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The Effect of Core Replacement on S64315, a Selective MCL-1 Inhibitor, and Its Analogues

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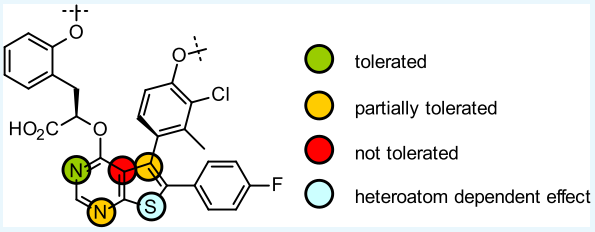
ABSTRACT: Following the identification of thieno[2,3-*d*]pyrimidine-based selective and potent inhibitors of MCL-1, we explored the effect of core swapping at different levels of advancement. During hit-to-lead optimization, X-ray-guided S-N replacement in the core provided a new vector, whose exploration led to the opening of the so-called deep-S2 pocket of MCL-1. Unfortunately, the occupation of this region led to a plateau in affinity and had to be abandoned. As the project approached selection of a clinical candidate, a series of core swap analogues were also prepared. The affinity and cellular activity of these compounds showed a significant dependence on the core structure. In certain cases, we also observed an increased and accelerated epimerization of the atropoisomers. The most potent core replacement analogues showed considerable *in vivo* PD response. One compound was progressed into efficacy studies and inhibited tumor growth.

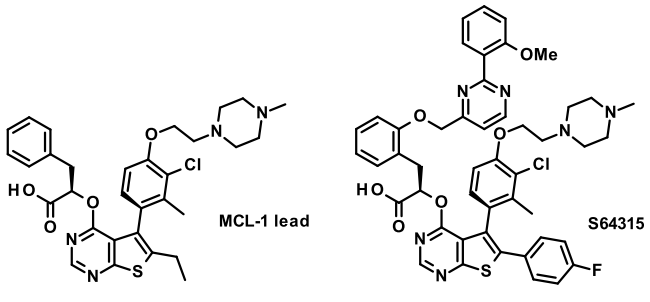


INTRODUCTION

The evasion of apoptosis, an evolutionary highly conserved form of programmed cell death used to eliminate cancer cells,[1] is linked to the development and sustained expansion of tumors.[2] The inhibition of prosurvival proteins associated with the blocking of apoptosis has long been recognized as a therapeutic approach and led to the identification of potent inhibitors of key family members BCL-2,[3] BCL-x_L,[4] and MCL-1[5] and to the approval of the selective BCL-2 inhibitor venetoclax for hematological malignancies.[6] Most of the chemotypes identified are protein−protein interaction inhibitors binding into the so-called BH3 groove of the target, and for each series of compounds, discovery was informed by structural information coming from X-ray crystallography and NMR spectroscopy. Some of the MCL-1 inhibitors, including our preclinical candidate S64315 derived from a thieno[2,3-*d*]pyrimidine-based lead compound (Scheme 1), were successfully progressed into the clinic recently.[7]

Around the time our fragment-based MCL-1 inhibitor discovery program reached the lead selection phase,[8] Abbott researchers patented (and later published)[9] a series of indolecarboxylic acid derivatives as selective MCL-1 inhibitors. Comparison of the Mcl-1-bound X-ray structures (Mcl-1 denoting the crystallization construct) of a representative example from their collection (PDB code 6B4L, Figure 1) and a close analogue of our lead (**1**) revealed that both compounds bind in the same region of Mcl-1 (the so-called S2 pocket). On the other hand, closer inspection of the structures showed that in the case of the indolecarboxylic acid derivative, the bottom of this pocket (coined the deep-S2 pocket) opened up to accommodate a bulky hydrophobic naphthalene moiety. This finding prompted us to seek an answer to the general question how the replacement of the thienopyrimidine core of our MCL-1 inhibitors would affect their efficiency and, in

Scheme 1. Structure of the Lead Compound and the Clinical Candidate S64315 Arising from Our MCL-1 Inhibitor Program



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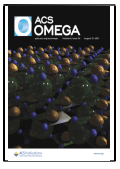


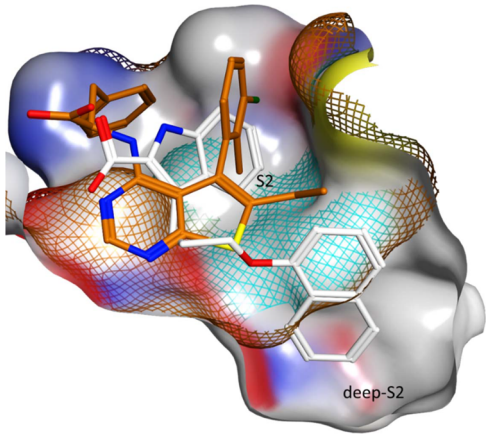


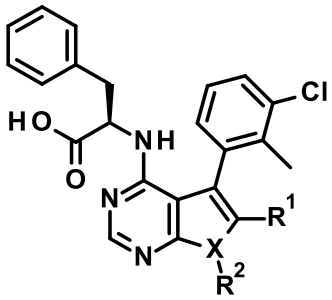
Figure 1. Overlay of the Mcl-1-bound structure of our lead-like compound (**1**, brown; PDB code: 7NB4) with a literature compound (white; PDB code: 6B4L). The binding pockets of Mcl-1 are shown in the solid surface for 6B4L and in mesh wire for our lead. Both compounds occupy the S2 pocket (cyan), whereas the naphthyl from 6B4L creates a deep-S2 pocket.

particular, to see if we could also achieve opening up of the deep-S2 pocket and gain affinity by filling it.

RESULTS AND DISCUSSION

To establish a robust comparison for the core swap experiments, we selected the lead-like thieno[2,3-*d*]pyrimidine derivative **1** as our benchmark. Due to the hindered rotation around the biaryl axis, this compound is a single diastereoisomer with a submicromolar affinity for MCL-1 in our primary FP assay, corroborated by ITC measurements. To be able to access the deep-S2 pocket, we had to replace the sulfur atom. The most trivial replacement was its swap to a nitrogen atom, leading to the pyrrolo[4,5-*b*]pyrimidine scaffold. The first analogue prepared carried a methyl group attached to the ring nitrogen. The atropoisomers of the compound (**2a** and **2b**) were separated and found to be stable under the testing conditions. During our discovery work on thieno[2,3-*d*]pyrimidines, we established a structure-based understanding of the difference in the affinities of the atropoisomers toward MCL-1. Based on this, we assigned the same relative conformation to the more active diastereoisomer, even in the absence of a direct proof, as in the thieno[2,3-*d*]pyrimidine series throughout this paper. We were happy to see that the more active stereoisomer maintained its affinity for MCL-1 at 8.7 μM, while the affinity of the other atropoisomer (**2a**) was significantly less (Table 1). Although one can assume that the more active diastereoisomer maintains the same axial chirality as observed in **1**, this has not been proven experimentally. Increasing the length of the substituent to allyl resulted in maintained affinity for the more active isomer **3b**, and interestingly, the less active form (**3a**) was only 2-fold less potent. We were interested to see the effect of variation in the R^1 substituent. Changing the ethyl group to bromine (**4a** and **4b**) had only a minor effect, leading to an increased separation of the stereoisomers' affinities. The 2.5 μM affinity of **4a** is a clear indication of the conformational flexibility of MCL-1. The introduction of the 2,2,2-trifluoroethyl substituent (**5a** and **5b**) led to very little change and an 8.5 μM affinity for the more potent isomer (**5b**). Changing the elongated allyl substituent to the bulkier isopropyl (**6a** and **6b**) was less tolerated and the compounds gave only partial

Table 1. Inhibition of MCL-1 by Compounds 1−12b



	X	R^1	R^2	FP MCL-1 K_i (μM)
1	S	Et		0.51/1.1[a]
2a	N	Et	Me	65%@50 μM
2b				8.7
3a	N	Et	allyl	18
3b				9.1
4a	N	Br	allyl	2.5
4b				66%@50 μM
5a	N	Et	trifluoroethyl	63%@50 μM
5b				8.5
6a	N	Et	*i*Pr	67%@50 μM
6b				78%@50 μM
7a	N	Et	2-butyn-4-yl	5.9
7b				0.33
8a	N	Et	Bn	6.5
8b				0.53
9a	N	Et	cyclopentylethyl	3.5
9b				0.79
10a	N	Et	1-naphthylmethyl	3.5
10b				0.26
11	N	$-(CH_2)_3-$		71%@50 μM
12a	N	$-(CH_2)_4-$		11
12b				5.9

[a] K_d measured by ITC (μM).

inhibition at the highest tested dose. On the other hand, if we attached an elongated, rigid substituent through a flexible linker (**7a** and **7b**), we observed a remarkable increase in affinity, the more active atropoisomer **7b** registering at 330 nM. We were able to cocrystallize **7b** with Mcl-1 and determine the X-ray structure of the complex (Figure 2), which confirmed the presence of the same axial chirality as in **1**.

The hypothesis of changing sulfur to nitrogen to explore the deep-S2 pocket is validated by the overlay of X-ray structures of compounds **1** and **7b** binding to Mcl-1 (Figure 2A). Not only do the bicyclic cores occupy exactly the same place, which is necessary for the sulfur-to-nitrogen swap to work, but also the alkyne motif installed at the pyrrolo nitrogen successfully opens up a deep-S2 pocket. Figure 2B illustrates the deep-S2 pocket created by the indole acid (6B4L) and by **7b**. The comparison of the protein surface shows that the deep-S2 pockets opened up by two completely different scaffolds are very similar in depth and shape. Inspection of the X-ray structure also shows that the butyne from **7b**, although near the bottom of the deep-S2 pocket, does not fill it completely.

Encouraged by the observed opening of the deep-S2 pocket by **7b** and that the end-groups of the different molecules overlay in the deep-S2 pocket, we introduced some bulkier substituents through a methylene linker onto the pyrrole ring. Our first choice, the benzyl-substituted compound (**8a** and

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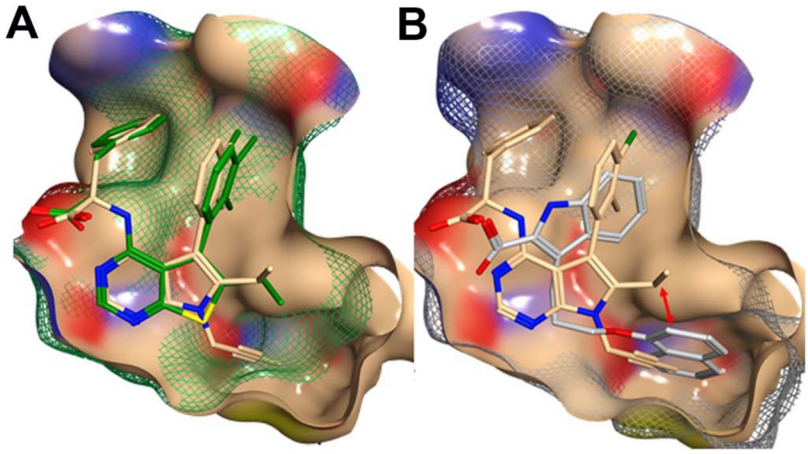


Figure 2. Comparison of the X-ray structures of the complexes of Mcl-1 and its inhibitors. (A) **7b** (beige; PDB: 7NB7) and **1** (green). (B) **7b** (beige) and literature structure 6B4L (gray). The protein surfaces are colored according to the bound ligands, respectively. Proximity of **7b** position-6 ethyl to 6B4L naphthyl is indicated by a red arrow.

8b), confirmed the hypothesis as the more active isomer (**8b**) registered at 530 nM. The less active atropoisomer (**8a**) showed a 20-fold drop in affinity, in line with our previous observations.

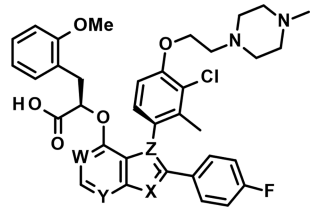
The increase in flexibility allowed the steric demand of the end-group in **9a** and **9b** to be tolerated, resulting only in a minor drop and retaining a submicromolar affinity for **9b**. The extension of the benzyl moiety to the bicyclic 1-naphthylmethyl substituent (**10a** and **10b**) was again well tolerated, resulting in a 260 nM affinity for **10b**.

While these compounds provide strong evidence of the conformational flexibility of MCL-1 and are interesting from a theoretical point of view, comparison of **7b** and **10b** highlights that they achieve the 300 nM affinity range with very different efficiency. Finally, we looked at some cyclized derivatives. In these compounds, the R^1 and R^2 substituents were replaced by a trimethylene (**11**) or tetramethylene (**12a** and **12b**) moiety. It is interesting to note that in **11**, the reduced bulk of the pyrrole substituent led to the facile interconversion of the atropoisomers in solution and we were unable to separate them, although they gave distinct chromatographic peaks. The bulkier substituent in **12**, on the other hand, allowed the separation of the atropoisomers. The affinity of these compounds was mediocre, the most potent one **12b** registering around 6 μM.

Although we could achieve improved affinity by filling the deep-S2 pocket, it required significant growth to reach 300 nM affinity. Comparing the X-ray structures with the SAR in Table 1 suggested that the 6-position of the bicyclic core (where R^1 is) may be competing against groups going into the deep-S2 pocket. Blocking position-6 is essential for obtaining the competent atropoisomer for MCL-1 binding. However, the proximity between 6-ethyl from **7b** and the naphthyl from 6B4L shown in Figure 2B made us wonder whether the pyrrolopyrimidine series designed to explore the deep-S2 pocket is limited by the necessary position of the 6-substitution. The crystallographic evidence clearly confirmed that the deep-S2 pocket can be opened by the pyrrolopyrimidine scaffold (Figure 2A). However, if this hydrophobic pocket is not filled satisfactorily due to space competition by position-6, then it is likely to incur a desolvation penalty, leading to the affinity leveling off earlier than expected. In addition, swapping in a nitrogen to the bicyclic core to enable deep-S2 exploration may also bring additional desolvation or electrostatic disadvantage. This is investigated in the following section.

Analysis of the X-ray structure of the **1**-Mcl-1 complex revealed that the heteroatoms in the thieno[2,3-*d*]pyrimidine core of **1** form no apparent interaction with the protein. Following the identification of desolvation as a potential issue with the deep-S2 pocket-accessing pyrrolopyrimidines, we explored whether removal of some of the polar heteroatoms by replacing the thienopyrimidine ring with benzofurane or indole could have a beneficial effect. To assess this, we selected compound **13** as our benchmark. **13** is an early compound from our lead optimization efforts and differs from our previous benchmark at three points: (i) it contains a fluorophenyl substituent in the 6-position that is a necessary modification to achieve high potency and activity; (ii) it has an ortho-substituent on the phenyl lactic acid moiety representing the vector needed to explore in lead optimization; (iii) it carries a piperazinoethoxy moiety on the benzene ring in the 5-position that is indispensable for cellular activity. By the selection of this benchmark, we could assess the effect of core swap both on affinity and cellular activity. The target compounds **14** and **15** were synthesized and isolated as single stereoisomers (Table 2). The 14 nM affinity of **13** for MCL-1 decreased to 820 and 47 nM for **14** and **15**, respectively.

Table 2. Inhibition of MCL-1 and Cell Killing by Compounds 13−15



ID	X	Z	Y	W	FP MCL-1 K_i (nM)	H929 MTT IC_{50} (nM)[a]
13	S	C	N	N	14	190
14	O	C	CH	CH	820	>1880
15	CH	N	CH	CH	47	>1880

[a]Measured in the presence of 10% CFS at 48 h.

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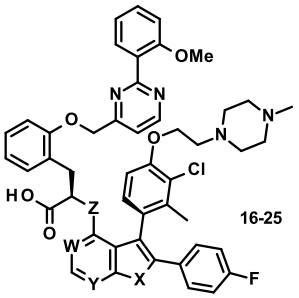
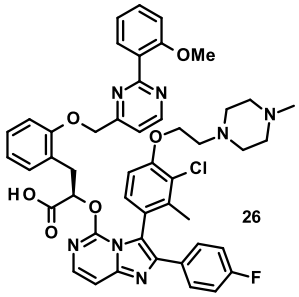
Unfortunately, the decrease in affinity was accompanied by a more than 10-fold loss of cellular activity compared to **13** (190 nM). With only these three compounds in hand, it is difficult to establish any structure−property relationship, but the complexity of the synthesis of **14** and **15** coupled with these discouraging results prompted us not to pursue the core replacement activities at this stage and only return to them once a candidate was identified.

Following the early-stage exploration of the core swap strategy with our MCL-1 inhibitors, we also looked at the replacement of the thieno[2,3-*d*]pyrimidine core once our preclinical candidate S64315 (**16a**) was identified. As an additional benchmark, we also included its amino acid analogue **16b** in our comparison. For such advanced compounds, we were able to compare affinities, cellular activities, and for the more active compounds, also their behavior in *in vivo* models (Table 3). The benchmark compounds showed high affinity (29 and 303 pM), good cellular activity (1.7 and 14 nM), and a robust *in vivo* PD response, the hydroxy acid (**16a**) being more active than the amino acid (**16b**). Replacement of the ring nitrogen in the 3-position by carbon (thieno[2,3-*d*]pyridines **17** and **18**) had only a minor effect on the *in vitro* parameters. In the case of **17**, we were able to separate the diastereoisomers and the measured properties belong to the more active one, while for the amino acid analogue, we could not separate the atropoisomers and **18** is a 7:3 mixture of diastereoisomers. Although we can assume that the axial chirality of the more active diastereoisomer **17** matches that of **16a**, it has not been proven experimentally.

Table 3. Inhibition of MCL-1, Cell Killing, and *In Vivo* PARP Activation by Compounds 16a−26



16-25



26

ID	X	Y	W	Z	QA MCL-1 K_i (nM)	H929 MTT IC_{50} (nM)[a]	PARP activation (fold)[b]
16a	S	N	N	O	0.029	1.7	285
16b	S	N	N	N	0.303	14	60
17	S	N	CH	O	0.10	9.1	12
18[c]	S	N	CH	N	0.10	11	NA
19[d]	S	CH	N	N	1.2	36	NA
20	S	CH	CH	O	1.8	25	156
21	O	CH	CH	O	1.3	47	NA
22	NMe	CH	CH	O	2.3	104	NA
23	NMe	N	N	O	0.64	32	5
24	O	N	N	O	0.036	24[e]	129
25	O	N	N	N	0.61	18	60
26				O	8.2	459	NA

[a]Measured in the presence of 10% CFS at 48 h. [b]Increase of cleaved PARP measured in AMO1 xenografted mice 16 h after i.v. bolus treatment at 12.5 mg/kg dose. [c]Present as a 7:3 mixture of atropoisomers. [d]Present as a 3:1 mixture of atropoisomers. [e]Diastereoisomers are separable by chromatography but equilibrate on the cellular experiment timescale in solution to give a 1:1 mixture of atropoisomers.

Both the measured affinity and cellular activity of **17** and **18** were alike, the former around 100 pM while the latter at 9.1 nM and 11 nM, respectively. The hydroxy acid **17** was also progressed into an *in vivo* PD experiment where we observed a 12-fold PARP activation 16 h after i.v. treatment at a dose of 12.5 mg/kg, the compound being considerably less active than **16a**. When we replaced the ring nitrogen of **16b** in the 1-position by carbon (thieno[3,2-*c*]pyridine **19**), we isolated the product again as a 3:1 mixture of atropoisomers. **19** showed a modest, 2−4 fold drop in affinity and cellular activity compared to **16b**. Removal of core nitrogens so far turned out to be deleterious, so it was interesting to test the effect when we replace both of the pyrimidine ring nitrogens by carbon (benzothiophene **20**, single more active stereoisomer). This compound had very similar affinity (1.8 nM vs 1.2 nM) and cellular activity (25 nM vs 36 nM) to **19**, corroborating the observation that the replacement of the nitrogen atom in position-3 has a more deleterious effect. We also tested **20** in the *in vivo* PD study and were delighted to see a marked effect (156-fold PARP activation.)

The next compound we prepared was the benzofurane analogue **21** (single, more active stereoisomer). The swap of the benzothiophene to benzofurane had only a marginal effect. The 1.3 nM affinity and 47 nM cellular activity of **21** were in the same range as **20**. To complete this sequence, we also prepared the indole analogue **22** (single, more active stereoisomer). For this compound, we observed a moderate, ca. 2-fold drop of on-target affinity and cellular activity (2.3 and 104 nM, respectively). Based on our previous observation, we anticipated that moving from indole to the pyrrolo[2,3-*d*]pyrimidine core (**23** single, more active stereoisomer) should improve both affinity and activity. Although we observed the anticipated amelioration, its magnitude was not marked. Compared to **16a**, **23** was about 20-fold less active. Further improvement could be anticipated by the replacement of the nitrogen in the five-membered ring by oxygen. The furo[2,3-*d*]pyrimidine analogue of our candidate **24** has a decreased atropoisomer stability, and its separated diastereoisomers equilibrate rapidly in solution to give a 1:1 mixture. **24** showed high, 36 pM affinity for MCL-1 as expected. Its cellular activity was also superior to **21** or **23** but 10-fold less than **16a** at 24 nM. Furthermore, this compound performed well in the *in vivo* PD experiment too, leading to a 129-fold PARP cleavage under the standard conditions.

We also prepared the amino acid analogue in the furo[2,3-*d*]pyrimidine series. We could separate the diastereoisomers and they were stable in solution. **25** (single, more active stereoisomer) showed decreased affinity (610 pM vs 36 pM), in line with the observations for the **16a**−**16b** compound pair, and maintained cellular activity. This compound was also tested *in vivo*. The observed PARP activation by the amino acid derivative was about 2-fold less than for the hydroxy acid analogue (60-fold vs 129-fold). Finally, we prepared a core swap analogue of **16a** carrying a nitrogen atom in the bridgehead position. The imidazo[1,2-*c*]pyrimidine analogue **26**, isolated as a mixture of atropoisomers, showed a 200-fold drop both in affinity and cellular activity compared to **16a**, registering at 8.2 nM vs 29 pM and 459 nM vs 1.7 nM, respectively.

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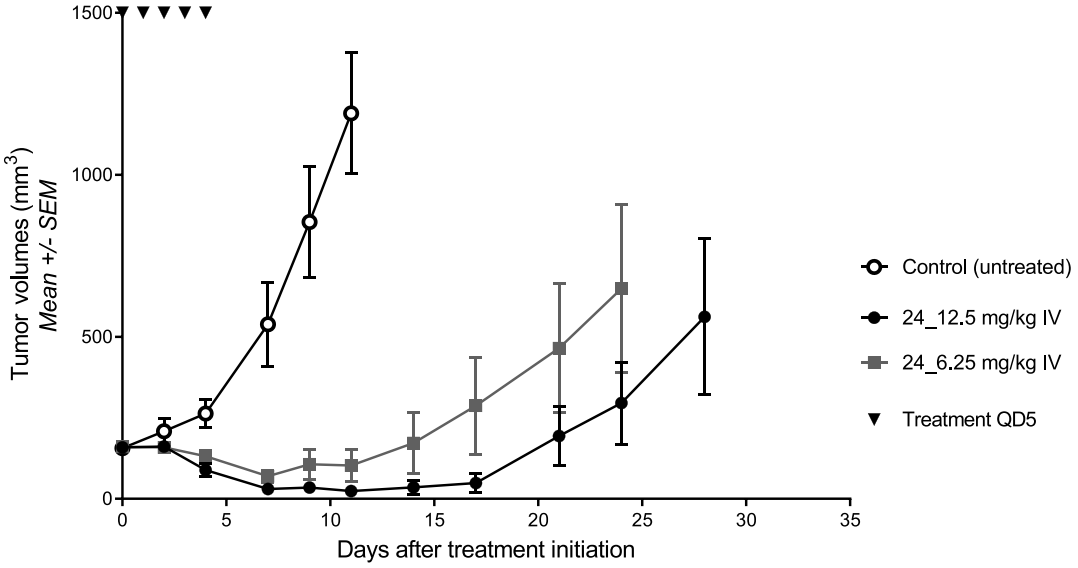

Figure 3. Tumor regression induced by the MCL-1 inhibitors **24** in AMO-1 xenografted mice following i.v. administration (QD5).

One of the more promising core swap analogues, **24**, was also assessed for its ability to induce tumor regression in mice with a human multiple myeloma cell line xenograft (AMO-1). Animals were treated at doses of 6.25 and 12.5 mg/kg i.v. daily for 5 days using freshly prepared solutions. While the compound is showing rapid antitumor activity in a dose−response manner, with complete regression observed in 6/8 animals treated at the dose of 12.5 mg/kg (Figure 3 and Table 4), this response was outperformed by compound **16a** (a.k.a. S64315/MIK665) compared in the same setting (data already published in ref 7a). Although inferior to **16a**, the observed *in vivo* efficacy of **24** can in part be attributed to its in vivo PK characteristics. At the 12.5 mg/kg dose, both its AUC and clearance were superior to **16a** (55,956 ng/mL·h and 2.5 mL/min·kg vs 33,975 ng/mL·h and 6.0 mL/min·kg, respectively).

Table 4. Tumor Growth Inhibition Data for Compounds Tested in the AMO-1 Efficacy Model (QD5, i.v. Bolus Treatment in Each Case)

compound	dose (mpk)	%TGI (day)	%TGI max (day)	time to reach 500 mm^3 (median of the group)
24	6.25	103.5 (D14)	122.7 (d7)	28
24	12.5	107.7 (D14)	184.8 (d2)	37

CONCLUSIONS

We explored the core replacement of our thieno[2,3-*d*]pyrimidine-based selective MCL-1 inhibitors in the hit-to-lead phase. We observed that the target protein was able to accommodate alternate bi- and tricyclic cores, and even substituents that were projected toward the bottom of the so-called S2 pocket, through its conformational flexibility. In general, the thieno[2,3-*d*]pyrimidine derivatives were superior both with respect to their affinity and also cellular activity compared to the studied analogues. A systematic modification of the central core was also repeated for the candidate. Variation of the nature and positioning of the heteroatoms in the 5 + 6 bicyclic core, while keeping the rest of the molecule unchanged, showed the different contribution of these elements to the affinity and cellular activity of our MCL-1 inhibitors. All the tested modifications led to a deterioration of properties. It is also interesting to note that the nature of the core had an influence on the stereochemical integrity of the molecule.

EXPERIMENTAL SECTION

MTT Cell Viability Assay of NCI H929 Cell Line. NCI-H929 cells (purchased from ATCC) were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated FBS, 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 10 mM Hepes (pH = 7.4) at 37 °C in 5% CO_2/95% air. Cells were grown at 37 °C in a humidified atmosphere with 5% CO_2. Cell viability was measured using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) colorimetric assay. Cells were seeded in 96-well microplates at a density to maintain control (untreated) cells in the exponential phase of growth during the entire experiment. Cells were incubated with compounds for 48 h followed by incubation with 1 mg/mL MTT for 4 h at 37 °C. Lysis buffer (20% SDS) was added and absorbance was measured at 540 nm 18 h later. All experiments were repeated at least two times in triplicates. The percentage of viable cells was calculated and averaged for each well, % growth = (O.D. treated cells/O.D. control cells) × 100, and IC_{50}, the concentration needed to reduce the optical density by 50%, was calculated by a linear regression performed on the linear zone of the dose−response curve.

Animals and Treatment Groups. Healthy female CB-17 SCID mice, 6−7 weeks old, were obtained from Charles Rivers. Mice were kept at the Servier Institute-specified pathogen-free animal area for mouse experimental purpose (facility license nos. B78-100-2 and A21231011EA). The care and use of animals used in this facility strictly applied the European and national regulation for the protection of vertebrate animals used for experimental and other scientific purposes (Directive 86/609 and 2003/65).

SCID mice were inoculated with 0.1 mL volume containing 5×10^6 cells subcutaneously in the right flank. AMO-1 cells were resuspended in a 50:50 mixture of growth media and Matrigel (BD Biosciences). The width and length of the tumor were measured two to three times a week using an electronic caliper. Tumor volume was calculated using the formula:

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length × width^2/2. When the tumor volume reached approximately 200 mm^3, mice were randomized in different groups before treatment (n = 3 for pharmacodynamic studies and n = 8 for efficacy studies). Compounds were formulated in 20% HPbCD (Fisher Scientific)/HCl (25 mM) and administrated with the doses and schedules described in the figure and table. At the first measurement higher than 2000 mm^3, mice were sacrificed. Once at least one mouse in a group had to be sacrificed for ethical reasons, the mean of tumor volume was not further represented on the graph.

Tumor growth inhibition (TGI) was calculated at the last day of the control group and at the greatest response (TGI_{max}) using the following equation:

$$1 - ((\text{median of treated at day } x - \text{median of treated at day } 0)/(\text{median of control at day } x - \text{median of control at day } 0)) \times 100$$

where day x is the day maximum where the number of animals per group in the control group is sufficient to calculate the TGI(%).

The tumor growth delay (TGD) was expressed as a percentage by which the treated group is delayed in attaining an arbitrary median volume of 500 mm^3 relative to the control group. It was determined using the following formula:

$$((\text{median times of treated to reach } 1000\ \text{mm}^3 - \text{median times of control to reach } 1000\ \text{mm}^3)/\text{median times of control to reach } 1000\ \text{mm}^3) \times 100$$

A complete tumor regression response was considered for the population with 25 mm^3 tumors for at least three consecutive measurements.

General Synthetic Remarks. All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying.

The reactions were monitored using LCMS and GCMS instruments. Analytical LC−MS: Agilent HP1200 LC with Agilent 6140 quadrupole MS, operating in positive or negative ion electrospray ionization mode. Molecular weight scan range was 100 to 1350 m/z. Parallel UV detection was done at 210 and 254 nm. Samples were supplied as a 1 mM solution in MeCN or in THF/water (1:1) with 5 μL loop injection. LCMS analyses were performed on two instruments, one of which was operated with basic and the other with acidic eluents.

Basic LCMS: Gemini-NX, 3 μm, C18, 50 mm × 3.00 mm i.d. column at 23 °C, at a flow rate of 1 mL min^{-1} using 5 mM aq. NH_4HCO_3 solution and MeCN as eluents.

Acidic LCMS: ZORBAX Eclipse XDB-C18, 1.8 μm, 50 mm × 4.6 mm i.d. column at 40 °C, at a flow rate of 1 mL min^{-1} using water and MeCN as eluents, both containing 0.02% (v/v) formic acid.

Combination gas chromatography and low-resolution mass spectrometry were performed on an Agilent 6850 gas chromatograph and Agilent 5975C mass spectrometer using a 15 m × 0.25 mm column with 0.25 μm HP-5MS coating and helium as a carrier gas. Ion source: EI$^+$, 70 eV; 230 °C; quadrupole: 150 °C; interface: 300 °C.

Flash chromatography was performed on an ISCO CombiFlash Rf 200i with pre-packed silica-gel cartridges (RediSep R_f Gold High Performance).

Preparative HPLC purifications were performed on an Armen Spot Liquid Chromatography system with a Gemini-NX 10 μm C18, 250 mm × 50 mm i.d. column running at a flow rate of 118 mL min^{-1} with UV diode array detection (210−400 nm).

^{1}H NMR and proton-decoupled ^{13}C NMR measurements were performed on a Bruker Avance III 500 MHz spectrometer and Bruker Avance III 400 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as a solvent. ^{1}H and ^{13}C NMR data are in the form of delta values, given in parts per million (ppm), using the residual peak of the solvent as the internal standard (DMSO-d_6: 2.50 ppm (^{1}H)/39.5 ppm (^{13}C); $CDCl_3$: 7.26 ppm (^{1}H)/77.0 ppm (^{13}C)). Splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sp (septet), m (multiplet), br s (broad singlet), dd (doublet of doublets), td (triplet of doublets), and qd (quartet of doublets). In some cases, two sets of signals appear in the spectra due to hindered rotation.

HRMS were determined on a Shimadzu IT-TOF; ion source temperature, 200 °C; ESI +/−; ionization voltage: (±)4.5 kV. Mass resolution min., 10,000.

All obtained products had an LC purity above 95% (for LC traces, see the Supporting Information) that was corroborated by their ^{1}H NMR spectrum, unless specifically mentioned otherwise.

General Procedure 1: Nucleophilic Substitution with Amino Acid. The appropriate 4-chloro-pyrrolo[2,3-*d*]-pyrimidine derivative (1 equiv), the appropriate amino acid derivative (3 equiv), DMSO (10 mL/mmol), and K_2CO_3 (4 equiv) were stirred at 150 °C until no further conversion was observed. The mixture was acidified with 1 M aq. HCl solution, and then the precipitate was filtered and oven-dried at 40 °C *in vacuo*. Purified via preparative reversed-phase chromatography using 25 mM aqueous NH_4HCO_3 solution and MeCN as eluents.

General Procedure 2: Suzuki Coupling on Bromo Pyrrolopyrimidines. The appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative (1 equiv), the appropriate boronic acid derivative (3 equiv), TBAOH (3 equiv), $Pd(OAc)_2$ (0.2 equiv), $PCy_3{\cdot}HBF_4$ (0.4 equiv), and DME (3.5 mL/mmol) were stirred under a N_2 atmosphere at 120 °C in an MW reactor until no further conversion was observed. Then, the mixture was filtered through Celite and washed with MTBE and water. The layers of the filtrate were separated, and the aqueous layer was washed with MTBE. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via preparative reversed-phase chromatography using 40 mM aq. NH_4OAc (pH = 4) solution and MeCN and then 0.1% aq. TFA solution and MeCN as eluents.

General Procedure 3: Mitsunobu Reaction on Pyrrolo[2,3-d]pyrimidine Derivatives. **R1a** (1.0 equiv), the appropriate alcohol (2.0 equiv), and PPh_3 (2.0 equiv) were dissolved in 10 mL/mmol dry THF under a N_2 atmosphere and cooled to 0 °C. Then, 2.0 equiv of DEAD (40% in toluene) was added dropwise. The mixture was stirred at 50 °C for 3−24 h. Then, the volatiles were removed under reduced pressure and the residue was purified via flash chromatography using either heptane and DCM or heptane and EtOAc as eluents to obtain

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the appropriate 5-bromo-4-chloro-6-ethyl-7-alkyl-pyrrolo[2,3-*d*]pyrimidine derivative.

***R1a**: 5-Bromo-4-chloro-6-ethyl-7H-pyrrolo[2,3-d]-pyrimidine. Step A: 5-Bromo-6-ethyl-7H-pyrrolo[2,3-d]-pyrimidin-4-ol.* 6-Ethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (1.63 g, 10.0 mmol) was dissolved in 20 mL of DMF and cooled to 0 °C. One milliliter of Br_2 (20.0 mmol) was added and the mixture was stirred at rt for 2 h. Then, it was diluted with 20 mL of water and 20 mL of sat. aq. $Na_2S_2O_3$ solution and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure to obtain 2.01 g of 5-bromo-6-ethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (8.30 mmol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.12 (s, 1H), 11.83 (s, 1H), 7.80 (d, J = 3.0 Hz, 1H), 2.60 (q, J = 7.3 Hz, 2H), 1.16 (t, J = 7.3 Hz, H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 157.1, 146.7, 143.5, 133.8, 105.6, 86.7, 18.8, 13.3. LRMS calculated for $C_8H_8BrN_3O$: 241.0; found: 241.8 (M + H).

Step B: 5-Bromo-4-chloro-6-ethyl-7H-pyrrolo[2,3-d]-pyrimidine. 5-Bromo-6-ethyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (1.93 g, 8.00 mmol), $POCl_3$ (4.5 mL, 48.0 mmol), and *N*,*N*-dimethylaniline (1 mL, 8.00 mmol) were placed in a flask and stirred at 100 °C for 30 min. The mixture was then poured onto ice-water and the precipitated material was collected by filtration to obtain 1.86 g of **R1a** (6.00 mmol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.9 (s, 1H), 8.56 (s, 1H), 2.78 (q, J = 7.6 Hz, 2H), 1.37 (t, J = 7.6 Hz, H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 150.8, 150.0, 148.6, 142.6, 114.2, 83.4, 19.7, 12.8. LRMS calculated for $C_8H_7BrClN_3$: 259.0; found: 260.0 (M + H).

***R1b**: 3-Bromo-2-(4-fluorophenyl)benzofuran-4-ol. Step A: 2-(4-Fluorophenyl)-1-benzofuran-4-ol.* 2-Bromoresorcinol (2.37 g, 12.5 mmol) was dissolved in 30 mL of dry THF under a N_2 atmosphere, and then 4.17 mL of TEA (30.0 mmol) and 1.92 mL of AcCl (27.0 mmol) were added. After stirring the mixture for 5 min, 2.40 g of 1-ethynyl-4-fluorobenzene (20.0 mmol), 561 mg of $Pd(OAc)_2$ (2.50 mmol), 1.45 g of $P^tBu_3{\cdot}HBF_4$ (5.00 mmol), 476 mg of CuI (2.50 mmol), and 10 mL of dry DIPA were added and the mixture was stirred at 80 °C until no further conversion was observed. Then, 2 g of $LiOH{\cdot}H_2O$ and 10 mL of water were added and the mixture was stirred at 80 °C for 2 days. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to give 992 mg of 2-(4-fluorophenyl)-1-benzofuran-4-ol (4.35 mmol, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.00 (s, 1H), 7.95−7.88 (m, 2H), 7.37 (s, 1H), 7.34−7.27 (m, 2H), 7.13−7.07 (m, 1H), 7.06−7.02 (m, 1H), 6.63 (dd, J = 7.7, 0.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.1, 155.8, 152.3, 151.3, 126.6, 126.5, 125.4, 118.2, 116.0, 108.0, 102.2, 99.5.

Step B: 2-(4-Fluorophenyl)-1-benzofuran-4-yl Acetate. 2-(4-Fluorophenyl)-1-benzofuran-4-ol (456 mg, 2.00 mmol) was dissolved in 10 mL of dry THF, and then 156 μL of AcCl (2.20 mmol) and 306 μL of TEA (2.20 mmol) were added carefully. The mixture was stirred under a N_2 atmosphere for 10 min to reach complete conversion. The solvent was then removed under reduced pressure, and the residue was purified via flash chromatography using heptane and EtOAc as eluents to obtain 350 mg of 2-(4-fluorophenyl)-1-benzofuran-4-yl acetate (1.30 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86−7.79 (m, 2H), 7.41 (d, J = 8.2 Hz, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.18−7.10 (m, 2H), 7.01 (d, J = 7.9 Hz, 1H), 6.85 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 168.8, 163.0, 156.0, 155.2, 143.4, 126.9, 126.3, 124.4, 122.9, 115.9, 115.4, 109.0, 98.2, 21.0.

Step C: 3-Bromo-2-(4-fluorophenyl)-1-benzofuran-4-yl Acetate. 2-(4-Fluorophenyl)-1-benzofuran-4-yl acetate (688 mg, 2.54 mmol) and NBS (589 mg, 3.31 mmol) were dissolved in 20 mL of MeCN and stirred at 70 °C for 30 min to reach complete conversion. The solvent was then removed under reduced pressure, and the residue was purified via flash chromatography using heptane and EtOAc as eluents to obtain 759 mg of 3-bromo-2-(4-fluorophenyl)-1-benzofuran-4-yl acetate (2.17 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.13−8.07 (m, 2H), 7.42 (dd, J = 8.4, 0.7 Hz, 1H), 7.36−7.30 (m, 1H), 7.22−7.14 (m, 2H), 7.00 (dd, J = 7.8, 0.7 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.7, 163.1, 154.4, 150.3, 143.5, 129.2, 125.5, 125.3, 121.4, 117.2, 115.7, 109.6, 21.0.

Step D: 3-Bromo-2-(4-fluorophenyl)-1-benzofuran-4-ol. 3-Bromo-2-(4-fluorophenyl)-1-benzofuran-4-yl acetate (551 mg, 1.58 mmol), 1 M NaOEt (1.5 mL) in EtOH solution, and EtOH (15 mL) were stirred at rt under a N_2 atmosphere for 10 min to reach complete conversion. The mixture was diluted with 50 mL of aq. cc. NH_4Cl solution and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated to give 486 mg of **R1b** (1.58 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.17 (br s, 1H), 8.13−8.06 (m, 2H), 7.43−7.35 (m, 2H), 7.21−7.15 (m, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.0, 154.3, 152.1, 147.3, 128.7, 126.6, 125.5, 116.1, 115.8, 108.9, 102.4, 90.9. LRMS calculated for $C_8H_7BrClN_3$: 306.0; found: 307.0 (M + H).

***R1c**: 3-Bromo-4-chloro-2-(4-fluorophenyl)thieno[2,3-b]-pyridine. Step A: 2-Chloro-3-[2-(4-fluorophenyl)ethynyl]-pyridine.* 3-Bromo-2-chloro-pyridine (3.85 g, 20.0 mmol), CuI (230 mg, 1.20 mmol), and $Pd(PPh_3)_2Cl_2$ (420 mg, 0.60 mmol) were stirred in 40 mL of dry TEA for 10 min, then 2.64 g of 1-ethynyl-4-fluoro-benzene (22.0 mmol) was added, and the solution was stirred at 100 °C overnight. Then, the mixture was cooled to rt and diluted with water, and then it was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 2.99 g of 2-chloro-3-[2-(4-fluorophenyl)ethynyl]-pyridine (12.9 mmol, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.44 (dd, J = 4.9, 1.9 Hz, 1H), 8.14 (dd, J = 7.7, 1.9 Hz, 1H), 7.70−7.65 (m, 2H), 7.51 (dd, J = 7.7, 4.9 Hz, 1H), 7.36−7.31 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.6, 150.8, 149.2, 142.1, 134.0, 123.1, 119.1, 117.8, 116.3, 95.2, 84.0. HRMS calculated for $C_{13}H_7ClFN$: 231.0251; found: 232.0310 (M + H).

Step B: 2-(4-Fluorophenyl)thieno[2,3-b]pyridine. 2-Chloro-3-[2-(4-fluorophenyl)ethynyl]pyridine (2.95 g, 12.7 mmol) and Na_2S (3.97 g, 51.0 mmol) were placed in a 250 mL flask. DMF (120 mL) was added and the mixture was stirred at 130 °C for 2 h. Then, the mixture was cooled to rt and diluted with water, and then it was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and

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filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.94 g of 2-(4-fluorophenyl)thieno[2,3-*b*]pyridine (8.46 mmol, 67%). LRMS calculated for $C_{13}H_8FNS$: 229.0; found: 230.2 (M + H).

Step C: 4-Chloro-2-(4-fluorophenyl)thieno[2,3-b]pyridine. 2-(4-Fluorophenyl)thieno[2,3-*b*]pyridine (1.94 g, 8.40 mmol) was dissolved in 50 mL of DCM and cooled to 0 °C. *m*CPBA (3.12 g, 12.6 mmol) was added portionwise and stirred at rt for 6 h. Then, it was concentrated under reduced pressure and purified via flash chromatography using DCM and MeOH as eluents. The obtained intermediate was dissolved in 50 mL of $CHCl_3$, then 15.7 mL of $POCl_3$ (25.8 g, 168 mmol) was added, and the mixture was stirred at a reflux temperature for 3 h. Then, it was cooled to rt, ice and sat. aq. $NaHCO_3$ solution was added, and it was extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using DCM and MeOH as eluents to obtain 1.18 g of 4-chloro-2-(4-fluorophenyl)thieno[2,3-*b*]pyridine (4.48 mmol, 53%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.50 (d, J = 5.2 Hz, 1H), 7.98−7.94 (m, 2H), 7.91 (s, 1H), 7.62 (d, J = 5.2 Hz, 1H), 7.39−7.34 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.8, 160.9, 147.4, 143.4, 137.0, 132.5, 129.2, 128.8, 120.7, 116.4, 115.3. HRMS calculated for $C_{13}H_7ClFNS$: 262.9972; found: 264.0047 (M + H).

Step D: 3-Bromo-4-chloro-2-(4-fluorophenyl)thieno[2,3-b]pyridine. 4-Chloro-2-(4-fluorophenyl)thieno[2,3-*b*]pyridine (1.46 g, 5.50 mmol) was dissolved in 20 mL of $CHCl_3$, and then 520 mg of K_2HPO_4 (3.00 mmol), 460 g of $NaHCO_3$ (5.50 mmol), and 1.12 g of $MgSO_4$ (9.20 mmol) were added. Then, 1.15 g of Br_2 (7.20 mmol) was added dropwise. Next, the mixture was stirred overnight at a reflux temperature. Then, it was cooled to rt and filtered. The filtrate was concentrated under reduced pressure and purified via flash chromatography using DCM and MeOH as eluents to obtain 1.67 g of **R1c** (4.89 mmol, 89%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (d, J = 5.1 Hz, 1H), 7.79−7.74 (m, 2H), 7.71 (d, J = 5.1 Hz, 1H), 7.46−7.74 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.7, 159.6, 147.9, 139.0, 138.1, 132.3, 128.2, 127.0, 123.1, 116.7, 100.7. HRMS calculated for $C_{13}H_6BrClFNS$: 340.9077; found: 341.9164 (M + H).

***R1d**: 5-Bromo-4-chloro-6-(4-fluorophenyl)furo[2,3-d]pyrimidine. Step A: 6-(4-Fluorophenyl)-3H-furo[2,3-d]pyrimidin-4-one.* 2-Amino-5-(4-fluorophenyl)furan-3-carbonitrile (1290 mg, 6.38 mmol) and acetic formic anhydride (25.5 mL) were placed in a flask and stirred at rt for 30 min. Then, the volatiles were evaporated under reduced pressure. The residue was dissolved in 51 mL of AcOH and heated in a MW reactor at 160 °C for 30 min and then at 180 °C for 15 min. Then, the mixture was cooled to rt, and the precipitate was filtered to obtain 960 mg of 6-(4-fluorophenyl)-3*H*-furo[2,3-*d*]pyrimidin-4-one (4.17 mmol, 65%). ^{1}H NMR (500 MHz, DMSO-d_6): 12.66 (br s, 1H), 8.15 (s, 1H), 7.93 (m, 2H), 7.47 (s, 1H), 7.36−7.29 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 164.4, 162.2, 158.2, 150.4, 146.7, 126.5, 125.6, 116.2, 109.5, 101.1.

Step B: 5-Bromo-4-chloro-6-(4-fluorophenyl)furo[2,3-d]pyrimidine. 6-(4-Fluorophenyl)-3*H*-furo[2,3-*d*]pyrimidin-4-one (1.70 g, 7.40 mmol) was stirred in 74 mL of AcOH, and then 1.18 g of Br_2 (7.40 mmol) was added. The mixture was stirred at 35 °C for 24 h, then an additional 745 mg of Br_2 was added, and the mixture was stirred for 4 days. Then, it was filtered, and the filtrate was concentrated under reduced pressure. The residue was digerated with 15 mL of MeOH, filtered, and dried in air. The obtained intermediate was dissolved in 12.7 mL of $POCl_3$ (136 mmol), 690 μL of *N*,*N*-dimethylaniline (5.44 mmol) was added, and the mixture was stirred at 110 °C for 20 min. Then, it was cooled to 0 °C and poured into ice-water. The crude product was isolated by filtration and then purified via flash chromatography using heptane and EtOAc as eluents to obtain 800 mg of **R1d** (2.43 mmol, 33%). ^{1}H NMR (400 MHz, DMSO-d_6): 8.87 (s, 1H), 8.20−8.12 (m, 2H), 7.52−7.45 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 164.5, 161.9, 153.5, 151.6, 150.3, 130.0, 123.6, 116.4.

***R2a**: Ethyl (2R)-2-Hydroxy-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoate. Step A: Ethyl (2R)-2-Acetoxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy]phenyl]propanoate.* Ethyl (2*R*)-2-acetoxy-3-(2-hydroxyphenyl)propanoate[7a] (30.3 g, 120 mmol), [2-(2-methoxyphenyl)pyrimidin-4-yl]methanol[7a] (38.9 g, 180 mmol), and PPh_3 (47.2 g, 180 mmol) were dissolved in 120 mL of dry toluene, and then 82 mL of DEAD (180 mmol, 40% in toluene) was added. The mixture was stirred at 50 °C under a N_2 atmosphere for 1 h. The volatiles were evaporated under reduced pressure. Then, 300 mL of Et_2O was added, the mixture was sonicated, and the formed PPh_3O precipitate was filtered off and washed with Et_2O. The filtrate was concentrated under reduced pressure, and then the residue was purified via flash chromatography using DCM and MeOH as eluents to obtain 32.0 g of ethyl (2*R*)-2-acetoxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoate (71.0 mmol, 59.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.94 (d, J = 5.2 Hz, 1H), 7.59 (d, J = 5.2 Hz, 1H), 7.56−7.53 (m, 1H), 7.50−7.44 (m, 1H), 7.29−7.21 (m, 2H), 7.18−7.14 (m, 1H), 7.11−7.03 (m, 2H), 6.98−6.92 (m, 1H), 5.27 (d, J = 3.0 Hz, 2H), 5.17 (dd, J = 8.6, 5.4 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 3.77 (s, 3H), 3.33−3.27 (m, 1H), 3.10 (dd, J = 13.8, 8.6 Hz, 1H), 2.00 (s, 3H), 1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 158.2, 131.8, 131.5, 131.3, 129.1, 121.5, 120.6, 115.9, 112.7, 112.5, 72.0, 69.5, 61.2, 56.1, 32.1, 20.7, 14.2. HRMS calculated for $C_{25}H_{26}N_2O_6$: 450.1791; found: 451.1862 (M + H).

Step B: Ethyl (2R)-2-Hydroxy-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoate. To a suspension of 620 mg of ethyl 2-acetoxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoate (1.38 mmol, 1.0 equiv) in 6 mL of EtOH was added 0.1 mL of NaOEt (1.0 M solution in EtOH, 0.100 mmol), and it was stirred at rt overnight. Water (18 mL) was added, and then the formed precipitate was filtered and purified via flash chromatography using DCM and MeOH as eluents to obtain 484 mg of **R2a** (1.185 mmol, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.98 (d, J = 5.1 Hz, 1H), 7.60 (d, J = 5.1 Hz, 1H), 7.56−7.53 (m, 1H), 7.49−7.44 (m, 1H), 7.23−7.18 (m, 2H), 7.17−7.14 (m, 1H), 7.08−7.03 (m, 2H), 6.93−6.88 (m, 1H), 5.53 (d, J = 6.6 HZ, 1H), 5.25 (d, J = 2.7 Hz, 1H), 4.37−4.31 (m, 1H), 4.09−4.01 (m, 2H), 3.15 (dd, J = 13.4, 5.5 Hz, 1H), 2.86 (dd, J = 13.4, 8.4 Hz, 1H), 1.11 (t, J =, 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 173.9, 166.0, 164.8, 157.8, 157.2, 155.6, 131.5, 131.0, 130.9, 128.4, 127.9, 125.8, 120.8, 120.2, 115.5, 112.2, 111.8, 69.9, 69.0, 60.0, 55.7,

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35.5, 14.1. HRMS calculated for $C_{23}H_{24}N_2O_5$: 408.1685; found: 409.1757 (M + H).

R2b: *Ethyl (2S)-2-Hydroxy-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoate.* **R2b** was synthesized starting from ethyl (2*S*)-2-acetoxy-3-(2-hydroxyphenyl)propanoate[7a] using steps A and B of **R2a**.

R2c: *(2R)-2-Amino-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoic Acid. Step A: Ethyl (2R)-2-Amino-3-(2-hydroxyphenyl)propanoate.* (2*R*)-2-Amino-3-(2-hydroxyphenyl)propanoic acid hydrochloride (653 mg, 3.00 mmol) was dissolved in 6 mL of HCl solution (1.25 M in EtOH, 7.50 mmol) and stirred at rt for 24 h. Then, the mixture was carefully diluted with 10% aq. $NaHCO_3$ solution and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure to obtain 165 mg of ethyl (2*R*)-2-amino-3-(2-hydroxyphenyl)propanoate (0.79 mmol, 26%). The product should be stored in the freezer. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.05−6.99 (m, 1H), 6.99−6.95 (m, 1H), 6.74−6.69 (m, 1H), 6.69−6.63 (m, 1H), 4.02 (q, J = 7.3 Hz, 2H), 3.65 (dd, J = 7.4, 4.8 Hz, 1H), 2.84 (dd, J = 13.7, 4.8 Hz, 1H), 2.78 (dd, J = 13.7, 7.4 Hz, 1H), 1.12 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 174.2, 156.4, 131.3, 127.8, 124.5, 118.4, 116.0, 60.2, 54.1, 37.2, 14.0. HRMS calculated for $C_{11}H_{15}NO_3$: 209.1052; found: 210.1128 (M + H).

Step B: Ethyl (2R)-2-Amino-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoate. Ethyl (2*R*)-2-amino-3-(2-hydroxyphenyl)propanoate (3.96 g, 18.9 mmol) was dissolved in 200 mL of dry toluene, then 5.69 g of PPh_3 (21.7 mmol) and 4.69 g of [2-(2-methoxyphenyl)pyrimidin-4-yl]methanol[7a] (21.7 mmol) were added, and the mixture was heated to 35 °C. Then, 5.00 g of DTBAD (21.7 mmol) was added, and the mixture was stirred at 45 °C for 3 h. Next, the mixture was concentrated under reduced pressure and purified via flash chromatography using EtOAc and MeOH as eluents to obtain 1.51 g of ethyl (2*R*)-2-amino-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoate (3.75 mmol, 20%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.92 (d, J = 5.1 Hz, 1H), 7.61 (d, J = 5.1 Hz, 1H), 7.55 (dd, J = 7.5, 1.8 Hz, 1H), 7.49−7.45 (m, 1H), 7.23−7.19 (m, 1H), 7.19−7.14 (m, 2H), 7.08−7.01 (m, 2H), 6.91 (td, J = 7.4, 0.9 Hz, 1H), 5.27 (d, J = 14.9 Hz, 1H), 5.23 (d, J = 14.9 Hz, 1H), 4.01 (q, J = 7.3 Hz, 2H), 3.76 (s, 3H), 3.68 (dd, J = 6.8, 0.9 Hz, 1H), 3.08 (br s, 2H), 3.03 (dd, J = 13.0, 6.7 Hz, 1H), 2.83 (dd, J = 13.0, 7.8 Hz, 1H), 1.07 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 158.6, 131.8, 131.5, 131.3, 128.3, 120.6, 116.1, 116.0, 112.7, 112.3, 69.5, 60.3, 56.2, 54.8, 36.7, 14.5. HRMS calculated for $C_{23}H_{25}N_3O_4$: 407.1845; found: 408.1928 (M + H).

Step C: (2R)-2-Amino-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoic Acid. Ethyl (2*R*)-2-amino-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy]phenyl]-propanoate (3.20 g, 7.85 mmol) was dissolved in 10 mL of THF, then 10 mL of water and 420 mg of $LiOH{\cdot}H_2O$ (10 mmol) were added, and the mixture was stirred at rt until the hydrolysis was complete. Then, it was diluted with water and neutralized with 2 M aq. HCl solution. The formed precipitate was filtered, washed with water, and dried to obtain 2.85 g of **R2c** (7.54 mmol, 96%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.88 (d, J = 5.1 Hz, 1H), 7.82 (d, J = 5.1 Hz, 1H), 7.54 (dd, J = 7.6, 1.7 Hz, 1H), 7.49−7.44 (m, 1H), 7.27 (dd, J = 7.6, 1.7 Hz, 1H), 7.23 (td, J = 7.6, 1.7 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.08−7.02 (m, 2H), 6.93 (t, J = 7.4 Hz, 1H), 5.26 (s, 2H), 3.76 (s, 3H), 3.59 (dd, J = 9.5, 4.1 Hz, 1H), 3.49 (dd, J = 14.2, 4.0 Hz, 1H), 2.83 (dd, J = 14.2, 9.8 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.1, 165.1, 158.4, 157.7, 156.3, 131.6, 131.5, 131.3, 128.6, 126.5, 121.5, 120.6, 116.4, 112.7, 112.4, 69.4, 56.2, 54.7, 32.9. HRMS calculated for $C_{21}H_{21}N_3O_4$: 379.1532; found: 380.1610 (M + H).

R3: *2-(3-Chloro-2-methyl-phenyl)-5,5-dimethyl-1,3,2-dioxaborinane.* (3-Chloro-2-methylphenyl)boronic acid (4.94 g, 29.0 mmol) and neopentyl-glycol (3.021 g, 29.0 mmol) were dissolved in 145 mL of 2-Me-THF and then stirred at rt in the presence of 100 mg of Amberlite 15H$^+$ ionic exchange resin (dried with toluene) for 4 h. The mixture was then filtered through Celite and washed with 2-Me-THF. The filtrate was concentrated under reduced pressure to obtain 6.47 g of **R3** (27.3 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (dd, J = 7.8, 0.9 Hz, 1H), 7.37 (dd, J = 7.8, 0.9 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 3.78 (s, 4H), 2.56 (s, 3H), 1.04 (s, 6H).

*(2R)-2-[[(5S$_a$)-5-(3-Chloro-2-methyl-phenyl)-6-ethyl-thieno[2,3-d]pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid (**1**).* **1** was prepared according to the published procedure.[8]

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**2a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**2b**). Step A: 5-Bromo-4-chloro-6-ethyl-7-methyl-pyrrolo[2,3-d]-pyrimidine.* **R1a** (1.303 g, 5.00 mmol) was dissolved in 20 mL of dry THF, and then 0.41 mL of MeOH was added under a N_2 atmosphere. Then, 10 mL of CMBP solution (10 mmol, 1.0 M in toluene) was added dropwise. The mixture was stirred at rt overnight. Then, the volatiles were removed under reduced pressure and the residue was purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.28 g of 5-bromo-4-chloro-6-ethyl-7-methyl-pyrrolo[2,3-*d*]pyrimidine (4.67 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.57 (s, 1H), 3.84, (s, 3H), 2.91 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.6, 150.4, 149.2, 142.1, 115.3, 85.7, 19.3, 13.2. LRMS calculated for $C_9H_9BrClN_3$: 273.0; found: 274.0 (M + H).

Step B: (2R)-2-[[5-Bromo-6-ethyl-7-methyl-pyrrolo[2,3-d]-pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.21 g of 5-bromo-4-chloro-6-ethyl-7-methyl-pyrrolo[2,3-*d*]pyrimidine (4.41 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 1.74 g of (2*R*)-2-[[5-bromo-6-ethyl-7-methyl-pyrrolo[2,3-*d*]-pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (4.06 mmol, 92%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.05 (br s, 1H), 8.17 (s, 1H), 7.32−7.25 (m, 2H), 7.25−7.18 (m, 3H), 6.32 (d, J = 7.5 Hz, 1H), 5.00−4.94 (m, 1H), 3.68, (s, 3H), 3.29 (dd, J = 13.9, 4.8 Hz, 1H), 3.18 (dd, J = 13.9, 7.0 Hz, 1H), 2.75 (q, J = 7.6 Hz, 2H), 1.13 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.0, 153.9, 151.0, 148.6, 136.7, 136.7, 129.4, 128.4, 126.8, 100.7, 82.7, 54.0, 36.7, 28.5, 17.7, 13.0. LRMS calculated for $C_{18}H_{19}BrN_4O_2$: 402.1; found: 403.0 (M + H).

*Step C: N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**2a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**2b**).* Using general procedure 2 and 250 mg of (2*R*)-2-[[5-

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bromo-6-ethyl-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (0.62 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **2a** (15.5 mg, 0.034 mmol, 5.6%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.86 (br s, 1H), 8.18 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.18−7.13 (m, 3H), 7.01 (d, J = 8.0 Hz, 1H), 6.68−6.62 (m, 2H), 4.82−4.76 (m, 1H), 4.70 (d, J = 8.0 Hz, 1H), 3.78, (s, 3H), 3.11 (dd, J = 13.8, 4.6 Hz, 1H), 2.73 (dd, J = 13.8, 7.4 Hz, 1H), 2.65−2.54 (m, 1H), 2.51−2.42 (m, 1H), 2.11 (s, 3H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 154.1, 150.6, 149.1, 136.3, 136.0, 135.7, 135.4, 134.4, 130.2, 128.9, 128.8, 128.3, 127.2, 126.5, 108.7, 101.5, 53.6, 36.9, 28.1, 17.3/17.3, 13.9. HRMS calculated for $C_{25}H_{25}ClN_4O_2$: 448.1666; found: 449.1753 (M + H).

The diastereoisomer eluted later was collected as **2b** (39 mg, 0.086 mmol, 14%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.82 (br s, 1H), 8.18 (s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.24−7.14 (m, 4H), 6.88−6.81 (m, 2H), 4.81−4.74 (m, 1H), 4.70 (d, J = 8.0 Hz, 1H), 3.72, (s, 3H), 3.15 (dd, J = 14.0, 4.4 Hz, 1H), 2.74 (dd, J = 14.0, 7.4 Hz, 1H), 2.62−2.52 (m, 1H), 2.48−2.38 (m, 1H), 1.91 (s, 3H), 1.01 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.9, 154.5, 150.5, 149.1, 136.6, 136.2, 135.7, 135.6, 134.4, 130.1, 129.0, 128.7, 128.3, 127.2, 126.5, 108.5, 101.6, 53.9, 36.8, 28.1, 17.3/17.3, 13.8. HRMS calculated for $C_{25}H_{25}ClN_4O_2$: 448.1666; found: 449.1752 (M + H).

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**3a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**3b**). Step A: 7-Allyl-5-bromo-4-chloro-6-ethyl-pyrrolo[2,3-d]pyrimidine.* **R1a** (1.37 g, 5.25 mmol) was dissolved in 20 mL of dry THF, and then 0.68 mL of prop-2-en-1-ol was added under a N_2 atmosphere. Then 10.5 mL CMBP solution (10.5 mmol, 1.0 M in toluene) was added dropwise. The mixture was stirred at rt overnight. Then, the volatiles were removed under reduced pressure and the residue was purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.16 g of 7-allyl-5-bromo-4-chloro-6-ethyl-pyrrolo[2,3-*d*]pyrimidine (3.86 mmol, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 6.06−5.96 (m, 1H), 5.17−5.11 (m, 1H), 5.01−4.95 (m, 2H), 4.86−4.77 (m, 1H), 2.85 (q, J = 7.7 Hz, 2H), 1.26 (t, J = 7.7 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 150.2, 150.1, 149.0, 143.5, 133.3, 116.6, 113.9, 84.6, 44.7, 18.3, 12.8. LRMS calculated for $C_{11}H_{11}BrClN_3$: 299.0; found: 300.0 (M + H).

Step B: (2R)-2-[[7-Allyl-5-bromo-6-ethyl-pyrrolo[2,3-d]-pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.09 g of 7-allyl-5-bromo-4-chloro-6-ethyl-pyrrolo[2,3-*d*]pyrimidine (3.61 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 1.58 g of (2*R*)-2-[[7-allyl-5-bromo-6-ethyl-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (3.43 mmol, 95%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.06 (br s, 1H), 8.16 (s, 1H), 7.33−7.26 (m, 2H), 7.26−7.19 (m, 3H), 6.35 (d, J = 7.5 Hz, 1H), 6.01−5.89 (m, 1H), 5.10 (dd, J = 10.2, 1.5 Hz, 1H), 5.01−4.93 (m, 1H), 4.87−4.80 (m, 2H), 4.77 (dd, J = 17.1, 1.5 Hz, 1H), 3.29 (dd, J = 13.7, 5.0 Hz, 1H), 3.18 (dd, J = 13.7, 7.2 Hz, 1H), 2.70 (q, J = 7.5 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.0, 154.0, 151.2, 148.4, 136.8, 136.4, 134.1, 129.4, 128.4, 126.8, 116.1, 100.7, 83.4, 54.0, 44.0, 36.7, 17.7, 13.4. LRMS calculated for $C_{20}H_{21}BrN_4O_2$: 428.1; found: 429.0 (M + H).

*Step C: N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**3a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**3b**).* Using general procedure 2 and 0.54 g of (2*R*)-2-[[7-allyl-5-bromo-6-ethyl-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (1.25 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **3a** (30 mg, 0.06 mmol, 5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.88 (br s, 1H), 8.16 (s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.19−7.14 (m, 3H), 7.11 (d, J = 7.7 Hz, 1H), 6.79−6.73 (m, 2H), 6.09−5.97 (m, 1H), 5.11 (dd, J = 10.4, 1.4 Hz, 1H), 4.93−4.78 (m, 2H), 4.78−4.67 (m, 3H), 3.11 (dd, J = 13.8, 4.5 Hz, 1H), 2.72 (dd, J = 13.8, 7.1 Hz, 1H), 2.59−2.49 (m, 1H), 2.47−2.39 (m, 1H), 2.11 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.7, 154.2, 150.8, 148.9, 135.7, 135.4, 134.5, 134.4, 130.2, 128.9, 128.8, 128.3, 127.3, 126.5, 115.6, 109.3, 101.5, 53.8, 43.6, 36.9, 17.3, 17.2, 14.4. HRMS calculated for $C_{27}H_{27}ClN_4O_2$: 474.1823; found: 475.1908 (M + H).

The diastereoisomer eluted later was collected as **3b** (89 mg, 0.19 mmol, 15%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.85 (br s, 1H), 8.17 (s, 1H), 7.56 (dd, J = 8.0, 0.9 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.25−7.15 (m, 4H), 6.87−6.81 (m, 2H), 6.09−5.97 (m, 1H), 5.11 (dd, J = 10.4, 1.3 Hz, 1H), 4.93−4.78 (m, 2H), 4.78−4.70 (m, 3H), 3.14 (dd, J = 14.0, 4.3 Hz, 1H), 2.74 (dd, J = 14.0, 7.0 Hz, 1H), 2.57−2.47 (m, 1H), 2.44−2.34 (m, 1H), 1.92 (s, 3H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 154.4, 148.8, 136.5, 135.9, 135.6, 134.5, 134.4, 130.1, 129.1, 128.7, 128.3, 127.3, 126.6, 115.6, 109.1, 101.6, 53.9/53.9, 43.6, 36.8, 17.3, 17.2, 14.2. HRMS calculated for $C_{27}H_{27}ClN_4O_2$: 474.1823; found: 475.1909 (M + H).

*N-[6-Bromo-(5S$_a$)-5-(3-chloro-2-methylphenyl)-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**4a**) and N-[6-Bromo-(5R$_a$)-5-(3-chloro-2-methylphenyl)-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**4b**). Step A: 7-Allyl-4-chloro-5-iodo-pyrrolo[2,3-d]pyrimidine.* 4-Chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (4.87 g, 15.0 mmol), K_2CO_3 (2.50 g, 18.15 mmol), allyl bromide (1.6 mL, 18.15 mmol), and dry DMF (23 mL) were stirred at rt under a N_2 atmosphere for 1 h. Then, the mixture was diluted with EtOAc and was filtered through a pad of silica. The filtrate was washed with water, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 4.02 g of 7-allyl-4-chloro-5-iodo-pyrrolo[2,3-*d*]pyrimidine (12.6 mmol, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.65 (s, 1H), 7.98 (s, 1H), 6.08−5.97 (m, 1H), 5.21−5.15 (m, 1H), 5.06−4.98 (m, 1H), 4.92−4.85 (m, 1H). ^{13}C NMR (125 MHz,

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DMSO-d_6) δ ppm: 151.0, 150.5, 150.3, 136.3, 133.1, 117.8, 116.1, 51.6, 46.8. LRMS calculated for $C_9H_7ClIN_3$: 318.9; found: 320.0 (M + H).

Step B: (2R)-2-[(7-Allyl-5-iodo-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 0.64 g of 7-allyl-4-chloro-5-iodo-pyrrolo[2,3-*d*]-pyrimidine as the appropriate 4-chloro-pyrrolo[2,3-*d*]-pyrimidine derivative (2.0 mmol) and *D*-phenylalanine as the appropriate amino acid derivative, 0.78 g of (2*R*)-2-[(7-allyl-5-iodo-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (1.75 mmol, 87%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.20 (br s, 1H), 8.19 (s, 1H), 7.42 (s, 1H), 7.31−7.18 (m, 5H), 6.48 (d, *J* = 7.1 Hz, 1H), 6.03−5.89 (m, 1H), 5.14 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.05−4.95 (m, 2H), 4.76−4.70 (m, 2H), 3.38 (dd, *J* = 14.0, 7.0 Hz, 1H), 3.14 (dd, *J* = 14.0, 6.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.9, 154.8, 151.6, 149.1, 136.6, 133.8, 129.6, 129.4, 128.4, 126.8, 117.3, 103.1, 54.0, 49.3, 46.1, 36.8. LRMS calculated for $C_{18}H_{17}IN_4O_2$: 448.0; found: 449.0 (M + H).

Step C: (2R)-2-[[7-Allyl-5-(3-chloro-2-methyl-phenyl)-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. (2*R*)-2-[(7-Allyl-5-iodo-pyrrolo[2,3-*d*]pyrimidin-4-yl)-amino]-3-phenyl-propanoic acid (715 mg, 1.60 mmol) and **R3** (1.145 g, 4.80 mmol) were dissolved in 11.2 mL of DME, then 4.8 mL of TBAOH solution (4.80 mmol, 1 M in water), 72 mg of $Pd(OAc)_2$ (0.32 mmol), and 228 mg of $BuPAd_2$ (0.64 mmol) were added, and the mixture was stirred under a N_2 atmosphere at a reflux temperature for 40 min to reach complete conversion. Then, the mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified via flash chromatography using DCM and MeOH as eluents to obtain 472 mg of (2*R*)-2-[[7-allyl-5-(3-chloro-2-methyl-phenyl)pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (1.06 mmol, 66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.87 (br s, 1H), 8.23 (s, 1H), 7.53−7.44 (m, 1H), 7.28−7.00 (m, 6H), 6.91−6.81 (m, 2H), 6.12−5.98 (m, 1H), 5.16 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.09−4.96 (m, 2H), 4.90−4.76 (m, 3H), 3.17 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.86 (dd, *J* = 13.6, 7.4 Hz, 1H), 2.23/2.04 (br s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.5, 151.6, 148.6, 135.7, 134.7, 134.1, 129.7, 128.7, 128.2, 127.4, 126.5, 124.2, 116.9, 116.7, 112.4, 67.3, 57.5, 45.9, 36.9, 17.6. LRMS calculated for $C_{25}H_{23}ClN_4O_2$: 446.2; found: 447.0 (M + H).

*Step D: N-[6-Bromo-(5S$_a$)-5-(3-chloro-2-methylphenyl)-7-(prop-2-en-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-Phenylalanine (**4a**) and N-[6-Bromo-(5R$_a$)-5-(3-chloro-2-methylphenyl)-7-(prop-2-en-1-yl)-7H-pyrrolo [2,3-d]pyrimidin-4-yl]-D-phenylalanine (**4b**).* (2*R*)-2-[[7-Allyl-5-(3-chloro-2-methyl-phenyl)pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (447 mg, 1.00 mmol) was dissolved in 5 mL of dry DMF, and then 196 mg of NBS (1.1 mmol) was added. The mixture was stirred at rt for 1.5 h. It was then poured into water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The formed diastereoisomers were purified and separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **4b** (120 mg, 0.23 mmol, 23%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.91 (br s, 1H), 8.25 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.20−7.16 (m, 3H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.84−6.79 (m, 2H), 6.05−5.95 (m, 1H), 5.16 (d, *J* = 10.6 Hz, 1H), 4.95−4-77 (m, 5H), 3.16 (dd, *J* = 13.9, 4.7 Hz, 1H), 2.86 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.5, 153.8, 151.9, 149.1, 136.3, 135.2, 134.5, 134.0, 133.2, 129.9, 129.5, 128.9, 128.3, 127.4, 126.5, 116.3, 113.0, 110.0, 101.9, 53.8, 45.2, 36.5, 17.2. HRMS calculated for $C_{25}H_{22}BrClN_4O_2$: 524.0615; found: 525.0675 (M + H).

The diastereoisomer eluted later was collected as **4a** (52 mg, 0.1 mmol, 10%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.89 (br s, 1H), 8.24 (s, 1H), 7.58 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.20−7.15 (m, 3H), 6.84−6.77 (m, 2H), 6.05−5.94 (m, 1H), 5.16 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.95−4-83 (m, 3H), 4.83−4.74 (m, 2H), 3.16 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.86 (dd, *J* = 14.0, 7.5 Hz, 1H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.6, 154.0, 151.9, 149.1, 136.5, 135.4, 134.5, 134.0, 133.1, 129.7, 129.6, 128.9, 128.7, 128.2, 127.6, 126.5, 116.3, 112.9, 110.2, 101.9, 54.0, 45.2, 36.6, 17.1. HRMS calculated for $C_{25}H_{22}BrClN_4O_2$: 524.0615; found: 525.0675 (M + H).

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**6a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**6b**). Step A: 5-Bromo-4-chloro-6-ethyl-7-isopropyl-pyrrolo-[2,3-d]pyrimidine.* Using general procedure 3 and 1.56 g of **R1a** (5.99 mmol) and 2-propanol as the appropriate alcohol, 1.15 g of 5-bromo-4-chloro-6-ethyl-7-isopropyl-pyrrolo[2,3-*d*]pyrimidine (3.65 mmol, 61%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.54 (s, 1H), 4.72 (sp, *J* = 7.0 Hz, 1H), 2.92 (q, *J* = 7.4 Hz, 2H), 1.72 (d, *J* = 7.0 Hz, 6H), 1.25 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.6, 150.4, 149.2, 142.1, 115.3, 85.7, 49.3, 21.4, 19.3, 13.2. LRMS calculated for $C_{11}H_{13}BrClN_3$: 301.0; found: 302.0 (M + H).

Step B: (2R)-2-[(5-Bromo-6-ethyl-7-isopropyl-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.10 g of 5-bromo-4-chloro-6-ethyl-7-isopropyl-pyrrolo[2,3-*d*]pyrimidine (3.64 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 1.52 g of (2*R*)-2-[(5-bromo-6-ethyl-7-isopropyl-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (3.53 mmol, 97%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.04 (br s, 1H), 8.14 (s, 1H), 7.33−7.26 (m, 2H), 7.26−7.18 (m, 3H), 6.33 (d, *J* = 7.7 Hz, 1H), 4.99−4.91 (m, 1H), 4.64 (sp, *J* = 6.8 Hz, 1H), 3.28 (dd, *J* = 13.9, 4.9 Hz, 1H), 3.17 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.76 (q, *J* = 7.4 Hz, 2H), 1.59 (d, *J* = 6.8 Hz, 6H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.1, 154.1, 150.3, 148.2, 136.8, 136.0, 129.3, 128.4, 126.7, 101.3, 82.8, 53.9, 48.1, 36.7, 21.3, 21.3, 18.1, 13.6. LRMS calculated for $C_{20}H_{23}BrN_4O_2$: 430.1; found: 431.2 (M + H).

*Step C: N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**6a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**6b**).* Using general procedure 2 and 0.53 g of (2*R*)-2-[(5-bromo-6-ethyl-7-isopropyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)-amino]-3-phenyl-propanoic acid (1.24 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **6a** (19 mg,

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0.04 mmol, 3.2%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.84 (br s, 1H), 8.15 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.26 (t, J = 7.9 Hz, 1H), 7.20−7.13 (m, 3H), 7.11 (d, J = 7.7 Hz, 1H), 6.78−6.72 (m, 2H), 4.78−4.70 (m, 1H) 4.70−4.54 (m, 2H), 3.08 (dd, J = 13.9, 4.3 Hz, 1H), 2.67 (dd, J = 13.9, 7.7 Hz, 1H), 2.61−2.51 (m, 1H), 2.48−2.37 (m, 1H), 2.10 (s, 3H), 1.67 (dd, J = 6.6, 4.5 Hz, 6H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 148.8, 136.3, 135.9, 135.6, 134.4, 130.3, 128.9, 128.7, 128.3, 127.3, 126.5, 108.6, 102.2, 53.7, 47.3, 37.0, 21.3, 21.2, 17.5, 17.4, 14.7. HRMS calculated for $C_{27}H_{29}ClN_4O_2$: 476.1979; found: 477.2057 (M + H).

The diastereoisomer eluted later was collected as **6b** (73 mg, 0.15 mmol, 12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.80 (br s, 1H), 8.17 (s, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.26−7.15 (m, 4H), 6.89−6.80 (m, 2H), 4.83−4.67 (m, 2H), 4.67−4.55 (m, 1H), 3.12 (dd, J = 14.2, 4.0 Hz, 1H), 2.70 (dd, J = 14.2, 7.8 Hz, 1H), 2.60−2.50 (m, 1H), 2.45−2.35 (m, 1H), 1.91 (s, 3H), 1.67 (dd, J = 6.7, 3.5 Hz, 6H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.9, 154.6, 149.6, 148.8, 136.6, 135.9, 135.7, 135.6, 134.4, 130.1, 129.0, 128.6, 128.3, 127.3, 126.5, 108.4, 102.3, 53.9, 47.3, 36.9, 21.3, 21.2, 17.5, 17.3, 14.5. HRMS calculated for $C_{27}H_{29}ClN_4O_2$: 476.1979; found: 477.2063 (M + H).

*N-[7-(But-2-yn-1-yl)-(5R$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**7a**) and N-[7-(But-2-yn-1-yl)-(5S$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**7b**). Step A: 5-Bromo-7-but-2-ynyl-4-chloro-6-ethyl-pyrrolo[2,3-d]pyrimidine.* Using general procedure 3 and 1.56 g of **R1a** (5.99 mmol) and 2-butyn-1-ol as the appropriate alcohol, 1.72 g of 5-bromo-7-but-2-ynyl-4-chloro-6-ethyl-pyrrolo[2,3-*d*]pyrimidine (5.51 mmol, 88%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.59 (s, 1H), 5.03 (q, J = 2.5 Hz, 2H), 2.99 (q, J = 7.6 Hz, 2H), 1.77 (t, J = 2.5 Hz, 3H), 1.33 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.7, 150.3/150.3, 142.4, 115.1, 86.7, 81.3, 72.7, 32.4, 19.0, 12.8, 3.5. LRMS calculated for $C_{12}H_{11}BrClN_3$: 311.0; found: 312.0 (M + H).

Step B: (2R)-2-[(5-Bromo-7-but-2-ynyl-6-ethyl-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.58 g of 5-bromo-7-but-2-ynyl-4-chloro-6-ethyl-pyrrolo[2,3-*d*]pyrimidine (5.00 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 2.10 g of (2*R*)-2-[(5-bromo-7-but-2-ynyl-6-ethyl-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (4.79 mmol, 95%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.25 (br s, 1H), 8.19 (s, 1H), 7.30−7.24 (m, 2H), 7.24−7.16 (m, 3H), 6.45 (d, J = 7.3 Hz, 1H), 5.02−4.96 (m, 2H), 4.96−4.89 (m, 1H), 3.30 (dd, J = 13.6, 5.0 Hz, 1H), 3.19 (dd, J = 13.6, 6.8 Hz, 1H), 2.80 (q, J = 7.6 Hz, 2H), 1.74 (t, J = 2.3 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.9, 154.0, 151.4, 148.0, 137.0, 135.9, 129.4, 128.3, 126.6, 100.7, 83.9, 80.2, 74.5, 54.2, 36.7, 31.4, 17.8, 13.1, 2.9. HRMS calculated for $C_{21}H_{21}BrN_4O_2$: 440.0848; found: 441.0906 (M + H).

*Step C: N-[7-(But-2-yn-1-yl)-(5R$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**7a**) and N-[7-(But-2-yn-1-yl)-(5S$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**7b**).* Using general procedure 2 and 0.55 g of (2*R*)-2-[(5-bromo-7-but-2-ynyl-6-ethyl-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (1.24 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 40 mM aq. NH_4OAc (pH = 4) solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **7a** (39 mg, 0.08 mmol, 6.5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.86 (br s, 1H), 8.20 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.20−7.14 (m, 3H), 7.12 (d, J = 8.0 Hz, 1H), 6.81−6.73 (m, 2H), 5.01 (s, 2H), 4.87−4.76 (m, 1H), 4.71 (d, J = 7.6 Hz, 1H), 3.10 (dd, J = 14.1, 4.6 Hz, 1H), 2.78−2.70 (m, 1H), 2.70−2.61 (m, 1H), 2.59−2.45 (m, 1H), 2.10 (s, 3H), 1.77 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.3, 153.8, 152.5, 148.2, 135.9, 135.1, 135.0, 134.0, 129.8, 128.6, 128.4, 127.9, 126.9, 126.1, 109.2, 101.2, 79.3, 74.4, 53.3, 36.5, 30.6, 16.9, 13.6, 2.6. HRMS calculated for $C_{28}H_{27}ClN_4O_2$: 486.1823; found: 487.1893 (M + H).

The diastereoisomer eluted later was collected as **7b** (52.5 mg, 0.11 mmol, 8.7%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.85 (br s, 1H), 8.20 (s, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.25−7.14 (m, 4H), 6.89−6.79 (m, 2H), 5.04 (d, J = 18.0 Hz, 1H), 4.98 (d, J = 18.0 Hz, 1H), 4.87−4.76 (m, 1H), 4.75−4.65 (m, 1H), 3.15 (dd, J = 13.6, 3.9 Hz, 1H), 2.80−2.70 (m, 1H), 2.70−2.57 (m, 1H), 1.90 (s, 3H), 1.77 (s, 3H), 1.04 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.4, 154.2, 150.4, 148.2, 136.2, 135.2, 135.1, 134.1, 129.6, 128.7, 128.3, 127.9, 126.9, 126.1, 109.0, 101.3, 79.3, 74.4, 53.6, 36.4, 30.7, 17.0, 16.8, 12.5, 2.6. HRMS calculated for $C_{28}H_{27}ClN_4O_2$: 486.1823; found: 487.1909 (M + H).

*N-[7-Benzyl-(5R$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**8a**) and N-[7-Benzyl-(5S$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**8b**). Step A: 7-Benzyl-5-bromo-4-chloro-6-ethyl-pyrrolo[2,3-d]-pyrimidine.* NaH (255 mg, 6.4 mmol, 60% in oil) and dry THF (50 mL) were charged into a 250 mL flask under a N_2 atmosphere and the slurry was cooled to 0 °C. Then, 1.79 g of **R1a** (5.80 mmol) was added. After stirring the mixture for 30 min at 0 °C, 773 μL of BnBr (6.40 mmol) was added and the mixture was allowed to warm up to rt and stirred overnight. The mixture was then diluted with sat. aq. NH_4Cl solution and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and acetone as eluents to obtain 600 mg of 7-benzyl-5-bromo-4-chloro-6-ethyl-pyrrolo[2,3-*d*]pyrimidine (1.70 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.60 (s, 1H), 7.35−7.23 (m, 3H), 7.09−7.02 (m, 2H), 5.54 (s, 2H), 2.79 (q, J = 7.6 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.4, 142.7, 136.3, 129.0, 128.0, 126.5, 86.7, 46.2, 19.1, 12.6. LRMS calculated for $C_{15}H_{13}BrClN_3$: 349.0; found: 349.8 (M + H).

Step B: (2R)-2-[(7-Benzyl-5-bromo-6-ethyl-pyrrolo[2,3-d]-pyrimidin-4-yl)amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.17 g of 7-benzyl-5-bromo-4-chloro-6-ethyl-pyrrolo[2,3-*d*]pyrimidine (3.35 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 1.59 g of

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(2*R*)-2-[(7-benzyl-5-bromo-6-ethyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (3.32 mmol, 99%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.07 (s, 1H), 8.19 (s, 1H), 7.33−7.26 (m, 4H), 7.27−7.19 (m, 4H), 7.08−7.02 (m, 2H), 6.40 (d, J = 6.9 Hz, 1H), 5.45 (br s, 2H), 5.02−4.94 (m, 1H), 3.31 (dd, J = 13.7, 5.0 Hz, 1H), 3.20 (dd, J = 13.7, 7.2 Hz, 1H), 2.69−2.61 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.0, 154.1, 151.5, 148.8, 137.7, 136.8, 136.4, 129.4, 128.7, 128.4, 127.4, 126.8, 126.5, 100.7, 83.8, 54.1, 44.9, 36.7, 17.9, 13.0. HRMS calculated for $C_{24}H_{23}N_4O_2Br$: 478.1004; found: 479.1059 (M + H).

*Step C: N-[7-Benzyl-(5R$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**8a**) and N-[7-Benzyl-(5S$_a$)-5-(3-chloro-2-methylphenyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**8b**).* Using general procedure 2 and 0.48 g of (2*R*)-2-[(7-benzyl-5-bromo-6-ethyl-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (1.00 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **8a** (74 mg, 0.13 mmol, 13%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.89 (s, 1H), 8.20 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.34−7.29 (m, 2H), 7.29−7.22 (m, 2H), 7.21−7.15 (m, 3H), 7.13 (d, J = 7.5 Hz, 1H), 7.10−7.03 (m, 2H), 6.80−6.74 (m, 2H), 5.53 (d, J = 16.3 Hz, 1H), 5.45 (d, J = 16.3 Hz, 1H), 4.84−4.70 (m, 2H), 3.12 (dd, J = 14.0, 4.4 Hz, 1H), 2.72 (dd, J = 14.0, 7.2 Hz, 1H), 2.53−2.43 (m, 1H), 2.43−2.32 (m, 1H), 2.12 (s, 3H), 0.80 (t, J = 7.5 Hz, H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 149.3, 138.1, 136.3, 135.8, 135.5, 135.4, 134.4, 130.2, 129.0, 128.8, 128.7, 128.3, 127.3, 127.2, 126.6, 126.2, 109.7, 101.5, 53.8, 44.5, 36.9, 17.4, 17.3, 14.1. HRMS calculated for $C_{31}H_{29}ClN_4O_2$: 524.1979; found: 525.2048 (M + H).

The diastereoisomer eluted later was collected as **8b** (130 mg, 0.23 mmol, 23%). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ ppm: 12.85 (s, 1H), 8.19 (s, 1H), 7.56 (dd, J = 8.0, 1.0 Hz, 1H), 7.34−7.28 (m, 3H), 7.27−7.16 (m, 5H), 7.09−7.03 (m, 2H), 6.88−6.82 (m, 2H), 5.52 (d, J = 16.4 Hz, 1H), 5.46 (d, J = 16.4 Hz, 1H), 4.83−4.71 (m, 2H), 3.15 (dd, J = 14.0, 4.2 Hz, 1H), 2.74 (dd, J = 14.0, 7.5 Hz, 1H), 2.50−2.40 (m, 1H), 2.39−2.28 (m, 1H), 1.93 (s, 3H), 0.79 (t, J = 7.5 Hz, H). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ ppm: 172.9, 154.6, 150.9, 149.4, 138.2, 136.6, 135.9, 135.6, 135.6, 134.4, 130.1, 129.1, 128.7, 128.7, 128.3, 127.3, 127.2, 126.6, 126.2, 109.5, 101.6, 54.0, 44.5, 36.9, 17.4, 17.3, 14.0. HRMS calculated for $C_{31}H_{29}ClN_4O_2$: 524.1979; found: 525.2064 (M + H).

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-7-(2-cyclopentylethyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**9a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-7-(2-cyclopentylethyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**9b**). Step A: 5-Bromo-4-chloro-7-(2-cyclopentylethyl)-6-ethyl-pyrrolo[2,3-d]pyrimidin.* Using general procedure 3 and 1.56 g of **R1a** (5.99 mmol) and 2-cyclopentylethanol as the appropriate alcohol, 1.90 g of 5-bromo-4-chloro-7-(2-cyclopentylethyl)-6-ethyl-pyrrolo[2,3-*d*]-pyrimidine (5.33 mmol, 89%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.56 (s, 1H), 4.31−4.20 (m, 2H), 2.89 (q, J = 7.6 Hz, 2H), 1.91−1.72 (m, 5H), 1.69−1.57 (m, 2H), 1.57−1.46 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H), 1.23−1.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.6, 150.5, 149.9, 142.3, 114.9, 85.8, 42.8, 37.6, 36.7, 32.6, 25.1, 18.9, 13.1. LRMS calculated for $C_{15}H_{19}BrClN_3$: 355.0; found: 356.0 (M + H).

Step B: (2R)-2-[[5-Bromo-7-(2-cyclopentylethyl)-6-ethyl-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.67 g of 5-bromo-4-chloro-7-(2-cyclopentylethyl)-6-ethyl-pyrrolo[2,3-*d*]-pyrimidine (4.7 mmol) as the appropriate 4-chloro-pyrrolo-[2,3-*d*]pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 2.25 g of (2*R*)-2-[[5-bromo-7-(2-cyclopentylethyl)-6-ethyl-pyrrolo[2,3-*d*]-pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (4.62 mmol, 98%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.04 (br s, 1H), 8.17 (s, 1H), 7.31−7.26 (m, 2H), 7.25−7.19 (m, 3H), 6.32 (d, J = 7.4 Hz, 1H), 5.00−4.92 (m, 1H), 4.17−4.09 (m, 2H), 3.29 (dd, J = 13.9, 4.9 Hz, 1H), 3.18 (dd, J = 13.9, 7.2 Hz, 1H), 2.74 (q, J = 7.5 Hz, 2H), 1.79−1.70 (m, 3H), 1.70−1.62 (m, 2H), 1.60−1.50 (m, 2H), 1.50−1.42 (m, 2H), 1.15 (t, J = 7.5 Hz, 3H), 1.12−1.01 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.0, 153.9, 151.0, 148.3, 136.8, 136.1, 129.4, 128.4, 126.8, 100.7, 83.1, 60.1, 54.0, 41.7, 40.4, 37.0, 36.7, 36.3, 36.2, 32.0, 24.7, 17.7, 13.4. HRMS calculated for $C_{24}H_{29}N_4O_2Br$: 484.1474; found: 487.1517 (M + H).

*Step C: N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-7-(2-cyclopentylethyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**9a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-7-(2-cyclopentylethyl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**9b**).* Using general procedure 2 and 0.60 g of (2*R*)-2-[[5-bromo-7-(2-cyclopentylethyl)-6-ethyl-pyrrolo-[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (1.24 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **9a** (31 mg, 0.05 mmol, 4.4%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.82 (br s, 1H), 8.17 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.25−7.14 (m, 3H), 7.10 (d, J = 7.6 Hz, 1H), 6.80−6.73 (m, 2H), 4.80−4.59 (m, 2H), 4.25−4.06 (m, 2H), 3.10 (dd, J = 13.9, 4.1 Hz, 1H), 2.71 (dd, J = 13.9, 7.8 Hz, 1H), 2.66−2.53 (m, 1H), 2.48−2.38 (m, 1H), 2.10 (s, 3H), 1.85−1.65 (m, 5H), 1.67−1.52 (m, 2H), 1.51−1.37 (m, 2H), 1.18−1.07 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 154.1, 150.5, 148.8, 136.3, 135.8, 135.3, 135.2, 134.3, 130.0, 128.7, 128.6, 128.1, 127.1, 126.4, 108.9, 101.1, 53.6, 41.1, 36.9, 36.3, 36.2, 32.0, 24.7, 17.2/17.2, 14.2. HRMS calculated for $C_{31}H_{35}ClN_4O_2$: 530.2449; found: 531.2528 (M + H).

The diastereoisomer eluted later was collected as **9b** (57 mg, 0.10 mmol, 8%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.78 (br s, 1H), 8.17 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.25−7.14 (m, 4H), 6.88−6.80 (m, 2H), 4.81−4.73 (m, 1H), 4.68 (d, J = 7.8 Hz, 1H), 4.23−4.10 (m, 2H), 3.13 (dd, J = 13.9, 4.1 Hz, 1H), 2.72 (dd, J = 13.9, 7.8 Hz, 1H), 2.65−2.53 (m, 1H), 2.48−2.38 (m, 1H), 1.91 (s, 3H), 1.86−1.67 (m, 5H), 1.62−1.52 (m, 2H), 1.52−1.41 (m, 2H), 1.18−1.07 (m, 2H), 1.15 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 154.5, 154.4, 150.4, 148.8, 136.5, 135.8, 135.6, 135.5, 134.3, 130.0, 128.9, 128.6, 128.2, 127.2, 126.4, 108.8, 101.6, 53.8, 41.2, 37.2, 36.9, 36.3,

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32.0, 24.7, 17.3, 17.2, 14.2. HRMS calculated for $C_{31}H_{35}ClN_4O_2$: 530.2449; found: 531.2547 (M + H).

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**5a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**5b**). Step A: 5-Bromo-4-chloro-6-ethyl-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-d]pyrimidine.* Using general procedure 3 and 1.56 g of **R1a** (5.99 mmol) and 2,2,2-trifluoroethanol as the appropriate alcohol, 1.00 g of 5-bromo-4-chloro-6-ethyl-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-*d*]-pyrimidine (2.70 mmol, 45%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.62 (s, 1H), 4.90 (q, J = 8.0 Hz, 2H), 2.94 (q, J = 7.7 Hz, 2H), 1.28 (t, J = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.6, 151.2, 150.8, 142.1, 122.9, 115.4, 88.3, 43.7, 18.5, 12.6. LRMS calculated for $C_{10}H_8BrClF_3N_3$: 341.0; found: 342.0 (M + H).

Step B: (2R)-2-[[5-Bromo-6-ethyl-7-(2,2,2-trifluoroethyl)-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 0.97 g of 5-bromo-4-chloro-6-ethyl-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-*d*]pyrimidine (2.82 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]-pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 1.28 g of (2*R*)-2-[[5-bromo-6-ethyl-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (2.70 mmol, 96%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.11 (br s, 1H), 8.23 (s, 1H), 7.32−7.19 (m, 5H), 6.44 (d, J = 7.5 Hz, 1H), 5.12 (q, J = 9.0 Hz, 2H), 5.00−4.93 (m, 1H), 3.30 (dd, J = 13.9, 5.0 Hz, 1H), 3.20 (dd, J = 13.9, 7.2 Hz, 1H), 2.78 (q, J = 7.4 Hz, 2H), 1.14 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.9, 154.1, 151.8, 149.3, 136.6, 129.4, 128.4, 126.8, 123.8, 101.1, 85.4, 54.1, 42.6, 36.6, 17.4, 12.9. HRMS calculated for $C_{19}H_{18}N_4O_2F_3Br$: 470.0565; found: 471.0613 (M + H).

*Step C: N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**5a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(2,2,2-trifluoroethyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-yl]-D-phenylalanine (**5b**).* Using general procedure 2 and 0.58 g of (2*R*)-2-[[5-bromo-6-ethyl-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (1.24 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **5a** (108 mg, 0.20 mmol, 16%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.87 (br s, 1H), 8.23 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.21−7.15 (m, 3H), 7.14 (d, J = 7.5 Hz, 1H), 6.80−6.73 (m, 2H), 5.20−5.05 (m, 2H), 4.84−4.77 (m, 1H), 4.74 (d, J = 7.2 Hz, 1H), 3.10 (dd, J = 13.9, 4.3 Hz, 1H), 2.73 (dd, J = 13.9, 7.4 Hz, 1H), 2.70−2.61 (m, 1H), 2.59−2.51 (m, 1H), 2.10 (s, 3H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.5, 154.3, 151.4, 149.8, 135.3, 135.0, 134.4, 129.9, 129.1, 128.9, 128.1, 127.3, 126.3, 125.2, 123.0, 110.7, 101.8, 54.0, 42.5, 42.2, 36.8, 17.2, 16.9, 13.8. HRMS calculated for $C_{26}H_{24}ClF_3N_4O_2$: 516.1540; found: 517.1624 (M + H).

The diastereoisomer eluted later was collected as **5b** (78 mg, 0.14 mmol, 11%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.85 (br s, 1H), 8.24 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.28−7.15 (m, 4H), 6.84 (d, J = 6.7 Hz, 2H), 5.20−5.05 (m, 2H), 4.84−4.72 (m, 2H), 3.10 (dd, J = 13.7, 3.8 Hz, 1H), 2.75 (dd, J = 13.7, 7.0 Hz, 1H), 2.69−2.59 (m, 1H), 2.56−2.45 (m, 1H), 1.91 (s, 3H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.3, 154.7, 151.3, 149.8, 135.5, 135.1, 134.4, 129.9, 129.2, 128.8, 128.2, 127.4, 126.3, 110.7, 101.9, 42.5, 42.2, 36.7, 17.0, 16.9, 13.8. HRMS calculated for $C_{26}H_{24}ClF_3N_4O_2$: 516.1540; found: 517.1605 (M + H).

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(naphthalen-1-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-Phenylalanine (**10a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(naphthalen-1-ylmethyl)-7H-pyrrolo[2,3-d]-pyrimidin-4-yl]-D-phenylalanine (**10b**). Step A: 5-Bromo-4-chloro-6-ethyl-7-(1-naphthylmethyl)pyrrolo[2,3-d]-pyrimidine.* Using general procedure 3 and 1.56 g of **R1a** (5.99 mmol) and 1-naphthalenemethanol as the appropriate alcohol, 1.64 g of 5-bromo-4-chloro-6-ethyl-7-(1-naphthylmethyl)-pyrrolo[2,3-*d*]pyrimidine (4.43 mmol, 74%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.58 (s, 1H), 8.14−8.06 (m, 1H), 7.95−7.89 (m, 1H), 7.83−7.75 (m, 1H), 7.66−7.54 (m, 2H), 7.32−7.26 (m, 1H), 6.45 (dd, J = 7.3, 1.0 Hz, 1H), 6.03 (s, 2H), 2.76 (q, J = 7.5 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.2, 150.9, 150.5, 143.1, 133.6, 131.4, 130.2, 129.1, 128.5, 126.8, 126.2, 125.4, 122.8, 122.1, 86.8, 44.0, 19.0, 12.9. LRMS calculated for $C_{19}H_{15}BrClN_3$: 399.0; found: 400.0 (M + H).

Step B: (2R)-2-[[5-Bromo-6-ethyl-7-(1-naphthylmethyl)-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 1.33 g of 5-bromo-4-chloro-6-ethyl-7-(1-naphthylmethyl)pyrrolo[2,3-*d*]pyrimidine (3.32 mmol) as the appropriate 4-chloro-pyrrolo[2,3-*d*]-pyrimidine derivative and *D*-phenylalanine as the appropriate amino acid derivative, 1.70 g of (2*R*)-2-[[5-bromo-6-ethyl-7-(1-naphthylmethyl)pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (3.21 mmol, 97%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.14 (br s, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.15 (s, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.66−7.56 (m, 2H), 7.37−7.20 (m, 6H), 6.48 (d, J = 7.5 Hz, 1H), 6.40 (d, J = 7.1 Hz, 1H), 5.94 (s, 2H), 5.02−4.95 (m, 1H), 3.33 (dd, J = 13.8, 5.0 Hz, 1H), 3.22 (dd, J = 13.8, 7.0 Hz, 1H), 2.62 (q, J = 7.0 Hz, 2H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.0, 154.2, 151.5, 148.9, 136.9, 136.7, 133.2, 133.1, 129.9, 129.4, 128.6, 128.4, 127.7, 126.8, 126.6, 126.2, 125.5, 123.0, 122.5, 100.9, 84.0, 54.2, 43.2, 40.4, 36.8, 17.9, 13.2. HRMS calculated for $C_{28}H_{25}N_4O_2Br$: 528.1161; found: 529.1224 (M + H).

*Step C: N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(naphthalen-1-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**10a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6-ethyl-7-(naphthalen-1-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**10b**).* Using general procedure 2 and 0.53 g of (2*R*)-2-[[5-bromo-6-ethyl-7-(1-naphthylmethyl)pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (1.0 mmol) as the appropriate 5-bromo-pyrrolo[2,3-*d*]pyrimidine derivative and **R3** as the appropriate boronic acid derivative, a mixture of diastereoisomers was obtained. The diastereoisomers were separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **10a** (77 mg, 0.12 mmol, 12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.92 (br s, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.15 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.5

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Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.24−7.13 (m, 4H), 6.83−6.75 (m, 2H), 6.42 (d, J = 7.2 Hz, 1H), 6.01 (d, J = 17.5 Hz, 1H), 5.94 (d, J = 17.5 Hz, 1H), 4.82 (s, 2H), 3.14 (dd, J = 13.7, 2.8 Hz, 1H), 2.74 (dd, J = 13.7, 6.9 Hz, 1H), 2.52−2.42 (m, 1H), 2.41−2.31 (m, 1H), 2.20 (s, 3H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 154.2, 149.3, 136.3, 136.2, 135.5, 135.5, 134.5, 133.6, 133.1, 130.3, 129.9, 129.1, 128.8, 128.6, 128.4, 127.5, 127.4, 126.6, 126.5, 126.2, 125.6, 123.0, 122.1, 109.9, 101.7, 53.8, 42.8, 37.0, 17.43, 17.36, 14.2. HRMS calculated for $C_{35}H_{31}ClN_4O_2$: 574.2136; found: 575.2211 (M + H).

The diastereoisomer eluted later was collected as **10b** (83 mg, 0.13 mmol, 13%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.87 (br s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.69−7.56 (m, 3H), 7.38−7.28 (m, 3H), 7.27−7.17 (m, 4H), 6.90−6.84 (m, 2H), 6.41 (d, J = 6.9 Hz, 1H), 6.00 (d, J = 17.4 Hz, 1H), 5.94 (d, J = 17.4 Hz, 1H), 4.85−4.77 (m, 2H), 3.17 (dd, J = 13.7, 4.0 Hz, 1H), 2.74 (dd, J = 13.7, 7.0 Hz, 1H), 2.48−2.39 (m, 1H), 2.38−2.28 (m, 1H), 2.00 (s, 3H), 0.80 (t, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.9, 154.7, 154.6, 150.9, 149.4, 136.6, 136.2, 135.6, 135.6, 134.5, 133.6, 133.1, 130.1, 129.9, 129.2, 128.7, 128.6, 128.4, 127.5, 127.4, 126.6, 126.5, 126.2, 125.6, 123.0, 122.1, 109.7, 101.8, 54.0, 42.8, 36.9, 17.5, 17.3, 14.1. HRMS calculated for $C_{35}H_{31}ClN_4O_2$: 574.2136; found: 575.2203 (M + H).

*N-[5-(3-Chloro-2-methylphenyl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-4-yl]-D-phenylalanine (**11**).* A 1:1 mixture of **4a** and **4b** (210 mg, 0.40 mmol) was dissolved in 3 mL of MeOH, then 70 μL of cc. H_2SO_4 (1.20 mmol) was added, and the mixture was stirred at rt overnight. Then, it was poured into icy water, neutralized with sat. aq. $NaHCO_3$ solution, and extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The obtained intermediate was dissolved in 2.5 mL of dry THF and was cooled to 0 °C. 9-BBN solution (3.8 mL, 1.9 mmol, 0.5 M in THF) was added and the mixture was allowed to reach rt in 1 h (in the case of noncomplete conversion to the appropriate boron species, addition of 9-BBN was repeated). Then, 2.7 mL of 2 M aq. NaOH solution (5.32 mmol) and 55.6 mg of $PdCl_2$·dppf (0.076 mmol) were added. The mixture was stirred at 80 °C for 2 h, and then it was cooled to rt. It was filtered through Celite and washed with EtOAc. The layers of the filtrate were separated, and the aqueous layer was acidified to pH 3 with 2 M aq. HCl solution and then extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via preparative reversed-phase chromatography using 40 mM aq. NH_4OAc solution (pH = 4, adjusted with AcOH) and MeCN as eluents to obtain 103 mg of **11** (0.23 mmol, 57%) as a mixture of diastereoisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.84 (br s, 1H), 8.15/8.13 (s, 1H), 7.50/7.45 (dd, J = 8.0/8.1, 1.3/0.8 Hz, 1H), 7.24/7.11 (t, J = 7.5 Hz, 1H), 7.22−7.01 (m, 4H), 6.86−6.79 (m, 2H), 4.91−4.74 (m, 2H), 4.15−4.06 (m, 2H), 3.18/3.13 (dd, J = 13.8/13.8, 5.0/4.3 Hz, 1H), 2.88−2.67 (m, 3H), 2.58−2.47 (m, 2H), 2.22/2.06 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.0/172.8, 154.7/154.2, 150.3/150.2, 145.51/145.47, 139.4/139.2, 136.6/136.5, 135.68/135.65, 135.0/134.7, 134.60/134.56, 129.6/129.5, 128.9/128.7, 128.5, 128.28/128.26, 127.2/127.1, 126.55/126.52, 105.5/105.3, 103.8/103.6, 54.0/53.7, 43.2, 36.8/36.7, 27.1, 23.1, 17.4/17.3. HRMS calculated for $C_{25}H_{23}ClN_4O_2$: 446.1510; found: 447.1590 and 447.1591 (M + H).

*N-[(5R$_a$)-5-(3-Chloro-2-methylphenyl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-4-yl]-D-phenylalanine (**12a**) and N-[(5S$_a$)-5-(3-Chloro-2-methylphenyl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-4-yl]-D-phenylalanine (**12b**). Step A: 7-But-3-enyl-4-chloro-5-iodo-pyrrolo[2,3-d]-pyrimidine.* 4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (5.0 g, 17 mmol), K_2CO_3 (2.84 g, 20.6 mmol), 4-bromo-1-butene (2.15 mL, 20.6 mmol), and dry DMF (26 mL) were stirred at rt under a N_2 atmosphere overnight. Then, the mixture was poured into water and extracted with EtOAc. The combined organic layer was washed with water, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 5.33 g of 7-but-3-enyl-4-chloro-5-iodo-pyrrolo[2,3-d]-pyrimidine (16.0 mmol, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.64 (s, 1H), 8.05 (s, 1H), 5.82−5.69 (m, 1H), 5.01−4.90 (m, 2H), 4.39−4.30 (m, 2H), 2.60−2.53 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 150.8, 150.4, 150.3, 136.5, 134.6, 117.5, 51.2, 43.9, 33.6. LRMS calculated for $C_{10}H_9ClIN_3$: 333.0; found: 334.0 (M + H).

Step B: (2R)-2-[(7-But-3-enyl-5-iodo-pyrrolo[2,3-d]-pyrimidin-4-yl)amino]-3-phenyl-propanoic Acid. Using general procedure 1 and 0.68 g of 7-but-3-enyl-4-chloro-5-iodo-pyrrolo[2,3-d]pyrimidine (2.00 mmol) as the appropriate 4-chloro-pyrrolo[2,3-d]pyrimidine derivative and D-phenylalanine as the appropriate amino acid derivative, 0.89 g of (2R)-2-[(7-but-3-enyl-5-iodo-pyrrolo[2,3-d]pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (1.92 mmol, 96%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.32 (s, 1H), 7.35−7.20 (m, 5H), 7.02 (s, 1H), 6.28 (d, J = 5.2 Hz, 1H), 5.80−5.67 (m, 1H), 5.09−5.05 (m, 1H), 5.04 (br s, 1H), 4.94−4.85 (m, 1H), 4.22 (t, J = 7.0 Hz, 2H), 3.51 (dd, J = 14.8, 5.0 Hz, 1H), 3.30 (dd, J = 14.8, 9.0 Hz, 1H), 2.54 (q, J = 7.1 Hz, 2H).

Step C: (2R)-2-[[7-But-3-enyl-5-(3-chloro-2-methyl-phenyl)pyrrolo[2,3-d]pyrimidin-4-yl]amino]-3-phenyl-propanoic Acid. (2R)-2-[(7-But-3-enyl-5-iodo-pyrrolo[2,3-d]-pyrimidin-4-yl)amino]-3-phenyl-propanoic acid (2.31 g, 5.00 mmol) and **R3** (3.60 g, 15.0 mmol) were dissolved in 35 mL of DME, then 15 mL of TBAOH solution (1 M in THF), 225 mg of $Pd(OAc)_2$ (1.00 mmol), and 715 mg of $BuPAd_2$ (2.00 mmol) were added, and the mixture was stirred at 100 °C under a N_2 atmosphere for 30 min. Then, it was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography using DCM and MeOH as eluents to obtain 2.39 g of (2R)-2-[[7-but-3-enyl-5-(3-chloro-2-methyl-phenyl)pyrrolo[2,3-d]-pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (4.65 mmol, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.86 (br s, 1H), 8.24 (s, 1H), 7.55−7.43 (m, 1H), 7.33−6.95 (m, 6H), 6.89−6.80 (m, 2H), 5.84−5.70 (m, 1H), 5.08−4.93 (m, 3H), 4.84 (br s, 1H), 4.37−4.15 (m, 2H), 3.22−3.10 (m, 1H), 2.85 (dd, J = 13.9, 7.4 Hz, 1H), 2.56 (q, J = 6.8 Hz, 2H), 2.27−1.98 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.8, 155.2, 154.8, 151.3, 149.0, 136.5, 135.8, 135.0, 134.5, 129.6, 128.8, 128.8, 128.6, 128.5, 128.3, 127.1, 126.5, 123.9, 117.2, 112.1, 101.5, 54.0, 53.9, 43.0, 36.7, 34.0, 17.4.

Step D: N-[6-Bromo-7-(but-3-en-1-yl)-(5R$_a$)-5-(3-chloro-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenyla-

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lanine and N-[6-Bromo-7-(but-3-en-1-yl)-(5S_a)-5-(3-chloro-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-D-phenylalanine. (2*R*)-2-[[7-But-3-enyl-5-(3-chloro-2-methyl-phenyl)-pyrrolo[2,3-*d*]pyrimidin-4-yl]amino]-3-phenyl-propanoic acid (512 mg, 1.10 mmol) was dissolved in 4.5 mL of dry DMF, and 187 mg of NBS (1.00 mmol) was added. The mixture was stirred at rt for 30 min. Then, it was poured into water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as *N*-[6-bromo-7-(but-3-en-1-yl)-(5R_a)-5-(3-chloro-2-methylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-*D*-phenylalanine (125 mg, 0.23 mmol, 21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.90 (br s, 1H), 8.26 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.20−7.14 (m, 3H), 7.04 (d, J = 7.6 Hz, 1H), 6.84−6.77 (m, 2H), 5.86−5.74 (m, 1H), 5.03−4.95 (m, 2H), 4.92−4.77 (m, 2H), 4.42−4.22 (m, 2H), 3.14 (dd, J = 14.0, 4.8 Hz, 1H), 2.82 (dd, J = 14.0, 7.0 Hz, 1H), 2.56 (q, J = 7.1 Hz, 2H), 2.11 (br s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.5, 153.7, 151.8, 136.3, 135.3, 134.5, 134.5, 134.1, 129.9, 129.4, 128.9, 128.3, 127.4, 126.6, 117.4, 112.8, 109.8, 101.9, 53.7, 42.6, 36.5, 33.7, 17.1. HRMS calculated for $C_{26}H_{24}BrClN_4O_2$: 538.0771; found: 541.0831 (M + H).

The diastereoisomer eluted later was collected as *N*-[6-bromo-7-(but-3-en-1-yl)-(5S_a)-5-(3-chloro-2-methylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-*D*-phenylalanine (95 mg, 0.18 mmol, 16%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.88 (br s, 1H), 8.25 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.23−7.13 (m, 4H), 6.83−6.76 (m, 2H), 5.86−5.73 (m, 1H), 5.03−4.94 (m, 2H), 4.92−4.84 (m, 1H), 4.83−4.74 (m, 2H), 4.38−4.25 (m, 2H), 3.15 (dd, J = 13.9, 4.7 Hz, 1H), 2.77 (dd, J = 13.9, 7.7 Hz, 1H), 2.52 (q, J = 7.2 Hz, 2H), 1.96 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.6, 154.0, 151.7, 149.1, 136.4, 135.5, 134.5, 134.5, 134.1, 129.7, 129.6, 128.7, 128.3, 127.5, 126.5, 117.5, 112.7, 110.0, 101.9, 54.0, 42.6, 36.6, 33.7, 17.0. HRMS calculated for $C_{26}H_{24}BrClN_4O_2$: 538.0771; found: 541.0835 (M + H).

*Step E: N-[(5R_a)-5-(3-Chloro-2-methylphenyl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-4-yl]-D-phenylalanine (**12a**) and N-[(5S_a)-5-(3-Chloro-2-methylphenyl)-6,7,8,9-tetrahydropyrimido[5,4-b]indolizin-4-yl]-D-phenylalanine (**12b**).* A 1:1 mixture of *N*-[6-bromo-7-(but-3-en-1-yl)-(5R_a)-5-(3-chloro-2-methylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-*D*-phenylalanine and *N*-[6-bromo-7-(but-3-en-1-yl)-(5S_a)-5-(3-chloro-2-methylphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl]-*D*-phenylalanine (1.29 g, 2.40 mmol) was dissolved in 10 mL of MeOH, then 0.4 mL of cc. H_2SO_4 (6.90 mmol) was added, and the mixture was stirred at rt overnight. Then, it was poured into icy water, neutralized with sat. aq. $NaHCO_3$ solution, and extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The obtained intermediate was dissolved in 12 mL of dry THF, cooled to 0 °C, and added dropwise to a solution of 9-BBN (24 mL, 12.0 mmol, 0.5 M in THF), which was previously cooled to 0 °C. Then, the mixture was allowed to reach rt in 1 h (in the case of incomplete conversion to the appropriate boron species, addition of 9-BBN solution was repeated). Then, 24 mL of 2 M aq. NaOH solution (48 mmol) and 351 mg of $PdCl_2$·dppf (0.48 mmol) were added and the mixture was stirred at 80 °C for 2 h. Then, it was cooled to rt, filtered through Celite, and washed with EtOAc. The layers of the filtrate were separated, and the aqueous layer was acidified to pH 3 with 2 M aq. HCl solution and then extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via preparative reversed-phase chromatography using 0.1% aq. TFA solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **12a** (76 mg, 0.16 mmol, 7%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.84 (br s, 1H), 8.17 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.20−7.13 (m, 4H), 7.04 (d, J = 7.7 Hz, 1H), 6.83−6.76 (m, 2H), 4.85−4.76 (m, 2H), 4.15−4.03 (m, 2H), 3.14 (dd, J = 13.8, 4.2 Hz, 1H), 2.80 (dd, J = 13.8, 6.6 Hz, 1H), 2.66−2.57 (m, 1H), 2.53−2.44 (m, 1H), 2.14 (s, 3H) 2.02−1.93 (m, 2H), 1.83−1.73 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.4, 153.7, 149.9, 148.3, 136.2, 130.5, 129.8, 128.6, 128.3, 128.0, 126.9, 126.2, 107.3, 53.4, 40.8, 36.5, 21.6, 22.0, 20.0, 17.0. HRMS calculated for $C_{26}H_{25}ClN_4O_2$: 460.1666; found: 461.1747 (M + H).

The diastereoisomer eluted later was collected as **12b** (72 mg, 0.16 mmol, 7%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.81 (br s, 1H), 8.16 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.20−7.14 (m, 4H), 6.85−6.78 (m, 2H), 4.87−4.71 (m, 2H), 4.16−4.00 (m, 2H), 3.14 (dd, J = 13.9, 4.2 Hz, 1H), 2.78 (dd, J = 13.9, 7.3 Hz, 1H), 2.62−2.53 (m, 1H), 2.50−2.42 (m, 1H), 2.01−1.93 (m, 5H), 1.82−1.71 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.4, 154.0, 149.8, 148.2, 136.3, 130.5, 129.4, 128.3, 127.9, 126.8, 126.1, 107.0, 53.6, 40.7, 36.4, 21.8, 21.5, 19.9, 16.7. HRMS calculated for $C_{26}H_{25}ClN_4O_2$: 460.1666; found: 461.1752 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)thieno[2,3-d]-pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**13**).* **13** was prepared according to the published procedure.[7a]

*(2R)-2-{[(3S_a)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**14**). Step A: Ethyl (2S)-3-(2-Methoxyphenyl)-2-[(4-methylbenzene-1-sulfonyl)oxy]propanoate.* Ethyl (2*S*)-2-hydroxy-3-(2-methoxyphenyl)propanoate[7a] (3.00 g, 13.4 mmol) was dissolved in 10 mL of pyridine, and then 2.93 g of TsCl (15.38 mmol) was added at 0 °C. The mixture was stirred at rt overnight to reach complete conversion. Then, the mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with 1 M aq. citric acid solution, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure to give 4.78 g of ethyl (2*S*)-3-(2-methoxyphenyl)-2-[(4-methylbenzene-1-sulfonyl)-oxy]propanoate (12.6 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.52−7.48 (m, 2H), 7.20−7.12 (m, 3H), 7.01 (dd, J = 7.4, 1.6 Hz, 1H), 6.79 (td, J = 7.4, 0.9 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 5.04 (dd, J = 9.1, 5.0 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.68 (s, 3H), 3.20 (dd, J = 13.7, 5.0 Hz, 1H), 2.96 (dd, J = 13.8, 9.2 Hz, 1H), 2.40 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H). MS (EI, 70 eV) m/z (% relative intensity, [ion]): 65 (7), 77 (14), 91 (49), 123 (33), 133 (33), 165 (100), 207 (65), 307 (13), 512 (7, [M^+]).

Step B: Ethyl (2R)-2-{[3-Bromo-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoate. **R1b** (153 mg, 0.50 mmol), ethyl (2*S*)-3-(2-methoxyphenyl)-2-[(4-methylbenzene-1-sulfonyl)oxy]propanoate (265 mg, 0.70 mmol), K_2CO_3 (138 mg, 1.00 mmol), and DMSO (5 mL)

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were stirred at 60 °C under a N_2 atmosphere for 2 h to reach complete conversion. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to give 240 mg of ethyl (2*R*)-2-{[3-bromo-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoate (0.47 mmol, 94%). MS (EI, 70 eV) *m*/*z* (% relative intensity, [ion]): 91 (56), 133 (41), 165 (100), 207 (93), 281 (26), 305 (9), 512 (3, [M^+]), 514 (3, [M^+]).

Step C: Ethyl (2R)-2-{[(3S$_a$)-3-(3-Chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoate. Ethyl (2*R*)-2-{[3-bromo-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoate (240 mg, 0.47 mmol) and 2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenol[7a] (180 mg, 0.70 mmol) were dissolved in 5 mL of THF, then 325 mg of Cs_2CO_3 (1.00 mmol) dissolved in 2 mL water was added, then 33 mg of AtaPhos (10 mol %, 0.047 mmol) was added, and the mixture was stirred under a N_2 atmosphere at 110 °C using microwave irradiation for 10 min to reach complete conversion. Then, it was diluted with brine, acidified to pH 5 with 2 M aq. HCl solution, and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer eluted later was collected as ethyl (2*R*)-2-{[(3S$_a$)-3-(3-chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)-propanoate (109 mg, 0.19 mmol, 41%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.25 (br s, 1H), 7.49−7.43 (m, 2H), 7.28−7.14 (m, 6H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.73 (td, *J* = 7.4, 0.9 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 6.40 (dd, *J* = 7.5, 1.6 Hz, 1H), 4.85 (dd, *J* = 8.1, 5.2 Hz, 1H), 4.07−3.95 (m, 2H), 3.77 (s, 3H), 2.90 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.54 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.01 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.0, 161.9, 157.0, 154.5, 153.0, 152.1, 148.0, 135.9, 131.1, 129.7, 128.3, 127.6, 126.7, 125.8, 124.2, 123.4, 120.7, 119.9, 119.0, 116.0, 113.7, 110.5, 105.1, 104.8, 74.9, 60.7, 55.4, 33.0, 17.6, 13.8. HRMS calculated for $C_{33}H_{28}ClFO_6$: 574.1558; found 575.1621 (M + H).

*Step D: (2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**14**).* Ethyl (2*R*)-2-{[(3S$_a$)-3-(3-chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-methoxyphenyl)propanoate (105 mg, 0.18 mmol), 2-(4-methylpiperazin-1-yl)ethan-1-ol (52 mg, 0.36 mmol), and PPh_3 (167 mg, 0.30 mmol, immobilized on resin, 3 mmol/g) were dissolved in 5 mL of toluene, then 92 mg of DTABD (0.40 mmol) was added, and the mixture was stirred under a N_2 atmosphere at 50 °C for 2.5 h to reach 96% conversion. It was filtered and washed with DCM. The filtrate was concentrated under reduced pressure and then purified via flash chromatography using heptane EtOAc and MeOH as eluents. Then, it was dissolved in 5 mL of dioxane, 150 mg of $LiOH·H_2O$ and 5 mL of water were added, and the mixture was stirred at rt for 3 h to reach complete conversion. Then, it was diluted with water, neutralized with 2 M aq. HCl solution, diluted with brine, and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents to obtain 70 mg of **14** (0.10 mmol, 57%) in a purity of 94.9%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.45−7.41 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.25−7.18 (m, 5H), 7.14−7.10 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.67−6.63 (m, 1H), 6.53 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.22 (dd, *J* = 7.5, 1.3 Hz, 1H), 4.70 (dd, *J* = 8.8, 4.1 Hz, 1H), 4.27−4.20 (m, 2H), 3.76 (s, 3H), 2.98 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.81−2.71 (m, 2H), 2.65−2.30 (m, 8H), 2.46 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.20 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.0, 161.9, 157.0, 154.5, 153.6, 152.8, 147.9, 136.0, 130.9, 130.2, 127.8, 127.6, 126.9, 126.1, 125.8, 124.5, 122.2, 119.7, 118.7, 116.0, 115.1, 110.9, 110.4, 104.9, 104.1, 75.4, 67.1, 56.1, 55.3, 54.1, 52.4, 45.0, 33.0, 17.6. HRMS calculated for $C_{38}H_{38}ClFN_2O_6$: 672.2402; found: 673.2486 (M + H).

*(2R)-2-{[(1R$_a$)-1-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1H-indol-7-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**15**). Step A: 3-Chloro-2-methyl-4-triisopropylsilyloxy-aniline.* (4-Bromo-2-chloro-3-methyl-phenoxy)-triisopropyl-silane[7a] (9.37 g, 24.8 mmol) and $BnNH_2$ (5.32 g, 49.6 mmol) were dissolved in 20 mL of dry toluene, then 558 mg of Pd_2dba_3 (0.62 mmol), 558 mg of X-Phos (1.24 mmol), and 12.11 g of Cs_2CO_3 (37.2 mmol) were added, and the mixture was stirred at 100 °C overnight. Then, it was filtered through Celite, and the filtrate was concentrated under reduced pressure and purified via flash chromatography using hexane and EtOAc as eluents. The obtained intermediate was dissolved in 100 mL of MeOH and 20 mL of EtOAc, then 80 mg of 10% Pd/C was added, and the mixture was stirred under 1 bar H_2 atmosphere overnight. Then, it was filtered through Celite, the filtrate was concentrated under reduced pressure, and the crude product was purified via flash chromatography using hexane and EtOAc as eluents to obtain 2.18 g of 3-chloro-2-methyl-4-triisopropylsilyloxy-aniline (6.93 mmol, 28%). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 6.63 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 3.38 (br s, 2H), 2.24 (s, 3H), 1.43−1.18 (m, 3H), 1.11 (d, *J* = 6.6 Hz, 18H). ^{1}H NMR (50 MHz, $CDCl_3$) δ ppm: 145.2, 139.1, 122.6, 117.6, 113.9, 18.3, 14.8, 13.2. LRMS calculated for $C_{16}H_{28}ClNOSi$: 313.2; found: 314.2 (M + H).

Step B: 3-Benzyloxy-2-bromo-benzaldehyde. 2-Bromo-3-hydroxybenzaldehyde (4.55 g, 22.7 mmol), benzyl bromide (4.26 g, 24.9 mmol), and K_2CO_3 (4.70 g, 34.0 mmol) were dissolved in 20 mL of DMSO and stirred at 50 °C for 1 h. Then, it was poured into water. The precipitate was filtered to give 5.90 g of 3-benzyloxy-2-bromo-benzaldehyde (20.3 mmol, 89%). MS (EI, 70 eV) *m*/*z* (% relative intensity, [ion]): 65 (10), 91 (100), 290 (5, [M^+]), 292 (5, [M^+]).

Step C: 3-Benzyloxy-2-(3-chloro-2-methyl-4-triisopropylsilyloxy-anilino) Benzaldehyde. 3-Benzyloxy-2-bromo-benzaldehyde (5.00 g, 17.2 mmol) and 3-chloro-2-methyl-4-triisopropylsilyloxy-aniline (5.39 g, 17.2 mmol) were dissolved in 85 mL of dry toluene, then 16.8 g of Cs_2CO_3 (51.5 mmol), 393 mg of Pd_2dba_3 (0.43 mmol), and 535 mg of rac-BINAP (0.86 mmol) were added, and the mixture was stirred at 120 °C under a N_2 atmosphere for 6 h. Then, the volatiles were removed under reduced pressure and the residue was purified via flash chromatography using heptane and EtOAc as eluents to obtain 7.72 g of 3-benzyloxy-2-(3-chloro-2-methyl-4-

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triisopropylsilyloxy-anilino) benzaldehyde (14.73 mmol, 86%). LRMS calculated for $C_{30}H_{38}ClNO_3Si$: 523.2; found: 524.2 (M + H).

Step D: N-[2-Benzyloxy-6-(2,2-dibromovinyl)phenyl]-3-chloro-2-methyl-4-triisopropylsilyloxy-niline. 3-Benzyloxy-2-(3-chloro-2-methyl-4-triisopropylsilyloxy-anilino) benzaldehyde (7.70 g, 14.7 mmol) and CBr_4 (7.31 g, 22.0 mmol) were dissolved in 160 mL of DCM at 0 °C, and then 11.6 g of PPh_3 (44.1 mmol) was added. The mixture was stirred at rt for 1 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in Et_2O. Then, heptane was added and the formed precipitate was filtered. The filtrate was concentrated under reduced pressure. Then heptane was added again, and the mixture was stirred for 10 min and filtered again. The filtrate was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to give 7.74 g of *N*-[2-benzyloxy-6-(2,2-dibromovinyl)phenyl]-3-chloro-2-methyl-4-triisopropylsilyloxy-aniline (11.4 mmol, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.28−7.23 (m, 5H), 7.20 (s, 1H), 7.14−7.10 (m, 2H), 7.05 (d, J = 7.7 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 6.42 (s, 1H), 6.23 (d, J = 8.9 Hz, 1H), 5.08 (s, 2H), 2.30 (s, 3H), 1.31−1.21 (m, 3H), 1.06 (d, J = 7.4 Hz, 18H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 151.8, 145.6, 139.5, 137.3, 135.5, 132.4, 130.3, 128.5, 127.7, 127.5, 125.0, 123.2, 121.8, 117.2, 116.6, 114.0, 70.2, 18.2, 15.6, 12.6. LRMS calculated for $C_{31}H_{38}Br_2ClNO_2Si$: 677.1; found: 678.0 (M + H).

Step E: [4-[7-Benzyloxy-2-(4-fluorophenyl)indol-1-yl]-2-chloro-3-methyl-phenoxy]-triisopropyl-silane. *N*-[2-Benzyloxy-6-(2,2-dibromovinyl)phenyl]-3-chloro-2-methyl-4-triisopropylsilyloxy-aniline (2720 mg, 4.00 mmol), 4-fluorophenylboronic acid (1119 mg, 8.00 mmol), K_3PO_4 (4245 mg, 20.0 mmol), $Pd(OAc)_2$ (90 mg, 0.40 mmol), and SPhos (328 mg, 0.80 mmol) were mixed in 60 mL of dry toluene under a N_2 atmosphere and stirred at 100 °C until no further conversion was observed. Then, the solvent was removed under reduced pressure, and the residue was purified via flash chromatography using heptane and EtOAc as eluents to give 2.61 g of [4-[7-benzyloxy-2-(4-fluorophenyl)indol-1-yl]-2-chloro-3-methyl-phenoxy]-triisopropyl-silane (70% purity, 2.98 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 (d, J = 7.8 Hz, 2H), 7.24−7.20 (m, 2H), 7.16−7.11 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.88−6.82 (m, 4H), 6.71 (s, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 4.91 (d, J = 11.5 Hz, 1H), 4.89 (d, J = 11.5 Hz, 1H), 1.93 (s, 3H), 1.30−1.23 (m, 3H), 1.11 (d, J = 7.6 Hz, 9H), 1.09 (d, J = 7.6 Hz, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 130.4, 127.8, 127.6, 126.6, 120.7, 116.2, 114.9, 113,5, 104.6, 103.0, 69.9, 17.9, 15.9, 12.9.

Step F: 4-[7-Benzyloxy-2-(4-fluorophenyl)indol-1-yl]-2-chloro-3-methyl-phenol. [4-[7-Benzyloxy-2-(4-fluorophenyl)-indol-1-yl]-2-chloro-3-methyl-phenoxy]-triisopropyl-silane (2.60 g, 2.96 mmol) was dissolved in 50 mL of THF, then 2.96 mL of TBAF solution (2.96 mmol, 1 M in THF) was added, and the mixture was stirred at rt for 10 min. The solvent was then removed under reduced pressure, and the residue was purified via flash chromatography using heptane and EtOAc as eluents to give 1.22 g of 4-[7-benzyloxy-2-(4-fluorophenyl)-indol-1-yl]-2-chloro-3-methyl-phenol (2.66 mmol, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.27 (br s, 1H), 7.28−7.18 (m, 6H), 7.10 (t, J = 7.7 Hz, 2H), 7.07−6.99 (m, 2H), 6.85−6.77 (m, 3H), 6.75 (s, 1H), 6.72 (d, J = 7.7 Hz, 1H), 4.95 (d, J = 11.4 Hz, 1H), 4.90 (d, J = 11.4 Hz, 1H), 1.75 (s, 3H). LRMS calculated for $C_{28}H_{21}ClFNO_2$: 457.1; found: 458.0 (M + H).

Step G: 7-Benzyloxy-1-[3-chloro-2-methyl-4-[2-(4-methyl-piperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indole. 4-[7-Benzyloxy-2-(4-fluorophenyl)indol-1-yl]-2-chloro-3-methyl-phenol (1.20 g, 2.10 mmol), 2-(4-methylpiperazin-1-yl)ethanol (606 mg, 4.20 mmol), and PPh_3 (2.10 g, 6.3 mmol) were dissolved in 50 mL of dry toluene under a N_2 atmosphere and the mixture was cooled to 0 °C. Then, 1.45 g of DTBAD (6.30 mmol) was added and the mixture was stirred at 45 °C for 2 h. The solvent was then removed under reduced pressure, and the residue was purified via flash chromatography using heptane, EtOAc, and MeOH as eluents to give 1.30 g of 7-benzyloxy-1-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl]-2-(4-fluorophenyl)indole (91% purity, 2.02 mmol, 95%). LRMS calculated for $C_{35}H_{35}ClFN_3O_2$: 583.2; found: 584.2 (M + H).

Step H: 1-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indol-7-ol. 7-Benzyloxy-1-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]-phenyl]-2-(4-fluorophenyl)indole (1.28 g, 2.02 mmol, 91% purity) was dissolved in 100 mL of EtOH, and then 100 mg of 10% Pd/C was added. The mixture was stirred under 1 bar H_2 atmosphere at rt overnight. Then, the mixture was filtered through Celite and the filtrate was concentrated to give 1.10 g of 1-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]-phenyl]-2-(4-fluorophenyl)indol-7-ol (89% purity, 1.98 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.05 (br s, 1H), 7.27−7.22 (m, 2H), 7.17−7.05 (m, 4H), 6.94 (d, J = 8.8 Hz, 1H), 6.80 (t, J = 7.7 Hz, 1H), 6.71 (s, 1H), 6.48 (d, J = 7.7 Hz, 1H), 4.17−4.09 (m, 2H), 2.73 (t, J = 5.7 Hz, 2H), 2.58−2.42 (m, 4H), 2.40−2.17 (m, 4H), 2.15 (s, 3H), 1.87 (s, 3H). LRMS calculated for $C_{28}H_{29}ClFN_3O_2$: 493.2; found: 494.2 (M + H).

Step I: Ethyl (2R)-2-[1-[3-Chloro-2-methyl-4-[2-(4-methyl-piperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indol-7-yl]-oxy-3-(2-methoxyphenyl)propanoate. 1-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indol-7-ol (494 mg, 0.89 mmol, 89% purity), ethyl (2*S*)-2-hydroxy-3-(2-methoxyphenyl)propanoate[7a] (449 mg, 2.00 mmol), and PPh_3 (786 mg, 3.00 mmol) were dissolved in 10 mL of dry toluene under a N_2 atmosphere, and the mixture was cooled to 0 °C. Then, 691 mg of DTBAD (3.00 mmol) was added and the mixture was heated to 45 °C and stirred for 4 h. The solvent was then removed under reduced pressure, and the residue was purified via flash chromatography using heptane, EtOAc, and MeOH as eluents to give 610 mg of ethyl (2*R*)-2-[1-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indol-7-yl]oxy-3-(2-methoxyphenyl)propanoate (90% purity, 0.78 mmol, 88%) as a mixture of atropoisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.43/6.98 (d, J = 8.8 Hz, 1H), 7.31−7.22 (m, 3H), 7.20−7.12 (m, 3H), 7.12/6.88 (d, J = 8.8 Hz, 1H), 6.96−6.89 (m, 2H), 6.79/6.78 (s, 1H), 6.77−6.71 (m, 1H), 6.61−6.51 (m, 1H), 6.46/6.40 (d, J = 7.5 Hz, 1H), 4.86−4.74 (m, 1H), 4.25−3.89 (m, 4H), 3.77/3.76 (s, 3H), 2.75−2.60 (m, 3H), 2.54−2.32 (m, 5H), 2.30−2.09 (m, 4H), 2.13/2.09 (s, 3H), 2.08/1.67 (s, 3H), 0.99/0.98 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.24/170.15, 162.6, 160.6, 157.12/157.11, 153.6/153.5, 144.8/144.6, 140.4/140.3, 137.3, 136.0, 132.8/132.6, 130.8/130.7, 130.5/130.4, 130.0/129.9, 129.5, 128.5, 128.4, 128.3, 127.6/127.4, 123.4/123.2, 121.4/121.3, 120.8/120.7, 120.0/119.9, 115.4/115.3,

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113.80/113.78, 110.52/110.46, 110.0/109.7, 104.4/103.8, 103.3/103.3, 74.6/74.4, 67.5/67.4, 60.6/60.5, 56.22/56.18, 55.4/55.3, 54.9/54.7, 53.02/53.00, 45.7, 33.0/32.9, 28.1/27.9, 15.7/15.2, 13.8/13.8. HRMS calculated for $C_{40}H_{43}ClFN_3O_5$: 699.2875; found: 700.2950 (M + H).

*Step J: (2R)-2-{[(1R$_a$)-1-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1H-indol-7-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**15**).* (2*R*)-2-[1-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl]-2-(4-fluorophenyl)indol-7-yl]oxy-3-(2-methoxyphenyl)propanoate (600 mg, 0.77 mmol, 90% purity) was dissolved in 20 mL of dioxane:water (1:1), and 600 mg of LiOH·H_2O (14.0 mmol) was added. The mixture was stirred at rt for 4 h. Then, it was diluted with water, acidified with 1 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **15** (80 mg, 0.12 mmol, 15%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.26−7.21 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.16−7.11 (m, 3H), 6.94 (t, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.76 (s, 1H), 6.71−6.67 (m, 1H), 6.45−6.42 (m, 2H), 4.65 (dd, *J* = 8.4, 5.1 Hz, 1H), 4.13−4.07 (m, 1H), 4.03−3.98 (m, 1H), 3.75 (s, 3H), 2.82 (dd, *J* = 14.2, 5.1 Hz, 1H), 2.67 (t, *J* = 5.5 Hz, 2H), 2.51−2.41 (m, 4H), 2.38−2.24 (m, 4H), 2.33 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.20 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.2, 161.5, 157.0, 153.4, 145.1, 140.2, 137.6, 132.9, 130.7, 130.2, 129.9, 128.5, 128.3, 127.8, 127.7, 124.4, 121.4, 120.8, 119.8, 115.3, 113.2, 110.3, 109.5, 103.8, 103.3, 74.9, 67.3, 56.1, 55.3, 54.3, 52.6, 45.2, 32.9, 16.0. HRMS calculated for $C_{38}H_{39}ClFN_3O_5$: 671.2562; found: 672.2618 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)thieno[2,3-d]-pyrimidin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**16a**).* **16a** was prepared according to the published procedure.[7a]

*N-[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**16b**).* **16b** was prepared according to the published procedure.[7a]

*(2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)thieno[2,3-b]-pyridin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}phenyl)propanoic Acid (**17**). Step A: 3-Bromo-2-(4-fluorophenyl)thieno[2,3-b]pyridin-4-ol.* The mixture of 206 mg of **R1c** (0.60 mmol), 492 mg of NaOAc (6.00 mmol), 12 mL of AcOH, and 0.18 mL of H_2O was heated at 150 °C via microwave irradiation for 5 h. Water was added and the product was collected by filtration to obtain 173 mg of 3-bromo-2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-ol (0.53 mmol, 88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 8.30 (br s, 1H), 7.77−7.67 (m, 2H), 7.42−7.35 (m, 2H), 6.87 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.3, 162.2, 148.9, 132.0, 128.7, 122.9, 122.7, 128.7, 115.9, 107.4.

Step B: Ethyl (2R)-2-[3-Bromo-2-(4-fluorophenyl)thieno-[2,3-b]pyridin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoate. 3-Bromo-2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-ol (324 mg, 1.00 mmol), **R2b** (613 mg, 1.50 mmol), DTBAD (691 mg, 3.00 mmol), and PPh_3 (787 mg, 3.00 mmol) were dissolved in 10 mL of dry THF under a N_2 atmosphere, and the mixture was stirred at rt for 30 min. The solvent was then removed under reduced pressure, and the residue was purified via flash chromatography using heptane and EtOAc as eluents to give 684 mg of ethyl (2*R*)-2-[3-bromo-2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]-phenyl]propanoate (0.96 mmol, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.86 (d, *J* = 5.1 Hz, 1H), 8.33 (d, *J* = 5.6 Hz, 1H), 7.74−7.69 (m, 2H), 7.61 (d, *J* = 5.1 Hz, 1H), 7.51 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.47−7.43 (m, 2H), 7.42−7.37 (m, 2H), 7.27−7.22 (m, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.05−7.01 (m, 1H), 6.95−6.91 (m, 1H), 6.88 (d, *J* = 5.9 Hz, 1H), 5.55 (dd, *J* = 8.4, 4.7 Hz, 1H), 5.30 (d, *J* = 14.8 Hz, 1H), 5.26 (d, *J* = 14.8 Hz, 1H), 4.20−4.11 (m, 2H), 3.75 (s, 3H), 3.58 (dd, *J* = 14.0, 4.7 Hz, 1H), 3.35 (dd, *J* = 14.0, 8.4 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.4, 165.7, 164.8, 162.5, 159.7, 159.3, 157.7, 157.2, 155.8, 149.2, 134.9, 132.1, 131.9, 131.0, 130.9, 128.7, 128.6, 128.4, 124.1, 120.93, 120.91, 120.1, 116.0, 115.8, 112.2, 112.0, 104.0, 99.6, 75.7, 69.2, 61.3, 55.7, 33.1, 13.9. HRMS calculated for $C_{36}H_{29}BrFN_3O_5S$: 713.0995; found: 714.1059 (M + H).

*Step C: (2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy] phenyl}-2-(4-fluorophenyl)thieno-[2,3-b]pyridin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**17**).* (2*R*)-2-[3-Bromo-2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]-propanoate (288 mg, 0.40 mmol), 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]-4-methyl-piperazine[7a] (472 mg, 1.20 mmol), AtaPhos (28 mg, 0.004 mmol), and Cs_2CO_3 (392 mg, 1.20 mmol) were dissolved in a mixture of 4 mL of dioxane and 3 mL of water and stirred at 70 °C under a N_2 atmosphere for 30 min. Then, the mixture was diluted with water and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. Then, it was purified via flash chromatography using DCM and MeOH as eluents. The obtained intermediate was dissolved in a mixture of 7 mL of dioxane and 7 mL of water, and then 168 mg of LiOH·H_2O (4 mmol) was added. The mixture was stirred at rt for 1 h. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated by preparative reversed-phase chromatography using 5 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted later was collected as **17** (171 mg, 0.20 mmol, 50%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.87 (d, *J* = 5.1 Hz, 1H), 8.26 (d, *J* = 5.5 Hz, 1H), 7.75−7.72 (m, 1H), 7.54−7.51 (m, 1H), 7.47−7.43 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.26−7.20 (m, 2H), 7.19−7.08 (m, 5H), 7.06−7.02 (m, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.74−6.69 (m, 2H), 6.35−6.31 (m, 1H), 5.23 (d, *J* = 15.0 Hz, 1H), 5.20 (d, *J* = 15.0 Hz, 1H), 4.97 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.23−4.09 (m, 2H), 3.75 (s, 3H), 3.16 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.75−2.62 (m, 2H), 2.62−2.34 (m, 8H), 2.42 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.22 (s, 3H), ,1.83 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 167.8, 165.9, 165.3, 164.7, 162.0, 160.68, 160.68, 162.0,

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156.5, 157.8, 157.2, 155.4, 153.2, 148.4, 136.1, 135.8, 135.4, 131.0, 130.9, 130.9, 130.7, 130.4, 129.8, 129.3, 129.2, 128.4, 127.9, 123.0, 121.8, 120.4, 120.2, 115.9, 115.8, 112.2, 111.7, 110.3, 103.7, 76.2, 68.10, 66.9, 55.9, 55.7, 53.8, 52.0, 44.6, 33.0, 17.6. HRMS calculated for $C_{48}H_{45}ClFN_5O_6S$: 873.2763; found 437.6441 (M + 2H).

*N-[3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl}-2-(4-fluorophenyl)thieno[2,3-b]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**18**). Step A: Ethyl N-[3-Bromo-2-(4-fluorophenyl)-thieno[2,3-b]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy}-D-phenylalaninate.* **R1c** (343 mg, 1.00 mmol) and **R2c** (455 mg, 1.20 mmol) were dissolved in 5 mL of dry DMSO, then 978 mg of Cs_2CO_3 (3.00 mmol) was added, and the mixture was stirred under a N_2 atmosphere at 100 °C for 3 h and then at rt overnight. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. Then, it was dissolved in 1.5 mL of 1.25 M HCl solution in EtOH, and the mixture was stirred at 60 °C for 2 h to reach complete conversion. Next, it was carefully neutralized with sat. aq. $NaHCO_3$ solution and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 190 mg of ethyl *N*-[3-bromo-2-(4-fluorophenyl)thieno-[2,3-*b*]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}-*D*-phenylalaninate (0.266 mmol, 27%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.77 (d, J = 5.2 Hz, 1H), 8.07 (d, J = 5.9 Hz, 1H), 7.62−7.57 (m, 2H), 7.49 (dd, J = 7.6, 1.7 Hz, 1H), 7.47−7.42 (m, 1H), 7.37 (d, J = 5.2 Hz, 1H), 7.36−7.31 (m, 2H), 7.27−7.22 (m, 2H), 7.13 (dd, J = 8.5, 0.6 Hz, 1H), 7.09 (dd, J = 8.7, 0.8 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 7.00 (td, J = 7.5, 1.0 Hz, 1H), 6.92 (td, J = 7.4, 0.9 Hz, 1H), 6.56 (d, J = 6.0 Hz, 1H), 5.23 (d, J = 14.6 Hz, 1H), 5.19 (d, J = 14.6 Hz, 1H), 4.95−4.89 (m, 1H), 4.17−4.07 (m, 2H), 3.73 (s, 3H), 3.44 (dd, J = 13.7, 5.6 Hz, 1H), 3.25 (dd, J = 13.7, 6.9 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.4, 165.3, 164.7, 162.3, 159.1, 157.5, 157.2, 156.0, 148.2, 148.1, 132.3, 131.9, 131.5, 131.1, 130.8, 128.7, 128.5, 128.3, 124.2, 121.0, 120.0, 116.1, 115.9, 115.4, 112.2, 112.1, 101.4, 98.9, 69.2, 61.2, 55.7, 54.9, 32.3, 13.9. HRMS calculated for $C_{36}H_{30}BrFN_4O_4S$: 712.1155; found: 357.0649 (M + 2H).

Step B: Ethyl N-[3-(3-Chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)thieno[2,3-b]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalaninate. Ethyl *N*-[3-bromo-2-(4-fluorophenyl)thieno[2,3-*b*]-pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}-*D*-phenylalaninate (178 mg, 0.249 mmol) and 2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol[7a] (107 mg, 0.400 mmol) were dissolved in 1 mL of 1,4-dioxane under a N_2 atmosphere, then 163 mg of Cs_2CO_3 (0.500 mmol), 0.5 mL of water, and 28 mg of AtaPhos (0.040 mmol) were added, and the mixture was stirred in a microwave reactor at 111 °C for 15 min. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 80 mg of ethyl *N*-[3-(3-chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-*D*-phenylalaninate (0.103 mmol, 41%) as a mixture of atropoisomers. HRMS calculated for $C_{43}H_{36}ClFN_4O_5S$: 774.2079; found: 388.1113 (M + 2H).

*Step C: N-[3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)thieno[2,3-b]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**18**).* Ethyl *N*-[3-(3-chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)thieno[2,3-*b*]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-*D*-phenylalaninate (80 mg, 0.103 mmol), 2-(4-methylpiperazin-1-yl)ethanol (43 mg, 0.30 mmol), and PPh_3 (79 mg, 0.30 mmol) were dissolved in 1 mL of dry toluene, then 69 mg of DTBAD (0.30 mmol) was added, and the mixture was stirred at rt under a N_2 atmosphere for 10 min to reach 96% conversion. Then, the mixture was concentrated under reduced pressure and the residue was purified via flash chromatography using EtOAc and MeOH as eluents. The obtained intermediate was dissolved in 1 mL of THF, then 80 mg of $LiOH·H_2O$ and 1 mL of water were added, and the mixture was stirred at rt for 4 h to reach complete conversion. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents to obtain 51 mg of **18** (0.058 mmol, 57%) as a 7:3 mixture of diastereoisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.85/8.73 (d/d, J = 5.1/5.1 Hz, 1H), 7.94/7.85 (d/d, J = 5.5/5.6 Hz, 1H), 7.56−6.32 (m, 16 H), 5.25−4.90 (m, 3H), 4.49−4.01 (m, 3H), 3.75/3.73 (s/s, 3H), 3.37−2.55 (m, 12H), 2.48/2.34 (s/s, 3H), 1.95/1.88 (s/s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.2, 165.3/165.0, 160.6, 160.1, 157.7/157.5, 157.22/157.16, 156.3/155.8, 154.4/154.3, 148.7/148.3, 147.6/147.5, 136.2/135.8, 132.1, 131.3, 131.06/131.02, 130.8/130.74, 130.66/130.5, 129.9, 129.6, 129.5/129.2, 128.42/128.37, 127.63/127.60, 127.56/127.1, 126.24/126.22, 123.04/123.01, 120.75/120.73, 120.14/120.07, 118.8/118.4, 116.1/115.4, 115.7/115.6, 112.23/112.18, 111.9/111.7, 111.5/111.0, 100.9/100.7, 69.37/69.33, 65.7, 55.70/55.67, 55.62, 55.5/55.3, 53.5, 43.5/43.1, 32.5/29.8, 17.42/17.38. HRMS calculated for $C_{48}H_{46}ClFN_6O_5S$: 872.2923; found: 437.1540 and 437.1538 (M + 2H).

*N-[3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl}-2-(4-fluorophenyl)thieno[3,2-c]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**19**). Step A: 3-Bromo-4-chloro-2-iodothieno[3,2-c]pyridine.* 3-Bromo-4-chloro-thieno[3,2-*c*]pyridine (4.97 g, 20.0 mmol) was dissolved in 50 mL of dry THF under an Ar atmosphere and the mixture was cooled to −45 °C. Then, 22 mL of Mg(TMP)Cl·LiCl solution (22 mmol, 1 M in THF) was added dropwise, the mixture was stirred for 1 h at −45 °C and then 1 h at 0 °C, and then it was cooled to −45 °C again. Then, 5.58 g of I_2 (22 mmol, dissolved in 20 mL of dry, cold THF) was added dropwise and the mixture was stirred at −45 °C for 2 h. Next, it was allowed to warm up to rt and concentrated under reduced pressure. The residue was poured onto 300 mL of brine and extracted with EtOAc. The combined organic phase was washed with sat. aq. $Na_2S_2O_3$ solution, sat. aq. NH_4Cl solution, and then water, then dried over Na_2SO_4, and filtered, and the filtrate was concentrated

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under reduced pressure. The crude product was purified via flash chromatography using hexanes and EtOAc as eluents to obtain 3.63 g of 3-bromo-4-chloro-2-iodothieno[3,2-*c*]pyridine (9.69 mmol, 48%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.27 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 5.4 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 153.2, 142.7, 142.6, 129.4, 117.7, 113.9, 93.4. HRMS calculated for $C_7H_2BrClINS$: 372.7824; found: 373.7916 (M + H).

Step B: 3-Bromo-4-chloro-2-(4-fluorophenyl)thieno[3,2-c]pyridine. 3-Bromo-4-chloro-2-iodothieno[3,2-*c*]pyridine (2.62 g, 7.00 mmol) and 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.33 g, 10.5 mmol) were dissolved in 18 mL of THF under an Ar atmosphere, then 6.84 g of Cs_2CO_3 (21.0 mmol), 18 mL of water, 79 mg of $Pd(OAc)_2$ (0.35 mmol), and 297 mg of ^{t}BuXPhos (0.70 mmol) were added, and the mixture was stirred at 70 °C overnight to reach complete conversion. Then, the volatiles were evaporated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic phase was washed with sat. aq. NH_4Cl solution and then with brine, then dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using hexanes and EtOAc as eluents to obtain 1.68 g of 3-bromo-4-chloro-2-(4-fluorophenyl)thieno[3,2-*c*]pyridine (4.89 mmol, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.35 (d, J = 5.4 Hz, 1H), 8.26 (d, J = 5.5 Hz, 1H), 7.76−7.72 (m, 2H), 7.45−7.40 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.7, 148.0, 144.1, 142.5, 140.5, 132.3, 129.7, 128.3, 118.0, 116.1, 102.5. HRMS calculated for $C_{13}H_6BrClFNS$: 340.9077; found: 341.9144 (M + H).

Step C: Ethyl N-[3-Bromo-2-(4-fluorophenyl)thieno[3,2-c]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}-D-phenylalaninate. 3-Bromo-4-chloro-2-(4-fluorophenyl)thieno[3,2-*c*]pyridine (343 mg, 1.00 mmol) and **R2c** (455 mg, 1.20 mmol) were dissolved in 5 mL of dry DMSO, then 978 mg of Cs_2CO_3 (3.00 mmol) was added, and the mixture was stirred under a N_2 atmosphere at 100 °C for 4 h and then at rt overnight. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. Then, it was dissolved in 1.5 mL of 1.25 M HCl solution in EtOH, and the mixture was stirred at 60 °C for 2 h and then at rt overnight. Next, it was carefully neutralized with sat. aq. $NaHCO_3$ solution and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 31 mg of ethyl *N*-[3-bromo-2-(4-fluorophenyl)thieno[3,2-*c*]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-*D*-phenylalaninate (0.043 mmol, 4.3%). HRMS calculated for $C_{36}H_{30}BrFN_4O_4S$: 712.1155; found: 713.1209 (M + H).

Step D: Ethyl N-[3-(3-Chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)thieno[3,2-c]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalaninate. Ethyl *N*-[3-bromo-2-(4-fluorophenyl)thieno[3,2-*c*]-pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}-*D*-phenylalaninate (31 mg, 0.043 mmol) and 2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol[7a] (24 mg, 0.09 mmol) were dissolved in 0.5 mL of 1,4-dioxane under a N_2 atmosphere, then 33 mg of Cs_2CO_3 (0.10 mmol), 0.5 mL of water, and 9.4 mg of AtaPhos (0.013 mmol) were added, and the mixture was stirred in a microwave reactor at 111 °C for 10 min. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 33 mg of ethyl *N*-[3-(3-chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)thieno[3,2-*c*]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-*D*-phenylalaninate as a mixture of atropoisomers (0.043 mmol, 99%). HRMS calculated for $C_{43}H_{36}ClFN_4O_5S$: 774.2079; found: 775.2134 (M + H).

*Step E: N-[3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)thieno[3,2-c]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**19**).* Ethyl *N*-[3-(3-chloro-4-hydroxy-2-methylphenyl)-2-(4-fluorophenyl)thieno[3,2-*c*]pyridin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-*D*-phenylalaninate (33 mg, 0.043 mmol), 2-(4-methylpiperazin-1-yl)ethanol (15 mg, 0.10 mmol), and PPh_3 (26 mg, 0.10 mmol) were dissolved in 1 mL of dry toluene, then 23 mg of DTBAD (0.10 mmol) was added, and the mixture was stirred at rt under a N_2 atmosphere for 1 h to reach complete conversion. Then, the mixture was concentrated under reduced pressure and the residue was purified via flash chromatography using EtOAc and MeOH as eluents. The obtained intermediate was dissolved in 1 mL of THF, then 80 mg of $LiOH·H_2O$ and 1 mL of water were added, and the mixture was stirred at rt for 4 h to reach complete conversion. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents to obtain 9.0 mg of **19** (0.010 mmol, 24%) as a 3:1 mixture of diastereoisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.84/8.77 (d/d, J = 5.1/5.1 Hz, 1H), 7.864/7.857 (d/d, J = 5.7/5.6 Hz, 1H), 7.60−7.43 (m, 3H), 7.29−7.10 (m, 9H), 7.08−6.97 (m, 2H), 6.93−6.82 (m, 1H), 6.73−6.67 (m, 1H), 5.19−4.91 (m, 3H), 4.77−4.72 (m, 1H), 4.36−4.06 (m, 2H), 3.77/3.75 (s/s, 3H), 3.47/3.29 (dd/dd, J = 13.2, 4.9 / 14.0, 5.2 Hz, 1H), 3.01−2.77 (m, 2H), 2.73/2.57 (dd/dd, J = 13.2, 5.6 / 14.0, 8.0 Hz, 1H), 2.73−2.30 (m, 8H), 2.33/2.17 (s/s, 3H), 1.96/1.84 (s/s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 174.1, 157.6, 141.7/141.4, 131.0, 130.8, 130.7, 130.6, 127.7, 120.2, 115.9, 115.7, 112.2, 111.5, 69.2/69.0, 66.7/66.3, 55.9, 55.7, 54.2, 53.8, 44.9/44.1, 32.4/30.9, 17.6/17.4. HRMS calculated for $C_{48}H_{46}ClFN_6O_5S$: 872.2923; found: 437.1549 and 437.1532 (M + 2H).

*(2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-benzothiophen-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}phenyl)propanoic Acid (**20**). Step A: (3-Bromophenyl) N,N-Diethylcarbamate.* 3-Bromophenol (5.00 g, 28.9 mmol) and diethylcarbamoyl chloride (4.31 g, 31.8 mmol) were dissolved in 50 mL of pyridine and stirred at 100 °C overnight. Then, the mixture was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 6.74 g of (3-bromophenyl) *N*,*N*-diethylcarbamate (24.8 mmol, 86%). MS (EI, 70 eV) m/z

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(% relative intensity, [ion]): 56 (9), 72 (42), 100 (100), 174 (4), 176 (4), 271 (4, [M^+]), 273 (4, [M^+]).

Step B: (3-Bromo-2-iodo-phenyl) N,N-Diethylcarbamate. (3-Bromophenyl) *N,N*-diethylcarbamate (2.72 g, 10 mmol) was dissolved in 50 mL of dry THF under a N_2 atmosphere and cooled to −78 °C. Six milliliters of LDA solution (12.0 mmol, 2 M in THF, heptane, PhEt) was added and the mixture was stirred at −78 °C for 30 min. Then, 3.18 g of I_2 (12.5 mmol) was added, the mixture was stirred at −78 °C for 30 min, and then it was allowed to warm up to rt. Next, the mixture was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 3.91 g of (3-bromo-2-iodo-phenyl) *N,N*-diethylcarbamate (9.82 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.60 (dd, J = 8.0, 1.5 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.0, 1.5 Hz, 1H), 3.47 (q, J = 7.1 Hz, 2H), 3.31 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 153.3, 152.0, 130.5, 129.8, 129.6, 122.3, 101.3, 41.8, 41.7, 14.3, 13.2.

Step C: [3-Bromo-2-[2-(4-fluorophenyl)ethynyl]phenyl] N,N-Diethylcarbamate. (3-Bromo-2-iodo-phenyl) *N,N*-diethylcarbamate (2.60 g, 6.53 mmol), 1-ethynyl-4-fluorobenzene (863 mg, 7.19 mmol), $Pd(PPh_3)_2Cl_2$ (229 mg, 0.33 mmol), CuI (130 mg, 0.65 mmol), and diethyl amine (1.43 g, 19.6 mmol) were dissolved in 25 mL of dry DMF and stirred at 50 °C overnight. The mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 2.50 g of [3-bromo-2-[2-(4-fluorophenyl)ethynyl]phenyl] *N,N*-diethylcarbamate (6.40 mmol, 98%). MS (EI, 70 eV) m/z (% relative intensity, [ion]): 56 (2), 72 (35), 100 (100), 261 (2), 263 (2), 389 (2, [M^+]), 391 (2, [M^+]).

Step D: [2-[2-(4-Fluorophenyl)ethynyl]-3-methylsulfanyl-phenyl] N,N-Diethylcarbamate. [3-Bromo-2-[2-(4-fluorophenyl)ethynyl]phenyl] *N,N*-diethylcarbamate (2.50 g, 6.56 mmol) was dissolved in 65 mL of dry THF and cooled to −78 °C, and then 4.3 mL ^{n}BuLi solution (6.88 mmol, 1.6 M in hexanes) was added. The mixture was stirred at −78 °C for 30 min. Then, 742 mg of S_2Me_2 (7.87 mmol) was added, the mixture was stirred at −78 °C for 30 min, and then it was allowed to warm up to rt. The mixture was then concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.15 g of [2-[2-(4-fluorophenyl)ethynyl]-3-methylsulfanyl-phenyl] *N,N*-diethylcarbamate (3.22 mmol, 49%). MS (EI, 70 eV) m/z (% relative intensity, [ion]): 56 (2), 72 (46), 100 (100), 342 (40), 357 (1, [M^+]).

Step E: [2-(4-Fluorophenyl)-3-iodo-benzothiophen-4-yl] N,N-Diethylcarbamate. [2-[2-(4-Fluorophenyl)ethynyl]-3-methylsulfanyl-phenyl] *N,N*-diethylcarbamate (1100 mg, 3.08 mmol) and I_2 (937 mg, 3.70 mmol) were dissolved in 20 mL of DCM and stirred at rt overnight. The mixture was then diluted with 10% aq. $Na_2S_2O_3$ solution and extracted with DCM. The combined organic layer was washed with brine and concentrated under reduced pressure to give 1.32 g of [2-(4-fluorophenyl)-3-iodo-benzothiophen-4-yl] *N,N*-diethylcarbamate (2.81 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.74 (dd, J = 8.0, 1.0 Hz, 1H), 7.59−7.53 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.21−7.11 (m, 2H), 7.12 (dd, J = 8.0, 1.0 Hz, 1H), 3.60 (q, J = 7.2 Hz, 2H), 3.46 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 164.3, 161.8, 154.4, 146.4, 142.3, 141.0, 132.3, 131.1, 125.2, 120.0, 119.8, 115.5, 42.2, 41.9, 14.3, 13.4. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 72 (42), 100 (100), 170 (16), 342 (37), 369 (5), 469 (1, [M^+]).

Step F: 3-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)benzothiophen-4-ol. [2-(4-Fluorophenyl)-3-iodo-benzothiophen-4-yl] *N,N*-diethylcarbamate (1.30 g, 2.77 mmol) and 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]-4-methyl-piperazine[7a] (1.64 g, 4.16 mmol) were dissolved in 20 mL of THF, then 1.80 g of Cs_2CO_3 (5.51 mmol), 196 mg of AtaPhos (0.277 mmol), and 10 mL of water were added, and the mixture was stirred under a N_2 atmosphere at 70 °C for 3 h. Then, it was diluted with water and extracted with DCM. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure and then purified via flash chromatography using heptane and EtOAc as eluents. The obtained intermediate was dissolved in 80 mL of EtOH, and 1.20 g of NaOH (30 mmol) was added. The mixture was stirred at 80 °C for 8 h. Then, the mixture was concentrated under reduced pressure and purified via flash chromatography using DCM and MeOH as eluents to obtain 480 g of 3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)benzothiophen-4-ol (0.94 mmol, 34%). LRMS calculated for $C_{28}H_{28}ClFN_2O_2S$: 510.2; found: 511.2.

*Step G: (2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-benzothiophen-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl] methoxy}phenyl)propanoic Acid (**20**).* 3-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)benzothiophen-4-ol (470 mg, 0.92 mmol), **R2b** (1.12 g, 2.76 mmol), and PPh_3 (726 mg, 2.76 mmol) were dissolved in 10 mL of dry toluene, and then 635 mg of DTBAD (2.76 mmol) was added. The mixture was stirred at 50 °C for 1 h. The mixture was then concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents. The obtained intermediate was dissolved in 10 mL of dioxane:water (1:1), 400 mg of LiOH·H_2O (9.5 mmol) was added, and the mixture was stirred at rt for 1 h. It was neutralized with 2 M aq. HCl solution and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted later was collected as **20** (55 mg, 0.063 mmol, 6.8%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.86 (d, J = 5.1 Hz, 1H), 7.64 (d, J = 5.1 Hz, 1H), 7.57−7.52 (m, 2H), 7.48−7.44 (m, 1H), 7.29−7.13 (m, 8H), 7.07−6.99 (m, 3H), 6.79−6.75 (m, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.55−6.51 (m, 1H), 5.24 (d, J = 15.1 Hz, 1H), 5.21 (d, J = 15.1 Hz, 1H), 4.89 (dd, J = 8.0, 5.2 Hz, 1H), 4.18−4.06 (m, 2H), 3.75 (s, 3H), 2.94 (dd, J = 13.7, 5.2 Hz, 1H), 2.69−2.60 (m, 2H), 2.48−2.38 (m, 4H), 2.42 (dd, J = 13.7, 8.0 Hz, 1H), 2.34−2.20 (m, 4H), 2.12 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.0, 164.8, 157.8, 157.3, 131.1, 130.1, 130.9, 130.8, 130.2, 128.4, 128.1, 125.8, 120.6, 120.2, 115.8, 115.7, 114.9, 112.3, 111.8, 110.3, 106.5, 75.1, 69.0, 67.1, 56.0, 55.7, 54.4, 52.6, 45.3, 32.8, 17.7. HRMS calculated for $C_{49}H_{46}ClFN_4O_6S$: 872.2811; found: 437.1491 (M + 2H).

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*(2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**21**). Step A: Ethyl (2R)-2-[3-Bromo-2-(4-fluorophenyl)benzofuran-4-yl]oxy-3-[2-[2-(2-methoxyphenyl)pyrimidin-4-yl]oxyphenyl]propanoate.* **R1b** (220 mg, 0.716 mmol), **R2b** (731 mg, 1.79 mmol), and PPh_3 (470 mg, 1.79 mmol) were dissolved in 14 mL of dry toluene under a N_2 atmosphere, then 413 mg of DTBAD (1.79 mmol) was added, and the mixture was stirred at 55 °C for 2 h. Then, it was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 479 mg of ethyl (2*R*)-2-[3-bromo-2-(4-fluorophenyl)-benzofuran-4-yl]oxy-3-[2-[2-(2-methoxyphenyl)pyrimidin-4-yl]oxyphenyl]propanoate (80% purity, 0.55 mmol, 77%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.86 (d, J = 5.1 Hz, 1H), 8.12−8.07 (m, 2H), 7.62 (d, J = 5.1 Hz, 1H), 7.55−7.51 (m, 1H), 7.49−7.44 (m, 2H), 7.43−7.38 (m, 2H), 7.27−7.23 (m, 2H), 7.22−7.17 (m, 1H), 7.17−7.13 (m, 1H), 7.11−7.08 (m, 1H), 7.06−7.02 (m, 1H), 6.97−6.92 (m, 1H), 6.62−6.60 (m, 1H), 5.32−5.24 (m, 3H), 4.13 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.55−3.49 (m, 1H), 3.33−3.28 (m, 1H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.2, 165.7, 164.8, 162.3, 157.7, 157.2, 155.8, 154.0, 151.6, 148.3, 132.1, 131.0, 130.9, 129.1, 128.5, 128.4, 126.6, 124.3, 120.9, 120.1, 120.0, 117.1, 116.0, 115.8, 112.2, 111.9, 106.0, 105.1, 75.8, 69.2, 61.0, 55.7, 33.5, 13.9. LRMS calculated for $C_{37}H_{30}BrFN_2O_6$: 696.1; found: 697.2 (M + H).

*Step B: (2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy] phenyl}-2-(4-fluorophenyl)-1-benzofuran-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**21**).* Ethyl (2*R*)-2-[3-bromo-2-(4-fluorophenyl)benzofuran-4-yl]oxy-3-[2-[2-(2-methoxyphenyl)pyrimidin-4-yl]oxyphenyl]propanoate (465 mg, 0.667 mmol) and 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]-4-methylpiperazine[7a] (342 mg, 0.866 mmol) were dissolved in 8 mL of dioxane, then 652 mg of Cs_2CO_3 (2.00 mmol), 48 mg of AtaPhos (0.068 mmol), and 8 mL of water were added, and the mixture was stirred under a N_2 atmosphere at 105 °C in an MW reactor for 25 min. Then, the mixture was acidified with 1 M aq. HCl solution and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The obtained intermediate was dissolved in 12 mL of dioxane, then 195 mg of $LiOH·H_2O$ (4.63 mmol) and 12 mL of water were added, and the mixture was stirred at 40 °C for 1.5 h. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with 2-MeTHF. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were separated and purified via preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted later was collected as **21** (65 mg, 0.076 mmol, 11%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.86 (d, J = 5.1 Hz, 1H). 7.70 (d, J = 5.1 Hz, 1H), 7.55−7.52 (m, 1H), 7.49−7.39 (m, 4H), 7.26−7.19 (m, 4H), 7.18−7.12 (m, 3H), 7.07−6.97 (m, 2H), 6.74−6.70 (m, 1H), 6.52−6.49 (m, 1H), 6.30−6.26 (m, 1H), 5.27−5.18 (m, 2H), 4.89−4.84 (m, 1H), 4.26−4.17 (m, 2H), 3.75 (s, 3H), 3.23−3.15 (m, 1H), 2.77−2.69 (m, 2H), 2.60−2.44 (m, 5H), 2.43−2.26 (m, 4H), 2.15 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 164.8, 161.9, 157.8, 157.3, 155.5, 136.1, 131.2, 131.1, 130.3, 129.9, 128.5, 128.0, 127.6, 126.2, 125.9, 125.1, 120.5, 120.2, 118.7, 116.0, 115.9, 112.3, 111.7, 111.0, 105.1, 104.2, 75.6, 69.1, 67.2, 56.2, 54.4, 52.7, 45.3, 33.4, 17.6. HRMS calculated for $C_{49}H_{46}ClFN_4O_7$: 856.3039; found: 429.1604 (M + 2H).

*(2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-methyl-1H-indol-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}phenyl)propanoic Acid (**22**). Step A: 1-(Benzenesulfonyl)-4-benzyloxy-indole.* 4-Benzyloxy-1*H*-indole (7.00 g, 31.4 mmol) was dissolved in 60 mL of dry DMF, and then 1.32 g of NaH (32.9 mmol, 60% in mineral oil) was added at 0 °C. The mixture was stirred for 1 h, then 6.09 g of benzenesulfonyl chloride (34.5 mmol) was added dropwise, and the mixture was stirred at 0 °C for 1 h. Then, it was diluted with water and extracted with DCM. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure and then purified via flash chromatography using heptane and EtOAc as eluents to obtain 9.23 g of 1-(benzenesulfonyl)-4-benzyloxy-indole (25.4 mmol, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.00−7.94 (m, 2H), 7.72 (d, J = 3.7 Hz, 1H), 7.71−7.67 (m, 1H), 7.63−7.56 (m, 2H), 7.54 (d, J = 8.3 Hz, 1H), 7.49−7.44 (m, 2H), 7.41−7.36 (m, 2H), 7.35−7.30 (m, 1H), 7.27 (t, J = 8.1 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 3.7 Hz, 1H), 5.20 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 151.8, 137.0, 136.9, 135.4, 134.7, 129.9, 128.5, 127.9, 127.5, 126.7, 126.0, 125.5, 120.7, 106.3, 106.1, 105.6, 69.4. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 77 (32), 91 (100), 141 (18), 222 (6), 272 (11), 363 (10, [M^+]).

Step B: 1-(Benzenesulfonyl)-4-benzyloxy-2-iodo-indole. 1-(Benzenesulfonyl)-4-benzyloxy-indole (5.08 g, 14.0 mmol) was dissolved in 140 mL of dry THF. LDA solution (8.54 mL, 15.4 mmol, 1.8 M in THF, heptane, PhEt) was added at −78 °C and the mixture was stirred for 1 h. Then, 4.26 g of I_2 (16.8 mmol) was added and the mixture was stirred for 1 h at −78 °C. Next, it was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with aq. $Na_2S_2O_3$ solution and water, then dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 5.80 g of 1-(benzenesulfonyl)-4-benzyloxy-2-iodo-indole (11.9 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.92−7.87 (m, 3H), 7.57−7.53 (m, 1H), 7.47−7.32 (m, 7H), 7.20−7.15 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 5.13 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 167.0, 150.7, 139.8, 138.2, 136.6, 134.0, 131.8, 129.1, 128.6, 128.1, 127.4, 127.2, 126.8, 125.8, 125.6, 125.5, 122.7, 121.4, 108.6, 105.2, 70.1.

Step C: 1-(Benzenesulfonyl)-4-benzyloxy-2-(4-fluorophenyl)indole. 1-(Benzenesulfonyl)-4-benzyloxy-2-iodo-indole (5.80 g, 11.9 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)fluorobenzene (3.16 g, 14.2 mmol) were dissolved in 75 mL of THF, then 7.73 g of Cs_2CO_3 (23.7 mmol), 420 mg of AtaPhos (0.59 mmol), and 25 mL of water were added, and the mixture was stirred at 70 °C under a N_2 atmosphere for 2 h. The mixture was then concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 5.30 g of 1-(benzenesulfonyl)-4-benzyloxy-2-(4-fluorophenyl)indole (11.6 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.79 (d, J = 8.3 Hz, 1H), 7.69−7.64 (m, 1H), 7.60−7.48 (m, 6H), 7.43−7.27 (m, 8H), 7.00 (d, J = 8.3 Hz, 1H), 5.76 (s, 1H),

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5.22 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.4, 151.7, 139.1, 137.5, 136.7, 136.6, 134.8, 133.8, 129.7, 129.3, 128.4, 128.3, 128.1, 127.74, 127.68, 127.3, 126.7, 126.4, 119.3, 114.8, 108.0, 107.1, 100.4, 69.7.

Step D: 1-(Benzenesulfonyl)-4-benzyloxy-2-(4-fluorophenyl)-3-iodo-indole. 1-(Benzenesulfonyl)-4-benzyloxy-2-(4-fluorophenyl)indole (4.92 g, 10.8 mmol), Ag_2SO_4 (3.69 g, 11.8 mmol), and iodine (3.00 g, 11.8 mmol) were stirred in 100 mL of EtOH at rt for 1 h. Then, the mixture was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 5.50 g of 1-(benzenesulfonyl)-4-benzyloxy-2-(4-fluorophenyl)-3-iodo-indole (9.43 mmol, 88%). LRMS calculated for $C_{27}H_{19}FINO_3S$: 583.0; found: 584.2 (M + H).

Step E: 1-(Benzenesulfonyl)-4-benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indole. 1-(Benzenesulfonyl)-4-benzyloxy-2-(4-fluorophenyl)-3-iodo-indole (5.50 g, 9.42 mmol) and 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]-4-methyl-piperazine[7a] (4.46 g, 11.3 mmol) were dissolved in 75 mL of THF, then 6.14 g of Cs_2CO_3 (18.8 mmol), 25 mL of water, and 354 mg of AtaPhos (0.50 mmol) were added, and the mixture was stirred at 70 °C under a N_2 atmosphere for 1 h. Then, it was concentrated under reduced pressure and purified via flash chromatography using heptane, EtOAc, and MeOH as eluents to obtain 6.50 g of 1-(benzenesulfonyl)-4-benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)indole (8.97 mmol, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.85 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 7.3 Hz, 1H), 7.61−6.90 (m, 2H), 7.53−7.47 (m, 4H), 7.40 (t, J = 8.2 Hz, 1H), 7.20−7.07 (m, 5H), 6.96 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 7.0 Hz, 2H), 4.96 (d, J = 12.3 Hz, 1H), 4.86 (d, J = 12.3 Hz, 1H), 4.11−4.05 (m, 1H), 4.00−3.95 (m, 1H), 3.54−3.17 (m, 4H), 2.75 (t, J = 5.4 Hz, 2H), 2.79−2.44 (m, 4H), 2.29 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 161.9, 153.1, 152.4, 137.9, 136.7, 136.3, 135.3, 134.5, 129.5, 128.8, 127.8, 127.2, 127.1, 127.0, 126.6, 126.2, 125.9, 124.1, 121.7, 120.0, 114.4, 109.6, 108.8, 106.9, 68.9, 67.1, 56.2, 54.3, 52.5, 21.1, 17.4.

Step F: 4-Benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1H-indole. 1-(Benzenesulfonyl)-4-benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-indole (6.50 g, 8.97 mmol) was dissolved in 100 mL of THF and 100 mL of MeOH, then 28.3 g of $Ba(OH)_2{\cdot}8H_2O$ (89.7 mmol) was added, and the mixture was stirred at 70 °C for 2 days. The mixture was then filtered, and the filtrate was concentrated under reduced pressure and purified via flash chromatography using DCM and MeOH as eluents to obtain 3.50 g of 4-benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1*H*-indole (5.99 mmol, 67%). LRMS calculated for $C_{35}H_{35}ClFN_3O_2$: 583.2; found: 584.2 (M + H).

Step G: 4-Benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1-methyl-indole. 4-Benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1*H*-indole (1.63 g, 2.78 mmol) was dissolved in 25 mL of dry DMF and cooled to 0 °C. Then, 123 mg of NaH (3.06 mmol, 60% in mineral oil) was added and the mixture was stirred for 1 h. Then, 395 mg of MeI (2.78 mmol) was added and the mixture was stirred for 1 h. Then, it was poured into water and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using DCM and MeOH as eluents to obtain 1.61 g of 4-benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1-methyl-indole (2.69 mmol, 97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.34−7.28 (m, 2H), 7.24−7.10 (m, 7H), 6.97 (d, J = 8.4 Hz, 1H), 6.83−6.76 (m, 3H), 6.68 (dd, J = 6.3, 2.4 Hz, 1H), 5.01 (d, J = 12.8 Hz, 1H), 4.93 (d, J = 12.8 Hz, 1H), 4.17−4.10 (m, 1H), 4.09−4.02 (m, 1H), 3.63 (s, 3H), 3.10−2.60 (m, 8H), 2.84 (br s, 2H), 2.58 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 152.6, 138.1, 137.3, 137.2, 135.6, 132.6, 135.4, 130.4, 129.9, 127.8, 126.9, 125.8, 122.7, 121.5, 117.1, 115.3, 112.8, 109.4, 103.7, 101.4, 68.5, 67.1, 55.8, 53.4, 35.8, 31.2, 30.9, 18.1.

Step H: 3-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1-methyl-indol-4-ol. 4-Benzyloxy-3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1-methyl-indole (1.60 g, 2.68 mmol) was dissolved in 10 mL of DCM, then 0.49 mL of HBr solution (2.68 mmol, 33% in AcOH) was added, and the mixture was stirred at rt for 1 h. Then, it was diluted with 10% aq. K_2CO_3 solution and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using DCM and MeOH as eluents and then via preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents to obtain 200 mg of 3-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]-phenyl]-2-(4-fluorophenyl)-1-methyl-indol-4-ol (0.39 mmol, 15%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.02 (s, 1H), 7.29−7.15 (m, 4H), 7.06−6.92 (m, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.38 (dd, J = 7.2, 1.1 Hz, 1H), 4.12−4.01 (m, 2H), 3.58 (s, 3H), 2.70 (t, J = 5.8 Hz, 2H), 2.58−2.40 (m, 4H), 2.40−2.19 (m, 4H), 2.14 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 151.5, 140.9, 138.7, 137.4, 136.4, 136.0, 135.1, 132.6, 130.4, 129.7, 127.8, 122.7, 115.3, 109.4, 104.3, 101.4, 66.9, 56.5, 54.8, 53.2, 45.8, 31.2, 18.2.

Step I: Ethyl (2S)-3-[2-[[2-(2-Methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]-2-(p-tolylsulfonyloxy)propanoate. **R2b** (3.67 g, 8.97 mmol) was dissolved in 12 mL of pyridine, and then 1.97 g of TsCl (10.3 mmol) was added at 0 °C. The mixture was stirred at rt for 3 days. Then, the mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with 1 M aq. citric acid solution, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure to give 2.94 g of ethyl (2*S*)-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]-phenyl]-2-(*p*-tolylsulfonyloxy)propanoate (5.23 mmol, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.93 (d, J = 5.0 Hz, 1H), 7.57 (dd, J = 7.6, 1.8 Hz, 1H), 7.52−7.45 (m, 2H), 7.43−7.34 (m, 2H), 7.24−7.15 (m, 4H), 7.13−7.04 (m, 2H), 6.92−6.83 (m, 2H), 5.12 (d, J = 15.0 Hz, 1H), 4.98 (dd, J = 9.5, 4.4 Hz, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.79 (s, 3H), 3.25 (dd, J = 13.9, 4.4 Hz, 1H), 3.00 (dd, J = 13.9, 9.5 Hz, 1H), 2.35 (s, 3H), 1.12 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 168.2, 165.5, 164.9, 157.8, 157.3, 155.4, 145.0, 131.6, 131.4, 131.1, 130.9, 129.9,

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128.8, 128.3, 127.3, 122.2, 121.0, 120.2, 115.4, 112.3, 111.8, 76.3, 69.0, 61.5, 55.7, 33.3, 21.1, 20.8, 14.1, 13.8.

*Step J: (2R)-2-{[(3S$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)-1-methyl-1H-indol-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**22**).* 3-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)-1-methyl-indol-4-ol (60 mg, 0.12 mmol), ethyl (2*S*)-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]-phenyl]-2-(*p*-tolylsulfonyloxy)propanoate (101 mg, 0.18 mmol), and Cs_2CO_3 (80 mg, 0.24 mmol) were dissolved in 2 mL of dry DMF and stirred at 50 °C for 3 h. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The obtained intermediate was dissolved in 3 mL of dioxane, 10 mg of LiOH·H_2O (0.24 mmol) and 3 mL of water were added, and it was stirred at rt for 3 h. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were separated and purified by preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted later was collected as **22** (4.3 mg, 0.0049 mmol, 4.1%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.85 (d, J = 5.2 Hz, 1H), 7.55−7.52 (m, 1H), 7.48−7.41 (m, 2H), 7.30−7.13 (m, 6H), 7.09−6.92 (m, 7H), 6.62−6.57 (m, 1H), 6.28 (d, J = 7.6 Hz, 1H), 6.08−6.03 (m, 1H), 5.21 (d, J = 15.1 Hz, 1H), 5.17 (d, J = 15.1 Hz, 1H), 4.67−4.56 (m, 1H), 4.18−4.08 (m, 2H), 3.76 (s, 3H), 3.61 (s, 3H), 3.21−3.16 (m, 1H), 2.67−2.62 (m, 2H), 2.49−2.37 (m, 5H), 2.31−2.15 (m, 4H), 2.08 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.5, 157.8, 138.3, 132.4, 131.0, 120.2, 119.6, 119.5, 116.5, 115.4, 115.3, 112.2, 109.9, 56.4, 55.7, 54.7, 53.0, 45.7, 32.9, 31.4, 18.0. HRMS calculated for $C_{50}H_{49}ClFN_5O_6$: 869.3355; found: 435.6767 (M + 2H).

*(2R)-2-[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(4-fluorophenyl)-7-methylpyrrolo[2,3-d]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoic Acid (**23**). Step A: Ethyl 2-Amino-5-(4-fluorophenyl)-1H-pyrrole-3-carboxylate.* Ethyl 3-amino-3-iminopropanoate hydrochloride (8.33 g, 50.0 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (10.9 g, 50.0 mmol) were dissolved in 100 mL of EtOH and stirred at rt for 30 min. Then, it was cooled to 0 °C and 50 mL of 1 M NaOEt solution in EtOH (50.0 mmol) was added. Next, it was stirred at 60 °C for 90 min. An additional 33 mL of 1 M NaOEt solution in EtOH (33.0 mmol) was added at rt and it was stirred at 60 °C for further 1 h. Then, it was concentrated under reduced pressure, diluted with water, and extracted with EtOAc. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography using heptane and EtOAc as eluents to obtain 6.97 g of ethyl 2-amino-5-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (28.1 mmol, 56%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.75 (br s, 1H), 7.55−7.48 (m, 2H), 7.18−7.10 (m, 2H), 6.44 (d, J = 2.9 Hz, 1H), 5.68 (br s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.25 (t, 3H).

Step B: 6-(4-Fluorophenyl)-3,7-dihydropyrrolo[2,3-d]pyrimidin-4-one. Ethyl 2-amino-5-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (6.83 g, 27.5 mmol) was dissolved in 12 mL of DMF, then 12 mL of HCOOH and 50 mL of $HCONH_2$ were added, and the mixture was stirred at 160 °C for 16 h in a sealed reaction vessel. Then, it was cooled to rt, 150 mL of ^{i}PrOH was added, and the formed precipitate was filtered, washed with heptane, and dried *in vacou* to obtain 5.50 g of 6-(4-fluorophenyl)-3,7-dihydropyrrolo[2,3-*d*]pyrimidin-4-one (24.0 mmol, 87%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.35 (s, 1H), 11.86 (s, 1H), 7.90−7.84 (m, 3H), 7.29−7.23 (m, 2H), 6.92 (d, J = 2.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 161.4, 158.2, 149.4, 143.8, 132.2, 128.1, 126.6, 115.8, 109.1, 99.2.

Step C: 4-Chloro-6-(4-fluorophenyl)-7H-pyrrolo[2,3-d]pyrimidine. The solution of 4.50 g of 6-(4-fluorophenyl)-3,7-dihydropyrrolo[2,3-*d*]pyrimidin-4-one (19.6 mmol) in 46 mL of $POCl_3$ (491 mmol) was stirred at 90 °C for 3 h. Then, it was concentrated under reduced pressure, and the residue was poured onto ice. The pH was adjusted to 7 using solid K_2CO_3, and then the mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure to give 4.47 g of 4-chloro-6-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (18.0 mmol, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 13.04 (br s, 1H), 8.60 (s, 1H), 8.12−8.04 (m, 2H), 7.40−7.33 (m, 2H), 7.10 (d, J = 2.0 Hz, 1H).

Step D: 4-Chloro-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-d]pyrimidine. 4-Chloro-6-(4-fluorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.87 g, 7.55 mmol) was dissolved in 38 mL of DMF, then 1.29 g of MeI (9.06 mmol) and 1.15 g of K_2CO_3 (8.30 mmol) were added, and it was stirred at rt for 1 h. Then, it was concentrated under reduced pressure. The residue was diluted with brine and then extracted with DCM. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Then, it was purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.45 g of 4-chloro-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-*d*]pyrimidine (5.54 mmol, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.69 (s, 1H), 7.83−7.75 (m, 2H), 7.46−7.39 (m, 2H), 6.80 (s, 1H), 3.83 (s, 3H).

Step E: 5-Bromo-4-chloro-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-d]pyrimidine. 4-Chloro-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-*d*]pyrimidine (1.36 g, 5.20 mmol) was dissolved in 16 mL of AcOH, then 5.46 mL of Br_2 solution (5.46 mmol, 1 M in AcOH) was added dropwise at 0 °C, and it was stirred at rt for 30 min. Then, it was concentrated under reduced pressure and diluted with sat. aq. $NaHCO_3$ solution, and it was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.66 g of 5-bromo-4-chloro-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-*d*]pyrimidine (4.87 mmol, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.72 (s, 1H), 7.73−7.66 (m, 2H), 7.50−7.43 (m, 2H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 162.9, 150.8, 150.3, 140.1, 133.0, 124.5, 116.0, 114.0.

Step F: Ethyl (2R)-2-[5-Bromo-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-d]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]-propanoate. 5-Bromo-4-chloro-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-*d*]pyrimidine (845 mg, 2.48 mmol) and **R2a**

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(1.27 g, 3.11 mmol) were dissolved in 10 mL of DMF, then 2.43 g of Cs_2CO_3 (7.44 mmol) was added, and the mixture was stirred at 60 °C for 6 h. Then, it was concentrated under reduced pressure, diluted with brine, and extracted with EtOAc. The combined organic phase was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.21 g of ethyl (2*R*)-2-[5-bromo-6-(4-fluorophenyl)-7-methyl-pyrrolo-[2,3-*d*]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoate (1.70 mmol, 69%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.91 (d, J = 5.1 Hz, 1H), 8.36 (s, 1H), 7.65−7.60 (m, 3H), 7.55−7.52 (m, 1H), 7.50−7.40 (m, 4H), 7.27−7.22 (m, 1H), 7.16−7.13 (m, 1H). 7.10−7.07 (m, 1H), 7.06−7.02 (m, 1H), 6.96−6.91 (m, 1H), 5.65 (dd, J = 9.3, 4.2 Hz, 1H), 5.33−5.22 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.60 (s, 3H), 3.60−3.54 (m, 1H), 3.26 (dd, J = 13.9, 9.3 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.9, 165.9, 164.8, 162.6, 160.5, 157.7, 157.2, 155.6, 151.1, 150.5, 136.4, 133.4, 132.3, 131.0, 130.8, 128.5, 128.3, 125.6, 124.3, 120.9, 120.1, 116.3, 115.4, 112.2, 111.9, 103.6, 85.1, 73.7, 69.1, 60.8, 55.7, 32.6, 30.4, 14.0. LRMS calculated for $C_{36}H_{31}BrFN_5O_5$: 711.1; found 712.0 (M + H).

*Step G: (2R)-2-[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-d]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoic Acid (**23**).* Ethyl (2*R*)-2-[5-bromo-6-(4-fluorophenyl)-7-methyl-pyrrolo[2,3-*d*]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoate (596 mg, 0.836 mmol) and 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]-4-methyl-piperazine[7a] (397 mg, 1.01 mmol) were dissolved in 8.5 mL of dioxane, then 689 mg of Cs_2CO_3 (2.11 mmol), 8.5 mL of water, and 59 mg of AtaPhos (0.084 mmol) were added, and the mixture was stirred at 75 °C under a N_2 atmosphere for 1.5 h. Then, it was neutralized with 1 M aq. HCl solution, diluted with brine, and extracted with THF. The combined organic layer was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Next, it was purified via flash chromatography using heptane, EtOAc, and MeOH as eluents and then via preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The obtained intermediate was dissolved in 6 mL of dioxane, 135 mg of LiOH·H_2O (3.21 mmol) and 6 mL of water were added, and it was stirred at rt for 2 h. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were separated and purified by preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **23** (110 mg, 0.126 mmol, 15%). Due to rapid isomerization, the compound showed only 90% purity in the LC measurements. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.89−8.86 (m, 1H), 8.33 (s, 1H), 7.76−7.72 (m, 1H), 7.54−7.51 (m, 1H), 7.48−7.43 (m, 1H), 7.41−7.36 (m, 2H), 7.28−7.22 (m, 2H), 7.16−7.01 (m, 3H), 6.97−6.94 (m, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 8.6 Hz, 1H), 6.56−6.52 (m, 1H), 5.95−5.91 (m, 1H), 5.31−5.16 (m, 3H), 4.21−4.09 (m, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 3.54−3.48 (m, 1H), 2.73 (t, 2H), 2.58−2.46 (m, 5H), 2.42 (s, 3H), 2.39−2.24 (m, 4H), 2.15 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 164.7, 162.0, 157.7, 157.2, 150.2, 135.4, 132.7, 131.3, 131.0, 130.8, 130.3, 127.9, 120.4, 120.1, 115.6, 115.5, 112.2, 111.6, 109.7, 73.6, 68.8, 67.2, 56.3, 55.7, 54.4, 52.7, 45.3, 33.0, 29.8, 18.3. HRMS calculated for $C_{48}H_{47}ClFN_7O_6$: 871.3260; found 436.6703 (M + 2H).

*(2R)-2-{[5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)furo[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-phenyl)propanoic Acid (**24**). Step A: Ethyl (2R)-2-[5-Bromo-6-(4-fluorophenyl)furo[2,3-d]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]-propanoate.* **R1d** (140 mg, 0.425 mmol), **R2a** (350 mg), ^{t}BuOH (5 mL), and Cs_2CO_3 (696 mg, 2.14 mmol) were placed in a flask and stirred at 55 °C for 90 min. Then, the mixture was concentrated under reduced pressure, neutralized with 1 M aq. HCl solution, diluted with brine, and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 270 mg of ethyl (2*R*)-2-[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]propanoate (0.386 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6): 8.92 (d, J = 5.1 Hz, 1H), 8.50 (s, 1H), 8.13−8.07 (m, 2H), 7.62 (d, J = 5.1 Hz, 1H), 7.52−7.41 (m, 5H), 7.29−7.23 (m, 1H), 7.16−7.08 (m, 2H), 7.05−7.00 (m, 1H), 6.99−6.94 (m, 1H), 5.72−5.67 (m, 1H), 5.33−5.23 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.63−3.57 (m, 1H), 1.15 (t, J = 7.1 Hz, 3H). LRMS calculated for $C_{35}H_{28}BrFN_4O_6$: 698.1; found 699.2 (M + H).

*Step B: (2R)-2-{[5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)furo[2,3-d]-pyrimidin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**24**).* Ethyl (2*R*)-2-[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]oxy-3-[2-[[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy]phenyl]-propanoate (239 mg, 0.342 mmol) and 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy]ethyl]-4-methyl-piperazine[7a] (162 mg, 0.410 mmol) were dissolved in 4 mL of dioxane, then 334 mg of Cs_2CO_3 (1.03 mmol), 4 mL of water, and 24 mg of AtaPhos (0.034 mmol) were added, and the mixture was stirred at 80 °C under a N_2 atmosphere for 20 min. Then, it was neutralized with 1 M aq. HCl solution, diluted with brine, and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. Then, it was purified via flash chromatography using heptane, EtOAc, and MeOH as eluents. The obtained intermediate was dissolved in 10 mL of dioxane, 97 mg of LiOH·H_2O (2.30 mmol) and 10 mL of water were added, and it was stirred at rt for 2 h. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents to obtain 94.3 mg of **24** (0.110 mmol, 32%) as a 1:1 mixture of diastereoisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.29 (br s, 1H), 8.90−8.86 (m, 1H), 8.48/8.47 (s, 1H), 7.78−7.72 (m, 1H), 7.56−6.93 (m, 12H), 6.71/6.60 (t, J = 7.4

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Hz, 1H), 6.26/6.00 (d, J = 7.4 Hz, 1H), 5.42/5.34 (dd, J = 10.1/10.6, 2.6/2.1 Hz, 1H), 5.28−5.17 (m, 2H), 4.32−4.21 (m, 2H), 3.754/3.744 (s, 3H), 3.58−3.52/3.46−3.41 (m, 1H), 2.84−2.75 (m, 2H), 2.70−2.28 (m, 9H), 2.44/2.22 (s, 3H), 2.20/1.96 (s, 3H). HRMS calculated for $C_{47}H_{44}ClFN_6O_7$: 858.2944; found: 430.1547 and 430.1555 (M + 2H).

*N-[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)furo[2,3-d]pyrimidin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**25**). Step A: (2R)-2-[[5-Bromo-6-(4-fluorophenyl)furo[2,3-d]pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)propanoic Acid.* **R1d** (1.97 g, 6.00 mmol) and (*R*)-2-amino-3-(2-hydroxy-phenyl)-propionic acid (1.93 g, 9.00 mmol) were dissolved in 12 mL of dry DMSO, and then 5.86 g of Cs_2CO_3 (18.0 mmol) was added. The mixture was stirred at 45 °C for 1 h, and then 120 mL of water was added. The pH was adjusted to 4 using 1 M aq. HCl solution, and then the precipitate was filtered, washed with water, and dried to obtain 2.52 g of (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)propanoic acid (5.32 mmol, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.34 (s, 1H), 8.08−8.00 (m, 2H), 7.46−7.38 (m, 2H), 7.08−7.04 (m, 1H), 7.04−6.98 (m, 1H), 6.85−6.82 (m, 1H), 6.70−6.64 (m, 1H), 4.49 (s, 1H), 3.27−3.20 (m, 1H), 3.13−3.05 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 173.3, 162.5, 156.1, 155.9, 154.5, 131.6, 128.7, 127.6, 124.6, 118.6, 116.2, 101.7, 56.0, 32.5.

Step B: Ethyl (2R)-2-[[5-Bromo-6-(4-fluorophenyl)furo[2,3-d]pyrimidin-4-yl]amino]-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-5-yl]methoxy]phenyl]propanoate. (2*R*)-2-[[5-Bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)propanoic acid (2.52 g, 5.32 mmol) was dissolved in 70 mL of HCl solution (1.25 M in EtOH) and stirred at 60 °C for 3 h. Then, it was concentrated under reduced pressure and then diluted with water. The precipitate was filtered and purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.95 g of ethyl (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]-amino]-3-(2-hydroxyphenyl)propanoate (3.90 mmol, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.79 (s, 1H), 8.31 (br s, 1H), 8.07−8.02 (m, 2H), 7.46−7.40 (m, 2H), 7.15−7.12 (m, 1H), 7.11−7.05 (m, 2H), 6.85−6.82 (m, 1H), 6.76−6.72 (m, 1H), 4.96−4.91 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.27−3.22 (m, 1H), 3.20−3.14 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.3, 162.5, 156.0, 155.3, 154.2, 145.3, 131.2, 128.9, 128.3, 124.4, 122.6, 119.2, 116.3, 114.8, 101.9, 88.9, 60.7, 54.8, 31.2, 14.0.

Step C: Ethyl (2R)-2-[[5-Bromo-6-(4-fluorophenyl)furo[2,3-d]pyrimidin-4-yl]amino]-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-5-yl]methoxy]phenyl]propanoate. Ethyl (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]-amino]-3-(2-hydroxyphenyl)propanoate (500 mg, 1.00 mmol), [2-(2-methoxyphenyl)pyrimidin-4-yl]methanol[7a] (540 mg, 2.50 mmol), and PPh_3 (656 mg, 2.50 mmol) were dissolved in 20 mL of dry toluene under a N_2 atmosphere, and then 576 mg of DTBAD (2.50 mmol) was added. The mixture was stirred at 60 °C for 40 min. Then, it was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to give 651 mg of ethyl (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]-amino]-3-[2-[[2-(2-methoxyphenyl)pyrimidin-5-yl]methoxy]-phenyl]propanoate (0.932 mmol, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.83 (d, J = 5.1 Hz, 1H), 8.28 (s, 1H), 7.97−7.92 (m, 2H), 7.47−7.42 (m, 3H), 7.40−7.34 (m, 2H), 7.30−7.28 (m, 1H), 7.27−7.22 (m, 1H), 7.14−7.09 (m, 2H), 7.00−6.97 (m, 1H), 6.96−6.93 (m, 1H), 6.83−6.80 (d, J = 7.5 Hz, 1H), 5.26−5.15 (m, 3H), 4.19−4.12 (m, 2H), 3.73 (s, 3H), 3.57 (dd, J = 8.7, 5.0 Hz, 1H), 3.33−3.27 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.3, 165.5, 164.7, 163.7, 162.5, 157.6, 157.2, 155.9, 154.1, 145.4, 131.4, 131.0, 130.8, 128.8, 128.8, 128.7, 128.3, 124.8, 124.3, 121.1, 120.0, 116.1, 115.2, 112.2, 112.1, 101.9, 88.8, 69.2, 61.0, 55.7, 53.8, 31.6, 14.0. HRMS calculated for $C_{35}H_{29}BrFN_5O_5$: 697.1336; found: 698.1402 (M + H).

*Step D: N-[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(4-fluorophenyl)furo[2,3-d]-pyrimidin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]-methoxy}-D-phenylalanine (**25**).* Ethyl (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)furo[2,3-*d*]pyrimidin-4-yl]amino]-3-[2-[[2-(2-methoxyphenyl)pyrimidin-5-yl]methoxy]phenyl]-propanoate (450 mg, 0.644 mmol) and 1-[2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenoxy]ethyl]-4-methyl-piperazine[7a] (305 mg, 0.773 mmol) were dissolved in 7 mL of THF, then 525 mg of Cs_2CO_3 (1.61 mmol), 7 mL of water, and 46 mg of AtaPhos (0.0644 mmol) were added, and the mixture was stirred at 70 °C under a N_2 atmosphere for 40 min. Then, it was diluted with brine, the pH was set to 4 with 1 M aq. HCl solution, and the mixture was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure and purified via flash chromatography using DCM and MeOH as eluents. The obtained intermediate was dissolved in 10 mL of dioxane, 168 mg of LiOH·H_2O (4.01 mmol) and 10 mL of water were added, and it was stirred at rt for 3 h. Then, it was diluted with brine, neutralized with 1 M aq. HCl solution, and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were separated and purified by preparative reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted earlier was collected as **25** (40 mg, 0.047 mmol, 5.4%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.84 (d, J = 5.1 Hz, 1H), 8.26 (s, 1H), 7.54−7.51 (m, 1H), 7.50 (d, J = 5.1 Hz, 1H), 7.48−7.41 (m, 3H), 7.29−7.11 (m, 6H), 7.06−7.01 (m, 1H), 6.99−6.92 (m, 2H), 6.84−6.79 (m, 1H), 5.58 (d, J = 6.0 Hz, 1H), 5.14−4.99 (m, 2H), 4.66−4.60 (m, 1H), 4.52−4.44 (m, 1H), 4.17−4.11 (m, 1H), 3.75 (s, 3H), 3.49 (dd, J = 14.0, 5.6 Hz, 1H), 3.01−2.91 (m, 4H) 2.82−2.55 (m, 8H), 2.38 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.2, 165.9, 164.5, 160.9, 157.6, 157.2, 156.2, 155.9, 154.5, 154.1, 144.4, 136.0, 131.0, 130.8, 130.4, 129.2, 128.4, 127.5, 127.3, 123.3, 120.6, 120.1, 116.1, 115.5, 113.5, 112.2, 112.0, 111.9, 102.8, 69.2, 66.1, 55.8, 55.7, 54.5, 44.2, 31.2, 17.2. HRMS calculated for $C_{47}H_{45}ClFN_7O_6$: 857.3104; found: 429.6637 (M + 2H).

*(2R)-2-{[(3R$_a$)-3-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-2-(4-fluorophenyl)imidazo[1,2-c]-pyrimidin-5-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**26**). Step A: 1-(2-Bromo-1,1-dimethoxyethyl)-4-fluorobenzene.* 2-Bromo-1-(4-fluorophenyl)ethan-1-one (8.68 g, 40.0 mmol) was dissolved in 80 mL of MeOH, then 8.75 mL of $CH(OMe)_3$ (80.0 mmol) and 380 mg of TsOH·H_2O (2.00 mmol) were added, and the mixture was stirred at a reflux temperature for 4 h to reach complete conversion. Then, it was concentrated

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under reduced pressure and diluted with Et_2O. It was washed with 10% aq. K_2CO_3 solution, dried over $MgSO_4$, and filtered, and the filtrate was concentrated under reduced pressure to obtain 10.16 g of 1-(2-bromo-1,1-dimethoxyethyl)-4-fluorobenzene (38.6 mmol, 97%). ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 7.53−7.43 (m, 2H), 7.12−7.00 (m, 2H), 3.60 (s, 2H), 3.22 (s, 6H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ ppm: 162.6, 134.4, 129.2, 114.8, 101.1, 49.3, 35.4.

Step B: 5-Chloro-2-(4-fluorophenyl)imidazo[1,2-c]pyrimidine. A high-pressure reaction vessel made of steel was charged with 633 mg of 2-chloropyrimidin-4-amine (4.89 mmol), 1.54 g of 1-(2-bromo-1,1-dimethoxyethyl)-4-fluorobenzene (5.87 mmol), 120 mg of $Sc(OTf)_3$ (0.24 mmol), and 50 mL of MeCN, and the mixture was stirred at 120 °C for 24 h to reach complete conversion. Then, it was diluted with DCM and washed with saturated aq. $NaHCO_3$ solution. The aqueous layer was extracted with DCM. The combined organic layer was dried over $MgSO_4$ and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using hexanes and EtOAc as eluents to obtain 229 mg of 5-chloro-2-(4-fluorophenyl)-imidazo[1,2-*c*]pyrimidine (0.93 mmol, 19%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.64 (s, 1H), 8.20−8.13 (m, 2H), 7.90 (d, J = 6.4 Hz, 1H), 7.69 (d, J = 6.4 Hz, 1H), 7.36−7.29 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.4, 145.9, 145.0, 139.3, 136.6, 129.0, 128.3, 115.8, 110.8, 107.7. HRMS calculated for $C_{12}H_7ClFN_3$: 247.0312; found: 248.0397 (M + H).

Step C: 3-Bromo-5-chloro-2-(4-fluorophenyl)imidazo[1,2-c]pyrimidine. 5-Chloro-2-(4-fluorophenyl)imidazo[1,2-*c*]-pyrimidine (198 mg, 0.80 mmol) was dissolved in 4.8 mL of DMF and then cooled to 0 °C. Then, 142 mg of NBS (0.80 mmol) was added and the mixture was allowed to warm up to rt and was stirred for 2 h to reach complete conversion. Next, the mixture was poured onto saturated aq. $NaHCO_3$ solution and the formed precipitate was filtered and washed with water. The crude product was purified via flash chromatography using hexanes and EtOAc as eluents to obtain 142 mg of 3-bromo-5-chloro-2-(4-fluorophenyl)imidazo[1,2-*c*]pyrimidine (0.43 mmol, 54%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.05−8.00 (m, 2H), 7.90 (d, J = 6.3 Hz, 1H), 7.73 (d, J = 6.3 Hz, 1H), 7.42−7.35 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 162.3, 147.4, 144.0, 139.3, 136.1, 130.7, 128.5, 115.6, 112.0, 91.4. HRMS calculated for $C_{12}H_6BrClFN_3$: 324.9418; found: 325.9496 (M + H).

Step D: Ethyl (2R)-2-{[3-Bromo-2-(4-fluorophenyl)-imidazo[1,2-c]pyrimidin-5-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)-propanoate. 3-Bromo-5-chloro-2-(4-fluorophenyl)imidazo-[1,2-*c*]pyrimidine (102 mg, 0.312 mmol) and **R2a** (140 mg, 0.344 mmol) were dissolved in 3 mL of dry DMSO under a N_2 atmosphere, then 305 mg of Cs_2CO_3 (0.936 mmol) was added, and the mixture was stirred at rt for 1 h to reach complete conversion. Then, it was diluted with brine and water, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 177 mg of ethyl (2*R*)-2-{[3-bromo-2-(4-fluorophenyl)imidazo[1,2-*c*]-pyrimidin-5-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoate (0.253 mmol, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.90 (d, J = 5.1 Hz, 1H), 8.06−8.00 (m, 2H), 7.62 (d, J = 5.1 Hz, 1H), 7.56 (d, J = 6.5 Hz, 1H), 7.50 (dd, J = 7.6, 1.8 Hz, 1H), 7.49 (dd, J = 7.4, 1.7 Hz, 1H), 7.42 (ddd, J = 8.4, 7.4, 1.9 Hz, 1H), 7.38−7.32 (m, 2H), 7.27 (ddd, J = 8.2, 7.6, 1.7 Hz, 1H), 7.23 (d, J = 6.5 Hz, 1H), 7.15−7.09 (m, 2H), 7.01 (td, J = 7.5, 1.0 Hz, 1H), 6.96 (td, J = 7.4, 1.0 Hz, 1H), 5.80 (dd, J = 9.2, 4.6 Hz, 1H), 5.31 (d, J = 14.7 Hz, 1H), 5.27 (d, J = 14.7 Hz, 1H), 4.22−4.11 (m, 2H), 3.75 (s, 3H), 3.62 (dd, J = 13.9, 4.5 Hz, 1H), 3.36 (dd, J = 14.0, 9.2 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.0, 165.6, 164.8, 162.2, 157.7, 157.2, 155.8, 147.8, 147.6, 142.5, 138.6, 132.0, 131.0, 130.8, 130.2, 128.8, 128.7, 128.3, 123.7, 121.0, 120.1, 115.51, 115.47, 112.2, 112.0, 107.0, 88.7, 75.9, 69.1, 61.3, 55.7, 32.4, 13.9. HRMS calculated for $C_{35}H_{29}BrFN_5O_5$: 697.1336; found: 698.1419 (M + H).

*Step E: (2R)-2-[(3R$_a$)-3-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-2-(4-fluorophenyl)imidazo-[1,2-c]pyrimidin-5-yl]oxy-3-[2-[[2-(2-methoxyphenyl)-pyrimidin-4-yl]methoxy]phenyl]propanoic Acid (**26**).* Ethyl (2*R*)-2-{[3-bromo-2-(4-fluorophenyl)imidazo[1,2-*c*]-pyrimidin-5-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoate (87 mg, 0.125 mmol) and 1-{2-[2-chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl}-4-methylpiperazine[7a] (118 mg, 0.300 mmol) were dissolved in 0.5 mL of 1,4-dioxane under a N_2 atmosphere, then 98 mg of Cs_2CO_3 (0.300 mmol), 0.2 mL of water, and 18 mg of AtaPhos (0.025 mmol) were added, and the mixture was stirred in a microwave reactor at 110 °C for 10 min. Then, the mixture was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. Then, it was purified via flash chromatography using heptane, EtOAc, and MeOH as eluents. The obtained intermediate was dissolved in 1 mL of THF, then 42 mg of $LiOH·H_2O$ and 1 mL of water were added, and the mixture was stirred at rt for 1 h to reach complete conversion. Then, it was diluted with brine, neutralized with 2 M aq. HCl solution, and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via reversed-phase chromatography using 25 mM aq. NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluted later was collected as **26** (4 mg, 0.0047 mmol, 4%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.90 (d, J = 5.2 Hz, 1H), 7.83 (d, J = 4.3 Hz, 1H), 7.57 (d, J = 6.4 Hz, 1H), 7.54 (dd, J = 7.5, 1.8 Hz, 1H), 7.53−7.48 (m, 3H), 7.46 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 6.4 Hz, 1H), 7.19−7.12 (m, 4H), 7.04 (td, J = 7.5, 0.9 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 7.3 Hz, 1H), 6.34 (d, J = 7.1 Hz, 1H), 5.43 (dd, J = 10.5, 2.7 Hz, 1H), 5.26 (d, J = 15.3 Hz, 1H), 5.21 (d, J = 15.3 Hz, 1H), 4.32−4.15 (m, 2H), 3.76 (s, 3H), 3.37−3.31 (m, 1H), 2.80−2.65 (m, 2H), 2.65−2.31 (m, 8H), 2.21 (s, 3H), 2.21−2.15 (m, 1H), 1.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.0, 164.6, 157.9, 157.2, 155.3, 154.4, 146.6, 141.0, 138.8, 137.4, 132.2, 131.0, 130.8, 130.4, 128.8, 128.4, 128.0, 124.3, 120.5, 120.1, 115.7, 115.4, 112.2, 111.8, 110.4, 105.8, 76.9, 68.9, 67.1, 56.1, 55.7, 54.0, 52.3, 44.8, 32.6, 17.6. HRMS calculated for $C_{47}H_{45}ClFN_7O_6$: 857.3104; found: 429.6638 (M + 2H).

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■ ASSOCIATED CONTENT

Supporting Information

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Molecular formula strings (XLSX)

Supplementary information available with description of data tables, structural determination details, LC chromatograms, and ^{1}H NMR spectra of key compounds (PDF)

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The X-ray structure mentioned in this paper has been deposited in the PDB with the following codes: **1**: 7NB4; **7b**: 7NB7. The authors will release the atomic coordinates and experimental data upon article publication.

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Notes

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■ ABBREVIATIONS USED

MCL-1, myeloid cell leukemia 1; Mcl-1, construct used for X-ray crystallography studies; BCL-2, B-cell lymphoma 2; BCL-x_L, B-cell lymphoma extra-large; BH3, BCL-2 homology domain 3; FBS, fetal bovine serum; FP, fluorescence polarization; QA, quench assay

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