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Discovery of S64315, a Potent and Selective Mcl-1 Inhibitor

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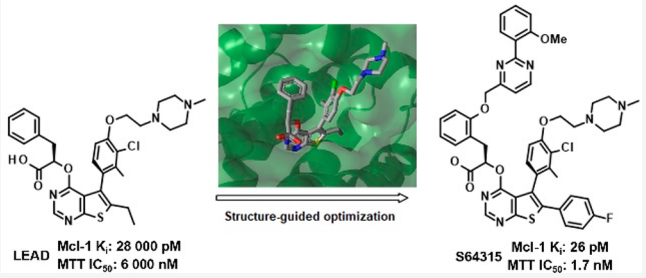
ABSTRACT: Myeloid cell leukemia 1 (Mcl-1) has emerged as an attractive target for cancer therapy. It is an antiapoptotic member of the Bcl-2 family of proteins, whose upregulation in human cancers is associated with high tumor grade, poor survival, and resistance to chemotherapy. Here we report the discovery of our clinical candidate S64315, a selective small molecule inhibitor of Mcl-1. Starting from a fragment derived lead compound, we have conducted structure guided optimization that has led to a significant (3 log) improvement of target affinity as well as cellular potency. The presence of hindered rotation along a biaryl axis has conferred high selectivity to the compounds against other members of the Bcl-2 family. During optimization, we have also established predictive PD markers of Mcl-1 inhibition and achieved both efficient in vitro cell killing and tumor regression in Mcl-1 dependent cancer models. The preclinical candidate has drug-like properties that have enabled its development and entry into clinical trials.



INTRODUCTION

Apoptosis, an evolutionary highly conserved form of programmed cell death, is an essential process for the elimination of no longer needed and dangerous cells.[1] Evasion of apoptosis is recognized as a critical element of the development as well as sustained expansion of tumors and also underlies resistance to diverse anticancer treatments.[2] Mcl-1 is a member of the Bcl-2 family, critical regulatory proteins of the mitochondrial apoptotic pathway, and is frequently upregulated in cancer.[3] Moreover increased expression of the MCL1 gene through transcriptional or post-transcriptional mechanisms was observed as a downstream consequence of several key oncogenic pathways.[4] Mcl-1 is needed to sustain the growth of diverse tumors, including acute myeloid leukemia (AML),[5] MYC-[6] or BCR-ABL-driven pre-B/B lymphomas,[7] certain breast cancers as well as non-small-cell lung carcinoma (NSCLC) derived cell lines that carry MCL1 gene amplifications.[8] Some compounds that broadly inhibit gene transcription or protein translation exert their cytotoxic effects in tumor cells (at least in part) by downregulating Mcl-1.[9]

In clinic, the highly promising activity of the Bcl-2-selective inhibitor venetoclax (Venclexta), which led to its approval in relapsed/refractory chronic lymphocytic leukemia (CLL) patients with 17p deletion and in AML in combination, has validated the concept of direct apoptosis activation in cancer therapy.[10] Until recently, only compounds showing weak cellular potency on Mcl-1 (high μM range) were available and therefore useful only as in vitro chemical tools.[11] Starting in late 2016, a series of potent and selective Mcl-1 inhibitors were disclosed (Figure 1) some of which have also recently entered clinical development.[12] The long-standing interest in Mcl-1 as a target and the late emergence of Mcl-1 targeting drug candidates suggest that drugging Mcl-1 is highly desirable but also very challenging. We have recently reported our successful efforts to establish a drug discovery platform for antiapoptotic targets[13] and its use in the identification of fragment hits for Mcl-1 and their development into a lead compound targeting Mcl-1.[14] The present manuscript describes our efforts to optimize this lead into a clinical candidate and details the unexpected events encountered in this process.

RESULTS AND DISCUSSION

Our starting point (**1a**) exhibited affinity on Mcl-1 (28 nM K_i)[14] and remarkable selectivity against other Bcl-2 family

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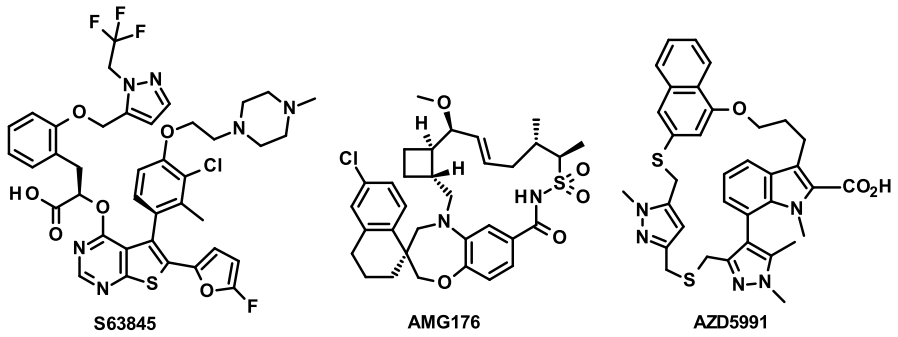

Figure 1. Structures of some recently disclosed potent and selective Mcl-1 inhibitors with reported in vivo efficacy.

members with an impact on the viability of Mcl-1 dependent multiple myeloma cell line H929[12a] at the single digit micromolar level. The primary objective of our lead optimization effort was to further enhance the affinity of our inhibitor. We determined the X-ray structure of **1a** bound to Mcl-1 (Figure 2), which suggested two main areas of

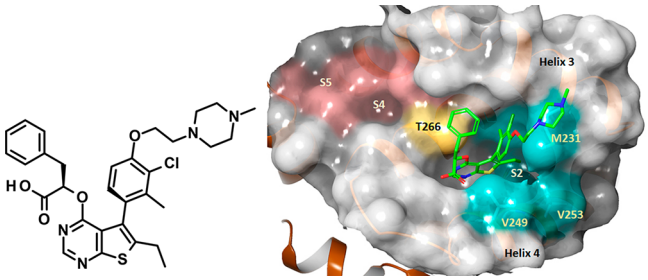

Figure 2. Structure of our Mcl-1 lead compound **1a** and the X-ray structure of its complex with Mcl-1 (PDB code 6QYO). S2 is highlighted in cyan, S4 and S5 are in pink. Residues of interest are as labeled.

exploitation: the more occluded hydrophobic S2 pocket that the 6-ethyl occupies and the more solvent exposed S4−S5 area extending from the benzyl across Thr266. The 6-ethyl moiety occupies the S2 pocket surrounded by hydrophobic residues (Val 249, Val253, Met231, and Met250) from helixes 3 and 4.

Our first attempts were directed at optimizing the filling of the S2 pocket. Since the X-ray structure of **1a** suggested that we only have limited space, a set of analogues (**1b−d**) carrying a small apolar substituent were synthesized and tested. While these modifications had only a minor effect on the target affinity, their influence on the cellular activity was more marked. The biggest improvement was achieved by the rigid 1-propynyl substituted analogue (**1d**), which improved activity 10-fold, probably through improved cell penetration. We also synthesized the cyclopropylated analogue **1e** that should not fit into the S2 pocket but surprisingly we observed no detrimental effect on the on-target affinity, suggesting that Mcl-1 was able to accommodate bigger substituents in this region through conformational rearrangement. In the next round we tested some sterically more demanding aromatic groups. The monocyclic furyl (**1f**), thienyl (**1g**), and phenyl (**1h**) substituents were equally accommodated by the protein resulting in affinities like **1a**, while their increased lipophilicity led to a marked improvement of their cellular activity. Further increasing the substituent to the bicyclic benzofurane (**1i**) resulted in a considerable drop in affinity marking the inability of Mcl-1 to rearrange sufficiently to accommodate a bicyclic moiety in this region. Further exploring the limits of this pocket, we investigated some monosubstituted aromatics. Introducing a methyl group next to the biaryl link of thiophene (**1j**) was detrimental, due probably to the fact that this change does not allow the two aromatic rings to adopt a beneficial coplanar conformation. If the substituent was shifted into the 3- or 4-position of the monocycle, then it was well tolerated on both the five (**1k**) and six membered (**1l**) substituent. On the other hand, the replacement of the phenyl ring of **1h** by 4-pyridyl (**1m**) resulted in a decrease of both the affinity and activity in H929 cells, due probably to the polarity of the latter leading to increased desolvation and decreased cell penetrance.

The next set of experiments explored the structure−activity relationship with analogues carrying a methoxy substituent on the lactic acid part (Table 1, **2a−l**). The reference compound **2a** exhibited an affinity for Mcl-1 of 20 nM, while its cellular activity was in the low micromolar range. The change of the 6-ethyl substituent to propynyl (**2b**) led to a similar change as observed for **1a**. The affinity was slightly decreased while the cellular activity improved considerably. Next we tested the fluorophenyl analogues **2c−f**. Neither the position of the fluorine on the benzene ring nor the number of fluorine substituents had a major effect. All four compounds had similar affinity for Mcl-1 (9−20 nM) and showed good cellular activity varying in a narrow range between 190 nM for **2c** and 230 nM for **2e**. Changing the fluorine to chlorine (**2g**) did not lead to significant changes. Replacement of the 3-chlorophenyl substituent by 3-pyridyl (**2h**) was well tolerated for target affinity but was detrimental for the cellular activity. Finally, we introduced a series of furane derivatives into the 6-position (**2i−l**). The parent compound **2j** showed a significant improvement both in affinity (4.0 nM vs 20 nM for **2a**) and in cellular activity (110 nM). The halogenated furane derivatives were equally potent. Their affinity for Mcl-1 ranged between 3 and 4 nM and achieved sub-100 nM cellular activities for the first time. The crystal structure of **2g** bound to Mcl-1 was obtained, and overlaying the bound structures of **1a** and **2g** (Figure 3) nicely demonstrated the conformational changes of Mcl-1 necessary to accommodate the latter compound. The superimposition revealed the movement of helix 4 as its backbone peels away from the binding site along with some side chain reorientation to give a more capacious pocket, which is necessary to hold a bigger group such as chlorophenyl from **2g**.

We also assessed the in vitro ADME properties of selected compounds (Table 1 in Supporting Information). In general, the modifications in the 6-position had only a minor effect on the predicted absorption (low to moderate) and liver

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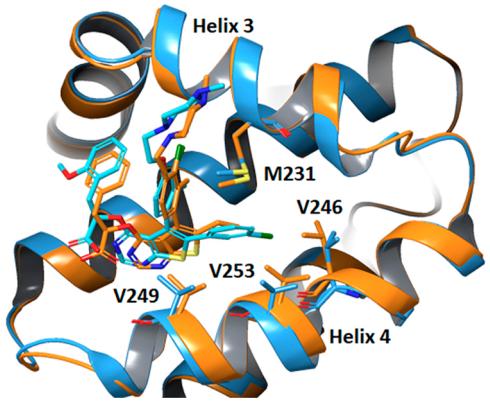

Figure 3. Comparison of the X-ray structures of the Mcl-1 inhibitors **1a** (orange, PDB code 6QYO) and **2g** (blue, 6YBG) bound to Mcl-1. The backbone and side chain movements of Helix 4 improve the binding of inhibitor **2g**.

microsomal stability (high in rodents, intermediate to low in human). Running the experiments with human hepatocytes for selected compounds in the presence of plasma resulted in high stability due probably to the very high plasma protein binding of these molecules (unbound fraction (fu) below 1%). The in vitro properties of **2i** (good cellular activity and high metabolic stability) suggested that this compound could also exhibit some activity in vivo. Mice bearing the Mcl-1 dependent human multiple myeloma AMO1[12a] tumors, as sensitive to Mcl-1 inhibition as H929, were treated intravenously with **2i** at 25 mg/kg and 75 mg/kg, respectively. The tumors were harvested 2 h after treatment, and the amount of cleaved PARP, a well-established apoptosis marker, was measured (Figure 4a). Marked cleaved PARP dose dependent effect was observed after **2i** treatment, with 80 and 120 fold increase (at 25 mg/kg and 75 mg/kg, respectively) compared to untreated tumors, showing in vivo apoptosis induction in the AMO-1 tumors after **2i** treatment.

Having optimized the substituent in the S2 pocket, we continued with the variation of the phenyllactic acid moiety for compounds bearing the 4-fluorofuryl (**3**) or the 4-fluorophenyl (**4**) moiety in position-6 in parallel (Table 2). We switched to a new assay format more suitable to assess the affinity of very potent binders toward Mcl-1, a static quenching assay. We introduced a set of five different substituents onto the ortho-position of the benzene ring, which was suggested to be the preferred vector toward the S4−S5 pockets based on the X-ray structures (Figure 2). The trifluoroethyl derivatives (**3a**, **4a**) showed a marked difference in affinity with **3a** being 10 times more potent, and its cellular activity was also markedly better (31 nM vs 114 nM, Table 2). A very similar behavior was observed for the tetrahydrofurylmethyl (**3b**, **4b**) and pyridylmethyl (**3c**, **4c**) molecule pairs. The fluorofuryl analogues (**3b**, **3c**) showed 4- to 5-fold higher affinity and 3−4 times higher cellular activity than the corresponding fluorophenyl derivatives **4b** and **4c**. Interestingly, replacing the pyridine by pyrazine (**3d** and **4d**) maintained the difference in the affinities (cf. 0.90 nM vs 5.0 nM), but the cellular activities became equipotent (36 nM vs 42 nM). Finally, replacing the pyrazine by *N*-methylpyrazole (**3e**, **4e**) broadened the gap in affinity (0.86 nM vs 21 nM). In cellular activity we observed a marked but smaller difference with **3e** registering at 44 nM and **4e** at 114 nM.

We selected a potent compound from each series, **3e** and **4d**, with similar ADME properties (Table 1 in Supporting Information) and assessed their activity in the in vivo PD study. Groups of xenografted mice bearing AMO1 tumors were

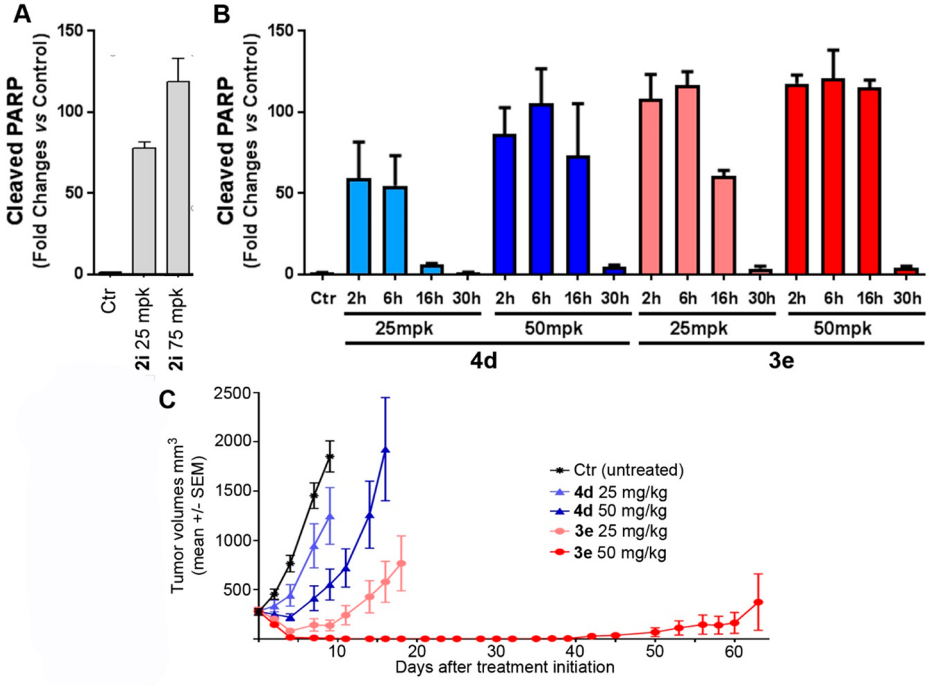

Figure 4. (A) Dose dependent apoptosis induction of **2i** in AMO1 xenografted mice evidenced through PARP cleavage induction 2 h after treatment (n = 3). (B) Time and dose dependent apoptosis induction by the Mcl-1 inhibitors **3e** and **4d** in AMO1 xenografted mice evidenced through PARP cleavage induction (n = 3). (C) Dose dependent antitumor activity of **3e** and **4d** in AMO1 xenografted mice following iv administration, for 5 consecutive days (n = 8).

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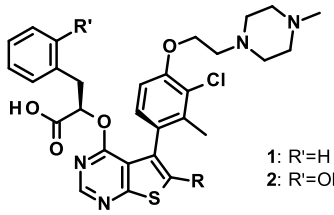
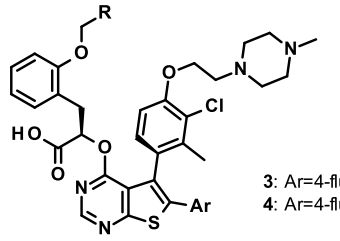
Table 1

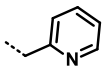
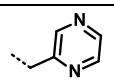
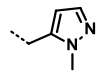


	R	Mcl-1 (nM)[1]	MTT IC_{50} (μM)[2]
1a		28	6.0
1b		34	2.3
1c		33	>37.5
1d		15	0.52
1e		22	1.1
1f		18	0.32
1g		40	0.95
1h		9.9	0.76
1i		73	3.3
1j		170	6.1
1k		50	2.9
1l		22	0.56
1m		82	>75
2a		20	2.8
2b		12	0.39
2c		20	0.19
2d		16	0.20
2e		12	0.23
2f		9.0	0.21
2g		13	0.19
2h		8.9	1.0
2i		8.1	0.11
2j		4.0	0.079
2k		3.0	0.070
2l		3.5	0.12

[1]K_i measured in Mcl-1 FP assay.[13] [2]Measured in H929 cell line with 10% FCS, 48 h.

Table 2



ID	R	Mcl-1 (nM)[1]	MTT IC_{50} (nM)[2]
3a	-CF_3	0.90	31
4a		11	114
3b		1.5	31
4b		8.1	136
3c		1.0	36
4c		4.4	168
3d		0.90	36
4d		5.0	42
3e		0.86	44
4e		21	114

[1]K_i measured in Mcl-1 quench assay. [2]Measured in H929 cell line with 10% CFS, 48 h.

treated with 25 mg/kg or 50 mg/kg doses, and the fold changes in the quantity of cleaved PARP were determined at different time points after iv bolus treatment. The results are shown in Figure 4b. In each case we observed a robust onset of apoptosis as evidenced by PARP cleavage registered after 6 h. For both compounds we observed a dose effect at the tested doses at time points 6 and 16 h. Interestingly, data suggest that in the PD study **3e** might be about twice as potent as **4d**, showing similar fold activation at the different time points at half the dose. In the case of **3e** we see a stronger dose dependence of PARP activation at 16 h than at 6 h. Irrespective of the compound or dose, the level of cleaved PARP after 30 h was close to the baseline in all samples. In order to test whether those PD results were predictive of antitumor activity, we evaluated **4d** and **3e** efficacy on AMO-1 grafted mice. Mice were treated intravenously (iv) with 25 mg/kg or 50 mg/kg of the respective compound for 5 consecutive days. In the case of **4d** we observed moderate dose dependent tumor growth inhibition (TGI_{max} = 96.2% and 125.6% at 25 mg/kg and 50 mg/kg, respectively) (Figure 4c and Table 4). The antitumor activity of **3e** was greater and led to tumor regression on treatment at the tested doses. At 25 mg/kg, the tumor regrew at the end of the treatment period, while at 50 mg/kg the effect was lasting, and the regrowth of the tumors started only 5 weeks later. The marked difference between antitumor activity of **3e** and **4d** suggests that evaluation of PARP cleavage 16 h after treatment might be used as a PD marker for compound screening.

To further explore the chemistry in these two subseries, we obtained the Mcl-1 bound X-ray structures of **3e** and **4d** (Figure 5). Both compounds bind in a similar manner to previous compounds of the series, and the heteroaromatic rings sit on top of the ridge between the so-called S2 and S4 pockets providing suitable vectors to grow into the latter region. The lasting tumor regression on **3e** treatment

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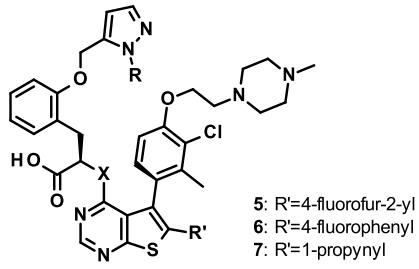
Table 3



compd	R	X	Mcl-1 (nM)[a]	MTT IC_{50} (nM)[b]	PARP 16 h[c]
5a	Et	O	0.077	21	
6a		O	0.34	44	
5b	*i*-Pr	O	0.12	13	32
6b		O	0.57	31	58
5c	Bu	O	0.014	4.8	
6c		O	0.088	16	
5d	*t*-Bu	O	0.046	7.8	118
6d		O	0.099	11	184
5e	CF_3-CH_2-	O	0.163	6.0	309
6e		O	0.76	41	151
5f	Bu	NH	0.42	47	125
7	Bu	O	0.023	18	107

[a]K_i measured in Mcl-1 quench assay. [b]Measured in H929 cell line with 10% CFS, 48 h. [c]Fold increase of cleaved PARP measured in AMO1 xenografted mice 16 h after iv bolus treatment at 12.5 mg/kg dose (n = 3).

prompted us to explore first the filling of the shallow S4 pocket through the variation of the substituent on the pyrazole ring. The methyl substituent in **3e** as shown in the X-ray does not directly interact with Mcl-1 We expected that the conformational flexibility of the two-atom linker should allow the pyrazole ring to flip and orient its substituent toward S4 to interact with Mcl-1 more productively. A collection of alkyl-substituted analogues was prepared and tested both in the 4-fluorofuryl (**5a**−**e**) and 4-fluorophenyl (**6a**−**e**) series. Increasing the length of the alkyl chain led to considerable improvement in both subseries. Growing from methyl (**3e**, **4e**) through ethyl (**5a**, **6a**) to butyl (**5c**, **6c**) resulted in a significant improvement of both affinity and cellular activity. Increasing the branching to isopropyl (**5b**, **6b**) and *tert*-butyl (**5d**, **6d**) was equally tolerated reaching sub-100 pM affinities of 10 nM or better cellular activity for both **5d** and **6d**. The trifluoroethyl-substituted molecules were also synthesized. In the fluorofuryl subseries with **5e** we reached 6 nM activity in the viability assay, while the fluorophenyl analogue **6e** was less active at 41 nM. At this stage we also wanted to see if the replacement of the hydroxy acid by an amino acid or the propynyl substitution in the 6-position that was beneficial for less decorated molecules (e.g., **1d** and **2b**) is tolerated in **5c**.

Table 4. Tumor Growth Inhibition Data for Compounds Tested in the AMO1 Efficacy Model[a]

compd	dose (mpk)	% TGI (day)	% TGI_{max} (day)	time to reach 500 mm^3 (median of the group)
3e	50	129.9 (d7)	154.9 (d2)	53
3e	25	120.5 (d7)	147.5 (d2)	23
4d	50	95 (d7)	125.6 (d2)	9
4d	25	63.6 (d7)	96.2 (d4)	7
5b	12.5	111.9 (d7)	173.1 (d2)	18
5e	12.5	118.9 (d7)	152.8 (d2)	32
8b	12.5	113.8 (d7)	120.5 (d2)	31
9b	12.5	120 (d7)	134.6 (d4)	28
9i	6.25	106 (d7)	132.4 (d2)	14
9m	6.25	189.5 (d4)	189.5 (d4)	38
9n	6.25	121.2 (d4)	130.8 (d2)	21
10b	6.25	116.8 (d4)	132.6 (d2)	28
11	6.25	142.5 (d4)	174.3 (d2)	32

[a]QD5, iv bolus treatment in each case, n = 8.

Changing the linker oxygen in **5c** to nitrogen (**5f**) led to a significant decrease of on-target affinity (0.42 nM vs 0.014 nM) as well as cellular activity (47 nM vs 4.8 nM). In contrast the replacement of the 4-fluorofuryl moiety by 1-propynyl (**7**) led to the highest affinity registered so far at 23 pM accompanied by a slightly disappointing 18 nM cellular activity.

Following the identification of several compounds that showed high cellular potency, a selection of them was assessed in the in vivo PD study in AMO1 xenografted mice with iv bolus treatment at 12.5 mg/kg. The fold activation results in the tumors harvested 16 h after treatment are listed in Table 3. Compounds **5b** and **6b** gave the weakest response with PARP increases at 32-fold and 58-fold, respectively. For compounds **5d**, **6d**, **5e**, and **6e** we observed a very strong apoptosis induction after 16 h with PARP increases between 118- and 309-fold, highlighting **5e** in particular. The amino acid analogue **5f** was also active in the PD study registering a 125-fold PARP increase. Replacing the aromatic moiety in the 6-position by an acetylene analogue (**7**) was well tolerated and gave strong apoptosis induction. In general, we can state that all studied compounds led to apoptosis induction and most of them showed a considerable pharmacodynamic effect.

To probe the predictive power of the PD data, two compounds were selected, **5b** as the least active and **5e** as the most active, and tested in the AMO1 efficacy model. Mice were treated with 12.5 mg/kg of the respective compound on 5 consecutive days using iv bolus administration. The measured efficacy data are listed in Table 4. Gratifyingly, both compounds induced rapid tumor regression evidenced by the respective TGI_{max} values of 173% and 153% observed 2 days after beginning of the treatment. This effect was persistent at day 7 corresponding to the last day of remaining mice in the

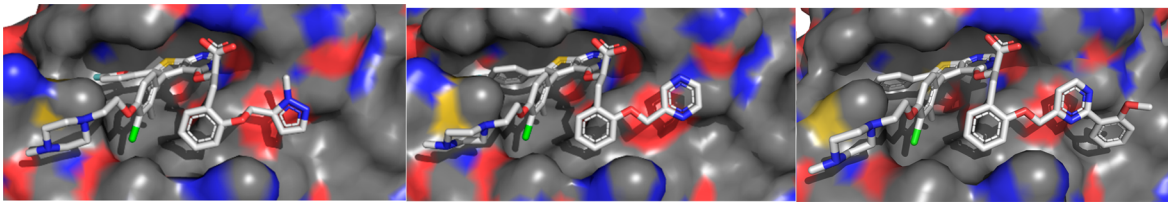


Figure 5. X-ray structures of the Mcl-1 inhibitors **3e** (PDB code 6YBJ), **4d** (6YBK), and **9m** (6YBL) bound to Mcl-1.

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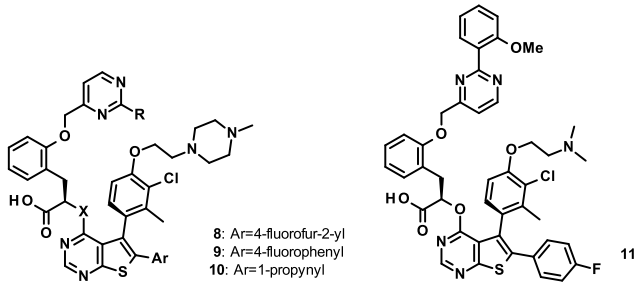
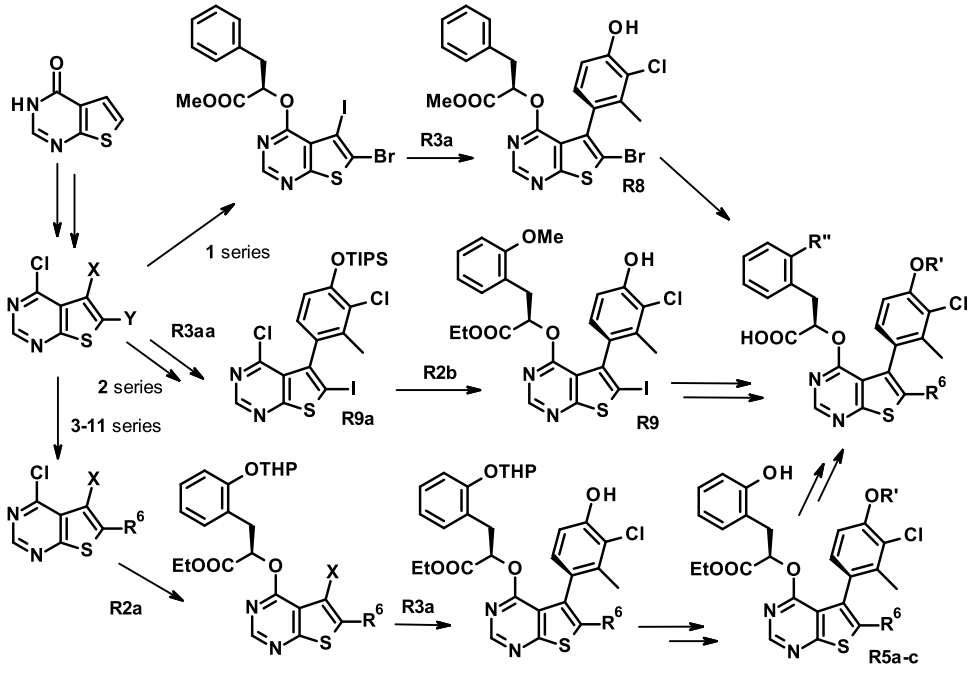
Table 5



compd	R	X	Mcl-1 (nM)[a]	MTT IC_{50} (nM)[b]	PARP 16 h[c]
8a	-OMe	O	0.12	15	NA
9a		O	0.36	24	NA
8b	morpholino	O	0.13	3.1	133
9b		O	0.64	14.4	129
8c	2-methoxyethyl	O	0.043	3.9	131
9c		O	0.72	5.7	78
8d	4-pyridyl	O	0.030	4.0	115
9d		O	0.036	3.7	NA
9e	2-pyridyl	O	0.052	12	32
9f	3-pyridyl	O	0.050	5.8	138
9g	2-furyl	O	0.081	8.1	141
9h	2-tolyl	O	0.055	4.7	151
9i	4-methylpyrid-3-yl	O	0.73	1.7	237
9j	3-methylpyrid-4-yl	O	0.034	3.5	120
9k	5-methoxy-2-methylpyrid-4-yl	O	0.048	5.7	25
9l	2-hydroxymethylphenyl	O	0.028	3.5	68
9m	2-methoxyphenyl	O	0.029	1.7	285
9n	2-methoxyphenyl	N	0.220	14	60
10a	2-methoxyphenyl	O	0.011	3.9	83
10b	2-methoxyphenyl	N	0.014	0.9	59
11			0.17	4.7	251

[a]K_i measured in Mcl-1 quench assay. [b]Measured in H929 cell line with 10% CFS, 48 h. [c]Fold increase of cleaved PARP measured in AMO1 xenografted mice 16 h after iv bolus treatment at 12.5 mg/kg dose (n = 3).

Scheme 1. Synthesis Strategies Followed in the Preparation of our Mcl-1 Inhibitors



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control group (TGI = 112% and 119% with **5b** and **5e**, respectively). Differentiation between the two compounds was observed on the time to relapse, as shown by the time to reach 500 mm^3. Indeed, while time to reach 500 mm^3 occurred 18 days after treatment for **5b**, this same size was reached 32 days after **5e** treatment showing a superiority of the latter compound.

Although **5e** showed very robust tumor regression, some of its other characteristics (e.g., light sensitivity) were suboptimal; therefore, we have also explored the further optimization of **4d**. As its Mcl-1 bound X-ray structure suggests (Figure 5), the vector for growing into S4 is the position meta to the oxymethyl moiety. We have established (data not shown) that replacing the pyrazine by pyrimidine is beneficial in terms of both affinity and compound behavior. For the first set of compounds bearing diverse substituents on the pyrimidine ring, we prepared both the fluorofuryl (**8a−d**) and fluorophenyl (**9a−d**) analogues. The small polar methoxy substituent (**8a**, **9a**) was tolerated in both series showing affinities in the several hundred picomolar range and 15 and 24 nM cellular activities, respectively (Table 5). Replacing methoxy by morpholine (**8b**, **9b**) had little effect on the affinity but improved the cellular activity of the compounds. The 2-methoxyethyl analogues showed an increase in affinity for **8c** registering at 43 pM while **9c** remained at 720 pM, which was accompanied by single digit nanomolar cellular potencies (3.9 and 5.7 nM, respectively). The introduction of an aromatic substituent, the 4-pyridyl moiety, was also beneficial. At this point the so far apparent difference in affinity between the fluorofuryl and fluorophenyl subseries disappeared, **8d** and **9d** having alike values of 30 pM and 36 pM, respectively, and their cellular activities were also very close (4.0 nM vs 3.7 nM).

To assess the predictivity of the in vitro assays, compounds **8b−c** and **9b−c** were tested in our PD model. They were injected at a dose of 12.5 mg/kg in AMO-1 grafted mice, and the tumors were harvested 16 h after the treatment. The fold increase values of cleaved PARP are described in Table 5. All four compounds showed strong apoptosis induction, slightly less pronounced for **9c** as compared to **8b**, **9b**, and **8c**, and it was difficult to correlate the PD response with their affinity or cellular activity. Interestingly, activity of those fluorophenyl derivatives matched the antitumor activity of the fluorofuryl compound **5e**.

It was reassuring to see that despite its lesser activity in the in vitro models, a fluorophenyl analogue could match the in vivo efficacy of the fluorofuryl derivatives, so at this point we decided to focus our efforts on the fluorophenyl subseries. First, we assessed the position of the nitrogen atom in the pyridyl substituent. The 2-pyridyl derivative (**9e**) showed a slight decrease of affinity (52 pM vs 36 pM for **9d**) and a more marked drop of cellular activity (12 nM vs 3.7 nM), while the 3-pyridyl analogue (**9f**) lay in between with an affinity of 50 pM and activity of 5.8 nM. Replacing 2-pyridyl by the 2-furyl moiety (**9g**) led to a modest drop in affinity (81 pM vs 52 pM) that was accompanied by an improvement of cellular activity. On the other hand, forcing the aromatic ring out of coplanarity with the *o*-tolyl substituent (**9h**) did not break the affinity (55 pM) with activity retained in the cellular assay at 4.7 nM. We also assessed the effect of methyl substitution on the pyridine substituent. Of the 4-methylpyrid-3-yl (**9i**), 3-methylpyrid-4-yl (**9j**), and 2-methyl-5-methoxypyrid-4-yl (**9k**) analogues, **9i** showed a marked drop in affinity while **9j** and **9k** were nearly equipotent registering at 34 pM and 48 pM, respectively. Interestingly the cellular activity of **9i** was very high showing a 1.7 nM IC_{50}, while **9j** and **9k** were in the expected activity range at 3.5 nM and 5.7 nM. Finally, we added an oxygen atom to the ortho-tolyl moiety of **9h** resulting in the hydroxymethylphenyl (**9l**) and methoxyphenyl (**9m**) substituted compounds. Compared to the tolyl analogue, both **9l** and **9m** showed some improvement in affinity (28 pM and 29 pM vs 55 pM) as well as in cellular activity (3.5 nM and 1.7 nM vs 4.7 nM), **9m** being the more potent compound.

Out of this diverse set of very potent Mcl-1 inhibitors we tested **9e−m** in our PD assay at 12.5 mg/kg. All of the tested compounds induced apoptosis, and the highest activities were observed for **9i** (237-fold) and **9m** (285-fold). Although **9i** and **9m** were the most active both in the cellular and in vivo PD assays, when we compared the ranking of the other compounds in the cellular and PD assays, it was difficult to see any correlation. We progressed **9i** and **9m** and tested their in vivo efficacy treating tumor bearing mice on 5 consecutive days with a dose of 6.25 mg/kg. Both compounds induced tumor growth inhibition, and **9m** showed the stronger efficacy considering both the magnitude and the duration of tumor growth inhibition (189.5% of TGI_{max} and 38 days to reach 500 mm^3).

Having identified **9m** as a very potent compound, we prepared some of its analogues including the amino acid **9n**, the hydroxy (**10a**) and amino acids (**10b**) bearing a propynyl substituent in the 6-position of the thienopyrimidine core instead of fluorophenyl, and the dimethylamino analogue **11**. Besides determining their affinity and cellular activity, these compounds were also characterized in the in vivo PD assay. By comparison of the hydroxy acid−amino acid pairs (**9m−9n**, **10a−10b**), **9m** showed higher affinity for the target and better cellular activity (1.7 nM vs 14 nM) than **9n**, while the affinity difference between **10a** and **10b** was marginal, and the propynyl compounds **10b** showed a remarkable 0.9 nM activity surpassing its hydroxy acid analogue **10a** (3.9 nM). Although the affinity of **11** toward Mcl-1 was only 170 pM, its cellular activity was quite good at 4.7 nM. In the in vivo setting **11** showed a remarkable PD response (251-fold PARP cleavage induction) as compared to the other compounds (**9n**, **10a−b**) (59- to 83-fold). As expected, **11** also showed the strongest antitumor activity at 6.25 mg/kg, although not reaching the in vivo efficacy of **9m**.

The synthesis strategies furnishing our Mcl-1 inhibitors are depicted in Scheme 1. All of the developed inhibitors could be constructed from four key building blocks: a halogenated thienopyrimidine core, a lactic acid derivative attached to the 4-position of the thienopyrimidine, a decorated *ortho*-tolylboronic acid or ester coupled to the 5-position of the core, and a smaller substituent in the 6-position connected to the core through a C−C bond. In the early stages of our work the late stage diversification of the 6-position was achieved in two ways. The synthesis of the **1** series started from 6-bromo-4-chloro-5-iodothieno[2,3-*d*]pyrimidine and followed a nucleophilic substitution (4-position), Suzuki coupling (5-position), Suzuki-coupling (6-position) sequence that was concluded by Mitsunobu coupling and ester hydrolysis to establish the correct substitution pattern. The formed diastereoisomers were separated after the first Suzuki coupling. A setback of this approach was the formation of 5,6-disubstituted byproducts in the first Suzuki coupling. The alternative route explored in the synthesis of the **2** series started from 4-chloro-5-iodothieno-

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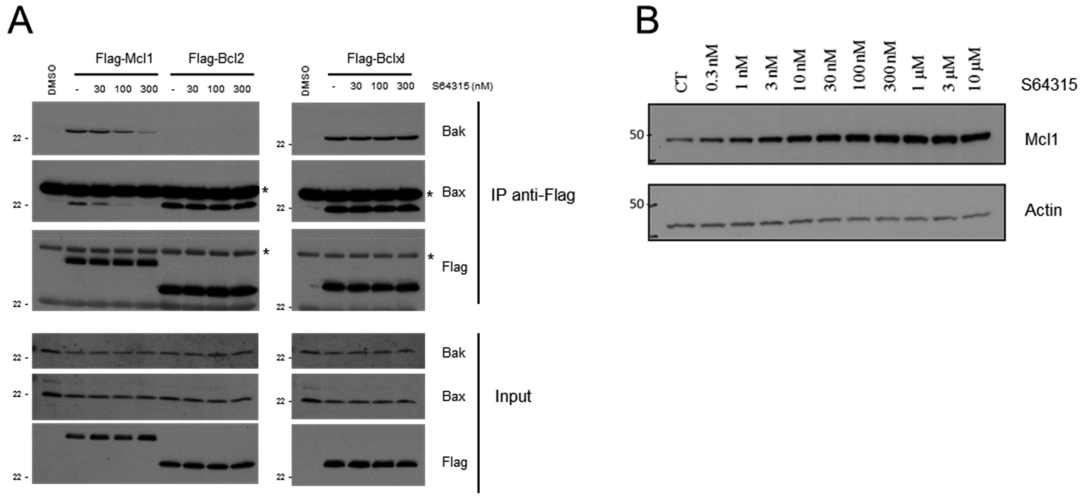

Figure 6. (A) Coimmunoprecipitation assay of HeLa cells expressing Flag-tagged Mcl-1, BCL-2 or BCL-X_L as indicated. Cells were treated with different concentrations of **9m** for 2 h before lysis. Cleared lysates were used for immunoprecipitation using anti-Flag antibody. The cell lysates (input) and immunoprecipitates (IPs) were analyzed by immunoblotting with anti-Bax, Bak, or Flag antibodies as indicated. ∗ indicates nonspecific bands. (B) Western blot analysis of endogenous Mcl-1 protein levels in HCT-116 cells treated with **9m** for 16 h at the indicated concentrations. Actin level is used as loading control.

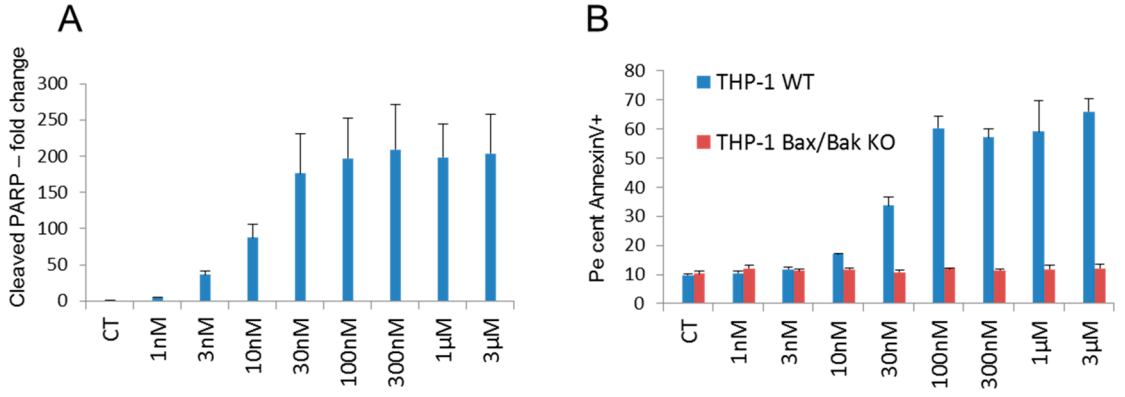

Figure 7. (A) H929 cells were treated for 6 h with increasing concentration of **9m**. Cleaved PARP was measured using MesoScale Discovery Apoptosis panel. Mean data of two independent biological experiments are represented. (B) Apoptosis induction in WT or BAX/BAK KO THP1 cells treated with **9m** at the indicated concentration for 2 h. Cells were analyzed by flow cytometry for PI and annexin V-FITC labeling. Mean and individual points from two biological replicates are shown. CT indicates that cells were treated with DMSO only.

[2,3-*d*]pyrimidine. On this compound the Suzuki coupling in the 5-position was selective, and subsequent iodination of the 6-position yielded **R9a**. Introduction of the homochiral lactic acid **R2b** by nucleophilic substitution was followed by the separation of the diastereoisomers (1:1 mixture), derivatization of the 6-position in a second Suzuki coupling, and the aforementioned concluding steps.

For the diversification of the phenyl lactate moiety in position 4 (**3**−**11** series) we used a different strategy. Exploiting the enhanced reactivity of the thienopyrimidine's 6-position in cross-coupling reactions, we started from the 6-iodo-4-chloro-thieno[2,3-*d*]pyrimidine bearing a bromine (**R1a**) or iodine (**R1b**) in the 6-position. Selective and high yielding Suzuki or Sonogashira coupling in the 6-position was followed by nucleophilic substitution in the 4-position using the THP-protected enantiopure lactate derivative **R2a**. We could exploit the stereochemical directing effect of the lactate in the following Suzuki coupling in the 5-position to obtain atropoisomer ratios up to 4:1 in our favor, which could be separated by flash column chromatography. Introduction of the solubilizer (mostly 2-(4-methylpiperazin-1-yl)ethanol) in Mitsunobu coupling and removal of the THP protecting group gave key intermediates **R5a**−**c**. Diversification of the 4-position followed by the hydrolysis of the ester gave the desired products. We carefully assessed that the stereochemical integrity of our compounds remained intact during the applied reaction conditions. The diastereomeric compounds that would arise from epimerization of one of the chirality elements are easy to detect due to their distinct chromatographic and NMR spectroscopic behavior. In the case of our most advanced compounds (i.e., **9m**), we also developed a chiral analytical method that was able to distinguish all four stereoisomers and that confirmed the stereochemical integrity of our compounds.

On the basis of the in vitro and in vivo data, **9m** was identified as a potential preclinical candidate and was further characterized. We obtained the X-ray structure of **9m** in complex with Mcl-1 (Figure 5). The thienopyridimine part of the **9m** binds exactly the same as in **1a**, **2g**, **3e**, and **4d**. The oxymethyl linker from the benzyl crosses the Thr266 ridge and positions the pyrimidine-methoxyphenyl in S4. While methoxyphenyl sits in a small hydrophobic cavity surrounded by

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Val220, Val265, and Phe319, the pyrimidine engages with Asn260 via two water molecules, one of which is further coordinated by the methoxy of the methoxyphenyl group.

The fact that **9m** inhibits the interaction of two proteins at a hydrophobic surface predicted a significant plasma protein binding that was in line with the measured free fractions of 0.05% and 0.04% in human and mice plasma, respectively. As a consequence, **9m** showed good PK properties in mice, in agreement with the very low in vitro hepatocytes clearance measured in the presence of plasma. Administered at 6.25 or 12.5 mg/kg in mice, the observed clearance was 5.3 and 6.0

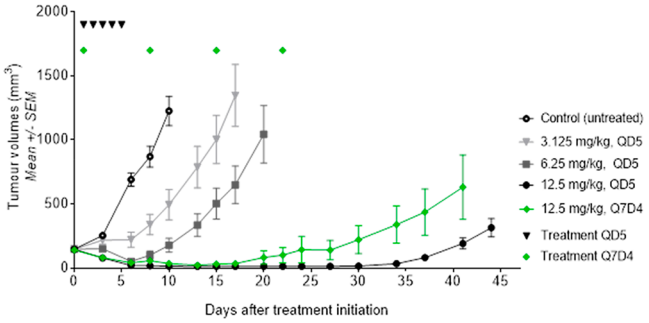

Figure 8. Antitumor activity of **9m** on AMO-1 grafted mice (n = 10). Mice were treated at different doses of **9m** by iv for 5 consecutive days (treatment QD) or weekly for 4 weeks (treatment Q7D4). Data are represented as the mean ± SEM.

mL min^{-1} kg^{-1} leading to high systemic exposures and a terminal half-life of around 5 h at both doses.

To confirm that **9m** acts in cells through selectively displacing proapoptotic BH3 domain containing proteins from Mcl-1, HeLa cells expressing Flag tagged Mcl-1, Bcl-2, and Bcl-x_L were treated with different doses of **9m**. Following immunoprecipitation using anti-Flag antibody, the endogenous Bak and Bax proteins complexed with Mcl-1, Bcl-2, and Bcl-x_L were monitored (Figure 6A). As expected on the basis of its low affinity toward Bcl-2 and Bcl-x_L (58 μM and 237 μM, respectively, in the FP assay[13]), **9m** displaced Bak and Bax proteins from Mcl-1 but not from Bcl-2 or Bcl-x_L complexes. The shift between the cytotoxic potency and the doses required to visualize Bax and Bak displacement from Bcl-2 family members is well documented[12a,15,16] and could be explained by two reasons. First an experimental bias coming from the fact that once the cell lysates are prepared, part of the compound can dissociate from Mcl-1 allowing Bax and Bak to reassociate, which would result in an apparent loss of potency in this Co-Ip setting. Second, it is not known how much Bax and/or Bak should be freed from Mcl-1 in order to induce cytotoxicity, and this amount might be very little and not easily detectable in a Western blot assay. Selective Mcl-1 inhibitors were also reported to stabilize Mcl-1 protein in a dose-dependent manner.[11a,12a,b] When the HCT116 cell line (not sensitive to Mcl-1 inhibition[12a]) was treated with different doses of **9m**, we observed a significant dose-dependent increase of the endogenous Mcl-1 protein. As reported earlier, this assay was very sensitive registering activity at doses as low as 0.3 nM. Having established Mcl-1 target hitting, we next assessed whether cell killing observed following **9m** treatment is the consequence of apoptosis induction. To this end, H929 multiple myeloma cell line was treated for 6 h with different doses of **9m**, and PARP cleavage, a commonly accepted apoptosis readout, was monitored. As shown in Figure 7A, **9m** induced PARP cleavage in a dose-dependent manner registering as early as 1 nM and with a maximal effect observed from 30 nM. Finally, to prove that the observed apoptosis was Bax/Bak dependent, THP1 cell line expressing Bax and Bak (WT) and also its BAX/BAK KO analogue were treated with different doses of **9m** for 2 h. Cells analysis by flow cytometry revealed a dose-dependent onset of apoptosis in the Bax/Bak WT cell line, while the cells devoid of Bax and Bak showed no sign of apoptosis (Figure 7B).

We have also analyzed the activity of **9m** in a panel of cell lines from different types of hematological malignancies (Table 4 in Supporting Information). We have considered the cell lines to be highly sensitive to **9m** when the IC_{50} was below 0.1 μM, moderately sensitive when the IC_{50} was between 0.1 μM and 1 μM, and insensitive when the IC_{50} was higher than 1 μM. Interestingly, all the AML and DLBCL cell lines tested and the majority of the multiple myeloma and other lymphoma cell lines were highly sensitive to **9m**. From the three ALL cell lines tested, one was highly sensitive, and two were insensitive, and all five CML cell lines were insensitive. These results are in line with previous data published by our team with the S63845 Mcl-1 inhibitor compound.[12a]

We next assessed the **9m** compound in AMO1 xenografted mice by treating the animals at different doses (3.125 mg/kg, 6.25 mg/kg, and 12.5 mg/kg) by iv for 5 consecutive days (Figure 8). A dose-dependent antitumor activity was observed with TGI_{max} of 89.1%, 115.8%, and 162.8% at 3.125 mg/kg, 6.25 mg/kg, and 12.5 mg/kg, respectively, with an outstanding complete regression for all treated animals lasting for 35 days observed at 12.5 mg/kg. Promisingly from a clinical perspective, animals treated at 12.5 mg/kg weekly for 4 weeks experienced similar tumor growth inhibition as compared to animals treated daily (TGI at D10 = 111.6% vs 108.4% after daily or weekly treatment, respectively). Taken together, those results highlight the potential of S64315 as an Mcl-1 inhibitor to be used weekly in hematological malignancies in clinic.

A preliminary assessment of the safety pharmacology profile (hERG and off target activity assays) was performed with **9m**. The first results showed no significant alerts: the hERG inhibition indicated IC_{50} > 3 μM (maximal solubility of **9m** in this assay) and the selectivity against all off targets was over 400-fold. The potential drug−drug interaction in human was assessed with a high throughput assay using human CYP450 transfected cells: **9m** was found mainly metabolized by CYP2C8 and exhibited an inhibitory potential toward CYP3A4 (IC_{50} = 1.8 μM, Table 3 in Supporting Information).

CONCLUSION

The systematic optimization of our lead Mcl-1 inhibitor that possessed nanomolar affinity and micromolar cellular activity led to the identification of the preclinical candidate S 64315/MIK665 (**9m**). The structure guided optimization revealed the plasticity of Mcl-1, enabling it to accommodate substituents that were not expected to be tolerated on the basis of prior X-ray structures. The filling of the S2 pocket resulted in a significant increase of activity. A significant part of our efforts was directed at growing our molecule into the S4−S5 region of Mcl-1. This part of the BH3 groove consists of more shallow pockets so the structural guidance was complemented by systematic modifications of our inhibitors. Our activities led to the identification of a series of selective and highly potent Mcl-

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1 inhibitors that showed strong apoptosis induction in in vivo models, which was also translated into efficient tumor growth inhibition. Of the compounds synthesized and tested, **9m** stood out and was selected as a preclinical candidate. Its mode of action was confirmed, and its other properties were also favorable for progressing it into preclinical development. This compound, also known as S64315/MIK665, is currently in clinical development against different hematological malignancies.

EXPERIMENTAL SECTION

MTT Cell Viability Assay of H929 Cell Line. 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% CO2/95% 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 2 times in triplicate. The percentage of viable cells was calculated and averaged for each well: % growth = (OD treated cells/OD control cells) × 100, and the IC_{50}, concentration reducing by 50% the optical density, was calculated by a linear regression performed on the linear zone of the dose−response curve.

MCL-1 Stabilization. HCT116 cells (purchased from ATCC) were seeded at 0.25× 10^6 cells in 35 mm dishes in RPMI 1640 medium supplemented with 10% decomplemented fetal bovine serum (FBS), 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 10 mM Hepes, pH = 7.4. Cells were grown at 37 °C in 5% CO_2/95% air. 48 h later, cells were treated with S64315 at the indicated doses for 16 h and harvested in lysis buffer (10 mM Hepes, pH7.4, 142.5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA, 1% NP40, and phosphatase and protease inhibitors). Lysates (20 μg) were analyzed by immunoblot using the following antibodies: anti-Mcl-1 (Santa Cruz sc-819) and anti-actin (Millipore MAB1501R).

Coimmunoprecipitation. HeLa cells (purchased from ATCC) were plated at 2.5 × 10^5 cells in 60 mm dishes 24 h before transfection in DMEM medium (containing 10% FCS, 1 mM Hepes, 100 U/mL penicillin, 100 μg/mL streptomycin) in 5% CO_2 incubator. HeLa cells were transiently transfected, using Effecten reagent (Qiagen), with Flag-tagged Mcl-1, Bcl-x_L or Bcl-2 expression vectors. 24 h later, cells were treated with S64315 during 2 h and harvested in lysis buffer (10 mM Hepes, pH 7.5, 150 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA, 0.4% TritonX100, protease inhibitors cocktail (Calbiochem 539134) and phosphatase inhibitors cocktail (Calbiochem 524625)). The cleared lysates were then subjected to immunoprecipitation with anti-Flag M2 agarose beads (Sigma). The immunoprecipitates and inputs were analyzed by immunoblot using the following antibodies: anti-Bax (Santa Cruz sc-493), anti-Bak (BD 556996) and anti-Flag M2 (Sigma).

Apoptosis Induction. H929 cells (purchased from ATCC) were seeded at 2 × 10^6 cells in 35 mm dishes in RPMI 1640 medium supplemented with 10% decomplemented fetal bovine serum (FBS), 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 10 mM Hepes, pH = 7.4. Cells were grown at 37 °C in 5% CO_2/95% air. 24 h after, cells were treated with S64315 for 6 h and harvested in lysis buffer (10 mM Hepes, pH 7.4, 142.5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA, 1% NP40, phosphatases and proteases inhibitors).

AMO-1 tumors collected after treatment at indicated time in the figures were frozen. Piece of tumor was homogenized in lysis buffer (10 mM Hepes, pH 7.5, 150 mM KCl, 5 mM $MgCl_2$, 1 mM EGTA, 0.4% Triton X-100) and centrifuged for dissociation at 6500 rpm for 30 s using Precellys.

Lysates (5 μg proteins) were assayed for immunodetection of cleaved PARP with MSD apoptosis panel whole cell lysate kit (MSD K15102D). Lysates were assayed in a MSD 96 well plate according to the manufacturer's instructions and analyzed on the Sector Image 2400. Data are expressed as relative light unit (RLU).

Bax/Bak Dependency. THP1 Bax/bak−/− generation was described in Casara et al.[17] Briefly, THP-1 (ATCC CCL-2) cells were first transduced with EF1a-Cas9- 2A neomycin (Sigma-Aldrich) and selected under neomycin for 10 days before being sorted as single-cells for the isolation of clones. One clone was then further transduced with pLV-U6g-EGFP-gRNA BAK1, and cells were sorted as single-cells based on the expression of the GFP reporter gene. Cells were then further transduced with pLV-U6g-Puromycin gRNA BAX and put under puromycin selection (1 μg/mL) for 9 days before being sorted as single-cells for the isolation of clones. BAX and BAK knockout efficiency on different clones was verified by Western blot.

THP-1 cells were treated with the indicated compounds for 2 h, centrifuged, and washed with binding buffer (10 mM Hepes, 140 mM NaCl, 2.5 mM $CaCl_2$). Cells were incubated with 200 μL of binding buffer containing annexin V-FITC (Invitrogen) and propidium iodide (PI, Sigma) during 15 min at 20 °C in the dark. THP-1 cells were incubated with 200 μL of binding buffer containing annexin V-APC (BD Biosciences) and DAPI (Sigma). 400 μL of binding buffer was added, and samples were kept at 4 °C before cytometric analysis. For each sample, 10^4 cells were analyzed by flow cytometry on Epics XL/MCL flow cytometer (Beckman Coulter, France). Fluorescence was collected at 520 nm (FITC), 630 nm (PI), 660 nm (APC), and 470 nm (DAPI). The number of apoptotic cells (addition of primary apoptosis, secondary apoptosis, and necrosis) was normalized to the total number of cells per tube.

Animals and Treatment Groups. Healthy female CB-17 SCID mice, 6−7 weeks old, were obtained from Charles River. Mice were kept either at Oncodesign or in the Servier Institute-specified pathogen-free animal area for mouse experimental purpose (facility license numbers B78-100-2 and A21231011EA). The care and use of animals used in this facility are strictly applying to European and national regulation for the protection of vertebrate animals used for experimental and other scientific purposes (Directives 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). Width and length of the tumor were measured 2−3 times a week using an electronic caliper. Tumor volume was calculated using the formula length × $width^2/2$. When tumor volume reached approximately 200 mm^3, mice were randomized in different groups before treatment (n = 3 for pharmacodynamic studies and n = 8 to 10 for efficacy studies). Compounds were formulated in HPbCD 20% (Fisher Scientifics)−HCl (25 mM) and administrated with the doses and schedules described in the figure.

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

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

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:

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[(median times of treated to reach 1000 mm^3 − median times of control to reach 1000 mm^3)/(median times of control to reach 1000 mm^3)] × 100

A complete tumor regression response was considered for the population with tumors of 25 mm^3 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 LCMS: 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 Agilent 6850 gas chromatograph and Agilent 5975C mass spectrometer using 15 m × 0.25 mm column with 0.25 μm HP-5MS coating and helium as carrier gas. Ion source: EI^+, 70 eV, 230 °C. Quadrupole: 150 °C. Interface: 300 °C.

Flash chromatography was performed on ISCO CombiFlash Rf 200i with prepacked silica-gel cartridges (Redi*Sep*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).

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

HRMS was determined on a Shimadzu IT-TOF, ion source temperature 200 °C, ESI±, ionization voltage (±)4.5 kV. Mass resolution min 10000.

All obtained products had an LC purity above 96% that was corroborated by their ^1H NMR spectrum unless specifically mentioned otherwise.

All reactions and workup procedures, where 5-fluoro-2-furyl moiety was present, were performed in the dark.

Reagent Synthesis and General Procedures. ***R1a:*** *5-Bromo-4-chloro-6-iodothieno[2,3-d]pyrimidine. Step A: 6-Iodo-3H-thieno-[2,3-d]pyrimidin-4-one.* A 2 L round bottomed flask equipped with mechanical stirrer, thermometer, and reflux condenser was charged with the solution of 433 mL AcOH, 13 mL cc. H_2SO_4, and 87 mL water. 69.3 g 3*H*-thieno[2,3-*d*]pyrimidin-4-one (0.455 mol), 51.9 g H_5IO_6 (0.228 mol) and 104 g I_2 (0.410 mol) were added to the stirred solution, and the mixture was heated to 60 °C for 1 h. The resulting suspension was cooled to rt, filtered off, washed with a mixture of AcOH and water (5:1) and then with Et_2O. The resulting beige crystalline solid was air-dried to give 95.6 g 6-iodo-3*H*-thieno[2,3-*d*]pyrimidin-4-one (0.344 mol, 76%). ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 12.57 (br s, 1H), 8.09 (s, 1H), 7.65 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 168.3, 155.9, 146.1, 130.8, 126.7, 76.4. HRMS calculated for $C_6H_3IN_2OS$: 277.9011; found 278.9088 (M + H).

Step B: 4-Chloro-6-iodothieno[2,3-d]pyrimidine. A 1 L round bottomed flask equipped with mechanical stirrer, thermometer, reflux condenser, and a tube filled with anhydrous $CaCl_2$ was charged with 113 mL $POCl_3$ and 35 mL *N,N*-dimethylaniline (0.29 mol). 75.5 g 6-iodo-3*H*-thieno[2,3-*d*]pyrimidin-4-one (0.271 mol) was added portionwise in 5 min. The reaction mixture was stirred at 105 °C for 1 h. The resulting suspension was cooled to 10 °C, filtered, and washed with hexane. The filtered solid was added to icy water and stirred for 10 min, filtered off, washed with cold water, Et_2O, and air-dried to give 75.1 g 4-chloro-6-iodothieno[2,3-*d*]pyrimidine as a beige crystalline solid (0.253 mol, 93%). ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 8.90 (s, 1H), 7.98 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.3, 152.8, 151.8, 131.0, 128.9, 86.5. MS (EI, 70 eV) *m/z* (% relative intensity, [ion]): 57 (9), 107 (27), 134 (13), 142 (15), 261 (48), 296 (100, [M^+]).

Step C: 5-Bromo-4-chloro-6-iodothieno[2,3-d]pyrimidine. A 2 L round bottomed flask equipped with mechanical stirrer, thermometer, and a bubbler was charged with 600 mL MeCN. 84.9 g 4-chloro-6-iodothieno[2,3-*d*]pyrimidine (0.286 mol), 50.9 g NBS (0.286 mol), and 8.5 mL $HBF_4{\cdot}Et_2O$ (62.5 mmol) were added. The reaction mixture was stirred at rt for 16 h. Additional 22.9 g NBS (0.129 mol) was added to the mixture in three portions in order to reach complete conversion. After cooling the suspension to 0 °C and stirring for 1 h, the precipitate was filtered off, washed with MeCN, and air-dried to give 86.9 g **R1a** as a beige crystalline solid (0.231 mol, 81%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.94 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 171.3, 152.9, 152.3, 126.0, 112.4, 92.9. HRMS calculated for $C_6HBrClIN_2S$: 373.7777; found 374.7853 (M + H).

R1b: *4-Chloro-5,6-diiodothieno[2,3-d]pyrimidine. Step A: 5,6-Diiodo-3H-thieno[2,3-d]pyrimidin-4-one.* To a well stirred slurry of 61.3 g 3*H*-thieno[2,3-*d*]pyrimidin-4-one (396 mmol), 92.4 g H_5IO_6 (405 mmol), 1 L AcOH, 200 mL water, 6 mL cc. H_2SO_4, and 203 g I_2 (799 mmol) were added. The reaction mixture was heated to 110 °C and stirred for 3 h. The suspension was cooled to rt and then 940 mL Et_2O was added and stirred further at 10 °C for 30 min. The precipitate was filtered off, washed with a 2:1 mixture of Et_2O and EtOH, finally with Et_2O, and air-dried to give 94.4 g 5,6-diiodo-3*H*-thieno[2,3-*d*]pyrimidin-4-one (234 mmol, 59%) as a tan powder. ^1H NMR (500 MHz, DMSO-d_6) δ ppm: 12.60 (br s, 1H), 8.13 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 168.0, 155.0, 146.4, 124.6, 89.4, 88.4.

Step B: 4-Chloro-5,6-diiodothieno[2,3-d]pyrimidine. To a well stirred slurry of 180 g 5,6-diiodo-3*H*-thieno[2,3-*d*]pyrimidin-4-one (445 mmol) in 2.5 L $POCl_3$ was added 64 mL *N,N*-dimethylaniline (507 mmol). The reaction mixture was heated to 105 °C and stirred for 1.5 h. The resulting suspension was cooled to rt, and 1.5 L hexane was added, and it was stirred for further 20 min. The precipitate was filtered off, washed with hexane and water, then air-dried to give 159.8 g **R1b** (378 mmol, 85%) as a gray crystalline solid. ^1H NMR (400 MHz, DMSO-d_6): 8.91 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 172.5, 152.5, 152.3, 129.1, 99.7, 89.9. MS (EI, 70 eV) *m/z* (% relative intensity, [ion]): 106 (43), 141 (38), 233 (14), 268 (19), 387 (25), 422 (100, [M^+]), 424 (37, [M^+]).

R1c: *5-Bromo-4-chloro-6-(4-fluorophenyl)thieno[2,3-d]-pyrimidine.* 75.08 g **R1a** (200 mmol), 53.63 g 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (240 mmol), 130 g Cs_2CO_3 (400 mmol), 2.245 g $Pd(OAc)_2$ (10 mmol), and 8.50 g ^{t}BuX-Phos (20 mmol) were placed in a 2 L flask. 600 mL THF and 200 mL water were added and then stirred overnight at 70 °C under Ar atmosphere. The volatiles were evaporated under reduced pressure, and then it was filtered. The solid was sonicated in 250 mL MeCN and filtered again. Finally it was crystallized from EtOH/THF (2:1) to give 52.57 g **R1c** as an off white solid (153 mmol, 76%). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.02 (s, 1H), 7.80−7.77 (m, 2H), 7.47−7.43 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 166.7,

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162.8, 153.9, 153.0, 139.3, 132.3, 127.6, 126.5, 116.2, 100.8. HRMS calculated for $C_{12}H_5BrClFN_2S$: 341.9029, found 342.9091 (M + H).

R1d: *4-Chloro-5-iodo-6-(prop-1-ynyl)thieno[2,3-d]pyrimidine.* 42.24 g **R1b** (100 mmol), 3.509 g $Pd(PPh_3)_2Cl$ (5.00 mmol), and 1.904 g CuI (10.0 mmol) were dissolved in 400 mL DIPA, then propyne was bubbled through the reaction mixture, which was stirred for 6 h at rt to reach complete conversion. Then the volatiles were evaporated under reduced pressure and the crude product was purified via flash chromatography using heptane and EtOAc as eluents to obtain 28.3 g **R1d** (84.6 mmol, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.92 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.9, 153.9, 153.1, 127.9, 126.9, 101.3, 82.1, 74.6, 4.8. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 75 (13), 86 (13), 93 (11), 100 (12), 106 (13), 127 (15), 144 (13), 145 (17), 180 (32), 207 (23), 334 (100, $[M^+]$), 336 (40, $[M^+]$).

R1e: *4-Chloro-5-iodothieno[2,3-d]pyrimidine.* 52.8 g **R1b** (125 mmol) was dissolved in 400 mL dry THF and cooled to 0 °C. 100 mL *t*BuMgCl (200 mmol, 2 M in Et_2O) was added over 15 min. Then 50 mL water was added and stirred for 10 min. The solution was decanted and concentrated under reduced pressure. The crude product was sonicated in a mixture of 200 mL MeCN and water (3:1) and then collected by filtration to yield 30.4 g **R1e** (102 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.95 (s, 1H), 8.45 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.6, 154.2, 152.6, 134.4, 127.3, 72.6.

R1f: *Methyl (2R)-2-[(5,6-diiodothieno[2,3-d]pyrimidin-4-yl)oxy]-3-phenylpropanoate.* 8.45 g **R1b** (20.0 mmol), 5.41 g methyl (2*R*)-2-hydroxy-3-phenylpropanoate (30.0 mmol), and 13.03 g Cs_2CO_3 (40.0 mmol) were placed in a flask. 20 mL DMSO was added, and the mixture was stirred at 60 °C for 35 min to reach complete conversion. Then the reaction mixture was diluted with water, the pH was set to 5 with 2 M aq HCl solution, and then it was extracted with DCM. The combined organic layer was dried over Na_2SO_4, 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 10.13 g **R1f** (17.9 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.49 (s, 1H), 7.45−7.39 (m, 2H), 7.34−7.21 (m, 3H), 5.78 (dd, J = 8.5, 4.8 Hz, 1H), 3.75 (s, 3H), 3.50−3.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.6, 170.2, 159.8, 152.8, 136.2, 129.5, 128.5, 127.1, 120.8, 90.4, 85.0, 76.0, 52.4, 37.6. HRMS calculated for $C_{16}H_{12}I_2N_2O_3S$: 565.8658; found 566.8734 (M + H).

R2a: *Ethyl (2R)-2-Hydroxy-3-(2-tetrahydropyran-2-yloxyphenyl)-propanoate. Step A: [2-(Bromomethyl)phenyl]acetate.* 60.07 g 2-methylphenyl acetate (400 mmol), 106.8 g NBS (600 mmol), and 500 mL cyclohexane were placed in a 1 L flask. Then 3.284 g AIBN (20 mmol) was added under vigorous stirring over 30 min. The mixture was stirred at 80 °C until no further conversion was observed, then it was cooled to rt. The precipitate was filtered off and washed with cyclohexane. The filtrate was concentrated under reduced pressure, and the overweight crude product (100 g) was used in step B without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.42 (dd, J = 7.8, 1.7 Hz, 1H), 7.35 (td, J = 7.8, 1.7 Hz, 1H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 7.14 (dd, J = 7.5, 1.2 Hz, 1H), 4.43 (s, 2H), 2.37 (s, 3H).

Step B: Ethyl (2R)-2-Acetoxy-3-(2-hydroxyphenyl)propanoate. 23.10 g anhydrous LiCl (545 mmol) and 65.36 g anhydrous $ZnCl_2$ (479.6 mmol) were placed in a 2 L flask, then dried at 160 °C under 0.1 mmHg for 1 h. After cooling to rt under Ar atmosphere, 26.49 g Mg turnings (1090 mmol) and 1 L dry, precooled (0 °C) THF were added. The resulting mixture was immersed into an ice-bath and then stirred for 30 min. Then 100 g [2-(bromomethyl)phenyl] acetate was dissolved in 120 mL dry THF and was added to the precooled inorganics over 15 min. After addition of the reagent the resulting mixture was stirred for 45 min while the temperature was kept between 0 and 5 °C. Then 64.82 mL ethyl 2-oxoacetate (654 mmol, 50% in toluene) was added over 5 min, and the resulting mixture was stirred for another 15 min. Then the insoluble inorganics were removed by filtration, and the filtrate was diluted with 500 mL MeOH. The mixture was stirred until the intramolecular acetyl group migration from the phenolic oxygen to the alkyl oxygen was complete. Then 30 mL AcOH was added and the volatiles were evaporated under reduced pressure. Then 350 mL water was added and the mixture was extracted with EtOAc. The combined organic layer was washed with saturated aq $NaHCO_3$ solution and with brine and then dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. Then 100 mL hexane was added, and it was stirred for 30 min at 0 °C. The formed white crystals were collected by filtration and washed with hexane yielding 23.2 g ethyl 2-acetoxy-3-(2-hydroxyphenyl)propanoate as a racemate (92.0 mmol, 23% for two steps). The enantiomers were separated via chiral chromatography. Column: OD. Eluents: heptane and EtOH. The enantiomer eluting later was collected as ethyl (2*R*)-2-acetoxy-3-(2-hydroxyphenyl)-propanoate with 99.9% ee. Retention times (Daicel Chiralcel OD-H 250 mm × 4.6 mm, 5 μm, eluent: ^{i}PrOH/heptane 50:50; flow rate 1.0 mL/min, detection wavelength: 210 nm, 276 nm; ambient temperature): 4.7 min (*S* enantiomer), 6.3 min (*R* enantiomer). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.53 (s, 1H), 7.08−7.03 (m, 2H), 6.79 (dd, J = 7.9, 0.8 Hz, 1H), 6.71 (td, J = 7.4, 1.1 Hz, 1H), 5.10 (dd, J = 8.3, 6.0 Hz, 1H), 4.05 (q, J = 7.1 Hz, 2H), 3.06 (dd, J = 13.7, 6.0 Hz, 1H), 2.94 (dd, J = 13.7, 8.3 Hz, 1H), 2.00 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.0, 169.6, 155.5, 131.1, 128.1, 121.8, 118.8, 114.8, 71.4, 60.7, 31.8, 20.3, 13.9. HRMS calculated for $C_{25}H_{26}N_2O_6$: 252.0998; found 275.0881 (M + Na).

Step C: Ethyl (2R)-2-Hydroxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate. 103.3 g ethyl (2*R*)-2-acetoxy-3-(2-hydroxyphenyl)propanoate (409.4 mmol) was dissolved in 280 mL DHP. 300 mg PTSA·H_2O (1.58 mmol, 0.39 mol %) was added, and the mixture was stirred until no further conversion was observed. Then it was diluted with 1 L EtOAc, washed with 200 mL saturated aq $NaHCO_3$ solution, then with 200 mL water. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Then it was purified via flash chromatography using heptane and EtOAc as eluents to give 139.7 g ethyl (2*R*)-2-acetoxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate, as a 1:1 mixture of diastereoisomers (contaminated with DHP oligomers).

This intermediate was dissolved in 600 mL EtOH, then 20 mL NaOEt solution (20 mmol, 1.0 M in EtOH) was added, and it was stirred at rt until no further conversion was observed. The mixture was concentrated under reduced pressure to half of its initial volume, then 300 mL water and 300 mL brine were added. It was extracted twice with EtOAc. The combined organic layer was washed with brine, then dried over Na_2SO_4, filtered and the filtrate was concentrated to give 110.2 g ethyl (2*R*)-2-hydroxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate as a 1:1 mixture of diastereoisomers (**R2a**, 374.4 mmol, 91% for two steps). The optical purity of the starting material was conserved. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.18−7.11 (m, 2H), 7.04 (d, J = 8.5 Hz, 1H), 6.89−6.84 (m, 1H), 5.52/5.50 (t, J = 3.0 Hz, 1H), 5.49−5.45 (m, 1H), 4.30−4.24 (m, 1H), 4.05/4.02 (q, J = 7.1 Hz, 2H), 3.77−3.69 (m, 1H), 3.59−3.51 (m, 1H), 3.06/3.04 (dd, J = 13.1, 5.2 Hz, 1H), 2.74/2.71 (dd, J = 13.1, 8.8 Hz, 1H), 2.00−1.89 (m, 1H), 1.85−1.74 (m, 2H), 1.68−1.50 (m, 3H), 1.12/1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.87/173.86, 154.43/154.41, 131.35/131.30, 127.6, 126.4/126.3, 120.8/120.7, 114.0/113.9, 95.2/95.0, 70.04/69.99, 61.2/61.1, 59.90/59.85, 35.7/35.6, 30.0/29.9, 24.8, 18.27/18.25, 13.98/13.96. HRMS calculated for $C_{16}H_{22}O_5$: 294.1467; found 317.1355 and 317.1356 (M + Na).

R2b: *Ethyl (2R)-2-Hydroxy-3-(2-methoxyphenyl)propanoate.* To a stirred mixture of 1.362 g 2-methoxybenzaldehyde (10.0 mmol) and 1.34 mL ethyl chloroacetate (12.5 mmol) in 10 mL dry THF at −78 °C, 12.5 mL NaHMDS solution (1.0 M in THF) was added dropwise. It was allowed to reach rt and stirred for 30 min. The mixture was quenched with sat. aq NH_4Cl solution, the layers were separated, the aq layer was extracted with EtOAc. Then the combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated. The obtained intermediate was dissolved in 20 mL EtOAc, then 0.2 g Pd/C (10%) was added, and the mixture was stirred at rt under 4.5 bar H_2 atmosphere. In the case of low conversion glacial AcOH and $Pd(OH)_2$ were added to the mixture, and hydrogenation was

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continued. After an overnight stirring under H_2 atmosphere the mixture was filtered through a pad of Celite, the Celite pad was successively washed with EtOAc, then the filtrate was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 1.04 g ethyl 2-hydroxy-3-(2-methoxyphenyl)propanoate (4.6 mmol, 46%) as a racemate. The enantiomers were separated via chiral chromatography. Column: AD. Eluent: ^{i}PrOH. The enantiomer eluting earlier was collected as **R2b** with 99.8% ee. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.19 (dt, J = 8.1, 1.7 Hz, 1H), 7.12 (dd, J = 7.3, 1.4 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.84 (dt, J = 7.3, 0.8 Hz, 1H), 5.45 (d, J = 6.5 Hz, 1H), 4.21 (dq, J = 6.5, 1.6 Hz, 1H), 4.01 (dq, J = 7.1, 1.6 Hz, 1H), 3.77 (s, 3H), 2.94 (dd, J = 13.3, 6.0 Hz, 1H), 2.77 (dd, J = 13.3, 8.0 Hz, 1H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.7, 157.3, 131.1, 127.8, 125.2, 120.0, 110.4, 69.7, 69.6, 59.9, 55.3, 35.2, 14.0.

***R3aa**: [2-Chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]triisopropylsilane. Step A: (4-Bromo-2-chlorophenoxy)triisopropylsilane.* 200 g 4-bromo-2-chlorophenol (0.964 mol) and 126 mL TIPSCl (1.18 mol) were dissolved in 1.6 L DCM. 167 g imidazole (2.45 mol) was added, and the mixture was stirred at rt for 2 h. Then the volatiles were evaporated under reduced pressure, and the residue was dissolved in 1.5 L EtOAc. The mixture was washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The formed TIPSOH impurity was removed by distillation (120 °C at 0.01 mmHg). The residue was filtered through a short pad of silica using hexane as eluent and the filtrate was concentrated under reduced pressure to give 350 g (4-bromo-2-chlorophenoxy)triisopropylsilane as a colorless oil (0.962 mol, 99.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.49 (d, J = 2.5 Hz, 1H), 7.21 (dd, J = 8.7, 2.5 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 1.31 (sp, J = 7.3 Hz, 3H), 1.14 (d, J = 7.3 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.4, 132.7, 130.4, 126.5, 121.2, 112.7, 17.9, 12.9. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 63 (30), 79 (24), 93 (41), 170 (17), 235 (19), 251 (16), 265 (24), 293 (23), 319 (77), 321 (100), 323 (28), 362 (1, [M^+]).

Step B: (4-Bromo-2-chloro-3-methylphenoxy)triisopropylsilane. 76.0 mL dry DIPA (0.54 mol) was dissolved in 1.2 L dry THF under Ar atmosphere, and 51.2 mL ^{n}BuLi solution (0.512 mol, 10 M in hexanes) was added dropwise at −78 °C. The mixture was stirred for 45 min at the same temperature. Then 178 g (4-bromo-2-chlorophenoxy)triisopropylsilane (0.489 mol) was added dropwise at −78 °C, and the white suspension was stirred until the regioselective deprotonation of the benzene ring was complete. Then 36.5 mL MeI (0.586 mol) was added at this temperature and the reaction mixture was stirred overnight without further cooling. The volatiles were evaporated under reduced pressure. The residue was dissolved in 1.5 L EtOAc, then washed with brine. The organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product was filtered through a short pad of silica using hexane as eluent and then concentrated under reduced pressure to obtain 172 g (4-bromo-2-chloro-3-methylphenoxy)triisopropylsilane as a pale yellow oil (0.455 mol, 93%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.45 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 2.44 (s, 3H), 1.30 (sp, J = 7.5 Hz, 3H), 1.06 (d, J = 7.5 Hz, 18H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 150.9, 136.3, 130.9, 125.6, 118.4, 115.5, 20.9, 17.7, 12.2. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 93 (31), 265 (17), 307 (15), 333 (81), 335 (100), 337 (31), 376 (1, [M^+]), 378 (1, [M^+]).

Step C: [2-Chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]triisopropylsilane. 178 g (4-bromo-2-chloro-3-methylphenoxy)triisopropylsilane (0.471 mol) was dissolved in 1.4 L dry THF under Ar atmosphere, and 52 mL ^{n}BuLi solution (0.520 mol, 10 M in hexanes) was added dropwise at −78 °C. The mixture was stirred for 5 min at this temperature. Then 116 mL 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.569 mol) was added and the mixture was allowed to warm up to rt. Then the volatiles were evaporated under reduced pressure, and the residue was dissolved in 1.5 L EtOAc. It was washed with brine, then the organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane impurity was removed by distillation (80 °C at 0.01 mmHg). The crude product was triturated in MeOH affording 160 g **R3aa** as a white solid (0.377 mol, 80%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.49 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 2.52 (s, 3H), 1.32 (sp, J = 7.4 Hz, 3H), 1.29 (s, 12H), 1.07 (d, J = 7.4 Hz, 18H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 153.5, 143.6, 135.1, 125.3, 116.5, 83.4, 24.6, 19.2, 17.7, 12.3. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 83 (53), 211 (15), 381 (100), 383 (42).

***R3a**: 2-Chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol.* 2.23 g **R3aa** (5.25 mmol) was dissolved in 10 mL dry THF, then 5.50 mL TBAF solution (5.50 mmol, 1 M in THF) was added, and the mixture was stirred at rt for 10 min. Then the solvent was evaporated under reduced pressure; the residue was dissolved in EtOAc, washed with saturated aq NH_4Cl solution and brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography using heptane and EtOAc as eluents to give 1.07 g **R3a** as a white solid (3.99 mmol, 76%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.40 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 2.49 (s, 3H), 1.27 (s, 12H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 156.0, 143.8, 135.6, 121.5, 113.7, 83.6, 25.1, 19.4. HRMS calculated for $C_{13}H_{18}BClO_3$: 268.1037; found 267.0972 (M − H).

***R3b**: 1-[2-[2-Chloro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]-4-methylpiperazine.* 5.77 g **R3a** (21.5 mmol), 9.29 g 2-(4-methylpiperazin-1-yl)ethanol (64.4 mmol) and 43.0 g polymer bound PPh_3 (1.5 mmol/g, 64.4 mmol) were stirred in 170 mL dry toluene, and then 14.79 g DTBAD (64.4 mmol) was added. The mixture was stirred at 50 °C under Ar atmosphere for 3 h. The crude reaction mixture was filtered, then the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography using DCM and MeOH as eluents. The resulting light brown oil was crystallized from hexane to give 5.58 g **R3b** (14.2 mmol, 66%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 7.56 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 4.15 (t, J = 5.8 Hz, 2H), 2.72 (t, J = 5.8 Hz, 2H), 2.51 (s, 3H), 2.50 (br s, 4H), 2.29 (br s, 4H), 2.13 (s, 3H), 1.29 (s, 12H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 156.0, 143.0, 135.3, 110.2, 83.4, 67.1, 56.2, 54.8, 53.1, 45.8, 24.6, 19.0. HRMS calculated for $C_{20}H_{32}BClN_2O_3$: 394.2195; found 395.2257 (M + H).

***R4**: Ethyl (2R)-2-[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate. Step A: Ethyl (2R)-2-[5-Bromo-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-tetra-hydropyran-2-yloxyphenyl)propanoate.* 48.45 g **R1c** (141 mmol), 45.63 g **R2a** (155 mmol), and 137.8 g Cs_2CO_3 (423 mmol) were placed in a 2 L flask. 1.4 L tBuOH was added and the mixture was stirred at 70 °C under N_2 atmosphere for 4.5 h to reach 98% conversion. Approximately 1 L solvent was evaporated under reduced pressure, then it was diluted with water, the pH was set to 8 with 2 M HCl, and then it was extracted with DCM. The combined organic layer was dried over Na_2SO_4, 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 62.19 g ethyl (2R)-2-[5-bromo-6-(4-fluorophenyl)thieno[2,3-d]-pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate diastereoisomer mixture as a white solid (103 mmol, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.67/8.66 (s, 1H), 7.76−7.72 (m, 2H), 7.43−7.39 (m, 3H), 7.20−7.16 (m, 1H), 7.08−7.06 (m, 1H), 6.90−6.87 (m, 1H), 5.81/5.69 (dd, J = 9.8, 3.8 Hz, 1H), 5.60−5.54 (m, 1H), 4.23−4.08 (m, 2H), 3.80−3.48 (m, 2H), 3.51/3.49 (dd, J = 13.8, 3.8 Hz, 1H), 3.19/3.17 (dd, J = 10.0, 1.8 Hz, 1H), 2.09−1.49 (m, 6H), 1.15/1.10 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.5, 165.84/165.82, 162.7, 162.0/161.9, 154.5/154.4, 153.2, 135.67/135.66, 132.1, 132.0, 128.34/128.35, 127.8, 124.6, 120.98/120.95, 117.5, 116.1, 114.00/113.97, 99.8, 95.3/94.9, 74.5/74.4, 61.21/61.17, 61.1/61.0, 32.95/32.89, 29.95/29.88, 24.8, 18.24/18.21, 13.89/13.86. HRMS calculated for $C_{28}H_{26}BrFN_2O_5S$: 600.0729; found 601.0809 and 601.0798 (M + H).

Step B: Ethyl (2R)-2-[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate. 186.6 g ethyl (2R)-2-[5-

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bromo-6-(4-fluorophenyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (310.3 mmol) and 99.99 g **R3a** (372.3 mmol) were dissolved in 1.2 L THF, then 202.2 g Cs_2CO_3 (620.6 mmol) dissolved in 300 mL water was added. Then 11.0 g AtaPhos (15.51 mmol) was added, and the mixture was stirred under N_2 atmosphere at 80 °C for 2 h to reach 98% conversion. Most of the volatiles were evaporated under reduced pressure, then it was diluted with DCM and brine. The pH of the aq phase was set to 8 with 2 M aq HCl solution. After phase separation the aq phase was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The atropoisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer pair eluting later was collected as **R4** (132.3 g, 199.5 mmol, 64%). ^{1}H NMR (500 MHz, DMSO-d_6, 1:1 mixture of diastereomers) δ ppm: 10.27 (br s, 1H), 8.60 (s, 1H), 7.32−7.28 (m, 2H), 7.24−7.19 (m, 2H), 7.14 (dd, J = 8.4, 6.6 Hz, 1H), 7.14−7.10 (m, 1H), 7.00 (dd, J = 8.4, 2.6 Hz, 1H), 6.96 (dd, J = 8.4, 2.6 Hz, 1H), 6.75−6.71 (m, 1H), 6.34/6.39 (dd, J = 7.4, 1.6 Hz, 1H), 5.55−5.51 (m, 1H), 5.41/5.39 (d, J = 4.5 Hz, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.70−3.65 (m, 2H), 3.10−3.05 (m, 1H), 2.44 (dd, J = 13.4, 9.2 Hz, 1H), 1.98/1.90 (br s, 1H), 1.85/1.83 (s, 3H), 1.79 (br s, 2H), 1.64 (br s, 1H), 1.59 (br s, 1H), 1.54 (br s, 1H), 1.09/1.08 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.3, 166.4, 162.54/162.50, 162.1, 154.14/154.13, 153.1, 152.7, 136.7, 135.7/135.6, 131.1/131.0, 131.02/131.00, 130.06/130.00, 129.1/128.9, 128.26/128.25, 125.9, 124.3, 120.7, 120.56/120.54, 118.83/118.82, 116.0, 113.9, 113.4, 95.1/94.8, 73.7/73.4, 61.2/61.0, 60.9/60.8, 32.7/32.6, 29.9/29.8, 24.8/24.7, 18.15/18.11, 17.6, 13.8. HRMS calculated for $C_{35}H_{32}ClFN_2O_6S$: 662.1653; found 663.1728 and 663.1717 (M + H).

***R5a**: Ethyl (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-hydroxyphenyl)propanoate.* 132.3 g **R4** (199.5 mmol), 43.17 g 2-(4-methylpiperazin-1-yl)ethanol (299.3 mmol), and 94.20 g PPh_3 (359.1 mmol) were dissolved in 1 L dry toluene, then 78.09 g DTBAD (339.2 mmol) was added. The mixture was stirred at 50 °C under N_2 atmosphere for 1 h to reach >97% conversion. 980 mL toluene was evaporated under reduced pressure, then 500 mL Et_2O was added, and the mixture was stirred and sonicated. The precipitated white crystals (PPh_3O) were filtered, washed with Et_2O. The filtrate was concentrated under reduced pressure and purified via flash chromatography using EtOAc and MeOH. The obtained intermediate was dissolved in 1 L EtOH, then 1 L 1.25 M HCl solution in EtOH was added and the mixture was stirred at rt for 1 h to reach >99% conversion. Most of the EtOH was evaporated, then 2 L Et_2O was added and the precipitated HCl salt (white solid) was filtered, washed with Et_2O. The HCl salt was carefully treated with 2 L sat. aq $NaHCO_3$ solution, then extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give 128 g **R5a** (181.5 mmol, 91% for two steps).^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.53 (br s, 1H), 8.60 (s, 1H), 7.32−7.28 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 7.24−7.19 (m, 2H), 7.16 (d, J = 8.8 Hz, 1H), 6.97 (td, J = 7.8, 1.6 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.53 (td, J = 7.4, 0.8 Hz, 1H), 6.18 (dd, J = 7.4, 1.6 Hz, 1H), 5.46 (dd, J = 9.0, 4.6 Hz, 1H), 4.25−4.18 (m, 2H), 4.07−4.00 (m, 2H), 2.92 (dd, J = 13.4, 4.8 Hz, 1H), 2.75 (t, J = 4.8 Hz, 2H), 2.53 (br s, 4H), 2.44 (dd, J = 13.6, 9.2 Hz, 1H), 2.36 (br s, 4H), 2.17 (s, 3H), 1.88 (s, 3H), 1.06 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.4, 166.5, 163.1, 162.6, 161.1, 155.2, 153.8, 152.8, 136.9, 136.0, 131.1, 130.3, 129.0, 128.5, 128.0, 127.6, 122.1, 121.7, 118.8, 118.5, 116.0, 114.7, 110.7, 73.3, 67.3, 60.8, 56.2, 32.3, 17.7, 13.9. HRMS calculated for $C_{37}H_{38}ClFN_4O_5S$: 704.2235; found 705.2288 (M + H).

***R5b**: Ethyl (2R)-2-[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate. Step A: 5-Bromo-4-chloro-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidine.* 26.3 g **R1a** (70.0 mmol) and 61.5 g 2-(5-fluoro-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[17] (290 mmol) were dissolved in 350 mL THF, then 29.3 g Cs_2CO_3 (90.0 mmol), 1.10 g $Pd(OAc)_2$ (4.90 mmol), 4.16 g *t*Bu-XPhos (9.80 mmol), and 120 mL water were added, and the mixture was stirred for 3 h at 70 °C under N_2 atmosphere. Most of the THF was removed under reduced pressure, EtOAc and water were added to the residue, and the resulting mixture was filtered through Celite. After separation of the phases, the aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified via flash chromatography using heptane and EtOAc as eluents to give a crude product which was finally crystallized from a mixture of heptane and Et_2O to obtain 10.5 g 5-bromo-4-chloro-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidine as a white solid (31.5 mmol, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.95 (s, 1H), 7.55 (t, J = 3.7 Hz, 1H), 6.23 (dd, J = 6.8, 3.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.6, 158.7, 154.6 (d, J = 268 Hz), 153.0, 136.8 (d, J = 1.5 Hz), 128.4, 126.7, 115.7, 97.6, 86.0 (d, J = 12.1 Hz). MS (EI, 70 eV) m/z (% relative intensity, [ion]): 106 (29), 198 (42), 225 (100), 253 (73), 332 (62, [M$^+$]), 334 (81, [M$^+$]), 336 (24, [M$^+$]).

Step B: Ethyl (2R)-2-[5-Bromo-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)-propanoate. 12.0 g 5-bromo-4-chloro-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidine (36.0 mmol), 11.8 g **R2a** (40.0 mmol), and 16.3 g Cs_2CO_3 (50 mmol) were mixed with 350 mL *t*BuOH, and the mixture was stirred at 35 °C under N_2 atmosphere for 4 h. Then the mixture was cooled to rt and diluted with brine, extracted with DCM, dried over Na_2SO_4, 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 17.1 g ethyl (2*R*)-2-[5-bromo-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate as a mixture of diastereoisomers (28.9 mmol, 80%). ^{1}H NMR (500 MHz, DMSO-d_6): 8.63/8.62 (s/s, 1H), 7.46−7.40 (m, 2H), 7.22−7.16 (m, 1H), 7.09−7.02 (m, 1H), 6.93−6.88 (m, 1H), 6.20−6.25 (m, 1H), 5.83−5.77/5.71−5.66 (m, 1H), 5.61/5.55 (t/t, J = 3.0/3.1 Hz, 1H), 4.20−4.07 (m, 2H), 3.78−3.40 (m, 3H), 3.23−3.14 (m, 1H), 2.06−1.33 (m, 6H), 1.17−1.09 (m, 3H). HRMS calculated for $C_{26}H_{24}BrFN_2O_6S$: 590.0522; found 591.0599 (M + H).

Step C: Ethyl (2R)-2-[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate. 14.0 g ethyl (2*R*)-2-[5-bromo-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (23.7 mmol) and 7.61 g **R3a** (28.3 mmol) were dissolved in 150 mL THF, then 13.0 g Cs_2CO_3 (40.0 mmol), 50 mL water, and 668 mg AtaPhos (0.94 mmol) were added, and the mixture was stirred under N_2 atmosphere at 80 °C for 1.5 h. Then the mixture was cooled to rt and diluted with brine. It was neutralized using 1 M aq HCl solution, then extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The atropisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer pair eluting later was isolated as ethyl (2*R*)-2-[(5S$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (1:1 mixture of diastereoisomers, 11.6 g, 17.8 mmol, 75%, white solid). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.40 (s, 1H), 8.58/8.57 (s, 1H), 7.17−7.12 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.04 (dm, J = 8.4 Hz, 1H), 7.01 (dm, J = 8.4 Hz, 1H), 6.83−6.78 (m, 1H), 6.38/6.36 (dd, J = 7.5, 1.7 Hz, 1H), 5.89 (dd, J = 6.9, 3.7 Hz, 1H), 5.69 (t, J = 3.7 Hz, 1H), 5.56/5.52 (m/t, J = 2.9 Hz, 1H), 5.56/5.43 (m/dd, J = 9.3, 4.0 Hz, 1H), 4.10−4.01 (m, 2H), 3.71−3.65 (m, 1H), 3.57−3.51 (m, 1H), 3.14/3.10 (dd, J = 13.6, 3.9/13.7, 3.6 Hz, 1H), 2.40−2.33 (m, 1H), 2.01−1.87 (m, 1H), 1.95/1.94 (s, 3H), 1.82−1.74 (m, 2H), 1.68−1.48 (m, 3H), 1.088/1.086 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.24/169.23, 165.93, 162.49/162.46, 156.5 (d, J = 278 Hz), 154.1, 153.5, 152.9, 138.0, 135.6, 131.1/130.9, 128.72/128.70, 128.3, 127.20/127.18, 126.0/125.8, 124.30/124.28, 120.83, 120.77, 118.67/118.65, 113.97, 113.95/113.88, 111.1, 95.1/94.8, 85.3 (d, J = 12.0 Hz), 73.7/73.4, 61.2, 61.0, 60.90/60.87, 32.8/32.7, 29.9/29.8,

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24.8/24.7, 18.12/18.07, 17.2, 13.8. HRMS calculated for $C_{33}H_{30}ClFN_2O_7S$: 652.1446; found 653.1485 and 653.1492 (M + H).

Step D: Ethyl (2R)-2-[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate. 11.6 g ethyl (2*R*)-2-[(5*S*$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (17.7 mmol), 5.77 g 2-(4-methylpiperazin-1-yl)ethanol (40 mmol), and 10.5 g PPh_3 (40 mmol) were dissolved in 100 mL dry toluene, then 9.21 g DTBAD (40 mmol) was added and the mixture was stirred at 50 °C under N_2 atmosphere for 1 h. Then the mixture was concentrated under reduced pressure, and the residue was purified via flash chromatography using heptane, EtOAc, and MeOH as eluents. The obtained intermediate was dissolved in 100 mL EtOH, then 100 mL HCl solution (1.25 M in EtOH) was added, and the mixture was stirred at rt for 2 h. Then most of the solvent was evaporated under reduced pressure, and then it was carefully neutralized with saturated aq $NaHCO_3$ solution and extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using DCM and MeOH as eluents to give 10.9 g **R5b** as a white solid (15.7 mmol, 89% for 2 steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.56 (s, 1H), 8.58 (s, 1H), 7.25 (s, 2H), 7.01−6.96 (m, 1H), 6.72 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.61−6.57 (m, 1H), 6.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.88 (dd, *J* = 6.8, 3.5 Hz, 1H), 5.71 (t, *J* = 3.5 Hz, 1H), 5.48 (dd, *J* = 9.4, 4.4 Hz, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 4.09−3.99 (m, 2H), 2.95 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.77 (t, *J* = 5.7 Hz, 2H), 2.53 (br s, 4H), 2.35 (dd, *J* = 13.6, 9.4 Hz, 1H), 2.29 (br s, 4H), 2.12 (s, 3H), 1.97 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.3, 165.9, 162.5, 156.6 (d, *J* = 278 Hz), 155.1, 154.1, 152.9, 137.9, 135.8, 131.0, 129.0, 128.0, 127.4, 126.8 (d, *J* = 3.6 Hz), 126.1, 122.4, 121.7, 118.63, 118.56, 114.7, 111.23, 111.21, 85.3 (d, *J* = 12.4 Hz), 73.3, 67.4, 60.8, 56.3, 54.7, 53.0, 45.6, 32.4, 17.3, 13.8. HRMS calculated for $C_{35}H_{36}ClFN_4O_6S$: 694.2028; found 695.2106 (M + H).

***R5c**: Ethyl (2R)-2-[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate. Step A: Ethyl (2R)-2-(5-Iodo-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl)oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate.* 8.92 g **R1d** (26.7 mmol), 8.83 g **R2a** (30.0 mmol), and 29.3 g Cs_2CO_3 (90.0 mmol) were placed in a 500 mL flask. 300 mL *t*BuOH was added, and the mixture was stirred at 65 °C under N_2 atmosphere for 4 h to reach >95% conversion. Brine was added, then it was extracted with DCM. The combined organic layer was dried over Na_2SO_4, 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 10.59 g ethyl (2*R*)-2-(5-iodo-6-prop-1-ynylthieno[2,3-*d*]-pyrimidin-4-yl)oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (17.9 mmol, 67%) as a mixture of diastereoisomers. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.64/8.63 (s, 1H), 7.52−7.49 (m, 1H), 7.22−7.17 (m, 1H), 7.09−7.05 (m, 1H), 6.91−6.87 (m, 1H), 5.82/5.71 (dd, *J* = 9.5, 4.1 Hz, 1H), 5.61/5.56 (t, *J* = 2.9 Hz, 1H), 4.18−4.08 (m, 2H), 3.77−3.65 (m, 1H), 3.59−3.46 (m, 2H), 3.21 (dd, *J* = 13.9, 9.5 Hz, 1H), 2.21 (s, 3H), 2.05−1.92 (m, 1H), 1.86−1.76 (m, 2H), 1.68−1.50 (m, 3H), 1.13/1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.4, 166.53/166.51, 161.4/161.3, 154.5/154.4, 153.69/153.67, 132.13/132.10, 128.43/128.40, 124.51/124.50, 123.68/123.66, 120.91/120.88, 119.1, 114.01/114.97, 98.94/98.93, 95.3/94.9, 79.6/79.5, 74.6/74.4, 74.3, 61.2/61.1, 61.04/61.01, 32.9, 29.9/29.8, 24.8, 18.21/18.19, 13.84/13.82, 4.7. HRMS calculated for $C_{25}H_{25}IN_2O_5S$: 592.0529; found 593.0606 (M + H).

Step B: Ethyl (2R)-2-[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate. 10.59 g ethyl (2*R*)-2-(5-iodo-6-prop-1-ynylthieno[2,3-*d*]pyrimidin-4-yl)oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (17.87 mmol) and 5.76 g **R3a** (21.45 mmol) were dissolved in 100 mL THF, then 11.64 g Cs_2CO_3 (35.74 mmol) dissolved in 30 mL water was added. Then 1.26 g AtaPhos (1.79 mmol) was added, and the mixture was stirred at 60 °C under N_2 atmosphere for 3 h to reach complete conversion. Then it was diluted with brine and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The atropoisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer pair eluting later was collected as 6.60 g ethyl (2*R*)-2-[(5*S*$_a$)-(3-chloro-4-hydroxy-2-methylphenyl)-6-prop-1-ynylthieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (10.9 mmol, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.31 (s, 1H), 8.62/8.61 (s, 1H), 7.15−7.11 (m, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.00−6.97 (m, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.76−6.70 (m, 1H), 6.25−6.22/6.20−6.17 (m, 1H), 5.54/5.51 (t, *J* = 2.6 Hz, 1H), 5.49/5.37 (dd/dd, *J* = 9.4, 4.1 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.71−3.61/3.56−3.49 (m, 2H), 3.14/3.11 (dd, *J* = 13.3 Hz, 4.1 Hz, 1H), 2.43 (dd, *J* = 13.3 Hz, 9.4 Hz, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 2.02−1.48 (m, 6H), 1.10/1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.26/169.25, 166.20/166.18, 162.15/162.11, 154.12, 154.09, 153.7/153.3, 135.91/135.87, 131.3/131.1, 129.62/129.56, 128.33/128.29, 128.26, 127.24/127.19, 125.63/125.63, 124.2, 120.6, 120.45/120.43, 119.36/119.35, 117.2, 113.9/113.0, 97.30/97.28, 95.0/94.8, 73.8/73.6, 71.9, 61.2/61.1, 60.93/60.90, 32.7/32.6, 29.86/29.82, 24.8/24.7, 18.1, 17.8, 14.0/13.8, 4.4. HRMS calculated for $C_{32}H_{31}ClN_2O_6S$: 606.1591; found 607.1685 and 607.1671 (M + H).

Step C: Ethyl (2R)-2-[(5S$_a$)-5-[3-cChloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate. 6.60 g ethyl (2*R*)-2-[(5*S*$_a$)-(3-chloro-4-hydroxy-2-methylphenyl)-6-prop-1-ynylthieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-tetrahydropyran-2-yloxyphenyl)propanoate (10.9 mmol), 2.88 g 2-(4-methylpiperazin-1-yl)ethanol (20.0 mmol), and 5.25 g PPh_3 (20.0 mmol) were dissolved in 50 mL dry toluene, then 4.61 g DTBAD (20.0 mmol) was added. The mixture was stirred at 50 °C under N_2 atmosphere for 1.5 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 100 mL EtOH, then 40 mL 1.25 M HCl solution in EtOH was added and the mixture was stirred at rt for 30 min to reach complete conversion. Then most of the solvent was evaporated under reduced pressure, and then it was carefully neutralized with saturated aq $NaHCO_3$ solution and extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using DCM and MeOH as eluents to give 5.90 g **R5c** (9.00 mmol, 84% for 2 steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.53 (s, 1H), 8.62 (s, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.99−6.95 (m, 1H), 6.71−6.68 (m, 1H), 6.54−6.50 (m, 1H), 6.07−6.04 (m, 1H), 5.41 (dd, *J* = 9.4, 4.3 Hz, 1H), 4.25 (t, *J* = 5.8 Hz, 2H), 4.11−4.00 (m, 2H), 2.97 (dd, *J* = 13.5, 4.3 Hz, 1H), 2.78−2.72 (m, 2H), 2.60−2.40 (m, 4H), 2.42 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.36−2.17 (m, 4H), 2.11 (s, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.4, 166.2, 162.2, 155.1, 153.9, 153.7, 136.1, 135.5, 131.1, 129.8, 128.0, 127.2, 122.0, 121.6, 119.5, 118.4, 117.2, 114.7, 110.3, 97.5, 73.4, 71.8, 67.4, 60.8, 56.3, 54.7, 53.1, 45.8, 32.2, 17.8, 13.9, 4.4. HRMS calculated for $C_{34}H_{37}ClN_4O_5S$: 648.2173; found 649.2275 (M + H).

***R6**: (E)-4-(Dimethylamino)-1,1-dimethoxybut-3-en-2-one.* 502.1 g 1,1-dimethoxypropan-2-one (4.25 mol) and 506.4 g 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (4.25 mol) were mixed in a 2 L flask and stirred at 105 °C for 3 h. The formed MeOH was removed continuously via distillation. When MeOH formation stopped (at 65 °C head temperature), the reaction mixture was vacuum distilled (decreasing the pressure slowly to 30 mbar) to remove side products and unreacted starting materials. The crude product was distilled at 0.1 mbar. Fractions were collected between 107 and 118 °C head temperature (bath temperature 160−165 °C) to give 488 g **R6** as a yellow oil (2.82 mol, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.59 (d, *J* = 12.5 Hz, 1H), 5.17 (d, *J* = 12.5 Hz, 1H), 4.42 (s, 1H), 3.25 (s, 6H), 3.09 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 189.1, 153.8, 103.9, 53.6, 44.4, 36.8. MS (EI, 70

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eV) m/z (% relative intensity, [ion]): 55 (9), 75 (14), 98 (100), 114 (22), 143 (14), 173 (1, [M^+]).

General Procedure 1: Acetal Deprotection and Reduction of the Formed Aldehyde. The appropriate acetal (1.0 equiv) was stirred with 2 M aq HCl solution (3 mL/mmol) at 60 °C until no further conversion was observed. Then the mixture was cooled to 0 °C, then NaOH (5.7 equiv) was added portionwise. The pH was adjusted to 8 using 10% aq K_2CO_3 solution, then $NaBH_4$ (2.0 equiv) was added portionwise while keeping the temperature under 5 °C and the mixture was stirred for 30 min at 0 °C. Then it was extracted with EtOAc, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents.

R6aa: 4-(Dimethoxymethyl)-2-methylsulfanylpyrimidine. 198 g NaOMe (3.67 mol) was dissolved in 3 L MeOH and cooled to 0 °C. 322 g thiocarbamide (4.23 mol) was added portionwise, and the mixture was stirred for 1 h. Then 488 g **R6** (2.82 mol) was added dropwise at 0 °C, then it was heated to 70 °C for 4 h. It was cooled to rt, 237 mL MeI (3.81 mol) was added dropwise, keeping the temperature below 28 °C, and the resulting mixture was stirred overnight at rt. It was filtered, and the filtrate was concentrated under reduced pressure, diluted with EtOAc, washed with water and brine. The combined aq layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 500 mL Et_2O, filtered through a pad of silica, using Et_2O as eluent. The filtrate was concentrated under reduced pressure to give 429 g **R6aa** (2.14 mol, 76%) as a light brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.69 (d, J = 5.1 Hz, 1H), 7.23 (d, J = 5.1 Hz, 1H), 5.22 (s, 1H), 3.33 (s, 6H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 171.3, 165.3, 158.5, 113.6, 102.3, 53.7, 13.5. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 110 (12), 125 (100), 152 (29), 200 (20, [M^+]).

R6a: (2-Methylsulfanylpyrimidin-4-yl)methanol. Using general procedure 1 and 1202 mg **R6aa** (6.00 mmol) as the appropriate acetal, 540 mg **R6a** (3.46 mmol, 58%) was obtained as white crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.61 (d, J = 5.1 Hz, 1H), 7.24 (d, J = 5.1 Hz, 1H), 5.63 (t, J = 6.0 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 172.1, 170.9, 158.3, 113.4, 63.7, 13.9. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 81 (24), 92 (18), 110 (19), 127 (15), 138 (100), 156 (55, [M^+]).

R6b: (2-(Morpholin-4-yl)pyrimidin-4-yl)methanol. Step A: 4-(Dimethoxymethyl)-2-methylsulfonylpyrimidine. 180 g **R6aa** (940 mmol) was dissolved in 1.5 L MeOH and 1.5 L water, then 752 g Oxone (1220 mmol) was added portionwise at −5 °C, then stirred at 0 °C overnight. The reaction mixture was concentrated under reduced pressure to half volume using a 30 °C bath and then the mixture was filtered, and the precipitate was washed with DCM. The filtrate was extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give 205 g 4-(dimethoxymethyl)-2-methylsulfonylpyrimidine (868 mmol, 92%) as a light brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.14 (d, J = 5.1 Hz, 1H), 7.86 (d, J = 5.1 Hz, 1H), 5.45 (s, 1H), 3.43 (s, 6H), 3.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.0, 165.4, 160.2, 121.3, 101.7, 54.0, 39.0. LRMS calculated for $C_8H_{12}N_2O_4$: 232.3; found 233.0 (M + H).

Step B: 4-[4-(Dimethoxymethyl)pyrimidin-2-yl]morpholine. 3.50 g 4-(dimethoxymethyl)-2-methylsulfonylpyrimidine (15.1 mmol) was stirred in 23 mL morpholine at rt for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified via flash chromatography using heptane and EtOAc as eluents to give 3.53 g 4-[4-(dimethoxymethyl)pyrimidin-2-yl]morpholine (14.8 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.42 (d, J = 4.9 Hz, 1H), 6.71 (d, J = 4.9 Hz, 1H), 5.06 (s, 1H), 3.71−3.62 (m, 8H), 3.31 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 165.6, 161.2, 158.8, 106.9, 103.0, 65.9, 53.6, 43.8.

Step C: (2-(Morpholin-4-yl)pyrimidin-4-yl)methanol. Using general procedure 1 and 3.53 g 4-[4-(dimethoxymethyl)pyrimidin-2-yl]morpholine (14.8 mmol) as the appropriate acetal, 2.33 g **R6b** (11.9 mmol, 81%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.35 (d, J = 5.0 Hz, 1H), 6.75 (d, J = 5.0 Hz, 1H), 5.42 (t, J = 6.0 Hz, 1H), 4.36 (d, J = 6.0 Hz, 2H), 3.69−3.61 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 171.6, 160.8, 158.2, 106.4, 66.0, 63.6, 43.8.

General Procedure 2: Conversion of Amidines to Pyrimidines. To the mixture of the appropriate amidine hydrochloride (1.2 equiv) and **R6** (1.0 equiv) in dry MeOH (0.5 mL/mmol), NaOMe (1.2 equiv) was added portionwise, and the mixture was stirred at 75 °C for 2 h. The reaction mixture was cooled and concentrated under reduced pressure. To the residue water was added, and it was extracted with DCM. The combined organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents.

R6c: [2-(2-Methoxyethyl)pyrimidin-4-yl]methanol. Step A: 4-(Dimethoxymethyl)-2-(2-methoxyethyl)pyrimidine. Using general procedure 2 and 25.0 g 3-methoxypropanamidine hydrochloride (180 mmol) as the appropriate amidine hydrochloride, 13.8 g 4-(dimethoxymethyl)-2-(2-methoxyethyl)pyrimidine (64.9 mmol, 36%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.78 (d, J = 5.1 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 5.25 (s, 1H), 3.80 (t, J = 6.6 Hz, 2H), 3.32 (s, 6H), 3.22 (s, 3H), 3.11 (t, J = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 167.9, 164.8, 158.1, 115.7, 102.6, 70.2, 57.9, 53.7, 38.8. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 75 (100), 135 (46), 165 (46), 167 (57), 182 (65), 197 (15).

Step B: [2-(2-Methoxyethyl)pyrimidin-4-yl]methanol. Using general procedure 1 and 13.8 g 4-(dimethoxymethyl)-2-(2-methoxyethyl)pyrimidine (64.9 mmol) as the appropriate acetal, 7.92 g **R6c** (47.1 mmol, 73%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.69 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 5.2 Hz, 1H), 5.60 (t, J = 5.8 Hz, 1H), 4.52 (d, J = 5.8 Hz, 2H), 3.78 (t, J = 6.5 Hz, 2H), 3.22 (s, 3H), 3.05 (t, J = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.9, 167.1, 157.5, 114.9, 70.3, 63.4, 57.8, 38.8. LRMS calculated for $C_8H_{12}N_2O2$: 168.2; found 169.2 (M + H).

R6d: [2-(2-Methoxyphenyl)pyrimidin-4-yl]methanol. Step A: 4-(Dimethoxymethyl)-2-(2-methoxyphenyl)pyrimidine. Using general procedure 2 and 4.435 g 2-methoxybenzamidine AcOH salt (21.1 mmol) as the appropriate amidine hydrochloride, 4.20 g 4-(dimethoxymethyl)-2-(2-methoxyphenyl)pyrimidine (19.42 mmol, 92%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.93 (d, J = 5.1 Hz, 1H), 7.55−7.43 (m, 3H), 7.16 (d, J = 8.3 Hz, 1H), 7.08−7.02 (m, 1H), 5.31 (s, 1H), 3.76 (s, 3H), 3.37 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 164.9, 164.8, 158.1, 157.3, 131.0, 130.9, 128.4, 120.2, 115.8, 112.3, 102.7, 55.7, 53.7. LRMS calculated for $C_{14}H_{16}N_2O_3$: 260.3; found 261.2 (M + H).

Step B: [2-(2-Methoxyphenyl)pyrimidin-4-yl]methanol. Using general procedure 1 and 2.36 g 4-(dimethoxymethyl)-2-(2-methoxyphenyl)pyrimidine (9.10 mmol) as the appropriate acetal, 1.71 g [2-(2-methoxyphenyl)pyrimidin-4-yl]methanol (**R6d**, 7.91 mmol, 87%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.84 (d, J = 5.2 Hz, 1H), 7.50−7.39 (m, 3H), 7.13 (d, J = 8.3 Hz, 1H), 7.06−6.99 (m, 1H), 5.65 (t, J = 5.9 Hz, 1H), 4.58 (d, J = 5.9 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 170.9, 164.4, 157.4, 157.1, 130.9, 130.6, 128.8, 120.1, 115.1, 112.2, 63.5, 55.7. LRMS calculated for $C_{12}H_{12}N_2O_2$: 216.2; found 217.2 (M + H).

R6e: [2-(4-Pyridyl)pyrimidin-4-yl]methanol. Using general procedure 2 and 2.50 g pyridine-4-carboxamidine hydrochloride (15.9 mmol) as the appropriate amidine hydrochloride, 1.74 g 4-(dimethoxymethyl)-2-(4-pyridyl)pyrimidine (7.53 mmol) was obtained which was treated as described in general procedure 1 to yield 1.23 g **R6e** (6.60 mmol, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.97 (d, J = 5.1 Hz, 1H), 8.78−8.74 (m, 2H), 8.26−8−23 (m, 2H), 7.62 (d, J = 5.1 Hz, 1H), 5.76 (t, J = 5.8 Hz, 1H), 4.68 (d, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 172.4, 161.2, 158.8, 151.0, 144.7, 122.0, 117.7, 63.9. LRMS calculated for $C_{10}H_9N_3O$: 187.2; found 188.2 (M + H).

General Procedure 3: Hydroxymethylation of Pyrazoles. To the solution of the appropriate alkyl pyrazole (1.0 equiv) in dry THF

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(1.5 mL/mmol) *n*-BuLi solution (1.10 equiv) was added dropwise at −70 °C. The mixture was stirred at −70 °C for 30 min, then allowed to warm up to 0 °C in 30 min, then cooled again to −70 °C. Then DMF (1.10 equiv) was added dropwise at −70 °C, then the reaction mixture was stirred at rt overnight. Then the mixture was cooled to 15 °C, then sat. aq NH_4Cl solution was added dropwise, and then the mixture was poured into sat. aq NH_4Cl solution. The phases were separated, and the aq layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Then it was dissolved in EtOH (0.5 mL/mmol), $NaBH_4$ (1.30 equiv) was added portionwise at −15 °C, and then the mixture was stirred at rt for 1 h. Then it was poured onto crushed ice and stirred for 16 h. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The oily phase was separated, and the aq layer was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated. The crude product was purified via flash chromatography, using heptane and EtOAc as eluents.

***R6f**: (1-Ethyl-1H-pyrazol-5-yl)methanol.* Using general procedure 3 and 1.93 g 1-ethylpyrazole (20.0 mmol) as the appropriate alkyl pyrazole, 1.67 g **R6f** (13.2 mmol, 66%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.31 (d, J = 1.8 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1H), 5.25 (t, J = 5.5 Hz, 1H) 4.55 (d, J = 5.5 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 2.99 (br s, 1H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 141.7, 137.2, 104.9, 53.7, 43.6, 15.6. LRMS calculated for $C_6H_{10}N_2O$: 126.2; found 127.2 (M + H).

***R6g**: [1-(Propan-2-yl)-1H-pyrazol-5-yl]methanol.* Using general procedure 3 and 2.20 g 1-isopropylpyrazole (20.0 mmol) as the appropriate alkyl pyrazole, 1.70 g **R6g** (12.1 mmol, 61%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.32 (d, J = 1.7 Hz, 1H), 6.10 (d, J = 1.7 Hz, 1H), 5.23 (t, J = 4.6 Hz, 1H), 4.60 (h, J = 6.6 Hz, 1H), 4.49 (d, J = 4.6 Hz, 2H), 1.36 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 141.1, 137.0, 104.5, 53.6, 49.3, 22.7. LRMS calculated for $C_7H_{12}N_2O$: 140.2; found 141.2 (M + H).

***R6h**: (1-Butyl-1H-pyrazol-5-yl)methanol.* Using general procedure 3 and 2.48 g 1-butylpyrazole (20.0 mmol) as the appropriate alkyl pyrazole, 1.76 g **R6h** (11.4 mmol, 57%) was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.30 (d, J = 1.7 Hz, 1H), 6.12 (d, J = 1.7 Hz, 1H), 5.24 (t, J = 5.5 Hz, 1H), 4.48 (d, J = 5.5 Hz, 2H), 4.05 (t, J = 7.2 Hz, 2H), 1.76−1.67 (m, 2H), 1.31−1.21 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 142.0, 137.2, 104.8, 53.8, 48.3, 32.0, 19.4, 13.6. LRMS calculated for $C_8H_{14}N_2O$: 154.2; found 155.2 (M + H).

***R6i**: (1-tert-Butyl-1H-pyrazol-5-yl)methanol. Step A: 1-tert-Butyl-5-(dimethoxymethyl)pyrazole.* 3.50 g *tert*-butylhydrazine hydrochloride (28.1 mmol) and 4.06 g **R6** (23.4 mmol) were dissolved in 15 mL dry MeOH, then 1.52 g NaOMe (28.1 mmol) was added portionwise and the mixture was stirred at 75 °C for 2 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. Then water was added, and it was extracted with DCM. The combined organic phase was dried over $MgSO_4$, 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 1.21 g 1-*tert*-butyl-5-(dimethoxymethyl)pyrazole (6.10 mmol, 26%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.34 (d, J = 1.7 Hz, 1H), 6.33 (d, J = 1.7 Hz, 1H), 5.74 (s, 1H), 3.23 (s, 6H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 139.2, 135.6, 107.4, 96.9, 60.6, 52.4, 29.9. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 111 (100), 167 (28), 198 (4, [M^+]).

Note: 2.42 g 1-*tert*-butyl-3-(dimethoxymethyl)pyrazole (12.2 mmol, 52%) was also obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.75 (d, J = 2.3 Hz, 1H), 6.18 (d, J = 2.3 Hz, 1H), 5.34 (s, 1H), 3.23 (s, 6H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 148.4, 126.9, 102.9, 99.6, 57.9, 52.5, 29.5.

Step B: (1-tert-Butyl-1H-pyrazol-5-yl)methanol. 1.21 g 1-*tert*-butyl-5-(dimethoxymethyl)pyrazole (6.10 mmol) was stirred with 18 mL 1 M aq HCl solution at 50 °C for 45 min. Then the mixture was cooled to 0 °C, then 700 mg NaOH (17.5 mmol) was added portionwise. The pH was adjusted to 8 using 10% aq K_2CO_3 solution, then 461 mg $NaBH_4$ (12.2 mmol) was added portionwise, while keeping the temperature under 5 °C, then it was stirred for 30 min at 0 °C. Then it was extracted with EtOAc, dried over Na_2SO_4, 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 830 mg **R6i** (5.38 mmol, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.26 (d, J = 1.6 Hz, 1H), 6.19 (d, J = 1.6 Hz, 1H), 5.31 (t, J = 5.5 Hz, 1H), 4.61 (d, J = 5.5 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 142.7, 135.6, 107.5, 59.8, 55.7, 29.8. MS (EI, 70 eV) m/z (% relative intensity, [ion]): 69 (40), 81 (100), 97 (35), 121 (37), 139 (11), 154 (20, [M^+]).

***R7**: Ethyl (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-methylsulfanylpyrimidin-4-yl)methoxy]phenyl]propanoate.* 1.39 g **R5a** (2.00 mmol), 0.94 g **R6a** (6.00 mmol) and 1.57 g PPh_3 (6.00 mmol) were dissolved in 40 mL dry toluene, then 1.38 g DTBAD (6.00 mmol) was added. The mixture was stirred at 50 °C under N_2 atmosphere for 1 h. The volatiles were evaporated under reduced pressure and the residue was purified via flash chromatography using DCM and MeOH as eluents to give 1.24 g **R7** (1.47 mmol, 74%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.70 (d, J = 5.2 Hz, 1H), 8.60 (s, 1H), 7.34 (d, J = 5.2 Hz, 1H), 7.33−7.28 (m, 3H), 7.25−7.14 (m, 4H), 6.98 (d, J = 8.2 Hz, 1H), 6.74 (t, J = 7.5 Hz, 1H), 6.31 (dd, J = 7.5, 1.3 Hz, 1H), 5.47 (dd, J = 9.3, 4.5 Hz, 1H), 5.17 (d, J = 14.9 Hz, 1H), 5.11 (d, J = 14.9 Hz, 1H), 4.25−4.12 (m, 2H), 4.10−4.00 (m, 2H), 3.12 (dd, J = 13.9, 4.2 Hz, 1H), 2.75−2.65 (m, 2H), 2.56 (dd, J = 13.7, 9.4 Hz, 1H), 2.50 (s, 3H), 2.46 (br s, 4H), 2.24 (br s, 4H), 2.10 (s, 3H), 1.86 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 169.3, 166.5, 166.3, 163.1, 161.7, 158.2, 155.3, 153.8, 152.7, 136.9, 135.9, 133.3, 131.0, 131.0, 130.2, 129.0, 128.8, 128.8, 128.5, 128.4, 127.6, 123.7, 122.1, 120.6, 118.8, 116.0, 113.3, 111.8, 110.7, 73.5, 68.7, 67.3, 60.9, 56.2, 54.6, 53.0, 45.6, 32.1, 17.6, 13.8, 13.5. HRMS calculated for $C_{43}H_{44}ClFN_6O_5S_2$: 842.2487; found 843.2660 (M + H).

***R8**: Methyl (2R)-2-[6-Bromo-(5S$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-phenylpropanoate. Step A: 6-Bromothieno[2,3-d]pyrimidin-4(3H)-one.* 10.0 g 3*H*-thieno[2,3-*d*]pyrimidin-4-one (65.7 mmol) was dissolved in 100 mL AcOH, then 4.04 mL Br_2 (78.8 mmol, dissolved in 20 mL AcOH) was added dropwise and the mixture was stirred at rt. Additional 3 mL Br_2 was added, and that was repeated until all starting material was consumed. Then it was poured onto icy water. The formed precipitate was filtered off, washed with water, AcOH, and Et_2O and then air-dried to give 14.9 g 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one (64.8 mmol, 98%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.63 (br s, 1H), 8.14 (d, J = 2.8 Hz, 1H), 7.55 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 164.9, 156.0, 146.3, 125.6, 124.5, 110.3.

Step B: 6-Bromo-4-chloro-5-iodothieno[2,3-d]pyrimidine. 1 L cc. H_2SO_4 was cooled with ice−water bath, and 72.0 g KI (0.434 mol) was added in portions during 15 min and then 32.4 g $NaIO_4$ (0.151 mol) during a 10 min period. The resulting mixture was stirred at rt for 30 min, then 80.0 g 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one (0.346 mol) was added to the mixture in portions in 30 min while the internal temperature was kept between −25 °C and −19 °C. The reaction mixture was stirred at −20 °C for 1.5 h. Ice was added to the suspension, then the precipitate was filtered off, washed with water, finally with Et_2O, and air-dried to give 116 g 6-bromo-5-iodothieno-[2,3-*d*]pyrimidin-4(3*H*)-one (0.325 mol, 94%). Then it was added to 910 mL $POCl_3$, then 41 mL *N*,*N*-dimethylaniline was added. The mixture was stirred at 100 °C for 1.5 h. The resulting suspension was cooled to rt, hexane was added, and it was stirred for further 20 min. The precipitate was filtered off, washed with hexane, water, and iPr_2O, finally air-dried to give 101.6 g 6-bromo-4-chloro-5-iodothieno[2,3-*d*]pyrimidine as a green shaded powder (0.270 mol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.94 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 168.9, 153.0, 152.5, 129.0, 123.4, 83.8.

Step C: Methyl (2R)-2-(6-Bromo-5-iodothieno[2,3-d]pyrimidin-4-yl)oxy-3-phenylpropanoate. 15.4 g 6-bromo-4-chloro-5-iodothieno-[2,3-*d*]pyrimidine (41.0 mmol), 11.1 g methyl (2*R*)-2-hydroxy-3-

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phenylpropanoate (61.6 mmol), and 26.7 g Cs_2CO_3 (82 mmol) were placed in a flask. 40 mL dry DMSO was added, and the mixture was stirred at 70 °C under Ar atmosphere for 30 min to reach complete conversion. The reaction mixture was poured onto 200 mL icy water, and then the pH was set to 5 with 2 M aq HCl solution Then it was extracted with DCM, dried over Na_2SO_4, 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 15.4 g methyl (2*R*)-2-(6-bromo-5-iodothieno[2,3-*d*]pyrimidin-4-yl)oxy-3-phenylpropanoate (29.7 mmol, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.64 (s, 1H), 7.49−7.45 (m, 2H), 7.33−7.28 (m, 2H), 7.26−7.21 (m, 1H), 5.71 (dd, J = 8.4, 4.8 Hz, 1H), 3.65 (s, 3H), 3.37−3.33 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.6, 168.4, 160.1, 153.0, 136.0, 129.6, 128.4, 126.9, 119.9, 119.0, 80.7, 75.9, 52.3, 37.0. LRMS calculated for $C_{16}H_{12}BrIN_2O_3S$: 517.9; found 518.9 (M + H).

Step D: Methyl (2R)-2-[6-Bromo-(5S$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-phenylpropanoate. 1.56 g methyl (2*R*)-2-(6-bromo-5-iodothieno[2,3-*d*]-pyrimidin-4-yl)oxy-3-phenylpropanoate (3.00 mmol) and 1.29 g **R3a** (4.80 mmol) were dissolved in dioxane, then 2.93 g Cs_2CO_3 (9.00 mmol) dissolved in 6 mL water and 219 mg Pd(ddpf)Cl_2 (0.30 mmol) were added and the mixture was stirred at 120 °C in a microwave reactor under N_2 atmosphere for 30 min to reach complete conversion. Then it was diluted with brine and the pH was set to 5 with 2 M aq HCl solution. Then it was extracted with DCM. The combined organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer eluting later was collected as **R8** (311 mg, 0.58 mmol, 19%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.38 (s, 1H), 8.61 (s, 1H), 7.17−7.13 (m, 3H), 7.09 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.67−6.63 (m, 2H), 5.47 (dd, J = 9.1, 3.1 Hz, 1H), 3.58 (s, 3H), 2.97 (dd, J = 14.2, 3.1 Hz, 1H), 2.63 (dd, J = 14.2, 9.2 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.3, 167.5, 161.2, 153.6, 153.0, 135.9, 135.7, 133.4, 129.4, 129.0, 128.1, 126.7, 125.2, 120.6, 117.6, 114.1, 113.4, 75.1, 52.1, 37.0, 17.6. LRMS calculated for $C_{23}H_{18}BrClN_2O_4S$: 531.0; found 532.0 (M + H).

***R9a**: [2-Chloro-4-(4-chloro-6-iodothieno[2,3-d]pyrimidin-5-yl)-3-methylphenoxy]triisopropylsilane. Step A: [2-Chloro-4-(4-chlorothieno[2,3-d]pyrimidin-5-yl)-3-methylphenoxy]-triisopropylsilane.* 34.50 g **R1e** (116.3 mmol), 59.32 g **R3aa** (139.6 mmol), 653 mg Pd(OAc)$_2$ (2.908 mmol), 2.085 g ^{n}BuPAd$_2$ (5.817 mmol), and 74.09 g K_3PO_4 (349.0 mmol) were placed in a 1 L flask. After addition of 450 mL DME and 150 mL water the reaction was stirred at 60 °C under N_2 atmosphere for 1 h. Then sat. aq NH_4Cl solution was added and it was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The obtained solid was sonicated in MeCN/water (3:1) and collected by filtration to give 38.41 g [2-chloro-4-(4-chlorothieno[2,3-*d*]pyrimidin-5-yl)-3-methylphenoxy]triisopropylsilane (82.6 mmol, 71%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.97 (s, 1H), 8.00 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 2.06 (s, 3H), 1.35 (sept, J = 7.4 Hz, 3H), 1.10 (dd, J = 7.4, 3.3 Hz, 18H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.1, 153.9, 152.8, 151.6, 136.9, 132.9, 129.5, 128.7, 128.2, 126.9, 124.7, 116.6, 17.8, 12.3.

Step B: [2-Chloro-4-(4-chloro-6-iodothieno[2,3-d]pyrimidin-5-yl)-3-methylphenoxy]triisopropylsilane. 38.00 g [2-chloro-4-(4-chlorothieno[2,3-*d*]pyrimidin-5-yl)-3-methylphenoxy]-triisopropylsilane (81.27 mmol) was dissolved in 1 L dry THF, then cooled to −78 °C under Ar atmosphere. 48.76 mL LDA (97.53 mmol, 2 M in THF, EtPh, hexanes) was added, and the mixture was stirred at −78 °C for 1 h. Then 24.75 g I_2 (97.53 mmol) was added and the mixture was allowed to warm up to rt. Sat. aq NH_4Cl solution was added, and it was extracted with EtOAc. The combined organic layer was washed with aq $Na_2S_2O_3$ solution, then dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The obtained solid was sonicated in MeCN/water (3:1) and collected by filtration to give 35.0 g **R9a** (159.3 mmol, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.93 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 1.99 (s, 3H), 1.36 (sept, J = 7.5 Hz, 3H), 1.10 (dd, J = 7.5, 5.4 Hz, 18H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.3, 152.8, 152.4, 151.9, 138.6, 136.8, 129.7, 129.7, 127.2, 125.0, 117.4, 91.4, 17.8, 12.3.

***R9**: Ethyl (2R)-2-[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-iodothieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-methoxyphenyl)-propanoate.* 6.39 g **R9a** (10.8 mmol), 2.90 g **R2b** (12.9 mmol), and 10.5 g Cs_2CO_3 (32.3 mmol) were placed in a 250 mL flask. 50 mL *t*BuOH was added, and the mixture was stirred at 70 °C for 3 h to reach complete conversion. It was diluted with icy water, the pH was set to 6 with 2 M aq HCl solution, and then it was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 150 mL THF, 13.6 mL TBAF (1 M solution in THF) was added, and the mixture was stirred at rt for 3 h. Approximately 100 mL solvent was evaporated under reduced pressure, then it was diluted with EtOAc, washed with water and brine. The organic layer was dried over Na_2SO_4, 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 eluting later was collected as **R9** (1.60 g, 2.5 mmol, 23%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.33 (s, 1H), 8.55 (s, 1H), 7.18 (dt, J = 7.9, 1.8 Hz, 1H), 7.02−6.96 (m, 2H), 6.90 (dd, J = 8.5, 0.8 Hz, 1H), 6.75 (dt, J = 7.4, 0.8 Hz, 1H), 6.29 (dd, J = 7.4, 1.6 Hz, 1H), 5.36 (dd, J = 9.2, 4.3 Hz, 1H), 4.09−3.97 (m, 2H), 3.76 (s, 3H), 2.99 (dd, J = 13.8, 4.2 Hz, 1H), 2.42 (dd, J = 13.8, 9.2 Hz, 1H), 1.97 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.3, 169.2, 160.8, 156.9, 153.3, 152.8, 138.7, 135.7, 130.9, 129.2, 128.4, 127.9, 123.2, 120.5, 119.9, 117.5, 113.3, 110.5, 85.9, 73.4, 60.8, 55.3, 32.2, 17.8, 13.8. HRMS calculated for $C_{25}H_{22}ClIN_2O_5S$: 623.9983; found 625.0055 (M + H).

General Hydrolysis Procedure. The obtained intermediate was dissolved in dioxane−water 1:1 (10 mL/mmol), and 10 equiv LiOH·H_2O was added. The mixture was stirred at rt until no further conversion was observed. Then it was diluted with brine, neutralized with 2 M aq HCl solution, extracted with DCM. The combined organic layer was dried over Na_2SO_4, 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.

General Procedure 4: Mitsunobu Reaction and Hydrolysis. 1 equiv of the appropriate phenol, 2 equiv of the appropriate alcohol, and 2 equiv PPh_3 were dissolved in dry toluene (0.2 M for the phenol), then 2 equiv DTBAD was added. The mixture was stirred at 50 °C under N_2 atmosphere until no further conversion was observed. The volatiles were evaporated under reduced pressure, and the crude intermediate was purified via flash chromatography using EtOAc and MeOH as eluents. The obtained intermediate was submitted to the general hydrolysis procedure to give the desired product.

General Procedure 5: Liebskind−Schrogl Reaction. 1 equiv **R7**, 3.0 equiv of the appropriate boronic acid derivative, and 3.0 equiv copper(I) thiophenecarboxylate were dissolved in dry THF (0.1 M for **R7**), then 0.15 equiv Pd$(PPh_3)_4$ was added. The mixture was stirred at 70 °C under N_2 atmosphere until no further conversion was observed. Then it was concentrated under reduced pressure, and the crude intermediate was purified via flash chromatography using DCM and MeOH as eluents. The obtained intermediate was submitted to the general hydrolysis procedure to give the desired product.

General Procedure 6: Suzuki Coupling−Mitsunobu Reaction−Hydrolysis Sequence. *Step A: Suzuki Coupling.* 1 equiv **R8**, 2.5 equiv of the appropriate boronic ester or boronic acid, and 2.5 equiv Cs_2CO_3 were dissolved in THF−water (4:1) (12.5 mL/mmol of **R8**), then 0.1 equiv Pd(dppf)Cl_2 was added. The mixture was stirred at 110 °C under N_2 atmosphere in a microwave reactor until no further conversion was observed. Then it was diluted with brine, neutralized with 2 M aq HCl solution, and extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product

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was purified via flash chromatography using heptane and EtOAc as eluents.

Step B: Mitsunobu Coupling−Hydrolysis. The product of step A was transformed following general procedure 4 using 2-(4-methylpiperazin-1-yl)ethanol as the appropriate alcohol.

General Procedure 7: Suzuki Coupling−Mitsunobu Reaction−Hydrolysis Sequence. *Step A: Suzuki Coupling.* 2.5 equiv of the appropriate boronic acid was dissolved in dry dioxane (5 mL/mmol **R9**), then 2.5 equiv pinacol and dry acidic Amberlyst (100 mg/mmol boronic acid) were added and the mixture was stirred at rt overnight, then it was filtered (if the appropriate boronic ester was available, then it was dissolved in dioxane (5 mL/mmol **R9**) and this solution was used instead of the filtrate). 1 equiv **R9**, 0.1 equiv $PdCl_2$·dppf, 2.5 equiv Cs_2CO_3, and water (2.5 mL/mmol) were added to the boronic ester solution, and the mixture was stirred at 110 °C under N_2 atmosphere in a microwave reactor until no further conversion was observed. Then it was diluted with brine, neutralized with 2 M aq HCl solution, and extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using heptane and EtOAc as eluents.

Step B: Mitsunobu Reaction and Hydrolysis. The product of step A was transformed following general procedure 4 using 2-(4-methylpiperazin-1-yl)ethanol as the appropriate alcohol.

Examples in the Manuscript. *(2R)-2-[((5S_a)-5-{3-cChloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-ethylthieno-[2,3-d]pyrimidin-4-yl)oxy]-3-phenylpropanoic Acid (**1a**).* **1a** was prepared according to the published procedure.[14]

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(2-methylprop-1-en-1-yl)thieno[2,3-d]-pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1b**).* Using general procedure 6, 202 mg **R8** (0.38 mmol) and 232 μL 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane (1.13 mmol) as the appropriate boronic ester, 49 mg **1b** (0.079 mmol, 21%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.53 (s, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.15−7.08 (m, 3H), 6.68−6.60 (m, 2H), 5.95 (br s, 1H), 5.30 (dd, *J* = 9.8 Hz, 2.8 Hz, 1H), 4.30−4.17 (m, 2H), 3.00 (dd, *J* = 14.1 Hz, 2.8 Hz, 1H), 2.83−2.70 (m, 2H), 2.70−2.32 (br, 8H), 2.53 (dd, *J* = 14.1 Hz, 9.8 Hz, 1H), 2.23 (s, 3H), 2.21 (s, 3H), 1.98 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.0, 166.7, 166.0, 154.1, 152.8, 140.3, 137.5, 136.6, 135.3, 130.7, 129.5, 129.3, 128.4, 128.3 126.8, 122.4, 118.1, 116.9, 110.8, 76.4, 67.5, 56.6, 54.5, 52.7, 45.3, 37.6, 27.9, 20.7, 18.2. HRMS calculated for $C_{33}H_{37}ClN_4O_4S$: 620.2224; found 621.2287 (M + H).

*(2R)-2-[(6-Acetyl-(5S_a)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}thieno[2,3-d]pyrimidin-4-yl)oxy]-3-phenylpropanoic Acid (**1c**). Step A: 1-[4-Chloro-5-(3-chloro-2-methyl-4-triisopropylsilyloxyphenyl)thieno[2,3-d]pyrimidin-6-yl]ethanone.* 935 mg **R9a** (2.0 mmol) was dissolved in 20 mL dry THF and then cooled to −78 °C under Ar atmosphere. 1.2 mL LDA solution (2.4 mmol, 2 M in THF, EtPh, hexanes) was added, and the mixture was stirred at −78 °C for 1 h. Then 265 mg AcOAc (2.6 mmol) was added and the mixture was allowed to warm up to rt. Then sat. aq NH_4Cl solution was added and the mixture was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, 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 289 mg 1-[4-chloro-5-(3-chloro-2-methyl-4-triisopropylsilyloxyphenyl)thieno[2,3-*d*]pyrimidin-6-yl]ethanone (0.57 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.94 (s, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 2.17 (s, 3H), 2.03 (s, 3H), 1.44−1.32 (m, 3H), 1.17 (d, *J* = 7.4 Hz, 18H).

Step B: Isopropyl (2R)-2-[6-Acetyl-(5S_a)-5-(3-chloro-4-hydroxy-2-methylphenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-phenylpropanoate. 278 mg 1-[4-chloro-5-(3-chloro-2-methyl-4-triisopropylsilyloxyphenyl)thieno[2,3-*d*]pyrimidin-6-yl]ethanone (0.55 mmol) was dissolved in 5 mL ^{i}PrOH, 118 mg methyl (2*R*)-2-hydroxy-3-phenyl-propanoate (0.65 mmol) and 538 mg Cs_2CO_3 (1.65 mmol) were added, and the mixture was stirred at rt until no further conversion was observed. It was diluted with water, the pH of the mixture was set to 4 with 2 M aq HCl solution, and then it was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude intermediate was purified via flash chromatography using heptane and EtOAc as eluents to obtain a mixture of diastereoisomers. It was dissolved in 10 mL THF, 0.6 mL TBAF solution (0.6 mmol, 1 M in THF) was added, and the mixture was stirred at rt until no further conversion was observed. Then it was diluted with EtOAc, washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer eluting later was collected as isopropyl (2*R*)-2-[6-acetyl-(5S_a)-5-(3-chloro-4-hydroxy-2-methylphenyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-phenylpropanoate (73 mg, 0.14 mmol, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.43 (br s, 1H), 8.71 (s, 1H), 7.22−7.17 (m, 3H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 5.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.78−4.71 (m, 1H), 2.86 (dd, *J* = 14.2, 4.2 Hz, 1H), 2.64 (dd, *J* = 14.2, 8.4 Hz, 1H), 2.03 (s, 3H), 1.94 (s, 3H), 1.07 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 192.6, 168.1, 167.9, 164.4, 155.2, 153.9, 139.2, 137.9, 135.5, 129.0, 128.6, 128.2, 126.7, 125.7, 120.8, 119.1, 113.5, 75.4, 68.7, 68.5, 36.8, 28.8, 21.3, 21.1, 17.8. HRMS calculated for $C_{27}H_{25}ClN_2O_5S$: 524.1173; found 525.1244 (M + H).

*Step C: (2R)-2-[(6-Acetyl-(5S_a)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}thieno[2,3-d]pyrimidin-4-yl)-oxy]-3-phenylpropanoic Acid (**1c**).* Using general procedure 4 and 63 mg isopropyl (2*R*)-2-[6-acetyl-(5S_a)-5-(3-chloro-4-hydroxy-2-methylphenyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy-3-phenylpropanoate (0.12 mmol) as the appropriate phenol and 2-(4-methylpiperazin-1-yl)ethanol as the appropriate alcohol, 15 mg **1c** (0.024 mmol, 20%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.69 (s, 1 H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.18−7.12 (m, 3H), 6.79 (d, *J* = 6.8 Hz, 1H), 5.39 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.26 (t, *J* = 5.4 Hz, 2H), 3.01 (dd, *J* = 14.4, 3.0 Hz, 1H), 2.82−2.74 (m, 2H), 2.62−2.37 (m, 9H), 2.22 (br s, 3H), 2.00 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 192.4, 170.1, 167.8, 165.3, 155.5, 154.3, 138.8, 137.7, 137.1, 135.6, 128.9, 128.8, 128.2, 127.7, 126.4, 122.3, 119.3, 110.8, 76.6, 67.2, 56.1, 54.2, 52.3, 45.0, 37.1, 28.9, 17.8. HRMS calculated for $C_{31}H_{33}ClN_4O_5S$: 608.186; found 609.194 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-phenylpropanoic Acid (**1d**). Step A: Methyl (2R)-2-{[5-Iodo-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoate.* 1.13 g **R1f** (2.00 mmol), 70 mg $Pd(PPh_3)_2Cl_2$ (5 mol %, 0.10 mmol), and 38 mg CuI (10 mol %, 0.20 mmol) were dissolved in 10 mL DIPA, then propyne gas was bubbled through the reaction mixture, which was stirred at 45 °C for 20 min to reach complete conversion. It was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 760 mg methyl (2*R*)-2-{[5-iodo-6-(prop-1-yn-1-yl)thieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (1.59 mmol, 79%). LRMS calculated for $C_{19}H_{15}IN_2O_3S$: 478; found 479 (M + H).

Step B: Methyl (2R)-2-{[(5S_a)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoate. 469 mg methyl (2*R*)-2-{[5-iodo-6-(prop-1-yn-1-yl)thieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (0.98 mmol) and 537 mg **R3a** (2.00 mmol) were dissolved in 10 mL 1,4-dioxane, then 815 mg Cs_2CO_3 (2.50 mmol) dissolved in 2 mL water was added followed by 71 mg AtaPhos (0.10 mmol) and the mixture was heated under N_2 atmosphere at 110 °C in a microwave reactor for 10 min to reach complete conversion. After dilution with DCM and brine the pH was set to 5 with 2 M aq HCl solution and the aq phase was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer eluting later was collected as methyl (2*R*)-2-{[(5S_a)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-(prop-1-yn-1-yl)-thieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (225 mg, 0.46

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mmol, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 10.35 (br s, 1H), 8.63 (s, 1H), 7.16−7.10 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.63−6.59 (m, 2H), 5.45 (dd, J = 8.9, 3.3 Hz, 1H), 3.57 (s, 3H), 2.97 (dd, J = 14.2, 3.3 Hz, 1H), 2.68 (dd, J = 14.2, 8.9 Hz, 1H), 2.09 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.3, 166.2, 162.1, 155.0, 153.6, 136.0, 135.9, 135.7, 129.6, 129.1, 128.1, 126.7, 120.5, 119.4, 117.2, 113.0, 97.3, 75.1, 71.9, 52.1, 37.0, 17.8, 4.4. HRMS calculated for $C_{26}H_{21}ClN_2O_4S$: 492.0911; found 493.0973 (M + H).

*Step C: (2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1d**).* Using general procedure 4 and 360 mg methyl (2*R*)-2-{[(5S$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-(prop-1-yn-1-yl)thieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (0.73 mmol) as the appropriate phenol and 2-(4-methylpiperazin-1-yl)ethanol as the appropriate alcohol, 338 mg **1d** (0.56 mmol, 77%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.38 (br s, 1H), 8.62 (s, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.12−7.07 (m, 3H), 6.60−6.56 (m, 2H), 5.30 (dd, J = 10.0, 2.7 Hz, 1H), 4.30−4.19 (m, 2H), 3.02 (dd, J = 14.2, 2.7 Hz, 1H), 2.85−2.74 (m, 2H), 2.80−2.50 (br m, 8H), 2.57 (dd, J = 14.2, 10.0 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.5, 166.0, 162.7, 153.9, 153.8, 136.9, 136.1, 135.6, 130.1, 128.9, 127.9, 127.4, 126.3, 121.9, 119.2, 117.2, 110.1, 97.2, 76.1, 71.9, 67.0, 55.9, 53.4, 51.4, 43.9, 37.1, 17.8, 4.4. HRMS calculated for $C_{32}H_{33}ClN_4O_4S$: 604.1911; found 605.2000 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(cyclopropylethynyl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1e**). Step A: Methyl (2R)-2-{[6-(Cyclopropylethynyl)-5-iodothieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoate.* 1.13 g **R1f** (2.00 mmol), 152 mg ethynylcyclopropane (2.30 mmol), 70 mg $Pd(PPh_3)_2Cl_2$ (5 mol %, 0.10 mmol), and 38 mg CuI (10 mol %, 0.20 mmol) were dissolved in 4 mL DIPA, and the mixture was stirred under N_2 atmosphere at 40 °C for 30 min to reach complete conversion. Then it was concentrated under reduced pressure and purified via flash chromatography using heptane and EtOAc as eluents to obtain 968 mg methyl (2*R*)-2-{[6-(cyclopropylethynyl)-5-iodothieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (1.92 mmol, 96%). LRMS calculated for $C_{21}H_{17}IN_2O_3S$: 504.0; found 505.0 (M + H).

Step B: Methyl (2R)-2-{[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-(cyclopropylethynyl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoate. 968 mg methyl (2*R*)-2-{[6-(cyclopropylethynyl)-5-iodothieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (1.92 mmol) and 670 mg **R3a** (2.50 mmol) were dissolved in 8 mL 2-Me-THF, then 2.5 mL TBAOH (1 M solution in water, 2.50 mmol) was added followed by 68 mg AtaPhos (5 mol %, 0.096 mmol). The mixture was heated under N_2 atmosphere at 110 °C in a microwave reactor for 10 min to reach complete conversion. Then it was diluted with DCM and brine, pH was set to 5 with 2 M aq HCl solution, and the aq phase was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer eluting later was collected as methyl (2*R*)-2-{[(5S$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-(cyclopropylethynyl)thieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-phenylpropanoate (297 mg, 0.57 mmol, 30%) with a purity of 95.0%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.51 (s, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.16−7.12 (m, 3H), 7.04 (d, J = 8.4 Hz, 1H), 6.65−6.60 (m, 2H), 5.76 (br s, 1H), 5.41 (dd, J = 10.4, 2.8 Hz, 1H), 3.71 (s, 3H), 3.03 (dd, J = 14.2, 2.8 Hz, 1H), 2.71 (dd, J = 14.2, 10.4 Hz, 1H), 2.18 (s, 3H), 1.40−1.34 (m, 1H), 0.90−0.82 (m, 2H), 0.73−0.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 170.4, 167.1, 162.3, 153.3, 151.2, 136.02, 135.98, 135.8, 130.6, 129.0, 128.2, 127.9, 126.7, 120.9, 120.3, 117.8, 112.5, 104.0, 75.3, 68.0, 52.4, 37.6, 18.0, 9.2, 9.1, 0.5. HRMS calculated for $C_{28}H_{23}ClN_2O_4S$: 518.1067; found 519.1176 (M + H).

*Step C: (2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(cyclopropylethynyl)thieno[2,3-d]-pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1e**).* Using general procedure 4 and 156 mg methyl (2*R*)-2-{[(5S$_a$)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-(cyclopropylethynyl)thieno[2,3-*d*]-pyrimidin-4-yl]oxy}-3-phenylpropanoate (0.30 mmol) as the appropriate phenol and 2-(4-methylpiperazin-1-yl)ethanol as the appropriate alcohol, 128 mg **1e** (0.20 mmol, 68%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.20 (br s, 1H), 8.61 (s, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.13−7.05 (m, 3H), 6.57−6.53 (m, 2H), 5.28 (dd, J = 10.1, 2.5 Hz, 1H), 4.32−4.20 (m, 2H), 3.03 (dd, J = 14.1, 2.5 Hz, 1H), 2.87−2.74 (m, 2H), 2.80−2.50 (br m, 8H), 2.58 (dd, J = 14.1, 10.1 Hz, 1H), 2.42 (s, 3H), 2.11 (s, 3H), 1.55−1.48 (m, 1H), 0.92−0.84 (m, 2H), 0.67−0.54 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.6, 166.0, 162.6, 153.80, 153.79, 136.9, 136.2, 136.1, 130.1, 128.9, 127.9, 127.4, 126.3, 121.8, 119.1, 117.1, 110.2, 104.1, 76.1, 67.7, 67.1, 55.8, 53.3, 51.2, 43.6, 37.1, 17.8, 9.01, 9.00, 0.0. HRMS calculated for $C_{34}H_{35}ClN_4O_4S$: 630.2068; found 631.2096 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(furan-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1f**).* Using general procedure 6 and 133 mg **R8** (0.25 mmol) and 2-(2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic ester, 35 mg **1f** (0.055 mmol, 22%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 7.80−7.77 (m, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.19−7.10 (m, 3H), 6.74−6.68 (m, 2H), 6.51 (dd, J = 3.5, 1.8 Hz, 1H), 5.64 (d, J = 3.5 Hz, 1H), 5.34 (dd, J = 10.0, 2.5 Hz, 1H), 4.32−4.22 (m, 2H), 3.02 (dd, J = 14.2, 2.5 Hz, 1H), 2.86−2.73 (m, 2H), 2.70−2.34 (m, 8H), 2.53−2.45 (m, 1H), 2.25 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 166.4, 163.6, 154.5, 153.4, 147.4, 144.3, 137.6, 136.3, 129.7, 129.3, 128.5, 128.4, 127.7, 127.2, 126.8, 122.7, 119.3, 113.2, 111.6, 109.5, 76.5, 67.6, 56.6, 54.5, 52.7, 45.3, 37.7, 17.7. HRMS calculated for $C_{33}H_{33}ClN_4O_5S$: 632.186; found 633.1939 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(thiophen-2-yl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-phenylpropanoic Acid (**1g**).* Using general procedure 6 and 133 mg **R8** (0.25 mmol) and 2-thienylboronic acid as the appropriate boronic acid, 21 mg **1g** (0.032 mmol, 13%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.55 (d, J = 5.0 Hz, 1H), 7.32 (d, J = 3.8 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 7.19−7.10 (m, 3H), 7.05 (dd, J = 5.0, 3.8 Hz, 1H), 6.75−6.70 (m, 2H), 5.32 (dd, J = 10.1, 2.4 Hz, 1H), 4.31−4.22 (m, 2H), 3.02 (dd, J = 14.2, 2.4 Hz, 1H), 2.84−2.72 (m, 2H), 2.70−2.30 (m, 8H), 2.50−2.43 (m, 1H), 2.20 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.2, 163.4, 154.8, 153.4, 137.6, 137.0, 134.5, 130.5, 129.7, 129.2, 128.5, 128.5, 127.9, 127.7, 126.8, 122.8, 111.6, 76.5, 67.6, 56.5, 54.7, 52.8, 45.5, 37.7, 17.8. HRMS calculated for $C_{33}H_{33}ClN_4O_4S_2$: 648.1632; found 649.172 (M + H).

*(2R)-2-[[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-phenylthieno[2,3-d]pyrimidin-4-yl)oxy]-3-phenylpropanoic Acid (**1h**).* Using general procedure 6 and 133 mg **R8** (0.25 mmol) and 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane as the appropriate boronic ester, 20 mg **1h** (0.031 mmol, 12%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.60 (s, 1H), 7.39−7.29 (m, 4H), 7.27−7.20 (m, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.13−7.07 (m, 3H), 6.68−6.61 (m, 2H), 5.34 (dd, J = 10.0, 2.6 Hz, 1H), 4.30−4.14 (m, 2H), 3.02 (dd, J = 14.0, 2.6 Hz, 1H), 2.82−2.68 (m, 2H), 2.55 (dd, J = 14.0, 10.0 Hz, 1H), 2.70−2.30 (m, 8H), 2.24 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 166.8, 163.6, 154.1, 153.2, 137.5, 136.3, 131.0, 128.9, 128.4, 122.4, 119.4, 111.0, 76.5, 67.5, 56.5, 54.5, 52.6, 45.2, 37.6, 18.0. HRMS calculated for $C_{35}H_{35}ClN_4O_4S$: 642.2068; found 643.2135 (M + H).

*(2R)-2-{[6-(1-Benzofuran-2-yl)-(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1i**).* Using general procedure 6 and 160 mg **R8** (0.300 mmol) and 2-(benzofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic ester, 23.5 mg **1i** (0.034 mmol, 11%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.62 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.37−7.32 (m, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.25−7.21 (m, 1H), 7.19−7.11 (m, 3H), 6.74 (d, J = 7.0 Hz,

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2H), 6.10 (s, 1H), 5.36 (dd, J = 9.9, 2.6 Hz, 1H), 4.36−4.25 (m, 2H), 3.04 (dd, J = 14.4, 2.6 Hz, 1H), 2.86−2.76 (m, 2H), 2.49 (d, J = 14.4, 9.9 Hz, 1H), 2.63−2.39 (m, 8H), 2.24 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.3, 166.5, 163.5, 154.2, 153.53, 153.45, 148.8, 135.7, 129.9, 129.2, 128.8, 128.1, 127.7, 126.6, 126.3, 125.9, 123.8, 122.5, 121.9, 119.0, 111.4, 111.1, 104.9, 76.4, 67.2, 56.1, 54.2, 52.4, 45.0, 37.2, 17.3. HRMS calculated for $C_{37}H_{35}ClN_4O_5S$: 682.2017; found 683.2084 (M + H)

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(3-methylthiophen-2-yl)thieno[2,3-d]-pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1j**).* Using general procedure 6 and 133 mg **R8** (0.249 mmol) and 4,4,5,5-tetramethyl-2-(3-methyl-2-thienyl)-1,3,2-dioxaborolane as the appropriate boronic ester, 54.7 mg **1j** (0.082 mmol, 34%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.51 (d, J = 5.1 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 7.11−7.07 (m, 3H), 6.90 (d, J = 5.1 Hz, 1H), 6.65−6.61 (m, 2H), 5.32 (dd, J = 10.2, 1.6 Hz, 1H), 4.27−4.11 (m, 2H), 3.03 (dd, J = 13.4, 1.6 Hz, 1H), 2.80−2.67 (m, 2H), 2.59−2.51 (m, 9H), 2.28 (s, 3H), 2.14 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.6, 166.8, 163.1, 153.8, 152.9, 137.4, 137.2, 136.3, 130.9, 130.6, 130.5, 130.4, 128.8, 127.9, 127.7, 127.1, 126.2, 121.8, 118.2, 110.3, 76.2, 67.0, 56.0, 53.8, 52.0, 44.5, 37.2, 17.6, 14.9. HRMS calculated for $C_{34}H_{35}ClN_4O_4S_2$: 662.1788; found 663.1882 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(2-methyl-1,3-thiazol-4-yl)thieno[2,3-d]-pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1k**).* Using general procedure 6 and 133 mg **R8** (0.25 mmol) and 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole as the appropriate boronic ester, 21 mg **1k** (0.032 mmol, 13%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.20−7.10 (m, 3H), 6.76−6.70 (m, 2H), 6.38 (s, 1H), 5.34 (dd, J = 10.0, 2.7 Hz, 1H), 4.30−4.23 (m, 2H), 3.02 (dd, J = 14.0, 2.7 Hz, 1H), 2.83−2.73 (m, 2H), 2.67 (s, 3H), 2.65−2.28 (m, 8H), 2.52−2.44 (m, 1H), 2.20 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.8, 166.9, 166.3, 163.6, 154.6, 153.4, 146.6, 137.6, 136.1, 133.2, 129.6, 129.2, 128.7, 128.5, 128.4, 126.8, 123.0, 119.5, 116.2, 111.9, 76.4, 67.7, 56.6, 54.7, 52.9, 45.6, 37.6, 19.0, 17.7. HRMS calculated for $C_{33}H_{34}ClN_5O_4S_2$: 663.1741; found 664.1823 (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-phenylpropanoic Acid (**1l**).* Using general procedure 6 and 133 mg **R8** (0.25 mmol) and 2-(4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic ester, 33 mg **1l** (0.05 mmol, 20%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.28−7.24 (m, 2H), 7.21−7.17 (m, 2H), 7.16 (d, J = 8.5 Hz, 1H), 7.10−7.07 (m, 1H), 6.87−6.84 (m, 1H), 6.65−6.61 (m, 1H), 5.33 (dd, J = 10.1, 2.7 Hz, 1H), 4.27−4.17 (m, 2H), 3.03 (dd, J = 14.2, 2.7 Hz, 1H), 2.79−2.70 (m, 2H), 2.63−236 (m, 8H), 2.54 (dd, J = 14.2, 10.1 Hz, 1H), 2.23 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.7, 166.3, 163.1, 161.0, 153.7, 152.8, 137.2, 136.5, 135.8, 131.0, 130.6, 129.1, 128.9, 128.6, 127.9, 127.7, 126.3, 122.0, 118.8, 115.9, 110.6, 76.3, 67.1, 56.0, 54.0, 52.2, 44.8, 37.2, 17.5. HRMS calculated for $C_{35}H_{34}ClFN_4O_4S$: 660.1973; found 661.2042 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(pyridin-4-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-phenylpropanoic Acid (**1m**).* Using general procedure 6 and 177 mg **R8** (0.30 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine as the appropriate boronic ester, 21 mg **1m** (0.03 mmol, 11%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.64 (s, 1H), 8.54−8.50 (m, 2H), 7.35 (d, J = 8.8 Hz, 1H), 7.21−7.16 (m, 3H), 7.13−7.08 (m, 3H), 6.69−6.64 (m, 2H), 5.35 (dd, J = 9.8, 2.8 Hz, 1H), 4.29−4.18 (m, 2H), 3.03 (dd, J = 14.3, 2.8 Hz, 1H), 2.81−2.71 (m, 2H), 2.66−2.31 (br m, 9H), 2.23 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.4, 166.7, 163.7, 153.9, 153.5, 150.2, 140.2, 137.2, 135.7, 134.4, 131.0, 130.2, 128.8, 128.0, 127.3, 126.3, 122.8, 122.2, 118.9, 110.7, 76.4, 67.1, 56.0, 54.0, 52.2, 44.8, 37.2, 17.5. HRMS calculated for $C_{34}H_{34}ClN_5O_4S$: 643.2020; found 644.2089 (M + H).

*(2R)-2-[((5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-ethylthieno[2,3-d]pyrimidin-4-yl)oxy]-3-(2-methoxyphenyl)propanoic Acid (**2a**). Step A: Ethyl (2R)-2-(6-Ethyl-5-iodothieno[2,3-d]pyrimidin-4-yl)oxy-3-(2-methoxyphenyl)-propanoate.* 100 mg 4-chloro-6-ethyl-5-iodothieno[2,3-d]-pyrimidine[2] (0.308 mmol), 104 mg **R2b** (0.462 mmol), and 502 mg Cs_2CO_3 (1.54 mmol) were placed in a 10 mL flask. 3.5 mL tBuOH was added, and the mixture was stirred at 65 °C under N_2 atmosphere for 3 h. Then the mixture was cooled to rt and concentrated under reduced pressure. It was diluted with water, extracted with DCM. The combined organic layer was dried over MgSO4, 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 110 mg ethyl (2R)-2-(6-ethyl-5-iodothieno[2,3-d]pyrimidin-4-yl)oxy-3-(2-methoxyphenyl)propanoate (0.215 mmol, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.45−7.42 (m, 1H), 7.26−7.21 (m, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.89−6.85 (m, 1H), 5.63 (dd, J = 8.8, 5.5 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.38 (dd, J = 13.8, 5.5 Hz, 1H), 3.24 (dd, J = 13.8, 8.8 Hz, 1H), 2.91 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 169.5, 166.6, 160.9, 157.3, 151.9, 144.8, 131.8, 128.5, 123.5, 120.1, 119.3, 110.6, 74.1, 71.4, 60.8, 55.4, 32.4, 26.5, 14.6, 13.9. HRMS calculated for $C_{20}H_{21}IN_2O_4S$: 512.0267; found 513.0340 (M + H).

*Step B: (2R)-2-[((5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy] phenyl}-6-ethylthieno[2,3-d]pyrimidin-4-yl)oxy]-3-(2-methoxyphenyl)propanoic Acid (**2a**).* 105 mg ethyl (2R)-2-(6-ethyl-5-iodothieno[2,3-d]pyrimidin-4-yl)oxy-3-(2-methoxyphenyl)propanoate (0.205 mmol) and 97 mg **R3b** (0.246 mmol) and 134 mg Cs_2CO_3 (0.410 mmol) were dissolved in 2 mL 1,4-dioxane and 0.4 mL water. Then 18 mg AtaPhos (0.025 mmol) was added under N_2 atmosphere. The mixture was stirred at 110 °C under N_2 atmosphere in a microwave reactor for 20 min to reach complete conversion. Then it was diluted with brine and extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Then it was hydrolyzed according to the general hydrolysis procedure. The diastereoisomer eluting later was collected as **2a** (41 mg, 0.066 mmol, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.51 (s, 1H), 7.10−7.24 (m, 3H), 6.89 (d, J = 8.2 Hz, 1H), 6.60−6.73 (m, 1H), 6.19 (d, J = 7.2 Hz, 1H), 5.31 (dd, J = 10.0, 3.1 Hz, 1H), 4.24 (t, J = 5.4 Hz, 2H), 3.76 (s, 3H), 3.09 (dd, J = 13.8, 3.1 Hz, 1H), 2.71−2.80 (m, 2H), 2.47−2.68 (m, 6H), 2.28−2.42 (m, 5H), 2.17 (s, 3H), 1.96 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.94, 165.9, 162.1, 156.9, 153.6, 152.1, 142.6, 135.9, 130.6, 129.7, 128.04, 127.96, 127.9, 124.3, 122.1, 119.7, 118.2, 110.6, 110.5, 73.9, 67.2, 56.2, 55.3, 54.3, 52.5, 45.2, 32.2, 21.6, 17.6, 15.5. HRMS calculated for $C_{32}H_{37}ClN_4O_5S$: 624.2173; found 625.2259 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-(2-methoxyphenyl)propanoic Acid (**2b**). Step A: Ethyl (2R)-2-{[5-Iodo-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoate.* 4.00 g **R1d** (12.0 mmol), 4.00 g **R2b** (17.8 mmol), and 11.7 g Cs_2CO_3 (36.0 mmol) were placed in a flask. 40 mL tBuOH was added, and the mixture was stirred at 50 °C under N_2 atmosphere for 2 h to reach complete conversion. Then it was diluted with water and the formed precipitate was filtered, washed with water, then dried *in vacuo* to obtain 6.16 g ethyl (2R)-2-{[5-iodo-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoate (11.8 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.52 (s, 1H), 7.38−7.35 (m, 1H), 7.26−7.20 (m, 1H), 6.90−6.83 (m, 2H), 5.79 (dd, J = 8.6, 5.7 Hz, 1H), 4.24−4.11 (m, 2H), 3.84 (s, 3H), 3.49 (dd, J = 13.8, 5.7 Hz, 1H), 3.39 (dd, J = 13.8, 8.6 Hz, 1H), 2.19 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 170.3, 167.1, 161.7, 157.8, 153.3, 131.8, 128.5, 125.0, 124.2, 120.3, 119.7, 110.1, 98.0, 76.0, 74.6, 74.6, 61.2, 55.3, 32.9, 14.0, 5.1. LRMS calculated for $C_{21}H_{19}IN_2O_4S$: 522.0; found 523.0 (M + H).

Step B: Ethyl (2R)-2-{[(5S$_a$)-5-(3-Chloro-4-hydroxy-2-methylphenyl)-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-

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methoxyphenyl)propanoate. 472 mg ethyl (2*R*)-2-{[5-iodo-6-(prop-1-yn-1-yl)thieno[2,3-*d*]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)-propanoate (0.90 mmol) and 403 mg **R3a** (1.50 mmol) were dissolved in 10 mL 1,4-dioxane, then 652 mg Cs_2CO_3 (2.00 mmol) dissolved in 2 mL water was added. Then 64 mg AtaPhos (10 mol %, 0.09 mmol) was added. The mixture was stirred at 110 °C under N_2 atmosphere in a microwave reactor for 10 min to reach complete conversion. Then it was diluted with DCM and brine, pH was set to 5 with 2 M aq HCl solution, and the aq phase was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The diastereoisomers were purified and separated via flash chromatography using heptane and EtOAc as eluents. The diastereoisomer eluting later was collected as ethyl (2*R*)-2-[(5S_a)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-prop-1-ynylthieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-methoxyphenyl)propanoate (248 mg, 0.46 mmol, 51%). ^{1}H NMR (500 MHz, DMSO-d_6): 10.34 (br s, 1H), 8.61 (s, 1H), 7.18−7.14 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.90−6.87 (m, 1H), 6.71−6.67 (m, 1H), 6.21−6.18 (m, 1H), 5.34 (dd, *J* = 9.3, 4.4 Hz, 1H), 4.11−3.99 (m, 2H), 3.75 (s, 3H), 3.00 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.52−2.46 (m, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.2, 166.2, 162.1, 156.9, 153.6, 153.2, 135.92, 135.89, 131.0, 129.6, 128.4, 125.6, 123.2, 120.4, 119.8, 119.3, 117.2, 113.0, 110.5, 97.3, 73.5, 71.9, 60.8, 55.3, 32.1, 17.8, 13.8, 4.4. HRMS calculated for $C_{28}H_{25}N_2O_5SCl$: 536.1173; found 537.1284 (M + H).

*Step C: (2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2b**).* Using general procedure 4 and 245 mg ethyl (2*R*)-2-[(5S_a)-5-(3-chloro-4-hydroxy-2-methylphenyl)-6-prop-1-ynylthieno[2,3-*d*]pyrimidin-4-yl]oxy-3-(2-methoxyphenyl)propanoate (0.46 mmol) as the appropriate phenol and 2-(4-methylpiperazin-1-yl)ethanol as the appropriate alcohol, 188 mg **2b** (0.30 mmol, 65%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 12.00 (br s, 1H), 8.62 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.15−7.10 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.65−6.61 (m, 1H), 6.00 (dd, *J* = 7.4, 1.4 Hz, 1H), 5.30 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.30−4.23 (m, 2H), 3.75 (s, 3H), 3.13 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.89−2.77 (m, 2H), 2.84−2.55 (m, 8H), 2.43 (s, 3H), 2.38 (dd, *J* = 13.8, 10.3 Hz, 1H), 2.10 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 166.1, 162.6, 156.9, 153.83, 153.79, 136.1, 135.5, 130.8, 130.0, 128.1, 127.3, 124.1, 121.8, 119.6, 119.2, 117.2, 110.5, 110.1, 97.3, 73.9, 71.9, 67.1, 55.8, 55.3, 53.3, 51.3, 43.7, 32.1, 17.8, 4.4. HRMS calculated for $C_{33}H_{35}ClN_4O_5S$: 634.2017; found 635.2082 (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 (**2c**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and 16 mg MeOH (0.50 mmol) as the appropriate alcohol, 63 mg **2c** (0.088 mmol, 35%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.26−7.23 (m, 2H), 7.20−7.16 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 6.08 (d, *J* = 7.6 Hz, 1H), 5.33 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.29−4.23 (m, 2H), 3.75 (s, 3H), 3.13 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.81−2.71 (m, 2H), 2.63−2.41 (m, 8H), 2.34 (dd, *J* = 13.8, 10.2 Hz, 1H), 2.25 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.3, 163.3, 163.0, 161.0, 156.9, 153.6, 152.9, 136.5, 135.7, 131.0, 130.6, 129.1, 128.6, 128.0, 127.7, 124.5, 122.0, 119.6, 118.8, 116.0, 110.6, 110.5, 74.1, 67.2, 56.0, 55.3, 53.9, 52.2, 44.7, 32.3, 28.1, 21.1, 17.5. HRMS calculated for $C_{36}H_{36}ClFN_4O_5S$: 690.2079; found 691.2147 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(3-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-(2-methoxyphenyl)propanoic Acid (**2d**).* Using general procedure 7 and 144 mg **R9** (0.249 mmol) and 2-(3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic acid derivative, 63 mg **2d** (0.091 mmol, 36%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.60 (s, 1H), 7.42−7.36 (m, 2H), 7.21−7.16 (m, 2H), 7.17−7.13 (m, 2H), 7.01−6.97 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.65−6.59 (m, 1H), 6.09 (d, *J* = 7.5 Hz, 1H), 5.34 (dd, *J* = 10.4, 3.2 Hz, 1H), 4.32−4.17 (m, 2H), 3.75 (s, 3H), 3.14 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.81−2.70 (m, 2H), 2.67−2.40 (m, 8H), 2.32 (dd, *J* = 13.8, 10.4 Hz, 1H), 2.24 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.4, 163.5, 161.8, 156.9, 153.7, 153.1, 135.9, 135.7, 135.0, 131.0, 130.6, 130.5, 129.4, 127.9, 127.6, 125.0, 124.6, 122.0, 119.6, 118.8, 115.6, 115.4, 110.6, 110.4, 74.3, 67.1, 56.1, 55.3, 53.9, 52.2, 44.7, 32.3, 17.5. HRMS calculated for $C_{36}H_{36}ClFN_4O_5S$: 690.2079; found 691.2152 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(2-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-(2-methoxyphenyl)propanoic Acid (**2e**).* Using general procedure 7 and 144 mg **R9** (2.49 mmol) and 2-(2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic acid derivative, 46 mg **2e** (0.067 mmol, 27%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.61 (s, 1H), 7.43−7.38 (m 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.28−7.24 (m, 1H), 7.25−7.21 (m, 1H), 7.18−7.14 (m, 1H), 7.12−7.06 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.63−6.58 (m, 1H), 6.09 (d, *J* = 7.5 Hz, 1H), 5.35 (dd, *J* = 10.0, 3.3 Hz, 1H), 4.26−4.21 (m, 1H), 4.17−4.10 (m, 1H), 3.75 (s, 3H), 3.12 (dd, *J* = 14.0, 3.3 Hz, 1H), 2.79−2.72 (m, 1H), 2.72−2.66 (m, 1H), 2.62−2.39 (m, 8H), 2.37 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.25 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 167.2, 163.4, 159.0, 156.9, 153.5, 153.1, 135.7, 132.3, 131.5, 131.4, 130.9, 130.6, 130.5, 127.9, 127.5, 124.7, 124.6, 121.6, 120.1, 119.6, 118.1, 116.1, 110.4, 110.1, 74.5, 66.9, 56.1, 55.3, 53.8, 52.1, 44.5, 32.2, 17.5. HRMS calculated for $C_{36}H_{36}ClFN_4O_5S$: 690.2079; found 691.2169 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(2,3,4-trifluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2f**).* Using general procedure 7 and 144 mg **R9** (2.49 mmol) and 4,4,5,5-tetramethyl-2-(2,3,4-trifluorophenyl)-1,3,2-dioxaborolane as the appropriate boronic acid derivative, 87 mg **2f** (0.120 mmol, 49%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.63 (s, 1H), 7.36−7.28 (m, 2H), 7.17−7.07 (m, 3H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.64−6.58 (m, 1H), 6.10 (d, *J* = 7.4 Hz, 1H), 5.36 (dd, *J* = 9.9, 3.2 Hz, 1H), 4.29−4.22 (m, 1H), 4.19−4.12 (m, 1H), 3.75 (s, 3H), 3.12 (dd, *J* = 13.9, 3.2 Hz, 1H), 2.80−2.73 (m, 1H), 2.73−2.66 (m, 1H), 2.65−2.40 (m, 8H), 2.37 (dd, *J* = 13.9, 9.9 Hz, 1H), 2.26 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 167.3, 163.6, 156.9, 153.6, 153.5, 150.5, 148.0, 139.0, 135.7, 132.4, 130.6, 130.4, 128.5, 127.9, 127.0, 126.8, 124.7, 121.7, 119.6, 118.2, 118.0, 113.1, 110.4, 110.2, 74.6, 67.0, 56.0, 55.3, 53.7, 52.0, 44.5, 32.2, 17.6. HRMS calculated for $C_{36}H_{34}ClF_3N_4O_5S$: 726.1891; found 727.1963 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(3-chlorophenyl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-(2-methoxyphenyl)propanoic Acid (**2g**).* Using general procedure 7 and 144 mg **R9** (2.49 mmol) and 2-(3-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic acid derivative, 57 mg **2g** (0.0805 mmol, 33%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.59 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.38−7.31(m, 2H), 7.21−7.14 (m, 3H), 7.11−7.07 (m, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.62−6.57 (m, 1H), 6.04 (d, *J* = 7.3 Hz, 1H), 5.33 (dd, *J* = 10.4, 2.9 Hz, 1H), 4.35−4.28 (m, 1H), 4.26−4.18 (m, 1H), 3.75 (s, 3H), 3.17 (dd, *J* = 13.7, 2.9 Hz, 1H), 2.83−2.71 (m, 2H), 2.67−2.40 (m, 8H), 2.30 (dd, *J* = 13.7, 10.4 Hz, 1H), 2.27 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.4, 166.4, 163.6, 156.9, 153.6, 153.1, 135.6, 134.7, 133.3, 130.66, 130.65, 130.6, 129.4, 128.5, 128.2, 127.9, 127.6, 127.4, 124.8, 122.1, 119.6, 118.8, 110.6, 110.4, 74.6, 67.2, 55.9, 55.3, 53.7, 52.0, 44.4, 32.4, 17.5. HRMS calculated for $C_{36}H_{36}Cl_2N_4O_5S$: 706.1783; found 707.1860 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(pyridin-3-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2h**).* Using general procedure 7 and 144 mg **R9** (0.25 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine as the appropriate boronic ester, 70 mg **2h** (0.10 mmol, 42%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 13.00 (br s, 1H), 8.61 (s, 1H), 8.49 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.37 (dd, *J* = 2.4, 0.7 Hz, 1H),7.67−7.63 (m, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.40−7.36 (m, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.12−7.08 (m,

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1H), 6.86 (d, J = 8.0 Hz, 1H), 6.61 (td, J = 7.5, 0.7 Hz, 1H), 6.09 (dd, J = 7.5, 1.3 Hz, 1H), 5.35 (dd, J = 10.5, 3.2 Hz, 1H), 4.31−4.17 (m, 2H), 3.75 (s, 3H), 3.15 (dd, J = 13.9, 3.2 Hz, 1H), 2.82−2.69 (m, 2H), 2.67−2.39 (m, 8H), 2.33 (dd, J = 13.9, 10.5 Hz, 1H), 2.25 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.6, 163.5, 156.9, 153.8, 153.2, 149.4, 148.9, 136.2, 135.6, 133.9, 130.7, 130.6, 129.9, 129.0, 127.9, 127.3, 124.6, 123.8, 122.0, 119.6, 118.7, 110.5, 110.4, 74.4, 67.0, 56.1, 55.3, 53.8, 52.1, 44.6, 32.3, 17.5. HRMS calculated for $C_{35}H_{36}ClN_5O_5S$: 673.2126; found 674.2205 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(furan-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2i**).* Using general procedure 7 and 205 mg **R9** (0.36 mmol) and 2-(2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the appropriate boronic ester, 127 mg **2i** (0.19 mmol, 54%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.78 (br s, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.17−7.10 (m, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.74−6.68 (m, 1H), 6.53−6.49 (m, 1H), 6.20 (br d, J = 7.4 Hz, 1H), 5.66−5.62 (m, 1H), 5.36 (dd, J = 10.5, 2.6 Hz, 1H), 4.34−4.20 (m, 2H), 3.76 (s, 3H), 3.14 (dd, J = 14.1, 2.6 Hz, 1H), 2.87−2.72 (m, 2H), 2.72−2.35 (br m, 8H), 2.32−2.20 (m, 1H), 2.27 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.6, 166.4, 163.8, 157.4, 154.4, 153.4, 147.4, 144.3, 136.2, 131.0, 129.7, 128.4, 127.6, 127.2, 125.1, 122.7, 119.6, 119.3, 113.2, 111.6, 110.9, 109.4, 74.6, 67.6, 56.6, 55.8, 54.3, 52.5, 45.0, 32.8, 17.7. HRMS calculated for $C_{34}H_{35}ClN_4O_6S$: 662.1966; found 663.2028 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2j**).* Using general procedure 4 and 556 mg **R5b** (0.8 mmol) as the appropriate phenol and MeOH as the appropriate alcohol, 237 mg **2j** (0.35 mmol, 43%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.17−7.11 (m, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.74−6.69 (m, 1H), 6.19 (d, J = 7.6 Hz, 1H), 5.86 (dd, J = 7.0, 3.6 Hz, 1H), 5.67 (t, J = 3.6 Hz, 1H), 5.33 (dd, J = 10.3, 3.2 Hz, 1H), 4.29−4.24 (m, 2H), 3.76 (s, 3H), 3.15 (dd, J = 14.2, 3.2 Hz, 1H), 2.79−2.76 (m, 2H), 2.63−2.29 (m, 8H), 2.25 (dd, J = 14.2, 10.3 Hz, 1H), 2.19 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 165.7, 163.4, 156.5, 154.0, 153.1, 138.1, 135.7, 130.5, 129.3, 127.9, 127.6, 127.1, 125.5, 124.8, 122.3, 119.8, 118.8, 111.1, 110.9, 110.5, 85.2, 74.5, 67.2, 56.2, 55.3, 54.2, 52.5, 45.1, 32.4, 17.2. HRMS calculated for $C_{34}H_{34}ClFN_4O_6S$: 680.1872; found 681.1947 (M + H).

*(2R)-2-{[6-(5-Chlorofuran-2-yl)-(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2k**).* 99.5 mg **2i** (0.15 mmol) was dissolved in 4 mL $CHCl_3$, then 300 mg NCS (2.25 mmol) was added and the mixture was stirred at rt in the dark for 2 h to reach complete conversion. Then it was diluted with DCM, washed with water, dried over Na_2SO_4, 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 20 mg **2k** (0.029 mmol, 19%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.16−7.11 (m, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 7.4 Hz, 1H), 6.54 (d, J = 3.6 Hz, 1H), 6.21 (dd, J = 7.4, 1.3 Hz, 1H), 5.70 (d, J = 3.6 Hz, 1H), 5.37 (dd, J = 10.4, 3.0 Hz, 1H), 4.31−4.23 (m, 2H), 3.76 (s, 3H), 3.13 (dd, J = 14.0, 3.0 Hz, 1H), 2.84−2.73 (m, 2H), 2.66−2.50 (br m, 4H), 2.50−2.34 (br m, 4H), 2.29 (dd, J = 14.0, 10.4 Hz, 1H), 2.21 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 166.0, 163.3, 156.9, 154.0, 153.2, 147.0, 135.8, 135.7, 130.5, 129.1, 128.0, 127.5, 125.6, 124.4, 122.3, 119.8, 118.7, 111.24, 111.18, 110.5, 109.9, 74.1, 67.2, 56.1, 55.3, 54.0, 52.2, 44.8, 32.3, 17.2. HRMS calculated for $C_{34}H_{34}Cl_2N_4O_6S$: 696.1576; found 697.1656 (M + H).

*(2R)-2-{[6-(5-Bromofuran-2-yl)-(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-methoxyphenyl)propanoic Acid (**2l**).* 1.33 g **2i** (2.00 mmol) was dissolved in 20 mL $CHCl_3$, then 534 mg NBS (3.00 mmol) was added. The resulting mixture was stirred at 0 °C until no further conversion was observed. Then the mixture was diluted with water and the pH was adjusted to 6 by the addition of 2 M aq HCl solution. The mixture was extracted with DCM, the combined organic layer was dried over Na_2SO_4, 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 1.37 g **2l** (1.90 mmol, 95%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.27−7.21 (m, 2H), 7.17−7.10 (m, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.74−6.68 (m, 1H), 6.63 (d, J = 3.6 Hz, 1H), 6.19 (br d, J = 7.5 Hz, 1H), 5.65 (d, J = 3.6 Hz, 1H), 5.35 (dd, J = 10.4, 3.0 Hz, 1H), 4.32−4.22 (m, 2H), 3.76 (s, 3H), 3.13 (dd, J = 13.8, 3.0 Hz, 1H), 2.83−2.72 (m, 2H), 2.67−2.22 (br m, 8H), 2.28 (dd, J = 13.8, 10.4 Hz, 1H), 2.17 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ ppm: 171.2, 166.5, 163.8, 157.4, 154.5, 153.6, 149.7, 136.2, 131.0, 129.5, 128.4, 128.0, 127.9, 126.1, 125.0, 123.3, 122.8, 120.2, 119.1, 115.2, 112.0, 111.7, 111.0, 74.7, 67.8, 56.7, 55.8, 54.8, 53.1, 45.7, 32.8, 17.7. HRMS calculated for $C_{34}H_{34}BrClN_4O_6S$: 740.1071; found 741.1165 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-[2-(2,2,2-trifluoroethoxy)phenyl]propanoic Acid (**3a**).* 209 mg **R5b** (0.30 mmol) and 138 mg K_2CO_3 (1.00 mmol) were dissolved in 2 mL DMF, then 232 mg 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.00 mmol) was added. The mixture was stirred at rt under N_2 atmosphere until no further conversion was observed. Then it was diluted with brine, neutralized with 2 M aq HCl solution, extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Then it was hydrolyzed according to the general hydrolysis procedure to obtain 92 mg **3a** (0.12 mmol, 40%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.20−7.15 (m, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.84−6.78 (m, 1H), 6.27 (br d, J = 7.7 Hz, 1H), 5.87 (dd, J = 6.8, 3.6 Hz, 1H), 5.66 (t, J = 3.6 Hz, 1H), 5.37 (dd, J = 10.1, 3.3 Hz, 1H), 4.82−4.64 (m, 2H), 4.32−4.20 (m, 2H), 3.12 (dd, J = 14.1, 3.3 Hz, 1H), 2.84−2.71 (m, 2H), 2.70−2.25 (br m, 8H), 2.36 (dd, J = 14.1, 10.1 Hz, 1H), 2.20 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 166.2, 163.6, 157.0, 155.2, 154.5, 153.5, 138.5, 136.2, 131.3, 129.6, 128.5, 128.0, 127.5, 125.5, 124.4, 122.7, 121.9, 119.1, 112.7, 111.6, 111.5, 85.7, 74.4, 67.7, 65.3, 56.6, 54.6, 52.9, 45.5, 32.5, 17.6. HRMS calculated for $C_{35}H_{33}ClF_4N_4O_6S$: 748.1745; found 749.1819 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-{2-[(2R)-tetrahydrofuran-2-ylmethoxy]phenyl}propanoic acid (**3b**).* Using general procedure 4 and 348 mg **R5b** (0.50 mmol) as the appropriate phenol and [(2R)-tetrahydrofuran-2-yl]methanol as the appropriate alcohol, 119 mg **3b** (0.16 mmol, 32%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.14−7.10 (m, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.73−6.69 (m, 1H), 6.23−6.20 (m, 1H), 5.87 (dd, J = 6.8, 3.7 Hz, 1H), 5.67 (t, J = 3.7 Hz, 1H), 5.39 (dd, J = 10.2, 3.4 Hz, 1H), 4.26 (t, J = 5.9 Hz, 2H), 4.17−4.11 (m, 1H), 3.96 (dd, J = 10.2, 4.5 Hz, 1H), 3.92 (dd, J = 10.2, 4.5 Hz, 1H), 3.78−3.74 (m, 1H), 3.69−3.65 (m, 1H), 3.11 (dd, J = 13.9, 3.4 Hz, 1H), 2.79−2.74 (m, 2H), 2.63−2.29 (m, 8H), 2.32 (dd, J = 13.9, 10.2 Hz, 1H), 2.17 (s, 3H), 2.03−1.96 (m, 1H), 1.93 (s, 3H), 1.92−1.87 (m, 1H), 1.86−1.77 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.8, 165.8, 163.1, 156.5, 156.3, 154.0, 153.1, 138.0, 135.7, 130.6, 129.1, 128.0, 127.5, 127.0, 125.7, 124.6, 122.3, 119.9, 118.7, 111.5, 111.2, 111.0, 85.2, 76.4, 74.0, 69.9, 67.7, 67.3, 56.2, 54.4, 52.6, 45.2, 32.4, 27.5, 25.5, 17.2. HRMS calculated for $C_{38}H_{40}ClFN_4O_7S$: 750.2290; found 751.2375 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-{2-[pyridin-2-ylmethoxy]phenyl}propanoic acid (**3c**).* Using general procedure 4 and 104 mg **R5b** (0.15 mmol) as the appropriate phenol and pyridin-2-yl methanol as the appropriate alcohol, 36 mg **3c** (0.05 mmol, 30%) was obtained with a purity of 94.3%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 8.55 (d,

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J = 4.4 Hz, 1H), 7.78 (td, *J* = 7.7, 1.6 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.34−7.30 (m, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.16−7.10 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 6.27 (d, *J* = 7.3 Hz, 1H), 5.87 (dd, *J* = 6.8, 3.6 Hz, 1H), 5.67 (t, *J* = 3.5 Hz, 1H), 5.48 (dd, *J* = 10.2, 3.2 Hz, 1H), 5.21 (d, *J* = 13.6 Hz, 1H), 5.16 (d, *J* = 13.6 Hz, 1H), 4.29−4.19 (m, 2H), 3.27 (dd, *J* = 13.9, 3.0 Hz, 1H), 2.81−2.69 (m, 2H), 2.64−2.30 (m, 9H), 2.20 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 165.7, 163.2, 157.0, 156.5, 155.6, 154.0, 153.1, 148.9, 138.0, 136.9, 135.7, 130.7, 129.1, 128.0, 127.6, 127.0, 125.7, 124.9, 122.8, 122.3, 120.9, 120.3, 118.7, 111.8, 111.2, 111.0, 85.2, 74.2, 70.0, 67.2, 56.1, 54.1, 52.4, 45.0, 32.5, 17.2. HRMS calculated for $C_{39}H_{37}ClFN_5O_6S$: 757.2137; found 379.6159 (M + 2H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-[2-(pyrazin-2-ylmethoxy)phenyl]propanoic acid (**3d**).* Using general procedure 4 and 280 mg **R5b** (0.4 mmol) as the appropriate phenol and pyrazin-2-ylmethanol as the appropriate alcohol, 98 mg **3d** (0.13 mmol, 32%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.94 (d, *J* = 1.4 Hz, 1H), 8.64 (dd, *J* = 2.6, 1.4 Hz, 1H), 8.62 (d, *J* = 2.6 Hz, 1H), 8.55 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.17−7.14 (m, 1H), 7.04−7.01 (m, 1H), 6.78−6.76 (m, 1H), 6.29−6.25 (m, 1H), 5.87 (dd, *J* = 6.9, 3.6 Hz, 1H), 5.67 (t, *J* = 3.6 Hz, 1H), 5.46 (dd, *J* = 10.3, 3.0 Hz, 1H), 5.30 (d, *J* = 13.7 Hz, 1H), 5.24 (d, *J* = 13.7 Hz, 1H), 4.28−4.22 (m, 2H), 3.27 (dd, *J* = 13.9, 3.0 Hz, 1H), 2.80−2.71 (m, 2H), 2.67−2.33 (m, 8H), 2.36 (dd, *J* = 13.9, 10.3 Hz, 1H), 2.20 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 165.7, 163.2, 156.5, 155.5, 154.0, 153.0, 152.4, 144.04, 143.97, 143.0, 138.0, 135.7, 130.8, 129.2, 128.4, 128.1, 127.6, 127.0, 125.7, 125.1, 122.3, 120.5, 118.7, 111.7, 111.2, 111.0, 85.2, 74.3, 68.4, 67.2, 56.1, 54.1, 52.3, 44.9, 32.6, 17.2. HRMS calculated for $C_{38}H_{36}ClFN_6O_6S$: 758.2090; found 759.2159 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-{2-[(1-methyl-1H-pyrazol-5-yl)methoxy]phenyl}propanoic Acid (**3e**).* Using general procedure 4 and 1.74 g **R5b** (2.50 mmol) as the appropriate phenol and (1-methyl-1*H*-pyrazol-5-yl)methanol as the appropriate alcohol, 1.22 g **3e** (1.61 mmol, 64%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.55 (s, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 7.28−7.21 (m, 2H), 7.19−7.13 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.78−6.72 (m, 1H), 6.41 (d, *J* = 1.7 Hz, 1H), 6.21 (br d, *J* = 7.7 Hz, 1H), 5.87 (dd, *J* = 6.7, 3.6 Hz, 1H), 5.68−5.65 (m, 1H), 5.38 (dd, *J* = 10.0, 3.3 Hz, 1H), 5.22−5.12 (m, 2H), 4.31−4.21 (m, 2H), 3.88 (s, 3H), 3.15 (dd, *J* = 14.0, 3.3 Hz, 1H), 2.82−2.71 (m, 2H), 2.64−2.35 (m, 8H), 2.28 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.20 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.8, 165.8, 163.2, 155.4, 154.0, 153.1, 138.1, 137.6, 137.5, 137.4, 130.9, 129.2, 128.0, 127.6, 127.0, 125.7, 124.9, 120.4, 118.7, 111.8, 111.2, 111.0, 106.7, 85.3, 74.2, 67.2, 60.2, 56.2, 54.1, 52.4, 44.9, 36.5, 32.5, 17.2. HRMS calculated for $C_{38}H_{38}ClFN_6O_6S$: 760.2246; found 761.2343 (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-(2,2,2-trifluoroethoxy)phenyl]propanoic Acid (**4a**).* 211 mg **R5a** (0.30 mmol) and 138 mg K_2CO_3 (1.00 mmol) were dissolved in 2 mL DMF, then 232 mg 2,2,2-trifluoroethyl trifluoromethanesulfonate (1.00 mmol) was added. The mixture was stirred at rt under N_2 atmosphere until no further conversion was observed. Then it was diluted with brine, neutralized with 2 M aq HCl solution, extracted with DCM, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Then it was hydrolyzed according to the general hydrolysis procedure to obtain 57 mg **4a** (0.076 mmol, 25%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.59 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.27−7.24 (m, 2H), 7.23−7.17 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.16−7.12 (m, 1H), 7.00−6.95 (m, 1H), 6.75−6.71 (m, 1H), 6.20−6.16 (m, 1H) 5.33 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.79−4.66 (m, 2H), 4.28−4.17 (m, 2H), 3.13 (dd, *J* = 14.1, 3.5 Hz, 1H), 2.79−2.70 (m, 2H), 2.56 (br s, 4H), 2.46 (br s, 4H), 2.42 (dd, *J* = 14.1, 10.0 Hz, 1H), 2.23 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.3, 163.4, 163.0, 162.2, 161.0, 154.7, 153.6, 152.9, 136.5, 135.8, 131.0, 130.5, 129.1, 128.6, 128.0, 127.7, 125.1, 122.0, 121.3, 118.8, 115.9, 112.2, 110.6, 74.1, 67.2, 64.9, 64.7, 56.0, 53.9, 52.2, 44.7, 32.0, 17.5. HRMS calculated for $C_{37}H_{35}ClF_4N_4O_5S$: 758.1953; found 759.1999 (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-[(2R)-tetrahydrofuran-2-ylmethoxy]phenyl}propanoic Acid (**4b**).* Using general procedure 4 and 705 mg **R5a** (1.00 mmol) as the appropriate phenol and [(2*R*)-tetrahydrofuran-2-yl]methanol as the appropriate alcohol, 234 mg **4b** (0.296 mmol, 30%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.60 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.22−7.29 (m, 2H), 7.17−7.22 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.06−7.11 (m 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.60−6.64 (m, 1H), 6.12 (d, *J* = 7.4 Hz, 1H), 5.38 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.17−4.28 (m, 2H), 4.12−4.17 (m, 1H), 3.89−3.98 (m, 2H), 3.73−3.79 (m, 1H), 3.64−3.69 (m, 1H), 3.11 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.69−2.79 (m, 2H), 2.41−2.61 (m, 8H), 2.38 (dd, *J* = 13.7, 10.0 Hz, 1H), 2.19 (s, 3H), 1.95−2.03 (m, 1H), 1.87−1.95 (m, 1H), 1.80 (s, 3H), 1.75−1.87 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.0, 166.3, 163.2, 162.0, 156.3, 153.6, 152.9, 136.5, 135.7, 131.0, 130.8, 130.5, 129.1, 128.6, 128.0, 127.7, 124.7, 122.0, 119.8, 118.8, 116.0, 111.4, 110.6, 76.4, 74.1, 69.9, 67.7, 67.2, 56.1, 54.2, 52.5, 45.0, 32.3, 27.5, 25.6, 17.5. HRMS calculated for $C_{40}H_{42}ClFN_4O_6S$: 760.2498; found 761.2550 (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-(pyridin-2-ylmethoxy)phenyl]propanoic Acid (**4c**).* Using general procedure 4 and 494 mg **R5a** (0.700 mmol) as the appropriate phenol and 2-pyridylmethanol as the appropriate alcohol, 159 mg **4c** (0.207 mmol, 30%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.59 (s, 1H), 8.55 (d, *J* = 4.9 Hz, 1H), 7.81−7.76 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.34−7.30 (m, 1H), 7.29−7.24 (m, 2H), 7.22−7.15 (m, 2H), 7.18−7.14 (m, 1H), 7.12−7.07 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.69−6.63 (m, 1H), 6.17 (d, *J* = 7.4 Hz, 1H), 5.47 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.22−5.13 (m, 2H), 4.28−4.22 (m, 1H), 4.21−4.14 (m, 1H), 3.27 (dd, *J* = 13.9, 3.4 Hz, 1H), 2.78−2.66 (m, 2H), 2.60−2.44 (m, 8H), 2.43 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.21 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.3, 163.2, 162.1, 157.0, 155.6, 153.6, 152.9, 149.0, 136.9, 136.5, 135.8, 131.0, 130.8, 130.5, 129.1, 128.6, 128.0, 127.7, 124.9, 122.8, 122.0, 120.9, 120.1, 118.9, 116.0, 111.7, 110.6, 74.2, 70.0, 67.2, 56.1, 54.1, 52.3, 44.9, 32.5, 17.5. HRMS calculated for $C_{41}H_{39}ClFN_5O_5S$: 767.2344; found 384.6257 (M + 2H).

*(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-(pyrazin-2-ylmethoxy)phenyl]propanoic Acid (**4d**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and 55 mg pyrazin-2-ylmethanol (0.5 mmol) as the appropriate alcohol, 77 mg **4d** was obtained (0.10 mmol, 40%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.94 (d, *J* = 1.2 Hz, 1H), 8.63 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.61 (d, *J* = 2.5 Hz, 1H), 8.57 (s, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.27−7.23 (m, 1H), 7.24 (d, *J* = 5.4 Hz, 1H), 7.20−7.15 (m, 2H), 8.63 (td, *J* = 8.0, 1.5 Hz, 1H), 7.00 (dm, *J* = 8.0 Hz, 1H), 6.67 (td, *J* = 7.4, 0.8 Hz, 1H), 6.16 (dd, *J* = 7.4, 1.5 Hz, 1H), 5.44 (dd, *J* = 10.0, 3.2 Hz, 1H), 5.29 (d, *J* = 13.5 Hz, 1H), 5.23 (d, *J* = 13.5 Hz, 1H), 4.28−4.16 (m, 2H), 3.28 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.78−2.69 (m, 2H), 2.62−2.38 (m, 8H), 2.42 (dd, *J* = 13.8, 10.0 Hz, 1H), 2.23 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm: 171.2, 166.2, 163.0, 162.2, 155.5, 153.6, 152.9, 152.4, 144.0, 144.0, 143.1, 136.5, 135.7, 130.9, 130.9, 130.6, 129.1, 128.6, 128.0, 127.7, 125.1, 122.0, 120.4, 118.8, 115.9, 111.7, 110.6, 74.4, 74.4, 68.4, 67.1, 56.0, 53.9, 52.1, 44.7, 32.5, 17.5. HRMS calculated for $C_{40}H_{38}ClFN_6O_5S$: 768.2297; found 769.2422 (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-[(1-methyl-1H-pyrazol-5-yl)methoxy]phenyl}propanoic Acid (**4e**).* Using general procedure 4 and 494 mg **R5a** (0.700 mmol) as the appropriate phenol and (1-methyl-1*H*-imidazol-5-yl)methanol as the appropriate alcohol, 229 mg **4e** (0.297 mmol, 42%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.38

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(d, J = 8.6 Hz, 1H), 7.36 (d, J = 1.7 Hz, 1H), 7.26−7.22 (m, 2H), 7.20−7.14 (m, 3H), 7.14−7.10 (m, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.67−6.62 (m, 1H), 6.40 (d, J = 1.8 Hz, 1H), 6.08 (d, J = 7.7 Hz, 1H), 5.36 (dd, J = 10.2, 3.2 Hz, 1H), 5.20−5.12 (m, 2H), 4.30−4.24 (m, 1H), 4.22−4.15 (m, 1H), 3.88 (s, 3H), 3.16 (dd, J = 13.7, 3.2 Hz, 1H), 2.81−2.68 (m, 2H), 2.47−2.37 (m, 8H), 2.33 (dd, J = 13.7, 10.2 Hz, 1H), 2.24 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 166.3, 163.3, 162.1, 155.4, 153.6, 152.8, 137.6, 137.4, 136.5, 135.7, 131.0, 130.9, 130.6, 129.1, 128.5, 127.9, 127.7, 125.0, 122.0, 120.2, 118.8, 115.9, 111.8, 110.5, 106.7, 74.3, 67.1, 60.2, 56.0, 53.8, 52.1, 44.6, 36.5, 32.4, 17.5. HRMS calculated for $C_{40}H_{40}ClFN_6O_5S$: 770.2453; found 771.2527 (M + H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-{2-[(1-ethyl-1H-pyrazol-5-yl)methoxy]phenyl}propanoic Acid (**5a**).* Using general procedure 4 and 348 mg **R5b** (0.50 mmol) as the appropriate phenol and **R6f** as the appropriate alcohol, 112 mg **5a** (0.14 mmol, 29%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.55 (s, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.18−7.13 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.77−6.73 (m, 1H), 6.41 (d, J = 1.7 Hz, 1H), 6.22 (dd, J = 7.4, 1.2 Hz, 1H), 5.87 (dd, J = 6.8, 3.7 Hz, 1H), 5.67 (t, J = 3.5 Hz, 1H), 5.38 (dd, J = 10.3, 3.2 Hz, 1H), 5.19 (d, J = 12.7 Hz, 1H), 5.14 (d, J = 12.7 Hz, 1H), 4.30−4.12 (m, 4H), 3.14 (dd, J = 13.9, 3.1 Hz, 1H), 2.83−2.71 (m, 2H), 2.66−2.35 (m, 8H), 2.30 (dd, J = 13.9, 10.3 Hz, 1H), 2.22 (s, 3H), 1.91 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 165.7, 163.2, 156.5, 155.5, 154.0, 153.0, 138.0, 137.7, 136.9, 135.7, 130.8, 129.2, 127.9, 127.5, 127.0, 125.7, 124.8, 122.3, 120.3, 118.7, 111.8, 111.1, 111.0, 106.6, 85.2, 74.1, 67.1, 60.1, 56.1, 54.0, 52.3, 44.8, 43.8, 32.4, 17.2, 15.4. HRMS calculated for $C_{39}H_{40}ClFN_6O_6S$: 774.2403; found 388.1265 (M + 2H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[1-(propan-2-yl)-1H-pyrazol-5-yl]methoxy}phenyl)-propanoic Acid (**5b**).* Using general procedure 4 and 229 mg **R5b** (0.33 mmol) as the appropriate phenol and **R6g** as the appropriate alcohol, 88 mg **5a** (0.11 mmol, 33%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.54 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.19−7.13 (m, 1H), 7.09 (d, J = 7.9 Hz, 1H), 6.78−6.71 (m, 1H), 6.39 (d, J = 1.6 Hz, 1H), 6.20 (br d, J = 7.3 Hz, 1H), 5.87 (dd, J = 6.8, 3.6 Hz, 1H), 5.66 (t, J = 3.6 Hz, 1H), 5.37 (dd, J = 10.3, 3.1 Hz, 1H), 5.18 (d, J = 12.5 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 4.67−4.57 (m, 1H), 4.30−4.21 (m, 2H), 3.14 (dd, J = 13.6, 3.1 Hz, 1H), 2.82−2.71 (m, 2H), 2.66−2.46 (br m, 4H), 2.46−2.26 (br m, 4H), 2.31 (dd, J = 13.6, 10.3 Hz, 1H), 2.18 (s, 3H), 1.91 (s, 3H), 1.40 (d, J = 6.5 Hz, 3H), 1.37 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 153.5, 138.0, 136.7, 131.4, 129.7, 128.4, 120.8, 112.2, 111.7, 111.5, 106.8, 85.7, 74.6, 67.7, 60.4, 56.7, 54.7, 53.0, 50.2, 45.6, 32.8, 23.3, 17.7. HRMS calculated for $C_{40}H_{42}ClFN_6O_6S$: 788.2559; found 789.2663 (M + H).

*(2R)-3-{2-[(1-Butyl-1H-pyrazol-5-yl)methoxy]phenyl}-2-{[(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}propanoic Acid (**5c**).* Using general procedure 4 and 521 mg **R5b** (0.75 mmol) as the appropriate phenol and **R6h** as the appropriate alcohol, 308 mg **5c** (0.38 mmol, 51%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.53 (s, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.18−7.14 (m, 1H), 7.08 (dm, J = 8.0 Hz, 1H), 6.77−6.72 (m, 1H), 6.41 (d, J = 1.8 Hz, 1H), 6.22−6.19 (m, 1H), 5.88 (dd, J = 6.9, 3.6 Hz, 1H), 5.66 (t, J = 3.6 Hz, 1H), 5.38 (dd, J = 10.5, 3.0 Hz, 1H), 5.18 (d, J = 12.7 Hz, 1H), 5.14 (d, J = 12.7 Hz, 1H), 4.29−4.22 (m, 2H), 4.17−4.07 (m, 2H), 3.14 (dd, J = 13.8, 3.0 Hz, 1H), 2.81−2.71 (m, 2H), 2.65−2.31 (m, 8H), 2.30 (dd, J = 13.8, 10.5 Hz, 1H), 2.18 (s, 3H), 1.91 (s, 3H), 1.77−1.71 (m, 2H), 1.30−1.23 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.8, 165.8, 163.2, 156.5, 155.5, 154.0, 153.0, 138.0, 137.6, 137.2, 135.7, 130.9, 129.2, 128.0, 127.5, 127.0, 125.7, 124.8, 122.3, 120.4, 118.7, 111.8, 111.2, 111.0, 106.5, 85.2, 74.1, 67.2, 60.2, 56.2, 54.2, 52.5, 48.6, 45.1, 32.3, 31.9, 19.4, 17.2, 13.5. HRMS calculated for $C_{41}H_{44}ClFN_6O_6S$: 802.2716; found 402.1447 (M + 2H).

*(2R)-3-{2-[(1-tert-Butyl-1H-pyrazol-5-yl)methoxy]phenyl}-2-{[(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}propanoic Acid (**5d**).* Using general procedure 4 and 417 mg **R5b** (0.60 mmol) as the appropriate phenol and **R6i** as the appropriate alcohol, 213 mg **5d** (0.27 mmol, 44%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.54 (s, 1H), 7.36 (d, J = 1.7 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.18−7.13 (m, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.77−6.72(m, 1H), 6.48 (d, J = 1.7 Hz, 1H), 6.22 (dd, J = 7.5, 1.4 Hz, 1H), 5.87 (dd, J = 6.8, 3.7 Hz, 1H), 5.67 (t, J = 3.5 Hz, 1H), 5.40 (dd, J = 10.2, 3.3 Hz, 1H), 5.25 (d, J = 12.7 Hz, 1H), 5.19 (d, J = 12.7 Hz, 1H), 4.30−4.20 (m, 2H), 3.17 (dd, J = 13.8, 3.2 Hz, 1H), 2.82−2.70 (m, 2H), 2.64−2.34 (m, 8H), 2.33 (dd, J = 13.8, 10.3 Hz, 1H), 2.20 (s, 3H), 1.92 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.8, 165.7, 163.2, 156.5, 155.5, 154.0, 153.0, 138.0, 137.3, 136.2, 135.7, 130.9, 129.2, 128.0, 127.5, 127.0, 125.7, 124.6, 122.3, 120.3, 118.7, 111.7, 111.1, 111.0, 108.9, 85.2, 74.1, 67.1, 61.9, 60.2, 56.1, 54.1, 52.3, 44.9, 32.4, 29.8, 17.2. HRMS calculated for $C_{41}H_{44}ClFN_6O_6S$: 802.2716; found 402.1422 (M + 2H).

*(2R)-2-[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidin-4-yl]-oxy-3-[2-[[2-(2,2,2-trifluoroethyl)pyrazol-3-yl]methoxy]phenyl]-propanoic Acid (**5e**).* **5e** was prepared according to the published procedure.[5]

*2-[(1-Butyl-1H-pyrazol-5-yl)methoxy]-N-[(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**5f**). Step A: 4-Chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl]thieno[2,3-d]pyrimidine.* 48 g **R1e** (160 mmol) and 76 g **R3b** (191 mmol) were dissolved in 2.4 L DME, then 101 g K_3PO_4 (478 mmol), 3.60 g $Pd(OAc)_2$ (16.0 mmol), 11.5 g nBuPAd$_2$ (32.0 mmol), and 800 mL water were added and the mixture was stirred at 60 °C until no further conversion was observed. Then the volatiles were evaporated under reduced pressure, filtered, washed with water and MeCN to give 60.0 g 4-chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]thieno[2,3-d]pyrimidine (139 mmol, 87%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.98 (s, 1H), 7.97 (s, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 4.25−4.16 (m, 2H), 2.76 (t, J = 5.8 Hz, 2H), 2.54 (br s, 4H), 2.32 (br s, 4H), 2.14 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ ppm: 178.2, 154.7, 151.9, 152.3, 137.0, 133.5, 130.0, 128.9, 126.8, 110.8, 91.9, 67.7, 56.9, 55.3, 53.6, 46.3, 18.5. HRMS calculated for $C_{20}H_{22}Cl_2N_4OS$: 436.0891; found 437.0980 (M + H).

Step B: 4-Chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-iodothieno[2,3-d]pyrimidine. 10.94 g 4-chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]-phenyl]thieno[2,3-d]pyrimidine (25.0 mmol) was dissolved in 250 mL dry THF and cooled to −78 °C. 25 mL LDA solution (50 mmol, 2 M in THF, heptane, EtPh) was added dropwise under Ar atmosphere, and the mixture was stirred for 15 min. Then 12.69 g I_2 (50 mmol) was added at −78 °C, and the mixture was allowed to warm up to rt. Then the mixture was diluted with EtOAc and was washed with sat. aq NH_4Cl solution, then with aq $Na_2S_2O_3$ solution, dried over Na_2SO_4, 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 11.8 g 4-chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl]-6-iodothieno[2,3-d]pyrimidine (21 mmol, 84%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.93 (s, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 4.22 (t, J = 5.8 Hz, 2H), 2.77 (t, J = 5.8 Hz, 2H), 2.56 (br s, 4H), 2.34 (br s, 4H), 2.16 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.3, 154.4, 152.8, 152.6, 138.7, 136.4, 129.8, 128.9, 127.2, 121.8, 110.7, 91.6, 67.2, 56.5, 54.8, 53.1, 45.8, 17.6. HRMS calculated for $C_{20}H_{21}Cl_2IN_4OS$: 561.9857; found 562.9935 (M + H).

Step C: 4-Chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(5-fluoro-2-furyl)thieno[2,3-d]pyrimidine. 5.61 g 4-chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-

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ethoxy]phenyl]-6-iodothieno[2,3-*d*]pyrimidine (10.0 mmol) and 8.60 g 2-(5-fluoro-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40.0 mmol) were dissolved in 80 mL 1,4-dioxane and 20 mL water, then 7.12 g Cs_2CO_3 (22.0 mmol) and 730 mg Pd(dppf)Cl_2 (1.00 mmol) were added and the mixture was stirred at 40 °C until no further conversion was observed. The mixture was then diluted with water and extracted with DCM. The combined organic layer was washed with water, dried over $MgSO_4$, 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 give 2.60 g 4-chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidine (5.00 mmol, 50%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.93 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 5.92 (dd, J = 6.8, 3.6 Hz, 1H), 5.68 (t, J = 3.5 Hz, 1H), 4.23 (t, J = 5.6 Hz, 2H), 2.79 (t, J = 5.6 Hz, 2H), 2.67−2.47 (m, 4H), 2.44−2.26 (m, 4H), 2.19 (s, 3H), 2.05 (s, 3H). HRMS calculated for $C_{24}H_{23}N_4O_2FSCl_2$: 520.0903; found 521.0972 (M + H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 167.0, 158.0, 156.9, 155.8, 154.6, 153.4, 152.8, 137.6, 136.4, 129.4, 129.2, 128.3, 126.5, 126.4, 122.2, 112.9, 111.5, 85.8, 67.2, 56.4, 54.7, 53.0, 45.6, 30.4, 17.3. HRMS calculated for $C_{24}H_{23}Cl_2FN_4O_2S$: 520.0903; found 521.0972 (M + H).

Step D: Ethyl (2R)-2-(tert-Butoxycarbonylamino)-3-(2-hydroxyphenyl)propanoate. 20.22 g (2*R*)-2-amino-3-(2-hydroxyphenyl)propanoic acid hydrochloride (93.0 mmol) was dissolved in 120 mL EtOH, then 18.2 mL $SOCl_2$ (224 mmol) was added slowly while vigorous stirring. Then it was heated at reflux temperature for 4 h. Then it was cooled to rt and the volatiles were removed under reduced pressure. Then it was dissolved in a biphasic mixture of 100 mL DCM and 100 mL water. The pH of the aq layer was set to 8 with $NaHCO_3$, then 20.31 g Boc_2O (93.0 mmol) was added and the mixture was stirred overnight at rt. The phases were separated, and the aq layer was extracted with DCM. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. Then it was sonicated with iPr$_2$O, when beige crystals were formed, which were collected by filtration to give 17.40 g ethyl (2*R*)-2-(*tert*-butoxycarbonylamino)-3-(2-hydroxyphenyl)propanoate (56.2 mmol, 60%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.50 (s, 1H), 7.13 (d, J = 7.9 Hz, 1H), 7.07−7.00 (m, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.68 (t, J = 7.3 Hz, 1H), 4.26−4.19 (m, 1H), 4.07−3.95 (m, 1H), 4.01 (dd, J = 9.2, 7.2 Hz, 1H), 2.97 (dd, J = 13.2, 5.8 Hz), 2.73 (dd, J = 13.5, 9.6 Hz, 1H), 1.33 (s, 9H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 172.5, 155.4, 131.1, 127.7, 123.5, 118.7, 114.7, 78.1, 60.1, 53.5, 31.9, 28.1, 14.0. HRMS calculated for $C_{16}H_{23}NO_5$: 309.1576; found 332.1438 (M + Na).

Step E: Ethyl (2R)-2-(tert-Butoxycarbonylamino)-3-[2-[(2-butylpyrazol-3-yl)methoxy]phenyl]propanoate. 928 mg ethyl (2*R*)-2-(*tert*-butoxycarbonylamino)-3-(2-hydroxyphenyl)propanoate (3.00 mmol), 925 mg **R6h** (6.00 mmol), and 1.57 g PPh_3 (6.00 mmol) were dissolved in 15 mL dry toluene under N_2 atmosphere. It was stirred at rt for 5 min, then 1.18 mL DIAD (1.21 g, 6.00 mmol) was added dropwise over a period of 2 min (exothermic reaction). Then the reaction mixture was stirred at 50 °C for 30 min to reach complete conversion. The reaction mixture was directly injected onto a preconditioned silica gel column, then it was purified via flash chromatography using heptane and EtOAc as eluents to give 890 mg ethyl (2*R*)-2-(*tert*-butoxycarbonylamino)-3-[2-[(2-butylpyrazol-3-yl)-methoxy]phenyl]propanoate (2.00 mmol, 66%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.88 (s, 1H), 7.41 (d, J = 1.8 Hz, 1H), 7.25−7.13 (m, 4H), 6.85 (t, J = 7.6 Hz, 1H), 6.41 (d, J = 1.6 Hz, 1H), 5.20 (d, J = 12.6 Hz, 1H) 5.17 (d, J = 12.6 Hz, 1H), 4.81−4.72 (m, 1H), 4.21−4.16 (m, 1H), 4.13 (t, J = 7.4 Hz, 2H), 4.01−3.94 (m, 1H), 3.98 (dd, J = 7.2, 1.8 Hz, 1H), 3.04 (dd, J = 13.4, 5.2 Hz, 1H), 2.72 (dd, J = 13.2, 10.0 Hz, 1H), 1.79−1.72 (m, 2H), 1.31 (s, 9H), 1.28−1.13 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 138.1, 131.6, 128.5, 121.0, 112.3, 106.9, 60.7, 60.7, 53.9, 49.0, 32.4, 32.2, 28.6, 19.8, 14.4, 14.0. HRMS calculated for $C_{24}H_{35}N_3O_5$: 445.2577; found 446.2654 (M + H).

Step F: (2R)-2-Amino-3-[2-[(2-butylpyrazol-3-yl)methoxy]-phenyl]propanoic Acid. 891 mg ethyl (2*R*)-2-(*tert*-butoxycarbonylamino)-3-[2-[(2-butylpyrazol-3-yl)methoxy]phenyl]propanoate (2.00 mmol) was dissolved in 5 mL dry DCM, then 5 mL trifluoroacetic acid was added in one portion. The mixture was stirred at rt for 2 h to reach complete conversion. It was concentrated under reduced pressure, then dissolved in 5 mL THF and 5 mL water. Then 840 mg LiOH·H_2O (20.0 mmol) was added, and it was stirred at 50 °C for 3 h to reach complete conversion. Then it was neutralized with 2 M aq HCl solution and purified via preparative reversed phase chromatography using 25 mM aq NH_4HCO_3 solution and MeCN as eluents to obtain 400 mg (2*R*)-2-amino-3-[2-[(2-butylpyrazol-3-yl)methoxy]-phenyl]propanoic acid (1.26 mmol, 63%). LRMS calculated for $C_{17}H_{23}N_3O_3$: 317.4; found 318.4 (M + H).

*Step G: 2-[(1-Butyl-1H-pyrazol-5-yl)methoxy]-N-[(5S$_a$)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]-D-phenylalanine (**5f**).* 520 mg 4-chloro-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl]-6-(5-fluoro-2-furyl)thieno[2,3-*d*]pyrimidine (1.00 mmol), 380 mg (2*R*)-2-amino-3-[2-[(2-butylpyrazol-3-yl)methoxy]-phenyl]propanoic acid (1.20 mmol), and 400 mg K_2CO_3 (3.00 mmol) were mixed in 10 mL dry DMSO and stirred at rt until no further conversion was observed. The mixture was then diluted with brine, acidified to pH 2 with 1 M aq HCl solution, and it was extracted with DCM. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure, then purified via preparative reversed phase chromatography using 25 mM aq NH_4HCO_3 solution and MeCN as eluents. The diastereoisomer eluting later was collected as **5f** (104 mg, 0.13 mmol, 13%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.21 (s, 1H), 7.37 (d, J = 1.7 Hz, 1H), 7.24 (d, J = 1.0 Hz, 2H), 7.14−7.11 (m, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.83−6.79 (m, 2H), 6.28 (d, J = 1.8 Hz, 1H), 5.8 (dd, J = 6.8, 3.6 Hz, 2H), 5.61 (t, J = 3.6 Hz, 1H), 5.04 (d, J = 12.5 Hz, 1H), 4.96 (d, J = 12.5 Hz, 1H), 4.54−4.47 (m, 2H), 4.18−4.15 (m, 2H), 4.06 (t, J = 7.2 Hz, 2H), 3.27 (dd, J = 14.5, 5.6 Hz, 1H), 3.12−3.07 (m, 1H), 2.99−2.95 (m, 1H), 2.82−2.54 (m, 8H), 2.75 (dd, J = 14.2, 6.0 Hz, 1H), 2.32 (s, 3H), 1.87 (s, 3H), 1.73−1.67 (m, 2H), 1.25−1.18 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.3, 172.8, 172.2, 172.2, 169.9, 164.0, 163.6, 160.7, 160.3, 159.3, 158.2, 157.3, 157.2, 156.0, 155.9, 155.1, 154.9, 153.9, 138.4, 137.6, 137.2, 135.7, 129.7, 128.7, 127.1, 126.4, 126.1, 123.3, 122.3, 120.4, 112.4, 111.8, 109.7, 106.6, 84.9, 84.8, 66.0, 60.0, 55.7, 54.1, 53.6, 49.9, 48.5, 43.9, 42.4, 31.9, 30.8, 19.3, 17.0, 13.5. HRMS calculated for $C_{41}H_{45}ClFN_7O_5S$: 801.2875; found 401.6505 (M + 2H).

*(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-[(1-ethyl-1H-pyrazol-5-yl)methoxy]phenyl}propanoic Acid (**6a**).* Using general procedure 4 and 3.526 g **R5a** (5.00 mmol) as the appropriate phenol and **R6f** as the appropriate alcohol, 3.02 g **6a** (3.85 mmol, 77%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.39−7−7.36 (m, 1H), 7.26−7.22 (m, 2H), 7.20−7.10 (m, 4H), 7.07−7.02 (m, 1H), 6.66−6.62 (m, 1H), 6.40 (d, J = 1.7 Hz, 1H), 6.11−6.07 (m, 1H), 5.37 (dd, J = 10.3, 3.3 Hz, 1H), 5.18 (d, J = 12.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 4.30−4.24 (m, 1H), 4.22−4.11 (m, 3H), 3.15 (dd, J = 13.9, 3.3 Hz, 1H), 2.81−2.69 (m, 2H), 2.55 (br s, 4H), 2.47 (br s, 4H), 2.35 (dd, J = 13.9, 10.3 Hz, 1H), 2.24 (s, 3H), 1.76 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 166.2, 163.3, 162.0, 155.5, 153.5, 152.8, 137.7, 136.9, 136.4, 135.7, 131.0, 130.9, 130.6, 129.1, 128.5, 127.9, 127.7, 124.9, 122.0, 120.2, 118.8, 115.9, 111.8, 110.5, 106.6, 74.2, 67.1, 60.1, 56.0, 53.8, 52.1, 44.6, 43.8, 32.3, 17.5, 15.5. HRMS calculated for $C_{41}H_{42}ClFN_6O_5S$: 784.2610; found 785.2679 (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-{[1-(propan-2-yl)-1H-pyrazol-5-yl]methoxy}phenyl)-propanoic Acid (**6b**).* Using general procedure 4 and 353 mg **R5a** (0.50 mmol) as the appropriate phenol and **R6g** as the appropriate

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alcohol, 222 mg **6b** (0.28 mmol, 56%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.29−7.23 (m, 2H), 7.23−7.16 (m, 2H), 7.16 (d, J = 8.6 Hz, 1H), 7.16−7.10 (m, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.68−6.63 (m, 1H), 6.38 (d, J = 1.6 Hz, 1H), 6.11 (br d, J = 7.6 Hz, 1H), 5.36 (dd, J = 10.2, 3.5 Hz, 1H), 5.17 (d, J = 12.5 Hz, 1H), 5.13 (d, J = 12.5 Hz, 1H), 4.67−4.57 (m, 1H), 4.30−4.16 (m, 2H), 3.13 (dd, J = 13.8, 3.5 Hz, 1H), 2.80−2.68 (m, 2H), 2.65−2.25 (br m, 8H), 2.38 (dd, J = 13.8, 10.2 Hz, 1H), 2.18 (s, 3H), 1.77 (s, 3H), 1.40 (d, J = 6.5 Hz, 3H), 1.37 (d, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 153.2, 138.0, 136.7, 131.5, 131.4, 131.0, 128.4, 120.6, 116.4, 111.0, 106.8, 74.4, 67.6, 60.4, 56.6, 54.7, 52.9, 50.2, 45.5, 32.7, 23.3, 18.0. HRMS calculated for $C_{42}H_{44}ClFN_6O_5S$: 798.2766; found 400.1469 (M + 2H).

*(2R)-3-{2-[(1-Butyl-1H-pyrazol-5-yl)methoxy]phenyl}-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}propanoic Acid (**6c**).* Using general procedure 4 and 529 mg **R5a** (0.75 mmol) as the appropriate phenol and **R6h** as the appropriate alcohol, 369 mg **6c** (0.45 mmol, 61%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.55 (s, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.27−7.23 (m, 2H), 7.21−7.10 (m, 4H), 7.08−7.05 (m, 1H), 6.67−6.63 (m, 1H), 6.40 (d, J = 1.7 Hz, 1H), 6.11−6.08 (m, 1H), 5.36 (dd, J = 10.1, 3.3 Hz, 1H), 5.17 (d, J = 12.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 4.27−4.07 (m, 4H), 3.14 (dd, J = 13.7, 3.3 Hz, 1H), 2.78−2.68 (m, 2H), 2.59−2.30 (m, 8H), 2.36 (dd, J = 13.7, 10.1 Hz, 1H), 2.18 (s, 3H), 1.77 (s, 3H), 1.76−1.71 (m, 2H), 1.31−1.23 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 166.3, 163.2, 162.0, 155.5, 153.6, 152.8, 137.6, 137.2, 136.5, 135.7, 131.0, 130.9, 130.6, 129.1, 128.5, 127.9, 127.6, 124.8, 122.0, 120.2, 118.8, 115.9, 111.8, 110.6, 105.5, 74.1, 67.2, 60.2, 56.1, 54.2, 52.5, 48.6, 45.0, 32.2, 31.9, 19.4, 17.5, 13.5. HRMS calculated for $C_{43}H_{46}ClFN_6O_5S$: 812.2923; found 407.1551 (M + 2H).

*(2R)-3-{2-[(1-tert-Butyl-1H-pyrazol-5-yl)methoxy]phenyl}-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}-propanoic Acid (**6d**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and **R6i** as the appropriate alcohol, 35 mg **6d** was obtained (0.043 mmol, 17%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.58 (s, 1H), 7.36−7.34 (m, 2H), 7.28−7.25 (m, 2H), 7.22−7.12 (m, 4H), 7.05 (d, J = 8.2 Hz, 1H), 6.66 (t, J = 7.5 Hz, 1H), 6.47 (d, J = 1.5 Hz, 1H), 6.14 (dd, J = 7.6, 1.0 Hz, 1H), 5.39 (dd, J = 10.0, 3.5 Hz, 1H), 5.25 (d, J = 12.5 Hz, 1H), 5.19 (d, J = 12.5 Hz, 1H), 4.26−4.18 (m, 2H), 3.15 (dd, J = 13.8, 3.5 Hz, 1H), 2.78−2.69 (m, 2H), 2.62−2.26 (m, 8H), 2.41 (dd, J = 13.8, 10.0 Hz, 1H), 2.17 (s, 3H), 1.78 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.8, 166.3, 163.0, 162.1, 155.5, 153.6, 152.8, 137.3, 136.5, 136.2, 135.7, 131.0, 130.5, 129.1, 128.6, 128.0, 127.6, 124.5, 122.0, 120.2, 118.8, 116.0, 111.7, 110.6, 109.0, 74.0, 67.2, 61.9, 60.3, 56.1, 54.2, 52.5, 45.1, 32.2, 29.9, 17.5. HRMS calculated for $C_{43}H_{46}ClFN_6O_5S$: 812.2923; found 813.3030 (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-{[1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl]methoxy}-phenyl)propanoic Acid (**6e**).* Using general procedure 4 and 423 mg **R5a** (0.60 mmol) as the appropriate phenol and [1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-5-yl]methanol as the appropriate alcohol, 311 mg **6e** (0.37 mmol, 62%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.56 (s, 1H), 7.57 (d, J = 1.7 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.27−7.23 (m, 2H), 7.21−7.11 (m, 4H), 7.06−7.02 (m, 1H), 6.69−6.65 (m, 1H), 6.57 (d, J = 1.7 Hz, 1H), 6.14−6.10 (m, 1H), 5.37 (dd, J = 10.3, 3.0 Hz, 1H), 5.23 (d, J = 13.3 Hz, 1H), 5.20 (d, J = 13.3 Hz, 1H), 5.18 (q, J = 9.0 Hz, 2H), 4.26−4.17 (m, 2H), 3.16 (dd, J = 13.6, 3.0 Hz, 1H), 2.79−2.69 (m, 2H), 2.65−2.32 (m, 8H), 2.36 (dd, J = 13.6, 10.3 Hz, 1H), 2.22 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.3, 163.2, 162.0, 155.4, 153.6, 152.8, 140.03, 139.98, 139.9, 136.5, 135.7, 131.0, 130.6, 129.1, 128.5, 127.8, 127.9, 125.0, 123.7, 122.0, 120.4, 118.8, 116.0, 111.8, 110.6, 107.2, 74.2, 67.1, 60.3, 56.0, 54.0, 52.3, 49.5, 44.8, 32.4, 17.5. HRMS calculated for $C_{41}H_{39}ClF_4N_6O_5S$: 838.2327; found 839.2389 (M + H).

*(2R)-3-{2-[(1-Butyl-1H-pyrazol-5-yl)methoxy]phenyl}-2-{[(5S_a)-5-{3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}propanoic Acid (**7**).* Using general procedure 4 and 389 mg **R5c** (0.6 mmol) as the appropriate phenol and **R6h** as the appropriate alcohol, 248 mg **7** (0.33 mmol, 55%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 7.38 (d, J = 1.7 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.14−7.10 (m, 1H), 7.08−7.04 (m, 1H), 6.68−6.63 (m, 1H), 6.40 (d, J = 1.7 Hz, 1H), 6.01−5.97 (m, 1H), 5.31 (dd, J = 10.5, 3.0 Hz, 1H), 5.16 (d, J = 12.7 Hz, 1H), 5.12 (d, J = 12.7 Hz, 1H), 4.28−4.19 (m, 2H), 4.16−4.06 (m, 2H), 3.17 (dd, J = 13.8, 3.0 Hz, 1H), 2.81−2.69 (m, 2H), 2.65−2.32 (m, 8H), 2.35 (dd, J = 13.8, 10.5 Hz, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.76−1.70 (m, 2H), 1.29−1.21 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 166.0, 162.9, 155.5, 153.8, 137.6, 137.2, 136.0, 135.6, 131.1, 130.1, 127.9, 127.3, 121.8, 120.2, 119.1, 117.2, 111.8, 110.1, 106.5, 97.2, 74.3, 71.9, 67.1, 60.2, 56.2, 54.1, 52.3, 48.6, 44.9, 32.3, 31.9, 19.4, 17.8, 13.6, 4.4. HRMS calculated for $C_{40}H_{45}ClN_6O_5S$: 756.2861; found 757.2953 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-{2-[(2-methoxypyrimidin-4-yl)methoxy]phenyl}propanoic Acid (**8a**).* Using general procedure 4 and 348 mg **R5b** (0.50 mmol) as the appropriate phenol and (2-methoxypyrimidin-4-yl)methanol as the appropriate alcohol, 95 mg **8a** (0.12 mmol, 24%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.61 (d, J = 5.1 Hz, 1H), 8.55 (s, 1H), 7.43 (d, J = 5.1 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.17−7.11 (m, 1H), 6.98−6.93 (m, 1H), 6.80−6.74 (m, 1H), 6.30−6.25 (m, 1H), 5.87 (dd, J = 6.7, 3.6 Hz, 1H), 5.67 (t, J = 3.6 Hz, 1H), 5.46 (dd, J = 10.3, 3.0 Hz, 1H), 5.16 (d, J = 15.3 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 4.30−4.18 (m, 2H), 3.91 (s, 3H), 3.31 (dd, J = 13.9, 3.0 Hz, 1H), 2.80−2.69 (m, 2H), 2.65−2.52 (br s, 4H), 2.47−2.30 (br s, 4H), 2.37 (dd, J = 13.9, 10.3 Hz, 1H), 2.20 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 170.9, 168.7, 165.7, 164.7, 163.2, 160.2, 157.6, 155.4, 155.2, 154.0, 153.1, 138.0, 135.7, 130.7, 129.2, 128.1, 127.6, 127.0, 125.7, 125.0, 122.3, 120.5, 118.7, 111.7, 111.0, 85.3, 85.2, 74.3, 68.6, 67.2, 56.1, 54.5, 54.2, 52.4, 45.0, 32.6, 17.2. HRMS calculated for $C_{39}H_{38}N_6O_7FSCl$: 788.2195; found 789.2289 (M + H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[2-(morpholin-4-yl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**8b**).* Using general procedure 4 and 486 mg **R5b** (0.7 mmol) as the appropriate phenol and **R6b** as the appropriate alcohol, 130 mg **8b** (0.15 mmol, 22%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.54 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.17−7.05 (m, 1H), 6.97 (d, J = 4.8 Hz, 1H), 6.94−6.85 (m, 1H), 6.80−6.69 (m, 1H), 6.29−6.18 (m, 1H), 5.91−5.80 (m, 1H), 5.71−5.62 (m, 1H), 5.52−5.39 (m, 1H), 5.03 (d, J = 15.0 Hz, 1H), 4.96 (d, J = 15.0 Hz, 1H), 4.32−4.13 (m, 2H), 3.68 (br s, 4H), 3.62 (br s, 4H), 3.36−3.24 (m, 1H), 2.82−2.67 (m, 2H), 2.66−2.37 (m, 8H), 2.37−2.28 (m, 1H), 2.25 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 166.6, 165.7, 163.5, 160.9, 158.7, 157.6, 155.4, 154.0, 153.1, 138.1, 135.7, 130.6, 129.3, 127.9, 127.7, 127.1, 125.6, 125.2, 122.3, 120.3, 118.8, 111.6, 111.0, 106.8, 85.2, 74.6, 68.9, 67.1, 66.0, 56.1, 53.8, 52.0, 44.5, 43.8, 32.7, 17.2. HRMS calculated for $C_{42}H_{43}ClFN_7O_7S$: 843.2617; found 422.6360 (M + 2H).

*(2R)-2-{[(5S_a)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[2-(2-methoxyethyl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**8c**).* Using general procedure 4 and 417 mg **R5b** (0.60 mmol) as the appropriate phenol and **R6c** as the appropriate alcohol, 249 mg **8c** (0.3 mmol, 50%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.74 (d, J = 5.2 Hz, 1H), 8.54 (s, 1H), 7.69 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.16−7.12 (m, 1H), 6.98−6.94 (m, 1H), 6.78−6.75 (m, 1H), 6.26−6.23 (m, 1H), 5.87 (dd, J = 6.8, 3.6 Hz, 1H), 5.67 (t, J = 3.6 Hz, 1H), 5.46 (dd, J = 10.6, 2.5 Hz, 1H), 5.19 (d, J = 15.2 Hz, 1H), 5.13 (d, J = 15.2 Hz, 1H), 4.30−4.20 (m, 2H), 3.79 (t, J = 6.7 Hz, 2H), 3.34 (dd, J = 13.8, 2.5 Hz, 1H), 3.21 (s, 3H), 3.10 (t, J = 6.7 Hz, 2H), 2.81−

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2.70 (m, 2H), 2.69−2.37 (m, 8H), 2.33 (dd, J = 13.8, 10.6 Hz, 1H), 2.24 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 167.6, 166.0, 165.7, 163.3, 157.9, 157.6, 155.4, 155.3, 154.0, 153.1, 138.1, 135.7, 130.7, 129.2, 128.1, 127.7, 127.1, 127.0, 125.6, 125.2, 122.3, 120.5, 118.8, 115.5, 111.7, 111.2, 110.9, 85.3, 85.2, 74.6, 70.2, 68.7, 67.2, 57.9, 56.1, 53.9, 52.1, 32.8, 17.2. HRMS calculated for $C_{41}H_{42}ClFN_6O_7S$: 816.2508; found 409.1335 (M + 2H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(5-fluorofuran-2-yl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[2-(pyridin-4-yl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**8d**).* Using general procedure 4 and 348 mg **R5b** (0.50 mmol) as the appropriate phenol and **R6e** as the appropriate alcohol, 217 mg **8d** (0.26 mmol 52%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.02 (d, J = 5.1 Hz, 1H), 8.76−8.74 (m, 2H), 8.52 (s, 1H), 8.25−8.23 (m, 2H), 7.92 (d, J = 5.1 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.18−7.14 (m, 1H), 7.05−7.02 (m, 1H), 6.81−6.77 (m, 1H), 6.30−6.27 (m, 1H), 5.87 (dd, J = 6.8, 3.6 Hz, 1H), 5.67 (t, J = 3.6 Hz, 1H), 5.48 (dd, J = 10.5, 2.6 Hz, 1H), 5.37 (d, J = 15.3 Hz, 1H), 5.29 (d, J = 15.3 Hz, 1H), 4.29−4.18 (m, 2H), 3.37 (dd, J = 14.1, 2.6 Hz, 1H), 2.79−2.68 (m, 2H), 2.62−2.34 (m, 8H), 2.37 (dd, J = 14.1, 10.5 Hz, 1H), 2.21 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 167.0, 165.7, 163.3, 161.1, 158.8, 156.5, 155.3, 154.0, 153.1, 150.5, 144.0, 138.1, 135.7, 130.7, 129.2, 128.1, 127.7, 127.1, 125.7, 125.3, 122.3, 121.6, 120.6, 118.8, 117.8, 111.8, 111.2, 110.9, 85.2, 74.6, 68.7, 67.2, 56.1, 54.0, 52.2, 44.8, 32.7, 17.2. HRMS calculated for $C_{43}H_{39}ClFN_7O_6S$: 835.2355; found 418.6246 (M + 2H).

*(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-methoxypyrimidin-4-yl)methoxy]phenyl}propanoic Acid (**9a**).* Using general procedure 4 and 353 mg **R5a** (0.50 mmol) as the appropriate phenol and (2-methoxypyrimidin-4-yl)methanol as the appropriate alcohol, 150 mg **9a** (0.19 mmol, 37%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.61 (d, J = 5.0 Hz, 1H), 8.57 (s, 1H), 7.43 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.30−7.24 (m, 2H), 7.22−7.16 (m, 3H), 7.14−7.08 (m, 1H), 6.95−6.90 (m, 1H), 6.71−6.65 (m, 1H), 6.19−6.15 (m, 1H), 5.45 (dd, J = 10.0, 3.0 Hz, 1H), 5.15 (d, J = 15.2 Hz, 1H), 5.09 (d, J = 15.2 Hz, 1H), 4.28−4.21 (m, 1H), 4.21−4.14 (m, 1H), 3.91 (s, 3H), 3.30 (dd, J = 13.5, 3.0 Hz, 1H), 2.78−2.66 (m, 2H), 2.61−2.52 (br s, 4H), 2.47−2.28 (br s, 4H), 2.42 (dd, J = 13.5, 10.0 Hz, 1H), 2.20 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 168.7, 166.2, 164.7, 163.3, 161.0, 160.2, 155.2, 153.6, 152.9, 136.5, 135.7, 131.0, 130.9, 130.8, 130.6, 129.1, 128.6, 128.0, 127.7, 125.8, 125.0, 122.0, 120.4, 118.9, 115.9, 111.7, 111.6, 110.6, 74.4, 68.6, 67.2, 56.0, 54.5, 54.1, 52.3, 44.9, 32.5, 17.5. HRMS calculated for $C_{41}H_{40}ClFN_6O_6S$: 798.2403; found 400.1284 (M + 2H).

*(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-(morpholin-4-yl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**9b**).* Using general procedure 4 and 1.06 g **R5a** (1.50 mmol) as the appropriate phenol and **R6b** as the appropriate alcohol, 335 mg **9b** (0.39 mmol, 26%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.57 (s, 1H), 8.37 (d, J = 5.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.30−7.23 (m, 2H), 7.22−7.14 (m, 3H), 7.12−7.06 (m, 1H), 6.92 (d, J = 5.0 Hz, 1H), 6.91−6.86 (m, 1H), 6.70−6.63 (m, 1H), 6.18−6.12 (m, 1H), 5.45 (dd, J = 10.2, 3.2 Hz, 1H), 5.03 (d, J = 14.9 Hz, 1H), 4.97 (d, J = 14.9 Hz, 1H), 4.28−4.21 (m, 1H), 4.21−4.13 (m, 1H), 3.72−3.66 (m, 4H), 3.65−3.60 (m, 4H), 3.28 (dd, J = 14.0, 3.2 Hz, 1H), 2.79−2.65 (m, 2H), 2.61−2.29 (m, 8H), 2.42 (dd, J = 10.2, 3.2 Hz, 1H), 2.20 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.5, 166.2, 163.3, 161.0, 160.9, 158.6, 155.4, 153.6, 152.9, 136.4, 135.7, 131.0, 130.8, 130.5, 129.1, 129.1, 128.6, 128.0, 127.7, 122.0, 120.2, 118.9, 116.0, 111.6, 110.5, 106.7, 74.3, 68.9, 67.2, 65.9, 63.7, 56.0, 54.0, 52.3, 44.9, 43.8, 32.4, 17.5. HRMS calculated for $C_{44}H_{45}ClFN_7O_6S$: 853.2825; found 427.6484 (M + 2H).

*(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-methoxyethyl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**9c**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and **R6c** as the appropriate alcohol, 72 mg **9c** (0.088 mmol, 35%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.74 (d, J = 5.2 Hz, 1H), 8.56 (s, 1H), 7.64 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.28−7.24 (m, 2H), 7.21−7.16 (m, 3H), 7.10 (td, J = 7.8, 1.5 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 6.68 (t, J = 7.4 Hz, 1H), 6.16 (d, J = 7.4 Hz, 1H), 5.45 (dd, J = 10.0, 3.0 Hz, 1H), 5.20 (d, J = 15.0 Hz, 1H), 5.12 (d, J = 15.0 Hz, 1H), 4.27−4.16 (m, 2H), 3.78 (t, J = 6.6 Hz, 2H), 3.34−3.29 (m, 1H), 3.20 (s, 3H), 3.09 (t, J = 6.6 Hz, 1H), 2.77−2.68 (m, 2H), 2.61−2.25 (m, 8H), 2.41 (dd, J = 13.8, 10.0 Hz, 1H), 2.22 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 167.6, 166.3, 165.9, 163.0, 162.1, 157.9, 155.3, 153.6, 152.9, 136.5, 135.7, 131.0, 130.8, 130.6, 129.1, 128.6, 128.1, 127.7, 125.1, 122.0, 120.4, 118.9, 116.0, 115.5, 111.7, 110.6, 74.4, 70.2, 68.7, 67.2, 57.9, 56.0, 54.0, 52.2, 44.8, 32.6, 17.5. HRMS calculated for $C_{43}H_{44}ClFN_6O_6S$: 826.2716; found 414.1439 (M + 2H).

*(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-(pyridin-4-yl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**9d**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and **R6e** as the appropriate alcohol, 93 mg **9d** (0.11, 44%) was obtained with a purity of 94.7%. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.02 (d, J = 5.0 Hz, 1H), 8.75 (dd, J = 4.4, 1.6 Hz, 1H), 8.54 (s, 1H), 8.24 (dd, J = 4.4, 1.6 Hz, 1H), 7.88 (d, J = 5.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.28−7.24 (m, 2H), 7.21−7.16 (m, 3H), 7.13 (td, J = 7.8, 1.6 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.19 (d, J = 7.8 Hz, 1H), 5.47 (dd, J = 10.2, 3.0 Hz, 1H), 5.36 (d, J = 15.2 Hz, 1H), 5.28 (d, J = 15.2 Hz, 1H), 4.26−4.14 (m, 2H), 3.36 (dd, J = 13.8, 2.5 Hz, 1H), 2.76−2.66 (m, 2H), 2.61−2.32 (m, 8H), 2.44 (dd, J = 13.8, 10.2 Hz, 1H), 2.21 (s, 3H), 1.79 (s, 3H). ^{1}H NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 167.0, 166.2, 162.2, 161.1, 158.8, 155.3, 153.6, 152.9, 150.6, 144.0, 136.5, 135.7, 131.0, 130.8, 130.6, 129.1, 128.6, 128.1, 127.8, 122.0, 121.6, 120.5, 118.9, 117.8, 116.0, 111.8, 110.6, 74.5, 68.8, 67.3, 67.1, 56.0, 54.0, 52.2, 44.8, 32.6, 17.5. HRMS calculated for $C_{45}H_{41}ClFN_7O_5S$: 845.2562; found 423.6358 (M + 2H).

*(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-(pyridin-2-yl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**9e**). Step A: [2-(2-Pyridyl)pyrimidin-4-yl]methanol.* Using general procedure 2 and 2.50 g pyridine-2-carboxamidine hydrochloride (15.9 mmol) as the appropriate amidine hydrochloride, 2.18 g 4-(dimethoxymethyl)-2-(2-pyridyl)pyrimidine (9.43 mmol) was obtained which was treated as described in general procedure 1 to yield 1.06 g [2-(2-pyridyl)pyrimidin-4-yl]methanol (5.66 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.94 (d, J = 5.1 Hz, 1H), 8.76−8.71 (m, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.00−7.93 (m, 1H), 7.60 (d, J = 5.1 Hz, 1H), 7.55−7.50 (m, 1H), 5.74 (t, J = 5.8 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H). LRMS calculated for $C_{10}H_9N_3O$: 187.2; found 188.2 (M + H).

*Step B: (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-(pyridin-2-yl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**9e**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and [2-(2-pyridyl)pyrimidin-4-yl]methanol as the appropriate alcohol, 61 mg **9e** (0.073 mmol, 29%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.99 (d, J = 5.0 Hz, 1H), 8.76−8.74 (m, 1H), 8.39−8.36 (m, 1H), 7.96 (td, J = 7.6, J = 1.8 Hz), 7.86 (d, J = 4.8 Hz, 1H), 7.55−7.52 (m, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.28−7.24 (m, 2H), 7.21−7.16 (m, 3H), 7.13 (td, J = 7.8, 1.5 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.19 (d, J = 7.4 Hz, 1H), 5.47 (dd, J = 10.2, 3.0 Hz, 1H), 5.34 (d, J = 15.2 Hz, 1H), 5.27 (d, J = 15.2 Hz, 1H), 4.27−4.15 (m, 2H), 3.37 (dd, J = 13.8, 2.5 Hz, 1H), 2.76−2.66 (m, 2H), 2.61−2.36 (m, 8H), 2.41 (dd, J = 13.8, 10.2 Hz, 1H), 2.21 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 166.8, 166.3, 166.2, 162.6, 162.2, 158.5, 155.3, 154.4, 153.6, 152.9, 149.7, 137.1, 136.5, 135.7, 131.0, 130.8, 130.6, 129.1, 128.6, 128.1, 127.8, 125.2, 123.5, 122.0, 120.5, 118.9, 117.1, 116.0, 111.8, 110.6, 74.6, 68.9, 67.1, 56.0, 54.0, 52.2, 52.2, 44.8, 32.6, 17.5. HRMS calculated for $C_{45}H_{41}ClFN_7O_5S$: 845.2562; found 423.6373 (M + 2H).

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*(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-(pyridin-3-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9f**). Step A: [2-(3-Pyridyl)pyrimidin-4-yl]methanol.* Using general procedure 2 and 2.50 g pyridine-3-carboxamidine hydrochloride (15.9 mmol) as the appropriate amidine hydrochloride, 1.67 g 4-(dimethoxymethyl)-2-(3-pyridyl)pyrimidine (7.23 mmol) was obtained which was treated as described in general procedure 1 to yield 1.19 g [2-(3-pyridyl)pyrimidin-4-yl]methanol (6.37 mmol, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.51−9.49 (m, 1H), 8.93 (d, J = 5.1 Hz, 1H), 8.73−8.70 (m, 1H), 8.68−8.63 (m, 1H), 7.58−7.53 (m, 2H), 5.73 (t, J = 5.8 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 172.2, 161.4, 158.7, 151.9, 149.4, 135.5, 133.1, 124.3, 116.8, 64.0. LRMS calculated for $C_{10}H_9N_3O$: 187.2; found 188.2 (M + H).

*Step B: (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-(pyridin-3-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9f**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and [2-(3-pyridyl)pyrimidin-4-yl]methanol as the appropriate alcohol, 110 mg **9f** (0.13 mmol, 52%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.50 (d, J = 2.2 Hz, 1H), 8.98 (d, J = 5.0 Hz, 1H), 8.71 (dd, J = 4.8, 1.7 Hz, 1H), 8.65 (dt, J = 8.0, 2.0 Hz, 1H), 8.54 (s, 1H), 7.82 (d, J = 5.0 Hz, 1H), 7.56−7.52 (m, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.28−7.24 (m, 2H), 7.21−7.16 (m, 3H), 7.13 (td, J = 7.6, 1.5 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.18 (d, J = 7.8 Hz, 1H), 5.47 (dd, J = 10.0, 3.0 Hz, 1H), 5.34 (d, J = 15.2 Hz, 1H), 5.27 (d, J = 15.2 Hz, 1H), 4.27−4.15 (m, 2H), 3.36 (dd, J = 13.8, 2.5 Hz, 1H), 2.76−2.66 (m, 2H), 2.61−2.36 (m, 8H), 2.41 (dd, J = 13.8, 10.0 Hz, 1H), 2.21 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.2, 166.8, 166.2, 163.0, 162.1, 161.4, 158.6, 155.3, 153.6, 152.9, 151.6, 149.0, 136.4, 135.7, 135.1, 132.4, 131.0, 130.8, 130.6, 129.1, 128.6, 128.1, 127.8, 125.2, 123.8, 122.0, 120.5, 118.9, 116.9, 116.0, 111.8, 110.6, 74.5, 68.8, 67.1, 56.0, 54.0, 52.2, 44.8, 32.6, 17.5. HRMS calculated for $C_{45}H_{41}ClFN_7O_5S$: 845.2562; found 423.6337 (M + 2H).

*(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-(furan-2-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9g**).* Using general procedure 5 and 1.10 g **R7** (1.30 mmol) and 0.58 g 2-furylboronic acid (5.2 mmol) as the appropriate boronic acid derivative, 358 mg **9g** (0.43 mmol, 33%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.84 (d, J = 5.1 Hz, 1H), 8.57 (s, 1H), 7.93 (dd, J = 1.7, 0.8 Hz, 1H), 7.67 (d, J = 5.0 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.31 (dd, J = 3.4, 0.8 Hz, 1H), 7.30−7.24 (m, 2H), 7.23−7.16 (m, 3H), 7.15−7.10 (m, 1H), 7.00−6.95 (m, 1H), 6.70 (dd, J = 3.4, 1.7 Hz, 1H), 6.73−6.67 (m, 1H), 6.22−6.16 (m, 1H), 5.46 (dd, J = 10.2, 3.0 Hz, 1H), 5.26 (d, J = 15.3 Hz, 1H), 5.19 (d, J = 15.3 Hz, 1H), 4.28−4.21 (m, 1H), 4.21−4.13 (m, 1H), 3.34 (dd, J = 13.7, 3.0 Hz, 1H), 2.78−2.65 (m, 2H), 2.61−2.27 (m, 8H), 2.43 (dd, J = 13.7, 10.2 Hz, 1H), 2.20 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.5, 166.2, 163.0, 161.0, 158.3, 156.4, 155.2, 153.6, 152.9, 151.5, 145.9, 136.4, 135.7, 131.0, 130.8, 130.6, 129.1, 128.6, 128.0, 127.7, 125.2, 122.0, 120.4, 118.9, 116.0, 115.6, 113.6, 112.5, 111.7, 110.6, 74.5, 68.7, 67.1, 56.0, 54.0, 52.3, 44.9, 32.5, 17.5. HRMS calculated for $C_{44}H_{40}ClFN_6O_6S$: 834.2403; found 418.1278 (M + 2H).

*(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-methylphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9h**).* Using general procedure 5 and 253 mg **R7** (0.30 mmol) and *o*-tolylboronic acid as the appropriate boronic acid derivative, 71 mg **9h** (0.083 mmol, 28%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.94 (d, J = 5.1 Hz, 1H), 8.55 (s, 1H), 7.81−7.77 (m, 1H), 7.76 (d, J = 5.1 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.39−7.34 (m, 1H), 7.33−7.25 (m, 4H), 7.23−7.16 (m, 3H), 7.15−7.09 (m, 1H), 7.01−6.96 (m, 1H), 6.73−6.66 (m, 1H), 6.23−6.16 (m, 1H), 5.46 (dd, J = 10.1, 3.0 Hz, 1H), 5.30 (d, J = 15.5 Hz, 1H), 5.24 (d, J = 15.5 Hz, 1H), 4.28−4.14 (m, 2H), 3.35 (dd, J = 13.8, 3.0 Hz, 1H), 2.76−2.65 (m, 2H), 2.60−2.24 (m, 9H), 2.47 (s, 3H), 2.16 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.0, 166.2, 166.0, 161.0, 157.9, 155.3, 153.6, 152.9, 137.6, 136.8, 136.4, 135.7, 131.1, 131.0, 130.8, 130.6, 130.4, 129.4, 129.1, 128.6, 128.0, 127.7, 125.7, 122.0, 120.4, 118.9, 116.0, 115.5, 111.7, 110.6, 68.8, 67.2, 56.1, 54.2, 52.5, 45.1, 32.5, 20.9, 17.5. HRMS calculated for $C_{47}H_{44}ClFN_6O_5S$: 858.2766; found 430.1464 (M + 2H).

*(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-(4-methylpyridin-3-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9i**).* Using general procedure 5 and 548 mg **R7** (0.65 mmol) and (4-methyl-3-pyridyl)boronic acid as the appropriate boronic acid derivative, 31 mg **9i** (0.036 mmol, 5.5%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.99 (d, J = 5.4 Hz, 1H), 8.92 (br s, 1H), 8.53 (s, 1H), 8.49 (br s, 1H), 7.84 (d, J = 4.6 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 4.2 Hz, 1H), 7.30−7.24 (m, 2H), 7.23−7.16 (m, 3H), 7.12 (td, J = 8.0, 1.4 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 7.5 Hz, 1H), 6.18 (d, J = 7.1 Hz, 1H), 5.46 (dd, J = 10.1, 2.8 Hz, 1H), 5.34 (d, J = 15.2 Hz, 1H), 5.27 (d, J = 15.2 Hz, 1H), 4.28−4.14 (m, 2H), 3.36 (dd, J = 13.7, 2.8 Hz, 1H), 2.77−2.65 (m, 2H), 2.60−2.24 (m, 9H), 2.47 (s, 3H), 2.16 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.3, 158.2, 155.3, 153.6, 152.8, 149.9, 136.4, 135.7, 131.0, 130.8, 130.6, 129.1, 128.6, 128.0, 122.0, 120.4, 118.9, 116.0, 115.9, 111.7, 110.6, 68.7, 67.2, 56.1, 54.2, 52.5, 45.1, 35.8, 32.6, 31.8, 20.2, 17.5. HRMS calculated for $C_{46}H_{43}ClFN_7O_5S$: 859.2719; found 430.6434 (M + 2H).

*(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-(3-methylpyridin-4-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9j**).* Using general procedure 5 and 250 mg **R7** (0.30 mmol) and (3-methyl-4-pyridyl)boronic acid as the appropriate boronic acid derivative, 52 mg **9j** (0.06 mmol, 20%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.01 (d, J = 5.1 Hz, 1H), 8.58−8.48 (m, 3H), 7.91 (d, J = 4.8 Hz, 1H), 7.76 (d, J = 5.1 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.30−7.23 (m, 2H), 7.23−7.15 (m, 3H), 7.12 (td, J = 8.0, 1.6 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.69 (t, J = 7.3 Hz, 1H), 6.16 (d, J = 7.3 Hz, 1H), 5.46 (dd, J = 10.3, 2.6 Hz, 1H), 5.34 (d, J = 15.4 Hz, 1H), 5.26 (d, J = 15.4 Hz, 1H), 4.29−4.14 (m, 2H), 3.38 (m, 1H), 2.78−2.66 (m, 2H), 2.65−2.29 (m, 9H), 2.48 (s, 3H), 2.20 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.3, 166.5, 166.2, 163.8, 163.0, 161.0, 158.3, 155.2, 153.6, 152.9, 152.1, 147.5, 143.9, 136.4, 135.7, 131.6, 130.9, 130.8, 130.7, 129.2, 128.6, 128.0, 127.8, 123.6, 122.0, 120.4, 118.9, 116.7, 115.9, 111.7, 110.6, 74.8, 68.7, 67.2, 56.0, 54.0, 52.3, 44.8, 32.7, 17.7, 17.5. HRMS calculated for $C_{46}H_{43}ClFN_7O_5S$: 859.2719; found 860.2808 (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-(5-methoxy-2-methylpyridin-4-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9k**). Step A: Ethyl (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-chloropyrimidin-4-yl)methoxy]phenyl]propanoate.* Using step A of general procedure 4 and 235 mg **R5a** (0.33 mmol) as the appropriate phenol and (2-chloropyrimidin-4-yl)methanol as the appropriate alcohol, 197 mg ethyl (2*R*)-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-chloropyrimidin-4-yl)methoxy]phenyl]propanoate (0.24 mmol, 71%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.89−8.85 (m, 1H), 8.60 (s, 1H), 7.71−7.66 (m, 1H), 7.36−7.09 (m, 6H), 7.03−6.86 (m, 2H), 6.79−6.68 (m, 1H), 6.33−6.24 (m, 1H), 5.47 (dd, J = 9.0, 4.2 Hz, 1H), 5.26 (d, J = 15.6 Hz, 1H), 5.20 (d, J = 15.6 Hz, 1H), 4.29−4.15 (m, 2H), 4.11−4.00 (m, 2H), 3.29−2.15 (m, 12H), 2.09 (s, 3H), 1.86 (s, 3H), 1.06 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.9, 169.5, 166.5, 162.3, 162.2, 161.1, 155.0, 153.8, 153.7, 152.7, 137.0, 136.0, 131.1, 131.0, 130.2, 129.5, 128.9, 128.8, 128.5, 128.0, 123.7, 122.0, 120.8, 118.8, 116.0, 111.9, 110.7, 73.8, 68.4, 67.3, 61.0, 56.3, 54.6, 52.9, 45.7, 32.3, 18.0, 13.9. HRMS calculated for $C_{42}H_{41}Cl_2FN_6O_5S$: 830.2220; found 831.2275 (M + H).

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*Step B: (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-(5-methoxy-2-methylpyridin-4-yl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**9k**).* 192 mg ethyl (2*R*)-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-chloropyrimidin-4-yl)methoxy]phenyl]propanoate (0.23 mmol), 115 mg 5-methoxy-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyridine (0.46 mmol), 16 mg $Pd(PPh_3)_2Cl_2$ (0.023 mmol), 0.6 mL 2 M aq Na_2CO_3 solution, and 0.6 mL dioxane were stirred at 90 °C under N_2 atmosphere for 2 h. Then 97 mg $LiOH·H_2O$ (2.30 mmol) was added and the mixture was stirred at rt for 2 h. Then it was diluted with brine, acidified with 2 M aq HCl solution, and extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure and purified via preparative reversed phase chromatography using 25 mM aq NH_4HCO_3 solution and MeCN as eluents to obtain 78 mg **9k** (0.088 mmol, 38%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.94 (d, J = 5.1 Hz, 1H), 8.56 (s, 1H), 8.38 (s, 1H), 7.83 (d, J = 5.1 Hz, 1H), 7.39 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.29−7.25 (m, 2H), 7.20 (t, J = 8.7 Hz, 2H), 7.20 (d, J = 8.4 Hz, 1H), 7.15−7.11 (m, 1H), 7.00−6.97 (m, 1H), 6.72−6.68 (m, 1H), 6.20−6.18 (m, 1H), 5.45 (dd, J = 10.1, 3.0 Hz, 1H), 5.28 (d, J = 15.2 Hz, 1H), 5.22 (d, J = 15.2 Hz, 1H), 4.27−4.16 (m, 2H), 3.84 (s, 3H), 3.34 (dd, J = 14.2, 3.0 Hz, 1H), 2.76−2.66 (m, 2H), 2.61−2.27 (m, 8H), 2.46 (s, 3H), 2.45−2.41 (m, 1H), 2.18 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.4, 166.3, 163.3, 162.8, 162.1, 158.1, 153.7, 152.9, 150.9, 150.2, 136.5, 135.1, 134.9, 131.0, 130.9, 130.6, 128.1, 127.8, 123.6, 120.5, 118.9, 116.6, 116.0, 111.8, 110.7, 74.5, 68.8, 67.2, 56.7, 56.1, 54.2, 52.5, 45.1, 32.6, 23.1, 17.5. HRMS calculated for $C_{47}H_{45}ClFN_7O_6S$: 889.2825; found 445.6481 (M + 2H).

*(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-(hydroxymethyl)phenyl]pyrimidin-4-yl}methoxy)-phenyl]propanoic Acid (**9l**).* Using general procedure 5 and 53 mg **R7** (0.063 mmol) and 2-(hydroxymethyl)phenylboronic acid as the appropriate boronic acid derivative, 24 mg **9l** (0.027 mmol, 43%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.96 (d, J = 5.2 Hz, 1H), 8.54 (s, 1H), 7.94 (dd, J = 7.7, 1.2 Hz, 1H), 7.84 (d, J = 5.0 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.50 (td, J = 7.7, 1.2 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.38 (td, J = 6.6, 1.2 Hz, 1H), 7.29−7.23 (m, 2H), 7.22−7.15 (m, 3H), 7.11 (td, J = 7.7, 1.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.68 (t, J = 7.4 Hz, 1H), 6.16 (d, J = 7.4 Hz, 1H), 5.45 (dd, J = 10.5, 2.7 Hz, 1H), 5.31 (d, J = 15.2 Hz, 1H), 5.22 (d, J = 15.2 Hz, 1H), 4.81 (s, 2H), 4.28−4.21 (m, 1H), 4.21−4.14 (m, 1H), 3.44−3.35 (m, 1H), 2.78−2.65 (m, 2H), 2.61−2.24 (m, 9H), 2.19 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.3, 166.2, 166.1, 165.0, 163.6, 163.0, 161.0, 158.0, 155.3, 153.6, 152.9, 142.0, 136.3, 135.9, 135.7, 130.9, 130.8, 129.8, 129.2, 128.7, 127.9, 127.8, 127.7, 126.6, 125.6, 122.0, 120.4, 118.9, 115.9, 115.6, 111.7, 110.6, 75.0, 68.8, 67.2, 61.7, 56.0, 54.0, 52.3, 44.9, 32.7, 17.5. HRMS calculated for $C_{47}H_{44}ClFN_6O_6S$: 874.2716; found 875.2804 (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 (**9m**).* Using general procedure 4 and 176 mg **R5a** (0.25 mmol) as the appropriate phenol and **R6d** as the appropriate alcohol, 91 mg **9m** (0.105 mmol, 42%) was obtained. ^{1}H NMR (500 MHz, DMSO-d6) δ ppm: 8.88 (d, J = 5.2 Hz, 1H), 8.57 (s, 1H), 7.72 (d, J = 5.2 Hz, 1H), 7.52 (dd, J = 7.5, 1.8 Hz, 1H), 7.47−7.43 (m, 1H), 7.38 (d, J = 8.5 Hz, 1H), 7.29−7.25 (m, 2H), 7.22−7.17 (m, 3H), 7.15−7.10 (m, 2H), 7.03 (td, J = 7.4, 1.0 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.19 (d, J = 7.4 Hz, 1H), 5.46 (dd, J = 10.0, 3.2 Hz, 1H), 5.25 (d, J = 15.0 Hz, 1H), 5.19 (d, J = 15.0 Hz, 1H), 4.26−4.16 (m, 2H), 3.75 (s, 3H), 3.33 (dd, J = 14.0, 3.0 Hz, 1H), 2.77−2.68 (m, 2H), 2.58−2.35 (m, 8H), 2.41 (dd, J = 14.0, 10.0 Hz, 1H), 2.20 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.1, 166.3, 166.0, 164.7, 162.1, 157.8, 157.2, 155.3, 153.6, 152.9, 136.5, 135.8, 131.0, 130.8, 130.6, 129.1, 128.6, 128.4, 128.1, 127.7, 122.0, 120.4, 120.1, 118.9, 116.0, 115.6, 112.2, 111.8, 110.6, 74.3, 68.9, 67.2, 56.0, 55.7, 54.1, 52.3, 44.9, 32.5, 17.5. HRMS calculated for $C_{47}H_{44}ClFN_6O_6S$: 874.2716; found 438.1415 (M + 2H).

*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 (**9n**). Step A: (2R)-2-[[5-Bromo-6-(4-fluorophenyl)thieno[2,3-d]-pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)propanoic Acid.* 2.899 g **R1c** (8.44 mmol), 2.755 g (2*R*)-2-amino-3-(2-hydroxyphenyl)-propanoic acid hydrochloride (12.66 mmol), and 3.500 g K_2CO_3 (25.32 mmol) were mixed in 84 mL DMSO and stirred at rt overnight. The mixture was then diluted with brine, acidified with 1 M aq HCl solution to pH 2. The formed precipitate was filtered to give 2.839 g (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)thieno[2,3-*d*]pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)propanoic acid (5.80 mmol, 69%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 11.20 (br s, 1H), 8.41 (s, 1H), 7.87 (d, J = 5.2 Hz, 1H), 7.73−7.66 (m, 2H), 7.45−7.34 (m, 2H), 7.10 (dd, J = 7.4, 1.6 Hz, 1H), 7.01 (td, J = 7.4, 1.6 Hz, 1H), 6.75 (dd, J = 8.0, 0.9 Hz, 1H), 6.68 (td, J = 7.4, 1.1 Hz, 1H), 4.72−4.60 (m, 1H), 3.27 (dd, J = 13.8, 5.1 Hz, 1H), 3.06 (dd, J = 13.7, 6.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.4, 163.7, 161.2, 156.0, 155.6, 154.0, 131.9, 131.5, 128.1, 127.7, 124.5, 118.7, 116.0, 115.8, 114.0, 99.5, 55.6, 32.2. LRMS calculated for $C_{21}H_{15}BrFN_3O_3S$: 487.0; found 488.0 (M + H).

Step B: Ethyl (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]amino]-3-(2-hydroxyphenyl)propanoate. 244 mg (2*R*)-2-[[5-bromo-6-(4-fluorophenyl)thieno[2,3-*d*]pyrimidin-4-yl]-amino]-3-(2-hydroxyphenyl)propanoic acid (0.50 mmol) and 237 mg **R3b** (0.60 mmol) were dissolved in 2.5 mL dioxane:water 2:1 mixture, then 489 mg Cs_2CO_3 (1.50 mmol) and 35.4 mg AtaPhos (0.05 mmol) were added and the mixture was stirred at 60 °C overnight. Then the mixture was neutralized with 1 M aq HCl solution and extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to yield a mixture of diastereoisomers, which were separated via flash chromatography using HILIC eluents. The diastereoisomer eluting later was collected, then dissolved in 5 mL 1.25 M HCl solution in EtOH and stirred at 40 °C overnight. Then it was carefully diluted with aq $NaHCO_3$ solution and extracted with DCM. The combined organic layer was dried over Na_2SO_4, 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 122 mg ethyl (2*R*)-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]amino]-3-(2-hydroxyphenyl)propanoate (0.17 mmol, 34%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.49 (s, 1H), 8.40 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.26−7.20 (m, 3H), 7.20−7.15 (m, 2H), 7.00 (td, J = 7.8, 1.6 Hz, 1H), 6.71 (dd, J = 7.8, 0.9 Hz, 1H), 6.60 (td, J = 7.8, 0.9 Hz, 1H), 6.39 (dd, J = 7.8, 1.6 Hz, 1H), 5.03 (d, J = 7.8 Hz, 1H), 4.96−4.89 (m, 1H), 4.26 (t, J = 5.5 Hz, 2H), 4.09−3.96 (m, 2H), 3.03 (dd, J = 13.7, 5.5 Hz, 1H), 2.78 (t, J = 5.5 Hz, 2H), 2.60−2.47 (m, 4H), 2.36 (dd, J = 13.7, 9.4 Hz, 1H), 2.39−2.19 (m, 4H), 2.12 (s, 3H), 1.83 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.4, 164.3, 162.9, 160.9, 156.4, 155.4, 154.6, 153.4, 136.6, 134.4, 130.7, 130.2, 129.6, 129.0, 128.0, 126.4, 123.2, 122.0, 118.6, 115.9, 115.6, 114.9, 111.7, 67.4, 60.7, 56.2, 54.7, 53.0, 52.4, 45.7, 32.8, 17.4, 13.9. HRMS calculated for $C_{37}H_{39}ClFN_5O_4S$: 703.2395; found 704.2450 (M + H).

*Step C: 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 (**9n**).* Using general procedure 4 and 63.4 mg ethyl (2*R*)-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]amino]-3-(2-hydroxyphenyl)propanoate (0.094 mmol) as the appropriate phenol and **R6d** as the appropriate alcohol, 32.4 mg **9n** (0.037 mmol, 39%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.85 (d, J = 5.2 Hz, 1H), 8.32 (s, 1H), 7.54 (dd, J = 7.5, 1.8 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.48−7.44 (m, 1H), 7.29−7.23 (m, 2H), 7.21−7.08 (m, 6H), 7.05 (td, J = 7.5, 0.9 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.91 (d, J

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= 7.5, 1.8 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 5.74 (d, J = 6.0 Hz, 1H), 5.12 (d, J = 14.9 Hz, 1H), 5.05 (d, J = 14.9 Hz, 1H), 4.63 (q, J = 6.0 Hz, 1H), 4.49−4.44 (m, 1H), 4.15−4.06 (m, 1H), 3.76 (s, 3H), 3.48 (dd, J = 13.8, 6.0 Hz, 1H), 3.11−3.00 (m, 1H), 2.98−2.87 (m, 2H), 2.86−2.53 (m, 8H), 2.34 (s, 3H), 1.84 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.3, 165.9, 164.7, 163.9, 160.8, 157.7, 157.2, 156, 155.9, 154.6, 153.7, 136.0, 132.8, 131.0, 130.8, 130.7, 130.1, 129.4, 129.2, 128.9, 128.4, 127.4, 126.5, 126.4, 123.1, 120.7, 120.1, 115.9, 115.8, 115.5, 112.2, 111.9, 111.8, 69.2, 65.9, 55.7, 55.6, 54.4, 53.7, 43.9, 31.2, 17.2. HRMS calculated for $C_{47}H_{45}ClFN_7O_5S$: 873.2875; found 437.6498 (M + 2H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]-oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**10a**).* Using general procedure 4 and 214 mg **R5c** (0.33 mmol) as the appropriate phenol and **R6d** as the appropriate alcohol, 133 mg **10a** (0.16 mmol, 49%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.89 (d, J = 5.4 Hz, 1H), 8.57 (s, 1H), 7.79 (d, J = 5.4 Hz, 1H), 7.52 (dd, J = 5.8, 1.8 Hz, 1H), 7.47−7.42 (m, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.15−7.70 (m, 2H), 7.02 (td, J = 7.5, 0.9 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.04 (d, J = 7.5 Hz, 1H), 5.40 (dd, J = 10.5, 2.7 Hz, 1H), 5.23 (d, J = 15.2 Hz, 1H), 5.17 (d, J = 15.2 Hz, 1H), 4.30−4.16 (m, 2H), 3.74 (s, 3H), 3.44−3.35 (m, 1H), 2.82−2.67 (m, 2H), 2.67−2.35 (m, 9H), 2.28 (s, 3H), 2.10 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.4, 166.0, 165.9, 164.7, 163.1, 157.9, 157.2, 155.3, 154.0, 153.8, 136.0, 135.7, 131.1, 130.9, 130.8, 130.2, 128.4, 128.0, 127.5, 125.4, 121.8, 120.4, 120.2, 119.0, 117.3, 115.7, 112.2, 111.7, 110.1, 97.1, 75.0, 72.0, 68.8, 67.0, 56.1, 55.7, 53.7, 51.9, 44.4, 32.8, 17.8, 4.4. HRMS calculated for $C_{44}H_{43}ClN_6O_6S$: 818.2653; found 410.1394 (M + 2H).

*N-[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)-ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**10b**). Step A: (2R)-3-(2-Hydroxyphenyl)-2-[(5-iodo-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl)amino]propanoic Acid.* 3.14 g **R1d** (9.38 mmol), 3.06 g (2R)-2-amino-3-(2-hydroxyphenyl)-propanoic acid (14.06 mmol), and 3.86 g K_2CO_3 (27.9 mmol) were mixed in 50 mL DMSO and stirred at 50 °C for 4 h. The mixture was then diluted with water, acidified with 1 M aq HCl solution to pH 1, and the formed precipitate was filtered to give 3.356 g (2R)-3-(2-hydroxyphenyl)-2-[(5-iodo-6-prop-1-ynylthieno[2,3-d]-pyrimidin-4-yl)amino]propanoic acid (7.00 mmol, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.41 (s, 1H), 7.93−7.84 (m, 1H), 7.09−7.04 (m, 1H), 7.03−6.97 (m, 1H), 6.75−6.70 (m, 1H), 6.69−6.63 (m, 1H), 4.76−4.68 (m, 1H), 3.30−3.22 (m, 1H), 3.04−2.95 (m, 1H), 2.18 (s, 3H). LRMS calculated for $C_{18}H_{14}IN_3O_3S$: 478.98; found 480.0 (M + H).

Step B: Ethyl (2R)-2-[[(5S$_a$)-5-[3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-prop-1-ynylthieno[2,3-d]-pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)propanoate. 2.39 g (2R)-3-(2-hydroxyphenyl)-2-[(5-iodo-6-prop-1-ynylthieno[2,3-d]-pyrimidin-4-yl)amino]propanoic acid (4.99 mmol) and 2.96 g **R3b** (7.50 mmol) were dissolved in 50 mL THF and 15 mL water, then 4.89 g Cs_2CO_3 (15.0 mmol) and 354 mg AtaPhos (0.050 mmol) were added under N_2 atmosphere and the mixture was stirred at 90 °C for 1 h. Then it was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The formed diastereoisomers were separated via flash chromatography using HILIC eluents. The diastereoisomer eluting later was collected and then dissolved in 20 mL 1.25 M HCl solution in EtOH and stirred at 40 °C overnight. The mixture was then diluted with aq $NaHCO_3$ solution and extracted with DCM. The combined organic layer was dried over Na_2SO_4, 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 1.02 g ethyl (2R)-2-[[(5S$_a$)-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)-propanoate (1.57 mmol, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 9.47 (s, 1H), 8.41 (s, 1H), 7.22−7.19 (m, 2H), 7.03−6.98 (m, 1H), 6.71−6.68 (m, 1H), 6.62−6.58 (m, 1H), 6.35−6.32 (m, 1H), 5.11 (d, J = 7.7 Hz, 1H), 4.92−4.86 (m, 1H), 4.27 (t, J = 5.7 Hz, 2H), 4.09−3.98 (m, 2H), 3.09−3.03 (m, 1H), 2.79 (t, J = 5.7 Hz, 2H), 2.71−2.47 (m, 4H), 2.43−2.36 (m, 1H), 2.36−2.23 (m, 4H), 2.12 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.11 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 171.3, 164.2, 155.9, 155.4, 154.6, 154.4, 136.6, 135.0, 130.2, 128.8, 128.1, 126.0, 123.1, 121.9, 118.6, 117.2, 114.9, 114.1, 111.3, 96.2, 71.7, 67.4, 60.8, 56.3, 54.8, 53.1, 52.5, 45.8, 32.6, 17.5, 14.0, 4.3. HRMS calculated for $C_{34}H_{38}ClN_5O_4S$: 647.2333; found 648.2385 (M + H).

*Step C: N-[(5S$_a$)-5-{3-Chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-6-(prop-1-yn-1-yl)thieno[2,3-d]pyrimidin-4-yl]-2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}-D-phenylalanine (**10b**).* Using general procedure 4 and 792 mg ethyl (2R)-2-[[(5S$_a$)-5-[3-chloro-2-methyl-4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl]-6-prop-1-ynylthieno[2,3-d]pyrimidin-4-yl]amino]-3-(2-hydroxyphenyl)-propanoate (1.22 mmol) as the appropriate phenol and **R6d** as the appropriate alcohol, 336 mg **10b** (0.410 mmol, 34%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.83 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 7.55−7.52 (m, 1H), 7.49−7.44 (m, 2H), 7.20−7.12 (m, 4H), 7.08−7.03 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 7.55 Hz, 1H), 6.85−6.80 (m, 1H), 5.80 (d, J = 6.2 Hz, 1H), 5.10 (d, J = 15.1 Hz, 1H), 5.02 (d, J = 15.1 Hz, 1H), 4.63−4.57 (m, 1H), 4.50−4.43 (m, 1H), 4.17−4.11 (m, 1H), 3.76 (s, 3H), 3.46 (dd, J = 14.0, 5.7 Hz, 1H), 3.10−3.02 (m, 1H), 2.98−2.89 (m, 2H), 2.83−2.56 (m, 8H), 2.36 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 173.2, 165.9, 164.7, 163.9, 157.7, 157.2, 155.9, 155.6, 154.7, 154.6, 136.0, 135.8, 131.0, 130.8, 130.2, 129.0, 128.4, 127.5, 126.3, 126.1, 122.9, 120.7, 120.1, 115.7, 115.4, 114.3, 112.2, 111.9, 111.5, 95.4, 71.9, 69.2, 66.1, 55.7, 55.6, 54.4, 53.6, 49.1, 43.9, 31.1, 17.2, 4.3. HRMS calculated for $C_{44}H_{44}ClN_7O_5S$: 817.2813; found 409.6494 (M + 2H).

*(2R)-2-{[(5S$_a$)-5-{3-Chloro-4-[2-(dimethylamino)ethoxy]-2-methylphenyl}-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)propanoic Acid (**11**). Step A: Ethyl (2R)-2-[(5S$_a$)-[3-Chloro-4-(2-dimethylaminoethyloxy)-2-methylphenyl]-6-(4-fluorophenyl)thieno[2,3-d]-pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate.* Using step A of general procedure 4 and 4.94 g **R4** (7.50 mmol) as the appropriate phenol and 2-(dimethylamino)ethanol as the appropriate alcohol, an intermediate was obtained, which was dissolved in 40 mL EtOH, then 20 mL 1.25 M HCl solution in EtOH was added and the mixture was stirred at rt overnight. Then water and saturated $NaHCO_3$ solution were added carefully and the mixture was extracted with DCM. The combined organic layer was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified via flash chromatography using EtOAc and MeOH as eluents to obtain 3.86 g ethyl (2R)-2-[(5S$_a$)-5-[3-chloro-4-(2-dimethylaminoethyloxy)-2-methylphenyl]-6-(4-fluorophenyl)thieno-[2,3-d]pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate (5.90 mmol, 79%). ^{1}H NMR (500 MHz, DMSO-d_6): 9.53 (br s, 1H), 8.61 (s, 1H), 7.32−7.27 (m, 3H), 7.24−7.19 (m, 2H), 7.16 (d, J = 8.7 Hz, 1H), 6.99−6.95 (m, 1H), 6.72−6.70 (m, 1H), 6.54−6.51 (m, 1H), 6.19−6.17 (m, 1H), 5.46 (dd, J = 9.0, 4.7 Hz, 1H), 4.20 (t, J = 5.7 Hz, 2H), 4.09−3.99 (m, 2H), 2.93 (dd, J = 13.6, 4.7 Hz, 1H), 2.69 (t, J = 5.7 Hz, 2H), 2.43 (dd, J = 13.6, 9.0 Hz, 1H), 2.22 (s, 6H), 1.88 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.4, 166.5, 162.6, 162.1, 155.2, 153.8, 152.8, 136.8, 135.9, 131.10, 131.07, 131.0, 129.0, 128.5, 128.0, 127.5, 122.0, 121.7, 118.8, 118.5, 116.0, 114.7, 110.6, 73.3, 67.4, 60.8, 57.4, 45.7, 32.2, 17.6, 13.9. HRMS calculated for $C_{34}H_{33}ClFN_3O_5S$: 649.1813; found 650.1887 (M + H).

Step B: Ethyl (2R)-2-[(5S$_a$)-5-[3-Chloro-4-(2-dimethylaminoethyloxy)-2-methylphenyl]-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-[2-[(2-methylsulfanylpyrimidin-4-yl)methoxy]phenyl]-propanoate. Using step A of general procedure 4 and 975 mg ethyl (2R)-2-[(5S$_a$)-5-[3-chloro-4-(2-dimethylaminoethyloxy)-2-methylphenyl]-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-(2-hydroxyphenyl)propanoate (1.50 mmol) as the appropriate phenol and 702 mg **R6a** (4.50 mmol) as the appropriate alcohol, 641 mg ethyl (2R)-2-[(5S$_a$)-5-[3-chloro-4-(2-dimethylaminoethyloxy)-2-methylphenyl]-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-

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[2-[(2-methylsulfanylpyrimidin-4-yl)methoxy]phenyl]propanoate (0.80 mmol, 54%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6): 8.69 (d, J = 5.1 Hz, 1H), 8.60 (s, 1H), 7.34 (d, 1H), 7.32−7.28 (m, 2H), 7.30 (d, J = 5.1 Hz, 1H), 7.24−7.20 (m, 2H), 7.19−7.14 (m, 2H), 6.99−6.97 (m, 1H), 6.76−6.72 (m, 1H), 6.30−6.28 (m, 1H), 5.47 (dd, J = 9.2, 4.2 Hz, 1H), 5.17 (d, J = 15.0 Hz, 1H), 5.11 (d, J = 15.0 Hz, 1H), 4.21−4.13 (m, 2H), 4.11−4.02 (m, 2H), 3.13 (dd, J = 13.7, 4.4 Hz, 1H), 2.64 (t, J = 5.7 Hz, 2H), 2.57−2.54 (m, 1H), 2.50 (s, 3H), 2.19 (s, 6H), 1.85 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 169.3, 166.5, 166.4, 162.4, 158.2, 155.3, 153.8, 152.7, 136.9, 131.1, 131.0, 130.3, 128.5, 127.5, 123.7, 120.6, 116.0, 113.3, 111.8, 110.6, 73.5, 68.7, 67.4, 60.1, 57.4, 45.7, 32.2, 17.6, 13.9, 13.5. HRMS calculated for $C_{40}H_{39}ClFN_5O_5S_2$: 787.2065; found 788.2148 (M + H).

*Step C: (2R)-2-{[(5S$_a$)-5-{3-Chloro-4-[2-(dimethylamino)ethoxy]-2-methylphenyl}-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy}-3-(2-{[2-(2-methoxyphenyl)pyrimidin-4-yl]methoxy}phenyl)-propanoic Acid (**11**).* Using general procedure 5 and 160 mg ethyl (2R)-2-[(5S$_a$)-5-[3-chloro-4-(2-dimethylaminoethyloxy)-2-methylphenyl]-6-(4-fluorophenyl)thieno[2,3-d]pyrimidin-4-yl]oxy-3-[2-[(2-methylsulfanylpyrimidin-4-yl)methoxy]phenyl]propanoate (0.20 mmol) instead of **R7**, (2-methoxyphenyl)boronic acid as the appropriate boronic acid derivative, 75 mg **11** (0.09 mmol, 46%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm: 8.86 (d, J = 5.1 Hz, 1H), 8.56 (s, 1H), 7.72 (d, J = 5.1 Hz, 1H), 7.53 (dd, J = 7.6, 1.8 Hz, 1H), 7.47−7.41 (m, 2H), 7.28−7.13 (m, 6H), 7.10−7.05 (m, 1H), 7.04 (td, J = 7.6, 0.9 Hz, 1H), 6.97−6.94 (m, 1H), 6.67−6.63 (m, 1H), 6.13 (d, J = 7.2 Hz, 1H), 5.44 (dd, J = 10.3, 2.8 Hz, 1H), 5.22 (d, J = 15.1 Hz, 1H), 5.13 (d, J = 15.1 Hz, 1H), 4.31−4.22 (m, 2H), 3.76 (s, 3H), 3.33 (dd, J = 13.8, 2.8 Hz, 1H), 2.84−2.79 (m, 2H), 2.43 (dd, J = 13.8, 10.3 Hz, 1H), 2.32 (s, 6H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm: 166.3, 165.9, 164.7, 162.2, 157.7, 157.2, 155.3, 153.6, 152.9, 135.7, 131.0, 130.8, 130.7, 128.5, 128.4, 128.0, 127.8, 122.0, 120.4, 120.2, 118.8, 115.9, 115.6, 112.2, 111.7, 110.6, 68.8, 66.9, 56.9, 55.7, 45.1, 17.5. HRMS calculated for $C_{44}H_{39}ClFN_5O_6S$: 819.2294; found 410.6206 (M + 2H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c01234.

Molecular formula strings and some data (CSV)

Data tables, structural determination details, LC chromatograms, and ^{1}H NMR spectra of key compounds (PDF)

Accession Codes

The X-ray structures mentioned in this paper have been deposited in the PDB with the following codes: **2g**, 6YBG; **3e**, 6YBJ; **4d**, 6YBK; **9m**, 6YBL. Authors will release the atomic coordinates and experimental data upon article publication

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

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

Mcl-1, myeloid cell leukemia 1; MCL1, Mcl-1 gene; Bcl-2, B-cell lymphoma 2; Bcl-x$_L$, B-cell lymphoma extra-large; BH3,

Bcl-2 homology domain3; Bim, Bcl-2-like protein 11; FBS, fetal bovine serum; FP, fluorescence polarization

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