IDIL mentor application for M1 or NéoM2
Original nucleoside analogues for cancer treatments

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Introduction

Cytotoxic nucleoside analogs were among the first chemotherapeutic agents to be introduced for the medical treatment of cancer (Fig, 1).[1] This family of compounds has grown to include a variety of purine and pyrimidine nucleoside derivatives with activity in both solid tumours and malignant disorders of the blood.

These agents behave as antimetabolites, compete with physiological nucleosides, and interact with a large number of intracellular targets to induce cytotoxicity (Fig. 2).

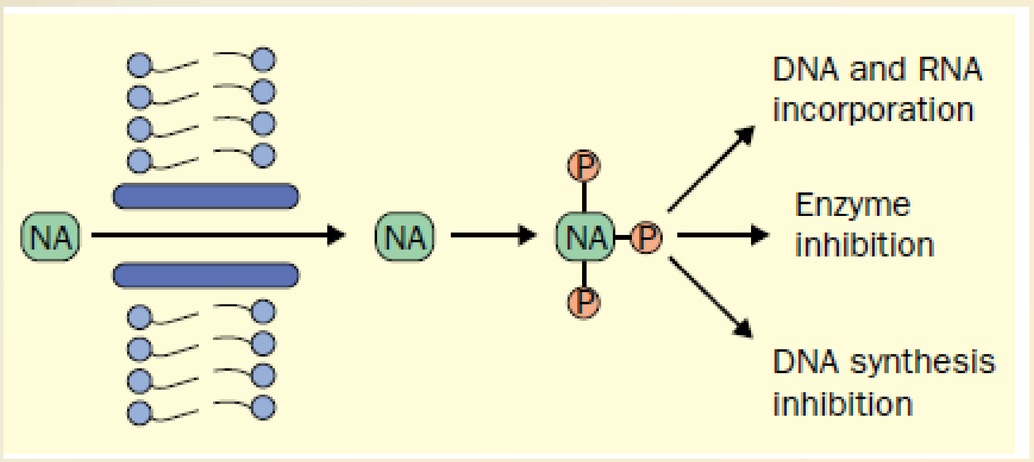


Figure 2. Metabolism and target interactions of nucleoside analogues

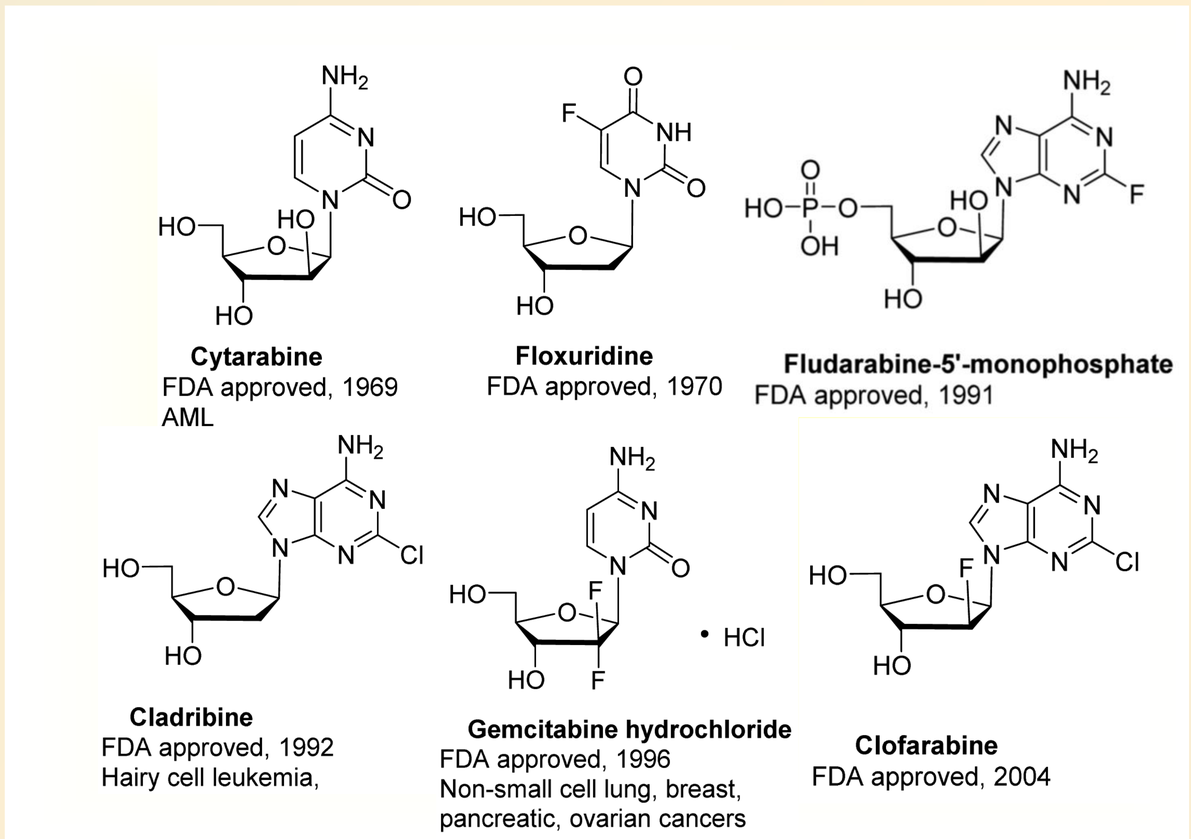


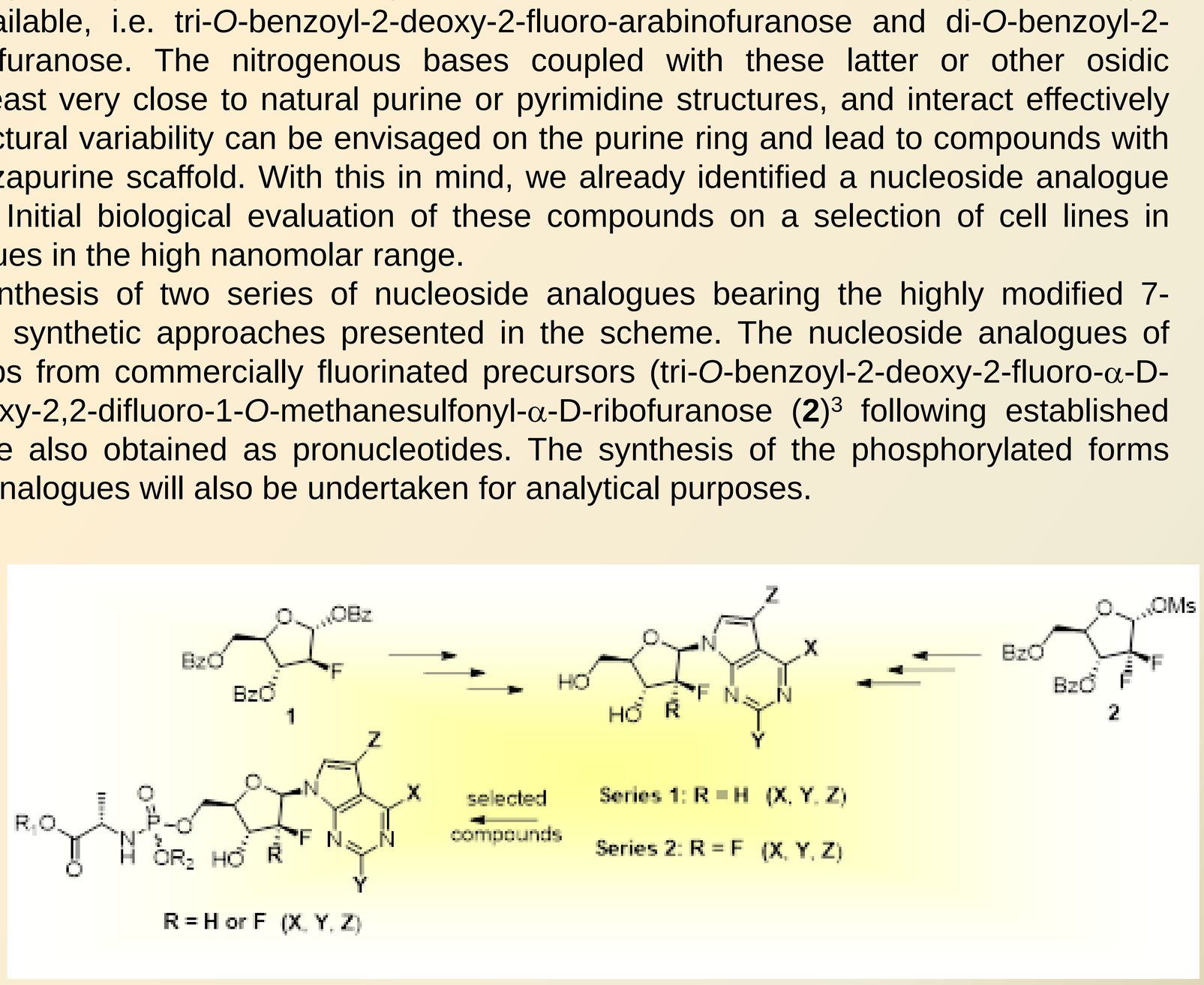
Figure 1. Cytoxic nucleoside analogues

Chemistry

Despite the tremendous development of new cancer therapies small cytotoxic compounds are still, and believed to remain, a cornerstone in the treatment of a large majority of cancer patients. Among the main synthetic pathway to access anticancer nucleoside analogs, the convergent approach which couples a nitrogenous base with a modified sugar precursor allows to access a rich synthetic diversity. Through this pathway, clofarabine and gemcitabine were obtained in a few steps from sugar precursors which are now commercially available, i.e. tri-*O*-benzoyl-2-deoxy-2-fluoro-arabinofuranose and di-*O*-benzoyl-2-deoxy-2,2-difluoro-1-*O*-methanesulfonyl-D-ribofuranose. The nitrogenous bases coupled with these latter or other osidic precursors are generally not modified, or at least very close to natural purine or pyrimidine structures, and interact effectively with cellular targets. However, a peculiar structural variability can be envisaged on the purine ring and lead to compounds with anticancer activities. This concerns the 7-deazapurine scaffold. With this in mind, we already identified a nucleoside analogue and its pronucleotide with biological interest. Initial biological evaluation of these compounds on a selection of cell lines in comparison with gemcitabine, showed IC_{50} values in the high nanomolar range.

Based on the expertise of the team, the synthesis of two series of nucleoside analogues bearing the highly modified 7-deazapurine scaffold will be undertaken. The synthetic approaches presented in the scheme. The nucleoside analogues of series **1** and **2** can be obtained in a few steps from commercially fluorinated precursors (tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (**1**)[2] and di-*O*-benzoyl-2-deoxy-2,2-difluoro-1-*O*-methanesulfonyl-α-D-ribofuranose (**2**)[3] following established protocols. The corresponding prodrugs will be also obtained as pronucleotides. The synthesis of the phosphorylated forms (mono, and 5-triphosphate) of the nucleoside analogues will also be undertaken for analytical purposes.

All new compounds will be evaluated on a selection of cancer cell lines identified as being overall sensitive to already approved drugs of this family. The courses supporting this project are HAC824C and HAC969C (Master 1 BM and Master 2 BM).



Scheme. Synthetic approach

References
- **1 . Galmarini *et al*., *Lancet Oncol,*** 2002**; 3: 415–24.**
- **2. Naus *et al*., *Bioorg. Med. Chem*.,** 2012, **20, 5202-5214.**
- **3. Quintiliani *et al*. *Bioorg. Med. Chem*.,** 2011**, 19, 4338-43456.**