Synthesis of 2-oxopurine adducts with structural resemblance to Efavirenz and DPC 961 as potential NNRT-inhibitors

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Dedicated to Professor Kjell Undheim on the Occasion of his 70th. birthday

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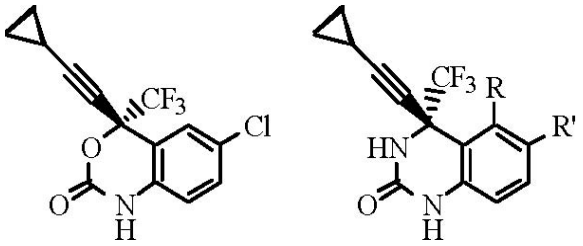
Abstract

6-Cyclopropylethynyl-6-trifluoromethyl dihydro-2-oxopurines have been prepared with completely regioselective addition of trimethyl(trifluoromethyl)silane and cyclopropylethynylmagnesium bromide to 1,9-dialkylated 2-oxopurines as key-steps. The target compounds are structurally related to the Non-Nucleoside reverse transcriptase inhibitors Efavirenz and DPC 961.

Keywords: 2-Oxopurines, regioselective addition, non-nucleoside reverse transcriptase inhibitors, Efavirenz, DPC 961

Introduction

Non-nucleoside reverse transcriptase inhibitors (NNRTI) are of increasing importance for the treatment of AIDS (acquired immune deficiency syndrome).[1] One of the NNRTIs approved as anti-HIV drug by the FDA is Efavirenz (Sustiva™) (Fig. 1). Several benzopyrimidinone adducts[2] including the second generation Efavirenz analogs DPC 961 and DPC 963[3] (Fig 1) also inhibit reverse transcriptase. DPC 961 exhibits increased potency and favourable plasma serum protein binding compared to Efavirenz. We have previously prepared 6-substituted adducts of 2-oxopurines[4] and as a continuance of this work we now report the synthesis of 6,6-disubstituted 2-oxopurine adducts with structural resemblance to Efavirenz, DPC 961 and DPC 963.



Efavirenz DPC 961: R=H, R'=Cl

DPC 963: R=R'=F

Figure 1

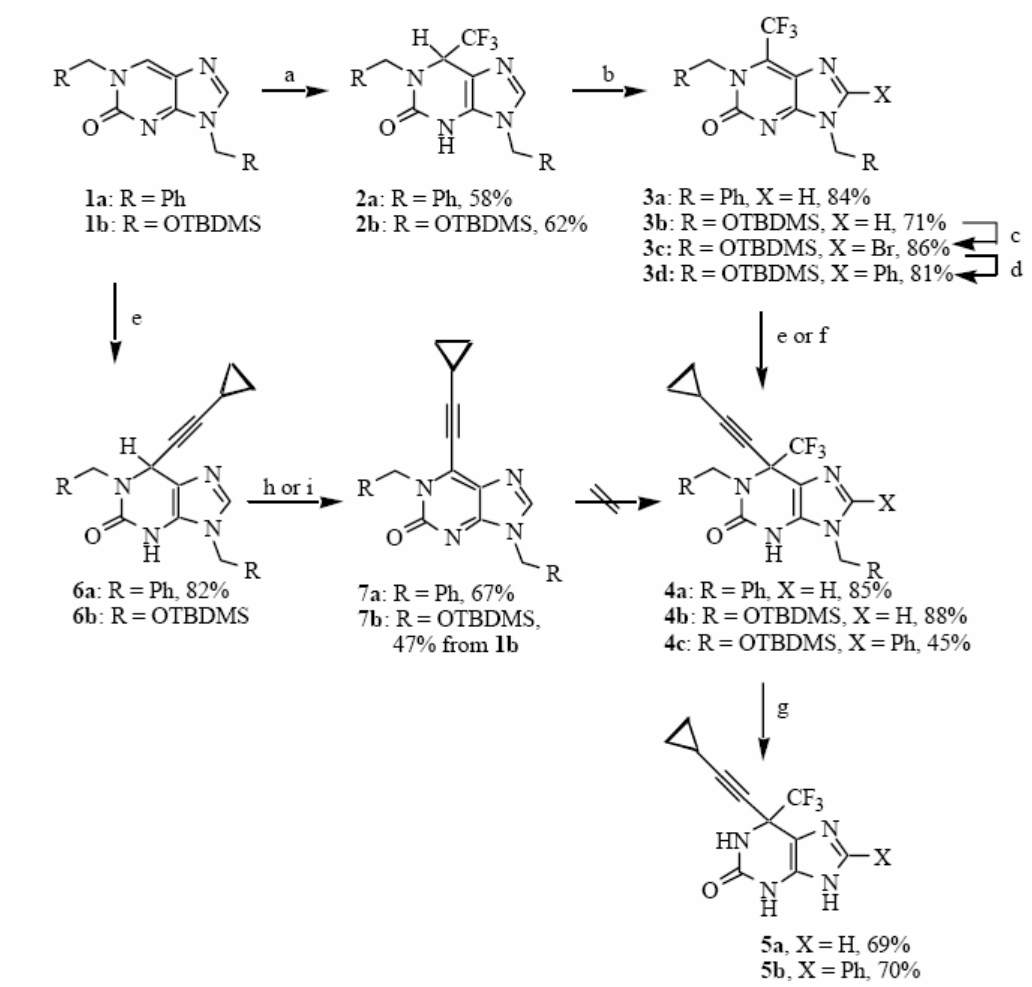
Results and Discussion

The synthesis of the target 2-oxopurines is outlined in Scheme 1. The 1,9-dialkylated 2-oxopurines 1 were prepared as previously reported[4,5] and reacted with trimethyl(trifluoromethyl)silane ($TMSCF_3$). Reactions of $TMSCF_3$ with carbonyl compounds are often performed in the presence of tetrabutylammonium fluoride (TBAF),[6] but attempts to employ a fluoride source (TBAF, Me_4NF or KF) in the addition to the purine 1a met with little success. Furthermore, fluoride ions would have been incompatible with the silicon based *N*-protecting groups in compound 1b. Potassium carbonate is known to catalyze the reaction between trifluoromethylsilanes and quinones,[7] and in the presence of K_2CO_3, the silane reacted with the 2-oxopurines in the 6-position exclusively to give compounds **2a** and **2b** in 58 and 62% yields respectively. The regiochemistry of compounds **2** as well as compound **4** below were established by HMQC and HMBC NMR spectroscopy.[4] After purification, adducts **2** were easily rearomatized with MnO2 to give compounds **6**. The use of DDQ in these oxidations resulted in complex mixtures and oxidation of crude **2** with MnO_2 was also less successful. The alkynyl substituent in compounds **4a** and **4b** were introduced when the purines **3a** or **3b** were reacted with cyclopropylethynylmagnesium bromide (generated *in situ* from cyclopropylethyne[8] and ethylmagnesium bromide). Again complete regioselectivity in the addition was observed.

Even though both addition reactions took place in the purine 6-position, a carbon substituent can also easily be introduced in the 8-position as demonstrated in the synthesis of the 8-phenylpurine **4c**. Bromination of the trifluoro compound **3b** gave the 8bromopurine **3c** which easily reacted with phenylboronic acid in a Suzuki type coupling.[9,10] The 8-substituted 2-oxopurine **3d** did not add cyclopropylethynylmagnesium bromide as described for compound **3a** and **3b** above, but the reaction with the corresponding organolithium reagent gave the desired adduct **4c** in 45% yields. No regioisomers were detected in the reaction mixture. Finally the silicon based protecting groups in compounds **4b** and **4c** were removed with Me_4NF to give the DPC 961 analogs **5**.

Reverse introduction of the purine 6-substituents was also attempted. Compounds **7** were readily available from addition of the ethynylmagnesium bromide reagent followed by oxidation,

but reaction of the alkynylpurines **7** with $TMSCF_3$ resulted only in complex mixtures.



Scheme 1. (a) $TMSCF_3$, K_2CO_3, DMF, 0 ^oC; (b) MnO_2, PhH; (c) Br_2, AcONa, AcOH; (d) $PhB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, PhMe, 90 ^oC; (e) cyclopropylCCMgBr, THF, –78 ^oC; (f) cyclopropylCCLi, THF, –78 ^oC; (g) Me_4NF, MeCN; (h) MnO_2 CH_2Cl_2; (i) DDQ, PhH.

Experimental Section

General Procedures. The ^{1}H-NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument. The ^{1}H decoupled ^{13}C-NMR spectra were recorded at 125, 75 or 50 MHz using the above mentioned spectrometers. ^{19}F-NMR spectra were recorded at 188 MHz at the Bruker Avance DPX 200 instrument. *J* values are given in Hz. ^{1}H- and ^{13}C-NMR spectra were referenced to the solvent and ^{19}F-NMR spectra were referenced to fluorotrichloromethane (freon 11). Mass spectra under electron impact conditions (EI) were

recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m*/*z* (% rel. int.). Methane was used for chemical ionisation (CI). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). Analytical thin layer chromatography was performed with E. Merck silica gel $60F_{254}$ 0.25 mm plates (Merck No. 1.05554).

Materials. THF was distilled from sodium-benzophenone, and DMF from BaO. Benzene and toluene were dried over a sodium-wire. CH_2Cl_2 was predried with $CaCl_2$, distilled from CaH_2 and stored over 4 Å molsieve. MeCN was distilled from CaH_2 and stored over 4 Å molsieve. Tetramethylammonium fluoride tetrahydrate was dried by azeotropic distillation with abs. EtOH and the residue was dissolved in dry MeCN. 1,9-dibenzyl-1,9-dihydro-2*H*-purin-2-one 1a,[4] 1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-2*H*-purin-2-one 1b[5] and cyclopropylethyne[8] were prepared according to literature procedures.

All other reagents were commercially available and used as received. Solvent mixtures are defined as volume ratios (v/v).

1,9-Dibenzyl-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (2a). To a mixture of 1,9-dibenzyl-1,9-dihydro-2*H*-purin-2-one (479 mg, 1.5 mmol) and K_2CO_3 (1.05 g, 7.5 mmol) in dry DMF (50 mL) under N_2 at 0 °C was added dropwise $TMSCF_3$ (3.8 mL, 7.5 mmol, 2 M solution in THF). The mixture was stirred for 17 h while slowly reaching ambient temperature and diluted with saturated aqueous ammonium chloride (50 mL) and EtOAc (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with saturated aqueous sodium chloride (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) to give the title compound (340 mg, 58%) as a colorless oil; ^{1}H-NMR (200 MHz; $CDCl_3$) δ 10.28 (1H, s, NH), 7.3-7.1 (10H, m, Ph), 7.11 (1H, s, 8-H), 5.45 [1H, d, *J* 15.4, HB in N(1)CH_2], 5.03 [2H, s, N(9)CH_2], 4.91 (1H, q, *J* 5.8, 6-H), 4.16 [1H, d, *J* 15.4, H_A in N(1)CH_2]; ^{19}FNMR (188 MHz; $CDCl_3$) δ –75.41 (d, *J* 5.7, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ 154.7 (2-C), 135.6 (C in Ph), 134.9 (C in Ph), 133.0 (8-C), 129.6 (4-C), 129.0 (CH in Ph), 128.8 (CH in Ph), 128.8 (CH in Ph), 128.3 (CH in Ph), 127.9 (CH in Ph), 127.7 (CH in Ph), 127.2 (CH in Ph), 126.4 (q, *J* 285.3, CF_3), 108.5 (5-C), 57.0 (q, *J* 31.9, 6-C), 50.3 [N(1)CH_2], 47.7 [N(9)CH_2]; MS (EI) *m/z*: 386 (M^+, 11%), 318 (13), 317 (59), 150 (6), 132 (6), 104 (6), 99 (15), 92 (9), 91 (100), 65 (11); Anal. Calcd for $C_{20}H_{17}F_3N_4O$: C, 62.17; H, 4.44. Found: C, 62.25; H, 4.50.

1,9-Di[(*tert*-butyldimethylsilyloxy)methyl]-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (2b). To a mixture of 1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-2*H*-purin-2-one (348 mg, 0.82 mmol) and K_2CO_3 (565 mg, 4.1 mmol) in dry DMF (35 mL) under N_2 at 0 °C was added dropwise $TMSCF_3$ (2.05 mL, 4.1 mmol, 2 M solution in THF). The mixture was stirred for 17 h while slowly reaching ambient temperature and diluted with saturated aqueous ammonium chloride (30 mL) and EtOAc (50 mL). The phases were separated and the aqueous

phase extracted with EtOAc (2×50 mL). The combined organic phases were washed with saturated sodium chloride (30 mL), dried ($MgSO_4$ and evaporated *in vacuo*. The product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (1:2) to give the title compound (250 mg, 62%) as colorless crystals; 170–3 °C; ^{1}H-NMR (300 MHz; $CDCl_3$ δ 8.97 (1H, s, NH), 7.25 (1H, s, 8-H), 5.69 [1H, d, *J* 9.3, H_B in N(1)CH_2 5.42 [2H, s, N(9)CH_2, 5.31 (1H, q, *J* 5.9, 6H), 4.76 [1H, d, *J* 9.3, H_A in N(1)CH_2, 0.85 (9H, s, Me in *t*-Bu), 0.84 (9H, s, Me in *t*-Bu), 0.08 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.04 (3 H, s, SiMe), 0.003 (3H, s, SiMe);^{19}F-NMR (188 MHz; $CDCl_3$) δ –75.52 (d, *J* 6.6, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ153.6 (2-C), 132.3 (8-C), 128.8 (4-C), 124.4 (q, *J* 284.3, CF_3), 109.4 (5-C), 70.7 [N(1)CH_2, 68.4 [N(9)CH_2], 54.4 (q, *J* 32.4, 6-C), 25.6 (Me in *t*-Bu), 25.3 (Me in *t*-Bu), 18.0 (C in *t*-Bu), 17.8 (C in *t*-Bu), –5.2 (SiMe), –5.5 (SiMe); MS (EI) *m/z*: 494 (M^+, 3%), 438 (29), 437 (100), 305 (42), 275 (37), 193 (18), 165 (31), 89 (22), 73 (41); Anal. Calcd for $C_{20}H_{37}F_3N_{43}Si_2$ C, 48.56; H, 7.54. Found: C, 48.55; H, 7.44.

1,9-Dibenzyl-1,9-dihydro-6-trifluoromethyl-2*H*-purin-2-one (3a). To a solution of 1,9-dibenzyl-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (120 mg, 0.31 mmol) in dry benzene (30 mL) was added MnO_2 (1.2 g, 13.8 mmol). The resulting mixture was stirred at ambient temperature for 23 hours, filtered and the product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) followed by EtOAc/hexane (3:2) to give the title compound (100 mg, 84%) as colorless crystals; 122– 4 °C; ^{1}H-NMR (200 MHz; $CDCl_3$) δ 7.95 (1H, s, 8-H), 7.4-7.1 (10H, m, Ph), 5.51 [2H, s, N(1)CH_2], 5.24 [2H, s, N(9)CH_2]; ^{19}F-NMR (188 MHz; $CDCl_3$) δ –59.45 (s, CF_3); ^{13}CNMR (75 MHz; $CDCl_3$) δ 160.6 (4-C), 155.1 (2-C), 149.9 (q, *J* 2.1, 8-C) , 135.9 (q, *J* 36.1, 6-C), 135.4 (C in Ph), 134.2 (C in Ph), 129.2 (CH in Ph), 128.8 (CH in Ph), 128.5 (CH in Ph), 128.3 (CH in Ph), 127.5 (CH in Ph), 126.2 (CH in Ph), 122.8 (5-C), 119.4 (q, *J* 277.4, CF_3), 51.1 [q, *J* 3.2, N(1)CH_2], 46.7 [N(9)CH_2]; MS (EI) *m/z*: 384 (M^+, 71%), 294 (16), 293 (84), 224 (21), 91 (100), 65 (12); Anal. Calcd for $C_{20}H_{15}F_3N4O$: C, 62.50; H, 3.93. Found: C, 62.28; H, 3.88.

1,9-Dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-6-trifluoromethyl-2*H*-purin-2-one (3b). To a solution of 1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (105 mg, 0.21 mmol) in dry benzene (25 mL) was added MnO_2 (1.0 g, 11.5 mmol). The resulting mixture was stirred at ambient temperature for 24 hours, filtered and the product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (1:2) to give the title compound (74 mg, 71%) as colorless crystals; 99–102 °C; ^{1}H-NMR (200 MHz; $CDCl_3$) δ 8.06 (1H, s, 8-H), 5.74 [2H, s, N(1)CH_2], 5.54 [2H, s, N(9)CH_2], 0.87 (9H, s, Me in *t*-Bu), 0.86 (9H, s, Me in *t*-Bu), 0.15 (6H, s, 2×SiMe), 0.12 (6H, s, 2×SiMe); ^{19}F-NMR (188 MHz; $CDCl_3$) δ –58.95 (s, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ 160.4 (4-C), 154.6 (2-C), 149.7 (8-C), 135.6 (q, *J* 36.8, 6C), 125.5 (q, *J* 400.4, CF_3), 121.3 (5-C), 71.1 [q, *J* 3.3, N(1)CH_2], 66.9 [N(9)CH_2], 25.4 (Me in *t*-Bu), 18.0 (C in *t*-Bu), 17.9 (C in *t*-Bu), –5.3 (SiMe), –5.5 (SiMe); MS (EI) *m/z*: 492 (M^+, 0.3%), 435 (22), 407 (11), 406 (28), 405 (100), 99 (12), 89 (13), 73 (22); Anal. Calcd for $C_{20}H_{35}F3N4O_3Si_2$: C, 48.75; H, 7.16. Found: C, 48.47; H, 7.54.

8-Bromo-1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-6-trifluoromethyl-2*H*-purin-2-one (3c). To a solution of 1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-6-trifluoromethyl-2*H*-purin-2-one (216 mg, 0.44 mmol) in acetic acid (12 mL) and sodium acetate (1.2 g) was added Br_2 (0.050 mL, 0.97 mmol). The solution was stirred for 2 hours at room temperature before diluting with EtOAc (40 mL) and water (40 mL). The resulting mixture was stirred vigorously and aqueous $NaHSO_3$ (5 %) was added until the solution became colorless. The phases were separated and the aqueous phase extracted with EtOAc (2×40 mL). The combined organic phases were washed with saturated aqueous sodium chloride (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (1:6) to give the title compound (215 mg, 86%) as colorless crystals; mp 99-103 ^oC; ^1H-NMR (300 MHz; $CDCl_3$) δ5.71 [2H, s, N(1)CH_2] 5.54 [2H, s, N(9)CH_2], 0.86 (9H, s, Me in *t*-Bu), 0.85 (9H, s, Me in *t*-Bu), 0.15 (6H, s, 2×SiMe), 0.14 (6H, s, 2×SiMe); ^{19}F-NMR (188 MHz; $CDCl_3$) δ –58.97 (s, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ161.0 (4-C), 154.3 (2-C), 139.3 (8-C), 134.3 (q, *J* 36.9, 6-C), 122.9 (5-C), 119.3 (q, *J* 277.5, CF_3), 71.2 [N(1)CH_2], 66.6 [N(9)CH_2], 25.5 (Me in *t*-Bu) ,18.1 (C in *t*-Bu), 18.0 (C in *t*-Bu), -5.2 (SiMe), -5.4 (SiMe); MS (CI) *m/z*: 573 (M+1, 100%), 572 (M^+, 29), 557 (29), 543 (27), 515 (30), 429 (27), 145 (39), 89 (26), 79 (36); Anal. Calcd for $C_{20}H_{34}BrF_3N_4O_3Si2$: C,42.02; H, 6.00. Found: C, 42.13; H, 6.13.

1,9-Dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-8-phenyl-6-trifluoromethyl-2*H*-purin-2-one (3d). A mixture of 8-bromo-1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-6-trifluoromethyl-2*H*-purin-2-one (190 mg, 0.33 mmol), phenylboronic acid (61 mg, 0.50 mmol), anhydrous K_2CO_3 (71 mg, 0.51 mmol), tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.017 mmol) and dry toluene (6 mL) was stirred under N_2 at 90 ^oC for 16 h, evaporated and chromatographed on silica gel eluting with EtOAc/hexane (1:6) to give the title compound (153 mg, 81%) as colorless crystals; mp 204-5 ^oC (CH_2Cl_2/hexane); R_F 0.24 (1:4 EtOAc/hexane); ^1H-NMR (300 MHz; $CDCl_3$) δ8.1 (2H, m, CH in Ph), 7.6-7.5 (3H, m, CH in Ph), 5.75 [2H, s, N(9)CH_2], 5.57 [2H, s, N(1)CH_2], 0.88 (9H, s, Me in *t*-Bu), 0.87 (9H, s, Me in *t*-Bu), 0.17 (12H, s, 4×SiMe); ^{19}F-NMR (188 MHz; CDCl3) δ –58.56 (s, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ162.7 (4-C), 161.0 (8-C), 154.8 (2-C), 134.0 (q, *J* 36.5, 6-C), 131.9 (C in Ph), 129.4 (CH in Ph), 128.9 (CH in Ph), 128.0 (C in Ph), 123.1 (5-C), 119.7 (q, *J* 277.4, CF_3), 71.0 [N(1)CH_2], 65.8 [N(9)CH_2], 25.5 (Me in *t*-Bu), 18.1 (C in *t*-Bu), 18.0 (C in *t*-Bu), -5.1 (SiMe), -5.4 (SiMe); MS (CI) *m/z*: 569 (M+1, 7%), 511 (100), 481 (61), 262 (4). HRMS: Found 511.1801 (M^+ -*t*-Bu), calc. for $C_{22}H_{30}F_3N_4O3Si_2$ 511.1809.

1,9-Dibenzyl-6-cyclopropylethynyl-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (4a). To a solution of 1,9-dibenzyl-1,9-dihydro-6-trifluoromethyl-2*H*-purin-2-one (90 mg, 0.23 mmol) in dry THF (4 mL) under N_2 at –78 ^oC was added cyclopropylethynylmagnesium bromide [generated *in situ* by adding cyclopropylethyne (140 mg, 1.27 mmol, 60 % solution in cyclohexane) in dry THF (1 mL) to a solution of ethylmagnesium bromide (1.1 mL, 1.15 mmol, 1.0 M solution in THF) in dry THF (2 mL) under N_2 and refluxing the resulting mixture for 2 hours before cooling to ambient temperature]. After stirring for 30 minutes at –78 ^oC and 30

minutes at ambient temperature, saturated aqueous ammonium chloride (10 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with EtOAc/hexane (1:1) gave the title compound (89 mg, 85%) as colorless crystals; 212–3 °C; ^{1}H-NMR (500 MHz; $CDCl_3$) δ10.64 (1H, s, NH), 7.3-7.0 (11H, m, CH in Ph and 8-H), 4.82 [1H, d, *J* 16.1, HB in N(1)CH_2], 4.78 [1H, d, *J* 16.1, H_A in N(1)CH_2], 4.68 [1H, d, *J* 15.4, H_B in N(9)CH_2], 4.64 [1H, d, *J* 15.4, H_A in N(9)CH_2], 1.20 (1H, m, CH in cyclopropyl), 0.63 (2H, m, CH_2 in cyclopropyl), 0.43 (2 H, m, CH_2 in cyclopropyl), ^{19}F-NMR (188 MHz; $CDCl_3$) δ –79.44 (s, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ 153.7 (2-C); 138.5 (C in Ph), 134.6 (C in Ph), 132.7 (8-C), 128.9 (CH in Ph or 4-C), 126.1 (CH in Ph or 4-C), 123.9 (q, *J* 288.7, CF_3), 110.3 (5-C), 93.5 (≡*C*-cyclopropyl), 66.2 (Pur-*C*≡), 62.9 (q, *J* 32.3, 6-C), 49.6 [N(1)CH_2], 47.6 [N(9)CH_2], 8.2 (CH_2 in cyclopropyl), 8.1 (CH_2 in cyclopropyl), –0.6 (CH in cyclopropyl); MS (EI) *m/z*: 450 (M^+, 2%), 381 (100), 210 (43), 193 (58), 165 (47), 147 (59), 120 (47), 93 (51), 91 (100), 81 (48); Anal. Calcd for $C_{25}H_{21}F_3N_4O$: C, 66.66; H, 4.70. Found: C, 66.32; H, 4.85.

6-Cyclopropylethynyl-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (4b). To a solution of 1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-6-trifluoromethyl-2*H*-purin-2-one (114 mg, 0.23 mmol) in dry THF (4 mL) under N_2 at –78 °C was added cyclopropylethynylmagnesium bromide [generated *in situ* by adding cyclopropylethyne (140 mg, 1.27 mmol, 60 % solution in cyclohexane) in dry THF (1 mL) to a solution of ethylmagnesium bromide (1.1 mL, 1.15 mmol, 1.0 M solution in THF) in dry THF (2 mL) under N_2 and refluxing the resulting mixture for 2 hours before cooling to ambient temperature]. After 30 minutes at –78 °C and 30 minutes at ambient temperature, saturated aqueous ammonium chloride (10 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with EtOAc/hexane (1:2) gave the title compound (114 mg, 88%) as colorless crystals; 166–9 °C; ^{1}H-NMR (500 MHz; $CDCl_3$) δ8.12 (1H, s, NH), 7.20 (1H, s, 8-H), 5.42 [1H, d, *J* 9.6, H_B in N(1)CH_2], 5.39 [2H, s, N(9)CH_2], 5.20 [1H, d, *J* 9.6, H_A in N(1)CH_2], 1.36 (1H, m, CH in cyclopropyl), 0.83-0.38 (22H, m, 2×CH_2 in cyclopropyl and Me in *t*-Bu), 0.12 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.06 (3H, s, SiMe), 0.02 (3H, s, SiMe); ^{19}F-NMR (188 MHz; $CDCl_3$) δ –80.12 (s, CF_3); ^{13}C-NMR (75 MHz; $CDCl_3$) δ 152.8 (2-C), 131.9 (8-C), 127.8 (4-C), 123.7 (q, *J* 287.6, CF_3), 111.4 (5-C), 93.3 (≡*C*-cyclopropyl), 70.0 [N(1)CH_2], 68.6 [N(9)CH_2], 65.9 (Pur-*C*≡), 61.9 (q, *J* 32.9, 6-C), 25.7 (Me in *t*-Bu), 25.3 (Me in *t*-Bu), 18.2 (C in *t*-Bu), 17.8 (C in *t*-Bu), 8.5 (2×CH2 in cyclopropyl), –0.4 (CH in cyclopropyl), –5.2 (SiMe), –5.5 (SiMe); MS (EI) *m/z*: 558 (M^+, 1%), 501 (30), 225 (30), 75 (100), 73 (42); Anal. Calcd for $C_{25}H_{41}F_3N_4O_3Si_2$: C, 53.73; H, 7.40. Found: C, 53.49; H, 7.54.

6-Cyclopropylethynyl-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-8-phenyl-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (4c). To a solution of 1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-8-phenyl-6-trifluoromethyl-2*H*-purin-2-one (120 mg, 0.21 mmol)

in dry THF (2 mL) under N_2 at -78 ^oC was added cyclopropylethynyllithium [generated *in situ* by adding *n*-butyllithium (0.54 mL, 0.84 mmol, 1.6 M solution in cyclohexane) to cyclopropylethyne (90 mg, 1.05 mmol, 80 % solution in cyclohexane) in dry THF (2 mL) under N_2 at 0 ^oC and stirring for 30 min at 0 ^oC and 1 h at ambient temperature]. After 30 minutes at -78 ^oC and 30 minutes at ambient temperature saturated aqueous ammonium chloride (10 mL) and CH_2Cl_2 (15 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL) and the combined organic phases dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with EtOAc/hexane (1:4) gave the title compound (61 mg, 45%) as a colorless oil; R_F 0.12 (1:5 EtOAc/hexane); 8.58 (1H, s, N-H), 7.6 (2H, m, CH in Ph), 7.4-7.3 (3H, m, CH in Ph), 5.45 [1H, d, *J* 9.6, H_B in N(1)CH_2], 5.43 [2 H, s, N(9)CH_2], 5.24 [1H, d, *J* 9.6, HA in N(1)CH_2], 1.36 (1H, m, CH in cyclopropyl), 0.88 (9H, s, Me in *t*-Bu), 0.81 (13H, m, 2×CH_2 in cyclopropyl and Me in *t*-Bu), 0.13 (3H, s, SiMe), 0.090 (3H, s, SiMe), -0.068 (3H, s, SiMe), -0.076 (3H, s, SiMe); ^{19}F-NMR (188 MHz; $CDCl_3$) δ –79.74 (s, CF_3); ^{13}C-NMR (125 MHz; $CDCl_3$) δ 151.9 (2-C), 143.5 (8-C), 129.5 (C in Ph), 129.2 (CH in Ph), 129.1 (4-C), 129.0 (CH in Ph), 128.6 (C in Ph), 123.7 (q, *J* 287.4, CF_3), 111.3 (5-C), 93.3 (≡*C*-cyclopropyl), 70.1 [N(1)CH_2], 68.4 [N(9)CH_2], 66.1 (Pur-*C*≡), 62.0 (q, *J* 32.8, C-6), 25.8 (Me in *t*-Bu), 25.4 (Me in *t*-Bu), 18.3 (C in *t*-Bu) ,17.8 (C in *t*-Bu), 8.5 (2×CH_2 in cyclopropyl), -0.2 (CH in cyclopropyl), -5.1 (SiMe), -5.5 (SiMe), -5.6 (SiMe); MS (EI) *m/z*: 635 (M^+, 1%), 577 (34), 566 (44), 565 (98), 480 (33), 89 (51), 75 (45), 73 (100); HRMS: Found 634.3012, calc. for $C_{31}H_{45}F_3N_4O_3Si_2$ 634.2982.

6-Cyclopropylethynyl-1,3,6,7-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (5a). To a solution of 6-cyclopropylethynyl-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-1,3,6,9-tetrahydro-6-trifluoro-methyl-2*H*-purin-2-one in dry MeCN (4 mL) was added tetramethylammonium fluoride (1.1 mL, 0.5 M solution in dry MeCN). After 22 hours at ambient temperature the solvent was evaporated *in vacuo* and the product isolated by flash chromatography on silica gel eluting with $CHCl_3$/MeOH (7:1) to give the title compound (27 mg, 69%) as colorless crystals; mp >250 ^oC (decomp.); ^{1}H-NMR (500 MHz; CD_3OD) δ 7.42 (1H, s, 8-H), 1.29 (1H, m, CH in cyclopropyl), 0.79 (2H, m, CH_2 in cyclopropyl), 0.68 (2 H, m, CH_2 in cyclopropyl), ^{19}F-NMR (188 MHz; $CDCl_3$) δ –80.34 (s, CF_3); ^{13}C-NMR (125 MHz; CD_3OD; T = 50 ^oC) δ 154.6 (2-C), 138.7 (br, 4-C), 136.2 (8-C), 124.7 (q, *J* 284.4, CF_3), 101.7 (br, 5-C), 92.7 (≡*C*-cyclopropyl), 68.8 (Pur-*C*≡), 57.6 (q, *J* 34.9, 6-C), 8.6 (2×CH_2 in cyclopropyl), –0.2 (CH in cyclopropyl); MS (EI) *m/z*: 270 (M^+, 7%), 202 (12), 201 (100), 140 (90), 135 (10); Anal. Calcd for $C_{11}H_9F_3N_4O$: C, 48.89; H, 3.36. Found: C, 48.46; H, 3.53.

6-Cyclopropylethynyl-8-phenyl-1,3,6,7-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (5b). To a solution of 6-cyclopropylethynyl-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-8-phenyl-1,3,6,9-tetrahydro-6-trifluoromethyl-2*H*-purin-2-one (47 mg, 0.074 mmol) in dry MeCN (2 mL) was added tetramethylammonium fluoride (0.6 mL, 0.5 M solution in dry MeCN, 0.3 mmol). After 20 hours at ambient temperature, tetramethylammonium fluoride (0.9 mL, 0.5 M solution in dry MeCN, 0.45 mmol) was added, and after another 20 hours the solvent was evaporated *in vacuo.* Flash chromatography on silica gel eluting with CHCl3/MeOH (100:1) followed by

$CHCl_3$/MeOH (50:1) and $CHCl_3$/MeOH (25:1) gave the title compound (18 mg, 70%) as pale yellow crystals; mp >150 °C (decomp.); RF 0.14 (25:1 $CHCl_3$/MeOH); ^{1}H-NMR (300 MHz; CD_3OD) δ 7.8-7.7 (2H, m, CH in Ph), 7.4-7.2 (3H, m, CH in Ph), 1.4-1.2 (1H, m, CH in cyclopropyl), 0.9-0.6 (4H, m, 2×CH_2 in cyclopropyl); ^{19}F-NMR (188 MHz; $CDCl_3$) δ -81.58 (s, CF_3); ^{13}C-NMR (125 MHz; CD_3OD; T = 50 °C) δ 154.5 (2-C),148.2 (8-C), 140.5 (br, 4-C), 131.1 (C in Ph), 130.1 (CH in Ph), 129.8 (CH in Ph), 126.9 (CH in Ph), 124.7 (q, *J* 284.9, CF_3), 101.5 (br, 5-C), 92.8 (≡*C*-cyclopropyl), 68.9 (Pur-*C*≡), 57.6 (br, 6-C), 8.7 (2×CH_2 in cyclopropyl), –0.2 (CH in cyclopropyl); MS (EI) *m/z*: 346 (M^+, 3%), 278 (17), 277 (100), 171 (14), 104 (10), 77 (8); HRMS: Found 346.1027, calc. for $C_{17}H_{13}F_3N_4O$ 346.1041.

6-Cyclopropylethynyl-1,9-dibenzyl-1,3,6,9-tetrahydro-2*H*-purin-2-one (6a). To a solution of 1,9-dibenzyl-1,9-dihydro-2*H*-purin-2-one (158 mg, 0.5 mmol) in dry THF (8 mL) under N_2 at –78 °C was added cyclopropylethynylmagnesium bromide [generated *in situ* by adding cyclopropylethyne (220 mg, 2.0 mmol, 60 % solution in cyclohexane) in dry THF (1 mL) to a solution of ethylmagnesium bromide (2.0 mL, 2.0 mmol, 1.0 M solution in THF) in dry THF (2 mL) under N_2 and refluxing the resulting mixture for 2 hours before cooling to ambient temperature]. After stirring for 30 minutes at –78 °C and 30 minutes at ambient temperature, saturated aqueous ammonium chloride (10 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with EtOAc/hexane (3:1) gave the title compound (157 mg, 82%) as yellow crystals; mp 120–2 °C; RF 0.18 (3:1 EtOAc/hexane); ^{1}H-NMR (300 MHz; $CDCl_3$) δ 9.78 (1H, s, NH) 7.4-7.2 (10H, m, CH in Ph), 7.10 (1H, s, 8-H), 5.29 (1H, d, *J* 1.5, 6-H), 5.25 [1H, d, *J* 15.1, HB in N(1)CH_2], 5.00 [2H, s, N(9)CH_2], 4.27 [1H, d, *J* 15.1, H_A in N(1)CH_2], 1.24 (1H, m, CH in cyclopropyl), 0.73 (2H, m, CH_2 in cyclopropyl), 0.66 (2H, m, CH_2 in cyclopropyl); ^{13}CNMR (75 MHz; $CDCl_3$) δ 153.8 (2-C), 136.5 (C in Ph), 135.3 (C in Ph), 131.9 (8-C), 128.8 (CH in Ph), 128.4 (CH in Ph), 128.1 (CH in Ph), 128.0 (CH in Ph), 127.5 (CH in Ph), 127.4 (CH in Ph), 126.4 (4-C), 112.9 (5-C), 89.0 (≡*C*-cyclopropyl), 71.8 (Pur-*C*≡), 48.9 (6-C), 48.3 [N(1)CH_2], 47.5 [N(9)CH_2], 8.3 (CH_2 in cyclopropyl), 8.2 (CH_2 in cyclopropyl), –0.5 (CH in cyclopropyl); MS (EI) *m/z*: 382 (M^+, 26%), 381 (11), 291 (43), 249 (11), 225 (14), 221 (13), 140 (69), 91 (100); HRMS: Found 382.1791, calc. for $C_{24}H_{22}N_4O$ 382.1794.

6-Cyclopropylethynyl-1,9-dibenzyl-1,9-dihydro-2*H*-purin-2-one (7a). To a solution of 6-cyclopropylethynyl-1,9-dibenzyl-1,3,6,9-tetrahydro-2*H*-purin-2-one (60 mg, 0.16 mmol) in dry CH_2Cl_2 (5 mL) was added MnO_2 (600 mg, 6.9 mmol). The resulting mixture was stirred at ambient temperature for 23 hours, filtered and the product was isolated by flash chromatography on silica gel eluting with $CHCl_3$/MeCN (3:1) to give the title compound (40 mg, 67%) as yellow crystals; mp 136–7 °C; ^{1}H-NMR (300 MHz; $CDCl_3$) δ7.71 (1H, s, 8-H), 7.2-7.4 (10H, m, CH in Ph), 5.45 [2H, s, N(1)CH_2], 5.11 [2 H, s, N(9)CH_2], 1.57 (1H, m, CH in cyclopropyl), 1.00 (2H, m, CH_2 in cyclopropyl), 0.88 (2H, m, CH_2 in cyclopropyl); ^{13}C-NMR (75 MHz; $CDCl_3$) δ 157.6 (4-C), 156.1 (2-C), 146.4 (8C), 136.0 (C in Ph), 134.7 (C in Ph), 134.4 (6-C), 129.0 (CH in Ph), 128.4 (2×CH in Ph), 128.0 (CH in Ph), 127.7 (CH in Ph), 127.6 (CH in Ph), 126.1 (5-C), 115.9

(≡*C*-cyclopropyl), 65.9 (Pur-*C*≡), 51.6 [N(1)CH_2], 46.5 [N(9)CH_2], 10.1 (2×CH_2 in cyclopropyl), 0.9 (CH in cyclopropyl); MS (EI) *m/z*: 380 (M^+, 45%), 379 (22), 289 (35), 155 (18), 91 (100), 65 (19); Anal. Calcd for $C_{24}H_{20}N_4O$: C, 75.77; H, 5.30. Found: C, 75.59; H, 5.40.

6-Cyclopropylethynyl-1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-2*H*-purin-2-one (7b). To a solution of 1,9-dihydro-1,9-di[(*tert*-butyldimethylsilyloxy)methyl]-2*H*-purin-2-one (100 mg, 0.32 mmol) in dry THF (4 mL) under N_2 at –78 °C was added dropwise a solution of cyclopropylethynylmagnesium chloride (0.48 mmol) in dry THF (4 mL) [generated *in situ* by adding cyclopropylethyne (56 mg, 0.51 mmol, 60 % solution in cyclohexane) in dry THF (2 mL) to a solution of isopropylmagnesium chloride (0.24 mL, 0.48 mmol, 2.0 M solution in THF) in dry THF (2 mL) under N_2 and refluxing the resulting mixture for 2 hours before cooling to ambient temperature]. After stirring for 1 hour at –78 °C and 20 hours at ambient temperature, saturated aqueous ammonium chloride (10 mL) and CH_2Cl_2 (20 mL) were added to the reaction mixture and the phases were separated. The organic phase was extracted with saturated sodium hydrogen carbonate (10 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product (6b) was dissolved in dry benzene (20 mL). DDQ (72 mg, 0.32 mmol) was added and the resulting mixture was stirred at ambient temperature for 3 hours, filtered and the solvent was evaporated *in vacuo*. The product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (2:1) to give the title compound (73 mg, 47%) as orange crystals; mp 140–2 °C; ^{1}H-NMR (500 MHz; $CDCl_3$) δ 8.10 (1H, s, 8-H), 5.76 [2H, s, N(1)CH_2], 5.51 [2H, s, N(9)CH_2], 1.66 (1H, m, CH in cyclopropyl), 1.04 (4H, m, 2×CH_2 in cyclopropyl), 0.86 (9H, s, Me in *t*-Bu), 0.85 (9H, s, Me in *t*-Bu), 0.12 (6H, s, 2×SiMe), 0.08 (6H, s, 2×SiMe); ^{13}C-NMR (75 MHz; $CDCl_3$) δ 157.9 (4-C), 155.3 (2-C), 146.2 (8C), 134.0 (6-C), 126.1 (5-C), 114.6 (≡*C*-cyclopropyl), 71.7 [N(1)CH_2], 66.8 [N(9)CH_2], 65.4 (Pur-*C*≡), 25.6 (Me in *t*-Bu), 25.5 (Me in *t*-Bu), 18.0 (C in *t*-Bu), 17.9 (C in *t*-Bu), 10.1 (2×CH_2 in cyclopropyl), 1.0 (CH in cyclopropyl), –5.3 (4×SiMe); MS (EI) *m/z*: 488 (M^+, 1%), 432 (34), 431 (100), 401 (79), 135 (79), 73 (37); Anal. Calcd for $C_{24}H_{40}N_4O_3Si_2$: C, 58.97; H, 8.25. Found: C, 58.70; H, 8.35.

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