Potent Tetracyclic Guanine Inhibitors of PDE1 and PDE5 Cyclic Guanosine Monophosphate Phosphodiesterases with Oral Antihypertensive Activity

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Received December 12, 1996[®]

Tetracyclic guanines have been shown to be potent and selective inhibitors of the cGMPhydrolyzing enzymes PDE1 and PDE5. In general, these compounds are inactive or only weakly active as inhibitors of PDE3, which is a major isozyme involved in cAMP hydrolysis. Structure– activity relationships are developed at N-1, C-2, N-3, and N-5 on the core nucleus. Compound **31**, with an IC₅₀ of 70 pM, is the most potent inhibitor of PDE1, while **50**, with an IC₅₀ of 4 nM, is the most potent inhibitor of PDE5. Compounds **20**, **22**, **30**, and **50** are potent dual inhibitors with IC₅₀ values below 30 nM for both PDE1 and PDE5. Compounds **12**, **20**, and **28** reduced blood pressure by more than 45 mmHg when administered orally at 10 mg/kg to the spontaneously hypertensive rat (SHR).

Introduction

Cyclic guanosine-3',5'-monophosphate (cGMP, i; Chart 1) plays a key role in the modulation of vascular function. Elevation of cGMP is directly correlated with vascular smooth muscle relaxation.^{1,2} Therapeutic manipulation of cGMP has been exploited in the management of angina pectoris, congestive heart failure, myocardial infarction, and hypertension. The evolving biology of cGMP and understanding of its mechanisms of regulation are opening up new opportunities for discovery of drugs which can produce therapeutically desirable effects through alteration of cGMP levels. At least two of the seven phosphodiesterase (PDE) families of cyclic nucleotide phosphodiesterases (designated PDE1 and PDE5) participate in the hydrolysis and inactivation of cGMP in smooth muscle. PDE1 is regulated by Ca^{2+} calmodulin and utilizes both cGMP and cAMP as substrate, showing a preference for cGMP, while PDE5 specifically hydrolyzes cGMP. Inhibitors of these phosphodiesterase enzymes have the potential to offer novel approaches toward treating cardiovascular diseases, since PDE1 is located in vascular tissue and PDE5 is located in vascular tissue and platelets. The field of cyclic nucleotide PDE inhibition as a therapeutic target has received considerable attention over the years and been the subject of recent reviews.^{3,4} More recently, the structure-activity relationships (SAR) of inhibitors of PDE1 and PDE5, from both the published and patent literature, have been extensively reviewed.⁵

The alkaloid vinpocetine (ii) is a weak but selective inhibitor of PDE1, which does not inhibit PDE5 or the cAMP-hydrolyzing enzyme PDE3. Zaprinast (M&B 22948, (iii) is an inhibitor of PDE5 which is selective relative to PDE3. The xanthine 8-MeOMeMIX (iv) is a weak inhibitor of both PDE1 and PDE5 which is also selective relative to PDE3. When examined in a preparation of rabbit aortic slices ii, iii, and iv showed





concentration dependent elevations in cGMP but not cAMP.⁶ More recently E4021 (**v**), a highly potent and selective PDE5 inhibitor, has been shown to elevate cGMP levels in and to directly relax porcine large coronary artery.⁷ When **iii** was administered at high doses (200 mg/kg/day po for 5 days) to the spontaneously hypertensive rat (SHR), significant (>30 mmHg) decreases in mean arterial pressure were observed.⁸ From this data we reasoned that a phosphodiesterase inhibitor which showed good potency for both PDE1 and PDE5 as well as improved oral activity could be potentially useful in the treatment of cardiovascular diseases.

[®] Abstract published in Advance ACS Abstracts, June 15, 1997.

Scheme 1^a



^a Reagents: (i) CH₃C(OEt)₃, DMF; (ii) CH₃CH₂CH₂CO₂H, EDCl, DMAP; (iii) POCl₃, DMF; (iv) amino alcohol, DIPEA, NMP; (v) SOCl₂, CH₂Cl₂; (vi) Pd(OH)₂/C, NH₄CO₂H, MeOH.

Whereas both structures iii and iv have a purine or azapurine nucleus, they are differentially substituted from each other as well as from cGMP around the purine nucleus. While iii is substituted at the purine 2-position, iv is substituted at positions 1, 3, and 8. With the goal of identifying structurally novel molecules which had both PDE1 and PDE5 inhibitory activity, we advanced the concept that a structure such as vi might incorporate both the features of iii and iv. We were additionally encouraged by the fact that a search of known ring structures indicated that a ring system such as vi had not been previously reported. Indeed, when we prepared one of our initial compounds with this novel ring system (8), we were pleased to observe that it not only retained the PDE profiles of iii and iv but also showed oral antihypertensive activity in a rat model of hypertension. In exploring this observation, we discovered the highly potent inhibitors of PDE1 and PDE5 which are described here.

Synthesis

Compounds 7–34 were prepared using the general method illustrated in Scheme 1 for compounds 7 and 8. Starting with the known 6-amino-5-(benzylamino)-3methylpyrimidine-2,4(1H,3H)-dione⁹ (1), acylation with either an orthoester or carboxylic acid afforded intermediate 2 or 3, respectively. The choice of acylating agent was dependent upon commercial availability, and both types of reagent worked well. In this scheme the orthoester leads to 7 and 8 while acylation produces the intermediate for 9 and 10. Subsequent reactions were identical and not dependent upon the acylation reagent used. The intermediates 2 and 3 were treated identically with excess POCl₃ to form the chloropurines 4 and 5. The third and fourth rings were added using the sequence starting with trans-2-aminocyclopentanol for compounds of type A or 1-amino-1-cyclopentanemethanol for compounds of type B. The chiral (-)-trans-2aminocyclopentanol¹⁰ displaced the ring chlorine to form intermediate 6, which upon activation with thionyl chloride underwent stereospecific displacement to give the (+)-*cis*-fused tetracylic guanine **7** having absolute configuration 6aR, 9aS. The diastereomeric *trans*-fused [3.3.0] ring system, which would result from retention of configuration at the displaced alcohol, was never observed. The synthesis was completed by catalytic hydrogenolysis of the N-3 benzyl group to give compound **8**.

Compounds **39–44** were prepared using the strategy outlined in Scheme 2. Intermediate **35**, which was prepared using the general reaction conditions of Scheme 1, was formylated to give the key intermediate **36**. Reduction to the alcohol **37**, chlorination (**38**), and displacement of chloride led to the heteroalkyl targets **39–42**. Reductive amination of the aldehyde with pyrrolidine directly yielded target compounds **43** and **44**.

Scheme 3 outlines the preparation of compounds **46** and **47** by lithiation of the C-2 position of intermediate **35** which was reacted with the protected imidazole **48** to give intermediate secondary alcohol **45**. Deoxygenation of the alcohol was accomplished by reduction of its mesylate to give **46**, which after hydrogenolysis of the benzyl group under the standard conditions yielded **47**.

As illustrated in Scheme 4 the arylacetylene compounds 50 and 52 were prepared by phenylacetylide anion displacement of the iodo (49) and bromo (51) intermediates, respectively. Compounds 53-58 were prepared by direct regioselective alkylation of the sterically less hindered N-3 nitrogen using the procedures described in the Experimental Section. For 53 dimethyl sulfate was used to alkylate the 2-bromotetracyclic guanine intermediate followed by 2-alkylation with benzyl bromide of the prepared organozinc species. Compounds 54 and 55 were prepared by alkylation using cyclohexylmethyl bromide and 2-bromoethanol, respectively. The catechol derivative 56 was prepared by alkylation with 2,3-dimethoxybenzyl bromide followed by demethylation with boron tribromide. Compound 57 was prepared using 3-(chloromethyl)pyridine as the alkylating reagent. Using 1-tosyl-2-(chlorometh-

Scheme 2^a



^{*a*} Reagents: (i) 1. *n*-BuLi, THF, 2. DMF; (ii) pyrrolidine, NaBH₃CN, MeOH; (iii) Pd(OH)₂/C, NH₄CO₂H, MeOH; (iv) NaBH₄, MeOH, CH₂Cl₂; (v) SOCl₂, CH₂Cl₂; (vi) NaOMe, MeOH or Me₂NH, THF.

Scheme 3^a



 a Reagents: (i) LDA, **48**, 60%; (ii) MsCl, Et_3N, CH₂Cl₂; (iii) LiBHEt_3, then 3% HCl, 35% (steps ii and iii); (iv) Pd(OH)_2/C, NH_4CO_2H, MeOH, reflux, 100%; (v) TsCl, Et_3N, 1,2-dichloro-ethane, reflux, 90%.

yl)imidazole as the alkylating reagent, compound **58** was afforded after removal of the tosyl protection.

The N-5-modified compounds **65**, **66**, **67** (Scheme 5), and **74** (Scheme 6) were prepared by building up the guanine nucleus through imidazole intermediates **61** and **70**. Cyclization to the xanthine structures **62** and **71** followed by completion of the ring system, under the general reaction conditions illustrated in Scheme 1, yielded the N-5-modified tetracyclic guanines.

Results and Discussion

Table 1 lists the structures and PDE isozyme inhibitory activity of tetracyclic guanines substituted on the imidazole C-2 carbon and N-1, N-3, and N-5 nitrogens. Variations included in this table at C-2 are lower alkyl (7-14), cycloalkylmethyl (15-22), aryl (25, 26), arylmethyl (27-34), arylalkynyl (50, 52), heteroalkyl (39-42), and heterocyclic (43-47). N-3 nitrogen substitutions for the above compounds are limited to hydrogen and benzyl for each of the C-2 variations. The structures are also varied with the presence of both fused, type A or spirofused, type B cyclopentyl rings. In the fused series (type A), the inhibitors (except for 23 and 24) are the enantiomerically pure *cis* (+) isomers with the absolute configuration 6aR,9aS as illustrated in the structural diagrams. Earlier work had suggested that the cis (+) isomers were about 10-fold more potent as PDE inhibitors than the *cis* (–) isomers.¹¹ However, since we did not examine each enantiomer for each target structure, we cannot be absolutely sure that this is true for all target compounds included in this study. General screening protocols in this study determined IC₅₀ values for PDE1 and PDE5 to evaluate effectiveness as inhibitors of cGMP hydrolysis and for PDE3 to evaluate selectivity against the enzyme responsible for cAMP hydrolysis in cardiac tissue. Included in Table 1 are the reference PDE inhibitors shown in Chart 1 along with isozyme inhibition data which had been determined previously in our laboratories.⁶

In general the tetracyclic guanines are much more effective inhibitors of PDE1 and PDE5 than PDE3. No consistent differences were observed between the fused and spirocyclopentyl series when comparable substitution patterns were present, and in general the SAR results were qualitatively similar. Within the alkyl

Scheme 4^a



^a Reagents: (i) LDA/THF; (ii) ClCH₂CH₂I, 67%, two steps; (iii) copper phenylacetylide, 120 °C; (iv) Pd(OH)₂/C, NH₄CO₂H, MeOH, reflux, 100%; (v) Br₂, NaOAc, HOAc, 50% °C, 90%; (vi) (phenyl-ethynyl)tributyltin, Pd(PPh₃)₄, NMP, 100 °C, 32%.

series (7-22) there is a trend for increasing potency with increasing carbon count when the nitrogen substitution is hydrogen. This trend is seen across the three enzymes. For the PDE1 enzyme benzyl substitution at N-3 increases potency for the small R₂ groups (7, 9, 15) but decreases it for the longer groups (11, 13,21) and has little effect on the sterically intermediate cyclopentylmethyl compounds (17, 19). The effect is somewhat similar for PDE5 where benzyl substitution generally decreases potency except for 7, 9, and 15. Only the N-3-benzylated trifluoromethylated compound 23showed good potency at PDE1 by comparison to the desbenzyl analog 24.

Among the C-2 aryl- and arylmethyl-substituted guanines (25-34), benzyl substitution at N-3 increased potency against both PDE1 and PDE3 except for the C-2 phenyl derivatives (25, 26) which are both inactive against PDE3. The effect on PDE5 is variable within this group. In most cases (27-34) decreases in potency are observed except for the C-2 phenyl compounds (25, 26) where N-benzylation results in increased potency. Compound **31**, with IC₅₀ = 70 pM, and compound **33**, with IC₅₀ = 0.6 nM, are the most potent inhibitors of PDE1. By comparison to their closest phenyl analogs (27 and 29, respectively), the additional phenyl group adds a 10–30-fold increase in potency for PDE1 but has only small and mixed effects for PDE3 and PDE5. This suggests a specific favorable interaction of the biphenyl

Journal of Medicinal Chemistry, 1997, Vol. 40, No. 14 2199

with the active site of PDE1 exists that is not mirrored in the active sites of the PDE3 and PDE5. Among the heteroalkyl-substituted inhibitors (39–44), the following trends can be observed: (i) N-3 benzyl substitution consistently increases the potency of PDE1 inhibition; (ii) inhibition for PDE5 is less than for PDE1 and responds variably to N-3 benzyl substitution; (iii) all are very weak inhibitors of PDE3. The imidazolylmethyl analogs (46, 47) are somewhat less potent than the arylmethyl analogs, while the phenylacetylides (50, 52) fall in between the imidazolylmethyl analogs and the most potent arylmethyl compounds. Although not the most potent at any single enzyme, it should be noted that compounds 20, 22, 30, and 50 are potent dual inhibitors with IC₅₀ values below 30 nM for both PDE1 and PDE5.

Table 1 also presents the activity of tetracyclic guanines with modifications at other positions on the core structure. Compounds 53-58 examine activity as a function of N-3 nitrogen substitution and supplement the hydrogen and benzyl examples 27-30. Methyl substitution at nitrogen (53) resulted in significantly reduced activity for the cGMP-hydrolyzing enzymes when compared to the hydrogen (30) or benzyl (29) analogs. Cyclohexylmethyl (54) showed a similar inhibition pattern to the isosteric benzyl (27) suggesting that this interaction is largely hydrophobic and not aryl specific. Dihydroxylation of the benzyl (56) reduces inhibition of PDE1 but has a minimal effect on PDE3 and PDE5. The polar hydroxyethyl group (55) on the imidazole nitrogen reduced activity at all enzymes, as did substitution with nitrogen-containing heteroarylmethyl groups (57, 58). These results are also consistent with a significant hydrophobic interaction at this position. The effect of groups larger than methyl on the pyrimidone N-5 nitrogen was examined in three compounds: 66, 67, and 74. A significant decrease in the inhibition of PDE1 was observed, with a much smaller effect on PDE3 and PDE5. Indeed, 67 and 74 are the most selective PDE5 inhibitors discovered in the tetracyclic guanine series. Finally, the effect of N-benzylation at the N-1 imidazole position was evaluated. Compound 65 is inactive for PDE1 and PDE3 and shows only weak activity for PDE5.

Nine PDE inhibitors (8, 12, 18, 20, 25, 28, 31, 33, 50) were selected for an expanded PDE profiling, adding PDE2 and PDE4, as well as for evaluation as antihypertensive agents when administered orally to the spontaneously hypertensive rat (SHR). As shown in Table 2, these compounds show modest to good selectivity for the PDE1 and PDE5 enzymes relative to PDE2, PDE3, and PDE4. The only exceptions within this group are compounds 31 and 33, which have similar activity for both PDE4 and PDE5 but are highly selective for PDE1. Certain inhibitors of PDE1 and PDE5 also demonstrate antihypertensive activity when administered orally at 10 mg/kg in the SHR. However, the magnitude of the maximum antihypertensive effect is not always correlated with the specific potency of the PDE inhibition within this limited group of compounds. For example, 25, 31, and 50 do not show significant blood pressure effects, while compounds 12, 20, and 28 reduced blood pressure by more than 45 mmHg. Most strikingly compounds 31 and 33, which are among the most potent PDE1 inhibitors and have similar profiles Scheme 5^a



^a Reagents: (i) Na₂S₂O₄, NaHCO₃, H₂O, 62%; (ii) CH₃C(OEt)₃, 100 °C, 71%; (iii) BnNH₂, EtOH, 80 °C, 52%; (iv) RNCO, NEt₃, PhH, 100 °C, then NaOMe, MeOH, reflux, 73%; (v) POCl₃, 100 °C, 54%; (vi) (1*R*,2*R*)-2-aminocyclopentanol, DIPEA, NMP, 96%; (vii) MsCl, NEt₃, CH₂Cl₂, 57%; (viii) Pd(OH)₂/C, NH₄HCO₂, MeOH, reflux, 78%.

Scheme 6^a



^{*a*} Reagents: (i) EtOH, HCl, 57%; (ii) ethyl 2-aminocyanoacetate; (iii) BnNH₂, 49% for two steps; (iv) EtNCO, 130 °C, 41%; (v) NaOMe, 98%; (vi) POCl₃, 100 °C, 55%; (vii) (–)-*trans*-2-aminocyclopentanol, DIPEA, 79%; (viii) MsCl, Et₃N, 65%; (ix) Pd(OH)₂/C, NH₄HCO₂, MeOH, reflux, 60%.

against PDE2, PDE3, PDE4, and PDE5, have completely different oral activities. This result suggests that the difference could be ascribed to the structural differences which include the N-3 benzyl and the spiro versus fused cyclopentane ring. It should be noted that in our hands the potent PDE5 inhibitor E4021 (Table 2) has not shown oral antihypertensive activity. A recent evaluation of the biological activity of a compound (SCH 51866), closely related to compound 28, indicated that in vivo biological activity is well correlated with plasma levels of PDE inhibitor.¹² However, pharmacokinetic/pharmacodynamic studies were not performed on the compounds presented here, and so variability in the absolute oral bioavailability, pharmacokinetics, and metabolic fate of these compounds could be reflected in the observed weak correlation between in vitro cGMP PDE inhibition and antihypertensive activity.

Conclusion

In summary, members of a series of tetracyclic guanines have been shown to be potent inhibitors of PDE1 or mixed inhibitors of PDE1 and PDE5 with high selectivity over other PDEs. General trends in the SAR demonstrate that (1) benzylation at N-1 is poorly tolerated, (2) a substantial enhancement of PDE1 activity is observed with hydrophobic arylmethyl groups at C-2, with biphenylmethyl being optimum, (3) N-3 benzylation tends to increase potency for PDE1 but has a mixed effect for PDE5, and (4) increasing the steric bulk of the alkyl group at N-5 enhances the selectivity for PDE5 over PDE1. Compounds **31** and **33** are potent and selective inhibitors of PDE1, with IC₅₀ values below 1 nM. Compounds **20**, **22**, **30**, and **50** are potent dual PDE1/PDE5 inhibitors with IC₅₀ values below 30 nM for both PDE1 and PDE5. Compounds **12**, **20**, and **28** reduced blood pressure by >45 mmHg when administered orally to the spontaneously hypertensive rat; however, other potent inhibitors had poor oral activity.

Given the important roles described for cGMP in cardiovascular regulation, it is evident that agents which modulate cGMP through inhibition of cGMPhydrolyzing PDEs should have desirable effects in cardiovascular diseases. Previously reported inhibitors have acted predominantly on PDE5.^{3.5.6} The tetracyclic guanines presented here inhibit both of the major isoenzyme classes (PDE1 and PDE5) which hydrolyze cGMP in vascular tissue and platelets. Furthermore, selected members of this family have good activity when administered orally and reduce blood pressure in hypertensive animals. Thus the potential for development of a new class of therapeutic agents is quite promising.
 Table 1. Structures and PDE1, PDE3, and PDE5 Inhibition of Tetracyclic Guanines Substituted at Positions 1, 2, 3, and 5

			$ \begin{array}{c} $	F 72	5 3 3 1 1 5 4 N 4 N 2 N N 1 R3 B			
Compound	Туре	-R ₁	-R ₂	-R₃	-R4		IC ₅₀ (nM)	
						PDE1	PDE3	PDE5
Vinpocetine [®]						19000	>300000	>300000
Zaprinast ^a						8000	122000	500
8-MeOMeMIX ^a						8000	240000	10000
E4021	_	_	211		211	>100000	>10000	4
7	Α	Bn	-CH ₃	-	CH₃	205	not tested	225
8	A	н	-CH3	-	CH₃	1250	>300000	2400
9	A	Bn	∽_ _{CH3}		CH₃	55	72000	510
10	A	н	CH3		CH3	350	80000	800
11	A	Bn	~~~~_CH3	-	CH3	100	35000	800
1 2	A	н	~~~сн₃	-	CH ₃	36	12000	10
13	Α	Bn	CH ₃	-	CH_3	80	25000	560
14	A	н	CH ₃	-	CH_3	15	15000	50
15	Α	Bn		-	CH_3	40	85000	420
16	Α	H	\sim	-	CH_3	300	50000	610
17	A	Bn	\sim	-	CH_3	36	130000	275
18	A	н	\sim	-	CH_3	30	30000	34
19	в	Bn	\sim	-	CH₃	37	36000	120
2 0	в	н	\sim	-	CH_3	14	57000	26
2 1	A	Bn	\sim		CH_3	1300	45000	590
2 2	A	н	\sim	-	CH_3	26	12000	19
23 ^b	A	Bn	-CF ₃	-	CH_3	39	50000	400
24 ^b	A	н	-CF ₃	-	CH₃	40000	>300000	6200

Compound	Туре	-R ₁	-R2	- R ₃	-R₄	IC₅₀ (nM)		
						PDE1	PDE3	PDE5
2 5	В	Bn	$-\langle \rangle$	-	CH_3	80	>300000	11
26	B	н		-	CH_3	5000	>100000	3300
27	Α	Bn	$\overline{\bigcirc}$	-	CH_3	2	17000	180
2 8	Α	Н	\sim	-	CH₃	100	80000	80
2 9	В	Bn	\sim	-	CH₃	7	11000	120
30	В	Н	\sim	-	CH_{3}	18	25000	19
31	A	Bn			CH₃	0.07	3500	305
32	A	Н		-	CH₃	16	1000	66
33	В	Bn		-	CH₃	0.6	7000	200
3 4	В	Н		-	CH_3	6	26000	43
39	A	Bn	∕o ^{_CH3}	-	CH3	125	150000	1000
40	A	н	∕_0 ^{,CH} ₃	-	CH₃	3000	>300000	13000
4 1	A	Bn	∽ _N , ^{CH} 3 cH3	-	CH_3	350	>100000	5600
4 2	A	н	∕_N, ^{СН} 3 с́Н3	-	CH_3	>10000	>100000	7500
43	A	Bn	N	-	CH₃	210	110000	1200
44	A	н	\sim N	-	CH_3	20000	150000	16000
4 6	A	Bn			CH₃	160	180000	1500
47	A	Н		-	CH_3	10000	>300000	26000
50	A	Bn		-	CH_3	21	110000	4
5 2	A	н		-	CH_3	150	250000	6000
53	В	CH_3	\sim	-	CH_3	1900	90000	4500

 Table 1. (Continued)

Compound	Type	-R1	-R ₂	- R 3	-R4	IC ₅₀ (nM)		
						PDE1	PDE3	PDE5
5 4	A	\frown	$\widehat{}$	-	CH_3	18	6000	110
55	A	ОН	$\widehat{}$	-	CH₃	4700	120000	10000
56	A	ОНОН	\sim		CH₃	70	32000	200
57	A	N	$\widehat{}$	-	CH₃	1100	>100000	4300
58	A	∕ , , , , , , , , , , , , , , , , , , ,	$\widehat{}$	-	CH₃	190	110000	4000
65	в	•	-CH ₃	Bn	-CH₃	>100000	>100000	2900
66	Α	н	-CH₃	-	∕сн₃	6900	111000	100
67	A	н	-CH₃	-		295000	175000	240
74	A	н	$\widehat{}$	-	∕сн₃	6500	30000	19

^{*a*} From ref 6. ^{*b*} Racemate.

Table 2. PDE1, PDE2, PDE3, PDE4, and PDE5 Inhibiton andOral Antihypertensive Effects in the SHR for Selected PDEInhibitors

		Λ mmHg				
compd	PDE1	PDE2	PDE3	PDE4	PDE5	@ 10 mg/kg
E4021	>100000	10900	>100000	5700	4	-7
8	1250	34000	>300000	82000	2400	-35
12	36	12000	11000	4800	10	-56
18	30	35000	30000	57000	34	-27
20	14	12000	57000	5200	26	-48
25	80	35000	>300000	9000	11	-10
28	100	1500	80000	8100	80	-47
31	0.07	2100	3500	700	305	-2
33	0.6	1800	7000	200	200	-33
50	21	3100	110000	not tested	4	-2

Experimental Section

Melting points were taken on a Thomas-Hoover or Mel-Temp II melting point apparatus and are uncorrected. The melting points of amorphous solids are generally not reported. Chromatography was performed over Universal Scientific or Selecto Scientific flash silica gel 32–63 µm. ¹H NMR spectra were determined with a Varian VXR 200, Gemini 300, or Gemini 400 MHz instrument using either Me₄Si or residual solvent signal as internal standard. IR spectra were obtained on a Perkin Elmer 727B series IR spectrophotometer or on a Nicolet 10 MX-FTIR. Rotations were determined on a Rudolph Autopol III or Perkin-Elmer 243B polarimeter. Mass spectra were obtained on a VG-ZAB-SE, Extrel-401, HP-MS Engine, or JEOL HX-110 mass spectrometer. Elemental analyses were determined by the Physical-Analytical Department of Schering-Plough Research Institute using either CEC 240-HA, CEC CE-440, or Fisons EA 1108 CHNS elemental analyzers and are within 0.4% of the theoretical value unless otherwise noted. Fractional solvent impurities reported in the molecular composition were identified by the characteristic peaks in the ¹H NMR and were quantitated by integration of the ¹H resonances. The reference PDE5 inhibitor, E4021, was prepared according to the patent procedure. $^{13}\,$ Several of the methods described in this section have been previously reported in the patent literature. $^{14}\,$

1,8-Dimethyl-7-(phenylmethyl)purine-2,6-dione (2). A solution of 6-amino-5-(benzylamino)-3-methylpyrimidine-2,4-(1H,3H)-dione (1) (24.60 g, 0.1 mmol) in DMF was heated to 60 °C, and triethyl orthoacetate (73 mL, 0.4 mol) was added. The reaction mixture was then heated at 110 °C for 5 h and cooled in an ice bath. The precipitate thus obtained was filtered and washed with methanol and diethyl ether to give the title compound (24.40 g, 90%) as a white solid: mp 293–295 °C; ¹H NMR (DMSO) δ 2.35 (s, 3H, CH₃), 3.15 (s, 3H, NCH₃), 5.50 (s, 2H, CH₂Ph), 7.15–7.40 (m, 5H, C₆H₅), 11.85 (bs, 1H, NH).

N-(6-Amino-3-methyl-2,4-dioxo-5-pyrimidinyl)-*N*-(phenylmethyl)butanamide (3). A mixture of 6-amino-3methyl-5-(benzylamino)pyrimidine-2,4-dione (1) (5.0 g, 20.33 mmol), butyric acid (1.79 g, 1.86 mL, 20.3 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.30 g, 22.4 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.25 g) in DMF (30 mL) was stirred at room temperature overnight. The reaction mixture was poured into ice-H₂O, filtered, washed with water, and dried *in vacuo* over P₂O₅ to give **3** (5.80 g, 90%): ¹H NMR (DMSO-*d*₆) δ 0.85 (t, 3H, CH₃), 1.50 (dt, 2H, CH₂CH₃), 2.05 (t, 2H, CH₂), 3.00 (s, 3H, NCH₃), 4.55 (AB, 2H, CH₂Ph), 6.15 (s, 2H, NH₂), 7.15-7.30 (m, 5H, C₆H₅),

2-Chloro-1,8-dimethyl-7-(phenylmethyl)purin-6(6H)one (4). A suspension of **2** (10.0 g) in POCl₃ (200 mL) was heated at reflux for 7 h; it was then concentrated under vacuum. The residue was partitioned between EtOAc and ice-water and the organic layer washed with water, dried, and concentrated. The crude product was purified by flash chromatography (1% MeOH/CH₂Cl₂) to give **4** (9.63 g, 90%) as a white solid: mp 166–168.5 °C; ¹H NMR (CDCl₃) δ 2.50 (s, 3H, CH₃), 3.75 (s, 3H, NCH₃), 5.60 (s, 2H, CH₂Ph), 7.15–7.40 (m, 5H, C₆H₅); MS (EI) m/z 290 (MH⁺).

2-Chloro-8-propyl-1-methyl-7-(phenylmethyl)purin-6(6*H***)-one (5). A suspension of 3** (2.0 g) in POCl₃ (50 mL) was heated at reflux for 7 h; it was then concentrated under

vacuum. The residue was partitioned between EtOAc and ice–water and the organic layer washed with water, dried, and concentrated. The crude product was purified by flash chromatography (1% MeOH/CH₂Cl₂) to give **5** (1.60 g, 80%): ¹H NMR (CDCl₃) δ 0.95 (t, 3H, CH₃), 1.55 (m, 2H), 2.55 (t, 2H, CH₂), 3.20 (s, 3H, NCH₃), 5.50 (AB, 2H, CH₂Ph), 7.15–7.35 (m, 5H, C₆H₅); MS (EI) *m*/*z* 318 (MH⁺).

2-[((1 *R***,2***R***)-2-Hydroxycyclopentyl)amino]-1,8-dimethyl-7-(phenylmethyl)purin-6(6***H***)-one (6). A mixture of 4** (6.0 g, 21 mmol), (1R,2R)-2-aminocyclopentanol¹⁰ (3.17 g, 31.4 mmol), and diisopropylethylamine (62 mmol) in *N*-methylpyrrolidone (20 mL) was heated at 130 °C until TLC indicated the complete consumption of **4**. The reaction mixture was poured into water, extracted with EtOAc, dried (MgSO₄), filtered, and concentrated. The crude product was purified by flash chromatography (5% MeOH/CH₂Cl₂) to give **6** (6.20 g, 85%): [α]²⁶_D +8.3° (*c* 1.0, EtOH); ¹H NMR (CDCl₃) δ 1.53–2.25 (m, 6H), 3.30 (s, 3H, NCH₃), 4.00 (m, 2H), 5.00 (d, 1H, OH), 5.50 (s, 2H, CH₂Ph), 6.45 (d, 1H, NH), 7.2–7.4 (m, 5H). Anal. (C₁₉H₂₃N₅O₂·0.5H₂O) C, H, N.

(6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (7). To a solution of 6 (8.0 g, 23 mmol) in CH₂Cl₂ (150 mL) was added SOCl₂ (8.1 g, 68 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h, diluted with CH₂Cl₂, treated with ice, and adjusted to pH 7–8 with 1 N NaOH. The CH₂Cl₂ layer was separated and the aqueous solution extracted with CH₂Cl₂. The combined organic solutions were washed with brine, dried (MgSO₄), filtered, and concentrated. The crude product was purified by flash chromatography (2% MeOH/CH₂Cl₂) to give 7 (7.20 g, 95%) as a white solid: mp 185.5–186.5 °C (CH₃CN); [α]²⁶_D +125.9° (*c* 1.0, EtOH); ¹H NMR (CDCl₃) δ 1.53–2.25 (m, 6H), 4.70 (t, 1H, J = 7.7 Hz), 4.81 (t, 1H, J = 7.3 Hz), 5.48 (s, 2H), 7.2–7.4 (m, 5H); MS (EI) *m*/*z* 335 (M⁺, 60). Anal. (C₁₉H₂₁N₅O) C, H, N.

(6a *R*,9a *S*)-5,6a,7,8,9,9a-Hexahydro-2,5-dimethylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (8). To a stirred suspension of 20% Pd(OH)₂/C (1.5 g) in methanol was added ammonium formate (9.5 g, 0.15 mol) followed by a solution of 7 (5.0 g, 15 mmol) in methanol. The mixture was stirred at reflux until TLC indicated the complete consumption of 7. The reaction mixture was filtered, washed with 10% MeOH/CH₂-Cl₂, and concentrated. The residue was diluted with CH₂Cl₂, washed with saturated NaHCO₃ and brine, dried (MgSO₄), filtered, and concentrated. Crude product was purified by flash chromatography (5% MeOH/CH₂Cl₂) to give **8** (3.30 g, 90%) as a white solid: $[\alpha]^{21}_{D} + 143.7^{\circ}$ (*c* 0.5, EtOH); ¹H NMR (CDCl₃) δ 1.6-2.25 (m, 6H), 2.55 (s, 3H), 3.44 (s, 3H), 4.81 (t, 1H, J = 7.1 Hz), 4.92 (t, 1H, J = 7.1 Hz); MS (CI, CH₄) m/z246 (MH⁺, 100). Anal. (C₁₂H₁₅N₅O·0.2H₂O) C, H, N.

(6a*R*,9a*S*)-2-Propyl-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (9): from compound 5 using the general methods described above for the conversion of 4 to 7; ¹H NMR (300 MHz, CDCl₃) δ 0.95 (t, 3H, J = 7.5 Hz, CH₃), 1.60–2.00 (m, 7H), 2.25 (dd, 1H, J = 7.5, 12.5 Hz), 2.60 (dd, 2H, CH₂CH₂), 3.32 (s, 3H, NCH₃), 4.70 (t, 1H, J = 7.0 Hz), 4.85 (t, 1H, J = 7.0 Hz), 5.50 (d, 2H, J = 12.5 Hz, NCH₂Ph), 7.15 (d, 2H, ArH), 7.28–7.30 (m, 3H, ArH); MS (FAB, thioglycerol matrix) m/z 364 (MH⁺). Anal. (C₂₁H₂₅N₅O) C, H, N.

(6a*R*,9a*S*)-2-Propyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (10): ¹H NMR (300 MHz, CDCl₃) δ 1.00 (t, 3H, J = 7.5 Hz, CH₃), 1.60–2.00 (m, 7H), 2.28 (dd, 1H, J = 7.5, 12.5 Hz), 2.80 (t, 2H, J = 7.5 Hz, CH₂CH₂), 3.30 (s, 3H, NCH₃), 4.72 (t, 1H, J = 7.0 Hz), 4.90 (t, 1H, J = 7.0 Hz); MS (FAB, thioglycerol matrix) m/z 274 (MH⁺). Anal. (C₁₄H₁₉N₅O) C, H, N.

(6a*R*,9a*S*)-2-Hexyl-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (11): ¹H NMR (CDCl₃) δ 0.85 (t, 3H, J = 6.7 Hz, CH₃), 1.2 (m, 6H, (CH₂)₃), 1.55 (m, 3H), 1.7 (m, 1H), 1.8 (m, 2H), 1.91 (dd, 1H, J = 12.4, 5.4 Hz, CH), 2.19 (dd, 1H, J = 13.6, 5.3 Hz, CH), 2.60 (t, 2H, J = 7.7 Hz, CH₂), 3.3 (s, 3H, NCH₃), 4.67 (t, 1H, J = 7.4 Hz, CH), 4.80 (t, 1H, J = 7.2 Hz, CH), 5.46 (AB, 2H, J = 15.8 Hz, PhCH₂), 7.12 (d, 2H, J = 6.95 Hz, ArH), 7.24–7.31 (m, 3H, ArH); HRMS FAB (C₂₄H₃₂N₅O) calcd 406.2607 (MH+), found 406.2620. Anal. ($C_{24}H_{31}N_5O)$ C, N; H: calcd, 7.7; found, 7.24.

(6a*R*,9a*S*)-2-Hexyl-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (12): ¹H NMR (CDCl₃) δ 0.84 (t, 3H, J = 6.4 Hz, CH₃), 1.34 (br, 6H, (CH₂)₃), 1.55 (m, 1H), 1.7–1.88 (m, 5H), 1.94 (m, 1H, CH), 2.23 (dd, 1H, J = 13.2, 5.5 Hz, CH), 2.79 (t, 2H, J = 7.7 Hz, CH₂), 3.37 (s, 3H, NCH₃), 4.72 (t, 1H, J = 7.3 Hz, CH), 4.87 (t, 1H, J = 7.5 Hz, CH); MS (CI) m/z 316 (M⁺). Anal. (C₁₇H₂₅N₅O·0.5 H₂O·0.25CH₃OH) C, H, N.

(6a*R*,9a.5)-2-(3-Methylbutyl)-5,6a,7,8,9,9a-hexahydro-5methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (13): ¹H NMR (CDCl₃) δ 0.81 (d, 6H, *J* = 6.5 Hz, CH(*CH*₃)₂), 1.38-2.22 (m, 9H, NCH(*CH*₂)₃CHN=, CH₂-*CH*₂*CH*(CH₃)₂), 2.58 (m, 2H, *CH*₂CH₂CH₂CH(CH₃)₂), 3.33 (s, 3H, CH₃N), 4.68 (t, 1H, *J* = 7.5 Hz, NC*H*(CH₂)₃CHN=), 4.81 (t, 1H, *J* = 7.3 Hz, NCH(CH₂)₃C*H*N=), 5.44 (d, 2H, *J* = 3.0 Hz, *CH*₂C₆H₅), 7.12 (d, 2H, *J* = 7.4 Hz, ArH), 7.25 (m, 3H, ArH); MS (CI) *m*/*z* 392 (MH⁺). Anal. (C₂₃H₂₉N₅O·0.50H₂O) C, H, N.

(6a*R*,9a*S*)-2-(3-Methylbutyl)-5,6a,7,8,9,9a-hexahydro-5methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (14): ¹H NMR (CDCl₃) δ 0.92 (d, 6H, J = 6.4 Hz, C(CH₃)₂), 1.53– 2.28 (m, 9H, NCH(*CH*₂)₃CHN=, CH₂*CH*₂*CH*(CH₃)₂), 2.82 (m, 2H, *CH*₂CH₂CH(CH₃)₂), 3.44 (s, 3H, CH₃N), 4.76 (t, 1H, J =7.1 Hz, N*CH*(CH₂)₃CHN=), 4.92 (t, 1H, J = 6.9 Hz, NCH-(CH₂)₃*CH*N=); MS (CI) *m*/*z* 302 (MH⁺). Anal. (C₁₆H₂₃N₅O-0.25CH₂Cl₂) C, H, N.

(6a*R*,9a.5)-2-(Cyclopropylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (15): ¹H NMR (CDCl₃) δ 0.11 (q, 2H, J = 5.0 Hz, cyclopropyl), 0.44 (m, 2H, J = 4.5 Hz, cyclopropyl), 0.95 (m, 1H, C*H*(CH₂)₂), 1.50–2.24 (m, 6H, NCH(*CH*₂)₃CHN=), 2.58 (t, 2H, J = 6.3 Hz, *CH*₂CH(CH₂)₂), 3.31 (s, 3H, CH₃N), 4.69 (t, 1H, J = 7.5 Hz, N*CH*(CH₂)₃CHN=), 4.83 (t, 1H, J =7.2 Hz, NCH(CH₂)₃*CH*N=), 5.47 (AB, 2H, J = 15.9 Hz, *CH*₂C₆H₅), 7.09 (d, 2H, J = 7.6 Hz, ArH), 7.25 (m, 3H, ArH); MS (CI) *m*/*z* 376 (MH⁺). Anal. (C₂₂H₂₅N₅O·0.80H₂O) C, H, N.

(6a*R*,9a*S*)-2-(Cyclopropylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (16): ¹H NMR (CDCl₃) δ 0.30 (q, 2H, J = 5.1 Hz, cyclopropyl), 0.56 (m, 2H, cyclopropyl), 1.17 (m, 1H, C*H*(CH₂)₂), 1.53–2.29 (m, 6H, NCH(*CH*₂)₃CHN=), 2.73 (d, 2H, J = 7.0 Hz, *CH*₂CH(CH₂)₂), 3.40 (s, 3H, CH₃N), 4.75 (t, 1H, J = 7.5 Hz, N*CH*(CH₂)₃CHN=), 4.91 (t, 1H, J = 7.0 Hz, NCH-(CH₂)₃CHN=); MS (CI) *m*/*z* 286 (MH⁺). Anal. (C₁₅H₁₉N₅O· 0.25CH₂Cl₂) C, H, N.

(6a*R*,9a*S*)-2-(Cyclopentylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (17): clear oil; $[\alpha]^{20}_{\rm D}$ +99° (*c* 0.57, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.09–2.27 (m, 15H), 2.65 (d, 2H, *J* = 7.4 Hz), 3.34 (s, 3H), 4.71 (t, 1H, *J* = 7.6 Hz), 4.84 (t, 1H, *J* = 7.2 Hz), 5.46 (d, 1H, *J* = 15.6 Hz), 5.54 (d, 1H, *J* = 15.9 Hz), 7.14 (d, 2H, *J* = 7.0 Hz), 7.26–7.35 (m, 3H); MS (CI) *m*/*z* 404 (MH⁺, 100). Anal. (C₂₄H₂₉N₅O·0.55CHCl₃) C, H; N: calcd, 14.93; found, 14.04.

(6a*R*,9a*S*)-2-(Cyclopentylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (18): clear oil; $[\alpha]^{20}_{\rm D}$ +127° (*c* 0.63, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.21–2.42 (m, 15H), 2.81 (d, 2H, *J* = 7.6 Hz), 3.40 (s, 3H), 4.74 (t, 1H, *J* = 7.4 Hz), 4.88 (t, 1H, *J* = 7.2 Hz); MS (CI) *m*/*z* 314 (MH⁺, 100). Anal. (C₁₇H₂₃N₅O·0.75CHCl₃) C, H, N.

5'-Methyl-2'-(cyclopentylmethyl)-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'H)-[3H]imidazo[2,1-*b***]purin]-4(5'H)one (19):** ¹H NMR (400 MHz, CDCl₃) δ 1.10 (m, 2H), 1.40– 1.95 (m, 14H), 2.20 (m, 1H), 2.55 (d, 2H, J = 7.4 Hz, $CH_2C_5H_9$), 3.34 (s, 3H, NCH₃), 3.90 (s, 2H, CH₂), 5.50 (s, 2H, CH_2Ph), 7.10, 7.28 (5H, m, ArH); MS (FAB, thioglycerol matrix) m/z418 (MH⁺). Anal. (C₂₅H₃₁N₅O) C, H, N.

5'-Methyl-2'-(cyclopentylmethyl)spiro[cyclopentane-1,7'(8'H)-[3H]imidazo[2,1-b]purin]-4'(5'H)-one (20): ¹H NMR (400 MHz, CDCl₃) δ 1.22 (m, 2H), 1.50–1.90 (m, 14H), 2.38 (m, 1H), 2.80 (d, 2H, J= 7.4 Hz, $CH_2C_5H_9$), 3.40 (s, 3H, NCH₃), 3.92 (s, 2H, CH₂); MS (FAB, thioglycerol matrix) m/z 328 (MH⁺). Anal. (C₁₈H₂₅N₅O) C, H, N.

(6a*R*,9a*S*)-2-(Cyclohexylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (21): white foam from silica gel column (2% MeOH in CH₂Cl₂); $[\alpha]^{22}_{\rm D}$ +99.1° (*c* 0.5, EtOH); ¹H NMR (CDCl₃) δ 0.9–2.0 (6m, 17H), 2.54 (d, 2H, *J* = 7.0 Hz), 3.34 (s, 3H), 4.72 (t, 1H, *J* = 7.0 Hz), 4.85 (t, 1H, *J* = 6.8 Hz), 5.35 (d, 2H, *J* = 5.8 Hz), 7.14–7.36 (m, 5H); MS (CI, CH₄) *m*/*z* 418 (MH⁺, 100). Anal. (C₂₅H₃₁N₅O·0.5CH₃OH) C, H, N.

(6a*R*,9a*S*)-2-(Cyclohexylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (22): beige foam from silica gel column (5% MeOH in CH₂Cl₂); $[\alpha]^{25}_{D}$ +127° (*c* 0.5 EtOH); ¹H NMR (CDCl₃) δ 1.0– 2.3 (6m, 17H), 2.70 (d, 2H, *J* = 7.1 Hz), 3.42 (s, 3H), 4.78 (t, 1H, *J* = 7.3 Hz), 4.90 (t, 1H, *J* = 7.1 Hz); MS (CI, CH₄) *m*/*z* 328 (MH⁺, 100). Anal. (C₁₈H₂₅N₅O·0.25CH₃OH) C, H, N.

rac-(6a*R**,9a*S**)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(trifluoromethyl)-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (23): white solid from silica gel column (2% MeOH in CH₂Cl₂); ¹H NMR (CDCl₃) δ 1.56 (m, 1H), 1.85 (m, 4H), 2.23 (m, 4H), 3.33 (s, 3H), 4.82 (t, 1H, *J* = 7.5 Hz), 5.68 (s, 2H), 7.2–7.4 (m, 5H); MS (CI, CH₄) *m*/*z* 390 (MH⁺, 100). Anal. (C₁₉H₁₈F₃N₅O) C, H, N.

rac-(6a*R**,9a*S**)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(trifluoromethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (24): white solid; ¹H NMR (400 MHz, CD₃OD) δ 1.66– 2.42 (m, 6H), 3.39 (s, 3H), 4.84 (t, 1H, *J* = 7.0 Hz), 5.21 (t, 1H, *J* = 7.1 Hz); MS (CI) *m*/*z* 300 (MH⁺, 100). Anal. (C₁₂H₁₂F₃N₅O· H₂O)C, H, N.

5'-Methyl-2'-phenyl-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'*H***)-[3***H***]imidazo[2,1-***b***]purin]-4(5'***H***)-one (25): white solid; mp 125.5–127.5 °C (from isopropyl ether); ¹H NMR (CDCl₃) \delta 1.67–1.95 (m, 8H), 3.36 (s, 3H), 3.95 (s, 2H), 5.59 (s, 2H), 7.03–7.56 (m, 10H); MS (CI, CH₄)** *m***/***z* **412 (MH⁺, 100). Anal. (C₂₅H₂₅N₅O·0.5CH₃OH) C, H, N.**

5'-Methyl-2'-phenylspiro[cyclopentane-1,7'(8'H)-[3H]-imidazo[2,1-*b***]purin]-4'(5'H)-one (26):** white solid; mp >300 °C (from EtOH); ¹H NMR (DMSO-*d*₆) δ 1.68–1.79 (m, 8H), 3.24 (s, 3H), 3.96 (s, 2H), 7.48 (m, 3H), 8.1 (d, 2H, *J* = 6.5 Hz), 13.5 (bs, 1H); MS (CI, isob) *m*/*z* 322 (MH⁺, 100). Anal. (C₁₈H₁₉N₅O· 0.1EtOH) C, H, N.

(6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2,3-bis-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (27): off-white solid; $[\alpha]^{25}_{D} + 237^{\circ}$ (*c* 0.50, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 1.55–2.40 (m, 6H), 3.52 (s, 3H), 4.07 (s, 2H), 4.84 (t, 1H, *J* = 7 Hz), 5.01 (t, 1H, *J* = 7 Hz), 5.37 (s, 2H), 7.08–7.13 (m, 4H), 7.24–7.34 (m, 6H); MS (EI) *m*/*z* 411 (M⁺, 48), 382 (100). Anal. (C₂₅H₂₅N₅O) C, H, N.

(6a*R*,9a*S*)-2-(Phenylmethyl)-5,6a,7,8,9,9a-hexahydro-5methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (28): ¹H NMR (200 MHz, CDCl₃ + 1 drop of CD₃OD) δ 1.50 (1H, m), 1.65–2.00 (5H, m), 2.28 (dd, 1H, J = 7.5, 12.5 Hz), 3.28 (s, 3H, NCH₃), 4.18 (s, 2H, CH₂Ph), 4.75 (t, 1H, J = 7.0 Hz), 4.90 (t, 1H, J = 7.0 Hz), 7.30 (m, 5H, ArH); MS (FAB, thioglycerol matrix) m/z 322 (MH⁺). Anal. (C₁₈H₁₉N₅O) C, H, N.

5'-Methyl-2',3'-bis(phenylmethyl)spiro[cyclopentane-1,7'(8'H)-[3H]imidazo[2,1-*b***]purin]-4'(5'H)-one (29): 'H NMR (300 MHz, DMSO-d_6) \delta 1.55–1.82 (m, 8H), 3.16 (s, 3H), 3.81 (s, 2H), 4.05 (s, 2H), 5.53 (s, 2H), 7.07–7.33 (m, 10H); MS (CI) m/z 426 (MH⁺). Anal. (C₂₆H₂₇N₅O·C₂H₅OH·0.5H₂O) C, H, N.**

5'-Methyl-2'-(phenylmethyl)spiro[cyclopentane-1,7'-(**8'H)-[3H]imidazo[2,1-b]purin]-4'(5'H)-one (30):** ¹H NMR (200 MHz, CDCl₃ + 1 drop of CD₃OD) δ 1.60–2.00 (m, 8H), 3.56 (s, 3H, NCH₃), 4.18 (bs, 2H, CH₂), 4.26 (s, 2H, CH₂Ph), 7.30 (m, 5H, ArH); MS (FAB, thioglycerol matrix) m/z 336 (MH⁺). Anal. (C₁₉H₂₁N₅O) C, H, N.

(6a*R*,9a*S*)-2-(Biphenylylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (31): colorless solid; $[\alpha]^{25}_{D}$ +86.6° (*c* 0.2, MeOH); ¹H NMR (CDCl₃) δ 1.61 (m, 1H, J = 6 Hz, CH₂), 1.72–2.02 (m, 4H, CH₂), 2.30 (dd, 1H, J = 5.2, 13.8 Hz, CH₂), 3.35 (s, 3H, NCH₃), 4.08 (s, 2H, CH₂Ar), 4.75 (t, 1H, J = 7.3 Hz, CH-N), 4.90 (t, 1H, J = 7.2 Hz, CH-N), 5.40 (s, 2H, NCH₂-Ar), 7.12 (m, 2H), 7.19 (m, 2H), 7.26–7.37 (m, 4H), 7.43 (m, 2H), 7.50 (m, 2H), 7.55 (m, 2H); MS (CI) m/z 488 (MH⁺). Anal. (C₃₁H₂₉N₅O·0.33H₂O) C, H, N.

(6a*R*,9a*S*)-2-(Biphenylylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (32): white powder; mp 225–227 °C; $[\alpha]^{25}_{D}$ +114.7° (*c* 0.2, MeOH); ¹H NMR (CDCl₃) δ 1.55 (m, 1H, CH₂), 1.68–1.92 (m, 4H, CH₂), 1.96 (m, 1H, CH₂), 2.27 (dd, 1H, CH₂), 3.38 (s, 3H, NCH₃), 4.20 (s, 2H, CH₂Ar), 4.72 (t, 1H, *J* = 7.6, CH-N), 4.87 (t, 1H, *J* = 7.4 Hz, CH-N), 7.35 (m, 1H, ArH), 7.42 (m, 4H, ArH), 7.55 (m, 4H, ArH); MS (CI) *m*/*z* 398 (MH⁺). Anal. (C₂₄H₂₃N₅O) C, H, N.

5'-Methyl-2'-(biphenylylmethyl)-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'H)-[3H]imidazo[2,1-b]purin]-4(5'H)one (33): ¹H NMR (CDCl₃) δ 1.60–1.76 (m, 4H), 1.82–2.00 (m, 4H), 3.37 (s, 3H), 3.94 (s, 2H), 4.05 (s, 2H), 5.43 (s, 2H), 7.13 (d, 2H, J = 6.2 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.30–7.40 (m, 4H), 7.48 (dd, 2H, J = 7.6 Hz), 7.53 (d, 2H, J = 8.2 Hz), 7.59 (d, 2H, J = 7.1 Hz); MS (CI) m/z 502 (MH⁺). Anal. (C₃₂H₃₁N₅O) C, H, N.

5'-Methyl-2'-(biphenylylmethyl)spiro[cyclopentane-1,7'(8'H)-[3H]imidazo[2,1-b]purin]-4'(5'H)-one (34): 1 H NMR (CDCl₃) δ 1.61–1.75 (m, 4H), 1.80–1.99 (m, 4H), 3.40 (s, 3H), 3.92 (s, 2H), 4.18 (s, 2H), 7.32 (m, 1H), 7.39–7.44 (m, 4H), 7.51–7.55 (m, 4H); MS (FAB) m/z 412.2 (MH⁺). Anal. (C₂₅H₂₅N₅O·CH₃OH) C, H, N.

(6a *R*, 9a *S*) -5, 6a, 7, 8, 9, 9a - Hexahydro-5 - methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (35). Intermediate 35 was prepared according to the general methods illustrated in Scheme 1, using triethyl orthoformate to form the imidazole ring, and recrystallized from CH₂Cl₂/hexane: mp 145–146 °C; $[\alpha]^{26}_{\rm D}$ +105.7° (*c* 0.5, MeOH); ¹H NMR (CDCl₃) δ 1.50 (m, 11H, CH₂), 1.61–1.92 (m, 4H, CH₂), 2.14 (dd, 1H, CH₂), 3.29 (s, 3H, NMe), 4.65 (t, 1H, J = 7 Hz, CH-N), 4.77 (t, 1H, J = 7 Hz, CH-N), 5.35 (d, 1H, J= 14 Hz, NCHPh), 5.40 (d, 1H, J = 14 Hz, CHPh), 7.27–7.34 (m, 5H, ArH), 7.42 (s, 1H, C2-H); MS (EI) *m*/*z* 321 (M⁺). Anal. (C₁₈H₁₉N₅O·0.1H₂O) C, H, N.

(6aR,9aS)-2-Formyl-cis-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one (36). A solution of N,N-diisopropylamine (7.15 mL, 51 mmol) in THF was cooled to 0 °C and treated with n-BuLi (2.5 M in hexanes, 20.4 mL) for 0.5 h. The reaction mixture was then cooled to -78 °C, and compound 35 (13.70 g, 42.60 mmol) in THF (100 mL) was added. The reaction mixture was stirred at -78 °C for 0.5 h, and DMF (5.30 mL, 68.0 mmol) was added. The reaction mixture was allowed to warm to room temperature over a period of 1 h and then treated with saturated NH₄Cl. The THF was removed under reduced pressure, and the residue was extracted with CH₂Cl₂. The CH₂Cl₂ layer was dried and evaporated. Flash chromatography (2% MeOH/CH₂Cl₂) gave 36 (10.70 g, 72%): ¹H NMR (400 MHz, CDCl₃) δ 1.75–2.0 (m, 5H), 2.20 (m, 1H), 3.40 (s, 3H, NCH₃), 4.75, 4.85 (2bt, 2H, J = 7.5 Hz, 2CH), 5.95 (AB, 2H, CH₂Ph), 7.20-7.30 (m, 5H, C₆H₅), 9.98 (s, 1H, CHO); MS (FAB, thioglycerol matrix) m/z 350 (MH⁺). Anal. (C₁₉H₁₉N₅O₂) C, H. N.

(6a*R*,9a.5)-2-(Hydroxymethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (37). To a solution of 36 (2.60 g, 7.0 mmol) in EtOH (100 mL) and CH_2Cl_2 (50 mL) was added sodium borohydride (2.68 g, 71 mmol) in two portions over 0.5 h. The reaction mixture was partially evaporated, and water was added. Solids were removed by filtration, and the filtrate was evaporated. The residue was extracted with CH_2Cl_2 , dried (MgSO₄), and evaporated to produce 37 (2.20 g, 85%): ¹H NMR (300 MHz, DMSO- d_8) δ 1.45–1.80 (m, 5H), 2.10 (m, 2H), 3.30 (s, 3H, NCH₃), 4.48 (d, 2H, CH₂OH), 4.55, 4.65 (2m, 2H), 5.52 (AB, 2H, J = 14.5 Hz, CH_2 Ph), 7.24, 7.30 (2m, 5H, C_6 H₅); MS (FAB, thioglycerol matrix) m/z 352 (MH⁺). Anal. ($C_{19}H_{21}N_5O_2$) *C*, H, N.

(6a*R*,9a.5)-2-(Chloromethyl)-5,6a,7,8,9,9a-hexahydro-5methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (38). To a solution of 37 (1.90 g, 5.14 mmol) in CH_2Cl_2 (60 mL) was added SOCl₂ (3.70 mL, 51 mmol), and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was evaporated; the residue was treated with saturated NaHCO₃, extracted with CH₂Cl₂ (3 × 100 mL), dried (MgSO₄), and evaporated to give **38** (1.70 g, 90%): ¹H NMR (300 MHz, CDCl₃) δ 1.50–2.00 (m, 5H), 2.20 (m, 2H), 3.38 (s, 3H, NCH₃), 4.50 (s, 2H, CH₂Cl), 4.75, 4.85 (2 bt, 2H, *J* = 7.5 Hz), 5.68 (2H, s, CH₂Ph), 7.22, 7.35 (2m, 5H, ArH); MS (FAB, thioglycerol matrix) m/z 370 (MH⁺). Anal. (C₁₉H₂₀-ClN₅O) C, H, N.

(6a*R*,9a.5)-5,6a,7,8,9,9a-Hexahydro-2-(methoxymethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (39). Compound 38 (0.30 g, 0.80 mmol) was added to a freshly prepared solution of sodium methoxide (0.07 g of sodium in 10 mL of MeOH), and the reaction mixture was refluxed for 1 h. The reaction mixture was evaporated, the residue was suspended in water, and the pH was adjusted to 8 with 1 N HCl. The suspension was extracted with CH₂Cl₂ (3 × 50 mL), dried (MgSO₄), and evaporated. Column chromatography (SiO₂, 3% MeOH/CH₂Cl₂) gave 39 (0.20 g, 70%): ¹H NMR (300 MHz, CDCl₃) δ 1.50–2.00 (m, 5H), 2.20 (m, 2H), 3.35 (s, 3H, NCH₃), 3.38 (s, 3H, OCH₃), 4.48 (s, 2H, CH₂O), 4.70, 4.82 (2bt, 2H *J* = 8.0 Hz), 5.62 (2H, s, CH₂Ph), 7.22, 7.32 (2m, 5H, ArH); MS (FAB, thioglycerol matrix) *m*/*z* 366 (MH⁺). Anal. (C₂₀H₂₃N₅O₂) C, H, N.

(6a*R*,9a.5)-5,6a,7,8,9,9a-Hexahydro-2-(methoxymethyl)-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (40). Compound **39** (0.20 g, 0.55 mmol) was reduced with ammonium formate/Pd(OH)₂, using the general procedure described for **8**, to give **40** (0.14 g, 92%): ¹H NMR (300 MHz, CDCl₃) δ 1.50–2.00 (m, 5H), 2.25 (m, 2H), 3.40 (s, 3H, NCH₃), 3.50 (s, 3H, OCH₃), 4.60 (s, 2H, CH₂O), 4.75, 4.85 (2 bt, 2H, *J* = 8.0 Hz); MS (FAB, thioglycerol matrix) *m*/*z* 276 (MH⁺). Anal. (C₁₃H₁₇N₅O₂) C, H, N.

(6a*R*,9a*S*)-2-[(*N*,*N*-Dimethylamino)methyl]-5,6a,7,8,9, 9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (41). A solution of compound **38** (1.0 g, 2.71 mmol) in THF and excess *N*,*N*dimethylamine (2 M in THF) was refluxed for 0.25 h, and the reaction mixture was evaporated. The residue was dissolved in CH₂Cl₂, washed with saturated NaHCO₃, dried (MgSO₄), and evaporated. Column chromatography of the residue (SiO₂, 2% MeOH/CH₂Cl₂) gave **41** (0.82 g, 80%): ¹H NMR (300 MHz, CDCl₃) δ 1.50–2.00 (m, 5H), 2.20 (m, 2H), 2.25 (s, 6H, N(CH₃)₂), 3.35 (s, 3H, NCH₃), 3.45 (s, 2H, NCH₂), 4.72, 4.85 (2 bt, 2H, *J* = 8.0 Hz), 5.75 (AB, 2H, *J* = 14.8 Hz, CH₂Ph), 7.20, 7.32 (2m, 5H, ArH); MS (FAB, thioglycerol matrix) *m*/*z* 379 (MH⁺). Anal. (C₂₁H₂₆N₆O) C, H, N.

(6a*R*,9a*S*)-2-[(*N*,*N*-Dimethylamino)methyl]-5,6a,7,8,9, 9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (42). Compound 41 was reduced with NH₄-HCO₂/Pd(OH)₂, using the general procedure described for 8, to give 42: ¹H NMR (300 MHz, CDCl₃) δ 1.50–2.00 (m, 5H), 2.25 (m, 2H), 2.35 (s, 6H, N(CH₃)₂), 3.40 (s, 3H, NCH₃), 3.65 (s, 2H, NCH₂), 4.75, 4.85 (2 bt, 2H, J = 8.0 Hz); MS (FAB, thioglycerol matrix) m/z 289 (MH⁺). Anal. (C₁₄H₂₀N₆O) C, H, N.

(6aR,9aS)-2-(1-Pyrrolidinylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-b]purin-4(3H)-one (43). To a solution of 36 (290 mg, 0.83 mmol) and pyrrolidine (168 mg, 2.37 mmol) in methanol was added acetic acid until pH 6-7. To the resulting red solution was added NaBH₃CN (68 mg, 1.08 mmol), and the yellow solution stirred at room temperature for 16 h. Methanol was evaporated, the residue was treated with CH₂Cl₂ and 1 N aqueous KOH, and the layers were separated. The combined aqueous solution was extracted with CH2Cl2, and the combined organic solution was dried (MgSO₄), filtered, and concentrated. The crude product was purified by flash column chromatography (3-7% MeOH/CH₂Cl₂) to give 43 (160 mg, 48%): ¹H NMR (CDCl₃) δ 1.52 (m, 1H), 1.65–1.8 (m, 7H), 1.85 (m, 1H, CH), 2.18 (dd, 1H, J = 13.2, 6.0 Hz, CH), 2.47 (bs, 4H, 2NCH₂), 3.30 (s, 3H, NCH₃), 3.60 (s, 2H, CH₂N), 4.67 (t, 1H, J = 7.3 Hz, CH), 4.80 (t, 1H, J = 7.6 Hz, CH), 5.68 (AB, 2H, J = 15 Hz, PhCH₂), 7.17 (d, 2H, J = 6.7 Hz, ArH), 7.29 (m, 3H, ArH); HRMS ($C_{23}H_{29}N_6O$) calcd 405.2403 (MH⁺), found 405.2415. Anal. (C23H28N6O) C, H, N.

(6a*R*,9a*S*)-2-(1-Pyrrolidinylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-

one (44). A solution of 43 (150 mg, 0.37 mmol) in methanol was added to a suspension of ammonium formate and Pd- $(OH)_2/C$ in methanol at room temperature. The mixture was heated at reflux for 15 h. The reaction mixture was poured into 10% MeOH/CH₂Cl₂ (500 mL), stirred at reflux for 10 min, filtered, and concentrated. The residue was dissolved in CH2-Cl₂ (200 mL) and washed with aqueous NaHCO₃. The aqueous solution was extracted with CH_2Cl_2 (3 \times 100 mL). The combined CH₂Cl₂ layers were dried (MgSO₄), filtered, and concentrated. Crude product was purified by flash chromatography (3-20% MeOH/CH₂Cl₂, then 10% MeOH (saturated with NH₃)/CH₂Cl₂) to give **44** (40 mg, 26%): ¹H NMR (CDCl₃) δ 1.51 (m, 1H), 1.60–1.80 (m, 7H), 1.81–1.95 (m, 1H), 2.18 (dd, 1H, J = 13.0, 6.0 Hz, CH), 2.58 (s, br, 4H, 2NCH₂), 3.29 (s, 3H, NCH₃), 3.75 (s, 2H, CH₂N), 4.65 (t, 1H, J = 7.2 Hz, CH), 4.79 (t, 1H, J = 7.5 Hz, CH); HRMS (C₁₆H₂₃N₆O) calcd 315.1933 (MH⁺), found 315.1926. Anal. (C₁₆H₂₂N₆O) C, H, Ν

(6a*R*,9a.5)-5,6a,7,8,9,9a-Hexahydro-2-(1*H*-imidazol-2-ylmethyl)-5-methyl-3-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (46). A mixture of 2-imidazolecarboxaldehyde (2.0 g, 21 mmol), TsCl (4.8 g, 25 mmol), and Et₃N (4.3 mL, 31 mmol) was refluxed in 1,2-dichloroethane (100 mL) for 24 h. The mixture was washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. Flash chromatography (20% EtOAc/hexanes, then 30% EtOAc/hexanes) gave **48** (4.7 g, 90%) as a pink solid: ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H), 7.31 (s, 1H), 7.37 (d, 2H, J = 8 Hz), 7.84 (s, 1H), 8.00 (d, 1H, J = 8 Hz), 9.78 (s, 1H); MS (CI) m/z 251 (MH⁺, 87), 155 (100). Anal. (C₁₁H₁₀N₂O₃S) C, H, N.

A solution of *n*-BuLi in hexanes (1.6 M, 2.3 mL, 3.7 mmol) was added to a solution of *i*-Pr₂NH (0.63 mL, 4.5 mmol) in dry THF (100 mL) at 0 °C under N₂ and stirred for 15 min. The solution was cooled to -78 °C, and a mixture of **35** (0.80 g, 2.5 mmol) in dry THF (40 mL) was added. The reaction mixture was stirred at -78 °C for 40 min. The color turned orange-red. A solution of the imidazole reagent **48** (0.94 g, 3.7 mmol) in dry THF (10 mL) was added at -78 °C, and the reaction mixture was stirred for 40 min. The reaction was quenched with saturated NH₄Cl and extracted with CH₂Cl₂. The organic extract was dried (MgSO₄), filtered, and concentrated. Flash chromatography (3% MeOH/CH₂Cl₂, then 5% MeOH/CH₂Cl₂) gave 0.86 g (60%) of **45** as a yellow solid: MS (CI) m/z 572 (MH⁺, 100).

MsCl (0.17 mL, 2.2 mmol) was added to a solution of **45** (0.64 g, 1.1 mmol) and Et_3N (0.47 mL, 3.3 mmol) in CH_2Cl_2 (20 mL) at room temperature under N_2 and stirred for 1 h. The solution was diluted with CH_2Cl_2 , washed with saturated NaHCO₃, dried (MgSO₄), and concentrated to give 0.67 g of crude product as a green solid.

A solution of LiBHEt₃ in THF (1.0 M, 3.4 mL, 3.3 mmol) was added to a solution of the above crude product (0.67 g) in dry THF (20 mL) at 0 °C under N₂ and stirred for 10 min. The reaction mixture turned red. The reaction was quenched with aqueous HCl (3%) and stirred at room temperature for 1 h. The mixture was basified with saturated NaHCO₃ and extracted with CH₂Cl₂. The organic extracts were dried (MgSO₄) and concentrated. Flash chromatography (3% MeOH/CH₂Cl₂, then 5% MeOH/CH₂Cl₂, then 7% MeOH/CH₂Cl₂) gave **46** (0.157 g, 35%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 1.45–2.14 (m, 6H), 3.27 (s, 3H), 4.22 (s, 2H), 4.69 (t, 1H, J = 7.5 Hz), 4.72 (t, 1H, J = 7.2 Hz), 5.25 (d, 1H, J = 15.5 Hz), 5.63 (d, 1H, J = 15.2 Hz), 7.00 (s, 2H), 7.20–7.33 (m, 5H); MS (EI) m/z 401 (M⁺, 25), 372 (36). Anal. (C₂₂H₂₃N₇O·0.20CH₂-Cl₂·0.90CH₃OH) C, H, N.

(6a*R*,9a.5)-5,6a,7,8,9,9a-Hexahydro-2-(1*H*-imidazol-2-ylmethyl)-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (47). To a stirred suspension of 20% Pd(OH)₂/C (0.16 g) in methanol (30 mL) was added ammonium formate (0.46 g, 7.3 mmol) followed by a solution of 46 (100 mg, 0.25 mmol) in methanol. The mixture was stirred at reflux for 20 h. The reaction mixture was diluted with CH₂Cl₂ (200 mL) and filtered. The solids were washed with 10% MeOH/CH₂Cl₂. The combined filtrate and washings were concentrated to give 47 as a yellow solid (78 mg, 100%): ¹H NMR (400 MHz, CD₃OD) δ 1.50–2.29 (m, 6H), 3.31 (s, 3H), 4.20 (s, *ca.* 1H), 4.72 (t, 1H, J = 7.2 Hz), 4.95 (t, 1H, J = 7.4 Hz), 6.97 (s, 2H); MS (EI) m/z 311 (M⁺, 27), 282 (100). Anal. (C₁₅H₁₇N₇O·2.35H₂CO₃) C, H, N.

(6aR.9aS)-5.6a.7.8.9.9a-Hexahvdro-5-methyl-2-iodo-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one (49). A solution of N,N-diisopropylamine (1.54 g, 11.4 mmol) in THF (15 mL) was cooled to 0 °C and treated with *n*-BuLi in hexanes (4.6 mL, 2.5 M, 11.4 mmol) for 0.5 h. The reaction mixture was then cooled to -78 °C, and a solution of 35 (3.05 g, 9.5 mmol) in THF (50 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 0.5 h to give a dark orange solution. To the reaction mixture was added a precooled solution of 1-chloro-2-iodoethane (2.7 g, 14 mmol) in THF (3 mL). The resulting yellow mixture was stirred at -78 °C for 2 h, quenched with aqueous ammonium chloride, and filtered. The precipitate was washed with H₂O and ether to give 49 (2.15 g, 51%) as an off-white solid. Ether and THF were evaporated from the filtrate. The resulting aqueous solution was extracted with 10% MeOH/CH₂Cl₂. The organic solution was dried (MgSO₄), filtered, and concentrated to give a yellow solid which was washed with ether and cold CH₃CN to give additional 49 (0.66 g, 16%): ¹H NMR (CDCl₃) δ 1.55 (m, 1H), 1.7-1.9 (m, 3H), 1.95 (dd, 1H), 2.21 (dd, 1H), 3.35 (s, 3H, NCH₃), 4.7 (t, 1H), 4.8 (t, 1H), 5.5 (s, 2H, PhCH₂), 7.35 (m, 5H, ArH); MS (EI) m/z 447 (M⁺), 418, 292, 91 (100).

(6aR,9aS)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(phenylethynyl)-3-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one (50). To a suspension of 49 (1.3 g, 2.9 mmol) in pyridine (5 mL) was added copper phenylacetylide (0.58 g, 3.5 mmol). The mixture was heated to 120 °C for 1 h. The cooled reaction mixture was partitioned with H₂O and EtOAc. The organic layer was separated and purified by silica gel flash chromatography (5% MeOH/CH₂Cl₂). The highly UV active fractions were concentrated to dryness, dissolved in EtOAc, and treated with Chelex 100 to remove any residual Cu. After stirring for several hours, the solution was filtered and concentrated to give 50 as a yellow solid: mp 193-194 °C; $[\alpha]^{25}_{D}$ +188° (c 0.12, EtOH); ¹H NMR (CDCl₃) δ 1.58 (m, 1H, CH2), 1.72-2.10 (m, 4H, CH2), 2.30 (dd, 1H, CH2), 3.45 (s, 3H, NCH₃), 4.77 (t, J = 7 Hz, 1H, CHN), 4.9 (t, J = 7 Hz, 1H, CHN), 5.62 (s, 2H, NCH₂Ar), 7.30-7.48 (m, 6H, ArH), 7.52 (d, 2H, ArH), 7.58 (d, 2H, ArH); MS (CI) *m*/*z* 422 (MH⁺). Anal. (C₂₆H₂₃N₅O·0.33 H₂O) C, H, N.

(6a *R*, 9a *S*) - 5, 6a, 7, 8, 9, 9a - Hexahydro - 5 - methyl - 2bromocyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (51). Compound 35 was debenzylated using the general methods described for 8. Bromine (0.91 mL, 17.5 mmol) was added to a solution containing desbenzyl-35 (3.38 g, 14.6 mmol) and NaOAc (1.44 g, 17.5 mmol) in HOAc (70 mL) at room temperature under nitrogen. The mixture was then stirred at 50 °C for 16 h. The solid was collected, washed with CHCl₃, and air-dried to give 51 as a white solid (3.75 g, 83%): $[\alpha]^{19.8}$ D +100.6° (*c* 0.63, MeOH); ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.68–2.24 (m, 6H), 3.32 (s, 3H), 4.81 (t, 1H, *J* = 7 Hz), 5.19 (t, 1H, *J* = 7 Hz), 10.18 (bs, 1H); MS (CI) *m*/*z* 312 (MH⁺, 25), 310 (27), 232 (100). Anal. (C₁₁H₁₂BrN₅O·1.02HBr) C, H, N.

(6aR,9aS)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(phenylethynyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)one (52). A mixture of the bromide 51 (178 mg, 0.574 mmol), (phenylethynyl)tributyltin (0.30 mL, 0.86 mmol), Pd(PPh₃)₄ (66 mg, 0.057 mmol), and PPh₃ (30 mg, 0.11 mmol) was heated in *N*-methylpyrrolidinone (5 mL) at 100 °C under N₂ for 5 h. The solvent was evaporated under reduced pressure. The residue was dissolved in 10% MeOH/CH2Cl2, washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. Preparative TLC $(5\% \text{ MeOH/CH}_2\text{Cl}_2)$ gave 52 (61 mg, 32%) as a light yellow solid: $[\alpha]^{24.5}_{D}$ +167° (c 0.56, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.62–2.51 (m, 6H), 3.54 (s, 3H), 4.92 (t, 1H, J = 7.3Hz), 5.13 (t, 1H, J = 7.4 Hz), 7.28-7.38 (m, 3H), 7.53 (d, 2H, J = 8.2 Hz); MS (CI) m/z 332 (MH⁺, 100); HRMS calcd for C19H17N5O 331.1433, found 331.1440. Anal. (C19H17N5O. 0.75H₂O) C, H; N: calcd, 20.31; found, 18.36.

3,5-Dimethyl-2'-(phenylmethyl)spiro[cyclopentane-1,7'-(8'H)-[3H]imidazo[2,1-b]purin]-4'(5'H)-one (53). 5'-Methyl-3'-(phenylmethyl)spiro[cyclopentane-1,7'(8'H)-[3H]imidazo-[2,1-b]purin]-4(5'H)-one was prepared according to the general reaction conditions of Scheme 1 (¹H NMR (400 MHz, CDCl₃) δ 1.65–2.04 (m, 8H), 3.44 (s, 3H), 3.98 (s, 2H), 7.69 (s, 1H)). This was directly brominated (conditions identical to preparation of 51) to give 5'-methyl-2'-bromospiro[cyclopentane-1,7'-(8'H)-[3H]imidazo[2,1-b]purin]-4(5'H)-one (1H NMR (400 MHz, CD₃OD) δ 1.78–2.18 (m, 8H), 3.48 (s, 3H), 4.41 (s, 2H); MS (CI) m/z 246 (100), 324 (81), 326 (73); Anal. (C₁₂H₁₄BrN₅O· HBr) C, H; N: calcd, 17.29; found: 16.03.). NaH (0.6 g, 15 mmol) was added to a solution of the brominated compound (1.23 g 3.78 mmol) and dimethyl sulfate (1.8 mL, 19 mmol) in DMF (50 mL) at room temperature and stirred under nitrogen for 3 h. The mixture was poured into cold saturated NaHCO₃ solution (300 mL). After several hours, the solids were filtered, washed with H₂O and ether, and air-dried to give 5'-methyl-2'-bromo-3'-methylspiro[cyclopentane-1,7'(8'H)-[3H]imidazo-[2,1-b]purin]-4(5'H)-one as a white solid (0.578 g, 45%): ¹H NMR (400 MHz, CDCl₃) & 1.63-2.03 (m, 8H), 3.38 (s, 3H), 3.87 (s, 2H), 3.91 (s, 3H); MS (CI) m/z 338 (100), 340 (92). Anal. $(C_{13}H_{16}BrN_5O \cdot 0.15Et_2O)$ C, H, N.

To a suspension of zinc dust (2.3 g) in dry THF (13 mL) at room temperature under nitrogen was added 1,2-dibromoethane (0.11 mL). The mixture was then stirred at 65 °C for 1 min. To this mixture at 0 °C was added dropwise a solution of benzyl bromide (3.5 mL). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. A portion of the cloudy supernatant (1.1 mL, ca. 2.4 mmol) was heated with the product of the previous reaction (0.162 g, 0.477 mmol), Pd-(PPh₃)₄ (0.056 g, 0.048 mmol), and PPh₃ (0.025 g, 0.095 mmol) in THF (2 mL) in a sealed tube at 120 °C under argon for 20 h. The solvent was evaporated. The residue was dissolved in CH₂Cl₂/MeOH (9:1), washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. The residue was separated by flash chromatography (2% MeOH/CHCl₃, then 3% MeOH/ CHCl₃) to give 53 as a yellow solid (0.061 g, 37%): ¹H NMR (400 MHz, CDCl₃) δ 1.58–1.96 (m, 8H), 3.33 (s, 3H), 3.72 (s, 3H), 3.88 (s, 2H), 4.09 (s, 2H), 7.14 (d, 2H, J = 8.2 Hz), 7.21-7.32 (m, 3H); MS (CI) m/z 350 (MH+, 100). Anal. (C₂₀H₂₃N₅O· 0.4CH₂Cl₂) C, H; N: calcd, 18.27; found, 17.41.

(6a*R*,9a*S*)-3-(Cyclohexylmethyl)-5,6a,7,8,9,9a-hexahydro-5-methyl-2-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (54). A mixture of 28 (179 mg, 0.558 mmol), cyclohexylmethyl bromide (0.39 mL, 2.8 mmol), and K₂CO₃ (0.77 g, 5.6 mmol) was heated in DMF (5 mL) at 60 °C under N₂ for 20 h. The DMF was evaporated. The residue was dissolved in CH₂Cl₂, washed with saturated NaHCO₃ solution, dried (MgSO₄), and concentrated. Flash chromatography (2% MeOH/CH₂Cl₂) gave 0.12 g (51%) of 54 as an off white solid: $[\alpha]^{23}_{D}$ +94° (*c* 0.62, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 0.90–2.30 (m, 17H), 3.34 (s, 3H), 3.91 (d, 2H, J = 7.4 Hz), 4.13 (s, 2H), 4.72 (t, 1H, J = 7.2 Hz), 4.86 (t, 1H, J = 7.2 Hz), 7.15 (d, 2H, J = 6.9 Hz), 7.21–7.33 (m, 3H); MS (EI) *m/z* 417 (M⁺, 62), 388 (100). Anal. (C₂₅H₃₁N₅O·0.39CH₂Cl₂) C, H, N.

(6a*R*,9a.5)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(phenyl-methyl)-3-(2-hydroxyethyl)cyclopent[4,5]imidazo[2,1-*b*]-purin-4(3*H*)-one (55): using the general procedure described above for 54 gave 55 as an off-white solid; ¹H NMR (400 MHz, CDCl₃) δ 1.52–2.35 (m, 6H), 3.10 (bs, 1H), 3.45 (s, 3H), 3.65–3.76 (m, 2H), 4.23 (s, 2H), 4.25–4.32 (m, 2H), 4.77 (t, 1H, *J* = 7 Hz), 4.96 (t, 1H, *J* = 7 Hz), 7.19 (d, 2H, *J* = 7.0 Hz), 7.21–7.33 (m, 3H); MS (FAB) *m*/*z* 366 (MH⁺). Anal. (C₂₀H₂₃N₅O₂·0.31CH₂Cl₂) C, H, N.

(6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(phenylmethyl)-3-[(2,3-dihydroxyphenyl)methyl]cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (56). Compound 28 was alkylated as above with 2,3-dimethoxybenzyl bromide to give (6a*R*,9a*S*)-5,6a,7,8,9,9a-hexahydro-5-methyl-2-(phenylmethyl)-3-[(2,3-dimethoxyphenyl)methyl]cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 1.52–2.31 (m, 6H), 3.32 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.04 (s, 2H), 4.73 (t, 1H, *J* = 7 Hz), 4.87 (t, 1H, *J* = 7.2 Hz), 5.40 (d, 1H, *J* = 15 Hz), 5.47 (d, 1H, *J* = 15 Hz), 6.41 (dd, 1H, *J* = 7.7, 1.2 Hz), 6.83 (dd, 1H, *J* = 8, 1.2 Hz), 6.94 (t, 1H, *J* = 8 Hz), 7.14 (d, 2H, *J* = 7 Hz), 7.18–7.28 (m, 3H); MS (FAB) m/z 472 (MH⁺, 100). A solution of BBr₃ in CH₂Cl₂ (3.5 mL, 1.0 M) was added to a solution of the product of the previous reaction (0.330 g, 0.7 mmol) in CH₂Cl₂ (10 mL) at -78 °C. The solution was stirred and allowed to warm up from -78 °C to room temperature over 18 h. The solution was then stirred with aqueous Na₂-CO₃ (10%) for 10 min. The organic layer was separated, dried (MgSO₄), and concentrated. Flash chromatography on silica gel (5% MeOH/EtOAc) gave 0.090 g (30%) of **56** as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 1.45–2.30 (m, 6H), 3.35 (s, 3H), 4.32 (s, 2H), 4.73 (t, 1H, J = 7 Hz), 4.90 (t, 1H, J = 7.2Hz), 5.24 (d, 1H, J = 14.7 Hz), 5.32 (d, 1H, J = 15.3 Hz), 6.59 (dd, 1H, J = 4.7, 2.1 Hz), 6.72 (t, 1H, J = 7.3 Hz), 6.87 (d, 1H, J = 7.3 Hz), 7.21 (d, 2H, J = 7.0 Hz), 7.24–7.33 (m, 3H); MS (FAB) m/z 444 (MH⁺). Anal. (C₂₅H₂₅N₅O₃·H₂O) C, H, N.

(6a*R*,9a.5)-5,6a,7,8,9,9a-Hexahydro-5-methyl-2-(phenylmethyl)-3-(3-pyridinylmethyl)cyclopent[4,5]imidazo[2,1*b*]purin-4(3*H*)-one (57). Compound **28** was alkylated by 3-(chloromethyl)pyridine, using the conditions previously described for **54**, to give **57** as an orange solid: $[\alpha]^{20}_{\rm D} + 105^{\circ}$ (*c* 0.23, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 1.52–2.30 (m, 6H), 3.32 (s, 3H), 4.07 (s, 2H), 4.72 (t, 1H, *J* = 7.0 Hz), 4.87 (t, 1H, *J* = 7.2 Hz), 5.35 (s, 2H), 7.10 (d, 2H, *J* = 6.6 Hz), 7.16–7.30 (m, 4H), 7.38 (dd, 1H, *J* = 7.9, 1.6 Hz), 8.34 (d, 1H, *J* = 1.8 Hz), 8.45 (dd, 1H, *J* = 4.8, 1.4 Hz); MS (CI) *m*/*z* 413 (MH⁺, 100). Anal. (C₂₄H₂₄N₆O-0.9H₂O) C, H; N: calcd, 19.60; found, 18.73.

(6a,R,9a,S)-5,6a,7,8,9,9a-Hexahydro-3(1*H*-imidazol-2-ylmethyl)-5-methyl-2-(phenylmethyl)cyclopent[4,5]imidazo-[2,1-*b*]purin-4(3*H*)-one (58). TFA (14 mL) was added to a solution of 48 (4.37 g, 17.5 mmol) and Et₃SiH (14 mL, 88 mmol) in CH₂Cl₂ (200 mL) at 0 °C. The solution was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. The solution was washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. Flash chromatography on silica gel (40% EtOAc/ hexanes, then 60% EtOAc/hexanes) gave 1-(tolylsulfonyl)-2-(hydroxymethyl)imidazole (3.29 g, 74%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H), 2.97 (bs, 1H), 4.86 (s, 2H), 7.00 (s, 1H), 7.37 (d, 2H, J = 8 Hz), 7.40 (s, 1H), 7.83 (d, 1H, J = 8 Hz); MS m/z (CI) 253 (MH⁺, 80), 235 (100).

A solution of PPh₃ (6.14 g, 23.4 mmol) in CH₂Cl₂ (40 mL) was added to a solution of 1-(tolylsulfonyl)-2-(hydroxymethyl)imidazole (4.92 g, 19.5 mmol) and CBr₄ (9.70 g, 29 mmol) in CH₂Cl₂ (200 mL) at 0 °C. The solution was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. The solution was concentrated. Flash chromatography on silica gel (20% EtOAc/hexanes, then 30% EtOAc/hexanes) gave 1-(tolylsulfonyl)-2-(bromomethyl)imidazole (2.89 g, 47%) as a clear oil: ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H), 4.81 (s, 2H), 7.04 (s, 1H), 7.37 (d, 2H, J = 8 Hz), 7.42 (s, 1H), 7.91 (d, 1H, J = 8 Hz); MS (CI) m/z 315 (MH⁺, 97), 317 (100).

Compound **28** was alkylated with 1-(tolylsulfonyl)-2-(bromomethyl)imidazole using the conditions described above to give (6aR, 9a.S)-5, 6a, 7, 8, 9, 9a-hexahydro-5-methyl-2-(phenylmethyl)-3-[[1-(tolylsulfonyl)imidazol-2-yl]methyl]cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one as a light yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 1.52–2.38 (m, 6H), 2.46 (s, 3H), 3.34 (s, 3H), 4.08 (s, 2H), 4.77 (t, 1H, J = 7 Hz), 4.95 (t, 1H, J = 7 Hz), 5.72 (s, 2H), 6.82 (s, 2H), 7.10 (d, 2H, J = 7 Hz), 7.18–7.32 (m, 4H), 7.39 (d, 2H, J = 8 Hz), 7.88 (d, 2H, J = 8 Hz); MS (FAB) m/z 556 (MH⁺, 100).

The tosylimidazole product of the previous reaction (0.38 g) was stirred with excess of KOH in MeOH (15 mL) at room temperature for 3 h. The solution was neutralized with dilute HCl and extracted with CH₂Cl₂. The organic layer was washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. Flash chromatography on silica gel (7% MeOH/CH₂Cl₂) gave **58** (0.24 g, 89%) as a light yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 1.48–2.28 (m, 6H), 3.48 (s, 3H), 4.40 (s, 2H), 4.76 (t, 1H, J = 7.6 Hz), 4.91 (t, 1H, J = 7.2 Hz), 5.28 (s, 2H), 7.02 (s, 2H), 7.25–7.35 (m, 5H); MS (FAB) m/z 402 (MH⁺, 78), 154 (100). Anal. (C₂₂H₂₃N₇O•0.6H₂O) C, H; N: calcd, 23.78; found, 22.45.

2-Cyanoglycine Ethyl Ester (59). $Na_2S_2O_4$ (15 g, 0.088 mol) was added portionwise to a solution of ethyl cyano-(hydroxyimino)acetate (12.45 g, 0.0877 mol) in saturated NaHCO₃ (80 mL) and H₂O (320 mL) and stirred at room

temperature for 1 h. More Na₂S₂O₄ (15 g) was added every 2 h until the reaction was shown to be complete by TLC (*ca.* 6 h). The solution was extracted with CH₂Cl₂. The organic extracts were dried (MgSO₄) and concentrated to give **59** (7.0 g, 62%) as an oil: ¹H NMR (200 MHz, CDCl₃) δ 1.36 (t, 3H, *J* = 7 Hz), 2.80–3.10 (bs, 2H), 4.35 (q, 2H, *J* = 7 Hz), 4.55 (s, 1H).

2-Cyano-*N***-(1-ethoxyethylidene)glycine Ethyl Ester** (60). The crude 59 (7.44 g, 0.0581 mol) was heated with triethyl orthoacetate (100 mL) at 100 °C for 16 h. The solution was concentrated. Flash chromatography on silica gel (20% EtOAc/hexanes) gave 60 (8.16 g, 71%) as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 1.19 (t, 3H, J = 7 Hz), 1.27 (t, 3H, J = 7 Hz), 1.92 (s, 3H), 4.07 (q, 2H, J = 7 Hz), 4.23 (q, 2H, J = 7 Hz), 4.82 (s, 1H).

Ethyl 5-Amino-2-methyl-1-(phenylmethyl)-1*H*-imidazole-4-carboxylate (61). Compound 60 (16 g, 0.081 mol) was heated with benzylamine (13.8 mL) in EtOH (200 mL) at 80 °C for 2 h. The solution was concentrated. The residue was dissolved in CH₂Cl₂, washed with saturated NaHCO₃ solution, dried (MgSO₄), and concentrated. Recrystallization from benzene gave 61 (11 g, 52%) as a solid: ¹H NMR (300 MHz, CDCl₃) δ 1.38 (t, 3H, J = 7 Hz), 2.34 (s, 3H), 4.34 (q, 2H, J =7 Hz), 4.69 (bs, 2H), 4.97 (s, 2H), 7.07 (d, 2H, J = 6 Hz), 7.26– 7.41 (m, 3H).

3,9-Dihydro-1,8-dimethyl-9-(phenylmethyl)purine-2,6-(**1***H***)dione (62).** The imidazole intermediate **61** (0.62 g, 2.4 mmol) was heated with methyl isocyanate (0.7 mL, 12 mmol) and Et₃N (1.7 mL, 12 mmol) in benzene (5 mL) at 100 °C for 18 h. The solution was concentrated. The residue was heated with NaOMe (0.65 g, 12 mmol) in refluxing MeOH for 1 h. The solution was concentrated. The residue was triturated with water, extracted with CH₂Cl₂, and adjusted to pH 6 with 10% HCl. The solids were filtered, washed with water and ether, and dried to give **62** (0.47 g, 73%) as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.22 (s, 3H), 3.20 (s, 3H), 5.32 (s, 2H), 7.10 (d, 2H, J = 7 Hz), 7.30–7.42 (m, 3H), 12.32 (s, 1H).

2-Chloro-1,9-dihydro-1,8-dimethyl-9-(phenylmethyl)purin-6(6*H***)-one (63**). Intermediate **62** (0.47 g, 1.7 mmol) was heated with POCl₃ (10 mL) at 100 °C for 25 h. The solution was cooled and diluted with hexanes (200 mL). The liquid layer was decanted. The residue was dissolved in CH₂-Cl₂, washed with saturated NaHCO₃ solution, dried (MgSO₄), and concentrated. Flash chromatography of the residue on silica gel (1% MeOH/CH₂Cl₂, then 2.5% MeOH/CH₂Cl₂) gave **63** (0.263 g, 54%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 2.42 (s, 3H), 3.78 (s, 3H), 5.27 (s, 2H), 7.10–7.36 (m, 5H).

1,9-Dihydro-2-[(1*R***,2***R***)-2-hydroxycyclopentyl)amino]-1,8-dimethyl-9-(phenylmethyl)purin-6(6***H*)-one (**64**). The intermediate **63** (0.263 g, 0.912 mmol) was heated at 130 °C with (1*R*,2*R*)-2-aminocyclopentanol hydrochloride (0.251 g, 1.8 mmol) and Et₃N (0.63 mL, 4.5 mmol) in NMP (20 mL) under N₂ for 16 h. The solution was concentrated. The residue was dissolved in CH₂Cl₂, washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. Flash chromatography of the residue on silica gel (6% MeOH/CH₂Cl₂) gave **64** (0.310 g, 96%) as a brown solid: ¹H NMR (300 MHz, CDCl₃) δ 1.45–2.45 (m, 6H), 2.36 (s, 3H), 3.48 (s, 3H), 3.95–4.05 (m, 1H), 4.22 (dd, 1H, J = 14, 7 Hz), 4.10–4.60 (bs, 1H), 5.14 (s, 2H), 5.71 (d, 1H, J = 4.7 Hz), 7.14 (d, 2H, J = 7 Hz), 7.25–7.35 (m, 3H).

(6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-2,5-dimethyl-1-(phenylmethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(1*H*)one (65). MsCl (0.135 mL, 1.76 mmol) was added dropwise to a solution of **64** (0.310 g, 0.878 mmol) and Et₃N (0.61 mL, 4.4 mmol) in CH₂Cl₂ (10 mL) at room temperature. The solution was stirred at room temperature for 16 h, diluted with CH₂Cl₂, washed with saturated NaHCO₃ solution, dried (Mg-SO₄), and concentrated. Flash chromatography of the residue on silica gel (6% MeOH/CH₂Cl₂) gave **65** (0.169 g, 57%) as a clear oil which solidified to an off-white solid: $[\alpha]^{23}_{D} + 137^{\circ}$ (*c* 0.05, EtOH); ¹H NMR (300 MHz, CDCl₃) δ 1.55–2.10 (m, 6H), 2.36 (s, 3H), 3.41 (s, 3H), 4.49 (t, 1H, *J* = 7.1 Hz), 4.65 (t, 1H, *J* = 6.8 Hz), 5.21 (d, 1H, *J* = 17.6 Hz), 5.30 (d, 1H, *J* = 17.7 Hz), 6.94 (d, 2H, *J* = 7.3 Hz), 7.32–7.43 (m, 3H); MS (FAB) *m*/*z* 336 (MH⁺, 100). Anal. (C₁₉H₂₁N₅O·0.50CH₂Cl₂) C, H, N. (6a*R*,9a*S*)-5-Ethyl-5,6a,7,8,9,9a-hexahydro-2-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one (66). This compound was prepared using a procedure analogous to that for 65 followed by hydrogenolysis of the N-1 benzyl group under the general conditions described above to give white crystals: mp 101–103 °C; $[\alpha]^{22}_{D}$ +133° (*c* 0.44, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.27 (t, 3H, *J* = 7.0 Hz), 1.45–2.28 (m, 6H), 2.51 (s, 3H), 4.02 (q, 2H, *J* = 7.0 Hz), 4.73 (t, 1H, *J* = 7.6 Hz), 4.83 (t, 1H, *J* = 7.2 Hz); MS (FAB) *m*/*z* 260 (MH⁺, 100). Anal (C₁₃H₁₇N₅O·0.2CH₂Cl₂) C, H, N.

(6a*R*,9a*S*)-5,6a,7,8,9,9a-Hexahydro-2-methyl-5-(1methylethyl)cyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)one (67). This compound was prepared using a procedure analogous to that for 65 followed by hydrogenolysis of the N-1 benzyl group under the general conditions described above to give a white solid: $[\alpha]^{22}_{\rm D}$ +124° (*c* 0.44, MeOH); ¹H NMR (300 MHz, CDCl₃) δ 1.45–2.28 (m, 6H), 1.54 (d, 6H, *J* = 7.0 Hz), 2.54 (s, 3H), 4.73 (t, 1H, *J* = 7.0 Hz), 4.83 (t, 1H, *J* = 6.6 Hz), 5.10 (septet, 1H, *J* = 6.9 Hz); MS (FAB) *m*/*z* 274 (MH⁺, 100). Anal. (C₁₄H₁₉N₅O·0.25H₂O) C, H, N.

α-**Ethoxybenene Ethanimine Hydrochloride (68).** An ice-cold solution of phenylacetonitrile (100 g, 0.85 mol) in EtOH (55 mL) was charged with anhydrous HCl (34.5 g, 0.97 mol). The reaction mixture was stored at 4 °C for 3 days. The solid mass was suspended in Et₂O, filtered, washed with Et₂O, and dried over P_2O_5 under vacuum. The imidate hydrochloride **68** (97 g, 57%) was used directly in the next step.

Ethyl 5-Amino-1,2-bis(phenylmethyl)-1*H*-imidazole-4carboxylate (69). A suspension of 68 (31.6 g, 0.16 mol) and ethyl aminocyanoacetate (22.5 g, 0.18 mol; prepared according to the literature procedure¹⁵) in CHCl₃ (700 mL) was refluxed under N₂ for 0.5 h. The suspension was filtered through Celite. To the filtrate was added benzylamine (20 g, 0.19 mol), and the reaction mixture was refluxed under N₂ for 16 h. The reaction mixture was refluxed under N₂ for 16 h. The reaction mixture was washed with 10% NaHCO₃ (2 × 200 mL), dried (MgSO₄), and concentrated. Purification by flash chromatography (4% MeOH/CH₂Cl₂) followed by crystallization from EtOAc/hexane gave imidazole **69** (21.6 g, 49%): ¹H NMR (CDCl₃) δ 1.40 (t, 3H, J = 7.1 Hz, CH₃), 4.04 (s, 2H, C*CH*₂Ph), 4.37 (q, 2H, J = 7.1 Hz, CO₂*CH*₂CH₃), 4.65 (s, 2H, NH₂), 4.75 (s, 2H, N*CH*₂Ph), 6.88 (m, 2H, ArH), 7.16–7.27 (m, 8H, ArH).

Ethyl 5-[[(Ethylamino)carbonyl]amino]-1,2-bis(phenylmethyl)-1*H*-imidazole-4-carboxylate (70). To a mixture of the amino ester **69** (3.0 g, 8.9 mmol) and Et₃N (1.4 mL, 10.0 mmol) in toluene (20 mL) was added ethyl isocyanate (1.4 mL, 18 mmol). The mixture was heated at 130 °C in a sealed tube under N₂ for 16 h and then allowed to cool. The reaction mixture was concentrated and the residue subjected to flash chromatography (3% MeOH/CH₂Cl₂) to give the urea **70** (1.47 g, 41%): ¹H NMR (CDCl₃) δ 1.09 (t, 3H, J= 7.3 Hz, CH_3CH_2N), 1.34 (t, 3H, J= 7.2 Hz, CO₂CH₂CH₃), 3.17 (m, 2H, CH₃CH₂N), 3.98 (s, 2H, CCH_2Ph), 4.30 (q, 2H, J= 7.2 Hz, CO₂CH₂CH₃), 4.97 (bs, 3H, NCH₂Ph + NH), 6.82 (m, 2H, ArH), 7.07 (m, 2H, ArH), 7.15–7.26 (m, 7H, ArH + NH).

1-Ethyl-3,9-dihydro-8,9-bis(phenylmethyl)-1*H***-purine-2,6-dione (71).** To a solution of NaOMe prepared from Na (0.10 g, 4.3 mmol) and MeOH (20 mL) was added urea **70** (0.91 g, 2.2 mmol). The reaction mixture was refluxed for 3.5 h and then evaporated to dryness. The residue was taken up in 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and evaporated to afford the xanthine **71** (0.79 g, 98%) as a white solid which was used directly in the next step: ¹H NMR (CDCl₃) δ 1.09 (t, 3H, J = 6.8 Hz, CH_3 -CH₂N), 3.89 (q, 2H, J = 6.8 Hz, CH_3 CH₂N), 4.20 (s, 2H, CCH₂-Ph), 5.35 (s, 2H, NCH₂Ph), 7.02 (m, 2H, ArH), 7.17 (m, 2H, ArH), 7.23–7.30 (m, 6H, ArH).

1-Ethyl-1,9-dihydro-2-[((1*R,2R*)-2-hydroxycyclopentyl)amino]-8-(phenylmethyl)purin-6(6*H*)-one (72). A suspension of xanthine 71 (0.896 g, 2.49 mmol) in POCl₃ (25 mL) was heated to 100 °C under N₂ for 18.5 h. The reaction mixture was allowed to cool, and the POCl₃ was removed by rotary evaporation at less than 40 °C. The resulting orange syrup was chilled in an ice bath, and saturated NaHCO₃ (50 mL) was added in portions with stirring. The whole was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography of the residue (CH₂Cl₂, then 0.5% MeOH/CH₂-Cl₂, then 5% MeOH/CH₂Cl₂) gave the chloropurine (0.522 g, 55%) as a yellow foam: ¹H NMR (CDCl₃) δ 1.39 (t, 3H, J = 7.1 Hz, CH₂CH₃), 4.04 (s, 2H, C*H*₂Ph), 4.41 (q, 2H, J = 7.1 Hz, *CH*₂CH₃), 5.04 (s, 2H, N*CH*₂Ph), 6.99 (m, 2H, ArH), 7.12 (m, 2H, ArH), 7.24–7.30 (m, 6H, ArH).

A mixture of the chloropurine (0.110 g, 0.29 mmol), (1R,2R)-2-aminocyclopentanol hydrochloride (59 mg, 0.43 mmol), and diisopropylethylamine (0.18 mL, 1.0 mmol) in NMP (0.4 mL) was heated at 110–120 $^\circ C$ in a sealed tube under $N_2.$ After 14 h the reaction mixture was allowed to cool and then diluted with H_2O (20 mL). The aqueous suspension was extracted with EtOAc (2×20 mL), and the combined organic extracts were washed with H_2O (5 \times 20 mL), dried (MgSO₄), filtered, and evaporated. Flash chromatography of the residue (linear gradient 1% MeOH/CH₂Cl₂ to 6% MeOH/CH₂Cl₂) gave the product 72 (91 mg, 79%) as an off-white solid: ¹H NMR (CDCl₃) δ 1.31 (t, 3H, J = 7.3 Hz, CH₂CH₃), 1.50 (dd, 1H, J =12.6, 8.2 Hz, cyclopentyl), 1.60-1.85 (m, 3H, cyclopentyl), 2.00 (m, 1H, cyclopentyl), 2.23 (m, 1H, cyclopentyl), 3.92-4.08 (m, 4H, CCH₂Ph, *CH*NH, *CH*OH), 4.11 (q, 2H, J = 7.4 Hz, *CH*₂-CH₃), 4.64 (bs, 1H, NH), 4.89 (d, 1H, J = 4.3 Hz, OH), 4.92 (s, 2H, NCH2Ph), 6.98 (m, 2H, ArH), 7.13 (m, 2H, ArH), 7.19-7.29 (m, 6H, ArH); MS (FAB) m/z 444.0 (MH⁺)

(6aR,9aS)-5-Ethyl-5,6a,7,8,9,9a-hexahydo-1,2-bis-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(1H)one (73). To a stirred suspension of alcohol 72 (169 mg, 0.38 mmol) and Et_3N (0.08 mL, 0.6 mmol) in ClCH₂CH₂Cl (5 mL) was added MsCl (65 mg, 0.57 mmol). The reaction mixture was refluxed for 3 h, then diluted with CH₂Cl₂ (10 mL), and washed with saturated NaHCO₃ (10 mL). The organic layer was dried (MgSO₄), filtered, and evaporated. Flash chromatography of the residue (2% MeOH/CH₂Cl₂, then 4% MeOH/ CH_2Cl_2) gave the tetracyclic guanine **73** (106 mg, 65%) as an off-white solid: ¹H NMR (CDCl₃) δ 1.26 (t, 3H, J = 7.6 Hz, CH₂CH₃), 1.49-1.79 (m, 5H, cyclopentyl), 1.80 (m, 1H, cyclopentyl), 4.00 (AB, 2H, J = 16.2 Hz, CCH₂Ph), 4.04 (m, 2H, CH_2CH_3 , 4.35 (dd, 1H, J = 6.7 Hz, NCHCH₂), 4.56 (dd, 1H, J = 6.7 Hz, NCHCH₂), 5.04 (AB, 2H, J = 17.7 Hz, NCH₂Ph), 6.80 (m, 2H, ArH), 7.15-7.36 (m, 8H, ArH); MS (FAB) m/z 426.2 (MH+).

(6aR,9aS)-5-Ethyl-5,6a,7,8,9,9a-hexahydro-2-(phenylmethyl)cyclopent[4,5]imidazo[2,1-b]purin-4(3H)-one (74). A mixture of the N-benzyl derivative 73 (87 mg, 0.20 mmol), HCO₂NH₄ (193 mg, 3.06 mmol), and 20% Pd(OH)₂/C (40 mg) in MeOH (15 mL) was refluxed for 0.5 h and then allowed to stir at room temperature overnight. The catalyst was removed by filtration through Celite, and the filter pad was washed with MeOH. The combined filtrate and washings were evaporated to dryness. The residue was taken up in EtOAc (20 mL) and washed with saturated NaHCO₃ (20 mL). The organic layer was dried (MgSO₄), filtered, and evaporated to give a foam which was crystallized from MeOH/Et₂O to give **74** (40 mg, 60%): $[\alpha]^{22}_{D}$ +129.3° (*c* 0.23, MeOH); ¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 7.0 Hz, CH₂CH₃), 1.53 (m, 1H, cyclopentyl), 1.97 (m, 1H, cyclopentyl), 2.25 (dd, 1H, J=13.2, 5.7 Hz, cyclopentyl), 7.22-7.34 (m, 5H, ArH), 1.70-1.87 (m, 3H, cyclopentyl), 4.02 (m, 2H, CH2CH3), 4.15 (s, 2H, CH2Ph), 4.73 (dd, 1H, J = 7.3 Hz, NCHCH₂), 4.87 (dd, 1H, J = 7.3 Hz, NCHCH₂); MS (FAB) m/z 336.0 (MH⁺). Anal. (C₁₉H₂₁N₅O· 0.5H₂O) C, H, N.

PDE Inhibition Assays. PDE assays were performed in a reaction medium containing 50 mM Tris-HCl (pH 7.5), 2 mM MgCl₂, 0.1 mg/mL BSA, and 1 μ M cGMP or cAMP, respectively. Assays were carried out for 30 min at 30 °C using the methods described by Thompson.¹⁶ Reaction mixture for assay of PDE1 activity also contained 1 mM CaCl₂ and 0.1 μ M calmodulin. The reaction mixture for assay of PDE2 contained 5 μ M cGMP. [³H]cGMP was used as the substrate in the assays for PDE1 and PDE5, while [³H]cAMP was used as the substrate for PDE2, PDE3, and PDE4. The concentration of compounds that produce 50% inhibition of enzyme activity (IC₅₀) was determined from the curve of percentage inhibition of enzyme activity *vs* log molar concentration of the compounds. All assays were carried out in duplicate, and reported values represent the mean of the two determinations. Measurements were reproducible on the average to $\pm 25\%$, except for the very weakest inhibitors where solubility limits were occasionally exceeded. PDE1, PDE2, PDE3, PDE4, and PDE5 utilized in the assays were purified from bovine aorta,6 recombinant bovine adrenal cortex,¹⁷ bovine heart,¹⁸ canine kidney,¹⁹ and bovine lung,²⁰ respectively. These preparations were free of substantial contaminating phosphodiesterase activities.

Antihypertensive Activity. PDE inhibitors were evaluated in the spontaneously hypertensive rat using the methodology previously described by Smith et al.21 and more recently by Vemulapalli et al.12 Reported values reflect peak changes in mean arterial pressure in comparison to a control group to which vehicle was administered. The compounds were adminstered orally as aqueous solutions or suspensions in 0.4% methylcellulose as the vehicle. In general differences of ≥ 10 mmHg are considered statistically significant. The drugs verapamil and nifedipine were routinely run as positive controls in this assay. Two hours after a 30 mg/kg oral dose of verapamil or nifedipine, reproducible falls in blood pressure of 70 \pm 4 and 58 \pm 5 mmHg (mean \pm SEM), respectively, were produced.

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JM9608467