HHS Public Access

Author manuscript

ChemistrySelect. Author manuscript; available in PMC 2020 March 30.

Published in final edited form as:

ChemistrySelect. 2018 November 30; 3(44): 12625–12629. doi:10.1002/slct.201802475.

Semisynthesis and Biological Evaluation of Platensimycin Analogues with Varying Aminobenzoic Acids

Kai Tian[a], **Youchao Deng**[a], **Lin Qiu**[a], **Xiangcheng Zhu**[a],[b], **Ben Shen**[d], **Yanwen Duan**[a],[b],[c], **Yong Huang**[a],[c]

[a]Xiangya International Academy of Translational Medicine, Central South University, Changsha, Hunan 410013 (China)

[b]Hunan Engineering Research Center of Combinatorial Biosynthesis and Natural Product Drug Discovery, Changsha, Hunan 410205 (China)

[c]National Engineering Research Center of Combinatorial Biosynthesis for Drug Discovery, Changsha, Hunan 410205 (China)

[d]Departments of Chemistry and Molecular Medicine, and Natural Products Library Initiative at The Scripps Research Institute, The Scripps Research Institute, Jupiter, FL 33458 (USA)

Abstract

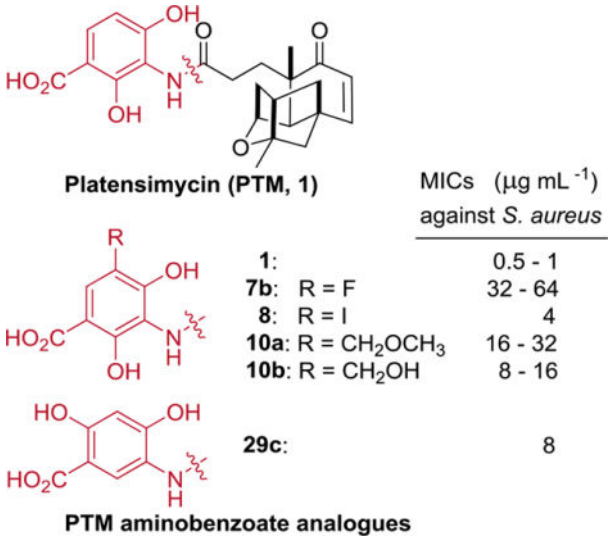
Platensimycin (PTM) is an excellent natural product drug lead against various gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. In this study, twenty PTM derivatives with varying aminobenzoic acids were semisynthesized. In contrast to all the previous reported inactive aminobenzaote analogues, a few of them showed moderate antibacterial activities against *S. aureus*. Our study suggested that modification of the conserved aminobenzoic acid remains a viable approach to diversify the PTM scaffold.

Graphical Abstract

jonghuang@csu.edu.cn or ywduan66@sina.com.

Supporting Information Summary

Detailed information about the experimental procedure, antibacterial activities, spectral characterization data such as ^{1}H-NMR and ^{13}C-NMR along with HRMS spectra of all synthesized products are provided



We have semisynthesized twenty PTM analogues with varying aminobenzoic acids and a few of them showed moderate antibacterial activities against *S. aureus*. Our results suggested that both electronegative properties and the steric hindrance of the substituents in the 5' position of the ADHBA moiety in these molecules would affect their binding to the target enzyme, while the former would probably play a major role; And the 4'-OH substituent in the ADHBA moiety of PTM is more important than the 2'-OH substituent. Our study suggested that modification of the conserved aminobenzoic acid remains a viable approach to diversify the PTM scaffold.

Keywords

semisynthesis; platensimycin; antibacterial activities

Platensimycin (PTM, **1**), a potent inhibitor of both bacterial and mammalian fatty acid synthases, was initially discovered from the soil-dwelling bacteria *Streptomyces platensis* MA7327 from South Africa by Merck scientists using a RNAi-based whole cell screening strategy, and it was later re-isolated from similar strains in China (Figure 1A).[1] It showed potent antibacterial activity against multi-drug resistant gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) in a mouse peritonitis model through continuously infusion, as well as antidiabetic effects in both diabetic mice and monkeys through oral administration.[1] PTM consists of a 2, 4-dihydroxyaminobenzoate (ADHBA) moiety and a unique tetracyclic terpene cage, connected though a propionylamide linker. The promising biological activities and novel structure of PTM have sparked interest to generate analogues to study the structure activity relationships, to improve its poor pharmacokinetic properties.[2]

The co-crystal structure of PTM with *Escherichia coli* β-ketoacyl-[acyl carrier protein] synthase II (FabF) (C163Q) revealed that the interaction between the active site residues of FabF and the ADHBA moiety is critical: the two His residues H340 and H303 form salt bridge with the carboxylate, while the C-4' phenol hydroxyl group is engaged with a hydrogen bond with D265 through H_2O (Figure 1B).[1a] The fine-tuned interaction in the

binding of ADHBA with the FabF active sites, makes generating ADHBA-modified active PTM analogues extremely difficult. Even minor perturbation of ADHBA leads to the abolishment of the antibacterial activities, despite dozens of aminobenzoate analogues have been obtained from fermentation or synthesis (Figure S1 and Table S1).[3] For example, compounds **2a-2c** synthesized by Nicolaou and co-workers displayed minimum inhibitory concentrations (MICs) above 82 μg mL^{-1} against MRSA, while other aminobenzoate analogues **2d-2h** from semisynthetic approaches also showed no antibacterial activities against MRSA. In contrast, the terpene cage was solvent-exposed and several terpene cage modified analogues were reported to have improved or comparable activities with PTM, such as the carbaplatensimycin, adamantaplatensimycin, the 7-phenyl- and 11-methyl-7-phenylplatensimycin, as well as the recent semisynthesized PTM sulfur analogues.[4] Since most of the previously obtained PTM aminobenzoate analogues suffered reduced structure complexity, such as compounds **2a-2h**, it appeared to us that the FabF active site could still accommodate more substitutions on the ADHBA moiety of PTM, which might lead to additional interactions with amino acid residues within the active site. Therefore our semisynthetic platform may enable the facile preparation of additional and complicated ADHBA analogues of PTM for biological evaluation, by taking advantage of its decagram-scale production from microbial fermentation using a high-yield mutant, and the gram-scale preparation of the key synthetic substrate platensic acid (PTMA, **3**) from PTM (Figure 1C).[3f, 4c, 5]

The synthesis of the 5'-F-substituted aniline derivative **6** started from the commercially available 2, 4, 5- trifluorobenzonitrile **4** (Scheme 1). Substitution of the 2-F and 4- F of **4** by benzyl alcohol, followed by high yield hydrolysis to convert nitrile to carboxylic acid and then methylation, afforded intermediate **5**.[6] Catalytic hydrogenation of **5** [H_2 (1.1 atm.), 10% Pd/C], followed by nitration with 65% HNO_3 and then catalytic hydrogenation again, delivered compound **6**.[7] HATU-mediated amide coupling of platensic acid **3** with aniline **6** yielded amide **7a**, which could be smoothly hydrolyzed with aqueous KOH in MeOH to furnish 5'-F-platensimycin **7b** in 23% overall yield in eight steps. No hydrolyzed product of amide **7a** was observed using aqueous LiOH in THF, which was used in the previous basic hydrolysis of the methyl esters of PTM analogues, such as carbaplatensimycin.[3c, 3g] The 5'-F-substituted aniline TMS ester of PTM could also be prepared, but it suffered low yield when coupled to **3** (Scheme S1).

Four additional aminobenzoate analogues of PTM **8–10** were smoothly synthesized from PTM in a one-step reaction (Scheme 2). Electrophilic iodination of PTM (I_2, DMAP, pyridine, CCl_4) afforded the 5'-I-platensimycin **8** in a good yield of 88%.[8] Treatment of PTM by 65% HNO_3 in 5 min furnished the 5'-nitro substituted PTM analogue **9** in 84% yield. Treatment of PTM by formaldehyde under basic conditions (HCHO, KOH, MeOH, $CaCl_2$), followed by quenching the reaction with NH_4OH led to the methoxylmethyl derivative of PTM **10a** with an excellent yield of 90%, while efficient synthesis of the similar hydroxymethyl PTM **10b** could be achieved in a similar procedure without NH_4OH treatment.[9]

Nine new aminobenozoic acid derivatives were synthesized from the known methyl esters **11**, **14**, **16**, **20** and **22** (Scheme 3). Basic hydrolysis of the methyl ester **11** (aq. LiOH, THF,

45 °C), followed by esterification with TMSE-OH (TMSE-OH, EDCI, Et_3N, DCM, 25°C) and catalytic hydrogenation, led to aniline **13** (Scheme 3A).[6c, 9] Aniline **15b** was prepared similarly by LiOH-mediated hydrolysis, followed by catalytic hydrogenation (Scheme 3B). Direct catalytic hydrogenation of methyl esters **14**, **16** and **20**, afforded the corresponding aniline methyl ester **15a**, **17a** and **21a**[7] in 95, 89 and 89% yield, respectively (Scheme 3B–3D). Starting from **16** and **20**, ester exchange under basic conditions (TMSE-OH, Bu_2SnO, toluene, 150°C), followed by catalytic hydrogenation, furnished anilines **17b** and **21b**.[10] Unfortunately, **14** and **23** could only be converted to the corresponding TMS esters in very low yields, when the above ester exchange conditions were used. The aniline derivative **19** was swiftly converted from the methyl ester **16**, by basic hydrolysis, demethylation mediated by $AlCl_3$ ($AlCl_3$, 1, 2-DCE, 90 °C), and catalytic hydrogenation.[7] Finally, selective benzylation of **22** (BnBr, K_2CO_3, acetone), followed by mild nitration ($Bi(NO_3)_3{\cdot}5H_2O$, MMT K10, DCM, 25 °C), provided the aniline **24** (Scheme 3E).[9]

With the nine aromatic fragments in hand, coupling to platensic acid via amidation would afford the corresponding PTM analogues. Analogues **25a**, **26a**, **27a**, **29a**, **29b** and **30** were efficiently prepared from their corresponding aniline derivatives **12**, **14**, **16**, **20** and **23**, with platensic acid **3** through HATU-mediated amide coupling (HATU, Et_3N, DMF) (Scheme 4). Deprotection of the resulting PTM TMS esters **25a**, **27b** and **29b** using fluoride (TBAF, DCM) furnished compounds **25b**, **27c** and **29c**.[10b] Alternatively, compounds **27c** and **29c** could be obtained by the hydrolysis of **27a** and **29a** using aqueous KOH in MeOH, in 74 and 34% yield, respectively. Inspired by the direct coupling of unprotected ADHBA with platencin core using DCC (DCC, DMAP, Et_3N, MeCN/DMF, rt), compounds **26b** and **28** were conveniently obtained by coupling of the respective aminobenzoic acids **15b** or **19** with **3** (PyBOP, Et_3N, DCM, rt, 30 min), in 80 and 75% yield, respectively.[7, 11]

The eighteen synthesized PTM analogues **8–10** and **25–30** were first tested against the gram-positive *S. aureus* ATCC 29213 and the gram-negative *Klebsiella pneumoniae* using the paper disc method, with 5 μg or 25 μg per disc, and PTM and linezolid (5 μg/disc) were used as controls (Figure S2). The 5'-Br-platensimycin and 5'-Cl-platensimycin were previously synthesized,[3b] but their antibacterial activities have not been reported (Figure S1). We also synthesized these two analogues according to the previous reported procedure and included them in our assay.

All of the twenty tested PTM analogues showed no antibacterial activities against the gram-negative pathogen *K. pneumoniae*, suggesting that these PTM ADHBA modified derivatives might share certain drug-efflux mechanisms with PTM against gram-negative pathogens, such as *Escherichia coli* (Figure S2).[1a] Interestingly, five ADHBA-modified analogues, including 5'-F-platensimycin **7b**, 5'-I-platensimycin **8**, 5'-methoxymethyl-platensimycin **10a**, 5'-hydroxymethylplatensimycin **10b** and 4', 6'- dihydroxyplatensimycin **29c** showed clean zone of inhibition, while 5'-Cl-platensimycin only showed a faint inhibition zone when applied against *S. aureus* ATCC 29213. The other tested PTM derivatives showed no antibacterial activities against the tested *S. aureus* strains.

The MICs of those active PTM derivatives **7b, 8, 10a, 10b** and **29c**, were determined against *S. aureus* ATCC 29213 and the clinical isolated methicillin-sensitive *S. aureus* (MSSA) and

MRSA, using PTM and linezolid as controls (Table 1).[12] Among them, the 5'-I-platensimycin **8** showed a MIC of 4 μg mL^{-1}, only 4–8 fold less potent than PTM, while 5'-F-platensimycin **7b** had a MIC of 64 μg mL^{-1} against the tested *S. aureus* strains. However, about 10% of 5'-I-platensimycin deiodinated to PTM due to the instability of C-I bond under the assay condition, suggesting that the observed antibacterial activities might be partly due to its parent compound PTM and an interesting pro-drug strategy to deliver PTM in vivo to improve its poor bioavailability (Figure. S3).[13] Both **10a** and **10b**, bearing slightly larger substituents in ADHBA moiety than 5'-I-PTM, have attenuated antibacterial activities with MICs ranging from 8–32 μg mL^{-1}. In contrast, 5'-Br-platensimycin, 5'-Cl-platensimycin and 5'-nitroplatensimycin did not show any antibacterial activities against *S. aureus*, while it is surprising that the 5'-F-platensimycin, with potentially enhanced bioavailability, still have weak antibacterial activity.[14] It was consistent with the complete loss of the antibacterial activities of 5'-Cl-platencin and 5'-Cl-iso-platencin, analogues of another potent fatty acid synthase inhibitor platencin, which shares the same ADHBA moiety with PTM.[3b, 15] Taken together, these results suggested that both electronegative properties and the steric hindrance of the substituents in the 5' position of the ADHBA moiety in these molecules would affect their binding to the target enzyme, while the former would probably play a major role.

The 4', 6'-dihydroxyplatensimycin **29c** had a MIC of 8 μg mL^{-1}, while 2', 6'-dihydroxyplatensimycin **26b** had no antibacterial activity under the tested conditions, suggesting that the 4'-OH substituent in the ADHBA moiety of PTM is more important than the 2'-OH substituent. It is consistent with the reported co-crystal structure of PTM and ecFabF (C163Q), in which the 4'-OH mediated a hydrogen bond with D265.[1a] It seemed that the 2'-OH in PTM and 6'-OH in **29c**, both ortho to the carboxylate of PTM or **29c**, are also needed for their respective antibacterial activities, because both the previous reported 4'-hydroxyplatensimycin by Nicolaou group and 4', 5'-dihydroxyplatensimycin **28** showed no antibacterial activity.[3c] Since the ortho phenolic hydroxy group in either PTM or **29c** could form a hydrogen bond with the carboxylate, as observed in their proton NMR spectroscopy, it remained to be determined what the role of the intramolecular hydrogen bond plays in the binding of PTM or **29c** to FabF.

In summary, we have semisynthesized twenty PTM analogues with varying aminobenzoic acids and a few of them showed moderate antibacterial activities against *S. aureus*. In contrast to all the previous reported PTM ADHBA analogues, including compounds **2a**-**2h**, as well as other analogues from PTM wild-type producer or the mutant strain through precursor-directed biosynthesis approaches (Figure S1), our study has resulted five active PTM ADHBA derivatives **7b, 8, 10a, 10b** and **29c**, with diverse functionality. However, they might still suffer the similar metabolic fate of rapid clearance or amide hydrolysis as PTM, challenges that have prevent PTM drug development to date. Our facile preparation of these active analogues would allow the study of their pharmacokinetics and pharmacodynamics in the future. Since PTM analogues could be prepared by convergent synthesis or biosynthetic routes, our discovery of several active ADHBA-modified PTM analogues would suggest the design of next generation of PTM analogues, by varying both ADHBA moiety and its terpene cage. It is further supported by our recent discovery of the active thioplatensimycin,

the natural congener of PTM.[20] The similar design principle might also be applicable to platencin. Since there are only a few effective inhibitors against type II PKSs, our generation of these active analogues may inspire the discovery of potent antibiotics targeting this essential pathway in major pathogens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by NSFC grants 81473124 (to Y.H.), the Chinese Ministry of Education 111 Project B0803420 (to Y.D.) and NIH Grant GM114353 (to B.S.). We thank the Center for Advanced Research in Central South University for the HRMS and NMR experiments.

References

[1]. a)Wang J, Soisson SM, Young K, Shoop W, Kodali S, Galgoci A, Painter R, Parthasarathy G, Tang YS, Cummings R, Ha S, Dorso K, Motyl M, Jayasuriya H, Ondeyka J, Herath K, Zhang C, Hernandez L, Allocco J, Basilio A. n., Tormo JR, Genilloud O, Vicente F, Pelaez F, Colwell L, Lee SH Michael B, Felcetto T, Gill C, Silver LL, Hermes JD, Bartizal K, Barrett, Schmatz D, Becker JW, Cully D, Singh SB, Nature 2006, 441, 358–361; [PubMed: 16710421] b)Wu M, Singh SB, Wang J, Chung CC, Salituro G, Karanam BV, Lee SH, Powles M, Ellsworth KP, Lassman ME, Miller C, Myers RW, Tota MR, Zhang BB, Li C, Proc. Natl. Acad. Sci. U.S.A 2011, 108, 5378–5383; [PubMed: 21389266] c)Singh SB, Kang L, Nawrocki AR, Zhou D, Wu M, Previs S, Miller C, Liu H, Hines CD, Madeira M, Cao J, Herath K, Spears LD, Semenkovich CF, Wang L, Kelley DE, Li C, Guan HP, PLoS One 2016, 11, e0164133; [PubMed: 27695056] d)Hindra T Huang D Yang JD Rudolf P Xie G Xie Q Teng JR Lohman X Zhu Y Huang L-X Zhao Y Jiang Y Duan B Shen, J. Nat. Prod2014, 77, 2296–2303. [PubMed: 25238028]

[2]. a)Nicolaou KC, Chen JS, Edmonds DJ, Estrada AA, Angew. Chem. Int. Ed 2009, 48, 660–719;b)Martens E, Demain AL, J. Antibiot. 2011, 64, 705–710 [PubMed: 21915133] c)Saleem M, Hussain H, Ahmed I, van Ree T, Krohn K, Nat. Prod. Rep 2011, 28, 1534–1579 [PubMed: 21808805] d)Singh S, in Expert. Opin. Ther. Pat, Vol. 20, 2010, pp. 1359–1371; [PubMed: 20653459] e)Rudolf JD, Dong L-B, Shen B, Biochem. Pharmacol 2017, 133, 139–151. [PubMed: 27865713]

[3]. a)Dong L-B, Rudolf JD, Shen B, Bioorg. Med. Chem 2016, 24, 6348–6353; [PubMed: 27134119] b)Singh SB, Herath KB, Wang J, Tsou N, Ball RG, Tetrahedron. Lett 2007, 48, 5429–5433;c)Nicolaou KC, Stepan AF, Lister T, Li A, Montero A, Tria GS, Turner CI, Tang Y, Wang J, Denton RM, Edmonds DJ, J. Am. Chem. Soc 2008, 130, 13110–13119; [PubMed: 18771264] d)Zhang C, Ondeyka J, Herath K, Jayasuriya H, Guan Z, Zink DL, Dietrich L, Burgess B, Ha SN, Wang J, Singh SB, J. Nat. Prod 2011, 74, 329–340 [PubMed: 21214253] e)Dong L-B, Rudolf JD, Shen B, Org. Lett 2016, 18, 4606–4609; [PubMed: 27599271] f)Qiu L, Tian K, Pan J, Jiang L, Yang H, Zhu X, Shen B, Duan Y, Huang Y, Tetrahedron 2017, 73, 771–775; [PubMed: 28626267] g)Nicolaou KC, Lister T, Denton RM, Montero A, Edmonds DJ, Angew. Chem. Int. Ed 2007, 46, 4712–4714.

[4]. a)Nicolaou KC, Tang Y, Wang J, Stepan AF, Li A, Montero A, J. Am. Chem. Soc 2007, 129, 14850–14851; [PubMed: 17988130] b)Jang KP, Kim CH, Na SW, Jang DS, Kim H, Kang H, Lee E, Bioorg. Med. Chem. Lett 2010, 20, 2156–2158; [PubMed: 20207542] c)Qiu L, Tian K, Wen Z, Deng Y, Kang D, Liang H, Zhu X, Shen B, Duan Y, Huang Y, J. Nat. Prod 2018, 81, 316–322; [PubMed: 29389125] d)Wang J, Sintim HO, Chem. Eur. J 2011, 17, 3352–3357. [PubMed: 21322068]

[5]. a)Shi J, Pan J, Liu L, Yang D, Lu S, Zhu X, Shen B, Duan Y, Huang Y, J. Ind. Microbiol. Biot 2016, 43, 1027–1035;b)Deng Y, Kang D, Shi J, Zhou W, Sun A, Ju J, Zhu X, Shen B, Duan Y, Huang Y, Med. Chem. Commun 2018, 9, 789–794.

[6]. a)Lee MM, Peterson BR, ACS Omega 2016, 1, 1266–1276; [PubMed: 28058293] b)Lignier P, Estager J, Kardos N, Gravouil L, Gazza J, Naffrechoux E, Draye M, Ultrason. Sonochem 2011, 18, 28–31; [PubMed: 20488745] c)Vaidyanathan G, McDougald D, Choi J, Pruszynski M, Koumarianou E, Zhou Z, Zalutsky MR, Org. Biomol. Chem 2016, 14, 1261–1271. [PubMed: 26645790]

[7]. Tiefenbacher K, Gollner A, Mulzer J, Chem. -Eur. J 2010, 16, 9616–9622. [PubMed: 20486112]

[8]. Liu H, Yan P, Li Y, Liu J, Sun Q, Wang X, Wang C, Monatsh. Chem 2012, 143, 1055–1059.

[9]. Yan Y, Qin B, Ren C, Chen X, Yip YK, Ye R, Zhang D, Su H, Zeng H, J. Am. Chem. Soc 2010, 132, 5869–5879. [PubMed: 20364840]

[10]. a)Nicolaou KC, Natarajan S, Li H, Jain NF, Hughes R, Solomon ME, Ramanjulu JM, Boddy CNC, Takayanagi M, Angew. Chem. Int. Ed 1998, 37, 2708–2714;b)Ghosh AK, Xi K, J. Org. Chem 2009, 74, 1163–1170. [PubMed: 19123842]

[11]. Hayashida J, Rawal VH, Angew. Chem. Int. Ed 2008, 47, 4373–4376.

[12]. Wiegand I, Hilpert K, Hancock RE, Nat. Protoc 2008, 3, 163–175. [PubMed: 18274517]

[13]. Cavina L, van der Born D, Klaren PHM, Feiters MC, Boerman OC, Rutjes F, Euro. J. Org. Chem 2017, 2017, 3387–3414.

[14]. Müller K, Faeh C, Diederich F, Science 2007, 317, 1881–1886. [PubMed: 17901324]

[15]. Wang J, Kodali S, Lee SH, Galgoci A, Painter R, Dorso K, Racine F, Motyl M, Hernandez L, Tinney E, Colletti SL, Herath K, Cummings R, Salazar O, González I, Basilio A, Vicente F, Genilloud O, Pelaez F, Jayasuriya H, Young K, Cully DF, Singh SB, Proc. Natl. Acad. Sci. U. S. A 2007, 104, 7612–7616. [PubMed: 17456595]

[16]. Sonar VN, Venkatraj M, Parkin S, Crooks PA, Acta Crystallogr., Sect. E: Struct. Rep. Online 2007, 63, o3227–o3227.

[17]. a)Wang L, Gong J, Deng L, Xiang Z, Chen Z, Wang Y, Chen J, Yang Z, Org. Lett 2009, 11, 1809–1812; [PubMed: 19296671] b)Kiss LE, Ferreira HS, Torrao L, Bonifacio MJ, Palma PN, Soares-da-Silva P, Learmonth DA, J. Med. Chem 2010, 53, 3396–3411. [PubMed: 20334432]

[18]. Giannis A, Heretsch P, Synthesis. 2007, 2007, 2614–2616.

[19]. Wang J, Kodali S, Lee SH, Galgoci A, Painter R, Dorso K, Racine F, Motyl M, Hernandez L, Tinney E, Colletti SL, Herath K, Cummings R, Salazar O, González I, Basilio A, Vicente F, Genilloud O, Pelaez F, Jayasuriya H, Young K, Cully DF, Singh SB. Proc. Natl. Acad. Sci. U.S.A 2007, 104, 7612–7616. [PubMed: 17456595]

[20]. Dong LB, Rudolf JD, Kang D, Wang N, He CQ, Deng Y, Huang Y, Houk KN, Dua Y, Shen B, Nat. Commun 2018, 9, 2362. [PubMed: 29915173]

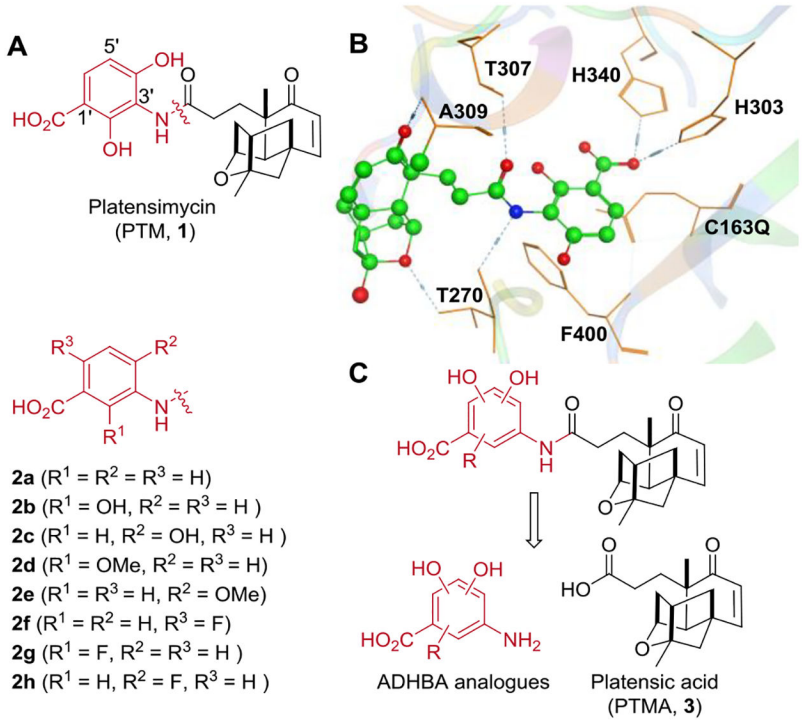
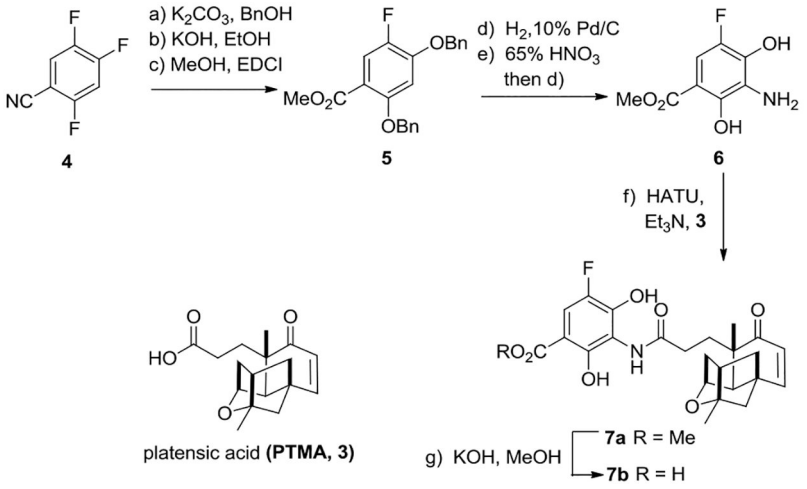


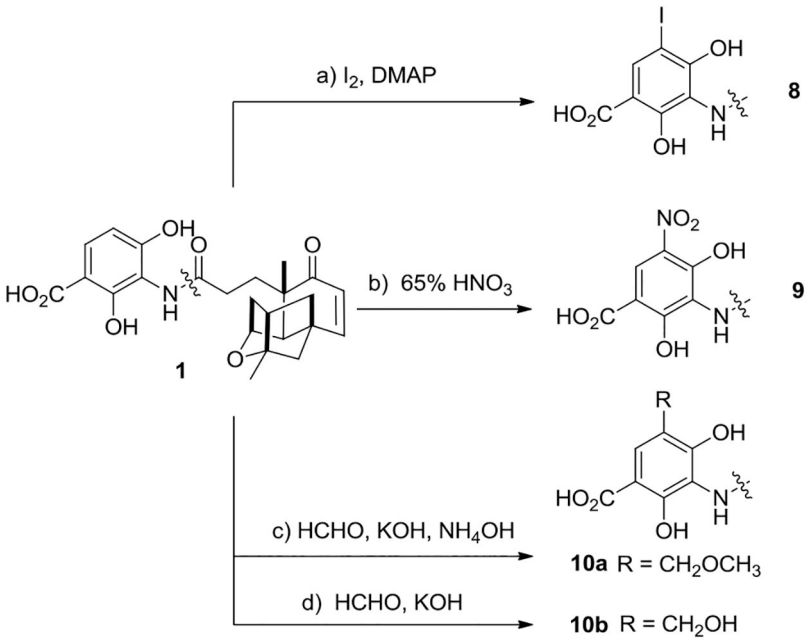
Figure 1.

The design of the aminobenzoate analogues of platensimycin. (A) The structures of platensimycin and selected platensimycin aminobenzoate analogues. (B) The co-crystal structure of PTM with *E. coli* FabF (C163Q). (C) The retrosynthetic analysis for the semisynthesis of most platensimycin analogues in this study.



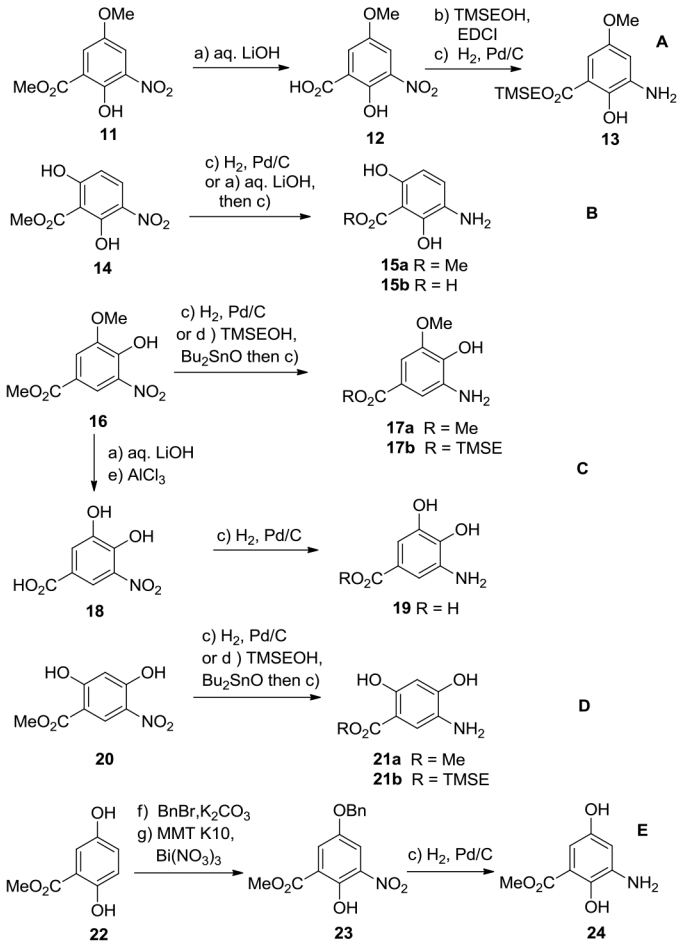
Scheme1. Synthesis of 5'-F-platensimycin 7b.

Reagents and conditions: (a) K_2CO_3 (5 equiv.), BnOH (2.5 equiv.), DMF, 105 °C, 16 h, 85%; (b) 6 N KOH, EtOH, 140 °C, 1.5 h, 95%; (c) MeOH, DMAP (0.1 equiv.), EDCI (1.2 equiv.), NEt_3 (2.5 equiv.), 10 h, 65%; (d) H_2 (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 °C, 3 h, 90%; (e) 65% HNO_3, $CHCl_3$, 5 min, 72%; (f) **3** (1.0 equiv.), HATU (2.0 equiv.), NEt_3 (3.0 equiv.), DCM, 25 °C, 12 h, 83%; (g) aq. KOH, MeOH, 45 °C, 4 h, 89%. Abbreviations: Bn = benzyl, DMF = *N,N*-dimethylformamide, DMAP = dimethylaminopyridine, EDCI = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HATU = 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, DCM = dichloromethane.



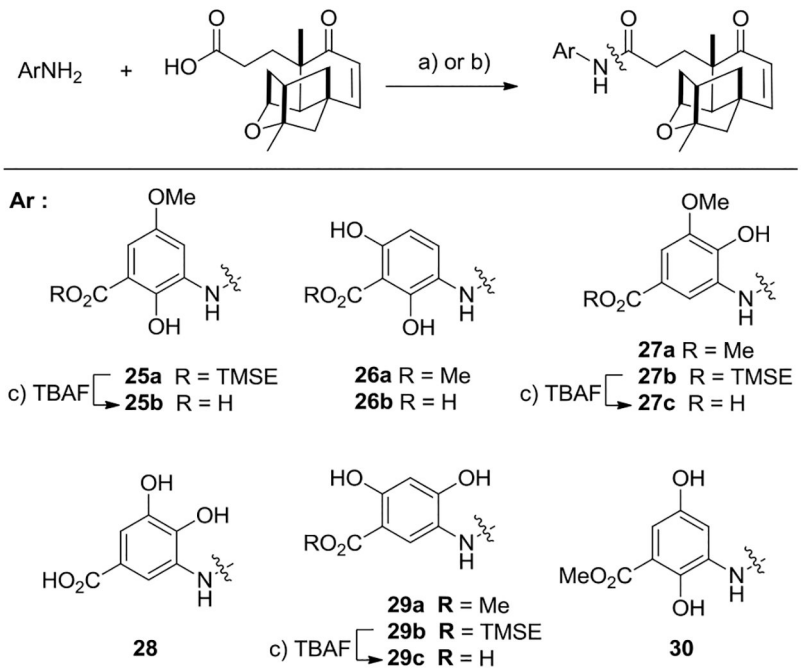
Scheme 2. Synthesis of platensimycin analogues 8–10.

Reagents and conditions: (a) CCl_4:pyridine (4:1), I_2 (3 equiv.), DMAP (0.2 equiv.), 110 °C, 4 h, 88%; (b) 65% HNO_3, $CHCl_3$, r.t. 5 min, 84%; (c) HCHO (3.0 equiv.), KOH (3.0 equiv.), $CaCl_2$ (3.0 equiv.), MeOH (2 ml), NH_4OH (10.0 equiv.), r.t. 4 h, 90%; (d) HCHO (3.0 equiv.), KOH (3.0 equiv.), $CaCl_2$ (3.0 equiv.), MeOH (2 ml), r.t. 4 h, 92%.



Scheme 3. Construction of aromatic fragments.

Reagents and conditions: (a) aq. LiOH, THF, 45 °C, 91–95%; (b) TMSEOH (1.2 equiv.), EDCI (1.0 equiv.), NEt_3 (2.0 equiv.), DCM, 25 °C, 12 h, 89%; (c) H_2 (1.1 atm.), 10% Pd/C (0.2 equiv.), MeOH, 25 °C, 3 h, 95% (for **13**), 91% (for **15a**), 89% (for **15b**), 93% (for **17a**), 82% (for **17b**), 89% (for **19**), 84% (for **21a**), 92% (for **21b**), 87% (for **24**); (d) TMSEOH (1.5 equiv.), toluene, Bu_2SnO (1.0 equiv.), 150 °C, 85–95%; (e) $AlCl_3$ (3.0 equiv.), 1,2-DCE, 90 °C, 85%; (f) BnBr, K_2CO_3, acetone, 3 h, 87%; (g) $Bi(NO_3)_3.5H_2O$ (1.0 equiv.), MMT K10 (1.0 equiv.), DCM, 25 °C, 2 h, 81%. Abbreviations: THF = tetrahydrofuran, TMSE = 2-(trimethylsilyl)ethyl, Bu = butyl, MMT K10 = bentonite clay K-10.



Scheme 4. Synthesis of platensimycin analogues 25–30.

Reagents and conditions: (a) HATU (2.0 equiv.), NEt_3 (3.0 equiv.), DMF, r.t, 8 h, 86% (for **25a**), 74% (for **26a**), 70% (for **27a**), 80% (for **27b**), 63% (for **29a**), 82% (for **29b**), 59% (for **30**); (b) PyBOP (0.9 equiv.), NEt_3 (2.0 equiv.), DCM, r.t, 30 min, 80% (for **26b**), 75% (for **28**); (c) TBAF, DCM, 12 h, 92% (for **25b**), 76% (for **27c**), 85% (for **29c**). Abbreviations: PyBOP =benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, TBAF = tetrabutylammonium fluoride.

Table 1.

The minimum inhibitory concentrations (MIC μg mL^{-1}) of platensimycin analogues against *S. aureus* ATCC 29213, and clinical MSSA and MRSA strains

Compounds	*S. aureus* ATCC 29213	MRSA	MSSA
PTM	1	0.5	1
Linezolid	1	1	1
7b	64	64	32
8	4	4	4
10a	32	16	16
10b	16	16	8
29c	8	8	8