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7-Phenylplatensimycin and 11-methyl-7-phenylplatensimycin: More potent analogs of platensimycin

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In memory of Professor Chi Sun Hahn

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ABSTRACT

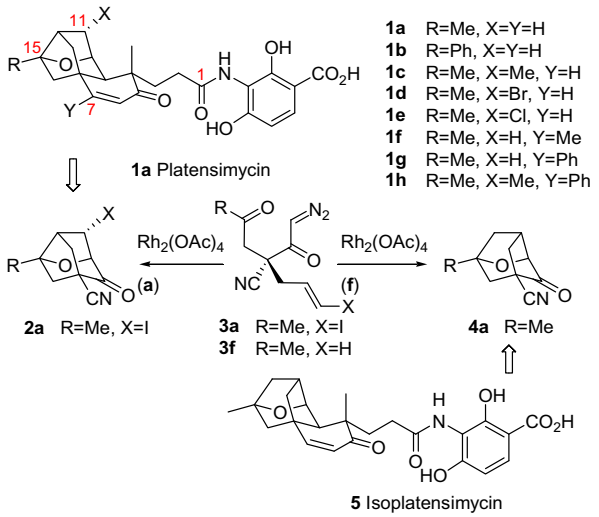
Carbonyl ylide cycloaddition strategy was employed in the synthesis of platensimycin analogs. 7-Phenylplatensimycin and 11-methyl-7-phenylplatensimycin are more potent analogs of platensimycin.

Platensimycin (**1a**, R = Me, X = Y = H) is a broad spectrum antibiotic (against Gram-positive bacteria) recently discovered from *Streptomyces platensis* by Merck scientists: it inhibits bacterial growth by selectively inhibiting the condensing enzyme FabF of the bacterial fatty acid synthesis pathway.[1] Platensimycin (**1a**) shows no cross-resistance to methicillin-resistant *Staphylococcus aureus*, vancomycin-intermediate *S. aureus*, and vancomycin-resistant enterococci. Due to the remarkable biological activities, intense activities were directed to the synthesis of platensimycin (**1a**)[2] and its analogs.[3]

Recently, we reported an efficient and concise synthetic route towards **1a**, in which the key tricyclic intermediate **2a** (R = Me, X = I) was prepared via intramolecular dipolar cycloaddition of the carbonyl ylide generated from the halogen-substituted olefinic intermediate **3a** (R = Me, X = I).[2h] In the absence of halogen substitution, regioselectivity in this key step is reversed, and an isomeric tricycle **4a** (R = Me) was obtained from **3f** (R = Me, X = H) (Scheme 1). The tricycle **4a** was used in the synthesis of isoplatensimycin (**5**), a novel analog of **1a** with subtle structural differences.[4]

A wide variety of analogs may easily be prepared using the method described in Scheme 1. In this Letter, we wish to report the synthesis of 15-phenyl-17-norplatensimycin (**1b**), 11-methylplatensimycin (**1c**), 11-bromoplatensimycin (**1d**), 11-chloroplatensimycin (**1e**), 7-methylplatensimycin (**1f**),[5] 7-phenylplatensimycin (**1g**), and 11-methyl-7-phenylplatensimycin (**1h**).

First, the key tetracyclic intermediates **11b–e** were prepared according to the known route from **6** to **11a** (R = Me, X = H) as



Scheme 1. Platensimycin and analogs.

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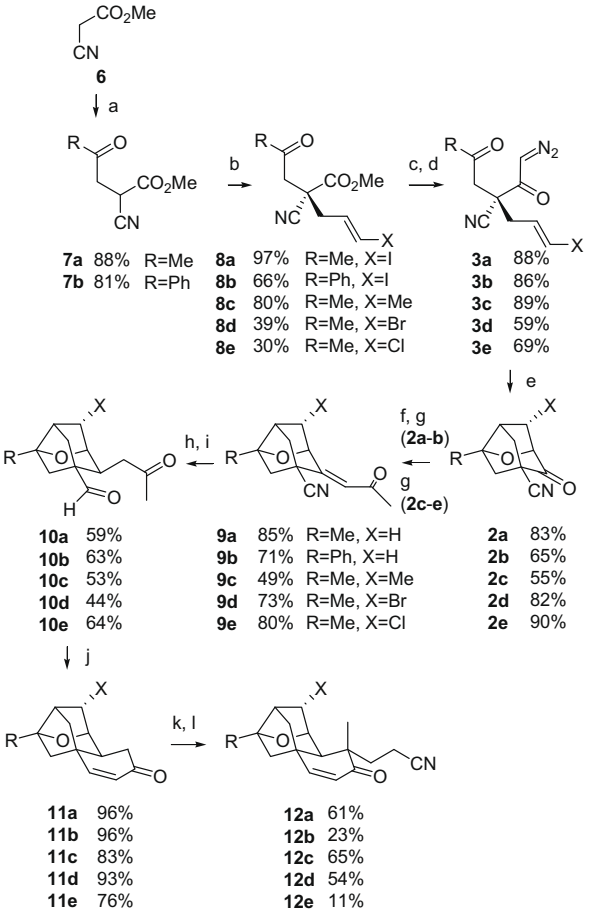
shown in Scheme 2. For synthesis of 15-phenyl-17-norplatensimycin (**1b**), α-chloroacetophenone was used in the alkylation of **6** in place of chloroacetone in Scheme 2. In the alkylation of **7a**, *E*/*Z* mixtures of crotyl bromide, 1,3-dibromopropene, and 1,3-dichloropropene were used as alkylating agents. The product **8c** was isolated as a mixture of *E*/*Z* mixture, but **8d** and **8e** were isolated as pure *E* isomers. Diazoketones **3b**–**e** were prepared from **8b**–**e** following the known procedure. The rhodium-catalyzed dipolar cycloaddition of **3b**–**e** proceeded uneventfully to produce tricycles **2b**–**e**. The preparation of enone **9b** from **2b** involved radical-mediated dehalogenation and Horner–Emmons reaction. Conversion of **2c**–**e** into **9c**–**e** required only the Horner–Emmons reaction. Rh(I)-catalyzed hydrosilylation of enones **9b**–**e**, DIBAL reduction, and careful imine hydrolysis was carried out under one-pot reaction conditions, and keto aldehydes **10b**–**e** were obtained after silyl enol ether hydrolysis. As noted in the preparation of **11a**, purification of ketoaldehyde intermediates **10b**–**e** was important for preparation of **11b**–**e** (Scheme 2). Conversion of **11a**–**e** to **12a**–**e** involved the use of acrylonitrile as used in the synthesis of isoplatensimycin (**5**).[4]

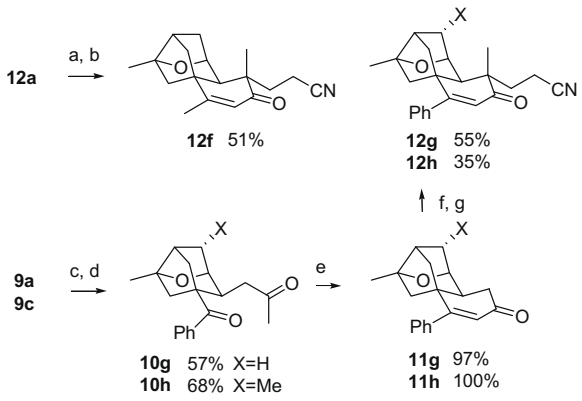
For introduction of a methyl group at C7, tetracycle **12a** was reacted with lithium dimethylcuprate in the presence of trimethylsilyl chloride. DDQ oxidation of the resulting silyl enol ether then produced a new tetracycle **12f**. For optimal introduction of a phenyl group at C7, a different route was adopted. The hydrosilylation intermediate from enone **9a** was allowed to react with phenyllithium to form **10g** after hydrolysis. The product **10g** was converted into the tetracycles **11g** under the acidic conditions. The known procedures as described in Scheme 2 were followed for the conversion of **11g** into **12g**. Synthesis of the intermediate **12h** also followed the same sequence of reactions starting from enone **9c** (Scheme 3).

Conversion of **12a**–**h** into the carboxylic acids **13a**–**h** was accomplished under alkaline conditions (Scheme 4). Platensimycin (**1a**) was prepared via amide coupling of **13a** with amine **14a** in the presence of HATU and TEA and subsequent basic hydrolysis. More generally, amide coupling of **13b**–**h** with (trimethylsilyl)ethyl ester **14b** and then treatment with TASF led to analogs **1b**–**h** as expected.

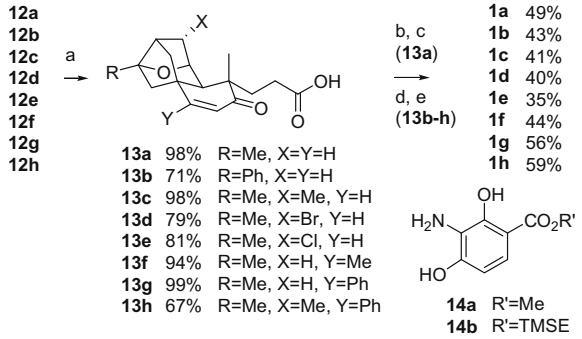
In vitro bioassay for testing analogs **1b**–**h** was carried out using strains of *S. aureus* and *Enterococcus faecalis* and *Enterococcus faecium*. Oxacillin (**15**) and vancomycin (**16**) were also tested as reference compounds for comparison (Table 1). Analogs **1b**–**h** displayed different levels of activities against *S. aureus* and *enterococci*. Substitution of the 15-methyl group (C17) with a phenyl group (i.e., **1b**) did not help to enhance the antibacterial activity, nor did 11-methyl-, 11-bromo-, 11-chloro-, and 7-methyl substitution (i.e., **1c**, **1d**, **1e**, **1f**) comparing with **1a**. Conspicuously, 7-phenylplatensimycin (**1g**) displayed higher activities than **1a** against methicillin-resistant *S. aureus* and vancomycin-insensitive *S. aureus*. 11-Methyl-7-phenylplatensimycin (**1h**) also showed similar activity



Scheme 2. Synthesis of tetracyclic intermediates. Reagents and conditions: (a) NaOMe, $MeCOCH_2Cl$ or $PhCOCH_2Cl$, MeOH; (b) NaH, (*E*)-$ICHCHCH_2I$ or $MeCHCHCH_2Br$ (*E*/*Z* = 5:1) or $BrCHCHCH_2Br$ (*E*/*Z* = 1:1), THF or NaH, $ClCHCHCH_2Cl$ (*E*/*Z* = 1:1), DMF; (c) 1 N KOH, MeOH; (d) $ClCO_2i$-Bu, TEA, THF, −20 °C; CH_2N_2, ether, 0 °C; (e) 3 mol % $Rh_2(OAc)_4$, CH_2Cl_2; (f) 1-ethylpiperidine, H_3PO_2, Et_3B, MeOH, 0 °C; (g) $MeCOCH_2PO(OMe)_2$, DIPEA, LiCl, MeCN; (h) Me_2PhSiH, 2 mol % $(Ph_3P)_3RhCl$, toluene, 60 °C; DIBAL, toluene, −40 °C; AcOH–H_2O (1:1), 0 °C; (i) 2 N HCl, THF, 0 °C; (j) *p*-TsOH, toluene, reflux; (k) KHMDS, THF–HMPA (5:1), −78 °C; MeI, −10 °C; (l) KOH, acrylonitrile, *t*-BuOH, 60 °C.



Scheme 3. Introduction of 7-substituents. Reagents and conditions: (a) Me_2CuLi, TMSCl, ether–THF, −78 °C; (b) DDQ, HMDS, benzene, reflux; (c) Me_2PhSiH, 2 mol % $(Ph_3P)_3RhCl$, benzene, 60 °C; PhLi, ether, −40 °C; AcOH–H_2O (1:1), 0 °C; (d) 2 N HCl, THF, 0 °C; (e) *p*-TsOH, toluene, reflux; (f) KHMDS, THF–HMPA (5:1), −78 °C; MeI, −10 °C; (g) KOH, acrylonitrile, *t*-BuOH, 60 °C.



Scheme 4. Synthesis of platensimycin and analogs. Reagents and conditions: (a) aq. KOH, MeOH, reflux; (b) **13a**, HATU, TEA, DMF; (c) 2 N KOH, 1,4-dioxane, 35 °C; (d) **13b**–**g**, HATU, TEA, DMF; (e) TASF, DMF, 40 °C.

Table 1
Bioassay of platensimycin (**1a**) and analogs

No.	Strain name	Drug sensitivity	MICs (μg/ml)								
			1a[f]	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**15**[g]	**16**[h]
1	*S. aureus*	MSSA[a]	1	2	0.25	1	1	0.5	0.25	<0.25	<0.25	NT[i]
2	*S. aureus*	MSSA	2	8	1	8	8	4	0.5	0.5	<0.25	NT
3	*S. aureus*	MSSA	8	8	8	32	8	2	2	0.5	<0.25	NT
4	*S. aureus*	MSSA	<0.25	1	<0.25	1	0.5	0.5	<0.25	<0.25	<0.25	NT
5	*S. aureus*	MRSA[b]	0.25	1	0.25	1	0.25	1	<0.25	<0.25	>32	NT
6	*S. aureus*	MRSA	0.25	2	0.5	2	0.5	0.5	<0.25	<0.25	>32	NT
7	*S. aureus*	MRSA	0.25	2	0.5	1	0.25	0.25	<0.25	<0.25	>32	NT
8	*S. aureus*	MRSA	1	4	1	4	4	2	0.5	<0.25	>32	NT
9	*S. aureus*	VISA[c]	2	16	2	8	8	4	1	1	>32	NT
10	*S. aureus*	VISA	2	16	8	16	8	4	1	4	>32	NT
11	*E. faecalis*	VSE[d]	⩽0.5	⩽0.5	1	4	2	⩽0.5	⩽0.5	8	NT	2
12	*E. faecalis*	VRE[e]	8	16	32	128	64	8	8	16	NT	64
13	*E. faecalis*	VRE	8	16	64	>128	64	16	16	8	NT	64
14	*E. feacium*	VRE	⩽0.5	8	2	4	8	2	2	2	NT	>128
15	*E. feacium*	VRE	⩽0.5	⩽0.5	1	16	2	⩽0.5	⩽0.5	⩽0.5	NT	>128

[a] MSSA: methicillin-sensitive *Staphylococcus aureus*.
[b] MRSA: methicillin-resistant *Staphylococcus aureus*.
[c] VISA: vancomycin-insensitive *Staphylococcus aureus*.
[d] VSE: vancomycin-sensitive *Enterococcus*.
[e] VRE: vancomycin-resistant *Enterococcus*.
[f] **1a** Platensimycin.
[g] **15** Oxacillin.
[h] **16** Vancomycin.
[i] NT: not tested.

profile. The present results are in contrast with those obtained for isoplatensimycin (**5**), which showed little activities against all strains of *S. aureus* and weak activities against vancomycin-resistant *E. faecium*.[4]

It is worth noting that 7-phenylplatensimycin (**1g**) and 11-methyl-7-phenylplatensimycin (**1h**) are the first analogs reported with better antimicrobial activities than the parent platensimycin (**1a**). From the present and previous studies, it may be concluded that the skeletal conservation/substituents appendage would be sensible future strategy for the development of useful analogs of platensimycin.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.02.037.

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