Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

The Discovery and Hit-to-Lead Optimization of Tricyclic Sulfonamides as Potent and Efficacious Potentiators of Glycine Receptors

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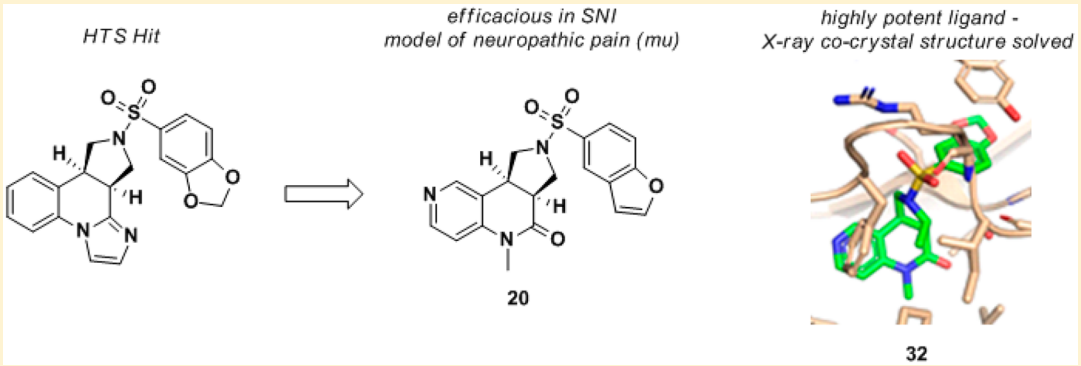
Supporting Information



ABSTRACT: Current pain therapeutics suffer from undesirable psychotropic and sedative side effects, as well as abuse potential. Glycine receptors (GlyRs) are inhibitory ligand-gated ion channels expressed in nerves of the spinal dorsal horn, where their activation is believed to reduce transmission of painful stimuli. Herein, we describe the identification and hit-to-lead optimization of a novel class of tricyclic sulfonamides as allosteric GlyR potentiators. Initial optimization of high-throughput screening (HTS) hit **1** led to the identification of **3**, which demonstrated ex vivo potentiation of glycine-activated current in mouse dorsal horn neurons from spinal cord slices. Further improvement of potency and pharmacokinetics produced in vivo proof-of-concept tool molecule **20** (AM-1488), which reversed tactile allodynia in a mouse spared-nerve injury (SNI) model. Additional structural optimization provided highly potent potentiator **32** (AM-3607), which was cocrystallized with human GlyR$\alpha 3_{cryst}$ to afford the first described potentiator-bound X-ray cocrystal structure within this class of ligand-gated ion channels (LGICs).

INTRODUCTION

Chronic, neuropathic pain represents a major unmet medical need. Current and most effective treatment plans include the administration of agents with undesirable psychotropic and physiological side effects.[1] The identification of novel anagelsic agents devoid of these side effects would provide an immensely positive societal impact. Strychnine-sensitive glycine receptors have been investigated as key regulators of spinal inhibitory neurotransmission in the adult CNS.[2,3] GlyRs functionally exist as homopentameric (GlyRα1 and GlyRα3) or heteropentameric (GlyR$\alpha 1\beta$ and GlyR$\alpha 3\beta$) channels with either a 3:2 or 2:3 ratio of α:β subunits. The reported enrichment of GlyRs in the spinal dorsal horn, the terminal point of afferent nociceptive sensitization and the reported role of GlyRα3 in inflammatory pain processing support targeting this receptor class.[4] The β-subunit is believed to localize the channel at the postsynaptic cleft by interacting with gephryn on the neuronal cell surface.[5] Because of these factors, we targeted potentiators of GlyR$\alpha 3\beta$ heteropentameric channels.

Positive modulators of GlyRs have been suggested as potential therapeutic agents to suppress pain signaling at the level of the spinal cord.[4,6,7] Reported GlyR modulators include volatile and intravenous anesthetics,[8] *n*-alcohols,[8] avermectins,[8] tropeines,[8] cannabinoid ligands,[9,10] bivalent cations,[8] glutamatergic ligands,[11] gelsemine,[12,13] mono and disaccharides,[14] and

Received: October 12, 2016

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

ginkolic acid.[15] Recent detailed functional behavioral pain studies suggested that the mechanism of analgesia afforded with the cannabinoid class of compounds, and gelsemine was primarily due to potentiation of GlyRα3.[9,10,12] Unfortunately, these reported modulators suffer from a lack of potency, selectivity, and/or pharmacokinetic (PK) properties favorable for in vivo profiling. Recently, Pfizer reported the identification of a few small molecule potentiator chemotypes via a high-throughput screening (HTS) campaign, with one sulfonamide displaying selectivity over $GABA_A$-R $\alpha1/3\beta3\gamma2$ without the disclosure of hit optimization efforts.[16] We sought to identify small molecule GlyRα3 positive modulators with selectivity over other ligand-gated ion channels (LGICs) suitable for oral dosing in a rodent pain model of neuropathic pain to establish target proof-of-concept (POC).

RESULTS AND DISCUSSION

In light of the paucity of reported, lead-like chemical matter for GlyRs, we initiated a HTS in search of potentiators with the goal of demonstrating in vivo POC. Our HTS and subsequent primary screening assay utilized HEK293T cells stably expressing human GlyR$\alpha3\beta$. Using a standard membrane potential dye that reports on net changes in membrane potential across the cell membrane due to GlyR-mediated ion flux, we designed an assay that enabled assessment of the ability of compound to directly activate GlyR$\alpha3\beta$ in the presence of low levels (EC_{10}) of the endogenous agonist glycine. The assay could also be performed in the absence of glycine, allowing for the detection of agonist activity. On-target activity was confirmed by reversal of activation with the known pan-GlyR antagonist, strychnine.[17−19] Compounds identified as on-target potentiators with suitable potency were advanced to a Schild shift assay which measured the ability of the compound to modulate the activity of the agonist glycine, i.e., individual glycine dose−response curves were generated in the presence of compound, applied at a range of concentrations (Figure 1).

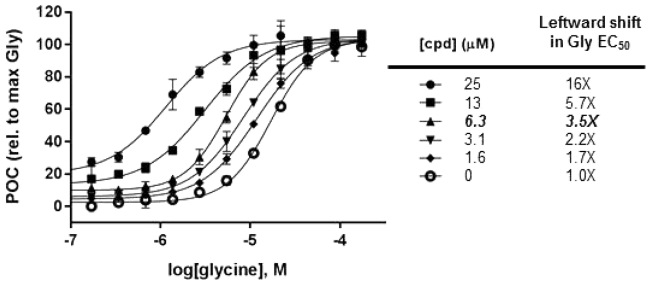


Figure 1. Representative glycine Schild shift plot. In this example, the mEC_3 (or minimum tested compound concentration to elicit a leftward shift in the Gly EC_{50} value ≥3×) corresponds to a compound concentration [cpd] of 6.3 μM.

The minimum tested concentration of potentiator required to left shift the glycine dose−response curve at least 3-fold (hereon referred to as mEC_3), a statistically relevant shift, was used to rank order potentiators (see Figure 1 for a representative example). All of the compounds described herein increased the glycine potency (effects in α) but not glycine maximum efficacy (no impact on β) in the Schild shift assay.[20] Therefore, the latter parameter was not utilized in our SAR analyses. Although the activities obtained in the Schild shift platform correlated well with dose−response values, confirmation of glycine modulation was required for compound advancement.[21]

Our HTS campaign led to the identification of modestly potent hit **1** (mEC_3 = 3.1 μM) with high passive permeability and low efflux ratios in breast cancer resistance protein (BCRP) and multidrug resistance protein 1 (MDR1) overexpressed Madin−Darby canine kidney (MDCK) cell lines (Table 1). Hit **1** suffered from high intrinsic clearance in mouse liver microsomes (MLM CL_{int} = 901 μL/min/mg), likely contributing to the observed low plasma exposure following intraperitoneal dosing in mice (plasma C_{max} unbound = 0.13 μM @ 30 mg/kg). Toward identifying a minimal structural core, replacement of the imidazole ring of the tetracycle with a methyl amide in **3** afforded improved potentiation (mEC_3 = 0.78 μM) as well as a moderate stereopreference, with the two cis pyrrolidine enantiomers **3** and **4** exhibiting a >10-fold potency difference. Like hit **1**, tricycle **3** suffered from high metabolic intrinsic clearance and poor in vivo exposure upon intraperitoneal dosing in mice (plasma C_{max} unbound = 0.07 μM @ 50 mg/kg). Despite the poor PK profile of **3**, it was considered an attractive lead molecule as the compound exhibited good cellular potency, permeability with low efflux ratio, and physicochemical properties conducive to CNS penetration.[22] Potency, as measured in HEK293T cells, was optimized for human GlyR$\alpha3\beta$, which correlated well with potency against human GlyRα3, GlyR$\alpha1\beta$, and GlyRα1 as well as rodent GlyR cell lines for all compounds described herein.[21]

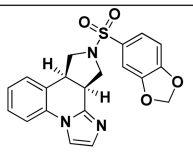
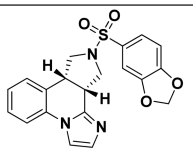
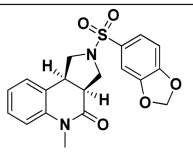
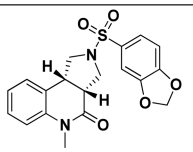
An in vitro metabolite profiling study using mouse liver microsomes (MLM) indicated that major metabolic pathways of **3** were oxidative metabolism on the quinolinone core, pyrrolidine ring, and benzodioxolane moiety.

Accordingly, initial efforts focused on suppressing the oxidative metabolism of the tricyclic aryl ring by increasing polarity and/or introducing a substituent at the relatively electron-rich C-6, which was believed to be a metabolic soft site (Table 2). 6-Hydroxy analogue **5** had decreased MLM CL_{int} and 2-fold increased potency (mEC_3 = 0.39 μM). The more polar 6-cyano analogue **6** had further reduced MLM CL_{int} but decreased potency (mEC_3 = 12.5 μM). The nonpolar 6-fluoro analogue **7** had retained potency but high intrinsic clearance (MLM CL_{int} = 761 μL/min/mg). An aza-walk around the quinolinone ring produced analogues with retained or improved potency coupled with markedly improved MLM CL_{int}, such as, 5-aza (**8**, mEC_3 = 0.78 μM, MLM CL_{int} = 136 μL/min/mg) and 6-aza (**9**, mEC3 = 0.20 μM, MLM CL_{int} = 151 μL/min/mg). This marked an important achievement: adding polarity and improving metabolic stability while improving activity. A significant loss of potency was observed with the 7-aza and 8-aza analogues, **10** and **11** (mEC_3 = 6.3 and 3.1 μM, respectively).

As a first step toward electrophysiological ex vivo validation of our in vitro cell-based functional potentiator assay, we assessed **9** and less active enantiomer (*ent*)-**9** in an ex vivo mouse spinal cord slice assay. In addition to good potency, **9** possessed high passive permeability (cell line Papp ave = 52 μcm/s) and solubility (PBS, FaSSIF = 235, 296 μM), rendering it suitable for this study. Neurons located in the upper layer of the dorsal horn (laminae I and II) were histologically identified and glycinergic profiles were further confirmed upon focal application of glycine (~EC_{30-40} = 20 μM) followed by confirmation of a reversal effect with the application of strychnine (10 μM). To further ensure that detected currents were a result of glycinergic signaling only, neurons were

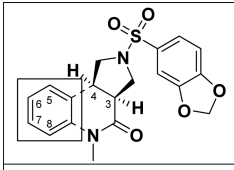
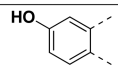
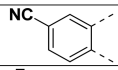
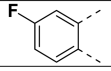
DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

Table 1. Profiles of Hit and Lead Compounds[a]

	Compd	hGlyRα3β mEC_3 (μM)	MW, LogD (pH =7.4), PSA	MLM CL_{int} (μL/min/mg)	MDCK Papp (ave, μcm/sec), Pgp ER, BCRP ER
	**1**	3.1	395, 4.0, 74	901	58, 1.7, 1.3
	**2**	6.3	395, 4.0, 74	1670	--
	**3**	0.78	386, 3.3, 76	1420	46, 0.8, 0.8
	**4**	6.3	386, 3.3, 76	2440	--

[a]Compounds are enantiopure unless otherwise noted as racemic.

Table 2. SAR and in Vitro PK Profiles of Quinolinone Ring[a]

	compd	hGlyRα3β mEC_3 (μM)	LogD (pH=7.4) PSA	MLM CL_{int} (μL/min/mg)	MDCK Papp (ave, μcm/sec), Pgp ER BCRP ER
	**3**	0.78	3.3 76	1420	46 0.8 0.8
	**5**	0.39	2.9 96	499	18 3.2 3.1
	(*rac*)-**6**	12.5	2.8 100	374	--
	(*rac*)-**7**	0.78	3.4 76	761	--
	**8**	0.78	1.8 89	136	45 1.5 1.0
	**9**	0.20	1.8 89	151	52 0.8 0.9
	(*ent*)-**9** (enantiomer of 9)	>25	1.8 89	213	14 1.0 0.9
	(*rac*)-**10**	6.3	1.8 89	225	--
	(*rac*)-**11**	3.1	1.8 89	760	--

[a]Compounds are enantiopure unless otherwise noted as racemic.

pretreated with a cocktail of inhibitors composed of tetrodotoxin (TTX), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), (2*R*)-amino-5-phosphonovaleric acid (APV), and bicuculine to silence TTX-sensitive sodium channels, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite receptors, *N*-methyl-D-aspartic acid (NMDA) receptors, and γ-

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

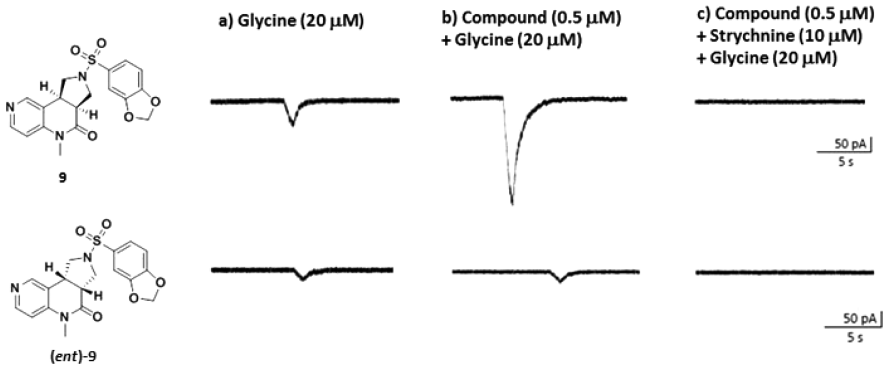


Figure 2. Potentiation of glycine evoked current in adult mouse spinal neurons. Representative postsynaptic current (PSC) amplitude (pA) modulation recorded from glycinergic neurons in an isolated adult mouse spinal cord slice: (a) glycine (20 μM), (b) glycine (20 μM) + **9** (0.5 μM) on the top and (ent)-**9** (0.5 μM) on the bottom, (c) glycine (20 μM) + **9** (0.5 μM) + strychnine (10 μM). On average, application of 0.5 μM of **9** led to a 4.9-fold increase of the PSC amplitude. This response was fully reversed in the presence of strychnine (n = 5 neurons, scale bars apply to all electrophysiological traces).

aminobutyric acid ($GABA_A$) receptors, respectively. Bath application of **9** at 0.5 μM with and without focal glycine application was assessed to confirm the potentiation mechanism. GlyR activation was assessed by calculating the mean ratio of postsynaptic current (PSC) amplitudes of 0.5 μM **9** or (*ent*)-**9** in the presence of 20 μM glycine (Figure 2b)/20 μM glycine application alone (Figure 2a), where a ratio of 1.0 equates to no potentiation. The activation was confirmed as glycine-dependent if the PSC amplitude could be fully reversed by strychnine (Figure 2c). In the presence of **9** at 0.5 μM, the mean PSC ratio calculated was 4.9 ± 3.7 (mean ratio ± STD; n = 5). This data confirmed that endogenous neuronal glycinergic receptors can be positively modulated by **9** and served to further validate our in vitro cell-based functional potentiator assays. Less active enantiomer (*ent*)-**9** (0.5 μM) did not evoke increased current in the presence of 20 μM glycine, which provided further support that the observed action of **9** was on mechanism via GlyR potentiation.

To identify compounds suitable for investigation in mouse models of neuropathic pain, compounds with favorable potency and microsomal stability such as **8** and **9** were advanced to mouse PK studies. Target coverage values were calculated using potentiation of mouse GlyRα3 rather than mouse GlyRα3β activities due to lack of heteropentamer protein availability.[23] At a 30 mg/kg oral dose, **8** had poor target coverage (mouse brain C_{max}(u)/muGlyRα3 EC_{50} = 0.006), likely attributed to solubility limited absorption (FaSSIF, PBS solubility = 28, 7 μM). In contrast, **9** had good solubility (FaSSIF, PBS = 296, 235 μM) and improved oral coverage at 30 mg/kg (mouse brain C_{max}(u)/muGlyRα3 EC_{50} = 0.62). Brain concentrations were measured due to target localization in the CNS. We next directed our efforts toward removing the oxidative metabolism liabilities imparted by the benzodioxolane sulfonamide moiety with the 6-aza substituted tricyclic core in place.

To guide our optimization of the sulfonamide portion of the molecule, we utilized emerging trends relating physiochemical properties with CL_{int}, Pgp, and BCRP efflux ratios. Analysis of correlation plots (Figure 3) indicated that by targeting cLogD (pH = 7.4)[24] ≤ 2, there was a high likelihood of achieving MLM CL_{int} < 200 μL/min/mg, and that by maintaining PSA < 90, Pgp and BCRP efflux ratios <3 were likely to be attained. Analogues containing hydrogen bond donors (depicted with green squares) tended to have poor passive permeability and high efflux. Our strategy toward exploring sulfonamide substitution SAR was guided by these trends and focused on small, systematic modifications relative to lead **9** with the goal of further improving potency and PK (Table 3).

Toward replacing the benzodioxolane moiety, a known structural alert,[25] other 6,5-bicyclic heteroaromatics were initially investigated. Benzimidazole and *N*-methyl benzimidazole replacements **12** and **13** suffered ∼10-fold reduced potency. Compound **12** had insufficient brain coverage over muGlyRα3 despite improved microsomal stability, likely as a result of poor passive permeability, and **13** suffered from high efflux. Benzoxazole **14** had retained potency and improved microsomal stability relative to **9** but was found to be unstable in mouse plasma and assay buffer.[26] Benzothiazole **15** suffered decreased potency (hGlyRα3β mEC_3 = 1.56 μM) and oral coverage over muGlyRα3 and imidazopyridine **16** had reduced potency (hGlyRα3β mEC_3 = 3.1 μM). The importance of each oxygen atom of the benzodioxolane was assessed by preparing dihydrobenzofurans **17** and **18**. Removal of either oxygen afforded a 5-fold drop in potency as well as slightly suppressed oral coverage. Interestingly, benzofuran analogue **20** (AM-1488)[27] had retained potency relative to **9** while its regioisomer **19** had reduced activity. Additionally, suitable coverage levels of **20** were achieved at lower doses relative to benzodioxolane **9** (mouse brain C_{max}(u) /muGlyRα3 EC_{50}: 1.2 @ 10 mg/kg vs 0.62 for **9** @ 30 mg/kg). It is likely that the improved exposure observed for **20** despite modest MLM stability was a result of saturation of metabolism, supported by greater than dose proportion increases in area under the curve (AUC) exposure when increasing dose from 5 to 10 mg/kg (po) and well over 100% calculated oral bioavailability. As was the case with our initial lead tricyclic sulfonamide, the enantiomer of **20**, (*ent*)-**20**, was significantly less active (hGlyRα3β EC_{50} > 20 μM, mEC_3 > 25 μM). Monocyclic sulfonamides, such as **21**, were identified with modest activity but with relatively high instrinsic clearance (MLM CL_{int} = 432 μL/min/mg).

Profiling of **20** across a range of CYS loop family receptors, voltage-gated ion channels, kinases, and GPCRs indicated a high degree of off-target selectivity (see Supporting Information Part 4). Additionally, **20** was selective over hERG, BSEP, CYPs, and PXR. Furthermore, **20** potentiated glycine-evoked current in adult mouse spinal neurons at 0.5 μM (4.4-fold increase in postsynaptic current amplitude relative to glycine alone).[27]

With suitable mouse PK and a favorable expanded selectivity profile, **20** was advanced as a potential in vivo proof-of-concept

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

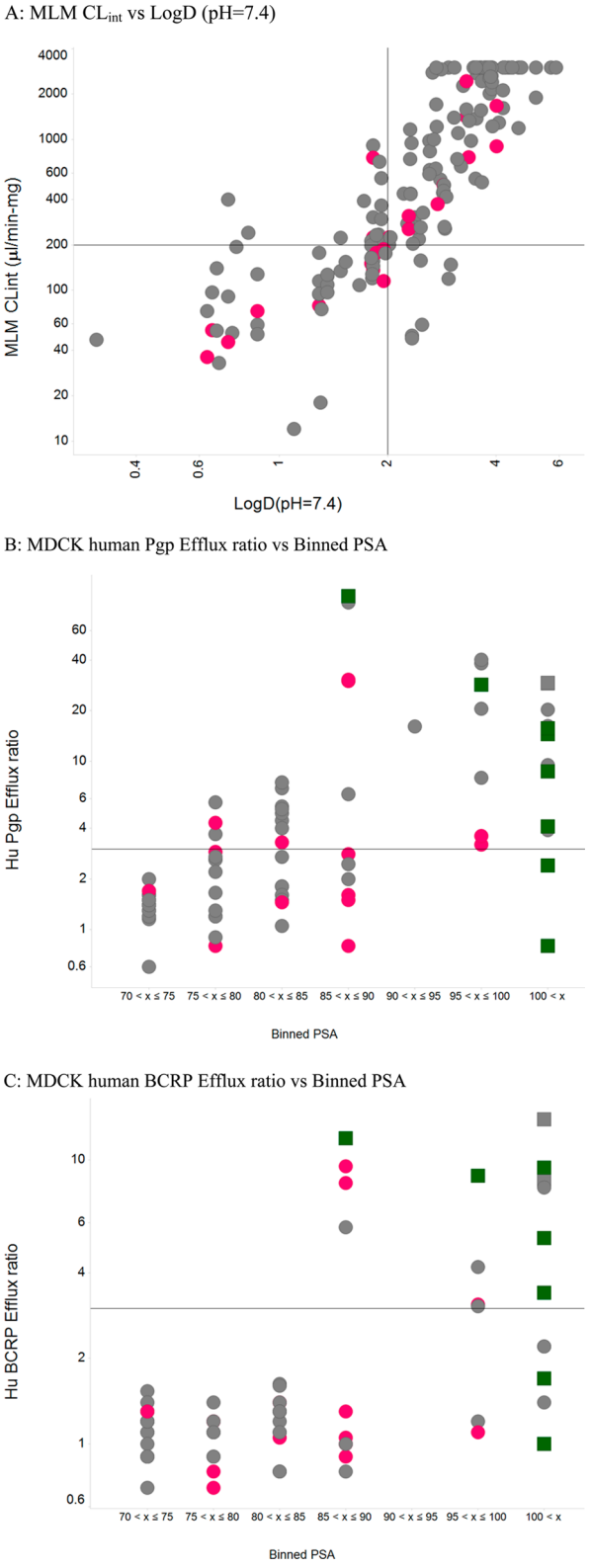
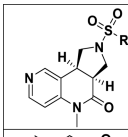
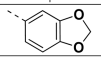
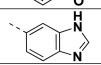
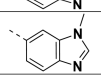
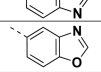
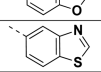
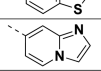
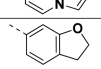
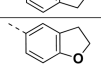
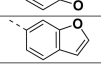
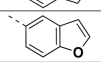
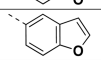
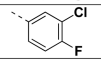


Figure 3. Physicochemical properties and in vitro PK trends. Pink, compounds described herein; gray, structurally related tricyclic sulfonamides (compounds not disclosed herein); green squares, analogues containing an H-bond donor. (A) MLM CL_{int} vs Log *D* (pH = 7.4). (B) MDCK human Pgp efflux ratio vs binned PSA. (C) MDCK human BCRP efflux ratio vs binned PSA.

tool and examined in the mouse SNI model of neuropathic pain (Figure 4). In SNI model, surgical ligation of the peroneal and

Table 3. Sulfonamide Substitutions: SAR and PK Profiles

	Compd	hGlyRα3β mEC_3 (μM)	LogD (pH =7.4)	PSA	MLM CL_{int} (μL/min/mg)	MDCK Papp (ave), Pgp ER, BCRP ER	Mouse brain C_{max} (u) / mu GlyRα3 EC_{50} (route, dose in mg/kg)[a]
	**9**	0.20	1.8	89	151	52 0.8 0.9	0.62 (PO, 30)
	**12**	3.1	0.7	99	<14	<1 -- --	0.047 (IP, 30)
	**13**	3.1	0.7	88	45	9 >31 >10	--
	**14**	0.39	0.9	97	73	25 3.6 1.1	--
	**15**	1.56	1.3	83	79	48 3.3 1.4	0.15 (PO, 60)
	**16**	3.1	0.6	87	36	16 30 8.3	--
	**17**	1.56	1.9	80	177	28 2.9 0.7	0.38 (PO, 60)
	**18**	3.1	2.0	80	225	50 4.3 1.2	0.19 (PO, 50)
	**19**	1.56	2.0	83	115	--	--
	**20 (AM-1488)**	0.20	2.0	83	188	69 1.5 1.1	1.2 (PO, 10)
	***(ent)*-20**	>25	2.0	83	--	--	--
	**21**	3.1	2.9	71	432	49 1.2 1.1	--

[a]Fraction unbound (f_u) in mouse brain was determined as described in Berry et al, 2010.[28] Mouse brains were collected at multiple time points following IP or PO administration. Drug concentrations in the brain were determined according to the method described by Huang et al.[29] brain C_u = total brain concentration × $f_{u\text{-brain}}$.

tibial nerves can generate tactile allodynia that can be reversed with a therapeutic agent.[30] In this model, active enantiomer **20** demonstrated significant reversal of tactile allodynia at an oral dose of 20 mg/kg (mouse brain *C*(u)/muGlyR*α*3 EC_{50}: 1.9), while the inactive enantiomer **21** did not elicit a significant effect at the same dose and with similar exposure *C*(u) plasma = 2.3 *μ*M (est. *C*(u) brain = 0.61 *μ*M). Notably, **20** did not significantly affect basic movements in naïve mice at an oral dose of 20 mg/kg.[27] These results suggest that the reversal of tactile allodynia was via potentiation of GlyRs and further validates GlyRs as a therapeutic target.

With the goal of improving metabolic stability and with guidance from metabolism identification studies, we pursued substitution of the pyrrolidine ring. Further, substitution at the pyrrolidine 1- or 2-position may impact both the vector and rotational freedom of the sulfonamide moiety potentially impacting activity. Exploration of pyrrolidine ring SAR was conducted concomitantly with the previously described sulfonamide SAR exploration and thus retained the benzodioxolane sulfonamide moiety (Table 4).

First, substitution at ring fusion carbon "3" was investigated. Both polar and nonpolar substitution at this position (**22**−**24**) resulted in markedly reduced potentiation (mEC_3 > 25 *μ*M). Similarly, methyl substitution at the ring fusion carbon "4" as in **25** was not tolerated (mEC_3 > 25 *μ*M). The chemistry employed en route to the majority of tricyclic core modifications was also suitable for rapidly accessing all eight diastereomeric *α*-methyl pyrrolidines. In fact, the initial synthesis afforded a nonstatistical mixture of all eight possible

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

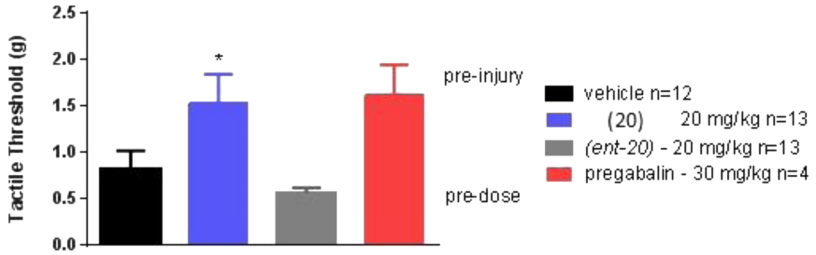
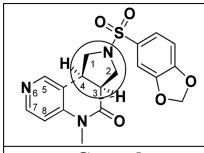


Figure 4. Reversal of SNI-induced tactile allodynia by **20** when dosed at 20 mg/kg (po). At 60 min post oral dosing, **20** dosed at 20 mg/kg (po) produced a significant increase in von Frey threshold (1.53 ± 0.31 g) relative to vehicle (0.82 ± 0.19 g) by ANOVA with Dunnett's Multiple Comparisons; $F_{2,35} = 4.7$, $p < 0.05$. The less active enantiomer (*ent*)-**20** also dosed at 20 mg/kg (po) did not reverse tactile allodynia. The positive control, pregabalin, dosed at 30 mg/kg (po), was not included in the statistical analysis because of low *n* but appeared effective. Exposure values were generated at 90 min post dose.

Table 4. Pyrrolidine Modifications: SAR[a]

					
Compd	**9**	**(*rac*)-22**	**23***	**(*rac*)-24**	**(*rac*)-25**
hGlyRα3β mEC$_3$ (μM)	0.2	>25	>25	>25	>25
					
Compound	**26**	**27**	**28**	**29**	
hGlyRα3β mEC$_3$ (μM)	>25	>25	>25	>25	
					
Compound	**30**	**31**	**32 (AM-3607)**	**33**	
hGlyRα3β mEC$_3$ (μM)	>25	>25	0.025	3.1	

[a]*Tricycle aryl contains C−H rather than aza at 6-position.

stereoisomers at positions "1" and "2", which were elaborated to a mixture of final compounds which were separated by chromatography, providing compounds **26**−**33**. Only one minor isomer out of the eight isolated (**32**, AM-3607),[27] representing 3% of the isomeric mixture, afforded improved potency, while the other seven isomers suffered a dramatic loss of potency. Furthermore, the potency of active *α*-methyl isomer **32** was almost an order of magnitude improved relative to its *des*-methyl congener **9** (hGlyR*α*3*β* mEC$_3$ = 0.025 vs 0.2 *μ*M) with an in vitro PK profile of **32** similar to that of **9** (MDCK P_{app} (av), 43.1; MDR1 ER, 1.6; HLM, MLM CL_{int}, 83, 254 *μ*L/min/mg). Two-dimensional NMR studies (ROESY and HMBC) indicated that the active analogue possessed a methyl *β* to the carbonyl which projected into the concave face of the tricyclic ring system.[31] Molecular modeling studies indicated that in addition to reducing the rotational freedom of the sulfonamide, the *α*-methyl substitution caused the structure to favor a different orientation of the tricycle, which we hypothesized to be the active binding conformation. For the *des*-methyl analogue **9**, the analogous conformation was found to be 3.08 kcal above its global minima (Figure 5).[32,33]

Toward enhancing our understanding of the binding properties of our molecules, we developed a surface plasmon resonance (SPR) assay using the crystallographic construct of human GlyR*α*3 channels.[27,34] The binding values we obtained

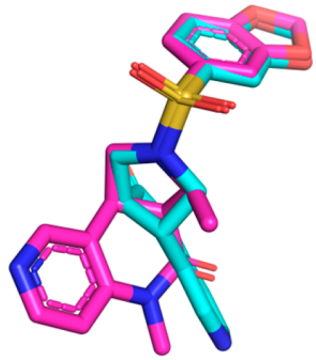


Figure 5. Overlay of global minima conformations of **32** (magenta) and **9** (cyan). Figures generated using PyMOL (The PyMOL Molecular Graphics System, version 1.7.05, Schrödinger, LLC).

were in good agreement with our measured cell-based assay potency for active leads and their less active isomers (Table 5), supporting that the compounds act through direct binding to the GlyR receptors. Furthermore, a 17-fold improved K_D is observed for **32** over **20**, consistent with the measured GlyRa3 EC_{50} values.

The X-ray cocrystal structure of **32** in complex with human GlyR*α*3 in the presence of the native agonist glycine was solved

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

Table 5. SPR Data for Active Leads and Their Less Active Isomers

compd	hGlyRα3 EC_{50} (μM)	SPR hGlyRα3 K_D[a] (μM)
20	0.45	0.19 ± 0.03
(*ent*)-**20**	>25	>20
32	0.050	0.011 ± 0.005
30	>25	>20

[a]Values are an average of three measurements with SEM values.

at high resolution (2.6 Å) (Figure 6).[27] This represented the first public disclosure of a potentiator-bound X-ray cocrystal structure with a human glycine receptor. **32** is bound in a novel induced-pocket and adopts a conformation very close to its calculated global minima conformation (0.05 kcal/mol difference).[35] The structure indicates H-bonding interactions with the sulfonamide and amide carbonyl groups (water-mediated) as well as hydrophobic interactions with the benzodioxolane, pyrrolidine−naphthyridinone core, and methyl groups. The ligand is bound at the interface between each of the five α-subunit protomers in the extracellular domain and in close proximity to bound glycine (10 Å away), which is in the canonical orthosteric ligand binding pocket. It was shown that upon binding of **32**, the GlyRα3 protein adopts a conformation which stabilizes glycine, thereby increasing binding affinity. The binding interactions identified in the X-ray crystal structure supported our SAR observations and design hypotheses. For example, the aza-naphthyridone carbonyl is engaged in a water-mediated hydrogen bond and removal of the carbonyl abolished activity (data not shown). Further, the nitrogen of the pyridine ring of the aza-naphthyridone is pointed toward the solvent, supporting the substitutional tolerance for both polar (aza (**32**), hydroxy (**5**)) and nonpolar substituents (fluoro, **7**). The pyridine ring nitrogen of aza-naphthyridones **10** and **11** are exposed to the hydrophobic binding pocket, explaining their significantly diminished activities.

CHEMISTRY

For the majority of the analogues described, a general route toward the tricyclic amine penultimate core was employed. The sequence began with either commercial or prepared quinolinones or naphthyridones (Scheme 1). The noncommercial 3-ethyl-carboxyl-quinolone and naphthyridone intermediates **34** were accessed by Friedlander synthesis of 2-formyl or 2-acetyl anilines with ethyl malonate.[36] The 3-cyano naphthyridone variant (**35**) was prepared under similar conditions with the anion of methyl 2-cyanoacetate as the nucleophile. The preparation of 3-fluoro-*N*-methyl-naphthyridone **37** began with S_NAr of 4-chloronicotinaldehyde with methyl amine providing 4-methylamino-pyridine **36**. Subsequent Horner−Wadsworth−Emmons olefination with the ylide generated upon deprotonation of ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate followed by intramolecular cyclization of the *E*-olefin isomer provided **37**.

The general sequence utilized to access tricyclic pyrrolidine cores is described in Scheme 2 and was inspired by established routes for the known tricycle core of **41a**.[37,38] Substituted and modified quinolinones (**34** or **35**) were *N*-methylated with iodomethane in the presence of cesium carbonate in DMF to give **38**. The key step was a [3 + 2] dipolar cycloaddition of **38** with the azo-methine ylide generated from the treatment of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine with TFA. This reliably provided tricyclic *N*-benzyl pyrrolidines **39** as the racemic syn isomers in generally good yields. In the synthesis of **39c**, the [3 + 2] dipolar cycloaddition and amide *N*-methylation steps were reversed.[27] Ester hydrolysis and decarboxylation under acidic conditions afforded **40**, and benzyl hydrogenolysis with catalytic palladium hydroxide furnished the penultimate tricyclic pyrrolidine core structure **41**. Because of the sensitivity of the nitrile functionality (R^3 = CN) under reductive conditions, a two-step, one pot debenzylation sequence was employed. Urethane formation by treatment with vinyl carbonochloridate and subsequent debenzylation of the formed salt was followed by urethane hydrolysis under acidic conditions to provide the α-cyano tricyclic core **41f**.

The syntheses of the α-methyl ring fusion, 4-cyano, and 4-hydroxy modified pyrrolidine cores employed late stage functionalization of the ring system (Scheme 3). Pyrrolidine nitrogen protecting group swap from benzyl to *tert*-butyl carbonate (Boc) under standard conditions provided **42**. Treatment with sodium hydride and excess iodomethane affected methylation of both the quinolinone nitrogen and the ring fusion carbon α to the carbonyl, affording α-methylated core tricycle **44**, following acid-mediated *N*-boc cleavage. Toward 4-substituted tricyclic core structures, the *N*-methylated tricycle of **42** was then regiospecifically brominated in the presence of *N*-bromosuccinimide to give **43**, which was cyanated under palladium-mediated conditions to furnish cyano substituted core **45**. The brominated intermediate **43** was alternatively converted to boronate ester **46** and subsequently oxidized with hydrogen peroxide and sodium hydroxide to hydroxylated core tricycle, then treated with HCl in dioxane to cleave the *N*-boc group and afford tricyclic amine intermediate **47**.

The syntheses of the 4-fluoro and 5-aza tricyclic pyrrolidine cores began with Still−Gennari modified Horner−Wads-

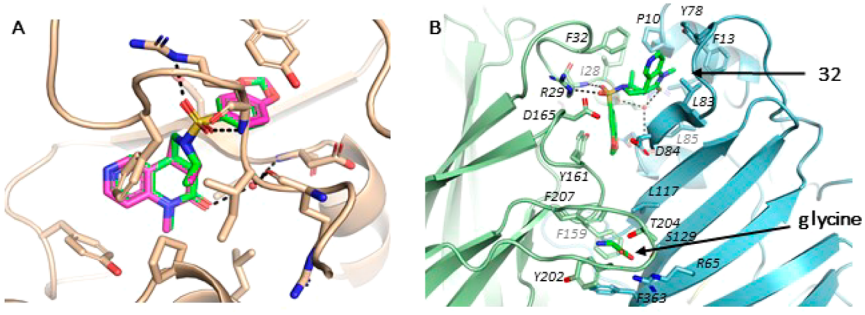
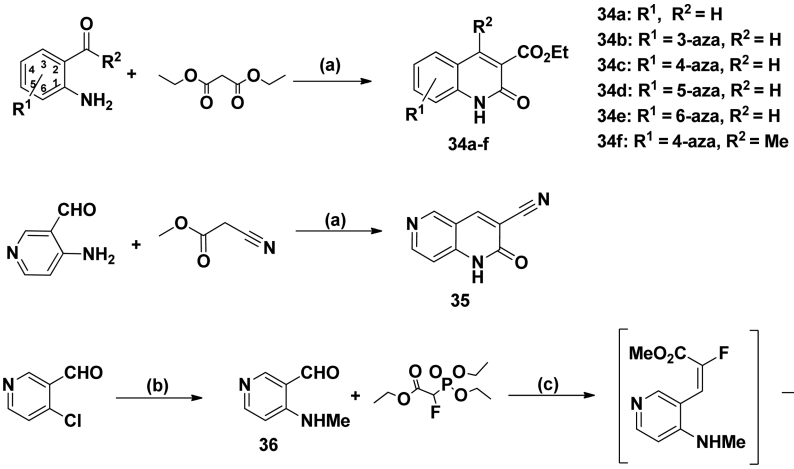


Figure 6. (A) Potentiator binding pocket in human GlyRα3. The bound conformation of **32** (green) is overlaid with the calculated minimum energy conformation (magenta). (B) X-ray of potentiator **32** and glycine bound to GlyRα3 (PDB codes: 5TIO and 5TIN).

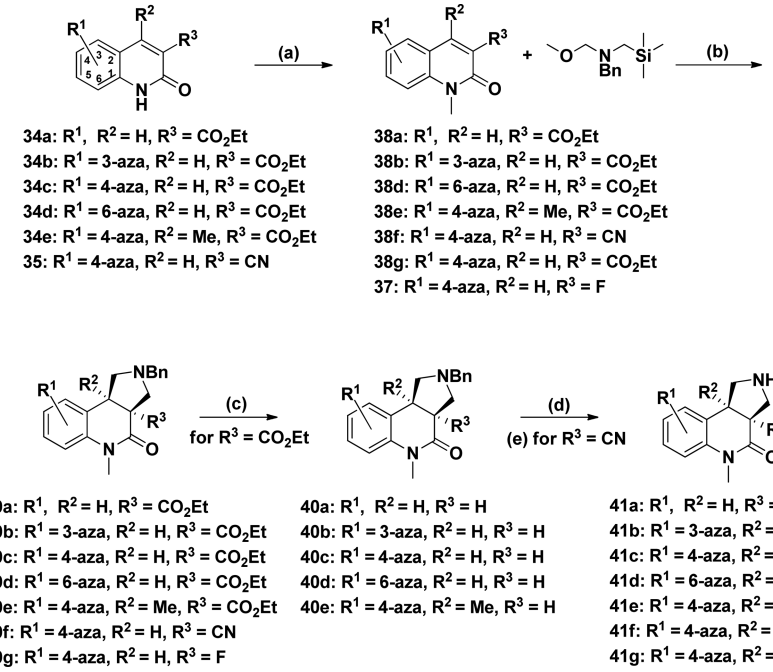
DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Preparation of Quinolinone and Naphthyridone Intermediates[a]



[a](a) piperidine, EtOH, reflux, 50−98%; (b) NH_3Me (40% in H_2O), MeOH−EtOH, 120 °C, sealed tube, 48%; (c) (i) NaH, ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate, THF, (ii) aldehyde **36**, 21%.

Scheme 2. Preparation of Tricyclic Pyrrolidine Cores[a]



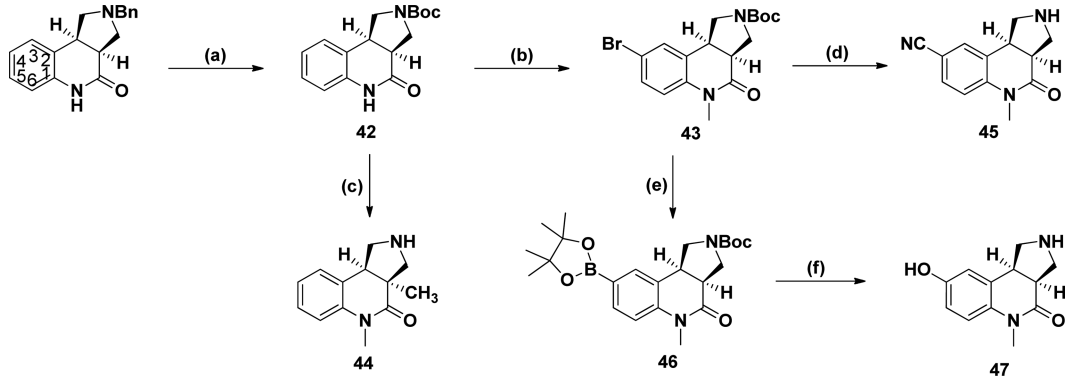
[a](a) Cs_2CO_3, MeI, DMF, 36−100%; (b) TFA, CH_2Cl_2, 52−100%, 18% for **39e**; (c) HCl (aq), 100 °C, 78−100%; (d) $Pd(OH)_2$, H_2, EtOH:H_2O (5 or 10:1), 40 psi, 40−60 °C, 83−100%; (e) (i) vinyl carbonochloridate, DCM, 0 °C−rt, (ii) EtOH, 6 N HCl, 100 °C, 70%.

worth−Emmons olefination of 2-nitro-4-fluoro benzaldehyde, affording olefin **48** as a mixture of *E* and *Z* isomers (4:1). Dipolar [3 + 2] cycloaddition of **48** with *N*-benzyl azo-methine ylide afforded *N*-benzyl pyrrolidine ester **49** (Scheme 4). Nitro reduction and intramolecular cyclization afforded tricyclic cores **50**, which were either methylated at the quinolone nitrogen via a protection, methylation, deprotection sequence to furnish penultimate 4-fluoro tricyclic core **51** or first sulfonylated at the secondary amine, then *N*-methylated to afford 5-aza analogue **10**.

The initial route toward α-methyl-pyrrolidine tricyclic pyrrolidine cores followed a very similar synthetic route as described for *des*-methyl pyrrolidine cores (Scheme 5). The known methylated azo-methine ylide precursor **53** was prepared following a published two-step protocol.[39] Alkylation of neat benzyl amine with (1-chloroethyl)trimethylsilane at 180 °C provided ethyl trimethylsilyl secondary amine **52**, which was then converted to an imminium salt by treatment with formaldehyde in the presence of potassium carbonate and trapped by methanol to afford **53**. This sensitive intermediate was used crude and in the presence of TFA decomposed to an azo-methine ylide which underwent dipolar [3 + 2] cycloaddition with naphthyridone **38g** to provide α-methyl-*N*-benzyl pyrrolidines as an 1:8:8:1 mixture of racemic stereoisomers. Cleavage of the *N*-benzyl group under standard hydrogenolysis conditions provided α-methyl-pyrrolidine tricyclic intermediate **54** as a mixture of stereoisomers. As described earlier, only one of the minor isomeric intermediates ((*rac*)-*cis*-**54d**) of this

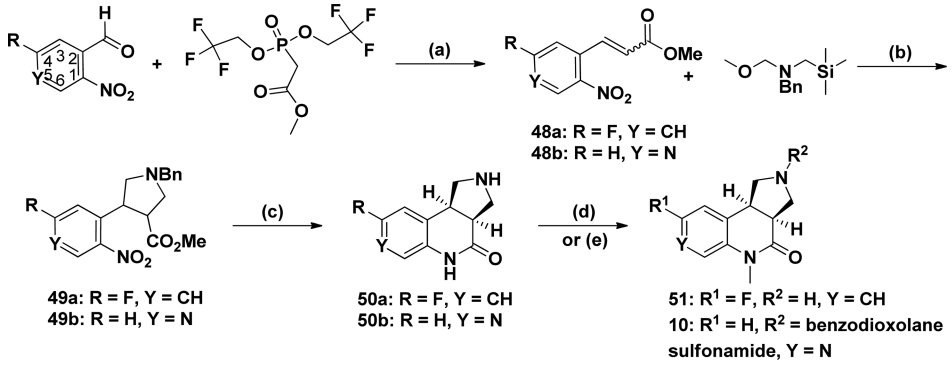
DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

Scheme 3. Preparation of α-Methyl Ring Fusion and 4-Cyano and 4-Hydroxyl Tricyclic Pyrrolidine Cores[a]



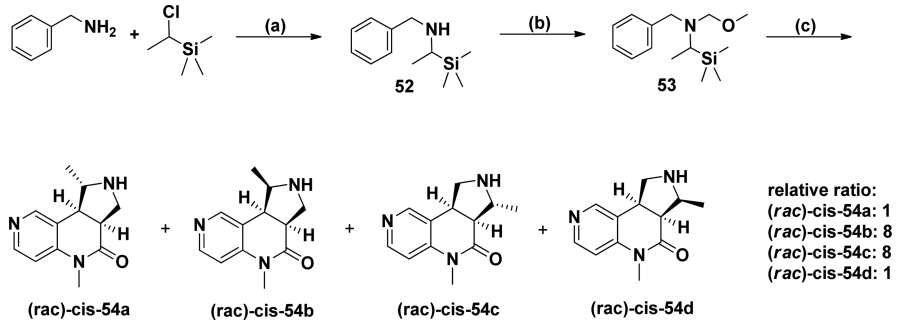
[a](a) Pd/C (10%), $Pd(OH)_2$, $(Boc)_2O$, H_2, EtOH, 50 psi, 96%; (b) (i) NaH, MeI, DCE, 59%, (ii) NBS, DCM, 92%; (c) (i) NaH, MeI, (ii) HCl in MeOH; (d) (i) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 100 °C, (ii) HCl/dioxane, 100%; (e) $(Bpin)_2$, $PdCl_2(dppf)$, KOAc, dioxane, 90 °C, 100%; (f) (i) H_2O_2, NaOH, THF/H_2O, (ii) HCl/dioxane, 60%.

Scheme 4. Preparation of 4-Fluoro Tricyclic Core and 5-Aza Tricyclic Core Analogue 10[a]



[a](a) K_2CO_3, 1,4-dioxane, 93% for **48a**, 24% for **48b**; (b) TFA, DCM, 87% for **49a**, 100% for **49b**; (c) (i) $Pd(OH)_2$ or Pd/C, H_2, EtOH, 60 °C, 55 psi, 100%, (ii) AcOH, 80 °C (for **49b** only), 99% (d) (i) $(Boc)_2O$, Et_3N, EtOH, (ii) NaH, MeI, DMF, (iii) HCl/dioxane, 56%; (e) (i) benzo[*d*][1,3]dioxole-5-sulfonyl chloride, Et_3N, DCM, (ii) NaH, MeI, DMF, 2%.

Scheme 5. Initial Route Towards Isomeric Mixture of α-Methyl Pyrrolidine Tricyclic Core[a]



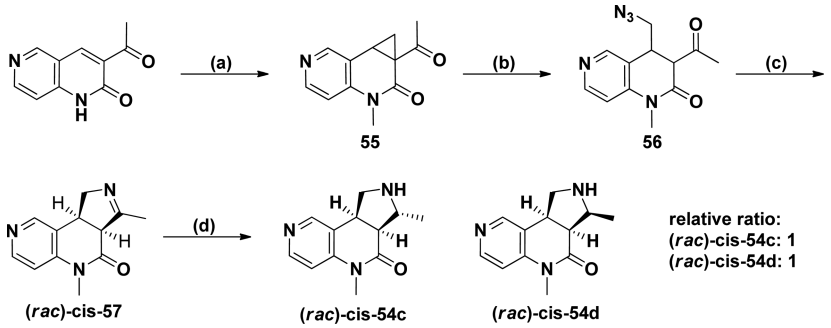
[a](a) Neat, 180 °C; (b) CH_2O (aq), K_2CO_3, MeOH; (c) (i) **38g**, TFA, DCM, 33%, (ii) 3 N HCl:dioxane (2:3), 90 °C, (iii) $Pd(OH)_2$, H_2, EtOH:H_2O (10:1), 40 °C, 40 psi, 96%, (over 2 steps).

mixture led to highly potent sulfonamide **32**. A revised synthesis was therefore developed to improve the relative yield of the active diastereomer (*rac*)-*cis*-**54d** (Scheme 6).

The complex isomeric mixture of methylated pyrrolidines was a result of both constitutional isomers (methyl group at either α-pyrrolidine position) and stereoisomers (methyl group projected into either the concave or convex face of tricyclic ring system). The active isomer contained a methyl group proximal to the carbonyl group and projected into the concave face of the ring system. By starting with a surrogate for the methyl group already present at the desired position, the regioisomer of choice would ultimately be prepared. Accordingly, commercial 3-acetyl-1,6-naphthyridin-2(1*H*)-one was *N*-methylated, then cyclopropanated under Corey–Chaykovsky[40] conditions with the ylide of trimethylsulfoxonium iodide to afford **55** (Scheme 6). Cyclopropane ring opening at the least sterically hindered carbon by sodium azide provided azide **56**. The crude azide was reduced with triphenylphosphine and the liberated amine condensed intramolecularly with the acetyl ketone to provide imine **57** as a racemic mixture of *cis*-

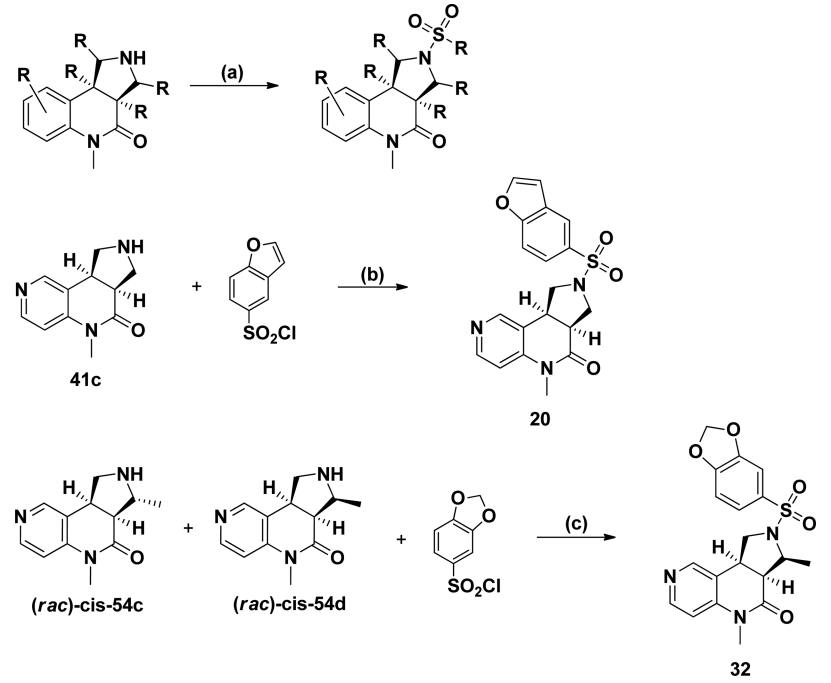
DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

Scheme 6. Improved Route Towards Isomeric Mixture of α-Methyl Pyrrolidine Tricyclic Core[a]



[a](a) (i) MeI, Cs_2CO_3, DMF, 51%, (ii) NaH, trimethylsulfoxonium iodide, THF, DMSO; (b) NaN_3, Et_3N, AcOH, DMF, 70 °C; (c) PPh_3, acetone, 60 °C; (d) $NaBH_4$, MeOH/DCE, (30% over 4 steps).

Scheme 7. Synthesis of Sulfonamides[a]



[a](a) Sulfonyl chloride, triethylamine, CH_3CN; (b) triethylamine, CH_3CN, 54%; (c) (i) triethylamine, CH_3CN, 75%, (ii) chiral SFC purification.

pyrrolidines. Compound **57** was susceptible to isomerization and oxidation to the pyrrole upon prolonged exposure to air. Reduction of the **57** with sodium borohydride afforded a 1:1 mixture of concave:convex methyl diastereomers, providing the penultimate racemic tricyclic intermediates ((*rac*)-*cis*-**54c** and (*rac*)-*cis*-**54d**). This route afforded improved relative ratio of the desired methylated tricyclic core with 25% of the desired single enantiomer as compared to 3% for the initial route.

The described tricyclic sulfonamides were prepared under the same general conditions, as generically depicted in Scheme 7. Sulfonylation was accomplished with sulfonyl chloride in the presence of triethylamine in acetonitrile. Either specific isomers or isomeric mixtures of tricyclic penultimate core intermediates were used in analogue synthesis. For example, the single active enantiomer of **41c** was used in the synthesis of **20** and the mixture of (*rac*)-cis-**54c** and (*rac*)-*cis*-**54d** was used toward the synthesis of **32**, which was obtained as a single enantiomer following chiral SFC purification. The relative and absolute configurations of the active species are as drawn in the schemes and were determined by two-dimensional NMR (ROESY and HMBC) and the described X-ray cocrystal structure, respectively.

CONCLUSION

Herein, we have detailed the discovery and synthesis of a novel class of orally available and CNS-penetrant tricyclic sulfonamides as selective allosteric potentiators of glycine receptors. Our property-guided hit-to-lead efforts delivered proof-of-concept ex vivo tool compound **3**, which potentiated postsynaptic currents in mouse spinal neurons of the dorsal horn, and in vivo tool molecule **20**, which demonstrated oral efficacy in a mouse spared-nerve injury model of neuropathic pain. Concurrent systematic exploration of the effects of core methylation on functional activity and binding affinity delivered highly potent ligand **32**, which facilitated the generation of the first potentiator-bound hGlyRα3 X-ray cocrystal structure to date. An efficient and scalable synthetic route to provide the penultimate methylated tricyclic intermediate (*rac*)-*cis*-**54d** was developed. This work provided methods and tools suitable for

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

the further investigation of the biology of GlyRs and the generation of GlyR modulators with improved drug-like properties.

EXPERIMENTAL SECTION

Functional Testing in FLIPR Assay. HEK293T cells expressing human GlyR$\alpha3\beta$ were cultured in T 225 cm^2 culture flasks under standard cell culture conditions of 37 °C, 5% v/v CO_2, and 95% humidity until 80−90% confluent. Prior to the assay, cells are harvested by briefly washing with DPBS followed by addition of TrypLE cell dissociation reagent for 2 min. Cells were then quantified using a ViCell and subsequently diluted in Cell Plating Media to achieve a plated cell density of ∼12000 cells/well. Using a Multidrop Combi, 25 μL of cell suspension was dispensed into Corning CellBIND 384-well ViewPlates and then incubated at 37 °C overnight under the standard cell culture conditions described above. The next day (∼18−24 h after plating), 5 μL of 6× Membrane Potential (MP) blue dye was dispensed into each cell culture plate using a Multidrop Combi. The cell plates were then incubated at 37 °C for 30 min and then allowed to equilibrate to room temperature for an additional 30 min prior to running the assay.

The membrane potential dye assay was performed on the FLIPR Tetra. The net membrane potential of the cells changes upon activation of GlyR$\alpha3\beta$, resulting in the increased flux of Cl^- ions out of the cell down a concentration gradient and a robust increase in fluorescence signal. All measurements were made using an exposure time of 0.4 s, 510−545 nm/565−625 nm excitation/emission filter set, excitation intensity of 40%, and camera gain of 50.

To examine the ability of compounds to directly activate GlyR$\alpha3\beta$ as agonists, dose−response plates of compound were prepared at 4× in assay buffer (10 mM Hepes, 60 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 1 mM $CaCl_2$, 10 mM D-glucose, 160 mM D-mannitol, pH 7.4) using a 1:2 stepwise dilution series of compounds in standard 384-well polypropylene plates. In a first addition step, 10 μL of 4× compound was transferred to a cell plate containing MP blue dye and fluorescence response (agonism) was measured for 2 min. Potentiation of GlyR$\alpha3\beta$ was measured in a subsequent addition step by transferring 10 μL of 5× EC_{10} glycine to the cell plate and monitoring fluorescence changes for 4 min. The maximum concentration of compound in this assay is 20 μM.

Schild assays were used to visualize the modulation of glycine potency by each compound. Glycine dose−response plates were prepared at 4× in assay buffer using a 1:2 stepwise dilution series in standard 384-well polypropylene plates. In this assay format, glycine and compound were premixed, simultaneously delivered to cells, and responses measured for 4 min. Glycine potency was then determined in the presence of varying concentrations of compound.

All FLIPR kinetic traces were processed using an area under the curve relative to baseline (AUC-BL) algorithm, where the baseline was the first 10 s of the kinetic measurement prior to a fluorescence change. Compound potencies were determined by normalizing responses to percent of control (POC) using the maximum achievable glycine response and baseline EC_{10} glycine response as references. POC normalized data were then plotted against log [compound], and data were fit to a nonlinear regression four-parameter Hill fit to determine the EC_{50}. All curve fitting was performed with the GraphPad Prism 6 software. Schild assay dose response curves for glycine were analyzed in a similar manner.

For human and mouse GlyR$\alpha3$ dose response assay protocols, surface plasmon resonance, off-target profiling, and X-ray crystallography protocols, see Huang et al.[27]

Mouse Spared Nerve Injury Model. Adult male C57BL/6 mice weighing 20−30 g were cared for in accordance to the Guide for the Care and Use of Laboratory Animals, eighth edition (National Research Council Committee for the Update of the Guide for the Care and Use of Laboratory Animals, 2011). Animals were housed at an Association for Assessment and Accreditation of Laboratory Animal Committee accredited facility in nonsterile ventilated microisolator housing. All research protocols were approved by the Institutional Animal Care and Use Committee. For protocol see Huang, Shaffer, DiMauro, Gingras et al.[27]

CL_{int} Determinations. CL_{int} was determined by spiking drug into a mixture of 0.25 mg/mL mouse liver microsomes, 1 mM reduced nicotinamide adenine dinucleotide phosphate, and 5 mM MgCl in 100 mM potassium phosphate buffer, pH 7.4, and incubating for various time points up to 40 min.

Passive Permeability Determinations. Bidirectional transport across Madin−Darby canine kidney cells transfected with control vector (VC-MDCK), human *MDR1* gene (MDR1-MDCK) and human *ABCG2* gene (BCRP-MDCK) was measured in triplicate at 5 μM. Average apparent permeability value (P_{app}) of both directions from VC-MDCK was used as passive permeability.

General Chemistry. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were obtained from Aldrich and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. Purity and reaction analyses were measured using Agilent 1100 series high performance liquid chromatography (HPLC) systems with UV detection at 254 and 215 nm (System A: Agilent Zorbax SB-C18 3.0 mm × 50 mm, 3.5 μm, 5−95% CH_3CN in H_2O with 0.1% TFA for 3.6 min at 1.5 mL/min or Halo Phenyl−Hexyl, 3 mm × 50 mm, 2.7 μm, 5−95% CH_3CN in H_2O with 0.1% TFA for 1.01 min at 2.0 mL/min. System B: Waters Xbridge C18, 3 mm × 50 mm, 3.5 μm, 5−95% CH_3CN in H_2O with 0.1% formic acid for 3.6 min at 1.5 mL/min.). Purities for final compounds were >95%. Exact mass confirmation was performed on an Agilent 1200 series high performance liquid chromatography (HPLC) system (Santa Clara, CA, U.S.) by flow injection analysis, eluting with a binary solvent system A and B (A, water with 0.1% FA; B, ACN with 0.1% FA) under isocratic conditions (50% A/50% B) at 0.2 mL/min with MS detection by an Agilent 6510-Q time-of-flight (TOF) mass spectrometer (Santa Clara, CA, U.S.). Silica gel chromatography was generally performed with prepacked silica gel cartidges (Biotage, Teledyne-Isco or Interchim). Chiral method development performed on an analytical Thar SFC/MS. Preparative chiral separations performed on Thar SFC Prep 80 or SFC Prep 350 instruments. Library purification methods: Preparative LC/MS, Waters autopurification system; liquid transfer system, Tecan; drying system, Genevac; prep. column: Xbridge (19 mm × 100 mm, C18, 10 μm); flow rate, 40 mL/min; general gradient, 5−95% B, 0.1% additive in both A and B; 10 min gradient. Mobile phase A, water; mobile phase B, acetonitrile; additive, TFA or NH_4OH. ^1H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer or a Varian 400 MHz spectrometer at ambient temperature, or the NMR spectra were collected with a Bruker Avance III spectrometer operating at a proton frequency of 500.13 MHz using a 10 mL Protasis CapNMR flow probe. NMR samples were delivered to the flow probe using a Protasis One-Minute NMR automation system comprised of a Discovery Tower Sample Manager and a Waters Liquid Handler is made by CTC, Switzerland (model 2777). All observed protons are reported as parts per million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Low-resolution mass spectral (MS) data were determined on an Agilent 1100 series LCMS with UV detection at 254 and 215 nm and a low resonance electrospray mode (ESI).

Chirality Naming Convention. Racemic mixtures are denoted with a "*rac*" chemical name prefix and refer to racemic mixtures of "cis" 5,6-ring fusions.

General Procedure for Sulfonylation. To a solution of the amine in DMF or MeCN was added the sulfonyl chloride at 0 °C followed by dropwise addition of triethylamine at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The resulting DMF suspension was filtered through a 0.45 μm frit. (When MeCN was the reaction solvent, the mixture was concentrated and the residue was suspended in DMF before filtration.) The filtrate was purified with RP-HPLC ramping ACN in H_2O, NH_4OH 0.1% to afford the

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

corresponding sulfonamide. Normal phase MPLC purification was alternately employed in some cases using EtOAc:EtOH (76:24) or EtOAc in heptane.

Synthesis of Intermediate (3a*R*,9b*R*)-5-Methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (41c).[27] Chiral separation conditions of **41c**. Note: This chiral separation was conducted on the free-base. The sample was processed using the following SFC conditions: column, Chiralpak AD, 5 μm, 2 cm i.d. × 15 cm length; flow rate, 80 mL/min; mobile phase, 60% methanol w/0.2% diethylamine, 40% CO_2; back pressure setting, 100 bar; sample dissolution, 60 g dissolved in 800 mL of methanol; injection volume, 1.75 mL. Analysis: column, Chiralpak AD, 5 μm, 4.6 mm × 100 mm; flow rate, 5 mL/min; mobile phase, 50% methanol w/0.2% diethylamine, 50% CO_2; back pressure setting, 100 bar. Peak 1 = (3a*S*,9b*S*)-**41c**.

(3a*S*,9b*S*)-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-one (3) and (3a*R*,9b*R*)-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-one (4). To a solution of **41a**[37,38] (0.204 g, 0.855 mmol) in DMF (8.55 mL) was added triethylamine (0.119 mL, 0.855 mmol). The mixture was stirred at rt for 5 min. Then 1,3-benzodioxole-5-sulfonyl chloride (0.207 g, 0.940 mmol) was added at 0 °C followed by dropwise addition of triethylamine (0.238 mL, 1.709 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The resulting mixture was diluted with water and extracted with DCM twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure. The crude material was adsorbed onto a plug of silica gel and purified by chromatography, eluting with a gradient of 0−50% EtOAc in heptane, to provide the racemic mixture of **3** and **4** (0.283 g, 0.732 mmol, 86% yield) as white solid. This solid was subjected to chiral resolution. Chiral SFC conditions: Chiralcel OJ, 2 cm × 15 cm, 30% methanol w/0.2% DEA, 80 mL/min, pressure drop = 54 bar, 254 nm detection, Sample dissolved in 20 mL of DCM:MeOH (1:1). Sample processed with 1 mL injection volume and cycle time of 2.5 min. Peak assignment determined by SFC on Chiralcel OJ with 30% methanol w/0.2% diethylamine modifier. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 1 = **3** (98 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25−7.37 (m, 4H), 7.07−7.12 (m, 2H), 7.07−7.14 (m, 2H), 7.01−7.06 (m, 1H), 6.15−6.25 (m, 2H), 3.89−3.96 (m, 1H), 3.63−3.71 (m, 1H), 3.44−3.52 (m, 2H), 3.18 (s, 4H), 2.78−2.89 (m, 1H). MS (ESI) m/z 387.0 $(M + H)^+$ HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_6S$ $(M + H)^+$ 387.1015; found 387.1021. Peak 2 = **4** (148 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24−7.38 (m, 4H), 7.08−7.12 (m, 2H), 7.01−7.07 (m, 1H), 6.16−6.23 (m, 2H), 3.86−3.95 (m, 1H), 3.62−3.70 (m, 1H), 3.45−3.53 (m, 2H), 3.18 (s, 4H), 2.80−2.88 (m, 1H). MS m/z (ESI) 387.0 $(M + H)^+$. HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_6S$ $(M + H)^+$ 387.1015; found 387.1012.

(3a*S*,9b*S*)-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-8-hydroxy-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-one (5). *Step 1: rac-(3aR,9bR)-tert-Butyl 8-Bromo-5-methyl-4-oxo-3,3a,4,5-tetrahydro-1H-pyrrolo[3,4-c]quinoline-2(9bH)-carboxylate (**43**).* To a solution of **42** (1.005 g, 3.49 mmol) in DMF (17.43 mL) at 0 °C was added sodium hydride, 60% suspension in mineral oil (0.137 g, 3.42 mmol). The mixture was stirred at rt for 30 min. Iodomethane (0.217 mL, 3.49 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with satd NH_4Cl at 0 °C, then stirred at rt for 30 min and extracted with EtOAc 3 times. The combined organics were washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated on vacuo to give 1.1 g of an off-white solid. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column 40g, eluting with a gradient of 0−35% EtOAc in heptane, to provide *rac*-(3aR,9bR)-*tert*-butyl 5-methyl-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-2(9b*H*)-carboxylate (0.617 g, 2.041 mmol, 59% yield) as colorless solid; m/z (ESI) 325.2 $(M + Na)^+$. To a 100 mL round-bottom flask was added *rac*-(3a*R*,9b*R*)-*tert*-butyl 5-methyl-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo-[3,4-*c*]quinoline-2(9b*H*)-carboxylate (2.0730 g, 6.86 mmol) and *N*-bromosuccinimide (0.584 mL, 6.86 mmol) in dichloroethane (34.3 mL). The resulting yellow solution was stirred at room temperature for 36 h. The mixture became a yellow suspension. The solvent was removed under reduced pressure. The resulting residue was partitioned between EtOAc and 2 N NaOH. The aqueous layer was extracted with EtOAc twice. The combined organics were washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure to provide a yellow solid. The crude material was adsorbed onto a plug of silica gel and purified by chromatography through a Redi-Sep prepacked silica gel column 40g, eluting with a gradient of 10−40% EtOAc in heptane, to provide **43** (2.406 g, 6.31 mmol, 92% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (d, J = 2.28 Hz, 1H), 7.49 (dd, J = 2.15, 8.68 Hz, 1H), 7.10 (d, J = 8.71 Hz, 1H), 3.90−4.08 (m, 1H), 3.58−3.77 (m, 2H), 3.49 (dt, J = 6.63, 10.65 Hz, 1H), 3.29 (s, 3H), 2.81−2.94 (m, 1H), 1.32−1.46 (m, 10H). MS (ESI) m/z 325.2 $(M - tBu + H)^{+1}$.

*Step 2: rac-tert-Butyl 5-Methyl-4-oxo-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,3a,4,5-tetrahydro-1H-pyrrolo[3,4-c]-quinoline-2(9bH)-carboxylate (**46**).* A reaction vessel was charged with **43** (0.518 g, 1.359 mmol), bis(pinacolato) diboron (0.690 g, 2.72 mmol), 1,1′-bis(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane adduct (0.044 g, 0.054 mmol), and potassium acetate (0.400 g, 4.08 mmol), then sealed. The vial was evacuated and backfilled with nitrogen twice prior to the addition of 1,4-dioxane (6.79 mL). The reaction mixture was stirred at 90 °C for 3.5 h. The resulting mixture was diluted with EtOAc and filtered. The filtrate was concentrated to give a dark oil. The crude material was purified with silica gel chromatography eluting with a gradient of 15−30% EtOAc in heptane, to provide **46** (0.712 g, 1.662 mmol, quantitative) as a white solid. MS (ESI) m/z 372.2 $(M - tBu + H)^+$.

*Step 3: rac-(3aS,9bS)-8-Hydroxy-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]quinolin-4(2H)-one (**47**).* A solution of **46** (0.205 g, 0.479 mmol) in THF (8 mL), water (2.3 mL), and 1 N NaOH (2.39 mL, 2.393 mmol) was treated with hydrogen peroxide solution (30%, w/w) (0.543 g, 4.79 mmol) at 0 °C. The resulting mixture was allowed to stir and warm to room temperature over 2 h. The resulting mixture was quenched by the addition of saturated NH_4Cl. Then 1 mL of 1 N HCl was added to adjust the pH to 4. The mixture was extracted with EtOAc 3 times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure to afford *rac-tert*-butyl 8-hydroxy-5-methyl-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo-[3,4-*c*]quinoline-2(9b*H*)-carboxylate (0.209 g, 0.656 mmol, quantitative) as a colorless oil. MS (ESI) m/z 263.1 $(M - tBu + H)^{+1}$. *rac-tert*-Butyl 8-hydroxy-5-methyl-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-2(9b*H*)-carboxylate (105 mg) was dissolved in MeOH (1 mL), and 4 N HCl in dioxane (1 mL, 4 mmol) was added. The reaction mixture was stirred at room temperature for 1h. The solvent was removed under reduced pressure to afford the HCl salt of **47** (0.073 g, 0.287 mmol, 59.9% yield). MS (ESI) m/z (ESI) 219.3 $(M + H)^+$

*Step 4: (3aS,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-8-hydroxy-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]quinolin-4(2H)-one (**5**).* To **47** (64 mg, 0.25 mmol) in DMF (2 mL) was added triethylamine (0.11 mL, 0.750 mmol) and benzo[*d*][1,3]dioxole-5-sulfonyl chloride (0.055 g, 0.250 mmol) following the general sulfonylation procedure to afford the racemic mixture of **5** (24 mg, 24% yield) which was subjected to chiral resolution. Chiral SFC conditions: Chiralpak AD-H, 2 cm × 15 cm, 45% methanol, 80 mL/min (column back pressure = 78 bar), 100 bar BPR, 255 nm; dissolution, 4 mL 1:1 MeOH:DCM. Peak assignment was determined by SFC on Column, AD-H; solvent, 45% methanol. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 2 = **5** (19 mg): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30−7.36 (m, 1H), 7.25−7.29 (m, 1H), 7.07−7.12 (m, 1H), 6.87−6.91 (m, 1H), 6.64−6.70 (m, 2H), 6.15−6.21 (m, 2H), 3.88−3.93 (m, 1H), 3.61−3.66 (m, 1H), 3.41−3.46 (m, 1H), 3.32−3.39 (m, 1H), 3.06−3.13 (m, 4H), 2.73−2.81 (m, 1H). MS (ESI) m/z (ESI)

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

403.0 $(M + H)^+$. HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_6S$ $(M + H)^+$ 403.0964; found 403.0959.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]quinoline-8-carbonitrile (6).** *Step 1: rac-5-Methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c]quinoline-8-carbonitrile (**45**).* To a 5 mL microwave vial was added **43** (0.165 g, 0.433 mmol), zinc cyanide (0.027 mL, 0.433 mmol), tetrakis(triphenylphosphine)palladium (0.050 g, 0.043 mmol), and DMF (2.164 mL). The solvent was purged with nitrogen for 5 min and sealed. The vessel was irradiated at 100 °C in a microwave oven for 1 h. The mixture was diluted with EtOAc and filtered. The filtrate was concentrated, and the crude material was purified with silica gel chromatography, eluting with a gradient of 0−40% EtOAc in heptane to provide *rac-tert*-butyl 8-cyano-5-methyl-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-2(9b*H*)-carboxylate as a yellow solid which was suspended in MeOH (4.5 mL) to which 4 N HCl in dioxane (2 mL, 8 mmol) was added. The suspension was stirred at room temperature overnight. The resulting mixture was concentrated to afford **45** as a hydrochloride salt (0.139 g, 0.527 mmol, quantitative) as a yellow solid which was used without further purification. MS (ESI) m/z 228.3 $(M + H)^+$

*Step 2: rac-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-5-methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c]quinoline-8-carbonitrile (**6**).* **45** (0.0685 g, 0.260 mmol) in DMF (2 mL) was treated with 1,3-benzodioxole-5-sulfonyl chloride (0.057 g, 0.260 mmol) and triethylamine (0.072 mL, 0.519 mmol) following the general sulfonylation procedure to afford **6** (17 mg, 16% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73−7.80 (m, 2H), 7.73−7.80 (m, 2H), 7.30−7.36 (m, 1H), 7.22−7.29 (m, 2H), 7.04−7.12 (m, 1H), 6.15−6.21 (m, 2H), 3.84−3.90 (m, 1H), 3.67−3.74 (m, 1H), 3.53−3.60 (m, 1H), 3.45−3.51 (m, 1H), 3.24−3.29 (m, 1H), 3.20 (s, 3H), 2.88−2.98 (m, 1H). MS (ESI) m/z (ESI) 412.1 $(M + H)^+$. HRMS (ESI) m/z calcd for $C_{20}H_{17}N_3O_5S$ $(M + H)^+$ 412.0967; found 412.0968.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-8-fluoro-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-one (7).** *Step 1: Methyl 3-(5-Fluoro-2-nitrophenyl)acrylate (**48a**).* A mixture of methyl *p*,*p*-bis(2,2,2-trifluoroethyl)-phosphonoacetate (10.74 mL, 29.6 mmol), 5-fluoro-2-nitrobenzaldehyde (5.0 g, 29.6 mmol), and potassium carbonate (8.19 g, 59.2 mmol) in 1,4-dioxane (233 mL) was refluxed overnight. The mixture was filtered, and the filtrate was concentrated. The residue was partitioned between water and EtOAc and extracted with EtOAc 3 times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure to afford **48a** (6.1 g, 93% yield) as a black solid. MS (ESI) m/z 226.1 $(M + H)^+$

*Step 2: Methyl 1-Benzyl-4-(5-fluoro-2-nitrophenyl)pyrrolidine-3-carboxylate (**49a**).* To a solution of **48a** (6.1 g, 27.1 mmol) in DCM (201 mL) at 0 °C under nitrogen flow was added trifluoroacetic acid (0.805 mL, 10.84 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (20.79 mL, 81 mmol). The resulting solution was stirred at rt overnight. The resulting mixture was diluted with satd aq $NaHCO_3$ and extracted with DCM twice. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of 10− 50% EtOAc/EtOH/NH_4OH (73:27:2) in heptane to provide **49a** (8.41g, 23.47 mmol, 87% yield) as a yellow oil. MS (ESI) m/z 359.1 $(M + H)^+$.

*Step 3: rac-8-Fluoro-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]-quinolin-4(2H)-one (**50a**).* A mixture of **49a** (8.41 g, 23.47 mmol), palladium hydroxide, 20 wt % Pd (dry basis) on carbon, and wet (0.8 g, 5.70 mmol) in EtOH (100 mL) was stirred at 60 °C under 55 psi of H_2 for 48 h. Additional palladium hydroxide, 20 wt % Pd (dry basis) on carbon, and wet (0.8 g, 5.70 mmol) was added. The mixture was stirred at 60 °C under 55 psi of H_2 for 3 additional days. The resulting mixture was filtered through Celite, and the filtrate was concentrated to provide **50a** (4.84 g, 23.47 mmol, quantitative) as a yellow solid, which was used without further purification. MS (ESI) m/z 207.2 $(M + H)^+$.

*Step 4: rac-8-Fluoro-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo-[3,4-c]quinolin-4(2H)-one (**51**).* A mixture of **50a** (4.84 g, 23.47 mmol), di-*tert*-butyl dicarbonate (7.68 g, 35.2 mmol), and triethylamine (6.53 mL, 46.9 mmol) in EtOH (235 mL) was stirred at rt overnight. The mixture was concentrated under reduced pressure, and the crude material was purified with silica gel chromatography eluting with a gradient of 0−50% EtOAc in heptane to provide *rac-tert*-butyl 8-fluoro-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-2-(9b*H*)-carboxylate (4.07 g, 13.29 mmol, 56.6% yield) as light-yellow solid. To a solution of *rac-tert*-butyl 8-fluoro-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-2(9b*H*)-carboxylate (1 g, 3.26 mmol) in DMF (16.32 mL) was added sodium hydride, 60% dispersion in mineral oil (0.131 g, 3.26 mmol) at 0 °C. The mixture was stirred at rt for 1 h prior to the addition of iodomethane (0.203 mL, 3.26 mmol). The reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford *rac-tert*-butyl 8-fluoro-5-methyl-4-oxo-3,3a,4,5-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-2(9b*H*)-carboxylate (1.3 g, 4.06 mmol, 124% yield) as a yellow oil which was dissolved in MeOH (10 mL). Hydrochloric acid, 4.0 M solution in 1,4-dioxane (10 mL, 40.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated to afford **51** (0.897 g, 3.49 mmol, quantitative) as a yellow solid which was used without further purification. MS (ESI) m/z 221.0 $(M + H)^+$.

*Step 5: rac-(3aR,9bR)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-8-fluoro-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]quinolin-4(2H)-one (**7**).* Compound **51** (0.072 g, 0.280 mmol) was dissolved in DMF (2 mL) and treated with 1,3-benzodioxole-5-sulfonyl chloride (0.062 g, 0.280 mmol) and triethylamine (0.117 mL, 0.841 mmol) following the general sulfonylation procedure to afford **7** (77 mg, 0.19 mmol, 68% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33 (dd, J = 1.69, 8.17 Hz, 1H), 7.27 (d, J = 1.62 Hz, 1H), 7.17−7.23 (m, 1H), 7.04−7.17 (m, 3H), 6.18 (d, J = 8.76 Hz, 2H), 3.87 (dd, J = 1.98, 10.02 Hz, 1H), 3.60−3.75 (m, 1H), 3.41−3.60 (m, 2H), 3.13−3.22 (m, 4H), 2.89 (t, J = 9.93 Hz, 1H). MS (ESI) m/z 405.0 $(M + H)^+$. HRMS (ESI) m/z calcd for $C_{19}H_{17}FN_2O_5S$ $(M + H)^+$ 405.0920; found 405.0921.

(6a*S*,9a*R*)-8-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-7,8,9,9a-tetrahydro-5*H*-pyrrolo[3,4-*c*][1,5]naphthyridin-6-(6a*H*)-one (8). *Step 1: Ethyl 2-Oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate (**34b**).* A mixture of 3-amino-pyridine-2-carbaldehyde (2 g, 16.38 mmol), diethyl malonate (4.97 mL, 32.8 mmol) and piperidine (0.404 mL, 4.09 mmol) in EtOH (27.3 mL) was refluxed for 18 h. The mixture was slowly cooled to rt with stirring and then filtered. The solid collected was washed with a small amount of EtOH and then with heptane to afford **34b** (2.246 g, 10.29 mmol, 62.9% yield) as a light-yellow solid. MS (ESI) m/z 219.2 $(M + H)^+$.

*Step 2: Ethyl 1-Methyl-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxylate (**38b**).* To a solution of **34b** (4.7 g, 21.54 mmol) in DMF (150 mL) was added sodium hydride, 60% dispersion in mineral oil (1.034 g, 25.8 mmol) portionwise at 0 °C. The reaction mixture was stirred at room temperature for 30 min. Iodomethane (1.405 mL, 22.62 mmol) was added dropwise via syringe. The reaction mixture was stirred at room temperature overnight. Additional iodomethane (0.1 mL) was added. After stirring at rt for 2 h, 5 mL of water was added and the resulting mixture stirred for 10 min. The solvents were removed under reduced pressure, and the resulting residue was suspended in water and extracted with DCM three times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure to afford 12 g of a green solid which was recrystallized from EtOAc to afford **38b** (3.55 g, 15.29 mmol, 71.0% yield). MS (ESI) m/z 233.1 $(M + H)^+$.

*Step 3: rac-Ethyl 8-Benzyl-5-methyl-6-oxo-6,6a,7,8,9,9a-hexahydro-5H-pyrrolo[3,4-c][1,5]naphthyridine-6a-carboxylate (**39b**).* To a solution of **38b** (3.55 g, 15.29 mmol) in DCM (113 mL) at 0 °C under N_2 was added trifluoroacetic acid (0.454 mL, 6.11 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (19.55 mL, 76 mmol). The resulting solution was stirred at rt overnight. The reaction mixture was diluted with satd aq $NaHCO_3$ and extracted with DCM twice. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

crude material was purified by silica gel chromatography eluting with a gradient of 10−50% EtOAc/EtOH/NH_4OH (73:27:2) in heptane to provide **39b** (5.70 g, 15.60 mmol, 102% yield) as light-yellow oil. MS (ESI) m/z 366.3 $(M + H)^+$.

*Step 4: rac-8-Benzyl-5-methyl-7,8,9,9a-tetrahydro-5H-pyrrolo-[3,4-c][1,5]naphthyridin-6(6aH)-one (**40b**).* A solution of **39b** (5.70 g, 15.60 mmol) in hydrochloric acid 6.0 N (130 mL, 780 mmol) was refluxed for 12 h. The mixture was concentrated under reduced pressure to afford **40b** (5.7 g, 15.56 mmol, quantitative) as an off-white solid. MS (ESI) m/z 294.4 $(M + H)^+$.

*Step 5: rac-5-Methyl-7,8,9,9a-tetrahydro-5H-pyrrolo[3,4-c][1,5]-naphthyridin-6(6aH)-one (**41b**).* A mixture of **40b** (5.7 g, 15.56 mmol) and palladium hydroxide, 20 wt % pd (dry basis) on carbon, wet (0.57 g, 0.812 mmol) in EtOH (50 mL), and water (10 mL) was stirred at 60 °C under 42 psi of H_2 for 12 h. The mixture was filtered through Celite and washed with water. The filtrate was concentrated to afford **41b** (4.32 g, 15.64 mmol, 101% yield) as an off-white solid which was used without further purification. MS (ESI) m/z 204.1 $(M + H)^+$.

*Step 6: (6aS,9aR)-8-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-5-methyl-7,8,9,9a-tetrahydro-5H-pyrrolo[3,4-c][1,5]naphthyridin-6(6aH)-one (**8**).* **41b** (0.3 g, 1.086 mmol) in MeCN (3.62 mL) was treated with benzo[*d*][1,3]dioxole-5-sulfonyl chloride (0.240 g, 1.086 mmol) and triethylamine (0.606 mL, 4.35 mmol) following the general sulfonylation procedure to afford a racemic mixture of **8** (0.2 g, 0.516 mmol, 47.5% yield). This was subjected to chiral resolution. Chiral SFC conditions: Chiralpak OJ-H, 2 cm × 25 cm, 25% methanol (0.1% DEA)/CO_2, 60 mL/min, 100 bar, 220 nm, inj vol 1.5 mL, 4 mg/mL 2:1 DCM/methanol. Peak assignment determined by SFC: Chiralpak OJ-H, 25% methanol w/0.2% diethylamine. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 1 = **8** (115 mg): ^1H NMR (400 MHz, DMSO-d_6) δ 8.12−8.16 (m, 1H), 7.46−7.50 (m, 1H), 7.30−7.35 (m, 2H), 7.25−7.26 (m, 1H), 7.06−7.09 (m, 1H), 6.18−6.21 (m, 2H), 3.58−3.64 (m, 3H), 3.53−3.57 (m, 1H), 3.46−3.52 (m, 1H), 3.34−3.38 (m, 1H), 3.18−3.21 (m, 3H), 3.18−3.20 (m, 3H). MS (ESI) m/z 388.1 $(M + H)^+$. HRMS calcd for $C_{18}H_{17}N_3O_5S$ $(M + H)^+$ 388.0967; found 388.0970.

(3a*S*,9b*S*)-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (9). To (3a*S*,9b*S*)-**41c** (0.073 M solution in MeCN (53 mL, 3.87 mmol) was added 1,3-benzodioxole-5-sulfonyl chloride (0.854 g, 3.87 mmol) followed by triethylamine (1.076 mL, 7.74 mmol). The reaction mixture was stirred at room temperature over 3 days. The mixture was concentrated under reduced pressure. The resulting residue was suspended in water and stirred for 30 min then filtered. The solid was washed with water and heptane successively. The solid was dried on vacuo to afford **9** (1.320 g, 3.41 mmol, 88% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.32−8.44 (m, 2H), 7.28−7.41 (m, 2H), 7.04−7.17 (m, 2H), 6.16−6.24 (m, 2H), 3.87−3.93 (m, 1H), 3.68−3.75 (m, 1H), 3.52−3.62 (m, 1H), 3.46−3.51 (m, 1H), 3.24−3.31 (m, 1H), 3.17 (s, 3H), 2.83−2.94 (m, 1H). MS (ESI) m/z 388.1 $(M + H)^+$. HRMS calcd for $C_{18}H_{17}N_3O_5S$ $(M + H)^+$ 388.0967; found 388.0963.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,7]naphthyridin-4(2*H*)-one (10).** *Step 1: (E)-Methyl 3-(3-nitropyridin-4-yl)acrylate (**48b**).* A mixture of 3-nitroisonicotinaldehyde (1 g, 6.57 mmol), methyl *p*,*p*-bis(2,2,2-trifluoroethyl)-phosphonoacetate (2.385 mL, 6.57 mmol) and potassium carbonate (1.817 g, 13.15 mmol) in 1,4-dioxane (51.8 mL) was refluxed overnight. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with satd aq $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and dried under reduced pressure. The crude material was purified with silica gel chromatography, eluting with a gradient of 20−50% EtOAc in heptane to provide **48b** (0.335 g, 1.609 mmol, 24.5% yield) as yellow solid. MS (ESI) m/z 209.1 $(M + H)^+$.

*Step 2: Methyl 1-Benzyl-4-(3-nitropyridin-4-yl)pyrrolidine-3-carboxylate (**49b**).* To a solution of **48b** (0.335 g, 1.609 mmol) in DCM (11.92 mL) at 0 °C under N_2 was added trifluoroacetic acid (0.048 mL, 0.644 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-benzylamine (2.059 mL, 8.05 mmol), and the resulting solution stirred at rt overnight. The mixture was diluted with satd $NaHCO_3$ and extracted with DCM twice. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of 0% to 40% EtOAc in heptane to provide **49b** (0.563 g, 1.649 mmol, quantitative) as yellow oil. MS (ESI) m/z 342.3 $(M + H)^+$.

*Step 3: rac-3,3a,5,9b-Tetrahydro-1H-pyrrolo[3,4-c][1,7]-naphthyridin-4(2H)-one (**50b**).* To a 100 mL pressure vessel was added **49b** (0.563 g, 1.649 mmol), EtOH (15 mL), and palladium 10 wt % on activated carbon (0.100 g, 0.940 mmol). The reaction mixture was stirred at 60 °C under 55 psi of H_2 overnight. Additional palladium 10 wt % on activated carbon (0.100 g, 0.940 mmol) was added. The reaction mixture was stirred at 60 °C under 55 psi of H_2 for an additional 48 h. The mixture was filtered through Celite and concentrated to afford 307 mg of a colorless oil. LCMS indicated complete hydrogenolysis but incomplete cyclization. The material was dissolved in AcOH (5 mL) and was stirred at 80 °C for 2 days. The resulting mixture was concentrated to provide a brown oil which was purified by strong cation exchange (SCX) catch and release by washing with MeOH, then eluting product with 2 M NH_3 in MeOH to afford **50b** (0.310 g, 1.638 mmol, 99% yield) as a yellow solid. MS (ESI) m/z 190.3 $(M + H)^+$.

*Step 4: rac-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,7]naphthyridin-4(2H)-one (**10**).* To a solution of **50b** (0.103 g, 0.544 mmol) in DCM (4 mL) was added 1,3-benzodioxole-5-sulfonyl chloride (0.120 g, 0.544 mmol) and triethylamine (0.151 mL, 1.089 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with water and extracted with EtOAc three times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified with silica gel chromatography eluting with a gradient of 0−80% EtOAc/EtOH/NH_4OH (73:17:2) in heptane to provide 2-(benzo[*d*][1,3]dioxol-5-ylsulfonyl)-3,3a,5,9b-tetrahydro-1*H*-pyrrolo-[3,4-*c*][1,7]naphthyridin-4(2*H*)-one (0.027 g, 0.072 mmol, 13% yield) as a tan solid. To this solid (0.027 g, 0.072 mmol) in DMF (1.45 mL) at 0 °C was added sodium hydride, 60% in mineral oil (2.89 mg, 0.072 mmol). The reaction mixture was stirred at room temperature for 30 min prior to the addition of iodomethane (4.49 μL, 0.072 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of a couple of drops of MeOH. The mixture was filtered through a 0.45 μm frit and purified with RP-HPLC ramping ACN in H_2O, with NH_4OH 0.1% to afford compound **10** (4 mg, 14% yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.34−8.38 (m, 1H), 8.20−8.25 (m, 1H), 7.26−7.35 (m, 3H), 7.25−7.35 (m, 3H), 7.06−7.11 (m, 1H), 6.16−6.21 (m, 2H), 3.80−3.85 (m, 1H), 3.66−3.72 (m, 1H), 3.53−3.59 (m, 1H), 3.45−3.51 (m, 1H), 3.45−3.51 (m, 1H), 3.23 (s, 4H), 2.95−3.00 (m, 1H), 2.92−3.03 (m, 1H). MS (ESI) m/z 388.0 $(M + H)^+$. HRMS calcd for $C_{18}H_{17}N_3O_5S$ $(M + H)^+$ 388.0967; found 388.0970.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,7]naphthyridin-4(2*H*)-one (11).** *Step 1: Ethyl 1-Methyl-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (**38d**).* A mixture of ethyl 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (5.0566 g, 23.17 mmol) and cesium carbonate (11.33 g, 34.8 mmol) in DMF (232 mL) was stirred at rt for 2 h with overhead stirring. Iodomethane (1.583 mL, 25.5 mmol) was added dropwise, and the resulting reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and water was added and the mixture stirred for 30 min, providing a suspension which was filtered. The solid was washed with water and heptane and dried to afford 4.410 g of solid. The filtrate was extracted with DCM three times. The combined organics was washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.025 g of yellow solid. The solids were combined to afford **38d** (5.435 g, 23.40 mmol, quantitative). MS (ESI) m/z 233.0 $(M + H)^+$.

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

*Step 2: rac-Ethyl 2-Benzyl-5-methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c][1,8]naphthyridine-3a-carboxylate (**39d**).* To a solution of **38d** (5.435 g, 23.40 mmol) in DCM (173 mL) at 0 °C under N_2 was added trifluoroacetic acid (0.695 mL, 9.36 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (29.9 mL, 117 mmol). The resulting solution was stirred at rt overnight. The resulting mixture was diluted with satd aq $NaHCO_3$ and extracted with DCM twice. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified with silica gel chromatography eluting with a gradient of 10−50% EtOAc/EtOH/NH_4OH (73:27:2) in heptane to provide **39d** (9.08 g, 24.7 mmol, quantitative) as light-yellow oil. MS (ESI) m/z 366.2 $(M + H)^+$.

*Step 3: rac-2-Benzyl-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo-[3,4-c][1,8]naphthyridin-4(2H)-one (**40d**).* A solution of **39d** (9.08 g, 24.85 mmol) in 6 N hydrochloric acid (207 mL, 1242 mmol) was refluxed for 16 h. The resulting mixture was concentrated to afford **40d** (9.02 g, 24.63 mmol, 99% yield) as a tan solid which was used without further purification. MS (ESI) m/z 294.3 $(M + H)^+$.

*Step 4: rac-5-Methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,8]-naphthyridin-4(2H)-one (**41d**).* A mixture of **40d** (9.02 g, 24.63 mmol) and palladium hydroxide, 20 wt % pd (dry basis) on carbon, wet (0.9 g, 1.282 mmol) in EtOH (50 mL) and water (10 mL) were stirred at 60 °C under 42 psi of H_2 for 12 h. The mixture was concentrated under reduced pressure to afford **41d** (6.65 g, 24.08 mmol, 98% yield) as an off white solid which was used without further purification. MS (ESI) m/z 204.1 $(M + H)^+$.

*Step 5: rac-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,7]naphthyridin-4(2H)-one (**11**).* **41d** (0.066 g, 0.203 mmol) in DMF (2 mL) was treated with benzo[*d*][1,3]dioxole-5-sulfonyl chloride (0.045 g, 0.203 mmol) and triethylamine (0.121 mL, 0.869 mmol) following the general sulfonylation procedure to afford **11** (0.088 mmol, 47% yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.27 (dd, J = 1.47, 4.86 Hz, 1H), 7.70 (d, J = 6.11 Hz, 1H), 7.33 (dd, J = 1.55, 8.11 Hz, 1H), 7.28 (d, J = 1.53 Hz, 1H), 7.00−7.12 (m, 2H), 6.19 (d, J = 4.64 Hz, 2H), 3.86 (dd, J = 2.15, 10.18 Hz, 1H), 3.62−3.75 (m, 1H), 3.40−3.58 (m, 2H), 3.15−3.29 (m, 4H), 2.91 (t, J = 9.87 Hz, 1H). MS (ESI) m/z 388.0 $(M + H)^+$. HRMS calcd for $C_{18}H_{17}N_3O_5S$ $(M + H)^+$ 388.0967; found 388.0961.

(3a*S*,9b*S*)-2-((1*H*-Benzo[*d*]imidazol-5-yl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (12). *rac*-**41c** (0.156 g, 0.565 mmol) in DMF (3.77 mL) was treated with triethylamine (0.393 mL, 2.82 mmol) and 1*H*-benzo[*d*]imidazole-5-sulfonyl chloride hydrochloride (0.143 g, 0.565 mmol) following the general sulfonylation procedure to afford the racemic mixture of **12** (0.199 g, 0.52 mmol, 92% yield). Chiral SFC conditions: Chiralcel OJ-H solvent, 35% methanol w/0.2% diethylamine. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 1 = **12** (49 mg), >96% ee: ^1H NMR (400 MHz, DMSO-d_6) δ 8.47−8.50 (m, 1H), 8.36−8.39 (m, 1H), 8.32−8.35 (m, 1H), 8.00−8.08 (m, 1H), 7.76−7.83 (m, 1H), 7.58−7.70 (m, 1H), 7.00−7.07 (m, 1H), 3.92−3.98 (m, 1H), 3.72−3.78 (m, 1H), 3.47−3.55 (m, 2H), 3.22−3.28 (m, 1H), 3.03 (s, 3H), 2.84−2.92 (m, 1H). MS (ESI) m/z 384.2 $(M + H)^+$. HRMS calcd for $C_{18}H_{17}N_5O_3S$ $(M + H)^+$ 384.1130; found 384.1127.

(3a*S*,9b*S*)-5-Methyl-2-((1-methyl-1*H*-benzo[*d*]imidazol-5-yl)-sulfonyl)-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]-naphthyridin-4(2*H*)-one (13). To a suspension of *rac*-**41c** (0.159 g, 0.576 mmol) in MeCN (3.84 mL) was added triethylamine (0.320 mL, 2.303 mmol). The reaction mixture was stirred at room temperature for 5 min prior to the addition of 1-methyl-1*H*-benzo[*d*]imidazole-5-sulfonyl chloride (0.133 g, 0.576 mmol). The resulting mixture was stirred at rt for 2 h then concentrated under reduced pressure. The resulting residue was suspended in water and filtered. The solid was washed with water and heptane successively and dried to give the racemic mixture of **13** (0.108 g, 0.27 mmol, 47% yield) as a white solid which was subjected to chiral purification conditions. Chiral SFC conditions: Chiralcel OJ-H solvent, 35% methanol, 70 mL/min, 220 nm, 179 bar, 108 mg dissolved in 6 mL of DCM/MeOH (3:2), 0.25 mL injected, and 40% methanol, 186 bar 1 mL injected. Peak assignment was determined by SFC on column OJ-H solvent, 20% methanol with ammonia. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 1 = **13** (53 mg) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 8.41−8.47 (m, 1H), 8.35−8.39 (m, 1H), 8.30−8.35 (m, 1H), 8.06−8.11 (m, 1H), 7.80−7.84 (m, 1H), 7.71−7.77 (m, 1H), 7.02−7.05 (m, 1H), 7.01−7.06 (m, 1H), 3.93 (s, 4H), 3.72−3.80 (m, 1H), 3.44−3.53 (m, 2H), 3.32 (s, 3H), 3.23−3.28 (m, 1H), 2.86−2.93 (m, 1H), 2.86−2.95 (m, 1H). MS (ESI) m/z 398.1 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_5O_3S$ $(M + H)^+$ 398.1287; found 398.1290.

(3a*S*,9b*S*)-2-(Benzo[*d*]oxazol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (14). *Step 1: rac-2-((4-Hydroxy-3-nitrophenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,7]naphthyridin-4(2H)-one.* To a suspension of *rac*-**41c** (0.380 g, 1.376 mmol) in MeCN (9.17 mL) was added triethylamine (0.383 mL, 2.75 mmol). The reaction mixture was stirred at room temperature for 5 min prior to the addition of 4-hydroxy-3-nitrobenzene-1-sulfonyl chloride (0.327 g, 1.376 mmol). The resulting mixture was stirred at rt for 2 h. The mixture was concentrated to afford crude 2-((4-hydroxy-3-nitrophenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,7]naphthyridin-4(2*H*)-one (1.24 g) as a yellow solid which was used without further purification. MS (ESI) m/z 405.1 $(M + H)^+$.

Step 2: rac-2-((3-Amino-4-hydroxyphenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,7]naphthyridin-4(2H)-one. A mixture of the 2-((4-hydroxy-3-nitrophenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,7]naphthyridin-4(2*H*)-one (1.24 g) and palladium hydroxide, 20 wt % pd (dry basis) on carbon, wet (0.124 g, 0.177 mmol) in acetic acid (1 mL, 17.32 mmol), EtOH (10 mL), and water (10 mL) was stirred at 40 °C under 42 psi of hydrogen gas overnight. The mixture was filtered through Celite and washed with EtOH and water. The filtrate was concentrated, and the residue was dissolved in MeOH and concentrated to facilitate removal of acetic acid. This was repeated 3 times until the residue became a dark solid. The material was further dried under high vacuo to provide 1.24 g of crude 2-((3-amino-4-hydroxyphenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,7]naphthyridin-4(2*H*)-one which was used without further purification. MS (ESI) m/z 375.2 $(M + H)^+$.

*Step 3: (3aS,9bS)-2-(Benzo[d]oxazol-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**14**).* A mixture of 2-((3-amino-4-hydroxyphenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,7]naphthyridin-4(2*H*)-one in ethyl orthoformate (10 mL, 60.1 mmol) was stirred at 120 °C for 5 h, and the resulting mixture was dried under reduced pressure. The residue was partitioned between water and EtOAc and extracted with EtOAc three times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure. The crude material was purified with silica gel chromatography eluting with a gradient of 20−100% EtOAc/EtOH/NH_4OH (73:27:2) in heptane to provide 0.2 g of the racemic product as white solid. Chiral SFC conditions: column OJ-H (2 cm × 25 cm), 40% methanol (0.1%)/CO_2, 100 bar, 60 mL/min, 220 nm, inj vol 2 mL, 10 mg/mL, 1:1 DCM:methanol. Peak assignment was determined by SFC on column OJ-H 40% methanol. Peak 1 contained the desired enantiomeric product (86 mg). Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. This material was further purified with RP-HPLC ramping ACN in H_2O, NH_4OH 0.1% to afford **14** (36 mg). ^1H NMR (500 MHz, DMSO-d_6) δ 8.95−9.02 (m, 1H), 8.35−8.39 (m, 1H), 8.30−8.34 (m, 1H), 3.92−3.99 (m, 1H), 3.75−3.82 (m, 1H), 3.50−3.60 (m, 2H), 3.34−3.44 (m, 1H).). MS (ESI) m/z 385.0 $(M + H)^+$. HRMS calcd for $C_{18}H_{16}N_4O_4S$ $(M + H)^+$ 385.0971; found 385.0970.

(3a*S*,9b*S*)-2-(Benzo[*d*]thiazol-6-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (15). (3aS,9bS)-**41c** (0.0736 M solution in MeCN, 6 mL, 0.442 mmol) was treated with 1,3-benzothiazole-6-sulfonyl chloride

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

(103 mg, 0.442 mmol) and triethylamine (0.123 mL, 0.883 mmol) following the general sulfonylation procedure to afford **15** (0.121 g, 0.30 mmol, 68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 8.74−8.80 (m, 1H), 8.32−8.42 (m, 2H), 8.24−8.31 (m, 1H), 7.89−7.97 (m, 1H), 6.98−7.08 (m, 1H), 3.94−4.02 (m, 1H), 3.75−3.84 (m, 1H), 3.51−3.63 (m, 2H), 3.25−3.30 (m, 1H), 3.25−3.30 (m, 1H), 2.94−3.03 (m, 4H). MS (ESI) m/z 401.0 (M + H)$^+$. HRMS calcd for $C_{18}H_{16}N_4O_3S_2$ (M + H)$^+$ 401.0742; found 401.0738.

(3a*S*,9b*S*)-2-(Imidazo[1,2-*a*]pyridin-7-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (16). (3a*S*,9b*S*)-**41c** (0.05 g, 0.246 mmol) in MeCN (3 mL) was treated with imidazo[1,2-*a*]pyridine-7-sulfonyl chloride (0.107 g, 0.492 mmol) and triethylamine (0.068 mL, 0.492 mmol) following the general sulfonylation procedure to afford **16** (0.027 g, 0.07 mmol, 29% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (d, J = 7.07 Hz, 1H), 8.30−8.44 (m, 2H), 8.21 (s, 1H), 7.99 (s, 1H), 7.84 (s, J = 6.42 Hz, 1H), 7.22 (d, J = 7.20 Hz, 1H), 7.05 (d, J = 5.64 Hz, 1H), 3.99 (d, J = 10.25 Hz, 1H), 3.75−3.89 (m, 1H), 3.52−3.70 (m, 2H), 3.17−3.29 (m, 1H), 2.98−3.09 (m, 4H). MS (ESI) m/z 384.2 (M + H)$^+$. HRMS calcd for $C_{18}H_{17}N_5O_3S$ (M + H)$^+$ 384.1130; found 384.1128.

(3a*S*,9b*S*)-2-((2,3-Dihydrobenzofuran-6-yl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (17). (3a*S*,9b*S*)-**41c** (0.0736 M solution in MeCN, 18.64 mL, 1.372 mmol) was treated with 2,3-dihydrobenzofuran-6-sulfonyl chloride (0.3 g, 1.372 mmol) and triethylamine (0.382 mL, 2.74 mmol) following the general sulfonylation procedure to afford **17** (0.310 g, 0.804 mmol, 59% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37−8.41 (m, 1H), 8.31−8.37 (m, 1H), 8.31−8.37 (m, 1H), 7.44 (d, J = 7.66 Hz, 1H), 7.22−7.29 (m, 1H), 7.03−7.15 (m, 2H), 4.57−4.70 (m, 2H), 3.87−3.94 (m, 1H), 3.66−3.74 (m, 1H), 3.51−3.59 (m, 1H), 3.44−3.50 (m, 1H), 3.25−3.29 (m, 3H), 3.24−3.28 (m, 2H), 3.16 (s, 3H), 2.88 (t, J = 10.06 Hz, 1H). MS (ESI) m/z 386.0 (M + H)$^+$. HRMS calcd for $C_{19}H_{19}N_3O_4S$ (M + H)$^+$ 386.1175; found 386.1176.

(3a*S*,9b*S*)-2-((2,3-Dihydrobenzofuran-5-yl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (18). (3a*S*,9b*S*)-**41c** (0.0736 M solution in MeCN, 6 mL, 0.442 mmol) was treated with 2,3-dihydro-1-benzofuran-5-sulfonyl chloride (0.100 g, 0.442 mmol) and triethylamine (0.123 mL, 0.883 mmol) following the general sulfonylation procedure to afford **18** (0.081 g, 0.21 mmol, 48% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28−8.49 (m, 2H), 7.66 (s, 1H), 7.55 (dd, J = 1.56, 8.37 Hz, 1H), 7.07 (d, J = 5.45 Hz, 1H), 6.92 (d, J = 8.37 Hz, 1H), 4.66 (dt, J = 2.01, 8.82 Hz, 2H), 3.88 (dd, J = 1.75, 10.19 Hz, 1H), 3.61−3.75 (m, 1H), 3.38−3.58 (m, 2H), 3.27 (t, J = 8.50 Hz, 3H), 3.15 (s, 3H), 2.87 (t, J = 10.02 Hz, 1H). MS (ESI) m/z 386.0 (M + H)$^+$. HRMS calcd for $C_{19}H_{19}N_3O_4S$ (M + H)$^+$ 386.1175; found 386.1174.

(3a*S*,9b*S*)-2-(Benzofuran-6-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (19). To a solution of **17** (100 mg, 0.259 mmol) in THF (1 mL) was added ceric ammonium nitrate (CAN) (284 mg, 0.519 mmol) and the resulting suspension shaken at 60 °C. After 3 h, additional CAN (4 equiv, 568 mg) was added and the mixture was shaken over three nights at room temperature. The resulting material was loaded directly onto a 25g ultra snap column and purified ramping DCM:MeOH (90:10) in DCM (0−100%, monitoring at 215 nm) affording product along with impurities. Repurification with RP-HPLC (ACN in H_2O, 5−95%, 0.1% NH_4OH modifier) provided **19** as a colorless film (10 mg, 10%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (br s, 2H), 8.29 (d, J = 2.1 Hz, 1H), 8.06 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.35 (br s, 1H), 7.16 (s, 1H), 3.96 (d, J = 10.2 Hz, 1H), 3.82−3.75 (m, 1H), 3.71−3.63 (m, 1H), 3.55 (dd, J = 6.7, 10.1 Hz, 1H), 3.34 (t, J = 6.7 Hz, 1H), 3.12 (s, 3H), 3.05 (t, J = 10.1 Hz, 1H) MS (ESI) m/z 384.0 (M + H)$^+$. HRMS calcd for $C_{19}H_{17}N_3O_4S$ (M + H)$^+$ 384.1018; found 384.1022.

(3a*R*,9b*R*)-2-(Benzofuran-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (20) and (3a*S*,9b*S*)-2-(Benzofuran-5-ylsulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (*ent*-20). To a vial charged with *rac*-**41c** (3.00 g, 14.76 mmol) was added MeCN (98 mL), Et_3N (8.23 mL, 59.0 mmol), and benzofuran-5-sulfonyl chloride (3.36 g, 15.50 mmol), respectively. The mixture was stirred at room temperature overnight, affording a white suspension (solution pinkish). To the mixture was added silica gel, and the mixture dried under reduced pressure. The adsorbed material was purified on MPLC ramping EtOAc:EtOH (76:24) in heptane (50−100%, 10% DCM throughout), affording racemic product (3.14 g, 55%). Chiral separation SFC conditions: Regis Whelk-O (s,s), 2 cm × 25 cm, 55% methanol w/0.2% DEA 80 mL/min (column back pressure = 117 bar), 100 bar BPR, 252 nm detection, dissolution 250 mL of 1:1 MeOH:DCM, sample processed with 4.0 mL injections and 4 min cycle time. Analytical data: Column dimensions, 4.6 mm × 100 mm; flow rate, 5 mL/min; instrument, SFC/MS-1. Column oven, 40 °C. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 1 = *ent*-**20**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 5.8 Hz, 1H), 8.34 (s, 1H), 8.19 (dd, J = 2.0, 8.7 Hz, 2H), 7.83 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.15 (dd, J = 0.8, 2.2 Hz, 1H), 7.03 (d, J = 5.7 Hz, 1H), 3.94 (dd, J = 1.7, 10.2 Hz, 1H), 3.79−3.70 (m, 1H), 3.60−3.45 (m, 2H), 3.26 (d, J = 6.6 Hz, 1H), 3.03 (s, 3H), 2.90 (t, J = 10.1 Hz, 1H). MS (ESI) m/z 384.1 (M + H)$^+$. HRMS calcd for $C_{19}H_{17}N_3O_4S$ 384.1018, found 384.102. Peak 2 = **20**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 5.8 Hz, 1H), 8.34 (s, 1H), 8.19 (dd, J = 2.0, 8.7 Hz, 2H), 7.83 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.15 (dd, J = 0.8, 2.2 Hz, 1H), 7.03 (d, J = 5.7 Hz, 1H), 3.94 (dd, J = 1.7, 10.2 Hz, 1H), 3.79−3.70 (m, 1H), 3.60−3.45 (m, 2H), 3.26 (d, J = 6.6 Hz, 1H), 3.03 (s, 3H), 2.90 (t, J = 10.1 Hz, 1H). MS (ESI) m/z 384.1 (M + H)$^+$. HRMS calcd for $C_{19}H_{17}N_3O_4S$ 384.1018, found 384.1016.

(3a*S*,9b*S*)-2-((3-Chloro-4-fluorophenyl)sulfonyl)-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (21). (3a*S*,9b*S*)- **41c** (0.0736 M solution in MeCN, 5 mL, 0.368 mmol) was treated with 3-chloro-4-fluorobenzenesulfonyl chloride (0.084 g, 0.368 mmol) and triethylamine (0.102 mL, 0.736 mmol) following the general sulfonylation procedure to afford **21** (0.091 g, 62% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.40 (d, J = 6.22 Hz, 1H), 8.36−8.37 (m, 1H), 8.01 (dd, J = 2.14, 6.81 Hz, 1H), 7.84 (ddd, J = 2.24, 4.46, 8.61 Hz, 1H), 7.65 (t, J = 8.61 Hz, 1H), 7.07 (d, J = 5.64 Hz, 1H), 3.89−4.00 (m, 1H), 3.70−3.81 (m, 1H), 3.59−3.69 (m, 1H), 3.55 (dd, J = 6.49, 10.38 Hz, 1H), 3.24−3.29 (m, 1H), 3.12 (s, 3H), 2.94 (t, J = 10.12 Hz, 1H). m/z 418.0 (M + Na)$^+$. HRMS calcd for $C_{17}H_{16}ClFN_3O_3S$ 396.0585, found 396.0578.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-3a-fluoro-5-methyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (22).** *Step 1: 4-(Methylamino)nicotinaldehyde (**36**).* To a vial charged with 4-chloronicotinaldehyde (0.884 g, 6.24 mmol) was added 2-methoxyethanol (3.57 mL) and methylamine, 40 wt % solution in water (13.51 mL, 156 mmol), respectively. The vessel was sealed and heated at 120 °C for 6 h. The orange solution was dried under reduced pressure and 1 N HCl (15 mL) was added, and the resulting mixture heated at 50 °C for 2 h. The mixture was cooled in an ice water bath and basified by the addition of satd aq $NaHCO_3$ (∼10 mL). The solution was extracted 2× with EtOAc. The combined organics were dried with Na_2SO_4, filtered, and dried under reduced pressure, affording **36** as a yellow oil which was used without further purification (0.408g, 48%). MS (ESI) m/z 137.1 (M + H)$^+$.

*Step 2: 3-Fluoro-1-methyl-1,6-naphthyridin-2(1H)-one (**37**).* A flask charged with dry THF (9.08 mL) was cooled in an ice−water bath prior to the addition of NaH (60% in mineral oil) (0.180 g, 4.50 mmol). To the suspension was added 2-fluoro-2-phosphonoacetic acid triethyl ester (0.912 mL, 4.50 mmol), faster than dropwise. The mixture was stirred for 30 min, then cooled in an ice/salt bath prior to the dropwise addition of a suspension of **36** (0.408 g, 3.00 mmol) in THF (5 mL), faster than dropwise while still stirring at ∼−10 °C. The mixture was allowed to stir for 1.5 h with slow warming. To the mixture was added water (∼5 mL) and the resulting orange solution dried under reduced pressure. The resulting residue was triturated with water, the filtrate was dried under reduced pressure and loaded onto a reverse phase column (55g, C18) and purified ramping ACN in H_2O (0−100%, 0.1% NH_4OH) with product eluting very early. This material was repurified by catch and release with a 10g SCX column,

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

loading with DCM/MeOH, washing with MeOH and eluting product with 2 M NH_3 in MeOH, affording **37** (110 mg, 21%) as a light-orange solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.78 (s, 1H), 8.62 (d, J = 5.96 Hz, 1H), 7.46 (d, J = 8.29 Hz, 1H), 7.22 (d, J = 6.01 Hz, 1H), 3.75 (s, 3H). MS (ESI) m/z 179.1 $(M + H)^+$.

*Step 3: rac-2-Benzyl-3a-fluoro-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**39g**).* To a vial charged with **37** (0.11 g, 0.617 mmol) was added DCM (1.764 mL) and TFA (0.019 mL, 0.247 mmol) and the resulting yellow suspension cooled in an ice−water bath prior to the addition of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzyl-amine (0.237 mL, 0.926 mmol), faster than dropwise. The mixture was stirred and allowed to slowly warm to room temperature (ice melt). After 3 h, additional *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzyl-amine (3 eq, 474 μL) was added and stirring continued at room temperature for 3 h then overnight at 40 °C. The mixture was dried under reduced pressure and purified by catch and release with a 10g SCX column, washing with MeOH, and then 2 M NH_3 in MeOH. The basic wash was dried under reduced pressure, affording **39g** (0.154g, 80%). MS (ESI) m/z 312.0 $(M + H)^+$.

*Step 4: rac-3a-Fluoro-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo-[3,4-c][1,6]naphthyridin-4(2H)-one (**41g**).* To a pressure vessel charged with **39g** (0.154 g, 0.495 mmol) as a turbid solution in EtOH (2.248 mL) was added water (0.225 mL) and palladium hydroxide, 20 wt % Pd (dry basis) on carbon, wet, Degussa type e101 ne/w (0.035 g, 0.049 mmol). The resulting mixture was heated to 40 °C under 40 psi of H_2 for 3 h. The mixture was filtered through Celite and dried under reduced pressure. The mixture was purified by catch and release with a 10g SCX column washing with MeOH, then 2 M NH_3 in MeOH to afford **41g** which was used without further purification, (95 mg, 0.429 mmol) (95 mg, 87%).

*Step 5: rac-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3a-fluoro-5-methyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**22**).* To a vial charged with **41g** (95 mg, 0.429 mmol) was added MeCN (2863 μL), Et_3N (239 μL, 1.718 mmol), and benzo[*d*][1,3]dioxole-5-sulfonyl chloride (95 mg, 0.429 mmol), respectively. The mixture was stirred at room temp for 1 h then dried under reduced pressure and purified with a 55g RP C-18 column, directly loading with IPA/DMSO and ramping with ACN in H_2O (0.1% in NH_4OH), providing product with minor close impurities. The material was repurified with RP-HPLC ramping ACN in H_2O (5−75%, 0.1% TFA), providing **22** as a white solid (85 mg, 49%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, J = 7.59 Hz, 2H), 7.22−7.35 (m, 3H), 7.02 (d, J = 8.11 Hz, 1H), 6.19 (s, 2H), 4.05 (d, J = 11.74 Hz, 2H), (broad water peak over 3 aliphatic H), 3.29 (s, 3H). MS (ESI) m/z 405.9 $(M + H)^+$. HRMS calcd for $C_{18}H_{16}FN_3O_5S$ = 406.0873, found 406.0875.

(3a*R*,9b*S*)-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-3a,5-dimethyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-one (23). *Step 1: rac-tert-Butyl 4-Oxo-3,3a,4,5-tetrahydro-1H-pyrrolo-[3,4-c]quinoline-2(9bH)-carboxylate (**42**).* To a mixture of *rac*-2-benzyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinolin-4(2*H*)-one (12 g, 0.0431 mmol), Pd/C (1.2 g, 10% on carbon), and $Pd(OH)_2$ (1.2 g) in EtOH (120 mL) was added $(Boc)_2O$ (14.09 mL, 0.064 mol, 1.5 equiv) and the mixture stirred at 50 psi under H_2 for 24 h. The resulting mixture was filtered and concentrated and the crude material was purified by column chromatography using petroleum ether:ethyl acetate (1:1) to afford **42** as an off-white solid (12 g, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.19 (td, J = 7.7, 1.4 Hz, 1H), 7.00−6.87 (m, 2H), 3.93 (t, J = 9.8 Hz, 1H), 3.60 (d, J = 8.5 Hz, 2H), 3.46 (ddd, J = 16.8, 10.5, 6.7 Hz, 1H), 3.14 (t, J = 6.7 Hz, 1H), 2.81 (td, J = 12.2, 10.4, 6.9 Hz, 1H), 1.38 (d, J = 14.5 Hz, 9H). MS (ESI) m/z 189.4 $(M + H - Boc)^+$.

*Step 2: rac-3a,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]quinolin-4(2H)-one (**44**).* To a solution of **42** (0.5 g, 1.734 mmol) in DMF (8.67 mL) at 0 °C was added sodium hydride 60% suspension in mineral oil (0.173 g, 4.34 mmol). The mixture was stirred at rt for 30 min prior to the addition of iodomethane (0.269 mL, 4.34 mmol). The resulting reaction mixture was stirred at room temperature for 2 h then quenched by the addition of satd aq NH_4Cl with ice bath cooling then extracted with diethyl ether three times. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure. To this residue was added 8 mL of 4 M HCl in MeOH (made from AcCl and MeOH), and the resulting solution was stirred at room temperature overnight. The resulting mixture was dried under reduced pressure and the residue purified by catch and release with an SCX column washing with MeOH, then 2 M NH_3 in MeOH. The basic wash was dried under reduced pressure to provide **44** (0.365 g, 1.688 mmol, 97% yield) as a thick brown oil. MS (ESI) m/z 217.2 $(M + 1)^+$.

*Step 3: (3aR,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3a,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]quinolin-4(2H)-one (**23**).* A solution of **44** (0.1 g, 0.462 mmol) in DMF (2 mL) was treated with 1,3-benzodioxole-5-sulfonyl chloride (0.112 g, 0.509 mmol) and triethylamine (0.193 mL, 1.387 mmol) following the general sulfonylation procedure to afford the racemate of **23** (0.143 g, 0.358 mmol, 77% yield). Then 50 mg of this material was subjected to chiral resolution by SFC on column (S,S) Whelk-O, 5 μ, 2 cm × 25 cm, 45% methanol w/0.2% DEA, 80 mL/min, 81 bar pressure drop, 100 bar BPR, 251 nm, sample dissolved in DCM:MeOH (1:1, 10 mL). Sample processed with 1.0 mL injection volume and cycle time of 6 min. Peak assignment determined by SFC on (S,S) Whelk-O with 45% methanol w/0.2% DEA modifer. Absolute configuration assigned by analogy based on in vitro activity and the known stereochemistry of active isomer **32** as determined by the X-ray cocrystal structure. Peak 1 = compound **23** (20 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25−7.38 (m, 4H), 7.03−7.16 (m, 3H), 6.15−6.22 (m, 2H), 4.10−4.16 (m, 1H), 3.63−3.70 (m, 1H), 3.21−3.28 (m, 1H), 3.10−3.18 (m, 4H), 2.77−2.87 (m, 1H), 0.95 (s, 3H). MS (ESI) m/z 401.1 $(M + H)^+$. HRMS calcd for $C_{20}H_{20}N_2O_5S$ $(M + H)^+$ 401.1171; found 401.1170.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5-methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridine-3a-carbonitrile (24).** *Step 1: 2-Oxo-1,2-dihydro-1,6-naphthyridine-3-carbonitrile (**35**).* To a vial charged with 4-amino-3-formylpyridine (0.90 g, 7.37 mmol) was added EtOH (12.28 mL), cyanoacetic acid methyl ester (1.312 mL, 14.74 mmol), and piperidine (0.182 mL, 1.842 mmol). The vial was sealed and heated with shaking to 120 °C overnight, affording a yellow precipitate. The mixture was cooled to room temperature and the solid collected via vacuum filtration and washed with heptane to afford **35** as a yellow solid (1.237 g, 7.23 mmol, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.70 (br s, 1 H), 8.89 (d, J = 0.7 Hz, 1 H), 8.92 (d, J = 0.7 Hz, 1 H), 8.59 (d, J = 5.9 Hz, 1 H), 7.26 (td, J = 0.7, 5.8 Hz, 1 H). MS (ESI) m/z 172.1 $(M + H)^+$.

*Step 2: 1-Methyl-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carbonitrile (**38f**).* To a vial charged with **35** (1.237 g, 7.23 mmol) was added DMF (20.65 mL) and Cs_2CO_3 (2.59 g, 7.95 mmol). The mixture was stirred at room temperature for 15 min prior to the addition of iodomethane (0.565 mL, 9.03 mmol). The resulting orange suspension was stirred for 1 h at room temp. The mixture was added to ice and the resulting solid collected via vacuum filtration and washed with water and the solid dried under a nitrogen/vacuum sweep, affording **38f** as a tan solid (1.121 g, 6.05 mmol, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.97 (d, J = 0.5 Hz, 1 H), 8.91 (s, 1 H), 8.72 (d, J = 6.1 Hz, 1 H), 7.60 (d, J = 6.2 Hz, 1 H), 3.62 (s, 3 H). MS (ESI) m/z 186.0 $(M + H)^+$.

*Step 3: rac-2-Benzyl-5-methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c][1,6]naphthyridine-3a-carbonitrile (**39f**).* To a vial charged with **38f** (1.12 g, 6.05 mmol) was added DCM (17.28 mL) and TFA (0.186 mL, 2.419 mmol) and the resulting yellow suspension cooled in an ice−water bath prior to the addition of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzyl-amine (2.321 mL, 9.07 mmol), faster than dropwise. The mixture was stirred and allowed to slowly warm to room temperature (ice melt). After 4 h, additional *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzyl-amine (1 equiv) was added and stirring at room temperature continued for 1 h. The reaction mixture was dried under reduced pressure, and the material was dissolved in MeOH/H_2O, filtered through a 0.45 μm frit, and loaded onto a Redisep load column and purified with a 120g RP Interchim C18, 30 μm, column ramping ACN in H_2O (0−100%, 0.1%

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

NH_4OH), providing **39f** as a yellow sticky foam (996 mg, 52%). MS (ESI) m/z 319.2 $(M + H)^+$.

*Step 4: rac-5-Methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo-[3,4-c][1,6]naphthyridine-3a-carbonitrile (**41f**).* To a vial charged with **39f** (0.10 g, 0.314 mmol) was added DCM (1.256 mL) and the resulting solution cooled in an ice−water bath prior to the addition of carbonochloridate (0.068 mL, 0.754 mmol) which was stirred for 10 min at 0 °C then overnight at 40 °C. The mixture was dried under reduced pressure and EtOH (1.5 mL) and 6 N HCl (0.3 mL) were added and the mixture shaken at 100 °C overnight. The mixture was cooled to room temperature and added to IPA (∼30 mL), affording a light-brown precipitate which was collected by vacuum filtration, rinsing with minimal IPA, providing **41f** as a brown solid (50 mg, 0.219 mmol, 69.7% yield). MS (ESI) m/z 229.2 $(M + H)^+$.

*Step 5: rac-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-5-methyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c][1,6]naphthyridine-3a-carbonitrile (**24**).* To a vial charged with **41f** (48 mg, 0.210 mmol) was added MeCN (1402 μL), Et_3N (117 μL, 0.841 mmol), and 1,3-benzodioxole-5-sulfonyl chloride (46.4 mg, 0.210 mmol), respectively. The mixture was shaken at room temperature for 90 min. The resulting mixture was dried under reduced pressure, dissolved in DMSO, filtered through a 0.45 μm frit, and purified with RP-HPLC ramping ACN in H_2O, NH_4OH 0.1%. Under these basic conditions, ∼50% of the product decomposed to the *des*-CN compound according to LC-MS. Repurification with RP-HPLC ramping ACN in H_2O, TFA 0.1% afforded **24** (18 mg, 16%). ^1H NMR (500 MHz, CD_3CN) δ = 3.33−3.39 (m, 4 H) 3.87−3.93 (m, 2 H) 4.18 (t, J = 8.17 Hz, 1 H) 4.24 (d, J = 10.77 Hz, 1 H) 6.15 (s, 2 H) 7.01 (d, J = 8.17 Hz, 1 H) 7.25 (d, J = 1.82 Hz, 1 H) 7.33−7.43 (m, 2 H) 8.55 (s, 1 H) 8.62 (d, J = 6.36 Hz, 1 H). MS (ESI) m/z 413.0 $(M + H)^+$, HRMS calcd for $C_{19}H_{16}N_4O_5S$ = 412.424, found 413.092.

***rac*-2-(Benzo[*d*][1,3]dioxol-5-ylsulfonyl)-5,9b-dimethyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (25).** *Step 1: Ethyl 4-Methyl-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (**34f**).* To a microwave vial was added 1-(4-aminopyridin-3-yl)ethanone (1.00 g, 7.34 mmol), diethyl malonate (5.58 mL, 36.7 mmol), and piperidine (0.182 mL, 1.836 mmol), respectively. The mixture was irradiated at 180 °C for 15 min, affording a tan precipitate. To the vessel was added water and the solid collected by vacuum filtration and washed with water to provide **34f** as a tan solid (0.848 g, 3.65 mmol, 49.7% yield), which was used without further purification. MS (ESI) m/z 233.1 $(M + H)^+$.

*Step 2: Ethyl 1,4-Dimethyl-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (**38e**).* To a vial charged with **34f** (0.675 g, 2.91 mmol) was added Cs_2CO_3 (1.326 g, 4.07 mmol) and DMF (8.30 mL), and the resulting suspension was cooled in an ice−water bath prior to the addition of iodomethane (0.182 mL, 2.91 mmol) dropwise. The mixture was allowed to stir while slowly warming to room temperature (ice melt) over 2 h. The mixture was diluted with water and purified by catch and release with a 10g SCX column, washing with MeOH, then 2 M NH_3 in MeOH to elute **38e**, obtained as a yellow solid (0.550 g, 2.233 mmol, 77% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 9.07 (s, 1 H), 8.68 (d, J = 5.9 Hz, 1 H), 7.54 (d, J = 6.0 Hz, 1 H), 4.35 (q, J = 7.2 Hz, 2 H), 3.60 (s, 3 H), 2.50 (s, 3 H), 1.31 (t, J = 7.1 Hz, 3 H). MS (ESI) m/z 247.1 $(M + H)^+$.

*Step 3: rac-Ethyl 2-Benzyl-5,9b-dimethyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c][1,6]naphthyridine-3a-carboxylate (**39e**).* To a vial charged with **38e** (0.500 g, 2.030 mmol) was added DCM (5.80 mL) and the resulting solution cooled in an ice−water bath prior to the addition of TFA (0.063 mL, 0.812 mmol) and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzyl-amine (2.60 mL, 10.15 mmol), faster than dropwise. The mixture was stirred and allowed to warm to room temperature (ice melt) over 4 h. The mixture was purified by catch and release by loading directly onto a 10g SCX column which was washed with MeOH, then 2 M NH_3 in MeOH. The basic wash was dried under reduced pressure and the mixture purified with a 55g C-18 RP column ramping ACN in H_2O (0−100%, 0.1% NH_4OH), affording **39e** as a yellow oil (0.134 g, 0.353 mmol, 17.39% yield). MS (ESI) m/z 380.1 $(M + H)^+$.

*Step 4: rac-2-Benzyl-5,9b-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**40e**).* To a vial charged with **39e** (0.134 g, 0.353 mmol) was added 6 N HCl (0.177 mL). The vial was sealed and shaken at 130 °C. After 2 h, additional 6 N HCl (2 mL) was added and the mixture heated to 130 °C, under nitrogen. After 2 more hours of concentration, HCl (2 mL) was added and the solution was stirred for 20 h at 130 °C. The resulting mixture was cooled in an ice−water bath while stirring and brought to basic pH by the addition of 6N NaOH. The resulting slurry was dried under reduced pressure and the solid (containing salts) shaken with DCM/MeOH and filtered to remove most of the salts. The filtrate was dried under reduced pressure and purified by catch and release with a 5g SCX column, loading with MeOH/DCM and washing with MeOH, water, MeOH, then 2 M NH_3 in MeOH, affording product elution. The solution was dried under reduced pressure and the resulting material (**40e**) used without further purification, obtained as a brown oil (85 mg, 78%). MS (ESI) m/z 308.1 $(M + H)^+$.

*Step 5: rac-5,9b-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**41e**).* To a pressure vessel charged with **40e** (0.085 g, 0.277 mmol) as a turbid solution in EtOH (1.257 mL) was added water (0.126 mL) and palladium hydroxide, 20 wt % Pd (dry basis) on carbon, wet, Degussa type e101 ne/w (0.019 g, 0.028 mmol). The resulting mixture was heated to 40 °C under 40 psi of H_2 for 4 h. The mixture was filtered through Celite and dried under reduced pressure. The crude material was purified by catch and release with a 5g SCX column washing with MeOH, then 2 M NH_3 in MeOH to afford **41e** with some minor impurities (∼75% pure, 50 mg, 83% yield). The material was used without further purification. MS (ESI) m/z 218.1 $(M + H)^+$.

*Step 6: rac-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-5,9b-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**25**).* To a vial charged with **41e** (50 mg, 0.230 mmol) was added MeCN (1534 μL), Et_3N (128 μL, 0.921 mmol), and benzo[*d*][1,3]-dioxole-5-sulfonyl chloride (50.8 mg, 0.230 mmol), respectively. The mixture was stirred at room temperature overnight. The yellow solution was dried under reduced pressure, dissolved in DMSO, filtered through a 0.25 μm frit, and purified with RP-HPLC ramping ACN in H_2O (0−100%, 0.1% NH_4OH), affording **25** as a pale-yellow film (25 mg, 0.062 mmol, 27.1% yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.40 (br s, 2H), 7.27 (dd, J = 1.72, 8.14 Hz, 1H), 7.20 (d, J = 1.62 Hz, 1H), 6.94−7.12 (m, 2H), 6.18 (d, J = 4.41 Hz, 2H), 3.58−3.70 (m, 2H), 3.46 (dd, J = 6.78, 10.09 Hz, 1H), 3.20 (s, 3H), 3.17 (s, 1H), 3.05 (t, J = 7.27 Hz, 1H), 1.22 (s, 3H). MS (ESI) m/z 402.1 $(M + H)^+$, HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1119.

Synthesis of (*rac*)-*cis*-52a, (*rac*)-*cis*-52b, (*rac*)-*cis*-52c, and (*rac*)-*cis*-52d via Initial Route, and Sulfonamides 26−33. *Step 1: N-Benzyl-1-(trimethylsilyl)ethanamine (**52**).* See Manzano et al., ref 39.

*Step 2: N-Benzyl-N-(methoxymethyl)-1-(trimethylsilyl)-ethanamine (**53**).* See Manzano et al., ref 39.

*Step 3: Ethyl 1-Methyl-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylate (**38g**).* To a flask charged with **34c** (5.08 g, 23.28 mmol) was added DMF (46.6 mL) and cesium carbonate (2.79 mL, 34.9 mmol). The resulting mixture was stirred for 15 min at room temperature, affording a thick yellow suspension which was cooled in an ice−water bath and placed under nitrogen prior to the addition of MeI (1.601 mL, 25.6 mmol), faster than dropwise. The resulting mixture was allowed to stir and warm slowly to room temperature (ice melt). After 2 h, the reaction was quenched by the addition of ice. The aqueous solution was extracted with EtOAc two times. The combined organics were dried with Na_2SO_4, filtered, and dried under reduced pressure. The organic layer was purified by catch and release with a 25g SCX column washing with MeOH, then 2 M NH_3 in MeOH, affording **38g** as a light-yellow solid (2.8 g, 36%). m/z (ESI) 233.1 $(M + H)^+$

Step 4: Diastereomeric Mixture of cis-Ring Fusion Isomers, rac-Ethyl 2-Benzyl-1,5-dimethyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c][1,6]naphthyridine-3a-carboxylate and rac-Ethyl 2-Benzyl-3,5-dimethyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,4-c][1,6]naphthyridine-3a-carboxylate. To a flask charged with **38g** (0.6 g, 2.58 mmol) was added DCM (7.38 mL) and TFA (0.080 mL, 1.033 mmol). The mixture was cooled to 0 °C prior to the addition of a solution of *N*-benzyl-*N*-(methoxymethyl)-1-(trimethylsilyl)-

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

ethanamine (1.624 g, 6.46 mmol) in DCM (1 mL), faster than dropwise. The mixture was stirred overnight at room temperature. The mixture was diluted with DCM, adsorbed onto silica gel, and purified with a 100g ultra snap column ramping EtOAc:EtOH (76:24) in heptane (0−30%, isocratic at 30%, then 30%−70%), affording product as a sticky yellow oil as a nonstatistical mixture of four racemic diastereomers (0.327 g, 0.862 mmol, 33.4% yield). MS (ESI) m/z 380.1 $(M + H)^+$.

Step 5: Diastereomeric Mixture of cis-Ring Fusion Isomers of 2-Benzyl-1,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]-naphthyridin-4(2H)-one and 2-Benzyl-3,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one. To a vial charged with *rac*-ethyl 2-benzyl-1,5-dimethyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridine-3a-carboxylate/*rac*-ethyl 2-benzyl-3,5-dimethyl-4-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridine-3a-carboxylate (291 mg, 0.767 mmol) was added 1,4-dioxane (4.18 mL) and 3 N HCl (2.8 mL), respectively. The vessel was sealed and heated at 90 °C over three nights. The resulting yellow solution was dried under reduced pressure and was used directly without further purification in the next step (yield not determined). MS (ESI) m/z 308.1 $(M + H)^+$.

*Step 6: rac-3,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c]-[1,6]naphthyridin-4(2H)-one and 1,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one/1,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one, (rac)-cis-**54a−d**.* To a pressure vessel charged with *rac*-2-benzyl-1,5-dimethyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one/*rac*-2-benzyl-3,5-dimethyl-3,3a,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,6]naphthyridin-4(2*H*)-one (0.261 g, 0.849 mmol (crude) as a turbid solution in EtOH (3.86 mL) was added water (0.386 mL) and palladium hydroxide, 20 wt % pd (dry basis) on carbon, wet, Degussa type e101 ne/w (0.060 g, 0.085 mmol). The resulting mixture was heated to 40 °C under 40 psi of H_2 for 3 h. The mixture was filtered through Celite and dried under reduced pressure. The crude residue was further purified by catch and release with a 5g SCX column washing with MeOH then 2 M NH_3 in MeOH, affording (*rac*)-*cis*-**54a−d** as pale-yellow upon drying under reduced pressure (160 mg, 0.736 mmol, 96% yield, 2 steps). MS (ESI) m/z 218.1 $(M + H)^+$.

*Step 7: Sulfonamides **26−33**.* To a vial charged with (*rac*)-*cis*-**54a−d** (160 mg, 0.736 mmol) was added MeCN (4.9 mL), Et_3N (0.4 mL, 2.95 mmol), and benzo[*d*][1,3]dioxole-5-sulfonyl chloride (162 mg, 0.736 mmol), respectively. The mixture was stirred at room temp for 2 h. The resulting mixture was dried under reduced pressure and purified with a 50g ultra snap column ramping EtOAc:EtOH (76:24) in heptane (0−100%, isocratic at 100%), affording desired product as a mixture of diastereomers light-yellow foam (211 mg, 71%). See the Supporting Information for chiral separation conditions and NMR structural confirmations.

Yields and analytical data for the individual diastereomers:

*(1S,3aS,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-1,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**26**) (Absolute Stereochemistry Arbitrarily Assigned).* Obtained 5 mg, 1.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 5.29 Hz, 1H), 8.32 (s, 1H), 7.24 (dd, J = 1.66, 8.19 Hz, 1H), 7.18 (d, J = 1.55 Hz, 1H), 6.98−7.06 (m, 2H), 6.17 (d, J = 11.71 Hz, 2H), 3.99 (d, J = 11.51 Hz, 1H), 3.69 (dd, J = 6.27, 11.25 Hz, 1H), 3.27−3.30 (m, 1H), 3.11−3.22 (m, 2H), 2.98 (s, 3H), 1.39 (d, J = 5.91 Hz, 3H). MS (ESI) m/z 402.2 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1118.

*(1R,3aR,9bR)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-1,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**27**) (Absolute Stereochemistry Arbitrarily Assigned).* Obtained 5 mg, 1.7% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 5.60 Hz, 1H), 8.32 (s, 1H), 7.24 (dd, J = 1.92, 8.14 Hz, 1H), 7.18 (d, J = 1.76 Hz, 1H), 6.98−7.06 (m, 2H), 6.17 (dd, J = 0.93, 11.92 Hz, 2H), 3.99 (dd, J = 1.55, 11.30 Hz, 1H), 3.69 (dd, J = 6.32, 11.20 Hz, 1H), 3.29 (s, 1H), 3.11−3.23 (m, 2H), 2.98 (s, 3H), 1.39 (d, J = 6.01 Hz, 3H). MS (ESI) m/z 402.2 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1122.

*(1R,3aS,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-1,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**28**) (Absolute Stereochemistry Arbitrarily Assigned).* Obtained 28 mg, 9.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, J = 5.60 Hz, 1H), 8.32 (s, 1H), 7.44 (dd, J = 1.87, 8.19 Hz, 1H), 7.40 (d, J = 1.66 Hz, 1H), 7.16 (d, J = 8.09 Hz, 1H), 7.13 (d, J = 5.70 Hz, 1H), 6.21 (dd, J = 1.04, 4.56 Hz, 2H), 3.99−4.11 (m, 2H), 3.40 (d, J = 8.71 Hz, 1H), 3.32 (m, 2H), 3.28 (s, 3H), 0.69 (d, J = 6.74 Hz, 3H). MS (ESI) m/z 402.0 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1123.

*(1S,3aR,9bR)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-1,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**29**) (Absolute Stereochemistry Arbitrarily Assigned).* Obtained 31 mg, 10.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, J = 5.70 Hz, 1H), 8.32 (s, 1H), 7.44 (dd, J = 1.87, 8.19 Hz, 1H), 7.40 (d, J = 1.66 Hz, 1H), 7.16 (d, J = 8.19 Hz, 1H), 7.13 (d, J = 5.70 Hz, 1H), 6.21 (dd, J = 0.93, 4.56 Hz, 2H), 3.99−4.12 (m, 2H), 3.38−3.45 (m, 1H), 3.32 (m, 2H), 3.28 (s, 3H), 0.69 (d, J = 6.74 Hz, 3H). MS (ESI) m/z 402.2 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1121.

*(3R,3aS,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**30**) (Absolute Stereochemistry Arbitrarily Assigned).* Obtained 34 mg, 11.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35−8.41 (m, 2H), 8.35−8.41 (m, 1H), 7.25 (dd, J = 1.87, 8.19 Hz, 1H), 7.18 (d, J = 1.87 Hz, 1H), 6.99−7.05 (m, 2H), 6.17 (dd, J = 0.93, 11.71 Hz, 2H), 4.29 (dq, J = 1.61, 6.51 Hz, 1H), 3.90 (td, J = 7.55, 10.08 Hz, 1H), 3.69 (dd, J = 7.72, 9.59 Hz, 1H), 3.02 (s, 3H), 2.96 (dd, J = 1.35, 7.26 Hz, 1H), 2.83 (t, J = 10.00 Hz, 1H), 1.38 (d, J = 6.63 Hz, 3H). MS (ESI) m/z 402.2 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1125.

*(3S,3aR,9bR)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**31**) (Absolute Stereochemistry Arbitrarily Assigned).* Obtained 46 mg, 15.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36−8.40 (m, 2H), 7.25 (dd, J = 1.87, 8.19 Hz, 1H), 7.18 (d, J = 1.66 Hz, 1H), 6.99−7.04 (m, 2H), 6.17 (dd, J = 0.88, 11.77 Hz, 2H), 4.29 (dq, J = 1.71, 6.58 Hz, 1H), 3.90 (td, J = 7.48, 10.13 Hz, 1H), 3.65−3.73 (m, 1H), 3.02 (s, 3H), 2.96 (dd, J = 1.45, 7.26 Hz, 1H), 2.83 (t, J = 10.05 Hz, 1H), 1.38 (d, J = 6.63 Hz, 3H). MS (ESI) m/z 402.2 $(M + H)^+$, HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1118.

*(3S,3aS,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**32**).* Obtained 5 mg, 1.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.43 (d, J = 5.49 Hz, 1H), 7.42 (dd, J = 1.87, 8.09 Hz, 1H), 7.39 (d, J = 1.66 Hz, 1H), 7.16 (d, J = 8.19 Hz, 1H), 7.09 (d, J = 5.60 Hz, 1H), 6.21 (s, 2H), 4.08 (dd, J = 1.76, 10.78 Hz, 1H), 3.89−3.99 (m, 1H), 3.69 (t, J = 7.46 Hz, 1H), 3.54 (dd, J = 6.58, 10.83 Hz, 1H), 3.26 (s, 3H), 3.05 (t, J = 9.07 Hz, 1H), 0.84 (d, J = 6.74 Hz, 3H). MS (ESI) m/z 402.2 $(M + H)^+$, HRMS calcd for $C_{19}H_{19}N_3O_5S$ 402.1124, found 402.1127.

*(3R,3aR,9bR)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**33**).* Obtained 6 mg, 2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.43 (d, J = 5.60 Hz, 1H), 7.42 (dd, J = 1.87, 8.09 Hz, 1H), 7.39 (d, J = 1.76 Hz, 1H), 7.16 (d, J = 8.19 Hz, 1H), 7.09 (d, J = 5.70 Hz, 1H), 6.21 (s, 2H), 4.08 (dd, J = 1.87, 10.78 Hz, 1H), 3.94 (qd, J = 6.74, 9.42 Hz, 1H), 3.69 (t, J = 7.31 Hz, 1H), 3.54 (dd, J = 6.58, 10.83 Hz, 1H), 3.26 (s, 3H), 3.05 (t, J = 9.07 Hz, 1H), 0.84 (d, J = 6.74 Hz, 3H). MS (ESI) m/z 402.1 $(M + H)^+$. HRMS calcd for $C_{19}H_{19}N_3O_5S$ = 401.44, found 402.1125

Synthesis of (*rac*)-*cis*-52c and (*rac*)-*cis*-52d via Improved Route (through Intermediates 55, 56, 57).[27] Chiral separation conditions for **54**: column, Chiralpak AD-H, 2 cm × 15 cm; modifier and percentage, 35% IPA w/0.2% DEA; flow rate (mL/min), 80; pressure drop (bar), 79; BPR (bar), 100; detection (nm), 257. Sample dissolution: ∼80 mL of 1:1:1 dichloromethane:IPA:MeOH. Test Injections: 0.25 mL (∼9 mg), 0.5 mL (∼18 mg). Then 3 mL ofDEA was added to sample solution to free base. Sample processing: volume (mL), 1; cycle time (min), 6. Desired peak was peak 3.

DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX

*Peak 1: (3R,3aR,9bR)-3,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**54**-d-Enantiomer of Active Intermediate).* Obtained 428 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 0.62 Hz, 1H), 8.33 (dd, J = 0.88, 5.65 Hz, 1H), 7.02 (d, J = 5.70 Hz, 1H), 3.54−3.65 (m, 2H), 3.43 (dd, J = 7.26, 11.51 Hz, 1H), 3.25 (s, 3H), 3.10−3.21 (m, 2H), 0.74 (d, J = 6.84 Hz, 3H).

*Peak 2: (3S,3aR,9bR)-3,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**54**-c-Less Active Diastereomer Peak 1 (Enantiomer Arbitrarily Assigned)).* Obtained 304 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31−8.38 (m, 2H), 7.04 (d, J = 5.60 Hz, 1H), 3.37−3.53 (m, 2H), 3.24 (s, 4H), 2.63 (dd, J = 6.06, 9.90 Hz, 1H), 2.52−2.57 (m, 1H), 1.26 (d, J = 6.43 Hz, 3H).

*Peak 3: (3S,3aS,9bS)-3,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**54**-d-Active Intermediate).* Obtained 267 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 0.62 Hz, 1H), 8.33 (dd, J = 0.88, 5.65 Hz, 1H), 7.02 (d, J = 5.70 Hz, 1H), 3.54−3.65 (m, 2H), 3.43 (dd, J = 7.26, 11.51 Hz, 1H), 3.25 (s, 3H), 3.10−3.21 (m, 2H), 0.74 (d, J = 6.84 Hz, 3H).

*Peak 4: (3R,3aS,9bS)-3,5-Dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**54**-c-Less Active Diastereomer Peak 2 (Enantiomer Arbitrarily Assigned)).* Obtained 298 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31−8.38 (m, 2H), 7.04 (d, J = 5.60 Hz, 1H), 3.37−3.53 (m, 2H), 3.24 (s, 4H), 2.63 (dd, J = 6.06, 9.90 Hz, 1H), 2.52−2.57 (m, 1H), 1.26 (d, J = 6.43 Hz, 3H).[27]

*(3S,3aS,9bS)-2-(Benzo[d][1,3]dioxol-5-ylsulfonyl)-3,5-dimethyl-3,3a,5,9b-tetrahydro-1H-pyrrolo[3,4-c][1,6]naphthyridin-4(2H)-one (**32**).* See Huang et al., ref 27.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.6b01496.

26−**33**, detailed chiral separation conditions; AM-3607, a detailed suite of 1D and 2D NMR data (PDF)
Molecular formula strings (CSV)

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All authors have contributed and have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the following people for their contributions: Grace Bi and Larry Miller for chiral resolution and compound purification support, Iain Campuzano for the generation of high-resolution mass spectroscopy data, Stephen Altmann for cell line validation work, Virginia Berry, Loren Berry, and Brett Janosky for PKDM support, Dr. Benjamin C. Milgram for useful chemistry discussions, and Dr. Margaret Chu-Moyer for critical review of the manuscript.

■ ABBREVIATIONS USED

μW, microwave; CL, clearance; CL_{int}, intrinsic clearance; PPB, plasma protein binding; DRG, dorsal root ganglion neuron; HLM, human liver microsomes; RLM, rat liver microsomes; MLM, mouse liver microsomes; MDR1, multidrug resistance protein 1; MDCK, Madin−Darby canine kidney; BCRP, breast cancer resistance protein; P_{app}, apparent passive permeability; LE, ligand efficiency; LipE, lipophilic efficiency; V_d, volume of distribution; TTX, tetrodotoxin; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione); APV, (2*R*)-amino-5-phosphonovaleric acid; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartic acid; GABA, γ-aminobutyric acid; S_NAr, nucleophilic aromatic substitution

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DOI: 10.1021/acs.jmedchem.6b01496
J. Med. Chem. XXXX, XXX, XXX−XXX