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Pharmacochemistry

Synthesis of New Dihydroxylated Derivatives of Ferulic and Isoferulic Acids

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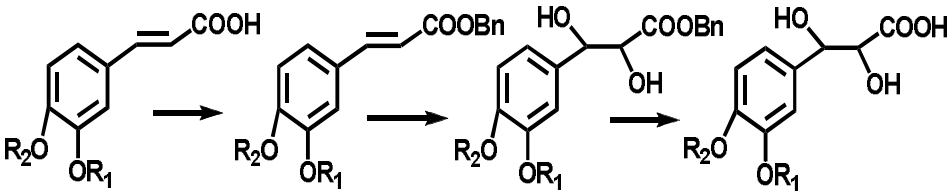
ABSTRACT. New racemic glyceric acid derivatives, namely, 2,3-dihydroxy-3-(4-hydroxy-3-methoxyphenyl)-propionic acid and 2,3-dihydroxy-3-(3-hydroxy-4-methoxyphenyl)-propionic acid were synthesized from *trans*-ferulic acid [*trans*-3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid] and *trans*-isoferulic acid [*trans*-3-(3-hydroxy-4-methoxyphenyl)-2-propenoic acid], respectively, via Sharpless dihydroxylation using the catalyst potassium osmiate and co-oxidant *N*-methylmorpholine-*N*-oxide (NMO). The structures of synthesized compounds were elucidated using IR, ^{1}H and ^{13}C NMR spectroscopy data. Continuing the search of highly active samples of phenolcarboxylic acids derivatives, racemic dihydrxylation of *trans*-ferulic acid and *trans*-isoferulic acid derivatives was performed for the purpose of elucidation of influence of hydroxyl groups on biological activities of these compounds. *© 2018 Bull. Georg. Natl. Acad. Sci.*

Key words: ferulic acid, isoferulic acid, dihydroxylation

Phenolcarboxylic acids such as 3,4-dihydroxycinnamic acid (caffeic acid), 4-hydroxy-3-methoxycinnamic acid (ferulic acid) 3-hydroxy-4-methoxycinnamic acid (isoferulic acid) and their derivatives exhibit antioxidant, anti-inflammatory properties and exert beneficial effects on human health through prevention of degenerative pathologies such as cardiovascular diseases and cancer [1-4]. Recently, caffeic acid-derived polymer-poly[oxy-1-carboxy-2-(3,4-dihydroxyphenyl)-ethylene (POCDPE) was isolated from species of Boraginaceae family *Symphytum asperum, S.officinale, S. Caucasicum, S.grandiflorum* and *Anchuza italica* [5-8]. It showed high immunomodulatory, antioxidant, anti-inflammatory and anticancer activities [9-12]. From aqueous organic extracts of roots and leaves of *S. asperum* and *S. Caucasicum*, low molecular phenolic compounds caffeic, rosmarinic, chlorogenic, lithospermic acids and oligomers of different structures were isolated as well [13].

The racemic and enantioselective syntheses of monomer of POCDPE namely, 2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propionic acid as well as virtually pure enantiomers, (+)-



1. R_1=CH_3, R_2=H 3. R_1=CH_3, R_2=Bn 5. R_1=CH_3, R_2=Bn 7. R_1=CH_3, R_2=H
2. R_1=H, R_2=CH_3 4. R_1=Bn, R_2=CH_3 6. R_1=Bn, R_2=CH_3 8. R_1=H, R_2=CH_3

Scheme 1. Synthesis of 2,3-dihydroxy-3-(4-hydroxy-3-methoxyphenyl)-propionic acid and 2,3-dihydroxy-3-(3-hydroxy-4-methoxyphenyl)-propionic acid from *trans*-ferulic and *trans*-isoferulic acids, respectively.

(*2R,3S*)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propionic acid and (-)-(*2S,3R*)-2,3-dihydroxy-3-(3,4-dihydroxyphenyl)-propionic acid were performed via sharpless asymmetric dihydroxylation of *trans*-caffeic acid derivatives using the enantiocomplementary catalysts, $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL, respectively [14]. All synthesized forms of monomeric compounds 3-(3,4-dihydroxyphenyl) glyceric acid (DPGA) exhibited higher antioxidant activity [14] than natural polymer, while POCDPE performed high anticancer activity against prostate cancer cells *in vitro* and *in vivo* [12]. Synthetic methylated analog of natural polymer 2-methoxycarbonyl-3-(3,4-dimethoxyphenyl)-oxirane poly(MCDMPO) [15] did not reveal any anticancer efficacy against prostate cancer [16].

Continuing search of highly active samples of derivatives of phenolcarboxilic acids, racemic dihydroxylation of *trans*-ferulic acid (**1**) and *trans*-isoferulic (**2**) acid derivatives was performed (scheme 1) for the purpose of elucidation of influence of hydroxyl groups on biological activities of these compounds.

Synthesis was realized from *trans*-ferulic (**1**) and *trans*-isoferulic acids (**2**) after preliminary protection of functional groups by benzylation, using benzylbromide in acetone and then dihydroxylation of obtained esters **3** and **4** using catalyst $K_2OsO_4 \cdot 2H_2O$ and co-oxidant *N*-methylmorpholine-*N*-oxide (NMO) in acetonitrile: acetone: water (3:1:1); removing of benzyl protecting groups from **5** and **6** carried out by using the catalytic hydrogenation procedure over Pd/C (10%) [14].

Structure elucidation of compounds **3-8** verified according to data of IR and NMR spectroscopy. The IR spectra of preparations contain absorption bands characteristic for functional groups. Strong absorptions at 1696, 1704, 1720 and 1725 cm^{-1} in compounds **3-6** indicated valent vibrations of C=O bonds of ester groups. Absorption bands at 3378, 3297 and 3408, 3303 cm^{-1} are characteristic for hydroxyl groups of substances **5** and **6,** respectively. Valent vibrations phenolic hydroxyls and secondary alcoholic groups of compounds **7** and **8** appear in the frequency domain 3400-3300 cm^{-1} and carbonyl group at 1725 cm^{-1}. Absorption bands of methoxy groups of substances **3-8** reveal in and around 2850-2858 cm^{-1}, C=C bond aromatic ring in the interval 1600 – 1450 cm^{-1} and aromatic C-H in region 890-815 cm^{-1}.

In the spectra of ^{1}H NMR signal of methyl group from O-CH_3 of compounds **3-8** visualized in the form of singlet with chemical shifts in the interval of δ 3.79-3,95 ppm, signals corresponding to aromatic protons of phenyl ring display in form doublet for H-5 in the interval δ 7.5-6.91ppm, with coupling constant J=1.8 Hz, and for H-2 in the interval δ 6.76-6.94 ppm, with coupling constant J=8.2 Hz, for H-6 in form doublet-doublet in the interval δ 6.84-7.13 ppm, with coupling constants

J=8.4 Hz and J=1.8 Hz. Olefinic protons at C-7 and C-8 side chain in compounds **3** and **4** reveal in the form doublet in the interval δ 7.65-7.71 ppm, with coupling constant J=15.9Hz and δ 6.32-6.40 ppm, with coupling constant J=15.9 Hz, respectively. Benzylic protons of CH_2 of compounds **3-6** reveal in the form of singlets in the intervals δ 5.20-5.29 ppm, and 10 aromatic protons benzylic groups in the forms of multiplets in the interval δ 7.19-7.49 ppm. Signals from protons C-7 and C-8 of side chain in compounds **5-8** exhibit in the form of doublet in the interval δ 4.06-5.0 ppm, with coupling constant J=3.4 Hz for β-C<u>H</u>OH and in the interval δ 3.51-4.29 with coupling constant J=3.4 Hz for α-C<u>H</u>OH.

In the spectra of ^{13}C NMR necessary emphasize signals ester groups of compounds **3-6** in the intervals of δ 167.1-173.03ppm, and free carboxylic groups of compounds **7** и **8** at δ 174.23 and 174.05 ppm, respectively. Signals of three non-linked carbon atoms of phenyl groups of compounds **7** and **8** develop at δ 120.18 and 118.50 ppm, - (C-6), 115.24 and 114.57 ppm, - (C-5), 111.39 and 111.84 ppm, - (C-2), respectively, and linked carbon atoms at δ 148.01 and 147.01 ppm., - (C-3), δ 146.26 and 147.57 ppm., - (C-4), δ 134.03 ppm., - (C-1), respectively. Signals aromatic carbon atoms of benzyl of compounds **3-6** belong in the region of δ 127.21 - 129.68 ppm., and benzylic CH_2 in the field of δ 66.6 -71.02 ppm. Signals of carbon atoms of secondary alcohol of compounds **5-8** display in the region of δ 55.7-56.28 ppm.

Studies of biological activities of new dihydroxylated ferulic and iso-ferulic acids are in progress.

Experimental

The melting points were recorded on an Gallenkamp. IR spectra were obtained using Magna-IR Spectrometer 550 in tablet with KBr. ^1H and ^{13}C spectra were obtained on a Brucker AC 500 (operating frequency 500 MHz by proton and 125 MHz by 13C). Chemical shifts are expressed in δ (parts per million) values relative to tetramethylsilane (TMS) as internal reference, solutions acetone d_6, $CDCl_3$ and coupling constants (J) are given in Hertz. The analysis data of all the compounds corresponded to the calculated ones. The reaction and the purity of the products were monitored by TLC on plates (60GF-254, Merck) in a petroleum ether: ethyl acetate system (5: 1).

Benzyl 3-(4-benzyloxy-3-methoxyphenyl)-propenoate (3). To the mixture of 0.97g (5.0 mmol) of ferulic acid and 7 g (50 mmol) K_2CO_3 in 30 ml acetone under stirring was added by dropwise 1.4 ml (11.7 mmol) benzylbromide in acetone and was refluxed 12 h; mixture was cooled to room temperature. The solid residues were filtered and washed (3X50 ml) with acetone and filtrate was evaporated on a rotary evaporator. After recristallization from ether-petroleum ether was obtained 1.77 g (95%) compound **3**. IR-spectrum (KBr, ν, cm^{-1}) 2858 (OCH_3), 1696 (C=O), 1602, 1513, 1456 (aromatic C=C), 855, 810 (aromatic C-H). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.71 (1H, d, J=15.9, H-7), 7.30-7.47(10H, m, aromatic protons), 7.11 (lH, d, J=1.8, H-5), 7.07 (1H, dd, J=8.4 and J=1.8, H-6), 6.91 (lH, d, J=8.2, H-2), 6.40 (lH, d, J=15.9, H-8), 5.29 (2H, s, OCH_2), 5.23 (2H, s, OCH_2), 3.95 (3H, s, OCH_3); ^{13}C NMR spectrum (δ, ppm): 167.1 (C=O), 150.3(C-4), 149.3 (C-3), 145.3 (C-7), 128.7-127.2 (aromatic carbons), 122.5 (C-8), 115.3 (C-6), 113.5(C-5), 110.3 (C-2), 71.4($O\underline{CH_2}C_6H_5$), 66.6 ($COO\underline{CH_2}C_6H_5$), 55.7($OCH_3$).

Benzyl 3-(3-benzyloxy-4-methoxyphenyl)-propenoate (4) was obtained similarly of synthesis of compound **3** from 0.97 g (5.0 mmol) iso-ferulic acid. Yield 95%. IR-spectrum (KBr, ν, cm^{-1}): 2850 (OCH_3), 1704(C=O), 1598, 1513, 1450 (aromatic C=C), 851, 810 (aromatic C-H). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.65 (lH, d J=15.9, H-7), 7.45-7.30 (10H, m, aromatic protons), 7.15 (lH, d, J=1.8, H-5), 7.13 (1H, dd, J=8.4 and J=1.8, H-6), 6.92 (lH, d, J=8.2, H-2),

6.32 (lH, J=15.9, H-8), 5.28 (2H, c, $COO\underline{CH_2}C_6H_5$), 5.20 (2H, s, $-O\underline{CH_2}C_6H_5$), 3.95 (3H, s, OMe); spectrum ^{13}C NMR (δ, ppm): 166.9 (C=O), 152.3(C-3), 149.3 (C-4), 145.3(C-7), 128.7-127.2 (aromatic carbons), 118.3(C-6), 115.3 (C-5), 111.3(C-2), 72.4 ($O\underline{CH_2}C_6H_5$), 67.6 ($COO\underline{CH_2}C_6H_5$), 55.7(OMe).

Benzyl 3-(4-benzyloxy-3-methoxyphenyl)-propionate (5). Mixture of 0.748 g (2 mmol) compound **3** and 0.315 g (1.5 mmol) of citric acid was dissolved in mixture of 5 ml acetonitrile: acetone: water (3:1:1), added 0,00074 g (0.1%) $K_2OsO_4 \cdot 2H_2O$ and then 0.45 ml (2.2 mmol) 4-methylmorpholine-N-oxide (NMO). 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 acidified with hydrochloric acid (1M, 12 ml) and extracted with ethyl acetate (2X50 ml). The combined organic extracts were dried over Na_2SO_4 and evaporated on a rotary evaporator. Yield 0.76 g (93%). IR (KBr, ν, cm^{-1}): 3378, 3297(OH), 2850 (OCH_3), 1720(C=O), 1598, 1513, 1450 (aromatic C=C), 871, 806 (aromatic C-H). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 7.49-7.30 (10H, m, aromatic protons), 6.96 (lH, d, J=1.8, H-5), 6.94 (1H, dd, J=8.4 and J=1.8, H-6), 6.88 (lH, d, J=8.2, H-2), 5.28 (2H, s, $COOC\underline{H_2}C_6H_5$), 5.25 (2H, s, $OC\underline{H_2}C_6H_5$), 4.06 (1H, d, J=3.4, β-C<u>H</u>OH), 3.51 (1H, d, J=3.4, α-C<u>H</u>OH), 3.79 (3H, s, OMe); ^{13}C NMR (δ, ppm): 173.03(C=O), 149.59 (C-4), 147.94(C-3), 133.03 (C-1), 129.68 - 127.21 (aromatic carbons), 115.83 (C-6), 113.4 (C-5), 109.9 (C-2) 75.01 (β-<u>C</u>HOH), 74.02 (α-<u>C</u>HOH), 71.65 ($O\underline{C}H_2C_6H_5$), 68.04 ($O\underline{C}H_2C_6H_5$), 56.07 (OMe).

Benzyl 2,3-dihydroxy-3-(3-benzyloxy-4-metoxyphenyl)-propionate (6) was obtained similarly of synthesis of compound **5** from benzyl 3-(3-benzyloxy-4-methoxyphenyl)-propenoate.

Yield 93%. IR (KBr, ν, cm^{-1}): 3408, 3303 (OH), 2850 (OCH_3), 1725 (C=O), 1595, 1504, 1450 (aromatic C=C), 890, 818 (aromatic C-H). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm J/Hz: 7.37-7.19 (10H, m, aromatic protons), 6.91 (lH, d, J=1.8, H-5), 6.84 (1H, dd, J=8.4 and J=1.8, H-6), 6.76 (lH, d, J=8.2, H-2), 5.11, s, (CH_2), 5.28 (2H, s, $COOC\underline{H_2}C_6H_5$), 5.25 (2H, s, $-OC\underline{H_2}C_6H_5$), 4.06 (1H, d, J=3.4, β-C<u>H</u>OH), 3.51(1H, d, J=3.4, α-C<u>H</u>OH) 3.79 (3H, s, OMe); ^{13}C NMR spectrum (δ, ppm): 172.5(C=O), 149.59 (C-4), 148.14 (C-3), 132.7 (C-1), 128.68, -127.41 (aromatic carbons), 119.23 (C-6), 112.4 (C-5), 111.5 (C-2) 74.8 (β-<u>C</u>HOH), 74.32 (α-<u>C</u>HOH), 71.02 ($O\underline{C}H_2C_6H_5$), 67.74 ($O\underline{C}H_2C_6H_5$), 56.03 (OMe).

2,3-dihydroxy-3-(4-hydroxy-3-methoxyphenyl)-propionate (7). Solution of 0.4 g (mmol) compound **5** in mixture EtOH-THF 1:1 (30ml) was added under stirring to 0.080 g of Pd/C (10%) suspension in the same solvent system (10 ml) from which the air was expelled in advance. Hydrogen was passed in the system for 2 h and mixture was stirred under hydrogen for the period of 24 h and then filtered through celite. Filtrate was evaporated on a rotary evaporator and precipitate was crystallized from EtOH. IR (KBr, ν, cm-1): 3408, 3303 (OH), 2852 (OCH_3), 1720(C=O), 1595, 1504,1456 (aromatic C=C), 885, 816 (aromatic C-H). 1H NMR (500 MHz, acetone d_6, δ, ppm, J/Hz): 7.13 (1H, d, J=1.8, H-5), 6.91 (1H, dd, J=8.4 and J=1.8, H-6), 6.84 (lH, d, J=8.2, H-2), 5.0 (1H, d, J=3.4, β-C<u>H</u>OH), 4.28 (1H, d, J=3.4, α-C<u>H</u>OH), 3.85 (3H, s, OMe). ^{13}C NMR (δ, ppm):174.23(CO), 148.01 (C-3), 146.26 (C-4), 134.03 (C-1), 120.18 (C-6), 115.24 (C-5), 111.39 (C-2), 76.09 (C-8), 74.92 (C-7), 56.07 (OMe).

2,3-Dihydroxy-3-(3-hydroxy-4-methoxyphenyl)-propionate (8) was obtained similarly of compound **7** from **benzyl 2,3-dihydroxy-3-(3-benzyloxy-4-metoxyphenyl)-propionate (6).** Yield 92%. IR (KBr, ν, cm^{-1}): 3405, 3300 (OH), 2852 (OCH_3), 1725(C=O), 1585, 1500,1450 (aromatic C=C), 875, 815 (aromatic C-H). ^1H NMR (500 MHz, acetone d_6, δ, ppm J/Hz): 7.5 (1H, d, J=1.8, H-5), 7.03 (1H, dd, J=8.4 and

J=1.8, H-6), 6.92 (lH, d, J=8.2, H-2), 4.99 (1H, d, J=3.4), 4.29 (1H, d, J=3.4), 3.86 (3H, s, OMe). ^{13}C NMR (δ, ppm): 174.05 (C=O), 147.57 (C-4), 147.01(C-3), 134.03(C-1), 118.50 (C-6), 114.57 (C-5), 111.84 (C-2), 75.95(C-8), 74.65 (C-7), 56.28(OMe).

ფარმაკოქიმია

ფერულის და იზოფერულის მჟავათა ახალი დიჰიდროქსი წარმოებულების სინთეზი

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(წარმოდგენილია აკადემიის წევრის ე. ქემერტელიძის მიერ)

ტრანს-ფერულის და *ტრანს*-იზოფერულის მჟავათა საფუძველზე, შარპლესის დიჰიდროქსილირების მეთოდით, კატალიზატორ კალიუმის ოსმეატის და თანადამჟანგველად *N*-მეთილმორფოლინ-*N*-ოქსიდის გამოყენებით სინთეზირებულია გლიცერინის მჟავას ახალი წარმოებულები, კერძოდ: 2,3-დიჰიდროქსი-3-(4-ჰიდროქსი-3-მეთოქსიფენილ) პროპიონის მჟავა და 2,3-დიჰიდროქსი-3-(3-ჰიდროქსი-4-მეთოქსიფენილ) პროპიონის მჟავა. სინთეზირებული ნაერთების სტრუქტურა დადგენილია იწ-, ^{1}H- და ^{13}C ბმრ სპექტროსკოპიის მონაცემების საფუძველზე. ვაგრძელებთ რა მაღალი აქტივობის მქონე ფენოლკარბოქსილის მჟავათა წარმოებულების კვლევას, განხორციელებულია *ტრანს*-ფერულისა და *ტრანს*-იზოფერულის მჟავას წარმოებულების რაცემული დიჰიდროქსილირება, მათ ბიოლოგიურ აქტივობაზე ჰიდროქსილის ჯგუფის გავლენის დადგენის მიზნით.

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