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Cyclic AMP Phosphodiesterase 4 Isoenzyme Inhibitory Activity of (*R*)- and (*S*)-Isomer of 7-Methyl- or 8-Alkyl-4,5,7,8-tetrahydroimidazo[2,1-*i*]-purin-5-one

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We investigated the structure–activity relationship of the (*R*)- and (*S*)-isomer of 7-methyl- and 8-alkyl-tetrahydroimidazo[2,1-*i*]purines for phosphodiesterase 4 (PDE4) inhibitors. (*S*)-8-Isopropyl-3,4-dipropyl-imizazo[2,1-*i*]purine (*S*)-2c exhibited both potent and selective PDE4 inhibitory activity.

Key words phosphodiesterase 4 inhibitor; condensed purine; imidazo[2,1-*i*]purine

cAMP-phosphodiesterase 4 (PDE4) is found in airway smooth muscle and inflammatory cells, and selective inhibitors of PDE4 are promising drugs for the treatment of asthma and inflammation.[1—3)]

During investigations of heterocycle condensed purines to obtain selective PDE4 inhibitors, we found that some heterocycle [*i*]-condensed purines inhibited PDE4 more effectively than did [*a*]-, [*b*]-, [*c*,*d*]- and [*g*,*h*]-condensed purines.[4)] Among heterocycle [*i*]-condensed purines, 3,4-dipropyl-4,5,7,8-terahydro-3*H*-imidazo[2,1-*i*]purine-5-one (**1**) showed selective PDE4 inhibitory activity and lacked some of the adverse reactions of xanthine derivatives.[5)] Additionally, **1** did not show emetic action, which is one in the development of PDE4 inhibitors. In the course of subsequent investigations, we found that tetrahydroimidazo[2,1-*i*]purines (*dl*-**2a**, *dl*-**2d** and *dl*-**3a**, *dl*-**3d**), with a methyl group at 7- or 8-position, although causing a decline in selectivity, affect the PDE4 inhibitory activities more strongly than does **1**.[4)]

The present study was undertaken to determine whether there is a difference between the PDE4 inhibitory activities of (*R*)- and (*S*)-isomers of 8-alkyl- (**2a**—**c**, **3a**—**c**) and those of 7-methyl-imidazo[2,1-*i*]purines (**2d**, **3d**). We report here on the synthesis and PDE4 inhibitory activity of imidazo[2,1-*i*]purines.

Chemistry Substituted imidazo[2,1-*i*]purines were prepared using the pathway we previously described.[4,5)] Treatment of 3-propyl-6-(1,2,4-triazol-4-yl)purine (**4**) or 6-chloro-3-propylpurine (**7**) with each of the (*R*)- and (*S*)-isomers of 2-amino-1-propanol, 2-amino-1-butanol, 2-amino-3-methyl-1-butanol, and 1-amino-2-propanol yielded the corresponding 6-(hydroxyethylamino)purines (**5a**—**d**, **8a**—**d**), which were used for the next reaction without purification. Ring closure of **5a**—**d** and **8a**—**d** with thionyl chloride yielded (*R*)- and (*S*)-isomers of imidazo[2,1-*i*]purines (**6a**—**d**, **3a**—**d**). *N*3-Propylation of **6a**—**d** with propyl bromide in the presence of potassium carbonate afforded the corresponding (*R*)- and (*S*)-isomers of **2a**—**d** (Chart 1).

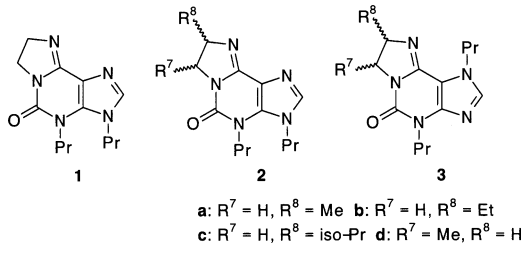
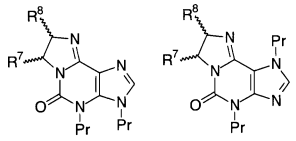


Fig. 1

BIOLOGICAL RESULTS AND DISCUSSION

The inhibitory activities of the imidazo[2,1-*i*]purines (**2a**—**d**, **3a**—**d**) against PDE1 and PDE4 isoenzymes from guinea-pig brain and PDE3 from guinea-pig heart were measured according to published methods.[6)] The results are shown in Table 1 together with the PDE inhibitory activities

Table 1



	R^7	R^8	IC_{50} (μM)		
			PDE1	PDE3	PDE4
(*R*)-**2a**	H	Me	22	20	1.4
(*S*)-**2a**	H	Me	20	30	5.6
(*R*)-**2b**	H	Et	11	76	1.8
(*S*)-**2b**	H	Et	5.6	65	1.7
(*R*)-**2c**	H	iso-Pr	16	47	4
(*S*)-**2c**	H	iso-Pr	21	>100	0.2
(*R*)-**2d**	Me	H	31	85	>100
(*S*)-**2d**	Me	H	37	50	0.6
(*R*)-**3a**	H	Me	28	37	1.8
(*S*)-**3a**	H	Me	13	23	1
(*R*)-**3b**	H	Et	8.9	59	1.6
(*S*)-**3b**	H	Et	4.5	27	1.4
(*R*)-**3c**	H	iso-Pr	9.3	>100	7.6
(*S*)-**3c**	H	iso-Pr	1.7	18	0.8
(*R*)-**3d**	Me	H	78	90	>100
(*S*)-**3d**	Me	H	51	>100	8.5
1	—	—	29	54	1.6
IBMX	—	—	6.8	2.3	6.8
Amrinone	—	—	>100	53	>100
Rolipram	—	—	>100	>100	3.7

Data are mean of three experiments.

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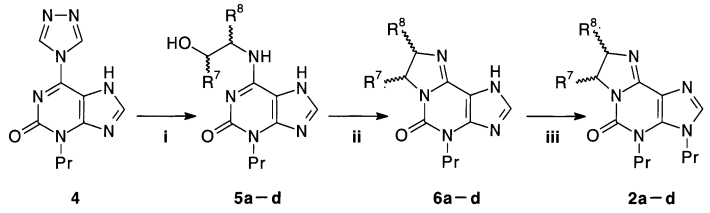
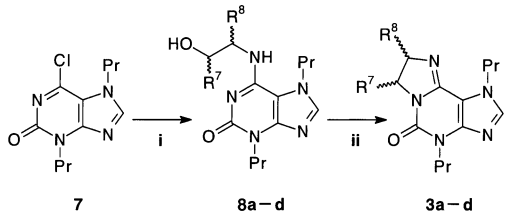


a: R^7 = H, R^8 = Me; **b:** R^7 = H, R^8 = Et
c: R^7 = H, R^8 = *iso*-Pr; **d:** R^7 = Me, R^8 = H



Reagents: (i) (2*R*)-, (2*S*)-2-amino-1-propanol, (2*R*)-, (2*S*)-2-amino-1-butanol, (2*R*)-, (2*S*)-2-amino-3-methyl-1-butanol or (2*R*)-, (2*S*)-1-amino-2-propanol, pyridine; (ii) $SOCl_2$, $CHCl_3$; (iii) Pr-Br, K_2CO_3, DMF

Chart 1

Table 2. Physicochemical Data for Tetrahydroiomidazo[2,1-*i*]purines (**6**, **2**, **3**)

Compd. no.	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
				C	H	N
(*R*)-**6a**	282—283	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.58)	6.48 (6.50)	30.02 (29.95)
(*S*)-**6a**	282—283	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.69)	6.48 (6.53)	30.02 (30.11)
(*R*)-**6b**	258—259	AcOEt–MeOH	$C_{12}H_{17}N_5O$	58.28 (58.33)	6.93 (7.01)	28.32 (28.31)
(*S*)-**6b**	253—254	AcOEt–MeOH	$C_{12}H_{17}N_5O$	58.28 (58.21)	6.93 (6.95)	28.32 (28.45)
(*R*)-**6c**	250—251	AcOEt–MeOH	$C_{13}H_{19}N_5O$	59.75 (59.82)	7.33 (7.19)	26.80 (26.84)
(*S*)-**6c**	255—256	AcOEt–MeOH	$C_{13}H_{19}N_5O$	59.75 (59.70)	7.33 (7.35)	26.80 (26.77)
(*R*)-**6d**	237—238	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.71)	6.48 (6.66)	30.02 (29.94)
(*S*)-**6d**	238—239	AcOEt–MeOH	$C_{11}H_{15}N_5O$	56.64 (56.68)	6.48 (6.51)	30.02 (30.11)
(*R*)-**2a**	125—126	pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.33)	7.69 (7.84)	25.43 (25.50)
(*S*)-**2a**	128—129	pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.21)	7.69 (7.78)	25.43 (25.38)
(*R*)-**2b**	120—121	pet. Ether	$C_{15}H_{23}N_5O$	62.26 (62.39)	8.01 (7.92)	24.20 (24.41)
(*S*)-**2b**	120—121	pet. Ether	$C_{15}H_{23}N_5O$	62.26 (62.13)	8.01 (7.99)	24.20 (24.34)
(*R*)-**2c**	126—127	pet. Ether	$C_{16}H_{25}N_5O$	63.34 (63.43)	8.31 (8.14)	23.08 (23.15)
(*S*)-**2c**	126—127	pet. Ether	$C_{16}H_{25}N_5O$	63.34 (63.31)	8.31 (8.47)	23.08 (23.01)
(*R*)-**2d**	Oil	—	$C_{14}H_{21}N_5O$		275.1746 275.1749[a)]	
(*S*)-**2d**	Oil	—	$C_{14}H_{21}N_5O$		275.1746 275.1744[a)]	
(*R*)-**3a**	129—130	pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.19)	7.69 (7.71)	25.43 (25.52)
(*S*)-**3a**	131—132	pet. Ether	$C_{14}H_{21}N_5O$	61.07 (61.17)	7.69 (7.61)	25.43 (25.54)
(*R*)-**3b**	117—118	pet. Ether	$C_{15}H_{23}N_5O$	62.26 (62.24)	8.01 (8.13)	24.20 (24.36)
(*S*)-**3b**	118—119	pet. Ether	$C_{15}H_{23}N_5O$	62.26 (62.09)	8.01 (8.12)	24.20 (24.34)
(*R*)-**3c**	129—130	pet. Ether	$C_{16}H_{25}N_5O$	63.34 (63.46)	8.31 (8.28)	23.08 (23.25)
(*S*)-**3c**	127—128	pet. Ether	$C_{16}H_{25}N_5O$	63.34 (63.28)	8.31 (8.40)	23.08 (23.22)
(*R*)-**3d**	Oil	—	$C_{14}H_{21}N_5O$		275.1746 275.1745[a)]	
(*S*)-**3d**	Oil	—	$C_{14}H_{21}N_5O$		275.1746 275.1747[a)]	

a) High resolution MS spectra data.

of **1**, non-selective PDE inhibitor IBMX, PDE3 inhibitor amrinone and PDE4 inhibitor rolipram, which were have been reported earlier.[7)]

The PDE4 inhibitory activities of (*R*)-**2a**, (*R*)-**2b** and (*S*)-**2b** on 3,4-dipropyl-imizazo[2,1-*i*]purines (**2a**—**d**) were as active that of as **1**. Moreover, (*S*)-**2c** and (*S*)-**2d** inhibited PDE4 more strongly than **1** or rolipram. The PDE1 inhibitory activity of (*R*)- and (*S*)-isomers of **2b** was stronger than that of **1**, while (*R*)- and (*S*)-isomers of **2a**, **2c** and **2d** were as active as **1**. PDE3 inhibitory activities of (*R*)- and (*S*)-isomers of **2b**, **2c** and **2d** were weaker than or the same as those of **1**. (*S*)-**2c** did not show a definite effect on PDE3 isoenzymes, although (*R*)- and (*S*)-isomers of **2a** showed somewhat stronger PDE3 inhibitory activities than did **1**.

The PDE4 inhibitory activities of (*S*)-**3a** and (*S*)-**3c** on 1,4-dipropyl-imizazo[2,1-*i*]purines (**3a**—**d**) were more potent than those of **1**, and those of other compounds similar except for (*R*)-**3c**, and (*R*)- and (*S*)-isomers of **3d**. However, (*R*)- and (*S*)-isomers of **3a**—**c** apart from (*R*)-**3c** induced an increase in PDE1 and PDE3 inhibitory activities.

In general, the PDE4 inhibitory potency of **2a**—**d** and **3a**—**d** was higher in (*S*)-isomers than (*R*)-isomers, except that of **2a**. A potential difference in PDE4 inhibitory activities between (*S*)- and (*R*)-isomers was observed for **2d** and **3d**, which have a methyl group at the 7-position. Further, the PDE1 and PDE3 inhibitory activity of (*S*)-**2d** was similar to those of **1**, and inhibited PDE4 more strongly than did **1**.

In our studies on the (*R*)- and (*S*)-isomers of 3,4-dipropyltetrahydroimidazo[2,1-*i*]purines (**2a**—**d**) and 1,4-dipropyltetrahyrdoimidazo[2,1-*i*]purines (**3a**—**d**), we found 8-isopropyl derivatives (*S*)-**2c** to be an effective inhibitor for PDE4. This finding indicates that the substituents on the dihydroimidazole ring and *N*3-propyl group may be important for the expression of potent and selective PDE4 inhibitory activities.

MATERIALS AND METHODS

Melting points were measured on a Yanagimoto micro melting points hot stage apparatus and were uncorrected. Infrared spectra (IR) were determined with a Horiba FT-720 spectrometer or a Hitachi 270-30 spectrometer. Mass spectra (MS) were measured with a JEOL-DX300. Nuclear magnetic response spectrometer (^{1}H-NMR) was recorded with a JEOL EX 90A. Chemical shifts are quoted in parts per million

Table 3. Spectral Data for Tetrahydroiomidazo[2,1-*i*]purines (**6**, **2**, **3**)

	IR (KBr) cm^{-1}	$[\alpha]_D$ (c=0.5)[b)]	^{1}H-NMR ($CDCl_3$) δ;
(*R*)-**6a**	3423, 1707, 1649	72.9	1.00 (3H, t, *J*=7.3 Hz), 1.54 (3H, d, *J*=6.1 Hz), 1.84 (2H, sext. *J*=7.3 Hz), 3.82 (1H, dd, *J*=5.7, 10.2 Hz), 4.03—4.60 (2H, m), 6.01 (1H, br s), 7.73 (1H, s).
(*S*)-**6a**	3450, 1707, 1678	−71.8	1.00 (3H, t, *J*=7.3 Hz), 1.54 (3H, d, *J*=6.1 Hz), 1.84 (2H, sext. *J*=7.3 Hz), 3.82 (1H, dd, *J*=5.7, 10.2 Hz), 4.03—4.60 (2H, m), 6.03 (1H, br s), 7.73 (1H, s).
(*R*)-**6b**	3448, 1709, 1684	82.8	1.00 (3H, t, *J*=7.3 Hz), 1.14 (3H, t, *J*=7.1 Hz), 1.63—2.04 (4H, m), 3.90—4.52 (4H, m), 7.94 (1H, s), 11.81 (1H, br s).
(*S*)-**6b**	3448, 1709, 1684	−79.6	1.00 (3H, t, *J*=7.3 Hz), 1.14 (3H, t, *J*=7.0 Hz), 1.63—2.04 (4H, m), 3.91—4.52 (4H, m), 7.94 (1H, s), 11.77 (1H, br s).
(*R*)-**6c**	3448, 1706, 1675	71.9	0.91—1.20 (9H, m), 1.61—2.04 (3H, m), 4.01—4.41 (5H, m), 7.93 (1H, s), 11.81 (1H, br s).
(*S*)-**6c**	3448, 1713, 1672	−68.8	0.91—1.20 (9H, m), 1.63—2.04 (3H, m), 4.01—4.41 (5H, m), 7.93 (1H, s), 11.85 (1H, br s).
(*R*)-**6d**[a)]	3448, 1712, 1675	86.2	0.99 (3H, t, *J*=7.2 Hz), 1.64 (3H, d, *J*=6.4 Hz), 1.82 (2H, sext. *J*=7.2 Hz), 3.78 (1H, dd, *J*=4.6, 11.4 Hz), 4.06—4.40 (2H, m), 4.74—5.04 (1H, m), 7.95 (1H, s), 11.33 (1H, br s).
(*S*)-**6d**[a)]	3405, 1707, 1655	−88.8	0.99 (3H, t, *J*=7.2 Hz), 1.64 (3H, d, *J*=6.4 Hz), 1.82 (2H, sext. *J*=7.2 Hz), 3.78 (1H, dd, *J*=4.4, 11.4 Hz), 4.06—4.41 (2H, m), 4.74—5.04 (1H, m), 7.95 (1H, s), 11.52 (1H, br s).
(*R*)-**3a**	1689, 1653	98.6	0.95 (3H, t, *J*=7.2 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.37 (3H, d, *J*=6.4 Hz), 1.64—2.04 (4H, m), 3.50 (1H, dd, *J*=7.0, 10.4 Hz), 3.86—4.28 (6H, m), 7.45 (1H, s).
(*S*)-**3a**	1685, 1653	−97.9	0.95 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.37 (3H, d, *J*=6.4 Hz), 1.64—2.04 (4H, m), 3.50 (1H, dd, *J*=7.2, 10.4 Hz), 3.86—4.28 (6H, m), 7.45 (1H, s).
(*R*)-**3b**	1682, 1655	82.1	0.94 (3H, t, *J*=7.4 Hz), 0.97 (3H, t, *J*=7.4 Hz), 1.56—2.04 (6H, m), 3.57 (1H, dd, *J*=6.7, 10.4 Hz), 3.86—4.32 (6H, m), 7.44 (1H, s).
(*S*)-**3b**	1685, 1654	−79.6	0.94 (3H, t, *J*=7.4 Hz), 0.97 (3H, t, *J*=7.4 Hz), 1.57—2.04 (6H, m), 3.57 (1H, dd, *J*=6.6, 10.3 Hz), 3.86—4.32 (6H, m), 7.44 (1H, s).
(*R*)-**3c**	1697, 1649	129.7	0.89—1.03 (12H, m), 1.56—2.04 (5H, m), 3.64 (1H, dd, *J*=7.2, 10.4 Hz), 3.77—4.26 (6H, m), 7.43 (1H, s).
(*S*)-**3c**	1687, 1649	−132.4	0.89—1.03 (12H, m), 1.56—2.04 (5H, m), 3.64 (1H, dd, *J*=7.2, 10.4 Hz), 3.77—4.26 (6H, m), 7.43 (1H, s).
(*R*)-**3d**	1693, 1655	63.1	0.95 (3H, t, *J*=7.3 Hz), 1.44 (3H, d, *J*=6.0 Hz), 1.65—2.05 (4H, m), 3.63 (1H, dd, *J*=4.3, 13.7 Hz), 3.87—4.48 (6H, m), 7.46 (1H, s).
(*S*)-**3d**	1712, 1668	−60.4	0.95 (3H, t, *J*=7.3 Hz), 1.44 (3H, d, *J*=6.0 Hz), 1.65—2.05 (4H, m), 3.63 (1H, dd, *J*=4.3, 13.7 Hz), 3.87—4.48 (6H, m), 7.46 (1H, s).
(*R*)-**2a**	1687, 1652	112.2	0.94 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.34 (3H, d, *J*=6.4 Hz), 1.64—2.04 (4H, m), 3.47 (1H, dd, *J*=6.8, 10.4 Hz), 3.86—4.28 (6H, m), 7.42 (1H, s).
(*S*)-**2a**	1686, 1654	−108.7	0.94 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.34 (3H, d, *J*=6.4 Hz), 1.64—2.04 (4H, m), 3.47 (1H, dd, *J*=6.8, 10.4 Hz), 3.86—4.28 (6H, m), 7.42 (1H, s).
(*R*)-**2b**	1686, 1655	103.3	0.86—1.06 (9H, m), 1.55—2.04 (6H, m), 3.57 (1H, dd, *J*=6.6, 10.3 Hz), 3.86—4.29 (6H, m), 7.44 (1H, s).
(*S*)-**2b**	1686, 1655	−97.7	0.86—1.06 (9H, m), 1.56—2.04 (6H, m), 3.56 (1H, dd, *J*=6.6, 10.3 Hz), 3.86—4.29 (6H, m), 7.44 (1H, s).
(*R*)-**2c**	1687, 1649	124.8	0.80—1.03 (12H, m), 1.60—2.04 (5H, m), 3.61 (1H, dd, *J*=6.9, 9.9 Hz), 3.76—4.38 (6H, m), 7.41 (1H, s).
(*S*)-**2c**	1687, 1648	−126.5	0.80—1.03 (12H, m), 1.60—2.04 (5H, m), 3.61 (1H, dd, *J*=7.0, 9.9 Hz), 3.76—4.38 (6H, m), 7.41 (1H, s).
(*R*)-**2d**	1691, 1658	80.0	0.95 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.42 (3H, d, *J*=5.9 Hz), 1.64—2.04 (4H, m), 3.62 (1H, dd, *J*=4.4, 13.9 Hz), 3.86—4.55 (6H, m), 7.42 (1H, s).
(*S*)-**2d**	1689, 1660	−75.8	0.95 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.2 Hz), 1.42 (3H, d, *J*=5.9 Hz), 1.64—2.04 (4H, m), 3.62 (1H, dd, *J*=4.4, 13.9 Hz), 3.86—4.55 (6H, m), 7.42 (1H, s).

a) ^{1}H-NMR spectra were recorded in DMSO-d_6. *b*) $[\alpha]_D$ was measured using MeOH as solvent.

(ppm) with tetramethyl silane as an internal standard. Specific rotation ($[\alpha]_D$) was measured with a JASCO DPI-370 automatic digital polarimeter using MeOH as solvent. Microanalyses were performed in the Micro Analytical Laboratory of our institute. The imidazo[2,1-*i*]purines [(*R*)-, (*S*)-**2a**—**d** and (*R*)-, (*S*)-**3a**—**d**] were synthesized according to the published procedures.[4] The amino alcohol used for synthesis of 6-hydroxyalkyl compounds was prepared with the method of Mckennin and Meyers.[7] IBMX and amrinone for PDE activity assay were purchased from Sigma Chemicals Co., and rolipram synthesized according to method of Crossland.[8] PDE activity was assayed by the method of Thompson and Appleman.[9] Physicochemical data of the imidazo[2,1-*i*]purines [(*R*)-, (*S*)-**6a**—**d**, (*R*)-, (*S*)-**2a**—**d** and (*R*)-, (*S*)-**3a**—**d**] are summarized in Tables 2 and 3.

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