# Iron-Catalyzed Remote C-H Alkylation of 8-Amidoquinolines with Cycloalkanes 

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Abstract An iron-catalyzed, peroxide-mediated cross-dehydrogenative coupling between 8 -amidoquinolines and cycloalkanes has been developed for the site-selective alkylation of the quinoline nucleus at the C5 position. The reaction tolerates various substituted $N$-(quinolin8 -yl)benzamides and $N$-(quinolin- 8 -yl)alkylamides, affording the corresponding C5-alkylation products in good yields. On the basis of control experiments, a reaction mechanism involving the addition of an alkyl radical to an iron-chelated intermediate is proposed.

Key words C-H functionalization, iron catalysis, quinolines, alkylation, radical reaction

The quinoline nucleus is widely present in pharmaceuticals and natural products. ${ }^{1}$ Consequently, direct and siteselective C-H functionalization of this privileged heterocycle has attracted considerable attention as a strategy to rapidly access structurally diverse quinoline derivatives. ${ }^{2}$ Among various $\mathrm{C}-\mathrm{H}$ functionalization reactions of quinolines, those employing 8 -amidoquinoline, which was originally popularized as an excellent $\mathrm{N}, \mathrm{N}$-bidentate directing group for chelation-assisted C-H functionalizations, ${ }^{3}$ have been extensively explored for the site-selective installation of various functional groups into the otherwise less reactive C5 position of the quinoline nucleus. Thus, since the seminal work by Stahl and co-workers on copper-catalyzed C5-selective chlorination through a single-electron-transfer mechanism, ${ }^{4}$ various methods for the C5-functionalization of 8 -amidoquinolines with halogen, ${ }^{5}$ oxygen, ${ }^{6}$ sulfur (and selenium), ${ }^{7}$ and nitrogen ${ }^{8}$ groups have been developed.

8-Amidoquinolines have also allowed for the C5-selective functionalization with alkyl groups. The most extensively studied reaction of this type is metal-catalyzed fluoroalkylation with fluoroalkyl bromides via a radical mechanism (Scheme 1a). ${ }^{9}$ Meanwhile, Zeng and co-workers
developed iron-catalyzed C5-allylation of 8-amidoquinolines with allyl alcohols, which likely operates by a nonradical mechanism (Scheme 1b). ${ }^{10}$ This was followed by the development of analogous metal-catalyzed C5-functionalization reactions using aminals, ${ }^{11}$ benzylamines, ${ }^{12}$ and benzyl acetates ${ }^{13}$ as electrophiles. Recently, Jeganmohan and co-workers disclosed ruthenium-catalyzed C5-H alkylation of 8 -amidoquinolines bearing an aroyl group with alkyl bromides, which was proposed to involve the addition of an alkyl radical to a ruthenacycle intermediate formed by bidentate chelation-assisted aromatic $\mathrm{C}-\mathrm{H}$ activation (Scheme 1c). ${ }^{5 g .14}$ Despite the above developments, C5alkylation of 8 -amidoquinolines with unfunctionalized


Transition-metal-catalyzed C-H fluoroalkylation


> b) Fe- or Rh-catalyzed C-H allylation and benzylation

c) Ru-catalyzed C-H alkylation with alkyl bromides

d) This work: Fe-catalyzed C-H alkylation with cycloalkanes


Scheme 1 Development of transition-metal-catalyzed C5-alkylation of 8 -amidoquinolines
alkanes via $\mathrm{C}\left(\mathrm{sp}^{3}\right)-\mathrm{H}$ bond cleavage, which can be categorized as $\mathrm{C}-\mathrm{H} / \mathrm{C}-\mathrm{H}$ coupling, ${ }^{15}$ remains elusive. Herein, we report on such a transformation using cycloalkanes as alkyl sources promoted by an iron catalyst in combination with di-tert-butyl peroxide (DTBP; Scheme 1d). The reaction tolerates 8 -amidoquinolines bearing various aroyl and alkanoyl groups and is proposed to involve the addition of an alkyl radical to an iron-chelated intermediate.

The present study commenced with exploration of the reaction of N -(quinolin-8-yl)benzamide (1a) in cyclooctane as the solvent and the alkylation agent (Table 1). In light of the capability of $\mathrm{Fe}(\mathrm{II}) /$ peroxide systems to generate alkoxy radical that can abstract hydrogen from aliphatic $\mathrm{C}-\mathrm{H}$ bonds, ${ }^{15,16}$ we initially performed the reaction in the presence of $\mathrm{Fe}(\mathrm{OAc})_{2}$ ( $20 \mathrm{~mol} \%$ ) and DTBP (4 equiv), which afforded, after 12 hours at $150^{\circ} \mathrm{C}$, the alkylation product 2 a in $43 \%$ yield with exclusive C5-selectivity (entry 1 ). While the addition of inorganic or organic base ( $40 \mathrm{~mol} \%$ ) to this system had detrimental or negligible effect in most cases (entries 2-8), $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ was found to improve the yield of $\mathbf{2 a}$ to $61 \%$ (entry 6). With $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ as the additive, we next explored ligand effects. While commercially available bipyri-

Table 1 C5-Alkylation of 8-Amidoquinoline 1a in Cyclooctane ${ }^{\text {a }}$


| Entry | Additive | Ligand | Yield (\%) |
| :---: | :--- | :--- | :--- |
| 1 | - | - | 43 |
| 2 | $\mathrm{Na}_{2} \mathrm{CO}_{3}$ | - | 28 |
| 3 | $\mathrm{~K}_{3} \mathrm{PO}_{4}$ | - | 30 |
| 4 | $\mathrm{~K}_{2} \mathrm{HPO}_{4}$ | - | 41 |
| 5 | $\mathrm{KH}_{2} \mathrm{PO}_{4}$ | - | 46 |
| 6 | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | - | 61 |
| 7 | $\mathrm{DABCO}^{2}$ | - | 39 |
| 8 | $\mathrm{DBU}^{2}$ | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | - |
| 10 | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | 1,10-phenanthroline | 39 |
| 11 | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | neocuproine | 45 |
| 12 | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | bathocuproine | 54 |
| 13 | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | $6,6^{\prime}$-dmbpy | 51 |
| 14 | $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ | $2,2^{\prime}$-biquinoline | 57 |

[^0]dine/phenanthroline-type ligands had only negative or negligible effect (entries 9-13), those bearing substituents near the nitrogen atoms were found to give marginally but consistently better results than 1,10-phenanthroline. Given this observation, we tested a bulkier ligand to find that $6,6^{\prime}-$ di-tert-butyl-2,2'-bipyridine (6,6'-dtbbpy) improved the yield to $77 \%$ (isolated; entry 14).

With the optimized conditions (Table 1, entry 14) in hand, we explored the scope for 8-amidoquinoline derivatives (Scheme 2). Various N -(quinolin-8-yl)benzamides containing electron-withdrawing ( $\mathrm{CF}_{3}, \mathrm{~F}$, and Cl ) or -donating ( OMe and Me ) groups on the aryl group at the ortho, para, or meta position afforded the corresponding C5-cyclooctylated products ( $\mathbf{2 b} \mathbf{- 2 1}$ ) in good yields ( $72-87 \%$ ). The alkylation reactions of amide substrates bearing a 1- or 2naphthyl group also proceeded smoothly to give the desired products ( $\mathbf{2 m}$ and $\mathbf{2 n}$ ) in $75 \%$ and $77 \%$ yield, respectively. For the reaction of N -(quinolin-8-yl)alkylamides, the use of $\mathrm{KH}_{2} \mathrm{PO}_{4}$ instead of $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ proved to give slightly better


2b ( $\mathrm{R}=\mathrm{OMe}$ ), 79\% 2c $(R=F), 83 \%$ 2d ( $\mathrm{R}=\mathrm{CF}_{3}$ ), 87\% 2e (R = CI), 84\%

2j ( $\mathrm{R}=\mathrm{Me}$ ), 75\%
2k ( $\mathrm{R}=\mathrm{F}$ ), $75 \%$
21 ( $\mathrm{R}=\mathrm{CF}_{3}$ ), 72\%

2n, 77\%

2f ( $\mathrm{R}=\mathrm{Me}, \mathrm{R}^{\prime}=\mathrm{H}$ ), 84\% 2g (R $\left.=\mathrm{OMe}, \mathrm{R}^{\prime}=\mathrm{H}\right), 86 \%$ 2h ( $\mathrm{R}=\mathrm{CF}_{3}, \mathrm{R}^{\prime}=\mathrm{H}$ ), 84\% $2 \mathbf{i}\left(\mathrm{R}=\mathrm{R}^{\prime}=\mathrm{OMe}\right), 82 \%$

2m, $75 \%$

20, 71\% ${ }^{\text {a }}$

$2 p, 76 \%^{a}$


2r, $77 \%^{a}$

2s, $73 \%{ }^{\text {a }}$


Scheme 2 Substrate scope for the cyclooctylation of 8-amidoquinoline derivatives. ${ }^{\text {a }} \mathrm{KH}_{2} \mathrm{PO}_{4}$ ( $40 \mathrm{~mol} \%$ ) was utilized instead of $\mathrm{NaH}_{2} \mathrm{PO}_{4}$. ${ }^{\text {b }}$ Cycloheptane was used instead of cyclooctane.
yields. Thus, amides bearing various alkyl substituents, such as methyl, isobutyl, isopropyl, cyclohexyl, tert-butyl, and 1-adamantyl groups, afforded the corresponding C5cyclooctylated products in good yields (20-2t). The alkylation of 1a also proceeded in cycloheptane to afford the C5cycloheptylated product $\mathbf{2 u}$ in $79 \%$ yield, whereas attempts at C5-cycloalkylation in cyclohexane or cyclopentane failed for unknown reasons. Note also that additional attempts to use aliphatic solvents such as THF and 1,4-dioxane as alkylating agents were futile under the present catalytic system.

To gain insight into the mechanism of the present C5alkylation, control experiments were performed. First, the reaction of 8 -aminoquinoline under the standard conditions failed to give any products including the C5-cyclooctylated derivative (Scheme 3a), which indicated the importance of the chelation effect of the amide moiety for the activation of the quinoline ring. Second, the addition of 2 equivalents of TEMPO completely shut down the reaction of 1a under the standard conditions (Scheme 3b), which suggested the involvement of radical species.

b)


Scheme 3 Control experiments

Based on the results of the control experiments and literature precedents, ${ }^{6 b, 16,17}$ we propose a possible reaction mechanism as shown in Scheme 4. The Fe(II) precatalyst A would be first oxidized by DTBP to an Fe (III) species B with concomitant generation of tert-butoxy radical. Deprotonation of 8 -amidoquinoline $\mathbf{1}$ by species $\mathbf{B}$ would form a chelate complex C. Meanwhile, tert-butoxy radical abstracts a hydrogen atom from the cycloalkane to generate an alkyl radical. The alkyl radical would then undergo addition to the C5 position of $\mathbf{C}$ to give radical species $\mathbf{D}$, which could be alternatively represented as Fe (II) chelate intermediate $\mathbf{D}^{\prime}$. Deprotonation of the C5 position and protonation of the amidate nitrogen, which might be assisted by the base, would furnish product 2 and regenerate species $\mathbf{A}$.


Scheme 4 Possible catalytic cycle

In summary, we have developed an iron-catalyzed C5selective alkylation of 8-amidoquinolines using cycloalkane as the alkylating agent under oxidative conditions. 8 -Amidoquinoline derivatives bearing a variety of aryl- and alkylamide moieties were tolerated, affording the desired alkylation products in moderate to good yields. The present study would hold a promise for further development of C5-alkylation of quinoline derivatives using a broader range of unactivated alkanes with the aid of different approaches of hydrogen atom abstraction/alkyl radical generation.


#### Abstract

All reactions dealing with air- and moisture-sensitive compounds were carried out in oven-dried reaction vessels under nitrogen atmosphere. Analytical TLC was performed on Merck 60 F254 silica gel plates. Flash column chromatography was performed using 40-63 $\mu \mathrm{m}$ silica gel (Si 60, Merck). ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on a JEOL ECA-400 or Bruker AV-400 ( 400 MHz ) NMR spectrometer, and are reported in parts per million (ppm) downfield from an internal standard (tetramethylsilane, 0 ppm ). GC analysis was performed on a Shimadzu GC-2010 system equipped with glass capillary column DB-5 (Agilent J\&W, 0.25 mm i.d. $\times 30 \mathrm{~m}, 0.25 \mu \mathrm{~m}$ film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-Tof Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers, and were used as received. 8-Amidoquinolines 1 were prepared according to a literature procedure. ${ }^{18} 6,6^{\prime}-$ Di-tert-butyl-2,2'-bipyridine was prepared according to the literature. ${ }^{19}$


## Iron-Catalyzed C5-Alkylation of 8-Amidoquinolines with Cycloalkanes; General Procedure

In a Schlenk tube were placed 8 -amidoquinoline 1 ( 0.1 mmol ), $\mathrm{Fe}(\mathrm{OAc})_{2}$ ( $5.2 \mathrm{mg}, 0.02 \mathrm{mmol}$ ), 6,6'-di-tert-butyl-2,2'-bipyridine ( 5.4 $\mathrm{mg}, 0.02 \mathrm{mmol}$ ), and $\mathrm{NaH}_{2} \mathrm{PO}_{4}$ [ $4.8 \mathrm{mg}, 0.04 \mathrm{mmol}$; $\mathrm{KH}_{2} \mathrm{PO}_{4}$ was used for N -(quinolin-8-yl)alkylamides] under nitrogen atmosphere. Di-tert-butyl peroxide ( $73 \mu \mathrm{~L}, 0.4 \mathrm{mmol}$ ) and cycloalkane ( 0.5 mL ) were added, and the resulting solution was stirred at $150{ }^{\circ} \mathrm{C}$ for 12 h . The reaction mixture was allowed to cool to room temperature, and then filtered through a short pad of silica gel, which was washed with

EtOAc ( 5 mL ). The filtrate was concentrated under reduced pressure. Silica gel chromatography (hexane/EtOAc, 5:1) of the crude product afforded the desired product 2.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)benzamide (2a)

Yellow oil; yield: 28 mg (77\%); $R_{f}=0.64$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.77(\mathrm{~s}, 1 \mathrm{H}), 8.87(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, 8.84 (dd, $J=4.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.47 (dd, $J=8.7,1.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.10-8.07 (m, 2 H$), 7.58-7.47(\mathrm{~m}, 5 \mathrm{H}), 3.53-3.46(\mathrm{~m}, 1 \mathrm{H}), 1.96-1.83(\mathrm{~m}, 6 \mathrm{H})$, 1.79-1.58 (m, 8 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.4,147.6,140.6,139.3,135.4,132.5$ (two signals overlapped), 131.8, 128.8, 127.4, 125.9, 124.3, 121.2, 116.6, 38.6, 34.2, 27.1, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{27} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 359.2123$; found: 359.2126.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-4-methoxybenzamide (2b)

Yellow oil; yield: 31 mg (79\%); $R_{f}=0.50$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.70(\mathrm{~s}, 1 \mathrm{H}), 8.89-8.81(\mathrm{~m}, 2 \mathrm{H}), 8.46$ (dd, $J=8.6,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.13-8.00(\mathrm{~m}, 2 \mathrm{H}), 7.54-7.42(\mathrm{~m}, 2 \mathrm{H}), 7.08-$ 6.98 (m, 2 H), 3.89 (s, 3 H ), 3.53-3.45 (m, 1 H ), 1.97-1.79 (m, 6 H ), 1.77-1.60 (m, 8 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.0,162.5,147.5,140.3,139.3$, $132.7,132.5,129.2,127.8,125.9,124.4,121.1,116.4,114.0,55.5,38.5$, 34.2, 27.1, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{2}[\mathrm{M}+\mathrm{H}]^{+}: 389.2229$; found: 389.2232.

## $\boldsymbol{N}$-(5-Cyclooctylquinolin-8-yl)-4-fluorobenzamide (2c)

Yellow solid; yield: 31 mg ( $83 \%$ ); mp $87-88{ }^{\circ} \mathrm{C} ; R_{f}=0.65$ (hexane/ EtOAc, 2:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.71(\mathrm{~s}, 1 \mathrm{H}), 8.91-8.71(\mathrm{~m}, 2 \mathrm{H}), 8.47$ (dd, $J=8.7,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.11-8.06(\mathrm{~m}, 2 \mathrm{H}), 7.52-7.46(\mathrm{~m}, 2 \mathrm{H}), 7.24-$ 7.19 (m, 2 H), 3.52-3.46 (m, 1 H), 1.95-1.76 (m, 6 H), 1.72-1.67 (m, 8 H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.0\left(\mathrm{~d},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=252.2 \mathrm{~Hz}\right), 164.3,147.6$, $140.8,139.2,132.6,132.4,131.6\left(\mathrm{~d},{ }^{4} J_{\mathrm{C}-\mathrm{F}}=3.0 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=9.0\right.$ $\mathrm{Hz}), 125.9,124.3,121.2,116.5,115.9\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=21.9 \mathrm{~Hz}\right), 38.6,34.2$, 27.0, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{OF}[\mathrm{M}+\mathrm{H}]^{+}: 377.2029$; found: 377.2027.
$\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-4-(trifluoromethyl)benzamide (2d) Yellow solid; yield: 37 mg ( $87 \%$ ); mp $142-143{ }^{\circ} \mathrm{C} ; R_{f}=0.60$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.81(\mathrm{~s}, 1 \mathrm{H}), 8.87-8.81(\mathrm{~m}, 2 \mathrm{H}), 8.49$ (dd, $J=8.6,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 8.18(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.81(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 2$ H), 7.54-7.47 (m, 2 H), 3.55-3.46 (m, 1 H), 1.99-1.83 (m, 6 H), 1.791.62 (m, 8 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=164.0,147.7,141.2,139.2,138.7,133.4$ $\left(\mathrm{q},{ }^{2} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=32.8 \mathrm{~Hz}\right), 132.6,132.1,127.8,125.91\left(\mathrm{q},{ }^{3} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.8 \mathrm{~Hz}\right)$, $125.90,124.3,123.8\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=272.6 \mathrm{~Hz}\right), 121.3,116.8,38.6,34.2,27.0$, 26.6, 26.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{OF}_{3}[\mathrm{M}+\mathrm{H}]^{+}$: 427.1997; found: 427.1999.

## 4-Chloro- $\boldsymbol{N}$-(5-cyclooctylquinolin-8-yl)benzamide (2e)

Yellow solid; yield: 33 mg ( $84 \%$ ); $\mathrm{mp} 110-111{ }^{\circ} \mathrm{C} ; R_{f}=0.62$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.73(\mathrm{~s}, 1 \mathrm{H}), 8.85-8.81(\mathrm{~m}, 2 \mathrm{H}), 8.47$ (dd, $J=8.8,1.5 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.04-7.99 (m, 2 H ), $7.53-7.45$ (m, 4 H ), 3.523.46 (m, 1 H ), 1.95-1.81 (m, 6 H$), 1.79-1.56(\mathrm{~m}, 8 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=164.2,147.6,140.9,139.2,138.0$, $133.8,132.6,132.2,129.1,128.8,125.9,124.3,121.2,116.6,38.6,34.2$, 27.0, 26.6, 26.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{OCl}[\mathrm{M}+\mathrm{H}]^{+}: 393.1734$; found: 393.1729.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-3-methylbenzamide (2f)

Yellow oil; yield: 31 mg (84\%); $R_{f}=0.67$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.73$ ( $\mathrm{s}, 1 \mathrm{H}$ ), 8.88-8.83 (m, 2 H ), 8.47 (d, J=7.7 Hz, 1 H), $7.89(\mathrm{~s}, 1 \mathrm{H}), 7.86(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.52-7.41(\mathrm{~m}$, $3 \mathrm{H}), 7.38$ (d, J = 7.6 Hz, 1 H), 3.53-3.46 (m, 1 H ), 2.48 (s, 3 H ), 1.97$1.80(\mathrm{~m}, 6 \mathrm{H}), 1.77-1.66(\mathrm{~m}, 8 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.6,147.6,140.6,139.3,138.7$, 135.4, 132.6, 132.52, 132.49, 128.7, 128.1, 125.9, 124.33, 124.27, 121.1, 116.6, 38.5, 34.2, 27.1, 26.6, 26.3, 21.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 373.2280$; found: 373.2284.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-3-methoxybenzamide (2g)

Yellow oil; yield: 33 mg (86\%); $R_{f}=0.67$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.75(\mathrm{~s}, 1 \mathrm{H}), 8.87-8.82(\mathrm{~m}, 2 \mathrm{H}), 8.47$ (dd, $J=8.6,1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.65-7.62 (m, 2 H), 7.52-7.42 (m, 3 H ), 7.11 (dd, $J=8.1,2.3 \mathrm{~Hz}, 1 \mathrm{H}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 3.53-3.46(\mathrm{~m}, 1 \mathrm{H}), 1.93-1.82$ (m, 6 H ), 1.78-1.62 (m, 8 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.2,160.1,147.6,140.7,139.3$, 136.9, 132.5 (two signals overlapped), 129.8, 125.9, 124.3, 121.2, $119.2,118.0,116.5,112.7,55.6,38.6,34.2,27.1,26.6,26.3$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}_{2}[\mathrm{M}+\mathrm{H}]^{+}: 389.2229$; found: 389.2226.
$\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-3-(trifluoromethyl)benzamide (2h) Yellow solid; yield: 36 mg ( $84 \%$ ); $\mathrm{mp} 80-81^{\circ} \mathrm{C} ; R_{f}=0.65$ (hexane/ EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.80(\mathrm{~s}, 1 \mathrm{H}), 8.86-8.83(\mathrm{~m}, 2 \mathrm{H}), 8.49$ (dd, J=8.7, 1.4 Hz, 1 H), 8.35 (s, 1 H ), 8.24 (d, $J=7.9 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.83 (d, $J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.69(\mathrm{t}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.54-7.47(\mathrm{~m}, 2 \mathrm{H}), 3.54-3.47$ (m, 1 H ), 1.98-1.83 (m, 6 H$), 1.78-1.64(\mathrm{~m}, 8 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=163.8,147.8,141.2,139.2,136.3$, $132.6,132.1,131.5\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=32.9 \mathrm{~Hz}\right), 130.3,129.4,128.3\left(\mathrm{q},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=3.4\right.$ $\mathrm{Hz}), 125.9,124.6\left(\mathrm{q},{ }^{3} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.6 \mathrm{~Hz}\right), 124.3,123.9\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=272.6 \mathrm{~Hz}\right)$, 121.3, 116.8, 38.6, 34.2, 27.0, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{OF}_{3}[\mathrm{M}+\mathrm{H}]^{+}$: 427.1997; found: 427.1999.
$\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-3,4-dimethoxybenzamide (2i)
Yellow oil; yield: 34 mg (82\%); $R_{f}=0.41$ (hexane/EtOAc, 2:1). ${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.72(\mathrm{~s}, 1 \mathrm{H}), 8.85-8.82(\mathrm{~m}, 2 \mathrm{H}), 8.46$ (dd, $J=8.8,1.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.68-7.64 (m, 2 H), 7.51-7.46 (m, 2 H$), 6.99$ $(\mathrm{d}, \mathrm{J}=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 4.00(\mathrm{~s}, 3 \mathrm{H}), 3.97(\mathrm{~s}, 3 \mathrm{H}), 3.52-3.45(\mathrm{~m}, 1 \mathrm{H}), 1.95-$ 1.83 (m, 6 H ), 1.75-1.66 (m, 8 H$)$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.0,152.0,149.2,147.5,140.4$, 139.3, 132.6, 132.5, 128.2, 125.9, 124.4, 121.1, 119.8, 116.3, 111.0, 110.5, 56.2, 56.1, 38.6, 34.2, 27.1, 26.6, 26.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{26} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}_{3}[\mathrm{M}+\mathrm{H}]^{+}$: 419.2335; found: 419.2337.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-2-methylbenzamide (2j)

Yellow oil; yield: 28 mg (75\%); $R_{f}=0.70$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.22(\mathrm{~s}, 1 \mathrm{H}), 8.87(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, $8.76(\mathrm{dd}, J=4.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.46(\mathrm{dd}, J=8.7,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.67(\mathrm{~d}, J=$ $7.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.50-7.46(\mathrm{~m}, 2 \mathrm{H}), 7.42-7.37(\mathrm{~m}, 1 \mathrm{H}), 7.32(\mathrm{t}, J=7.3 \mathrm{~Hz}$, $2 \mathrm{H}), 3.53-3.46(\mathrm{~m}, 1 \mathrm{H}), 2.60(\mathrm{~s}, 3 \mathrm{H}), 1.96-1.83$ (m, 6 H$), 1.71-1.62$ ( $\mathrm{m}, 8 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=168.1,147.6,140.7,139.1,136.9$, 136.7, 132.7, 132.4, 131.4, 130.2, 127.3, 126.0, 125.8, 124.2, 121.1, 116.5, 38.6, 34.2, 27.0, 26.6, 26.3, 20.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 373.2280; found: 373.2283.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-2-fluorobenzamide (2k)

Yellow oil; yield: 28 mg (75\%); $R_{f}=0.67$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=11.16(\mathrm{~d}, J=12.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.90(\mathrm{~d}, J=$ $8.1 \mathrm{~Hz}, 1 \mathrm{H}), 8.86(\mathrm{dd}, J=4.1,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.47(\mathrm{dd}, J=8.7,1.4 \mathrm{~Hz}, 1 \mathrm{H})$, 8.22 (td, $J=7.8,1.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.57-7.46(\mathrm{~m}, 3 \mathrm{H}), 7.35-7.31(\mathrm{~m}, 1 \mathrm{H})$, 7.27-7.21 (m, 1 H ), 3.53-3.47 (m, 1 H ), 1.98-1.81 (m, 6 H), 1.76-1.68 ( $\mathrm{m}, 8 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR $\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=161.5\left(\mathrm{~d},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=3.2 \mathrm{~Hz}\right), 160.6\left(\mathrm{~d},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=\right.$ 249.1 Hz ), 147.8, 141.0, 139.3, 133.5, 132.7, 132.4, 132.1, 125.9, 124.9 $\left(\mathrm{d},{ }^{3} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.4 \mathrm{~Hz}\right), 124.3,122.4\left(\mathrm{~d},{ }^{2} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=11.7 \mathrm{~Hz}\right), 121.2,117.3,116.4$ $\left(\mathrm{d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=24.5 \mathrm{~Hz}\right), 38.7,34.2,27.1,26.6,26.3$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{OF}[\mathrm{M}+\mathrm{H}]^{+}$: 377.2029; found: 377.2027.
$\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-2-(trifluoromethyl)benzamide (21)
Yellow solid; yield: 31 mg (72\%); mp $189-190{ }^{\circ} \mathrm{C} ; R_{f}=0.60$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.17(\mathrm{~s}, 1 \mathrm{H}), 8.85(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, $8.74(\mathrm{~d}, J=4.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.46(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.79(\mathrm{~d}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.75(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.68(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H})$, 7.50-7.45 (m, 2 H), 3.53-3.47 (m, 1 H), 1.96-1.83 (m, 6 H), 1.78-1.64 ( $\mathrm{m}, 8 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.8,147.6,141.3,139.0,136.4$, $132.5,132.3,132.2,130.1,128.6,127.8\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=32.3 \mathrm{~Hz}\right), 126.7(\mathrm{q}$, $\left.{ }^{3} J_{\mathrm{C}-\mathrm{F}}=4.7 \mathrm{~Hz}\right), 125.8,124.2,123.7\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=273.8 \mathrm{~Hz}\right), 121.2,116.9$, 38.6, 34.2, 27.0, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{25} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{OF}_{3}[\mathrm{M}+\mathrm{H}]^{+}$: 427.1997; found: 427.1998.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-1-naphthamide (2m)

Yellow solid; yield: $31 \mathrm{mg}\left(75 \%\right.$ ); $\mathrm{mp} 91-92{ }^{\circ} \mathrm{C} ; R_{f}=0.55$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.43(\mathrm{~s}, 1 \mathrm{H}), 8.98(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, 8.73 (dd, $J=4.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.55-8.51(\mathrm{~m}, 1 \mathrm{H}), 8.47(\mathrm{dd}, J=8.7,1.5$ $\mathrm{Hz}, 1 \mathrm{H}), 8.00(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.94-7.90(\mathrm{~m}, 2 \mathrm{H}), 7.60-7.51(\mathrm{~m}, 4$ H), 7.47 (dd, J = 8.6, $4.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.55-3.49 (m, 1 H ), 1.98-1.85 (m, 6 H), 1.78-1.65 (m, 8 H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=167.7,147.6,140.9,139.1,135.0$, $134.0,132.8,132.5,131.0,130.5,128.4,127.3,126.6,125.9,125.7$, 125.6, 125.0, 124.3, 121.2, 116.7, 38.6, 34.2, 27.1, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 409.2280$; found: 409.2281.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)-2-naphthamide (2n)

Yellow solid; yield: 31 mg (77\%); mp $104-105{ }^{\circ} \mathrm{C} ; R_{f}=0.60$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.92(\mathrm{~s}, 1 \mathrm{H}), 8.92(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, 8.88 (dd, $J=4.1,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.60(\mathrm{~s}, 1 \mathrm{H}), 8.49(\mathrm{dd}, J=8.6,1.3 \mathrm{~Hz}, 1$ H), 8.14 (dd, $J=8.6,1.8 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.05 (dd, $J=6.3,2.9 \mathrm{~Hz}, 1 \mathrm{H}), 8.00$ (d, $J=8.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.95-7.90(\mathrm{~m}, 1 \mathrm{H}), 7.62-7.56(\mathrm{~m}, 2 \mathrm{H}), 7.54-7.49(\mathrm{~m}$, $2 \mathrm{H}), 3.54-3.48$ (m, 1 H$), 2.01-1.81(\mathrm{~m}, 6 \mathrm{H}), 1.78-1.66$ (m, 8 H$)$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.5,147.6,140.7,139.3,135.0$, 132.9, 132.7, 132.6, 132.5, 129.3, 128.7, 128.0, 127.87, 127.85, 126.8, 125.9, 124.4, 123.9, 121.2, 116.6, 38.6, 34.2, 27.1, 26.6, 26.3.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}\left[\mathrm{M}+\mathrm{H}^{+}\right.$: 409.2280; found: 409.2279.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)acetamide (20)

Yellow oil; yield: 21 mg (71\%); $R_{f}=0.70$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=9.78(\mathrm{~s}, 1 \mathrm{H}), 8.78(\mathrm{dd}, J=4.1,1.5 \mathrm{~Hz}, 1$ H), 8.67 (d, $J=8.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.44 (dd, $J=8.6,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.47$ (dd, $J=$ $8.6,4.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.41 (d, J = $8.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.49-3.43 (m, 1 H ), 2.33 ( $\mathrm{s}, 3$ H), 1.92-1.80 (m, 6 H), 1.76-1.61 (m, 8 H$)$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=168.7,147.4,140.3,138.8,132.5$, $132.4,125.8,124.2,121.0,116.4,38.4,34.2,27.0,26.6,26.2,25.2$.
HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{19} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 297.1967; found: 297.1969.

## $\boldsymbol{N}$-(5-Cyclooctylquinolin-8-yl)-3-methylbutanamide (2p)

Yellow oil; yield: 26 mg (76\%); $R_{f}=0.72$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=9.79(\mathrm{~s}, 1 \mathrm{H}), 8.79(\mathrm{dd}, J=4.2,1.5 \mathrm{~Hz}, 1$ H), 8.72 (d, $J=8.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.44 (dd, $J=8.7,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.47$ (dd, $J=$ 8.6, 4.1 Hz, 1 H), $7.41(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.49-3.43(\mathrm{~m}, 1 \mathrm{H}), 2.42(\mathrm{~d}$, $J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.36-2.27(\mathrm{~m}, 1 \mathrm{H}), 1.94-1.78(\mathrm{~m}, 6 \mathrm{H}), 1.76-1.62(\mathrm{~m}$, $8 \mathrm{H}), 1.06(\mathrm{~d}, \mathrm{~J}=6.6 \mathrm{~Hz}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=171.2,147.4,140.2,138.8,132.5$, $132.4,125.8,124.3,121.0,116.4,47.7,38.6,34.2,27.1,26.6,26.4$, 26.2, 22.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 339.2436$; found: 339.2435 .

## N -(5-Cyclooctylquinolin-8-yl)isobutyramide (2q)

Yellow oil; yield: 25 mg (76\%); $R_{f}=0.72$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=9.91(\mathrm{~s}, 1 \mathrm{H}), 8.79(\mathrm{dd}, J=4.1,1.4 \mathrm{~Hz}, 1$ H), $8.71(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.47-8.42(\mathrm{~m}, 1 \mathrm{H}), 7.47(\mathrm{dd}, J=8.6,4.1 \mathrm{~Hz}$, 1 H ), 7.42 (dd, $J=7.9,3.4 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.48-3.43 (m, 1 H ), 2.80-2.70 (m, 1 H), 1.93-1.80 (m, 6 H$), 1.75-1.67(\mathrm{~m}, 8 \mathrm{H}), 1.34(\mathrm{~d}, J=6.8 \mathrm{~Hz}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=175.7,147.4,140.2,139.0,132.5$, $132.4,125.8,124.3,121.0,116.4,38.5,37.2,34.2,27.1,26.6,26.2$, 19.8.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{21} \mathrm{H}_{29} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 325.2280; found: 325.2283.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)cyclohexanecarboxamide (2r)

Yellow oil; yield: $28 \mathrm{mg}(77 \%)$; $R_{f}=0.72$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=9.89(\mathrm{~s}, 1 \mathrm{H}), 8.79(\mathrm{dd}, J=4.1,1.3 \mathrm{~Hz}, 1$ H), 8.71 (d, $J=8.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.44 (d, $J=8.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.47 (dd, $J=8.6,4.1$ $\mathrm{Hz}, 1 \mathrm{H}$ ), 7.41 (d, J = $8.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 3.49-3.43 (m, 1 H ), 2.50-2.42 (m, 1 H), 2.10-2.06 (m, 2 H), 1.94-1.80 (m, 8 H), 1.77-1.64 (m, 10 H ), 1.451.25 (m, 4 H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=174.8,147.4,140.1,139.0,132.6$, 132.4, 125.8, 124.3, 121.0, 116.4, 47.0, 38.5, 34.2, 29.9, 27.1, 26.6, 26.2, 25.9 (two signals overlapped).

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 365.2593$; found: 365.2594.

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)pivalamide (2s)

Yellow oil; yield: $25 \mathrm{mg}(73 \%) ; R_{f}=0.73$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.28(\mathrm{~s}, 1 \mathrm{H}), 8.80(\mathrm{~d}, J=3.5 \mathrm{~Hz}, 1 \mathrm{H})$, 8.72 (d, $J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 8.43$ (d, $J=8.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.46$ (dd, $J=8.6,4.2 \mathrm{~Hz}$, $1 \mathrm{H}), 7.41(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.49-3.42(\mathrm{~m}, 1 \mathrm{H}), 1.92-1.80(\mathrm{~m}, 6 \mathrm{H})$, 1.74-1.65 (m, 8 H), 1.42 (s, 9 H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=177.1,147.5,140.1,139.3,132.6$, $132.4,125.8,124.3,121.0,116.2,40.3,38.3,34.2,27.8,27.0,26.5$, 26.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 339.2436$; found: 339.2440 .

## $\mathbf{N}$-(5-Cyclooctylquinolin-8-yl)adamantane-1-carboxamide (2t)

Yellow oil; yield: 33 mg (80\%); $R_{f}=0.80$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.23(\mathrm{~s}, 1 \mathrm{H}), 8.81(\mathrm{~d}, \mathrm{~J}=4.1 \mathrm{~Hz}, 1 \mathrm{H})$, $8.74(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 8.43(\mathrm{~d}, J=8.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.46$ ( $\mathrm{dd}, J=8.6,4.1 \mathrm{~Hz}$, $1 \mathrm{H}), 7.41(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.49-3.42(\mathrm{~m}, 1 \mathrm{H}), 2.15-2.09(\mathrm{~m}, 8 \mathrm{H})$, 1.94-1.78 (m, 13 H ), 1.75-1.65 (m, 8 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=176.7,147.5,140.0,139.4,132.6$, 132.4, 125.8, 124.3, 121.0, 116.3, 42.3, 39.4, 38.8, 36.6, 34.2, 28.4, 27.1, 26.6, 26.2.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{28} \mathrm{H}_{37} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}: 417.2906$; found: 417.2908.

## $\mathbf{N}$-(5-Cycloheptylquinolin-8-yl)benzamide (2u)

Yellow solid; yield: 27 mg (79\%); mp 91-92 ${ }^{\circ} \mathrm{C}$; $R_{f}=0.80$ (hexane/EtOAc, 2:1).
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=10.76(\mathrm{~s}, 1 \mathrm{H}), 8.86(\mathrm{~d}, \mathrm{~J}=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, 8.84 (dd, $J=4.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.46 ( $\mathrm{dd}, J=8.6,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $8.10-8.06$ (m, 2 H), 7.58-7.53 (m, 3 H), 7.52-7.47 (m, 2 H), 3.44-3.32 (m, 1 H), 2.05-2.01 (m, 2 H), 1.93-1.85 (m, 2 H), 1.83-1.76 (m, 4 H), 1.72-1.65 (m, 4H).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=165.4,147.6,140.3,139.2,135.4$, $132.5,132.4,131.8,128.8,127.4,125.9,123.8,121.2,116.6,40.6,36.5$, 27.9, 27.6.

HRMS (ESI): $m / z$ calcd for $\mathrm{C}_{23} \mathrm{H}_{25} \mathrm{~N}_{2} \mathrm{O}[\mathrm{M}+\mathrm{H}]^{+}$: 345.1967 ; found: 345.1969.

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## Supporting Information

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[^0]:    ${ }^{\text {a }}$ Reaction conditions: 1 a ( 0.10 mmol ), Fe( OAc$)_{2}$ ( $20 \mathrm{~mol} \%$ ), DTBP ( 0.40 mmol ), additive ( $40 \mathrm{~mol} \%$ ), ligand ( $20 \mathrm{~mol} \%$ ), cyclooctane ( 0.5 mL ), $150^{\circ} \mathrm{C}$, 12 h. DABCO: 1,4-diazabicyclo[2.2.2]octane; DBU: 1,8-diazabicyclo-[5.4.0]undec-7-ene; 6,6'-dmbpy: 6,6'-dimethyl-2,2'-bipyridine; 6,6'dtbbpy: 6,6'-di-tert-butyl-2,2'-bipyridine.
    ${ }^{\mathrm{b}}$ Determined by GC using tridecane as an internal standard.
    ${ }^{\text {c }}$ Isolated yield.

