SYNTHESIS OF ACYLHYDRAZONES FROM LUPANE AND 19β,28-EPOXY-18α-OLEANANE 2,3-*seco*-ALDEHYDONITRILES

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*2,3-seco-Triterpene acylhydrazones, which are interesting as new biologically active compounds, were prepared by reaction of lupane and 19*β*,28-epoxy-18*α*-oleanane 2,3-seco-aldehydonitriles with acylated hydrazines.*

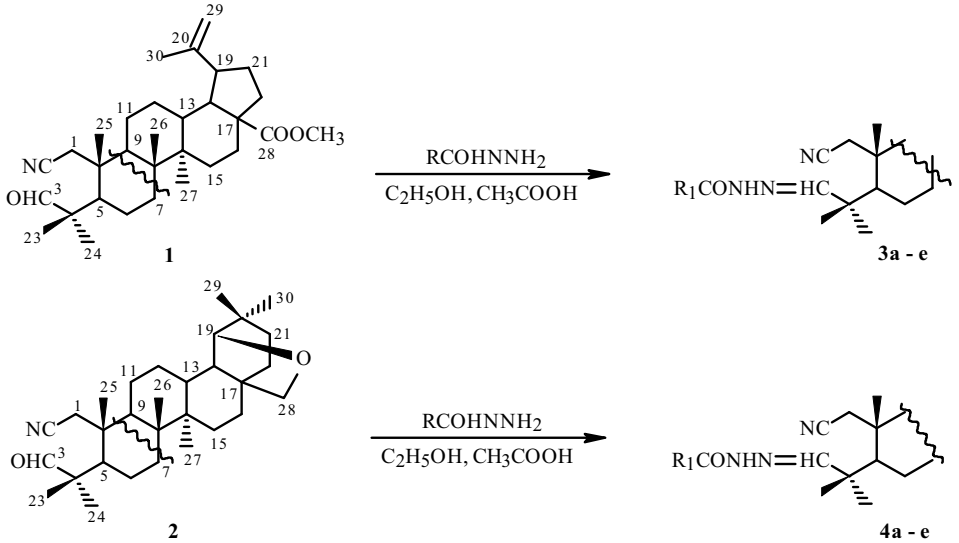
Keywords: A-*seco*-triterpenoids, 2,3-*seco*-aldehydonitriles, betulin, betulinic acid, allobetulone, acylhydrazines, hydrazones.

Lupane triterpenoids are a valuable source of new pharmacologically active derivatives among low-molecular-weight compounds of plant origin. Functionalization of their more available representatives betulin and betulinic acid at C-3, C-28, and C-30 produced numerous derivatives with anti-HIV, antitumor, immunostimulating, and anti-inflammatory activity [1].

More drastic changes of the C skeleton of betulin have been investigated much less frequently. Moreover, lupane *seco*-derivatives were detected in extracts of medicinal plants [2, 3] and among cytotoxic products from microbial transformation of betulin and betulinic acid [4]. High cytotoxic and antiviral activity was reported for semi-synthetic 2,3-*seco*-dicarboxylic acids of the oleanane and lupane type [5, 6] and 2,3-*seco*-aldehydonitriles and their derivatives obtained from betulonic acid and its methyl ester [7–9].

In continuation of research on chemical transformation of 2,3-*seco*-triterpenoids and in consideration of the reported high anti-angiogenic and antiviral activity of betulonic acid hydrazones and hydrazides [10–12], we synthesized 2,3-*seco*-triterpene acylhydrazones based on 2,3-*seco*-3-oxo-1-cyano lupane (**1**) and 19β,28-epoxy-18α-oleanane (**2**) derivatives.

Triterpene 2,3-*seco*-acylhydrazones **3a**–**e** and **4a**–**e** were prepared by reaction of acylated hydrazines with 2,3-*seco*-aldehydonitriles **1** or **2** in EtOH in the presence of catalytic amounts of glacial acetic acid [13]. The reaction was carried out at room temperature with yields of 20-68% of **3a**–**e** and **4a**–**e** after purification by chromatography.



R_1 = CH_3- (**a**); $C_4H_9CH(C_2H_5)$- (**b**); $C_{10}H_{21}$- (**c**); $C_{14}H_{29}$- (**d**); C_6H_5- (**e**)

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The structures of synthesized hydrazones **3a**–**e** and **4a**–**e** were confirmed by IR and NMR spectroscopy. IR spectra of the hydrazones contained absorption bands at 1653–1682, 2233–2244, and 3192–3236 cm^{-1} that corresponded to stretching vibrations of CH=N, C=N, and NH bonds, respectively. The PMR spectra showed resonances for protons typical of lupane or 19β,28-epoxy-18α-oleanane, an acyl substituent, a singlet for C-3 at 7.15–7.70 ppm, and a broad singlet for the amino proton at 8.54–9.32. ^{13}C NMR spectra exhibited characteristic resonances for nitrile (118.23–118.80 ppm), C-3 (154.16–160.64), and the carbonyl C atom of the acyl substituent (163.62–176.57).

Thus, the studies resulted in the synthesis of 2,3-*seco*-triterpene acylhydrazones that are of interest as new biologically active agents.

EXPERIMENTAL

IR spectra were recorded in mineral oil mulls on a Bruker IFS 66/S IR-Fourier spectrometer (Germany). PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury+ spectrometer (USA) at operating frequency 300 or 75.5 MHz with HMDS internal standard. Melting points were measured on a PTP melting-point apparatus (Russia). Specific optical rotation was determined for $CHCl_3$ solutions on a Perkin–Elmer 341 polarimeter (USA) at 589 nm. Elemental analyses (C, H, N) were performed using a Leco CHNS-9321P analyzer (Netherlands) and agreed with those calculated.

Column chromatography (CC) was performed over silica gel (Merck, 0.35–0.70 mm) with a compound:sorbent ratio of ≈ 1:50 with elution by a mixture selected individually for each compound. TLC used Sorbfil plates (Russia) and detection by spraying with an ethanol solution of phosphomolybdic acid (20%) and subsequent heating at 100–120°C for 2–3 min. 2,3-*seco*-Aldehydonitriles **1** and **2** were synthesized by the literature method [7].

General Method for Preparing Acylhydrazones (3a–e, 4a–e). A solution of **1** or **2** (0.44 mmol) in EtOH (15 mL) was treated with acylhydrazine (0.44 mmol) and glacial acetic acid (2 drops) and left at room temperature for 7 h. The course of the reaction was monitored by TLC. Solvent was evaporated. The solid was purified by CC.

Acetylhydrazone of 2,3-*seco*-28-methoxycarbonyl-1-cyanolup-20(29)-en-3-al (3a), $C_{33}H_{51}N_3O_3$. Yield after purification by CC, 0.26 g (48%), R_f 0.34 (hexane:EtOAc, 5:1), mp 120–122°C (hexane:EtOAc, 5:1), $[\alpha]_D^{21}$ +9.5° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1653 (CH=NNHCO), 1726 ($COOCH_3$), 2237 (C≡N), 3236 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90, 0.92, 1.00, 1.16, 1.18 (5 × 3H, 5s, $5CH_3$), 1.67 (3H, s, CH_3-30), 2.22 (3H, s, CH_3), 2.29 and 2.56 (2H, 2d, J_{AB} = 18.3, H_2-1, AB-system), 2.99 (1H, td, J = 10.5, 5.1, CH-19), 3.66 (3H, s, $COOC\underline{H}_3$), 4.60 and 4.72 (2H, 2s, H_2-29), 7.21 (1H, s, H-3), 9.24 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 14.54, 15.80, 18.43, 19.18, 20.15, 20.32, 21.77, 22.44, 25.46, 28.24, 29.58, 29.64, 30.41, 31.88, 33.33, 36.80, 38.17, 40.61, 42.32, 42.44, 42.74, 44.73, 46.85, 49.12, 51.27, 51.47, 56.46, 109.83 (C-29), 118.30 (C-2), 150.21 (C-20), 154.59 (C-3), 173.29 ($\underline{C}ONH$), 176.58 (C-28).

2-Ethylpentanoylhydrazone of 2,3-*seco*-28-methoxycarbonyl-1-cyanolup-20(29)-en-3-al (3b), $C_{39}H_{63}N_3O_3$. Yield after purification by CC, 0.37 g (59%), R_f 0.4 (hexane:EtOAc, 7:3), mp 86–88°C (hexane:EtOAc, 7:3), $[\alpha]_D^{21}$ +2.0° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1666 (CH=NNHCO), 1725 ($COOCH_3$), 2237 (C≡N), 3202 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83, 0.86 (2 × 3H, 2t, J = 7.1, $2CH_3$), 0.89, 0.92, 1.00, 1.17, 1.19 (5 × 3H, 5s, $5CH_3$), 1.67 (3H, s, CH_3-30), 2.26 and 2.51 (2H, 2d, J_{AB} = 18.0, H_2-1, AB-system), 2.98 (1H, td, J = 9.0, 5.7, H-19), 3.10–3.22 (1H, m, $C_4H_9C\underline{H}(C_2H_5)CONHN{=}CH$), 3.66 (3H, s, $COOC\underline{H}_3$), 4.60 and 4.70 (2H, 2s, H_2-29), 7.20 (3H, s, H-3), 9.25 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 11.91, 12.01, 13.96, 14.03, 14.53, 15.79, 18.31, 19.18, 20.18, 21.79, 22.65, 22.70, 25.45, 28.26, 28.37, 29.62, 29.79, 30.42, 31.83, 31.88, 33.33, 36.80, 38.19, 40.62, 42.40, 42.56, 42.76, 44.68, 46.85, 49.14, 51.26, 51.40, 56.47, 109.82 (C-29), 118.23 (C-2), 150.19 (C-20), 154.16 (C-3), 176.57 ($\underline{C}ONH$), 178.77 (C-28).

Undecanoylhydrazone of 2,3-*seco*-28-methoxycarbonyl-1-cyanolup-20(29)-en-3-al (3c), $C_{42}H_{69}N_3O_3$. Yield after purification by CC, 0.29 g (43%), R_f 0.41 (hexane:EtOAc, 10:1), mp 142–144°C (hexane:EtOAc, 10:1), $[\alpha]_D^{21}$ +5.4° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1670 (CH=NNHCO), 1725 ($COOCH_3$), 2237 (C≡N), 3211 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87 (3H, t, J = 7.5, CH_3), 0.90, 0.93, 1.00, 1.16, 1.19 (5 × 3H, 5s, $5CH_3$), 1.67 (1H, s, CH_3-30), 2.29 and 2.56 (2H, 2d, J_{AB} = 18.2, H_2-1, AB-system), 2.99 (1H, td, J = 10.2, 6.0, H-19), 3.66 (3H, s, $COOC\underline{H}_3$), 4.60 and 4.73 (2H, 2s, H_2-29), 7.20 (1H, s, H-3), 9.21 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 14.06, 14.54, 15.79, 18.39, 19.19, 20.21, 21.80, 22.55, 22.63, 24.84, 25.48, 28.22, 29.27, 29.29, 29.34, 29.36, 29.48, 29.53, 29.55, 29.60, 30.43, 31.86, 32.79,, 33.33, 36.80, 38.20, 40.63, 42.36, 42.44, 42.76, 44.72, 46.86, 49.15, 51.26, 51.43, 56.47, 109.83 (C-29), 118.25 (C-2), 150.20 (C-20), 154.44 (C-3), 176.22 (CONH), 176.57 (C-28).

Pentadecanoylhydrazone of 2,3-*seco*-28-methoxycarbonyl-1-cyanolup-20(29)-en-3-al (3d), $C_{46}H_{77}N_3O_3$. Yield after purification by CC, 0.32 g (44%), R_f 0.44 (hexane:EtOAc, 10:1), yellow paste, $[\alpha]_D^{21}$ +3.1° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1670 (CH=NNHCO), 1730 ($COOCH_3$), 2242 (C≡N), 3202 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, t, J = 6.9, CH_3), 0.90, 0.93, 1.00, 1.16, 1.18 (5 × 3H, 5s, $5CH_3$), 1.67 (3H, s, CH_3-30), 2.26 and 2.56 (2H, 2d, J_{AB} = 18.2, H_2-1, AB-system), 2.99 (1H, td, J = 11.1, 5.7, H-19), 3.66 (3H, s, $COOCH_3$), 4.60 and 4.72 (2H, 2s, H_2-29), 7.18 (3H, s, CH-3), 9.08 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 14.07, 14.55, 15.81, 18.41, 19.20, 20.20, 21.80, 22.55, 22.65, 24.84, 25.49, 28.23, 29.32 (2C), 29.34 (2C), 29.37, 29.49, 29.60 (2C), 29.61 (2C), 29.65 (2C), 30.44, 31.88, 32.81, 33.36, 36.81, 38.21, 40.64, 42.37, 42.45, 42.77, 44.74, 46.86, 49.16, 51.26, 51.45, 56.48, 109.83 (C-29), 118.26 (C-2), 150.20 (C-20), 154.39 (C-3), 176.17 (CONH), 176.57 (C-28).

Benzoylhydrazone of 2,3-*seco*-28-methoxycarbonyl-1-cyanolup-20(29)-en-3-al (3e), $C_{38}H_{53}N_3O_3$. Yield after purification by CC, 0.24 g (68%), R_f 0.26 (hexane:EtOAc, 5:1), mp 128–131°C (hexane:EtOAc, 10:1), $[\alpha]_D^{21}$ +4.2° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1653 (CH=NNHCO), 1726 ($COOCH_3$), 2233 (C≡N), 3236 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.91 (2 × 3H, s, $2CH_3$), 0.99, 1.18, 1.25 (3 × 3H, 3s, $3CH_3$), 1.67 (3H, s, CH_3-30), 2.25 and 2.54 (2H, 2d, J_{AB} = 18.2, H_2-1, AB-system), 2.99 (1H, td, J = 10.7, 5.1, H-19), 3.66 (3H, s, $COOCH_3$), 4.60 and 4.72 (2H, 2s, H_2-29), 7.42 (2H, t, J = 7.2, arom.), 7.50 (1H, t, J = 7.2, arom.), 7.70 (1H, s, H-3), 7.84 (2H, d, J = 6.9, arom.), 9.32 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 14.54, 15.79, 18.56, 19.21, 19.71, 21.63, 25.40, 28.50, 29.46, 29.57, 30.43, 31.89, 33.47, 36.81, 38.10, 40.63, 42.49, 42.73 (2C), 44.88, 46.84, 49.15, 51.28, 51.55, 56.46, 109.81 (C-29), 118.79 (C-2), 127.29 (2C arom.), 128.62 (2C arom.), 131.82 (arom.), 133.21 (arom.), 150.23 (C-20), 160.38 (C-3), 163.62 (CONH), 176.54 (C-28).

Acetylhydrazone of 1-cyano-2,3-*seco*-19β,28-epoxy-18α-olean-3-al (4a), $C_{32}H_{51}N_3O_2$. Yield 0.23 g (45%), R_f 0.12 ($CHCl_3$:EtOAc, 10:1), mp 65–67°C ($CHCl_3$:EtOAc, 10:1), $[\alpha]_D^{21}$ +30.0° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1676 (CH=N), 2240 (C≡N), 3208 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78, 0.92, 0.95, 0.97, 1.17, 1.19, 1.24 (7 × 3H, 7s, $7CH_3$), 2.23 (3H, s, CH_3), 2.32 and 2.60 (2H, 2d, J_{AB} = 18.2, H_2-1, AB-system), 3.44 and 3.75 (2H, 2d, J_{AB} = 7.8, H_2-28, AB-system), 3.52 (1H, s, H-19), 7.19 (1H, s, H-3), 8.87 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 13.39, 15.70, 18.73, 20.17, 20.31, 21.88, 22.59, 24.50, 26.13, 26.35, 26.42, 28.18, 28.76, 29.85, 32.64, 32.88, 34.27, 36.24, 36.61, 40.55, 41.10, 41.45, 42.36, 42.51, 45.25, 46.58, 51.61, 71.23 (C-28), 87.83 (C-19), 118.28 (C-2), 154.61 (C-3), 173.37 (CONH).

2-Ethylpentanoylhydrazone of 1-cyano-2,3-*seco*-19β,28-epoxy-18α-olean-3-al (4b), $C_{38}H_{63}N_3O_2$. Yield 0.12 g (20%), R_f 0.4 ($CHCl_3$:EtOAc, 10:1), mp 73–75°C ($CHCl_3$:EtOAc, 10:1), $[\alpha]_D^{21}$ +18.6° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1668 (CH=N), 2244 (C≡N), 3204 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78, 0.95, 0.97, 1.18, 1.19 (5 × 3H, 5s, $5CH_3$), 0.86 and 0.88 (2 × 3H, 2t, J = 6.6, $2CH_3$), 0.92 (2 × 3H, s, $2CH_3$), 2.30 and 2.58 (2H, 2d, J_{AB} = 17.7, H_2-1, AB-system), 3.02–3.22 (1H, m, =NNHCOCH(C_2H_5)C_4H_9), 3.44 and 3.75 (2H, 2d, J_{AB} = 7.8, H_2-28, AB-system), 3.52 (1H, s, H-19), 7.15 (1H, s, H-3), 8.54 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 12.03, 13.38, 13.98, 15.67, 18.60, 20.13, 21.87, 22.65, 22.69, 24.48, 26.11, 26.32, 26.40, 28.34, 28.73, 29.62, 29.76, 31.68, 31.79, 32.62, 32.85, 34.24, 36.21, 36.59, 40.51, 41.07, 41.42, 42.41, 42.46, 42.54, 45.16, 46.54, 51.51, 71.20 (C-28), 87.81 (C-19), 118.23 (C-2), 154.28 (C-3), 178.97 (CONH).

Undecanoylhydrazone of 1-cyano-2,3-*seco*-19β,28-epoxy-18α-olean-3-al (4c), $C_{41}H_{69}N_3O_2$. Yield 0.32 g (50%), R_f 0.34 ($CHCl_3$:EtOAc, 10:1), mp 143–145°C ($CHCl_3$:EtOAc, 10:1), $[\alpha]_D^{21}$ +22.9° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1682 (CH=N), 2242 (C≡N), 3196 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78, 0.95, 0.97, 1.17, 1.19 (5 × 3H, 5s, $5CH_3$), 0.86 (3H, t, J = 6.6, CH_3), 0.92 (2 × 3H, s, $2CH_3$), 2.31 and 2.59 (1H, d, J_{AB} = 18.3, H-1), 2.58 (2H, t, J = 7.5, $COCH_2(CH_2)_9CH_3$), 3.44 and 3.75 (2H, 2d, J_{AB} = 7.7, H_2-28, AB-system), 3.52 (1H, s, H-19), 7.16 (1H, s, H-3), 8.67 (1H br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 13.38, 14.07, 15.68, 18.67, 20.18, 21.87, 22.64, 24.48, 24.85, 26.12, 26.34, 26.42, 28.22, 28.74, 29.28, 29.35 (2C), 29.38, 29.49, 29.56 (2C), 29.79, 31.87, 32.63, 32.83, 34.26, 36.22, 36.60, 40.53, 41.08, 41.43, 42.35, 42.48, 45.20, 46.56, 51.54, 71.21 (C-28), 87.81 (C-19), 118.26 (C-2), 154.20 (C-3), 176.07 (CONH).

Pentadecanoylhydrazone of 1-cyano-2,3-*seco*-19β,28-epoxy-18α-olean-3-al (4d), $C_{45}H_{77}N_3O_2$. Yield 0.17 g (24%), R_f 0.4 ($CHCl_3$:EtOAc, 10:1), yellow paste, $[\alpha]_D^{21}$ +19.0° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1674 (CH=N), 2244 (C≡N), 3200 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78, 0.95, 0.97, 1.17, 1.19 (5 × 3H, 5s, $5CH_3$), 0.87 (3H, t, J = 6.8, CH_3), 0.92 (2 × 3H, s, $2CH_3$), 2.31 and 2.60 (1H, d, J = 18.0, H_2-1), 2.55–2.64 (2H, m, $COCH_2(CH_2)_{13}CH_3$), 3.44 and 3.75 (2H, 2d, J_{AB} = 8.0, H_2-28, AB-system), 3.52 (1H, s, H-19), 7.15 (1H, s, H-3), 8.60 (1H br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 13.40, 14.09, 15.71, 18.72, 20.19, 21.89, 22.67, 24.50, 24.85, 26.14, 26.36, 26.44, 28.23, 28.76, 29.34 (2C), 29.37 (2C), 29.52, 29.64 (3C), 29.68 (3C), 29.81, 31.91, 32.66, 32.85, 34.29, 36.25, 36.63, 40.56, 41.11, 41.45, 42.39, 42.52, 45.23, 46.58, 51.55, 71.23 (C-28), 87.84 (C-19), 118.26 (C-2), 154.27 (C-3), 176.09 (CONH).

Benzoylhydrazone of 1-cyano-2,3-*seco*-19β,28-epoxy-18α-olean-3-al (4e), $C_{37}H_{53}N_3O_2$. Yield 0.25 g (43%), R_f 0.28 ($CHCl_3$:EtOAc, 10:1), mp 247–249°C ($CHCl_3$:EtOAc, 10:1), $[\alpha]_D^{21}$ +7.6° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1654 (CH=N), 2236 (C≡N), 3192 (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78, 0.92, 0.96, 1.21, 1.24 (5 × 3H, 5s, $5CH_3$), 0.98 (2 × 3H, s, $2CH_3$), 1.86 and 2.60 (1H, d, J = 18.1, H_2-1), 3.44 and 3.75 (2H, 2d, J_{AB} = 18.0, H_2-28, AB-system), 3.51 (1H, s, H-19), 7.44 (2H, t, J = 7.2, arom.), 7.52 (1H, t, J = 6.6, arom.), 7.70 (1H, s, H-3), 7.82 (2H, d, J = 7.5, arom.), 8.95 (1H, br.s, NH).

^{13}C NMR spectrum (75.5 MHz, $CDCl_3$, δ, ppm): 13.39, 15.65, 18.85, 19.75, 20.64, 21.75, 24.48, 26.10, 26.31, 26.38, 28.44, 28.73, 29.65, 32.62, 33.00, 34.17, 36.21, 36.60, 40.30, 41.06, 41.42, 42.54, 42.75, 45,39, 46.50, 51.70, 71.19 (C-28), 87.81 (C-19), 118.80 (C-2), 127.33 (2C, arom.), 128.69 (2C, arom.), 131.89 (arom.), 133.20 (arom.), 160.64 (C-3), 164.15 (CONH).

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