In-Silico Studies toward the Improvement of the Antibacterial Activity of Pristinamycin IIB †

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1. Introduction

The streptogramin antibiotics are naturally occurring compounds isolated from Streptomyces and are classified as A and B groups according to their basic primary structure [1]. The first antibiotic mixture of streptogramin antibiotics was isolated from the producer strain Streptomyces graminofaciens from a soil sample in Texas [2].

Natural Pristinamycin IIB- group A is among the most interesting antibiotics in the streptogramin family [3]. Nevertheless, it presents numerous problems related to its chemical structure, such as instability to most pHs, weak solubility in aqueous media and resistance exhibited by bacteria [4,5].

In order to improve its poor pharmacological characteristics as therapeutic agents and overcome resistance mechanisms, we have designed new analogues of Pristinamycin IIB, based most importantly on the introduction of fluorine atoms.

Following studies in the late 1990s that indicated that poor pharmacokinetics and toxicity were important causes of costly late-stage failures in drug development, it has become widely appreciated that data on absorption, distribution, metabolism, excretion (ADME) and toxicity (T) should be considered as early as possible in the drug discovery process [6].

Interestingly, SwissADME was recently introduced as a web-based tool for ADMET modeling and it presents one of the most practical tools recently developed for ADMET prediction [7].

SwissADME uses quantum mechanical methods to assess the potential for interaction between small molecules under consideration and proteins known to be involved in ADME processes, such as cytochrome P450s. Moreover, it enables the prediction of physicochemical properties, in addition to lipophilicity (logP) and water solubility (logS). PK models and drug-likeness filters are other features available in this tool. Additionally, medicinal chemistry alerts are given, such as PAINS, the Brenk structural alert [8], lead-likeness [9] and synthetic accessibility.
2. Discussion

Accordingly, we have started this investigation by selecting Pristinamycin IIB as our lead compound to which we introduced two fluorine atoms at C15, along with other modifications, hence providing several fluorinated analogues.

Subsequently, using some predictive models, we computed the physico-chemistry and estimated the pharmacokinetics, drug-likeness and medicinal chemistry friendliness of the newly designed analogues of Pristinamycin IIB.

Thus, we submitted Pristinamycin IIB along with its two lead analogues (Figure 1) to the online SwissADME (http://www.swissadme.ch/, accessed on 15 November 2021) for evaluation.

![Figure 1. Pristinamycin IIB with its two newly designed lead analogues.](image)

For each structure submitted to SwissADME, we obtained over 31 data, some of which we did not report in Table 1 for practical reasons (Table 1).

| Physicochemical properties | Pristinamycin IIB | Analogue 1 | Analogue 2 |
|----------------------------|-------------------|-----------|-----------|
| Molecular weight (ESOL)    | C₂₈H₃₇N₅O₇        | C₂₈H₃₅F₂N₅O₇ | C₂₈H₃₅F₂N₅O₆ |
| Molar Refractivity          | 148.14            | 148.28    | 149.66    |
| Consensus Log Po/w          | 1.91              | 2.36      | 1.78      |
| Water Solubility            |                   |           |           |
| Log S (ESOL)                | −4.64             | −5.32     | −5.29     |
| Solubility                  | 1.22 × 10⁻² mg/mL; | 2.70 × 10⁻³ mg/mL; | 2.97 × 10⁻³ mg/mL; |
| Class                       | Moderately soluble| Moderately soluble| Moderately soluble|
| Log S (Ali)                 | −4.93             | −5.70     | −5.46     |
| Solubility                  | 2.31 × 10⁻⁵ mol/L | 4.79 × 10⁻⁶ mol/L | 5.17 × 10⁻⁶ mol/L |
| Class                       | Moderately soluble| Moderately soluble| Moderately soluble|
| TPSA                        | 139.04 Å²         | 139.04 Å² | 143.72 Å² |
| Lipophilicity               |                   |           |           |
| No. rotatable bonds         | 5                 | 5         | 11        |
| No. H-bond donors           | 2                 | 2         | 2         |
| No. H-bond acceptors        | 8                 | 10        | 10        |
| Fraction Csp                | 0.54              | 0.54      | 0.50      |
| No. heavy atoms             | 38                | 40        | 41        |
| No. arom. heavy atoms       | 5                 | 5         | 11        |

| Pharmacokinetics            | Pristinamycin IIB | Analogue 1 | Analogue 2 |
|----------------------------|-------------------|-----------|-----------|
| GI absorption               | High              | Low       | Low       |
| BBB permeant                | No                | No        | No        |
| P-gp substrate              | Yes               | Yes       | Yes       |
| CYP1A2 inhibitor            | No                | No        | No        |
Table 1. Cont.

|                      | Pristinamycin IIB | Analogue 1 | Analogue 2 |
|----------------------|-------------------|------------|------------|
| CYP2C19 inhibitio    | No                | No         | No         |
| CYP2C9 inhibitio     | No                | No         | No         |
| CYP2D6 inhibitio     | No                | No         | No         |
| CYP3A4 inhibitio     | No                | Yes        | No         |
| Drug-likeness        |                   |            |            |
| Lipinski             | Yes               | Yes        | No         |
| Ghose                | No                | No         | No         |
| Veber                | Yes               | Yes        | No         |
| Egan                 | No                | No         | No         |
| Muegge               | Yes               | Yes        | Yes        |
| Medicinal Chemistry  |                   |            |            |
| PAINS                | 0 alert           | 0 alert    | 0 alert    |
| Brenk                | 0 alert           | 0 alert    | 0 alert    |
| Lead-likeness        | No; 1 violation:  | No; 1 violation: | No; 1 violation: |
|                      | MW > 350          | MW > 350   | MW > 350   |
|                      |                   | 350        |            |
| Synthetic accessibility | 6.92              | 6.97       | 6.88       |

Our analysis indicated that the primarily designed molecules do not possess all the required drug-likeness, bioavailability, synthetic accessibility and ADMET features. Nevertheless, the data derived from the established study was employed in suggesting some new modifications in order to create other promising new analogues.

On the other side, our group has started the total synthesis of some fluorinated analogues. Our multistep synthetic approach relies on a convergent assembly of three main fragments using a few key reactions, namely a Wittig reaction, a Grubbs reaction, and a hydroxy, -difluoro API (Advanced Pharmaceutical Intermediate) synthesis.

3. Conclusions

At this stage, computational approaches are the only option for accessing information about ADMET properties, but it is also acceptable that the predictions are not perfect, which is a convergent opinion with others reported in the literature.

These primary studies and results obtained during this work encourage us to complete the synthesis of these novel antibiotic analogues and work towards further optimization of a clinical candidate.

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