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Research Article

SYNTHESIS OF 7-HYDROXY/METHOXY-8-[2' (4,6-DIMETHYL-3-CARBOXY-5-CARBETHOXY-2,3-DIHYDROPYRIDYL)]ISOFLAVONES

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ABSTRACT

7-Hydroxy/methoxy-8-formylisoflavones **(2a-e & 6a-c)** react with ethyl-3-aminocrotanate **(3)** by a modified Hantzsch reaction gave 7-hydroxy/methoxy-8-[2' (4, 6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydropyridyl] isoflavones**(4a-e & 7a-c)**

Keywords: 7-Hydroxy-8-formylisoflavones, 7-methoxy-8-formylisoflavones, ethyl-3-aminocrotanate, Hantzsch reaction, Pyridines.

INTRODUCTION

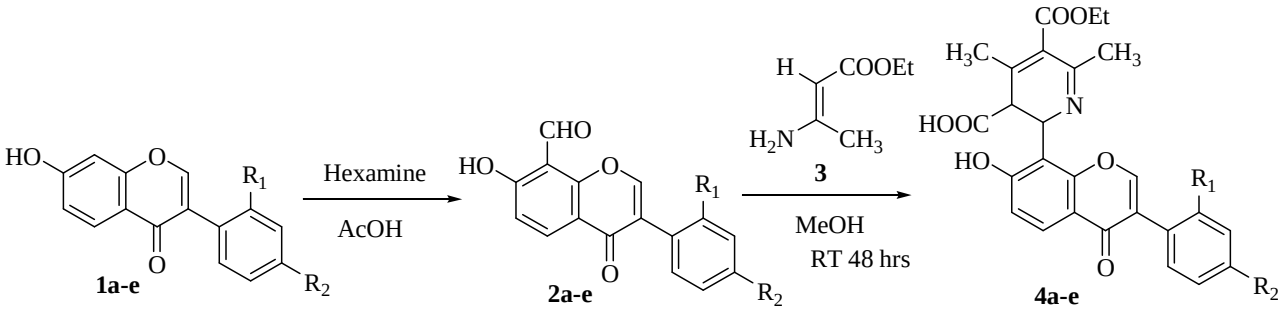
Flavones and isoflavones constitute an important class of oxygen heterocyclics. Substituted as well as heterocyclic ring fused flavones and isoflavones have a wide range of pharmacological activity. Flavones and isoflavones with medicinal use are Khellin a coronary vasodilator. Chromenes-2-carboxylate spasnolitic agent and disodium chromo glycate and anti elergitic drug. Genstein having estrogen hormonal activity, and 7-isopropoxy isoflavones for treatment of postmenopausal and senile osteoporosis.

In view of the substituted isoflavones show a variety of biological activity, such as dopamine antihypertensive, ATP sensitive potassium channel openers antitumor and gastro protective agent. In the present study 7-hydroxy-8-formylisoflavones and substituted isoflavones are synthesized by the Hantzsch reaction involves the reaction of a ethyl-3-aminocrotonate and glacial acetic acid to gave 7-hydroxy/methoxy-8-[2'(4,6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydropyridyl]isoflavones

RESULTS AND DISCUSSION

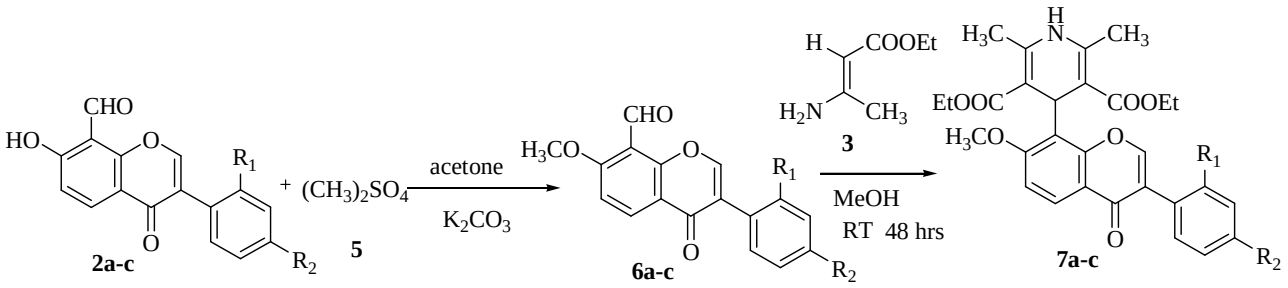
Synthesis of 7-hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydro pyridyl)) isoflavones (4a-e)

7-Hydroxy-8-formylisoflavones **(2a-e)** and ethyl-3-aminocrotanate **(3)** in methanol on stirring at room temperature to gave 7-hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydropyridyl)]isoflavones **(4a-e)** . In the IR spectrum, ester carbonyl peak appeared at 1742 cm^{-1} and isoflavone C=O at 1651cm^{-1}. In the UV spectrum absorption maxima appeared at 238 nm (log ε 4.8) and 272 nm (log ε 4.6). In the ^{1}H NMR spectrum of **4a** recorded in (300 MHz) ($CDCl_3$), signals due to the newly formed 2,3-dihydropyridyl moiety at 8-position are as follows. The H-2" appeared as a doublet at δ 3.05 (J=3.9Hz) and the H-3" appeared as a doublet at δ 4.62 (J=3.9 Hz). The protons of the 4-CH_3 and 6-CH_3 groups appeared at δ 1.88 and δ 1.25. Signals due to one COOEt appeared at δ 1.30(CH_3) as triplet with (J=7.0 Hz) and the OCH_2 protons appeared at δ 4.15 as quartet (J=7.0Hz). A COOH proton appeared as a broad singlet at δ 8.90 and the 7-hydroxyl proton appeared as a broad singlet at δ 5.80. The other signals are due to the isoflavone moiety. The H-2 appeared as singlet at δ 8.0. The H-5 appeared as doublet at δ 7.95 (J=9.0 Hz) .In the ^{13}C NMR (75.5MHz) ($CDC1_3$) spectrum of the product **4a** there is evidence for the pyridyl ring carbons. The signal assignments are as follows: δ 45.83 (C-2"), 60.13 (C-3"), 168.69 (C-3"-COOH), 152.81 (C-4"), 19.81 (C-4"CH_3), 133.01 (C-5"), 154.31 (C-5"COO), 61.13 (C-5"-OCH_2), 14.21 (C-5"CH_3), 169.0 (C-6"), 25.07 (C-6"-CH_3). The carbon signal assignment due to isoflavone moiety are as follows δ 174.72 (C-4), 155.73 (C-7), 155.33 (C-8a), 152.81 (C-2), 135.25 (C-2'), 135.12 (C-4'), 127.10 (C-6'), 129.69 (C-5'), 129.32 (C-1'), 125.97 (C-5), 125.97 (C-3), 123.35 (C-3'), 118.36 (C-4a), 116.27(C-6), 114.32 (C-8).The MS of **(4a)** showed the $[M+H]^+$ ion at m/z 531, M-l at m/z 529. The other ions at m/z 483, 223.



1,2,4 **a**= R_1 = Cl R_2= Cl
b= R_1 =H R_2=H
c =R_1 = H R_2 = OCH_3
d= R_1 =H R_2 = Cl
e= R_1 =Cl R_2 = H

Scheme 1



2,6,7 **a** = R_1 =H R_2= H
b = R_1 =Cl R_2=Cl
c = R_1 = Cl R_2 =H

Scheme 2

EXPERIMENTAL SECTION (4a-e)

General: - Melting points were determined on a Polmon instrument (model no. MP 96).IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer, and ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) were recorded on a VarianGemini 200 spectrometer using TMS as internal standard (chemical shifts and ppm). UV spectra were obtained on a Shimadzu UV-visible spectrophotometer (model UV-1601). Mass spectra were recorded on a VG micromass70-70H instrument.

General procedure for the synthesis of 7-hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydro pyridyl)] isoflavones (4a-e)

i) ***7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-2',4'- dichloroisoflavone*** **(4a)**

A mixture of 7-hydroxy-8-formyl-2',4'-dichloroisoflavone**(2a)** (2.6g,10.0mmol), ethyl-3-aminocrotanate **(3)** (20 mmol) in methanol (20ml) stirred at room temperature for 48 hrs. The reaction mixture was poured on to crushed ice. Pale yellow solid separated out. It was filtered washed with water and chromatographed over silica gel by eluting with pet ether : ethyl acetate to give7-hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-2',4'-dichloroisoflavone**(4a)**. (2.0g,50-70%) yield which was recrystallized from methanol as pale yellow needles mp 162 °C.

IR (KBr): 1651cm^{-1} isoflavone(C=O), 1742 cm^{-1} (=C-O ester)

UV (MeOH): 238 nm (log ε 4.8), 272 nm (log ε 4.6)

^{1}H NMR (300 MHz) ($CDCl_3$) : δ 8.90 (bs,COOH), 8.01 (s,H-2), 7.95 (d. J=9.0Hz, H-5), 7.20-7.60 (m.H-3',5',6'), 6.85 (d,J=9.0Hz,H-6), 5.80 (bs,OH-7), 1.30 (t, J=7.0Hz, CH_3 ($COOC_2H_5$), 3.05 (d,J=3.9Hz,H-2"), 4.62 (d,J-3.9Hz,H-3"), 4.15 (q,J=7.0Hz,OCH_2 ($COOC_2H_5$), 1.88 (s,CH_3-4"), 1.25(s,CH_3-6').

^{13}C NMR (75.5 MHz) ($CDC1_3$) : δ 174.72 (C-4), 169.0 (C-6"), 168.69 (C-3"COOH), 155.73 (C-7), 154.31 (C-5"COO), 155.33 (C-8a), 152.81 (C-4"), 152.81 (C-2), 135.25 (C-2'), 135.12 (C-4'), 133.01 (C-5"), 129.69 (C-5'), 129.32 (C-l'), 127.10 (C-6'), 125.97 (C-5), 125.97 (C-3), 123.35 (C-3'),118.36(C-4a),116.27(C-6),114.32(C-8),60.13 (C-3"), 61.13 (C-5"-OCH_2), 45.83 (C-2"), 25.07 (C-6"-CH_3), 19.81 (C-4"-CH_3), 14.21 (C-5"-CH_3).

MS: $[M+H]^+$ m/z 531, M-l 529, 483, 223.

Employing the similar procedure as mentioned as mentioned for **(4a)** compounds **(4b-e)** were synthesized from **(2b-e)** in 50-75% yields.

ii) 7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]isoflavone **(4b)**

Recrystallized from methanol gave pale yellow needles mp. 130 °C.

IR (KBr): 1645 cm^{-1} isoflavone (C=O), 1740 cm^{-1} (=C-O, ester).

UV (MeOH): 280 nm (log ε 5.0), 296 nm (log ε 5.0).

^{1}H NMR (300 MHz; ($CDC1_3$): δ 8.85 (bs,COOH), 8.26 (s,H-2), 7.55 (m,2-H.H-2',6') 7.40 (m,3-H,H-3',4',5'), 7.93 (d,J=9.0Hz,H-5), 6.85 (d,J=9.0Hz,H-6), 6.15 (b,s,7-OH), 4.15 (q,J=7.0Hz,5"-OCH_2), 4.60 (d,J=3.9 H-2"), 3.25 (d,J=3.9Hz, H-3"), 2.22 (s,CH_3 6"), 1.85 (s,CH_3 4"), 1-24 (t J=7.0Hz,CH_3 (5"-COOEt).

^{13}C NMR (75.5MHz) ($CDCl_3$): δ 175.6 (C-4), 169.0 (C-6"), 168.8 (C-3"COOH), 151.48 (C-4"), 155.5(C-5"COO), 151.4 (C-2), 155.4 (C-7), 154.0 (C-8a), 131.5 (C-5"), 128.0 (C-1'), 128.4 (C-2',6'), 129.0 (C-3',5'), 126.0 (C-4'), 125.0 (C-5), 124.5 (C-3). 118.5 (C-4a), 116.0 (C-6), 114.0 (C-8), 61.09 (C-5"-OCH_2), 45.82 (C-2"), 29.31 (C-3"), 22.64 (C-6"-CH_3), 19.78(C-4"-CH_3), 11.20(C-5"-CH_3).

MS: $[M+H]^+$ m/z 462.

iii) 7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-4'-methoxyisoflavone **(4c)**

Recrystallized from methanol pale yellow needles mp150 °C.

IR (KBr): 1635 cm^{-1} isoflavone (C=O), 1740 cm^{-1} (=C-O, ester).

UV (MeOH): 257 nm (log ε 5.2).

^{1}H NMR (300 MHz) ($CDC1_3$): δ 8.90 (bs,COOH),8.05 (d,J=9.0Hz,H-5), 7.90 (s,H-2), 7.45 (d,J=9.0,Hz, H-2',6"), 6.90 (d,J=9.0Hz,H-3',5'), 6.85 (d,J=9.0Hz,H-6), 5.70 (bs,OH-7), 4.60 (d,J=3.9Hz,H-3"), 4.20 (q,OCH_2,$COOC_2H_5$), 3.80 (s,4'-OCH_3), 3.05 (d.J=3.9Hz,H-2"), 2.25 (s,CH_3-6"), 1.90 (s,CH_3-4"), 1.30 (t,J=7Hz,CH_3 ($COOC_2H_5$).

^{13}C NMR (75.5 MHz) ($CDC1_3$): δ 175.8 (C-4), 168.78 (C-3"COOH), 168.78 (C-6"), 159.6 (C-4'), 155.3 (C-8a), 154.1 (C-5"COO), 150.82 (C-4"), 150.82 (C-2), 155.1 (C-7), 130.13 (C-2',6'), 130.13 (C-5"), 125.95 (C-5), 124.0 (C-3), 118.5 (C-4a), 115.88 (C-6), 114.02 (C-8), 125.2 (C-1'), 113.98 (C-3',5'), 61.09 (C-5"-OCH_2), 45.56 (C-2"), 31.12 (C-3"), 55.33 (C-4'-OCH_3), 25.15 (C-6"-CH_3), 19.81 (C-4"-CH_3), 14.22 (C-5"-CH_3).

MS: $[M+H]^+$ m/z 492.

iv)*7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-4'-chloroisoflavone* **(4d)**

Recrystallized from methanol as pale yellow needles mp.138 °C.

IR (KBr): 1630 cm^{-1} isoflavone (C=O), 1742 cm^{-1}(=C-O, ester).

UV (MeOH): 250 nm (log ε 5.0), 273 nm (log ε 4.8).

^{1}H NMR (300 MHz) ($CDCl_3$): δ 8.96 (bs,COOH), 8.07 (d,J=9.0H-5), 7.94 (s,H-2), 7.48(d,J=8.5Hz,H-2',6'), 7.41 (d,J=8.5,H-3',5'), 6.89

(d,J=9.0Hz,H-6), 5.80 (bs,OH-7), 4.64 (d, J=3.9Hz,H-2"), 4.20 (q,J=7.0Hz,$OCH_2COOC_2H_5$), 1.93 (s, CH_3-4"), 2.29 (s,CH_3-6"), 3.12 (d, J=3.9Hz, H-3"), 1.27 (t, J=7.0Hz, CH_3, $COOC_2H_5$).

^{13}C NMR (75.5 MHz) ($CDCl_3$): δ 175.35 (C-4), 168.71 (C-6"), 161.4 (C-3"COOH), 155.6 (C-8a), 155.2 (C-5"COO), 154.2 (C-7), 152.1 (C-4"), 151.40 (C-2), 134.2 (C-4'), 130.20 (C-5"), 130.1 (C-2',6'), 128.65 (C-3',5'), 125.8 (C-5), 125.9 (C-1'), 124.7 (C-3), 118.41 (C-4a), 116.13 (C-6), 114.21 (C-8), 45.80 (C-2"), 31.11 (C-3"), 19.79 (C-4"-CH_3), 61.12 (C-5"-OCH_2), 14.21(C-5"-CH_3),25.11 (C-6"-CH_3).

MS: $[M+H]^+$ m/z 496.

v)*7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethxy-2,3-dihydropyridyl)]-2'-chloroisoflavone* (4e)

Recrystallized from methanol as pale yellow needles mp. 130 °C.

IR (KBr): 1625 cm^{-1} isoflavone (C=O), 1734 cm^{-1} (=C-O, ester).

UV (MeOH): 255 nm (log ε 5.2).

^{1}H NMR (300 MHz) ($CDCl_3$): δ 8.80 (bs,COOH), 8.10 (s,H-2), 7.40 (m,4H-H-3',4', 5',6'), 6.88 (d,J=9.0Hz,H-6), 6.30(bs,OH-7), 4.64 (d,J=3.9Hz,H-2"), 4.60 (d,J=3.9 Hz, H-3"), 4.12 (q,J=7.0Hz,$OCH_2COOC_2H_5$),1.85 (s,CH_3-4"), 2.20 (s,CH_3-2"), 2.28 (s,CH_3-6"), 1.25 (t, J=7.0Hz,CH_3-$COOC_2H_5$).

^{13}C NMR (75.5 MHz) ($CDC1_3$): δ 174.95 (C-4), 169.02 (C-6"), 168.72 (C-3"COOH), 155.58 (C-7), 155.43 (C-8a), 154.30 (C-5"COO), 152.73 (C-4"), 152.73 (C-2), 130.75 (C-5"), 134.48 (C-2'), 132.20 (C-3'), 130.55 (C-4'), 129.81 (C-5'), 129.76 (C-6'), 125.97 (C-5), 124.55 (C-3), 124.31 (C-1'), 118.43 (C-4a), 116.10 (C-6), 114.28 (C-8), 61.08 (C-5"-OCH_2), 45.81 (C-2"), 29.24 (C-3"), 25.03 (C-6"-CH_3), 19.76 (C-4"-CH_3), 14.20 (C-5"-CH_3).

MS: $[M+H]^+$ m/z 496.

Synthesis of 7-methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)] isoflavones (7a-c)

i) *7-Methoxy -8- [2'-(3", 5"-dimethyl-4', 6 '-dicarbethoxypyridyl)] isoflavone* (7a)

7-Methoxy-8-formylisoflavone (**6a)** (2.7g, 10.0mmol), ethlyl-3-aminocrotanate **(3)** (20mmol) in methanol (20ml), stirred at room temperature for 48 hrs. The reaction mixture was poured on to crushed ice. Pale yellow solid separated out which was chromatographed over silicagel by eluting with pet ether: ethyl acetate to give 7-methoxy-8-[2'-(3'',5"-dimethyl-4',6'-dicarbethoxypyridyl)] isoflavone **(7a)**. (2.5g, 40-60%) was recrystallized from methanol as pale yellow needles mp. 185 °C.

IR (KBr): 1632 cm^{-1}(C=O), 1681 cm^{-1} (C=O, ester).

UV (MeOH): 480 nm (log ε 3.6).

^{1}H NMR (300 MHz) ($CDC1_3$) : δ 8.15 (d,J=9.0Hz,H-5), 8.02 (s,H-2), 7.52 (m,2-H, H-2',6'), 7.40, (m,3H, H-3',4',5'), 6.98 (d,J=9.0 Hz, H-6), 5.80 (s,C-H), 5.65 (bs, N-H), 3.95 (q,OCH_2), 3.95 (s,7-OCH_3), 2.25 (s, CH_3), 1.08 (t J=7.0Hz, CH_3 3"-$COOEtx_2$).

^{13}C NMR (75.5 MHz) ($CDCl_3$): δ 176.42 (C-4), 167.86 (C-7), 162.81 (C=O of (COOEt), 154.66 (C-8a), 152.73 (C-2), 145.48 (C-2",6"), 132.26 (C-l'), 128.97 (C-3',5'), 128.44 (C-2',6'), 127.99 (C-4'), 125.71 (C-5), 124.38 (C-3), 122.65 (C-8), 118.06 (C-4a), 109.95 (C-6), 100.28 (C-3",5"), 59.38 (OCH_2), 55.98 (7-OCH_3), 30.41 (C-4"), 19.70 (CH_3-C-2",6"), 14.26 (CH_2CH_3).

MS: $[M+H]^+$ m/z 504, 474, 252, 224, 196.

Employing the similar procedure as mentioned for **7a**, compounds **7b-c** were obtained from **6b-c** solids in 40-60% yield.

ii) *7-Methoxy-8-[2'-(3",5''-dimethyl-4',6 '-dicarbethoxypyridyl)]-2', 4'-dichloroisoflavone* (7b)

Recrystallized from chloroform as pale yellow needles mp.195 °C.

IR (KBr): 1634 cm^{-1} (C=O), 1724 cm^{-1} (=C-O, ester).

UV (MeOH): 368 nm (log ε 4. 4).

^{1}H NMR (300 MHz) ($CDCl_3$): δ 8.10 (d, J=9.0Hz, H-5), 7.95 (s, H-2), 7.20-7.50 (4-H, m, H-3', 4', 5', 6'), 7.00 (d,J=9.0 Hz, H-6). 5.80 (s,C-H), 5.65 (bs,N-H), 3.92 (q,J-7.0Hz, OCH_2), 3.90 (s,7-OCH_3), 2.30 (s,CH_3), 1.10 (t J=7.0Hz,CH_3 3" COOEt x 2).

^{13}C NMR (75.5 MHz) ($CDCl_3$): δ 175.64(C-4), 167.79 (C-7), 163.21 (C=O) of COOEt); 154.17 (C-2), 154.57 (C-8a), 145.55 (C-2",6"), 135.27 (C-2'), 133.08 (C-1'), 134.91 (C-4'), 132.93 (C-6'), 129.81 (C-5'), 129.69 (C-3'), 127.11 (C-5), 125.73 (C-3), 122.76 (C-8), 118.89 (C-4a), 110.22 (C-6), 100.24 (C-3".5"), 59.41 (OCH_2), 56.02 (7-OCH_3), 30.15 (C-1"), 19.76(CH_3-C-2",6"), 14.47(CH_2CH_3).

MS: $[M+H]^+$ m/z 573.

iii) *7-Methoxy-8-[2'-(3 ",5"-dimethyl-4',6 '-dicarbethoxypyridyl)]-2 '-chloroisoflavone* (7c)

Recrystallized from chloroform as pale yellow needles, mp.195 °C.

IR (KBr): 1631 cm^{-1} (C=O), 1724 cm^{-1}(=C-O, ester).

UV (MeOH):368nm (log ε 4.4).

^{1}H NMR (300 MHz) ($CDC1_3$): δ 8.10 (d, J=9.0Hz,H-5), 7.95 (s, H-2), 7.20-7.50 (m.4H, H-3',4',5',6'), 7.00 (d,J=9.0Hz,H-6). 5.80 (s,C-H), 5.65 (bs,N-H), 3.92 (q,J=7Hz, OCH_2), 3.90 (s.7-OCH_3), 2.30 (s,CH_3), 1.05 (t,J-7.0Hz,CH_3-3"-$COOEtx_2$).

^{13}C NMR (75.5 MHz) ($CDC1_3$): δ 175.81 (C-4), 167.82 (C-7), 163.10 (C=O of COOEt), 156.78 (C-8a), 154.09 (C-2), 145.67 (C-2",6"), 138.29 (C-2'), 134.55 (C-1'), 132.27 (C-3'),131.28 (C-4'),130.64 (C-5'), 127.37 (C-6'), 125.70 (C-5), 123.78 (C-3), 122.56 (C-8), 117.93 (C-4a), 109.27 (C-6), 100.15 (C-3",5"), 59.35 (OCH_2), 30.40 (C-4"), 56.97 (7-OCH_3), 19.65 (CH_3-C-2",6"), 14.27 (CH_2CH_3).

MS: $[M+H]^+$ m/z 538.

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