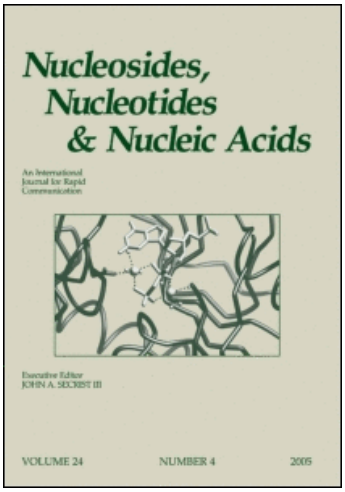

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Synthesis of 3-Deazaclitocwe [2-Amino-3-nitro-4-(β-D-ribofuranosylamino)pyridine] as Cytotoxic Agent

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SYNTHESIS OF 3-DEAZACLITOCINE [2-AMINO-3-NITRO-4-(ß-D-RIBOFURANOSYLAMINO)PYRIDINE] AS CYTOTOXIC AGENT.

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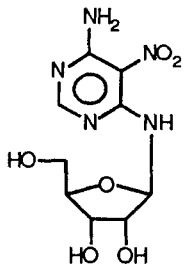
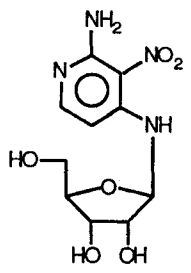
ABSTRACT: The 2-amino-3-nitro-4-(β-D-ribofuranosylamino)pyridine (**2**) was synthesized by glycosylation of 2,4-diamino-3-nitropyridine with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose. The 4-amino-3-nitro-1-(β-D-ribofuranosyl)-2(1H)pyridinimine (**6**) and its tautomer **7** were also obtained. *In vitro* antitumor activity of compounds **2** and **7** was evaluated.

In order to investigate the structure-activity relationships of clitocine (**1**), an antitumor exocyclic nucleoside isolated from *Clitocybe inversa*,[1a,b] we have synthesized its 3-deazaanalogue (**2**) starting from 2,6-diamino-3-nitropyridine[2] (**3**) (Scheme 1).

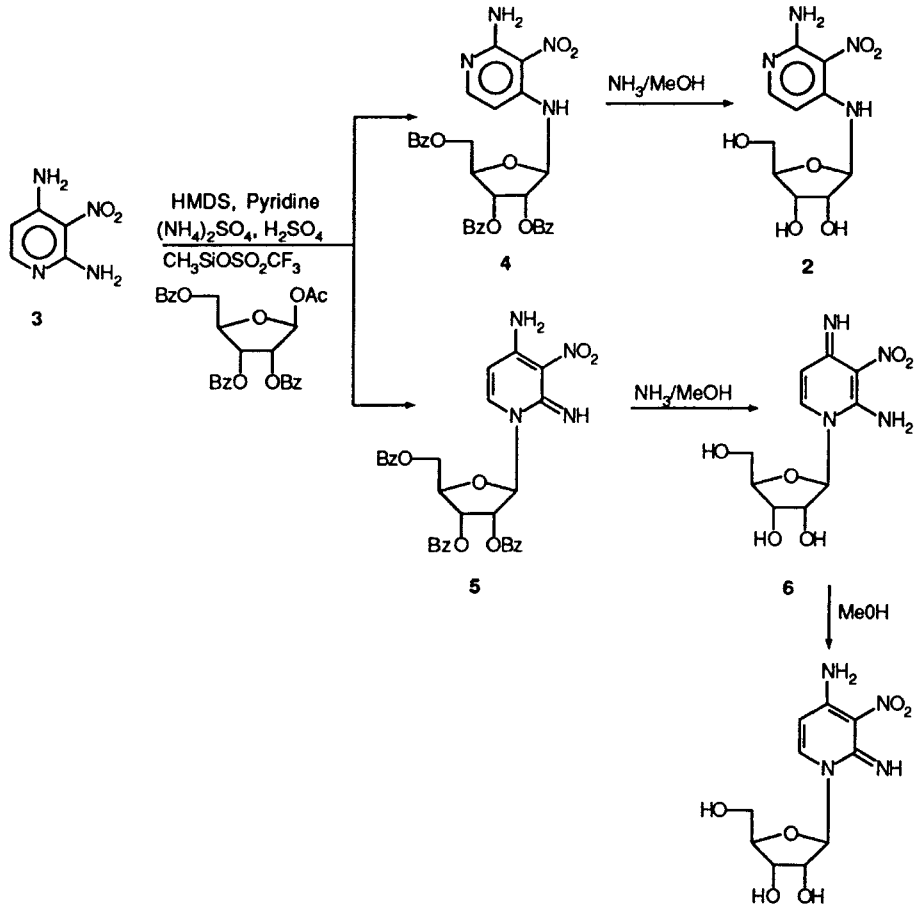


1



2

Compound **3** was silylated and then directly glycosylated with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose to give a complex mixture of glycosylated products. Chromatographic separation of this mixture yielded the blocked nucleosides **4** and **5**.



Scheme 1

Deprotection of compounds **4** and **5** with a saturated solution of ammonia in methanol gave 2-amino-3-nitro-4-(ß-D-ribofuranosyl-amino)pyridine (**2**) and 4-amino-3-nitro-1-(ß-D-ribofuranosyl)-4-(1H)pyridinimine (**6**). Compound **6** was easily converted to the tautomer **7** upon crystallization from methanol.

Compounds **2** and **7** have been evaluated *in vitro* for their ability to inhibit the growth of *murine leukemia* P388 and *human promyelocytic leukemia* HL60. Compound **2** was found to be less active than clitocine (ID_{50} , 8.8 x 10^{-5} M and 7.5 x 10^{-5} M).

Compound **7** (a 3-deazacytosine derivative) appears to be more active against both the tumoral cell lines (ID_{50} , 2.8 x 10^{-5} M and 8.5 x 10^{-6}).

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