

AMIDES OF *N*-DEACETYLLAPPAONITINE AND UNSATURATED FATTY ACIDS

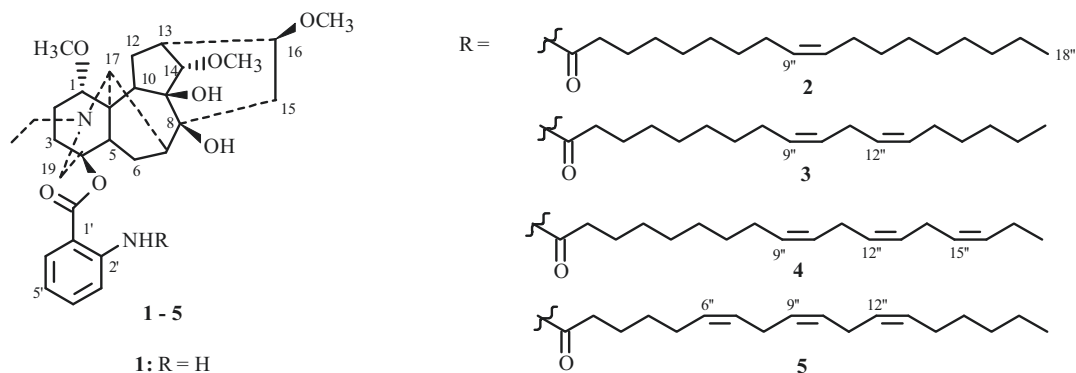
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Amides were prepared from N-deacetylappaconitine and unsaturated oleic, linoleic, α -linolenic, and γ -linolenic fatty acids.

Keywords: diterpene alkaloids, *N*-deacetylappaconitine, oleic acid, linoleic acid, α -linolenic acid, γ -linolenic acid.

Conjugates combining different pharmacophores represent a modern approach to new drug design. They are potentially capable of expanding spectra of biological activity of known drugs, affecting the number of pathogenesis mechanisms, and reducing the number of drugs used in complex therapy.

N-Deacetylappaconitine (**1**), the main metabolite of allapinine, is just as active in most arrhythmia models as allapinine, less toxic, and faster in onset of antiarrhythmic effects but has a shorter duration of action [1]. Modification of **1** is interesting for producing new derivatives combining high arrhythmic activity, prolonged duration of action, and lower toxicity [2, 3]. Unsaturated fatty-acid chlorides could be used for modification and were previously added to the 8-position of aconitine-type diterpene alkaloids [4].



Linoleic and α -linolenic essential polyunsaturated fatty acids (PUFAs) are known to be progenitors of two families of higher PUFAs, i.e., ω -3 and ω -6, a deficiency of which could lead to a broad spectrum of illnesses. They are precursors of prostaglandins and possess potent antisclerotic and cardioprotective activity. They reduce inflammation and cholesterol level and decrease platelet aggregation. In general, this reduces the risk of cardiovascular diseases [5, 6].

Free fatty acids (FAs), primarily linoleic and palmitic [7], and lipid diterpene alkaloids with fatty-acid residues in the 8-position [8] were observed in plants of the genus *Aconitum* among the natural constituents.

Unsaturated-acid chlorides [oleic (OA), linoleic (LA), α -linolenic (ALA), and γ -linolenic (GLA)] were chosen as the modifiers for producing previously unreported amides. Commercial olive, sunflower, flaxseed, and *Borago officinalis* seeds, lipids of which were characterized by significant contents of GLA [9, 10], were the main sources of the acids.

Neutral lipids were extracted by hexane from ground seeds. Fatty acids were isolated from the neutral lipids by hydrolysis and as urea clathrates from the corresponding FA mixtures to produce fractions enriched in one acid or another [11]. The compositions of the FA fractions were monitored by GC of methyl esters. The total starting FAs used to produce the concentrates were also analyzed (Table 1).

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TABLE 1. Compositions of Fatty-Acid Concentrates of Neutral Lipids Before and After Separation of Clathrates, % of Σ FA

Acid	Oil						Seeds	
	olive		sunflower		flaxseed		<i>B. officinalis</i>	
	1	2	1	2	1	2	1	2
16:0	12.9	–	5.8	–	4.2	–	11.4	–
16:1	3.0	–	–	–	–	–	–	–
17:0	–	–	–	–	–	–	0.5	–
18:0	5.6	–	3.9	–	3.2	–	4.6	–
18:1	57.0	96.5	22.5	8.5	21.0	0.7	20.8	–
α -18:2	18.6	3.5	67.0	91.5	15.3	17.0	36.9	33.6
γ -18:3	–	–	–	–	–	–	19.9	65.1
α -18:3	2.9	–	–	–	55.4	82.3	0.6	1.3
20:0	–	–	0.2	–	0.2	–	3.3	–
22:0	–	–	0.6	–	0.2	–	2.0	–
Σ_{mono}	60.0	96.5	22.5	8.5	21.0	–	20.8	–
Σ_{dien}	18.6	3.5	67.0	91.5	15.3	17.0	36.9	33.6
Σ_{trien}	2.9	–	–	–	55.4	82.3	20.5	66.4

1) Initial FA composition; 2) FA composition of concentrate.

Reaction of the OA, LA, ALA, and GLA concentrates with an excess of oxalyl chloride in anhydrous C_6H_6 produced the acid chlorides. The solvent and excess of oxalyl chloride were evaporated. The chlorides were used without further separation in reactions with *N*-deacetylappaconitine (**1**, CH_2Cl_2 , Et_3N , 4 h).

Corresponding amides **2–4** were obtained in 58–63% yield; amide **5**, in a mixture with **3** (2:1 ratio) in 59% yield. The structures of the amides were established using PMR, ^{13}C NMR, and DEPT and 2D COSY, HSQC, HMBC, and NOESY correlation spectra and IR and mass spectra.

IR spectra of amides **2–5** showed NHCO stretching bands at 1681–1682 cm^{-1} . The acyl groups in these compounds were confirmed by additional resonances in PMR and ^{13}C NMR spectra for CH_3 at δ_H 0.87–0.88 ppm and δ_C 14.1–14.3 ppm and proton and C-atom resonances of double bonds (δ_H 5.32–5.38 ppm; δ_C 127.1–131.9 ppm).

PMR and ^{13}C NMR spectra of **2–5** had proton and C-atom chemical shifts for the basic C skeleton including the aromatic ring and practically did not change except for the appearance of an Ar-NH-fragment at weak field of δ_H 11 ppm. The appearance in this region that was analogous to that observed for ArNHAc of lappaconitine confirmed that the N atoms were acylated to form the corresponding amides.

EXPERIMENTAL

GC analysis of methyl esters of FAs used a GC-2014 chromatograph (Shimadzu) with an Omegawax TM 250 capillary column (30.0 m \times 0.25 mm, Supelco), stationary phase poly(ethylene glycol) L (0.25 μ m), column temperature 205°C, vaporizer 250°C, detector 260°C, and carrier gas He at flow rate 30 mL/min. IR spectra were recorded from films on a Shimadzu Prestige 21 FT-IR spectrophotometer in the range 4000–400 cm^{-1} . Mass spectra were measured using direct sample introduction into the ion source of a Thermo Finnigan MAT 95 XP mass spectrometer with programmed temperature from 50 to 270°C and ionizing potential 70 eV. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker Avance III-500 spectrometer [500.13 MHz (1H), 125.76 MHz (^{13}C)].

Resonances in PMR and ^{13}C NMR spectra were accurately assigned using NMR spectral recording methods embedded in the spectrometer operating system, i.e., ^{13}C -DEPT 135 and DEPT 90 with full proton decoupling, where the chemical shifts (CSs) of methyl, methylene, methine, and quaternary C atoms are determined unambiguously. Then, 2D HSQC CH-correlation spectroscopy was used to find the CSs of protons bonded to the corresponding C atoms. The 1H - 1H COSY spectrum confirmed the proton couplings. The HMBC spectrum indicated the correctness of the proton CS assignments from their couplings with geminal and vicinal C atoms. Thus, proton CSs in the Experimental section were determined from 2D HSQC spectra.

GC analyses and spectral studies used equipment at the Khimiya CUC, UIC, RAS. Dried and freshly distilled solvents were used in the work. Benzene was dried by distillation over CaH_2 under Ar. Seed oil from *B. officinalis* was obtained by

extracting ground seeds in a Soxhlet apparatus. Commercially available olive, sunflower, and flaxseed oils were used to isolate OA, LA, and ALA. FAs were isolated from oils by hydrolysis with KOH/MeOH (10%). Concentrates of OA, LA, ALA, and GLA were produced by treating the corresponding acid mixture with saturated urea solution in EtOH (FA-urea, 1:3; 60°C, 1 h; room temp., 3 h; 10°C, 24 h). The concentrate of the corresponding acid was extracted from the mother liquor (H₂O, HCl, Et₂O) as before [11]. The quantitative content of acid in the mother liquor was estimated by methylating it with CH₂N₂ and analyzing it by GC.

General Method for Preparing FA Acid Chlorides. A solution of the appropriate FA (0.002 mol) in anhydrous C₆H₆ (15 mL) was stirred, treated with oxalyl chloride (0.19 mL, 0.0022 mol), held at room temperature under Ar for 6 h, and evaporated in a rotary evaporator. The product was again dissolved in C₆H₆ and evaporated to remove traces of oxalyl chloride and dissolved in anhydrous CH₂Cl₂ (15 mL) for subsequent acylation of *N*-deacetylappaconitine (**1**).

General Method for Acylation of *N*-deacetylappaconitine (1**) by FA Chlorides.** A solution of **1** (2 mmol) and Et₃N (0.26 mL, 2 mmol) in anhydrous CH₂Cl₂ (15 mL) was treated with a solution of the appropriate FA chloride. The mixture was stirred at room temperature under Ar for 4 h. The course of the reaction was monitored by TLC. The mixture was washed with soda solution (10%, 10 mL), dried over Na₂SO₄, and evaporated. The residue was dried *in vacuo* and purified by column chromatography over SiO₂ (60/150 μm) using C₆H₆-MeOH (0.5–2 vol%).

***N*-9-Octadecamonoenoyl-*N*-deacetylappaconitine (**2**).** Yield 58%. Mass spectrum (EI, 70 eV), *m/z* (*I*_{rel}, %): 806 (M⁺, 1), 405 (100). IR spectrum (KBr, ν, cm⁻¹): 1700 (C=O), 1681 (NHCO), 1130–1080 (C–O). ¹H NMR spectrum (500 MHz, CDCl₃, δ, ppm, J/Hz): 0.88 (3H, t, J = 7.0, H-18''), 1.13 (3H, t, J = 7.1, CH₃CH₂N), 1.60 (1H, dd, J = 15.0, 8.2, H_a-6), 1.81 (1H, m, H_a-3), 1.99 (1H, m, H_a-12), 2.04 (1H, m, H_a-15), 2.11 (1H, m, H-10), 2.17 (1H, m, H-7), 2.18 (1H, m, H_a-2), 2.30 (1H, m, H_b-2), 2.38 (1H, m, H-13), 2.40 (1H, m, H_b-15), 2.42 (1H, m, H-5), 2.51 (1H, m, H_b-12), 2.52 (1H, m, CH₃CH_aN), 2.57 (1H, d, J = 11.4, H_a-19), 2.58 (1H, m, CH₃CH_bN), 2.67 (1H, m, H_b-3), 2.71 (1H, dd, J = 15.0, 7.5, H_b-6), 3.02 (1H, s, H-17), 3.19 (1H, m, H-1), 3.30 (3H, s, 1-OCH₃), 3.31 (1H, m, H-16), 3.32 (3H, s, 16-OCH₃), 3.41 (3H, s, 14-OCH₃), 3.45 (1H, d, J = 4.6, H-14), 3.60 (1H, d, J = 11.4, H_b-19), 5.34 (2H, m, H-9'', 10''), 7.02 (1H, t, J = 7.6, H-5'), 7.49 (1H, t, J = 7.4, 8.2, H-4'), 7.92 (1H, d, J = 8.1, H-6'), 8.70 (1H, d, J = 8.5, H-3'), 11.07 (1H, s, NH). ¹³C NMR spectrum (125 MHz, CDCl₃, δ, ppm): 84.2 (CH, C-1), 26.8 (CH₂, C-2), 31.8 (CH₂, C-3), 84.5 (C, C-4), 48.5 (CH, C-5), 24.1 (CH₂, C-6), 47.6 (CH, C-7), 75.6 (C, C-8), 78.6 (C, C-9), 49.8 (CH, C-10), 51.0 (C, C-11), 26.2 (CH₂, C-12), 36.3 (CH, C-13), 90.1 (CH, C-14), 44.8 (CH₂, C-15), 82.9 (CH, C-16), 61.5 (CH, C-17), 55.5 (CH₂, C-19), 49.0 (CH₂, C-21), 13.6 (CH₃, C-22), 56.6 (CH₃, 1-OCH₃), 57.9 (CH₃, 14-OCH₃), 56.1 (CH₃, 16-OCH₃), 167.5 (C, 4-OCO), 115.8 (C, C-1'), 141.8 (C, C-2'), 120.3 (CH, C-3'), 134.4 (CH, C-4'), 122.2 (CH, C-5'), 131.1 (CH, C-6'), 172.3 (C, NHCO), 38.7 (CH₂, C-2''), 25.5 (CH₂, C-3''), 29.2–29.8 (6 × CH₂, C-4'', 5'', 6'', 13'', 14'', 15''), 29.8 (2 × CH₂, C-7'', 12''), 27.1 (2 × CH₂, C-8'', 11''), 129.8 (CH, C-9''), 130.0 (CH, C-10''), 31.9 (CH₂, C-16''), 22.7 (CH₂, C-17''), 14.1 (CH₃, C-18'').

***N*-9,12-Octadecadienoyl-*N*-deacetylappaconitine (**3**).** Yield 63%. Mass spectrum (EI, 70 eV), *m/z* (*I*_{rel}, %): 804 (M⁺, 1), 405 (100). IR spectrum (KBr, ν, cm⁻¹): 1700 (C=O), 1682 (NHCO), 1130–1180 (C–O). ¹H NMR spectrum (500 MHz, CDCl₃, δ, ppm, J/Hz): 0.88 (3H, t, J = 7.0, H-18''), 1.12 (3H, t, J = 7.1, CH₃CH₂N), 1.59 (1H, dd, J = 15.1, 8.3, H_a-6), 1.80 (1H, m, H_a-3), 1.98 (1H, m, H_a-12), 2.01 (1H, m, H_a-15), 2.10 (1H, m, H-10), 2.15 (1H, m, H-7), 2.17 (1H, m, H_a-2), 2.29 (1H, m, H_b-2), 2.37 (1H, m, H-13), 2.39 (1H, m, H-5), 2.40 (1H, m, H_b-15), 2.50 (1H, m, H_b-12), 2.51 (1H, m, CH₃CH_aN), 2.54 (1H, d, J = 11.4, H_a-19), 2.56 (1H, m, CH₃CH_bN), 2.64 (1H, m, H_b-3), 2.68 (1H, dd, J = 15.1, 7.4, H_b-6), 3.00 (1H, s, H-17), 3.18 (1H, m, H-1), 3.29 (3H, s, 1-OCH₃), 3.30 (1H, m, H-16), 3.31 (3H, s, 16-OCH₃), 3.40 (3H, s, 14-OCH₃), 3.44 (1H, d, J = 4.7, H-14), 3.58 (1H, d, J = 11.4, H_b-19), 5.35 (4H, m, H-9'', 10'', 12'', 13''), 7.01 (1H, t, J = 7.6, H-5'), 7.48 (1H, t, J = 7.9, H-4'), 7.92 (1H, d, J = 8.1, H-6'), 8.70 (1H, d, J = 7.9, H-3'), 11.06 (1H, s, NH). ¹³C NMR spectrum (125 MHz, CDCl₃, δ, ppm): 84.2 (CH, C-1), 26.8 (CH₂, C-2), 31.8 (CH₂, C-3), 84.5 (C, C-4), 48.6 (CH, C-5), 24.1 (CH₂, C-6), 47.6 (CH, C-7), 75.6 (C, C-8), 78.6 (C, C-9), 49.8 (CH, C-10), 51.0 (C, C-11), 26.2 (CH₂, C-12), 36.3 (CH, C-13), 90.1 (CH, C-14), 44.9 (CH₂, C-15), 82.9 (CH, C-16), 61.5 (CH, C-17), 55.5 (CH₂, C-19), 49.0 (CH₂, C-21), 13.6 (CH₃, C-22), 56.6 (CH₃, 1-OCH₃), 57.9 (CH₃, 14-OCH₃), 56.1 (CH₃, 16-OCH₃), 167.5 (C, 4-OCO), 115.8 (C, C-1'), 141.8 (C, C-2'), 120.3 (CH, C-3'), 134.4 (CH, C-4'), 122.2 (CH, C-5'), 131.1 (CH, C-6'), 172.2 (C, NHCO), 38.7 (CH₂, C-2''), 25.5 (CH₂, C-3''), 29.2–29.8 (5 × CH₂, C-4'', 5'', 6'', 7'', 15''), 27.2 (2 × CH₂, C-8'', 14''), 130.0 (CH, C-9''), 128.0 (CH, C-10''), 26.5 (CH₂, C-11''), 128.8 (CH, C-12''), 130.1 (CH, C-13''), 31.5 (CH₂, C-16''), 22.6 (CH₂, C-17''), 14.1 (CH₃, C-18'').

***N*-9,12,15-Octadecatrienoyl-*N*-deacetylappaconitine (**4**).** Yield 61%. Mass spectrum (EI, 70 eV), *m/z* (*I*_{rel}, %): 802 (M⁺, 1), 405 (100). IR spectrum (KBr, ν, cm⁻¹): 1700 (C=O), 1682 (NHCO), 1130–1080 (C–O). ¹H NMR spectrum (500 MHz, CDCl₃, δ, ppm, J/Hz): 0.87 (3H, t, J = 6.8, H-18''), 1.11 (3H, t, J = 7.5, CH₃CH₂N), 1.59 (1H, dd, J = 15.1, 8.3, H_a-6), 1.80 (1H, m, H_a-3), 2.00 (1H, m, H_a-12), 2.02 (1H, m, H_a-15), 2.09 (1H, m, H-10), 2.16 (1H, m, H-7), 2.18 (1H, m,

H_a-2), 2.29 (1H, m, H_b-2), 2.37 (1H, m, H-13), 2.39 (1H, m, H-5), 2.40 (1H, m, H_b-15), 2.49 (1H, m, H_b-12), 2.51 (1H, m, CH₃CH_aN), 2.54 (1H, d, J = 11.4, H_a-19), 2.56 (1H, m, CH₃CH_bN), 2.65 (1H, m, H_b-3), 2.69 (1H, dd, J = 15.1, 7.4, H_b-6), 3.00 (1H, s, H-17), 3.18 (1H, m, H-1), 3.29 (3H, s, 1-OCH₃), 3.30 (1H, m, H-16), 3.31 (3H, s, 16-OCH₃), 3.40 (3H, s, 14-OCH₃), 3.44 (1H, d, J = 4.6, H-14), 3.58 (1H, d, J = 11.4, H_b-19), 5.32–5.38 (6H, m, H-9'', 10'', 12'', 13'', 15'', 16''), 7.01 (1H, t, J = 7.4, 7.8, H-5'), 7.48 (1H, t, J = 7.3, 7.9, H-4'), 7.91 (1H, d, J = 7.9, H-6'), 8.69 (1H, d, J = 8.5, H-3'), 11.06 (1H, s, NH). ¹³C NMR spectrum (125 MHz, CDCl₃, δ, ppm): 84.2 (CH, C-1), 26.8 (CH₂, C-2), 31.8 (CH₂, C-3), 84.5 (C, C-4), 48.6 (CH, C-5), 24.1 (CH₂, C-6), 47.6 (CH, C-7), 75.6 (C, C-8), 78.6 (C, C-9), 49.8 (CH, C-10), 50.9 (C, C-11), 26.2 (CH₂, C-12), 36.3 (CH, C-13), 90.1 (CH, C-14), 44.8 (CH₂, C-15), 82.9 (CH, C-16), 61.6 (CH, C-17), 55.5 (CH₂, C-19), 49.0 (CH₂, C-21), 13.6 (CH₃, C-22), 56.6 (CH₃, 1-OCH₃), 57.9 (CH₃, 14-OCH₃), 56.1 (CH₃, 16-OCH₃), 167.4 (C, 4-OCO), 115.8 (C, C-1'), 141.7 (C, C-2'), 120.3 (CH, C-3'), 134.4 (CH, C-4'), 122.2 (CH, C-5'), 131.1 (CH, C-6'), 172.3 (C, NHCO), 38.7 (CH₂, C-2''), 25.5 (CH₂, C-3''), 29.2–29.6 (4 × CH₂, C-4'', 5'', 6'', 7''), 27.2 (CH₂, C-8''), 130.3 (CH, C-9''), 128.3 (CH, C-10''), 25.6 (CH₂, C-11''), 127.7 (CH, C-12''), 128.3 (CH, C-13''), 25.5 (CH₂, C-14''), 127.1 (CH, C-15''), 131.9 (CH, C-16''), 20.5 (CH₂, C-17''), 14.3 (CH₃, C-18'').

N-6,9,12-Octadecatrienoyl-N-deacetylappaconitine (5). Mass spectrum (EI, 70 eV), *m/z* (*I*_{rel}, %): 802 (*M*⁺, 1), 405 (100). IR spectrum (KBr, ν, cm⁻¹): 1700 (C=O), 1682 (NHCO), 1130–1080 (C–O). ¹H NMR spectrum (500 MHz, CDCl₃, δ, ppm, J/Hz): 0.87 (3H, t, J = 6.7, H-18''), 1.11 (3H, t, J = 7.1, CH₃CH₂N), 1.60 (1H, dd, J = 15.1, 8.2, H_a-6), 1.80 (1H, m, H_a-3), 1.96 (1H, m, H_a-12), 2.02 (1H, m, H_a-15), 2.09 (1H, m, H-10), 2.15 (1H, m, H-7), 2.18 (1H, m, H_a-2), 2.29 (1H, m, H_b-2), 2.37 (1H, m, H-13), 2.39 (1H, m, H-5), 2.40 (1H, m, H_b-15), 2.49 (1H, m, H_b-12), 2.51 (1H, m, CH₃CH_aN), 2.54 (1H, d, J = 11.4, H_a-19), 2.56 (1H, m, CH₃CH_bN), 2.65 (1H, m, H_b-3), 2.69 (1H, dd, J = 15.1, 7.4, H_b-6), 3.00 (1H, s, H-17), 3.19 (1H, m, H-1), 3.29 (3H, s, 1-OCH₃), 3.30 (1H, m, H-16), 3.31 (3H, s, 16-OCH₃), 3.40 (3H, s, 14-OCH₃), 3.44 (1H, d, J = 4.7, H-14), 3.59 (1H, d, J = 11.4, H_b-19), 5.32–5.38 (6H, m, H-6'', 7'', 9'', 10'', 12'', 13''), 7.01 (1H, t, J = 7.4, H-5'), 7.48 (1H, t, J = 7.5, 8.0, H-4'); 7.91 (1H, d, J = 7.7, H-6'), 8.69 (1H, d, J = 8.5, H-3'), 11.07 (1H, s, NH). ¹³C NMR spectrum (125 MHz, CDCl₃, δ, ppm): 84.2 (CH, C-1), 26.8 (CH₂, C-2), 31.8 (CH₂, C-3), 84.5 (C, C-4), 48.5 (CH, C-5), 24.1 (CH₂, C-6), 47.6 (CH, C-7), 75.7 (C, C-8), 78.6 (C, C-9), 49.8 (CH, C-10), 51.0 (C, C-11), 26.2 (CH₂, C-12), 36.3 (CH, C-13), 90.1 (CH, C-14), 44.8 (CH₂, C-15), 82.9 (CH, C-16), 61.6 (CH, C-17), 55.5 (CH₂, C-19), 49.0 (CH₂, C-21), 13.5 (CH₃, C-22), 56.6 (CH₃, 1-OCH₃), 57.9 (CH₃, 14-OCH₃), 56.1 (CH₃, 16-OCH₃), 167.5 (C, 4-OCO), 115.8 (C, C-1'), 141.7 (C, C-2'), 120.3 (CH, C-3'), 134.4 (CH, C-4'), 122.3 (CH, C-5'), 131.1 (CH, C-6'), 172.1 (C, NHCO), 38.5 (CH₂, C-2''), 25.1 (CH₂, C-3''), 29.2 (CH₂, C-4''), 27.2 (CH₂, C-5''), 130.4 (CH, C-6''), 128.4 (CH, C-7''), 25.6 (CH₂, C-8''), 128.1 (CH, C-9''), 128.1 (CH, C-10''), 25.6 (CH₂, C-11''), 127.6 (CH, C-12''), 129.7 (CH, C-13''), 27.2 (CH₂, C-14''), 29.6 (CH₂, C-15''), 31.5 (CH₂, C-16''), 22.6 (CH₂, C-17''), 14.1 (CH₃, C-18'').

ACKNOWLEDGMENT

The work was performed under state task topic No. AAAA-A-17-117011910025-6.

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