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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 such a family, it presents numerous problems related to its chemical structure such as instability to most pHs, weak solubility in water, and resistance by bacteria. As a response to the need of 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 a dihydroxy, -difluoro API (Advanced Pharmaceutical Intermediate) synthesis

Keywords: Streptogramins; Pristinamycins IIB; fluorine

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 a moderate bacteriostatic activity by binding to the bacterial 50S ribosomal subunit, whereas the synergic combination of both substances provides a bactericidal activity [1].

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

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

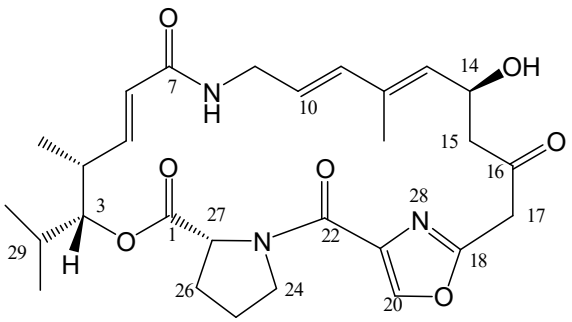

Figure 1. Pristinamycin IIB.

We have established a convergent synthetic approach of our new analogue. Strategically, the new analogue 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 9 steps.

So far, we have accomplished the preparation of the two first precursor using Diethyl phosphonate, ethyl bromoacetate and Select Fluor as started materials.

Triethyl phosphonoacetate and its mono-fluorinated analogue 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.

References

1. Mast, Y.; Wohlleben, W. Streptogramins-Two are better than one! *Int. J. Med. Microbiol.* **2014**, *304*, 44–50. doi:10.1016/j.ijmm.2013.08.008.
2. Fass, R.J. In vitro activity of RP 59500, a semisynthetic injectable pristinamycin, against Staphylococci, Streptococci, and Enterococci. *Antimicrob. Agents Chemother.* **1991**, *35*, 553–559. doi:10.1128/AAC.35.3.553.
3. Moellering, R.C. Discovering new antimicrobial agents. *Int. J. Antimicrob. Agents* **2011**, *37*, 2–9. doi:10.1016/j.ijantimicag.2010.08.018.
4. Mezghani Maalej, S.; Malbruny, B.; Leclercq, R.; Hammami, A. Emergence of Staphylococcus aureus strains resistant to pristinamycin in Sfax (Tunisia). *Pathol. Biol.* 2012, 60, e71–e74. doi:10.1016/j.patbio.2011.10.012.
5. Thal, L.A.; Zervos, M.J. Occurrence and epidemiology of resistance to virginiamycin and streptogramins. *J. Antimicrob. Chemother.* **1999**, *43*, 171–176. doi:10.1093/jac/43.2.171.
6. Cohen, R.J.; Fox, D.L.; Eubank, J.F.; Salvatore, R.N. Mild and efficient Cs2CO3-promoted synthesis of phosphonates. *Tetrahedron Lett.* **2003**, *44*, 8617–8621. doi:10.1016/j.tetlet.2003.09.045.
7. Marma, M.S.; Khawli, L.A.; Harutunian, V.; Kashemirov, B.A.; McKenna, C.E. Synthesis of α-fluorinated phosphonoacetate derivatives using electrophilic fluorine reagents: Perchloryl fluoride versus 1-chloromethyl-4- fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®). *J. Fluor. Chem.* **2005**, *126*, 1467–1475. doi:10.1016/j.jfluchem.2005.04.002.