საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 11, №3, 2017
BULLETIN OF THE GEORGIAN NATIONAL ACADEMY OF SCIENCES, vol. 11, no. 3, 2017

Organic Chemistry

Synthesis of 5 (6)-Hydroxymethyl-, 5 (6)-Carboxy-2-(1–adamantyl)benzimidazole, Ethyl Carboxylate and some Amide Derivatives

Marina Soselia[*], Ivane Gogolashvili[*], Davit Zurabishvili[*], Shota Samsoniya[**]

** Department of Chemistry, Faculty of Exact and Natural Sciences, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia*
*** Academy Member, Department of Exact and Natural Sciences , Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia*

ABSTRACT. 5 (6)-R-2-(1-Adamantyl)benzimidazole derivatives were synthesized (R=CH_2OH, COOH, COOEt, $CONH_2$, CONHAd, CONH(N-Me-piperazinyl). The synthesis of ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate was fulfilled by three methods: a) via one-step esterification-cyclization of 4-amino-3-(1-adamantanecarboxamido) benzoic acid, b) using 4 synthetic steps started from coupling of 1-adamantane carboxylic acid chloride with ethyl 4-aminobenzoate and further nitration, reduction and cyclization of obtained amide, g) direct esterification of 5 (6)-carboxy-2-(1–adamantyl) benzimidazole. 5 (6)-carboxy-2-(1–adamantyl) benzimidazole was synthesized via cyclization of 3,4-diaminobenzoic acid's adamantoylation product. Coupling of the resulted acid with some amines gave corresponding amides and reduction of carboxylic group by $LiAlH_4$ - 5(6)-hydroxymethyl-2-(1–adamantyl) benzimidazole. © *2017 Bull. Georg. Natl. Acad. Sci.*

Key words: benzimidazole, adamantane, organic synthesis, cyclization reaction, amides, esters

Adamantane derivatives are distinguished with wide spectrum of biological activity. Medications containing this unique bulk core are used for the prophylaxis and treatment of various viral diseases [1], parkinsonism and other neurodegenerative disorders [2] and type 2 diabetes mellitus [3] since its discovery in 1933. Many adamantyl-based compounds are studied as potential anti-hypertensive and anti-inflammatory, anticancer, anti-malaria and tuberculosis agents as well as a therapeutics for neurological and iron overload conditions [4].

The bioactivity of adamantane-containing compounds originates from the bulk and high lipophilic wireframe structure of adamantane core. Incorporation of the adamantane fragment in the molecule enhance lipophilicity and stability of the drugs, improves their pharmacokinetics, helps poorly absorbed drugs to penetrate into the lipid bi layer of the cell

membrane and in most cases decreases the toxicity of the molecule [5, 6].

In direction of searching the new biological active molecules the aim of our work was the synthesis of adamantane-core containing some benzimidazole derivatives via involving obtaining potent bioactive amides in synthetic steps. Literature survey conformed that plenty of benzimidazole derivatives containing ester group on 5 position at benzimidazole ring revealed actimicrobial [7], antileukemic [8], potent anti-breast cancer [9], Antituberculosis [10] activity, while amide derivatives of adamantane carboxylic acid are good inhibitors of the soluble epoxide hydrolase [11], also act as anti-inflammatory [12] and anti-microbal [13] agents.

In presented article was studied the synthesis of ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate by two ways – via direct one-step esterification-cyclization of 4-amino-3-(1-adamantanecarboxamido) benzoic acid **1** in ethanol in the presence of thionyl chloride according to scheme 1 and using 5 synthetic steps as depicted in scheme 2. After esterification of para-aminobenzoic acid **3**, incorporation of adamantane core was fulfilled by conversion of 1-adamantane carboxylic acid to acyl anhydride by heating at 40-50°C in $SOCl_2$ and coupling with resulted ethyl 4-aminobenzoate **4** in CH_2Cl_2 in the presence of Et_3N at room temperature. Nitration reaction of obtained amide **5** by nitrating agent (65% HNO_3 / 98% H_2SO_4, 1 / 1.2) in acetic acid / acetic anhydride mixture gave the nitro product **6**. After reduction of nitro group by molecular H_2 on Pd/C in EtOH at room temperature, the corresponding aminoamide **7** was isolated. The cyclization of compound **7** in toluene in the presence of acetic acid gave the desired benzimidazole **2**.

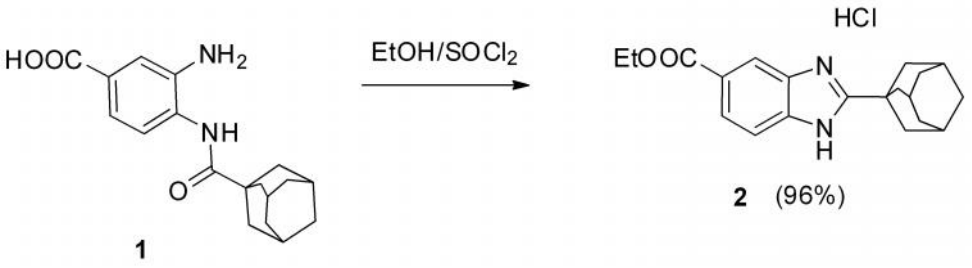
The synthetic pathway of 5(6)-carboxy-2-(1-adamantyl)benzimidazole **8** and some transformations on carboxylic group are outlined in Scheme 3. The coupling of 1-adamantane carboxylic acid with 3,4-diaminobenzoic acid gave the mixture of three isomers which were refluxed, without separation, in toluene in the presence of trifluoroacetic acid and gave benzimidazole **8**. The latter one was converted to compound **9** by reduction of carboxylic group using $LiAlH_4$ in Et_2O. Esterification of 5(6)-carboxy-2-(1-adamantyl)benzimidazole **8** by ethyl alcohol gave compounds **2**. Finally, after conversion of carboxylic group into the acyl chloride using thionyl chloride and further coupling with some amines in dioxane new amide derivatives **10**, **11** and **12** were obtained.

In order to obtain potent biological active compound, new derivatives of 5(6)-R-2-(1-adamantyl) benzimidazole were synthesized. Since ester group is more active than carboxy one in biological point of view, the first synthetic pathway included preparation of ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate in one-step and also by multiple step synthesis and new ethyl ester derivatives were obtained. The second synthetic route provided the synthesis of 5(6)-carboxy-2-(1-adamantyl)benzimidazole and its ethyl ester and some amide derivatives, while reduction of carboxylic group went to 5(6)-hydroxymethyl-2-(1-adamantyl)benzimidazole. Hydroxymethyl group in the final product is perspective for further transformation and the synthesis of new benzimidazole based biological active derivatives.

Experimental Part

TLC was performed on Merck aluminium plates coated with SiO_2 F_{254}. Preparative column chromatography was carried out using Merck SiO_2 (35–70 μm, type 60 Å) with n-hexane and EtOAc as eluents. ^1H- and ^{13}C-NMR spectra were recorded on Bruker Avance DRX 500 instruments at 23°C in $CDCl_3$. Multiplicities of carbon signals were determined with DEPT experiments. MS and HRMS spectra were obtained with a Finnigan MAT95 (EI) and a Waters Q-TOF Premier (ESI, all in positive mode) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. Elemental analyses were measured with a Euro EA-CHNS instrument from HEKAtech. Melting points of crystalline compounds were determined on

Scheme 1. The synthesis of ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate via one-step esterification-cyclization reactions.



a Gallenkamp Melting Point Apparatus and are uncorrected.

Reagents and starting materials were purchased from common commercial suppliers and used without further purification. Solvents were purified and dried following standard procedure.

Ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate (2).

Method A (scheme 1). The suspension of 0.20 g (1.24 mmol) 4-(adamantan-1-carboxamido)-3-aminobenzoic acid **1** and 1.4 ml $SOCl_2$ in ethanol was refluxed for 3 h. Afterwards, the solvent was evaporated and the residue was washed with hexane and dried. 0.43 g (1.19 mmol) white crystals of compound **2** as hydrochloric salt were obtained in 96% yield.

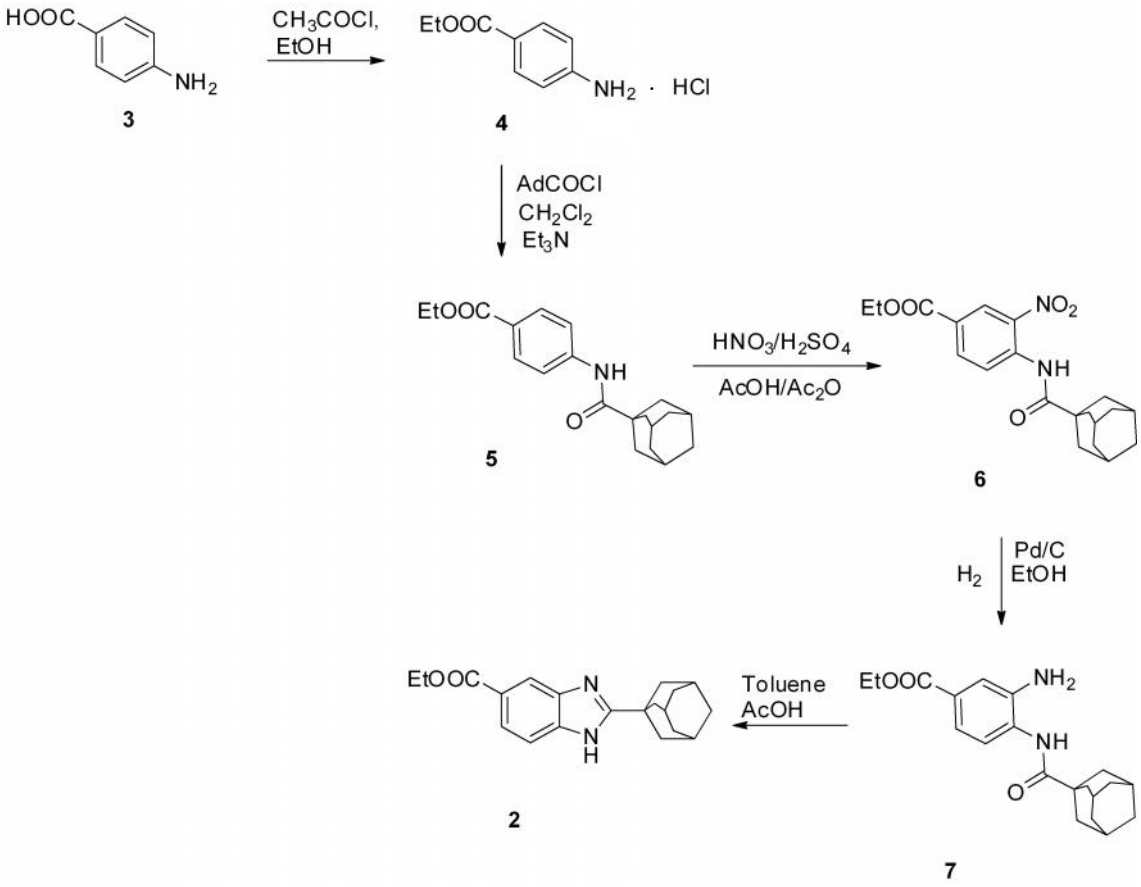
Method B (scheme 2). A mixture of 0.21 g (0.61 mmol) ethyl 3-(adamantane-1-carboxamido)-4-aminobenzoate **7** and 0.30 ml (100 %, 5.20 mmol) acetic acid in toluene (10 ml) was refluxed for 11 h. The reaction mixture was cooled and the precipitate was filtered off, washed with acetone and dried to afford the title compound **2** (0.17 g, 0.52 mmol, 84 %) as colorless solid.

Method C (scheme 3). In a solution of 1.50 g (5.00 mmol) compound **8** in absolute ethanol (50 ml) was added drop wise 3.6 ml (50.00 mmol) of $SOCl_2$ over 20 min and the reaction mixture was refluxed for 3 h. The crude reaction mixture was then concentrated, treated with aqueous sat. $NaHCO_3$ solution and then extracted with EtOAc (150 ml, 3×50). The organic layer were combined, washed with brine, dried over anhydrous $MgSO_4$ and evaporated to dryness to obtain 1.31 g (4.00 mmol, 80%) of the compound **2** as colorless solid. T_{melt}.=246-248°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 12.32 (br, s, 1H), 7.98-8.22 (m, 1H), 7.78 (br, s, 1H), 7.40-7.65 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.06-2.12 (m, 9H), 1.75-1.84 (m, 6H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (DMSO-d_6, 125 MHz), δ, ppm: 165.24 (C), 142.70 (C), 141.88 (C), 137.79 (C), 122.56 (C), 121.96 (CH), 119.95 (CH), 117.73 (CH), 60.05 (CH_2), 40.58 (3 CH_2), 36.03 (3 CH_2), 34.98 (C), 27.59 (3 CH), 14.09 (CH_3). IR spectrum, ν, cm^{-1}: 3300, 2899, 2848, 1696, 1622, 1519. MS (ESI. pos. Mode): calcd. 347.1735 (for $C_{20}H_{24}N_2NaO_2$), found 347.2493 [M + Na+]. Anal. For $C_{20}H_{24}N_2O_2$ (324.42): calcd., %: C 74.04, H 7.46, N 8.64; found C 73.67, H 7.55, N 8.78.

Ethyl 4-aminobenzoate hydrochloride (4). (CAS #: 23239-88-5). Acetyl chloride (1.43 g, 18.00 mmol) was dropwise added to cold (ice-bath) ethanol (50 ml) with stirring. Ten minutes later, 0.82 g (6.00 mmol) p-aminobenzoic acid was added and reaction mixture was refluxed for 5 h. Afterwards, the solvent was removed at reduced pressure and resulting methyl ester hydrochloride recrystallized from ethanol to give 1.10 g (91 %, 5.45 mmol) compound **4** as colorless crystals. T_{melt}.=183-185°C (ethanol), (lit.: 195°C [14]). ^{1}H NMR (300 MHz, Methanol-d_4), δ, ppm: 7.75 (d, J =8.5 Hz, 2H), 6.64 (d, J = 8.5 Hz, 2H), 4.41 (q, J = 7.1, 2H), 1.41 (t, J = 7.1, 3H).

Ethyl 4-(adamantane-1-carboxamido)benzoate (5). 1-Adamantanecarboxylic acid (0.54 g, 3.00 mmol) was dissolved in 5 ml of $SOCl_2$ and the mixture was refluxed for 1 h. The $SOCl_2$ was removed in *vacuo*. The crude acid chloride was dissolved in CH_2Cl_2 (5 ml) and then added dropwise into a solution of compound **4** (0.50 g, 3.00 mmol) and triethylamine (0.30 g,

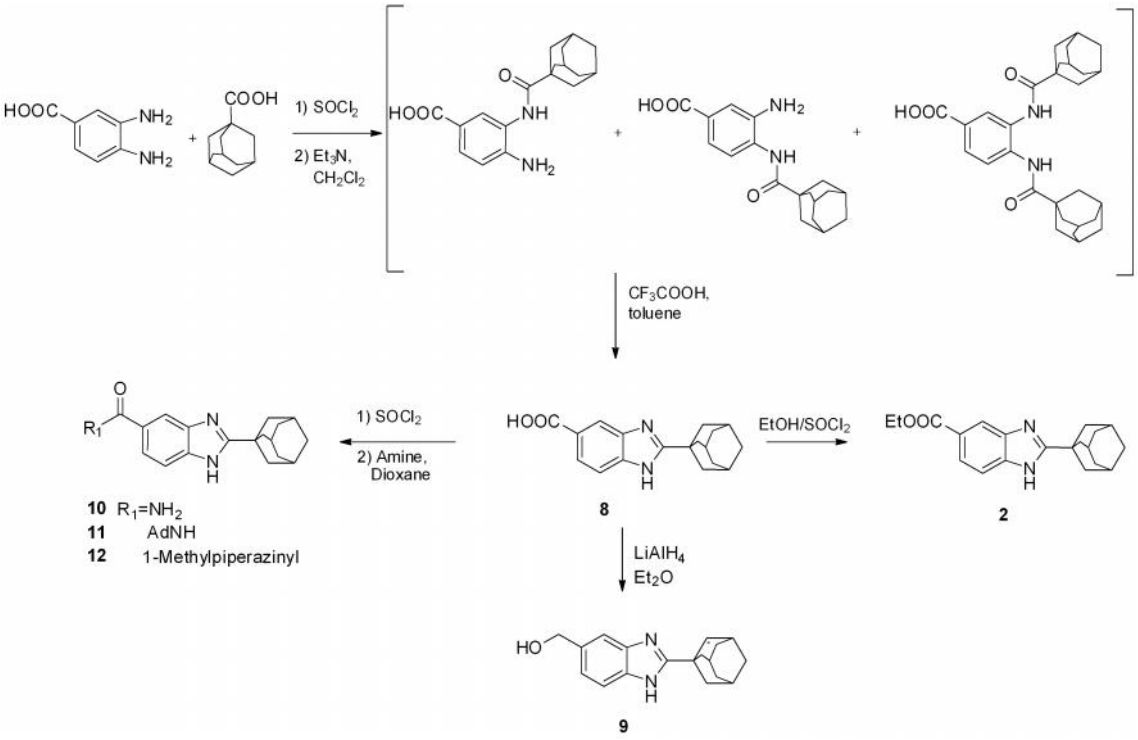
Scheme 2. The synthesis pathway of ethyl 2-(1-adamantyl)-1H-benzimidazole-5-carboxylate via 5 synthetic steps.



3.00 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 2 h at room temperature. Afterwards, it was poured into water (15 ml). After separation of two layers, the organic part was dried over anhydrous Na_2SO_4, filtered and evaporated in *vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc / hexane 1 / 3, R_f = 0.80) to give the title compound **5** (0.70 g, 2.13 mmol, 71%) as colorless crystals. T_{melt}.=188-190°C (Lit.: 186-188 [15], 192°C [11]). ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.93 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.38 (s,br, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.00-2.09 (m, 3H), 1.84-1.98 (m, 6H), 1.60-1.78 (m, 6H), 1.32 (t, J = 7.1 Hz, 3H).

Ethyl 4-(adamantane-1-carboxamido)-3-nitrobenzoate (6). A nitrating agent consisting of HNO_3 (65%, 0.15 ml, 3.45 mmol) and H_2SO_4 (98%, 0.22 ml, 4.10 mmol) was added dropwise over 15 min to an ice-cooled suspension of 0.49 g (1.50 mmol) compound **5** in the mixture of acetic acid (2 ml) and acetic anhydride (1 ml). After 30 min cooling the reaction mixture was stirred for 3 h at room temperature. Subsequently, it was poured into ice-water (50 ml) and the yellow participate was filtered off and washed with water (100 ml). The crude product was purified by chromatography (silica gel, hexane / EtOAc 8 / 1, R_f = 0.65) to yield 0.40 g (1.10 mmol, 72 %) of the title compound **6** as yellow solid. T_{melt}.=121-123°C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 10.90 (s, 1H), 9.00 (d, J = 8.9 Hz, 1H), 8.91 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 4.44 (q, J = 6.8 Hz, 2H), 2.12-2.21 (m, 3H), 1.97-2.09 (m, 6H), 1.75-1.91 (m, 6H), 1.45 (t, J = 6.9 Hz, 3H) ppm. ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz), δ, ppm: 177.55 (C), 164.25 (C), 138.77 (C), 136.43 (CH), 135.56 (C), 127.46 (CH), 124.93 (C), 121.68 (CH), 61.65 (CH_2), 42.68 (CH), 39.04 (3 CH_2), 36.26 (3 CH_2), 27.99 (3 CH), 14.27 (CH_3) ppm. IR spectrum, ν, cm^{-1}: 3354, 2926, 2849, 2353, 2323. MS (ESI. pos. Mode): calcd. 395.1583 (for $C_{20}H_{24}N_2NaO_5$), found 395.2888 [M + Na^+]. Anal. For $C_{20}H_{24}N_2O_5$

Scheme 3. Preparation of 5(6)-carboxy-2-(1-adamantyl)benzimidazole and its further transformations.



(372.41): calcd., %: C 64.60, H 6.50, N 7.52; found C 64.85, H 6.64, N 7.77.

Ethyl 4-(adamantane-1-carboxamido)-3-aminobenzoate (7). 0.34 g (0.90 mmol) of compound **6** and 0.04 g (10% Pd) Pd/C in ethanol (30 ml) were stirred under hydrogen atmosphere for 24 h at room temperature. The mixture was then filtered and the filtrate was evaporated in *vacuo*. The crude product was recrystallized from ethanol (10 ml) to give 0.21 g (0.61 mmol, 68%) the title compound **7** as colorless solid. T_{melt}.=286-288°C. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 7.58-7.76 (m, 3 H), 4.35 (q, J = 7.1 Hz, 2H), 1.86-2.24 (m, 9 H), 1.62-1.86 (m, 6 H), 1.39 (t, J = 7.1 Hz, 3 H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz), δ, ppm: 176.78 (C), 166.34 (C), 139.23 (C), 129.85 (C), 128.09 (C), 123.78 (CH), 121.63 (CH), 119.81 (CH), 60.90 (CH_2), 41.63 (C), 39.39 (3 CH_2), 36.46 (3 CH_2), 28.14 (3 CH), 14.31 (CH_3). IR spectrum, ν, cm^{-1}: 3426, 3363, 3289, 2903, 2849, 2321. MS (ESI. pos. Mode): calcd. 365.1841 (for $C_{20}H_{26}N_2NaO_3$), found 366.1063 [M + Na^+]. Anal. For $C_{20}H_{26}N_2O_3$ (342.43): calcd., %: C 70.15, H 7.65, N 8.18; found C 70.33, H 7.83, N 8.39.

5(6)-Carboxy-2-(1–adamantyl)benzimidazole (8). 2.16 g (12.00 mmol) Adamantane-1-carboxylic acid in $SOCl_2$ (4 ml) was heated for 30 min at 50°C. The $SOCl_2$ was removed in *vacuo* and the crude acid chloride was dissolved in CH_2Cl_2 (30 ml) and then added dropwise over 1 h into a solution of 1.83 g (12.00 mmol) 3,4-diaminobenzoic acid and 3 ml triethylamine (20.00 mmol) in CH_2Cl_2 (200 ml). The reaction mixture was stirred for 3 h at room temperature. Subsequently, water (30 ml) was added and resulted two layers were separated. The organic part was washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated in *vacuo*. 2.61 g residue was dissolved in the mixture of CF_3COOH (5 ml) and toluene (35 ml) refluxed for 9 h. The resulted precipitate was filtered, washed with water and hexane and dried. 1.60 g (5.40 mmol) colorless crystals were obtained. T_{melt}.=298-300°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.66 (br., 1H), 8.19 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 2.0 – 1.90 (m, 9H), 1.78 – 1.70 (m, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6), δ, ppm: 167.45 (C), 163.41 (C), 138.66 (C), 135.39 (C), 125.30 (C), 124.11 (CH), 116.10 (CH),

114.04 (CH), 35.78 (3 CH_2), 35.16 (C), 27.43 (3 CH). IR spectrum, ν, cm^{-1}: 2904, 2847, 1690, 1625, 1491.

5(6)-Hydroxymethyl-2-(1-adamantyl) benzimidazole (9). 0.20 g (0.67 mmol) compound **8** was added slowly to a stirred suspension of 0.19 g lithium aluminum hydride in dry Et_2O (80 ml). The reaction mixture was refluxed for 6 h. After cooling, KOH (3 ml, 15%) and water (2 ml) were added slowly and the mixture was further stirred for 24 h. Afterwards, the white precipitate of aluminum salt was filtered off and washed with mixture of EtOAc and Et_2O. The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resulted crude product was purified by column chromatography (SiO_2, EtOAc / hexane, 2 / 1, R_f = 0.55) and yielded 0.10 g (0.35 mmol, 53%) as beige solid. T_{melt}.=138-140°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: (two tautomers), 11.94 (br, s, 1H), 9.00 (s, 1H), 8.95 (s, 1H), 7.81 – 7.55 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 8.2, 1.9 Hz, 1H), 7.05 (d, J = 8.2, 1H), 5.21 (t, J = 5.7, 1H), 5.07 (t, J = 5.7, 1H), 4.55 (d, J = 5.5, 2H), 4.46 (d, J = 5.5, 2H), 2.10–1.99 (m, 6H), 1.92-1.83 (m, 12 H), 1.78-1.63 (m, 12 H). ^{13}C {^{1}H} NMR (DMSO-d_6, 125 MHz), δ, ppm: (two tautomers) 139.55 (C), 139.52 (C), 132.32 (C), 131.63 (C), 131.50 (C), 130.92 (C), 130.83 (C), 129.50(C), 129.46 (C), 128.57 (C), 125.04 (C), 125.00 (CH), 123.10 (CH). 122.99 (CH), 67.31 (CH_2), 62.26 (CH_2), 40.76 (3 CH), 40.60 (3 CH), 38.73 (C), 38.00 (C), 36.09 (3 CH), 35.95 (3 CH), 27.64 (3 CH), 27.53 (3 CH). IR spectrum, ν, cm^{-1}: 3440, 3286, 2904, 2848, 1653, 1608, 1519. HR-MS (ESI. pos. Mode): calcd. 283.1810 (for $C_{18}H_{23}N_2O$), found 283.1812 [M + H^+].

General method of preparation of amides 10, 11 and 12. 0.50 g (0.50 mmol) compound **8** in 2 ml $SOCl_2$ was refluxed for 1 h. Afterwards, Thionyl chloride was evaporated *in vacuo* and the yellow residue was dissolved in dioxane and amine (1.00 mmol) was added. Reaction mixture was stirred at room temperature for 3 h. Then, water (30 ml) was added and resulted suspension was extracted with EtOAc (30 ml×3). The organic layer was washed with water, dried over Na_2SO_4, filtered and evaporated. The resulted residue was recrystallized from hexane.

5 (6)-Carboxamido-2-(1-adamantyl)benzimidazole 10. T_{melt}.=170-172°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: (two tautomers), 12.31 (br, s, 2H), 8.06 (s, 2H), 7.89 (s, 1H), 7.80-7.66 (m, 2H), 7.62-7.31 (m, 2H), 7.19 (s, 1H), 2.17-1.77 (m, 18H), 1.82-1.70 (m, 12H). ^{13}C {^{1}H} NMR (DMSO-d_6, 125 MHz), δ, ppm: (two tautomers) 168.48 (2 C), 156.47 (C), 153.94 (C), 141.93 (C), 139, 97 (C), 133.03 (C), 131.51 (C), 128.58 (C), 127.34 (C), 121.09 (CH), 120.98 (CH), 118.06 (2 CH), 111.13 (2 CH), 41.17 (6 CH_2), 36.59 (6 CH_2), 35.53 (2 C), 28.14 (6 CH_2). IR spectrum, ν, cm^{-1}: 3340, 3185, 2923, 2852, 1658. HR-MS (ESI. pos. Mode): calcd. 296.1763 (for $C_{18}H_{22}N_3O$), found 296.1717 [M + H^+].

N-(1-Adamantyl)-2-(1-adamantyl)-1H-benzimidazole-5 (6)-carboxamide 11. T_{melt}.=318-320°C, ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 7.92 (d, J = 8.6 Hz, 1H), 7.89 (s, 1H), 7.77 (d, J = 8.5 Hz, 1H), 5.76 (s, 1H), 2.15 – 2.05 (m, 15H), 1.8 – 1.75 (m, 15H). ^{13}C {^{1}H} NMR (DMSO-d_6, 125 MHz), δ, ppm: 165.34 (C), 161.34 (C), 151.84 (C), 126.03 (C), 124.59 (C), 119.09 (CH), 113.41 (CH), 103.47 (CH), 40.86 (3 CH_2), 36.09 (C), 35.42 (C), 35.13 (6 CH_2), 28.91 (3 CH_2), 28.31 (6 CH_2).

IR spectrum, ν, cm^{-1}: 3367, 3072, 3050, 2904, 2848, 1632. HR-MS (ESI. pos. Mode): calcd. 430.2858 (for $C_{28}H_{36}N_3O$), found 430.2850 [M + H^+].

5 (6)-(N-Methylpiperazine) carboxamido-2-(1-adamantyl) benzimidazole 12. T_{melt}.=244-246°C ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 10.90 (br, s, 1H), 7.59 (br, s, 2H), 7.17 (d, J = 8.08, 1H), 3.95-3.45 (m, 4H), 2.55-2.34 (m, 4H), 2.31 (s, 3H), 2.07-1.99 (m, 9H), 1.79-1.70 (m, 6H). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz), δ, ppm: 164.29 (C), 129.47 (C), 128.60 (2 C), 121.02 (C), 120.92 (CH), 117.71 (CH), 116. 04 (CH), 55.02 (2 CH_2), 54.90 (CH_3), 45.93 (2 CH_2), 41.09 (3 CH_2), 36.43 (3 CH_2), 35.41(C), 28.12 (3 CH_2). IR spectrum, ν, cm^{-1}: 3429, 2923, 2850, 1724, 1611. HR-MS (ESI. pos. Mode): calcd. 379.2498 (for $C_{23}H_{31}N_4O$), found 379.2429 [M + H^+].

Acknowledgement.

This work was supported by Shota Rustaveli National Scientific Foundation PhD scholarships: "PhDF2016_155" and grant FR/154/6-420/13.

ორგანული ქიმია

5(6)-ჰიდროქსიმეთილ-, 5(6)-კარბოქსი-2-(1–ადამანტილ)ბენზიმიდაზოლის, მისი ეთილ კარბოქსილატის და ზოგიერთი ამიდის სინთეზი

მ. სოსელია*, ი. გოგოლაშვილი*, დ. ზურაბიშვილი*, შ. სამსონია**

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

სინთეზირებულ იქნა 5 (6)-R-2-(1-ადამანტილ) ბენზიმიდაზოლის წარმოებულები (R= CH_2OH, COOH, COOEt, $CONH_2$, CONHAd, CONH(N-Me-piperazinyl). ეთილ 2-(1-ადამანტილ)-1H-ბენზიმიდაზოლ-5-კარბოქსილატი სინთეზი განხორციელდა სამი მეთოდით: ა) 4-ამინო-3-(1-ადამანტანკარბოქსამიდო) ბენზოის მჟავას ერთდროული ეთერიფიკაცია-ციკლიზაციის გზით, ბ) ოთხსაფეხურიანი სინთეზის გავლით დაწყებული ადამანტან-1-კარბონმჟავას ქლორანჰიდრიდის კონდენსაციით ეთილ 4-ამინობენზოის მჟავასთან და მიღებული ამიდის შემდგომი ნიტრირების, აღდგენის და ციკლიზაციით, გ) 5 (6)-კარბოქსი-2-(1–ადამანტილ) ბენზიმიდაზოლის პირდაპირ ესთერიფიკაციით. 5 (6)-კარბოქსი-2-(1–ადამანტილ) ბენზიმიდაზოლი სინთეზირებულ იქნა 3,4-დიამინობენზოის მჟავას ადამანტოილირებით მიღებული პროდუქტების ციკლიზაციით. მიღებული მჟავას კონდენსაციით ზოგიერთ ამინთან გამოყოფილ იქნა შესაბამისი ამიდები, ხოლო კარბოქსილის ჯგუფის $LiAlH_4$-ით აღდგენით - 5 (6)-ჰიდროქსიმეთილ-2-(1–ადამანტილ) ბენზიმიდაზოლი.

REFERENCES

1. Spasov A. A., Khamidovaf T. V., Bugaeva L. I., Morozov I. S. (2000) Adamantane derivatives: pharmacological and toxicological properties. *Pharm. Chem. J.* **34**, 1: 1-7.
2. Morozov I. S., Ivanova I. A., Lukicheva T. A. (2001) Actoprotector and adaptogen properties of adamantane derivatives. *Pharm. Chem. J.* **35**, 5: 235-238.
3. Zettl H., Schubert-Zsilavecz M., Steinhilber D. (2010) Medicinal chemistry of incretin mimetics and DPP-4 inhibitors. *Chem. Med. Chem*. **5:** 179-185.
4. Liu J., Obando D., Liao V., Lifa T., Codd R. (2011) The many faces of the adamantyl group in drug design. *Euro. J. Med. Chem*. **46**: 1949-1963.
5. Lamoureux G., Artavia G. (2010) Use of the adamantane structure in medicinal chemistry. *Curr. Med. Chem*. **17**: 2967-2978.
6. Wanka L., Iqbalb Kh., Schreiner P. R. (2013) The lipophilic bullet hits the targets: medicinal chemistry of adamantane derivatives. *Chem Rev*. **113**, 5: 3516–3604.
7. Ozden S., Atabey D., Y1ld1z S., Goker H. (2005) Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1H-benzimidazole-5-carboxylates derivatives carrying amide or amidine groups. *Bioorg. & Med. Chem*. **13**: 1587–1597.

8. Thimme Gowda N.R., Kavitha C.V., Chiruvella K. K., Joy O., Rangappa K. S., Raghavan S. C. (2009) Synthesis and biological evaluation of novel 1-(4-methoxyphenethyl)-1h-benzimidazole-5-carboxylic acid derivatives and their precursors as antileukemic agents. *Bioorg. & Med. Chem. Letters*. **19**, 16: 4594-4600.
9. Karthikeyan Ch., Solomon V. R., Lee H., Trivedi P. (2013) Synthesis and biological evaluation of 2-(phenyl)-3H-benzo[d]imidazole-5-carboxylic acids and its methyl esters as potent anti-breast cancer agents. *Arab. J. Chem*.: 1-6.
10. Yoon Y. K., Ali M. A., Choon T. S., Ismail R., Wei A. Ch., Kumar R. S., Osman H., Beevi F. (2013) Antituberculosis: synthesis and antimycobacterial activity of novel benzimidazole derivatives. *BioMed Res. Intern*.: 1-6.
11. Kim I., Park Y., Hammock B. D., Nishi K. (2011) Structure-activity relationships of cycloalkylamide derivatives as inhibitors of the soluble epoxide hydrolase. *J. Med. Chem*. **54**: 1752–1761.
12. Ermokhin V.A., Purygin P.P. Zarubin Y.P. (2006) Adamantanovye proizvodnye jefirov i amidov 4-aminobenzoinoi kisloty. *Vestn. Samar. Gos. Tekhn. Univ*. - Estestvenno-Nauchnaya Ser. **9**, 49: 92-96 (in Russian).
13. Goryachkina A.A., Ermokhin V.A., Purygin P.P. (2012) Sintez N-nitrofenil'nykh proizvodnykh 1-adamantilsoderzhashikh amidov. *Vestn. Samar. Gos. Tekhn. Univ*. - Estestvenno-Nauchnaya Ser. **3/1**, 94: 132-136 (in Russian).
14. Zafar A., Melendez R., Geib S. J., Hamilton A. D. (2002) Hydrogen bond controlled aggregation of guanidinium-carboxylate derivatives in the solid state. *Tetrahedron*, **58**, 4: 683–690.
15. Ermokhin V., Purygin P., Vishnyakov V. (2000) Sintez amidow 1-adamantankarbonowoi kisloty. *Vestn. Samar. Gos. Tekhn. Univ*. – Estestvenno-Nauchnaya Ser. **2**, 16: 146-148 (in Russian).

Received April, 2017