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Organic Chemistry

Synthesis of Some Caffeic and 2,3-Dihydroxy-3-(3,4-Dihydroxyphenyl)-Propanoic Acids Amides

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(Presented by Academy Member Devi Ugrekhelidze)

ABSTRACT. Synthesis of some new amides of caffeic acid and 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid with potential antioxidant activity has been carried out. The structures of synthesized compounds were established by NMR and IR spectroscopy. *© 2011 Bull. Georg. Natl. Acad. Sci.*

Key words: *caffeic acid,* 2,3-*dihydroxy*-3-(3,4-*dihydroxyphenyl*)-*propanoic acid, amides, synthesis*

Caffeic acid and its analogues are widely distributed in the plant kingdom and are potential natural antioxidants with multiple mechanisms involving free radical scavenging, metal ion chelation, and inhibitory actions on specific enzymes that induce free radical and lipid hydroperoxide formation. They are known as compounds possessing antibacterial, antiviral, anti-inflammatory, antiatherosclerotic, antioxidative, antiproliferative, neuroprotective, and immunostimulatory properties [1-3].

Recently, high-molecular (>1000 kDa) water-soluble preparations with impressive immunomodulatory (anti-complementary) and antioxidant activity were isolated from the roots and stems of *Symphytum asperum and S. caucasicum* [4,5]. The main constituent of these preparations was found to be a regular caffeic acid-derived polyether, namely, poly[3-(3,4-dihydroxyphenyl)-glyceric acid] or poly-[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)-ethylene]. This polymer is a representative of a new class of natural polyethers with a residue of 3-(3,4-dihydroxyphenyl)-glyceric acid as the repeating unit.

In order to compare antioxidant activities of the above mentioned natural polymer and its synthetic monomer (1), containing the characteristic dihydroxyphenyl moiety of caffeic acid with well-known antioxidant activities, we have synthesized racemic 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid (1) and its enantiomers: (2R,3S)-2,3-dihy-droxy-3-(3,4-dihydroxyphenyl)-propanoic acid (2) and (2S,3R)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid (3) (Fig. 1). It has been shown that the novel racemic propanoic acid derivative (1) as well as its enantiomeric pure derivatives (2) and (3) possess strong antioxidant activities against reactive oxygen species, such as hypochlorite or free radicals such as DPPH. The inhibitory effect of racemic product (1) and the corresponding enantiomers appeared to be about 40-fold and three-fold higher than that of polyether and trans-caffeic acid, respectively [6]. Such pronounced antioxidant properties provide appropriate background for further deep investigation of the biological activity of the above mentioned phenolic compounds as well as their derivatives.

It is known that the structural feature responsible for the antioxidative and free radical scavenging activity of caffeic acid is the ortho-dihydroxyl functionality in the catechol ring. The antioxidative activity of caffeic acid analogues, however, depends on several other factors

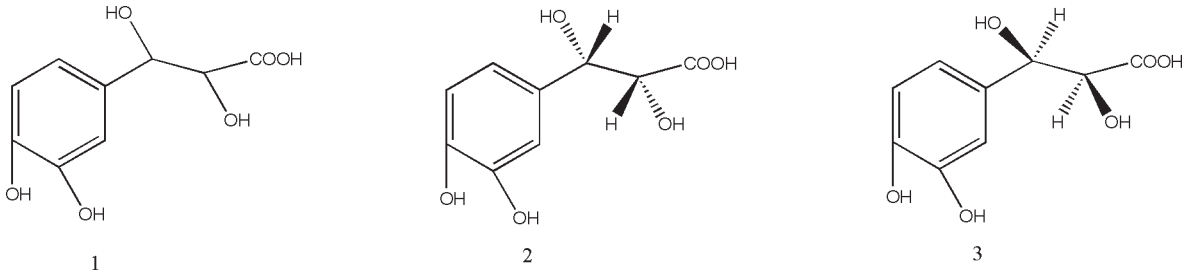
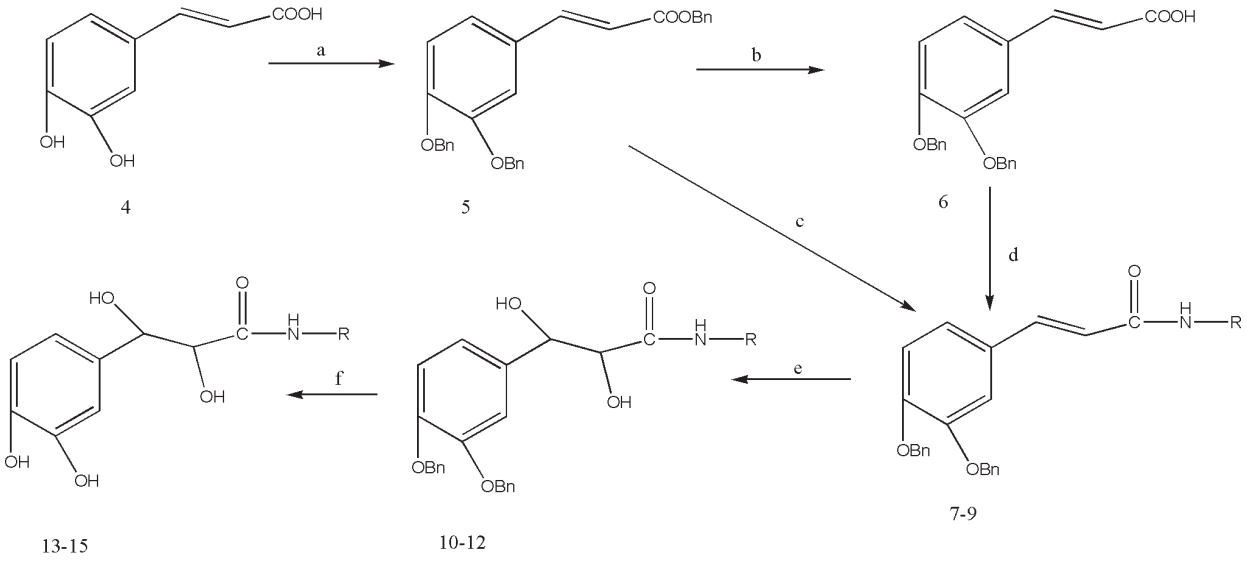


Fig. 1. Racemic 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid (1) and its enantiomers: (2R,3S)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid (2) and (2S,3R)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid (3).

such as the electron-donating and withdrawing substituents on the catechol ring, the number of hydroxyl groups or catechol moieties and the involvement of other H-donating groups (-NH, -SH) [5].

Results and Discussion. In order to study the antiradical and antioxidative activity and to better understand the effects of involvements of H-donating groups some 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid amides on the basis of caffeic acid have been synthesized (Scheme 1).

The amides were synthesized from protected caffeic acid (5) and the corresponding amines (either in the free base or hydrochloride form) using benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate (BOP) as coupling reagent. Protection of starting caffeic acid (4) was performed with benzylbromide in acetone. Hydrolysis of obtained esteric group (5) by KOH in DMF gave benzylated caffeic acid with free carboxylic group (6). Condensation of acid (6) with appropriate amines gave amides (7-9). The protected amides (10-12) were dihydroxylated according with Sharpless dihydroxylation procedure using a potassium osmate [7]. The desired amides (13-15) were obtained by the removing of protected groups of amides (10-12) by catalytic hydrogena-



R=$CH_2COOC_2H_5$ (7, 10, 13)

R=$CH_2CH_2C_6H_5$ (8, 11, 14)

R=CH_2CH_2OH (9, 12, 15)

a) BnBr, K_2CO_3, $(CH_3)_2CO$ b) NaOH, DMF c) $H_2NCH_2CH_2OH$, DMF d) amine, BOP, DMF, $(C_2H_5)_3N$, CH_2Cl_2

e) $K_2OsO_4{\cdot}2H_2O$, NMO, CH_3CN:$(CH_3)_2CO$:H_2O (3:3:1) f) Pd/C, THF:EtOH (1:1)

Scheme 1. Synthesis of some 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propanoic acid amides.

tion on Pd/C. Antioxidant activity of compounds (10-15) will be examined in our further research.

Materials and Methods. ^{1}H and ^{13}C NMR spectra were obtained on a Brucker Avance DRX-500 spectrometer (Brucker AG, Karlsruhe,Germany). Chemical shifts are expressed in δ (parts per million, ppm) values relative to tetramethylsilane (TMS) as internal reference and coupling constants (J) are given in Hertz. IR spectra were obtained using Perkin Elmer 283 FT-IR spectrometer (Waltham, MA). The melting points were recorded on an Electrothermal apparatus and are uncorrected (Engineering Ltd., VT). All reactions were monitored by TLC on 0.25 mm precoated silicagel plates Merck 60, GF-254 (Merck, Darmstadt, Germany) and visualized with UV light.

Benzyl 3-(3,4-dibenzyloxyphenyl)-propenoate (5). A mixture containing trans-caffeic acid 4 (1.8 g, 10 mmol), 50 ml acetone, powdered potassium carbonate (4.55 g), benzyl bromide (3.91 ml) was reûuxed overnight under stirring. The solid residues were ûltered and washed three times with 50 ml portions of acetone. The solvent was evaporated, and the resulted viscous yellowish residues were puriûed by crystallization in diethyl ether—petroleum ether. Yield: 4.05 g (90%), mp. 80–82^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.16 (2H, s, benzylic protons,). 5.19 (2H, s, benzylic protons), 5.22 (2H, s, benzylic protons), 6.26 (1H, d, J=15.9), 6.92 (1H, d, J=8.2), 7.06 (1H, dd, J=8.4, 1.8), 7.11 (1H, d, J=1.8), 7.30–7.45 (15H, m, aromatic protons), 7.59 (1H, d, J=15.9). ^{13}C NMR (125 MHz, $CDCl_3$): δ=66.6 (benzylic—CH_2), 71.3 (benzylic—CH_2), 71.7 (benzylic—CH_2), 114.1, 114.6, 116.1, 123.3, 127.14, 127.2– 128.6, 136.7, 136.8, (complex area, aromatic carbons), 145.3, 149.3, 151.5 (olefinic carbon), 167.1 (CO, ester group). IR (KBr), ν_{max} (cm-^{1}): 3068, 3025, 2907, 2857, 1683 (carbonyl group), 1595, 1516, 1445, 1390, 1272, 1130, 1021, 946, 871, 840, 816.

(3,4-Dibenzyloxyphenyl)-propenoic acid (6). 1g (2.22mmole) of benzyl 3-(3,4-dibenzyloxyphenyl)-propenoate (5) was dissolved in 10 ml DMF and 0.24g (4.44 mmole) KOH and 1 ml water. Mixture was boiled for 15h, cooled, poured into 50 ml water, filtered and washed with water. Yield: 0.66g, (90%), m.p. 190^{0}C-192^{0}C. ^{1}HNMR (500 MHz, $CDCl_3$): δ=5.21 (2H, s, benzylic protons), 5.23 (2H, s, benzylic protons), 6.26 (1H, d, J=15.9), 6.92 (1H, d, J=8.2), 7.06 (1H, dd, J=8.4, 1.8), 7.11 (1H, d, J=1.8), 7.30–7.5 (10H, m, aromatic protons), 7.59 (1H, d, J=15.9). ^{13} C NMR (125 MHz, $CDCl_3$): δ=71.3 (benzylic —CH_2), 71.7 (benzylic —CH_2), 114.1, 114.6, 116.1, 123.3, 129.0–127.0 (aromatic carbons), 145.3, 147.3, 151.5 (olefinic carbons), 171.1 (COOH). IR spectrum (KBr), ν_{max} (cm-^{1}): 3280, 3065, 2988, 2866, 1732 (CO), 1647, 1619, 1594, 1480, 1390, 1257, 1196, 1027, 1001, 968, 916, 840, 816.

General Synthetic Procedure for Caffeic Acid Amide Analogues. The amides were synthesized from protected caffeic acid (6) and the corresponding amines using BOP as coupling reagent. Briefly, 10 mmol of compound (6) was dissolved in 20 mL of DMF and 1.4-2.8 mL (10-20 mmol) of triethylamine. The solution was cooled in an ice-water bath and 10 mmol of the amine was added followed by 10 mmol of BOP dissolved in 20 mL of dichloromethane. The reaction mixture was stirred at 0 °C for 30 min and then stirred at room temperature for 2 h. Dichloromethane was removed under reduced pressure, and the residual solution was diluted with 150 mL of water. The crude product was then extracted with ethyl acetate, washed successively with 1 N HCl, water, 1 M $NaHCO_3$, and water, then dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on a silica gel column using a mixture of ethyl acetate/n-hexane (1:1 or 2:1) as eluents.

3-(3,4-Dibenzyloxyphenyl)-N-(acetylethylester)-propenoic acid amide (7). Yield: 3.96g, (84.4%), m.p. 130-132^{0}C. ^{1} H NMR (500 MHz, $CDCl_3$): δ=1.3 (m, 3H), 4.17 (s, 2H), 4.25 (d, 2H, J=6.4), 5.17 (2H, s, benzylic protons), 5.20 (2H, s, benzylic protons), 6.26 (1H, d, J=15.9), 6.92 (1H, d, J=8.2, 7.06 (1H, dd, J=8.4, 1.8), 7.11 (1H, d, J=1.8), 7.30–7.45 (10H, m, aromatic protons), 7.59 (1H, d, J=15.9). ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.6, 41.5, 62.0, 71.4, 71.8, 114.3, 114.8, 118.3, 122.8, 126.6–128.8 aromatic carbons), 137.1, 141.9, 149.3, 151.3 166.1, 170.1. IR spectrum (KBr), ν_{max} (cm-^{1}): 3278, 1740, 1651, 1614, 1537, 1517, 1516, 1445, 1375, 1265, 1199, 1134, 968, 920, 842, 813.

3-(3,4-Dibenzyloxyphenyl)-N-(2-phenethyl)-propenoic acid amide (8). Yield: 3.05g, (66%), m.p. 168-170^{0}C. ^{1} H NMR (500 MHz, $CDCl_3$): δ=2,92 (t, J=7.8, 2H, CH_2-Ar), 3,59 (dd, J=5,9 2H, -NH-CH), 5.20 (2H, s, benzylic protons), 5.22 (2H, s, benzylic protons),6.15 (d, 1H, J=15.9), 6.93 (d, 1H, J=8.2), 7.06 (dd, 1H, J=8.4, 1.8), 7.11 (d, 1H, J=1.8), 7.22-7.26 (5H, H-2', H-6', H-3', H-5', H-4'), 7.55 (d, 1H, J=15.9), 7.3 (s, 1H, N-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=35.5, 40.7, 71.0, 71.4, 113.9, 114.7, 118.7, 122.2,126.5, 127.2, 128.8, 140.6, 149.0, 150.5, 166.6. IR spectrum (KBr), ν_{max} (cm^{-1}): 3293, 3069,3037, 2882, 1651, 1619, 1545, 1517, 1456, 1428, 1379, 1334, 1127, 1216, 993, 972, 924, 847. 806, 753.

3-(3,4-Dibenzyloxyphenyl)-N-(ethanolyl)-propenoic acid amide (9). 1g (2,22 mmol) of compound (5) was dissolved in 8ml DMF and 1ml (16,5mmol) of ethanolamine was added. The mixture was refluxed for 24 h, cooled and poured into cold water. Precipitate was filtered, washed with water, dried and recrystallized from chloroform: diethyl ether mixture. Yield: 0.7g (59%), amorphous comp. ^{1}HNMR (500 MHz, $CDCl_3$): δ=3.58 (2H, t, CH_2), 3.77 (2H, t, CH_2), 5.16 (2H, s, benzylic protons), 5.17 (2H, s, benzylic protons), 6.26 (1H, d, J=15.9), 6.92 (1H, d, J=8.2), 7.06 (1H, dd,

J=8.4, 1.8), 7.11 (1H, d, J =1.8), 7.30–7.45 (10H, m, aromatic protons), 7.55 (1H, d, J=15.9). ^{13}C NMR (125 MHz, $CDCl_3$): δ=43.3, 63.1, 71.4, 71.8, 114.3, 114.7, 118.6, 122.7, 127.6, 127.7, 128.3, 128.9, 141.6, 167.5. IR spectrum (KBr), ν_{max} (cm-^{1}): 3288, 3065, 3028, 2935, 2874, 1655, 1598, 1541, 1517, 1257, 1208, 1009, 964, 924, 847, 802.

Typical Procedure for Dihydroxylation. The protected trans-caffeic acid derivatives (7-9) were dihydroxylated according to a Sharpless procedure. Brieûy, the alkylated caffeic acid derivatives (7-9) (2.22 g, 10 mmol) and citric acid (3 g, 7.5 mmol) were dissolved in 10 ml of a 3:3:1 mixture of acetonitrile–acetone–water in a 100 ml Erlenmeyer flask. Potassium osmate (3.7 mg, 0.1 mol %) was then added, followed by 50% water solution of NMO (2.28 ml,1.1 mmol). The reaction mixture turned bright green. After stirring at room temperature for 4 hours the reaction mixture became nearly colorless. The organic solvents were removed on a rotary evaporator and the aqueous residue was then acidiûed with hydrochloric acid (1M, 12 ml) and extracted with ethyl acetate (2X50 ml). The combined organic extracts were dried with sodium sulfate and

***Syn*-2,3-dihydroxy-3-(3,4-dibenzyloxyphenyl)-N-(acetylethylester)-propanoic acid amide (10).** Yield: 4.6g, (93%), amorphous comp. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.26 (m, 3H), 4.17 (s, 2H), 4.25 (d, 2H, J=6.4), 5.17 (2H, s, benzylic protons), 5.20 (2H, s, benzylic protons), 6.26 (1H, d, J=15.9), 6.92 (1H, d, J=8.2), 7.06 (1H, dd, J=8.4, 1.8), 7.11 (1H, d, J=1.8), 7.30–7.45 (10H, m, aromatic protons), 7.59 (1H, d, J= 15.9). ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.6, 41.5, 62.0, 71.4, 71.8, 114.3, 114.8, 118.3, 122.8, 126.6–128.8, 137.1, 141.9, 149.3, 151.3 166.1, 170.1. IR-spectrum (KBr), ν_{max}(cm-^{1}): 3333, 3183,1740, 1651, 1578, 1513, 1464, 1338, 1265. 1188, 1131, 1070, 1029, 977, 907, 887, 855.

***Syn*-2,3-dihydroxy-3-(3,4-dibenzyloxyphenyl)-N-(2-phenethyl)-propanoic acid amide (11)**. Yield: 4.72g, (95%), m.p. 140-42^{0}C ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.76 (t, J=7.8, 2H, CH_2-Ar), 3.49 (dd, J=5,9 2H, -NH-CH), 4.14 (d, 1H, J=3.4, α-CHOH), 5.02(d, 1H, J=3.4, β-CHOH), 5.18 (4H, s, benzylic protons), 6.88 (d, 1H, J=8.9) 6.93 (dd, 1H, J=7.7, 1.8), 7.04 (d, 1H,), 7.26 (s, 1H, N-H), 7.30-7.50 (m, aromatic protons). ^{13} C NMR (125 MHz, $CDCl_3$): δ=35.5, 40.7, 71.0, 73.7,75.1 113.2, 114.7, 119.3, 126.9, 127.2,-128.8 ,137.6, 147.0, 171.6. IR-spectrum (KBr), ν_{max}(cm-^{1}): 3378, 3065, 3024, 2931, 1651, 1614, 1562, 1517, 1448, 1387, 1338, 1257, 1163, 1127, 1107, 912, 855, 814, 749.

***Syn*-2,3-dihydroxy-3-(3,4-dibenzyloxyphenyl)-N-(ethanolyl)-propanoic acid amide (12).** Yield: amorphous comp. ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.15 (2H, t, CH_2), 3.39 (2H, t, CH_2), 3.90 (s, 2H), 4.83 (d, 2H, J=6.4), 4.14 (d,1H, J=3.4, α-CHOH), 5.02(d, 1H, J=3.4, α-CHOH), 5.16 (2H, s, benzylic protons), 5.17 (2H, s, benzylic protons), 6.92 (1H, d, J=8.2), 7.06 (1H, dd, J=8.4, 1.8), 7.11 (1H, d, J=1.8), 7.30–7.45 (10H, m, aromatic protons), 7.59 (1H, d, J=15.9). ^{13}C NMR (125 MHz, $CDCl_3$): δ=41.9, 60.6, 71.1, 71.4, 73.6, 76.5, 114.1, 114.9, 120.6, 128.2, 128.4, 128.5, 128.6, 1292.9, 137.2, 138.4, 148.9, 173.5. IR-spectrum (KBr), ν_{max}(cm-^{1}): 3490-3200, 3100-3000, 1650, 1625-1540, 1500, 1200, 1163, 1127, 1107, 912, 855, 814.

Typical Procedure for Removing Benzyl Groups. In brief, a solution of products (10, 11 or 12) (2.0 mmol) in a 1:1 mixture of ethanol–tetrahydrofuran (30 ml) was added to a stirred suspension of palladium/carbon (10 mol %) in the same solvent system (20 ml) that had previously been evacuated, purged with hydrogen, and stirred for 30 min under a hydrogen atmosphere. The reaction mixture was stirred overnight and then ûltered through celite. The organic extracts were concentrated under vacuum, and the resulting residue was puriûed by crystallization in ethanol.

***Syn*-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-N-(acetylethylester)-propanoic acid amide (13).** Yield: 2.69g, (90%), m.p. 90-92^{0}C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.26 (m, 3H), 4.17 (s, 2H), 3,49 (dd, J=5.9, 2H, -NH-CH), 4,14 (d, 1H, J= 3.4, α-CHOH), 5.02(d,1H, J=3.4, β-CHOH), 6.88 (d, 1H, J=8.9) 6.93 (dd, 1H, J=7.7, 1.8), 7.04 (d, 1H, 7.3 (s, 1H, N-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.6, 41.5, 62.0, 71.7, 72.1, 114.7, 118.3, 122.8, 137.1, 141.9, 149.3, 166.1, 170.1. IR-spectrum (KBr), ν_{max}(cm-^{1}): 3450, 3443, 3373, 3337, 1740, 1651, 1578, 1513, 1464, 1338, 1265. 1188, 1131, 1070, 1029, 977, 907, 887, 855.

***Syn*-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-N-(2-[phenyl]ethyl)-propanoic acid amide (14).** Yield: 2.69g, (85%), amorphous comp. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2,76 (t, J=7.8, 2H, CH_2-Ar), 3,49 (dd, J=5.9, 2H, -NH-CH), 4,14 (d, 1H, J= 3.4, α-CHOH), 5.02 (d, 1H, J=3.4, β-CHOH), 6.88 (d, 1H, J=8.9) 6.93(dd, 1H, J=7.7, 1.8), 7.04 (d, 1H,), 7.22-7.26 (5H, H-2', H-6', H-3', H-5', H-4'), 7.3 (s, 1H, N-H). ^{13} C NMR (125 MHz, $CDCl_3$): δ=35.5, 40.7, 71.0, 73.7, 75.1, 113.2, 114.7, 119.3, 126.2-128.4, 132.9, 143.9, 144.1, 166.2. IR-spectrum (KBr), ν_{max}(cm-^{1}): 3445, 3374, 3337, 1650, 1614, 1562, 1517, 1448, 1387, 1338, 1257, 1163, 1127, 1107, 912, 855, 814, 749.

***Syn*-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-N-(ethanolyl)-propanoic acid amide (15).** Yield: 2.05g, (85%), amorphous comp. ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.15 (2H, t, CH_2) 3.39 (2H, t, CH_2), 3.90 (s, 2H), 4.83 (d, 2H, J=6.4), 4,14 (d, 1H, J=3.4, α-CHOH), 5.02 (d, 1H, J=3.4, β-CHOH), 6.88 (d, 1H, J=8.9) 6.93 (dd, 1H, J=7.7, 1.8), 7.04 (d, 1H), 7.3 (s, 1H, N-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=41.9, 60.6, 71.1, 71.4, 113.2, 117.7, 121.3, 132.9, 143.9, 144.1, 167.2. IR-spectrum (KBr), δ_{max} (cm-^{1}): 3490-3300, 3100-3000, 1650, 1625, 1540, 1550, 1250, 1163, 1127, 1107, 912, 855, 814.

ორგანული ქიმია

კოფეინის მჟავას და 2,3-დიჰიდროქსი-3-(3,4-დიჰიდროქსიფენილ)-პროპიონის მჟავას ამიდების სინთეზი

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(წარმოდგენილია აკადემიის წევრის დ. უგრეხელიძის მიერ)

განხორციელებულია კოფეინის და 2,3-დიჰიდროქსი-3-(3,4-დიჰიდროქსიფენილ)-პროპიონის მჟავას პოტენციური ანტიოქსიდანტური აქტივობის მქონე ზოგიერთი ახალი ამიდის სინთეზი. სინთეზირებული ნაერთების აღნაგობა დადასტურებულია ბმრ- და იწ-სპექტროსკოპიის მონაცემების საფუძველზე.

REFERENCES

1. *Ch.Hung, W.J.Tsai, Y.L.Kuo, Y.H.Kuo* (2005), Bioorg. Med. Chem., **13**, 5: 1791-1797.
2. *P.J.Ley* (2001), International Journal of Cosmetic Science, **23**, 1: 35-48.
3. *Ch.Siquet, F.Paiva-Martins, L.F.C.Jose, F. Borges* (2006), Free Radical Research, **40**, 4 : 433-442.
4. *V. Barbakadze, E. Kemertelidze, I. Targamadze, et. al.* (2005), Molecules, **10,** 9: 1135-1144.
5. *V. Barbakadze, E. Kemertelidze, I. Targamadze, et. al.* (2005), Chemistry of Natural Compounds, **41,** 4: 374-377.
6. *M. Merlani, V. Barbakadze, L. Amiranashvili, et. al.* (2010), Chirality, **22**, 8: 717-725.
7. *S. Son, B. Lewis* (2002), J. Agric. Food Chem., **50**, 3: 468-472.

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