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Article

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Detailed Exploration around 4-Aminoquinolines Chemical Space to Navigate the Lysine Methyltransferase G9a and DNA Methyltransferase Biological Spaces.

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ABSTRACT

Epigenetic regulators that exhibit aberrant enzymatic activities or expression profiles are potential therapeutic targets for cancers. Specifically, enzymes responsible for methylation at histone-3 lysine-9 (like G9a) and aberrant DNA hypermethylation (DNMTs) have been implicated in a number of cancers. Recently, molecules bearing a 4-aminoquinoline scaffold were reported as dual inhibitors of these targets and showed a significant *in-vivo* efficacy in animal models of hematological malignancies. Here, we

report a detailed exploration around three growing vectors born by this chemotype. Exploring this chemical space led to the identification of features to navigate G9a and DNMT1 biological spaces; not only their corresponding exclusive areas, selective compounds, but also common spaces. Thus, we identified from selective G9a and first-in-class DNMT1 inhibitors, > 1 log unit between their IC_{50} values, with IC_{50} < 25nM (e.g. **43** and **26**, respectively) to equipotent inhibitors with IC_{50} < 50nM for both targets (e.g. **13**). Their ADME/Tox profiling and antiproliferative efficacies, *versus* some cancer cell lines, are also reported.

INTRODUCTION

Methyltransferases are responsible for the methylation of their corresponding substrates (histones, proteins for protein methyltransferases (PMTs); or DNA, for DNA methyltransferases (DNMTs)) using S-adenosyl-L-methionine (SAM or AdoMet) as cofactor; thus acting as epigenetic writers that control epigenetic gene regulation and carcinogenesis.[1,2] G9a (also known as KMT1C or EHMT2) catalyzes mono- or dimethylation of histone H3 lysine 9 (H3K9) and other protein targets such as p53.[3] G9a upregulation and overexpression is present in a variety of cancers.[4] DNMT1, a protein catalyzing methylation of C5-cytosine of DNA, binds G9a and both proteins cooperate in promoting transcriptional silencing of target genes.[5] Moreover, pharmacologic or siRNA-mediated inhibition of G9a synergises with DNMT1 inhibition in reducing cell proliferation.[6,7] All these observations strongly suggested that dual inhibitors of both targets could be valuable anticancer agents and we sought to identify such compounds. A number of selective G9a inhibitors have been reported,[8] with substrate-competitive inhibitors **1** (UNC-0638)[9] and **2** (A-366)[10] being extensively used as chemical probes to

investigate the biological role of G9a in multiple diseases beyond cancer (Chart 1). The development of potent reversible DNMT inhibitors is more appealing as most advanced compounds include nucleoside mimetics such as **3** (Azacytidine) and **4** (Decitabine) that incorporate into DNA and irreversible bind to DNMT1. As an alternative, current reversible non-nucleoside DNMT1 inhibitors lack potency, with IC_{50} values in the low micromolar range.[11,12]

We recently reported the discovery of the quinoline-based lead compound **5** (CM-272) as an inhibitor of G9a (IC_{50} = 8 nM) and DNMT1 (IC_{50} = 382 nM) with *in vivo* efficacy in Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL) and Diffuse Large B-cell Lymphoma-(DLBCL) xenogeneic models.[6] Competition assays and microscale thermophoresis demonstrated that inhibitors of this chemical series bind to the substrate binding site of both targets.[6,13] Our efforts to identify this lead compound utilized a combination of knowledge- and structure-based approaches, starting from the chemical structure of compound **1**. Initial structure-activity relationship (SAR) studies were focused on determining the optimal substitution pattern at the 2-position of the quinoline not only to achieve G9a and DNMT1 enzymatic inhibition but also a cellular response and a suitable pharmacokinetic (PK) profile for *in vivo* proof-of-concept.[13] Additional SAR exploration around the 4-, 6- and 7-positions of the quinoline scaffold, aimed at further DNMT1 potency optimization and target selectivity modulation, identified key chemical features that confer selectivity towards G9a or DNMT1 (where selectivity involves >1 log unit difference between corresponding IC_{50} values). In fact, first-in-class DNMT1 potent (low nanomolar, IC_{50} < 25 nM), selective and reversible inhibitors are achieved. In addition, antiproliferative activities in cancer cells and preliminary ADME/Tox of this exploration are discussed. Furthermore, novel R-groups mimicking the lysine side chain of histone substrate (G9a)

or the cytosine of DNA (DNMT1) are introduced. Our results and compounds not only represent interesting, and first-in-class, tools for targeting relevant epigenetic enzymes but also constitute valuable alternatives for the design of epigenetic inhibitors targeting the substrate-binding site of other methyltransferases.

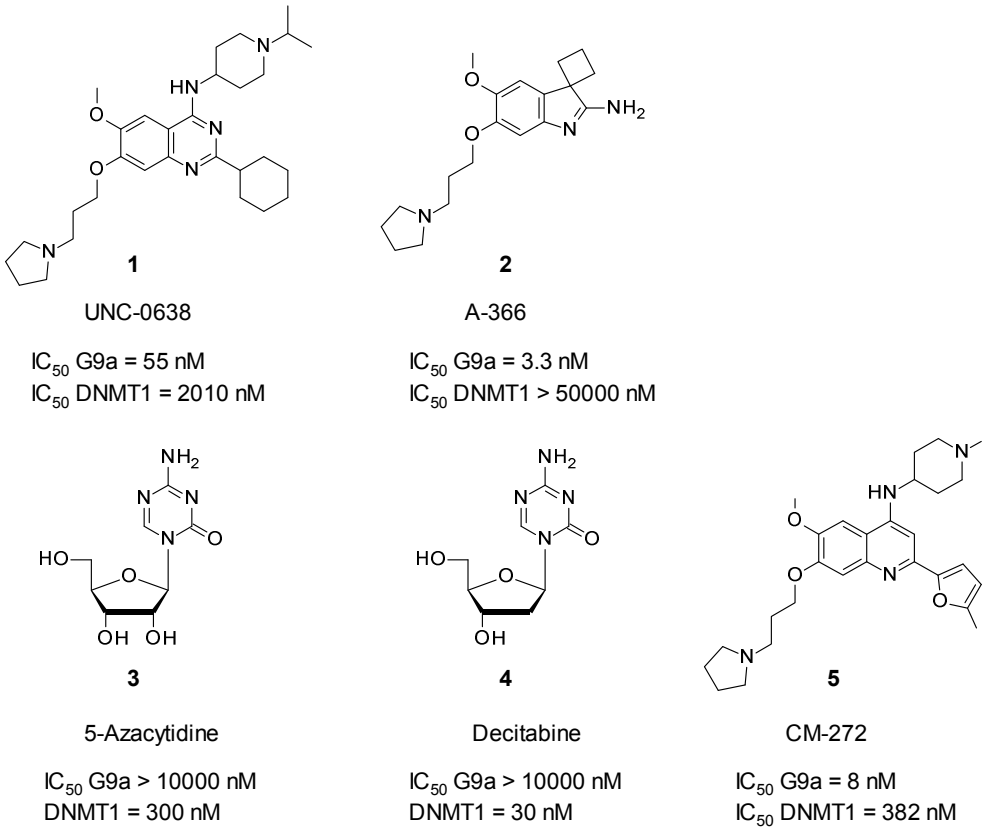


Chart 1. Known G9a inhibitors (**1**, **2**), nucleoside DNMT1 inhibitors (**3**, **4**) and inhibitor (**5**). G9a IC_{50} values of **1**, **3**, **4** and **5** and DNMT1 IC_{50} values for **1** and **5** as determined internally (see footnote in Table 1). Alternatively, the reported IC_{50} value for compound **1** (UNC-0638) was < 15 nM (G9a, using a SAHH-coupled assay) and 1287 nM (DNMT1, using a radioactive methyl transfer assay).[14] Discrepancies with initially reported DNMT1 IC_{50} values for **1** (IC_{50} = 107,000 nM) have been attributed to a different assay format.[9] IC_{50} values for compound **2**[10] (G9a, DNMT1) and **3**,[15] **4**[15] (DNMT1, corresponding to the lower concentration at which DNA hypomethylation is observed) have been previously reported.

RESULTS

SAR in Biochemical G9a and DNMT1 Assays

SAR examination of the 2-position of the quinoline scaffold revealed 5-alkyl-2-furyl groups (5-methyl in **5** and 5-ethyl in **6**, Table 1) as the optimal groups for yielding functional cellular activity.[13] Thus, we decided to alternatively use these substituents as initial reference points for subsequent SAR exploration of the 4-, 6- and 7-positions of the quinoline scaffold, using a sequential approach (Chart 2).

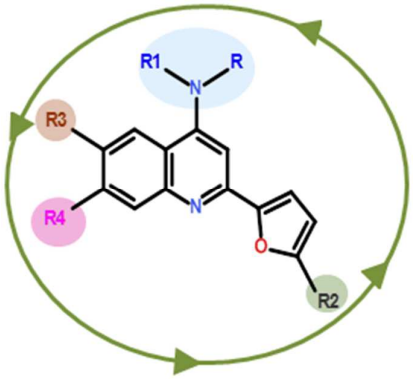


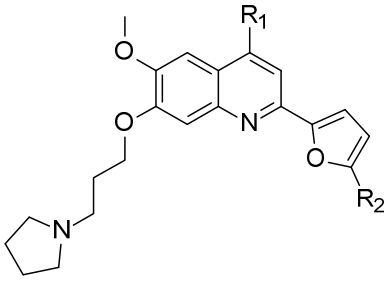
Chart 2. Sequential SAR exploration strategy for positions 4, 6 and 7 of the quinoline scaffold; position 2 is fixed with a 2-furyl ring substituted at position 5 (where R_2 is methyl or ethyl)

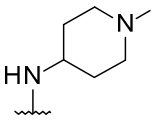
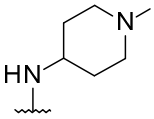
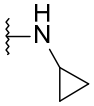
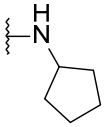
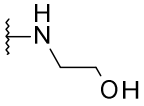
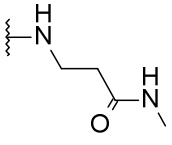
The 4-amino moiety was first explored (Table 1). According to the predicted binding mode of **5**[6] and **6** (Figure 1A-B) into both methyltransferases and X-ray structure of **1** and related quinazoline analogues into G9a,[9] this position extends out toward the so called solvent accessible area, suggesting that chemically diverse groups, exploring the biological space,[16] could be well-tolerated. Removal of the basic nitrogen of **5** (compounds **7-11**, **16**) caused a significant drop in activity against both targets, and only the piperidone derivative **11** retained potent DNMT1 activity (IC_{50} < 500 nM). This result is consistent with the predicted binding mode of **6** with G9a, as the positively

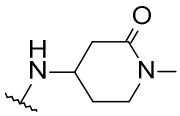
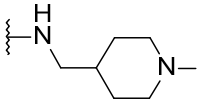
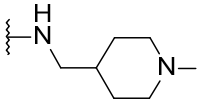
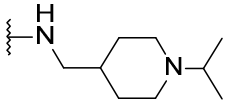
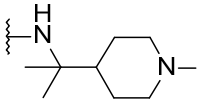
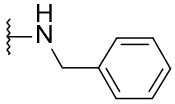
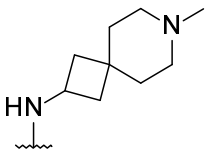
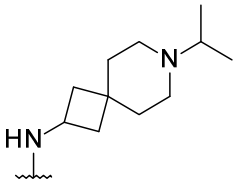
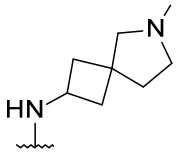
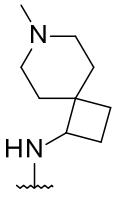
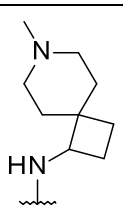
charged nitrogen of the piperidine ring interacts with Asp1078 (Figure 1A). With respect to DNMT1, no explicit contacts were predicted by docking between the piperidine ring and the protein (Figure 1B), although a negative electrostatic potential is observed in this area (Figure 1C). Homologation of the piperidine ring of **5** with a methylene linker (compounds **12**[6]**-13**) greatly improved DNMT1 activity (IC_{50} < 50 nM) while causing minor potency loss against G9a (IC_{50} ~ 15 nM). Given the poor pharmacokinetic profile of **12**,[6] the gem-dimethyl analogue **15** was synthesized as the methylene linker was viewed as a potential metabolic liability. As **15** was significantly less potent against both targets, we concentrated on alternatives to the piperidine ring by limiting molecular flexibility[17] with spiropiperidines (**17**, **18**, **20**, **21**), spiropyrrolidines (**19**, **22**) and bridged piperazines (**23-26**). In general, these conformationally constrained analogs share a biochemical profile similar to that of **5**, especially in terms of selectivity towards G9a over DNMT1. Exceptionally, racemic analogs **20-22**, whose basic nitrogen predictably positions more distant from that of the piperidine (in green in Figure 1D compared to the other docked spiro derivatives in orange and **5** in violet, that overlap well), were less potent against G9a (IC_{50} > 50 nM). DNMT1 SAR was flat, with no general improvements in activity (200-300 nM, pIC_{50} ranging between 6.5 and 6.7, with less than 0.3 log units compared to **5** and **6**) except for some remarkable analogs such as the homologated 3-azabicyclo[3.2.1]octane of **25** (IC_{50} = 80 nM). As expected,[18] loss of the hydrogen bond donor of the 4-amino group of **5** by methylation (**27**) or replacement by an oxygen atom (**28**)[6] was detrimental for G9a activity. Interestingly, similar results were observed against DNMT1 and are in agreement with a predicted contact between this 4-amino group and Ser1233 of DNMT1 (Ser1230 in human DNMT1, hDNMT1, Figure 1B), what might explain the decreased DNMT1 activity of **27** and **28**. In summary, this exploration of the 4-position either mainly retained the selectivity profile

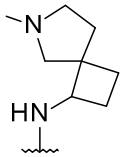
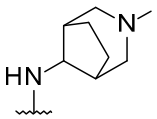
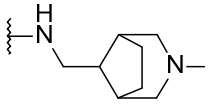
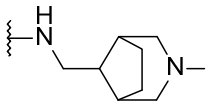
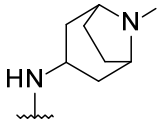
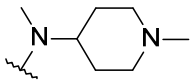
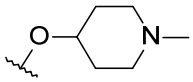
of lead compound **5** (e.g. with constrained rings) or equally potent compounds were obtained at the cost of losing G9a activity (e.g. **11**). Only the homologated compounds **12** and **13** exhibit both G9a and DNMT1 activities in the low nanomolar range (< 50 nM) and can be regarded as non-selective, especially in comparison with their counterparts **5** and **6** (absolute pIC_{50} differences between both targets of 0.3 for **12** and **13** versus 1.7 (**5**) and 2.1 (**6**)).

Table 1. Exploration of the 4-position



Cpd	R1	R2	G9a IC_{50} (nM)	DNMT1 IC_{50} (nM)
5[6,13]		Me	8	382
6[13]		Et	2	234
7		Me	436	1030
8		Me	735	1790
9		Me	244	781
10		Me	105	1080

Cpd	R1	R2	G9a IC_{50} (nM)	DNMT1 IC_{50} (nM)
11		Me	146	297
12[6]		Me	16	32
13		Et	18	40
14		Me	13	205
15		Me	115	722
16		Me	699	624
17		Me	15	140
18		Me	7	211
19		Me	11	201
20		Me	63	123
21		Et	94	220

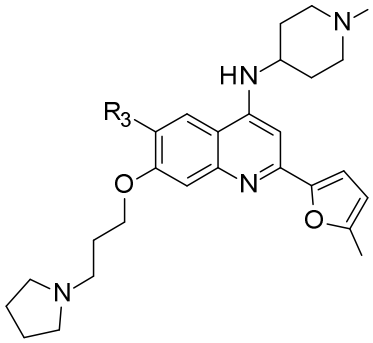
Cpd	R1	R2	G9a IC_{50} (nM)	DNMT1 IC_{50} (nM)
22		Me	76	290
23		Me	41	235
24		Me	21	261
25		Et	5	80
26		Me	13	234
27		Me	935	1320
28[6]		Me	2870	1870

For data in Tables 1-4 and Chart 1, all biochemical results are the average of at least two independent replicates performed at different days. If absolute pIC_{50} difference was higher than 0.3 log units, additional replicates were performed until satisfying the experimental error (by discarding individual results with values outside 2 MADs of the mean value).

Exploration of the 6-position with small groups (**29-33**, Table 2), designed to modulate ADME properties, produced a notable decrease in activity, especially against G9a, affording equally potent compounds against both targets in the mid-nanomolar or low-micromolar range. Only replacement of the methoxy group by chlorine (**31**) had negligible impact on DNMT1 activity (IC_{50} = 298 nM) compared to **5**, so no further exploration around this position was continued. Inspection of the binding cavity for this derivatization position did not reveal any specific contacts between this substitution

pattern and both proteins as to rationalize the weaker activities observed against both of them.

Table 2. Exploration of the 6-position

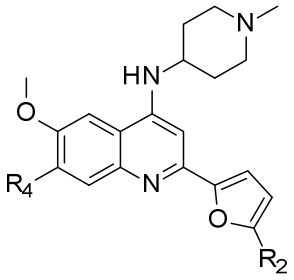


Cpd	R3	G9a IC_{50} (nM)	DNMT1 IC_{50} (nM)
29	H	532	950
30	OH	859	645
31	Cl	342	298
32	OCF_3	6110	2080
33	CN	1450	588

Finally, we modulated the 7-(3-pyrrolidin-1-ylpropoxy) moiety that predictably mimics the lysine side chain (G9a) or the cytosine of DNA (DNMT1) (Table 3). The 7-methoxy analogue **34**, lacking the basic nitrogen of **5** at the 7-position, was considerably less potent against G9a (IC_{50} = 2060 nM, absolute pIC_{50} difference of 2.4 log units), likely as a result of missing interactions with Leu1086 (hydrogen-bond) and Tyr1154 (cation-π interaction) (Figure 1A). The impact of this moiety on DNMT1 was less notorious (IC_{50} raising from 382 nM for **5** to 750 nM for **34**, < 0.3 log units), suggesting that the predicted interaction between the basic nitrogen of pyrrolidine and catalytic Glu1269 (Glu1266 in hDNMT1, Figure 1B) was not so important for the inhibitory activity of this chemical series. Thus, we speculated that selective DNMT1 inhibitors could be

developed by exploring amine analogs of pyrrolidine with different basicity and distance extension from the quinoline core. Compounds in Table 3 were designed and synthesized. G9a potency was attenuated in all cases, with piperidine **37** being the only replacement retaining G9a IC_{50} value below 100 nM. Interestingly, the 4-piperidyl (**40**), 1-methyl-4-piperidyl (**41**), 2-methyl-2-azaspiro[3.3]heptan-6-yl (**43**) and 2-isopropyl-2-azaspiro[3.3]heptan-6-yl (**44**) groups conferred high DNMT1 potency (< 100 nM), yielding compounds selective for DNMT1 over G9a (> 1 log units). The reduced basicity of all these groups (estimated pK_a with Pipeline Pilot[19] for the amine nitrogen at position 7 of 6.33, 8.75, 7.26 for **40**, **41** and **43**, respectively), compared to that of the pyrrolidin ring of **5** (pK_a of 12.1) and **37** (pK_a of 11.8) seems to play a major role on target selectivity, as on the other hand the cationic environment overlaps well among all these derivatives (Figure 1E). While some of these amines in Table 3 have already been examined as lysine mimetics[10,18,20] that reduce the lipophilicity of the parent compound **5** (acyclic amine **35**, piperidine **37**, morpholine **38**, 3-(3-fluoropyrrolidin-1-yl)propyl **39**), the DNMT1 potency of the spirocyclic derivative **43** (IC_{50} = 21 nM) was considered as a key SAR finding and a novelty in epigenetic drug design. Decreasing its basicity with N-isopropyl (**44**) and N-cyclopropyl (**45**) capping groups correlated with loss of potency. Compounds **46-50** were obtained by combining the identified optimal groups at positions 4 and 7 (Table 4). Unfortunately, the excellent DNMT1 potency of **43** was not retained when this group was combined with the most potent 4-substituents in Table 1 to afford analogues **47-50**, suggesting non-additive SAR effects.[21] Despite lower DNMT1 inhibitory activity (between 187 and 501 nM for **47-50**), all these compounds displayed DNMT1 selectivity over G9a comparable to that of **43**.

Table 3. Exploration of the 7-position



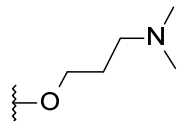
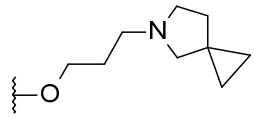
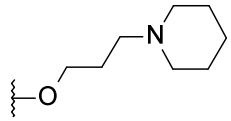
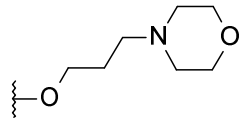
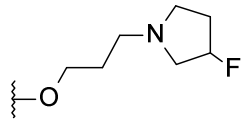
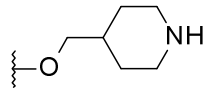
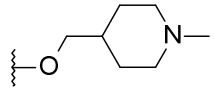
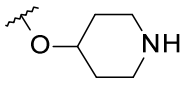
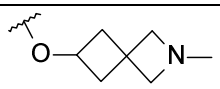
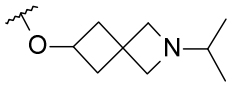
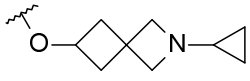
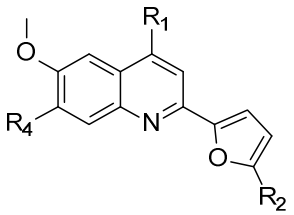
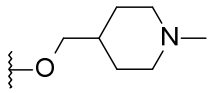
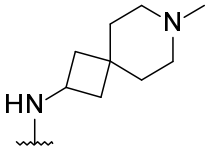
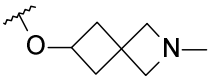
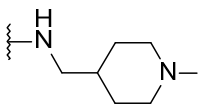
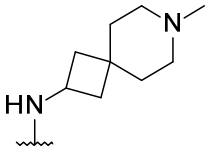
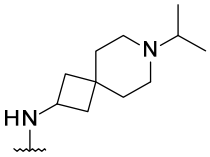
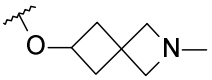
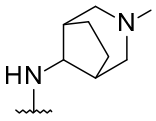
Cpd	R4	R2	G9a IC_{50} (nM)	DNMT1 IC_{50} (nM)
34		Me	2060	750
35		Et	123	425
36		Et	599	212
37		Et	21	247
38		Et	3910	446
39		Me	1470	833
40		Me	838	73
41		Me	1150	83
42		Me	7550	414
43		Me	351	21
44		Me	378	83
45		Me	3260	494

Table 4. Combined exploration of positions 4 and 7



Cpd	R4	R1	R2	G9a IC_{50} (nM)	DNMT1 IC_{50} (nM)
46			Me	3080	200
47			Me	3220	475
48			Me	3450	250
49			Me	5130	187
50			Me	5410	501

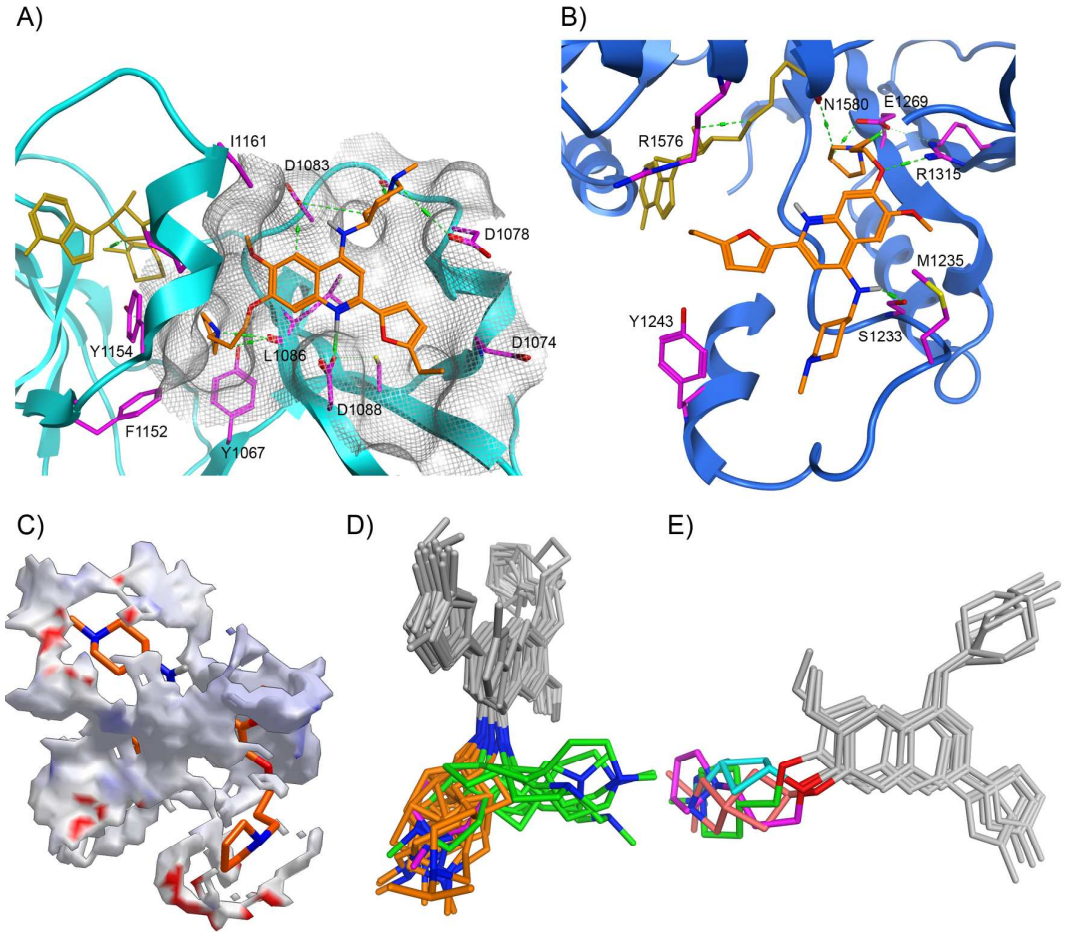


Figure 1. Predicted complex of **6** with G9a (A, PDB entry 3RJW) and DNMT1 (B, PDB entry 4DA4). (C) Electrostatic potential of DNMT1 (only negative, in red), especially at the regions accommodating both basic centers of compound **6**. (D) Overlaid conformations of docked spirocyclic and bridged derivatives in Table 1 to compound **5** (violet), showing that the basic nitrogen of compounds **20-22** (green, all stereoisomers considered) lies distal to the basic nitrogen of the rest of spirocycles and bridged structures (**17-19**, **23-26**, orange). (E) Overlaid conformations of docked compounds **5**, **41**, **43** and **44** showing that the basic nitrogen overlays well among them.

Having identified interesting compounds with different selectivity profiles towards G9a and/or DNMT1 (**13**, **43**), we analyzed their selectivity at 10 μM against a panel of epigenetic targets comprising 14 lysine and arginine methyltransferases, DNMTs

(DNMT3A, DNMT3B), bromodomains (BRD2, CREBBP and BAZ2B) and histone demethylases (JMJD2C, JMJD3, JMJD1A) (Supplementary Table 1). Despite we initially anticipated potent GLP inhibition (as for **12**[6]), given the close similarity among G9a and GLP, compounds **13** and **43** displayed high selectivity towards G9a (GLP IC_{50} values higher than 20 μM). Reasons for this selectivity are not clear considering the high structural similarity between **12** and **13**. Oppositely, in agreement with initial prediction, all three compounds are potent inhibitors of DNMT3A and DNMT3B (>95% inhibition at 10 μM). For the remaining targets, inhibition values were < 50%, with the exception of PRMT1 for **13** (84%) and JMJD3 for **43** (71%).

Antiproliferative effect and preliminary ADME

Following our screening funnel, the antiproliferative response of compounds with potent inhibitory activity (G9a < 100 nM and DNMT1 < 500 nM) was tested against ALL cell lines (CEMO-1) and DLBCL (OCI-Ly3 and OCI-Ly10) cell lines (Table 5). All selected compounds displayed potent antiproliferative effects, with GI_{50} values below 1 μM against at least one cell line. However, no evident correlation was found between G9a/DNMT1 activity/selectivity, passive membrane permeability of compounds as measured using the parallel artificial membrane permeation assay (PAMPA), and phenotypic response, this last being greatly dependent on the cell type. For example, compounds **12** and **43**, two of the most interesting compounds from the viewpoint of G9a/DNMT1 selectivity, mainly differing in their G9a activity (16 nM versus 351 nM) and being equally very potent against DNMT1 (32 versus 21 nM), have the same growth inhibitory activity against CEMO-1 (GI_{50} ~ 75 nM) but diverse response against DLBCL cell lines: OCI-Ly10 cell line (< 31 nM versus 253 nM for **12** and **43**, respectively) and the opposite response against OCI-Ly3 (202 versus 74 nM for

12 and **43**, respectively). Low toxicity of compounds, assayed against the non-tumoural hepatic cell line THLE-2 (Table 5), was regarded as a requisite for further compound progression into *in vitro* preliminary ADME, ideally affording a therapeutic window (absolute difference between pGI_{50} and pLC_{50}) of a least one log unit against one out of the four tumoural cell lines (mostly CEMO-1, Table 6). Selected compounds in Table 6 showed low cytochrome P450 inhibition of five major isoforms (< 25% at 10 μM) and were inactive against hERG (pIC_{50} < 4), thus limiting the potential for cardiotoxicity. As no compound with a novel selectivity profile (e.g. **43**) improved the metabolic stability of lead compound **5**, especially in human liver microsomes, compounds were not further progressed into PK studies.

Table 5. Antiproliferative response of selected compounds against cancer cell lines and non-tumoural hepatic cell line THLE-2

Cpd	CEMO-1 GI_{50} (nM)[a]	OCI-Ly3 GI_{50} (nM)[a]	OCI-Ly10 GI_{50} (nM)[a]	THLE-2 LC_{50} (nM) 72 h[b]	PAMPA Pe (nm/s)[c]	G9a pIC_{50} – DNMT1 pIC_{50}
5[6]	218	409	455	1780	12.9	1.7
6[13]	56	95	64	2320	23.9	2.1
11	172	215	170	7950	3.4	0.3
12[6]	75	202	<31	1300	11.0	0.3
13	93	277	133	954	16.2	0.3
14	659	N.D.	N.D.	777	19.2	1.2
17	235	243	100	992	10.5	1.0
18	426			841	19.3	1.5
19	768	374	257	8380	3.3	1.3
20	424	246	112	731	15.9	0.3
21	186	237	638	517	37.7	0.4
22	252	205	131	1980	7.6	0.6
23	156	557	313	527	33.7	0.8
25	115	N.D.	N.D.	<164	36.1	1.2
26	671	N.D.	N.D.	4150	3.6	1.3

31	782	N.D.	N.D.	2310	24.5	-0.1
35	370	86	1100	3520	14.9	0.5
36	184	230	596	2040	36.6	-0.5
37	196	271	576	1380	8.3	1.1
40	1070	<63	1380	24800	2.9	-1.1
41	272	N.D.	N.D.	1030	12	-1.1
43	73	74	253	698	7.1	-1.2
46	504	12	186	2530	14.9	-1.2
49	452	N.D.	N.D.	4650	11.1	-1.4

N.D. = Not Determined. [a] Proliferation assays are the average of three replicates at different days. [b] THLE-2 cytotoxicity results after 72 hours of incubation are the average of at least two independent experiments performed at 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). [c] 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.[22]

Table 6. ADME profile of selected compounds

Cpd	1A2 (%) [a]	2C9 (%) [a]	2C19 (%) [a]	2D6 (%) [a]	3A4 (%) [a]	HLM (%) [b]	MLM (%) [b]	hERG IC_{50} (μM)
5[6,13]	2.8	0.56	2.5	4.9	0.0	99.7	70.9	>100
11	9.3	3.2	6.5	22.4	1.2	82.7	71.9	>100
13	7.1	16.8	23.1	19.3	2.2	69.0	59.1	N.D.
17	0	0	0	0	0	68.6	40.6	>100

20	0	0	2.5	5.3	0	80.4	53.3	N.D.
26	0	0	6.3	0	0	60.3	43.9	N.D.
31	7.2	3.8	0	0	0	81.7	81.7	N.D.
43	6.1	6.3	0	21.5	6.9	49.8	43.3	N.D.

N.D. = Not Determined. [a] % inhibition at 10 μM. [b] % compound remaining after a 20-min incubation in human or mouse liver microsomes (HLM and MLM respectively). All assays were performed in duplicate, with the exception of hERG binding data (n=1).

Finally, the functional cellular potency of selected compounds was assessed by quantifying the global levels of H3K9me2 (Western Blot) and 5-methylcytosine (5mC) (Dot Blot) in the CEMO-1 cell line following 96 h of exposure. As an example, the selected reference compounds **13** and **43** were tested. Both compounds reduced the H3K9me2 and 5mC levels in a concentration-dependent manner (Figure 2); Western Blots are quantized and reported in the Supplementary Information (Figure S1). In summary, these results demonstrate the functional dual effect of compounds **13** and **43** against the methyltranferase activity of G9a and DNMTs.

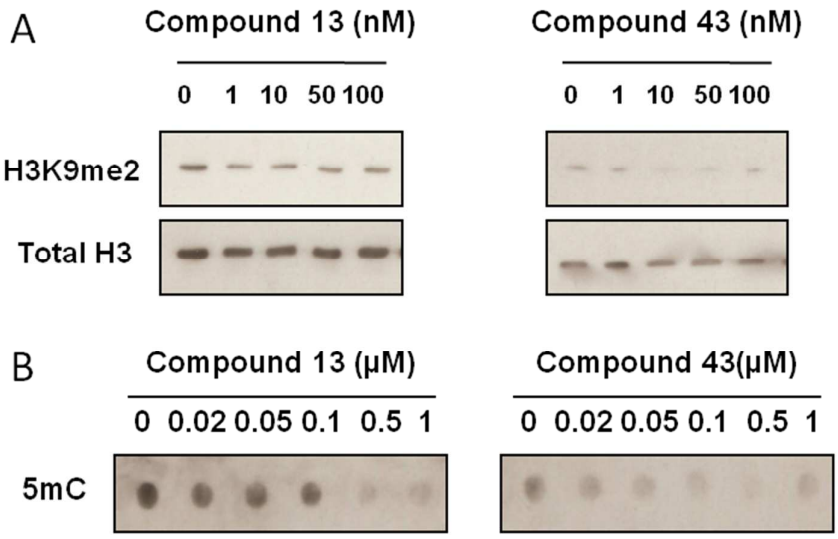
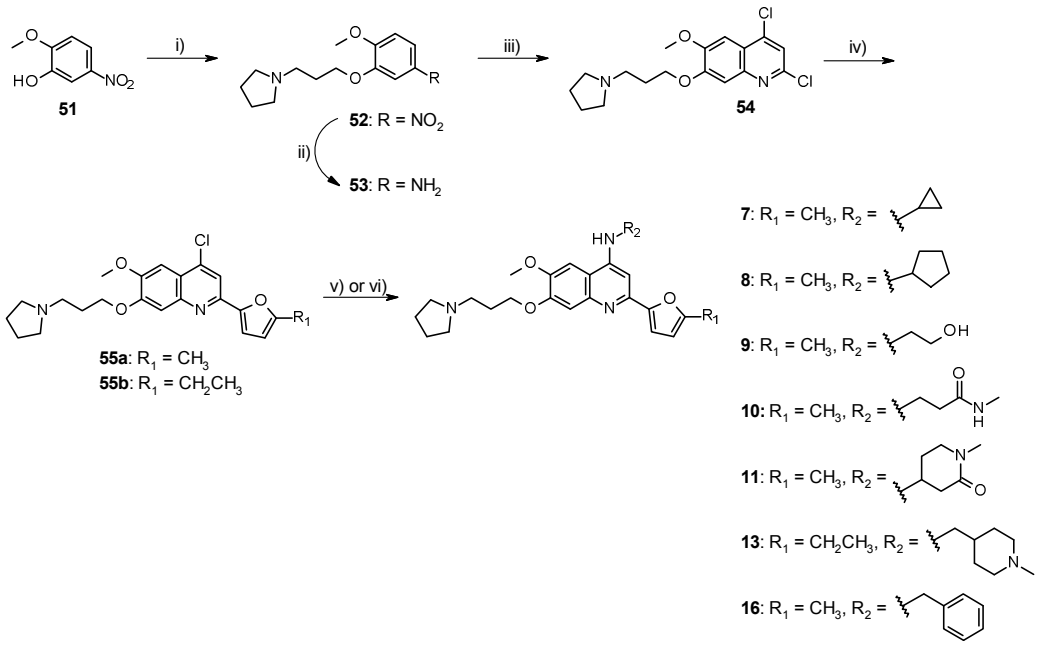


Figure 2. H3K9me2 and 5mC hallmarks in the CEMO-1 cell line after treatment with compounds **13** and **43**. A) H3K9me2 levels after 96 hours of treatment with different doses of compounds **13** and **43** in CEMO-1 cell line. H3 total was used as loading control. B) 5mC levels after 96 hours of treatment with different doses of compounds **13** and **43**.

Chemistry

Preparation of compounds **7-11**, **13** and **16** with different substituents at 4-position of the quinoline were prepared as outlined in Scheme 1 from commercially available 2-methoxy-5-nitro-phenol (**51**). This alcohol was first converted into compound **52** through Mitsunobu reaction and then intermediate **54** was achieved after hydrogenation and reaction with $POCl_3$ in malonic acid. Then, Suzuki coupling with boronic esters 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane or 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane afforded compounds **55a** and **55b** which were finally converted into desired 4-aminoquinolines **7-11**, **13** and **16** by Pd-coupling reaction using different amines.

Scheme 1. Synthesis of compounds **7**-**11**, **13** and **16**.

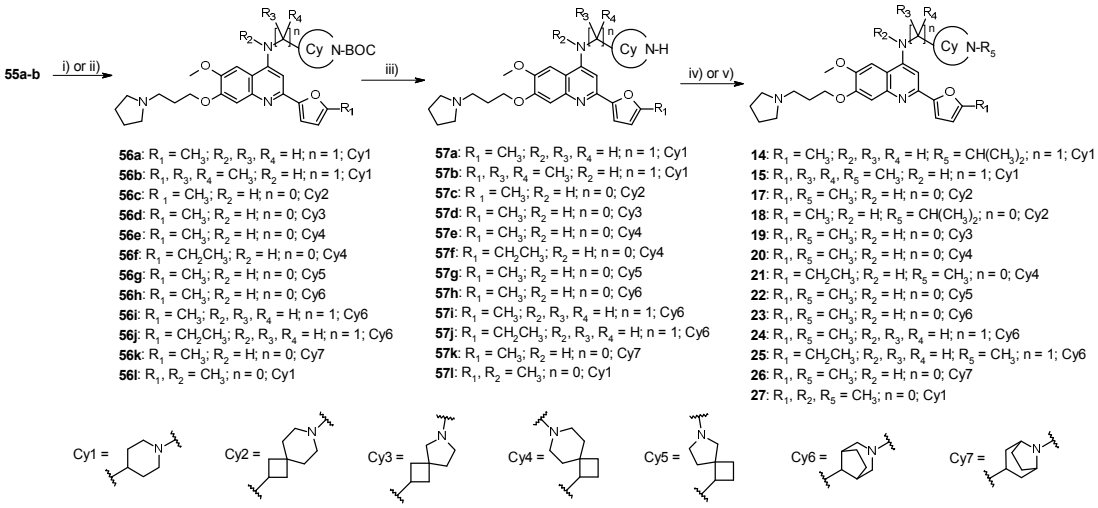


Conditions: i) 3-pyrrolidin-1-yl-propan-1-ol, PPh_3, DEAD, THF, rt, 5 h; ii) Pd/C, H_2 (1 atm), MeOH, rt, 3 h; iii) $POCl_3$, malonic acid, rt, 4 h, then, 90 ºC, overnight; iv) 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane or 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, Na_2CO_3 or K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane or 1,4-dioxane /H_2O (15:1), 110 ºC, MW or conventional heating, 4-12 h; v) corresponding amine, Cs_2CO_3, BINAP, $Pd_2(dba)_3$, 1,4-dioxane, 120-130 ºC, MW or conventional heating , 3-12 h; vi) corresponding amine, *t*-BuONa, xantphos, $Pd_2(dba)_3$, toluene, 100 ºC, MW, 2 h.

Synthesis of isopropyl analogue **14**, gem-dimethyl analogue **15**, spiropiperidines **17**, **18**, **20** and **21**, spiropyrrolidines **19** and **22**, bridged piperazines **23**-**26** and methylated analogue **27** is described in Scheme 2. Starting from previously described 4-chloroquinolines **55a** or **55b**, BOC-protected amines **56a-k** were prepared by Buchwald-Hartwig amination and tertiary amine **56l** using tert-butyl 4-(methylamino)piperidine-1-carboxylate and PTSA in *t*-BuOH. Then, the BOC protecting group was removed under acidic conditions and desired methyl or isopropyl substituent was installed by reductive amination. All analogues with chiral centers and

pseudostereocenters in this manuscript (**11**, **19-26**, **39**, **50**) were prepared as racemic mixtures.

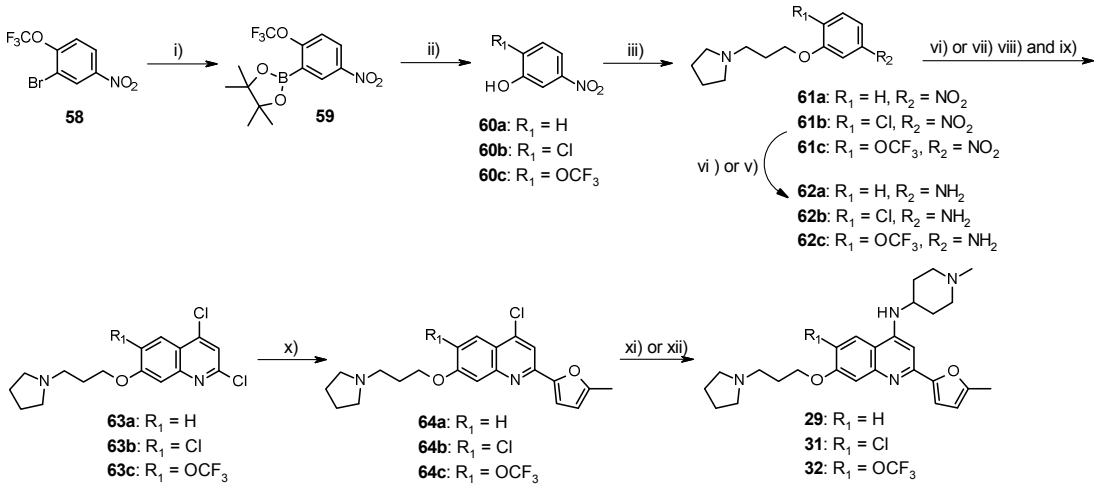
Scheme 2. Synthesis of compounds **14**, **15** and **17-27**.



Conditions: i) corresponding amine, Cs_2CO_3, BINAP, $Pd_2(dba)_3$, 1,4-dioxane, 115-130 ºC, MW or conventional heating , 5-48 h; ii) tert-butyl 4-(methylamino)piperidine-1-carboxylate, PTSA, *t*-BuOH, 120 ºC, 48 h; iii) HCl/EtOAc (1.0 or 2.0 M) or HCl/MeOH (2.0 or 4.0 M), 16-25 ºC, 1-16 h; iv) acetone, $NaBH_3CN$, AcOH, *i*-PrOH, 50-60 ºC, 15-16 h; v) $(HCHO)_n$, HCOOH, $NaBH(OAc)_3$, MeOH, rt or 60 ºC, 12 h or overnight.

Compounds with a hydrogen atom, a chlorine atom and a $-OCF_3$ group at position 6 of the quinoline (**29**, **31** and **32** respectively) were synthesized from intermediates **60a-c** through Mitsunobu reaction and reduction of nitro group (Scheme 3). Then, key intermediates **63a-b** were achieved after heating with $POCl_3$ and malonic acid and compound **63c** by a three step protocol (reaction with ethyl 3-chloro-3-oxo-propanoate, ester hydrolysis and reaction with $POCl_3$). Subsequent reaction with 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane and Buchwald-Hartwig amination led us to desired compounds **29**, **31** and **32**.

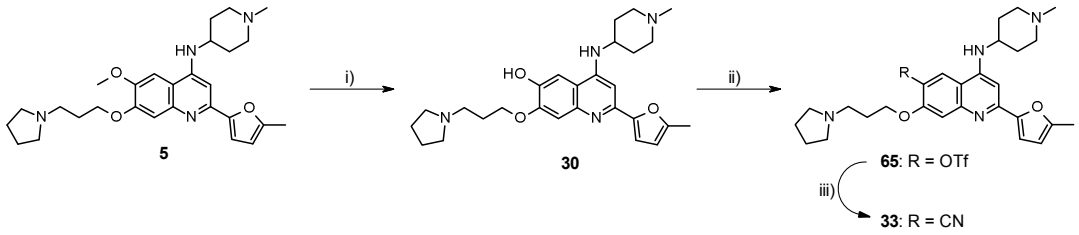
Scheme 3. Synthesis of compounds **29**, **31** and **32**.



Conditions: i) 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane, KOAc, $Pd(dppf)Cl_2$, 1,4-dioxane, 90 ºC, 10 h; ii) NaOH, H_2O_2, THF, 30 minutes, 22 ºC; iii) 3-pyrrolidin-1-ylpropan-1-ol, PPh_3, DEAD or DIAD, THF, 0 ºC or rt, 5-10 h; iv) Pd/C, H_2 (40 Psi), MeOH, rt, 2-15 h; v) Fe, NH_4Cl, EtOH/H_2O (4:1), rt, 3 h; vi) $POCl_3$, malonic acid, rt, 4 h, then 90 ºC, overnight; vii), DMAP, pyridine, CH_2Cl_2, -70 ºC, 1 h, then ethyl 3-chloro-3-oxo-propanoate, 20 ºC, 15 h; viii) $LiOH \cdot H_2O$, THF/MeOH/H_2O (4:2:3), 20 ºC, 15 h; ix) $POCl_3$, 100 ºC, 3 h; x) 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, Na_2CO_3 or K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O (5:1, 15:1 or 10:1), 80-110 ºC, MW or conventional heating, 2-15 h; xi) 1-methylpiperidin-4-amine, x-Phos, $Pd_2(dba)_3$, *t*-BuOK, 1,4-dioxane, 130 ºC, MW, 4 h; xii) 1-methylpiperidin-4-amine, BINAP, $Pd_2(dba)_3$, Cs_2CO_3, 1,4-dioxane, 80-110 ºC, 12-15 h.

Compounds with a hydroxy and a cyano substituent at position 6 of the quinoline (compounds **30** and **33**) were also prepared. As illustrated in Scheme 4, from previously described **5**, compound **30** was afforded using BBr_3 in CH_2Cl_2. Then, trifluoromethanesulfonate intermediate **65**, obtained by reaction with $PhN(OTf)_2$, was converted into desired compound **33** using $Zn(CN)_2$ and $Pd(PPh_3)_4$ in DMF.

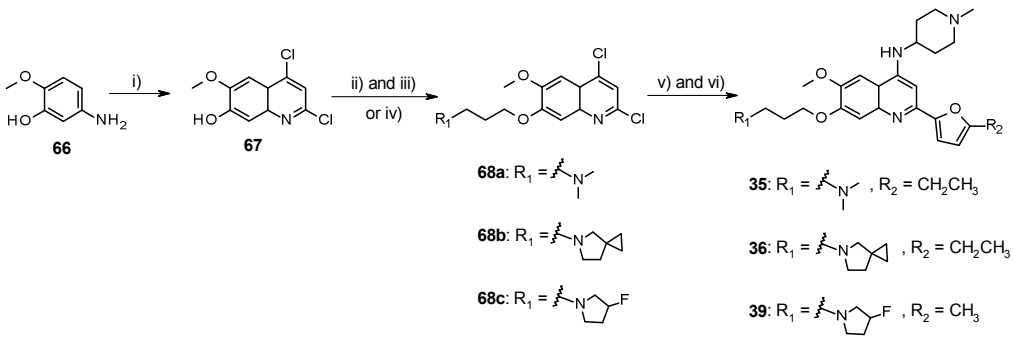
Scheme 4. Synthesis of compounds **30** and **33**.



Conditions: i) BBr_3, CH_2Cl_2, 0 ºC, 2 h; ii) $PhN(OTf)_2$, DIEA, DMF, 0 ºC, 2 h, then 25 ºC, 12h; iii) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 110 ºC, 12 h.

To continue with exploration at position 7 of the quinoline, compounds **35**, **36** and **39** were synthesized (Scheme 5). Starting from commercially available 5-amino-2-methoxy-phenol (**66**), intermediate **67** was prepared by reaction with $POCl_3$. Substitution at position 7 was then installed using 1,3-dibromopropane and N-methylmethanamine or 5-azaspiro[2.4]heptane to obtain compounds **68a-b**. On the other hand, intermediate **68c** was achieved in only one step by Mitsunobu reaction with 3-(3-fluoropyrrolidin-1-yl)propan-1-ol. Then, dichloroquinolines **68a-c** were converted into desired compounds **35**, **36** and **39** by the two step protocol previously described: Suzuki coupling and Buchwlad-Hartwig amination.

Scheme 5. Synthesis of compounds **35**, **36** and **39**.

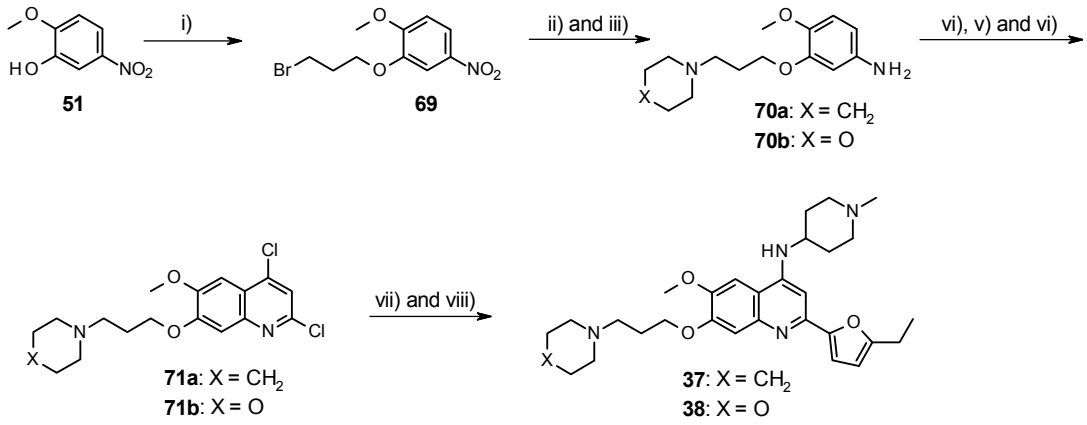


Conditions: i) $POCl_3$, malonic acid, 95 ºC, 12 h; ii) 1,3-dibromopropane, K_2CO_3, CH_3CN, 60 ºC, 88 h; iii) corresponding amine, K_2CO_3, CH_3CN, 60 ºC, 16 h; iv) 3-(3-fluoropyrrolidin-1-yl)propan-1-ol, PPh_3, DEAD, THF, 20 ºC 16 h; v) 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl- 1,3,2-dioxaborolane or 4,4,5,5-

tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane, K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane/H_2O (1:1 or 10:1), 110 ºC, 16 h; vi) 1-methylpiperidin-4-amine, Cs_2CO_3, $Pd_2(dba)_3$, BINAP, 1,4-dioxane, 120 ºC, 12-16 h.

Compounds with a piperidine or morpholine at position 7 were also prepared as outlined in Scheme 6. Conversion of commercially available 2-methoxy-5-nitro-phenol (**51**) to intermediate **69** was first achieved by reaction with 1,3-dibromopropane. Then, substitution by piperidine or morpholine and subsequent hydrogenation led us to compounds **70a-b** which were converted into corresponding 2,4-dichloroanilines **71a-b** after reaction with ethyl 3-chloro-3-oxo-propanoate, ester hydrolysis and reaction with $POCl_3$. Finally, desired 4-aminoquinolines **37** and **38** were isolated through Suzuki coupling and amination under Buchwald-Hartwig conditions.

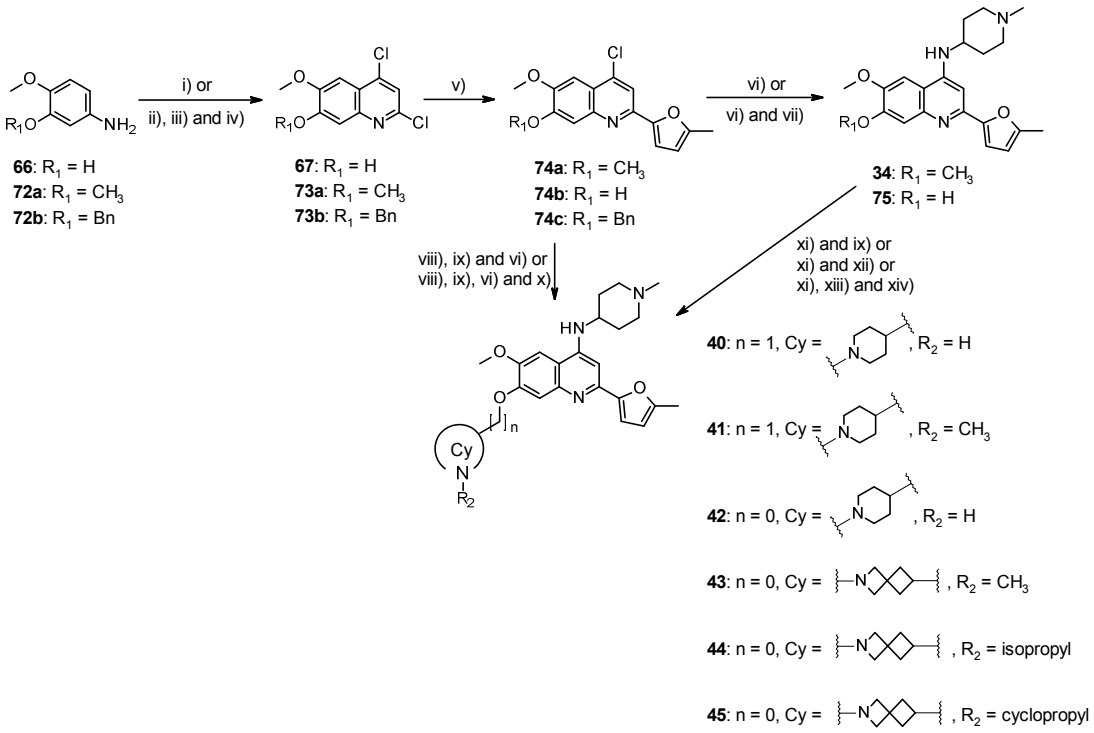
Scheme 6. Synthesis of compounds **37** and **38**.



Conditions: i) 1,3-dibromopropane, Cs_2CO_3, DMF, 20 ºC, 16 h; ii) piperidine or morpholine, Cs_2CO_3, CH_3CN, 90 ºC, 16 h; iii) Pd/C, MeOH, H_2 (30 Psi), 15 ºC, 2 h; iv) DMAP, pyridine, CH_2Cl_2, -78 ºC, then ethyl 3-chloro-3-oxo-propanoate, 15 ºC, 16 h; v) $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (20:20:13 or 3:3:2), 15 ºC, 16 h; vi) $POCl_3$, 100 ºC, 2 h; vii) 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane or 1,4-dioxane/H_2O (1:1), 110 ºC, 16 h; viii) 1-methylpiperidin-4-amine, Cs_2CO_3, $Pd_2(dba)_3$, BINAP, 1,4-dioxane, 120 ºC, 16 h.

Preparation of compounds **34**, **40-45** is shown in Scheme 7. In this case the synthesis started with commercially available anilines **72a-b** and **66** which were transformed into 2,4-dichloroanilines **73a-b** and **67** following methods described above. Then, 5-methyl-2-furyl at position 2 was installed through Suzuki coupling to afford intermediates **74a-c**. Compound **34** with a methoxy group at position 7 of the quinoline, was then prepared from intermediate **74a** by Buchwald-Hartwig amination using 1-methylpiperidin-4-amine as in other cases. 4-Piperidyl derivatives **40** and **41** were synthesized from intermediate **74b** through Mitsunobu reaction with tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate, coupling with 1-methylpiperidin-4-amine, removal of BOC protecting group under acidic conditions and reductive amination in the case of methylated derivative **41**. Compound **42** was prepared from intermediate **75** (obtained from **74c** by Suzuki coupling and hydrogenation), after reaction with tert-butyl 4-methylsulfonyloxypiperidine-1-carboxylate and acidic removal of BOC protecting group. Finally, 2-azaspiro[3.3]heptan-6-yl derivatives **43-45** were isolated after reaction of intermediate **75** with tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate and methylation using $LiAlH_4$ for compound **43** or deprotection with TFA and reductive amination or cyclopropanation for compounds **44** and **45** respectively.

Scheme 7. Synthesis of compounds **34**, **40-45**.

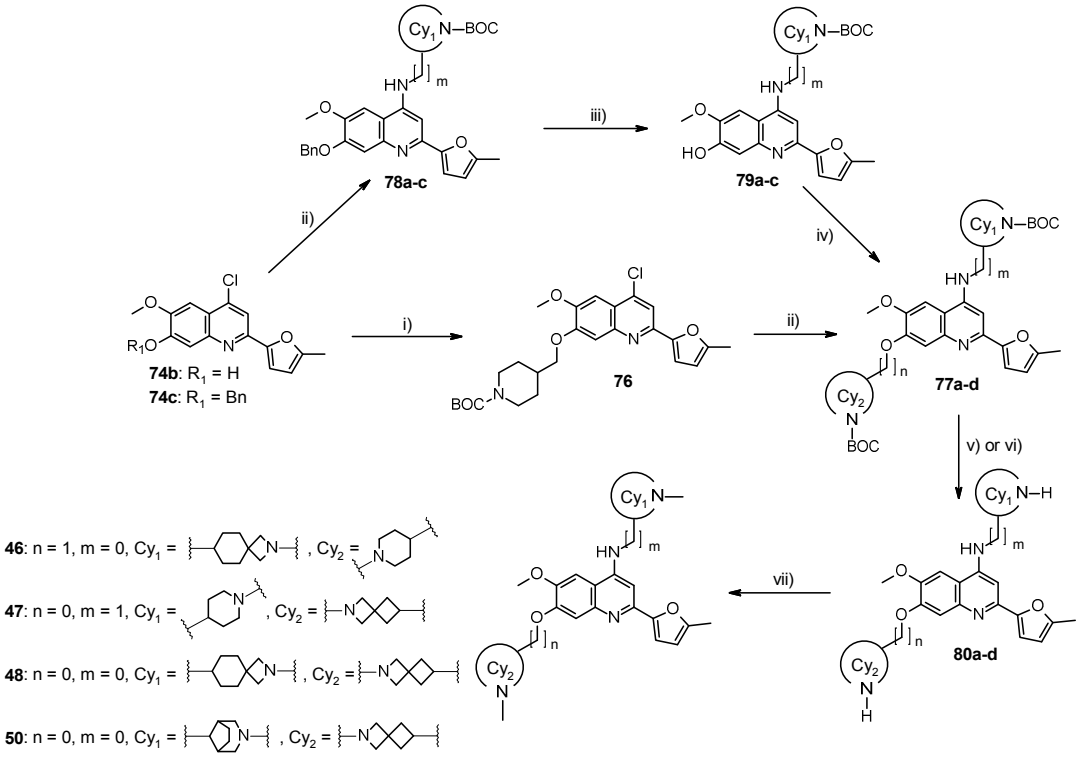


Conditions: i) $POCl_3$, malonic acid, rt, 4 h, then 90 ºC, overnight or 95 ºC, 12 h; ii) Et_3N, ethyl 3-chloro-3-oxo-propanoate, CH_2Cl_2, 25 ºC, 12 h; iii) $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (3:3:2), 25 ºC, 16 h; iv) $POCl_3$, 90 ºC, 2 h; v) 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane, Na_2CO_3 or K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane or 1,4-dioxane/H_2O (15:1), 100-120 ºC, MW or conventional heating, 2-16 h; vi) 1-methylpiperidin-4-amine, Cs_2CO_3, BINAP, $Pd_2(dba)_3$, 1,4-dioxane, 110-120 ºC, MW or conventional heating, 3-16h; vii) Pd/C, H_2 (50 Psi), MeOH, 25 ºC, 16 h; viii) tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate, PPh_3, DIAD, THF, 0 ºC, 8 h; ix) HCl/EtOAc (1.0 or 2.0 M), 25 ºC, 2-3 h; x) $(HCHO)_n$, $NaBH(OAc)_3$, HCOOH, 1,4-dioxane, 100 ºC, 2 h; xi) tert-butyl 4-methylsulfonyloxypiperidine-1-carboxylate or tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate, Cs_2CO_3, DMF, 100 ºC, 16 h; xii) $LiAlH_4$, THF, 70 ºC, 16 h; xiii) TFA, CH_2Cl_2, 18 ºC, 2 h; xiv) acetone or (1-ethoxycyclopropoxy)-trimethyl-silane, $NaBH_3CN$, AcOH, *i*-PrOH or *t*-BuOH, 60 ºC, 16 h.

Synthesis of analogues **46-48** and **50** was performed as described in Scheme 8. From intermediate **74b**, compound **46** was prepared through Mitsunobu reaction, Pd mediated coupling with tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate, deprotection in

acidic media and reductive amination. On the other hand, compounds **47**, **48** and **50** were prepared from **74c**. In this case, this intermediate was transformed into compounds **79a-c** after amination with different BOC- protected amines and hydrogenation. Then, substituent at position 7 was installed by reaction with tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate. Finally, BOC protecting groups were removed using TFA and free secondary amines were methylated through reductive amination.

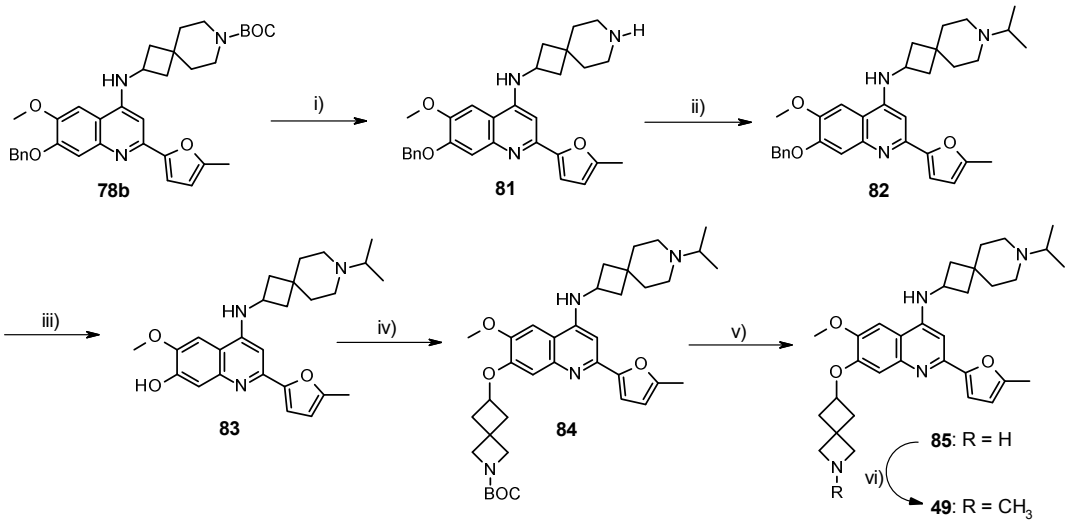
Scheme 8. Synthesis of compounds **46**-**48** and **50**.



Conditions: i) tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate, PPh_3, DIAD, THF, 0 ºC, 8 h; ii) corresponding amine, Cs_2CO_3, BINAP, $Pd_2(dba)_3$, or $Pd(dba)_2$, 1,4-dioxane, 110-130 ºC, 12-16 h; iii) Pd/C, MeOH, H_2 (50 Psi), 25 ºC, 16 h; iv) tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate, Cs_2CO_3, DMF, 100 ºC, 16 h; v) HCl/EtOAc (2.0 M), 25 ºC, 2 h; vi) TFA, CH_2Cl_2, 18 ºC, 2 h; vii) $(HCHO)_n$, $NaBH_3CN$ or $NaBH(OAc)_3$, HCOOH, MeOH, 60-70 ºC, 12-16 h.

Finally, derivative **49** was synthesized as outlined in Scheme 9. To prepare this compound, BOC protecting group of intermediate **78b** was removed and then an isopropyl group was installed by reductive amination. Compound **83** was then achieved after hydrogenation. Subsequent Mitsunobu reaction using tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate led us to intermediate **84** which was finally converted into desired analogue **49** by acidic deprotection and reductive amination.

Scheme 9. Synthesis of compound **49**.



Conditions: i) HCl/EtOAc (2.0 M), 18 ºC, 2 h; ii) acetone, $NaBH_3CN$, AcOH, *i*-PrOH, 60 ºC, 16 h; iii) Pd/C, MeOH, H_2 (50 Psi), 20 ºC, 8 h; iv) tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate, Cs_2CO_3, DMF, 100 ºC, 16 h; v) TFA, DCM, 18 ºC, 2 h; vi) $(HCHO)_n$, $NaBH(OAc)_3$, HCOOH, MeOH, 60 ºC, 16 h.

DISCUSSION AND CONCLUSIONS

In summary, we present a detailed exploration around three main growing vectors born by the 2-(2-furyl)-4-aminoquinoline scaffold. Exploring this chemical space led to the identification of key chemical features (substructures) that guide our navigation to well-

defined biological spaces covering the above mentioned epigenetic targets; thus, we discovered selective G9a inhibitors (**5, 6** and **26**), first-in-class potent and selective DNMT1 inhibitors (**43**) as well as equipotent dual inhibitors targetting G9a and DNMT1 (**12** and **13**). These molecules are valuable tools for comparative cellular studies and to investigate the mechanistic role and function of these targets in different diseases. In this regard, all the above mentioned compounds showed remarkable antiproliferative effects against different hematological cancer cell lines and an adequate therapeutic window. Thus, these first-in-class substrate competitive and reversible inhibitors, covering different activity profiles, may serve as valuable starting points for drug discovery programs.

EXPERIMENTAL SECTION

Chemistry. General Procedure.

Unless otherwise noted, all reagents and solvents were of the highest commercial quality and used without further purification. All experiments dealing with moisture sensitive compounds were conducted under N_2. Flash column chromatography was performed on silica gel, particle size 60 Å, mesh = 230-400 (Merck) 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 performed in a Biotage Smith Synthesis microwave reactor. The NMR spectroscopic data were recorded on a Bruker AV400 or VARIAN 400MR spectrometer with standard pulse sequences, operating at 400 MHz. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. The abbreviations used to explain

multiplicities are s = singlet, d = doublet, t = triplet, m = multiplet. Coupling constants (J) are in hertz. HPLC-analysis was performed using a Shimadzu LC-20AB or LC-20AD with a Luna-C18(2), 5 μm, 2.0*50 mm column at 40 ºC and UV detection at 215, 220 and 254 nm. Flow from the column was split to a MS spectrometer. The MS detector (Agilent 1200, 6110MS or Agilent 1200, 6120MS Quadropole) was configured with an electrospray source or API/APCI. N_2 was used as the nebulizer gas. The source temperature was maintained at 50 ºC. Data acquisition was accomplished with ChemStation LC/MSD quad software. All tested compounds possessed a purity of at least 95% established by HPLC or LCMS unless otherwise noted. Reported yields were not optimized, the emphasis being on purity of product rather than quantity.

N-cyclopropyl-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (7)

To a solution of compound **55a** (200 mg, 0.5 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (325 mg, 1 mmol), BINAP (67 mg, 0.1 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol) and cyclopropanamine (60 mg, 1 mmol) and the reaction mixture was stirred at 120 ºC for 5 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to obtain pure compound **7** (35 mg, 17%) as yellow solid; m.p. 103-104 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.69 (s, 1H), 7.49 (d, *J* = 2.8 Hz, 1H), 7.47 (s, 1H), 7.31 (s, 1H), 6.43 (d, *J* = 2.8 Hz, 1H), 4.36-4.33 (m, 2H), 4.01 (s, 3H), 3.85-3.78 (m, 2H), 3.51-3.47 (m, 2H), 3.20-3.10 (m, 2H), 2.91-2.89 (m, 1H), 2.50 (s, 3H), 2.39-2.34 (m, 2H), 2.24-2.17 (m, 2H), 2.09-2.05 (m,

2H), 1.11-1.09 (m, 2H), 0.85-0.82 (m, 2H). ESI-MS *m/z* 422.3 $[M+H]^+$ calc. for $C_{25}H_{31}N_3O_3$.

N-cyclopentyl-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (8)

To a solution of compound **55a** (90 mg, 0.225 mmol) in toluene (5 mL) was added *t*-BuONa (43 mg, 0.45 mmol), xantphos (45 mg, 0.07 mmol), $Pd_2(dba)_3$ (64 mg, 0.07 mmol), and cyclopentanamine (40 mg, 0.45 mmol) and the solution was heated to 100 ºC for 2 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 2 described in supporting information) to obtain pure compound **8** (7.2 mg, 7%) as yellow oil. ^1H NMR (CD_3OD, 400 MHz): δ 7.83 (s, 1H), 7.52-7.51 (m, 1H), 7.46 (s, 1H), 6.99 (s, 1H), 6.43-6.42 (m, 1H), 4.37-4.33 (m, 3H), 4.04 (s, 3H), 3.90-3.75 (m, 2H), 3.55-3.45 (m, 2H), 3.25-3.10 (m, 2H), 2.51 (s, 3H), 2.45-2.35 (m, 2H), 2.35-2.15 (m, 4H), 2.15-2.00 (m, 2H), 2.00-1.70 (m, 6H). ESI-MS *m/z* 450.3 $[M+H]^+$ calc. for $C_{27}H_{35}N_3O_3$.

2-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]ethanol (9)

To a solution of compound **55a** (200 mg, 0.5 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (325 mg, 1 mmol), BINAP (67 mg, 0.1 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol) and 2-aminoethanol (61 mg, 1 mmol) and the reaction mixture was stirred at 120 ºC for 3 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous

Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to obtain compound **9** (60 mg, 28%) as a yellow solid; m.p. 112-113 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.73 (s, 1H), 7.50-7.49 (m, 2H), 7.06 (s, 1H), 6.42 (d, *J* = 2.8 Hz, 1H), 4.36-4.33 (m, 2H), 4.06 (s, 3H), 3.93-3.89 (m, 2H), 3.86-3.78 (m, 2H), 3.77-3.74 (m, 2H), 3.52-3.47 (m, 2H), 3.21-3.13 (m, 2H), 2.49 (s, 3H), 2.40-2.36 (m, 2H), 2.25-2.16 (m, 2H), 2.11-2.05 (m, 2H). ESI-MS *m/z* 426.3 $[M+H]^+$ calc. for $C_{24}H_{31}N_3O_4$.

3-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-N-methyl-propanamide (10)

To a solution of compound **55a** (200 mg, 0.5 mmol) in 1,4-dioxane (10 mL) was added Cs_2CO_3 (325 mg, 1 mmol), BINAP (67 mg, 0.1 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol) and 3-amino-N-methylpropanamide (204 mg, 1 mmol) and the solution was heated to 130 ºC for 5 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to obtain pure compound **10** (40 mg, 17%) as yellow solid; m.p. 105-106 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.68 (s, 1H), 7.55 (d, *J* = 3.2 Hz, 1H), 7.49 (s, 1H), 7.01 (s, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 4.38-4.34 (m, 2H), 4.05 (s, 3H), 3.94-3.80 (m, 4H), 3.54-3.50 (m, 2H), 3.23-3.12 (m, 2H), 2.75-2.65 (m, 5H), 2.53 (s, 3H), 2.43-2.38 (m, 2H), 2.27-2.17 (m, 2H), 2.12-2.05 (m, 2H). ESI-MS *m/z* 467.3 $[M+H]^+$ calc. for $C_{26}H_{34}N_4O_4$.

4-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-methyl-piperidin-2-one (11)

To a solution of compound **55a** (200 mg, 0.5 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (325 mg, 1 mmol), BINAP (67 mg, 0.1 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol) and 4-amino-1-methylpiperidin-2-one (128 mg, 1 mmol) and the reaction mixture was stirred at 120 ºC for 3 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to obtain pure compound **11** (20 mg, 8%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.83 (s, 1H), 7.58 (d, *J* = 3.2 Hz, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 6.44 (d, *J* = 3.2 Hz, 1H), 4.57-4.51 (m, 1H), 4.40-4.34 (m, 2H), 4.07 (s, 3H), 3.89-3.80 (m, 2H), 3.62-3.48 (m, 4H), 3.21-3.12 (m, 2H), 3.04 (s, 3H), 2.99-2.93 (m, 1H), 2.64-2.53 (m, 4H), 2.44-2.27 (m, 3H), 2.24-2.07 (m, 5H). ESI-MS *m/z* 493.3 $[M+H]^+$ calc. for $C_{28}H_{36}N_4O_4$.

2-(5-ethyl-2-furyl)-6-methoxy-N-[(1-methyl-4-piperidyl)methyl]-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (13)

To a solution of compound **55b** (207 mg, 0.5 mmol) in 1,4-dioxane (15 mL) was added Cs_2CO_3 (325 mg, 1 mmol), BINAP (33.75 mg, 0.05 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol) and (1-methylpiperidin-4-yl)methanamine (128 mg, 1.0 mmol) and the solution was heated to 120 ºC for 12 hours. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 3 described in supporting information) to obtain pure compound **13** (110 mg, 43%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.73 (s, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.48 (s, 1H), 6.99 (s, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 4.37-4.31 (m, 3H), 4.04 (s, 3H), 3.86-3.74 (m, 2H), 3.61-3.52 (m, 4H), 3.50-3.42 (m, 2H), 3.23-3.12 (m, 2H),

3.11-2.98 (m, 2H), 2.91-2.83 (m, 5H), 2.42-2.32 (m, 2H), 2.26-2.11 (m, 5H), 2.11-2.02 (m, 2H), 1.65-1.55 (m, 2H), 1.38-1.34 (m, 3H). ESI-MS *m/z* 507.3 $[M+H]^+$ calc. for $C_{30}H_{42}N_4O_3$.

N-[(1-isopropyl-4-piperidyl)methyl]-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (14)

To a mixture of compound **57a** (125 mg, 0.261 mmol) and acetone (85 mg, 1.46 mmol) in *i*-PrOH (20 mL) were added $NaBH_3CN$ (92 mg, 1.46 mmol) and AcOH (88 mg, 1.46 mmol) and the mixture was stirred at 50 °C for 15 hours under N_2. Then, the solution was cooled to 16 °C, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (method 4 described in supporting information) to afford the desired compound **14** (42.0 mg, 31%) as a yellow oil. ^1H NMR (CD_3OD, 400 MHz): δ 7.73 (s, 1H), 7.56-7.48 (m, 2H), 6.96 (s, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.34-4.29 (m, 2H), 4.03 (s, 3H), 3.90-3.78 (m, 2H), 3.62-3.55 (m, 2H), 3.53-3.49 (m, 5H), 3.16 (m, 2H), 3.09-3.03 (m, 2H), 2.50 (s, 3H), 2.42-2.33 (m, 2H), 2.20-2.17 (m, 4H), 2.10-2.01 (m, 2H), 1.72-1.64 (m, 2H), 1.42-1.32 (m, 7H). ESI-MS *m/z* 521.4 $[M+H]^+$ calc. for $C_{31}H_{44}N_4O_3$.

6-methoxy-2-(5-methyl-2-furyl)-N-[1-methyl-1-(1-methyl-4-piperidyl)ethyl]-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (15)

A mixture of **57b** (15.0 mg, 0.029 mmol), $(HCHO)_n$ (5.3 mg, 0.059 mmol), HCOOH (0.28 mg, 5.92 μmol) and $NaBH(OAc)_3$ (12.55 mg, 0.059 mmol) in MeOH (5.00 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 60 °C for 12 hours. Then, the reaction mixture was filtrated and the filtrate was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (method 5 described in supporting information) to afford compound **15** (4.5 mg, 30%) as a yellow

oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.74 (s, 1H), 7.56 (d, *J* = 3.54 Hz, 1H), 7.47 (s, 1H), 7.09 (s, 1H), 6.44-6.42 (m, 1H), 4.35 (t, *J* = 5.2 Hz, 2H), 4.03 (s, 3H), 3.85-3.76 (m, 2H), 3.58-3.44 (m, 4H), 3.18-3.10 (m, 2H), 3.06-2.96 (m, 2H), 2.83 (s, 3H), 2.62-2.54 (m, 1H), 2.50 (s, 3H), 2.40-2.33 (m, 2H), 2.23-2.16 (m, 2H), 2.10-1.95 (m, 4H), 1.84-1.71 (m, 2H), 1.64 (s, 6H). ESI-MS *m/z* 521.4 $[M+H]^+$ calc. for $C_{31}H_{44}N_4O_3$.

N-benzyl-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (16)

To a solution of compound **55a** (200 mg, 0.5 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (325 mg, 1 mmol), BINAP (67 mg, 0.1 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol) and phenylmethanamine (107 mg, 1 mmol) and the reaction mixture was stirred at 120 ºC for 3 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to obtain pure compound **16** (60 mg, 26%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.78 (s, 1H), 7.32 (s, 7H), 6.92 (s, 1H), 6.38 (d, *J* = 2.8 Hz, 1H), 4.79 (s, 2H), 4.36-4.33 (m, 2H), 4.04 (s, 3H), 3.87-3.78 (m, 2H), 3.52-3.47 (m, 2H), 3.19-3.13 (m, 2H), 2.46 (s, 3H), 2.42-2.35 (m, 2H), 2.26-2.19 (m, 2H), 2.11-2.04 (m, 2H). ESI-MS *m/z* 472.3 $[M+H]^+$ calc. for $C_{29}H_{33}N_3O_3$.

6-methoxy-N-(7-methyl-7-azaspiro[3.5]nonan-2-yl)-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (17)

To a solution of compound **57c** (50.4 mg, 0.1 mmol) in MeOH (10 mL) was added $(HCHO)_n$ (9 mg, 0.3 mmol) and the solution was stirred at room temperature for 1 hour.

Then, $NaBH(OAc)_3$ (63 mg, 0.3 mmol) was added and the mixture was stirred at room temperature overnight. The solution was extracted with EtOAc and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in the supporting information) to afford pure compound **17** (25 mg, 48%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.85 (s, 1H), 7.55 (d, *J* = 2.8 Hz, 1H), 7.51 (s, 1H), 6.85 (s, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 4.55-4.53 (m, 1H), 4.40-4.33 (m, 2H), 4.06 (s, 3H), 3.89-3.82 (m, 2H), 3.53-3.50 (m, 3H), 3.46-3.43 (m, 1H), 3.18-3.15 (m, 3H), 3.05-2.98 (m, 1H), 2.90 (s, 3H), 2.87-2.84 (m, 1H), 2.58-2.54 (m, 1H), 2.53 (s, 3H), 2.40 (s, 2H), 2.28-2.25 (m, 4H), 2.18-2.09 (m, 3H), 1.98-1.95 (m, 3H). ESI-MS *m/z* 519.3 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

N-(7-isopropyl-7-azaspiro[3.5]nonan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (18)

A mixture of **57c** (200 mg, 0.396 mmol), acetone (128 mg, 2.22 mmol), $NaBH_3CN$ (139 mg, 2.22 mmol) and AcOH (133 mg, 2.22 mmol) in *i*-PrOH (5 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 60 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 6 described in supporting information) to afford pure compound **18** (32 mg, 15%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.82 (s, 1H), 7.54 (d, *J* = 3.6 Hz, 1H), 7.48 (s, 1H), 6.81 (s, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 4.52-4.50 (m, 1H), 4.35-4.34 (m, 2H), 4.04 (s, 3H), 3.83 (br s, 2H), 3.52-3.47 (m, 6H), 3.17-3.14 (m, 4H), 2.98-2.93 (m, 1H), 2.82-2.78 (m, 1H), 2.55-2.50 (m, 4H), 2.38-2.36 (m, 2H), 2.29-2.26 (m, 2H), 2.23-2.20 (m, 2H), 2.10-2.08 (m, 2H), 2.00-1.98 (m, 2H), 1.39-1.37 (m, 6H). ESI-MS *m/z* 547.5 $[M+H]^+$ calc. for $C_{33}H_{46}N_4O_3$.

6-methoxy-N-(6-methyl-6-azaspiro[3.4]octan-2-yl)-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (19)

To a solution of compound **57d** (80 mg, 0.16 mmol) in MeOH (10 mL) was added $(HCHO)_n$ (15 mg, 0.48 mmol) and the solution was stirred at room temperature for 1 hour. Then, $NaBH(OAc)_3$ (170 mg, 0.8 mmol) was added and the reaction mixture was stirred at room temperature overnight. Then, the solution was extracted with EtOAc and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford compound **19** (15 mg, 19%) as yellow oil. ^1H NMR (CD_3OD, 400 MHz): δ 7.80 (s, 1H), 7.55-7.54 (m, 1H), 7.47 (s, 1H), 6.85-6.83 (m, 1H), 6.44-6.43 (m, 1H), 4.54-4.46 (m, 1H), 4.36-4.33 (m, 2H), 4.04 (s, 3H), 3.83-3.70 (m, 4H), 3.52-3.47 (m, 2H), 3.19-3.16 (m, 4H), 3.00-2.94 (m, 3H), 2.80-2.65 (m, 3H), 2.60-2.50 (m, 4H), 2.39-2.38 (m, 3H), 2.25-2.21 (m, 3H), 2.12-2.08 (m, 2H). ESI-MS *m/z* 505.3 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

6-methoxy-N-(7-methyl-7-azaspiro[3.5]nonan-3-yl)-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (20)

To a solution of compound **57e** (50.5 mg, 0.1 mmol) in MeOH (10 mL) was added $(HCHO)_n$ (9 mg, 0.3 mmol) and the solution was stirred at room temperature for 1 hour. Then, $NaBH(OAc)_3$ (63 mg, 0.3 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solution was extracted with EtOAc and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford pure compound **20** (25 mg, 48%) as

yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.90 (s, 1H), 7.51 (s, 2H), 7.01 (s, 1H), 6.47 (s, 1H), 4.63-4.56 (m, 1H), 4.40-4.32 (m, 2H), 4.08 (s, 3H), 3.89-3.81 (m, 2H), 3.55-3.40 (m, 4H), 3.26-3.12 (m, 3H), 3.08-2.96 (m, 1H), 2.83 (s, 3H), 2.61-2.48 (m, 5H), 2.46-2.28 (m, 3H), 2.26-2.03 (m, 7H), 1.94-1.82 (m, 1H), 1.70-1.61 (m, 1H). ESI-MS *m/z* 519.3 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

2-(5-ethyl-2-furyl)-6-methoxy-N-(7-methyl-7-azaspiro[3.5]nonan-3-yl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (21)

A mixture of **57f** (50 mg, 0.096 mmol), $(HCHO)_n$ (26.1 mg, 0.289 mmol), $NaBH(OAc)_3$ (61 mg, 0.289 mmol) and HCOOH (4.6 mg, 0.96 mmol) in MeOH (5 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 60 °C for 16 hours. Then, the solution was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **21** (12.5 mg, 24%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.88 (s, 1H), 7.51-7.50 (m, 2H), 6.98 (s, 1H), 6.44 (d, J = 3.2 Hz, 1H), 4.58-4.55 (m, 1H), 4.37-4.34 (m, 2H), 4.05 (s, 3H), 3.85-3.80 (m, 2H), 3.49-3.42 (m, 4H), 3.17-3.14 (m, 4H), 3.03-2.97 (m, 1H), 2.86-2.81 (m, 5H), 2.58-2.52 (m, 2H), 2.40-2.37 (m, 2H), 2.22-2.06 (m, 7H), 1.89-1.86 (m, 1H), 1.68-1.64 (m, 1H), 1.36 (t, J = 14.8 Hz, 3H). ESI-MS *m/z* 533.5 $[M+H]^+$ calc. for $C_{32}H_{44}N_4O_3$.

6-methoxy-N-(6-methyl-6-azaspiro[3.4]octan-3-yl)-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (22)

To a solution of compound **57g** (49.1 mg, 0.1 mmol) in MeOH (10 mL) was added $(HCHO)_n$ (9 mg, 0.3 mmol) and the solution was stirred at room temperature for 1 hour.

Then $NaBH(OAc)_3$ (63 mg, 0.3 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solution was extracted with EtOAc and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford pure compound **22** (15 mg, 30%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.98 (s, 1H), 7.60-7.52 (m, 2H), 7.11-7.08 (m, 1H), 6.48 (s, 1H), 4.41-4.32 (m, 2H), 4.09 (s, 3H), 3.89-3.79 (m, 4H), 3.55-3.46 (m, 3H), 3.24-3.12 (m, 4H), 2.93-2.82 (m, 3H), 2.54-2.35 (m, 7H), 2.26-2.03 (m, 8H). ESI-MS *m/z* 505.3 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

6-methoxy-N-(3-methyl-3-azabicyclo[3.2.1]octan-8-yl)-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (23)

A mixture of **57h** (150 mg, 0.306 mmol), $(HCHO)_n$ (82 mg, 0.917 mmol), $NaBH(OAc)_3$ (194 mg, 0.917 mmol) and HCOOH (14 mg, 0.305 mmol) in MeOH (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 60 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 7 described in supporting information) to afford pure compound **23** (22.5 mg, 14%) as a white solid; m.p. 120-121 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.94 (s, 1H), 7.61 (d, J = 3.6 Hz, 1H), 7.54 (s, 1H), 6.99 (s, 1H), 6.44 (d, J = 2.8 Hz, 1H), 4.37-4.35 (m, 2H), 4.10 (s, 3H), 4.04-4.00 (m, 1H), 3.86-3.77 (m, 2H), 3.54-3.49 (m, 4H), 3.40-3.37 (m, 2H), 3.18-3.14 (m, 2H), 2.92-2.89 (m, 5H), 2.51 (s, 3H), 2.41-2.38 (m, 2H), 2.27-2.22 (m, 4H), 2.06-1.99 (m, 4H). ESI-MS *m/z* 505.4 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

6-methoxy-N-[(3-methyl-3-azabicyclo[3.2.1]octan-8-yl)methyl]-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (24)

A mixture of **57i** (300 mg, 0.55 mmol), $(HCHO)_n$ (149 mg, 1.66 mmol), $NaBH(OAc)_3$ (352 mg, 1.66 mmol) and HCOOH (26 mg, 0.554 mmol) in MeOH (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 60 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 8 described in supporting information) to afford compound **24** (47 mg, 16%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.79-7.76 (m, 1H), 7.57-7.56 (m, 1H), 7.50 (s, 1H), 7.08-7.02 (m, 1H), 6.44-6.43 (m, 1H), 4.36-4.34 (m, 2H), 4.04-4.01 (m, 4H), 3.86-3.78 (m, 2H), 3.53-3.41 (m, 6H), 3.16-3.13 (m, 3H), 2.93-2.83 (m, 3H), 2.55-2.37 (m, 8H), 2.22-2.20 (m, 3H), 2.10-2.08 (m, 3H), 1.90-1.89 (m, 2H). ESI-MS *m/z* 519.4 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

2-(5-ethyl-2-furyl)-6-methoxy-N-[(3-methyl-3-azabicyclo[3.2.1]octan-8-yl)methyl]-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (25)

A mixture of **57j** (360 mg, 0.649 mmol), $(HCHO)_n$ (175 mg, 1.95 mmol), $NaBH(OAc)_3$ (412 mg, 1.95 mmol) and HCOOH (31 mg, 0.648 mmol) in MeOH (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 60 °C overnight. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 8 described in supporting information) to afford compound **25** (48 mg, 14%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.79-7.75 (m, 1H), 7.59-7.57 (m, 1H), 7.50 (s, 1H), 7.07-7.02 (m, 1H), 6.46-6.44 (m, 1H), 4.36-4.34 (m, 2H), 4.04-4.01 (m, 4H), 3.86-3.77 (m, 2H), 3.53-3.41 (m, 6H), 3.16-3.13 (m, 3H), 2.93-2.83 (m, 5H), 2.55-2.37 (m, 5H), 2.21-2.20 (m, 3H), 2.10-2.07 (m,

3H), 1.90-1.89 (m, 2H), 1.36 (t, *J* = 14.8 Hz, 3H). ESI-MS *m/z* 533.4 $[M+H]^+$ calc. for $C_{32}H_{44}N_4O_3$.

6-methoxy-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (26)

To a solution of compound **57k** (200 mg, 0.408 mmol) in MeOH (10 mL) were added HCOOH (18 mg, 0.379 mmol), $NaBH(OAc)_3$ (241 mg, 1.14 mmol) and $(HCHO)_n$ (103 mg, 1.14 mmol) at 20 °C under N_2 and the mixture was stirred at 60 °C for 16 hours. Then, the mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (method 9 described in supporting information) to afford pure compound **26** (61.6 mg, 30%) as a yellow solid; m.p. 120-121 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.80-7.78 (m, 1H), 7.60 (d, *J* = 3.2 Hz, 1H), 7.50 (s, 1H), 7.08 (s, 1H), 6.42 (d, *J* = 3.2 Hz, 1H), 4.60-4.55 (m, 1H), 4.33 (t, *J* = 5.2 Hz, 2H), 4.08-4.04 (m, 5H), 3.87-3.77 (m, 2H), 3.49 (t, *J* = 7.2 Hz, 2H), 3.17-3.13 (m, 2H), 2.87 (s, 3H), 2.51 (s, 3H), 2.42-2.34 (m, 8H), 2.25-2.15 (m, 3H), 2.15-1.99 (m, 3H). ESI-MS *m/z* 505.3 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

6-methoxy-N-methyl-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (27)

To a solution of compound **57l** (40 mg, 0.083 mmol) in MeOH (5 mL) were added HCOOH (4 mg, 0.083 mmol), $NaBH(OAc)_3$ (53 mg, 0.25 mmol) and $(HCHO)_n$ (23 mg, 0.25 mmol) and the mixture was stirred at 60 °C for 16 hours under N_2. Then, mixture was concentrated under reduced pressure and the resulting residue was purified by prep-HPLC (method 10 described in supporting information) to afford pure compound **27** (8.2 mg, 20%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.60 (d, *J*

= 14.8 Hz, 2H), 7.31 (d, *J* = 9.2 Hz, 2H), 6.46 (s, 1H), 4.46-4.32 (m, 3H), 4.04 (s, 3H), 3.86-3.77 (m, 2H), 3.67 (d, *J* = 13.6 Hz, 2H), 3.54-3.47 (m, 2H), 3.29-3.10 (m, 7H), 2.91 (s, 3H), 2.54-2.49 (m, 3H), 2.46-2.35 (m, 4H), 2.28-2.13 (m, 4H), 2.12-2.03 (m, 2H). ESI-MS *m/z* 493.3 $[M+H]^+$ calc. for $C_{29}H_{40}N_4O_3$.

2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (29)

To a solution of compound **64a** (140 mg, 0.38 mmol) in 1,4-dioxane (10 mL) was added *t*-BuOK (1.0 M, 1.14 mL, 1.14 mmol), x-Phos (54 mg, 0.114 mmol), $Pd_2(dba)_3$ (69 mg, 0.076 mmol) and 1-methylpiperidin-4-amine (252 mg, 2.2 mmol) and the solution was heated to 130 ºC for 4 hours under Microwave. Then, the mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 2 described in supporting information) to afford pure compound **29** (18.7 mg, 11%) as a yellow solid; m.p. 98-99 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.34 (d, *J* = 9.2 Hz, 1H), 7.64 (s, 1H), 7.46 (s, 1H), 7.30-7.25 (m, 1H), 7.07 (s, 1H), 6.45 (d, *J* = 2.8 Hz, 1H), 4.32-4.29 (m, 3H), 3.73-3.66 (m, 4H), 3.48-3.44 (m, 2H), 3.26-3.25 (m, 1H), 3.15-3.10 (m, 2H), 2.93 (s, 3H), 2.51 (s, 3H), 2.34-2.31 (m, 4H), 2.18-2.17 (m, 4H), 2.16-2.14 (m, 2H). ESI-MS *m/z* 449.3 $[M+H]^+$ calc. for $C_{27}H_{36}N_4O_2$.

2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-(3-pyrrolidin-1-ylpropoxy)quinolin-6-ol (30)

To a solution of compound **5** (50 mg, 0.101 mmol) in CH_2Cl_2 (10 mL) was added BBr_3 (254 mg, 1.01 mmol) slowly at 0 ºC and the solution was stirred for 2 hours at 0 ºC

under N_2. Then, the reaction was quenched with water and concentrated to give the crude product which was purified by prep-HPLC (method 2 described in supporting information) to afford pure compound **30** (11 mg, 23%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 1H), 7.58 (d, *J* = 3.2 Hz, 1H), 7.52 (s, 1H), 7.07 (s, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 4.41-4.32 (m, 2H), 4.34-4.24 (m, 2H), 3.87-3.71 (m, 4H), 3.58-3.51 (m, 2H), 3.32-3.25 (m, 2H), 3.20-3.09 (m, 2H), 2.97 (s, 3H), 2.50 (s, 3H), 2.44-2.33 (m, 4H), 2.24-2.04 (m, 6H). ESI-MS *m/z* 465.3 $[M+H]^+$ calc. for $C_{27}H_{36}N_4O_3$.

6-chloro-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (31)

To a solution of compound **64b** (100 mg, 0.25 mmol) in 1,4-dioxane (15 mL) was added Cs_2CO_3 (161 mg, 0.49 mmol), BINAP (31 mg, 0.049 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and 1-methylpiperidin-4-amine (128 mg, 1.12 mmol) and the mixture was stirred at 110 ºC for 12 hours under N_2. Then, the mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 2 described in supporting information) to afford pure compound **31** (10 mg, 8%) as a yellow solid; m.p. 109-110 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.54-8.47 (m, 1H), 7.54-7.44 (m, 2H), 7.10-7.02 (m, 1H), 6.42-6.35 (m, 1H), 4.43-4.35 (m, 2H), 4.26-4.17 (m, 1H), 3.93-3.82 (m, 2H), 3.60-3.42 (m, 6H), 3.25-3.13 (m, 4H), 2.89 (s, 3H), 2.51 (s, 3H), 2.45-2.30 (m, 3H), 2.20-2.03 (m, 5H). ESI-MS *m/z* 483.3 $[M+H]^+$ calc. for $C_{27}H_{35}ClN_4O_2$.

2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-(3-pyrrolidin-1-ylpropoxy)-6-(trifluoromethoxy)quinolin-4-amine (32)

To a solution of compound **64c** (195 mg, 0.43 mmol) in 1,4-dioxane (15.00 mL) were successively added 1-methylpiperidin-4-amine (108 mg, 1.03 mmol), $Pd_2(dba)_3$ (39 mg, 0.04 mmol), BINAP (53 mg, 0.086 mmol) and Cs_2CO_3 (350 mg, 1.08 mmol) and the resulting mixture was stirred at 80 °C for 15 hours under N_2. Then, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to obtain the crude product which was purified by prep-HPLC (method 2 described in supporting information) to afford pure compound **32** (64.4 mg, 28%) as a yellow solid; m.p. 195-196 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.52 (s, 1H), 7.75-7.70 (m, 2H), 7.14 (s, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 4.42-4.39 (m, 2H), 4.36-4.28 (m, 1H), 3.76-3.68 (m, 4H), 3.47-3.43 (m, 2H), 3.31-3.26 (m, 2H), 3.19-3.10 (m, 2H), 2.95 (s, 3H), 2.53 (s, 3H), 2.42-2.36 (m, 4H), 2.19-2.16 (m, 4H), 2.08-2.07 (m, 2H). ESI-MS *m/z* 533.2 $[M+H]^+$ calc. for $C_{28}H_{35}F_3N_4O_3$.

2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-(3-pyrrolidin-1-ylpropoxy)quinoline-6-carbonitrile (33)

To a solution of compound **65** (100 mg, 0.168 mmol) in DMF (5 mL) was added $Zn(CN)_2$ (39 mg, 0.336 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and the solution was heated at 110 ºC for 12 hours. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **33** (58 mg, 73%) as yellow solid; m.p. 123-124 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.88 (s, 1H), 7.75 (d, *J* = 3.6 Hz, 1H), 7.62 (s, 1H), 7.15 (s, 1H), 6.51 (d, *J* = 3.6 Hz, 1H), 4.46-4.42 (m, 2H), 4.38-4.27 (m, 1H), 3.83-3.76 (m, 1H), 3.73-3.64 (m, 2H), 3.54-3.46 (m,

2H), 3.21-3.12 (m, 4H), 2.94 (s, 3H), 2.52 (s, 3H), 2.45-2.33 (m, 4H), 2.21-2.02 (m, 6H). ESI-MS *m/z* 474.3 $[M+H]^+$ calc. for $C_{28}H_{35}N_5O_2$.

6,7-dimethoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (34)

To a solution of compound **74a** (70 mg, 0.23 mmol) in 1,4-dioxane (5 mL) was added Cs_2CO_3 (226 mg, 0.69 mmol), BINAP (423 mg, 0.69 mmol), $Pd_2(dba)_3$ (38 mg, 0.041 mmol) and 1-methylpiperidin-4-amine (52 mg, 0.46 mmol) and the mixture was heated to 110 ºC for 3 hours under Microwave. Then, the mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by the prep-HPLC (method 2 described in supporting information) to afford pure compound **34** (7.8 mg, 9%) as yellow solid; m.p. 21-220 ºc. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 1H), 7.56-7.54 (d, *J* = 8 Hz, 1H), 7.47 (s, 1H), 7.08 (s, 1H), 6.45 (s, 1H), 4.04-4.02 (m, 7H), 3.73-3.68 (m, 2H), 3.27-3.20 (m, 2H), 2.96 (s 3H), 2.52 (s, 3H), 2.45-2.30 (m, 2H), 2.20-2.05 (m, 2H). ESI-MS *m/z* 382.3 $[M+H]^+$ calc. for $C_{22}H_{27}N_3O_3$.

7-[3-(dimethylamino)propoxy]-2-(5-ethyl-2-furyl)-6-methoxy-N-(1-methyl-4-piperidyl)quinolin-4-amine (35)

A mixture of **68a** (150 mg, 0.455 mmol), 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (121 mg, 0.546 mmol), K_2CO_3 (157 mg, 1.14 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.045 mmol) in 1,4-dioxane/H_2O (1:1, 10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 110 °C for 16 hours. Then, the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue which

was purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) to afford pure intermediate 3-[[4-chloro-2-(5-ethyl-2-furyl)-6-methoxy-7-quinolyl]oxy]-N,N-dimethyl-propan-1-amine (150 mg, 85%) as a yellow solid. ESI-MS *m/z* 389.3 $[M+H]^+$ calc. for $C_{21}H_{25}ClN_2O_3$. A mixture of this intermediate (150 mg, 0.385 mmol), 1-methylpiperidin-4-amine (88 mg, 0.771 mmol), Cs_2CO_3 (251 mg, 0.7712 mmol), $Pd_2(dba)_3$ (35 mg, 0.038 mmol) and BINAP (24 mg, 0.038 mmol) in 1,4-dioxane (5 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 120 °C for 16 hours. Then, reaction mixture was concentrated in vacuum to give a residue which was successively purified by prep-TLC (CH_2Cl_2:MeOH = 7:1) and prep-HPLC (method 3 described in supporting information) to afford pure compound **35** (6 mg, 3%) as a yellow oil. ^1H NMR (CD_3OD, 400 MHz): δ 7.82 (s, 1H), 7.60 (d, *J* = 3.2 Hz, 1H), 7.52 (s, 1H), 7.09 (s, 1H), 6.46 (d, *J* = 3.6 Hz, 1H), 4.36-4.34 (m, 3H), 4.05 (s, 3H), 3.72-3.69 (m, 2H), 3.44-3.42 (m, 2H), 3.00 (s, 6H), 2.95 (s, 3H), 2.88 (q, *J* = 7.6 Hz, 15.2 Hz, 2H), 2.40-2.38 (m, 6H), 2.17-2.14 (m, 2H), 1.36 (t, *J* = 14.8 Hz, 3H). ESI-MS *m/z* 467.4 $[M+H]^+$ calc. for $C_{27}H_{38}N_4O_3$.

7-[3-(5-azaspiro[2.4]heptan-5-yl)propoxy]-2-(5-ethyl-2-furyl)-6-methoxy-N-(1-methyl-4-piperidyl)quinolin-4-amine (36)

A mixture of **68b** (100 mg, 0.262 mmol), 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl- 1,3,2-dioxaborolane (70 mg, 0.314 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) and K_2CO_3 (90 mg, 0.655 mmol) in 1,4-dioxane/H_2O (1:1, 12 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 110 °C for 16 hours under N_2 atmosphere. Then, the reaction mixture was concentrated in vacuum to give a residue which was purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) to afford intermediate 7-[3-(5-azaspiro[2.4]heptan-5-yl)propoxy]-4-chloro-2-(5-ethyl-2-furyl)-6-methoxy-quinoline

(230 mg, containing some impurities) as a yellow solid. ESI-MS *m/z* 441.3 $[M+H]^+$ calc. for $C_{25}H_{29}ClN_2O_3$. Then, a mixture of this intermediate (130 mg, 0.294 mmol), 1-methylpiperidin-4-amine (67 mg, 0.589 mmol), $Pd_2(dba)_3$ (27 mg, 0.029 mmol), BINAP (18 mg, 0.029 mmol) and Cs_2CO_3 (192 mg, 0.589 mmol) in 1,4-dioxane (5 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 120 ℃ for 16 hours under N_2 atmosphere. Then, the reaction mixture was concentrated and successively purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) and prep-HPLC (method 3 described in supporting information) to afford pure compound **36** (10 mg, 6%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.82 (s, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.51 (s, 1H), 7.09 (s, 1H), 6.47 (d, *J* = 3.6 Hz, 1H), 4.36-4.31 (m, 3H), 4.05 (s, 3H), 4.04-3.96 (m, 2H), 3.72-3.69 (m, 2H), 3.55-3.52 (m, 3H), 3.43-3.39 (m, 1H), 2.96 (s, 3H), 2.90-2.82 (m, 2H), 2.42-2.38 (m, 4H), 2.19-2.06 (m, 6H), 1.36 (t, *J* = 14.8 Hz, 3H), 0.83-0.78 (m, 4H). ESI-MS *m/z* 519.4 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

2-(5-ethyl-2-furyl)-6-methoxy-N-(1-methyl-4-piperidyl)-7-[3-(1-piperidyl)propoxy]quinolin-4-amine (37)

A mixture of **71a** (200 mg, 0.541 mmol), 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (144 mg, 0.650 mmol), $Pd(PPh_3)_4$ (62 mg, 0.054 mmol) and K_2CO_3 (187 mg, 1.35 mmol) in 1,4-dioxane (3 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 110 ℃ for 16 hours. 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 intermediate 4-chloro-2-(5-ethyl-2-furyl)-6-methoxy-7-[3-(1-piperidyl)propoxy]quinoline (220 mg, 94%) as a yellow solid. ESI-MS *m/z* 429.3 $[M+H]^+$ calc. for $C_{24}H_{29}ClN_2O_3$. Then, a mixture of this intermediate (220 mg, 0.513 mmol), 1-methylpiperidin-4-amine (117 mg, 1.03 mmol), $Pd_2(dba)_3$ (47 mg,

0.051 mmol), BINAP (32 mg, 0.051 mmol) and Cs_2CO_3 (334 mg, 1.03 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 120 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was successively purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) and prep-HPLC (method 3 described in supporting information) to afford pure compound **37** (15.1 mg 6%) as a yellow solid; m.p. 127-128 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (s, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.51 (s, 1H), 7.09 (s, 1H), 6.47 (d, *J* = 3.6 Hz, 1H), 4.35-4.32 (m, 3H), 4.04 (s, 3H), 3.69-3.67 (m, 4H), 3.39-3.37 (m, 3H), 3.31-3.26 (m, 1H), 3.00-2.96 (m, 5H), 2.86 (q, *J* = 7.6 Hz, 14.8Hz, 2H), 2.41-2.38 (m, 4H), 2.16-1.80 (m, 7H), 1.59-1.51 (m, 1H), 1.36 (t, *J* = 14.8 Hz, 3H). ESI-MS *m/z* 507.4 $[M+H]^+$ calc. for $C_{30}H_{42}N_4O_3$.

2-(5-ethyl-2-furyl)-6-methoxy-N-(1-methyl-4-piperidyl)-7-(3-morpholinopropoxy)quinolin-4-amine (38)

A mixture of **71b** (200 mg, 0.539 mmol), 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (143 mg, 0.6465 mmol), $Pd(PPh_3)_4$ (62 mg, 0.054 mmol) and K_2CO_3 (186 mg, 1.35 mmol) in 1,4-dioxane/H_2O (1:1, 6 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 110 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by TLC (CH_2Cl_2:MeOH = 12:1) to give intermediate 4-[3-[[4-chloro-2-(5-ethyl-2-furyl)-6-methoxy-7-quinolyl]oxy]propyl]morpholine (190 mg, 81%) as a yellow solid. ESI-MS *m/z* 431.1 $[M+H]^+$ calc. for $C_{23}H_{27}ClN_2O_4$. Then, a mixture of this intermediate (190 mg, 0.441 mmol), 1-methylpiperidin-4-amine (100 mg, 0.882 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), BINAP (27 mg, 0.044 mmol) and Cs_2CO_3 (287 mg, 0.882 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 3 times and the mixture was

stirred at 120 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was successively purified by TLC (CH_2Cl_2:MeOH = 10:1) and prep-HPLC (method 3 described in supporting information) to afford pure compound **38** (25.7 mg 11%) as a yellow solid; m.p. 121-122 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (s, 1H), 7.59 (d, *J* = 3.2 Hz, 1H), 7.51 (s, 1H), 7.09 (s, 1H), 6.47 (d, *J* = 3.6 Hz, 1H), 4.37-4.31 (m, 3H), 4.04 (s, 3H), 3.91-3.82 (m, 3H), 3.72-3.69 (m, 3H), 3.48-3.45 (m, 3H), 3.26-3.13 (m, 3H), 2.96 (s, 3H), 2.88 (q, *J* = 7.2 Hz, 14.8Hz, 2H), 2.42-2.38 (m, 6H), 2.16-2.12 (m, 2H), 1.36 (t, *J* = 14.8 Hz, 3H). ESI-MS *m/z* 509.4 $[M+H]^+$ calc. for $C_{29}H_{40}N_4O_4$.

7-[3-(3-fluoropyrrolidin-1-yl)propoxy]-6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (39)

A mixture of **67c** (400 mg, 1.07 mmol), 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (156 mg, 0.75 mmol), $Pd(PPh_3)_4$ (123 mg, 0.107 mmol) and K_2CO_3 (296 mg, 2.14 mmol) in 1,4-dioxane/H_2O (10:1, 55 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 110 °C for 16 hours. Then, the mixture was concentrated and the residue was extracted with EtOAc. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give intermediate 4-chloro-7-[3-(3-fluoropyrrolidin-1-yl)propoxy]-6-methoxy-2-(5-methyl-2-furyl)quinoline (400 mg, 89%) as a yellow solid. ESI-MS *m/z* 419.1 $[M+H]^+$ calc. for $C_{22}H_{24}ClFN_2O_3$. A mixture of this intermediate (50 mg, 0.119 mmol), 1-methylpiperidin-4-amine (41 mg, 0.358 mmol), $Pd_2(dba)_3$ (22 mg, 0.024 mmol), Cs_2CO_3 (78 mg, 0.239 mmol) and BINAP (15 mg, 0.024 mmol) in 1,4-dioxane (5.00 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 120 °C for 12 hours. Then, the reaction mixture was filtrated and the filtrate was

concentrated under vacuum to give the crude product. The crude product was purified by prep-HPLC (method 11 described in supporting information) to afford compound **39** (5.0 mg, 8%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.83 (s, 1H), 7.61 (d, *J* = 3.2 Hz, 1H), 7.51 (s, 1H), 7.11 (s, 1H), 6.45 (d, *J* = 3.2 Hz, 1H), 5.58-5.45 (m, 1H), 4.36 (d, *J* = 4.8 Hz, 3H), 4.10-4.00 (m, 5H), 3.73-3.67 (m, 2H), 3.60-3.50 (m, 6H), 2.95 (s, 3H), 2.62-2.55 (m, 1H), 2.51 (s, 3H), 2.49-2.26 (m, 5H), 2.26-2.09 (m, 2H). ESI-MS *m/z* 497.3 $[M+H]^+$ calc. for $C_{28}H_{37}FN_4O_3$.

6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-(4-piperidylmethoxy)quinolin-4-amine (40)

To a mixture of **74b** (650 mg, 2.24 mmol), tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (540 mg, 2.51 mmol) and PPh_3 (1.18 g, 4.48 mmol) in THF (50 mL), was added DIAD (907 mg, 4.48 mmol) and the mixture was stirred at 0 ºC for 8 hours. Then, the mixture was concentrated and extracted with EtOAc. The combined organic phase was washed with saturated brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 2/1) to afford intermediate tert-butyl 4-[[4-chloro-6-methoxy-2-(5-methyl-2-furyl)-7-quinolyl]oxymethyl]piperidine-1-carboxylate (700 mg, 64%). ESI-MS *m/z* 487.3 $[M+H]^+$ calc. for $C_{26}H_{31}ClN_2O_5$. To a mixture of this intermediate (250 mg, 0.51 mmol) and 1-methylpiperidin-4-amine (120 mg, 1.06 mmol) in 1,4-dioxane (20 mL) was added Cs_2CO_3 (344 mg, 1.06 mmol) and $Pd(dba)_2$ (30 mg, 0.052 mmol). The mixture was stirred at 120 ºC for 12 hours. Then, the solution was concentrated and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 10/1) to afford intermediate tert-butyl 4-[[6-methoxy-2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-quinolyl]oxymethyl]piperidine-1-carboxylate (100 mg, 34%) as

yellow solid. ESI-MS *m/z* 565.2 $[M+H]^+$ calc. for $C_{32}H_{44}N_4O_5$. Finally, to a solution of this intermediate (160 mg, 0.283 mmol) in EtOAc (10 mL) was added HCl/EtOAc (10 mL, 2.0 M) and the mixture was stirred at 25 ºC for 3 hours. Then, the solution was concentrated and the residue was purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **40** (100 mg, 75%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.79 (s, 1H), 7.58 (d, *J* = 3.2 Hz, 1H), 7.48 (s, 1H), 7.08 (s, 1H), 6.43 (d, *J* = 3.2 Hz, 1H), 4.37-4.26 (m, 1H), 4.14-4.10 (m, 2H), 4.01 (s, 3H), 3.74-3.65 (m, 2H), 3.54-3.46 (m, 2H), 3.35-3.27 (m, 2H), 3.16-3.02 (m, 2H), 2.95 (s, 3H), 2.50 (s, 3H), 2.45-2.23 (m, 3H), 2.20-2.08 (m, 4H), 1.79-1.69 (m, 2H). ESI-MS *m/z* 465.3 $[M+H]^+$ calc. for $C_{27}H_{36}N_4O_3$.

6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-[(1-methyl-4-piperidyl)methoxy]quinolin-4-amine (41)

To a solution of compound **40** (80 mg, 0.172 mmol) in 1,4-dioxane (5 mL) was added $(HCHO)_n$ (46.5 mg, 0.516 mmol), $NaBH(OAc)_3$ (109 mg, 0.516 mmol) and HCOOH (8.3 mg, 0.172 mmol) and the mixture was stirred at 100 ºC for 2 hours. Then, the solution was concentrated and the residue was purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **41** (15.0 mg, 18%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.81 (s, 1H), 7.62 (d, *J* = 3.6 Hz, 1H), 7.50 (s, 1H), 7.09 (s, 1H), 6.43 (d, *J* = 2.4 Hz, 1H), 4.39-4.30 (m, 1H), 4.13-4.08 (m, 2H), 4.02 (s, 3H), 3.71-3.63 (m, 2H), 3.62-3.55 (m, 2H), 3.35-3.28 (m, 2H), 3.13-3.04 (m, 2H), 2.95 (s, 3H), 2.90 (s, 3H), 2.50 (s, 3H), 2.38-2.10 (m, 7H), 1.84-1.71 (m, 2H). ESI-MS *m/z* 479.4 $[M+H]^+$ calc. for $C_{28}H_{38}N_4O_3$.

6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)-7-(4-piperidyloxy)quinolin-4-amine (42)

To a mixture of **75** (100 mg, 0.272 mmol) and tert-butyl 4-methylsulfonyloxypiperidine-1-carboxylate (91 mg, 0.326 mmol) in DMF (5.00 mL) was added Cs_2CO_3 (177 mg, 0.544 mmol) and the mixture was stirred at 100 °C for 16 hours under N_2. Then, the mixture was concentrated and purified by prep-TLC (CH_2Cl_2:MeOH = 10:1) to afford intermediate tert-butyl 4-[[6-methoxy-2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-quinolyl]oxy]piperidine-1-carboxylate (50 mg, 33%) as a yellow solid. ESI-MS *m/z* 551.3 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_5$. Then, a solution of this intermediate (50 mg, 0.091 mmol) in HCl/EtOAc (5.00 mL, 1.0 M) was stirred at 25 °C for 2 hours under N_2. The mixture was concentrated and purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **42** (10.0 mg, 24%) as a yellow solid; m.p. 150-151 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.84 (s, 1H), 7.61 (s, 2H), 7.09 (s, 1H), 6.45 (s, 1H), 4.96-4.90 (m, 2H), 4.32 (s, 1H), 4.04 (s, 3H), 3.72-3.65 (m, 2H), 3.48-3.43 (m, 2H), 3.31 (s, 1H), 2.95 (s, 3H), 2.50 (s, 3H), 2.40-2.19 (m, 10H). ESI-MS *m/z* 451.3 $[M+H]^+$ calc. for $C_{26}H_{34}N_4O_3$.

6-methoxy-7-[(2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy]-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (43)

To a mixture of compound **75** (100 mg, 0.272 mmol) and tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (95 mg, 0.326 mmol) in DMF (5.0 mL) was added Cs_2CO_3 (177 mg, 0.544 mmol) and the mixture was stirred at 100 °C for 16 hours. Then, the mixture was concentrated and purified by TLC to give intermediate tert-butyl 6-[[6-methoxy-2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-quinolyl]oxy]-2-azaspiro[3.3]heptane-2-carboxylate (60.0 mg,

39%). ESI-MS *m/z* 563.3 $[M+H]^+$ calc. for $C_{32}H_{42}N_4O_5$. A mixture of this intermediate (100 mg, 0.177 mmol), and $LiAlH_4$ (34 mg, 0.89 mmol) in dry THF (10.0 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 70 °C for 16 hours under N_2 atmosphere. Then, the reaction was quenched with water and concentrated. The residue was purified by prep-HPLC (method 2 described in supporting information) to afford pure compound **43** (21 mg, 25%) as a yellow oil. ^1H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 1H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.35 (s, 1H), 7.07 (s, 1H), 6.42 (d, *J* = 4.4 Hz, 1H), 4.46-4.43 (m, 1H), 4.35-4.31 (m, 2H), 4.17-4.10 (m, 2H), 4.00 (s, 3H), 3.70-3.67 (m, 2H), 3.35-3.28 (m, 3H), 3.07-3.01 (m, 2H), 2.95 (s, 3H), 2.92 (s, 3H), 2.57-2.55 (m, 2H), 2.49 (s, 3H), 2.38-2.35 (m, 2H), 2.17-2.14 (m, 2H). ESI-MS *m/z* 477.4 $[M+H]^+$ calc. for $C_{28}H_{36}N_4O_3$.

7-[(2-isopropyl-2-azaspiro[3.3]heptan-6-yl)oxy]-6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (44)

To a solution of intermediate tert-butyl 6-[[6-methoxy-2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-quinolyl]oxy]-2-azaspiro[3.3]heptane-2-carboxylate (described in the synthesis of compound **43**) (170 mg, 0.302 mmol) in CH_2Cl_2 (12 mL) was added TFA (2.6 g) at 0 °C and the mixture was stirred at 18 °C for 2 hours. Then, the mixture was concentrated to obtain intermediate 7-(2-azaspiro[3.3]heptan-6-yloxy)-6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (500 mg, crude) as yellow oil. ESI-MS *m/z* 463.3 $[M+H]^+$ calc. for $C_{27}H_{34}N_4O_3$. Then, to a solution of this intermediate (150 mg, 0.325 mmol) in *i*-PrOH (4 mL) were added $NaBH_3CN$ (98 mg, 1.56 mmol), acetone (91 mg, 1.56 mmol) and AcOH (94 mg, 1.56 mmol) at 18 °C under N_2 and the mixture was stirred at 60 °C for 16 hours. Then, the mixture was concentrated. The residue was purified by prep-HPLC (method 12

described in supporting information) to afford pure compound **44** (23 mg, 14%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.78 (s, 1H), 7.58 (d, *J* = 3.53 Hz, 1H), 7.34 (s, 1H), 7.07 (s, 1H), 6.43 (d, *J* = 3.53 Hz, 1H), 4.31 (br. s, 1H), 4.26 (d, *J* = 19.41 Hz, 2H), 4.20 (s, 2H), 4.01 (s, 3H), 3.69 (d, *J* = 12.35 Hz, 2H), 3.43-3.39 (m, 1H), 3.32 (br. s, 1H), 3.29-3.23 (m, 1H), 3.12-3.07 (m, 1H), 2.99 (br. s, 1H), 2.94 (s, 3H), 2.91-2.86 (m, 1H), 2.64-2.49 (m, 5H), 2.38 (d, *J* = 13.23 Hz, 2H), 2.19-2.08 (m, 2H), 1.23 (dd, *J* = 7.94 Hz, *J* = 6.62 Hz, 6H). ESI-MS *m/z* 505.4 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

7-[(2-cyclopropyl-2-azaspiro[3.3]heptan-6-yl)oxy]-6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (45)

To a solution of intermediate 7-(2-azaspiro[3.3]heptan-6-yloxy)-6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (described in the synthesis of compound **44**, 100 mg, 0.216 mmol) and (1-ethoxycyclopropoxy)-trimethyl-silane (226 mg, 1.30 mmol) in *t*-BuOH (10 mL) were added $NaBH_3CN$ (81 mg, 1.30 mmol) and AcOH (77 mg, 1.30 mmol) and the mixture was stirred at 60 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (method 13 described in supporting information) to afford compound **45** (30 mg, 27%) as a yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.78 (s, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.34 (s, 1H), 7.07 (s, 1H), 6.43 (d, *J* = 3.6 Hz, 1H), 4.35-4.28 (m, 6H), 4.01 (s, 3H), 3.71-3.68 (m, 2H), 3.36-3.29 (m, 2H), 3.04-2.99 (m, 3H), 2.95 (s, 3H), 2.58-2.55 (m, 2H), 2.50 (s, 3H), 2.39-2.36 (m, 2H), 2.16-2.10 (m, 2H), 0.92-0.85 (m, 4H). ESI-MS *m/z* 503.3 $[M+H]^+$ calc. for $C_{30}H_{38}N_4O_3$.

6-methoxy-N-(7-methyl-7-azaspiro[3.5]nonan-2-yl)-2-(5-methyl-2-furyl)-7-[(1-methyl-4-piperidyl)methoxy]quinolin-4-amine (46)

To a solution of **80a** (30.0 mg, 0.061 mmol) in MeOH (5.0 mL), was added HCOOH (6 mg, 0.13 mmol), $NaBH(OAc)_3$ (78 mg, 0.367 mmol) and $(HCHO)_n$ (33 mg, 0.367 mmol) and the mixture was stirred at 70 ºC for 12 hours. Then, the mixture was concentrated and the residue was purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **46** (8.0 mg, 25%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.80 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 6.81 (s, 1H), 6.43 (s, 1H), 4.53 (d, *J* = 7.6 Hz 1H), 4.13 (d, *J* = 5.2 Hz, 2H), 4.02 (s, 3H), 3.64-3.55 (m, 2H), 3.53-3.48 (m, 2H), 3.44-3.36 (m, 2H), 3.16-3.02 (m, 4H), 3.00-2.80 (m, 6H), 2.80-2.71 (m, 1H), 2.51 (s, 3H), 2.31-2.09 (m, 6H), 2.01-1.84 (m, 2H), 1.83-1.73 (m, 2H). ESI-MS *m/z* 519.4 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

6-methoxy-7-[(2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy]-2-(5-methyl-2-furyl)-N-[(1-methyl-4-piperidyl)methyl]quinolin-4-amine (47)

To a solution of compound **80b** (150 mg, 0.325 mmol) in MeOH (10 mL) were added $NaBH_3CN$ (49 mg, 0.780 mmol), HCOOH (12 mg, 0.260 mmol) and $(HCHO)_n$ (70 mg, 0.780 mmol) and the mixture was stirred at 60 °C for 16 hours. Then, the mixture was concentrated and the residue was purified by prep-HPLC (method 14 described in supporting information) to afford pure compound **47** (9.5 mg, 6%) as yellow solid; m.p. 158-160 ºC. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.70 (s, 1H), 7.56 (d, *J* = 3.53 Hz, 1H), 7.33 (s, 1H), 6.98 (s, 1H), 6.45-6.39 (m, 1H), 4.47-4.34 (m, 2H), 4.14 (br. s., 2H), 4.01 (s, 3H), 3.64-3.52 (m, 4H), 3.14-2.94 (m, 5H), 2.92 (s, 3H), 2.86 (s, 3H), 2.57 (d, *J* = 12.35 Hz, 2H), 2.50 (s, 3H), 2.16 (d, *J* = 13.23 Hz, 3H), 1.70-1.60 (m, 2H). ESI-MS *m/z* 491.4 $[M+H]^+$ calc. for $C_{29}H_{38}N_4O_3$.

6-methoxy-7-[(2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy]-N-(7-methyl-7-azaspiro[3.5]nonan-2-yl)-2-(5-methyl-2-furyl)quinolin-4-amine (48)

To a solution of compound **80c** (150 mg, 0.249 mmol) in MeOH (10 mL) were added $NaBH(OAc)_3$ (317 mg, 1.49 mmol), HCOOH (12 mg, 0.249 mmol) and $(HCHO)_n$ (135 mg, 1.49 mmol) and the mixture was stirred at 60 °C for 16 hours. Then, the mixture was concentrated and the residue was purified by prep-HPLC (method 15 described in supporting information) to afford pure compound **48** (6.8 mg, 5%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.79 (s, 1H), 7.54 (d, *J* = 3.2 Hz, 1H), 7.31 (s, 1H), 6.80 (s, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.52-4.48 (m, 1H), 4.44 (d, *J* = 15.6 Hz, 1H), 4.36 (d, *J* = 10.4 Hz, 1H), 4.13 (d, *J* = 5.6 Hz, 2H) 4.01 (s, 3H), 3.52-3.38 (m, 3H), 3.16-3.11 (m, 1H), 2.97 (d, *J* = 5.2 Hz, 1H), 2.92 (s, 3H), 2.87 (s, 3H), 2.80-2.75 (m, 1H), 2.60-2.53 (m, 3H), 2.50 (s, 3H), 2.31-2.21 (m, 3H), 2.15-2.10 (m, 1H), 2.00-1.88 (m, 4H). ESI-MS *m/z* 517.4 $[M+H]^+$ calc. for $C_{31}H_{40}N_4O_3$.

N-(7-isopropyl-7-azaspiro[3.5]nonan-2-yl)-6-methoxy-7-[(2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy]-2-(5-methyl-2-furyl)quinolin-4-amine (49)

To a solution of compound **85** (250 mg, 0.471 mmol) in MeOH (15 mL) were added $NaBH(OAc)_3$ (300 mg, 1.41 mmol), HCOOH (22 mg, 0.471.08 mmol) and (HCHO)n (127 mg, 1.41 mmol) and the mixture was stirred at 60 °C for 16 hours under N_2. Then, the mixture was concentrated and the residue was purified by prep-HPLC (method 16 described in supporting information) to afford pure compound **49** (14.4 mg, 5%) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.79 (s, 1H), 7.54 (br s, 1H), 7.31 (s, 1H), 6.79 (s, 1H), 6.42 (br s, 1H), 4.52-4.43 (m, 2H), 4.36 (d, *J* = 10.6 Hz, 1H), 4.17-4.07 (m, 2H), 4.01 (s, 3H), 3.53-3.45 (m, 2H), 3.39 (d, *J* = 12.4 Hz, 1H), 3.15-3.05 (m, 2H), 2.97 (br s, 2H), 2.92 (s, 3H), 2.79 (br s, 1H), 2.61-2.48 (m, 6H), 2.32-2.23 (m, 2H), 2.14-2.09

(m, 1H), 2.07-1.86 (m, 4H), 1.38 (d, J = 6.6 Hz, 6H). ESI-MS *m/z* 545.4 $[M+H]^+$ calc. for $C_{33}H_{44}N_4O_3$.

6-methoxy-N-(3-methyl-3-azabicyclo[3.2.1]octan-8-yl)-7-[(2-methyl-2-azaspiro[3.3]heptan-6-yl)oxy]-2-(5-methyl-2-furyl)quinolin-4-amine (50)

To a solution of compound **80d** (150 mg, 0.254 mmol) in MeOH (10 mL) were added $NaBH_3CN$ (48 mg, 0.764 mmol), HCOOH (12 mg, 0.254 mmol) and $(HCHO)_n$ (69 mg, 0.764 mmol) and the mixture was stirred at 60 °C for 16 hours. Then, the mixture was concentrated and the residue was purified by prep-HPLC (method 17 described in supporting information) to afford pure compound **50** (10 mg, 7%) as yellow oil. ^1H NMR (CD_3OD, 400 MHz): δ 7.81 (s, 1H), 7.51 (d, J = 3.53 Hz, 1H), 7.29 (s, 1H), 6.89 (s, 1H), 6.37-6.31 (m, 1H), 4.36 (d, J = 10.58 Hz, 1H), 4.27 (d, J = 10.14 Hz, 1H), 4.08-4.01 (m, 2H), 3.98 (s, 3H), 3.93 (t, J = 4.19 Hz, 1H), 3.43-3.38 (m, 2H), 3.31-3.26 (m, 2H), 2.96 (dd, J = 11.03, 4.85 Hz, 1H), 2.93-2.84 (m, 2H), 2.83 (s, 3H), 2.82-2.77 (m, 5H), 2.52-2.45 (m, 2H), 2.41 (s, 3H), 2.22-2.15 (m, 2H), 1.93-1.86 (m, 2H). ESI-MS *m/z* 503.4 $[M+H]^+$ calc. for $C_{30}H_{38}N_4O_3$.

1-[3-(2-methoxy-5-nitro-phenoxy)propyl]pyrrolidine (52)

To a solution of commercially available 2-methoxy-5-nitro-phenol (**51**) (39.2 g, 0.24 mol) in THF (1.0 L), PPh_3 (121 g, 0.46 mol), 3-pyrrolidin-1-yl-propan-1-ol (41.08 g, 0.32 mol) and DEAD (79.12 g. 0.46 mmol) were added at 0 ºC and the reaction mixture was stirred at room temperature for 5 hours. Then, the reaction mixture was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by silica gel column chromatography to obtain pure compound **52**

(40 g, 60%) as yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, *J* = 2.4 Hz, 1H), 7.89 (s, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 4.23-4.14 (m, 2H), 3.97 (s, 3H), 2.70-2.60 (m, 2H), 2.58-2.50 (m, 4H), 2.15-2.05 (m, 2H), 1.85-1.75 (m, 4H). ESI-MS *m/z* 281.2 $[M+H]^+$ calc. for $C_{14}H_{20}N_2O_4$.

4-methoxy-3-(3-pyrrolidin-1-ylpropoxy)aniline (53)

To a solution of compound **52** (28 g, 0.1 mol) in MeOH (500 mL) was added Pd/C (5 g) and the solution was stirred at room temperature for 3 hours under H_2 atmosphere (1 atm). Then, the solution was filtered and the filtrate was concentrated to give compound **53** (21 g, 84%) as yellow oil which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.70 (d, *J* = 8.4 Hz, 1H), 6.34 (s, 1H), 6.22 (d, *J* = 8.4 Hz, 1H), 4.08-4.00 (m, 2H), 3.79 (s, 3H), 2.70-2.60 (m, 2H), 2.59-2.52 (m, 4H), 2.10-2.02 (m, 2H), 1.90-1.70 (m, 4H). ESI-MS *m/z* 251.2 $[M+H]^+$ calc. for $C_{14}H_{22}N_2O_2$.

2,4-dichloro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinoline (54)

To a solution of compound **53** (20 g, 0.08 mol) in $POCl_3$ (130 mL) was added malonic acid (10.3 g, 0.098 mol) at room temperature and the mixture was stirred for 4 hours. Then, the solution was heated to 90 ºC and stirred for overnight. $POCl_3$ was removed by distillation under vacuum and the residue was poured into ice-water. The resulting 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 compound **54** (7 g, 24%) as pale yellow solid which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.28 (m, 2H), 7.19 (s, 1H), 4.20-4.10

(m, 2H), 3.96 (s, 3H), 2.80-2.60 (m, 6H), 2.20-2.10 (m, 2H), 1.95-1.75 (m, 4H). ESI-MS *m/z* 355.3 $[M+H]^+$ calc. for $C_{17}H_{20}Cl_2N_2O_2$.

4-chloro-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinoline (55a)

To a solution of compound **54** (600 mg, 1.7 mmol) in 1,4-dioxane/H_2O (15:1, 16 mL) were added Na_2CO_3 (0.54 g, 5.1 mmol), $Pd(PPh_3)_4$ (0.22 g, 0.17 mmol) and 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (0.39 g, 1.87 mmol) and the mixture was stirred at 110 ºC for 4 hours under Microwave. Then, the mixture was quenched with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to obtain compound **55a** (400 mg, 59%) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.83 (s, 1H), 7.47 (s, 1H), 7.36 (s, 1H), 7.19 (d, *J* = 3.2 Hz, 1H), 6.31 (d, *J* = 3.2 Hz, 1H), 4.30-4.22 (m, 2H), 3.96 (s, 3H), 3.65-3.55 (m, 2H), 3.35-3.26 (m, 2H), 3.08-2.98 (m, 2H), 2.39 (s, 3H), 2.23-2.16 (m, 2H), 2.05-1.95 (m, 2H), 1.91-1.82 (m, 2H). ESI-MS *m/z* 401.2 $[M+H]^+$ calc. for $C_{22}H_{25}ClN_2O_3$.

4-chloro-2-(5-ethyl-2-furyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinoline (55b)

To a solution of compound **54** (354 mg, 1 mmol) and 2-(5-ethyl-2-furyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (222 mg, 1 mmol) in 1,4-dioxane (15 mL) was added K_2CO_3 (280 mg, 2 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.030 mmol) and the solution was heated to 110 ºC for 12 hours. Then, the mixture was concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting

information) to afford pure compound **55b** (150 mg, 36%) as a yellow solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 8.02 (s, 1H), 7.59-7.52 (m, 2H), 7.38 (s, 1H), 6.35-6.40 (m, 1H), 4.40-4.30 (m, 2H), 4.07 (s, 3H), 3.85-3.75 (m, 2H), 3.51-3.45 (m, 2H), 3.18-3.10 (m, 2H), 2.85-2.75 (m, 2H), 2.41-2.32 (m, 2H), 2.25-2.15 (m, 2H), 2.10-2.00 (m, 2H), 1.37-1.31 (m, 3H). ESI-MS *m/z* 415.2 $[M+H]^+$ calc. for $C_{23}H_{27}ClN_2O_3$.

Tert-butyl 4-[[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]piperidine-1-carboxylate (56a)

To a solution of compound **55a** (120 mg, 0.3 mmol) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (160 mg, 0.75 mmol) in 1,4-dioxane (15 mL) were successively added $Pd_2(dba)_3$ (55 mg, 0.06 mmol), Cs_2CO_3 (243 mg, 0.75 mmol) and BINAP (75 mg, 0.12 mmol) and the mixture was stirred at 115 °C for 18 hours under N_2 and at 125 °C for 10 hours. Then, the solution was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, filtered and concentrated to give crude product which was purified by prep-TLC (CH_2Cl_2:MeOH = 5:1) to obtain pure compound **56a** (125.0 mg, 72%) as a yellow solid. ESI-MS *m/z* 579.3 $[M+H]^+$ calc. for $C_{33}H_{46}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 4-[1-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-1-methyl-ethyl]piperidine-1-carboxylate (56b)

A mixture of **55a** (50 mg, 0.125 mmol), tert-butyl 4-(1-amino-1-methyl-ethyl)piperidine-1-carboxylate (36 mg, 0.149 mmol), Cs_2CO_3 (81 mg, 0.25 mmol), BINAP (16 mg, 0.024 mmol) and $Pd_2(dba)_3$ (11 mg, 0.012 mmol) in 1,4-dioxane (3.00 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at

120 °C for 24 hours under N_2 atmosphere. Then, the reaction mixture was filtrated and the filtrate was concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (method 18 described in supporting information) to afford compound **56b** (5.0 mg, 7%) as a yellow solid. ESI-MS *m/z* 607.4 $[M+H]^+$ calc. for $C_{35}H_{50}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 2-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (56c)

To a solution of compound **55a** (400 mg, 1 mmol) in 1,4-dioxane (10 mL) was added Cs_2CO_3 (650 mg, 2 mmol), BINAP (70 mg, 0.11 mmol), $Pd_2(dba)_3$ (100 mg, 0.11 mmol) and tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate (240 mg, 1 mmol) and the solution was heated to 130 ºC for 5 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford compound **56c** (200 mg, 33%) as yellow solid. ESI-MS *m/z* 605.3 $[M+H]^+$ calc. for $C_{35}H_{48}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 2-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-6-azaspiro[3.4]octane-6-carboxylate (56d)

To a solution of compound **55a** (400 mg, 1 mmol) in 1,4-dioxane (10 mL) was added Cs_2CO_3 (650 mg, 2 mmol), BINAP (70 mg, 0.11 mmol), $Pd_2(dba)_3$ (100 mg, 0.11 mmol) and tert-butyl 2-amino-6-azaspiro[3.4]octane-6-carboxylate (226 mg, 1 mmol) and the solution was heated to 130 ºC for 5 hours under Microwave. Then, the solution

was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford pure compound **56d** (100 mg, 17%) as yellow solid. ESI-MS *m/z* 591.3 $[M+H]^+$ calc. for $C_{34}H_{46}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 3-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (56e)

To a solution of compound **55a** (400 mg, 1 mmol) in 1,4-dioxane (10 mL) was added Cs_2CO_3 (650 mg, 2 mmol), BINAP (70 mg, 0.11 mmol), $Pd_2(dba)_3$ (100 mg, 0.11 mmol) and tert-butyl 3-amino-7-azaspiro[3.5]nonane-7-carboxylate (224 mg, 1 mmol) and the solution was heated to 130 ºC for 5 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford compound **56e** (200 mg, 33%) as yellow solid. ESI-MS *m/z* 605.3 $[M+H]^+$ calc. for $C_{35}H_{48}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 3-[[2-(5-ethyl-2-furyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (56f)

A mixture of **55b** (550 mg, 1.33 mmol), tert-butyl 3-amino-7-azaspiro[3.5]nonane-7-carboxylate (637 mg, 2.65 mmol), Cs_2CO_3 (863 mg, 2.65 mmol), $Pd_2(dba)_3$ (121 mg, 0.133 mmol) and BINAP (83 mg, 0.133 mmol) in 1,4-dioxane (50 mL) was degassed

and purged with N_2 for 3 times and then the mixture was stirred at 120 °C for 16 hours. Then, the mixture was concentrated and purified by silica gel column chromatography (CH_2Cl_2:MeOH = 200:1 - 1:1) to afford pure compound **56f** (200 mg, 24%) as a white solid. ESI-MS *m/z* 619.4 $[M+H]^+$ calc. for $C_{36}H_{50}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 3-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-6-azaspiro[3.4]octane-6-carboxylate (56g)

To a solution of compound **55a** (400 mg, 1 mmol) in 1,4-dioxane (10 mL) was added Cs_2CO_3 (650 mg, 2 mmol), BINAP (70 mg, 0.11 mmol), $Pd_2(dba)_3$ (100 mg, 0.11 mmol) and tert-butyl 1-amino-6-azaspiro[3.4]octane-6-carboxylate (226 mg, 1 mmol) and the solution was heated to 130 ºC for 5 hours under Microwave. Then, the solution was concentrated and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 1 described in supporting information) to afford pure compound **56g** (150 mg, 25%) as yellow solid. ESI-MS *m/z* 591.3 $[M+H]^+$ calc. for $C_{34}H_{46}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 8-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-3-azabicyclo[3.2.1]octane-3-carboxylate (56h)

A mixture of **55a** (200 mg, 0.5 mmol), tert-butyl 8-amino-3-azabicyclo[3.2.1]octane-3-carboxylate (226 mg, 1.0 mmol), Cs_2CO_3 (325 mg, 1.0 mmol), $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and BINAP (31 mg, 0.05 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 120 °C for 16 hours.

Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 5:1) to obtain pure compound **56h** (200 mg, 67%) as a yellow solid. ESI-MS *m/z* 591.4 $[M+H]^+$ calc. for $C_{34}H_{46}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 8-[[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-3-azabicyclo[3.2.1]octane-3-carboxylate (56i)

A mixture of **55a** (300 mg, 0.75 mmol), tert-butyl 8-(aminomethyl)-3-azabicyclo[3.2.1]octane-3-carboxylate (359 mg, 1.50 mmol), Cs_2CO_3 (487 mg, 1.5 mmol), $Pd_2(dba)_3$ (137 mg, 0.15 mmol) and BINAP (186 mg, 0.3 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 120 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-TLC (CH_2Cl_2:MeOH = 5:1) to afford compound **56i** (300 mg, 66%) as a yellow solid. ESI-MS *m/z* 605.4 $[M+H]^+$ calc. for $C_{35}H_{48}N_4O_5$.

Tert-butyl 8-[[[2-(5-ethyl-2-furyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]methyl]-3-azabicyclo[3.2.1]octane-3-carboxylate (56j)

A mixture of **55b** (300 mg, 0.72 mmol), tert-butyl 8-(aminomethyl)-3-azabicyclo[3.2.1]octane-3-carboxylate (347 mg, 1.45 mmol), Cs_2CO_3 (471 mg, 1.45 mmol), $Pd_2(dba)_3$ (132 mg, 0.144 mmol) and BINAP (180 mg, 0.289 mmol) in 1,4-dioxane (10 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 120 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was purified by TLC (CH_2Cl_2:MeOH = 5:1) to afford

pure compound **56j** (360 mg, 80%) as a yellow solid. ESI-MS *m/z* 619.4 $[M+H]^+$ calc. for $C_{36}H_{50}N_4O_5$.

Tert-butyl 3-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (56k)

To a solution of compound **55a** (200 mg, 0.5 mmol) in 1,4-dioxane (10 mL) were added $Pd_2(dba)_3$ (46 mg, 0.05 mmol), Cs_2CO_3 (325 mg, 1.0 mmol), tert-butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (226 mg, 1.0 mmol) and BINAP (31 mg, 0.05 mmol) and the mixture was stirred at 120 ºC for 16 hours under N_2. Then, the mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (CH_2Cl_2: MeOH = 10:1) to afford pure compound **56k** (200 mg, 67%) as a yellow solid. ESI-MS *m/z* 591.5 $[M+H]^+$ calc. for $C_{36}H_{46}N_4O_5$. This compound was used in the next step without further characterization.

Tert-butyl 4-[[6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]-methyl-amino]piperidine-1-carboxylate (56l)

A mixture of compound **55a** (300 mg, 0.75 mmol), tert-butyl 4-(methylamino)piperidine-1-carboxylate (192 mg, 0.897 mmol) and PTSA (155 mg, 0.9 mmol) in *t*-BuOH (7.5 mL) was degassed and purged with N_2 for 3 times and then the mixture was stirred at 120 ℃ for 48 hours. Then, the reaction mixture was concentrated in vacuum to give crude product which was purified by prep-HPLC (method 10 described in supporting information) to afford pure compound **56l** (40 mg 9%) as a yellow solid. ESI-MS *m/z* 579.5 $[M+H]^+$ calc. for $C_{33}H_{46}N_4O_5$.

6-methoxy-2-(5-methyl-2-furyl)-N-(4-piperidylmethyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57a)

A solution of compound **56a** (125.0 mg, 0.21 mmol) in HCl/EtOAc (2.0 M, 30 mL) was stirred at 16 °C for 8 hours. Then, the solution was concentrated to give compound **57a** (125.0 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 479.3 $[M+H]^+$ calc. for $C_{28}H_{38}N_4O_3$.

6-methoxy-2-(5-methyl-2-furyl)-N-[1-methyl-1-(4-piperidyl)ethyl]-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57b)

A solution of **56b** (15.00 mg, 0.024 mmol) in HCl/MeOH (2.0 M, 5.00 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 25 °C for 12 hours. Then, the solution was concentrated under vacuum to give compound **57b** (10.0 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 507.4 $[M+H]^+$ calc. for $C_{30}H_{42}N_4O_3$.

N-(7-azaspiro[3.5]nonan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57c)

To a solution of compound **56c** (60.4 mg, 0.1 mmol) in MeOH (10 mL) was added HCl/MeOH (5 mL, 4.0 M) and the solution was stirred at room temperature for 5 hours. Then, the mixture was concentrated to give compound **57c** (49 mg, crude) as yellow solid which was used in the next step without further purification. ESI-MS *m/z* 505.3 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

N-(6-azaspiro[3.4]octan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57d)

To a solution of compound **56d** (100 mg, 0.17 mmol) in MeOH (5 mL) was added HCl/MeOH (5 mL, 4.0 M) and the solution was stirred at room temperature for 5 hours. Then, the solution was concentrated to give compound **57d** (90 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 491.3 $[M+H]^+$ calc. for $C_{29}H_{38}N_4O_3$.

N-(7-azaspiro[3.5]nonan-3-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57e)

To a solution of compound **56e** (60.4 mg, 0.1 mmol) in MeOH (10 mL) was added HCl/MeOH (5 mL, 4.0 M) and the solution was stirred at room temperature for 5 hours. Then, the solution was concentrated to give compound **57e** (49 mg, crude) as yellow solid which was used in the next step without further purification. ESI-MS *m/z* 505.3 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

N-(7-azaspiro[3.5]nonan-3-yl)-2-(5-ethyl-2-furyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57f)

A solution of **56f** (80 mg, 0.129 mmol) in HCl/EtOAc (5.00 mL, 1.0 M) was stirred at 20 ºC for 16 hours. Then, the reaction mixture was concentrated to dryness under vacuum to obtain compound **57f** (60 mg, crude) as a yellow solid which was used in next step without further purification. ESI-MS *m/z* 519.4 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

N-(6-azaspiro[3.4]octan-3-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57g)

To a solution of compound **56g** (150 mg, 0.25 mmol) in MeOH (10 mL) was added HCl/MeOH (5 mL, 4.0 M) and the solution was stirred at room temperature for 5 hours. Then, the solution was concentrated to give compound **57g** (110 mg, crude) as yellow solid which was used in the next step without further purification. ESI-MS *m/z* 491.3 $[M+H]^+$ calc. for $C_{29}H_{38}N_4O_3$.

N-(3-azabicyclo[3.2.1]octan-8-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57h)

A solution of **56h** (200 mg, 0.338 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 15 °C for 2 hours. Then, the reaction mixture was concentrated in vacuum to give compound **57h** (150 mg, crude) which was used in the next step without further purification. ESI-MS *m/z* 491.4 $[M+H]^+$ calc. for $C_{29}H_{38}N_4O_3$.

N-(3-azabicyclo[3.2.1]octan-8-ylmethyl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57i)

A solution of **56i** (300 mg, 0.496 mmol) in HCl/EtOAc (5.00 mL, 2.0 M) was stirred at 18 °C for 2 hours. Then, the reaction mixture was concentrated in vacuum to give compound **57i** (300 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 505.4 $[M+H]^+$ calc. for $C_{30}H_{40}N_4O_3$.

N-(3-azabicyclo[3.2.1]octan-8-ylmethyl)-2-(5-ethyl-2-furyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57j)

A solution of **56j** (360 mg, 0.581 mmol) in HCl/EtOAc (5 mL, 2.0 M) was stirred at 18 °C for 2 hours. Then, the reaction mixture was concentrated in vacuum to give

compound **57j** (360 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 519.4 $[M+H]^+$ calc. for $C_{31}H_{42}N_4O_3$.

N-(8-azabicyclo[3.2.1]octan-3-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57k)

A solution of compound **56k** (200 mg, 0.338 mmol) in HCl/EtOAc (10 mL, 2.0 M) was stirred at 20 °C for 2 hours. Then, the mixture was concentrated under vacuum to give compound **57k** (200 mg, crude) as a yellow solid which was used in next step without further purification. ESI-MS *m/z* 491.4 $[M+H]^+$ calc. for $C_{29}H_{38}N_4O_3$.

6-methoxy-N-methyl-2-(5-methyl-2-furyl)-N-(4-piperidyl)-7-(3-pyrrolidin-1-ylpropoxy)quinolin-4-amine (57l)

A solution of compound **56l** (40 mg, 0.0692 mmol) in HCl/EtOAc (4 mL, 2.0 M) was stirred at 20 °C for 1 hour. Then, the mixture was concentrated under vacuum to give compound **57l** (40 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 479.4 $[M+H]^+$ calc. for $C_{28}H_{38}N_4O_3$.

4,4,5,5-tetramethyl-2-[5-nitro-2-(trifluoromethoxy)phenyl]-1,3,2-dioxaborolane (59)

A mixture of commercially available 2-bromo-4-nitro-1-(trifluoromethoxy)benzene (**58**) (12.20 g, 42.66 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (13.00 g, 51.19 mmol), KOAc (9.21 g, 93.85 mmol) and $Pd(dppf)Cl_2$ (3.12 g, 4.27 mmol) in 1,4-dioxane (200 mL) was de-gassed and heated to 90 °C for 10 hours under N_2. Then, the reaction was quenched with water and extracted with EtOAc. The organic phase was washed with saturated brine, dried over anhydrous

Na_2SO_4, filtered and concentrated in vacuum to give a residue, which was purified by silica gel column chromatography (PE:EtOAc = 100:1 - 20:1) to afford the compound **59** (13.00 g, 91%) as a yellow solid. ESI-MS *m/z* 334.1 $[M+H]^+$ calc. for $C_{13}H_{15}BF_3NO_5$. This compound was used in the next step without further characterization.

5-nitro-2-(trifluoromethoxy)phenol (60c)

A schenk flask was charged with compound **59** (17.10 g, 52.2 mmol) and NaOH (12.53 g, 313.2 mmol) and the mixture was dissolved in THF (200 mL). Then, an aqueous solution of H_2O_2 (33%, 35.51 g, 313.2 mmol) was added dropwise under N_2 and the reaction mixture was stirred for 30 minutes at 22 °C. Then, the mixture was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and filtered. The solvents were removed under reduced pressure and the crude product was purified by silica gel column chromatography (PE:EtOAc = 9:1 - 3:1) to afford compound **60c** (10.40 g, 89%) as a yellow solid. ESI-MS *m/z* 224.1 $[M+H]^+$ calc. for $C_7H_4F_3NO_4$. This compound was used in the next step without further characterization.

1-[3-(3-nitrophenoxy)propyl]pyrrolidine (61a)

To a solution of commercially available 3-nitrophenol (**60a**) (4.9 g, 0.035 mol) in THF (500 mL) was added PPh_3 (11.1 g, 0.042 mol), 3-pyrrolidin-1-ylpropan-1-ol (5 g, 0.038 mol) and DEAD (7.3 g. 0.042 mol) at 0 ºC and the solution was stirred at room temperature for 10 hours. Then, the reaction mixture was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was

purified by silica gel column chromatography to afford compound **61a** (3.3 g, 37%) as yellow solid. ESI-MS *m/z* 251 $[M+H]^+$ calc. for $C_{13}H_{18}N_2O_3$. This compound was used in the next step without further characterization.

1-[3-(2-chloro-5-nitro-phenoxy)propyl]pyrrolidine (61b)

To a solution of commercially available 2-chloro-5-nitro-phenol (**60b**) (20 g, 0.12 mol) in THF (1000 mL) was added PPh_3 (60.45 g, 0.23 mol), 3-pyrrolidin-1-ylpropan-1-ol (22.33 g, 0.17 mol) and DEAD (40.14 g. 0.23 mmol) at 0 ºC and the solution was stirred at room temperature for 5 hours. Then, the reaction mixture was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by silica gel column chromatography to afford pure compound **61b** (20 g, 58%) as yellow solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.90 (d, *J* = 2.4Hz, 1H), 7.85 (s, 1H), 7.68 (d, *J* = 2.4Hz, 1H), 4.28-4.20 (m, 2H), 2.76-2.70 (m, 2H), 2.61-2.45 (m, 4H), 2.13-2.06 (m, 2H), 1.85-1.75 (m, 4H). ESI-MS *m/z* 285 $[M+H]^+$ calc. for $C_{13}H_{17}ClN_2O_3$.

1-[3-[5-nitro-2-(trifluoromethoxy)phenoxy]propyl]pyrrolidine (61c)

To a mixture of compound **60c** (9.20 g, 41.24 mmol), 3-pyrrolidin-1-ylpropan-1-ol (6.39 g, 49.48 mmol) and PPh_3 (21.63 g, 82.47 mmol) in THF (350 mL), was added DIAD (16.68 g, 82.47 mmol) in one portion at 0 °C under N_2 and the mixture was stirred at 0 °C for 8 hours. Then, the mixture was quenched with water and extracted with EtOAc. The combined organic phase was washed with saturated brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE:EtOAc = 1:3) to afford pure compound **61c** (8.60 g,

62%) as a yellow liquid. ESI-MS *m/z* 335.1 $[M+H]^+$ calc. for $C_{14}H_{17}F_3N_2O_4$. This compound was used in the next step without further characterization.

3-(3-pyrrolidin-1-ylpropoxy)aniline (62a)

To a solution of compound **61a** (3.3 g, 0.013 mol) in MeOH (20 mL) was added Pd/C (1.5 g) and the solution was stirred at room temperature for 2 hours under H_2 atmosphere (40 Psi). Then, the solution was filtered and the filtrate was concentrated to give compound **62a** (3 g, 96%) as yellow oil. ESI-MS *m/z* 221 $[M+H]^+$ calc. for $C_{13}H_{20}N_2O$. This compound was used in the next step without further characterization.

4-chloro-3-(3-pyrrolidin-1-ylpropoxy)aniline (62b)

To a solution of compound **61b** (5 g, 17.56 mmol) in EtOH/H_2O (4:1, 250 mL) was added Fe (2.94 g, 56.28 mmol) and NH_4Cl (2.82 g, 56.28 mmol) slowly and the mixture was stirred at room temperature for 3 hours under N_2 atmosphere. Then, the solution was filtered and the filtrate was concentrated to give compound **62b** (2 g, 44%) as yellow solid. ^1H NMR (CD_3OD, 400 MHz): δ 7.36 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 6.76-6.73 (m, 1H), 4.22-4.18 (m, 2H), 3.81-3.72 (m, 2H), 3.48-3.42 (m, 2H), 3.19-3.08 (m, 2H), 2.34-2.26 (m, 2H), 2.24-2.13 (m, 2H), 2.14-1.98 (m, 2H). ESI-MS *m/z* 255 $[M+H]^+$ calc. for $C_{13}H_{19}ClN_2O$.

3-(3-pyrrolidin-1-ylpropoxy)-4-(trifluoromethoxy)aniline (62c)

To a solution of compound **61c** (8.60 g, 25.73 mmol) in MeOH (100 mL) was added Pd/C (1.50 g) and the mixture was stirred at room temperature for 15 hours under H_2 atmosphere (40 Psi). Then, the mixture was filtered and the filtrate was concentrated to

give compound **62c** (7.80 g, 99%) as a gray liquid which was used for the next step without further purification. ESI-MS *m/z* 305.0 $[M+H]^+$ calc. for $C_{14}H_{19}F_3N_2O_2$.

2,4-dichloro-7-(3-pyrrolidin-1-ylpropoxy)quinoline (63a)

To a solution of compound **62a** (3 g, 0.013 mol) in $POCl_3$ (40 mL) was added malonic acid (2.1 g, 0.020 mol) and the mixture was stirred at room temperature for 4 hours and then at 90 ºC overnight. Then, the solution was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give compound **63a** (1.5 g, 34%) as pale yellow solid. ^1H NMR (DMSO-d_6, 400 MHz): δ 8.09 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.44-7.40 (m, 2H) 4.29-4.26 (m, 2H), 3.55-3.49 (m, 2H), 3.34-3.25 (m, 2H), 3.10-2.91 (m, 2H), 2.26-2.22 (m, 2H), 2.00-1.89 (m, 4H). ESI-MS *m/z* 325 $[M+H]^+$ calc. for $C_{16}H_{18}Cl_2N_2O$.

2,4,6-trichloro-7-(3-pyrrolidin-1-ylpropoxy)quinoline (63b)

To a solution of compound **62b** (3 g, 11.78 mmol) in $POCl_3$ (30mL) was added malonic acid (1.84 g, 17.86 mmol) and the mixture was stirred at room temperature for 4 hours and at 90 ºC overnight. Then, the solution was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give compound **63b** (1 g, 24%) as pale yellow solid. ^1H NMR (CD_3OD, 400 MHz): δ 8.29 (s, 1H), 7.66 (s, 1H), 7.52 (s, 1H), 4.48-4.37 (m, 2H), 3.85-3.74 (m, 2H), 3.56-3.45 (m, 2H), 3.26-3.13 (m, 2H), 2.48-2.37 (m, 2H), 2.27-2.17 (m, 2H), 2.16-2.02 (m, 2H). ESI-MS *m/z* 359 $[M+H]^+$ calc. for $C_{16}H_{17}Cl_3N_2O$.

2,4-dichloro-7-(3-pyrrolidin-1-ylpropoxy)-6-(trifluoromethoxy)quinoline (63c)

DMAP (129 mg, 1.06 mmol) and pyridine (5.86 g, 74.07 mmol) were added to a stirred suspension of compound **62c** (9.20 g, 30.16 mmol) in CH_2Cl_2 (60 mL) at -70 °C over a period of 10 minutes under nitrogen. The resulting solution was stirred at -70 °C for 1 hour, and then ethyl 3-chloro-3-oxo-propanoate (3.35 g, 22.22 mmol) was added over a period of 10 minutes under nitrogen. The resulting solution was stirred at 20 °C for 15 hours. Then, the reaction was quenched with water then extracted with CH_2Cl_2. The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to afford pure intermediate ethyl 3-oxo-3-[3-(3-pyrrolidin-1-ylpropoxy)-4-(trifluoromethoxy)anilino]propanoate (5.40 g, 42%) as a yellow solid. ESI-MS *m/z* 419.0 $[M+H]^+$ calc. for $C_{19}H_{25}F_3N_2O_5$. To a solution of this intermediate (5.40 g, 12.91 mmol) in THF/MeOH/H_2O (4:2:3, 45 mL) was added $LiOH \cdot H_2O$ (1.63 g, 38.73 mmol) and the resulting mixture was stirred at 20 °C for 15 hours. Then, the mixture was diluted with water and adjusted pH to 4~5 with 1.0 N HCl. The solution was extracted with EtOAc and the combined organic layer was washed with brine and concentrated to afford the desired intermediate 3-oxo-3-[3-(3-pyrrolidin-1-ylpropoxy)-4-(trifluoromethoxy)anilino]propanoic acid (4.89 g, 97%) as a yellow solid. ESI-MS *m/z* 391.1 $[M+H]^+$ calc. for $C_{17}H_{21}F_3N_2O_5$. A solution of this intermediate (4.80 g, 12.30 mmol) in $POCl_3$ (60 mL) was then stirred at 100 ºC for 3 hours. Then, the solution was concentrated to give the crude compound which was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to afford pure compound **63c** (2.10 g, 41%) as a yellow solid. ESI-MS *m/z* 409.1 $[M+H]^+$ calc. for $C_{17}H_{17}Cl_2F_3N_2O_2$. This compound was used in the next step without further characterization.

4-chloro-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinoline (64a)

To a solution of compound **63a** (400 mg, 1.23 mmol) in 1,4-dioxane/H_2O (5:1, 18 mL) was added Na_2CO_3 (196 mg, 1.8 mmol), $Pd(PPh_3)_4$ (138 mg, 0.12 mmol) and 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (288 mg, 1.36 mmol) and the solution was heated at 110 ºC for 2 hours under Microwave. Then, the mixture was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-TLC to afford compound **64a** (0.4 g, 88%) as pale yellow solid. ESI-MS *m/z* 371 $[M+H]^+$ calc. for $C_{21}H_{23}ClN_2O_2$. This compound was used in the next step without further characterization.

4,6-dichloro-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)quinoline (64b)

To a solution of compound **63b** (180 mg, 0.5 mmol) in 1,4-dioxane/H_2O (15:1, 16 mL) was added K_2CO_3 (0.138 g, 1 mmol), $Pd(PPh_3)_4$ (100.1 mg, 0.1 mmol) and 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (104 mg, 1 mmol) under N_2 and the mixture was stirred at 110 ºC for 12 hours. The mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by prep-HPLC (method 2 described in supporting information) to afford compound **64b** (100 mg, 49%) as a yellow solid. ^1H NMR (CD_3OD, 400 MHz): δ 8.23 (s, 1H), 7.92 (s, 1H), 7.58 (s, 1H), 7.27-7.25 (m, 1H), 6.31-6.29 (m, 1H), 4.43-4.37 (m, 2H), 3.80-3.74 (m, 2H), 3.55-3.49 (m, 2H), 3.23-3.09 (m, 2H), 2.46-2.33 (m, 5H), 2.25-2.16 (m, 2H), 2.13-2.02 (m, 2H). ESI-MS *m/z* 405 $[M+H]^+$ calc. for $C_{21}H_{22}Cl_2N_2O_2$.

4-chloro-2-(5-methyl-2-furyl)-7-(3-pyrrolidin-1-ylpropoxy)-6-(trifluoromethoxy)quinoline (64c)

To a solution of compound **63c** (1.50 g, 3.67 mmol) in 1,4-dioxane/H_2O (10:1, 55 mL) were successively added 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (800 mg, 3.85 mmol), $Pd(PPh_3)_4$ (423 mg, 0.366 mmol) and K_2CO_3 (1.27 g, 9.16 mmol) and the resulting mixture was stirred at 80 °C for 15 hours under N_2. Then, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to obtain the crude product which was purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to afford pure compound **64c** (1.36 g, 81%) as a yellow solid. ESI-MS *m/z* 455.2 $[M+H]^+$ calc. for $C_{22}H_{22}ClF_3N_2O_3$. This compound was used in the next step without further characterization.

[2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]-7-(3-pyrrolidin-1-ylpropoxy)-6-quinolyl] trifluoromethanesulfonate (65)

To a solution of compound **30** (232 mg, 0.5 mmol) in DMF (5 mL) was added DIEA (202 mg, 1.56 mmol) and $PhN(OTf)_2$ (270 mg, 0.75 mmol) at 0 ºC and the solution was stirred at 0 ºC for 2 hours and at 25 ºC for 12 hours. Then, the solution was concentrated to give the crude product which was purified by prep-HPLC (method 3 described in supporting information) to afford pure compound **65** (180 mg, 60%) as a yellow solid. ESI-MS *m/z* 597.3 $[M+H]^+$ calc. for $C_{28}H_{35}F_3N_4O_5S$. This compound was used in the next step without further characterization.

2,4-dichloro-6-methoxy-quinolin-7-ol (67)

To a mixture of commercially available 5-amino-2-methoxy-phenol (**66**) (4.91 g, 35.29 mmol) and malonic acid (7.34 g, 70.57 mmol) was added $POCl_3$ (70 mL) and the mixture was stirred at 95 ºC for 12 hours under N_2. Then, the mixture was concentrated in reduced pressure to remove $POCl_3$. The residue was poured into water and stirred for 20 minutes. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with saturated brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 2/1) to afford compound **67** (2.10 g, 247%). ESI-MS *m/z* 244.0 $[M+H]^+$ calc. for $C_{23}H_{27}ClN_2O_3$. This compound was used in the next step without further characterization.

3-[(2,4-dichloro-6-methoxy-7-quinolyl)oxy]-N,N-dimethyl-propan-1-amine (68a)

To a solution of **67** (3 g, 12.29 mmol) and 1,3-dibromopropane (2.98 g, 14.75 mmol) in CH_3CN (60 mL) was added K_2CO_3 (4.25 g, 30.73 mmol) and the mixture was stirred at 60 °C for 88 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was diluted with water and filtered. The filter cake was dried in vacuum and further purified by silica gel column chromatography (from PE:EtOAc (30:1) to pure MeOH) to afford intermediate 7-(3-bromopropoxy)-2,4-dichloro-6-methoxy-quinoline (1 g, 22%) as a white solid. ESI-MS *m/z* 364.1 $[M+H]^+$ calc. for $C_{13}H_{12}BrCl_2NO_2$. To a solution of this intermediate (200 mg, 0.550 mmol) and N-methylmethanamine hydrochloride (67 mg, 0.821 mmol) in CH_3CN (20 mL) was added K_2CO_3 (189 mg, 1.37 mmol) and the mixture was stirred at 60 °C for 16 hours. Then, mixture was concentrated in vacuum to give a residue. The residue was diluted with water and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give compound **68a** (150 mg, 83%) as a white

solid which was used in next step without further purification. ESI-MS *m/z* 329.2 $[M+H]^+$ calc. for $C_{15}H_{18}Cl_2N_2O_2$.

7-[3-(5-azaspiro[2.4]heptan-5-yl)propoxy]-2,4-dichloro-6-methoxy-quinoline (68b)

To a solution of 7-(3-bromopropoxy)-2,4-dichloro-6-methoxy-quinoline (intermediate described in the synthesis of **68a**, 598 mg, 1.64 mmol) and 5-azaspiro[2.4]heptane hydrochloride (328 mg, 2.46 mmol) in CH_3CN (20 mL) was added K_2CO_3 (680 mg, 4.92 mmol) and the mixture was stirred at 60 °C for 16 hours. Then, the mixture was concentrated in vacuum to give a residue. The residue was dissolved in CH_2Cl_2 and filtered through a Celite pad. The filtrate was concentrated in vacuum and the residue was purified by prep-HPLC (method 3 described in supporting information) to afford compound **68b** (150 mg, 24%) as a purple solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.56 (s, 1H), 7.46 (s, 1H), 7.33 (s, 1H), 4.35-4.32 (m, 2H), 4.04 (s, 3H), 3.97-3.95 (m, 1H), 3.54-3.51 (m, 3H), 3.43-3.40 (m, 1H), 3.30-3.29 (m, 1H), 2.40-2.35 (m, 2H), 2.22-2.20 (m, 1H), 2.05-2.02 (m, 1H), 0.86-0.76 (m, 4H). ESI-MS *m/z* 381.2 $[M+H]^+$ calc. for $C_{19}H_{22}Cl_2N_2O_2$.

2,4-dichloro-7-[3-(3-fluoropyrrolidin-1-yl)propoxy]-6-methoxy-quinoline (68c)

A mixture of **67** (829 mg, 3.40 mmol), 3-(3-fluoropyrrolidin-1-yl)propan-1-ol (500 mg, 3.40 mmol) and PPh_3 (1.16 g, 4.42 mmolq) in THF (30.0 mL) was degassed and purged with N_2 for 3 times. Then, DEAD (769 mg, 4.42 mmol) was added at 0 °C under N_2 and the mixture was stirred at 20 °C for 16 hours. Then, reaction was quenched with water and the mixture was concentrated to give a residue. The residue was extracted with EtOAc and the combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude product. The crude

product was purified by silica gel column chromatography (PE/EtOAc = 100:1 - 0:1, CH_2Cl_2/Methanol = 1/0 - 10:1) to afford pure compound **68c** (700 mg, 55%) as a yellow solid. ESI-MS *m/z* 373.1 $[M+H]^+$ calc. for $C_{17}H_{19}Cl_2FN_2O_2$. This compound was used in the next step without further characterization.

2-(3-bromopropoxy)-1-methoxy-4-nitro-benzene (69)

A mixture of commercially available 2-methoxy-5-nitro-phenol (**51**) (30.63 g, 181.10 mmol), 1,3-dibromopropane (47.53 g, 235.43 mmol) and Cs_2CO_3 (118.01 g, 362.20 mmol) in DMF (500 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 20 °C for 16 hours. Then, the mixture was poured into water and extracted with MTBE. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (PE:EtOAc = 40:1 - 5:1) to afford pure compound **69** (20 g, 38%) as a black solid. ESI-MS *m/z* 290.1 $[M+H]^+$ calc. for $C_{10}H_{12}BrNO_4$. This intermediate was used in the next step without further characterization.

4-methoxy-3-[3-(1-piperidyl)propoxy]aniline (70a)

To a solution of **69** (10 g, 34.47 mmol) and piperidine (4.4 g, 51.71 mmol) in CH_3CN (100 mL) was added Cs_2CO_3 (22.46 g, 68.94 mmol) and the mixture was stirred at 90 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (PE:EtOAc = 20:1 - pure EtOAc) to afford pure intermediate 1-[3-(2-methoxy-5-nitro-phenoxy)propyl]piperidine (6.3 g, 62%) as a white solid. ESI-MS *m/z* 295.3 $[M+H]^+$ calc. for $C_{15}H_{22}N_2O_4$. Then, to a solution of this intermediate (6.3 g,

21.40 mmol) in MeOH (150 mL) was added Pd/C (10%, 1.3 g) and the suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (30 Psi) at 15 °C for 2 hours. Then, the reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuum to give compound **70a** (4.8 g, 84%) as a brown solid which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.72-6.68 (m, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.22 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 4.03-4.00 (m, 2H), 3.78 (s, 3H), 3.40 (br s, 2H), 2.50-2.46 (m, 2H), 2.40 (br s, 4H), 2.03-2.00 (m, 2H), 1.62-1.56 (m, 4H), 1.45-1.42 (m, 2H). ESI-MS *m/z* 265.3 $[M+H]^+$ calc. for $C_{15}H_{24}N_2O_2$.

4-methoxy-3-(3-morpholinopropoxy)aniline (70b)

To a solution of **69** (10 g, 34.47 mmol) and morpholine (4.5 g, 51.71 mmol) in CH_3CN (100 mL) was added Cs_2CO_3 (22.46 g, 68.94 mmol) and the mixture was stirred at 90 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue which was purified by silica gel column chromatography (PE:EtOAc = 20:1 - pure EtOAc) to afford intermediate 4-[3-(2-methoxy-5-nitro-phenoxy)propyl]morpholine (5 g, 49%) as a white solid. ESI-MS *m/z* 297.3 $[M+H]^+$ calc. for $C_{14}H_{20}N_2O_5$. Then, to a solution of this intermediate (5.0 g, 16.87 mmol) in MeOH (150 mL) was added Pd/C (10%, 1g) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times and then the mixture was stirred under H_2 (30 psi) at 15 °C for 2 hours. Then, the reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuum to give compound **70b** (4.4 g, 98%) as a yellow solid which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.33 (d, *J* = 2.4

Hz, 1H), 6.23 (dd, *J* = 2.8 Hz, 8.4 Hz, 1H), 4.05-4.01 (m, 2H), 3.78 (s, 3H), 3.72-3.70 (m, 4H), 3.45 (br s, 2H), 2.54-2.50 (m, 2H), 2.46 (br s, 4H), 2.04-1.99 (m, 2H). ESI-MS *m/z* 267.3 $[M+H]^+$ calc. for $C_{14}H_{22}N_2O_3$.

2,4-dichloro-6-methoxy-7-[3-(1-piperidyl)propoxy]quinoline (71a)

To a solution of **70a** (4.6 g, 17.40 mmol) in CH_2Cl_2 (50 mL) were added pyridine (4.82 g, 60.90 mmol) and DMAP (212 mg, 1.74 mmol) at -78 °C. Then ethyl 3-chloro-3-oxo-propanoate (3.14 g, 20.88 mmol) was added drop wise into above solution and the mixture was stirred at 15 °C for 16 hours. Then, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give intermediate ethyl 3-[4-methoxy-3-[3-(1-piperidyl)propoxy]anilino]-3-oxo-propanoate (2.3 g, 34%) as a black solid. ESI-MS *m/z* 379.3 $[M+H]^+$ calc. for $C_{20}H_{30}N_2O_5$. To a solution of this intermediate (2.3 g, 6.08 mmol) in THF/MeOH/H_2O (20:20:13, 53 mL) was added $LiOH{\cdot}H_2O$ (510 mg, 12.16 mmol) and the mixture was stirred at 15 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give intermediate 3-[4-methoxy-3-[3-(1-piperidyl)propoxy]anilino]-3-oxo-propanoic acid (2 g, 93%) as a black solid. ESI-MS *m/z* 351.3 $[M+H]^+$ calc. for $C_{18}H_{26}N_2O_5$. Finally, a solution of this intermediate (2 g, 5.71 mmol) in $POCl_3$ (8.75 g, 57.08 mmol) was stirred at 100 °C for 2 hours. Then, the reaction mixture was concentrated in vacuum to give a residue. The residue was dissolved in EtOAc and poured slowly into water. The resulting mixture was adjust to pH = 8 with NaOH (2.0 M) and then extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and concentrated to give a residue which was purified by silica gel column chromatography (PE:EtOAc = 1:1 to CH_2Cl_2:MeOH = 10:1) to afford pure compound **71a** (1.2 g, 56%) as a brown solid. ^1H NMR (CD_3OD,

400 MHz): δ 7.57 (s, 1H), 7.48 (s, 1H), 7.35 (s, 1H), 4.34-4.32 (m, 2H), 4.03 (s, 3H), 3.70-3.67 (m, 2H), 3.41-3.37 (m, 2H), 3.04-2.98 (m, 2H), 2.40-2.35 (m, 2H), 2.03-1.99 (m, 2H), 2.87-2.78 (m, 3H), 1.59-1.55 (m, 1H). ESI-MS *m/z* 369.2 $[M+H]^+$ calc. for $C_{18}H_{22}Cl_2N_2O_2$.

4-[3-[(2,4-dichloro-6-methoxy-7-quinolyl)oxy]propyl]morpholine (71b)

To a solution of **70b** (4.3 g, 16.14 mmol) in CH_2Cl_2 (10.0 mL) were added pyridine (4.47 g, 56.51 mmol) and DMAP (197 mg, 1.61 mmol) at -78 °C and then ethyl 3-chloro-3-oxo-propanoate (2.92 g, 19.37 mmol) was added drop wise into above solution. The reaction mixture was stirred at 15 °C for 16 hours. Then, the mixture was poured into water and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give intermediate ethyl 3-[4-methoxy-3-(3-morpholinopropoxy)anilino]-3-oxo-propanoate (6 g, 98%) as a brown oil. ESI-MS *m/z* 381.3 $[M+H]^+$ calc. for $C_{19}H_{28}N_2O_6$. To a solution of this intermediate (6 g, 15.77 mmol) in THF/MeOH/H_2O (3:3:2, 80 mL) was added $LiOH{\cdot}H_2O$ (1.32 g, 31.54 mmol) and the mixture was stirred at 15 °C for 16 hours. Then, the reaction mixture was concentrated in vacuum to give intermediate 3-[4-methoxy-3-(3-morpholinopropoxy)anilino]-3-oxo-propanoic acid (5 g, 90%) as a brown solid. ESI-MS *m/z* 353.3 $[M+H]^+$ calc. for $C_{17}H_{24}N_2O_6$. Finally, a solution of this intermediate (5 g, 14.19 mmol) in $POCl_3$ (21.76 g, 141.89 mmol) was stirred at 100 °C for 2 hours. Then, the reaction mixture was concentrated in vacuum to give a residue which was dissolved in EtOAc and poured into water slowly. The mixture was adjust to pH = 8 with NaOH (2.0 M) and then extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue which was purified by silica gel column chromatography (PE:EtOAc = 1:1 to CH_2Cl_2:MeOH = 10:1) to afford

pure compound **71b** (3.8 g, 72%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.60 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 4.36-4.35 (m, 2H), 4.13-4.10 (m, 2H), 4.03 (s, 3H), 3.71-3.64 (m, 4H), 3.48-3.46 (m, 2H), 3.26-3.23 (m, 2H), 2.43 (br s, 2H). ESI-MS *m/z* 371.2 $[M+H]^+$ calc. for $C_{17}H_{20}Cl_2N_2O_3$.

2,4-dichloro-6,7-dimethoxy-quinoline (73a)

To a solution of commercially available 3,4-dimethoxyaniline (**72a**) (8 g, 52 mmol) in $POCl_3$ (100 mL) was added malonic acid (6.69 g, 64 mmol) and the solution was heated for 4 hours at room temperature and overnight at 90 ºC. Then, the mixture was concentrated and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by the silica gel column chromatography to afford pure compound **73a** (8 g, 60%) as a pale yellow solid. ESI-MS *m/z* 258 $[M+H]^+$ calc. for $C_{11}H_9Cl_2NO_2$. This compound was used in the next step without further characterization.

7-benzyloxy-2,4-dichloro-6-methoxy-quinoline (73b)

To a mixture of commercially available 3-benzyloxy-4-methoxy-aniline (**72b**) (35 g, 0.153 mol) and TEA (30.87 g, 0.306 mol) in CH_2Cl_2 (1 L) was added drop wise ethyl 3-chloro-3-oxo-propanoate (25.25 g, 0.168 mol) at 0 °C and the mixture was stirred at 25 °C for 12 hours. Then, the reaction was poured into water and extracted with CH_2Cl_2. The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford intermediate ethyl 3-(3-benzyloxy-4-methoxy-anilino)-3-oxo-propanoate (40 g, 76%) which was used in the next step without further purification. ESI-MS *m/z* 344.2 $[M+H]^+$ calc. for $C_{19}H_{21}NO_5$. To a mixture of this intermediate (20.40 g, 59.41 mmol) in THF/MeOH/H_2O (3:3:2, 267 mL) was added

$LiOH \cdot H_2O$ (3.74 g, 89.12 mmol) and the mixture was stirred at 25 °C for 16 hours. Then, the solvent was removed and the residue was poured into ice-water. The resulting slurry was filtered and the filter cake was dried under vacuum to afford intermediate 3-(3-benzyloxy-4-methoxy-anilino)-3-oxo-propanoic acid (19.30 g, crude) as a white solid. ESI-MS *m/z* 316.2 $[M+H]^+$ calc. for $C_{17}H_{17}NO_5$. Finally, this intermediate (7.00 g, 22.20 mmol) was suspended in $POCl_3$ (68.08 g, 444 mmol) in a 500 mL single-necked round bottom flask and the mixture was stirred at 90 °C for 2 hours under N_2. The reaction mixture was cooled and concentrated to remove $POCl_3$. The residue was further purified by silica gel column chromatography (PE:EtOAc = 50:1 - 10:1) to give afford pure **73c** (2.50 g, 33%). ESI-MS *m/z* 334.2 $[M+H]^+$ calc. for $C_{17}H_{13}Cl_2NO_2$. This compound was used in the next step without further characterization.

4-chloro-6,7-dimethoxy-2-(5-methyl-2-furyl)quinoline (74a)

To a solution of compound **73a** (150 mg, 0.58 mmol) in 1,4-dioxane/H_2O (15:1, 16 mL) was added Na_2CO_3 (189 mg, 1.75 mmol), $Pd(PPh_3)_4$ (75 mg, 0.064 mmol) and 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (120 mg, 0.58 mmol) and the mixture was stirred at 110 ºC for 2 hours under Microwave. Then, the mixture was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product which was purified by the prep-TLC to afford pure compound **74a** (70 mg, 40%) as a yellow solid. ESI-MS *m/z* 304 $[M+H]^+$ calc. for $C_{16}H_{14}ClNO_3$. This compound was used in the next step without further characterization.

4-chloro-6-methoxy-2-(5-methyl-2-furyl)quinolin-7-ol (74b)

To a mixture of **67** (6.00 g, 24.58 mmol), 4,4,5,5-tetramethyl -2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (5.63 g, 27.04 mmol) and $Pd(PPh_3)_4$ (2.86 g, 2.46 mmol) in 1,4-dioxane (90 mL) was added K_2CO_3 (3.40 g, 24.64 mmol) in H_2O (30 mL) and the mixture was stirred at 120 ºC for 12 hours. Then, the mixture was extracted with EtOAc and the combined organic phase was washed with saturated brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 2:1) to afford pure compound **74b** (2.10 g, 30%) as yellow solid. ESI-MS *m/z* 290.1 $[M+H]^+$ calc. for $C_{15}H_{12}ClNO_3$. This compound was used in the next step without further characterization.

7-benzyloxy-4-chloro-6-methoxy-2-(5-methyl-2-furyl)quinoline (74c)

A mixture of compound **73b** (900 mg, 2.69 mmol), 4,4,5,5-tetramethyl-2-(5-methyl-2-furyl)-1,3,2-dioxaborolane (588 mg, 2.83 mmol), K_2CO_3 (558 mg, 4.04 mmol) and $Pd(PPh_3)_4$ (311 mg, 0.27 mmol) in 1,4-dioxane (10 mL) was de-gassed and heated to 100 °C for 16 hours under N_2. Then, the reaction mixture was poured into water and extracted with EtOAc. The combined organic phase was washed with saturated brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue, which was purified by silica gel column chromatography (PE:EtOAc = 30:1 - 5:1) to afford the pure compound **74c** (500 mg, 49%). ESI-MS *m/z* 380.1 $[M+H]^+$ calc. for $C_{22}H_{18}ClNO_3$. This compound was used in the next step without further characterization.

6-methoxy-2-(5-methyl-2-furyl)-4-[(1-methyl-4-piperidyl)amino]quinolin-7-ol (75)

A solution of compound **74c** (500 mg, 1.32 mmol), 1-methylpiperidin-4-amine (300 mg, 2.63 mmol), $Pd_2(dba)_3$ (120 mg, 0.13 mmol), BINAP (82 mg, 0.13 mmol) and Cs_2CO_3

(858 mg, 2.63 mmol) in 1,4-dioxane (10 mL) was stirred at 110 ºC for 16 hours under N_2. Then, the reaction mixture was concentrated and purified by silica gel column chromatography (CH_2Cl_2:MeOH = 10:1) to afford intermediate 7-benzyloxy-6-methoxy-2-(5-methyl-2-furyl)-N-(1-methyl-4-piperidyl)quinolin-4-amine (400 mg, 66%). ESI-MS *m/z* 458.2 $[M+H]^+$ calc. for $C_{28}H_{31}N_3O_3$. Then to a solution of this intermediate (457 mg, 1.0 mmol) in MeOH (50 mL) was added Pd/C (120 mg) and the mixture was stirred under H_2 (50 psi) at 25 ℃ for 16 hours. Then, the reaction mixture was filtered and the filter was concentrated. The crude product was purified by silica gel column chromatography (PE/EtOAC = 5:1) to afford pure compound **75** (350 mg, 95%) as yellow solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.77 (s, 1H), 7.53 (s, 1H), 7.36 (s, 1H), 7.02 (s, 1H), 6.43 (s, 1H), 4.29 (s, 1H), 4.06 (s, 3H), 3.72-3.69 (m, 2H), 2.95 (s, 3H), 2.50 (s, 3H), 2.41-2.37 (m, 3H), 2.15-2.12 (m, 3H). ESI-MS *m/z* 368.2 $[M+H]^+$ calc. for $C_{21}H_{25}N_3O_3$.

Tert-butyl 4-[[4-chloro-6-methoxy-2-(5-methyl-2-furyl)-7-quinolyl]oxymethyl]piperidine-1-carboxylate (76)

To a mixture of **74b** (650 mg, 2.24 mmol), tert-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (540 mg, 2.51 mmol) and PPh_3 (1.18 g, 4.48 mmol) in THF (50 mL), was added DIAD (907 mg, 4.48 mmol) in one portion at 0 ºC under N_2 and the mixture was stirred at 0 ºC for 8 hours. Then, the mixture was concentrated and extracted with EtOAc. The combined organic phase was washed with saturated brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (PE/EtOAc = 2/1) to afford compound **76** (700 mg, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (s, 1H), 7.42 (s, 1H), 7.37 (s, 1H), 7.03 (s,

1H), 6.17 (s, 1H), 5.01-4.95 (m, 1H), 4.19-4.13 (m, 2H), 4.04 (s, 3H), 2.81-2.74 (m, 2H), 2.45 (s, 3H), 2.19-2.13 (m, 2H), 1.93-1.85 (m, 2H), 1.75-1.66 (m, 2H), 1.48 (s, 9H). ESI-MS *m/z* 487.3 $[M+H]^+$ calc. for $C_{26}H_{31}ClN_2O_5$.

Tert-butyl 2-[[7-[(1-tert-butoxycarbonyl-4-piperidyl)methoxy]-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (77a)

To a mixture of **76** (100 mg, 0.205 mmol) and tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate (99 mg, 0.410 mmol) in 1,4-dioxane (10 mL), was added $Pd(dba)_2$ (12 mg, 0.021 mmol), BINAP (13 mg, 0.021 mmol) and Cs_2CO_3 (133 mg, 0.410 mmol) and the mixture was stirred at 110 ºC for 12 hours. Then, the mixture was concentrated and the residue was purified by prep-TLC (CH_2Cl_2/MeOH = 15/1) to afford compound **77a** (80.0 mg, 56%) as yellow solid. ESI-MS *m/z* 691.4 $[M+H]^+$ calc. for $C_{39}H_{54}N_4O_7$. This compound was used in the next step without further characterization.

Tert-butyl 6-[[4-[(1-tert-butoxycarbonyl-4-piperidyl)methylamino]-6-methoxy-2-(5-methyl-2-furyl)-7-quinolyl]oxy]-2-azaspiro[3.3]heptane-2-carboxylate (77b)

To a solution of compound **79a** (50 mg, 0.107 mmol) in DMF (10 mL) were added Cs_2CO_3 (70 mg, 0.214 mmol) and tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (47 mg, 0.160 mmol) and the mixture was stirred at 100 °C for 16 hours. Then, the mixture was concentrated to give crude compound **77b** (100 mg, crude) as yellow solid which was used for next step without further purification. ESI-MS *m/z* 663.4 $[M+H]^+$ calc. for $C_{37}H_{50}N_4O_7$.

Tert-butyl 2-[[7-[(2-tert-butoxycarbonyl-2-azaspiro[3.3]heptan-6-yl)oxy]-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (77c)

To a solution of compound **79b** (190 mg, 0.385 mmol) in DMF (15 mL) were added Cs_2CO_3 (251 mg, 0.770 mmol) and tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (168 mg, 0.577 mmol) and the mixture was stirred at 100 ℃ for 16 hours under N_2. Then, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by prep-TLC (CH_2Cl_2:MeOH = 20:1) to afford pure compound **77c** (200 mg 75%) as yellow solid. ESI-MS *m/z* 689.4 $[M+H]^+$ calc. for $C_{39}H_{52}N_4O_7$. This compound was used in the next step without further characterization.

Tert-butyl 8-[[7-[(2-tert-butoxycarbonyl-2-azaspiro[3.3]heptan-6-yl)oxy]-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-3-azabicyclo[3.2.1]octane-3-carboxylate (77d)

To a solution of compound **79c** (110 mg, 0.229 mmol) in DMF (10 mL) were added Cs_2CO_3 (149 mg, 0.458 mmol) and tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (100 mg, 0.344 mmol) and the mixture was stirred at 100 ℃ for 16 hours. Then, the reaction mixture was filtered and the filtrate was concentrated to afford crude compound **77d** (160 mg, crude) as yellow solid which was used for next step without further purification. ESI-MS *m/z* 675.4 $[M+H]^+$ calc. for $C_{38}H_{50}N_4O_7$.

Tert-butyl 4-[[[7-benzyloxy-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]piperidine-1-carboxylate (78a)

To a solution of compound **74c** (300 mg, 0.790 mmol), in 1,4-dioxane (20 mL) were added Cs_2CO_3 (515 mg, 1.58 mmol), BINAP (49 mg, 0.079 mmol), $Pd_2(dba)_3$ (72 mg, 0.079 mmol) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (338 mg, 1.58 mmol) and the mixture was stirred at 130 °C for 16 hours. Then, the mixture was concentrated and extracted with EtOAc. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude product. The residue was purified by silica gel column chromatography (CH_2Cl_2:Methanol = 50:1 to 20:1) to afford pure compound **78a** (130 mg 29%) as yellow solid. ESI-MS *m/z* 558.4 $[M+H]^+$ calc. for $C_{33}H_{39}N_3O_5$. This compound was used in the next step without further characterization.

Tert-butyl 2-[[7-benzyloxy-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (78b)

To a solution of compound **74c** (400 mg, 1.05 mmol) in 1,4-dioxane (10 mL) were added Cs_2CO_3 (686 mg, 2.11 mmol), BINAP (66 mg, 0.105 mmol), $Pd_2(dba)_3$ (96 mg, 0.105 mmol) and tert-butyl 2-amino-7-azaspiro[3.5]nonane-7-carboxylate (506 mg, 2.11 mmol) and the mixture was stirred at 120 °C for 16 hours. Then, the solution was extracted with EtOAc and the combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude product. The residue was purified by prep-TLC (SiO_2, CH_2Cl_2:MeOH = 20:1) to afford pure compound **78b** (300 mg, 49%) as yellow solid. ESI-MS *m/z* 584.3 $[M+H]^+$ calc. for $C_{35}H_{41}N_3O_5$. This compound was used in the next step without further characterization.

Tert-butyl 8-[[7-benzyloxy-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-3-azabicyclo[3.2.1]octane-3-carboxylate (78c)

To a solution of compound **74c** (300 mg, 0.790 mmol**)** in 1,4-dioxane (20 mL) were added Cs_2CO_3 (514.7 mg, 1.58 mmol), BINAP (49 mg, 0.079 mmol), $Pd_2(dba)_3$ (72 mg, 0.079 mmol) and tert-butyl 8-amino-3-azabicyclo[3.2.1]octane-3-carboxylate (357 mg, 1.58 mmol) and the mixture was stirred at 130 °C for 16 hours. Then, the mixture was concentrated and extracted with EtOAc. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give the crude product which was purified by silica gel column chromatography (CH_2Cl_2:Methanol = 30:1 to 10:1) to afford pure compound **78c** (210 mg, 47%) as a yellow solid. ESI-MS *m/z* 570.4 $[M+H]^+$ calc. for $C_{34}H_{39}N_3O_5$. This compound was used in the next step without further characterization.

Tert-butyl 4-[[[7-hydroxy-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]methyl]piperidine-1-carboxylate (79a)

To a solution of compound **78a** (130 mg, 0.233 mmol) in MeOH (15 mL) was added Pd/C (150 mg, 50%) and the suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 25 °C for 16 hours. Then, the reaction mixture was filtered and the filtrate was concentrated to give compound **79a** (50 mg, 46%) as yellow solid which was used in the next step without further purification. ESI-MS *m/z* 468.3 $[M+H]^+$ calc. for $C_{26}H_{33}N_3O_5$.

Tert-butyl 2-[[7-hydroxy-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-7-azaspiro[3.5]nonane-7-carboxylate (79b)

To a solution of compound **78b** (300 mg, 0.514 mmol) in MeOH (30 mL) was added Pd/C (100 mg, 10%) and the suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 25 °C for 16 hours. Then, the reaction

mixture was filtered and the filtrate was concentrated to give the compound **79b** (190 mg, 75%) as yellow solid which was used in the next step without further purification. ESI-MS *m/z* 494.4 $[M+H]^+$ calc. for $C_{28}H_{35}N_3O_5$.

Tert-butyl 8-[[7-hydroxy-6-methoxy-2-(5-methyl-2-furyl)-4-quinolyl]amino]-3-azabicyclo[3.2.1]octane-3-carboxylate (79c)

To a solution of compound **78c** (210 mg, 0.368 mmol) in MeOH (15 mL) was added Pd/C (200 mg, 50%) and the suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 25 °C for 16 hours. Then, the reaction mixture was filtered and the filtrate was concentrated to give compound **79c** (110 mg, 62%) as yellow solid which was used in the next step without further purification. ESI-MS *m/z* 480.3 $[M+H]^+$ calc. for $C_{27}H_{33}N_3O_5$.

N-(7-azaspiro[3.5]nonan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)-7-(4-piperidylmethoxy)quinolin-4-amine (80a)

To a mixture of **77a** (50.0 mg, 0.072 mmol) in EtOAc (10.0 mL), was added EtOAc/HCl (2.0 M, 5 mL) and the mixture was stirred at 25 °C for 2 hours under N_2. Then, the mixture was concentrated and purified by prep-HPLC (method 3 described in supporting information) to afford compound **80a** (15.0 mg, 42%) as yellow solid. ^1H NMR (CD_3OD, 400 MHz): δ 7.80 (s, 1H), 7.54 (d, *J* = 3.6 Hz 1H), 7.46 (s, 1H), 6.81 (s, 1H), 6.44 (d, *J* = 2.8 Hz 1H), 4.53 (d, *J* = 8.0 Hz 1H), 4.13 (d, *J* = 5.6 Hz 2H), 4.02 (s, 3H), 3.53-3.47 (m, 2H), 3.31-3.22 (m, 2H), 3.16-3.07 (m, 4H), 2.73-2.64 (m, 2H), 2.51 (s, 3H), 2.27 (br s, 1H), 2.23-2.11 (m, 4H), 2.09-2.05 (m, 2H), 1.94-1.86 (m, 2H), 1.81-1.68 (m, 2H). ESI-MS *m/z* 491.4 $[M+H]^+$ calc. for $C_{29}H_{38}N_4O_3$.

7-(2-azaspiro[3.3]heptan-6-yloxy)-6-methoxy-2-(5-methyl-2-furyl)-N-(4-piperidylmethyl)quinolin-4-amine (80b)

To a solution of compound **77b** (100 mg, 0.151 mmol) in CH_2Cl_2 (8 mL) was added TFA (3.1 g) at 0 °C and the mixture was stirred at 18 °C for 2 hours. Then, the mixture was concentrated to give crude compound **80b** (150 mg, crude) as yellow oil which was used for next step without further purification. ESI-MS *m/z* 463.4 $[M+H]^+$ calc. for $C_{37}H_{50}N_4O_7$.

7-(2-azaspiro[3.3]heptan-6-yloxy)-N-(7-azaspiro[3.5]nonan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)quinolin-4-amine (80c)

To a solution of compound **77c** (200 mg, 0.290 mmol) in CH_2Cl_2 (16 mL) was added TFA (6.12 g) at 0 °C and the mixture was stirred at 18 °C for 2 hours. Then, the mixture was concentrated to give the crude compound **80c** (180 mg, crude) as yellow oil which was used in the next step without further purification. ESI-MS *m/z* 489.3 $[M+H]^+$ calc. for $C_{29}H_{36}N_4O_3$.

N-(3-azabicyclo[3.2.1]octan-8-yl)-7-(2-azaspiro[3.3]heptan-6-yloxy)-6-methoxy-2-(5-methyl-2-furyl)quinolin-4-amine (80d)

To a solution of compound **77d** (110 mg, 0.163 mmol) in CH_2Cl_2 (8 mL) was added TFA (3.06 g) at 0 °C and the mixture was stirred at 18 °C for 2 hours. Then, the mixture was concentrated to afford crude compound **80d** (150 mg, crude) as yellow oil which was used for next step without further purification. ESI-MS *m/z* 475.4 $[M+H]^+$ calc. for $C_{28}H_{34}N_4O_3$.

N-(7-azaspiro[3.5]nonan-2-yl)-7-benzyloxy-6-methoxy-2-(5-methyl-2-furyl)quinolin-4-amine (81)

Compound **78b** (650 mg, 1.11 mmol) was dissolved in HCl/EtOAc (2.0 M, 10 mL) and the mixture was stirred at 18 °C for 2 hours. Then, the mixture was concentrated to afford crude compound **81** (650 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 484.3 $[M+H]^+$ calc. for $C_{30}H_{33}N_3O_3$.

7-benzyloxy-N-(7-isopropyl-7-azaspiro[3.5]nonan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)quinolin-4-amine (82)

To a solution of compound **81** (650 mg, 1.25 mmol) in *i*-PrOH (15 mL) were added CH_3COOH (450 mg, 7.50 mmol), acetone (436 mg, 7.50 mmol) and $NaBH_3CN$ (471 mg, 7.50 mmol) and the mixture was stirred at 60 °C for 16 hours under N_2. Then, the mixture was concentrated and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel column chromatography (CH_2Cl_2:Methanol = 50:1 to 1:1) to afford compound **82** (300 mg, 46%) as a yellow solid. ESI-MS *m/z* 526.4 $[M+H]^+$ calc. for $C_{33}H_{39}N_3O_3$. This compound was used in the next step without further characterization.

4-[(7-isopropyl-7-azaspiro[3.5]nonan-2-yl)amino]-6-methoxy-2-(5-methyl-2-furyl)quinolin-7-ol (83)

To a solution of compound **82** (300 mg, 0.571 mmol) in MeOH (50 mL) was added Pd/C (10%, 100 mg) and the suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 20 °C for 8 hours. Then, the reaction mixture was filtered and the filtrate was concentrated to give crude compound **83** (200

mg, 81%) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 436.3 $[M+H]^+$ calc. for $C_{26}H_{33}N_3O_3$.

Tert-butyl 6-[[4-[(7-isopropyl-7-azaspiro[3.5]nonan-2-yl)amino]-6-methoxy-2-(5-methyl-2-furyl)-7-quinolyl]oxy]-2-azaspiro[3.3]heptane-2-carboxylate (84)

To a solution of compound **83** (150 mg, 0.344 mmol) in DMF (10 mL) were added Cs_2CO_3 (224 mg, 0.689 mmol) and tert-butyl 6-methylsulfonyloxy-2-azaspiro[3.3]heptane-2-carboxylate (151 mg, 0.516 mmol) and the mixture was stirred at 100 °C for 16 hours under N_2. Then, the reaction mixture was filtered and the filtrate was concentrated to give crude compound **84** (300 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS *m/z* 631.5 $[M+H]^+$ calc. for $C_{37}H_{50}N_4O_5$.

7-(2-azaspiro[3.3]heptan-6-yloxy)-N-(7-isopropyl-7-azaspiro[3.5]nonan-2-yl)-6-methoxy-2-(5-methyl-2-furyl)quinolin-4-amine (85)

To a solution of compound **84** (300 mg, 0.476 mmol) in CH_2Cl_2 (8 mL) was added TFA (3.08 g, 27.01 mmol) at 0 °C and the mixture was stirred at 18 °C for 2 hours. Then, the mixture was concentrated to afford compound **85** (300 mg, crude) as yellow oil which was used in the next step without further purification. ESI-MS *m/z* 531.5 $[M+H]^+$ calc. for $C_{32}H_{42}N_4O_3$.

G9a and DNMT1 docking

Compound **6** was superposed to the conformation of UNC0638 in the co-crystal structure of the G9-UNC0638-SAH complex (Protein Data Bank, PDB, entry 3RJW) with the MOE program (Chemical Computing Group, http://www.chemcomp.com).

Then, the overlaid conformation of the compound was translated into the G9a-UNC0638-SAH crystal in order to analyze the key interactions between the ligand and the methyltransferase.

The GoldSuite 5.2 program (Cambridge Crystallographic Data Centre, https://www.ccdc.cam.ac.uk/pages/Home.aspx) was used to carry out docking of compounds to DNMT1 and G9a. For G9a, the PDB entry 3RJW was used, with the ChemScore function and a cavity of 10-Å around the carboxylate oxygen of Asp1088. The setting was validated after reproducing the binding mode of UNC0638. The crystal structure of Mouse DNMT1 bound to hemimethylated CpG DNA (PDB entry 4DA4) was chosen. In order to explore both, different binding pockets and different binding modes, a range of docking set ups where considered with emphasis on keeping adequate volume occupancy of the different binding pockets and considering protein-ligand interactions, especially those involving conserved catalytic residues. The docking configuration was, when adequate, validated by reproducing the crystallographic binding mode of SAH. In the final selected set-up, the docking region used was a 20-Å sphere around the carboxylate oxygen of Glu1269. The PLP scoring function was used to rank docking poses, and protein hydrogen bond constraints for binding to carboxylate of Glu-1269 were imposed on the ligand. The top twenty best docked structures out of 100 independent genetic algorithm runs were retrieved and visually inspected. The high-scoring pose was finally chosen as it has a plausible binding mode with key interactions with DNMT1 and a high degree of convergence (rmsd < 2 Å) was observed among the top three ranked poses.

Calculation of the electrostatic potential of DNMT1

A customized python script using OpenEye Toolkits[23] was programmed to calculate the void volume between DNMT1 cavity bound to compound **6** and color coded it by electrostatic potential. For the purpose of clarity, only negative potentials are shown in red in Figure 1C.

G9a enzyme activity assay

The biochemical assay to measure G9a enzyme activity relies on time-resolved fluorescence energy transfer (TR-FRET) between europium cryptate (donor) and XL665 (acceptor). TR-FRET is observed when biotinylated histone monomethyl-H3K9 peptide is incubated with cryptate-labeled anti- H3K9me2 antibody (CisBio Cat# 61KB2KAE) and streptavidin XL665 (CisBio Cat#610SAXLA), after enzymatic reaction of G9a.

The assay was carried out during 1 hour at room temperature, in a final volume of 20 µL, with 0.2 nM human G9a enzyme, 40nM biotinylated histone monomethyl-H3K9 peptide, 20 µM S-adenosylmethionine (SAM) and different final concentrations of tested compounds in assay buffer (50 mM Tris-HCl, 10 mM NaCl, 4 mM DTT, 0.01% Tween-20 pH 9). The final percentage of DMSO was 0.5%. After incubation time enzyme activity was stopped by adding 150 nM of cryptate-labeled anti-H3K9me2 antibody and 16 µM of streptavidin XL665 beads. After one hour of incubation at room temperature, fluorescence was measured at 620 nm and 665 nm. A ratio (665 nm / 620 nm) was then calculated in order to minimize medium interferences. Positive control was obtained in the presence of the vehicle of the compounds. Negative control was obtained in the absence of G9a enzyme activity. Calculated IC_{50} values were determined using GraphPrism using 4-parameters inhibition curve. Compounds were tested in duplicate at different days, within an experimental error of 0.3 log units. If absolute

pIC_{50} difference was higher than 0.3 log units, additional replicates were performed until satisfying the experimental error (by discarding individual results with values outside 2 MADs of the mean value).

DNMT1 enzyme activity assay

The biochemical assay to measure DNMT1 enzyme activity relies on time-resolved fluorescence energy transfer (TR-FRET) between lumi4-Tb (donor) and d2 (acceptor) using the EPIgeneous methyltransferase assay (CisBio Cat#62SAHPEB). TR-FRET is observed when antibody specific to S-adenosylhomocysteine labeled with Lumi4-Tb is incubated with d2-labeled S-adenosylhomocysteine. TR-FRET signal is inversely proportional to the concentration of SAH, product of DNMT1 enzyme activity, in the sample.

The assay was carried out during 15 minutes at 37 ºC, in a final volume of 20 µL, with 20 nM human DNMT1enzyme, 1 µg/mL poly-deoxy inosine poly-deoxy cytosine (pdI-pdC) DNA, 1 µM S-adenosylmethionine (SAM) and different final concentrations of tested compounds in assay buffer (50 mM Tris-HCl, 1 mM EDTA, 1 mM DTT, 0.1% Triton X-100, 5% glycerol pH 7.5).The final percentage of DMSO was 0.5%. After incubation time enzyme activity was stopped by adding 2 µL of buffer one of the EPIgeneous methyltransferase kit assay. After 10 minutes at room temperature, it was added 4 µL of antibody specific to S-adenosylhomocysteine labeled with Lumi4-Tb 50 x and 4 µL of d2-labeled S-adenosylhomocysteine 31x both diluted in buffer two of the EPIgeneous methyltransferase kit. Fluorescence was measured at 620 nm and 665 nm one hour later. A ratio (665 nm / 620 nm) was then calculated in order to minimize medium interferences. Positive control was obtained in the presence of the vehicle of the compounds. Negative control was obtained in the absence of DNMT1 enzyme

activity. Calculated IC50 values were determined using GraphPrism using 4-parameters inhibition curve. Compounds were tested in duplicate, within an experimental error of 0.3 log units. If absolute pIC_{50} difference was higher than 0.3 log units, additional replicates were performed until satisfying the experimental error (by discarding individual results with values outside 2 MADs of the mean value).

Epigenetics Selectivity Panel

Selectivity of **13** and **43** against methyltransferases (MLL1, SET7/9, SUV39H1, SUV39H2, PRMT1, PRMT3, PRMT4, PRMT5, PRMT6, PRMT8, EZH1, EZH2, SETD2), DNMTs (DNMT1, DNMT3A, DNMT3B), bromodomains (BRD2, CREBBP, BAZ2B) and histone demethylases (JMJD2C, JMJD3 and JMJD1A) was performed by BPS Bioscience (http://www.bpsbioscience.com/index.ph). Binding experiments were performed in duplicate at each concentration. GLP IC_{50} determination for **13** and **43** was carried out at Eurofins (https://www.eurofins.com/) in duplicate.

Cell culture

CEMO-1 cell lines were cultured with RPMI 1640 medium supplemented with 20% fetal bovine serum and OCI-Ly10 and OCI-Ly3 cells with IMDM supplemented with 20% human serum and 55 μM of β-mercaptoethanol. All cell lines were maintained in culture at 37 °C in a humid atmosphere containing 5% CO_2 and were tested for mycoplasma.

Cell Proliferation Assay – MTS

Cell proliferation was analyzed after 48 hours of *in vitro* treatment using the CellTiter 96 Aqueous One Solution Cell Proliferation Assay (Promega). This is a colorimetric method for determining the number of viable cells in proliferation. For the assay, cells

were cultured by triplicate at a density of $1x10^6$ cells/mL in 96-well plates (100.000 cells/well, 100µL/well), except for OCI-Ly3 and OCI-Ly10 cell lines which were cultured at a density of $0.5x10^6$ cells/mL (50.000 cells/well, 100 µL/well). In all cases, only the 60 inner wells were used to avoid any border effects. After 48 hours of treatment, plates were centrifuged at 800g for 10 minutes and medium was removed. Then, cells were incubated with 100 µL/well of medium and 20 µL/well of CellTiter 96 Aqueous One Solution reagent. After 1-3 hours of incubation at 37 ºC, absorbance was measured at 490 nm in a 96-well plate reader. The background absorbance was measured in wells with only cell line medium and solution reagent. Data was calculated as a percentage of total absorbance of treated cell / absorbance of non-treated cells.

CYP Inhibition

The inhibitory effect of the compounds on five human cytochrome P450s (1A2, 2C9, 2C19, 2D6, and 3A4) was evaluated in human liver microsomes at WuXi (http://www.wuxi.com/). Compounds were prepared at 10 µM, and the corresponding substrates for each P450 isoform (20 µL) were incubated with 140 µL of liver microsomes (0.286 mg/mL; BD Gentest) and NADPH cofactor (20 µL, 1 mM) for 10 min at 37 °C. The reaction was terminated by adding 400 µL of cold stop solution (200 ng/mL tolbutamide in ACN), and samples were centrifuged at 1500g for 20min. Supernatants were analyzed by LC-MS/MS (Shimadzu LC 20-AD−API 4000) using the peak area ratio of the analyte/internal standard. Compounds and positive controls were tested in duplicate. The percentage of inhibition was calculated as the ratio of substrate metabolite detected in treated and non-treated wells.

hERG Blockade Assay

The effect of the compounds on the hERG potassium channel was determined using a PredictorTM hERG fluorescence polarization commercial assay kit (Life Technologies, catalogue no. PV5365). The assay was carried out in black 384-well plates (Corning, catalogue no. 3677 PS), monitoring changes in the fluorescence polarization properties of the labeled hERG ligand between its soluble and bound states. The compounds, which will compete with the fluorescently labeled hERG, were solubilized in 100% DMSO across a 16-point concentration curve and then diluted 1:25 with hERG assay buffer. The assay contained 5 μL/well of studied compound, 10 μL/well of hERG membranes, and 5 μL/well of hERG Tracer Red. The plate was incubated 2 h at rt and protected from light. Fluorescence polarization signals were recorded with an Envision plate reader (PerkinElmer).

Metabolic Stability

Test compounds (1 μM, 5% MeOH in potassium phosphate buffer) were incubated with human (catalogue no. 452161 from BD Gentest) and mouse (catalogue no. M1000, Xenotech) liver microsomes at 37 °C for 10 min. Liver microsomes were at a final assay concentration of 0.7 mg protein/mL. The reaction was started by the addition of 90 μL of NADP cofactor solution and stopped by the addition of 300 μL of stop solution (ACN at 4 °C, including 100 ng/mL tolbutamide as an internal standard) after 20 min of incubation. The samples were shaken for 5 min and then centrifuged for 20 min at 1500g. A 100 μL aliquot of the supernatant was transferred to eight new 96-well plates with 300 μL of HPLC water and centrifuged at 1500g for LC-MS/MS analysis (Shimadzu LC 10-AD−API 4000). An injection volume of 10 μL was added to a Phenomenex Synergi C18 column eluting with formic acid in water or ACN at a flow rate of 800 μL/min. The percent loss of parent compound was calculated from the peak

area ratio of the analyte/internal standard. Compounds and positive controls were tested in duplicate.

PAMPA Permeability

The permeability of compounds was evaluated with the parallel artificial membrane permeation assay (PAMPA) as an *in vitro* model of passive diffusion. Donor solutions of test compounds (180 µL. 50 µM in PBS/EtOH 70:30) were added to each well of the donor plate, whose PVDF membrane was precoated with 4 µL of a 20 $mg \times mL^{-1}$ PBL/dodecane mixture. PBS/EtOH (180 µL) was added to each well of the PTFE acceptor plate. The donor and acceptor plates were combined together and incubated for 18 h at 20 ºC without shaking. In each plate, compounds and controls were tested in duplicate. Drug concentration in the acceptor, the donor, and the reference wells was determined using the UV plate reader with 130 µL of acceptor and donor samples. Permeability rates (Pe in nm s^{-1}) were calculated with Equation (1). The permeability rate of each compound is the averaged value of three independent measurements.

Equation (1) $P_e = C \times \left(-ln\left(1 - \frac{[drug]_{acceptor}}{[drug]_{equilibrium}}\right)\right) \times 10^7$;

where $C = \frac{V_D \times V_A}{(V_D + V_A) \times Area \times time}$; V_D = 0.18 mL; V_A = 0.18 mL; Area = 0.32 cm^2; time = 64800 s; D_F = 180/130; $[drug]_{equilibrium} = ([drug]_{donor} \times V_D + [drug]_{acceptor} \times V_A) / (V_D + V_A)$; $[drug]_{donor} = (A_a/A_i * D_F)_{donor}$; $[drug]_{acceptor} = (A_a/A_i * D_F)_{acceptor}$; $A_{a\ donor} = Abs_{donor} - Abs_{vehicle}$; $A_{a\ acceptor} = Abs_{acceptor} - Abs_{vehicle}$, $Ai = Abs_{withoutPBL} - Abs_{vehicle}$.

Interference compound assessment

Potential PAINS (Pan Assay Interference Compounds) liability of reported compounds was assessed according to the structural filters defined by Baell & Holloway[24] (Charts 3 and 4 and Tables 1-3 of this reference) using a customized Pipeline Pilot protocol.[19] No compound reported in the manuscript matches any of these substructures.

Western blot

After 96 hours of treatment, CEMO-1 cells were washed twice with PBS, being the last centrifugation of 4000 rpm for 10 min at 4 ºC. Histone extraction was performed as recommended by Upstate Biotechnology. Briefly, cells were homogenized in 5 volumes of lysis buffer (10 mM HEPES, pH 7.9; 1.5 mM $MgCl_2$; 10 mM KCl; 0.5 mM DTT; protease inhibitor cocktail (Complete Mini, Cat No 11836153301, Roche) and HCl was added to a final concentration of 0.2 M. After incubation on ice for 30 min, the homogenate was centrifuged at 11000 g for 10 min at 4 ºC, and the supernatant was first dialyzed twice against 0.1 M glacial acetic acid (1 hour each time) and then three times against water for 1 hour, 3 hours and overnight, respectively. The histone concentration in the extract was measured using the dye-binding assay of Bradford. 10 µg of histone was separated on 15 % SDS-PAGE gel and transferred to a nitrocellulose membrane. The membrane, after being blocked with Tropix I-block blocking reagent (Cat No AI300, Tropix) in PBS with 0.1 % of Tween-20 and 0.02 NaN_3, was incubated with the primary antibody against H3K9me2 (Mouse monoclonal antibody to Histone H3 dimethyl K9, Cat No ab1220, Abcam) diluted 1:2000 overnight at 4 ºC and then with alkaline phosphatase-conjugated secondary antibodies. Bound antibodies were revealed by a chemiluminiscent reagent (Tropix) and detected using HyperfilmTM enhanced chemilumincescence. Total H3 was used as a loading control (diluted 1:50000 overnight at 4 ºC or for 1 hour at rt) (Anti-Histone H3, CT, pan, rabbit polyclonal, Cat No 07-690, Millipore).

Dot blot

After 96h of treatment, cells were washed twice with PBS and genomic DNA was extracted using a DNA kit (Nucleo Spin Tissue, Cat No 74095250, Macherey-Nagel) following the manufacturer's instructions. DNA purity and concentration was measured using a NanoDrop spectrophotometer (Thermo Scientific). 500 ng of genomic DNA was loaded onto a nitrocellulose membrane (Amersham Hybond_N+, RPN203B, GE Healthcare), pre-wetted in 6X SSC for 10 min, using the Bio-Dot microfiltration apparatus (Cat No 170-6545, BioRad) following the manufacturer's instructions. Then the membrane was incubated with 2X SSC for 5 min and was cross-linked for 2 h at 80 ºC. The membrane, after being blocked with Tropix I-block blocking reagent (Cat No AI300, Tropix) in PBS with 0.1 % of Tween-20 and 0.02 NaN_3, was incubated with the primary antibody against 5-methylcytosine (Monoclonal antibody 5-Methylcytidine, Cat No BI-MECY-1000, Eurogentec) diluted 1:4000 overnight at 4 ºC and then with alkaline phosphatase-conjugated secondary antibody. Bound antibodies were revealed by a chemiluminiscent reagent (Tropix) and detected using HyperfilmTM enhanced chemilumincescence.

ASSOCIATED CONTENT

Supporting Information

Protocols for preparative HPLC purification methods (S1)

Method for High Resolution Mass Spectrometry of final compounds (S2)

Methods for LCMS, analytical HPLC and UHPLC (S3)

HRMS and purities of final compounds (S4)

HPLC traces of final compounds (S5)

Selectivity of compounds **13** and **43** against epigenetic targets (S6)

Molecular formula strings and some data (CSV)

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Notes

These authors declare no competing financial interest.

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ABBREVIATIONS

AcOH, acetic acid; ADME, absorption, distribution, metabolism and excretion; AML; acute myeloid leukemia; BINAP, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; BOC, *tert*-butoxycarbonyl; Cp, compound; dba, dibenzylideneacetone; DEAD, diisopropyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DLBCL, diffuse large B-cell lymphoma; DMAP, 4-dimethylaminopyridine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DNA, deoxyribonucleic Acid; DNMT, DNA methyltransferase; DTT, *dithiothreitol;* EDTA, ethylenediaminetetraacetic acid; EHMT2, euchromatic histone methyltransferase 2; ESI-MS, electrospray ionisation mass spectrometry, EtOAc, ethyl acetate; EtOH, etanol; HPLC, High-performance liquid chromatography; *i*-PrOH, propan-2-ol; KMT1C, lysine methyltransferase 1C; KOAc, potassium acetate; LCMS, liquid chromatography–mass spectrometry, MeOH, methanol; m.p., melting point; MW, microwave; NMR, nuclear magnetic resonance; PAMPA, parallel artificial membrane permeability assay; PBS, phosphate buffered saline; PE, petroleum eter; Ph, phenyl; PK, pharmacokinetic; PMT, protein methyltransferase; PTFE, polytetrafluoroethylene; PTSA, p-toluenesulfonic acid; PVDF, polyvinylidene difluoride; rt, room temperature; Rt, retention time; SAM, S-adenosyl methionine; SAR, structure-activity relationship; *t*-BuOH, *tert*-butanol; *t*-BuOK, potassium *tert*-butoxide; *t*-BuONa, sodium *tert*-butoxide; THF, tetrahydrofuran; TFA, trifluoroacetic acid; TLC, thin layer chromatography; TMS, tetramethylsilane; TR-FRET, time-resolved fluorescence resonance energy transfer; UPLC, ultra performance liquid chromatography; UV, ultraviolet; xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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