A New Synthesis of Pteridines

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A new synthesis of pteridines possessing a (substituted) (*Z*)-3-hydroxyprop-1-enyl group at C(6) is based on the acylation of 4-amino-5-nitrosopyrimidines with dienoic acid chlorides, followed by a high-yielding intramolecular hetero-*Diels–Alder* cycloaddition and cleavage of the N–O bond leading to **4**. Thermolysis of the resulting pteridines **4** possessing a benzyloxy group at C(4) led to the products **5**, resulting from isomerisation of the 3-hydroxyprop-1-enyl to an 3-oxopropyl side chain, while the analogous pteridine **8** possessing an NH_2 group at C(4) remained unaffected.

Introduction. – Pteridines occur widely, play essential roles in growth processes and the metabolism of one-carbon units [1–4], and are in clinical use as anticancer, antiviral, antibacterial, and diuretic drugs [5]. A number of methods allow the synthesis of pteridines either from pyrimidine or from pyrazine precursors [2][3]. 4-Amino-5-nitrosopyrimidines are common, crucial intermediates in the synthesis of purines and pteridines. They were reduced to 4,5-diaminopyrimidines, as in the *Traube* [6] and related *Pfleiderer* purine syntheses [7], and in the *Gabriel–Isay* and *Viscontini* pteridine syntheses [8][9], transformed to pyrimido-oxadiazinones that react with enamines or enol ethers to form lumazines [10][11], or used directly, as in our improved modification of the *Traube* purine synthesis [12] and in the *Timmis* condensation with carbonyl compounds [13] that leads regioselectively to substituted pteridines. Recent years have seen a rapid increase in studies devoted to pteridines[1]) while synthetic innovation has, with few exceptions, been directed at improving known methods [10][11][27–33]. In the context of our interest in 8-substituted guanines, we considered a new access to pteridines. The high reactivity of nitroso (NO) groups as heterodienophiles in [4+2] cycloadditions [34] should allow a facile intramolecular hetero-*Diels–Alder* cycloaddition of amides resulting from *N*-acylation of 4-amino-5-nitrosopyrimidines with penta-2,4-dienoyl chlorides and lead regioselectively to *C(6)*- and/or *C(7)*-substituted pteridines. As most naturally occurring pteridines, such as folic acids, biopterin, and neopterin, as well as the anticancer drug methotrexate are substituted at C(6) [5], this would constitute a potentially useful new synthesis of pteridines.

Results and Discussion. – We examined a few conditions for the acylation with sorbyl chloride [35][36] of the poorly soluble 6-(benzyloxy)-5-nitrosopyrimidine-2,4-

[1]) See, *e.g.*, [1][14–26]. A search in the *Web of Science* (January 2006) produced 352 references for the period of 2000–2006.

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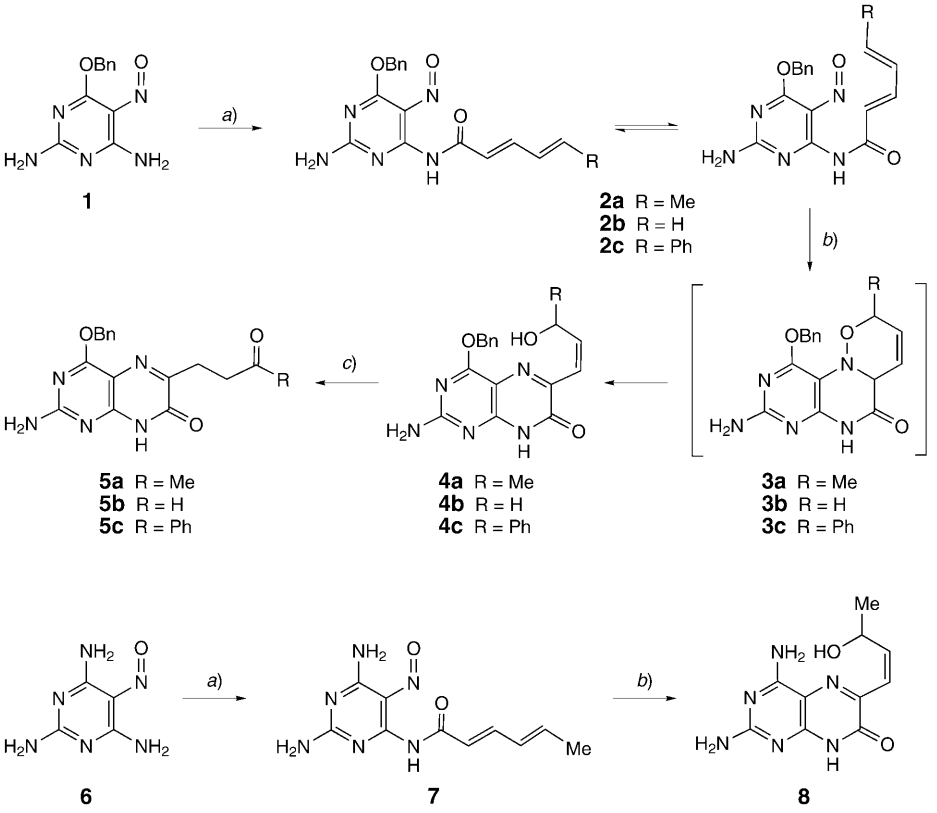
Scheme



a) RCH=CH–CH=CH–COCl (R = Me, H, or Ph), pyridine; 60–70% of **2a**–**2c** and **7**. *b*) Suspension in toluene, 100°; *ca*. 98% of **4a**–**4c** and **8**. *c*) Suspension in *o*-xylene, 120°; *ca*. 98% of **5a**–**5c**.

diamine (**1**) [37] (*Scheme*) that we already used in our synthesis of 8-substituted purines. We obtained satisfactory results, also for the acylation by penta-3,4-dienoyl [38] and 5-phenylpenta-4,5-dienoyl chloride [39], by treating a pyridine solution of **1** at $-10°$ with a cold pyridine solution of 1.1 equiv. of the acyl chloride.

The expected amides **2a**–**2c** were obtained as green powders. They were not stable in solution, as judged by a progressive colour change to yellow and the formation of precipitates during chromatography, or in solution, and were not characterized. The precipitates were very polar, insoluble in many organic solvents, and strongly fluorescent, suggesting a facile intramolecular [4+2] cycloaddition. The precipitates proved complex mixtures. They were not separated. Fortunately, heating the crude acylation products **2a**–**2c** in toluene under reflux led almost quantitatively to the pure pteridines

4a–**4c**. The products **3a**–**3c** of the expected [4+2] cycloaddition appear to undergo a rapid eliminative cleavage of the weak N–O bond[2]), followed by tautomerisation.

The 5-nitrosopyrimidine-2,4,6-triamine (**6**) [41] was similarly acylated with sorbyl chloride. Heating the resulting amide **7** in toluene induced a similar, more sluggish transformation, leading to the diaminopteridine **8**, again in high yields, as precipitates that were purified by washing with H_2O, AcOEt, and Et_2O.

Remarkably, continued heating of **4a**–**4c**[3]), best performed in boiling *o*-xylene, led in high yields to the ketones **5a**–**5c**[3]). The transformation of **4** to **5** is rationalised by a [1,5]-sigmatropic H shift, followed by tautomerisation of the intermediate enol enamine to the imino ketones **5**. A precedent for such a transformation is found in the tautomerisation reported by *Coppola* and *Damon* [42]. The diaminopteridine **8** did not undergo such a transformation. Longer heating or higher temperatures led to its progressive decomposition.

The structure of the pteridine derivatives **4** and **8** follows unambiguously from their spectroscopic data. Thus, the constitution of the secondary alcohol **4a** is evidenced by high-resolution MALDI-MS, elemental analysis, IR bands at 3420 cm^{-1} (OH; NH bands at 3323 and 3208 cm^{-1}), a comparison of their UV spectra with those of related pteridines [27][43], and the ^{1}H- and ^{13}C-NMR data (*Tables 1 and 2* in the *Exper. Part*). No ^{13}C-NMR spectra of pteridin-7(8*H*)-ones were found by a Beilstein X-fire search. The assignment of the ^{13}C *s*s of **4** and **5** to the six quaternary C-atoms was first based on the predictions of ChemDraw Ultra V. 9 and on a comparison, for C(2) and C(4), with the C(2) and C(6) signals of O^6-methylguanosines [44] and then revised – for the assignment of C(2) and C(7) – on the basis of an HMBC spectrum of **4a**. It shows cross-peaks between the two *d*s of PhCH_2 and the *s* at 164.51 ppm (C(4)), between the *s* of NH_2 and the *s*s at 164.51, 161.39 (C(8a)), and 150.62 ppm (C(2)), and between the *dd* of H–C(1′) and the *s*s at 157.13 ppm (C(7)) and 146.08 (C(6)). J(1′,2′) of the olefinic H-atom of 12.3 Hz is in keeping with the (*Z*)-configuration as evidenced by a comparison with the data of related 2-(3-hydroxyprop-1-enyl)pyridines [45]. The structure of **8** is evidenced by the high-resolution MALDI mass spectrum, an ATR-IR OH band at 3460 cm^{-1}, and broader NH bands at 3327 and 3175 cm^{-1}, and the NMR spectra ((D$_6$)DMSO) where the Me group resonates at 1.23 ppm as a *d* (J=6.3 Hz), the olefinic H-atom at 6.56 (*dd*, J=12.0 and 1.2 Hz) and 5.87 ppm (*dd*, J=12.0 and 7.8 Hz), and the allylic H-atom at 5.15 ppm (*m*), in keeping with a ^{13}C *q* at 22.43 ppm, and *d*s at 118.76, 144.01, and 63.07 ppm.

Also the structure of the ketones **5** follows unambiguously from their analytical data. Thus, the 3-oxobutyl substituent of **5a** is evidenced by the disappearance of the

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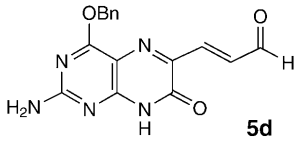
[2]) See [40] for a base-promoted eliminative cleavage of a N–O bond.

[3]) In contact with air, the aldehyde **5b** is easily oxidised to the corresponding (*E*)-configured α,β-unsaturated aldehyde **5d** that was also formed in small amounts from **4b**.



5d

signals corresponding to the olefinic C=C bond of **4a**, a Me *s* at 2.07 ppm, and two *triplet*-like signals of an isolated ethylene group at 2.81 and 2.71 ppm. The PhCH_2 of **5a** resonate as a *s* at 5.43 ppm (^{13}C-NMR: *t* at 67.42 ppm), while PhCH_2 of **4a** resonates as two *d*s at 5.49 and 5.44 ppm. The C=O group of **5a** is evidenced by a ^{13}C *s* at 207.77 ppm and an IR band at 1708 cm^{-1}. The ATR-IR OH/NH band of **4a** at 3420 cm^{-1} is replaced by a much weaker NH band at 3427 cm^{-1} for **5a**.

This synthesis of pteridines possessing a configurationally defined 3-hydroxyprop-1-enyl substituent at C(6) should allow a convenient access to naturally occurring pteridines and their analogues; work towards this goal is in progress.

We thank the *ETH Zürich* and *F. Hoffmann-La Roche*, Basel, for generous support, *Thomas Steinlin* for checking the transformations of **1** to **4a**–**4c** and to **5a**–**5c**, and for the UV spectra of these compounds, and Dr. *Bruno Bernet* for checking the analytical data.

Experimental Part

General. See [46]. UV Spectra: MeOH, λ_{max} (log ε).

General Procedure for the Preparation of the Pteridin-7-ones **4a**–**4c** *and* **8**. A soln. of **1** [37] (245 mg, 1.0 mmol) or **6** [41] (154 mg, 1.0 mmol) in dry pyridine (10 ml) was cooled to −10°, treated with the 2,4-dienoyl chloride (1.1 mmol), and stirred for 12 h. The soln. was diluted with CH_2Cl_2 (50 ml), washed with brine (3×20 ml), dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/MeOH 100:1) of the blue residue gave green powders of **2a**–**2c** and **7** (60–70%), resp. A suspension of **2a**–**2c** and **7** (1 mmol) in toluene was heated for 3–5 h to 100°, when a yellow suspension was formed. After evaporation, the solid yellow residue was washed with H_2O, AcOEt, and Et_2O. Drying of the residue *in vacuo* (*i.v.*) gave **4a**–**4c** and **8** (*ca.* 98%), resp. Yellow powders.

General Procedure for the Transformation of **4a**–**4c** *to the Carbonyl Compounds* **5a**–**5c**. A suspension of **4a**–**4c** (1 mmol) in *o*-xylene was degassed, heated for 12 h to 120°, and evaporated. The solid yellow residue was washed with H_2O and Et_2O. Drying of the residue *i.v.* gave **5a**–**5c** (*ca*. 98%). Yellow powders.

*2-Amino-6-[(Z)-3-hydroxybut-1-enyl]-4-(phenylmethoxy)pteridin-7(8*H*)-one* (**4a**). M.p. 242° (dec.). UV: 376 (4.18), 285 (3.84), 208 (4.46). IR (ATR): 3420*m*, 3323*w*, 3208*m*, 2834*w*, 2737*w* (br.), 1802*w*, 1670*w*, 1614*s*, 1560*s*, 1538*m*, 1496*m*, 1490*m*, 1464*m*, 1428*s*, 1387*m*, 1356*s*, 1327*m*, 1307*m*, 1182*s*, 1052*s*, 975*m*, 927*m*, 905*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*; additionally, 7.54–7.31 (*m*, 5 arom. H); 5.49, 5.44 (2*d*, *J* = 12.6, PhCH_2). ^{13}C-NMR ((D$_6$)DMSO, 100 MHz; assignments based on a HSQC and a HMBC spectrum): see *Table 2*; additionally, 136.31 (*s*); 128.23 (2*d*); 127.77 (*d*); 127.36 (2*d*); 67.32 (*t*, Ph*C*H$_2$). HR-MALDI-MS: 362.1223 (82, $[M+Na]^+$, $C_{17}H_{17}N_5NaO_3^+$; calc. 362.1229), 340.1402 (35, $[M+H]^+$, $C_{17}H_{18}N_5O_3^+$; calc. 340.1410), 322.1299 (100, $[M-OH]^+$, $C_{17}H_{16}N_5O_2^+$; calc. 322.1304). Anal. calc. for $C_{17}H_{17}N_5O_3$ (339.35): C 60.17, H 5.05, N 20.64; found: C 60.38, H 5.15, N 20.50.

*2-Amino-6-[(Z)-3-hydroxyprop-1-enyl]-4-(phenylmethoxy)pteridin-7(8*H*)-one* (**4b**). M.p. 220° (dec.). UV: 360 (3.91), 287 (3.70), 216 (4.43). IR (ATR): 3367*m*, 3330*m*, 3193*m*, 2888*w*, 2832*w*, 2766*w* (br.), 1673*m*, 1650*s*, 1610*s*, 1561*s*, 1534*s*, 1489*s*, 1440*s*, 1388*m*, 1343*s*, 1325*m*, 1265*m*, 1189*s*, 1086*m*, 1064*m*, 1037*m*, 1016*s*, 950*m*, 913*s*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*; additionally, 7.50–7.31 (*m*, 5 arom. H); 5.49 (*s*, PhCH_2); weak signals at 9.69 (*d*, *J* = 7.8), 7.68 (*d*, *J* = 16.2), and 7.12 (*dd*, *J* = 16.2, 7.8) denote a contamination by 5 to 10% of **5d**. ^{13}C-NMR ((D$_6$)DMSO, 100 MHz): see *Table 2*; additionally, 136.58 (*s*); 128.42 (2*d*); 127.78 (*d*); 127.30 (2*d*); 67.10 (*t*, Ph*C*H$_2$). HR-MALDI-MS: 348.1066 (43, $[M+Na]^+$, $C_{16}H_{15}N_5NaO_3^+$; calc. 348.1073), 326.1247 (56, $[M+H]^+$, $C_{16}H_{16}N_5O_3^+$; calc. 326.1253), 308.1140 (100, $[M-OH]^+$, $C_{16}H_{14}N_5O_2^+$; calc. 308.1147).

*2-Amino-6-[(Z)-3-hydroxy-3-phenylprop-1-enyl]-4-(phenylmethoxy)pteridin-7(8*H*)-one* (**4c**). M.p. 205° (dec.). UV: 381 (4.16), 280 (3.91), 233 (4.22), 211 (4.55). IR (ATR): 3422*w*, 3323*w*, 3206*m*, 2734*w* (br.), 1662*m*, 1613*s*, 1561*s*, 1487*s*, 1432*s*, 1394*m*, 1354*s*, 1326*m*, 1264*m*, 1178*m*, 1090*m*, 1046*m*, 1002*m*, 938*m*, 908*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*; additionally, 12.46 (*s*, HN(8)); 7.58–7.06

Table 1. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the Pteridin-7(8*H*)-ones* **4a**–**4c**, **5a**–**5c**, *and* **8** *in (D$_6$)DMSO*

	4a	**4b**	**4c**	**5a**	**5b**	**5c**	**8**
H–N(8)	12.40	12.38	12.46	12.34	12.37	12.35	12.12
H_2N–C(2)	7.24	7.20	[a])	7.08	7.09	7.06	7.29[b])
H–C(1′)	6.61	6.68	6.68	2.81	2.90	2.99	6.56
H–C(2′)	5.95	6.09	6.02	2.71	2.76	3.40	5.87
H–C(3′)	5.15	4.53	6.36	–	9.73	–	5.15
HO–C(3′)	4.89	4.92	5.48	–	–	–	4.81
Me(4′)	1.20	–	–	2.07	–	–	1.23
J(1′,2′)	12.3	12.0	12.0	6.3	6.6	6.6	12.0
J(1′,3′)	1.2	2.4	0	–	–	–	1.2
J(2′,3′)	7.5	5.4	9.0	–	1.2	–	7.8
J(3′,OH)	4.2	[c])	4.2	–	–	–	4.5
J(3′,4′)	6.3	–	–	–	–	–	6.3

[a]) Hidden by the arom. signals at 7.58–7.06 ppm. [b]) $\delta(H_2N–C(4)) = 6.64$ ppm. [c]) Not assigned.

Table 2. *Selected ^{13}C-NMR Chemical Shifts* [ppm] *of the Pteridin-7(8*H*)-ones* **4a**–**4c**, **5a**–**5c**, *and* **8** *in (D$_6$)DMSO*

	4a[a])	**4b**	**4c**	**5a**	**5b**	**5c**[b])	**8**[b])
C(2)	150.62	150.65	151.01	151.92	151.72	152.03	148.88
C(4)	164.51	164.53	164.61	164.25	164.27	164.14	160.63
C(4a)	107.54	107.71	107.56	106.70	106.82	106.71	106.49
C(6)	146.08	146.52	145.83	151.17	151.27	151.13	143.68
C(7)	157.13	157.17	157.26	157.02	157.03	157.01	157.79
C(8a)	161.39	161.37	161.41	161.17	161.18	161.06	162.20
C(1′)	118.56	119.18	118.50	26.64	25.17	26.44	118.76
C(2′)	145.75	142.63	142.50	38.25	39.18	34.17	144.01
C(3′)	63.45	60.28	67.45	207.77	202.53	199.01	63.07
C(4′)	22.26	–	–	30.16	–	–	22.43

[a]) Assignments based on a HSQC and a HMBC spectrum. [b]) Assignments based on a HSQC spectrum.

(*m*, 10 arom. H, NH_2); 5.64, 5.43 (2*d*, *J* = 12.6, PhCH_2). ^{13}C-NMR ((D$_6$)DMSO, 100 MHz): see *Table 2*; additionally, 144.33, 136.22 (2*s*); 128.41 (2*d*); 128.16 (2*d*); 127.97 (*d*); 127.70 (2*d*); 126.50 (*d*); 126.44 (2*d*); 67.52 (*t*, PhCH_2). HR-MALDI-MS: 424.1376 (40, $[M+Na]^+$, $C_{22}H_{19}N_5NaO_3^+$; calc. 424.1386), 402.1555 (45, $[M+H]^+$, $C_{22}H_{20}N_5O_3^+$; calc. 402.1566), 384.1450 (100, $[M-OH]^+$, $C_{22}H_{18}N_5O_2^+$; calc. 384.1460).

*2-Amino-6-(3-oxobutyl)-4-(phenylmethoxy)pteridin-7(8*H*)-one* (**5a**). M.p. 245° (dec.). UV: 343 (4.08), 284 (3.78), 212 (4.40). IR (ATR): 3427*w*, 3322*w*, 3202*w*, 2900*w*, 2835*w*, 2760*w* (br.), 1708*w*, 1666*m*, 1615*s*, 1557*s*, 1498*m*, 1431*s*, 1391*m*, 1354*s*, 1307*m*, 1253*m*, 1178*m*, 1087*m*, 1058*m*, 978*m*, 930*m*, 911*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*; additionally, 7.51–7.32 (*m*, 5 arom. H); 5.44 (*s*, PhCH_2). ^{13}C-NMR ((D$_6$)DMSO, 100 MHz): see *Table 2*; additionally, 136.34 (*s*); 128.42 (2*d*); 128.38 (2*d*); 128.10 (*d*); 67.42 (*t*, PhCH_2). HR-MALDI-MS: 362.1222 (49, $[M+Na]^+$, $C_{17}H_{17}N_5NaO_3^+$; calc. 362.1229), 340.1398 (100, $[M+H]^+$, $C_{17}H_{18}N_5O_3^+$; calc. 340.1410).

*2-Amino-6-(3-oxopropyl)-4-(phenylmethoxy)pteridin-7(8*H*)-one* (**5b**). M.p. 210° (dec.). UV: 345 (3.89), 282 (3.74), 209 (4.37). ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*; additionally, 7.49–7.31

(*m*, 5 arom. H); 5.43 (*s*, PhCH_2). ^{13}C-NMR ((D$_6$)DMSO, 100 MHz): see *Table 2*; additionally, 136.46 (*s*); 128.41 (2*d*); 128.12 (2*d*); 127.98 (*d*); 67.20 (*t*, PhCH_2). HR-MALDI-MS: 348.1067 (31, $[M+Na]^+$, $C_{16}H_{15}N_5NaO_3^+$; calc. 348.1073), 326.1249 (79, $[M+H]^+$, $C_{16}H_{16}N_5O_3^+$; calc. 326.1253).

*2-Amino-6-(3-oxo-3-phenylpropyl)-4-(phenylmethoxy)pteridin-7(8*H*)-one* (**5c**). M.p. 255° (dec.). UV: 343 (3.57), 279 (3.35), 235 (3.75), 204 (4.19). IR (ATR): 3414*w*, 3322*w*, 3204*w*, 2916*w*, 2831*w*, 2736*w* (br.), 1684*m*, 1662*m*, 1644*s*, 1619*s*, 1559*s*, 1511*m*, 1497*m*, 1433*s*, 1392*m*, 1355*s*, 1298*s*, 1205*m*, 1183*s*, 1088*m*, 1055*s*, 987*m*, 920*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*; additionally, 7.98–7.29 (*m*, 10 arom. H); 5.38 (*s*, PhCH_2). ^{13}C-NMR ((D$_6$)DMSO, 125 MHz; assignments based on HSQC spectrum): see *Table 2*; additionally, 136.81, 136.33 (2*s*); 132.83 (*d*); 128.51 (2*d*); 128.21 (2*d*); 127.78 (3*d*); 127.72 (2*d*); 66.96 (*t*, PhCH_2). HR-MALDI-MS: 424.1380 (59, $[M+Na]^+$, $C_{22}H_{19}N_5NaO_3^+$; calc. 424.1386), 402.1563 (100, $[M+H]^+$, $C_{22}H_{20}N_5O_3^+$; calc. 402.1566).

*2,4-Diamino-6-[(*Z*)-3-hydroxybut-1-enyl)pteridin-7(8*H*)-one* (**8**). M.p. 210° (dec.). IR (ATR): 3460*w*, 3327*m*, 3175*m*, 2969*w*, 2924*w*, 2847*w*, 2721*w* (br.), 1826*w*, 1615*s*, 1556*s*, 1530*s*, 1480*s*, 1454*s*, 1401*s*, 1323*m*, 1257*m*, 1153*m*, 1108*m*, 1048*s*, 930*m*, 903*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): see *Table 1*. ^{13}C-NMR ((D$_6$)DMSO, 100 MHz; assignments based on HSQC spectrum): see *Table 2*. HR-MALDI-MS: 271.0914 (26, $[M+Na]^+$, $C_{10}H_{12}N_6NaO_2^+$; calc. 271.0919), 249.1093 (37, $[M+H]^+$, $C_{10}H_{13}N_6O_2^+$; calc. 249.1100), 231.0991 (100, $[M-OH]^+$, $C_{10}H_{11}N_6O^+$; calc. 231.0994).

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