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HIGH SELECTIVITY OF NOVEL ISOGUANOSINE ANALOGUES FOR THE ADENOSINE A_1 RECEPTOR

Vasu Nair*[1] and Allen J. Fasbender
Department of Chemistry, The University of Iowa
Iowa City, Iowa 52242

and

Leonard P. Miller and Jennifer L. Bruce
Department of CNS Studies, Gensia Pharmaceuticals Inc.
San Diego, California 92121

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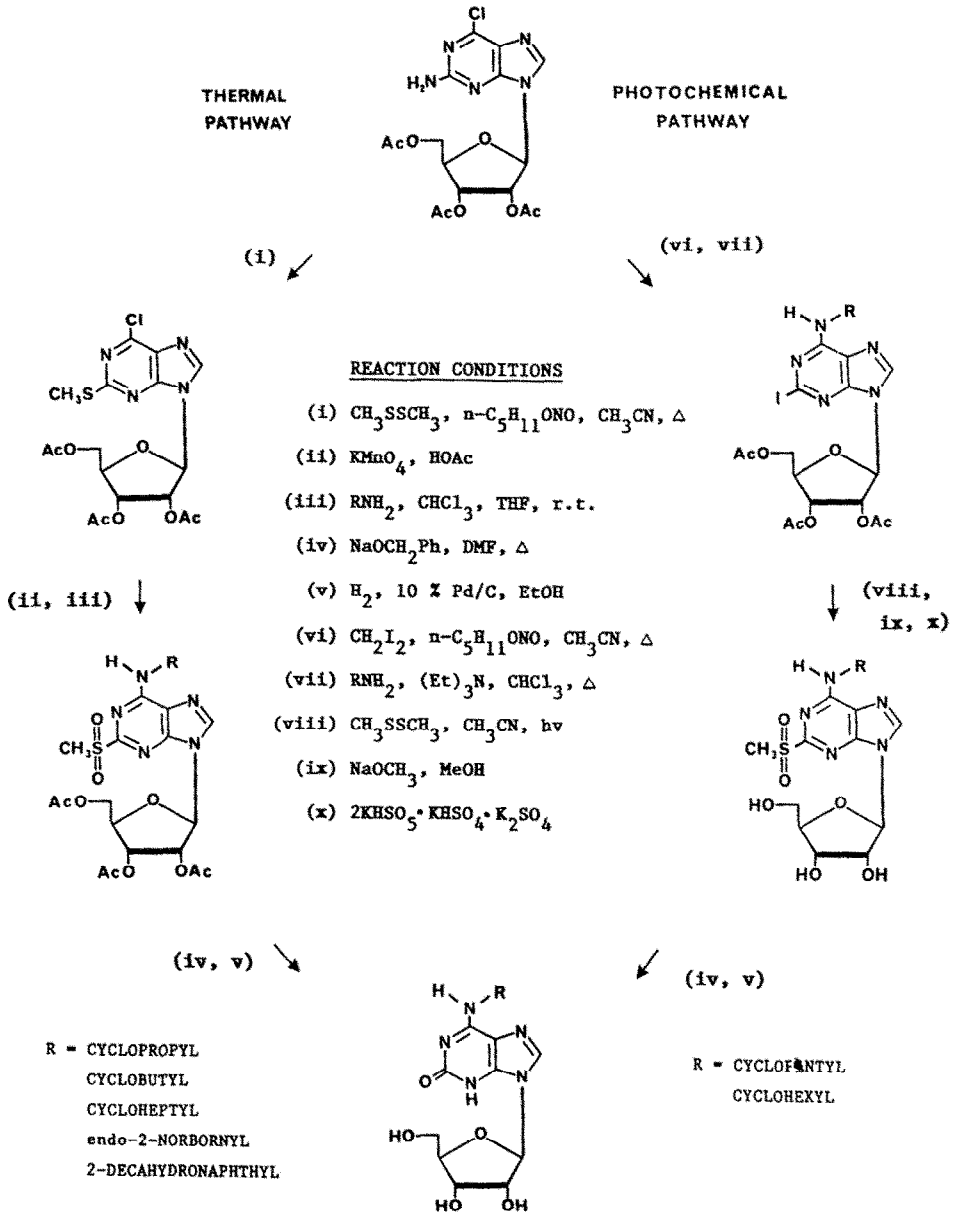
Abstract. N^6-Cyclosubstituted isoguanosines have been synthesized in high yields from 2-amino-6-chloropurine ribonucleoside. Compounds containing five- and six-membered rings at the N^6-position exhibit high adenosine A_1 receptor affinity and excellent A_2/A_1 selectivity.

The natural nucleoside, adenosine, apparently exerts many of its physiological effects through the involvement of extracellular receptors referred to as A_1 and A_2 which are distributed throughout a wide variety of tissues in the human system.[2-6] The A_1 and A_2 receptors have been associated with a decrease or an increase, respectively, of intracellular levels of cyclic AMP. Adenosine has been approved clinically for the treatment of paroxysmal supraventricular tachycardia; however, its therapeutic usefulness is limited by poor receptor selectivity, and a very short metabolic lifetime because of its hydrolytic deamination by the ubiquitous mammalian enzyme, adenosine deaminase.[7] The natural minor nucleoside, isoguanosine (2-hydroxyadenosine) has been reported to have hypotensive properties greater than adenosine and to be metabolically resistant to deamination by adenosine deaminase.[8-10] There has been considerable interest in developing adenosine receptor agonists that have better pharmacological properties than adenosine both in terms of metabolic stability and in terms of A_1, A_2 receptor binding and specificity. Adenosine agonists with high selectivity for the A_1 or A_2 receptor are of potential interest as antiarrhythmics, anticonvulsants, antihypertensives and as other therapeutic agents.[11-15] Several recent reports of highly

active and selective nucleoside systems for both A_1 and A_2 receptors have focused attention on 2- and/ or N^6-modified adenosines.[16-19] However, very few examples of agonists which are isoguanosine analogues are known. This communication reports on the synthesis and A_1, A_2 receptor binding activities of novel N^6-cyclosubstituted isoguanosine compounds.

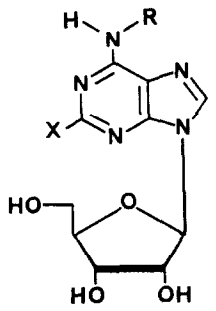
The synthetic design for the target compounds incorporated a series of N^6-cyclic and bicyclic substitutions on the parent isoguanosine molecule to increase receptor affinity and selectivity through hydrophobic and related interactions. Synthetic approaches to the target compounds utilized 2-amino-6-chloropurine ribonucleoside triacetate as the starting compound (Scheme 1). Thermally-induced radical deamination-thioalkylation on this precursor yielded the 2-methylthio compound which was converted <u>via</u> its sulfone[20] to the target compounds as shown in Scheme 1 (-14 % overall yield). Alternatively, a synthetic plan utilizing a photochemical thioalkylation step[21] was also used for some of the analogues (-11 % overall yield).[22]

The affinities of the isoguanosine analogues[23] and related compounds in A_1, A_2 receptor binding are summarized in Table 1. Comparisons are also shown in the table with adenosine, N^6-cyclopentyladenosine, N^6-cyclohexyladenosine, NECA, and isoguanosine. The data clearly show that a number of the N^6-cyclosubstituted isoguanosines show excellent A_1 agonist activity. There is a clear trend in terms of correlation of ring size with receptor binding for the monocyclosubstituted compounds with the highest selectivity being obtained for the five- and six-membered ring compounds (**7**, **8**). Decreases in specificity occurs on either side of this N^6-ring size with greater loss in selectivity for the seven membered ring compound (see **6** and **9**). The decalin system **11**, showed poor A_1 agonist activity and poor A_2/A_1 selectivity. However, the <u>endo</u>-norbornyl compound, **10**, showed excellent A_1 receptor binding (35 nm) and high A_2/A_1 selectivity (2,286). Its receptor binding selectivity is comparable to that of another one of our compounds, 2-iodo-N^6-cyclopentyladenosine, **5**. Our results suggest that


THERMAL PATHWAY
PHOTOCHEMICAL PATHWAY
(i)
(vi, vii)
(ii, iii)
(viii, ix, x)
(iv, v)
(iv, v)
REACTION CONDITIONS
(i) CH_3SSCH_3, n-$C_5H_{11}ONO$, CH_3CN, Δ
(ii) $KMnO_4$, HOAc
(iii) RNH_2, $CHCl_3$, THF, r.t.
(iv) $NaOCH_2Ph$, DMF, Δ
(v) H_2, 10 % Pd/C, EtOH
(vi) CH_2I_2, n-$C_5H_{11}ONO$, CH_3CN, Δ
(vii) RNH_2, $(Et)_3N$, $CHCl_3$, Δ
(viii) CH_3SSCH_3, CH_3CN, hv
(ix) $NaOCH_3$, MeOH
(x) $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
R = CYCLOPROPYL
CYCLOBUTYL
CYCLOHEPTYL
endo-2-NORBORNYL
2-DECAHYDRONAPHTHYL
R = CYCLOPENTYL
CYCLOHEXYL

Scheme 1

Table 1. Affinities of Isoguanosine Analogues and Related Compounds in A_1, A_2 Receptor Binding Assays[a]



COMPOUNDS	X	R	K_i (nM) A_1	A_2	A_2/A_1
1	H	H	12.8[b]	37[b]	2.9[9]
2	H		0.6	462	783[24]
3	H		1.3	363	277[24]
4	OH	H	94	331	3.5[9]
5	I		20	40,000	2,000
6	OH		55	15,000	273
7	OH		19	7,500	395
8	OH		40	15,000	375
9	OH		70	6,000	85.7
10	OH		35	80,000	2,286
11	OH		30,000	140,000	4.7

a) A_1 affinities were determined in [^{3}H]-N^6-cyclohexyladenosine binding to rat brain membranes and A_2 affinities were determined in [^{3}H]-5'-N-ethylcarboxamidoadenosine (NECA) binding to rat striatal membranes.

b) The binding affinities for adenosine cannot be determined directly and these are estimated values (see ref. 9).

there may be specific binding involving both the 2- and 6-positions of the adenosine system involving the A_1 receptor. Hydrophobic groups at the N^6 position, particularly those with five- or six-membered mono or bicyclic rings, appear to interact hydrophobically and be accomodated into the S1, S2 and S3 subregions[25] within the A_1 receptor. Certain electronegative groups capable of hydrogen bonding at the 2-position (e.g. Cl, I, in some cases, O) may contribute to enhanced binding to the A_1 receptor and/ or a decreased affinity for the A_2 receptor. Alternatively, the absence of large hydrophobic groups on nitrogen or oxygen at the 2-position (e.g. 2-phenylamino, 2-phenethoxy) contribute to decreasing A_2 receptor affinity. Other studies to further delineate the structural requirements of the hydrogen bonding recognition site and the hydrophobic pocket in terms of biological activity are currently in progress.

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22. Direct displacement of the sulfone intermediate with hydroxide ions gave low yields (30-40%) only of the target compounds. Photochemical hydration of the 2-iodo-N^6-cyclosubstituted purine nucleosides also resulted in low yields of products (< 20%, cf. Nair, V.; Young, D.A. *J. Org. Chem.* **1985**, 50, 406).

23. Representative Physical Data. 6-(endo-2-Norbornylamino)-2-oxo-9-(ß-D-ribofuranosyl)purine: m.p. 179-186 °C (dec.); ^{1}H-NMR (Me_2SO-d_6) δ 1.38-2.17 (m, 11H), 3.58 (m, 2H), 3.92 (m, 1H), 4.09 (m, 1H), 4.50 (t, 1H), 4.96-5.48 (m, 3H), 5.68 (d, 1H), 7.96 (m, 2H); UV (EtOH) 249 nm (ϵ 11,542), 284 nm (ϵ 10,635), 302 nm (ϵ 9,579); IR (KBr) 1634 cm^{-1}. 6-Cyclohexylamino-2-oxo-9-(ß-D-ribofuranosyl)purine: m.p. 170-172 °C; ^{1}H-NMR (Me_2SO-d_6) δ 1.32-1.88 (m, 11H), 3.60 (m, 2H), 3.95 (m, 1H), 4.10 (m, 1H), 4.49 (m, 1H), 5.12-5.38 (m, 3H), 5.69 (d, 1H), 7.64 (m, 1H), 7.97 (s, 1H); UV (EtOH) 248 nm (ϵ 9,290), 284 nm (ϵ 7,770), 302 nm (ϵ 7,990); IR (KBr) 1643 cm^{-1}.

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