Facile and General Syntheses of 3- and/or 5-Substituted 7-β-D-Ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purines as a New Class of Potential Xanthine Oxidase Inhibitors

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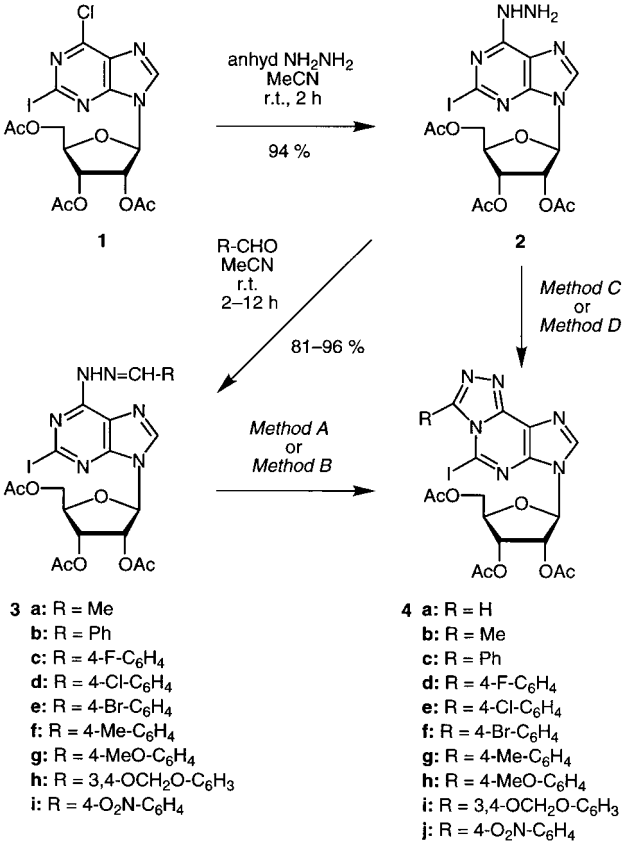
Abstract: Novel, general, and facile syntheses of 3- and/or 5-substituted 7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purines (**5–8**) via compounds **4** as a new class of potential xanthine oxidase inhibitors are described. The key intermediates **4b–j** were prepared by oxidative cyclization of the aldehyde hydrazones **3a–i**, derived from 6-hydrazino-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purines (**2**) and an appropriate aldehyde, with diethyl azodicarboxylate (DEAD) (Method A) or lead tetraacetate (Method B) in good yields. The intermediates **4a–j** were also synthesized from heating of **2** with triethyl orthoesters (Method C) or with aldehydes and DEAD in one-pot reactions (Method D).

Key words: purine nucleosides, *s*-triazolo[3,4-*i*]purine nucleosides, oxidative cyclization, xanthine oxidase inhibitor

In connection with ongoing work aimed at the synthesis and biological evaluation of novel fused purine systems,[1,2] we tried to prepare the angular type purine analogues, 7*H*-[1,2,4]triazolo[3,4-*i*]purine nucleosides, which have very recently been investigated as a new class of potential xanthine oxidase (XO) / xanthine dehydrogenase (XDH) inhibitors in our laboratory.[3] Some of them showed more potent bovine milk XO inhibitory activity than that of allopurinol. Allopurinol and oxypurinol are known to inhibit xanthine oxidase,[4] and allopurinol is now widely employed in treatment of gout and hyperuricemia resulting from uric acid.[5–7] Although XO / XDH inhibitory activities have recently been discovered in some synthetic compounds,[8–12] no clinically effective XO inhibitors for the treatment of hyperuricemia have been developed since allopurinol was introduced for clinical use in 1963.[4] Here we report a new, convenient, and general synthesis of the tricyclic purine compounds, 3- and/or 5-substituted 7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purines (**5–8**) as a new class of the xanthine oxidase inhibitors.

Since the first report[13] on the synthesis of compounds having a 7*H*-[1,2,4]triazolo[3,4-*i*]purine ring system in 1965, which is of interest in view of the chemical and biological properties, only two reports[14, 15] have hitherto appeared in the literature. Halogenated purine nucleosides are good synthetic intermediates for the synthesis of a number of the purine nucleoside derivatives. Thus the availability of 6-chloro-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (**1**)[16] for the starting material enabled us to synthesize the tricyclic purine derivatives **4a–j** as shown in Scheme 1.



Method A: DEAD, MeCN, reflux, 5–10 h; *Method B*: $Pb(OAc)_4$, dioxane, reflux, 1–15 h; *Method C*: $RC(OEt)_3$, HOAc, 55–80 °C, 4–7 h; *Method D*: RCHO, MeCN, r.t., 5 h, then with DEAD, reflux, 5–24 h

Scheme 1

Treatment of compound **1** with excess anhydrous hydrazine (2.3 mol equiv) in acetonitrile at room temperature afforded 6-hydrazino-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (**2**) in 94% yield. The structure was verified by satisfactory spectral and analytical data. In particular, the IR spectrum showed the characteristic N-H bands at ν_{as} = 3410, ν_s = 3360, ν = 3260, and δ = 1610 cm^{-1} for the $NHNH_2$ group, and the structure was substantiated by the appearance of the molecular ion peak (MH^+: *m/z* = 535), which was attributable to the 6-hydrazino derivative **2** rather than 2-hydrazino derivative (MH^+: *m/z* =

Table 1 Formation and Physical Data of Compounds **3a–i**

Product[a]	Yield[b] (%)	mp (°C)[c]	Recrystallization[d] Solvent	MS-FAB[e] *m/z* MH^+
3a	96	85– 88	benzene	561
3b	92	103–106	benzene	623
3c	85	119–121	EtOH/H_2O	641
3d	89	115–118	DMF/H_2O	657, 659
3e	90	109–111	DMF/H_2O	701, 703
3f	93	172–173	EtOH/H_2O	637
3g	87	109–112	EtOAc	653
3h	92	114–115	DMF/H_2O	667
3i	81	260–262	DMF/H_2O	668

[a] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.29, N ± 0.30.
[b] Yield based on the isolated product after column chromatography.
[c] Uncorrected.
[d] All products were obtained as colorless powder except for **3i** (yellow).
[e] FAB MS was measured with glycerol as a matrix.

443 and 445), in the FAB mass spectrum. Subsequent treatment of the 6-hydrazino derivative **2** with an appropriate alkylaldehyde (3 mol equiv) or arylaldehyde (1.3 mol equiv) in acetonitrile at room temperature for 2–12 h gave the corresponding 6-aldehyde hydrazones **3a–i** in 81–96% yields as shown in Table 1. All new compounds exhibited satisfactory elemental combustion analyses and MS, IR, and ^{1}H NMR spectral data consistent with the structures indicated (Table 4). Heating the hydrazones **3** thus obtained with diethyl azodicarboxylate (DEAD) (2.5 mol equiv) in anhydrous acetonitrile at reflux for 5–10 h afforded the desired tricyclic purine derivatives, 5-iodo-7-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofurano-syl)-7*H*-[1,2,4]triazolo[3,4-*i*]purines **4**, after isolation by column chromatography (Merck Kieselgel 60, eluent: benzene/ethyl acetate, 1:1) in 70–79% yields as disclosed in the experimental examples **4d, f, i, j** and indicated in the Table 2 (*Method A*). The oxidative cyclization of the hydrazones **3** could also be accomplished by heating at reflux for 1–15 h with lead tetraacetate (2 mol equiv) in anhydrous dioxane and work up in a similar manner as above to get the triazolopurines **4** in 66–73% yields as disclosed in the experimental examples **4b, c, e, g, h** (*Method B*). Moreover, the triazolopurines **4** were obtained by heating the 6-hydrazino derivative **2** with triethyl orthoesters (107 mol equiv) and glacial acetic acid (5 parts) at 55–80 °C in 63–77% yields as disclosed in the experimental examples **4a, b** (*Method C*). The present procedures were further simplified by the following technique. Thus a solution of the hydrazinopurine **2** with an appropriate aldehyde (1.3 mol equiv) in anhydrous acetonitrile was stirred at r.t. for 5 h, followed by heating with DEAD (3 mol equiv) at reflux for 5–24 h in one-pot reactions to yield the corresponding triazolopurines **4c–j** in 44–82% yields (*Method D*). The structures of the tricyclic compounds **4a–j** were confirmed by satisfactory analytical and spectral data as shown in Tables 2 and 4. Especially, the ^{1}H NMR spectra can be used to establish

Table 2 Preparation and Physical Data of Compounds **4a–j**

Starting Material	Method[a]	Reaction Conditions: Solvent	Temp (°C)	Time (h)	Product[b]	Yield[c] (%)	mp (°C)[d] (Appearance)	Recrystallization Solvent	MS-FAB[e] *m/z* MH^+
2	C	AcOH	55	4	**4a**	77	180–182 (colorless powder)	EtOH	545
3a	B	dioxane	reflux	1	**4b**	66	119–121 (colorless powder)	EtOAc/benzene	559
2	C	AcOH	80	7		63			
3b	B	dioxane	reflux	5	**4c**	73	126–130 (pale yellow powder)	EtOAc/benzene	621
2	D	MeCN	reflux	18		82			
3c	A	MeCN	reflux	10	**4d**	79	192–195 (colorless powder)	EtOAc	639
2	D	MeCN	reflux	17		63			
3d	B	dioxane	reflux	10	**4e**	73	174–177 (colorless powder)	benzene	655, 657
2	D	MeCN	reflux	24		79			
3e	A	MeCN	reflux	8	**4f**	70	113–115 (pale yellow powder)	EtOAc/benzene	699, 701
2	D	MeCN	reflux	5		53			
3f	B	dioxane	reflux	15	**4g**	68	106–109 (pale yellow powder)	EtOAc/benzene	635
2	D	MeCN	reflux	24		44			
3g	B	dioxane	reflux	12	**4h**	71	146–148 (pale yellow powder)	EtOAc/benzene	651
2	D	MeCN	reflux	16		75			
3h	A	MeCN	reflux	5	**4i**	73	122–125 (pale yellow powder)	EtOAc/benzene	665
2	D	MeCN	reflux	6		65			
3i	A	MeCN	reflux	10	**4j**	75	119–122 (pale yellow powder)	EtOAc	666
2	D	MeCN	reflux	17		61			

[a] Method A: DEAD; Method B: $Pb(OAc)_4$; Method C: $RC(OEt)_3$; Method D: RCHO, MeCN, r.t., then with DEAD, reflux.
[b] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.34, N ± 0.31.
[c] Yield based on the isolated product after column chromatographic separation (Merck Kieselgel 60, eluent: benzene/EtOAc, 1:1).
[d] Uncorrected.
[e] FAB MS was measured with glycerol as a matrix.

the structures between the products **3** and **4**. Namely, the spectra of the products **3** in DMSO-d_6 showed the presence of two broad singlet signals, each one proton. The signal at δ = 7.7–8.4 was attributable to the NHN=C*H*, while the other at δ =11.6–12.2 was attributable to the N*H*N=CH. On the other hand, such two broad singlet signals in the spectra of the products **4** disappeared.

The iodo group of compounds **4** was easily displaced by several nucleophiles, e.g. sodium methoxide, liquid ammonia, aqueous potassium hydroxide, and thiourea to afford the corresponding substituted triazolopurine nucleosides **5–8** (Scheme 2). Namely, treatment of compounds **4a, c–j** with sodium methoxide (7 mol equiv) in anhydrous methanol at 0–5 °C for 2 h and neutralization with 10% hydrochloric acid afforded the corresponding 5-methoxy-7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purines (**5a–i**) in 67–95% yields (Table 3). Similarly reaction of compounds **4a, c** with excess liquid ammonia provided the corresponding 5-amino triazolopurine nucleosides **6a, b** in 82–95% yields, while reaction of compound **4a** with morpholine (4 mol equiv) and potassium carbonate (2 mol equiv) in dioxane at reflux for 20 h yielded 5-morpholino derivative **6c** in 49% yield. In the ^{1}H NMR spectra, the structures **5a–i** and **6a, b** were ascertained explicitly by the presence of three protons singlet signals at δ = ca. 4.3 attributable to the methoxy group and the presence of two protons singlet signals at δ = ca. 7.9 attributable to the amino group, respectively, at their 5-positions. While the structure **6c** was ascertained by the presence of two multiplet signals at δ = 3.83 and 3.91 for each four protons attributable to CH_2OCH_2 and CH_2NCH_2 of the morpholino, respectively, at the 5-position. Hydrolysis of the iodo group of compounds **4** to get the desired 5-oxo triazolopurine nucleosides **7a–c** was achieved by treatment of compounds **4a, c, e** (1 mmol) with 5% aqueous potassium hydroxide (20 mL) at room temperature and neutralization with 10% hydrochloric acid in 70–86% yields. Moreover, heating the compounds **4a, c–e, h** with thiourea (2 mol equiv) in ethanol at 75 °C and then treatment of the reaction residue with 10% aqueous sodium hydroxide and 10% hydrochloric acid gave the corresponding 5-thioxo triazolopurine nucleosides **8a–e** in 50–91% yields. The structures of new compounds **5–8** were assigned on the basis of elemental analyses and satisfactory spectral data (Tables 3 and 4).

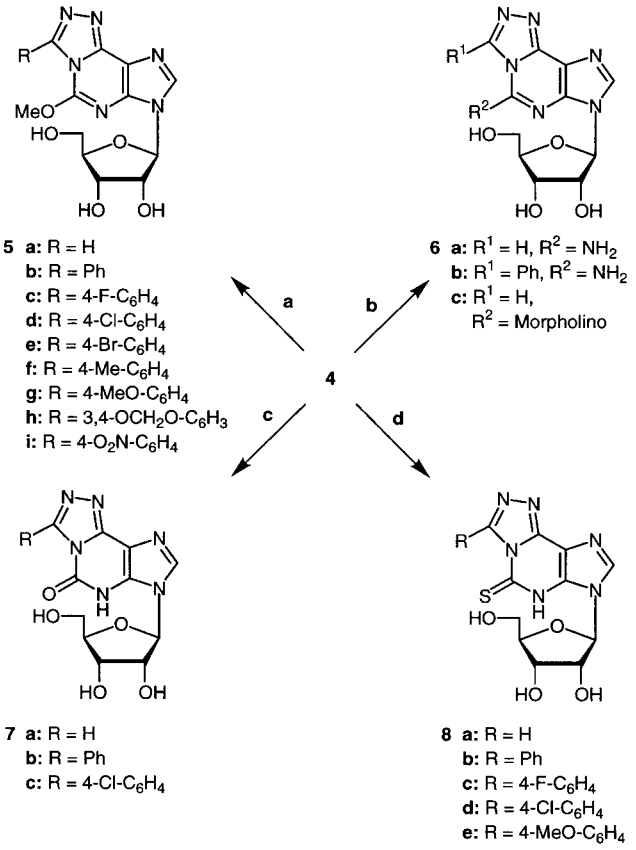
Thus, we have demonstrated the first general syntheses of 7*H*-[1,2,4]triazolo[3,4-*i*]purine nucleosides, namely, 3- and/or 5-substituted 7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purines via 6-hydrazino-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purines as a new class of potential xanthine oxidase inhibitors. Some of them showed more potent bovine milk XO inhibitory activity than that of allopurinol.[3] Further investigations along this line are now in progress and the results of the inhibitory activities of the compounds described in this paper will be reported elsewhere.

Mps were obtained on a Yanagimoto micro melting point apparatus and were uncorrected. Microanalyses were measured by Yanaco

Table 3 Preparation and Physical Data of Compounds **5a–i**, **6a–c**, **7a-c** and **8a-e**

Starting Material	Reaction Conditions			Product[a]	Yield[b] (%)	mp (°C)[c]	Recrystallization Solvent	Appearance	MS-FAB[d] *m/z* MH^+
	Solvent	Temp (°C)	Time (h)						
4a	MeOH	0–5	2	**5a**	95	219–221	EtOH	colorless needles	323
4c	MeOH	0–5	2	**5b**	91	220–222	DMF/H_2O	colorless crystals	399
4d	MeOH	0–5	2	**5c**	95	238–241	EtOH	colorless crystals	417
4e	MeOH	0–5	2	**5d**	85	237–240	EtOH	colorless crystals	433, 435
4f	MeOH	0–5	2	**5e**	82	250–253	EtOH	colorless crystals	477, 479
4g	MeOH	0–5	2	**5f**	85	221–224	EtOH	colorless crystals	413
4h	MeOH	0–5	2	**5g**	95	198–200	EtOH	colorless crystals	429
4i	MeOH	0–5	2	**5h**	93	206–208	EtOH	colorless crystals	443
4j	MeOH	0–5	2	**5i**	67	> 300	EtOH	pale yellow crystals	444
4a	none	r.t.	6	**6a**	95	220–221	DMF/H_2O	colorless crystals	308
4c	none	r.t.	6	**6b**	82	245–247	DMF/H_2O	colorless crystals	384
4a	dioxane	reflux	20	**6c**	49	224–226	EtOH/H_2O	colorless crystals	378
4a	H_2O	r.t.	5	**7a**	85	228–231	DMF/H_2O	colorless crystals	309
4c	H_2O	r.t.	9	**7b**	86	248–251	DMF/H_2O	colorless crystals	385
4e	H_2O	r.t.	10	**7c**	70	208–210	DMF/H_2O	colorless crystals	419, 421
4a	EtOH	75	4	**8a**	50	205–208	DMF/H_2O	colorless crystals	325
4c	EtOH	75	4	**8b**	88	203–206	DMF/H_2O	pale yellow crystals	401
4d	EtOH	75	4	**8c**	70	> 235 (dec)	DMF	pale grey crystals	419
4e	EtOH	75	4	**8d**	91	200–203	DMF	pale grey crystals	435, 437
4h	EtOH	75	4	**8e**	77	222–225	DMF	colorless crystals	431

[a] Satisfactory microanalyses obtained for **5**: C ± 0.39, H ± 0.28, N ± 0.26, for **6**: C ± 0.34, H ± 0.23, N ± 0.24, for **7**: C ± 0.30, H ± 0.29, N ± 0.33 and for **8**: C ± 0.34, H ± 0.33, N ± 0.34.
[b] Yield based on the isolated product.
[c] Uncorrected.
[d] FAB MS was measured with 3-nitrobenzyl alcohol as a matrix and MH^+ - H_2O ion was observed in the spectra of compounds **6a,b**, **7a–c**



a: MeONa, MeOH, 0–5 °C, 2 h, then 10% HCl; **b**: liquid NH_3, r.t., 6 h or morpholine, K_2CO_3, dioxane, reflux, 20 h; **c**: 5% aq KOH, r.t., 5–10 h, then 10% HCl; **d**: $(H_2N)_2C=S$, EtOH, 75 °C, 4 h, then 10% aq NaOH and 10% HCl

Scheme 2

CHN Corder MT-5 apparatus. Mass spectra were recorded at 70 eV ionizing voltage with FAB ionization using a VG-70SE spectrometer. IR spectra were recorded on a JASCO IRA-102 spectrometer. ^{1}H NMR spectra were obtained using a Varian VXR 500 MHz spectrometer with TMS as an internal standard. In all cases, chemical shifts are in ppm downfield to TMS. *J* values are given in Hz and signals are quoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. All reagents were of commercial quality from freshly opened containers and were used without further purification. Organic solvents were dried by standard methods and distilled before use. Reaction progress was monitored by analytical thin layer chromatography (TLC) on Merck silica gel 60 F_{254} plates and products were visualized by UV light. Column chromatography was run on Kieselgel 60 (70–230 mesh ASTM, Merck).

6-Hydrazino-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (2)

To a solution of anhyd hydrazine (1.36 g, 42.7 mmol) in MeCN (300 mL) was added 6-chloro-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine[16] (**1**; 10.0 g, 18.6 mmol) and the mixture was stirred at r.t. for 2 h. The solvent was removed in vacuo and crystallization of the residue from anhyd EtOH afforded the 6-hydrazinopurine nucleoside **2** as colorless crystals; yield: 9.32 g (94%); mp 71–73 °C; TLC (benzene/EtOH, 2:1): R_f 0.60.

IR (KBr): ν = 3410 (as, NH_2), 3360 (s, NH_2), 3260 (NH), 1745 (C=O), 1730 ^{sh} (C=O) and δ = 1610 cm^{-1} (NH_2).

^{1}H NMR (DMSO-d_6/TMS): δ = 2.02 (s, 3H, 5′-OCOMe), 2.04 (s, 3H, 3′-OCOMe), 2.11 (s, 3H, 2′-OCOMe), 4.22–4.27 (m, 1H, 5′-H_a), 4.33–4.40 (m, 2H, 4′-H, 5′-H_b), 4.60 (br s, 2H, NH_2, exchangeable with D_2O), 5.57 (dd, 1H, $J_{2',3'}$ = 5.6 Hz, $J_{3',4'}$ = 5.1 Hz, 3′-H), 5.84 (dd, 1H, $J_{1',2'}$ = 5.4 Hz, $J_{2',3'}$ = 5.6 Hz, 2′-H), 6.12 (d, 1H, $J_{1',2'}$ = 5.4 Hz, 1′-H), 8.27 (s, 1H, 8-H), 9.43 (br s, 1H, NH, exchangeable with D_2O).

MS (FAB, glycerol matrix): *m/z* = 535 (MH^+).

Anal. Calcd for $C_{16}H_{19}IN_6O_7$ (534.3): C 35.97, H 3.58, N 15.73. Found: C 35.95, H 3.63, N 15.78.

6-Alkylidenehydrazino- and 6-Benzylidenehydrazino-2-iodo-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purines 3a–i; General Procedure

A solution of the hydrazinopurine (**2**; 1.0 g, 1.87 mmol) and an appropriate alkylaldehyde (5.6 mmol) or arylaldehyde (2.4 mmol) in anhyd MeCN (60 mL) was stirred at r.t. for 2–12 h. All reactions were monitored by analytical TLC (benzene/EtOH, 2:1 or CH_2Cl_2/EtOAc, 1:1). After the reaction was complete, the solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: benzene/EtOAc, 1:1) to give the corresponding hydrazones **3a–i**. The isolated products were recrystallized from the solvents given in Table 1.

5-Iodo-7-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)-7*H*-[1,2,4]triazolo[3,4-*i*]purine (4a) and its 3-Substituted Derivatives 4b–j; General Procedure

Method A: A mixture of the hydrazone (**3**; 2.0 mmol) and DEAD (0.87 g, 5.0 mmol) in anhyd MeCN (50 mL) was heated at reflux for 5–10 h. After the reaction was complete, the solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: benzene/EtOAc, 1:1) to give the corresponding triazolopurines **4d, f, i, j**. The isolated products were recrystallized from the solvents given in Table 2.

Method B: A mixture of the hydrazone (**3**; 1.8 mmol) and $Pb(OAc)_4$ (1.6 g, 3.6 mmol) in anhyd dioxane (50 mL) was heated at reflux for 1–15 h. After the reaction was complete, the solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: benzene/EtOAc, 1:1) to give the corresponding triazolopurines **4b, c, e, g, h** (Tables 2 and 4).

Method C: A mixture of the hydrazinopurine (**2**; 1.0 g, 1.87 mmol) and triethyl orthoformate or triethyl orthoacetate (200 mmol) in glacial HOAc (5 mL) was heated at 55–80 °C for 4–7 h. After cooling, the formed precipitates were collected by filtration and washed with anhyd EtOH to afford the corresponding triazolopurines **4a, b**. Furthermore, the filtrate was concentrated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: benzene/EtOAc, 1:1) to yield the second crop of the triazolopurines **4a, b** (Tables 2 and 4).

Method D: A solution of the hydrazinopurine (**2**; 1.0 g, 1.87 mmol) and an appropriate arylaldehyde (2.4 mmol) in anhyd MeCN (60 mL) was stirred at r.t. for 5 h, followed by heating the mixture with DEAD (0.98 g, 5.6 mmol) at reflux for 5–24 h in one-pot reactions. After the reaction was complete, the solvent was evaporated in vacuo and the residue was subjected to column chromatography on silica gel (eluent: benzene/EtOAc, 1:1) to give the corresponding triazolopurines **4c–j** (Tables 2 and 4).

5-Methoxy-7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purine (5a) and its 3-Aryl Derivatives 5b–i; General Procedure

To a solution of MeONa prepared from Na (0.16 g, 7.0 mmol) and anhyd MeOH (15 mL) was added an appropriate triazolopurine (**4**; 1.0 mmol) under cooling with ice-water. After stirring at 0–5 °C for 2 h, the deposited solid was collected by filtration, washed with anhyd MeOH, and recrystallized from EtOH or DMF to afford the cor-

Table 4 IR and ^{1}H NMR Spectral Data for the New Products **3a–i**, **4a–j**, **5a–i**, **6a–c**, **7a–c**, and **8a–e** Prepared

Product	IR (KBr) ν (cm^{-1})[a]	^{1}H NMR (500 MHz) (DMSO-d_6/TMS)[b] δ, *J* (Hz)
3a	3260 (NH); *1760*, 1740, *1730* (C=O); 1210, 1090, 1040 (C-O-C)	1.96 (d, 3H, *J* = 5.37, CH*Me*), 2.03, 2.06, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.26 (dd, 1H, J_{gem} = 13.1, $J_{4',5'a}$ = 6.8, 5'-H_a), 4.38 (m, 2H, 4'-H, 5'-H_2), 5.60 (dd, 1H, $J_{2',3'}$ = 5.7, $J_{3',4'}$ = 5.1, 3'-H), 5.86 (t, 1H, *J* = 5.6, 2'-H), 6.17 (d, 1H, $J_{1',2'}$ = 5.4, 1'-H), 7.70 (br s, 1H, C*H*Me), 8.38 (s, 1H, 8-H), 11.60 (s, 1H, NH, exchangeable with D_2O)
3b	3260 (NH); *1760*, 1750, *1740* (C=O); 1235, 1110, 1050 (C-O-C)	2.03, 2.06, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.26 (dd, 1H, J_{gem} = 13.1, $J_{4',5'a}$ = 6.8, 5'-H_a), 4.40 (m, 2H, 4'-H, 5'-H_b), 5.61 (dd, 1H, $J_{2',3'}$ = 5.9, $J_{3',4'}$ = 4.8, 3'-H), 5.88 (t, 1H, *J* = 5.6, 2'-H), 6.20 (d, 1H, $J_{1',2'}$ = 5.3, 1'-H), 7.46 (m, 3H, PhH), 7.76 (m, 2H, PhH), 8.30 (br s, 1H, C*H*Ph), 8.46 (s, 1H, 8-H) , 12.14 (s, 1 H, NH, exchangeable with D_2O)
3c	3270 (NH); *1760*, 1745, *1730* (C=O); 1220, 1100, 1050 (C-O-C)	2.04, 2.07, 2.13 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.28 (dd, 1H, J_{gem} = 13.1, $J_{4',5'a}$ = 6.8, 5'-H_a), 4.40 (m, 2H, 4'-H, 5'-H_b), 5.61 (dd, 1H, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 5.0, 3'-H), 5.89 (t, 1H, *J* = 5.6, 2'-H), 6.20 (d, 1H, $J_{1',2'}$ = 5.3, 1'-H), 7.31 (t, 2H, *J* = 8.8 Hz, Ar-*m*H), 7.82 (br t, 2H, Ar-*o*H), 8.30 (br s, 1H, C*H*Ar), 8.47 (s, 1H, 8-H), 12.10 (br, 1H, NH, exchangeable with D_2O)
3d	3280 (NH); *1760*, 1755, *1730* (C=O); 1240, 1095, 1055 (C-O-C)	2.03, 2.05, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.27 (dd, 1H, J_{gem} = 13.3, $J_{4',5'a}$ = 7.1, 5'-H_a), 4.39 (m, 2H, 4'-H, 5'-H_b), 5.60 (dd, 1H, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 4.8, 3'-H), 5.88 (t, 1H, *J* = 5.6, 2'-H), 6.19 (d, 1H, $J_{1',2'}$ = 5.3, 1'-H), 7.52 (d, 2H, *J* = 8.4, Ar-*m*H), 7.77 (d, 2H, *J* = 8.4, Ar-*o*H), 8.25 (br s, 1H, C*H*Ar), 8.46 (s, 1H, 8-H), 12.10 (br, 1H, NH, exchangeable with D_2O)
3e	3260 (NH); *1755*, 1740, *1725* (C=O); 1230, 1090, 1045 (C-O-C)	2.02, 2.05, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.27 (dd, 1H, J_{gem} = 13.1, $J_{4',5'a}$ = 6.9, 5'-H_a), 4.39 (m, 2H, 4'-H, 5'-H_b), 5.60 (dd, 1H, $J_{2',3'}$ = 5.7, $J_{3',4'}$ = 4.8, 3'-H), 5.88 (t, 1H, *J* = 5.6, 2'-H), 6.19 (d, 1H, $J_{1',2'}$ = 5.3, 1'-H), 7.65 (d, 2H, *J* = 7.9, Ar-*m*H), 7.70 (d, 2H, *J* = 7.9, Ar-*o*H), 8.25 (br s, 1H, C*H*Ar), 8.47 (s, 1H, 8-H), 12.12 (br, 1H, NH, exchangeable with D_2O)
3f	3260 (NH); *1755*, 1745, *1720* (C=O); 1230, 1090, 1050 (C-O-C)	2.03, 2.06, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 2.34 (s, 3H, Ph*Me*), 4.27 (dd, 1H, J_{gem} = 13.2, $J_{4',5'a}$ = 6.9, 5'-H_a), 4.39 (m, 2H, 4'-H, 5'-H_b), 5.60 (dd, 1H, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 5.0, 3'-H), 5.87 (t, 1H, *J* = 5.6 , 2'-H), 6.19 (d, 1H, $J_{1',2'}$ = 5.3, 1'-H), 7.26 (d, 2H, *J* = 7.9 , Ar-*m*H), 7.64 (d, 2H, *J* = 7.9 , Ar-*o*H), 8.26 (br, 1H, C*H*Ar), 8.45 (s, 1H, 8-H), 12.10 (br, 1H, NH, exchangeable with D_2O)
3g	3270 (NH); *1755*, 1745, *1720* (C=O); 1240, 1100, 1040 (C-O-C)	2.04, 2.07, 2.13 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 3.81 (3H, s, OMe), 4.28 (dd, 1H, J_{gem} = 13.2, $J_{4',5'a}$ = 6.8, 5'-H_a), 4.40 (m, 2H, 4'-H, 5'-H_b), 5.61 (dd, 1H, $J_{2',3'}$ = 5.9, $J_{3',4'}$ = 5.0, 3'-H), 5.89 (t, 1H, *J* = 5.6, 2'-H), 6.20 (d, 1H, $J_{1',2'}$ = 5.4, 1'-H), 7.03 (d, 2H, *J* = 8.3, Ar-*m*H), 7.70 (d, 2H, *J* = 8.3, Ar-*o*H), 8.25 (br, 1H, C*H*Ar), 8.45 (s, 1H, 8-H) , 12.09 (br, 1 H, NH, exchangeable with D_2O)
3h	3260 (NH); *1755*, 1740, *1725* (C=O); 1230, 1090, 1035 (C-O-C)	2.03, 2.05, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.26 (dd, 1H, J_{gem} = 13.1, $J_{4',5'a}$ = 6.8, 5'-H_a), 4.39 (m, 2H, 4'-H, 5'-H_b), 5.59 (dd, 1H, $J_{2',3'}$ = 5.6, $J_{3',4'}$ = 4.9, 3'-H), 5.87 (t, 1H, *J* = 5.6, 2'-H), 6.08 (s, 2H, OCH_2O), 6.18 (d, 1H, $J_{1',2'}$ = 5.3, 1'-H), 6.98 (d, 1H, *J* = 7.9, Ar-*m*H), 7.16 (dd, 1H, *J* = 1.8, 7.9, Ar-*o*H), 7.38 (s, 1H, *J* = 1.8, Ar-*o*H), 8.15 (br, 1H, C*H*Ar), 8.45 (s, 1H, 8-H) , 12.10 (br, 1H, NH, exchangeable with D_2O)
3i	3300 (NH); *1755*, 1745, *1725* (C=O); 1230, 1105, 1060 (C-O-C)	2.04 , 2.07, 2.14 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.29 (dd, 1H, J_{gem} = 13.2, $J_{4',5'a}$ = 6.9, 5'-H_a), 4.41 (m, 2H, 4'-H, 5'-H_b), 5.62 (dd, 1H, $J_{2',3'}$ = 5.6, $J_{3',4'}$ = 4.8, 3'-H), 5.90 (t, 1H, *J* = 5.6, 2'-H), 6.23 (d, 1H, $J_{1'2'}$= 5.3, 1'-H), 8.02 (d, 2H, *J* = 8.9, Ar-*m*H), 8.32 (d, 2H, *J* = 8.9, Ar-*o*H), 8.38 (br, 1H, C*H*Ar), 8.53 (s, 1H, 8-H)) , 12.15 (br, 1 H, NH, exchangeable with D_2O)
4a	*1750*, 1740, *1720* (C=O); 1225, 1100, 1040 (C-O-C)	2.03, 2.07, 2.14 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.29 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 5.3, 5'-H_a), 4.43 (m, 2H, 4'-H, 5'-H_b), 5.66 (t, 1H, *J* = 5.4, 3'-H), 5.90 (t, 1H, *J* = 5.5, 2'-H), 6.34 (d, 1H, $J_{1',2'}$ = 5.0, 1'-H), 8.59 (s, 1H, 8-H), 9.46 (s, 1H, 3-H)
4b	*1760*, 1740, *1730* (C=O); 1230, 1100, 1045 (C-O-C)	2.04, 2.08, 2.14 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 3.05 (s, 3H, 3-Me), 4.29 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 6.5, 5'-H_a), 4.43 (m, 2H, 4'-H, 5'-H_b), 5.66 (t, 1H, *J* = 5.5, 3'-H), 5.88 (t, 1H, *J* = 5.4, 2'-H), 6.31 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 8.51 (s, 1H, 8-H)
4c	*1760*, 1745, *1725* (C=O); 1230, 1090, 1045 (C-O-C)	2.01, 2.06, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.26 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 6.2, 5'-H_a), 4.41 (m, 2H, 4'-H, 5'-H_b), 5.62 (t, 1H, *J* = 5.4, 3'-H), 5.88 (t, 1H, *J* = 5.5, 2'-H), 6.33 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 7.57 (m, 3H, PhH), 7.65 (m, 2H, PhH), 8.57 (s, 1H, 8-H)
4d	*1755*, 1745, *1725* (C=O); 1220, 1080, 1040 (C-O-C)	2.01, 2.06, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.25 (dd, 1H, J_{gem} = 12.9, $J_{4',5'a}$ = 6.3, 5'-H_a), 4.42 (m, 2H, 4'-H, 5'-H_b), 5.62 (t, 1H, *J* = 5.6, 3'-H), 5.87 (t, 1H, *J* = 5.5, 2'-H), 6.33 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 7.43 (t, 2H, *J* = 8.9, Ar-*m*H), 7.44 (dd, 2H, $J_{H,F}$ = 5.5, $J_{H,H}$ = 8.6, Ar-*o*H), 8.57 (s, 1H, 8-H)

Table 4 (continued)

Product	IR (KBr) ν (cm^{-1})[a]	^{1}H NMR (500 MHz) (DMSO-d_6/TMS)[b] δ, *J* (Hz)
4e	*1755*, 1745, *1725* (C=O); 1230, 1090, 1045 (C-O-C)	2.01, 2.06, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.26 (dd, 1H, J_{gem} = 12.9, $J_{4',5'a}$ = 6.2, 5'-H_2), 4.41 (m, 2H, 4'-H, 5'-H_b), 5.62 (t, 1H, *J* = 5.7, 3'-H), 5.87 (t, 1H, *J* = 5.4, 2'-H), 6.33 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 7.66 (d, 2H, *J* = 8.5, Ar-*m*H), 7.72 (d, 2H, *J* = 8.5, Ar-*o*H), 8.58 (s, 1H, 8-H)
4f	*1760*, 1750, *1730*, (C=O); 1230, 1100, 1045 (C-O-C)	2.01, 2.06, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.25 (dd, 1H, J_{gem} = 12.9, $J_{4',5'a}$ = 6.2, 5'-H_a), 4.41 (m, 2H, 4'-H, 5'-H_b), 5.61 (t, 1H, *J* = 5.6, 3'-H), 5.87 (t, 1H, *J* = 5.5, 2'-H), 6.32 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 7.64 (d, 2H, *J* = 8.4, Ar-*m*H), 7.80 (d, 2H, *J* = 8.4, Ar-*o*H), 8.58 (s, 1H, 8-H)
4g	*1750*, 1740, *1720* (C=O); 1220, 1090, 1040 (C-O-C)	2.01, 2.06, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 2.42 (s, 3H, Ph*Me*), 4.26 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 6.1, 5'-H_a), 4.41 (m, 2H, 4'-H, 5'-H_b), 5.61 (t, 1H, *J* = 5.6, 3'-H), 5.87 (t, 1H, *J* = 5.5, 2'-H), 6.32 (d, 1H, $J_{1',2'}$ = 4.8, 1'-H), 7.38 (d, 2H, *J* = 8.1, Ar-*m*H), 7.54 (d, 2H, *J* = 8.1, Ar-*o*H), 8.57 (s, 1H, 8-H)
4h	*1755*, 1745, *1720* (C=O); 1230, 1100, 1045 (C-O-C)	2.01, 2.06, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 3.05 (s, 3H, OMe), 4.25 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 6.1, 5'-H_a), 4.40 (m, 2H, 4'-H, 5'-H_b), 5.61 (t, 1H, *J* = 5.6, 3'-H), 5.87 (t, 1H, *J* = 5.5, 2'-H), 6.32 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 7.12 (d, 2H, *J* = 8.7, Ar-*m*H), 7.57 (d, 2H, *J* = 8.7, Ar-*o*H), 8.56 (s, 1H, 8-H)
4i	*1750*, 1740, *1725* (C=O); 1230, 1100, 1030 (C-O-C)	2.03, 2.07, 2.12 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.27 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 6.2, 5'-H_a), 4.42 (m, 2H, 4'-H, 5'-H_b), 5.63 (t, 1H, *J* = 5.6, 3'-H), 5.88 (t, 1H, *J* = 5.4, 2'-H), 6.16 (s, 2H, OCH_2O), 6.33 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 7.11 (d, 1H, *J* = 8.1, Ar-*m*H), 7.15 (dd, 1H, *J* = 1.7, 8.1, Ar-*o*H), 7.23 (d, 1H, *J* = 1.7, Ar-*o*H), 8.57 (s, 1H, 8-H)
4j	*1755*, 1740, *1725* (C=O); 1220, 1090, 1040 (C-O-C)	2.02, 2.07, 2.11 (each s, each 3H, 5'-, 3'- and 2'-OCO*Me*), 4.26 (dd, 1H, J_{gem} = 12.8, $J_{4',5'a}$ = 6.1, 5'-H_a), 4.42 (m, 2H, 4'-H, 5'-H_b), 5.62 (t, 1H, *J* = 5.6, 3'-H), 5.88 (t, 1H, *J* = 5.4, 2'-H), 6.34 (d, 1H, $J_{1',2'}$ = 4.9, 1'-H), 8.03 (d, 2H, *J* = 8.8, Ar-*m*H), 8.45 (d, 2H, *J* = 8.8, Ar-*o*H), 8.60 (s, 1H, 8-H)
5a	3360, 1100, 1050 (OH)	3.59 [br dd (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'a}$ = 4.4), 1H, 5'-H_a], 3.69 [br dd (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'b}$ = 4.3), 1H, 5'-H_b], 3.97 (q, 1H, *J* = 3.9, 4'-H), 4.24 [t (dd after addition of D_2O, $J_{2,3'}$ = 4.9, $J_{3',4'}$ = 3.9), 1H, *J* = 4.3, 3'-H], 4.28 (s, 3H, OMe), 4.64 (t, 1H, *J* = 5.3, 2'-H), 5.07 (br, 1H, 5'-OH, exchangeable with D_2O), 5.40 (br, 1H, 3'-OH, exchangeable with D_2O), 5.65 (br, 1H, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.6, 1'-H), 8.54 (s, 2H, 3-H, 8-H)
5b	3350, 1115, 1050 (OH)	3.59 [m (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'a}$ = 4.4), 1H, 5'-H_a], 3.69 [m (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'b}$ = 4.3), 1H, 5'-H_b], 3.97 (q, 1H, *J* = 4.1, 4'-H), 4.23 [q (dd after addition of D_2O, $J_{2',3'}$ = 4.9, $J_{3',4'}$ = 3.9), 1H, *J* = 4.6, 3'-H], 4.29 (s, 3H, OMe), 4.65 [q (t after addition of D_2O, *J* = 5.3), 1H, *J* = 5.6, 2'-H], 5.01 (t, 1H, $J_{5',OH}$ = 5.4, 5'-OH, exchangeable with D_2O), 5.29 (d, 1H, $J_{3',OH}$ = 5.0, 3'-OH, exchangeable with D_2O), 5.54 (d, 1H, $J_{2',OH}$ = 6.1, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.7, 1'-H), 7.55 (m, 3H, PhH), 8.25 (m, 2H, PhH), 8.54 (s, 1H, 8-H)
5c	3400, *1110*, 1060 (OH)	3.59 [br dd (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'a}$ = 4.4), 1H, 5'-H_a], 3.66 [br dd (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'b}$ = 4.3), 1H, 5'-H_b], 3.96 (q, 1H, *J* = 3.9, 4'-H), 4.22 (t, 1H, *J* = 4.3, 3'-H), 4.29 (s, 3H, OMe), 4.63 (t, 1H, *J* = 5.4, 2'-H), 5.08 (br, 1H, 5'-OH, exchangeable with D_2O), 5.36 (br, 1H, 3'-OH, exchangeable with D_2O), 5.50 (br, 1H, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.8, 1'-H), 7.40 (t, 2H, *J* = 8.9, Ar-*m*H), 8.25 (dd, 2H, $J_{H,F}$ = 5.7, $J_{H,H}$ = 8.4, Ar-*o*H), 8.54 (s, 1H, 8-H)
5d	3350, 1090, 1060 (OH)	3.60 (dd, 1H, J_{gem} = 11.9, $J_{4',5'a}$ = 4.4, 5'-H_a), 3.70 (dd, 1H, J_{gem} = 11.9, $J_{4',5'b}$ = 4.3, 5'-H_b), 3.98 (q, 1H, *J* = 4.0, 4'-H), 4.24 (t, 1H, *J* = 4.4, 3'-H), 4.30 (s, 3H, OMe), 4.65 (t, 1H, *J* = 5.3, 2'-H), 5.03 (br, 1H, 5'-OH, exchangeable with D_2O), 5.40 (br, 1H, 3'-OH, exchangeable with D_2O), 5.50 (br, 1H, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.7, 1'-H), 7.64 (d, 2H, *J* = 8.5, Ar-*m*H), 8.27 (d, 2H, *J* = 8.5, Ar-*o*H), 8.56 (s, 1H, 8-H)
5e	3400, 1120, 1070 (OH)	3.60 (dd, 1H, J_{gem} = 11.9, $J_{4',5'a}$ = 4.3, 5'-H_a), 3.70 (dd, 1H, J_{gem} = 11.9, $J_{4',5'b}$ = 4.3, 5'-H_b), 3.98 (q, 1H, *J* = 3.9, 4'-H), 4.23 (t, 1H, *J* = 4.2, 3'-H), 4.30 (s, 3H, OMe), 4.65 (t, 1H, *J* = 5.2, 2'-H), 5.05 (br, 1H, 5'-OH, exchangeable with D_2O), 5.39 (br, 1H, 3'-OH, exchangeable with D_2O), 5.53 (br, 1H, 2'-OH, exchangeable with D_2O), 6.01 (d, 1H, $J_{1',2'}$ = 5.8, 1'-H), 7.78 (d, 2H, *J* = 8.5, Ar-*m*H), 8.20 (d, 2H, *J* = 8.5, Ar-*o*H), 8.56 (s, 1H, 8-H)

Table 4 (continued)

Product	IR (KBr) ν (cm^{-1})[a]	^1H NMR (500 MHz) (DMSO-d_6/TMS)[b] δ, *J* (Hz)
5f	3350, *1100*, 1050 (OH)	3.59 [br dd (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'a}$ = 4.4), 1H, 5'-H_a], 3.69 [br dd (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'b}$ = 4.3), 1H, 5'-H_b], 3.98 (q, 1H, *J* = 4.0, 4'-H), 4.25 (t, 1H, *J* = 4.3, 3'-H), 4.30 (s, 3H, OMe), 4.65 (t, 1H, *J* = 5.3, 2'-H), 5.08 (br, 1H, 5'-OH, exchangeable with D_2O), 5.42 (br, 1H, 3'-OH, exchangeable with D_2O), 5.56 (br, 1H, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.6, 1'-H), 7.38 (d, 2H, *J* = 8.1, Ar-*m*H), 8.15 (d, 2H, *J* = 8.1, Ar-*o*H), 8.55 (s, 1H, 8-H)
5g	3300, *1100*, 1050 (OH)	3.60 [m (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'a}$ = 4.4), 1H, 5'-H_a], 3.69 [m (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'b}$ = 4.3), 1H, 5'-H_b], 3.85 (s, 3H, Ar-O*Me*), 3.98 (q, 1H, *J* = 3.8, 4'-H), 4.24 [q (t after addition of D_2O, *J* = 4.3), 1H, *J* = 4.5, 3'-H], 4.30 (s, 3H, 5-OMe), 4.66 [q (t after addition of D_2O, *J* = 5.3), 1H, *J* = 5.6, 2'-H], 5.06 (t, 1H, $J_{5',OH}$ = 5.4, 5'-OH, exchangeable with D_2O), 5.33 (d, 1H, $J_{3',OH}$ = 4.8, 3'-OH, exchangeable with D_2O), 5.59 (d, 1H, $J_{2',OH}$ = 6.0, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.7, 1'-H), 7.12 (d, 2H, *J* = 8.8, Ar-*m*H), 8.20 (d, 2H, *J* = 8.8, Ar-*o*H), 8.54 (s, 1H, 8-H)
5h	3400, 1090, 1040 (OH)	3.60 (dd, 1H, J_{gem} = 11.9, $J_{4',5'a}$ = 4.3, 5'-H_a), 3.69 (dd, 1H, J_{gem} = 11.9, $J_{4',5'b}$ = 4.3, 5'-H_b), 3.97 (q, 1H, *J* = 4.0, 4'-H), 4.23 (t, 1H, *J* = 4.3, 3'-H), 4.29 (s, 3H, OMe), 4.65 (t, 1H, *J* = 5.3, 2'-H), 5.04 (br, 1H, 5'-OH, exchangeable with D_2O), 5.40 (br, 1H, 3'-OH, exchangeable with D_2O), 5.50 (br, 1H, 2'-OH, exchangeable with D_2O), 6.00 (d, 1H, $J_{1',2'}$ = 5.6, 1'-H), 6.14 (s, 2H, OCH_2O), 7.10 (d, 1H, *J* = 8.2, Ar-*m*H), 7.68 (d, 1H, *J* = 1.6, Ar-*o*H), 7.83 (dd, 1H, *J* = 1.6, 8.2, Ar-*o*H), 8.54 (s, 1H, 8-H)
5i	3400, 1100, 1050 (OH)	3.60 [m (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'a}$ = 4.4), 1H, 5'-H_a], 3.70 [m (dd after addition of D_2O, J_{gem} = 11.8, $J_{4',5'b}$ = 4.3), 1H, 5'-H_b], 3.98 (q, 1H, *J* = 3.9, 4'-H), 4.25 (t , 1H, *J* = 4.2, 1H, 3'-H), 4.32 (s, 3H, OMe), 4.65 (t , 1H, *J* = 5.0, 2'-H), 5.10 (br, 1H, 5'-OH, exchangeable with D_2O), 5.44 (br, 1H, 3'-OH, exchangeable with D_2O), 5.70 (br, 1H, 2'-OH, exchangeable with D_2O), 6.02 (d, 1H, $J_{1',2'}$ = 5.6, 1'-H), 8.43 (d, 2H, *J* = 8.9, Ar-*m*H), 8.53 (d, 2H, *J* = 8.9, Ar-*o*H), 8.59 (s, 1H, 8-H)
6a	3300, 1095, 1055 (OH); 3150, 3100, 1640 (NH_2)	3.56 [m (dd after addition of D_2O, J_{gem} = 11.9, $J_{4',5'a}$ = 4.2), 1H, 5'-H_a], 3.66 [m (dd after addition of D_2O, J_{gem} = 11.9, $J_{4',5'b}$ = 4.2), 1H, 5'-H_b], 3.92 (q, 1H, *J* = 4.0, 4'-H), 4.15 [q (t after addition of D_2O, *J* = 4.3), 1H, *J* = 4.5, 3'-H], 4.49 [q (t after addition of D_2O, *J* = 5.4), 1H, *J* = 5.5, 2'-H], 5.04 (t, 1H, $J_{5',OH}$ = 5.5, 5'-OH, exchangeable with D_2O), 5.19 (d, 1H, $J_{3',OH}$ = 4.8, 3'-OH, exchangeable with D_2O), 5.47 (d, 1H, $J_{2',OH}$ = 6.0, 2'-OH, exchangeable with D_2O), 5.88 (d, 1H, $J_{1',2'}$ = 5.7, 1'-H), 7.98 (s, 2H, NH_2, exchangeable with D_2O), 8.23 (s, 1H, 8-H), 9.30 (s, 1H, 3-H)
6b	3300, 1110, 1050 (OH); 3200, 3150, 1620 (NH_2)	3.57 (dd, 1H, J_{gem} = 11.9, $J_{4',5'a}$ = 4.1, 5'-H_a), 3.66 (dd, 1H, J_{gem} = 11.9, $J_{4',5'b}$ = 4.2, 5'-H_b), 3.93 (q, 1H, *J* = 3.9, 4'-H), 4.15 (t, 1H, *J* = 4.3, 3'-H), 4.51 (t, 1H, *J* = 5.4, 2'-H), 5.05 (br, 1H, 5'-OH, exchangeable with D_2O), 5.20 (br, 1H, 3'-OH, exchangeable with D_2O), 5.48 (br, 1H, 2'-OH, exchangeable with D_2O), 5.93 (d, 1H, $J_{1',2'}$ = 5.9, 1'-H), 7.56 (m, 3H, PhH), 7.87 (s, 2H, NH_2, exchangeable with D_2O), 8.27 (m, 2H, PhH), 8.35 (s, 1H, 8-H)
6c	3400, 1118, 1070 (OH)	3.57 [m (dd after addition of D_2O, J_{gem} = 11.9, $J_{4',5'a}$ = 4.2), 1H, 5'-H_a], 3.67 [m (dd after addition of D_2O, J_{gem} = 11.9, $J_{4',5'b}$ = 4.2), 1H, 5'-H_2], 3.83 (m, 4H, CH_2OCH_2), 3.91 (m, 4H, CH_2NCH_2), 3.95 (q, 1H, *J* = 4.1, 4'-H), 4.20 [q (t after addition of D_2O, *J* = 4.3), 1H, *J* = 4.6, 3'-H], 4.62 [q (t after addition of D_2O, *J* = 5.3), 1H, *J* = 5.6, 2'-H], 5.00 (t, 1H, $J_{5',OH}$ = 5.4, 5'-OH, exchangeable with D_2O), 5.27 (d, 1H, $J_{3',OH}$ = 5.0, 3'-OH, exchangeable with D_2O), 5.49 (d, 1H, $J_{2',OH}$ = 6.1, 2'-OH, exchangeable with D_2O), 5.97 (d, 1H, $J_{1',2'}$ = 5.6, 1'-H), 8.45 (s, 1H, 8-H), 8.52 (s, 1H, 3-H)
7a	3350, *1090*, 1060 (OH); *3130* (NH); 1655 (C=O)	3.52 (dd, 1H, J_{gem} = 12.3, $J_{4',5'a}$ = 2.7, 5'-H_a), 3.66 (dd, 1H, J_{gem} = 12.3, $J_{4',5'b}$ = 2.6, 5'-H_b), 3.95 (q, 1H, *J* = 2.5, 4'-H), 4.11 (dd, 1H, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 2.5, 3'-H), 4.64 (dd, 1H, $J_{1',2'}$ = 6.7, $J_{2',3'}$ = 5.0, 2'-H), 5.00 (br, 1H, 5'-OH, exchangeable with D_2O), 5.16 (br, 1H, 3'-OH, exchangeable with D_2O), 5.45 (br, 1H, 2'-OH, exchangeable with D_2O), 5.70 (d, 1H, $J_{1',2'}$ = 6.7, 1'-H), 7.79 (s, 1H, 8-H), 7.98 (s, 1H, 3-H)
7b	3300, 1070, 1045 (OH); *3100* (NH); 1657 (C=O)	3.53 (dd, 1H, J_{gem} = 12.4, $J_{4',5'a}$ = 2.6, 5'-H_a), 3.67 (dd, 1H, J_{gem} = 12.4, $J_{4',5'b}$ = 2.5, 5'-H_b), 3.96 (q, 1H, *J* = 2.4, 4'-H), 4.11 (dd, 1H, $J_{2',3'}$ = 4.9, $J_{3',4'}$ = 2.5, 3'-H), 4.61 (t, 1H, *J* = 5.0, 2'-H), 5.07 (br, 1H, 5'-OH, exchangeable with D_2O), 5.10 (br, 1H, 3'-OH, exchangeable with D_2O), 5.49 (br, 1H, 2'-OH, exchangeable with D_2O), 5.69 (d, 1H, $J_{1',2'}$ = 6.7, 1'-H), 7.05 (m, 3H, PhH), 7.78 (s, 1H, 8-H), 8.11 (m, 2H, PhH)
7c	3300, 1080, 1060 (OH); *3120* (NH); 1655 (C=O)	3.55 (dd, 1H, J_{gem} = 12.4, $J_{4',5'a}$ = 2.6, 5'-H_a), 3.69 (dd, 1H, J_{gem} = 12.4, $J_{4',5'b}$ = 2.5, 5'-H_b), 4.07 (q, 1H, *J* = 2.4, 4'-H), 4.14 (dd, 1H, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 2.4, 3'-H), 4.39 (dd, 1H, $J_{1',2'}$ = 6.7, $J_{2',3'}$ = 5.0, 2'-H), 5.02 (br, 1H, 5'-OH, exchangeable with D_2O), 5.07 (br, 1H, 3'-OH, exchangeable with D_2O), 5.51 (br, 1H, 2'-OH, exchangeable with D_2O), 5.91 (d, 1H, $J_{1',2'}$ = 6.7, 1'-H), 7.62 (d, 2H, *J* = 8.5, Ar-*m*H), 8.14 (s, 1H, 8-H), 8.21 (d, 2H, *J* = 8.5, Ar-*o*H)

Table 4 (continued)

Product	IR (KBr) ν (cm^{-1})[a]	^{1}H NMR (500 MHz) (DMSO-d_6/TMS)[b] δ, *J* (Hz)
8a	3350, 1085, *1060* (OH); 3120 (NH); 1225 (C=S)	3.68 (m, 1H, 5'-H_a), 3.71 (m, 1H, 5'-H_b), 4.06 (q, 1H, *J* = 2.5, 4'-H), 4.15 (dd, 1H, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 2.7, 3'-H), 4.40 (dd, 1H, $J_{1',2'}$ = 5.9, $J_{2',3'}$ = 5.0, 2'-H), 5.30 (br, 1H, 5'-OH, exchangeable with D_2O), 5.78 (br, 1H, 3'-OH, exchangeable with D_2O), 6.10 (d, 1H, $J_{1',2'}$ = 5.9, 1'-H), 6.25 (br, 1H, 2'-OH, exchangeable with D_2O), 8.43 (s, 1H, 8-H), 8.54 (s, 1H, 3-H)
8b	3300, *1070*, 1060 (OH); *3100* (NH); 1210 (C=S)	3.71 (m, 2H, 5'-H_a, 5'-H_b), 4.07 (q, 1H, *J* = 2.7, 4'-H), 4.15 (dd, 1H, $J_{2',3'}$ = 5.1, $J_{3',4'}$ = 2.8, 3'-H), 4.22 (dd, 1H, $J_{1',2'}$ = 5.9, $J_{2',3'}$ = 5.1, 2'-H), 5.60 (br, 1H, 5'-OH, exchangeable with D_2O), 5.82 (br, 1H, 3'-OH, exchangeable with D_2O), 6.11 (d, 1H, $J_{1',2'}$ = 5.9, 1'-H), 6.22 (br, 1H, 2'-OH, exchangeable with D_2O), 7.58 (m, 3H, PhH), 8.25 (m, 2H, PhH), 8.43 (s, 1H, 8-H)
8c	3350, 1090, *1050* (OH); 3100 (NH); 1220 (C=S)	4.33 (m, 2H, 5'-H_a, 5'-H_b), 4.67 (q, 1H, *J* = 2.4, 4'-H), 4.99 (t, 1H, *J* = 5.3, 3'-H), 5.23 (t, 1H, *J* = 4.9, 2'-H), 6.61 (d, 1H, $J_{1',2'}$ = 4.5, 1'-H), 7.39 (m, 2H, Ar-*m*H), 8.33 (m, 2H, Ar-*o*H), 9.35 (s, 1H, 8-H)
8d	3330, 1080, *1050* (OH); *3130* (NH); 1215 (C=S)	3.69 (m, 2H, 5'-H_a, 5'-H_b), 4.10 (q, 1H, *J* = 2.4, 4'-H), 4.15 (dd, 1H, $J_{2',3'}$ = 4.9, $J_{3',4'}$ = 2.3, 3'-H), 4.43 (t, 1H, *J* = 5.1, 2'-H), 5.56 (br s, 1H, 5'-OH, exchangeable with D_2O), 5.81 (br s, 1H, 3'-OH, exchangeable with D_2O), 5.94 (d, 1H, $J_{1',2'}$ = 6.7, 1'-H), 6.25 (br s, 1H, 2'-OH, exchangeable with D_2O), 7.63 (d, 2H, *J* = 8.6, Ar-*m*H), 8.21 (d, 2H, *J* = 8.6, Ar-*o*H), 8.67 (s, 1H, 8-H)
8e	3370, 1080, *1060* (OH); *3140* (NH); 1250 (C=S)	3.69 (dd, 1H, J_{gem} = 11.8, $J_{4',5'a}$ = 2.4, 5'-H_a), 3.74 (dd, 1H, J_{gem} = 11.8, $J_{4',5'b}$ = 2.7, 5'-H_b), 4.08 (q, 1H, *J* = 2.6, 4'-H), 4.15 (dd, 1H, $J_{2',3'}$ = 4.7, $J_{3',4'}$ = 2.7, 3'-H), 4.40 (t, 1H, *J* = 5.5, 2'-H), 5.50 (br, 1H, 5'-OH, exchangeable with D_2O), 5.83 (br, 1H, 3'-OH, exchangeable with D_2O), 6.10 (d, 1H, $J_{1',2'}$ = 6.3, 1'-H), 6.22 (br, 1H, 2'-OH, exchangeable with D_2O), 7.13 (d, 2H, *J* = 8.8, Ar-*m*H), 8.18 (d, 2H, *J* = 8.8, Ar-*o*H), 8.41 (s, 1H, 8-H)

[a] The values in italics refer to wave numbers at which shoulders or inflexions occur in the absorption.
[b] All products were measured in DMSO-d_6 as the measurement solvent except for product **8c** (trifluoroacetic acid-*d*).

responding 5-methoxy derivatives **5a–i** (Tables 3 and 4). Furthermore, the filtrate was neutralized with 10% HCl to yield a second crop of the 5-methoxy derivatives **5a–i**.

5-Amino-7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purine (6a) and its 3-Phenyl Derivative 6b; General Procedure

An appropriate triazolopurine (**4**; 1.0 mmol) was transfered to a 200 mL stainless steel cylinder, and the reaction cylinder was cooled to – 78 °C. Then anhyd liquid NH_3 (30 mL) was added to the cylinder and the sealed mixture was allowed to warm to r.t. After standing at r.t. for 6 h, the residual solid was collected by filtration, washed with anhyd EtOH, and recrystallized from DMF/H_2O to afford the corresponding 5-amino derivatives **6a, b** (Tables 3 and 4).

5-Morpholino-7-β-D-ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purine (6c)

A mixture of the triazolopurine (**4a**; 1.0 g, 1.84 mmol), morpholine (0.64g, 7.35 mmol), and K_2CO_3 (0.51 g, 3.68 mmol) in dioxane (20 mL) was refluxed for 20 h. After the reaction was complete, the solvent was evaporated in vacuo and the residual oil was triturated with EtOAc. The formed crystals were collected by filtration and recrystallized from EtOH/H_2O to give the 5-morpholino derivative **6c** as colorless crystals (Tables 3 and 4).

7-β-D-Ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purin-5(6*H*)-one (7a) and its 3-Aryl Derivatives 7b, c; General Procedure

A mixture of an appropriate triazolopurine (**4**; 1.0 mmol) with 5% aq KOH (20 mL) was stirred at r.t. for 5–10 h. After the reaction was complete, the solution was adjusted to pH 1 with 10% HCl to afford the precipitates, which were filtered by suction, washed with cold H_2O, and recrystallized from DMF/H_2O to get the corresponding pure the 5-oxo derivatives **7a–c** (Tables 3 and 4).

7-β-D-Ribofuranosyl-7*H*-[1,2,4]triazolo[3,4-*i*]purine-5(6*H*)-thione (8a) and its 3-Aryl Derivatives 8b–e; General Procedure

A mixture of an appropriate triazolopurine (**4**; 1.0 mmol) with thiourea (0.15 g, 2.0 mmol) in anhyd EtOH (50 mL) was heated at 75 °C for 4 h. After the reaction was complete, the solution was concentrated in vacuo and stirred with 10% aq NaOH (20 mL) at r.t. for 30 min. Then, the solution was adjusted to pH 1 with 10% HCl to afford the precipitates, which were filtered by suction, washed with cold H_2O, and recrystallized from DMF to get the corresponding pure the 5-thioxo derivatives **8a–e** (Tables 3 and 4).

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