New [*c*,*d*]-Fused Purinediones: 2-Substituted 9-Methyl-4,5-dihydro-6*H*,8*H*-pyrimido-[1,2,3-*cd*]purine-8,10(9*H*)-diones

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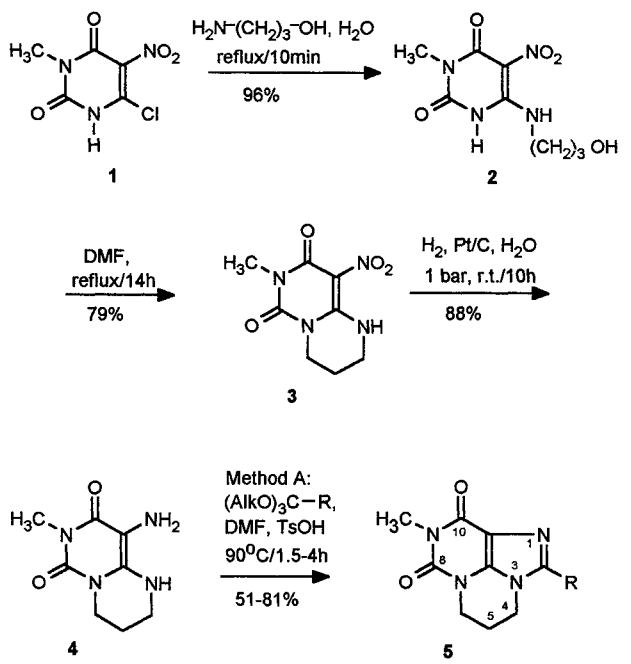
2-Alkyl- or 2-aryl-9-methyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones **5** were obtained either by a four-step synthesis starting from 6-chloro-5-nitro-3-methylpyrimidine-2,4(1*H*,3*H*)-dione **(1)** via 9-amino-7-methyl-3,4-dihydro-2*H*-pyrimido[1,6-*a*]pyrimidine-6,8(1*H*,7*H*)-dione **(4)** and its reaction with the respective orthocarboxylates, or, alternatively, by a four-step process from 6-[(3-hydroxypropyl)amino]-3-methyl-5-nitrosopyrimidine-2,4(1*H*,3*H*)-dione via 8-alkyl- or 8-aryl-9-mesyloxypropyl-1-methyl-3,9-dihydro-1*H*-purine-2,6-diones **9** and their intramolecular alkylation in dimethylformamide (DMF) in the presence of potassium carbonate.

So far only two types of compounds with a pyrimido[1,2,3-*cd*]purine ring system have been reported, *viz.* 4,9-dimethyl-5,6-dihydropyrimidopurine[1] and the partly unsaturated 9-alkyl-4-substituted aryl derivatives;[2] the last-mentioned compounds revealed interesting anxiolytic and antihypertensive effects.

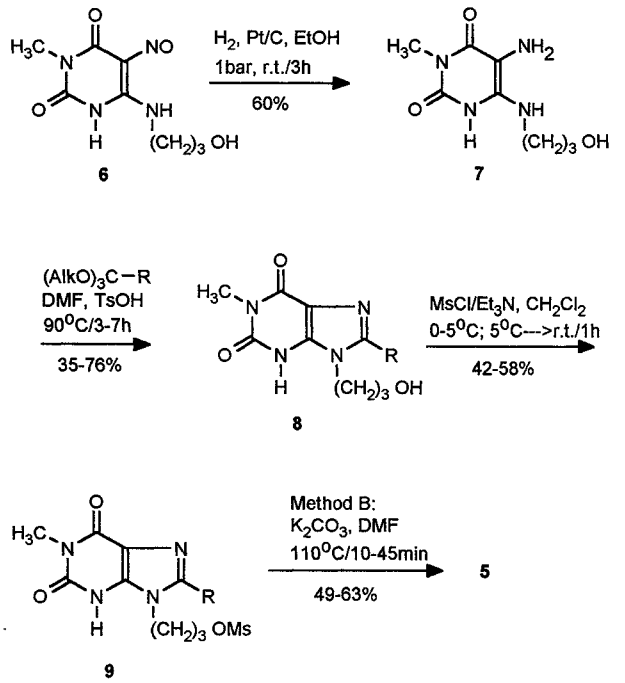
In extention of our studies on annulated purinediones,[3-6] we wish to present two new synthetic approaches to the pyrimido[1,2,3-*cd*]purine ring system. 2-Substituted 9-methyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones **5** were obtained from 6-chloro-5-nitro-3-methylpyrimidine-2,4-(1*H*,3*H*)-dione[7] **(1)**, which was converted into the corresponding 6-[(3-hydroxypropyl)amino]-5-nitro derivative **2** by a nucleophilic replacement with 3-aminopropanol. Lengthy reflux of the latter in DMF resulted in elimination of water originating from the side-chain hydroxy group in position 6 and the proton at N_1 of the pyrimidine derivative **2** and formation of 7-methyl-9-nitro-3,4-dihydro-2*H*-pyrimido[1,6-*a*]pyrimidine-6,8(1*H*,7*H*)-dione **(3)**. The nitro group in position 5 of compounds **2** is prerequisite for closure of the second ring of pyrimidine, because it enhances acidity of the N_1 proton and thus stimulates the elimination of water. The analogous 6-(3-hydroxypropyl)amino derivative without the nitro group resisted condensation attempts, and even quadrupled reaction time (60 h) did not afford the required dehydration product. Nevertheless, cyclization of a derivative analogous to our intermediate **2**, but without the methyl group in position 3 has already been reported;[8] it was, however, necessary to extend the reaction time by three times (14 h). Hydrogenation of the nitro group of compound **3** yielded the bicyclic diamine **4**, which is the precursor to formation of the third imidazole ring of the final products **5**. The third ring was formed by reacting the intermediate **4** with orthocarboxylates in aprotic solvents under acid catalysis and elevated temperature.

The second method leading to products **5** is based upon closure of the third pyrimidine ring in the suitably 9-substituted purinedione precursor. The starting 9-(3-functionalized propyl) 8-substituted 1-methyl-3,9-dihyd-



Scheme 1

5	R	5	R
a	H	d	Pr
b	Me	e	Bu
c	Et	f	Ph



Scheme 2

8,9	R	8,9	R
a	H	d	Pr
b	Me	e	Bu
c	Et	f	Ph

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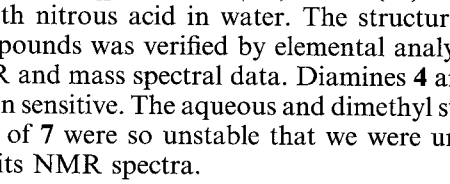
ro-1*H*-purine-2,6-dione **9** was obtained from the known[9] 6-[(3-hydroxypropyl)amino]-3-methyl-5-nitrosopyrimidine-2,4(1*H*,3*H*)-dione **(6)** by hydrogenation to the corresponding 5-amino derivative **7**. Similarly to the first method, compound **7** was reacted with orthocarboxylates in an aprotic solvent and traces of acid at elevated temperature to yield 8-substituted 9-(3-hydroxypropyl)-1-methyl-3,9-dihydro-1*H*-purine-2,6-diones **8**. Mesylation with mesyl chloride in the presence of an organic base afforded the corresponding 9-(3-mesyloxypropyl) derivatives **9**, and subsequent intramolecular alkylation in the presence of alkali metal carbonate in an aprotic solvent at 110 °C gave the final products **5**. The cyclization of compounds **9** producing the pyrimidine ring proceeded smoothly and without formation of byproducts. On the other hand, attempts to convert 9-(3-hydroxypropyl) derivatives into the respective 9-(3-chloropropyl) analogues failed.

The bicyclic diamine **4** was also the starting material for the preparation of 9-methyl-4,5-dihydro-6*H*,8*H*-2-azapyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione **(10)** by nitrosation with nitrous acid in water. The structure of the new compounds was verified by elemental analysis, ^{1}H, ^{13}C NMR and mass spectral data. Diamines **4** and **7** are air-oxygen sensitive. The aqueous and dimethyl sulfoxide solutions of **7** were so unstable that we were unable to measure its NMR spectra.



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Scheme 3

Reagents were obtained from commercial suppliers and were used without further purification. Mps were determined with a hot stage microscope (Boetius) and are uncorrected. The ^{1}H (300 MHz) and ^{13}C (75.45 MHz) NMR spectra were obtained on a Bruker AM-300 spectrometer. Chemical shifts were related to tetramethylsilane as an internal standard. Signals of compounds **5e**, **8e** and **9e** were assigned by means of 2D COSY experiments. Mass spectra were obtained on a Finnigan MAT SSQ 710 instrument using the electron impact ionization technique (100–210 °C, 70 eV). TLC was carried out on plates SILUFOL UV_{254} (Kavalier, Votice, Czech Republic) in $CHCl_3$/MeOH (9:1).

Satisfactory elemental analyses were obtained for all new compounds: C ± 0.39, H ± 0.30, N ± 0.33, S ± 0.37 %.

6-[(3-Hydroxypropyl)amino]-3-methyl-5-nitropyrimidine-2,4(1*H*,3*H*)-dione (2):

3-Aminopropanol (30.0 g, 0.40 mol) was added to a stirred suspension of 6-chloro-3-methyl-5-nitropyrimidine-2,4(1*H*,3*H*)-dione (**1**; 20.5 g, 0.10 mol) in H_2O (165 mL). Dissolution of compound **1** was slightly exothermic. The mixture was refluxed for 10 min, cooled to 40 °C, and acidified with 5 M aq HCl to pH 1. The separated crystals were filtered off and crystallized from H_2O (330 mL). Yield: 5.9 g (79 %), mp 189–191 °C (H_2O/EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.83 (quin, 2H, NCH_2CH_2), 3.18 (s, 3H, N–CH_3), 3.59 (t, 2H, NCH_2), 3.66 (br t, 2H, CH_2OH), 10.2 (br s, 1H, 6-NH).

^{13}C NMR (DMSO-d_6): δ = 27.0 (N–CH_3), 30.9 (NCH_2CH_2), 40.0 (NCH_2), 58.3 (CH_2OH), 109.3 (C-5), 148.4 (C-6), 151.8 (C-2), 155.9 (C-4).

MS: *m/z* (%) = 244 (M^+, 67), 226 (100), 208 (57), 198 (25), 196 (26), 180 (64), 167 (17), 136 (19), 123 (27), 111 (30), 96 (25), 83 (75).

7-Methyl-9-nitro-3,4-dihydro-2*H*-pyrimido[1,6-*a*]pyrimidine-6,8(1*H*,7*H*)-dione (3):

Compound **2** (8.3 g, 34 mmol) in DMF (85 mL) was refluxed for 14 h, the solvent was removed under diminished pressure and the dry residue was crystallized from H_2O (150 mL, charcoal). Yield: 5.9 g (79 %), mp 239–241 °C (H_2O/EtOH).

^{1}H NMR (DMSO-d_6): δ = 2.07 (m, 2H, H-3), 3.22 (s, 3H, N7-CH_3), 3.58 (m, 2H, H-2), 3.96 (m, 2H, H-4), 10.5 (br s, 1H, N1-H).

^{13}C NMR (DMSO-d_6): δ = 18.2 (C-3), 27.7 (N7-CH_3), 39.8 (C-2), 41.6 (C-4), 109.3 (C-9), 148.4 (C-9a), 151.2 (C-6), 155.0 (C-8).

MS: *m/z* (%) = 226 (M^+, 45), 208 (85), 196 (20), 180 (11), 165 (9), 151 (7), 124 (17), 122 (16), 95 (18), 85 (39), 83 (100).

9-Amino-7-methyl-3,4-dihydro-2*H*-pyrimido[1,6-*a*]pyrimidine-6,8(1*H*,7*H*)-dione (4):

A suspension of compound **3** (6.1 g, 27 mmol) in H_2O (320 mL) was hydrogenated over Pt/C (410 mg, 10 %) at 1 bar and r.t. for ca. 10 h; the originating amine dissolved in the medium. The catalyst was then filtered off and the aqueous solution, concentrated to 15 mL, was stored in a refrigerator overnight and the separated crystals were filtered off. Yield: 4.7 g (88 %), mp 170–172 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.99 (m, 2H, H-3), 3.21 (s, 3H, N7-CH_3), 3.35 (m, 2H, H-2), 3.83 (m, 2H, H-4), 6.7 (br s, 1H, N1-H).

^{13}C NMR (DMSO-d_6): δ = 20.5 (C-3), 27.3 (N7-CH_3), 38.4 (C-2), 40.6 (C-4), 93.4 (C-9), 144.2 (C-9a), 149.5 (C-6), 158.8 (C-8).

MS: *m/z* (%) = 196 (M^+, 100), 181 (4), 167 (7), 137 (6), 123 (5), 111 (14), 96 (9), 84 (40), 85 (38).

5-Amino-6-[(3-hydroxypropyl)amino]-3-methylpyrimidine-2,4(1*H*,3*H*)-dione (7):

A suspension of 6-[(3-hydroxypropyl)amino]-3-methyl-5-nitrosopyrimidine-2,4(1*H*,3*H*)-dione (**6**; 10.5 g, 46 mmol) in EtOH (210 mL) was hydrogenated over Pt/C (730 mg, 10 %) at 1 bar and r.t. for ca. 3 h, during which the purple-red suspension turned light brown. The mixture was evaporated to dryness under reduced pressure and the product was crystallized from H_2O (180 mL), after removal of the catalyst. Yield: 5.9 g (60 %), mp 197–199 °C (H_2O/EtOH).

MS: *m/z* (%) = 214 (M^+, 100), 196 (64), 183 (39), 169 (64), 155 (73), 128 (9), 110 (11), 98 (23), 84 (27).

8-Alkyl- or 8-Aryl-9-(3-hydroxypropyl)-1-methyl-3,9-dihydro-1*H*-purine-2,6-diones 8; General Procedure:

A mixture containing compound **7** (2.15 g, 10 mmol), DMF (25 mL), trimethyl or triethyl orthoalkanoate or orthobenzoate (15 mmol) and *p*-toluenesulfonic acid (8–12 mg) was heated with stirring at 90 °C (3 h for **8e, f**; 4 h for **8a, c, d**; 7 h for **8b**). The volatile components were distilled off under reduced pressure after the catalytical amount of *p*-toluenesulfonic acid was neutralized with ethanolic ammonia. The dry residue was crystallized from a suitable solvent in the presence of charcoal.

8-Unsubstituted Derivative **(8a):**

Yield: 76 %; mp 248–250 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.91 (quin, 2H, NCH_2CH_2), 3.26 (s, 3H, N1-CH_3), 3.48 (t, 2H, N9-CH_2), 4.18 (t, 2H, CH_2OH), 7.76 (s, 1H, H-8).

^{13}C NMR (DMSO-d_6): δ = 27.0 (N1-CH_3), 32.4 (NCH_2CH_2), 41.1 (N9-CH_2), 57.3 (CH_2OH), 114.9 (C-5), 137.0 (C-8), 138.6 (C-4), 150.8 (C-2), 157.5 (C-6).

MS: *m/z* (%) = 224 (M^+, 84), 206 (29), 194 (7), 179 (25), 166 (7), 149 (50), 139 (35), 122 (100), 109 (35), 95 (10).

8-Methyl Derivative **(8b):**

Yield: 61 %; mp 195–197 °C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.85 (quin, 2H, NCH_2CH_2), 2.42 (s, 3H, C8-CH_3), 3.23 (s, 3H, N1-CH_3), 3.49 (t, 2H, N9-CH_2), 4.11 (t, 2H, CH_2OH).

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^{13}C NMR (DMSO-d_6): δ = 12.9 (C8-CH_3), 27.0 (N1-CH_3), 32.0 (NCH_2CH_2), 40.3 (N9-CH_2), 57.4 (CH_2OH), 113.0 (C-5), 139.2 (C-4), 144.2 (C-8), 150.8 (C-2), 157.2 (C-6).

MS: *m/z* (%) = 238 (M^+, 77), 207 (7), 193 (13), 179 (9), 164 (10), 153 (35), 137 (100), 122 (20), 109 (24), 96 (8).

8-Ethyl Derivative **(8c)**:

Yield: 41%; mp 218–219°C (EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.43 (t, 3H, CH_2CH_3), 1.85 (quin, 2H, NCH_2CH_2), 2.79 (q, 2H, C8-CH_2), 3.28 (s, 3H, N1-CH_3), 3.50 (t, 2H, N9-CH_2), 4.12 (t, 2H, CH_2OH).

^{13}C NMR (DMSO-d_6): δ = 11.1 (CH_2CH_3), 19.3 (C8-CH_2), 27.0 N1-CH_3), 32.2 (NCH_2CH_2), 40.0 (N9-CH_2), 57.4 (CH_2OH), 113.1 (C-5), 139.2 (C-4), 148.2 (C-8), 150.8 (C-2), 157.3 (C-6).

MS: *m/z* (%) = 252 (M^+, 100), 234 (4), 221 (13), 207 (21), 193 (8), 179 (21), 167 (42), 150 (20), 136 (17), 123 (68), 109 (7).

8-Propyl Derivative **(8d)**:

Yield: 48%; mp 211–213°C (dioxane/EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.06 (t, 3H, $CH_2CH_2CH_3$), 1.81 (sext, 2H, C8-CH_2CH_2), 1.84 (quin, 2H, N9-CH_2CH_2), 2.73 (C8-CH_2), 3.27 (t, 2H, N1-CH_3), 3.50 (t, 2H, N9-CH_2), 4.12 (t, 2H, CH_2OH).

^{13}C NMR (DMSO-d_6): δ = 13.7 ($CH_2CH_2CH_3$), 19.9 (C8-CH_2CH_2), 26.9 (C8-CH_2), 27.7 (N1-CH_3), 32.3 (N9-CH_2CH_2), 40.0 (N9-CH_2), 113.2 (C-5), 139.1 (C-4), 147.2 (C-8), 150.7 (C-2), 157.2 (C-6).

MS: *m/z* (%) = 266 (M^+, 30), 238 (10), 235 (17), 221 (10), 194 (100), 180 (32), 162 (17), 150 (5), 137 (24), 122 (8), 109 (4).

8-Butyl Derivative **(8e)**:

Yield: 45%; mp 190–192°C (THF/methyl *tert*-butyl ether).

^{1}H NMR (DMSO-d_6): δ = 1.02 (t, 3H, $CH_2CH_2CH_3$), 1.48 (sext, 2H, C8-$CH_2CH_2CH_2$), 1.78 (quin, 2H, C8-CH_2CH_2), 1.83 (quin, 2H, N9-CH_2CH_2), 2.76 (t, 2H, C8-CH_2), 3.28 (s, 3H, N1-CH_3), 3.51 (t, 2H, N9-CH_2), 4.12 (t, 2H, CH_2OH).

^{13}C NMR (DMSO-d_6): δ = 13.7 ($CH_2CH_2CH_3$), 21.7 (C8-$CH_2CH_2CH_2$), 25.5 (C8-CH_2CH_2), 26.9 (C8-CH_2), 27.0 (N1-CH_3), 32.3 (N9-CH_2CH_2), 40.0 (N9-CH_2), 57.4 (CH_2OH), 113.2 (C-5), 139.1 (C-4), 147.3 (C-8), 150.7 (C-2), 157.2 (C-6).

MS: *m/z* (%) = 280 (M^+, 13), 265 (2), 251 (13), 238 (29), 221 (12), 207 (6), 194 (100), 180 (35), 162 (9), 150 (4), 122 (4), 109 (3).

8-Phenyl Derivative **(8f)**:

Yield: 34%; mp 298–301°C (H_2O/EtOH).

^{1}H NMR (DMSO-d_6): δ = 1.80 (quin, 2H, N9-CH_2CH_2), 3.32 (s, 3H, N1-CH_3), 3.41 (t, 2H, N9-CH_2), 4.28 (t, 2H, CH_2OH), 7.6–7.8 (m, 5H, H_{arom}).

^{13}C NMR (DMSO-d_6): = 27.1 (N1-CH_3), 32.2 (N9-CH_2CH_2), 41.7 (N9-CH_2), 57.5 (CH_2OH), 114.4 (C-5), 128.5, 128.7, 129.4, 129.5, (C_6H_5), 140.2 (C-4), 145.8 (C-8), 150.8 (C-2), 157.5 (C-6).

MS: *m/z* (%) = 300 (M^+, 100), 282 (58), 255 (24), 242 (14), 225 (39), 215 (12), 198 (47), 194 (26), 185 (11), 162 (18), 144 (31), 129 (16), 117 (43), 104 (87).

8-Alkyl- or 8-Aryl-9-(3-mesyloxypropyl)-1-methyl-3,9-dihydro-1*H*-purine-2,6-diones 9; General Procedure:

Et_3N (0.30 g, 0.42 mL, 3 mmol) added to a stirred and cooled (0–5°C) suspension of compound **8** (2 mmol) in CH_2Cl_2 (15 mL for **8c–e**, 20 mL for **8a, b, f**) afforded a solution into which mesyl chloride (0.25 g, 0.17 mL, 2.2 mmol) in CH_2Cl_2 (7 mL) was dripped at the same temperature over 15 min. The mixture was stirred without cooling (5°C → r.t.) for 1 h and the solvent was removed under diminished pressure. Water (3 mL) was added to the dry residue, the crystalline product **(9a, b, f)** was filtered off, or the solution was stored in a refrigerator overnight and the crystals formed were filtered off **(9c, d)**, or the product was taken from the solution with CH_2Cl_2 (2 × 15 mL), the solvent was concentrated to about 4 mL under reduced pressure and the crystals formed after addition of methyl *tert*-butyl ether (20 mL) were filtered off **(9e)**.

8-Unsubstituted Derivative **(9a)**:

Yield: 58%; mp 163–165°C (MeOH/EtOH).

^{1}H NMR ($CDCl_3$): δ = 2.20 (quin, 2H, N9-CH_2CH_2), 3.30 (s, 3H, N1-CH_3), 3.32 (s, 3H, SO_2CH_3), 4.25 (t, 2H, N9-CH_2), 4.31 (t, 2H, OCH_2), 7.81 (s, 1H, H-8).

^{13}C NMR ($CDCl_3$): δ = 27.1 (N1-CH_3), 29.0 (SO_2CH_3), 36.7 (N9-CH_2CH_2), 47.6 (N9-CH_2), 67.3 (OCH_2), 115.1 (C-5), 136.9 (C-8), 138.6 (C-4), 150.8 (C-2), 157.6 (C-6).

MS: *m/z* (%) = 206 (M – CH_3SO_3H, 76), 177 (3), 149 (100), 121 (61), 93 (9).

8-Methyl Derivative **(9b)**:

Yield: 72%; mp 165–167°C (MeOH).

^{1}H NMR ($CDCl_3$): δ = 2.14 (quin, 2H, N9-CH_2CH_2), 2.45 (s, 3H, C8-CH_3), 3.26 (s, 3H, N1-CH_3), 3.27 (s, 3H, SO_2CH_3), 4.18 (t, 2H, N9-CH_2), 4.38 (t, 2H, OCH_2).

^{13}C NMR ($CDCl_3$): δ = 12.9 (C8-CH_3), 27.0 (N1-CH_3), 28.6 (SO_2CH_3), 36.6 (N9-CH_2CH_2), 45.7 (N9-CH_2), 67.4 (OCH_2), 113.0 (C-5), 139.2 (C-4), 143.9 (C-8), 150.8 (C-2), 157.1 (C-6).

MS: *m/z* (%) = 220 (M – CH_3SO_3H, 100), 163 (99), 135 (50), 107 (5), 83 (65).

8-Ethyl Derivative **(9c)**:

Yield: 62%; mp 142–144°C (acetone).

^{1}H NMR ($CDCl_3$): δ = 1.34 (t, 3H, C8-CH_2CH_3), 2.13 (quin, 2H, N9-CH_2CH_2), 2.79 (q, 2H, C8-CH_2), 3.27 (s, 3H, N1-CH_3), 3.28 (s, 3H, SO_2CH_3), 4.17 (t, 2H, N9-CH_2), 4.35 (t, 2H, OCH_2).

^{13}C NMR ($CDCl_3$): δ = 11.0 (C8-CH_2CH_3), 19.3 (C8-CH_2), 27.0 (N1-CH_3), 28.7 (SO_2CH_3), 36.6 (N9-CH_2CH_2), 45.8 (N9-CH_2), 67.4 (OCH_2), 113.0 (C-5), 139.2 (C-4), 148.2 (C-8), 150.8 (C-2), 157.2 (C-6).

MS: *m/z* (%) = 234 (M – CH_3SO_3H, 100), 177 (95), 149 (30), 121 (3), 98 (38), 96 (77).

8-Propyl Derivative **(9d)**:

Yield: 52%; mp 141–143°C (acetone).

^{1}H NMR ($CDCl_3$): δ = 1.05 (t, 3H, C8-$CH_2CH_2CH_3$), 1.82 (sext, 2H, C8-CH_2CH_2), 2.13 (quin, 2H, N9-CH_2CH_2), 2.73 (t, 2H, C8-CH_2), 3.27 (s, 3H, N1-CH_3), 3.28 (s, 3H, SO_2CH_3), 4.18 (t, 2H, N9-CH_2), 4.34 (t, 2H, OCH_2).

^{13}C NMR ($CDCl_3$): δ = 13.7 (C8-$CH_2CH_2CH_3$), 19.9 (C8-CH_2CH_2), 27.0 (N1-CH_3), 27.7 (C8-CH_2), 28.9 (SO_2CH_3), 36.6 (N9-CH_2CH_2), 45.7 (N9-CH_2), 67.4 (OCH_2), 113.1 (C-5), 139.1 (C-4), 147.1 (C-8), 150.8 (C-2), 157.2 (C-6).

MS: *m/z* = 248 (M – CH_3SO_3H, 45), 220 (100), 191 (45), 162 (14), 135 (12), 107 (7), 96 (20).

8-Butyl Derivative **(9e)**:

Yield: 55%; mp 131–133°C (acetone/MeOH).

^{1}H NMR ($CDCl_3$): δ = 1.01 (t, 3H, $CH_2CH_2CH_3$), 1.48 (sext, 2H, C8-$CH_2CH_2CH_2$), 1.78 (quin, 2H, C8-CH_2CH_2), 2.15 (quin, 2H, N9-CH_2CH_2), 2.80 (t, 2H, C8-CH_2), 3.28 (2 s, 6H, N1-CH_3, SO_2CH_3), 4.19 (t, 2H, N9-CH_2), 4.36 (t, 2H, OCH_2).

^{13}C NMR ($CDCl_3$): δ = 13.7 ($CH_2CH_2CH_3$), 21.7 (C8-$CH_2CH_2CH_2$), 25.3 (C8-CH_2CH_2), 27.0 (N1-CH_3), 28.6 (C8-CH_2), 28.8 (SO_2CH_3), 36.6 (N9-CH_2CH_2), 45.8 (N9-CH_2), 67.4 (OCH_2), 112.1 (C-5), 139.0 (C-4), 147.5 (C-8), 150.7 (C-2), 156.7 (C-6).

MS: *m/z* (%) = 262 (M – CH_3SO_3H, 17), 233 (16), 220 (100), 162 (17), 135 (17), 107 (5), 96 (17).

8-Phenyl Derivative **(9f)**:

Yield: 85%; mp 179–180°C (MeOH).

^{1}H NMR ($CDCl_3$): δ = 2.10 (quin, 2H, N9-CH_2CH_2), 3.17 (s, 3H, N1-CH_3), 3.32 (s, 3H, SO_2CH_3), 4.00 (t, 2H, N9-CH_2), 4.22 (t, 2H, OCH_2), 7.60–7.95 (m, 5H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 27.1 (N1-CH_3), 28.7 (SO_2CH_3), 36.5 (N9-CH_2CH_2), 45.6 (N9-CH_2), 67.1 (OCH_2), 114.4 (C-5), 128.6, 128.8, 129.2, 129.8 (C_6H_5), 140.1 (C-4), 145.6 (C-8), 150.8 (C-2), 157.4 (C-6).

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MS: *m/z* (%) = 282 (M – CH_3SO_3H, 100), 225 (69), 197 (30), 144 (51), 117 (77), 113 (17).

2-Alkyl- or 2-Aryl-9-methyl-4,5-dihydro-6*H*,8*H*-pyrimido[1,2,3-*cd*]purine-8,10(9*H*)-diones 5; General Procedures:

Method A:

A mixture of compound **4** (1.96 g, 10 mmol), DMF (15 mL), trimethyl or triethyl orthoalkanoate or orthobenzoate (15 mmol) and *p*-toluenesulfonic acid (10–15 mg) was heated with stirring (1.5 h for **5d**; 2.5 h for **5a, e**; 3 h for **5b**; 3.5 h for **5c**; 4 h for **5f**). The cooled mixture was neutralized with ethanolic ammonia and the volatile components were distilled off under diminished pressure. The dry distillation residue was crystallized from a suitable solvent.

Method B:

Compound **9** (2.0 mmol) in DMF (16 mL) was stirred with K_2CO_3 (0.33 g, 2.4 mmol) and heated to 110 °C (10 min for **5f**; 20 min for **5d**; 30 min for **5b**; 60 min for **5c**; 90 min for **5a**). DMF was distilled off in vacuo, the residue was extracted with $CHCl_3$ (3 × 100 mL), the solvent was removed under reduced pressure and the dry residue was crystallized from a suitable solvent (charcoal) (**5a–c, f**), or the chloroformic solution was concentrated to a minimal volume to which methyl *tert*-butyl ether was added. The solution was stored overnight and the separated crystals were filtered off (**5d**).

2-Unsubstituted Derivative (**5a**):

Yield: 57% (Method A); 52% (B); mp 321–322 °C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 2.29 (quin, 2H, H-5), 3.30 (s, 3H, N9-CH_3), 3.92 (t, 2H, H-4), 4.20 (t, 2H, H-6), 7.85 (s, 1H, H-2).

^{13}C NMR ($CDCl_3$): δ = 20.5 (C-5), 27.5 (N9-CH_3), 38.6 (C-4), 39.7 (C-6), 113.1 (C-10a), 135.6 (C-2), 138.0 (C-10b), 149.8 (C-8), 156.8 (C-10).

MS: *m/z* = 206 (M^+, 73), 149 (100), 121 (71), 93 (10).

2-Methyl Derivative (**5b**):

Yield: 67% (A); 59% (B); mp 337–339 °C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 2.28 (quin, 2H, H-5), 2.43 (s, 3H, C2-CH_3), 3.28 (s, 3H, N9-CH_3), 3.92 (t, 2H, H-4), 4.08 (t, 2H, H-6).

^{13}C NMR ($CDCl_3$): δ = 12.4 (C2-*C*H_3), 20.6 (C-5), 27.5 (N9-CH_3), 38.6 (C-4), 39.7 (C-6), 114.0 (C-10a), 138.4 (C-10b), 148.0 (C-2), 149.7 (C-8), 156.5 (C-10).

MS: *m/z* (%) = 220 (M^+, 100), 163 (99), 135 (53), 83 (70).

2-Ethyl Derivative (**5c**):

Yield: 51% (A); 39% (B); mp 199–200 °C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 1.33 (t, 3H, C2-CH_2CH_3), 2.29 (quin, 2H, H-5), 2.78 (q, 2H, C2-CH_2), 3.30 (s, 3H, N9-CH_3), 3.90 (t, 2H, H-4), 4.10 (t, 2H, H-6).

^{13}C NMR ($CDCl_3$): δ = 10.9 (C2-CH_2CH_3), 19.4 (C2-*C*H_2CH_3), 20.6 (C-5), 27.4 (N9-CH_3), 38.6 (C-4), 39.7 (C-6), 111.7 (C-10a), 138.4 (C-10b), 147.8 (C-2), 149.7 (C-8), 156.6 (C-10).

MS: *m/z* = 234 (M^+, 93), 177 (100), 149 (47), 97 (70), 96 (65).

2-Propyl Derivative (**5d**):

Yield: 63% (A); 58% (B); mp 159–162 °C (dioxane)

^{1}H NMR ($CDCl_3$): δ = 1.14 (t, 3H, $CH_2CH_2CH_3$), 1.78 (sext, 2H, C2-CH_2CH_2), 2.29 (quin, 2H, H-5), 2.73 (t, 2H, C2-CH_2), 3.28 (s, 3H, N9-CH_3), 3.90 (t, 2H, H-4), 4.10 (t, 2H, H-6).

^{13}C NMR ($CDCl_3$): δ = 13.6 ($CH_2CH_2CH_3$), 19.9 (C2-CH_2CH_2), 20.5 (C-5), 27.4 (N9-CH_3), 27.8 (C2-CH_2), 38.6 (C-4), 39.7 (C-6), 111.8 (C-10a), 138.3 (C-10b), 146.7 (C-2), 149.7 (C-8), 156.6 (C-10).

MS: *m/z* = 248 (M^+, 52), 220 (82), 219 (49), 191 (72), 162 (42), 135 (20), 107 (9), 96 (11).

2-Butyl Derivative (**5e**):

Yield: 56% (A); mp 150–151 °C (EtOH).

^{1}H NMR ($CDCl_3$): δ = 1.02 (t, 3H, $CH_2CH_2CH_3$), 1.48 (sext, 2H, $CH_2CH_2CH_3$), 1.75 (quin, 2H, C-2-CH_2CH_2), 2.29 (quin, 2H, H-5), 2.76 (t, 2H, C2-CH_2), 3.29 (s, 3H, N9-CH_3), 3.92 (t, 2H, H-4), 4.11 (t, 2H, H-6).

^{13}C NMR ($CDCl_3$): δ = 13.6 ($CH_2CH_2CH_3$), 20.6 (C-5), 21.6 ($CH_2CH_2CH_3$), 25.5 (C2-CH_2CH_2), 27.4 (N9-CH_3), 28.5 (C2-CH_2), 38.6 (C-4), 39.7 (C-6), 118.8 (C-10a), 138.3 (C-10b), 146.8 (C-2), 149.7 (C-8), 156.6 (C-10).

MS: *m/z* = 262 (M^+, 29), 233 (27), 220 (100), 162 (34), 135 (38), 83 (45).

2-Phenyl Derivative (**5f**):

Yield: 81% (A); 85% (B); mp 276–280 °C (EtOH/H_2O).

^{1}H NMR ($CDCl_3$): δ = 2.30 (quin, 2H, H-5), 3.33 (s, 3H, N9-CH_3), 4.00 (t, 2H, H-4), 4.40 (t, 2H, H-6), 7.40–7.95 (m, 5H, C2-Ph).

^{13}C NMR ($CDCl_3$): δ = 20.9 (C-5), 27.6 (N9-CH_3), 39.7 (C-4), 42.8 (C-6), 113.3 (C-10a), 128.8, 128.9, 129.3, 129.5 (C_6H_5), 134.3 (C-8), 139.5 (C-10b), 149.7 (C-8), 158.8 (C-10).

MS: *m/z* = 282 (M^+, 89), 225 (67), 197 (20), 145 (64), 144 (64), 117 (100), 113 (24), 103 (20), 89 (14), 77 (18).

9-Methyl-4,5-dihydro-6*H*,8*H*-2-azapyrimido[1,2,3-*cd*]purine-8,10(9*H*)-dione (10):

Conc. HCl (0.9 mL, 10 mmol) was dripped into a suspension of compound **4** (1.96 g, 10 mmol) in H_2O (30 mL). A solution of $NaNO_2$ (0.76 g, 11 mmol) in H_2O (2 mL) was added to the violet solution of **4** · HCl with stirring at 10 °C over 5 min. The violet colour of the solution disappeared and a colourless fine-crystalline product separated. Stirring was continued at 10 °C for 1 h until the reaction was complete and the filtered product was crystallized from H_2O. Yield: 1.01 g (49%), mp 268–269 °C (H_2O).

^{1}H NMR ($CDCl_3$): δ = 2.38 (quin, 2H, H-5), 3.32 (s, 3H, N9-CH_3), 3.96 (t, 2H, H-4), 4.55 (t, 2H, H-6).

^{13}C NMR ($CDCl_3$): δ = 20.4 (C-5), 27.9 (N9-CH_3), 39.2 (C-4), 43.1 (C-6), 122.4 (C-10a), 139.8 (C-10b), 149.6 (C-8), 155.4 (C-10).

MS: *m/z* = 207 (M^+, 100), 179 (23), 151 (24), 123 (43), 108 (34), 94 (23).

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