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Biocatalytical diversification of 4'-thiouridine gives access to halogenated pyrimidine and purine derivates

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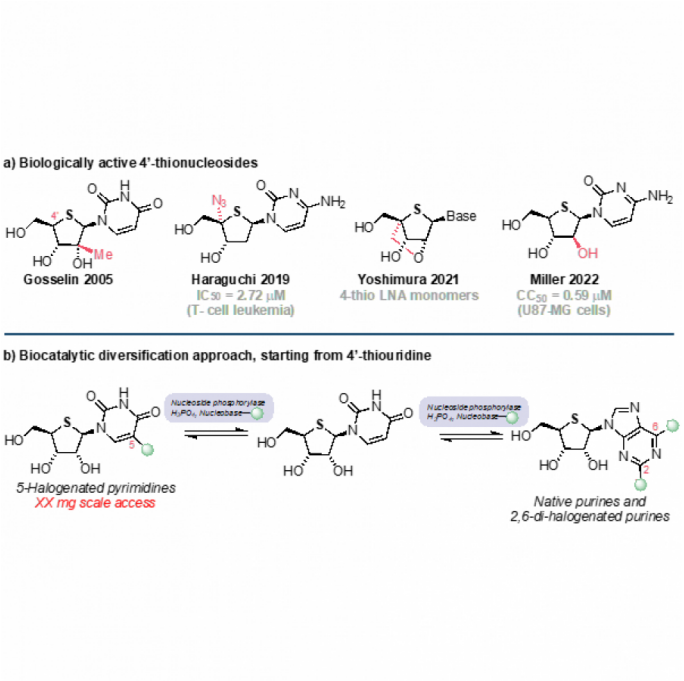
PURPOSE OF THE ABSTRACT

The key role of nucleosides and their analogues in cell proliferation and viral replication renders this class of small molecules prominent drug candidates. While a wide range of nucleoside analogues are approved drugs, only a small number features 4'-modified sugar residues, namely the 4'-C derivates Entecavir and Ticagrelor and the 4´-N derivative Forodesine (De Jonghe and Herdewijn, 2022). Recently, the interest in 4'-thio nucleosides analogues was revived, and a new up-scalable chemical synthesis route for pyrimidine derivates was developed (Guinan et al., 2022). While this methodology gives access to a wide range of 2'-modified 4'-thiopyrimidines, obtaining 4'-thiopurine nucleosides remains a challenge.

To fill this gab, 4'-thiouridine was chosen as starting compound in a proof-of-concept study focussing on biocatalytical diversification of the uracil base. To this end, we applied thermostable nucleoside phosphorylases to cleave this nucleoside analogue into uracil and 4'-thioribo-1'-phosphate. The latter served as substrate for a second reaction, where diverse modified bases were attached. The synthesis of 4'-thio-5-Iodouridine was up-scaled to 100 mg product to enable additional chemical diversification reactions.

While enzymatic synthesis on itself is not new, as Van Draanen and colleagues (Van Draanen et al. 1996) used it before to produce 2'-deoxy-4'-thio-6-Cl-2-aminopurine nucleoside, we were focussing on a directed reaction optimization by characterizing the two reaction steps thermodynamically. This enabled the development of an ecological up-scaling process by avoiding usage of disproportional amounts of substrate.

FIGURES



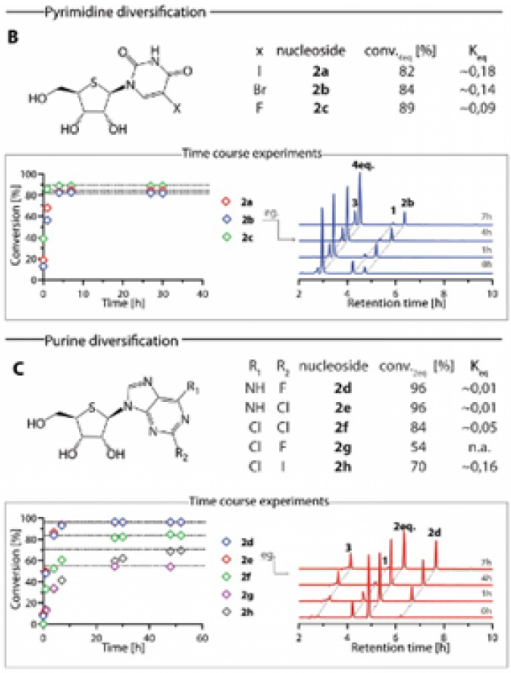


FIGURE 1

Concept

a) Examples of biologically relevant 4-thionucleoside analogues, with furanose ring modification replacing oxygen with sulfur, and additional structural modifications (shown in red); b) Strategy undertaken here to deliver heterobase-modified 4-thionucle

FIGURE 2

Diversification Results

Reaction equilibrium and apparent K_eq of the target molecules. HPLC chromatograms highlight absence of unwanted side products, and the time course shows reaching of reaction equilibrium under chosen conditions for halogenated B) Pyrimidines and C) Purin

KEYWORDS

4'-thianucleoside | Nucleoside Phosphorylase | biocatalysis | drug diversification

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