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DIIMIDAZO[1,2-*c*:4',5'-*e*]PYRIMIDINES: N^6-N1 CONFORMATIONALLY RESTRICTED ADENOSINES

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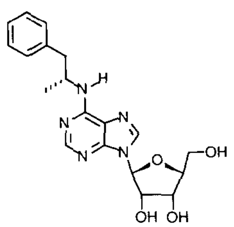
Abstract: Tethering the N^6-substituents of N^6-substituted adenosines to N1 has resulted in a series of conformationally restricted adenosine analogues. The resultant diimidazo[1,2-*c*:4',5'-*e*]pyrimidines were shown to be adenosine A_1 selective.

Numerous substituted adenosines have been developed as specific ligands for adenosine receptors *viz.* A_1, A_{2A}, A_{2B}, and A_3.[1] Highly selective synthetic analogues such as R-PIA and CGS21680[2] act as pharmacological tools for defining the precise physiological and pathophysiological role of adenosine. Because adenosine receptors occur on almost all cells and tissue, new classes of therapeutic agents, acting via these receptors are likely to contribute to meeting the disease challenges of the 21st century.[3]

N^6-(*R*)-(Phenylisopropyl)adenosine [R-PIA] **1** is a selective A_1 receptor ligand. It is important to note that changing the stereochemistry of the hydrophobic phenylisopropyl substituent to the (*S*)-configuration results in a decrease, both in potency and selectivity, at this receptor.[4]

Constraining the relatively mobile phenylisopropyl group onto the framework of 1-phenylpyrazolopyrimidines and 9-phenylpurines has been achieved in two ways.[5] Tethering the phenylisopropyl group at the benzylic position (route A) produced **2** while the methyl "anchor" (route B) yielded **3** and **4**. The compounds **2**–**4** had affinity at A_1 and A_{2A} adenosine receptors (Table 1).



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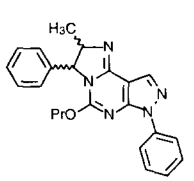

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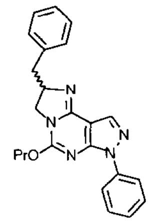

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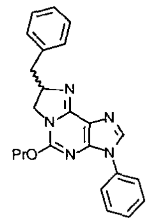

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Table 1. Binding data for compounds **2–4**[5]

Compound	A_1 receptor K_i μM	A_{2A} receptor K_i μM	K_i A_{2A}/ K_i A_1
2a 8-(*R*)-methyl-7-(*R*)-phenyl	7.4	11	1.5
2b 8-(*S*)-methyl-7-(*S*)-phenyl	33	45	1.4
3a 8-(*R*)-benzyl	0.62	>100	>100
3b 8-(*S*)-benzyl	9.4	3.3	0.35
4a 8-(*R*)-benzyl	3.2	72	22
4b 8-(*S*)-benzyl	9.0	1.6	0.18

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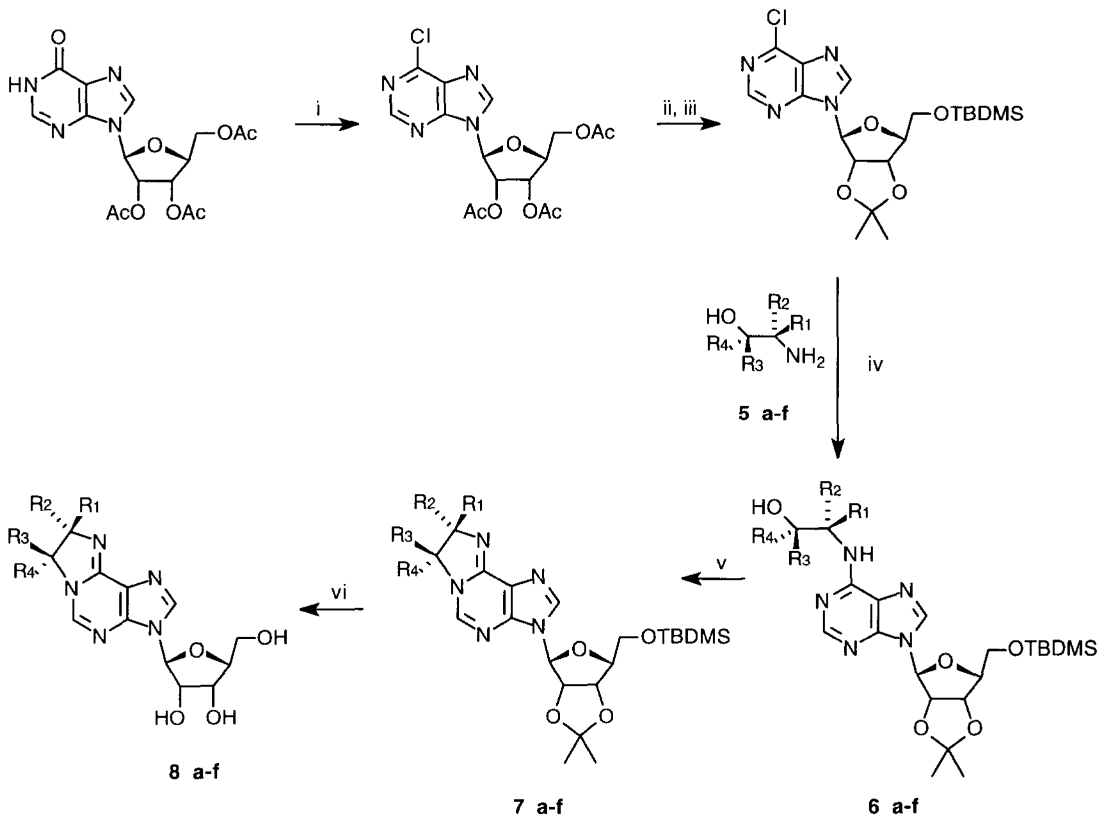
Compounds **2–4** contain two hydrophobic groups (phenyl and phenylisopropyl) as opposed to the single hydrophobic group and sugar moiety of R-PIA. We now report the synthesis and binding data for a series of diimidazo[1,2-*c*:4',5'-*e*]pyrimidines in which the hydrophobic group is conformationally constrained in the presence of the ribose.

The target compounds[6] were synthesised by reaction of an amino alcohol (**5a–f**) with a suitably protected 6-chloroadenosine as depicted in Scheme 1. In the case of route A tethered derivatives, both (1*S*,2*R*)- and (1*R*,2*S*)-norephedrine (**5a** and **5b** respectively) were employed. For the B tethered route, (*R*)- and (*S*)-phenylalaninol (**5c** and **5d**) and (*R*)- and (*S*)-phenylglycinol (**5e** and **5f**) were used. The six amino alcohols thus generate a series where the hydrophobic moieties occupy different zones above and below the plane of the heterocycle relative to the ribose.



Scheme 1. Synthesis of Conformationally Restricted Adenosines

(i) Vilsmeier's reagent, $CHCl_3$, reflux, 3 h, 90%; (ii) saturated methanolic NH_3, 4 °C, 16 h then 2,2-dimethoxypropane, *p*-TsOH, acetone, 24 °C, 45 min, 91%; (iii) TBDMSCl, imidazole, DMF, 35 °C, 16 h, 72%; (iv) Hunig's base, EtOH, 70 °C, 16 h, 92–99%; (v) **6a-f**, MsCl, Hunig's base, CH_2Cl_2, 0–24°C, 16 h, 46-65%; (vi) **7a–f**, HCO_2H:H_2O (7:3), 24 °C, 3 h, 30-76%.

Table 2. K_i values of Binding to Adenosine A_1 Receptors from Rat Brain and Adenosine A_{2A} Receptors from Rat Striata[7]

Compound	R^1	R^2	R^3	R^4	K_i (A_1) μM	K_i (A_{2A}) μM	K_i (A_{2A})/ K_i (A_1)
8a 8-(*R*)-methy-7-(*R*)-phenyl	Me	H	H	Ph	12.6 ± 1.1	55.5 ± 32.8	4.4
8b 8-(*S*)-methyl-7-(*S*)-phenyl	H	Me	Ph	H	11.2 ± 1.6	45%, 10^{-3} M[a]	~70
8c 8-(*R*)-benzyl	Bz	H	H	H	2.23 ± 0.31	13.5 ± 8.8	6
8d 8-(*S*)-benzyl	H	Bz	H	H	2.99 ± 0.38	57.1 ± 22.7	19
8e 8-(*R*)-phenyl	Ph	H	H	H	3.82 ± 0.41	17.5 ± 4.8	4.6
8f 8-(*S*)-phenyl	H	Ph	H	H	4.54 ± 0.47	189 ± 37.8	42

[a] 10^{-3} M.maximum concentration tested.

Binding to adenosine A_1 receptors was observed with the following rank order: **8c** = **8d** = **8e** = **8f** > **8a** = **8b** (Table 2). In the compounds based on PIA, **8c** and **8d** in which the methyl from PIA was tethered in the ring bound more strongly to the A_1 receptor than **8a** and **8b**, containing the free methyl group. The phenyl substituted compounds from (*R*)- and (*S*)-phenylglycinol (**8e** and **8f**, respectively) bound at the same affinity to the A_1 receptor as the benzyl substituted compounds **8c** and **8d**. The 8-(*S*)-phenyl **8d** and 8-(*S*)-benzyl **8f** had reduced A_{2A} binding resulting in an increase A_1 selectivity compared to the corresponding 8-(*R*) isomers. All diimidazo[1,2-*c*:4',5'-*e*]pyrimidines were A_1 selective as opposed to the previous bishydrophobic compounds **2**–**4**, where A_{2A} selectivity was found in some cases.[5]

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4. Moos, W. M.; Szotek, D. S.; Bruns, R. F. *J. Med. Chem.* **1985**, *28*, 1383.
5. Peet, N. P.; Lentz, N. L.; Sunder, S.; Dudley, M. W.; Ogden, A. M. L. *J. Med. Chem.* **1992**, *35*, 3263.
6. Spectral data for **8a**: 7,8-Dihydro-3-ribofuranose-7-(*R*)-phenyl-8-(*R*)-methyl-3H-diimidazo[1,2-*c*:4',5'-*e*] pyrimidine. ^{1}H NMR (600 MHz, CD_3OD) δ 1.51 (d, 3H, *J* = 6.6 Hz, CH_3), 3.78 (dd, 1H, *J* = 3.2 Hz, 12.4 Hz, $CH_{5'}$), 3.90 (dd, 1H, *J* = 3.2 Hz, 12.4 Hz, $CH_{5'}$), 4.17 (q, 1H, *J* = 3 Hz, $CH_{4'}$) 4.23 (p, 1H, *J* = 6.8 Hz, CH_3CH), 4.34 (dd, 1H, *J* = 3.2 Hz, 5.1 Hz, $CH_{3'}$), 4.65 (t, 1H, *J* = 5.3 Hz, $CH_{2'}$), 5.13 (d, 1H, CH_3CHCH), 5.98 (d, 1H, $CH_{1'}$), 7.39–7.52 (m, 5H, CH_{arom}), 7.71 (s, 1H, H_5), 8.25 (s, 1H, H_2). ^{13}C NMR (150 MHz, CD_3OD) δ 22.1 (CH_3), 63.1 ($C_{5'}$), 71.2 (C_7), 72.3 (C_8), 72.5 ($C_{3'}$), 76.1 ($C_{2'}$), 87.7 ($C_{4'}$), 90.7 ($C_{1'}$), 121.1 (C_{1a}), 127.8 (C_{ortho}), 129.9 (C_{para}), 130.6 (C_{meta}), 140.5 (C_2), 141.7 (C_{ipso}), 145.7 (C_5), 145.9 (C_{3a}), 151.3 (C_{10}). MS (electrospray) *m/z* 384 (M^+ + 1), 418 (M^+ + 35). Anal. calcd for ($C_{19}H_{21}N_5O_4.3/2H_2O$): C, 55.6; H, 5.8; N, 17.0. Found C, 56.0; H, 5.5; N, 16.9.
   Spectral data for **8b**: 7,8-Dihydro-3-ribofuranose-7-(*S*)-phenyl-8-(*S*)-methyl-3H-diimidazo[1,2-*c*:4',5'-*e*] pyrimidine. ^{1}H NMR (600 MHz, CD_3OD) δ 1.50 (d, 3H, *J* = 6.6 Hz, CH_3), 3.78 (dd, 1H, *J* = 3.2 Hz, 12.4 Hz, $CH_{5'}$), 3.90 (dd, 1H, *J* = 3.2 Hz, 12.4 Hz, $CH_{5'}$), 4.17 (q, 1H, *J* = 3 Hz, $CH_{4'}$) 4.23 (p, 1H, *J* = 6.7 Hz, CH_3CH), 4.34 (dd, 1H, *J* = 3.2 Hz, 5.1 Hz, $CH_{3'}$), 4.65 (t, 1H, *J* = 5.3 Hz, $CH_{2'}$), 5.13 (d, 1H, CH_3CHCH), 5.98 (d, 1H, $CH_{1'}$), 7.39–7.52 (m, 5H, CH_{arom}), 7.72 (s, 1H, H_5), 8.25 (s, 1H, H_2). ^{13}C NMR (150 MHz, CD_3OD) δ 22.2 (CH_3), 63.2 ($C_{5'}$), 71.2 (C_7), 72.3 (C_8), 72.5 ($C_{3'}$), 76.1 ($C_{2'}$), 87.6 ($C_{4'}$), 90.7 ($C_{1'}$), 121.2 (C_{1a}), 127.8 (C_{ortho}), 129.9.7 (C_{para}), 130.6 (C_{meta}), 140.6 (C_2), 141.7 (C_{ipso}), 145.7

(C_5), 145.9 (C_{3a}), 151.3 (C_{10}). MS (electrospray) *m/z* 384 (M^+ + 1), 418 (M^+ + 35). Anal. calcd for ($C_{19}H_{21}N_5O_4.3/2H_2O$): C, 55.6; H, 5.8; N, 17.0. Found C, 56.0; H, 5.6; N, 17.0.

Spectral data for **8c**: 7,8-Dihydro-3-ribofuranose-8-(*R*)-(phenylmethyl)-3H-diimidazo[1,2-*c*:4',5'-*e*] pyrimidine. ^{1}H NMR (200 MHz, CD_3OD) δ 2.78 (dd, 1H, *J* = 8.1 Hz, 13.5 Hz, PhCH*H*), 3.09 (dd, 1H, *J* = 4.9 Hz, 13.5 Hz, PhCH*H*), 3.70 (dd, 1H, *J* = 3.1 Hz, 12.4 Hz $CH_{5'}$), 3.85 (dd, 1H, *J* = 3.1 Hz, 12.4 Hz $CH_{5'}$), 3.95 (dd, 1H, *J* = 7.0 Hz, 11.2 Hz, NCH*H*), 4.07-4.18 (m, 2H, NCH*H*, $CH_{4'}$), 4.27 (dd, 1H, *J* = 3.0 Hz, 5.1 Hz $CH_{3'}$), 4.53–4.58 (m, 2H, CH_2CHCH_2, $CH_{2'}$), 5.87 (d, 1H, $CH_{1'}$), 7.20–7.28 (m, 5H, CH_{arom}), 7.88 (s, 1H, H_5), 8.12 (s, 1H, H_2). ^{13}C NMR (50 MHz, CD_3OD) δ 43.0 (CH_2Ph), 51.9 (C_7), 63.2 ($C_{5'}$), 67.1 (C_8), 72.3 ($C_{3'}$), 76.1 ($C_{2'}$), 87.7 ($C_{4'}$), 90.7 ($C_{1'}$), 120.8 (C_{1a}), 127.6 (C_{para}), 129.5 (C_{meta}), 130.6 (C_{ortho}), 138.8 (C_2), 140.3 (C_{ipso}), 145.7 (C_5), 146.1 (C_{3a}), 151.9 (C_{10}). MS (electrospray) *m/z* 384 (M^+ + 1), 418 (M^+ + 35). Anal. calcd for ($C_{19}H_{21}N_5O_4.3/2H_2O$): C, 55.6; H, 5.8; N, 17.0. Found C, 55.9; H, 5.6; N, 16.9.

Spectral data for **8d**: 7,8-Dihydro-3-ribofuranose-8-(*S*)-(phenylmethyl)-3H-diimidazo[1,2-*c*:4',5'-*e*] pyrimidine. ^{1}H NMR (200 MHz, CD_3OD) δ 2.78 (dd, 1H, *J* = 8.3 Hz, 13.6 Hz, PhCH*H*), 3.12 (dd, 1H, *J* = 4.9 Hz, 13.6 Hz, PhCH*H*), 3.70 (dd, 1H, *J* = 3.1 Hz, 12.4 Hz $CH_{5'}$), 3.85 (dd, 1H, *J* = 3.1 Hz, 12.4 Hz $CH_{5'}$), 3.94 (dd, 1H, *J* = 7.0 Hz, 11.2 Hz, NCH*H*), 4.07–4.18 (m, 2H, NCH*H*, $CH_{4'}$), 4.27 (dd, 1H, *J* = 3.0 Hz, 5.1 Hz $CH_{3'}$), 4.50–4.58 (m, 2H, CH_2CHCH_2, $CH_{2'}$), 5.87 (d, 1H, $CH_{1'}$), 7.17–7.27 (m, 5H, CH_{arom}), 7.88 (s, 1H, H_5), 8.12 (s, 1H, H_2). ^{13}C NMR (50 MHz, CD_3OD) δ 42.9 (CH_2Ph), 51.9 (C_7), 63.1 ($C_{5'}$), 66.9 (C_8), 72.3 ($C_{3'}$), 75.9 ($C_{2'}$), 87.6 ($C_{4'}$), 90.6 ($C_{1'}$), 120.8 (C_{1a}), 127.5 (C_{para}), 129.4 (C_{meta}), 130.5 (C_{ortho}), 138.7 (C_2), 140.3 (C_{ipso}), 145.7 (C_5), 146.0 (C_{3a}), 151.9 (C_{10}). MS (electrospray) *m/z* 384 (M^+ + 1). Anal. calcd for ($C_{19}H_{21}N_5O_4.3/2H_2O$): C, 55.6; H, 5.8; N, 17.0. Found C, 56.0; H, 5.6; N, 16.9.

Spectral data for **8e**: 7,8-Dihydro-3-ribofuranose-8-(*R*)-(phenyl)-3H-diimidazo[1,2-*c*:4',5'-*e*] pyrimidine. ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.55 (dd, 1H, *J* = 3.0 Hz, 12.1 Hz $CH_{5'}$), 3.67 (dd, 1H, *J* = 3.0 Hz, 12.5 Hz $CH_{5'}$), 3.95–4.20 (m, 3H, $CH_{3'}$, $CH_{4'}$, NCH*H*), 4.48 (t, 1H, *J* = 5.6 Hz, $CH_{2'}$), 4.81 (t, 1H, *J* = 11.2 Hz, NCH*H*), 5.44 (m, 1H, CH_2CH), 5.88 (d, 1H, J = 5.6 Hz, $CH_{1'}$), 7.32–7.40 (m, 5H, CH_{arom}), 8.34 (s, 1H, H_5), 8.46 (s, 1H, H_2). ^{13}C NMR (50 MHz, DMSO-d_6) δ 54.4 (C_7), 61.2 ($C_{5'}$), 64.4 (C_8), 70.3 ($C_{3'}$), 74.2 ($C_{2'}$), 85.8 ($C_{4'}$), 87.8 ($C_{1'}$), 118.0 (C_{1a}), 126.9 (C_{ortho}), 127.8 (C_{para}), 128.7 (C_{meta}), 140.3 (C_2), 141.9 (C_{ipso}), 144.7 (C_5), 146.8 (C_{3a}), 150.1 (C_{10}). MS (electrospray) *m/z* 370 (M^+ + 1). Anal. calcd for ($C_{18}H_{19}N_5O_4.3/2H_2O$): C, 54.5; H, 5.6; N, 17.6. Found C, 54.7; H, 5.2; N, 17.3.

Spectral data for **8f**: 7,8-Dihydro-3-ribofuranose-8-(*S*)-(phenyl)-3H-diimidazo[1,2-*c*:4',5'-*e*] pyrimidine. ^{1}H NMR (200 MHz, CD_3OD) δ 3.72 (dd, 1H, *J* = 3.0 Hz, 12.5 Hz $CH_{5'}$), 3.85 (dd, 1H, *J* = 3.0 Hz, 12.5 Hz $CH_{5'}$), 4.07 (dd, 1H, *J* = 8.1 Hz, 11.2 Hz, NCH*H*), 4.12 (q, 1H, $CH_{4'}$), 4.30 (dd, 1H, *J* = 3.3 Hz, 5.1 Hz $CH_{3'}$), 4.60 (br t, 1H, $CH_{2'}$), 4.68 (t, 11.2 Hz, NCH*H*), 5.40 (dd, 1H, *J* = 7.9 Hz, 10.7 Hz, CH_2CH), 5.93 (d, 1H, $CH_{1'}$), 7.27–7.37 (m, 5H, CH_{arom}), 8.03 (s, 1H, H_5), 8.19 (s, 1H, H_2). ^{13}C NMR (50 MHz, CD_3OD) δ 55.9 (C_7), 63.1 ($C_{5'}$), 68.3 (C_8), 72.2 ($C_{3'}$), 76.2 ($C_{2'}$), 87.7 ($C_{4'}$), 90.7 ($C_{1'}$), 120.8 (C_{1a}), 127.8 (C_{ortho}), 128.9 (C_{para}), 129.9 (C_{meta}), 141.0 (C_2), 144.0 (C_{ipso}), 145.6 (C_5), 146.9 (C_{3a}), 152.5 (C_{10}). MS (electrospray) *m/z* 370 (M^+ + 1), 404 (M^+ + 35). Anal. calcd for ($C_{18}H_{19}N_5O_4.3/2H_2O$): C, 54.5; H, 5.6; N, 17.6. Found C, 54.5; H, 5.4; N, 17.3.

7. [^{3}H]R-PIA binding to A_1 receptors in whole rat brain membranes and [^{3}H]CGS21680 binding to A_{2A} receptors in rat striatal membranes was measured at 23 °C.[8] Values are means ± SEM from two experiments, each with triplicate determinations. K_i values were calculated using the Cheng-Prusoff equation, assuming K_d values of 1 nM and 15.5 nM for [^{3}H]R-PIA and [^{3}H]CGS21680, respectively.

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