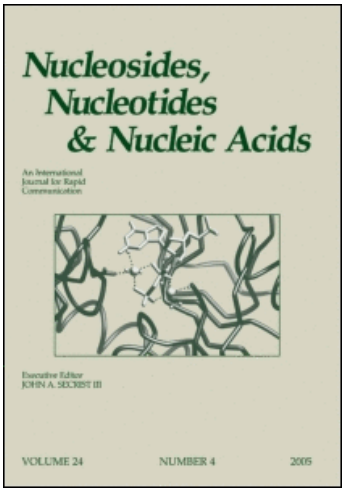

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Synthesis and Antitumor Activity of 6-Substituted Purine and Deazapurine Nucleosides

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SYNTHESIS AND ANTITUMOR ACTIVITY OF 6-SUBSTITUTED PURINE AND DEAZAPURINE NUCLEOSIDES

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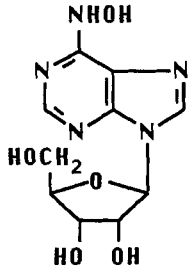
Abstract. A series of 6-hydroxylamino purine and deazapurine nucleosides were synthesized and tested for their antitumor and adenosine deaminase inhibitory activity. All the examined molecules displayed an *in vitro* activity comparable to that of the reference compounds HAPR and ara-A, their ID_{50} ranging from 0.9μM (**9**) to ~100μM (**5**).

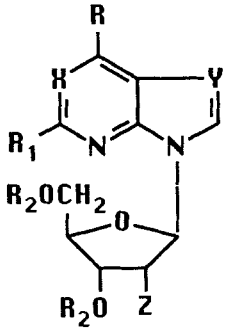
The growth-inhibitory effect and toxicity of 6-hydroxylaminopurine and of its 9-ß-D-ribofuranosyl derivative (HAPR) are well documented.[1,2] HAPR is readily deaminated in vivo by the enzyme adenosine deaminase (ADA) with formation of inosine and free hydroxylamine, which induces blood cell hemolysis.



HAPR

Since the presence of a chlorine atom in position 2 of adenosine makes the compound resistant to ADA we prepared the

TABLE 1. *In vitro* antitumor activity by hydroxylamino and nitro nucleosides.



compd	R	R1	X	Y	R2	R3	P388 [a] ID50, μM [b]	L1210 [a] ID50, μM [b]
1	NHOH	Cl	N	N	OH	OH	75.5	94.4
2	NHOH	Cl	N	N	H	OTol	10.4	4.9
3	NHOH	H	CH	N	OH	OH	4.9	5.3
4	NHOH	Cl	CH	N	OH	OH	60.0	91.0
5	NHOH	H	CH	N	H	OH	67.6	>100.0
6	NHOH	Cl	CH	N	H	OTol	4.3	4.8
7	NHOH	H	CH	CH	H	OH	35.2	39.9
8	NO_2	Cl	CH	N	OH	OH	1.5	0.9
9	NO_2	H	CH	N	H	OH	20.6	14.9
10	NO_2	H	CH	CH	H	OH	32.7	41.5
11	NHOH	H	CH	N	H	OTol	16.9	22.5
HAPR	NHOH	H	N	N	OH	OH	1.6	3.1
Ara-A							16.8	21.7

[a] 5×10^{-5} Exponentially growing cells were exposed to varying concentration of drug for 72 h. The cells were then counted with Coulter Counter. [b] Inhibitory dose 50 is the concentration of the compound in the culture media that produces 50% inhibition of the tumor cell growth as compared to the untreated controls.

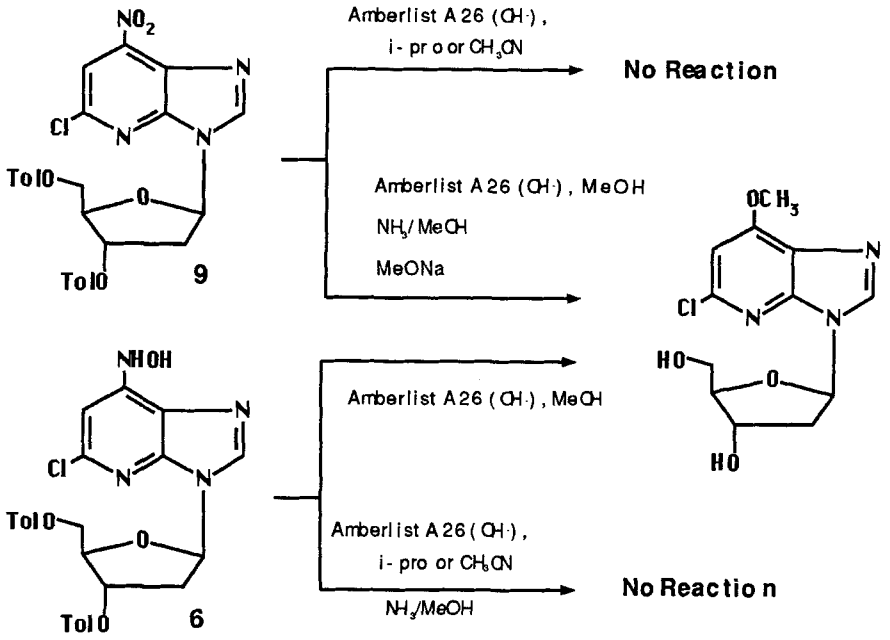


FIG. 1

2-chloro-6-hydroxylamino-9-ß-D-ribofuranosylpurine (**1**) and the corresponding 2'-deoxyribofuranosyl derivative **2**.

Since we have previously reported that 1-deazaadenosine is an inhibitor of ADA,[3] and is also endowed with antitumor activity in vitro,[4] the synthesis of N^6-hydroxylamino derivatives of 1-deazaadenosine was undertaken leading to compounds **3-6, 8, 9, 11** (Table 1).

The synthesis of nitro and hydroxylamino derivatives of 1,7-dideazaadenosine [5] was also carried out to obtain compounds **7** and **10**.

CHEMISTRY

The synthesis of 2-chloro-6-hydroxylamino-9-ß-D-ribofuranosylpurine (**1**) was accomplished in two steps starting from 2,6-dichloro-9-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-purine.[6]

The synthesis of 2-chloro-6-hydroxylamino-9-(2-deoxy-3,5-di-p-toluoyl-ß-D-*erythro*-pentofuranosyl)-purine (**2**) was carried out by treatment of 2,6-dichloro-9-(2-deoxy-3,5-di-p-toluoyl-ß-D-*ery*-

thro-pentofuranosyl)-purine[7] with refluxing ethanolic hydroxylamine. Attempts to remove the toluoyl blocking groups of **6** under many conditions (methanolic ammonia, sodium methylate, triethylamine or Amberlist A26 OH^-) were unsuccessful, leading surprisingly to 6-amino-2-chloro-9-(2-deoxy-ß-D-*erythro*-pentofuranosyl)-purine.

The hydroxylamino derivatives of the 1-deaza and 1,7-dideaza nucleosides (**3-7**) were prepared starting from the corresponding nitro derivatives. The reduction was carried out with sodium hypophosphite in tetrahydrofurane and 5% Pd/C as a catalyst. As in the case of compound **2**, attempts to remove the toluoyl blocking groups, both from the nitro compound **9** and from 5-chloro-7-hydroxylamino-3-(2-deoxy-3,5-di-p-toluoyl-ß-D-*erythro*-pentofuranosyl)-3H-imidazo[4,5-b]pyridine (**6**), under many conditions were unsuccessful as reported in Fig. 1.

Compounds **2** and **6** were tested as still protected nucleosides and in order to clarify the influence of the toluoyl groups on the antitumor activity, the protected derivative **11**, corresponding to the O-detoluoylated nucleoside **5**, was also synthesized and tested.

Details on the syntheses and experimental part are reported elsewhere.[8]

BIOLOGICAL RESULTS

The antitumor activity of the new hydroxylamino derivatives **1-7, 11** and of the nitro derivatives **8-10** was evaluated in vitro in murine leukemia cell lines (P388 and L1210). All the examined molecules displayed an activity comparable to that of the reference compounds HAPR and ara-A, their ID_{50} ranging from 0.9µM (**9**) to ~100µM (**5**). The results are reported in TABLE 1.

The presence of toluoyl groups increases the in vitro activity (**11** $ID_{50} \approx 22.5$ µM versus **5** $ID_{50} > 100$ µM).

Enzymatic tests on adenosine deaminase from calf intestine were also performed. The 6-hydroxylamino derivatives of deazapurines **3-5, 7** and also the blocked compound **11** are inhibitors of ADA whereas the purine derivatives **1** and **2** and the nitro compounds **8-10** are resistant to the enzyme.

In conclusion, the isosteric substitution of the nitrogen atom in position 1 or the disubstitution in position 1 and 7 of purine moiety of HAPR or the introduction of a chlorine atom in position 2 led to compounds which are not affected by ADA while maintaining antitumor activity. In vivo tests are in progress.
Details on the biological results are reported elsewhere.[8]

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