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Tackling Pristinamycin IIB Problems: Synthetic Studies toward Some Fluorinated Analogs †

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Abstract: Streptogramins are potent antibiotics against numerous highly resistant pathogens and therefore are used in last-resort human therapy. These antibiotics are formed of both A- and B-group compounds named pristinamycins that differ in their basic primary structures. Although pristinamycin IIB is among the most interesting antibiotics in this family, it presents numerous problems related to its chemical structure, such as instability at most pH levels, weak solubility in water, and resistance by bacteria. As a response to the need for developing new antimicrobial agents, we have designed a new analog of pristinamycin IIB, based most importantly on the introduction of fluorine atoms. We conjectured indeed that the introduced modifications may solve the above-mentioned problems exhibited by pristinamycin IIB. Our multistep synthetic approach relies on few key reactions, namely a Wittig reaction, a Grubbs reaction, and dihydroxy, -difluoro API (Advanced Pharmaceutical Intermediate) synthesis

Keywords: streptogramins; pristinamycins IIB; fluorine

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The first antibiotic mixture of streptogramin antibiotics was isolated from the producer strain Streptomyces graminofaciens from a soil sample in Texas [1].

Streptogramins are unique in their mode of action: each component alone exhibits moderate bacteriostatic activity by binding to the bacterial 50S ribosomal subunit, whereas the synergic combination of both substances provides bactericidal activity [1].

Natural mixtures such as pristinamycin are highly active against a wide range of Gram-positive bacteria. They are used for the treatment of cutaneous, bone, and respiratory infectious diseases, mostly those caused by staphylococci [2].

As a response to the need for developing new antimicrobial agents, we have designed a new analog of pristinamycin IIB group A relying on chemical modification of the known pristinamycin; see Figure 1 [3]. These modifications should potentially solve the problems associated with this antimicrobial agent and its derivatives present on the market, particularly instability at different pH levels and antibiotic resistance [4,5]. This derivative is also supposed to improve the solubility of the drugs in water since pure streptogramin compounds are insoluble in aqueous medium [1].

We have established a convergent synthetic approach for our new analog. Strategically, the new analog was envisioned to derive from a convergent assembly of three key subunits according to a Wittig and Grubbs reaction after being prepared separately.

We have started the practical work by the preparation of the first fragment following nine steps.

Thus far, we have accomplished the preparation of the two first precursors using Diethyl phosphonate, ethyl bromoacetate, and Select Fluor as starting materials.

Triethyl phosphonoacetate and its mono-fluorinated analog were obtained as a yellow oil in 82% and 40% yield, respectively [6,7].

The primary studies and results obtained during this work confirm our initial hypothesis and encourage us to complete the synthesis of this novel antibiotic.

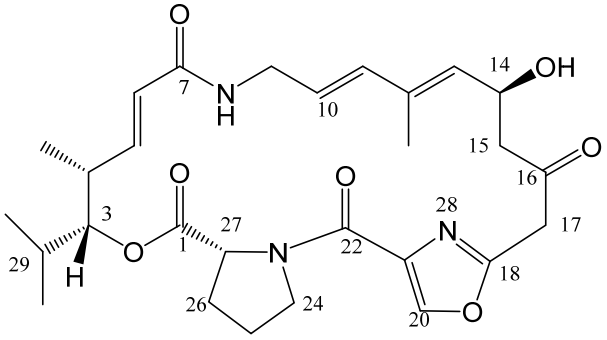

Figure 1. Pristinamycin IIB.

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