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N^6-(5,6-EPOXYNORBORNYL)ADENOSINE ANALOGS AS A_1 ADENOSINE AGONISTS

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Abstract: A range of related adenosines and 5′-N-ethylcarboxamidoadenosines bearing oxygenated substituents in the N^6 position have been synthesised and evaluated as A_1-adenosine receptor ligands. Compound **9** emerged with potent affinity (EC_{50} = 1.1 nM).

Adenosine (marketed as Adenocard™) is currently used for the therapy and diagnosis of certain cardiac arrhythmias such as paroxysmal supraventricular tachycardia.[1] As a result of adenosine's extremely short duration of action up to 35% of tachycardias recur within two minutes of administration.[1] In an attempt to identify longer acting A_1-adenosine receptor agonists, we recently designed and synthesised ENAdo.[2] Whilst ENAdo proved to be a potent A_1-adenosine receptor agonist, the more active 2S-*endo* isomer was found to degrade upon standing to a polar by-product.[2] This degradation is believed to involve N1 cyclising with the epoxide. In order to obtain more stable analogs of ENAdo we have targeted a range of related adenosines in which the N^6-substituent was less reactive or the reactivity of N1 was masked (by oxidation to the corresponding N-oxide). It has been shown that 5′-N-ethylcarboxamidoadenosine (NECA) has increased potency for the A_1-adenosine receptor and metabolic stability as compared to adenosine.[3] Therefore, we have also targeted the corresponding N^6-substituted NECA derivatives. All compounds were tested for their potency to inhibit cAMP accumulation in DDT_1 MF-2 cells, an A_1-adenosine receptor mediated response.[4]

N^6-Substituted adenosines were prepared by alkylation of the appropriate amine with 6-chloropurine riboside. N^6-Substituted NECAs were prepared by alkylation of 2′,3′-O-isopropylidene-N-ethyl-6-chloropurine-5'uronamide[5] followed by deprotection using aqueous acid. The required amines were either commercially available or were synthesised by literature procedures.[2,6] The alkenes of the N^6-(5-norbornen-2-yl) compounds (**1** and **7**) and N^6-(3-cyclohexenyl) compounds (**3** and **9**) were transformed to the corresponding epoxides by treatment with dimethyldioxirane. Peracid oxidation (*m*-CPBA) was used in the synthesis of compound **6** as it effected epoxidation and N1 oxide formation simultaneously.

In general, the epoxides proved to be 3–5 times less potent than the corresponding alkenes in the series of adenosines and NECAs. NECAs possessed significantly greater affinity for the A_1-adenosine receptor than the corresponding adenosines. This ranged from around threefold for the N^6-(5,6-epoxynorborn-2-ylmethyl)

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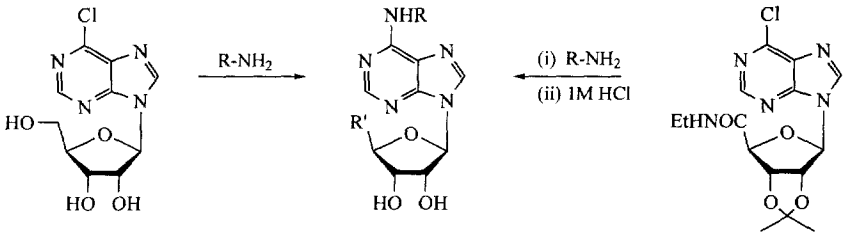
compounds (compare **2** and **8**) to nearly sevenfold for the N^6-(cyclohex-3-enyl) compounds (compare **3** and **9**). Of the other oxygenated N^6-substituents, only morpholinoethyl possessed significant potency with an EC_{50} of 18 nM. N^6-(*exo*-5,6-Epoxynorborn-2-yl)-N-ethylcarboxamidoadenosine-1-oxide (**6**) was found to have quite poor affinity for the A_1-adenosine receptor (EC_{50} = 217 nM). All of the target molecules proved to be stable on the shelf—no degradation was observed upon standing over several months.

Table 1.



	R	R'	N1	Yield[a]	EC_{50} (nM)[b]
CPA	cyclopentyl	-CH_2OH			2.8 ± 0.8 (7)
1	5-norbornen-2-ylmethyl	-CH_2OH		73	188 ± 22 (4)
2	5,6-epoxynorborn-2-ylmethyl	-CH_2OH		75	537 ± 77 (6)
3	3-cyclohexenyl	-CH_2OH		98	7.2 ± 1.7 (3)
4	3,4-epoxycyclohexyl	-CH_2OH		35	37 ± 6 (7)
5	tetrahydro-2*H*-pyranylmethyl	-CH_2OH		57	3092 ± 588 (3)
6	5,6-epoxynorborn-2-yl	-CONHEt	N-oxide	59	217 ± 42 (4)
7	5-norbornen-2-ylmethyl	-CONHEt		97	35 ± 9 (5)
8	5,6-epoxynorborn-2-ylmethyl	-CONHEt		60	159 ± 36 (4)
9	3-cyclohexenyl	-CONHEt		91	1.1 ± 0.4 (7)
10	3,4-epoxycyclohexyl	-CONHEt		25	5.9 ± 1.6 (6)
11	tetrahydro-2*H*-pyranylmethyl	-CONHEt		43	641 ± 53 (6)
12	furfurylmethyl	-CONHEt		92	262 ± 34 (4)
13	morpholino-N-ethyl	-CONHEt		85	18 ± 4 (5)

[a]All compounds were purified by column chromatography. Microanalyses obtained on final products were within 0.4% of the calculated values. [b]DDT_1 MF-2 cells were incubated with 1 μM (-) isoproterenol, 50 mM rolipram and varying concentrations of the agonists for 10 min at 37 °C. The concentration of each agonist that inhibited (-) isoproterenol-stimulated cAMP accumulation by 50% (EC_{50}) was calculated from nonlinear regression analysis. Basal cAMP accumulated was typically less than 5% of the total accumulated in the presence of 1 μM (-) isoproterenol. Data are the mean ± SE and the number in parentheses are the experimental N.

References and Notes

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