DEC LSI-11 computer over 20-s intervals every 5 min, continuously for 24 h. Antihypertensive activity was calculated as the percent fall in blood pressure from predrug control value and is reported as the mean value acquired from six rats per dose; the maximum antihypertensive effect noted during the 0–6 h postdrug time period is an indication of drug potency, whereas the antihypertensive effect during the 6–18 h postdrug time period is an indication of duration of action of the drug (determined as the average of the maximum percent fall in blood pressure during the 6–12 and 12–18 h postdrug time periods). The antihypertensive effects for **12a**, amlodipine, and nifedipine were also evaluated as area-over-the-curve for the mean data points calculated from the peak effect (antihypertension) detected over 30-min intervals (six consecutive 5-min data intervals) and plotted against the corresponding dose levels, thereby generating a dose–response relationship (Figure 2).

Crystal Structure Analysis. Crystals of **29a** were obtained from isopropyl ether/hexane. Unit cell parameters were obtained through a least squares analysis of the experimental diffractometer settings of 25 high angle reflections using CuKα monochromatic radiation (λ = 1.5418 Å): a = 17.116 (2), b = 16.366 (2), c = 9.032 (1) Å, V = 2530.0 (9) Å^3. Space group $P2_12_12$ was assigned on the basis of systematic absences of Weissenberg films and confirmed by the full structure analysis. The crystal density, D_{obs} = 1.32 g cm^{-3} was measured by flotation in carbon tetrachloride/hexane mixtures (D_{calc} = 1.324 for Z = 4, $C_{26}H_{28}N_3O_4F_3$). A total of 2011 reflections were measured on an Enraf-Nonius CAD4 diffractometer at 23 °C with the θ–2θ variable scan technique and were corrected for Lorentz polarization factors. Background counts were collected at the extremes of the scan for half the time of the scan. Two standard reflections were monitored for decay; no decrease of intensity was observed during the course of the measurements. Calculations utilized the SDP program package with minor local modifications.[18] The structure was solved by direct methods and refined on the basis of 1499 "observed" reflections with $I \geq 3\sigma(I)$. Although some hydrogen positions were evident in difference maps, all hydrogens were introduced in idealized positions and their scattering was taken into account in the terminal stages of refinement. Least squares weights, $w = \sigma^{-2}(F_o)$ were calculated with the assumption that $\sigma^2 = \epsilon^2 + (\rho I)^2$ where ϵ is the statistical counting error and ρ = 0.04. The function minimized in the least squares refinements was $\sum_w(|F_o| - |F_c|)^2$. R is defined as $\sum||F_o| - |F_c||/\sum|F_o|$ while $R_w = [\sum_w(|F_o| - |F_c|)^2/\sum_w|F_o|^2]^{1/2}$. The refinements converged at R = 0.044, R_w = 0.051. The final difference map contained no significant features. Tables of atomic coordinates, thermal parameters, bond distances and angles are included as supplementary material. Relative to the known configuration of the R-(+)-α-methylbenzylamine used in the synthesis, the configuration at C4 is also R.

Acknowledgment. The authors with to thank Dr. Michael Porubcan and his associates for nuclear magnetic resonance spectra, Ms. Mary Young and Mr. Terrence McCormick and their associates for microanalytical data, Mr. Russell J. Brittain, Ms. Dianne Henry, and Ms. Diane McMullen for technical assistance in providing the in vitro biological data, and Mr. Thomas Schaffer and Ms. S. Clow for technical assistance in providing the in vivo SHR data.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances and bond angles, and perspective ORTEP drawing of **29a** (6 pages). Ordering information is given on any current masthead page.

(18) SDP, Structure Determination Package, A. Frenz & Associates, College Station, TX.

Conformationally Restrained, Chiral (Phenylisopropyl)amino-Substituted Pyrazolo[3,4-*d*]pyrimidines and Purines with Selectivity for Adenosine A_1 and A_2 Receptors

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Two modes of tethering a chiral (phenylisopropyl)amino substituent in pyrazolo[3,4-*d*]pyrimidines and purines have been explored. One mode gave (*S*)-2,7-dihydro-7-phenyl-2-(phenylmethyl)-5-propoxy-3*H*-imidazo[1,2-c]pyrazolo-[4,3-*e*]pyrimidine (**12a**) and its corresponding *R*-enantiomer **12b**, which were selective for A_2 and A_1 adenosine receptors, respectively. The corresponding diimidazo[1,2-*c*:4′,5′-*e*]pyrimidines **12e** and **12f** were analogously selective. This is the first example where a single chiral recognition unit provides enantiomers with opposite selectivities for adenosine receptors. The second mode gave (2*S*-*trans*)-2,7-dihydro-2-methyl-3,7-diphenyl-5-propoxy-3*H*-imidazo[1,2-c]-pyrazolo[4,3-*e*]pyrimidine (**12c**) and its corresponding *R*-enantiomer **12d**. Compounds **12c** and **12d** were significantly less potent than **12a** and **12b** at A_1 receptors, and were nonselective.

Chiral recognition units at the C^6-N position of adenosine play a role in the determination of A_1/A_2 selectivity for adenosine receptors. Thus, N^6-[(*R*)-1-methyl-2-phenylethyl]adenosine (*R*-PIA) is more potent and selective for A_1 receptors (A_1 K_i value of 1.15 nM; A_2 K_i value of 124 nM) than is N^6-[(*S*)-1-methyl-2-phenylethyl]-adenosine (*S*-PIA) (A_1 K_i value of 47.6 nM; A_2 K_i value of 1810 nM).[1] We felt that the affinity and the selectivity for an adenosine receptor ligand bearing a chiral phenylisopropyl substituent may be enhanced by approximating the preferred spatial orientation for the relatively flexible chiral recognition unit through conformational restraint.[2]

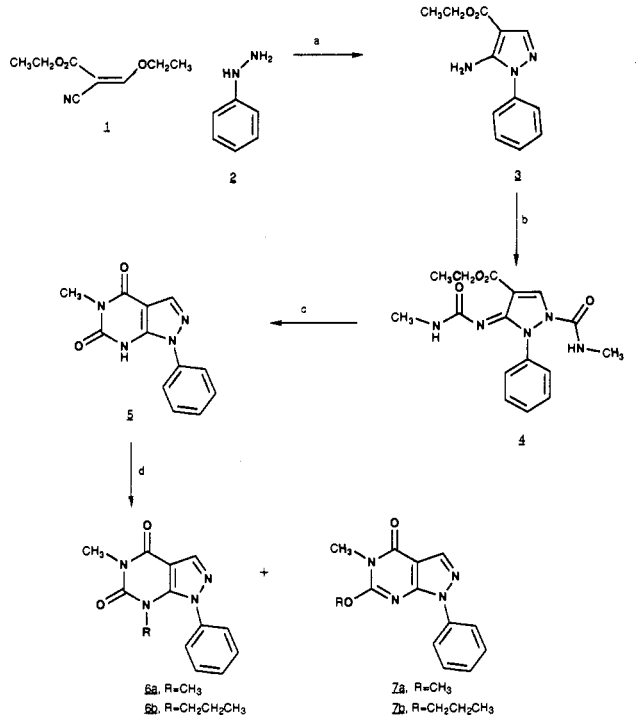
Two different ways of tethering the chiral (phenylisopropyl)amino side chain to the pyrimidine ring were proposed. Connection of the methyl carbon to N^1 as shown by tether A in the general structure would give a ben-

(1) Moos, W. H.; Szotek, D. S.; Bruns, R. F. N^6-Cycloalkyladenosines. Potent, A_1-Selective Adenosine Agonists. *J. Med. Chem.* **1985**, *28*, 1383–1384.

(2) Conformational restraint has been previously employed with R-PIA by a connection in the phenylisopropyl unit between the phenyl and methyl groups. See: (a) Daly, J. W.; Padgett, W.; Thompson, R. D.; Kusachi, S.; Bugni, W. J.; Olsson, R. A. Structure–Activity Relationships for N^6-Substituted Adenosines at a Brain A_1-Adenosine Receptor with a Comparison to an A_2-Adenosine Receptor Regulating Coronary Blood Flow. *Biochem. Pharmacol.* **1986**, *35*, 2467–2481. (b) Trivedi, B. K.; Blankley, C. J.; Bristol, J. A.; Hamilton, H. W.; Patt, W. C.; Kramer, W. J.; Johnson, S. A.; Bruns, R. F.; Cohen, D. M.; Ryan, M. J. N^6-Substituted Adenosine Receptor Agonists: Potential Antihypertensive Agents. *J. Med. Chem.* **1991**, *34*, 1043–1049.

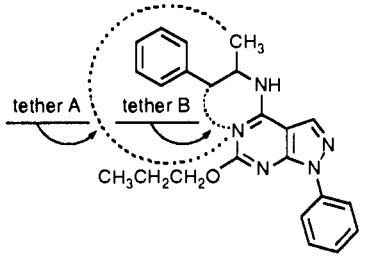
0022-2623/92/1835-3263$03.00/0

Scheme I[a]



[a] Reagents: (a) Ethanol, reflux; (b) methyl isocyanate, triethylamine, chloroform, sealed tube (120 °C); (c) 2 N sodium hydroxide, reflux; (d) sodium hydride, dimethylformamide, alkyl iodide.

zyl-substituted imidazoline. An imidazoline substituted with phenyl and methyl groups would follow from connection of N^1 to the benzyl methylene group, as shown by tether B in the general structure.

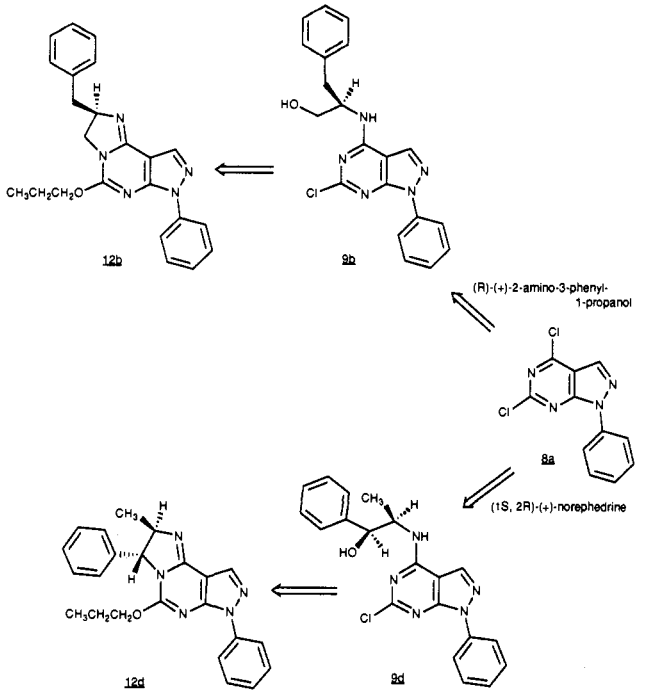


This report describes the syntheses of and adenosine A_1 and A_2 receptor affinities for chiral imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines and diimidazo[1,2-*c*:4′,5′-*e*]pyrimidines, wherein imidazo fusions represent constrained phenylisopropyl units.

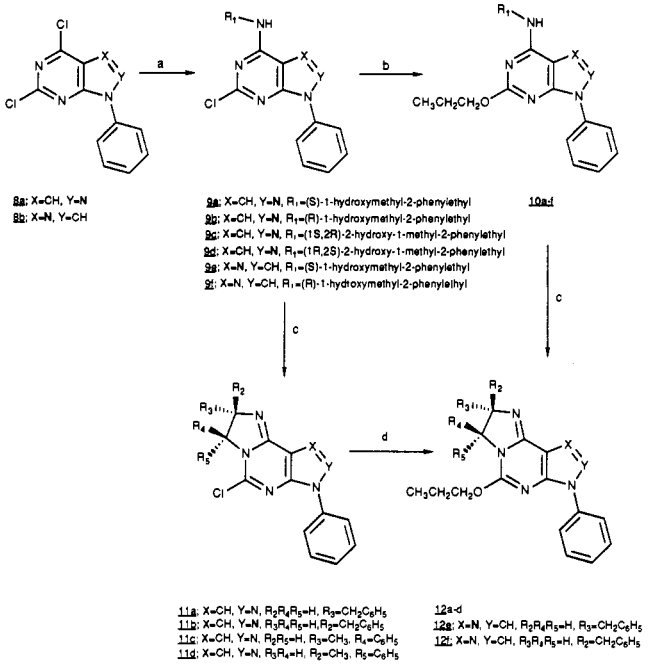
Chemistry

Compounds synthesized as shown in Scheme I were prepared to determine the optimal placement of a substituent on the pyrimidine ring. Treatment of ethyl (ethoxymethylene)cyanoacetate (1) with phenylhydrazine (2) gave 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (3).[3] Aminopyrazole **3**, when treated with excess methyl isocyanate, gave the bisurea **4**. Cyclization of **4** with aqueous sodium hydroxide gave 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**5**).[4] Alkylation of the anion of **5**, generated with sodium hydride in dimethylformamide, gave a mixture of **6a** and **7a**, which were readily separated by flash chromatography. Likewise, alkylation of **5** with iodopropane gave **6b** and **7b**.

Scheme II



Scheme III[a]



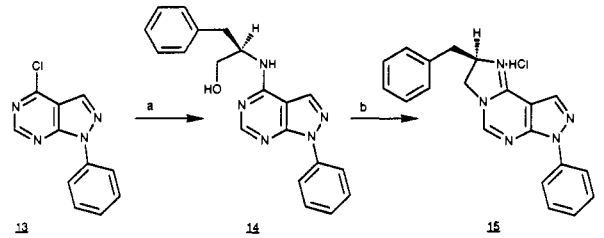
[a] Reagents: (a) R_1-NH_2, ethanol, reflux; (b) excess sodium propoxide, 90 °C; (c) thionyl chloride, chloroform, room temperature; (d) 1.5 equiv of sodium propoxide, room temperature.

Retrosynthetic analysis of the imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine **12b**, with tether A in place, is shown in Scheme II. Opening the imidazole ring of **12b** gives amino alcohol **9b**, which would derive from 4,6-dichloro-1-phenylpyrazolo[3,4-*d*]pyrimidine (**8a**) by displacement of chloride at the most reactive center with (*R*)-(+)-2-amino-3-phenyl-1-propanol. Similarly, the isomeric imidazopyrazolopyrimidine **12d**, which has tether B in place, upon internal disconnection leads to amino alcohol **9d**, which also could be prepared from **8a** by a displacement

(3) Schmidt, P.; Druey, J. Heilmittelchemische Untersuchungen in der heterocyclischen Reihe. XIV. Pyrazolo[3,4-*d*]pyrimidines. *Helv. Chim. Acta.* **1956**, *39*, 986–991.

(4) Capuano, L.; Welter, M.; Zander, R. Synthese von Thieno-, Tetrahydrobenzothieno-, Pyrazolo-, Triazolo- and Pyrido-pyrimidinen sowie Naphth- und Thien-oxazinen. *Chem. Ber.* **1969**, *102*, 3698–3706.

Scheme IV[a]



[a] Reagents: (a) (*R*)-(+)-2-amino-3-phenyl-1-propanol, triethylamine, ethanol, reflux; (b) thionyl chloride, chloroform, reflux.

reaction with (1*S*,2*R*)-(+)-norephedrine. Thus, **8a** is the projected common starting material for the construction of both tethered systems.

Syntheses of the imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidines and the diimidazo[1,2-*c*:4′,5′-*e*]pyrimidines, which were targeted as conformationally restricted (phenylisopropyl)amino-substituted pyrazolo[3,4-*d*]pyrimidines and purines, respectively, are shown in Scheme III. Treatment of **8a**[5] and 2,6-dichloro-9-phenylpurine (**8b**)[6] with (*S*)-(−)-2-amino-3-phenyl-1-propanol gave **9a** and **9e**, respectively; the *R*-enantiomers **9b** and **9f** were prepared in analogous fashion.

Treatment of **8a** with (1*R*,2*S*)- and (1*S*,2*R*)-1-hydroxy-2-methyl-1-phenylethylamines gave **9c** and **9d**, respectively. When **9a–f** were treated with sodium propoxide, compounds **10a–f** were produced. Cyclization of **9a–d** with thionyl chloride gave the fused imidazolines **11a–d**, which were treated with sodium propoxide to afford the target compounds **12a** and **12b**, with tether A in place, and target compounds **12c** and **12d**, with tether B in place. Alternatively, tether A compounds could be accessed from **10**. Treatment of **10e** and **10f** with thionyl chloride gave diimidazopyrimidines **12e** and **12f**.

Cyclizations of **9c** and **9d** to **11c** and **11d**, respectively, represent *net inversion of configuration* at the benzylic hydroxyl-bearing carbon. This stereochemical outcome suggests that intramolecular displacement is occurring either via single S_N2 displacement or by an S_N1 (carbonium ion) mechanism.

X-ray crystal structure data were obtained for (*R*)-2,7-dihydro-7-phenyl-2-(phenylmethyl)-3*H*-imidazo[1,2-*c*]-pyrazolo[4,3-*e*]pyrimidine hydrochloride salt (**15**). As shown in Scheme IV, 4-chloro-1-phenylpyrazolo[3,4-*d*]-pyrimidine (**13**)[7] was treated with (*R*)-(+)-2-amino-3-phenyl-1-propanol to give **14**, which was cyclized to **15** with thionyl chloride. The ORTEP drawing of **15**[8] shown in Figure 1 clearly rules out other potential cyclization products or skeletal rearrangement products which could have been produced during the thionyl chloride-induced cyclization of **14**.

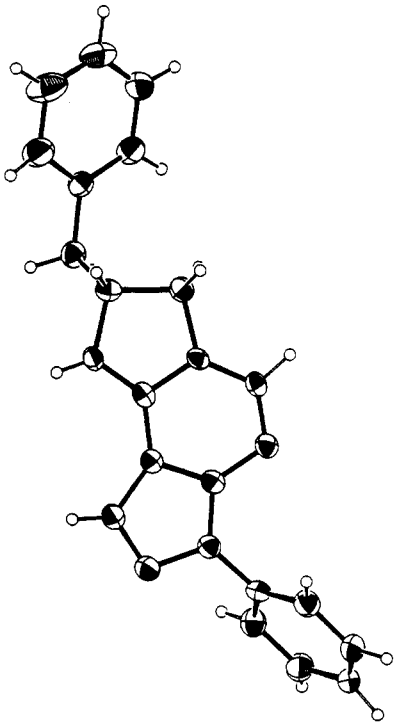
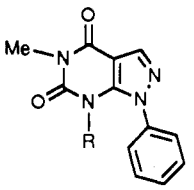
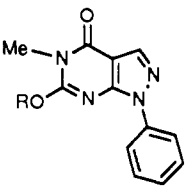


Figure 1. ORTEP drawing for (*R*)-2,7-dihydro-7-phenyl-2-(phenylmethyl)-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine hydrochloride salt (**15**).

Table I. Binding Constants for Simple Imidazopyrimidines at Adenosine A_1 Receptors





compd	R	IC_{50},[a] μM	compd	R	IC_{50},[a] μM
6a	Me	33	**7a**	Me	4.8
6b	Pr	35	**7b**	Pr	4.3

[a] Assay measures inhibition of [^{3}H]CHA binding to rat cerebral cortical membranes. See ref 2a. Values were determined from a single competition experiment with concentrations run in triplicate.

Biological Results and Discussion

Prior to incorporating a conformationally restricted (phenylisopropyl)amino substituent into pyrazolo[3,4-*d*]-pyrimidine and purine ring systems, we optimized substituents at positions 1, 6, and 7, using the pyrazolo[3,4-*d*]pyrimidine nucleus.

A phenyl group was chosen for the 1-position after exploring several aryl groups at that position and on the basis of work by Davies et al.,[9,10] who reported adenosine receptor affinity with 1-phenyl-1*H*-pyrazolo[4,5-*e*]pyrimi-

(5) Cheng, C. C.; Robins, R. K. Potential Purine Antagonists. XII. Synthesis of 1-Alkyl(aryl)-4,6-disubstituted Pyrazolo[3,4-*d*]-pyrimidines. *J. Org. Chem.* **1958**, *23*, 852–861.

(6) Koppel, H. C.; Robins, R. K. Potential Purine Antagonists. XI. Synthesis of Some 9-Aryl(alkyl)-2,6-disubstituted Purines. *J. Am. Chem. Soc.* **1958**, *80*, 2751–2755.

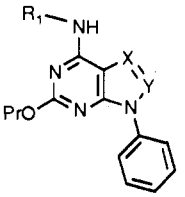
(7) Cheng, C. C.; Robins, R. K. Potential Purine Antagonists. VI. Synthesis of 1-Alkyl- and 1-Aryl-4-substituted Pyrazolo[3,4-*d*]pyrimidines. *J. Org. Chem.* **1956**, *21*, 1240–1256.

(8) Crystallography studies on compound **15** were performed by Dr. J. C. Huffman of Indiana University. Complete crystallographic details are available in microfiche form from the Chemistry Library, Indiana University, Bloomington, IN 47405: request MSC Report No. 88708. The diffractometer, data-handling techniques, and general procedure have previously been described. See: Huffman, J. C.; Lewis, L. N.; Caulton, K. G. A Donor Semibridge Molecular Structures of Dicyclopentadienyldivanadiumtetracarbonyltriphenylphosphine and Dicyclopentadienyldivanadiumpentacarbonyl. *Inorg. Chem.* **1980**, *19*, 2755–2762.

(9) Davies, L. P.; Chow, S. C.; Skeritt, J. H.; Brown, D. J.; Johnston, G. A. R. Pyrazolo[3,4-*d*]pyrimidines as Adenosine Antagonists. *Life Sci.* **1984**, *34*, 2117–2128.

(10) Davies, L. P.; Brown, D. J.; Chow, S. C.; Johnston, G. A. R. Pyrazolo[3,4-*d*]pyrimidines, a New Class of Adenosine Antagonists. *Neurosci. Lett.* **1983**, *41*, 189–193.

Table II. Binding Constants for Pyrazolopyrimidines 10a–d and Imidazopyrimidines 10e and 10f at Adenosine A_1 and A_2 Receptors



10a: X = CH, Y = N, R_1 = (*S*)-1-(hydroxymethyl)-2-phenylethyl
b: X = CH, Y = N, R_1 = (*R*)-1-(hydroxymethyl)-2-phenylethyl
c: X = CH, Y = N, R_1 = (1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl
d: X = CH, Y = N, R_1 = (1*R*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl
e: X = N, Y = CH, R_1 = (*S*)-1-(hydroxymethyl)-2-phenylethyl
f: X = N, Y = CH, R_1 = (*R*)-1-(hydroxymethyl)-2-phenylethyl

compd	K_i, μM		A_2/A_1
	A_1 receptor[a]	A_2 receptor[b]	
10a	1.6 ± 0.11	4.2 ± 1.4	2.6
10b	0.35 ± 0.034	0.37 ± 0.03	1.0
10c	6.3 ± 0.99	1.4 ± 0.16	0.22
10d	1.0 ± 0.63	0.31 ± 0.04	0.31
10e	0.096 ± 0.018	5.6 ± 0.75	58
10f	0.44 ± 0.07	30 ± 5.1	68

[a] Binding of [^{3}H]CHA in whole rat brain membranes was measured at 25 °C. Values are geometric means from a single determination run in triplicate ± standard error. See: Goodman, R.; Cooper, M.; Gavish, M.; Snyder, S. *Mol. Pharmacol.* **1982**, *21*, 329. [b] Binding of [^{3}H]NECA was measured in rat brain striatum at 25 °C. Values are geometric means from a single determination run in triplicate ± standard error. See: Bruns, R. F.; Lu, G. H.; Pugsley, T. A. *Mol. Pharmacol.* **1986**, *29*, 331.

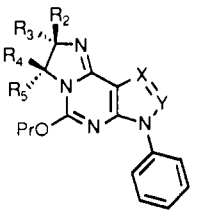
dines. The C^6-alkoxy substituent was chosen on the basis of affinities of compounds synthesized via Scheme I.

Binding constants for these simple pyrazolopyrimidines (**6a**, **6b**, **7a**, and **7b**) at adenosine A_1 receptors are shown in Table I. 6-Alkoxy compounds **7a** and **7b** have better affinity for A_1 receptors than the corresponding compounds **6a** and **6b**, where the alkyl group resides on the nitrogen atom at the 7-position. Thus, we chose the 6-alkoxy substituent for incorporation in subsequent compounds.

Table II shows binding constants for compounds **10a–f**, the precursors to tricyclic compounds **12a–f**. For pyrazolopyrimidines **10a** and **10b**, the *R*-enantiomer (**10b**) was more potent at the A_1 and A_2 receptors, although neither compound was selective. The corresponding imidazopyrimidines **10e** and **10f** displayed selectively for the adenosine A_1 receptor, but in this pair, it was the *S*-enantiomer (**10e**) which was more potent at both A_1 and A_2 receptors. This reversal in the relationship of stereochemistry to potency is interesting, but reasons for this difference are only speculative at this time. Potencies of pyrazolopyrimidines **10c** and **10d** were consistent with those of **10a** and **10b**, wherein diastereomer **10d**, with the *R*-stereocenter adjacent to the nitrogen atom at the 4-position, was more potent at both A_1 and A_2 receptors. In terms of overall A_1 potency and selectivity, imidazopyrimidine **10e** was the best compound of the group in Table II.

The biological results for the tricyclic imidazopyrazolopyrimidines and diimidazopyrimidines are shown in Table III. Interestingly, potency and selectivity for either A_1 or A_2 adenosine receptors were generally better with dihydroimidazoles bearing a benzyl substituent (**12a**, **12b**, **12e**, and **12f**) than for the dihydroimidazoles bearing the phenyl and methyl substituents (**12c** and **12d**). This suggests that the former compounds better approximate biologically relevant conformations of *R*-PIA and *S*-PIA than do the latter compounds.[11] In fact, dihydroimidazo

Table III. Binding Constants for Imidazopyrazolopyrimidines 12a–d and Diimidazopyrimidines 12e and 12f at Adenosine A_1 and A_2 Receptors



12a: X = CH, Y = N, R_2, R_4, R_5 = H, R_3 = $CH_2C_6H_5$
b: X = CH, Y = N, R_3, R_4, R_5 = H, R_2 = $CH_2C_6H_5$
c: X = CH, Y = N, R_2, R_5 = H, R_3 = CH_3, R_4 = C_6H_5
d: X = CH, Y = N, R_3, R_4 = H, R_2 = CH_3, R_5 = C_6H_5
e: X = N, Y = CH, R_2, R_4, R_5 = H, R_3 = $CH_2C_6H_5$
f: X = N, Y = CH, R_3, R_4, R_5 = H, R_2 = $CH_2C_6H_5$

compd	K_i, μM		A_2/A_1
	A_1 receptor[a]	A_2 receptor[b]	
12a	9.4 ± 1.7	3.3 ± 0.17	0.35
12b	0.62 ± 0.04	>100	>100
12c	33 ± 5.7	45 ± 7.2	1.4
12d	7.4 ± 0.53	11 ± 6.8	1.5
12e	9.0 ± 0.38	1.6 ± 0.19	0.18
12f	3.2 ± 0.46	72 ± 2.6	22

[a] Binding of [^{3}H]CHA in whole rat brain membranes was measured at 25 °C. Values are geometric means from a single determination run in triplicate ± standard error. See: Goodman, R.; Cooper, M.; Gavish, M.; Snyder, S. *Mol. Pharmacol.* **1982**, *21*, 329. [b] Binding of [^{3}H]NECA was measured in rat brain striatum at 25 °C. Values are geometric means from a single determination run in triplicate ± standard error. See: Bruns, R. F.; Lu, G. H.; Pugsley, T. A. *Mol. Pharmacol.* **1986**, *29*, 331.

compounds **12c** and **12d** had similar and weak affinities for both adenosine A_1 and A_2 receptors, and stereochemistry was not influential. However, stereochemistry was an important factor with the benzyl-substituted dihydroimidazolines **12a**, **12b**, **12e**, and **12f**. *Interestingly, the S-enantiomers (**12a** and **12e**) were A_2 selective whereas the R-enantiomers (**12b** and **12f**) were A_1 selective.*

The effect of stereochemistry on receptor selectivity with dihydroimidazolines **12a**, **12b**, **12e**, and **12f** suggests that the conformationally restrained phenylisopropyl units could be interacting with the same area of the adenosine receptors as are the phenylisopropyl groups of *R*-PIA and *S*-PIA. Compounds **12a** and **12e** are the first ligands bearing the phenylisopropyl chiral recognition unit which are A_2 selective. We have recently reported A_1-selective xanthines[12] with phenylisopropyl chiral recognition units[13,14] at the 8-position, and have proposed a binding mode for these compounds such that the phenylisopropyl group at the 8-position of the xanthine occupies the same receptor space as does the phenylisopropyl group of *R*-PIA.

(11) This idea was supported but not established by molecular modeling studies. The phenylisopropyl portion of an energy-minimized conformation of R-PIA appeared to overlay better on the dihydroimidazo ring of **12e** than it did on the dihydroimidazo ring of **12f**.

(12) Peet, N. P.; Lentz, N. L.; Meng, E. C.; Dudley, M. W.; Ogden, A. M. L.; Demeter, D. A.; Weintraub, H. J. R.; Bey, P. A Novel Synthesis of Xanthines. Support for a New Binding Mode for Xanthines with Respect to Adenosine at Adenosine Receptors. *J. Med. Chem.* **1990**, *33*, 3127–3130.

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In summary, we have described the syntheses and adenosine receptor affinities for chiral tricyclic molecules containing conformationally restrained phenylisopropyl units. One mode of restriction provides *S*-enantiomers with A_2 selectivity and corresponding *R*-enantiomers with A_1 selectivity.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 727B spectrophotometer and NMR spectra with Varian Gemini 300 and Varian VXR-300 spectrometers; MS data were collected at 70 eV with a Finnigan TCQ GC/MS/MS instrument, and HRMS data were collected at 70 eV with a VG ZABZ-SE spectrometer, using computerized peak matching with perfluorokerosene as the reference and a resolution of 10 000. Chemical shifts for ^{1}H NMR signals are reported in ppm downfield from TMS (δ). Analytical TLC was performed using Merck silica gel 60F-254 glass backed plates of 0.25-mm thickness. Flash chromatography was performed using Merck silica gel 230–400 mesh. A Model 7924T Chromatotron from Harrison Research was used for radial chromatography. Combustion analyses fell within ±0.4% of the calculated values.

5-Amino-1-phenyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (3). A mixture of 89.6 g (0.550 mol) of ethyl (ethoxymethylene)cyanoacetate (1), 54.0 g (0.500 mol) of phenylhydrazine (2), and 600 mL of ethanol was heated at reflux for 15 h. The mixture was filtered hot and the filtrate was concentrated to half-volume and cooled. The resulting crystalline solid was collected and dried to give 66.8 g (58%) of 3, mp 98–100 °C (lit.[3] mp 99–101 °C).

2,3-Dihydro-1-[(methylamino)carbonyl]-3-[[(methylamino)carbonyl]imino]-2-phenyl-1*H*-pyrazole-4-carboxylic Acid Ethyl Ester (4). To a solution of 23.1 g (0.100 mol) of 3 in 25 mL of $CHCl_3$ in a glass tube was added 20 mL of methyl isocyanate. The tube was sealed and heated at 120 °C for 62 h. The tube was cooled, and the contents were removed and cooled. The resulting solid was collected and dried to afford 7.1 g (50%) of 4, mp 159–160 °C (lit.[4] mp 157 °C).

5-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6-(5*H*,7*H*)-dione (5). A mixture of 3.80 g (11.0 mmol) of 4 and 38 mL of 2 N NaOH was heated at reflux for 4 min. The clear solution was diluted with 38 mL of water and acidified with acetic acid. The resulting solid was collected, washed with water, and dried to give 2.56 g (96%) of 5, mp 289–290 °C (lit.[4] mp 296 °C).

5,7-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (6a) and 1,5-Dihydro-6-methoxy-5-methyl-1-phenyl-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (7a). To a mixture of 0.82 g (34 mmol) of NaH in 15 mL of DMF was added 6.10 g (25.0 mmol) of 5. After 10 min of stirring, 3.55 g (25.0 mmol) of CH_3I was added to the clear solution. After 3 h of stirring the mixture was diluted with water and the resulting solid was collected and dried to give 6.41 g (100%) of a mixture of 6a and 7a. Separation by flash chromatography on silica gel (1:1 hexane/EtOAc) gave, as the first component to elute, 0.98 g (15%) of 7a: mp 185–186 °C; IR (Nujol) 1700 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.23 (s, 1 H, C3-H), 8.10 (m, 2 H, C2′-H and C6′-H), 7.57 (m, 2 H, C3′-H and C5′-H), 7.40 (C4′-H), 4.09 (s, 3 H, OCH_3), 3.37 (s, 3 H, NCH_3); MS (70 eV, CI, CH_4) *m/z* 257 (M^+ + 1), 285 (M^+ + 29), 297 (M^+ + 41). Anal. ($C_{13}H_{12}N_4O_2$) C, H, N.

Fractions containing the second component were combined and concentrated to give 3.75 g (58%) of 6a: mp 212–213 °C; IR (Nujol) 1705 (C=O), 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.14 (s, 1 H, C3-H), 7.60 (m, 5 H, phenyl), 3.24 (s, 3 H, NCH_3), 2.97 (s, 3 H, NCH_3); MS (70 eV, CI, CH_4) *m/z* 257 (M^+ + 1), 285 (M^+ + 25), 297 (M^+ + 41). Anal. ($C_{13}H_{12}N_4O_2$) C, H, N.

5-Methyl-1-phenyl-7-propyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (6b) and 1,5-Dihydro-5-methyl-1-phenyl-6-propoxy-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (7b). To a mixture of 0.82 g (34 mmol) of NaH in 15 mL of DMF was added 6.10 g (25.0 mmol) of 5. After 15 min of stirring, 6.80 g (40.0 mmol) of iodopropane was added to the clear solution. The solution was stirred at room temperature, heated at 100 °C for 30 min, and cooled. The mixture was diluted with water and the resulting precipitate was collected and dried to give 6.60 g (93%) of a mixture of 6b and 7b. The mixture was separated by flash chromatography on silica gel to give, as the fast-moving component, 3.50 g (49%) of 7b: mp 134–135 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.20 (s, 1 H, C2-H), 8.05 (m, 2 H, C2′-H and C6′-H), 7.53 (m, 2 H, C3′-H and C5′-H), 7.38 (m, 1 H, C4′-H), 4.41 (t, J = 6.3 Hz, 2 H, OCH_2), 3.35 (s, 3 H, NCH_3), 1.81 (m, 2 H, OCH_2CH_2), 1.01 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$); MS (70 eV, EI) *m/z* 284 (molecular ion). Anal. ($C_{15}H_{16}N_4O_2$) C, H, N.

Fractions containing the slower-moving component were combined and concentrated to give 1.21 g (17%) of 6b: mp 155 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.14 (s, 1 H, C2-H), 7.64 (m, 5 H, phenyl), 3.45 (t, J = 8.1 Hz, 2 H, NCH_2), 3.25 (s, 3 H, NCH_3), 1.29 (m, 2 H, NCH_2CH_2), 0.33 (t, J = 7.2 Hz, 3 H, $NCH_2CH_2CH_3$); MS (70 eV, EI) *m/z* 284 (molecular ion). Anal. ($C_{15}H_{16}N_4O_2$) C, H, N.

(*S*)-β-[(1-Phenyl-6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]benzenepropanol (9a). A suspension of 2.50 g (9.43 mmol) of 4,6-dichloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine[5] (8a) in 60 mL of ethanol was treated with 4.28 g (28.3 mmol) of (*S*)-(−)-2-amino-3-phenyl-1-propanol with stirring at room temperature. After 24 h, the solvent was removed under vacuum and the crude oil was purified by flash chromatography [10, 15, 20% isopropyl alcohol (IPA)/hexane] to yield 3.5 g (97%) of 9a as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.1 Hz, 2 H), 7.98 (s, 1 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.20–7.38 (m, 7 H), 5.88 (br s, 1 H) 4.62 (br s, 1 H), 3.86 (dd, J = 11.2, 3.9 Hz, 1 H), 3.76 (dd, J = 11.2, 4.7 Hz, 1 H), 3.05 (d, J = 6.8 Hz, 2 H); MS (70 eV, CI, CH_4) *m/z* 380 (M^+ + 1), 408 (M^+ + 29), 420 (M^+ + 41), 362 (loss of H_2O), 344 (loss of HCl).

(*R*)-β-[(1-Phenyl-6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]benzenepropanol (9b). A suspension of 2.81 g (10.6 mmol) of 8a in 60 mL of ethanol was treated with (*R*)-(+)-2-amino-3-phenyl-1-propanol with stirring at room temperature. After 48 h, the solvent was removed under vacuum and the crude oil was purified by flash chromatography (2, 5, 7% MeOH/$CHCl_3$) to yield 3.80 g (95%) of 9b as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.9 Hz, 2 H), 7.98 (s, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.20–7.38 (m, 7 H), 5.88 (br s, 1 H), 4.62 (br s, 1 H), 3.81 (dd, J = 11.3, 3.9 Hz, 2 H), 3.06 (d, J = 6.8 Hz, 2 H); MS (70 eV, CI, CH_4) *m/z* 380 (M^+ + 1), 408 (M^+ + 29), 420 (M^+ + 420), 362 (loss of H_2O), 344 (loss of HCl).

[*S*-(*R,*S**)]-α-[1-[(1-Phenyl-6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]ethyl]benzenemethanol (9c).** A suspension of 1.00 g (3.77 mmol) of 8a in 25 mL of ethanol was treated with 1.71 g (11.3 mmol) of (1*R*,2*S*)-(−)-norephedrine with stirring at room temperature. After 24 h, the solvent was removed under vacuum and the crude oil was purified by radial chromatography (40, 50, 60, 70% Et_2O/hexane, 4-mm plate) to yield 1.17 g (82%) of 9c as a white solid: mp 164–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.9 Hz, 2 H), 7.89 (s, 1 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.20–7.42 (m, 7 H), 5.78 (br s, 1 H), 4.96 (d, J = 2.9 Hz, 1 H), 4.78 (br s, 1 H), 3.00 (br s, 1 H), 1.09 (d, J = 6.4 Hz, 3 H); MS (70 eV, CI, CH_4), *m/z* 380 (M^+ + 1), 408 (M^+ + 29), 420 (M^+ + 41), 344 (loss of HCl).

[*R*-(*S,*R**)]-α-[1-[(1-Phenyl-6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]ethyl]benzenemethanol (9d).** A solution of 828 mg (4.41 mmol) of (1*S*,2*R*)-(+)-norephedrine hydrochloride in 100 mL of H_2O was made basic with 10% KOH. The aqueous phase was extracted with 100 mL of Et_2O. The organic phase was then dried over anhydrous $MgSO_4$, filtered, and concentrated to yield an oil. This was added to a stirring suspension of 390 mg (1.47 mmol) of 8a in 15 mL of ethanol at room temperature. After 4 h the reaction mixture became clear and the solvent was removed under vacuum. The crude oil was purified by radial chromatography (5, 10, 20% IPA/hexane, 4-mm plate) to yield 535 mg (96%) of 9d as an oil: MS (70 eV, CI, CH_4) *m/z* 380 (M^+ + 1), 408 (M^+ + 29), 420 (M^+ + 41), 344 (loss of HCl).

(*S*)-β-[(9-Phenyl-2-chloro-1*H*-purin-6-yl)amino]-benzenepropanol (9e). A suspension of 2.00 g (7.54 mmol) of 2,6-dichloro-9-phenylpurine[6] (8b) in 70 mL of ethanol was treated with 1.15 g (7.54 mmol) of (*S*)-(−)-2-amino-3-phenyl-1-propanol and 1.13 mL (7.54 mmol) of Et_3N with stirring. The reaction was heated to reflux for 4 h. After cooling, the solvent was removed under vacuum and the crude residue was purified by flash

chromatography (3–5% MeOH/$CHCl_3$) to yield 2.77 g (96%) of **9e**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.19–7.62 (m, 10 H), 7.00 (br s, 1 H), 4.64 (br s, 1 H), 4.33 (br s, 1 H), 3.97 (d, J = 11.2 Hz, 1 H), 3.79 (m, 1 H), 3.08 (m, 2 H); MS (70 eV, EI) m/z 379 (M^+), 348 ($M^+ - CH_2OH$), 288 ($M^+ - CH_2C_6H_5$).

(*R*)-β-[(9-Phenyl-2-chloro-1*H*-purin-6-yl)amino]benzenepropanol (9f). A suspension of 1.24 g (4.70 mmol) of **8b** in 50 mL of ethanol was treated with 0.710 g (4.70 mmol) of (*R*)-(+)-2-amino-3-phenyl-1-propanol and 0.700 mL (5.05 mmol) of Et_3N. The reaction was heated to reflux for 5 h. After cooling, the solvent was removed under vacuum and the crude residue was purified by flash chromatography (5% MeOH/$CHCl_3$) to yield 1.47 g (82%) of **9f**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.19–7.62 (m, 10 H), 6.84 (br s, 1 H), 4.62 (br s, 1 H), 3.95 (br d, J = 11.5 Hz, 2 H), 3.77 (t, J = 5.3 Hz, 1 H), 3.08 (m, 2 H); MS (70 eV, CI, CH_4) m/z 380 (M^+ + 1), 408 (M^+ + 29), 420 (M^+ + 41), 362 (loss of H_2O), 344 (loss of HCl).

(*S*)-β-[(1-Phenyl-6-propoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]benzenepropanol (10a). Sodium *n*-propoxide was freshly prepared by adding 314 mg (13.7 mmol) of sodium spheres to 25 mL of dry *n*-propanol under N_2. After the sodium had completely reacted, 650 mg (1.71 mmol) of **9a** in 10 mL of *n*-propanol was added with stirring. The reaction was heated to 90 °C for 2 h. After cooling, the reaction was poured into 100 mL of saturated NaCl and extracted with 200 mL of $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude oil was purified by radial chromatography (10–20% IPA/hexane, 4-mm plate) to yield, after recrystallization from 30% IPA/hexane and drying under vacuum at 60 °C for 72 h, 319 mg (46%) of **10a**: mp 155–157 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.9 Hz, 2 H), 7.86 (s, 1 H), 7.49 (t, J = 7.1 Hz, 2 H), 7.20–7.40 (m, 7 H), 5.55 (br s, 1 H), 4.60 (br s, 1 H), 4.35 (t, J = 6.9 Hz, 2 H), 3.80 (m, 2 H), 3.06 (d, J = 7.1 Hz, 2 H), 1.88 (m, 2 H), 1.06 (t, J = 7.5 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 404 (M^+ + 1), 432 (M^+ + 29), 386 (loss of H_2O). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

(*R*)-β-[(1-Phenyl-6-propoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]benzenepropanol (10b). Following the general procedure for **10a**, 773 mg (2.04 mmol) of **9b** was treated with excess sodium propoxide. Radial chromatography (10, 20, 30% IPA/hexane, 4-mm plate) followed by recrystallization from 30% IPA/hexane yielded 217 mg (26%) of **10b** as a white solid: mp 158–159 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8 Hz, 2 H), 7.78 (s, 1 H), 7.40 (t, J = 7.7 Hz, 2 H), 7.20–7.40 (m, 7 H), 5.58 (br s, 1 H), 4.60 (br s, 1 H), 4.27 (t, J = 6.8 Hz, 2 H), 3.80 (m, 2 H), 2.96 (d, J = 6.9 Hz, 2 H), 1.88 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 404 (M^+ + 1), 432 (M^+ + 29). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

[*S*-(*R,*S**)]-α-[1-[(1-Phenyl-6-propoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]ethyl]benzenemethanol (10c).** Following the general procedure for **10a**, 400 mg (1.05 mmol) of **9c** was treated with excess sodium propoxide. Radial chromatography (5, 10, 20% IPA/hexane, 4-mm plate) followed by recrystallization from 20% Et_2O/hexane yielded 122 mg (29%) of **10c** as a white solid: mp 136–138 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.1 Hz, 2 H), 7.90 (s, 1 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.22–7.40 (m, 6 H), 5.40 (br s, 1 H), 5.02 (s, 1 H), 4.80 (br s, 1 H), 4.39 (t, J = 6.7 Hz, 2 H), 4.1 (br s, 1 H), 1.89 (m, 2 H), 1.20 (d, J = 6.9 Hz, 3 H), 1.05 (t, J = 7.3 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 404 (M^+ + 1), 432 (M^+ + 29), 444 (M^+ + 41), 386 (loss of H_2O). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

[*R*-(*S,*R**)]-α-[1-[(1-Phenyl-6-propoxy-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)amino]ethyl]benzenemethanol (10d).** Following the general procedure for **10a**, 341 mg (0.900 mmol) of **9d** was treated with excess sodium propoxide. Radial chromatography (5, 10, 20% IPA/hexane, 2-mm plate) followed by recrystallization from 20% Et_2O/hexane yielded 205 mg (56%) of **10d** as a white solid: mp 137–140 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.3 Hz, 2 H), 7.90 (s, 1 H), 7.49 (t, J = 7.7 Hz, 2 H), 7.22–7.40 (m, 6 H), 5.40 (br s, 1 H), 5.02 (s, 1 H), 4.80 (br s, 1 H), 4.39 (t, J = 7.0 Hz, 2 H), 4.1 (br s, 1 H), 1.89 (m, 2 H), 1.20 (d, J = 6.8 Hz, 3 H), 1.07 (t, J = 7.5 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 404 (M^+ + 1), 432 (M^+ + 29), 444 (M^+ + 41), 386 (loss of H_2O). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

(*S*)-β-[(2-Propoxy-9-phenyl-1*H*-purin-6-yl)amino]benzenepropanol (10e). Following the general procedure for **10a**, 2.76 g (7.27 mmol) of **9e** was treated with excess sodium propoxide. Flash chromatography (2% MeOH/$CHCl_3$) followed by recrystallization from 5% IPA/hexane yielded 1.78 g (61%) of **10e** as a white solid: mp 126–128 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.67 (d, J = 8.0 Hz, 2 H), 7.52 (t, J = 7.5 Hz, 2 H), 7.20–7.45 (m, 6 H), 6.20 (br s, 1 H), 4.68 (br s, 1 H), 4.27 (t, J = 7.5 Hz, 2 H), 3.90 (m, 1 H), 3.72 (m, 2 H), 3.06 (d, J = 7.52 Hz, 2 H), 1.81 (m, 2 H), 1.02 (t, J = 7.5 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 404 (M^+ + 1), 432 (M^+ + 29), 444 (M^+ + 41), 386 (loss of H_2O). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

(*R*)-β-[(2-Propoxy-9-phenyl-1*H*-purin-6-yl)amino]benzenepropanol (10f). Following the general procedure for **10a**, 1.40 g (3.69 mmol) of **9f** was treated with excess sodium propoxide. Flash chromatography (2% MeOH/$CHCl_3$) followed by recrystallization from 5% IPA/hexane yielded 1.05 g (71%) of **10f** as a white solid: mp 127–128 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.67 (d, J = 8.3 Hz, 2 H), 7.52 (t, J = 7.4 Hz, 2 H), 7.20–7.45 (m, 6 H), 6.35 (br s, 1 H), 4.68 (br s, 1 H), 4.27 (t, J = 6.9 Hz, 2 H), 3.90 (m, 2 H), 3.72 (m, 1 H), 3.06 (dd, J = 6.8, 2.3 Hz, 2 H), 1.81 (m, 2 H), 1.01 (t, J = 7.4 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 404 (M^+ + 1), 432 (M^+ + 29), 444 (M^+ + 41), 386 (loss of H_2O). Anal. ($C_{23}H_{25}N_5O_2$) C, H, N.

(*S*)-2,7-Dihydro-7-phenyl-2-(phenylmethyl)-5-chloro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (11a). A solution of 6.60 g (17.4 mmol) of **9a** in 300 mL of $CHCl_3$ was cooled with ice. To the solution was added 8.9 mL (120 mmol) of thionyl chloride with stirring. The reaction was allowed to warm to room temperature overnight. The reaction was cooled to −20 °C and then suction filtered. The product was rinsed with $CHCl_3$ and dried under vacuum over P_2O_5 to yield 4.94 g (78%) of **11a** as a white solid (TLC 5% MeOH/$CHCl_3$, R_f = 0.53): mp 248–251 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1 H), 7.88 (d, J = 7.8 Hz, 2 H), 7.20–7.50 (m, 8 H), 5.05 (br s, 1 H), 4.66 (t, J = 10.4 Hz, 1 H), 4.30 (m, 1 H), 3.35 (dd, J = 14.6, 3.7 Hz, 1 H), 3.17 (dd, J = 14.3, 7.3 Hz, 1 H); MS (70 eV, CI, CH_4) m/z 362 (M^+ + 1), 390 (M^+ + 29), 402 (M^+ + 41).

(*R*)-2,7-Dihydro-7-phenyl-2-(phenylmethyl)-5-chloro-3*H*-imidazo[1,2-c]pyrazolo[4,3-*e*]pyrimidine (11b). Following the general procedure for **11a**, 4.40 g (11.6 mmol) of **9b** was treated with excess thionyl chloride to yield 4.04 g (96%) of **11b** as a white solid: mp 253 °C; ^1H NMR ($CDCl_3$) δ 8.90 (s, 1 H), 7.91 (d, J = 7 Hz, 2 H), 7.20–7.52 (m, 8 H), 4.95 (br s, 1 H), 4.50 (br s, 1 H), 4.30 (m, 1 H), 3.35 (dd, J = 14 Hz, J = 3 Hz, 1 H), 3.15 (m, 1 H); MS (70 eV, CI, CH_4) m/z 362 (M^+ + 1), 390 (M^+ + 29), 402 (M^+ + 41).

(2*S*-*trans*)-2,7-Dihydro-2-methyl-3,7-diphenyl-5-chloro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (11c). A solution of 700 mg (1.8 mmol) of **9c** in 50 mL of CH_3CN was treated with 0.26 mL (3.7 mmol) of thionyl chloride with stirring at room temperature. After 24 h, the reaction was concentrated under vacuum and the residue was purified by radial chromatography (20, 30, 50% ethyl acetate/hexane, 4-mm plate) to yield 210 mg (32%) of **11c**: TLC, 50% ethyl acetate/hexane, R_f = 0.28; MS (70 eV, CI, CH_4) m/z 362 (M^+ + 1), 390 (M^+ + 29).

(2*R*-*trans*)-2,7-Dihydro-2-methyl-3,7-diphenyl-5-chloro-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (11d). Following the general procedure for **11c**, 1.9 g (5.0 mmol) of **9d** was treated with excess thionyl chloride to yield, after flash chromatography (50% ethyl acetate/hexane), 0.85 g (47%) of **11d** as a clear viscous oil: TLC 50% ethyl acetate/hexane, R_f = 0.21; MS (70 eV, CI, CH_4) m/z 362 (M^+ + 1), 390 (M^+ + 29), 402 (M^+ + 41).

(*S*)-2,7-Dihydro-7-phenyl-2-(phenylmethyl)-5-propoxy-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (12a). To 3 mL of a 0.29 M solution of freshly prepared sodium propoxide (0.87 mmol) at 0 °C was added 209 mg (0.580 mmol) of **11a** with stirring under nitrogen. After 1 h, the reaction was poured into 100 mL of saturated NaCl and extracted with 200 mL of $CHCl_3$. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by radial chromatography (5–10% MeOH/$CHCl_3$, 2-mm plate) to yield 168 mg (75%) of **12a** as a viscous oil: TLC 5% MeOH/$CHCl_3$, R_f = 0.22; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 3 H), 7.46 (t, J = 7.8 Hz, 2 H), 7.20–7.40 (m, 6 H), 4.62 (m, 1 H), 4.35 (m, 2 H), 3.84 (t, J = 10.2 Hz, 1 H), 3.61 (dd, J = 11.7 Hz, J = 7.7 Hz, 1 H), 3.30 (dd, J = 14.4, 4.7 Hz, 1 H), 2.75 (dd, J = 14.1, 9.3 Hz, 1 H), 1.80 (m, 2 H), 1.00 (t, J = 7.3 Hz, 3 H); MS (70 eV, CI, CH_4) m/z

386 ($M^+ + 1$), 414 ($M^+ + 29$), 426 ($M^+ + 41$); HR MS $m/z + 1$ calcd for $C_{23}H_{24}N_5O$ 386.1980, found 386.1966.

(*R*)-2,7-Dihydro-7-phenyl-2-(phenylmethyl)-5-propoxy-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (12b). Following the general procedure for **12a**, 650 mg (1.80 mmol) of **11b** was treated with a slight excess of sodium propoxide. Aqueous workup followed by radial chromatography (10, 20, 30% IPA/hexane, 4-mm plate) and recrystallization (10% Et_2O/hexane) yielded 132 mg (19%) of **12b** as a white solid: mp 45–48 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 3 H), 7.45 (t, J = 8.6 Hz, 2 H), 7.20–7.40 (m, 6 H), 4.62 (m, 1 H), 4.35 (td, J = 6.5 Hz, J = 2.1 Hz, 2 H), 3.85 (t, J = 10.8 Hz, 1 H), 3.60 (dd, J = 11.3 Hz, J = 7.4 Hz, 1 H), 3.30 (dd, J = 13.9, 4.8 Hz, 1 H), 2.72 (dd, J = 13.9, 9.3 Hz, 1 H), 1.78 (m, 2 H), 1.00 (t, J = 7.5 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 386 ($M^+ + 1$), 414 ($M^+ + 29$), 426 ($M^+ + 41$); HR MS m/z calcd for $C_{23}H_{23}N_5O$ 385.1902, found 385.1900.

(2*S*-*trans*)-2,7-Dihydro-2-methyl-3,7-diphenyl-5-propoxy-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (12c). Following the general procedure for **12a**, 209 mg (0.580 mmol) of **11c** was treated with a slight excess of sodium propoxide. Aqueous workup followed by radial chromatography (2% MeOH/$CHCl_3$, 2 mm plate) yielded 180 mg (80%) of **12c** as a foam: TLC 5% MeOH/$CHCl_3$, R_f = 0.46; ^1H NMR (300 MHz, DMSO-d_6) δ 8.10 (s, 1 H), 8.02 (d, J = 8.3 Hz, 2 H), 7.52 (t, J = 7.5 Hz, 2 H), 7.20–7.40 (m, 6 H), 4.86 (d, J = 5.4 Hz, 1 H), 4.15 (m, 2 H), 3.95 (m, 1 H), 1.40 (m, 2 H), 1.33 (d, J = 6.5 Hz, 3 H), 0.52 (t, J = 7.2 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 386 ($M^+ + 1$), 414 ($M^+ + 29$), 426 ($M^+ + 41$); HR MS $m/z + 1$, calcd for $C_{23}H_{24}N_5O$ 386.1980, found 386.1980.

(2*R*-*trans*)-2,7-Dihydro-2-methyl-3,7-diphenyl-5-propoxy-3*H*-imidazo[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine (12d). Following the general procedure in **12a**, 670 mg (1.85 mmol) of **11d** was treated with a slight excess of sodium propoxide. Aqueous workup followed by radial chromatography (2×) (30, 50, 70, 90% of ethyl acetate/hexane, 2 mm plate) yielded 220 mg (31%) of **12d** as a foam: TLC, 50% ethyl acetate/hexane, R_f = 0.27; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1 H), 8.05 (d, J = 8.8 Hz, 2 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.20–7.40 (m, 6 H), 4.71 (d, J = 5.6 Hz, 1 H), 4.15 (m, 2 H), 1.45 (m, 2 H), 1.40 (d, J = 6.9 Hz, 3 H), 0.62 (t, J = 7.5 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 386 ($M^+ + 1$), 414 ($M^+ + 29$), 426 ($M^+ + 41$); HR MS $m/z + 1$ calcd for $C_{23}H_{24}N_5O$ 386.1980, found 386.1979.

(*S*)-7,8-Dihydro-3-phenyl-8-(phenylmethyl)-5-propoxy-3*H*-diimidazo[1,2-*c*:4′,5′-*e*]pyrimidine (12e). A solution of 1.20 g (2.97 mmol) of **10e** in 60 mL of dry CH_2Cl_2 was treated with 1.52 mL (20.8 mmol) of thionyl chloride. The reaction was heated to reflux under nitrogen for 4 h. The solvent was then removed under vacuum. The residue was purified by flash chromatography (5% MeOH/$CHCl_3$) to yield 437 mg (38%) of **12e** as a white solid: mp 74–80 °C; TLC, 5% MeOH/$CHCl_3$, R_f = 0.21; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.60 (d, J = 8.5 Hz, 2 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.20–7.35 (m, 6 H), 4.70 (m, 1 H), 4.25 (ddd, J = 8.4, 6.6, 2.0 Hz, 2 H), 3.89 (t, J = 10.8 Hz, 1 H), 3.65 (dd, J = 11.2, 7.6 Hz, 1 H), 3.35 (dd, J = 13.8, 4.9 Hz, 1 H), 2.76 (dd, J = 13.8, 9.9 Hz, 1 H), 1.75 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 386 ($M^+ + 1$), 414 ($M^+ + 29$), 426 ($M^+ + 41$); HR MS $m/z + 1$ calcd for $C_{23}H_{24}N_5O$ 386.1980, found 386.1974.

(*R*)-7,8-Dihydro-3-phenyl-8-(phenylmethyl)-5-propoxy-3*H*-diimidazo[1,2-*c*:4′,5′-*e*]pyrimidine (12f). Following the general procedure for **12e**, 750 mg (1.86 mmol) was treated with excess thionyl chloride to yield, after radial chromatography (3–6% MeOH/$CHCl_3$, 2-mm plate), 60 mg (8%) of **12f** as a light brown foam: TLC, 5% MeOH/$CHCl_3$, R_f = 0.21; ^1H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 7.15–7.50 (m, 10 H), 5.15 (s, 1 H), 4.26 (t, J = 6.7 Hz, 2 H), 4.07 (t, J = 11.0 Hz, 1 H), 3.90 (dd, J = 11.9, 6.4 Hz, 1 H), 3.55 (d, 1 H), 2.89 (dd, J = 13.4, 9.1 Hz, 1 H), 1.72 (m, 2 H), 0.94 (t, J = 7.5 Hz, 3 H); MS (70 eV, CI, CH_4) m/z 386 ($M^+ + 1$), 414 ($M^+ + 29$), 426 ($M^+ + 41$); HR MS $m/z + 1$ calcd for $C_{23}H_{24}N_5O$ 386.1980, found 386.1959.

(*R*)-2,7-Dihydro-7-phenyl-2-(phenylmethyl)-3*H*-imidazo-[1,2-*c*]pyrazolo[4,3-*e*]pyrimidine Hydrochloride Salt (15). To 60 mL of ethanol were added 1.13 g (4.88 mmol) of 1-phenyl-6-chloropyrazolo[3,4-*d*]pyrimidine (**13**), 0.740 g (4.88 mmol) of (*R*)-(+)-2-amino-3-phenyl-1-propanol, and 0.67 mL (4.9 mmol) of triethylamine with stirring. The reaction was heated on a steam bath for 4 h. After cooling, the solvent was removed under vacuum and the residue was purified by flash chromatography (10–20% IPA/hexane) to yield 1.24 g (74%) of **14**, which was immediately carried on to the cyclization step. A solution of 1.24 g (3.59 mmol) of **14** in 60 mL of CH_2Cl_2 was treated with 1.82 mL (25.1 mmol) of thionyl chloride. The reaction was heated to reflux for 4 h. After cooling, the solvent was removed under vacuum and the residue was triturated with butanone. The white precipitate was collected and recrystallized from 5% MeOH/butanone to yield, after drying at 85 °C under vacuum, 229 mg (18%) of **15** as long, flat, clear needles: mp >270 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1 H), 8.79 (s, 1 H), 8.59 (s, 1 H), 8.00 (d, J = 8.1 Hz, 2 H), 7.62 (t, J = 8.1 Hz, 2 H), 7.45 (t, J = 7.1 Hz, 1 H), 7.20–7.40 (m, 5 H), 4.90 (m, 1 H), 4.70 (t, J = 11.0 Hz, 1 H), 4.44 (dd, J = 11.5, 6.5 Hz, 1 H), 3.10 (d, J = 6.5 Hz, 2 H); MS (70 eV, CI, CH_4) m/z 328 ($M^+ + 1$), 356 ($M^+ + 29$), 368 ($M^+ + 41$). Anal. ($C_{20}H_{18}ClN_5$) C, H, N.

Biochemical Assays. Stock solutions of all test compounds were prepared (millimolar concentration range) in dimethyl sulfoxide and stored in the freezer. Solutions were warmed to room temperature prior to dilution in water for testing. Inhibition of binding of [^3H]CHA to adenosine A_1 receptors in rat cerebral cortical membranes was performed as described.[2a] For the adenosine A_2 receptor assay, inhibition of [^3H]NECA in whole rat brain membranes was measured.[15]

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