Journal of Medicinal Chemistry

ARTICLE

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Design and Synthesis of Novel *N*-Hydroxy-Dihydronaphthyridinones as Potent and Orally Bioavailable HIV-1 Integrase Inhibitors

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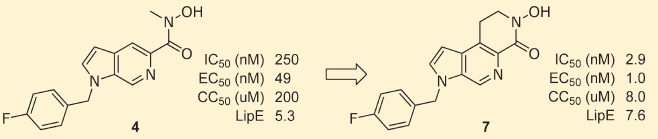
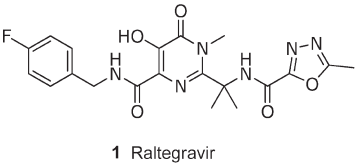
ABSTRACT: HIV-1 integrase (IN) is one of three enzymes encoded by the HIV genome and is essential for viral replication, and HIV-1 IN inhibitors have emerged as a new promising class of therapeutics. Recently, we reported the synthesis of orally bioavailable azaindole hydroxamic acids that were potent inhibitors of the HIV-1 IN enzyme. Here we disclose the design and synthesis of novel tricyclic *N*-hydroxy-dihydronaphthyridinones as potent, orally bioavailable HIV-1 integrase inhibitors displaying excellent ligand and lipophilic efficiencies.

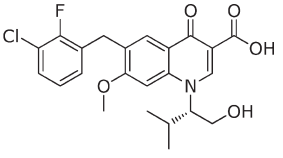


INTRODUCTION

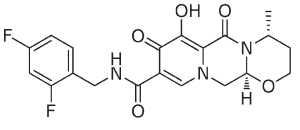
Human immunodeficiency virus type 1 (HIV-1), the causative pathogen of AIDS, replicates utilizing three essential enzymes encoded in the HIV pol gen: reverse transcriptase (RT), protease (PR), and integrase (IN). Many anti-HIV agents target either RT[1] or PR.[2] Recently, inhibitors of the integrase enzyme have emerged as a new promising class of therapeutics for the treatment of AIDS,[3,4] highlighted by the recent approval of Raltegravir (**1**)[5,6] and encouraging phase II clinical trial results with Elvitegravir (**2**)[7] and S/GSK-1349572 (**3**).[8−10] Several drivers remain, however, to discover new chemical classes with complementary or improved properties regarding resistance,[11] dosing, and tolerability.



1 Raltegravir



2 Elvitegravir



3 GSK-1349572

We recently disclosed the discovery of azaindole *N*-methyl hydroxamic acids[12] such as **4** and described subsequent improvements in ADME properties leading to **5**.[13] As shown in Table 1, the introduction of an appropriate side chain onto the pyrrolyl-β-position of **4** results in the aminomethyl **5** with significant alterations to the calculated log *P*, log *D*, and tPSA values. These changes lead to a dramatic improvement in the extraction ratio (ER) as measured with human hepatocytes. The improved stability exhibited by **5** allowed us to examine the pharmacokinetic profile of **5** in the dog. Amide **5** exhibited moderate clearance (Cl = 15 mL/min/kg), a moderate volume of distribution (Vdss = 2.32 L/kg), and a moderate half-life ($T_{1/2}$ = 6.2 h). Unfortunately, the side chain additions are also associated with a loss in enzymatic activity (IC_{50}) and a diminution in antiviral activity (EC_{50}). In the present article, we describe the design, synthesis, and identification of highly potent, ligand and lipophilic efficient, and metabolically stable HIV-1 integrase inhibitors belonging to the *N*-hydroxy-dihydronaphthyridinone class.

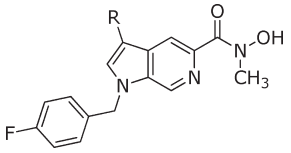
RESULTS AND DISCUSSION

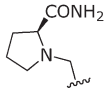
Bis-Metal Binder Design. The catalytic core domain of IN contains two aspartate (Asp64, Asp116) and one glutamate (Glu152) residues that are critical for the catalytic activity of IN and are believed to bind Mg^{2+} and Mn^{2+} ions.[14] More recently, data suggests that Mg^{2+} is the biologically relevant divalent metal critical for IN activity.[15] It is generally believed that IN inhibitors such as diketo acids (DKA (A)) or the dihydroxy pyrimidines carboxamide class (B) bind these two metal ions in the active site while the hydrophobic aryl group participates in a specific interaction with an adjacent hydrophobic pocket or surface (Figure 1).[16,17] Using these notions, we can represent our previously disclosed azaindole hydroxamate class (C) as shown in Figure 1.

In addition to the dipole−dipole interactions which must be dealt with as the precursors of (A), (B), and (C) traverse the path from their global minima to a binding conformation, the azaindole hydroxamates, as shown in (C) (Figure 1), develop an A-strain type of steric interaction as the hydroxamate *N*-methyl begins to eclipse the 4-H of the pyridine portion of

Received: February 23, 2011
Published: March 29, 2011

Table 1. A Comparison of Azaindole Hydroxamates and 3-Substituted Azaindole Hydroxamates



Cmpd	R	Log D	tPSA	IC_{50} (nM)[a]	EC_{50} (nM)[b]	ER (Hhep)[c]
4	H	2.04	58.36	250	32	1.0
5		1.70	104.69	558	94	0.36

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CL_{int})/(Q + (fu × CL_{int})).

the bicyclic system. To better understand the energetic costs of this binding requirement and to estimate the impact it might have on measured enzymatic and antiviral activity, we undertook the conformational analysis[18] of a simplified picolinamide-*N*-methyl hydroxamate system **6** (Figure 2).

As might have been predicted, the global minimum calculated for hydroxamate **6** was found to be a pyridine−N-H-bonded conformer **a** (NCCO torsion = −179.42°, ONCO torsion = −178.77°) with all relevant atoms from the pyridine-N to the hydroxamate-O in essentially the same plane. Conformer **a** was assigned a relative ΔE = 0.0 kcal/mol. Conformer **b** (NCCO torsion −16.26°, ONCO torsion −33.65°), which presents the carbonyl on the same face of the molecule as the pyridine-N but significantly twisted out of planarity, was calculated to be ΔE = 1.057 kcal/mol higher in energy than **a**. Conformer **c** (NCCO torsion = −159.68°, ONCO torsion = 1.44°), a carbonyl-H-bonded relative of **a**, was found to be ΔE = 1.804 kcal/mol higher in energy than **a**. Still higher in energy (ΔE = 3.108 kcal/mol; NCCO torsion = 163.46°, OCNO torsion = −31.80°) was conformer **d**, devoid of an H-bond but exhibiting the carbonyl and pyridine-N in relatively close proximity to a binding mode. Finally, conformer **e**, in which we have constrained the atoms comprising the bis-metal binding domain to be essentially coplanar (NCCO torsion = 0.34°, ONCO torsion = −0.32°) was calculated to be ΔE = 5.926 kcal/mol higher in energy than the global minimum **a**. We surmise that the energetic penalty that must be paid for molecules such as **4** or **5** to assume the putative bis-metal binding conformation might be responsible for the modest enzymatic and antiviral activities obtained in the azaindole hydroxamate series. If we wish to avail ourselves of the improved characteristics offered by the 3-substituted azaindoles such as **5**, we must design more potent molecules.

Should the bis-metal binding conformation be difficult to access due to the energetic considerations described above, we should be easily able to correct this problem through the introduction of a conformational restriction, a ring. Hence we will endeavor to alter the structure of the azaindole hydroxamates such as **4** to arrive at the conformationally locked tetrahydropyrrolo-naphthyridinone **7** (Figure 3).

Chemistry. Our initial synthesis of the target tetrahydropyrrolo-naphthyridinone **7** is shown in Scheme 1. The commercial

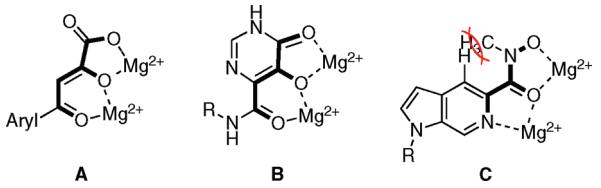


Figure 1. Metal binding of DKA (A), dihydroxypyrimidine carboxamide (B), and azaindole hydroxamate (C).

pyrrole **8** was easily benzylated to provide 4-F-Bn-pyrrole **9** in 95% yield. A two-phase tribromination ((1) pyrrolyl dibromination NBS, EtOAc; (2) benzylic bromination $(PhCO_2)_2$, reflux) gave **10** (88%), which was smoothly coupled with *N*-Ts-glycine methyl ester (KO*t*-Bu) to provide dibromo-pyrrole **11** (81%). Despite extensive experimentation, we discovered that we could not avoid electrophilic aromatic bromination, a reaction which proceeded much faster than benzylic halogenation, hence we resorted to this two-phase procedure. Cyclization to the dibromoazaindole **12** (LiHMDS, 86%) and hydrogenolysis of the dibromide afforded azaindole **13** (95%), setting the stage for the addition of the third ring via a Stille reaction[19] with (*Z*)-2-ethoxyvinyl-tributylstannane.[20] Pyridinol **13** was treated with Tf_2O to provide triflate **14** (90%), which was coupled with (*Z*)-2-ethoxyvinyl-tributylstannane to afford enol ether **15** (70%). Closure to the tricyclic enol lactone was realized after ester hydrolysis and treatment of the resulting acid with HOAc to give **16** (92%). Hydrogenation of the enol lactone gave **17** (81%) and exposure of the lactone to H_2NOTHP and LiHMDS led to the ring-opened, protected hydroxamate **18** (57%). A nonselective (*O*- vs *N*-) Mitsunobu closure provided the *N*-OTHP-tetrahydro-pyrrolo-naphthyridinone **19** in a disappointing 37% yield. The sequence was concluded with an acidic hydrolysis of the THP-ether to give the target *N*-OH compound **7** (24%). The sequence successfully provided the first member of this targeted class of conformationally locked pyridyl hydroxamates, however, at 13 steps and 1.3% overall yield, it did not auger well for a profitable analogue program. The length and poor yield of the sequence was troubling, especially in light of the additional steps required to functionalize at the pyrrolyl-β-position. Of particular concern was the use of tin in the Stille coupling (**14** to **15**), the tedious conversion of the enol ether-ester **15** to the protected hydroxamate **18**, the total lack of selectivity in the Mitsunobu closure of **18** to give **19**, and the poor yield of **7** from the hydrolysis of the *O*-THP congener **19**. We targeted these areas for improvement, and the chemistry developed to circumvent these difficulties is presented in Scheme 2.

Tin could be readily eliminated from the sequence of Scheme 1 by utilizing the β-selective enol ether Heck reaction reported by Fu.[21] In the event, triflate **14** was coupled with butyl vinyl ether to afford the desired enol ether **20** with <5% of the undesired α-coupled enol ether detected in the crude mixture. To avoid the *N*- vs *O*-cyclization conundrum which plagued the **18** to **19** closure (Scheme 1), we envisioned installing the protected hydroxylamine utilizing the butyl enol ether as a acetaldehyde equivalent, with oximino-ether reduction and cyclization completing the formation of the third ring. The first two steps envisioned were poorly precedented in the literature and required a series of reagent and optimization studies that eventually culminated in the successful formation of the cyclic protected *N*-hydroxy-dihydronaphthyridinone **22** in excellent yield. Our plan called for an exchange of the enol ether to afford

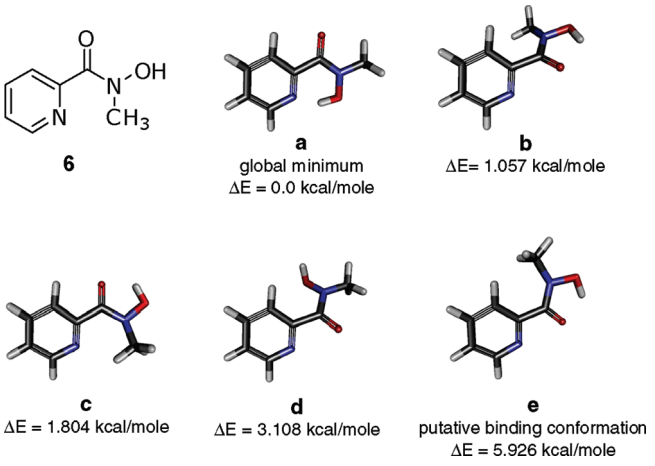
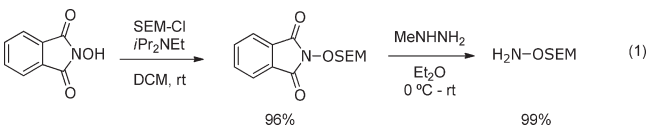


Figure 2. Conformational analysis of picolinamide-*N*-methyl hydroxamate **6**.

an oximino-ether upon treatment of **20** with a selected H_2NOR. The H_2NOR blocking group must survive acid-mediated exchange, oximino-ether reduction, and subsequent cyclization, yet be of sufficient fragility to provide **7** in yields decidedly better than the 24% hydrolysis of **19** to **7** in Scheme 1. A SEM blocking group in the form of H_2N-OSEM seemed to be ideally suited to our needs, however, this entity was unknown. SEM-blocked hydroxylamine was readily prepared as shown in eq 1. SEM-protection of *N*-OH phthalimide provided the desired *N*-OSEM phthalimide in 96% yield. The target H_2OSEM was then easily prepared (99%) upon treatment of the phthalimide with $MeNHNH_2$.[22] Treatment of the butyl vinyl ether **20** with SEM protected hydroxyl amine under acidic conditions (*p*-TsOH, THF) formed the oximino-ether **21** (94%), which was reduced using sodium cyanoborohydride/HOAc and subsequently cyclized in situ to give the desired product **22** in excellent yield. It is interesting to note that many reducing agents were used to attempt the reduction-cyclization sequence, but only sodium cyanoborohydride was found to effect the reduction while other reagents provided starting material or significant byproduct formation. The sequence was completed by the treatment of **22** with HCl in THF to give the target *N*-OH **7** in 80% yield. Alternatively, compound **7** can be prepared directly from **20** in good yield by treatment with hydroxylamine and hydrochloride acid in ethanol at reflux, followed by treatment of the oximino-ether intermediate with acetic acid and sodium cyanoborohydride in methanol at room temperature. The chemistry described shortens the route to nine steps and 34% overall yield to achieve a useful intermediate **22** for an analogue effort vs the 12 steps and 5% overall yield to **19** shown in Scheme 1.

Equation 1: Formation of NH_2OSEM



During our study of azaindole hydroxamates,[12] we had examined a variety of benzylic groups on the pyrrolyl-*N*-position. It was likely that we would also desire to examine an assortment of benzylic groups in the tricyclic tetrahydro-pyrrolo-naphthyridinone class; however, the chemistry of Schemes 1 and 2 was

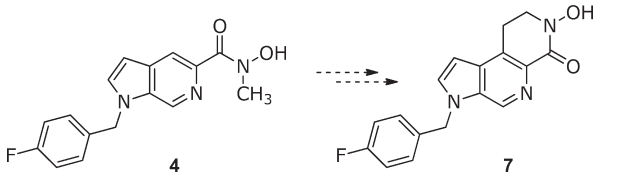


Figure 3. Evolution of azaindole hydroxamate based HIV-integrase inhibitors.

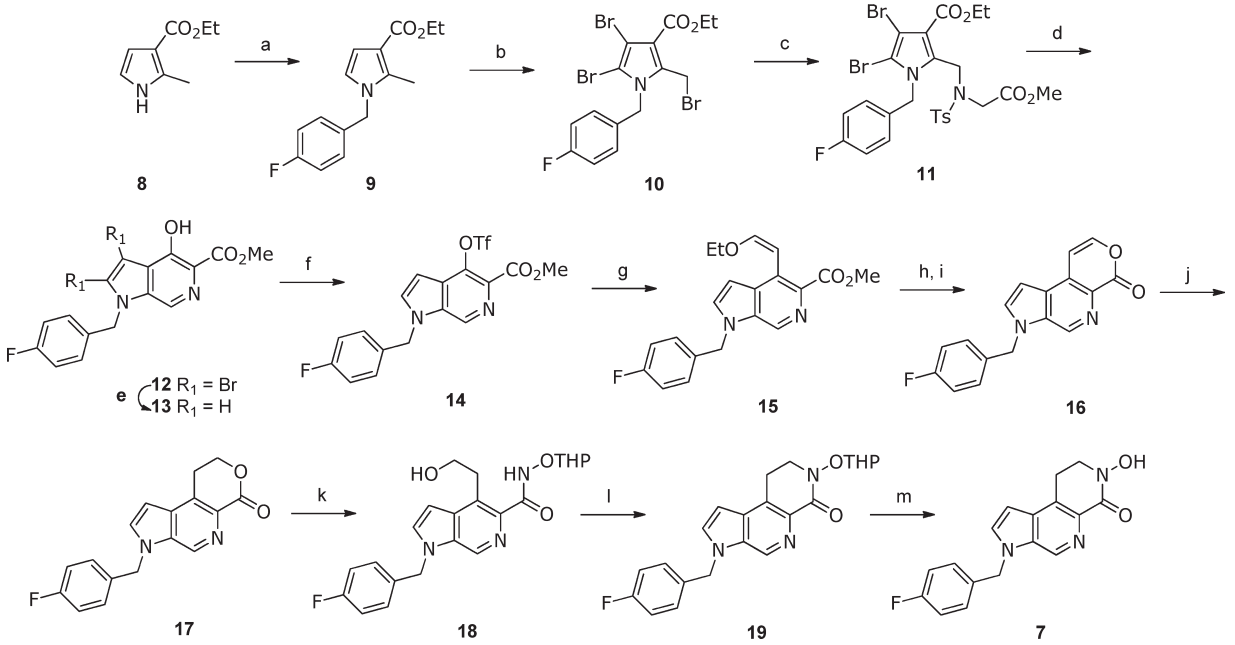
poorly suited to such a study as the benzylic diversity is introduced in step 1 of the nine-step sequence. We selected a benzenesulfonyl blocking group for the pyrrolyl-*N* for its relative stability but ease of removal under basic conditions late in the synthesis endeavor.[23] The chemistry developed for these purposes is presented in Scheme 3.

Pyrrole **8** sulfonylation proceeded smoothly ($PhSO_2Cl$, phase transfer) to provide the protected pyrrole **23** in good yield, and this was followed by benzylic bromination (NBS, benzoyl peroxide), leading to bromide **24** in 92% yield. It is noteworthy that sulfonylation completely suppressed the aromatic electrophilic substitution which was observed in the benzylic bromination of Scheme 1. Alkylation with tosyl glycine provided the coupled product **25** (81%), which was transformed into the phenol **26** in good yield by treatment with lithium hexamethyl disilazide in tetrahydrofuran at low temperature. Activation of the phenol with triflic anhydride and triethyl amine gave the azaindole triflate **27** (86%), which was selectively coupled with butyl vinyl ether, as previously described ($Pd_2(dba)_3$, $(c\text{-}C_6H_{11})_2NMe$, $(t\text{-}Bu)_3PHBF_4$, LiCl, 1,4-dioxane, 70 °C) to yield enol ether **28** (84%). Deprotection of the benzene sulfonyl protecting group was accomplished in 81% yield using a solution of sodium ethoxide in ethanol to give the *N*-H azaindole **29** (84%), which was subjected to H_2NOSEM, and *p*-TsOH as described in Scheme 2, to form the oximino ether **30**. Reductive cyclization of **30** ($NaBH_3CN$, HOAc) gave the *N*-H tricyclic compound **31** in 76% yield, setting the stage for the introduction of the benzylic function deep within the synthetic sequence. Tricycle **31** was readily alkylated with 2-CN, 4-F-benzyl bromide (NaH, THF), yielding **32** (74%) which suffered *O*-SEM cleavage after exposure to sulfuric acid in *i*-PrOH to provide the target tricycle **33** (88%). Utilizing the chemistry of Scheme 3, a small group of modified benzylic analogues were prepared as shown in Table 3.

Having secured reasonable sequences to the target tricyclic cores, we wished to examine the impact of altering physicochemical properties of our putative HIV integrase inhibitors via the incorporation of a side chain at the pyrrolyl β-position as we had described for our azaindole hydroxamates.[13] Tricycle **22** should suffer ready aminomethylation as well as iodination and bromination, setting the stage for facile functionalization. Tricycle **22** was treated with *N*,*N*-dimethyl(methylene)ammonium chloride (MeCN)[24] to give (Scheme 4) the desired aminomethyl compound **34** in good yield (89%); likewise, the exposure of **22** to *N*-iodo-succinimide (NIS) or *N*-bromosuccinimide (NBS) in DMF results in smooth iodination or bromination of the reactive pyrrolyl ring to afford **35a** or **35b** in excellent yields.

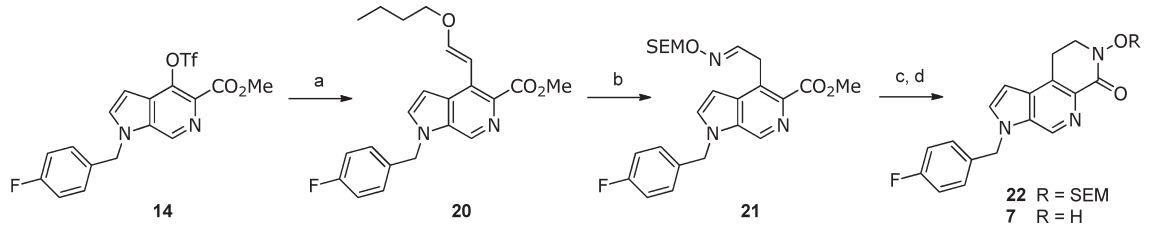
Dimethylaminomethyl-tetrahydro-pyrrolo-naphthyridinone **34** provided access to the compounds of this study as shown in Scheme 5. Treatment of **34** with EtOCOCl or PhOCOCl in DCM[25,26] afforded the reactive intermediate benzylic chloride **36**, which was directly coupled with selected nucleophiles in situ.

Scheme 1. The Synthesis of Tetrahydro-pyrrolo-naphthyridinone 7[a]



[a] Reagents and conditions: (a) 4-FPhCH$_2$Br, KO*t*-Bu, THF, 95%; (b) (1) NBS (3 equiv), EtOAc, rt; (2) (PhCO$_2$)$_2$, reflux, 88%; (c) TsNHCH$_2$CO$_2$Me, KO*t*-Bu, THF, rt, 81%; (d) LiHMDS, THF, −78 °C, 86%; (e) H$_2$ (40 psi), Pd/C, MeOH, 95%; (f) Tf$_2$O, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 90%; (g) PdCl$_2$(PPh$_3$)$_2$, LiCl, (*Z*)-EtOCHCHSn(*n*-Bu)$_3$, 1,4-dioxane, 70 °C, 70%; (h) LiOH, aq MeOH, 50 °C; (i) HOAc, 100 °C, 92%; (j) H$_2$ (35 psi), Pd/Al$_2$O$_3$, MeOH, 81%; (k) H$_2$NOTHP, LiHMDS, THF, 57%; (l) D*t*-BAD, PPh$_3$, THF, rt, 1:1 *N*- vs *O*-, 37% isolated; (m) 1 N aq HCl, 24%.

Scheme 2. Improved End-Game for the Synthesis of Tetrahydro-pyrrolo-naphthyridinone 7[a]



[a] Reagents and conditions: (a) C$_4$H$_9$OCH═CH$_2$ Pd$_2$(dba)$_3$, (*c*-C$_6$H$_{11}$)$_2$NMe, (*t*-Bu)$_3$PHBF$_4$, LiCl, 1,4-dioxane, 70 °C, 86%; (b) H$_2$NOSEM, *p*-TsOH, THF, 94%; (c) NaBH$_3$CN, HOAc, rt, 84%; (d) HCl, THF, rt, 80%.

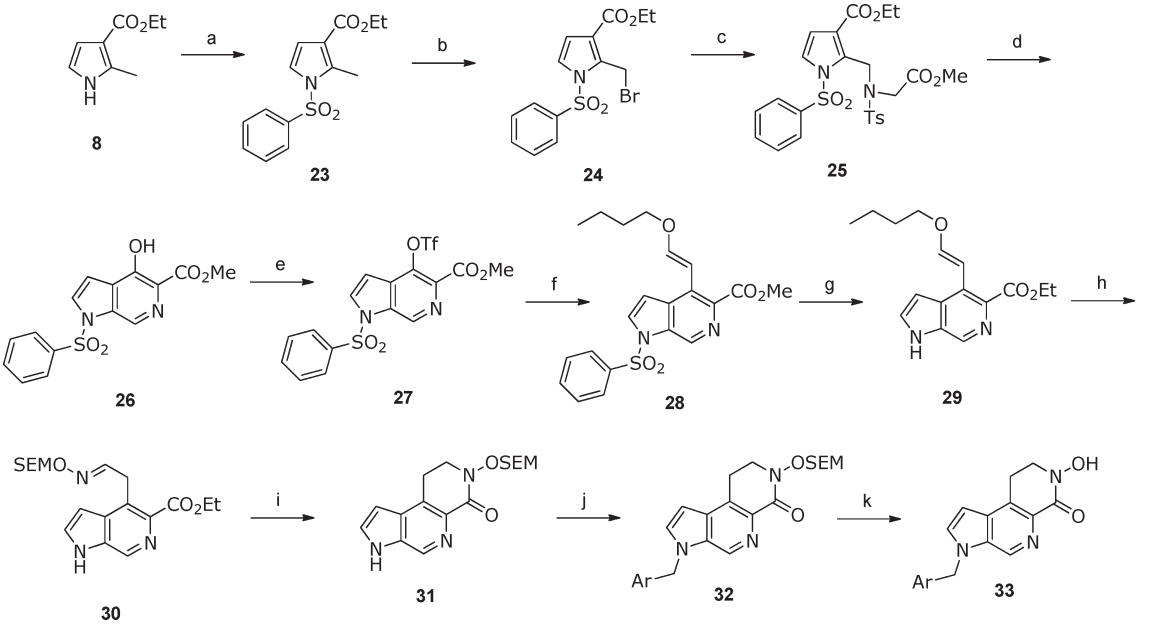
The reaction of **36** with a primary or secondary amine in the presence of *i*-Pr$_2$NEt gave the aminomethyl analogue precursors **37** in good yields. SEM removal as described above led to the target structures **38**. Similarly, the treatment of **36** with an alcohol or water in the presence of *i*-Pr$_2$NEt led to SEM-blocked ethers **39** in good yields. Removal of the SEM-blocking group then afforded ethers **40**.

The preparation of analogues with longer carbon chains at the 1-position of the 3-(4-fluorobenzyl)-7-hydroxy-8,9-dihydro-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6(7*H*)-one core was achieved via the palladium mediated coupling of iodide **35a** with alkynes (Sonogashira reaction) and alkenes (Heck reaction, Scheme 6). Iodide **35a** was easily converted to alkynes **41** under standard Sonogashira conditions, and these alkynes were readily converted to targeted analogues **44** after hydrogenation and SEM removal. Likewise, iodide **35a** afforded alkenes **42**, which provided carbon chain extended analogues **44** after hydrogenation and deprotection.

The final analogues designed for this study were planned to alter physical properties through the incorporation of a sulfonamide moiety at the pyrrolyl-*β*-position. Although we had considered the incorporation of an amide moiety to achieve these ends, our experience with amides in the azaindole series[13] caused us to consider sulfonamides in their stead. The preparation of these sulfonamide containing entities is illustrated in Scheme 7. The conditions required for chlorosulfonylation at the azaindole pyrrolyl-*β*-position were sufficiently acidic (ClSO$_3$H, SOCl$_2$) that we were concerned for the survival of the NO-SEM moiety of the cyclic hydroxamate **22**. Therefore, we elected to start the chemistry of Scheme 7 with the less advanced, but more stable, lactone **17**. Lactone **17** was exposed to chlorosulfonic acid and thionyl chloride, a modification of literature conditions[27] required to drive the reaction to completion, leading to sulfonyl chloride **45** in quantitative yield. Sulfonyl chloride **45** readily provided sulfonamides **46** (R$_1$R$_2$NH, Et$_3$N, DMF), which suffered smooth lactone opening when reacted with

dx.doi.org/10.1021/jm200208d |*J. Med. Chem.* 2011, 54, 3393–3417

Scheme 3. Late Stage Functionalization: The Synthesis of Differentially Benzyl Substituted Tetrahydro-pyrrolo-naphthyridinones[a]



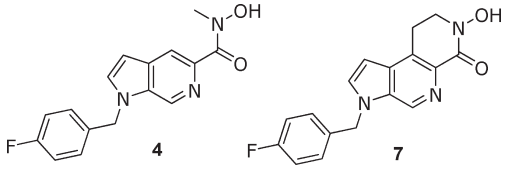
[a] Reagents and conditions: (a) $PhSO_2Cl$, *n*-Bu_4NBr, toluene, aq NaOH, 86%; (b) (1) NBS, CCl_4, $(PhCO_2)_2$, reflux, 92%; (c) $TsNHCH_2CO_2Me$, KO*t*-Bu, THF, rt, 81%; (d) LiHMDS, THF, −78 °C, 63%; (e) Tf_2O, Et_3N, CH_2Cl_2, 0 °C, 86%; (f) $C_4H_9OCH{=}CH_2$ $Pd_2(dba)_3$, $(c\text{-}C_6H_{11})_2NMe$, $(t\text{-Bu})_3PHBF_4$, LiCl, 1,4-dioxane, 70 °C, 84%; (g) NaOEt, ethanol, 84%; (h) H_2NOSEM, *p*-TsOH, THF; (i) $NaBH_3CN$, HOAc, rt, 76%; (j) $ArCH_2Br$, NaH, THF, 40−72%; (k) H_2SO_4, *i*-PrOH, 78−95%.

H_2NOTHP/LiHMDS (THF), giving OTHP-hydroxamates **47** in reasonable yields. Ring closure (*p*-TsCl, *i*-Pr_2NEt, CH_2Cl_2) led to 7-OTHP-naphthyridinones **48**, and the target sulfonamido-substituted tricycles **49** were obtained after OTHP hydrolysis (*p*-TsOH, aq MeOH).

In Vitro Potency, Efficiency, and ADME. We theorized (vide supra) that tethering of the *N*-Me group of compound **4** back onto the azaindole core to give **7** (Table 2) would provide a more rigid, more potent integrase inhibitor by locking the metal binding motif into the most productive binding conformation. We were gratified by the large enhancement in potency from the acyclic *N*-methyl hydroxamate **4** (IC_{50} 250 nM) to the cyclic *N*-hydroxy-dihydronaphthyridinone **7** (IC_{50} 2.9 nM), representing a nearly 100-fold improvement. This progression in potency was also coupled to a significant increase in the LipE[28] from the acyclic **4** (LipE 5.3) to the cyclic **7** (LipE 7.6) metal binding motifs, resulting from a concomitant improvement in antiviral potency and a lowering of log *D*. The change in LipE observed in the transition from the azaindole **4** to the tricycle **7** (2.3 log units) is in excess with respect to the impact on LipE expected as a result of the Δ log *D* (0.65 log units), hence our surmise regarding stronger metal binding and a resulting improvement in antiviral activity appears to be validated.

In addition to the six-membered *N*-hydroxy-dihydronaphthyridinone **7**, both the seven-membered and the five-membered analogues were prepared. Interestingly, the seven-membered ring retained low nanomolar biochemical and cellular potencies (IC_{50} 23 nM and EC_{50} 18 nM, respectively), while the five-membered ring lost significant potency, presumably directly related to the modified "bite" angles differentially affecting the metal-binding abilities (Figure 1). The six-membered ring was ultimately pursued over the seven-membered ring based on synthetic complexity considerations.

Table 2. Enzymatic and Antiviral Activity, Metabolic Stability and Lipophilic Ligand Efficiency of the Acyclic Azaindole *N*-Methyl Hydroxamate 4 and the Cyclic *N*-Hydroxy-dihydronaphthyridinone 7



4 7

Cmpd	Log D	IC_{50} (nM)[a]	EC_{50} (nM)[b]	CC_{50} (μM)[b]	HLM ER	hHEP ER[c]	LipE[d]
4	2.04	250	49	200	0.57	1.00	5.3
7	1.39	2.9	1.0	8.0	<0.40	0.87	7.6

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = $(fu \times CL_{int})/(Q + (fu \times CL_{int}))$. [d] LipE = $-\log EC_{50} - \log D$.

Moderate human liver microsome clearance and high human hepatic clearance for **4** and **7** (Table 2) prompted investigation into route and extent of clearance in vitro. As with our previous series of uncyclized azaindole *N*-methyl hydroxamates,[13] the cyclic *N*-hydroxy-dihydronaphthyridinones are cleared mostly via glucuronidation of the relatively acidic *N*-hydroxy group. Studies of glucuronidation rates with catechols in rat liver concluded that rates are highest for hydrophobic catechols with a pK_a between 8 and 9.[29,30] Because the *N*-hydroxy functionality (typical pK_a between 8 and 9)[31] was critical for activity, we

dx.doi.org/10.1021/jm200208d |*J. Med. Chem.* 2011, 54, 3393–3417

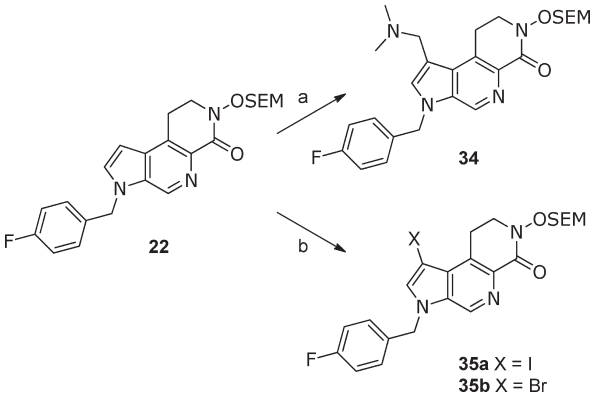
explored whether metabolic rates could be altered by modifying physical properties, for example basicity/acidity/lipophilicity as expressed in a log *D* value. In general, we focused on human hepatocyte clearance measurements to assess glucuronidation while monitoring oxidative clearance via human liver microsomes, although phase I-type clearance seemed to be less relevant based on low in vitro clearance values obtained and metabolic identification studies.

The large improvement in LipE increased our confidence that we could produce a low molecular weight, potent tricyclic inhibitor with acceptable ADME properties by minor modifications to the relatively simple tricycle analogue **7**.[32] Our objective is defined as lowering clearance without compromising antiviral activity or permeability.

Fortuitously, both the fluorobenzyl group and the β position (R_β) in the azaindole ring were readily accessible for introduction of a variety of functional groups covering a range of polarities and it was our assumption, based upon our prior experience,[12,13] that this could be accomplished without substantial loss in antiviral activity. We surveyed an assortment of substituents in the β position of the pyrrole or fluorobenzyl substitutions through parallel medicinal chemistry and singleton synthesis, and wish to report potencies and metabolic stabilities (determined in human hepatocytes) of representative examples.

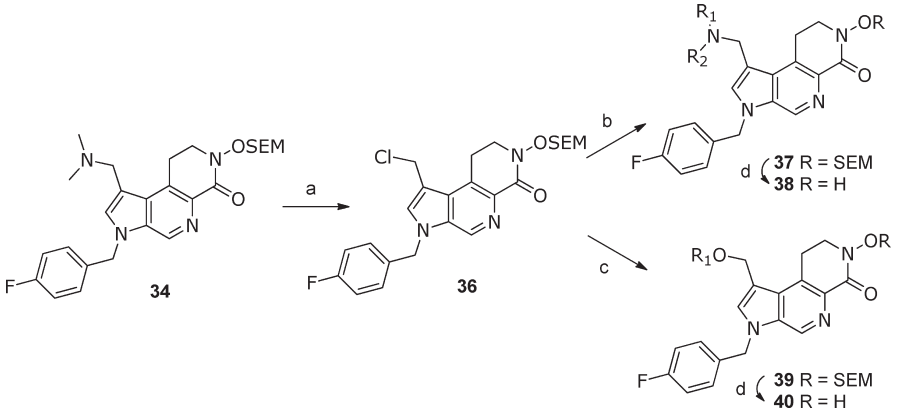
Table 3 highlights potency, stability, permeability, and lipophilic efficiency comparisons of the fluorobenzyl substituted analogues **33a**−**d**. Fluorobenzyl modifications are well tolerated, and all compounds displayed excellent biochemical and cellular potencies. Also, compounds **33a** and **33b** provided comparable LipE values to the original tricyclic lead **7**. Although analogue **33a** and **33b** lost potency relative to the original tricyclic lead, both provide low molecular weight analogues, significantly lower clearance, and reveal good in vitro permeability.[32] In general, clearance values changed with a lowering of log *D*, especially in human hepatocytes, wherein phase II type metabolism is assessed. Oxidative metabolism, as measured by human liver microsome clearance, was not an issue in the *N*-hydroxy-dihydronaphthyridinone series unless

Scheme 4. β-Functionalization of the Pyrrolo-Ring of 22[a]



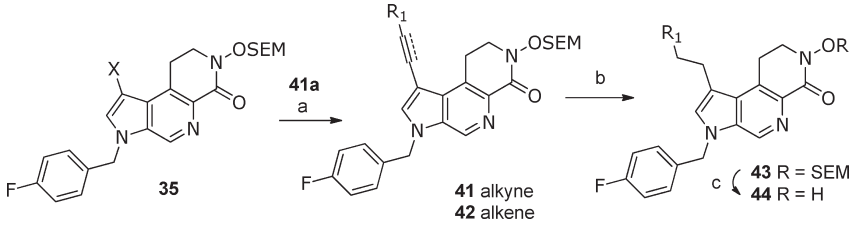
[a] Reagents and conditions: (a) $Me_2N{=}CH_2$ Cl, MeCN, reflux, 89%; (b) NIS, DMF, 92% or NBS, DMF, 97%.

Scheme 5. Synthesis of 1-Substituted 3-(4-fluorobenzyl)-7-hydroxy-8,9-dihydro-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6(7*H*)-ones from Compound 34[a]



[a] Reagents and conditions: (a) EtOCOCl or PhOCOCl, DCM, rt; (b) R_1R_2NH, *i*-Pr_2NEt; (c) R_1OH, *i*-Pr_2NEt, THF; (d) HCl, 1,4-dioxane.

Scheme 6. Synthesis of Carbon Chain Extended 1-Substituted 3-(4-fluorobenzyl)-7-hydroxy-8,9-dihydro-3*H*-pyrrolo[2,3-*c*]-[1,7]naphthyridin-6(7*H*)-ones from Compounds 35 via Palladium Chemistry[a]



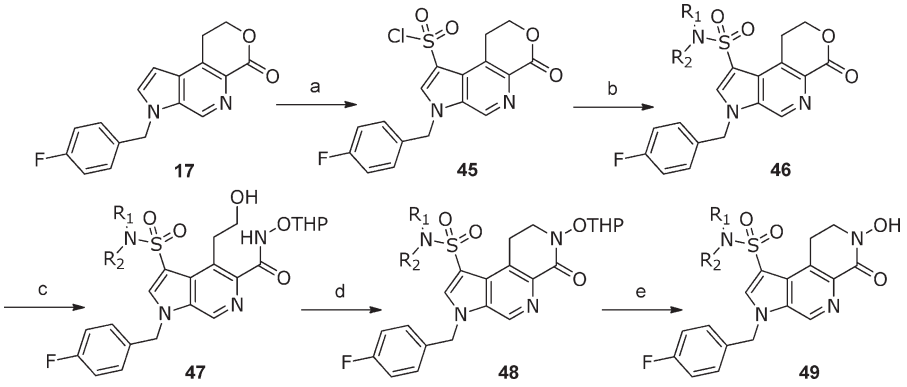
[a] Reagents and conditions: (a) R_1-alkyne, $PdCl_2(Ph_3P)_2$, CuI-SMe_2, Et_3N, DMF, or R_1-$CH_2{=}CH_2$, tri-*o*-tolylphosphine, $Pd(OAc)_2$, Et_3N, DMF; (b) H_2 (1 atm), $Pd(OH)_2$, MeOH; (c) HCl, 1,4,-dioxane, MeOH.

log *D* values were higher or the inhibitors contained metabolic soft spots.

Likewise, substitution on the β-position of the pyrrole allowed property modulation without loss of antiviral potency. A variety of amines with differing pK_a values were prepared and fully characterized regarding potency and in vitro ADME. The biochemical and cellular potencies for the aminomethyl analogues (**38a**−**f**, Table 4) highlight the tolerability of this position to substitution, and the similar LipE numbers (6.9−7.6) calculated underscore the parallel impact of lipophilicity on the cellular potencies in this series. Compounds **38c** and **38f** represent good combinations of antiviral potency, clearance in both human liver microsomes and human hepatocytes, and in vitro permeability, a discernible improvement over the parent *N*-hydroxy-dihydronaphthyridinone **7**.

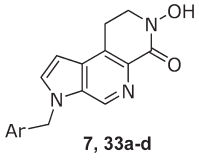
Ethers **40a**−**f** were also prepared, providing a subseries (Table 5) with slightly higher log *D* values due to the absence of the amine found in the aminomethyl series illustrated. As an expected consequence of elevated log *D* values, the in vitro clearance, both in human liver microsomes and human hepatocytes, were slightly elevated. Consequently, cellular potencies and permeabilities were improved, and as expected there

Scheme 7. The Synthesis of 1-Sulfonamido-substituted 3-(4-fluorobenzyl)-7-hydroxy-8,9-dihydro-3*H*-pyrrolo[2,3-*c*]-[1,7]naphthyridin-6(7*H*)-ones from Lactone 17[a]



[a] Reagents and conditions: (a) $ClSO_3H$, $SOCl_2$, 100%; (b) R_1R_2NH, Et_3N, DMF, 69−78%; (c) H_2NOTHP, LiHMDS, THF, 40−57%; (d) *p*-TsCl, *i*-Pr_2NEt, CH_2Cl_2, 33−40%; (e) *p*-TsOH, MeOH, H_2O, 39−45%.

Table 3. Enzymatic and Antiviral Activity and Lipophilic Ligand Efficiency of the 3-Substituted 3,7,8,9-Tetrahydro-7-hydroxy-6*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6-ones 7 and 33a−d

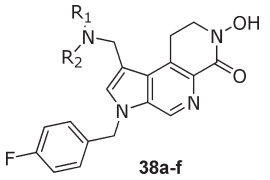


Cmpd	Ar	Log D	tPSA	IC_{50} (nM)[a]	EC_{50} (nM)[b]	CC_{50} (μM)[b]	HLM ER	hHEP ER[c]	Perm AB flux (10^{-6} cm/s)[d]	LipE[e]
33a		0.60	71	32	14	6.0	<0.29	0.13	8.81 (M)	7.3
33b		0.77	71	18	5.0	>3.2	<0.28	0.40	7.65 (M)	7.5
33c		1.15	82	50	14	8.8	<0.28	0.20	8.03 (M)	6.7
7		1.39	54	2.9	1.0	8.0	<0.40	0.87	15.3 (H)	7.6
33d		1.70	82	17	14	9.7	<0.28	0.33	ND	6.2

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CL_{int})/(Q + (fu × CL_{int})). [d] Permeability assessed using Caco-2 flux assay. [e] LipE = −log EC_{50} − log *D*.

dx.doi.org/10.1021/jm200208d |*J. Med. Chem.* 2011, 54, 3393–3417

Table 4. Enzymatic and Antiviral Activity, Metabolic Stability and Lipophilic Ligand Efficiency of 1-Aminomethyl Substituted 3,7,8,9-Tetrahydro-7-hydroxy-6*H*-Pyrrolo[2,3-*c*][1,7]naphthyridin-6-ones 38a−f



38a-f

Cmpd	R_1 R_2	Log D	tPSA	IC_{50} (nM)[a]	EC_{50} (nM)[b]	CC_{50} (μM)[b]	HLM ER	hHEP ER[c]	Perm AB flux (10^{-6} cm/s)[d]	LipE[e]
38a		0.89	62	81	5.0	5.0	<0.26	<0.22	1.81 (L)	7.4
38b		0.67	82	15	4.9	6.9	ND	<0.11	0.44 (L)	7.6
38c		1.15	62	15	3.0	2.2	<0.55	0.25	2.28 (L)	7.4
38d		1.46	71	26	3.2	>3.7	<0.36	0.46	3.52 (M)	7.0
38e		1.52	62	35	3.0	2.0	<0.28	0.67	4.19 (M)	7.0
38f		2.02	62	11	1.2	6.8	0.32	0.02	5.87 (M)	6.9

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CL_{int})/(Q + (fu × CL_{int})). [d] Permeability assessed using Caco-2 flux assay. [e] LipE = −log EC_{50} − log *D*.

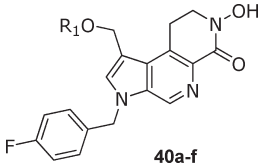
was a parallel relationship between improvements in EC_{50} and increases in log *D* resulting in LipE values clustered around the LipE = 7 line. Overall, compound **40d** provided good cellular potency, in vitro clearance values, and in vitro permeability.

Despite the excellent potencies and in vitro ADME data displayed by the aminomethyl (Table 4) and ether subseries (Table 5), the potential for this chemotype to undergo transformation to reactive intermediates was recognized.[33] The ejection of the corresponding amines or alcohols, whether through metabolic activation or not, could afford reactive intermediates that produce toxicities in vivo. Although metabolic activation was performed in the presence of glutathione,[34] no reactive metabolite glutathione adducts were observed. We must also point to the good yields of final compounds obtained under strongly acidic *N*-OSEM deblocking conditions wherein the possibility of forming reactive intermediates is obvious and palpable. Despite these results, the lingering potential to form reactive metabolites convinced us to explore other β-pyrrolyl substitution offering mechanistic exclusion from reactive imino-methide formation so reminiscent of gramines.

Table 6 features a variety of 3-carbon analogues that were prepared allowing further exploration of this chemical space and also alternatives to the 1-carbon variants that may show unpredictable toxicities. Overall, antiviral potencies were excellent and LipE values were high, confirming that this 3-substitution was also well tolerated. Both compound **44a** and **44b** showed higher-than-usual LipE values. Considering each subseries (Table 4−7), there is a general trend toward higher LipE values at lower log *D*, which is of interest and perhaps is counterintuitive. The increased polarity in the β-substituted moeity and the impact on log *D* is well-tolerated relative to other protein−ligand interactions. Perhaps the β substituent is solvent exposed, not requiring extensive desolvation for binding; however, additional interactions with the protein or metal bound to the protein cannot be discounted. It is also possible that the components of LipE, lipophilicity and potency, have varying contributions over large log *D* ranges or at very low log *D* values. It is very surprising, given the low in vitro permeability measurements, that we are observing any substantial antiviral potencies for these very polar substrates. A possible explanation for the discrepancy between the poor permeability assessment using Caco2 AB data and the excellent antiviral cellular potency, may rest in the time course of the two experiments. The antiviral assay is performed over a three-day period, while the Caco2 assay is on the order of minutes. Although the acid afforded excellent cellular potency along with low in vitro clearance, the resulting significant drop in lipophilicity (log *D*) caused the in vitro permeability to suffer, obliging us to deprioritize these potentially poorly orally absorbed compounds. A number of the compounds in Table 6 offer a reasonable combination of cellular potency and clearance properties (**44b**, **44c**, **44d**), however A to B permeability for these compounds falls into the low bin. The trifluoropropyl analogue **44f**, the simplest analogue in Table 6, offered a good combination of cellular potency and permeability data with somewhat improved clearance vs **7**.

Finally, a series of sulfonamides (**49a**−**e**) were tested for their ability to inhibit HIV integrase and also for their in vitro ADME properties (Table 7). In general, the sulfonamides demonstrated good antiviral potencies and good LipE values relative to the fluorobenzyl analogues (Table 4) and the other β pyrrole-substituted analogues (Tables 4−6). While lower log *D* compounds exhibited good in vitro clearance values in the human

Table 5. Enzymatic and Antiviral Activity, Metabolic Stability and Lipophilic Ligand Efficiency of 1-Alkoxymethyl Substituted 3,7,8,9-Tetrahydro-7-hydroxy-6*H*-Pyrrolo[2,3-*c*][1,7]naphthyridin-6-ones 40a−f

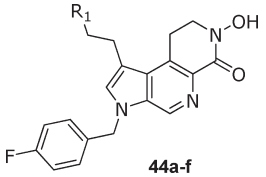


40a-f

Cmpd	R_1	Log D	tPSA	IC_{50} (nM)[a]	EC_{50} (nM)[b]	CC_{50} (μM)[b]	HLM ER	hHEP ER[c]	Perm AB flux (10^{-6} cm/s)[d]	LipE[e]
40a		1.56	80	12	1.5	6.3	0.64	0.35	6.81 (M)	7.3
40b		1.63	80	11	0.83	>1.0	0.48	0.57	9.52 (M)	7.5
40c		1.83	77	14	0.41	7.9	0.44	0.60	4.24 (M)	7.6
40d		2.12	77	17	0.52	>1.0	0.49	0.28	9.52 (M)	7.2
40e		2.15	80	14	4.7	>1.0	0.76	0.49	1.91 (L)	6.2
40f		2.47	68	16	0.84	2.1	0.69	0.67	ND	6.6

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CL_{int})/(Q + (fu × CL_{int})). [d] Permeability assessed using Caco-2 flux assay. [e] LipE = −log EC_{50} − log *D*.

Table 6. Enzymatic and Antiviral Activity, Metabolic Stability and Lipophilic Ligand Efficiency of 1-(3-Carbon) Substituted 3,7,8,9-Tetrahydro-7-hydroxy-6*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6-ones 44a−f



44a-f

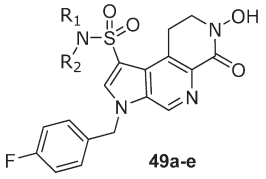
Cmpd	R_1	Log D	tPSA	IC_{50} (nM)[a]	EC_{50} (nM)[b]	CC_{50} (μM)[b]	HLM ER	hHEP ER[c]	Perm AB flux (10^{-6} cm/s)[d]	LipE[e]
44a		-0.74	96	13	6.0	>100	<0.28	<0.10	0.08 (L)	9.0
44b		0.10	71	13	2.1	6.0	<0.28	0.54	2.07 (L)	8.6
44c		0.76	79	14	5.9	>1.0	<0.28	0.41.	4.08 (L)	7.5
44d		1.67	79	8.8	0.67	>2.1	<0.28	0.42	1.69 (L)	7.5
44e		2.10	77	14	0.85	>1.0	0.38	0.89	3.08 (L)	7.0
44f		2.32	58	13	0.50	6.30	<0.364	0.71	10.6 (H)	7.0

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CL_{int})/(Q + (fu × CL_{int})). [d] Permeability assessed using Caco-2 flux assay. [e] LipE = −log EC_{50} − log *D*.

hepatocyte assay, the increase in tPSA resulted in very poor permeability for this series in general. Compounds in this class, such as **49a**, were ultimately withheld from in vivo studies based on predicted poor absorption from in vitro permeability assessments in the Caco2-AB cell flux assay.

In Vivo PK. Encouraged by the reduction in glucuronidation rates in vitro coupled with excellent antiviral potency, compound **38c** emerged as an early candidate for further assessment of its pharmacokinetic (PK) parameters in animal species. Unlike our previous series of bicyclic analogues (i.e., **4**) that were hydrolyzed

Table 7. Enzymatic and Antiviral Activity, Metabolic Stability, and Ligand Lipophilic Efficiency of Sulfonamide Substituted 3,7,8,9-Tetrahydro-7-hydroxy-6*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6-ones 49a−e



49a-e

Cmpd	R_1, R_2	Log D	tPSA	IC_{50} (nM)[a]	EC_{50} (nM)[b]	CC_{50} (μM)[b]	HLM ER	hHEP ER[c]	Perm AB flux (10^{-6} cm/s)[d]	LipE[e]
49a		0.18	113	43	7.5	>10	0.24	0.57	0.0 (L)	7.9
49b		1.14	113	66	5.6	>10	0.63	0.51	0.11 (L)	7.1
49c		1.29	104	13	4.0	30	ND	0.32	0.44 (L)	7.1
49d		1.63	104	22	6.3	24.0	0.26	0.92	0.29 (L)	6.6
49e		2.14	104	36	1.5	20	0.78	0.85	0.75 (L)	6.7

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CL_{int})/(Q + (fu × CL_{int})). [d] Permeability assessed using Caco-2 flux assay. [e] LipE = −log EC_{50} − log *D*.

to their corresponding carboxylic acids in rodent plasma,[35,36] most likely mediated by carboxyesterases, the tricyclic *N*-hydroxy-dihydronaphthyridinones were stable in rat plasma. Despite stability in rat plasma and low in vitro rat microsomal stability, we observed clearance at rat liver blood flow in rat PK studies and were obliged to perform in vivo studies in dog. Pharmacokinetic studies in dog for **38c** showed improved in vivo parameters (Table 8), predicting favorable human pharmacokinetics via single species scaling. Ultimately, compound **38c** provided comparable in vivo human PK predictions relative to **5** (Cl 5.5 mL/min/kg; Vdss 2.2 L/kg; *F* 41%; $T_{1/2}$ 4.5 h)[13] but offered a 300-fold improvement in antiviral potency resulting in a significantly improved predicted human dose[37] (32 mg, BID) and safety margins.

Selectivity Profile against Relevant Targets. Because HIV integrase is a metal dependent DNA processing enzyme and **38c** has a metal binding motif, the selectivity of **38c** for HIV integrase was determined by testing the inhibitor against a variety of human DNA modifying and metal-dependent enzymes.[38] Results from these experiments indicate that **38c** demonstrates no inhibition of any of these enzymes up to the highest concentrations tested (Table 8). Additionally, 10 μM **38c** was tested against 102 human Mg-dependent protein kinases, included in the CEREP profile, and no inhibition was observed.

CONCLUSION

N-Hydroxy-dihydronaphthyridinones are potent HIV integrase inhibitors with antiviral cell-based activities comparable to the currently marketed HIV integrase inhibitor Raltegravir **1** (EC_{50} 10 nM). We were able to dramatically improve LipE through cyclization of the *N*-methyl hydroxamate **4** to the restricted rotamer *N*-hydroxy-dihydronaphthyridinone **7**, locking the metal binding motif into the bioactive conformation. We were also able to attenuate clearance rates in human hepatocytes through introduction of groups at the β-pyrrolyl position of the azaindole core and fluorobenzyl group modification without significant loss in antiviral potencies, endowing several inhibitors with in vitro potency and ADME improvements over the original leads **4** and **7**. Alignment of in vitro ADME and antiviral potency coupled with favorable pharmacokinetic parameters displayed by **38c**, culminated in a substantially lower predicted dose and improved safety margins.

Table 8. Pharmacokinetic Profile of Compound 38c in Dog and Human PK Prediction Using Single-Species Scaling

Species	Cl (mL/min/kg)[b]	Vdss (L/kg)[c]	$T_{1/2}$ (h)[d]	F (%)[e]
dog[a]	30	6.7	2.6	33
human (predicted)	9.1	3.1	4.0	50

[a] Dose: iv, 1.0 mg/kg, citrate buffer, pH = 4; po, 4.2 mg/kg, citrate buffer, pH = 4. [b] Plasma clearance. [c] Volume of distribution. [d] Effective half-life. [e] Oral bioavailability.

EXPERIMENTAL SECTION

Biology. Compounds were assessed for activity against the purified HIV-1 enzyme in a strand-transfer scintillation proximity assay. Data is reported as the mean IC_{50}. All other enzymatic data is IC_{50} of the curve

fit parameter from replicate compound doses in a single experiment. The antiviral activities were determined in a HIV-1 cell protection assay using the RF strain if HIV-1, CEM-SS cells, and the XTT dye-reduction method.[39] Compounds were tested in one or more independent experiments. Variability was typically less than 30% for replicate data.

Integrase Strand-Transfer Scintillation Proximity Assay (SPA). A detailed description of the integrase strand-transfer scintillation proximity assay is described[40] and briefly summarized here. Full-length HIV-1 integrase constructed with an amino terminal 6-histidine tag and mutations described by Chen et al.[41] was expressed in *E. coli* and purified following standard methods. Double-stranded donor DNA (ds-DNA) representing preprocessed ds-DNA derived from the LTR U5 sequence of the viral genome was synthesized (TriLink BioTechnologies; San Diego, CA) as a 5′ biotinylated strand and a CA base-pair overhang at the 5′ end of the nonbiotinylated strand. A 3′ dideoxy derivative of the donor DNA was generated as a control ds-DNA to test for nonspecific interactions. Target ds-DNA was prepared as a [^{3}H]-thymidine labeled product (PerkinElmer Life Sciences Inc., Boston, MA) from enzymatic extension of overhanging 3′ ends of poly(dA) DNA. The final product consists of 5′-blunt end ds-DNA with six [^{3}H]-thymidine nucleotides at both 5′ ends and specific activity of >900 Ci/mmol. Biotinylated donor ds-DNA bound to streptavidin-coated polyvinyltoluene SPA beads (Amersham Pharmacia; Piscataway, NJ) was incubated with enzyme 15 min at 22 °C to form an integrase−donor DNA complex. The strand-transfer reaction was initiated by addition of [^{3}H]-thymidine labeled target DNA. Final assay conditions were 2 pmol donor DNA, 246 nM integrase, and 50 nM target DNA in 22.5 mM MOPS (pH 7.2), 20 mM NaCl, 4 mM CHAPS, 0.05% NP40, 4 mM $MgCl_2$, 1% DMSO, and 10 mM DTT. Reactions were for 50 min at 37 °C, followed by addition of 150 mM EDTA, 90 mM NaOH, and 6 M CsCl to stop the reaction and dissociate integrase−DNA complexes. Compounds solvated and diluted in 100% DMSO were transferred to the assay well in 10% DMSO prior to addition of assay components. Activity was measured in the TopCount plate-based scintillation counter programmed with quench correction to normalize data for potential color absorption of the compounds (PerkinElmer Life Sciences Inc., Boston, MA). Compounds are tested as 2−3 replicates per concentration in 1 or more independent experiments. The corrected percentage inhibition for a compound was fit to a four-parameter logistic equation with variable Hill slope using GraphPad Prism software (GraphPad Software, La Jolla, CA). Acceptable criteria for a curve fit is a percent correlation coefficient (R^2) exceeding 92%. Data is reported as the mean IC_{50}. All other enzymatic data is IC_{50} of the curve fit parameter from replicate compound doses in a single experiment.

HIV-1 Cytopathic Effect (CPE) Inhibition Assay. The antiviral activities of potential modulator compounds (test compounds) were determined as a function of their ability to protect T-cells from the cytopathic effects of HIV-1 infection using the XTT dye reduction method.[39] CEM-SS cells seeded at 2×10^4 cells per well into 96-well plates were mock infected or infected with HIV-1 RF virus at an moi resulting in 90% cell death after 6 days. Test compounds at two or more replicate wells per half-log dilution were added to the cells at the time of seeding and prior to the mock or HIV-1 RF virus infection. On day 6, 50 μL of XTT (1 mg/mL XTT tetrazolium and 0.02 nM phenazine methosulfate) was added to the wells for additional 4 h incubation. Cell viability, as determined by the amount of XTT formazan produced, was quantified spectrophotometrically by absorbance at 450 nm. Data from CPE assays were expressed as the percent of formazan produced in compound-treated cells compared to formazan produced in wells of uninfected, compound-free cells. The 50% effective concentration (EC_{50}) was calculated as the concentration of compound that increased the percentage of formazan production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells. The 50% cytotoxic concentration (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in uninfected, compound-treated cells compared to uninfected, compound-free cells. Compounds were tested in one or more independent experiments. Variability was typically less than 30% for replicate data.

Chemistry. Starting materials and other reagents were purchased from commercial suppliers and were used without further purification unless otherwise indicated. All reactions were performed under a positive pressure of nitrogen, argon, or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, unless otherwise indicated. Analytical thin-layer chromatography was performed on glass-backed Silica Gel 60 °F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high-performance liquid chromotagraphy (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain. Microwave assisted reactions were run in a SmithCreator (Personal Chemistry). ^{1}H NMR spectra were recorded on a Bruker instrument operating at 300 MHz unless otherwise indicated. ^{1}H NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions as indicated (reported in ppm), using chloroform as the reference standard (7.25 ppm) or DMSO-d_6 (2.50 ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in hertz. The mass spectra were obtained using liquid chromatography mass spectrometry (LC-MS) on an Agilent instrument using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI). High resolution mass measurements were carried out on an Agilent TOF 6200 series with ESI. All test compounds showed ≥95% purity as determined by combustion analysis or by high-performance liquid chromatography (HPLC). HPLC conditions were as follows: Eclipse XDB C8, 4.6 mm × 150 mm, 5 μm, 5% → 95% CH_3CN/H_2O/0.1% TFA, 10 min run, flow rate 1.5 mL/min, UV detection (λ = 254, 224 nm), or 5% → 95% CH_3CN/H_2O/0.1%TFA, 9 min run, hold 95% CH_3CN/H_2O/0.1%TFA for 3 min, flow rate 1.5 mL/min. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia).

*Ethyl 1-(4-Fluorobenzyl)-2-methyl-1H-pyrrole-3-carboxylate (**9**).* To a solution of ethyl 2-methyl-1*H*-pyrrole-3-carboxylate **8** (106.26 g, 0.694 mol) (prepared by the method of Wee, et al.[42]) in anhydrous THF (1.0 L), under nitrogen, was added solid potassium *t*-butoxide (85.6 g, 0.763 mol) in five portions over 1 h. The mixture was allowed to stir for 30 min, and then 4-fluorobenzyl bromide (131.13 g, 0.694 mol) in anhydrous THF (0.2 L) was added via pressure equalized addition funnel over 45 min. The mixture was allowed to stir at room temperature for 16 h after the addition was complete and then was poured into water (1.4 L) in a 4 L separatory funnel. The mixture was extracted with diethyl ether (5 × 1.0 L), and the combined organic phases were washed with brine (3.0 L) and dried (Na_2SO_4). Filtration, rinsing of the filter cake with diethyl ether (0.5 L), and concentration in vacuo (house vacuum) gave the crude product as an orange oil. The crude product was purified by chromatography on a column of silica gel (125 mm OD, 1 kg 230−400 mesh, packed with hexanes/EtOAc 95:5) eluted with hexanes/EtOAc (95:5, 2.0 L) and hexanes/EtOAc (90:10, 8.0 L) while collecting 500 mL fractions, using the flash technique. Fractions **4**−**18** were combined to afford ethyl 1-(4-fluorobenzyl)-2-methyl-1*H*-pyrrole-3-carboxylate **9** (172.3 g, 95%) as a clear, pale-yellow, viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.06 Hz, 3H), 2.43 (s, 3H), 4.26 (q, J = 7.06 Hz, 2H), 5.00 (s, 2H), 6.52 (d, J = 3.20 Hz, 1H), 6.58 (d, J = 3.20 Hz, 1H), 6.92−7.04 (4H). LC-MS (APCI) m/z 262.1 $(M + H)^+$. Anal. Calcd for $C_{15}H_{16}FNO_2$: C, 68.95; H, 6.17; N, 5.36. Found: C, 69.21; H, 6.43; N, 5.07.

*Ethyl 4,5-Dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1H-pyrrole-3-carboxylate (**10**).* NBS (267.5 g, 1.503 mol, 3 equiv) was added in

five portions over 1.5 h to a solution ethyl 1-(4-fluorobenzyl)-2-methyl-1*H*-pyrrole-3-carboxylate **9** (130.9 g, 0.501 mol) in EtOAc (2 L), in a 5 L 3 N round-bottom flask, equipped with an internal temperature monitoring probe and reflux condenser. The internal temperature rose to 43 °C during the addition and a transient red color developed, which faded upon completion of the addition. The mixture was allowed to stir for 15 min, and then benzoyl peroxide (1.21 g, 5 mmol, 0.01 equiv) was added and the mixture was heated to reflux and maintained at that temperature for 1.5 h. At this time point, LC-MS (APCI) indicated complete reaction. The mixture was cooled to room temperature, poured into hexanes (2 L), and the precipitated solid was removed by filtration, the filter cake was rinsed with hexanes/EtOAc (0.3 L 90:10), and the combined filtrates were concentrated in vacuo to give the crude tribromide as a red−brown semisolid. The crude material was treated with dichloromethane (50 mL) and hexanes (250 mL) to produce a tan solid and a red−brown liquid. The solid was isolated by filtration, rinsed with dichloromethane/hexanes (10:90, 0.5 L), and was dried in vacuo at room temperature to furnish 216.8 g (88%) of ethyl 4,5-dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1*H*-pyrrole-3-carboxylate **10** as a pale, tan solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, J = 7.16 Hz, 3H), 4.35 (q, J = 7.16 Hz, 2H), 4.77 (s, 2H), 5.36 (s, 2H), 6.96−7.07 (4H). LC-MS (APCI) m/z 416.0 $(M + H)^+$.

*Ethyl 4,5-Dibromo-1-(4-fluorobenzyl)-2-({(2-methoxy-2-oxoethyl)[(4-methylphenyl)sulfonyl]amino}methyl)-1H-pyrrole-3-carboxylate (**11**).* To a stirring solution of methyl *N*-[(4-methylphenyl)sulfonyl]glycinate (51.75 g, 0.213 mol, prepared by the method of Ginzel, et al.[43]) in anhydrous THF (0.5 L) was added solid potassium *t*-butoxide (24.13 g, 0.215 mol) in one portion. The mixture was allowed to stir for 30 min (warms and returns to room temperature), at which time a solution ethyl 4,5-dibromo-2-(bromomethyl)-1-(4-fluorobenzyl)-1*H*-pyrrole-3-carboxylate **10** (105.92 g, 0.213 mol) in anhydrous THF (0.5 L) was added over 1 h. The mixture was allowed to stir at room temperature for 16 h, and then the THF was removed in vacuo and the oily residue was dissolved in dichloromethane (0.75 L), and the solution was washed with satd aq NH_4Cl (0.5 L), brine (0.5 L), and dried (Na_2SO_4). Filtration and concentration in vacuo provided the crude alkylated material as a viscous reddish oil. The crude material was heated in the presence of MeOH (0.75 L) until the MeOH was boiling, and then dichloromethane was added slowly until solution was achieved. The red solution was cooled to room temperature (see off-white crystals), and the crystallization was completed by cooling in a refrigerator (4 °C) for 16 h. The ivory solid was isolated by filtration, the solid was rinsed with diethyl ether/hexanes (0.5 L, 10:90), and the solid was dried in a vacuum oven (house vacuum, 50 °C) overnight to furnish ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-methoxy-2-oxoethyl)[(4-methylphenyl) sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate 11 (113.8 g, 81%) as a free-flowing, fine ivory solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.16 Hz, 3H), 2.14 (s, 3H), 3.49 (s, 3H), 3.89 (s, 2H), 4.19 (q, J = 7.16 Hz, 2H), 4.55 (s, 2H), 7.02 (d, J = 2.45 Hz, 2H), 7.04 (s, 2H), 7.28 (d, J = 8.19 Hz, 2H), 7.59 (d, J = 8.19 Hz, 2H). LC/MS m/z 680.8 $(M + Na)^+$. Anal. Calcd for $C_{25}H_{25}Br_2FN_2O_6S$: C, 45.47; H, 3.82; N, 4.24. Found: C, 45.81; H, 4.06; N, 4.13.

*Methyl 2,3-Dibromo-1-(4-fluorobenzyl)-4-hydroxy-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**12**).* To solid LiHMDS (61.27 g, 0.366 mol), in a 3 L 3-neck round-bottom flask equipped with a 0.5 L pressure equalized addition funnel and an internal temperature probe, was added anhydrous THF (0.5 L). The mixture was placed under nitrogen and immersed in a dry ice-*i*-PrOH bath. The solution was allowed to stir until the internal temperature reached −78 °C (1.25 h). To this stirring cold solution was added a solution of ethyl 4,5-dibromo-1-(4-fluorobenzyl)-2-({(2-methoxy-2-oxoethyl)[(4-methylphenyl) sulfonyl]amino}methyl)-1*H*-pyrrole-3-carboxylate **11** (107.63 g, 0.163 mol) in anhydrous THF (0.5 L) at such a rate that the internal temperature does not exceed −70 °C (2 h). During the course of the addition, a yellow color was first noticed giving way to an orange−yellow solution, which then produced a precipitate and an orange−yellow solution. The reaction was allowed to stir for 30 min after the addition was complete, at which point HPLC/MS (sample taken at 15 min after addition) indicated the reaction was complete. The mixture was rapidly poured into a 6 L separatory funnel, which had been charged with satd aq NH_4Cl (1.5 L) and dichloromethane/methanol (95:5, 2 L). The mixture was rapidly shaken to distribute the reaction mixture and quench the reaction. The organic phase was separated, the aqueous layer was extracted with dichloromethane/methanol (95:5, 1 L), and the combined organic phases were filtered to remove a fine white precipitate and then were dried (Na_2SO_4). Concentration in vacuo afforded the crude cyclized material as a yellow solid which was triturated with EtOH (0.6 L) and the resulting white solid was isolated by filtration, washed with anhydrous ethyl ether (50 mL), and dried in a vacuum oven (house vacuum, 50 °C, 16 h) to give 51.15 g (68.5%) of methyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **12** as a powdery white solid after drying in a vacuum oven . The filtrate was concentrated in vacuo, and the residue was triturated with diethyl ether/hexanes (50:50, 0.25 L) to give 10.68 g (14.3%) of **12** as a powdery white solid after drying in a vacuum oven (house vacuum, 50 °C, 16 h). The filtrate was again treated under the same conditions (0.1 L, 50:50 diethyl ether/hexanes) to give an additional 2.39 g (3.2%) of **12** for a total yield of 64.22 g (86%). TLC (Merck, CH_2Cl_2/EtOAc 50:50, UV±, cerium molybdate±): R_f = 0.57. LC-MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc)/CH_3CN, 5 min, ESI, + mode): RT 3.790 min, m/e = 456.9 (55), 458.8 (base), 459.9 (15) − M+, 480.9 − $(M + Na)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3H), 5.48 (s, 2H), 7.00 (m, 2H), 7.08 (m, 2H), 8.28 (s, 1H), 11.60 (s, 1H). Anal. Calcd for $C_{16}H_{11}Br_2FN_2O_3$: C, 41.95; H, 2.42; N, 6.12. Found: C, 42.13; H, 2.71; N, 5.88.

*Methyl 1-(4-Fluorobenzyl)-4-hydroxy-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**13**).* To a 2.5 L Parr flask was added methyl 2,3-dibromo-1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **12** (67.34 g, 0.147 mol), methanol (1.5 L), and triethyl amine (32.70 g, 0.323 mol). Into this mixture was bubbled nitrogen for 10 min, and then 10% Pd/C (15.6 g) was carefully added. The bottle was placed on a Parr apparatus, evacuated/purged with nitrogen (3×), and hydrogen was added to 40 psi. Shaking was commenced, and after 5 min, the pressure had gone to zero and the bottle was repressurized to 40 psi. This was repeated two times, at which point the pressure lowered to 35 psi and remained. TLC and LC/MS then indicated the reaction was complete (total time ca. 1 h). The palladium was removed by filtration through a pad of Celite, the filter cake was rinsed with dichloromethane (1.0 L), and the combined filtrates were concentrated in vacuo to give the crude product **12** plus amine salts. The mixture was taken into EtOAc (2 L) and water (1.0 L), the organic phase was separated, the aqueous layer was extracted with EtOAc (0.6 L), and the combined organic phases were washed with brine (1.0 L) and dried (Na_2SO_4). Filtration and concentration in vacuo gave a powdery white solid which was dried in a vacuum oven (house vacuum, 50 °C, 16 h) to afford 41.93 g (95%) of methyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **13** as a free-flowing, powdery white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 5.36 (s, 2H), 6.83 (d, J = 3.10 Hz, 1H), 6.99 (2H), 7.11 (2H), 7.17 (d, J = 3.10 Hz, 1H), 8.31 (s, 1H), 11.40 (s, 1H). LC/MS (APCI) m/z 301.1 $(M + H)^+$. Anal. Calcd for $C_{16}H_{13}FN_2O_3$: C, 64.00; H, 4.36; N, 9.33. Found: C, 64.27; H, 4.69; N, 9.15.

*Methyl 1-(4-Fluorobenzyl)-4-(trifluoromethylsulfonyloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**14**).* To a stirred solution of the methyl 1-(4-fluorobenzyl)-4-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **13** (19.13 g, 63.7 mmol) and triethylamine (44.4 mL, 318.5 mmol) in dichloromethane (150 mL) at 0 °C was added trifluoromethanesulfonic anhydride (32.0 mL, 190.1 mmol) dropwise, and the reaction stirred for 1 h. The reaction was quenched with water (100 mL), the organic phase

was separated, the aqueous phase was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by flash column chromatography (silica gel, ethyl acetate/hexane 1:1) to provide the title compound **14** as a pale-brown solid (24.8 g, 90% yield), which was employed directly without additional purification. ^{1}H NMR (DMSO-d_6) δ 4.11 (s, 3H), 5.64 (s, 2H), 6.74 (d, J = 3.10 Hz, 1H), 7.18 (t, J = 3.10 Hz, 2H), 7.41 (m, 2H), 8.08 (m, 1H), 8.10 (s, 1H). LC/MS (APCI) m/z 433.0 $(M + H)^+$.

*(Z)-Methyl 4-(2-Ethoxyvinyl)-1-(4-fluorobenzyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**15**).* A mixture of triflate **14** (4.32 g, 10 mmol), *Z*-2-ethoxy-vinyl-tributylstannane (3.97 g, 11 mmol, 1.1 equiv), and anhydrous LiCl (1.27 g, 30 mmol) were dissolved in anhydrous DMF (50 mL), and the solution was sparged with argon for 10 min. To this oxygen-free mixture was added $PdCl_2(PPh_3)_2$ (0.35 g, 0.5 mmol, 5 mol %), and the flask was placed in an oil bath which had been heated to 60 °C and was stirred for 18 h. DMF was removed in vacuo to give a dark, viscous oil which was triturated with CH_2Cl_2 (100 mL). The solvent was removed in vacuo, and the residue was dissolved in a minimum of CH_2Cl_2 and was purified by chromatography on a column of silica gel using the flash technique (70 mm OD, 500 g, 230−400 mesh, 0−50% EtOAc/CH_2Cl_2, 100 mL fractions). Fractions **20**−**24** were combined to provide 2.48 g (70%) of **15** as a clear, colorless, viscous oil. ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (t, J = 7.06 Hz, 3H), 3.90 (s, 3H), 4.02 (q, J = 7.06 Hz, 2H), 5.53 (s, 2H), 5.86 (d, J = 6.97 Hz, 1H), 6.46 (d, J = 6.97 Hz, 1H), 6.71 (m, 1H), 7.05 (m, 2H), 7.25 (m, 2H), 7.60 (m, 1H), 8.52 (s, 1H). LC/MS (APCI) m/z 355.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}FN_2O_3$: C, 67.79; H, 5.40; N, 7.91. Found: C, 67.66, H, 5.43; N, 8.04.

*7-(4-Fluorobenzyl)pyrano[3,4-b]pyrrolo[3,2-d]pyridin-4(7H)-one (**16**).* (a) To a stirring solution of (*E*)-methyl 4-(2-ethoxyvinyl)-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (10.0 g, 28.2 mmol) **15** in methanol (150 mL) was added 3 M aq LiOH (28.2 mL, 84.6 mmol, 3 equiv). The resulting mixture was heated to an oil bath temperature of 60 °C until hydrolysis was complete by LCMS (5 h). When the reaction was complete, the mixture was cooled to room temperature, and the solvent was removed in vacuo and evaporated under reduced pressure, and the residue was taken into DCM (0.25 L) (Li^+ salt is organic soluble). The organic material was washed with water (0.25 L), brine (0.25 L), and was then dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give a slightly sticky, ivory solid. The residue was triturated with hexanes (3×) and dried in a vacuum oven to afford the crude lithium salt (10.2 g), which was carried into the next step without any further purification or characterization. LC/MS (APCI) m/z 341.1 $(M + H)^+$. (b) The crude lithium salt of (*E*)-4-(2-ethoxyvinyl)-1-(4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (10.2 g), prepared in (a) above, was taken into AcOH (100 mL), and the solution was heated to reflux. After 6 h, the reaction was checked by LCMS and was determined to be complete. At this point, the reaction was cooled to room temperature, and an ivory solid precipitated upon cooling. The solid was filtered and washed with hexanes (3×) and dried in a vacuum oven at 75 °C overnight to provide 7.55 g (91%) of the target 7-(4-fluorobenzyl)pyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(7*H*)-one (**16**) as an ivory powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.66 (s, 2H), 7.12−7.25 (m, 4H), 7.36 (dd, J = 8.57, 5.56 Hz, 2H), 7.73 (d, J = 5.46 Hz, 1H), 7.97 (d, J = 3.01 Hz, 1H), 9.13 (s, 1H). LC/MS (APCI) m/z 295.1 $(M + H)^+$. Anal. Calcd for $C_{17}H_{11}FN_2O_2$: C, 69.38; H, 3.77; N, 9.52. Found: C, 69.12; H, 3.57; N, 9.23.

*7-(4-Fluorobenzyl)-1,7-dihydropyrano[3,4-b]pyrrolo[3,2-d]pyridin-4(2H)-one (**17**).* A solution/suspension of 7-(4-fluorobenzyl)pyrano-[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(7*H*)-one **16** (17.90 g, 60.82 mmol) in THF/MeOH/H_2O (1 L, 85:14:1) was sparged with nitrogen for 15 min in a 2 L Parr hydrogenation bottle. To this solution, under N_2, was added 5% Pd/Al_2O_3 (1.79 g, 10 wt %), and the mixture was hydrogenated under 35 psi of H_2 for 18 h. HPLC and HPLC/MS indicated completion of the reaction, the mixture was sparged with nitrogen, filtered through a pad of Celite (wet with CH_2Cl_2/MeOH 95:5), and the Parr bottle was rinsed with CH_2Cl_2/MeOH (750 mL, 95:5) and the combined filtrates were concentrated in vacuo to afford the crude product as a tan/pale-yellow foam. The crude material was purified by Biotage chromatography in three portions (4 g, 65 + M column gradient CH_2Cl_2/MeOH 99:1 to 95:5, 120 mL fractions), fractions **24**−**27** afforded 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one **17** as a clear−colorless oil which solidified and was recrystallized from ether/CH_2Cl_2 to furnish the target compound as white plates. The 4 g purification was repeated (65 + M column gradient CH_2Cl_2/MeOH 99:1 to 95:5, 120 mL fractions), fractions **25**−**27** afforded the desired lactone as a clear−colorless oil which was seeded with saturated lactone and recrystallized from ether/CH_2Cl_2 to furnish the target compound as white plates. The remaining 11 g of crude product was purified on the Biotage (65 + M column gradient CH_2Cl_2/MeOH 99:1 to 95:5, 120 mL fractions), fractions **25**−**28** gave the desired lactone as a clear−colorless oil which was seeded with saturated lactone and recrystallized from ether/CH_2Cl_2 to furnish the target compound as white plates. The combined material was recrystallized from ether/CH_2Cl_2 to afford 14.7 g (81%) of 7-(4-fluorobenzyl)-1,7-dihydropyrano[3,4-*b*]pyrrolo[3,2-*d*]pyridin-4(2*H*)-one **17** as white plates. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (t, J = 6.12 Hz, 2H), 4.64 (t, J = 6.12 Hz, 2H), 5.45 (s, 2H), 6.68 (d, J = 3.01 Hz, 1H), 7.02 (m, 2H), 7.13 (m, 2H), 7.39 (d, J = 3.01 Hz, 1H), 8.79 (s, 1H). LC/MS (APCI) m/z 297.1 $(M + H)^+$. Anal. Calcd for $C_{17}H_{13}FN_2O_2$: C, 68.91; H, 4.42; N, 9.45. Found: C, 69.02; H, 4.57; N, 9.21.

*1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-N-(tetrahydro-2H-pyran-2-yloxy)-1H-pyrrolo[2,3c]pyridine-5-carboxamide (**18**).* Lactone **17** (3.50 g, 11.81 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (2.77 g, 23.62 mmol, 2 equiv) were rigorously dried by evaporation from anhydrous THF (3 × 20 mL), and the mixture was then dissolved in anhydrous THF (80 mL). The resulting solution was treated with solid LiHMDS (3.95 g, 23.62 mmol, 2 equiv) to give a cloudy orange solution which was warmed to near reflux and then was allowed to cool to room temperature with stirring overnight. The mixture was concentrated in vacuo to provide an orange oil which was dissolved in CH_2Cl_2/MeOH (250 mL, 95:5), and the organic phase was washed satd aq NH_4Cl (200 mL), $^1/_2$ saturated brine (200 mL), brine (200 mL), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded crude **18** as a brown oil which was purified by flash chromatography on a column of silica gel, eluting with a gradient from CH_2Cl_2 to CH_2Cl_2/MeOH (98:2) to provide **18** (3.81 g, 78%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44−1.72 (3H), 1.81−2.02 (3H), 3.67 (m, 2H), 3.86−4.13 (4H), 5.12 (s, 1H), 5.38 (s, 2H), 6.69 (m, 1H), 6.96−7.20 (4H), 7.31 (m, 1H), 8.42(s, 1H), 10.46 (s, 1H). LC/MS m/z 414.2 $(M + H)^+$. Anal. Calcd for $C_{22}H_{24}FN_3O_4$: C, 63.91; H, 5.85; N, 10.16. Found: C, 63.75; H, 5.77; N, 10.02.

*3-[(4-Fluorophenyl)methyl]-3,7,8,9-tetrahydro-7-[(tetrahydro-2H-pyran-2-yl)oxy]-6H-Pyrrolo[2,3-c][1,7]naphthyridin-6-one (**19**).* To a stirred solution of alcohol **18** (1.60 g, 3.9 mmol) in anhydrous THF (100 mL) was added triphenylphosphine (1.20 g, 4.6 mmol) followed by the addition of a solution diisopropyl azodicarboxylate (0.9 mL, 0.94 g, 4.6 mmol) in anhydrous THF (10 mL) over 10 min. The mixture was allowed to stir at room temperature for 1 h, and then the solvent was removed in vacuo to provide crude **19** as a viscous oil. The crude material was purified by chromatography on a Biotage SP-4 (gradient CH_2Cl_2/MeOH 99:1 to 95:5, 10 mL fractions) to give 0.57 g (37%) of **19** as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52−1.72 (3H), 1.80−2.01 (3H), 3.40 (m, 2H), 3.66 (m, 1H), 3.92−4.20 (3H), 5.28 (s, 1H), 5.42 (s, 2H), 6.64 (m, 1H), 7.02 (m, 2H), 7.26 (m, 2H), 7.32 (m, 1H), 8.78 (s, 1H). LC/MS m/z 396.2 $(M + H)^+$. Anal. Calcd for $C_{22}H_{22}FN_3O_3$: C, 66.82; H, 5.61; N, 10.63. Found: C, 66.91; H, 5.70; N, 10.65.

*3-[(4-Fluorophenyl)methyl]-3,7,8,9-tetrahydro-7-hydroxy-6H-Pyrrolo[2,3-c][1,7]naphthyridin-6-one (**7**).* To a solution of THP/ether **19** (0.12 g, 0.30 mmol) in MeOH (2 mL), was added HCl in dioxane (4.0 M, 0.45 mL, 1.8 mmol, 6 equiv) at room temperature. LC-MS showed complete conversion to the product after stirring overnight at room temperature. The solution was concentrated in vacuo, treated with saturated aqueous sodium bicarbonate solution (10 mL), and extracted with DCM (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide crude **7**. The crude product was purified by prep-HPLC to afford 0.023 g, 24% of **7** as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.30 (m, 2H), 3.80 (m, 2H), 5.57 (s, 2H), 6.72 (d, J = 3.0 Hz, 1H), 7.15 (m, 2H), 7.21 (m, 2H), 7.85 (d, J = 3.0 Hz, 1H), 8.84 (s, 1H), 9.87 (s, 1H). LC/MS (APCI) m/z 312.1 $(M + H)^+$. HRMS Calcd for $C_{17}H_{15}FN_3O_2$ $(M + H)^+$: 312.1148. Found: 312.1158.

*Methyl 4-[(E)-2-Butoxyvinyl]-1-(4-fluorobenzyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**20**).* To a three-neck round-bottom flask equipped with a stir bar, a dry ice coldfinger, two rubber septa, under a blanket of N_2, was added **14** (51.77 g, 0.12 mol), $Pd_2(dba)_3$ (3.29 g, 3.6 mmol, 0.03 equiv), $(t\text{-Bu})_3P\cdot HBF_4$ (1.042 g, 3.59 mmol, 0.03 equiv), LiCl (15.23 g, 359.23 mmol, 3 equiv), and anhydrous 1, 4-dioxane (780 mL, 6.5 mL/mmole of **14**). With stirring, *n*-butyl vinyl ether (48.1 g, 0.48 mol, 4 equiv) and Cy_2NMe (26.48 g, 156 mmol, 1.13 equiv) were added. The dry ice coldfinger was filled with dry ice and IPA, and the reaction was heated in an oil bath to an external temperature of 70 °C. After 60 min of heating, the reaction changed from dark-red to a yellow−green. The reaction was checked by HPLC and LCMS and was complete. The reaction was removed from the oil bath and allowed to cool to room temperature. When room temperature was reached, the reaction was filtered through pad of Celite, and the filter cake was washed with EtOAc until no color was observed coming from the filter. The solvents were evaporated under reduced pressure to provide a viscous oil. The oil was dissolved (sonication was used to help dissolve the viscous oil) in EtOAc (1 L). The solution was stirred rapidly for 2−3 h at which time a solid precipitated. The solid was removed by filtration, and the filtrate was concentrated in vacuo to provide crude **20** as a sticky solid. The crude material was purified by flash chromatography eluting with 100% DCM and increasing polarity with EtOAc (0−100%). The pure fractions were concentrated in vacuo to yield an oily solid. The solid was recrystallized from EtOAc to give off **20** (39.4 g, 86%) as off-white needles. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (t, J = 7.2 Hz, 3H), 1.43 (m, 2H), 1.72 (m, 2H), 4.03 (s, 3H), 4.06 (t, J = 7.2 Hz, 2H), 5.78 (s, 2H), 6.63 (d, J = 12.4 Hz, 1H), 7.20 (m, 2H), 7.33 (d, J = 2.6 Hz, 1H), 7.42 (m, 2H), 7.54 (d, J = 12.4 Hz, 1H), 8.41 (d, J = 2.6 Hz, 1H), 9.15 (s, 1H). LC/MS m/z 383.2 $(M + H)^+$. Anal. Calcd for $C_{22}H_{23}FN_2O_3$: C, 68.09; H, 6.06; N, 7.33. Found: C, 68.21; H, 4.29; N, 7.19.

2-((2-(Trimethylsilyl)ethoxy)methoxy)isoindoline-1,3-dione. To a 2 L 3-neck round-bottom flask, equipped with a stir bar, addition funnel (w/N_2 line attached), and digital thermometer, under a static head of nitrogen, was added *N*-hydroxyphthalimide (51.13 g, 0.313 mmol), SEM chloride (73.07 mL, 73.07 g, 0.438 mmol), and dichloromethane (700 mL). The flask was cooled to 0 °C, and then triethyl amine (60.96 mL, 44.32 g, 0.438 mmol) was placed in the addition funnel and added dropwise to the suspension at such a rate that the internal temperature does not exceed 10 °C. During the addition, a transient red color is observed, remaining in the presence of an excess of amine base. Once the addition was complete, the cooling bath was removed and the reaction was stirred at room temperature for 4 h. The reaction was checked by adding an additional 1 mL of triethyl amine, if any red color is observed, then the mixture was allowed to stir for an additional hour and then the test was repeated. Once the reaction was complete, it was cast into dichloromethane (0.5 L) and washed with satd aq $NaHCO_3$ (750 mL) and brine (750 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. The crude solid was recrystallized from hexanes, and the crystals were filtered, washed with cold hexanes, and dried to provide 2-((2-(trimethylsilyl)ethoxy)methoxy)isoindoline-1,3-dione, 88.1 g (96%) as a white crystalline solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.01 (s, 9H), 0.89 (m, 2H), 3.93 (m, 2H), 5.11 (s, 2H), 7.86−7.95 (4H). LC/MS m/z 294.1 $(M + H)^+$. Anal. Calcd for $C_{14}H_{19}NO_4Si$: C, 57.31; H, 6.53; N, 4.77. Found: C, 57.33; H, 6.61; N, 4.62.

O-{[2-(Trimethylsilyl)ethoxy]methyl}hydroxylamine. To a 2 L three-neck round-bottom flask, equipped with an overhead stirrer, an addition funnel (w/N_2 line attached), and a digital thermometer was added 2-((2-(trimethylsilyl)ethoxy)methoxy)isoindoline-1,3-dione 1 (77.69 g, 0.265 mmol) and Et_2O (700 mL). The mixture was cooled in an ice−salt bath (to ca. 0 °C) and *N*-methyl hydrazine (20.9 mL, 18.29 g, 0.397 mmol) was added (with rapid stirring) at such a rate that the internal temperature did not exceed 5 °C. When the addition was complete, the bath was removed and the reaction was allowed to stir at room temperature for 4 h. The white precipitate, which was formed during the reaction, was removed by filtration, rinsed with Et_2O (0.5 L), and the combined filtrates were concentrated in vacuo to furnish the crude product as a pale-yellow oil. The crude oil was purified by distillation (55−58 °C, 760 mmHg) to give *O*-{[2-(trimethylsilyl)ethoxy]methyl}hydroxylamine (39.4 g, 91%) as a clear colorless liquid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.00 (s, 9 H), 0.87 (m, 2 H), 3.57 (m, 2 H), 4.60 (s, 2 H), 6.04 (s, 2 H). LC/MS (APCI) m/z 164.1 $(M + H)^+$. Anal. Calcd for $C_6H_{17}NO_2Si$: C, 44.14; H, 10.49; N, 8.58. Found: C, 43.99; H, 10.52; N, 8.52.

*Methyl 1-(4-Fluorobenzyl)-4-(2-((2-(trimethylsilyl)ethoxy)methoxyimino)ethyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**21**).* To (*E*)-methyl 1-(4-fluorobenzyl)-4-(2-butoxyvinyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **20** (10.00 g, 26.15 mmol) in anhydrous THF (250 mL) was added in order H_2NOSEM (4.91 g, 30.07 mmol, d = 0.81 g/mL, 6.06 mL) and *p*-TsOH−H_2O (12.93 g, 67.99 mmol). HPLC-MS after 1 h showed no reaction. HPLC-MS after 14.5 h suggested 20% conversion to the target compound and a clean reaction. At 24 h, HPLC-MS suggested ca. 35% conversion; 38.5 h, ca. 60% completion. Stirring was continued for an additional ca. 22 h (60 h total), at which time HPLC-MS suggested that the reaction was complete (RT = 1.76 min, m/e = 472). The mixture was diluted with ether (0.25 L) and was cast into CH_2Cl_2 (0.5 L) and satd aq $NaHCO_3$ (0.75 L). The organic phase was separated, the aqueous layer was extracted with CH_2Cl_2 (0.5 L), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo to furnish the crude product as a tan oil. The crude material was triturated with ether, producing a fine, brown solid which was removed by filtration. Removal of the ether from the filtrate gave a beige oil. The crude product was purified by a short, flash column (50 mm OD, 100 g 230−400 mesh, packed DCM; eluted ether/DCM 10:90, 1.0 L; ether/DCM 17.5:82.5 1.0 L; 50 mL fractions). Fractions **14**−**24** were combined to afford the desired product **21** as a clear, colorless, viscous oil 10.0 g (94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.98 (m, 2H), 3.68 (m, 1H), 3.77 (m, 1H), 4.01 (s, 3H), 4.26 (d, J = 6.22 Hz, 1H), 4.43 (d, J = 5.09 Hz, 1H), 5.11 (m, 1H), 5.28 (m, 1H), 5.42 (m, 2H), 6.92 (m, 1H) 7.04 (m, 2H) 7.15 (m, 2H) 7.34 (d, J = 3.20 Hz, 1H) 8.69 (d, J = 3.96 Hz, 1H). LC/MS (APCI) m/z 472.2 $(M + H)^+$. Anal. Calcd for $C_{24}H_{30}FN_3O_4Si$: C, 61.12; H, 6.41; N, 8.91. Found: C, 61.38; H, 6.73; N, 8.76.

*3-(4-Fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**22**).* To methyl 1-(4-fluorobenzyl)-4-(2-((2-(trimethylsilyl)ethoxy)methoxyimino)ethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **21** (7.48 g, 15.86 mmol) in glacial HOAc (125 mL) was added sodium cyanoborohydride (2.10 g, 95%, 31.72 mmol) in two portions (2 × 1.05 g) at the start of the reaction and after 1 h. The reaction was monitored by HPLC and HPLC-MS and

appeared to be ca. 80−90% complete after 1 h. After the addition of the second equivalent of $NaBH_3CN$, the mixture was allowed to stir for 1 additional hour, at which time HPLC-MS suggested that the reaction was complete. The HOAc was then removed at full pump vacuum to give a clear, yellow viscous oil which was treated with 1.0 L of 95:5 ether/DCM and 0.8 L of satd aq $NaHCO_3$. The mixture was placed in a 2 L separatory funnel, shaken, and the organic phase was separated, the aqueous phase was extracted with an additional 0.5 L of DCM, and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo gave the crude product **22** as a pale-yellow glass, which provided a white foam upon exposure to pump vacuum. The crude product was purified by Biotage (65, gradient 2% MeOH to 12% MeOH; 98% to 88% DCM over 12 column volumes, collection by UV, 240 mL fractions). UV detection initiated collection at ca. 5% MeOH in DCM, and collection continued until the gradient reached 6+% MeOH in DCM, a total of two fractions. Concentration in vacuo afforded 5.86 g (84%) of the target compound **22** as a clear, colorless glass/foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9H), 0.97 (m, 2H), 3.38 (t, J = 6.88 Hz, 2H), 3.85 (m, 2H), 3.99 (t, J = 6.88 Hz, 2H), 5.11 (s, 2 H), 5.40 (s, 2H), 6.62 (d, J = 3.20 Hz, 1H), 6.98 (t, J = 8.67 Hz, 2H), 7.09 (m, 2H), 7.33 (d, J = 3.20 Hz, 1H), 8.78 (s, 1H). LC/MS (APCI) m/z 442.2 $(M + H)^+$. Anal. Calcd for $C_{23}H_{28}FN_3O_3Si$: C, 62.56; H, 6.39; N, 9.52. Found: C, 62.79; H, 6.61; N, 9.33.

3-(4-Fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (***7***). To a stirring solution of the SEM-protected *N*-hydroxy-dihydropyridone **22** (1.00 g, 2.26 mmol) in isopropyl alcohol (20 mL) was added sulfuric acid (0.604 mL, 11.30 mmol) and the reaction stirred at room temperature. After 24 h, LCMS showed no remaining starting material. Diethyl ether (100 mL) was added, and the resulting solid hydrogen sulfate salt of the product was filtered through a medium glass fritted filter, rinsed with diethyl ether (100 mL), and dried overnight in a vacuum oven at 40 °C to provide the salt of the desired product **7** as a white solid (700 mg, 80%). ^{1}H NMR (300 MHz, CD_3OD) δ 3.62 (t, J = 7.5 Hz, 2H), 4.10 (t, J = 7.5 Hz, 2H), 5.74 (s, 2H), 7.12 (m, 2H), 7.20 (dd, J = 3.3, 0.8 Hz, 1H), 7.37 (m, 2H), 8.32 (d, J = 3.3 Hz, 1H), 9.08 (s, 1H). LC/MS (APCI) m/z 312.2 $(M + H)^+$. Anal. Calcd for $C_{17}H_{14}FN_3O_2-H_2SO_4-H_2O$: C, 47.77; H, 4.24; N, 9.83. Found: C, 47.59; H, 4.31; N, 9.76.

Ethyl 2-Methyl-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate (***23***). To a solution of ethyl 2-methyl-1*H*-pyrrole-3-carboxylate **8** (15.2 g, 99.3 mmol) and tetra-*n*-butylammonium bromide (3.2 g, 9.9 mmol) in toluene (500 mL) was added benzenesulfonyl chloride (26.4 g, 14.9 mmol) followed by a solution of sodium hydroxide (38 g, 0.95 mol) in water (50 mL). The mixture was vigorously stirred for 45 min. The reaction was monitored by TLC (20% ethyl acetate in hexanes). Upon completion, water (250 mL) was added to the reaction mixture and the organic layer separated. The aqueous was extracted with a further portion of toluene (100 mL). The combined organics were dried over sodium sulfate, and the solvent was removed to afford the product as a viscous oil that was purified by passing through a plug of silica gel, eluting with ethyl acetate/heptanes (initially 10% being increased to 15%). Upon concentration in vacuo, the product began to crystallize from solution, evaporation was halted, and the mixture was cooled in an ice−water bath. The resulting solid was collected by filtration and washed with heptanes to provide the desired product **23** (22.12 g, 76%) as a colorless solid. On standing, a second crop of product (2.75 g, 10%, total 24.87 g, 86%) was isolated. LC/MS (APCI) m/z 294.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7.16 Hz, 3H), 2.63 (s, 3H), 4.25 (q, J = 7.16 Hz, 2H), 6.63 (d, J = 3.58 Hz, 1H), 7.31 (d, J = 3.58 Hz, 1H), 7.56 (m, 2H), 7.62 (m, 1H), 7.84 (m, 2H). HPLC (254, 224 nm): >95% purity.

Ethyl 2-(Bromomethyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate (***24***). To ethyl 2-methyl-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate **23** (30.0 g, 100 mmol) in 400 mL of carbon tetrachloride was added *N*-bromosuccinimide (27.3 g, 153 mmol) and benzoyl peroxide (0.743 mg, 3.07 mmol). The suspension was heated to reflux (oil bath, 100 °C) for 2 h, after which time the reaction mixture was allowed to cool to room temperature and the solid was removed by filtration. The filtrate was concentrated in vacuo, and the resulting residue was dissolved in ethyl acetate (0.5 L) and washed with saturated sodium bicarbonate solution (2 × 0.5 L). The combined aqueous layers were extracted with an additional portion of ethyl acetate (0.25 L). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to give an oily solid. The resulting solid was precipitated from diethyl ether/hexanes solution using sonication and was then filtered and dried to provide the title compound **24** (36.4 g, 96%). LC/MS (APCI) m/z 372.0 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J = 7.16 Hz, 3H), 4.32 (q, J = 7.16 Hz, 2H), 5.19 (s, 2H), 6.71 (d, J = 3.58 Hz, 1H), 7.37 (d, J = 3.58 Hz, 1H), 7.57 (m, 2H), 7.66 (m, 1H) 7.97 (m, 2H). HPLC (254, 224 nm): >95% purity.

Ethyl 2-({(2-Methoxy-2-oxoethyl)[(4-methylphenyl)sulfonyl]amino}methyl)-1-(phenylsulfonyl)-1H-pyrrole-3-carboxylate (***25***). Ethyl 2-(bromomethyl)-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate **24** (30.0 g, 80.6 mmol) and tosyl-glycine methyl ester (19.6 g, 80.6 mmol) were dissolved in DMF (220 mL) and added over 1 h to sodium hydride (6.45 g, 161 mmol, 60% in mineral oil which was washed by hexanes three times) suspended in DMF (100 mL) and cooled in a dry ice-*i*-PrOH bath to −20 °C internal. During the addition, the temperature was kept between −20 °C and −10 °C by altering the rate of addition. After the addition was complete, the mixture was transferred to an ice−water bath and stirring was continued for 2 h. Saturated aqueous ammonium chloride was then added to the reaction mixture (1 L), and the mixture was extracted with ethyl acetate (2 × 1 L). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product as an oily solid. The material was triturated with hexanes and dried in vacuo overnight to afford 31.5 g (73%) of **25** as a white solid. LC/MS (APCI) m/z 535.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.16 Hz, 3H), 2.44 (s, 3H), 3.27 (s, 3H), 3.69 (s, 2H), 4.20 (q, J = 7.16 Hz, 2H), 5.08 (s, 2H), 6.64 (d, J = 3.58 Hz, 1H), 7.33 (m, 2H), 7.39 (d, J = 3.58 Hz, 1H), 7.59 (m, 2H) 7.67 (m, 1H), 7.72 (m, 2H), 8.03 (m, 2H). HPLC (254, 224 nm): >95% purity.

Methyl 4-Hydroxy-1-(phenylsulfonyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (***26***). To a stirring solution of ethyl 2-((*N*-(2-methoxy-2-oxoethyl)-4-methylphenylsulfonamido)methyl)-1-(phenylsulfonyl)-1*H*-pyrrole-3-carboxylate **25** (31.84 g, 59.56 mmol) in THF (400 mL), cooled in a dry ice-*I*-PrOH bath, was added LiHMDS (178 mL, 178 mmol, 1.0 M in THF) via a jacketed (dry ice-*I*-PrOH) addition funnel over 2 h. The resulting mixture was allowed to stir at −78 °C for an additional 1 h, after which time reaction was quenched with aqueous ammonium chloride (400 mL). The resulting mixture was extracted with ethyl acetate (2 × 600 mL), the combined organic layers were washed with water (2 × 400 mL), and the combined aqueous layers were extracted with additional ethyl acetate (2 × 400 mL). The resulting organic layers were combined, washed with saturated sodium chloride solution (1 L), dried over Na_2SO_4, filtered, and concentrated in vacuo until crystalline material was present. The remaining solution was then cooled to room temperature and left in a refrigerator overnight to provide the title compound **26** as a white crystalline solid 12.47 g (63%). LC/MS (APCI) m/z 333.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3H), 6.95 (d, J = 3.58 Hz, 1H), 7.50 (m, 2H), 7.62 (m, 1H), 7.67 (d, J = 3.58 Hz, 1H), 7.95 (m, 2H), 8.96 (s, 1H), 11.25 (s, 1H). HPLC (254, 224 nm): >95% purity.

Methyl 1-(Phenylsulfonyl)-4-{[(trifluoromethyl)sulfonyl]oxy}-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (***27***). A solution of phenol **26** (20.00 g, 60.02 mmol), triethylamine (42.00 mL, 300.0 mmol), and anhydrous dichloromethane (400 mL) was cooled to −5 °C in an ice/brine bath. To the mixture was added triflic anhydride (25.40 mL, 150.4 mmol) at a rate such that the internal temperature of the mixture was

kept below 0 °C. After addition was complete, the reaction mixture was stirred for an additional 30 min. Sodium bicarbonate solution (satd, 600 mL) was added and the mixture was extracted with dichloromethane (3 × 400 mL). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to provide the crude product as an oil which purified by column chromatography (silica gel, 3:1 hexanes/EtOAc) to provide **27** (24.78 g, 86%) as a viscous oil. LC/MS (APCI) m/z 465.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3H), 6.89 (d, J = 3.58 Hz, 1H), 7.56 (m, 2H), 7.68 (m, 1H), 7.86 (d, J = 3.58 Hz, 1H), 7.97 (m, 2 H), 9.37 (s, 1 H) . HPLC (254, 224 nm): >95% purity.

*Methyl 4-[(E)-2-Butoxyethenyl]-1-(phenylsulfonyl)-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**28**).* To a solution of the triflate **27** (1.00 g, 2.15 mmol, 1.00 equiv) in anhydrous 1,4-dioxane (20 mL, degassed with argon balloon and needle) in a Teflon, capped, and sealed tube was added LiCl (274 mg, 6.46 mmol, 3.00 equiv), $Pd_2(dba)_3$ (0.099 g, 0.100 mmol, 0.03 equiv), and $(t\text{-Bu})_3$P-HBF$_4$ (62.4 mg, 0.20 mmol, 0.05 equiv). While stirring, *n*-butyl vinyl ether (2.78 mL, 21.6 mmol, 10 equiv) and Cy2Nme (0.56 mL, 2.6 mmol, 1.20 equiv) were added and the resulting mixture was heated to 80 °C for 16 h and was then allowed to cool. Sodium bicarbonate solution was then added, and the mixture was extracted with ethyl acetate to provide a red−black oil. The residue was dissolved in dichloromethane and purified by flash chromatography (silica gel, 2:1 hexanes/EtOAc to 1:1 hexanes/EtOAc) to provide the title compound **28** as a viscous, colorless glass 0.499 g (56% yield). LC-MS (APCI) m/z 415.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.65 (4H), 3.96 (s, 3H), 5.93 (d, J = 12.4 Hz, 1H), 6.52 (d, J = 12.4 Hz, 1H), 6.78 (m, 1H), 7.41−7.53 (2H), 7.59 (m, 1H), 7.70 (m, 1H), 7.89−7.99 (2H), 9.21 (s, 1H). HRMS Calcd for $C_{21}H_{22}N_2O_5S$ + H^+: 415.1328. Found: 415.1334.

*Ethyl 4-[(E)-2-Butoxyethenyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**29**).* To a solution of methyl 4-[(*E*)-2-butoxyethenyl]-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (**28**) (3.76 g, 9.06 mmol) in anhydrous EtOH (65 mL) was added NaOEt (2.60 M in EtOH, 4.40 mL, 11.8 mmol). The reaction mixture was stirred at room temperature for 8 h, then was quenched by the addition of satd aq NH_4Cl (0.25 L). Then the mixture was extracted by 2 × 300 mL of EtOAc. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to provide the crude products that was further purified by ISCO 180 g flash column (3% to 5% MeOH/DCM) to yield yellow fine crystal of the desired product (**29**) 2.06 g (79%). LC-MS m/z 289.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.06 Hz, 3H), 1.40−1.65 (4H), 3.95 (t, J = 7.16 Hz, 2H) 4.46 (q, J = 7.16 Hz, 2H), 5.93 (d, J = 12.4 Hz, 1H), 6.51 (d, J = 12.4 Hz, 1H), 6.72 (d, J = 3.01 Hz, 1H) 7.43 (d, J = 3.01 Hz, 1H), 8.79 (s, 1H), 9.05 (brs, 1H). HPLC (254, 224 nm): >95% purity.

*Ethyl 4-[(9E)-2,2-Dimethyl-5,7-dioxa-8-aza-2-siladec-9-en-10-yl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylate (**30**).* To a clear yellow solution of ethyl 4-[(*E*)-2-butoxyethenyl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (2.77 g, 9.64 mmol) in anhydrous 1,4-dioxane (80 mL) was added H_2NOSEM (2.09 mL, 10.6 mmol) and *p*-TsOH-H_2O (4.77 g, 25.1 mmol). After stirring 5.5 h at room temperature, the reaction was complete. It was quenched by saturated sodium bicarbonate solution (0.5 L) and extracted with ethyl acetate (2 × 400 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give crude product (contaminated by leftover NH_2OSEM) as a light-yellow solid (3.64 g). LC-MS (APCI) m/z 378.2 $(M + H)^+$. The crude product was carried on to the next step without further purification.

*7-{[2-(Trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**31**).* To ethyl 4-[(9*E*)-2,2-dimethyl-5,7-dioxa-8-aza-2-siladec-9-en-10-yl]-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate **30** (2.59 g, 7.13 mmol) in glacial acetic acid (25 mL) was added sodium cyanoborohydride (0.896 g, 14.26 mmol) in two portions, and the resulting reaction mixture was stirred at room temperature for 2 h. The acetic acid was removed, and the residue was dissolved in EtOAc (0.25 L) and washed with satd aq sodium bicarbonate solution (0.25 L). The aqueous layer was extracted with EtOAc (0.125 L), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was treated with 1.0 L of 95:5 ether/DCM and 0.8 L of saturated aqueous sodium bicarbonate. The mixture was placed in a 2 L separatory funnel, shaken, and the organic phase was separated. The aqueous phase was extracted with an additional 0.5 L of DCM, and the combined organic phases were dried over sodium sulfate, filtered, and the residue was dried in vacuo. The crude product was purified by chromatography (100% EtOAc then 20% MeOH/DCM as eluant) to provide **31** as a solid (0.95 g, 76% yield, two steps). LC-MS (APCI) m/z 334.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 1.00 (m, 2H), 3.42 (t, J = 6.78 Hz, 2H), 3.85 (m, 2H), 4.02 (t, J = 6.88 Hz, 2H), 5.16 (s, 2H), 6.63 (d, J = 3.01 Hz, 1H), 7.69 (d, J = 2.83 Hz, 1H), 9.16 (s, 1H). HPLC (254, 224 nm): >95% purity.

*5-Fluoro-2-[(6-oxo-7-{[2-(trimethylsilyl)ethoxy]methoxy}-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-3-yl)methyl]benzonitrile (**32c**).* To a solution of 7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6*H*-pyrrolo[3,2-*f*]isoquinolin-6-one **31** (2.5 g, 6.75 mmol) in anhydrous THF (50 mL), cooled in an ice−water bath, was added NaH as a 60% mineral oil dispersion (1.44 g, 8.10 mmol). After stirring for 30 min, 2-(bromomethyl)-5-fluorobenzonitrile (1.44 g, 6.75 mmol) was added and reaction was stirred for 1 h and then was quenched with saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (3 × 125 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide crude **32c** which purified by chromatography (silica gel, 2% to 6% MeOH/DCM) to provide the title compound **32c** as white solid (2.34 g, 74% yield). LC-MS m/z 467.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (9H), 1.02 (m, 2H), 3.43 (t, J = 6.78 Hz, 2H), 3.89 (m, 2H), 4.04 (t, J = 6.78 Hz, 2H), 5.17 (s, 2H), 5.65 (s, 2H), 6.70 (dd, J = 3.20, 0.75 Hz, 1H), 7.04 (dd, J = 8.76, 5.18 Hz, 1H), 7.22 (m, 1H), 7.45 (m, 2H), 8.82 (s, 1H). HPLC (254, 224 nm): >95% purity.

*5-Fluoro-2-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-3-yl)methyl]benzonitrile (**33c**).* To a solution of 5-fluoro-2-[(6-oxo-7-{[2-(trimethylsilyl)ethoxy]methoxy}-6,7,8,9-tetrahydro-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-3-yl)methyl]benzonitrile **32c** (2.33 g, 4.99 mmol) in isopropyl alcohol (50 mL) was added sulfuric acid (1.33 mL, 25.0 mmol). The reaction mixture was stirred at 40 °C for 22 h. The reaction mixture was then cooled to room temperature, and diethyl ether (40 mL) was added. The mixture was filtered to provide the title compound **33c** as white solid sulfate salt (2.426 g). The salt of **33** was dissolved in DCM (300 mL) and washed with satd aq sodium bicarbonate (2 × 300 mL). The aqueous layers were combined and extracted with DCM (4 × 300 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give **33c** as a white solid (1.48 g, 88% yield). LC-MS m/z 337.2 $(M + H)^+$. ^{1}H NMR (300 MHz, CD_3OD) δ 3.48 (t, J = 7.06 Hz, 2H), 4.00 (m, 2H), 5.82 (s, 2H), 6.86 (d, J = 3.20 Hz, 1H), 7.23 (dd, J = 8.67, 5.27 Hz, 1H), 7.42 (td, J = 8.67, 2.73 Hz, 1H), 7.70 (m, 2H) 8.77 (s, 1H). HRMS Calcd for $C_{18}H_{13}FN_4O_2$ + H^+: 337.1095. Found: 337.1092.

*3-[(5-Fluoropyridin-2-yl)methyl]-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**32a**).* According to the procedure described for the preparation of **32d**, **31** and 2-(bromomethyl)-5-fluoropyridine were combined to provide **32a** in 65% yield. LC-MS m/z 443.2 $(M + H)^+$. ^{1}H NMR (300 MHz, CD_3Cl) δ 0.06 (9H), 1.01 (m, 2H), 3.42 (t, J = 6.78 Hz, 2H), 3.88 (dd, J = 9.42, 7.72 Hz, 2H), 4.02 (t, J = 6.78 Hz, 2H), 5.16 (s, 2H), 5.55 (s, 2H), 6.67 (m, 1H), 6.98 (dd, J = 8.67, 4.14 Hz, 1H), 7.32 (td, J = 8.34, 2.92 Hz, 1H), 7.47 (d, J = 2.92 Hz, 1H), 8.42 (d, J = 2.64 Hz, 1H), 8.84 (s, 1H). HPLC (254, 224 nm): >95% purity.

*3-[(5-Fluoropyridin-2-yl)methyl]-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**33a**).* According to the procedure described for the preparation of **33c**, **32b** provided **33a** in 95% yield. LC-MS m/z 313.2 $(M + H)^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.51 (brs, 2H), 4.01 (t, J = 7.06 Hz, 2H), 5.94 (s, 2H), 7.23 (d, J = 2.83 Hz, 1H), 7.58 (dd, J = 8.67, 4.52 Hz, 1H), 7.80 (td, J = 8.67, 2.83 Hz, 1H), 8.48 (m, 2H), 9.32 (s, 1H). HRMS, Calcd for $C_{16}H_{13}FN_4O_2$ + H^+: 313.1095. Found: 313.1094.

*3-[(3,5-Difluoropyridin-2-yl)methyl]-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**32b**).* As described for the preparation of **32d**, **31** and 2-bromomethyl-3,5-difluoropyridine hydrobromide were reacted to provide **32b** in 72% yield. LC/MS (APCI) 461.4 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (9H), 1.01 (m, 2H), 3.42 (t, J = 6.76 Hz, 2H), 3.88 (dd, J = 9.42, 7.72 Hz, 2H), 4.02 (t, J = 6.76 Hz, 2H), 5.17 (s, 2H), 5.62 (s, 2H), 7.16 (m, 1H), 7.32 (m, 1H), 8.15 (m, 1H), 8.42 (m, 1H), 8.84 (s, 1H). HPLC (254, 224 nm): >95% purity.

*3-[(3,5-Difluoropyridin-2-yl)methyl]-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**33b**).* As described for the preparation of **33c**, **32b** was hydrolyzed to provide **33c** in 78% yield. LC/MS (APCI) 331.1 $(M + H)^+$. ^{1}H NMR (300 MHz, DMDSO-d_6) δ 3.35 (m, 2H), 3.90 (m, 2H), 5.67 (s, 2H), 6.68 (m, 1H), 7.50−7.70 (2H), 8.25 (brs, 1H), 8.79 (s, 1H). HPLC (254, 224 nm): >95% purity.

*5-Fluoro-6-chloro-2-[(6-oxo-7-{[2-(trimethylsilyl)ethoxy]methoxy}-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-3-yl)methyl]benzonitrile (**32d**).* As described for the preparation of **32d**, **31** was reacted with 6-(bromomethyl)-2-chloro-3-fluorobenzonitrile to give **32d** in 40% yield. LC-MS m/z 501.2 $(M + H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 9H), 0.97 (m, 2H), 3.39 (t, J = 6.69 Hz, 2H), 3.85 (m, 2H), 4.00 (t, J = 6.69 Hz, 2H), 5.12 (s, 2H), 5.61 (s, 2H), 6.67 (d, J = 3.20 Hz, 1H), 6.83 (dd, J = 8.67, 4.52 Hz, 1H), 7.24 (m, 1H), 7.42 (d, J = 3.20 Hz, 1H), 8.76 (s, 1H). HPLC (254, 224 nm): >95% purity.

*5-Fluoro-6-chloro-2-[(7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-3-yl)methyl]benzonitrile (**33d**).* According to the proceedure described for the preparation of **33c**, **32d** gave **33d** in 95% yield. LC-MS m/z 371.2 $(M + H)^+$. ^{1}H NMR (300 MHz, CD_3OD) δ 3.62 (t, J = 7.06 Hz, 2H), 4.09 (t, J = 7.06 Hz, 2H), 5.98 (s, 2H), 7.23 (m, 2H), 7.58 (t, J = 8.76 Hz, 1H), 8.23 (d, J = 3.01 Hz, 1H), 9.21 (s, 1H). HRMS. Calcd for $C_{18}H_{12}ClFN_4O_2 + H^+$: 371.0706. Found: 371.0709.

*3-(4-Fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**34**).* To 3-(4-fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6(7*H*)-one **22** (7.82 g, 17.71 mmol) in acetonitrile (0.3 L) was added *N*,*N*-dimethyliminium chloride (Fluka, 6.63 g, 70.84 mmol). The mixture was allowed to stir under nitrogen at room temperature for 21 h, at which point HPLC-MS suggested ca. 40−45% conversion to the desired dimethylaminomethyl compound. The flask was equipped with a reflux condenser, and the mixture was immersed in a 90 °C oil bath and warmed to reflux (under N_2) for 4 h, HPLC-MS at this time point suggested complete reaction, hence reflux was discontinued. The cooled reaction mixture was concentrated in vacuo, and the resulting semisolid was partitioned between EtOAc/DCM (1 L, 95:5) and satd aq sodium bicarbonate (0.75 L). The organic phase was separated, washed with brine (0.75 L), and dried (Na_2SO_4). HPLC-MS analysis of the organic phase and the initial $NaHCO_3$ wash suggested that all target material was present in the initial organic phase. Concentration in vacuo then afforded the crude dimethylaminomethyl-substituted-SEM-blocked dihydro tricycle **34** as a tan solid. The crude solid (1 peak by LC-MS was further purified by trituration with hot ether/hexanes (90:10) to give 3-(4-fluorobenzyl)-1-((dimethylamino)methyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3*H*-pyrrolo[2,3-c][1,7]naphthyridin-6(7*H*)-one **34** (6.82 g) as fine ivory needles. The filtrate was passed through a small Biotage column (40M, 2−10% MeOH/DCM over 19 column volumes, 3 CV to waste, then collect 50 mL fractions). Fraction **12** [9CV] provided an additional 1.17 g of **34** as a tan crystalline solid. Total purified yield 7.89 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.03 (m, 2H), 2.23 (s, 6H), 3.51 (s, 2H), 3.77 (t, J = 6.03 Hz, 2H), 3.92 (m, 4H), 5.15 (d, J = 2.07 Hz, 2H), 5.35 (s, 2H), 7.00 (m, 2H), 7.03−7.17 (3H), 8.74 (s, 1H). LC-MS (APCI) m/z 499.2 $(M + H)^+$. Anal. Calcd for $C_{26}H_{35}FN_4O_3Si$: C, 62.62; H, 7.07; N, 11.24. Found: C, 62.91; H, 7.28; N, 10.99.

*3-(4-Fluorobenzyl)-1-iodo-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**35a**).* To a stirring solution of SEM protected tricycle **22** (4.23 g, 9.58 mmol) in DMF (100 mL) was added NIS (4.31 g, 19.16 mmol). The reaction was stirred for 1 h at room temperature and was then checked by LCMS and determined to be complete. The reaction was diluted with DCM (250 mL) and washed with a satd aq solution of sodium thiosulfate (2 × 150 mL), satd aq sodium bicarbonate (2 × 150 mL), and brine (1 × 100 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo, yielding crude **35a** as an orange oil. The crude **35a** was purified on a Biotage SP4 (column: 75+S, eluent: 100% DCM 2CV then 0−10% MeOH in DCM over 12CV). The purified material came off in one fraction and was pure by HPLC. The material was concentrated in vacuo, yielding the desired iodide **35a** as a pale-yellow solid (5.03 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.96 (m, 2H), 3.83 (m, 2H), 3.86 (m, 2H), 3.92 (m, 2H), 5.10 (s, 2H), 5.10 (s, 2H), 6.98 (m, 2H), 7.09 (m, 2H), 7.32 (s, 1H), 8.75 (s, 1H). LC-MS (APCI) m/z 568.2 $(M + H)^+$. Anal. Calcd for $C_{23}H_{27}FIN_3O_3Si$: C, 46.68; H, 4.80; N, 7.40. Found: C, 47.04; H, 5.13; N, 7.12.

*3-(4-Fluorobenzyl)-1-bromo-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**35b**).* To a solution of 3-(4-fluorobenzyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridin-6(7*H*)-one **22** (10.00 g, 22.65 mmol) in anhyd DMF (110 mL) was added *N*-bromosuccinimide (4.43 g, 24.9 mmol), and the reaction was stirred under nitrogen atmosphere at room temperature overnight. The reaction was monitored by LCMS, which indicated starting material consumption and complete conversion of starting material to the desired product. The reaction mixture was concentrated in vacuo to afford a viscous reddish semisolid which was dissolved in dichloromethane (250 mL), washed with 10% sodium carbonate solution (3 × 500 mL), brine (1 × 500 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give **35b** as an off-white solid (11.5 g, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.02 (m, 2H), 3.85 (m, 2H), 3.89 (m, 2H), 3.99 (q, J = 6.6 Hz, 2H), 5.15 (s, 2H), 5.37 (s, 2H), 7.04 (m, 2H), 7.15 (m, 2H), 7.30 (s, 1H), 8.79 (s, 1H), LC-MS (APCI) m/z 521.2 $(M + H)^+$. HRMS m/z Calcd for $C_{23}H_{27}BrFN_3O_3Si$: 520.1067 $(M + H)^+$. Found: 520.1074.

*1-[(Dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**38a**).* To a stirring solution of the protected dihydronaphthyridinone **34** (1.45 g, 2.3 mmol) in methanol (15 mL) was added hydrogen chloride solution (4 M in dioxane, 10 mL, 40 mmol) at room temperature and the mixture was stirred for 5 h, at which time LC-MS confirmed complete conversion to the desired product. The mixture was concentrated, treated with satd aq sodium bicarbonate solution (200 mL), and extracted with dichloromethane (2 × 200 mL). The organic layers were combined, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was suspended in diethyl ether:dichloromethane and filtered to provide 1-[(dimethylamino)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6*H*-pyrrolo[2,3-*c*]-1,7-naphthyridin-6-one **38a** as a white solid (0.53 g, 48%). ^{1}H NMR (400 MHz, CD_3OD) δ 2.16 (s, 6H), 3.47 (brs, 2H), 3.63 (m, 2H), 3.77 (m, 2H), 5.52 (s, 2H), 7.13 (m, 2H), 7.29 (m, 2H), 7.71 (brs, 1H), 8.80 (s, 1H), 9.71 (s, 1H). LC/MS (APCI) m/z: 369.2 $(M + H)^+$. HRMS calcd for $C_{20}H_{21}FN_4O_2$ $(M + H)^+$ 369.1722; found 369.1713. Anal. Calcd for: $C_{20}H_{21}FN_4O_2$: C, 65.20; H, 5.75; N, 15.21. Found: C, 65.42; H, 5.66; N, 14.81.

*1-{[(Cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**37e**).* To a stirring solution of the SEM protected 3-dimethylaminomethylpyridone **34** (2.5 g, 5.0 mmol) in dichloromethane (15 mL) was added phenyl chloroformate (0.77 mL, 5.45 mmol). The mixture was allowed to stir for 0.5 h at room temperature to generate the desired chloride **36**, then cyclopropylmethyl methyl amine hydrochloride (1.22 g, 10 mmol) and DIEA (10 mL, 57 mmol) were added and the mixture was allowed to stir for 1 h at room temperature, at which time the reaction was judged to be complete. The solution was diluted with DCM (75 mL) and washed with satd aq $NaHCO_3$ (75 mL). The aq phase was extracted with DCM (75 mL) and the combined organic phases were washed with brine (150 mL), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude **37e** as a viscous oil which was purified by silica gel chromatography with MeOH in DCM (5−10%) as eluent to provide **37e** as an amorphous white solid (0.99 g, 37%). LC/MS (APCI) m/z 539.4 $(M + H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 0.03 (s, 9H), 0.46 (m, 2H), 0.48 (m, 2H), 0.92 (m, 2H), 2.14 (s, 3H), 2.25 (d, J = 6.6 Hz, 2H), 3.59 (s, 2H), 3.75 (t, J = 6.0 Hz, 2H), 3.75 (d, J = 6.0 Hz, 2H), 3.79−3.88 (4H), 4.99 (s, 2H), 5.53 (s, 2H), 7.17 (m, 2H), 7.29 (m, 2H), 7.72 (s, 1H), 8.83 (s, 1H). HPLC (254, 224 nm): >95% purity.

*1-{[(Cyclopropylmethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**38e**).* Prepared from **37e** (1.29 g, 2.39 mmol) according to the procedure for the preparation of **38a** to give **38e** (0.695 g, 71%). ^1H NMR (300 MHz, DMSO-d_6) δ −0.07 (m, 2H), 0.45 (m, 2H), 0.86 (m, 1H), 2.16 (s, 3H), 2.25 (d, J = 6.59 Hz, 2H), 3.59 (s, 2H), 3.66−3.86 (4H), 5.53 (s, 2H), 7.17 (m, 2H), 7.31 (m, 2H), 7.71 (s, 1H), 8.81 (s, 1H), 9.71 (s, 1H). LC/MS (APCI) m/z 409.2 $(M + H)^+$. Anal. Calcd for $C_{23}H_{25}FN_4O_2$: C, 67.63; H, 6.17; N, 13.72. Found: C, 67.49; H, 6.18; N, 13.58.

*3-(4-Fluorobenzyl)-7-hydroxy-1-{[(2-hydroxyethyl)(methyl)amino]methyl}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**38b**).* Prepared from **37b** according to general procedure for **38a** to provide the *N*-hydroxynaphthyridinone **38b** in 29% yield. ^1H NMR (300 MHz, CD_3OD) δ 2.43 (m, 2H), 2.56 (s, 3H), 3.66 (m, 2H), 3.73 (m, 2H), 3.91 (s, 2H), 3.96 (m, 2H), 5.50 (s, 2H), 7.01 (m, 2H), 7.21 (m, 2H), 7.66 (s, 1H), 8.69 (s, 1H). LC/MS (APCI) m/z 399.2 $(M + H)^+$. HPLC (254, 222 nm): >95% purity. HRMS Calcd for $C_{21}H_{22}FN_4O_3 + H^+$: 399.1827. Found: 399.1838.

*1-{[(2-Methoxy-ethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo-[2,3-c][1,7]naphthyridin-6-one (**37d**).* Compound **34** (2.0 g, 4.01 mmol) was converted to the chloromethyl entity **36** as described for **37e** and then reacted with *N*-methyl-*N*-2-methoxyethyl amine (1.43 g, 16 mmol) in DIEA (10 mL, 57 mmol) to give **37d**, which was purified by silica gel chromatography with MeOH in DCM (5−10%) as eluent to provide **37d** as a sticky pale-yellow solid which was recrystallized (hexanes/ether, 90:10) to give **37d** (2.01 g, 92%) as a pale-yellow solid. LC/MS (APCI) m/z 543.4 $(M + H)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.99 (m, 2H), 2.20 (s, 3H), 2.60 (m, 2H), 3.33 (s, 3H), 3.30−4.00 (12H), 5.35 (s, 2H), 6.98 (m, 2H), 7.05−7.20 (3H), 8.77 (s, 1H). HPLC (254, 224 nm): >95% purity.

*1-{[(2-Methoxy-ethyl)(methyl)amino]methyl}-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**38d**).* Prepared from **37d** (2.48 g, 4.58 mmol) according to general procedure for **38a** to provide, after neutralization and trituration with diethyl ether, the *N*-hydroxynaphthyridinone **38d** (0.99 g, 53%) as an amorphous, tan solid. LC/MS (APCI) m/z 413.20 $(M + H)^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 2.14 (s, 3H), 2.60 (m, 2H), 3.19 (s, 3H), 3.10−3.90 (6H), 5.52 (s, 2H), 7.15 (m, 2H), 7.30 (m, 2H), 7.70 (s, 1H), 8.80 (s, 1H), 9.69 (brs, 1H). HPLC (254, 224 nm): >95% purity.

*1-[(3,3-Difluoropyrrolidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**37f**).* As described for the preparation of **37e**, compound **34** (0.1 g, 0.2 mmol) was treated with phenyl chloroformate (250 μL, 0.20 mmol) to provide the related chloromethyl compound **36**. Compound **36** was reacted with 3,3-difluoropyrrolidine hydrochloride (0.058 g, 0.40 mmol) and diisopropyl ethylamine (0.14 mL, 0.81 mmol) in DMF (5.0 mL) to give **37f**, which was filtered through a short plug of silica gel and used in the next reaction without further characterization or purification. LC/MS (APCI) m/z 561.4 $(M + H)^+$.

*1-[(3,3-Difluoropyrrolidin-1-yl)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**38f**).* Prepared from **37f** according to general procedure for the preparation of **38a** to provide the *N*-hydroxynaphthyridinone **38f** in 13% yield. ^1H NMR (300 MHz, CD_3OD) δ 2.28 (m, 2H), 2.76 (m, 2H), 2.91 (m, 2H), 3.86−3.93 (4H), 3.96 (m, 2H), 5.55 (s, 2H), 7.07 (m, 2H), 7.27 (m, 2H), 7.79 (m, 1H), 8.78 (s, 1H). LCMS m/z 431.2 $(M + H)^+$. HPLC (254, 450 nm): >98% purity. HRMS calcd for $C_{22}H_{21}F_3N_4O_2 + H^+$ 431.1689; found, 431.1693.

*3-(4-Fluorobenzyl)-1-(piperidin-1-ylmethyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**37c**).* Prepared from **34** (11.2 g, 2.25 mmol) according to general procedure for the preparation of **37e** to provide the 3-piperidinomethyl substituted **37c** (4.0 g, 33%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.03 (s, 9H), 0.92 (m, 2H), 1.30−1.56 (6H), 2.22−2.43 (4H), 3.52 (s, 2H), 3.69 (t, J = 6.69 Hz, 2H), 3.78−3.92 (4H), 5.00 (s, 2H), 5.52 (s, 2H), 7.16 (m, 2H), 7.32 (m, 2H), 7.69 (s, 1H), 8.83 (s, 1H). LC/MS (APCI) m/z 539.4 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-7-hydroxy-1-(piperidin-1-ylmethyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**38c**).* Prepared from **37c** (3.40 g, 6.35 mmol) according to general procedure for the preparation of **38a** to provide the *N*-hydroxynaphthyridinone **38c** (2.77 g, 91%) as a bis-HCl salt. ^1H NMR (300 MHz, CD_3OD) δ 1.61 (m, 2H), 1.77−2.13 (4H), 3.04−3.17 (4H), 3.65 (m, 2H), 3.91 (m, 2H), 4.25 (s, 2H), 5.54 (s, 2H), 7.05 (m, 2H), 7.26 (m, 2H), 7.82 (m, 1H), 8.68 (s, 1H). LC/MS (APCI) m/z 409.2 $(M + H)^+$. HRMS calcd for $C_{23}H_{25}FN_4O_2$ $(M + H)^+$ 409.2034; found, 409.2046. Anal. Calcd for $C_{23}H_{25}FN_4O_2$: C, 67.63; H, 6.17; N, 13.72. Found: C, 67.39; H, 6.12; N, 13.62.

*1-[[2-(2-Pyridinyl)ethoxy]methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy] methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**39a**).* To a stirring solution of **34** (0.45 g, 0.902 mmol) in DCM (10 mL) was added phenyl chloroformate (0.143 g, 0.115 mL, 0.902 mmol) in one portion. The mixture was allowed to stir for 1 h at room temperature, at which point clean conversion to **36** had been realized (LC-MS). To the stirring solution was added DIEA (0.41 g, 0.55 mL, 3.16 mmol) followed by 2-(2-pyridyl)-ethanol (0.278 g, 2.256 mmol) and DMF (10 mL). The reaction mixture was then immersed in a preheated 50 °C oil bath and was allowed to stir for 16 h. The mixture was cooled to room temperature, was diluted with DCM (70 mL) and was cast into water (65 mL) and brine (10 mL). The organic phase was separated, the aqueous phase was extracted with DCM (2 × 70 mL), and the combined organic layers were washed with satd aq $NaHCO_3$ (150 mL) and brine (150 mL) and dried (Na_2SO_4). Filtration and concentration in vacuo afforded crude **39a** as a yellow oil, which was purified by chromatography on a Biotage SP1 (0−5% MeOH/DCM) to give **39a** (0.39 g, 75%) as a clear, colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.03 (m, 2H), 3.05 (m, 2H), 3.52 (m, 2H), 3.77 (t, J = 6.03 Hz, 2H), 3.92 (m, 4H), 4.68 (s, 2H), 5.15 (m, 2H), 5.35 (s, 2H), 7.00 (m, 2H), 7.03−7.22 (5H), 7.58 (m, 1H), 8.44 (m, 1H), 8.74 (s, 1H). LC/MS (APCI) m/z 577.8 $(M + H)^+$. Anal. Calcd for $C_{31}H_{37}FN_4O_4Si$: C, 64.56; H, 6.47; N, 9.71. Found. C, 64.73; H, 6.82; N, 9.59.

*1-[[2-(2-Pyridinyl)ethoxy]methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**40a**).* To a stirring solution of **39a** (0.34 g, 0.589 mmol) in MeOH (30 mL) was added HCl in dioxane (4 M, 2.5 mL, 10 mmol), and the resulting solution was allowed to stir at room temperature for 15 h. The solvent was removed in vacuo, and the crude pale-yellow solid was recrystallized from *i*-PrOH to provide the bis-HCl salt of **40a** (0.153 g, 50%) as pale-yellow needles. ^1H NMR (300 MHz, DMSO-d_6) δ 3.17 (m, 2H), 3.30

(m, 2H), 3.81 (m, 2H), 3.90 (m, 2H), 4.80 (s, 2H), 5.79 (s, 2H), 7.21 (m, 2H), 7.43 (m, 2H), 7.60 (m, 1H), 7.65−7.75 (2H), 8.13 (m, 1H), 8.43 (brs, 1H), 8.61 (m, 1H). LC/MS (APCI) m/z 447.2 $(M + H)^+$. Anal. Calcd for: $C_{25}H_{23}FN_4O_3 \cdot 2HCl$: C, 57.81; H, 4.85; N, 10.79. Found: C, 57.81; H, 4.91; N, 10.86.

*1-[(2-Pyridinylmethoxy)methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**39b**).* As described for the preparation of **39a**, dimethylaminomethyl compound **34** (0.90 g, 1.80 mmol) was converted to chloromethyl compound **36**, which was reacted with 2-pyridyl-methanol (0.49 g, 4.50 mmol) to provide SEM−ether **39b** (0.82 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 0.96 (m, 2H), 3.55 (m, 2H), 3.80−4.00 (4H), 4.68 (s, 2H), 4.80 (s, 2H), 5.15 (s, 2H), 5.30 (s, 2H), 7.00 (m, 2H), 7.04−7.22 (5H), 7.58 (m, 1H), 8.60 (brs, 1H), 8.80 (s, 1H). LC/MS (APCI) m/z 563.2 $(M + H)^+$. Anal. Calcd for $C_{30}H_{35}FN_4O_4Si$: C, 64.03; H, 6.27; N, 9.96. Found: C, 64.14; H, 6.39; N, 9.78.

*1-[(2-Pyridinylmethoxy)methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**40b**).* As described for the preparation of **40a**, SEM−ether **39b** (0.70 g, 1.24 mmol) was treated with HCl in dioxane to give the bis-HCl salt of **40b** (0.48 g, 76%) as a pale-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.67 (m, 2H), 3.95 (m, 2H), 4.76 (s, 2H), 4.95 (s, 2H), 5.77 (s, 2H), 7.20 (m, 2H), 7.40 (m, 2H), 7.53 (m, 1H), 7.65 (m, 1H), 8.06 (m, 1H), 8.54 (brs, 1H), 8.65 (m, 1H), 9.36 (s, 1H). LC/MS (APCI) m/z 433.2 $(M + H)^+$. Anal. Calcd for $C_{24}H_{21}FN_4O_3 \cdot 2HCl$: C, 57.04; H, 4.59; N, 11.09. Found: C, 57.01; H, 4.73; N, 10.72.

*1-(Tetrahydro-2H-pyran-4-yl)methoxy]methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-Pyrrolo-[2,3-c][1,7]naphthyridin-6-one (**39c**).* As described for the preparation of **39a**, dimethylaminomethyl compound **34** (1.00 g, 2.00 mmol) was converted to chloromethyl compound **36**, which was reacted with (tetrahydro-2*H*-pyran-4-yl)methanol (0.58 g, 5.00 mmol) to provide SEM−ether **39c** (0.97 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 0.97 (m, 2H), 1.30 (m, 4H), 1.55−2.00 (6H), 3.20−3.42 (4H), 3.52 (m, 1H), 3.67 (m, 2H), 4.62 (s, 2H), 5.15 (s, 2H), 5.35 (s, 2H), 6.95−7.05 (3H), 7.12 (m, 2H), 8.79 (s, 1H). LC/MS (APCI) m/z 570.3 $(M + H)^+$. Anal. Calcd for $C_{30}H_{40}FN_3O_5Si$: C, 63.24; H, 7.08; N, 7.38. Found: C, 63.19; H, 7.21; N, 7.29.

*1-(Tetrahydro-2H-pyran-4-yl)methoxy]methyl]-3-(4-fluorobenzyl)-7-hydroxy3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**40c**).* As described for the preparation of **40a**, SEM−ether **39c** (0.75 g, 1.31 mmol) was treated with HCl in dioxane to give the HCl salt of **40c** (0.42 g, 61%) as an ivory solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.16 (m, 2H), 1.55 (m, 2H), 1.78 (m, 1H), 3.15−3.32 (4H), 3.64 (m, 2H), 3.77 (m, 2H), 3.96 (m, 2H), 4.69 (s, 2H), 5.75 (s, 2H), 7.20 (m, 2H), 7.40 (m, 2H), 8.44 (s, 1H), 9.35 (s, 1H), 10.35 (brs, 1H)). LC/MS (APCI) m/z 440.2 $(M + H)^+$. Anal. Calcd for $C_{24}H_{26}FN_3O_4 \cdot HCl$: C, 60.57; H, 5.72; N, 8.83. Found: C, 60.62; H, 5.69; N, 8.91.

*1-[[2-(1-Methylethoxy)ethoxy]methyl]-3-(4-fluorobenzyl)-)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**39d**).* As described for the preparation of **39a**, dimethylaminomethyl compound **34** (0.40 g, 0.79 mmol) was converted to chloromethyl compound **36**, which was reacted with 2-isopropoxyethanol (0.21 g, 1.98 mmol) to provide SEM−ether **39d** (0.35 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.97 (m, 2H), 1.15 (d, J = 7.0 Hz, 6H), 1.30 (m, 4H), 3.50−3.75 (7H), 3.85 (m, 2H), 3.97 (m, 2H), 4.69 (s, 2H), 5.13 (s, 2H), 5.34 (s, 2H), 6.98 (m, 2H), 7.18 (m, 2H), 7.27 (s, 1H), 8.82 (s, 1H). LC/MS (APCI) m/z 558.2 $(M + H)^+$. Anal. Calcd for $C_{29}H_{40}FN_3O_5Si$: C, 62.45; H, 7.23; N, 7.53. Found: C, 62.47; H, 7.29; N, 7.36.

*1-[[2-(1-Methylethoxy)ethoxy]methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**40d**).* As described for the preparation of **40a**, SEM−ether **39d** (0.324 g, 0.58 mmol) was treated with HCl in dioxane to give the HCl salt of **40d** (0.135 g, 50%) as an ivory solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (d, J = 7.0 Hz, 6H), 3.40−3.55 (7H), 3.75 (m, 2H), 4.62 (s, 2H), 5.52 (s, 2H), 7.16 (m, 2H), 7.81 (s, 1H), 8.85 (s, 1H), 9.74 (s, 1H). LC/MS (APCI) m/z 428.2 $(M + H)^+$. Anal. Calcd for $C_{23}H_{26}FN_3O_4 \cdot HCl$: C, 59.54; H, 5.87; N, 9.06. Found: C, 59.38; H, 5.59; N, 8.93.

*1-[[3-(2-Pyridinyl)propoxy]methyl]-3-(4-fluorobenzyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**39e**).* As described for the preparation of **39a**, dimethylaminomethyl compound **34** (0.80 g, 1.58 mmol) was converted to chloromethyl compound **36**, which was reacted with 3-(2-pyridyl)-propan-1-ol (0.54 g, 3.95 mmol) to provide SEM−ether **39e** (0.72 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.97 (m, 2H), 1.85 (m, 2H), 2.87 (m, 2H), 3.50−3.75 (6H), 3.90 (m, 2H), 4.71 (s, 2H), 5.10 (s, 2H), 5.36 (s, 2H), 7.00 (m, 2H), 7.10−7.20 (3H), 7.24−7.32 (2H), 7.60 (m, 1H), 8.39 (m, 1H), 8.79 (s, 1H). LC/MS (APCI) m/z 591.2 $(M + H)^+$. Anal. Calcd for $C_{32}H_{39}FN_3O_4Si$: C, 65.06; H, 6.65; N, 9.48. Found: C, 65.04; H, 6.72; N, 9.36.

*1-[[3-(2-Pyridinyl)propoxy]methyl]-3-(4-fluorobenzyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**40e**).* As described for the preparation of **40a**, SEM−ether **39e** (0.60 g, 1.01 mmol) was treated with HCl in dioxane to give the bis-HCl salt of **40e** (0.275 g, 51%) as a pale-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.94 (m, 2H), 2.76 (m, 2H). 3.45−3.62 (4H), 3.81 (m, 2H), 4.62 (s, 2H), 5.54 (s, 2H), 7.10−7.22 (4H), 7.32 (m, 2H), 7.60 (m, 1H), 7.83 (s, 1H), 8.44 (m, 1H), 8.88 (s, 1H), 9.77 (brs, 1H). LC/MS (APCI) m/z 461.2 $(M + H)^+$. Anal. Calcd for $C_{26}H_{25}FN_4O_3 \cdot 2HCl$: C, 58.54; H, 5.10; N, 10.50. Found: C, 58.15; H, 5.14; N, 10.43.

*1-[[(2-Fluorophenyl)methoxy]methyl]-3-(4-fluorobenzyl)-3,7,8,9-tetrahydro-7-{[2-(trimethylsilyl)ethoxy]methoxy}-6H-pyrrolo[2,3-c]-[1,7]naphthyridin-6-one (**37f**).* As described for the preparation of **39a**, dimethylaminomethyl compound **34** (0.45 g, 0.90 mmol) was converted to chloromethyl compound **36**, which was reacted with 2-fluoro-benzyl alcohol (0.29 g, 2.25 mmol) to provide SEM−ether **39f** (0.41 g, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.01 (m, 2H), 3.61 (m, 2H), 3.80−3.92 (4H), 4.60 (s, 2H), 4.70 (s, 2H), 5.14 (s, 2H), 5.34 (s, 2H), 6.95−7.15 (6H), 7.23 (m, 1H), 7.27 (s, 1H), 7.35 (m, 1H), 8.76 (s, 1H). LC/MS (APCI) m/z 580.2 $(M + H)^+$. Anal. Calcd for $C_{31}H_{35}F_2N_3O_4Si$: C, 64.23; H, 6.09; N, 7.25. Found: C, 64.19; H, 6.18; N, 7.22.

*1-[[(2-Fluorophenyl)methoxy]methyl]-3-(4-fluorobenzyl)-3,7,8,9-tetrahydro-7-hydroxy-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**40f**).* As described for the preparation of **40a**, SEM−ether **39f** (0.340 g, 0.58 mmol) was treated with HCl in dioxane to give the HCl salt of **40f** (0.141 g, 50%) as an ivory solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.62 (m, 2H), 3.92 (m, 2H), 4.61 (s, 2H), 4.80 (s, 2H), 5.76 (s, 2H), 7.10−7.22 (4H), 7.30−7.46 (4H), 8.49 (s, 1H), 9.35 (s, 1H), 10.56 (brs, 1H). LC/MS (APCI) m/z 450.2 $(M + H)^+$. Anal. Calcd for $C_{25}H_{21}F_2N_3O_3 \cdot HCl$: C, 61.79; H, 4.56; N, 8.65. Found: C, 61.84; H, 4.49; N, 8.63.

*3-(4-Fluorobenzyl)-1-(3-(4-morpholinyl)-prop-1-yn-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**41b**).* To a stirring solution of iodide **35a** (9.97 g, 17.6 mmol), 4-prop-2-yn-1-ylmorpholine (2.20 g, 17.6 mmol), and TEA (3.56 g, 4.90 mL, 35.2 mmol) in DMF (100 mL) was added $Pd(PPh_3)_2Cl_2$ (0.625 g, 0.88 mmol) and CuI (0.334 g, 1.76 mmol). After the addition was complete, the color of the solution went from pale-yellow, to orange, to black, and after 20 min, the reaction was judged to be complete by HPLC-MS analysis. The reaction was diluted with dichloromethane (1.0 L), washed with a satd aq ammonium chloride (2 × 1.0 L), water (1.0 L), and brine (0.75 L), dried over sodium sulfate, and concentrated in vacuo, yielding a brown residue. The crude **41b** was purified on silica gel using a Biotage SP4 chromatography system (eluent: 0−6% EtOH in DCM over 16CV). The purified fractions were combined

and concentrated in vacuo, yielding the desired alkyne **41b** (7.71 g, 78%) as pale-yellow solid. TLC: (Merck, CH_2Cl_2/MeOH 98:2, UV) R_f = 0.30. LC/MS: (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN, 3 min, APCI, + mode), RT 1.608 min, m/e = 565.4 ($M + H^+$, base). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.02 (m, 2H), 2.64 (m, 4H), 3.54 (m, 2H), 3.60−3.80 (6H), 3.88 (m, 2H), 3.99 (s, 2H), 5.15 (s, 2H), 5.36 (s, 2H), 7.04 (m, 2H), 7.14 (m, 2H), 7.43 (s, 1H), 8.77 (s, 1H). Anal. Calcd for $C_{30}H_{37}FN_4O_4Si$: C, 63.80; H, 6.60; N 9.92%. Found: C, 64.11; H, 6.89; N, 10.01%.

*3-(4-Fluorobenzyl)-1-(3-morpholin-4-ylpropyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**43b**).* To a rapidly stirring solution of alkyne **41b** (7.70 g, 13.65 mmol) in methanol (150 mL) was added palladium hydroxide (1.54 g, 20 wt %), and the mixture was placed under 1 atm of hydrogen. After 2 h, the reduction was determined to be complete by HPLC-MS. The catalyst was removed by filtration through a pad of Celite. The filter cake was rinsed with DCM (0.5 L), and the combined filtrates were concentrated in vacuo to furnish crude **43b** as a sticky, pale-yellow solid. Crude **43b** was purified by flash chromatography (eluent: 0−6% EtOH in DCM) to furnish **43b** (4.68 g, 60%) as an amorphous white solid. TLC: (Merck, CH_2Cl_2:MeOH 98:2, UV) R_f = 0.139. LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc): CH_3CN, 3 min, APCI, + mode): RT 1.247 min, m/e = 569.0 ($M + H^+$, base). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.02 (m, 2H), 1.87 (m, 2H), 2.37−2.47 (6H), 2.89 (m, 2H), 3.60 (t, J = 6.69 Hz, 2H), 3.72 (m, 4H), 3.89 (m, 2H), 3.98 (t, J = 6.69 Hz, 2H), 5.16 (s, 2H), 5.33 (s, 2H), 6.97−7.13 (5H), 8.75 (s,1H). Anal. Calcd for $C_{30}H_{41}FN_4O_4Si$: C, 63.35; H, 7.27; N 9.85%. Found: C, 63.27; H, 7.33; N, 9.77.

*3-(4-Fluorobenzyl)-7-hydroxy-1-(3-morpholin-4-ylpropyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**44b**).* As described for the hydrolysis of **38a**, SEM−ether **43b** (4.68 g 8.23 mmol) was treated with HCl in methanol to provide **44b** (2.66 g, 72%) as an ivory powder after neutralization of the bis-HCl salt and trituration with diethyl ether. LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc) CH_3CN 3 min, APCI, + mode): RT0.549 min, m/e = 439.0 ($M + H^+$, base). ^1H NMR (300 MHz, $CDCl_3$) δ 1.86 (m, 2H), 2.38−2.52 (6H), 2.88 (t, J = 7.63 Hz, 2H), 3.60 (t, J = 6 0.97 Hz, 2H), 3.72 (m, 4H), 3.99 (t, J = 6.97 Hz, 2H), 5.34 (s, 2H), 6.97−7.13 (5H), 8.72 (s, 1H). Anal. Calcd for $C_{24}H_{27}FN_4O_3 \cdot 0.50H_2O$: C, 64.41; H, 6.31; N 12.52%. Found: C, 64.24; H, 6.25; N, 12.15.

*(E)-tert-Butyl 3-(3-(4-Fluorobenzyl)-6-oxo-7-((2-(trimethylsilyl)ethoxy)methoxy)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-1-yl) acrylate (**42a**).* Compound **35a** (2.0 g, 3.524 mmol) was stirred with *tert*-butylacrylate (0.516 mL, 3.52 mmol), tri-*o*-tolylphosphine (0.043 g, 0.141 mmol), $Pd(OAc)_2$ (0.016 g, 0.0705 mmol) in triethylamine (10 mL), and DMF (50 mL) at 80 °C under nitrogen for 3 h. The dark-red solution was concentrated and the residue diluted with ethyl acetate (100 mL). The organic solution was washed with water (2 × 100 mL) and brine (75 mL). The organic solution was dried over sodium sulfate and concentrated in vacuo, yielding a red residue. The red residue was purified on silica gel using a Biotage SP4 chromatography system. The purified fractions were combined and concentrated in vacuo, yielding the desired alkene **42a** (1.528 g, 76%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 1.03 (m, 2H), 1.53 (s, 9H), 3.66 (t, J = 6.78 Hz, 2H), 3.89 (m, 2H), 4.00 (t, J = 6.78 Hz, 2H), 5.15 (s, 2H), 5.40 (s, 2H), 6.18 (d, J = 15.64 Hz, 1H), 7.05 (m, 2H), 7.16 (m, 2H), 7.59 (s, 1H), 7.95 (d, J = 15.64 Hz, 1H), 8.80 (s, 1H). LC/MS (APCI) m/z 568.4 ($M + H)^+$. Anal. Calcd for $C_{30}H_{38}FN_3O_5Si$: C, 63.47; H, 6.75; N, 7.40. Found: C, 63.72; H, 6.89; N, 7.22.

*tert-Butyl 3-(3-(4-Fluorobenzyl)-6-oxo-7-((2-(trimethylsilyl)ethoxy)methoxy)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-1-yl) propanoate (**43a**).* Compound **42a** (1.528 g, 2.691 mmol) was reduced as described for the preparation of **43b**, yielding **43a** as an ivory foam (1.327 g, 87%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.01 (m, 2H), 1.40 (s, 9H), 2.59 (t, J = 7.54 Hz, 2H), 3.16 (t, J = 7.44 Hz, 2H), 3.62 (t, J = 6.78 Hz, 2H), 3.89 (m, 2H), 3.99 (t, J = 6.78 Hz, 2H), 5.15 (s, 2H), 5.32 (s, 2H), 6.99 (t, J = 8.67 Hz, 2H), 7.09 (m, 3H), 8.75 (s, 1 H). LC/MS (APCI) m/z 570.4 ($M + H)^+$. Anal. Calcd for $C_{30}H_{40}FN_3O_5Si$: C, 63.24; H, 7.08; N, 7.38. Found: C, 63.59; H, 7.23; N, 7.03.

*3-(3-(4-Fluorobenzyl)-7-hydroxy-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-1-yl)propanoic acid (**44a**).* Compound **43a** (1.322 g, 2.32 mmol) was stirred in isopropyl alcohol (20 mL) with sulfuric acid (0.6 mL) at 40 °C for 24 h and then heated to reflux for a further 3 h. The solution was concentrated to give a green oil which was diluted with water (10 mL), and the pH was adjusted to ca. pH 10 with sodium carbonate. The aqueous phase was extracted with DCM:MeOH (95:5 4 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford a brown foam. The foam was dissolved in methanol (40 mL) and water (10 mL) added. After the addition of 3 M aq LiOH solution (1.0 mL, 2.95 mmol), the solution was stirred at room temperature for 24 h and then warmed to 45 °C overnight. The reaction mixture was filtered through Celite to remove particulates and then was concentrated to remove methanol. The aqueous solution was treated with 1 M HCl (4.5 mL, 4.5 mmol) to ca. pH 4. An off-white solid precipitated which was isolated by filtration, washed with water and isopropyl alcohol, then dried under vacuum at 75 °C overnight to give **44a** as an off-white powder (0.765 g, 86%). ^1H NMR (300 MHz, DMSO-d_6) δ 2.62 (s, 2H), 3.12 (s, 2H), 3.52 (s, 2H), 3.81 (s, 2H), 5.54 (s, 2H), 7.16 (s, 2H), 7.32 (s, 2H, 7.63 (s, 1H), 8.83 (s, 1H), 9.75 (s, 1H), 12.20 (s, 1H). LC/MS (APCI) m/z 384.0 ($M + H)^+$. HPLC (254, 222 nm): >95% purity. Anal. Calcd for $C_{20}H_{18}FN_3O_4 \cdot 1.54H_2O$: C, 58.44; H, 5.17; N 10.22%. Found: C, 58.43; H, 5.02; N, 10.01%.

*3-(4-Fluorobenzyl)-1-(3-(N-methyl-acetamido)-prop-1-yn-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**41c**).* Iodide **35a** (1.00 g, 1.77 mmol) was coupled with *N*-methyl-*N*-2-propyn-1-yl-acetamide (0.20 g, 1.77 mmol) according to the procedure for the preparation of **41b** to provide **41c** (0.94 g, 96%) as an ivory solid after chromatography on a Biotage SP-4, exhibiting ^1H NMR signals of amide rotamers. LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN, 3 min, APCI, + mode): RT 1.818 min, m/e = 551.40 ($M + H^+$, base). ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.01 (m, 2H), 2.08−2.22 (3H), 2.87−3.14 (5H), 3.60−4.45 (6H), 5.15 (s, 2H), 5.35 (s, 2H), 7.02 (m, 2H), 7.14 (m, 2H), 7.67 (s, 1H), 8.77 (s, 1H).). Anal. Calcd for $C_{29}H_{35}FN_4O_4Si$: C, 63.25; H, 6.41; N 10.17%. Found: C, 63.37; H, 6.44; N, 9.94.

*3-(4-Fluorobenzyl)-1-(3-(N-methyl-acetamido)-propyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**43c**).* As described for the preparation of **43b**, alkyne **41c** (1.06 g, 1.92 mmol) was hydrogenated to provide **43c** (0.92 g, 86%) as an amorphous white solid after flash chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 1.00 (m, 2H), 1.85 (m, 2H), 2.05 (m, 2H), 2.08 (s, 3H), 2.77−3.10 (4H), 2.99 (s, 3H), 3.48 (m, 2H), 3.97 (m, 2H), 5.13 (s, 2H), 5.33 (s, 2H), 6.95 (m, 2H), 7.08 (m, 2H), 7.21 (s, 1H), 8.72 (s, 1H). LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN, 3 min, APCI, + mode): RT 1.726 min, m/e = 555.4 ($M + H^+$, base). Anal. Calcd for $C_{29}H_{39}FN_4O_4Si$: C, 62.79; H, 7.09; N 10.10%. Found: C, 63.04; H, 7.19; N, 9.87.

*3-(4-Fluorobenzyl)-1-(3-(N-methyl-acetamido)-propyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**44c**).* As described for the hydrolysis of **43a**, SEM−ether **43c** (1.36 g 2.45 mmol) was treated with sulfuric acid in *i*-PrOH to provide the hydrogen sulfate salt of **44c** (1.00 g, 96%) as an ivory powder after trituration with diethyl ether. ^1H NMR (300 MHz, DMSO-d_6) δ 1.94 (brs, 1H), 1.91 (m, 2H), 1.96 (s, 3H), 2.89 (m, 2H), 2.96 (s, 3H), 3.35 (m, 2H), 3.65 (m, 2H), 3.96 (m, 2H), 5.73 (s, 2H), 7.18 (m, 2H), 7.35 (m, 2H), 8.35 (s, 1H), 9.28 (s, 1H). LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN, 3 min, APCI, + mode):

RT 1.246 min, m/e = 425.2 ($M + H^+$, base). Anal. Calcd for $C_{23}H_{25}FN_4O_4 \cdot H_2SO_4$: C, 52.87; H, 5.21; N 10.72%. Found: C, 52.92; H, 5.04; N, 10.45.

*3-(4-Fluorobenzyl)-1-(3-hydroxy-3-methylbut-1-ynyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**41d**).* Iodide **35a** (1.51 g, 2.66 mmol) was coupled to 2-methyl-3-butyn-2-ol (0.650 mL, 6.65 mmol) under the standard conditions as described for the preparation of **41b**, yielding the desired alkyne **41d** (0.907 g, 70%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.01 (m, 2H), 1.52 (s, 3H), 1.64 (s, 3H), 3.80 (m, 2H), 3.90 (m, 2H), 4.00 (m, 2H), 5.15 (s, 2H), 5.34 (s, 2H), 7.02 (m, 2H), 7.13 (m, 2H), 7.42 (bs, 1H), 8.76 (bs, 1H). LC/MS (APCI) m/z 524.3 $(M + H)^+$. HPLC (254, 222 nm): >95% purity. Anal. Calcd for $C_{28}H_{34}FN_3O_4Si$: C, 64.22; H, 6.54; N, 8.02. Found: C, 64.49; H, 6.72; N, 7.84.

*3-(4-Fluorobenzyl)-1-(3-hydroxy-3-methylbutyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**43d**).* Compound **41d** (0.907 g, 1.85 mmol) was reduced as described for the preparation of **43b**, yielding a yellow oil which crystallized upon cooling. The crude crystals were recrystallized from hot ethyl acetate, giving **43d** (0.965 g, 99%) as white needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 9H), 1.03 (m, 2H), 1.34 (s, 6H), 1.85 (m, 2H), 2.98 (m, 2H), 3.64 (m, 2H), 3.89 (m, 2H), 3.99 (m, 2H), 5.16 (s, 2H), 5.34 (s, 2H), 6.98−7.13 (5H), 7.42 (bs, 1H), 8.76 (bs, 1H), LC/MS (APCI) m/z 528.4 $(M + H)^+$. HPLC (254, 222 nm): >95% purity. Anal. Calcd for $C_{28}H_{38}FN_3O_4Si$: C, 63.73; H, 7.26; N, 7.96. Found: C, 63.98; H, 7.49; N, 7.73.

*3-(4-Fluorobenzyl)-7-hydroxy-1-(3-hydroxy-3-methylbutyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**44d**).* To a stirring solution of **43d** (0.907 mg, 1.72 mmol) in THF (50 mL) was added HF−pyridine (3.0 mL, 35 mmol). The solution was stirred at room temperature for 2 h at 40 °C for an additional 2 h. The reaction was diluted in 7:2:1 EtOAc/DCM/MeOH (100 mL) and the organic solution washed with satd aq sodium bicarbonate (100 mL). The organic solution was separated and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo and purified by prep HPLC, yielding the desired product **44d** as an ivory powder (0.284 g, 39%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18 (s, 6H), 2.87 (m, 2H), 3.52 (m, 2H), 3.76 (m, 2H), 5.49 (s, 2H), 7.15 (m, 2H), 7.31 (m, 2H), 7.57 (s, 1H), 8.79 (s, 1H), 9.74 (bs, 1H). LC/MS (APCI) m/z 398.2 $(M + H)^+$. HPLC (254, 222 nm): >95% purity. Anal. Calcd for $C_{20}H_{17}F4N_3O_2 \cdot 0.8H_2O$: C, 64.16; H, 6.27; N 10.20%. Found: C, 63.89; H, 6.08; N, 9.94.

*3-(4-Fluorobenzyl)-1-(3-(tetrahydro-2H-pyran-4-yl)oxy]-1-propyn-1-yl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**41e**).* Iodide **35a** (1.32 g, 1.77 mmol) was coupled with propyn-3-ol (0.15 g, 2.71 mmol) according to the procedure for the preparation of **41b** to provide **41e** (1.03 g, 95%) as a pale-yellow solid after chromatography on a Biotage SP-4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 1.00 (m, 2H), 1.64 (m, 2H), 1.92 (m, 2H), 3.45 (m, 2H), 3.72−3.80 (3H), 3.82−4.00 (6H), 4.44 (s, 2H), 5.14 (s, 2H), 5.35 (s, 2H), 7.01 (m, 2H), 7.12 (m, 2H), 7.45 (s, 1H), 8.75 (s, 1H). LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN, 3 min, APCI, + mode): RT 1.945 min, m/e = 580.4 ($M + H^+$, base). Anal. Calcd for $C_{31}H_{38}FN_3O_5Si$: C, 64.22; H, 6.61; N 7.25%. Found: C, 64.29; H, 6.43; N, 7.18.

*3-(4-Fluorobenzyl)-1-(3-(tetrahydro-2H-pyran-4-yl)oxy-propyl)-7-{[2-(trimethylsilyl)ethoxy]methoxy}-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**43e**).* As described for the preparation of **43b**, alkyne **41e** (1.37 g, 2.76 mmol) was hydrogenated to provide **43e** (0.83 g, 60%) as an ivory solid after flash chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 0.99 (m, 2H), 1.47−1.72 (4H), 1.81−1.99 (4H), 2.92 (m, 2H), 3.37−3.52 (6H), 3.62 (t, J = 6.69 Hz, 2H), 3.81−4.01 (6H), 5.16 (s, 2H), 5.34 (s, 2H), 6.95−7.26 (5H), 8.76 (s, 1H). LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN 3 min, APCI, + mode): RT 1.892 min, m/e = 584.4 ($M + H^+$, base). Anal. Calcd for $C_{31}H_{42}FN_3O_5Si$: C, 63.78; H, 7.25; N 7.20%. Found: C, 63.94; H, 7.43; N, 6.98.

*3-(4-Fluorobenzyl)-1-(3-(tetrahydro-2H-pyran-4-yl)oxy-propyl)-7-hydroxy-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**44e**).* As described for the hydrolysis of **43a**, SEM−ether **43e** (0.838 g 1.43 mmol) was treated with sulfuric acid in *i*-PrOH to provide the hydrogensulfate salt of **44e** (0.579 g, 89%) as a white powder after trituration with diethyl ether. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38 (m, 2H), 1.70−1.95 (4H), 2.96 (t, J = 7.63 Hz, 2H), 3.20−3.50 (6H), 3.68 (m, 2H), 3.78 (m, 2H), 3.95 (t, J = 6.95 Hz, 2H), 5.72 (s, 2H), 7.18 (m, 2H), 7.36 (m, 2H), 8.28 (s, 1H), 9.28 (s, 1H), 10.51 (brs, 1H). LC/MS (Eclipse XDB-C8, 0.8 mL/min, gradient 80:20 to 5:95 H_2O (+0.1% HOAc):CH_3CN 3 min, APCI, + mode): RT 1.383 min, m/e = 454.2 ($M + H^+$, base). Anal. Calcd for $C_{25}H_{28}FN_3O_4 \cdot H_2SO_4$: C, 54.44; H, 5.48; N 7.62%. Found: C, 54.19; H, 5.27; N, 7.39.

*3-(4-Fluorobenzyl)-1-(3,3,3-trifluoroprop-1-ynyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**41f**).* Diisopropylamine (0.89 mL, 5.98 mmol) was stirred in tetrahydrofuran (10 mL) under nitrogen at −78 °C, and 1.6 M *n*-butyl lithium (2.39 mL, 5.98 mmol) was added, keeping temperature below −55 °C. After 15 min, 2-bromo-3,3,3-trifluoro-1-propene (0.28 mL, 2.72 mmol) was added in tetrahydrofuran (2 mL), keeping the temperature below −60 °C, giving a dark-red suspension. After 10 min, a 0.5 M solution of zinc chloride (5.98 mL, 2.99 mmol) was added, keeping the temperature below −65 °C. The reaction was stirred at −78 °C for 30 min and then allowed to warm to room temperature. After a further 30 min, **35a** (1.029 g, 1.813 mmol) and $Pd(PPh_3)_4$ (0.0105 g, 0.0907 mmol) was added and the brown solution heated to 50 °C for 7 h. The reaction was diluted to 80 mL with the addition of ethyl acetate. The organic solution was washed with a saturated solution of ammonium chloride (2 × 100 mL), water (100 mL), and brine (75 mL). The organic solution was dried over sodium sulfate and concentrated in vacuo, yielding a brown residue. The brown residue was purified on silica gel using a Biotage SP4 chromatography system. The purified fractions were combined and concentrated in vacuo, yielding the desired alkyne **41f** (0.205 g, 21%) 60% purity contaminated with residual **35a**. LC/MS (APCI) m/z 534.2 $(M + H)^+$.

*3-(4-Fluorobenzyl)-1-(3,3,3-trifluoropropyl)-7-((2-(trimethylsilyl)ethoxy)methoxy)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**43f**).* Compound **41f** (0.205 g, 0.25 mmol) was hydrogenated as described for the preparation of **43b** to give a orange oil which was purified on silica gel using a Biotage SP4 chromatography system. The purified fractions were combined and concentrated in vacuo, yielding the desired product **43f** (0.130 g, 100%) 60% purity contaminated with residual des-iodo **22**. LC/MS (APCI) m/z 538.2 $(M + H)^+$.

*3-(4-Fluorobenzyl)-7-hydroxy-1-(3,3,3-trifluoropropyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**44f**).* Compound **43f** (0.130 g, 0.145 mmol) was stirred for 24 h at room temperature in methanol (10 mL) with 4 M HCl in dioxane (0.39 mL, 1.54 mmol). The solution was concentrated in vacuo, yielding a yellow solid. The yellow residue was purified by prep HPLC yielding the TFA salt of **44f** as an ivory powder (0.055 g, 93%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.68 (m, 2H), 3.13 (m, 2H), 3.53 (t, J = 6.78 Hz, 2H), 3.80 (t, J = 6.78 Hz, 2H), 5.53 (s, 2 H), 7.16 (t, J = 8.76 Hz, 2H), 7.32 (dd, J = 8.48, 5.46 Hz, 2H), 7.78 (s, 1 H), 8.88 (s, 1H), 9.83 (s, 1H). LC/MS (APCI) m/z 408.4 $(M + H)^+$. HPLC (254, 222 nm): >95% purity. Anal. Calcd For $C_{20}H_{17}F_4N_3O_2 - CF_3CO_2H$: C, 50.68; H, 3.48; N 8.06%. Found: C, 50.37; H, 3.23; N, 7.86%.

*7-(4-Fluorobenzyl)-4-oxo-1,2,4,7-tetrahydropyrano[3,4-b]pyrrolo[3,2-d]pyridine-9-sulfonyl Chloride (**45**).* To a stirring solution of azaindole lactone **17** (1.00 g, 3.39 mmol) in chlorosulfonic acid (3 mL) was slowly added thionyl chloride (1.50 mL) and the reaction mixture stirred overnight at room temperature. The reaction was quenched by dropwise addition of the reaction mixture onto ice. A precipitate formed, which

was filtered and dried under vacuum to provide the product **45** as an off-white solid (1.33 g, 100%). The material was carried to the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.00 (m, 2H), 4.78 (m, 2H), 5.80 (s, 2H), 7.22 (m, 2H), 7.50 (m, 2H), 8.51 (s, 1H), 9.55 (s, 1H). LC/MS (APCI) m/z 395.0 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*7-(4-Fluorobenzyl)-N,N-dimethyl-4-oxo-1,2,4,7-tetrahydropyrano[3,4-b]pyrrolo[3,2-d]pyridine-9-sulfonamide (**46c**).* To a stirring solution of the sulfonyl chloride **45** (0.137 g, 0.35 mmol) and dimethylamine hydrochloride (0.031 g, 0.38 mmol) in DMF (mL) at room temperature was added triethylamine (0.146 mL, 1.05 mmol) dropwise. The reaction was stirred overnight and judge to be complete by LCMS. The mixture was concentrated under reduced pressure. The crude material was dissolved in dichloromethane and washed with water and then brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the product **46c** as a colorless semisolid (0.107 g, 75%). LC/MS (APCI) m/z 404.0 $(M + H)^+$. HPLC >95% purity. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.71 (s, 6H), 3.21 (m, 2H), 4.60 (m, 2H), 5.45 (s, 2H), 7.35 (m, 2H), 7.45 (m, 2H), 8.30 (s, 1H), 9.20 (s, 1H). HPLC (254, 224 nm): >95% purity.

*3-(Dimethylsulfamoyl)-1-(4-fluorobenzyl)-4-(2-hydroxyethyl)-N-(tetrahydro-2H-pyran-2-yloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide (**47c**).* To a stirring suspension of dimethylsulfamide **46c** (0.100 g, 0.25 mmol) in THF (2 mL) was added *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (NH_2OTHP, 0.059 g, 0.50 mmol), followed by lithium hexamethyl disilazide (LiHMDS, 0.084 g, 0.50 mmol), and the mixture was stirred until LCMS showed complete disappearance of starting material and formation of the desired product. The reaction was quenched with water, and dichloromethane was added. The dichloromethane was washed with saturated ammonium chloride solution and then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was purified by flash chromatography (silica gel, 1−5% methanol:chloroform) to provide the product **47c** as a white solid (0.070 g, 54%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.60 (m, 2H), 1.75 (m, 4H), 2.60 (s, 6H), 3.65 (m, 2H), 3.82 (s, 1H), 3.90 (m, 2H), 4.00 (m, 2H), 5.15 (s, 1H), 5.80 (s, 2H), 7.15 (m, 2H), 7.30 (m, 2H), 8.05 (s, 1H), 10.55 (brs, 1H). LC-MS m/z 521.1 $(M + H)^+$. HPLC > 95% purity. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-N,N-dimethyl-6-oxo-7-(tetrahydro-2H-pyran-2-yloxy)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridine-1-sulfonamide (**48c**).* To a stirring solution of the alcohol **47c** (0.88 g, 1.69 mmol) and di-isopropyl ethylamine (0.88 mL, 5.07 mmol) in dichloromethane (16 mL) at room temperature was added toluenesulfonyl chloride (0.35 g, 1.86 mmol) and the reaction stirred overnight. The reaction mixture was diluted with dichloromethane, washed with water, and dried over sodium sulfate. The dichloromethane was filtered and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (silica gel, 5% methanol: chloroform) to provide pure cyclized product **48c** (0.276 g, 33%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, m), 1.95 (3H, m), 2.80 (s, 6H), 3.70 (m, 1H), 3.80 (m, 2H), 3.95 (m, 2H), 4.15 (m, 1H), 5.25 (s, 1H), 5.45 (s, 2H), 7.05 (m, 2H), 7.20 (m, 2H), 7.95 (s, 1H), 8.80 (s, 1H). LC-MS m/z 503.10 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-7-hydroxy-N,N-dimethyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c]-1,7-naphthyridine-1-sulfonamide (**49c**).* To a stirring solution of the THP protected *N*-hydroxydihydropyridone **48c** (0.276 g, 0.55 mmol) in methanol/water (1:1, 1 mL) was added *p*-toluenesulfonic acid monohydrate (0.209 g, 1.10 mmol) and the reaction stirred overnight at room temperature. The mixture was concentrated under reduced pressure to provide a white solid that was filtered to provide the pure product **49c** as the tosylate salt (0.133 g, 40%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.75 (s, 6H), 3.63 (m, 2H), 3.82 (m, 2H), 5.69 (s, 2H), 7.21 (m, 2H), 7.47 (m, 2H), 8.63 (s, 1H), 9.01 (s, 1H). LC-MS m/z 419.2 $(M + H)^+$. HRMS Calcd for $C_{19}H_{20}FN_4O4S + H^+$: 419.1184. Found: 419.1181.

*7-(4-Fluorobenzyl)-9-(morpholin-4-ylsulfonyl)-1,7-dihydropyrano-[3,4-b]pyrrolo[3,2-d]pyridin-4(2H)-one (**46a**).* As described for the preparation of **46c**, sulfonyl chloride **45** was reacted with morpholine (DMF), in the presence of Et_3N, to give **46a** in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (m, 1H), 3.15 (m, 4H), 3.60−3.75 (5H), 4.61 (m, 2H), 5.48 (s, 2H), 7.11 (m, 2H), 7.19 (m, 2H), 7.96 (s, 1H), 8.93 (s, 1H). LC-MS m/z 446.0 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-3-(morpholin-4-ylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide (**47a**).* As described for the preparation of **47c**, sulfonamide **46a**, as a solution in THF, was treated with H_2NOTHP and LiHMDS to give **47a** in 51% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30−1.90 (8H), 3.55−3.70 (6H), 3.70 (m, 2H), 3.90 (m, 4H), 4.75 (m, 1H), 5.65 (s, 2H), 7.12 (m, 2H), 7.24 (m, 2H), 7.81 (s, 1H), 8.71 (s, 1H), 10.62 (brs, 1H). LC/MS (APCI): m/z 563.2 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-1-(morpholin-4-ylsulfonyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**48a**).* As described for the preparation of **48c**, sulfonamide **47a** was cyclized by treatment with *p*-TsCl and *i*-Pr_2NEt in CH_2Cl_2 to give *N*-OTHP lactam **48a** in 35% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30−1.90 (8H), 3.55−3.70 (6H), 3.95 (m, 4H), 4.10 (m, 4H), 4.73 (m, 1H), 5.67 (s, 2H), 7.12 (m, 2H), 7.24 (m, 2H), 7.79 (s, 1H), 8.82 (s, 1H). LC/MS (APCI) m/z 545.1 $(M + H)^+$. HPLC (254, 224 nM) >95% purity. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-7-hydroxy-1-(morpholinosulfonyl)-8,9-dihydro-3H-pyrrolo[2,3-c][1,7]naphthyridin-6(7H)-one (**49a**).* Procedure followed according to the preparation of **49c** to provide the product **49a** as the tosylate salt (41%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.47−3.80 (4H), 3.85−4.27 (8H), 5.51 (s, 2H), 7.04 (m, 2H), 7.18−7.30 (3H), 8.00 (s, 1H), 9.29 (s, 1H). LC/MS (APCI) m/z 461.0 $(M + H)^+$. HPLC (260, 222 nm): >95% purity.

*7-(4-Fluorobenzyl)-N-(2-methoxyethyl)-N-methyl-4-oxo-1,2,4,7-tetrahydropyrano[3,4-b]pyrrolo[3,2-d]pyridine-9-sulfonamide (**46b**).* As described for the preparation of **46c**, sulfonyl chloride **45** was reacted with *N*-methyl-2-methoxyethylamine (DMF), in the presence of Et_3N, to give **46b** in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (m, 1H), 2.90 (m, 1H), 2.92 (s, 3H), 3.21 (s, 3H), 3.40 (m, 1H), 3.49 (m, 1H), 3.74 (m, 2H), 4.61 (m, 2H), 5.46 (s, 2H), 7.10 (m, 2H), 7.21 (m, 2H), 7.97 (s, 1H), 8.58 (s, 1H). LC/MS (APCI) m/z 448.1 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-3-[(2-methoxyethyl)(methyl) sulfamoyl]-N-(tetrahydro-2H-pyran-2-yloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide (**47b**).* As described for the preparation of **47c**, sulfonamide **46b**, as a solution in THF, was treated with H_2NOTHP and LiHMDS to give **47b** in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.95 (6H), 2.91 (s, 3H), 3.28 (s, 3H), 3.30−3.85 (6H), 3.93 (m, 2H), 4.05 (m, 2H), 5.10 (m, 1H), 5.40 (s, 2H), 7.05−7.25 (4H), 8.00 (s, 1H), 8.52 (s, 1H), 10.36 (brs, 1H). LC/MS (APCI) m/z: 565.1 $(M + H)^+$. HPLC (260, 222 nm): >95% purity.

*3-(4-Fluorobenzyl)-N-(2-methoxyethyl)-N-methyl-6-oxo-7-(tetrahydro-2H-pyran-2-yloxy)-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridine-1-sulfonamide (**48b**).* As described for the preparation of **48c**, sulfonamide **47b** was cyclized by treatment with *p*-TsCl and *i*-Pr_2NEt in CH_2Cl_2 to give *N*-OTHP lactam **48b** in 37% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30−1.95 (6H), 2.75 (s, 3H), 3.17 (s, 3H), 3.30 (m, 1H), 3.60−3.75 (5H), 3.95 (m, 2H), 4.13 (m, 2H), 4.90 (m, 1H), 5.50 (s, 2H), 7.12 (m, 2H), 7.24 (m, 2H), 7.64 (s, 1H), 8.81 (s, 1H). LC/MS (APCI) m/z: 546.1 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-7-hydroxy-N-(2-methoxyethyl)-N-methyl-6-oxo-6,7,8,9-tetrahydro-3H-pyrrolo[2,3-c][1,7]naphthyridine-1-sulfonamide (**49b**).* Procedure followed according to the preparation of **49c** to

provide the product **49b** as the tosylate salt (39%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.86 (s, 3H), 3.19 (s, 3H), 3.36 (m, 2H), 3.47 (m, 2H), 3.69 (m, 2H), 3.94 (m, 2H), 5.65 (s, 2H), 6.94 (m, 2H), 7.26 (m, 2H), 8.16 (s, 1H), 9.64 (s, 1H). LC/MS (APCI) m/z: 463.1 $(M + H)^+$. HPLC (260, 222 nm): >95% purity.

*7-(4-Fluorobenzyl)-9-(pyrrolidin-1-ylsulfonyl)-1,7-dihydropyrano-[3,4-b]pyrrolo[3,2-d]pyridin-4(2H)-one (**46d**).* As described for the preparation of **46c**, sulfonyl chloride **45** was reacted with pyrrolidine (DMF), in the presence of Et_3N, to give **46d** in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (m, 4H), 3.29 (m, 4H), 3.77 (m, 2H), 4.61 (m, 2H), 5.47 (s, 2H), 7.09 (m, 2H), 7.20 (m, 2H), 7.95 (s, 1H), 8.91 (s, 1H). LC/MS (APCI) m/z: 430.1 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-3-(pyrrolidin-1-ylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide (**47d**).* As described for the preparation of **47c**, sulfonamide **46d**, as a solution in THF, was treated with H_2NOTHP and LiHMDS to give **47d** in 44% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.31−1.95 (12H), 2.70 (m, 2H), 2.95 (m, 2H), 3.63 (m, 2H), 3.74 (m, 2H), 3.96 (m, 2H), 4.77 (m, 1H), 5.52 (s, 2H), 7.09 (m, 2H), 7.24 (m, 2H), 7.78 (s, 1H), 8.71 (s, 1H). LC/MS (APCI) m/z 547.2 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-1-(pyrrolidin-1-ylsulfonyl)-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**48d**).* As described for the preparation of **48c**, sulfonamide **47d** was cyclized by treatment with *p*-TsCl and *i*-Pr_2NEt in CH_2Cl_2 to give *N*-OTHP lactam **48d** in 34% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36−2.00 (12H), 2.71 (m, 2H), 2.96 (m, 2H), 3.55−3.65 (6H), 4.00 (m, 2H), 4.12 (m, 2H), 4.97 (m, 1H), 5.52 (s, 2H), 7.09 (m, 2H), 7.25 (m, 2H), 7.75 (s, 1H), 8.84 (s, 1H). LC/MS (APCI) m/z 529.1 $(M + H)^+$. HPLC (254, 224 nM) >95% purity.

*3-(4-Fluorobenzyl)-7-hydroxy-1-(pyrrolidin-1-ylsulfonyl)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**49d**).* Procedure followed according to the preparation of **49c** to provide the product **49d** as the tosylate salt (42%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.83 (m, 4H), 3.23 (m, 4H), 3.75 (m, 2H), 3.98 (m, 2H), 5.78 (s, 2H), 7.24 (m, 2H), 7.47 (m, 2H), 8.84 (s, 1H), 9.24 (s, 1H). LC/MS (APCI) m/z 445.0 $(M + H)^+$. HPLC (254, 224 nM) >95% purity.

*7-(4-Fluorobenzyl)-9-[(4-methylpiperidin-1-yl)sulfonyl]-1,7-dihydropyrano[3,4-b]pyrrolo[3,2-d]pyridin-4(2H)-one (**46e**).* As described for the preparation of **46c**, sulfonyl chloride **45** was reacted with 4-methylpiperidine (DMF), in the presence of Et_3N, to give **46e** in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 6.0 Hz, 3H), 1.10−1.90 (5H), 2.66 (m, 2H), 3.60−3.80 (4H), 4.61 (m, 2H), 5.47 (s, 2H), 7.10 (m, 2H), 7.21 (m, 2H), 7.94 (s, 1H), 8.91 (s, 1H). LC/MS (APCI) m/z 458.1 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*1-(4-Fluorobenzyl)-4-(2-hydroxyethyl)-3-[(4-methylpiperidin-1-yl) sulfonyl]-N-(tetrahydro-2H-pyran-2-yloxy)-1H-pyrrolo[2,3-c]pyridine-5-carboxamide (**47e**).* As described for the preparation of **47c**, sulfonamide **46e**, as a solution in THF, was treated with H_2NOTHP and LiHMDS to give **47e** in 57% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (d, J = 7.07 Hz, 3H), 1.20−1.92 (13H), 3.06 (m, 2H), 3.63 (m, 2H), 3.73 (m, 2H), 3.96 (m, 2H), 4.77 (m, 1H), 5.,52 (s, 2H), 7.10 (m, 2H), 7.23 (m, 2H), 7.93 (s, 1H), 8.71 (s, 1H). LC/MS (APCI): m/z 575.2 $(M + H)^+$. HPLC (254, 224 nm): >95% purity.

*3-(4-Fluorobenzyl)-1-[(4-methylpiperidin-1-yl)sulfonyl]-7-(tetrahydro-2H-pyran-2-yloxy)-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c][1,7]naphthyridin-6-one (**48e**).* As described for the preparation of **48c**, sulfonamide **47e** was cyclized by treatment with *p*-TsCl and *i*-Pr_2NEt in CH_2Cl_2 to give *N*-OTHP lactam **48e** in 40% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (d, J = 7.06 Hz, 3H), 1.20−1.96 (13H), 3.07 (m, 2H), 3.55−3.75 (6H), 4.00 (m, 2H), 4.11 (m, 2H), 4.96 (m, 1H), 5.53 (s, 2H), 7.11 (m, 2H), 7.24 (m, 2H), 7.90 (s, 1H), 8.84 (s, 1H). LC/MS (APCI) m/z 557.1 $(M + H)^+$. HPLC (254, 224 nM) >95% purity.

*3-(4-Fluorobenzyl)-7-hydroxy-1-[(4-methylpiperidin-1-yl)sulfonyl]-3,7,8,9-tetrahydro-6H-pyrrolo[2,3-c]-1,7-naphthyridin-6-one (**49e**).* Procedure followed according to the preparation of **49c** to provide the product **49e** as the tosylate salt (45%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (d, J = 6.25 Hz, 3H), 1.16 (m, 2H), 1.47 (m, 1H), 1.40 (m, 2H), 2.62 (m, 2H), 3.96 (m, 2H), 5.79 (s, 2H), 7.22 (m, 2H), 7.44 (m, 2H), 8.90 (s, 1), 9.32 (s, 1H). LC/MS (APCI) m/z: 473.1 $(M + H)^+$. HPLC (254, 224 nM) >95% purity.

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ACKNOWLEDGMENT

We thank Dr. Martin Edwards, Dr. Simon Bailey, and Dr. Stacie Canan for helpful discussions.

ABBREVIATIONS USED

CC_{50}, 50% cytotoxic concentration; CPE, cytopathic effect; DCM, dichloromethane; DIEA, di-isopropyl ethylamine; D*t*BAD, di-*t*-butyl azodicarboxylate; DMAP, dimethylamino pyridine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; EC_{50}, 50% effective concentration; EtOAc, ethyl acetate; ER, extraction ratio; *F*, bioavailability; *H*, high; HIV, human immunodeficiency virus; HIV-1, human immunodeficiency virus type 1; hHEP, human hepatocyte; HLM, human liver microsome; HPLC, high-performance liquid chromatography; IC_{50}, 50% inhibitory concentration; IN, integrase; *L*, low; LC-MS, liquid chromatography−mass spectrometry; LipE, lipophilic efficiency; log *D*, octanol:buffer (pH 7.4) distribution coefficient; *M*, medium; NIS, *N*-iodosuccinimide; NMM, *N*-methyl morpholine; PR, protease; PK, pharmacokinetic; RT, reverse transcriptase; rt, room temperature; SEM, 2-(trimethylsilyl)ethoxymethyl; SFC, supercritical fluid chromatography; SPA, scintillation proximity assay; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin-layer chromatography; tPSA, topological polar surface area; Vdss, volume of distribution

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