Journal of Medicinal Chemistry

Article

5,6,7,8-Tetrahydro-1,6-naphthyridine Derivatives as Potent Allosteric Site HIV-1 Integrase Inhibitors

Kevin Peese, Christopher Allard, Timothy Connolly, Barry Johnson, Chen Li, Manoj Patel, Margaret Sorensen, Michael Walker, Nicholas A. Meanwell, Brian McAuliffe, Beatrice Minassian, Mark Krystal, Dawn Parker, Hal A. Lewis, Kevin Kish, Ping Zhang, Robert T Nolte, Jean Simmermacher, Susan Jenkins, Christopher Cianci, and B Narasimhulu Naidu

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.8b01473 • Publication Date (Web): 04 Jan 2019

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

5,6,7,8-Tetrahydro-1,6-naphthyridine Derivatives as Potent Allosteric Site HIV-1 Integrase Inhibitors

Kevin M. Peese,[*,†,§] Christopher W. Allard,[‡] Timothy Connolly,[†] Barry L. Johnson,[†] Chen Li,[†] Manoj Patel,[†,§] Margaret E. Sorensen,[†] Michael A. Walker,[†] Nicholas A. Meanwell,[†] Brian McAuliffe,[†,§] Beatrice Minassian,[‡] Mark Krystal,[†,§] Dawn D. Parker,[†,§] Hal A. Lewis,[†] Kevin Kish,[†] Ping Zhang,[†] Robert T. Nolte,[◊] Jean Simmermacher,[†,§] Susan Jenkins,[†,§] Christopher Cianci,[‡] and B. Narasimhulu Naidu[†,§]

[†] Bristol-Myers Squibb Research & Development, Department of Discovery Chemistry, 5 Research Parkway, Wallingford, Connecticut 06492

[‡] Bristol-Myers Squibb Research & Development, Department of Virology Discovery Biology, 5 Research Parkway, Wallingford, Connecticut 06492

[◊] GlaxoSmithKline, Protein Cellular and Structural Sciences, 1250 South Collegeville Rd., Collegeville, PA 19426

[§] Current address: ViiV Healthcare, 36 East Industrial Road, Branford, Connecticut, 06405

KEYWORDS: ALLINI, LEDGIN, NCINI, HIV integrase inhibitor, HIV integrase, LEDGF, allosteric inhibitor.

ABSTRACT: A series of 5,6,7,8-tetrahydro-1,6-naphthyridine derivatives targeting the allosteric lens epithelium-derived growth factor p75 (LEDGF/p75) binding site on HIV-1 integrase, an attractive target for antiviral chemotherapy, was prepared and screened for activity against HIV-1 infection in cell culture. Small molecules that bind within the LEDGF/p75 binding site promote aberrant multimerization of the integrase enzyme and are of significant interest as HIV-1 replication inhibitors. SAR studies and rat pharmacokinetic studies of lead compounds are presented.

INTRODUCTION

Infection with HIV-1 represents a substantial global health challenge. By the end of 2016, the World Health Organization (WHO) estimated that there were approximately 36.7 million people living with HIV-1 infection, including 1.8 million newly-infected people in 2016.[1] In recent years, significant advances have been made in the treatment of HIV-1 infection; however, due to the emergence of resistance and issues associated with drug tolerability there remains a need for new antiviral agents.[2,3] HIV-1 integrase, one of three essential enzymes encoded in the HIV-1 genome, is an attractive target for chemotherapeutic intervention.[4-7] Currently, four HIV-1 integrase inhibitors are approved for clinical use in combination with other antiviral agents, including raltegravir, elvitegravir, dolutegravir, and, most recently, bictegravir.[8-12] All of the clinically-approved inhibitors bind to the active site of integrase, blocking the strand transfer step in which viral DNA is integrated into the host genome, and are designated integrase as strand transfer inhibitors (INSTIs). Recently, allosteric inhibition of HIV-1 integrase has emerged as a promising, complementary approach to active site-based inhibitors of strand transfer.[13-16] Allosteric integrase inhibitors (ALLINIs), alternatively known as lens epithelium-derived growth factor (LEDGF) inhibitors (LEDGINs), non-catalytic site integrase inhibitors (NCINIs), and IN-LEDGF/p75 allosteric inhibitors (INLAIs), are mechanistically differentiated, presenting a biochemical profile that is distinct from active site inhibitors and therefore offer the promise to provide an important clinical complement to INSTIs in drug combinations for the treatment of HIV-1 infection.[13,14,17] In the time since the initial disclosure of this class, ALLINIs have become a focus of active research, delivering the clinical candidate BI-224436 (**1**) while multiple preclinical candidates have been described (Figure 1).[15-17]

LEDGF is a ubiquitous host transcriptional co-activator nuclear protein that is a cellular co-factor taken advantage of by HIV-1 virus to direct the activity of integrase.[13,14] LEDGF exists as two distinct isoforms, p75 and p52, of which only p75 has been shown to bind to HIV-1 integrase.[21,22] Binding of LEDGF/p75 to integrase promotes organization of the enzyme as a tetramer and tethers the integration complex to chromatin, thereby facilitating viral integration into host cell DNA.[23] Disruption of the integrase-LEDGF/p75 protein-protein interaction inhibiting integration is a conceptually attractive approach to inhibit integration and block viral replication.[13,14,18-20] Studies of early disclosed allosteric integrase inhibitors demonstrated, however, that while these agents do indeed bind to the LEDGF/p75 interface on integrase in vitro, the primary antiviral effect is to block viral particle maturation, i.e. a late mechanism of action.[18,24-26] Further elucidation of the mechanism revealed that ALLINIs induce aberrant multimerization of integrase during viral particle assembly, ultimately leading to the production of structurally defective, non-infectious virions.

Through a program of structure-based drug design employing known inhibitors, including **1** and **2**, we identified 5,6,7,8-

tetrahydro-1,6-naphthyridine **3** as an inhibitor of HIV-1 integrase that binds to the LEDGF/p75 binding pocket. Encouragingly, **3** exhibited modest antiviral activity in cell culture against NL4-3 virus, establishing it as a useful lead molecule. Consideration of a computational model of **3** bound to integrase within the LEDGF/p75 binding site suggested that the *N*-phenyl ring of **3** lies in a relatively open hydrophobic pocket of the integrase protein bounded on the front and bottom by threonine 124/threonine 125 (T124/T125), on the back by tryptophan 131 (W131), and underneath by alanine 128 (A128) (Figure 2). The projection of the phenyl ring in compound **3** differs considerably from contemporary reports of inhibitors represented by **4** and **5** where substitution was directed in a complementary vector away from this pocket.[20] Analysis of the model inspired a strategy designed to further explore this region of the LEDGF/p75 binding pocket. The goal of this exercise was to improve the antiviral potency of this series based upon the hypothesis that projection of the *N*-phenyl ring further away from the core heterocycle would more completely fill the binding pocket and result in a concomitant increase in binding efficiency. Consequently, we set out to explore approaches to introduce linker elements between the phenyl ring and the 5,6,7,8-tetrahydro-1,6-naphthyridine core designed to project the *N*-aryl group of **3** deeper into the hydrophobic pocket of HIV-1 integrase.

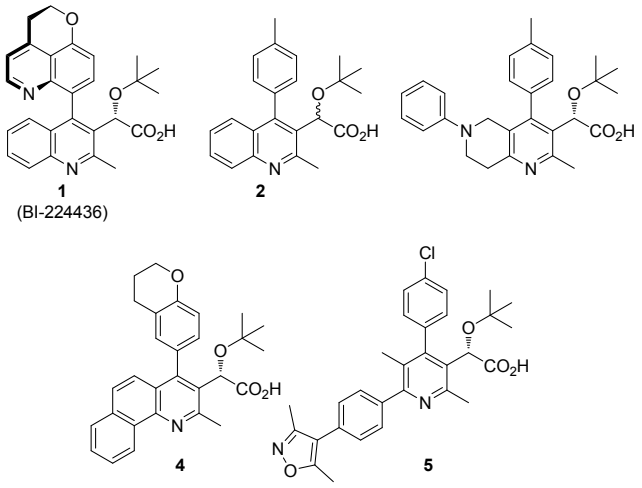


Figure 1. Compounds **1**–**5**.

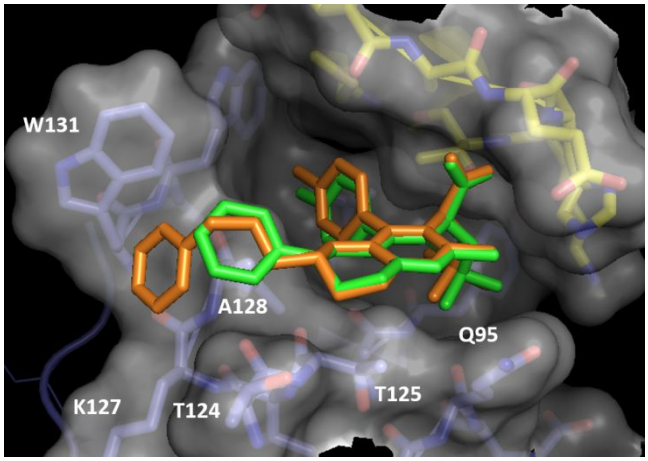


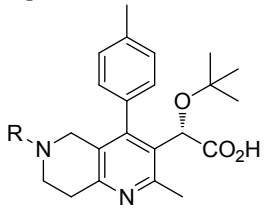
Figure 2. Overlay of compounds **3** and **8** docked in the LEDGF/p75 binding pocket of HIV-1 integrase.

RESULTS AND DISCUSSION

Efforts to project the *N*-aryl ring of **3** further into the hydrophobic LEDGF/p75 binding pocket began with a study of the homologous series of linker elements between the phenyl ring and the piperidine *N* atom (Table 1). These compounds were evaluated in both a biochemical binding assay and in a cell culture antiviral activity assay. The binding assay evaluated compounds for their ability to displace a tritiated version of compound **2** from the LEDGF/p75 binding site on integrase. The cell culture antiviral activity assay evaluated the ability of compounds to inhibit viral outgrowth of the NL4-3 HIV-1 strain replication in MT-2 cells. As antiviral activity is the ultimate driver of efficacy for antiretroviral agents, the cell culture antiviral assay was used as the primary means of evaluating new compounds. Both the one and two carbon-linked compounds **6** and **7**, respectively, demonstrated similar antiviral activity to the prototype **3**. However, the three carbon homolog **8** delivered an almost 50-fold increase in antiviral activity, with an EC_{50} value of 0.010 μM. The next series of analogs explored variation of the three atom spacer motif in **8**. Replacement of the benzylic carbon with an oxygen atom to afford the ether **9** resulted in reduced antiviral activity, as did the introduction of an unsaturation into the spacer, alkene **10**. In both cases, the conformational preferences associated with these molecular edits, which are similar in effect, presumably compromises the optimal presentation of the phenyl ring to the hydrophobic pocket of the enzyme.[28-30] Conformational constraints proximal to the heterocyclic core, examined in the context of amide **11**, carbamate **12**, and urea **13**, resulted in lower potency compared to **8**, with the EC_{50} values recorded for these compounds comparable to the prototype **3**. The incorporation of a phenyl ring in the tether was also evaluated in an effort to further illuminate the preferred binding conformation. Both the *para*-biphenyl **14** and *meta*-biphenyl **15** exhibited antiviral activity comparable to **3** while the *ortho*-biphenyl isomer **16**, in which the proximal phenyl ring is attached to the tetrahydronaphthyridine ring via a methylene spacer, demonstrated potent antiviral activity, EC_{50} = 0.070 μM, although still attenuated relative to the activity of the phenylpropyl-based **8**. Finally, a series of analogs in which the terminal phenyl ring was either replaced with alkyl substituents or excised completely were probed in order to assess the importance of an aromatic element at this site. Replacement of the aryl ring of **8** with a cyclopentyl ring (**17**) was tolerated, although this compound was 4-fold less active than the prototype **8**, while the simple *n*-pentyl analog **18** was 20-fold less potent than **8**. Finally, the *N*-methylamine **19**, the acetamide **20**, the methyl carbamate **21**, and the sulfonamide **22** all displayed reduced antiviral potency with EC_{50} values above 1 μM, consistent with the hypothesized advantage of occupying the hydrophobic pocket. The results from the binding assay generally tracked within 3-fold of the cell culture antiviral assay, the primary exceptions being compounds lacking a terminal aryl ring. However, SAR trends were generally more consistent and interpretable in the cell culture assay, supporting the decision to rely primarily on the cell culture assay.

In an effort to further optimize the potency of the chemotype, attention focused on evaluating the effect of substitution on the aryl ring of **8** (Table 2). This phase of the survey was performed in the context of the 8-fluoro-5-methylchromane group at C-4 of the core heterocycle rather than the simpler tolyl substituent. Adoption of the 8-fluoro-5-methylchromane group was based on the description of this motif as a highly optimized substituent

identified in the course of the discovery of **2** that conferred a significant increase in antiviral potency.[19,31] As has been observed by others, the atropisomeric stereogenic axis is stable and must be in the *R*-configuration in order to obtain potent antiviral activity.[32] Replacement of the tolyl ring of **8** by the chromane group gave **23** as the prototype of this series, a



Compound	R	IC_{50} (μM)[a,b]	EC_{50} (μM)[c]	EC_{50} SD (μM)[d]	CC_{50} (μM)[e]
1	NA	0.071	0.052	0.021	>40
2	NA	-	0.15	0.053	>40
3	Ph	0.23	0.47	0.17	>40
6	$PhCH_2$	0.83	0.30	0.15	>40
7	$PhCH_2CH_2$	0.85	0.24	-	>40
8	$PhCH_2CH_2CH_2$	0.070	0.010	0.0037	>40
9	$PhOCH_2CH_2$	0.17	0.20	0.084	>40
10	$PhCH{=}CHCH_2$	0.16	0.12	0.044	>40
11	$PhCH_2CH_2CO.$	0.76	0.34	0.071	>40
12	$PhCH_2OCO.$	0.14	0.23	0.055	>40
13	$PhCH_2NHCO.$	0.31	0.50	-	>40
14	4-Ph-C_6H_4	0.22	0.32	-	>40
15	3-Ph-C_6H_4	0.43	0.28	0.049	>40
16	2-Ph-$C_6H_4CH_2$	0.08	0.070	0.017	>40
17	*c*-$C_5H_9CH_2CH_2CH_2$	0.24	0.039	0.002	>40
18	$CH_3CH_2CH_2CH_2CH_2$	1.1	0.21	0.053	>40
19	CH_3	5.8	2.1	-	>40
20	$CH_3CO.$	17	1.9	-	>40
21	$CH_3OCO.$	4.2	1.6	-	>40
22	CH_3SO_2	2.2	2.6	-	>40

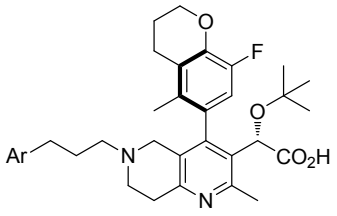
Table 1. Antiviral activity of **3** and **6-22** in a biochemical binding assay measuring the capacity of test compounds to displace tritiated **2** from integrase and activity in a cell culture antiviral HIV-1 infectivity assay.

[a] Binding assay which evaluated compounds for the ability to displace a tritiated version of compound **2** from the LEDGF binding site on integrase. [b] Binding assay values based on single replicant. [c] Cell culture antiviral activity assay which evaluated the ability of compounds to inhibit viral outgrowth of the NL4-3 HIV-1 strain in MT-2 cells. [d] Cell culture activity values based on multiple replicants- see supplemental data for details. [e] Measured in MT-2 cells up to a maximal concentration of 40 μM of test substrate.

structural edit associated with potent antiviral potency, with an EC_{50} value of 0.004 μM. An effort to constrain the pendent phenyl ring in the hypothesized active conformation through introduction of a syn cyclopropyl group in the tether provided **24**, prepared as a 1:1 mixture of diastereomers. While the strategic deployment of cyclopropyl rings for conformational restriction has been reported in numerous medicinal chemistry settings, in our context minimal or no enhancement of antiviral activity compared to prototype **23** was observed.[33] However, **24** experienced no loss in activity, an observation consistent with the importance of the correct presentation of the phenyl ring that further supports the conformational rationale presented regarding the diminished antiviral activity of the ether (**9**) and olefin (**10**) linkers in the tolyl series. Substitution of the phenyl ring of **23** at the 2-, 3-, or 4-positions with fluoro or methyl, explored with compounds **25-31**, provided only modest or no improvement compared to the parent **23**. Interestingly, the disubstituted 4-methyl, 3-fluorophenyl analog **27** was an exception, with an EC_{50} of 0.001 μM in the cell culture assay. In contrast to the effects of substitution at the 4- or 3-positions, substitution at the 2-position was a more productive approach to improving antiviral activity. The 2-fluorophenyl analogue **29** demonstrated an EC_{50} of 0.001 μM while the 2-methylphenyl derivative **30** demonstrated an EC_{50} value of 0.002 μM in the antiviral assay. In addition, replacement of the phenyl ring with a pyridine heterocycle resulted in compound **32** with reduced antiviral potency, a result consistent with the importance of complementing the hydrophobic pocket of the LEDGF/p75 binding site with a lipophilic moiety.

HIV-1 integrase is highly polymorphic at threonine 124 (T124) and threonine 125 (T125) (NL4-3 sequence) which are located in the LEDGF/p75 binding pocket of the catalytic core domain (CCD) of HIV-1 integrase. Evaluation of **8** and **23** against the five most common polymorphic substitutions

observed clinically demonstrated that this tetrahydronaphthyridine-based series is relatively insensitive to these mutations (Table 3). The most challenging integrase polymorph for the tolyl-substituted prototype **8** was the T124A/T125A variant for which the EC_{50} value was 0.034 μM, representing a 3-fold loss of antiviral activity compared to wild-type virus. Similarly, the chromane derivative **23** exhibited an EC_{50} of 0.004 μM for wild type T124/T125 integrase and an EC_{50} of 0.007 μM for the



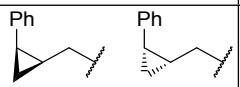
Compound	Ar	IC_{50} (μM)[a,b]	EC_{50} (μM)[c]	EC_{50} SD (μM)[d]	CC_{50} (μM)[e]
23	Ph	0.016	0.004	0.0015	>40
24	 1:1	0.024	0.005	0.0010	>40
25	4-F-Ph	0.015	0.004	-	>40
26	4-Me-Ph	0.012	0.002	0.0007	>40
27	3-F-Ph	0.044	0.004	-	>40
28	3-Me-Ph	0.029	0.002	0.0001	>40
29	2-F-Ph	0.008	0.001	-	>40
30	2-Me-Ph	0.019	0.002	0.0004	>40
31	3-F,4-Me-Ph	0.011	0.001	0.0001	>40
32[f]	4-C_5H_4N	0.040	0.058	0.028	>40

Table 2. Activity of **23-32** in a biochemical binding assay measuring the capacity of test compounds to displace tritiated **2** from integrase and activity in a cell culture antiviral HIV-1 infectivity assay.

[a] Binding assay which evaluated compounds for the ability to displace a tritiated version of compound **2** from the LEDGF binding site on integrase. [b] Binding assay values based on single replicant. [c] Cell culture antiviral activity assay which evaluated the ability of compounds to inhibit viral outgrowth of the NL4-3 HIV-1 strain in MT-2 cells. [d] Cell culture activity values and standard deviations (SD) based on multiple replicants- see supplemental data for details. [e] Measured in MT-2 cells up to a maximal concentration of 40 μM of test substrate. [f] 1:1 mixture of atropisomers.

T125A polymorph. Polymorph potency shifts of 3-fold or less are considered to be modest in nature, demonstrating that the tetrahydronaphthyridine series is associated with broad polymorph coverage. This polymorph antiviral activity profile differs markedly from published series where the aryl substituent projects in the southwest direction, as the molecules are drawn. Compound **5** is a representative example, experiencing a 12-fold loss in antiviral activity for the T124N polymorph, a difference that further highlights a potential advantage of the tetrahydronaphthyridine series.[26]

To gain insight into the antiviral activity of the tetrahydronaphthyridine series, a cocrystal structure of **24** bound to HIV-1 integrase was obtained (Figure 3). The X-ray crystal structure was solved at 2.0 Å resolution by soaking crystals of a construct of the CCD of HIV-1 integrase with the diastereomeric mixture of **24**, selectively binding a single diastereomer of **24**. The crystal structure of **24** confirmed that the tetrahydronaphthyridine series binds to the LEDGF/p75 recognition pocket in a fashion comparable to previously disclosed reports of structurally similar inhibitors.[18] Importantly, the crystal structure of **24** bound to integrase demonstrated projection of the terminal aryl ring into the hydrophobic pocket adjacent to the LEDGF/p75 binding site in support of the binding mode hypothesis developed for this series, adopting a conformation very similar to that predicted for the phenylpropyl analog **8** bound to integrase (Figure 3).[28] The terminal aryl ring of **24** projects towards tryptophan 131 in an edge to π face conformation and establishes close van der Waals contacts with threonine 124, threonine 125, and alanine 128. The crystal structure of **24** bound to integrase provided validation of the hypothesis that projecting a lipophilic aryl ring deeper into the hydrophobic pocket of LEDGF/p75 would result in increased binding efficiency, confirmed by the measured antiviral activity.

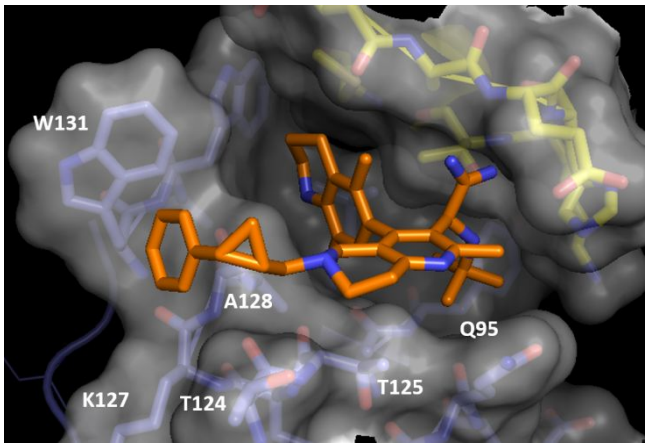


Figure 3. X-ray cocrystal structure of a single diastereomer of compound **24** bound to the HIV-1 integrase CCD.

Several compounds were profiled in rat pharmacokinetic studies designed to further assess the potential of this tetrahydronaphthyridine chemotype (Table 4). Both the phenyl derivative **23** and the 4-fluorophenyl homologue **25** exhibited high clearance (CL) of 82 and 92 mL/min/kg and moderate to high volumes of distribution (Vss) of 6 and 1 L/kg, respectively, following IV ad-ministration. This high CL was unexpected as

Compound	Wild type EC_{50} (μM)	T124A EC_{50} (μM)	T125A EC_{50} (μM)	T124A/T125A EC_{50} (μM)	T124N EC_{50} (μM)	T124A/T125N EC_{50} (μM)
8	0.010	0.017	0.021	0.034	0.020	0.031
23	0.004	0.004	0.007	0.006	0.006	0.004

Table 3. Cell culture antiviral activity of **8** and **23** toward NL4-3 viruses incorporating mutations in HIV-1 integrase within the pol gene.

both **23** and **25** displayed good metabolic stability in an in vitro rat liver microsome assay with 78% of each remaining after a 10 minute incubation period at a concentration of 0.5 μM. Togain insight into the observed rat pharmacokinetic SAR, further compounds with a range of structural features were also profiled in rat in vivo studies. Analogs **3**, **6**, and **16**, which place the pendent aryl ring in close proximity to the core tetrahydronaphthyridine, exhibited moderate CL values of 24, 21, and 24 mL/min/kg, respectively. In contrast, analogs **8**, **11**, and **12** in which the aryl ring is spaced three atoms from the tetrahydronaphthyridine ring demonstrated high CL values. The hybrid biphenyl analog **16**, which possesses an aryl proximal to the tetrahydronaphthyridine in addition to a more distant terminal aryl ring, delivered an improvement in the IV pharmacokinetic profile with a moderate CL value of 24 mL/min/kg. Finally, replacement of the aryl ring with a cyclopentyl ring, exemplified by **17**, did not improve the pharmacokinetic profile since this compound is also subject to rapid clearance. The key finding of these pharmacokinetic studies was that placement of an aryl ring close to the tetrahydronaphthyridine was central to obtaining a good pharmacokinetic profile. Most importantly, the hybrid biphenyl **16** recovered a positive pharmacokinetic profile, with low CL that provides insight into a potential path forward for future studies. As observed with **23** and **25**, the in vitro rat liver microsome stability profiles of **3**, **6**, **8**, **11**, **12**, **16**, and **17** were not predictive of in vivo pharmacokinetic profiles. The lack of correlation between the in vitro-derived microsomal stability data and the high in vivo clearance values suggests that the clearance is likely not driven by CYP-mediated oxidative processes. This result is consistent with published data for **2** and related compounds for which enterohepatic recirculation and biliary excretion of the unmodified parent and the corresponding acyl glucuronide were found to be the primary drivers of in vivo clearance.[34] While we have no direct evidence for glucuronidation or enterohepatic recirculation, biliary clearance might be considered to be the likely primary mode of in vivo clearance for this series considering the generally high in vitro metabolic stability of representative compounds.

Table 4. Rat pharmacokinetic profiles of test compounds dosed at 1 mg/kg IV and 5 mg/kg PO.[a]

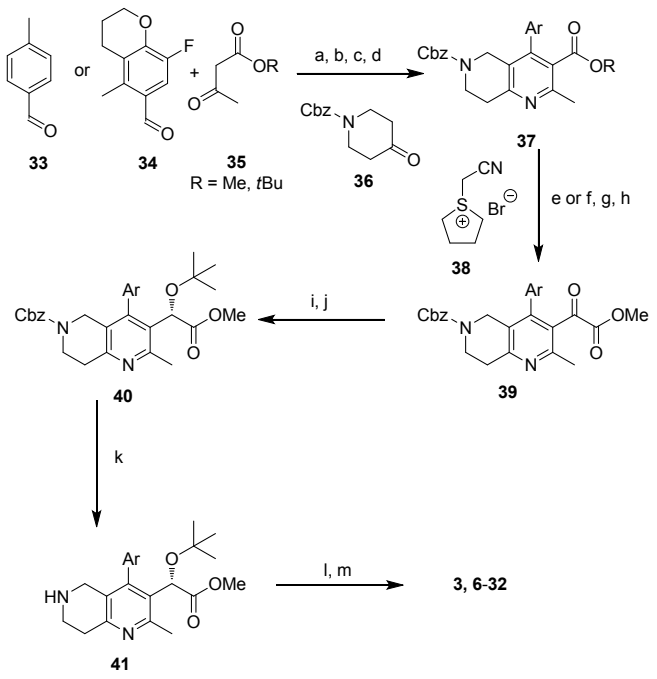
Compound	CL (mL/min/kg)[b]	Vss (L/kg)[c]	%F[d]
3	24	3	NA[e]
6	21	7	35%
8	171	16	NA[e]
11	163	2	NA[e]
12	118	19	71%
16	24	9	25%
17	152	66	32%
23	82	6	10%
25	92	1	10%

[a] All compounds evaluated *in vivo* are included in Table 4. [b] Clearance (CL). [c] Steady state volume of distribution (Vss). [d] Oral bioavailability. [e] PO arm was not evaluated.

Tetrahydronaphthyridines **3** and **6**-**32** were readily prepared following the synthetic procedures outlined in Scheme 1. Piperidine-catalyzed Knoevenagel condensation of tolyl aldehyde **33** or chromane aldehyde **34** with ketoester **35** provided the respective enoate products. The lithium enolate of ketone **36**, generated by deprotonation with LiHMDS, was added to the enoate. Treatment of the addition products with NH_4OAc/AcOH produced the dihydropyridines which were readily oxidized with ceric ammonium nitrate (CAN) to deliver the pyridine products **37**. Following saponification of the alkyl ester, Bode homologation of the carboxylate provided the keto esters **39**.[35] Asymmetric reduction of the ketone utilizing the Corey–Bakshi–Shibata (CBS) (*R*)-borane reagent gave the chiral alcohol which was alkylated with *t*-butyl acetate/perchloric acid to produce the *t*-butyl ethers **40**.

Deprotection of the benzyl carbamate (Cbz) under standard hydrogenation conditions provided the highly versatile amines **41**. Using either reductive amination or acylation chemistry followed by saponification of the ester led to target compounds **3** and **6-32**.

Scheme 1. Preparation of **3**, **6-32**.



Reagents. a) piperidine, DCM; b) **36**, LiHMDS, THF, -78 °C; NH_4OAc, AcOH, 60 °C; d) CAN, MeCN; e) LiCl, lutadine, DMSO, 130 °C; f) TFA; g) $(COCl)_2$, DMF (cat.), DCM; **38**, DIPEA, DCM; h) Oxone, MeOH, water; i) (*R*)-CBS borane, catechol borane, toluene, -20 °C; j) 70% $HClO_4$, t-BuOAc; k) 10% Pd/C, H_2, MeOH; l) reductive amination or acylation; m) 10 N NaOH, MeOH, 60 °C.

CONCLUSION

In conclusion, we have identified a new series of tetrahydronaphthyridine inhibitors of the interaction of HIV-1 integrase with LEDGF/p75 that exhibit potent antiviral activity in cell culture and display activity to-ward clinically-relevant integrase polymorphic viruses. The discovery of this series was based upon the rational structure-based hypothesis of exploring extension of **3** toward occupation of a hydrophobic portion of the LEDGF/p75 binding pocket on integrase, a strategy that differs from previous optimization campaigns which explored an alternative direction for structural optimization. Lead compounds from this series were profiled in rat pharmacokinetic studies but, as with other representatives of this inhibitor class, balancing potent antiviral activity with an acceptable pharmacokinetic profile remains a key challenge in moving the series forward.

EXPERIMENTAL SECTION

General Information. All materials were obtained from commercial suppliers and used without purification. Dry organic solvents were purchased from Sigma-Aldrich packaged under nitrogen in Sure Seal bottles. NMR spectra were obtained on Bruker 400 MHz or 500 MHz NMR spectrometers. The chemical shifts of ^1H and ^{13}C NMR signals are cited relative to internal $CHCl_3$ (δ = 7.26) and $CDCl_3$ (δ = 77.0). LCMS obtained on Shimadzu LCMS 2020 system run with 2%-98% MeCN/water gradient [0.05% TFA]. Purity of final compounds was ≥95% based on analytical HPLC and NMR analysis.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-phenyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (3). A solution of methyl 2-(*tert*-butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.040 g, 0.095 mmol, 1 equiv), Et_3N (0.013 mL, 0.095 mmol, 1 equiv) and bromobenzene (0.020 mL, 0.191 mmol, 2 equiv) was added to a mixture of trisdibenzylideneacetone-dipalladium chloroform complex (5 mg, 4.77 µmol, 0.05 equiv), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-Phos) (4 mg, 9.55 µmol, 0.10 equiv) and sodium *t*-butoxide (0.018 g, 0.191 mmol, 2 equiv) in toluene (2 mL). The resulting mixture was stirred at 110 °C for 4 h then cooled to room temperature, diluted with EtOAc, and washed with water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to provide the product (0.051 g) as a yellow oil. LCMS (ESI, M+1): 459.1. The crude coupling product was taken up in dioxane (2 mL) and 1 N NaOH (1.1 mL, 1.11 mmol) was added. The reaction was heated at 75 °C for 4 h. Upon cooling to ambient temperature, the crude mixture was purified via preparative HPLC to provide the product (17 mg, 41%). ^1H NMR (500 MHz, DMSO-d_6) δ 7.38 (dd, *J* = 7.6, 15.0 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J*=7.63 Hz, 1H), 7.17 (t, *J*=7.93 Hz, 2H), 6.66-6.82 (m, 3H), 4.80 (s, 1H), 4.07 (d, *J*=16.17 Hz, 1H), 3.63-3.73 (m, 2H), 3.55 (td, *J*=6.33, 12.97 Hz, 1H), 2.96 (br. s., 2H), 2.50 (s, 3H), 2.43 (s, 3H), 0.89 (s, 9H). LCMS (ESI, M+1): 445.2.

(S)-2-(6-Benzyl-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (6). To a solution of methyl 2-(*tert*-butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.042 g, 0.100 mmol, 1 equiv) in acetonitrile (2.5 mL) were added BnBr (0.014 mL, 0.120 mmol, 1.2 equiv) followed by DIPEA (0.052 mL, 0.300 mmol, 3 equiv). After 1.5 h, the reaction was diluted with EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give methyl 2-(6-benzyl-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(*tert*-butoxy)acetate (0.048 g) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.45 (m, 1H), 7.25-7.32 (m, 5H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.14-7.21 (m, 1H), 7.05 (dd, *J* = 1.7, 7.8 Hz, 1H), 4.96 (s, 1H), 3.70 (s, 3H), 3.44-3.66 (m, 2H), 3.12-3.41 (m, 2H), 2.96-3.08 (m, 2H), 2.63-2.85 (m, 2H), 2.62 (s, 3H), 2.44 (s, 3H), 0.98 (s, 9H). LCMS (ESI, M+1): 473.4. To a solution of the crude benzylation product in dioxane (3 mL) was added 1 N NaOH (1.0 mL, 1.00 mmol, 10 equiv). The mixture was heated at 70 °C for 1 h. Upon cooling ambient temperature, the mixture was quenched with 1 mL 1 N HCl and purified via preparative HPLC to provide the product (30 mg, 65%). ^1H NMR (500 MHz, DMSO-d_6) δ 7.20-7.35 (m, 7H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.09 (dd, *J* = 1.5, 7.6 Hz, 1H), 4.77 (s, 1H), 3.44-3.58 (m, 2H), 3.30 (br. s., 1H), 2.99 (d, *J* = 15.6 Hz, 1H), 2.81-2.89 (m, 2H), 2.75 (td, *J* = 5.5, 11.0 Hz, 1H), 2.56-2.65 (m, 1H), 2.48 (s, 3H), 2.37 (s, 3H), 0.87 (s, 9H). LCMS (ESI, M+1): 459.3.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-phenethyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (7). To a solution of methyl 2-(*tert*-butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.030 g, 0.072 mmol, 1 equiv) in THF (0.7 mL) was

added 2-phenylethanal (0.014 mL, 0.107 mmol, 1.5 equiv), acetic acid (0.239 mL) and sodium triacetaoxyborohydride (0.024 g, 0.107 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 2 h. The mixture was concentrated and purified by preparative HPLC to provide the tertiary amine. The amine was taken up in dioxane (1 mL) and 1 N NaOH (0.700 mL, 0.700 mmol, 10 equiv) was added. The reaction was heated at 75 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 M HCl (0.7 mL) and then purified by preparative HPLC to provide the product (16 mg, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29-7.38 (m, 2H), 7.21-7.26 (m, 2H), 7.09-7.21 (m, 5H), 4.77 (s, 1H), 3.26 (s, 1H), 2.95 (d, J = 15.0 Hz, 1H), 2.88 (br. s., 3H), 2.62-2.76 (m, 3H), 2.58 (d, J = 7.0 Hz, 2H), 2.48 (s, 3H), 2.40 (s, 3H), 0.87 (s, 9H). LCMS (ESI, M+1): 473.1.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-(3-phenylpropyl)-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (8). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.030 g, 0.072 mmol, 1 equiv) in acetonitrile (2 mL) was added K_2CO_3 (0.022 g, 0.158 mmol, 2.2 equiv) followed by (3-chloropropyl)benzene (0.010 ml, 0.072 mmol, 1 equiv). The resulting mixture was stirred at 75 °C for 48 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc and water. The organic fraction was dried (Na_2SO_4) and concentrated *in vacuo* to give methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-6-(3-phenylpropyl)-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate as a colorless oil which was carried on without purification. LCMS (ESI, M+1): 501.4. A solution of the crude tertiary amine and 1 N NaOH (0.720 mL, 0.720 mmol, 10 equiv) in dioxane (2 mL) was heated at 75 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 N HCl (0.75 mL) and concentrated and *in vacuo*. The crude product was purified by preparative HPLC to provide the product (16 mg, 46%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (d, J = 7.93 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.19-7.28 (m, 3H), 7.09-7.18 (m, 4H), 4.76 (s, 1H), 3.20 (d, J = 15.6 Hz, 1H), 2.83-2.94 (m, 3H), 2.79 (td, J = 5.15, 10.8 Hz, 1H), 2.56-2.64 (m, 1H), 2.54 (br. s., 2H), 2.48 (s, 3H), 2.39 (s, 3H), 2.32 (t, J = 6.7 Hz, 2H), 1.63 (quin, J = 7.3 Hz, 2H), 0.87 (s, 9H). LCMS (ESI, M+1): 487.1.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-(2-phenoxyethyl)-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (9). To a suspension of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.050 g, 0.119 mmol, 1 equiv) in acetonitrile (1 mL) was added DIPEA (0.104 mL, 0.597 mmol, 5 equiv) followed by (2-iodoethoxy)benzene (0.089 g, 0.358 mmol, 3 equiv). After stirring the solution for 21 h, MeOH (1 mL), water (0.1 mL), and LiOH monohydrate (0.050 g, 1.19 mmol, 10 equiv) were added. After stirring at ambient temperature for 4 d, the reaction was neutralized with 1 N HCl (1.2 mL) and concentrated and *in vacuo*. The crude product was purified by preparative HPLC to provide the product (55 mg, 91%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.25 (dd, J = 8.5, 7.3 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.91 (t, J = 7.3 Hz, 1H), 6.76 (d, J = 7.6 Hz, 2H), 4.78 (s, 1H), 4.08 - 3.96 (m, 2H), 3.39 - 3.37 (m, 2H), 2.96 - 2.86 (m, 3H), 2.76 (t, J = 5.6 Hz, 3H), 2.48 (s, 3H), 2.41 (s, 3H), 0.87 (s, 9H); LCMS (ESI, M+1): 489.6.

(S)-2-(tert-Butoxy)-2-(6-cinnamyl-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (10). To a suspension of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.125 g, 0.298 mmol, 1 equiv) in acetonitrile (9 mL) was added DIPEA (0.156 mL, 0.895 mmol, 3 equiv) followed by (*E*)-(3-chloroprop-1-en-1-yl)benzene (0.055 g, 0.358 mmol, 1.2 equiv). After stirring 6 h, the solution was diluted with EtOAc and washed with water (x2), brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (0-100% EtOAc/hexane) to provide the product (72 mg, 48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) □□7.29-7.41 (m, 4H), 7.26 (s, 2H), 7.14-7.23 (m, 2H), 7.06 (dd, J = 1.7, 7.82 Hz, 1H), 6.49 (d, J = 15.9 Hz, 1H), 6.23 (td, J = 6.7, 15.9 Hz, 1H), 4.96 (s, 1H), 3.69 (s, 3H), 3.36 (d, J = 15.4 Hz, 1H), 3.02-3.29 (m, 5H), 2.92 (td, J = 5.5, 11.31 Hz, 1H), 2.78 (td, J = 5.7, 11.3 Hz, 1H), 2.62 (s, 3H), 2.42 (s, 3H), 0.98 (s, 9H). LCMS (ESI, M+1): 499.7. A mixture of methyl (*S,E*)-2-(*tert*-butoxy)-2-(6-cinnamyl-2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate (60 mg, 0.120 mmol, 1 equiv) and 1 N NaOH (1.20 mL, 1.20 mmol, 10 equiv) in MeOH was heated at 65 °C for 1.5 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 N HCl and concentrated *in vacuo*. The crude product was purified by preparative HPLC to provide the product (25 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.95 (br. s., 1H), 7.23-7.41 (m, 6H), 7.04-7.22 (m, 3H), 6.48 (d, J = 15.9 Hz, 1H), 6.09-6.33 (m, 1H), 4.84 (br. s., 1H), 2.99-3.52 (m, 7H), 2.82 (br. s., 1H), 2.65 (s, 3H), 2.37 (s, 3H), 0.98 (s, 9H). LCMS (ESI, M+1): 485.7.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-(3-phenylpropanoyl)-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (11). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.030 g, 0.072 mmol, 1 equiv) and DIPEA (0.038 mL, 0.215 mmol, 3 equiv) in DCM (2 mL) was added 3-phenylpropanoyl chloride (0.013 g, 0.079 mmol, 1.1 equiv). After stirring 4 h, the reaction was diluted with DCM, washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product which was carried on without purification. LCMS (ESI, M+1): 515.4. A solution of the crude amide and 1 N NaOH (0.720 mL, 0.720 mmol, 10 equiv) in dioxane (2 mL) was heated at 75 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 N HCl (0.72 mL) and concentrated *in vacuo*. The crude product was purified by preparative HPLC to provide the product (19 mg, 52%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.11-7.42 (m, 8H), 7.04 (d, J = 7.3 Hz, 1H), 4.71-4.83 (m, 1H), 3.87-4.38 (m, 2H), 3.74-3.84 (m, 1H), 3.59-3.73 (m, 1H), 2.59-2.97 (m, 6H), 2.49 (s, 3H), 2.39-2.43 (m, 3H), 0.87 (s, 9H). LCMS (ESI, M+1): 501.3.

(S)-2-(6-((Benzyloxy)carbonyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (12). A solution of benzyl (*S*)-3-(1-(*tert*-butoxy)-2-methoxy-2-oxoethyl)-2-methyl-4-(*p*-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (**41a**) (25 mg, 0.048 mmol) and 1 N NaOH (0.48 mL, 0.480 mmol, 10 equiv) in MeOH (1.5 mL) was stirred at 65 °C for 1 h. Upon cooling to ambient temperature, the mixture was stirred a further 18 h. The mixture was diluted with water and EtOAc and neutralized with 1 N HCl (0.48 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to provide the crude product. The crude product was purified by preparative HPLC to provide the product (21 mg, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.59 (m, 8H), 7.05 (br. s., 1H), 5.13 (br. s., 2H), 5.03 (s, 1H), 4.44 (d, J = 18.1 Hz, 1H), 4.13

(d, *J* = 18.1 Hz, 1H), 3.22-3.47 (m, 2H), 2.85 (s, 3H), 2.48 (s, 3H), 1.01 (s, 9H). LCMS (ESI, M+1): 503.1.

(S)-2-(6-(Benzylcarbamoyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (13). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.030 g, 0.072 mmol, 1 equiv) and TEA (0.040 mL, 0.286 mmol, 4 equiv) in DCM (2 mL) was added (isocyanatomethyl)benzene (0.010 mL, 0.079 mmol, 1.1 equiv). After stirring 4 h, the reaction was diluted with DCM, washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product which was carried on without purification. A solution of the crude urea and 1 N NaOH (0.720 mL, 0.720 mmol, 10 equiv) in dioxane (2 mL) was heated at 75 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 N HCl (0.72 mL) and concentrated *in vacuo*. The crude product was purified by preparative HPLC to provide the product (28 mg, 77%). LCMS (ESI, M+1): 516.3. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.11-7.41 (m, 10H), 4.78 (s, 1H), 4.11-4.24 (m, 3H), 3.98 (d, *J* = 17.1 Hz, 1H), 3.71-3.81 (m, 1H), 3.50-3.63 (m, 1H), 2.80-2.96 (m, 2H), 2.49 (s, 3H), 2.40 (s, 3H), 0.87 (s, 9H). LCMS (ESI, M+1): 502.3.

(S)-2-(6-([1,1'-Biphenyl]-4-yl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (14). A solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.040 g, 0.095 mmol, 1 equiv), TEA (0.013 mL, 0.095 mmol, 1 equiv) and 4-bromo-1,1'-biphenyl (0.032 mL, 0.191 mmol, 2 equiv) in toluene (2 mL) was added to a mixture of trisdibenzylideneacetone dipalladium chloroform complex (4.94 mg, 0.048 mmol, 0.05 equiv), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-Phos) (3.92 mg, 0.096 mmol, 0.10 equiv) and sodium *t*-butoxide (0.018 g, 0.191 mmol, 2 equiv). The reaction was heated to 110 °C for 21 h. Upon cooling to ambient temperature, the reaction was diluted with EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to provide the product (0.035 g) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.60 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.21-7.40 (m, 5H), 7.14 (dd, *J* = 1.7, 7.8 Hz, 1H), 6.98-7.08 (m, 2H), 6.79 (dd, *J* = 2.0, 8.3 Hz, 1H), 5.01 (s, 1H), 4.11 (d, *J* = 16.4 Hz, 1H), 3.86 (d, J=16.4 Hz, 1H), 3.58-3.82 (m, 5H), 3.19 (q, *J* = 5.8 Hz, 2H), 2.65 (s, 3H), 2.48 (s, 3H), 1.01 (s, 9H). LCMS (ESI, M+1): 535.1. The amine was taken up in dioxane (2 mL) and 1 N NaOH (0.65 mL, 0.650 mmol, 6.8 equiv) was added. The reaction was heated at 75 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 M HCl (0.75 mL) and then purified by preparative HPLC to provide the product (16 mg, 33%). ^{1}H NMR (500 MHz, DMSO-d_6) δ .53 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.33-7.43 (m, 3H), 7.22-7.33 (m, 3H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.77 (dd, *J* = 2.1, 8.2 Hz, 1H), 4.85 (s, 1H), 4.15 (d, *J* = 16.2 Hz, 1H), 3.78-3.86 (m, 1H), 3.75 (d, *J* = 16.5 Hz, 1H), 3.66 (td, *J* = 6.5, 13.3 Hz, 1H), 2.93-3.03 (m, 2H), 2.47-2.50 (m, 3H), 2.43 (s, 3H), 0.90 (s, 9H). LCMS (ESI, M+1): 521.1.

(S)-2-(6-([1,1'-Biphenyl]-3-yl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (15). A solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.040 g, 0.095 mmol, 1 equiv), TEA (0.013 mL, 0.095 mmol, 1 equiv) and 3-bromo-1,1'-biphenyl (0.032 mL, 0.191 mmol, 2 equiv) in toluene (2 mL) was added to a mixture of trisdibenzylideneacetone dipalladium chloroform complex (4 mg, 0.048 mmol, 0.05 equiv), 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (S-Phos) (3.92 mg, 0.096 mmol, 0.10 equiv) and sodium *t*-butoxide (0.018 g, 0.191 mmol, 2 equiv). The reaction was heated to 110 °C for 21 h. Upon cooling to ambient temperature, the reaction was diluted with EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to provide the crude product as a brown oil. LCMS (ESI, M+1): 535.8. The amine was taken up in dioxane (2 mL) and MeOH (2 mL). 1 N NaOH (0.95 mL, 0.950 mmol, 10 equiv) was added. The reaction was heated at 75 °C for 4.5 h. Upon cooling to ambient temperature, the reaction was neutralized with 1 M HCl and then purified by preparative HPLC to provide the product (21 mg, 41%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.42 - 7.32 (m, 3H), 7.31 - 7.18 (m, 3H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.90 (s, 1H), 6.76 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.84 (s, 1H), 4.14 (d, *J* = 16.2 Hz, 1H), 3.83 - 3.77 (m, 1H), 3.74 (d, *J* = 16.2 Hz, 1H), 3.68 - 3.62 (m, 1H), 2.97 (br. s., 2H), 2.49 (s, 3H), 2.42 (s, 3H), 0.89 (s, 9H). LCMS (ESI, M+1): 521.5.

(S)-2-(6-([1,1'-Biphenyl]-2-ylmethyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (16). A solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.030 g, 0.078 mmol, 1 equiv), 2-phenylbenzaldehyde (0.029 g, 0.157 mmol, 2 equiv), and DIPEA (0.014 mL, 0.078 mmol, 1 equiv) in DCE (0.5 mL) was added a solution of sodium triacetoxyborohyride (62 mg, 0.235 mmol, 3 equiv) in DCE (0.5 mL). After stirring 24 h, the reaction was concentrated. The residue was dissolved in MeOH (0.75 mL) and 1 N NaOH (0.75 mL) was added. The reaction was heated to 65 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with AcOH (0.1 mL) and then purified by preparative HPLC to provide the product (23 mg, 55%). ^{1}H NMR (500 MHz, DMSO-d_6) □ 7.49 - 7.42 (m, 1H), 7.40 - 7.21 (m, 9H), 7.19 - 7.16 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.76 (s, 1H), 3.43 - 3.38 (m, 1H), 3.21 - 3.10 (m, 2H), 2.88 - 2.79 (m, 3H), 2.72 - 2.64 (m, 1H), 2.56 - 2.53 (m, 1H), 2.47 (s, 3H), 2.40 (s, 3H), 0.87 (s, 9H); LCMS (ESI,M+1): 535.4.

(S)-2-(tert-Butoxy)-2-(6-(3-cyclopentylpropyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (17). To a solution of (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (**S3**) (20 mg, 0.54 mmol, 1 equiv), 3-cyclopentylpropanal (12 mg, 0.95 mmol, 1.75 mmol), and AcOH (0.016 mL, 0.271 mmol, 5 equiv) in MeOH (1 mL) was added sodium cyanoborohydride (17 mg, 0.271 mmol, 5 equiv). After stirring 18 h, the mixture was purified by preparative HPLC to provide the product (13 mg, 50%) as an off white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.41 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 4.80 (s, 1H), 3.92 (d, *J* = 15.3 Hz, 1H), 3.51-3.61 (m, 2H), 3.26-3.31 (m, 2H), 3.11-3.17 (m, 1H), 2.88-3.05 (m, 2H), 2.64 (s, 3H), 2.45 (s, 3H), 1.69-1.80 (m, 3H), 1.49-1.67 (m, 7H), 1.31 (m, 2H), 1.00-1.10 (m, 2H), 0.92 (s, 9H); LCMS (ESI, M+1): 479.5.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-pentyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (18). A solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-

5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.030 g, 0.078 mmol, 1 equiv), pentanal (0.014 g, 0.157 mmol, 2 equiv), and DIPEA (0.014 mL, 0.078 mmol, 1 equiv) in DCE (0.5 mL) was added a solution of sodium triacetoxyborohyride (62 mg, 0.235 mmol, 3 equiv) in DCE (0.5 mL). After stirring 24 h, the reaction was concentrated. The residue was dissolved in MeOH (0.75 mL) and 1 N NaOH (0.75 mL) was added. The reaction was heated to 65 °C for 1 h. Upon cooling to ambient temperature, the reaction was neutralized with AcOH (0.1 mL) and then purified by preparative HPLC to provide the product (28 mg, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) □ 7.33 (dd, J = 17.4, 7.9 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.13 (dd, J = 7.9, 1.5 Hz, 1H), 4.77 (s, 1H), 3.23 - 3.16 (m, 1H), 2.93 - 2.84 (m, 3H), 2.81 - 2.74 (m, 1H), 2.62 - 2.55 (m, 1H), 2.48 (s, 3H), 2.40 (s, 3H), 2.29 (t, J = 7.2 Hz, 2H), 1.33 (quin, J = 7.2 Hz, 2H), 1.27 - 1.15 (m, 4H), 0.88 (s, 9H), 0.82 (t, J = 6.9 Hz, 3H); LCMS (ESI, M+1): 439.4.

(S)-2-(tert-Butoxy)-2-(2,6-dimethyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (19). To a solution of methyl 2-(*tert*-butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.042 g, 0.10 mmol, 1 equiv) in THF (1 mL) and acetic acid (0.33 mL) was added 37% formaldehyde (0.011 mL, 0.150 mmol, 1.5 equiv) and $NaBH(OAc)_3$ (0.033 g, 0.150 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 2 h. The mixture was then purified by preparative HPLC to provide the product (0.040 g) as a white paste. The tertiary amine was then taken up in dioxane (3 mL) and 1 N NaOH (0.10 mL, 0.100 mmol, 1 equiv) was added. The reaction was heated to 70 °C for 1 h. Upon cooling to ambient temperature, the mixture was neutralized with 1 N HCl and then purified by preparative HPLC to give the product (14 mg, 39%). ^{1}H NMR (500 MHz, DMSO-d_6) □ 7.32 (dd, J = 7.9, 15.6 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.12 (dd, J=1.5, 7.63 Hz, 1H), 4.73 (s, 1H), 3.16 (s, 1H), 2.77-2.95 (m, 2H), 2.68-2.77 (m, 1H), 2.54-2.60 (m, 1H), 2.48 (s, 3H), 2.39 (s, 3H), 2.21 (s, 3H), 0.86 (s, 9H). LCMS (ESI, M+1): 383.3.

(S)-2-(6-Acetyl-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(tert-butoxy)acetic acid (20). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl (**41a**) (0.040 g, 0.095 mmol, 1 equiv) in DCM (2 mL) was added DIPEA (0.050 mL, 0.286 mmol, 3 equiv) followed by acetyl chloride (0.007 mL, 0.105 mmol, 1.1 equiv). The reaction was stirred for 18 h. Additional acetyl chloride (0.007 mL, 0.105 mmol, 1.1 equiv) and DIPEA (0.050 mL, 0.286 mmol, 3 equiv) was added. The reaction was stirred an additional 6 h. The mixture was dilted with EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give crude amide. The amide was taken up in dioxane (2 mL) and 1 N NaOH (0.95 mL, 0.95 mmol, 10 equiv) was added. The reaction was heated to 70 °C for 1 h. Upon cooling to ambient temperature, the mixture was neutralized with 1 N HCl (0.95 mL) and then purified by preparative HPLC to give the product (7 mg, 18%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36 (dd, J = 7.5, 16.0 Hz, 2H), 7.10-7.29 (m, 2H), 4.74-4.85 (m, 1H), 3.57-3.84 (m, 2H), 2.79-3.02 (m, 2H), 2.54-2.68 (m, 2H), 2.50 (br. s., 3H), 2.42 (s, 3H), 1.81-2.08 (m, 3H), 0.82-0.93 (m, 9H); LCMS (ESI, M+1): 411.1.

(S)-2-(tert-Butoxy)-2-(6-(methoxycarbonyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (21). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-(2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl (**41a**) (0.040 g, 0.095 mmol, 1 equiv.) in THF (2 mL) was added TEA (0.032 mL, 0.229 mmol, 2.2 equiv) and methyl chloroformate (11 mg, 0.115 mmol, 1.2 equiv). The reaction was stirred at room temperature for 1 h and then diluted with EtOAc. The mixture was washed with water and the organic phase was dried (Na_2SO_4 and concentrated *in vacuo*. LCMS (ESI, M+1): 441.1. The crude carbamate was taken up in dioxane (2 mL) and 1 N NaOH (0.95 mL, 0.95 mmol, 10 equiv) was added. The reaction was heated to 75 °C for 1 h. Upon cooling to ambient temperature, the mixture was neutralized with 1 N HCl (1.9 mL) and then purified by preparative HPLC to give the product (23 mg, 56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21-7.43 (m, 3H), 7.15 (d, J = 7.9 Hz, 1H), 4.73 (br. s., 1H), 4.14-4.34 (m, 1H), 3.87-3.99 (m, 1H), 3.67-3.82 (m, 1H), 3.56 (br. s., 4H), 2.87 (t, J = 5.8 Hz, 2H), 2.49 (s, 3H), 2.41 (s, 3H), 0.86 (s, 9H); LCMS (ESI, M+1): 427.3.

(S)-2-(tert-Butoxy)-2-(2-methyl-6-(methylsulfonyl)-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (22). To a solution of methyl 2-(*tert*-butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41a**) (0.042 g, 0.100 mol, 1 equiv) in DCM (2 mL) was added TEA (0.049 mL, 0.350 mmol). The solution cooled to 0 °C (ice/water) and MsCl (8 µl, 0.100 mmol, 1 equiv) was added. After 1.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The reaction was partitioned between EtOAc and water. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to provide the product (0.052 g) as a colorless oil that crystallized upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.35 (m, 2H), 7.16 (dd, J = 1.8, 7.7 Hz, 1H), 7.04 (dd, J = 1.71, 7.6 Hz, 1H), 4.93 (s, 1H), 4.11 (d, J = 16.1 Hz, 1H), 3.84 (d, J=16.1 Hz, 1H), 3.70 (s, 3H), 3.51-3.69 (m, 2H), 3.15 (t, J = 6.0 Hz, 2H), 2.76 (s, 3H), 2.62 (s, 3H), 2.44 (s, 3H), 0.98 (s, 9H). LCMS (ESI, M+1): 461.3. The sulfonamide was taken up in dioxane (3 mL) and 1 N NaOH (1.0 mL, 1.00 mmol, 10 equiv) was added. The reaction was heated to 70 °C for 1 h. Upon cooling to ambient temperature, the mixture was neutralized with 1 N HCl and then purified by preparative HPLC to give the product (39 mg, 88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36 (dd, J = 7.9, 15.6 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.17 (dd, J = 1.7, 7.8 Hz, 1H), 4.75 (s, 1H), 4.11 (d, J = 15.6 Hz, 1H), 3.69 (d, J = 15.6 Hz, 1H), 3.56 (td, J = 5.7, 11.9 Hz, 1H), 3.40-3.47 (m, 1H), 3.00 (t, J = 6.0 Hz, 2H), 2.86 (s, 3H), 2.52 (d, J = 1.8 Hz, 3H), 2.41 (s, 3H), 0.87 (s, 9H). LCMS (ESI, M+1): 447.3.

(S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(3-phenylpropyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (23). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (30 mg, 0.066 mmol, 1 equiv), 3-phenylpropionaldehyde (0.026 mL, 0.197 mmol, 3 equiv), and DIPEA (0.034 mL, 0.197 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (21 mg, 0.329 mmol, 5 equiv). After 2 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.5 mL) and water (0.1 mL). Lithium hydroxide monohydrate (28 mg, 0.661 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 2 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (25 mg,

54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 - 7.24 (m, J = 7.6 Hz, 2H), 7.19 - 7.13 (m, J = 8.2 Hz, 3H), 6.71 (d, J = 11.0 Hz, 1H), 4.20 (t, J = 5.2 Hz, 2H), 2.93 - 2.86 (m, J = 5.5 Hz, 3H), 2.73 - 2.64 (m, J = 3.7, 1.6, 1.6 Hz, 4H), 2.58 - 2.53 (m, 2H), 2.43 - 2.40 (m, 2H), 2.39 - 2.32 (m, 4H), 2.02 (dd, J = 6.7, 4.6 Hz, 2H), 1.79 (s, 3H), 1.70 - 1.63 (m, J = 6.4 Hz, 2H); LCMS (ESI, M+1): 561.5.

(S)-2-(tert-butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(((1S,2R)-2-phenylcyclopropyl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid and (S)-2-(tert-butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(((1R,2S)-2-phenylcyclopropyl)methyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (24, 1:1 mixture). A solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 2-phenylcyclopropanecarbaldehyde (**S9**) (9 mg, 0.061 mmol, 1.5 equiv), sodium cyanoborohydride (13 mg, 0.203, 5 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (1 mL) was stirred for 2 h. More 2-phenylcyclopropanecarbaldehyde (**S9**) (9 mg, 0.061 mmol, 1.5 equiv) and sodium cyanoborohydride (13 mg, 0.203, 5 equiv) were added. After 1 h, more 2-phenylcyclopropanecarbaldehyde (**S9**) (9 mg, 0.061 mmol, 1.5 equiv) and sodium cyanoborohydride (13 mg, 0.203, 5 equiv) were added. After 1 h, the reaction was added to saturated sodium bicarbonate and extracted with DCM (x3). The combined DCM extracts were dired (Na_2SO_4) and concentrated *in vacuo*. The crude amine was taken up in MeOH (1 mL) and water (0.1 mL). Lithium hydroxide monohydrate (17 mg, 0.406 mmol, 10 equiv) was added and the reaction was heated at 60 °C for 40 min. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (12 mg, 52%) as a diastereomeric mixture. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 - 7.05 (m, 4H), 6.92 - 6.91 (m, 1H), 6.63 - 6.57 (m, 1H), 4.67 (d, J = 4 Hz, 1H), 4.20 (d, J = 4 Hz, 2H), 2.89 – 1.69 (m, 18H), 1.15 (m, 1H), 0.99 (s, 9H), 0.93 – 0.89 (m, 1H), 0.71 – 0.67 (m, 1H); LCMS (ESI, M+1): 573.6.

(S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-6-(3-(4-fluorophenyl)propyl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (25). To a solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (30 mg, 0.066 mmol, 1 equiv), 1-fluoro-4-(3-iodopropyl)benzene (52 mg, 0.197 mmol, 3 equiv), and DIPEA (0.034 mL, 0.197 mmol, 3 equiv) in MeCN (0.5 mL) was added sodium cyanoborohydride (19 mg, 0.330 mmol, 5 equiv). THe reaction was stirred for 6 d. Upon completion, the reaction was concentrated *in vacuo*. The crude amine was taken up in MeOH (0.5 mL) and water (0.1 mL). Lithium hydroxide monohydrate (28 mg, 0.661 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 2 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (30 mg, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.20 - 7.15 (m, J = 8.5, 5.8 Hz, 2H), 7.09 - 7.04 (m, 2H), 6.69 (d, J = 11.3 Hz, 1H), 4.72 (s, 1H), 4.21 (t, J = 5.2 Hz, 2H), 2.98 (d, J = 15.0 Hz, 1H), 2.90 - 2.85 (m, 2H), 2.82 (d, J = 15.3 Hz, 1H), 2.72 - 2.63 (m, 4H), 2.56 - 2.53 (m, 4H), 2.31 (t, J = 7.0 Hz, 2H), 2.06 - 1.99 (m, J = 5.2 Hz, 2H), 1.75 (s, 3H), 1.64 (quin, J = 7.4 Hz, 2H), 1.02 (s, 9H); LCMS (ESI, M+1): 579.4.

(S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(3-(p-tolyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (26). To a of solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 3-(*p*-tolyl)propanal (18 mg, 0.122 mmol, 3 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (13 mg, 0.203 mmol, 5 equiv). After 18 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.4 mL) and water (0.04 mL). Lithium hydroxide (10 mg, 0.391 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 2 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (18 mg, 76%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.06 - 7.02 (m, 2H), 7.02 - 6.98 (m, 2H), 6.66 (d, J = 11.3 Hz, 1H), 4.69 (s, 1H), 4.20 (t, J = 5.0 Hz, 2H), 2.96 (d, J = 15.3 Hz, 1H), 2.89 - 2.79 (m, 3H), 2.70 - 2.61 (m, 4H), 2.54 (s, 3H), 2.49 - 2.45 (m, 2H), 2.29 (t, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.02 (q, J = 5.5 Hz, 2H), 1.75 (s, 3H), 1.61 (quin, J = 7.1 Hz, 2H), 1.01 (s, 9H); LCMS (ESI, M+1): 575.6.

(S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-6-(3-(3-fluorophenyl)propyl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (27). To a of solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 3-(3-fluorophenyl)propanal (19 mg, 0.122 mmol, 3 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (13 mg, 0.203 mmol, 5 equiv). After 18 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.4 mL) and water (0.04 mL). Lithium hydroxide (10 mg, 0.391 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 1 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (30 mg, 100%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 (dd, J = 7.9, 7.0 Hz, 1H), 6.97 (d, J = 11.0 Hz, 3H), 6.66 (d, J = 11.9 Hz, 1H), 4.69 (s, 1H), 4.19 (t, J = 4.9 Hz, 3H), 2.96 (d, J = 15.9 Hz, 2H), 2.89 - 2.80 (m, 4H), 2.65 (dd, J = 18.9, 11.3 Hz, 3H), 2.58 - 2.53 (m, 6H), 2.30 (t, J = 6.7 Hz, 2H), 2.01 (d, J = 5.5 Hz, 2H), 1.74 (s, 3H), 1.69 - 1.60 (m, 2H), 1.00 (s, 9H); LCMS (ESI, M+1): 579.6.

(S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(3-(m-tolyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (28). To a of solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 3-(*m*-tolyl)propanal (18 mg, 0.122 mmol, 3 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (13 mg, 0.203 mmol, 5 equiv). After 18 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.4 mL) and water (0.04 mL). Lithium hydroxide (9 mg, 0.391 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 1 h. Upon cooling to ambient temperature, the mixture was purified by preparative

HPLC to give the product (20 mg, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.86 (t, J = 7.5 Hz, 1H), 6.73 - 6.66 (m, 2H), 6.63 (d, J = 7.3 Hz, 1H), 6.39 (d, J = 11.3 Hz, 1H), 4.43 (s, 1H), 3.92 (br. s., 2H), 2.72 (d, J = 15.0 Hz, 1H), 2.64 - 2.54 (m, 3H), 2.42 (br. s., 2H), 2.37 (br. s., 2H), 2.30 - 2.27 (m, 3H), 2.25 (br. s., 3H), 2.24 - 2.20 (m, 2H), 2.04 (t, J = 6.7 Hz, 2H), 1.98 (s, 3H), 1.74 (d, J = 5.2 Hz, 2H), 1.48 (s, 3H), 1.39 - 1.32 (m, J = 6.9, 6.9 Hz, 2H), 0.74 (s, 9H); LCMS (ESI, M+1): 575.6.

S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-6-(3-(2-fluorophenyl)propyl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (29). To a of solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 3-(2-fluorophenyl)propanal (19 mg, 0.122 mmol, 3 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (13 mg, 0.203 mmol, 5 equiv). After 18 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.4 mL) and water (0.04 mL). Lithium hydroxide (9 mg, 0.391 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 2 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (15 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.28 (dd, J = 9.2, 7.3 Hz, 1H), 7.01 - 6.93 (m, 3H), 6.66 (d, J = 11.3 Hz, 1H), 4.69 (s, 1H), 4.19 (t, J = 4.9 Hz, 2H), 2.97 (d, J = 15.3 Hz, 1H), 2.88 - 2.79 (m, 3H), 2.68 (t, J = 5.6 Hz, 2H), 2.66 - 2.61 (m, 2H), 2.59 - 2.53 (m, 5H), 2.30 (t, J = 6.6 Hz, 2H), 2.01 (d, J = 4.9 Hz, 2H), 1.75 (s, 3H), 1.65 (quin, J = 7.2 Hz, 2H), 1.01 (s, 9H); LCMS (ESI, M+1): 579.6.

(S)-2-(tert-Butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(3-(o-tolyl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (30). To a of solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 3-(o-tolyl)propanal (18 mg, 0.122 mmol, 3 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (13 mg, 0.203 mmol, 5 equiv). After 18 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.4 mL) and water (0.04 mL). Lithium hydroxide (9 mg, 0.391 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 1 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (19 mg, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.87 - 6.76 (m, 4H), 6.40 (d, J = 11.3 Hz, 1H), 4.42 (s, 1H), 3.94 (br. s., 2H), 2.74 (d, J = 15.6 Hz, 1H), 2.64 (s, 1H), 2.63 - 2.54 (m, 3H), 2.48 (s, 1H), 2.46 - 2.33 (m, 3H), 2.10 (t, J = 6.6 Hz, 2H), 1.94 (s, 3H), 1.76 (d, J = 4.6 Hz, 2H), 1.50 (s, 3H), 1.36 - 1.28 (m, J = 6.7 Hz, 2H), 0.75 (s, 9H); LCMS (ESI, M+1): 575.6.

(S)-2-(tert-Butoxy)-2-((R)-6-(3-(3-fluoro-4-methylphenyl)propyl)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (31). To a of solution of methyl (*S*)-2-(*tert*-butoxy)-2-((*R*)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (20 mg, 0.041 mmol, 1 equiv), 3-(3-fluoro-4-methylphenyl)propanal (20 mg, 0.122 mmol, 3 equiv), and DIPEA (0.021 mL, 0.122 mmol, 3 equiv) in MeOH (0.5 mL) was added sodium cyanoborohydride (13 mg, 0.203 mmol, 5 equiv). After 18 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The ether layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude amine was taken up in MeOH (0.4 mL) and water (0.04 mL). Lithium hydroxide (9 mg, 0.391 mmol, 10 equiv) was added and the reaction was heated at 80 °C for 1 h. Upon cooling to ambient temperature, the mixture was purified by preparative HPLC to give the product (19 mg, 66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 9.2 Hz, 2H), 6.66 (d, J = 11.3 Hz, 1H), 4.68 (s, 1H), 4.20 (t, J = 4.9 Hz, 2H), 2.98 (d, J = 15.3 Hz, 1H), 2.89 - 2.79 (m, 3H), 2.72 - 2.60 (m, 4H), 2.54 (s, 3H), 2.30 (t, J = 6.7 Hz, 2H), 2.18 (s, 3H), 2.06 - 1.97 (m, J = 5.2 Hz, 2H), 1.75 (s, 3H), 1.62 (quin, J = 7.1 Hz, 2H), 1.01 (s, 9H); LCMS (ESI, M+1): 593.6.

(2S)-2-(tert-butoxy)-2-(4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-6-(3-(pyridin-4-yl)propyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid, 1:1 mixture of atropisomers (32). To a of solution of 1 mixture of atropisomers of methyl (*S*)-2-(*tert*-butoxy)-2-(4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate, HCl salt (**41b**) (26 mg, 0.049 mmol, 1 equiv), 3-(pyridin-4-yl)propanal (20 mg, 0.1472 mmol, 3 equiv), and TEA (0.246 mL, 0.122 mmol, 5 equiv) in MeOH (1 mL) was added sodium cyanoborohydride (15 mg, 0.246 mmol, 5 equiv). After 2 h, the reaction was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine. The ethyl acetate layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude amine was taken up in MeOH (1 mL) and water (0.1 mL). Lithium hydroxide (21 mg, 0.491 mmol, 10 equiv) was added and the reaction was stirred for 18 h. The mixture was purified by preparative HPLC to give the product (7 mg, 25%) as a mixture of atropisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 – 8.47 (m, 2H), 7.10 – 7.08 (m, 2H), 6.99 - 6.91 (m, 1H, atropisomer 1), 6.59 - 6.57 (m, 1H, atropisomer 2), 4.67 (bs, 1H), 4.30 – 4.26 (m, 2H), 3.20 – 1.72 (m, 19H), 1.12 (s, 9H, atropisomer 1), 1.01 (s, 9H, atropisomer 2); LCMS (ESI, M+1): 562.2.

8-fluoro-5-methylchromane-6-carbaldehyde (34). To a solution of 6-bromo-8-fluoro-5-methylchroman (10 g, 36.7 mmol, 1 equiv) (*prepared following the procedure in WO2010130842*) in THF (200 mL) at -78 °C IPA/dry ice) was added *n*-BuLi (22 mL of a 2.5 M solution in hexane, 55.1 mmol, 1.5 equiv) dropwise. After stirring for 30 min, DMF (5.69 mL, 73.4 mmol, 2 equiv) was added dropwise. Upon complete addition, the reaction was warmed to 0°C (ice bath). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with ether, washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to provide the crude product as a reddish brown crystalline solid. The crude product was triturated in a small amount of ether and hexane to deliver the product (6.7 g, 94%) as creamy tan crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 11.3 Hz, 1H), 4.33 - 4.26 (m, 2H), 2.74 (t, J = 6.7 Hz, 2H), 2.51 (s, 3H), 2.15 - 2.08 (m, 2H).

6-Benzyl 3-methyl 2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-3,6(5H)-dicarboxylate (37a). A solution of LiHMDS (4.72 mL of a 1 N solution in THF, 4.72 mmol, 1.1 equiv) in THF (3 mL) was cooled to -78 °C. A solution of

benzyl 4-oxopiperidine-1-carboxylate (1.0 g, 4.29 mmol, 1 equiv) in THF (3.00 mL) was added dropwise over several minutes. After stirring for 10 min at -78 °C, the solution was allowed to warm to -20 °C and stirred for 15 min before cooling to -78 °C again. A cold (-78 °C) solution of methyl 2-(4-methylbenzylidene)-3-oxobutanoate (0.936 g, 4.29 mmol, 1 equiv) in THF (1.5 mL) was added via cannula and the resulting yellow solution was stirred at -40 °C for 3 h. The reaction was quenched with AcOH (1.23 mL, 21.44 mmol, 5 equiv) and allowed to warm to ambient temperature. Water was added and the aqueous phase was extracted with EtOAc (x3). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the Michael addition product as a brown oil (LCMS [M+1] = 452.4). The oil was taken up in EtOH (12 mL) and stirred with NH_4OAc (2.64 g, 34.3 mmol, 8 equiv) and *p*-toluenesulfonic acid monohydrate (0.041 g, 0.214 mmol, 0.05 equiv) at 80 °C. After 70 h, the mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to provide the dihydropyridine intermediate as a thick amber oil. To the residue dissolved in DCM (20 mL) was added cerium(IV) diammonium nitrate (4.70 g, 8.57 mmol, 2 equiv) and TFA (0.330 mL, 4.29 mmol, 1 equiv). The resulting mixture stirred for 1.5 h. The reaction mixture was then washed with water and the aqueous phase was extracted with DCM (x2). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (0-100% EtOAc/hexane) to give 6-benzyl 3-methyl 2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-3,6(5*H*)-dicarboxylate (1.25 g, 67%) as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.4 Hz, 5H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 5.13 (s, 2H), 4.36 (s, 2H), 3.82 (t, *J* = 6.0 Hz, 2H), 3.54 (s, 3H), 3.07 (br. s., 2H), 2.57 (s, 3H), 2.41 (s, 3H). LCMS (ESI, M+1): 431.4.

6-Benzyl 3-tert-butyl 4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-7,8-dihydro-1,6-naphthyridine-3,6(5H)-dicarboxylate (37b). To a solution of LHMDS (9.9 mL of a 1 M solution in THF, 9.87 mmol, 1.1 equiv) in THF (15 mL) at -78 °C (IPA/dry ice) was added dropwise a solution of benzyl 4-oxopiperidine-1-carboxylate (2.09 g, 8.97 mmol, 1 equiv) in THF (15 mL). After stirring 10 min, the temperature was raised to -20 °C (IPA/dry ice) for 15 min and then recooled to -78 °C. A solution of *tert*-butyl 2-((8-fluoro-5-methylchroman-6-yl)methylene)-3-oxobutanoate (**S4**) (3.0 g, 8.97 mmol, 1 equiv) in THF (15 mL) was added dropwise. After stirring 10 min, the temperature was raised to -40 °C (MeCN/dry ice) and stirred for 3 h. The reaction was then quenched with AcOH and added to water. The aqueous mixture was extracted with ether (x2). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was taken up in EtOH (30 mL) and ammonium acetate (6.9 g, 90 mmol, 10 equiv) was added. The reaction was heated at reflux for 16 h. Upon cooling to ambient temperature, the solution was concentrated *in vacuo*. The residue was triturated with DCM and filtered. The filtrate was then concentrated *in vacuo*. The crude dihydropyridine was then taken up in MeOH (30 mL) and CAN (9.8 g, 17.9 mmol, 2 equiv) was added. After stirring 1 h, the mixture was added to saturated aqueous sodium bicarbonate and extracted with ether (x3). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (0-100% EtOAc/hexane) to provide the product (2.30 g, 47%) as a tan solid. 1H NMR (400 MHz, CDCl3) δ 7.42 - 7.30 (m, 5H), 6.64 (d, *J* = 11.0 Hz, 1H), 5.17 - 5.09 (m, 2H), 4.30 - 4.23 (m, 2H), 4.22 - 4.15 (m, 2H), 3.97 - 3.84 (m, 1H), 3.79 - 3.63 (m, 1H), 3.13 - 2.98 (m, 2H), 2.76 - 2.60 (m, 1H), 2.57 (s, 3H), 2.16 - 2.08 (m, 2H), 1.90 - 1.71 (m, 4H), 1.22 (s, 9H); LCMS (ESI, M+1): 547.35.

Benzyl 3-(2-methoxy-2-oxoacetyl)-2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (39a). To a suspension of 6-((benzyloxy)carbonyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylic acid (**S1**) (1.88 g, 4.51 mmol, 1 equiv) and DMF (cat.) in DCM (30 mL) was added oxalyl chloride (11.3 mL of a 2 M solution in DCM, 22.55 mmol, 5 equiv). After 1 h, the mixture was concentrated *in vacuo* and azeotroped with toluene (x2) to remove unreacted oxalyl chloride. The residue was taken up in DCM (30 mL). DIPEA (4.7 mL, 0.893 mmol, 6 equiv) and 1-(cyanomethyl)tetrahydro-1H-thiophen-1-ium, bromide salt (**38**) (1.74 g, 13.53 mmol, 3 equiv) were added. The reaction was stirred for 20 h. The reaction was diluted with DCM, washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to give an amber oil. The oil was dissolved in MeOH (60 mL). A solution of Oxone (5.55 g, 9.02 mmol, 2 equiv) in water (30 mL) was added. The resulting suspension was stirred for 2 h. The methanol was removed *in vacuo* and the remaining solution extracted with EtOAc (x3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (0-100% EtOAc/hexane) to the product (1.82 g, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.51 (m, 7H), 6.92-7.11 (m, 2H), 5.13 (br. s., 2H), 4.28-4.52 (m, 2H), 3.44 (s, 3H), 3.25-3.38 (m, 2H), 3.11 (br. s., 2H), 2.50-2.63 (m, 3H), 2.41 (s, 3H); LCMS (ESI, M+1): 459.3.

Benzyl 4-(8-fluoro-5-methylchroman-6-yl)-3-(2-methoxy-2-oxoacetyl)-2-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (39b). To a solution of 6-((benzyloxy)carbonyl)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylic acid (**S5**) (2.42 g, 4.00 mmol, 1 equiv) from previous step and DMF (0.046 mL, 0.60 mmol, 0.15 equiv) in DCM (40 mL) was added oxalyl chloride (1.40 mL, 16.0 mmol, 4 equiv). Gas evolution! After 1 h, the solution was concentrated *in vacuo*. The crude acid chloride was taken up in DCM (40 mL) and DIPEA (4.19 mL, 24.0 mmol, 6 equiv) and 1-(cyanomethyl)tetrahydro-1H-thiophen-1-ium, bromide salt (**38**) (2.50 g, 12.0 mmol, 3 equiv). The mixture was stirred for 1 h, and then washed with saturated aqueous sodium bicarbonate. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (acetone) to provide the sulfur ylide (1.11 g) as a tan solid. LCMS (ESI, M+1): 600.35. The sulfur ylide was taken up in MeOH (19 mL) and water (1 mL). Oxone (2.28 g, 3.70 mmol, 2 equiv) added. Reaction is an orange slurry. After 18 h, the mixure was cautiously added to saturated aqueous sodium bicarbonate and extracted with ether (x3). The combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo* to provide the product (1.07 g, 50% over 2 steps) as a tan foam. 1H NMR (400 MHz, CDCl3) δ 7.43 - 7.29 (m, 5H), 6.58 (d, *J* = 10.8 Hz, 1H), 5.13 (br. s., 2H), 4.25 (t, *J* = 5.1 Hz, 4H), 3.91 (d, *J* = 3.5 Hz, 1H), 3.72 (s, 1H), 3.55 (s, 3H), 3.11 (br. s., 2H), 3.07 - 3.01 (m, 1H), 2.64 (s, 3H), 2.56 (s, 3H), 2.27 - 2.21 (m, 1H), 2.13 - 2.07 (m, 2H); LCMS (ESI, M+1): 533.35.

Benzyl (S)-3-(1-(tert-butoxy)-2-methoxy-2-oxoethyl)-2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (40a). To a solution of benzyl 3-(1-hydroxy-2-

methoxy-2-oxoethyl)-2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (**S2**) (0.10 g, 0.217 mmol, 1 equiv) in DCM (3 mL) was added *tert*-butyl acetate (2.05 mL, 15.2 mmol, 70 equiv) followed by 70% $HClO_4$ (0.056 mL, 0.651 mmol, 3 equiv). The flask was sealed and stirred at room temperature for 2.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (gas evolution observed). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (0-30% EtOAc/hexanes) to provide the product (82 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01-7.78 (m, 9H), 5.13 (s, 2H), 4.97 (s, 1H), 4.29-4.32 (m, 1H), 4.05-4.10 (m, 1H), 3.78-3.81 (m, 2H), 3.71 (s, 3H), 3.06 (bs, 2H), 2.64 (s, 3H), 2.45 (s, 3H) 0.99 (s, 9H). LCMS (ESI, M+1): 517.4.

Benzyl (R)-3-((S)-1-(tert-butoxy)-2-methoxy-2-oxoethyl)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (40b). To a solution of (*R*)-benzyl 4-(8-fluoro-5-methylchroman-6-yl)-3-((S)-1-hydroxy-2-methoxy-2-oxoethyl)-2-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (**S6**) (0.91 g, 1.71 mmol, 1 equiv) in DCM (10 ml) and *tert*-butyl acetate (16 ml) was added 70% perchloric acid (0.44 mL, 5.12 mmol, 3 equiv). After 1 h, the reaction is a white slurry so chloroform (10 mL) was added. Reaction is now a homogenous solution. After stirring 2 h more, the reaction was diluted with DCM and washed with saturated aqueous sodium bicarbonate, water, and brine. The organic layer was dried (Na_2SO4) and concentrated *in vacuo*. The crude product was purified by flash column silica gel chromatography (0-100% EtOAc/hex) to provide the product (0.49 g, 49%) as an off white solid. Starting alcohol was also recovered (0.31 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.29 (m, 5H), 6.59 (d, *J* = 11.0 Hz, 1H), 5.12 (br. s., 2H), 4.93 (s, 1H), 4.34 - 4.24 (m, *J* = 4.8 Hz, 2H), 4.05 (br. s., 2H), 3.86 (dt, *J* = 13.3, 5.9 Hz, 1H), 3.72 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.61 (s, 3H), 3.10 - 2.96 (m, 2H), 2.69 (s, 3H), 2.14 (br. s., 2H), 1.86 - 1.67 (m, 3H), 1.55 (s, 3H), 1.11 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.06 (br. s., 1F); LCMS (ESI, M+1): 591.45.

Methyl 2-(tert-Butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate (41a). To a solution of benzyl 3-(1-(*tert*-butoxy)-2-methoxy-2-oxoethyl)-2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (**40a**) (0.100 g, 0.194 mmol, 1 equiv) in DCM (2 mL) and methanol (2 mL) was added 10% Pd/C (10 mg, 0.0097 mol, 0.05 equiv) followed by 12 M HCl (0.024 mL, 0.290 mmol, 1 equiv). The mixture was shaken on a Parr shaker under H_2 (50 psi) for 3 h. Celite was added and the mixture was filtered through Celite eluting with methanol. The filtrate was concentrated *in vacuo*. The crude product was triturated with Et_2O and the solids were collected by filtration to provide the product as the presumed HCl salt (0.066 g, 74%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (t, *J* = 8.4 Hz, 2H), 7.24 (dd, *J* = 6.9, 18.3 Hz, 2H), 5.08 (s, 1H), 4.10-4.26 (m, 1H), 3.70-3.85 (m, 4H), 3.57-3.70 (m, 2H), 3.21-3.31 (m, 2H), 2.66 (s, 3H), 2.47 (s, 3H), 0.99 (s, 9H). LCMS (ESI, M+1): 383.1.

Methyl (S)-2-(tert-butoxy)-2-((R)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetate (41b). A solution of benzyl (*R*)-3-((S)-1-(*tert*-butoxy)-2-methoxy-2-oxoethyl)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (**40b**) (0.77 g, 1.31 mmol, 1 equiv), 1 M HCl (2.1 mL, 2.10 mmol, 1.6 equiv), and 10% Pd/C (0.14 g, 0.131 mmol, 0.1 equiv) in MeOH (12 mL) was stirred under a balloon of hydrogen for 2 h. The reaction was then filtered through Celite eluting with MeOH. The filtrate was concentrated *in vacuo* to provide the HCl salt of the product (0.56 g, 86%) as a white solid. LCMS (ESI, M+1): 457.35.

6-((Benzyloxy)carbonyl)-2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylic acid (S1). A mixture of 6-benzyl 3-methyl 2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-3,6(5*H*)-dicarboxylate (**37a**) (0.48 g, 1.12 mmol, 1 equiv) and lithium chloride (0.48 g, 11.19 mmol, 10 equiv) in 2,6-lutadine (10 mL) and DMSO (10 mL) was stirred at 130 °C for 2 h. The mixture was allowed to cool to ambient temperature, diluted with water, and washed with EtOAc. The aqueous phase was made acidic with 1 N HCl and extracted with EtOAc (x2) and DCM (x1). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to provide the product (74 mg, 15%) as an amber oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (br. s., 4H), 7.24 (d, *J* = 7.8 Hz, 3H), 7.13 (d, *J* = 7.6 Hz, 2H), 5.11 (s, 2H), 4.36 (s, 2H), 3.78 (t, *J* = 5.6 Hz, 2H), 3.30 (br. s., 2H), 2.80 (br. s., 3H), 2.38 (s, 3H); LCMS (ESI, M+1): 417.4.

Benzyl 3-(1-hydroxy-2-methoxy-2-oxoethyl)-2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (S2). A solution of benzyl 3-(2-methoxy-2-oxoacetyl)-2-methyl-4-(p-tolyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (**39a**) (2.53 g, 5.52 mmol, 1 equiv) and *R*-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (2.21 mL of a 1 M solution in toluene, 2.21 mmol, 0.4 equiv) in toluene (100 mL) was cooled to -35 °C. Catecholborane (1.65 mL of a 50% weight solution in toluene, 7.73 mmol, 1.5 equiv) was added dropwise and the solution stirred at -35 °C for 30 min then at -15 °C for 2 h. The reaction was diluted with EtOAc and stirred vigorously with saturated aqueous Na_2CO_3 for 1 h. The organic phase was washed with saturated aqueous Na_2CO_3 (x2), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (0-100% EtOAc/hexane) to provide the product (1.29 g, 50%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.49 (m, 7H), 7.08 (t, *J* = 8.7 Hz, 2H), 5.11 (d, *J* = 15.7 Hz, 3H), 4.22 (br. s., 2H), 3.67-3.89 (m, 5H), 3.14 (d, *J* = 2.5 Hz, 1H), 2.99-3.11 (m, 2H), 2.55 (s, 3H), 2.43 (s, 3H). LCMS (ESI, M+1): 461.0.

(S)-2-(tert-butoxy)-2-(2-methyl-4-(p-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)acetic acid (S3). To a solution of (*S*)-2-(6-((benzyloxy)carbonyl)-2-methyl-4-(*p*-tolyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-2-(*tert*-butoxy)acetic acid (**12**) (0.34 g, 0.668 mmol, 1 equiv) in MeOH (5 mL) was added 10% Pd/C (7 mg, 0.67 mmol, 0.1 equiv). The reaction was stirred under a balloon of hydrogen for 2 h. The mixture was then filtered through a pad of Celite eluting with MeOH and the filtrate was concentrated *in vacuo* to provide the product (0.21 g, 85%) as an off white glass. LCMS (ESI, M+1) 369.4.

tert-Butyl 2-((8-fluoro-5-methylchroman-6-yl)methylene)-3-oxobutanoate (S4). A solution of 8-fluoro-5-methylchromane-6-carbaldehyde (**34**) (4.0 g, 21.3 mmol, 1 equiv), *tert*-butyl acetoacetate (4.2 mL, 25.5 mmol, 1.2 equiv), and piperidinium acetate (0.31 g, 0.257 mmol, 0.1 equiv) in benzene (53 mL) was refluxed for 18 h with a Dean-Stark trap. More *tert*-butyl acetoacetate (4.2 mL, 25.5 mmol, 1.2 equiv) and piperidinium acetate (0.31 g, 0.257 mmol, 0.1 equiv) were added. After heating at reflux for another 24 h, the reaction was allowed to cool to ambient temperature and concentrated *in*

vacuo. Crude product was purified by silica gel flash column chromatography (0-20% EtOAc/hexane and 20-100% DCM/hexane) to provide the major geometric isomer (2.28 g, 32%) as a yellow solid and the minor geometric isomer (0.70 g, 10%) as a yellow oil. Major isomer: 1H NMR (400 MHz, CDCl3) δ 7.72 (s, 1H), 7.11 (d, *J* = 11.8 Hz, 1H), 4.28 - 4.21 (m, 2H), 2.70 (t, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 2.19 (s, 3H), 2.13 - 2.07 (m, 2H), 1.50 (s, 9H). Minor isomer: 1H NMR (500 MHz, CDCl3) δ 7.77 (s, 1H), 6.85 (d, *J* = 11.7 Hz, 1H), 4.28 - 4.22 (m, 2H), 2.71 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 3H), 2.21 (s,3H), 2.13 - 2.08 (m, 2H), 1.56 (s, 9H).

6-((Benzyloxy)carbonyl)-4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylic acid (S5). An orange solution of 6-benzyl 3-*tert*-butyl 4-(8-fluoro-5-methylchroman-6-yl)-2-methyl-7,8-dihydro-1,6-naphthyridine-3,6(5H)-dicarboxylate (**37b**) (2.3 g, 4.21 mmol, 1 equiv) in TFA (21 mL) was stirred for 18 h. The solution was concentrated *in vacuo* and triturated with ether to provide the putative TFA salt of the product (2.42 g, 95%) as a tan solid. LCMS (ESI, M+1): 491.35.

Benzyl (R)-4-(8-fluoro-5-methylchroman-6-yl)-3-((S)-1-hydroxy-2-methoxy-2-oxoethyl)-2-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (S6). To a solution of benzyl 4-(8-fluoro-5-methylchroman-6-yl)-3-(2-methoxy-2-oxoacetyl)-2-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (**39b**) (2.50 g, 4.69 mmol, 1 equiv) and (*R*)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole (1.88 mL of a 1 M solution in toluene, 1.88 mmol, 0.4 equiv) in toluene (45 mL) at -30 °C (IPA/dry ice) was added catecholborane (3.15 mL of a 50% solution in toluene, 6.57 mmol, 1.4 equiv). The reaction was placed in a freezer (-15 to -20 °C) for 4 d. The reaction was quenched with saturated aqueous sodium carbonate. EtOAc was added and the mixture was allowed to warm to ambient temperature. After stirring vigorously for 1 h, the emulsion was filtered through Celite. The organic layer was separated and stirred vigorously with saturated aqueous sodium carbonate for 1 h. The organic layer was separated and then again stirred vigorously with saturated aqueous sodium carbonate for 1 h. The organic layer was seperated and washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product as ~1:1 mixture of atropisomers was carefully purified by silica gel flash chromatography (5% TFE/DCM) to provide the product the desired product as the lower Rf spot and the undesired atropisomer as the higher Rf spot. The desired atropisomer was isolated (1.12 g, 45%) as a white solid. The undesired atropisomer/diastereomer was also isolated (1.22 g, 49%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.30 (m, 5H), 6.62 (d, *J* = 10.8 Hz, 1H), 5.16 - 5.07 (m, *J* = 17.3 Hz, 2H), 5.00 (d, *J* = 2.3 Hz, 1H), 4.27 (t, *J* = 4.3 Hz, 2H), 4.19 - 4.03 (m, 2H), 3.93 - 3.84 (m, 1H), 3.73 (s, 3H), 3.10 - 3.00 (m, 3H), 2.68 (br. s., 1H), 2.52 (s, 3H), 2.11 (br. s., 2H), 1.84 (br. s., 1H), 1.72 (br. s., 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -139.11 (d, *J* = 12.1 Hz, 1F); LCMS (ESI, M+1): 535.35. Other atropisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.30 (m, 5H), 6.64 (d, *J* = 11.0 Hz, 1H), 5.12 (d, *J* = 9.3 Hz, 2H), 4.97 (d, *J* = 2.5 Hz, 1H), 4.27 (t, *J* = 5.0 Hz, 2H), 4.21 - 4.02 (m, 2H), 3.93 - 3.83 (m, 1H), 3.75 (s, 3H), 3.17 (d, *J* = 2.5 Hz, 1H), 3.05 (br. s., 2H), 2.70 (br. s., 1H), 2.50 (s, 3H), 2.11 (br. s., 2H), 1.89 - 1.73 (m, 3H), 1.59 (s, 3H); LCMS (ESI, M+1): 535.35.

Ethyl (syn)-2-phenyl-cyclopropanecarboxylate (S7). Following the procedure in *J. Med. Chem.* **2009**, *52*, 1885. A solution of $Cu(acac)_2$ (0.24 g, 0.90 mmol, 0.03 equiv) and phenyl hydrazine (6 drops) in DCM (60 mL) was heated to reflux to produce a dark blue solution. Styrene (3.4 mL, 30 mmol, 1 equiv) was added. Ethyl diazoacetate (4.7 mL, 45 mmol, 1.5 equiv) was then added by syringe pump over 40 min. After 5 h, the reaction was allowed to cool to ambient temperature and washed with saturated aqueous sodium bicarbonate and brine. The DCM layer was dried (Na_2SO_4) and concentrated *in vacuo*. NMR of the crude product indicated ~2:1 anti:syn cyclopropanation. The crude product was purified by silica gel flash chromatography (0-10% ether/hexane) to provide the product as a colorless oil (0.88 g, 15%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 - 7.16 (m, 5H), 3.89 (q, *J* = 7.1 Hz, 2H), 2.70 - 2.51 (m, 1H), 2.10 (ddd, *J* = 9.3, 7.8, 5.6 Hz, 1H), 1.81 - 1.69 (m, 1H), 1.34 - 1.31 (m, 1H), 0.99 (t, *J* = 1.0 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H).

Syn (2-phenylcyclopropyl)methanol (S8). To a solution of **S7** (0.88 g, 4.63 mmol, 1 equiv) in THF (23 mL) was added $LiBH_4$ (4.6 mL of a 2 M solution in THF, 9.25 mmol, 2 equiv) followed by methanol (0.37 mL, 9.25 mmol, 2 equiv). Gas evolution. The reaction was heated to 60 °C for 1 h. Upon cooling to ambient temperature, the reaction was diluted with ether and washed with 1 N HCl and brine. The ether layer was dried (Na_2SO_4) and concentrated *in vacuo* to provide the product (0.32 g, 47%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.18 (m, 5H), 3.50 (dd, *J* = 11.8, 6.3 Hz, 1H), 3.29 (dd, *J* = 11.5, 8.5 Hz, 1H), 2.37 - 2.26 (m, 1H), 1.56 -1.47 (m, 1H), 1.11 - 1.03 (m, 1H), 0.90 (q, *J* = 5.6 Hz, 1H).

Syn 2-phenylcyclopropanecarbaldehyde (S9). To a solution of **S8** (0.32 g, 2.16 mmol, 1 equiv) in DCM (11 mL) was added Dess-Martin periodinane (1.28 g, 3.02 mmol, 1.4 equiv). After 1 h, the reaction was diluted with ether and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (0-30% ethyl acetate/hexane) to provide the product as a yellow oil (0.15 g, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 6.6 Hz, 1H), 7.36 - 7.26 (m, 5H), 2.89 - 2.82 (m, 1H), 2.20 - 2.13 (m, 1H), 1.91 (dt, *J* = 7.3, 5.3 Hz, 1H), 1.65 - 1.60 (m, 1H).

ASSOCIATED CONTENT

Supporting Information. Methods for binding assay, cell assay, cytoxicity assay, in vitro metabolic stability assay, in vivo pharmacokinetic study, crystallography, and modeling. **Accession Codes.** The coordinates of the crystal structure of **24** bound with integrase CCD (PDB ID 6NCJ) have been deposited in the Protein Data Bank (www.pdb.org). Authors will release the atomic coordinates and experimental data upon article publication. Molecular Formula Strings available.

AUTHOR INFORMATION

Corresponding Author

* Email: kevin.m.peese@viivhealthcare.com.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

Wade Blair is acknowledged for helpful discussion regarding biology and mechanism of action. David Langley, Prasanna Siva, Eric Arnault, and Eugene Stewart are acknowledged for helpful discussions regarding molecular modeling. Mian Gao is acknowledged for protein expression efforts. The Bristol-Myers Squibb Department of Chemical Synthesis is acknowledged for synthetic support.

ABBREVIATIONS

ALLINI, allosteric integrase inhibitor; CAN, ceric ammonium nitrate; CBS, Corey–Bakshi–Shibata; Cbz, benzyl carbamate; CCD, catalytic core domain; CL, clearance; CYP, cytochrome P450; DNA, deoxyribonucleic acid; HIV, Human Immunodeficiency Virus; IN, integrase; INLAI, IN-LEDGF/p75 inhibitor; INSTI, integrase strand transfer inhibitors; IV, intravenous; LEDGF, lens epithelium-derived growth factor; LEDGIN, LEDGF inhibitor; LiHMDS, lithium bis(trimethylsilyl)amide; NCINI, non-catalytic site integrase inhibitor; PO, oral; SAR, structure activity relationship; Vss, steady state volume of distribution; WHO, World Health Organization

REFERENCES

(1) WHO website. HIV/AIDS fact sheet. http://www.who.int/mediacentre/factsheets/fs360/en/ (last accessed May 3, 2018).

(2) Wainberg, M. A.; Zaharatos, G. J.; Brenner, B. G. Development of antiretroviral drug resistance. *N. Engl. J. Med.* **2011**, *365*, 637–646.

(3) Barton, K. M.; Burch, B. D.; Soriano-Sarabia, N.; Margolis, D. M. Prospects for treatment of latent HIV. *Clin. Pharmacol. Ther.* **2013**, *93*, 46–56.

(4) McColl, D. J.; Chen, X. Strand transfer inhibitors of HIV-1 integrase: bringing IN a new era of antiretroviral therapy. *Antiviral Research* **2010**, *8*, 101–118.

(5) Pendri, A.; Meanwell, N. A.; Peese, K. M.; Walker, M. A. New first and second generation inhibitors of human immunodeficiency virus-1 integrase. *Expert Opin. Ther. Pat.* **2011**, *21*, 1173–1189.

(6) Quashie, P. K.; Sloan, R. D.; Wainberg, W. A. Novel therapeutic strategies targeting HIV integrase. *BMC Medicine* **2012**, *10*, 34–44.

(7) Blanco, J.-L.; Varghese, V.; Rhee, S.-Y.; Gatell, J. M.; Shafer, R. W. HIV-1 integrase inhibitor resistance and its clinical implications. *J. Infect. Dis.* **2011**, *203*, 1204–1214.

(8) Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore,F.; Gardelli, C.; Paz, O. G.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteagudo, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley M. Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIV-AIDS infection. *J. Med. Chem.* **2008**, *51*, 5843–5855.

(9) Rowley, M. The discovery of raltegravir, an integrase inhibitor for the treatment of HIV infection. *Prog. Med. Chem.* **2008**, *46*, 1–26.

(10) Sato, M.; Kawakami, H.; Motomura, T.; Aramaki, H.; Matsuda, T.; Yamashita, M.; Ito, Y.; Matsuzaki, Y.; Yamataka, K.; Ikeda, S.; Shinkai H. Quinolone carboxylic acids as a novel monoketo acid class of human immunodeficiency virus type 1 integrase inhibitors. *J. Med. Chem.* **2009**, *52*, 4869–4882.

(11) Johns, B. A.; Kawasuji, T.; Weatherhead, J. G.; Taishi, T.; Temelkoff, D. P.; Yoshida, H.; Akiyama, T.; Taoda, Y.; Murai, H.; Kiyama, R.; Fuji, M.; Tanimoto, N.; Jeffrey, J.; Foster, S. A.; Yoshinaga, T.; Seki, T.; Kobayashi, M.; Sato, A.; Johnson, M. N.; Garvey, E. P.; Fujiwara, T. Carbamoyl pyridone HIV‐1 integrase inhibitors 3. A diastereomeric approach to chiral nonracemic tricyclic ring systems and the discovery of dolutegravir (S/GSK1349572) and (S/GSK1265744). *J. Med. Chem.* **2015**, *56*, 5901–5916.

(12) Tsiang, M.; Jones, G. S.; Goldsmith, J.; Mulato, A.; Hansen, D.; Kan, E.; Tsai, L.; Bam, R. A.; Stepan, G.; Stray, K. M. ; Niedziela-Majka, A.; Yant, S. R.; Yu, H.; Kukolj, G.; Cihlar, T.; Lazerwith, S. E.; White, K. L.; Jin, H. Antiviral activity of bictegravir (GS-9883), a novel potent hiv-1 integrase strand transfer inhibitor with an improved resistance profile. *Antimicrob. Agents Chemother*. **2016**, *60*, 7086–7097.

(13) Christ, F.; Debyser, Z. The LEDGF/p75 integrase interaction, a novel target for anti-HIV therapy. *Virology* **2013**, *435*, 102–109.

(14) Demeulemeester, J.; Chaltin, P.; Marchand, A.; De Maeyer, M.; Debyser, Z.; Christ, F. LEDGINs, non-catalytic site inhibitors of HIV-1 integrase: a patent review (2006-2014). *Exp. Opin. Ther. Patents* **2014**, *24*, 609-632.

(15) Le Rouzic, E.; Bonnard, D.; Chasset, S.; Bruneau, J.-M.; Chevreuil, F.; Le Strat, F.; Nguyen, J.; Beauvoir, R.; Amadori, C.; Brias, J.; Vomscheid1, S.; Eiler, S.; Lévy, N.; Delelis, O.; Deprez, E.; Saïb, A.; Zamborlini, A.; Emiliani, S.; Ruff, M.; Ledoussal, B.; Moreau, F.; Benarous, R. Dual inhibition of HIV-1 replication by integrase-LEDGF allosteric inhibitors is predominant at the post-integration stage. *Retrovirology* **2013**, *10*, 144.

(16) Feng, L.; Larue, R. C.; Slaughter, A.; Kessl, J. J.; Kvaratskhelia, M. HIV-1 integrase multimerization as a therapeutic target. *Curr. Top. Microbiol. Immunol.* **2015**, *389*, 93–119.

(17) Bonnard, D.; Le Rouzic, E.; Eiler, S.; Amadori, C.; Orlov, I.; Bruneau, J.-M.; Brias, J.; Barbion, J.; Chevreuil, F.; Spehner, D.; Chasset, S.; Ledoussal, B.; Moreau, F.; Saïb, A.; Klaholz, B. P.; Emiliani, S.; Ruff, M.; Zamborlini, A.; Benarous, R. Structure-function analyses unravel distinct effects of allosteric inhibitors of HIV-1 integrase on viral maturation and integration. *J. Biol. Chem.* **2018**, *293*, 6172–6186.

(18) Christ, F.; Voet, A.; Marchand, A.; Nicolet, S.; Desimmie, B. A.; Marchand, D.; Bardiot, D.; Van der Veken, N. J.; Van Remoortel, B.; Strelkov, S. V.; De Maeyer, M.; Chaltin, P.; Debyser, Z. Rational design of small-molecule inhibitors of the LEDGF/p75-integrase interaction and HIV replication. *Nat. Chem. Biol.* **2010**, *6*, 442–448.

(19) a) Fader, L. D.; Malenfant, E.; Parisien, M.; Carson,R.; Bilodeau, F.; Landry, S.; Pesant, M.; Brochu, C.; Morin, S.; Chabot, C.; Halmos, T.; Bousquet, Y.; Bailey, M. D.; Kawai, S. H.; Coulombe, R.; LaPlante, S.; Jakalian, A.; Bhardwaj, P. K.; Wernic, D.; Schroeder, P.; Amad, M.; Edwards, P.; Garneau, M.; Duan, J.; Cordingley, M.; Bethell, R.; Mason, S. W.; Bös, M.; Bonneau, P.; Poupart, M.-A.; Faucher, A.-M.; Simoneau, B.; Fenwick, C.; Yoakim, C.; Tsantrizos, Y. Discovery of BI 224436, a noncatalytic site integrase inhibitor (NCINI) of HIV-1. *ACS Med. Chem. Lett.* **2014**, *5*, 422-427. b) Fenwick, C.; Amad, M.; Bailey, M. D.; Bethell, R.; Bös, M.; Bonneau, P.; Cordingley, M.; Coulombe, R.; Duan, J.; Edwards, P.; Fader, L. D.; Faucher, A.-M.; Garneau, M.; Jakalian, A.; Kawai, S.; Lamorte, L.; LaPlante, S.; Luo, L.; Mason, S.; Poupart, M.-A.; Rioux, N.; Schroeder, P.; Simoneau, B.; Tremblay, S.; Tsantrizos, Y.; Witvrouw, M.; Yoakim, C. Preclinical profile of BI 224436, a novel HIV-1 non-catalytic-site integrase inhibitor. *Antimicrob. Agents Chemother*. **2014**, *58*, 3233–3244.

(20) Mitchell, M.; Balakrishnan, M.; Brizgys, G.; Cai, R.; Lansdon, E.; Mulato, A.; Osier, M.; Wang, J.; Yu, H.; Sakowicz, R. Novel non-catalytic site integrase inhibitor with improved resistance profile. Presented at the *24th Conference on Retroviruses and Opportunistic Infections* (CROI), Seattle, Washington, February 13-16, 2017. Poster 434.

(21) Engelman A.; Cherepanov, P. The lentiviral integrase binding protein LEDGF/p75 and HIV-1 replication. *PLoS Pathog.* **2008**, *4*, e1000046.

(22) Poeschla, E. M. Integrase, LEDGF/p75 and HIV replication. *Cell Mol. Life Sci.* **2008**, *65*, 1403–1424.

(23) Maertens, G. N.; Hare, S.; Cherepanov, P. The mechanism of retroviral integration from X-ray structures of its key intermediates. *Nature* **2010**, *468*, 326–329.

(24) Jurado, K. A.; Wang, H.; Slaughter, A.; Feng, L.; Kessl, J. J.; Koh, Y.; Wang, W.; Ballandras-Colas, A.; Patel, P. A.; Fuchs, J. R.; Kvaratskhelia, M.; Engelman, A. Allosteric integrase inhibitor potency is determined through the inhibition of HIV-1 particle maturation. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 8690–8695.

(25) Balakrishnan, M.; Yant, S. R.; Tsai, L.; O'Sullivan, C.; Bam, R. A.; Tsai, A.; Niedziela-Majka, A.; Stray, K. M.; Sakowicz, R.; Cihlar T. Non-catalytic site HIV-1 integrase inhibitors disrupt core maturation and induce a reverse transcription block in target cells. *PLoS One* **2013**, 8, e74163.

(26) Jurado, K. A.; Engelman, A. Multimodal mechanism of action of allosteric HIV-1 integrase inhibitors. *Expert Rev. Mol. Med.* **2013**, *26*, e14.

(27) Fader, L. D.; Carson, R.; Morin, S.; Bilodeau, F.; Chabot, C.; Halmos, T.; Bailey, M. D.; Kawai, S. H.; Coulombe, R.; Laplante, S.; Mekhssian, K.; Jakalian, A.; Garneau, M.; Duan, J.; Mason, S. W.; Simoneau, B.; Fenwick, C.; Tsantrizos, Y.; Yoakim, C. Minimizing the contribution of enterohepatic recirculation to clearance in rat for the NCINI class of inhibitors of HIV. *ACS Med. Chem. Lett*. **2014**, *5*, 711–716.

(28) Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. Small molecule conformational preferences derived from crystal structure data. A medicinal chemistry focused analysis. *J. Chem. Inf. Model*. **2008**, *48*, 1–24.

(29) a) Anderson, G. M., III; Kollman, P. A.; Domelsmith, L. N.; Houk, K. N. Methoxy group nonplanarity in *o*-dimethoxybenzenes. Simple predictive models for conformations and rotational barriers in alkoxyaromatics. *J. Am. Chem. Soc.* **1979**, *101*, 2344–2352. (b) Hummel, W.; Huml, K.; Bürgi, H.-B. Conformational flexibility of the methoxyphenyl group studies by statistical analysis of crystal structure data. *Helv. Chim. Acta* **1988**, *71*, 1291–1302.

(30) Bryan, R. F.; Freyberg, D. P. Crystal structures of α-*trans*- and *p*-methoxy-cinnamic acids and their relation to thermal mesomorphism. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1835–1840.

(31) a) De La Rosa, M. A.; Johns, B. A.; Kazmierski, W. M.; Samano, V.; Suwandi, L.; Temelkoff, D.; Velthuisen, E.; Weatherhead, J. G. Compounds and Methods For Treating HIV. WO2014/9794, 2014. b) Bardiot, D.; Chaltin, P.; Christ, F.; Debyser, Z.; De Maeyer, M.; Marchand, A.; Marchand, D.; Voet, A. Thieno [2, 3-*b*] Pyridine Derivatives as Viral Replication Inhibitors. WO2010/130842, 2010.

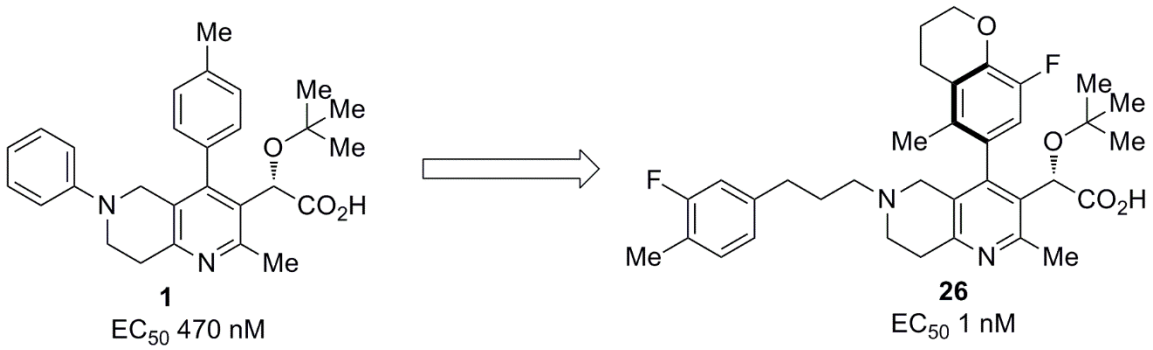
(32) Fandrick, K. R.; Li, W.; Zhang, Y.; Tang, W.; Gao, J.; Rodriguez, S.; Patel, N. D.; Reeves, D. C.; Wu, J.-P.; Sanyal, S.; Gonnella, N.; Qu, B. Haddad, N.; Lorenz, J. C.; Sidhu, K.; Wang, J.; Ma, S.; Grinberg, N. Lee, H.; Tsantrizos, Y.; Poupart, M.-A., Busacca, C. A.; Yee, N. K.; Lu, B. Z.; Senanayake, C. H. Concise and practical asymmetric synthesis of a challenging atropisomeric HIV integrase inhibitor. *Angew. Chem. Int. Ed.* **2015**, *54*, 7144–7148.

(33) Talele, T. T. The "Cyclopropyl Fragment" is a versatile player that frequently appears in preclinical/clinical drug molecules. *J. Med. Chem*. **2016**, *59*, 8712–8756.

(34) Fader, L. D.; Bailey, M.; Beaulieu, E.; ois Bilodeau, F.; Bonneau, P.; Bousquet, Y.; Carson, R. J.; Chabot, C.; Coulombe, R.; Duan, J.; Fenwick, C.; Garneau, M.; Halmos, T.; Jakalian, A.; James, C.; Kawai, S. H.; Landry, S.; LaPlante, S. R.; Mason, S. W.; Morin, S.; Rioux, N.; Simoneau, B.; Surprenant, S.; Thavonekham, B.; Thibeault, C.; Trinh, T.; Tsantrizos, Y.; Tsoung, J.; Yoakim, C.; Wernic, D. Aligning potency and pharmacokinetic properties for pyridine-based NCINIs. *ACS Med. Chem. Lett*. **2016**, *7*, 797–801.

(35) Ju, L.; Lippert, A. R.; Bode, J. W. Stereoretentive synthesis and chemoselective amide-forming ligations of C-terminal peptide alpha-ketoacids. *J. Am. Chem. Soc.* **2008**, *130*, 4253–4255.

Table of Contents graphic



1
EC_{50} 470 nM

26
EC_{50} 1 nM