf=0.49 (ethyl acetate/hexane ½), yellowish crystal. IR **(cm-1):** 3335(N-H), 3060 (Ar C-H), 2912-2856 (Ad, CH_2, CH_3), 1670, 1637(C=O), 1535, 1337 (NO_2); ^{1}H NMR: 11.90 (s, 1H), 8.54 (t, *J* = 6.0 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.49 (dq, *J* = 8.4, 1.0 Hz, 1H), 7.33 (m, 1H), 7.25 (m, 1H), 7.10 (m, 1H), 7.09 (m, 1H), 5.22 (s, 1H), 4.10 (s 2H),4.07(s, 2H), 3.88 (s, 3H), 1.93 – 1.79 (m, 4H), 1.49 (m, 8H), 1.19 (m, 4H), 0.94 (m, 3H). ^{13}CNMR: 176.1, 169.5, 160.7, 139.3, 131.1, 127.0, 125.3, 125.0, 122.3, 120.6, 110.9, 110.4, 109.7, 77.5, 60.4, 40.6, 40.5, 36.0, 31.5, 30.3, 27.5, 18.7, 16.9, 14.0 ppm. LC-MS: found, *m*/*z:* 572.21, calculated, *m*/*z*: 572.26;

Compound 5e. 29% Rf=0.49 (ethyl acetate/hexane ½), yellowish crystal. IR **(cm-1):** 3452 (OH), 3245(N-H), 3060 (Ar C-H), 2918-2886 (Ad, CH_2, CH_3), 1650 (C=O), 1530, 1380 (NO_2);; ^{1}H NMR: 11.87 (s, 1H), 9.00 (s, 1H), 7.76 – 7.66 (m, 1H), 7.50 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.42 (dd, *J* = 6.0, 3.5 Hz, 2H), 7.34 – 7.26 (m, 2H), 7.19 (q, *J* = 3.2, 2.5 Hz, 1H), 7.10 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 5.06 (d, *J* = 4.7 Hz, 1H), 4.12-4.07 (m, 4H), 3.88 (s, 3H), 2.05 – 1.97 (m, 3H), 1.90 (d, *J* = 2.9 Hz, 9H), 1.69 (d, *J* = 3.2 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}CNMR: 169.5, 168.6, 160.5, 147.8, 140. 1, 135.3, 130.6, 129.6, 128.2, 127.3, 120.9, 117.5, 111.3, 110.4, 63.0, 61.7, 59.6, 41.5, 38.0, 36.9, 31.4, 28.1, 14.0 ppm;

Compound 6a. White crystal, 55%**,** Rf=0.36 (ethyl acetate/hexane ½),.**IR (cm-1):** 3250 (N-H), 3050 (Ar C-H), 2908-2846 (Ad, CH_2, CH_3); 1622 (C=O); ^{1}H NMR: 11.92 (s, 1H), 8.56 (t, *J* = 5.9 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.31 – 7.24 (m, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 5.22 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 4H), 3.88 (d, *J* = 6.0 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 6H); ^{13}CNMR: 169.5, 169.4, 160.9, 137.4, 126.6, 124.8, 122.0, 121.7, 120.5, 119.6, 112.6, 108.6, 83.7, 60.4, 40.5, 33.8, 29.4, 17.4, 13.9 ppm;

Compound 6b. White crystal, 56%**,** Rf=0.35 (ethyl acetate/hexane ½),.**IR (cm-1):** , 3229 (N-H), 3060 (Ar C-H), 2910-2843 (Ad, CH_2, CH_3); 1625 (C=O); ^{1}H NMR: 8.0 (s, 1H), 7.64 (dt, *J* = 8.1, 1.0 Hz, 2H), 7.37 (s, 2H), 7.35 – 7.29 (m, 3H), 7.11 (ddd, *J* = 8.0, 5.8, 2.1 Hz, 2H), 6.64 (s, 1H), 5.43 (t, *J* = 6.0 Hz, 1H), 4.15 (t, *J* = 7.2 Hz, 3H), 4.03 (s, 4H), 0.91 (s, 3H); ^{13}CNMR: 169.8, 167.2, 160.9, 136.6, 133.2, 129.9, 128.7, 127.6, 125.7, 125.1, 119.3, 111.5, 110.7, 75.5, 61.1, 40.6, 40.7, 33.6, 14.2 ppm;

Compound 6c. White crystal, 55%**,** Rf=0.37 (ethyl acetate/hexane ½),**IR (cm-1):** 3456(OH), 3250 (N-H), 3050 (Ar C-H), 2911-2846 (Ad, CH_2, CH_3); 1622 (C=O); ^{1}H NMR: 11.25 (s, 1H), 9.00 (s, 1H), 8.52 (t, *J* = 5.9 Hz, 1H), 7.73 (dt, *J* = 8.1, 1.0 Hz, 2H), 7.61 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.43 (d, *J* = 0.9 Hz, 2H), 7.41 – 7.32 (m, 2H), 7.20 – 7.13 (m, 2H), 5.20 (t, *J* = 6.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 4H), 3.87 (dd, *J* = 5.9, 2.2 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}CNMR: 178.1, 169.5, 160.4, 157.2, 134.1, 133.7, 129.1, 128.6, 125.4, 124.6, 122.5, 121.1, 119.7, 116.8, 110.5, 109.5, 68.2, 61.1, 40.6, 33.2, 14.9 ppm**;**

Compound 6d. White crystal, 51%**,** Rf=0.41 (ethyl acetate/hexane ½),.**IR (cm-1):** 3270 (N-H), 3045 (Ar C-H), 2911-2858 (Ad, CH_2, CH_3); 1622 (C=O), 1537, 1368 (NO_2); ^{1}H NMR: 9.0 (s, 1H), 8.49 (t, *J* = 5.9 Hz, 2H), 7.74 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.61 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.44 (d, *J* = 0.9 Hz, 1H), 7.38 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 2H), 7.16 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 2H), 5.05 (d, *J* = 4.5 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 3H),

2.04 (s, 4H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}CNMR: 169.2, 167.6, 160.1, 147.3, 141.6, 132.9, 130.5, 128.6, 125.1, 124.6, 121.9, 120.2, 119,7, 110.9, 109.4, 74.2, 61.7, 40.7, 33.6, 14.8 ppm;

Compound 6e. White crystal, 33%**,** Rf=0.46 (ethyl acetate/hexane ½), **IR (cm-1):** 3489(OH), 3236 (N-H), 3075 (Ar C-H), 2905-2861 (Ad, CH_2, CH_3); 1640 (C=O), 1517, 1345 (NO_2); ^{1}H NMR: 11.0 (s, 1H), 9.2 (s, 1H), 8.57 (t, *J* = 5.9 Hz, 1H), 7.85 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.56 (d, *J* = 0.9 Hz, 1H), 7.28 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 2H), 7.24 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 2H), 5.05 (d, *J* = 4.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.0 (s, 3H), 3.76 (d, *J* = 6.0 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}CNMR: 172.1, 167.5, 162.1, 147.3, 141.6, 132.9, 130.5, 128.5, 125.6, 124.3, 121.9, 120.2, 119.7, 110.9, 109.4, 74.2, 61.7, 40.7, 33.1, 14.8 ppm;

Compound 7a. White crystal, Rf=0.25 (ethyl acetate/hexane ½),.**IR (cm-1):** 3050 (Ar C-H), 2913-2849 (Ad, CH_2, CH_3); 1622 (C=O); ^{1}H NMR: 11.00 (s, 1H), 7.54 – 7.42 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.26 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.01 (td, *J* = 7.4, 6.9, 1.1 Hz, 1H), 6.84 (s, 1H), 4.19 (m, 4H), 3.98 (s, 3H), 3.78 (s, 2H), 2.12 (m, 3H); ^{13}CNMR: 169.8, 160.2, 144.2, 136.8, 125.2, 122.3, 120.4, 119.7, 115.9, 110.4, 61.5, 40.6, 36.2, 18.7ppm;

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ორგანული ქიმია

ინდოლისა და ადამანტანის შემცველი ზოგიერთი დიპეპტიდის სინთეზი იზოციანიდების ბაზაზე მულტიკომპონენტური რეაქციით (IMCR)

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**სან დიეგოს სახელმწიფო უნივერსიტეტი საქართველოში, ქიმია-ბიოქიმიის ფაკულტეტი, თბილისი, საქართველო

§აკადემიის წევრი, ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, თბილისი, საქართველო

წარმოდგენილ სამუშაოში აღწერილია N-მეთილ-1H-ინდოლის და ადამანტანის ფრაგმენტის შემცველი ახალი დიპეპტიდების სინთეზი იზოციანიდების ბაზაზე მულტიკომპონენტური რეაქციით (IMCR), რომელიც ჩატარდა ეკვიმოლური თანაფარდობით ამინო-1-ადამანტანის, ალდეჰიდების, N-მეთილ-1H-ინდოლკარბონმჟავას და ეთილიზოციანო-აცეტატის გამოყენებით. შემუშავდა სინთეზის პრეპარატული მეთოდი და რეაქციის ოპტიმალური პირობები. სარეაქციო ნარევიდან სვეტური ქრომატოგრაფიით გამოყოფილ იქნა დიპეპტიდები, პასერინის სამკომპონენტიანი რეაქციის პროდუქტები, ინდოლშემცველი ამიდი და ადამანტანის შემცველი შიფის ფუძეები. სინთეზირებული ნაერთების სტრუქტურები დადგინდა ინფრაწითელი, ბირთვულ მაგნიტური რეზონანსული სპექტრით და LC-MS ანალიზით.

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