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SYNTHESIS OF NEW AMIDOETHANESULFONAMIDES OF BETULONIC ACID

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New potentially biologically active amidoethanesulfonamides of betulonic acid were synthesized by the acid chloride method via conjugation of betulonic acid with 2-aminoethanesulfonamides as the free bases.

Keywords: pentacyclic triterpenoids, betulonic acid, 2-aminoethanesulfonamides, amidoethanesulfonamides.

Pentacyclic lupane-type triterpenoids form a promising platform for development of biologically active compounds with various types and mechanisms of antiviral activity [1], including against influenza viruses [2, 3], hepatitis B and D [4], human immunodeficiency [5–7], Dengue and Chikungunya flaviviruses [8], and corona viruses HCoV-229E [9] and SARS-CoV-2 [10]. Currently, expansion of the library of modified triterpenes and identification among them of novel antiviral agents are becoming especially critical. One approach to the synthesis of antiviral compounds consists of introducing a sulfonamide group into a triterpenoid structure. The sulfonamide group is the basis of various antimicrobial, antitumor, anti-inflammatory, antiviral, and many other medicines and biologically active compounds [11–13]. HIV-1 maturation inhibitors were observed among derivatives of lupane triterpenoids with a C-3 or C-28 sulfonamide group [14, 15].

In continuation of research on the modification of lupane triterpenoids to develop biologically active compounds, new sulfonamide derivatives of betulonic acid (**1**) were synthesized by us. The sulfonamide group was bonded to the triterpene skeleton through an amidoethane spacer. Previously, sulfonamides of this series were first prepared in low yields by us using the reaction of betulinic and betulonic acids with 2-aminoethanesulfonamide hydrochlorides in the presence of Mukaiyama reagent [16].

The present article demonstrates the syntheses of amidoethanesulfonamides of betulonic acid **2a**–**d** via the acid chloride method using 2-aminoethanesulfonamides **3a**–**d** as the free bases. Compounds **3a**–**d** were obtained in 30–51% yields from phthalic anhydride and 2-aminoethanesulfonic acid (taurine) through 2-phthalimidoethanesulfonyl chloride (**4**) and 2-phthalimidoethanesulfonamides **5a**–**d** using the literature method [17]. The phthalyl protection of the amine in **5a**–**d** was removed by hydrazine hydrate upon refluxing in EtOH. The target amidoethanesulfonamides **2a**–**d** were obtained in 49–78% yields after purification by column chromatography over silica gel.

The structures of conjugates **2a**–**d** were confirmed by 1D and 2D NMR spectroscopy (^{1}H, ^{13}C {^{1}H}, ^{13}C DEPT, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{15}N HSQC, ^{1}H–^{15}N HMBC) and high-resolution mass spectrometry. Resonances in PMR and ^{13}C NMR spectra of all synthesized sulfonamides **2a**–**d** were fully assigned. Characteristic resonances of $NH(CH_2)_2SO_2$ in proton spectra included a quartet at 3.71–3.75 ppm (2H-2″) and a multiplet at 3.00–3.05 (2H-1″, for **2a**, **c**, **d**) or two doublets of triplets for diastereotopic protons H-1a″ and H-1b″ at 3.22 and 3.29 ppm (for **2b**). ^{13}C NMR spectra showed resonances for C-2″ at 33.56–33.95 ppm while the C-1″ chemical shifts varied from 43.12 to 51.46 ppm, depending on the amine substituent on the S atom.

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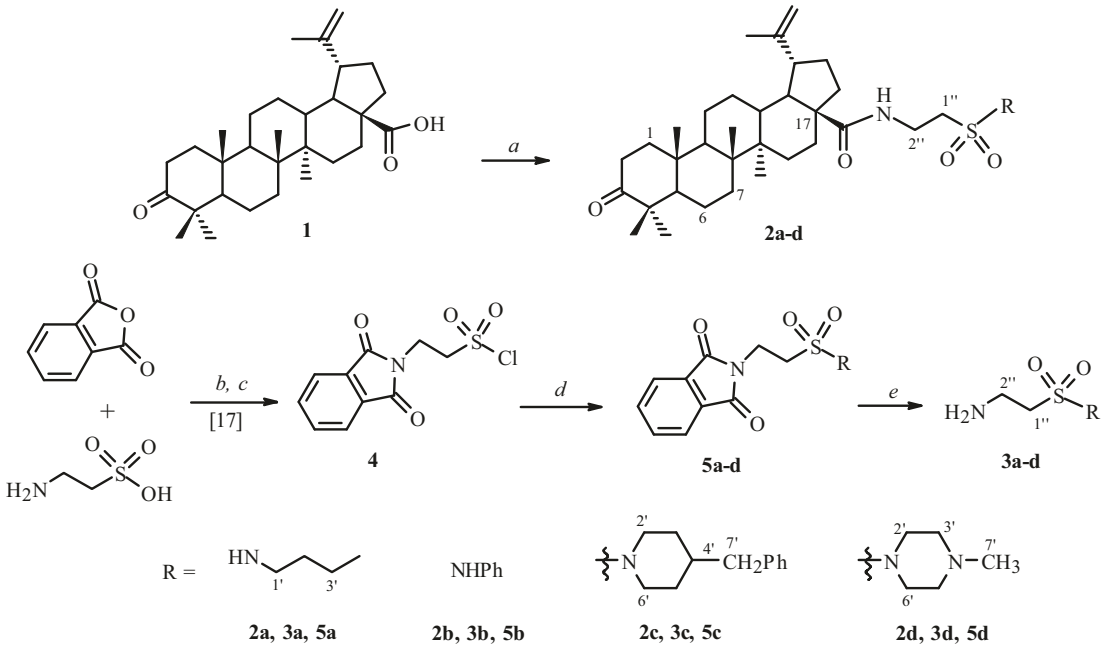

a. 1. $(COCl)_2$, CH_2Cl_2; 2. **3a–d**, CH_2Cl_2, Et_3N; *b.* AcONa, AcOH; *c.* PCl_5, toluene, reflux; *d.* amine, CH_2Cl_2, Et_3N, reflux; *e.* $NH_2NH_2 \cdot H_2O$, EtOH, reflux.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded using TMS as an internal standard or NH_3 (for ^{15}N) as an external standard on an Avance III-500 (Bruker, Germany) at operating frequency 500.13 MHz (^1H), 125.47 MHz (^{13}C), and 50.68 MHz (^{15}N) or AMXIII-300 spectrometer (Bruker, Germany) at operating frequency 300.13 MHz (^1H) and 75.47 MHz (^{13}C). Positive-ion mass spectra were measured on an Agilent 1260 Infinity II/6530-LC/Q-TOF high-resolution mass spectrometer or an LCMS-2010EV liquid chromatograph-mass spectrometer (Shimadzu). Rotation angles were measured on a PerkinElmer 341C instrument. Column chromatography used SiO_2 (L grade, 40/60 μm, Russia). TLC used Sorbfil plates (OOO Imid, Krasnodar, Russia). Chromatograms were detected in a thin layer using anisaldehyde, I_2, and UV light. Melting points were determined on a Boetius instrument (Germany). 2-Phthalimidoethanesulfonamides **5a** and **5b** were prepared by the literature methods [18 and 17, respectively].

Preparation of 5c and 5d. A suspension of sulfonyl chloride **4** (1.827 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated with the appropriate amine (1.827 mmol) and Et_3N (3.654 mmol), stirred for 5 h, left overnight, and treated with H_2O (10 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to afford **5c** and **5d**.

2-[2-(4-Benzylpiperidin-1-ylsulfonyl)ethyl]isoindoline-1,3-dione (5c), yield 88%. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.29 (2H, m, H_a-3′, 5a′), 1.50–1.93 (3H, m, H-3b′, 5b′, H-4′), 2.54 (2H, d, J = 6.6, H-7′), 2.75 (2H, t, J = 11.8, H-2a′, 6a′), 3.31 (2H, t, J = 6.8, H-1″), 3.78 (2H, d, J = 11.8, H-2b′, 6b′), 4.12 (2H, t, J = 6.8, H-2″), 7.14 (2H, d, J = 7.3, Ph: H-2, 6), 7.23 (1H, t, J = 7.3, Ph: H-4), 7.27 (2H, m, Ph: H-3, 5), 7.75 (2H, m, Ar), 7.87 (2H, m, Ar).

2-[2-(4-Methylpiperazin-1-ylsulfonyl)ethyl]isoindoline-1,3-dione (5d), yield 70 %. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.35 (3H, s, H-7′), 2.54 (4H, m, 2H-3′, 5′), 3.37 (6H, m, 2H-1″, 2H-2′, 6′), 4.14 (2H, m, H-2″), 7.74 (2H, m, Ar), 7.87 (2H, m, Ar). APCI-MS *m/z* 338.1 $[M + H]^+$ (calcd for $C_{15}H_{20}N_3O_4S$, 338.1).

Preparation of 2-Aminoethanesulfonamides 3a–d. A suspension of the appropriate 2-phthalimidoethanesulfonamide **5a**–**d** (1.189 mmol) was dissolved with heating in EtOH (10 mL), treated with $N_2H_4 \cdot H_2O$ (1.43 mmol), refluxed for 8–15 h until a voluminous white precipitate formed, and cooled. The precipitate was filtered off. The filtrate was evaporated. The solid was dissolved in $CHCl_3$ or MTBE (for **3c**). The insoluble precipitate was filtered off. The filtrate was evaporated to afford **3a**–**d**.

2-Amino-*N*-butylethanesulfonamide (3a), yield 37%. The ^{1}H NMR spectrum agreed with the literature [18].

2-Amino-*N*-phenylethanesulfonamide (3b), yield 51%. The ^{1}H NMR spectrum agreed with the literature [19].

2-(4-Benzylpiperidin-1-ylsulfonyl)ethanamine (3c), yield 45%. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.29 (2H, m, H_a-3a′, 5a′), 1.58–1.77 (3H, m, H-3b′, 5b′, H-4′), 2.53 (2H, m, NH_2), 2.55 (2H, d, J = 7.2, H-7′), 2.67 (2H, t, J = 12.0, H-2a′, 6a′), 2.99 (2H, m, H-1″), 3.16 (2H, m, H-2″), 3.76 (2H, d, J = 12.0, H-2b′, 6b′), 7.12 (2H, d, J = 7.4, Ph: H-2, 6), 7.19 (1H, t, J = 7.4, Ph: H-4), 7.26 (1H, t, J = 7.4, Ph: H-3*), 7.27 (1H, t, J = 7.4, Ph: H-5*). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 31.72 (C-3′, 5′), 36.61 (C-2″), 37.52 (C-4′), 42.70 (C-1″), 45.97 (C-2′, 6′), 51.96 (C-7′), 126.09 (Ph: C-4), 128.30 (Ph: C-3, 5), 129.02 (Ph: C-2, 6), 139.69 (Ph: C-1).

2-(4-Methylpiperazin-1-ylsulfonyl)ethanamine (3d), yield 30%. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.95 (2H, br.s, NH_2), 2.31 (3H, s, H-7′), 2.48 (4H, t, J = 4.3, H-3′, 5′), 3.03 (2H, t, J = 6.1, H-1″), 3.19 (2H, t, J = 6.1, H-2″), 3.29 (4H, t, J = 4.3, H-2′, 6′). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 36.49 (C-2″), 45.55 (C-2′, 6′), 45.87 (C-7′), 51.73 (C-1″), 54.48 (C-3′, 5′).

General Method for Preparing Conjugates 2a–d. A solution of acid **1** (0.229 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with $(COCl)_2$ (0.2 mL, 2.290 mmol), stirred for 2 h, and evaporated. The resulting betulonic acid chloride was dissolved in anhydrous CH_2Cl_2 (5 mL), treated with the appropriate sulfonamide (**3a**–**d**, 0.344 mmol) in anhydrous CH_2Cl_2 (3 mL) and Et_3N (0.10 mL, 0.687 mmol), stirred for 4 h, left overnight, and evaporated. The solid was chromatographed over SiO_2 (hexane–EtOAc, 5:1, 3:1, 2:1).

***N*-[2-(*N*-Butylsulfamoyl)ethyl]-3-oxolup-20(29)-ene-17*β*-carboxamide (2a)**, yield 61%, mp 97–99°C, $[\alpha]_D^{20}$ +20.5° (*c* 0.43, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.92, 1.01, 1.06, 1.68 (3H each, s, CH_3-25*, 24, 23, 30), 0.97 (6H, s, CH_3-26*, 27), 0.94 (3H, t, J = 7.4, H-4′), 1.04 (1H, m, H-12a), 1.17 (1H, ddd, J = 13.3, 2.8, H-15a), 1.24–1.50 (14H, m, H-1a, 21a, 16a, 15b, 2H-6, 7, 11, H-5, 9, 2H-3′), 1.54 (1H, dd, J = 13.5, 2.6, H-22a), 1.57 (3H, m, H-18, H-2′), 1.73 (1H, dd, J = 11.2, 2.0, H-12b), 1.79 (1H, ddd, J = 12.2, 8.5, 1.9, H-16b), 1.85–1.95 (2H, m, H-1b, 21b), 1.98 (1H, dt, J = 13.5, 3.0, H-22b), 2.40 (1H, ddd, J = 15.6, 7.5, 4.4, H-2a), 2.48 (2H, m, H-2b, 13), 3.10 (1H, td, J = 11.2, 4.3, H-19), 3.05–3.25 (4H, m, H-1′, 1″), 3.72 (2H, q, J = 5.3, H-2″), 4.59, 4.73 (1H each, s, H-29), 4.70 (1H, br.s, NHBu), 6.47 (1H, t, J = 5.8, NH). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 13.63 (C-4′), 14.57 (C-27), 15.99 (C-25, 26), 19.46 (C-30), 19.66 (C-6), 19.78 (C-3′), 21.04 (C-24), 21.49 (C-11), 25.62 (C-12), 26.66 (C-23), 29.39 (C-15), 30.82 (C-21), 32.37 (C-2′), 33.14 (C-16), 33.38 (C-22), 33.68 (C-7), 33.95 (C-2″), 34.17 (C-2), 36.93 (C-10), 37.82 (C-13), 39.64 (C-1), 40.73 (C-8), 42.52 (C-14), 43.12 (C-1′), 46.71 (C-19), 47.35 (C-4), 49.97 (C-9, 18), 52.18 (C-1″), 54.97 (C-5), 55.71 (C-17), 109.53 (C-29), 150.75 (C-20), 176.70 (C-28), 218.37 (C-3). ^{15}N (50.68 MHz, $CDCl_3$, δ, ppm): 93.74 (NHBu), 105.94 (C(O)NH). HR-ESI-MS *m/z* 617.4351 $[M + H]^+$ (calcd for $C_{36}H_{61}N_2O_4S$, 617.4347).

***N*-[2-(*N*-Phenylsulfamoyl)ethyl]-3-oxolup-20(29)-ene-17*β*-carboxamide (2b)**, yield 78%, mp 125–127°C, $[\alpha]_D^{20}$ +12.7° (*c* 0.83, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95, 1.02, 1.07, 1.66 (3H each, s, CH_3-27, 24, 23, 30), 0.89 (6H, s, CH_3-25, 26), 1.00 (1H, dd, J = 11.2, 4.6, H-12a), 1.13 (1H, dt, J = 13.5, 2.9, H-15a), 1.18–1.56 (12H, m, H-1a, 21a, 16a, H-15b, 2H-6, 7, 11, H-5, 9), 1.52 (1H, dd, J = 13.4, 2.9, H-22a), 1.56 (1H, t, J = 11.3, H-18), 1.70 (1H, dd, J = 11.2, 2.8, H-12b), 1.76 (1H, ddd, J = 12.2, 8.2, 1.8, H-16b), 1.82–1.91 (2H, m, H-1b, 21b), 1.96 (1H, dt, J = 13.6, 2.7, H-22b), 2.39 (1H, ddd, J = 15.5, 7.5, 4.3, H-2a), 2.47 (2H, m, H-2b, 13), 3.05 (1H, td, J = 11.2, 4.2, H-19), 3.22 (1H, dt, J = 14.5, 5.6, H-1a″), 3.29 (1H, dt, J = 14.5, 5.6, H-1b″), 3.75 (2H, q, J = 5.6, H-2″), 4.58, 4.70 (1H each, s, H-29), 6.42 (1H, t, J = 5.9, NH), 7.54 (1H, s, N<u>H</u>Ph), 7.18 (1H, t, J = 7.3, Ph: H-4), 7.28 (2H, d, J = 7.3, Ph: H-2, 6), 7.34 (2H, t, J = 7.3, Ph: H-3, 5). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 14.54 (C-27), 15.86 (C-26*), 15.97 (C-25*), 19.44 (C-30), 19.65 (C-6), 21.04 (C-24), 21.44 (C-11), 25.60 (C-12), 26.66 (C-23), 29.36 (C-15), 30.76 (C-21), 33.39 (C-22), 33.63 (C-2″), 33.78 (C-7), 34.17 (C-2), 36.92 (C-10), 37.36 (C-13), 38.09 (C-16), 39.63 (C-1), 40.71 (C-8), 42.49 (C-14), 46.64 (C-19), 47.35 (C-4), 49.97 (C-9, 18), 51.46 (C-1″), 54.99 (C-5), 55.71 (C-17), 109.51 (C-29), 121.28 (Ph: C-2, 6), 125.56 (Ph: C-4), 129.69 (Ph: C-3, 5), 136.59 (Ph: C-1), 150.67 (C-20), 176.93 (C-28), 218.50 (C-3). ^{15}N (50.68 MHz, $CDCl_3$, δ, ppm): 104.40 (C(O)NH), 115.74 (NHPh). HR-ESI-MS *m/z* 637.4041 $[M + H]^+$ (calcd for $C_{38}H_{57}N_2O_4S$, 637.4034).

***N*-[2-(4-Benzylpiperidin-1-ylsulfonyl)ethyl]-3-oxolup-20(29)-ene-17*β*-carboxamide (2c)**, yield 49%, mp 108–110°C, $[\alpha]_D^{20}$ +12.6° (*c* 0.49, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89, 0.95, 0.96, 1.00, 1.05, 1.66 (3H each, s, CH_3-26*, 27, 25*, 24, 23, 30), 1.04 (1H, m, H-12a), 1.17 (1H, dt, J = 13.4, 2.8, H-15a), 1.23–1.48 (14H, m, H-1a, 16a, 21a, H-15b, 2H-6, 7, 11, H-5, 9, H-3a′, 5a′), 1.51 (1H, dd, J = 13.4, 3.1, H-22a), 1.56 (1H, t, J = 11.0, H-18), 1.65 (1H, m, H-4′), 1.69 (2H, m, H-3b′, 5b′), 1.71 (1H, dd, J = 11.3, 2.8, H-12b), 1.78 (1H, ddd, J = 12.3, 8.5, 1.9, H-16b), 1.84–1.94 (2H, m, H-1b, 21b), 1.98 (1H, dt, J = 13.4, 3.1, H-22b), 2.38 (1H, ddd, J = 15.4, 7.5, 4.4, H-2a), 2.46 (2H, m, H-2b, 13), 2.56 (2H, d, J = 7.2, H-7′), 2.68 (2H, t, J = 12.4, H-2a′, 6a′), 3.00 (2H, m, H-1″), 3.07 (1H, td, J = 11.0, 4.2, H-19), 3.71 (2H, q, J = 5.2, H-2″), 3.74 (2H,

td, J = 12.4, 3.1, H-2b′, 6b′), 4.5, 4.72 (1H each, s, H-29), 6.43 (1H, t, J = 5.7, NH), 7.12 (2H, d, J = 7.3, Ph: H-2, 6), 7.19 (1H, t, J = 7.3, Ph: H-4), 7.28 (2H, t, J = 7.3, Ph: H-3, 5). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 14.55 (C-27), 15.97 (C-26*), 16.00 (C-25*), 19.43 (C-30), 19.64 (C-6), 21.04 (C-24), 21.48 (C-11), 25.60 (C-12), 26.64 (C-23), 29.40 (C-15), 30.80 (C-21), 31.73 (C-3′), 31.74 (C-5′), 33.35 (C-22), 33.56 (C-2′′), 33.69 (C-7), 34.14 (C-2), 36.91 (C-10), 37.49 (C-4′), 37.80 (C-13), 38.11 (C-16), 39.62 (C-1), 40.71 (C-8), 42.51 (C-14), 42.71 (C-7′), 46.05 (C-2′, 6′), 46.69 (C-19), 47.32 (C-4), 48.61 (C-1′′), 49.90 (C-18), 49.96 (C-9), 54.96 (C-5), 55.71 (C-17), 109.51 (C-29), 126.19 (Ph: C-4), 128.32 (Ph: C-3, 5), 129.05 (Ph: C-2, 6), 139.61 (Ph: C-1), 150.75 (C-20), 176.56 (C-28), 218.15 (C-3). ^{15}N (50.68 MHz, $CDCl_3$, δ, ppm): 105.20 (C(O)NH). HR-ESI-MS *m/z* 719.4825 $[M + H]^+$ (calcd for $C_{44}H_{67}N_2O_4S$, 719.4816).

***N*-[2-(4-Methylpiperazin-1-ylsulfonyl)ethyl]-3-oxolup-20(29)-ene-17*β*-carboxamide (2d)**, yield 64%, mp118–119°C, $[\alpha]_D^{20}$ +17.5° (*c* 0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.91, 0.95, 0.96, 1.00, 1.05, 1.67 (3H each, s, CH_3-26, 27, 25, 24, 23, 30), 1.01 (1H, m, H-1a), 1.16 (1H, dt, J = 13.3, 2.8, H-15a), 1.23–1.47 (12H, m, H-1a, 16a, 21a, H-15b, 2H-6, 7, 11, H-5, 9), 1.52 (1H, dd, J = 13.3, 3.1, H-22a), 1.57 (1H, t, J = 11.3, H-18), 1.71 (1H, dd, J = 11.1, 2.5, H-12b), 1.79 (1H, ddd, J = 12.2, 8.6, 1.9, H-16b), 1.85–1.95 (2H, m, H-1b, 21b), 1.97 (1H, dt, J = 13.5, 3.1, H-22b), 2.33 (3H, s, H-7′), 2.38 (1H, ddd, J = 15.5, 7.4, 4.3, H-2a), 2.46 (2H, m, H-2b, 13), 2.50 (4H, t, J = 3.5, H-2′, 6′), 3.04 (2H, m, H-1′′), 3.07 (1H, td, J = 11.2, 4.4, H-19), 3.30 (4H, t, J = 3.5, H-3′, 5′), 3.73 (2H, q, J = 5.8, H-2′′), 4.58, 4.72 (1H each, s, H-29), 6.39 (1H, t, J = 5.8, NH). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 14.53 (C-27), 15.94 (C-26), 16.00 (C-25), 19.43 (C-30), 19.63 (C-6), 21.02 (C-24), 21.46 (C-11), 25.60 (C-12), 26.62 (C-23), 29.39 (C-15), 30.79 (C-21)*, 33.37 (C-22)*, 33.48 (C-7), 33.70 (C-2′′), 34.13 (C-2), 36.92 (C-10), 37.79 (C-13), 38.08 (C-16), 39.62 (C-1), 40.72 (C-8), 42.51 (C-14), 45.50 (C-2′, 6′), 45.80 (C-7′), 46.67 (C-19), 47.32 (C-4), 48.32 (C-1′′), 49.91 (C-18), 49.97 (C-9), 54.37 (C-5), 54.98 (C-3′, 5′), 55.71 (C-17), 109.51 (C-29), 150.72 (C-20), 176.55 (C-28), 218.13 (C-3). ^{15}N (50.68 MHz, $CDCl_3$, δ, ppm): 35.60 (N-4′), 91.90 (N-1′), 105.50 (C(O)NH). HR-ESI-MS *m/z* 644.4464 $[M + H]^+$ (calcd for $C_{37}H_{62}N_3O_4S$, 644.4456).

Resonances of atoms in ^{1}H and ^{13}C NMR spectra marked with an "*" could change places.

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REFERENCES

1. S. Xiao, Z. Tian, Y. Wang, L. Si, L. Zhang, and D. Zhou, *Med. Res. Rev.*, **38**, 951 (2018).
2. Y. Chen, X. Wang, Y. Zhu, L. Si, B. Zhang, Y. Zhang, L. Zhang, D. Zhou, and S. Xiao, *Mol. Pharmaceutics*, **17** (7), 2546 (2020).
3. H. Wang, R. Xu, Y. Shi, L. Si, P. Jiao, Z. Fan, X. Han, X. Wu, X. Zhou, F. Yu, Y. Zhang, L. Zhang, L. Zhang, D. Zhou, and S. Xiao, *Eur. J. Med. Chem.*, **110**, 376 (2016).
4. M. Kirstgen, K. A. A. T. Lowjaga, S. F. Muller, N. Goldmann, F. Lehmann, S. Alakurtti, J. Yli-Kauhaluoma, D. Glebe, and J. Geyer, *Sci. Rep.*, **10**, 21772 (2020).
5. I. Dicker, J. L. Jeffrey, T. Protack, Z. Lin, M. Cockett, Y. Chen, S.-Y. Sit, M. Gartland, N. A. Meanwell, A. Regueiro-Ren, D. Drexler, J. Cantone, B. McAuliffe, and M. Krystal, *Antimicrob. Agents Chemother.*, **66** (1), 1876 (2022).
6. A. Regueiro-Ren, S.-Y. Sit, Y. Chen, J. Chen, J. J. Swidorski, Z. Liu, B. L. Venables, N. Sin, R. A. Hartz, T. Protack, Z. Lin, S. Zhang, Z. Li, D.-R. Wu, P. Li, J. Kempson, X. Hou, A. Gupta, R. Rampulla, A. Mathur, H. Park, A. Sarjeant, Y. Benitex, S. Rahematpura, D. Parker, T. Phillips, R. Haskell, S. Jenkins, K. S. Santone, M. Cockett, U. Hanumegowda, I. Dicker, N. A. Meanwell, and M. Krystal, *J. Med. Chem.*, **65**, 11927 (2022).
7. Q. Wang, Y. Li, L. Zheng, X. Huang, Y. Wang, C.-H. Chen, Y.-Y. Cheng, S. L. Morris-Natschke, and K.-Hsiung Lee, *ACS Med. Chem. Lett.*, **11** (11), 2290 (2020).
8. M. W. C. Loe, E. Hao, M. Chen, C. Li, R. C. H. Lee, I. X. Y. Zhu, Z. Y. Teo, W.-X. Chin, X. Hou, J. Deng, and J. J. H. Chu, *Antiviral Res.*, **184**, 104954 (2020).

9. A. Stevaert, B. Krasniqi, B. Van Loy, T. Nguyen, J. Thomas, J. Vandeput, D. Jochmans, V. Thiel, R. Dijkman, W. Dehaen, A. Voet, and L. Naesens, *J. Med. Chem.*, **64**, 5632 (2021).
10. M. Kadela-Tomanek, M. Jastrzebska, K. Marciniec, E. Bebenek, E. Chrobak, and S. Boryczka, *Crystals*, **11**, 76 (2021).
11. C. Zhao, K. P. Rakesh, L. Ravidar, W.-Y. Fang, and H.-L. Qin, *Eur. J. Med. Chem.*, **162**, 679 (2019).
12. S. Apaydin and M. Torok, *Bioorg. Med. Chem. Lett.*, **29**, 2042 (2019).
13. A. K. Timiri, S. Selvarasu, M. Kesherwani, V. Vishwanathan, B. N. Sinha, D. Velmurugan, and V. Jayaprakash, *Bioorg. Chem.*, **62**, 74 (2015).
14. N. Sin, Z. Liu, et al., US Pat. Appl. 20130296554A1, Nov. 7, 2013.
15. A. Reguerio-Ren, J. Swidorski, et al., US Pat. 8,754,068 B2, Jun. 17, 2014.
16. N. G. Komissarova, S. N. Dubovitskii, O. V. Shitikova, and A. V. Orlov, *Chem. Nat. Compd.*, **57**, 712 (2021).
17. R. A. Smits, M. Adami, E. P. Istyastono, O. P. Zuiderveld, C. M. E. van Dam, F. J. J. de Kanter, A. Jongejan, G. Coruzzi, R. Leurs, and I. J. P. de Esch, *J. Med. Chem.*, **53** (6), 2390 (2010).
18. R. Goschke, S. Stutz, V. Rasetti, N.-C. Cohen, J. Rahuel, P. Rigollier, H.-P. Baum, P. Forgiarini, C. R. Schnell, T. Wagner, M. G. Gruetter, W. Fuhrer, W. Schilling, F. Cumin, J. M. Wood, and J. Maibaum, *J. Med. Chem.*, **50** (20), 4818 (2007).
19. T. Sugimoto, N. Sasamoto, et al., WO Pat. 2012115256A1, Aug. 30, 2012.