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Structure-Based Optimization of Naphthyridones into Potent ATAD2 Bromodomain Inhibitors

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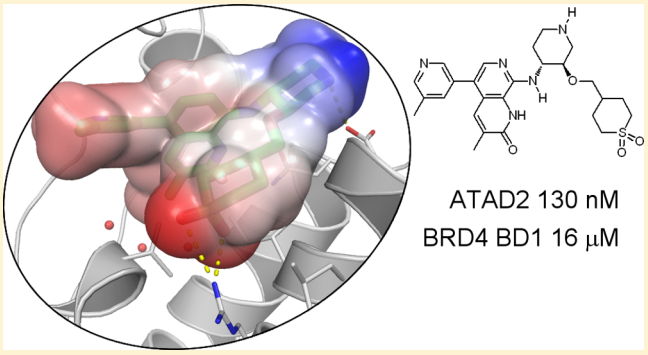
Supporting Information

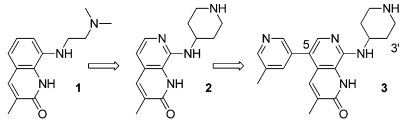
ABSTRACT: ATAD2 is a bromodomain-containing protein whose overexpression is linked to poor outcomes in a number of different cancer types. To date, no potent and selective inhibitors of the bromodomain have been reported. This article describes the structure-based optimization of a series of naphthyridones from micromolar leads with no selectivity over the BET bromodomains to inhibitors with sub-100 nM ATAD2 potency and 100-fold BET selectivity.



INTRODUCTION

The bromodomain-containing protein ATAD2 (ATPase family, AAA domain containing 2), also known as ANCCA (AAA nuclear coregulator cancer-associated protein), is a promising oncology target. Increased expression correlates with poor outcome in a range of cancers, and ATAD2 knockdown has been shown to modulate multiple relevant tumor cell growth factors.[1−3] The fact that ATAD2 contains a bromodomain makes it an attractive area for research, as similar modules are known to be tractable to drug discovery in the tandem-bromodomain BET (bromodomain and extra terminal) family proteins (BRD2,3,4 and T).[4,5] Despite this, relatively little work has been published, and there is a great need for small molecules with which to investigate phenotypic responses to inhibition of the ATAD2 bromodomain. Until very recently, the most potent inhibitors of the ATAD2 bromodomain were weak (≥200 μM) fragments, which are not suitable for use as cellular chemical probes and for which no optimization has been reported.

In our preceding article, we described the discovery of the first reported low-micromolar inhibitors of the ATAD2 bromodomain (Figure 1).[6] A weak hit **1** (Figure 1) was synthesized within an ATAD2-targeted portion of an array based upon a quinolinone template. The crystallographic binding mode to the bromodomain of ATAD2 of analogues such as **2** was characterized, confirming that the napthyridone acts as an acetyl-lysine (KAc) mimetic via direct and through-water hydrogen-bonded interactions to Asn1064 and Tyr1021 (Figure 2b). The basic piperidine substituent makes an important additional contribution to ATAD2 binding through its interaction with Asp1071. Exploration of SAR at the C5 position of the naphthyridone demonstrated that 3-pyridyl derivatives provided a further boost to ATAD2 activity and resulted in the micromolar ATAD2 lead **3**.



	1	2	3
ATAD2 (Peptide) pIC_{50}	4.0	4.9	5.9
ATAD2 (Ligand) pIC_{50}	4.1	4.8	5.7
BRD4-BD1 pIC_{50}	4.6	5.4	5.6

Figure 1. From hit to micromolar ATAD2 inhibitor. pIC_{50}s of compounds **1**−**3** in ATAD2 peptide- and ligand-based TR-FRET assays and against BRD4 BD1.

Because of the extensive effects of BET inhibitors,[7] high selectivity over these proteins is required in chemical probes of other bromodomains. In a cellular probe for ATAD2, we aimed to achieve at least 100-fold selectivity over the BET family.

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Attempts to gain this selectivity through further exploration of the C5-position met with limited success, with most analogues being more active against the BET family, exemplified by the N-terminal bromodomain of BRD4 (BRD4 BD1), than ATAD2. We now continue the story of our attempts to increase ATAD2 potency and introduce selectivity over the BET bromodomains.

RESULTS AND DISCUSSION

As this work progressed, we moved away from the peptide-based assay we had used to develop compound **3** to an alternative TR-FRET competition binding assay, in which a fluorescently labeled naphthyridone analogue of **3** was used instead of a peptide. Data generated for compounds in both assays showed that the two were in good agreement (r^2 = 0.94 for 386 compounds over the TR-FRET IC_{50} range 100 μM to 100 nM; see Figure S1a, Supporting Information). ATAD2 pIC_{50} data reported here were generated using the ligand-based TR-FRET assay. For completeness, data from the peptide-based assay is also shown in Table S1, Supporting Information.

Throughout the optimization, we also confirmed that the activity against the recombinant bromodomain was retained against ATAD2 protein from a more physiological source. The ATAD2 *Bromosphere* assay measures competitive binding to endogenous full-length ATAD2 from cell lysate. The correlation between the ATAD2 *Bromosphere* assay and the recombinant TR-FRET assay was also good (r^2 > 0.67 for 237 compounds over a range of TR-FRET IC_{50} between 100 μM and 100 nM; Figure S1b, Supporting Information).

Exploration of the 3′ Position to Find Lipophilic Interactions with the RVF Shelf. Having found difficulty in improving on the 3-pyridyl substituent at the naphthyridone C5 position of **3**, we considered ways to interact with other parts of the ATAD2 binding site. For the BET-family bromodomains, some areas outside the immediate KAc site have proved to be valuable in optimizing potency. One such area is the WPF shelf, named after the conserved Trp−Pro−Phe motif located nearby (Figure 2a).[8] In the BRD4 N-terminal bromodomain (BRD4 BD1), key residues of the WPF shelf include Trp81 and Pro82 of the WPF motif, Met149, and especially Ile146. Potent BET inhibitors typically exploit the WPF shelf using aromatic or lipophilic substituents. In one recent example, aniline substituents projecting from a tetrahydroquinoline core onto the BET WPF shelf gained significant extra potency, and a similarly positioned phenyl ring is an essential part of first-generation BET inhibitors I-BET762 (Figure 2a) and JQ-1.[9−11]

A similar shallow shelf exists in ATAD2, but the amino acids surrounding it differ considerably from the BET bromodomains. As the BET WPF motif is replaced by RVF (Arg1007−Val1008−Phe1009) in ATAD2, this region has been called the RVF shelf.[12] Another important difference is the presence of Arg1077 in ATAD2 instead of Met149 (BRD4 numbering) (Figure 2b and Figure S2, Supporting Information). Together, these changes result in a more polar and flexible environment on the RVF shelf in ATAD2 that is more challenging to interact with productively than in BRD4. While the rims of the two bromodomain shelves differ considerably, the floors are more similar. In ATAD2, the floor is formed by gatekeeper residue Ile1074 (Figure 2b), which is identical to the corresponding residue in the second BET bromodomains, and only conservatively differs from the first (Ile146 and Val439 in BRD4 BD1 and BD2, respectively).

We inspected the ATAD2 crystal structure complex with **3** to find ways to target the RVF shelf. The C3′ equatorial position of the piperidine seemed to offer a suitable vector (Figure 2b). We first tried to interact with the lipophilic part of the RVF shelf surface produced by Ile1074, which is the closest part of the shelf to the piperidine ring of **3**. Modeling suggested that an ether linker could direct lipophilic groups toward this position in a low-energy conformation.

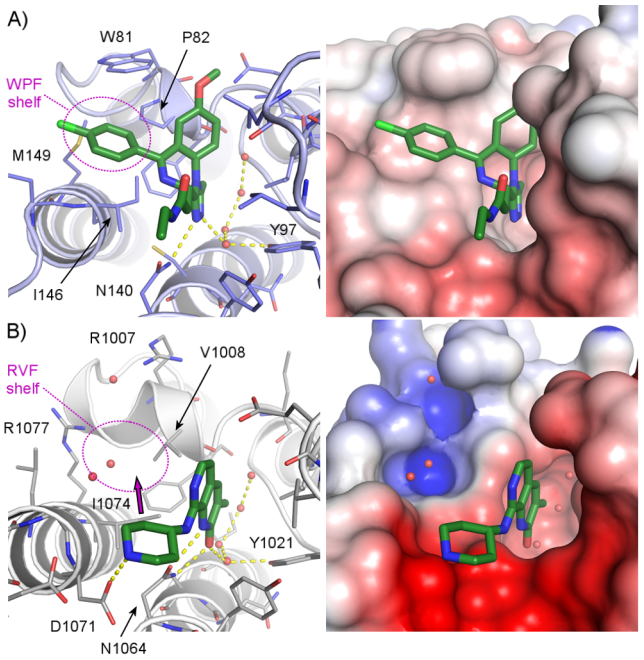

Figure 2. (A) Acetyl-lysine binding site of BRD4 BD1 bound to literature inhibitor I-BET762 (PDB code 3p5o)[10] showing detailed interactions (left) and electrostatic charge colored protein surface (right). (B) X-ray structure of ATAD2 bound to **2** (PDB code 5a5q), in the same orientation. Hydrogen bonds are shown as yellow dashed lines.

This hypothesis could be explored rapidly in the C5-H naphthyridone template, via O-alkylation of the trans azido protected hydroxy-piperidine **5**, which was easily accessible from the known epoxide **4** (Scheme 1).[13] Reduction of the azide generated protected 3-alkoxy 4-amino piperidines **6** suitable for palladium-catalyzed coupling with the chloro naphthyridines **7a,b**, as previously described.[6] Deprotection then followed under acidic conditions. As well as giving access to racemic products, this route also enabled the isolation of inhibitors as single enantiomers, since the enantiomers of the azides, BOC-protected naphthyridines, or the final compounds could be easily separated by chiral chromatography.

The SAR (Table 1) shows a size- and lipophilicity-dependent increase in potency up to a point, with acyclic groups producing relatively ineffective ATAD2 inhibitors (**9**−**12**). Alpha branching (as in **10**) was especially poorly tolerated compared to linear or β-branched alkyl chains (e.g., **11** and **12**). The cyclohexyl derivative **13** appeared to be the optimal cycloalkyl group, being marginally more ligand-efficient than the cyclopentyl (**14**) and comparable to the cycloheptyl (**15**). After separation of the two enantiomers of compound **13**, one enantiomer (**17**) was significantly more active than the other (**16**) by a factor of 1.3 logs. We judged that although the increase in potency in moving from **2** to **17** was achieved at the expense of some ligand efficiency and was driven by lipophilicity, this was acceptable to counter the hydrophilicity

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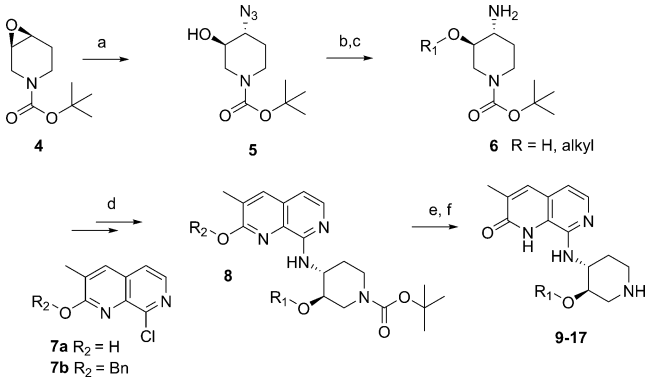
Scheme 1. Synthesis of Key Trans Piperidines[a]



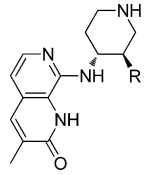
[a]Reagents and conditions: (a) NaN_3, DMF/acetone/water, 80°C, 63%; (b) NaH, DMF, 0°C then RI or ROTf, 0 °C to room temperature, 10−100%; (c) Pd/C, MeOH, H_2 (1 bar), 69−100% or PPh_3, THF, room temperature then water, reflux, 69−79%; (d) for R_2 = H: LiHMDS, Caddick catalyst, THF, 80−120 °C, microwave, 13−95%; or for R_2 = Bn: BrettPhos, BrettPhos precatalyst, THF, *t*BuONa, room temperature, 65−95%; (e) for R_2 = H: TFA, CH_2Cl_2, room temperature, 73−92%; (f) for R_2 = Bn: H_2, Pd/C, MeOH, room temperature, 99% then TFA, CH_2Cl_2, room temperature, 84%.

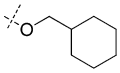
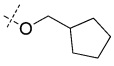
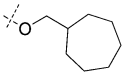
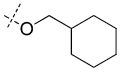
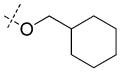
of the naphthyridone core, producing more balanced molecules with greater logD to promote cell permeability.

A 2.0 Å crystal structure of ATAD2 bound to compound **13** was rapidly solved (Figure 3a). The addition of the 3′ substituent does not change the overall binding mode of the naphthyridone, which is unmoved relative to the bound structure of **2**. Interestingly, only the single (*R*,*R*) isomer of the trans racemic compound **13** was seen to bind in the ATAD2 active site (Figure S3, Supporting Information). The structure confirmed our intended binding mode, with the 3′-substituent cyclohexyl group positioned on the RVF shelf, in direct hydrophobic contact with Ile1074. The addition of the cyclohexyl substituent displaces two water molecules from ATAD2 that were visible in the complex with **2**. Both appear to be weakly bound. For example, one displaced water molecule, labeled $H_2O_{(R1077)}$ in Figure 3a, forms only a single visible hydrogen bond to the Arg1077 guanidine group and is otherwise surrounded by the aliphatic side chains of Val1008, Leu1073, and Ile1074.

For comparison, the BRD4 BD1 X-ray crystal structure with compound **13** was obtained by cocrystallization (Figure 3b). The naphthyridone of **13** binds to the acetyl-lysine pocket of BRD4 in a similar way to that of **3**.[6] As with ATAD2, the

Table 1. Data for C3′-Substituents in the C5-H Naphthyridone Series[a]



Compound	R	Enantiomer	ATAD2 pIC_{50}	ATAD2 LE	BRD4 BD1 pIC_{50}	Solubility μM	LogD
2	H	-	4.8	0.33	5.4	≥ 274	0.6
9	OCH_3	Enantiomer 1	5.0	0.33	5.2	≥ 306	0.9
10		Racemate	4.2	0.25	4.6	207	1.8
11		Racemate	4.6	0.27	5.2	≥ 280	1.8
12		Racemate	4.8	0.27	5.2	≥ 290	2.3
13		Racemate	5.5	0.28	5.3	285	3.3
14		Racemate	5.1	0.27	5.0	≥ 275	3.1
15		Racemate	5.7	0.28	5.3	≥ 316	4.0
16		Enantiomer 1	4.3	0.22	4.9	140	3.3
17		Enantiomer 2	5.6	0.28	5.4	220	3.3

[a]Ligand efficiency (LE) ≈ 1.37 × pIC_{50}/(number of heavy atoms). For statistics, see Table S1, Supporting Information.

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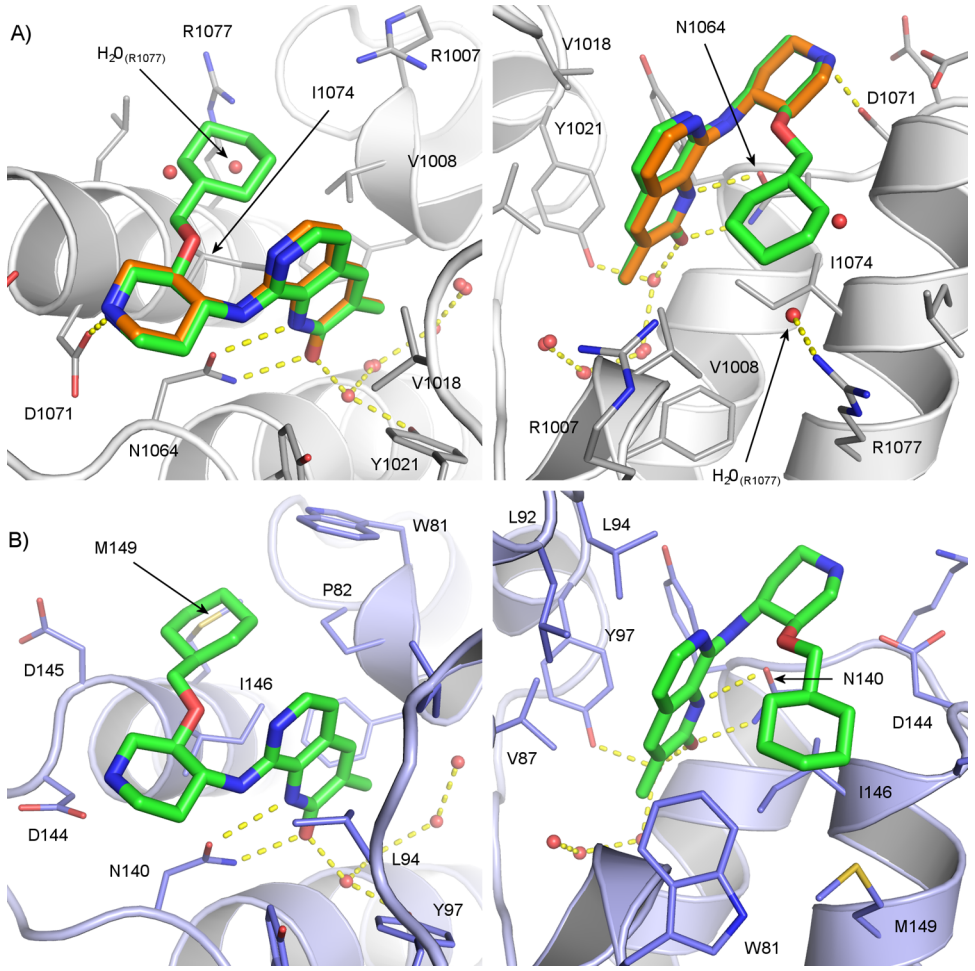

Figure 3. (A) Crystal structure of ATAD2 bound to **13** (green, PDB code 5a81), superimposed on that of **2** (orange, PDB code 5a5q) using alpha-carbon atoms of the active sites. The water molecule labeled $H_2O_{(R1077)}$ on the RVF shelf close to Arg1077 is present in the complex with **2** and is displaced by **13**. (B) Crystal structure of BRD4 BD1 bound to **13** (green, PDB code 5a85). Dashed yellow lines indicate hydrogen bonds.

electron density in the BRD4 BD1 X-ray structure was consistent with the (*R*,*R*) enantiomer. The cyclohexyl ring binds on the BRD4 BD1 WPF shelf, making lipophilic contact with the Ile146 side chain. As this hydrophobic interaction (with Ile1074 and Ile146 in ATAD2 and BRD4 BD1, respectively) is similar in both bromodomains, it is not surprising that the BRD4 BD1 potency tracks the ATAD2 potency closely for these and similar compounds (Table 1).

From the mixture of the two trans enantiomers of **13**, the (*R*,*R*) enantiomer was found to bind to both ATAD2 and BRD4 crystallographically. We assumed that this was the more potent of the two separated enantiomers and that, therefore, the more potent of the two separated enantiomers, **17**, had (*R*,*R*) stereochemistry. Later synthesis of enantiomerically pure material via chiral separation of azide intermediate **5** (Scheme 1)[14] followed by crystallographic binding mode determination of the most active enantiomer showed that, indeed, the most potent single enantiomer was always the one associated with (*R*,*R*) stereochemistry (data not shown). We checked periodically to ensure that this remained true. From hereon, it is assumed that the (*R*,*R*) enantiomer is systematically more potent against ATAD2 than (*S*,*S*).

Combining C5 and Lipophilic C3′ Substituents. Seeing little difference in the position of the naphthyridone between the ATAD2-bound X-ray structures of **2** and **13**, we hoped that the improvements in potency from modification at the C3′ position could be boosted further if other changes were additive. In our previous article, we described SAR at the naphthyridone C5-position.[6] We introduced some of our favored C5-substituents, including the 3-pyridyl group of **3**, into C3′-derivatized molecules according to Scheme 2. The derivatives **8** were selectively brominated at C5 to give **18**, which could be coupled with the required boronic acids to give **19.** Acidic deprotection of these intermediates gave the corresponding inhibitors in moderate to good yields.

Data for two example C5, C3′ disubstituted derivatives are presented in Table 2. As reported previously for the 3′-H piperidine analogues, the addition of 3-pyridyl substituents at the C-5 position improved ATAD2 potency significantly, conserving ligand efficiency (compare **20** and **22** to **17**). Consistent with the data shown in Table 1 for 5-H naphthyridones, in the C5-(3-pyridyl) analogues the (*R*,*R*) enantiomer **20** was 1.3 logs more potent than the (*S*,*S*) enantiomer **21**. For the first time, these compounds clearly demonstrated the possibility of achieving our target ATAD2 activity (pIC_{50} >7.0). In the case of compound **22**, this milestone was confirmed by potent activity measured against endogenous ATAD2 in the chemoproteomic *Bromosphere* assay (Table 2).

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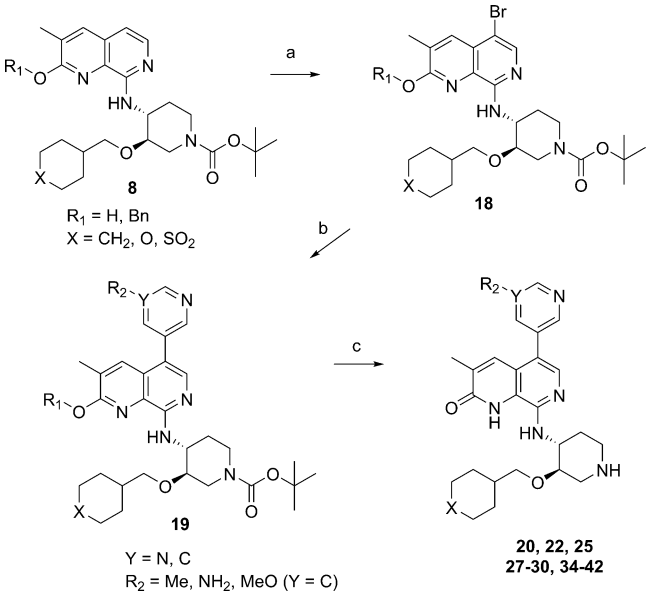
Scheme 2[a]

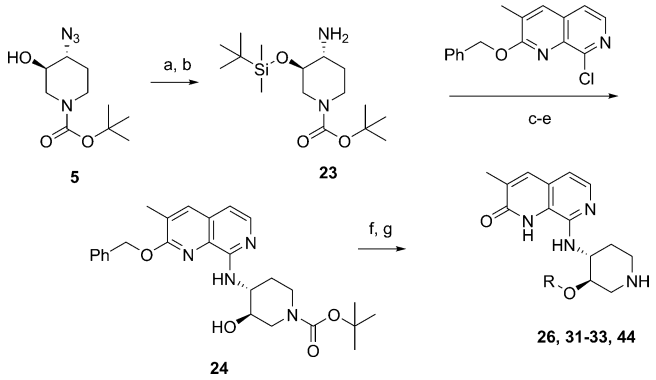


[a]Reagents and conditions: (a) NBS, $CHCl_3$, −10 °C, 84−95%; (b) $Pd(OAc)_2$, K_2CO_3, cataCXium A, $ArB(OH)_2$, 1,4-dioxane/water, 100 °C, microwave, 46−87%; (c), TFA, CH_2Cl_2, room temperature (R_1 = H, 26−90%) or TFA reflux (R_1 = Bn, 39−99%).

Also for the first time, the combination of C5 and C3′ groups in compounds **20** or **22** gave a modest but significant window of selectivity for ATAD2 over BRD4 (≥0.7 log difference between the two pIC_{50} values in TR-FRET assays). While encouraging, we felt that this level of selectivity was still too small to be able to distinguish any phenotypic readout due to ATAD2 from residual BET activity. We therefore looked for ways to widen the selectivity window. Up to this point, the selection of substituents at the 3′ position had been quite limited and did not seek to exploit the differences between the ATAD2 RVF shelf and the BET WPF shelf outlined above. The ATAD2 environment is significantly more polar, due to the presence of Arg1007 and Arg1077, than in BRD4 (Trp81 and Met149). Figure 3 shows the different surroundings of the 4-position of the 3′-cyclohexyl moiety of **13** when bound to ATAD2 and BRD4. As mentioned above, the loss of a water molecule $H_2O_{(R1077)}$ bound to the Arg1077 side chain had been seen upon the addition of the cyclohexyl C3′ substituent. We speculated that introducing hydrogen-bond acceptor groups in this region might improve ATAD2 activity either through direct or water-bridged interactions with Arg1077. If direct or indirect H-bonds could not be formed, then we hoped at least that electronegative groups would be more tolerated in ATAD2 because of the more positive electrostatic surface in this area while being detrimental to BET activity by virtue of its greater lipophilicity.

Polar C3′ Substituents. As before, derivatives were first synthesized in the naphthyridone C5-H template. In most cases, these were prepared from the racemic trans hydroxy azido piperidine **5** (Scheme 1), and the enantiomers were separated for selected examples. In some cases (examples **26**, **31−33**, **44**), the alkylation with the C3′ substituent was performed after the Buchwald coupling between **7b** and the protected amine **23**, which was derived from the hydroxyl derivative **5** (Scheme 3). Deprotection of the secondary alcohol gave **24**, which, after alkylation and further deprotection, gave the desired inhibitors.

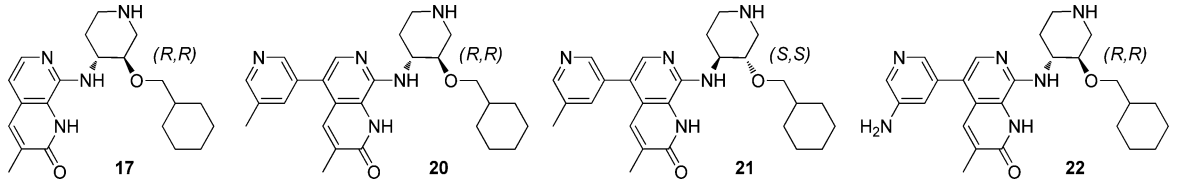
Scheme 3[a]



[a]Reagents and conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, room temperature, 71%; (b) H_2, Pd/C, EtOH, room temperature, 95%; (c) BrettPhos, BrettPhos precatalyst, *t*BuONa, THF, room temperature to 60 °C, 97%; (d) TBAF, THF, room temperature, 71%; (e) chiral separation of enantiomers; (f) ROTf, *t*BuOK, THF, 0 °C to room temperature, 10−65% or NaH, THF (or DMF), 0 °C then ROTf, 0 °C to room temperature, 37−65%; (g) TFA, 60 °C to reflux, 45−94%.

Examples of such compounds with increased polarity in their C3′ substituents are shown in Table 3. Most of the racemic mixtures (e.g., **25−27**) had ATAD2 activity comparable to that of the racemic cyclohexyl benchmark **13** (pIC_{50} 5.5). As before, when the mixtures were separated, most of the activity resided in a single enantiomer (compare **29** to **28**). The most

Table 2. Effect of C5-(3-Pyridine) Substituents[a]



Compound	ATAD2 pIC_{50}	ATAD2 LE	ATAD2 *Bromosphere* pIC_{50}	BRD4 BD1 pIC_{50}	Δ	Solubility μM	LogD
17	5.6	0.28	5.4	5.4	0.2	220	3.3
20	6.7	0.27	6.5	5.8	0.9	170	4.0
21	5.4	0.22		4.9	0.5	196	4.2
22	6.9	0.28	7.4	6.2	0.7	494	2.2

[a]Δ = difference between ATAD2 and BRD4 BD1 FRET pIC_{50}. For statistics, see Table S1, Supporting Information.

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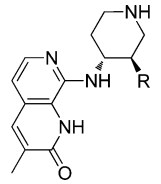
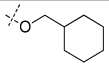
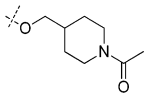
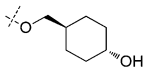
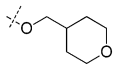
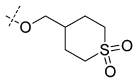
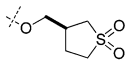
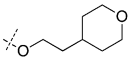
Table 3. Polar C3′ Substituents[a]



R	Chirality	Compound	ATAD2 pIC_{50}	ATAD2 LE	ATAD2 *Bromosphere* pIC_{50}	BRD4 BD1 pIC_{50}	Δ	Solubility μM	LogD
	Enantiomer 2	**17**	5.6	0.28	5.4	5.4	0.2	220	3.3
	Racemate	**25**	5.1	0.23		5.0	0.1	≥ 392	1.2
	Racemate	**26**	5.3	0.26		4.9	0.4	≥ 323	0.7
	Racemate	**27**	5.2	0.26		5	0.2	298	1.7
	Enantiomer 1	**28**	4.2	0.21		4.9	- 0.7	≥ 352	1.5
	Enantiomer 2	**29**	5.4	0.27	5.8	4.8	0.6	≥ 406	1.5
	Racemate	**30**	5.6	0.26	6.0	5.2	0.4	≥ 309	1.0
	Enantiomer 1	**31**	4.3	0.20		5.3	-1.0	≥ 531	1.1
	Enantiomer 2	**32**	6.1	0.29	6.3	4.9	1.2	≥ 421	1.0
	Racemate	**33**	5.3	0.26		4.9	0.4	≥ 328	1.0
	Racemate	**34**	4.8	0.23		4.6	0.2	≥ 327	1.5

[a]Δ = difference between ATAD2 and BRD4 BD1 FRET pIC_{50}. For statistics, see Table S1, Supporting Information

promising polar analogue was the cyclic sulfone **30**. When chirally separated, the more active enantiomer **32** showed improved ATAD2 activity over the chiral cyclohexyl **17**. More importantly, consistent with our strategy for increasing selectivity over BRD4 by increasing negative polarity, both the tetrahydropyran **29** and cyclic sulfone **32** showed lower BRD4 activity than **17**. Further analogues using similar ring systems (e.g., **33**) did not show any advantage, as was also the case when extending the linker between the piperidine and the substituent (e.g., **34**).

To better understand the interactions made by the cyclic sulfone and to confirm the identity of the more active enantiomer, a soak of the racemic cyclic sulfone **30** into ATAD2 crystals led to the X-ray structure shown in Figure 4. The binding mode is very similar to that of **13**. Again, the (*R*,*R*) isomer can be seen unambiguously binding within the active site (Figure S3, Supporting Information). The main differences from the structure of **13** are the polar interactions made by the sulfone oxygen atoms, each of which accepts hydrogen bonds from the guanidinium group of Arg1077. The first sulfone oxygen lies in the position occupied by $H_2O_{(R1077)}$, the Arg1077-bound water molecule in the complex with **2** (Figure 4c). The second sulfone oxygen also hydrogen bonds to the Arg1077 terminal NH_2 group and is able to make a second interaction with the terminal NH_2 group of Arg1007, which moves slightly toward the sulfone.

The enhanced selectivity over BRD4 of **32** relative to **17** is due to both increased ATAD2 potency and decreased BET activity (Table 3). The ATAD2 potency gain arises from the new direct hydrogen bonds to the arginines and the displacement of the weakly bound water molecules. The reduction of BET activity presumably results from placing polar sulfone oxygen atoms in an unfavorable lipophilic location near Trp81 and Met149 (Figure 3b). The tetrahydropyran **29** is intermediate in polarity between the cyclohexyl **17** and cyclic sulfone **32** and shows intermediate selectivity.

Combining C5 and Polar C3′ Substituents. The tetrahydropyran and the cyclic sulfone C3′ substituents offered the best compromise of structural complexity, ATAD2 activity, and BET selectivity. Next, we assessed the impact of reintroduction of C5-(3-pyridine) groups on the overall profile of our fully functionalized inhibitors, prepared according to Scheme 2. In agreement with earlier results, C5-(3-pyridyl) substituents were about 1 log more potent against ATAD2 than

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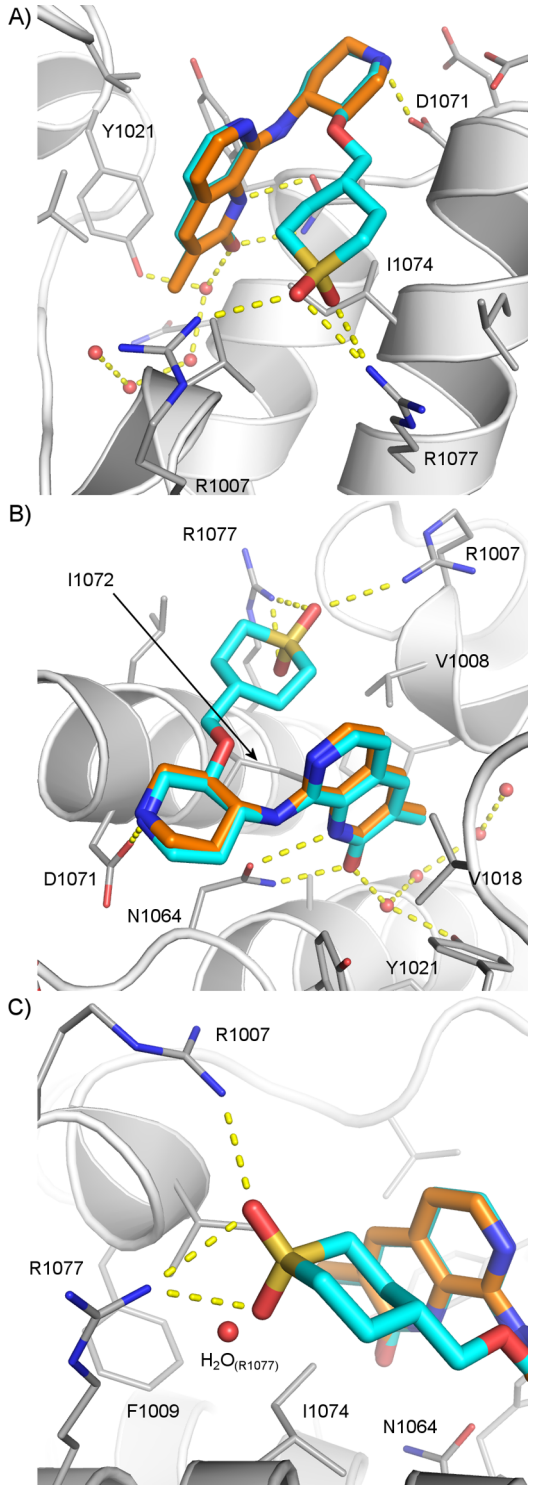

Figure 4. (A–C) Three different views of the X-ray structure of ATAD2 bound to **30** (cyan, PDB code 5a82), superimposed on **2** (orange, PDB code 5a5q). In (C), a water molecule $H_2O_{(R1077)}$ is shown. This lies near Arg1077 in the complex with **2** and is displaced by **30**.

the direct C5-H analogues (Table 4: compare **20** to **17**, **37** to **29**, and **38** to **32**). As was found for the 5-H analogues, the most potent C5-(3-pyridyl)-substituted compounds were the C3′-cyclic sulfones (**36**, **38**, and **40**, all with ATAD2 pIC_{50} 6.9). The 3′ tetrahydopyran derivatives were uniformly slightly lower in potency than the cyclic sulfones by ∼0.3 logs (compare **35** to **36**, **37** to **38**, and **39** to **40**).

Unexpectedly, addition of C5-(3-pyridine) substituents to compounds with polar C3′ groups also improved the selectivity for ATAD2 over BRD4 BD1 (compare, e.g., **38** to **32**). **38** was the first compound whose activity in the ATAD2 FRET assay was over 2 logs greater than in BRD4 BD1. Interestingly, introduction of the (3,5)-pyrimidine at C5 gave somewhat improved BET selectivity (in the case of the tetrahydropyran **41** compared to **35**, **37**, or **39**), but this came at the expense of some ATAD2 potency. This is in line with the effects of the C5-pyrimidine in the 3′-unsubstituted naphthyridone (compound 67 in our preceding article).[6]

Compound **38** almost matched our ATAD2 TR-FRET target activity and possessed even greater activity when measured against endogenous ATAD2 in the *Bromosphere* assay (Table 4). It also met our probe criteria of 2 logs of selectivity over BRD4 BD1. While this was encouraging, concerns remained over the polarity of the C3′ cyclic sulfone and its possible impact on cell permeability. For early analogues such as **3** that retained significant BRD4 BD1 potency, IL-6 inhibitory activity in LPS-stimulated PBMCs was consistent with this BET-driven readout, showing that they were cell-permeable.[6] Less polar analogues, such as C3′-cyclohexyl **20** or tetrahydropyran derivatives **37** and **39**, possess measurable artificial membrane permeability (Table 4) and also have expected levels of BET-driven IL-6 activity (Table S1, Supporting Information). However, these have insufficient ATAD2 potency and/or BET selectivity to meet our probe criteria. For selective ATAD2 inhibitors such as **36**, **38** and **40**, BET-driven cellular IL-6 activity would be expected to be minimal, so this could no longer be used as an indication of cell penetration. The low logD and artificial membrane permeability of these sulfone-containing compounds (Table 4) did suggest that their concentration within cells could be relatively limited.

Increasing Permeability. Because of these concerns, we attempted to increase the permeability of the sulfone-bearing inhibitors by reducing the polar surface area and the number of hydrogen bond donors and acceptors. In parallel, we tried to increase logD by finding areas where small lipophilic substituents could be tolerated. Table 5 highlights some results of this strategy. First, to remove one heteroatom, the naphthyridone core was changed back to the quinolinone (as in the original hit **1**). The resulting compounds included the direct quinolinone analogue of **38** (the racemic **42** and its most potent single enantiomer, **43**). Although the removal of the naphthyridone nitrogen did increase logD by ∼0.5, this did not translate into measurable artificial membrane permeability.

A crystal structure of **42** was solved in ATAD2. As before, the (*R*,*R*) enantiomer was observed to bind (Figure S3, Supporting Information). The binding mode is very similar to that of **30** (Figure 5). The key protein contacts made by the quinolinone of **42** and the naphthyridone of **30** are essentially identical. The piperidines of each compound also overlay perfectly. The increase of potency conferred by the C5-(3-pyridyl) group can be rationalized in the same way as that previously used to explain the increase in potency for **3** over **2**.[6] The pyridine nitrogen forms a direct hydrogen bond with the backbone NH group of Asp1014 in the ZA loop of ATAD2 (Figure 5).

On the RVF shelf, the hydrogen bonds between Arg1077 and the sulfone of **42** are also the same as seen in the complex with **30** (Figure 5). Unexpectedly, the side chain of Arg1007 moves away from the sulfone in the complex with **42**, suggesting that

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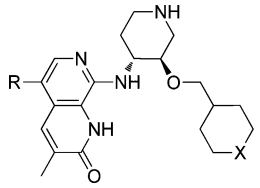
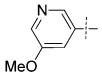
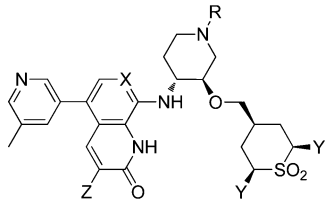
Table 4. Combinations of Optimal C5 and C3′ Substituents[a]



R	Compound	X	ATAD2 pIC_{50}	ATAD2 LE	ATAD2 *Bromosphere* pIC_{50}	BRD4 BD1 pIC_{50}	Δ	Solubility μM	LogD	Permeability (nm/s, pH 7.4)
	17	CH_2	5.6	0.28	5.4	5.4	0.2	220	3.3	130
H	**29**	O	5.4	0.27	5.8	4.8	0.6	≥406	1.5	<10
	32	SO_2	6.1	0.29	6.3	4.9	1.2	≥421	1.0	<6.5
	**35**	O	6.6	0.27	6.7	5.2	1.4	≥465	1.6	<3
	36	SO_2	6.9	0.27	7.0	5.0	1.9	≥315	1.3	<3
	**20**	CH_2	6.7	0.27	6.5	5.8	0.9	170	4.0	138
	37	O	6.5	0.26	6.6	5.0	1.5	254	1.9	32.5
	38	SO_2	6.9	0.26	7.5	4.8	2.1	179	1.6	<3
	**39**	O	6.6	0.26	6.5	5.1	1.5	≥418	2.0	33.5
	40	SO_2	6.9	0.26	7.0	5.1	1.8	≥269	1.7	<3
	**41**	O	6.0	0.25	6.1	4.3	1.7	≥414	1.0	<3

[a]All are the most potent single enantiomers. Δ = difference between ATAD2 and BRD4 BD1 FRET pIC_{50}. For statistics, see Table S1, Supporting Information

Table 5. Increasing Lipophilicity in the Sulfone Series[a]



Compound	X	Y	Z	R	ATAD2 pIC_{50}	ATAD2 LE	ATAD2 *Bromophere* pIC_{50}	BRD4 BD1 pIC_{50}	Δ	Solubility μM	LogD	Permeability (nm/s, pH 7.4)
38	N	H	CH_3	H	6.9	0.26	7.5	4.8	2.1	179	1.6	<3
42	CH	H	CH_3	H	6.8	0.26	7.4	5.4	1.4	217	2.0	<3
43	CH	H	CH_3	H	7.2	0.27	7.4	5.4	1.8	≥266	2.1	<3
44	N	CH_3	CH_3	H	7.0	0.25	7.2	4.6	2.4	30	1.7	<3
45	N	H	C_2H_5	H	7.1	0.26	7.3	5.0	2.1	323	1.8	<3
46	N	H	CH_3	CH_3	6.5	0.24	7.0	4.1	2.4	≥341	2.3	<10

[a]All are single (*R*,*R*) enantiomers except for **42**, which is a racemic mixture of trans enantiomers. Δ = difference between ATAD2 and BRD4 BD1 FRET pIC_{50}. LE ≈ 1.37 × pIC_{50}/(number of heavy atoms). For statistics, see Table S1, Supporting Information.

their direct interaction seen in the complex with **30** is not critical for sulfone recognition.

The ATAD2 activity of **43**, the (*R*,*R*) enantiomer of **42**, is similar to that of **38** (Table 5). This is as expected given the lack of any visible interactions in the X-ray structures involving the naphthyridone N7 atom or the corresponding quinolinone C7 atom. For reasons not well understood, a small but consistent decrease in selectivity over BET was observed for the quinolinones relative to the naphthyridones (compare **43** to **38**, and other analogues not shown).

Finding no advantage in the quinolinone series over the naphthyridones, we investigated the addition of small lipophilic substituents elsewhere in the structure. These were tolerated at some positions on the C3′ substituent with no impact on activity or selectivity. For example, we tried to mask some of the polarity of the cyclic sulfone by methylation upon either side (**44**). This change was tolerated in terms of potency, but it did not affect measured logD or permeability, and it was somewhat detrimental to solubility, which was otherwise good in this series. Perhaps more surprisingly, replacement of the naphthyridone C3-methyl group, which binds in the acetyl-lysine methyl pocket, with a bulkier ethyl substituent (**45**) was also well tolerated. Unfortunately, this did not improve the measured permeability. Finally, small piperidine N-alkyl substituents were introduced. Piperidine N-methylation led to a modest loss of potency at ATAD2 for compound **46** relative

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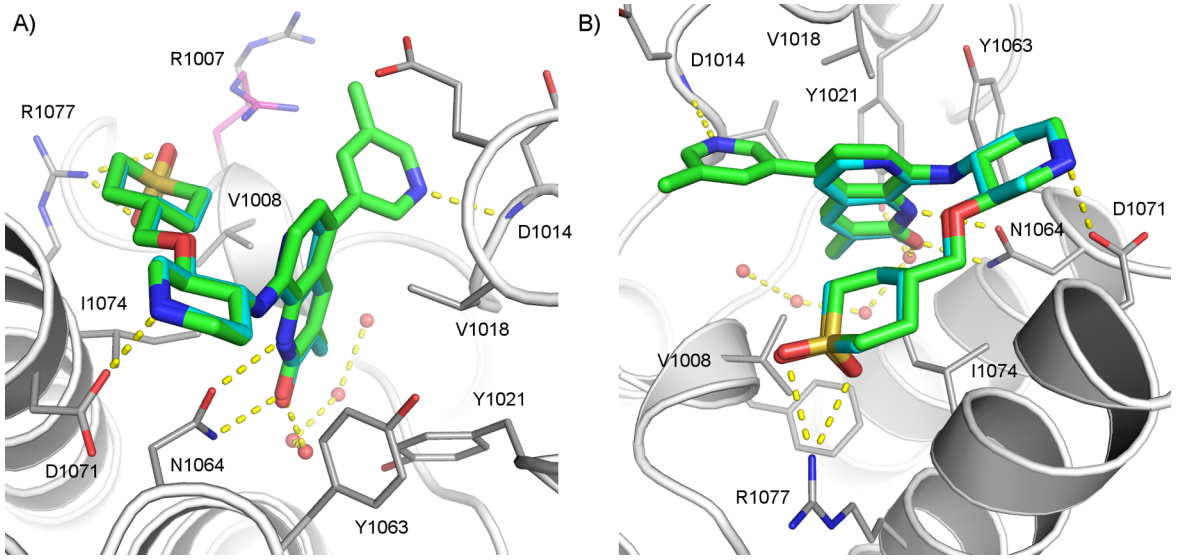

Figure 5. (A, B) Two orientations of the ATAD2 X-ray complex with **42** (green, PDB code 5a83), superimposed on the structure of **30** (cyan, PDB code 5a82). The position of the mobile side chain of Arg1007 in the complex with **30** is shown in magenta.

to **38**, probably due to the close proximity of the N-methyl group to the side chain of Asp1071 (Figure 5). A similar reduction was seen in the *Bromosphere* assay (Table 5). Although not quite reaching our ATAD2 target potency, **46** had higher logD than **38** and lower BRD4 BD1 activity, resulting in a slightly wider selectivity window.

Further Characterization. This work was primarily driven by activity against the ATAD2 bromodomain, measured in the TR-FRET assay, as well as in the *Bromosphere* assay as described above. For some compounds, pK_d values were also derived by monitoring direct binding to the ATAD2 bromodomain using surface plasmon resonance (SPR). SPR pK_d values were in excellent agreement with the TR-FRET pIC_{50}s (r^2 > 0.95, Table 6 and Figure S1c, Supporting Information). This confirmed the sub-100 nM ($pIC_{50} \geq 7.0$) potency of key molecules such as **38**. Much of the important SAR also tracked, for example, the decrease in potency caused by the piperidine N-methylation of **38** to give **46**.

Table 6. ATAD2 SPR Binding Constants Compared to TR-FRET pIC_{50} Values

Compound	ATAD2 SPR K_d μM	ATAD2 SPR pK_d	ATAD2 TR-FRET pIC_{50}
13	2.9	5.5	5.5
17	2.3	5.6	5.6
22	0.05	7.3	6.9
29	3.2	5.5	5.4
32	1.1	6.0	6.1
38	0.09	7.1	6.9
43	0.06	7.2	7.2
46	0.20	6.7	6.5

The selectivity of **46** against the wider bromodomain family was assessed in the BROMO*scan* panel (Figure 6 and Table S2, Supporting Information).[15] The ATAD2 pK_i of 7.7 (K_i 20 nM) in this format was slightly more potent than in other assays. Similar activity was found against the closest homologue of ATAD2, ATAD2B (pK_i 7.4), which was expected given the high sequence similarity between the two bromodomains (73% identity, with only conservative changes in the KAc site, see

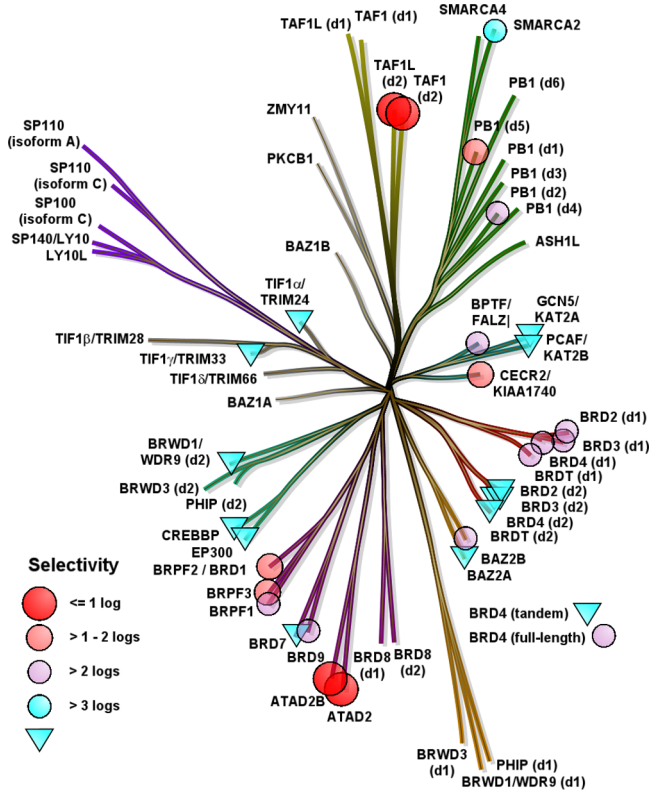

Figure 6. Selectivity of **46** against other bromodomains. The color scale ranges from pK_i 7.7 (red) to <4.3 (blue, triangles denote "<" modifier).

Figure S2, Supporting Information). Selectivity over the BET bromodomains was confirmed, with a window of at least 2.6 logs (>400-fold), BRD4 BD1 being the most potent (pK_i 5.1). For the other bromodomains tested, the highest activity was with the second bromodomains of TAF1 and TAF1L (pK_i 7.3 and 6.9, respectively). Weaker activity remained against the BRPF family (pK_i 5.3/6.4/6.1 against BRPF1/2/3, respectively) and CECR2 (pK_i 6.1). The cellular consequences of inhibition of these bromodomains is currently unknown, so we

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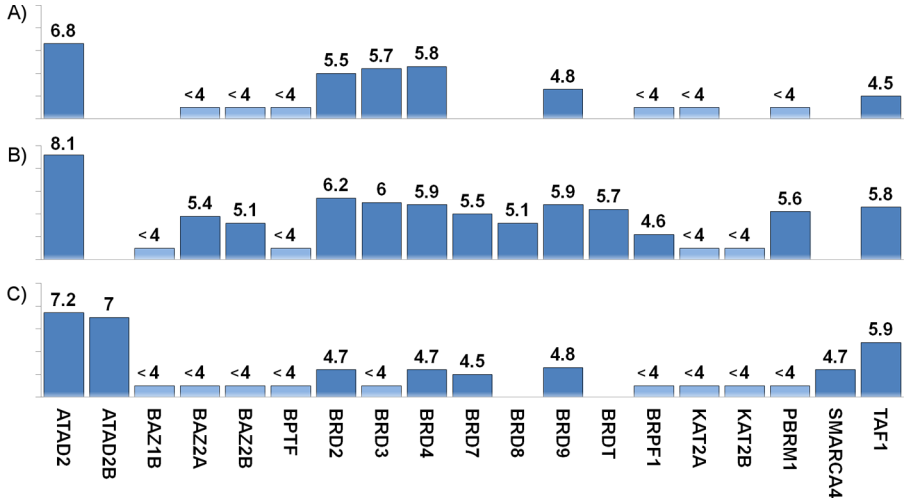
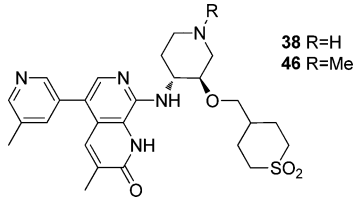


Figure 7. Selectivity of (A) **20**, (B) **43**, and (C) **46** for ATAD2 against other bromodomain containing proteins using MS-detected pull downs from cell lysates. Specified values are apparent pK_ds. Values <4 indicate that no pK_d was determined up to 100 μM compound concentration. No bar indicates that protein was not identified.

Table 7. Summary of Properties of 38 and 46



	38	46
ATAD2 pIC_{50} (TR-FRET)	6.9	6.5
ATAD2 pIC_{50} (Peptide FRET)	6.9	6.6
ATAD2 pIC_{50} (*Bromosphere*)	7.5	7.0
ATAD2 pK_d (SPR)	7.1	6.7
ATAD2 pK_i (BROMO*scan*)		7.7
BRD2 BD1/BD2 pIC_{50} (TR-FRET)	4.5/<4.5	<4.3/<4.3
BRD3 BD1/BD2 pIC_{50} (TR-FRET)	<4.3/<4.3	<4.3/<4.3
BRD4 BD1/BD2 pIC_{50} (TR-FRET)	4.8/5.3	4.1/<3.3
BRDT BD1/BD2 pIC_{50} (TR-FRET)	4.5/<4.3	<4.3/< 4.3
Chrom LogD (pH 7.4)	1.6	2.3
Artificial membrane permeability (nm/s, pH 7.4)	<3	<10
CLND solubility (μM)	179	≥341

were satisfied to find this highly restricted off-target profile among the bromodomain family and to verify the excellent selectivity over the BET bromodomains.

In parallel, we assessed the selectivity of **46** and other examples against a panel of endogenous bromodomain-containing proteins present in cell lysates using a *Bromosphere* chemoproteomic assay. A focused panel of immobilized, unselective bromodomain inhibitors was able to pull down 19 of these proteins, as detected using mass spectrometry. The pK_d values of **20**, **43**, and **46** for those full-length proteins were determined using competition dose−response experiments. **46** shows clearly improved selectivity over **20** (Figure 7c), as also found for the BET bromodomains by TR-FRET. For **46**, the bromodomains detected to bind most strongly are consistent with those found in the BROMO*scan* panel, although, pleasingly, it appears that the compound shows greater selectivity for ATAD2 and ATAD2B when measured using endogenous proteins.

CONCLUSIONS

Here, we have presented the first report of successful optimization of inhibitors of the ATAD2 bromodomain to sub-100 nMaffinity. Potency and BET selectivity were improved with the help of extensive crystallography in ATAD2 and BRD4 BD1. This led to the identification of compounds such as **38** (Table 7), which matched our potency and selectivity criteria, showing >100-fold selectivity over the BET bromodomains. This selectivity was achieved by optimizing the 3′ substituent for complementarity with the ATAD2 site and against the BET site, resulting in the C3′-cyclic sulfone moiety found within **38**. However, this came at the expense of greater hydrophilicity, and the passive permeability of the sulfone-containing members of this series remained concerningly low for use in cellular assays. We were partly able to mitigate this in compound **46**, although the potency was lower than we had hoped and some off-target activity remained against other bromodomains. The conclusion

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of the optimization of this series to generate a cell-permeable and significantly more selective ATAD2 chemical probe will be the subject of our next publication.

EXPERIMENTAL SECTION

Protein Expression, SPR, BET Bromodomain Assays, PBMC IL6 Assay, and Physicochemical Property Measurement. These were carried out as described previously.[6]

ATAD2 Synthetic Ligand Competition TR-FRET Binding Assay. Compounds were titrated from 10 mM in 100% DMSO, and 100 nL was transferred to a low-volume black 384-well microtiter plate using a Labcyte Echo 555. A Thermo Scientific Multidrop Micro was used to dispense 5 μL of 5 nM FLAG-6His-Tev-ATAD2(981−1121) in 50 mM Hepes, 150 mM NaCl, 5% Glycerol, 1 mM CHAPS, and 1 mM DTT, pH 7.4, in the presence of 100 nM Alexa Fluor 488-labeled ligand. After equilibrating for 30 min in the dark at room temperature, the ATAD2 protein−fluorescent ligand interaction was detected using TR-FRET following a 5 μL addition of 1.5 nM Lanthascreen Elite Tb-anti His antibody (Invitrogen, PV5863) in assay buffer. Time-resolved fluorescence (TRF) was then detected on a TRF laser equipped PerkinElmer Envision multimode plate reader (excitation = 337 nm; emission 1 = 520 nm; emission 2 = 495 nm; dual wavelength bias dichroic = 400, 505 nm). TR-FRET ratio was calculated using the following equation: ratio = ((acceptor fluorescence at 520 nm)/(donor fluorescence at 495 nm)) × 1000. TR FRET ratio data was normalized to a mean of 16 replicates per microtiter plate of both 10 μM GSK3190320 (a potent naphthyridone ATAD2 inhibitor similar to **37**; see Figure S4, Supporting Information) and 1% DMSO controls, and IC_{50} values were determined for each of the compounds tested by fitting the fluorescence ratio data to a four-parameter model, $y = a + ((b - a)/(1 + (10^x/10^c)^d))$, where a is the minimum, b is the Hill slope, c is the IC_{50}, and d is the maximum.

Preparation of Cell Fractions for Chemoproteomic Profiling. Nuclear extract was produced from HuT78 cells grown at 1×10^6 to 5×10^6 cells/mL in spinner flasks. Cells were collected by centrifugation, washed with PBS, and resuspended in three volumes with hypotonic buffer A (10 mM Tris-Cl, pH 7.4, 1.5 mM $MgCl_2$, 10 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM DTT, and 1 Roche protease inhibitor tablet per 25 mL). After 15 min, cells were homogenized with a Dounce homogenizer. Nuclei were collected by centrifugation (2500*g*), washed with hypotonic buffer A, and homogenized in one volume of extraction buffer B (50 mM Tris-Cl, pH 7.4, 1.5 mM $MgCl_2$, 20% glycerol, 420 mM NaCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM DTT, 400 units/mL DNase I, and 1 Roche protease inhibitor tablet per 25 mL). Extraction was allowed to proceed under agitation for 30 min at 4 °C before the extract was clarified by centrifugation at 13 000*g*. The extract was diluted in buffer D (50 mM Tris-Cl, pH 7.4 (RT), 1.5 mM $MgCl_2$, 25 mM NaF, 1 mM Na_3VO_4, 0.6% NP-40, 1 mM DTT, and Roche protease inhibitors), and aliquots were snap-frozen in liquid nitrogen and stored at −80 °C. Tight chromatin-associated protein-enriched fractions were prepared by resuspending the remaining pellet in 10 volumes of high-salt extraction buffer (20 mM Hepes, pH 7.4, 1.5 mM $MgCl_2$, 1 M KCl, 10% glycerol, 0.1% NP40, 0.5 mM DTT, and Roche protease inhibitors) with 8−10 cycles of 10 s on/50 s off sonication with an ultrasound homogenizer (Bandelin Sonoplus). After sonication and incubation for 45 min at 4 °C, the homogenate was clarified at 8000*g*. The salt concentration was adjusted to 150 mM KCl through stepwise dialysis before ultracentrifugation at 100 000*g* for 20 min. Aliquots were snap-frozen in liquid nitrogen and stored at −80 °C.

ATAD2 *Bromosphere* Assay.[16] The ATAD2 *Bromosphere* competition binding assay was performed in a 384-well format using an antibody-based array readout. Briefly, 60−120 μg HuT-78 chromatin lysate and 1.5 μL of ATAD2 capturing matrix (immobilized GSK2998821 on NHS Sepharose, structure not shown) per well (final volume 75 μL) were incubated in the absence or presence of inhibitor compound at 4 °C. Compounds were tested in a dose−response format with a starting concentration of 100−200 μM, applying 1:3 dilution steps for, in total, 10 or 11 data points. DMSO concentration was 1% (v/v). After 2 h incubation, the nonbound fraction was removed by washing the beads with lysis buffer (50 mM Tris-HCl (pH 7.4), 0.1% (v/v) Igepal-CA630, 5% (v/v) glycerol, 150 mM NaCl, 1.5 mM $MgCl_2$, 25 mM NaF, 1 mM sodium vanadate, 1 mM dithiothreitol). Proteins retained on the beads were eluted in SDS sample buffer (100 mM Tris (pH 7.4), 4% (w/v) SDS, 20% (v/v) glycerol, 0.01% (w/v) bromophenol blue, 50 mM dithiothreitol) and spotted on nitrocellulose membranes (400 nL per spot) using an automated pin-tool liquid transfer (Biomek FX, Beckman). After drying, the membranes were rehydrated in 20% (v/v) ethanol and processed for detection with a specific anti-ATAD2 antibody (Sigma; 29424 (1:300) in the presence of 0.4% Tween) followed by incubation with an IRDye 800-labeled secondary antibody for visualization (anti-rabbit 926-32211, LICOR (1:5000)) in the presence of 0.2% Tween. Spot intensities were quantified using a LiCOR Odyssey scanner.

Chemoproteomic Assay with Dose-Dependent Competition. Affinity profiling assays were performed as described previously.[16,17] Briefly, sepharose beads were derivatized with nonselective bromodomain inhibitors of various chemotypes containing a primary amine handle (e.g., 0.6 mM GSK2975292 or 2 mM GSK2893910 or 1 mM GSK3040504, structures not shown) via amide-bond formation on activated NHS beads. Increasing concentrations of tested ATAD2 inhibitor compounds were spiked into HuT-78 mixed chromatin and nuclear extracts and incubated for 45 min at 4 °C. Derivatized sepharose beads (35 μL beads per sample) were equilibrated in lysis buffer and incubated with cell extract containing compound. Beads were washed with lysis buffer containing 0.2% NP-40 and eluted with 2× SDS sample buffer supplemented with DTT.

Mass Spectrometry and Data Analysis for Chemoproteomic Assay. Sample preparation, labeling with TMT isobaric mass tags, peptide fractionation, and mass spectrometric analyses were performed essentially as described earlier.[18] The pooled peptide samples were either fractionated with a reverse phase at pH 12 as described previously[19] and subsequently analyzed by LC-MS with a 1D plus (Eksigent) LC connected to a Orbitrap XL (Thermo Scientific) or directly analyzed using Nanoacquity UPLC system (Waters) connected to an Orbitrap Elite mass spectrometer (Thermo Scientific). In both cases, the peptides were separated on custom-made 50 cm × 100 μM reversed-phase columns (Reprosil) at 40 °C. Gradient elution was performed from 2 to 40% acetonitrile in 0.1% formic acid over 2 h. A targeted data acquisition strategy was applied as described[20] for protein identification using a list of 20 peptide charge mass combinations per bromodomain protein. Mascot 2.3.02 (Matrix Science) was used for protein identification, using 10 ppm mass tolerance for peptide precursors and 20 mDa (HCD) or 0.8 Da (CID) mass tolerance for fragment ions. Carbamidomethylation of cysteine residues and TMT modification of lysine residues were set as fixed modifications, and methionine oxidation, N-terminal acetylation of proteins, and TMT modification of peptide N-termini were set as variable modifications. The search database consisted of a customized version of the IPI protein sequence database combined with a decoy version of this database created using a script supplied by Matrix Science. All identified proteins were quantified; FDR for quantified proteins was ≪0.1%. For dose-dependent experiments, dose−response curves were fitted using R (http://www.r-project.org/) and the drc package (http://www.bioassay.dk), as described previously.[21] IC_{50} values were corrected for the influence of the immobilized ligand on the binding equilibrium using the Cheng−Prusoff relationship.[22]

ATAD2 Crystallography. Apo crystals of ATAD2 981−1108, expressed and detagged as described previously,[6] were typically grown at 4 °C in 96-well MRC plates using well solutions under a range of conditions spanning 0.1 M Tris-HCl, pH 7.0−8.0, 1.2−1.5 M ammonium sulfate, and 20−25% PEG3350. The sitting drops were made up of 3:1 ratio of protein/well solution, and the hexagonal crystals often grew from phase-separated drops. Compounds were soaked into apo crystals overnight either from solid or using 1−5 mM ligand solution diluted from a 100−200 mM DMSO stock solution. Soaked crystals were harvested in a cryo-loop, briefly transferred into a cryoprotectant buffer of 20% ethylene glycol + 80% well solution,

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before being plunge-frozen in liquid nitrogen. Data from single crystals were collected at 100 K on an in-house Rigaku FR-E+ SuperBright/Saturn A200 detector/ACTOR robotic system or at the Diamond Light Source (Oxford) or the Europeon Synchrotron Radiation Facility (Genoble). Data processing was performed using DENZO,[23] MOSFLM,[24] or XDS[25] (within AUTOPROC [Global Phasing Limited]) and scaled using either SCALEPACK,[23] SCALA,[26] or AIMLESS[27] [within the CCP4 programming suite[28]]. Structures were solved by Fourier synthesis using REFMAC[29] (via CCP4) starting from a previously determined in-house structure; model-building was performed using COOT,[30] and refinement, using REFMAC via CCP4. The statistics for the data collection and refined coordinates are given in Table S3, Supporting Information, and OMIT maps are provided in Figure S3. The final crystal structures have been deposited in the Protein Data Bank under the accession codes shown in Table S3, Supporting Information.

BRD4 BD1 Crystallography. Detagged BRD4-BD1(44−168), generated as previously described,[31] was cocrystallized with at least 3:1 excess of compound at 9−10 mg/mL in sitting drops using a 96-well MRC plate with a well solution indicated in Table S4. Crystals were briefly transferred into a cryoprotectant solution consisting of well solution with 20% ethylene glycol added prior to flash freezing in liquid nitrogen. Data from single crystals at 100 K on an in-house Rigaku FR-E$^+$ SuperBright/Saturn A200 detector/ACTOR robotic system or at the Europeon Synchrotron Radiation Facility (Genoble) were processed using XDS[25] and scaled using SCALA[26] or AIMLESS[27] within the CCP4 programming suite.[28] Molecular replacement solutions were determined with a previously collected in-house structure. The $P2_12_12_1$ cells have a single molecule in the asymmetric unit. Manual model building was performed using COOT[30] and refined using REFMAC[29] via CCP4. There was clear difference density for the ligands in the acetylated lysine binding site, allowing the ligand to be unambiguously modeled. The statistics for the data collection and refined coordinates are given in Table S4, Supporting Information, and electron density maps are shown in Figure S3, Supporting Information. The final crystal structures have been deposited in the Protein Data Bank under the accession codes shown in Table S3, Supporting Information.

Chemistry. All solvents were purchased from Sigma-Aldrich (Hy-Dry anhydrous solvents), and commercially available reagents were used as received. All reactions were followed by TLC analysis (TLC plates GF254, Merck) or LCMS (liquid chromatography mass spectrometry) using a Waters ZQ instrument. NMR spectra were recorded on a Bruker nanobay 400 MHz or a Bruker AVII+ 600 MHz spectrometers and are referenced as follows: ^{1}H NMR (400 or 600 MHz), internal standard TMS at δ = 0.00; ^{13}C NMR (100.6 or 150.9 MHz), internal standard $CDCl_3$ at δ = 77.23 or DMSO-d_6 at δ = 39.70. Column chromatography was performed on prepacked silica gel columns (30−90 mesh, IST) using a biotage SP4. Mass spectra were recorded on Waters ZQ (ESI-MS) and Q-Tof 2 (HRMS) spectrometers. Mass-directed auto prep was performed on a Waters 2767 with a MicroMass ZQ mass spectrometer using a Supelco LCABZ++ column.

Synthetic Methods and Characterization of Compounds. Abbreviations for multiplicities observed in NMR spectra: s; singulet; br s, broad singulet; d, doublet; t, triplet; q, quadruplet; p, pentuplet; spt, septuplet; m, multiplet. The purity of all compounds was determined by LCMS and ^{1}H NMR and was always >95%. See Supporting Information.

LCMS. UPLC analysis was conducted on an Acquity UPLC BEH C18 column (50 mm × 2.1 mm, i.d. 1.7 μm packing diameter) at 40 °C. Formate method: solvents employed were A = 0.1% v/v solution of formic acid in water and B = 0.1% v/v solution of formic acid in acetonitrile. High-pH method: the solvents employed were A = 10 mM ammonium hydrogen carbonate in water adjusted to pH 10 with ammonia solution and B = acetonitrile. For both methods, the gradient employed is shown in Table 8.

The UV detection was a summed signal from wavelength of 210 to 350 nm. Mass spectra were obtained on a Waters ZQ instrument; ionization mode, alternate-scan positive and negative electrospray; scan range, 100−1000 AMU; scan time, 0.27 s; inter scan delay, 0.10 s.

Table 8. LCMS Gradients Employed

time (min)	flow rate (mL/min)	% A	% B
0	1	99	1
1.5	1	3	97
1.9	1	3	97
2.0	1	0	100

MDAP. Formate method: HPLC analysis was conducted on either a Sunfire C18 column (100 mm × 19 mm, i.d. 5 μm packing diameter) or a Sunfire C18 column (150 mm × 30 mm, i.d. 5 μm packing diameter) at ambient temperature. The solvents employed were A = 0.1% v/v solution of formic acid in water and B = 0.1% v/v solution of formic acid in acetonitrile. Run as a gradient over either 15 or 25 min (extended run) with a flow rate of 20 mL/min (100 mm × 19 mm, i.d 5 μm packing diameter) or 40 mL/min (150 mm × 30 mm, i.d. 5 μm packing diameter). High-pH method: HPLC analysis was conducted on either an Xbridge C18 column (100 mm × 19 mm, i.d. 5 μm packing diameter) or a Xbridge C18 column (100 mm × 30 mm, i.d. 5 μm packing diameter) at ambient temperature. The solvents employed were A = 10 mM ammonium bicarbonate in water, adjusted to pH 10 with ammonia solution, and B = acetonitrile. Run as a gradient over either 15 or 25 min (extended run) with a flow rate of 20 mL/min (100 mm × 19 mm, i.d. 5 μm packing diameter) or 40 mL/min (100 mm × 30 mm, i.d. 5 μm packing diameter). For both methods, the UV detection was a summed signal from wavelength of 210 to 350 nm. Mass spectra were obtained on a Waters ZQ instrument; ionization mode, alternate-scan positive and negative electrospray; scan range, 100−1000 AMU; scan time, 0.50 s; inter scan delay, 0.20 s.

(3*R*,4*R*)-*tert*-Butyl 4-Azido-3-hydroxypiperidine-1-carboxylate (5). A solution of *tert*-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (**4**[13]) (11 g, 55 mmol) in DMF (100 mL) at room temperature was treated with a solution of sodium azide (6 g, 92 mmol) in water (40 mL) and acetone (60 mL), and the resulting mixture was stirred at 80 °C for 2 h and was then cooled to room temperature and diluted with EtOAc (200 mL) and water (200 mL). The layers were separated, and the organic phase was washed with water (200 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a pale yellow liquid. Purification of this residue by flash chromatography on silica gel (340 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (8.4 g, 63%) as a white solid. Later eluting fractions were combined and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 3-azido-4-hydroxy piperidine-1-carboxylate (1.9 g, 14%) as a colorless solid. ^{1}H NMR (T = 120 °C, 400 MHz, DMSO-d_6) δ ppm 4.97 (br s, 1H) 3.89−4.01 (m, 1H), 3.82 (d, J = 13.3 Hz, 1H), 3.27−3.44 (m, 2H), 2.83−2.90 (m 1H), 2.69 (dd, J = 12.8, 9.1 Hz, 1H), 1.84−2.01 (m, 1H), 1.44 (s, 9H), 1.27−1.40 (m, 1H). The racemic mixture was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralpak AD-H (4.6 mm i.d. × 25 cm), using 20% EtOH in heptane at a flow rate of 1 mL/min. The material (4.9 g) was dissolved in a mixture of EtOH/heptane (1:1) (500 mg in 2 mL). The purification was carried out on a Chiralpak AD-H (30 mm × 25 cm), using 20% EtOH in heptane at a flow rate of 30 mL/min, and 2 mL of solution was injected at a time. The appropriate fractions were combined and concentrated under reduced pressure to give the fastest running enantiomer, (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (2.3 g), and the slowest running enantiomer, (3*S*,4*S*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (2.4 g).

8-Chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (7a) and 2-(Benzyloxy)-8-chloro-3-methyl-1,7-naphthyridine (7b). The synthesis of these two compounds is described in the preceding article.[6]

8-(((3*R*,4*R*)-3-Methoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (9). Step 1: A solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (0.54 g, 2.23 mmol) in DMF (10 mL) at 0 °C under nitrogen was treated with NaH (60% w/w in mineral oil, 0.116 g, 2.90 mmol), and the resulting

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mixture was stirred at this temperature for 20 min. Iodomethane (0.153 mL, 2.45 mmol) was then added, and the solution was stirred for 16 h at room temperature. The mixture was then diluted with water (20 mL), and the aqueous phase was extracted with EtOAc (20 mL). The organic phase was washed with water (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-methoxypiperidine-1-carboxylate (0.48 g, 84%) as a colorless oil. Step 2: (3*R*,4*R*)-*tert*-butyl 4-azido-3-methoxypiperidine-1-carboxylate (0.45 g, 1.76 mmol) was dissolved in MeOH (40 mL) and hydrogenated in the H-Cube (1 mL/min, 10% Pd/C cartridge, full H_2 mode), and then MeOH was concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-amino-3-methoxypiperidine-1-carboxylate (**6**, R_1=Me) (0.38 g, 94%) as a colorless oil. Step 3: A suspension of 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) (0.08 g, 0.41 mmol), (3*R*,4*R*)-*tert*-butyl 4-amino-3-methoxypiperidine-1-carboxylate (**6**, R_1=Me) (0.156 mL, 0.617 mmol), and Caddick catalyst (0.024 g, 0.041 mmol) in THF (2 mL) in a microwave vial at room temperature under nitrogen was treated with LiHMDS (1N in THF, 1.23 mL, 1.23 mmol), and the resulting mixture was stirred at 120 °C for 30 min under microwave irradiation and then cooled to room temperature. The mixture was diluted with a saturated NH_4Cl aqueous solution (10 mL), and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 3-methoxy-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (63 mg, 39%) as a beige solid. LCMS (high-pH method): t_R 0.99 min, $[M + H]^+$ = 389.3. Step 4: A solution of (3*S*,4*S*)-*tert*-butyl 3-methoxy-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (76 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL), and the resulting mixture was stirred at this temperature for 1 h and then concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 8-(((3*S*,4*S*)-3-methoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1H)-one (48 mg, 85%) as a pale yellow solid. The racemic mixture was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralpak AD-H (4.6 mm i.d. × 25 cm), using 40% EtOH (+0.2% isopropylamine) in heptane at a flow rate of 1 mL/min. The material (34 mg) was dissolved in a mixture of EtOH/heptane (2:1). The purification was carried out on a Chiralpak AD-H (30 mm × 25 cm), using 40% EtOH (+ 0.2% isopropylamine) in heptane at a flow rate of 30 mL/min, and 3 mL of solution was injected. The appropriate fractions were combined and concentrated under reduced pressure to give the fastest running enatiomer, 8-(((3*R*,4*R*)-3-methoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**9**) (12 mg, 0.042 mmol, 21%), as a white solid. LCMS (high-pH method): t_R 0.62 min, $[M + H]^+$ = 289.2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.78 (d, J = 5.4 Hz, 1H), 7.72 (d, J = 1.0 Hz, 1H), 6.79 (d, J = 5.6 Hz, 1H), 4.12−4.20 (m, 1H), 3.45 (s, 3H), 3.37 (m, 4H), 2.99−3.06 (m, 1H), 2.69−2.78 (m, 1H), 2.51−2.58 (m, 1H), 2.24 (d, J = 1.2 Hz, 3H). Three NH not seen.

8-(((3*R*,4*R*)-3-Isopropoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (10). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (0.54 g, 2.2 mmol) in DMF (10 mL) at 0 °C under nitrogen was treated with sodium hydride (60% w/w in mineral oil, 0.116 g, 2.90 mmol), and the resulting mixture was stirred for 20 min at this temperature. 2-Iodopropane (0.245 mL, 2.45 mmol) was then added, and the solution was stirred at room temperature for 16 h. The mixture was then stirred at 70 °C for 2 h before being cooled to room temperature and treated with water (30 mL). The aqueous phase was extracted with EtOAc (30 mL). The organic phase was then washed with water (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-isopropoxypiperidine-1-carboxylate (55 mg, 9%) as a colorless oil. Step 2: (3*R*,4*R*)-*tert*-butyl 4-azido-3-isopropoxypiperidine-1-carboxylate (50 mg, 0.18 mmol) was dissolved in MeOH (20 mL) and hydrogenated in the H-Cube (1 mL/min flow rate, 10% Pd/C cartridge, full H_2 mode). The solution was then concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-amino-3-isopropoxypiperidine-1-carboxylate (**6**, R_1 = *i*-Pr) (42 mg, 92%) as a colorless oil. Step 3: a microwave vial was charged with 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) (0.035 g, 0.18 mmol), (3*R*,4*R*)-*tert*-butyl 4-amino-3-isopropoxypiperidine-1-carboxylate (**6**, R_1 = *i*-Pr) (0.053 mL, 0.19 mmol), and Caddick catalyst (10.6 mg, 0.018 mmol) and filled with THF (2 mL), and the resulting suspension was treated at room temperature under nitrogen with LiHMDS (1N in THF, 0.54 mL, 0.54 mmol). The resulting mixture was stirred at 120 °C for 30 min under microwave irradiation and was then cooled to room temperature. The mixture was then diluted with a saturated NH_4Cl aqueous solution (10 mL), and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave 8-(((3*R*,4*R*)-3-isopropoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (12 mg, 21%) (**10**) as a beige solid. LCMS (high-pH method): t_R 0.75 min, $[M + H]^+$ = 317.2. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.86 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 1.0 Hz, 1H), 6.88 (d, J = 5.4 Hz, 1H), 4.39 (d, J = 4.4 Hz, 1H), 4.05−4.10 (m, 1H), 3.92−4.01 (m, 1H), 3.41−3.51 (m, 2H), 3.21−3.28 (m, 1H), 3.17 (dd, J = 13.1, 4.5 Hz, 1H), 2.41−2.51 (m, 1H), 2.25 (d, J = 0.7 Hz, 3H), 1.97−2.05 (m, 1H), 1.24 (d, J = 6.1 Hz, 6H). Three NH not seen.

3-Methyl-8-(((3*R*,4*R*)-3-propoxypiperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (11). Step 1: a solution of (3*S*,4*S*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (1.94 g, 8.00 mmol) in DMF (30 mL) at room temperature under nitrogen was treated with sodium hydride (60% w/w in mineral oil, 0.384 g, 9.60 mmol) and then, after 10 min, with allyl bromide (1.04 mL, 12.0 mmol). The solution was stirred at room temperature for 1 h before being quenched with MeOH (1 mL) and diluted with water. The aqueous phase was extracted four times with Et_2O, and the combined organics were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give (3*S*,4*S*)-*tert*-butyl 3-(allyloxy)-4-azidopiperidine-1-carboxylate (2.32 g, 103%) as a clear oil, which was used in the next step without further purification. Step 2: a solution of (3*S*,4*S*)-*tert*-butyl 3-(allyloxy)-4-azidopiperidine-1-carboxylate (2.32 g, 8.22 mmol) in THF (40 mL) at room temperature was treated with triphenylphosphine (3.23 g, 12.3 mmol), and the resulting mixture was stirred at this temperature for 16 h. Water (3 mL) was then added, and the solution was refluxed for 2.5 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, dried over $MgSO_4$, and concentrated *in vacuo* to give a white solid. This residue was loaded on to a 50 g SCX column, washed with MeOH, and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give the desired amine still contaminated with triphenylphosphine oxide. Purification of this residue by flash chromatography on silica gel (50 g column, gradient: 10 to 40% (20% (2 N NH_3 in MeOH) in CH_2Cl_2) in CH_2Cl_2) gave (3*S*,4*S*)-*tert*-butyl 3-(allyloxy)-4-aminopiperidine-1-carboxylate (1.45 g, 69%) as a colorless oil. Step 3: (3*S*,4*S*)-*tert*-butyl 3-(allyloxy)-4-aminopiperidine-1-carboxylate (300 mg, 1.17 mmol) was dissolved in MeOH (40 mL) and hydrogenated in the H-Cube on full hydrogen mode with 10% Pd/C cartridge at 1 mL/min flow rate. The eluent was evaporated *in vacuo* to give a colorless oil. The product was redissolved in MeOH (40 mL), and hydrogenation was repeated under the same conditions to give (3*S*,4*S*)-*tert*-butyl 4-amino-3-propoxypiperidine-1-carboxylate (**6**, R_1 = Pr) (285 mg, 94%). Step 4: a microwave vial was charged with 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) (0.043 g, 0.22 mmol), (3*R*,4*R*)-*tert*-butyl 4-amino-3-propoxypiperidine-1-carboxylate (66 mg, 0.25 mmol), and Caddick catalyst (0.020 g, 0.033 mmol) and was then filled with THF (2 mL). The resulting mixture was treated with LiHMDS (1 N in THF, 0.77 mL, 0.77 mmol) and was then stirred at 80 °C for 30 min under nitrogen and microwave irradiation before being cooled to room temperature and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with a saturated NH_4Cl aqueous solution, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash

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chromatography on silica gel (25 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-propoxypiperidine-1-carboxylate (73 mg, 79%) as a brown solid. This product was dissolved in CH_2Cl_2 (2 mL) and treated at room temperature with TFA (1 mL). The mixture was stirred at this temperature for 1 h and was then concentrated *in vacuo*. The residue obtained was loaded on to a 5 g SCX-2 cartridge, which was washed with MeOH (10 mL) and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 3-methyl-8-(((3*R*,4*R*)-3-propoxypiperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (**11**) (51 mg, 73%) as a pale yellow solid. LCMS (high-pH method): t_R 0.72 min, $[M + H]^+$ = 317.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.95 (d, J = 5.4 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 6.50 (d, J = 7.3 Hz, 1H), 4.40−4.52 (m, 1H), 3.59 (dt, J = 9.2, 6.5 Hz, 1H), 3.45−3.54 (m, 2H), 3.34−3.42 (m, 1H), 3.09−3.18 (m, 1H), 2.83 (ddd, J = 12.7, 10.1, 2.9 Hz, 1H), 2.67−2.75 (m, 1H), 2.37 (d, J = 0.7 Hz, 3H), 2.21−2.30 (m, 1H), 1.60−1.72 (m, 1H), 1.43−1.54 (m, 2H), 0.74 (t, J = 7.5 Hz, 3H). Two NH not seen.

8-(((3*R*,4*R*)-3-Isobutoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (12). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (0.70 g, 2.89 mmol) in DMF (10 mL) at 0 °C was treated with NaH (60% w/w in mineral oil, 0.139 g, 3.47 mmol), and the resulting mixture was stirred for 20 min at 0 °C before 1-bromo-2-methylpropane (0.396 g, 2.89 mmol) was added. The mixture was stirred at this temperature for 2 h and was then diluted with water (40 mL). The aqueous phase was extracted with EtOAc (40 mL), and the organic layer was washed with water (40 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-isobutoxypiperidine-1-carboxylate (90 mg, 10%). Step 2: a suspension of 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) (0.050 g, 0.26 mmol), (3*R*,4*R*)-*tert*-butyl 4-amino-3-isobutoxypiperidine-1-carboxylate (0.078 g, 0.29 mmol), and Caddick catalyst (0.017 g, 0.029 mmol) in THF (2 mL) at room temperature was treated with LiHMDS (1N in THF, 0.86 mL, 0.86 mmol), and the resulting mixture was stirred at 120 °C under microwave irradiation for 1 h, cooled to 0 °C, and quenched with a saturated NH_4Cl aqueous solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 3-isobutoxy-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (51 mg, 41%) as a pale yellow solid. Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 3-isobutoxy-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-piperidine-1-carboxylate (50 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL), and the resulting mixture was stirred at this temperature for 1 h and concentrated *in vacuo*. The residue was loaded on to a 5 g SCX-2 cartridge, washed with MeOH (20 mL), and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-isobutoxypiperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**12**) (31 mg, 81%) as a pale yellow solid. LCMS (high-pH method): t_R 0.80 min, $[M + H]^+$ = 331.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 (d, J = 5.4 Hz, 1H), 7.67 (d, J = 1.2 Hz, 1H), 6.68 (d, J = 5.4 Hz, 1H), 6.62 (d, J = 7.3 Hz, 1H), 4.13 (m, 1H), 3.35(br s, 1H), 3.30 (dd, J = 8.9, 6.5 Hz, 2H), 3.13−3.23 (m, 3H), 2.81−2.90 (m, 1H), 2.44−2.50 (m, 1H), 2.25−2.35 (m, 1H), 2.11 (d, J = 0.7 Hz, 3H), 1.97 (dd, J = 13.0, 3.7 Hz, 1H), 1.62 (dt, J = 13.2, 6.6 Hz, 1H), 1.22−1.35 (m, 1H), 0.69 (dd, J = 8.6, 6.8 Hz, 6H).

8-(((3*R*,4*R*)-3-(Cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (13). Step 1: a solution of cyclohexylmethanol (10 g, 88 mmol) in CH_2Cl_2 (150 mL) at 0 °C under nitrogen was treated with pyridine (7.8 mL, 96 mmol), and the resulting mixture was stirred for 5 min before being treated with the dropwise addition of Tf_2O (16.3 mL, 96 mmol) over 10 min. The resulting mixture was stirred for 1 h at this temperature and was then warmed to room temperature. The organic phase was washed with water (2 × 50 mL) and then brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give cyclohexylmethyl trifluoromethanesulfonate (20 g, 93%) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.35 (d, J = 6.1 Hz, 2H), 1.76−1.89 (m, 5H), 1.69−1.76 (m, 1H), 1.17−1.38 (m, 3H), 0.99−1.12 (m, 2H). Step 2: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (15 g, 62 mmol) in DMF (50 mL) and THF (20 mL) was cooled to 0 °C and treated with sodium hydride (60% w/w in mineral oil, 3.2 g, 80 mmol) in small portions over 10 min. The resulting mixture was stirred at this temperature for 30 min. A solution of cyclohexylmethyl trifluoromethanesulfonate (20 g, 81 mmol) in THF (30 mL) was then added dropwise over 20 min, and the resulting mixture was allowed to slowly warm to room temperature over 2 h before being diluted with water (500 mL). The aqueous phase was extracted with Et_2O (2 × 300 mL), and the combined organics were washed with water (2 × 400 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. Purification of this residue by flash chromatography on silica gel (330 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cyclohexylmethoxy) piperidine-1-carboxylate (20.5 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.97−4.34 (m, 1H), 3.84−3.94 (m, 1H), 3.36−3.38 (m, 2H), 3.32−3.39 (m, 1H), 3.10−3.20 (m, 1H), 2.84−2.96 (m, 1H), 2.60−2.83 (m, 1H), 1.88−1.97 (m, 1H), 1.75 (t, J = 13.1 Hz, 5H), 1.53−1.64 (m, 1H), 1.48 (s, 9H), 1.11−1.45 (m, 4H), 0.97 (d, J = 11.7 Hz, 2H). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cyclohexylmethoxy)piperidine-1-carboxylate (20.5 g, 60.6 mmol) in THF (200 mL) at room temperature was treated with triphenylphosphine (19.1 g, 72.7 mmol), and the resulting solution was allowed to stand at room temperature over 2 days; then, water (30 mL) was added, and the resulting mixture was refluxed for 3 h before being cooled to room temperature and concentrated *in vacuo*. The residue obtained was partitioned between EtOAc (200 mL) and brine (200 mL), and the layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a colorless solid. This solid was triturated with Et_2O (200 mL) for 30 min and then filtered off to remove triphenylphosphine oxide. The filtrate was concentrated *in vacuo*. Purification of the residue obtained by flash chromatography on silica gel (340 g column, gradient: 0 to 10% (2N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-amino-3-(cyclohexylmethoxy)piperidine-1-carboxylate (**6**, R_1 = cyclohexylmethyl) (14.9 g, 79%) as a pale yellow oil that crystallized on standing overnight. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13−4.49 (m, 1H), 3.93−4.09 (m, 1H), 3.42−3.50 (m, 1H), 3.25 (dd, J = 9.0, 6.6 Hz, 1H), 2.80−2.90 (m, 1H), 2.73 (br s, 2H), 2.31−2.53 (m, 1H), 1.64−1.87 (m, 6H), 1.53−1.63 (m, 1H), 1.43−1.50 (m, 9H), 1.10−1.38 (m, 6H), 0.87−1.02 (m, 2H). Step 4: a flask was charged with 2-(benzyloxy)-8-chloro-3-methyl-1,7-naphthyridine (**7b**) (530 mg, 1.86 mmol), sodium *tert*-butoxide (537 mg, 5.58 mmol), Brettphos palladacycle (74.3 mg, 0.093 mmol), Brettphos (50.0 mg, 0.093 mmol), and (3*S*,4*S*)-*tert*-butyl 4-amino-3-(cyclohexylmethoxy)-piperidine-1-carboxylate (756 mg, 2.42 mmol) and then filled with THF (10 mL), and the resulting mixture stirred was for 1 h at room temperature. The color of the reaction changed from deep green to orange during this time. The mixture was then diluted with EtOAc (20 mL), and the organic phase was washed with water (20 mL) and then dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-(cyclohexylmethoxy) piperidine-1-carboxylate (1.02 g, 98%) as a pale yellow solid. LCMS (high-pH method): t_R 1.73 min, $[M + H]^+$ = 561. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 1.2 Hz, 1H), 7.50 (d, J = 7.1 Hz, 2H), 7.39−7.44 (m, 2H), 7.36 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 5.6 Hz, 1H), 6.37 (d, J = 7.3 Hz, 1H), 5.47−5.56 (m, 2H), 4.18−4.32 (m, 1H), 3.85 (s, 1H), 3.40−3.49 (m, 1H), 3.29−3.37 (m, 1H), 3.22 (dd, J = 8.9, 6.5 Hz, 2H), 2.42−2.51 (m, 1H), 2.40 (d, J = 0.7 Hz, 3H), 1.47−1.66 (m, 18H), 1.05 (d, J = 8.3 Hz, 3H), 0.68−0.86 (m, 2H). Step 5: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-(cyclohexylmethoxy) piperidine-1-carboxylate (1.02 g, 1.82 mmol) in MeOH (100

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mL) was hydrogenated using a H-Cube apparatus, on full hydrogen mode, running at 1 mL/min with a 10% Pd/C cartridge. The eluent was evaporated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-piperidine-1-carboxylate (0.85 g, 99%) as a pale yellow solid which was used in the next step without further purification. LCMS (high-pH method): t_R 1.47 min, $[M + H]^+$ = 471. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.06−11.22 (m, 1H), 7.76 (d, J = 5.3 Hz, 1H), 7.65 (d, J = 1.0 Hz, 1H), 6.73 (d, J = 5.3 Hz, 1H), 6.46 (d, J = 7.0 Hz, 1H), 4.29−4.38 (m, 1H), 3.76−3.84 (m, 1H), 3.60−3.69 (m, 1H), 3.39 (dd, J = 9.3, 6.5 Hz, 1H), 3.14−3.36 (m, 4H), 2.15 (d, J = 1.0 Hz, 3H), 1.97−2.08 (m, 1H), 1.59 (d, J = 7.5 Hz, 5H), 1.39−1.53 (m, 11H), 1.02−1.22 (m, 3H), 0.89 (br s, 2H). Step 6: a solution of (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (50 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL), and the resulting mixture was stirred at this temperature for 1 h and then concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL) and loaded onto a 5g SCX-2 cartridge. The cartridge was washed with MeOH (20 mL) and was then eluted with a 2 N NH_3 solution in MeOH (10 mL). The ammoniac fractions were concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-(cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**13**) (33 mg, 84%) as a yellow solid. LCMS (high-pH method): t_R 0.95 min, $[M + H]^+$ = 371.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 7.96 (d, J = 5.4 Hz, 1H), 7.65 (d, J = 1.0 Hz, 1H), 6.69 (d, J = 5.6 Hz, 1H), 6.45 (d, J = 6.4 Hz, 1H), 4.46 (d, J = 5.1 Hz, 1H), 3.34−3.49 (m, 3H), 3.29 (dd, J = 9.2, 6.5 Hz, 1H), 3.09−3.17 (m, 1H), 2.78−2.88 (m, 1H), 2.70 (dd, J = 12.1, 8.4 Hz, 1H), 2.38 (d, J = 0.7 Hz, 3H), 2.20−2.28 (m, 1H), 1.62−1.77 (m, 2H), 1.39−1.61 (m, 5H), 0.88−1.13 (m, 3H), 0.65−0.83 (m, 2H). One NH not seen.

8-(((3*R*,4*R*)-3-(Cyclopentylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (14). Step 1: a solution of cyclopentylmethanol (1.55 g, 15.5 mmol) in CH_2Cl_2 (30 mL) was cooled in an ice bath and was then treated with pyridine (1.38 mL, 17.0 mmol) followed by trifluoromethanesulfonic anhydride (2.88 mL, 17.0 mmol). The resulting mixture was stirred at this temperature for 2 h and was then washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give cyclopentylmethyl trifluoromethanesulfonate (3.02 g, 84%) as a colorless oil, which was used in the next step without further purification. Step 2: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (1.8 g, 7.4 mmol) in DMF (5 mL) was cooled in an ice bath and was then treated with NaH (60% w/w in mineral oil, 0.232 g, 9.66 mmol), and the resulting mixture was stirred at this temperature for 20 min before being treated with cyclopentylmethyl trifluoromethanesulfonate (2 g, 8.61 mmol). After stirring at 0 °C for 2 h, the reaction mixture was allowed to warm to room temperature. The reaction mixture was then diluted with water (15 mL), and the aqueous phase was extracted with EtOAc (20 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cyclopentylmethoxy)piperidine-1-carboxylate (1.01 g, 42%) as a colorless oil. Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cyclopentylmethoxy)piperidine-1-carboxylate (1.01 g, 3.11 mmol) in MeOH (80 mL) was hydrogenated in the H-Cube on full hydrogen mode over a 10% Pd/C cartridge at 1 mL/min flow rate. The eluent was concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-amino-3-(cyclopentylmethoxy) piperidine-1-carboxylate (**6**, R_1 = cyclopentylmethyl) (0.92 g, 99% yield) as a colorless oil. Step 4: a microwave vial was charged with 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) (65 mg, 0.33 mmol), (3*R*,4*R*)-*tert*-butyl4-amino-3-(cyclopentylmethoxy) piperidine-1-carboxylate (130 mg, 0.43 mmol), and Caddick catalyst (15 mg, 0.33 mmol) and flushed with nitrogen for 10 min. THF (2 mL) followed by LiHMDS (1N in THF, 1.34 mL, 1.34 mmol) was added, and the reaction mixture was stirred at 80 °C for 30 min under microwave irradiation and then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated NH_4Cl aqueous solution (10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 3-(cyclopentylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (145 mg, 95%) as a yellow glass. A solution of (3*R*,4*R*)-*tert*-butyl 3-(cyclopentylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-piperidine-1-carboxylate (145 mg, 0.32 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL), and the resulting mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The residue was loaded on to a 5 g SCX-2 cartridge, washed with MeOH, and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were combined and concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-(cyclopentylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**14**) (110 mg, 92%) as a yellow solid. LCMS (high-pH method): t_R 0.89 min, $[M + H]^+$ = 357. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (d, J = 5.4 Hz, 1H), 7.66 (s, 1H), 6.69 (d, J = 5.4 Hz, 1H), 6.48 (d, J = 7.1 Hz, 1H), 4.51−4.40 (m, 1H), 3.54−3.43 (m, 2H), 3.42−3.32 (m, 2H), 3.17−3.07 (m, 1H), 2.87−2.77 (m, 1H), 2.74−2.65 (m, 1H), 2.38 (s, 3H), 2.30−2.21 (m, 1H), 2.11−1.97 (m, 1H), 1.73−1.61 (m, 1H), 1.59−1.43 (m, 2H), 1.43−1.30 (m, 4H), 1.13−1.01 (m, 2H). Two NH not seen.

8-(((3*R*,4*R*)-3-(Cycloheptylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (15). Step 1: a solution of cycloheptane carboxylic acid (3 g, 21 mmol) in THF (50 mL) was cooled to 0 °C using an ice bath and was then treated under nitrogen with LAH (1 N in THF, 36 mL, 36 mmol) dropwise over 10 min. The resulting mixture was stirred at this temperature for 1 h and was then stirred at room temperature for 16 h. The reaction mixture was quenched by the dropwise addition of water (1.4 mL) over 10 min, followed by a 15% w/w NaOH aqueous solution (1.4 mL). After stirring for 20 min, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give cycloheptylmethanol (2.55 g, 94%) as a colorless oil. Step 2: cycloheptylmethyl trifluoromethanesulfonate was prepared from cycloheptylmethanol using the same procedure as that for the synthesis of cyclopentylmethyl trifluoromethanesulfonate from cyclopentylmethanol (preparation of **14**, step 1) (5.2 g, 95%, colorless oil). Step 3: (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cycloheptylmethoxy) piperidine-1-carboxylate was prepared from cycloheptylmethyl trifluoromethanesulfonate and (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) using the same procedure as that for the synthesis of (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cyclopentylmethoxy)-piperidine-1-carboxylate from cyclopentylmethyl trifluoromethanesulfonate (preparation of **14**, step 2) (3.4 g, 78%, colorless oil). Step 4: (3*R*,4*R*)-*tert*-butyl 4-amino-3-(cycloheptylmethoxy)piperidine-1-carboxylate was prepared from (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cycloheptylmethoxy)piperidine-1-carboxylate using the same procedure as that for the synthesis of (3*R*,4*R*)-*tert*-butyl 4-amino-3-(cyclopentylmethoxy)piperidine-1-carboxylate from (3*R*,4*R*)-*tert*-butyl 4-azido-3-(cyclopentylmethoxy)piperidine-1-carboxylate (preparation of **14**, step 3). Purification of the crude amine by flash chromatography on silica gel (25 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-amino-3-(cycloheptylmethoxy) piperidine-1-carboxylate (1.35 g, 97%) as a colorless oil. Step 5: 8-(((3*R*,4*R*)-3-(cycloheptylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one was prepared from (3*R*,4*R*)-*tert*-butyl 4-amino-3-(cycloheptylmethoxy) piperidine-1-carboxylate and 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) using the same procedure as that for the synthesis of 8-(((3*R*,4*R*)-3-(cyclopentylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (preparation of **14**, step 4). Purification of the crude amine by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-(cycloheptyl methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (18 mg, 13%) as a yellow oil. LCMS (high-pH method): t_R 1.01 min, $[M + H]^+$ = 385. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.72 (d, J = 5.4 Hz, 1H), 7.67 (s, 1H), 6.67 (d, J = 5.4 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.19−4.08 (m, 1H), 3.22−3.12 (m, 3H), 2.90−2.81 (m, 1H), 2.49−2.43 (m, 1H), 2.34−2.24 (m, 1H), 2.11 (s, 3H), 1.99−1.90 (m, 1H), 1.57−1.11 (m, 13H), 1.01−0.87 (m, 2H). Two NH not seen.

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8-(((3*S*,4*S*)-3-(Cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (16) and 8-(((3*R*,4*R*)-3-(Cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (17). Step 1: the racemic mixture of the Boc-protected compound **13** (**8**, R_1 = methylcyclohexyl, R_2 = H) was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralpak IC (4.6 mm i.d. × 25 cm), using 20% EtOH in heptane at a flow rate of 1 mL/min. The material (100 mg) was dissolved in a mixture of EtOH/heptane (1:1) (4 mL). The purification was carried out on a Chiralpak IC (2 cm × 25 cm), using 20% EtOH in heptane at a flow rate of 15 mL/min, and 1 mL of solution was injected at a time. The appropriate fractions were combined and concentrated under reduced pressure to give the fastest running enantiomer, (3*S*,4*S*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (28 mg, 0.059 mmol), and the slowest running enantiomer, (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (20 mg, 0.042 mmol). Step 2: (3*S*,4*S*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (28 mg, 0.059 mmol) and (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (20 mg, 0.042 mmol) were each dissolved in CH_2Cl_2 (3 mL) at room temperature and then were treated with TFA (1 mL). The mixtures were stirred at this temperature for 30 min and were then concentrated *in vacuo*. The residue were dissolved in MeOH (3 mL), loaded onto a 5 g SCX-2 cartridge, washed with MeOH (10 mL), and finally eluted with a 2 N NH_3 solution in MeOH (10 mL). The ammoniac fractions were in each case concentrated *in vacuo* to give 8-(((3*S*,4*S*)-3-(cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**16**) (21 mg, 95%) as a pale yellow solid and 8-(((3*R*,4*R*)-3-(cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**17**) (15 mg, 68) as pale yellow solid.

8-(((3*R*,4*R*)-3-(Cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (20). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-piperidine-1-carboxylate (208 mg, 0.442 mmol) in $CHCl_3$ (20 mL) at −10 °C was treated with NBS (79 mg, 0.44 mmol), and the resulting solution was stirred at this temperature for 1 h, treated with a saturated sodium metabisulfate aqueous solution, and stirred for another 10 min. The layers were separated, and the organic phase was dried using a phase separator and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((5-bromo-3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(cyclohexylmethoxy)piperidine-1-carboxylate (232 mg, 96%) as a pale yellow solid, which was used in the next step without further purification. LCMS (high-pH method): t_R 1.56 min, $[M + H]^+$ = 549 (1 Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 8.08 (s, 1H), 8.03 (d, J = 1.0 Hz, 1H), 6.50−6.63 (m, 1H), 4.38−4.53 (m, 1H), 3.97−4.09 (m, 1H), 3.40−3.50 (m, 2H), 3.29 (d, J = 6.6 Hz, 2H), 3.02−3.18 (m, 2H), 2.36 (s, 3H), 2.15−2.26 (m, 2H), 1.48−1.64 (m, 15H), 1.07 (d, J = 12.6 Hz, 3H), 0.76 (br s, 2H). Step 2: a microwave vial was charged with (3*R*,4*R*)-*tert*-butyl 4-((5-bromo-3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(cyclohexylmethoxy)piperidine-1-carboxylate (100 mg, 0.182 mmol), $Pd(OAc)_2$ (4.09 mg, 0.018 mmol), cataCXium A (6.53 mg, 0.018 mmol), 5-methylpyridine-5-boronic acid (49.8 mg, 0.364 mmol), and K_2CO_3 (75 mg, 0.55 mmol) and then filled with 1,4-dioxane (3 mL) and water (0.5 mL). The resulting mixture was stirred at 100 °C for 30 min under nitrogen and microwave irradiation and was then cooled to room temperature. The mixture was diluted with CH_2Cl_2 (10 mL), and the organic phase was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave a residue that was further purified by flash chromatography on silica gel (10 g column, gradient: 0 to 10% (2 N NH_3 in MeOH)) to give (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-5-(5-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (**19**, R_1 = H, X = CH_2, Y = C, R_2 = Me) (65 mg, 64%) as a yellow gum. LCMS (method formic): t_R 1.11 min, $[M + H]^+$ = 562. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 8.52 (d, J = 1.5 Hz, 1H), 8.47 (d, J = 1.7 Hz, 1H), 7.91 (s, 1H), 7.71 (d, J = 1.0 Hz, 1H), 7.53 (s, 1H), 6.66−6.77 (m, 1H), 4.50−4.65 (m, 1H), 4.22−4.46 (m, 1H), 3.98−4.08 (m, 1H), 3.41−3.54 (m, 2H), 3.23−3.34 (m, 1H), 2.75−3.19 (m, 2H), 2.47 (s, 2H), 2.28 (d, J = 0.7 Hz, 2H), 2.20−2.26 (m, 1H), 1.99−2.05 (m, 3H), 1.77 (br s, 3H), 1.61−1.73 (m, 3H), 1.39−1.60 (m, 14H). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-5-(5-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (65 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL), and the resulting mixture was stirred for 1 h at this temperature and then concentrated *in vacuo*. The residue was dissolved in MeOH (10 mL) and loaded onto a 5 g SCX-2 cartridge, which was washed with MeOH (10 mL) and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were combined and concentrated *in vacuo*. Purification of this residue by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-(cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (**20**) (14 mg, 26%) as a yellow solid. LCMS (high-pH method): t_R 0.98 min, $[M + H]^+$ = 462. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.5 (br s, 1H), 8.52 (d, J = 1.5 Hz, 1H), 8.48 (d, J = 1.7 Hz, 1H), 7.91 (s, 1H), 7.71 (d, J = 1.0 Hz, 1H), 7.53 (s, 1H), 6.65−6.74 (m, 1H), 4.46−4.56 (m, 1H), 3.36−3.50 (m, 3H), 3.31 (dd, J = 9.3, 6.6 Hz, 1H), 3.14 (br s, 1H), 2.85 (br s, 1H), 2.71 (dd, J = 12.2, 8.6 Hz, 1H), 2.47 (s, 3H), 2.34 (d, J = 0.7 Hz, 3H), 2.23−2.31 (m, 1H), 1.71 (d, J = 9.8 Hz, 1H), 1.43−1.64 (m, 6H), 0.94−1.19 (m, 3H), 0.68−0.85 (m, 2H). One NH not seen.

8-(((3*S*,4*S*)-3-(Cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (21). This compound was obtained in an analogous manner as that for compound **20**, starting from (3*S*,4*S*)-*tert*-butyl 3-(cyclohexylmethoxy)-4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-piperidine-1-carboxylate.

5-(5-Aminopyridin-3-yl)-8-(((3*R*,4*R*)-3-(cyclohexylmethoxy)-piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (22). A 20 mL microwave vial was charged with (5-aminopyridin-2-yl)boronic acid (40.2 mg, 0.291 mmol), (3*R*,4*R*)-*tert*-butyl 4-((5-bromo-3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(cyclohexylmethoxy)piperidine-1-carboxylate (**18**, R_1 = H, X = CH_2) (80 mg, 0.15 mmol), K_2CO_3 (80 mg, 0.582 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)-phosphine (cataCXium A) (5.22 mg, 0.015 mmol) and was then filled with 1,4-dioxane (4 mL) and water (2 mL). The resulting mixture was degassed for 20 min with nitrogen and was then stirred at 110 °C for 30 min under microwave irradiation before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic phase was dried using an hydrophobic frit and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-((5-(5-aminopyridin-3-yl)-3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(cyclohexylmethoxy)piperidine-1-carboxylate (57 mg, 70%) as a yellow solid. This compound was dissolved in CH_2Cl_2 (3 mL), and the resulting solution was treated with TFA (1 mL). The mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL) and loaded onto a 5 g SCX-2 cartridge. This cartridge was washed with MeOH (10 mL) and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 5-(5-aminopyridin-3-yl)-8-(((3*R*,4*R*)-3-(cyclohexylmethoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**21**) (33 mg, 71%) as a yellow solid. LCMS (method TFA): t_R 0.57 min, $[M + H]^+$ = 463.4. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.02 (d, J = 2.7 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.68−7.74 (m, 2H), 7.12 (br s, 1H), 4.27−4.37 (m, 1H), 3.43−3.50 (m, 1H), 3.35−3.42 (m, 2H), 3.22−3.29 (m, 1H), 3.03−3.12 (m, 1H), 2.71−2.81 (m, 1H), 2.50−2.63 (m, 1H), 2.21 (d, J = 1.0 Hz, 4H), 1.54 (br s, 6H), 1.34−1.42 (m, 1H), 0.95−1.19 (m, 4H), 0.68−0.85 (m, 2H). Four NH not seen.

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8-(((3*R*,4*R*)-3-((1-Acetylpiperidin-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (25). Step 1: a solution of piperidin-4-ylmethanol (5.00 g, 43.4 mmol) and triethylamine (9.00 mL, 64.6 mmol) in CH_2Cl_2 (100 mL) was cooled in an ice bath and was then treated with acetic anhydride (4.10 mL, 43.4 mmol), and the resulting mixture was allowed to warm to room temperature and stirred under nitrogen for 16 h. The solution was then washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give 1-(4-(hydroxymethyl)piperidin-1-yl)ethanone (4.56 g, 67%) as a pale yellow gum. Step 2: a solution of 1-(4-(hydroxymethyl)piperidin-1-yl)ethanone (2.00 g, 12.7 mmol) and pyridine (1.24 mL, 15.3 mmol) in CH_2Cl_2 (40 mL) under nitrogen was cooled in an ice bath and then treated with trifluoromethanesulfonic anhydride (2.36 mL, 14.0 mmol) dropwise over 10 min. The resulting mixture was stirred at this temperature for 30 min and then washed with water (50 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to give (1-acetylpiperidin-4-yl)methyl trifluoromethanesulfonate (1.79 g, 49%) as a brown gum, which was used in the next step without further purification. Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (1.5 g, 6.2 mmol) in DMF (5 mL) was cooled in an ice bath and then treated with NaH (60% w/w in mineral oil, 0.19 g, 8.05 mmol), and the resulting mixture stirred at this temperature for 20 min before (1-acetylpiperidin-4-yl)methyl trifluoromethanesulfonate (1.79 g, 6.19 mmol) was added as a solution in DMF (5 mL). The solution was stirred at 0 °C for 2 h and was then allowed to warm to room temperature and diluted with water (15 mL). The aqueous phase was extracted with EtOAc (20 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 100% EtOAc in cyclohexane followed by 5 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 3-((1-acetylpiperidin-4-yl)methoxy)-4-azidopiperidine-1-carboxylate (0.43 g, 18% yield) as a yellow gum. This azide was dissolved in MeOH (20 mL) and hydrogenated in the H-Cube on full hydrogen mode, using a 10% Pd/C cartridge, at 1 mL/min flow rate; then, the eluent was concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl3-((1-acetylpiperidin-4-yl)methoxy)-4-aminopiperidine-1-carboxylate (0.34 g, 15%). Step 4: (3*R*,4*R*)-*tert*-butyl 3-((1-acetylpiperidin-4-yl)methoxy)-4-aminopiperidine-1-carboxylate (225 mg, 0.632 mmol), sodium *tert*-butoxide (152 mg, 1.580 mmol), and BrettPhos precatalyst (21 mg, 0.026 mmol) were added to a solution of 2-(benzyloxy)-8-chloro-3-methyl-1,7-naphthyridine (**7b**) (150 mg, 0.527 mmol) in THF (3 mL) at 0 °C under nitrogen. After stirring at room temperature for 3 h, the mixture was concentrated *in vacuo*, and the residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The layers were separated, and the organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 3-((1-acetylpiperidin-4-yl)methoxy)-4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)-amino)piperidine-1-carboxylate (182 mg, 57%) as a yellow solid. LCMS (high-pH method): t_R 1.38 min, $[M + H]^+$ = 604.4. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.86 (s, 1H), 7.82 (d, J = 5.5 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H),7.26−7.43 (m, 3H), 6.80 (d, J = 5.5 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 5.62 (d, J = 2.8 Hz, 2H), 4.20−4.33 (m, 1H), 3.78−3.96 (m, 3H), 3.67−3.76 (m, 1H), 3.42−3.54 (m, 2H), 3.33 (dd, J = 9.3, 6.3 Hz, 1H), 3.14−3.26 (m, 2H), 3.08 (dd, J = 13.3, 8.1 Hz, 1H), 2.82 (br s, 2H), 2.65 (br s, 1H), 2.51 (d, J = 1.5 Hz, 1H), 2.37 (s, 3H), 2.13 (d, J = 4.0 Hz, 1H), 1.58−1.71 (m, 2H), 1.41−1.56 (m, 11H), 0.89−1.04 (m, 2H). Step 5: a solution of (3*R*,4*R*)-*tert*-butyl 3-((1-acetylpiperidin-4-yl)methoxy)-4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (180 mg, 0.298 mmol) in TFA (2 mL) was heated at 50 °C for 2 h and then cooled to room temperature and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-((1-acetylpiperidin-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (85 mg, 69%) as a yellow solid. LCMS (high-pH method): t_R 0.63 min, $[M + H]^+$ = 414. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.74 (d, J = 5.3 Hz, 1H), 7.60 (s, 1H), 6.67 (d, J = 5.3 Hz, 1H), 6.39 (d, J = 6.5 Hz, 1H), 4.23 (br s, 1H), 3.88 (br s, 2H), 3.46−3.40 (m, 1H), 3.37−3.18 (m, 3H), 2.98−2.89 (m, 1H), 2.82 (br s, 1H), 2.70 (br s, 2H), 2.62−2.53 (m, 1H), 2.47−2.39 (m, 1H), 2.16 (s, 3H), 2.05−1.97 (m, 1H), 1.90 (s, 3H), 1.71−1.59 (m, 1H), 1.58−1.47 (m, 2H), 1.48−1.38 (m, 1H), 1.05−0.92 (m, 2H). One NH not seen.

8-(((3*R*,4*R*)-3-(((*trans*)-4-Hydroxycyclohexyl)methoxy)-piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (26). Step 1: A solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (1 g, 4.1 mmol) in CH_2Cl_2 (30 mL) at room temperature was treated with imidazole (0.309 g, 4.54 mmol) and TBDMSCl (0.684 g, 4.54 mmol), and the resulting mixture was stirred at this temperature for 24 h. The organic phase was then washed with water (30 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (1.05 g, 71%) as a colorless oil. Step 2: (3*R*,4*R*)-*tert*-butyl 4-azido-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (0.43 g, 1.2 mmol) was dissolved in EtOH (40 mL) and hydrogenated in the H-Cube (flow rate 1 mL/min, Pd/C cartridge, full H_2 mode). The solvent was then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-amino-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (**23**) (0.38 g, 95%) as a colorless oil. Step 3: A flask was charged with (3*R*,4*R*)-*tert*-butyl 4-amino-3-((*tert*-butyldimethylsilyl)oxy) piperidine-1-carboxylate (**23**) (6.04 g, 18.3 mmol), 2-(benzyloxy)-8-chloro-3-methyl-1,7-naphthyridine (**7b**) (4.0 g, 14 mmol), sodium *tert*-butoxide (4.05 g, 42.1 mmol), Brettphos (0.649 g, 1.21 mmol), and Brettphos palladacycle (0.4 g, 0.5 mmol) and then filled with THF (10 mL). The resulting mixture was stirred under nitrogen at room temperature for 2 h. $Pd_2(dba)_3$ (0.643 g, 0.702 mmol) and Brettphos (0.649 g, 1.21 mmol) were further added, and the mixture was stirred at 50 °C for 2 h, cooled to room temperature, and diluted with a saturated NH_4Cl aqueous solution (20 mL). The aqueous phase was extracted with EtOAc (40 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-piperidine-1-carboxylate (8.05 g, 99%) as a yellow foam. LCMS (high-pH method): t_R 1.79 min, $[M + H]^+$ = 579.4. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (d, J = 5.9 Hz, 1H), 7.67 (d, J = 1.0 Hz, 1H), 7.50 (d, J = 7.1 Hz, 2H), 7.39−7.46 (m, 2H), 7.35 (s, 1H), 6.73 (d, J = 5.9 Hz, 1H), 6.16−6.26 (m, 1H), 5.51 (d, J = 16.9 Hz, 2H), 4.23−4.36 (m, 1H), 3.86−4.20 (m, 2H), 3.60−3.72 (m, 1H), 3.11−3.22 (m, 1H), 2.92−3.09 (m, 1H), 2.41 (d, J = 1.0 Hz, 3H), 2.21−2.31 (m, 1H), 1.45 (s, 9H), 0.77 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). One NH not seen. Step 4: A solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-piperidine-1-carboxylate (8.0 g, 14 mmol) in THF (50 mL) at room temperature was treated with TBAF (1N in THF, 20 mL, 20 mmol), and the resulting mixture was stirred at this temperature for 3 h and then concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (100 mL), and the layers were separated. The organic phase was washed with water (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (100 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate. The racemic mixture was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralcel OD-H (4.6 mm i.d. × 25 cm), using 25% EtOH in heptane at a flow rate of 1 mL/min. The material (5.3 g) was dissolved in a mixture of EtOH/heptane (1:1) (250 mg in 1 mL). The purification was carried out on a Chiralcel OD (5 cm × 25 cm), using 25% EtOH in heptane at a flow rate of 50 mL/min, and 2 mL of solution was injected at a time. The appropriate fractions were combined and concentrated *in vacuo*. The residues were dissolved with CH_2Cl_2 and concentrated under reduced

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pressure to give the fastest running enantiomer, (3*S*,4*S*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (2.4 g), and the slowest running enantiomer, (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)-amino)-3-hydroxypiperidine-1-carboxylate (**24**) (2.2 g). LCMS (high-pH method): t_R 1.40 min, $[M + H]^+$ = 465.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (d, J = 5.9 Hz, 1H), 7.69 (d, J = 1.0 Hz, 1H), 7.50 (d, J = 7.1 Hz, 2H), 7.32−7.44 (m, 3H), 6.81 (d, J = 5.9 Hz, 1H), 6.30 (d, J = 4.2 Hz, 1H), 5.42−5.61 (m, 2H), 4.18−4.49 (m, 2H), 3.74−3.87 (m, 1H), 3.50−3.61 (m, 1H), 2.63−2.90 (m, 2H), 2.42 (d, J = 0.7 Hz, 3H), 1.99−2.06 (m, 1H), 1.72−1.86 (m, 1H), 1.51 (s, 9H). One H not seen. Step 5: 1,4-dioxaspiro[4.5]decan-8-ylmethyl trifluoromethanesulfonate was prepared from 1,4-dioxaspiro[4.5]decan-8-ylmethanol using the same procedure as that for the synthesis of (1-acetylpiperidin-4-yl)methyl trifluoromethanesulfonate from 1-(4-(hydroxymethyl)piperidin-1-yl)ethanone (see synthesis of **25**, steps 1 and 2) (1.78 g, 100%, pale yellow oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.38 (d, J = 6.6 Hz, 2H), 3.86−4.05 (m, 4H), 1.76−1.95 (m, 5H), 1.59 (td, J = 13.4, 4.3 Hz, 2H), 1.32−1.48 (m, 2H). Step 6: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (100 mg, 0.215 mmol; see compounds **31** and **32**, steps 1−4) at 0 °C under nitrogen in THF (3 mL) was treated with sodium hydride (60% w/w in mineral oil, 21.5 mg, 0.538 mmol), and the resulting mixture was stirred for 20 min at this temperature before being treated with 1,4-dioxaspiro[4.5]-decan-8-ylmethyl trifluoromethanesulfonate (131 mg, 0.431 mmol) as a solution in THF (2 mL). After stirring at 0 °C for 2 h, the mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 3-(1,4-dioxaspiro[4.5]-decan-8-ylmethoxy)-4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (87 mg, 65%) as a colorless gum. LCMS (high-pH method): t_R 1.56 min, $[M + H]^+$ = 619.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 0.7 Hz, 1H), 7.51 (d, J = 7.1 Hz, 2H), 7.38−7.44 (m, 2H), 7.35 (d, J = 7.3 Hz, 1H), 6.75 (d, J = 5.9 Hz, 1H), 6.33−6.38 (m, 1H), 5.50 (d, J = 4.4 Hz, 2H), 4.18−4.31 (m, 1H), 3.79−3.92 (m, 5H), 3.43−3.55 (m, 2H), 3.31−3.38 (m, 2H), 3.19−3.28 (m, 2H), 2.40 (d, J = 0.7 Hz, 3H), 1.55−1.85 (m, 6H), 1.45 (s, 9H), 1.26−1.42 (m, 1H), 1.22−1.34 (m, 2H), 1.04−1.21 (m, 2H). Step 7: a solution of (3*R*,4*R*)-*tert*-butyl 3-(1,4-dioxaspiro[4.5]decan-8-ylmethoxy)-4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate (40 mg, 0.065 mmol) in CH_2Cl_2 (5 mL) at room temperature was treated with TFA (0.5 mL), and the resulting mixture was stirred at this temperature for 1 h and then concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL), cooled to 0 °C using an ice bath, and treated with $NaBH_4$ (12.2 mg, 0.323 mmol). After stirring for 2 h at this temperature, the mixture was diluted with water (10 mL), and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in MeOH (30 mL) and hydrogenated in the H-cube on full hydrogen mode over a 10% Pd/C cartridge at 1 mL/min flow rate. The eluent was concentrated *in vacuo*, and the residue was purified by MDAP (high-pH method) to give 8-(((3*R*,4*R*)-3-(((1*R*,4*R*)-4-hydroxycyclohexyl) methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**26**) (4 mg, 16%). LCMS (high-pH method): t_R 0.63 min, $[M + H]^+$ = 387. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 13.2 (br s, 1H), 7.73 (d, J = 5.1 Hz, 1H), 7.67 (s, 1H), 6.68 (d, J = 5.1 Hz, 1H), 6.59 (d, J = 7.7 Hz, 1H), 4.35 (d, J = 4.4 Hz, 1H), 4.17−4.08 (m, 1H), 3.34−3.28 (m, 1H) 3.22−3.13 (m, 4H), 2.89−2.83 (m, 1H), 2.49−2.44 (m, 1H), 2.32−2.26 (m, 1H), 2.12 (s, 3H), 1.99−1.93 (m, 1H), 1.68−1.62 (m, 2H), 1.55−1.45 (m, 2H), 1.34−1.19 (m, 2H), 1.00−0.91 (m, 2H), 0.78−0.69 (m, 2H). One NH not seen.

3-Methyl-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)-methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (27). Step 1: a solution of (tetrahydro-2*H*-pyran-4-yl)methanol (7.0 g, 60 mmol) in CH_2Cl_2 (50 mL) at 0 °C under nitrogen was treated with pyridine (5.36 mL, 66.3 mmol) and, after 5 min, with the dropwise addition of Tf_2O (11.2 mL, 66.3 mmol) over 10 min. The resulting mixture was stirred at this temperature for 1 h and was then warmed to room temperature. The organic phase was washed with water (2 × 50 mL) and then brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give (tetrahydro-2*H*-pyran-4-yl)methyl trifluoromethanesulfonate (14.2 g, 95%) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.38 (d, J = 6.6 Hz, 2H), 3.99−4.09 (m, 2H), 3.43 (td, J = 11.9, 2.0 Hz, 2H), 2.06−2.18 (m, 1H), 1.65−1.75 (m, 2H), 1.36−1.51 (m, 2H). Step 2: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (10 g, 41 mmol) in DMF (50 mL) and THF (50 mL) at 0 °C under nitrogen was treated portionwise with sodium hydride (60% w/w in mineral oil, 2.2 g, 55 mmol). The resulting mixture was stirred at this temperature for 30 min before being treated with the dropwise addition of a solution of (tetrahydro-2*H*-pyran-4-yl)methyl trifluoromethanesulfonate (13.3 g, 53.7 mmol) in THF (50 mL) over 20 min. The resulting mixture was then slowly allowed to warm to room temperature over 2 h and then diluted with water (500 mL). The aqueous phase was extracted with Et_2O (2 × 300 mL), and the combined organics were washed with water (2 × 400 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. Purification of this residue by flash chromatography on silica gel (330 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (12.8 g, 91%) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.09−4.34 (m, 1H), 3.95−4.03 (m, 3H), 3.85−3.94 (m, 1H), 3.48−3.57 (m, 1H), 3.34−3.47 (m, 4H), 3.12−3.22 (m, 1H), 2.85−2.96 (m, 1H), 2.61−2.82 (m, 1H), 1.77−1.99 (m, 2H), 1.61−1.73 (m, 2H), 1.47 (s, 9H), 1.29−1.43 (m, 2H). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (12.8 g, 37.6 mmol) in THF (100 mL) at room temperature was treated with triphenylphosphine (10.8 g, 41.4 mmol), and the resulting mixture was stirred at room temperature for 16 h. Water (30 mL) was then added, and the mixture was refluxed for 24 h before being cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in Et_2O (200 mL), and the solution was diluted with cyclohexane (150 mL). Some solid separated after standing for 1 h at room temperature, and the solvent was partially evaporated, causing further precipitation of triphenylphosphine oxide. The solid was filtered off, and the filtrate was concentrated *in vacuo* to give a pale yellow oil. Purification of this residue by flash chromatography on silica gel (2 × 100 g column, gradient: 0 to 10% (2N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-amino-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (8.7 g, 74%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13−4.47 (m, 1H), 3.92−4.09 (m, 3H), 3.49−3.60 (m, 1H), 3.40 (td, J = 11.7, 2.2 Hz, 2H), 3.31 (dd, J = 9.2, 6.5 Hz, 1H), 2.83−2.93 (m, 1H), 2.76 (br s, 2H), 2.35−2.55 (m, 1H), 1.80−1.88 (m, 2H), 1.61−1.72 (m 2H), 1.52 (s, 2H), 1.47 (s, 9H), 1.23−1.43 (m, 3H). Step 4: a mixture of (3*R*,4*R*)-*tert*-butyl 4-amino-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (2.3 g, 7.3 mmol), 2-(benzyloxy)-8-chloro-3-methyl-1,7-naphthyridine (**7b**) (1.5 g, 5.3 mmol), sodium 2-methylpropan-2-olate (1.52 g, 15.8 mmol), $Pd_2(dba)_3$ (0.241 g, 263 mmol), and BrettPhos (0.283 g, 0.527 mmol) in THF (20 mL) was stirred at room temperature under nitrogen for 1 h and was then stirred at 60 °C for 3 h before being cooled to room temperature and diluted with a saturated NH_4Cl aqueous solution. The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0 to 70% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (2.72 g, 92%) as a pale yellow foam. LCMS (high-pH method): t_R 1.50 min, $[M + H]^+$ = 563. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (d, J = 5.9 Hz, 1H), 7.68 (d, J = 1.0 Hz, 1H), 7.49 (d, J = 7.1 Hz, 2H), 7.38−7.44 (m, 2H), 7.35 (d, J = 7.1 Hz, 1H), 6.75 (d, J = 5.9 Hz, 1H), 6.28−6.36 (m, 1H), 5.51 (s, 2H), 4.25−4.37 (m, 1H), 3.75−3.88 (m 2H), 3.43−3.52 (m,

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1H), 3.32 (d, J = 3.9 Hz, 1H), 3.12−3.27 (m, 3H), 2.89−3.11 (m, 1H), 2.41 (d, J = 0.7 Hz, 3H), 2.28−2.38 (m, 1H), 1.58−1.93 (m, 2H), 1.49−1.54 (m, 11H), 1.23−1.48 (m, 3H), 0.96−1.22 (m, 2H). Step 5: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)-methoxy)piperidine-1-carboxylate (0.18 g, 0.320 mmol) in MeOH (40 mL) was hydrogenated in the H-Cube on full mode using a 10% Pd/C cartridge. The eluant was evaporated *in vacuo* to give a colorless glass. This material was dissolved in CH_2Cl_2 (10 mL), and the resulting solution was treated with TFA (2 mL). The mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 3-methyl-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)-amino)-1,7-naphthyridin-2(1*H*)-one (**27**) (35 mg, 29%) as a yellow solid. LCMS (high-pH method): t_R 0.67 min, $[M + H]^+$ = 373.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.96 (d, J = 5.4 Hz, 1H), 7.66 (s, 1H), 6.68−6.74 (m, 1H), 6.29−6.49 (m, 1H), 4.37−4.51 (m, 1H), 3.73−3.87 (m, 2H), 3.43−3.50 (m, 2H), 3.33−3.42 (m, 2H), 3.18−3.29 (m, 2H), 3.09−3.17 (m, 1H), 2.77−2.87 (m, 1H), 2.65−2.74 (m, 1H), 2.38 (s, 3H), 2.19−2.28 (m, 1H), 1.58 (m, 6H), 1.06−1.26 (m, 2H).

3-Methyl-8-(((3*S*,4*S*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)-piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (28) and 3-Methyl-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)-piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (29). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)-piperidine-1-carboxylate (1.76 g, 3.13 mmol) in MeOH (100 mL) was treated with 10% w/w palladium on charcoal (0.30 g, 0.282 mmol), and the resulting mixture was stirred at room temperature under an atmosphere of hydrogen (1 bar) for 3 h. The catalyst was filtered off using a 2.5 g pad of Celite and rinsed with MeOH. The combined organics were concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((2-hydroxy-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (1.50 g, 100%).

The racemic mixture was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralpak IC (4.6 mm i.d. × 25 cm), using 20% EtOH (+0.2% isopropylamine) in heptane at a flow rate of 1 mL/min. The material (40 mg) was dissolved in a mixture of EtOH/heptane (1:1) (1 mL). The purification was carried out on a Chiralpak IC (30 mm × 25 cm), using 20% EtOH (+0.2% isopropylamine) in heptane at a flow rate of 30 mL/min, and 1 mL of solution was injected. The appropriate fractions were combined and concentrated under reduced pressure to give the fastest running enantiomer, (3*S*,4*S*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (10 mg, 0.021 mmol), and the slowest running enantiomer, (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (10 mg, 0.021 mmol). LCMS (high-pH method): t_R 1.47 min, $[M + H]^+$ = 473. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 7.96 (d, J = 5.4 Hz, 1H), 7.67 (d, J = 1.0 Hz, 1H), 6.71 (d, J = 5.6 Hz, 1H), 6.49−6.59 (m, 1H), 4.49−4.62 (m, 1H), 3.95−4.44 (m, 2H), 3.70−3.88 (m, 2H), 3.44−3.56 (m, 2H), 3.21 (d, J = 11.7 Hz, 4H), 2.32 (d, J = 0.7 Hz, 3H), 2.13−2.25 (m, 1H), 1.60−1.79 (m, 2H), 1.51 (s, 9H), 0.99−1.26 (m, 5H). Step 2: (3*S*,4*S*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (10 mg, 0.021 mmol) and (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (10 mg, 0.021 mmol) were dissolved in CH_2Cl_2 and treated with TFA (0.5 mL) at room temperature. The solutions were stirred at this temperature for 2 h and then concentrated *in vacuo*. The residues were dissolved in MeOH (2 mL) and loaded on to two 5 g SCX-2 cartridges. The cartridges were washed with MeOH and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 3-methyl-8-(((3*S*,4*S*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (**28**) (7 mg, 89%) and 3-methyl-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (**29**) (7 mg, 89%).

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (30). Step 1: a solution of (tetrahydro-2*H*-thiopyran-4-yl)methanol (10 g, 76 mmol) in MeOH (200 mL) at room temperature was treated with a solution of sodium periodate (32.4 g, 151 mmol) in water (300 mL), and the resulting suspension was stirred at 50 °C for 60 h, cooled to room temperature, and concentrated *in vacuo* to leave a white, granular solid. This solid was suspended in EtOAc (200 mL), stirred for 10 min, and then filtered off. The solid obtained was then suspended in 10% MeOH in CH_2Cl_2 (200 mL), stirred for 10 min, and then filtered off. The combined filtrates were concentrated *in vacuo* to give 4-(hydroxymethyl)-tetrahydro-2*H*-thiopyran 1,1-dioxide (11.2 g, 90%) as a colorless, crystalline solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.59 (d, J = 6.4 Hz, 2H), 3.06−3.15 (m, 2H), 2.93−3.05 (m, 2H), 2.16−2.27 (m, 2H), 1.84−1.97 (m, 2H), 1.71−1.81 (m, 2H). Step 2: a solution of 4-(hydroxymethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (3.0 g, 18.3 mmol) in CH_2Cl_2 (20 mL) cooled at −10 °C using an acetone/ice bath under nitrogen was treated with pyridine (1.62 mL, 20.1 mmol) and then with Tf_2O (3.4 mL, 20.1 mmol) dropwise, and the resulting mixture was stirred at this temperature for 1 h and then allowed to warm to room temperature. The solution was then washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl trifluoromethanesulfonate (5.2 g, 96%) as a colorless solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.42 (d, J = 6.1 Hz, 2H), 3.11−3.22 (m, 2H), 2.96−3.10 (m, 2H), 2.19−2.31 (m, 2H), 1.95−2.17 (m, 3H). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (2.28 g, 9.41 mmol) in THF (10 mL) at 0 °C under nitrogen was treated with potassium *tert*-butoxide (1 N in THF, 14.1 mL, 14.1 mmol), and the resulting mixture was stirred at this temperature for 20 min. (1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl trifluoromethanesulfonate (4.18 g, 14.1 mmol) was then added in small portions over 10 min, and the resulting mixture was stirred at 0 °C for 2 h. Water (30 mL) was added, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. Purification of this residue by flash chromatography on silica gel (50 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-azido-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (3.32 g, 91%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.82−4.00 (m, 1H), 3.53−3.65 (m, 1H), 3.39−3.52 (m, 2H), 3.15−3.23 (m, 1H), 3.04−3.14 (m, 3H), 2.87−3.03 (m, 3H), 2.70−2.81 (m, 2H), 2.19 (d, J = 12.2 Hz, 2H), 1.79−2.01 (m, 4H), 1.38−1.51 (m, 9H). Step 4: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (3.3 g, 8.5 mmol) in MeOH (100 mL) was treated with palladium on charcoal (5% w/w, 50% wet, 1 g), and the resulting mixture was stirred under an atmosphere of hydrogen (1 bar) for 2 h. The catalyst was filtered off using a pad of Celite (2.5 g), and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-amino-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (2.34 g, 76%) as a colorless crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13−4.43 (m, 1H), 3.92−4.08 (m, 1H), 3.54−3.65 (m, 1H), 3.39 (dd, J = 9.2, 6.0 Hz, 1H), 3.05−3.14 (m, 2H), 2.87−3.04 (m, 3H), 2.71−2.85 (m, 2H), 2.41−2.55 (m, 1H), 2.11−2.23 (m, 2H), 1.91−2.02 (m, 2H), 1.78−1.88 (m, 2H), 1.42−1.61 (m, 11H), 1.25−1.41 (m, 1H). Step 5: a mixture of (3*R*,4*R*)-*tert*-butyl 4-amino-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (1.7 g, 4.7 mmol), 2-(benzyloxy)-8-chloro-3-methyl-1,7-naphthyridine (**7b**) (1.10 g, 3.86 mmol), sodium 2-methylpropan-2-olate (1.11 g, 11.6 mmol), BrettPhos (0.207 g, 0.386 mmol), and $Pd_2(dba)_3$ (0.177 g, 0.193 mmol) in THF (20 mL) was stirred under nitrogen at room temperature for 1 h and was then stirred at 60 °C for

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3 h before being cooled to room temperature and diluted with a saturated NH_4Cl aqueous solution. The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0 to 70% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (2.31 g, 98%) as a pale yellow foam. LCMS (high-pH method): t_R 1.38 min, $[M + H]^+$ = 611. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.90 (d, J = 5.6 Hz, 1H), 7.69 (s, 1H), 7.47−7.52 (m, 2H), 7.41 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 7.3 Hz, 1H), 6.75 (d, J = 5.6 Hz, 1H), 6.22 (d, J = 8.6 Hz, 1H), 5.46−5.58 (m, 2H), 4.30−4.41 (m, 1H), 3.89−4.11 (m, 1H), 3.76−3.87 (m, 1H), 3.46−3.57 (m, 1H), 3.31 (d, J = 3.7 Hz, 4H), 2.67 (br s, 4H), 2.42 (s, 3H), 2.17−2.28 (m, 1H), 1.86−1.99 (m, 1H), 1.74−1.83 (m, 1H), 1.39−1.72 (m, 13H). Step 6: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidine-1-carboxylate (26 mg, 0.043 mmol) in TFA (2 mL) was stirred at 50 °C for 2 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in MeOH and loaded on to a 5 g SCX-2 cartridge. The cartridge was washed with MeOH and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo*. Purification of the residue obtained by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**30**) (7.5 mg, 42%) as a beige solid. LCMS (high-pH method): t_R 0.62 min, $[M + H]^+$ = 421.1. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 7.95 (d, J = 5.4 Hz, 1H), 7.67 (d, J = 1.0 Hz, 1H), 6.62−6.77 (m, 2H), 4.45−4.60 (m, 1H), 3.54−3.63 (m, 2H), 3.44 (dd, J = 8.9, 6.0 Hz, 2H), 3.24 (d, J = 12.7 Hz, 1H), 2.71−2.98 (m, 6H), 2.33−2.38 (m, 3H), 2.22−2.31 (m, 1H), 1.93−2.10 (m, 2H), 1.60−1.84 (m, 4H). One NH not seen.

8-(((3*S*,4*S*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (31) and 8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (32). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (75 mg, 0.16 mmol) (see steps 1−4 of compound **26**) and a solution of (3*S*,4*S*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (75 mg, 0.16 mmol) in DMF (5 mL) at 0 °C under nitrogen were treated with sodium hydride (60% w/w in mineral oil, 21.5 mg, 0.538 mmol), and the resulting mixtures were stirred at this temperature for 10 min; then, (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl trifluoromethanesulfonate (96 mg, 0.323 mmol) was added as a solution in DMF (1 mL) to each reaction. The mixtures were allowed to warm to room temperature over 2 and were then diluted with water (10 mL) and extracted with EtOAc (10 mLl). In each case, the organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of each residue by flash chromatography on silica gel (10 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*S*,4*S*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (40 mg, 41%) as a colorless glass and (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (37 mg, 37%) as a colorless glass. Step 2: (3*S*,4*S*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidine-1-carboxylate (40 mg, 0.065 mmol) and (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (35 mg, 0.057 mmol) were each dissolved in TFA (3 mL), and the solutions were stirred at 60 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. The residues were dissolved in MeOH (2 mL) and loaded on to two 5 g SCX-2 cartridges. The cartridges were washed with MeOH and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 8-(((3*S*,4*S*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**31**) (26 mg, 94%) and 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**32**) (12.4 mg, 45%) as beige solids.

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydrothiophen-3-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (33). Step 1: (1,1-dioxidotetrahydrothiophen-3-yl)methyl trifluoromethanesulfonate was prepared from 3-(hydroxymethyl)-tetrahydrothiophene 1,1-dioxide using the same procedure as that for the synthesis of (1-acetylpiperidin-4-yl)methyl trifluoromethanesulfonate from 1-(4-(hydroxymethyl)piperidin-1-yl)ethanone (1.72 g, 92%, pale yellow crystalline solid). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 4.52−4.65 (m, 2H), 3.22−3.38 (m, 2H), 3.07−3.20 (m, 1H), 2.94−3.05 (m, 1H), 2.86−2.94 (m, 1H), 2.41−2.52 (m, 1H), 2.07 (dq, J = 13.6, 9.4 Hz, 1H). Step 2: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (**24**) (450 mg, 0.969 mmol) in THF (5 mL) under nitrogen was cooled to 0 °C using an ice bath and was then treated with potassium *tert*-butoxide (239 mg, 2.13 mmol). After stirring for 10 min, (1,1-dioxidotetrahydrothiophen-3-yl)methyl trifluoromethanesulfonate (547 mg, 1.94 mmol) was added, and the resulting mixture was stirred for 2 h at this temperature. After standing over 2 days at room temperature under a nitrogen atmosphere, the reaction mixture was concentrated *in vacuo*. Purification of the residue obtained by flash chromatography on silica gel (25 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydrothiophen-3-yl)methoxy)piperidine-1-carboxylate (55 mg, 10% yield) as a pale yellow gum. LCMS (high-pH method): t_R 1.38 min, $[M + H]^+$ = 597.4. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (d, J = 5.6 Hz, 1H), 7.69 (s, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.34 (d, J = 7.3 Hz, 1H), 6.98 (dd, J = 17.1, 10.8 Hz, 1H), 6.77 (d, J = 5.9 Hz, 1H), 5.45−5.54 (m, 2H), 4.32−4.44 (m, 1H), 4.09−4.20 (m, 1H), 3.95−4.05 (m, 1H), 3.59−3.94 (m, 2H), 3.27−3.51 (m, 2H), 3.14−3.26 (m, 2H), 2.99−3.12 (m, 1H), 2.75−2.97 (m, 2H), 2.25−2.43 (m, 4H), 2.14−2.24 (m, 1H), 1.93−2.12 (m, 1H), 1.68−1.84 (m, 1H), 1.51 (s, 9H), 1.23−1.37 (m, 1H). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydrothiophen-3-yl)methoxy)piperidine-1-carboxylate (55 mg, 0.092 mmol) in TFA (1 mL) was refluxed for 2 h, cooled to room temperature, and concentrated *in vacuo*. The residue was loaded on to a 5 g SCX cartridge, washed with MeOH, and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were combined and concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydrothiophen-3-yl)methoxy)piperidin-4-yl)amino)-3-methyl-1,7-naphthyridin-2(1*H*)-one (**33**) (17 mg, 45%) as a beige glass. LCMS (high-pH method): t_R 0.61 min, $[M + H]^+$ = 407. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, J = 5.4 Hz, 1H), 7.67 (s, 1H), 6.72 (d, J = 5.4 Hz, 1H), 6.60 (d, J = 7.3 Hz, 1H), 4.55−4.43 (m, 1H), 3.79−3.67 (m, 1H), 3.67−3.59 (m, 1H), 3.58−3.52 (m, 1H), 3.44−3.32 (m, 1H), 3.21−3.11 (m, 1H), 3.06−2.91 (m, 2H), 2.91−2.66 (m, 4H), 2.66−2.56 (m, 1H), 2.36 (s, 3H), 2.28−2.20 (m, 1H), 2.17−2.06 (m, 1H), 1.94−1.77 (m, 1H), 1.70 (d, J = 10.0 Hz, 1H). Two NH not seen.

3-Methyl-8-(((3*R*,4*R*)-3-(2-(tetrahydro-2*H*-pyran-4-yl)-ethoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (34). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-hydroxypiperidine-1-carboxylate (**5**) (0.64 g, 2.64 mmol) in DMF (10 mL) under nitrogen was cooled at 0 °C using an ice bath and then treated with sodium hydride (60% w/w in mineral oil, 0.14 g, 3.50 mmol). The resulting mixture was stirred at this temperature for 20 min; then, 4-(2-bromoethyl)tetrahydropyran (0.61 g, 3.17 mmol) was added. After stirring at 0 °C for 2 h, the reaction mixture was allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was then treated with water (30 mL), and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organics were washed with water (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of this residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave

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(3*R*,4*R*)-*tert*-butyl 4-azido-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)-piperidine-1-carboxylate (0.55 g, 59% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.04−4.41 (m, 1H), 3.96 (s, 3H), 3.67−3.80 (m, 1H), 3.53−3.64 (m, 1H), 3.34−3.46 (m, 3H), 3.12−3.22 (m, 1H), 2.81−2.92 (m, 1H), 2.70 (br s, 1H), 1.87−1.99 (m, 1H), 1.52−1.78 (m, 5H), 1.40−1.51 (m, 10H), 1.25−1.39 (m, 2H). Step 2: a solution of (3*R*,4*R*)-*tert*-butyl 4-azido-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)piperidine-1-carboxylate (0.52 g, 1.467 mmol) in MeOH (80 mL) was hydrogenated in the H-cube on full hydrogen mode over a 10% Pd/C cartridge at 1 mL/min flow rate. The eluant was concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-amino-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)piperidine-1-carboxylate (0.48 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.13−4.55 (m, 1H), 4.00−4.09 (m, 1H), 3.96 (dd, J = 11.2, 3.9 Hz, 2H), 3.68−3.78 (m, 1H), 3.47−3.54 (m, 1H), 3.39 (t, J = 11.6 Hz, 2H), 2.84−2.93 (m, 1H), 2.68−2.80 (m, 2H), 2.35−2.56 (m, 1H), 1.79−1.87 (m, 1H), 1.52−1.74 (m, 6H), 1.45−1.50 (m, 10H), 1.25−1.40 (m, 3H). Step 3: a suspension of 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) (40 mg, 0.21 mmol), (3*R*,4*R*)-*tert*-butyl 4-amino-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)piperidine-1-carboxylate (101 mg, 0.308 mmol) and Caddick catalyst (12 mg, 0.021 mmol) in THF (250 mL) at room temperature under nitrogen was treated with LiHMDS (1 M in THF, 0.62 mL, 0.62 mmol) and was then stirred at 60 °C for 3 h before being cooled to 0 °C and quenched with a saturated NH_4Cl aqueous solution. The mixture was diluted with EtOAc (30 mL), and the insoluble material was filtered off and then washed with EtOAc (2 × 50 mL) to give (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)piperidine-1-carboxylate (52 mg, 52%) as a pale yellow solid. LCMS (high-pH method): t_R 1.07 min, $[M + H]^+$ = 487.4. Step 4: a solution of (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)piperidine-1-carboxylate (52 mg, 0.107 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL). The resulting mixture was stirred at room temperature for 1 h and was then concentrated *in vacuo*. The residue was loaded on to a 5 g SCX cartridge, washed with MeOH (20 mL), and eluted with a 2 N NH_3 solution in MeOH (20 mL). The ammoniac fractions were concentrated *in vacuo* to give 3-methyl-8-(((3*R*,4*R*)-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (**34**) (35 mg, 85% yield) as a brown solid. LCMS (high-pH method): t_R 0.68 min, $[M + H]^+$ = 387. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.98−1.18 (m, 2H), 1.27−1.75 (m, 7H), 2.14−2.25 (m, 1H), 2.36 (s, 3H), 2.63−2.73 (m, 1H), 2.80 (br t, J = 10.3 Hz, 1H), 2.94 (br t, J = 12.0 Hz, 1H), 3.04−3.13 (m, 1H), 3.09−3.18 (m, 1H), 3.37−3.47 (m, 2H), 3.51−3.60 (m, 1H), 3.63−3.71 (m, 2H), 3.75 (br dd, J = 11.4, 3.7 Hz, 1H), 4.37−4.52 (m, 1H), 6.41 (br s, 1H), 6.69 (d, J = 5.5 Hz, 1H), 7.65 (q, J = 1.5 Hz, 1H), 7.94 (d, J = 5.4 Hz, 1H), 13.09 (br s, 1H).

3-Methyl-5-(pyridin-3-yl)-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (35). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (2.7 g, 4.8 mmol) in CH_2Cl_2 at 0 °C was treated with NBS (0.683 g, 3.84 mmol), and the resulting mixture was stirred at this temperature for 30 min. Further NBS (50 mg, 0.28 mmol) was added, and the mixture was stirred for another 10 min, warmed to room temperature, and washed with a saturated sodium metabisulphite aqueous solution. The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (2.92 g, 95%) as a beige foam, which was used in the next step without further purification. LCMS (high-pH method): t_R 1.68 min, $[M + H]^+$ = 641/643 (1 Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (s, 1H), 7.99 (d, J = 1.2 Hz, 1H), 7.46−7.50 (m, 2H), 7.38−7.44 (m, 2H), 7.36 (d, J = 7.1 Hz, 1H), 6.29 (d, J = 7.8 Hz, 1H), 5.52 (s, 2H), 4.17−4.30 (m, 1H), 3.82 (d, J = 7.6 Hz, 3H), 3.43−3.52 (m, 1H), 3.30 (d, J = 3.9 Hz, 1H), 3.14−3.25 (m, 3H), 2.46 (d, J = 1.0 Hz, 2H), 2.26−2.36 (m, 1H),1.60−1.72 (m, 2H), 1.52 (s, 11H), 1.50 (br s, 4H), 0.96−1.25 (m, 2H). Step 2: a 20 mL microwave vial was charged with K_2CO_3 (172 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 0.031 mmol), 3-pyridineboronic acid pinacol ester (128 mg, 0.623 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)-amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (200 mg, 0.312 mmol), and di((3S,5S,7S)-adamantan-1-yl)-(butyl)phosphine (cataCXium A) (11.18 mg, 0.031 mmol) and was then filled with 1,4-dioxane (8 mL) and water (4 mL). The reaction mixture was degassed for 20 min with nitrogen and then stirred under microwave irradiation at 100 °C for 1 h before being cooled to room temperature. The solvent was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The layers were separated, and the organic phase was dried using a hydrophobic frit and then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 8% MeOH in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(pyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (133 mg, 60%). LCMS (high-pH method): t_R 1.45 min, $[M + H]^+$ = 640. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.59−8.66 (m, 2H), 7.84−7.88 (m, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.80 (s, 1H), 7.50−7.58 (m, 3H), 7.37−7.43 (m, 2H), 7.33 (s, 1H), 6.93−6.98 (m, 1H), 5.59−5.73 (m, 2H), 4.26−4.36 (m, 1H), 3.76−3.87 (m, 1H), 3.58−3.66 (m, 2H), 3.45−3.54 (m, 1H), 3.38−3.44 (m, 1H), 3.19−3.26 (m, 1H), 3.06 (br s, 3H), 2.31 (d, J = 0.7 Hz, 3H), 2.10−2.23 (m, 1H), 2.01−2.09 (m, 1H), 1.88−1.98 (m, 1H), 1.53−1.77 (m, 2H), 1.44 (s, 9H), 1.26−1.36 (m, 2H), 0.83−1.04 (m, 2H). Step 3: a flask was charged with (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(pyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (102 mg, 0.159 mmol) and then filled with TFA (2 mL), and the resulting mixture was stirred at 80 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 3-methyl-5-(pyridin-3-yl)-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (34 mg, 47%) as a colorless foam. LCMS (high-pH method): t_R 0.66 min, $[M + H]^+$ = 450. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.50 (br s, 1H), 8.62 (dd, J = 4.8, 1.6 Hz, 1H), 8.59 (d, J = 1.7 Hz, 1H), 7.80 (s, 1H), 7.72 (s, 1H), 7.50−7.55 (m, 2H), 6.84−6.88 (m, 1H), 4.13−4.27 (m, 1H), 3.62−3.72 (m, 2H), 3.37−3.43 (m, 1H), 3.07−3.29 (m, 5H), 2.84−2.93 (m, 1H), 2.26−2.36 (m, 1H), 2.09 (d, J = 1.2 Hz, 3H), 1.96−2.05 (m, 1H), 1.56−1.69 (m, 1H), 1.32−1.41 (m, 3H), 0.93−1.10 (m, 2H). Two NH not seen.

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-5-(pyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (36). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (2.6 g, 4.3 mmol) in CH_2Cl_2 (50 mL) at −10 °C was treated with NBS (0.66 g, 3.71 mmol), and the resulting mixture stirred at this temperature for 30 min before being treated with a saturated sodium metabisulphite aqueous solution (50 mL). The resulting mixture was stirred for 20 min at room temperature, and the layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)-amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidine-1-carboxylate (2.71 g, 92%) as an orange solid. LCMS (high-pH method): t_R 1.54 min, $[M + H]^+$ = 688/690 (1 Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (s, 1H), 8.00 (d, J = 1.2 Hz, 1H), 7.46−7.50 (m, 2H), 7.38−7.44 (m, 2H), 7.36 (d, J = 7.3 Hz, 1H), 6.21 (d, J = 8.3 Hz, 1H), 5.47−5.57 (m, 2H), 4.24−4.35 (m, 1H), 3.85−4.10 (m, 1H), 3.76−3.84 (m, 1H), 3.47−3.56 (m, 1H), 3.03−3.34 (m, 3H), 2.88−2.97 (m, 1H), 2.65−2.86 (m, 3H), 2.48 (d, J = 0.7 Hz, 3H), 2.17−2.26 (m, 1H), 1.89−2.01 (m, 1H), 1.77−1.86 (m, 1H), 1.64−1.76 (m, 1H), 1.52 (s, 9H), 1.45−1.65 (m, 4H). Step 2: a 20 mL microwave vial was charged with pyridin-3-ylboronic acid (21.4 mg, 0.174 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (80 mg, 0.12 mmol),

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K_2CO_3 (64.1 mg, 0.464 mmol), $Pd(OAc)_2$ (2.6 mg, 0.012 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (4.2 mg, 0.012 mmol) and then filled with 1,4-dioxane (4 mL) and water (2 mL). The resulting mixture was degassed under vacuum, quenched with nitrogen for 20 min, and stirred under nitrogen and microwave irradiation at 100 °C for 30 min before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic layer was dried using a hydrophobic frit and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 10% (2 N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-4-((3-methyl-2-oxo-5-(pyridin-3-yl)-1,2-dihydro-1,7-naphthyridin-8-yl)amino)piperidine-1-carboxylate. This derivative was dissolved in TFA (2 mL), and the resulting solution was stirred at reflux for 16 h, cooled to room temperature, and concentrated *in vacuo*. The residue was loaded on a 5 g SCX cartridge, washed with MeOH, and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-5-(pyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (**36**) (32 mg, 55%) as yellow solid. LCMS (high-pH method): t_R 0.61 min, $[M + H]^+$ = 498. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.50 (br s, 1H), 8.55−8.68 (m, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.73 (s, 1H), 7.47−7.58 (m, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 4.19 (br s, 1H), 3.46 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.21−3.28 (m, 2H), 3.17 (d, *J* = 2.4 Hz, 1H), 2.94−3.05 (m, 2H), 2.82−2.93 (m, 3H), 2.29−2.41 (m, 1H), 2.09 (s, 3H), 1.99−2.06 (m, 1H), 1.82−1.96 (m, 2H), 1.67−1.79 (m, 1H), 1.47−1.49 (m, 1H), 1.41−1.55 (m, 3H), 1.35 (d, *J* = 9.3 Hz, 2H).

3-Methyl-5-(5-methylpyridin-3-yl)-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (37). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (1.5 g, 3.2 mmol) in $CHCl_3$ (20 mL) at −10 °C was treated with NBS (0.508 g, 2.86 mmol), and the resulting mixture was stirred at this temperature for 1 h and then treated with a saturated sodium metabisulphite aqueous solution (20 mL). The biphasic mixture was warmed to room temperature and stirred for 10 min, and the layers were separated. The organic phase was dried using a phase separator and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((5-bromo-3-methyl-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (1.63 g, 93%) as a yellow solid, which was used in the next step without further purification. LCMS (high-pH method): t_R 1.22 min, $[M + H]^+$ = 551/553 (1 Br). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 13.21 (br s, 1H), 8.08 (s, 1H), 8.04 (s, 1H), 6.58 (d, *J* = 7.1 Hz, 1H), 4.41−4.54 (m, 1H), 4.15−4.35 (m, 2H), 3.96−4.06 (m, 1H), 3.82 (br s, 2H), 3.41−3.56 (m, 2H), 3.03−3.35 (m, 4H), 2.36 (s, 3H), 2.15−2.25 (m, 1H), 1.67 (br s, 2H), 1.52 (s, 9H), 1.33−1.48 (m, 2H), 1.03−1.25 (m, 2H). Step 2: a 20 mL microwave vial was charged with (5-methylpyridin-3-yl)boronic acid (64.6 mg, 0.471 mmol), (3*R*,4*R*)-*tert*-butyl 4-((5-bromo-2-hydroxy-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (200 mg, 0.363 mmol), K_2CO_3 (150 mg, 1.09 mmol), $Pd(OAc)_2$ (8.1 mg, 0.036 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (13 mg, 0.036 mmol) and then filled with 1,4-dioxane (4 mL) and water (2 mL). The resulting mixture was degassed for 20 min under vacuum, quenched with nitrogen, and stirred at 100 °C for 30 min under microwave irradiation before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic phase was dried using a hydrophobic frit and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 10% (2N NH_3 in MeOH) in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-5-(5-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)-amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (0.178 g, 87%) as a pale yellow solid. The racemic mixture was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralpak IC (4.6 mm i.d. × 25 cm), using 40% EtOH in heptane at a flow rate of 1 mL/min. The material (120 mg) was dissolved in a mixture of EtOH/heptane (2:1) (1 mL). The purification was carried out on a Chiralpak IC (30 mm × 25 cm), using 40% EtOH in heptane at a flow rate of 30 mL/min, and 1 mL of solution was injected at a time. The appropriate fractions were combined and concentrated *in vacuo* to give the fastest running enantiomer, (3*S*,4*S*)-*tert*-butyl 4-((3-methyl-5-(5-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (58 mg), and the slowest running enantiomer, (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-5-(5-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)-piperidine-1-carboxylate (53 mg). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-((3-methyl-5-(5-methylpyridin-3-yl)-2-oxo-1,2-dihydro-1,7-naphthyridin-8-yl)amino)-3-(2-(tetrahydro-2*H*-pyran-4-yl)ethyl)-piperidine-1-carboxylate (58 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) at room temperature was treated with TFA (1 mL), and the resulting mixture was stirred at this temperature for 30 min and then concentrated *in vacuo*. The residue was loaded on a 2 g SCX-2 cartridge, washed with MeOH, and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were combined and concentrated *in vacuo* to give 3-methyl-5-(5-methylpyridin-3-yl)-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)-amino)-1,7-naphthyridin-2(1*H*)-one (**37**) (43 mg, 90%). LCMS (method TFA): t_R 0.48 min, $[M + H]^+$ = 464. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 8.52 (d, *J* = 1.5 Hz, 1H), 8.47 (d, *J* = 1.7 Hz, 1H), 7.91 (s, 1H), 7.72 (s, 1H), 7.53 (s, 1H), 6.69 (d, *J* = 6.6 Hz, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 3.76−3.89 (m, 2H), 3.39 (dd, *J* = 9.3, 6.6 Hz, 2H), 3.26 (qd, *J* = 11.8, 2.0 Hz, 2H), 3.10−3.18 (m, 1H), 2.83 (t, *J* = 10.1 Hz, 1H), 2.70 (dd, *J* = 12.2, 8.8 Hz, 1H), 2.47 (s, 3H), 2.35 (m, 4H), 2.22−2.30 (m, 1H), 1.64−1.84 (m, 3H), 1.41−1.56 (m, 2H), 1.07−1.29 (m, 2H). One NH not seen.

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (38). A 20 mL microwave vial was charged with (5-methylpyridin-3-yl)boronic acid (34.2 mg, 0.249 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (see preparation of **36**) (86 mg, 0.12 mmol), K_2CO_3 (68.9 mg, 0.499 mmol), $Pd(OAc)_2$ (2.8 mg, 0.012 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (4.5 mg, 0.012 mmol) and then filled with 1,4-dioxane (4 mL) and water (2 mL). The reaction mixture was stirred and degassed for 20 min with nitrogen and was then stirred at 100 °C for 30 min under microwave irradiation before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic phase was dried through a hydrophobic frit and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 10% (2N NH_3 in MeOH) in CH_2Cl_2 gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate as a pale yellow solid. This residue was dissolved in TFA (3 mL), and the resulting solution was refluxed for 2 h before being cooled to room temperature and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (**38**) (47 mg, 74%) as a pale yellow solid. LCMS (method TFA): t_R 0.68 min, $[M + H]^+$ = 512.3. ^1H NMR (400 MHz, CD_3OD) δ ppm 8.77−8.80 (m, 1H), 8.73−8.76 (m, 1H), 8.40−8.46 (m, 1H), 7.82−7.86 (m, 1H), 7.77−7.80 (m, 1H), 4.44−4.55 (m, 1H), 3.87−3.95 (m, 1H), 3.64−3.76 (m, 2H), 3.46−3.59 (m, 2H), 3.21−3.30 (m, 2H), 3.11−3.19 (m, 1H), 2.91−3.11 (m, 2H), 2.79−2.89 (m, 1H), 2.64 (s, 3H), 2.39−2.50 (m, 1H), 2.30 (s, 3H), 2.09−2.21 (m, 1H), 2.01−2.09 (m, 1H), 1.91−2.00 (m, 1H), 1.73−1.90 (m, 2H), 1.56−1.71 (m, 1H). Three NH protons not seen.

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5-(5-Methoxypyridin-3-yl)-3-methyl-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (39). Step 1: a 20 mL microwave vial was charged with K_2CO_3 (172 mg, 1.25 mmol), $Pd(OAc)_2$ (7.0 mg, 0.031 mmol), 3-methoxypyridine-5-boronic acid pinacol ester (147 mg, 0.623 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)-methoxy)piperidine-1-carboxylate (200 mg, 0.312 mmol), and di-((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (11.2 mg, 0.031 mmol) and then filled with 1,4-dioxane (8 mL) and water (4 mL). The resulting mixture was degassed under vacuum, quenched with nitrogen over 20 min, and stirred under microwave irradiation at 100 °C for 1 h before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic phase was dried using a hydrophobic frit and then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 2 to 8% MeOH in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-(5-methoxypyridin-3-yl)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (120 mg, 46%) as a pale yellow solid. LCMS (method TFA): t_R 1.47 min, $[M + H]^+$ = 670. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (d, J = 2.9 Hz, 1H), 8.22 (d, J = 1.7 Hz, 1H), 7.87 (d, J = 1.0 Hz, 1H), 7.82 (s, 1H), 7.54 (d, J = 7.1 Hz, 2H), 7.37−7.44 (m, 3H), 7.30−7.36 (m, 1H), 6.92−6.99 (m, 1H), 5.59−5.74 (m, 2H), 4.25−4.36 (m, 1H), 3.90−4.15 (m, 2H), 3.89 (s, 3H), 3.76−3.85 (m, 1H), 3.57−3.66 (m, 2H), 3.45−3.54 (m, 1H), 3.37−3.44 (m, 1H), 3.20−3.26 (m, 1H), 3.07 (m, 2H), 2.70−3.12 (m, 1H), 2.32 (d, J = 0.7 Hz, 3H), 2.00−2.09 (m, 1H), 1.52−1.66 (m, 2H), 1.44 (s, 9H), 1.26−1.37 (m, 2H), 0.88−1.05 (m, 2H). Step 2: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-(5-methoxypyridin-3-yl)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (130 mg, 0.194 mmol) in TFA (2 mL) was stirred at 80 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 5-(5-methoxypyridin-3-yl)-3-methyl-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (**39**) (66 mg, 71%) as a colorless foam. LCMS (high-pH method): t_R 0.70 min, $[M + H]^+$ = 480. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.50 (br s, 1H), 8.32−8.36 (m, 1H), 8.13−8.20 (m, 1H), 7.72−7.78 (m, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.37 (dd, J = 2.7, 2.0 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 4.13−4.27 (m, 1H), 3.89 (s, 3H), 3.63−3.73 (m, 2H), 3.40 (dd, J = 9.3, 6.6 Hz, 1H), 3.18−3.29 (m, 3H), 3.14 (tt, J = 11.7, 2.4 Hz, 2H), 2.89 (d, J = 12.5 Hz, 1H), 2.26−2.37 (m, 1H), 2.10 (d, J = 1.0 Hz, 3H), 2.00 (d, J = 8.8 Hz, 1H), 1.63 (br s, 2H), 1.28−1.44 (m, 3H), 0.95−1.10 (m, 2H). One NH not seen.

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-5-(5-methoxypyridin-3-yl)-3-methyl-1,7-naphthyridin-2(1*H*)-one (40). Step 1: a 20 mL microwave vial was charged with (5-methoxypyridin-3-yl)boronic acid (26.6 mg, 0.174 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (see preparation of **36**) (80 mg, 0.116 mmol), K_2CO_3 (64.1 mg, 0.464 mmol), $Pd(OAc)_2$ (2.60 mg, 0.012 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (4.2 mg, 0.012 mmol) and then filled with 1,4-dioxane (4 mL) and water (2 mL). The resulting mixture was degassed under vacuum, quenched with nitrogen for 20 min, and stirred under nitrogen and microwave irradiation at 100 °C for 30 min before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic layer was dried using a hydrophobic frit and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 10% (2N NH_3 in MeOH) in CH_2Cl_2) gave 4-((((3*R*,4*R*)-4-((2-(benzyloxy)-5-(5-methoxypyridin-3-yl)-3-methyl-1,7-naphthyridin-8-yl)amino)piperidin-3-yl)oxy)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide. This derivative was dissolved in TFA (2 mL), and the resulting solution was refluxed for 16 h, cooled to room temperature, and concentrated *in vacuo*. The residue was loaded on a 5 g SCX cartridge, washed with MeOH, and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-5-(5-methoxypyridin-3-yl)-3-methyl-1,7-naphthyridin-2(1*H*)-one (28 mg, 46%) as yellow solid. LCMS (high-pH method): t_R 0.70 min, $[M + H]^+$ = 528. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.20 (br s, 1H), 8.39 (d, J = 2.7 Hz, 1H), 8.27 (s, 1H), 7.92 (s, 1H), 7.77 (s, 1H), 7.26 (d, J = 1.5 Hz, 1H), 6.75 (d, J = 7.3 Hz, 1H), 4.76 (br s, 1H), 4.51 (d, J = 3.7 Hz, 1H), 3.95 (s, 3H), 3.51−3.62 (m, 2H), 3.48 (dd, J = 8.7, 6.2 Hz, 1H), 3.38−3.44 (m, 1H), 3.16 (d, J = 12.5 Hz, 1H), 2.75−2.99 (m, 5H), 2.69 (dd, J = 11.7, 9.0 Hz, 1H), 2.34 (s, 3H), 2.25 (d, J = 10.0 Hz, 1H), 2.05 (t, J = 12.3 Hz, 2H), 1.62−1.90 (m, 4H).

3-Methyl-5-(pyrimidin-5-yl)-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (41). Step 1: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (2.7 g, 4.8 mmol) in CH_2Cl_2 at 0 °C was treated with NBS (0.683 g, 3.84 mmol), and the resulting solution was stirred at this temperature for 30 min. Further NBS (50 mg, 0.28 mmol) was added. The solution was stirred at 0 °C for 10 min before being treated with a saturated sodium metabisulphite aqueous solution. The layers were separated, and the organic phase was dried using a phase separator and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)-methoxy)piperidine-1-carboxylate (2.92 g, 95%) as a beige foam, which was used in the next step without further purification. LCMS (high-pH method): t_R 1.67 min, $[M + H]^+$ = 643.5 (1 Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.03 (s, 1H), 7.99 (d, J = 1.2 Hz, 1H), 7.46−7.50 (m, 2H), 7.38−7.44 (m, 2H), 7.36 (d, J = 7.1 Hz, 1H), 6.29 (d, J = 7.8 Hz, 1H), 5.52 (s, 2H), 4.14−4.31 (m, 1H), 3.82 (d, J = 7.6 Hz, 2H), 3.41−3.54 (m, 1H), 3.30 (d, J = 3.9 Hz, 1H), 2.92−3.25 (m, 4H), 2.46 (d, J = 1.0 Hz, 2H), 2.26−2.36 (m, 1H), 1.61−1.71 (m, 2H), 1.33−1.55 (m, 15H), 1.11−1.24 (m, 1H), 0.98−1.10 (m, 1H). Step 2: a 20 mL microwave vial was charged with K_2CO_3 (172 mg, 1.25 mmol), $Pd(OAc)_2$ (7.00 mg, 0.031 mmol), pyrimidine-5-boronic acid (77 mg, 0.62 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (200 mg, 0.312 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (11 mg, 0.031 mmol) and then filled with 1,4-dioxane (8 mL) and water (4 mL). The resulting mixture was stirred, degassed for 20 min with nitrogen, and stirred at 100 °C under microwave irradiation for 1 h before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic phase was dried using a hydrophobic frit and then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 2 to 8% MeOH in CH_2Cl_2) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(pyrimidin-5-yl)-1,7-naphthyridin-8-yl)amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (120 mg, 60%). LCMS (high-pH method): t_R 1.40 min, $[M + H]^+$ = 641.6. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (s, 1H), 9.23 (s, 1H), 8.91 (s, 2H), 7.89 (d, J = 1.0 Hz, 1H), 7.85 (s, 1H), 7.55 (d, J = 7.1 Hz, 2H), 7.38−7.44 (m, 2H), 7.34 (s, 1H), 7.01−7.09 (m, 1H), 5.59−5.74 (m, 2H), 4.26−4.38 (m, 1H), 3.88−4.19 (m, 1H), 3.77−3.87 (m, 1H), 3.57−3.67 (m, 2H), 3.47−3.55 (m, 1H), 3.38−3.45 (m, 1H), 3.20−3.27 (m, 1H), 3.07 (br s, 2H), 2.70−2.97 (m, 1H), 2.32 (s, 3H), 1.99−2.09 (m, 1H), 1.53−1.67 (m, 2H), 1.38−1.48 (m, 9H), 1.27−1.36 (m, 2H), 0.87−1.06 (m, 2H). Step 3: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(pyrimidin-5-yl)-1,7-naphthyridin-8-yl)-amino)-3-((tetrahydro-2*H*-pyran-4-yl)methoxy)piperidine-1-carboxylate (120 mg, 0.187 mmol) in TFA (2 mL) was stirred at 80 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 3-methyl-5-(pyrimidin-5-yl)-8-(((3*R*,4*R*)-3-((tetrahydro-2*H*-pyran-4-yl)-methoxy)piperidin-4-yl)amino)-1,7-naphthyridin-2(1*H*)-one (**41**) (20 mg, 41%) as a colorless oil. LCMS (high-pH method): t_R 0.57 min, [M

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+ H]$^+$ = 451.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (s, 1H), 8.86 (s, 2H), 7.76 (s, 1H), 7.59 (d, J = 1.2 Hz, 1H), 6.91−6.98 (m, 1H), 4.14−4.25 (m, 1H), 3.63−3.73 (m, 2H), 3.37−3.43 (m, 1H), 3.08−3.29 (m, 6H), 2.84−2.92 (m, 1H), 2.26−2.36 (m, 1H), 2.10 (d, J = 1.0 Hz, 3H), 1.95−2.05 (m, 1H), 1.58−1.70 (m, 1H), 1.28−1.44 (m, 3H), 0.95−1.09 (m, 2H). Two NH not seen.

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)quinolin-2(1*H*)-one (42). Step 1: a solution of 2-methyl-3-phenylacryloyl chloride (11 g, 60.9 mmol) in CH_2Cl_2 (300 mL) at 0 °C under nitrogen was treated with NEt_3 (9.34 mL, 67.0 mmol) and then, after 10 min, with 2-bromoaniline (10.5 g, 60.9 mmol). The resulting solution was stirred at this temperature for 4 h, washed successively with water (300 mL), a 5% w/w Na_2CO_3 aqueous solution (300 mL), and a 1 N HCl aqueous solution (300 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give *N*-(2-bromophenyl)-2-methyl-3-phenylacrylamide (18.5 g, 96%) as a dark brown oil that crystallized on standing and that was used in the next step without further purification. Step 2: a solution of *N*-(2-bromophenyl)-2-methyl-3-phenylacrylamide (16.0 g, 50.6 mmol) in chlorobenzene (40 mL) at 0 °C was treated with $AlCl_3$ (40.5 g, 304 mmol), and the resulting mixture was stirred at this temperature for 20 min and then at 120 °C for 2 h. The reaction mixture was cooled to room temperature and then added very cautiously to ice (500 g). The mixture was agitated thoroughly to ensure complete hydrolysis of aluminum chloride. The mixture was then extracted with CH_2Cl_2 (200 mL), and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (330 g column, 0 to 100% gradient EtOAc in cyclohexane) gave 8-bromo-3-methylquinolin-2(1*H*)-one (6.9 g, 57%) as a pink solid. LCMS (method formate): t_R 0.82 min, [M + H]$^+$ = 238.0 (1 Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.04 (br s, 1H), 7.66 (dd, J = 7.8, 1.1 Hz, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.47 (dd, J = 1.0, 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 2.29 (d, J = 1.2 Hz, 3H). Step 3: a suspension of 8-bromo-3-methylquinolin-2(1*H*)-one (1.0 g, 4.2 mmol) DMF (5 mL) at room temperature was treated with K_2CO_3 (0.71 g, 5.1 mmol), and the resulting mixture was stirred at this temperature for 10 min before (bromomethyl)benzene (0.55 mL, 4.6 mmol) was added. The resulting mixture was then stirred for 72 h at room temperature. The precipitate was filtered off, the mother liquors were diluted with water (50 mL) and EtOAc (50 mL), and the layers were separated. The organic phase was washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, 0 to 100% gradient EtOAc in cyclohexane) gave 2-(benzyloxy)-8-bromo-3-methylquinoline (1.17 g, 85%) as a pink solid and 1-benzyl-8-bromo-3-methylquinolin-2(1*H*)-one (40 mg, 3%) as a milky white gum. LCMS (method formate): t_R 1.57 min, [M + H]$^+$ = 328.0 (1 Br).^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 (dd, J = 7.8, 1.7 Hz, 1H), 7.55 (d, J = 1.2 Hz, 1H), 7.47 (dd, J = 7.7, 1.5 Hz, 1H), 7.18−7.31 (m, 3H), 7.10 (m, 2H), 7.04 (dd, J = 7.7, 7.7 Hz, 1H), 6.06 (s, 2H), 2.29 (d, J = 1.2 Hz, 3H). Step 4: a mixture of (3*R*,4*R*)-*tert*-butyl 4-amino-3-((*tert*-butyldimethylsilyl)-oxy)piperidine-1-carboxylate (1.21 g, 3.66 mmol), 2-(benzyloxy)-8-bromo-3-methylquinoline (1.0 g, 3.0 mmol), sodium *tert*-butoxide (0.878 g, 9.14 mmol), BrettPhos (0.164 g, 0.305 mmol), and BrettPhos precatalyst (0.243 g, 0.305 mmol) in THF (2 mL) was stirred at room temerature for 1 h, stirred at 60 °C for 3 h, cooled to room temperature, and diluted with a saturated NH_4Cl aqueous solution. The aqueous phase was extracted with EtOAc (2 × 50 mLl), and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 0−25% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (1.70 g, 97%) as a pale yellow foam. LCMS (high-pH method): t_R 1.90 min, [M + H]$^+$ = 578. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 (d, J = 0.7 Hz, 1H), 7.49 (s, 2H), 7.39 (s, 2H), 7.30−7.35 (m, 1H), 7.17−7.23 (m, 1H), 6.93−6.99 (m, 1H), 6.72−6.77 (m, 1H), 5.62−5.68 (m, 1H), 5.55 (d, J = 8.8 Hz, 2H), 3.72−3.93 (m, 2H), 3.59−3.67 (m, 1H), 3.48−3.57 (m, 1H), 3.16−3.27 (m, 1H), 3.05−3.14 (m, 1H), 2.40 (s, 3H), 1.60−1.76 (m, 2H), 1.52 (s, 9H), 0.84 (s, 9H), −0.09 (s, 6H). Step 5: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)-amino)-3-((*tert*-butyldimethylsilyl)oxy)piperidine-1-carboxylate (1.60 g, 2.77 mmol) in THF (50 mL) at room temperature was treated with TBAF (1 N in THF, 5.54 mL, 5.54 mmol), and the resulting mixture was stirred at this temperature for 2 h and then concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (100 mL), and the layers were separated. The organic phase was dried under $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient 0−50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (0.91g, 71%) as a colorless oil. LCMS (high-pH method): t_R 1.47 min, [M + H]$^+$ = 464. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (d, J = 0.7 Hz, 1H), 7.50 (d, J = 7.3 Hz, 2H), 7.36−7.43 (m, 2H), 7.33 (d, J = 7.3 Hz, 1H), 7.19−7.25 (m, 1H), 7.01−7.07 (m, 1H), 6.84 (d, J = 7.3 Hz, 1H), 5.50−5.59 (m, 2H), 5.42−5.49 (m, 1H), 4.28−4.39 (m, 1H), 3.92−4.22 (m, 1H), 3.58−3.69 (m, 1H), 3.41−3.53 (m, 1H), 2.83−3.02 (m, 2H), 2.59−2.73 (m, 1H), 2.41 (d, J = 1.0 Hz, 3H), 2.03−2.13 (m, 1H), 1.52 (s, 9H), 1.30−1.43 (m, 1H). Step 6: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (420 mg, 0.906 mmol) in THF (10 mL) at 0 °C was treated with potassium *tert*-butoxide (224 mg, 1.99 mmol). The resulting mixture was stirred at this temperature for 10 min, treated with (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl trifluoromethanesulfonate (537 mg, 1.81 mmol), and allowed to warm to room temperature over 2 h before being diluted with water (10 mL). The aqueous phase was extracted with EtOAc (10 mL). The organic layer was washed with water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (0.47 g, 85%) as a pale green oil. LCMS (high-pH method): t_R 1.51 min, [M + H]$^+$ = 610.5. Step 7: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (0.47 g, 0.77 mmol) in CH_2Cl_2 (20 mL) at −10 °C was treated with NBS (0.123 g, 0.694 mmol), and the resulting mixture was stirred at this temperature for 20 min before being treated with a saturated sodium metabisulphite aqueous solution (20 mL). The biphasic mixture was stirred at room temperature for 10 min, and the layers were separated. The organic phase was dried using a phase separator and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methylquinolin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (370 mg, 70%) as a pale yellow gum. LCMS (high-pH method): t_R 1.55 min, [M + H]$^+$ = 688/690. Step 8: a 20 mL microwave vial was charged with (5-methylpyridin-3-yl)boronic acid (53.7 mg, 0.392 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methylquinolin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (180 mg, 0.261 mmol), K_2CO_3 (144 mg, 1.04 mmol), $Pd(OAc)_2$ (5.9 mg, 0.026 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (9.4 mg, 0.026 mmol) and then filled with 1,4-dioxane (4 mL) and water (2 mL). The resulting mixture was degassed under vacuum over 20 min, quenched with nitrogen, and stirred at 100 °C for 30 min under microwave irradiation before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), and the layers were separated. The organic phase was dried using a hydrophobic frit and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10 g column, gradient: 0 to 100% EtOAc in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(5-methylpyridin-3-yl)quinolin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (125 mg, 68%) as a pale yellow solid. LCMS (high-pH method): t_R 1.48 min, [M + H]$^+$ = 701.6. Step 9: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(5-methylpyridin-3-

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yl)quinolin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (125 mg, 0.178 mmol) in TFA (1 mL) was refluxed for 2 h, cooled to room temperature, and concentrated *in vacuo*. The residue was dissolved in MeOH and loaded onto a 5 g SCX-2 cartridge, which was washed with MeOH (20 mL) and eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)quinolin-2(1*H*)-one (**42**) (90 mg, 99%) as a yellow solid. LCMS (high-pH method): t_R 0.68 min, $[M + H]^+$ = 511, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.70 (br s, 1H), 8.51 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 1.2 Hz, 1H), 7.52 (s, 1H), 6.99−7.06 (m, 2H), 4.24 (br s, 1H), 3.58−3.65 (m, 1H), 3.36−3.56 (m, 4H), 3.20 (br s, 1H), 2.94−3.14 (m, 5H), 2.57−2.66 (m, 1H), 2.55−2.57 (m, 1H), 2.52 (dd, J = 11.5, 9.5 Hz, 1H), 2.46 (s, 3H), 2.07−2.31 (m, 4H), 1.75−1.90 (m, 3H), 1.53−1.62 (m, 2H).

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)quinolin-2(1*H*)-one (43). This compound was obtained in an anlogous manner as that for compound **42** following the separation of the two enantiomers of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (step 5, compound **42**), which was performed as follows: The racemic mixture was separated by chiral HLPC. The HPLC analysis was carried out on a Chiralpak IC (4.6 mm i.d. × 25 cm), using 25% EtOH in heptane at a flow rate of 1 mL/min. The material (910 mg) was dissolved in a mixture of EtOH/heptane (2:1) (1 mL). The purification was carried out on a Chiralpak IC (30 mm × 25 cm), using 25% EtOH in heptane at a flow rate of 30 mL/min, and 1 mL of solution was injected at a time. The appropriate fractions were combined and concentrated *in vacuo* to give the fastest running enantiomer, (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (422 mg), and the slowest running enantiomer, (3*S*,4*S*)-*tert*-butyl 4-((2-(benzyloxy)-3-methylquinolin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (423 mg).

8-(((3*R*,4*R*)-3-(((2*R*,4*R*,6*S*)-2,6-Dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (44). Step 1: a solution of 4-(hydroxymethyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (1.0 g, 6.1 mmol) in CH_2Cl_2 (30 mL) at room temperature was treated with imidazole (0.497 g, 7.31 mmol) and DMAP (0.074 g, 0.61 mmol). The mixture was stirred at this temperature for 20 min; then, TBDMSCl (1.10 g, 7.31 mmol) was added, and the resulting suspension was stirred for 2 h. The organic phase was then washed with water (30 mL), dried using a phase separator, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 0 to 50% EtOAc in cyclohexane) gave 4-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (1.62 g, 96%) as a colorless oil. Step 2: a solution of 4-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-2*H*-thiopyran 1,1-dioxide (1.4 g, 5.0 mmol) in THF (10 mL) at −78 °C under nitrogen was treated with LiHMDS (1 N in THF, 6.54 mL, 6.54 mmol). The resulting mixture was stirred at this temperature for 30 min before being treated with MeI (0.503 mL, 8.04 mmol). The mixture was stirred at −78 °C for 2 h and was then allowed to warm to room temperature. The solution was diluted with water (30 mL), and the aqueous phase was extracted with EtOAc (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give (2*R*,6*S*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (contaminated with a mixture of monomethylated adducts) (1.45 g, 95%) as a pale yellow oil, which was used in the next step without further purification. Step 3: a solution of (2*R*,6*S*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,6-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.50 g, 1.7 mmol) in THF (10 mL) at room temperature was treated with a 2 N HCl aqueous solution (10 mL), and the resulting mixture was stirred at this temperature for 18 h and then concentrated *in vacuo* to give (2*R*,6*S*)-4-(hydroxymethyl)-2,6-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.186 g, 61%) as a colorless solid (contaminated with a mixture of monomethylated adducts), which was used in the next step without further purification. Step 4: a solution of (2*R*,6*S*)-4-(hydroxymethyl)-2,6-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.186 g, 1.04 mmol) in CH_2Cl_2 (10 mL) under nitrogen was cooled using an acetone/ice bath (−10 °C) then was treated with pyridine (0.093 mL, 1.15 mmol) and Tf_2O (0.194 mL, 1.15 mmol) dropwise. The resulting mixture was stirred at this temperature for 1 h and then allowed to warm to room temperature. The organic phase was washed with brine (10 mL), dried using a phase separator, and concentrated *in vacuo* to give ((2*R*,6*S*)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl trifluoromethanesulfonate (0.32 g, 99%) as a pale yellow oil (contaminated with a mixture of monomethylated adducts), which was used in the next step without further purification. Step 5: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-hydroxypiperidine-1-carboxylate (0.30 g, 0.65 mmol) in THF (10 mL) at 0 °C under nitrogen was treated with tBuOK (0.152 g, 1.36 mmol), and the resulting mixture was stirred at this temperature for 10 min before being treated with a solution of ((2*R*,6*S*)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methyl trifluoromethanesulfonate (0.301 g, 0.969 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 30 min before being quenched with water. The aqueous phase was extracted with EtOAc. The organic phase was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient 0 to 70% EtOAc in hexanes) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-(((2*R*,6*S*)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (0.19 g, 47%) as a pale yellow gum contaminated with a mixture of monomethylated adducts. LCMS (high-pH method): t_R 1.43 min, $[M + H]^+$ = 639.5. Step 6: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-1,7-naphthyridin-8-yl)amino)-3-(((2*R*,6*S*)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidine-1-carboxylate (0.19 g, 0.30 mmol) in CH_2Cl_2 (10 mL) at −10 °C was treated with NBS (0.049 g, 0.27 mmol), and the resulting mixture was stirred at this temperature for 40 min and then treated with a saturated sodium metabisulphite aqueous solution. The biphasic mixture was allowed to warm to room temperature and stirred for 10 min. The layers were separated, and the organic phase was dried using a phase separator and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-(((2*R*,6*S*)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidine-1-carboxylate (180 mg, 84%) as a pale yellow gum (contaminated with a mixture of monomethylated adducts), which was used in the next step without further purification. LCMS (high-pH method): t_R 1.57 min, $[M + H]^+$ = 719.4 (1 Br). Step 7: a 20 mL microwave vial was charged with (5-methylpyridin-3-yl)boronic acid (0.070 g, 0.51 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-methyl-1,7-naphthyridin-8-yl)amino)-3-((2-methyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (0.18 g, 0.26 mmol), K_2CO_3 (0.141 g, 1.02 mmol), $Pd(OAc)_2$ (5.74 mg, 0.026 mmol), and di((3*S*,5*S*,7*S*)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (9.2 mg, 0.026 mmol) and then filled with 1,4-dioxane (4 mL) and water (2 mL). The resulting mixture was degassed under vacuum for 20 min and quenched with nitrogen before being stirred at 100 °C for 30 min under microwave irradiation.. The mixture was then cooled to room temperature and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-(((2*R*,6*S*)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (140 mg, 76%) contaminated with a mixture of monomethylated adducts. The mixture was further purified by chiral HLPC. The HPLC analysis was carried out on a Chiralpak IB (4.6 mm i.d. × 25 cm), using 10% EtOH (+0.2% isopropylamine) in heptane at a flow rate of 1 mL/min. The material (140 mg) was dissolved in a mixture of EtOH (100 mg in mL). The purification was carried out on a Chiralpak IB (2 cm × 25 cm), using 10% EtOH (+0.2% isopropylamine) in heptane at a flow rate of 20 mL/min, and 1 mL of solution was injected. The appropriate fractions were combined and concentrated under reduced

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pressure to give (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-(((2R,4R,6S)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidine-1-carboxylate (80 mg, 43%). LCMS (high-pH method): t_R 1.43 min, $[M + H]^+$ = 730.6. Step 8: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-(((2R,4r,6S)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (70 mg, 0.096 mmol) in TFA (2 mL) was refluxed for 2 h and then cooled to room temperature and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-(((2R,4r,6S)-2,6-dimethyl-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (**44**) (20 mg, 39%) as a bright yellow solid. LCMS (method TFA): t_R 0.47 min, $[M + H]^+$ = 540. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 8.53 (d, J = 1.5 Hz, 1H), 8.48 (d, J = 1.7 Hz, 1H), 7.90−7.94 (m, 1H), 7.75 (d, J = 1.0 Hz, 1H), 7.54 (s, 1H), 6.75 (d, J = 6.4 Hz, 1H), 4.52 (br s, 1H), 3.46−3.59 (m, 2H), 3.32−3.45 (m, 2H), 3.09−3.17 (m, 1H), 2.77−2.92 (m, 3H), 2.63−2.71 (m, 1H), 2.47 (s, 3H), 2.34 (d, J = 0.7 Hz, 3H), 2.19−2.27 (m, 1H), 1.84−1.94 (m, 3H), 1.60−1.76 (m, 2H), 1.30−1.54 (m, 2H), 1.23 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H).

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-ethyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (45). Step 1: (*E*)-ethyl 2-((3-((*tert*-butoxycarbonyl)amino)-2-chloropyridin-4-yl)methylene)butanoate was obtained from *tert*-butyl (2-chloro-4-formylpyridin-3-yl)carbamate in an anaogous manner as that for (*E*)-ethyl 3-(3-((*tert*-butoxycarbonyl)amino)-2-chloropyridin-4-yl)-2-methyl acrylate (see synthesis of **7a** in preceding article[6]) using ethyl 2-(diethoxyphosphoryl)butanoate (15 g, 57%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.33 (d, J = 4.8 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 4.8 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.27 (d, J = 7.5 Hz, 2H), 1.39 (br s, 7H), 1.25 (t, J = 7.1 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H). Step 2: (*E*)-ethyl 2-((3-amino-2-chloropyridin-4-yl)methylene)butanoate was obtained from (*E*)-ethyl 2-((3-((*tert*-butoxycarbonyl)amino)-2-chloropyridin-4-yl)methylene)butanoate using the same procedure as that for the synthesis of (*E*)-ethyl 3-(3-amino-2-chloropyridin-4-yl)-2-methyl acrylate from ethyl 3-(3-((*tert*-butoxycarbonyl)amino)-2-chloropyridin-4-yl)-2-methyl acrylate (see synthesis of **7a** in preceding article[6]) (8.1 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.63 (d, J = 1.0 Hz, 1H), 7.34 (s, 1H), 6.98 (d, J = 1.0 Hz, 1H), 5.50 (s, 2H), 4.19−4.25 (m, 2H), 2.26−2.34 (m, 2H), 1.29 (t, J = 1.0 Hz, 3H), 1.03 (t, J = 1.0 Hz, 3H). Step 3: 8-chloro-3-ethyl-1,7-naphthyridin-2(1*H*)-one was obtained from (*E*)-ethyl 2-((3-amino-2-chloropyridin-4-yl)methylene)butanoate using the same procedure as that for the synthesis of 8-chloro-3-methyl-1,7-naphthyridin-2(1*H*)-one (**7a**) from (*E*)-ethyl 3-(3-amino-2-chloropyridin-4-yl)-2-methyl acrylate (5 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.35 (s, 1H), 8.13 (d, J = 5.0 Hz, 1H), 7.83 (s, 1H), 7.64 (d, J = 5.0 Hz, 1H), 2.53−2.60 (m, 2H), 1.19 (t, J = 7.5 Hz, 3H). Step 4: a solution of (3*R*,4*R*)-*tert*-butyl 4-amino-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidine-1-carboxylate (249 mg, 0.686 mmol) in THF (4 mL) was treated with 2-(benzyloxy)-8-chloro-3-ethyl-1,7-naphthyridine (248 mg, 0.830 mmol), sodium *tert*-butoxide (203 mg, 2.11 mmol), $Pd_2(dba)_3$ (34 mg, 0.037 mmol), and BrettPhos (39 mg, 0.074 mmol). The resulting mixture was stirred at room temperature for 1 h and was then refluxed for 3 h before being cooled to room temperature and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (50 g column, gradient: 15 to 70% EtOAc in cyclohexane) gave a first residue, which was further purified by flash chromatography on silica gel (50 g column, gradient: 15 to 70% EtOAc in cyclohexane) to give (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-ethyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (69.1 mg, 16%) as a yellow oil. LCMS (method formic): t_R 1.04 min, $[M + H]^+$ = 625.6. Step 5: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-ethyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (6.1 mL, 0.096 mmol) in CH_2Cl_2 (5 mL) was cooled to −10 °C using an NaCl ice bath and then treated with NBS (10.6 mg, 0.060 mmol), and the resulting mixture was stirred at this temperature for 30 min. NBS (3.6 mg, 0.020 mmol) was further added, and the mixture was stirred at the same temperature for 30 min before being treated with a saturated sodium metabisulfite aqueous solution (5 mL). The reaction mixture was stirred for 20 min and then warmed to room temperature. The layers were separated, and the organic phase was dried using a hydrophobic frit and concentrated *in vacuo* to give (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-ethyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (59.4 mg, 88%) as a yellow oil, which was used in the next step without further purification. LCMS (method formic): t_R 1.46 min, $[M + H]^+$ = 705.6 (1 Br). Step 6: a 5 mL microwave vial was charged with (5-methylpyridin-3-yl)boronic acid (15 mg, 0.11 mmol), (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-5-bromo-3-ethyl-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidine-1-carboxylate (59 mg, 0.084 mmol), $Pd(OAc)_2$ (2.0 mg, 8.9 μmol), K_2CO_3 (51 mg, 0.37 mmol), and di((3S,5S,7S)-adamantan-1-yl)(butyl)phosphine (cataCXium A) (3.0 mg, 8.4 μmol) and then filled with 1,4-dioxane (2 mL) and water (1 mL), and the resulting mixture was degassed by bubbling nitrogen through it for 30 min. The mixture was then stirred under microwave irradiation at 100 °C for 30 min before being cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (8 mL) and water (8 mL), and the layers were separated. The organic phase was dried using a hydrophobic frit and then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (25 g column, gradient: 12 to 63% (3:1 EtOAc/EtOH) in cyclohexane) gave (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-ethyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-8-yl)amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)piperidine-1-carboxylate (25.6 mg, 42%) as a yellow oil. LCMS (high-pH method): t_R 1.45 min, $[M + H]^+$ = 717.7. Step 7: a solution of (3*R*,4*R*)-*tert*-butyl 4-((2-(benzyloxy)-3-ethyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-8-yl)-amino)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidine-1-carboxylate (25 mg, 0.036 mmol) in TFA (1 mL) was refluxed at 80 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. The residue was again dissolved in TFA (1 mL), and the mixture was refluxed for another 3 h before being cooled to room temperature and concentrated *in vacuo*. The residue was loaded on to a 500 mg SCX-2 cartridge, which was washed with MeOH (5 mL) and then eluted with a 2 N NH_3 solution in MeOH. The ammoniac fractions were combined and concentrated *in vacuo* to give 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)piperidin-4-yl)amino)-3-ethyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (**45**) (12.1 mg, 64%) as a yellow solid. LCMS (method formic): t_R 0.51 min, $[M + H]^+$ = 526. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.46 (d, J = 1.5 Hz, 1H), 8.41 (d, J = 1.7 Hz, 1H), 7.75−7.79 (m, 2H), 7.61 (s, 1H), 4.30−4.38 (m, 1H), 3.60 (dd, J = 9.2, 5.5 Hz, 1H), 3.38−3.46 (m, 2H), 3.05−3.12 (m, 1H), 2.82−3.01 (m, 4H), 2.72−2.81 (m, 1H), 2.64 (q, J = 7.8 Hz, 2H), 2.54−2.60 (m, 1H), 2.47 (s, 4H), 2.16−2.25 (m, 1H), 1.93−2.02 (m, 2H), 1.75 (ddd, J = 8.4, 5.6, 2.9 Hz, 1H), 1.58−1.70 (m, 3H), 1.19 (t, J = 7.5 Hz, 3H). Three NH not seen.

8-(((3*R*,4*R*)-3-((1,1-Dioxidotetrahydro-2*H*-thiopyran-4-yl)-methoxy)-1-methylpiperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (46). A solution of 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-piperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (110 mg, 0.215 mmol) in $CHCl_3$ was treated with formic acid (11 μL, 0.28 mmol) and with a formaldehyde solution in water, containing 10−15% MeOH as stabilizer (37% w/w, 19 μL, 0.26 mmol). The resulting mixture was stirred under microwave irradiation at 80 °C for 2 h, cooled to room temperature, and concentrated *in vacuo*. Purification of the residue by MDAP (high-pH method) gave 8-(((3*R*,4*R*)-3-((1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)methoxy)-1-methylpiperidin-4-yl)amino)-3-methyl-5-(5-methylpyridin-3-yl)-1,7-naphthyridin-2(1*H*)-one (**46**) (67 mg, 59%) as a yellow solid. LCMS (method TFA): t_R 0.77 min, $[M + H]^+$ = 526. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 13.2 (br s, 1H), 8.52 (d, J = 1.5 Hz, 1H), 8.46 (d, J =

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1.7 Hz, 1H), 7.90 (s, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 0.7 Hz, 1H), 6.64 (d, J = 7.6 Hz, 1H), 4.32−4.43 (m, 1H), 3.70 (td, J = 9.1, 4.3 Hz, 1H), 3.55−3.61 (m, 1H), 3.48−3.54 (m, 1H), 3.17 (dd, J = 10.9, 3.3 Hz, 1H), 2.75−2.98 (m, 6H), 2.47 (s, 3H), 2.38 (s, 3H), 2.34 (d, J = 1.0 Hz, 3H), 2.21−2.32 (m, 3H), 2.16 (t, J = 10.1 Hz, 1H), 1.98−2.11 (m, 2H), 1.66−1.86 (m, 2H).

■ ASSOCIATED CONTENT

Supporting Information

Table S1, parts 1 and 2: Full data for exemplified compounds in main tables. Table S2: Selectivity profile of compound **46** in the BromoSCAN panel. Table S3: Data collection and refinement statistics for ATAD2 X-ray structures. Table S4: Data collection and refinement statistics for BRD4 BD1 structure. Figure S1: Correlation plots between ATAD2 assays. Figure S2: KAc site amino acids of ATAD2, ATAD2B, BRD4 BD1, and BRD4 BD2 bromodomains. Figure S3: OMIT maps for ATAD2 and BRD4 BD1 X-ray structures. Figure S4: GSK3190320, the synthetic ligand used in the ATAD2 TR-FRET assay. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b00773.

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Notes

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■ ABBREVIATIONS USED

ANCCA, AAA nuclear coregulator cancer-associated protein; ATAD2, ATPase family AAA domain containing 2; BET, bromodomain and extra terminal domain; BRD4, bromodomain-containing protein 4; BRPF1/2/3, bromodomain and PHD finger containing 1/2/3; CECR2, cat eye syndrome chromosome region, candidate 2; KAc, acetyl lysine. pIC_{50}, $-\log_{10} IC_{50}$; SPR, surface plasmon resonance; TAF, TATA box binding protein (TBP)-associated factor

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