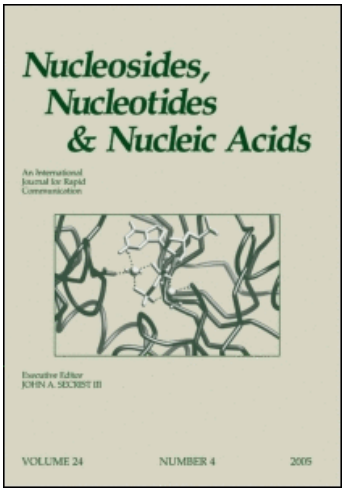

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Biological Activity of 1-Deazapurine Nucleosides: Role of Deoxycytidine Kinase?

AM. Bergman[a]; G. Cristalli[b]; S. Vittori[b]; J. Wang[c]; S. Eriksson[c]; Gj Peters[a]
[a] Dept. Oncology, University Hospital VU, Amsterdam, The Netherlands [b] Dept. Vet. Med. Chem., Swed. Univ. Agric. Sci., Uppsala, Sweden [c] Dip. Scienze Chim., Univ. Camerino, Italy

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BIOLOGICAL ACTIVITY OF 1-DEAZAPURINE NUCLEOSIDES : ROLE OF DEOXYCYTIDINE KINASE?

AM. Bergman§, G Cristalli#, S Vittori#, J Wang@, S Eriksson@, GJ Peters §*,.
§, Dept. Oncology, University Hospital VU, PO Box 7057, 1007 MB Amsterdam, the Netherlands; @Dept. Vet. Med. Chem., Swed. Univ. Agric. Sci., Uppsala, Sweden, #Dip. Scienze Chim., Univ. Camerino, Italy.

ABSTRACT: Several 1-deazapurine nucleosides were tested for their biological activity; anti-HIV-1, cytotoxicity and inhibition of adenosine deaminase (ADA). A2780 human ovarian cancer cells and the deoxycytidine kinase (dCK) deficient variant AG6000, used to determine whether dCK plays a role in their activation, showed a similar sensitivity to the analogs. This is in line with substrate specificity tests, which revealed a very low affinity of dCK.

Several 1-deazapurine nucleosides were modified at the amino group (R), the 2-position (R1) and 3'-position (R2)[1](FIG. 1). Since deoxyadenosine (dA) is a substrate for dCK, they were tested for their biological activity in A2780 ovarian cancer cells and the dCK deficient variant AG6000[2], for their substrate specificity for dCK, anti-HIV-1, and ADA inhibitory activity.

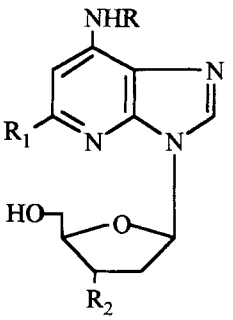

FIG. 1

Experimental: Synthesis of the derivatives was described previously[1]. Growth inhibition was assessed using the sulphorhodamide B protein assay using 72 hr exposure to the drugs[2]. The phosphoryl transfer assay using 100 μM Υ^{32}P-ATP as phosphate donor and pure recombinant human dCK was performed as previously described[3,4]. The activity of 5 ng dCK with 100 μM dCyd as a substrate was set at 100%. Anti-HIV-1, and ADA inhibitory activity were determined as described previously[1].

TABLE 1. Anti-HIV-1, ADA inhibitory activity, and growth inhibition of A2780 cells and its dCK deficient variant, of 1-deazapurine nucleosides.

Cpd (AAG)	R	R_1	R_2	ADA inhib.K_i	anti-HIV-1 [a]EC_{50}	C8166 cells [b]IC_{50}	A2780 cells [b]IC_{50}	AG6000 cells [b]IC_{50}
125	cC5H9	Cl	OH	>100	0.8	7	32	50
129	cC5H9	H	OH	22	40	400	>60	>60
137	cC5H9	Cl	H	>100	20	50	15	45
140	cC5H9	H	H	>100	80	500	>60	>60
143	cC7H13	Cl	OH	>100	0.2	5	22	23
144	cC7H13	H	OH	42	30	80	>60	>60
165	cC7H13	Cl	H	>100	0.8	8	12	17

[a]EC50 represents the concentration of drug which reduced HIV-1 gp120 plague formation by 50% in infected cell cultures. [b]IC_{50} represents the concentration of drugs which reduced cell growth by 50%. All values in μM.

RESULTS AND DISCUSSION: The chloro-substituted compounds were the most active against A2780, AG6000 and C8166 cells (TABLE 1.). They were more active than their respective non-substituted compounds. However, AAG129 and AAG144 were the strongest ADA inhibitors. The long chain substituted compounds were more cytotoxic than their respective short chain substituted compounds. Moreover, AAG143 and AAG165 had the highest anti-HIV-1 activity. Since AAG137 was more active in A2780 than in AG6000, some involvement of dCK may be present, but the difference is small. The substrate specificity of the dA analogs was less than 1% compared to deoxycytidine, while dA had a 500% substrate specificity. Therefore dCK is unlikely to play a major role in the biological activity of these compounds. In conclusion, the 2-chlorinated, 2'3'-dideoxy 1-deazapurines showed a relatively good activity in both wild type and dCK deficient cells. The 2'-deoxy-compounds were all inactive. The higher lipophilicity of AAG143 and AAG165 may partly explain their somewhat greater potency.

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