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Chemistry & Drug Discovery

Supporting Information

Bisubstrate Inhibitors of the Enzyme Catechol *O*-Methyltransferase (COMT): on the Crucial Role of the Ribose Structural Unit for Inhibitor Binding Affinity

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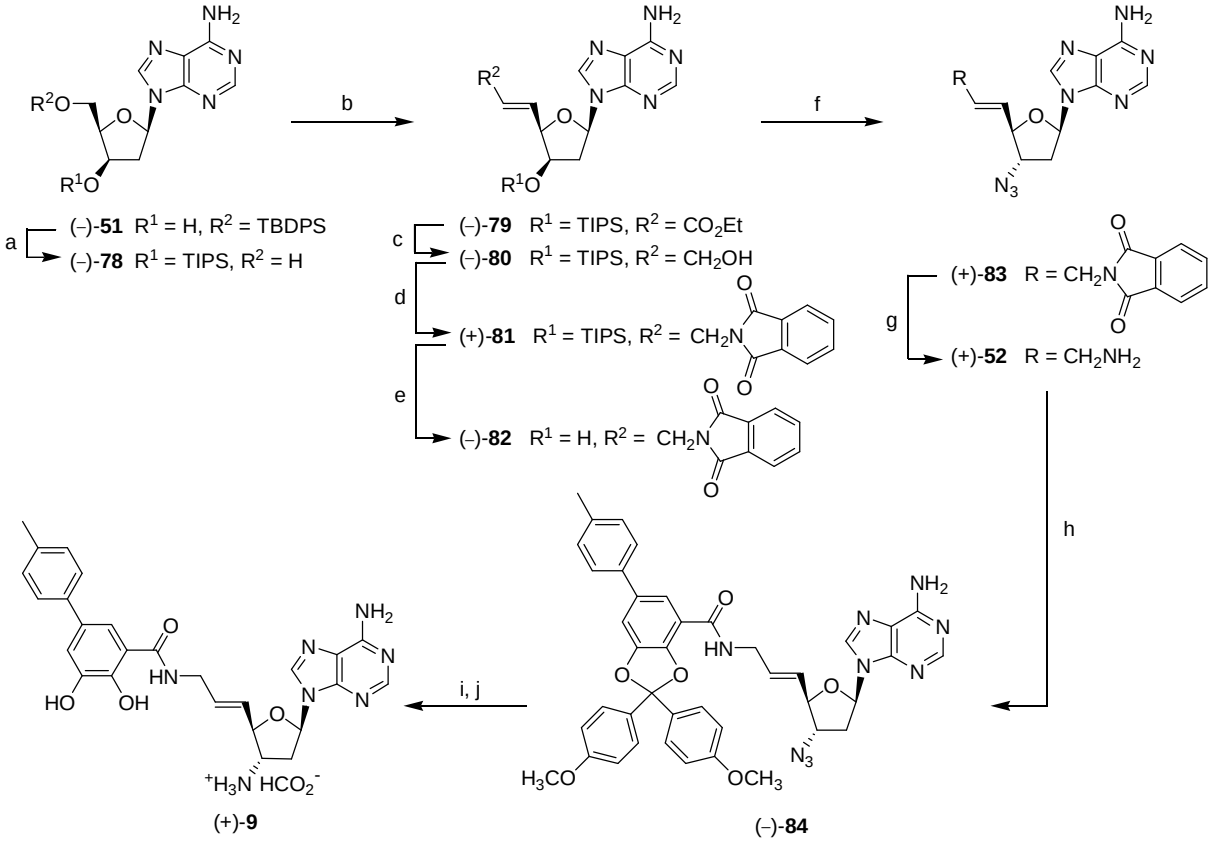
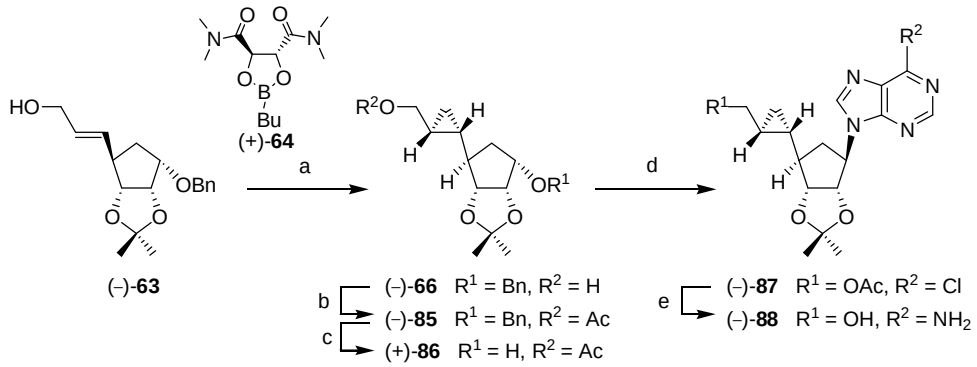
Supporting Information

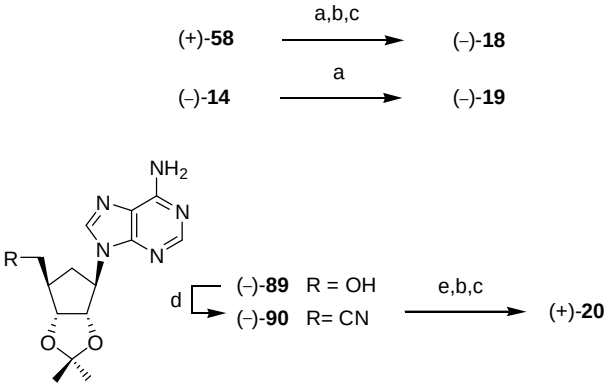
Table of Contents



Scheme 1SI Synthesis of inhibitor (+)-**9**. a) 1. TIPS-OTf, imidazole, DMF, 16 h, 20 °C; 2. NaOH, MeOH, 8 h, 20 °C, 77%; b) $Ph_3P{=}CHCO_2Et$, IBX, DMSO, 16 h, 20 °C, 96%; c) DIBAL-H, CH_2Cl_2, 3 h, -78 °C, 96%; d) PPh_3, DIAD, phthalimide, THF, 16 h, 20 °C, 85%; e) TBAF, THF, 5 min, 0 °C, 85%; f) PPh_3, DIAD, $(PhO)_2PON_3$, THF, 16 h, 20 °C, 77%; g) $MeNH_2$, EtOH, 16 h, 20 °C, 84%; h) 1. **28**, EDC·HCl, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 20 °C; 2. (+)-**52**, Et_3N, CH_2Cl_2, 16 h, 20 °C, 51%; i) 1,3-propanedithiol, Et_3N, MeOH, 16 h, 20 °C; j) TFA/H_2O 1:1, 60 min, 0 °C, 50%.



Scheme 2SI Synthesis of building block (–)-**88**. a) (+)-**64**, Et_2Zn, DME, CH_2I_2, CH_2Cl_2, 30 min, -30 °C, then 18 h, 20 °C, 97% (84% de); b) Ac_2O, pyridine, DMAP, 14 h, 20 °C, 81%; c) H_2, Pd/C, 14 h, 20 °C, 61%; d) PPh_3, DIAD, 6-chloropurine, THF, 16 h, 20 °C, then 24 h, 60 °C, 39%; e) NH_3, MeOH, 14 h, 20 °C, then 24 h, 100 °C, 71%.



Scheme 3SI. Synthesis of inhibitors (–)-**18**, (–)-**19**, and (+)-**20**. a) H_2, Pd/C, MeOH, 16 h, 20 °C, 45%; b) TFA/H_2O 1:1, 60 min, 0 °C; c) **53**, Et_3N, DMF, 16 h, 20 °C, 22-32%; d) PPh_3, DIAD, acetone cyanohydrine, THF, 16 h, 20 °C, 77%; e) H_2, PtO_2, THF/AcOH 1:2, 18 h, 20 °C; (for a published synthesis of (–)-**90**, see: S. F. Wnuk, C.-S. Yuan, T. R. Borchardt, M. J. Robins, *Nucleosides Nucleotides* **1998**, *17*, 99-114).

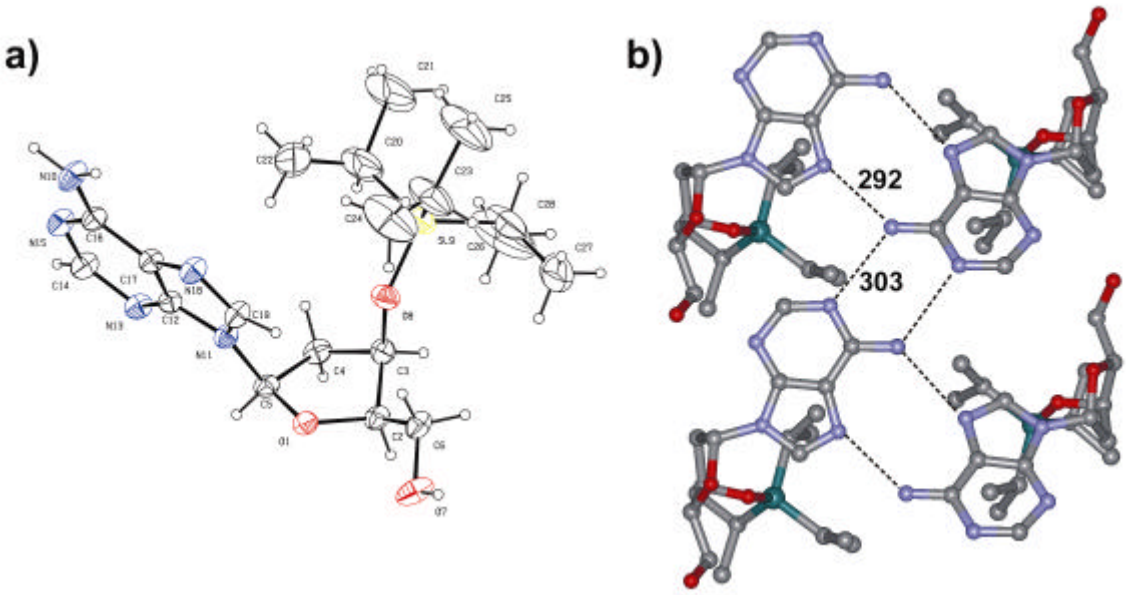


Figure 1SI X-ray crystal structure of (–)-**78**. Crystals (space group $P2_122_1$) of intermediate (–)-**78** (Scheme 1 SI) suitable for X-ray analysis were obtained by slow evaporation of a concentrated MeOH solution. a) ORTEP plot. Arbitrary numbering. Thermal ellipsoids are shown at the 50% probability level. The adenine moiety adopts the *anti* conformation with respect to the ribose (c = -162.9°). b) H-bonding network observed in the crystal packing. N···N distances are given in pm. Each adenine undergoes H-bonding interactions in both the Watson-Crick and the Hoogsteen modes with two neighboring adenines, leading to the formation of a layered, ribbon-type structure.

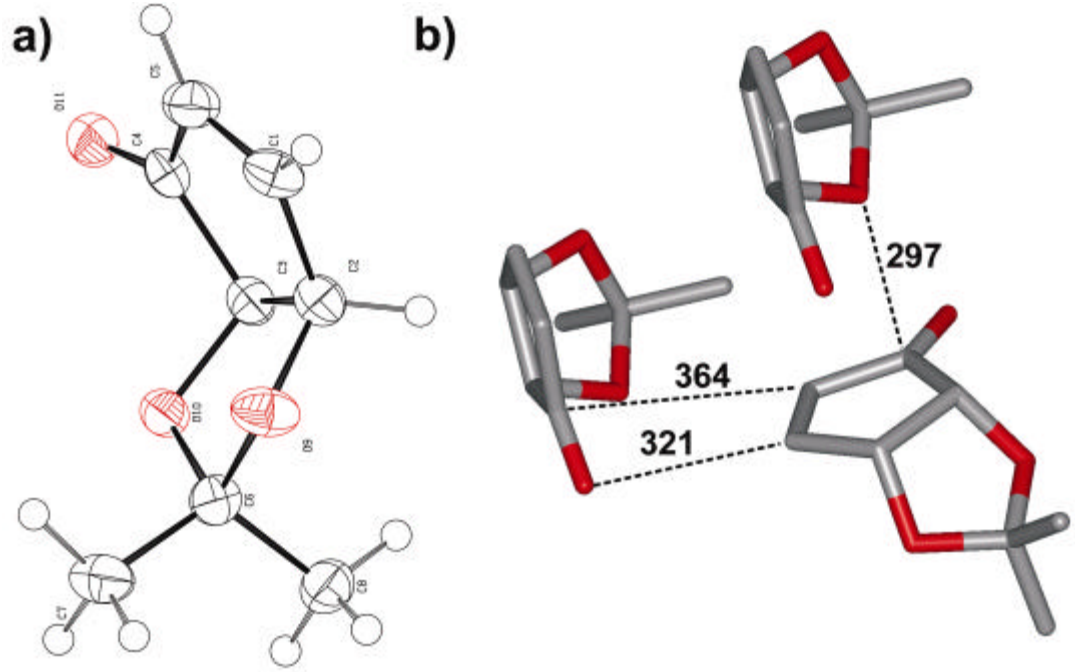


Figure 2SI. X-ray crystal structure analysis of cyclopentenone (–)-**91** (space group $P2_1$), a key intermediate in the synthetic route to (–)-**54**. a) ORTEP plot. Arbitrary numbering. Thermal ellipsoids are shown at 50% probability level. b) Dipolar interactions observed in the crystal packing. Distances are given in pm. Carbonyl and conjugated olefin units of adjacent molecules (2_1 axis) are arranged in a sheared antiparallel orientation (d(C···O) = 321 pm, d(C···C) = 364 pm), giving rise to a stabilizing dipolar interaction. In addition, a remarkable, short orthogonal dipolar contact is observed between one of the ether oxygen atoms and the carbonyl group (d(O···C) = 297 pm, angle (O-C-O) = 97°) (see: R. Paulini, K. Müller, F. Diederich, *Angew. Chem.* **2005**, *117*, 1820-1839; *Angew. Chem. Int. Ed.* **2005**, *44*, 1788-1805).

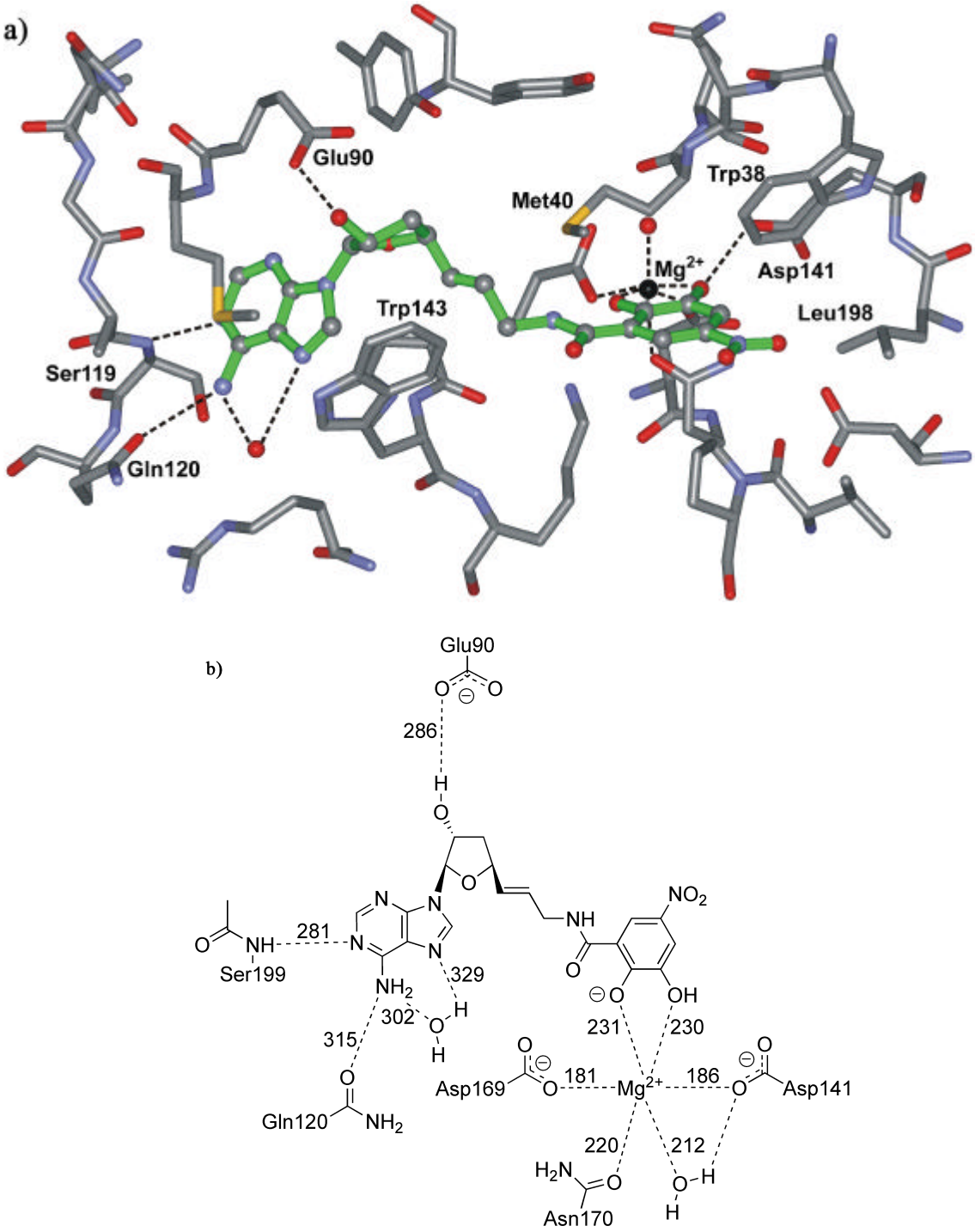


Figure 3SI Computer model (MOLOC) of inhibitor (–)-**6** in complex with COMT and a Mg^{2+} ion. a) Ball-and-stick representation and b) schematic representation of H-bonding interactions. Distances are given in pm. Color code: inhibitor skeleton: green, C-atoms: gray, O-atoms: red, N-atoms: blue, S-atoms: yellow, Mg atom: black.

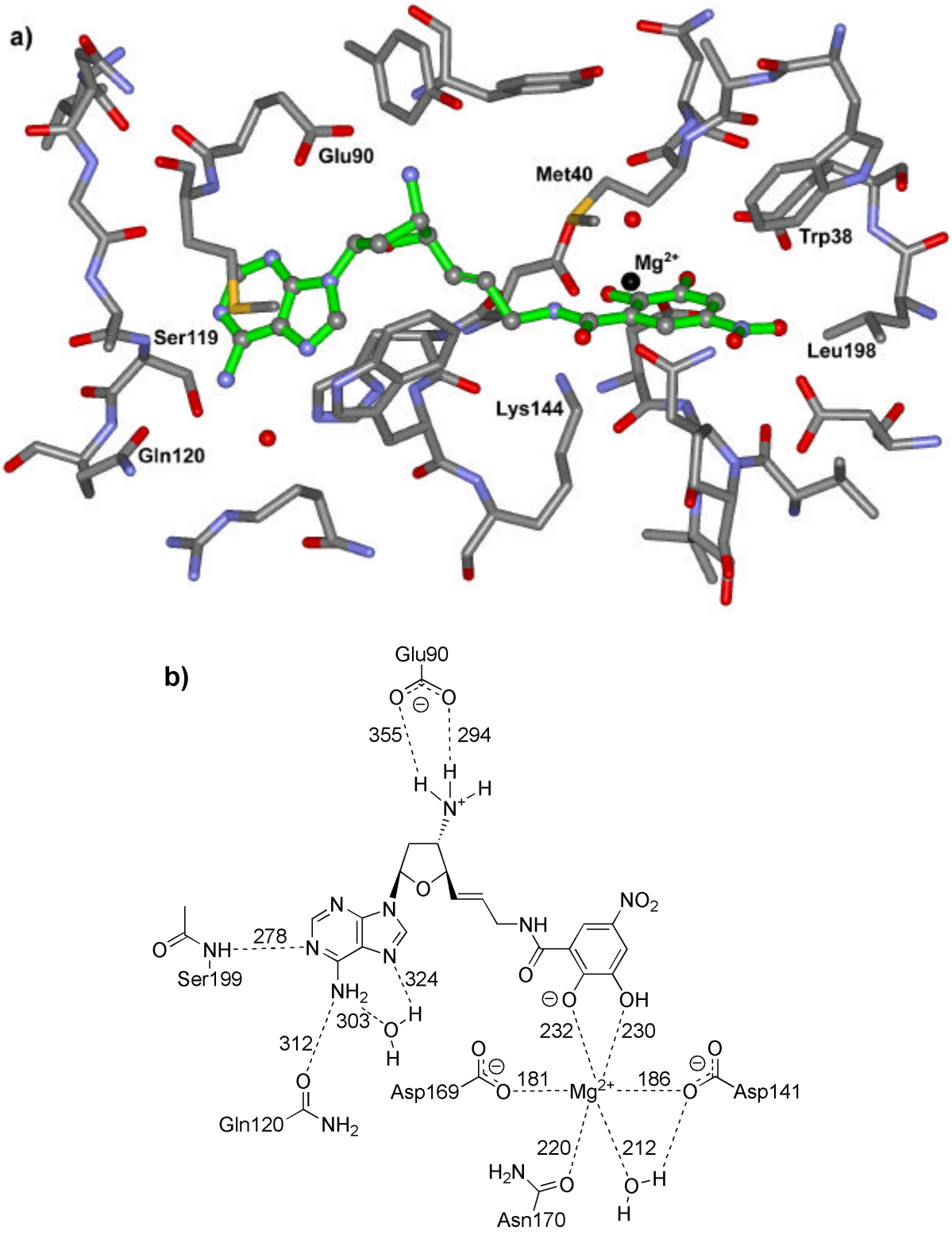


Figure 4SI. Computer model (MOLOC) of inhibitor (–)-**8** in complex with COMT and a Mg^{2+} ion. a) Ball-and-stick representation and b) schematic representation of H-bonding interactions. Distances are given in pm. Color code: inhibitor skeleton: green, C-atoms: gray, O-atoms: red, N-atoms: blue, S-atoms: yellow, Mg atom: black.

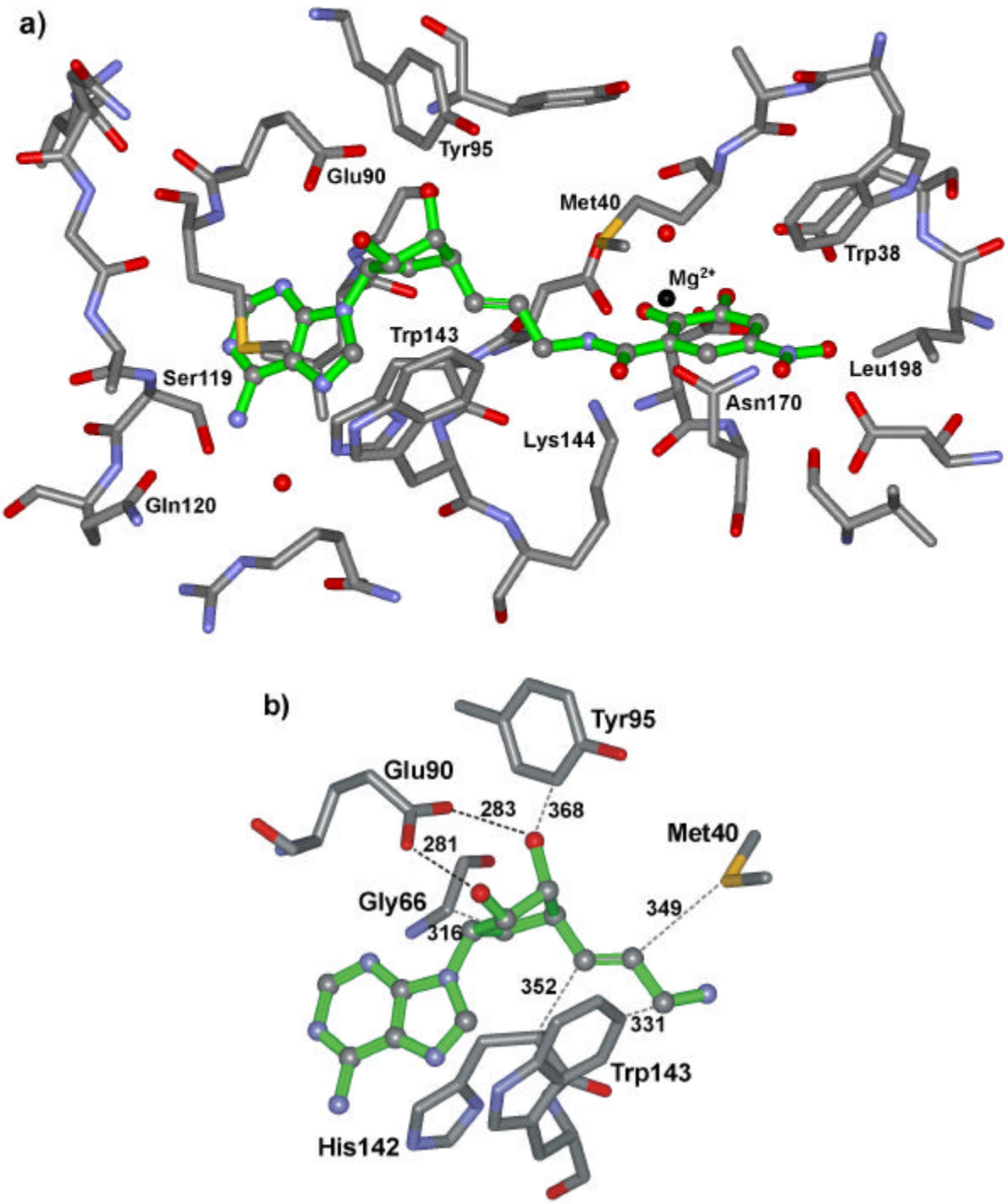
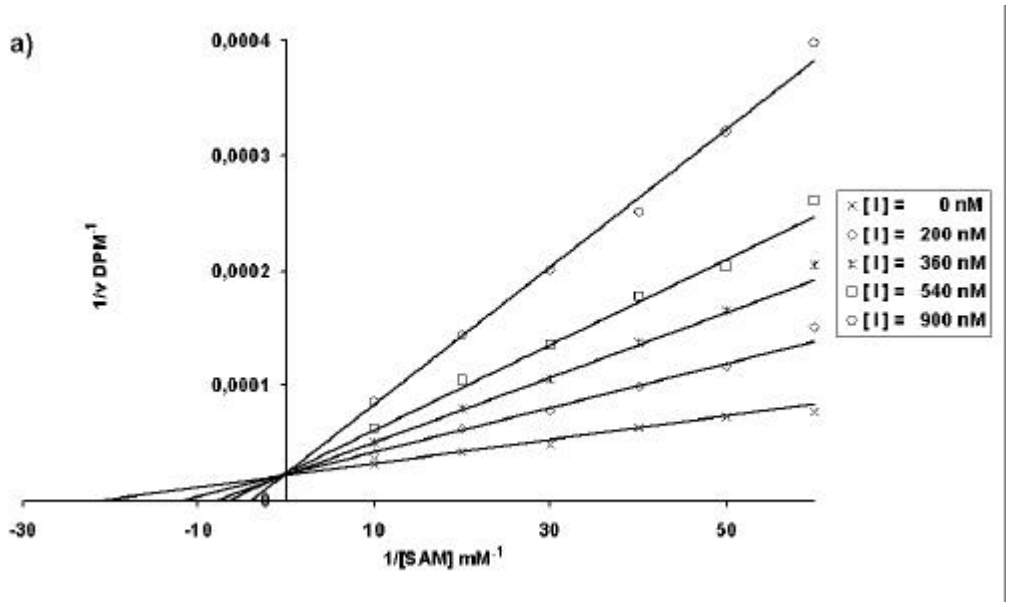


Figure 5SI. Computer model (MOLOC) of inhibitor (–)-**13** in complex with COMT and a Mg^{2+} ion. Ball-and-stick representation of a) the active site and b) of close contacts in the ribose binding pocket. Distances are given in pm. Color code: inhibitor skeleton: green, C-atoms: gray, O-atoms: red, N-atoms: blue, S-atoms: yellow, Mg atom: black.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-30
-10
10
30
50
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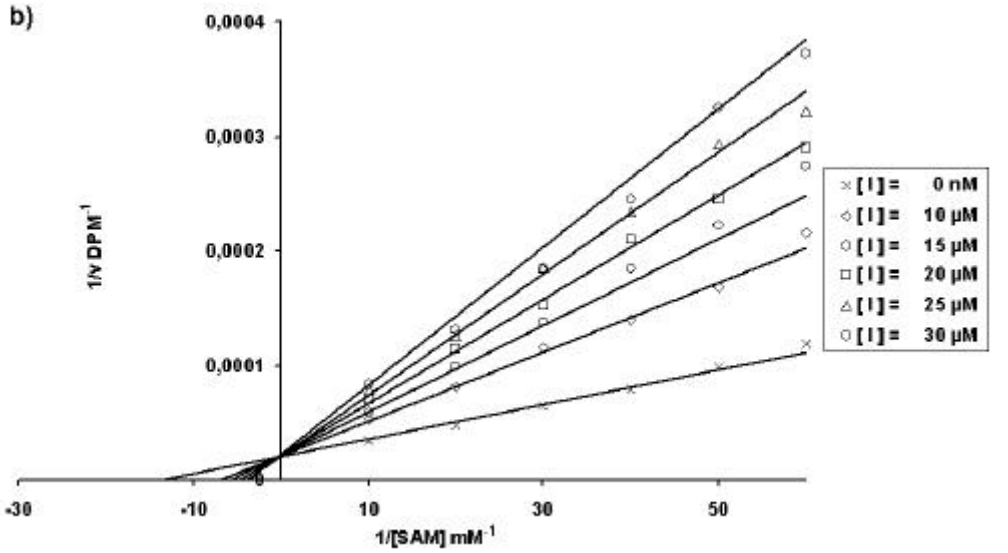
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0,0003
0,0002
0,0001
0
1/v DPM-1
-30
-10
10
30
50
1/[SAM] mM-1
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[I] = 10 µM
[I] = 15 µM
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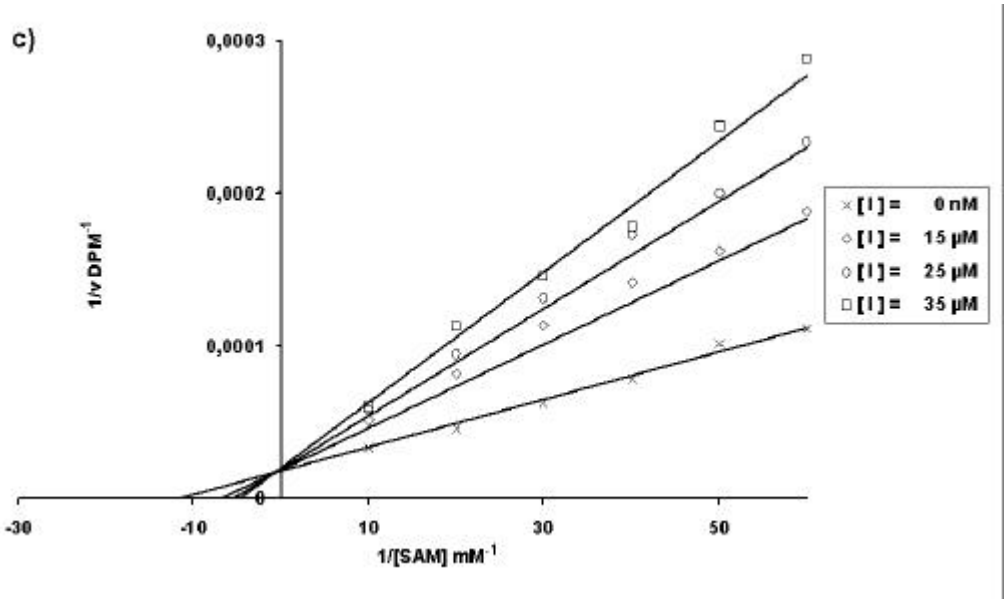
[I] = 30 µM


c)
0,0003
0,0002
0,0001
0
1/v DPM-1
-30
-10
10
30
50
1/[SAM] mM-1
[I] = 0 nM
[I] = 15 µM
[I] = 25 µM
[I] = 35 µM

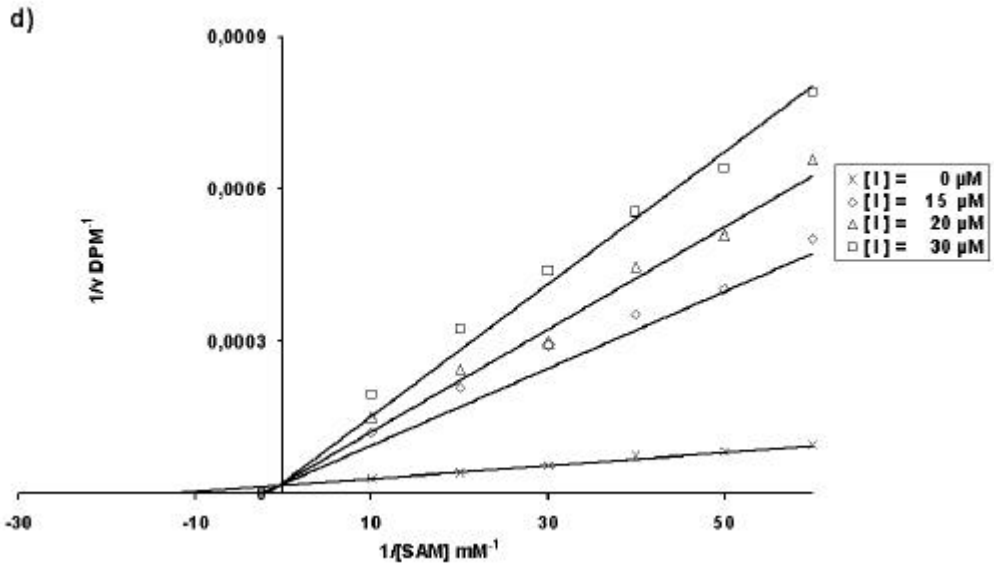


Figure 6SI. Lineweaver-Burk plots of reciprocal enzymatic activity vs. reciprocal concentration of the cofactor (SAM) for varying concentrations of inhibitors (–)-**7** (a), (–)-**11** (b), (–)-**12** (c), and (+)-**16** (d) at saturating benzene-1,2-diol concentrations. DMP = decays per min.

Experimental Section of the Supporting Information

***N*-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxamide ((–)-30).**

Compound **28** (203 mg, 0.43 mmol), EDC·HCl (125 mg, 0.65 mmol), *N*-hydroxysuccinimide (65 mg, 0.56 mmol), and (–)-**26** (130 mg, 0.33 mmol) were reacted according to *GP F*. Workup, followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) yielded (–)-**30** (190 mg, 68%) as a colorless foam. $[a]_D^{20}$ = -3.1 (c = 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.10 (*s*, 3 H), 0.14 (*s*, 3 H), 0.91 (*s*, 9 H), 2.05 (*m*, 2 H), 2.37 (*s*, 3 H), 3.78 (*s*, 3 H), 3.79 (*s*, 3 H), 4.17 (*m*, 2 H), 4.79 (*m*, 1 H), 4.94 (*m*, 1 H), 5.63 (*bs*, 2 H), 5.94 (*m*, 3 H), 6.89 (*d*, *J* = 8.7 Hz, 2 H), 6.90 (*d*, *J* = 8.7 Hz, 2 H), 7.21 (*d*, *J* = 8.0 Hz, 2 H), 7.22 (*d*, *J* = 1.7 Hz, 1 H), 7.26 (*t*, *J* = 5.4 Hz, 1 H), 7.45 (*m*, 6 H), 7.82 (*d*, *J* = 1.7 Hz, 1 H), 7.87 (*s*, 1 H), 8.31 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = -4.8, -4.6, 18.0, 21.2, 25.8, 39.5, 40.9, 55.3, 76.9, 80.8, 92.5, 110.4, 113.6, 115.2, 119.1, 120.3, 120.7, 126.6, 128.1, 129.3, 130.0, 130.3, 130.9, 135.7, 136.9, 137.1, 138.5, 144.1, 147.9, 149.2, 152.8, 155.1, 160.4, 163.4 ppm; IR (neat): *n* = 2929*w*, 1634*m*, 1598*m*, 1512*m*, 1466*s*, 1249*s*, 1206*m*, 1172*s*, 1083*w*, 1027*m*, 1004*m*, 830*s*, 777*m*, 721*w*, 647*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{47}H_{53}N_6O_7Si^+$: 841.3740; found: 841.3735 $[MH]^+$.

***N*-{(2*E*)-3-[(2*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-4-hydroxytetrahydrofuran-2-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxamide ((+)-32).**

A solution of (–)-**30** (115 mg, 0.137 mmol) in THF (10 mL) was treated with 0.68 mL of a 1M solution of *n*-Bu_4NF in THF. The mixture was stirred for 2 h at 20 °C, then aq. $NaClO_4$ solution was added and the resulting precipitate removed by filtration. The residue was partitioned between CH_2Cl_2 and H_2O and the org. phase washed with sat. aq. NH_4Cl solution and sat. aq. NaCl solution, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified using CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield (+)-**32** as a colorless foam (86 mg, 86%). $[\alpha]_D^{20}$ = +8.3 (c = 0.61, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 2.10 (*m*, 1 H), 2.29 (*m*, 1 H), 2.37 (s, 3 H), 3.78 (*s*, 3 H), 3.79 (*s*, 3 H), 4.17 (*m*, 2 H), 4.69 (*m*, 1 H), 4.99 (*q*, *J* = 6.9 Hz, 1 H), 5.25 (*bs*, 2 H), 5.86 (*m*, 1 H), 5.88 (*d*, *J* = 3.1 Hz, 1 H), 5.96 (*dt*, *J* = 15.6 Hz, 5.0 Hz, 1 H), 6.89 (*d*, *J* = 8.9 Hz, 4 H), 7.20 (*d*, *J* = 8.0 Hz, 2 H), 7.22 (*d*, *J* = 1.8 Hz, 1 H), 7.26 (*t*, *J* = 5.1 Hz, 1 H), 7.44 (*m*, 6 H), 7.81 (*d*, *J* = 1.8 Hz, 1 H), 7.95 (*s*, 1 H), 8.30 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 21.0, 37.9, 40.7, 55.3, 76.1, 80.5, 92.6, 110.5, 113.7, 115.2, 119.2, 120.2, 120.7, 126.7, 128.2, 129.5, 130.2, 130.4, 131.0, 135.9, 137.1, 137.2, 138.3, 144.2, 148.0, 148.9, 152.6, 155.5, 160.6, 163.6 ppm; IR (neat): *n* = 3331*w*, 2930*w*, 1634*m*, 1608*m*, 1512*m*, 1466*m*, 1249*s*, 1206*m*, 1172*s*, 1025*m*, 1004*m*, 828*m*, 721*w*,

647*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{41}H_{38}N_6NaO_7Si^+$: 749.2694; found: 749.2703 [*M* + Na]$^+$.

_N_-{(2_E_)-3-[(2_S_,4_R_,5_R_)-5-(6-Amino-9_H_-purin-9-yl)-4-hydroxytetrahydrofuran-2-yl]prop-2-en-1-yl}-4,5-dihydroxy-4'-methylbiphenyl-3-carboxamide ((–)-7).

Compound (+)-**32** (70 mg, 0.1 mmol) was reacted according to *GP G* to yield (–)-**7** (28 mg, 59%) as a fluffy white solid after lyophilization. $[a]_D^{20}$ = -8.0 (c = 0.21, $(CH_3)_2SO$); ^{1}H NMR (500 MHz, CD_3OD): *d* = 2.22 (*m*, *2* H), 2.35 (*s*, 3 H), 4.06 (*d*, *J* = 3.8 Hz, 2 H), 4.73 (*m*, 1 H), 4.96 (*m*, 1 H), 5.94 (*m*, 2 H), 6.05 (*d*, *J* = 1.3 Hz, 1 H), 7.20 (*d*, *J* = 8.0 Hz, 2 H), 7.21 (*d*, *J* = 2.2 Hz, 1 H), 7.47 (*d*, *J* = 8.0 Hz, 2 H), 7.52 (*d*, *J* = 2.2 Hz, 1 H), 8.30 (*s*, 1 H), 8.31 ppm (*s*, 1 H); ^{13}C NMR (125 MHz, CD_3OD): *d* = 21.1, 39.8, 41.6, 77.2, 82.5, 93.7, 116.9, 118.1, 120.6, 127.4, 130.4 (2x), 130.9, 131.7, 133.3, 137.8, 138.8, 142.5, 147.6, 147.7, 149.5, 149.7, 153.5, 171.3 ppm; IR (neat): *n* = 3313*br w*, 1678*s*, 1593*m*, 1543*m*, 1477*w*, 1314*w*, 1197*s*, 1137*m*, 1038*w*, 968*w*, 817*m*, 721*m*, 640*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{26}H_{26}N_6NaO_5^+$: 525.1857; found: 525.1865 [*M*Na]$^+$.

Methyl 2,2-bis[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxylate (37).

4,4′-Dimethoxybenzophenone (1.4 g, 5.6 mmol) and oxalyl chloride (2.9 mL, 34 mmol) were stirred at 60 °C for 50 min, then the temperature was raised to 110 °C to remove excess

oxalyl chloride. Compound **35** (1 g, 4.7 mmol) was added to the mixture, and the dark red solution was stirred at 160 °C for 30 min. After cooling, EtOAc was added to the viscous mixture and the solution was washed with sat. aq. NaCl solution, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified using CC (SiO_2; hexane/EtOAc 9:1) to yield **37** as a yellow solid (1.48 g, 89%). M.p. 49-51 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 3.81 (*s*, 6 H), 3.97 (*s*, 3 H), 6.91 (*d*, *J* = 9.0 Hz, 4 H), 7.46 (*d*, *J* = 9.0 Hz, 4 H), 7.81 (*d*, *J* = 2.4 Hz, 1 H), 8.45 ppm (*d*, *J* = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): *d* = 52.8, 55.3, 107.5, 111.4, 114.0, 119.9, 121.3, 128.0, 129.7, 141.9, 148.8, 152.3, 160.5, 162.5 ppm; IR (neat): *n* = 3088*w*, 2827*w*, 1728*m*, 1608*w*, 1532*w*, 1511*m*, 1450*m*, 1338*m*, 1318*m*, 1282*m*, 1238*s*, 1204*m*, 1169*s*, 1068*w*, 1023*m*, 1002*m*, 933*w*, 851*m*, 834*m*, 802*w*, 743*m*, 715*w*, 647*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{23}H_{20}NO_8^+$: 438.1183; found: 438.1179 $[MH]^+$; elemental analysis calcd (%) for $C_{23}H_{19}NO_8$ (437.11): C 63.16, H 4.38, N 3.20; found: C 63.02, H 4.44, N 3.31.

2,2-Bis[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxylic acid (27).

The biphasic mixture of a solution of **37** (900 mg, 2.06 mmol) in THF (15 mL) and a solution of $LiOH \cdot H_2O$ (1 g, 21 mmol) in H_2O (15 mL) was heated to reflux for 3 h. Sat. aq. NH_4Cl solution was added, and the mixture was partitioned between EtOAc and H_2O. The aq. layer was extracted twice with EtOAc (20 mL), and

the combined organic fractions were washed twice with sat. aq. NaCl solution before being dried over $MgSO_4$ and evaporated *in vacuo* to yield **27** as a yellowish solid (872 mg, quant.). M.p. 106-107 °C; ^{1}H NMR (300 MHz, $(CD_3)_2SO$): *d* = 3.73 (*s*, 6 H), 6.95 (*bs*, 4 H), 7.40 (*d*, *J* = 8.4 Hz, 4 H), 7.86 (*bs*, 1 H), 8.33 ppm (*bs*, 1 H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): *d* = 55.2, 105.1, 113.7, 119.8, 121.1, 127.8, 130.2, 131.7, 141.1, 148.1, 151.8, 160.1, 170.1 ppm; IR (neat): *n* = 2930*w*, 1609*m*, 1512*m*, 1461*m*, 1412*m*, 1333*m*, 1245*s*, 1209*m*, 1171*s*, 1029*s*, 1049*s*, 1003*m*, 933*w*, 827*m*, 805*m*, 712*m*, 687*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{22}H_{18}NO_8^+$: 424.1027; found: 424.1021 [*M*H]$^+$.

_N_-{(2_E_)-3-[(2_S_,4_R_,5_R_)-5-(6-Amino-9_H_-purin-9-yl)-4-azidotetrahydrofuran-2-yl]prop-2-en-1-yl}-2-[3-(methoxy)phenyl]-2-[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxamide ((–)-50).

Amide coupling of (–)-**48** (100 mg, 0.33 mmol) with **28** (203 mg, 0.43 mmol), using EDC·HCl (124 mg, 0.65 mmol) and *N*-hydroxysuccinimide (56 mg, 0.56 mmol) according to *GP F* yielded (–)-**50** (105 mg, 42%) as a colorless foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 20:1). $[a]_D^{20}$ = -11.9 (c = 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 2.28 (*m*, 2 H), 2.37 (s, 3 H), 3.79 (*s*, 3 H), 3.80 (*s*, 3 H), 4.17 (*m*, 2 H), 4.84 (*m*, 2 H), 5.61 (*bs*, 2 H), 5.86 (*dd*, *J* = 15.4, 6.9 Hz, 1 H), 5.97 (*d*, *J* = 1.7 Hz, 1 H), 6.00 (*dt*, *J* = 15.4, 5.1 Hz, 1 H), 6.89 (*dd*, *J* = 9.0, 2.8 Hz, 4 H), 7.21 (*d*, *J* = 8.3 Hz, 2

H), 7.23 (*d*, *J* = 1.9 Hz, 1 H), 7.26 (*t*, *J* = 3.4 Hz, 1 H), 7.45 (*m*, 6 H), 7.81 (*d*, *J* = 1.9 Hz, 1 H), 7.88 (*s*, 1 H), 8.31 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 21.2, 36.2, 40.8, 55.4, 65.6, 80.8, 89.9, 110.5, 113.6, 115.1, 119.1, 120.3, 120.7, 126.6, 128.1, 129.0, 129.4, 130.9, 131.3, 135.6, 137.0, 137.1, 138.6, 144.1, 147.9, 149.0, 153.1, 155.2, 160.4, 163.4 ppm; IR (neat): *n* = 2924*w*, 2105*m*, 1660*m*, 1598*m*, 1513*m*, 1467*m*, 1251*s*, 1207*m*, 1174*s*, 1049*m*, 1004*w*, 831*w*, 630*w* cm^{-1}; HR-ESI-MS: *m/z*: calcd for $C_{41}H_{37}N_9NaO_6^+$: 774.2759; found: 774.2763 [*M* + Na]$^+$.

(2*R*,3*R*,5*S*)-2-(6-Amino-9*H*-purin-9-yl)-5-[(1*E*)-3-{[(4,5-dihydroxy-4'-methylbiphenyl-3-yl)carbonyl]amino}prop-1-en-1-yl]tetrahydrofuran-3-aminium Trifluoroacetate ((–)-12).

Reaction of (–)-**50** (60 mg, 0.080 mmol) with 1,3-propanedithiol (87 mg, 0.80 mmol) and Et_3N (81 mg, 0.80 mmol) in MeOH (5 mL) according to *GP E*, *Method B*, followed by acid-catalyzed ketal deprotection according to *GP G* and subsequent purification by RP-HPLC (0.1% TFA in H_2O/CH_3CN) yielded (–)-**12** (33 mg, 69%) as a fluffy white solid after lyophilization. $[a]_D^{20}$ = -10.3 (c = 0.6, $(CD_3)_2SO$); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): *d* = 2.32 (*s*, 3 H), 2.35 (*m*, *1* H), 2.55 (*m*, 1 H), 3.95 (*t*, *J* = 5.4 Hz, 2 H), 4.5 (*m*, 1 H), 4.85 (*td*, *J* = 8.6, 6.4 Hz, 1 H), 5.82 (*m*, 2 H), 6.14 (*d*, *J* = 3.8 Hz, 1 H), 7.21 (*d*, *J* = 2.1 Hz, 1 H), 7.23 (*d*, *J* = 8.0 Hz, 2 H), 7.51 (*d*, *J* = 8.0 Hz, 2 H), 7.62 (*d*, *J* = 2.1 Hz, 1 H), 7.80 (*bs*, 1 H), 8.23 (*s*, 1 H), 8.41 (*s*, 1 H), 8.50 (*bs*, 2 H), 9.16 ppm (*t*, *J* = 5.4 Hz, 1 H); ^{13}C NMR (125 MHz,

$(CD_3)_2SO$): *d* = 20.6, 35.3, 54.1, 78.9, 86.1, 114.8, 114.9, 116.8, 118.9, 129.3, 129.6, 130.1, 136.0, 136.6, 140.4, 146.5, 148.9, 149.2, 151.1, 154.8, 169.6 ppm; two peaks missing due to overlap; IR (neat): *n* = 3071*br w*, 1673*s*, 1538*w*, 1433*w*, 1316*w*, 1195*s*, 1133*s*, 970*w*, 838*w*, 819*w*, 798*m*, 722*m*, 641*w* cm^{-1}; HR-ESI-MS: *m/z*: calcd for $C_{28}H_{29}N_7O_4^+$: 502.2197; found: 502.2190 $[MH]^+$.

9-{2-Deoxy-3-*O*-[tris(1-methylethyl)silyl]-ß-D-*threo*-pentofuranosyl}-9*H*-purin-6-amine ((–)-78).

TIPS-OTf (4 g, 13.1 mmol) was added to a solution of (–)-**51** (5.5 g, 10.9 mmol) and imidazole (890 mg, 13.1 mmol) in dry DMF (10 mL), and the mixture was stirred for 16 h at 20 °C. The mixture was partitioned between sat. aq. $NaHCO_3$ solution and EtOAc, and the org. phase was washed with sat. NaCl solution, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was redissolved in MeOH (80 mL), cooled to 0 °C, and NaOH (6.4 g, 160 mmol) was added. The mixture was stirred for 7 h at 20 °C, then volatiles were removed under reduced pressure and the residue was partitioned between H_2O and EtOAc. The org. phase was washed with H_2O (2 x 50 mL), sat. aq. NaCl solution, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified using CC (SiO_2; CH_2Cl_2/MeOH 20:1) to yield (–)-**78** as a white solid (3.4 g, 77%). M.p. 224°C; $[a]_D^{20}$ = -36.5 (c = 0.79, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD): *d* = 0.98 (*m*, 21 H), 2.56 (*dt*, *J* = 14.3, 2.0 Hz, 1 H),

2.79 (*ddd*, *J* = 14.3, 7.2, 5.0 Hz, 1 H), 3.99 (*m*, 2 H), 4.24 (*ddd*, *J* = 6.6, 4.6, 3.9 Hz, 1 H), 4.74 (*m*, 1 H), 6.35 (*dd*, *J* = 7.2, 2.0 Hz, 1 H), 8.19 (*s*, 1 H), 8.35 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, CD_3OD): *d* = 13.3, 18.4, 43.7, 62.4, 73.2, 86.1, 87.5, 120.3, 140.6, 149.5, 153.4, 157.0 ppm; IR (neat): *n* = 3256*w*, 3118*m*, 2941*m*, 2865*m*, 1688*s*, 1606*s*, 1572*w*, 1462*w*, 1420*w*, 1383*w*, 1338*m*, 1305*m*, 1248*w*, 1205*m*, 1175*m*, 1114*s*, 1054*s*, 1010*w*, 981*w*, 945*s*, 885*m*, 847*w*, 797*w*, 774*w*, 687*s*, 653*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{19}H_{34}N_5O_3Si^+$: 408.2425; found: 408.2421 $[MH]^+$; elemental analysis calcd (%) for $C_{19}H_{33}N_5O_3Si$ (407.24): C 55.99, H 8.16, N 17.18; found: C 56.26, H 7.95, N 16.96.

Ethyl (2*E*)-3-[(2*R*,3*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-{[tris(1-methylethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-enoate ((–)-79).

Compound (–)-**78** (3.6 g, 8.83 mmol), $Ph_3P{=}CHCO_2Et$ (7.7 g, 22.1 mmol), and IBX (6.15 g, 22.1 mmol) were dissolved in Me_2SO (50 mL) and reacted according to *GP A*. Workup, followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (+)-**79** (4.12 g, 96%) as a white solid. M.p. 174-175 °C; $[a]_D^{20}$ = -13.9 (c = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.99 (*m*, 21 H), 1.28 (*t*, *J* = 7.1 Hz, 3 H), 2.50 (*ddd*, *J* = 14.5, 2.0, 1.2 Hz, 1 H), 2.82 (*ddd*, *J* = 14.5, 7.9, 4.8 Hz, 1 H), 4.21 (*qd*, *J* = 7.1, 1.4 Hz, 2 H), 4.70 (*m*, 2 H), 5.73 (*bs*, 2 H), 6.15 (*dd*, *J* = 15.7, 1.4 Hz, 1 H), 6.52 (*dd*, *J* = 7.9, 2.1 Hz, 1 H), 7.11 (*dd*, *J* = 15.7, 5.3 Hz, 1 H), 8.32 (*s*, 1 H), 8.35 ppm (*s*, 1 H); ^{13}C NMR (75

MHz, $CDCl_3$): *d* = 12.1, 14.3, 17.9, 43.0, 60.6, 73.4, 83.4, 84.5, 119.5, 124.0, 139.4, 141.9, 149.3, 152.7, 155.1, 165.4 ppm; IR (neat): *n* = 3297*w*, 3136*w*, 2942*w*, 2866*w*, 1706*s*, 1666*s*, 1602*m*, 1572*w*, 1472*m*, 1423*w*, 1367*w*, 1305*s*, 1265*m*, 1214*m*, 1175*s*, 1116*s*, 1069*m*, 1042*s*, 1011*m*, 977*m*, 940*m*, 917*m*, 877*m*, 819*m*, 798*w*, 675*m*, 649*m*, 627*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{23}H_{37}N_5NaO_4Si^+$: 498.2507; found: 498.2501 $[M + Na]^+$.

(2*E*)-3-[(2*R*,3*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-{[tris(1-methylethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-ol ((–)-80).

A solution of (–)-**79** (2.76 g, 5.8 mmol) in dry CH_2Cl_2 (80 mL) and DIBAL-H (47 mL of a 1M solution in CH_2Cl_2) were reacted according to *GP B*. Workup, followed by CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (–)-**80** (2.41 g, 96%) as a colorless solid. M.p. 182-183 °C; $[a]_D^{20}$ = -2.9 (c = 1.13, CH_3OH); ^1H NMR (300 MHz, CD_3OD): *d* = 0.96 (*m*, 21 H), 2.51 (*d*, *J* = 14.4 Hz, 1 H), 2.82 (*ddd*, *J* = 14.4, 7.5, 4.6 Hz, 1 H), 4.14 (*d*, *J* = 4.6 Hz, 2 H), 4.62 (*m*, 2 H), 6.00 (*dd*, *J* = 15.6, 4.6 Hz, 1 H), 6.12 (*ddt*, *J* = 15.6, 6.7, 1.2 Hz, 1 H), 6.36 (*dd*, *J* = 7.5, 1.2 Hz, 1 H), 8.20 (*s*, 1 H), 8.37 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, CD_3OD): *d* = 13.2, 18.4, 44.0, 62.8, 74.9, 85.9, 88.0, 120.1, 126.7, 136.1, 140.7, 149.5, 153.5, 157.0 ppm; IR (neat): *n* = 3307*w*, 3148*w*, 2942*w*, 2865*w*, 1668*s*, 1600*s*, 1569*w*, 1464*w*, 1417*w*, 1368*w*, 1326*w*, 1302*m*, 1241*w*, 1210*m*, 1180*m*, 1071*m*, 1051*m*, 994*s*, 976*s*, 958*m*, 914*w*, 880*s*, 846*w*, 799*w*, 765*w*, 717*w*, 691*m*, 656*m*,

624*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{21}H_{36}N_5O_3Si^+$: 434.2587; found: 434.2581 $[MH]^+$; elemental analysis calcd (%) for $C_{21}H_{35}N_5O_3Si$ (433.25): C 58.17, H 8.14, N 16.15; found: C 58.13, H 7.95, N 16.17.

2-{(2*E*)-3-[(2*R*,3*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-{[tris(1-methylethyl)silyl]oxy}tetrahydrofuran-2-yl]prop-2-en-1-yl}-1*H*-isoindole-1,3(2*H*)-dione ((+)-81).

Compound (–)-**80** (2.55 g, 5.88 mmol), DIAD (1.78 g, 8.82 mmol), PPh_3 (2.32 g, 8.82 mmol), and phthalimide (1.54 g, 8.82 mmol) in THF (60 mL) were reacted according to *GP C*. Solvent removal under reduced pressure and CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (+)-**81** (3.04 g, 92%) as a colorless foam. $[a]_D^{20}$ = +0.3 (c = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.91 (*m*, 21 H), 2.46 (*dt*, *J* = 14.4, 1.8 Hz, 1 H), 2.74 (*ddd*, *J* = 14.4, 7.9, 4.9 Hz, 1 H), 4.35 (*d*, *J* = 4.1 Hz, 2 H), 4.51 (*m*, 2 H), 5.72 (*bs*, 2 H), 6.01 (*m*, 2 H), 6.40 (*dd*, *J* = 7.9, 1.8 Hz, 1 H), 7.72 (*dd*, *J* = 5.5, 3.1 Hz, 2 H), 7.86 (*dd*, *J* = 5.5, 3.1 Hz, 2 H), 8.27 (*s*, 1 H), 8.32 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 11.9, 17.8, 38.7, 42.9, 73.1, 83.3, 85.6, 119.7, 123.3, 128.4, 129.4, 132.1, 134.0, 139.6, 149.4, 152.8, 155.2, 167.7 ppm; IR (neat): *n* = 3142*br w*, 2943*w*, 1711*s*, 1643*m*, 1596*m*, 1467*w*, 1393*m*, 1329*w*, 1296*w*, 1244*w*, 1211*w*, 1184*w*, 1109*m*, 1057*m*, 954*w*, 881*m*, 798*w*, 717*m*, 681*m*, 649*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{29}H_{38}N_6NaO_4Si^+$: 585.2616; found: 585.2611 [*M* +

Na]$^+$; elemental analysis calcd (%) for $C_{29}H_{38}N_6O_4Si$ (562.27): C 61.90, H 6.81, N 14.93; found: C 61.67, H 6.81, N 14.72.

2-{(2*E*)-3-[(2*R*,3*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-hydroxytetrahydrofuran-2-yl]prop-2-en-1-yl}-1*H*-isoindole-1,3(2*H*)-dione ((–)-82).

A solution of (+)-**81** (2.96 g, 5.26 mmol) in dry THF (40 mL) was cooled to 0 °C and treated with *n*-Bu_4NF (6.3 mL of a 1M sol. in THF). After stirring for 5 min at 0 °C, the reaction was quenched by addition of sat. aq. NH_4Cl solution (20 mL) and the mixture was partitioned between CH_2Cl_2 and H_2O. The org. phase was washed with H_2O (40 mL), then sat. aq. NaCl solution (40 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified using CC (SiO_2; CH_2Cl_2/MeOH 19:1) to yield the title compound as a colorless foam (1.81 g, 85%). $[a]_D^{20}$ = -13.7 (c = 0.9, $(CD_3)_2SO$); ^{1}H NMR (300 MHz, $(CD_3)_2SO$): *d* = 2.27 (*dd*, *J* = 14.5, 1.9 Hz, 1 H), 2.79 (*ddd*, *J* = 14.5, 8.7, 5.5 Hz, 1 H), 4.22 (*m*, 3 H), 4.34 (*m*, 1 H), 5.81 (*m*, 2 H), 5.99 (*d*, *J* = 5.7 Hz, 1 H), 6.19 (*dd*, *J* = 8.7, 1.9 Hz, 1 H), 7.32 (*bs*, 2 H), 7.85 (*m*, 4 H), 8.10 (*s*, 1 H), 8.31 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $(CD_3)_2SO$): *d* = 38.6, 40.7, 70.8, 82.2, 84.2, 118.7, 123.0, 128.0, 131.4, 134.3, 139.8, 148.3, 152.0, 155.9, 167.1 ppm; one peak missing due to overlap; IR (neat): *n* = 3313*w*, 3106*w*, 2915*w*, 1769*w*, 1708*s*, 1669*m*, 1601*m*, 1577*m*, 1485*w*, 1430*w*, 1396*m*, 1367*m*, 1301*w*, 1258*m*, 1180*w*, 1112*w*,

1053*m*, 949*w*, 863*w*, 795*w*, 719*m*, 645*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{20}H_{19}N_6O_4^+$: 407.1462; found: 407.1458 $[MH]^+$.

2-{(2*E*)-3-[(2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-azidotetrahydrofuran-2-yl]prop-2-en-1-yl}-1*H*-isoindole-1,3(2*H*)-dione ((+)-83).

Compound (–)-**82** (1.46 g, 3.59 mmol), DIAD (1.09 g, 5.39 mmol), PPh_3 (1.41 g, 5.39 mmol), and $(PhO)_2PON_3$ (1.48 g, 5.39 mmol) were reacted according to *GP C*. Solvent removal under reduced pressure and CC (SiO_2; CH_2Cl_2/MeOH 19:1) provided (+)-**83** (1.18 g, 77%) as a colorless foam. $[a]_D^{20}$ = +18.7 (c = 1.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 2.51 (*ddd*, *J* = 13.9, 6.9, 6.7 Hz, 1 H), 3.04 (*ddd*, *J* = 13.9, 6.7, 5.1 Hz, 1 H), 4.32 (*dd*, *J* = 2.4, 1.5 Hz, 2 H), 4.41 (*m*, 2 H), 5.93 (*m*, 4 H), 5.96 (*dd*, *J* = 6.9, 5.1 Hz, 1 H), 7.72 (*dd*, *J* = 5.5, 3.1 Hz, 2 H), 7.85 (*dd*, *J* = 5.5, 3.1 Hz, 2 H), 7.88 (*s*, 1 H), 8.25 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 36.8, 38.8, 63.9, 84.2, 84.4, 120.3, 123.3, 128.5, 130.3, 131.8, 134.0, 139.1, 149.2, 152.9, 155.4, 167.6 ppm; IR (neat): *n* = 3323*w*, 3121*br w*, 2101*m*, 1769*w*, 1705*s*, 1634*m*, 1595*m*, 1469*w*, 1425*w*, 1393*m*, 1329*m*, 1246*m*, 1055*m*, 937*m*, 798*w*, 720*m*, 648*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{20}H_{18}N_9O_3^+$: 432.1527; found: 432.1530 $[MH]^+$.

9-{(2*R*,4*S*,5*R*)-5-[(1*E*)-3-Aminoprop-1-en-1-yl]-4-azidotetrahydrofuran-2-yl}-9*H*-purin-6-amine ((+)-52).

Reaction of (+)-**83** (800 mg, 1.85 mmol) with $MeNH_2$ (25 mL of a 8M solution in EtOH) and purification according to *GP D*, *Method B*, afforded (+)-**52** (470 mg, 84%) as a colorless foam. $[a]_D^{20}$ = +26.5 (c = 0.9, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$): *d* = 1.42 (*bs*, 2 H), 2.54 (*dt*, *J* = 14.1, 7.2 Hz, 1 H), 3.06 (*ddd*, *J* = 14.1, 7.1, 4.4 Hz, 1 H), 3.35 (*dd*, *J* = 5.2, 1.5 Hz, 2 H), 4.42 (*m*, 2 H), 5.80 (*ddt*, *J* = 15.4, 7.3, 1.5 Hz, 1 H), 6.00 (*bs*, 2 H), 6.01 (dtd, J = 15.4, 5.2, 0.6 Hz, 1 H), 6.25 (*dd*, *J* = 7.2, 4.4 Hz, 1 H), 7.89 (*s*, 1 H), 8.34 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 37.1, 43.3, 63.8, 84.1, 85.1, 120.3, 125.7, 137.6, 139.1, 149.1, 152.9, 155.5 ppm; IR (neat): *n* = 3307*w*, 3148*w*, 2099*s*, 1644*s*, 1595*s*, 1573*s*, 1472*m*, 1418*w*, 1364*w*, 1329*m*, 1296*m*, 1247*m*, 1054*m*, 968*m*, 929*m*, 797*w*, 726*w*, 702*w*, 646*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{12}H_{16}N_9O^+$: 302.1472; found: 302.1469 $[MH]^+$.

_N_-{(2_E_)-3-[(2_R_,3_S_,5_R_)-5-(6-Amino-9_H_-purin-9-yl)-3-azidotetrahydrofuran-2-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxamide ((–)-84).

Amide coupling of (+)-**52** (100 mg, 0.33 mmol) with **28** (203 mg, 0.43 mmol), using EDC·HCl (124 mg, 0.65 mmol) and *N*-hydroxysuccinimide (56 mg, 0.56 mmol) according to *GP F* yielded (–)-**84** (127 mg, 62%) as a colorless foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 19:1). $[a]_D^{20}$ = -1.7 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): *d* = 2.36 (s, 3 H), 2.52

(*m*, 1 H), 3.01 (*m*, 1 H), 3.79 (*s*, 6 H), 4.17 (*m*, 2 H), 4.39 (*m*, 2 H), 5.88 (*m*, 3 H), 6.02 (*dt*, *J* = 15.6, 5.1 Hz, 1 H), 6.26 (*dd*, *J* = 7.1, 4.9 Hz, 1 H), 6.89 (*d*, *J* = 8.9 Hz, 4 H), 7.20 (*d*, *J* = 7.9 Hz, 2 H), 7.23 (*d*, *J* = 1.9 Hz, 1 H), 7.26 (*t*, *J* = 3.1 Hz, 1 H), 7.44 (*m*, 6 H), 7.81 (*d*, *J* = 1.9 Hz, 1 H), 7.87 (*s*, 1 H), 8.26 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 21.0, 36.8, 40.8, 55.4, 63.9, 84.0, 84.6, 110.5, 113.6, 115.1, 119.2, 120.4, 120.7, 126.7, 128.1, 128.2, 129.4, 130.9, 131.0, 132.1, 135.8, 137.0, 137.2, 144.2, 148.0, 149.3, 153.1, 155.5, 160.6, 163.6 ppm; IR (neat): *n* = 3323*w*, 2930*w*, 2101*m*, 1633*m*, 1608*m*, 1512*m*, 1467*m*, 1248*s*, 1207*m*, 1172*s*, 1025*m*, 1004*w*, 932*w*, 829*w*, 774*w*, 725*w*, 648*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{41}H_{38}N_9O_6^+$: 752.2940; found: 752.2931 $[MH]^+$.

(2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2-[(1*E*)-3-{[(4,5-dihydroxy-4'-methylbiphenyl-3-yl)carbonyl]amino}prop-1-en-1-yl]tetrahydrofuran-3-aminium Formate ((+)-9).

Reaction of (–)-**84** (80 mg, 0.106 mmol) with 1,3-propanedithiol (115 mg, 1.06 mmol) and Et_3N (110 mg, 1.06 mmol) in MeOH (5 mL) according to *GP E*, *Method B*, followed by acid-catalyzed ketal deprotection using dichloroacetic acid (0.4 mL) in a mixture of MeOH/H_2O (2:1, 3 mL) and subsequent purification by RP-HPLC (0.1% HCO_2H in H_2O/CH_3CN) yielded (+)-**9** (29 mg, 50%) as a fluffy white solid after lyophilization. $[a]_D^{20}$ = +9.4 (c = 0.24, $(CH_3)_2SO$); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): *d* = 2.32 (*m*, 4 H), 2.75 (*ddd*, *J* = 13.5, 7.0, 4.7 Hz, 1 H), 3.68 (*q*, *J* = 6.5 Hz),

3.96 (*q*, *J* = 5.4 Hz, 2 H), 4.14 (*t*, *J* = 6.5 Hz, 1 H), 5.79 (*dt*, *J* = 15.5, 5.4 Hz, 1 H), 5.86 (*dd*, *J* = 15.5, 6.5 Hz, 1 H), 6.33 (*dd*, *J* = 7.0, 4.7 Hz, 1 H), 7.18 (*d*, *J* = 2.2 Hz, 1 H), 7.22 (*d*, *J* = 8.1 Hz, 2 H), 7.23 (*bs*, 2 H), 7.50 (*d*, *J* = 8.1 Hz, 2 H), 7.62 (*d*, *J* = 2.2 Hz, 1 H), 8.12 (*s*, 1 H, H), 8.23 (*bs*, 1 H), 8.27 (*s*, 1 H), 9.31 ppm (*t*, *J* = 5.4 Hz, 1 H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): *d* = 20.6, 38.9, 55.5, 82.5, 86.2, 114.9, 115.1, 116.2, 119.1, 125.9, 129.3, 129.4, 129.7, 136.8, 136.8, 139.2, 146.8, 149.0, 149.9, 152.5, 156.0, 163.9, 169.5 ppm; one peak missing due to signal overlap; IR (neat): *n* = 3073*br w*, 1674*s*, 1591*s*, 1475*m*, 1297*m*, 1247*m*, 1037*w*, 970*w*, 818*w*, 796*w*, 726*w*, 646*w* cm^{-1}; HR-ESI-MS: *m/z*: calcd for $C_{28}H_{29}N_7O_4^+$: 502.2197; found: 502.2191 $[MH]^+$.

9-{(3a*S*,4*R*,6*R*,6a*R*)-6-[(1*E*)-3-Aminoprop-1-en-1-yl]-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}-9*H*-purin-6-amine ((+)-58).

Compound(+)-**57** (380 mg, 1.15 mmol), DIAD (610 mg, 3.05 mmol), PPh_3 (800 mg, 3.05 mmol), and phthalimide (450 mg, 3.05 mmol) were reacted according to *GP C*. Reaction of the product with $MeNH_2$ (15 mL of a 8M solution in EtOH) and purification according to *GP D*, *Method B*, afforded (+)-**58** (170 mg, 63%) as a colorless foam. $[a]_D^{20}$ = +23.7 (c = 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 1.25 (*s*, 3 H), 1.52 (*s*, 3 H), 2.42 (*m*, 2 H), 2.74 (*m*, 1 H), 3.26 (*m*, 2 H), 4.58 (*t*, *J* = 7.2 Hz, 1 H), 4.72 (*ddd*, J = 11.5, 7.0, 5.2 Hz, 1 H), 5.04 (*dd*, *J* = 7.2, 5.2

Hz, 1 H), 5.62 (*dd*, *J* = 15.5, 5.9 Hz, 1 H), 5.71 (*dt*, J = 15.5, 4.8 Hz, 1 H), 6.47 (*s*, 2 H), 7.79 (*s*, 1 H), 8.27 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 24.9, 27.3, 36.9, 43.6, 46.9, 61.3, 83.3, 84.0, 113.9, 120.2, 128.9, 133.1, 139.6, 149.8, 152.9, 155.8 ppm; IR (neat): *n* = 3311*w*, 3140*w*, 2982*w*, 2931*w*, 1660*m*, 1594*s*, 1478*w*, 1414*w*, 1376*m*, 1299*w*, 1254*w*, 1205*s*, 1157*w*, 1064*s*, 1007*w*, 968*w*, 858*m*, 796*w*, 726*w*, 646*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{16}H_{23}N_6O_2^+$: 331.1877; found: 331.1871 $[MH]^+$.

_N_-{(2_E_)-3-[(3a_R_,4_R_,6_R_,6a_S_)-6-(6-Amino-9_H_-purin-9-yl)-2,2-dimethyltetrahydro-3a_H_-cyclopenta[_d_][1,3]dioxol-4-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxamide ((+)-59).

Amide coupling of (+)-**58** (70 mg, 0.21 mmol) with **27** (98 mg, 0.23 mmol), using EDC·HCl (70 mg, 0.35 mmol), and *N*-hydroxysuccinimide (35 mg, 0.30 mmol) according to *GP F* yielded (+)-**59** (53 mg, 38%) as a yellowish foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 19:1). $[a]_D^{20}$ = +19.4 (c = 0.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 1.27 (*s*, 3 H), 1.54 (*s*, 3 H), 2.46 (*m*, 2 H), 2.78 (*m*, 1 H), 3.78 (*s*, 3 H), 3.79 (*s*, 3 H), 4.12 (*m*, 2 H), 4.57 (*t*, *J* = 7.3 Hz, 1 H), 4.74 (*ddd*, *J* = 11.5, 7.0, 5.1 Hz, 1 H), 5.07 (*dd*, *J* = 7.3, 5.1 Hz, 1 H), 5.77 (*m*, 2 H), 5.96 (*bs*, 2 H), 6.91 (*dd*, *J* = 8.9, 3.1 Hz, 4 H), 7.10 (*t*, *J* = 5.7 Hz, 1 H), 7.41 (*dd*, *J* = 8.9, 3.1 Hz, 4 H), 7.81 (*s*, 1 H), 7.82 (*d*, *J* = 2.3 Hz, 1 H), 8.25 (*s*, 1

H), 8.58 ppm (*d*, *J* = 2.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 25.0, 27.3, 36.7, 41.2, 47.0, 55.3, 61.3, 83.3, 83.8, 106.5, 113.8, 114.1, 114.9, 120.3 (2×), 122.2, 127.3, 128.1, 129.6, 131.4, 139.8, 142.9, 148.2, 149.5, 149.8, 152.7, 155.5, 160.9, 161.2 ppm; IR (neat): *n* = 3424*w*, 2934*w*, 2838*w*, 1643*m*, 1607*m*, 1516*s*, 1464*m*, 1338*s*, 1250*s*, 1209*m*, 1175*s*, 1027*w*, 832*m*, 749*w*, 649*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{38}H_{38}N_7O_9^+$: 736.2726; found: 736.2712 $[MH]^+$.

_N_-{(2_E_)-3-[(3a_R_,4_R_,6_R_,6a_S_)-6-(6-Amino-9_H_-purin-9-yl)-2,2-dimethyltetrahydro-3a_H_-cyclopenta[_d_][1,3]dioxol-4-yl]prop-2-en-1-yl}-2,2-bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxamide ((+)-60).

Amide coupling of (+)-**58** (70 mg, 0.21 mmol) with **28** (113 mg, 0.24 mmol), using EDC·HCl (70 mg, 0.35 mmol), and *N*-hydroxysuccinimide (36 mg, 0.31 mmol) according to *GP F* yielded (+)-**60** (84 mg, 51%) as a colorless foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 19:1). $[a]_D^{20}$ = +20.0 (c = 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 1.28 (*s*, 3 H), 1.56 (*s*, 3 H), 2.37 (*s*, 3 H), 2.43 (*m*, 2 H), 2.81 (*m*, 1 H), 3.78 (*s*, 3 H), 3.79 (*s*, 3 H), 4.14 (*m*, 2 H), 4.58 (*t*, *J* = 7.3 Hz, 1 H), 4.75 (*ddd*, J = 11.7, 7.0, 5.1 Hz, 1 H), 5.06 (*dd*, *J* = 7.3, 5.1 Hz, 1 H), 5.79 (*m*, 4 H), 6.91 (*dd*, *J* = 9.0, 2.6 Hz, 4 H), 7.21 (*d*, J = 8.0 Hz, 2 H), 7.22 (d, J = 1.8 Hz, 1 H), 7.46 (*m*, 6 H), 7.80 (*s*, 1 H), 7.81 (*d*, J = 1.8 Hz, 1 H), 8.28 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 21.2, 25.2, 27.6,

37.0, 41.1, 47.1, 55.4, 61.5, 83.4, 84.0, 110.4, 113.6, 114.1, 115.4, 119.0, 120.3, 120.7, 126.7, 128.0, 128.2, 129.4, 130.7, 131.1, 135.7, 136.9, 137.1, 139.7, 144.1, 147.9, 149.8, 152.7, 155.4, 160.5, 163.3 ppm; IR (neat): *n* = 3421*w*, 3318*w*, 3183*w*, 2933*w*, 2837*w*, 1645*m*, 1598*m*, 1513*m*, 1467*m*, 1437*w*, 1417*w*, 1374*w*, 1250*s*, 1207*s*, 1174*s*, 1114*w*, 1050*m*, 1028*m*, 1004*w*, 951*w*, 864*w*, 832*m*, 754*s*, 648*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{45}H_{45}N_6O_7^+$: 781.3344; found: 781.3330 $[MH]^+$.

_N_-{(2_E_)-3-[(1_R_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]prop-2-en-1-yl}-2,3-dihydroxy-5-nitrobenzamide ((–)-13).

Deprotection of (+)-**59** (40 mg, 54 µmol) according to *GP G* yielded (–)-**13** (25 mg, 98%) as a fluffy yellowish solid after HPLC purification and lyophilization of product-containing fractions. $[a]_D^{20}$ = -1.8 (c = 1.0, $(CH_3)_2SO$); ^1H NMR (300 MHz, CD_3OD): *d* = 2.07 (*dt*, *J* = 12.9, 10.3 Hz, 1 H), 2.47 (*dt*, *J* = 12.9, 8.0 Hz, 1 H), 2.74 (*m*, 1 H), 4.02 (*dd*, *J* = 11.0, 5.5 Hz, 2 H), 4.47 (*dd*, *J* = 7.2, 6.1 Hz, 1 H), 4.89 (*m*, 2 H), 5.74 (*dt*, *J* = 15.4, 5.5 Hz, 1 H), 5.89 (*dd*, *J* = 15.4, 7.5 Hz, 1 H), 7.74 (*d*, *J* = 2.6 Hz, 1 H), 8.30 (*s*, 1 H), 8.34 (*d*, J = 2.6 Hz, 1 H), 8.36 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, CD_3OD): *d* = 33.1, 42.0, 47.3, 62.7, 76.0, 76.2, 112.9, 115.1, 115.6, 120.1, 127.1, 134.3, 140.3, 144.0, 145.8, 147.7, 149.9, 152.3, 155.9, 169.0 ppm; IR (neat): *n* = 3313*br w*, 3094*w*, 2946*w*, 1691*s*, 1641*s*, 1613*s*, 1512*m*, 1472*m*, 1415*m*, 1330*s*, 1285*s*, 1195*s*, 1133*s*,

970*w*, 837*s*, 799*s*, 721*s*, 644*s* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{20}H_{22}N_7O_7^+$: 472.1575; found: 472.1577 [*M*H]$^+$.

_N_-{(2_E_)-3-[(1_R_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]prop-2-en-1-yl}-4,5-dihydroxy-4'-methylbiphenyl-3-carboxamide ((–)-14).

Deprotection of (+)-**60** (32 mg, 31 µmol) according to *GP G* yielded (–)-**14** (16 mg, 76%) as a fluffy white solid after HPLC purification and lyophilization of product-containing fractions. $[a]_D^{20}$ = -1.1 (c = 1.0, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): *d* = 2.06 (*dt*, *J* = 13.0, 10.2 Hz, 1 H), 2.35 (*s*, 3 H), 2.46 (*dt*, *J* = 13.0, 8.1 Hz, 1 H), 2.74 (*dt*, *J* = 13.0, 7.5 Hz, 1 H), 4.02 (*dd*, *J* = 11.1, 5.4 Hz, 2 H), 4.48 (*dd*, *J* = 7.5, 5.9 Hz, 1 H), 4.89 (*m*, 2 H), 5.75 (*dt*, *J* = 15.4, 5.4 Hz, 1 H), 5.88 (*dd*, *J* = 15.4, 7.5 Hz, 1 H), 7.20 (*d*, *J* = 8.0, 1 H), 7.21 (*d*, *J* = 2.1 Hz, 2 H), 7.46 (*d*, *J* = 8.0 Hz, 2 H), 7.53 (*d*, *J* = 2.1 Hz, 1 H), 8.27 (*s*, 1 H), 8.36 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, CD_3OD): *d* = 21.1, 33.4, 42.1, 47.7, 63.1, 76.4, 76.7, 116.9, 118.1, 120.6, 127.4, 128.1, 130.5, 133.3, 134.3, 134.4, 137.8, 138.8, 144.6, 146.0, 147.7, 149.6, 150.5, 152.7, 171.3 ppm; IR (neat): *n* = 3319*br w*, 3096*w*, 1679*s*, 1594*m*, 1544*w*, 1477*w*, 1413*w*, 1314*w*, 1194*s*, 1132*s*, 970*w*, 819*m*, 720*m*, 645*m*, 610*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{27}H_{29}N_6O_5^+$: 517.2194; found: 517.2203 [*M*H]$^+$.

{(1*R*,2*R*)-2-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methyl Acetate ((–)-69).

Compound (–)-**68** (1.0 g, 3.7 mmol), DIAD (1.50 g, 7.4 mmol), PPh_3 (1.94 g, 7.4 mmol), and 6-chloropurine (860 mg, 5.55 mmol) in dry THF (10 mL) were reacted according to *GP H*. Solvent removal under reduced pressure and CC (SiO_2; EtOAc/hexane 1:1) provided (–)-**69** (600 mg, 40%) as a colorless oil. $[a]_D^{20}$ = -17.4 (c = 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.59 (*dt*, *J* = 8.5, 5.2 Hz, 1 H), 0.68 (*dt*, *J* = 8.5, 5.2 Hz, 1 H), 0.86 (*m*, 1 H), 1.03 (*m*, 1 H), 1.28 (*s*, 3 H), 1.51 (*s*, 3 H), 1.71 (*m*, 1 H), 1.99 (*s*, 3 H), 2.44 (*m*, 2 H), 3.82 (*dd*, *J* = 11.5, 7.7 Hz, 1 H), 3.98 (*dd*, *J* = 11.5, 6.7 Hz, 1 H), 4.61 (*dd*, *J* = 7.3, 5.6 Hz, 1 H), 4.73 (*ddd*, *J* = 12.6, 7.1, 5.6 Hz, 1 H), 5.05 (*dd*, *J* = 7.3, 5.6 Hz, 1 H), 8.17 (*s*, 1 H), 8.71 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.2, 16.4, 20.1, 21.0, 25.0, 27.4, 36.2, 47.5, 62.2, 67.9, 83.3, 83.6, 113.9, 132.2, 144.3, 151.0, 151.5 (2x), 170.8 ppm; IR (neat): *n* = 2984*w*, 2935*w*, 1732*s*, 1589*s*, 1557*s*, 1491*w*, 1437*w*, 1399*w*, 1372*m*, 1336*m*, 1236*s*, 1201*s*, 1149*m*, 1070*s*, 1032*m*, 937*m*, 863*m*, 837*m*, 752*w*, 695*w*, 637*m*, 609*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{19}H_{24}ClN_4O_4^+$: 407.1481; found: 407.1474 $[MH]^+$.

{(1*R*,2*R*)-2-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methanol ((–)-70).

A solution of (–)-**69** (560 mg, 1.38 mmol) in MeOH (40 mL) was saturated with NH_3 and stirred for 14 h at 20 °C. The mixture was then cooled to 0°C, resaturated with NH_3, and reacted according to *GP I*. Solvent removal and CC (SiO_2; CH_2Cl_2/MeOH 19:1) yielded (–)-**70** (350 mg, 74%) as a colorless foam. $[a]_D^{20}$ = -19.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.43 (*dt*, *J* = 8.9, 4.9 Hz, 1 H), 0.53 (*dt*, *J* = 8.9, 4.9 Hz, 1 H), 0.73 (*m*, 1 H), 0.95 (*m*, 1 H), 1.24 (*s*, 3 H), 1.47 (*s*, 3 H), 1.64 (*m*, 1 H), 2.37 (*m*, 2 H), 3.28 (*dd*, *J* = 11.2, 7.6 Hz, 1 H), 3.58 (*dd*, *J* = 11.2, 6.1 Hz, 1 H), 4.22 (*bs*, 1 H), 4.59 (*m*, 2 H), 5.00 (*dd*, *J* = 7.0, 5.3 Hz, 1 H), 6.77 (*bs*, 2 H), 7.88 (*s*, 1 H), 8.25 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 8.7, 19.7, 19.8, 24.8, 27.2, 35.8, 47.6, 61.7, 65.7, 83.7, 84.0, 113.3, 119.9, 139.6, 149.6, 152.6, 155.8 ppm; IR (neat): *n* = 3324*w*, 3180*w*, 2988*w*, 2930*w*, 1641*s*, 1597*s*, 1476*m*, 1415*w*, 1375*m*, 1329*w*, 1300*m*, 1247*m*, 1206*s*, 1156*m*, 1061*s*, 860*s*, 798*m*, 724*m*, 648*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{17}H_{24}N_5O_3^+$: 346.1874; found: 346.1869 $[MH]^+$.

2-({(1*R*,2*R*)-2-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methyl)-1*H*-isoindole-1,3(2*H*)-dione ((+)-71).

Compound (–)-**70** (310 mg, 0.9 mmol), DIAD (370 mg, 1.8 mmol), PPh_3 (470 mg, 8.82 mmol), and phthalimide (264 mg, 1.8 mmol) in THF (20 mL) were reacted according to *GP C*. Solvent removal under reduced pressure and CC (CH_2Cl_2/MeOH 19:1) provided (+)-

71 (289 mg, 68%) as a colorless foam. $[\alpha]_D^{20}$ = +22.1 (c = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.62 (*dt*, *J* = 8.4, 5.2 Hz, 1 H), 0.68 (*dt*, *J* = 8.4, 5.2 Hz, 1 H), 0.97 (*m*, 1 H, H-C(5′)), 1.09 (*m*, 1 H), 1.26 (*s*, 3 H), 1.48 (*s*, 3 H), 1.59 (*m*, 1 H), 2.29 (*m*, 2 H), 3.50 (*dd*, *J* = 14.1, 7.4 Hz, 1 H), 3.62 (*dd*, *J* = 14.1, 6.9 Hz, 1 H), 4.59 (*m*, 2 H), 5.03 (*dd*, *J* = 7.1, 5.8 Hz, 1 H), 6.07 (*bs*, 2 H), 7.65 (*dd*, *J* = 5.5, 3.0 Hz, 2 H), 7.78 (*m*, 3 H), 8.26 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.8, 16.9, 20.7, 25.0, 27.4, 36.5, 41.7, 47.6, 61.4, 83.5, 83.8, 113.7, 120.2, 123.2, 131.9, 133.9, 139.5, 149.9, 152.7, 155.6, 168.3 ppm; IR (neat): *n* = 3323*w*, 3158*br w*, 2986*w*, 2930*w*, 1769*w*, 1705*s*, 1634*m*, 1596*m*, 1470*w*, 1373*m*, 1329*m*, 1247*w*, 1207*m*, 1157*w*, 1065*m*, 967*w*, 862*m*, 798*m*, 720*s*, 649*s* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{25}H_{27}N_6O_4^+$: 475.2088; found: 475.2080 [*M*H]$^+$.

9-{(3a*S*,4*R*,6*R*,6a*R*)-6-[(1*R*,2*R*)-2-(Aminomethyl)cyclopropyl]-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}-9*H*-purin-6-amine ((–)-72).

Reaction of (+)-**71** (267 mg, 0.56 mmol) with $MeNH_2$ (20 mL of a 8M solution in EtOH) and purification according to *GP D*, *Method B*, afforded (–)-**72** (150 mg, 77%) as a colorless foam. $[\alpha]_D^{20}$ = -17.3 (c = 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.37 (*dt*, *J* = 8.4, 4.9 Hz, 1 H), 0.50 (*dt*, *J* = 8.4, 4.9 Hz, 1 H), 0.66 (*m*, 1 H), 0.76 (*m*, 1 H), 1.25 (*s*, 3 H), 1.47 (*s*, 3 H), 1.64 (*m*, 1 H), 2.37 (*m*, 2 H), 2.50 (*bs*, 2 H), 4.60 (*m*, 2 H), 5.04 (*dd*, *J* = 7.3, 5.5 Hz, 1 H), 6.58 (*bs*, 2 H), 7.81 (*s*, 1 H),

8.26 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.1, 19.9, 21.0, 25.0, 27.4, 36.5, 46.1, 47.6, 61.6, 83.4, 83.8, 113.4, 120.1, 139.5, 149.6, 152.5, 155.7 ppm; IR (neat): *n* = 3322*br w*, 3168*br w*, 2987*w*, 2932*w*, 1640*s*, 1596*s*, 1475*m*, 1414*w*, 1374*m*, 1328*w*, 1299*m*, 1246*m*, 1206*s*, 1157*m*, 1064*s*, 908*w*, 861*s*, 796*w*, 751*m*, 647*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{17}H_{25}N_6O_2^+$: 345.2034; found: 345.2028 [*M*H]$^+$.

_N_-({(1_R_,2_R_)-2-[(3a_R_,4_R_,6_R_,6a_S_)-6-(6-Amino-9_H_-purin-9-yl)-2,2-dimethyltetrahydro-3a_H_-cyclopenta[_d_][1,3]dioxol-4-yl]cyclopropyl}methyl)-2,2-bis[4-(methoxy)phenyl]-6-nitro-1,3-benzodioxole-4-carboxamide ((+)-76).

Amide coupling of (–)-**72** (60 mg, 0.17 mmol) with **27** (113 mg, 0.26 mmol), using EDC·HCl (75 mg, 0.39 mmol), and *N*-hydroxysuccinimide (39 mg, 0.34 mmol) according to *GP F* yielded (+)-**76** (74 mg, 57%) as an orange foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 19:1). $[a]_D^{20}$ = +1.2 (c = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.58 (*dt*, *J* = 8.4, 5.0 Hz, 1 H), 0.66 (*dt*, *J* = 8.4, 5.0 Hz, 1 H), 0.91 (*ddd*, *J* = 12.6, 8.8, 5.0 Hz, 1 H), 1.02 (*m*, 1 H), 1.27 (*s*, 3 H), 1.50 (*s*, 3 H), 1.66 (*m*, 1 H), 2.38 (*m*, 2 H), 3.25 (*ddd*, J = 13.9, 7.1, 5.4 Hz, 1 H), 3.55 (*dt*, J = 13.9, 6.2 Hz, 1 H), 3.79 (*s*, 6 H), 4.59 (*m*, 2 H), 5.02 (*dd*, *J* = 7.3, 5.5 Hz, 1 H), 6.17 (*bs*, 2 H), 6.86 (*dd*, *J* = 8.9, 2.1 Hz, 4 H), 7.14 (*t*, *J* = 5.4 Hz, 1 H), 7.36 (*m*, 4 H), 7.76 (*d*, *J* = 2.2 Hz, 1 H), 7.77 (*s*, 1 H), 8.24 (*s*, 1 H), 8.54 ppm (*d*, *J* = 2.2 Hz, 1 H); ^{13}C NMR (75

MHz, $CDCl_3$): *d* = 9.0, 17.4, 20.3, 25.0, 27.4, 36.5, 43.7, 47.7, 55.4, 61.5, 83.4, 83.6, 106.4, 113.7 (2x), 114.9, 120.1, 120.2, 122.0, 127.9, 129.4, 139.5, 142.8, 148.0, 149.3, 149.6, 152.5, 155.5, 160.7, 161.1 ppm; IR (neat): *n* = 3421*w*, 3327*br w*, 3103*w*, 1639*m*, 1607*m*, 1514*m*, 1462*m*, 1336*m*, 1245*s*, 1206*m*, 1172*s*, 1067*m*, 1025*m*, 1003*m*, 949*w*, 863*w*, 829*m*, 726*m*, 648*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{39}H_{40}N_7O_9^+$: 750.2882; found: 750.2868 $[MH]^+$.

_N_-({(1_R_,2_R_)-2-[(3a_R_,4_R_,6_R_,6a_S_)-6-(6-Amino-9_H_-purin-9-yl)-2,2-dimethyltetrahydro-3a_H_-cyclopenta[_d_][1,3]dioxol-4-yl]cyclopropyl}methyl)-2,2-bis[4-(methoxy)phenyl]-6-(4-methylphenyl)-1,3-benzodioxole-4-carboxamide ((–)-77).

Amide coupling of (–)-**72** (50 mg, 0.14 mmol) with **28** (122 mg, 0.26 mmol), using EDC·HCl (75 mg, 0.39 mmol) and *N*-hydroxysuccinimide (40 mg, 0.34 mmol) according to *GP F* yielded (–)-**77** (60 mg, 52%) as a colorless foam after purification by CC (SiO_2; CH_2Cl_2/MeOH 19:1). $[a]_D^{20}$ = -1.7 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): *d* = 0.60 (*dt*, *J* = 8.3, 4.9 Hz, 1 H), 0.67 (*dt*, *J* = 8.3, 4.9 Hz, 1 H), 0.91 (*m*, 1 H), 1.04 (*m*, 1 H), 1.28 (*s*, 3 H), 1.52 (*s*, 3 H), 1.68 (*m*, 1 H), 2.38 (*m*, 3 H), 3.29 (*ddd*, *J* = 13.9, 6.9, 5.5 Hz, 1 H), 3.55 (*dt*, *J* = 13.9, 6.2 Hz, 1 H), 3.79 (*s*, 6 H), 4.60 (*m*, 2 H), 5.02 (*dd*, *J* = 7.2, 5.7 Hz, 1 H), 6.08 (*bs*, 2 H), 6.86 (*d*, *J* = 8.9 Hz, 4 H), 7.18 (*m*, 3 H), 7.26 (*t*, *J* = 5.5 Hz, 1 H)), 7.42 (*m*, 6 H), 7.76 (*s*, 1 H), 7.79 (*d*, *J* = 1.8 Hz, 1 H), 8.27 ppm

(*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.0, 17.6, 20.2, 21.1, 25.1, 27.5, 36.5, 43.4, 47.7, 55.3, 61.5, 83.5, 83.7, 110.2, 113.5, 113.7, 115.3, 118.8, 120.2, 120.5, 126.5, 128.0, 129.3, 130.9, 135.6, 136.8, 137.0, 139.5, 143.9, 147.7, 149.7, 152.5, 155.4, 160.3, 163.3 ppm; IR (neat): *n* = 3421*w*, 3323*br w*, 2932*w*, 1634*m*, 1609*m*, 1513*m*, 1466*m*, 1416*m*, 1372*w*, 1249*s*, 1206*s*, 1172*s*, 1025*m*, 1004*m*, 951*w*, 905*w*, 863*w*, 828*s*, 774*w*, 726*m*, 647*m*, 617*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{46}H_{47}N_6O_7^+$: 795.3501; found: 795.3511 [*M*H]$^+$.

_N_-({(1_R_,2_R_)-2-[(1_R_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]cyclopropyl}methyl)-2,3-dihydroxy-5-nitrobenzamide ((+)-15).

Deprotection of (+)-**76** (52 mg, 65 µmol) according to *GP G* yielded (+)-**15** (31 mg, 98%) as a fluffy yellowish solid after HPLC purification and lyophilization of product-containing fractions. $[a]_D^{20}$ = +35.8 (c = 0.79, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): *d* = 0.65 (*m*, 2 H), 1.02 (*m*, 2 H), 1.50 (*m*, 1 H), 1.97 (*ddd*, *J* = 13.3, 10.0, 7.6 Hz, 1 H), 2.56 (*dt*, *J* = 13.3, 8.6 Hz, 1 H), 3.17 (*dd*, *J* = 13.8, 8.2 Hz, 1 H), 3.46 (*dd*, *J* = 13.8, 5.7 Hz, 1 H), 4.03 (*dd*, *J* = 5.2, 2.9 Hz, 1 H), 4.68 (*dd*, *J* = 9.0, 5.2 Hz, 1 H), 4.80 (*dd*, *J* = 18.7, 9.0 Hz, 1 H), 7.67 (*d*, *J* = 2.6, 1 H), 8.18 (*d*, *J* = 2.6 Hz, 1 H), 8.23 (*s*, 1 H), 8.30 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, CD_3OD): *d* = 11.1, 18.8, 23.3, 33.7, 44.6, 48.2, 62.6, 76.2, 76.6, 113.0, 115.4, 116.3, 120.4, 140.4, 144.4, 146.0, 147.9, 150.2, 152.5, 155.9, 169.2

ppm; IR (neat): $\tilde{\nu}$ = 3379*br w*, 3094*w*, 1681*s*, 1511*m*, 1471*w*, 1414*w*, 1329*s*, 1283*m*, 1191*s*, 1134*s*, 1091*m*, 1038*w*, 835*m*, 799*m*, 721*m*, 643*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{21}H_{24}N_7O_7^+$: 486.1732; found: 486.1723 $[M\mathrm{H}]^+$.

_N_-({(1_R_,2_R_)-2-[(1_R_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]cyclopropyl}methyl)-4,5-dihydroxy-4'-methylbiphenyl-3-carboxamide ((+)-16).

Deprotection of (–)-**77** (35 mg, 44 µmol) according to *GP G* yielded (+)-**16** (21 mg, 90%) as a fluffy white solid after HPLC purification and lyophilization of product-containing fractions. $[\alpha]_D^{20}$ = +41.3 (c = 0.67, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD): δ = 0.66 (*m*, 2 H), 1.03 (*m*, 2 H), 1.48 (*td*, *J* = 9.0, 2.3 Hz, 1 H), 2.05 (*ddd*, *J* = 13.4, 9.9, 7.2 Hz, 1 H), 2.34 (*s*, 3 H), 2.60 (*dt*, *J* = 13.4, 9.0 Hz, 1 H), 3.16 (*dd*, *J* = 13.8, 8.8 Hz, 1 H), 3.47 (*dd*, *J* = 13.8, 5.4 Hz, 1 H), 4.03 (*dd*, *J* = 5.0, 2.3 Hz, 1 H), 4.68 (*dd*, *J* = 9.2, 5.0 Hz, 1 H), 4.80 (*dd*, *J* = 18.6, 9.2 Hz, 1 H), 7.12 (*d*, *J* = 8.0 Hz, 2 H), 7.13 (*d*, *J* = 2.2 Hz, 1 H), 7.29 (*d*, *J* = 8.0 Hz, 2 H), 7.34 (*d*, *J* = 2.2 Hz, 1 H), 8.09 (*s*, 1 H), 8.26 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, CD_3OD): δ = 11.4, 19.1, 21.1, 23.4, 33.7, 44.3, 48.1, 62.8, 76.2, 76.7, 116.6, 117.0, 117.6, 120.4, 127.0, 130.2, 132.8, 137.6, 138.2, 144.7, 145.0, 147.3, 149.0, 150.0, 151.9, 171.0 ppm; IR (neat): $\tilde{\nu}$ = 3318*br w*, 3173*br w*, 2985*w*, 1678*s*, 1597*m*, 1546*w*, 1478*w*, 1411*w*, 1311*w*, 1195*s*, 1136*s*, 1073*m*, 1042*m*, 820*m*,

721*m*, 644*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{28}H_{31}N_6O_5^+$: 531.2350; found: 531.2341 $[MH]^+$.

[(1*R*,2*S*)-2-{(3a*R*,4*R*,6*S*,6a*S*)-2,2-Dimethyl-6-[(phenylmethyl)oxy]tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}cyclopropyl]methanol ((–)-66).

Et_2Zn (23 mL of a 1M solution in hexane) was slowly added to a solution of DME (2.4 g, 26.7 mmol) in dry CH_2Cl_2 (17 mL) at –25 °C (internal temperature), followed by CH_2I_2 (4.22 mL, 52.4 mmol). The mixture was stirred for 20 min at –25 °C, before being slowly transferred via cannula to a solution of (+)-**64** (2.24 g, 8.2 mmol) and (–)-**63** (1.40 g, 4.6 mmol) in dry CH_2Cl_2 (14 mL) at –30 °C, while maintaining the internal temperature between –30 °C and –25 °C. The mixture was stirred for 18 h at 20 °C, then the reaction was quenched by addition of sat. aq. NH_4Cl solution and partitioned between H_2O and Et_2O. The aq. phase was extracted with Et_2O (2 x 100 mL), and the combined organic fractions were concentrated to ca. 200 mL. A 5M KOH solution (200 mL) was added, and the biphasic mixture was vigorously stirred for 6 h at 20 °C. The org. phase was washed with sat. aq. NaCl solution, dried over $MgSO_4$, and concentrated *in vacuo*. The diastereoisomeric excess was determined by analytical HPLC (84%). CC (SiO_2; EtOAc/hexane 1:2) using analytical HPLC to verify the purity of the product fractions yielded (–)-**66** (1.42 g, 97%) as a colorless oil. t_R = 11.9 min; $[a]_D^{20}$ = -18.5 (c = 1.36, $CHCl_3$); ^1H NMR (300 MHz,

$CDCl_3$): *d* = 0.40 (*m*, 3 H), 0.88 (*m*, 1 H), 1.33 (*m*, 4 H), 1.50 (*s*, 3 H), 1.78 (*dd*, *J* = 12.0, 5.8 Hz, 1 H), 2.05 (*m*, 1 H), 3.39 (*m*, 2 H), 3.90 (*m*, 1 H), 4.40 (*d*, *J* = 5.3 Hz, 1 H), 4.64 (*m*, 3 H), 7.33 ppm (*m*, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): *d* = 10.0, 20.0, 21.2, 24.3, 26.3, 32.8, 45.8, 66.3, 71.7, 78.3, 84.5, 111.0, 127.8, 128.4, 128.5, 138.5 ppm; IR ($CHCl_3$): *n* = 3007*w*, 2927*m*, 2873*w*, 1455*w*, 1374*m*, 1108*m*, 1008*m*, 909*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{19}H_{24}NaO_4^+$: 341.1723; found: 341.1720 $[M Na]^+$.

[(1*S*,2*S*)-2-{(3a*R*,4*R*,6*S*,6a*S*)-2,2-Dimethyl-6-[(phenylmethyl)oxy]tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}cyclopropyl]methyl acetate ((–)-85).

Ac_2O (2.7 mL, 28.3 mmol) and DMAP (17 mg, 0.14 mmol) were added to a solution of (–)-**66** (900 mg, 2.83 mmol) in dry pyridine (15 mL). The mixture was stirred for 14 h at 20 °C and subsequently partitioned between H_2O and EtOAc. The org. phase was washed with sat. aq. $KHCO_3$ solution (2 x 50 mL) and sat. aq. NH_4Cl solution (2 x 50 mL), before being dried over $MgSO_4$ and evaporated under reduce pressure. CC (SiO_2; EtOAc/hexane 1:2) yielded (–)-**85** (830 mg, 81%) as a colorless oil. $[a]_D^{20}$ = -23.1 (c = 0.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): *d* = 0.44 (*m*, 3 H), 0.99 (*m*, 1 H), 1.33 (*m*, 4 H), 1.49 (*s*, 1 H), 1.76 (*dd*, *J* = 12.4, 5.9 Hz, 1 H), 2.03 (*m*, 4 H), 3.76 (*dd*, *J* = 11.4, 7.7 Hz, 1 H), 3.90 (*m*, 2 H), 4.36 (*d*, *J* = 5.6 Hz, 1 H), 4.60 (*d*, *J* = 12.3 Hz, 1 H), 4.61 (*t*, *J* = 5.1 Hz, 1 H), 4.70 (*d*, *J* = 12.3

Hz, 1 H), 7.32 ppm (*m*, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 10.2, 17.4, 20.6, 21.0, 24.2, 26.2, 32.7, 45.6, 67.9, 71.6, 78.2, 78.3, 84.3, 110.8, 127.5, 127.7, 128.3, 138.3, 171.0 ppm; IR (neat): *n* = 2985*w*, 2935*w*, 1735*s*, 1452*w*, 1369*m*, 1235*s*, 1164*w*, 1114*m*, 1029*m*, 878*w*, 739*w*, 670*w*, 633*w* cm^{-1}; HR-EI-MS: *m/z*: calcd for $C_{21}H_{28}O_5^+$: 360.1932; found: 360.1935 $[M]^+$; elemental analysis calcd (%) for $C_{21}H_{28}O_5$ (360.19): C 69.98, H 7.83; found: C 69.78, H 8.01.

{(1*S*,2*S*)-2-[(3a*R*,4*R*,6*S*,6a*S*)-6-Hydroxy-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methyl Acetate ((+)-86).

Pd/C (10%, 75 mg) was added to a solution of (–)-**85** (760 mg, 2.11 mmol) in MeOH (20 mL), and the mixture was stirred for 14 h at 20 °C under a H_2 atmosphere. Filtration of the mixture over Celite and concentration under reduced pressure provided (+)-**86** (350 mg, 61%) as a colorless oil. $[a]_D^{20}$ = +60.2 (c = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 0.42 (*m*, 3 H), 0.63 (*m*, 1 H), 1.13 (*m*, 1 H), 1.27 (*s*, 3 H), 1.44 (*s*, 3 H), 1.76 (*m*, 2 H), 2.02 (*s*, 3 H), 2.35 (*bs*, 1 H), 3.86 (*dd*, *J* = 11.4, 7.7 Hz, 1 H), 3.93 (*m*, 1 H), 3.98 (*dd*, *J* = 11.4, 6.9 Hz, 1 H), 4.43 (*m*, 1 H), 4.53 ppm (*m*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 7.5, 15.7, 18.6, 21.1, 24.0, 25.8, 33.0, 44.4, 68.4, 77.4, 77.5, 78.7, 109.8, 171.0 ppm; IR (neat): *n* = 3501*br w*, 2988*w*, 2936*w*, 2835*w*, 1734*s*, 1371*s*, 1235*s*, 1208*s*, 1036*s*, 1143*w*, 1102*w*, 970*w*, 878*m*, 826*m*, 633*w* cm^{-1}; HR-EI-MS: *m/z*: calcd for $C_{14}H_{22}O_5^+$:

270.1462; found: 270.1499 [*M*]$^+$; elemental analysis calcd (%) for $C_{14}H_{22}O_5$ (270.15): C 62.20, H 8.20; found: C 62.33, H 8.21.

{(1*S*,2*S*)-2-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methyl Acetate ((–)-87).

Compound (+)-**86** (300 mg, 1.11 mmol), DIAD (450 mg, 2.22 mmol), PPh_3 (582 mg, 2.22 mmol), and 6-chloropurine (260 mg, 1.66 mmol) in dry THF (10 mL) were reacted according to *GP H*. Solvent removal under reduced pressure and CC (SiO_2; EtOAc/hexane 1:1) provided (–)-**87** (175 mg, 39%) as a colorless foam. $[a]_D^{20}$ = -70.4 (c = 0.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = -0.12 (*ddd*, *J* = 12.7, 8.8, 5.0 Hz, 1 H), 0.29 (*dt*, *J* = 8.6, 5.0 Hz, 1 H), 0.38 (*dt*, *J* = 8.6, 5.0 Hz, 1 H), 1.04 (*m*, 1 H), 1.35 (*s*, 3 H), 1.49 (*s*, 3 H), 2.11 (*m*, 6 H), 3.44 (*dd*, *J* = 11.7, 8.1 Hz, 1 H), 3.87 (*dd*, *J* = 11.7, 6.3 Hz, 1 H), 4.77 (*m*, 1 H), 5.17 (*m*, 2 H), 8.14 (*s*, 1 H), 8.71 ppm (*m*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.0, 15.8, 16.4, 21.0, 23.6, 26.1, 37.0, 45.7, 65.7, 67.7, 80.7, 84.3, 110.3, 131.7, 146.4, 151.3, 151.7 (2×), 170.8 ppm; IR (neat): *n* = 2945*w*, 1726*s*, 1593*s*, 1557*s*, 1496*w*, 1445*w*, 1368*m*, 1342*w*, 1245*s*, 1202*s*, 1177*m*, 1141*m*, 1091*w*, 1069*m*, 1047*m*, 1028*m*, 970*w*, 934*s*, 882*s*, 851*s*, 791*m*, 767*w*, 694*w*, 668*m*, 637*s* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{19}H_{24}ClN_4O_4^+$: 407.1481; found: 407.1480 [*M* + Na]$^+$; elemental analysis calcd (%) for $C_{19}H_{24}ClN_4O_4$ (407.15): C 65.09, H 5.70, N 13.77; found: C 56.15, H 5.83, N 13.48.

{(1*S*,2*S*)-2-[(3a*R*,4*R*,6*R*,6a*S*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]cyclopropyl}methanol ((–)-88).

A solution of (–)-**87** (150 mg, 0.37 mmol) in MeOH (20 mL) was saturated with NH_3 and stirred for 14 h at 20 °C. The mixture was then cooled to 0 °C, resaturated with NH_3, and reacted according to *GP I*. Solvent removal and CC (SiO_2; CH_2Cl_2/MeOH 19:1) yielded (–)-**88** (90 mg, 71%) as a colorless foam. $[a]_D^{20}$ = -19.2 (c = 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = -0.19 (*ddd*, *J* = 12.7, 8.7, 4.9 Hz, 1 H), 0.25 (*dt*, *J* = 8.7, 4.9 Hz, 1 H), 0.36 (*dt*, *J* = 8.7, 4.9 Hz, 1 H), 1.03 (*m*, 1 H), 1.33 (*s*, 3 H), 1.47 (*s*, 3 H), 1.98 (*m*, 3 H), 2.90 (*dd*, *J* = 10.9, 8.4 Hz, 1 H), 3.53 (*dd*, *J* = 10.9, 4.4 Hz, 1 H), 3.95 (*bs*, 1 H), 4.83 (*m*, 1 H), 5.06 (*m*, 2 H), 6.38 (*bs*, 2 H), 7.75 (*s*, 1 H), 8.28 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 8.2, 15.9, 21.4, 23.7, 26.0, 36.5, 46.1, 64.0, 65.8, 80.3, 84.6, 110.3, 119.2, 140.7, 150.1, 153.1, 155.8 ppm; IR (neat): *n* = 3331*w*, 3178*w*, 2988*w*, 1642*s*, 1598*s*, 1479*m*, 1415*w*, 1373*m*, 1331*s*, 1204*s*, 1166*m*, 1042*s*, 910*m*, 856*s*, 797*m*, 728*m*, 645*s* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{17}H_{24}N_5O_3^+$: 346.1874; found: 346.1880 $[MH]^+$.

9-{(3a*S*,4*R*,6*R*,6a*R*)-6-[(1*S*,2*S*)-2-(Azidomethyl)cyclopropyl]-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}-9*H*-purin-6-amine ((–)-75).

Compound (–)-**73** (70 mg, 0.2 mmol), DIAD (103 mg, 0.51 mmol), PPh_3 (122 mg, 0.46 mmol), and $(PhO)_2PON_3$ (128 mg, 0.46 mmol) in THF (8 mL) were reacted according to *GP C*. Solvent removal under reduced pressure and CC (CH_2Cl_2/MeOH 19:1) provided (–)-**75** (35 mg, 47%) as a colorless foam. $[a]_D^{20}$ = -58.9 (c = 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* = -0.14 (*ddd*, *J* = 12.4, 8.7, 5.0 Hz, 1 H), 0.29 (*dt*, *J* = 8.5, 5.2 Hz, 1 H), 0.41 (*dt*, *J* = 8.5, 5.2 Hz, 1 H), 0.96 (*m*, 1 H), 1.33 (*s*, 3 H), 1.48 (*s*, 3 H), 2.09 (*m*, 3 H), 2.80 (*dd*, *J* = 12.8, 7.3 Hz, 1 H), 2.93 (*dd*, *J* = 12.8, 6.5 Hz, 1 H), 4.75 (*m*, 1 H), 5.11 (*m*, 2 H), 6.08 (*bs*, 2 H), 7.75 (*s*, 1 H), 8.29 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.6, 15.8, 16.9, 23.8, 26.3, 36.9, 45.5, 54.8, 64.6, 80.7, 84.8, 110.1, 119.6, 140.9, 150.0, 152.7, 155.5 ppm; IR (neat): *n* = 3320*br w*, 3168*br w*, 2985*w*, 2935*w*, 2090*s*, 1639*s*, 1594*s*, 1475*m*, 1414*w*, 1371*m*, 1329*w*, 1248*m*, 1205*s*, 1168*m*, 1043*s*, 977*w*, 910*m*, 855*m*, 798*w*, 767*w*, 729*m*, 641*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{17}H_{23}N_8O_2^+$: 371.1938; found: 371.1934 $[MH]^+$.

9-{(3a*S*,4*R*,6*R*,6a*R*)-6-[(1*S*,2*S*)-2-(Aminomethyl)cyclopropyl]-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl}-9*H*-purin-6-amine ((–)-74).

Compound (–)-**75** (32 mg, 86 µmol) and PPh_3 (68 mg, 0.36 mmol) were dissolved in dioxane (4 mL) and reacted according to *GP E*, *Method A*, to yield (–)-**74** (25 mg, 86%) as a colorless foam. $[a]_D^{20}$ = -24.0 (c = 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): *d* =

-0.24 (*ddd*, *J* = 12.7, 8.8, 4.7 Hz, 1 H), 0.13 (*dt*, *J* = 8.4, 4.9 Hz, 1 H), 0.26 (*dt*, J = 8.4, 4.9 Hz, 1 H), 0.79 (*m*, 1 H), 1.34 (*s*, 3 H), 1.49 (*s*, 3 H), 1.75 (*bs*, 2 H), 2.09 (*m*, 4 H), 2.41 (*dd*, *J* = 12.9, 6.0 Hz, 1 H), 4.77 (*m*, 1 H), 5.09 (*s*, 2 H), 7.78 (*s*, 1 H), 8.31 ppm (*s*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 9.1, 15.5, 21.1, 23.7, 26.1, 36.9, 45.7, 45.8, 64.6, 80.6, 84.9, 110.1, 119.5, 141.1, 150.1, 152.8, 155.4 ppm; IR (neat): *n* = 3319*w*, 3170*w*, 2986*w*, 2931*w*, 2848*w*, 1737*w*, 1641*s*, 1595*s*, 1476*m*, 1435*w*, 1414*w*, 1371*m*, 1329w, 1301*m*, 1251*m*, 1205*s*, 1168*m*, 1119*w*, 1045*s*, 976*w*, 908*m*, 873*m*, 855*m*, 798*w*, 722*s*, 695*s*, 643*m* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{17}H_{25}N_6O_2^+$: 345.2034; found: 345.2028 $[MH]^+$.

_N_-({(1_S_,2_S_)-2-[(1_R_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]cyclopropyl}methyl)-2,3-dihydroxy-5-nitrobenzamide ((+)-17).

Amide coupling of (–)-**74** (21 mg, 61 µmol) with **27** (39 mg, 91 µmol), using EDC·HCl (27 mg, 137 µmol) and *N*-hydroxysuccinimide (14 mg, 119 µmol) according to *GP F*, and deprotection of the product according to *GP G* yielded (+)-**17** (4 mg, 13%) as a fluffy yellowish solid after HPLC purification and lyophilization of product-containing fractions. $[a]_D^{20}$ = +33.2 (c = 0.37, $(CD_3)_2SO$); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): *d* = 0.19 (*dt*, *J* = 8.2, 4.7 Hz, 1 H), 0.24 (*dt*, *J* = 8.2, 4.7 Hz, 1 H), 0.31 (*m*, 1 H), 0.41 (*ddd*, *J* = 12.9, 9.2, 4.7 Hz, 1 H), 1.90 (*m*, 4 H), 2.43 (*dt*, *J* = 13.8, 4.8 Hz,

1 H), 4.03 (*t*, *J* = 3.7 Hz, 1 H), 4.78 (*dd*, *J* = 9.6, 3.7 Hz, 1 H), 4.90 (*t*, *J* = 9.6 Hz, 1 H), 7.67 (*d*, *J* = 2.3 Hz, 1 H), 8.29 (*d*, *J* = 2.4 Hz, 1 H), 8.32 (*bs*, 2 H), 8.39 (*s*, 1 H), 8.57 (*s*, 1 H), 9.03 ppm (*t*, *J* = 5.2 Hz, 1 H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): *d* = 8.8, 17.0, 18.6, 36.3, 41.1, 41.7, 61.2, 69.8, 74.7, 111.7, 113.9, 114.3, 118.6, 138.0, 142.3, 146.8, 147.9, 149.8, 152.6, 156.4, 167.6 ppm; IR (neat): *n* = 3095*br m*, 1674*s*, 1512*m*, 1475*w*, 1414*w*, 1332*m*, 1196*s*, 1133*s*, 838*w*, 798*w*, 743*w*, 720*m*, 641*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{21}H_{24}N_7O_7^+$: 486.1732; found: 486.1724 [*M*H]$^+$.

_N_-{3-[(1_S_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]propyl}-2,3-dihydroxy-5-nitrobenzamide ((–)-18).

Pd/C (25 mg, 10%) was added to a solution of (+)-**58** (25 mg, 75.7 µmol) in MeOH (3 mL), and the mixture was stirred 14 h at 20°C under a H_2 atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue (12 mg) was redissolved in TFA/H_2O (2 mL, 1:1) and the mixture stirred for 60 min at 0 °C. Volatiles were removed under high vaccum at 20 °C, and the residue was redissolved in dry DMF (2.5 mL). Catechol **53** (13 mg, 43 µmol) and Et_3N (0.1 mL) were added to the solution, and the mixture was stirred for 14 h at 20 °C. Purification by RP-HPLC (0.1% TFA in H_2O/CH_3CN) yielded (–)-**18** (8 mg, 22%) as a fluffy yellowish solid after lyophilization of product-

containing fractions. $[\alpha]_D^{20}$ = -17.7 (c = 0.26, $(CH_3)_2SO$); ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 1.36 (*m*, 1 H), 1.55 (*m*, 4 H), 1.83 (*m*, 1 H), 2.23 (*m*, 1 H), 3.28 (*m*, 2 H), 3.64 (*m*, 1 H), 4.24 (*t*, *J* = 6.0 Hz, 1 H), 4.64 (*m*, 1 H), 7.63 (*s*, 1 H), 8.26 (*s*, 1 H), 8.36 (*s*, 1 H), 8.39 (*bs*, 2 H), 8.41 (*s*, 1 H), 9.20 ppm (*bs*, 1 H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$): δ = 27.0, 31.3, 32.5, 40.4, 42.8, 60.1, 74.4, 74.6, 112.0, 114.1, 114.3, 118.8, 138.3, 142.2, 147.0, 147.1, 149.0, 152.1, 156.4, 168.1 ppm; IR (neat): ν = 3093*br m*, 1681*s*, 1511*m*, 1473*m*, 1328*s*, 1195*s*, 1131*s*, 890*w*, 836*w*, 797*w*, 743*w*, 721*m*, 641*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{20}H_{24}N_7O_7^+$: 474.1732; found: 474.1742 $[MH]^+$.

_N_-{3-[(1_S_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]propyl}-4,5-dihydroxy-4'-methylbiphenyl-3-carboxamide ((–)-19).

Pd/C (10%, 10 mg) was added to a solution of (–)-**14** (8 mg, 15.5 µmol) in MeOH (2 mL), and the mixture was stirred for 14 h at 20 °C under a H_2 atmosphere. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure provided (–)-**19** (3.6 mg, 45%) as a colorless, fluffy solid after HPLC purification and lyophilization of product-containing fractions. $[\alpha]_D^{20}$ = -6.6 (c = 0.46, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.56 (*m*, 1 H), 1.77 (*m*, 3 H), 1.86 (*m*, 1 H), 2.09 (*m*, 1 H), 2.35 (s, 3 H), 2.49 (*dt*, *J* = 12.8, 7.9 Hz, 1 H), 3.45 (*m*, 2 H), 3.90 (*dd*, *J* = 5.9, 4.0 Hz, 1 H), 4.49 (*dd*, *J* = 8.6, 6.0 Hz, 1 H), 4.86 (*m*, 1 H), 7.20 (*d*, *J* = 2.1

Hz, 1 H), 7.21 (*d*, *J* = 8.4 Hz, 2 H), 7.46 (*d*, *J* = 8.4 Hz, 2 H), 7.50 (*d*, *J* = 2.1 Hz, 1 H), 8.28 (*s*, 1 H), 8.37 ppm (*s*, 1 H); ^{13}C NMR (125 MHz, CD_3OD): *d* = 21.1, 28.8, 32.8, 33.6, 40.4, 44.5, 62.8, 76.3 (2 x), 116.8, 117.0, 118.0, 120.5, 127.4, 130.4, 133.2, 137.8, 138.8, 144.6, 145.9, 147.6, 149.5, 150.6, 152.6, 171.5 ppm; IR (neat): *n* = 3096*br w*, 1678*s*, 1594*m*, 1549*m*, 1477*w*, 1413*w*, 1315*w*, 1198*s*, 1133*s*, 895*w*, 819*w*, 798*w*, 722*w*, 641*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{27}H_{29}N_6O_5^-$: 517.2205; found: 517.2214 [*M*H]$^-$.

_N_-{2-[(1_S_,2_R_,3_S_,4_R_)-4-(6-Amino-9_H_-purin-9-yl)-2,3-dihydroxycyclopentyl]ethyl}-2,3-dihydroxy-5-nitrobenzamide ((+)-20).

PtO_2 (50 mg, 0.22 mmol) was added to a solution of (–)-**90** (70 mg, 0.22 mmol) in THF/AcOH (6 mL, 1:2) and the mixture stirred for 18 h at 20° C under a H_2 atmosphere. Following filtration and evaporation of the solvents under reduced pressure, the residue was treated with TFA/H_2O (3 mL, 1:1) for 1 h at 0 °C. Volatiles were removed under high vacuum at 20 °C, and the residue was redissolved in dry DMF (3 mL). Catechol **53** (73 mg, 0.24 mmol) and Et_3N (0.3 mL) were added to the solution, and the mixture was stirred for 14 h at 20 °C. Purification by RP-HPLC (0.1% TFA in H_2O/CH_3CN) yielded (+)-**20** (33 mg, 32%) as a fluffy yellowish solid after lyophilization of product-containing fractions. $[a]_D^{20}$ = +1.1 (c = 0.87, $(CD_3)SO$); ^{1}H NMR (300 MHz, $(CD_3)SO$): *d* = 1.68 (*m*, 2 H), 1.94

(*m*, 2 H), 1.39 (*dt*, *J* = 12.7, 7.7 Hz, 1 H), 3.39 (*m*, 2 H), 3.77 (*dd*, *J* = 5.9, 4.2 Hz, 1 H), 4.33 (*dd*, *J* = 8.0, 5.9 Hz, 1 H), 4.73 (*dt*, *J* = 10.3, 8.0 Hz, 1 H), 7.71 (*d*, *J* = 2.5 Hz, 1 H), 8.36 (*s*, 1 H), 8.44 (*d*, *J* = 2.5 Hz, 1 H), 8.51 (*s*, 1 H), 9.32 ppm (*t*, *J* = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $(CD_3)SO$): *d* = 32.5, 33.4, 37.9, 40.7, 60.1, 74.5, 74.6, 111.9, 114.0, 114.2, 118.7, 138.1, 142.0, 146.8, 146.9, 148.8, 151.9, 156.2, 167.9 ppm; IR (neat): *n* = 3097*br w*, 1678*s*, 1512*m*, 1473*w*, 1416*w*, 1328*s*, 1195*s*, 1132*s*, 891*w*, 837*w*, 798*w*, 743*w*, 721*w*, 642*w* cm^{-1}; HR-MALDI-MS: *m/z*: calcd for $C_{19}H_{22}N_7O_7^+$: 560.1575; found: 460.1567 $[MH]^+$.

Experimental details of the in vitro assay

Enzyme preparations were preincubated for 15 min at 37 °C with inhibitor concentrations varying from 10^{-3} to 10^{-9} mol L^{-1}. The reaction was started by addition of substrate (benzene-1,2-diol, 0.025 mol L^{-1}) and radiolabeled cofactor [^{1}H]/[^{3}H]SAM, reaching a final substrate concentration of 2.5 mM and a final [^{1}H]/[^{3}H]SAM concentration of 183 µM. After the vials had been incubated in a water-bath at 37 °C for 15 min, the reaction was stopped by addition of acetic acid (5.7%) containing guaiacol (0.1 g L^{-1}). IC_{50} values were obtained by nonlinear curve fit to a plot of enzymatic activity vs. logarithmic inhibitor concentration.