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Discovery of Azetidinyl Ketolides for the Treatment of Susceptible and Multidrug Resistant Community-Acquired Respiratory Tract Infections

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Respiratory tract bacterial strains are becoming increasingly resistant to currently marketed macrolide antibiotics. The current alternative telithromycin (**1**) from the newer ketolide class of macrolides addresses resistance but is hampered by serious safety concerns, hepatotoxicity in particular. We have discovered a novel series of azetidinyl ketolides that focus on mitigation of hepatotoxicity by minimizing hepatic turnover and time-dependent inactivation of CYP3A isoforms in the liver without compromising the potency and efficacy of **1**.

Introduction

The macrolide class of antibiotics has been very successful in the treatment of serious bacterial infections.[1] These natural product agents, first discovered over 50 years ago,[2] target the bacterial ribosome to inhibit protein synthesis. Two of the most successful members of this class are azithromycin and clarithromycin, first put on the market in the early 1990s and used extensively to treat community-acquired respiratory tract infections. The antibacterial spectrum is targeted primarily against Gram-positive bacterial strains including *Streptococcus pneumoniae* and *S. pyogenes*, fastidious Gram-negative strains including *Haemophilus influenzae* and *Moraxella catarrhalis*, atypicals *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophilia,* and *Helicobacter pylori*.[3] However, these older agents are becoming less effective as resistance has emerged over time, creating a medical need for novel macrolides addressing these resistant strains.[4] The two primary macrolide resistance mechanisms expressed in streptococci are erythromycin ribosome methylation (erm[a])[5] and active efflux (mef).[6] Newer or "third" generation macrolides (ketolides) have the advantage that they are poor inducers of the erm resistance mechanism and are also poor substrates for mef efflux-mediated resistance. Telithromycin (**1**, Figure 1)[7] is a third generation macrolide that covers macrolide sensitive and resistant strains and is currently the only marketed ketolide. Unfortunately, although a promising compound, **1** has been plagued by safety concerns.[8] Cethromycin (**2**) is the next most advanced ketolide and is currently in late stage development.[9] Both structures derive the moniker ketolide from the ketone function at position C3. Both also have bicyclic aryl rings tethered to the macrocylic ring, but in the case of **1** the tether springs from the N11 of the 11,12-carbamate fused to the macrocycle, while for **2** the attachment point is the O6 position. This disclosure focuses on the discovery of a novel series of N11 ketolides addressing some of the safety issues facing **1**.

Synthetic Chemistry

The synthesis of the azetidinyl ketolide template (**5**) began with the conversion of the clarithromycin starting material (**3**) to the known acylimidazole intermediate (**4**),[10] as shown in Scheme 1. This was carried out by bis-acetylation of the desosamine and cladinose sugars of **3** followed by dehydration of the 10-hydroxyl and concomitant transformation of the 11-hydroxyl to the acyl imidazole utilizing 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and carbonyl diimidazole (CDI). These reactions proceeded very smoothly in near-quantitative yield, requiring no further purification for the subsequent steps. Incorporation and cyclization of 1-benzhydrylazetidine-3-ylamine into intermediate **4** were unsuccessful under the standard conditions (triethylamine or diisopropylethylamine in acetonitrile with heating) for reacting amine tethers with this system likely because of steric crowding intrinsic to the azetidinylamine and its large benzhydryl protecting group. A stronger organic base (DBU) proved to be very effective for both the displacement of the imidazole and cyclization steps. Subsequent removal of the 4″-acetylcladinose using aqueous

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[a] Abbreviations: erm, erythromycin ribosome methylation genotype; mef, macrolide efflux genotype; RTI, respiratory tract infection; OM, otitis media; ER, in vitro human hepatic microsomal extraction ratio; TDI, time-dependent inhibition of cytochrome P450; CYP3A, cytochrome P450 isoform 3A (includes 3A4 and 3A5); DDI, drug−drug interactions; AO, aldehyde oxidase.

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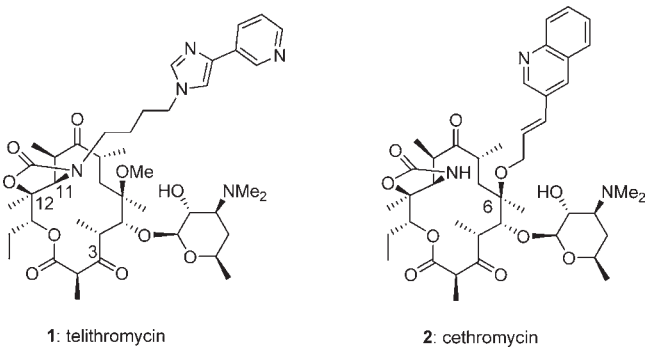
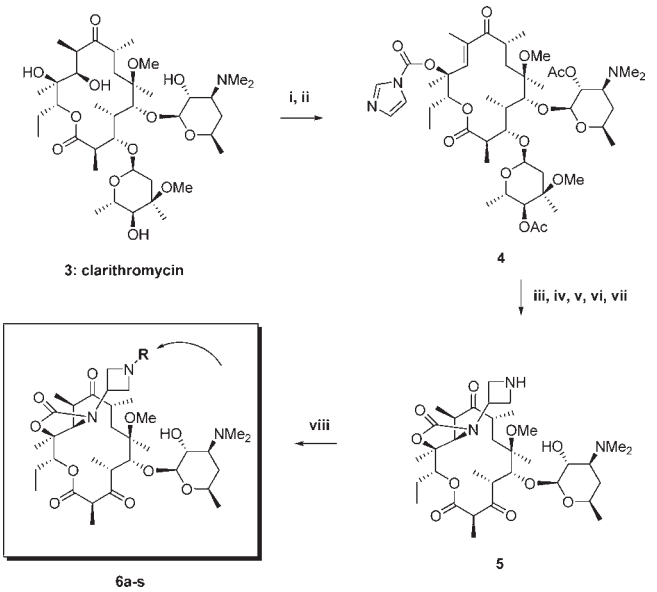


Figure 1. Structures of leading ketolides.

Scheme 1. Synthesis of the Azetidinyl Ketolide Template[a]



[a] Reagents and conditions: (i) Ac_2O, TEA, DMAP, DCM; (ii) DBU, CDI, THF, isopropyl ether; (iii) DBU, 1-benzhydrylazetidine-3-ylamine, MeCN, 50 °C; (iv) 2 N HCl, EtOH, 40 °C; (v) DMSO, pyridinium trifluoroacetate, EDC; (vi) MeOH, 50 °C; (vii) Pearlman's catalyst, H_2 (40 psi), MeOH, conc aq HCl (2−3 equiv) in Parr shaker at 35 °C, 2 h, then TEA (3 equiv), 35% yield over five steps; (viii) aldehyde or ketone, HOAc, TEA, 4 Å powdered molecular sieves, $Na(OAc)_3BH$, 30−70% yields.

HCl and ethanol yielded the C3 hydroxyl intermediate, which was oxidized to the C3 ketone using DMSO, pyridinium triflouroacetate, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After removal of the 2′-acetyl group by heating in methanol, the benzhydryl protecting group was removed by hydrogenolysis using Pearlman's catalyst to give the azetidinyl template **5**. From this template target analogues **6a**−**s** were synthesized by reductive amination using standard conditions.

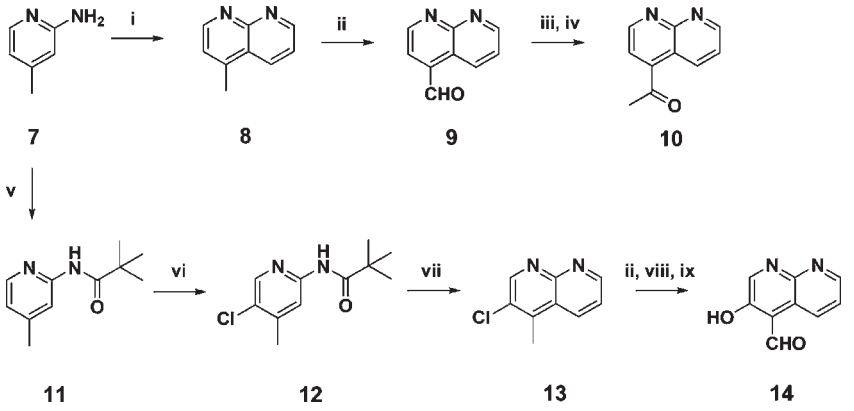
Many of the coupling partners for the azetidinyl template **5** were either commercially available or synthesized using well precedented chemistries. The naphthyridine aromatic headpieces, however, had to be constructed from more basic building blocks as illustrated in Schemes 2 and 3. The [1,8]naphthyridines were initially accessed via the Skraup reaction[11] on **7**, although in poor yields as is typical for such systems. The Skraup product **8** was subsequently converted to **9** (used to make **6m**, Figure 2) by way of selenium dioxide benzylic oxidation. Aldehyde **9** was further homologated to the methyl ketone **10**, used in the synthesis of diastereomeric isomers **6p** and **6q**. The isomers were separated by reverse-phase HPLC and the more active **6q** recrystallized from ethyl acetate to unambiguously assign the structure (see Supporting Information). For the synthesis of the 3-hydroxy intermediate **14** a modified Friedlander reaction[12] was found to be much more efficient than the Skraup approach. Thus, converting **7** to pivalamide **11** followed by treatment with chlorine gas yielded the 3-chloro intermediate **12**, which was dilithiated with *tert*-butyllithium in ethyl ether and subsequently condensed with 3-dimethylaminopropenal. Upon treatment with strong acid the intermediate obtained from the anion addition collapsed in relatively good overall yield to the [1,8]naphthyridine **13**. Selenium dioxide oxidation followed by methoxide displacement of the chloride proceeded smoothly. Methyl ether cleavage was then carried out in 6 N HCl to yield **14**.

The route used to access the [1,5]naphthyridine coupling partner **22**, used in the synthesis of **6s**, is given in Scheme 3. Thus, treatment of dibromide **15** with sodium methoxide in DMF gave **16** in good yield, which in turn was converted to **17** using palladium-catalyzed coupling of *tert*-butyl carbamate. Installation of a methyl group at the 4-position via dilithiation and methyl iodide treatment yielded **18** after acidic removal of the protecting group. The Skraup reaction to form the [1,5]naphthyridine system was generally better than the [1,8] disposition, and this was particularly true with an electron donating group in the 5-position (methoxy in this case). Thus, the conversion of **18** to **19** was affected in modest but workable (45%) yield. Oxidation of **19** with selenium dioxide was not successful, so we then resorted to a longer sequence of bromination followed by displacement with potassium acetate and ester hydrolysis to give the benzylic alcohol **20**. Oxidation of **20** with IBX yielded aldehyde **21**, which was subsequently treated with strong acid to cleave the methyl ether, giving **22**.

Results and Discussion

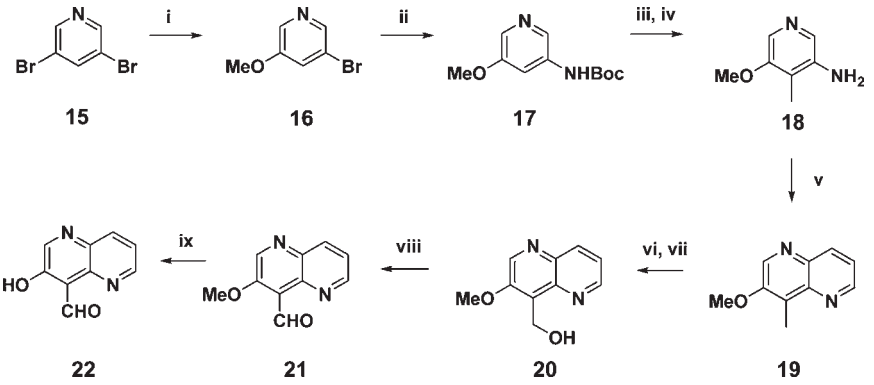
Gram-positive potency criteria for advancement of a compound was MIC ≤ 1 μg/mL against sensitive and resistant streptococcal strains, including the constitutive erm strain of *S. pyogenes* 1079 (superior to **1**, MIC = 32 μg/mL). The fastidious Gram-negative *H. influenzae*, with its restriction on entry into and efflux out of the bacterium, has always been a challenge for large molecules such as macrolides.[13] The *H. influenzae* 1325 strain (Table 1) was one of the least susceptible in our laboratories, and its modal MIC values were more or less representative of the MIC_{90} results obtained from larger populations of this pathogen ($N \geq 30$ strains). Thus, MIC ≤ 4 μg/mL vs *H. influenzae* 1325 was the standard for further advancement of a compound, matching the Gram-negative profile of **1** for its least susceptible strain. Because **1** has generated serious safety concerns,[8] particularly with respect to its hepatotoxicity profile,[14] we focused on lowering the liabilities of our analogues by reducing its elevated hepatic turnover and the high degree of time-dependent inactivation (TDI) of cytochrome P450 liver enzymes (specifically 3A isoforms). In addition to mitigating the hepatic liabilities associated with **1**, this strategy would have the added benefit of improving the pharmacokinetics through reduction of metabolic clearance and drug−drug interactions (DDI). Human liver microsomes were used to screen compounds for metabolic clearance.[15] The measured human liver microsomal extraction ratio (ER) of **1** was 0.7, consistent with the

Scheme 2. Synthesis of [1,8]Naphthyridines[a]



[a] Reagents and conditions: (i) *m*-nitrobenzene sodium sulfonate, conc H_2SO_4, glycerol, 120 °C, 8 h, then basify, 11% yield; (ii) SeO_2, dioxane, water, 80 °C, 77% yield; (iii) MeMgBr, toluene, THF, 24% yield; (iv) IBX, EtOAc, 80 °C, 86% yield; (v) pivoyl chloride, TEA, DCM, 82% yield; (vi) Cl_2(g), Na_2HPO_4, water, DCM; 86% yield; (vii) *t*-BuLi (2.1 equiv), Et_2O, −65 to −15 °C, then add 3-dimethylaminopropenal, −15 °C to room temp, treat with concentrated HCl, 52% yield; (viii) NaOMe, MeOH, 67% yield; (ix) 6 N HCl, reflux, 98% yield.

Scheme 3. Synthesis of [1,5]Naphthyridines[a]



[a] Reagents and conditions: (i) NaOMe, DMF, 50 °C, 90% yield; (ii) $BocNH_2$, $Pd_2(dba)_3$−$CHCl_3$, xantphos, Cs_2CO_3, dioxane, 100 °C for 30 h, 84% yield; (iii) *n*-BuLi, THF, MeI, MTBE, 100% yield; (iv) 4 N HCl, MeOH, 84% yield; (v) sodium 3-nitrobenzenesulfonate, $MeSO_3H$, $FeSO_4 \cdot 7H_2O$, glycerol, 125−130 °C, 45% yield; (vi) NBS, dibenzoyl peroxide, CCl_4, 95% yield; (vii) KOAc, DMF, MeOH, K_2CO_3, 63% yield; (viii) IBX, EtOAc; (ix) 6 N HCl, reflux, 90% yield combining steps viii and ix.

relatively high clearance observed in human.[16] CYP3A TDI was assessed using human liver microsomes with midazolam as a probe substrate for CYP3A. Compounds were evaluated for time- and concentration-dependent inhibition of midazolam metabolism, and K_I and k_{inact} values were determined. These parameters were then used to predict clinical DDI.[17] TDI measurements of **1** yielded K_I = 2.4 μM and k_{inact} = 0.04 min^{-1}, resulting in a predicted 6-fold increase in area under the curve (AUC) for a concomitantly administered CYP3A substrate, consistent with clinical observations.[18] In order to improve on the druglike properties of our analogues relative to **1**, the advancement criteria included in vitro microsomal ER ≤ 0.3 and TDI values resulting in predicted AUC increase of ≤3-fold for concomitantly administered CYP3A substrates. The cardiotoxicity liabilities (QTc) of **1** are not intrinsic to the compound but appear to be a function of its TDI and the effect this has on CYP3A object drugs.[18] Thus, the QTc potential of new analogues was monitored in a hERG patch-clamp assay with the goal of not exceeding that of **1** (IC_{50} ≥ 40 μM). Finally, the most promising compounds were evaluated in preclinical infection models using clinically relevant respiratory strains: *S. pneumoniae* 1095 (erm) in a murine respiratory tract infection (RTI) model and *H. influenzae* 1325 (least susceptible of all strains) in a gerbil otitis media (OM) model to ensure that they demonstrated equivalent or superior oral efficacy to that of **1**.

With a clear strategy in mind we then set out by cyclizing the tether connecting the critical aryl−alkyl group to the macrocylic ring system.[19] Additionally, a nitrogen was placed into the conformationally constrained tether to introduce polarity and to provide a convenient point of attachment for rapid SAR exploration and, significantly, modulation of the physicochemical properties of the final analogues. After considerable empirical evaluation of tether systems, the azetidine ring proved to be a rich vein for the program and is the focus of the present disclosure.[20] The unsubstituted azetidinyl template **5** had excellent activity against the susceptible strain of *S. pneumoniae* (1016), moderate activity against the mef strain (1175), but very poor erm potency (*S. pneumoniae* 1095 and *S. pyogenes* 1079; Table 1), which is not unexpected given the well-established need for an aryl ring to capture erm strains from a macrolide template. Appendage of a simple benzyl substituent (**6a**) gave a dramatic improvement in the erm *S. pneumoniae* profile, which was not improved upon with the corresponding pyridylmethyl analogues (**6b**,**c**). Introduction of a bromine ortho to the methylene bridge of **6c**, however, resulted in **6d**, which began to show good streptococcal potency, including against erm *S. pyogenes* 1079.

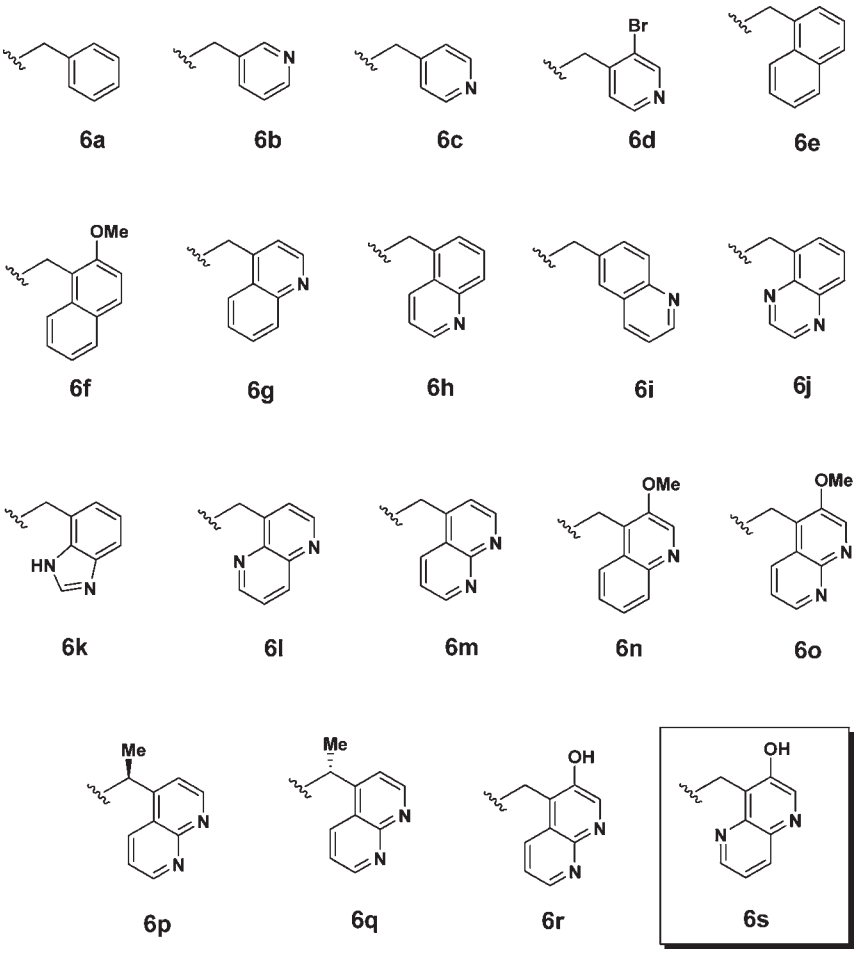


Figure 2. Aryl−alkyl attachments to intermediate **5** (Scheme 1) representing key test compounds **6a**−**s**.

Encouragingly, this level of erm potency was clearly differentiated from that of **1**.

The metabolism of **6d**, however, was high (ER > 0.8), and this compound was not pursued any further. Extension into bicyclic aromatics quickly pointed to the advantages of fused systems, which cover the rest of the analogues (**6e**−**s**) in Table 1. Similar to the *o*-bromine effect on the monocyclic ring of **6d**, halogens (not shown) and in particular a methoxy substituent (identified by synthesis of a library array) on the bicyclic-fused rings ortho to the methylene bridge demonstrated a distinct potency advantage (**6e** vs **6f**). Quinolines **6g** and **6h** showed a relative insensitivity to the placement of the nitrogen, although the attachment point to the macrolide made a significant difference, with the α ring junction being consistently preferred over β (**6h** vs **6i**). To reduce the lipophilicity of the target compounds, more polar heterocycles were subsequently incorporated. The benzimidazole **6k** was one such example; however, it lacked the requisite in vitro potency. The [1,5]naphthyridine analogue **6l** appeared more promising except that both the ER (0.7) and TDI (5-fold) measurements indicated no differentiation from **1** (Table 2). The [1,8]naphthyridine analogue **6m** also met the potency criteria and showed a distinct advantage over **6l** in the TDI assay (2-fold) but still had a high ER (0.6). Combining the *o*-methoxy substituent of **6f** with quinoline **6g** and [1,8]naphthyridine **6m** gave analogues **6n** and **6o**, respectively. While both **6n** and **6o** had extremely good Gram-positive potencies, their *H. influenzae* MICs were slightly elevated; furthermore, both had high ERs (**6n** = 0.6; **6o** = 0.8). Considering the potential for metabolism at the benzylic methylene bridge connecting the aryl ring to the azetidinyl nitrogen, methyl substitution was used at this position to block metabolism, yielding the diastereomers **6p** and **6q**. Not unexpectedly, the diastereomers displayed differential activities in the MIC panel, with **6q** having a clear potency advantage. This strategy also resulted in lowering the ER of **6q** relative to the parent **6m** considerably (0.3 vs 0.6); additionally **6q** maintained a reasonable TDI value (3-fold) as well as a hERG IC_{50} (43 μM) comparable to that of **1**. Consequently **6q** was profiled in the preclinical in vivo RTI and OM models. The oral efficacy results of **6q** compared to **1** and negative control **3** are given in Table 3 and were sufficiently encouraging (in combination with its predicted human clearance and safety properties) to nominate **6q** for clinical development. Single dose studies in humans, however, were disappointing, with plasma exposures upon oral dosing (300−1000 mg) achieving only approximately 20% of the predicted AUC. Subsequent investigation revealed extensive nonmicrosomally mediated metabolism of **6q** catalyzed by aldehyde oxidase (AO),[21] which halted development of the compound. Because AO is a cytosolic rather than microsomal enzyme, an in vitro assay with human liver cytosol was retroactively used to analyze the structure−metabolism relationships, in both the presence and absence of an AO inhibitor (raloxifene[22]), revealing a clear pattern of vulnerability of the [1,8]naphthyridine system to AO metabolism (Table 2). Thus, although the 3-hydroxy[1,8]naphthyridinyl **6r** had very promising in vitro potency, it too was revealed to be a substrate for AO and was not progressed further as a consequence. Encouragingly, the 3-hydroxy substituent imparted very favorable ER

Table 1. Minimum Inhibitory Concentrations (MICs, μg/mL) of Telithromycin (**1**), Clarithromycin (**3**), the Azetidinyl Ketolide Template (**5**), and the Azetidinyl Ketolide Analogues with Varying Aryl−Alkyl Substituents (**6a**−**s**) against Susceptible and Resistant Respiratory Pathogens

compd	*S. pneumoniae* 1016 (susceptible)	*S. pneumoniae* 1095 (ermB)	*S. pneumoniae* 1175 (mefA)	*S. pyogenes* 1079 (ermB)	*H. influenzae* 1325
1	≤0.06	≤0.06	≤0.06	32	4
3	≤0.06	>64	16	>64	16
5	≤0.06	64	2	>64	16
6a	≤0.06	≤0.06	0.12	>64	16
6b	≤0.06	≤0.06	2	>64	8
6c	≤0.06	0.12	0.5	>64	4
6d	≤0.06	≤0.06	≤0.06	1	8
6e	≤0.06	0.12	≤0.06	8	16
6f	≤0.06	0.12	≤0.06	1	16
6g	≤0.06	≤0.06	0.25	4	4
6h	≤0.06	≤0.06	≤0.06	4	8
6i	≤0.06	≤0.06	0.25	16	16
6j	≤0.06	≤0.06	≤0.06	2	8
6k	≤0.06	0.125	0.5	8	8
6l	≤0.06	≤0.06	≤0.06	1	8
6m	≤0.06	≤0.06	0.12	1	4
6n	≤0.06	≤0.06	≤0.06	≤0.06	8
6o	≤0.06	≤0.06	≤0.06	≤0.06	8
6p	≤0.06	≤0.06	0.25	16	16
6q	≤0.06	≤0.06	0.25	1	4
6r	≤0.06	≤0.06	≤0.06	0.25	4
6s	≤0.06	≤0.06	≤0.06	0.5	4

Table 2. Summary of Screening Data Used for Compound Selection[a]

compd	hepatic ER	AO metabolism	CYP3A K_I (μM)	CYP3A k_{inact} (min^{-1})	predicted fold ↑AUC for CYP3A substrate	hERG IC_{50} (μM)
1	0.7	no	2.4	0.04	6	40
6l	0.7	no	1.2	0.02	5	196
6m	0.6	yes	5.6	0.02	2	80
6q	0.3	yes	5.3	0.03	3	43
6r	<0.3	yes	25	0.03	≤2	140
6s	<0.3	no	24	0.02	≤2	67

[a] Methods provided in Supporting Information.

Table 3. Oral Efficacies in Preclinical Infection Models for **1**, **3**, **6q**, and **6s**

compd	PD_{50} ((mg/kg)/dose)[a] in murine RTI model: *S. pneumoniae* 1095	ED_{50} ((mg/kg)/dose)[a] in gerbil OM model: *H. infuenzae* 1325
1	31.2 ± 5.6[b]	37.5 ± 11.6[c]
3	>100	>100
6q	54.5 ± 24.1[c]	35.6[d]
6s	26.8[e]	53.6[e]

[a] Mean ± standard deviation ($N > 2$ studies) or average ($N \leq 2$ studies). [b] $N = 5$ studies. [c] $N = 3$ studies. [d] $N = 1$ study. [e] $N = 2$ studies.

(<0.3) and TDI (≤2-fold) properties to the molecule. Putting all of these elements together in one molecule, the 3-hydroxy-[1,5]naphthyridine analogue **6s** was found to meet all of the in vitro criteria for advancement, including antimicrobial potency, ER (<0.3), TDI (≤2-fold), hERG, and AO (no turnover, Table 2). Furthermore, in vivo profiling of **6s** demonstrated the required efficacy with oral dosing in both mouse RTI and gerbil OM models (Table 3), comparable to **1**. Consequently **6s** was advanced into development and is currently in phase 1 clinical trials.

Conclusion

In conclusion, we have discovered a novel azetidinyl tethered ketolide series addressing the problem of resistant respiratory pathogens for the treatment of community-acquired infections. The key analogues from this series generally matched the in vitro potency of **1** against the common susceptible- and macrolide-resistant strains and exceeded **1** versus the very resistant erm *S. pyogenes*. We devised a strategy of focusing on lowering hepatic metabolism and time-dependent inactivation of hepatic enzymes, specifically CYP3A isoforms, to address the hepatic safety issues associated with the first marketed drug from the ketolide class, telithromycin (**1**). Our first clinical candidate from this effort (**6q**) contained the [1,8]naphthyridine aryl group which was subsequently found to be extensively metabolized by AO. We have subsequently selected the 3-hydroxy[1,5]naphthyridine analogue (**6s**), which is differentiated from **6q** in that it is not an AO substrate and which further is differentiated from **1** in both predicted hepatic ER and CYP3A TDI while not compromising on its antibacterial potency or preclinical in vivo efficacy.

Experimental Section

General Chemistry Methods. All NMR spectra were recorded on a Varian Inova 400 MHz spectrometer unless otherwise specified. Reported data for **6s** were recorded on a Bruker DRX 600 MHz spectrometer. All final test compounds were purified to ≥98% analytical purity using preparative HPLC (Waters autopurification, Luna C-18 column, 250 mm × 21 mm, flow rate of 28 mL/min, gradient from 10% to 90% MeOH in 0.1% formic acid aqueous eluant). MS experiments were

performed using a Waters Micromass ZMD (electrospray ionization, chromatography on a Varian Polaris 5 C-18 column with MeCN, and 0.1% formic acid aqueous gradient eluant). Reagents were obtained from commercial sources unless otherwise noted. All reactions were performed under nitrogen unless otherwise noted.

11-Deoxy-2′,4″-diacetyl-10,11-didehydro-12-*O*-((1*H*-imidazol-1-yl)carbonyl)-6-*O*-methylerythromycin A (4). To a solution of clarithromycin (6-*O*-methylerythromycin A, **3**, 150 g, 201 mmol) in anhydrous dichloromethane (934 mL) cooled in an ice−water bath were added triethylamine (68.1 mL, 487 mmol), acetic anhydride (60 mL, 636 mmol), and DMAP (0.49 g, 4 mmol). The mixture was allowed to warm to ambient temperature for 48 h, then diluted with 0.5 M NaH_2PO_4 (1500 mL) and extracted with $CHCl_3$ (3 × 1 L). The organic layers were combined and dried over sodium sulfate, filtered, and concentrated to under vacuum to give clean 2′,4″-diacetyl-6-*O*-methylerythromycin A as an amorphous solid (167 g, 200 mmol). 2′,4″-Diacetyl-6-*O*-methylerythromycin A (100 g, 120 mmol) was dissolved in anhydrous THF (300 mL) and diisopropyl ether (700 mL), then treated with 1,1′-carbonyldiimidazole (97.4 g, 601 mmol) and DBU (53.9 mL, 366 mmol), and the resulting mixture was heated to 40 °C for 2 h. The reaction mixture was then stirred at ambient temperature for 48 h before diluting with ethyl acetate (1 L) and water (1 L). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (2 × 1 L). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum to yield the title compound and some imidazole-related impurities (121 g total). This material was of sufficient purity to use in subsequent reactions and was used as such. MS (ESI+) for *m*/*z* 908.50 $(M + H)^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 0.88−0.95 (m, 6 H), 1.11 (s, 1 H), 1.12−1.13 (m, 6 H), 1.17 (d, 6 H, *J* = 6.00), 1.23 (d, 3 H, *J* = 6.80), 1.34−1.59 (br, 4 H), 1.61−1.67 (m, 6 H), 1.76 (s, 3 H), 1.83−1.99 (br, 6 H), 2.01 (s, 3 H), 2.10 (s, 3 H), 2.24 (s, 6 H), 2.39 (d, 2H, *J* = 15.2), 3.11 (s, 3 H), 3.32 (s, 3 H), 3.55−3.65 (br, 3 H), 4.33 (m, 1 H), 4.58−4.72 (m, 3 H), 4.96 (br, 1 H), 5.79 (dd, 1 H, *J* = 2.80, *J* = 10.40), 6.63 (s, 1 H), 7.05 (s, 1 H), 7.35 (s, 1 H), 8.06 (s, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl(azetidin-3-yl)imino)erythromycin A Dihydrochloride (5). Step 1. DBU (10 mL, 67 mmol) was added to 1-benzhydrylazetidin-3-ylamine (9.0 g, 37.8 mmol) dissolved in anhydrous MeCN (100 mL) at ambient temperature. To this solution was added 11-deoxy-2′,4″-diacetyl-10,11-didehydro-12-*O*-((1*H*-imidazol-1-yl)carbonyl)-6-*O*-methylerythromycin A (**4**) (32.5 g, 35.8 mmol), and the resulting mixture was heated (50 °C) for 7.5 h, then allowed to stir overnight at ambient temperature. A white precipitate was collected by filtration (21 g, 19.5 mmol). The filtrate was concentrated to about 25 mL before adding water (20 mL) and saturated aqueous $NaHCO_3$ solution (30 mL) and extracting the resulting mixture with DCM (dichloromethane, 50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over sodium sulfate, and concentrated under vacuum to a tan foam. MS (ESI+) for *m*/*z* 540 $(M/2 + H)^+$.

Step 2. The product from step 1 was dissolved in EtOH (100 mL) and 2 N HCl (100 mL), heated (40 °C) for 3 h, then cooled to 30 °C and stirred overnight. The resulting mixture was concentrated under vacuum, maintaining the bath at 28 °C, to about half of the original volume. To the resulting concentrate was added DCM (100 mL), followed by careful addition of solid potassium carbonate to basify the aqueous layer (to pH 10). The organic layer was separated, and the aqueous layer was re-extracted with DCM (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to a white foam. MS (ESI+) for *m*/*z* 440 $(M/2 + H)^+$.

Step 3. The crude product from step 2 was redissolved in anhydrous DCM (200 mL) and to which were added anhydrous DMSO (20 mL, 282 mmol), pyridinium trifluoroacetate (15 g, 77.7 mmol), and finally 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 g, 156.5 mmol). The mixture was stirred at ambient temperature for 3 h and then treated with saturated aqueous $NaHCO_3$ solution (30 mL) and water (30 mL). The resulting mixture was separated, the aqueous layer was re-extracted with DCM (3 × 75 mL), and the combined organic layers were washed with water (50 mL). After the organics were dried over sodium sulfate, the solvent was removed under vacuum to yield a yellow foam. MS (ESI+) for *m*/*z* 439 $(M/2 + H)^+$.

Step 4. The yellow foam from step 3 was redissolved in MeOH (200 mL) and heated (50 °C) for 24 h, then concentrated under vacuum to dryness. This solid material was rinsed with hexanes/diethyl ether (2/1) and treated with MeOH (50 mL) and the resulting slurry heated on a steam bath up to the boiling point, then cooled to ambient temperature. The resulting white solid of 3-descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-benzhydrylazetidin-3-yl)imino)erythromycin A was filtered and dried under vacuum (10.5 g, 12.6 mmol, 35% yield over four steps). MS (ESI+) for *m*/*z* 418 $(M/2 + H)^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 4.60 (s, 1 H), 4.88 (br d, 1 H), 7.16 (m, 2 H), 7.21 (m, 4 H), 7.41 (m, 4 H).

Step 5a. The white solid from step 4 was dissolved in MeOH and treated with concentrated 37 wt % HCl (2.4 mL, 28 mmol). To this was added palladium hydroxide (20% weight Pd, about 6 g), and the slurry was subjected to hydrogen gas (40−50 psi) in a Parr shaker while heating (35 °C) for up to 2 h. The Parr flask was cooled to room temperature and purged with nitrogen, and the solids were filtered off. The filtrate was treated with TEA (6.0 mL, 43 mmol) and concentrated under vacuum to yield the title compound (**5**) along with diphenylmethane (1 equiv) and the hydrochloride salt of TEA (2.2 equiv) as a free-flowing crude solid (14 g total, approximately 59% by weight the title compound **5**). This material was used in subsequent coupling reactions. MS (ESI+) for *m*/*z* 335 $(M/2 + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 4.16 (br t, 1 H), 4.27 (d, 1 H), 4.33 (d, 1 H), 4.48 (br t, 1 H), 4.71−4.59 (m, 2 H).

Alternatively, the benzhydryl was removed using the procedure in step 5b.

Step 5b. Palladium hydroxide (5.18 kg; 20% on carbon, 50% water wet) was charged to a 200 L reactor (water wet, nitrogen purged). To a 100 L glass-lined reactor was charged MeOH (82.9 L) and concentrated 37 wt % HCl (2.24 L). 3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-benzhydrylazetidin-3-yl)imino)erythromycin A (10.29 kg, 12.3 mol) was then added. The resulting solution was transferred to the 200 L reactor and the dark slurry heated to 40−50 °C for 2 h, then cooled to 20−25 °C. The mixture was filtered over Celite and rinsed with MeOH (2 × 50 L). To a Hastelloy pressure reactor (prewet with water), palladium hydroxide (1.03 kg; 20% on carbon, 50% water wet) and the filtrate obtained above were added. After nitrogen and hydrogen purge, the reaction mixture was warmed to 40−50 °C. The mixture was held at 50 psi of hydrogen for 2 h, then cooled to 20−25 °C. After nitrogen purge, the slurry was filtered through Celite and washed with MeOH (2 × 20 L). The filtrate was concentrated and solvent-exchanged with THF (100 L) to a final volume of ∼40 L (water from the wet catalyst was removed during the azeotropic distillation at 250 mmHg, 45−50 °C). The resulting mixture was cooled to 20−25 °C and stirred for 3 h. The batch was filtered and the filter cake rinsed with THF (10 L). The solids were dried under vacuum to afford 8.27 kg of desired **5** as a pure dihydrochloride salt (8.27 kg, 11.1 mol, 94%). MS (ESI+) for *m*/*z* 668.4 $(M + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.78 (t, 3H, *J* = 7.46 Hz), 0.91 (d, 3H, *J* = 6.64 Hz), 1.06 (d, 3H, *J* = 6.64 Hz), 1.08−1.30 (m, 11H), 1.32−1.79 (m, 2H), 1.95 (m, 1H), 2.38−2.54 (m, 1H), 2.59 (s, 3H), 2.68 (s, 3H). 2.77 (s, 3H), 3.02−3.39 (m, 6H), 3.52−3.65 (m, 3H), 3.94 (q, 1H, *J* = 7.46 Hz), 4.03−4.30 (m, 5H), 4.42 (t, 2H, *J* = 6.64 Hz), 4.51−4.63 (m, 2H), 4.78−4.93 (m, 2H).

Typical Reductive Amination Coupling Procedure: 3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((phenyl)methyl)azetidin-3-yl)imino)erythromycin A (6a). Intermediate **5** (1310 mg, 1.83 mmol) was dissolved in anhydrous

THF (40 mL), followed by TEA (0.78 mL, 5.58 mmol), acetic acid (0.32 mL, 5.58 mmol), benzaldehyde (0.203 mL, 2.01 mmol), and powdered molecular sieves (4 Å, 1310 mg). The resulting mixture was heated (49 °C) and stirred for 4 h, whereupon sodium triacetoxyborohydride (1971 mg, 9.30 mmol) was added with continued heating for an additional 1 h, then cooled to ambient temperature overnight. The reaction mixture was diluted with DCM (40 mL), filtered to remove solids, and extracted with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). The aqueous layer was separated and re-extracted with DCM (4 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to afford 1.29 g of crude coupled product, which was purified by reverse phase preparative HPLC to afford desired titled compound **6a** (650 mg, 0.86 mmol, 47% yield). MS (ESI+) for m/z 379.7 $(M/2 + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.84−0.96 (m, 6 H), 1.02 (d, J = 6.63 Hz, 3 H), 1.16 (d, J = 7.02 Hz, 3 H), 1.23−1.39 (m, 17 H), 1.44−1.54 (m, 1 H), 1.57 (s, 2 H), 1.62−1.73 (m, 1 H), 1.77 (d, J = 6.83 Hz, 1 H), 1.81−1.93 (m, 1 H), 2.00−2.09 (m, 1 H), 2.56 (s, 1 H), 2.62−2.69 (m, 2 H), 2.82 (s, 6 H), 3.17 (s, 2 H), 3.34−3.52 (m, 2 H), 3.67 (s, 1 H), 3.73 (br s, 1 H), 4.01−4.16 (m, 2 H), 4.24 (t, J = 8.10 Hz, 1 H), 4.31 (s, 1 H), 4.38 (s, 2 H), 4.42−4.52 (m, 2 H), 4.56 (s, 1 H), 4.96 (dd, J = 10.44, 2.24 Hz, 1 H), 7.26−7.74 (m, 5 H).

Final test compounds **6b**−**o**,**r** were synthesized with the same procedure used for **6a**. The procedures for **6p**−**q**,**s** were altered as described below.

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((pyridin-3-yl)methyl)azetidin-3-yl)imino)erythromycin A (6b). MS (ESI+) for m/z 380 $(M/2 + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.89 (t, J = 7.32 Hz, 2 H), 1.00 (d, J = 6.64 Hz, 2 H), 1.15 (d, J = 7.03 Hz, 2 H), 1.23−1.38 (m, 7 H), 1.40−1.57 (m, 3 H), 1.61−1.72 (m, 1 H), 1.75 (d, J = 7.03 Hz, 1 H), 3.65 (s, 1 H), 3.70−3.78 (m, 1 H), 3.93−4.00 (m, 1 H), 4.00−4.08 (m, 2 H), 4.12−4.17 (m, 1 H), 4.31 (d, J = 8.01 Hz, 1 H), 4.38 (d, J = 6.64 Hz, 1 H), 4.94 (dd, J = 10.54, 2.54 Hz, 1 H), 7.39−7.53 (m, 1 H), 7.84−7.91 (m, 1 H), 8.51 (dd, J = 5.08, 1.56 Hz, 1 H), 8.56 (d, J = 1.76 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((pyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6c). MS (ESI+) for m/z 380 $(M/2 + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.86−0.94 (m, 3 H), 1.01 (d, J = 6.83 Hz, 3 H), 1.12−1.20 (m, 3 H), 1.23−1.39 (m, 13 H), 1.55 (s, 3 H), 1.62−1.72 (m, 1 H), 1.76 (d, J = 6.83 Hz, 2 H), 1.82−1.93 (m, 1 H), 2.00−2.10 (m, 1 H), 2.55 (s, 1 H), 2.66 (s, 3 H), 2.82 (s, 6 H), 3.18 (s, 2 H), 3.35−3.53 (m, 2 H), 3.67 (s, 1 H), 3.70−3.82 (m, 2 H), 3.90 (br s, 1 H), 3.98−4.25 (m, 6 H), 4.35 (dd, J = 27.05, 7.32 Hz, 2 H), 4.94 (dd, J = 10.45, 2.64 Hz, 1 H), 7.43 (d, J = 6.05 Hz, 2 H), 8.45−8.61 (m, 2 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((3-bromopyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6d). MS (ESI+) for m/z 419.9 $(M/2 + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.86−0.97 (m, 4 H), 1.02 (d, J = 6.83 Hz, 3 H), 1.19 (d, J = 7.03 Hz, 3 H), 1.27−1.38 (m, 15 H), 1.56 (s, 3 H), 1.61−1.71 (m, 1 H), 1.75−1.82 (m, 2 H), 1.82−1.99 (m, 2 H), 2.58 (br s, 7 H), 2.70 (s, 3 H), 3.12−3.26 (m, 2 H), 3.60−3.75 (m, 4 H), 3.86−3.97 (m, 3 H), 4.05 (s, 2 H), 4.13−4.24 (m, 1 H), 4.29−4.40 (m, 2 H), 4.94 (dd, J = 10.45, 2.64 Hz, 1 H), 7.49 (d, J = 5.08 Hz, 1 H), 8.48 (d, J = 5.08 Hz, 1 H), 8.65 (s, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((naphth-1-yl)methyl)azetidin-3-yl)imino)erythromycin A (6e). MS (ESI+) for m/z 404.7 $(M/2 + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.87−0.96 (m, 6 H), 1.03 (d, J = 6.83 Hz, 3 H), 1.16 (d, J = 7.03 Hz, 3 H), 1.21−1.40 (m, 18 H), 1.52 (d, J = 10.94 Hz, 1 H), 1.57 (s, 2 H), 1.65−1.74 (m, 1 H), 1.76 (d, 1 H), 1.81−1.96 (m, 1 H), 2.02 (d, J = 9.96 Hz, 1 H), 2.50−2.59 (m, 1 H), 2.62 (s, 2 H), 2.81 (s, 5 H), 3.11−3.25 (m, 2 H), 3.34−3.51 (m, 2 H), 3.67 (s, 1 H), 3.69−3.81 (m, 1 H), 3.87−3.97 (m, 1 H), 4.01−4.11 (m, 1 H), 4.16−4.28 (m, 1H), 4.28−4.41 (m, 4 H), 4.48 (t, J = 8.40 Hz, 1 H), 4.64−4.80 (m, 2 H), 4.97 (dd, J = 10.64, 2.64 Hz, 1 H), 7.45−7.69 (m, 4 H), 7.89−8.00 (m, 2 H), 8.21 (d, J = 8.40 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((2-methoxynaphth-1-yl)methyl)azetidin-3-yl)imino)erythromycin A (6f). MS (ESI+) for m/z 839.3 $(M + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.86−0.91 (m, 5 H), 0.99 (d, J = 6.64 Hz, 3 H), 1.14 (d, J = 7.03 Hz, 3 H), 1.27−1.32 (m, 15 H), 1.50 (q, J = 11.72 Hz, 1 H), 1.56 (s, 3 H), 1.63−1.72 (m, 1 H), 1.76 (d, J = 7.03 Hz, 2 H), 1.81−1.90 (m, 1 H), 2.02 (br d, J = 12.31 Hz, 1 H), 2.53 (q, J = 7.10 Hz, 1 H), 2.61 (s, 3 H), 2.79 (s, 6 H), 3.11−3.19 (m, 2 H), 3.37 (dd, J = 12.01, 4.00 Hz, 1 H), 3.41−3.45 (m, 1 H), 3.65 (s, 1 H), 3.69−3.73 (m, 1 H), 4.04 (d, J = 6.84 Hz, 1 H), 4.07 (s, 3 H), 4.17−4.27 (m, 2 H), 4.29 (d, J = 8.01 Hz, 1 H), 4.36 (d, J = 7.03 Hz, 1 H), 4.54−4.60 (m, 1 H), 4.71 (t, J = 10.25 Hz, 1 H), 4.75−4.79 (m, 1 H), 4.90 (dd, J = 10.54, 2.44 Hz, 1 H), 4.99 (s, 2 H), 7.43 (t, J = 7.52 Hz, 1 H), 7.51 (d, J = 9.18 Hz, 1 H), 7.90 (d, J = 7.81 Hz, 1 H), 8.05 (d, J = 9.18 Hz, 1 H), 8.19 (d, J = 8.59 Hz, 1 H), 8.49 (s, 2 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((quinolin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6g). MS (ESI+) for m/z 810.2 $(M + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.86−0.91 (m, 4 H), 1.01 (d, J = 6.64 Hz, 3 H), 1.16 (d, J = 7.03 Hz, 3 H), 1.28−1.33 (m, 13 H), 1.47−1.51 (m, 1 H), 1.55 (s, 3 H), 1.62−1.70 (m, 1 H), 1.76 (d, J = 7.82 Hz, 2 H), 1.82−1.91 (m, 1 H), 1.99 (br d, J = 14.65 Hz, 1H), 2.51−2.59 (m, 1 H), 2.64 (s, 3 H), 2.75 (s, 6 H), 3.15−3.22 (m, 2 H), 3.25−3.28 (m, 1 H), 3.42 (dd, J = 10.55, 7.23 Hz, 1 H), 3.60−3.64 (m, 1 H), 3.67 (s, 1 H), 3.69−3.72 (m, 1 H), 4.01−4.07 (m, 1 H), 4.18 (m, 1 H), 4.28−4.37 (m, 4 H), 4.96 (br d, J = 12.89 Hz, 1 H), 7.53 (d, J = 4.49 Hz, 1 H), 7.61−7.68 (m, 1 H), 7.79 (t, J = 8.24 Hz, 1 H), 8.04 (d, J = 7.81 Hz, 1 H), 8.22 (d, J = 8.98 Hz, 1 H), 8.53 (s, 1 H), 8.80 (d, J = 4.69 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((quinolin-5-yl)methyl)azetidin-3-yl)imino)erythromycin A (6h). MS (ESI+) for m/z 810.2 $(M + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.89−0.93 (m, 4 H), 1.01 (d, J = 6.84 Hz, 3 H), 1.15 (d, J = 7.03 Hz, 3 H), 1.28−1.33 (m, 14 H), 1.43−1.53 (m, 1 H), 1.56 (s, 3 H), 1.63−1.71 (m, 1 H), 1.75 (d, J = 7.03 Hz, 2 H), 1.83−1.92 (m, 1 H), 2.03 (br d, J = 15.63 Hz, 1 H), 2.49−2.56 (m, 1 H), 2.60 (s, 3 H), 2.82 (s, 6 H), 3.12−3.22 (m, 2 H), 3.38−3.46 (m, 2 H), 3.66 (s, 1 H), 3.68−3.76 (m, 2 H), 3.99−4.07 (m, 2 H), 4.15−4.21 (m, 3 H), 4.30 (d, J = 8.01 Hz, 1 H), 4.37 (d, J = 6.64 Hz, 1 H), 4.48 (d, J = 13.28 Hz, 1 H), 4.57 (d, J = 13.48 Hz, 1 H), 4.95 (br d, J = 10.35 Hz, 1 H), 7.63 (dd, J = 8.59, 4.30 Hz, 1 H), 7.68 (d, J = 7.81 Hz, 1 H), 7.76−7.79 (m, 1 H), 8.05 (d, J = 8.04 Hz, 1 H), 8.41 (br s, 2 H), 8.74 (br d, J = 10.94 Hz, 1 H), 8.90 (dd, J = 4.30, 1.55 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((quinolin-6-yl)methyl)azetidin-3-yl)imino)erythromycin A (6i). MS (ESI+) for m/z 810.2 $(M + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.89−0.91 (m, 5 H), 1.01 (d, J = 6.84 Hz, 3 H), 1.15 (d, J = 7.03 Hz, 3 H), 1.27−1.33 (m, 15 H), 1.47−1.53 (m, 1 H), 1.56 (s, 3 H), 1.63−1.71 (m, 1 H), 1.74 (d, J = 7.03 Hz, 2 H), 1.82−1.88 (m, 1 H), 2.02 (br d, J = 12.69 Hz, 1 H), 2.53 (dd, J = 14.16, 6.93 Hz, 1 H), 2.58 (s, 3 H), 2.81 (s, 6 H), 3.12−3.19 (m, 2 H), 3.35−3.46 (m, 2 H), 3.65 (br s, 1 H), 3.68−3.74 (m, 1 H), 4.01−4.06 (m, 2 H), 4.22−4.26 (m, 1 H), 4.28 (d, J = 8.01 Hz, 1 H), 4.36 (d, J = 6.64 Hz, 1 H), 4.39−4.44 (m, 2 H), 4.48 (d, J = 3.71 Hz, 1 H), 4.50−4.55 (m, 1 H), 4.95 (br d, J = 10.45 Hz, 1 H), 7.59 (dd, J = 8.40, 4.30 Hz, 1 H), 7.83 (dd, J = 8.69, 1.86 Hz, 1 H), 8.06 (d, J = 1.76 Hz, 1 H), 8.08 (d, J = 8.60 Hz, 1 H), 8.42 (dd, J = 8.40, 1.17 Hz, 1 H), 8.89 (dd, J = 4.39, 1.66 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((quinoxalin-5-yl)methyl)azetidin-3-yl)imino)erythromycin A (6j). MS (ESI+) for m/z 405.7 $(M/2 + H)^+$. ^1H NMR (CD_3OD) δ ppm: 0.88 (t, J = 7.32 Hz, 3 H), 0.99 (d, J = 6.83 Hz, 3 H), 1.16 (d, 3 H), 1.20−1.37 (m, 14 H), 1.48−1.92 (m,8 H), 2.38 (s, 6 H), 2.47−2.77 (m, 6 H), 3.07−3.29 (m, 3 H), 3.49−3.70 (m, 4 H), 3.87−4.06 (m, 2 H), 4.15 (s, 1 H), 4.24−4.33 (m, 2 H),

4.37−4.55(m, 2 H), 4.85−4.96 (m, 1 H), 7.77−7.89 (m, 2 H), 8.03 (dd, J = 7.13, 2.83 Hz, 1 H), 8.91 (dd, J = 20.89, 1.76 Hz, 2 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-(([1,5]naphthyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6l). MS (ESI+) for m/z 406.4 $(M/2 + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.89 (t, J = 7.41 Hz, 3 H), 1.03 (d, J = 6.83 Hz, 3 H), 1.12−1.20 (m, 4 H), 1.24−1.38 (m, 13 H), 1.47−1.60 (m, 4 H), 1.61 −1.91 (m, 5 H), 2.00−2.09 (m, 1 H), 2.66 (s, 2 H), 2.83 (s, 6 H), 3.11−3.23 (m, 2 H), 3.39−3.50 (m, 2 H), 3.67−3.80 (m, 2 H), 4.01−4.10 (m, 1 H), 4.24−4.34 (m, 2 H), 4.39 (d, J = 6.83 Hz, 1 H), 4.59−4.63 (m, 1 H), 4.64−4.75 (m, 2 H), 4.95 (dd, J = 10.54, 2.34 Hz, 1 H), 5.07 (s, 2 H), 7.84−7.93 (m, 2 H), 8.53 (dd, J = 8.59, 1.76 Hz, 1 H), 9.04 (d, J = 4.29 Hz, 1 H), 9.09 (dd, J = 4.20, 1.66 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-(([1,8]naphthyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6m). MS (ESI+) for m/z 406.7 $(M/2 + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.90 (t, J = 7.41 Hz, 3 H), 0.98−1.07 (m, 3 H), 1.12−1.21 (m, 3 H), 1.26−1.40 (m, 13 H), 1.49−1.60(m, 4 H), 1.62−1.93 (m, 4 H), 1.99−2.09 (m, 1 H), 2.50−2.60 (m, 1 H), 2.62 (s, 2 H), 2.83 (s, 6 H), 3.13−3.24 (m, 2 H), 3.36−3.50 (m, 2 H), 3.59−3.79 (m, 4 H), 3.94−4.09 (m, 3 H), 4.13−4.22 (m, 1 H), 4.28−4.45 (m, 4 H), 4.96 (dd, J = 10.24, 2.63 Hz, 1 H), 7.64 (d, J = 4.49 Hz, 1 H), 7.69 (dd, J = 8.39, 4.29 Hz, 1 H), 8.79 (dd, J = 8.49, 1.85 Hz, 1 H), 9.03 (d, J = 4.49 Hz, 1 H), 9.08 (dd, J = 4.29, 1.76 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-(([1,5]naphthyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6n). MS (ESI+) for m/z 420.2 $(M/2 + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.87 (t, J = 7.42 Hz, 3 H), 0.97 (d, J = 6.64 Hz, 3 H), 1.07−1.38 (m, 16 H), 1.52 (s, 3 H), 1.56−1.89 (m, 5 H), 2.33 (s, 5 H), 2.45−2.69 (m, 5 H), 3.08−3.27 (m, 3 H), 3.35 (s, 1 H), 3.41 (t, 1 H), 3.53−3.66 (m, 3 H), 3.85 (d, J = 7.81 Hz, 2 H), 3.98−4.17 (m, 5H), 4.21−4.34 (m, 4 H), 4.82−4.89 (m, 2 H), 7.58−7.67 (m, 2 H), 7.94−8.02 (m, 1 H), 8.14−8.23 (m, 1 H), 8.84 (s, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-(([1,5]naphthyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6o). MS (ESI+) for m/z 420.7 $(M/2 + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.87 (t, J = 7.42 Hz, 3 H), 0.96 (d, 3 H), 1.08−1.37 (m, 17 H), 1.52 (s, 3 H), 1.57−1.87 (m, 5 H), 2.33 (s, 6 H), 2.45−2.54 (m, 1 H), 2.54−2.58 (m, 3 H), 2.57−2.66 (m, 1 H), 3.07−3.26 (m, 3 H), 3.36−3.43 (m, 1 H), 3.52−3.64 (m, 3 H), 3.79−3.87 (m, 2 H), 3.97−4.10 (m, 2 H), 4.13−4.19 (m, 3 H), 4.23−4.32 (m, 3 H), 4.83−4.89 (m, 1 H), 7.62 (dd, J = 8.49, 4.20 Hz, 1 H), 8.71 (dd, J = 8.59, 1.76 Hz, 1 H), 8.92 (dd, J = 4.10, 1.76 Hz, 1 H), 9.05 (s, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-(1*S*-([1,8]naphthyridin-4-yl)ethyl)azetidin-3-yl)imino)erythromycin A (6p) and 3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-(1*R*-([1,8]naphthyridin-4-yl)-ethyl)azetidin-3-yl)imino)erythromycin A (6q). Intermediate **5** (4.21 g) was treated with anhydrous THF (35 mL), 1-[1,8]naphthyridin-4-ylethanone (**10**) (0.7 g, 4.07 mmol), acetic acid (0.33 mL, 5.8 mmol), TEA (1.55 mL, 11.1 mmol), and powdered 4 Å powdered molecular sieves (4.5 g), and the slurry was heated with stirring for 4 h at 49 °C. At this point, sodium triacetoxyborohydride (2.35 g, 11 mmol) was added, and heating was continued for another hour before removing the heat source and allowing the reaction flask to come to ambient temperature overnight with continuous stirring. The solids were then filtered off, and to the filtrate were added saturated aqueous $NaHCO_3$ (15 mL) and water (15 mL), and the layers were separated. The aqueous layer was re-extracted with DCM (5 × 40 mL). The solid filtrant was rinsed into a separatory funnel and extracted as the filtrate was. The combined organic layers were dried (sodium sulfate), filtered, and concentrated under vacuum to give 4 g of a crude mixture of diastereomers. The diastereomers were separated by reverse phase preparative HPLC multiple injections (using gradient from 8% to 30% A in B over 10 min, where A = acetonitrile containing 0.1% formic acid and B = water containing 0.1% formic acid). The more polar peak (**6q**) eluted at 4.00 min (1.1 g total collected) and the less polar peak (**6p**) just after at 4.38 min (1.0 g total collected). After recrystallization from ethyl acetate, the structure of the more potent **6q** was assigned unambiguously by X-ray (Supporting Information): MS (ESI+) for m/z 825.2 $(M + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.85 (t, J = 7.33 Hz, 3 H), 1.04 (d, J = 6.64 Hz, 3 H), 1.17 (d, J = 7.03 Hz, 3 H), 1.24−1.29 (m, 13 H), 1.42 (d, J = 6.44 Hz, 3 H), 1.54 (s, 3 H), 1.60−1.68 (m, 1 H), 1.71−1.85 (m, 4 H), 2.33 (s, 6 H), 2.35 (s, 3 H), 2.52−2.64 (m, 2 H), 3.07−3.15 (m, 1 H), 3.18−3.25 (m, 3 H), 3.55−3.58 (m, 1 H), 3.60 (br s, 1 H), 3.85−3.89 (m, 1 H), 3.98−4.03 (m, 1 H), 4.14−4.19 (m, 2 H), 4.25 (d, J = 7.42 Hz, 2 H), 4.51 (q, J = 6.45 Hz, 1 H), 4.99 (br d, J = 10.55 Hz, 1 H), 7.69−7.72 (m, 2 H), 8.97 (d, J = 8.59 Hz, 1 H), 9.04 (d, J = 4.69 Hz, 1 H), 9.09 (dd, J = 4.20, 1.66 Hz, 1 H). The structure of the **6p** diastereomer was assigned by inference: MS (ESI+) for m/z 825.4 $(M + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.91−0.94 (m, 6 H), 1.15 (d, J = 7.03 Hz, 3 H), 1.30−1.32 (m, 6 H), 1.34−1.36 (m, 6 H), 1.39 (d, J = 6.64 Hz, 3), 1.54 (s, 3 H), 1.64−1.70 (m, 1 H), 1.72−1.81 (m, 2 H), 1.85−1.92 (m, 2 H), 2.56 (s, 6 H), 2.73 (s, 3 H), 2.95−3.03 (m, 1 H), 3.17−3.25 (m, 2 H), 3.34−3.37 (m, 1 H), 3.57 (t, J = 7.62 Hz, 1 H), 3.65−3.77 (m, 4 H), 4.05−4.10 (m, 1 H), 4.11−4.19 (m, 1 H), 4.35 (d, J = 7.23 Hz, 2 H), 4.51−4.55 (m, 1 H), 4.99 (br d, J = 10.55 Hz, 1 H), 7.70 (dd, J = 8.40, 4.20 Hz, 1 H), 7.78 (d, J = 4.69 Hz, 1 H), 8.55 (s, 1 H), 8.95 (dd, J = 8.60, 1.76 Hz, 1 H), 9.06 (d, J = 4.69 Hz, 1 H), 9.09 (dd, J = 4.20, 1.86 Hz, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((3-hydroxy[1,8]naphthyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A (6r). MS (ESI+) for m/z 414.2 $(M/2 + H)^+$. ^{1}H NMR (CD_3OD) δ ppm: 0.87 (t, J = 7.42 Hz, 3 H), 0.99 (d, J = 6.64 Hz, 3 H), 1.14 (d, J = 7.03 Hz, 3 H), 1.24−1.36 (m, 11 H), 1.39−1.51 (m, 1 H), 1.54 (s, 3 H), 1.59−1.69 (m, 1 H), 1.71−1.78 (m, 2 H), 1.79−1.91 (m, 1 H), 1.92−2.02 (m, 1 H), 2.47−2.59 (m, 1 H), 2.61 (s, 2 H), 2.65 (s, 3 H), 2.71 (s, 5 H), 3.11−3.28 (m, 3 H), 3.36- 3.45 (m, 1 H), 3.60−3.76 (m, 3 H), 3.86 (t, J = 7.81 Hz, 1 H), 3.97−4.23 (m, 4 H), 4.26−4.39 (m, 2 H), 4.49 (s, 2 H), 4.87−4.96 (m, 1 H), 7.53−7.60 (m, 1 H), 8.48−8.60 (m, 2 H), 8.68 (s, 1 H), 8.76−8.84 (m, 1 H).

3-Descladinosyl-11,12-dideoxy-6-*O*-methyl-3-oxo-12,11-(oxycarbonyl-(1-((3-hydroxy[1,5]naphthyridin-4-yl)methyl)azetidin-3-yl)imino)erythromycin A Tosylate Salt (6s). 3-Hydroxy-[1,5]naphthyridine-4-carbaldehyde (**22**) (10 g, 57.6 mmol) and intermediate **5** prepared by step 5b (41 g, 55.3 mmol) were combined in THF (410 mL). TEA (21.9 mL, 157 mmol) was then added. The mixture was stirred for 30 min, followed by the addition of pivalic acid (21.4 g, 210 mmol). The mixture was heated to reflux, and approximately 600 mL of solvent was removed by concentration under atmospheric pressure to ensure complete removal of water (400 mL of additional amount of anhydrous THF was added during the concentration). The mixture was then cooled to 20−25 °C and transferred to a reaction flask that contained sodium triacetoxyborohydride (55.5 g, 262 mmol), acetonitrile (164 mL), and EtOAc (1230 mL) at 20−25 °C under agitation. After the mixture was stirred for 30 min, 5% aqueous sodium bicarbonate (205 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (205 mL). The combined organic phase was treated with anhydrous $MgSO_4$, and then active carbon (10.3 g) was added. The mixture was filtered and concentrated under vacuum. The resulting residue was purified by reverse-phase chromatography (column, Kromasil C-18; mobile phase, A (acetonitrile) and B (0.06% phosphoric acid in water); gradient, 15% A for 0−2 min to 90% A over 30 min, hold 90% A for 3 min, return to 10% A, and hold for 5 min). Desired fractions were combined, and the acetonitrile was removed by concentration in vacuo under 20 °C. The remaining aqueous mixture was pH adjusted to 8.34 using 4% aqueous sodium bicarbonate solution, then extracted with EtOAc (3 × 400 mL).

The combined organic phase was washed with saturated brine solution, dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was dissolved in acetone (350 mL), and a solution of tolunesulfonic acid hydrate (5.90 g, 31 mmol) in acetone (90 mL) was added dropwise. After the addition was complete, the mixture was stirred for 2 h at 20−25 °C. The product that crystallized out was filtered, rinsed with cold acetone (100 mL), and dried under vacuum to give the desired product (23.2 g, 23.2 mmol, 42% yield). FTMS (ESI+) for m/z 826.459 85 $(M + H)^+$ for $C_{43}H_{64}N_5O_{11}$ (theoretical = 826.459 69). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm: 0.80 (t, J = 7.42 Hz, 3 H), 0.89 (d, J = 6.66 Hz, 3 H), 1.10 (d, J = 7.17 Hz, 3 H), 1.18−1.24 (m, 12 H), 1.36 (dd, J = 12.29, 10.75 Hz, 1 H), 1.48 (s, 3 H), 1.55−1.60 (m, 1 H), 1.60−1.64 (m, 1 H), 1.65−1.71 (m, 1 H), 1.71−1.77 (m, 1 H), 1.90 (dd, J = 10.24, 3.07 Hz, 1 H), 2.29 (s, 3 H), 2.44 (dd, J = 7.17, 2.56 Hz, 1 H), 2.51 (s, 3 H), 2.61 (s, 6 H), 3.05−3.12 (m, 2 H), 3.16−3.26 (m, 1 H), 3.29 (dd, J = 10.75, 7.68 Hz, 1 H), 3.46 (s, 1 H), 3.60−3.66 (m, 1 H), 3.69 (dd, J = 6.61 Hz, 1 H), 3.83 (dd, J = 6.62 Hz, 1 H), 3.96−4.00 (m, 1 H), 4.00−4.05 (m, 2 H), 4.06 (q, J = 6.66 Hz, 1 H), 4.12 (d, J = 8.19 Hz, 1 H), 4.27 (d, J = 7.17 Hz, 1 H), 4.65 (s, 2 H), 4.79 (dd, J = 10.24, 0.66 Hz, 1 H), 5.97 (br s, 1 H), 7.07−7.14 (m, 2 H), 7.44−7.52 (m, 2 H), 7.56 (dd, J = 8.19, 4.35 Hz, 1 H), 8.29 (dd, J = 8.19, 1.54 Hz, 1 H), 8.64 (s, 1 H), 8.88 (dd, J = 4.35, 1.79 Hz, 1 H). ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm: 10.20, 13.45, 13.60, 13.93, 15.35, 17.62, 19.48, 20.74, 21.66, 29.80, 37.78, 38.11, 40.05, 44.63, 45.33, 46.43, 49.11, 50.07, 52.19, 57.36, 58.90, 61.74, 64.38, 67.74, 68.76, 75.76, 77.69, 77.78, 82.61, 102.60, 120.48, 121.26, 125.47, 127.99, 136.84, 136.85, 137.53, 142.83, 144.73, 145.76, 150.57, 153.66, 155.13, 169.61, 204.18, 216.04.

4-Methyl[1,8]naphthyridine (8). *m*-Nitrobenzene sodium sulfonate (202 g, 897 mmol) was weighed into a 3 L three-necked flask equipped with an overhead stirrer, and the flask was immersed in an ice−water bath before adding concentrated sulfuric acid (260 mL), glycerol (145 mL, 1987 mmol), 4-methylpyridin-2-ylamine **7** (50 g, 463 mmol), and finally water (260 mL). The mixture was heated to 120 °C for 8 h, then cooled to ambient temperature to yield a chocolate brown slurry. Aqueous sodium hydroxide (20 N) was added slowly with cooling (such that the temperature did not exceed 40 °C) until the pH of the mixture approximated 10. The resulting sludge was filtered through Celite and the filtrate extracted with DCM (3 × 100 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum to a black oil. The desired product **8** (7.32 g, 50.8 mmol, 11% yield) was isolated by silica gel chromatography (DCM/MeOH, 95:5). MS (ESI+) for m/z 145 $(M + H)^+$.

[1,8]Naphthyridin-4-carbaldehyde (9). 4-Methyl[1,8]naphthyridine (**8**) (0.743 g, 5.15 mmol) was dissolved in dioxane (32 mL) and water (4 mL). Selenium dioxide (1.14 g, 103 mmol) was added, and the solution was heated to 80 °C for 1 h. Subsequently more selenium dioxide (0.020 g, 1.80 mmol) was added and the solution heated for 30 min and then allowed to cool to room temperature. The solution was passed through a syringe filter to remove solids and poured into a solution of water/saturated aqueous $NaHCO_3$ (1:1) (60 mL). The organic layer was separated, and the remaining aqueous layer extracted with DCM (2 × 100 mL and 1 × 50 mL). The organic fractions were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum. The product was purified (silica gel chromatography using MeCN/hexanes in 1:1 ratio) to yield the title compound (0.63 g, 3.99 mmol, 77% yield). MS (ESI+) for m/z 159 $(M + H)^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 7.61 (dd, 1 H), 7.85 (d, 1 H), 9.16 (d, 1H), 9.37−9.39 (m, 2H), 10.39 (s, 1H).

1-[1,8]Naphthyridin-4-yl-ethanone (10). Step 1. [1,8]Naphthyridin-4-carbaldehyde (**9**) (0.300 g, 1.90 mmol) was dissolved in a mixture of anhydrous toluene (10 mL) and anhydrous THF (10 mL). The solution was cooled to 0 °C. Methylmagnesium bromide (1.62 mL of 1.4 M in THF/toluene) was added slowly and the solution stirred for 1 h while warming to ambient temperature. Saturated aqueous ammonium chloride was added until the solution reached a bright-yellow color and precipitate was apparent. The solution was passed through a syringe filter and into water, then extracted with EtOAc (3 × 30 mL). The combined organic fractions were dried over sodium sulfate, filtered, and concentrated under vacuum. The product was purified (silica gel with MeCN/hexanes eluant in 1:1 ratio initially, then to DCM/MeOH/NH_4OH eluant (89:10:1), yielding the title compound (0.079 g, 0.45 mmol, 24% yield). MS (ESI+) for m/z 175 $(M + H)^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 1.48 (s, 3 H), 5.58 (dd, 1 H), 6.32 (br s, 1 H), 7.25 (dd, 1 H), 7.52 (d, 1 H), 8.38 (m, 1 H), 8.64 (d, 1 H), 8.73 (m, 1 H).

Step 2. 1-[1,8]Naphthyridin-4-ylethanol (1.44 g, 8.26 mmol) was dissolved in ethyl acetate (250 mL), treated with 2-iodoxybenzoic acid (7.8 g, 24.8 mmol) and heated to 80 °C for 6 h. The solution was cooled to ambient temperature, and the solids were removed by filtration. The product was purified (silica gel using MeCN eluant) yielding the title compound (1.22 g 7.09 mmol, 86% yield). MS (ESI+) for m/z 173 $(M + H)^+$. ^{1}H NMR ($CDCl_3$) δ ppm: 2.64 (s, 3 H), 7.46 (dd, 1 H), 7.70 (d, 1 H), 8.85 (dd, 1 H), 9.03 (dd, 1 H), 9.13 (d, 1 H).

***N*-(4-Methylpyridin-2-yl)pivalamide (11).** To a solution of 4-methylpyridin-2-ylamine (**7**) (150 g, 1.40 mol) in DCM (1.5 L) was added triethylamine (205 mL, 1.50 mol). Pivoyl chloride (190 mL, 1.55 mol) was added dropwise over ∼1 h with stirring under nitrogen and under cooling with an ice−water bath. The resulting pale-yellow suspension was warmed to room temperature and stirred overnight. The reaction mixture was poured into water (500 mL) and saturated sodium bicarbonate (400 mL). The clear orange-yellow organic layer was separated, washed with saturated sodium bicarbonate (500 mL), saturated brine (300 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting off-white solid product was recrystallized from heptanes to afford pure **11** as pale-yellow needles (220 g, 1.14 mol, 82% yield). ^{1}H NMR ($CDCl_3$) δ ppm: 1.32 (s, 9H), 2.35 (s, 3H), 6.85 (d, 1H), 7.96 (br s, 1H), 8.11 (m, 2H).

***N*-(5-Chloro-4-methylpyridin-2-yl)pivalamide (12).** *N*-(4-Methylpyridin-2-yl)pivalamide **11** (252 g, 1.31 mol) was suspended in water (4 L). Na_2HPO_4 (468 g, 3.3 mol) was added, followed by DCM (1.5 L). The mechanically stirred mixture was cooled to 0 °C, and a gentle stream of chlorine gas was slowly passed through the reaction mixture for ∼75 min, during which the reaction mixture turned pale-yellow. The aqueous layer was separated and extracted with DCM (2 × 500 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The crude orange oil (∼350 g) was purified by silica gel chromatography (heptanes/EtOAc, 9:1 to 3:1) to afford **12** as an orange solidifying oil (253 g, 1.11 mol, 86% yield). ^{1}H NMR ($CDCl_3$): δ ppm: 1.32 (s, 9H), 2.39 (s, 3H), 7.98 (br s, 1H), 8.15 (s, 1H), 8.21 (s, 1H).

3-Chloro-4-methyl[1,8]naphthyridine (13). A solution of **12** (129 g, 0.57 mol) in diethyl ether (1.25 L) was cooled to −65 °C. To the resulting yellow suspension was slowly added a 1.5 M solution of *tert*-butyllithium (800 mL, 1.2 mol, 2.1 equiv). The resulting mixture was warmed to 15 °C when 3-dimethylaminopropenal (77.3 mL, 90% purity, 0.69 mol) was added neat under the cooling of an ice−water bath. After the mixture was stirred at room temperature overnight, the solvents were removed under reduced pressure, and the resulting yellow powder was treated with water (700 mL), followed by concentrated HCl (325 mL) while cooling the mixture in ice. The resulting dark-red reaction mixture was heated to 80 °C for 1 h, cooled in ice, and basified to pH 8 with NaOH. The mixture was extracted with DCM (4 × 1 L), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by silica gel chromatography (EtOAc eluant) to afforded **13** as a yellow solid (52.6 g, 0.295 mol, 52% yield). ^{1}H NMR ($CDCl_3$) δ ppm: 2.78 (s, 3H), 7.55 (dd, 1H), 8.41 (dd, 1H), 9.02 (s, 1H), 9.11 (dd, 1H).

3-Hydroxy[1,8]naphthyridine-4-carbaldehyde Hydrochloride Salt (14). Step 1. To an orange-red solution of **13** (14.4 g, 81 mmol) in 4:1 dioxane/water (200 mL) was added selenium dioxide (28.3 g, 0.242 mol), and the resulting mixture was heated at gentle reflux (T_{intern} = 90 °C) for 3 h. The resulting dark mixture was cooled to room temperature and carefully poured into saturated sodium bicarbonate (150 mL) and water (150 mL). The mixture was treated with DCM (400 mL), filtered over Celite, which was then rinsed with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The crude green product was purified by silica gel chromatography (1:1 DCM/MeCN) to afford 3-chloro-[1,8]naphthyridine-4-carbaldehyde as an orange solid (4.0 g, 21 mmol, 26% yield). MS (ESI+) for m/z 192 $(M + H)^+$. ^1H NMR ($CDCl_3$) δ: 7.67 (dd, 1H), 9.18 (dd, 1H), 9.22 (s, 1H), 9.33 (dd, 1H), 10.84 (s, 1H).

Step 2. To a solution of 3-chloro[1,8]naphthyridine-4-carbaldehyde (23.4 g, 121 mmol) in methanol (400 mL) was added a 5.4 M solution of sodium methoxide in methanol (112 mL, 0.607 mol, 5 equiv), and the resulting mixture was heated at 80 °C for 1 h. After cooling, the dark red reaction mixture was evaporated to $\sim^1/_2$ volume, acidified with acetic acid, and evaporated to dryness. The orange residue was partitioned between EtOAc (1 L) and saturated sodium bicarbonate (1 L). The aqueous layer was extracted with EtOAc (1 L and 3 × 500 mL). The combined organic layers were washed with saturated brine (1 L), dried over Na_2SO_4, filtered, and concentrated to dryness to give 3-methoxy[1,8]naphthyridine-4-carbaldehyde as an orange-brown solid (15.3 g, 81 mmol, 67% yield). MS (ESI+) for m/z 188 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ ppm: 4.26 (s, 3H), 7.57 (dd,1H), 9.03 (dd,1H), 9.25 (s, 1H), 9.43 (dd,1H), 10.85 (s, 1H).

Step 3. A mixture of 3-methoxy[1,8]naphthyridine-4-carbaldehyde (21.5 g, 114 mmol) and 6 N HCl was stirred at gentle reflux (T_{bath} = 155 °C) for 2 h. The volatiles were removed under reduced pressure (< 50 °C) and the resulting black solid was dried in vacuo to give **14** (23.6 g, as crude HCl salt and hydrate used directly in coupling to the **5**). MS (ESI+) for m/z 175 $(M + H)^+$.

3-Bromo-5-methoxypyridine (16). To a solution of 3,5-dibromopyridine (100 g, 0.42 mol) in DMF (1.0 L) was added sodium methoxide (5.4 M in methanol, 125 mL, 0.68 mol), and the resulting mixture was heated to 50 °C for 5 h and cooled to room temperature overnight. Water (4 L) was then added, and the mixture was extracted with MTBE (3 × 1 L). The combined organic layers were washed with saturated brine (2×), dried over Na_2SO_4, filtered, and evaporated to dryness. This afforded crude **16** as a yellow solidifying oil, recrystallized from pentane (71.1 g, 0.38 mol, 90% yield). ^1H NMR ($CDCl_3$) δ ppm: 3.85 (s, 3H), 7.36 (m, 1H), 8.24 (m, 1H), 8.28 (m, 1H).

***tert*-Butyl 5-Methoxypyridin-3-ylcarbamate (17).** A mixture of *tert*-butyl carbamate (67.9 g, 0.58 mol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.48 g, 2.4 mmol), xantphos (4.17 g, 7.2 mmol), and Cs_2CO_3 (220 g, 0.68 mol) was stirred under vacuum for 20 min. The flask was filled with N_2. This evacuation/backfill sequence was repeated twice. Next, a solution of 16 (90.9 g, 0.48 mol) in dry, degassed 1,4-dioxane (500 mL) was added, and the resulting suspension was heated to 100 °C for 30 h (followed by TLC). After cooling, the orange-red suspension was diluted with DCM (1 L), filtered over Celite, and evaporated to dryness. The crude orange solid product (130 g) was combined with that of a 0.87 mol batch to a total of 386 g and purified by silica gel chromatography (1:1 heptanes/EtOAc) to afford pure **17** as a pale-yellow solid (255 g, 1.14 mol, 84% for the combined yield). ^1H NMR ($CDCl_3$) δ ppm: 1.53 (s, 9H), 3.86 g (s, 3H), 6.55 (br s, 1H), 7.71 (br s, 1H), 7.95 (m, 1H), 7.99 (m, 1H).

3-Amino-5-methoxy-4-methylpyridine (18). Step 1. A solution of **17** (67.5 g, 0.30 mol) in THF (1.5 L) was cooled to −70 °C. Then *n*-BuLi (2.5 M, 300 mL, 0.75 mol, 2.5 equiv) was added dropwise, keeping T_{int} < −65 °C. The resulting mixture was warmed to −25 °C and stirred at that temperature for 1 h. The yellow-green solution was cooled to −78 °C, and a 2.0 M solution of MeI in MTBE (225 mL, 0.45 mol, 1.5 equiv) was added dropwise, keeping T_{int} < −70 °C. The resulting cloudy yellow solution was stirred for 1 h at −70 °C and next quenched by addition of water (250 mL). The mixture was poured into water (750 mL) and DCM (1.5 L). The aqueous layer was extracted with DCM (3 × 0.5 L). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated to dryness to afford *tert*-butyl 5-methoxy-4-methylpyridin-3-ylcarbamate as an orange-yellow sticky oil (73 g, 0.30 mol, 100% yield). ^1H NMR ($CDCl_3$) δ ppm: 1.52 (s, 9H), 2.13 (s, 3H), 3.91 (s, 3H), 6.17 (br s, 1H), 8.01 (s, 1H), 8.58 (s, 1H).

Step 2. To a cooled (0 °C) solution of *tert*-butyl 5-methoxy-4-methylpyridin-3-ylcarbamate (70 g, 0.29 mol) in methanol (450 mL) was added 4 N HCl in dioxane (450 mL, 1.8 mol) in one portion. The resulting effervescent solution was stirred overnight at room temperature. The solvents were removed under reduced pressure, and the pale-yellow solid residue was triturated with diethyl ether and dried in vacuo. This afforded the HCl salt as a pale-yellow solid. The HCl salt was suspended in water (250 mL), basified to pH 10 with 25% NaOH, and extracted with DCM (3 × 250 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and evaporated to dryness, giving **18** as an orange oil (33.7 g, 0.24 mol, 84% yield). ^1H NMR ($CDCl_3$) δ ppm: 2.03 (s, 3H), 3.61 (br s, 2H), 3.87 (s, 3H), 7.71 (s, 1H), 7.76 (s, 1H).

3-Methoxy-4-methyl[1,5]naphthyridine (19). *m*-Nitrobenzene sodium sulfonate (35 g, 0.16 mol) was added to methanesulfonic acid (125 mL) at room temperature, followed by powdered $FeSO_4 \cdot 7H_2O$ (2.0 g, 7.2 mmol). This addition was slightly exothermic, causing T_{int} to rise to 27 °C. To the resulting mixture was added **18** (33.7 g, 0.24 mol) in portions over ~20 min, during which T_{int} increased to 55−60 °C. After being stirred for 15 min, the dark reaction mixture was heated to 125−130 °C, and glycerol (50 mL; 0.68 mol) was added dropwise over ~5 h. ^1H NMR of a sample (poured into saturated sodium bicarbonate, extracted with EtOAc, dried over Na_2SO_4, filtered, evaporated) indicated approximately 60% conversion of starting material to the desired product. The mixture was reheated at 125 °C for 20 h, after which ^1H NMR of a sample indicated full conversion. The dark reaction mixture was cooled to room temperature, diluted with water (150 mL), and basified with 10 M NaOH, keeping T_{int} < 10 °C. The dark mixture was next filtered over Celite, rinsed with MTBE, and extracted with MTBE (4 × 300 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated to dryness. This afforded **19** as a yellow-brown crystalline solid (19.0 g, 0.109 mol, 45% yield). ^1H NMR ($CDCl_3$) δ ppm: 2.71 (s, 3H), 4.11 (s, 3H), 7.50 (dd, 1H), 8.32 (dd, 1H), 8.81 (s, 1H), 8.95 (dd, 1H).

(3-Methoxy[1,5]naphthyridin-4-yl)methanol (20). Step 1. Nitrogen was bubbled through a solution of purified **19** (note: must be very pure) (10.6 g, 61 mmol) in CCl_4 for 10 min. *N*-Bromosuccinimide (freshly recrystallized from water; 16.2 g, 92 mmol) and dibenzoyl peroxide (75%, 5.9 g, 18.3 mmol) were then added, and the resulting mixture was heated to gentle reflux (T_{int} = 75 °C) for 4 h. TLC/^1H NMR indicated full conversion, and the orange reaction mixture was cooled to 10−15 °C and filtered to remove insoluble material. The filtrate was diluted with DCM (500 mL) and washed with saturated sodium bicarbonate (750 mL). The aqueous layer was extracted with DCM (2 × 400 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. This afforded (3-methoxy[1,5]naphthyridin-4-yl)methyl bromide as a yellow solid (14.7 g, 58 mmol, 95% yield). ^1H NMR ($CDCl_3$) δ ppm: 4.21 (s, 3H), 5.19 (s, 2H), 7.55 (dd, 1H), 8.35 (dd, 1H), 8.90 (s, 1H), 9.02 (dd, 1H).

Step 2. To an orange solution of (3-methoxy[1,5]-naphthyridin-4-yl)methyl bromide (14.7 g, 58 mmol) from step 1 in DMF (325 mL) was added KOAc (42 g, 0.43 mol), and the

resulting mixture was heated to $T_{int} = 70-72$ °C for 4 h until ^{1}H NMR/TLC indicated full conversion. DMF was evaporated under reduced pressure, and the dark residue was partitioned between water (400 mL) and EtOAc (400 mL), filtered, separated, and the aqueous layer was extracted with EtOAc (3 × 400 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated to dryness to afford crude acetate as a dark oil (12.8 g, 55 mmol, 95%), which was then dissolved in methanol (500 mL). K_2CO_3 (40 g, 0.29 mol) was added, and the resulting mixture was stirred at room temperature overnight. The mixture was filtered to remove insoluble material and concentrated under reduced pressure ($T_{bath} = 25-30$ °C). The residue was diluted with water (400 mL) and extracted with EtOAc (4 × 250 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated to dryness. The product was combined with another batch (from starting from 38.5 mmol (3-methoxy[1,5]naphthyridin-4-yl)methyl bromide) and the composite crude material purified by silica gel chromatography (EtOAc/heptane, 1:1 to 9:1), affording **20** as a pale-yellow solid (10.7 g, 56 mmol, 63% yield). ^{1}H NMR ($CDCl_3$) δ ppm: 4.12 (s, 3H), 5.31 (d, 2H), 5.78 (br t, 1H), 7.54 (dd, 1H), 8.38 (dd, 1H), 8.86 (s, 1H), 8.87 (dd, 1H).

3-Hydroxy[1,5]naphthyridine-4-carbaldehyde (22). To a solution of 20 (2.0 g, 10.5 mmol) in EtOAc (175 mL) was added 2-iodoxybenzoic acid (8.8 g, 32 mmol), and the resulting suspension was heated to gentle reflux for 3.5 h ($T_{int} = 76$ °C). TLC indicated full conversion of starting material, and the mixture was cooled to room temperature overnight. The mixture was cooled to 0 °C, filtered over a P4 glass filter, and rinsed with cold EtOAc. The filtrate was concentrated in vacuo to afford a yellow solid. ^{1}H NMR analysis revealed the product to be a mixture of desired intermediate aldehyde (**21**) and reagent-derived benzoic acid residues. Several attempts to remove the latter impurity by dissolve−cool−filter sequences failed. The mixture was therefore dissolved in 6 N HCl (80 mL), extracted with EtOAc (4 × 50 mL), filtered, and evaporated to dryness. The orange-yellow residue was taken up in 6 N HCl (60 mL), heated to gentle reflux ($T_{bath} = 155$ °C) for 2 h, cooled, evaporated to dryness, and stripped with toluene (2×) to afford **22** as a dark-green solid pure enough to couple to the macrolide template (2.0 g, 9.5 mmol, 90% yield). MS (ESI+) for m/z 175 $(M + H)^+$. ^{1}H NMR (D_2O) δ ppm: 7.46−7.56 (m, 1 H), 8.32 (s, 1 H), 8.40−8.46 (m, 1 H), 8.46−8.54 (m, 1 H), 10.04 (s, 1H).

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Supporting Information Available: Methods for measurement of MIC, ER, AO, TDI; in vivo efficacy data (RTI, OM); and single crystal X-ray data for **6q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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