Journal of Medicinal Chemistry

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Design and Synthesis of Novel Epigenetic Inhibitors Targeting Histone Deacetylases, DNA Methyltransferase 1, and Lysine Methyltransferase G9a with *In Vivo* Efficacy in Multiple Myeloma

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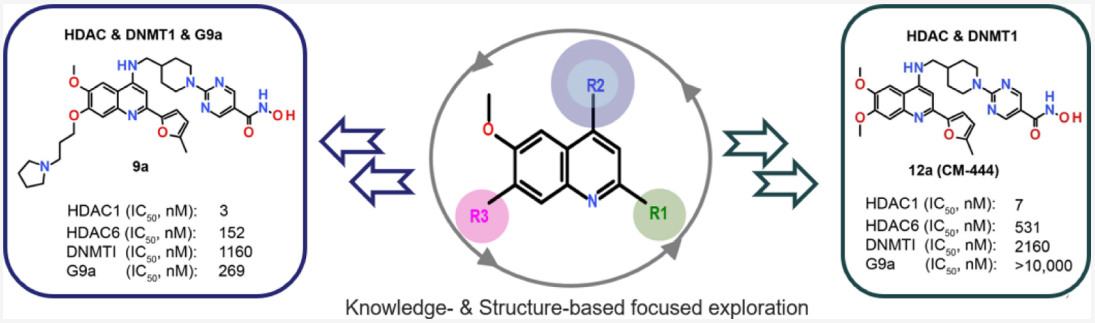

ABSTRACT: Concomitant inhibition of key epigenetic pathways involved in silencing tumor suppressor genes has been recognized as a promising strategy for cancer therapy. Herein, we report a first-in-class series of quinoline-based analogues that simultaneously inhibit histone deacetylases (from a low nanomolar range) and DNA methyltransferase-1 (from a mid-nanomolar range, IC_{50} < 200 nM). Additionally, lysine methyltransferase G9a inhibitory activity is achieved (from a low nanomolar range) by introduction of a key lysine mimic group at the 7-position of the quinoline ring. The corresponding epigenetic functional cellular responses are observed: histone-3 acetylation, DNA hypomethylation, and decreased histone-3 methylation at lysine-9. These chemical probes, multitarget epigenetic inhibitors, were validated against the multiple myeloma cell line MM1.S, demonstrating promising *in vitro* activity of **12a** (CM-444) with GI_{50} of 32 nM, an adequate therapeutic window (>1 log unit), and a suitable pharmacokinetic profile. *In vivo*, **12a** achieved significant antitumor efficacy in a xenograft mouse model of human multiple myeloma.

INTRODUCTION

Epigenetic modifications play an important role in the regulation of gene expression and transcription and are implicated in cancer and many other diseases. Due to the reversibility of epigenetic alterations, there has consequently been a focus upon directing probe and drug discovery efforts toward the identification of novel antitumor targets. Among the many epigenetic protein families, DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), enzymes that respectively add methylation marks to DNA and erase acetylation marks from histones, were strongly implicated in cancer through extensive studies of their biological mechanisms and target validation via epigenetic medicinal chemistry. As a result, both are molecular targets of FDA-approved drugs for the treatment of hematologic malignancies, with a considerable number of active clinical trials and many inhibitors under development.[1] Approved DNMT inhibitors (DNMTi), Azacitidine and Decitabine, are nucleoside analogues that, following conversion to the triphosphate, incorporate into the DNA and covalently bind to DNMTs. Such non-specific mechanism of action translates into significant toxicity limiting the dose and efficacy. Despite recent progress in the development of non-nucleoside-based DNMTi binding to the catalytic site of DNMTs, none has entered into clinical phases.[2] For HDACs, the pipeline is more advanced: a considerable number of potent HDAC inhibitors (HDACi) have been discovered; the pharmacophore pattern to inhibit them is well-established and five HDACi have been

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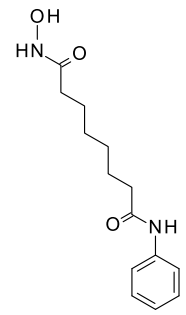
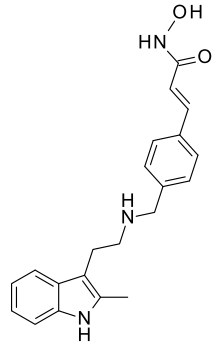
Chart 1. pan-HDACi (1,[30] 2,[31] 3[32]), Dual DNMT, and HDACi (4),[19] Dual G9a and DNMT1 Inhibitors (5, 6),[21] G9a Inhibitor (7)[24] and Dual G9a and HDACi (8);[23] IC_{50} Values for 4 Were Determined Internally (See Footnote in Table 1) and the Rest of the Biochemical IC_{50} Values Extracted from the Corresponding References; for 8, the Enzymatic Activity of HDAC Was Measured in Intact Cells by the Homogeneous Cellular HDAC Assay Method Using the K562 Cell Line and the Ability to Block G9a by H3K9me2 Cell Immunofluorescence In-Cell Western (ICW) Assays Using the MDA-MB-231 Cell Line[23]



1

SAHA

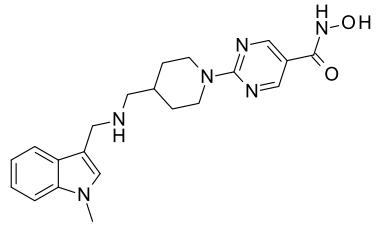
HDAC1 IC_{50} = 30nM
HDAC2 IC_{50} = 170nM
HDAC3 IC_{50} = 100nM
HDAC6 IC_{50} = 38nM



2

Panobinostat

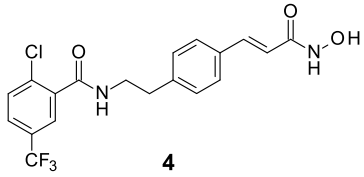
HDAC1 IC_{50} = 2.5nM
HDAC2 IC_{50} = 13.2nM
HDAC3 IC_{50} = 2.1nM
HDAC6 IC_{50} = 10.5nM



3

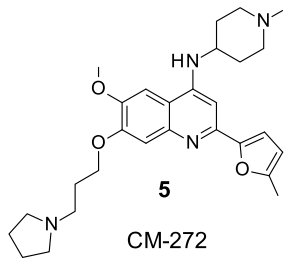
Quisinostat

HDAC1 IC_{50} = 0.11nM
HDAC2 IC_{50} = 0.33nM
HDAC3 IC_{50} = 4.86nM
HDAC6 IC_{50} = 76.8nM



4

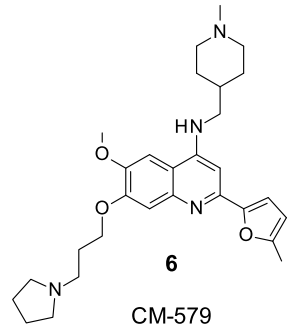
DNMT1 69.88% at 100 μM
DNMT3A 23.39% at 100 μM
DNMT3B 48.53% at 100 μM
HDAC1 IC_{50} = 56.84 nM
HDAC6 IC_{50} = 17.39 nM



5

CM-272

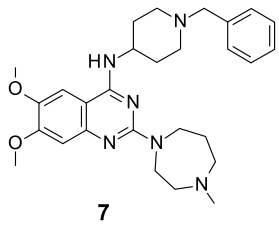
IC_{50} G9a = 8 nM
IC_{50} DNMT1 = 382 nM



6

CM-579

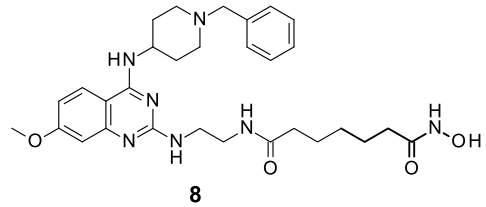
IC_{50} G9a = 16 nM
IC_{50} DNMT1 = 32 nM



7

BIX-01294

IC_{50} G9a = 1200 nM
IC_{50} DNMT1 > 10000 nM



8

IC_{50} G9a (H3K9Me2 ICW) = 7.136 μM
IC_{50} HDAC (cellular histone deacetylase assay) = 5.735 μM

approved: SAHA (Vorinostat, **1**), Belinostat, Panobinostat (LBH-589, **2**), Romidepsin (Depsipeptide), and Chidamide,[3,4] the latter in China only. The clinical development of HDACi is hampered by dose-limiting toxicity, which can lead to poor single agent efficacy. Given that combination regimens are the mainstay of modern cancer therapy to achieve optimal clinical efficacy and the interplay between DNA methylation and histone deacetylation,[5,6] combination studies of HDACi and DNMTi have been pursued, which demonstrate a synergistic *in vitro* and *in vivo* antitumor activity and the induction of tumor suppressor genes (TSGs).[6−11] As additive toxicity is often observed with combination therapy,[12] dual DNMT and HDACi may overcome this hurdle.[13]

Only a few compounds have been reported having this dual DNMT/HDAC inhibitory profile: psammaplins[14] (although its DNMT inhibitory activity is controversial[15]) and related

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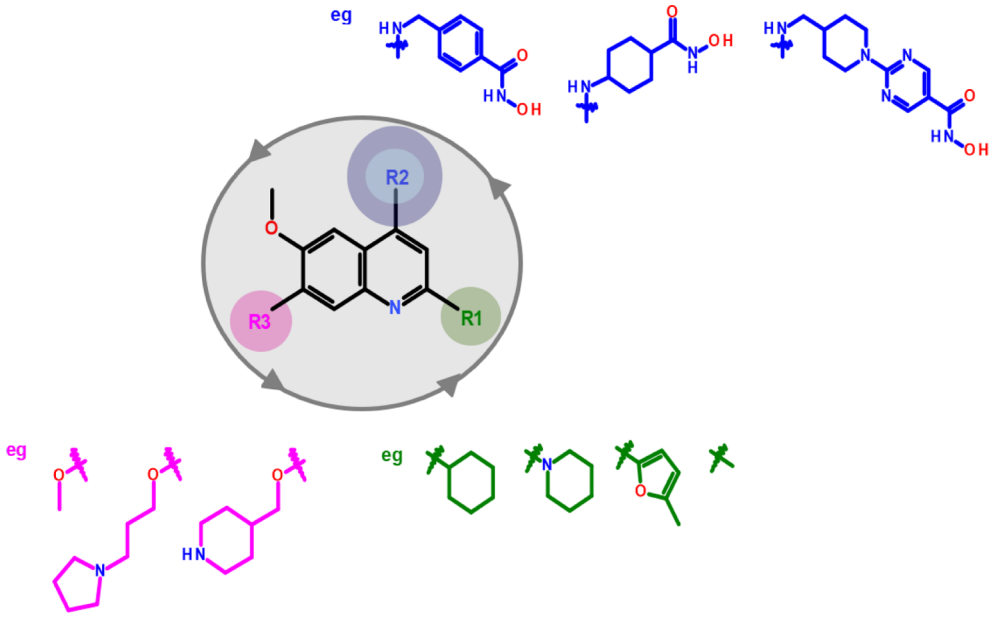

Figure 1. Focused exploration around three diversity points (R1, R2, and R3) of the quinoline ring to achieve first-in-class multitarget epigenetic inhibitors targeting DNMT1, HDAC, and, optionally, G9a—some examples are illustrated.

analogues,[16] (−)-epigallocatechin-3-gallate,[17] DC-517,[18] and NSC-319745-based hydroxamic acid derivatives,[19] these last being claimed as the first *de novo*-designed dual DNMT−HDAC molecules. However, as exemplified with the advanced compound **4** in Chart 1, the NSC-319745-based chemical series still lacks potent DNMT1 inhibitory activity (e.g., <70% inhibition at 100 μM). In the same line, DC-517-based analogues (e.g., C02S) have IC_{50} values in the low micromolar range against DNMTs and HDAC1.[18]

Here, considering polypharmacology as an attractive strategy to overcome the main limitations of the single target therapy leading to a superior therapeutic effect and a reduction of potential mechanism(s) of drug resistance,[20] we set out with the goal of designing novel molecules able to inhibit DNMT and HDAC simultaneously. The chemical structures of our proprietary non-nucleoside epigenetic inhibitors CM-272 (**5**) and CM-579 (**6**) served as starting points because of their good potency against DNMT1 (IC_{50} of 382 nM and 32 nM, respectively, Chart 1) and because they reversibly bind at the substrate-binding site.[21] Of note, these compounds display also nanomolar inhibitory activity against G9a (EHMT2), a histone methyltransferase responsible for the mono- and di-methylation of the lysine 9 of the histone 3 (H3K9).[21,22] We postulated that combined H3K9 hypomethylation and hyperacetylation as a result of concurrent inhibition of G9a and HDAC should additionally contribute to relieve transcriptional repression of TSG in cancer. In fact, the anticancer response of dual G9a/HDAC inhibitory profile has also been examined for a series of quinazoline derivatives of BIX-01294 (**7**), exemplified by compound **8** in Chart 1.[23] Therefore, achieving first-in-class molecules as DNMT1, HDAC and, optionally, G9a inhibitors targeting two or three different epigenetic marks simultaneously should expectedly result in chemical probes to validate the feasibility of the proposed multitarget epigenetic inhibition (dual and triple inhibition, IC_{50} < 10 μM against each target of interest) as well as to study epigenetic targets from a mechanistic perspective (e.g., role in gene transcription) and to analyze their phenotypic and antiproliferative responses.

Based on the well-established pharmacophore of HDACi and structural information available, incorporation of HDAC inhibitory activity to our chemical series seemed initially achievable considering the predicted binding mode of compounds **5** and **6** at the substrate-binding site of both methyltransferases; then, to achieve this goal, we explored around R2 (Figure 1). Moreover, owing to the structural knowledge gained from the SAR exploration of our lead compounds **5** and **6** and the optimization of **7** toward more potent G9a inhibitors,[24,25] we hypothesized that the inhibitory activity against G9a might be compatible with DNMT1 and HDAC inhibition to yield a triple epigenetic inhibitor; therefore, an exploration around R3 was also performed (Figure 1).

Thus, using knowledge- and structure-based approaches, we designed a synthetically feasible focused exploration around the quinoline scaffold; the synthetic approach enables to explore three diversity points (Figure 1) that are key for primary activities. This exploration led to first-in-class multitarget epigenetic inhibitors targeting G9a, DNMT1, and HDAC. Herein, we report the discovery of chemical probes (e.g., **9a** and **12a**) that confirm the feasibility of the proposed multitarget epigenetic inhibition, which was not only validated by biochemical assays but also by their corresponding functional cellular responses: activities *versus* these epigenetic targets, in both validation scenarios, range from nM to low μM (up to ∼1−2 μM). In addition, this initial exploration led to basic SAR guidelines to achieve these two target compound profiles, (a) G9a, DNMT1, and HDAC inhibition as well as (b) DNMT1 and HDAC inhibition, and to identify absorption, distribution, metabolism, and excretion (ADME) properties that may require an optimization (e.g., permeability and solubility). From a drug discovery perspective, these chemical probes are key starting points to become optimized lead compounds according to project requirements (e.g., specific inhibition profile for selected targets, therapeutic window, ADME properties, etc.), fulfilling the corresponding target product profile.

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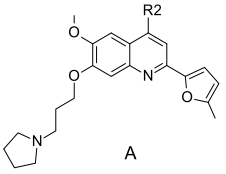
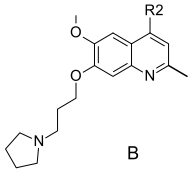
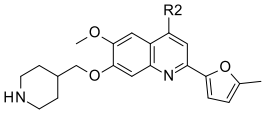
Table 1. Hybrid Compounds with Triple HDAC, DNMT1, and G9a Inhibitory Activity: Exploring Around R2 and R3 Positions[a]







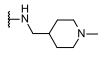
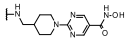
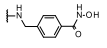
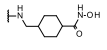
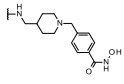
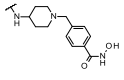
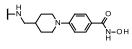
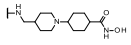
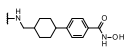
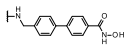
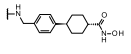
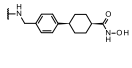
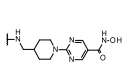
Cpd	Core	R2	G9a IC_{50} nM	DNMT1 IC_{50} nM	HDAC1 IC_{50} nM	HDAC2 IC_{50} nM	HDAC3 IC_{50} nM	HDAC6 IC_{50} nM
1[30,b]			>10000	>10000	43.9 *(7.4)*	93.6 *(24.5)*	63.9 *(14.8)*	3.9 *(0.8)*
5[21,b]	A		8 *(4.4)*	382 *(74.1)*	>10000	>10000	>10000	>10000
6[21,b]	A		16 *(8.7)*	32 *(10.6)*	>10000	>10000	>10000	>10000
9a	A		269 *(71)*	1160 *(300)*	3 *(0.4)*	21 *(1.1)*	5 *(1.3)*	152 *(5.6)*
9b	A		471 *(43.1)*	795 *(119)*	9 *(3.3)*	60 *(0.3)*	21 *(4)*	11 *(1.2)*
9c	A		55 *(8.2)*	531 *(67.2)*	22 *(2.8)*	159 *(3.5)*	109 *(14)*	34 *(22.1)*
9d	A		46 *(0.7)*	167 *(7.1)*	524 *(137)*	N.D.	N.D.	53 *(9.1)*
9e	A		47 *(3.1)*	318 *(9.9)*	147 *(24.1)*	N.D.	N.D.	39 *(12.7)*
9f	A		269 *(26.2)*	417 *(29.7)*	78 *(11.9)*	N.D.	N.D.	67 *(31.3)*
9g	A		38 *(0.2)*	566 *(146)*	>20000	N.D.	N.D.	>20000
9h	A		3100 *(1018)*	2760 *(919)*	34 *(0.8)*	N.D.	N.D.	122 *(27.6)*
9i	A		2240 *(459.6)*	2570 *(488)*	45 *(2.6)*	N.D.	N.D.	127 *(29)*
9j-*trans*	A		1650 *(346.5)*	2270 *(297)*	3320 *(750)*	N.D.	N.D.	9620 *(792)*
9j-*cis*	A		1920 *(360.6)*	1431 *(719)*	115 *(0.7)*	N.D.	N.D.	351 *(77.8)*
9k	A		25 *(11)*	691 *(190)*	415 *(70.7)*	N.D.	N.D.	133 *(37.5)*
10a	B		4 *(0.8)*	555 *(211)*	7 *(0.4)*	N.D.	N.D.	350 *(201)*
10b	B		34 *(6.4)*	2040 *(205)*	17 *(6.9)*	N.D.	N.D.	118 *(15.6)*
11	C		2065 *(813.2)*	1140 *(315)*	6 *(0.5)*	N.D.	N.D.	351 *(37.5)*

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Table 1. continued

[a]For data in Tables 1−3 and Chart 1, all IC_{50} values are the average of at least two independent replicates performed at different days. If the absolute pIC_{50} difference was higher than 0.3 log units, additional measurements were performed until satisfying the experimental error (by discarding individual results with values outside 2 MADs of the mean value). Standard Deviations are reported together with the corresponding IC_{50} values in brackets and *in italics*. N.D. = not determined. [b]**1** (reference pan-HDACi),[30] **5** (dual G9a and DNMT1 inhibitor, potent G9a inhibition),[21] and **6** (dual G9a and DNMT1 inhibitor, potent DNMT1 inhibition)[21] are utilized as positive controls for all biochemical assays reported in Tables 1−3. Synthetic approaches for all new molecules are shown in Scheme 1 (compounds **9a−k**), Scheme 2 (**10a−b**) and Scheme 3 (**11**).

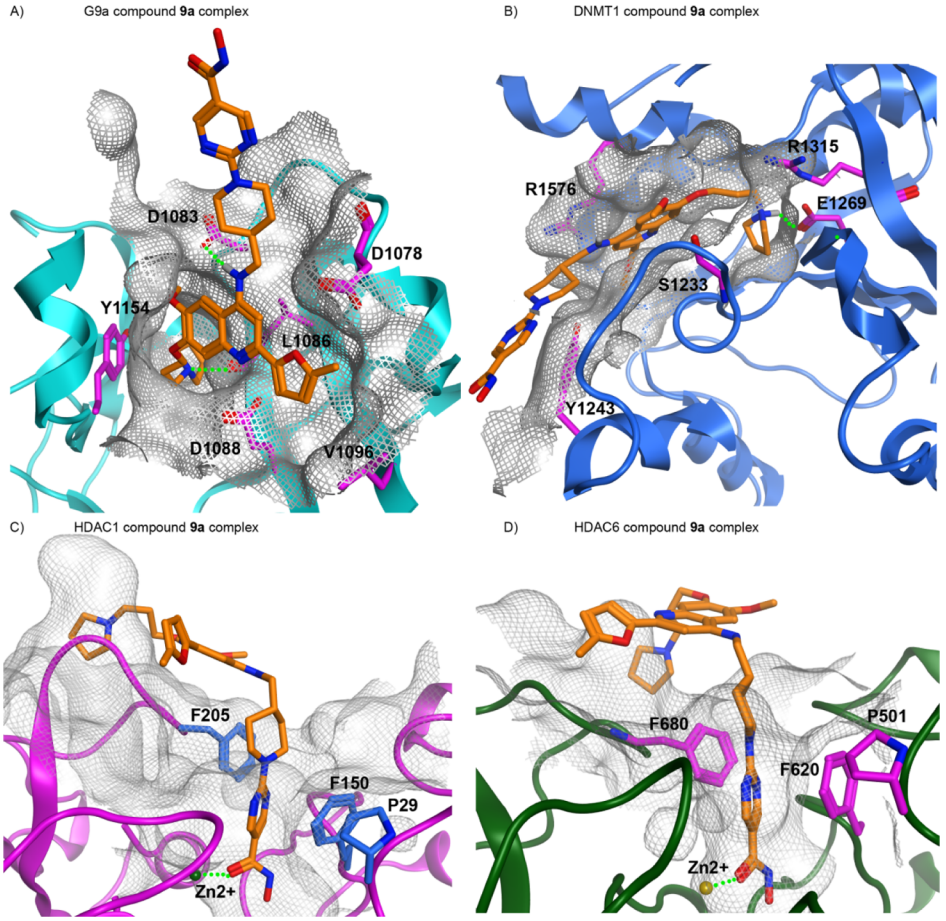

Figure 2. Predicted complex of compound **9a** with G9a [(A) PDB accession code: 3RJW],[25] DNMT1 [(B) PDB accession code: 4DA4],[36] HDAC1 [(C) PDB accession code: 4BKX][37] and HDAC6 [(D) PDB accession code: 5EDU][38]—experimental validation of proposed binding modes will be experimentally performed by biophysical methods in due course.

As mentioned above, DNMT1 and HDAC are molecular targets of FDA-approved drugs for the treatment of hematologic malignancies; however, multiple myeloma (MM) still remains incurable.[26] Despite approval by the FDA and the EMA of the pan-HDACi **2** in combination with bortezomib and deixamethasone for the treatment of relapsed or refractory MM,[27] this is still an unmet medical need. Taking into account that not only histone 3 (H3) acetylation is altered in MM patients but also the DNA methylation pattern,[28,29] a combination of HDAC and DNMT1 inhibition may be an adequate therapeutic strategy. In fact, very recently it was shown that a combination of azacitine and BG45 (HDACi) exhibited synergistic cell growth inhibition of MM tumor cells and induced cell growth inhibition in *in vivo* models.[6]

Thus, the antiproliferative response of these chemical probes was tested against MM tumor cells MM1.S. Those molecules with a potent antiproliferative response (GI_{50}), **9a** as a triple inhibitor and **12a** as a dual inhibitor, were selected to monitor their corresponding functional cellular responses: histone-3 acetylation, DNA hypomethylation, and decreased histone-3 methylation at lysine-9. This exploration also led to the identification of compound **12a** (CM-444) as a pharmacological tool compound: suboptimal but adequate ADME and pharmacokinetic (PK) profiles as well as therapeutic window to perform an *in vivo* proof of concept. *In vivo* efficacy of **12a** was assessed in a xenograft mouse model of human MM.

RESULTS

Rational Design of Hybrid Compounds with HDAC, DNMT1, and G9a Inhibitory Activity. The classical pharmacophore for HDAC inhibition consists of a (i) a zinc-binding group (ZBG) that chelates the zinc ion in the active site, (ii) a recognition capping group that interacts with the rim of the catalytic tunnel, and (iii) a hydrophobic linker connecting the ZBG and the cap group. This pharmacophore pattern has been successfully exploited to derive a plethora of

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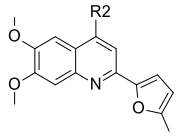
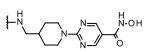
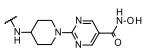
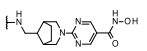
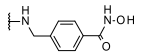
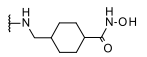
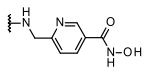
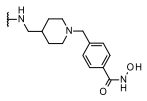
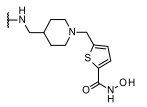
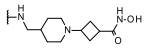
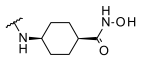
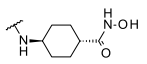
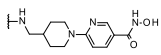
Table 2. Hybrid Compounds with Dual DNMT1 and HDAC Activity: Exploration of the 4 Position[a]



Cpd	R2	G9a IC50 μM	DNMT1 IC50 nM	HDAC1 IC50 nM	HDAC2 IC50 nM	HDAC3 IC50 nM	HDAC6 IC50 nM
12a		>10	2160 *(648)*	7 *(2.7)*	51 *(1)*	18 *(5.4)*	531 *(67.2)*
12b		>10	7140 *(827)*	63 *(2.7)*	409 *(30.4)*	73 *(18.9)*	343 *(78.5)*
12c		>10	1680 *(14.1)*	22 *(0.1)*	125 *(2.1)*	33 *(7.5)*	239 *(99)*
12d		>10	5400 *(1570)*	14 *(2.6)*	91 *(11.9)*	44 *(10)*	22 *(16.5)*
12e		>10	2850 *(183.9)*	38 *(7)*	274 *(14.1)*	206 *(30.4)*	41 *(6.5)*
12f		>10	>10000	87 *(3)*	N.D.	N.D.	204 *(79.9)*
12g		>10	267 *(30.4)*	330 *(90.5)*	N.D.	N.D.	84 *(17.9)*
12h		>10	323 *(20.5)*	303 *(39.6)*	N.D.	N.D.	66 *(19.2)*
12i		>10	540 *(65.1)*	453 *(14.9)*	N.D.	N.D.	3180 *(1032)*
12j-*cis*		>10	2660 *(191)*	396 *(7.1)*	N.D.	N.D.	2890 *(735)*
12j-*trans*		>10	4180 *(381.8)*	>4000	N.D.	N.D.	>20000
12k		>10	8410 *(721.2)*	144 *(10.6)*	N.D.	N.D.	465 *(82)*

[a]N.D. = not determined. A corresponding synthetic approach is shown in Scheme 4 (compounds **12a**–**k**).

novel multifunctional HDACi compounds, most of them bearing a hydroxamic group as the ZBG.[10,33] Compounds **5** and **6** are substrate competitive inhibitors against G9a and DNMTs, with predicted binding modes established by docking and consistent with SAR.[21,34,35] Examination of these protein–ligand complex models suggested that linking a hydroxamic moiety to the methylpiperidine (position 4 of the quinoline ring; R2 in Figure 1) would project this ZBG substituent toward the solvent exposed area of both, G9a and DNMT, and be well tolerated from a potency perspective. From the viewpoint of HDAC inhibitory activity, the quinoline core of **5** and **6** would serve as a cap group. Following this rationale, and owing to its chemical similarity, the pyrimidylhydroxamic acid of quisinostat (**3**) was incorporated into **6** to yield compound **9a** (Table 1 and synthesis in the Chemistry Section). As shown in Figure 2, this compound retains the binding mode of the parent compound into G9a and DNMT1 and fits predictably well into the binding site cavities of HDAC1 and HDAC6. These two HDAC isoforms were chosen for routinely biochemical screening as representative of class I (HDAC1)

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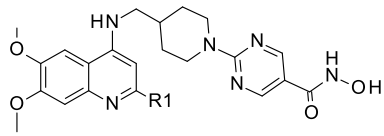
and class IIb (HDAC6) HDAC isoforms. In fact, compound **9a** is a potent HDACi, with a preference for class I (HDAC1, HDAC2, and HDAC3 IC_{50} of 3, 21, and 5 nM) over class IIb isoform (HDAC6 IC_{50} of 152 nM). For the G9a and DNMT1 profiles, a significant drop in activity was observed compared to the parent compound **6** although **9a** satisfies our initial requirement of targeting the three epigenetic families (respective G9a and DNMT1 IC_{50} values of 269 and 1160 nM, compared to 16 and 32 nM for **6**). On this basis, various analogues with different linker rings with varying lengths, hydrophobicities, and flexibilities were synthesized (compounds **9b**−**9k**, Table 1). In general, flexible alkyl rings (**9c**) and methylene-homologated rings (**9d**, **9e**) yielded compounds with improved G9a (IC_{50} < 100 nM), DNMT1 (IC_{50} < 500 nM) and HDAC6 (IC_{50} < 100 nM) potencies compared to that of compound **9a**, although at the cost of losing at least one log unit of HDAC1 activity. Conserving the basic nitrogen of the piperidine ring confers the highest potency against G9a (**9d**, **9e**, and **9g**),[34,35] with the striking exception of the cyclohexyl moiety of **9c** (G9a IC_{50} of 55 nM), the triple inhibitor compound in Table 1 with the most promising well-balanced biochemical profile against all targets. Substitution of the 5-methyl-2-furyl group of the initial hit **9a** by methyl to yield **10a** was beneficial for G9a and DNMT activities while retaining a similar HDAC inhibitory profile to that of **9a**. Finally, compound **11** was designed in an attempt to increase the DNMT1 potency of **9a** by incorporation of a 4-piperidyl moiety at the 7 position.[35] As this replacement of the 7-(3-pyrrolidin-1-ylpropoxy) group did not meet the expected improvement, SAR exploration of the 7 position (R3, Figure 1) with alternative groups with basic nitrogens was no longer continued.

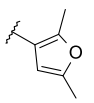
Hybrid Compounds with Dual HDAC and DNMT1 Inhibitory Activity. During the course of our SAR exploration around compounds **5** and **6**, it was noticed that removal of the basic nitrogen at position 7 of the quinoline scaffold (R3, Figure 1) was detrimental for G9a activity.[35] This is consistent with the predicted role of the 7-(3-pyrrolidin-1-ylpropoxy) group mimicking the lysine side chain (Figure 2A). Similar conclusions were drawn during the optimization of **7**[25] that can be explained on the basis of missing key interactions with Leu1086 (hydrogen-bond) and Tyr1154 (cation−π interaction) (Figure 2A). The impact of replacing this lysine mimic group by a methoxy group was initially less impacting on DNMT1 activity for the quinoline analogues.[35] With the goal of blocking G9a inhibitory activity, a handful of 7-methoxyquinolines with the optimal linkers from previous SAR explorations were prepared (**12a**, **12d**, **12e**, **12g**, Table 2), as well as some additional linkers designed to constrain the conformation of the hydroxamic moiety (**12b** and **12j**, Table 2). As expected, all of them were inactive against G9a (IC_{50} > 10 μM). DNMT1 activity was less affected, spanning mid-nanomolar (again, for the flexible methylene-homologated rings of **12g** and **12h**) to low-micromolar ranges. For HDACs, inhibitory profiles between corresponding matched pairs in Table 1 are in general consistent (e.g., **12a** vs **9a**, **12d** vs **9b** and **12e** vs **9c**), highlighting the minimal impact of the methoxy group moiety at the rim surface of the HDACs.

Considering a well-balanced contribution of the primary targets, compounds **12g** and **12h** had an adequate profile (IC_{50} ∼ 300 nM vs DNMT1 and HDAC1; and, ∼100 nM against HDAC6). On the other hand, giving special emphasis to HDAC1 inhibition (IC_{50} < 50 nM), the pyrimidylhydroxamic group of **12a**, its azabicyclo analogue **12c**, and the cyclohexyl linker (**12e**) were among the best compounds in Table 2 (their IC_{50} vs DNMT1 are ∼1−3 μM).

Finally, a small exploration of the 2-position of the quinoline (R1, Figure 1) was carried out by keeping constant the initial pyrimidylhydroxamic group of **12a** and replacing its heteroaryl ring, 5-methyl-2-furyl, by a methyl (**13a**), cyclohexyl (**13b**), phenyl (**13c**), N-linked piperidine (**13d**), 2,5-dimethyl-3-furyl (**13e**), and 5-methylthiophen-2-yl (**13f**) (Table 3). However,

Table 3. Hybrid Compounds: Exploration of the 2 Position (R1)[a]



Cpd	R1	G9a IC_{50} μM	DNMT1 IC_{50} μM	HDAC1 IC_{50} nM	HDAC6 IC_{50} nM
13a	-CH_3	7.2 *(0.9)*	>10	3 *(0.03)*	253 *(55.1)*
13b		>10	>10	2 *(0.06)*	111 *(14.1)*
13c		>10	>10	3 *(0.02)*	230 *(48.8)*
13d		>10	>10	3 *(0.01)*	234 *(2.1)*
13e		>10	>10	5 *(0.6)*	126 *(24.1)*
13f		>10	>10	17 *(3.5)*	1258 *(879)*

[a]Corresponding synthetic approach is shown in Scheme 5 (compounds **13a**−**f**).

compared to **12a**, this exploration had a minor impact on the HDAC profile (HDAC1 IC_{50} values are ∼10 nM); all these substitutions were detrimental to DNMT1 inhibition: IC_{50} values > 10 μM for all these new molecules are reported in Table 3, resulting in HDAC inhibition alone.

These initial explorations around these three diversity points (R1, R2, and R3) borne by the quinoline scaffold, represented in Figure 1 and exemplified in Tables 1−3, led to some key general conclusions; a preliminary SAR guideline:

- Substituents at R1, position 2 of the quinoline ring, have a huge impact on DNMT1 activity; in fact, among all explored analogues (Table 3), only the 5-methy-2-furyl (**12a**) was able to maintain a capacity of inhibition (IC_{50} < 10 μM).
- The classical pharmacophore for HDAC inhibition (containing a ZBG, e.g., hydroxamic acid[33,39] or *ortho*-aminoanilides[40,41]) should be located at R2, position 4

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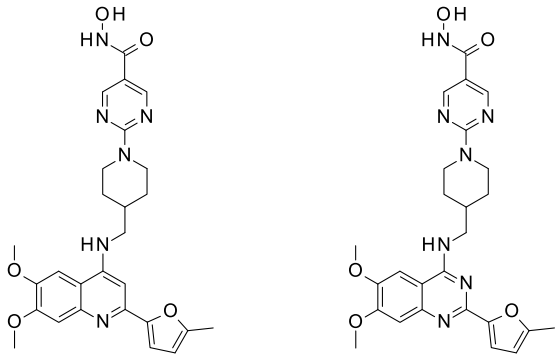
of the quinoline ring, thus causing minimal impact on G9a and DNMT1 inhibition (solvent exposed according to the proposed binding modes) and, on the other hand, quinoline serves as the cap group for binding to HDAC—as described in Figure 2. This substitution pattern led to potent inhibition of HDAC enzymatic activity (Tables 1−3)

- The 7-(3-pyrrolidin-1-ylpropoxy) group mimics the lysine side chain; then, as previously reported by our group,[35] removal of the basic nitrogen at position 7 of the quinoline scaffold (located at R3) was detrimental for G9a activity. Thus, as illustrated in Table 1 *versus* Table 2, we can easily modulate the G9a inhibitory activity.

Finally, we also explored an alternative scaffold to the quinoline ring: quinazoline. Interestingly, the corresponding quinazoline-based pair of the selected compound **12a** (details below), compound **14** (Chart 2 and synthesis in the Scheme 6), does not exhibit DNMT1 activity (IC_{50} > 10 μM), thereby indicating the impact of the quinoline scaffold on the DNMT1 activity—as previously reported for G9a and DNMT1 inhibitors.[34]

Chart 2. Selected compound 12a and its corresponding quinazoline-matched pair 14.



12a

IC_{50} DNMT1 = 2160 nM

IC_{50} G9a > 10 μM

IC_{50} HDAC1 = 7 nM
IC_{50} HDAC2 = 51 nM
IC_{50} HDAC3 = 18 nM
IC_{50} HDAC6 = 531 nM

14

IC_{50} DNMT1 > 10 μM

IC_{50} G9a > 10 μM

IC_{50} HDAC1 = 7 nM
IC_{50} HDAC2 = 38 nM
IC_{50} HDAC3 = 21 nM
IC_{50} HDAC6 = 506nM

Cellular Response: Antiproliferative Effect and Functional Hallmarks. New molecules fulfilling target compound profiles, (a) G9a, DNMT1, and HDAC inhibition or (b) DNMT1 and HDAC inhibition (Tables 1 and 2), and covering diversity in terms of chemical space and biological responses were selected to test their antiproliferative activity using human cancer cells of MM, cell line MM1.S. From Table 1, only four triple inhibitors did not progress to the cellular assay against MM1.S: those chemical probes which IC_{50} values are >1 μM for more than one target of interest (compounds **9g**, **9h**, **9j-*trans*** and **9j-*cis***); **9i** and **11** were exceptions, diversity in chemical space, and were tested. From Table 2, we also discarded four double inhibitors: compounds the IC_{50} values of which are >8 μM *versus* DNMT1 (**12f** and **12k**) and those molecules the IC_{50} values of which are >1 μM for more than one target of interest (compounds **12j-*trans*** and **12j-*cis***). Exploration around the R1 position (Figure 1) only led to HDACi lack of DNMT1 inhibition (IC_{50} values > 10 μM). Then, for comparison purposes, only the most potent compound from Table 3 progressed to the cellular assay against MM1.S: **13b**.

As seen in Table 4, triple inhibitors exhibited GI_{50} values in the low micromolar range (**9a−i**) comparable to that achieved by G9a-DNMT1 inhibitors **5** and **6** or were inactive below 10 μM (**10a−b**,**11**) possibly due to their poor PAMPA permeability (Pe ∼ <1 nm/s). Dual HDAC-DNMT1 compounds (**12a−12g**) with reduced molecular weight and slightly higher permeability (although still poor permeators, with Pe < 10 nm/s) mostly tended to show GI_{50} < 1 μM. Among them, compound **12a** achieved the most potent antiproliferative response (GI_{50} = 32 nM) close to the reference compound **2** (panobinostat, GI_{50} = ∼ 9 nM), ∼0.5 log units difference, and with decreased toxicity against the healthy hepatic cell line THLE-2 (LC_{50} 794 vs 22 nM); in fact, the therapeutic window of compound **12a** (1.4 log units) is 3 times larger than the corresponding therapeutic window of **2** (0.4 log units)—Table 4. Furthermore, a pairwise comparison between **12a** and the most potent HDAC selective inhibitor of this chemical series (**13b**, Table 3) shows that dual inhibition leads to a more potent antiproliferative activity against MM1.S (>0.75 log units difference) and a better therapeutic window (Table 4). On the other hand, we should also highlight that **12a** is >1.5 log units more potent against MM1.S than reference dual G9a and DNMT1 inhibitors (compounds **5** and **6**).

When tested against other MM cell lines (JJN3, KMS28BM, and H929), compound **12a** also showed good antiproliferative activity with GI_{50} values between 100 and 550 nM. **9a**, as representative of the triple inhibitors (described below), which was also tested *versus* these cell lines and showed more modest activities; in fact, GI_{50} values are between 1 and 6 μM (Table 5).

Finally, in order to assess the functional cellular response of inhibiting these epigenetic targets (Tables 1 and 2), two chemical probes were selected as representatives: **9a**, as G9a, DNMT1 and HDACi; and, **12a**, as DNMT1 and HDACi. In fact, **12a** is the most potent molecule among dual inhibitors *versus* MM1.S. On the other hand, **9a** and **9i** are the most potent chemical probes among triple inhibitors; but, because **9a** is >0.9 log units more potent *versus* G9a than **9i**, **9a** was selected as the representative triple inhibitor to monitor its corresponding functional hallmarks. Further biochemical profiling *versus* two DNMT and seven HDAC additional isoforms was also performed (described in Table S1, Supporting Information) for these two selected chemical probes, **9a** and **12a**. These results suggest that inhibition of these DNMT and HDAC additional isoforms may contribute to antiproliferative efficacy against MM1.S cell line as well as to monitor cellular functional responses.

The global levels of histone-3 lysine-9 acetylation (H3K9Ac) and H3K9me2 hallmarks were monitored by Western Blot in MM1.S cells after 48 h of exposure of the selected compounds in a concentration-dependent manner (Figure 3A) as well as in comparison with the reference compounds for each target: decitabine as DNMTi,[2] panobinostat as HDACi[3,4] and A-366 as G9a inhibitor[42] (Figure S1 in the Supporting Information). As shown in Figure 3A, both compounds led to an increase in

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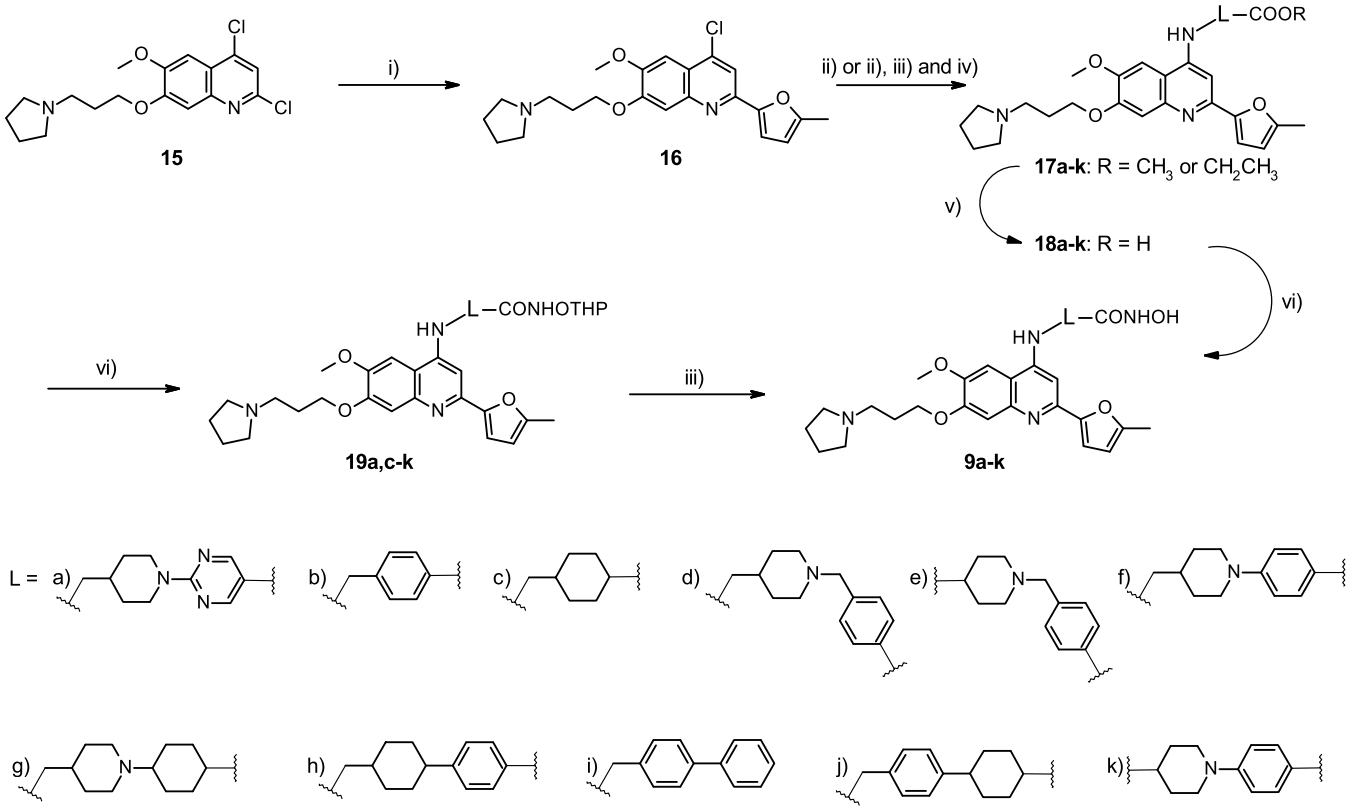
Scheme 1. Synthesis of Compounds 9a−k[a]



[a]Conditions: (i) 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, Na_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O (15:1), 110 °C, MW, 4 h; (ii) corresponding amine, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, 1,4-dioxane, 110−120 °C, 16 h; (iii) HCl/EtOAc(2.0 M) or HCl/MeOH (2.0 M), 20 °C, 30 min to 16 h; (iv) ethyl 4-oxocyclohexanecarboxylate, $ZnCl_2$/diethyl ether, $NaBH_3CN$, MeOH, 40 °C, 15.5 h; (v) LiOH·H_2O, EtOH/H_2O (2:1) or THF/MeOH/H_2O (5:1:3 or 3:1:1), 20−25 °C, 1−16 h; (vi) $THPONH_2$, HOBt, DIEA, EDCI, DMF, 20 °C, 2−16 h.

H3K9Ac at concentrations above 500 nM (**12a**) and 1 μM (**9a**), such as the control compound panobinostat (Figure S1 in the Supporting Information). The higher dose required for compound **9a** might be due to its poorer permeability, given that both compounds are equally active against HDAC1, HDAC2, and HDAC3. In line with the lack of biochemical activity of **12a** against G9a (as reported in Table 2), no alteration of H3K9me2 mark was detected, while this mark was significantly reduced after treatment with doses of compound **9a** above 1 μM (Figure 3A), such as the reference compound A-366 (Figure S1 in the Supporting Information).

On the other hand, DNA methylation alteration was monitored in MM1.S cells by pyrosequencing analysis of several CpGs located in the promoter region of the *POU4F2* gene, which is differentially methylated in MM and involved in the TP53 pathway deregulation. As previously reported,[34] doses below their IC_{50} values and long incubation times of treating every day were used to avoid cell killing and thus to be able to monitor their impact on DNA methylation; in this case, **9a** was tested at 2 μM and **12a** at 10 nM were used for 5 days. Pyrosequencing analysis was focused on the promoter area *POU4F2* (Figure 3B) where treatment with compound **9a** clearly leads to hypomethylation, ∼15%, of the CpG position "3" and incubation with **12a** hypomethylates CpG positions "4" and "5" in ∼10% each. This DNA hypomethylating activity, monitored by *POU4F2* pyrosequencing, was also observed in the JJN.3 cell line treated with **9a** (at 1 μM) and **12a** (at 100 nM) for 5 days (Figure S2 in the Supporting Information).

***In Vivo* Antitumoral Efficacy in MM.** As shown in Table 4, compound **12a** exhibited a potent antiproliferative response against the MM1.S cell line (GI_{50} = 32 nM) and an acceptable therapeutic window (>1 log unit); thus, this molecule was selected to test the efficacy in an *in vivo* xenogeneic mouse model. Compound **9a**, the selected triple inhibitor, exhibited a moderate antiproliferative response (GI_{50} ∼ 2 μM) as well as therapeutic window (<1 log unit), an identical profile to **9i**. A preliminary PK study was performed for **9a**, but the mice (n = 5) died 10 min after its administration at 10 mg/kg (i.p.). Then, the dose was reduced to 5 mg/kg (i.p.); but, 15 min after administration of **9a**, during the blood extraction process, the mice (n = 5) also died (data not shown). Thus, any efforts for *in vivo* testing of **9a** were discontinued.

Before the *in vivo* efficacy test, the corresponding PK study of the compound **12a** was done; in addition, a preliminary ADME profile was also performed (Table 6). This ADME data show that **12a** inhibits two P450 isoforms (1A2 and 3A4) by more than 50% at 10 μM; then, P450 inhibition should be taken into account during the optimization process. Moreover, the reported ADME profiling highlights two key critical aspects: (i) **12a** metabolic stability, in human and mouse cryopreserved hepatocytes (≤50% remaining after 60 min, respectively), is not optimal and (ii) its solubility is poor (below the limit of quantification), <0.987 μg/mL.

These two factors led to suboptimal PKs. The low metabolic stability in hepatocytes translated in a high clearance and a reduced half-life when administered to BALB/c-RAG2$^{-/-}\gamma c^{-/-}$

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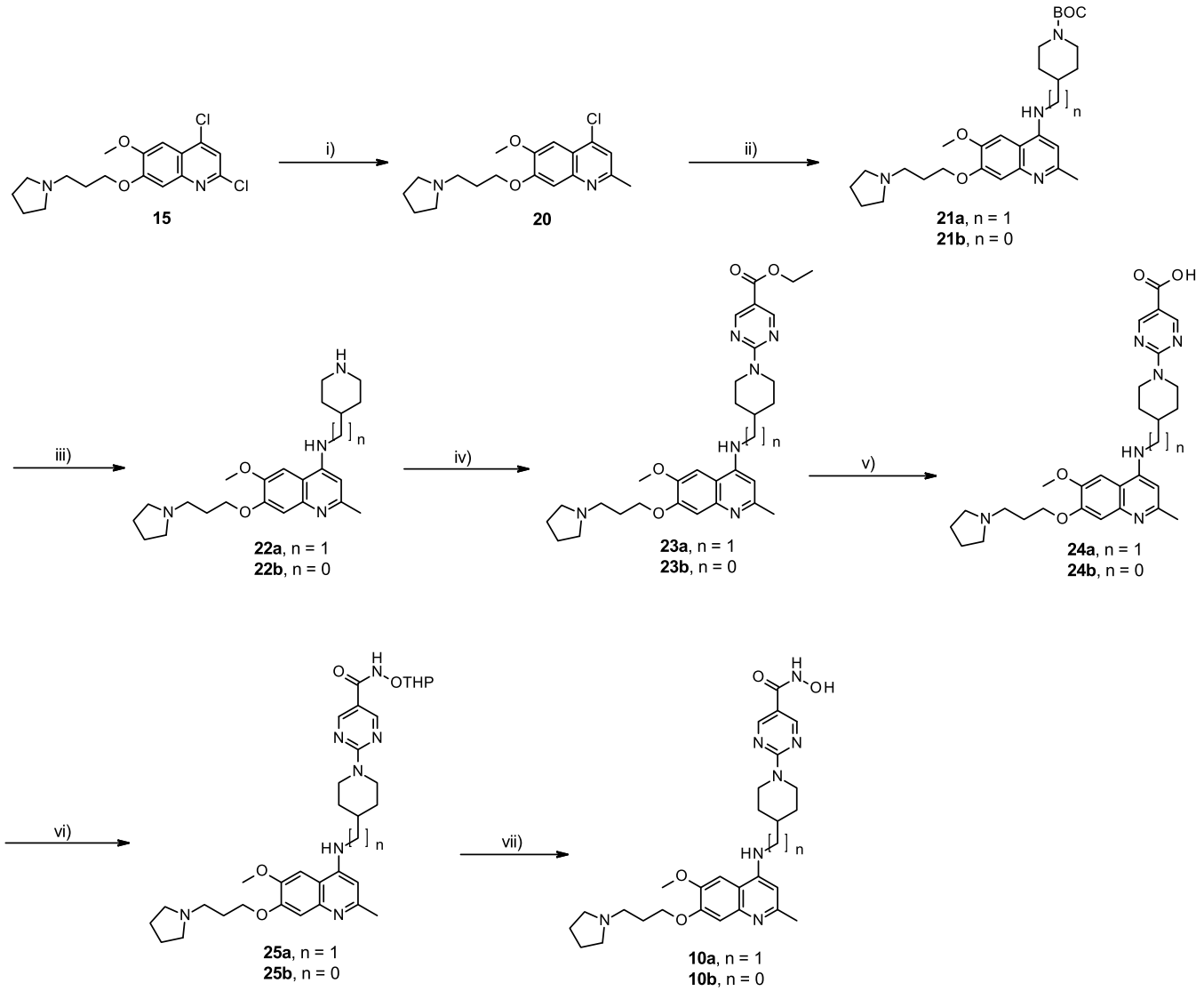
Scheme 2. Synthesis of Compounds 10a–b[a]



[a]Conditions: (i) methyl boronic acid, K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O (10:1), 110 °C, MW, 3 h; (ii) corresponding amine, *t*-BuONa, xantphos, $Pd_2(dba)_3$, toluene, 110 °C, MW, 1–2 h; (iii) HCl/1,4-dioxane (4.0 M), rt, 1–3 h; (iv) ethyl 2-chloropyrimidine-5-carboxylate, K_2CO_3, CH_3CN, rt, 3 h; (v) LiOH·H_2O, THF/MeOH/H_2O (10:1:3), rt, overnight; (vi) $THPONH_2$, HOBt, NMM, EDC·HCl, DMF, rt, overnight; (vii) HCl/1,4-dioxane (4.0 M), rt, 1 h.

mice for PK profiling (Table 7; details are described in the Supporting Information, Tables S2 and S3); in addition, the poor solubility of compound **12a** also precludes its use in an *in vivo* efficacy assay when resuspended in a 100% saline solution. However, if the vehicle is not only a saline solution but also DMSO and Tween 20 (10% each) then, **12a** revealed an acceptable profile with an adequate half-life (~8.5 h) and an acceptable exposure (AUC_{0-24h} = 916.15) to achieve *in vivo* efficacy *versus* the MM1.S cell line with GI_{50} value of 32 nM. Compared with the PK profile of **12a** using the 100% saline solution, the formulation containing DMSO and Tween 20 leads to a half-life that is twice longer as well as to an exposure 1.5 times higher. Additional medicinal chemistry efforts are required to optimize this molecule and should focus, among others, on three critical factors: metabolic stability, solubility, and permeability (its PAMPA, Table 4, is also poor).

Given the acceptable PK profile of **12a**, using saline together with 10% DMSO and 10% Tween 20 as vehicle, this compound was utilized as a pharmacological tool compound to test the *in vivo* efficacy and its mechanism of action (dual DNMT and HDAC inhibition) in terms of tumor growth in a mouse model using human MM xenografts, one of the most widely used models for the evaluation of *in vivo* efficacy of anticancer drugs.[43]

The mouse model showed that tumor growth is prevented using this inhibitor **12a** in tumors induced by subcutaneously injecting 10×10^6 MM1.S cells in BALB/c-RAG2$^{-/-}\gamma c^{-/-}$ mice, a model previously used in several studies.[44] The treatment with compound **12a** started when all mice presented tumors 12 days after myeloma cell inoculation. These mice were then treated with 10 mg/kg (i.p.) of compound **12a** administered daily during 5 consecutive days followed by 2 rest days and sacrificed at day 35 after cell inoculation. The mice were controlled for signs of morbidity (behavior and body weight loss), not observing differences in the body weight of the animals (Figure S3 in the Supporting Information), and the

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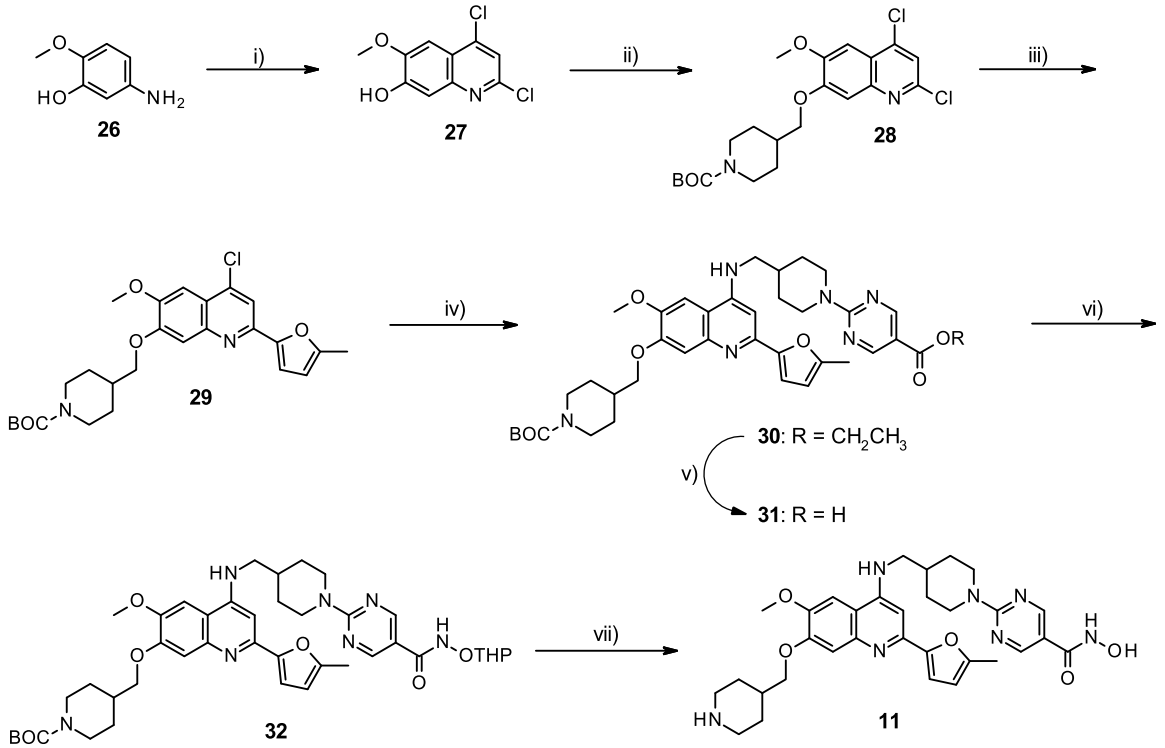
Scheme 3. Synthesis of Compound 11[a]



[a]Conditions: (i) $POCl_3$, malonic acid, 95 °C, 12 h; (ii) *tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate, Cs_2CO_3, DMF, 80 °C, 16 h; (iii) 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane/H_2O (4:1), 90 °C, 16 h; (iv) ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, 1,4-dioxane, 110 °C, 16 h; (v) LiOH·H_2O, THF/H_2O (2:1), 15 °C, 16 h; (vi) $THPONH_2$, HOBt, DIEA, EDCI, DMF, 15 °C, 16 h; (vii) HCl/EtOAc (1.0 M), 15 °C, 16 h.

tumor volume was monitored every 3−5 days. As shown in Figure 4, treatment with **12a** produced a significant (p value < 0.05) overall tumor growth inhibition, average tumor volumes at day 35 of 1788 ± 1164 and 3836 ± 1696 mm^3 for treated and control groups, respectively.

DISCUSSION AND CONCLUSIONS

We presented a detailed account of knowledge- and structure-based design of first-in-class multitarget epigenetic inhibitors targeting DNMT1, HDAC and, optionally, G9a. Synthetic approaches, schemes described below, enabled to explore three diversity points around the quinoline scaffold (Figure 1). These explorations not only identified the impact of each substitution pattern but also the role of each of the growing vectors (R1, R2, and R3) on different epigenetic targets (preliminary SAR described above). In addition, these focused explorations led to chemical probes fulfilling our initial objective (dual and triple inhibition, IC_{50} < 10 μM against each target of interest) as well as to other compounds that only inhibit HDACs (IC_{50} values for DNMT1 and G9a are >10 μM). Furthermore, replacement of the quinoline scaffold by quinazoline eliminates DNMT1 inhibitory activity (IC_{50} > 10 μM), thereby validating the quinoline ring as the central core for the achievement of this multitarget epigenetic inhibition.

Two chemical probes fulfilling the established target compound profiles, (i) **9a** as triple inhibitor (G9a, DNMT1 and HDAC) and (ii) **12a** as double inhibitor (DNMT1 and HDAC), were selected to validate their functional cellular responses and clearly showed the impact on their corresponding epigenetic marks: global levels of H3K9Ac and H3K9me2 as well as DNA methylation levels; assay concentrations, for both chemical probes, ranged from nanomolars to low micromolars (up to ∼1−2 μM).

Taking into account that MM remains still incurable[26] and that different epigenetic layers are altered in MM patients,[28,29] a combination of HDAC and DNMT1 inhibition may be an adequate therapeutic strategy. Thus, those novel multitarget inhibitors showing potent double and triple inhibitory activities were tested *versus* the MM1.S cell line and **12a** showed a potent antiproliferative activity (GI_{50} is 32 nM). Furthermore, pairwise comparisons between molecules of this chemical series, for example, reference G9a and DNMT1 inhibitors (**5** and **6**) as well as the most potent HDAC selective inhibitor of this chemical series (**13b**) *versus* **12a**, show that dual DNMT and HDAC inhibition leads to more potent antiproliferative activity against MM1.S.

Compound **12a** shows a potent antiproliferative activity, exhibits an adequate therapeutic window (>1 log unit) and, based on a special vehicle, a suitable PK was achieved. Thus, **12a** was assayed *in vivo* as a pharmacological tool compound to test its antitumor efficacy in a xenograft mouse model of human MM; a significant efficacy was achieved. However, **12a** is a chemical probe and requires an optimization process to evolve and become a new molecule with optimized drug-like properties: a lead compound. In fact, to overcome its poor ADME profile (special stress on solubility, permeability, and metabolic stability) and achieve an optimal PK, a focused exploration around R2 and R3 positions is currently *on-going*.

The reported chemical probes are key tool compounds (i) to validate the feasibility of this proposal: multitarget epigenetic inhibition, (ii) to define a preliminary SAR guideline (focused

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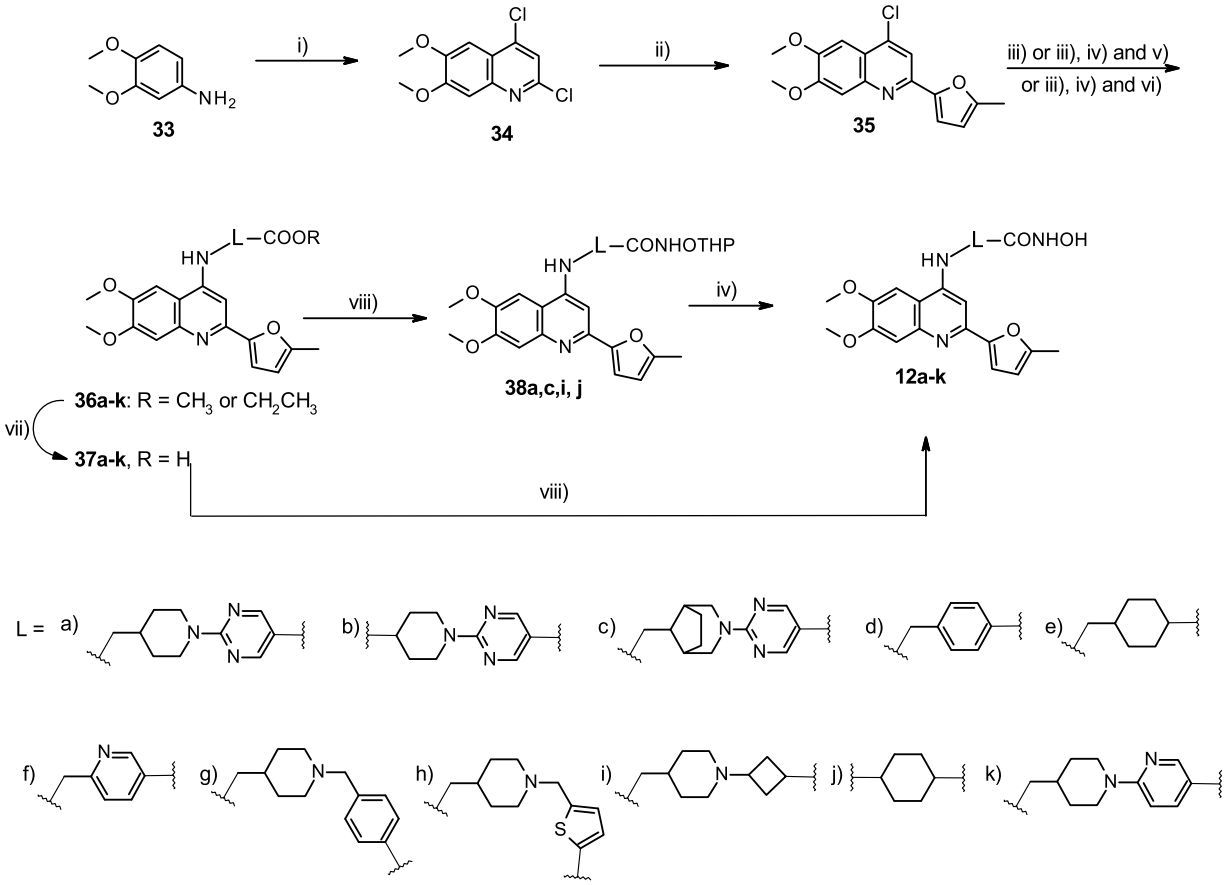
Scheme 4. Synthesis of Compounds 12a−k[a]



[a]Conditions: (i) $POCl_3$, malonic acid, 100 °C, 16 h; (ii) 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane/H_2O (10:1), 90 °C, 16 h; (iii) corresponding amine, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, 1,4-dioxane, 120−140 °C, 12−16 h; (iv) HCl/MeOH (2.0 M) or HCl/EtOAc (1.0 or 2.0 M), 20−25 °C, 20 min −16 h; (v) ethyl 2-chloropyrimidine-5-carboxylate, K_2CO_3, DMF or CH_3CN, 40−50 °C, 12−16 h; (vi) corresponding aldehyde or ketone, $NaBH_3CN$, CH_3COOH or $ZnCl_2$, MeOH, 40−70 °C, 2−15.5 h; (vii) $LiOH·H_2O$, THF/H_2O (2:1) or THF/MeOH/H_2O (6:1:1 or 3:1:1), 15−25 °C, 2−16 h; (viii) $THPONH_2$, HOBt, DIEA, EDCI, DMF, 15−25 °C, 2−16 h.

on a double and triple inhibition: DNMT1, HDAC and, optionally, G9a), as well as to identify critical ADME issues (e.g., permeability and solubility). and (iii) to initiate a new drug discovery project that requires a multitarget epigenetic inhibitor as starting points (e.g., as **12a** for MM) to progress to an optimized lead molecule fulfilling the corresponding target product profile. Thus, these first-in-class molecules are paving the way for achieving multitarget epigenetic inhibition (DNMT1, HDAC, and, optionally, G9a) according to requirements that every drug discovery project may need (e.g., inhibition profile of selected targets, ADME properties, etc.)

CHEMISTRY

The preparation of target compounds is summarized in the following schemes. Compounds **9a−k** (Scheme 1) were synthesized from previously described 2,4-dichloroquinoline **15**,[21] which was converted into the desired key intermediate **16**[34,35] through Suzuki coupling. Then, different substitutions at the 4-position of the quinoline were installed using Buchwald−Hartwig amination conditions and esters **17a−k** were isolated. Hydrolysis of these esters led us to corresponding carboxylic acids **18a−k**. Finally, the desired hydroxamates **9a−k** were obtained by reaction with $THPONH_2$ and acidic cleavage of the protecting group.

Synthesis of compounds **10a** and **10b** is shown in Scheme 2. In this case, compound **15** was reacted with methyl boronic acid and intermediate **20**[34,35] was isolated. Then, amines **22a** and **22b**[35] were prepared by reaction with *tert*-butyl 4-aminopiperidine-1-carboxylate or *tert*-butyl 4-(aminomethyl)-piperidine-1-carboxylate respectively using $Pd_2(dba)_3$ as the catalyst and subsequent deprotection of corresponding intermediates **21a**[35] and **21b**[35] in acidic media. These amines were then substituted with a pyrimidyl ester to obtain compounds **23a** and **23b**. Finally, the desired hydroxamates were obtained by ester hydrolysis, synthesis of THP-protected intermediates **25a** and **25b**, and acidic deprotection.

Next, compound **11** with a 4-piperidyl moiety at the 7-position was prepared as outlined in Scheme 3. In this case, the synthesis started from commercially available aniline **26**, which was converted into 2,4-dichloroquinoline **27**[35] by reaction with $POCl_3$. Then, the piperidyl group at position 7 and 5-methyl-2-furyl group at position 2 of the quinoline were installed under standard conditions to obtain compound **29**.[35] Conversion of this intermediate into desired hydroxamate **11** was achieved using the similar synthetic procedure as described above (Buchwald−Hartwig amination, ester hydrolysis, synthesis of protected hydroxamic acid and removal of THP protecting group).

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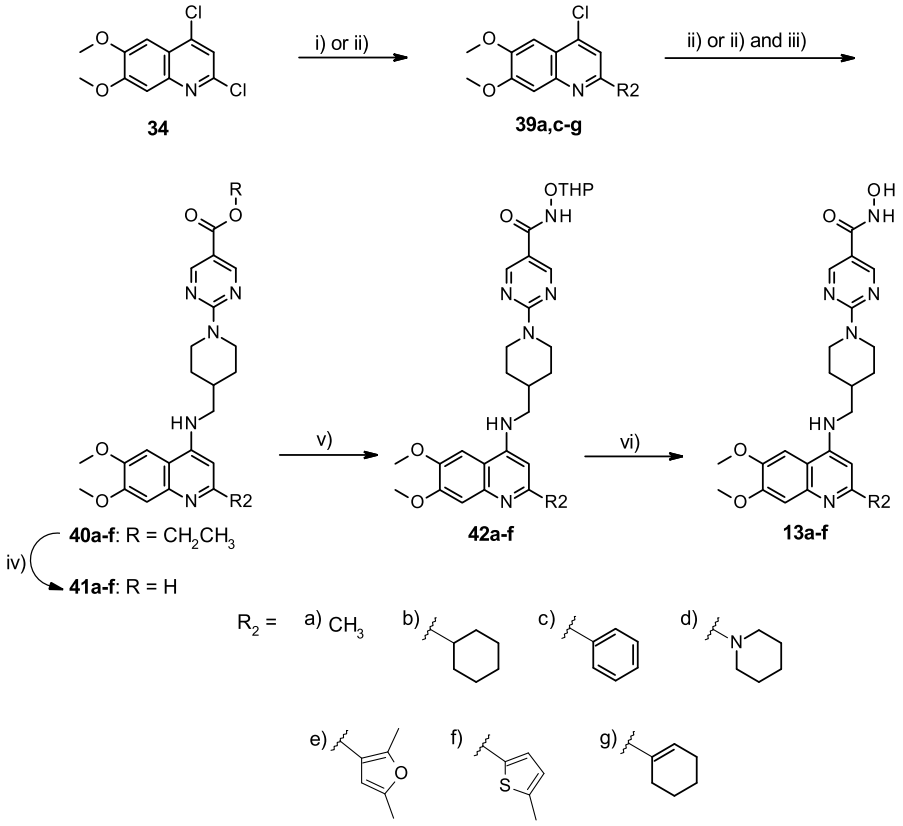
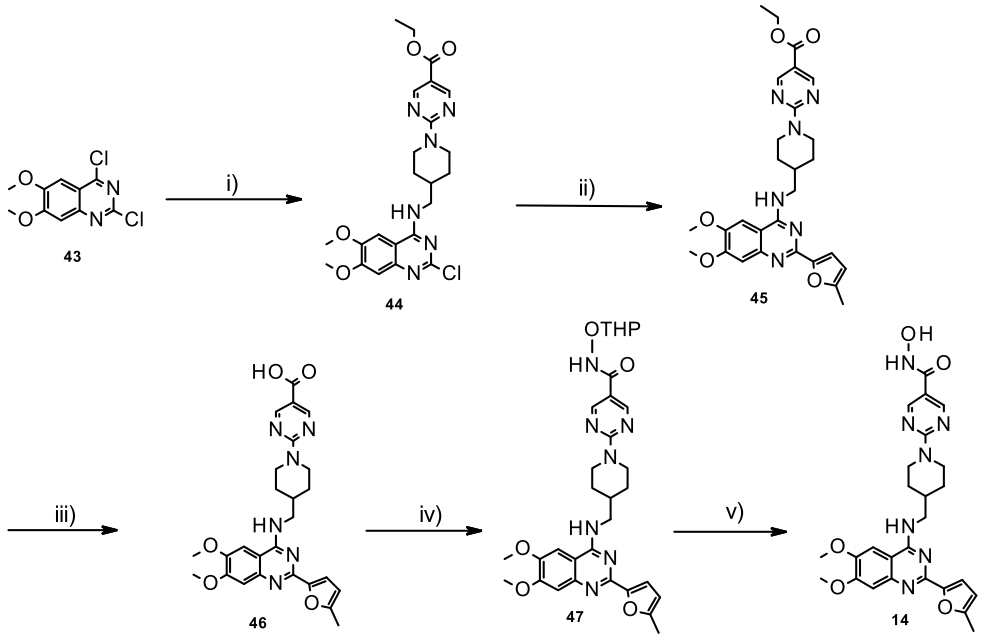
Scheme 5. Synthesis of Compounds 13a−f[a]



[a]Conditions: (i) corresponding boronic ester, $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane/H_2O (10:1 or 5:1), 90−100 °C, 6−16 h; (ii) piperidine or ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, 1,4-dioxane,100−140 °C, 12−48 h; (iii) Pd/C, H_2 (15 Psi), MeOH, 20 °C, 16 h; (iv) LiOH·H_2O, THF/MeOH/H_2O (3:1:1) or THF/H_2O (2:1), 15−25 °C, 16 h; (v) $THPONH_2$, HOBt, DIEA, EDCI, DMF, 15−20 °C, 12−16 h; (vi) HCl/EtOAc (1.0 or 2.0 M), 15−25 °C, 4−16 h.

Scheme 6. Synthesis of Compound 14[a]



[a]Conditions: (i) ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate, K_2CO_3, DMF, 80 °C, 12 h; (ii) 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 100 °C, 12 h; (iii) LiOH·H_2O, THF/H_2O (2:1), 25 °C, 12 h; (iv) $THPONH_2$, HOBt, DIEA, EDCI, DMF, 25 °C, 12 h; (v) TFA, CH_3CN/H_2O (1:1), 60 °C, 5 min.

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Table 4. Antiproliferative Response of Selected Hybrid Compounds against the MM1.S MM Cancer Cell Line and the Healthy Hepatic Cell Line THLE-2

Cpd	MM1.S GI_{50} nM[b]	MM1.S pGI_{50}[c]	THLE-2 LC_{50} nM 72 h[d]	THLE-2 pLC_{50}[e]	PAMPA Pe (nm/s)[f]	therapeutic window[g]
2	8.9 (*0.1*)	8.05	22 (*14.5*)	7.66	14.2 (*0.7*)	0.39
5[21,34]	1041 (*62.1*)	5.97	1780 (*596*)	5.75	12.9 (*1.4*)	0.22
6[21,35]	3842 (*92.1*)	5.42	1300 (*590*)	5.89	11.0 (*0.7*)	toxic[h]
9a	2077 (*409.5*)	5.68	10,900 (*1980*)	4.96	0 (*0*)	0.72
9b	4505 (*2181*)	5.35	11,300 (*2496*)	4.95	1.0 (*0.2*)	0.40
9c	>10,000	<5	26,100 (*5940*)	4.58	0 (*0*)	N.A.[i]
9d	3571 (*1417*)	5.45	3890 (*516.2*)	5.41	0 (*0*)	0.04
9e	4207 (*97*)	5.38	22,050 (*9970*)	4.66	0 (*0*)	0.72
9f	3763 (*42.5*)	5.43	9700 (*367.7*)	5.01	0.5 (*0.7*)	0.42
9i	1811 (*199*)	5.74	13,500 (*0.5*)	4.87	1.1 (*0.9*)	0.87
9k	>10,000	<5	6656 (*82*)	5.18	0.14 (*0.2*)	toxic[h]
10a	>10,000	<5	>100,000	<4	0 (*0*)	N.A.[i]
10b	>10,000	<5	33,250 (*7778*)	4.48	0.75 (*0.6*)	N.A.[i]
11	>10,000	<5	19,700 (*282*)	4.71	0.25 (*0.3*)	N.A.[i]
12a	32 (*27.3*)	7.50	794 (*17.0*)	6.10	5.04 (*0.5*)	1.40
12b	1025 (*73.2*)	5.99	3090 (*438.4*)	5.51	5.96 (*0.58*)	0.48
12c	459 (*19.9*)	6.34	1350 (*21.2*)	5.87	9.59 (*0.66*)	0.47
12d	520 (*29.6*)	6.28	2330 (*155.6*)	5.63	5.34 (*0.5*)	0.65
12e	5826 (*920*)	5.24	9600 (*1590*)	5.02	3.93 (*0.76*)	0.22
12g	217 (*32.3*)	6.66	204 (*110.3*)	6.69	5.56 (*0.32*)	toxic[h]
12h	1938 (*272*)	5.71	2227 (*129*)	5.65	4.01 (*0.1*)	0.06
12i	1985 (*458*)	5.70	10,410 (*1797*)	4.98	0.68 (*0.5*)	0.72
13b	195 (*53.2*)	6.71	2298 (*277*)	5.64	2.1 (*0.7*)	1.07

[a]N.D. = not determined. [b]MM1.S proliferation assays are the average of three replicates on different days. [c]Antiproliferative efficacy *vs* MM1.S (GI_{50} values) are also reported in log units, as pGI_{50}. [d]THLE-2 cytotoxicity results after 72 h of incubation are the average of at least two independent experiments performed on different days. If absolute pLC_{50} difference was higher than 1 log unit, additional replicates were performed until satisfying the experimental error (by discarding individual results with values outside 3 MADs of the mean value). [e]Cytotoxicity *vs* THLE-2 (LC_{50} values) are also reported in log units, as pLC_{50}. [f]The PAMPA assay was performed in triplicate. Depending on permeability values (Pe, nm/s), compounds can be regarded as poor (Pe < 10 nm/s); moderate (10 < Pe < 30 nm/s), or good (>30 nm/s) permeators.[33] [g]The therapeutic Window describes the difference between efficacy (pGI_{50} values vs MM1.S) and toxicity (pLC_{50} values vs THLE-2). [h]Antiproliferative effects against the healthy cell line (THLE-2) are more potent than, or equal to, the tumor cell line (MM1.S): Toxicity. [i]N.A. = not applicable (GI_{50} or/and LC_{50} are undetermined). Standard deviations are reported together with the corresponding experimental values (GI_{50}, LC_{50} and Pe) in brackets and *in italics*.

Table 5. GI_{50} Values of Compounds 9a and 12a *vs* Additional Cell Lines of MM[a]

compound	JJN3, GI_{50} (nM)	KMS28BM, GI_{50} (nM)	H929, GI_{50} (nM)
9a	6035 (*856*)	1299 (*151*)	981 (*189*)
12a	482 (*230*)	547 (*30.5*)	103 (*19.5*)

[a]These results are the average of three replicates on different days. Standard deviations are reported together with the corresponding experimental GI_{50} values in brackets and *in italics*.

Finally, preparation of compounds **12a−k** and **13a−f** with a methoxy group at position 7 and following the same synthetic strategy as described for compounds above is outlined in Schemes 4 and 5. Synthetic strategy for intermediates **51**, **54**, **57**, **60**, **64**, **68**, **73** and **75** is described in Scheme 7.

EXPERIMENTAL SECTION

Chemistry. *General Procedure.* Unless otherwise noted, all starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. Air-sensitive reactions were conducted under N_2. Flash column chromatography was performed on silica gel (230−400 mesh particle size) under standard techniques. Automated flash column chromatography was performed using ready-to-connect cartridges from Varian on irregular silica gel, particle size 15−40 μm (normal phase disposable flash columns) on a Biotage SPX flash purification system. Microwave-assisted reactions were obtained in a Biotage Smith Synthesis microwave reactor. The ^{1}H NMR spectroscopic data were recorded on a Bruker AV400 or VARIAN 400MR spectrometer with standard pulse sequences and ^{13}C NMR on a Bruker AVII-600 equipped with a 5 mm TCI cryoprobe and processed using MestreNova. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and relative to the residual protons of deuterated reagents, which are corrected by tetramethylsilane (TMS). The abbreviations used to explain multiplicities are s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. Coupling constants (*J*) are in hertz. HPLC-analysis was performed using a Shimadzu LC-20AB with a Luna-C18(2), 5 μm, 2.0 × 50 mm column at 40 °C and UV detection. Flow from the column was split to the MS detector (Agilent 1200, 6110MS or Agilent 1200, 6120MS Quadropole), configured with an electrospray source or API/APCI (N2 as the nebulizer gas, with the source temperature at 50 °C, ChemStation LC/MSD quad software). UHPLC-analysis was carried out using a BEH C18, 1.7 mm, 2.1 × 50 column at 40 °C and UV detection. The HPLC or UHPLC purity of all reported compounds, which were subjected to pharmacological evaluation, is ≥95% except for compound **42**, the purity of which is 94.53. No effort was put on yield optimization.

*2-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**9a**).* A solution of compound **19a** (80 mg, 0.114 mmol) in HCl/MeOH (10 mL, 2.0 M) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 10 described in the Supporting Information) to afford pure compound **9a** (29.6 mg, 42%)

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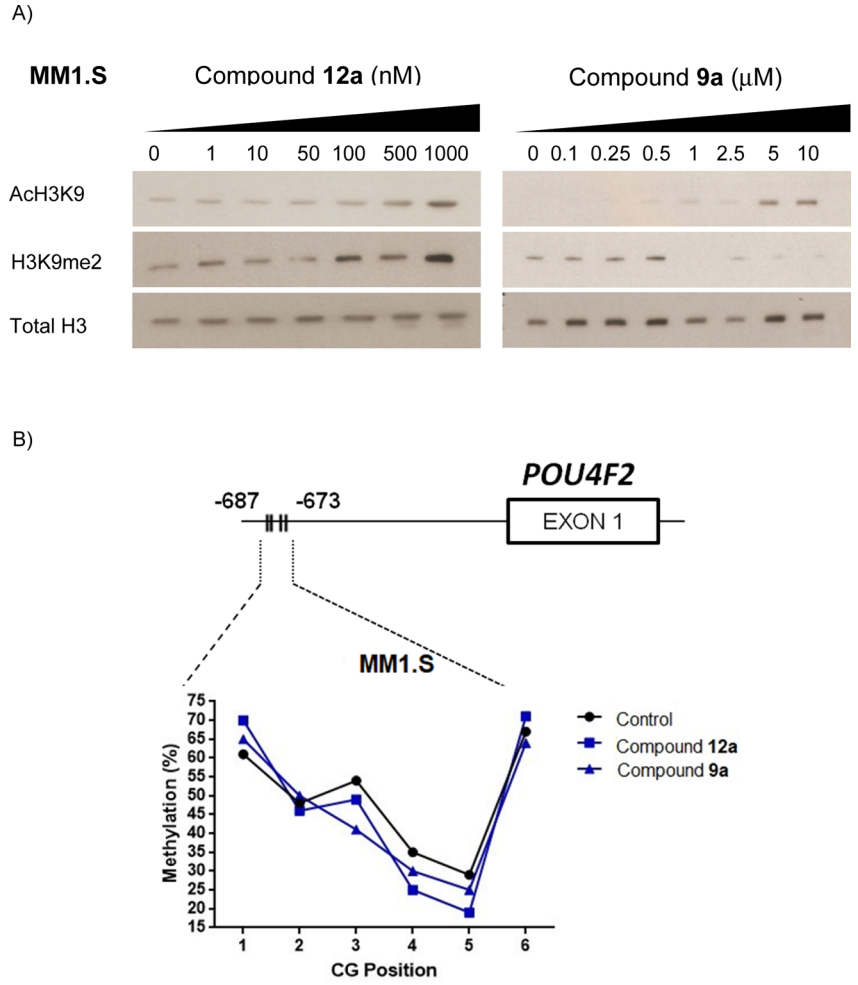

Figure 3. Changes in the epigenetic hallmarks following treatment of MM1.S cells with compounds **12a** and **9a**. (A) H3K9Ac and H3K9me2 dose−response western blots after incubation for 48 h with the indicated dose range of **12a** and **9a**. (B) *POU4F2* gene pyrosequencing after treatment with **12a** at 10 nM and **9a** at 2 μM for 5 days. All assays were performed in duplicate.

Table 6. ADME Profile of Compound 12a

Cpd	1A2 (%)[a]	2C9 (%)[a]	2C19 (%)[a]	2D6 (%)[a]	3A4 (%)[a]	HH (%)[b]	HH ($t_{1/2}$)[c]	HH (CLint)[d]	MH (%)[b]	MH ($t_{1/2}$)[c]	MH (CLint)[d]	kinetic solubility (μg/mL)[e]
12a	58.8	0.0	5.6	10.8	50.8	50.8 (*10*)	71.1	54.2	14.3 (*0.9*)	22.8	410.7	<0.987

[a]% inhibition at 10 μM. [b]% compound remaining after a 60 min incubation in pooled human or C57 mouse hepatocytes (HH and MH respectively); standard deviations are reported in brackets and *in italics*. [c]Half-life (min) in HH and MH. [d]*In vivo* CLint (mL/min/kg) in HH and MH. [e]Below the limit of quantification (BLQ), which is 0.987 μg/mL. All assays were performed in duplicate.

Table 7. PK Profile of Compound 12a[a]

Cpd	route	vehicle	dose (mg/kg)	AUC_{0-24h} (nM h)	$t_{1/2}$ (h)	Cl/F (L/h)	Vz/F (L)
12a	i.p.	saline	10	591.1	3.8	0.8	4.6
12a	i.p.	80% saline, 10% Tween20 and 10% DMSO	10	916.15	8.46	0.53	6.56

[a]Species: BALB/c-RAG2$^{-/-}\gamma c^{-/-}$ mice; i.p. means intraperitoneal administration, saline: NaCl 0.9%; n = 5 and time points: 0.25, 1, 2, 4, 8, and 24 h.

as a yellow solid; mp 126−127 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.64 (s, 2H), 7.74 (s, 1H), 7.53 (d, J = 3.6 Hz, 1H), 7.48 (s, 1H), 7.00 (s, 1H), 6.42 (t, J = 3.2 Hz, 1H), 4.35 (t, J = 5.6 Hz, 2H), 4.05 (s, 3H), 3.85−3.78 (m, 2H), 3.56−3.48 (m, 4H), 3.19−3.10 (m, 3H), 3.02−2.92 (m, 3H), 2.53 (s, 3H), 2.40−2.38 (m, 2H), 2.36−2.23 (m, 3H), 2.09−2.07 (m, 2H), 1.99−1.96 (m, 2H), 1.37−1.31 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ^{13}C NMR (151 MHz, MeOD): δ 164.04, 161.50, 157.63, 156.94 (2C), 154.55, 153.66, 149.46, 144.11, 140.00, 134.50, 115.66, 113.43, 110.62, 109.59, 101.55, 100.51, 91.81, 66.67, 55.73, 54.08 (2C), 53.06, 48.38, 43.61 (2C), 35.78, 29.59 (2C), 25.22, 22.64 (2C), 12.41. ESI-MS m/z: calcd for $C_{33}H_{41}N_7O_5$, 615.3; m/z: found, 616.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.01 min and purity is 98.97%. HRMS $[M + H]^+$: calcd, 616.3242; found, 616.3235, Δ = 1.1 ppm.

*4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]benzenecarbohydroxamic Acid (**9b**).* A mixture of compound **18b** (80 mg, 0.155 mmol), $THPONH_2$(27 mg, 0.232 mmol), HOBt (25 mg, 0.186 mmol), EDCI (36 mg, 0.186 mmol), and DIEA (40 mg, 0.310 mmol) in DMF (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 5 h. Then, the mixture was

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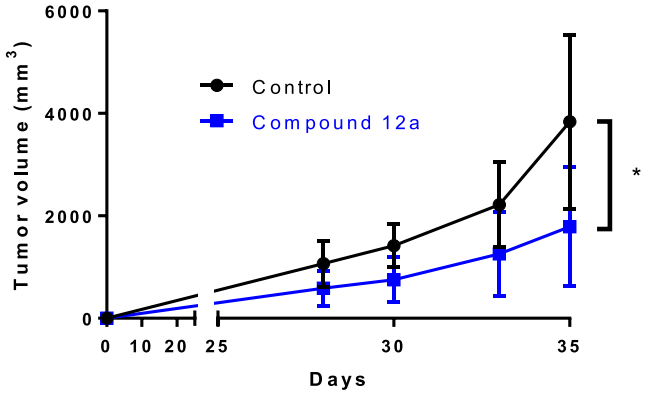


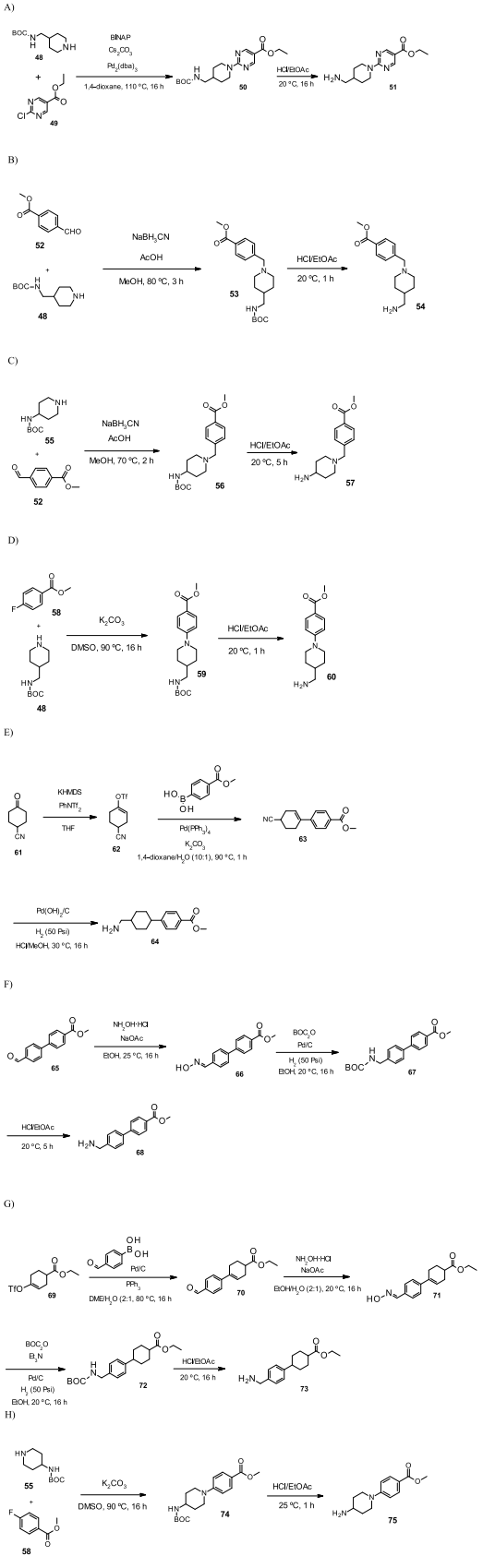
Figure 4. Compound **12a** shows *in vivo* efficacy in an MM1.S tumor model. The tumor volume of MM1.S cells subcutaneously injected and treated with the vehicle (80% saline, 10% Tween 20, and 10% DMSO) or compound **12a** (10 mg/Kg for 5 consecutive days followed by 2 rest days) (n = 9). Statistical significance was calculated by a two-tailed Student's t-test. *p-value ≤ 0.05.

concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 30 described in the Supporting Information) to afford pure compound **9b** (22.4 mg, 27%) as a yellow solid; mp 100−101 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.36 (s, 1H), 11.22 (s, 1H), 9.43 (s, 1H), 7.89 (s, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.63 (s, 2H), 7.53 (d, J = 8.4 Hz, 2H), 6.99 (s, 1H), 6.52 (s, 1H), 4.93 (d, J = 6.0 Hz, 2H), 4.26−4.24 (m, 2H), 3.98 (s, 3H), 3.67−6.64 (m, 2H), 3.37−3.35 (m, 2H), 3.10−3.07 (m, 2H), 2.47 (s, 3H), 2.28−2.26 (m, 2H), 2.08−2.06 (m, 2H), 1.90−1.89 (m, 2H). ESI-MS m/z: calcd for $C_{30}H_{34}N_4O_5$, 530.2; m/z: found, 531.3 $[M + H]^+$. HPLC (*method 1*): Rt is 1.75 min and purity is 96.17%. HRMS $[M + H]^+$: calcd, 531.2602; found, 531.2643, Δ = 7.7 ppm.

*4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]cyclohexanecarbohydroxamic Acid (**9c**).* A solution of compound **19c** (60 mg, 0.097 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 3 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 25 described in the Supporting Information) to afford pure compound **9c** (9.6 mg, 18%) as a yellow solid; mp 127−128 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.73 (d, J = 4.4 Hz, 1H), 7.51 (d, J = 3.6 Hz, 1H), 7.46 (s, 1H), 6.93 (s, 1H), 6.43 (d, J = 3.2 Hz, 1H), 4.36−4.33 (m, 2H), 4.04 (s, 3H), 3.83 (m, 2H), 3.51−3.46 (m, 4H), 3.17 (m, 2H), 2.50 (s, 3H), 2.39−2.36 (m, 2H), 2.21 (m, 2H), 2.09−2.06 (m, 3H), 2.01−1.99 (m, 2H), 1.86−1.83 (m, 3H), 1.62−1.56 (m, 2H), 1.22−1.13 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z:calcd for $C_{30}H_{40}N_4O_5$, 536.3; m/z: found, 537.5 $[M + H]^+$. HPLC (*method 2*): Rt is 3.02 min and purity is 97.84%. HRMS $[M + H]^+$: calcd, 537.3071; found, 537.3126, Δ = 10.2 ppm.

*4-[[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]methyl]-benzenecarbohydroxamic Acid (**9d**).* A solution of compound **19d** (65 mg, 0.091 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 20 °C for 0.5 h. Then, the solution was concentrated to give the residue, which was purified by prep-HPLC (method 31 described in the Supporting Information) to afford pure compound **9d** (15.4 mg, 27%) as a yellow solid; mp 135−136 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.84 (d, J = 8.0 Hz, 2H), 7.71 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 3.6 Hz, 1H), 7.47 (s, 1H), 6.98 (s, 1H), 6.42 (d, J = 3.6 Hz, 1H), 4.41−4.28 (m, 4H), 4.02 (s, 3H), 3.81 (s, 2H), 3.66−3.44 (m, 6H), 3.23−2.91 (m, 4H), 2.49 (s, 3H), 2.43−2.31 (m, 2H), 2.29−1.98 (m, 7H), 1.65 (d, J = 12.4 Hz, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z: calcd for $C_{36}H_{45}N_5O_5$, 627.3; m/z: found, 628.3 $[M + H]^+$. HPLC (*method 1*): Rt is 1.443

Scheme 7. (a−h) Synthesis of Intermediates: 51, 54, 57, 60, 64, 68, 73, and 75[a]



[a]Specific reaction conditions for each synthetic step are explicitly detailed in each scheme (a−h).

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min and purity is 97.63%. HRMS $[M + H]^+$: calcd, 628.3493; found, 628.3558, Δ = 10.3 ppm.

*4-[[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]methyl]-benzenecarbohydroxamic Acid (**9e**).* A solution of compound **19e** (80 mg, 0.115 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 32 described in the Supporting Information) to afford pure compound **9e** (9.3 mg, 13%) as a yellow solid; mp 137−138 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 3.2 Hz, 1H), 7.50 (s, 1H), 7.07 (s, 1H), 6.44 (d, *J* = 2.8 Hz, 1H), 4.47 (s, 2H), 4.36−4.29 (m, 3H), 4.03 (s, 3H), 3.83 (s, 2H), 3.66 (s, 2H), 3.51−3.47 (m, 2H), 3.32−3.31 (m, 2H), 3.17−3.14 (m, 2H), 2.51 (s, 3H), 2.40−2.37 (m, 4H), 2.21−2.06 (m, 6H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m*/*z*:calcd for $C_{35}H_{43}N_5O_5$, 613.3; *m*/*z*: found, 614.4 $[M + H]^+$. HPLC (*method 1*): Rt is 1.428 min and purity is 98.36%. HRMS $[M + H]^+$: calcd, 614.3337; found, 614.3387, Δ = 8.1 ppm.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-benzenecarbohydroxamic Acid (**9f**).* A solution of compound **19f** (85 mg, 0.122 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 20 °C for 0.5 h. Then, the mixture was concentrated to give a residue, which was purified by prep-HPLC (method 25 described in the Supporting Information) to afford pure compound **9f** (25.1 mg, 33%) as a yellow solid; mp 125−126 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.73 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.53 (s, 1H), 7.47 (s, 1H), 7.02−6.95 (m, 3H), 6.42 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 2H), 4.04 (s, 3H), 3.92 (d, *J* = 13.0 Hz, 2H), 3.85 (m, 2H), 3.58 (d, *J* = 6.4 Hz, 2H), 3.50 (t, *J* = 7.0 Hz, 2H), 3.18 (m, 2H), 2.88 (t, *J* = 12.0 Hz, 2H), 2.50 (s, 3H), 2.39 (d, *J* = 5.6 Hz, 2H), 2.22 (m, 2H), 2.09 (m, 3H), 1.98 (d, *J* = 12.0 Hz, 2H), 1.60−1.44 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m*/*z*: calcd for $C_{35}H_{43}N_5O_5$, 613.3; *m*/*z*: found, 614.4 $[M + H]^+$. HPLC (*method 1*): Rt is 1.797 min and purity is 98.70%. HRMS $[M + H]^+$: calcd, 614.3337; found, 614.3369, Δ = 5.2 ppm.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-cyclohexanecarbohydroxamic Acid (**9g**).* A solution of compound **19g** (50 mg, 0.071 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 0.5 h. Then, the solution was concentrated to give a residue, which was purified by prep-HPLC (method 33 described in the Supporting Information) to afford pure compound **9g** (5.3 mg, 12%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 1H), 7.59 (d, *J* = 3.2 Hz, 1H), 7.51 (s, 1H), 6.99 (s, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 4.36 (t, *J* = 5.2 Hz, 2H), 4.04 (s, 3H), 3.83 (s, 2H), 3.64−3.60 (m, 5H), 3.58−3.49 (m, 2H), 3.18−3.09 (m, 5H), 2.50 (s, 3H), 2.40 (d, *J* = 6.0 Hz, 2H), 2.21−2.17 (m, 6H), 2.08 (d, *J* = 8.8 Hz, 5H), 1.95 (d, *J* = 8.8 Hz, 2H), 1.73−1.63 (m, 4H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m*/*z*:calcd for $C_{35}H_{49}N_5O_5$, 619.4; *m*/*z*: found, 620.4 $[M + H]^+$. HPLC (*method 1*): Rt is 1.464 min and purity is 98.13%. HRMS $[M + H]^+$: calcd, 620.3806; found, 620.3818, Δ = 1.9 ppm.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]cyclohexyl]-benzenecarbohydroxamic Acid (**9h**).* A solution of compound **19h** (15 mg, 0.022 mmol) in HCl/EtOAc (3 mL, 2.0 M) was stirred at 20 °C for 1 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 34 described in the Supporting Information) to afford pure compound **9h** (8.5 mg, 64%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.75 (d, *J* = 6.4 Hz, 1H), 7.70−7.68 (m, 2H), 7.51 (d, *J* = 3.6 Hz, 1H), 7.47−7.46 (m, 2H), 7.43−7.33 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 4.37−4.34 (m, 2H), 4.05−4.04 (m, 3H), 3.84 (s, 2H), 3.76−3.74 (m, 1H), 3.56−3.54 (m, 1H), 3.50−3.48 (m, 2H), 3.31−3.18 (m, 2H), 2.77−2.62 (m, 1H), 2.51−2.48 (m, 3H), 2.40−2.37 (m, 2H), 2.22 (s, 3H), 2.09−2.07 (m, 2H), 1.94−1.92 (m, 2H), 1.84−1.82 (m, 4H), 1.59−1.57 (m, 1H), 1.36−1.33 (m, 1H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m*/*z*:calcd for $C_{36}H_{44}N_4O_5$, 612.3; *m*/*z*: found, 613.4 $[M + H]^+$. HPLC (*method 1*): Rt is 2.127 min and purity is 99.19%. HRMS $[M + H]^+$: calcd, 613.3384; found, 613.3408, Δ = 3.9 ppm.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]benzenecarbohydroxamic Acid (**9i**).* A solution of compound **19i** (80 mg, 0.116 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 20 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 10 described in the Supporting Information) to afford pure compound **9i** (22.9 mg, 32%) as a yellow solid; mp 119−120 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 3H), 7.67−7.65 (m, 4H), 7.55−7.53 (m, 2H), 7.46−7.38 (m, 2H), 6.91 (d, *J* = 3.6 Hz, 1H), 6.39 (s, 1H), 4.36 (s, 2H), 4.06 (s, 3H), 3.87 (s, 2H), 3.53−3.50 (m, 2H), 3.17 (s, 2H), 2.47−2.39 (m, 6H), 2.23−2.09 (m, 5H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m*/*z*:calcd for $C_{36}H_{38}N_4O_5$, 606.3; *m*/*z*: found, 607.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.009 min and purity is 100%. HRMS $[M + H]^+$: calcd, 607.2915; found, 607.2961, Δ = 7.6 ppm.

*rac-trans 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]-cyclohexanecarbohydroxamic Acid (**9j-trans**) and rac-cis 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]cyclohexanecarbohydroxamic Acid (**9j-cis**).* A solution of compound **19j** (105 mg, 0.150 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 0.5 h. Then, the solution was concentrated and the residue was purified by prep-HPLC (method 10 described in the Supporting Information) to afford pure compound **9j-*cis*** (11.9 mg, 13%) as a yellow solid and pure compound **9j-*trans*** (3.3 mg, 4%) as a yellow solid. **9j-*trans***: mp 93−94 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.78 (s, 1H), 7.46 (s, 1H), 7.40−7.34 (m, 3H), 7.31−7.29 (m, 2H), 6.95 (s, 1H), 6.40 (d, *J* = 3.4 Hz, 1H), 4.82 (s, 2H), 4.36 (t, *J* = 5.4 Hz, 2H), 4.04 (s, 3H), 3.83 (m, 2H), 3.52−3.49 (m, 2H), 3.19−3.14 (m, 2H), 2.67 (m, 1H), 2.47 (s, 3H), 2.46−2.37 (m, 3H), 2.23 (m, 3H), 2.10−1.85 (m, 6H), 1.75−1.69 (m, 4H); two exchangeable protons were not observed. ESI-MS *m*/*z*:calcd for $C_{36}H_{44}N_4O_5$, 612.3; *m*/*z*: found, 613.4 $[M + H]^+$. HPLC (*method 1*): Rt is 2.100 min and purity is 100%. HRMS $[M + H]^+$: calcd, 613.3384; found, 613.3451. **9j-*cis***: mp 134−135 °C.^{1}H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 1H), 7.46 (s, 1H), 7.39−7.37 (m, 3H), 7.27−7.25 (m, 2H), 6.93 (s, 1H), 6.39 (d, *J* = 3.4 Hz, 1H), 4.81 (s, 2H), 4.35 (m, 2H), 4.03 (s, 3H), 3.83 (s, 2H), 3.52−3.48 (m, 2H), 3.21−3.10 (m, 2H), 2.55 (m, 1H), 2.47 (s, 3H), 2.38 (m, 3H), 2.22 (s, 2H), 2.07 (m, 3H), 1.80−1.93 (m, 4H), 1.68 (m, 2H), 1.55−1.49 (m, 2H); two exchangeable protons were not observed. ESI-MS *m*/*z*:calcd for $C_{36}H_{44}N_4O_5$, 612.3; *m*/*z*: found, 613.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.040 min and purity is 100%. HRMS $[M + H]^+$: calcd, 613.3384; found, 613.3407, Δ = 3.8 ppm.

*4-[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]benzenecarbohydroxamic Acid (**9k**).* A solution of compound **19k** (100 mg, 0.146 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 20 °C for 3 h. Then, the solution was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 5 described in the Supporting Information) to afford pure compound **9k** (23.4 mg, 27%) as a yellow solid; mp 138−139 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.79 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.56 (s, 1H), 7.48 (br, 1H), 7.10 (s, 1H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.43 (s, 1H), 4.35 (s, 2H), 4.24 (m, 1H), 4.07−4.02 (m, 5H), 3.83 (m, 2H), 3.51−3.48 (m, 2H), 3.18−3.12 (m, 4H), 2.51 (s, 3H), 2.38 (m, 2H), 2.21−2.18 (m, 4H), 2.07 (m, 2H), 1.95−1.92 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m*/*z*:calcd for $C_{34}H_{41}N_5O_5$, 599.3; *m*/*z*: found, 600.4 $[M + H]^+$. HPLC (*method 1*): Rt is 1.862 min and purity is 98.07%. HRMS $[M + H]^+$: calcd, 600.3180; found, 600.3245, Δ = 10.8 ppm.

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*2-[4-[[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**10a**).* A solution of compound **25a** (50 mg, 0.080 mmol) in HCl/1,4-dioxane (10 mL, 4.0 M) was stirred at room temperature for 1 h. Then, the reaction mixture was concentrated to give compound **10a** (20 mg, 46%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.67 (s, 2H), 7.69 (s, 1H), 7.19 (s, 1H), 6.66 (s, 1H), 4.30 (m, 2H), 4.04 (s, 3H), 3.47 (m, 2H), 3.09 (m, 8H), 2.65 (s, 3H), 2.26 (m, 3H), 1.96 (m, 8H), 1.34 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*: calcd for $C_{29}H_{39}N_7O_4$, 549.3; *m/z*: found, 550.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.85 min and purity is 95.59%. HRMS $[M + H]^+$: calcd, 550.3136; found, 550.3161, Δ = 4.5 ppm.

*2-[4-[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**10b**).* A solution of compound **25b** (60 mg, 0.097 mmol) in HCl/1,4-dioxane (10 mL, 4.0 M) was stirred at room temperature for 1 h. Then, the reaction mixture was concentrated to give the desired compound **10b** (31 mg, 60%) as a white solid; mp 192−193 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.73 (s, 2H), 7.83 (s, 1H), 7.23 (s, 1H), 6.89 (s, 1H), 4.37−4.28 (m, 3H), 4.04 (s, 3H), 3.86 (m, 2H), 3.52 (m, 2H), 3.33 (m, 4H), 3.19 (m, 2H), 2.71 (s, 3H), 2.41 (m, 2H), 2.23 (m, 4H), 2.11 (m, 2H), 1.89 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*: calcd for $C_{28}H_{37}N_7O_4$, 535.3; *m/z*: found, 536.3 $[M + H]^+$. HPLC (*method 2*): Rt is 2.80 min and purity is 95.69%. HRMS $[M + H]^+$: calcd, 536.2980; found, 536.3024, Δ = 8.2 ppm.

*2-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(4-piperidylmethoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**11**).* A solution of compound **32** (300 mg, 0.381 mmol) in HCl/EtOAc (1.0 M, 10 mL) was stirred at 15 °C for 16 h. Then, the reaction mixture was concentrated to give a residue, which was purified by prep-HPLC (method 35 described in the Supporting Information) to afford pure compound **11** (13 mg, 5%) as a yellow solid; mp 155−156 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 2H), 7.71 (s, 1H), 7.52 (d, *J* = 3.6 Hz, 1H), 7.45 (s, 1H), 6.99 (s, 1H), 6.42 (s, 1H), 4.95−4.93 (m, 1H), 4.13 (d, *J* = 5.6 Hz, 2H), 4.02 (s, 3H), 3.58−3.56 (m, 2H), 3.52−3.49 (m, 2H), 3.13−3.01 (m, 4H), 2.50 (s, 3H), 2.31−2.23 (br s, 2H), 2.18−2.14 (m, 2H), 1.99−1.96 (m, 2H), 1.79−1.73 (m, 2H), 1.40−1.30 (m, 3H); four exchangeable protons were not observed. ESI-MS *m/z*: calcd for $C_{32}H_{39}N_7O_5$, 601.3; *m/z*: found, 602.4 $[M + H]^+$. UHPLC (*method 3*): Rt is 2.36 min and purity is 96.28%. HRMS $[M + H]^+$: calcd, 602.3085; found, 602.3063, Δ = 3.6 ppm.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**12a**).* A mixture of compound **38a** (80 mg, 0.133 mmol, 1.00 eq) in HCl/EtOAc (5.00 mL, 2M) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 3 h under an N_2 atmosphere. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (method 5 described in the Supporting Information) to afford pure compound **12a** (39.10 mg, 0.061 mmol, 45.91% yield, 98.74% purity) as a white solid; mp 136−137 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 2H), 7.69 (s, 1H), 7.54 (d, *J* = 3.54 Hz, 1H), 7.43 (s, 1H), 6.99 (s, 1H), 6.42 (dd, *J* = 3.54 Hz, 0.88 Hz, 1H), 4.95−4.89 (m, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.56 (d, *J* = 7.06 Hz, 2H), 3.05−2.96 (m, 2H), 2.85−2.71 (m, 1H), 2.50 (s, 3H), 2.29−2.18 (m, 1H), 2.02−1.94 (m, 2H), 1.43−1.29 (m, 2H); two exchangeable protons were not observed. ^{13}C NMR (151 MHz, MeOD): δ 163.59, 161.07, 157.03, 156.49 (2C), 154.59, 153.89, 149.08, 143.55, 139.27, 134.07, 115.01, 113.04, 109.71, 109.03, 100.80, 98.99, 91.14, 55.08, 54.93, 47.93, 43.05 (2C), 35.14, 29.10 (2C), 11.88. ESI-MS *m/z*: calcd for $C_{27}H_{30}N_6O_5$, 518.2; *m/z*: found, 519.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.37 min and purity is 98.74%. HRMS $[M + H]^+$: calcd, 519.2361; found, 519.2335, Δ = 5.0 ppm.

*2-[4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**12b**).* A mixture of compound **37b** (70 mg, 0.143 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine hydrochloride (44 mg, 0.286 mmol), EDCI (41 mg, 0.214 mmol), DIEA (37 mg, 0.286 mmol), and HOBt (29 mg, 0.214 mmol) in DMF (5.00 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 12 h. Then, the reaction mixture was concentrated in vacuum to give a residue, which was purified by prep-HPLC (method 15 described in the Supporting Information) to afford pure compound **12b** (40.6 mg, 56%) as a yellow solid; mp 181−182 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.70 (s, 2H), 7.72 (s, 1H), 7.56−7.54 (m, 2H), 7.43 (s, 1H), 7.12 (s, 1H), 6.44 (d, *J* = 2.88 Hz, 1H), 5.07−4.97 (m, 2H), 4.38−4.29 (m, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.27−3.20 (m, 2H), 2.52 (s, 3H), 2.25−2.16 (m, 2H), 1.85−1.72 (m, 2H); two exchangeable protons were not observed. ESI-MS *m/z*:calcd for $C_{26}H_{28}N_6O_5$, 504.2; *m/z*: found, 505.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.12 min and purity is 96.03%. HRMS $[M + H]^+$: calcd, 505.2194; found, 505.2179, Δ = 3.0 ppm.

*2-[8-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-3-azabicyclo[3.2.1]octan-3-yl]pyrimidine-5-carbohydroxamic Acid (**12c**).* A solution of compound **38c** (0.1 g, 0.159 mmol) in HCl/EtOAc (10 mL, 1.0 M) was stirred at 15 °C for 2 h. Then, the reaction mixture was concentrated to give a residue, which was purified by prep-HPLC (method 16 described in the Supporting Information) to afford pure compound **12c** (15 mg, 17%) as a white solid; mp 180−181 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.69−8.65 (m, 2H), 7.76−7.74 (d, *J* = 6 Hz, 1H), 7.56−7.50 (m, 1H), 7.45 (s, 1H), 7.06−7.03 (m, 1H), 6.44−6.41 (m, 1H), 4.64−4.62 (m, 1H), 4.37−4.34 (m, 1H), 4.04−4.01 (m, 7H), 3.53−3.44 (m, 2H), 3.08−3.05 (m, 1H), 2.51−2.50 (d, *J* = 5.2 Hz, 3H), 2.46 (br s, 1H), 2.42−2.39 (m, 2H), 1.97−1.90 (m, 2H), 1.66−1.58 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*:calcd for $C_{29}H_{32}N_6O_5$, 544.2; *m/z*: found, 545.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.357 min and purity is 99.30%. HRMS $[M + H]^+$: calcd, 545.2507; found, 545.2495, Δ = 2.2 ppm.

*4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]benzenecarbohydroxamic Acid (**12d**).* A mixture of compound **37d** (60 mg, 0.143 mmol), $THPONH_2$ (20 mg, 0.172 mmol), HOBt (23 mg, 0.172 mmol), EDCI (33 mg, 0.172 mmol), and DIEA (37 mg, 0.287 mmol) in DMF (3 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 20 °C for 3 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 10 described in the Supporting Information) to afford pure compound **12d** (27.1 mg, 44%) as a yellow solid; mp 180−181 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.26 (s, 1H), 11.22 (s, 1H), 9.36 (s, 1H), 7.86 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.59 (s, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 6.98 (s, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 4.92 (d, *J* = 5.2 Hz, 2H), 3.97 (s, 6H), 2.47 (s, 3H); one exchangeable proton was not observed. ESI-MS *m/z*: calcd for $C_{24}H_{23}N_3O_5$, 433.2; *m/z*: found, 434.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.01 min and purity is 97.66%. HRMS $[M + H]^+$: calcd, 434.1710; found, 434.1746, Δ = 8.3 ppm.

*4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]cyclohexanecarbohydroxamic Acid (**12e**).* A mixture of compound **37e** (50 mg, 0.118 mmol), $THPONH_2$ (28 mg, 0.235 mmol), HOBt (19 mg, 0.141 mmol), EDCI (27 mg, 0.141 mmol), and DIEA (30 mg, 0.235 mmol) in DMF (20 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 3 h. Then, the mixture was concentrated in reduced pressure at 40 °C to give a residue, which was purified by prep-HPLC (method 10 described in the Supporting Information) to afford compound **12e** (17.2 mg, 33%) as a yellow solid; mp 148−149 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.20 (s, 1H), 10.39 (s, 1H), 8.75 (d, *J* = 5.6 Hz, 1H), 7.75 (s, 1H), 7.69 (d, *J* = 3.2 Hz, 1H), 7.55 (s, 1H), 6.86 (s, 1H), 6.50 (d, *J* = 3.2 Hz, 1H), 3.94 (s, 6H), 3.45−3.40 (m, 2H), 2.50−2.47 (m, 3H), 2.01−1.95 (m, 1H), 1.89−1.86 (m, 2H), 1.72−1.68 (m, 3H), 1.42−1.39 (m, 2H), 1.10−1.05 (m, 2H). ESI-MS *m/z*: calcd for $C_{24}H_{29}N_3O_5$, 439.2; *m/z*: found, 440.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.13 min and purity is 96.86%. HRMS $[M + H]^+$: calcd, 440.2180; found, 440.2204, Δ = 5.5 ppm.

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*6-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]pyridine-3-carbohydroxamic Acid (**12f**).* A mixture of compound **37f** (50 mg, 0.119 mmol), $THPONH_2$(28 mg, 0.238 mmol), EDCI (46 mg, 0.238 mmol), HOBt (32 mg, 0.238 mmol), and DIEA (46 mg, 0.357 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 20 °C for 16 h. Then, the reaction mixture was quenched with water (2 mL) and concentrated in vacuum to give a residue. The residue was dissolved in 0.5 M HCl aqueous solution and stirred for 30 min. Then, the reaction mixture was concentrated in vacuum to give a residue, which was purified by prep-HPLC (method 42 described in the Supporting Information) to afford pure compound **12f** (3.5 mg, 6%) as a white solid.mp 138−139 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.92 (s, 1H), 8.17 (d, J = 8 Hz, 1H), 7.72 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.38 (d, J = 3.6 Hz, 1H), 6.94 (s, 1H), 6.39 (d, J = 3.2 Hz, 1H), 5.02 (s, 2H), 4.04 (s, 6H), 2.46 (s, 3H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z: calcd for $C_{23}H_{22}N_4O_5$, 434.2; m/z: found, 435.2 $[M + H]^+$. UHPLC (*method 3*): Rt is 2.35 min and purity is 96.76%. HRMS $[M + H]^+$: calcd, 435.1663; found, 435.1639, Δ = 5.5 ppm.

*4-[[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]methyl]benzenecarbohydroxamic Acid (**12g**).* A mixture of compound **37g** (50 mg, 0.097 mmol), $THPONH_2$ (13 mg, 0.116 mmol), HOBt (15 mg, 0.116 mmol), EDCI (22 mg, 0.116 mmol), and DIEA (25 mg, 0.194 mmol) in DMF (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 18 described in the Supporting Information) to afford pure compound **12g** (21.5 mg, 41%) as a yellow solid; mp 162−163 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.85 (d, J = 7.6 Hz, 2H), 7.66 (s, 1H), 7.61 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 3.6 Hz, 1H), 7.44 (s, 1H), 6.97 (s, 1H), 6.43 (d, J = 3.6 Hz, 1H), 4.37 (s, 2H), 4.03−4.02 (s, 3H), 4.02−4.01 (s, 3H), 3.63−3.50 (m, 4H), 3.09−3.03 (m, 2H), 2.50 (s, 3H), 2.18−2.14 (m, 3H), 1.66−1.63 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z: calcd for $C_{30}H_{34}N_4O_5$, 530.3; m/z: found, 531.4 $[M + H]^+$. UHPLC (*method 3*): Rt is 2.04 min and purity is 100%. HRMS $[M + H]^+$: calcd, 531.2602; found, 531.2620, Δ = 3.4 ppm.

*5-[[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]methyl]thiophene-2-carbohydroxamic Acid (**12h**).* A mixture of compound **37h** (60 mg, 0.115 mmol), $THPONH_2$ (16 mg, 0.138 mmol), HOBt (19 mg, 0.138 mmol), EDCI (26 mg, 0.138 mmol), and DIEA (18 mg, 0.138 mmol) in DMF (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 19 described in the Supporting Information) to afford pure compound **12h** (5.0 mg, 8%) as a yellow solid; mp 165−166 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.68 (s, 1H), 7.55 (s, 1H), 7.52 (d, J = 3.2 Hz, 1H), 7.45 (s, 1H), 7.32 (d, J = 2.8 Hz, 1H), 6.97 (s, 1H), 6.42 (d, J = 3.2 Hz, 1H), 4.58 (s, 2H), 4.03−4.01 (m, 6H), 3.60 (m, 4H), 3.13−3.06 (m, 2H), 2.50 (s, 3H), 2.20−2.16 (m, 3H), 1.68 (s, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z: calcd for $C_{28}H_{32}N_4O_5S$, 536.2; m/z: found, 537.2 $[M + H]^+$. HPLC (*method 1*): Rt is 1.76 min and purity is 95.42%. HRMS $[M + H]^+$: calcd, 537.2166; found, 537.2132, Δ = 6.3 ppm.

*3-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]cyclobutanecarbohydroxamic Acid (**12i**).* A solution of compound **38i** (50 mg, 0.086 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 20 min. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 17 described in the Supporting Information) to afford pure compound **12i** (14.7 mg, 34%) as a yellow solid; mp 150−151 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.67 (d, J = 3.6 Hz, 1H), 7.52 (d, J = 3.6 Hz, 1H), 7.44 (s, 1H), 6.97 (s, 1H), 6.42 (d, J = 3.6 Hz, 1H), 4.01 (d, J = 5.2 Hz, 6H), 3.61−3.55 (m, 4H), 2.86−2.77 (m, 3H), 2.59−2.42 (m, 8H), 2.21−2.18 (m, 3H), 1.66−1.55 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z: calcd for $C_{27}H_{34}N_4O_5$, 494.3; m/z: found, 495.4 $[M + H]^+$. HPLC (*method 1*): Rt is 1.644 min and purity is 100%. HRMS $[M + H]^+$: calcd, 495.2602; found, 495.2636, Δ = 6.9 ppm.

*rac-cis 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]cyclohexanecarbohydroxamic Acid (**12j-cis**).* A solution of compound **38j-*cis*** (30 mg, 0.059 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 3 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 20 described in the Supporting Information) to afford pure compound **12j-*cis*** (5.4 mg, 21%) as a yellow solid; mp 173−174 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.74 (s, 1H), 7.53 (d, J = 3.2 Hz, 1H), 7.42 (s, 1H), 7.01 (s, 1H), 6.42 (d, J = 2.8 Hz, 1H), 4.02 (d, J = 3.6 Hz, 6H), 3.97−3.94 (m, 1H), 2.51 (s, 3H), 2.23−2.16 (m, 3H), 1.96−1.80 (m, 4H), 1.68−1.63 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z:calcd for $C_{23}H_{27}N_3O_5$, 425.2; m/z: found, 426.2 $[M + H]^+$. HPLC (*method 1*): Rt is 2.069 min and purity is 100%. HRMS $[M + H]^+$: calcd, 426.2023; found, 426.2070, Δ = 11.0 ppm.

*rac-trans 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]cyclohexanecarbohydroxamic Acid (**12j-trans**).* A solution of compound **38j-*trans*** (20 mg, 0.039 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 3 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 21 described in the Supporting Information) to afford pure compound **12j-*trans*** (3.6 mg, 21%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.80 (s, 1H), 7.49 (d, J = 3.2 Hz, 1H), 7.42 (s, 1H), 6.96 (s, 1H), 6.41 (d, J = 2.4 Hz, 1H), 4.04 (s, 1H), 4.03 (s, 6H), 2.50 (s, 3H), 2.42 (s, 1H), 2.15−2.06 (m, 4H), 1.95−1.93 (m, 2H), 1.80−1.79 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS m/z: calcd for $C_{23}H_{27}N_3O_5$, 425.2; m/z: found, 426.2 $[M + H]^+$. HPLC (*method 1*): Rt is 2.131 min and purity is 100%. HRMS $[M + H]^+$: calcd, 426.2023; found, 426.2052, Δ = 6.8 ppm.

*6-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]pyridine-3-carbohydroxamic Acid (**12k**).* A solution of compound **37k** (95 mg, 0.189 mmol, 1 equiv), *O*-tetrahydropyran-2-ylhydroxylamine (44.29 mg, 0.378 mmol, 2 equiv), HOBt (51.08 mg, 0.378 mmol, 2 equiv), EDCI (72.47 mg, 0.378 mmol, 2 equiv), and DIEA (73.29 mg, 0.567 mmol, 98.78 μL, 3 equiv) in DMF (5 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 25 °C for 12 h under an N_2 atmosphere. The reaction mixture was adjusted to pH ∼ 5 with aq HCl (1 M) and concentrated to give a residue, which was purified by prep-HPLC (method 17 described in the Supporting Information). Compound **12k** was obtained as a light yellow solid: 19.4 mg, 0.038 mmol, 19.8% yield, 99.94% purity; mp 183−184 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.40 (s, 1H), 8.05 (d, J = 9.5 Hz, 1H), 7.71 (s, 1H), 7.52 (d, J = 3.4 Hz, 1H), 7.45 (s, 1H), 7.15 (d, J = 9.4 Hz, 1H), 6.99 (s, 1H), 6.42 (d, J = 2.6 Hz, 1H), 4.42 (d, J = 13.7 Hz, 2H), 4.03 (s, 3H), 4.02 (s, 3H), 3.59 (d, J = 7.0 Hz, 2H), 3.18 (t, J = 12.1 Hz, 2H), 2.50 (s, 3H), 2.28 (m, 1H), 2.12−2.01 (m, 2H), 1.54−1.42 (m, 2H); three exchangeable protons were not observed. ESI-MS m/z:calcd for $C_{28}H_{31}N_5O_5$, 517.2; m/z: found, 518.3 $[M + H]^+$. HPLC (*method 1*): Rt is 1.553 min and purity is 99.94%. HRMS $[M + H]^+$: calcd, 518.2398; found, 518.2409, Δ = 2.1 ppm.

*2-[4-[[(6,7-Dimethoxy-2-methyl-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**13a**).* A solution of compound **42a** (300 mg, 0.559 mmol) in HCl/EtOAc (10 mL, 1.0 M) was stirred at 20 °C for 16 h. Then, the reaction mixture was concentrated in vacuum and the residue was purified by prep-HPLC (method 8 described in the Supporting Information) to afford pure compound **13a** (4 mg, 2%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 2H), 7.68 (s, 1H), 7.13 (s, 1H), 6.68 (s, 1H), 4.95−

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4.93 (m, 2H), 4.01−4.00 (m, 6H), 3.49−3.47 (m, 2H), 3.02−2.96 (m, 2H), 2.64 (s, 3H), 2.21−2.17 (m, 1H), 1.96−1.93 (m, 2H), 1.37−1.30 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*: calcd for $C_{23}H_{28}N_6O_4$, 452.2; *m/z*: found, 453.3 $[M + H]^+$. HPLC (*method 1*): Rt is 1.528 min and purity is 98.28%. HRMS $[M + H]^+$: calcd, 453.2245; found, 453.2209, Δ = 7.9 ppm.

*2-[4-[[(2-Cyclohexyl-6,7-dimethoxy-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**13b**).* A solution of compound **42b** (50 mg, 0.083 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 4 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 6 described in the Supporting Information) to afford pure compound **13b** (9 mg, 21%) as a yellow solid; mp 155−156 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 2H), 7.67 (s, 1H), 7.24 (s, 1H), 6.62 (s, 1H), 4.91 (d, *J* = 13.2 Hz, 2H), 4.01 (d, *J* = 2.4 Hz, 6H), 3.51 (d, *J* = 6.8 Hz, 2H), 3.03−2.97 (m, 2H), 2.87−2.84 (m, 1H), 2.19 (m, 1H), 2.03−1.94 (m, 6H), 1.72−1.50 (m, 3H), 1.49−1.32 (m, 5H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*:calcd for $C_{28}H_{36}N_6O_4$, 520.3; *m/z*: found, 521.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.351 min and purity is 100%. HRMS $[M + H]^+$: calcd, 521.2871; found, 521.2837, Δ = 6.5 ppm.

*2-[4-[[(6,7-Dimethoxy-2-phenyl-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**13c**).* A solution of compound **42c** (60 mg, 0.100 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 4 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 7 described in the Supporting Information) to afford pure compound **13c** (23.3 mg, 45%) as a yellow solid; mp 165−166 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.64 (s, 2H), 7.91 (t, *J* = 5.2 Hz, 2H), 7.75 (s, 1H), 7.66−7.65 (m, 3H), 7.39 (s, 1H), 6.96 (s, 1H), 4.92−4.89 (m, 2H), 4.04 (s, 6H), 3.59 (d, *J* = 6.8 Hz, 2H), 3.00 (d, *J* = 12.0 Hz, 2H), 2.24 (s, 1H), 1.97 (d, *J* = 12.0 Hz, 2H), 1.39−1.31 (s, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*: calcd for $C_{28}H_{30}N_6O_4$, 514.3; *m/z*: found, 515.2 $[M + H]^+$. HPLC (*method 1*): Rt is 2.157 min and purity is 100%. HRMS $[M + H]^+$: calcd, 515.2401; found, 515.2363, Δ = 7.4 ppm.

*2-[4-[[[6,7-Dimethoxy-2-(1-piperidyl)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**13d**).* A solution of compound **42d** (0.3 g, 0.495 mmol) in HCl/EtOAc (10 mL, 1.0 M) was stirred at 15 °C for 16 h. Then, the reaction mixture was concentrated in vacuum to give a residue, which was purified by prep-HPLC (method 8 described in the Supporting Information) to afford pure compound **13d** (65.6 mg, 25%) as a white solid; mp 129−130 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (m, 2H), 7.56 (s, 1H), 7.25 (s, 1H), 5.91 (s, 1H), 4.92 (s, 2H), 3.96 (s, 6H), 3.67 (s, 4H), 3.41−3.39 (m, 2H), 3.03−2.97 (m, 2H), 2.21−2.19 (br s, 1H), 1.96−1.94 (m, 2H), 1.77 (s, 6H), 1.36−1.30 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*: calcd for $C_{27}H_{35}N_7O_4$, 521.3; *m/z*: found, 522.4 $[M + H]^+$. HPLC (*method 1*): Rt is 2.233 min and purity is 98.77%. HRMS $[M + H]^+$: calcd, 522.2823; found, 522.2834, Δ = 2.1 ppm.

*2-[4-[[[2-(2,5-dimethyl-3-furyl)-6,7-dimethoxy-4-quinolyl]-amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**13e**).* To a solution of compound **42e** (0.6 g, 0.973 mmol, 1 equiv) in MeCN (5 mL) and water (10 mL) was added TFA (770.00 mg, 6.75 mmol, 0.5 mL, 6.94 equiv).The mixture was stirred at 60 °C for 1 h. LCMS showed that the reaction was completed and one main peak with the desired *m/z* was detected. MeCN was removed in vacuum, the residue was freeze-dried by the lyophilizer. Compound **13e** was obtained as a light yellow solid: 0.42 g, 0.789 mmol, 81.1% yield and 100% purity; its mp is 176−177 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 2H), 7.71 (s, 1H), 7.32 (s, 1H), 6.68 (s, 1H), 6.47 (s, 1H), 4.92 (br d, *J* = 13.2 Hz, 2H), 4.03 (s, 6H), 3.53 (br d, *J* = 7.1 Hz, 2H), 2.99 (br t, *J* = 11.9 Hz, 2H), 2.56 (s, 3H), 2.35 (s, 3H), 2.21 (br d, *J* = 4.2 Hz, 1H), 1.96 (br d, *J* = 11.0 Hz, 2H), 1.38−1.30 (m, 2H); three exchangeable protons were not observed. ESI-MS *m/z*: calcd for $C_{28}H_{32}N_6O_5$, 532.2; *m/z*: found, 533.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.288 min and purity is 100%. HRMS $[M + H]^+$: calcd, 533.2518; found, 533.2549, Δ = 5.8 ppm.

*2-(4-(((6,7-Dimethoxy-2-(5-methylthiophen-2-yl)quinolin-4-yl)-amino)methyl)piperidin-1-yl)-N-hydroxypyrimidine-5-carboxamide (**13f**).* To a solution of compound **42f** (40 mg, 0.065 mmol, 1 equiv) in MeCN (5 mL) and water (5 mL) was added TFA (73.71 mg, 0.647 mmol, 47.86 μL, 10 equiv). The mixture was stirred at 60 °C for 5 min. HPLC showed that the starting material was consumed completely and one main peak was detected. The solvent was removed. The residue was purified by prep-HPLC (method 45 described in the Supporting Information) to afford pure compound **13f** (24.8 mg, 0.046 mmol, 71.06% yield and 98.54% purity) as an off-yellow solid; its mp is 177−178 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.65 (s, 2H), 7.80 (d, *J* = 3.8 Hz, 1H), 7.70 (s, 1H), 7.39 (s, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 6.83 (s, 1H), 4.94 (br s, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.56 (d, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 12.2 Hz, 2H), 2.62 (s, 3H), 2.22 (br s, 1H), 1.97 (d, *J* = 12.7 Hz, 2H), 1.37−1.34 (m, 2H); three exchangeable protons were not observed. ESI-MS *m/z*: calcd for $C_{27}H_{30}N_6O_4S$, 534.2; *m/z*: found, 535.3 $[M + H]^+$. HPLC (*method 1*): Rt is 2.186 min and purity is 98.543%. HRMS $[M + H]^+$: calcd, 535.2122; found, 535.2138, Δ = 3.0 ppm.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)quinazolin-4-yl]-amino]methyl]-1-piperidyl]pyrimidine-5-carbohydroxamic Acid (**14**).* To a solution of **47** (130 mg, 0.215 mmol) in CH_3CN/H_2O (1:1, 10 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL) and the mixture was stirred at 60 °C for 5 min. Then, the residue was purified by prep-HPLC (method 14 described below) to afford pure compound **42** (64.3 mg, 56%) as an off-white solid; mp 160−161 °C. ^{1}H NMR (MeOD, 400 MHz): δ 8.64 (s, 2H), 7.71 (s, 1H), 7.58 (d, *J* = 3.5 Hz, 1H), 7.35 (s, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 4.90 (br s, 2H), 4.04 (s, 3H), 4.01 (s, 3H), 3.78 (d, *J* = 6.8 Hz, 2H), 3.01 (br t, *J* = 11.5 Hz, 2H), 2.53 (s, 3H), 2.22 (br s, 1H), 1.94 (br d, *J* = 11.7 Hz, 2H), 1.39−1.31 (m, 2H); three exchangeable protons (NH from 4-aminoquinoline and NH−OH from hydroxamic group) were not observed. ESI-MS *m/z*: calcd for $C_{26}H_{29}N_7O_5$, 519.2; *m/z*: found, 520.3 $[M + H]^+$. HPLC (*method 1*): Rt is 1.897 min and purity is 94.528%. HRMS $[M + H]^+$: calcd, 520.2303; found, 520.2309, Δ = 1.2 ppm.

*Ethyl 2-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-yl-propoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**17a**).* A mixture of compound **16**[34,35] (200 mg, 0.499 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 198 mg, 0.748 mmol), $Pd_2(dba)_3$ (46 mg, 0.050 mmol), BINAP (31 mg, 0.050 mmol), and Cs_2CO_3 (325 mg, 0.998 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C to give a residue and this residue was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 23 described in the Supporting Information) to afford pure compound **17a** (80 mg, 25%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{35}H_{44}N_6O_5$, 628.3; *m/z*: found, 629.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-yl-propoxy)-4-quinolyl]amino]methyl]benzoate (**17b**).* A mixture of compound **16**[34,35] (100 mg, 0.249 mmol), ethyl 4-(aminomethyl)-benzoate (58 mg, 0.324 mmol), Cs_2CO_3 (162 mg, 0.499 mmol), BINAP (15 mg, 0.025 mmol), and $Pd_2(dba)_3$ (23 mg, 0.025 mmol) in 1,4-dioxane (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was filtrated and the filtrate was concentrated in reduced pressure at 40 °C to give compound **17b** (100 mg, 74%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{32}H_{37}N_3O_5$, 543.3; *m/z*: found, 544.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-yl-propoxy)-4-quinolyl]amino]methyl]cyclohexanecarboxylate (**17c**).*

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A mixture of compound **16**[34,35] (200 mg, 0.499 mmol), ethyl 4-(aminomethyl)cyclohexanecarboxylate (139 mg, 0.748 mmol), BINAP (31 mg, 0.050 mmol), $Pd_2(dba)_3$ (46 mg, 0.050 mmol), and Cs_2CO_3 (325 mg, 0.998 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. The mixture was cooled to 20 °C and concentrated in reduced pressure at 40 °C. The residue was poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine (20 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to afford compound **17c** (200 mg, 73%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{32}H_{43}N_3O_5$, 549.3; *m/z*: found, 550.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Methyl 4-[[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]methyl]benzoate (**17d**).* A mixture of compound **16**[34,35] (140 mg, 0.349 mmol), methyl 4-[[4-(aminomethyl)-1-piperidyl]methyl]benzoate (**54**, 92 mg, 0.349 mmol), $Pd_2(dba)_3$ (32 mg, 0.035 mmol), BINAP (22 mg, 0.035 mmol), and Cs_2CO_3 (228 mg, 0.698 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was filtered and the filtrate was concentrated. The residue was diluted with water (10 mL) and extracted with EtOAc (15 mL). The organic phase was acidized with aqueous HCl (1.0 N) to pH = 3 and the organic phase was separated. The aqueous phase was alkalized by saturated $NaHCO_3$ solution to pH = 8 and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford compound **17d** (220 mg, crude) as a yellow solid. ESI-MS *m/z*: calcd for $C_{37}H_{46}N_4O_5$, 626.4; *m/z*: found, 627.4 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Methyl 4-[[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]methyl]benzoate (**17e**).* A mixture of compound **16**[34,35] (200 mg, 0.499 mmol), methyl 4-[(4-amino-1-piperidyl)methyl]benzoate (**57**, 248 mg, 0.998 mmol), BINAP (31 mg, 0.050 mmol), $Pd_2(dba)_3$ (46 mg, 0.050 mmol), and Cs_2CO_3 (325 mg, 0.998 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 110 °C for 16 h. The mixture was cooled to 20 °C and concentrated in reduced pressure at 40 °C. The residue was poured into water (20 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue, which was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford pure compound **17e** (150 mg, 49%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{36}H_{44}N_4O_5$, 612.3; *m/z*: found, 613.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*Methyl 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]benzoate (**17f**).* A mixture of compound **16**[34,35] (300 mg, 0.748 mmol), methyl 4-[4-(aminomethyl)-1-piperidyl]benzoate (**60**, 204 mg, 0.823 mmol), $Pd_2(dba)_3$ (69 mg, 0.075 mmol), BINAP (47 mg, 0.075 mmol), and Cs_2CO_3 (488 mg, 1.50 mmol) in 1,4-dioxane (30 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was filtered and the filtrate was concentrated to give a residue, which was washed with a solution of PE/EtOAc = 10/1 to afford compound **17f** (220 mg, 48%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{36}H_{44}N_4O_5$, 612.3; *m/z*: found, 613.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-cyclohexanecarboxylate (**17g**).* A mixture of compound **16**[34,35] (500 mg, 1.25 mmol), *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (267 mg, 1.25 mmol), $Pd_2(dba)_3$ (114 mg, 0.125 mmol), BINAP (78 mg, 0.125 mmol), and Cs_2CO_3 (813 mg, 2.49 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was filtered and the filtrate was concentrated to give a residue. The residue was washed with a solution of PE/EtOAc = 15/1 to afford intermediate *tert*-butyl 4-[[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]piperidine-1-carboxylate (250 mg, 34%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{33}H_{46}N_4O_5$, 578.4; *m/z*: found, 579.4 $[M + H]^+$. Then, a solution of this intermediate (250 mg, 0.432 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 20 °C for 1 h. The mixture was concentrated to give the crude product. The crude product was diluted with MeOH (15 mL) and $NaHCO_3$ solid was added into the mixture to pH = 8. The mixture was filtered and the filtrate was concentrated to give intermediate 6-methoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidylmethyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine(180 mg, 87%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{28}H_{38}N_4O_3$, 478.3; *m/z*: found, 479.3 $[M + H]^+$. Finally, to a solution of $ZnCl_2$/diethyl ether (1.0 M, 20 μL) was added $NaBH_3CN$ (52 mg, 0.827 mmol) in MeOH (10 mL) and the mixture was stirred at 20 °C for 30 min. Then, a mixture of ethyl 4-oxocyclohexanecarboxylate (70 mg, 0.414 mmol) and intermediate 6-methoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidylmethyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (180 mg, 0.376 mmol) in MeOH (40 mL) was added into the reaction solution. The mixture was heated at 40 °C for 15.5 h. Then, the reaction was quenched with water (10 mL) and the mixture was filtered. The filtrate was concentrated and extracted with a solution of CH_2Cl_2/MeOH = 3:1. The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford compound **17g** (155 mg, 65%) as a white solid. ESI-MS *m/z*: calcd for $C_{37}H_{52}N_4O_5$, 632.4; *m/z*: found, 633.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Methyl 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]cyclohexyl]benzoate (**17h**).* A mixture of compound **16**[34,35] (200 mg, 0.499 mmol), methyl 4-[4-(aminomethyl)cyclohexyl]benzoate (**64**, 185 mg, 0.748 mmol), BINAP (31 mg, 0.050 mmol), $Pd_2(dba)_3$ (46 mg, 0.050 mmol), and Cs_2CO_3 (325 mg, 0.998 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C; the residue was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue, which was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 5:1) to afford pure compound **17h** (150 mg, 49%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{37}H_{45}N_3O_5$, 609.3; *m/z*: found, 610.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*Methyl 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]benzoate (**17i**).* A mixture of compound **16**[34,35] (200 mg, 0.499 mmol), methyl 4-[4-(aminomethyl)phenyl]benzoate (**68**, 180 mg, 0.748 mmol), BINAP (31 mg, 0.050 mmol), $Pd_2(dba)_3$ (46 mg, 0.050 mmol), and Cs_2CO_3 (325 mg, 0.998 mmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 110 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C; the residue was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue, which was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford pure compound **17i** (200 mg, 66%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{37}H_{39}N_3O_5$, 605.3; *m/z*: found, 606.2 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]-cyclohexanecarboxylate (**17j**).* A mixture of compound **16**[34,35] (400 mg, 0.998 mmol), ethyl 4-[4-(aminomethyl)phenyl]-cyclohexanecarboxylate (**73**, 261 mg, 0.998 mmol), $Pd_2(dba)_3$ (92 mg, 0.100 mmol), BINAP (62 mg, 0.100 mmol), and Cs_2CO_3 (650 mg, 2.00 mmol) in 1,4-dioxane (50 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then,

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the mixture was filtered and the filtrate was concentrated to give a residue, which was washed with a solution of PE/EtOAc = 10/1 to give compound **17j** (162 mg, 26%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{38}H_{47}N_3O_5$, 625.3; *m/z*: found, 626.2 $[M + H]^+$. This compound was used in the next step without further purification or characterization.

*Methyl 4-[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]benzoate (**17k**).* A mixture of compound **16**[34,35] (300 mg, 0.748 mmol), methyl 4-(4-amino-1-piperidyl)benzoate (**7S**, 210 mg, 0.898 mmol), BINAP (93 mg, 0.150 mmol), $Pd_2(dba)_3$ (137 mg, 0.150 mmol), and Cs_2CO_3 (488 mg, 1.50 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 110 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C; the residue was poured into water (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine (20 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue, which was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford pure compound **17k** (200 mg, 44%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{35}H_{42}N_4O_5$, 598.3; *m/z*: found, 599.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*2-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**18a**).* To a solution of compound **17a** (100 mg, 0.155 mmol) in THF/MeOH/H_2O (5:1:3, 9.0 mL) was added LiOH·H_2O (10 mg, 0.233 mmol) and the mixture was stirred at 25 °C for 12 h. Then, the reaction mixture was concentrated and the pH was adjusted pH to 3−4 with 3.0 M aqueous HCl and the solid was precipitated. The solid was collected to give compound **18a** (90 mg, 94%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{33}H_{40}N_6O_5$, 600.3; *m/z*: found, 601.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]benzoic Acid (**18b**).* A mixture of compound **17b** (100 mg, 0.184 mmol) and LiOH·H_2O (15 mg, 0.368 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was poured into water (2 mL) and extracted with EtOAc (3 mL). The mixture was adjusted to pH 3 with 2.0 M HCl. Then, the solution was filtered and the filter cake was concentrated to dryness to give compound **18b** (80 mg, 84%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{30}H_{33}N_3O_5$, 515.2; *m/z*: found, 516.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]cyclohexanecarboxylic Acid (**18c**).* A mixture of compound **17c** (200 mg, 0.364 mmol) and LiOH·H_2O (45 mg, 1.09 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was poured into water (3 mL) and extracted with EtOAc (5 mL). The mixture was acidified to pH = 3−4 with 1 N HCl and filtered. The filter cake was concentrated to dryness to give compound **18c** (100 mg, 52%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{30}H_{39}N_3O_5$, 521.3; *m/z*: found, 522.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]methyl]benzoic Acid (**18d**).* To a mixture of compound **17d** (220 mg, 0.351 mmol) in EtOH/H_2O (2:1, 6.0 mL) was added LiOH·H_2O (29 mg, 0.702 mmol) and the mixture was stirred at 20 °C for 1 h. Then, the solution was concentrated to give a residue. The residue was acidized with 1.0 M aqueous HCl to pH = 3. Then, the mixture was concentrated to give compound **18d** (140 mg, 65%) as a white solid. ESI-MS *m/z*: calcd for $C_{36}H_{44}N_4O_5$, 612.3; *m/z*: found, 613.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]methyl]benzoic Acid (**18e**).* A mixture of compound **17e** (150 mg, 0.245 mmol) and LiOH·H_2O (31 mg, 0.735 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (0.5 mL) and extracted with EtOAc (3 mL). The aqueous layer was acidified to pH = 3−4 with 1 N HCl and concentrated to dryness to afford compound **18e** (150 mg, crude) as a yellow solid. ESI-MS *m/z*: calcd for $C_{35}H_{42}N_4O_5$, 598.3; *m/z*: found, 599.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]benzoic Acid (**18f**).* To a solution of compound **17f** (220 mg, 0.359 mmol) in EtOH/H_2O (2:1, 6.0 mL) was added LiOH·H_2O (31 mg, 0.718 mmol) and the mixture was stirred at 20 °C for 3 h. Then, the solution was concentrated to give a residue. The residue was acidized with 1.0 M aqueous HCl to pH = 3 and the mixture was concentrated to give compound **18f** (155 mg, 72%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{35}H_{42}N_4O_5$, 598.3; *m/z*: found, 599.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]cyclohexanecarboxylic Acid (**18g**).* To a solution of compound **17g** (155 mg, 0.245 mmol) in EtOH/H_2O (2:1, 12.0 mL) was added LiOH·H_2O (21 mg, 0.490 mmol) and the mixture was stirred at 20 °C for 2 h. Then, the solution was concentrated to give a residue. The residue was acidized with 1.0 M aqueous HCl to pH = 3 and the mixture was concentrated to give compound **18g** (105 mg, 71%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{35}H_{48}N_4O_5$, 604.4; *m/z*: found, 605.4 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]cyclohexyl]benzoic Acid (**18h**).* A mixture of compound **17h** (150 mg, 0.245 mmol) and LiOH·H_2O (31 mg, 0.735 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (2 mL) and extracted with EtOAc (3 mL). The aqueous layer was acidified to pH = 3−4 with 1.0 N HCl. The filter was concentrated to dryness to give a residue, which was purified by prep-HPLC (method 24 described in the Supporting Information) to afford pure compound **18h** (60 mg, 41%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{36}H_{43}N_3O_5$, 597.3; *m/z*: found, 598.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]benzoic Acid (**18i**).* A mixture of compound **17i** (200 mg, 0.330 mmol) and LiOH·H_2O (41 mg, 0.990 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was stirred at 20 °C for 5 h. Then, the mixture was concentrated and the residue was diluted with water (0.5 mL) and extracted with EtOAc (3 mL). The aqueous phase was acidified to pH = 3−4 with 1.0 *N* HCl and concentrated to dryness to give compound **18i** (150 mg, 77%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{36}H_{37}N_3O_5$, 591.3; *m/z*: found, 592.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]cyclohexanecarboxylic Acid (**18j**).* To a solution of compound **17j** (160 mg, 0.256 mmol) in EtOH/H_2O (2:1, 6.0 mL) was added LiOH·H_2O (21 mg, 0.511 mmol), which was stirred at 20 °C for 2 h. Then, the mixture was acidized with 1.0 M HCl to pH = 3 and concentrated to give a residue. The residue was diluted with MeOH (5 mL), filtered, and the filtrate was concentrated to give compound **18j** (135 mg, 88%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{36}H_{43}N_3O_5$, 597.3; *m/z*: found, 598.3 $[M + H]^+$. This compound was used in the next step without further purification or characterization.

*4-[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]benzoic Acid (**18k**).* A mixture of compound **17k** (200 mg, 0.334 mmol) and LiOH·H_2O (42 mg, 1.00 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (0.5 mL) and extracted with EtOAc (3 mL). The

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aqueous phase was acidified to pH = 3−4 with 1.0 N HCl and concentrated to dryness to afford compound **18k** (150 mg, 76%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{34}H_{40}N_4O_5$, 584.3; *m/z*: found, 585.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**19a**).* A mixture of compound **18a** (80 mg, 0.133 mmol), DIEA (34 mg, 0.266 mmol), HOBt (21 mg, 0.160 mmol), $THPONH_2$ (23 mg, 0.200 mmol), and EDCI (30 mg, 0.160 mmol) in DMF (5.00 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C to give a residue that was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 25 described in the Supporting Information) to afford pure compound **19a** (60 mg, 64%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{38}H_{49}N_7O_6$, 699.4; *m/z*: found, 700.4 $[M + H]^+$.This compound was used in the next step without further characterization.

*4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-N-tetrahydropyran-2-yloxy-cyclohexanecarboxamide (**19c**).* A mixture of compound **18c** (100 mg, 0.192 mmol), $THPONH_2$ (45 mg, 0.383 mmol), HOBt (31 mg, 0.230 mmol), EDCI (44 mg, 0.230 mmol), and DIEA (50 mg, 0.383 mmol) in DMF (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C. The residue was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC (method 26 described in the Supporting Information) to afford pure compound **19c** (60 mg, 50%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{35}H_{48}N_4O_6$, 620.4; *m/z*: found, 621.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]methyl]-N-tetrahydropyran-2-yloxy-benzamide (**19d**).* A mixture of compound **18d** (140 mg, 0.229 mmol), $THPONH_2$ (30 mg, 0.251 mmol), EDCI (45 mg, 0.251 mmol), HOBt (44 mg, 0.321 mmol), and DIEA (56 mg, 0.457 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated and the residue was diluted with water (10 mL) and extracted with EtOAc (15 mL). The organic phase was concentrated to give a residue, which was purified by prep-HPLC (method 27 described in the Supporting Information) to afford pure compound **19d** (65 mg, 40%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{41}H_{53}N_5O_6$, 711.4; *m/z*: found, 712.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]methyl]-N-tetrahydropyran-2-yloxy-benzamide (**19e**).* A mixture of compound **18e** (150 mg, 0.250 mmol), $THPONH_2$ (55 mg, 0.472 mmol), HOBt (38 mg, 0.283 mmol), EDCI (54 mg, 0.283 mmol), and DIEA (37 mg, 0.283 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 5 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 19 described in the Supporting Information) to afford pure compound **19e** (80 mg, 46%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{40}H_{51}N_5O_6$, 697.4; *m/z*: found, 698.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-benzamide (**19f**).* A mixture of compound **18f** (120 mg, 0.200 mmol), $THPONH_2$ (26 mg, 0.220 mmol), EDCI (40 mg, 0.220 mmol), HOBt (38 mg, 0.300 mmol), and DIEA (49 mg, 0.400 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL). The organic phase was separated and the aqueous phase was concentrated to give the residue, which was purified by prep-HPLC (method 10 described in the Supporting Information) to afford pure compound **19f** (85 mg, 61%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{40}H_{51}N_5O_6$, 697.4; *m/z*: found, 698.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-cyclohexanecarboxamide (**19g**).* A mixture of compound **18g** (105 mg, 0.174 mmol), $THPONH_2$ (22 mg, 0.191 mmol), EDCI (37 mg, 0.191 mmol), HOBt (35 mg, 0.260 mmol), and DIEA (45 mg, 0.347 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated and the residue was purified by prep-HPLC (method 18 described in the Supporting Information) to afford pure compound **19g** (50 mg, 41%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{40}H_{57}N_5O_6$, 703.4; *m/z*: found, 704.5 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]cyclohexyl]-N-tetrahydropyran-2-yloxy-benzamide (**19h**).* A mixture of compound **18h** (60 mg, 0.1 mmol), $THPONH_2$ (20 mg, 0.168 mmol), HOBt (14 mg, 0.101 mmol), EDCI (19 mg, 0.101 mmol), and DIEA (22 mg, 0.101 mmol) in DMF (5 mL) was degassed and purged with N_2 3 times and then the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 28 described in the Supporting Information) to afford pure compound **19h** (15 mg, 21%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{41}H_{52}N_4O_6$, 696.4; *m/z*: found, 697.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]-N-tetrahydropyran-2-yloxy-benzamide (**19i**).* A mixture of compound **18i** (150 mg, 0.253 mmol), $THPONH_2$ (56 mg, 0.477 mmol), HOBt (39 mg, 0.286 mmol), EDCI (55 mg, 0.286 mmol), and DIEA (37 mg, 0.286 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 3 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 5 described in the Supporting Information) to afford pure compound **19i** (80 mg, 46%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{41}H_{46}N_4O_6$, 690.4; *m/z*: found, 691.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]phenyl]-N-tetrahydropyran-2-yloxy-cyclohexanecarboxamide (**19j**).* A mixture of compound **18j** (135 mg, 0.226 mmol), $THPONH_2$ (27 mg, 0.234 mmol), EDCI (45 mg, 0.234 mmol), HOBt (43 mg, 0.319 mmol), and DIEA (55 mg, 0.425 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated to give a residue, which was purified by prep-HPLC (method 29 described in the Supporting Information) to afford pure compound **19j** (105 mg, 67%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{41}H_{52}N_4O_6$, 696.4; *m/z*: found, 697.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*4-[4-[[6-Methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]-N-tetrahydropyran-2-yloxy-benzamide (**19k**).* A mixture of compound **18k** (200 mg, 0.342 mmol), $THPONH_2$(75 mg, 0.644 mmol), HOBt (52 mg, 0.387 mmol), EDCI (74 mg, 0.387 mmol), and DIEA (50 mg, 0.387 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 24 described in the Supporting Information) to afford pure compound **19k** (100 mg, 43%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{39}H_{49}N_5O_6$, 683.4; *m/z*: found, 684.4 $[M + H]^+$. This compound was used in the next step without further characterization.

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*6-Methoxy-2-methyl-N-(4-piperidylmethyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (**22a**).* A solution of compound **21a**[35] (250 mg, 0.49 mmol) in HCl/1,4-dioxane (10 mL, 4.0 M) was stirred at room temperature for 1 h. Then, the reaction mixture was concentrated to give compound **22a** (200 mg, 99%) as a white solid. ESI-MS *m/z*: calcd for $C_{24}H_{36}N_4O_2$, 412.3; *m/z*: found, 413 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[4-[[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**23a**).* To a solution of compound **22a** (41 mg, 0.1 mmol) in acetonitrile (10 mL) were added K_2CO_3 (69 mg, 0.5 mmol) and ethyl 2-chloropyrimidine-5-carboxylate(37 mg, 0.2 mmol) and the solution was stirred at room temperature for 3 h. Then, the mixture was concentrated to give compound **23a** (50 mg, 89%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{31}H_{42}N_6O_4$, 562.3; *m/z*: found, 563 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[4-[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]pyrimidine-5-carboxylate (**23b**).* To a solution of compound **22b**[35] (120 mg, 0.3 mmol) in acetonitrile (15 mL) were added K_2CO_3 (138 mg, 1 mmol) and ethyl 2-chloropyrimidine-5-carboxylate (88 mg, 0.45 mmol) and the mixture was stirred at room temperature for 3 h. Then, the mixture was concentrated to give compound **23b** (0.15 g, 91%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{30}H_{40}N_6O_4$, 548.3; *m/z*: found, 549 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**24a**).* To a solution of compound **23a** (56 mg, 0.1 mmol) in THF/MeOH/H_2O (10:1:3, 10 mL) was added LiOH·H_2O (21 mg, 0.5 mmol) and the resulting mixture was stirred at room temperature overnight. Then, the mixture was diluted with water and the pH was adjusted to 2−3 with 1.0 N aqueous HCl. Then, the mixture was extracted with EtOAc and the combined organic layers were concentrated to give compound **24a** (45 mg, 83%). ESI-MS *m/z*: calcd for $C_{29}H_{38}N_6O_4$, 534.3; *m/z*: found, 535 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]pyrimidine-5-carboxylic Acid (**24b**).* To a solution of compound **23b** (0.2 g, 0.365 mmol) in THF/MeOH/H_2O (10:1:3, 10 mL) was added LiOH·H_2O (78 mg, 1.82 mmol) and the resulting mixture was stirred at room temperature overnight. Then, the mixture was diluted with water and the pH was adjusted to 2−3 with 1.0 N aqueous HCl. Then, the mixture was extracted with EtOAc and the combined organic phase was concentrated to give compound **24b** (0.15 g, 79%). ESI-MS *m/z*: calcd for $C_{28}H_{36}N_6O_4$, 520.3; *m/z*: found, 521 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**25a**).* To a solution of compound **24a** (45 mg, 0.084 mmol) in DMF (10 mL) were added EDC·HCl (29 mg, 0.17 mmol), HOBt (23 mg, 0.17 mmol), $THPONH_2$ (20 mg, 0.17 mmol), and NMM (34 mg, 0.34 mmol) and the mixture was stirred at room temperature overnight. Then, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue, which was purified by prep-HPLC (method 41 described in the Supporting Information) to afford pure compound **25a** (25 mg, 48%). ESI-MS *m/z*: calcd for $C_{34}H_{47}N_7O_5$, 633.4; *m/z*: found, 634 $[M + H]^+$. This compound was used in the next step without further characterization.

*2-[4-[[6-Methoxy-2-methyl-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**25b**).* To a solution of compound **24b** (104 mg, 0.2 mmol) in DMF (10 mL) were added EDC·HCl (69 mg, 0.4 mmol), HOBt (54 mg, 0.4 mmol), $THPONH_2$ (35 mg, 0.3 mmol), and NMM (61 mg, 0.6 mmol) and the mixture was stirred at room temperature overnight. Then, the mixture was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue, which was purified by prep-HPLC (method 39 described in the Supporting Information) to afford pure compound **25b** (60 mg, 48%). ESI-MS *m/z*: calcd for $C_{33}H_{45}N_7O_5$, 619.3; *m/z*: found, 620 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 2-[4-[[[7-[(1-tert-Butoxycarbonyl-4-piperidyl)methoxy]-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**30**).* A mixture of compound **29**[35] (270 mg, 0.554 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]-pyrimidine-5-carboxylate (**51**, 293 mg, 1.11 mmol), $Pd_2(dba)_3$ (51 mg, 0.055 mmol), BINAP (34 mg, 0.055 mmol), and Cs_2CO_3 (451 mg, 1.39 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 110 °C for 16 h. Then, the reaction mixture was concentrated in vacuum and the residue was dissolved in EtOAc (50 mL) and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified by prep-TLC (CH_2Cl_2/MeOH = 10:1) to afford pure compound **30** (200 mg, 50%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{39}H_{50}N_6O_7$, 714.4; *m/z*: found, 715.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*2-[4-[[[7-[(1-tert-Butoxycarbonyl-4-piperidyl)methoxy]-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]-1-piperidyl]-pyrimidine-5-carboxylic Acid (**31**).* To a solution of compound **30** (200 mg, 0.280 mmol) in THF/H_2O (2:1, 30.0 mL) was added LiOH·H_2O (23 mg, 0.559 mmol) and the mixture was stirred at 15 °C for 16 h. Then, the reaction mixture was adjusted to pH 6 with 0.1 M HCl aqueous solution and concentrated in vacuum to obtain compound **31** (200 mg, crude) as a yellow solid. ESI-MS *m/z*: calcd for $C_{37}H_{46}N_6O_7$, 686.3; *m/z*: found, 687.4 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*tert-Butyl 4-[[6-Methoxy-2-(5-methyl-2-furyl)-4-[[1-[5-(tetrahydropyran-2-yloxycarbamoyl)pyrimidin-2-yl]-4-piperidyl]-methylamino]-7-quinolyl]oxymethyl]piperidine-1-carboxylate (**32**).* A mixture of compound **31** (200 mg, 0.291 mmol), $THPONH_2$(68 mg, 0.582 mmol), EDCI (112 mg, 0.582 mmol), HOBt (79 mg, 0.582 mmol), and DIEA (113 mg, 0.873 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 15 °C for 16 h. Then, the reaction mixture was quenched with water (10 mL) and concentrated in vacuum to give compound **32** (300 mg, crude) as a yellow oil. ESI-MS *m/z*: calcd for $C_{42}H_{55}N_7O_8$, 785.5; *m/z*: found, 786.5 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**36a**).* A mixture of compound **35**[35] (100 mg, 0.329 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 104.43 mg, 0.395 mmol, 1.20 equiv), $Pd_2(dba)_3$ (30.15 mg, 0.033 mmol, 0.10 equiv), BINAP (41.00 mg, 0.066 mmol, 0.20 equiv), and Cs_2CO_3 (214.54 mg, 0.658 mmol, 2.00 equiv) in 1,4-dioxane (3.00 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 140 °C for 12 h under an N_2 atmosphere. The reaction mixture was filtrated and the filtrate was concentrated in vacuo to give the compound **36a** (120.00 mg, 0.225 mmol, 68.6% yield) as a yellow solid. ESI-MS *m/z*: calcd for $C_{29}H_{33}N_5O_5$, 531.3; *m/z*: found, 532.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]-1-piperidyl]pyrimidine-5-carboxylate (**36b**).* A mixture of compound **35**[35] (250 mg, 0.823 mmol), *tert*-butyl 4-aminopiperidine-1-carboxylate(247 mg, 1.23 mmol), $Pd_2(dba)_3$ (75 mg, 0.082 mmol), BINAP (102 mg, 0.164 mmol), and Cs_2CO_3 (536 mg, 1.65 mmol) in 1,4-dioxane (10.0 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 12 h. Then, the reaction mixture was filtrated and the filtrate was concentrated under vacuum to give intermediate *tert*-butyl 4-[[6,7-dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]piperidine-1-carboxylate (350 mg, 91%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{26}H_{33}N_3O_5$, 467.2; *m/z*:

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found, 468.3 $[M + H]^+$. Then, a mixture of this intermediate (350 mg, 0.748 mmol) in HCl/MeOH (10.0 mL, 2.0 M) was degassed and purged with N_2 3 times and the mixture was stirred at 25 °C for 5 h. The reaction mixture was concentrated under vacuum and the residue was extracted with water (5 mL × 4) and washed with EtOAc (5 mL × 3). The combined aqueous phase was concentrated under reduced pressure to give intermediate 6,7-dimethoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidyl)quinolin-4-amine (220 mg, 80%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{21}H_{25}N_3O_3$, 367.2; *m/z*: found, 368.3 $[M + H]^+$. Finally, a mixture of this intermediate (100 mg, 0.272 mmol), ethyl 2-chloropyrimidine-5-carboxylate (66 mg, 0.354 mmol), and K_2CO_3 (113 mg, 0.816 mmol) in DMF (10.0 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 50 °C for 12 h. Then, the reaction mixture was concentrated under vacuum and the residue was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with water (10 mL × 1), dried over Na_2SO_4, filtered, and concentrated to afford compound **36b** (100 mg, 71%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{28}H_{31}N_5O_5$, 517.2; *m/z*: found, 518.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[8-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]-3-azabicyclo[3.2.1]octan-3-yl]pyrimidine-5-carboxylate (**36c**).* A mixture of compound **35**[35] (200 mg, 0.658 mmol), *tert*-butyl 8-(aminomethyl)-3-azabicyclo[3.2.1]octane-3-carboxylate (190 mg, 0.790 mmol), Cs_2CO_3 (429 mg, 1.32 mmol), BINAP (41 mg, 0.066 mmol), and $Pd_2(dba)_3$ (60 mg, 0.066 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C; the residue was poured into water (100 mL) and extracted with EtOAc (30 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford intermediate *tert*-butyl 8-[[[6,7-dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]-3-azabicyclo[3.2.1]octane-3-carboxylate (250 mg, 75%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{29}H_{37}N_3O_5$, 507.3; *m/z*: found, 508.3 $[M + H]^+$. Then, a solution of this intermediate (250 mg, 0.492 mmol) in HCl/EtOAc (20 mL, 2.0 M) was stirred at 20 °C for 16 h and then, the mixture was concentrated in reduced pressure at 40 °C to afford *N*-(3-azabicyclo[3.2.1]octan-8-ylmethyl)-6,7-dimethoxy-2-(5-methyl-2-furyl)quinolin-4-amine (200 mg, 99%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{24}H_{29}N_3O_3$, 407.3; *m/z*: found, 408.3 $[M + H]^+$. Finally, to a solution of this amine (500 mg, 1.23 mmol) in CH_3CN (20 mL) were added K_2CO_3 (509 mg, 3.68 mmol) and ethyl 2-chloropyrimidine-5-carboxylate (343 mg, 1.84 mmol) and the mixture was stirred at 40 °C for 16 h. Then, the reaction mixture was filtered and concentrated in vacuum to give compound **36c** (0.4 g, 58%) as a yellow oil. ESI-MS *m/z*: calcd for $C_{31}H_{35}N_5O_5$, 557.3; *m/z*: found, 558.2 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*Ethyl 4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]benzoate (**36d**).* A mixture of compound **35**[35] (100 mg, 0.329 mmol), ethyl 4-(aminomethyl)benzoate (77 mg, 0.428 mmol), Cs_2CO_3 (214 mg, 0.658 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), and BINAP (20 mg, 0.033 mmol) in 1,4-dioxane (3 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C to afford compound **36d** (100 mg, 68%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{26}H_{26}N_2O_5$, 446.2; *m/z*: found, 447.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]cyclohexanecarboxylate (**36e**).* A mixture of compound **35**[35] (100 mg, 0.329 mmol), ethyl 4-(aminomethyl)-cyclohexanecarboxylate (122 mg, 0.659 mmol), BINAP (20 mg, 0.033 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), and Cs_2CO_3 (214 mg, 0.658 mmol) in 1,4-dioxane (5 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C to give compound **36e** (100 mg, 67%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{26}H_{32}N_2O_5$, 452.2; *m/z*: found, 453.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Methyl 6-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]pyridine-3-carboxylate (**36f**).* A mixture of compound **35**[35] (50 mg, 0.164 mmol), commercially available methyl 6-(aminomethyl)pyridine-3-carboxylate (55 mg, 0.329 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), BINAP (31 mg, 0.049 mmol), and Cs_2CO_3 (134 mg, 0.411 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h. Then, the reaction mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (CH_2Cl_2/MeOH = 10:1) to afford pure compound **36f** (40 mg, 56%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{24}H_{23}N_3O_5$, 433.2; *m/z*: found, 434.2 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 4-[[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]-1-piperidyl]methyl]benzoate (**36g**).* A mixture of compound **35**[35] (500 mg, 1.65 mmol), *tert*-butyl 4-(aminomethyl)-piperidine-1-carboxylate (530 mg, 2.47 mmol), Cs_2CO_3 (1.08 g, 3.30 mmol), BINAP (102 mg, 0.165 mmol), and $Pd_2(dba)_3$ (151 mg, 0.165 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was poured into water (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give the crude product, which was purified by silica gel column chromatography (PE/EtOAc = 1:0 to 0:1, CH_2Cl_2/MeOH = 1:0 to 1:1) to afford pure intermediate *tert*-butyl 4-[[[6,7-dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]piperidine-1-carboxylate (500 mg, 63%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{27}H_{35}N_3O_5$, 481.3; *m/z*: found, 482.3 $[M + H]^+$. Then, a solution of this intermediate (500 mg, 1.04 mmol) in HCl/MeOH (20 mL, 2.0 M) was degassed and purged with N_2 3 times and then stirred at 20 °C for 5 h. Then, the mixture was concentrated in reduced pressure at 40 °C to give intermediate 6,7-dimethoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidylmethyl)quinolin-4-amine (400 mg, crude) as a yellow solid. ESI-MS *m/z*: calcd for $C_{22}H_{27}N_3O_3$, 381.2; *m/z*: found, 382.2 $[M + H]^+$. Finally, a mixture of this amine (100 mg, 0.262 mmol), ethyl 4-formylbenzoate (93 mg, 0.524 mmol), CH_3COOH (16 mg, 0.262 mmol), and $NaBH_3CN$ (49 mg, 0.786 mmol) in MeOH (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 70 °C for 2 h. Then, the solution was concentrated in reduced pressure at 40 °C to give a residue, which was purified by prep-HPLC (method 10 described in the Supporting Information) to afford pure compound **36g** (70 mg, 49%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{32}H_{37}N_3O_5$, 543.3; *m/z*: found, 544.2 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 5-[[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]-1-piperidyl]methyl]thiophene-2-carboxylate (**36h**).* A mixture of 6,7-dimethoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidylmethyl)quinolin-4-amine (62 mg, 0.163 mmol, intermediate described in the synthesis of compound **36g**), ethyl 5-formylthiophene-2-carboxylate (60 mg, 0.325 mmol), CH_3COOH (9 mg, 0.163 mmol), and $NaBH_3CN$ (30 mg, 0.488 mmol) in MeOH (3 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 70 °C for 2 h. Then, the solution was concentrated in reduced pressure at 40 °C to afford compound **36h** (60 mg, 76%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{30}H_{35}N_3O_5S$, 549.2; *m/z*: found, 550.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Methyl 3-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]-1-piperidyl]cyclobutanecarboxylate (**36i**).* To a solution of $NaBH_3CN$ (72 mg, 1.15 mmol) was added $ZnCl_2$ (78 mg, 0.576 mmol) in MeOH (5 mL) and the mixture was stirred at 20 °C for 30 min. Then, a mixture of 6,7-dimethoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidylmethyl)quinolin-4-amine(200 mg, 0.524 mmol, intermediate described in the synthesis of compound **36g**) and methyl

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3-oxocyclobutanecarboxylate (73 mg, 0.576 mmol) in MeOH (10 mL) was added and the solution was stirred at 40 °C for 15.5 h. Then, the mixture was filtered and concentrated in vacuum to give compound **36i** (200 mg, 77%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{28}H_{35}N_3O_5$, 493.3; *m/z*: found, 494.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*rac-cis Ethyl 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]cyclohexanecarboxylate (**36j-cis**) and rac-trans Ethyl 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-cyclohexanecarboxylate (**36j-trans**).* A mixture of compound **35**[35] (200 mg, 0.658 mmol), ethyl 4-aminocyclohexanecarboxylate (169 mg, 0.987 mmol), Cs_2CO_3 (429 mg, 1.32 mmol), BINAP (41 mg, 0.066 mmol), and $Pd_2(dba)_3$ (60 mg, 0.066 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 120 °C for 16 h. Then, the mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (method 11 described in the Supporting Information) to afford pure compound **36j-*cis*** (100 mg, 34%) as a yellow solid and **36j-*trans*** (50 mg, 17%) as a yellow solid. **36j-*cis***: ^{1}H NMR (CD_3OD, 400 MHz): δ 7.74 (s, 1H), 7.52 (d, J = 3.2 Hz, 1H), 7.42 (s, 1H), 6.99 (s, 1H), 6.41 (d, J = 2.4 Hz, 1H), 4.18−4.13 (m, 2H), 4.01 (d, J = 2.0 Hz, 6H), 2.50 (s, 3H), 2.41−2.38 (m, 1H), 2.22−2.13 (m, 4H), 1.78−1.62 (m, 5H), 1.29−1.25 (m, 3H); one exchangeable proton was not observed. ESI-MS *m/z*: calcd for $C_{25}H_{30}N_2O_5$, 438.2; *m/z*: found, 439.2 $[M + H]^+$. **36j-*trans***: ^{1}H NMR (CD_3OD, 400 MHz): δ 7.77−7.76 (m, 1H), 7.52 (d, J = 3.2 Hz, 1H), 7.44−7.43 (m, 1H), 7.02−7.00 (m, 1H), 6.43 (d, J = 2.8 Hz, 1H), 4.24−4.19 (m, 2H), 4.03 (d, J = 5.6 Hz, 6H), 2.76 (s, 1H), 2.52 (s, 3H), 2.32 (s, 2H), 2.29−2.24 (m, 1H), 2.05−2.00 (m, 2H), 1.85−1.74 (m, 4H), 1.33−1.29 (m, 3H); one exchangeable proton was not observed. ESI-MS *m/z*: calcd for $C_{25}H_{30}N_2O_5$, 438.2; *m/z*: found, 439.2 $[M + H]^+$.

*Methyl 6-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]methyl]-1-piperidyl]pyridine-3-carboxylate (**36k**).* A mixture of compound **35**[35] (0.2 g, 0.659 mmol, 1 equiv), tertbutyl 4-(aminomethyl)piperidine-1-carboxylate (282.22 mg, 1.32 mmol, 2 equiv), $Pd_2(dba)_3$ (120.59 mg, 0.132 mmol, 0.2 equiv), BINAP (123.00 mg, 0.198 mmol, 0.3 equiv), and Cs_2CO_3 (536.35 mg, 1.65 mmol, 2.5 equiv) in dioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired *m/z* was detected. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (ISCO, 20 g SepaFlash Silica Flash Column) using as eluent a 0−70% ethylacetate/petroleum ether gradient at 100 mL/min. Compound *tert*-butyl 4-[[[6,7-dimethoxy 2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]piperidine-1-carboxylate (0.2 g, 0.415 mmol, 63.07% yield) was obtained as a pure light yellow solid. ESI-MS *m/z*: calcd for $C_{27}H_{35}N_3O_5$, 481.3; *m/z*: found, 482.3 $[M + H]^+$. Then, a solution of this intermediate (0.2 g, 0.415 mmol, 1 eq) in HCl/EtOAc (4.0 M, 10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for1 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired *m/z* was detected. The solvent was removed and the pure intermediate, 6,7-dimethoxy-2-(5-methyl-2-furyl)-*N*-(4-piperidylmethyl)quinolin-4-amine (140 mg, 0.335 mmol, 80.66% yield), was obtained as a light yellow solid. ESI-MS *m/z*: calcd for $C_{22}H_{27}N_3O_3$, 381.2; *m/z*: found, 382.0 $[M + H]^+$. Finally, to a mixture of this amine (140 mg, 0.335 mmol, 1 equiv) in DMF (10 mL) were added K_2CO_3 (138.89 mg, 1.00 mmol, 3 equiv) and methyl 6-chloropyridine-3-carboxylate (68.97 mg, 0.402 mmol, 1.2 equiv). The mixture was stirred at 50 °C for 12 h. HPLC and LC−MS showed that the reaction was completed and one main peak with the desired *m/z* was detected. The mixture was filtered and the filtrate was concentrated to give a residue, which was purified by prep-HPLC (method 43 described in the Supporting Information) to afford the pure compound **36k** (0.1 g, 0.194 mmol, 57.8% yield) as a light yellow solid.^{1}H NMR (CD_3OD, 400 MHz): δ 8.66 (d, J = 1.9 Hz, 1H), 8.03 (dd, J = 2.4, 9.2 Hz, 1H), 7.69 (s, 1H), 7.51 (d, J = 3.3 Hz, 1H), 7.44 (s, 1H), 6.99 (s, 1H), 6.87 (d, J = 9.3 Hz, 1H), 6.42 (dd, J = 0.9, 3.5 Hz, 1H), 4.54 (d, J = 13.1 Hz, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.86 (s, 3H), 3.57 (d, J = 7.2 Hz, 2H), 3.08−2.97 (m, 2H), 2.50 (s, 3H), 2.23 (m, 1H), 1.99 (br d, J = 10.9 Hz, 2H), 1.47−1.34 (m, 2H); one exchangeable proton was not observed. ESI-MS *m/z*: calcd for $C_{29}H_{32}N_4O_5$, 516.2; *m/z*: found, 517.3 $[M + H]^+$.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**37a**).* A mixture of compound **36a** (120.00 mg, 0.226 mmol, 1.00 equiv) and LiOH·H_2O (18.94 mg, 0.452 mmol, 2.00 equiv) in THF/MeOH/H_2O (10.00/1.00/1.00 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 12 h under an N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove THF and MeOH to give a residue. The residue was diluted with water 3 mL and quenched by 2 M HCl to adjust the pH to 4. Then, the yellow solid was precipitated and collected. The yellow solid was concentrated in vacuo to give the compound **37a** (90.00 mg, 0.179 mmol, 79.2% yield) as a yellow solid. ESI-MS *m/z*: calcd for $C_{27}H_{29}N_5O_5$, 503.2; *m/z*: found, 504.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-1-piperidyl]pyrimidine-5-carboxylic Acid (**37b**).* A mixture of compound **36b** (100 mg, 0.193 mmol) and LiOH·H_2O (24 mg, 0.579 mmol) in THF/MeOH/H_2O (6:1:1, 4.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 h. Then, the reaction mixture was concentrated in vacuum and the residue was adjusted to pH 4 with 4.0 M HCl. The obtained solid was filtrated and collected to afford compound **37b** (70 mg, 74%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{26}H_{27}N_5O_5$, 489.2; *m/z*: found, 490.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[8-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-3-azabicyclo[3.2.1]octan-3-yl]pyrimidine-5-carboxylic Acid (**37c**).* To a solution of compound **36c** (0.4 g, 0.717 mmol) in THF/H_2O (2:1, 30 mL) was added LiOH·H_2O (45 mg, 1.08 mmol) and the mixture was stirred at 15 °C for 2 h. Then, the pH was adjusted to 6 with 1.0 M HCl aqueous solution and the mixture was concentrated in vacuum to afford compound **37c** (0.4 g, crude) as a brown solid. ESI-MS *m/z*: calcd for $C_{29}H_{31}N_5O_5$, 529.2; *m/z*: found, 530.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]benzoic Acid (**37d**).* A mixture of compound **36d** (100 mg, 0.224 mmol) and LiOH·H_2O (19 mg, 0.448 mmol) in THF/MeOH/H_2O (3:1:1, 2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 5 h. Then, the mixture was concentrated, the residue was diluted with water (2 mL) and the residue was extracted with EtOAc (3 mL). The aqueous phase was adjusted pH to 3−4 with 2.0 M HCl and the obtained yellow solid was precipitated and filtrated. The filter cake was concentrated to dryness to give compound **37d** (60 mg, 64%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{24}H_{22}N_2O_5$, 418.2; *m/z*: found, 419.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]cyclohexanecarboxylic Acid (**37e**).* A mixture of compound **36e** (100 mg, 0.221 mmol) and LiOH·H_2O (18 mg, 0.442 mmol) in THF/MeOH/H_2O (3:1:1, 5.0 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with H_2O (2 mL) and extracted with EtOAc (5 mL). Then pH of the aqueous phase was adjusted to 3−4 with 2.0 M HCl. The obtained solid was filtered and concentrated to dryness to give compound **37e** (50 mg, 53%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{24}H_{28}N_2O_5$, 424.2; *m/z*: found, 425.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*6-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]pyridine-3-carboxylic Acid (**37f**).* To a solution of compound **36f** (40 mg, 0.092 mmol) in THF/H_2O (2:1, 15 mL) was added LiOH·H_2O (8 mg, 0.184 mmol) and the mixture was stirred at 20 °C

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for 16 h. Then, the reaction mixture was adjust to pH 6 and concentrated in vacuum to give compound **37f** (50 mg, crude) as a yellow solid. ESI-MS *m/z*: calcd for $C_{23}H_{21}N_3O_5$, 419.2; *m/z*: found, 420.2 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*4-[[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]methyl]benzoic Acid (**37g**).* A mixture of compound **36g** (70 mg, 0.129 mmol) and $LiOH·H_2O$ (11 mg, 0.257 mmol) in THF/MeOH/H_2O (3:1:1, 2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (0.5 mL) and extracted with EtOAc (3 mL). Then aqueous phase was acidified with 2.0 M HCl to adjust pH to 3−4. The solution was filtered and the filter cake was concentrated to dryness to give compound **37g** (50 mg, 75%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{30}H_{33}N_3O_5$, 515.3; *m/z*: found, 516.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*5-[[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]methyl]thiophene-2-carboxylic Acid (**37h**).* A mixture of compound **36h** (100 mg, 0.182 mmol) and $LiOH·H_2O$ (23 mg, 0.545 mmol) in THF/MeOH/H_2O (3:1:1, 2.5 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (2 mL) and extracted with EtOAc (3 mL). The aqueous layer was acidified to pH = 3−4 with 1 N HCl and filtered. The filter cake was concentrated to dryness to give compound **37h** (60 mg, 63%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{28}H_{31}N_3O_5S$, 521.2; *m/z*: found, 522.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*3-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]cyclobutanecarboxylic Acid (**37i**).* A mixture of compound **36i** (200 mg, 0.405 mmol) and $LiOH·H_2O$ (51 mg, 1.22 mmol) in MeOH/THF/H_2O (1:3:1, 15.0 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with H_2O (2 mL) and extracted with EtOAc (3 mL). Then the aqueous layer was acidified to pH = 3−4 with 1 N HCl and filtered. The filter cake was concentrated to dryness to give compound **37i** (100 mg, 51%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{27}H_{33}N_3O_5$, 479.2; *m/z*: found, 480.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*rac-cis 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]cyclohexanecarboxylic Acid (**37j-cis**).* A mixture of compound **36j-*cis*** (70 mg, 0.160 mmol) and $LiOH·H_2O$ (20 mg, 0.479 mmol) in MeOH/THF/H_2O (1:3.1, 10.0 mL) was stirred at 20 °C for 3 h. Then, the mixture was concentrated and the residue was diluted with water (3 mL) and extracted with EtOAc (5 mL). Then the aqueous layer was acidified to pH = 3−4 with 1 N HCl and filtered. The filter was concentrated to dryness to afford compound **37j-*cis*** (60 mg, 91%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{23}H_{26}N_2O_5$, 410.2; *m/z*: found, 411.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*rac-trans 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]cyclohexanecarboxylic Acid (**37j-trans**).* A mixture of compound **36j-*trans*** (50 mg, 0.114 mmol) and $LiOH·H_2O$ (14 mg, 0.342 mmol) in MeOH/THF/H_2O (1:3:1, 8.0 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (3 mL) and extracted with EtOAc (5 mL). Then the aqueous layer was acidified to pH = 3−4 with 1 N HCl and filtered. The filter was concentrated to dryness to give compound **37j-*trans*** (50 mg, crude) as a yellow solid. ESI-MS *m/z*: calcd for $C_{23}H_{26}N_2O_5$, 410.2; *m/z*: found, 411.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*6-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]pyridine-3-carboxylic Acid (**37k**).* To a solution of compound **36k** (0.1 g, 0.194 mmol, 1 equiv) in THF (5 mL) and water (5 mL) was added $LiOH·H_2O$ (24.37 mg, 0.581 mmol, 3 equiv). The mixture was stirred at 20 °C for 12 h. The mixture was adjusted pH ∼ 6 with HCl (2 M) and extracted with ethyl acetate (10 mL, three times). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. Compound **37k** (95 mg, 0.189 mmol, 97.7% yield) was obtained as a light yellow solid. ESI-MS *m/z*: calcd for $C_{28}H_{30}N_4O_5$, 502.2; *m/z*: found, 503.3 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**38a**).* A mixture of compound **37a** (120.00 mg, 0.238 mmol, 1.00 equiv), *O*-tetrahydropyran-2-ylhydroxylamine (54.91 mg, 0.358 mmol, 1.50 equiv—as hydrochloride), HOBt (48.30 mg, 0.358 mmol, 1.50 equiv), EDCI (68.53 mg, 0.358 mmol, 1.50 equiv) and DIEA (61.60 mg, 0.477 mmol, 83.24 μL, 2.00 equiv) in DMF (10.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 12 h under N_2 atmosphere. LC−MS showed 70% of desired compound was detected. The reaction mixture was filtrated and the filtrate was concentrated in vacuo to give a residue. The residue was extracted with EtOAc (20 mL, 3 times) and washed with water (10 mL, twice). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by HPLC (method 2 described in the Supporting Information) to afford compound **38a** (80.00 mg, 0.133 mmol, 55.7% yield) as a yellow solid. ESI-MS *m/z*: calcd for $C_{32}H_{38}N_6O_6$, 602.3; *m/z*: found, 603.3 $[M + H]^+$.

*2-[8-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-3-azabicyclo[3.2.1]octan-3-yl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**38c**).* A mixture of compound **37c** (200 mg, 0.378 mmol), $THPONH_2$ (88 mg, 0.755 mmol), EDCI (109 mg, 0.566 mmol), HOBt (76 mg, 0.566 mmol), and DIEA (146 mg, 1.13 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15 °C for 16 h. Then, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (20 mL × 3). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum to obtain compound **38c** (0.1 g, 42%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{34}H_{40}N_6O_6$, 628.3; *m/z*: found, 629.3 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*3-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-cyclobutanecarboxamide (**38i**).* A mixture of compound **37i** (90 mg, 0.188 mmol), $THPONH_2$ (44 mg, 0.375 mmol), DIEA (48 mg, 0.375 mmol), HOBt (30 mg, 0.225 mmol), and EDCI (43 mg, 0.225 mmol) in DMF (5 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (10 mL), and it was extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by prep-HPLC (method 12 described in the Supporting Information) to afford pure compound **38i** (50 mg, 46%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{32}H_{42}N_4O_6$, 578.3; *m/z*: found, 579.3 $[M + H]^+$. This intermediate was used in the next step without further characterization.

*rac-cis 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]-N-tetrahydropyran-2-yloxy-cyclohexanecarboxamide (**38j-cis**).* A mixture of compound **37j-*cis*** (60 mg, 0.146 mmol), $THPONH_2$(34 mg, 0.292 mmol), DIEA (38 mg, 0.292 mmol), HOBt (24 mg, 0.175 mmol), and EDCI (34 mg, 0.175 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 13 described in the Supporting Information) to afford compound **38j-*cis*** (30 mg, 40%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{28}H_{35}N_3O_6$, 509.3; *m/z*: found, 510.3 $[M + H]^+$. This intermediate was used in the next step without further characterization.

rac-trans 4-[[6,7-Dimethoxy-2-(5-methyl-2-furyl)-4-quinolyl]-amino]-N-tetrahydropyran-2-yloxy-cyclohexanecarboxamide

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*(**38j-trans**)*. A mixture of compound **37j-*trans*** (50 mg, 0.122 mmol), $THPONH_2$(29 mg, 0.244 mmol), DIEA (31 mg, 0.244 mmol), HOBt (20 mg, 0.146 mmol), and EDCI (28 mg, 0.146 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times and the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 3 described in the Supporting Information) to afford pure compound **38j-*trans*** (20 mg, 32%) as a yellow solid. ESI-MS *m*/*z*: calcd for $C_{28}H_{35}N_3O_6$, 509.3; *m*/*z*: found, 510.3 $[M + H]^+$. This intermediate was used in the next step without further characterization.

*4-Chloro-6,7-dimethoxy-2-(1-piperidyl)quinoline (**39d**)*. A mixture of compound **34**[35] (1.00 g, 3.87 mmol), piperidine (330 mg, 3.87 mmol), Cs_2CO_3 (2.52 g, 7.75 mmol), $Pd_2(dba)_3$ (355 mg, 0.387 mmol), and BINAP (241 mg, 0.387 mmol) in 1,4-dioxane (100 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 48 °C and the residue was poured into water (200 mL). The aqueous phase was extracted with EtOAc (100 mL × 3) and the combined organic phase was concentrated in reduced pressure at 48 °C to afford compound **39d** (300 mg, 25%) as a yellow solid, which was used in the next step without further purification. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.56 (s, 1H), 7.47 (s, 1H), 7.42 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H), 3.84 (s, 4H), 1.82 (s, 6H). ESI-MS *m*/*z*: calcd for $C_{16}H_{19}ClN_2O_2$, 306.1; *m*/*z*: found, 307.1 $[M + H]^+$.

*4-Chloro-2-(2,5-dimethyl-3-furyl)-6,7-dimethoxy-quinoline (**39e**)*. A mixture of compound **34**[35] (2 g, 7.75 mmol, 1 equiv), 2-(2,5-dimethyl-3-furyl)-4,4,5,5 tetramethyl-1,3,2-dioxaborolane (1.72 g, 7.75 mmol, 1 equiv), K_2CO_3 (2.14 g, 15.50 mmol, 2 equiv), $Pd(PPh_3)_4$ (895.44 mg, 0.775 mmol, 0.1 equiv) in dioxane (20 mL), and water (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 80 °C for 2 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired *m*/*z* was detected. The mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO, 40 g SepaFlash Silica Flash Column) using as eluent a 0−15% ethylacetate/petroleum ether gradient at 100 mL/min. Compound **39e** was obtained as a light yellow solid: 1 g, 3.15 mmol, 40.61% yield. ESI-MS *m*/*z*: calcd for $C_{17}H_{16}ClNO_3$, 317.1; *m*/*z*: found, 318.1 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 2-[4-[[(6,7-Dimethoxy-2-methyl-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**40a**)*. A mixture of compound **39a**[45,46] (200 mg, 0.841 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 334 mg, 1.26 mmol), $Pd_2(dba)_3$ (154 mg, 0.168 mmol), BINAP (157 mg, 0.252 mmol), and Cs_2CO_3 (548 mg, 1.68 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 48 h. Then, the reaction mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford pure compound **40a** (230 mg, 59%) as a yellow oil. ESI-MS *m*/*z*: calcd for $C_{25}H_{31}N_5O_4$, 465.2; *m*/*z*: found, 466.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 2-[4-[[(2-Cyclohexyl-6,7-dimethoxy-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**40b**)*. A mixture of compound **39g**[46] (300 mg, 0.987 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 313 mg, 1.19 mmol), Cs_2CO_3 (643 mg, 1.98 mmol), BINAP (61 mg, 0.099 mmol), and $Pd_2(dba)_3$ (90 mg, 0.099 mmol) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h. Then, the mixture was filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford pure intermediate ethyl 2-[4-[[[2-(cyclohexen-1-yl)-6,7-dimethoxy-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (300 mg, 57%) as a yellow solid. ESI-MS *m*/*z*: calcd for $C_{30}H_{37}N_5O_4$, 531.3; *m*/*z*: found, 532.4 $[M + H]^+$. To a solution of this intermediate (300 mg, 0.564 mmol) in MeOH (20 mL) was added Pd/C (10%, 30 mg) under an H_2 atmosphere. The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (15 Psi) at 20 °C for 16 h. Then, the mixture was filtered and concentrated in vacuum to afford compound **40b** (200 mg, 66%) as a yellow solid. ESI-MS *m*/*z*: calcd for $C_{30}H_{39}N_5O_4$, 533.3; *m*/*z*: found, 534.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[4-[[(6,7-Dimethoxy-2-phenyl-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**40c**)*. A mixture of compound **39c**[46] (150 mg, 0.500 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]-pyrimidine-5-carboxylate (**51**, 145 mg, 0.550 mmol), Cs_2CO_3 (326 mg, 1.00 mmol), BINAP (31 mg, 0.050 mmol), and $Pd_2(dba)_3$ (45 mg, 0.050 mmol) in 1,4-dioxane (15 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 16 h. Then, the mixture was filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2, CH_2Cl_2/MeOH = 10:1) to afford pure compound **40c** (200 mg, 76%) as a yellow solid. ESI-MS *m*/*z*: calcd for $C_{30}H_{33}N_5O_4$, 527.3; *m*/*z*: found, 528.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 2-[4-[[[6,7-Dimethoxy-2-(1-piperidyl)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**40d**)*. A mixture of compound **39d** (250 mg, 0.815 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 323 mg, 1.22 mmol), $Pd_2(dba)_3$ (75 mg, 0.081 mmol), BINAP (51 mg, 0.081 mmol), and Cs_2CO_3 (531 mg, 1.63 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 16 h. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-TLC (CH_2Cl_2/MeOH = 10:1) to afford pure compound **40d** (270 mg, 62%) as a yellow solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.78 (s, 2H), 7.37 (s, 1H), 7.07 (s, 1H), 6.92 (s, 1H), 4.35−4.29 (m, 2H), 3.92 (s, 6H), 3.72 (s, 1H), 3.58 (br s, 4H), 3.30−3.27 (m, 2H), 3.04−2.98 (m, 2H), 2.22 (s, 2H), 1.98−1.95 (m, 2H), 1.87−1.86 (m, 1H), 1.70 (s, 6H), 1.36 (s, 3H), 1.31−1.27 (m, 2H). ESI-MS *m*/*z*: calcd for $C_{29}H_{38}N_6O_4$, 534.3; *m*/*z*: found, 535.3 $[M + H]^+$.

*Ethyl 2-[4-[[[2-(2,5-Dimethyl-3-furyl)-6,7-dimethoxy-4-quinolyl]-amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**40e**)*. A mixture of compound **39e** (1 g, 3.15 mmol, 1 equiv), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 1.23 g, 4.09 mmol, 1.3 equiv), $Pd_2(dba)_3$ (576.35 mg, 0.629 mmol, 0.2 equiv), BINAP (587.86 mg, 0.944 mmol, 0.3 equiv), and Cs_2CO_3 (3.08 g, 9.44 mmol, 3 equiv) in 1,4-dioxane (20 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 12 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired *m*/*z* was detected. The mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO, 40 g SepaFlash Silica Flash Column) using as eluent a 0−100% ethylacetate/petroleum ether gradient at 100 mL/min. Compound **40e** was obtained as a light yellow solid: 0.8 g, 1.47 mmol, 46.6% yield. ESI-MS *m*/*z*: calcd for $C_{30}H_{35}N_5O_5$, 545.3; *m*/*z*: found, 546.2 $[M + H]^+$. This compound was used in the next step without further characterization.

*Ethyl 2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-thienyl)-4-quinolyl]-amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**40f**)*. A mixture of compound **39f**[46] (0.17 g, 0.532 mmol, 1 equiv), ethyl 2-[4-(aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**, 207.86 mg, 0.691 mmol, 1.3 equiv), $Pd_2(dba)_3$ (97.35 mg, 0.106 mmol, 0.2 equiv), BINAP (99.3 mg, 0.160 mmol, 0.3 equiv), and Cs_2CO_3 (519.6 mg, 1.59 mmol, 3 equiv) indioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 120 °C for 12 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired *m*/*z* was detected. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (ISCO, 12 g SepaFlash Silica Flash Column) using as eluent a 0−80% ethylacetate/petroleum ether gradient at 50 mL/min. Compound **40f** was obtained as a light yellow solid (0.15 g, 0.274 mmol, 51.5% yield), which was used in the next step without further purification. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.85 (s, 2H), 7.44 (br s, 1H), 7.37 (s, 1H), 6.86 (s, 1H), 6.79−6.78 (m, 1H), 6.75 (s, 1H), 4.99 (d, *J* = 13.2 Hz, 2H), 4.75 (br s, 1H), 4.35

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(q, J = 7.2 Hz, 2H), 4.02 (s, 6H), 3.34 (t, J = 6.2 Hz, 2H), 3.03−2.97 (m, 2H), 2.55 (s, 3H), 2.15−2.05 (m, 1H), 2.01 (d, J = 11.9 Hz, 2H), 1.38 (t, J = 7.2 Hz, 5H). ESI-MS m/z: calcd for $C_{29}H_{33}N_5O_4S$, 547.2; m/z: found, 548.3 $[M + H]^+$.

*2-[4-[[(6,7-Dimethoxy-2-methyl-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**41a**).* To a solution of compound **40a** (230 mg, 0.494 mmol) in THF/H_2O (2:1, 30 mL) was added LiOH·H_2O (41 mg, 0.988 mmol) and the mixture was stirred at 20 °C for 16 h. Then, the reaction mixture was adjusted to pH 6 and concentrated in vacuum to give compound **41a** (300 mg, crude) as a yellow solid that was used in the next step without further purification. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.91 (s, 2H), 7.76 (s, 1H), 7.20 (s, 1H), 6.69 (s, 1H), 4.82−4.80 (m, 2H), 4.02−4.00 (m, 6H), 3.53−3.51 (m, 2H), 3.28−3.21 (m, 2H), 2.66 (s, 3H), 2.35 (s, 1H), 2.08−2.05 (m, 2H), 1.50−1.48 (m, 2H); two exchangeable protons were not observed. ESI-MS m/z: calcd for $C_{23}H_{27}N_5O_4$, 437.2; m/z: found, 438.3 $[M + H]^+$.

*2-[4-[[(2-Cyclohexyl-6,7-dimethoxy-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**41b**).* A mixture of compound **40b** (200 mg, 0.375 mmol) and LiOH·H_2O (47 mg, 1.12 mmol) in MeOH/THF/H_2O (1:3:1, 5 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (2 mL) and extracted with EtOAc (3 mL). Then, the aqueous phase was acidified to pH = 3−4 with 1 N HCl and filtered. The filter cake was concentrated to dryness to give compound **41b** (120 mg, 63%) as a yellow solid. ESI-MS m/z: calcd for $C_{28}H_{35}N_5O_4$, 505.3; m/z: found, 506.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[(6,7-Dimethoxy-2-phenyl-4-quinolyl)amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**41c**).* A mixture of compound **40c** (200 mg, 0.379 mmol) and LiOH·H_2O (47 mg, 1.14 mmol) in MeOH/THF/H_2O (1:3:1, 8 mL) was stirred at 20 °C for 16 h. Then, the mixture was concentrated and the residue was diluted with water (5 mL) and extracted with EtOAc (10 mL). The aqueous phase was acidified to pH = 3−4 with 1 N HCl and filtered. The filter cake was concentrated to dryness to afford compound **41c** (150 mg, 79%) as a yellow solid. ESI-MS m/z: calcd for $C_{28}H_{29}N_5O_4$, 499.2; m/z: found, 500.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6,7-Dimethoxy-2-(1-piperidyl)-4-quinolyl]amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**41d**).* To a solution of compound **40d** (270 mg, 0.505 mmol) in THF/H_2O (2:1, 15 mL) was added LiOH·H_2O (32 mg, 0.757 mmol) and the mixture was stirred at 15 °C for 16 h. Then, the pH was adjusted to 5 with 2.0 M HCl aqueous solution and the mixture was concentrated in vacuum to obtain crude compound **41d** (300 mg, crude) as a yellow oil. ESI-MS m/z: calcd for $C_{27}H_{34}N_6O_4$, 506.3; m/z: found, 507.3 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[2-(2,5-Dimethyl-3-furyl)-6,7-dimethoxy-4-quinolyl]-amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**41e**).* To a solution of **40e** (0.8 g, 1.47 mmol, 1 equiv) in THF (10 mL)and water (5 mL) was added LiOH·H_2O (307.61 mg, 7.33 mmol, 5 equiv).The mixture was stirred at 25 °C for 12 h. LC−MS showed that the reaction was completed and one main peak with the desired m/z was detected. The mixture was adjusted to pH ∼ 5 with aqueous HCl (2 M) at room temperature. Some precipitate was formed and, after filtration, the solid was collected to afford compound **41e** as a light yellow solid: 0.6 g, 1.16 mmol, 79.1% yield. ESI-MS m/z: calcd for $C_{28}H_{31}N_5O_5$, 517.2; m/z: found, 518.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-thienyl)-4-quinolyl]amino]-methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**41f**).* To a solution of **40f** (150 mg, 0.274 mmol, 1 equiv) in THF (8 mL) and water (4 mL) was added LiOH·H_2O (57.46 mg, 1.37 mmol, 5 equiv). The mixture was stirred at 25 °C for 12 h. LC−MS showed that the reaction was completed and one main peak with the desired m/z was detected. The mixture was adjusted to pH ∼ 5 with aqueous HCl (2 M) at room temperature and then filtered. Compound **41f** was obtained as a yellow solid: 120 mg, 0.231 mmol, 84.3% yield. ESI-MS m/z: calcd for $C_{27}H_{29}N_5O_4S$, 519.2; m/z: found, 520.2 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[(6,7-Dimethoxy-2-methyl-4-quinolyl)amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**42a**).* A mixture of compound **41a** (300 mg, 0.685 mmol), $THPONH_2$ (161 mg, 1.37 mmol), EDCI (263 mg, 1.37 mmol), HOBt (185 mg, 1.37 mmol), and DIEA (265 mg, 2.06 mmol) in DMF (30 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 20 °C for 16 h. Then, the reaction mixture was quenched with water (10 mL) and concentrated in vacuum to give a residue. The residue was extracted with EtOAc (3 mL × 3) and the organic layers were dried over Na_2SO_4 and concentrated in vacuum to give compound **42a** (300 mg, 82%) as a yellow oil. ESI-MS m/z: calcd for $C_{28}H_{36}N_6O_5$, 536.3; m/z: found, 537.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[(2-Cyclohexyl-6,7-dimethoxy-4-quinolyl)amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**42b**).* A mixture of compound **41b** (120 mg, 0.237 mmol), $THPONH_2$ (56 mg, 0.475 mmol), DIEA (61 mg, 0.475 mmol), HOBt (38 mg, 0.285 mmol), and EDCI (55 mg, 0.295 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 3 described in the Supporting Information) to afford pure compound **42b** (50 mg, 35%) as a yellow solid. ESI-MS m/z: calcd for $C_{33}H_{44}N_6O_5$, 604.3; m/z: found, 605.4 $[M + H]^+$. This compound was used in the next step without further characterization.

*2-[4-[[(6,7-Dimethoxy-2-phenyl-4-quinolyl)amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**42c**).* A mixture of compound **41c** (150 mg, 0.300 mmol), $THPONH_2$ (70 mg, 0.600 mmol), DIEA (77 mg, 0.600 mmol), HOBt (48 mg, 0.360 mmol), and EDCI (69 mg, 0.360 mmol) in DMF (15 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C and the residue was purified by prep-HPLC (method 4 described in the Supporting Information) to afford pure compound **42c** (60 mg, 33%) as a yellow solid. ESI-MS m/z: calcd for $C_{33}H_{38}N_6O_5$, 598.3; m/z: found, 599.3 $[M + H]^+$. This compound was used in the next step without further characterization.

*2-[4-[[[6,7-Dimethoxy-2-(1-piperidyl)-4-quinolyl]amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**42d**).* A mixture of compound **41d** (300 mg, 0.592 mmol), $THPONH_2$ (139 mg, 1.18 mmol), EDCI (227 mg, 1.18 mmol), HOBt (160 mg, 1.18 mmol), and DIEA (229 mg, 1.78 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 15 °C for 16 h. Then, the reaction mixture was quenched with water (5 mL) and concentrated in vacuum to give a residue. The residue was dissolved in 20 mL of CH_3CN (20 mL) and filtered. The filtrate was concentrated in vacuum to afford compound **42d** (500 mg, crude) as a brown oil. ESI-MS m/z: calcd for $C_{32}H_{43}N_7O_5$, 605.3; m/z: found, 606.4 $[M + H]^+$.This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[2-(2,5-Dimethyl-3-furyl)-6,7-dimethoxy-4-quinolyl]-amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**42e**).* A mixture of compound **41e** (0.6 g, 1.16 mmol, 1 equiv), *O*-tetrahydropyran-2-ylhydroxylamine (271.60 mg, 2.32 mmol, 2 equiv), HOBt (313.28 mg, 2.32 mmol, 2 equiv), EDCI (444.46 mg, 2.32 mmol, 2 equiv), and DIEA (749.11 mg, 5.80 mmol, 1.01 mL, 5 equiv) in DMF (8 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 12 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired m/z was detected. The residue was poured into ice-water (w/w = 1/1) (30 mL). The aqueous phase was extracted with ethyl acetate (20 mL, three times). The combined organic phase was washed with brine (30 mL), dried with anhydrous

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Na_2SO_4, concentrated in vacuum, and purified by prep-HPLC (method 44 described in the Supporting Information) to afford the pure compound **42e**, as a light yellow solid: 0.6 g, 0.973 mmol, 83.9% yield. ESI-MS *m/z* calcd for $C_{33}H_{40}N_6O_6$, 616.3; *m/z*: found, 617.3 $[M + H]^+$.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-thienyl)-4-quinolyl]amino]-methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**42f**).* A mixture of compound **41f** (50 mg, 0.096 mmol, 1 equiv), *O*-tetrahydropyran-2-ylhydroxylamine (22.54 mg, 0.192 mmol, 2 equiv), HOBt (26.0 mg, 0.192 mmol, 2 equiv), EDCI (36.89 mg, 0.192 mmol, 2 equiv), and DIEA (62.18 mg, 0.481 mmol, 83.8 μL, 5 equiv) in DMF (5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 12 h under an N_2 atmosphere. LC−MS showed that the reaction was completed and one main peak with the desired *m/z* was detected. The residue was poured into ice-water (w/w = 1/1) (6 mL). The aqueous phase was extracted with ethyl acetate (5 mL, 3 times). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. Compound **42f** was obtained as a light yellow solid (40mg). ESI-MS *m/z*: calcd for $C_{32}H_{38}N_6O_5S$, 618.3; *m/z*: found, 619.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*Ethyl 2-[4-[[(2-Chloro-6,7-dimethoxy-quinazolin-4-yl)amino]-methyl]-1-piperidyl]pyrimidine-5-carboxylate (**44**).* A mixture of commercially available 2,4-dichloro-6,7-dimethoxy-quinazoline (**43**) (0.2 g, 0.772 mmol), ethyl 2-[4-(aminomethyl)-1-piperidyl]-pyrimidine-5-carboxylate (**51**, 232 mg, 0.772 mmol, HCl), and K_2CO_3(320 mg, 2.32 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 80 °C for 12 h under an N_2 atmosphere. Then, the mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO; 12 g SepaFlash Silica FlashColumn, Eluent of 0−40% EtOAc/PE gradient at 100 mL/min) to obtain pure **44** (200 mg, 53%) as a light yellow solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.83 (s, 2H), 7.15 (s, 1H), 6.85 (s, 1H), 5.73 (br s, 1H), 4.94 (br d, *J* = 13.2 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.63 (t, *J* = 6.4 Hz, 2H), 3.02−2.95 (m, 2H), 2.13−2.12 (m, 1H), 1.93 (br d, *J* = 11.2 Hz, 2H), 1.39−1.32 (m, 5H). ESI-MS *m/z*: calcd for $C_{23}H_{27}ClN_6O_4$, 486.2; *m/z*: found, 487.2 $[M + H]^+$.

*Ethyl 2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)quinazolin-4-yl]-amino]methyl]-1-piperidyl]pyrimidine-5-carboxylate (**45**).* A mixture of **44** (150 mg, 0.308 mmol),4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (64 mg, 0.308), K_2CO_3 (128 mg, 0.924 mmol) and $Pd(PPh_3)_4$ (36 mg, 0.031 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 12 h under an N_2 atmosphere. Then, the mixture was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (ISCO; 12 g SepaFlash Silica FlashColumn, eluent of 0−40% EtOAc/PE gradient at 75 mL/min) to obtain pure **45** (140 mg, crude) as a light yellow solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.83 (s, 2H), 7.36 (s, 1H), 7.16 (d, *J* = 3.3 Hz, 1H), 6.88 (s, 1H), 6.15 (dd, *J* = 0.9, 3.1 Hz, 1H), 5.58 (br s, 1H), 4.94 (br d, *J* = 13.5 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 0.9 Hz, 6H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.02−2.95 (m, 2H), 2.46 (s, 3H), 2.20−2.17 (m, 1H), 1.96 (br d, *J* = 10.8 Hz, 2H), 1.41−1.33 (m, 5H). ESI-MS *m/z*: calcd for $C_{28}H_{32}N_6O_5$, 532.2; *m/z*: found, 533.3 $[M + H]^+$.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)quinazolin-4-yl]-amino]methyl]-1-piperidyl]pyrimidine-5-carboxylic Acid (**46**).* To a solution of **45** (190 mg, 0.356 mmol) in THF/H_2O (2:1, 12 mL) was added LiOH·H_2O (45 mg, 1.07 mmol) and the mixture was stirred at 25 °C for 12 h. Then, the mixture was adjusted to pH ∼ 5 with aqueous HCl (2 M) and extracted with EtOAc (5 mL × 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to afford **46** (150 mg, 83%) as a light yellow solid. ESI-MS *m/z*: calcd for $C_{26}H_{28}N_6O_5$, 504.2; *m/z*: found, 505.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

*2-[4-[[[6,7-Dimethoxy-2-(5-methyl-2-furyl)quinazolin-4-yl]-amino]methyl]-1-piperidyl]-N-tetrahydropyran-2-yloxy-pyrimidine-5-carboxamide (**47**).* A mixture of **46** (150 mg, 0.297 mmol), $THPONH_2$ (70 mg, 0.594 mmol), HOBt (80 mg, 0.594 mmol), EDCI (114 mg, 0.594 mmol), and DIEA (192 mg, 1.49 mmol) in DMF (10 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 12 h under an N_2 atmosphere. Then, the residue was poured into ice-water (w/w = 1/1) (10 mL) and the aqueous phase was extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to afford **47** (130 mg, crude) as a light yellow solid. ESI-MS *m/z*: calcd for $C_{31}H_{37}N_7O_6$, 603.3; *m/z*: found, 604.3 $[M + H]^+$. This intermediate was used in the next step without further purification or characterization.

Synthesis of Intermediates. *Ethyl 2-[4-[(tert-Butoxycarbonylamino)methyl]-1-piperidyl]pyrimidine-5-carboxylate (**50**).* A mixture of *tert*-butyl *N*-(4-piperidylmethyl)carbamate (**48**, 1.00 g, 4.67 mmol), ethyl 2-chloropyrimidine-5-carboxylate (**49**, 870 mg, 4.67 mmol), BINAP (290 mg, 0.467 mmol), Cs_2CO_3 (3.04 g, 9.34 mmol), and $Pd_2(dba)_3$ (427 mg, 0.467 mmol) in 1,4-dioxane (100 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 110 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (50 mL), and it was extracted with EtOAc (30 mL × 3). The combined organic phase was washed with brine (30 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 1:0 to 2:1) to afford pure **50** (1.20 g, 70%) as a yellow solid. ESI-MS *m/z*: calcd for $C_{18}H_{28}N_4O_4$, 364.2; *m/z*: found, 365.2 $[M + H]^+$.

*Ethyl 2-[4-(Aminomethyl)-1-piperidyl]pyrimidine-5-carboxylate (**51**).* A solution of **50** (1.20 g, 3.29 mmol) in HCl/EtOAc (30 mL, 2.0 M) was stirred at 20 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (20 mL), and it was extracted with EtOAc (10 mL × 3). The aqueous phase was concentrated in vacuum and then dissolved in MeOH (20 mL). $NaHCO_3$ (200 mg) was added and the mixture was stirred at 25 °C for 1 h. The mixture was filtered and concentrated in vacuum to afford **51** (700 mg, 80%) as a white solid, which was used for the synthesis of target compounds without further purification. ^1H NMR (CD_3OD, 400 MHz): δ 8.77 (d, *J* = 8.0 Hz, 2H), 4.95−4.91 (m, 2H), 4.35−4.29 (m, 2H), 3.04−2.97 (m, 2H), 2.78−2.77 (m, 2H), 1.95−1.86 (m, 3H), 1.37−1.34 (m, 3H), 1.24−1.20 (m, 2H). ESI-MS *m/z*: calcd for $C_{13}H_{20}N_4O_2$, 264.2; *m/z*: found, 265.2 $[M + H]^+$.

*Methyl 4-[[4-[(tert-Butoxycarbonylamino)methyl]-1-piperidyl]-methyl]benzoate (**53**).* To a solution of methyl 4-formylbenzoate (**52**, 200 mg, 1.22 mmol) in MeOH (20 mL) were added $NaBH_3CN$ (230 mg, 3.66 mmol), AcOH (77 mg, 1.28 mmol), and *tert*-butyl *N*-(4-piperidylmethyl)carbamate (**48**, 275 mg, 1.28 mmol) and the mixture was stirred at 80 °C for 3 h. Then, the reaction was quenched with water (5 mL) and MeOH was removed. The residue was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was purified by prep-TLC (SiO_2, PE/EtOAc = 1/1) to afford pure **53** (220 mg, 50%) as a white solid. ESI-MS *m/z*: calcd for $C_{20}H_{30}N_2O_4$, 362.2; *m/z*: found, 363.1 $[M + H]^+$.

*Methyl 4-[[4-(Aminomethyl)-1-piperidyl]methyl]benzoate (**54**).* A solution of **53** (220 mg, 0.607 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 1 h. Then, the mixture was concentrated to give a residue. The residue was diluted with MeOH and the pH was adjusted to 7−8 with $NaHCO_3$. Then, the mixture was filtered and the filtrate was concentrated to give **54** (140 mg, 88%) as a white solid, which was used for the synthesis of compound **17d** without further purification. ^1H NMR (CD_3OD, 400 MHz): δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 3.91 (s, 3H), 3.58 (d, *J* = 6.4 Hz, 2H), 2.94−2.90 (m, 2H), 2.56−2.53 (m, 2H), 2.08−2.02 (m, 2H),

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1.77−1.74 (m, 2H), 1.19−1.15 (m, 3H). ESI-MS *m*/*z*: calcd for $C_{15}H_{22}N_2O_2$, 262.2; *m*/*z*: found, 263.3 $[M + H]^+$.

*Methyl 4-[[4-(tert-Butoxycarbonylamino)-1-piperidyl]methyl]-benzoate (**56**).* A mixture of *tert*-butyl *N*-(4-piperidyl)carbamate (**55**, 1.00 g, 4.99 mmol), methyl 4-formylbenzoate (**52**, 820 mg, 4.99 mmol), $NaBH_3CN$ (941 mg, 14.98 mmol), and CH_3COOH (315 mg, 5.24 mmol) in MeOH (30 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 70 °C for 2 h. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (50 mL), and it was extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine (50 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give **56** (1.00 g, 57%) as a white solid. ESI-MS *m*/*z*: calcd for $C_{19}H_{28}N_2O_4$, 348.2; *m*/*z*: found, 349.2$[M + H]^+$.

*Methyl 4-[(4-Amino-1-piperidyl)methyl]benzoate (**57**).* A solution of **56** (1.00 g, 2.87 mmol) in HCl/EtOAc (30 mL, 2.0 M) was stirred at 20 °C for 5 h under an N_2 atmosphere. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was dissolved in MeOH (50 mL) and $NaHCO_3$ (400 mg) was added. The reaction mixture was stirred at 25 °C for 1 h. The mixture was filtered and concentrated in vacuum to give **57** (300 mg, 42%) as a white solid, which was used for the synthesis of compound **17e** without further purification. ^1H NMR (CD_3OD, 400 MHz): δ 8.02 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 2H), 3.19−3.14 (m, 3H), 2.56−2.50 (m, 2H), 2.11−2.08 (m, 2H), 1.87−1.80 (m, 2H). ESI-MS *m*/*z*: calcd for $C_{14}H_{20}N_2O_2$, 248.2; *m*/*z*: found, 249.1 $[M + H]^+$.

*Methyl 4-[4-[(tert-Butoxycarbonylamino)methyl]-1-piperidyl]-benzoate (**59**).* To a solution of methyl 4-fluorobenzoate (**58**, 500 mg, 3.24 mmol) in DMSO (35 mL) were added K_2CO_3 (897 mg, 6.49 mmol) and **48** (695 mg, 3.24 mmol) and the mixture was stirred at 90 °C for 16 h. Then, the mixture was filtered and the filtrate was diluted with the water (10 mL) and it was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1 to 2:1) to afford pure **59** (430 mg, 38%) as a white solid. ESI-MS *m*/*z*: calcd for $C_{19}H_{28}N_2O_4$, 348.2; *m*/*z*: found, 349.2$[M + H]^+$.

*Methyl 4-[4-(Aminomethyl)-1-piperidyl]benzoate (**60**).* A solution of **59** (430 mg, 1.23 mmol) in HCl/EtOAc (15 mL, 2.0 M) was stirred at 20 °C for 1 h. Then, the mixture was concentrated to give a residue, which was diluted with MeOH (15 mL) and alkalized with a saturated aqueous $NaHCO_3$ solution. The mixture was filtered, and the filtrate was concentrated to give **60** (230 mg, 75%) as a white solid, which was used for the synthesis of compound **17f** without further purification. ESI-MS *m*/*z*: calcd for $C_{14}H_{20}N_2O_2$, 248.2; *m*/*z*: found, 249.3 $[M + H]^+$.

*(4-Cyanocyclohexen-1-yl)trifluoromethanesulfonate (**62**).* To a stirred solution of the commercially available 4-oxocyclohexanecarbonitrile (4.00 g, 32.48 mmol) and KHMDS (1.0 M, 42.87 mL) in THF (200 mL) under N_2 at −78 °C was added $PhNTf_2$ (14.85 g, 41.57 mmol) and the mixture was stirred for 8 h at 20 °C. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (100 mL), and it was extracted with EtOAc (100 mL × 3). The combined organic phase was washed with brine (100 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 50:1 to 1:1) to give **62** (3.00 g, 36%) as a colorless oil. ESI-MS *m*/*z*: calcd for $C_8H_8F_3NO_3S$, 255.0; *m*/*z*: found, 256.1$[M + H]^+$.

*Methyl 4-(4-Cyanocyclohexen-1-yl)benzoate (**63**).* A mixture of **62** (2.50 g, 9.80 mmol), (4-methoxycarbonylphenyl)boronic acid (1.47 g, 8.16 mmol), $Pd(PPh_3)_4$ (943 mg, 0.816 mmol), and K_2CO_3 (2.26 g, 16.33 mmol) in 1,4-dioxane/H_2O (10:1, 55 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90 °C for 1 h. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (50 mL), and it was extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine (50 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give a crude product, which was purified by silica gel column chromatography (PE/EtOAc = 40:1 to 2:1) to afford pure **63** (2.00 g, crude) as a yellow solid. ESI-MS *m*/*z*: calcd for $C_{15}H_{15}NO_2$, 241.1; *m*/*z*: found, 242.1 $[M + H]^+$.

*Methyl 4-[4-(Aminomethyl)cyclohexyl]benzoate (**64**).* To a solution of **63** (1.50 g, 6.22 mmol) in HCl (1.23 mL, 36% purity) and MeOH (20 mL) was added $Pd(OH)_2/C$ (10%, 500 mg) under an H_2 atmosphere. The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (50 Psi) at 30 °C for 16 h. Then, the reaction mixture was concentrated in vacuum to give a residue, which was purified by prep-HPLC (method 37 described in the Supporting Information) to afford pure **64** (200 mg, 13%) as a white solid. ^1H NMR (CD_3OD, 400 MHz): δ 7.94−7.92 (m, 2H), 7.37−7.32 (m, 2H), 3.88 (s, 3H), 2.81 (d, J = 7.2 Hz, 1H), 2.70 (s, 1H), 2.60 (d, J = 6.4 Hz, 1H), 1.96−1.91 (m, 2H), 1.76−1.69 (m, 5H), 1.55−1.52 (m, 1H), 1.15−1.12 (m, 1H). ESI-MS *m*/*z*: calcd for $C_{15}H_{21}NO_2$, 247.2; *m*/*z*: found, 248.2 $[M + H]^+$.

*Methyl 4-[4-[(E)-Hydroxyiminomethyl]phenyl]benzoate (**66**).* A mixture of the commercially available methyl 4-(4-formylphenyl)-benzoate (1.00 g, 4.16 mmol), $NH_2OH{\cdot}HCl$ (289 mg, 4.16 mmol), and NaOAc (273 mg, 3.33 mmol) in EtOH (40 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 25 °C for 16 h. Then, the mixture was concentrated in reduced pressure at 40 °C, the residue was poured into water (10 mL), and it was extracted with CH_2Cl (10 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give **66** (500 mg, 47%) as a yellow solid. ESI-MS *m*/*z*: calcd for $C_{15}H_{13}NO_3$, 255.1; *m*/*z*: found, 256.1$[M + H]^+$.

*Methyl 4-[4-[(tert-Butoxycarbonylamino)methyl]phenyl]-benzoate (**67**).* To a solution of **66** (500 mg, 1.96 mmol) and BOC_2O (427 mg, 1.96 mmol) in EtOH (30 mL) was added Pd/C (10%, 200 mg) under an H_2 atmosphere. The suspension was degassed and purged with H_2 3 times and then the mixture was stirred under H_2 (50 Psi) at 20 °C for 16 h. Then, the mixture was filtered and concentrated under vacuum to give a residue, which was purified by silica gel column chromatography (PE/EtOAc = 1:0 to 5:1) to afford pure **67** (400 mg, 59%) as a white solid. ESI-MS *m*/*z*: calcd for $C_{20}H_{23}NO_4$, 341.2; *m*/*z*: found, 342.2 $[M + H]^+$.

*Methyl 4-[4-(Aminomethyl)phenyl]benzoate (**68**).* A solution of **67** (400 mg, 1.17 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 5 h under an N_2 atmosphere. Then, the reaction mixture was concentrated in vacuum to give a residue, which was dissolved in MeOH (20 mL). Then, $NaHCO_3$ (200 mg) was added and the solution was stirred at 25 °C for 1 h. The mixture was filtered and concentrated in vacuum to give **68** (250 mg, 88%) as a white solid, which was used for the synthesis of compound **17i** without further purification. ^1H NMR (CD_3OD, 400 MHz): δ 8.12−8.10 (m, 2H), 7.79−7.76 (m 4H), 7.59−7.57 (m, 2H), 4.19 (s, 2H), 3.93 (s, 3H). ESI-MS *m*/*z*: calcd for $C_{15}H_{15}NO_2$, 241.1; *m*/*z*: found, 242.1 $[M + H]^+$.

*Ethyl 4-(4-Formylphenyl)cyclohex-3-ene-1-carboxylate (**70**).* A mixture of (4-formylphenyl)boronic acid (1 g, 6.67 mmol), the commercially available ethyl 4-(trifluoromethylsulfonyloxy)cyclohex-3-ene-1-carboxylate (2.42 g, 8.00 mmol), Pd/C (100 mg, 10% purity), and PPh_3 (157 mg, 0.600 mmol) in DME (50 mL) and H_2O (25 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 80 °C for 16 h. Then, the mixture was filtered and the filtrate was concentrated to give a residue, which was purified by silica gel column chromatography (PE/EtOAc = 20:1 to 5:1) to afford **70** (950 mg, 55%) as a yellow solid.^1H NMR ($CDCl_3$, 400 MHz): δ 9.99 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 6.30 (s, 1H), 4.19 (q, J = 7.4 Hz, 2H), 2.71−2.59 (m, 1H), 2.54−2.53 (m, 4H), 2.27−2.15 (m, 1H), 1.95−1.79 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). ESI-MS *m*/*z*: calcd for $C_{16}H_{18}O_3$, 258.2; *m*/*z*: found, 259.2 $[M + H]^+$.

*Ethyl 4-[4-[(E)-Hydroxyiminomethyl]phenyl]cyclohex-3-ene-1-carboxylate (**71**).* To a solution of **70** (950 mg, 3.68 mmol) in EtOH (5 mL) and H_2O (2.5 mL) were added $NH_2OH{\cdot}HCl$ (256 mg,

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3.68 mmol) and NaOAc (241 mg, 2.94 mmol) and the mixture was stirred at 20 °C for 16 h. Then, the reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with water (30 mL) and it was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give a residue, which was purified by silica gel column chromatography (PE/EtOAc = 10:1 to 5:1) to afford pure **71** (980 mg, 97%) as a yellow solid.^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 6.19 (s, 1H), 4.18 (q, J = 7.0 Hz, 2H), 2.68−2.56 (m, 1H), 2.51 (m, 4H), 2.25−2.16 (m, 1H), 1.92−1.77 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). ESI-MS m/z: calcd for $C_{16}H_{19}NO_3$, 273.1; m/z: found, 274.2 $[M + H]^+$.

*Ethyl 4-[4-[(tert-Butoxycarbonylamino)methyl]phenyl]-cyclohexanecarboxylate (**72**).* To a solution of BOC_2O (822 mg, 3.76 mmol) in EtOH (20 mL) were added **71** (980 mg, 3.59 mmol), Et_3N (544 mg, 5.4 mmol), and Pd/C (10% purity, 100 mg) under an N_2 atmosphere. The suspension was degassed and purged with H_2 3 times and then the mixture was stirred under H_2 (50 Psi) at 20 °C for 16 h. Then, the mixture was filtered and the filtrate was concentrated to give a residue, which was purified by silica gel column chromatography (PE/EtOAc = 5:1 to 2:1) to afford pure compound **72** (950 mg, 73%) as a yellow oil. ESI-MS m/z: calcd for $C_{21}H_{31}NO_4$, 361.2; m/z: found, 262.2 $[M - BOC]^+$.

*Ethyl 4-[4-(Aminomethyl)phenyl]cyclohexanecarboxylate (**73**).* A solution of **72** (950 mg, 2.63 mmol) in HCl/EtOAc (20 mL, 2.0 M) was stirred at 20 °C for 16 h. Then, the mixture was concentrated to give **73** (350 mg, 51%) as a light yellow oil, which was used for the synthesis of compound **17j** without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−7.23 (m, 2H), 7.22−7.17 (m, 2H), 4.25−4.12 (m, 2H), 3.88−3.81 (m, 2H), 2.71 (s, 1H), 2.62−2.48 (m, 1H), 2.27 (d, J = 9.4 Hz, 1H), 1.84−1.76 (m, 1H), 1.74−1.47 (m, 6H), 1.35−1.23 (m, 3H). ESI-MS m/z: calcd for $C_{16}H_{23}NO_2$, 261.2; m/z: found, 262.2 $[M + H]^+$.

*Methyl 4-[4-(tert-Butoxycarbonylamino)-1-piperidyl]benzoate (**74**).* To a solution of *tert*-butyl *N*-(4-piperidyl)carbamate (**55**, 2.00 g, 9.99 mmol) in DMSO (50 mL) were added K_2CO_3 (3.45 g, 24.98 mmol) and methyl 4-fluorobenzoate (**58**, 1.85 g, 11.99 mmol) and the mixture was stirred at 90 °C for 16 h. Then, the reaction mixture was poured into water (200 mL) and filtered. The solution was concentrated in vacuum to give **74** (1.40 g, 42%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92−7.89 (m, 2H), 6.87−6.85 (m, 2H), 3.87 (s, 3H), 3.82−3.79 (m, 2H), 3.01−2.94 (s, 2H), 2.06−2.04 (m, 2H), 1.54−1.46 (m, 12H). ESI-MS m/z: calcd for $C_{18}H_{26}N_2O_4$, 334.2; m/z: found, 335.2 $[M + H]^+$.

*Methyl 4-(4-Amino-1-piperidyl)benzoate (**75**).* Compound **74** (1.40 g, 4.19 mmol) was dissolved in HCl/EtOAc (20 mL, 2.0 M) and the mixture was stirred at 25 °C for 16 h. Then, the reaction mixture was concentrated in vacuum to give a residue, which was dissolved in MeOH (50 mL). Then, $NaHCO_3$ (400 mg) was added and the mixture solution was stirred at 25 °C for 1 h. The mixture was filtered and concentrated in vacuum to afford **75** (500 mg, 51%), which was used for the synthesis of compound **17k** without further purification.^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 9.2 Hz, 2H), 4.03−3.99 (m, 2H), 3.83 (s, 3H), 3.29−3.26 (m, 1H), 2.99−2.92 (m, 2H), 2.08−2.05 (m, 2H), 1.70−1.61 (m, 2H). ESI-MS m/z: calcd for $C_{13}H_{18}N_2O_2$, 234.1; m/z: found, 235.1 $[M + H]^+$.

Docking and Biological Assays. Details on the following assays are reported: (a) docking set-up protocols into G9a and DNMT1,[21,34,35] and HDAC1[33] and HDAC6;[39] (b) G9a,[21,34,35] DNMT1,[21,34,35] DNMT3A,[21] DNMT3B,[21] HDAC1,[33] HDAC2,[33] HDAC3,[33] and HDAC6[33] enzyme activity assays; (c) cytotoxicity in THLE-2 cells;[21,34,35] (d) PAMPA permeability;[34] (e) cytochrome P450s inhibition;[34] (f) metabolic stability;[34] (g) kinetic solubility;[47] (h) Western blot (WB) to monitor H3K9me2[21] and H3K9Ac,[33] (i) DNA methylation analysis by pyrosequencing,[21] (j) cell proliferation assay[21] (MM1.S cells were cultured at a density of 0.4 × 10^6 cells/mL), and (k) a PK study after approval from the Animal Care and Ethics Committee of the University of Navarra (protocol numbers 158-12 and 009-16) in a plasma sample.[40] Other tests are explicitly described (below).

***In Vivo* Experiments.** All animal studies had previous approval from the Animal Care and Ethics Committee of the University of Navarra (protocol number: 041-15). For the human subcutaneous MM1.S MM model, 10 × 10^6 MM1.S cells diluted in 100 μL of saline solution were subcutaneously inoculated in the back left flank of female BALB/cA-Rag2$^{-/-}\gamma c^{-/-}$ mice between 6 and 8 weeks of age (n = 18). When the tumors became palpable, the mice were randomized into two groups, control and compound **12a**, (9 animals/group). The treatment with 10 mg/kg of compound **12a** was started 12 days after cell inoculation when all mice presented subcutaneous tumors and was administered for 5 consecutive days followed by 2 rest days (n = 9) during 3 weeks. The control group (n = 9) received only 80% saline solution, 10% DMSO, and 10% Tween20 (diluents of compound **12a**). The tumor size was analyzed every 5 days using the following method: $V1/4\ D\_d2/2$, where D and d corresponded to the longest and shorter diameters, respectively. The mice were killed 35 days after cell inoculation.

Interference Compound Assessment. No compound reported matches any of the structural filters for potential PAINS as defined by Baell & Holloway[48] and implemented in a customized Pipeline Pilot protocol.[49]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c02255.

Protocols for preparative HPLC purification methods; method for high-resolution mass spectrometry (HRMS) of the final compounds; methods for analytical HPLC and UHPLC; HPLC or UHPLC traces of the final compounds; NMR spectra (^{1}H & ^{13}C) of the final compounds; biochemical profiling of **9a** and **12a** *versus* DNMT and HDAC isoforms; H3K9me2 and H3Ac marks after treatment with A-366, Panobinostat, and Decitabine in MM1.S cells; hypomethylating activity of compounds **9a** and **12a** in JJN3 cells; body weight of mice treated with compound **12a**; and plasmatic concentrations of **12a** after administration (PDF)

Molecular formula strings together with their IC_{50} values (CSV)

Results from docking studies reported in Figure 2:
G9a compound **9a** complex (PDB)
DNMT1 compound **9a** complex (PDB)
HDAC1 compound **9a** complex (PDB)
HDAC6 compound **9a** complex (PDB)

Accession Codes

PDB ID Codes: **1**, 4LXZ; **2**, 5EF8; **3**, 6HSH; G9a, 3RJW; DNMT1, 4DA4; HDAC1, 4BKX; HDAC6, 5EDU.

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Notes

The authors declare no competing financial interest.

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All animal experiments performed in the manuscript were conducted in compliance with institutional guidelines (as reported above)

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■ ABBREVIATIONS

ADME, absorption, distribution, metabolism, and excretion; AML, acute myeloid leukemia; BINAP, 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl; BOC, *tert*-butoxycarbonyl; Cpd, compound; dba, dibenzylideneacetone; DIEA, *N*,*N*-diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DNA, deoxyribonucleic acid; DNMT, DNA methyltransferase; EDCI, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; EHMT2, euchromatic histone methyltransferase 2; ESI-MS, electrospray ionization mass spectrometry; EtOAc, ethyl acetate; EtOH, ethanol; HOBt, hydroxybenzotriazole; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; HPLC, high-performance liquid chromatography; HRMS, high-resolution mass spectrometry; ICW, in-cell Western; LCMS, liquid chromatography−mass spectrometry; MeOH, methanol; mp, melting point; MTBE, methyl *tert*-butyl ether; MM, multiple myeloma; MW, microwave; NMM, *N*-methylmorpholine; NMR, nuclear magnetic resonance; PAMPA, parallel artificial membrane permeability assay; PDB, Protein Data Bank; PE, petroleum ether; Ph, phenyl; HH, human hepatocytes; MH, mouse hepatocytes; prep., preparative; rt, room temperature; Rt, retention time; SAR, structure−activity relationship; *t*-BuONa, sodium *tert*-butoxide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; $THPONH_2$, *O*-(tetrahydro-2*H*-pyran-2-yl)-hydroxylamine; TLC, thin-layer chromatography; TMS, tetramethylsilane; UHPLC, ultraperformance liquid chromatography; UV, ultraviolet; ZBG, zinc-binding group

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