DOI 10.1007/s10600-020-03169-x
Chemistry of Natural Compounds, Vol. 56, No. 5, September, 2020

SYNTHETIC TRANSFORMATIONS OF SESQUITERPENE LACTONES. 11.* CONJUGATES BASED ON CAFFEINE AND EUDESMANOLIDES WITH *N*-CONTAINING LINKERS

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8-(Aminoalkylamino)caffeine or 8-(piperazinyl)caffeine were formed in high yields by reacting 8-bromo- or 8-chlorocaffeine with linear and cyclic diamines using microwave-assisted organic synthesis. These amines were highly reactive in Michael reactions with sesquiterpene lactones containing active methylene groups. Conjugates with caffeine and eudesmanolide moieties bonded by a N*-containing linker were synthesized.*

Keywords: caffeine, eudesmanolides, methylenelactones, Michael reaction.

The alkaloid caffeine (**1**) is an available natural methylxanthine and an interesting lead compound for designing new derivatives with valuable biological activity and lower toxicity. It was used as a platform to synthesize agents to treat cancer of the lungs, liver, and breast and compounds enhancing stomach secretions and reducing the risk of developing gallstone disease [2]. Research on caffeine derivatives showed that compounds with various substituents in the C-8 position were antagonists of adenosine receptors [3, 4] and acetylcholine esterase [5, 6] and monoamine oxidase inhibitors [7]. 8-(2-Phenethyl)-1,3,7-trimethylxanthine and 8-(phenoxymethyl)-1,3,7-trimethylxanthine were found to exhibit affinity for A_1 and A_2 adenosine receptors [8], confirming the hypothesis that modification of the caffeine C-8 substituent structure could lead to agents with increased affinity and selectivity for A_1, A_{2A}, A_{2B}, or A_3 adenosine receptors. 8-Aminocaffeine and 8-alkylmercaptocaffeine derivatives belong to this pharmacologically promising subclass [9].

The present article reports the regioselective synthesis of a series of eudesmane-xanthine conjugates using Michael reactions of diamino-substituted caffeine derivatives with eudesmane-type lactones, e.g., isoalantolactone (**2**), 4,15-epoxyisoalantolactone (**3**), and 3-hydroxyisoalantolactone (**4**). The presence of an activated methylene in lactones **2**–**4** enabled them to undergo Michael reactions. The nucleophiles were the *N*-nucleophiles 8-(aminoalkylamino)caffeine and 8-(piperazinyl)caffeine.

The 8-aminocaffeine derivatives were prepared by heating 8-chlorocaffeine (**5**) with an excess (5 eq.) of an amine at 175–180°C [7] followed by workup with AcOH. Syntheses of caffeine diamino derivatives **6** and **7** by refluxing with an excess of ethylenediamine (**8**) or hexamethylenediamine (**9**) (5 mmol) and 2-bromocaffeine (**10**) in EtOH were previously reported [10]. In our hands, **6** and **7** were formed by reacting 8-chlorocaffeine (**5**) with diamines **8** and **9** (2 eq.) in 2-methoxyethanol using microwave-assisted organic synthesis (MAOS) (120°C, 3 h). Compounds **6** and **7** were isolated in 80–93% yields after column chromatography (Scheme 1). Their analytical characteristics were analogous to those in the literature [10]. This reaction also occurred readily with cyclic amines. The reaction of 8-halocaffeine **5** or **10** with piperazine (**11**) or morpholine (**12**) under the noted conditions gave 8-(piperazin-1-yl)caffeine **13** or 8-morpholinocaffeine **14** in 86–90% yields. Disubstituted 8,8′-(ethane-1,2-diamino)*bis*[1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione] (4% yield) was isolated from the reaction of 8-chlorocaffeine with ethylenediamine (**8**). An analysis of the reactions of morpholine (**12**) with 8-chlorocaffeine (**5**) or 8-bromocaffeine (**10**) found no difference in the course of the reaction depending on the 8-halocaffeine. The conversion of the starting halogens and yields of **14** differed insignificantly.

*For No. 10, see the literature [1].

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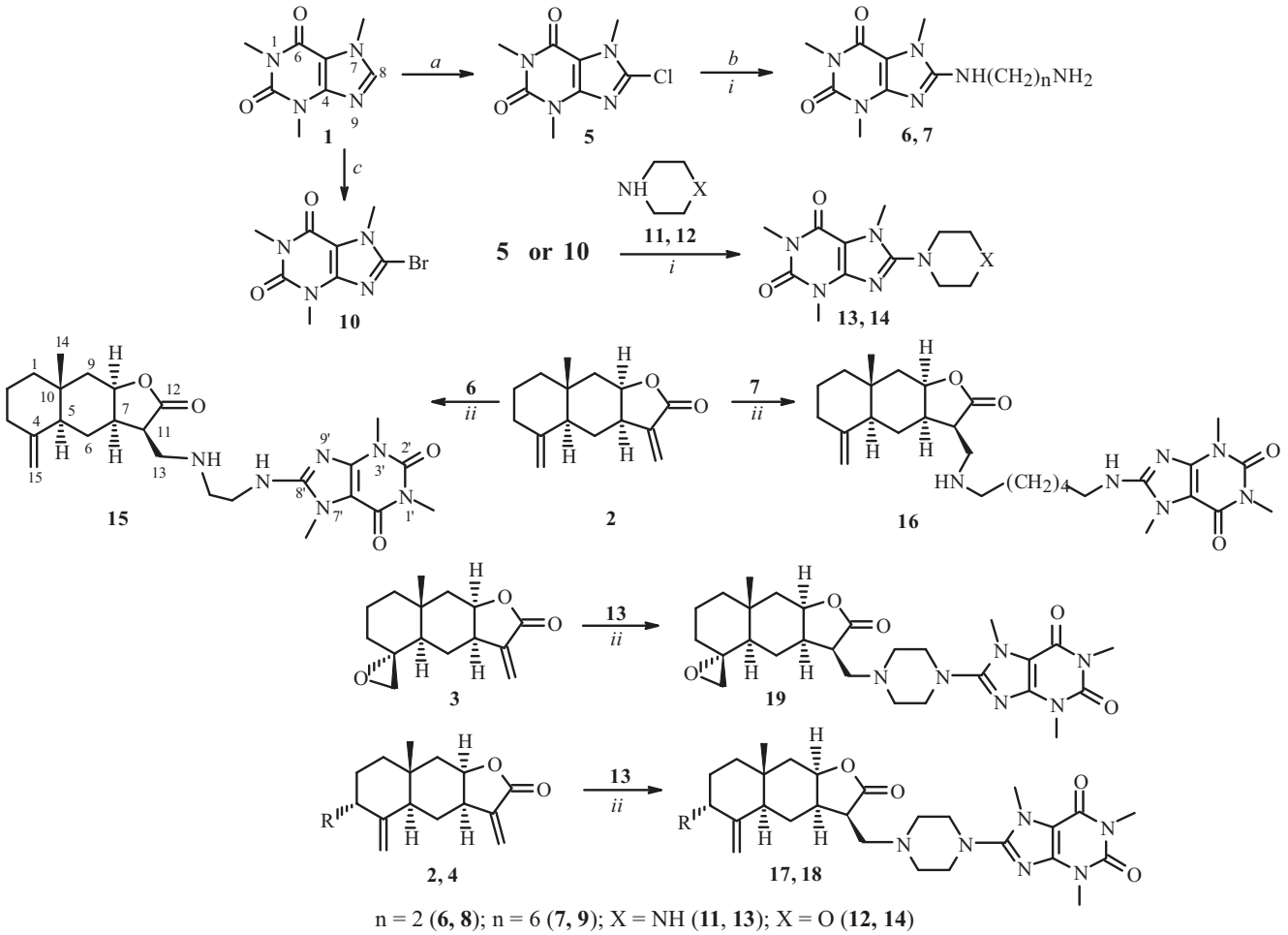


n = 2 (**6, 8**); n = 6 (**7, 9**); X = NH (**11**, **13**); X = O (**12, 14**)
2, 17: R = H; **4, 18:** R = OH

a. NCS, H_2O–CH_2Cl_2, 24 h; *b*. $NH_2(CH_2)_nNH_2$ (**8** or **9**); *c*. NBS
i. 2-methoxyethanol, MAOS, 120°C, 3 h; *ii*. Et_3N, EtOH, 55°C, 3 h

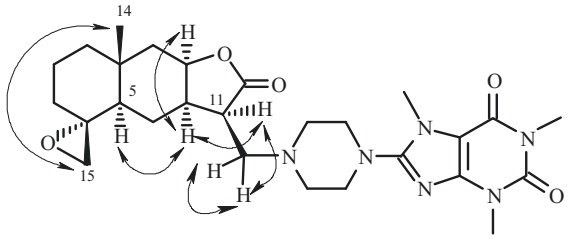
Scheme 1

Conjugates **15** and **16** with fragments of the natural compounds isoalantolactone (**2**) and caffeine (**1**) linked by ethylenediamine or hexamethylenediamine were obtained by an aza-Michael reaction of **2** with 8-(2-aminoethylamino)caffeine (**6**) or 8-(6-aminohexylamino)caffeine (**7**) in the presence of Et_3N in EtOH at 55°C for 3 h.

The degree of conversion of **2** was monitored by TLC. Conjugates **15** and **16** were isolated by column chromatography over silica gel in 65 and 44% yields, respectively (Scheme 1). The reaction of **2** with aliphatic primary and secondary amines (e.g., with morpholine [11]) is known to occur in alcohols at reduced temperature without a catalyst. The temperature had to be increased and an excess of Et_3N had to be used for complete conversion of **2** with amines **6** and **7**.

The reaction of methylenelactones **2**–**4** with 8-(piperazinyl)caffeine (**13**) in the presence of Et_3N formed conjugates **17**–**19**, which were isolated in 44–60% yields. It can be seen that the yields of aza-Michael reaction products of eudesmane methylenelactones **2**–**4** were practically independent of the methylenelactone structure.

The structures of the synthesized compounds were elucidated using physicochemical methods, i.e., IR, UV, PMR, and ^{13}C NMR spectroscopy [including two-dimensional (2D) NOESY, COSY, and COXH experiments] and high-resolution mass spectrometry (see Experimental). PMR spectra of **15**–**19** showed resonances of protons in the products on C-11 (in the range 2.9–3.2 ppm as a doublet of triplets for **15** and **16** or a doublet of doublets of doublets for **17**–**19**) and C-13 (CH_2N groups as a doublet of doublets at δ 2.75–3.09 ppm with geminal SSCC J = 11.7–13.2 Hz and vicinal SSCC J = 4.1–7.7 Hz and a doublet of doublets in the range 2.57–3.04 with the given geminal constant and vicinal constant J = 5.8–10.5 Hz). The stereochemistry of the new asymmetric center (11*R*) in **15**–**19** was established using the NOE-effect (cross-peaks) between H(5)-H(7)-H(8)-H(11), which indicated they were *cis*-positioned (Fig. 1).



19

Fig. 1. Structurally significant NOE correlations for **19**.

Cross-peaks between H(14)-H(15) confirmed the structure of the oxirane fragment and the *R*-configuration of C(4). The resonances and multiplicities of the other protons of the starting lactone and the caffeine derivatives remained the same and corresponded to the proposed structures.

High-resolution mass spectra contained strong peaks for the molecular ion, caffeine diamine, and the corresponding sesquiterpene lactone and confirmed the empirical formula of the amination products.

EXPERIMENTAL

IR spectra (ν, cm^{-1}) were taken from KBr pellets on a Vector-22 Fourier spectrometer. UV absorption spectra [λ_{max}, nm (log ε)] were obtained on an HP 8453 UV-Vis spectrometer in EtOH solution. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ ($CDCl_3$ + CD_3OD for **6** and **7**) with TMS internal standard on Bruker AV-400 [400.13 (^1H) and 100.78 MHz (^{13}C)] and AV-600 [600.30 (^1H) and 150.96 MHz (^{13}C)] (**16** and **19**) spectrometers. The structures of the synthesized compounds were elucidated by analyzing PMR and ^{13}C NMR spectra and using 2D ^1H–^1H and ^{13}C–^1H correlation spectroscopy (COSY, COXH, NOESY, mixing time 1 s, delay between pulses 2 s). PMR and ^{13}C NMR spectra were described using atomic numbering of the backbone and substituents given for the structures of **1** and **15**.

Mass spectra were recorded and molecular masses and elemental compositions were determined using a DFS high-resolution mass spectrometer (Thermo Scientific) (vaporizer temperature 190–270°C, electrospray ionization source).

Melting points were measured on a Mettler Toledo FP900 apparatus. Specific rotation $[\alpha]_D$ was measured on a PolAAr3005 polarimeter and were expressed in deg·mL/g·dm. Concentrations were given in g per 100 mL of solution. The spectral analytical studies were performed at the Khimiya Common Use Center of the SB, RAS.

The reactions of **5** with **8** or **9** were performed in an Anton Paar Monowave 300 microwave reactor.

The course of reactions and purity of products were monitored using TLC on Silufol UV-254 plates, $CHCl_3$–EtOH (9:1) or C_6H_6–EtOAc (3:1) eluent, and detection by I_2 vapor or UV radiation. Reaction products were isolated by column chromatography over silica gel (Acros, 0.035–0.240 mm) with elution by $CHCl_3$–EtOH (100:0→75:25).

Solvents (2-methoxyethanol, EtOH, CH_2Cl_2, $CHCl_3$) were purified by standard methods and distilled under Ar immediately before use in reactions. The reagents caffeine, *N*-bromosuccinimide, *N*-chlorosuccinimide, morpholine, piperazine, ethylenediamine, and hexamethylenediamine were purchased (Alfa Aesar).

Isoalantolactone (**2**) [mp 104–106°C (petroleum ether), $[\alpha]_D$ +173° (*c* 5.1, $CHCl_3$)] that was obtained via extraction from *Inula helenium* L. followed by purification of the morpholine adduct using the literature method [11] was used in the work. 4,15-Epoxyisoalantolactone (**3**) was prepared via epoxidation of **2** by the literature method [12]; 3-hydroxyisoalantolactone (**4**), via oxidation of **2** by selenium dioxide by the literature method [13]; 8-chlorocaffeine (**5**) and 8-bromocaffeine (**10**), by reacting **1** with *N*-chlorosuccinimide or *N*-bromosuccinimide by a modified literature method [14]. The characteristics of **5** [15] and **10** [14] agreed with those in the literature.

Synthesis of 8-Amino-substituted Caffeine Derivatives. General Method. 8-Chlorocaffeine (**5**, 0.44 mmol, 100 mg) and the appropriate amine [ethylenediamine (**8**), hexamethylenediamine (**9**), piperazine (**11**), or morpholine (**12**)] (1.76 mmol) were dissolved in methoxyethanol (3.5 mL). The mixture was stirred for 3 h in a microwave reactor at 120°C and cooled. The resulting precipitate of disubstitution product (0.5–4% yield) was filtered off and rinsed with EtOH (3 × 5 mL). The mother liquor was evaporated. The residue was worked up with H_2O and extracted with $CHCl_3$ (3 × 20 mL). The organic fractions were combined, dried over $MgSO_4$, and evaporated. Compounds **6**, **7**, **13**, and **14** were purified by column chromatography over silica gel ($CHCl_3$–EtOH eluent, 100:0→70:30).

8-(2-Aminoethyleneamino)caffeine [8-(2-Aminoethylamino)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione] (6). Yield 93%, white powder, mp 167–170°C. IR spectrum (KBr, ν, cm^{-1}): 3309 (N-H), 2947, 1697 (C=O), 1649 (C=O), 1608, 1574, 1549, 1489, 1446, 1387, 1217, 1028, 754. UV spectrum (EtOH, λ_{max}, nm) (log ε): 213 (4.57), 293 (4.44). ^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 3.76 (2H, dd, J = 5.5, 7.1, CH_2), 3.70 (3H, s, NCH_3), 3.51 (3H, s, NCH_3), 3.35 (3H, s, NCH_3), 3.27 (2H, dd, J = 5.5, 7.1, CH_2), 2.75 (2H, br.s, NH_2). ^{13}C NMR spectrum (100 MHz, δ, ppm): 153.8 (C-6), 153.8 (C-8), 151.5 (C-2), 148.4 (C-4), 103.0 (C-5), 42.1 (CH_2), 40.0 (CH_2), 29.4 (NMe), 29.3 (NMe), 27.3 (NMe). Mass spectrum (*m/z*, $I_{отн.}$, %): 252 (47), 223 (17), 222 (100), 209 (18), 195 (9), 165 (10), 82 (13), 67 (18), 42 (12), 36 (14); found *m/z* 252.1331 $[M]^+$; calcd for $C_{10}H_{16}N_6O_2$, 252.1329 $[M]^+$.

The reaction of **5** with ethylenediamine (**8**) also afforded the disubstitution product 8,8′-(ethane-1,2-diamino)*bis*[1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione] (4% yield), mp 370°C (dec.). Found, %: C 49.30; H 6.05; N 30.60. $C_{18}H_{24}N_{10}O_4$. Calcd, %: C 48.64; H 5.44; N 31.51.

8-(6-Aminohexamethyleneamino)caffeine [8-(6-Aminohexylamino)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione] (7). Yield 80%, white powder, mp 153–156°C. IR spectrum (KBr, ν, cm^{-1}): 3369 (N-H), 2935, 1703 (C=O), 1661 (C=O), 1614, 1580, 1545, 1479, 1460, 1431, 1221, 1036, 750. UV spectrum (EtOH, λ_{max}, nm) (log ε): 217 (4.56), 297 (4.49). ^{1}H NMR spectrum (400 MHz, $CDCl_3$ + CD_3OD, δ, ppm, J/Hz): 3.81 (2H, dd, J = 7.1, 7.8, C<u>H</u>$_2$NH), 3.54 (3H, s, NCH_3), 3.43 (3H, s, NCH_3), 3.34 (2H, dd, J = 7.1, 7.8, CH_2), 3.27 (3H, s, NCH_3), 2.65 (2H, dd, J = 7.1, 8.6, CH_2), 1.56 (2H, m, CH_2), 1.45 (2H, m, CH_2), 1.30–1.32 (2H, m, CH_2), 1.17 (2H, t, J = 7.1, 8.3, CH_2). ^{13}C NMR spectrum (100 MHz, δ, ppm): 154.1 (C-6), 153.8 (C-8), 151.6 (C-2), 148.9 (C-4), 102.8 (C-5), 42.6 (CH_2), 40.6 (CH_2), 30.9 (CH_2), 29.4 (CH_2), 29.2 (2 × NCH_3), 27.3 (NCH_3), 26.0 (CH_2), 25.9 (CH_2). Mass spectrum (*m/z*, I_{rel}, %): 308 (100), 278 (16), 236 (21), 223 (11), 222 (65), 209 (40), 165 (7), 82 (13), 67 (9), 42 (7); found *m/z* 308.1958 $[M]^+$; calcd for $C_{14}H_{24}N_6O_2$, 308.1955 $[M]^+$.

1,3,7-Trimethyl-8-(piperazin-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (13). Yield 90%, white powder, mp 173.7°C. IR spectrum (ν, cm^{-1}): 3317 (NH), 1695 (C=O), 1657 (C=O), 1610, 1516, 910, 746 (C=C, C=N). UV spectrum ($\lambda_{max.}$, nm) (log ε): 206 (4.20), 223 (4.26), 293 (4.19). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 5.10 (m, NH), 3.72 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 3.36 (3H, s, NCH_3), 3.20–3.22 (4H, m, 2 × CH_2), 2.99–3.01 (4H, m, 2 × CH_2). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 156.5 (C-6), 154.9 (C-8), 151.7 (C-2), 147.4 (C-4), 105.2 (C-5), 50.8 (2 × CH_2), 45.5 (2 × CH_2), 32.4 (NCH_3), 29.5 (NCH_3), 27.6 (NCH_3). Mass spectrum (*m/z*, I_{rel}, %): 278 (100), 236 (28), 223 (26), 222 (100), 209 (48), 207 (12), 67 (20), 57 (20), 56 (20), 42 (13); found *m/z* 278.1485 $[M]^+$; calcd for $C_{12}H_{18}N_6O_2$, 278.1486 $[M]^+$.

1,3,7-Trimethyl-8-morpholino-1*H*-purine-2,6(3*H*,7*H*)-dione (14). Yield 86%, white powder, mp 152.0–154.9°C. IR spectrum (ν, cm^{-1}): 1701 (C=O), 1653 (C=O), 1612, 1514, 1445, 912, 748 (C=C, C=N). UV spectrum (λ_{max}, nm) (log ε): 206 (4.18), 222 (4.29), 291 (4.19). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.82 (4H, dd, J = 4.6, 6.2, 2 × CH_2), 3.73 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 3.36 (3H, s, NCH_3), 3.23 (4H, dd, J = 4.6, 6.2, 2 × CH_2). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 155.7 (C-6), 154.8 (C-8), 151.5 (C-2), 147.1 (C-4), 105.3 (C-5), 66.1 (2 × CH_2), 49.8 (2 × CH_2), 32.2 (NCH_3), 29.4 (NCH_3), 27.5 (NCH_3). Mass spectrum (*m/z*, I_{rel}, %): 279 (100), 264 (11), 234 (6), 222 (19), 221 (8), 220 (8), 194 (6), 193 (4), 67 (7), 42 (6), ; found *m/z* 279.1320 $[M]^+$; calcd for $C_{12}H_{17}N_5O_3$, 279.1326.

Synthesis of Conjugates 15–19. General Method. Caffeine derivative **6**, **7**, or **13** (1 mmol), the appropriate lactone **2**, **3**, or **4** (0.9 mmol), and Et_3N (2.0 mmol) were dissolved in EtOH (10 mL). The reaction mixture was stirred at 55°C for 3 h and at room temperature for 12 h. When the reaction was finished, the mixture was evaporated in a rotary evaporator. The residue was chromatographed over silica gel ($CHCl_3$–EtOH eluent, 100:0→75:25).

1,3,7-Trimethyl-8-(2-{[(3*R*,3a*R*,4a*S*,8a*R*,9a*R*)-8a-methyl-5-methylene-2-oxododecahydronaphtho[2,3-*b*]furan-3-yl]methylamino}ethylamino)-1*H*-purine-2,6(3*H*,7*H*)-dione (15). Yield 65%, white powder, mp 194°C; $[\alpha]_{589}^{23}$ +44° (*c* 0.37, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3431 (NH), 2931, 1763 (C=O), 1697 (C=O), 1653 (C=O), 1622, 1578, 1549, 1489, 1456, 1221, 1165, 910, 720. UV spectrum (λ_{max}, nm) (log ε): 216 (4.54), 296 (4.45). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.67 (1H, d, J = 1.5, H-15), 4.52 (1H, ddd, J = 1.7, 4.2, 5.1, H-8), 4.32 (1H, d, J = 1.5, H-15), 3.65 (2H, t, J = 4.6, CH_2), 3.60 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 3.30–3.44 (2H, m, NH), 3.26 (3H, s, NCH_3), 3.20 (1H, dt, J = 6.4, 7.0, H-11), 3.07–3.12 (3H, m, H-13, CH_2), 3.04 (1H, dd, J = 5.8, 12.1, H-13), 2.57 (1H, dtd, J = 4.0, 6.0, 6.1, 12.5, H-7), 2.24 (1H, d, J = 13.6, H-3), 2.08 (1H, dd, J = 1.8, 15.5, H-9), 1.89 (1H, ddd, J = 5.1, 12.6, 14.5, H-3), 1.72 (1H, d, J = 12.0, H-5), 1.43–1.50 (4H, m, H-1, 2, 2, 6), 1.41 (1H, dd, J = 4.0, 15.5, H-9), 1.15 (1H, ddd, J = 4.3, 13.2, 14.3, H-1), 1.06 (1H, dd, J = 12.6, 12.8, H-6), 0.68 (3H, s, CH_3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 177.5 (C-12), 153.6 (C-6′), 152.8 (C-8′), 151.3 (C-2′), 148.5 (C-4), 148.0 (C-4′), 106.0 (C-15), 103.0 (C-5′), 78.6 (C-8), 48.3 (C-13), 45.7 (C-11), 44.6 (C-5), 44.1 (CH_2), 41.6 (C-1), 40.6 (C-9), 39.7 (CH_2), 38.6 (C-7), 36.1 (C-3), 34.2 (C-10), 29.4 (NCH_3), 29.2 (NCH_3), 27.2 (NCH_3), 22.1 (C-2), 20.7 (C-6), 17.2

(CH_3). Mass spectrum (*m/z*, I_{rel}, %): 484 (6), 252 (57), 232 (46), 223 (32), 222 (100), 209 (40), 190 (60), 93 (34), 91 (32), 79 (32); found *m/z* 484.2790 $[M]^+$; calcd for $C_{25}H_{36}N_6O_4$, 484.2793.

1,3,7-Trimethyl-8-(6-{[(3*R*,3a*R*,4a*S*,8a*R*,9a*R*)-8a-methyl-5-methylene-2-oxododecahydronaphtho[2,3-*b*]furan-3-yl]methylamino}hexylamino)-1*H*-purine-2,6(3*H*,7*H*)-dione (16). Yield 44%, oily compound, $[\alpha]_{589}^{23}$ +23° (*c* 1.50 $CHCl_3$). IR spectrum (ν, cm^{-1}): 3348 (NH), 1751 (C=O), 1709 (C=O), 1661 (C=O), 1614, 1581, 1547, 1481, 1454, 1373, 1221, 1161, 1032, 968, 744. UV spectrum (λ_{max}, nm) (log ε): 217 (4.60), 297 (4.54). ^{1}H NMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.71 (1H, d, J = 1.3, H-15) 4.61 (1H, s, NH), 4.44 (1H, ddd, J = 1.5, 3.9, 4.7, H-8), 4.39 (1H, d, J = 1.3, H-15), 3.59 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.39 (2H, dt, J = 6.2, 7.0, CH_2), 3.30 (3H, s, NCH_3), 2.95 (1H, dd, J = 7.7, 11.7, H-13), 2.86 (1H, dt, J = 6.7, 7.0, H-11), 2.71 (1H, dd, J = 7.0, 11.7, H-13), 2.56–2.63 (2H, m, CH_2), 2.44 (1H, dtd, J = 4.4, 6.0, 6.3, 12.2, H-7), 2.26 (1H, d, J = 13.6, H-3), 2.14–2.10 (1H, m, NH), 2.09 (1H, dd, J = 1.8, 15.4, H-9), 1.92 (1H, ddd, J = 5.4, 12.5, 14.0, H-3), 1.72 (1H, d, J = 12.0, H-5), 1.57–1.62 (2H, m, CH_2), 1.46–1.53 (6H, m, H-1, 2, 2, 6, CH_2), 1.41 (1H, dd, J = 4.1, 15.5, H-9), 1.33–1.35 (4H, m, 2 × CH_2), 1.16–1.18 (1H, m, H-1), 1.16 (1H, dd, J = 12.8, 13.1, H-6), 0.73 (3H, s, CH_3). ^{13}C NMR spectrum (150 MHz, $CDCl_3$, δ, ppm): 178.3 (C-12), 153.9 (C-6′), 153.5 (C-8′), 151.6 (C-2′), 149.1 (C-4), 148.6 (C-4′), 106.2 (C-15), 102.8 (C-5′), 78.2 (C-8), 49.7 (C-13), 47.2 (C-11), 46.3 (C-5), 45.2 (CH_2), 43.0 (CH_2), 42.0 (C-1), 41.2 (C-9), 39.0 (C-7), 36.5 (C-3), 34.6 (C-10), 29.6 (CH_2), 29.5 (CH_2), 29.4 (NCH_3), 29.3 (NCH_3), 27.4 (NCH_3), 26.6 (CH_2), 26.3 (CH_2), 22.4 (C-2), 21.0 (C-6), 17.6 (CH_3). Mass spectrum (*m/z*, I_{rel}, %): 541 (13), 540 (86), 309 (14), 308 (100), 278 (15), 236 (19), 232 (13), 222 (57), 209 (32), 190 (18), 41 (12); found *m/z* 540.3416 $[M]^+$; calcd for $C_{29}H_{44}N_6O_4$, 540.3419.

1,3,7-Trimethyl-8-(4-{[(3*R*,3a*R*,4a*S*,8a*R*,9a*R*)-8a-methyl-5-methylene-2-oxododecahydronaphtho[2,3-*b*]furan-3-yl]methyl}piperazin-1-yl)-1*H*-purine-2,6(3*H*,7*H*)-dione (17). Yield 58%, white powder, mp 144.9°C, $[\alpha]_{589}^{23}$ +53° (*c* 0.24, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1757 (C=O), 1707 (C=O), 1662 (C=O), 1610, 1520, 1448, 1375, 1311, 1281, 1219, 1175, 1157, 1142, 986, 964, 750. UV spectrum (λ_{max}, nm) (log ε): 202 (4.25), 222 (4.25), 293 (4.15). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.75 (1H, d, J = 1.1, H-15), 4.47 (1H, ddd, J = 1.7, 4.0, 4.9, H-8), 4.43 (1H, d, J = 1.1, H-15), 3.71 (3H, s, NCH_3), 3.48 (3H, s, NCH_3), 3.34 (3H, s, NCH_3), 3.20–3.28 (4H, m, 2 × CH_2), 2.95 (1H, ddd, J = 4.4, 6.1, 10.4, H-11), 2.80 (1H, dd, J = 4.4, 13.0, H-13), 2.71–2.73 (2H, m, CH_2), 2.69 (1H, dd, J = 10.4, 13.0, H-13), 2.52–2.57 (2H, m, CH_2), 2.51 (1H, dtd, J = 4.2, 6.0, 6.1, 12.2, H-7), 2.32 (1H, d, J = 12.8, H-3), 2.15 (1H, dd, J = 1.7, 15.5, H-9), 1.97 (1H, ddd, J = 7.0, 12.4, 14.1, H-3), 1.78 (1H, d, J = 12.0, H-5), 1.68 (1H, ddd, J = 2.0, 5.7, 13.2, H-6), 1.50–1.58 (3H, m, H-1, 2, 2), 1.45 (1H, dd, J = 4.2, 15.5, H-9), 1.21 (1H, ddd, J = 6.0, 12.7, 13.4, H-1), 1.14 (1H, dd, J = 12.6, 13.0, H-6), 0.77 (3H, s, CH_3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 177.4 (C-12), 156.0 (C-6′), 154.8 (C-8′), 151.6 (C-2′), 149.3 (C-4), 147.2 (C-4′), 106.3 (C-15), 105.3 (C-5′), 78.2 (C-8), 53.0 (C-13), 52.5 (2 × CH_2), 49.5 (2 × CH_2), 46.4 (C-11), 45.2 (C-5), 42.1 (C-1), 41.4 (C-9), 39.2 (C-7), 36.6 (C-3), 34.7 (C-10), 32.4 (NCH_3), 29.5 (NCH_3), 27.6 (NCH_3), 22.5 (C-2), 20.8 (C-6), 17.7 (CH_3). Mass spectrum (*m/z*, I_{rel}, %): 510 (58), 302 (27), 288 (25), 278 (67), 232 (18), 223 (22), 222 (100), 209 (90), 190 (25), 91 (21), 84 (28); found *m/z* 510.2944 $[M]^+$; calcd for $C_{27}H_{38}N_6O_4$, 510.2949.

8-(4-{[(3*R*,3a*R*,4a*R*,6*R*,8a*R*,9a*R*)-6-Hydroxy-8a-methyl-5-methylene-2-oxododecahydronaphtho[2,3-*b*]furan-3-yl]methyl}piperazin-1-yl)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)) (18). Yield 44%, white powder, mp 100.5–103.2°C, $[\alpha]_{589}^{23}$ +40° (*c* 1.36, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3446 (OH), 1765 (C=O), 1699 (C=O), 1657 (C=O), 1612, 1520, 1448, 1391, 1375, 1313, 1283, 1221, 1167, 1051, 1038, 987, 966, 910, 750. UV spectrum (λ_{max}, nm) (log ε): 202 (4.18), 222 (4.25), 292 (4.16). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.98 (1H, s, H-15), 4.57 (1H, s, H-15), 4.48 (1H, ddd, J = 1.6, 4.0, 4.9, H-8), 4.31 (1H, t, J = 2.4, H-3), 3.71 (3H, s, NCH_3), 3.48 (3H, s, NCH_3), 3.34 (3H, s, NCH_3), 3.19–3.28 (4H, m, 2 × CH_2), 2.95 (1H, ddd, J = 4.6, 6.1, 10.3, H-11), 2.80 (1H, dd, J = 4.3, 13.2, H-13), 2.70–2.72 (2H, m, CH_2), 2.68 (1H, dd, J = 10.5, 13.2, H-13), 2.51–2.56 (3H, m, H-7, 2H - CH_2), 2.36 (1H, d, J = 12.1, H-5), 2.16 (1H, dd, J = 1.4, 15.4, H-9), 1.64–1.82 (4H, m, H-1, 2, 2, 6), 1.52 (1H, dd, J = 4.2, 15.5, H-9), 1.30 (1H, dt, J = 3.2, 12.7, H-1), 1.12 (1H, dd, J = 12.6, 12.8, H-6), 0.76 (3H, s, CH_3). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 177.4 (C-12), 156.0 (C-6′), 154.8 (C-8′), 151.6 (C-2′), 150.4 (C-4), 147.2 (C-4′), 109.5 (C-15), 105.2 (C-5′), 78.1 (C-8), 73.0 (C-3), 53.0 (C-13), 52.5 (2 × CH_2), 49.4 (2 × CH_2), 45.2 (C-11), 41.0 (C-9), 40.3 (C-5), 39.2 (C-7), 35.6 (C-1), 34.6 (C-10), 32.4 (NCH_3), 29.6 (NCH_3), 29.0 (C-2), 27.6 (NCH_3), 20.4 (C-6), 16.9 (CH_3). Mass spectrum (*m/z*, I_{rel}, %): 526 (11), 362 (17), 278 (100), 248 (26), 236 (14), 223 (19), 222 (98), 209 (72), 138 (15), 123 (14); found *m/z* 526.2903 $[M]^+$; calcd for $C_{27}H_{38}N_6O_5$, 526.2898.

1,3,7-Trimethyl-8-[4-({(2′*R*,3*R*,3a*R*,4a*R*,8a*R*,9a*R*)-8a-methyl-2-oxodecahydro-2*H*-spiro[naphtho[2,3-*b*]furan-5,2′-oxiran]-3-yl}methyl)piperazin-1-yl]-1*H*-purine-2,6(3*H*,7*H*)-dione (19). Yield 60%, white powder, mp 108.5°C, $[\alpha]_{589}^{23}$ +9° (*c* 0.11, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1759 (C=O), 1707 (C=O), 1662 (C=O), 1510, 1448, 1437, 1377, 1313, 1284, 1217, 1194, 1146, 1009, 987, 970, 752. UV spectrum (λ_{max}, nm) (log ε): 204 (4.13), 222 (4.22), 293 (4.12). ^{1}H NMR spectrum (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.45 (1H, ddd, J = 1.9, 4.2, 4.6, H-8), 3.70 (3H, s, NCH_3), 3.48 (3H, s, NCH_3), 3.34 (3H, s,

NCH_3), 3.19–3.28 (4H, m, 2 × CH_2), 2.93 (1H, ddd, J = 4.3, 6.1, 9.6, H-11), 2.75 (1H, dd, J = 4.1, 13.2, H-13), 2.66–2.70 (2H, m, CH_2), 2.64 (1H, dd, J = 1.6, 4.5, H-15), 2.57 (1H, dd, J = 9.9, 13.1, H-13), 2.54–2.56 (2H, m, CH_2), 2.53 (1H, d, J = 4.5, H-15), 2.43 (1H, dtd, J = 4.1, 5.7, 6.0, 12.4, H-7), 2.14 (1H, dd, J = 1.6, 15.5, H-9), 1.85 (1H, dd, J = 10.0, 10.6, H-3), 1.53–1.69 (5H, m, H-1, 2, 2, 5, 6), 1.44 (1H, dd, J = 4.3, 15.5, H-9), 1.32 (1H, d, J = 12.6, H-3), 1.16 (1H, ddd, J = 8.0, 9.3, 13.2, H-1), 0.92 (3H, s, CH_3), 0.65 (1H, dd, J = 12.4, 12.7, H-6). ^{13}C NMR spectrum (150 MHz, $CDCl_3$, δ, ppm): 177.3 (C-12), 156.0 (C-6′), 154.8 (C-8′), 151.6 (C-2′), 147.2 (C-4′), 105.2 (C-5′), 77.8 (C-8), 58.5 (C-4), 52.8 (C-13), 52.4 (2 × CH_2), 50.6 (C-15), 49.3 (2 × CH_2), 45.4 (C-11), 44.3 (C-5), 41.8 (C-1), 41.2 (C-9), 39.3 (C-7), 35.1 (C-3), 34.7 (C-10), 32.4 (NCH_3), 29.5 (NCH_3), 27.6 (NCH_3), 20.2 (C-2), 18.5 (CH_3), 16.4 (C-6). Mass spectrum (*m/z*, I_{rel}, %): 526 (88), 422 (19), 318 (30), 304 (21), 290 (29), 278 (83), 248 (8), 233 (34), 223 (18), 222 (76), 209 (100), 91 (6), 84 (4); found *m/z* 526.2899 $[M]^+$; calcd for $C_{27}H_{38}N_6O_5$, 526.2898.

ACKNOWLEDGMENT

The work was financially supported by RFBR grants (Project No. 18-03-01012) and the RFBR and Novosibirsk Region Government (Project No. 19-43-543042). We thank the Khimiya Common Use Center, NIOCh, SB, RAS, for spectral and analytical studies.

REFERENCES

1. S. Kishkentayeva, E. E. Shults, Y. V. Gatilov, S. S. Patrushev, S. Karim, and S. M. Adekenov, *Chem. Heterocycl. Compd*., **52**, 788 (2016).
2. J. Monteiro, M. G. Alves, P. F. Oliveira, and B. M. Silva, *Crit. Rev. Food Sci. Nutr.*, **59**, 2597 (2019).
3. R. Harmse, M. M. van der Walt, J. P. Petzer, and G. Terre′Blanche, *Bioorg. Med. Chem. Lett.*, **26**, 5951 (2016).
4. J. Jiang, C. J. Seel, A. Temirak, V. Namasivayam, A. Arridu, J. Schabikowski, Y. Baqi, S. Hinz, J. Hockemeyer, and C. E. Muller, *J. Med. Chem*., **62**, 4032 (2019).
5. M. I. Rodriguez-Franco, M. I. Fernandez-Bachiller, C. Perez, A. Castro, and A. Martinez, *Bioorg. Med. Chem*., **13**, 6795 (2005).
6. S. S. Patrushev, T. V. Rybalova, I. D. Ivanov, V. A. Vavilin, and E. E. Shults, *Tetrahedron*, **73**, 2717 (2017).
7. H. P. Booysen, C. Moraal, G. Terre′Blanche, A. Petzer, J. J. Bergh, and J. P. Petzer, *Bioorg. Med. Chem*., **19**, 7507 (2011).
8. M. M. Van der Walt and G. Terre′Blanche, *Bioorg. Med. Chem*., **23**, 6641 (2015).
9. M. M. van der Walt and G. Terre′Blanche, *Eur. J. Med. Chem.*, **125**, 652 (2017).
10. B. Jasiewicz, A. Sierakowska, W. Jankowski, M. Hoffman, W. Pioronska, A. Gornicka, A. Bielawska, K. Bielawski, and L. Mrowczynska, *Free Radical Res.*, **52**, 724 (2018).
11. S. C. Srivastava, M. M. Mehra, G. K. Trivedi, and S. C. Bhattacharyya, *Indian J. Chem*., **9**, 512 (1971).
12. A. T. Kulyyasov, T. S. Seitembetov, K. M. Turdybekov, and S. M. Adekenov, *Chem. Nat. Compd*., **32**, 869 (1996).
13. X. Li, C. Lu, S. Liu, S. Liu, C. Su, T. Xiao, Z. Bi, P. Sheng, M. Huang, X. Liu, Y. Wei, L. Zhao, S. Miao, J. Mao, K. Huang, S. Gao, N. Liu, M. Qi, T. Liu, S. Qin, L. Wei, T. Sun, W. Ning, G. Yang, H. Zhou, and C. Yang, *Eur. J. Med. Chem*., **157**, 229 (2018).
14. M. N. S. Rad, S. Behrouz, and A.-R. Nekoei, *Synlett*, **23**, 1191 (2012).
15. S. M. Maddox, C. J. Nalbandian, D. E. Smith, and J. L. Gustafson, *Org. Lett.,* **17**, 1042 (2015).