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

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Abstract: Pristinamycin IIB (PIIB) is a potent antibiotic with limited use due to some structural problems, and also to the bacterial resistance exhibited toward the antibiotic. A thorough study led to the design of novel analogues of PIIB, based on the introduction of a difluorostatone moiety. Herein, we describe the initial in silico studies toward these novel analogues using ADMET modeling predictive models in order to compute the physico-chemistry and estimate the pharmacokinetics, drug-likeness and medicinal chemistry friendliness of these newly designed analogues.

Keywords: Pristinamycin IIB; fluorine; difluoroanalogues; ADMET; SwissADME

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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 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 (http://www.swissadme.ch/index.php) 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,

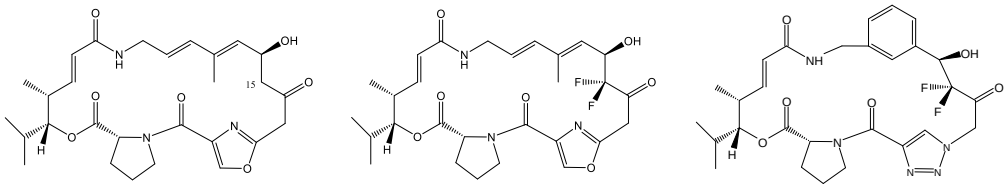
medicinal chemistry alerts are given, such as PAINS, Brenk structural alert [8], lead-likeness [9] and synthetic accessibility.

2. Discussion

Accordingly, we have started this investigation by selecting Pristinimycin 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 Pristinimycin IIB.

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



Pristinamycin IIB **Analogue 1** **Analogue 2**

Figure 1. Pristinamycin IIB with its two lead newly designed analogues.

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).

Table 1. SwissADME data.

	Pristinamycin IIB	**Analogue 1**	**Analogue 2**
Physicochemical Properties			
Formula	$C_{28}H_{37}N_3O_7$	$C_{28}H_{35}F_2N_3O_7$	$C_{28}H_{33}F_2N_5O_6$
Molecular weight	527.61 g/mol	563.59 g/mol	573.59 g/mol
Num. heavy atoms	38	40	41
Num. arom. heavy atoms	5	5	11
Fraction Csp	0.54	0.54	0.50
Num. rotatable bonds	1	1	1
Num. H-bond acceptors	8	10	10
Num. H-bond donors	2	2	2
Molar Refractivity	148.14	148.28	149.66
TPSA	139.04 Å²	139.04 Å²	143.72 Å²
Lipophilicity			
Consensus Log Po/w	1.91	2.36	1.78
Water Solubility			
Log S (ESOL)	−4.64	−5.32	−5.29
Solubility	1.22e-02 mg/mL ; 2.31e-05 mol/L	2.70e-03 mg/mL ; 4.79e-06 mol/L	2.97e-03 mg/mL ; 5.17e-06 mol/L
Class	Moderately soluble	Moderately soluble	Moderately soluble
Log S (Ali)	−4.93	−5.70	−5.46
Solubility	6.19e-03 mg/mL ; 1.17e-05 mol/L	1.13e-03 mg/mL ; 2.00e-06 mol/L	1.97e-03 mg/mL ; 3.43e-06 mol/L
Class	Moderately soluble	Moderately soluble	Moderately soluble
Log S (SILICOS-IT)	−4.19	−4.70	−5.21
Solubility	3.38e-02 mg/mL ; 6.40e-05 mol/L	1.13e-02 mg/mL ; 2.01e-05 mol/L	3.50e-03 mg/mL ; 6.11e-06 mol/L
Class	Moderately soluble	Moderately soluble	Moderately soluble
Pharmacokinetics			
GI absorption	High	Low	Low

BBB permeant	No	No	No
P-gp substrate	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibito	No	No	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	Yes	No
Druglikeness			
Lipinski	Yes	Yes	No
Ghose	No	No	No
Veber	Yes	Yes	No
Egan	No	No	No
Muegge	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.17
Medicinal Chemistry			
PAINS	0 alert	0 alert	0 alert
Brenk	0 alert	0 alert	0 alert
Leadlikeness	No; 1 violation: MW > 350	No; 1 violation: MW > 350	No; 1 violation: MW > 350
Synthetic accessibility	6.92	6.97	6.88

Our analysis indicates that the primary 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 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 at this stage, 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 further optimization towards a clinical candidate.

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