Bisubstrate Inhibitors for the Enzyme Catechol *O*-Methyltransferase (COMT): Dramatic Effects of Ribose Modifications on Binding Affinity and Binding Mode

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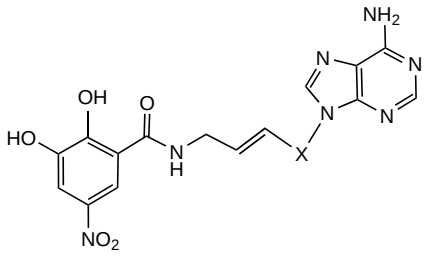
Dedicated, on the occasion of his 80th birthday, to Professor *Jack D. Dunitz*, a postdoctoral fellow in the *Diederich* group since 1992

Inhibition of the enzyme catechol *O*-methyltransferase (COMT) is of significant interest in the therapy of *Parkinson*'s disease. Described herein are structural analogs of the potent bisubstrate inhibitor (−)-**1** (IC_{50} = 9 nM; *Table 1*) for COMT, with target modifications of the central ribose moiety. Their synthesis involves, as key intermediates, adenosine derivatives, which are transformed to the potential bisubstrate inhibitors by a similar sequence of six steps (*Schemes 1–4*). The compounds were submitted to an enzymatic assay for determination of their *in vitro* inhibitory activity against COMT, and the inhibition mechanism with respect to the binding side of the cofactor *S*-adenosylmethionine (SAM) was analyzed by kinetics measurements (*Fig. 3*). Both binding affinity and binding mode were exceedingly sensitive towards modifications of the ribose moiety (*Table 1*). Removal of the 2′-OH group upon changing from (−)-**1** to (−)-**2** (IC_{50} = 28 μM) led to a reduction in binding affinity by more than three orders of magnitude. At the same time, competitive inhibition kinetics with respect to the SAM binding site was maintained, thereby supporting a bisubstrate binding mode. Unlike (−)-**2**, the dideoxyribose inhibitor (−)-**3** (IC_{50} = 3 μM) showed a mixed and the cyclopentane derivative (+)-**4** (IC_{50} = 1 μM) an uncompetitive inhibition mechanism with respect to the SAM binding site. In the complex of the latter, the adenine-substituted cyclopentane ring orients most probably towards the surface of the enzyme into the surrounding solution. The enantiomeric compounds (−)-**5** (IC_{50} = 43 μM) and (+)-**5** (IC_{50} = 141 μM), wherein the ribose had been replaced by a pyrrolidine ring, showed only low binding affinity.

1. Introduction. – The enzyme catechol *O*-methyltransferase (COMT) catalyzes the transfer of a Me group from the cofactor *S*-adenosylmethionine (SAM) to a OH group of biologically active catechols in the presence of a Mg^{2+} ion. The inhibition of COMT reduces the peripheral degradation of L-dopa and increases its supply to the brain, which is of significant interest for the L-dopa-based therapy of *Parkinson*'s disease [1]. NO_2-Substituted catechols were found to be potent COMT inhibitors, and two of them are currently in therapeutic use [2]. Based on the X-ray crystal structure of COMT [3],

we developed the first effective bisubstrate inhibitor that binds to both cofactor and catechol binding sites of the enzyme [4]. Further optimization of the linker between the nucleoside and catechol moieties subsequently led to the highly active bisubstrate inhibitor (−)-**1** (IC_{50} = 9 nM; IC_{50} = concentration of inhibitor at which 50% V_{max} is observed) [5]. The bisubstrate binding mode of (−)-**1** was confirmed by kinetic studies and the X-ray crystal structure of the ternary complex formed between COMT, (−)-**1**, and a Mg^{2+} ion [5].



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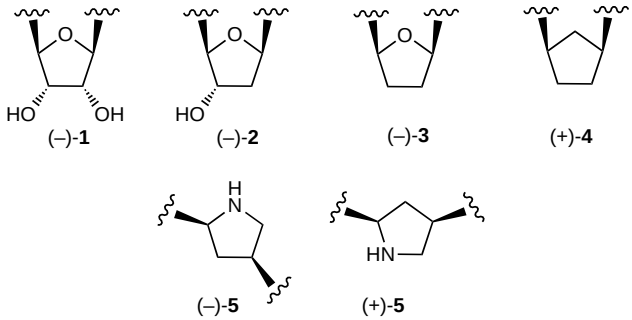


In this paper, we present the synthesis and biological activity of a series of derivatives of (−)-**1**, in which the ribose moiety has been modified. Compounds (−)-**2**, (−)-**3**, and (+)-**4** were designed to probe the energetic contribution of the two H-bonds formed between the two ribose OH-groups in (−)-**1** with the side-chain carboxylate of Glu90 in COMT, as seen in the X-ray crystal structure of the ternary complex [5]. Computer modeling, with the molecular-modeling program MOLOC with the MAB force field [6], suggested that the 2′-deoxyribose derivative (−)-**2** would adopt a bisubstrate binding mode similar to the one observed for (−)-**1**, with the 3′-OH group undergoing H-bonding to the side-chain carboxylate of Glu90 (*Fig. 1*). On the other hand, the effect of removing both ribose OH-groups in (−)-**3** and (+)-**4**, thereby eliminating any H-bonding to Glu90, was difficult to predict at the design stage. It is, however, well-known that ribose pockets at the ATP binding sites of some kinases tolerate the occupancy by highly lipophilic residues, even in the presence of side-chain carboxylates [7]. A possible re-orientation of the side chain of Glu90 away from the ribose pocket in the complexes of (−)-**3** and (+)-**4**, lacking H-bonding OH groups, could not be excluded *a priori*. On the other hand, making the inhibitors more lipophilic seemed attractive for further enhancing their binding affinity and bioavail-

ability [8]. The modeling suggested that both enantiomers of **5** would be capable of forming a salt bridge between their protonated pyrrolidine ring and the side-chain of Glu90.

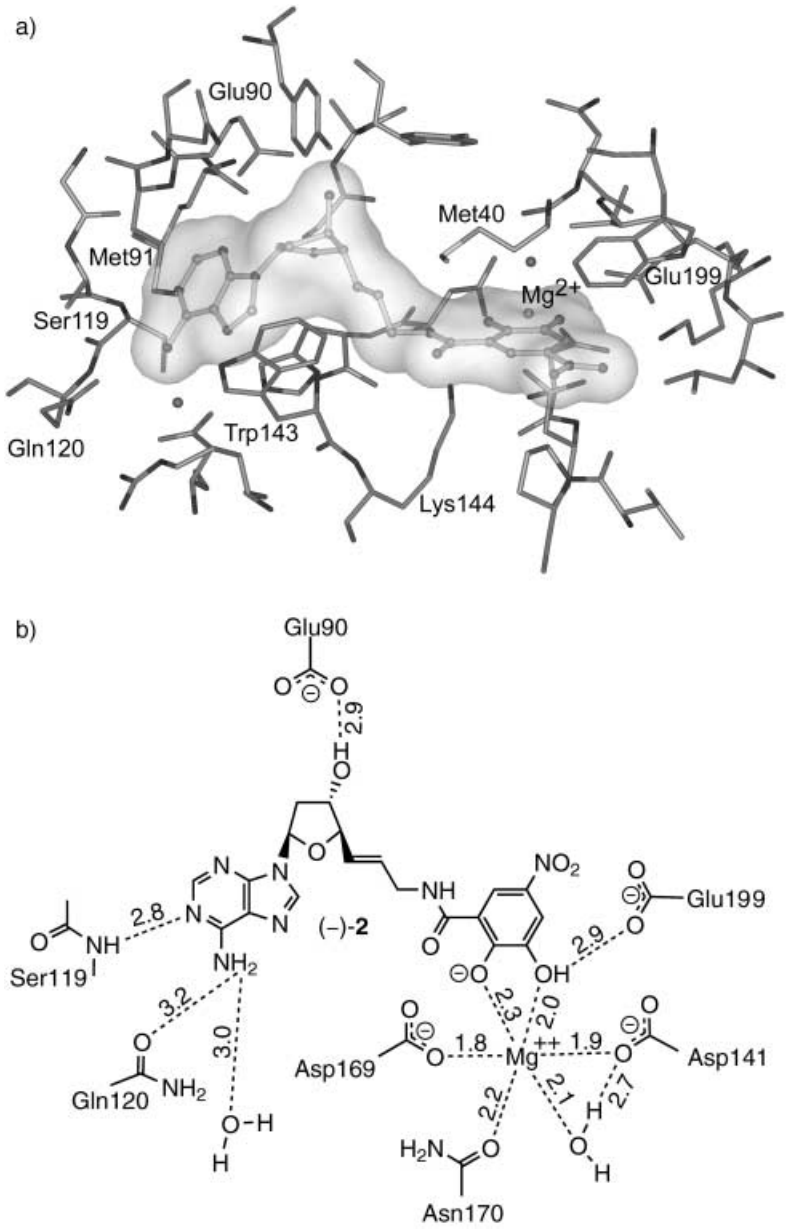


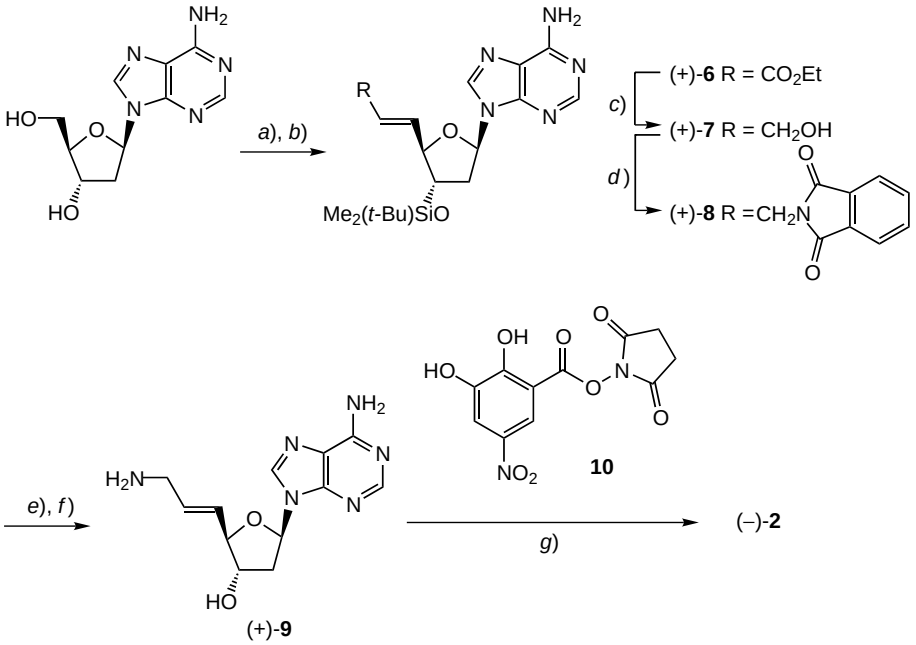
Fig. 1. a) *Computer-modeled ternary complex between COMT, Mg^{2+}, and bisubstrate inhibitor (–)-***2**. The *Connolly* surface of the inhibitor is shown. b) *Schematic drawing of the H-bonding and metal-ion interactions* (dashed lines) *in the ternary complex*. Distances are given in Å.

Here, we show that ribose substitutions in bisubstrate inhibitors of COMT are extremely challenging, and that even small changes alter dramatically both binding affinity and binding mode of the inhibitors.

2. Results and Discussion. – 2.1. *Synthesis.* In analogy to the synthesis of (−)-**1** [5], the preparation of (−)-**2** started with the selective one-pot 5′-oxidation of 2′-deoxyadenosine with *ortho*-iodoxybenzoic acid (IBX) and olefination with Ph_3PCHCO_2Et [9], followed by protection of the 3′-OH group, to give the ester (+)-**6** (62%) (*Scheme 1*). Crystals of (+)-**6** suitable for X-ray analysis were obtained by slow evaporation of a concentrated solution in MeOH. The compound crystallized in the space group $P2_12_12_1$. In the X-ray crystal structure (*Fig. 2, a*), the adenine moiety adopts the *syn* conformation with respect to the deoxyribose ring. The crystal lattice shows a layered structure of H-bonded pairs of nucleosides, with one adenine binding in the *Watson–Crick* and the other in the *Hoogsteen* mode (*Fig. 2, b*).

Reduction of (+)-**6** with DIBAL-H (diisobutylaluminum hydride) provided allylic alcohol (+)-**7** (73%), which was transformed into phthalimide (+)-**8** by a *Mitsunobu* reaction (84%). Phthalimide (+)-**8** was cleaved to the amine with $MeNH_2$ [10], and the silyl protective group was removed with Bu_4NF. In the workup, addition of an aqueous solution of $NaClO_4$ led to precipitation of Bu_4NClO_4, which was removed conveniently

Scheme 1. *Synthesis of the Inhibitor (−)-***2**



a) *o*-Iodoxybenzoic acid (IBX), $Ph_3P{=}CHCO_2Et$, Me_2SO, 20°, 70 h. *b*) Me_2(*t*-Bu)SiCl, 1*H*-imidazole, DMF, 20°, 21 h; 62%. *c*) DIBAL-H, hexane, CH_2Cl_2, −78°, 4 h; 73%. *d*) Phthalimide, diethyl azodicarboxylate (DEAD), PPh_3, THF, 20°, 14 h; 84%. *e*) $MeNH_2$, EtOH, 20°, 35 h. *f*) Bu_4NF, THF, 20°, 16 h; 99%. *g*) **10**, $NaHCO_3$, DME, H_2O, 20°, 20 h; 26%.

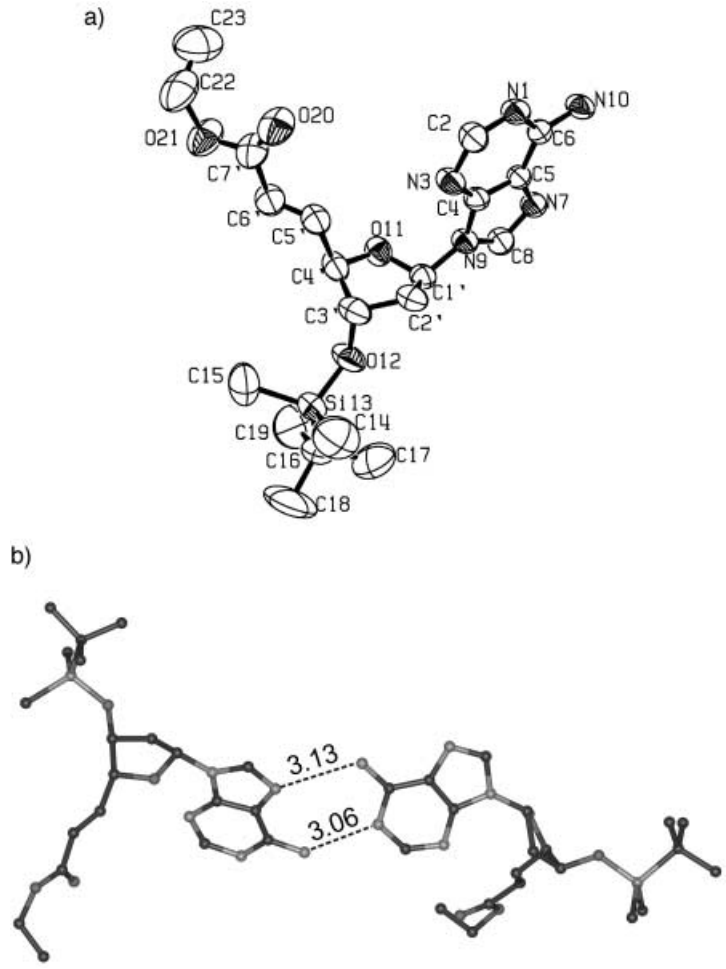


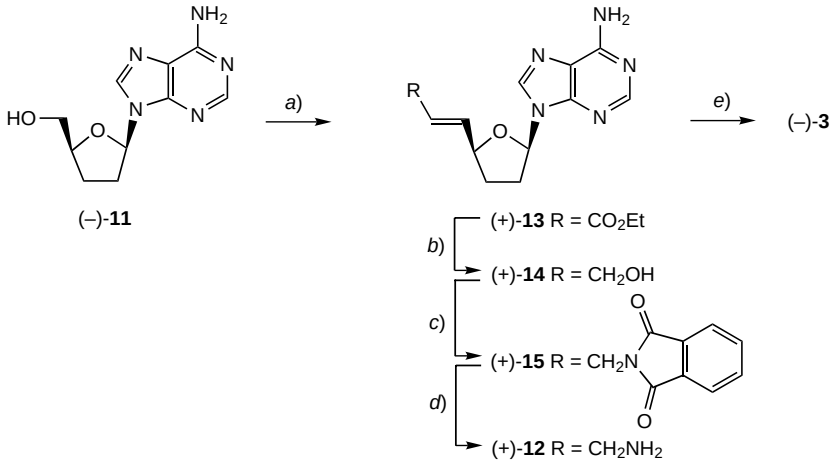
Fig. 2. a) *X-Ray crystal structure of (+)*-**6**. Arbitrary numbering. Atomic displacement parameters obtained at 295 K are drawn at the 50% probability level. b) *H-Bonding between pairs of molecules in the crystal packing of (+)*-**6**. N···N Distances in Å.

by filtration [11]. The polar, fully deprotected amine (+)-**9** was isolated in quantitative yield after purification by ion-exchange chromatography. The activated ester **10** [4] reacted selectively with the primary amino group of (+)-**9** to give the inhibitor (−)-**2** (26%). Similar yields of (−)-**2** were obtained with either 1,2-dimethoxyethane (DME)/H_2O as solvent with $NaHCO_3$ as a base [12], or DMF together with Et_3N [4].

For the synthesis of (−)-**3** (*Scheme 2*), 2′,3′-dideoxyadenosine ((−)-**11**) was prepared according to the procedure described in [13]. Following the protocol for (+)-**9** (*Scheme 1*), amine (+)-**12** was obtained *via* the sequence (+)-**11** → (+)-**13** → (+)-**14** → (+)-**15** → (+)-**12**, and reaction with activated ester **10** afforded inhibitor (−)-**3**. First attempts to purify (−)-**3** by reversed-phase chromatography on *SiO_2 100 C_{18}* with

MeCN/1% aqueous HCOOH or MeCN/0.1% aqueous CF_3COOH (TFA) mixtures as eluent failed due to decomposition of the acid-labile product. Purification was eventually achieved with a volatile triethylammonium carbonate buffer, which was readily obtained by bubbling CO_2 through aqueous Et_3N solution. Nevertheless, subsequent buffer removal proved problematic as ^{1}H-NMR product analysis showed residual traces of buffer even after repeated lyophilization. It was, however, possible to remove any residual buffer *via* ion exchange on *Dowex® 50W × 2* (NH_4^+).

Scheme 2. *Synthesis of Inhibitor (–)*-**3**.

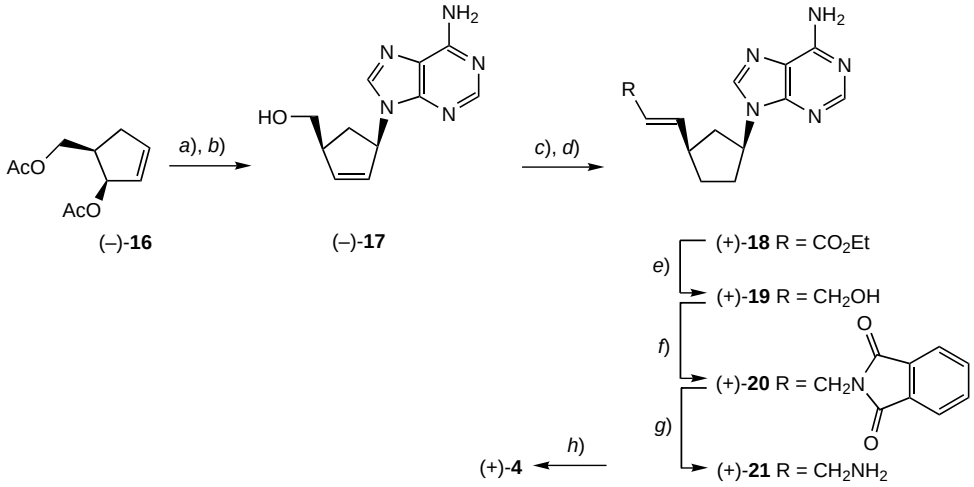


a) IBX, $Ph_3P{=}CHCO_2Et$, Me_2SO, 20°, 37 h; 57% *b*) DIBAL-H, hexane, CH_2Cl_2, −78°, 1 h; 67%. *c*) Phthalimide, DEAD, PPh_3, THF, 20°, 18 h; 96%. *d*) $MeNH_2$, EtOH, 20°, 16 h; 83%. *e*) **10**, Et_3N, DMF, 20°, 16 h; 63%.

The synthesis of the inhibitor (+)-**4** (*Scheme 3*) was achieved starting from the enantiomerically pure building block (−)-**16**, which was prepared according to an elegant procedure introduced by *Crimmins et al.* [14], involving an asymmetric aldol addition [15] and a ring-closing metathesis reaction (for formation of the five-membered ring) as key steps. Stereo- and regioselective introduction of the adenine moiety by Pd-catalyzed substitution of the allylic acetate gave (−)-**17** [16]. The best results (55%) in this conversion were obtained with NaH as base and $[Pd(PPh_3)_4]$ as catalyst; in the absence of base or in the presence of weaker bases such as Et_3N or Cs_2CO_3, no conversion to the desired product was observed. Reduction of the C=C bond by catalytic hydrogenation, followed by the sequence of transformations as described above for (−)-**2** ((−)-**17** → (+)-**18** → (+)-**19** → (+)-**20** → (+)-**21**), afforded amine (+)-**21**, which reacted with **10** to give target compound (+)-**4**.

For the synthesis of the pure enantiomers (−)-**5** and (+)-**5**, intermediates (−)-**22** [17] and (+)-**22** [18], respectively, were prepared according to literature procedures. Different leaving groups (methylsulfonyl (Ms), *para*-toluenesulfonyl (Ts), *para*-bromobenzenesulfonyl (Bs), and *para*-nitrobenzenesulfonyl (Ns)) were tested for the activation of the OH group in (−)-**22**, for the subsequent nucleophilic displacement with adenine. The *para*-nitrobenzenesulfonyl (nosyl, Ns) group was found to be the

Scheme 3. *Synthesis of the Inhibitor (+)*-**4**.



a) Adenine, NaH, $[Pd(PPh_3)_4]$, THF, 45°, 3 h. *b*) NaOH, H_2O; 55%. *c*) H_2, Pd/C, MeOH, 20°, 3 h. *d*) IBX, $Ph_3P{=}CHCO_2Et$, Me_2SO, 20°, 15 h; 71% *e*) DIBAL-H, hexane, CH_2Cl_2, −78°, 1 h; 38%. *f*) Phthalimide, DEAD, PPh_3, THF, 20°, 15 h; 75%. *g*) $MeNH_2$, EtOH, 20°, 16 h; 99%. *h*) **10**, Et_3N, DMF, 20°, 16 h; 25%.

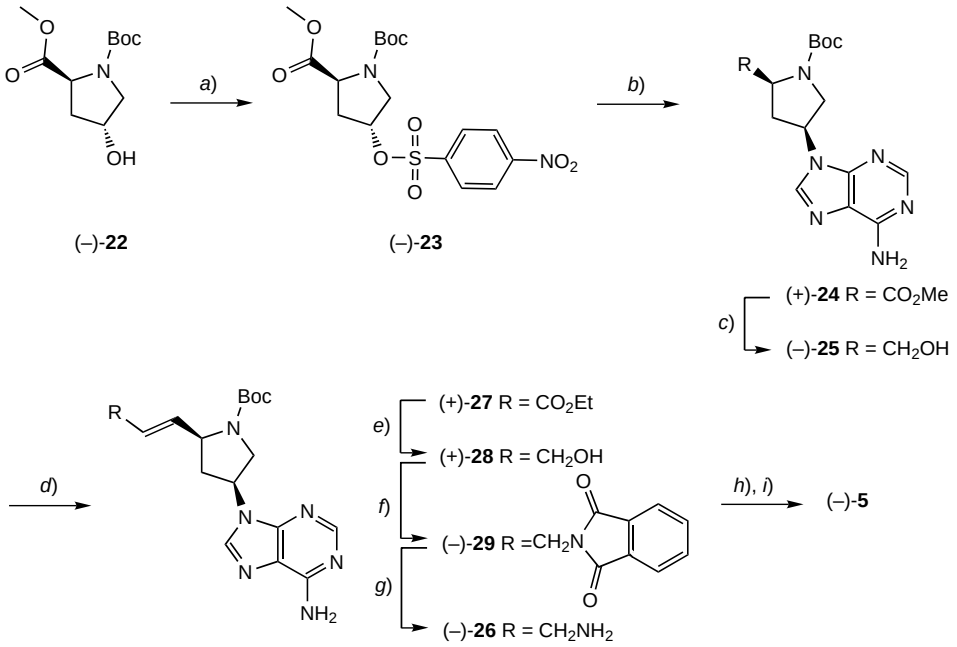
best in this case. High yields for its introduction, leading to compound (−)-**23** (87%), and for the substitution step, providing (+)-**24** (72%), were obtained. According to ^{13}C-NMR spectroscopy, adenine reacted regioselectively at the desired N(9) position [19]. Ester (+)-**24** was reduced in 89% yield to the primary alcohol (−)-**25** with $NaBH_4$ in the presence of LiCl; in the absence of LiCl, no conversion was observed. Following the sequence described above for the synthesis of (−)-**2**, amine (−)-**26** was obtained *via* (−)-**25** → (+)-**27** → (+)-**28** → (−)-**29** → (−)-**26**. Coupling the amine (−)-**26** to **10** and subsequent removal of the Boc protecting group provided (−)-**5** (71%). Enantiomer (+)-**5** was obtained analogously.

2.2. *Biological Activity.* All newly synthesized inhibitors were tested for *in vitro* inhibitory activity against COMT obtained from rat liver. The IC_{50} values were determined in a radiochemical assay as reported in [4][20] and are listed in the *Table*.

Table. IC_{50} *Values* (uncertainties ± 5%) *Determined by Radiochemical Assay with Preincubation for the Inhibitors of COMT*

Compound	IC_{50} [μM]
(−)-**1**	0.009
(−)-**2**	28
(−)-**3**	3
(+)-**4**	1
(−)-**5**	43
(+)-**5**	141

Scheme 4. *Synthesis of the Inhibitor (−)*-**5** (the synthesis of (+)-**5** follows the same procedure, starting from (+)-**22**; yields are given in parentheses)



a) NsCl, pyridine, 4°, 14 h; 87% (85%). *b*) Adenine, K_2CO_3, 18-crown-6, DMF, 80°, 6 h; 72% (60%). *c*) $NaBH_4$, LiCl, THF, EtOH, 0°, 1 h then 55°, 11 h; 89% (85%). *d*) IBX, $Ph_3P{=}CHCO_2Et$, Me_2SO, 20°, 42 h; 54% (53%). *e*) DIBAL-H, hexane, CH_2Cl_2, −78°, 1 h; 50% (68%). *f*) Phthalimide, DEAD, PPh_3, THF, 20°, 16 h; 92% (75%). *g*) $MeNH_2$, EtOH, 20°, 20 h; 74% (74%). *h*) **10**, Et_3N, DMF, 20°, 20 h. *i*) TFA, H_2O, 20°, 2 h; 71% (84%).

Removal of the 2′-OH group leads to a dramatic loss in binding affinity, with the ternary complex formed by COMT, Mg^{2+}, and (−)-**2** (IC_{50} = 28 μM) being three orders of magnitude less stable than the one formed by (−)-**1** (IC_{50} = 9 nM). Increasing the hydrophobicity by removing the second OH group ((−)-**3**: IC_{50} = 3 μM) and replacing the ribose by a cyclopentane ring ((+)-**4**: IC_{50} = 1 μM) slightly increases the binding affinity relative to (−)-**2**. Compounds (−)-**5** (IC_{50} = 43 μM) and (+)-**5** (IC_{50} = 141 μM), wherein the ribose had been replaced by a pyrrolidine ring, are the least active in this series of inhibitors. Clearly, changes in the ribose substitution pattern have dramatic, unfavorable effects on binding affinity. Also, replacement of the ribose moiety by a pyrrolidium ring, which, in protonated form, could undergo ion pairing with the side-chain carboxylate of Glu90, leads to a disappointingly low activity of the designed bisubstrate inhibitors.

Kinetic studies were performed with (−)-**2**, (−)-**3**, and (+)-**4** [4] to determine the inhibition mechanism with respect to the cofactor binding site. Similar measurements were not conducted with respect to the catechol binding site, since the competitive occupation of this site by nitrocatechols is amply documented [2][4][5]. In the inhibition experiments, the concentration of SAM was varied at saturating benzene-1,2-

diol concentration for different concentrations of inhibitor. Initial velocities were determined without preincubation. K_i Values were calculated by globally fitting the data to *Eqns. 1*, *2*, or *3*, corresponding to linear competitive, uncompetitive, or mixed inhibition, respectively [21]. In these equations, K_{ic} and K_{iu} are the competitive and uncompetitive inhibition constants, respectively.

$$v = V[S]/(K_m(1 + [I]/K_{ic}) + [S]) \quad (1)$$

$$v = V[S]/(K_m + [S](1 + [I]/K_{iu})) \quad (2)$$

$$v = V[S]/(K_m(1 + [I]/K_{ic}) + [S](1 + [I]/K_{iu})) \quad (3)$$

Bisubstrate inhibitors in our previous studies had shown a competitive inhibition mechanism with respect to the SAM binding site, and, in the case of (−)-**1**, this binding mode had been confirmed by X-ray crystallography [5]. Similarly, (−)-**2**, although lacking the 2′-OH group, shows a competitive mechanism with respect to the SAM binding site (crossing of the lines on the *y*-axis in the *Lineweaver–Burk* plot; *Fig. 3, a*). The calculated inhibition constant is $K_i = K_{ic} = 14 \pm 1$ μM. Although the elimination of the 2′-OH group upon changing from (−)-**1** to (−)-**2** reduces the binding free energy by as much as *ca.* 5 kcal mol^{-1}, the deoxyadenosine derivative is still competing for the SAM cofactor binding site. On the other hand, compound (+)-**4**, with a cyclopentyl ring substituting for the ribose moiety, is no longer capable of occupying the SAM binding site. This is clearly reflected by uncompetitive inhibition kinetics (parallel lines in the *Lineweaver–Burk* plot; $K_i = K_{iu} = 0.56 \pm 0.03$ μM). Only the catechol substrate binding site is occupied by (+)-**4**, whereas the adenine-substituted cyclopentane ring most probably orients towards the periphery of the enzyme, into the surrounding solution. Dideoxyadenosine derivative (−)-**3** showed a mixed inhibition mechanism, $K_i = K_{ic} = K_{iu} = 2.7 \pm 0.1$ μM (lines in the *Lineweaver–Burk* plot cross on the *x*-axis); this case is often referred to as a noncompetitive inhibition mechanism, although the use of this terminology is disfavored [21]. These results demonstrate that a meaningful, comparative discussion of the inhibition properties of bisubstrate inhibitors requires detailed knowledge of the inhibition kinetics.

3. Conclusions. – Biological assays and kinetic studies show that both binding affinity and binding mode of potential bisubstrate inhibitors for COMT are extremely sensitive towards changes of the ribose moiety. Thus, the dramatic decrease in affinity by more than three orders of magnitude upon changing from ribose derivative (−)-**1** to 2′-deoxyribose derivative (−)-**2** – both are bisubstrate inhibitors as revealed by the enzyme kinetics – strongly suggests that H-bonding of the *two* OH groups of the ribose moiety to the side-chain carboxylate of Glu90 is necessary for efficient binding. Apparently, a single OH group as in (−)-**2** is not sufficient to 'solvate' the carboxylate, which obviously cannot adopt another orientation by turning away from the ribose pocket. In future work, we intend to prepare the 3′-deoxyadenosine derivative to further underline this statement. Most remarkably, a series of small changes in the ribose ring – while keeping the adenine and catechol moieties the same – changes the inhibition kinetics from competitive ((−)-**2**), to mixed ((−)-**3**), and to uncompetitive

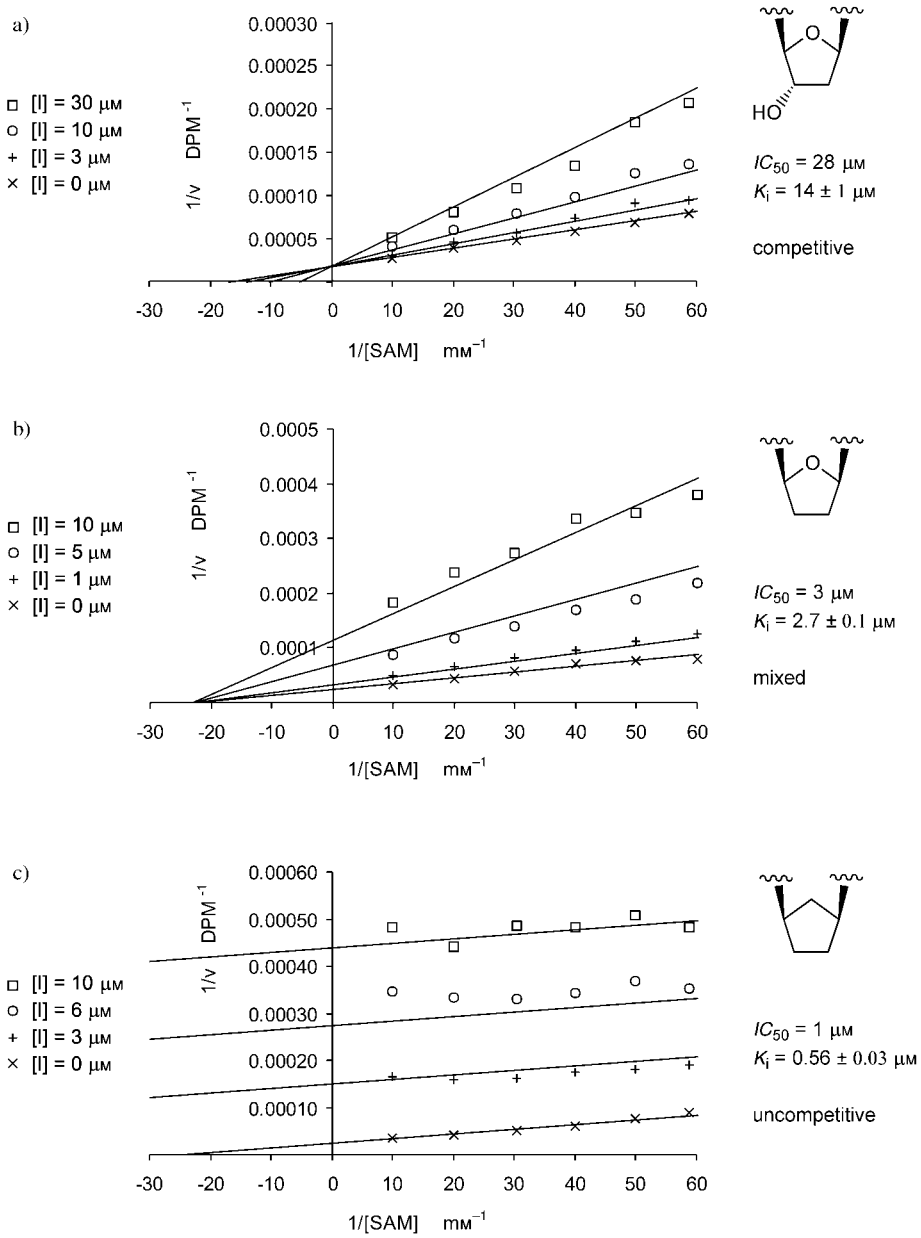


Fig. 3. Lineweaver–Burk *plots of reciprocal enzymatic activity* vs. *reciprocal SAM concentration for varying concentrations of inhibitors (–)*-**2** (a), *(–)*-**3** (b), *and (+)*-**4** (c) *at saturating benzene-1,2-diol concentration*. DPM = decays per min.

((+)-**4**). The different inhibition mechanisms of (−)-**3** and (+)-**4** suggest that the O-atom in the furan ring is also relevant for recognition in the ribose pocket. The pyrrolidine rings of (−)-**5** and (+)-**5** are poor replacements for the ribose moiety and most probably are pointing towards the surface of the enzyme into the surrounding solution rather than into the SAM binding site. These investigations clearly show that modifications of the ribose moiety in bisubstrate inhibitors of COMT are delicate and remain a true challenge for future investigations.

Experimental Part

General. Solvents and reagents were purchased reagent-grade and used without further purification. All reactions were carried out under an Ar atmosphere. The following compounds were prepared according to literature procedures: **10** [4] [22], (−)-**11** [13], (−)-**16** [14], (−)-**22** [17], (+)-**22** [18], and IBX [23]. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Anh. Me_2SO and DMF, stored over molecular sieves, were purchased from *Fluka*. Evaporation *in vacuo* was performed at *ca.* 20 Torr. All products were dried under high vacuum (0.05 Torr) before anal. characterization. Thin-layer chromatography (TLC) was performed on glass plates coated with *Merck SiO_2 60 F_{254}*. Column chromatography (CC) was performed with *Fluka SiO_2 60* (230–400 mesh, 0.040–0.063 mm). Reversed-phase CC was performed with *Fluka SiO_2 100 C_{18}* (230–400 mesh, 0.040–0.063 mm). M.p. were determined with a *Büchi B-540* melting-point apparatus and are uncorrected. Optical rotations were measured on a *Perkin-Elmer 241* polarimeter at $\lambda = 365$, $\lambda = 589$, or $\lambda = 578$ nm and are given in 10^{-1} deg cm^2 g^{-1}. IR Spectra: *Perkin-Elmer 1600-FT-IR* spectrometer. ^{1}H- and ^{13}C-NMR Spectra (δ [ppm]; J [Hz]): *Varian Gemini 300*, *Varian Mercury 300*, or *Varian Gemini 200* spectrometers. MALDI Mass spectra: *IonSpec Ultima* instrument with 2,5-dihydroxybenzoic acid (DHB) or 2,4,5-trihydroxyacetophenone/diammonium citrate 2:1 (THA) as a matrix. Elemental analyses were performed by the Mikrolabor at the Laboratorium für Organische Chemie, ETH Zürich. The nomenclature was generated with the computer program *ACD-Name (ACD/Labs)*.

General Procedure A (*GP A*) *for the Oxidation of Primary Alcohols and Subsequent* Horner-Wittig *Olefination.* To a soln. of primary alcohol (40 mmol) in dry Me_2SO (100 ml), $Ph_3P{=}CHCO_2Et$ (42.8 g, 100 mmol) and IBX (27.8 g, 100 mmol) were added. The mixture was stirred at 20° for 15–70 h. H_2O (500 ml) was added, and the mixture was extracted with AcOEt (2 × 500 ml). The combined org. phases were dried (Na_2SO_4) and concentrated to a residue, which was purified by CC.

General Procedure B (*GP B*) *for the Reduction of α,β-Unsaturated Esters to Allylic Alcohols.* To a soln. of unsaturated ester (1 mmol) in CH_2Cl_2 (3 ml), a 1M soln. of DIBAL-H in hexane (4 ml, 4 mmol) was added dropwise. The mixture was stirred at −78° for 1–4 h and then quenched with MeOH (5 ml). A sat. aq. soln. of potassium sodium tartrate monohydrate (*Rochelle* salt, 50 ml) was added and the resulting suspension was stirred vigorously for 16 h at 20°, then extracted with AcOEt (3 × 50 ml). The combined org. phases were dried (Na_2SO_4) and evaporated to dryness.

General Procedure C (*GP C*) *for the* Mitsunobu *Reaction of Allylic Alcohols with Phthalimide.* DEAD (0.234 ml, 97%, 1.46 mmol) was added dropwise to a stirred suspension of allylic alcohol (1.46 mmol), phthalimide (215 mg, 1.46 mmol), and Ph_3P (383 mg, 1.46 mmol) in THF (7 ml). After stirring for 14–18 h at 20°, the mixture was evaporated to dryness and the residue purified by CC.

General Procedure D (*GP D*) *for the Cleavage of* N-*Alkylated Phthalimides with $MeNH_2$.* To *N*-alkylated phthalimide (1.91 mmol), a soln. of $MeNH_2$ in EtOH (33%, 30 ml) was added, and the mixture was stirred at 20° for 16–35 h. *Method A:* After evaporation, the residue was dissolved in MeOH (10 ml) and loaded onto a column of *Dowex® 50W × 4* (NH_4^+, 1 cm × 25 cm). Washing with MeOH/H_2O 1:1 (400 ml) and elution with MeOH/13% aq. NH_3 soln. 1:1, followed by evaporation of MeOH, left an aq. product-containing soln. that was lyophilized. *Method B:* After evaporation, the residue was dissolved in $CHCl_3$ (20 ml) and extracted with 10% aq. AcOH (30 ml). The aq. phase was washed with $CHCl_3$ (3 × 25 ml), adjusted to pH > 12 with 2N NaOH, and then extracted again with $CHCl_3$ (4 × 25 ml). The combined org. phases were dried (Na_2SO_4) and evaporated to dryness.

General Procedure E for the Amide Synthesis with N-*Hydroxysuccinimide Ester* **10**. *Method A:* To a soln. of amine (0.3 mmol) in dry DMF (5 ml), Et_3N (1 mmol) and **10** (0.3 mmol) were added, and the resulting red mixture was stirred at 20° for 16–20 h. H_2O (100 ml) was added, and the mixture was adsorbed on a column with reversed-phase SiO_2 (1 cm × 25 cm). After washing with 1% aq. HCOOH (200 ml), the amide was eluted with

MeCN/1% aq. HCOOH 2:8 → 3:8. Product-containing fractions were evaporated to dryness by lyophilization. *Method B:* To a soln. of amine (0.1 mmol) and $NaHCO_3$ (17 mg, 0.2 mmol) in H_2O (0.8 ml), a soln. of **10** (30 mg, 0.1 mmol) in DME (1 ml) was added dropwise. The mixture was stirred at 20° for 20 h. After evaporation of DME, the remaining aq. soln. was purified as described in *Method A*.

*Ethyl (*E*)-3-((2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-[[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2,3,4,5-tetrahydrofuran-2-yl)prop-2-enoate* ((+)-**6**). According to *GP A*, a soln. of 2′-deoxyadenosine (5.0 g, 19 mmol), IBX (15.5 g, 56 mmol), and $Ph_3P{=}CHCO_2Et$ (14.3 g, 41 mmol) in Me_2SO (55 ml) was stirred for 70 h. H_2O (900 ml) was added. The resulting precipitate was removed by filtration and washed with CH_2Cl_2/MeOH/Et_3N 90:9:1 (3 × 100 ml). The aq. phase was extracted with AcOEt (8 × 500 ml). The combined org. phases were dried (Na_2SO_4) and evaporated to dryness. The resulting brown oil, (*t*-Bu)Me_2SiCl (6.72 g, 44 mmol), and 1*H*-imidazole (1.52 g, 22 mmol) were dissolved in DMF (40 ml). The mixture was stirred for 21 h at 20°. H_2O (600 ml) was added, and the aq. layer was extracted with AcOEt (4 × 200 ml). The combined org. phases were evaporated and purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 95:4:1) to afford (+)-**6** (5.04 g, 62%). White solid. M.p. 125–126° (Et_2O). $[\alpha]_D^{20} = +27.0$ ($c = 1$, $CHCl_3$). IR (KBr): 3334*s*, 3162*s*, 2930*m*, 2856*w*, 1718*s*, 1667*s*, 1601*s*, 1573*m*, 1480*m*, 1442*m*, 1365*s*, 1328*m*, 1306*m*, 1252*s*, 1206*m*, 1191*m*, 1098*s*, 1052*s*, 984*m*, 951*m*, 926*w*, 864*w*, 834*m*, 776*m*, 724*w*, 654*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.11 (*s*, 6 H); 0.92 (*s*, 9 H); 1.28 (*t*, *J* = 7.1, 3 H); 2.40–2.48 (*m*, 1 H); 2.85–2.95 (*m*, 1 H); 4.20 (*q*, *J* = 7.1, 2 H); 4.50–4.58 (*m*, 2 H); 5.85 (br. *s*, 2 H); 6.07 (*dd*, *J* = 15.6, 1.6, 1 H); 6.43 (*t*, *J* = 6.5, 1 H); 7.04 (*dd*, *J* = 15.6, 5.3, 1 H); 7.93 (*s*, 1 H); 8.36 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −4.8; 14.2; 18.0; 25.8; 39.7; 60.8; 75.6; 84.8; 86.3; 120.6; 122.8; 139.4; 144.1; 150.0; 153.4; 155.8; 166.3. HR-MALDI-MS: 434.2228 ($[M+H]^+$, $C_{20}H_{32}N_5O_4Si^+$; calc. 434.2224). Anal. calc. for $C_{20}H_{31}N_5O_4Si$ (433.58): C 55.40, H 7.21, N 16.15; found: C 55.58, H 7.20, N 16.16. X-Ray: see *Fig. 2*.

*(*E*)-3-((2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-[[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2,3,4,5-tetrahydrofuran-2-yl)prop-2-en-1-ol* ((+)-**7**). According to *GP B*, a soln. of (+)-**6** (4.39 g, 10 mmol) in CH_2Cl_2 (50 ml) was treated with a 1M soln. of DIBAL-H in hexane (40 ml, 40 mmol). The mixture was stirred at −78° for 4 h. Workup followed by CC (SiO_2; CH_2Cl_2/MeOH 9:1), provided (+)-**7** (2.90 g, 73%). Pale-yellow solid. M.p. 74–76°. $[\alpha]_D^{20} = +30.6$ ($c = 1$, $CHCl_3$). IR (KBr): 3443*s*, 3322*s*, 3178*s*, 2929*s*, 2856*s*, 2356*w*, 1664*s*, 1602*m*, 1473*m*, 1422*m*, 1372*m*, 1337*m*, 1306*m*, 1253*m*, 1156*m*, 1102*m*, 1036*m*, 836*s*, 778*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.09 (*s*, 6 H); 0.91 (*s*, 9 H); 1.95 (br. *s*, 1 H); 2.43 (*ddd*, *J* = 13.2, 6.3, 4.2, 1 H); 2.84 (*dt*, *J* = 13.2, 6.3, 1 H); 4.19 (*d*, *J* = 3.7, 2 H); 4.39–4.48 (*m*, 2 H); 5.83 (br. *s*, 2 H); 5.89–6.00 (*m*, 2 H); 6.38 (*t*, *J* = 6.3, 1 H); 7.94 (*s*, 1 H); 8.34 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −4.7; 18.1; 25.8; 40.0; 62.3; 75.9; 84.5; 87.6; 120.1; 127.9; 133.4; 139.1; 149.5; 153.0; 155.6. HR-MALDI-MS: 414.1936 ($[M+Na]^+$, $C_{18}H_{29}N_5NaO_3Si^+$; calc. 414.1937). Anal. calc. for $C_{18}H_{29}N_5O_3Si$ (391.54): C 55.22, H 7.47, N 17.89; found: C 55.27, H 7.37, N 17.71.

*2-[(*E*)-3-((2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3-[[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}tetrahydrofuran-2-yl)prop-2-enyl]-2,3-dihydro-1*H*-isoindole-1,3-dione* ((+)-**8**). According to *GP C*, a soln. of (+)-**7** (1.451 g, 3.7 mmol), phthalimide (655 mg, 4.5 mmol), and PPh_3 (1.167 g, 4.5 mmol) in THF (10 ml) was treated with DEAD (0.7 ml, 4.5 mmol) and stirred for 14 h. A white solid precipitated. The suspension was filtered, and the product (+)-**8** (839 mg, 43%) was washed with Et_2O (3 × 15 ml). The filtrate was evaporated and purified by CC (SiO_2; CH_2Cl_2/MeOH 19:1) to afford additional (+)-**8** (789 mg, 41%). White solid. M.p. 219° (dec.). $[\alpha]_D^{20} = +21.9$ ($c = 1$, $CHCl_3$). IR (KBr): 3313*m*, 3200*m*, 2928*m*, 2856*m*, 1764*m*, 1711*s*, 1676*m*, 1601*m*, 1467*w*, 1398*m*, 1257*m*, 1107*m*, 1055*m*, 936*w*, 836*m*, 777*w*, 722*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.05 (*s*, 6 H); 0.85 (*s*, 9 H); 2.40 (*ddd*, *J* = 13.0, 6.5, 4.7, 1 H); 2.74–2.83 (*dt*, *J* = 13.0, 6.5, 1 H); 4.30 (*d*, *J* = 3.7, 2 H); 4.33–4.45 (*m*, 2 H); 5.85–5.87 (*m*, 2 H); 6.00 (br. *s*, 2 H); 6.36 (*t*, *J* = 6.5, 1 H); 7.71, 7.85 (*AA′BB′*, *J* = 5.4, 3.0, 4 H); 7.92 (*s*, 1 H); 8.25 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −4.8; 18.0; 25.7; 38.8; 39.9; 75.7; 84.4; 87.0; 120.3; 123.4; 127.0; 131.3; 132.0; 134.1; 139.1; 149.6; 153.0; 155.6; 167.8. HR-MALDI-MS: 543.2140 ($[M+Na]^+$, $C_{26}H_{32}N_6NaO_4Si^+$; calc. 543.2152). Anal. calc. for $C_{26}H_{32}N_6O_4Si$ (520.66): C 59.98, H 6.19, N 16.14; found: C 60.01, H 6.02, N 16.14.

*(2*R*,3*S*,5*R*)-2-[(*E*)-3-Aminoprop-1-enyl]-5-(6-amino-9 H-purin-9-yl)-2,3,4,5-tetrahydrofuran-3-ol* ((+)-**9**). According to *GP D*, (+)-**8** (579 mg, 1.1 mmol) was dissolved in $MeNH_2$ in EtOH (33%, 25 ml). The mixture was stirred for 35 h and then evaporated. To the residue, a 1M soln. of Bu_4NF in THF (11 ml, 11 mmol) was added. The soln. was stirred for 16 h at 20° and then evaporated. The residue was dissolved at 0° in an aq. phosphate buffer (pH 7.2) containing $NaClO_4$. The resulting precipitate was removed by filtration. Purification by ion-exchange chromatography according to *GP D* (*Method A*) afforded (+)-**9** (300 mg, 99%). Brown oil. $[\alpha]_D^{20} = +15.0$ ($c = 1$, MeOH). IR (KBr): 3354*s*, 1652*s*, 1600*s*, 1578*s*, 1477*s*, 1333*m*, 1300*m*, 1250*m*, 1091*m*, 1033*m*, 967*w*, 928*w*, 649*m*. ^{1}H-NMR (300 MHz, CD_3OD): 2.44 (*ddd*, *J* = 13.7, 6.5, 4.6, 1 H); 2.82 (*dt*, *J* = 13.7, 6.5, 1 H); 3.24 (*d*, *J* = 4.4, 2 H); 4.35 (*t*, *J* = 4.3, 1 H); 4.43 (*m*, 1 H); 5.81–5.85 (*m*, 2 H); 6.40 (*t*, *J* = 6.5, 1 H); 8.18 (*s*, 1 H); 8.24 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 40.2; 43.6; 75.9; 85.3; 88.7; 120.6; 130.0; 134.3; 141.0; 150.5; 153.9; 157.4. HR-ESI-MS: 299.1233 ($[M+Na]^+$, $C_{12}H_{16}N_6NaO_2^+$; calc. 299.1227).

*N-{(*E*)-3-[(2*R*,3*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-3-hydroxyfuran-2-yl]prop-2-enyl}-2,3-dihydroxy-5-nitrobenzamide* ((−)-**2**). According to *GP E* (*Method B*), a soln. of (+)-**9** (28 mg, 0.1 mmol) and $NaHCO_3$ (17 mg, 0.2 mmol) in H_2O (0.8 ml) was treated with a soln. of **10** (30 mg, 0.1 mmol) in DME (1 ml). The mixture was stirred for 20 h. Workup according to *GP E* afforded (−)-**2** (12 mg, 26%). Yellow solid. M.p. 172° (dec.). $[\alpha]_D^{20} = -29.0$ ($c = 0.5$, MeOH). IR (KBr): 3370*s*, 1689*w*, 1638*s*, 1594*m*, 1561*m*, 1477*m*, 1417*w*, 1294*s*, 1264*s*, 1081*w*, 1039*w*, 972*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 2.25–2.30 (*m*, 1 H); 2.80–2.88 (*m*, 1 H); 3.94 (*t*, $J = 5.3$, 2 H); 4.25–4.36 (*m*, 2 H); 5.52 (br. *s*, 1 H); 5.72–5.90 (*m*, 2 H); 6.32 (*t*, $J = 6.7$, 1 H); 7.29 (br. *s*, 2 H); 7.38–7.41 (*m*, 1 H); 8.10 (*s*, 1 H); 8.31 (*s*, 1 H); 8.36 (*d*, $J = 2.8$, 1 H); 9.43 (*t*, $J = 5.3$, 1 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 73.8; 74.1 83.3; 86.8; 111.9; 114.2; 114.4; 128.6; 129.8; 138.3; 141.2; 146.9; 147.8; 148.4; 152.4; 156.1; 167.8. HR-MALDI-MS: 480.1230 ($[M + Na]^+$, $C_{19}H_{19}N_7NaO_7^+$; calc. 480.1244).

*Ethyl (*E*)-3-[(2*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydofuran-2-yl]prop-2-enoate* ((+)-**13**). According to *GP A*, a soln. of (−)-**11** (1.856 g, 7.9 mmol), IBX (6.590 g, 23.7 mmol), and $Ph_3P{=}CHCO_2Et$ (4.120 g, 11.8 mmol) in Me_2SO (24 ml) was stirred for 37 h. Workup and purification by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 94:5:1) gave (+)-**13** (1.36 g, 57%). White solid. M.p. 103–105° ($CHCl_3$/hexane 1:2). $[\alpha]_D^{20} = +16.8$ ($c = 1$, $CHCl_3$). IR (KBr): 3310*m*, 3116*s*, 2978*m*, 1718*s*, 1648*s*, 1600*s*, 1479*m*, 1415*m*, 1371*m*, 1302*s*, 1257*m*, 1180*m*, 1089*m*, 1045*m*, 977*m*, 799*w*, 644*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.29 (*t*, $J = 7.2$, 3 H); 2.03–2.10 (*m*, 1 H); 2.32–2.42 (*m*, 1 H); 2.56–2.63 (*m*, 2 H); 4.21 (*q*, $J = 7.2$, 2 H); 4.76–4.79 (*m*, 1 H); 5.86 (br. *s*, 2 H); 6.07 (*dd*, $J = 15.6$, 1.6, 1 H); 6.37 (*t*, $J = 4.8$, 1 H); 7.04 (*dd*, $J = 15.6$, 5.1, 1 H); 7.97 (*s*, 1 H); 8.36 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.2; 30.1; 32.6; 60.7; 80.0; 85.6; 120.1; 122.1; 138.7; 145.2; 149.3; 152.4; 155.1; 166.0. HR-MALDI-MS: 326.1206 ($[M + Na]^+$, $C_{14}H_{17}N_5NaO_3^+$; calc. 326.1229). Anal. calc. for $C_{14}H_{17}N_5O_3$ (303.32): C 55.44, H 5.65, N 23.09; found: C 55.51, H 5.74, N 23.03.

*(*E*)-3-[(2*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydrofuran-2-yl]prop-2-en-1-ol* ((+)-**14**). According to *GP B*, a soln. of (+)-**13** (702 mg, 2.0 mmol) in CH_2Cl_2 (11 ml) was treated with a 1M soln. of DIBAL-H in hexane (9.3 ml, 9.3mmol). The mixture was stirred at −78° for 1 h. Workup, followed by CC (SiO_2; $CHCl_3$/MeOH 92:8) provided (+)-**14** (407 mg, 67%). White solid. M.p. 141–143°. $[\alpha]_D^{20} = +18.0$ ($c = 1$, MeOH). IR (KBr): 3306*s*, 3131*s*, 1671*s*, 1605*s*, 1574*m*, 1474*m*, 1421*m*, 1375*m*, 1338*m*, 1301*m*, 1215*m*, 1048*m*, 958*m*, 862*w*, 797*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87–1.94 (*m*, 1 H); 2.19–2.27 (*m*, 1 H); 2.49–2.56 (*m*, 2 H); 3.4 (br. *s*, 1 H); 4.21 (*d*, $J = 4.1$, 2 H); 4.60–4.67 (*m*, 1 H); 5.85–6.00 (*m*, 2 H); 6.17 (br. *s*, 2 H); 6.30 (*t*, $J = 4.5$, 1 H); 7.97 (*s*, 1 H); 8.31 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.2; 33.1; 62.2; 81.9; 85.6; 120.0; 129.3; 133.2; 138.5; 149.1; 153.0; 155.6. HR-MALDI-MS: 262.1300 ($[M + H]^+$, $C_{12}H_{16}N_5O_2^+$; calc. 262.1304).

*2-{(*E*)-3-[(2*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydrofuran-2-yl]prop-2-enyl}-2,3-dihydro-1*H*-isoindole-1,3-dione* ((+)-**15**). According to *GP C*, a soln. of (+)-**14** (134 mg, 0.5 mmol), PPh_3 (160 mg, 0.6 mmol), and phthalimide (90 mg, 0.6 mmol) in THF (2 ml) was treated with DEAD (92 µl, 0.6 mmol). The mixture was stirred for 18 h. Workup followed by CC (SiO_2; $CHCl_3$/MeOH 95:5) afforded (+)-**15** (192 mg, 96%). Colorless solid. M.p. 169–170°. $[\alpha]_D^{20} = +26.3$ ($c = 1$, $CHCl_3$). IR (KBr): 3385*s*, 3156*s*, 1765*m*, 1709*s*, 1654*s*, 1598*s*, 1468*m*, 1397*s*, 1338*m*, 1295*m*, 1212*m*, 1062*m*, 935*m*, 800*w*, 723*m*, 654*m*, 529*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.89–1.97 (*m*, 1 H); 2.20–2.26 (*m*, 1 H); 2.48–2.55 (*m*, 2 H); 4.32 (*d*, $J = 4.4$, 2 H); 4.57–4.64 (*m*, 1 H); 5.82–5.96 (*m*, 2 H); 6.10 (br. *s*, 2 H); 6.29 (*t*, $J = 4.7$, 1 H); 7.71, 7.87 (*AA′BB′*, $J = 5.4$, 3.0, 4 H); 7.96 (*s*, 1 H); 8.31 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.1; 33.0; 38.9; 81.2; 85.5; 120.2; 123.5; 126.7; 132.0; 132.8; 134.1; 138.6; 149.2; 153.0; 155.6; 167.9. HR-MALDI-MS: 391.1507 ($[M + H]^+$, $C_{20}H_{19}N_6O_3^+$; calc. 391.1519). Anal. calc. for $C_{20}H_{18}N_6O_3$ (390.40): C 61.53, H 4.65, N 21.53; found: C 61.27, H 4.77, N 21.52.

*9-{(2*R*,5*S*)-5-[(*E*)-3-Aminoprop-1-enyl]-2,3,4,5-tetrahydrofuran-2-yl}-9*H*-purin-6-amine* ((+)-**12**). According to *GP D*, (+)-**15** (561 mg, 1.7 mmol) was dissolved in $MeNH_2$ in EtOH (33%, 26 ml). The mixture was stirred for 16 h. Workup and ion-exchange chromatography according to *GP D* (*Method A*) gave (+)-**12** (363 mg, 83%). White solid. M.p. 110–115°. $[\alpha]_D^{20} = +21.0$ ($c = 1$, $CHCl_3$). IR (KBr): 3355*s*, 3167*s*, 1652*s*, 1596*s*, 1474*s*, 1330*m*, 1303*m*, 1246*m*, 1210*m*, 1055*m*, 796*w*, 696*m*, 649*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.86–1.99 (*m*, 1 H); 2.17–2.27 (*m*, 1 H); 2.45–2.60 (*m*, 2 H); 3.39 (*d*, $J = 5.1$, 2 H); 4.61 (*q*, $J = 6.9$, 1 H); 5.75 (*dd*, $J = 15.4$, 6.9, 1 H); 5.92 (*dt*, $J = 15.4$, 5.1, 1 H); 6.30 (*dd*, $J = 5.5$, 3.6, 1 H); 7.98 (*s*, 1 H); 8.33 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.3; 33.1; 43.2; 82.2; 85.5; 120.2; 128.3; 135.6; 138.6; 149.2; 153.0; 155.5. HR-MALDI-MS: 283.1282 ($[M + Na]^+$, $C_{12}H_{16}N_6NaO^+$; calc. 283.1283).

*N-{(*E*)-3-[(2*S*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydrofuran-2-yl]prop-2-enyl}-2,3-dihydroxy-5-nitrobenzamide* ((−)-**3**). According to *GP E* (*Method A*), a mixture of (+)-**12** (219 mg, 0.84 mmol), **10** (235 mg, 0.79 mmol), and Et_3N (320 µl, 2.4 mmol) in DMF (15 ml) was stirred for 16 h. The product was purified according to *GP E*, with the acid component of the aqueous mobile phase replaced with volatile triethylammonium carbonate buffer (pH 8, adjusted by bubbling CO_2 through a 0.3M soln. of Et_3N in H_2O). After lyophilization, the residue was dissolved in H_2O (50 ml), evaporated, taken up in MeOH/H_2O 1:1

(20 ml), filtered over an ion-exchange column (*DOWEX 50W* × *2*, NH_4^+, 2 cm × 45 cm), and eluted with MeOH. MeOH was evaporated, and H_2O was added (10 ml). Lyophilization gave (−)-**3** (219 mg, 63%). Yellow solid. M.p. 125° (i-PrOH/Et_2O). $[\alpha]_D^{20} = -20.0$ ($c = 0.5$, MeOH). IR (KBr): 3367*s*, 3211*s*, 1639*s*, 1544*m*, 1478*m*, 1439*m*, 1333*m*, 1249*s*, 1077*m*, 977*w*, 794*w*, 699*w*, 644*w*, 560*w*. ^{1}H-NMR (300 MHz, CD_3OD): 1.97–2.10 (*m*, 1 H); 2.22–2.31 (*m*, 1 H); 2.45–2.55 (*m*, 2 H); 4.08 (*d*, $J = 2.8$, 2 H); 4.62–4.67 (*m*, 1 H); 5.93–5.95 (*m*, 2 H); 6.30 (*dd*, $J = 6.5$, 2.8, 1 H); 7.49 (*d*, $J = 2.8$, 1 H); 8.18 (*s*, 1 H); 8.26 (*s*, 1 H); 8.50 (*d*, $J = 2.8$, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 31.5; 33.8; 41.4; 83.4; 86.7; 108.5; 116.7; 120.8; 121.7; 131.1; 132.1; 133.8; 140.8; 150.3; 150.8; 154.1; 157.6; 168.8; 170.0. HR-MALDI-MS: 464.1293 ($[M + Na]^+$, $C_{19}H_{19}N_7NaO_6^+$; calc. 464.1294).

*[(1*S*,4*R*)-4-(6-Amino-9*H*-purin-9-yl)cyclopent-2-enyl]methanol* ((−)-**17**). A suspension of NaH (66% in mineral oil, 96 mg, 2.4 mmol) and adenine (364 mg, 2.6 mmol) in degassed dry Me_2SO (6 ml) was stirred at 45° for 15 min. A soln. of $[Pd(PPh_3)_4]$ (112 mg, 0.1 mmol) and (−)-**16** (396 mg, 2 mmol) in degassed THF (6 ml) was added. The mixture was stirred at 45° for 3 h. H_2O (25 ml) was added, and the mixture was extracted with AcOEt (9 × 30 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. 1M NaOH (5 ml) was added to the residue. The mixture was stirred at 20° for 45 min. H_2O (200 ml) was added, and the mixture was extracted with AcOEt (8 × 250 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. The residue was purified by CC (SiO_2; MeOH/$CHCl_3$ 1:9) to give (−)-**17** (265 mg, 55%). Colorless solid. M.p. 183–185° (MeOH/$CHCl_3$) ([24]: 183–186°). ^{1}H-NMR (200 MHz, CD_3OD): 1.71 (*dt*, $J = 13.7$, 5.6, 1 H); 2.78 (*dt*, $J = 13.7$, 8.7, 1 H); 2.99–3.05 (*m*, 1 H); 3.49–3.70 (*m*, 2 H); 5.65–5.73 (*m*, 1 H); 5.92–5.97 (*m*, 1 H); 6.20–6.24 (*m*, 1 H); 8.13 (*s*, 1 H); 8.20 (*s*, 1 H).

*Ethyl (*E*)-3-[(1R,3S)-3-(6-Amino-9 H-purin-9-yl)cyclopentyl]prop-2-enoate* ((+)-**18**). A soln. of (−)-**17** (503 mg, 2.18 mmol) in MeOH (45 ml) was hydrogenated (6 bar H_2) in the presence of 10% Pd/C (145 mg) for 3 h. The catalyst was removed by filtration and the solvent evaporated. According to *GP A*, the residue was reacted with IBX (1.831 g, 6.54 mmol) and $Ph_3P{=}CHCO_2Et$ (1.519 g, 4.36 mmol) in dry Me_2SO (22 ml). The mixture was stirred for 15 h. Workup and CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 94:5:1) provided (+)-**18** (467 mg, 71%). Brown oil. $[\alpha]_D^{20} = +6.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3412*w*, 2995*m*, 1710*m*, 1630*s*, 1472*w*, 1437*w*, 1265*m*, 1048*m*, 693*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.26 (*t*, $J = 7.2$, 3 H); 1.85–2.18 (*m*, 4 H); 2.29–2.46 (*m*, 2 H); 2.81–2.89 (*m*, 1 H); 4.17 (*q*, $J = 7.2$, 2 H); 4.91–4.97 (*m*, 1 H); 5.85 (*d*, $J = 15.6$, 1 H); 5.94 (br. *s*, 2 H); 7.00 (*dd*, $J = 15.6$, 7.8, 1 H); 7.84 (*s*, 1 H); 8.31 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.3; 30.0; 31.7; 38.9; 40.9; 55.5; 60.5; 121.1; 129.6; 133.8; 138.8; 150.8; 153.1; 155.9; 166.8. HR-MALDI-MS: 302.1613 ($[M + H]^+$, $C_{15}H_{20}N_5O_2^+$: 302.1617).

*(*E*)-3-[(1*R*,3*S*)-3-(6-Amino-9*H*-purin-9-yl)cyclopentyl]prop-2-en-1-ol* ((+)-**19**). According to *GP B*, (+)-**18** (381 mg, 1.47 mmol) in CH_2Cl_2 (10 ml) was treated with a 1M soln. of DIBAL-H in hexane (5.92 ml, 5.92 mmol). The mixture was stirred at −78° for 1 h. Workup followed by CC (SiO_2; MeOH/$CHCl_3$ 1:9) gave (+)-**19** (143 mg, 38%). Colorless solid. M.p. 118–121°. $[\alpha]_D^{20} = +23.8$ ($c = 0.48$, MeOH). IR (KBr): 3197*m*, 1667*m*, 1606*w*, 1566*w*, 1479*w*, 1414*w*, 1340*w*, 1310*w*, 1256*w*, 985*w*, 668*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.73–2.13 (*m*, 4 H); 2.29–2.52 (*m*, 2 H); 2.70–2.76 (*m*, 1 H); 4.14 (*d*, $J = 5.0$, 2 H); 4.92–4.98 (*m*, 1 H); 5.68–5.83 (*m*, 4 H); 7.87 (*s*, 1 H); 8.35 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 31.8; 32.5; 40.6; 42.6; 57.1; 63.6; 120.5; 130.0; 135.9; 141.0; 150.7; 153.5; 157.3. HR-MALDI-MS: 260.1505 ($[M + H]^+$, $C_{13}H_{18}N_5O^+$; calc. 260.1511).

*2-{(*E*)-3-[(1*R*,3*S*)-3-(6-Amino-9*H*-purin-9-yl)cyclopentyl]prop-2-enyl}-2,3-dihydro-1*H*-isoindole-1,3-dione* ((+)-**20**). According to *GP C*, a mixture of (+)-**19** (26 mg, 0.1 mmol), phthalimide (18 mg, 0.12 mmol), PPh_3 (31 mg, 0.12 mmol), and DEAD (19 µl, 0.12 mmol) in THF (1 ml) was stirred for 15 h. Workup and CC (SiO_2; $CHCl_3$/MeOH 9:1) gave (+)-**20** (29 mg, 75%). Colorless crystals. M.p. 207–209°. $[\alpha]_D^{20} = +21.1$ ($c = 0.37$, MeOH). IR (KBr): 3111 (br.), 1716*m*, 1672*w*, 1603*w*, 1396*w*, 725*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.65–2.06 (*m*, 4 H); 2.21–2.45 (*m*, 2 H); 2.61–2.67 (*m*, 1 H); 4.22 (*d*, $J = 5.9$, 2 H); 2.82–4.93 (*m*, 1 H); 5.50–5.82 (*m*, 2 H); 6.39 (br. *s*, 2 H); 7.65–7.69 (*m*, 2 H); 7.76–7.81 (*m*, 2 H); 7.82 (*s*, 1 H); 8.27 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.3; 156.0; 153.0; 150.3; 138.7; 137.4; 134.2; 132.4;123.5; 123.2;120.1; 55.3; 40.9; 39.5; 39.4; 31.9; 30.4. HR-MALDI-MS: 389.1718 ($[M + H]^+$, $C_{21}H_{21}N_6O_2^+$; calc. 389.1726).

*9-{(1*S*,3*R*)-3-[(*E*)-3-Aminoprop-1-enyl]cyclopentyl}-9*H*-purin-6-amine* ((+)-**21**). According to *GP D* (*Method B*), (+)-**20** (200 mg, 0.51 mmol) was dissolved in $MeNH_2$ in EtOH (33%, 20 ml). The mixture was stirred for 12 h. Workup afforded (+)-**21** (144 mg, 99%). Colorless oil. $[\alpha]_D^{20} = +20.1$ ($c = 1$, MeOH). IR (KBr): 3329 (br.), 1647*m*, 1594*m*, 1475*m*, 1414*w*, 1303*w*, 1250*w*, 972*w*, 798*w*, 650*w*. ^{1}H-NMR (300 MHz, CD_3OD): 1.76–2.15 (*m*, 4 H); 2.25–2.44 (*m*, 2 H); 2.69–2.73 (*m*, 1 H); 3.18–3.31 (*m*, 2 H); 4.84–4.98 (*m*, 1 H); 5.58–5.74 (*m*, 2 H); 8.19 (*s*, 1 H); 8.21 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 31.9; 32.5; 40.6; 42.7; 44.2; 57.1; 120.5; 130.4; 135.6; 141.0; 150.7; 153.5; 157.3. HR-MALDI-MS: 259.1669 ($[M + H]^+$, $C_{13}H_{19}N_6^+$; calc. 259.1671).

N-*{(*E*)-3-[(1*R*,3*S*)-3-(6-Amino-9*H*-purin-9-yl)cyclopentyl]prop-2-enyl}-2,3-dihydroxy-5-nitrobenzamide* ((+)-**4**). According to *GP E* (*Method A*), a mixture of (+)-**21** (26 mg, 0.1 mmol), Et_3N (42 µl, 0.3 mmol), and **10**

(30 mg, 0.1 mmol) in DMF (1.5 ml) was stirred for 15 h. Workup according to *GP E* gave (+)-**4** (11 mg, 25%). Yellow solid. 208–209° (dec.). $[\alpha]_D^{20} = +11.8$ ($c = 1$, Me_2SO). IR (KBr): 3398*s*, 3100*s*, 1700*s*, 1617*m*, 1513*m*, 1422*w*, 1339*s*, 1278*m*, 1200*s*, 1133*m*, 967*w*, 889*w*, 833*w*, 794*w*, 723*m*. ^{1}H-NMR (300 MHz, CD_3OD): 1.75–2.08 (*m*, 4 H); 2.18–2.36 (*m*, 2 H); 2.67–2.73 (*m*, 1 H); 3.90–3.95 (*m*, 2 H); 4.91–4.96 (*m*, 1 H); 5.59 (*dt*, $J = 15.3$, 5.3, 1 H); 5.76 (*dd*, $J = 15.3$, 7.2, 1 H); 7.71 (*d*, $J = 2.5$, 1 H); 8.34 (*s*, 1 H); 8.46 (*d*, $J = 2.5$, 1 H); 8.49 (*s*, 1 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 30.3; 31.1; 40.7; 40.8; 48.6; 55.3; 112.0; 114.3; 114.5; 118.7; 124.8; 135.2; 138.4; 146.9; 148.6; 151.7; 156.2; 158.1; 158.3; 167.8. HR-MALDI-MS: 440.1681 ($[M+H]^+$, $C_{20}H_{22}N_7O_5^+$; calc. 440.1682).

*1-(1,1-Dimethylethyl) 2-Methyl (2*S*,4*R*)-4-{[(4-Nitrophenyl)sulfonyl]oxy}-2,3,4,5-tetrahydro-1*H*-pyrrole-1,2-dicarboxylate* ((−)-**23**). To (−)-**22** (12.264 g, 50 mmol) in pyridine (90 ml), 4-nitrobenzenesulfonyl chloride (18.395 g, 83 mmol) was added at 0°. The mixture was stored at 4° for 14 h. The reaction was quenched with H_2O (90 ml), AcOEt (250 ml) was added, and the org. phase was washed with 0.5N HCl (250 ml), H_2O (250 ml), and sat. aq. NaCl soln. (250 ml), dried (Na_2SO_4), and evaporated. The residue was recrystallized from Et_2O/pentane to yield (−)-**23** (18.8 g, 87%). Reddish crystals. M.p. 96° (Et_2O/pentane). $[\alpha]_D^{20} = -31.9$ ($c = 1$, $CHCl_3$). IR (KBr): 2975*w*, 1741*s*, 1700*s*, 1533*s*, 1405*s*, 1288*m*, 1184*s*, 1044*m*, 912*m*, 747*m*, 687*w*, 620*m*, 577*m*, 464*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36, 1.40 (2*s*, 9 H, rotamers); 2.16–2.25 (*m*, 1 H); 2.40–2.61 (*m*, 1 H); 3.58–3.66 (*m*, 2 H); 3.71 (*s*, 3 H); 4.31–4.41 (*m*, 1 H); 5.15 (*s*, 1 H); 8.08, 8.39 (*AA′BB′*, $J = 8.7$, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.2, 28.3 (rotamers); 36.1, 37.3 (rotamers); 51.8, 52.2 (rotamers); 52.4, 52.6 (rotamers); 57.0, 57.3 (rotamers); 79.9, 80.4 (rotamers); 81.0; 124.6; 129.0; 142.0; 150.7; 153.0, 153.6 (rotamers); 172.3. ESI-MS: 453 ($[M+Na]^+$). Anal. calc. for $C_{17}H_{22}N_2O_9S$ (430.43): C 47.44, H 5.15, N 6.51; found: C 47.58, H 5.26, N 6.45.

*1-(1,1-Dimethylethyl) 2-Methyl (2*R*,4*S*)-4-{[(4-Nitrophenyl)sulfonyl]oxy}-2,3,4,5-tetrahydro-1*H*-pyrrole-1,2-dicarboxylate* ((+)-**23**). The procedure as for ((−)-**23**), starting from (+)-**22**, gave ((+)-**23**) in 85% yield. M.p. 93–95° (Et_2O/pentane). $[\alpha]_D^{20} = +30.8$ ($c = 1$, $CHCl_3$).

*1-(1,1-Dimethyethyl) 2-Methyl (2*S*,4*S*)-4-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-1*H*-pyrrole-1,2-dicarboxylate* ((+)-**24**). A suspension of adenine (337 mg, 2.5 mmol), K_2CO_3 (346 mg, 2.5 mmol), 18-crown-6 (105 mg, 0.4 mmol), and (−)-**23** (430 mg, 1 mmol) in DMF (5 ml) was stirred at 80° for 6 h. $CHCl_3$ (25 ml) and H_2O (25 ml) were added. The layers were separated, and the aq. phase was extracted with $CHCl_3$ (25 ml). The combined org. phases were dried (Na_2SO_4) and evaporated. The residue was purified by CC (SiO_2; MeOH/CH_2Cl_2 8:100), then recrystallized from AcOEt/hexane to afford (+)-**24** (261 mg, 72%). Colorless crystals. M.p. 187° (AcOEt/hexane). $[\alpha]_D^{20} = +17.3$ ($c = 1$, $CHCl_3$). IR (KBr): 3325*m*, 3176*m*, 2976*w*, 1749*s*, 1699*s*, 1598*s*, 1475*m*, 1401*s*, 1300*m*, 1257*m*, 1158*s*, 896*w*, 798*w*, 727*w*, 648*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39 (*s*, 9 H); 2.34–2.54 (*m*, 1 H); 2.75–2.90 (*m*, 1 H); 3.59 (*s*, 3 H); 3.75–3.99 (*m*, 1 H); 4.03–4.17 (*m*, 1 H); 4.31–4.49 (*m*, 1 H); 5.05–5.18 (*m*, 1 H); 6.33 (*s*, 2 H); 7.93 (*s*, 1 H); 8.27 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 28.1, 28.2 (rotamers); 35.1, 36.3 (rotamers); 50.2, 50.9 (rotamers); 51.6; 52.3, 52.5 (rotamers); 57.3, 57.8 (rotamers); 81.0; 119.6, 120.0 (rotamers); 138.3; 149.8, 150.0 (rotamers); 152.9; 153.2, 153.8 (rotamers); 155.8; 172.3. ESI-MS: 363 ($[M+H]^+$). Anal. calc. for $C_{16}H_{22}N_6O_4$ (362.39): C 53.03, H 6.12, N 23.19; found: C 53.15, H 6.31, N 23.13.

*1-(1,1-Dimethylethyl) 2-Methyl (2*R*,4*R*)-4-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-1*H*-pyrrole-1,2-dicarboxylate* ((−)-**24**). The procedure as for ((+)-**24**), starting from (+)-**23**, gave (−)-**24** in 60% yield. M.p. 183–187° (AcOEt/hexane). $[\alpha]_D^{20} = -13.0$ ($c = 1$, $CHCl_3$).

*1,1-Dimethylethyl (2*S*,4*S*)-4-(6-amino-9*H*-purin-9-yl)-2-(hydroxymethyl)-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((−)-**25**). A soln. of (+)-**24** (257 mg, 0.7 mmol) in THF (2 ml) was cooled to 0°, then LiCl (89 mg, 2.1 mmol) and $NaBH_4$ (79 mg, 2.1 mmol) were added. After addition of EtOH (4 ml), the mixture was stirred at 0° for 1 h, followed by 11 h at 55°. The mixture was cooled to 20°. Aq. AcOH (10%, 15 ml) was added, and the soln. was concentrated and purified by CC (SiO_2; MeOH/CH_2Cl_2 7:93 → 10:90). Recrystallization from Et_2O/hexane afforded (−)-**25** (208 mg, 89%). Colorless crystals. M.p. 110° (Et_2O/hexane). $[\alpha]_D^{20} = -8.5$ ($c = 1$, MeOH). IR (KBr): 3329*m*, 3176*m*, 2975*w*, 1651*m*, 1598*w*, 1475*w*, 1418*m*, 1163*m*. ^{1}H-NMR (300 MHz, CD_3OD): 1.48 (*s*, 9 H); 2.48–2.63 (*m*, 1 H); 2.64–2.77 (*m*, 1 H); 3.59–3.69 (*m*, 1 H); 3.70–3.89 (*m*, 2 H); 3.98–4.09 (*m*, 1 H); 4.19–4.28 (*m*, 1 H); 4.97–5.10 (*m*, 1 H); 8.19 (*s*, 1 H); 8.23 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 28.5; 33.8, 34.6 (rotamers); 51.7, 52.0 (rotamers); 53.3; 59.0; 63.7; 81.4; 120.0; 140.4; 150.4; 153.3; 155.8; 156.9. ESI-MS: 335 ($[M+H]^+$). Anal. calc. for $C_{15}H_{22}N_6O_3$ (334.38): C 53.88, H 6.63, N 25.13; found: C 53.88, H 6.69, N 25.27.

*1,1-Dimethylethyl (2*R*,4*R*)-4-(6-Amino-9*H*-purin-9-yl)-2-(hydroxymethyl)-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((+)-**25**). The procedure as for ((−)-**25**), starting from (−)-**24**, gave (+)-**25** in 85% yield. M.p. 107–109° (Et_2O/hexane). $[\alpha]_D^{20} = +8.1$ ($c = 1$, MeOH).

*1,1-Dimethylethyl (2*S*,4*S*)-4-(6-Amino-9*H*-purin-9-yl)-2-[(*E*)-3-ethoxy)-3-oxoprop-1-enyl]-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((+)-**27**). According to *GP A*, a soln. of (−)-**25** (321 mg, 0.96 mmol) in Me_2SO

(3.9 ml), IBX (806 mg, 2.88 mmol), and $Ph_3P{=}CHCO_2Et$ (669 mg, 1.92 mmol) was stirred for 42 h. Workup and CC (SiO_2; MeOH/AcOEt 10:90) yielded (+)-**27** (208 mg, 54%). Colorless crystals. M.p. 97° (CH_2Cl_2/pentane). $[\alpha]_D^{20} = +11.3$ ($c = 1$, $CHCl_3$). IR (KBr): 3328*m*, 3179*m*, 2978*w*, 1699*s*, 1645*s*, 1597*m*, 1475*m*, 1394*s*, 1368*m*, 1301*m*, 1265*m*, 1162*m*, 1125*w*, 1040*w*, 980*w*, 865*w*, 798*w*, 648*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*t*, $J = 7.2$, 3 H); 1.38 (*s*, 9 H); 2.36–2.46 (*m*, 1 H); 2.68–2.77 (*m*, 1 H); 3.79–3.69 (*m*, 1 H); 4.08–4.20 (*m*, 3 H); 4.50 (br. *s*, 1 H); 4.95–5.05 (*m*, 1 H); 5.86 (*d*, $J = 15.5$, 1 H); 6.48 (*s*, 2 H); 6.83 (*dd*, $J = 15.5, 6.7$, 1 H); 7.82 (*s*, 1 H); 8.26 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.4; 28.5; 37.6; 50.3; 52.3; 57.0; 60.7; 81.0; 120.1; 121.7; 138.3; 147.6; 150.2; 153.1; 154.2; 156.0; 166.2. HR-MALDI-MS: 425.1906 ($[M + Na]^+$), $C_{19}H_{26}N_6NaO_4^+$; calc. 425.1913). Anal. calc. for $C_{19}H_{26}N_6O_4$ (402.45): C 56.70, H 6.51, N 20.88; found C 56.85, H 6.42, N 20.79.

*1,1-Dimethylethyl (2*R*,4*R*)-4-(6-Amino-9*H*-purin-9-yl)-2-[(*E*)-3-ethoxy-3-oxoprop-1-enyl]-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((−)-**27**). The procedure as for (+)-**27**, starting from alcohol (+)-**25** gave (−)-**27** in 53% yield. M.p. 98° (CH_2Cl_2/pentane). $[\alpha]_D^{20} = -12.6$ ($c = 1$, $CHCl_3$).

*1,1-Dimethylethyl (2*S*,4*S*)-4-(6-Amino-9*H*-purin-9-yl)-2-[(*E*)-3-hydroxyprop-1-enyl]-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((+)-**28**). According to *GP B*, (+)-**27** (5.6 g, 13.9 mmol) in THF (60 ml) was treated with a 1M DIBAL-H soln. in hexane (73.9 ml, 73.9 mmol). The mixture was stirred at −78° for 1 h. Workup and CC (SiO_2; MeOH/AcOEt 15:85 → 18:82) gave (+)-**28** (2.51 g, 50%). Colorless foam. $[\alpha]_D^{20} = +20.9$ ($c = 1$, $CHCl_3$). IR (KBr): 3326*m*, 3181*m*, 2976*m*, 1690*s*, 1645*s*, 1598*m*, 1576*m*, 1476*m*, 1411*s*, 1366*m*, 1331*m*, 1301*m*, 1256*m*, 1162*m*, 1117*w*, 1013*w*, 976*w*, 874w, 798*w*, 649*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.42 (*s*, 9 H); 2.28–2.39 (*m*, 1 H); 2.61–2.73 (*m*, 1 H); 3.73–3.83 (*m*, 1 H); 4.08–4.18 (*m*, 3 H); 4.44 (br. *s*, 1 H); 5.01 (*t*, $J = 7.5$, 1 H); 5.66 (br. *s*, 2 H); 6.15 (br *s*, 2 H); 7.85 (*s*, 1 H); 8.28 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.6; 38.0; 50.8; 52.7; 57.5; 62.6; 80.6; 120.0; 130.7; 131.5; 138.7; 150.2; 153.2; 154.6; 155.8. HR-MALDI-MS: 383.1815 ($[M + Na]^+$, $C_{17}H_{24}N_6NaO_3^+$; calc. 383.1813).

*1,1-Dimethylethyl (2*R*,4*R*)-4-(6-Amino-9*H*-purin-9-yl)-2-[(*E*)-3-hydroxyprop-1-enyl]-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((−)-**28**). The procedure as for (+)-**28**, starting from (−)-**27** gave (−)-**28** in 68% yield. M.p. 99–101°. $[\alpha]_D^{20} = -19.6$ ($c = 1$, $CHCl_3$).

*1,1-Dimethylethyl (2*S*,4*S*)-4-(6-Amino-9*H*-purin-9-yl)-2-[(*E*)-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindole-2-yl)-prop-1-enyl]-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((−)-**29**). According to *GP C*, a soln. of (+)-**28** (360 mg, 1 mmol), phthalimide (177 mg, 1.2 mmol), and PPh_3 (315 mg, 1.2 mmol) in THF (4 ml) was treated with DEAD (187 µl, 1.2 mmol). The mixture was stirred for 16 h. Workup and CC (SiO_2; MeOH/AcOEt 10:90) afforded (−)-**29** (452 mg, 92%). Yellowish foam. $[\alpha]_D^{20} = -3.9$ ($c = 1$, $CHCl_3$). IR (KBr): 3324*m*, 3175*m*, 2976*m*, 2930*w*, 1772*m*, 1717*s*, 1638*s*, 1595*m*, 1574*m*, 1469*m*, 1394*s*, 1366*m*, 1330*m*, 1299*m*, 1252*m*, 1162*s*, 1112*m*, 1046*w*, 956*w*, 874*w*, 798*w*, 722*m*, 648*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.38 (*s*, 9 H); 2.28–2.40 (*m*, 1 H); 2.65–2.77 (*m*, 1 H); 3.68–3.77 (*m*, 1 H); 4.12–4.32 (*m*, 3 H); 4.41 (br. *s*, 1 H); 5.00 (*t*, $J = 7.5$, 1 H); 5.57–5.76 (*m*, 2 H); 6.17 (br. *s*, 2 H); 7.70, 7.84 (*AA′BB′*, $J = 5.6, 3.1, 4$ H); 7.84 (*s*, 1 H); 8.29 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.3; 37.8; 38.8; 50.5; 52.1; 57.2; 80.4; 119.8; 123.2; 124.5; 131.9; 133.9; 134.2; 138.2; 149.9; 152.8; 154.0; 155.5; 167.6. HR-MALDI-MS: 390.1675 ($[M + Na]^+$, $C_{25}H_{27}N_7NaO_4^+$; calc. 390.1673).

*1,1-Dimethylethyl (2*R*,4*R*)-4-(6-Amino-9*H*-purin-9-yl)-2-[(*E*)-3-(1,3-dioxo-2,3-dihydro-1*H*-isoindole-2-yl)prop-1-enyl]-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((+)-**29**). The procedure as for (−)-**29**, starting from (−)-**28**, gave (+)-**29** in 75% yield. M.p. 101–110°. $[\alpha]_D^{20} = +3.2$ ($c = 1$, $CHCl_3$).

*1,1-Dimethylethyl (2*S*,4*S*)-2-[(*E*)-3-aminoprop-1-enyl]-4-(6-amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((−)-**26**). According to *GP D*, (−)-**29** (1.000 g, 2.04 mmol) was dissolved in $MeNH_2$ in EtOH (33%, 47 ml). The mixture was stirred for 20 h. Workup and ion-exchange chromatography according to *GP D* (*Method A*) afforded (−)-**26** (542 mg, 74%). Colorless solid. M.p. 127–134° (Et_2O). $[\alpha]_{Hg365}^{20} = -1.7$ ($c =$ 1, MeOH). IR (KBr): 3322*m*, 3171*m*, 2975*w*, 2919*w*, 2359*m*, 2336*m*, 1681*s*, 1650*s*, 1597*m*, 1572*m*, 1471*m*, 1399*s*, 1365*m*, 1329*m*, 1298*m*, 1253*m*, 1158*m*, 1110*w*, 965*w*, 870*w*, 772*w*, 724*w*, 646*w*. ^{1}H-NMR (300 MHz, CD_3OD): 1.46 (*s*, 9 H); 2.43–2.53 (*m*, 1 H); 2.66–2.77 (*m*, 1 H); 3.20 (*d*, $J = 6.0$, 2 H)); 3.82 (*dd*, $J = 11.0, 9.0$, 1 H); 4.16 (*dd*, $J = 11.0, 7.0$, 1 H); 4.42 (*dd*, $J = 13.0, 7.5$, 1 H); 4.97–5.08 (*m*, 1 H); 5.54–5.73 (*m*, 2 H); 8.19 (*s*, 1 H); 8.19 (*s*, 1 H). ^{13}C-NMR (75 MHz, CD_3OD): 28.6; 38.2; 43.5; 51.0; 53.8; 58.9; 81.3; 120.1; 131.9; 140.6; 150.4; 153.3; 155.8; 156.9; one peak is missing due to signal overlap. HR-MALDI-MS: 260.1620 ($[M + H]^+$, $C_{17}H_{26}N_7O_2^+$; calc. 260.1618).

*1,1-Dimethylethyl (2*R*,4*R*)-2-[(*E*)-3-Aminoprop-1-enyl]-4-(6-amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-1*H*-pyrrole-1-carboxylate* ((+)-**26**). The procedure as for (−)-**26**, starting from (+)-**29**, gave (+)-**26** in 74% yield. M.p. 126° (MeOH/Et_2O). $[\alpha]_{Hg365}^{20} = +1.6$ ($c = 1$, MeOH).

N-*{(E)-3-[(2*S*,4*S*)-4-(6-Amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-1*H*-pyrrol-2-yl]prop-2-enyl}-2,3-dihydroxy-5-nitrobenzene-1-carboxamide* ((−)-**5**). According to *GP E* (*Method A*), a soln. of (−)-**26** (50 mg, 0.14 mmol), Et_3N (58 µl, 0.42 mmol), and **10** (41 mg, 0.14 mmol) in DMF (3 ml) was stirred for 20 h. The

mixture was evaporated to dryness. H_2O (0.8 ml) and TFA (2.0 ml) were added, and the soln. was stirred at 20° for 2 h. The solvent was evaporated, and the residue was purified by prep. reversed-phase HPLC (2.5 cm × 28 cm; 200 ml 0.5% HCOOH in H_2O, then 1% HCOOH in H_2O/MeCN 100 : 0 → 0 : 100 in 100 min) to give (−)-**5** (44 mg, 71%). Yellow solid. M.p. 217–222° (dec., MeOH/Et_2O). $[\alpha]_{Hg578}^{20} = -9.7$ ($c = 0.3$, TFA/Me_2SO 1:20). IR (KBr): 3419*m*, 3188*m*, 1635*s*, 1600*m*, 1473*m*, 1418*w*, 1331*m*, 1261*s*, 1076*w*, 982*w*, 901*w*, 825*w*, 794*w*, 648*w*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$ + 1 drop CF_3COOD): 2.28–2.50 (*m*, 1 H); 2.68–2.84 (*m*, 1 H); 3.56–3.67 (*m*, 1 H); 3.74–3.87 (*m*, 1 H); 3.94–4.04 (*m*, 2 H); 4.24–4.38 (*m*, 1 H); 5.37–5.50 (*m*, 1 H); 5.88 (*dd*, $J = 16.0$, 8.0, 1 H); 6.00–6.12 (*m*, 1 H); 7.75 (*d*, $J = 2.5$, 1 H); 8.45 (*d*, $J = 2.5$, 1 H); 8.53 (*s*, 1 H); 8.64 (*s*, 1 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$ + 1 drop CF_3COOD): 36.1; 47.9; 52.1; 59.6; 64.9; 112.0; 114.4; 118.4; 124.0; 133.7; 138.5; 142.3; 145.0; 146.8; 148.3; 150.2; 155.5; 167.7. HR-MALDI-MS: 441.1632 ($[M+H]^+$, $C_{19}H_{21}N_8O_5^+$; calc. 441.1629).

N-*{(*E*)-3-[(2*R*,4*R*)-4-(6-amino-9*H*-purin-9-yl)-2,3,4,5-tetrahydro-1*H*-pyrrol-2-yl]prop-2-enyl}-2,3-dihydroxy-5-nitrobenzene-1-carboxamide* ((+)-**5**). The procedure as for (−)-**5**, starting from (+)-**26**, gave (+)-**5** in 84% yield. M.p. 217–225° (dec., MeOH/Et_2O). $[\alpha]_{Hg578}^{20} = +9.7$ ($c = 0.3$, TFA/Me_2SO 1:20).

X-Ray Crystal Structure of (+)-**6**. Crystals were grown by slow evaporation of a soln. of (+)-**6** in MeOH. *X*-Ray crystal data for $C_{20}H_{31}N5O_4Si$ (M_r 433.6): orthorhombic space group $P2_12_12_1$, $D_c = 1.171$ g cm^{-3}, $Z = 4$, $a = 8.473(5)$, $b = 16.350(12)$, $c = 17.753(12)$ Å, $V = 2459(3)$ Å^3, CuK_α radiation, $\lambda = 1.54178$ Å, $3.68° \leq \theta \leq 50.03°$, 1460 unique reflections, $T = 293$ K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXTL PLUS (VMS)). All heavy atoms were refined anisotropically, H-atoms isotropically; H-positions are based on stereochemical considerations. Final $R(F) = 0.0401$, w$R(F2) = 0.1039$ for 272 parameters and 1384 reflections with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre*, deposition No. CCDC-198755. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: + 44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

Enzymatic Studies. Full experimental details of the radiochemical assay to determine IC_{50} values and the kinetic measurements for determining the enzyme inhibition mechanisms are given in [4][20].

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