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A facile semi-synthetic approach towards halogen-substituted aminobenzoic acid analogues of platensimycin

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ABSTRACT

Platensimycin (PTM), produced by several strains of *Streptomyces platensis*, is a promising drug lead for infectious diseases and diabetes. The recent pilot-scale production of PTM from *S. platensis* SB12026 has set the stage for the facile semi-synthesis of a focused library of PTM analogues. In this study, gram-quantity of platensic acid (PTMA) was prepared by the sulfuric acid-catalyzed ethanolysis of PTM, followed by a mild hydrolysis in aqueous lithium hydroxide. Three PTMA esters were also obtained in near quantitative yields in a single step, suggesting a facile route to make PTMA aliphatic esters. 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU)-catalyzed coupling of PTMA and 33 aminobenzoates resulted in the synthesis of 28 substituted aminobenzoate analogues of PTM, among which 26 of them were reported for the first time. Several of the PTM analogues showed weak antibacterial activity against methicillin-resistant *Staphylococcus aureus*. Our study supported the potential utility to integrate natural product biosynthetic and semi-synthetic approaches for structure diversification.

1. Introduction

Fatty acids, such as palmitate, are essential building blocks of various lipids, membrane proteins and many intracellular signal molecules for all cells, and play important roles in physiology and diseases.[1,2] Fatty acids in bacteria and plants are biosynthesized by type II fatty acid synthases (FASIIs), while multifunctional type I FASs consisting of individual functional domains exist in fungi and animals.[3] Due to their importance in *de novo* fatty acid synthesis, FASs are viable targets for infective diseases, metabolic disorders and cancer.[4–7] Therefore there is great interest to identify novel FASs inhibitors with potentially broad pharmacological application.

Platensimycin (PTM), consisting of a 3-amino-2,4-dihydroxy benzoate (ADHBA) and a novel tetracyclic terpene cage moiety (platensic acid, PTMA, **1d**), was isolated from *Streptomyces platensis* by Singh and his co-workers, using an antisense differential screening strategy against an essential enzyme β-Ketoacyl-Acyl Carrier Protein (ACP) Synthase II (FabF) in FASII (Fig. 1).[8] It was firstly shown to possess potent antibacterial activity against Gram-positive bacteria including the methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci*, in comparison to clinically used antibiotic linezolid. Later it showed promising antidiabetic activity in mouse models, suggesting its application in metabolic diseases, such as obesity and diabetes.[9] Platencin (PTN), a PTM structure analogue with a different tricyclic terpene moiety, was similarly discovered.[10] Note that PTN is a dual inhibitor for FabF and β-Ketoacyl-ACP Synthase I (FabH) against many Gram-positive pathogens. The recent discovery of dedicated terpene synthases for

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PTM and PTN biosynthesis showcased how those elegant molecules were naturally produced.[11,12]

Joining the growing family of natural FabF or FabH inhibitors, including cerulenin, thiolactomycin and phomallenic acids, PTM and PTN were under intense investigation mainly due to their promising biological activities and unprecedented molecular complexity.[13] In order to improve their biological activities or poor pharmacokinetic properties, many PTM and PTN analogues were thus prepared via various approaches. For example, dozens of PTM or PTN congeners have been obtained from its native producers or engineered mutant strains (Fig. 1B).[14–19] Many elegant approaches towards the synthesis of their analogues were reported.[20–36] These work resulted in a few PTM analogues with improved antibacterial activity, such as 7-phenyl- and 11-methyl 7-phenylplatensimycin,[29] as well as PTM D1, a PTM pseudo-dimer.[18] Furthermore, Nicolaou and his co-workers prepared a few PTM analogues with various molecular complexities,[36] supporting the importance of the ADHBA moiety and the wisdom of making PTM analogues, since there were only a very limited number of natural or synthetic PTM aminobenzoates, especially those halogenated analogues.[16,26,27,36] In addition, other molecular scaffolds, such as anthranilic acid derivatives, acylhydrozones or thiolactomycin derivatives, were also potent bacterial FabF or FabH inhibitors by binding to the active sites (Fig. 1C).[37–39] Therefore, introduction of diverse functionality via halogen-substituted aminobenzoates to PTM molecular scaffold may improve our understanding of the structure-activity relationship about this important natural product.

2. Results and discussion

2.1. Synthesis of PTMA esters (*1a*–*1c*) and PTMA (*1d*)

With ample PTM in hands from the fermentation of *S. platensis* SB12026,[40,41] we began our investigation to obtain gram-quantity of PTMA (**1d**) for semi-synthesis of PTM analogues with varying aminobenzoate moieties (Scheme 1). Singh and his co-workers

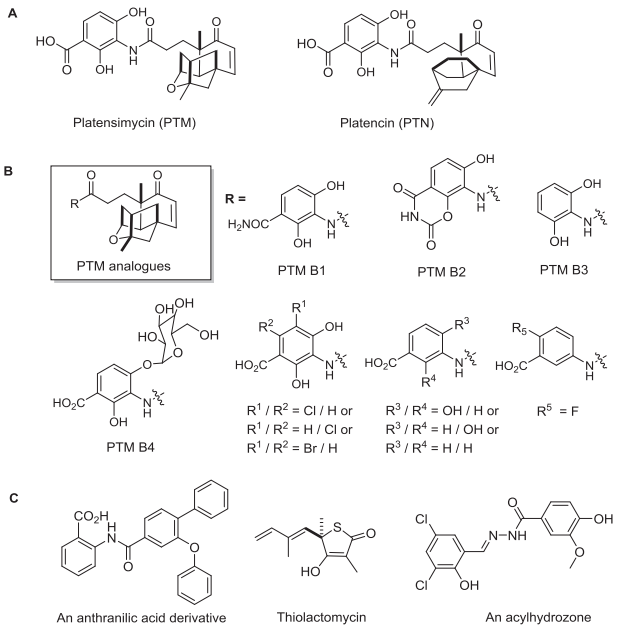


Fig. 1. Structures of selected FAS inhibitors and their analogues. (**A**) Structures of PTM and PTN; (**B**) PTM aminobenzoate analogues from fermentation broth or semi-synthesis; (**C**) Structures of an anthranilic acid derivative, thiolactomycin and an acylhydrozone.

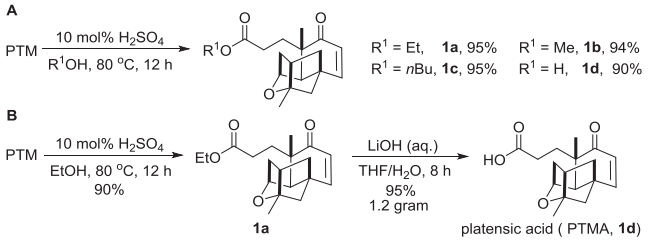
obtained PTMA via a mild amide hydrolysis through $NaNO_2$/CH_3COOH/Ac_2O with a moderate yield of about 60%.[27] In order to improve the reaction yield, we first discovered that 10 mol% sulfuric acid efficiently converted PTM into corresponding PTMA esters when several alcohols were used as solvents under elevated temperature (Scheme 1A). Methanol (MeOH), ethanol (EtOH) and n-butanol (*n*BuOH) were all tolerated for this reaction except isopropanol and phenol. The PTMA esters **1a**, **1b** and **1c** were obtained in near quantitative yields. Note that the PTMA methyl ester **1b** was further modified to increase the terpene diversity.[28] Since many aliphatic alcohols are basic building blocks in organic synthesis, this method may potentially be used to obtain other PTMA esters as well.

The direct hydrolysis was equally effective for this reaction, and PTMA (**1d**) was obtained in 90% yield under 0.1 mmol scale (Scheme 1A). However, the yield decreased dramatically for a large scale synthesis, which was probably due to the low solubility for PTM under acid conditions.[16,41] Therefore, EtOH was used as the solvent to make PTMA ethyl ester **1a**, followed by the LiOH-mediated hydrolysis in a large scale synthesis. Thus 1.2 g of PTMA was obtained from 2.11 g of PTM with 85% overall yield in two steps (Scheme 1B). The synthetic PTMA displayed the similar Cotton effect to that of the PTM observed by Circular dichroism (CD), supporting the retention of the PTM-like absolute stereochemistry during the reactions (Supporting Information, Fig. S1). Comparing to the heroic efforts to make PTMA via total synthesis,[13] our semi-synthesis approach could take advantage of microbial fermentation and set the stage to rapidly diversify the aminobenzoate moiety of PTM.

2.2. Synthesis of PTM 3-aminobenzoate analogues

Organofluorine was known to affect the binding affinity and selectivity of small molecules to their targets, as well as to change their physical and pharmacokinetic properties.[42] Therefore, several fluorine-containing methyl esters of PTM analogues were first synthesized by coupling of PTMA (**1d**) with substituted 3-aminobenzoic acid methyl esters (**2b-1, 2d-1, 2e-1**), with the ratio of methyl esters: PTMA: HATU: Et_3N = 1.5: 1.0:1.2: 1.5 (entries 2, 4, 5). PTM analogues **3b-1**, **3d-1**, **3e-1** with different F substitutions on the aromatic rings were obtained with various yields ranging from 34% to 43%. The 4-Cl substituted compound **3c-1** was obtained with a comparable yield of 34% (entry 3). However, these yields were much lower than those for coupling of PTMA with protected ADHBA during the PTM synthesis, typically 50%–70% under similar coupling conditions.[13,36] The possible reason is that the inductive effects of fluoride and chloride reduce the basicity of the 3-amino group, since the coupling of 3-aminobenzoic acid methyl ester to PTMA resulted in a decent yield of 87% (entry 1) (see Table 1).

PTM and its analogues were often prepared by the hydrolysis of their methyl esters in the last step of synthesis.[13] Due to the low yield for preparing the halogen-substituted PTM aminobenzoic methyl esters (**3b-1** - **3e-1**), we next tested if unprotected



Scheme 1. Semi-synthesis of PTMA or PTMA esters from PTM.