Synthesis and Antimicrobial Activity of Novel Puromycin Analogs

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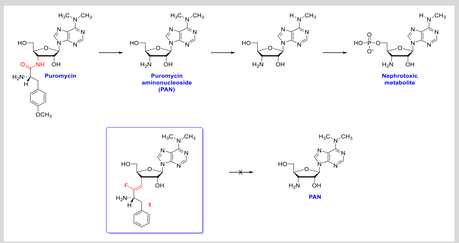
OBJECTIVE

To synthesize a novel puromycin analog lacking the nephrotoxic effects of the parent compound, and to evaluate its antimicrobial activity against selected Gram-positive and Gram-negative microorganisms.

BACKGROUND

Puromycin is a peptidyl nucleoside antibiotic produced by *Streptomyces alboniger* that is capable of inhibiting peptidyl transfer on both prokaryotic and eukaryotic ribosomes.[1] A number of natural peptidyl nucleoside antibiotics share similar properties with puromycin (Figure 1). Commonly used as a basic tool in biochemistry and molecular biology, puromycin has been evaluated as antimicrobial and possible antitumor agent with disappointing results. The major drawback of puromycin is the nephrotoxicity of the metabolite puromycin aminonucleoside (PAN).[2,3] As part of our efforts to improve the toxicity profile of puromycin,[4,5] we have isosterically replaced the amide functionality of puromycin with a fluorovinyl group. The resulting analog is incapable of undergoing metabolism to PAN (Figure 1) but still retains the antimicrobial activity of puromycin.

Figure 1. Nephrotoxicity of puromycin[2,3] and isosteric replacement of the amide functionality



METHODS

The target molecule 1 was synthesized in a 10-step process starting from D-xylose (Scheme 1). The key step of the synthesis was a regio- and stereoselective difluorination/dehydrofluorination of the intermediate ketone 2. The stereochemistry of the resulting fluoride 3 was confirmed by NMR techniques (Figure 2). In preliminary evaluation of antimicrobial activity, the target compound showed antimicrobial activity against *S. epidermidis*, multi-drug resistant *S. aureus* (MRSA), *E. coli*, and *P. aeruginosa* strains (Figure 3).

RESULTS

Scheme 1. Synthesis of 1.

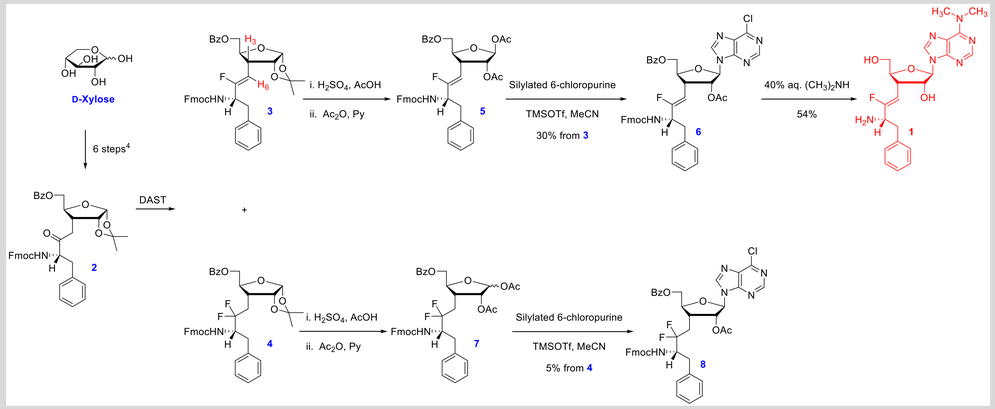


Figure 3. MIC and MBC evaluation of molecule 1 compared to puromycin.

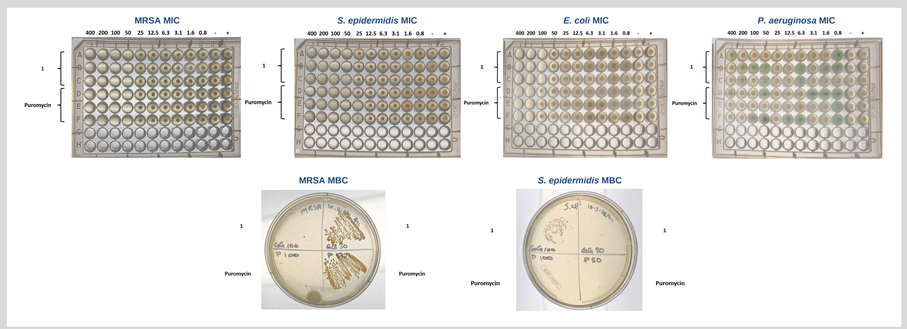


Figure 2. Proton NMR, COSY, and Fluorine NMR of molecule 3.

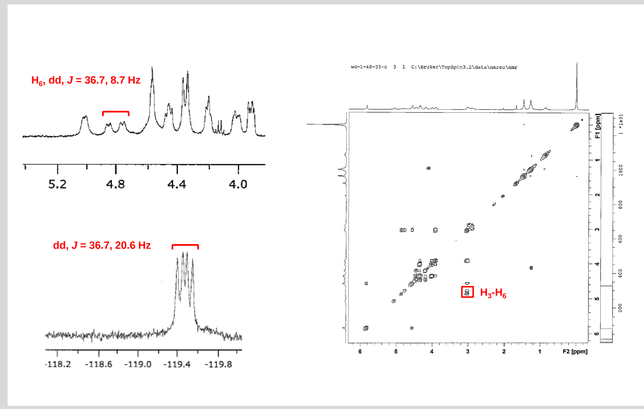
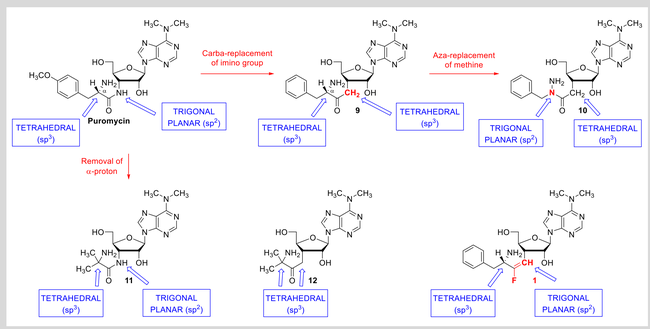


Figure 4. Structure-Activity Relationships of Puromycin Analogs.



CONCLUSIONS

1. The novel fluorinated puromycin analog **1** was synthesized in 10 steps from D-xylose.
2. The target compound was prepared via a regio- and stereoselective fluorination step.
3. Analog **1** shows antimicrobial activity comparable to puromycin against MRSA, *S. epidermidis*, and *E. coli*.
4. Unlike puromycin, **1** cannot be metabolized to the nephrotoxic aminonucleoside PAN.
5. The synthesis and evaluation of **1** adds to our understanding of the structure-activity relationships of puromycin analogs (figure 4).

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