Novel Antibacterial Class: A Series of Tetracyclic Derivatives

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We describe the synthesis and antibacterial activity of a series of tetracyclic naphthyridones. The members of this series act primarily via inhibition of bacterial translation and belong to the class of novel ribosome inhibitors (NRIs). In this paper we explore the structure−activity relationships (SAR) of these compounds to measure their ability both to inhibit bacterial translation and also to inhibit the growth of bacterial cells in culture. The most active of these compounds inhibit *Streptococcus pneumoniae* translation at concentrations of <5 μM and have minimum inhibitory concentrations (MICs) of <8 μg/mL against clinically relevant strains of bacteria.

Introduction

Bacteria resistant to known therapies are a growing threat across the globe. An increasing fraction of bacterial isolates show reduced susceptibility to our most trusted antibiotics.[1,3,4] Although it was once believed that we had conquered bacteria and that they no longer posed a threat to human health,[2] the shortsightedness of that belief is now clear. An unavoidable consequence of the length of the bacterial life cycle compared with the length of our own is that bacteria can adapt to their environment vastly faster than humans. The antibiotics that seemed infallible 30 years ago are much less effective today and will become even less effective in the future. Our best weapon against this threat is continually to develop new antibiotics against which bacteria have not yet developed resistance.

Nowhere is the rise in resistant strains of bacteria more evident than in the treatment of respiratory tract infections. Respiratory infections are responsible for millions of deaths each year. *Streptococcus pneumoniae* is the most commonly identified pathogen associated with community-acquired pneumonia, and resistance in *S. pneumoniae* to traditional therapies continues to increase.[3,4] Overall rates of resistance in *S. pneumoniae* are as high as 36% for penicillin and 31% for the macrolide antibiotics.[1] The rates of resistance toward fluoroquinolones are still quite low; however, they too are rising.[5] A new class of antimicrobial agent that is not cross-resistant to drug-resistant strains of *S. pneumoniae* would be a powerful tool to treat community-acquired respiratory infections.

The goal of our research for the past several years has been the discovery of a new class of antibiotic to treat community-acquired respiratory infections. The traits of this new drug should ideally include efficacy against a variety of relevant bacterial strains and a mechanism of action different from those employed by known therapies. Toward this end, we have discovered the novel ribosome inhibitors (NRIs; Figure 1).[6]

The NRIs are a class of compounds with a core structure similar to quinolone antibiotics, but they function predominantly by a different cellular mechanism than quinolones. The NRIs inhibit translation in bacterial cells by interacting with the ribosome. In contrast, the quinolone antibiotics inhibit bacterial topoisomerases II and IV.[7] These two mechanisms are not mutually exclusive. A compound could be a potent inhibitor of either or both pathways. What we have observed in our work is a series of compounds that act predominantly via translation inhibition. A thorough study was performed to prove this point for two lead compounds in this series.[6] The topic of this paper is a series of NRIs with substitution linking the 6- and the 7-positions.

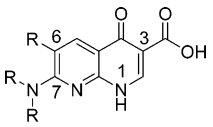

Figure 1. General structure of the novel ribosome inhibitors (NRIs).

Results and Discussion

Synthesis of Tetracyclic NRIs. A general synthesis is outlined in Scheme 1. The protected 7-chloronaphthyridine, **10** or **11**, was reacted with an unprotected prolinol with optional substitution. The substitution on the prolinol greatly affected the difficulty of this reaction. Unsubstituted prolinol reacted readily with the core (**10**) in acetonitrile in the presence of diisopropylethylamine at room temperature over the course of 2 days to afford the desired compound (**1b**) in 88% yield. In contrast, compound **22** (R_3 = allyl, $R_4 = R_5$ = H, $n = 1$) reacted with the core (**11**) only very slowly in dimethylacetamide (DMA) with diisopropylethylamine at 110 °C, affording the desired products, compounds **19a** and **20a**, in only 20% yield after 6 days.

The next step in the sequence is closure of the fourth ring. While this reaction generally does not work with the C-3 ester in place, initial hydrolysis of the ester followed by cyclization afforded the desired products cleanly.[10] The esters could be hydrolyzed with lithium hydroxide in a mixture of ethanol and water. The ring closure was effected by the addition of sodium hydride to a solution of the acid in *N*,*N*-dimethylformamide (DMF), followed by heating to afford the cyclized products (**1c**, **4c**−**6c**, and **14c**−**22c**).

To complete the synthesis, the N-1 protecting group was removed. For the cleavage of the 2,4-dimethoxybenzyl and *tert*-butyl groups, the protected intermediates were dissolved in trifluoroacetic acid and warmed as necessary. This reaction was greatly accelerated by the addition of a catalytic amount of concentrated sulfuric acid.

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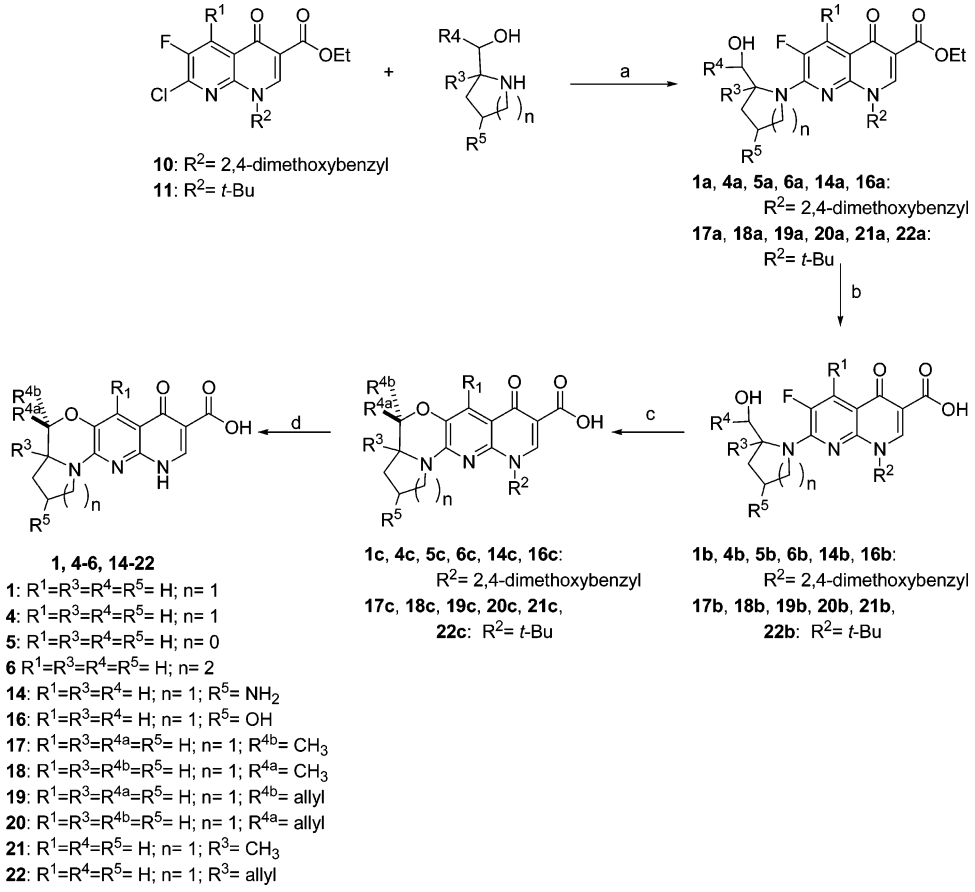
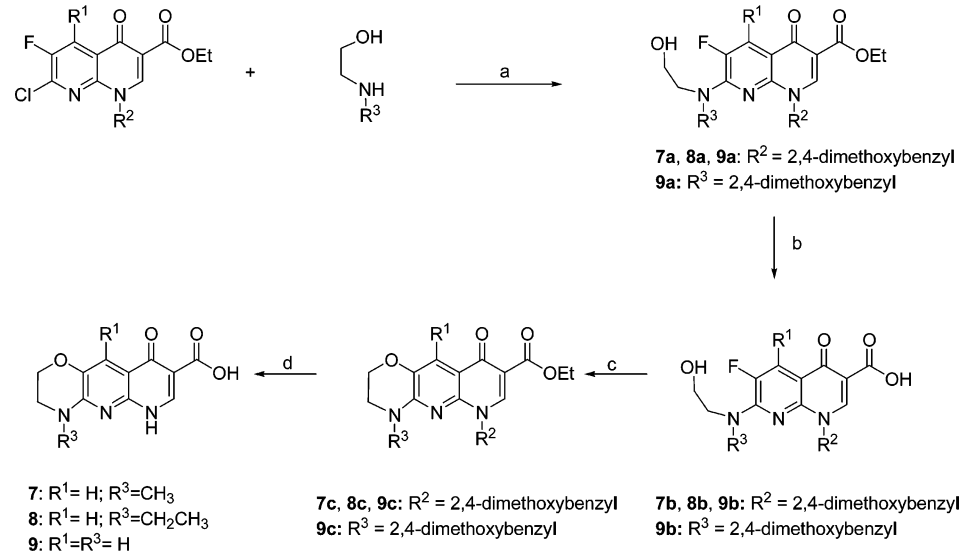
Scheme 1. Synthesis of Tetracyclic NRIs[a]



[a] (a) R_3N, CH_3CN; (b) LiOH, EtOH; (c) NaH, DMF, Δ; (d) TFA.

Scheme 2. Synthesis of Tricyclic NRIs[a]

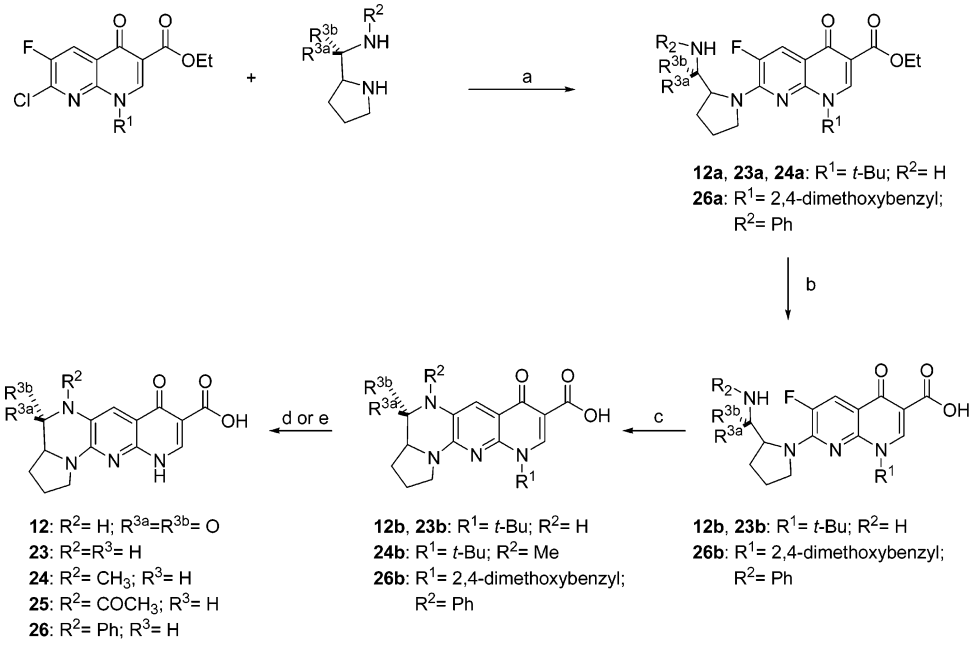


[a] (a) R_3N, CH_3CN; (b) LiOH, EtOH; (c) NaH, DMF, Δ; (d) TFA.

Synthesis of Tricyclic NRIs. Synthesis of the tricyclic analogues was similar to that of the tetracycles. In general, the cyclization chemistry was more difficult but could ultimately be accomplished as shown in Scheme 2. When R^3 was hydrogen, cyclization was not successful, even with prolonged heating. To obviate this difficulty, we used a 2,4-dimethoxybenzyl protecting group at R^3. The cyclization proceeded and the protecting group was removed in the final step.

Synthesis of Amino Tetracyclic NRIs. Synthesis of the nitrogen analogues of the tetracycles is shown in Scheme 3. The primary difference in the synthesis came in the cyclization reaction. While in the synthesis of compound **1** and its analogues it was necessary to deprotonate the alcohol to effect cyclization, deprotonation of amine **23** resulted in a slower and less clean cyclization reaction. As with the oxygen analogue, these reactions were performed on the carboxylate, not on the acid.

Scheme 3. Synthesis of Amino Tetracyclic NRIs[a]

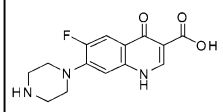
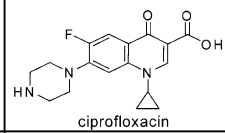
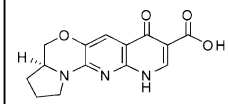
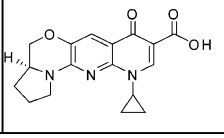


[a] (a) R_3N, CH_3CN; (b) LiOH, EtOH; (c) NaH, DMF, Δ; (d) TFA, cat. H_2SO_4; Ac_2O, Et_3N; (e) NaH, MeI; TFA, cat. H_2SO_4.

For best results, the monodeprotonated amino acid was slurried in DMF and warmed to 100 °C overnight. After cyclization, substituents could be installed on the nitrogen by deprotonation of the nitrogen followed by its reaction with an electrophile. This procedure worked for most substituents; however, acyl groups proved to be unstable to the subsequent deprotection conditions and these groups were best installed after deprotection.

Biochemical and Antibacterial Activity of Tetracyclic and Tricyclic NRIs. Three primary assays were used to evaluate the compounds in this series. The compounds were tested in a cell-free, uncoupled *S. pneumoniae* translation assay to determine their biochemical potency as inhibitors of bacterial translation. This assay is sensitive only to compounds that inhibit bacterial translation and not to those that inhibit transcription. The assay used mRNA encoding the luciferase gene to monitor translation. Test compounds were dried in 96-well plates and treated with a cell-free S30 extract, mRNA encoding luciferase protein, and a complete amino acid mix. The reactions were incubated to allow for translation and then stopped by the addition of kanamycin. Finally, luciferin reagent was added and the wells were read by flash luminescence. A complete description of the assay procedure can be found in an earlier paper in this series.[6] In addition to cell-free biochemical potency, we were interested in the antimicrobial activities of the compounds. To assess this activity, we used minimum inhibitory concentrations (MICs) to evaluate the compounds' ability to inhibit bacterial growth in vitro. MICs were determined by the broth microdilution method as described by the National Committee for Clinical Laboratory Standards.[11] In this paper, we present data for three clinically relevant bacterial strains associated with community-acquired pneumonia. Two strains of *S. pneumoniae* are included. *S. pneumo* 6303 is quinolone-susceptible and *S. pneumo* 7257 is resistant to inhibition by quinolone antibiotics. *Haemophilus influenzae* 1435 is a quinolone-susceptible strain. Data for *H. influenzae* are presented to demonstrate that the NRIs not only inhibit Gram-positive organisms but also can inhibit the growth of a clinically relevant, Gram-negative organism. The final assay we employed was a Jijoye B-cell cytotoxicity assay. The procedure for the toxicity assay is also described in detail elsewhere.[6]

Table 1. SAR of N-1 Alkyl and N-1 H in Quinolones and NRIs

Compound	Structure	*S. pneumo* translation inhibition (μM)	*S. pneumo* ATCC 7257 (Q-R) MIC (μg/mL)	*S. pneumo* ATCC 6303 MIC (μg/mL)
27		141	>64	>64
28	 ciprofloxacin	200	16	2
1		5.2	1	4
29		>100	8	>64

The compounds presented in this paper follow the structure−activity relationship (SAR) pattern of the NRIs and not the pattern common to quinolones. A hallmark of the quinolones is the importance to activity of an alkyl substituent at the 1-position. A comparison of compounds **27** and **28** illustrates this point. Compound **28**, ciprofloxacin, shows a typical pattern of minimum inhibitory concentrations (MICs). The quinolone-susceptible strain of *S. pneumoniae* (*S. pneumo* 6303) is inhibited at a concentration of 2 μg/mL. In contrast, the quinolone-resistant strain of *S. pneumomoniae* (*S. pneumo* 7257) requires a concentration of 16 μg/mL to achieve inhibition. *S. pneumo*

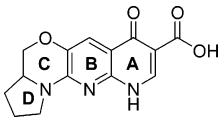
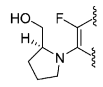


Figure 2. Compound **1**.

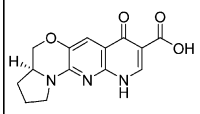
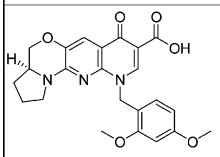
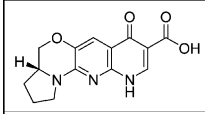
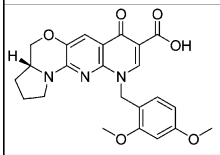
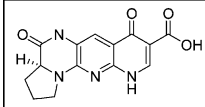
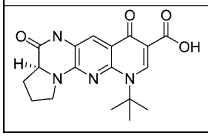
Table 2. SAR of Tetracyclic NRIs

Compound	Structure	*S. pneumo* translation inhibition (μM)	*S. pneumo* ATCC 7257 (Q-R) MIC (μg/mL)	*S. pneumo* ATCC 6303 MIC (μg/mL)	*H. influenzae* 1435 MIC (μg/mL)	Human B-cell cytotoxicity LD_{50} (μg/mL)
1		5.2	1	4	2	>100
2		75[a]	>64	>64	>64	>100
3		10	4	16	<1	>100
4		10.5	1	8	4	>100
5		7.5	2	16	8	>100
6		63	16	>64	8	>100
7		70	32	>64	32	>100
8		84	32	>64	64	>100
9		100	>64	>64	32	>100

[a] Value for a transcription/translation coupled assay.

7257 is a strain with mutant topoisomerase II and IV that demonstrates reduced susceptibility to quinolones. Removal of the cyclopropyl group at the 1-position of ciprofloxacin affords compound **27**. From the data shown in Table 1, we see a profound effect upon removing the alkyl substitution at the 1-position of ciprofloxicin. The overall ability of the compound to inhibit bacterial growth is significantly compromised. MICs for compound **27** are greater than 64 μg/mL for both resistant and susceptible strains of *S. pneumoniae*. This observation is well-precedented in the quinolone literature.[8] When the predominant cause of bacterial growth inhibition is topoisomerase II inhibition, as we see with the quinolones, removal of the alkyl group at the 1-position results in less inhibition of bacterial growth and higher MICs. In contrast, when the driving force for bacterial growth inhibition is inhibition of bacterial translation, removal of the alkyl group at the 1-position gives greater bacterial growth inhibition and lower MICs. This pattern is common to the NRIs and we see it when we compare compound **1** with compound **29** (Table 1).[6,9] Examination of compounds

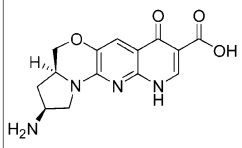
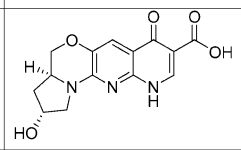
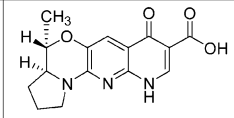
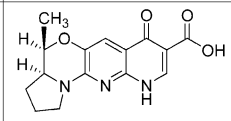
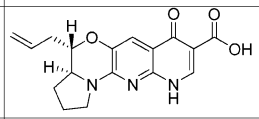
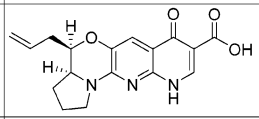
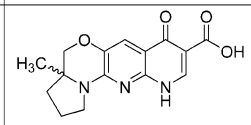
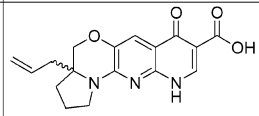
Table 3. SAR of Substitution at the N-1 Position of Tetracyclic NRI's

Structure	*S. pneumo* translation inhibition (μM)	*S. pneumo* ATCC 7257 (Q-R) MIC (μg/mL)	*S. pneumo* ATCC 6303 MIC (μg/mL)	*H. influenzae* 1435 MIC (μg/mL)	Human B-cell cytotoxicity LD_{50} (μg/mL)
	5.2	1	4	2	>100
	57	32	>64	>64	12
	10.5	1	8	4	>100
	229	16	>64	>64	6
	22	>64	>64	>64	>100
	>200	>64	>64	>32	>100

1 and **29** affords a parallel comparison. Compound **29** has an alkyl group favored for the quinolones at the 1-position but is not very active as a quinolone. According to the precedent from quinolone SAR, removal of the cyclopropyl group should result in an even less active antimicrobial compound.[8] In fact, removal of the cyclopropyl group affords compound **1**, which shows significantly improved MICs in both susceptible (*S. pneumo* 6303) and resistant (*S. pneumo* 7257) strains of *S. pneumoniae*. This increase in activity against *S. pneumoniae* is accompanied by improved inhibition of *S. pneumoniae* translation, measured in a cell-free, biochemical assay. Compound **1** has an IC_{50} of 5.7 μM against *S. pneumoniae* translation and also shows antibacterial activity with MICs of 1 μg/mL for the quinolone-resistant (7257) and 4 μg/mL for the quinolone-susceptible (6303) strains of *S. pneumoniae*. Furthermore, as one might expect from a mechanism unrelated to topoisomerase II inhibition, the quinolone-resistant strain of *S. pneumoniae* (7257) is no longer resistant. In fact, the quinolone-resistant strain (7257) is actually more susceptible to this series of compounds. One possible explanation for the greater susceptibility of the quinolone-resistant strain of *S. pneumoniae* (7257) is that this strain could be intrinsically less hardy and thus its growth is more easily inhibited by mechanisms not relying on topoisomerase II inhibition. Although it is possible, and even likely, that the NRIs retain some inhibition of topoisomerase II, this activity is weak compared with quinolone antibiotics and the data point to bacterial translation inhibition as the primary mechanism of antimicrobial activity in *Steptococcus pneumoniae* by the NRIs.

The general structure of this class of NRI has four rings that can be labeled A−D as shown in Figure 2. This group of

Table 4. Substitution SAR of Tetracyclic NRIs

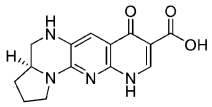
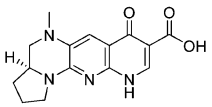
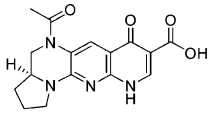
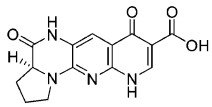
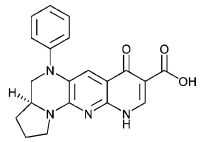
Compound	Structure	*S. pneumo* translation inhibition (μM)	*S. pneumo* ATCC 7257 MIC (Q-R) (μg/mL)	*S. pneumo* ATCC 6303 MIC (μg/mL)	*H. influenzae* 1435 MIC (μg/mL)	Human B-cell cytotoxicity LD_{50} (μg/mL)
14		2.7	>64	>64	>64	>100
16		6.9	16	64	16	>100
17		8.7	4	8	32	>100
18		125	32	64	64	>100
19		47	8	>64	64	>100
20		>300	>64	>64	>64	>100
21		107	32	>64	32	>100
22		>300	>64	>64	>64	>100

compounds is distinct from the greater class of NRIs by the presence of the C-ring.[9] To highlight the effect of the C-ring, a direct comparison of compound **1** with an analogue lacking the C-ring (compound **3**) is shown in Table 2. When compounds **1** and **3** are compared, the C-ring offers a modest but still significant improvement. It appears to be critical to have the pyrrolidine ring in, or nearly in, the plane of the core. In fact, the slight improvement in activity seen in compound **1** over compound **3** may be the result of the C-ring locking the pyrrolidine and the core into an almost coplanar conformation. Further supporting this theory are the data for compound **2**. Compound **2** has a hydroxymethyl group similar to compound **1**, but its pyrrolidine ring is most likely locked out of plane with the A,B-rings for steric reasons, and it has no activity at the highest concentration tested. Changes in the D-ring also have a noticeable effect on activity. Compounds lacking the D-ring are markedly less active analogues. Further, the size of the D-ring has an effect on activity. While four- and five-membered rings are both tolerated, the six-membered ring is 10-fold less active. The stereochemistry at the C,D-ring juncture has little effect on activity. From these data, we can conclude that the presence of both the C- and D-rings is advantageous and that, for optimum activity, the D-ring should be either a four- or a five-membered ring.

One of the earliest trends that we observed with the NRIs is that substitution on the nitrogen at the 1-position significantly reduces both biochemical potency and antibacterial activity[9] (Table 3). This trend holds true for the tetracycles. We have direct comparisons with *tert*-butyl and 2,4-dimethoxybenzyl groups at N-1 compared to the N-1 H analogues. Substitution reduces biochemical activity in the translation assay by more than 10-fold, and this reduction usually translates to weaker antibacterial activity.

We were interested to see the effect of substitution on the B-, C-, and D-rings (Table 4). In general, substitution on the C-ring, α to the oxygen, with groups larger than a methyl group resulted in a loss of activity. Furthermore, the stereochemical configuration of this site affected activity. Compound **17** shows good biochemical activity with little loss in antibacterial activity compared with compound **1**. In contrast, diastereoisomer **18**

Table 5. SAR of Amino Tetracyclic NRIs

Compound	Structure	*S. pneumo* translation inhibition (μM)	*S. pneumo* ATCC 7257 (Q-R) MIC (μg/mL)	*S. pneumo* ATCC 6303 MIC (μg/mL)	*H. influenzae* 1435 MIC (μg/mL)	Human B-cell cytotoxicity LD_{50} (μg/mL)
23		10	8	16	8	18
24		0.89	2	8	8	>100
25		7	2	16	4	>100
12		22	>64	>64	>64	>100
26		64	>64	>64	>64	>100

loses much biochemical and antibacterial activity. We observe a similar correlation between stereochemical configuration and activity in another set of diastereoisomers, **19** and **20**. Substitution at the C−D ring juncture, even with just a methyl group (**21**), causes an almost complete loss of activity.

Interestingly, the change that resulted in the best biochemical activity did not translate into improved MIC's. Compound **14** has excellent biochemical activity, but has little antibacterial activity in intact cells. This observation may be the result of the physiochemical properties of this particular compound. One possibility is that compound **14** may not cross the cell membrane as readily as other compounds, and this feature would have caused its intracellular concentration to be lower than other compounds, resulting in lower activity. Alternatively, compound **14** may be less soluble in aqueous media than other compounds and thus the bacterial cells may have been exposed to a lower effective concentration of compound **14** than of other compounds. To determine the exact reason for the lack of agreement between biochemical activity and MIC's in compound **14** and others like it, further experiments will be required.

We also made a small set of compounds that contained two nitrogen atoms in the C-ring. The results from this set are summarized in Table 5. The simple substitution of a nitrogen atom for an oxygen atom (compare compound **1** with compound **23**) resulted in a modest loss of activity. The addition of a methyl group on the C-ring nitrogen (**24**) gave a compound with improved biochemical activity but without the corresponding improvement in antibacterial activity. Acylation of the amine gave a compound (**25**) with similar biochemical activity and weaker antibacterial activity. The addition of larger groups on the nitrogen (**26**) appeared detrimental, although the set of nitrogen-substituted analogues is small. Finally, acylation of the nitrogen by oxidizing the α carbon in the C-ring affords a compound (**12**) that maintains relatively good biochemical potency but loses all antibacterial activity. As discussed for compound **14** earlier, physiochemical properties may explain the lack of antibacterial activity observed for compound **12**. From our results, it is evident that the nitrogen-containing tetracycles are likely to be a promising area for future research. Our research will focus on expanding our understanding of this chemistry as well as that of the oxygen-containing tetracycles.

Conclusion. We have reported a series of tri- and tetracyclic antibacterial compounds with surprising activity. While structurally similar to the quinolone antibiotics, they behave very differently. These compounds are more active in strains of bacteria resistant to quinolones and their SAR runs contrary to trends common to all quinolones. Further, their antimicrobial activity tracks with their ability to inhibit bacterial translation. These data show these compounds to be novel ribosome inhibitors (NRIs).[6] The series of NRIs presented in this paper contain four rings. These compounds give improved activity relative to the parent compounds that lack the fourth ring.[9] The improvement is seen both in a cell-free, biochemical assay to assess translation inhibition and in experiments measuring antibacterial activity in intact cells (MIC). This series of compounds shows translation inhibitions ranging from <1 μM to >100 μM. The MICs of this series of compounds range from 1 μg/mL to >64 μg/mL. The most active compound in this series is slightly less active than ciprofloxacin in the quinolone-susceptible strain of *S. pneumoniae* (*S. pneumo* 6303) and significantly more active than ciprofloxacin against the quinolone-resistant strain of *S. pneumoniae* (*S. pneumo* 7257).

Experimental Section

Synthetic Materials and Methods. Unless otherwise specified, reactions were performed under an inert atmosphere of nitrogen and monitored by thin-layer chromatography (TLC) or by liquid chromatography−mass spectrometry (LC-MS). All reagents were

purchased from commercial suppliers and used as provided. Flash column chromatography was performed either on a Biotage Flash 40 system using 50 or 90 g prepacked silica columns or on an Alltech Extract-Clean vacuum manifold with 5 and 10 g prepacked silica cartridges with HPLC-grade solvents. Analytical LC-MS was performed on a Agilent Series 1100 HPLC system equipped with an autosampler and coupled to a Finnegan Thermoquest atmospheric pressure chemical ionization (APCI) mass spectrometer. Peak detection was by ultraviolet absorption at 220 and 254 nm and by evaporative light scattering (ELS) detection. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker ARX spectrometer (300 MHz) or on a Varian Inova Spectrometer (500 MHz), are given in parts per million (ppm), and are referenced to residual solvent peaks (DMSO-d_6, δ 2.50 ppm) or to an internal standard of tetramethylsilane (TMS, δ 0.00 ppm). ^{1}H−^{1}H couplings are assumed to be first−order, and peak multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Electrospray ionization (ESI) and desorption chemical ionization (DCI) mass spectrometry were performed on Finnigan SSQ700 single-quadrupole mass spectrometers. Elemental analyses were performed by Roberston Microlit Laboratories (Madison, NJ) and by Qualitative Technologies Inc. (Whitehouse, NJ). All of the compounds reported were analyzed by LC-MS, ^{1}H NMR, and mass spectrometry and are consistent with the proposed structures in each case. Purity (>99% for all compounds reported) was assessed by analytical LC-MS on a Agilent 1100−Finnigan Navigator HPLC-MS system with ELS detection (Sedere Sedex 75), on a Phenomenex Luna C8(2) column (2.0 × 30 mm, 5 μM, 100 Å) by either method A (linear gradient 10−100% MeCN with 0.1% TFA over 3 min + 1 min hold at 100% MeCN, at 1.5 mL/min) or method B (linear gradient 10−100% MeCN with 10 mM NH_4OAc over 3 min + 1 min hold at 100% MeCN, at 1.5 mL/min).

General Procedure for Displacement of the Chloride of Naphthyridine 10 or 11 with Prolinols. Compound **10** was partially dissolved in CH_3CN (0.1 M). To this mixture was added the prolinol (1.2 equiv), producing a mixture that turned bright orange. Addition of ^{i}Pr$_2$EtN (3.3 equiv) provided a solution that was stirred at room temperature for 3 days before being diluted with water. If the product precipitated, it was collected by filtration. If the product did not precipitate, the mixture was extracted with CH_2Cl_2 and the organic phase was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and H_2O, and concentrated in vacuo to give a yellow semisolid. The crude material was taken up in hot CH_3CN and water was added until the product precipitated. The product was collected by filtration.

General Procedure for the Hydrolysis of Ethyl Esters. The ethyl ester was dissolved in ethanol (~0.05 M). To this solution was added aqueous LiOH (0.1 M in water, 2 equiv). The mixture was stirred for 1 day and then brought to pH 3 by the addition of 1 N HCl. Generally, a white precipitate formed and was collected by filtration.

General Procedure for the Cyclization of the C-ring by Displacement of Fluorine by the Hydroxyl Group of a Substituted Prolinol. The alcohol was dissolved in DMF (0.04 M) and cooled to 0 °C. Sodium hydride (60% in oil, 2.6 equiv) was added. After 30 min at room temperature, the mixture was warmed to 90 °C. The mixture was kept between 90 and 115 °C until the reaction was complete (generally 1 h−3 days). The mixture was cooled to room temperature, diluted with one solvent volume of H_2O, and brought to pH 3 with aqueous 1 N HCl. A precipitate formed and was collected by filtration. If a precipitate did not form, the product could be isolated by standard organic extraction. The crude product could be further purified by column chromatography or trituration with a variety of standard, organic solvents.

General Procedure for the Deprotection of the Dimethoxybenzyl Protecting Group. The 2,4-dimethoxybenzyl-protected substrate was dissolved or slurried in trifluoroacetic acid (0.05 M) and the mixture was warmed to 70 °C. The mixture became a clear, purple solution. After 3 h at 70 °C, the mixture was cooled and concentrated. The purple residue was taken up in CH_3CN and treated with H_2O. A gray precipitate formed and was collected by filtration. The crude product could be purified by column chromatography (5−10% methanol in CH_2Cl_2) and also by trituration with a variety of standard, organic solvents.

General Procedure for the Deprotection of the *tert*-Butyl Protecting Group. The *tert*-butyl-protected substrate was dissolved in TFA (0.05 M), treated with several drops of concentrated sulfuric acid, stirred at room temperature for 2−4 h, and concentrated in vacuo. The crude product could be purified by column chromatography (5−10% methanol in CH_2Cl_2) and also by trituration with a variety of standard, organic solvents.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(*S*)-2-hydroxymethylpyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (1a). Compound **1a** was prepared according to the general procedure from chloride **10** and (*S*)-2-hydroxymethylpyrrolidine (7 mmol scale) in 91% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (t, J = 7.12 Hz, 3H), 1.90 (m, 2H), 2.04 (m, 2H), 3.29 (m, 1H), 3.39 (m, 1H), 3.52 (m, 1H), 3.63 (m, 1H), 3.74 (m, 3H), 3.80 (m, 3H), 4.19 (q, J = 7.12 Hz, 2H), 4.37 (m, 1H), 4.81 (t, J = 5.76 Hz, 1H), 5.38 (m, 2H), 6.48 (dd, J = 8.14, 2.37 Hz, 1H), 6.60 (m, 1H), 7.12 (d, J = 8.14 Hz, 1H), 7.83 (d, J = 13.6 Hz, 1H), 8.62 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 22.5, 27.0, 48.8, 49.2, 55.2, 55.4, 59.6, 60.5, 61.2, 98.5, 104.7, 109.96, 113.3, 116.1, 118.8 (d, J = 21 Hz), 130.4, 144.9, 145.1 (d, J = 256 Hz), 147.7 (d, J = 12 Hz), 148.2, 158.3, 160.5, 164.3, 171.9. Anal. ($C_{25}H_{28}FN_3O_3$) C, H, N, F.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(S)-2-hydroxymethylpyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (1b). Carboxylic acid **1b** was prepared from ethyl ester **1a** according to the general procedure (4 mmol scale) in 100% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.08 (m, 2H), 3.42 (m, 1H), 3.54 (m, 1H), 3.67 (m, 1H), 3.74 (m, 3H), 3.76 (m, 3H), 3.85 (m, 1H), 4.41 (m, 1H), 4.86 (m, 1H), 5.51 (m, 2H), 6.51 (dd, J = 8.48, 2.37 Hz, 1H), 6.60 (d, J = 2.37 Hz, 1H), 7.16 (d, J = 8.48 Hz, 1H), 7.96 (d, J = 13.22 Hz, 1H), 8.81 (m, 1H), 15.44 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.5, 27.0, 49.3, 49.4, 49.8, 55.3, 55.5, 60.9, 98.6, 104.9, 107.3, 110.8, 115.3, 117.6 (d, J = 22 Hz), 130.8, 145.8, 145.8 (d, J = 259 Hz), 147.5, 148.6 (d, J = 12 Hz), 158.4, 160.8, 166, 176.1. Anal. ($C_{23}H_{24}FN_3O_3$) C, H, N, F.

10-(2,4-Dimethoxybenzyl)-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (1c). Compound **1c** was prepared from **1b** according to the general displacement conditions (3 mmol scale) in 100% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (m, 1H), 1.54 (m, 1H), 1.97 (m, 1H), 2.15 (m, 2H), 3.63 (m, 2H), 3.73 (m, 3H), 3.77 (m, 3H), 3.84 (m, 1H), 4.64 (dd, J = 10.51, 3.73 Hz, 1H), 5.52 (m, 2H), 6.54 (m, 2H), 7.34 (d, J = 8.48 Hz, 1H), 7.53 (m, 1H), 8.86 (m, 1H), 15.86 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2, 27.5, 46.0, 49.6, 54.9, 55.1, 55.2, 67.3, 98.5, 105.0, 106.9, 111.1, 113, 115.4, 131.2, 137.9, 143.3, 145.6, 148.0, 158.4, 160.6, 165.8, 175.7. Anal. ($C_{23}H_{23}N_3O_3$) C, H, N, F.

7-Oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (1). Compound **1** was prepared from 2,4-dimethoxybenzyl-protected **1c** according to the general procedure (0.6 mmol scale) in 52% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.56 (m, 1H), 2.00 (m, 1H), 2.10 (m, 1H), 2.19 (m, 1H), 3.58 (m, 1H), 3.68 (m, 2H), 3.84 (m, 1H), 4.63 (dd, J = 10.99, 3.66 Hz, 1H), 7.50 (m, 1H), 8.34 (m, 1H), 12.67 (br s, 1H), 15.67 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.22, 27.49, 45.88, 55.12, 67.35, 107.21, 110.42, 112.47, 138.12, 141.15, 145.72, 148.82, 165.88, 176.26. Anal. ($C_{14}H_{13}N_3O_4$) C, H, calcd for N 14.63, found 13.49. HPLC [retention time (RT) given in minutes] (method A) RT = 1.24, (method B) RT = 1.19.

6-Fluoro-7-(2-hydroxymethylpyrrolidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (2). Compound **2** was prepared from compound **1b** according to the general procedure (0.23 mmol scale) in 10% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.99 (m, 4H), 3.55 (m, 2H), 3.76 (m, 2H), 4.42 (m, 1H), 4.85 (t, J = 5.1 Hz, 1H), 7.95 (d, J = 13.2 Hz, 1H), 8.47 (s, 1H), 13.18 (s, 1H), 15.52 (s, 1H). Anal. ($C_{14}H_{14}FN_3O_4\cdot 0.5H_2O$) C, H, N. HPLC (method A) RT = 1.45, (method B) RT = 0.59.

1-(2,4-Dimethoxybenzyl)-6-fluoro-4-oxo-7-pyrrolidin-1-yl-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (3a). To a suspension of chloride **10** (30 g, 71 mmol) in 750 mL of acetonitrile was added potassium carbonate (25 g, 181 mmol) followed by pyrrolidine (15.2 g, 214 mmol). The reaction mixture was stirred at room temperature for 2 days and then the solvent was concentrated to ca. $^1/_4$ volume. The concentrated mixture was treated with CH_2Cl_2 and water, and the phases were separated. The organic phase was washed twice with 10% aqueous citric acid, water, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The produce was crystallized from a mixture of CH_2Cl_2/Et_2O/hexanes to afford a yellow solid (85% yield). ^{1}H NMR (300 MHz, chloroform-*d*) δ 1.39 (t, J = 7.12 Hz, 3H), 1.94−2.05 (m, 4H), 3.72−3.81 (m, 5H), 3.79 (s, 3H), 3.84 (s, 3H), 4.36 (q, J = 7.12 Hz, 2H), 5.37 (s, 2H), 6.41 (dd, J = 8.14, 2.37 Hz, 1H), 6.47 (d, J = 2.37 Hz, 1H), 7.21 (d, J = 8.48 Hz, 1H), 8.05 (d, J = 12.89 Hz, 1H), 8.63 (s, 1H).

1-(2,4-Dimethoxybenzyl)-6-fluoro-4-oxo-7-pyrrolidin-1-yl-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (3b). To a suspension of compound **3a** (17.9 g, 39 mmol) in 750 mL of tetrahydrofuran (THF) was added a solution of 1 N aqueous LiOH (196 mL, 196 mmol). After 5 min, the reaction mixture was treated with 80 mL of methanol. After 1.5 h, the precipitate was filtered and washed with THF and THF/water to afford the lithium salt of the product (16.6 g, 98%). The lithium salt was suspended in 30 mL of a 1:2 mixture of water and CH_2Cl_2 and treated with 1 N aqueous HCl. After 15 min, the phases were separated, and the organic phase was washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford a white solid (702 mg, 92%). ^{1}H NMR (300 MHz, chloroform-*d*) δ 2.0−2.11 (m, 4H), 3.79 (s, 3H), 3.80−3.89 (m, 4H), 3.84 (s, 3H), 5.45 (s, 2H), 6.40−6.48 (m, 2H), 7.23 (d, J = 8.14 Hz, 1H), 7.99 (d, J = 12.89 Hz, 1H), 8.84 (s, 1H).

6-Fluoro-4-oxo-7-pyrrolidin-1-yl-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (3). Compound **3** was prepared from 2,4-dimethoxybenzyl-protected **3b** according to the general procedure (6.0 mmol scale) in 96% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.93−1.98 (m, 4H), 3.60−3.83 (m, 4H), 7.92 (d, J = 13.2 Hz, 1H), 8.43 (s, 1H), 15.52 (br s, 1H). Anal. ($C_{13}H_{12}FN_3O_3$) C, H, N, F.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(*R*)-2-hydroxymethylpyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (4a). Compound **4a** was prepared according to the general procedure from compound **10** (7 mmol scale) in 88% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (t, J = 7.12 Hz, 3H), 1.90 (m, 2H), 2.04 (m, 2H), 3.29 (m, 1H), 3.39 (m, 1H), 3.52 (m, 1H), 3.63 (m, 1H), 3.74 (m, 3H), 3.80 (m, 3H), 4.19 (q, J = 7.12 Hz, 2H), 4.37 (m, 1H), 4.81 (t, J = 5.76 Hz, 1H), 5.38 (m, 2H), 6.48 (dd, J = 8.14, 2.37 Hz, 1H), 6.60 (m, 1H), 7.12 (d, J = 8.14 Hz, 1H), 7.83 (d, J = 13.56 Hz, 1H), 8.62 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 22.5, 27.0, 48.8, 49.2, 55.2, 55.4, 59.6, 60.5, 61.2, 98.5, 104.7, 109.96, 113.3, 116.1, 118.8 (d, J = 21 Hz), 130.4, 144.9, 145.1 (d, J = 256 Hz), 147.7 (d, J = 12 Hz), 148.2, 158.3, 160.5, 164.3, 171.9. Anal. ($C_{25}H_{28}FN_3O_3$) C, H, N, F.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(*R*)-2-hydroxymethylpyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (4b). Carboxylic acid **4b** was prepared from ethyl ester **4a** according to the general procedure (4 mmol scale) in 94% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (m, 2H), 2.08 (m, 2H), 3.42 (m, 1H), 3.54 (m, 1H), 3.67 (m, 1H), 3.74 (m, 3H), 3.76 (m, 3H), 3.85 (m, 1H), 4.41 (m, 1H), 4.86 (m, 1H), 5.51 (m, 2H), 6.51 (dd, J = 8.48, 2.37 Hz, 1H), 6.60 (d, J = 2.37 Hz, 1H), 7.16 (d, J = 8.48 Hz, 1H), 7.96 (d, J = 13.22 Hz, 1H), 8.81 (m, 1H), 15.44 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.5, 27.0, 49.3, 49.4, 49.8, 55.3, 55.5, 60.9, 98.6, 104.9, 107.3, 110.8, 115.3, 117.6 (d, J = 22 Hz), 130.8, 145.8, 145.8 (d, J = 259 Hz), 147.5, 148.6 (d, J = 12 Hz), 158.4, 160.8, 166, 176.1. Anal. ($C_{23}H_{24}FN_3O_3$) C, H, N, F.

10-(2,4-Dimethoxybenzyl)-7-oxo-2,3,(*R*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (4c). Compound **4c** was prepared from **4b** according to the general displacement conditions (3 mmol scale) in 100% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.81 (m, 1H), 1.54 (m, 1H), 1.97 (m, 1H), 2.15 (m, 2H), 3.63 (m, 2H), 3.73 (m, 3H), 3.77 (m, 3H), 3.84 (m, 1H), 4.64 (dd, J = 10.51, 3.73 Hz, 1H), 5.52 (m, 2H), 6.54 (m, 2H), 7.34 (d, J = 8.48 Hz, 1H), 7.53 (m, 1H), 8.86 (m, 1H), 15.86 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.2, 27.5, 46.0, 49.6, 54.9, 55.1, 55.2, 67.3, 98.5, 105.0, 106.9, 111.1, 113, 115.4, 131.2, 137.9, 143.3, 145.6, 148.0, 158.4, 160.6, 165.8, 175.7. Anal. ($C_{23}H_{23}N_3O_3$) C, H, N, F.

7-Oxo-2,3,(*R*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (4). Compound **4** was prepared from 2,4-dimethoxybenzyl-protected **4c** according to the general procedure (0.6 mmol scale) in 52% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.56 (m, 1H), 2.00 (m, 1H), 2.10 (m, 1H), 2.19 (m, 1H), 3.58 (m, 1H), 3.68 (m, 2H), 3.84 (m, 1H), 4.63 (dd, J = 10.99, 3.66 Hz, 1H), 7.50 (m, 1H), 8.34 (m, 1H), 12.67 (br s, 1H), 15.67 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 22.22, 27.5, 45.9, 55.1, 67.4, 107.2, 110.4, 112.5, 138.1, 141.2, 145.7, 148.8, 165.9, 176.3. Anal. ($C_{14}H_{13}N_3O_4$) C, H, calcd for N 14.63, found 13.22. HPLC (method A) RT = 1.27, (method B) RT = 0.96.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[2-(*S*)-hydroxymethylazetidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (5a). *N-tert*-Butoxycarbonyl-2-hydroxymethylazetidine (1.0 g, 5.4 mmol) was dissolved in 3 mL of CH_2Cl_2 and added dropwise to 25 mL of 4 N HCl in dioxane that had been cooled to 0 °C. The cooling bath was removed, and after 1 h the mixture was concentrated. Chloride **10** (1.6 g, 3.8 mmol) was mostly dissolved in 25 mL of acetonitrile. In a separate flask, the 2-(*S*)-hydroxymethylazetidine hydrochloride was dissolved in 20 mL of acetonitrile, treated with diisopropylethylamine (4 mL, 23 mmol), and added to the solution of **10** in CH_3CN. After 3 days, the mixture was diluted with 350 mL of H_2O and filtered to afford a white solid, which was purified by column chromatography (3% MeOH in CH_2Cl_2) to give the desired product (1.0 g, 58%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7.12 Hz, 3H), 2.35 (m, 2H), 3.64 (m, 1H), 3.74 (s, 3H), 3.79 (s, 3H), 3.85 (m, 1H), 4.21 (q, J = 7.12 Hz, 2H), 4.21 (m, 2H), 4.59 (m, 1H), 4.92 (t, J = 5.76 Hz, 1H), 5.34 (m, 2H), 6.49 (m, 1H), 6.58 (m, 1H), 7.15 (d, J = 8.14 Hz, 1H), 7.80 (d, J = 11.87 Hz, 1H), 8.64 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 19.8, 49.2, 50.0, 55.2, 55.5, 59.6, 61.6, 65.2, 98.5, 104.7, 109.9, 113.7, 116.0, 117.9 (d, J = 16 Hz), 130.9, 145.3, 145.4 (d, J = 255 Hz), 148.3, 149.6 (d, J = 14 Hz), 158.4, 160.5, 164.3, 172.0. Anal. ($C_{24}H_{26}FN_3O_6$) C, H, N, F.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-(2-(*S*)-hydroxymethylazetidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (5b). Carboxylic acid **5b** was prepared from ethyl ester **5a** according to the general procedure (2 mmol scale) in 97% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (m, 2H), 3.64 (m, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.89 (m, 1H), 4.27 (m, 2H), 4.65 (m, 1H), 4.98 (m, 1H), 5.48 (m, 2H), 6.54 (m, 2H), 7.19 (m, 1H), 7.94 (d, J = 11.87 Hz, 1H), 8.85 (s, 1H), 15.45 (s, 1H). Anal. ($C_{22}H_{22}FN_3O_6$) C (calcd for 59.59, found 59.03), H, N, F.

9-(2,4-Dimethoxybenzyl)-6-oxo-1,2,(*S*)-2a,3,6,9-hexahydro-4-oxa-9,10,10b-triazacyclobuta[*a*]anthracene-7-carboxylic Acid (5c). Compound **5c** was prepared from compound **5b** according to the general displacement conditions (2 mmol scale) in 93% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.51 (m, 2H), 3.62 (m, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 4.28 (m, 1H), 4.52 (m, 2H), 4.78 (m, 1H), 5.44 (m, 2H), 6.51 (m, 2H), 7.33 (d, J = 8.09 Hz, 1H), 7.58 (s, 1H), 8.84 (s, 1H), 15.59 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.0, 50.7, 53.6, 55.2, 55.5, 60.1, 66.4, 98.4, 104.8, 106.7, 112.9, 115.2, 116.0, 132.4, 140.0, 145.2, 147.0, 151.5, 158.9, 160.8, 166.3, 176.5.

Sodium 6-Oxo-1,2,(*S*)-2a,3,6,9-hexahydro-4-oxa-9,10,10b-triazacyclobuta[a]anthracene-7-carboxylate (5). Compound **5** was prepared from 2,4-dimethoxybenzyl-protected **5c** according to the general procedure (0.6 mmol scale) in 74% yield. The parent compound was converted to the sodium salt: acid **5** (91 mg, 0.33 mmol) was slurried in 60 mL of H_2O. To this mixture was added sodium hydroxide (300 μL, 1.037 M, 0.31 mmol). The mixture had a pH of 7.0−7.5 and was filtered through a 0.45 μM filter. The clear solution was lyophilized to afford the sodium salt (80

mg, 74% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.37 (m, 1H), 2.60 (m, 1H), 3.66 (t, J = 10.51 Hz, 1H), 4.21 (m, 1H), 4.38 (m, 2H), 4.65 (m, 1H), 7.57 (s, 1H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.4, 53.2, 59.8, 66.7, 106.3, 112.6, 115.6, 139.1, 151.9, 151.9, 155.4, 170.4, 173.2. HPLC (method A) RT = 1.08, (method B) RT = 0.96.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-(2-hydroxymethylpiperidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (6b). Chloride **10** (2.15 g, 5.1 mmol) was slurried in 50 mL of acetonitrile. To this mixture was added 2-hydroxymethylpiperidine (890 mg, 7.7 mmol) and diisopropylethylamine (2.5 mL, 14 mmol). After 20 h at room temperature, the mixture was warmed to 75 °C for 5 days and then cooled and diluted with 200 mL of H_2O. The mixture was extracted with 200 mL of CH_2Cl_2, and the organic phase was washed with H_2O, 1 N HCl, and H_2O and concentrated in vacuo. The crude material was taken up in 110 mL of EtOH and lithium hydroxide (90 mL, 0.1 M, 9 mmol) was added. After 16 h, the pH was adjusted to 3 and the mixture was extracted with CH_2Cl_2. The organic phase was concentrated in vacuo. The crude material was recrystallized from EtOAc/hexanes to afford the desired material as pale crystals (1.62 g, 74%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (m, 6H), 3.17 (m, 2H), 3.62 (m, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 4.30 (m, 1H), 4.64 (m, 1H), 4.78 (t, J = 5.43 Hz, 1H), 5.53 (m, 2H), 6.49 (m, 1H), 6.59 (m, 1H), 7.16 (d, J = 8.48 Hz, 1H), 7.99 (d, J = 13.90 Hz, 1H), 8.86 (s, 1H), 15.35 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.7, 25.1, 41.8, 41.9, 49.9, 55.3, 55.5, 59.2, 98.5, 104.9, 107.3, 111.9, 115.3, 118.6, 118.8 (d, J = 23 Hz), 118.9, 130.7, 145.2, 147.8, 149.8 (d, J = 182 Hz), 150.9, 158.3, 160.7, 166.0, 176.1. Anal. ($C_{24}H_{26}FN_3O_6$) C, H, N, F.

11-(2,4-Dimethoxybenzyl)-8-oxo-1,2,3,4,4a,5,8,11-octahydro-6-oxa-11,12,12b-triazabenzo[*a*]anthracene-9-carboxylic Acid (6c). Compound **6c** was prepared according to the general procedure from alcohol **6b** (2.1 mmol scale). The crude material was recrystallized from 900 mL of EtOAc to give the desired product in 68% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (m, 6H), 2.84 (m, 1H), 3.59 (m, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 3.97 (dd, J = 11.19, 6.78 Hz, 1H), 4.33 (dd, J = 11.53, 3.73 Hz, 1H), 4.83 (m, 1H), 5.54 (m, 2H), 6.52 (m, 2H), 7.15 (d, J = 8.48 Hz, 1H), 7.50 (s, 1H), 8.86 (s, 1H), 15.73 (s, 1H).

Sodium 8-Oxo-1,2,3,4,4a,5,8,11-octahydro-6-oxa-11,12,12b-triazabenzo[*a*]anthracene-9-carboxylate (6). Acid **6c** (217 mg, 0.48 mmol) was dissolved in 10 mL of TFA. After 16 h at room temperature, the solution was concentrated in vacuo. The purple residue was slurried in acetone and the solvent was decanted. This process was repeated with CH_2Cl_2. The crude product was isolated as a gray solid. The gray solid (113 mg, 0.38 mmol) was slurried in 100 mL of H_2O. To this mixture was added sodium hydroxide (290 μL, 1.002 M in H_2O, 0.29 mmol) and the mixture was sonicated for 2 h. The cloudy solution was filtered through a 0.45 μM filter and lyophilized to give the desired product as a fluffy, white solid (110 mg, 91%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.22 (m, 1H), 1.47 (m, 2H), 1.78 (m, 3H), 2.68 (m, 1H), 3.42 (m, 1H), 3.91 (dd, J = 11.03, 7.72 Hz, 1H), 4.26 (dd, J = 11.03, 3.31 Hz, 1H), 4.83 (m, 1H), 7.42 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.8, 24.3, 26.9, 43.1, 52.3, 68.2, 106.4, 111.5, 113.8, 138.3, 149.4, 151.5, 154.6, 170.5, 172.4. HPLC (method A) RT = 1.47, (method B) RT = 1.42.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(2-hydroxyethyl)methylamino]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (7a). A solution of chloride **10** (2 g, 4.75 mmol), *N*-methylaminoethanol (572 μL, 7.13 mmol), and triethylamine (2 mL, 14.25 mmol) in acetonitrile (50 mL) was stirred at 25 °C for 18 h and then filtered. The solid was washed with acetonitrile and air-dried to give off-white crystals (2.09 g, 96%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (t, J = 7.12 Hz, 3H), 3.24 (d, J = 3.05 Hz, 3H), 3.60 (m, 2H), 3.67 (m, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 4.20 (q, J = 7.12 Hz, 2H), 4.77 (t, J = 5.43 Hz, 1H), 5.38 (s, 2H), 6.48 (dd, J = 8.31, 2.54 Hz, 1H), 6.60 (d, J = 2.37 Hz, 1H), 7.06 (d, J = 8.14 Hz, 1H), 7.83 (d, J = 13.90 Hz, 1H), 8.65 (s, 1H).

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(2-hydroxyethyl)methylamino]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (7b). Acid **7b** was prepared from ester **7a** (4.6 mmol scale) according to the general procedure in 92% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.29 (d, J = 3.05 Hz, 3H), 3.61 (q, J = 5.65 Hz, 2H), 3.74 (s, 3H), 3.74 (m, 2H), 3.76 (s, 3H), 4.81 (t, J = 5.26 Hz, 1H), 5.53 (s, 2H), 6.49 (dd, J = 8.14, 2.37 Hz, 1H), 6.60 (d, J = 2.37 Hz, 1H), 7.10 (d, J = 8.48 Hz, 1H), 7.98 (d, J = 13.90 Hz, 1H), 8.86 (s, 1H), 15.39 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 39.4 (d, J = 6 Hz), 49.8, 54.3 (d, J = 7 Hz), 55.2, 55.5, 58.8, 98.6, 104.8, 107.3, 111.2, 115.4, 118.3 (d, J = 22 Hz), 130.3, 145.3, 146.2 (d, J = 237 Hz), 147.7, 150.1 (d, J = 10 Hz), 158.2, 160.7, 166.0, 176.1. IR (microscopy) 3481, 1698, 1629 cm^{-1}. Anal. ($C_{21}H_{22}FN_3O_6$) C, H, N, F.

5-(2,4-Dimethoxybenzyl)-4-methyl-8-oxo-3,4,5,8-tetrahydro-2*H*-1-oxa-4,5,10-triazaanthracene-7-carboxylic Acid (7c). Compound **7c** was prepared from compound **7b** (2.3 mmol scale) according to the general procedure in 30% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 3.66 (t, J = 4.78 Hz, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 4.26 (t, J = 4.78 Hz, 2H), 5.55 (s, 2H), 6.50 (dd, J = 8.27, 2.39 Hz, 1H), 6.59 (d, J = 2.57 Hz, 1H), 7.21 (d, J = 8.46 Hz, 1H), 7.47 (s, 1H), 8.83 (s, 1H), 15.81 (s, 1H).

4-Methyl-8-oxo-3,4,5,8-tetrahydro-2*H*-1-oxa-4,5,10-triazaanthracene-7-carboxylic Acid (7). Compound **7** was prepared from compound **7c** according to the general procedure (0.7 mmol scale) in 38% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3H), 3.66 (dd, J = 5.15, 4.41 Hz, 2H), 4.27 (dd, J = 4.41, 4.41 Hz, 2H), 7.44 (s, 1H), 8.39 (d, J = 6.99 Hz, 1H), 13.07 (d, J = 5.15 Hz, 1H), 15.87 (s, 1H); ^{13}C NMR (125 MHz, CF_3COOD) δ 40.3, 51.2, 66.3, 107.2, 112.7, 114.8, 145.7, 145.9, 150.1, 155.8, 172.4, 173.0. Anal. ($C_{12}H_{11}N_3O_4$) C, H, N.

1-(2,4-Dimethoxybenzyl)-7-[ethyl(2-hydroxyethyl)amino]-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (8a). A solution of chloride **10** (2 g, 4.75 mmol), 2-(ethylamino)ethanol (556 μL, 5.7 mmol), and triethylamine (1.98 mL, 14.25 mmol) in acetonitrile (47.5 mL) at 25 °C was stirred for 18 h, treated with more 2-(ethylamino)ethanol (556 μL, 5.7 mmol), heated at 55−75 °C for 4 days, cooled to 25 °C, and filtered with acetonitrile rinsing to give a white solid (1.96 g, 87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (t, J = 6.95 Hz, 3H), 1.26 (t, J = 7.12 Hz, 3H), 3.60 (m, 6H), 3.73 (s, 3H), 3.80 (s, 3H), 4.19 (q, J = 7.12 Hz, 2H), 4.78 (m, 1H), 5.38 (s, 2H), 6.47 (dd, J = 8.14, 2.37 Hz, 1H), 6.61 (d, J = 2.37 Hz, 1H), 6.93 (d, J = 8.48 Hz, 1H), 7.84 (d, J = 13.90 Hz, 1H), 8.62 (s, 1H).

1-(2,4-Dimethoxybenzyl)-7-[ethyl(2-hydroxyethyl)amino]-6-fluoro-4-oxo-1 ,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (8b). Acid **8b** was prepared from ester **8a** according to the general procedure (4.2 mmol scale) in 100% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.14 (t, J = 6.95 Hz, 3H), 3.68 (m, 6H), 3.74 (s, 3H), 3.77 (s, 3H), 4.82 (m, 1H), 5.52 (s, 2H), 6.48 (dd, J = 8.48, 2.37 Hz, 1H), 6.61 (d, J = 2.37 Hz, 1H), 6.97 (d, J = 8.48 Hz, 1H), 8.00 (d, J = 14.24 Hz, 1H), 8.83 (s, 1H), 15.39 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.9, 46.2 (d, J = 4.89 Hz), 49.7, 52.2 (d, J = 7.3 Hz), 55.3, 55.5, 59.1, 98.6, 104.8, 107.5, 111.2 (d, J = 2.4 Hz), 115.5, 118.6 (d, J = 12.9 Hz), 129.6, 145.5, 146.1 (d, J = 258.8 Hz), 147.7, 149.4 (d, J = 9.7 Hz), 158, 160.6, 166, 176.2. Anal. ($C_{22}H_{24}N_3O$) C, H, N.

5-(2,4-Dimethoxybenzyl)-4-ethyl-8-oxo-3,4,5,8-tetrahydro-2*H*-1-oxa-4,5,10-triazaanthracene-7-carboxylic Acid (8c). A solution of **8b** (1.14 g, 2.56 mmol) in DMF (45 mL) at 25 °C was treated with 60% oily sodium hydride (215 mg, 5.37 mmol), stirred for 4 h, heated at 100 °C for 2 days, cooled to 25 °C, treated with more 60% oily sodium hydride (100 mg, 2.50 mmol), stirred for 4 h, heated at 100 °C for 2 days, cooled to 25 °C, treated with water, adjusted to pH 3.5 with 1 M HCl, and filtered; the filtrant was purified by flash chromatography on silica gel with 0−4% methanol/dichloromethane to give a white solid (498 mg, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.11 (t, J = 6.99 Hz, 3H), 3.69 (m, 4H), 3.73 (s, 3H), 3.78 (s, 3H), 4.24 (t, J = 4.60 Hz, 2H), 5.54

(s, 2H), 6.48 (dd, $J = 8.46$, 2.21 Hz, 1H), 6.60 (d, $J = 2.21$ Hz, 1H), 7.05 (d, $J = 8.46$ Hz, 1H), 7.48 (s, 1H), 8.84 (s, 1H), 15.83 (s, 1H).

Sodium 4-Ethyl-8-oxo-3,4,5,8-tetrahydro-2*H*-1-oxa-4,5,10-triazaanthracene-7-carboxylate (8). A solution of **8c** (498 mg, 1.17 mmol) in TFA (20 mL) was stirred at 25 °C for 18 h and concentrated; the concentrate was azeotroped with toluene, concentrated, and triturated first with acetone and then with methanol to give the crude product as a white powder (498 mg). To a suspension of the crude material (200 mg) in water (200 mL) was added 1.002 N NaOH solution (412.5 μL), and the mixture was sonicated and heated for 6 h. The resulting pH 7.5 suspension was filtered through a 0.45 μM syringe filter and the filtrate was lyophilized to give the sodium salt (89.3 mg, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (t, $J = 7.17$ Hz, 3H), 3.56 (m, 2H), 3.72 (q, $J = 7.11$ Hz, 2H), 4.20 (m, 2H), 7.40 (s, 1H), 8.56 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.6, 41.8, 44.5, 63.4, 106.2, 110.7, 113.3, 137.8, 148.5, 151.3, 155.0, 170.6, 172.2. Anal. ($C_{13}H_{12}N_3NaO_4$) C, H, N, Na.

7-Chloro-1-(2,4-dimethoxybenzyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (10). Commercially available 3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropionic acid ethyl ester [CAS 96568-04-6] (40 g, 143 mmol) was slurried in 100 mL of acetic anhydride, treated with triethylorthoformate (27 mL, 163 mmoL), and heated to reflux for 14 h. The mixture was cooled and concentrated in vacuo to afford a brown oil. The oil was dissolved in 500 mL of CH_2Cl_2, and the flask was placed in an ice bath. The mixture was treated with 2,4-dimethoxybenzylamine (22 mL, 147 mmol), stirred at room temperature for 1 h, and concentrated in vacuo. The residue was dissolved in 250 mL of acetonitrile and treated with potassium carbonate (40 g, 289 mmol), heated to reflux for 14 h, and cooled. The solution was diluted with EtOAc, washed with H_2O and 10% aqueous citric acid, dried over Na_2SO_4, and concentrated in vacuo. The crude material was recrystallized from 300 mL of EtOAc to afford an off-white powder (19 g, 32% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, $J = 7.1$ Hz, 3H), 3.74 (s, 3H), 3.80 (s, 3H), 4.25 (q, $J = 7.1$ Hz, 2H), 5.43 (s, 2H), 6.51 (dd, $J = 8.5$, 2.4 Hz, 1H), 6.59 (d, $J = 2.4$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 8.43 (d, $J = 7.8$ Hz, 1H), 8.89 (s, 1H).

1-*tert*-Butyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (11). Compound **11** was synthesized as described for compound **10** (143 mmol scale), with *tert*-butyl amine (15 mL, 143 mmol) in place of 2,4-dimethoxybenzylamine to afford the product as a white solid (17.6 g, 38% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.29 (t, $J = 7.1$ Hz, 3H), 1.83 (s, 9H), 4.25 (q, $J = 7.1$ Hz, 2H), 8.47 (d, $J = 8.1$ Hz, 1H), 8.83 (s, 1H).

1-*tert*-Butyl-7-(2-carbamoylpyrrolidin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Ethyl Ester (12a). Compound **12a** was prepared from chloride **10** and L-prolinamide according to the general procedure (12.2 mmol scale) in 75% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, $J = 7.17$ Hz, 3H), 1.81 (s, 9H), 1.84 (m, 1H), 1.97 (m, 2H), 2.26 (m, 1H), 3.75 (m, 1H), 3.94 (m, 1H), 4.21 (q, $J = 7.23$ Hz, 2H), 4.66 (m, 1H), 7.08 (s, 1H), 7.51 (s, 1H), 7.89 (d, $J = 13.24$ Hz, 1H), 8.68 (s, 1H). Anal. ($C_{20}H_{25}FN_4O_4$) C, H, N, F.

1-*tert*-Butyl-7-(2-carbamoylpyrrolidin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid (12b). Compound **12b** was prepared from ester **12a** according to the general procedure (5 mmol scale) in 89% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 9H), 2.00 (m, 3H), 2.27 (m, 1H), 3.83 (m, 1H), 3.97 (m, 1H), 4.74 (m, 1H), 7.13 (s, 1H), 7.56 (s, 1H), 8.02 (d, $J = 12.87$ Hz, 1H), 8.85 (s, 1H), 15.37 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.0 (br), 28.9, 32.0 (br), 50.6 (br), 62.5 (br), 65.5, 106.7, 113, 117.6 (d, $J = 20.8$ Hz), 144.6, 145.7 (d, $J = 258.8$ Hz), 146.5, 148.0 (d, $J = 11.0$ Hz), 166.3, 173.4, 175.8. Anal. ($C_{18}H_{21}FN_4O_4$) C, H, N, F.

10-*tert*-Butyl-4,7-dioxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (12c). A solution of **12b** (500 mg, 1.33 mmol) in DMF (20 mL) was treated with 60% oily sodium hydride (112.0 mg, 2.79 mmol), stirred for 2 h, heated at 100−130 °C for 6 days, cooled to 25 °C, treated with water, adjusted to pH 3.5 with 1 M HCl, and filtered. The crude material was purified by silica gel chromatography and eluted with 0−10% methanol in dichloromethane to give a white solid (111 mg, 23%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.89 (s, 9H), 2.03 (m, 3H), 2.30 (m, 1H), 3.76 (m, 2H), 4.45 (m, 1H), 7.66 (s, 1H), 8.78 (s, 1H), 10.99 (s, 1H), 15.76 (s, 1H). Anal. ($C_{14}H_{13}N_3O_5 \cdot 0.25H_2O$) C, H, N.

4,7-Dioxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (12). Compound **12** was prepared from compound **12c** according to the general procedure (0.3 mmol scale) in 64% yield. ^{1}H NMR (300 MHz, 1:1 CF_3COOD/DMSO-d_6) δ 15.93 (s, 1H), 8.42 (s, 1H), 7.61 (s, 1H), 4.42 (m, 1H), 3.77 (m, 1H), 3.65 (m, 1H), 2.32 (m, 1H), 2.03 (m, 3H). HPLC (method A) RT = 0.44 min, (method B) RT = 0.30 min.

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(*R*)-4-hydroxy-(*S*)-2-hydroxymethylpyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl ester (16a). Compound **16a** was prepared from chloride **10** and (*S*)-5-hydroxymethylpyrrolidin-(*R*)-3-ol[12] according to the general procedure (5.4 mmol scale) in 42% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25 (t, $J = 10.51$ Hz, 3H), 1.91(m, 1H), 2.16 (m, 1H), 3.48 (m, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.85 (m, 1H), 4.10 (q, $J = 10.51$ Hz, 2H), 4.44 (m, 2H), 4.72 (t, $J = 5.76$ Hz, 1H), 4.99 (d, 4.07 Hz, 1H), 5.39 (m, 2H), 6.48 (dd, $J = 8.48$, 2.37 Hz, 1H), 6.60 (d, $J = 2.03$ Hz, 1H), 7.05 (d, $J = 8.48$ Hz, 1H), 7.85 (d, $J = 13.22$ Hz, 1H), 8.63 (s, 1H).

1-(2,4-Dimethoxybenzyl)-6-fluoro-7-[(*R*)-4-hydroxy-(*S*)-2-hydroxymethylpyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (16b). A suspension of the ethyl ester **16a** (0.698 g, 1.39 mmol) and 1 M NaOH (4.2 mL) in ethanol (35 mL) was stirred for 18 h. Water (20 mL) was added and the mixture heated at 50 °C for 5 h. More water (20 mL) was added, and the solution adjusted to pH 3 with 1 M HCl and then extracted with dichloromethane (3 × 50 mL). The organic extracts were dried and concentrated to give a yellow solid (578 mg, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.94 (m, 1H), 2.18 (m, 1H), 3.45 (m, 1H), 3.64 (m, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 3.83 (m, 1H), 4.46 (m, 2H), 4.76 (s, 1H), 5.02 (s, 1H), 5.52 (dd, $J = 21.33$, 14.34 Hz, 2H), 6.50 (dd, $J = 8.46$, 2.21 Hz, 1H), 6.61 (d, $J = 2.57$ Hz, 1H), 7.10 (d, $J = 8.46$ Hz, 1H), 8.01 (d, $J = 12.87$ Hz, 1H), 8.80 (s, 1H), 15.44 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 49.7, 55.3, 55.5, 58.0 (d, $J = 9$ Hz), 60.0, 98.6, 104.9, 107.4, 111.0, 115.3, 117.7 (d, $J = 22$ Hz), 130.5, 146.1 (d, $J = 243$ Hz), 145.7, 149.1 (d, $J = 7$ Hz), 158.3, 160.8, 166.0, 176.1. Anal. ($C_{23}H_{24}FN_3O_7$) C, H, N, F.

10-(2,4-Dimethoxybenzyl)-(*R*)-2-hydroxy-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (16c). Compound **16c** was prepared from compound **16b** (1.1 mmol scale) according to the general procedure in 55% yield. This reaction required an unusually long heating time to effect cyclization. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.67 (m, 1H), 2.06 (dd, $J = 12.32$, 5.33 Hz, 1H), 3.61 (m, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 3.82 (m, 1H), 4.05 (m, 1H), 4.53 (m, 1H), 4.66 (dd, $J = 10.66$, 3.68 Hz, 1H), 5.25 (d, $J = 3.31$ Hz, 1H), 5.53 (dd, $J = 14.34$, 2.57 Hz, 2H), 6.51 (dd, $J = 8.27$, 2.39 Hz, 1H), 6.58 (d, $J = 2.57$ Hz, 1H), 7.32 (d, $J = 8.09$ Hz, 1H), 7.54 (s, 1H), 8.86 (s, 1H), 15.85 (s, 1H).

10-(2,4-Dimethoxybenzyl)-(*S*)-2-amino-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic acid (14c). To a solution of **16c** (519 mg, 1.15 mmol) and triethylamine (398.5 μL, 2.88 mmol) in dichloromethane (5 mL) at 0 °C was added dropwise mesyl chloride (177.4 μL, 2.3 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 18 h. The reaction was diluted with dichloromethane (15 mL) and the organic phase was washed with aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated in vacuo. To a solution of the crude mesylate in DMF (14 mL) was added sodium azide (724.8 mg, 11.5 mmol). The resulting gelatinous mixture was stirred at 65 °C for 18 h. The mixture was cooled to room temperature and diluted with water (100 mL), and the resulting

solid was collected by vacuum filtration. The solid was washed with water and dried to give the crude azide. To a solution of the crude azide (147.3 mg) in THF (3 mL) and water (100 μL) was added triphenylphosphine (97 mg, 0.37 mmol). The solution was stirred at 50 °C for 18 h. The mixture was cooled to room temperature and concentrated in vacuo, and the residue was triturated with ether (three portions) to give a pale yellow solid, which was further purified by reversed phase (RP) HPLC (100 mg, 15%). ^{1}H NMR [of free amine] (300 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.50 (s, 1H), 7.30 (d, J = 8.46 Hz, 1H), 6.58 (d, J = 2.21 Hz, 1H), 6.51 (dd, J = 8.46, 2.21 Hz, 1H), 5.51 (dd, J = 14.34, 1.84 Hz, 2H), 4.58 (dd, J = 10.30, 3.68 Hz, 1H), 3.88 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.69 (m, 2H), 2.24 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (75 MHz, 5% CH_3OD in DMSO-d_6) δ 37.8, 49.9, 50.7, 53.8, 55.2, 67.7, 98.3, 104.3, 107.1, 112.4, 114.9, 132.3, 138.5, 145.4, 145.9, 146.0, 148.0, 159.0, 161.3, 168.1, 176.4. Anal. ($C_{23}H_{24}N_4O_6$·1.5CF_3COOH) C, H, N.

(*S*)-2-Amino-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (14). A solution of crude **14c** (65 mg, 0.14 mmol) in TFA (10 mL) was stirred for 3 days and then concentrated. The concentrate was azeotroped with acetonitrile (3×). The residue was suspended in water (100 mL) and the suspension was washed with ether. The aqueous layer was filtered through a 0.45 μM syringe filter and then lyophilized to give a white powder, which was further purified by RP HPLC (23.6 mg, 39%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 15.8 (br s, 1H), 8.44 (s, 1H), 8.23 (br s, 2H), 7.58 (s, 1H), 4.67 (dd, J = 10.66 Hz, 3.68 Hz, 1H), 4.13−3.85 (m, 3H), 3.80−3.64 (m, 2H), 2.52 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.5, 47.7, 49.4, 54.0, 67.2, 107.4, 111.2, 113.5, 138.4, 142.0, 145.8, 148.4, 166.4, 176.7; Anal. ($C_{14}H_{14}N_4O_4$·1.75 CF_3COOH) C, H, N, F.

(*R*)-2-Hydroxy-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (16). A solution of **16c** (267 mg, 0.59 mmol) in TFA (5 mL) was heated at 55 °C for 1 h, cooled to 25 °C, stirred for 18 h, and concentrated. The concentrate was azeotroped with toluene, sonicated for 2 h in water (300 mL) and 1 M NaOH (1.36 mL, 1.35 mmol), washed with diethyl ether, adjusted to pH 3.5 with 1 M HCl, and filtered. The crude material was triturated with acetone and then further purified by RP HPLC (44.4 mg, 25%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.16 (m, 1H), 8.37 (d, J = 4.07 Hz, 2H), 7.53 (m, 1H), 4.67 (dd, J = 10.51, 3.73 Hz, 1H), 4.49 (m, 1H), 4.08 (m, 1H), 3.68 (m, 4H), 2.07 (dd, J = 12.55, 5.09 Hz, 1H), 1.67 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 37.0, 54.0, 55.7, 67.5, 67.8, 107.3, 110.7, 112.9, 138.6, 141.6, 146.1, 149.2, 166.6, 176.6. Anal. ($C_{14}H_{13}N_3O_5$·0.4H_2O) C, H, N.

1-*tert*-Butyl-6-fluoro-7-[2-(1-hydroxyethyl)pyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (17a, 18a). A solution of 2-(1-hydroxyethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester[13] (0.94 g, 4.37 mmol) and *p*-toluenesulfonic acid monohydrate (1.25 g, 6.58 mmol) in acetonitrile (10 mL) was refluxed for 2 h and cooled to room temperature, and the solution was used in the next reaction.

A solution of **11** (0.952 g, 2.92 mmol), crude 1-pyrrolidin-2-ylethanol *p*-toluenesulfonate salt (approximately 4.37 mmol in 10 mL of acetonitrile), and triethylamine (1.62 mL, 11.6 mmol) in acetonitrile (15 mL) at 55 °C was stirred for 3 days, adsorbed onto silica gel and eluted with 0−10% methanol/dichloromethane. This gave diastereomer A as a 3:1 mixture (0.486 g, 41%) and diastereomer B as a 9:1 mixture (0.55 g, 47%).

Data for diastereomer A (17a): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.03 (d, J = 6.3 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.83 (s, 9H), 1.95 (m, 4H), 3.75 (m, 3H), 4.21 (q, J = 7.1 Hz, 3H), 4.45 (m, J = 3.7 Hz, 1H), 4.77 (d, J = 4.8 Hz, 1H), 7.84 (d, J = 13.6 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.3, 19.1, 22.2, 26.2, 29.0, 45.5, 49.5, 59.7, 63.2 (d, J = 7.3 Hz,), 63.6, 67.2, 109.3, 115.5, 118.6 (d, J = 20.8 Hz), 144.6 (d, J = 236.8 Hz), 144.9, 145.6, 147.5 (d, J = 9.7 Hz), 165.0, 171.6. Anal. ($C_{21}H_{28}FN_3O_4$) C, H, N, F.

Data for diastereomer B (18a): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (d, J = 6.3 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.82 (s, 9H), 1.89 (m, 2H), 2.10 (m, 2H), 3.78 (m, 2H), 4.03 (m, 1H), 4.21 (q, J = 7.2 Hz, 2H), 4.28 (m, 1H), 4.73 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 13.6 Hz, 1H), 8.67 (s, 1H). Anal. ($C_{21}H_{28}FN_3O_4$) C, H, N, F.

1-*tert*-Butyl-6-fluoro-7-[(*S*)-2-[(*S*)-1-hydroxyethyl]pyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (17b). Compound **17b** (3:1 mixture of diastereomers) was prepared from **17a** according to the general procedure (1.2 mmol scale) in 95% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.07 (d, J = 5.9 Hz, 3H), 1.89 (s, 9H), 1.97 (m, 4H), 3.78 (m, 3H), 4.47 (m, 1H), 4.85 (d, J = 4.4 Hz, 1H), 7.95 (d, J = 13.2 Hz, 1H), 8.83 (s, 1H), 15.46 (s, 1H).

1-*tert*-Butyl-6-fluoro-7-[(*S*)-2-[(*R*)-1-hydroxyethyl]pyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (18b). Compound **18b** (9:1 mixture of diastereomers) was prepared from **18a** according to the general procedure (1.4 mmol scale) in 75% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (d, J = 6.6 Hz, 3H), 1.87 (s, 9H), 1.93 (m, 2H), 2.15 (m, 2H), 3.83 (m, 2H), 4.05 (m, 1H), 4.34 (m, 1H), 4.79 (d, J = 4.8 Hz, 1H), 8.04 (d, J = 13.2 Hz, 1H), 8.84 (s, 1H), 15.40 (s, 1H).

10-*tert*-Butyl-(*S*)-4-methyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (17c). Compound **17c** (3:1 mixture of diastereomers) was prepared from **17b** according to the general procedure (0.9 mmol scale) in 121% yield (contaminated with mineral oil) as a 4:1 mixture of diastereomers. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.42 (d, J = 5.9 Hz, 3H), 1.59 (m, 1H), 1.90 (s, 9H), 2.00 (m, 1H), 2.16 (m, 2H), 3.51 (m, 1H), 3.76 (m, 3H), 7.57 (s, 1H), 8.78 (s, 1H), 15.85 (s, 1H).

10-*tert*-Butyl-(*R*)-4-methyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (18c). Compound **18c** (15:1 mixture of diastereomers) was prepared from **18b** according to the general procedure (1 mmol scale) in 127% yield (contaminated with mineral oil) as a 15:1 mixture of diastereomers. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.06 (d, J = 6.6 Hz, 3H), 1.61 (m, 1H), 1.90 (s, 9H), 1.99 (m, 1H), 2.15 (m, 2H), 3.68 (m, 1H), 3.83 (m, 1H), 4.00 (m, 1H), 4.83 (m, 1H), 7.58 (s, 1H), 8.78 (s, 1H), 15.87 (s, 1H).

(*S*)-4-Methyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (17). Compound **17** was prepared from compound **17c** (4:1 mixture of diastereomers) according to the general procedure (0.9 mmol scale) in 68% yield (94:6 ratio of diastereomers). ^{1}H NMR (500 MHz, 1:1 CF_3CO_2D/DMSO-d_6) δ 1.52 (d, J = 7.0 Hz, 3H), 1.68 (m, 1H), 2.12 (m, 1H), 2.25 (m, 1H), 2.31 (m, 1H), 3.59 (m, 1H), 3.78 (m, 1H), 3.92 (m, 1H), 7.64 (s, 1H), 8.87 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 17.6, 22.8, 29.0, 46.3, 61.1, 74.3, 106.3, 110.4, 112.6, 137.5, 148.1, 151.1, 155.4, 170.6, 172.5. HPLC (method A) RT = 1.42 min, (method B) RT = 1.32 min.

(*R*)-4-Methyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (18). Compound **18** was prepared from compound **18c** (95:5 mixture of diastereomers) according to the general procedure (1 mmol scale) in 62% yield (>95:5 mixture of diastereomers). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (d, J = 6.6 Hz, 3H), 1.59 (m, 1H), 2.04 (m, 3H), 3.63 (m, 1H), 3.75 (m, 1H), 3.98 (m, 1H), 4.80 (m, 1H), 7.49 (s, 1H), 8.36 (d, J = 6.6 Hz, 1H), 13.17 (d, J = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 13.0, 22.8, 28.0, 46.5, 58.0, 69.9, 107.3, 110.9, 113.7, 136.3, 141.5, 146.0, 148.9, 166.6, 176.4. HPLC (method A) RT = 1.34 min, (method B) RT = 1.22 min.

1-*tert*-Butyl-6-fluoro-7-[(*S*)-2-(1-hydroxybut-3-enyl)pyrrolidin-1-yl]-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (19a and 20a). *N*-(*tert*-Butoxycarbonyl)-L-prolinal (5.0 g, 25 mmol)was dissolved in 100 mL of THF and cooled to −78 °C. Allylmagnesium bromide (30 mL, 1.0 M in Et_2O, 30 mmol) was added, and the mixture was stirred for 2 h at −78 °C and for 1 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The organic phases were washed with H_2O, dried over

Na_2SO_4, and concentrated to afford a clear oil (6.3 g). A portion of this crude material (3.45 g, 14.3 mmol) was dissolved in 40 mL of ethanol and treated with *p*-toluenesulfonic acid (4.1 g, 22 mmol), and the mixture was warmed to 60 °C for 2 h. Because the reaction was not complete, an additional aliquot of *p*-toluenesulfonic acid (510 mg, 2.7 mmol) was added and the mixture was warmed to 80 °C for 1 h. The solution was concentrated to afford the *p*-toluenesulfonic acid salt of 1-pyrrolidin-2-ylbut-3-en-1-ol, and this material was used without further purification.

1-Pyrrolidin-2-ylbut-3-en-1-ol *p*-toluenesulfonic acid salt (4.5 g, 14.3 mmol) was slurried in CH_3CN and treated with chloride **11** (4.0 g, 12.2 mmol) and triethylamine (7 mL, 50 mmol). After 2 h at room temperature, the mixture was warmed to 50 °C for 1 day. The mixture was cooled and diluted with 150 mL of H_2O. A precipitate formed and was collected by filtration. This solid was a 2:1 mixture of diastereomers with diastereomer A predominating. This material could be recrystallized from EtOAc to afford analytically clean material, still as a 2:1 mixture of diastereomers.

Diastereomer A (*R* Configuration at the Alcohol Center): 1-*tert*-Butyl-6-fluoro-7-{(*S*)-2-[(*R*)-1-hydroxybut-3-enyl)]pyrrolidin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (20a). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7.35 Hz, 3H), 1.82 (s, 9H), 1.94 (m, 2H), 2.14 (m, 4H), 3.76 (m, 2H), 3.92 (m, 1H), 4.21 (q, J = 7.35 Hz, 2H), 4.34 (m, 1H), 4.87 (d, J = 5.52 Hz, 1H), 5.03 (m, 2H), 5.83 (m, 1H), 7.91 (d, J = 13.60 Hz, 1H), 8.66 (s, 1H). Anal. ($C_{23}H_{30}N_3O_4$) C, H, N.

The filtrate from the above procedure was extracted with EtOAc and the organic phase was concentrated. This material was recrystallized from EtOAc and hexanes to afford clean desired compound as a 1:3 mixture of diastereomers, now with diastereomer B predominating.

Diastereomer B: (*S* Configuration at the Alcohol Center): 1-*tert*-Butyl-6-fluoro-7-{(*S*)-2-[(*S*)-1-hydroxybut-3-enyl)]pyrrolidin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (19a). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 6.99 Hz, 3H), 1.83 (s, 9H), 1.94 (m, 4H), 2.14 (m, 2H), 3.75 (m, 3H), 4.20 (q, J = 6.99 Hz, 2H), 4.49 (m, 1H), 4.91 (d, J = 5.15 Hz, 1H), 5.03 (m, 2H), 5.83 (m, 1H), 7.83 (d, J = 13.24 Hz, 1H), 8.67 (s, 1H).

1-*tert*-Butyl-6-fluoro-7-{(*S*)-2-[(*R*)-1-hydroxybut-3-enyl)]pyrrolidin-1-yl}-4 -oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (20b). Carboxylic acid **20b** was prepared from ethyl ester **20a** according to the general procedure (2.8 mmol scale) to afford an 89% yield of a 4:1 mixture of diastereomers, favoring 20b. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 9H), 1.95 (m, 2H), 2.15 (m, 4H), 3.82 (m, 3H), 4.38 (m, 1H), 4.91 (d, J = 5.52 Hz, 1H), 5.04 (m, 2H), 5.82 (m, 1H), 8.00 (d, J = 13.24 Hz, 1H), 8.81 (s, 1H), 15.36 (s, 1H). Anal. ($C_{21}H_{26}N_3O_4$) C, H, N.

1-*tert*-Butyl-6-fluoro-7-{(*S*)-2-[(*S*)-1-hydroxybut-3-enyl)]pyrrolidin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (19b). Carboxylic acid **19b** was prepared from ethyl ester **19a** according to the general procedure (2.7 mmol scale) to afford a 95% yield of a 1.5:1 mixture of diastereomers, favoring 19b. ^{1}H NMR [major diastereomer] (300 MHz, DMSO-d_6) δ 1.87 (s, 9H), 2.11 (m, 6H), 3.70 (m, 3H), 4.52 (m, 1H), 5.01 (m, 3H), 5.84 (m, 1H), 7.94 (d, J = 13.24 Hz, 1H), 8.82 (s, 1H), 15.47 (s, 1H). Anal. ($C_{21}H_{26}FN_3O_4$) C, H, N.

(*R*)-4-Allyl-10-*tert*-butyl-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (20c). Compound **20c** was prepared from **20b** according to the general procedure (2.3 mmol scale) to afford an 81% yield of a 6:1 mixture of diastereomers favoring **20c**. The material could further be recrystallized from EtOAc and hexanes to give analytically pure desired compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.74 (m, 1H), 1.90 (s, 9H), 1.99 (m, 2H), 2.14 (m, 2H), 2.38 (m, 1H), 3.68 (m, 1H), 3.81 (m, 1H), 4.05 (m, 1H), 4.73 (dt, J = 10.30, 4.04 Hz, 1H), 5.03 (m, 2H), 5.85 (m, 1H), 7.55 (s, 1H), 8.78 (s, 1H), 15.84 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.8, 27.8, 29.0, 31.2, 46.7, 57.8, 65.4, 72.8, 106.5, 113.0, 114.6, 117.7, 133.5, 135.3, 142.7, 146.0, 147.0, 166.7, 175.5. Anal. ($C_{21}H_{25}N_3O_4$) C, H, N.

(*S*)-4-Allyl-10-*tert*-butyl-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (19c). Compound **19c** was prepared from **19b** according to the general procedure (2.3 mmol scale) to afford a 28% yield of a 3:1 mixture of diastereomers favoring **19c**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.64 (m, 2H), 1.89 (s, 9H), 2.00 (m, 1H), 2.16 (m, 2H), 2.62 (m, 1H), 3.70 (m, 4H), 5.22 (m, 2H), 5.97 (m, 1H), 7.57 (s, 1H), 8.78 (s, 1H), 15.85 (s, 1H).

(*R*)-4-Allyl-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (20). Compound **20** was prepared from compound **20c** (0.19 mmol scale) to afford a 66% yield of a 10:1 mixture of diastereomers, favoring **20**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.68 (m, 1H), 1.92 (m, 2H), 2.04 (m, 1H), 2.13 (m, 1H), 2.30 (m, 1H), 3.60 (m, 1H), 3.72 (m, 1H), 4.01 (m, 1H), 4.65 (dt, J = 10.38, 3.66 Hz, 1H), 4.96 (m, 2H), 5.80 (m, 1H), 7.46 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.8, 27.7, 31.1, 46.4, 57.9, 72.5, 107.3, 111.0, 113.9, 117.7, 133.5, 136.1, 141.6, 146.1, 149.1, 166.5, 176.4.

(*S*)-4-Allyl-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (19). Compound **19** was prepared from compound **19c** (0.2 mmol scale) to afford a 100% yield of a 10:1 mixture of diastereomers, favoring **19**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.57 (m, 1H), 1.98 (m, 1H), 2.14 (m, 2H), 2.43 (m, 1H), 2.61 (m, 1H), 3.56 (m, 2H), 3.72 (m, 2H), 5.22 (m, 2H), 5.97 (m, 1H), 7.48 (s, 1H), 8.40 (s, 1H), 16.14 (s, 1H); ^{13}C (125 MHz, DMSO-d_6 with TFA-*d*) δ 25.5, 31.7, 38.7, 50.7, 64.0, 81.4, 107.5, 112.2, 114.1, 121.5, 134.5, 145.2, 145.7, 149.8, 153.2, 172.3, 172.6.

1-*tert*-Butyl-6-fluoro-7-(2-hydroxymethyl-2-methylpyrrolidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (21a). *N*-(*tert*-Butoxycarbonyl)-DL-proline methyl ester (3.0 g, 13.0 mmol) was dissolved in 50 mL of THF and cooled to −78 °C. To this solution was added lithium diisopropylamide (8.5 mL, 2.0 M in heptane, 17 mmol). After 3 h at −78 °C, methyl iodide (1.6 mL, 25.7 mmol) was added and the mixture was warmed to 0 °C. After 2.5 h at 0 °C, the reaction was quenched by the addition of H_2O and the mixture was extracted with EtOAc. The organic phase was washed with 1 N HCl and H_2O, dried over Na_2SO_4, and concentrated to afford an amber oil (3.4 g). The crude material was dissolved in 50 mL of THF and cooled to −78 °C. To this solution was added DiBAl (32 mL, 1.0 M in toluene, 32 mmol). After 15 min, the cooling bath was removed and the mixture was stirred at room temperature for 2.5 h. The reaction was quenched by the addition of H_2O and saturated aqueous Rochelle's salt. The mixture was extracted with EtOAc, and the organic phase was washed with H_2O and concentrated to afford an orange oil (2.8 g). The crude material (1.5 g, 7.0 mmol) was dissolved in 20 mL of ethanol, and *p*-toluenesulfonic acid (1.8 g, 9.4 mmol) was added. The mixture was warmed to 60 °C for 3 h, and the mixture was then treated with an additional aliquot of *p*-toluenesulfonic acid (220 mg, 1.1 mmol). The mixture was left at 60 °C for 2 h, cooled, and concentrated to afford (2-methylpyrrolidin-2-yl)methanol as the *p*-toluenesulfonic acid salt.

Chloride **11** (2.0 g, 6.12 mmol) was dissolved in 20 mL of DMA, and the toluenesulfonic acid of (2-methylpyrrolidin-2-yl)methanol (2.0 g, 7 mmol) and diisopropylethylamine (4.5 mL, 26 mmol) were added. The mixture was warmed to 110 °C for 6 days. The mixture was cooled and diluted with H_2O, and a white precipitate formed. The precipitate was collected by filtration and chromatographed on SiO_2 with 1−4% MeOH in CH_2Cl_2 to afford the desired product (1.0 g, 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7.35 Hz, 3H), 1.38 (d, J = 2.21 Hz, 3H), 1.70 (m, 1H), 1.82 (s, 9H), 1.95 (m, 2H), 2.37 (m, 1H), 3.57 (m, 1H), 3.77 (m, 3H), 4.21 (q, J = 6.99 Hz, 2H), 4.86 (t, J = 5.52 Hz, 1H), 7.93 (d, J = 13.97 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 21.7, 22.9, 28.9, 38.6, 53.5, 59.7, 63.5, 64.7, 66.9, 109.2, 116.2, 119.7 (d, J = 23 Hz), 145.4, 145.5, 145.1 (d, J = 255 Hz), 147.1 (d, J = 12 Hz), 164.9, 171.6. Anal. ($C_{21}H_{28}FN_3O_6$) C, H, N, F.

1-*tert*-Butyl-6-fluoro-7-(2-hydroxymethyl-2-methylpyrrolidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (21b). Carboxylic acid **21b** was prepared from ethyl ester **21a**

according to the general procedure (0.5 mmol scale) in 80% yield. ^{1}H NMR (500 MHz, acetone-d_6) δ 1.38 (m, 3H), 1.65 (m, 1H), 1.77 (s, 9H), 1.90 (m, 2H), 2.29 (m, 1H), 3.71 (m, 3H), 4.62 (m, 1H), 7.97 (m, 1H), 8.84 (m, 1H). Anal. ($C_{19}H_{24}FN_3O_6$) C, H, N, F.

3a-Methyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (21). Alcohol **21b** (65 mg, 0.17 mmol) was dissolved in 5 mL of DMF, and sodium hydride (20 mg, 60% in oil, 0.5 mmol) was added. After 2 h at room temperature, the mixture was warmed to 50 °C for 18 h. The mixture was allowed to cool and diluted to 80 mL with H_2O, and the pH was adjusted to 3 with 1 N HCl. A yellow precipitate formed and was collected by filtration. A portion of this yellow solid (50 mg, 0.14 mmol) was dissolved in 5 mL of TFA and a few drops of sulfuric acid was added. After 2 h, the mixture concentrated in vacuo and the crude product was purified by chromatography on SiO_2 with 0−5% MeOH in CH_2Cl_2 to afford the desired product (18 mg, 43%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (s, 3H), 1.73 (m, 1H), 1.94 (m, 1H), 2.15 (m, 2H), 3.68 (m, 3H), 4.45 (d, J = 10.30 Hz, 1H), 7.56 (s, 1H), 8.37 (s, 1H), 13.17 (br s, 1H), 15.95 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 22.0, 34.4, 46.1, 59.7, 72.1, 107.2, 110.5, 112.9, 137.9, 141.7, 146.2, 148.6, 166.6, 176.5. Anal. ($C_{15}H_{15}N_3O_3$) C (calcd 59.79, found 59.29), H, N.

7-(2-Allyl-2-hydroxymethylpyrrolidin-1-yl)-1-*tert*-butyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (22a). Chloride **11** (2.0 g, 6.12 mmol) was dissolved in DMA and treated with diisopropylethylamine (4.5 mL, 26 mmol) and (2-allylpyrrolidin-2-yl)methanol toluenesulfonic acid salt (2.2 g, 7 mmol), and the mixture was warmed to 110 °C for 6 days. The mixture was cooled and diluted with H_2O. A precipitate formed and was collected by filtration and washed with Et_2O. The filtrate was extracted with CH_2Cl_2; the organic phase was concentrated and then taken up in EtOAc, washed with water, and concentrated to give a brown oil. The combined crude material was chromatographed on SiO_2 with 0−3% MeOH in CH_2Cl_2 to afford the desired material (247 mg, 20%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 6.99 Hz, 3H), 1.81 (s, 9H), 1.96 (m, 3H), 2.25 (m, 1H), 2.56 (m, 1H), 2.72 (m, 1H), 3.63 (m, 1H), 3.78 (m, 3H), 4.21 (q, J = 7.35 Hz, 2H), 4.93 (m, 3H), 5.67 (m, 1H), 7.95 (d, J = 13.97 Hz, 1H), 8.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.2, 21.9, 28.9, 34.6, 39.2, 53.9, 59.7, 63.5, 64.6, 64.7, 69.5, 109.3, 116.3, 118.2, 119.7 (d, J = 22 Hz), 133.8, 145.3, 145.4, 145.5 (d, J = 254 Hz), 147.4 (d, J = 12 Hz), 164.9, 171.5. Anal. ($C_{23}H_{30}FN_3O_4$) C, H, N, F.

7-(2-Allyl-2-hydroxymethylpyrrolidin-1-yl)-1-*tert*-butyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (22b). Carboxylic acid **22b** was prepared from ethyl ester **22a** according to the general procedure (0.63 mmol scale) in 82% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.86 (s, 9H), 2.00 (m, 3H), 2.28 (m, 1H), 2.57 (m, 1H), 2.74 (m, 1H), 3.63 (m, 1H), 3.83 (m, 3H), 4.98 (m, 3H), 5.71 (m, 1H), 8.10 (d, J = 13.60 Hz, 1H), 8.87 (s, 1H), 15.29 (s, 1H).

3a-Allyl-10-*tert*-butyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triaza-cyclopenta[*a*]anthracene-8-carboxylic Acid (22c). Compound **22c** was prepared from compound **22b** according to the general displacement conditions (0.5 mmol scale) in 82% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.65 (m, 1H), 1.90 (m, 9H), 2.20 (m, 5H), 3.59 (d, J = 10.66 Hz, 1H), 3.79 (m, 2H), 4.55 (d, J = 10.66 Hz, 1H), 5.15 (m, 2H), 5.88 (m, 1H), 7.65 (m, 1H), 8.79 (m, 1H), 15.81 (m, 1H); ^{13}C (125 MHz, DMSO-d_6) δ 21.0, 28.9, 31.5, 38.8, 46.9, 62.4, 65.3, 69.6, 106.4, 112.7, 113.8, 119.4, 133.1, 137.3, 142.8, 146.0, 146.6, 166.7, 175.7.

3a-Allyl-7-oxo-2,3,3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (22). Compound **22** was prepared from compound **22c** (0.14 mmol scale) in 49% yield according to the general procedure. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (m, 1H), 2.08 (m, 3H), 2.30 (m, 2H), 3.56 (d, J = 11.03 Hz, 1H), 3.74 (m, 2H), 4.52 (d, J = 11.03 Hz, 1H), 5.14 (m, 2H), 5.86 (m, 1H), 7.57 (s, 1H), 8.38 (d, J = 6.62 Hz, 1H), 13.18 (d, J = 6.62 Hz, 1H), 15.88 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.1, 31.5, 38.9, 46.6, 62.3, 69.5, 107.3, 110.7, 113.1, 119.5, 133.2, 138.0, 141.7, 146.1, 148.7, 166.5, 176.6. HPLC (method A) RT = 1.65, (method B) RT = 1.60.

7-(2-Aminomethylpyrrolidin-1-yl)-1-*tert*-butyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (23a). Chloride **11** (2.72 g, 8.3 mmol) was slurried in 50 mL of acetonitrile and cooled to 0 °C. To this mixture was added triethylamine (3 mL, 22 mmol) and 2-(*S*)-(aminomethyl)pyrrolidine (0.96 g, 9.6 mmol). The cooling bath was allowed slowly to warm to room temperature and the mixture was stirred for 3 days. The mixture was diluted with water and extracted with EtOAc. The organic phase was washed with water and concentrated in vacuo to give 2.6 g. The crude material was chromatographed with 5−8% MeOH in CH_2Cl_2 to afford the desired material as an oil (22%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (t, J = 7.0 Hz, 3H), 1.83 (s, 9H), 2.02 (m, 4H), 2.57 (m, 1H), 2.77 (m, 1H), 3.63 (m, 1H), 3.83 (m, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.30 (m, 1H), 7.89 (d, J = 13.6 Hz, 1H), 8.66 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.3, 21.7, 27.4, 29, 44, 49.6, 59.7, 61.1, 63.6, 109.4, 115.4, 119.1 (d, J = 21 Hz), 144.8 (d, J = 268 Hz), 145, 145.8, 146.5, 165, 171.5.

10-*tert*-Butyl-7-oxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (23c). Ester **23a** (2.8 g, 7.7 mmol) was dissolved in 50 mL of ethanol and treated with aqueous lithium hydroxide (7.5 mL, 1 M). After 2 days, an additional aliquot of lithium hydroxide (2 mL, 1 M) was added. After an additional 3 h, the mixture was concentrated in vacuo to afford crude lithium carboxylate of acid **23b**. The crude lithium carboxylate of **23b** (2.1 g, 5.7 mmol) was slurried in 100 mL of DMF and warmed to 100 °C. After 20 h, the mixture was cooled, diluted with ∼300 mL of H_2O, brought to pH 4 with 1 N HCl, and filtered to afford the desired product as a yellow solid (48%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (m, 1H), 1.62 (s, 9H), 1.81 (m, 3H), 2.48 (m, 1H), 3.40 (m, 4H), 6.29 (m, 1H), 7.01 (s, 1H), 8.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.6, 29.0, 29.8, 43.4, 46.6, 56.8, 65.0, 106.0, 107.2, 113.3, 129.7, 140.24, 144.1, 146.8, 167.4, 174.9.

7-Oxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic acid (23). Compound **23c** was deprotected to afford compound **23** according to the general procedure (0.49 mmol scale) in 41% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (m, 1H), 2.04 (m, 3H), 2.74 (m, 1H), 3.66 (m, 4H), 6.55 (s, 1H), 7.21 (s, 1H), 8.23 (d, J = 7.0 Hz, 1H), 12.98 (d, J = 6.3 Hz, 1H). HPLC (method A) RT = 1.15, (method B) RT = 0.58.

10-*tert*-Butyl-5-methyl-7-oxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (24c). Amine **23c** (150 mg, 0.44 mmol) was dissolved in 2 mL of DMF. To this solution were added methyl iodide (100 μL, 1.6 mmol) and triethylamine (300 μL, 2.2 mmol). After 24 h at room temperature, more methyl iodide (100 μL, 1.6 mmol) was added and the mixture was warmed to 60 °C. After 16 h, the mixture was cooled to room temperature and diluted with H_2O. A precipitate formed and was collected by filtration. The crude material was chromatographed with 0−5% MeOH in CH_2Cl_2 to give the desired product (92 mg, 56%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (m, 1H), 1.90 (m, 9H), 2.09 (m, 3H), 2.77 (m, 1H), 2.95 (m, 3H), 3.76 (m, 4H), 7.14 (m, 1H), 8.70 (m, 1H), 16.34 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.1, 30.2, 31.5, 39.7, 49.4, 53.6, 58.5, 70.3, 103.7, 105.1, 113.0, 134.9, 141.5, 148.4, 150.6, 168.0, 171.9. HPLC (method A) RT = 1.34, (method B) RT = 1.28. Anal. ($C_{19}H_{24}N_4O_3 \cdot 0.5H_2O$): C, H, N.

5-Methyl-7-oxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (24). In a 25-mL flask, amine **24c** (56 mg, 0.15 mmol) was dissolved in 3 mL of TFA. A few drops of sulfuric acid was added. After 4 days, the mixture was concentrated in vacuo. The crude mixture was chromatographed on 10 g of SiO_2 with 5−10% MeOH in CH_2Cl_2 to give a yellow film. The film was triturated and sonicated with Et_2O and then with water to give the desired product (21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.54 (m, 1H), 1.97 (m, 1H), 2.08 (m, 1H), 2.19 (m, 1H), 2.78 (m, 1H), 2.96 (s, 3H), 3.61 (dd, J =

11.60, 4.27 Hz, 1H), 3.68 (m, 2H), 3.85 (m, 1H), 7.08 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.9, 29.3, 38.2, 46.1, 51.9, 55.6, 104.8, 107.2, 111.0, 131.5, 139.1, 144.1, 148.9, 166.6, 175.5.

5-Acetyl-7-oxo-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (25). Amine **23** (47 mg, 0.16 mmol) was dissolved in 1.5 mL of DMF and treated with acetic anhydride (100 μL, 1.1 mmol) and triethylamine (150 μL, 1.1 mmol). The mixture was stirred at room temperature for 2 h, at 100 °C for 2 h, and at room temperature for 2 days. The reaction was quenched by the addition of water, and the mixture was extracted with 30 mL of EtOAc. The organic phase was washed with water and concentrated in vacuo. The crude material was chromatographed (3−10% MeOH in CH_2Cl_2) to afford the desired product (6 mg, 11%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.55 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.15 (m, 1H), 2.75 (t, 1H), 3.28 (s, 3H), 3.7 (m, 4H), 6.55 (s, 1H), 8.22 (s, 1H).

1-(2,4-Dimethoxybenzyl)-6-fluoro-4-oxo-7-[(S)-2-phenylaminomethylpyrrolidin-1-yl]-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (26a). Compound **26a** was prepared according to the general procedure from chloride **10** and (*S*)-phenylpyrrolidin-2-ylmethylamine (5.3 mmol scale) in 100% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.26 (t, J = 7.12 Hz, 3H), 1.99 (m, 4H), 3.07 (m, 1H), 3.23 (m, 1H), 3.63 (m, 1H), 3.68 (s, 3H), 3.76 (s, 3H), 3.84 (m, 1H), 4.19 (q, J = 7.12 Hz, 2H), 4.63 (m, 1H), 5.39 (m, 2H), 5.63 (m, 1H), 6.38 (m, 1H), 6.52 (m, 4H), 6.99 (t, J = 7.46 Hz, 2H), 7.09 (d, J = 8.48 Hz, 1H), 7.86 (d, J = 13.22 Hz, 1H), 8.60 (s, 1H). Anal. ($C_{31}H_{33}FN_4O_5$) C, H, N, F.

1-(2,4-Dimethoxybenzyl)-6-fluoro-4-oxo-7-[(S)-2-phenylaminomethylpyrrolidin-1-yl]-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (26b). Acid **26b** was prepared according to the general procedure from ethyl ester **26a** (5.3 mmol scale) in 90% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.02 (m, 4H), 3.12 (m, 1H), 3.26 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 3.87 (m, 1H), 4.67 (m, 1H), 5.51 (m, 2H), 5.67 (m, 1H), 6.49 (m, 5H), 6.99 (t, J = 7.80 Hz, 3H), 7.13 (d, J = 8.48 Hz, 1H), 7.97 (d, J = 12.89 Hz, 1H), 8.77 (s, 1H), 15.42 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 26.9 (br), 27.6 (v br), 49.2, 49.2, 49.6, 55.2, 55.5, 59.0, 98.6, 104.8, 107.3, 110.9, 111.9, 115.1, 115.7, 117.62 (d, J = 21 Hz), 128.8, 130.8, 145.7, 145.8 (d, J = 257 Hz), 148.7, 158.4, 160.8, 165.9, 176.0. Anal. ($C_{29}H_{29}FN_4O_5$) C (calcd 65.40, found 64.80), H, F, N.

10-(2,4-Dimethoxybenzyl)-7-oxo-5-phenyl-1,2,3,(*S*)-3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (26c). Amine **26b** (1.0 g, 1.9 mmol) was dissolved in 50 mL of DMF. To this solution was added sodium hydride (230 mg, 60% in oil, 5.8 mmol), and the mixture was warmed to 100 °C for 16 h. The mixture was cooled and diluted with 150 mL of H_2O, and the pH was adjusted to 4 with 1 N HCl. A brown precipitate formed and was collected by filtration. The crude material was recrystallized from EtOAc to afford the desired product (800 mg, 83%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.59 (m, 1H), 2.01 (m, 1H), 2.17 (m, 2H), 3.32 (m, 1H), 3.74 (m, 2H), 3.74 (s, 3H), 3.78 (s, 3H), 3.92 (m, 2H), 5.55 (m, 2H), 6.55 (m, 2H), 7.27 (m, 5H), 7.49 (m, 2H), 8.76 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.5, 31.9, 49.9, 53.2, 54.6, 56.9, 57.1, 59.5, 100.6, 105.2, 106.9, 107.1, 111.9, 116.5, 127.2, 128.8, 132.4, 134.7, 135.2, 145.9, 146.7, 148.5, 152.5, 161.8, 164.4, 168.4, 172.2.

7-Oxo-5-phenyl-1,2,3,3a,4,5,7,10-octahydro-5,10,11,11b-tetraazacyclopenta[*a*]anthracene-8-carboxylic Acid (26). Compound **26** was prepared from 2,4-dimethoxybenzyl-protected **26c** according to the general procedure (0.86 mmol scale) in 60% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.60 (m, 1H), 2.08 (m, 3H), 3.27 (m, 1H), 3.71 (m, 2H), 3.92 (m, 2H), 7.19 (s, 1H), 7.26 (m, 1H), 7.34 (m, 2H), 7.50 (m, 2H), 8.29 (s, 1H), 13.05 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.9, 29.0, 46.2, 50.4, 55.9, 107.0, 108.8, 110.4, 123.7, 124.5, 129.0, 129.2, 139.7, 144.5, 144.9, 148.9, 166.0, 175.5. Anal. ($C_{19}H_{18}N_4O_3$) C, H, N (calcd 15.46, found 14.84). HPLC (method A) RT = 1.82 min, (method B) RT = 1.75.

1-(2-Cyanoethyl)-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Ethyl Ester (27a). Commercially available 3-oxo-3-(2,4,5-trifluorophenyl)propionic acid ethyl ester [CAS 98349-24-7] (20 g, 81 mmol) was slurried in 50 mL of acetic anhydride, treated with triethylorthoformate (15 mL, 90 mmoL), and heated to reflux for 18 h. The mixture was cooled and concentrated in vacuo to afford an oil. The oil (1.3 g, 4 mmol) was dissolved in 5 mL of CH_2Cl_2. The solution was treated with 3-aminopropionitrile (312 mg, 4.5 mmol), stirred at room temperature for 1 h, and concentrated in vacuo. The residue (1 g, 3 mmol) was dissolved in 20 mL of THF, cooled to 0 °C, treated with sodium hydride (130 mg, 60% in oil, 3.4 mmol), stirred for 15 h, quenched by the addition of water, and filtered to afford the desired product (655 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3H), 3.00 (t, J = 6.8 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.52 (t, J = 6.8 Hz, 2H), 7.40 (dd, J = 11.0, 5.9 Hz, 1H), 8.31 (dd, J = 10.2, 8.8 Hz, 1H), 8.58 (s, 1H).

7-[(4-*tert*-Butoxycarbonyl)piperazin-1-yl]-1-(2-cyanoethyl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Ethyl Ester (27b). Compound **27a** (1.0 g, 3.3 mmol) was dissolved in 10 mL of DMSO, treated with piperazine-1-carboxylic acid *tert*-butyl ester (1.8 g, 9.8 mmol), heated to 90 °C for 18 h, cooled, diluted with Et_2O, and filtered to afford the desired product (1.33 g, 85% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (t, J = 7.0 Hz, 3H), 1.43 (s, 9H), 3.13 (t, J = 6.4 Hz, 2H), 3.22 (m, 4H), 3.52 (m, J = 4.7 Hz, 4H), 4.23 (q, J = 7.1 Hz, 2H), 4.72 (t, J = 6.4 Hz, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 13.2 Hz, 1H), 8.68 (s, 1H).

7-[(4-tert-Butoxycarbonyl)piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (27c). Compound **27b** (1.3 g, 2.8 mmol) was slurried in 50 mL of ethanol, heated to 70 °C, treated with 1 M aqueous lithium hydroxide (8 mL, 8 mmol), stirred for 30 min, treated with more lithium hydroxide (8 mL, 8 mmol), heated to reflux for 4 h, cooled, and concentrated. The residue was suspended in EtOAc, washed with 1 N HCl and H_2O, and concentrated in vacuo to afford the product (1.0 g, 97% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (s, 9H), 3.20 (m, 4H), 3.53 (m, 4H), 7.24 (d, J = 7.5 Hz, 1H), 7.85 (d, J = 13.6 Hz, 1H), 8.81 (s, 1H), 15.48 (s, 1H).

6-Fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylic Acid (27). Compound **27c** (95 mg, 0.24 mmol) was slurried in 3 mL of 4 N HCl in dioxane, stirred for 1 h, and then filtered to afford **27** as the hydrochloride salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.32 (m, 4H), 3.44 (m, 4H), 7.36 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 12.9 Hz, 1H), 8.85 (d, J = 6.8 Hz, 1H), 9.10 (s, 2H), 13.36 (d, J = 7.1 Hz, 1H). Anal. ($C_{14}H_{15}FN_3O_3$) C, H, N.

1-Cyclopropyl-6-fluoro-7-(2-hydroxymethylpyrrolidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid Ethyl Ester (29a). 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester[14] (1.0 g, 3.4 mmoL) was slurried in 30 mL of acetonitrile, treated with (*S*)-2-hydroxymethylpyrrolidine (0.4 mL, 4.0 mmol) and *i*-Pr_2EtN (1.7 mL, 9.8 mmol), stirred for 2 days, treated with (*S*)-2-hydroxymethylpyrrolidine (0.1 mL, 1 mmol), stirred for 1 day, quenched by the slow addition of 200 mL of H_2O, and filtered to afford the product as a white solid (1.06 g, 84% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (m, 1H), 1.03 (m, 1H), 1.13 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.93 (m, 2H), 2.05 (m, 2H), 3.45 (m, 1H), 3.54 (m, 1H), 3.69 (m, J = 8.1, 4.1 Hz, 2H), 3.84 (m, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.43 (m, 1H), 4.78 (t, J = 5.6 Hz, 1H), 7.82 (d, J = 13.6 Hz, 1H), 8.35 (s, 1H).

1-Cyclopropyl-6-fluoro-7-(2-hydroxymethylpyrrolidin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (29b). Acid **29b** was prepared according to the general procedure from ethyl ester **29a** (2.7 mmol scale) in 97% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (m, 1H), 1.11 (m, 1H), 1.19 (m, 2H), 1.95 (m, 2H), 2.07 (m, 2H), 3.50 (m, 1H), 3.68 (m, 2H), 3.77 (m, J = 8.0, 3.6 Hz, 1H), 3.88 (m, J = 6.1 Hz, 1H), 4.48 (m, 1H), 4.82 (m, 1H), 7.97 (d, J = 13.2 Hz, 1H), 8.56 (s, 1H), 15.40 (s, 1H). Anal. ($C_{17}H_{18}FN_3O_4 \cdot 0.65H_2O$) C, H, N.

10-Cyclopropyl-7-oxo-2,3,(*S*)-3a,4,7,10-hexahydro-1*H*-5-oxa-10,11,11b-triazacyclopenta[*a*]anthracene-8-carboxylic Acid (29). Compound **29** was prepared from **29b** according to the general displacement conditions (1.5 mmol scale) in 84% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.09 (m, 2H), 1.17 (m, 2H), 1.57 (m, 1H),

2.02 (m, 1H), 2.15 (m, 2H), 3.61 (m, 1H), 3.72 (m, 3H), 3.85 (m, 1H), 4.68 (dd, J = 10.5, 3.7 Hz, 1H), 7.53 (s, 1H), 8.49 (s, 1H), 15.82 (s, 1H). Anal. ($C_{17}H_{17}N_3O_4$) C, H, N.

Supporting Information Available: Tabular listing of analytical procedures performed for target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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