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Cobalt-Induced Synthesis of 6-(Pyridin-2-yl)purines by Microwave-Enhanced [2+2+2] Cyclotrimerization

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A novel, efficient, and atom-economic methodology for the preparation of a large series of diversely substituted (pyridin-2-yl)purines has been developed. Thus, microwave-enhanced [2+2+2] cyclotrimerization of 6-(diynyl)purines with nitriles in the presence of a stoichiometric or catalytic amount of $[CpCo(CO)_2]$ afforded the corresponding products in good yields. The reactions carried out with various alkyl, aryl, and heteroaryl cyanides poceeded with exclusive regioselectivity, affording 6-(pyridin-2-yl)purines. In an analogous manner, [2+2+2] cyclotrimerizations of 1,8-bis(purinyl)-1,7-octadiynes with nitriles were conducted, yielding 1,4-bis(purin-6-yl)-5,6,7,8-tetrahydroisoquinolines.

Introduction

The cyclotrimerization of alkynes catalyzed by transition-metal compounds is a convenient method for assembling aromatic molecules with a high degree of complexity within a single step under mild reaction conditions.[1] Since the seminal work of Wakatsuki and Yamazaki[2] and Vollhardt and Bergman[3] this process has also been extended to cobalt-catalyzed reactions of alkynes with substrates bearing unsaturated C–N bonds such as nitriles, opening up a straightforward and atom-economic route for the synthesis of heteroaromatics.[1,4,5] The synthetic attraction of this method is supported by its numerous applications in the synthesis of natural compounds.[5] Nonetheless, its potential has not been exhausted yet and could inspire the development of new, biologically active compounds.

6-Arylpurines and their derivatives exhibit a broad spectrum of biological activities, including antitumor, antiviral, antimycobacterial, and receptor-modulating activities.[6] Several purine ribonucleosides bearing five- or six-membered heterocycles in the 6-position possess significant cytostatic and anti-HCV activity.[7] Among them, the 6-(pyridin-2-yl)purine nucleoside is one of the most active cytostatics with moderate antiviral activity. As the mechanism of action is not yet known, one way to gain more insight into the structure–activity relationships (SARs) of this class of compounds is to synthesize a larger series of modified derivatives by adding additional structural features onto the pyridine ring. Herein, we would like to report a pathway for the synthesis of new 6-pyridylpurines based on cobalt-induced cyclotrimerization under microwave conditions.

Results and Discussion

We have demonstrated that substituted 6-arylpurines can be prepared by a transition-metal-catalyzed [2+2+2] cyclotrimerization of 6-alkynylpurines with alkynes or diynes under mild reaction conditions.[8] Clearly, the same strategy can be envisioned for the synthesis of 6-heteroarylpurines. Generally, there are two possible cyclotrimerization approaches to 6-(pyridin-2-yl)purines (Scheme 1): (i) Reaction of 6-cyanopurines with α,ω-diynes and (ii) reaction of purinyldiynes with nitriles (Scheme 1). The former was attempted by studying the reactions of 9-benzyl-6-cyanopurine[9] with diverse diynes catalyzed by $[CpCo(CO)_2]$.[1a,3] However, none of the reactions gave any cyclotrimerization product probably due to the electron-withdrawing effect of the purine moiety on the CN group. Therefore we decided to pursue the latter approach starting from purinyldiynes.

Interestingly, the synthesis of the starting diynes **1** was not as simple a task as had initially been assumed. Although the Sonogashira reaction[10] of 6-halopurines with terminal alkynes has been reported to proceed well to give 6-alkynylpurines in good yields,[11] the same reaction involving α,ω-diynes often furnished the corresponding monopurinyldiynes in rather low yields. Thus, the coupling

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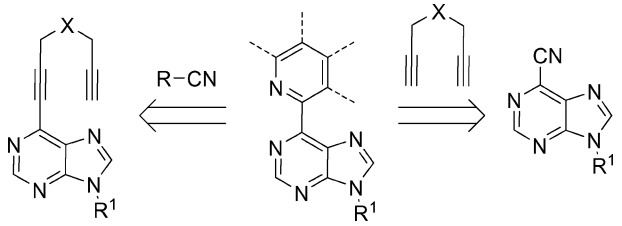
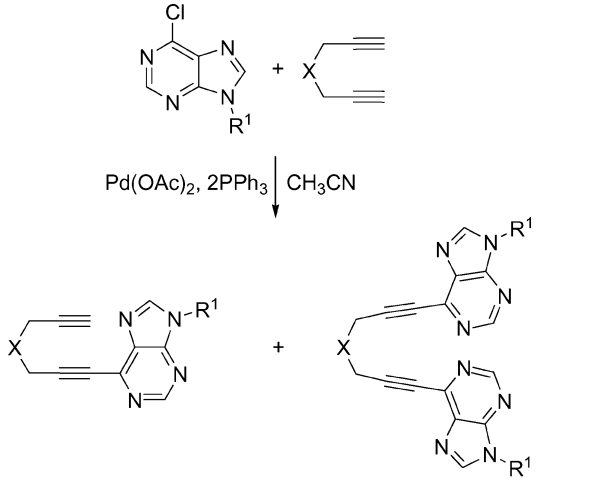
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. Retrosynthetic analysis of [2+2+2] cyclotrimerization approaches to 6-(pyridin-2-yl)purines.

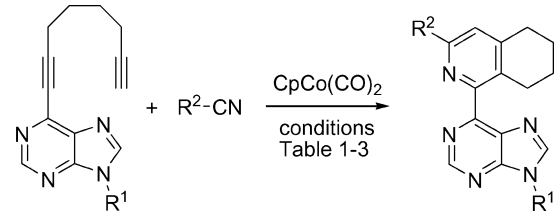
reactions of benzyl- or THP-protected 6-chloropurines with 1,7-octadiyne were carried out initially in DMF, but the corresponding products **1a** (28%) or **1b** (35%) along with small amounts of the hitherto unreported 1,8-bis(purinyl)-1,7-octadiynes **2a** (14%) or **2b** (19%) were formed in rather low yields. Nonetheless, after considerable effort we found that the use of MeCN as solvent and copper-free reaction conditions allowed the synthesis of 6-octadiynylpurines **1a** (benzyl protecting group) and **1b** (THP protecting group) in reasonable yields of 53 and 58% yields, respectively (Scheme 2). In addition, 1,8-bis(purinyl)-1,7-octadiynes **2a** and **2b** were obtained in increased yields of 25 and 28%, respectively. The dipropargyl ether derivative **1c** was prepared under the same conditions in a low yield of 17%; note that under the former conditions it was obtained in only 8% yield. When 6-iodo-9-benzylpurine was coupled with 1,7-octadiyne under the above-mentioned conditions, compounds **2a** and **2b** were obtained in yields of 66 and 27%, respectively.



1a, X = $(CH_2)_2$, R^1 = Bn, 53% **2a**, X = $(CH_2)_2$, R^1 = Bn, 25%
1b, X = $(CH_2)_2$, R^1 = THP, 58% **2b**, X = $(CH_2)_2$, R^1 = THP, 28%
1c, X = O, R^1 = THP, 17%

Scheme 2. Synthesis of octadiynylpurines **1a**–**1c** and bis(purinyl)-octadiynes **2a** and **2b**.

Initially we tried to cyclotrimerize 6-octadiynyl-9-benzylpurine (**1a**) with an excess of benzonitrile (**3a**) in the presence of a catalytic amount of [$CpCo(CO)_2$] (20 mol-%) under standard thermal conditions (140 °C, 6 h). However, the product **4aa** was obtained in only 22% yield. The reaction was also carried out with a stoichiometric amount of the Co complex to increase the yield, but **4aa** was obtained in just 43% yield. The use of a mixture of the complex with a stabilizing ligand (PPh_3) gave exactly the same result. Although these results were not encouraging, we found that heating of the reaction mixture accompanied by light irradiation in mesitylene resulted in a considerable improvement of the product yields. The results of the cyclotrimerizations of various nitriles (Scheme 3) with **1a** are presented in Table 1 (conditions A). Thus **4aa** was isolated in 74% yield when the reaction was conducted in excess PhCN as solvent. Cyclotrimerizations with other nitriles such as **3c**, **3e**, **3f**, and **3i** were carried out in mesitylene and the corresponding pyridylpurines **4ac**, **4ae**, **4af**, and **4ai** were obtained in reasonable isolated yields of 56, 37, 36, and 58%, respectively. Interestingly, the reaction with acetonitrile **3h** did not yield the desired product.



1a, R^1 = Bn
1b, R^1 = THP

3a, R^2 = C_6H_5
3b, R^2 = 4-$MeOC_6H_4$
3c, R^2 = 4-$MeOOCC_6H_4$
3d, R^2 = 4-$CF_3CC_6H_4$
3e, R^2 = 2-furyl
3f, R^2 = 4-pyridyl
3h, R^2 = Me
3g, R^2 = 3-pyridyl
3i, R^2 = Et

4xy
x = R^1
y = R^2

Scheme 3. Cyclotrimerization of **1** with nitriles **3** to yield pyridylpurines **4**.

Table 1. Thermal- and microwave-initiated cyclotrimerization of **1a**,**1b** with nitriles **3** in the presence of [$CpCo(CO)_2$].

Nitrile	Purine	Yield [%][a] A[b]	B[c]	Purine	% Yield[a] B[c]
3a	**4aa**	74[d]	77[d]	**4ba**	89[d]
3b				**4bb**	29
3c	**4ac**	56	39	**4bc**	30
3d				**4bd**	57
3e	**4ae**	37	34	**4be**	40
3f	**4af**	36	39	**4bf**	47
3g	**4ag**		36		
3h	**4ah**	0	71[e]	**4bh**	50[e]
3i	**4ai**	58	53[f]	**4bi**	50[f]

[a] Isolated yields. [b] Conditions A: [$CpCo(CO)_2$] (100 mol-%), *hv*, 140 °C, mesitylene unless otherwise noted. [c] Conditions B: [$CpCo(CO)_2$] (100 mol-%), MW irradiation, 200 °C, THF unless otherwise noted. [d] In PhCN. [e] In MeCN. [f] In EtCN.

Nonetheless, a desire to shorten the reaction times (usually 6 or more hours) prompted us to look for new reaction conditions. It has been shown before that "CpCo" is the active species involved in the cyclotrimerization process and its formation is caused by CO dissociation from the mother complex.[4a] It is well known that microwave irradiation has

positive effects on the course of various reactions.[12] It is most likely that its effect on the enhancement of CO dissociation from [$CpCo(CO)_2$] is the underlying strategy for its successful application in the cyclotrimerizations of alkynes with nitriles to pyridines reported by us[13] and others.[14] In this regard we were interested to know whether its application could also be successful for the above-mentioned cyclotrimerizations. Gratifyingly, cyclotrimerization under microwave irradiation proceeded successfully in all cases within 10 min to give the corresponding pyridylpurines **4a*y*** in 34–77% isolated yields (Table 1, conditions B). The yields of the pyridines obtained were in the range of those obtained under light irradiation. However, it is noteworthy that under these conditions it was possible to carry out the cyclotrimerization of acetonitrile **3h** to afford **4ah** in a good 71% yield.

Next, the cyclotrimerization was carried out with the synthetically more attractive THP-protected purine derivative **1b** under identical conditions (Table 1). The corresponding THP-protected pyridylpurines **4b*y*** were obtained in good-to-excellent yields (30–89%). The structure **4ba** was confirmed by single-crystal X-ray analysis (Figure 1). In addition, the cyclotrimerization of the dipropargyl ether derivative **1c** with benzonitrile **3a** to pyridylpurine **4ca** under the same reaction conditions was successfully carried out (Scheme 4).

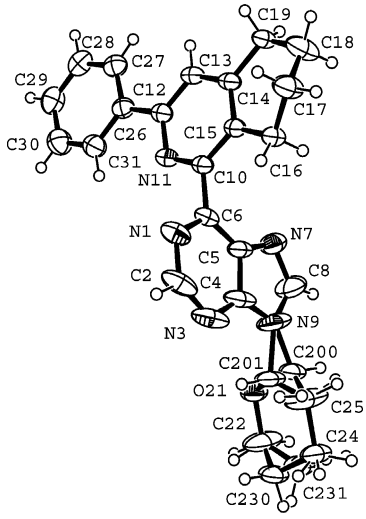
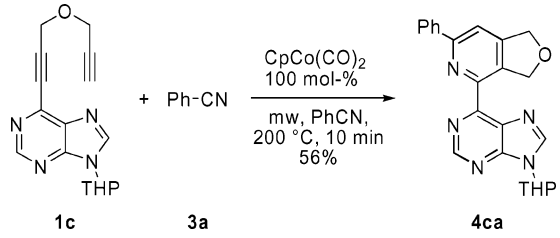


Figure 1. ORTEP drawing of **4ba**. Thermal ellipsoids are drawn at the 50% probability level.

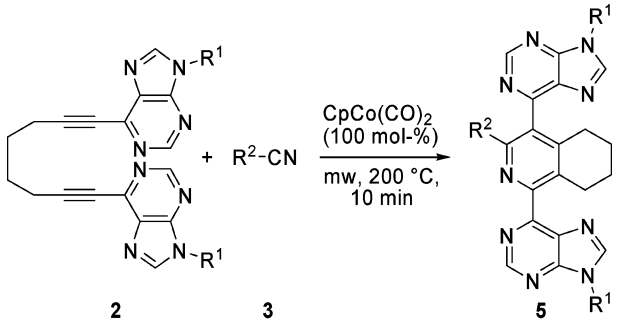


1c 3a 4ca

Scheme 4. Cyclotrimerization of **1c** with **3a** to **4ca**.

It has been shown before that "CpCo" is the species involved in the cyclotrimerization reaction and its formation is caused by CO dissociation from the mother complex.[4a] In this regard it is reasonable to assume that the increased reaction rate of cyclotrimerization is related to the enhancement of CO dissociation by microwave irradiation.

Bis(purinyl)octadiynes **2a** and **2b** were also subjected to the above-mentioned cyclotrimerization protocol (Scheme 5). Reaction of the benzyl-protected substrate **2a** with benzonitrile (**3a**) and acetonitrile (**3h**) afforded the 2,5-bis(purinyl)pyridines **5aa** and **5ah** in reasonable yields of 31 and 33%, respectively. Similar results were obtained with the THP-protected substrate **2b** in its reactions with benzonitrile (**3a**) and 4-trifluorobenzonitrile (**3d**); the corresponding 2,5-bis(purinyl)pyridines **5ba** and **5bd** were isolated in 42 and 28%, respectively.



2 3 5

5aa, R^1 = Bn, R^2 = Ph, 31%
5ah, R^1 = Bn, R^2 = Me, 33%
5ba, R^1 = THP, R^2 = Ph, 42%
5bd, R^1 =THP, R^2 = 4-CF_3Ph, 28%

Scheme 5. Cyclotrimerization of bis(purinyl)diynes **2** with nitriles **3** to terpyridines **5**.

Although, the early results obtained from the thermal- and light-initiated reactions did not provide strong support for the idea of developing a catalytic cyclotrimerization reaction using [$CpCo(CO)_2$], we were curious as to whether the use of microwave irradiation would prove otherwise. Thus, the cyclotrimerizations of 6-octadiynyl-9-benzylpurine (**1a**) and 6-octadiynyl-9-(tetrahydropyranyl)purine (**1b**) with nitriles **3** were carried out in the presence of a catalytic amount of [$CpCo(CO)_2$] (20 mol-%) under microwave irradiation (Table 2). Gratifyingly, in all cases the yields of the corresponding products **4a*y*** and **4b*y*** were comparable to those obtained with a stoichiometric amount of the catalyst or even better. The most pronounced improvement was observed for the cyclotrimerization of acetonitrile (**3h**) and propionitrile (**3i**) for which the 6-pyridylpurines **4ah**, **4ai**, and **4bh** were isolated in 75, 64, and 61% yields, respectively.

Note that the application of a recently published procedure for the cyclotrimerization of diynes with nitriles catalyzed by a system composed of [$CoCl_2 \cdot 6H_2O$]/dppe/Zn[4d] for the reaction of **1b** with **3a** afforded only a small amount of the expected product **4ab** (18%, as determined by ^1H NMR of an inseparable mixture of the product and diyne).

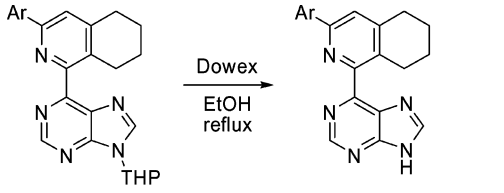
Table 2. Microwave-initiated catalytic cyclotrimerization of nitriles **3** with **1a** and **1b**.[a]

Nitrile	Purine	% Yield[b]	Purine	% Yield[b]
3a	**4aa**	79[c]	**4ba**	91[c]
3b			**4bb**	32
3c	**4ac**	31	**4bc**	43
3d			**4bd**	46
3e	**4ae**	39	**4be**	42
3f	**4af**	42	**4bf**	47
3g	**4ag**	42		
3h	**4ah**	75[d]	**4bh**	61[d]
3i	**4ai**	64[e]		

[a] Conditions C: $[CpCo(CO)_2]$ (20 mol-%), MW irradiation, 200 °C, THF unless otherwise noted. [b] Isolated yields. [c] In PhCN. [d] In MeCN. [e] In EtCN.

This clearly indicates the superiority of the above-mentioned procedure. In addition, an attempt to cyclotrimerize the same substrates by catalysis with [Cp*RuCl(cod)][15] did not yield pyridylpurine **4ab**.

Finally, two selected THP-protected pyridylpurines, **4ba** and **4bd**, were deprotected to the free bases **6a** and **6d** in good 70 and 67% isolated yields, respectively (Scheme 6).



4ba, 4bd

6a, Ar = C_6H_5, 70%
6d, Ar = 4-$CF_3C_6H_4$, 67%

Scheme 6. Deprotection of **4** leading to free bases **6**.

In vitro cytostatic activity tests of some representative examples of the prepared 6-pyridylpurines were performed using the following cell cultures: Human cervix carcinoma HeLa S3 cells (ATCC CCL 2.2), human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119), and human promyelocytic leukemia HL60 cells (ATCC CCL 240). Unfortunately, none of the prepared pyridylpurines showed any desirable activity. On the other hand two of the starting alkynes, **1c** (HeLa, IC_{50} = 3–4 μM; CEM, IC_{50} = 1.2–1.6 μM) and **2a** (HeLa, IC_{50} = 1.2–1.8 μM), were found to exhibit interesting levels of activity.

Conclusions

In conclusion, we have shown that various 6-pyridylpurines can be conveniently synthesized by cobalt-mediated or -catalyzed cyclotrimerization of diynylpurines with nitriles under microwave conditions. In some cases it was even possible to carry out the reaction with substrates that did not react under thermal of photochemical conditions. From a synthetic point of view, the above-mentioned results provide new insights into the cyclotrimerization reactions of heterocyclic alkyne substrates with nitriles and it could also prompt a revision of previous unsuccessful attempts to carry out transition-metal-mediated or -catalyzed [2+2+2] cycloaddition reactions. Although, the prepared compounds did not exhibit any interesting biological activity, these results could provide useful information for the further elaboration of the pyridine ring of the most active 6-pyridylpurines.

Experimental Section

General: All reaction under microwave irradiation were carried in a microwave reactor Biotage Initiator (300 W). ^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400, AVANCE 500, or AVANCE 600 spectrometer. Mass spectra were recorded with a ZAB-SEQ (VG-Analytical) instrument. Infrared spectra were recorded with a Bruker IFS 55 spectrometer. 1,7-Octadiyne and $CpCo(CO)_2$ were purchased from Aldrich.

General Procedure for the Cross-Coupling Reactions of 6-Chloropurine with Diynes. Method B: (The results obtained by Method A are presented in the Supporting Information.) Acetonitrile (18 mL), diyne (12 mmol), and triethylamine (2.5 mL) were added to an argon-purged mixture of 9-benzyl-6-chloro- or 6-chloro-9-(tetrahydropyran-2-yl)purine (6 mmol), PPh_3 (63 mg, 0.24 mmol), and $[Pd(OAc)_2]$ (27 mg, 0.12 mmol) and the mixture was stirred at 70 °C overnight. The solvents were evaporated under reduced pressure and the residue was purified by chromatography on silica gel column.

9-Benzyl-6-(octa-1,7-diyn-1-yl)-9*H*-purine (1a) and 1,8-Bis(9-benzyl-9*H*-purin-6-yl)octa-1,7-diyne (2a): Column chromatography on silica gel (hexane/EtOAc, 1:1) afforded 1006 mg (53%) of **1a** as a yellowish solid and further elution (EtOAc/MeOH, 10:1) gave 390 mg (25%) of **2a** as a brownish solid. Recrystallization of **1a** from EtOAc/heptane gave yellowish crystals.

1a: M.p. 94–95 °C (EtOAc/heptane). R_f (EtOAc) = 0.54. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75, 1.85 (2 m, 2×2 H, 4′-H and 5′-H), 1.95 (t, $J_{8',6'}$ = 2.7 Hz, 1 H, 8′-H), 2.26 (td, $J_{6',5'}$ = 6.9, $J_{6',8'}$ = 2.7 Hz, 2 H, 6′-H), 2.65 (t, $J_{3',4'}$ = 6.9 Hz, 2 H, 3′-H), 5.45 (s, 2 H, CH_2-Ph), 7.27–7.40 (m, 5 H, Ph), 8.07 (s, 1 H, 8-H), 8.93 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.94 (CH_2-6′), 19.45 (CH_2-3′), 27.00 (CH_2-4′), 27.55 (CH_2-5′), 47.36 (CH_2Ph), 68.66 (CH-8′), 76.33 (C-1′), 83.89 (C-7′), 100.75 (C-2′), 127.80 (CH-*m*-Ph), 128.68 (CH-*p*-Ph), 129.18 (CH-*o*-Ph), 134.22 (C-5), 134.86 (C-*i*-Ph), 142.33 (C-6), 144.81 (CH-8), 151.47 (C-4), 152.74 (CH-2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3308, 2234, 1584, 1498, 1405, 1329 cm^{-1}. MS (FAB): *m*/*z* (%) = 315 (40) $[M + H]^+$, 91 (100). HRMS (FAB): calcd. for $C_{20}H_{19}N_4$ $[M + H]^+$ 315.1610; found 315.1617. $C_{20}H_{18}N_4$: C 76.41, H 5.77, N 17.82; found C 76.09, H 5.78, N 17.37.

2a: M.p. 198–201 °C. R_f (EtOAc/MeOH, 5:1) = 0.50. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.95 (m, 4 H, 4′-H), 2.68 (m, 4 H, 3′-H), 5.44 (s, 4 H, CH_2Ph), 7.29 (m, 4 H, *o*-Ph-H), 7.31–7.39 (m, 6 H, *m*,*p*-Ph-H), 8.06 (s, 2 H, 8-H), 8.92 (s, 2 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.49 (CH_2-3′), 27.22 (CH_2-4′), 47.34 (CH_2Ph), 76.47 (C-1′), 100.67 (C-2′), 127.79 (CH-*o*-Ph), 128.66 (CH-*p*-Ph), 129.17 (CH-*m*-Ph), 134.23 (C-5), 134.88 (C-*i*-Ph), 142.32 (C-6), 144.80 (CH-8), 151.46 (C-4), 152.73 (CH-2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2996, 2234, 1584, 1498, 1444, 1405, 1329 cm^{-1}. MS (FAB): *m*/*z* (%) = 523 (13) $[M + H]^+$, 91 (100). HRMS (FAB): calcd. for $C_{32}H_{27}N_8$ $[M + H]^+$ 523.2359; found 523.2368.

6-(Octa-1,7-diyn-1-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (1b) and 1,8-Bis[9-(tetrahydropyran-2-yl)-9*H*-purin-6-yl]octa-1,7-diyne (2b):

Column chromatography on silica gel (hexane/EtOAc, 1:1) afforded 1064 mg (58%) of **1b** a yellowish oil and further elution (EtOAc/MeOH, 10:1) afforded **2b** as a yellowish oil, which after co-evaporation with acetone gave 422 mg (28%) of a white foam.

1b: R_f (EtOAc) = 0.54. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.64–1.89 (m, 7 H, 4′-H, 5′-H and CH_2-THP), 1.96 (t, $J_{8',6'}$ = 2.7 Hz, 1 H, 8′-H), 2.03–2.19 (m, 3 H, CH_2-THP), 2.27 (td, $J_{6',5'}$ = 7.1, $J_{6',8'}$ = 2.7 Hz, 2 H, 6′-H), 2.65 (t, $J_{3',4'}$ = 7.1 Hz, 2 H, 3′-H), 3.79 (td, J = 11.8, 2.6 Hz, 1 H, CH_aH_bO-THP), 4.19 (ddt, J = 11.8, 4.4, 1.9 Hz, 1 H, CH_aH_bO-THP), 5.80 (dd, J = 10.5, 2.5 Hz, 1 H, CHO-THP), 8.31 (s, 1 H, 8-H), 8.90 (s, 1 H, 2-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 17.93 (CH_2-6′), 19.44 (CH_2-3′), 22.68 and 24.78 (CH_2-THP), 26.98 (CH_2-4′), 27.54 (CH_2-5′), 31.79 (CH_2-THP), 68.65 (CH-8′), 68.84 (CH_2O-THP), 76.29 (C-1′), 82.02 (CHO-THP), 83.89 (C-7′), 100.75 (C-2′), 134.39 (C-5), 142.29 (C-6), 142.80 (CH-8), 150.59 (C-4), 152.52 (CH-2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3308, 2233, 1586, 1443, 1333, 1326, 1087, 1046 cm^{-1}. MS (FAB): m/z (%) = 309 (22) $[M + H]^+$, 225 (100). HRMS (FAB): calcd. for $C_{18}H_{21}N_4O$ $[M + H]^+$ 309.1715; found 309,1724.

2b: R_f (EtOAc/MeOH, 5:1) = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.87 (m, 6 H, CH_2-THP), 1.96 (m, 4 H, 4′-H), 2.01–2.20 (m, 6 H, CH_2-THP), 2.69 (m, 4 H, 3′-H), 3.79 (td, J = 11.6, 2.6 Hz, 2 H, CH_aH_bO-THP), 4.19 (ddt, J = 11.6, 4.1, 1.9 Hz, 2 H, CH_aH_bO-THP), 5.79 (dd, J = 10.2, 2.5 Hz, 2 H, CHO-THP), 8.30 (s, 2 H, 8-H), 8.89 (s, 2 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.49 (CH_2-3′), 22.68 and 24.80 (CH_2-THP), 27.23 (CH_2-4′), 31.80 (CH_2-THP), 68.82 (CH_2O-THP), 76.45 (C-1′), 82.04 (CHO-THP), 100.65 (C-2′), 134.43 (C-5), 142.30 (C-6), 142.79 (CH-8), 150.60 (C-4), 152.50 (CH-2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2995, 2953, 2234, 1585, 1443, 1334, 1326, 1087, 1046 cm^{-1}. MS (FAB): m/z (%) = 511 (15) $[M + H]^+$, 343 (32), 93 (100). HRMS (FAB): calcd. for $C_{28}H_{31}N_8O_2$ $[M + H]^+$ 511.2570; found 511.2562.

6-[3-(Prop-2-ynyloxy)prop-1-ynyl]-9-(tetrahydropyran-2-yl)-9*H*-purine (1c): Column chromatography on silica gel (hexane/EtOAc, 2:3) afforded 300 mg (17%) of a yellowish solid. Recrystallization from EtOAc/heptane gave colorless crystals, m.p. 80–82 °C (EtOAc/heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.88 and 2.01–2.21 (2 m, 2 × 3 H, CH_2-THP), 2.49 (t, $J_{7',5'}$ = 2.4 Hz, 1 H, 7′-H), 3.80 (td, J = 11.7, 2.7 Hz, 1 H, CH_aH_bO-THP), 4.20 (ddt, J = 11.7, 4.4, 1.8 Hz, 1 H, CH_aH_bO-THP), 4.41 (d, $J_{5',7'}$ = 2.4 Hz, 2 H, 5′-H), 4.66 (s, 2 H, 3′-H), 5.80 (dd, J = 10.3, 2.5 Hz, 1 H, CHO-THP), 8.34 (s, 2 H, 8-H), 8.94 (s, 2 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.67, 24.79, and 31.81 (CH_2-THP), 56.88 (CH_2-5′), 57.03 (CH_2-3′), 68.87 (CH_2O-THP), 75.35 (CH-7′), 78.68 (C-6′), 81.49 (C-1′), 82.15 (CHO-THP), 93.68 (C-2′), 134.57 (C-5), 140.97 (C-6), 143.31 (CH-8), 150.86 (C-4), 152.52 (CH-2) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3308, 2238, 1585, 1443, 1352, 1342, 1334, 1087, 1046 cm^{-1}. MS (FAB): m/z (%) = 297 (9) $[M + H]^+$, 185 (27), 93 (100). HRMS (FAB): calcd. for $C_{16}H_{17}N_4O_2$ $[M + H]^+$ 297.1352; found 297.1359. $C_{16}H_{16}N_4O_2$: C 64.85, H 5.44, N 18.91; found C 64.81, H 5.39, N 18.65. R_f (EtOAc) = 0.53.

General Procedure for the [$CpCo(CO)_2$]-Catalyzed Cyclotrimerization of 6-Diynylpurines 1 with Nitriles 3 under Microwave Irradiation. Method C: Procedure with THF as Solvent (Method C1): (The results obtained by Method A and B are presented in the Supporting Information.) Diynylpurine **1** (0.4 mmol) was placed in a vial filled with argon. Then nitrile **3** (2 mmol), THF (4 mL), and the cobalt catalyst [$CpCo(CO)_2$] (11 μL, 0.08 mmol) were added to the starting material under argon. Vial was placed into the microwave reactor and irradiated for 10 min. Then the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to give the corresponding product **4**.

Procedure with Nitrile 3 as Solvent (Method C2): Diynylpurine **1** (0.4 mmol) was placed in a vial filled with argon. Then nitrile **3** (4 mL) and the cobalt catalyst [$CpCo(CO)_2$] (11 μL, 0.08 mmol) were added to the starting material under argon. The vial was placed in the microwave reactor and irradiated for 10 min. Then the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to give the corresponding product **4**.

9-Benzyl-6-(3-phenyl-5,6,7,8-tetrahydroisoquinolin-1-yl)-9*H*-purine (4aa) (Method C2): Column chromatography on silica gel (hexane/EtOAc/$CHCl_3$, 5:5:1) afforded 132 mg (79%) of a white solid. Recrystallization from CH_2Cl_2/heptane gave white crystals, m.p. 225–226 °C (CH_2Cl_2/heptane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76 (m, 2 H, 7′-H), 1.86 (m, 2 H, 6′-H), 2.75 (t, J_{vic} = 6.4 Hz, 2 H, 8′-H), 2.92 (t, J_{vic} = 6.2 Hz, 2 H, 5′-H), 5.49 (s, 2 H, CH_2-Bn), 7.30–7.42 (m, 8 H, Bn and *m* + *p*-H-Ph), 7.54 (s, 1 H, 4′-H), 7.96 (m, 2 H, *o*-H-Ph), 8.08 (s, 1 H, 8-H), 9.13 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.08 (CH_2-6′), 22.72 (CH_2-7′), 25.88 (CH_2-8′), 29.63 (CH_2-5′), 47.35 (CH_2-Bn), 121.81 (CH-4′), 127.12 (CH-*o*-Ph), 127.99, 128.32, 128.47, 128.64, and 129.17 (CH-Ph), 130.96 (C-8′a), 132.26 (C-5), 135.05 (C-*i*-Bn), 139.58 (C-*i*-Ph), 144.88 (CH-8), 148.01 (C-4′a), 152.32 (C-4), 152.51 (CH-2), 152.88 (C-1′), 154.37 (C-3′), 157.60 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2987, 2944, 1591, 1580, 1553, 1500, 1434, 1328, 728, 698 cm^{-1}. MS (EI): m/z (%) = 417 (91) $[M]^+$, 389 (5), 326 (100), 91 (55). HRMS: calcd. for $C_{27}H_{23}N_5$ $[M]^+$ 417.1953; found 417.1944. $C_{27}H_{23}N_5$: C 77.67, H 5.55, N 16.77; found: C 77.22, H 5.45, N 16.58. R_f (hexane/EtOAc, 1:3) = 0.55.

9-Benzyl-6-[3-(4-methoxycarbonylphenyl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9*H*-purine (4ac) (Method C1): Column chromatography on silica gel (hexane/EtOAc/$CHCl_3$, 5:5:1) afforded a yellowish solid, which after co-evaporation with acetone formed 59 mg (31%) of a yellowish foam. Crystallization from CH_2Cl_2/heptane gave yellowish crystals, m.p. 168–171 °C (CH_2Cl_2/heptane). R_f (hexane/EtOAc, 1:3) = 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73–1.90 (m, 4 H, 7′-H and 6′-H), 2.76 (t, J_{vic} = 6.3 Hz, 2 H, 8′-H), 2.94 (t, J_{vic} = 6.3 Hz, 2 H, 5′-H), 3.91 (s, 3 H, CH_3O), 5.50 (s, 2 H, CH_2-Ph), 7.35–7.42 (m, 5 H, Ph), 7.60 (s, 1 H, 4′-H), 8.06 (s, 4 H, *o*,*m*-C_6H_4-H), 8.10 (s, 1 H, 8-H), 9.14 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.00 and 22.63 (CH_2-6′ and CH_2-7′), 25.95 (CH_2-8′), 29.65 (CH_2-5′), 47.41 (CH_2-Ph), 52.05 (CH_3O), 122.16 (CH-4′), 126.98 (CH-*o*-C_6H_4), 128.03 (CH-*o*-Ph), 128.69 (CH-*p*-Ph), 129.19 (CH-*m*-Ph), 129.79 (C-*p*-C_6H_4), 129.84 (CH-*m*-C_6H_4), 131.98 (C-8′a), 132.22 (C-5), 134.99 (C-*i*-Ph), 143.71 (C-*i*-C_6H_4), 144.99 (CH-8), 148.30 (C-4′a), 152.38 (C-4), 152.53 (CH-2), 152.99 (C-3′), 153.19 (C-1′), 157.28 (C-6), 167.04 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2989, 2952, 1718, 1590, 1581, 1500, 1437, 1328, 1281, 1192, 1117, 1107 cm^{-1}. MS (FAB): m/z (%) = 476 (15) $[M + H]^+$, 91 (100). HRMS (FAB): calcd. for $C_{29}H_{25}N_5O_2$ $[M + H]^+$ 476.2087; found 476.2092.

9-Benzyl-6-[3-(furan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9*H*-purine (4ae) (Method C1): Column chromatography on silica gel (hexane/EtOAc/chloroform, 5:5:1) afforded a yellowish oil, which after co-evaporation with acetone formed 64 mg (39%) of a yellowish foam. Crystallization from CH_2Cl_2/heptane gave yellowish crystals, m.p. 182–185 °C (CH_2Cl_2/heptane). R_f (hexane/EtOAc, 1:3) = 0.44. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 and 1.83 (2 m, 4 H, 7′-H and 6′-H), 2.69 (t, J_{vic} = 6.2 Hz, 2 H, 8′-H), 2.89 (t, J_{vic} = 6.4 Hz, 2 H, 5′-H), 5.49 (s, 2 H, CH_2-Ph), 6.45 (dd, $J_{4,3}$ = 3.4, $J_{4,5}$ = 1.8 Hz, 1 H, 4-furyl-H), 6.95 (dd, $J_{3,4}$ = 3.4, $J_{3,5}$ = 0.8 Hz, 1 H, 3-furyl-H), 7.32–7.42 (m, 5 H, Ph), 7.47 (dd, $J_{5,4}$ = 1.8, $J_{5,3}$ = 0.8 Hz, 1 H, 5-furyl-H), 7.51 (s, 1 H, 4′-H), 8.07 (s, 1 H, 8-H), 9.13

(s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.99 and 22.64 (CH_2-6′ and CH_2-7′), 25.99 (CH_2-8′), 29.52 (CH_2-5′), 47.35 (CH_2-Ph), 108.26 (CH-3-furyl), 111.69 (CH-4-furyl), 119.67 (CH-4′), 127.96 (CH-*o*-Ph), 128.64 (CH-*p*-Ph), 129.17 (CH-*m*-Ph), 130.93 (C-8′a), 132.21 (C-5), 135.05 (C-*i*-Ph), 142.78 (CH-5-furyl), 144.87 (CH-8), 146.32 (C-3′), 147.94 (C-4′a), 152.33 (C-4), 152.56 (CH-2), 152.91 (C-1′), 153.56 (C-2-furyl), 157.26 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2989, 2944, 1593, 1582, 1499, 1329 cm^{-1}. MS (FAB): *m*/*z* (%) = 408 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{25}H_{22}N_5O$ [M + H]$^+$ 408.1824; found 408,1834.

9-Benzyl-6-[3-(pyridin-4-yl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9*H*-purine (4af) (Method C1): Column chromatography on silica gel (EtOAc/MeOH/$CHCl_3$, 10:1:1) afforded a brownish oil, which after co-evaporation with $CHCl_3$ formed 70 mg (42%) of a brownish foam. Crystallization from CH_2Cl_2/heptane gave brownish crystals, m.p. 248–253 °C (CH_2Cl_2/heptane). R_f (EtOAc/MeOH, 5:1) = 0.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74–1.91 (m, 4 H, 7′-H and 6′-H), 2.77 (t, J_{vic} = 6.5 Hz, 2 H, 8′-H), 2.94 (t, J_{vic} = 6.2 Hz, 2 H, 5′-H), 5.51 (s, 2 H, CH_2-Ph), 7.34–7.43 (m, 5 H, Ph), 7.62 (s, 1 H, 4′-H), 7.91 (br. m, 2 H, *m*-H-Py), 8.11 (s, 1 H, 8-H), 8.67 (br. m, 2 H, *o*-H-Py), 9.14 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.91 and 22.53 (CH_2-6′ and CH_2-7′), 26.03 (CH_2-8′), 29.65 (CH_2-5′), 47.44 (CH_2-Ph), 121.36 (CH-*m*-Py), 122.01 (CH-4′), 128.05 (CH-*m*-Ph), 128.72 (CH-*p*-Ph), 129.20 (CH-*o*-Ph), 132.18 (C-5), 133.07 (C-8′a), 134.93 (C-*i*-Ph), 145.08 (CH-8), 146.51 (C-*p*-Py), 148.59 (C-4′a), 150.25 (CH-*o*-Py), 151.32 (C-3′), 152.40 (C-4), 152.51 (CH-2), 153.45 (C-1′), 156.99 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2985, 2947, 1591, 1581, 1500, 1329 cm^{-1}. MS (EI): *m*/*z* (%) = 418 (55) [M]$^+$, 326 (100), 91 (39). HRMS (EI): calcd. for $C_{26}H_{22}N_6$ [M]$^+$ 418.1906; found 418.1891.

9-Benzyl-6-[3-(pyridin-3-yl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9*H*-purine (4ag) (Method C1): Column chromatography on silica gel (EtOAc/MeOH/$CHCl_3$, 10:1:1) afforded a brownish oil, which after co-evaporation with $CHCl_3$ formed 70 mg (42%) of a yellowish foam. Crystallization from CH_2Cl_2/heptane gave yellowish crystals, m.p. 179–182 °C (CH_2Cl_2/heptane). R_f (EtOAc/MeOH, 5:1) = 0.37. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.78 and 1.87 (2 m, 4 H, 7′-H and 6′-H), 2.77 (t, J_{vic} = 6.4 Hz, 2 H, 8′-H), 2.94 (t, J_{vic} = 6.3 Hz, 2 H, 5′-H), 5.51 (s, 2 H, CH_2-Ph), 7.33 (br. dd, $J_{5,4}$ = 7.9, $J_{5,6}$ = 4.8 Hz, 1 H, 5-py-H), 7.34–7.41 (m, 5 H, Ph), 7.57 (s, 1 H, 4′-H), 8.11 (s, 1 H, 8-H), 8.31 (ddd, $J_{4,5}$ = 7.9, $J_{4,6}$ = 2.2, $J_{4,2}$ = 1.7 Hz, 1 H, 4-py-H), 8.59 (br. m, 1 H, 6-py-H), 9.14 (s, 1 H, 2-H), 9.16 (br. m, 1 H, 2-py-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.94 and 22.57 (CH_2-6′ and CH_2-7′), 25.91 (CH_2-8′), 29.62 (CH_2-5′), 47.40 (CH_2-Ph), 121.80 (CH-4′), 123.45 (CH-5-py), 128.01 (CH-*o*-Ph), 128.68 (CH-*p*-Ph), 129.18 (CH-*m*-Ph), 131.95 (C-8′a), 132.16 (C-5), 134.66 (CH-4-py), 134.94 (C-*i*-Ph), 135.04 (C-3-py), 145.04 (CH-8), 148.25 (CH-2-py), 148.51 (C-4′a), 149.40 (CH-6-py), 151.53 (C-3′), 152.34 (C-4), 152.51 (CH-2), 153.35 (C-1′), 157.12 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2986, 2946, 1590, 1580, 1500, 1329 cm^{-1}. MS (FAB): *m*/*z* (%) = 419 (100) [M + H]$^+$, 91 (18). HRMS (FAB): calcd. for $C_{26}H_{23}N_6$ [M + H]$^+$ 419.1984; found 419.1992.

9-Benzyl-6-(3-ethyl-5,6,7,8-tetrahydroisoquinolin-1-yl)-9*H*-purine (4ai) (Method C2): Column chromatography on silica gel (EtOAc/chloroform, 10:1) afforded 95 mg (64%) of a yellowish oil. R_f (EtOAc/MeOH, 10:1) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J_{vic} = 7.6 Hz, 3 H, CH_3CH$_2$), 1.72 (m, 2 H, 7′-H), 1.81 (m, 2 H, 6′-H), 2.63 (t, J_{vic} = 6.4 Hz, 2 H, 8′-H), 2.82 (t, J_{vic} = 6.8 Hz, 2 H, 5′-H), 2.83 (q, J_{vic} = 7.6 Hz, 2 H, CH$_2$CH$_3$), 5.48 (s, 2 H, CH_2-Ph), 7.01 (s, 1 H, 4′-H), 7.31–7.41 (m, 5 H, Ph), 8.06 (s, 1 H, 8-H), 9.11 (s, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.27 (*C*H$_3$CH$_2$), 22.09 (CH_2-6′), 22.74 (CH_2-7′), 25.68 (CH_2-8′), 29.37 (CH_2-5′), 30.97 (*C*H$_2$CH$_3$), 47.34 (CH_2-Ph), 122.89 (CH-4′), 127.97 (CH-*o*-Ph), 128.64 (CH-*p*-Ph), 129.15 (CH-*m*-Ph), 129.29 (C-8′a), 132.07 (C-5), 135.04 (C-*i*-Ph), 144.83 (CH-8), 147.64 (C-4′a), 152.20 and 152.23 (C-4 and C-1′), 152.70 (CH-2), 157.71 (C-6), 160.02 (C-3′) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2974, 2942, 1592, 1580, 1500, 1329 cm^{-1}. MS (FAB): *m*/*z* (%) = 370 (100) [M + H]$^+$, 91 (90). HRMS (FAB): calcd. for $C_{23}H_{24}N_5$ [M + H]$^+$ 370.2032; found 370.2039.

6-(3-Phenyl-5,6,7,8-tetrahydroisoquinolin-1-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (4ba) (Method C2): Column chromatography on silica gel (hexane/EtOAc/$CHCl_3$, 10:10:1) afforded 149 mg (91%) of a yellowish solid. Recrystallization from CH_2Cl_2/heptane gave colorless crystals, m.p. 182–187 °C (CH_2Cl_2/heptane). R_f (hexane/EtOAc, 2:5) = 0.37. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.89 (m, 7 H, 6′,7′-H and CH_2-THP), 2.06–2.22 (m, 3 H, CH_2-THP), 2.70 and 2.75 (2 dt, J_{gem} = 17.2, J_{vic} = 6.1 Hz, 2 H, 8′-H), 2.92 (t, J_{vic} = 6.2 Hz, 2 H, 5′-H), 3.83 (td, J = 11.7, 2.6 Hz, 1 H, CH$_a$H$_b$O-THP), 4.21 (ddt, J = 11.7, 4.3, 1.9 Hz, 1 H, CH$_a$H$_b$O-THP), 5.88 (dd, J = 10.4, 2.8 Hz, 1 H, CHO-THP), 7.33 (m, 1 H, *p*-H-Ph), 7.39 (m, 2 H, *m*-H-Ph), 7.54 (s, 1 H, 4′-H), 7.96 (m, 2 H, *o*-H-Ph), 8.39 (s, 1 H, 8-H), 9.09 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.09 (CH_2-6′), 22.71 (CH_2-7′), 22.77 and 24.88 (CH_2-THP), 25.84 (CH_2-8′), 29.64 (CH_2-5′), 31.89 (CH_2-THP), 68.87 (CH_2O-THP), 82.05 (CHO-THP), 121.74 (CH-4′), 127.12 (CH-*o*-Ph), 128.31 (CH-*p*-Ph), 128.46 (CH-*m*-Ph), 130.94 (C-8′a), 132.48 (C-5), 139.59 (C-*i*-Ph), 142.87 (CH-8), 147.99 (C-4′a), 151.49 (C-4), 152.36 (CH-2), 152.88 (C-1′), 154.35 (C-3′), 157.67 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2984, 2948, 1591, 1579, 1496, 1434, 1332, 1326, 1086, 1045 cm^{-1}. MS (EI): *m*/*z* (%) = 411 (8) [M]$^+$, 327 (95), 224 (27), 57 (100). HRMS (EI): calcd. for $C_{25}H_{25}N_5O$ [M]$^+$ 411.2059; found 411.2080.

6-[3-(4-Methoxyphenyl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9-(tetrahydropyran-2-yl)-9*H*-purine (4bb) (Method C1): Column chromatography on silica gel (hexane/EtOAc/$CHCl_3$, 10:10:1) afforded 57 mg (32%) of a yellowish oil. Crystallization from EtOAc/heptane gave greyish crystals, m.p. 146–151 °C (EtOAc/heptane). R_f (EtOAc) = 0.59. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.90 (m, 7 H, 7′,6′-H and CH_2-THP), 2.06–2.23 (m, 3 H, CH_2-THP), 2.68 and 2.78 (2 dt, J_{gem} = 17.2, $J_{8',7'}$ = 6.0 Hz, 2 H, 8′-H), 2.90 (t, $J_{5',6'}$ = 6.2 Hz, 2 H, 5′-H), 3.82 (s, 3 H, CH_3O), 3.83 (td, J = 11.3, 2.3 Hz, 1 H, CH$_a$H$_b$O-THP), 4.21 (ddt, J = 11.3, 4.2, 1.7 Hz, 1 H, CH$_a$H$_b$O-THP), 5.88 (dd, J = 10.6, 2.5 Hz, 1 H, CHO-THP), 6.92 (m, 2 H, *m*-C_6H_4OMe-H), 7.48 (s, 1 H, 4′-H), 7.92 (m, 2 H, *o*-C_6H_4OMe-H), 8.32 (s, 1 H, 8-H), 9.09 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.11 and 22.74 (CH_2-6′ and CH_2-7′), 22.77 and 24.86 (CH_2-THP), 25.79 (CH_2-8′), 29.62 (CH_2-5′), 31.87 (CH_2-THP), 55.26 (CH_3O), 68.87 (CH_2O-THP), 82.00 (CHO-THP), 113.82 (CH-*m*-C_6H_4OMe), 121.02 (CH-4′), 128.30 (CH-*o*-C_6H_4OMe), 130.21 (C-8′a), 132.29 (C-*i*-C_6H_4OMe), 132.43 (C-5), 142.82 (CH-8), 147.85 (C-4′a), 151.43 (C-4), 152.35 (CH-2), 152.67 (C-1′), 153.98 (C-3′), 157.77 (C-6), 159.95 (C-*p*-C_6H_4OMe) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2981, 2947, 1610, 1591, 1580, 1515, 1496, 1441, 1332, 1326, 1249, 1207, 1176, 1086, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 442 (24) [M + H]$^+$, 358 (72), 57 (100). HRMS (FAB): calcd. for $C_{26}H_{28}N_5O_2$ [M + H]$^+$ 442.2243; found 442.2259.

6-[3-(4-Methoxycarbonylphenyl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9-(tetrahydropyran-2-yl)-9*H*-purine (4bc) (Method C1): Column chromatography on silica gel (hexane/EtOAc/$CHCl_3$, 10:10:1) afforded 80 mg (43%) of a yellowish oil. Crystallization from EtOAc/heptane gave white crystals, m.p. 204–206 °C (EtOAc/heptane). R_f (EtOAc) = 0.62. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.66–1.90 (m, 7 H, 7′,6′-H and CH_2-THP), 2.07–2.28 (m, 3 H, CH_2-THP), 2.71

and 2.77 (2 dt, J_{gem} = 17.4, $J_{8',7'}$ = 6.5 Hz, 2 H, 8′-H), 2.93 (t, $J_{5',6'}$ = 6.2 Hz, 2 H, 5′-H), 3.83 (td, J = 11.7, 2.6 Hz, 1 H, CH_aH_bO-THP), 3.92 (s, 3 H, CH_3O), 4.22 (ddt, J = 11.7, 4.3, 1.7 Hz, 1 H, CH_aH_bO-THP), 5.88 (dd, J = 10.4, 2.5 Hz, 1 H, CHO-THP), 7.60 (s, 1 H, 4′-H), 8.07 (m, 4 H, *o*,*m*-C_6H_4COOMe-H), 8.34 (s, 1 H, 8-H), 9.10 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.99 and 22.59 (CH_2-6′ and CH_2-7′), 22.76 and 24.85 (CH_2-THP), 25.90 (CH_2-8′), 29.63 (CH_2-5′), 31.86 (CH_2-THP), 52.05 (CH_3O), 68.89 (CH_2O-THP), 82.04 (CHO-THP), 122.12 (CH-4′), 126.96 (CH-*o*-C_6H_4COOMe), 129.76 (C-*p*-C_6H_4COOMe), 129.83 (CH-*m*-C_6H_4COOMe), 131.94 (C-8′a), 132.40 (C-5), 143.00 (CH-8), 143.70 (C-*i*-C_6H_4COOMe), 148.28 (C-4′a), 151.50 (C-4), 152.37 (CH-2), 152.95 (C-3′), 153.17 (C-1′), 157.32 (C-6), 167.04 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2952, 2933, 1718, 1591, 1579, 1496, 1437, 1331, 1326, 1281, 1116, 1107, 1086, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 470 (6) [M + H]$^+$, 386 (29), 57 (100). HRMS (FAB): calcd. for $C_{27}H_{28}N_5O_3$ [M + H]$^+$ 470.2195; found 470.2188. $C_{27}H_{27}N_5O_3$: C 69.07, H 5.80, N 14.92; found C 68.73, H 5.71, N 14.72.

6-{3-[4-(Trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-1-yl}-9-(tetrahydropyran-2-yl)-9*H*-purine (4bd) (Method C1): Column chromatography on silica gel (hexane/EtOAc/$CHCl_3$, 10:10:1) afforded 88 mg (46%) of a colorless oil. R_f (hexane/EtOAc, 2:5) = 0.45. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67–1.90 (m, 7 H, 7′,6′-H and CH_2-THP), 2.04–2.23 (m, 3 H, CH_2-THP), 2.72 and 2.77 (2 dt, J_{gem} = 17.4, $J_{8',7'}$ = 6.4 Hz, 2 H, 8′-H), 2.94 (td, $J_{5',6'}$ = 6.3, $J_{5',4'}$ = 0.8 Hz, 2 H, 5′-H), 3.84 (td, J = 11.9, 2.6 Hz, 1 H, CH_aH_bO-THP), 4.22 (ddt, J = 11.9, 4.4, 1.9 Hz, 1 H, CH_aH_bO-THP), 5.89 (dd, J = 10.4, 2.3 Hz, 1 H, CHO-THP), 7.58 (t, $J_{4',5'}$ = 0.8 Hz, 1 H, 4′-H), 7.65 (m, 2 H, *m*-$C_6H_4CF_3$-H), 8.09 (m, 2 H, *o*-$C_6H_4CF_3$-H), 8.34 (s, 1 H, 8-H), 9.10 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.98 and 22.59 (CH_2-6′ and CH_2-7′), 22.77 and 24.86 (CH_2-THP), 25.90 (CH_2-8′), 29.66 (CH_2-5′), 31.88 (CH_2-THP), 68.91 (CH_2O-THP), 82.06 (CHO-THP), 122.00 (CH-4′), 124.27 (q, $J_{C,F}$ = 272 Hz, CF_3), 125.44 (q, $J_{C,F}$ = 4 Hz, CH-*m*-$C_6H_4CF_3$), 127.32 (CH-*o*-$C_6H_4CF_3$), 130.20 (q, $J_{C,F}$ = 32 Hz, C-*p*-$C_6H_4CF_3$), 132.04 (C-8′a), 132.40 (C-5), 142.81 (C-*i*-$C_6H_4CF_3$), 143.04 (CH-8), 148.41 (C-4′a), 151.52 (C-4), 152.38 (CH-2), 152.66 (C-3′), 153.20 (C-1′), 157.27 (C-6) ppm. ^{19}F NMR (470.3 MHz, $CDCl_3$): δ = –62.96 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2986, 2948, 1590, 1580, 1496, 1434, 1379, 1326, 1168, 1130, 1085, 1069, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 480 (7) [M + H]$^+$, 396 (100). HRMS (FAB): calcd. for $C_{26}H_{25}N_5OF_3$ [M + H]$^+$ 480.2011; found 480.1997.

6-[3-(Furan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9-(tetrahydropyran-2-yl)-9*H*-purine (4be) (Method C1): Column chromatography on silica gel ($CHCl_3$/diethyl ether, 5:1) afforded 68 mg (42%) of a yellowish oil, which after co-evaporation with $CHCl_3$ formed a white foam. Crystallization from CH_2Cl_2/heptane gave greyish crystals, m.p. 193–194 °C (CH_2Cl_2/heptane). R_f (EtOAc) = 0.50. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.66–1.89 (m, 7 H, 7′,6′-H and CH_2-THP), 2.05–2.21 (m, 3 H, CH_2-THP), 2.65 and 2.70 (2 dt, J_{gem} = 17.2, $J_{8',7'}$ = 6.4 Hz, 2 H, 8′-H), 2.89 (td, $J_{5',6'}$ = 6.3, $J_{5',4'}$ = 0.9 Hz, 2 H, 5′-H), 3.83 (td, J = 11.8, 2.6 Hz, 1 H, CH_aH_bO-THP), 4.21 (ddt, J = 11.8, 4.3, 2.0 Hz, 1 H, CH_aH_bO-THP), 5.87 (dd, J = 10.4, 2.8 Hz, 1 H, CHO-THP), 6.45 (dd, $J_{4,3}$ = 3.4, $J_{4,5}$ = 1.8 Hz, 1 H, 4-furyl-H), 6.95 (dd, $J_{3,4}$ = 3.4, $J_{3,5}$ = 0.9 Hz, 1 H, 3-furyl-H), 7.47 (dd, $J_{5,4}$ = 1.8, $J_{5,3}$ = 0.9 Hz, 1 H, 5-furyl-H), 7.52 (t, $J_{4',5'}$ = 0.9 Hz, 1 H, 4′-H), 8.31 (s, 1 H, 8-H), 9.09 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.99 and 22.62 (CH_2-6′ and CH_2-7′), 22.76 and 24.85 (CH_2-THP), 25.94 (CH_2-8′), 29.51 (CH_2-5′), 31.88 (CH_2-THP), 68.87 (CH_2O-THP), 82.02 (CHO-THP), 108.25 (CH-3-furyl), 111.69 (CH-4-furyl), 119.64 (CH-4′), 130.89 (C-8′a), 132.40 (C-5), 142.76 (CH-5-furyl), 142.88 (CH-8), 146.32 (C-3′), 147.93 (C-4′a), 151.45 (C-4), 152.39 (CH-2), 152.89 (C-1′), 153.57 (C-2-furyl), 157.30 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2987, 2948, 1594, 1580, 1497, 1410, 1332, 1326, 1234, 1207, 1087, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 402 (30) [M + H]$^+$, 318 (100). HRMS (FAB): calcd. for $C_{23}H_{24}N_5O_2$ [M + H]$^+$ 402.1930; found 402.1927.

6-[3-(Pyridin-4-yl)-5,6,7,8-tetrahydroisoquinolin-1-yl]-9-(tetrahydropyran-2-yl)-9*H*-purine (4bf) (Method C1): Column chromatography on silica gel (EtOAc/MeOH/$CHCl_3$, 10:1:1) afforded 78 mg (47%) of a yellowish oil. Crystallization from CH_2Cl_2/heptane gave yellowish crystals, m.p. 179–184 °C (CH_2Cl_2/heptane). R_f (EtOAc/MeOH, 5:1) = 0.32. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.67–1.90 (m, 7 H, 7′,6′-H and CH_2-THP), 2.03–2.24 (m, 3 H, CH_2-THP), 2.73 and 2.78 (2 dt, J_{gem} = 17.5, $J_{8',7'}$ = 6.3 Hz, 2 H, 8′-H), 2.95 (t, $J_{5',6'}$ = 6.3 Hz, 2 H, 5′-H), 3.84 (td, J = 11.8, 2.6 Hz, 1 H, CH_aH_bO-THP), 4.22 (ddt, J = 11.8, 4.3, 1.9 Hz, 1 H, CH_aH_bO-THP), 5.89 (dd, J = 10.5, 2.7 Hz, 1 H, CHO-THP), 7.62 (s, 1 H, 4′-H), 7.89 (m, 2 H, 3,5-Py-H), 8.35 (s, 1 H, 8-H), 8.65 (m, 2 H, 2,6-Py-H), 9.11 (s, 1 H, 2-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.89 and 22.49 (CH_2-6′ and CH_2-7′), 22.78 and 24.89 (CH_2-THP), 25.97 (CH_2-8′), 29.61 (CH_2-5′), 31.84 (CH_2-THP), 68.90 (CH_2O-THP), 82.02 (CHO-THP), 121.24 (CH-3,5-Py), 121.98 (CH-4′), 132.35 (C-5), 133.01 (C-8′a), 143.09 (CH-8), 146.46 (C-4-Py), 148.56 (C-4′a), 150.17 (CH-2,6-Py), 151.29 (C-3′), 151.51 (C-4), 152.35 (CH-2), 153.41 (C-1′), 157.02 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2983, 2949, 1594, 1580, 1496, 1441, 1332, 1326, 1086, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 413 (38) [M + H]$^+$, 356 (31), 329 (100). HRMS (FAB): calcd. for $C_{24}H_{25}N_6O$ [M + H]$^+$ 413.2090; found 413.2084.

6-(3-Methyl-5,6,7,8-tetrahydroisoquinolin-1-yl)-9-(tetrahydropyran-2-yl)-9*H*-purine (4bh) (Method C2): Column chromatography on silica gel (EtOAc/MeOH/$CHCl_3$, 20:2:1) afforded a yellowish oil, which after co-evaporation with $CHCl_3$ formed 85 mg (61%) of a white foam. R_f (EtOAc/MeOH, 5:1) = 0.34. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65–1.88 (m, 7 H, 7′,6′-H and CH_2-THP), 2.04–2.20 (m, 3 H, CH_2-THP), 2.54 (s, 3 H, CH_3), 2.60 and 2.66 (2 dt, J_{gem} = 17.1, $J_{8',7'}$ = 6.3 Hz, 2 H, 8′-H), 2.81 (td, $J_{5',6'}$ = 6.3, $J_{5',4'}$ = 0.8 Hz, 2 H, 5′-H), 3.82 (td, J = 11.8, 2.6 Hz, 1 H, CH_aH_bO-THP), 4.21 (ddt, J = 11.8, 4.5, 1.8 Hz, 1 H, CH_aH_bO-THP), 5.86 (dd, J = 10.3, 2.6 Hz, 1 H, CHO-THP), 6.99 (s, 1 H, 4′-H), 8.30 (s, 1 H, 8-H), 9.07 (s, 1 H, 2-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.04 and 22.70 (CH_2-6′ and CH_2-7′), 22.73 (CH_2-THP), 23.97 (CH_3), 24.84 (CH_2-THP), 25.60 (CH_2-8′), 29.23 (CH_2-5′), 31.89 (CH_2-THP), 68.86 (CH_2O-THP), 82.01 (CHO-THP), 124.38 (CH-4′), 129.17 (C-8′a), 132.22 (C-5), 142.87 (CH-8), 147.58 (C-4′a), 151.33 (C-4), 152.23 (C-1′), 152.48 (CH-2), 154.70 (C-3′), 157.60 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2982, 2948, 1594, 1579, 1497, 1441, 1331, 1326, 1086, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 350 (27) [M + H]$^+$, 266 (100). HRMS (FAB): calcd. for $C_{20}H_{24}N_5O$ [M + H]$^+$ 350.1981; found 350.1975.

General Procedure for the [$CpCo(CO)_2$]-Mediated Cyclotrimerization of Bis(purinyl)diynes 2 with Nitriles 3 Under Microwave Irradiation. Method D: Procedure with THF as Solvent (Method D1): Bis(purinyl)diyne **2** (0.4 mmol) was placed in a vial filled with argon. Then nitrile **3** (2 mmol), THF (4 mL), and the cobalt catalyst [$CpCo(CO)_2$] (52 μL, 0.4 mmol) were added to the starting material under argon. The vial was placed in the microwave reactor and irradiated for 10 min. Then the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel to give the corresponding product **5**.

Procedure with Nitrile 3 as Solvent (Method D2): Bis(purinyl)diyne **2** (0.4 mmol) was placed in a vial filled with argon. Then nitrile **3** (4 mL) and the cobalt catalyst [$CpCo(CO)_2$] (52 μL, 0.4 mmol)

were added to the starting material under argon. The vial was placed in the microwave reactor and irradiated for 10 min. Then the solvent was evaporated under reduced pressure and the residue purified by chromatography on silica gel to give the corresponding product **5**.

1,4-Bis(9-benzyl-9*H*-purin-6-yl)-3-phenyl-5,6,7,8-tetrahydroisoquinoline (5aa) (Method D2): Column chromatography on silica gel (EtOAc/MeOH/$CHCl_3$, 10:1:1) afforded a brownish oil, which after co-evaporation with $CHCl_3$ formed 78 mg (31%) of a brownish foam. R_f (EtOAc/MeOH, 5:1) = 0.59. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.70–1.80 (m, 4 H, 6′,7′-H), 2.45 and 2.80 (2 m, 2 H, 8′-H), 2.86 (m, 2 H, 5′-H), 5.40 and 5.49 (2 s, 2×2 H, CH_2-Ph), 6.96–7.03 (m, 3 H, *m*,*p*-Ph-H), 7.17 (m, 2 H, *o*-Bn-H), 7.27 (m, 2 H, *o*-Ph-H), 7.32–7.40 (m, 8 H, 2×*m*,*p*-Bn-H and *o*-Bn-H), 7.88 and 8.09 (2 s, 2×1 H, 8-H), 9.00 and 9.14 (2 s, 2×1 H, 2-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.91 and 22.99 (CH_2-6′ and CH_2-7′), 26.38 (CH_2-5′), 27.68 (CH_2-8′), 47.14 and 47.31 (CH_2-Ph), 127.10 (CH-*p*-Ph), 127.36 (CH-*o*-Ph), 127.59 and 127.98 (CH-*o*-Bn), 128.54 and 128.60 (CH-*p*-Bn), 129.10 and 129.14 (CH-*m*-Bn), 129.25 (CH-*m*-Ph), 130.30 (C-8′a), 130.97 (C-4′), 132.35 and 133.04 (C-5), 134.98 and 135.03 (C-*i*-Bn), 140.28 (C-*i*-Ph), 144.54 and 144.87 (CH-8), 146.58 (C-4′a), 151.51 and 152.35 (C-4), 152.44 and 152.50 (CH-2), 153.32 (C-1′), 154.87 (C-3′), 157.24 and 157.60 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2988, 2944, 1589, 1579, 1500, 1330 cm^{-1}. MS (FAB): *m*/*z* (%) = 626 (40) [M + H]$^+$, 91 (100). HRMS (FAB): calcd. for $C_{39}H_{32}N_9$ [M + H]$^+$ 626.2781; found 626.2764.

1,4-Bis(9-benzyl-9*H*-purin-6-yl)-3-methyl-5,6,7,8-tetrahydroisoquinoline (5ah) (Method D2): Column chromatography on silica gel (EtOAc/MeOH/$CHCl_3$, 10:1:1) afforded a brownish oil, which after co-evaporation with $CHCl_3$ formed 75 mg (33%) of a brownish foam. R_f (EtOAc/MeOH, 5:1) = 0.28. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.66–1.73 (m, 4 H, 6′,7′-H), 2.30 (s, 3 H, CH_3), 2.40 and 2.57 (2 m, 2 H, 8′-H), 2.77 (m, 2 H, 5′-H), 5.486 (d, J_{gem} = 14.9 Hz, 1 H, CH_aH_b-Ph), 5.494 (s, 2 H, CH_2-Ph), 5.51 (d, J_{gem} = 14.9 Hz, 1 H, CH_aH_b-Ph), 7.33–7.44 (m, 10 H, Ph), 8.06 and 8.09 (2 s, 2×1 H, 8-H), 9.14 and 9.15 (2 s, 2×1 H, 2-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.86 and 22.01 (CH_2-6′ and CH_2-7′), 23.03 (CH_3), 26.22 (CH_2-5′), 27.50 (CH_2-8′), 47.31 and 47.48 (CH_2-Ph), 127.96 and 128.19 (CH-*o*-Ph), 128.60 and 128.75 (CH-*p*-Ph), 129.13 and 129.23 (CH-*m*-Ph), 129.75 (C-8′a), 130.79 (C-4′), 132.13 and 132.63 (C-5), 134.80 and 135.04 (C-*i*-Ph), 144.67 and 144.85 (CH-8), 145.87 (C-4′a), 151.79 and 152.30 (C-4), 152.63 (CH-2), 152.65 (C-1′), 152.84 (CH-2), 152.92 (C-3′), 157.29 and 157.51 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2990, 2944, 1588, 1579, 1500, 1329 cm^{-1}. MS (FAB): *m*/*z* (%) = 564 (100) [M + H]$^+$, 91 (58). HRMS (FAB): calcd. for $C_{34}H_{30}N_9$ [M + H]$^+$ 564.2624; found 564.2618.

1,4-Bis[9-(tetrahydropyran-2-yl)-9*H*-purin-6-yl]-3-phenyl-5,6,7,8-tetrahydroisoquinoline (5ba) (Method D2): Column chromatography on silica gel (EtOAc/acetone/$CHCl_3$, 10:1:1) afforded 104 mg (42%) of a yellowish foam (mixture of four diastereoisomers). R_f (EtOAc/acetone, 5:2) = 0.18. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.64–1.94 (m, 40 H, 7′,6′-H and CH_2-THP), 2.02–2.20 (m, 24 H, CH_2-THP), 2.38–2.48 and 2.59–2.70 (2 m, 8 H, 8′-H), 2.77–2.91 (m, 8 H, 5′-H), 3.76–3.86 (m, 4 H, CH_aH_bO-THP), 4.15–4.23 (m, 4 H, CH_aH_bO-THP), 5.75–5.81 and 5.86–5.89 (2 m, 4 H, CHO-THP), 6.98–7.04 (m, 12 H, *m*,*p*-Ph-H), 7.28–7.31 (m, 8 H, *o*-Ph-H), 8.167, 8.176, 8.184, 8.195, 8.341, 8.345 and 8.346 (7s, 8 H, 8-H), 8.94, 8.959, 8.960, 8.976, 9.106, 9.107, and 9.109 (7s, 8 H, 2-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.85, 21.89, and 21.94 (CH_2-6′ and CH_2-7′), 22.71, 22.76, 24.79, and 24.85 (CH_2-THP), 26.33 (CH_2-5′), 27.64 (CH_2-8′), 31.32, 31.33, 31.74, 31.76, and 31.83 (CH_2-THP), 68.81 and 68.84 (CH_2O-THP), 81.62, 81.93, and 82.07 (CHO-THP), 127.15, 127.27, 127.43, 127.53, and 127.54 (CH-*m*,*p*-Ph), 129.23, 129.26, 129.28, and 129.31 (CH-*o*-Ph), 130.23, 130.25, and 130.27 (C-4′), 130.82, 130.84, 130.93, and 130.95 (C-8′a), 132.52, 133.21, 133.23, 133.28, and 133.31 (C-5), 140.17 and 140.27 (C-*i*-Ph), 142.38, 142.41, 142.54, 142.57, and 142.85 (CH-8), 146.56, 146.57, 146.69, and 146.70 (C-4′a), 150.54, 150.58, 150.67, 150.72, 151.48, 151.49, and 151.52 (C-4), 152.27, 152.33, and 152.35 (CH-2), 153.26 and 153.28 (C-1′), 154.66, 154.68, 154.80, and 154.81 (C-3′), 157.28, 157.30, 157.31, 157.62, 157.67, and 157.68 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2979, 2950, 2931, 1590, 1581, 1497, 1406, 1332, 1326, 1207, 1085, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 614 (23) [M + H]$^+$, 530 (15), 446 (36), 57 (100). HRMS (FAB): calcd. for $C_{35}H_{36}N_9O_2$ [M + H]$^+$ 614.2992; found 614.2999.

1,4-Bis[9-(tetrahydropyran-2-yl)-9*H*-purin-6-yl]-3-[4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinoline (5bd) (Method D1): Column chromatography on silica gel (EtOAc/acetone/$CHCl_3$, 10:1:1) afforded 76 mg (28%) of a yellowish foam (mixture of four diastereoisomers). R_f (EtOAc/acetone, 5:2) = 0.31. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.65–1.88 (m, 40 H, 7′,6′-H and CH_2-THP), 2.02–2.23 (m, 24 H, CH_2-THP), 2.40–2.50 and 2.60–2.74 (2 m, 8 H, 8′-H), 2.79–2.93 (m, 8 H, 5′-H), 3.77–3.86 (m, 4 H, CH_aH_bO-THP), 4.15–4.24 (m, 4 H, CH_aH_bO-THP), 5.77–5.82 and 5.86–5.90 (2 m, 4 H, CHO-THP), 7.26–7.31 (m, 8 H, *m*-$C_6H_4CF_3$-H), 7.41–7.46 (m, 8 H, *o*-$C_6H_4CF_3$-H), 8.17, 8.19, 8.20, 8.21, 8.349, 8.353, and 8.355 (7s, 8 H, 8-H), 8.95, 8.97, 8.98, 8.99, 9.110, 9.111, and 9.114 (7s, 8 H, 2-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.77, 21.81, and 21.87 (CH_2-6′ and CH_2-7′), 22.69, 22.74, 22.76, 24.78, and 24.85 (CH_2-THP), 26.38, 26.40, and 26.42 (CH_2-5′), 27.66 and 27.67 (CH_2-8′), 31.33, 31.34, 31.71, 31.74, and 31.84 (CH_2-THP), 68.80, 68.81, 68.83, 68.84, and 68.87 (CH_2O-THP), 81.68, 81.69, 81.98, and 82.16 (CHO-THP), 124.08 (q, $J_{C,F}$ = 272 Hz, CF_3), 124.40, 124.42, 124.57, and 124.58 (q, $J_{C,F}$ = 4 Hz, CH-*m*-$C_6H_4CF_3$), 129.11 and 129.23 (q, $J_{C,F}$ = 32 Hz, C-*p*-$C_6H_4CF_3$), 129.60, 129.62, 129.65, and 129.68 (CH-*o*-$C_6H_4CF_3$), 130.38, 130.39, and 130.41 (C-4′), 131.72, 131.74, 131.85, and 131.89 (C-8′a), 132.47, 132.48, 133.12, 133.18, 133.21, and 133.27 (C-5), 142.64, 142.66, 142.88, 142.89, and 143.01 (CH-8), 143.77 and 143.86 (C-*i*-$C_6H_4CF_3$), 147.01, 147.02, 147.15, and 147.16 (C-4′a), 150.68, 150.73, 150.79, 150.83, 151.54, 151.55, and 151.58 (C-4), 152.36, 152.40, and 152.43 (CH-2), 153.23, 153.25, 153.32, and 153.33 (C-3′), 153.50 and 153.54 (C-1′), 156.88, 156.89, 156.90, 156.92, 156.93, 156.94, and 156.95 (C-6) ppm. ^{19}F NMR (470.3 MHz, $CDCl_3$): δ = –63.17, –63.16 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2983, 2950, 1590, 1580, 1497, 1408, 1325, 1168, 1129, 1086, 1066, 1045 cm^{-1}. MS (FAB): *m*/*z* (%) = 682 (27) [M + H]$^+$, 598 (28), 514 (100). HRMS (FAB): calcd. for $C_{36}H_{35}N_9O_2F_2$ [M + H]$^+$ 682.2866; found 682.2863.

General Procedure for Deprotection of the 9-THP-6-pyridylpurines: A reaction mixture composed of 9-THP-6-pyridylpurine **4by** (0.5 mmol) and Dowex D-50 (100 mg) in EtOH (10 mL) was heated at reflux for 1 h or until the starting material had been consumed (followed by TLC). The reaction mixture was filtered through a frit and the residue was washed with hot EtOH (3×10 mL). Finally, the combined organic fractions were concentrated under reduced pressure.

6-(3-Phenyl-5,6,7,8-tetrahydroisoquinolin-1-yl)-9*H*-purine (6a): The deprotection of **4ba** (218 mg, 0.53 mmol) afforded 121 mg (70%) of the title compound as a white solid. Recrystallization from EtOH/toluene gave white crystals, m.p. 239–240 °C (EtOH/toluene). ^{1}H NMR (500 MHz, [D$_6$]DMSO + DCl): δ = 1.71 (m, 2 H, 6′-H), 1.80

(m, 2 H, 7′-H), 2.87 (t, J_{vic} = 6.2 Hz, 2 H, 8′-H), 3.00 (t, J_{vic} = 6.2 Hz, 2 H, 5′-H), 7.44–7.52 (m, 3 H, *m*,*p*-Ph-H), 8.05 (s, 1 H, 4′-H), 8.09 (m, 2 H, *o*-Ph-H), 9.31 (s, 1 H, 2-H), 9.40 (s, 1 H, 8-H) ppm. ^{13}C NMR (125.7 MHz, [D$_6$]DMSO + DCl): δ = 21.65 (CH_2-7′), 22.20 (CH_2-6′), 25.83 (CH_2-8′), 29.59 (CH_2-5′), 123.86 (CH-4′), 126.24 (C-5), 127.60 (CH-*o*-Ph), 129.23 (CH-*m*-Ph), 130.15 (CH-*p*-Ph), 133.63 (C-8′a), 136.75 (C-*i*-Ph), 148.02 (C-1′), 148.53 (CH-8), 149.98 (C-4), 151.19 (CH-2), 152.04 (C-4′a), 152.62 (C-3′), 154.95 (C-6) ppm. IR (KBr): $\tilde{\nu}$ = 2940, 2918, 1601, 1588, 1583, 1562, 1547, 1482, 1465, 1435, 1427, 1397, 1384, 1322, 1266, 1250, 1230, 1125 cm^{-1}. MS (FAB): *m*/*z* (%) = 328 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{20}H_{18}N_5$ [M + H]$^+$ 328.1562; found 328.1563.

6-{3-[4-(Trifluoromethyl)phenyl]-5,6,7,8-tetrahydroisoquinolin-1-yl}-9*H*-purine (6d): The deprotection of **4bd** (240 mg, 0.5 mmol) afforded 133 mg (67%) of the title compound as a white solid. Recrystallization from EtOH/toluene gave white crystals, m.p. 208–210 °C (EtOH/toluene). ^{1}H NMR (600 MHz, [D$_6$]DMSO + DCl): δ = 1.67 (m, 2 H, 6′-H), 1.76 (m, 2 H, 7′-H), 2.87 (t, J_{vic} = 6.3 Hz, 2 H, 8′-H), 2.95 (t, J_{vic} = 6.3 Hz, 2 H, 5′-H), 7.79 (m, 2 H, *m*-$C_6H_4CF_3$-H), 8.07 (s, 1 H, 4′-H), 8.30 (m, 2 H, *o*-$C_6H_4CF_3$-H), 9.33 (s, 1 H, 2-H), 9.55 (s, 1 H, 8-H) ppm. ^{13}C NMR (151 MHz, [D$_6$]DMSO + DCl): δ = 21.94 (CH_2-7′), 22.50 (CH_2-6′), 26.24 (CH_2-8′), 29.70 (CH_2-5′), 124.40 (CH-4′), 124.93 (q, $J_{C,F}$ = 272 Hz, CF_3), 125.60 (C-5), 126.26 (q, $J_{C,F}$ = 3 Hz, CH-*m*-$C_6H_4CF_3$), 128.43 (CH-*o*-$C_6H_4CF_3$), 130.03 (q, $J_{C,F}$ = 32 Hz, C-*p*-$C_6H_4CF_3$), 134.76 (C-8′a), 141.84 (C-*i*-$C_6H_4CF_3$), 148.74 (C-1′), 148.80 (CH-8), 150.72 (C-4), 151.31 (C-4′a), 151.33 (CH-2), 151.95 (C-3′), 154.63 (C-6) ppm. ^{19}F NMR (470.3 MHz, [D$_6$]DMSO + DCl): δ = –61.55 ppm. IR (KBr): $\tilde{\nu}$ = 2936, 1613, 1591, 1562, 1476, 1427, 1379, 1335, 1326, 1163, 1127, 1108, 1070 cm^{-1}. MS (FAB): *m*/*z* (%) = 396 (100) [M + H]$^+$. HRMS (FAB): calcd. for $C_{21}H_{17}N_5F_3$ [M + H]$^+$ 396.1436; found 396.1420.

Supporting Information (see also the footnote on the first page of this article): Details of all experimental procedures for the cyclotrimerization reactions, X-ray data, and spectral characteristics of the prepared compounds.

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