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Metal-, Photocatalyst-, and Light-Free Minisci C–H Alkylation of *N*-Heteroarenes with Oxalates

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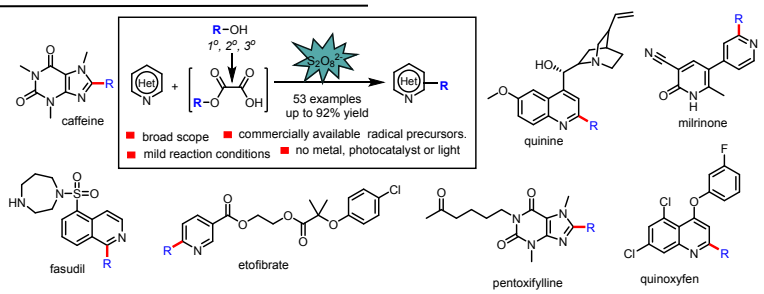
Supporting Information Placeholder

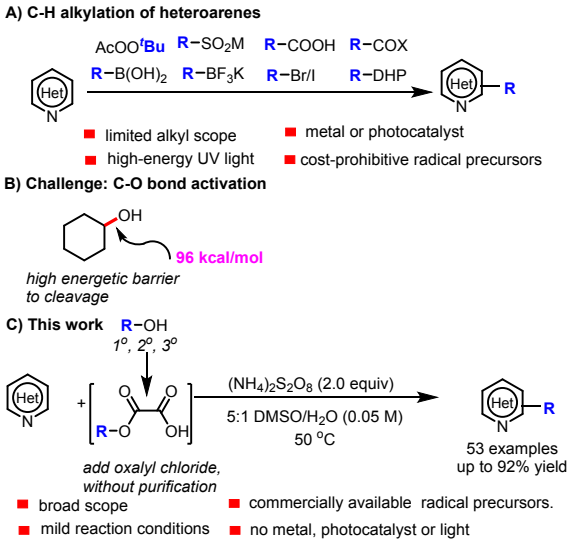
ABSTRACT: Herein, we report a mild protocol for metal-, photocatalyst-, and light-free Minisci C–H alkylation reactions of *N*-heteroarenes with alkyl oxalates derived from primary, secondary, and tertiary alcohols. The protocol uses environmentally benign persulfate as a stoichiometric oxidant and does not require high temperatures or large excesses of either of the substrates, making the procedure suitable for late-stage C–H alkylation of complex molecules. Notably, several pharmaceuticals and natural products could be functionalized or prepared with this protocol, thus demonstrating its utility.



Heteroaryl motifs are present in a wide variety of natural products, functional materials, small-molecule drugs, and ligands for metal catalysts.[1] Therefore, rapid, mild, and selective methods for direct C–H functionalization of these motifs are highly sought-after for late-stage modification of pharmaceuticals and other molecules.[2] One useful tool for this purpose is the Minisci reaction, in which a protonated *N*-heteroarene is attacked by an alkyl radical under oxidative conditions.[3] Minisci C–H alkylation reactions of *N*-heteroarenes with alkyl peroxides, sulfonates, aliphatic carboxylic acids, activated esters, boronic acids, alkyltrifluoroborates, alkyl halides, and 1,4-dihydropyridines as the alkyl radical sources have been reported (Scheme 1A).[4] However, most of the previously reported protocols require high temperatures, (sub)stoichiometric amounts of expensive metal salts, excesses of the radical precursors, expensive photocatalysts, or high-energy UV light for good yields, or they are limited in scope with respect to the alkyl source; therefore, their utility for late-stage functionalization of complex molecules is limited. Moreover, few structurally complex radical precursors (e.g., trifluoroborates and boronic acids) are commercially available or cost-effective.

Alcohols are among the most widely occurring, naturally abundant organic compounds, and they are often used as feedstock chemicals.[5] Because alcohols, from the simple to the complex, are inexpensive, abundant, stable, nontoxic, and readily available, the prospect of using them as alkyl radical sources is appealing. However, few Minisci C–H alkylation reactions using alcohols as the alkyl radical sources have been reported, because such reactions require cleavage of the relatively strong C–O bonds of the alcohols (~96 kcal/mol) (Scheme 1B).[6] Yokoyama's group achieved the first alkylation of heterocycles with alcohols by generating half esters of oxalic acid with strongly oxidizing hypervalent iodine(III) reagents.[7] However, this reaction is performed under refluxing benzene with a large excesses of the *N*-heterocycles and the oxalic acid monoesters, which narrows the functional group tolerance and thus limits the substrate scope. Furthermore, the yields are low, especially for primary alcohols (<20%). MacMillan's group reported a method for photoredox-catalyzed C–H alkylation of heteroarenes with excess alcohol as the radical source,[8] but this method is limited to primary alcohols. Therefore, the development of a practical, mild protocol for C–H alkylation of heteroarenes with primary, secondary, and tertiary alcohols with broad functional group tolerance would be a significant advance.

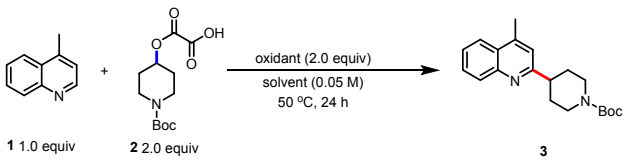
Scheme 1. Methods for Minisci C–H Alkylation of *N*-Heteroarenes.



We speculated that alkyl oxalates could be used for this purpose. Reaction of alcohols with oxalyl chloride results in the generation of activated alcohols that can be used for radical

generation.[9] Recently, Macmillan's group reported that the relatively strong C–O bonds of alkyl oxalates can generally be cleaved to form sp^3 carbon radical fragments for the construction of C–C bonds.[10] Very recently, Overman's group describes the use of tert-alkyl oxalate salts, derived from tertiary alcohols, to introduce tertiary substituents into a variety of heterocyclic substrates.[11] Our group is interested in Minisci reactions, and we recently reported C–H alkylation reactions of heteroarenes with alkyl halides.[12] On the basis of recent successful examples of C–H alkylation reactions of *N*-heteroarenes with alkylcarboxylic acids,[13] we envisioned that a simple, mild protocol for metal-, photocatalyst-, and light-free C–H alkylation of heteroarenes could be achieved by using alkyl oxalates as alcohol-activating groups. In addition, we wanted to use an environmentally benign oxidant and avoid the need for high temperatures and large excesses of the *N*-heteroarenes and alkyl oxalates. Herein, we report a protocol for Minisci C–H alkylation of *N*-heteroarenes with alkyl oxalates derived from primary, secondary, and tertiary alcohols (Scheme 1C). The high efficiency, broad substrate scope, excellent functional group tolerance, and mildness of this protocol make it particularly suitable for late-stage functionalization of complex nitrogen-containing natural products and drugs.

Table 1. Optimization of Reaction Conditions[a]

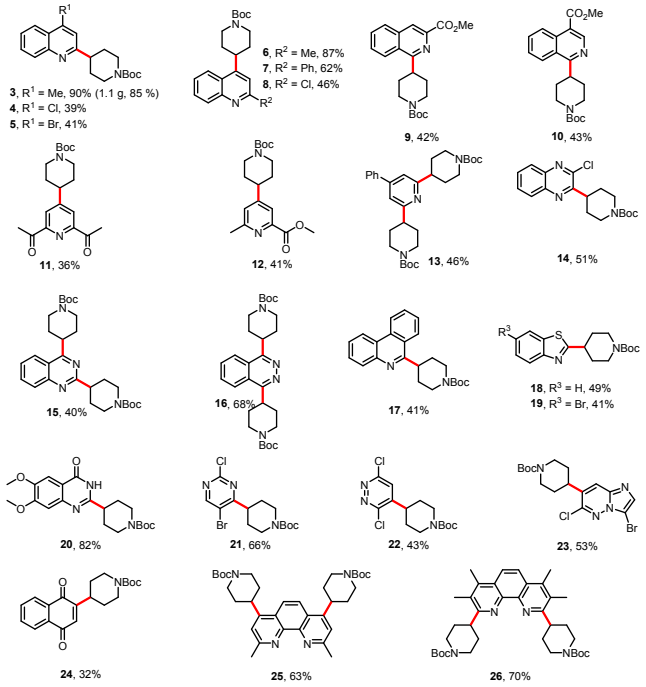


entry	oxidant	solvent	yield (%)[b]
1	$(NH_4)_2S_2O_8$	toluene	<5%
2	$(NH_4)_2S_2O_8$	CH_3CN	NR
3	$(NH_4)_2S_2O_8$	DCE	NR
4	$(NH_4)_2S_2O_8$	DMSO	84
5	$Na_2S_2O_8$	DMSO	52
6	$K_2S_2O_8$	DMSO	28
7	$PhI(CH_3CO_2)_2$	DMSO	<5
8	$PhI(CF_3CO_2)_2$	DMSO	<5
9	$(NH_4)_2S_2O_8$	100:1 DMSO/H_2O	88
10	$(NH_4)_2S_2O_8$	10:1 DMSO/H_2O	91
11	**$(NH_4)_2S_2O_8$**	**5:1 DMSO/H_2O**	**93 (90)[c]**
12[d]	$(NH_4)_2S_2O_8F_6$	5:1 DMSO/H_2O	39

[a]General conditions, unless otherwise noted: **1** (0.3 mmol), **2** (0.6 mmol), oxidant (0.6 mmol), and DMSO (6 mL) under air atmosphere. [b]Determined by ^1H NMR spectroscopy using dibromomethane as an internal standard. NR = no reaction. [c]Isolated yields are given. [d]Reaction performed at room temperature.

We began by investigating the alkylation reaction between lepidine (**1**) and *N*-Boc-4-hydroxypiperidine monooxalate (**2**; formed in situ from *N*-Boc-4-hydroxypiperidine, oxalyl chloride, and water) in the presence of $(NH_4)_2S_2O_8$ in toluene at 50 °C for 24 h (Table 1). Unfortunately, the yield of desired product **3** under these conditions was poor (entry 1). However, when we tested various other solvents (entries 2–4), we found that **3** could be obtained in 84% yield in DMSO (entry 4). In fact, DMSO was the only solvent in which the reaction proceeded; none of the typical Minisci solvents worked. The use of a different persulfate (sodium persulfate or potassium persulfate) had a deleterious effect on the yield (entries 5 and 6). Although strongly oxidizing hypervalent iodine(III) reagents are often used in classical Minisci reactions,[4d,7,14] we obtained poor yields of **3** with these reagents, and the reactions gave mainly the quinoline-4-carbaldehyde by-product (entries 7 and 8). We tried adding various amounts of H_2O as a co-solvent to increase the solubility of $(NH_4)_2S_2O_8$ in the solvent, and these experiments revealed that 5:1 (v/v) DMSO/H_2O was optimal (entries 9–11). Finally, performing the reaction at room temperature rather than at 50 °C decreased the yield to 39% (entry 12). It should be noted that the absence of exogenous strong acid (e.g., H_2SO_4, TFA, or HCl which is often employed in traditional Minisci conditions) enabled the reaction to proceed under such mild conditions.

Scheme 2. Scope of the Reaction with Respect to the *N*-Heteroarene.[a]



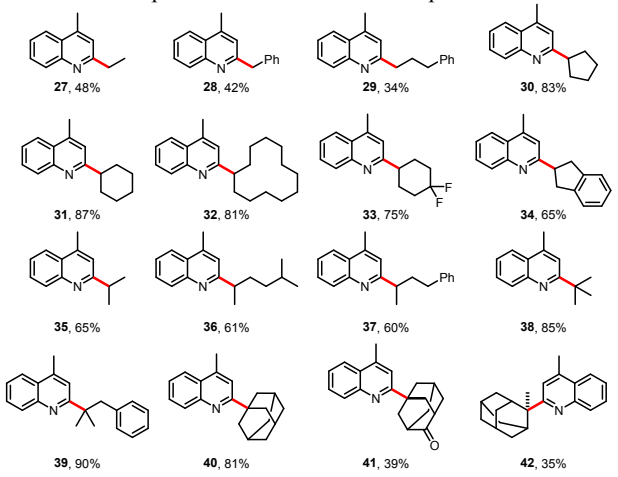
[a]Reactions were performed on a 0.3 mmol scale. Isolated yields are given. See Supplementary Information for experimental details.

With the optimized conditions in hand, we investigated the scope of the reaction with respect to the *N*-heteroarene (Scheme 2). Various electron-deficient heteroarenes were readily alkylated at the most electrophilic position with *N*-Boc-4-hydroxypiperidine monooxalate (**2**), giving the desired products in fair to excellent yields. Quinoline substrates with electron-withdrawing or electron-donating substituents underwent selective alkylation at C2 and C4, respectively (giving **3–8** in 39–90% yields). Reactions of **2** with 3-methoxycarbonyl- and 4-methoxycarbonyl-substituted isoquinolines afforded products of selective alkylation at C1 (**9** and **10**, respectively, in 42% and 43% yields). Notably, pyridine derivatives also participated in this reaction, giving moderate yields of products **11–13**. The protocol could also be used for *N*-heterocycles containing two nitrogen atoms: 2-chloroquinoxaline (**14**, 51%), quinazoline (**15**, 40%), and phthalazine (**16**, 68%). Phenanthridine (**17**, 41%), benzothiazoles (**18**, 49%; **19**, 41%), 4-

hydroxyquinazoline (**20**, 82%), pyrimidine (**21**, 66%), 3,6-dichloropyridazine (**22**, 43%), chloroimidazo[1,2-*b*]pyridazine (**23**, 53%), and 1,4-naphthoquinone (**24**, 32%) were also acceptable substrates. Notably, the reaction could be used to modify commercially available phenanthroline ligands, as demonstrated by the bialkylation with **2** to afford fair to good yields of **25**–**26**. The selective bialkylation of these phenanthroline ligands suggests that this protocol may find applications in the synthesis of ligands for catalysis. The reaction between **1** and **2** could be carried out on a gram scale with no decrease in the yield of **3**.

Next, we explored the scope of the alkylation reaction with respect to the alcohol by using lepidine (**1**) as the heteroarene (Scheme 3). To our delight, both cyclic and acyclic primary, secondary, and tertiary alcohols were found to be amenable to the standard reaction conditions, affording fair to excellent yields of functionalized lepidine derivatives. For example, linear primary alcohols afforded corresponding alkylated heteroarenes **27**–**29** in 34–48% yields. Alkylation reactions of secondary and tertiary alcohols also proceeded under the standard conditions to afford corresponding alkylated heteroarenes **30**–**42** in moderate to excellent yields. Notably, fluorine heteroatoms were tolerated, which is typically not the case for Minisci reactions.[15] The relatively low yields of compounds **41** and **42** compared to **40** may be due to the addition of alkyl radicals to carbonyl group and relatively large steric hindrance, respectively.

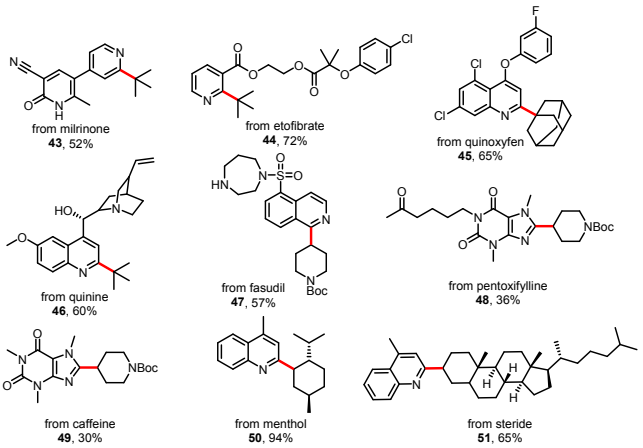
Scheme 3. Scope of the Reaction with Respect to the Alcohol.[a]



[a]Reactions were performed on a 0.3 mmol scale. Isolated yields are given. See Supplementary Information for experimental details.

As shown in Scheme 4, our Minisci C–H alkylation protocol could be readily used to functionalize complex natural products and drug molecules.[4,16] For instance, milrinone, a phosphodiesterase 3 inhibitor and vasodilator, could be alkylated to afford a moderate yield of **43**. Etofibrate, which contains clofibrate and niacin moieties, was selectively alkylated on the pyridine ring to give **44** in 72% yield. The fungicide quinoxyfen was alkylated at C2 of the quinoline ring to give **45** in good yield. Quinine, an alkaloid with a free OH group as well as amine and vinyl groups, could be selectively alkylated at the C2 position (**46**). Fasudil, a potent vasodilator, was selectively alkylated at C1 to give a fair yield of **47**. Notably, the analgesic pentoxifylline was transformed into alkylated analogue **48** in 36% yield. Caffeine, a challenging substrate for previously reported Minisci protocols, could be selectively alkylated at C2 to afford **49**. Naturally occurring alcohols L-menthol and steride were successfully alkylated to afford **50** and **51**, respectively, in good yields. Because alcohols are readily available and inexpensive, this new Minisci protocol may prove highly useful in drug discovery research.[17]

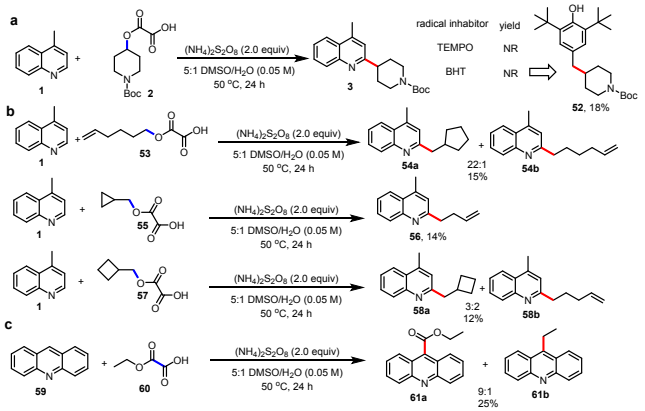
Scheme 4. Use of the Minisci C–H Alkylation Protocol for Functionalization of Natural Products and Drug Molecules.[a]



[a]Reactions were performed on a 0.3 mmol scale. Isolated yields are given. See Supplementary Information for experimental details.

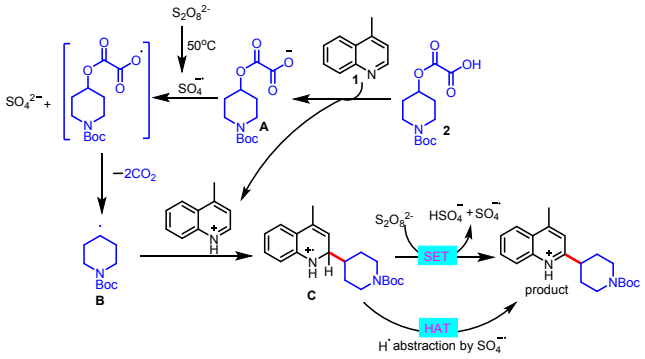
Having explored the substrate scope and utility of the reaction, we turned our attention to the mechanism. When a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT), was present in a reaction mixture containing **1** and **2**, the formation of **3** was completely inhibited; and instead the corresponding product of radical trapping, *tert*-butyl 4-(3,5-di-*tert*-butyl-4-hydroxybenzyl)piperidine-1-carboxylate (**52**), was isolated in 18% yield (Scheme 5a). To gain additional information about the mechanism, we carried out radical clock experiments (Scheme 5b).[12] Alkylation of **1** with 2-(hex-5-en-1-yloxy)-2-oxoacetic acid (**53**) resulted in 5-*exo*-*trig* cyclization prior to heteroarene addition and afforded a 22:1 mixture of **54a** and **54b**. Alkylation of **1** with 2-(cyclopropylmethoxy)-2-oxoacetic acid (**55**) under the standard conditions gave ring-opened product **56** in 14% yield. In the reaction of **1** with 2-(cyclobutylmethoxy)-2-oxoacetic acid **57**, the cyclobutane ring remained partly unopened, and **58a** and **58b** were obtained in a 3:2 ratio. When we use acridine (**59**) as N-heteroarene and 2-ethoxy-2-oxoacetic acid (**60**) as as radical sources, a 9:1 mixture of acyl radical addition product (**61a**) and alkyl radical addition product (**61b**) was afforded in 25% yield. These experiments clearly point to a radical pathway.

Scheme 5. Mechanistic Experiments.



On the basis of these observations and literature reports,[11] we propose the mechanism depicted in Scheme 6. The standard Minisci reaction is thought to commence with decomposition of persulfate $S_2O_8^{2-}$ to sulfate radical anion ($SO_4^{-\bullet}$), traditionally under metal mediation or photolysis.[3,13a] However, we believe that in our case, the decomposition under mild conditions without catalysis is achievable because the rate of decomposition is solvent-dependent, and $S_2O_8^{2-}$ has in fact been reported to decompose much more readily in DMSO than in other solvents.[18] The sulfate radical anion can then oxidize *N*-Boc-4-hydroxypiperidine monooxalate anion (**A**) to form alkyl radical **B** and extrude two equiv of CO_2. Radical **B** then adds to the protonated electron-deficient heteroarene via a Minisci-type pathway to afford radical cation **C**. Product **3** can form either via H radical abstraction by sulfate radical anion or via a single electron transfer (SET) reaction with persulfate.

Scheme 6. Proposed Mechanism for Direct C–H Alkylation of *N*-Heteroarenes.



In conclusion, we have developed a mild protocol for Minisci C–H alkylation of *N*-heteroarenes with readily available, inexpensive alcohols as the alkyl radical sources without the need for a metal, a photocatalyst, or light. A broad range of cyclic and acyclic primary, secondary, and tertiary alkyl groups can be efficiently incorporated into various *N*-heteroarenes, and the protocol is scalable to the gram level. The high efficiency and broad substrate scope of the reaction, and the fact that neither high temperatures nor large excesses of the alkyl oxalates are required, make the procedure suitable for late-stage C–H alkylation of complex molecules, as demonstrated by the functionalization of various nitrogen-containing natural products and drugs.

EXPERIMENTAL SECTION

General Method and Materials. Reagents were purchased from commercial sources and were used as received. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance 400 Ultrashield NMR spectrometers. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. High-resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 microscope melting point apparatus and are uncorrected. Conversion was monitored by thin layer chromatography (TLC). Flash column chromatography was performed over silica gel (100-200 mesh).

Preparation of Oxalates from Alcohols. The oxalate was synthesized according to literature report.[7,10,11] The spectral data of the oxalate is consistent with the literature data. A round-bottom flaskwas charged with alcohol (10 g, 49.7 mmol 1.0 equiv) followed by the addition of Et_2O (250 mL) and dichloromethane (80 mL). The solution was cooled to 0 °C. Next, oxalyl chloride (8.41 mL, 99.0 mmol, 2.0 equiv) was added dropwise. The homogeneous reaction mixture was allowed to warm to ambient temperature and stir for 18 h. The reaction was cooled to 0 °C and quenched by slow addition of H_2O (100 mL). After stirring for 1 h at ambient temperature, the resulting mixture was transferred to a separatory funnel, and the aqueous layer mixture was extracted with three portions of Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure affording the title compound. All the oxalates were used without further purification.

Experimental Procedures and Product Characterization

General Procedure for the alkylation of N-heteroarenes. To a 15 mL glass vial was added heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.6 mmol, 2.0 equiv), $(NH_4)_2S_2O_8$ (137 mg, 0.6 mmol, 2.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. The reaction mixture was sealed with PTFE cap and then stirred rapidly at 50 °C for 24 h (heating mantle). The mixture was diluted with 20 mL of aqueous 1 M $NaHCO_3$ solution, and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.

Product Characterization

*tert-butyl 4-(4-methylquinolin-2-yl)piperidine-1-carboxylate **(3)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] White solid (88.0 mg, 90%). M.p. = 59 – 60 °C. R_f 0.50 (Petroleum ether/EtOAc, 5/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.56 – 7.43 (m, 1H), 7.13 (s, 1H), 4.30 (s, 2H), 3.00 (tt, J = 12.0, 3.6 Hz, 1H), 2.94 – 2.79 (m, 2H), 2.66 (s, 3H), 2.00 – 1.91 (m, 2H), 1.84 (ddd, J = 25.2, 12.4, 4.4 Hz, 2H), 1.49 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.2, 154.8, 147.6, 144.6, 129.5, 129.1, 127.1, 125.7, 123.6, 120.0, 79.3, 45.4, 44.1, 31.6, 28.5, 18.8. **HRMS** (ESI) calcd for $C_{20}H_{27}N_2O_2$ [M + H]$^+$ 327.2067, found 327.2069.

*tert-butyl 4-(4-chloroquinolin-2-yl)piperidine-1-carboxylate **(4)***. According to the *general procedure*. Colorless oil (40.5 mg, 39%). R_f 0.40 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.66 – 7.55 (m, 1H), 7.41 (s, 1H), 4.31 (s, 2H), 3.15 – 2.78 (m, 3H), 1.99 (d, J = 12.4 Hz, 2H), 1.91 – 1.76 (m, 2H), 1.50 (s, 9H). **^{13}C NMR{^{1}H}** (100 MHz, $CDCl_3$) δ 164.7, 154.9, 148.8, 143.0, 130.5, 129.5, 127.0, 125.3, 124.0, 119.7, 79.6, 45.4, 43.9, 31.6, 28.6. **HRMS** (ESI) calcd for $C_{19}H_{24}ClN_2O_2$ [M + H]$^+$ 347.1521, found 347.1520.

*tert-butyl 4-(4-bromoquinolin-2-yl)piperidine-1-carboxylate **(5)***. According to the *general procedure*. Colorless oil (48.0 mg, 41%). R_f 0.20 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 7.2 Hz, 1H), 7.64 – 7.52 (m, 2H), 4.29 (s, 2H), 3.02 (tt, J = 12.0, 3.6 Hz, 1H), 2.89 (s, 2H), 2.06 – 1.93 (m, 2H), 1.90 – 1.76 (m, 2H), 1.49 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.7, 154.9, 148.6, 134.6, 130.5, 129.6, 127.3, 126.7, 123.6, 79.6, 45.3, 44.0, 31.6, 28.6. **HRMS** (ESI) calcd for $C_{19}H_{24}BrN_2O_2$ $[M + H]^+$ 391.1016, found 391.1012.

*tert-butyl 4-(2-methylquinolin-4-yl)piperidine-1-carboxylate **(6)***. According to the *general procedure*. White solid (85.1 mg, 87%). M.p. = 108 – 109 °C. R_f 0.30 (Petroleum ether/EtOAc, 5/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 11.6, 8.4 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.14 (s, 1H), 4.34 (s, 2H), 3.44 (ddd, J = 12.0, 9.2, 3.2 Hz, 1H), 2.95 (s, 2H), 2.72 (s, 3H), 1.95 (d, J = 12.8 Hz, 2H), 1.85 – 1.68 (m, 2H), 1.50 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 158.9, 154.8, 151.0, 148.3, 129.8, 129.0, 125.6, 124.9, 122.4, 118.5, 79.7, 44.3, 37.2, 32.4, 28.5, 25.6. **HRMS** (ESI) calcd for $C_{20}H_{27}N_2O_2$ $[M + H]^+$ 327.2067, found 327.2069.

*tert-butyl 4-(2-phenylquinolin-4-yl)piperidine-1-carboxylate **(7)***. According to the *general procedure*. White solid (72.2 mg, 62%). M.p. = 124 – 125 °C R_f 0.35 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 7.2 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.58 – 7.49 (m, 3H), 7.45 (t, J = 7.2 Hz, 1H), 4.37 (s, 2H), 3.50 (ddd, J = 12.0, 9.2, 3.2 Hz, 1H), 2.97 (s, 2H), 2.01 (d, J = 12.8 Hz, 2H), 1.92 – 1.74 (m, 2H), 1.51 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.4, 154.8, 151.6, 148.7, 140.0, 130.9, 129.3, 129.3, 128.9, 127.6, 126.2, 125.6, 122.5, 115.6, 79.8, 44.4, 37.5, 32.5, 28.6. **HRMS** (ESI) calcd for $C_{25}H_{29}N_2O_2$ $[M + H]^+$ 389.2224, found 389.2221.

*tert-butyl 4-(2-chloroquinolin-4-yl)piperidine-1-carboxylate **(8)***. According to the *general procedure*. White solid (47.7 mg, 46%). M.p. = 92 – 93 °C. R_f 0.20 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 7.73 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.24 (s, 1H), 4.35 (s, 2H), 3.45 (t, J = 11.6 Hz, 1H), 2.95 (s, 2H), 1.97 (d, J = 12.4 Hz, 2H), 1.73 (ddd, J = 15.6, 12.4, 3.2 Hz, 2H), 1.50 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 154.8, 154.6, 151.1, 148.3, 130.3, 129.8, 126.9, 125.4, 122.8, 118.9, 79.9, 44.4, 37.5, 32.2, 28.6. **HRMS** (ESI) calcd for $C_{19}H_{24}ClN_2O_2$ $[M + H]^+$ 347.1521, found 347.1520.

*methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)isoquinoline-3-carboxylate **(9)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[4d] White solid (46.6 mg, 42%). M.p. = 127 – 128 °C. R_f 0.60 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.29 – 8.21 (m, 1H), 8.00 – 7.94 (m, 1H), 7.74 (p, J = 6.8 Hz, 2H), 4.33 (s, 2H), 4.03 (s, 3H), 3.79 – 3.63 (m, 1H), 3.00 (t, J = 11.6 Hz, 2H), 2.16 (s, 2H), 1.96 (d, J = 12.8 Hz, 2H), 1.50 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.8, 164.0, 154.8, 140.8, 136.2, 130.4, 129.4, 129.3, 127.7, 124.6, 122.9, 79.5, 52.8, 44.1, 40.2, 31.2, 28.6.
HRMS (ESI) calcd for $C_{21}H_{27}N_2O_4$ $[M + H]^+$ 371.1965, found 371.1960

*methyl 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)isoquinoline-4-carboxylate **(10)***. According to the *general procedure*. White solid (47.7 mg, 43%). M.p. = 110 – 111 °C. R_f 0.60 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.99 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 4.33 (s, 2H), 4.01 (s, 3H), 3.75 (dd, J = 15.6, 8.4 Hz, 1H), 2.98 (s, 2H), 2.04 (s, 2H), 1.92 (d, J = 10.0 Hz, 2H), 1.50 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.4, 167.1, 154.7, 145.8, 134.3, 131.3, 127.4, 125.9, 125.8, 124.5, 119.0, 79.4, 52.2, 44.3, 40.2, 31.3, 28.5. **HRMS** (ESI) calcd for $C_{21}H_{27}N_2O_4$ $[M + H]^+$ 371.1965, found 371.1964.

*tert-butyl 4-(2,6-diacetylpyridin-4-yl)piperidine-1-carboxylate **(11)***. According to the *general procedure*. Colorless oil (37.4 mg, 36%). R_f 0.25 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 4.27 (s, 2H), 3.73 – 3.65 (m, 1H), 2.86 (s, 2H), 2.79 (s, 3H), 2.75 (s, 3H), 1.83 (d, J = 12.8 Hz, 2H), 1.67 – 1.56 (m, 2H), 1.49 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 202.1, 199.2, 154.8, 151.1, 150.3, 145.4, 136.6, 124.0, 79.7, 44.3, 41.3, 37.1, 32.7, 28.8, 28.6, 28.5, 25.6. **HRMS** (ESI) calcd for $C_{19}H_{26}N_2NaO_4$ $[M + Na]^+$ 369.1785, found 369.1781.

*methyl 4-(1-(tert-butoxycarbonyl)piperidin-4-yl)-6-methylpicolinate **(12)**.* According to the *general procedure*. White solid (41.1 mg, 41%). M.p. = 95 – 96 °C. R_f 0.25 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.24 (s, 2H), 3.90 (s, 3H), 3.76 – 3.64 (m, 1H), 2.85 (s, 2H), 2.55 (s, 3H), 1.93 (dt, J = 21.2, 10.4 Hz, 2H), 1.75 (d, J = 12.4 Hz, 2H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.4, 164.8, 161.6, 154.9, 138.6, 121.9, 120.4, 79.2, 52.2, 44.3, 40.8, 31.4, 28.6, 24.9. **HRMS** (ESI) calcd for $C_{18}H_{27}N_2O_4$ $[M + H]^+$ 335.1965, found 335.1963.

*di-tert-butyl 4,4'-(4-phenylpyridine-2,6-diyl)bis(piperidine-1-carboxylate) **(13)***. According to the *general procedure*. Heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.9 mmol, 3.0 equiv), $(NH_4)_2S_2O_8$ (205 mg, 0.9 mmol, 3.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. White solid (71.9 mg, 46%). M.p. = 115 – 116 °C. R_f 0.40 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.52 – 7.38 (m, 3H), 7.19 (s, 2H), 4.26 (s, 4H), 3.01 – 2.76 (m, 6H), 1.96 (d, J = 12.4 Hz, 4H), 1.84 – 1.70 (m, 4H), 1.49 (s, 18H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.5, 155.0, 149.6, 139.1, 129.1, 128.9, 127.2, 116.8, 79.5, 44.7, 44.2, 31.9, 28.6. **HRMS** (ESI) calcd for $C_{31}H_{44}N_3O_4$ $[M + H]^+$ 522.3326, found 522.3331.

*tert-butyl 4-(3-chloroquinoxalin-2-yl)piperidine-1-carboxylate **(14)***. According to the *general procedure*. Yellow solid (53.1 mg, 51%). M.p. = 126 – 127 °C. R_f 0.60 (Petroleum ether/EtOAc, 5/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 8.02 (m, 1H), 8.01 – 7.95 (m, 1H), 7.79 – 7.70 (m, 2H), 4.33 (s, 2H), 3.50 (ddd, J = 15.2, 11.2, 4.0 Hz, 1H), 2.94 (s, 2H), 2.04 – 1.86 (m, 4H), 1.50 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.2, 154.8, 147.1, 141.1, 140.8, 130.3, 130.2, 128.9, 128.2, 79.6, 43.7, 40.8, 30.2, 28.6. **HRMS** (ESI) calcd for $C_{18}H_{23}ClN_3O_2$ $[M + H]^+$ 348.1473, found 348.1472.

*di-tert-butyl 4,4'-(quinazoline-2,4-diyl)bis(piperidine-1-carboxylate) **(15)***. According to the *general procedure*. Heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.9 mmol, 3.0 equiv), $(NH_4)_2S_2O_8$ (205 mg, 0.9 mmol, 3.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. White solid (59.5 mg, 40%). M.p. = 76 – 77 °C. R_f 0.20 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 2H), 7.95 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 4.31 (s, 4H), 3.71 (t, J = 10.8 Hz, 1H), 3.32 (t, J = 10.4 Hz, 1H), 3.08 – 2.86 (m, 4H), 2.12 – 1.82 (m, 8H), 1.50 (d, J = 5.6 Hz, 18H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.9, 168.4, 155.1, 154.9, 150.7, 133.4, 129.2, 126.8, 123.7, 121.5, 79.7, 79.4, 45.8, 44.3, 39.4, 30.9, 28.6. **HRMS** (ESI) calcd for $C_{28}H_{41}N_4O_4$ $[M + H]^+$ 497.3122, found 497.3116.

*di-tert-butyl 4,4'-(phthalazine-1,4-diyl)bis(piperidine-1-carboxylate) **(16)***. According to the *general procedure*. Heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.9 mmol, 3.0 equiv), $(NH_4)_2S_2O_8$ (205 mg, 0.9 mmol, 3.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. Yellow sollid (101.2 mg, 68%). M.p. = 55 – 56 °C. R_f 0.20 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 6.4, 3.2 Hz, 2H), 7.92 (dd, J = 6.4, 3.2 Hz, 2H), 4.33 (s, 4H), 3.92 – 3.82 (m, 1H), 3.73 (dd, J = 12.8, 6.4 Hz, 1H), 3.06 – 2.93 (m, 4H), 2.27 – 1.96 (m, 8H), 1.50 (d, J = 3.2 Hz, 18H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.5, 154.8, 131.7, 124.8, 124.0, 79.5, 43.9, 38.7, 30.9, 28.5. **HRMS** (ESI) calcd for $C_{28}H_{41}N_4O_4$ $[M + H]^+$ 497.3122, found 497.3119.

*tert-butyl 4-(phenanthridin-6-yl)piperidine-1-carboxylate **(17)***. According to the *general procedure*. White solid (44.5 mg, 41%). M.p. = 136 – 137 °C. R_f 0.30 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.4 Hz, 1H), 8.53 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.82 (t, J = 7.2 Hz, 1H), 7.70 (ddd, J = 11.6, 5.2, 2.4 Hz, 2H), 7.64 – 7.57 (m, 1H), 4.35 (s, 2H), 3.75 (ddd, J = 14.8, 11.2, 3.6 Hz, 1H), 3.02 (s, 2H), 2.26 – 1.92 (m, 4H), 1.51 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.2, 154.9, 143.8, 133.2, 130.2, 130.1, 128.7, 127.4, 126.6, 125.3, 124.6, 123.5, 122.9, 121.9, 79.5, 44.5, 40.1, 31.3, 28.7. **HRMS** (ESI) calcd for $C_{23}H_{27}N_2O_2$ [M + H]$^+$ 363.2067, found 363.2063.

*tert-butyl 4-(benzo[d]thiazol-2-yl)piperidine-1-carboxylate **(18)***. According to the *general procedure*. White solid (46.7 mg, 49%). M.p. = 72 – 73 °C. R_f 0.20 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 4.23 (s, 2H), 3.25 (t, J = 11.6 Hz, 1H), 2.92 (t, J = 11.6 Hz, 2H), 2.15 (d, J = 12.4 Hz, 2H), 1.85 (ddd, J = 15.6, 12.4, 4.0 Hz, 2H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.2, 154.8, 153.2, 134.6, 126.1, 124.9, 122.8, 121.7, 79.8, 43.7, 41.6, 32.2, 28.6. **HRMS** (ESI) calcd for $C_{17}H_{23}N_2O_2S$ [M + H]$^+$ 319.1475, found 319.1470.

*tert-butyl 4-(6-bromobenzo[d]thiazol-2-yl)piperidine-1-carboxylate **(19)***. According to the *general procedure*. Yellow solid (48.7 mg, 41%). M.p. = 83 – 84 °C. R_f 0.40 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 8.8, 1.6 Hz, 1H), 4.23 (s, 2H), 3.23 (ddd, J = 11.6, 8.0, 3.6 Hz, 1H), 2.92 (s, 2H), 2.15 (d, J = 12.4 Hz, 2H), 1.92 – 1.76 (m, 2H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.8, 154.8, 152.1, 136.3, 129.6, 124.3, 123.9, 118.5, 79.8, 43.6, 41.6, 32.1, 28.6. **HRMS** (ESI) calcd for $C_{17}H_{22}BrN_2O_2S$ [M + H]$^+$ 397.0580, found 397.0577.

*tert-butyl 4-(6,7-dimethoxy-4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **(20)***. According to the *general procedure*. White solid (95.7 mg, 82%). M.p. = 199 – 200 °C. R_f 0.40 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.16 (s, 1H), 7.59 (s, 1H), 7.12 (s, 1H), 4.30 (s, 2H), 4.03 (d, J = 4.0 Hz, 6H), 3.07 – 2.80 (m, 3H), 2.13 – 1.87 (m, 4H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.7, 157.3, 155.5, 154.8, 149.0, 146.0, 113.9, 108.0, 105.1, 79.7, 56.4, 43.7, 42.2, 29.8, 28.6. **HRMS** (ESI) calcd for $C_{20}H_{28}N_3O_5$ [M + H]$^+$ 390.2023, found 390.2022.

*tert-butyl 4-(5-bromo-2-chloropyrimidin-4-yl)piperidine-1-carboxylate **(21)***. According to the *general procedure*. White solid (74.3 mg, 66%). M.p. = 87 – 88 °C. R_f 0.30 (Petroleum ether/EtOAc, 15/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 4.29 (s, 2H), 3.29 – 3.15 (m, 1H), 2.84 (s, 2H), 1.82 (s, 4H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.4, 160.8, 159.9, 154.6, 119.0, 79.7, 43.9, 42.4, 29.4, 28.5. **HRMS** (ESI) calcd for $C_{14}H_{19}BrClN_3NaO_2$ [M + Na]$^+$ 398.0241, found 398.0235.

*tert-butyl 4-(3,6-dichloropyridazin-4-yl)piperidine-1-carboxylate **(22)***. According to the *general procedure*. Yellow solid (42.7 mg, 43%). M.p. = 91 – 92 °C. R_f 0.50 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 4.32 (s, 2H), 3.04 (tt, J = 12.0, 3.2 Hz, 1H), 2.86 (s, 2H), 1.94 (d, J = 12.8 Hz, 2H), 1.55 – 1.51 (m, 2H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.5, 156.4, 154.5, 146.7, 127.3, 80.0, 43.6, 38.6, 30.6, 28.5. **HRMS** (ESI) calcd for $C_{14}H_{20}Cl_2N_3O_2$ [M + H]$^+$ 332.0927, found 332.0923.

*tert-butyl 4-(3-bromo-6-chloroimidazo[1,2-b]pyridazin-7-yl)piperidine-1-carboxylate **(23)***. According to the *general procedure*. Yellow solid (65.8 mg, 53%). M.p. = 74 – 75 °C. R_f 0.60 (Petroleum ether/EtOAc, 3/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 6.91 (s, 1H), 4.31 (s, 2H), 3.50 (tt, J = 12.4, 3.2 Hz, 1H), 2.93 (s, 2H), 2.10 – 1.98 (m, 2H), 1.78 – 1.65 (m, 2H), 1.49 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 154.7, 148.5, 146.2, 138.4, 133.8, 115.2, 101.6, 79.9, 43.7, 36.8, 30.9, 28.6. **HRMS** (ESI) calcd for $C_{16}H_{21}BrClN_4O_2$ [M + H]$^+$ 415.0531, found 415.0534.

*tert-butyl 4-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)piperidine-1-carboxylate **(24)***. According to the *general procedure*. Yellow oil (32.7 mg, 32%). R_f 0.30 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 – 8.01 (m, 2H), 7.75 (dd, J = 5.6, 3.2 Hz, 2H), 6.73 (s, 1H), 4.25 (s, 2H), 3.07 (ddd, J = 12.0, 9.2, 2.8 Hz, 1H), 2.86 (s, 2H), 1.82 (d, J = 12.8 Hz, 2H), 1.52 – 1.44 (m, 11H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 185.3, 184.7, 154.9, 154.3, 134.0, 133.9, 133.6, 132.5, 132.0, 126.9, 126.2, 79.9, 44.1, 35.3, 31.1, 28.6. **HRMS** (ESI) calcd for $C_{20}H_{23}NNaO_4$ [M + Na]$^+$ 364.1519, found 364.1512**.**

*di-tert-butyl 4,4'-(2,9-dimethyl-1,10-phenanthroline-4,7-diyl)bis(piperidine-1-carboxylate) **(25)***. According to the *general procedure*. Heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.9 mmol, 3.0 equiv), $(NH_4)_2S_2O_8$ (205 mg, 0.9 mmol, 3.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. Yellow oil (108.5 mg, 63%). R_f 0.40 (CH_2Cl_2/MeOH, 30/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.34 (s, 2H), 4.36 (s, 4H), 3.50 (t, J = 12.0 Hz, 2H), 3.03 – 2.87 (m, 10H), 2.01 (d, J = 11.2 Hz, 4H), 1.79 (d, J = 9.6 Hz, 4H), 1.51 (s, 18H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 159.4, 154.9, 150.9, 146.4, 124.4, 120.2, 120.0, 79.9, 44.4, 37.7, 32.6, 28.6, 26.4. **HRMS** (ESI) calcd for $C_{34}H_{47}N_4O_4$ [M + H]$^+$ 575.3592, found 575.3582.

*di-tert-butyl 4,4'-(3,4,7,8-tetramethyl-1,10-phenanthroline-2,9-diyl)bis(piperidine-1-carboxylate) **(26)***. According to the *general procedure*. Heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.9 mmol, 3.0 equiv), $(NH_4)_2S_2O_8$ (205 mg, 0.9 mmol, 3.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. White solid (126.4 mg, 70%). M.p. = 82 – 83 °C. R_f 0.60 (CH_2Cl_2/MeOH, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (s, 2H), 4.28 (d, J = 11.2 Hz, 4H), 3.34 (s, 2H), 3.05 (s, 4H), 2.66 (s, 6H), 2.50 (s, 6H), 2.35 – 1.94 (m, 8H), 1.50 (s, 18H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 162.0, 155.3, 143.7, 141.3, 128.0, 125.9, 121.6, 79.2, 44.6, 41.7, 30.6, 28.7, 15.3, 15.1. **HRMS** (ESI) calcd for $C_{36}H_{51}N_4O_4$ [M + H]$^+$ 603.3905, found 603.3900.

*2-ethyl-4-methylquinoline **(27)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[4i] Colorless oil (24.6 mg, 48%). R_f 0.50 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 8.4, 0.8 Hz, 1H), 7.66 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.14 (s, 1H), 2.95 (q, J = 7.6 Hz, 2H), 2.66 (s, 3H), 1.38 (t, J = 7.6 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.8, 147.8, 144.4, 129.5, 129.1, 126.9, 125.5, 123.7, 121.6, 32.4, 18.8, 14.2. **HRMS** (ESI) calcd for $C_{12}H_{14}N$ [M + H]$^+$ 172.1121, found 172.1120.

*2-benzyl-4-methylquinoline **(28)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12]

Yellow oil (29.4 mg, 42%). R_f 0.30 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.95 – 7.87 (m, 1H), 7.72 – 7.63 (m, 1H), 7.56 – 7.45 (m, 1H), 7.34 – 7.26 (m, 4H), 7.25 – 7.19 (m, 1H), 7.05 (s, 1H), 4.29 (s, 2H), 2.58 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 160.9, 147.7, 144.7, 139.5, 129.6, 129.3, 129.3, 128.7, 127.0, 126.5, 125.8, 123.7, 122.3, 45.6, 18.8. **HRMS** (ESI) calcd for $C_{17}H_{16}N$ [M + H]$^+$ 234.1277, found 234.1276.

*4-methyl-2-(3-phenylpropyl)quinoline **(29)***. According to the *general procedure*. Heteroarene (0.3 mmol, 1.0 equiv), oxalate (0.9 mmol, 3.0 equiv), $(NH_4)_2S_2O_8$ (205 mg, 0.9 mmol, 3.0 equiv), 5.0 mL of DMSO and 1.0 mL of H_2O. Yellow oil (26.6 mg, 34%). R_f 0.30 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 7.13 (s, 1H), 3.03 – 2.91 (m, 2H), 2.74 (t, J =

7.6 Hz, 2H), 2.67 (s, 3H), 2.15 (dt, *J* = 15.6, 7.6 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 162.3, 147.9, 144.4, 142.3, 129.5, 129.2, 128.6, 128.5, 126.9, 125.9, 125.6, 123.7, 122.2, 38.9, 35.9, 31.7, 18.8. **HRMS** (ESI) calcd for $C_{19}H_{20}N$ $[M + H]^+$ 262.1590, found 262.1586.

2-cyclopentyl-4-methylquinoline ***(30)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] Yellow oil (52.5 mg, 83%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.04 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.52 – 7.44 (m, 1H), 7.17 (s, 1H), 3.41 – 3.27 (m, 1H), 2.67 (s, 3H), 2.17 (ddd, *J* = 10.8, 9.2, 2.4 Hz, 2H), 1.97 – 1.81 (m, 4H), 1.81 – 1.66 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 166.0, 147.6, 144.2, 129.5, 129.0, 127.1, 125.4, 123.6, 120.7, 48.9, 33.7, 26.1, 18.9. **HRMS** (ESI) calcd for $C_{15}H_{18}N$ $[M + H]^+$ 212.1434, found 212.1436.

2-cyclohexyl-4-methylquinoline ***(31)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] Yellow oil (58.7 mg, 87%). R_f 0.40 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.95 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.47 (m, 1H), 7.42 – 7.30 (m, 1H), 7.04 (s, 1H), 2.77 (tt, *J* = 12.0, 3.2 Hz, 1H), 2.54 (s, 3H), 1.97 – 1.86 (m, 2H), 1.78 (dd, *J* = 10.0, 2.8 Hz, 2H), 1.72 – 1.62 (m, 1H), 1.52 (ddd, *J* = 24.8, 12.4, 2.8 Hz, 2H), 1.42 – 1.29 (m, 2H), 1.28 – 1.19 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 166.5, 147.7, 144.2, 129.6, 128.9, 127.1, 125.4, 123.6, 120.3, 47.7, 32.9, 26.6, 26.2, 18.9. **HRMS** (ESI) calcd for $C_{16}H_{20}N$ $[M + H]^+$ 226.1590, found 226.1594.

2-cyclododecyl-4-methylquinoline ***(32)***. According to the *general procedure*. White solid (75.1 mg, 81%). M.p. = 72 – 73 °C.

R_f 0.60 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.06 (d, *J* = 8.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 7.12 (s, 1H), 3.09 (p, *J* = 6.8 Hz, 1H), 2.66 (s, 3H), 1.96 – 1.84 (m, 2H), 1.75 – 1.67 (m, 2H), 1.50 – 1.29 (m, 18H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 166.8, 147.8, 143.8, 129.8, 128.8, 127.1, 125.4, 123.6, 121.5, 43.2, 30.3, 24.1, 24.0, 23.8, 23.5, 23.0, 18.9. **HRMS** (ESI) calcd for $C_{22}H_{32}N$ $[M + H]^+$ 310.2529, found 310.2523.

2-(4,4-difluorocyclohexyl)-4-methylquinoline ***(33)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[13a] Yellow oil (58.7 mg, 75%). R_f 0.50 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.03 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 2.96 (t, *J* = 11.2 Hz, 1H), 2.69 (s, 3H), 2.27 (dt, *J* = 10.8, 7.6 Hz, 2H), 2.13 – 1.94 (m, 5H), 1.93 – 1.81 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 164.0, 147.7, 144.8, 129.7, 129.3, 127.2, 125.9, 123.7, 119.9, 45.2, 33.9 (dd, *J* = 25.1, 23.1 Hz), 28.9, 28.8, 18.9. **HRMS** (ESI) calcd for $C_{16}H_{18}F_2N$ $[M + H]^+$ 262.1402, found 262.1400.

2-(2,3-dihydro-1H-inden-2-yl)-4-methylquinoline ***(34)***. According to the *general procedure*. Yellow solid (50.5 mg, 65%). M.p. = 40 – 41 °C. R_f 0.50 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 3.2 Hz, 2H), 7.21 – 7.14 (m, 3H), 4.01 (p, *J* = 8.8 Hz, 1H), 3.42 (qd, *J* = 16.0, 8.8 Hz, 4H), 2.62 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 164.6, 147.6, 144.6, 142.9, 129.6, 129.2, 127.1, 126.6, 125.7, 124.5, 123.6, 120.6, 48.0, 39.8, 18.9. **HRMS** (ESI) calcd for $C_{19}H_{18}$ N $[M + H]^+$ 260.1434, found 260.1431.

2-isopropyl-4-methylquinoline ***(35)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] Yellow oil (36.1 mg, 65%). R_f 0.30 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.05 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.53 – 7.44 (m, 1H), 7.17 (s, 1H), 3.21 (hept, *J* = 7.2 Hz, 1H), 2.68 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 167.5, 147.7, 144.4, 129.6, 129.0, 127.1, 125.5, 123.7, 119.9, 37.4, 22.7, 18.9. **HRMS** (ESI) calcd for $C_{13}H_{16}N$ $[M + H]^+$ 186.1277, found 186.1276.

(R)-4-methyl-2-(5-methylhexan-2-yl)quinoline ***(36)***. According to the *general procedure*. Yellow oil (44.1 mg, 61%). R_f 0.60 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.06 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 3.07 – 2.93 (m, 1H), 2.67 (s, 3H), 1.81 (tdd, *J* = 12.8, 7.6, 5.2 Hz, 1H), 1.73 – 1.60 (m, 1H), 1.53 (tt, *J* = 13.2, 6.8 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.25 (dd, *J* = 12.0, 6.0 Hz, 1H), 1.13 – 1.01 (m, 1H), 0.84 (dd, *J* = 6.8, 3.2 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 167.0, 147.7, 144.2, 129.7, 128.9, 127.1, 125.4, 123.6, 120.2, 43.3, 37.1, 35.0, 28.3, 22.7, 20.9, 18.9. **HRMS** (ESI) calcd for $C_{17}H_{24}N$ $[M + H]^+$ 242.1903, found 242.1898.

(R)-4-methyl-2-(4-phenylbutan-2-yl)quinoline ***(37)***. According to the *general procedure*. Yellow oil (49.5 mg, 60%). R_f 0.40 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.08 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.16 – 7.11 (m, 4H), 3.16 – 3.02 (m, 1H), 2.71 – 2.63 (m, 4H), 2.58 – 2.47 (m, 1H), 2.19 (dtd, *J* = 10.4, 8.4, 5.6 Hz, 1H), 1.99 (ddd, *J* = 16.8, 12.8, 6.4 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 166.3, 147.8, 144.4, 142.6, 129.7, 129.0, 128.5, 128.3, 127.1, 125.7, 125.5, 123.7, 120.4, 42.6, 38.8, 34.1, 21.0, 18.9. **HRMS** (ESI) calcd for $C_{20}H_{22}N$ $[M + H]^+$ 276.1747, found 276.1744.

2-(tert-butyl)-4-methylquinoline ***(38)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] Colorless oil (50.7 mg, 85%). R_f 0.70 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.34 (s, 1H), 2.66 (s, 3H), 1.45 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 169.0, 147.5, 143.7, 130.1, 128.8, 126.7, 125.5, 123.5, 119.0, 38.0, 30.3, 19.1. **HRMS** (ESI) calcd for $C_{14}H_{18}N$ $[M + H]^+$ 200.1434, found 200.1431.

4-methyl-2-(2-methyl-1-phenylpropan-2-yl)quinoline ***(39)***. According to the *general procedure*. Yellow oil (74.3 mg, 90%). R_f 0.50 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.68 – 7.61 (m, 1H), 7.51 – 7.44 (m, 1H), 7.18 (s, 1H), 7.10 (dd, *J* = 6.4, 3.6 Hz, 3H), 6.91 (dd, *J* = 6.4, 2.8 Hz, 2H), 3.14 (s, 2H), 2.62 (s, 3H), 1.43 (s, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 167.6, 147.5, 143.5, 139.4, 130.6, 130.2, 128.8, 127.7, 126.7, 125.9, 125.6, 123.6, 119.7, 49.1, 42.2, 27.6, 19.0. **HRMS** (ESI) calcd for $C_{20}H_{22}N$ $[M + H]^+$ 276.1747, found 276.1744.

2-(adamantan-1-yl)-4-methylquinoline ***(40)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] White solid (67.3 mg, 81%). M.p. = 105 – 106 °C. R_f 0.65 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.33 (s, 1H), 2.69 (s, 3H), 2.20 – 2.08 (m, 9H), 1.84 (s, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 168.80, 147.68, 143.66, 130.11, 128.73, 126.84, 125.44, 123.53, 118.63, 41.95, 39.68, 37.05, 29.00, 19.09. **HRMS** (ESI) calcd for $C_{20}H_{24}N$ $[M + H]^+$ 278.1903, found 278.1900.

5-(4-methylquinolin-2-yl)adamantan-2-one ***(41)***. According to the *general procedure*. White solid (34.0 mg, 39%). M.p. = 130 – 131 °C. R_f 0.40 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.04 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.29 (s, 1H), 2.77 – 2.65 (m, 5H), 2.49 – 2.38 (m, 4H), 2.33 (s, 3H), 2.17 (d, *J* = 12.0 Hz, 2H), 2.08 (d, *J* = 12.4 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) *δ* 218.2, 165.6, 147.5, 144.3, 129.9, 129.0, 126.8, 125.8, 123.5, 118.0, 46.7, 43.2, 40.8, 39.3, 38.7, 28.2, 19.0.

HRMS (ESI) calcd for $C_{20}H_{22}NO$ $[M + H]^+$ 292.1696, found 292.1694.

*4-methyl-2-(2-methyladamantan-2-yl)quinoline **(42)***. According to the *general procedure*. White solid (30.6 mg, 35%). M.p. = 100 – 101 °C. R_f 0.40 (Petroleum ether/EtOAc, 10/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.29 (s, 1H), 2.75 – 2.58 (m, 5H), 2.26 (d, J = 12.4 Hz, 2H), 1.94 (s, 1H), 1.81 (dd, J = 24.0, 12.4 Hz, 4H), 1.73 – 1.66 (m, 3H), 1.62 (d, J = 12.4 Hz, 2H), 1.30 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.5, 147.9, 143.7, 130.0, 128.6, 126.5, 125.4, 123.5, 119.1, 46.7, 39.0, 34.7, 34.2, 33.3, 28.4, 28.1, 27.9, 19.2. **HRMS** (ESI) calcd for $C_{21}H_{26}N$ $[M + H]^+$ 292.2060, found 292.2055.

*2'-(tert-butyl)-2-methyl-6-oxo-1,6-dihydro-[3,4'-bipyridine]-5-carbonitrile **(43)***. According to the *general procedure*. White solid (41.7 mg, 52%). M.p. = 180 – 181 °C. R_f 0.60 (CH_2Cl_2/MeOH, 40/1). **^{1}H NMR** (400 MHz, MeOD) δ 8.53 (d, J = 5.2 Hz, 1H), 8.08 (s, 1H), 7.46 (s, 1H), 7.23 (d, J = 5.2 Hz, 1H), 2.37 (s, 3H), 1.40 (s, 9H). **^{13}C NMR{^{1}H}** (100 MHz, MeOD) δ 169.6, 161.1, 150.9, 149.6, 148.3, 145.1, 121.4, 120.0, 117.9, 115.1, 101.3, 37.1, 29.1, 17.1. **HRMS** (ESI) calcd for $C_{16}H_{18}N_3O$ $[M + H]^+$ 268.1444, found 268.1442.

*2-((2-(4-chlorophenoxy)-2-methylpropanoyl)oxy)ethyl 6-(tert-butyl)nicotinate **(44)***. According to the *general procedure*. Colorless oil (90.5 mg, 72%). R_f 0.65 (Petroleum ether/EtOAc, 5/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.09 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.4, 2.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.80 – 6.73 (m, 2H), 4.53 (q, J = 5.6 Hz, 4H), 1.60 (s, 6H), 1.39 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.4, 173.9 165.2, 154.0, 150.0, 137.3, 129.2, 127.3, 122.6, 120.3, 118.8, 79.4, 63.2, 62.5, 38.1, 30.1, 25.4. **HRMS** (ESI) calcd for $C_{22}H_{27}ClNO_5$ $[M + H]^+$ 420.1572, found 420.1575.

*2-(adamantan-1-yl)-5,7-dichloro-4-(3-fluorophenoxy)quinolone **(45)***. According to the *general procedure*. Colorless oil (86.0 mg, 65%). R_f 0.40 (Petroleum ether/EtOAc, 100/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.15 (dd, J = 11.2, 6.0 Hz, 2H), 7.11 – 7.06 (m, 2H), 6.74 (s, 1H), 2.08 (s, 3H), 1.94 – 1.91 (m, 6H), 1.80 – 1.71 (m, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.0, 162.1, 159.8 (d, J = 244 Hz), 151.4, 150.9, 134.6, 129.8, 128.7, 128.0, 121.7, 121.6, 117.2, 116.9, 116.9, 104.6, 41.6, 40.0, 36.8, 28.7. **HRMS** (ESI) calcd for $C_{25}H_{23}Cl_2FNO$ $[M + H]^+$ 442.1135, found 442.1136.

*(1S)-(2-(tert-butyl)-6-methoxyquinolin-4-yl)((1S,4S)-5-vinylquinuclidin-2-yl)methanol **(46)***. According to the *general procedure*. Yellow solid (68.4 mg, 60%). M.p. = 120 – 121 °C. R_f 0.30 (CH_2Cl_2/MeOH, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.61 (d, J = 9.2 Hz, 1H), 6.80 (dd, J = 9.2, 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.34 (s, 1H), 6.05 (s, 1H), 5.52 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.10 – 4.85 (m, 2H), 4.54 (t, J = 9.6 Hz, 1H), 3.49 (s, 3H), 3.41 (dd, J = 13.2, 10.8 Hz, 1H), 3.31 – 3.22 (m, 1H), 3.10 (td, J = 11.6, 5.6 Hz, 1H), 2.98 (dd, J = 13.2, 2.8 Hz, 1H), 2.67 (s, 1H), 2.26 (t, J = 10.8 Hz, 1H), 2.14 (dd, J = 13.2, 7.2 Hz, 1H), 2.06 (d, J = 2.4 Hz, 1H), 1.83 (t, J = 9.6 Hz, 1H), 1.47 (s, 9H), 1.33 – 1.28 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 165.7, 157.4, 143.3, 143.1, 137.4, 131.3, 123.2, 121.5, 117.3, 115.7, 99.0, 66.2, 60.3, 56.9, 54.9, 44.1, 37.9, 37.4, 30.3, 27.2, 24.4, 18.1. **HRMS** (ESI) calcd for $C_{24}H_{33}N_2O_2$ $[M + H]^+$ 381.2537, found 381.2543.

*tert-butyl 4-(5-((1,4-diazepan-1-yl)sulfonyl)isoquinolin-1-yl)piperidine-1-carboxylate **(47)***. According to the *general procedure*. Yellow oil (81.1 mg, 57%). R_f 0.20 (CH_2Cl_2/MeOH, 20/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 6.0 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.36 – 8.23 (m, 2H), 7.68 (t, J = 8.0 Hz, 1H), 4.32 (s, 2H), 3.72 (t, J = 10.8 Hz, 1H), 3.57 – 3.39 (m, 4H), 3.21 – 2.88 (m, 7H), 2.04 (s, 2H), 1.90 (dd, J = 14.4, 8.8 Hz, 4H), 1.49 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.5, 154.8, 143.9, 135.5, 132.4, 132.3, 129.8, 126.9, 125.5, 116.0, 79.5, 50.8, 50.2, 47.6, 47.4, 43.9, 40.3, 31.6, 30.9, 28.5. **HRMS** (ESI) calcd for $C_{24}H_{35}N_4O_4S$ $[M + H]^+$ 475.2374, found 475.2369.

*tert-butyl 4-(3,7-dimethyl-2,6-dioxo-1-(5-oxohexyl)-2,3,6,7-tetrahydro-1H-purin-8-yl)piperidine-1-carboxylate **(48)***. According to the *general procedure*. White solid (49.8 mg, 36%). M.p. = 128 – 129 °C. R_f 0.60 (CH_2Cl_2/MeOH, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.21 (s, 2H), 3.97 (t, J = 6.4 Hz, 3H), 3.92 (s, 3H), 3.51 (s, 3H), 2.85 (dd, J = 12.4, 8.8 Hz, 3H), 2.47 (t, J = 6.8 Hz, 2H), 2.11 (s, 3H), 1.90 – 1.76 (m, 4H), 1.64 – 1.60 (m, 3H), 1.45 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 208.8, 156.1, 155.4, 154.6, 151.5, 148.1, 107.4, 79.8, 43.3, 42.8, 40.7, 33.9, 31.6, 30.0, 29.9, 29.7, 28.5, 27.6, 21.1. **HRMS** (ESI) calcd for $C_{23}H_{36}N_5O_5$ $[M + H]^+$ 462.2711, found 462.2708.

*tert-butyl 4-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)piperidine-1-carboxylate **(49)***. According to the *general procedure*. White solid (33.9 mg, 30%). M.p. = 208 – 209 °C.

R_f 0.60 (CH_2Cl_2/MeOH, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.23 (s, 2H), 3.96 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 2.88 (td, J = 10.8, 5.2 Hz, 3H), 1.99 – 1.78 (m, 4H), 1.48 (s, 9H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.0, 155.6, 154.7, 151.8, 148.0, 107.4, 79.9, 43.4, 34.0, 31.6, 30.0, 29.8, 28.6, 27.9. **HRMS** (ESI) calcd for $C_{18}H_{28}N_5O_4$ $[M + H]^+$ 378.2136, found 378.2130.

*2-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-4-methylquinoline **(50)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[13d] Yellow oil (79.2 mg, 94%). R_f 0.60 (Petroleum ether/EtOAc, 20/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.12 (s, 1H), 2.86 (t, J = 11.2 Hz, 1H), 2.68 (s, 3H), 2.01 – 1.69 (m, 4H), 1.56 (s, 1H), 1.41 – 1.19 (m, 3H), 1.09 (dd, J = 24.0, 11.6 Hz, 1H), 0.91 (d, J = 6.0 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.0, 147.9, 144.1, 129.7, 128.9, 127.2, 125.4, 123.7, 120.7, 51.0, 46.6, 43.5, 35.3, 33.1, 28.3, 24.7, 22.6, 21.6, 19.0, 15.8. **HRMS** (ESI) calcd for $C_{20}H_{28}N$ $[M + H]^+$ 282.2216, found 282.2213.

*2-((3S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)-4-methylquinoline **(51)***. According to the *general procedure*. The spectral Data is consistent with the literature data.[12] White solid (100.0 mg, 65%). M.p. = 167 – 168 °C. R_f 0.60 (Petroleum ether/EtOAc, 40/1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.17 (s, 1H), 3.01 – 2.84 (m, 1H), 2.66 (s, 3H), 1.98 (d, J = 12.4 Hz, 1H), 1.90 – 1.76 (m, 4H), 1.71 – 1.48 (m, 6H), 1.44 – 1.25 (m, 9H), 1.20 – 0.96 (m, 10H), 0.95 – 0.89 (m, 7H), 0.87 (dd, J = 6.4, 1.2 Hz, 6H), 0.67 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.4, 147.8, 144.3, 129.7, 129.0, 127.2, 125.5, 123.6, 120.3, 56.7, 56.5, 54.7, 48.0, 46.9, 42.7, 40.2, 39.7, 38.8, 36.3, 36.0, 35.9, 35.7, 35.1, 32.3, 29.0, 28.5, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 21.2, 19.0, 18.8, 12.7, 12.2. **HRMS** (ESI) calcd for $C_{37}H_{56}N$ $[M + H]^+$ 514.4407, found 514.4413.

Gram-scale Reaction. To a 250 mL glass vial was added lepidine **1** (0.8 mL, 6 mmol, 1.0 equiv), N-Boc-4-hydroxypiperidine **2** (3.3 g, 12 mmol, 2.0 equiv), $(NH_4)_2S_2O_8$ (2.7 g, 12 mmol, 2.0 equiv), 100 mL of DMSO and 20 mL of H_2O. The reaction mixture was stirred rapidly at 50 °C for 24 h (heating mantle). The mixture was diluted with 100 mL of aqueous 1 M $NaHCO_3$ solution, and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated in vacuo. After purification by flash column chromatography on silica gel, the product **3** (1.1 g) was obtained in 85% yield.

ASSOCIATED CONTENT

Supporting Information Available: NMR spectra for known compounds and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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