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Synthesis Of N-Methyl-1h-Indole And Adamantane Fragment Containing Derivatives Via UGI-4CR.

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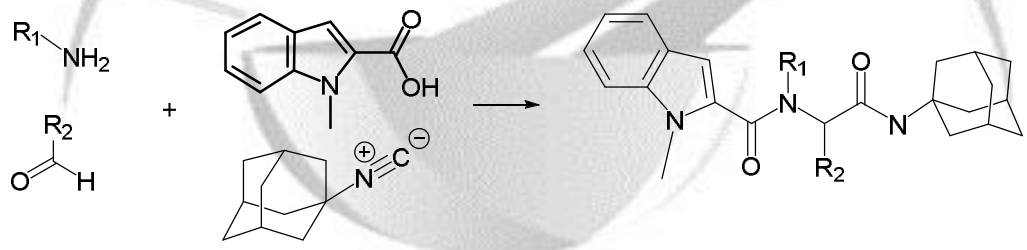
ABSTRACT

In the present study, an efficient synthesis of N-Methyl-1H-indole and adamantane containing dipeptides obtained via Ugi-four component reaction (U4-CR) by the interaction of an amine, aldehyde, N-methyl-1H-indole-2-carboxylic acid and adamantyl-1-isonitrile is described. U4-CR involves a one-pot condensation of an amine, a carbonyl compound, a carboxylic acid, and an isocyanide to provide a substituted peptide-like product. For N-methyl-1H-indole and adamantane containing dipeptides were established the feasibility of the strategy and was optimized the reaction conditions including temperature, solvents and the influence of bases.



Keywords: Adamantan-1-amine, N-methyl-1H-indole-2-carboxylic acid, Ugi four-component reaction (U-4CR); Adamantyl-1-isonitrile

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INTRODUCTION

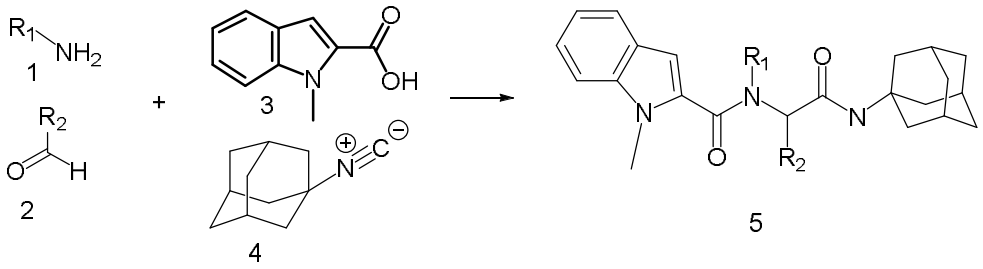
It is known that indoles are one of the most important alkaloids molecules found extensively in biological systems, which play vital role in many of the biochemical process [1]. Indole and its derivatives comprise a major group of heterocyclic aromatic compounds which provides privileged scaffolds in drug discovery, for the synthesis of pharmaceuticals, dyes, and industrial solvents [2-4]. There are also amazing numbers of indole containing drugs in the market as well as compounds in clinical evaluation [5].

Adamantane derivatives are known to have a broad spectrum of biological activity including antiviral, antimicrobial, anticarcinogenic, anticataleptic, immunotropic, neuro-psychotropic and other effects. The wide spectrum of pharmacological activities of adamantane line derivatives are conditioned by the structure of their molecules. The diamond-like firm cyclic structure determines their unique physical, chemical and biological properties [6-8]. The incorporation of an adamantyl fragment into several molecules results in compounds with relatively high lipophilicity, which in turn can modify the biological availability of these molecules. The high lipophilicity and unique geometry of the adamantane skeleton enhances considerably the permeability and adsorption of this type of compounds with respect to cell membranes [9-12]. This property of adamantane became of a great interest of scientists to use adamantane fragment for delivering the medicinal remedies inside cells and enhancing their pharmacological properties [13-15].

In recent years, synthesized peptides, especially indole and adamantane fragment containing peptides, have gained popularity as promising building blocks for the design and development of novel materials with potential application in diverse areas ranging from drug design to biotechnology. Many methods for synthesis of peptides are known but multicomponent reaction (MCR) on the basis of isocyanides named as the Ugi reaction is the most interesting [16-26]. It has attracted considerable attention from the synthetic organic chemistry. The MCRs are highly flexible, often selective and operationally simple. The Ugi reaction is widely used in the synthesis of bioactive compounds, in pharmaceutical industry for preparing compounds with interesting properties. This reaction involves a one-pot condensation of an amine, a carbonyl compound, a carboxylic acid, and an isocyanide to provide a substituted peptide-like product. [27-30].

In the present study, we have made an attempt to study the synthesis of N-Methyl-1H- indole and adamantane containing dipeptides obtained via Ugi-four component reaction (U4-CR) (Scheme 1). For this reaction initially, as an amine **1** adamantan-1-amine, glycine ethyl ester hydrochloride, alanine ethyl ester hydrochloride and phenylalanine ethyl ester hydrochloride were chosen. As an aldehyde **2** benzaldehyde, salicylic aldehyde and isobutyl aldehyde were taken. As an acid, N-methyl-1H-indole-2-carboxylic acid **(3)** was synthesized according to the scheme 2 and as an isocyanide **4** adamantyl-1-isonitrile **(4)** was synthesized from adamantan-1-amine according to the scheme **3**.

Scheme 1: U4-IMCRs among amine (1), aldehyde (2), N-methyl-1H-indole carboxylic acid (3) and adamantyl-1-isonitrile (4)



MATERIALS AND METHODS

Chemical reagents and apparatus

Chemical reagents used in the study were supplied from Sigma Sigma-Aldrich and VWR. Melting points were taken in,,Stuart™ melting point apparatus SMP10'' in open capillary method and are uncorrected. ^{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 and $CDCl_3$ as solvent and relative to TMS as the internal standard. High-resolution mass spectra were recorded on a Finnigan MAT 95, CI (reagent gas – methane). Infrared spectra were recorded on a Thermo Nicolet-Is5 FTIR instrument. Agilent Technologies 6460C Triple Quad coupled with HPLC (Agilent 1260 series). Pure substance was injected to MS without HPLC column. Methanol +0.1% ormic acid at 0/2 ml/min was used as mobile phase. ESI Jet Stream source was used as ion source, at mass range 10 to 800 mas range and 20V fragmentor voltage was used. Thin layer chromatography (TLC) was performed on Merck precoated silica gel 60F254 plates (ethyl acetate/hexane 1:3) and spots were visualized by ultraviolet light and iodine. Synthesized products purification was conducted by flash chromatography (ethyl acetate/hexane 1:9) and recrystallization was carried out from ethanol/water.

EXPERIMENTAL

The synthesis of compounds 3a-3 (scheme 2), 4a-4 (scheme 3)

the desired product. White solid; mp 120-122 oC (lit.1 mp 121-123 oC); IR (KBr) nmax/cm-1 3463, 3431, 2929, 1711 and 1695; 1H NMR (CDCl3, 400 MHz) d 1.41 (t, 3H, J 6.8 Hz), 4.39 (q, 2H, J 6.8 Hz), 7.23-7.16 (m, 1H), 7.29-7.33 (m, 2H), 7.49-7.56 (m, 1H), 7.69 (d, 1H, J 9.6 Hz), 9.41 (br s, 1H); 13C NMR (CDCl3, 75 MHz) d 161.7, 135.4, 128.2, 126.5, 122.6, 121.7, 121.1, 110.6, 109.2, 62.3, 14.7; MALDI-TOF MS m/z 189 (M+); Anal. calcd. for C11H11NO2: C 69.83, H 5.86, N 7.40; found: C 70.01, H 5.69, N 7.21

Ethyl 1H-indole-2-carboxylate (3d). Ethyl 2-(2-phenylhydrazono)-propanoate (3c) was obtained by interaction of phenyl hydrazine (3a) (2.16 g, 0.02 mol) with ethyl pyruvate (3b) (2.55g, 0.022 mol) in glacial acetic acid (30 g, 0.5 mol). After 2 h stirring reaction mixture was neutralized with 1 M NaOH, diluted with water (300 mL) and formed precipitate was filtered, washed with water and dried. Then PPEE (1.1 ml, 0.012 mole) was added to the crude product of compound **3c** (1.02 gm, 0.004 mole). The reaction mixture was stirred at 70-75 ^{0}C for 1 h and poured into the ice water, neutralized with saturated $NaHCO_3$ and formed white precipitate was filtered and recrystallized from Methanol. Ethyl 1H-indole-2-carboxylate (3d) was obtained 0. 87g (92%), m.p. 122-124˚C. [Lit.: 31,32], **IR** (cm^{-1}): 3463, 3431, 2929, 1711 and 1695; [33]. LC-MS: Found, m/z: 189.08, calculated, m/z: 189.08.

White solid; mp 120-122 oC (lit.1 mp 121-123 oC); IR (KBr) nmax/cm-1 3463, 3431, 2929, 1711 and 1695; 1H NMR (CDCl3, 400 MHz) d 1.41 (t, 3H, J 6.8 Hz), 4.39 (q, 2H, J 6.8 Hz), 7.23-7.16 (m, 1H), 7.29-7.33 (m, 2H), 7.49-7.56 (m, 1H), 7.69 (d, 1H, J 9.6 Hz), 9.41 (br s, 1H); 13C NMR (CDCl3, 75 MHz) d 161.7, 135.4, 128.2, 126.5, 122.6, 121.7, 121.1, 110.6, 109.2, 62.3, 14.7; MALDI-TOF MS m/z 189 (M+); Anal. calcd. for C11H11NO2: C 69.83, H 5.86, N 7.40; found: C 70.01, H 5.69, N 7.21

Ethyl 1-methyl-1H-indole-2-carboxylate (3e). To a suspension of ground potassium hydroxide (0.58 g, 10.3 mmol) in DMSO (20 mL) was added compound **3d** (0.49 g, 2.6 mmol) and the resulting suspension was stirred at 40 °C. After 30 min, a solution of methyl iodide (0.92 g, 6.5 mmol) in DMSO (20 mL) was added slowly over a period of 2 h, and the resulting mixture was stirred overnight at 40 °C. The viscous gel-like suspension was poured into ice-water, filtered and washed with water. Ethyl 1-methyl-1H-indole-2-carboxylate (**3e)** was obtained 0.5g, 92% yield after recrystallization. m.p. 133-134˚C, **IR** (cm^{-1})**:** 3040, 2936, 1646, 1518, 1465, 1426; LC-MS: found, m/z: 204.08, calculated, m/z: 204.08

1-Methyl indole carboxylic acid (3). A solution of NaOH (1.6, 0.04 mol) in methanol (10 mL,) was mixed with a solution of the compound **3e** (2.0 g, 0.01 mol) in methanol (10 mL) and the mixture was stirred at the 35-40°C. The course of the reaction was followed by TLC analysis (EtOAc/hexane 1:2) until the starting material was consumed. When the reaction was complete, the reaction mixture was cooled and diluted with water. The aqueous layer was acidified with 1 N HCl to get the acid. The mixture was stirred 3 h at 40 °C, then was poured into ice-water, filtered and washed with water. 1-methyl indole carboxylic acid **(3)** was obtained 1.56g, (91 %). M.p. 198-200 ˚C. IR (cm^{-1}): 365,053, 2948, 1660, 1515 LC-MS: found m/z: 175.07, calculated, m/z: 175.06.

Adamantyl-1-isonitrile (4). Method a). At first step of reaction compound **4a** (18.77g, 0.1 mol) and p-toluene sulphonyl acid monohydrate (0.01g, 0.06 mmol) were dissolved in 50 ml ethyl format. TEA (11.1g, 0.11 mol) was slowly added by drop wise over a period of 2 h. Reaction mixture was stirred at 60°C for 20 h and monitored by TLC (hexane/ ethyl acetate 4/1). Reaction mixture was cooled and filtrated. Filtrate was concentrated under the reduced pressure and white powder of compound N-(adamantan-1-yl)-formamide **(4c)**

was obtained 16.11 g (90 %) mp.132-134°C; IR (cm^{-1}): 2900-2870, 1600-1550, 1380-1350, 1100; ^{1}HNMR: 8.28 (1H, d, J = 12), 8.03 (1 H d, J = 1.6 Hz), 6.9 (br. s, 1 H,), 2.24 (m, 6 H,) 1.44 (m, 9 H,) ppm.; ^{13}C NMR: 162.4, 160.33, 52.2, 50.8, 44.1, 41.8, 36.2, 35.9, 29.3 ppm. LC-MS: found, m/z: 179.18, calculated, m/z: 179.13;

In second step TEA (20.8g, 0.02 mol) by dropwise was added to the suspension of compound **4c** (15g, 0.083m) in CH_2Cl_2 (250 mL) at 0°C temperature. The reaction mixture was stirred 1h and further with Na_2CO_3 (16.6g, 0.16 mol) in water (166ml) was treated and stirred at room temperature at half hour. The reaction mixture was diluted with 300 ml of water. The formed suspension was extracted with CH_2Cl_2 (3 x 100 ml), the organic layer was dried over Na_2SO_4 and concentrated. Formed residue was filtered and washed with hexane. 1-isocyanoadamantane (4) was obtained 10.11 g (75%), m.p. 187-190°C. IR (cm^{-1})**:** 2900-2800, 2130, 1490, 1380, 1200 ^{1}H NMR: 2.05-2.02 (9H m. Ad), 1.71 (6H, m Ad); ^{13}CNMR: 145, 77, 46, 36.5, 29; LC-MS: found, m/z: 161.13, calculated, m/z: 161.12;

Adamantyl-1-isonitrile (4). Method b). Compound **4a** (9.4g, 0.05 mol) with tetrabutylammonium bromide (0.16g, 0.5 mmol) was diluted in 300 ml of dichloromethane and NaOH 50 % (115ml) and chloroform (9.5g, 0.08mol) were added. The mixture was stirred for 6 h at room temperature and afterwards the water (300 ml) was added. Organic phase was separated through the separation funnel, washed twice with water (2 x 150ml) and then the brine. It was dried over MgSO4 and concentrated in vacuum. The obtained residue was recrystallized from chloroform. The compound 9 was obtained 6.25g, (83%) yield.

General procedure for synthesis of Ugi product (5a-b) and dipeptides (5c-e) (Table 1)

To a solution of primary amine **1** (2 mmol) in 5 mL of ethanol was added aldehyde **2** successively and the mixture was stirred at room temperature for 1 h. Then acid **3** (2 mmol) was added, and stirring was continued for 20 min, afterwards the isonitrile 4 (2 mmol) was added and the reaction mixture was heating and stirring for 24 h at 40°C. The regular control of the reaction progress by TLC. From the reaction mixture pure compound **8** was separated by filtration and filtrate was diluted with CH_2Cl_2 and washed 1M $NaHSO_3$ and saturated $NaHCO_3$. Organic phase was separated through the separation funnel, washed twice with water (2 x 150ml) and then the brine. It was dried over MgSO4 and concentrated in vacuum. Compounds 5, 6, 7, 8 and 9 were separated by column chromatography.

Compound 5a, Yellowish crystal, 65%, R_f =0.52, m.p. 224-226°C decomposition. **IR** (cm^{-1})**:** 3254 3057, 2907 & 2848, 1629 & 1608; ^{1}H NMR: 15.93 (1H), 8.55 (1H), 7.54 (1H, d, j=8), 7.38 (1H, d, j=12), 7.28 (2H, t, j=12), 7.14 (1H, t, j=12), 6.98 (1H, t, j=16); 6.78 (3H, dd, j=12, j=16), 4.04 (3H, s), 2.07 (16H, m), 1.99 (6H, m, Ad), 1.76 (6H, m, Ad), 1.66 (3H, m, Ad), ^{13}CNMR: 164.78, 163.9, 163.23, 132.5, 129.26, 121.73, 120,81, 119.01, 118.03, 117.23, 116.94, 110.04, 104.37, 57.56, 52.50, 50.19, 40.67, 35.69, 31.08, 28.90, 28.48 Found, m/z: 591.3386 [M]+. $C_{38}H_{45}O_3N_2$. Calculated, m/z: 591.3455.

Compound 5b. Yellowish crystal, 63% R_f =0.42, m.p. <300 °C. IR (cm^{-1})**:** 3200, 3057, 2913 & 2852, 1650 & 1608; ^{1}H NMR: 8.56 (1H), 7.51 (1H, d, j=8), 7.38 (1H, d, j=12), 7.30 (1H, t, j=12), 7.14 (1H, t, j=12), 6.76 (1H, d, j=12), 4.85 (1H, m), 4.05 (3H, s), 2.08 (14H, m), 2.00 (6H, m, Ad), 1.77 (5H, m, Ad), 1.59 (12H, m, Ad), ^{13}CNMR: 177.39, 164.36, 144.27, 132.94, 129.69, 122.17, 121,25, 117.38, 110.48, 57.99, 52.94, 50.63, 42.98, 41.28, 36.13, 35.72, 31.52, 29.33, 29.22, 28.92 Found, m/z: 541.3339. $C_{35}H_{47}O_3N_2$. Calculated, m/z: 541.3668;

General procedure for synthesis of dipeptides (5c-e)

The synthesis was performed using the method described above by interaction of amino acids ethyl esters hydrochloride (2 mmol) in presence of TEA (2,4 mmol) with aldehyde (2 mmol), acid 3 (2mmol) and isonitrile 4 (2 mmol). Compounds 5, 6, 7 and 9 were separated and purified via column chromatography.

Compound 5c, Yellowish crystal, 55 % R_f =0.44, m.p. 140-142°C decomposition. IR (cm^{-1})**:** 3264, 3002, 2910 & 2850, 1741, 1663 &1623; ^{1}H NMR: 9.01 (1H), 8.49 (2H, d, j=8), 7.74 (2H, d, j=8), 7.61 (5H, d, j=8), 7.42 (1H, d, j=8), 5.06 (2H, s), 4.08 (2H, s), 3.98 (2H, m), 3.87 (1H, s), 2.60 (3H, m), 2.25 (3H, m), 1.89 (5H, m), 1.71 (5H, m), 1.18(3H, m); ^{13}CNMR: 170.38, 169.52, 160.66, 140.07, 126.49, 125.76, 125.61, 122.75, 120,89, 110.88, 110.35, 73.56, 61.66, 41.07, 39.38, 36.44, 34.06, 31.65, 28.11, 18.21, 14.08, 13.74; Found, m/z: 527.2784. $C_{32}H_{37}O_4N_3$. Calculated, m/z: 527.2703.

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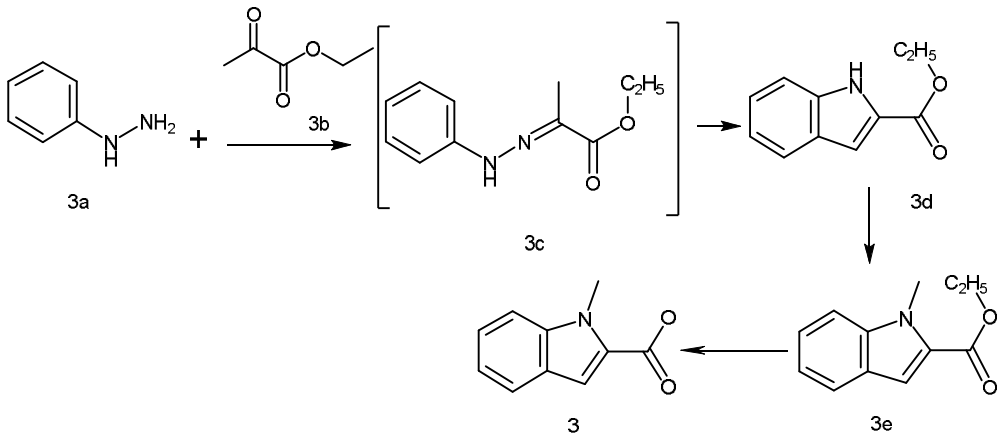
Compound 5d, Yellowish crystal, 53 % Rf =0.43, m.p. 173-176°C. IR (cm^{-1})**:** 3339, 3200, 3082, 2973, 2922 & 2877, 1744, 1680 &1663; ^{1}H NMR: 11.89 (1H), 8.50 (1H, d, j=12), 7.95 (1H, d, j=4), 7.69 (2H, d, j=8), 7.49 (2H, d, j=8), 7.29 (3H,m), 7.08 (1H, m), 5.06 (1H, s), 4.05 (3H, s), 3.86 (3H, m), 2.29 (6H, m), 2.23 (2H, m), 2.08 (3H, m), 1.67 (3H, m), 1.56(5H, m); 1.18(6H, m); ^{13}CNMR: 169.46, 169.09, 160.52, 137.44, 126.60, 124.78, 122.03, 120.19, 112.53, 108.63, 77.50, 60.35, 50.85, 40.52, 34.99, 30.37, 28.22, 18.56, 16.93, 13.94; Found, m/z: 569.3287. $C_{35}H_{43}O_4N_3$. Calculated, m/z: 569.3254.

Compound 5e. Yellowish crystal, 57 % Rf =0.42, m.p. 145-147°C. IR (cm^{-1})**:** 3333, 3264, 3084, 2956, 2932 & 2871, 1751, 1697 &1667; ^{1}H NMR: 11.92 (1H), 8.56 (1H, d, j=12), 7.68 (2H, d, j=8), 7.48 (2H, d, j=8), 7.28 (4H, d, j=8), 7.09 (1H,m), 5.22 (2H, s), 4.08 (3H, s), 3.88 (3H, m), 1.88 (3H, m), 1.74 (4H, m), 1.48 (3H, m), 1.20 (5H, m), 1.18(5H, m); ^{13}CNMR: 169.85, 169.48, 160.39, 137.44, 126.63, 124.82, 122.07, 120.21, 112.55, 108.66, 73.17, 60.40, 40.52, 33.68, 29.48, 17.64, 13.95, 13.58; Found, m/z: 541.2949 [M]+. $C_{35}H_{43}O_4N_3$. Calculated, m/z: 541.2941.

RESULTS AND DISCUSSION

Target compounds, N-methyl-1H-indole-2-carboxylic acid (**3)** was synthesis by the Fisher indolization reaction according to the scheme **2** [31, 32]. The interaction of a phenyl hydrazine (3a) with an ethyl pyruvate (3b) in glacial acetic acid at high temperature initially forms intermediate ethyl 2-(2-phenylhydrazono)-propanoate (3c) with a high yield. The formation of ethyl 1H-indole-2-carboxylate (3d) in excellent yields was afforded by the cyclization of compound **3c** with the loss of ammonia in the presence of PPAEE (polyphosphoric acid ethyl ester). The compound **3d** was obtained by the interaction of ethyl 1H-indole-2-carboxylate (**3d**) with methyl iodide in the presence of KOH in DMSO in which hydrolysis in acid area desire N-methyl-1H-indole-2-carboxylic acid (**3**) with a high yield was obtained [33-36].

Scheme 2: Synthesis of 1-methyl-1H-indole-2-carboxylic acid via Fisher idolization reaction:



The second starting materials for the Ugi-4CRs is very important due to the presence of an isocyano group with ambiphilic reactivity, which enables them to react with electrophiles, nucleophiles and radicals. The desire adamantyl-1-isonitrile was synthesized from adamantane-1-amine hydrochloride (4a) in two different ways (I and II) according to the scheme 3. According to the method **I** the reaction is in two steps. In the first step of reaction N-(adamantan-1-yl)-formamide **(4)** with in high yield is obtained by the interaction of compound 4a with ethyl format **(4b)** in presence of TEA and p-toluenesulfonic acid monohydrate in the area of excess ethyl format.

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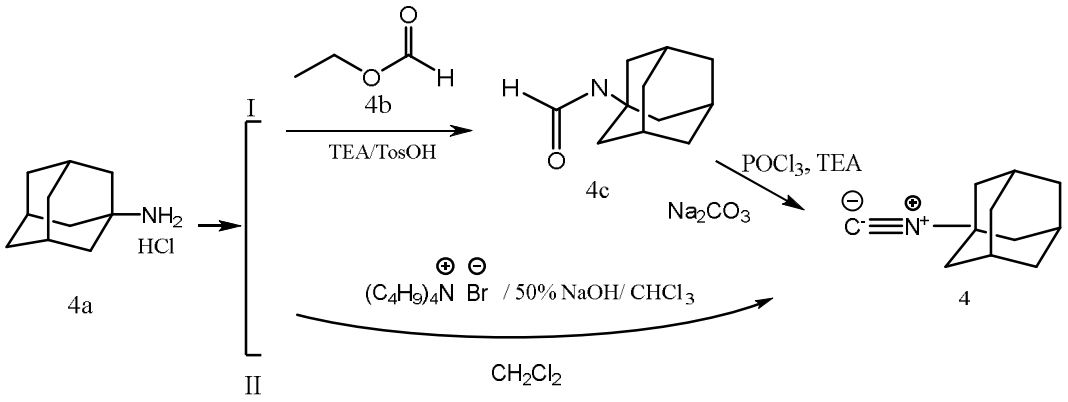
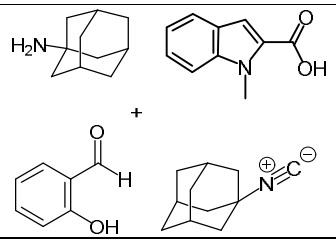
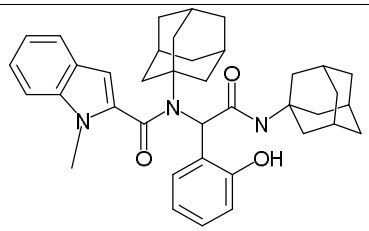
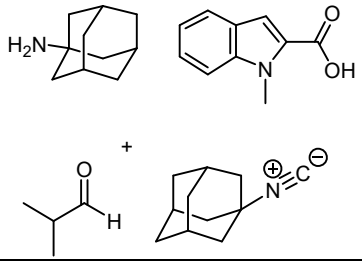
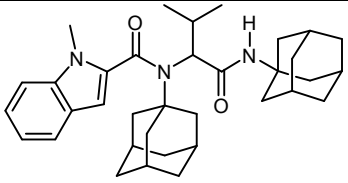
Scheme 3: Synthesis of adamantyl-1-isonitrile



In the second step, equimolar ration of $POCl_3$ was added to the solution of compound **4c** in CH_2Cl_2 in presence of TEA. After 1 hour of stirring the reaction mixture was processing with aqueous Na_2CO_3 and extracted with CH_2Cl_2. Organic layer was concentrated and compound **4** with **65 %** yield was obtained. Also compound **4** with 85% yield was obtained by the method **II**. The interaction of compound **4a** with equimolar ratio of $CHCl_3$ in the presence of tetrabutylammoniums bromide salt and 3 tames more equimolar ration of aqueous NaOH in CH_2Cl_2 was carried out at room temperature and adamantyl-1-isonitrile **(4)** with in high yield was obtained.

Ugi four component reaction were conducted between in equimolar ration of amine, aldehyde, N-methyl-1H-indole-2-carboxylic acid and adamatyl-1-isonitrile in methanol area at 40°C temperature and desire products (**5a-e**) were obtained in 53-65% yield (Table 1). By flash chromatography also were separated some side products -6, 7, 8 and 9 according to scheme 4.

Table 1:N-methyl-1H-Indole and adamantane containing Ugi product and dipeptides synthesized via Ugi-4CR

Entry	Substrate	Ugi product	Yield, %
5a			65
5b			63

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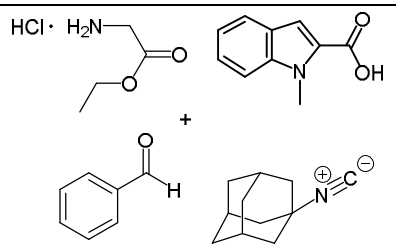
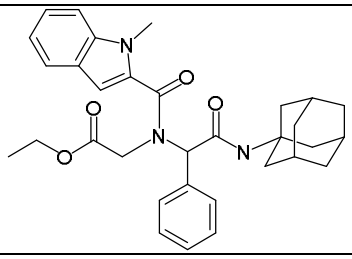
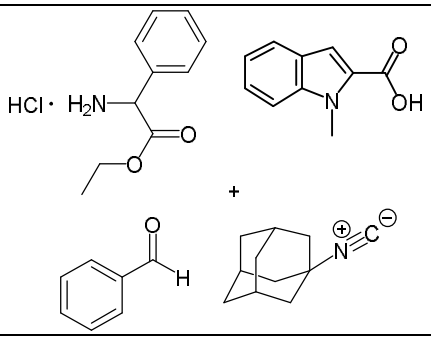
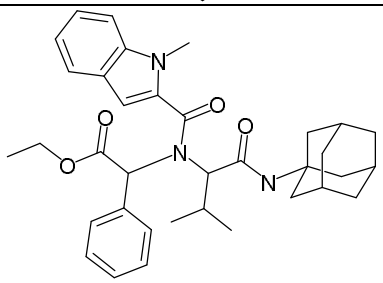
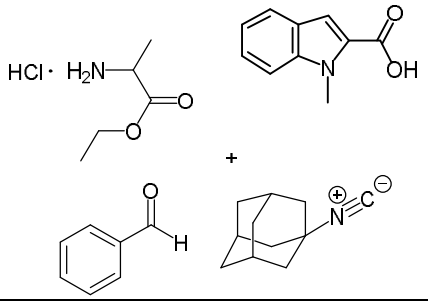
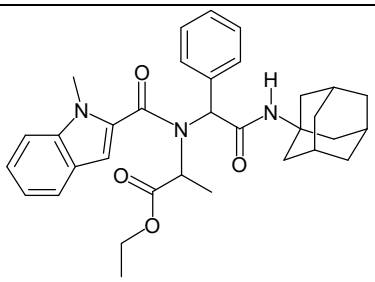
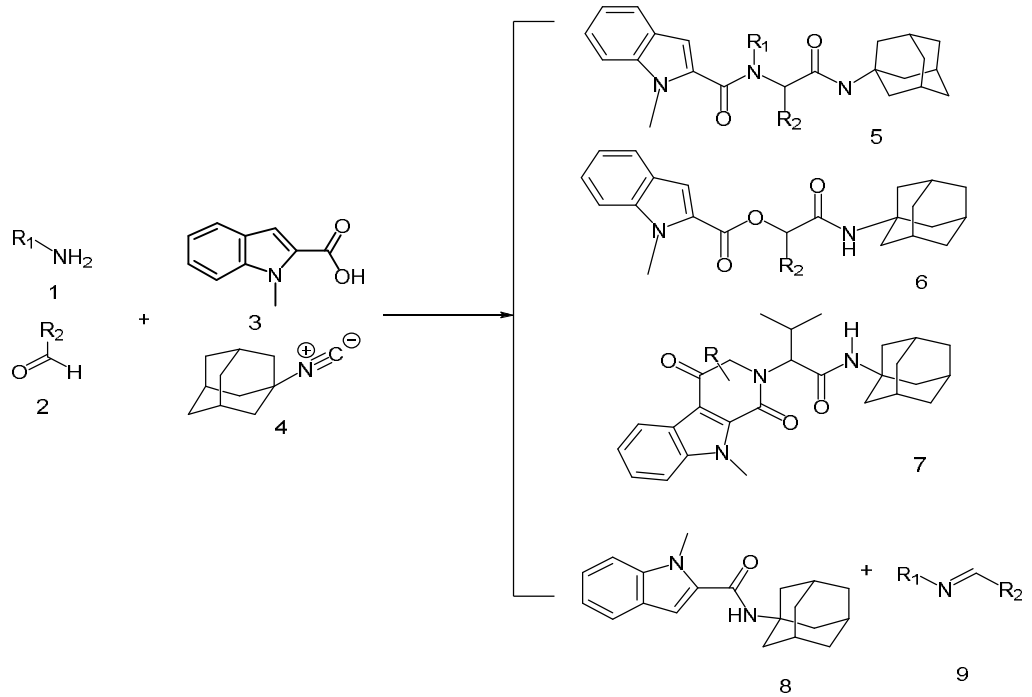
5c			55
5d			53
5e			57

Scheme 4: The obtained derivatives via Ugi-4CRs



R_1=Ad, R_1 =-$CH_2COOC_2H_5$, -$CH(CH_3)COOC_2H_5$, -$CH(C_6H_5)COOC_2H_5$; R_2 =-C_6H_4OH, -i-C_3H_7, -C_6H_5;

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For Ugi-4CR was established the feasibility of the strategy and was optimized the reaction conditions including temperature, solvents (Table 2) and the influence of bases during of using amino acids esters hydrochloride (Table 3). It was found that when the reaction was carried out in methanol at room temperature the compound 5a was obtained 52 % and as a side product were isolated Passerine product (6) (10%) and Amin amide (8) (35 %) even after 24 h (Table 2, entry 1). At 40°C temperature the amount of the same products was 65, 25 and 9% (Table 2, entry 2). At 55°C temperature the yield of desire product 5a was less than in entry 1 and 2 and among the side product some colored tar was formed (Table 2, entry 3). This model of reaction was examined in CH_2Cl_2 too, it was found that in room temperature only Amin amide (8) and Schiff bases (9) around 72% were formed even after 24 h (Table 2, entry 4).

Table 2: Optimization of reaction conditions for the synthesis of indole-adamantane containing Ugi product.

entry	solvent	time	t°	Yield %		
				5	6	8/9
1	MeOH	24	r.t	52	10	35
2	MeOH	24	40	65	25	9
3	MeOH	24	55	60	23	7
4	Cl_2CH_2	24	Rt	trace	trace	72

Then, we carried out this model reaction by employing of amino acids hydrochloride with bases (Table 3, entries 5-8). In the presence of TEA, the mixture of desired dipeptides (5) and cyclized product (7) were obtained. We reasoned that addition of base not only neutralized the amino acids esters hydrochloride, but also accelerated the cyclization step. It was found that when the reaction was carried out in methanol in presence of TEA 1.2 molar ration at room temperature dipeptides (5) and cyclized product (7) about ~41-35 % was obtained (Table 2, entry 5). At 40°C the yield of desire product was 57% and for cyclized product was formed 39% yield. But at 55°C the yield of compound 5 and 7 were less and addition the colored tar was formed.

Table 3: Optimization of reaction conditions for the synthesis of indole-adamantane containing dipeptides

entry	solvent	Base (molar ration) 1:1.2	time	t°	Yield %		
					5	7	8/9
5	MeOH	TEA	24	r.t	41	35	20
6	MeOH	TEA	24	40	57	39	2
7	MeOH	TEA	24	55	48	43	3
8	Cl_2CH_2	TEA	24	rt	10	15	60

To see the effect of solvents, we examined our reaction in methanol and CH_2Cl_2. When the reaction solvent was changed from MeOH to CH_2Cl_2, there was a significant decrease in the yield of isolated products (Table 2, entries 4; table 3, entry 8). This suggests that between MeOH and CH_2Cl_2 , MeOH is the favored solvent system.

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