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Palladium-Catalyzed Direct Arylation of C(sp^3)-H Bonds of α-Cyano Aliphatic Amides

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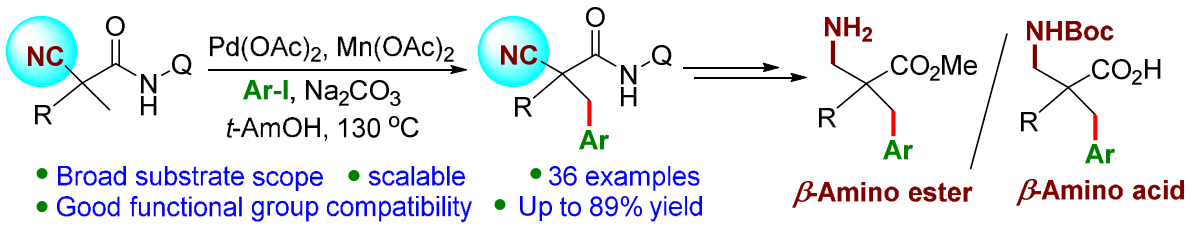


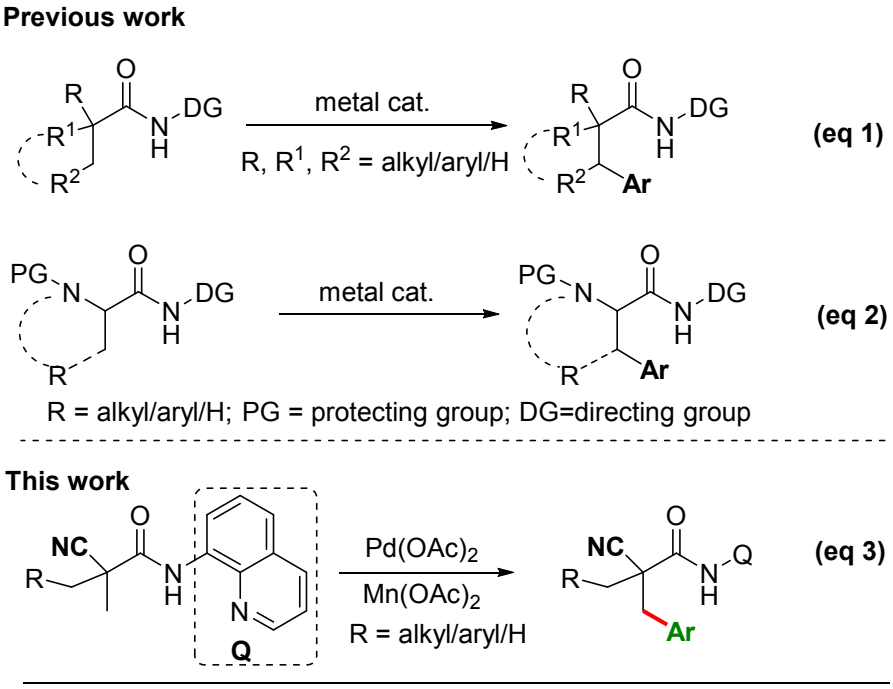
ABSTRACT: Pd(OAc)$_2$-catalyzed arylation of C(sp^3)-H bonds in α–cyano–α–methyl aliphatic amides is achieved in the presence of 8-aminoquinoline, as a removable directing group, using Mn(OAc)$_2$ and Na_2CO_3. The current strategy enables the placement of an aryl/heteroaryl group at the β–position of α–cyano aliphatic acids for the first time. Wide functional group tolerance and easily accessible starting materials provide an efficient protocol for the synthesis of arylated α–cyano amides. Furthermore, the synthetic utility of the products has been demonstrated by their efficient conversions to medicinally important α, α–dialkylated acid and β–amino acid derivatives.

INTRODUCTION

Transition metal-catalyzed functionalization of carbon-hydrogen bonds is an emerging topic in recent years.[1] The C-H bond activation protocol shortens the synthetic pathway and simplifies the retrosynthetic strategy by elimination of pre-functionalization of the starting materials. Over the years, functionalization of C(sp^2)-H bonds has developed as a means to construct carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds. Significant work has been done in the area of unactivated C(sp^2)-H bond functionalization.[2] The construction of C-C and C-X bonds using unactivated C(sp^3)-H bonds,

however, is a challenging task in modern synthetic and organometallic chemistry due to the ubiquity of C(sp^3)-H bonds in nature.[3] In this context, various transition metal catalysts have been extensively utilized in metal-catalyzed C-H functionalizations. Among these, palladium complexes play a significant role in this field. More recently, a number of C(sp^3)-H bond to C(sp^3)-C and C(sp^3)-X transformations have been reported on carboxylic acid derivatives.[4-10] In particular, arylation of acyclic and cyclic aliphatic carboxylic acids[4] (Scheme 1, eq 1), amino acids[5] (Scheme 1, eq 2) and heterocyclic carboxylic acid derivatives[6] using a bidentate directing group have been reported, since a seminal article by Daugulis in 2005.[4g] The pioneering work of Yu,[11] Chatani,[12] Daugulis,[4g] and others[13] has demonstrated that C(sp^3)-H bond functionalization could be accomplished through the use of an appropriate directing group. Despite developments in C(sp^3)-H bond functionalization of various acid derivatives, the functionalization of new classes of biologically significant synthons is beneficial, and further elucidation of this method is warranted.

2-Cyanoacetic acid derivatives are a class of active methylene compounds that can serve not only as versatile intermediates in pharmaceuticals and functional materials,[14] but also as handy precursors in synthetic chemistry[15] due to their ability to undergo a broad range of functional group transformations.[16] Small molecules bearing a nitrile group comprise a considerable proportion of therapeutic drugs.[17] It is important to develop a substrate with diverse functional groups capable of further modification. Inspired by the pioneering work and our interest in C-H functionalization, we envisioned that the β–C(sp^3)-H bonds of cyanoacetic acid derivatives could undergo arylation with bidentate auxiliary assistance. In this line, herein, we disclose the direct arylation of unactivated C(sp^3)-H bonds in α–cyano–α–methyl carboxylic acid amides using 8-aminoquinoline (-Q) as a directing group with aryl/heteroaryl iodides under palladium catalysis (Scheme 1, eq 3).



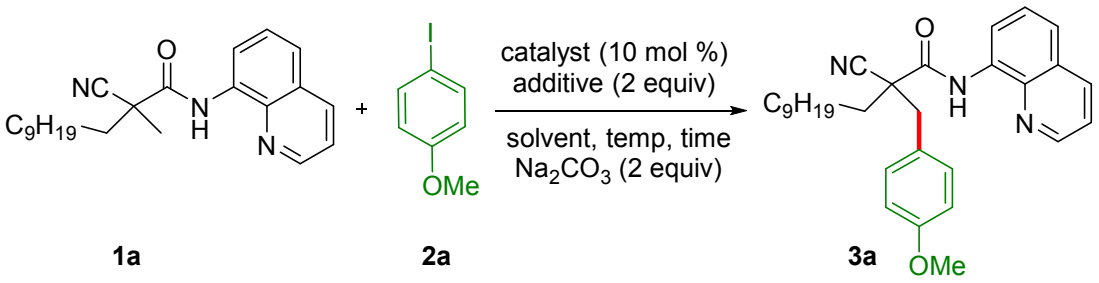
Scheme 1. Transition metal-catalyzed arylation of unactivated C(sp^3)-H bonds of aliphatic amides

RESULTS AND DISCUSSION

We commenced our investigation with the reaction of 2-cyano-2-methyl-*N*-(quinolin-8-yl)dodecanamide (**1a**), (prepared from commercially available ethyl 2-cyanopropanoate with 1-bromodecane under K_2CO_3/CH_3CN conditions, followed by ester hydrolysis and amide formation, Scheme 7) and 4-iodoanisole (**2a**), as a model substrate to establish the initial reaction parameters, in the presence of $Pd(OAc)_2$, Na_2CO_3 as base and AgOAc as additive at 120 ^oC in toluene for 24 h (entry 1, Table 1). The expected mono arylated product **3a** was isolated, although in only 18% yield. We then examined the effects of various additives on product formation using $Pd(OAc)_2$ as catalyst and either $Cu(OAc)_2$, $K_2S_2O_8$ or $Mn(OAc)_2$ at 130 ^oC in toluene for 24 h. Unsatisfactory yields were obtained with $Cu(OAc)_2$ as well as $K_2S_2O_8$ (entries 2 and 3). However, $Mn(OAc)_2$ greatly aided the conversion of **1a**, affording **3a** in 54% yield (entry 4). This is significant since iodide scavenging is accomplished without the need for silver salts. Next, prolongation of the reaction time with $Pd(OAc)_2$ and $Mn(OAc)_2$ in toluene resulted in **3a** in 68% yield (entry 5). Subsequently, based on the screening of a series of solvents including 1,4-dioxane, CF_3CH_2OH, *t*-AmOH and 1,2-dichloroethane with $Pd(OAc)_2$ and $Mn(OAc)_2$ at

different temperatures for 30 hours (entries 6-9), we concluded that *t*-AmOH was the solvent of choice, providing **3a** in 85% yield (entry 8, Table 1). In addition, employing coupling partners such as 4-bromoanisole (23%) or 4-chloroanisole (no reaction) instead of **2a** was ineffective (entry 8, Table 1) and replacing $Pd(OAc)_2$ with $Pd(TFA)_2$, $Pd(OPiv)_2$ or $PdCl_2$ resulted in lower yields (entries 10-12). From the series of above examinations, the combination of 10 mol % of $Pd(OAc)_2$, $Mn(OAc)_2$ (2 equiv) and Na_2CO_3 (2 equiv) in *t*-AmOH at 130 ^oC for 30 hours was determined to be the optimal reaction conditions.[18]

Table 1. Optimization of reaction conditions[a]

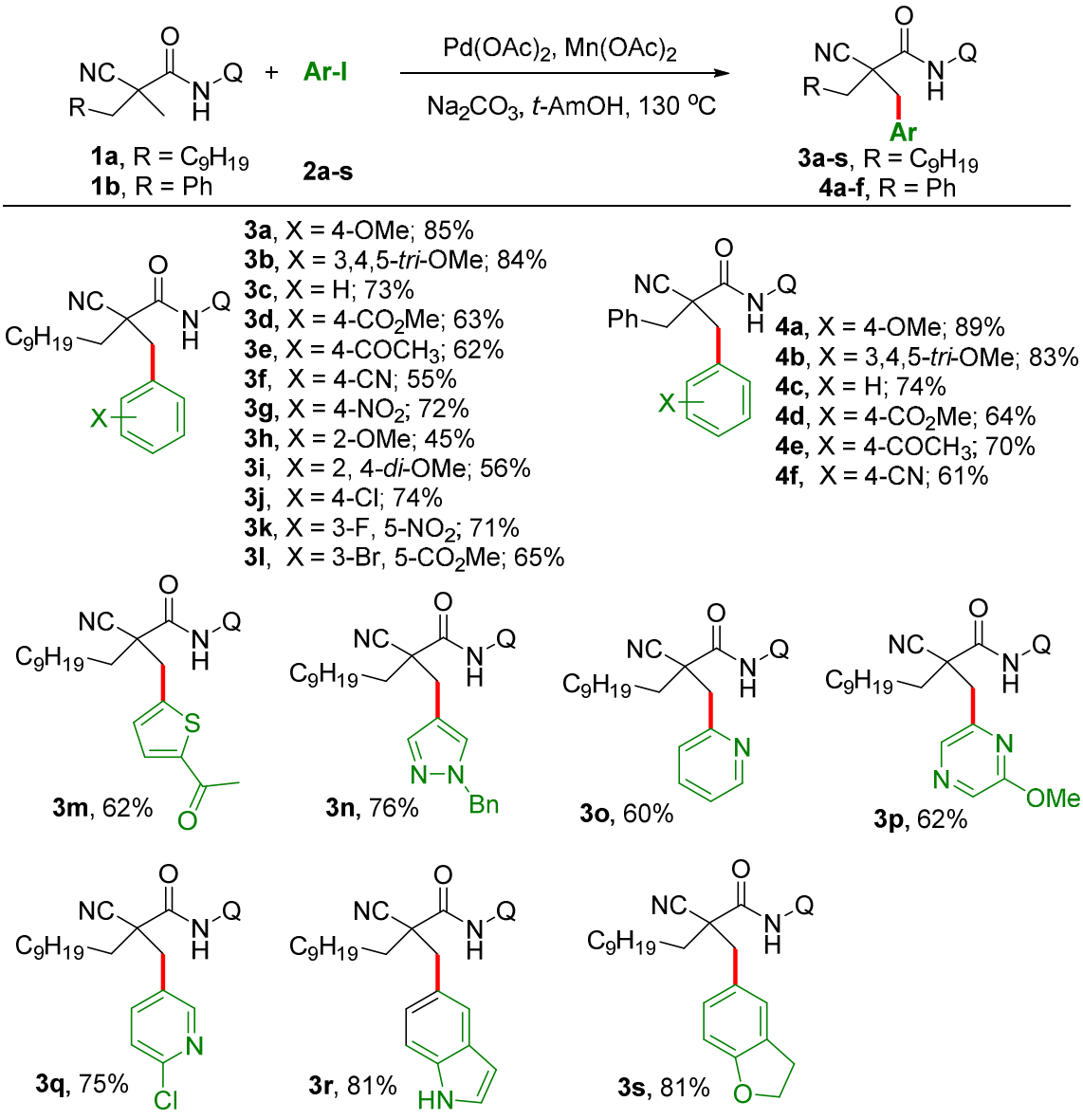


1a **2a** **3a**

entry	catalyst	additive	solvent	temp (^oC)	time (h)	yield (%)[b]
1	$Pd(OAc)_2$	AgOAc	toluene	120	24	18
2	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	130	24	15
3	$Pd(OAc)_2$	$K_2S_2O_8$	toluene	130	24	Trace
4	$Pd(OAc)_2$	$Mn(OAc)_2$	toluene	130	24	54
5	$Pd(OAc)_2$	$Mn(OAc)_2$	toluene	130	30	68
6	$Pd(OAc)_2$	$Mn(OAc)_2$	1,4-dioxane	130	30	72
7	$Pd(OAc)_2$	$Mn(OAc)_2$	CF_3CH_2OH	110	30	81
8	**$Pd(OAc)_2$**	**$Mn(OAc)_2$**	***t*-AmOH**	**130**	**30**	**85, (23)[c],(0)[d]**
9	$Pd(OAc)_2$	$Mn(OAc)_2$	DCE	110	30	79
10	$Pd(TFA)_2$	$Mn(OAc)_2$	*t*-AmOH	130	30	51
11	$Pd(OPiv)_2$	$Mn(OAc)_2$	*t*-AmOH	130	30	46
12	$PdCl_2$	$Mn(OAc)_2$	*t*-AmOH	130	30	40

[a]Reaction conditions: Cyanoamide **1a** (0.4 mmol), 4-iodoanisole (**2a**) (1.2 mmol), catalyst (10 mol %), additive (0.8 mmol), Na_2CO_3 (0.8 mmol), solvent (4 mL); [b]All the products were characterized by ^1H, ^{13}C NMR, IR and MS; [c]4-bromoanisole used as aryl halide; [d]4-chloroanisole used as aryl halide.

We next examined the scope and generality of an extensive range of aryl iodides with α–cyano amides **1a** and **1b** using the optimized conditions. Results are summarized in Scheme 2. Substrates with electron donating and electron withdrawing substituents are well tolerated under the optimal reaction conditions. The 4-OMe and 3,4,5-*tri*-OMe iodobenzene derivatives (**2a** and **2b**) reacted cleanly to give the corresponding products in excellent yields (**3a** and **3b**). Iodobenzene **2c** was also subjected to the optimized conditions and provided the corresponding product (**3c**) in 73% yield.



[a]Reaction conditions: Cyanoamide **1** (0.4 mmol), Iodoarene **2** (1.2 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.8 mmol), Na_2CO_3 (0.8 mmol) *t*-AmOH (4 mL), 130 °C, 30 h; All the products were characterized by ^1H, ^{13}C NMR, IR and MS.

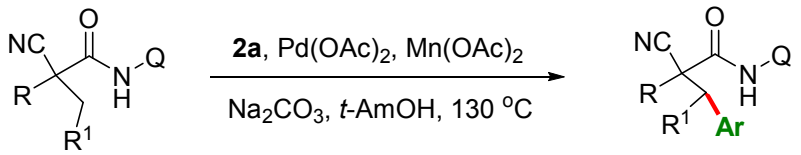
Scheme 2. Reactivity of different aryl/heteroaryl iodides with **1a** and **1b**[a]

Diverse electron withdrawing groups on the aryl iodide (**2d-g**, 4-CO_2Me, 4-$COCH_3$, 4-CN and 4-NO_2) were all well tolerated with **1a** to give the appropriate products in moderate to good yields (**3d-3g**). Importantly, *ortho* substituted aryl iodides (2-OMe, **2h** and 2,4-*di*-OMe, **2i**) were also compatible in the present protocol to afford the desired products in moderate to low yields (**3h** and **3i**), presumably due to steric effects. The 4-chloro-, 3-fluoro-5-nitro- and 3-bromo-5-methylcarboxylate aryl iodides (**2j-l**) successfully gave the corresponding arylated products (**3j-3l**) with reasonably good yields from **1a**. Moreover, α–cyano amide derivative **1b** was also tested under these optimal conditions, with aryl iodides (**2a-f**), bearing electron rich and electron poor groups, to afford the corresponding products in good yields (**4a-4f**). Auspiciously, the reaction of diverse heteroaromatic iodides (**2m-s**) with **1a** smoothly furnished the corresponding heteroaryl substituted, α–cyano amides in synthetically useful yields: substituted thiophene-amide (**3m**, 62%), 1-benzyl-1*H*-pyrazole-amide (**3n**, 76%), 2-pyridine-amide (**3o**, 60%), 6-methoxypyrazine-amide (**3p**, 62%), 2-chloropyridine-amide (**3q**, 75%), *N*-unprotected indole-amide (**3r**, 81%), and 2,3-dihydrobenzofuran-amide (**3s**, 79%), respectively. It is noteworthy to mention here that the obtained products provide a critical handle for further structural elaboration.

A variety of α–cyano carboxylic acid derivatives were successfully arylated with 8-aminoquinoline as a directing group under the optimal reaction conditions with **2a** (Table 2). α–Cyano amides bearing aliphatic long chains (**1c** and **1d**) were well tolerated to afford the corresponding products **5a** and **5b** in excellent yields. 2-Cyano-3-cyclohexylpropanamide derivative **1e** was coupled with **2a** to give **5c** in 78% yield, while 4-phenylbutaramide (**1f**) and 5-phenylpentanamide (**1g**) derivatives afforded the arylated products **5d** and **5e**, respectively, in good yields. Interestingly, 2-cyano-2-methyl-*N*-(quinolin-8-yl)propanamide (**1h**), treated with **2a** under palladium-catalyzed conditions, furnished a mixture of mono-arylated amide (**5f**) in 50% and diarylated amide (**5g**) in 29% yields. Further, the mono-arylated product (**5f**) was treated separately with **2a** under optimal conditions to afford **5g** in 86% yield. α–Cyano-2,5-dimethyl amide analog (**1i**) gave the arylated **5h** in 81% yield. We further examined the

utility of this method by examining the reactivity of monomethylene systems at the β-position (**1j** and **1k**). Treatment of **1j** or **1k** with **2a** under standard reaction conditions failed to give the arylated products (**5i** and **5j**, respectively), presumably due to an active C-H proton at the α-position of the substrates. Only starting materials were recovered from the reaction. Interestingly, the reaction of **3a** (containing two methylene systems at the β-position, 0.1 mmol) and **2a** (0.15 mmol) did afford the corresponding mono-arylated product **5k** at the benzylic position, although in only 20% yield.

Table 2. Arylation of various α–cyanoacetic acid derivatives with 2a[a]

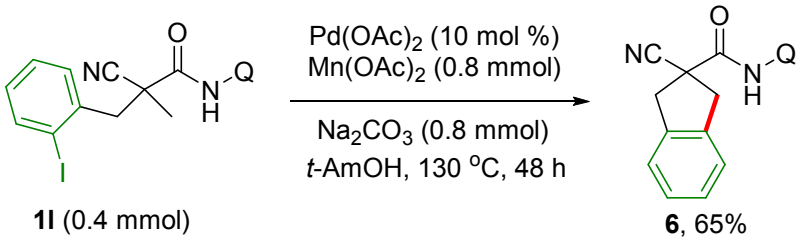


1c-k, 3a, 5f **5a-k**

entry	α–cyanoamide	product (**5**)	yield[a]
1	**1c**, R = *n*-C_5H_{11}-; R^1 = H	**5a**, R = *n*-C_5H_{11}-; R^1 = H	77
2	**1d**, R = *n*-$C_{16}H_{33}$-; R^1 = H	**5b,** R = *n*-$C_{16}H_{33}$; R^1 = H	83
3	**1e**, R = Cyclohexylmethylene-; R^1 = H	**5c**, R = Cyclohexylmethylene-; R^1 = H	78
4	**1f**, R = $PhCH_2$-; R^1 = H	**5d**, R = $PhCH_2$-; R^1 = H	82
5	**1g**, R = $Ph(CH_2)_2$-; R^1 = H	**5e**, R = $Ph(CH_2)_2$-; R^1 = H	84
6	**1h**, R = CH_3, R^1 = H	**5f**, R = CH_3, R^1 = H	50[b]
7	**5f**, R = 4-*MeO*-C_6H_4-; R^1 = H	**5g**, R = 4-*MeO*-C_6H_4-; R^1 = H	86
8	**1i**, R = *i*-Bu; R^1 = H	**5h**, R = *i*-Bu; R^1 = H	81
9	**1j**, R = H; R^1 = $PhCH_2$-	**5i**, R = H; R^1 = $PhCH_2$-	0[c]
10	**1k**, R = H; R^1 = C_9H_{19}-	**5j**, R = H; R^1 = C_9H_{19}-	0[d]
11	**3a**, R = $C_{10}H_{21}$-; R^1 = 4-*MeO*-C_6H_4-	**5k**, R = $C_{10}H_{21}$-; R^1 = 4-*MeO*-C_6H_4-	20[e]

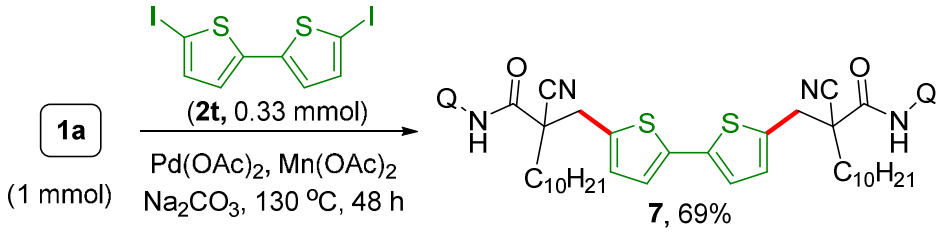
[a]Reaction conditions: α-cyanoamide (0.4 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (10 mol %), $Mn(OAc)_2$ (0.8 mmol), Na_2CO_3 (0.8 mmol), *t*-AmOH (4 mL), 130 °C, 30 h; **Ar-** = 4-*MeO*-C_6H_4-. All the products were characterized by ^1H, ^{13}C NMR, IR and MS. [b]di-arylated product **5g** also formed in 29% yield. [c]45% of **1j** was recovered, [d]89% of **1k** was recovered, [e]0.1 mmol of **3a,** 0.15 mmol of **2a** were used.

Encouraged by the successful utilization of various aryl iodides and α–cyanoamide derivatives for palladium-catalyzed C(sp^3)-H functionalization, we turned our attention to the more challenging intramolecular C(sp^3)-H arylation reaction (Scheme 3). We prepared an α–cyano substrate [2-cyano-3-(2-iodophenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide)] **1l**, embedded with an iodoarene and treated it with 10 mol % $Pd(OAc)_2$, $Mn(OAc)_2$ (2 equiv) and Na_2CO_3 (2 equiv) in *t*-AmOH at 130 ^oC for 48 hours. The reaction proceeded smoothly to give the 2-cyano-2,3-dihydro-1*H*-indene-2-carboxamide derivative (**6**) in 65% yield.



Scheme 3. Intramolecular C(sp^3)-H arylation reaction

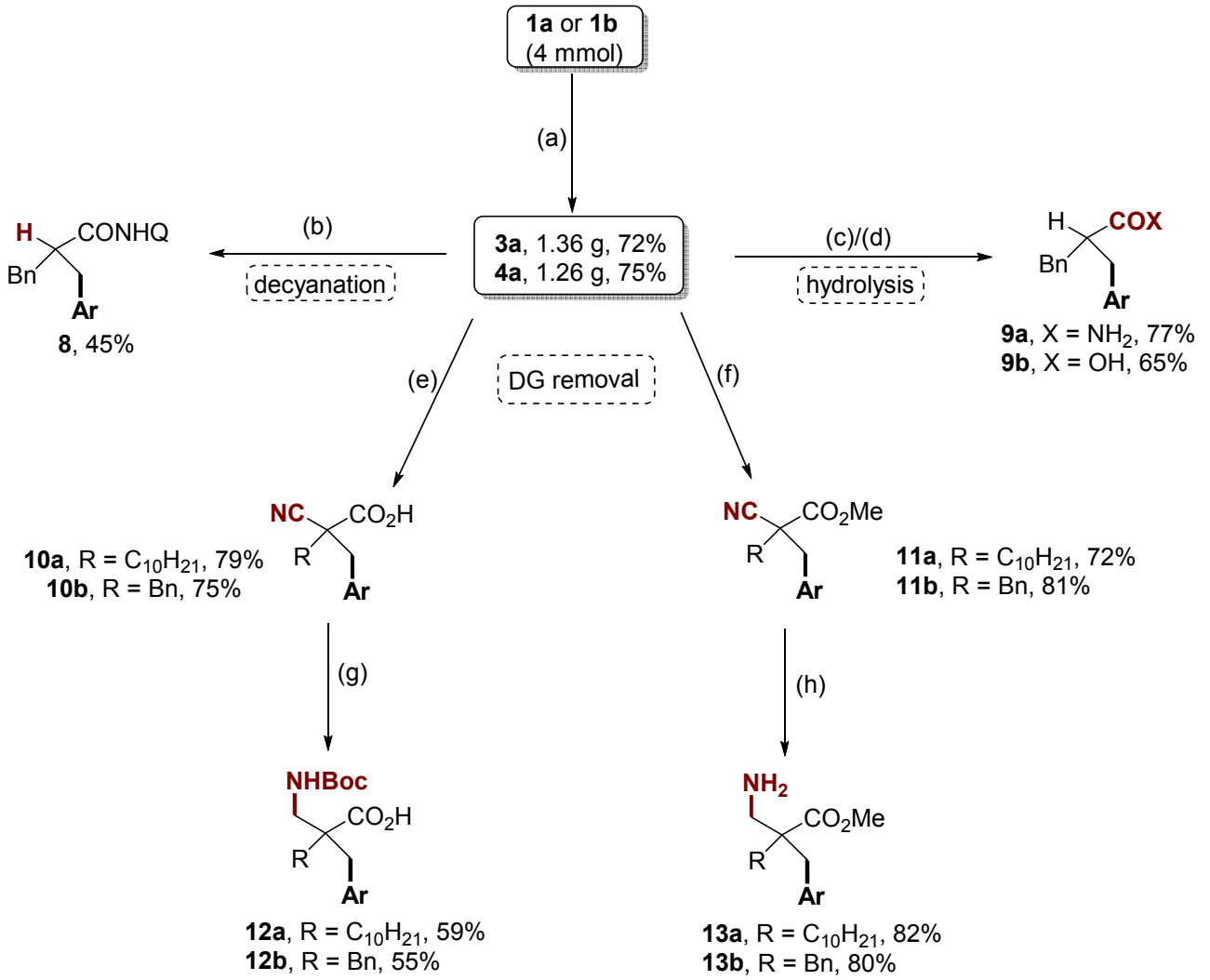
Next, we used 5,5'-diiodo-2,2'-bisthiophene (**2t**) as an aryl iodide to test the structural generality of the reaction under the optimized conditions, as shown in Scheme 4. The reaction of **1a** (3 mmol) with **2t** (1 mmol), proceeded smoothly to give the di-functionalized product (**7**) in 69% yield.



Scheme 4. Arylation of **1a** with diiodo-bisthiophene

Remarkably, we also successfully applied the current protocol to the gram-scale synthesis of arylated compounds **3a** and **4a** using 4 mmoles of **1a** and **1b**, separately, under the optimal conditions with **2a**, resulting in 1.36 g of **3a** (72%) and 1.26 g of **4a** (75%), respectively (Scheme 5). The synthetic usefulness of these representative compounds was demonstrated through various functional group

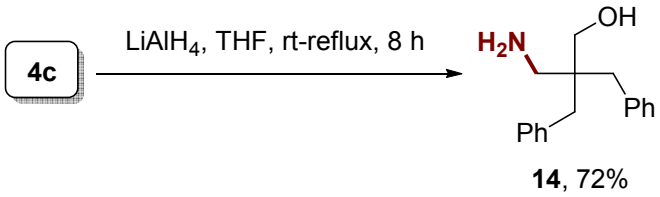
transformations. Initially, elimination of the nitrile group in **4a** resulted in the dialkylated amide (**8**) in 45% yield. We also found that **4a** under strongly basic conditions led to hydrolysis of both nitrile and amide groups, followed by decarboxylation of the acid functional group to afford the α,α–disubstituted amide (**9a**) in 77% yield and acid (**9b**) in 65% yield with longer reaction time. Additionally, in both compounds **3a** and **4a**, the auxiliary 8-aminoquinoline group was easily removed using KOH/*t*-AmOH conditions to generate versatile acid motifs **10a** (79%) and **10b** (75%) in good yields, while the nitrile group remained intact. Similarly, removal of the auxiliary in **3a** and **4a** using HCl/MeOH reflux conditions gave the corresponding methyl esters in excellent yields (**11a**, **11b**). Interestingly, cyanoacids **10a** and **10b** or cyanoesters **11a** and **11b** could be subjected to hydrogenation (Pd-C in MeOH) to give the corresponding *N*-Boc-β-amino acids, **12a** (59%) and **12b** (55%) or β–amino esters, **13a** (82%) and **13b** (80%), respectively.



Reaction conditions: (a) **2a**, $Pd(OAc)_2$, $Mn(OAc)_2$, Na_2CO_3, *t*-AmOH, 130 °C, 30 h. (b) SmI_2, HMPA: THF, 0 °C-rt, 6 h. (c) KOH, *t*-AmOH, 120 °C, 24 h. (d) KOH, *t*-AmOH, 130 °C, 40 h. (e) KOH, *t*-AmOH, 90 °C, 3 h. (f) HCl, MeOH, reflux, 20 h. (g) 10% Pd-C, H_2, $(Boc)_2O$, DIPEA, MeOH, rt, 36-40 h. (h) 10% Pd-C, H_2, HCl, MeOH, rt, 24 h.

Scheme 5. Gram-scale syntheses of **3a** and **4a** and their synthetic utility

To further elaborate the applicability of the obtained products, compound **4c** was subjected to $LiAlH_4$ to provide the 1,3-amino alcohol **14** in 72% yield (Scheme 6).



Scheme 6. Synthesis of 1,3-amino alcohol **14**

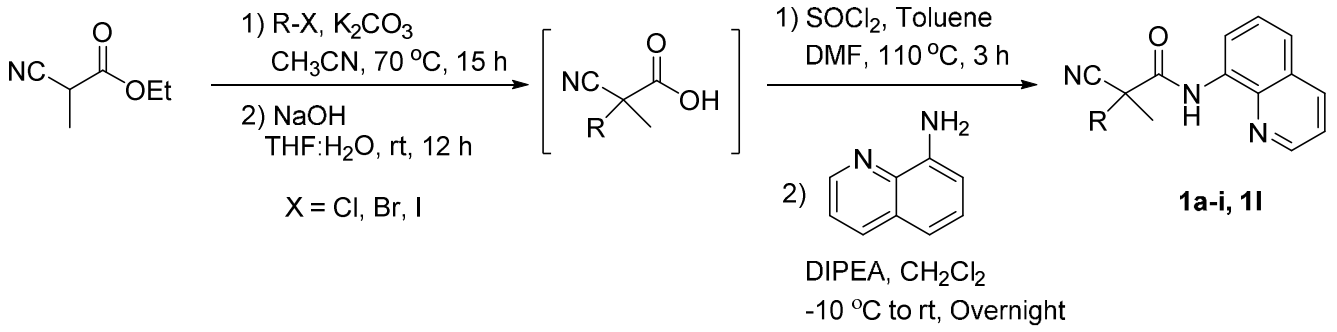
CONCLUSION

In summary, we have developed an 8-aminoquinoline-directed arylation of unactivated C(sp^3)-H bonds of α–cyano aliphatic amides with aryl/heteroaryl iodides under palladium catalysis. The reaction offers wide functional group compatibility, broad substrate scope (including heterocyclic substrates) and provides arylated α–cyano amides in good to excellent yields, even on gram scale. The obtained products can be utilized for the development of various synthetically useful compounds and privileged motifs in pharmaceuticals, such as disubstituted α–cyano acids, α,α–dialkylated acid derivatives, β–amino acid derivatives and amino alcohols. Further applications of this method are underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. All reactions were conducted in glassware that was dried in an oven (120 °C), heated under reduced pressure, and cooled under a stream of argon before use. Reactions were monitored by thin-layer chromatography on silica gel plates using UV-light (254 nm) and ceric sulfate or β-naphthol for visualization. Column chromatography was performed on a flash chromatography system with silica gel columns using *n*-hexane and ethyl acetate as eluent. Evaporation of solvents was conducted under reduced pressure at 50 °C using rotary evaporators. FTIR spectra were recorded neat, wave numbers are indicated in cm^{-1}. NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C). Deuterated chloroform was used as the solvent, and spectra were calibrated against the residual solvent peak 7.26 ppm for ^1H and 77.0 ppm for ^{13}C or against TMS. Chemical shifts (δ) and coupling constants (J) are given in ppm (parts per million) and Hz (Hertz), respectively. The following abbreviations were used to explain multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, bs=broad singlet. Low resolution mass spectra were obtained by electrospray ionization (ESI) in positive mode. High resolution mass spectra (HRMS) were performed with an orbitrap mass analyzer by electrospray ionization (ESI).

General Procedure for the Preparation of Starting Materials:[19]



Scheme 7. Preparation of starting compounds **1a-i, 1l**

To a solution of ethyl 2-cyanopropionate (635 mg, 0.629 mL, 5 mmol) in acetonitrile (20 mL) was added K_2CO_3 (1.38 g, 10 mmol) and alkyl halide (6 mmol). After the addition, the mixture was warmed to 70 ^oC and stirred overnight. The mixture was cooled to room temperature (RT), and the solvent was removed under vacuum. Water (20 mL) was added and the product extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under vacuum. The crude residue was purified by flash column chromatography to provide the corresponding ester. The ester was dissolved in THF (15 mL), and treated with a solution of NaOH (800 mg, 20 mmol, 9 mL of water). The mixture was stirred at RT for 12 h. After removal of THF *in vacuo*, the pH of the aqueous layer was adjusted to 4.0 with 2.0 M HCl. The mixture was extracted with DCM (20 mL x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the crude carboxylic acid, which was used in the next reaction without further purification.

$SOCl_2$ (0.51 mL, 7 mmol) was added slowly to a stirred solution of the carboxylic acid in toluene (15 mL) and DMF (0.1 mL) at room temperature. The mixture was stirred for 3 h at 110 °C and the solvent evaporated *in vacuo*. The residue was then dissolved in toluene (5 mL), evaporated *in vacuo* twice to give the crude acid chloride. The acid chloride was added dropwise to a solution of 8-aminoquinoline (720 mg, 5 mmol) and DIPEA (1.26 g, 1.74 mL, 10 mmol) in CH_2Cl_2 (20 mL) at -10 ^oC over 15 min. The resulting solution was warmed to RT and stirred overnight. The mixture was diluted with CH_2Cl_2 (15 mL) and washed successively with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), HCl (0.5 M,

20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:9, v/v), to afford the corresponding 2-cyano-2-methyl-8-aminoquinolinyl amides **1**.

*2-Cyano-2-methyl-N-(quinolin-8-yl)dodecanamide (**1a**)*: 1-Bromodecane (1.32 g, 1.23 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a brown oil, 1.44 g, 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.88 (s, 1H), 8.89 (dd, J = 4.2, 2.4 Hz, 1H), 8.75 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (td, J = 12.3, 4.5 Hz, 1H), 1.85 (td, J = 12.2, 4.5 Hz, 1H), 1.74 (s, 3H), 1.68-1.57 (m, 1H), 1.51-1.40 (m, 1H), 1.38-1.20 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 166.6, 148.9, 138.8, 136.2, 133.5, 127.9, 127.1, 122.7, 121.9, 121.4, 116.7, 45.5, 38.6, 31.8, 29.5, 29.4, 29.3, 29.3, 29.2, 25.6, 24.1, 22.6, 14.1; FTIR (neat): 3307, 2924, 2853, 2235, 1688, 1529, 1486, 1424, 1327, 1132, 1057, 825, 791, 698 cm^{-1}; MS (ESI): *m/z* 366 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{23}H_{32}ON_3$ $(M+H)^+$: 366.2540, found: 366.2539.

*2-Cyano-2-methyl-3-phenyl-N-(quinolin-8-yl)propanamide (**1b**)*: Benzyl bromide (1.02 g, 0.71 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a brown solid, mp = 82-84 ^{o}C, 1.27 g, 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.79 (dd, J = 4.2, 1.7 Hz, 1H), 8.71 (dd, J = 6.3, 2.7 Hz, 1H), 8.14 (dd, J = 8.3, 1.6 Hz, 1H), 7.57-7.51 (m, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 7.38-7.33 (m, 2H), 7.30-7.18 (m, 3H), 3.44 (d, J = 13.5 Hz, 1H), 3.12 (d, J = 13.5 Hz, 1H), 1.77 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 166.6, 148.8, 138.7, 136.1, 134.5, 133.5, 130.1, 130.0, 128.6, 127.8, 127.0, 122.7, 121.9, 120.9, 116.7, 46.9, 43.9, 23.7; FTIR (neat): 3275, 3028, 2928, 2234, 1687, 1539, 1485, 1331, 1205, 1174, 1072, 882, 792, 699 cm^{-1}; MS (ESI): *m/z* 316 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{18}ON_3$ $(M+H)^+$: 316.1444, found: 316.1440.

*2-Cyano-2-methyl-N-(quinolin-8-yl)heptanamide (**1c**)*: 1-Iodopentane (1.18 g, 0.781 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a dark brown oil, 1.06 g, 72%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.2, 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (td, J = 12.3, 4.5 Hz, 1H), 1.87 (td, J = 12.3, 4.5 Hz, 1H), 1.74 (s, 3H), 1.70-1.57 (m, 1H), 1.52-1.42 (m, 1H), 1.36-1.28 (m, 4H),

0.87 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.6, 148.8, 138.8, 136.2, 133.6, 127.9, 127.1, 122.6, 121.9, 121.4, 116.7, 45.5, 38.5, 31.4, 25.3, 24.1, 22.3, 13.9; FTIR (neat): 3274, 3062, 2929, 2234, 1687, 1537, 1486, 1266, 1174, 1072, 824, 792, 699 cm^{-1}; MS (ESI): *m/z* 296 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{22}ON_3$, $(M+H)^+$: 296.1757, found: 296.1753.

*2-Cyano-2-methyl-N-(quinolin-8-yl)octadecanamide (**1d**)*: 1-Bromohexadecane (1.83 g, 1.83 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow solid, mp = 48-49 ^{o}C, 1.84 g, 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.88 (s, 1H), 8.89 (dd, J = 4.2, 1.7 Hz, 1H), 8.72 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.60-7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (td, J = 12.3, 4.5 Hz, 1H), 1.86 (td, J = 12.3, 4.4 Hz, 1H), 1.74 (s, 3H), 1.68-1.58 (m, 1H), 1.52-1.41 (m, 1H), 1.39-1.19 (m, 26H), 0.87 (t, J = 13.7 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.6, 148.9, 138.8, 136.2, 133.6, 127.9, 127.1, 122.6, 121.9, 121.4, 116.7, 45.5, 38.6, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 25.6, 24.1, 22.7, 14.1; FTIR (neat): 3306, 2914, 2850, 2230, 1709, 1693, 1532, 1466, 1330, 1151, 822, 782 cm^{-1}; MS (ESI): *m/z* 450 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{44}ON_3$ $(M+H)^+$: 450.3479, found: 450.3482.

*2-Cyano-3-cyclohexyl-2-methyl-N-(quinolin-8-yl)propanamide (**1e**)*: (Bromomethyl)cyclohexane (1.06 g, 0.834 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil, 1.25 g, 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.93 (s, 1H), 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.71 (dd, J = 7.1, 1.8 Hz, 1H), 8.18 (dd, J = 8.3, 1.6 Hz, 1H), 7.60-7.52 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 2.13 (dd, J = 14.7, 7.2 Hz, 1H), 1.91 (d, J = 12.8 Hz, 1H), 1.79-1.53 (m, 8H), 1.30-0.93 (m, 6H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.8, 148.9, 138.8, 136.2, 133.6, 127.9, 127.1, 122.6, 121.9, 121.7, 116.7, 45.3, 44.1, 35.4, 34.0, 33.0, 26.0, 25.9, 25.9, 25.8; FTIR (neat): 3308, 2922, 2850, 2234, 1690, 1526, 1424, 1326, 1260, 1132, 922, 825, 755 cm^{-1}; MS (ESI): *m/z* 322 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}ON_3$ $(M+H)^+$: 322.1914, found: 322.1915.

*2-Cyano-2-methyl-4-phenyl-N-(quinolin-8-yl)butanamide (**1f**)*: (2-Bromoethyl)benzene (1.11 g, 0.82 mL, 6 mmol) used as the alkyl halide and the product was obtained as a pale yellow oil, 1.40 g, 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.94 (s, 1H), 8.90 (dd, J = 5.8, 2.6 Hz, 1H), 8.72 (dd, J = 7.2, 1.7 Hz, 1H),

8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.61-7.53 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 7.28-7.14 (m, 5H), 2.94 (td, J = 12.6, 4.8 Hz, 1H), 2.79 (td, J = 12.6, 5.0 Hz, 1H), 2.57 (td, J = 12.4, 5.0 Hz, 1H), 2.13 (td, J = 12.6, 4.8 Hz, 1H), 1.79 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.1, 148.9, 139.8, 138.7, 136.2, 133.4, 128.5, 128.4, 127.8, 127.0, 126.3, 122.8, 121.9, 121.1, 116.8, 45.3, 40.3, 32.0, 24.4; FTIR (neat): 3306, 3029, 2934, 2233, 1687, 1527, 1485, 1326, 1261, 1156, 1055, 790, 697 cm^{-1}; MS (ESI): *m/z* 330 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{20}ON_3$ $(M+H)^+$: 330.1601, found: 330.1602.

*2-Cyano-2-methyl-5-phenyl-N-(quinolin-8-yl)pentanamide (**1g**)*: (3-Bromopropyl)benzene (1.19 g, 0.915 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil, 1.39 g, 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.88 (s, 1H), 8.86 (dd, J = 4.2, 1.6 Hz, 1H), 8.71 (dd, J = 7.0, 1.9 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.58-7.50 (m, 2H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.27-7.22 (m, 2H), 7.19-7.13 (m, 3H), 2.78-2.61 (m, 2H), 2.22-2.14 (m, 1H), 2.02-1.76 (m, 3H), 1.72 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.3, 148.8, 141.0, 138.7, 136.2, 133.5, 128.4, 128.3, 127.8, 127.0, 126.0, 122.7, 121.9, 121.3, 116.7, 45.3, 38.0, 35.3, 27.2, 24.1; FTIR (neat): 3308, 3063, 2935, 2962, 2235, 1687, 1527, 1485, 1326, 1262, 1132, 1029, 929, 825, 750 cm^{-1}; MS (ESI): *m/z* 344 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{22}ON_3$ $(M+H)^+$: 344.1757, found: 344.1764.

*2-Cyano-2-methyl-N-(quinolin-8-yl)propanamide (**1h**)*: Iodomethane (0.85 g, 0.373 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a brown oil, 0.78 g, 65%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.81 (s, 1H), 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.70 (dd, J = 7.0, 1.9 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.60-7.52 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 1.78 (s, 6H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.6, 148.8, 138.7, 136.3, 133.6, 127.9, 127.1, 122.7, 122.0, 121.9, 116.7, 40.0, 25.3; FTIR (neat): 3276, 2984, 2235, 1686, 1531, 1485, 1424, 1327, 1243, 1156, 918, 899, 791, 640 cm^{-1}; MS (ESI): *m/z* 240 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}ON_3$ $(M+H)^+$: 240.1131, found: 240.1132.

*2-Cyano-2,5-dimethyl-N-(quinolin-8-yl)hexanamide (**1i**)*: 1-Bromo-3-methylbutane (0.91 g, 0.758 mL, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil, 1.16 g, 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 8.89 (dd, J = 5.8, 2.6 Hz, 1H), 8.73 (dd, J = 7.1, 1.8 Hz, 1H), 8.13 (dd, J = 8.2, 1.6 Hz, 1H), 7.60-7.52 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 2.14 (td, J = 12.3, 4.6

Hz, 1H), 1.85 (td, *J* = 12.8, 4.4 Hz, 1H), 1.75 (s, 3H), 1.65-1.55 (m, 1H), 1.54-1.47 (m, 1H), 1.41-1.31 (m, 1H), 0.91 (dd, *J* = 6.5, 3.4 Hz, 6H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.6, 148.8, 138.8, 136.2, 133,6, 127.8, 127.1, 122.6, 121.9, 121.4, 116.7, 45.5, 36.6, 34.3, 28.0, 24.1, 22.4; FTIR (neat): 3310, 2956, 2870, 2235, 1688, 1527, 1486, 1466, 1326, 1154, 918, 825, 790, 755 cm^{-1}; MS (ESI): *m/z* 296 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{22}ON_3$ $(M+H)^+$: 296.1757, found: 296.1753.

*2-Cyano-3-(2-iodophenyl)-2-methyl-N-(quinolin-8-yl)propanamide (**1l**)*: 2-Iodobenzyl bromide (1.78 g, 6 mmol) was used as the alkyl halide and the product was obtained as a pale yellow oil, 1.65 g, 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.80 (s, 1H), 8.79 (dd, *J* = 5.8, 2.5 Hz, 1H), 8.75 (dd, *J* = 6.4, 2.5 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.84 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.60-7.53 (m, 2H), 7.48-7.43 (m, 2H), 7.25 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.91 (dd, *J* = 7.7, 1.6 Hz, 1H), 3.62 (d, *J* = 14.2 Hz, 1H), 3.52 (d, *J* = 14.2 Hz, 1H), 1.84 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 165.7, 148.7, 140.1, 138.7, 137.8, 136.1, 133.4, 130.4, 130.3, 129.4, 128.5, 127.8, 127.0, 122.7, 121.8, 120.7, 116.7, 102.6, 46.4, 23.7; FTIR (neat): 3299, 3050, 2988, 2236, 1686, 1527, 1485, 1326, 1241, 1126, 1012, 904, 789 cm^{-1}; MS (ESI): *m/z* 442 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}ION_3$ $(M+H)^+$: 442.0411, found: 442.0416.

*2-Cyano-4-phenyl-N-(quinolin-8-yl)butanamide (**1j**)*: To a solution of ethyl 2-cyanoacetate (565 mg, 0.538 mL, 5 mmol) in acetonitrile (20 mL) was added K_2CO_3 (138 mg, 1 mmol) and (2-bromoethyl)benzene (185 mg, 0.14 mL, 1 mmol). After the addition, the mixture was warmed to 70 ^{o}C and stirred overnight. The mixture was cooled to room temperature (RT), and the solvent was removed under vacuum. Water (20 mL) was added and the product extracted with ethyl acetate (10 ml x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography to provide the corresponding ester. The ester was dissolved in THF (5 mL), and treated with a solution of NaOH (160 mg, 4 mmol, 3 mL of water). The mixture was stirred at RT for 12 h. After removal of THF *in vacuo*, the pH of the aqueous layer was adjusted to 4.0 with 2.0 M HCl. The mixture was extracted with DCM (10 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and

evaporated to give the crude carboxylic acid, which was used in the next reaction without further purification.

A mixture of the crude 2-cyano-4-phenylbutanoic acid (190 mg, 1 mmol), 8-aminoquinoline (145 mg, 1 mmol), EDCI (163 mg, 1.05 mmol), HOBt•H_2O (161 mg, 1.05 mmol), and DIPEA (387 mg, 3 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at RT overnight. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/hexane (1:9, v/v), to give the title compound **1j** as a brown solid (233 mg, 74 % yield). mp = 62-63 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 7.2, 1.7 Hz, 1H), 8.18 (dd, J = 8.3, 1.6 Hz, 1H), 7.59-7.50 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 7.34-7.19 (m, 5H), 3.65 (dd, J = 8.5, 5.9 Hz, 1H), 3.03-2.84 (m, 2H), 2.54-2.37 (m, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 162.6, 148.6, 139.2, 138.3, 136.5, 133.3, 128.7, 128.6, 127.8, 127.1, 126.7, 122.8, 121.9, 117.5, 116.9, 38.9, 32.8, 31.8; FTIR (neat): 3308, 2925, 2853, 2250, 1667, 1536, 1499, 1322, 1239, 827, 790 cm^{-1}; MS (ESI): *m/z* 316 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{18}ON_3$ $(M+H)^+$: 316.1444, found: 316.1445.

*2-Cyano-N-(quinolin-8-yl)dodecanamide (**1k**)*: To a solution of ethyl 2-cyanoacetate (565 mg, 0.538 mL, 5 mmol) in acetonitrile (20 mL) was added K_2CO_3 (138 mg, 1 mmol) and 1-bromodecane (220 mg, 0.20 mL, 1 mmol). After the addition, the mixture was warmed to 70 ^oC and stirred overnight. The mixture was cooled to room temperature (RT), and the solvent was removed under vacuum. Water (20 mL) was added and the product extracted with ethyl acetate (10 ml x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under vacuum. The crude residue was purified by flash column chromatography to provide the corresponding ester. The ester was dissolved in THF (5 mL), and treated with a solution of NaOH (160 mg, 4 mmol, 3 mL of water). The mixture was stirred at RT for 12 h. After removal of THF *in vacuo*, the pH of the aqueous layer was adjusted to 4.0 with 2.0 M HCl. The mixture was extracted with DCM (10 mL x 2). The combined organic layers were

washed with brine (10 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give the crude carboxylic acid, which was used in the next reaction without further purification.

A mixture of the crude 2-cyanododecanoic acid (225 mg, 1 mmol), 8-aminoquinoline (145 mg, 1 mmol), EDCI (163 mg, 1.05 mmol), HOBt•H_2O (161 mg, 1.05 mmol), and DIPEA (387 mg, 3 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at RT overnight. Water was added and the mixture was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/hexane (1:9, v/v), to give the title compound **1k** asa brown solid (245 mg, 70% yield). mp = 89-90 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.52 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 7.0, 1.8 Hz, 1H), 8.17 (dd, J = 8.2, 1.6 Hz, 1H), 7.60-7.51 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 3.70 (dd, J = 7.6, 6.4 Hz, 1H), 2.19-2.07 (m, 2H), 1.67-1.54 (m, 2H), 1.43-1.20 (m, 14H), 0.87 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 162.9, 148.7, 138.5, 136.3, 133.4, 127.8, 127.3, 122.7, 121.9, 117.8, 116.8, 40.0, 31.8, 30.4, 29.5, 29.4, 29.3, 29.2, 28.9, 26.9, 22.7, 14.1; FTIR (neat): 3303, 3006, 2929, 2250, 1948, 1663, 1552, 1492, 1295, 827, 640 cm^{-1}; MS (ESI): *m/z* 352 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{30}ON_3$ $(M+H)^+$: 352.2383, found: 352.2384.

General procedure for the synthesis of arylated cyanoacetic acid derivatives:

To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added the amide derivative (**1**, 0.4 mmol), iodoarene (**2**, 1.2 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), $Mn(OAc)_2$ (138 mg, 0.8 mmol), Na_2CO_3 (85 mg, 0.8 mmol) and *t*-AmOH (4 mL). The mixture was stirred for 30 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and the product extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1 to 6/1) to afford the desired arylated product (**3a-s**, **4a-f** and **5a-5j**).

*2-Cyano-2-(4-methoxybenzyl)-N-(quinolin-8-yl)dodecanamide (**3a**)*: 160 mg, 85%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.64 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 5.9, 3.0 Hz, 1H), 8.12 (dd, J = 8.3, 1.7 Hz, 1H), 7.56-7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 3.66 (s, 3H), 3.36 (d, J = 13.5 Hz, 1H), 3.06 (d, J = 13.5 Hz, 1H), 2.20 (td, J = 13.1, 4.4 Hz, 1H), 1.85 (td, J = 12.3, 4.2 Hz, 1H), 1.70-1.59 (m, 1H), 1.51-1.38 (m, 1H), 1.37-1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.7, 159.1, 148.8, 138.7, 136.0, 133.5, 131.0, 127.8, 127.1, 126.7, 122.7, 121.8, 120.5, 116.6, 113.9, 55.1, 53.2, 42.7, 37.4, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 25.6, 22.7, 14.4; FTIR (neat): 3306, 2924, 2853, 2232, 1686, 1612, 1529, 1325, 1178, 1034, 909, 790 cm^{-1}; MS (ESI): *m/z* 472 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{30}H_{38}O_2N_3$ $(M+H)^+$: 472.2959, found: 472.2959.

*2-Cyano-N-(quinolin-8-yl)-2-(3,4,5-trimethoxybenzyl)dodecanamide (**3b**)*: 178 mg, 84%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.71 (dd, J = 6.9, 1.9 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56-7.48 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 6.53 (s, 2H), 3.67 (s, 6H), 3.56 (s, 3H), 3.31 (d, J = 13.4 Hz, 1H), 3.05 (d, J = 13.4 Hz, 1H), 2.25 (td, J = 12.9, 4.4 Hz, 1H), 1.89 (td, J = 12.3, 4.2 Hz, 1H), 1.75-1.63 (m, 1H), 1.55-1.43 (m, 1H), 1.41-1.20 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.5, 152.9, 148.8, 138.6, 137.2, 136.0, 133.4, 130.2, 127.8, 126.8, 122.7, 121.9, 120.5, 116.4, 106.7, 60.5, 55.9, 53.2, 44.2, 37.4, 31.9, 29.5, 29.4, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 3302, 2960, 2924, 2853, 2232, 1686, 1590, 1529, 1422, 1326, 1240, 1123, 1007, 826, 791 cm^{-1}; MS (ESI): *m/z* 532 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{32}H_{42}O_4N_3$ $(M+H)^+$: 532.3170, found: 532.3172.

*2-Benzyl-2-cyano-N-(quinolin-8-yl)dodecanamide (**3c**)*: 128 mg, 73%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 6.1, 2.8 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56-7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.36-7.32 (m, 2H), 7.25-7.20 (m, 2H), 7.19-7.14 (m, 1H), 3.42 (d, J = 13.4 Hz, 1H), 3.11 (d, J = 13.4 Hz, 1H), 2.21 (td, J = 13.1, 4.1 Hz, 1H), 1.86 (td, J = 12.3, 4.2 Hz, 1H), 1.71-1.58 (m, 1H), 1.51-1.40 (m, 1H), 1.37-1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.5, 148.8, 138.7, 136.0, 134.6, 133.4, 130.0,

128.5, 127.7, 127.5, 126.9, 122.6, 121.8, 120.3, 116.6, 52.9, 43.4, 37.5, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 3303, 3030, 2924, 2853, 2235, 1686, 1529, 1485, 1326, 1206, 1170, 910, 825, 699 cm^{-1}; MS (ESI): *m/z* 442 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{36}ON_3$ $(M+H)^+$: 442.2855, found: 442.2854.

*Methyl 4-(2-cyano-2-(quinolin-8-ylcarbamoyl)dodecyl)benzoate (**3d**)*: 125 mg, 63%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (s, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.58-7.50 (m, 2H), 7.44-7.39 (m, 3H), 3.82 (s, 3H), 3.48 (d, *J* = 13.3 Hz, 1H), 3.14 (d, *J* = 13.3 Hz, 1H), 2.24 (td, *J* = 13.0, 4.5 Hz, 1H), 1.88 (td, *J* = 12.3, 4.2 Hz, 1H), 1.70-1.58 (m, 1H), 1.53-1.40 (m, 1H), 1.37-1.18 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 166.7, 165.0, 148.8, 139.8, 138.9, 136.0, 133.2, 130.0, 129.8, 129.4, 127.8, 126.9, 122.8, 121.8, 120.0, 116.7, 52.6, 52.0, 43.2, 37.7, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.6, 22.7, 14.1; FTIR (neat): 3304, 2924, 2854, 2234, 1721, 1687, 1529, 1486, 1325, 1276, 1106, 1021, 791, 637 cm^{-1}; MS (ESI): *m/z* 500 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{31}H_{38}O_3N_3$ $(M+H)^+$: 500.2908, found: 500.2908.

*2-(4-Acetylbenzyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**3e**)*: 119 mg, 62%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (s, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.58-7.51 (m, 2H), 7.46-7.40 (m, 3H), 3.48 (d, *J* = 13.3 Hz, 1H), 3.15 (d, *J* = 13.3 Hz, 1H), 2.47 (s, 3H), 2.26 (td, *J* = 13.0, 4.4 Hz, 1H), 1.89 (td, *J* = 12.3, 4.2 Hz, 1H), 1.71-1.61 (m, 1H), 1.52-1.41 (m, 1H), 1.38-1.17 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.7, 165.0, 148.8, 140.1, 138.6, 136.3, 136.1, 133.2, 132.5, 130.2, 128.7, 128.5, 127.8, 126.9, 122.8, 121.9, 120.0, 116.7, 52.6, 43.1, 37.8, 31.8, 29.5, 29.5, 29.4, 29.3, 29.2, 26.5, 25.6, 22.6, 14.1; FTIR (neat): 3303, 2954, 2924, 2853, 2234, 1682, 1529, 1486, 1325, 1263, 1018, 826, 611 cm^{-1}; MS (ESI): *m/z* 484 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{31}H_{38}O_2N_3$ $(M+H)^+$: 484.2959, found: 484.2954.

*2-Cyano-2-(4-cyanobenzyl)-N-(quinolin-8-yl)dodecanamide (**3f**)*: 102 mg, 55%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.60 (s, 1H), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 7.3, 1.6 Hz, 1H),

8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.65-7.39 (m, 7H), 3.48 (d, *J* = 13.3 Hz, 1H), 3.13 (d, *J* = 13.3 Hz, 1H), 2.25 (td, *J* = 13.0, 4.4 Hz, 1H), 1.90 (td, *J* = 12.3, 4.2 Hz, 1H), 1.74-1.61 (m, 1H), 1.53-1.41 (m, 1H), 1.39-1.17 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 164.7, 148.9, 140.1, 138.6, 136.1, 133.0, 132.2, 131.1, 127.8, 126.9, 123.0, 122.0, 119.8, 118.5, 116.7, 111.6, 52.6, 43.1, 37.8, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.5, 22.6, 14.1; FTIR (neat): 3303, 2924, 2853, 2229, 1686, 1529, 1485, 1425, 1326, 1170, 910, 825, 790, 608 cm^{-1}; MS (ESI): *m/z* 467 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{30}H_{35}ON_4$ $(M+H)^+$: 467.2805, found: 467.2791.

*2-Cyano-2-(4-nitrobenzyl)-N-(quinolin-8-yl)dodecanamide (**3g**)*: 140 mg, 72%; pale yellow solid, mp = 140-141 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (s, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.59-7.53 (m, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.53 (d, *J* = 13.3 Hz, 1H), 3.18 (d, *J* = 13.3 Hz, 1H), 2.26 (td, *J* = 13.1, 4.4 Hz, 1H), 1.92 (td, *J* = 12.3, 4.3 Hz, 1H), 1.74-1.64 (m, 1H), 1.54-1.42 (m, 1H), 1.39-1.18 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 164.6, 148.9, 147.4, 142.1, 138.6, 136.1, 133.0, 130.9, 127.8, 126.9, 123.7, 123.0, 122.0, 119.8, 116.7, 52.6, 42.8, 37.9, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 3320, 2924, 2853, 2236, 1690, 1530, 1487, 1425, 1299, 1007, 827, 792, 757 cm^{-1}; MS (ESI): *m/z* 487 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}O_3N_4$ $(M+H)^+$: 487.2704, found: 487.2707.

*2-Cyano-2-(2-methoxybenzyl)-N-(quinolin-8-yl)dodecanamide (**3h**)*: 84 mg, 45%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 8.79-8.73 (m, 2H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56-7.51 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28-7.25 (m, 1H), 7.15 (td, *J* = 15.6, 1.7 Hz, 1H), 6.82 (td, *J* = 7.4, 1.0 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 3.69 (s, 3H), 3.35 (dd, *J* = 14.9, 13.6 Hz, 2H), 2.25 (td, *J* = 12.5, 4.4 Hz, 1H), 1.86 (td, *J* = 12.2, 4.2 Hz, 1H), 1.70-1.59 (m, 1H), 1.51-1.40 (m, 1H), 1.37-1.18 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.0, 157.9, 148.7, 138.7, 136.0, 133.7, 131.6, 129.0, 127.7, 127.0, 123.3, 122.4, 121.8, 120.4, 120.3, 116.5, 110.4, 55.1, 52.2, 37.2, 37.0, 31.8, 29.7, 29.5, 29.4, 29.3, 29.2, 25.6, 22.6, 14.4; FTIR (neat): 3305, 2923, 2855, 2233, 1687, 1529, 1425,

1291, 1157, 825, 757 cm^{-1}; MS (ESI): *m/z* 472 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{30}H_{38}O_2N_3$ $(M+H)^+$: 472.2959, found: 472.2959.

*2-Cyano-2-(2,4-dimethoxybenzyl)-N-(quinolin-8-yl)dodecanamide (**3i**)*: 112 mg, 56%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.64 (s, 1H), 8.79-8.73 (m, 2H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.57-7.50 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.34 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 3.68 (s, 3H). 3.64 (s, 3H), 3.28 (dd, *J* = 17.6, 13.6 Hz, 2H), 2.24 (td, *J* = 13.1, 4.4 Hz, 1H), 1.84 (td, *J* = 12.3, 4.2 Hz, 1H), 1.70-1.58 (m, 1H), 1.50-1.39 (m, 1H), 1.37-1.18 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 166.1, 160.4, 158.8, 148.6, 138.7, 136.0, 133.7, 132.0, 127.8, 127.0, 122.4, 121.7, 120.6, 116.5, 115.7, 104.1, 98.3, 55.2, 55.1, 52.5, 37.1, 36.7, 31.8, 29.5, 29.5, 29.4, 29.3, 29.2, 25.7, 22.7, 14.1; FTIR (neat): 3308, 2924, 2853, 2233, 1687, 1528, 1424, 1290, 1208, 1157, 1035, 825, 790, 756 cm^{-1}; MS (ESI): *m/z* 502 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{31}H_{40}O_3N_3$ $(M+H)^+$: 502.3064, found: 502.3066.

*2-(4-Chlorobenzyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**3j**)*: 140 mg, 74%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (s, 1H), 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.69 (dd, *J* = 6.9, 1.9 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58-7.50 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 3.39 (d, *J* = 13.5 Hz, 1H), 3.06 (d, *J* = 13.5 Hz, 1H), 2.21 (td, *J* = 12.9, 4.4 Hz, 1H), 1.86 (td, *J* = 12.9, 4.4 Hz, 1H), 1.73-1.59 (m, 1H), 1.52-1.39 (m, 1H), 1.37-1.16 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.2, 148.8, 148.6, 138.6, 136.0, 133.6, 133.2, 133.1, 131.3, 128.6, 127.8, 126.9, 122.8, 121.9, 120.1, 116.6, 52.8, 42.6, 37.6, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 2924, 2853, 2233, 1686, 1529, 1486, 1326, 1092, 910, 806, 790 cm^{-1}; MS (ESI): *m/z* 476 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}ClON_3$ $(M+H)^+$: 476.2463, found: 476.2466.

*2-Cyano-2-(3-fluoro-5-nitrobenzyl)-N-(quinolin-8-yl)dodecanamide (**3k**)*: 143 mg, 71%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.66 (s, 1H), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.68 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.03 (s, 1H), 7.72 (dt, *J* = 8.2, 2.2 Hz, 1H), 7.60-7.52 (m, 2H), 7.47-7.42 (m, 2H), 3.55 (d, *J* = 13.5 Hz, 1H), 3.16 (d, *J* = 13.5 Hz, 1H), 2.26 (td, *J* = 13.0, 4.5 Hz, 1H), 1.90

(td, J = 12.3, 4.2 Hz, 1H), 1.75-1.66 (m, 1H), 1.55-1.43 (m. 1H), 1.40-1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 164.4, 163.3, 160.8, 148.9, 138.7, 136.2, 132.8,127.8, 127.1, 123.5, 123.1, 121.9, 120.9, 119.5, 116.9, 110.8, 110.5, 52.4, 42.4, 37.8, 31.8, 29.7, 29.4, 29.4, 29.2, 29.2, 25.5, 22.6, 14.1; FTIR (neat): 3299, 2924, 2854, 2235, 1687, 1529, 1485, 1352, 1147, 882, 790 cm^{-1}; MS (ESI): *m/z* 505 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{34}FO_3N_4$ $(M+H)^+$: 505.2609, found: 505.2610.

*Methyl 3-bromo-5-(2-cyano-2-(quinolin-8-ylcarbamoyl)dodecyl)benzoate (**3l**)*: 150 mg, 65%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.60 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 6.6, 2.3 Hz, 1H), 8.14 (dd, J = 8.3, 1.6 Hz, 1H), 7.92 (dt, J = 12.0, 3.3 Hz, 1H), 7.66 (t, J = 1.6 Hz, 1H), 7.59-7.51 (m, 2H), 7.44 (dd, J = 8.3, 4.2 Hz, 1H), 3.78 (s, 3H), 3.42 (d, J = 13.4 Hz, 1H), 3.10 (d, J = 13.4 Hz, 1H), 2.24 (td, J = 13.4, 4.5 Hz, 1H), 1.87 (td, J = 12.8, 4.2 Hz, 1H), 1.73-1.61 (m, 1H), 1.54-1.41 (m. 1H), 1.40-1.19 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 165.3, 164.9, 148.8, 138.6, 137.7, 137.0, 136.0, 133.0, 132.0, 131.9, 129.7. 126.9, 122.9, 122.5, 121.9, 119.7, 116.9, 52.6, 52.3, 42.7, 37.4, 31.8, 29.5, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 2924, 2853, 1726, 1686, 1528, 1485, 1425, 1280, 1204, 886, 825, 763 cm^{-1}; MS (ESI): *m/z* 578 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{31}H_{37}BrO_3N_3$ $(M+H)^+$: 578.2013, found: 578.2014.

*2-((5-Acetylthiophen-2-yl)methyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**3m**)*: 121 mg, 62%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.81 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.74 (dd, J = 7.1, 1.8 Hz, 1H), 8.19 (dd, J = 8.3, 1.6 Hz, 1H), 7.63-7.55 (m, 1H), 7.52-7.46 (m, 2H), 7.10 (d, J = 3.8 Hz, 1H), 3.70 (d, J = 14.5 Hz, 3H), 3.35 (d, J = 14.5 Hz, 1H), 2.44 (s, 3H), 2.21 (td, J = 13.4, 4.4 Hz, 1H), 1.95 (td, J = 12.3, 4.3 Hz, 1H), 1.75-1.65 (m, 1H), 1.55-1.42 (m. 1H), 1.41-1.18 (m, 14H), 0.87 (t, J = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 164.7, 148.9, 145.2, 144.1, 138.7, 136.1, 133.2, 132.6, 129.1, 127.8, 127.0, 122.9, 121.9, 119.8, 116.9, 52.7, 37.7, 37.7, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 29.1, 26.6, 25.5, 22.6, 14.1; FTIR (neat): 2955, 2924, 2853, 2235, 1686, 1660, 1528, 1485, 1326, 1273, 928, 825, 790 cm^{-1}; MS (ESI): *m/z* 490 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{36}N_3O_2S$ $(M+H)^+$: 490.2523, found: 490.2525.

*2-((1-Benzyl-1H-pyrazol-4-yl)methyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**3n**)*: 158 mg, 76%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 7.4, 1.5 Hz, 1H), 8.16 (dd, J = 8.3, 1.6 Hz, 1H), 7.59-7.49 (m, 3H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 7.37 (s, 1H), 7.14-7.09 (m, 1H), 7.07-7.01 (m, 2H), 6.99-6.96 (m, 2H), 5.14 (s, 2H), 3.28 (d, J = 14.3 Hz, 1H), 2.99 (d, J = 14.3 Hz, 1H), 2.16 (td, J = 13.1, 4.4 Hz, 1H), 1.87 (td, J = 12.2, 4.2 Hz, 1H), 1.70-1.59 (m, 1H), 1.51-1.38 (m, 1H), 1.36-1.16 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.7, 148.8, 140.3, 138.7, 136.3, 136.1, 133.3, 129.3, 128.5, 127.8, 127.7, 127.3, 127.0, 122.7, 121.9, 120.7, 116.6, 114.6, 55.9, 53.1, 37.3, 33.0, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 3304, 2923, 2853, 2232, 1684, 1529, 1485, 1455, 1326, 1170, 909, 825, 790, 696 cm^{-1}; MS (ESI): *m/z* 522 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{33}H_{40}ON_5$ $(M+H)^+$: 522.3227, found: 522.3226.

*2-Cyano-2-(pyridin-2-ylmethyl)-N-(quinolin-8-yl)dodecanamide (**3o**)*: 106 mg, 60%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.85 (s, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.73 (dd, J = 6.7, 2.2 Hz, 1H), 8.45 (d, J = 4.2 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.58-7.51 (m, 3H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.07 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 3.66 (d, J = 14.2 Hz, 1H), 3.33 (d, J = 14.2 Hz, 1H), 2.26 (td, J = 13.3, 4.6 Hz, 1H), 1.96 (td, J = 12.5, 4.3 Hz, 1H), 1.77-1.63 (m, 1H), 1.57-1.44 (m, 1H), 1.39-1.17 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.9, 155.3, 149.4, 148.8, 138.8, 136.4, 136.0, 133.7, 127.8, 127.0, 123.8, 122.5, 122.2, 121.8, 120.3, 116.7, 51.0, 44.7, 37.9, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 25.4, 22.6, 14.1; FTIR (neat): 3292, 2948, 2920, 2851, 2240, 1678, 1589, 1529, 1426, 1325, 1256, 910, 834, 778 cm^{-1}; MS (ESI): *m/z* 443 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{35}ON_4$ $(M+H)^+$: 443.2805, found: 443.2806.

*2-Cyano-2-((6-methoxypyrazin-2-yl)methyl)-N-(quinolin-8-yl)dodecanamide (**3p**)*: 117 mg, 62%; brown solid, mp = 60-61 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.90 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.69 (dd, J = 7.3, 1.6 Hz, 1H), 8.17 (dd, J = 8.3, 1.6 Hz, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.59-7.50 (m, 2H), 7.48 (dd, J = 8.3, 4.2 Hz, 1H), 3.66 (s, 3H), 3.65 (d, J = 15.1 Hz, 1H), 3.26 (d, J = 15.1 Hz, 1H), 2.23 (td, J = 13.1, 4.1 Hz, 1H), 1.99 (td, J = 12.6, 4.2 Hz, 1H), 1.88-1.68 (m, 1H), 1.59-1.46 (m, 1H), 1.41-

1.19 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 165.7, 159.7, 148.8, 147.4, 138.6, 136.2, 135.6, 134.1, 133.5, 127.8, 127.1, 122.6, 121.9, 120.3, 116.6, 53.7, 49.6, 40.7, 38.5, 31.8, 29.5, 29.4, 29.3, 29.2, 29.2, 25.3, 22.6, 14.1; FTIR (neat): 3299, 2924, 2854, 2236, 1686, 1541, 1485, 1302, 1245, 1009, 905, 799, 665 cm^{-1}; MS (ESI): *m/z* 474 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}O_2N_5$ $(M+H)^+$: 474.2864, found: 474.2864.

2-((6-Chloropyridin-3-yl)methyl)-2-cyano-N-(quinolin-8-yl)dodecanamide ***(3q)***: 143 mg, 75%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 8.80 (dd, J = 4.2, 1.6 Hz, 1H), 8.68 (dd, J = 7.3, 1.5 Hz, 1H), 8.35 (d, J = 2.2 Hz, 1H), 8.15 (dd, J = 8.3, 1.6 Hz, 1H), 7.65 (dd, J = 8.2, 2.5 Hz, 1H), 7.60-7.50 (m, 2H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 3.44 (d, J = 13.7 Hz, 1H), 3.07 (d, J = 13.7 Hz, 1H), 2.23 (td, J = 12.9, 4.5 Hz, 1H), 1.91 (td, J = 12.9, 4.4 Hz, 1H), 1.75-1.61 (m, 1H), 1.53-1.41 (m, 1H), 1.40-1.18 (m, 14H), 0.86 (t, J = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 164.6, 151.0, 150.8, 148.9, 140.2, 138.6, 136.2, 129.4, 127.8, 126.9, 124.7, 123.2, 121.9, 119.7, 116.8, 52.5, 39.6, 37.8, 31.9, 29.5, 29.4, 29.4, 29.3, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 2924, 2853, 2232, 1686, 1529, 1460, 1386, 1105, 825, 790 cm^{-1}; MS (ESI): *m/z* 477 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{34}ClON_4$ $(M+H)^+$: 477.2416, found: 477.2416.

2-((1H-Indol-5-yl)methyl)-2-cyano-N-(quinolin-8-yl)dodecanamide ***(3r)***: 155 mg, 81%; brown semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.65 (s, 1H), 8.73 (dd, J = 6.7, 2.2 Hz, 1H), 8.60 (dd, J = 4.2, 1.6 Hz, 1H), 8.15 (s, 1H), 8.01 (dd, J = 8.3, 1.6 Hz, 1H), 7.60 (s, 1H), 7.51-7.44 (m, 2H), 7.29 (dd, J = 8.3, 4.2 Hz, 1H), 7.18-7.11 (m, 2H), 7.04 (t, J = 2.9 Hz, 1H), 6.39 (t, J = 4.5 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 3.21 (d, J = 13.6 Hz, 1H), 2.23 (td, J = 13.1, 4.5 Hz, 1H), 1.84 (td, J = 12.5, 4.2 Hz, 1H), 1.69-1.58 (m, 1H), 1.51-1.39 (m, 1H), 1.35-1.16 (m, 14H), 0.84 (t, J = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.1, 148.7, 138.7, 136.0, 135.3, 133.5, 128.0, 127.8, 127.0, 125.8, 124.6, 124.0, 122.6, 122.2, 121.7, 120.8, 116.7, 111.0, 102.5, 53.6, 43.8, 37.4, 31.9, 29.7, 29.5, 29.4, 29.3, 29.3, 25.7, 22.7, 14.2; FTIR (neat): 3379, 3304, 2923, 2853, 2233, 1686, 1528, 1485, 1326, 1965, 908, 825, 729 cm^{-1}; MS (ESI): *m/z* 481 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{31}H_{37}ON_4$ $(M+H)^+$: 481.2962, found: 481.2964.

*2-Cyano-2-((2,3-dihydrobenzofuran-5-yl)methyl)-N-(quinolin-8-yl)dodecanamide (**3s**)*: 156 mg, 81%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 6.1, 2.8 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.56-7.50 (m, 2H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, J = 8.2, 1.8 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.45-4.37 (m, 1H), 4.36-4.28 (m, 1H), 3.32 (d, J = 13.6 Hz, 1H), 3.12-3.03 (m, 1H), 3.02 (d, J = 13.6 Hz, 1H), 2.90-2.80 (m, 1H), 2.20 (td, J = 13.1, 4.4 Hz, 1H), 1.85 (td, J = 12.2, 4.2 Hz, 1H), 1.71-1.59 (m, 1H), 1.52-1.40 (m, 1H), 1.37-1.15 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.7, 159.5, 148.7, 138.6, 136.0, 133.5, 129.7, 127.8, 127.1, 126.9, 126.5, 122.6, 121.8, 120.5, 116.6, 109.1, 71.1, 53.3, 43.2, 37.2, 31.8, 29.7, 29.5, 29.4, 29.4, 29.3, 29.2, 29.2, 25.6, 22.7, 14.1; FTIR (neat): 3306, 2923, 2853, 2233, 1686, 1528, 1487, 1325, 1243, 1105, 982, 825, 790, 693 cm^{-1}; MS (ESI): *m/z* 484 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{31}H_{38}O_2N_3$ $(M+H)^+$: 484.2959, found: 484.2954.

*2-Benzyl-2-cyano-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (**4a**)*: 149 mg, 89%; brown solid, mp = 117-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.35 (s, 1H), 8.70-8.66 (m, 2H), 8.08 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 4.2 Hz, 2H), 7.40-7.33 (m, 3H), 7.30-7.12 (m, 5H), 6.74 (d, J = 8.5 Hz, 2H), 3.66 (s, 3H), 3.51 (dd, J = 16.5, 13.1 Hz, 2H), 3.12 (dd, J = 15.7, 13.7 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 164.9, 159.0, 148.6, 138.6, 135.9, 134.5, 133.3, 131.2, 130.0, 128.5, 127.6, 127.6, 126.9, 126.5, 122.6, 121.7, 119.8, 116.6, 113.9, 55.0, 54.7, 42.9, 42.4; FTIR (neat): 3304, 3030, 2942, 2830, 2233, 1686, 1530, 1426, 1325, 1179, 1035, 790 cm^{-1}; MS (ESI): *m/z* 422 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{24}O_2N_3$ $(M+H)^+$: 422.1863, found: 422.1863.

*2-Benzyl-2-cyano-N-(quinolin-8-yl)-3-(3,4,5-trimethoxyphenyl)propanamide (**4b**)*: 159 mg, 83%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37 (s, 1H), 8.69 (dd, J = 5.6, 3.3 Hz, 1H), 8.66 (dd, J = 4.2, 1.6 Hz, 1H), 8.06 (dd, J = 8.3, 1.6 Hz, 1H), 7.52-7.47 (m, 2H), 7.40 (d, J = 7.0 Hz, 2H), 7.36 (dd, J = 8.3, 4.2 Hz, 1H), 7.30-7.19 (m, 3H), 6.53 (s, 2H), 3.66 (s, 6H), 3.58 (d, J = 13.4 Hz, 1H), 3.53 (s, 3H), 3.43 (d, J = 13.4 Hz, 1H), 3.18 (d, J = 13.5 Hz, 1H), 3.08 (d, J = 13.4 Hz, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 164.9, 152.9, 148.7, 138.5, 137.2, 135.9, 134.5, 133.3, 130.2, 129.9, 128.6, 127.7, 127.6, 126.7, 122.7, 121.8, 119.8, 116.3, 106.7, 60.5, 55.9, 54.5, 43.8, 42.8; FTIR (neat): 2936, 2837,

2248, 1683, 1590, 1528, 1485, 1326, 1240, 1124, 1004, 826, 698 cm^{-1}; MS (ESI): *m/z* 482 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{28}O_4N_3$ $(M+H)^+$: 482.2074, found: 482.2076.

*2-Benzyl-2-cyano-3-phenyl-N-(quinolin-8-yl)propanamide (**4c**)*: 116 mg, 74%; brown solid, mp = 129-130 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 8.69 (dd, J = 5.4, 3.3 Hz, 1H), 8.64 (d, J = 2.9 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.55-7.49 (m, 2H), 7.40-7.32 (m, 5H), 7.27-7.12 (m, 6H), 3.55 (d, J = 13.4 Hz, 2H), 3.15 (d, J = 13.4 Hz, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 164.8, 148.6, 138.5, 135.8, 134.4, 133.2, 130.1, 128.5, 127.6, 127.5, 126.8, 122.6, 121.7, 119.7, 116.5, 54.4, 43.0; FTIR (neat): 3274, 3063, 2933, 2235, 1679, 1530, 1514, 1455, 1327, 1249, 1091, 1030, 910, 823, 758 cm^{-1}; MS (ESI): *m/z* 392 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{26}H_{22}ON_3$ $(M+H)^+$: 392.1757, found: 392.1755.

*Methyl 4-(2-benzyl-2-cyano-3-oxo-3-(quinolin-8-ylamino)propyl)benzoate (**4d**)*: 115 mg, 64%; white solid, mp = 191-192 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 8.67 (t, J = 4.5 Hz, 1H), 8.62 (dd, J = 4.2, 1.6 Hz, 1H), 8.06 (dd, J = 8.3, 1.6 Hz, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 4.2 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.39-7.31 (m, 3H), 7.26-7.21 (m, 2H), 7.20-7.15 (m, 1H), 3.81 (s, 3H), 3.51 (dd, J = 15.0, 13.4 Hz, 2H), 3.17 (dd, J = 13.3, 7.5 Hz, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 166.7, 164.4, 148.6, 139.7, 138.5, 135.9, 134.1, 133.0, 130.1, 130.1, 129.8, 129.4, 128.6, 127.8, 127.6, 126.8, 122.8, 121.7, 119.4, 116.6, 54.1, 52.0, 43.3, 42.7; FTIR (neat): 3340, 3048, 3009, 2941, 2233, 1690, 1712, 1524, 1487, 1289, 1172, 1111, 983, 823, 738 cm^{-1}; MS (ESI): *m/z* 450 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}O_3N_3$ $(M+H)^+$: 450.1812, found: 450.1814.

*2-(4-Acetylbenzyl)-2-cyano-3-phenyl-N-(quinolin-8-yl)propanamide (**4e**)*: 121 mg, 70%; white solid, mp = 172-173 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 8.67 (dd, J = 5.1, 3.8 Hz, 1H), 8.60 (dd, J = 4.2, 1.6 Hz, 1H), 8.05 (dd, J = 8.3, 1.6 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.54-7.48 (m, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 7.0 Hz, 2H), 7.33 (dd, J = 8.2, 4.2 Hz, 1H), 7.26-7.21 (m, 2H), 7.20-7.15 (m, 1H), 3.59 (dd, J = 14.6, 13.4 Hz, 2H), 3.18 (dd, J = 13.2, 9.7 Hz, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.6, 164.4, 148.6, 139.9, 138.5, 136.3, 135.9, 134.1, 133.0, 130.3, 130.1, 128.6, 128.5, 127.8, 127.6, 126.8, 122.8, 121.7, 119.4, 116.6, 54.1, 43.3, 42.7, 26.5; FTIR (neat): 3337, 3042,

2924, 2852, 223, 1691, 1675, 1523, 1486, 1269, 1172, 1089, 960, 822, 739, 632 cm^{-1}; MS (ESI): *m/z* 434 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}O_2N_3$ $(M+H)^+$: 434.1863, found: 434.1863.

*2-Benzyl-2-cyano-3-(4-cyanophenyl)-N-(quinolin-8-yl)propanamide (**4f**)*: 101 mg, 61%; white solid, mp = 170-171 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H), 8.69-8.61 (m, 2H), 8.10 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.55-7.51 (m, 2H), 7.50-7.43 (m, 4H), 7.42-7.35 (m, 3H), 7.29-7.17 (m, 3H), 3.59 (dd, *J* = 13.2, 10.9 Hz, 2H), 3.21 (d, *J* = 13.4 Hz, 1H), 3.13 (d, *J* = 13.4 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 164.1, 148.7, 140.0, 138.5, 136.0, 133.9, 132.9, 132.3, 130.9, 130.1, 128.7, 128.0, 127.7, 126.8, 123.0, 121.9, 119.3, 118.5, 116.6, 111.7, 54.1, 43.4, 42.7; FTIR (neat): 3274, 3060, 2225, 1679, 1526, 1486, 1328, 1208, 1174, 1019, 915, 824, 699 cm^{-1}; MS (ESI): *m/z* 417 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}ON_4$ $(M+H)^+$: 417.1710, found: 417.1712.

*2-Cyano-2-(4-methoxybenzyl)-N-(quinolin-8-yl)heptanamide (**5a**)*: 123 mg, 77%; brown oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (s, 1H), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.72 (dd, *J* = 5.9, 3.0 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56-7.50 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 3.66 (s, 3H), 3.36 (d, *J* = 13.5 Hz, 1H), 3.06 (d, *J* = 13.5 Hz, 1H), 2.20 (td, *J* = 13.6, 4.8 Hz, 1H), 1.85 (td, *J* = 12.2, 4.3 Hz, 1H), 1.70-1.59 (m, 1H), 1.51-1.39 (m, 1H), 1.37-1.26 (m, 4H), 0.85 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.6, 158.9, 148.7, 138.7, 136.0, 133.4, 131.0, 127.6, 126.9, 126.6, 122.6, 121.8, 120.4, 116.6, 113.8, 55.0, 53.2, 42.7, 37.3, 31.5, 25.3, 22.3, 13.9; FTIR (neat): 3306, 2928, 2859, 2233, 1685, 1528, 1485, 1325, 1247, 1178, 1033, 909, 825, 790 cm^{-1}; MS (ESI): *m/z* 402 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}O_2N_3$ $(M+H)^+$: 402.2176, found: 402.2176.

*2-Cyano-2-(4-methoxybenzyl)-N-(quinolin-8-yl)octadecanamide (**5b**)*: 184 mg, 83%; brown oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.63 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.75 (dd, *J* = 5.2, 3.7 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.56-7.49 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 3.65 (s, 3H), 3.36 (d, *J* = 13.6 Hz, 1H), 3.05 (d, *J* = 13.6 Hz, 1H), 2.20 (td, *J* = 13.0, 4.4 Hz, 1H), 1.85 (td, *J* = 12.4, 4.2 Hz, 1H), 1.70-1.58 (m, 1H), 1.51-1.39 (m, 1H), 1.38-1.18 (m, 26H), 0.87 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.6, 159.0, 148.7, 138.7,

136.0, 133.4, 131.0, 127.7, 127.0, 126.7, 122.6, 121.8, 120.4, 116.6, 113.8, 55.0, 53.2, 42.7, 37.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.3, 25.6, 22.7, 14.1; FTIR (neat): 3337, 2922, 2852, 2233, 1689, 1528, 1513, 1486, 1327, 1250, 1178, 960, 824, 757 cm^{-1}; MS (ESI): *m/z* 556 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{36}H_{50}O_2N_3$ $(M+H)^+$: 556.3898, found: 556.3894.

*2-Cyano-3-cyclohexyl-2-(4-methoxybenzyl)-N-(quinolin-8-yl)propanamide (**5c**)*: 132 mg, 78%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.60 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.68 (dd, *J* = 5.7, 3.2 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.57-7.49 (m, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 3.62 (s, 3H), 3.32 (d, *J* = 13.5 Hz, 1H), 3.02 (d, *J* = 13.5 Hz, 1H), 2.21 (td, *J* = 13.9, 7.2 Hz, 1H), 1.92 (d, *J* = 12.6 Hz, 1H), 1.82-1.55 (m, 7H), 1.27-0.93 (m, 6H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.9, 159.0, 148.7, 138.7, 136.0, 133.5, 131.1, 127.7, 127.0, 126.4, 122.6, 121.8, 120.6, 116.6, 113.8, 55.0, 51.7, 44.1, 43.9, 35.5, 34.0, 33.1, 26.0, 26.0, 25.9; FTIR (neat): 3305, 2923, 2850, 2233, 1686, 1612, 1527, 1512, 1463, 1326, 1249, 1178, 1033, 908, 825, 608 cm^{-1}; MS (ESI): *m/z* 428 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}O_2N_3$ $(M+H)^+$: 428.2333, found: 428.2332.

*2-Cyano-2-(4-methoxybenzyl)-4-phenyl-N-(quinolin-8-yl)butanamide (**5d**)*: 143 mg, 82%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.72 (dd, *J* = 5.4, 3.5 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.55-7.49 (m, 2H), 7.40 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.28-7.12 (m, 7H), 6.73 (d, *J* = 8.7 Hz, 2H), 3.64 (s, 3H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.09 (dd, *J* = 13.6 Hz, 1H), 2.94 (td, *J* = 12.9, 4.6 Hz, 1H), 2.77 (td, *J* = 12.7, 4.9 Hz, 1H), 2.54 (td, *J* = 13.4, 5.0 Hz, 1H), 2.13 (td, *J* = 12.5, 4.6 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.2, 159.0, 148.7, 139.9, 138.7, 136.0, 133.3, 131.0, 128.5, 128.4, 127.7, 126.9, 126.4, 126.3, 122.7, 121.8, 120.2, 116.7, 113.9, 55.0, 52.9, 42.8, 39.0, 31.0; FTIR (neat): 3303, 3029, 2930, 2836, 2234, 1684, 1528, 1424, 1326, 1178, 908, 790, 697 cm^{-1}; MS (ESI): *m/z* 436 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{26}O_2N_3$ $(M+H)^+$: 436.2020, found: 436.2020.

*2-Cyano-2-(4-methoxybenzyl)-5-phenyl-N-(quinolin-8-yl)pentanamide (**5e**)*: 150 mg, 84%; pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ 10.62 (s, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 5.8, 1.2

Hz, 1H), 8.10 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.55-7.49 (m, 2H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.26-7.20 (m, 4H), 7.16-7.12 (m, 3H), 6.73 (d, *J* = 8.7 Hz, 2H), 3.65 (s, 3H), 3.55 (d, *J* = 13.6 Hz, 1H), 3.05 (dd, *J* = 13.6 Hz, 1H), 2.74-2.59 (m, 2H), 2.32-2.22 (m, 1H), 2.05-1.74 (m, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 165.4, 159.0, 148.7, 141.0, 138.7, 136.0, 133.3, 131.0, 128.4, 128.3, 127.7, 126.9, 126.5, 126.0, 122.7, 121.8, 120.3, 116.7, 113.9, 55.0, 53.0, 42.7, 36.9, 35.4, 27.2; FTIR (neat): 3030, 2931, 2836, 2233, 1684, 1611, 1528, 1485, 1325, 1178, 1031, 908, 825, 698 cm^{-1}; MS (ESI): *m/z* 450 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{29}H_{28}O_2N_3$ $(M+H)^+$: 450.2176, found: 450.2176.

*2-Cyano-3-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)propanamide (**5f**)*: **5f** was obtained according to the general procedure as a pale yellow solid 69 mg (50%) along with the diarylated product **5g** (29%); mp = 104-105 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.66 (s, 1H), 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58-7.51 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.29-7.24 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 3.70 (s, 3H), 3.38 (d, *J* = 13.6 Hz, 1H), 3.06 (d, *J* = 13.6 Hz, 1H), 1.76 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 166.0, 159.0, 148.7, 138.7, 136.1, 133.4, 131.1, 127.7, 127.0, 126.6, 122.6, 121.8, 121.0, 116.7, 113.9, 55.1, 47.1, 43.3, 23.6; FTIR (neat): 3287, 2931, 2835, 2234, 1684, 1532, 1511, 1487, 1331, 1252, 1123, 1028, 806, 761 cm^{-1}; MS (ESI): *m/z* 346 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{20}O_2N_3$ $(M+H)^+$: 346.1550, found: 346.1550.

*2-Cyano-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (**5g**)*: **5g** was obtained according to the general procedure as a pale yellow solid, 155 mg (86%) from **5f** and 52 mg (29%) from **1h** along with mono arylated compound **5f**; mp = 110-111 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.39 (s, 1H), 8.70-8.64 (m, 2H), 8.07 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.51 (d, *J* = 3.8 Hz, 2H), 7.36 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.26 (d, J = 8.7 Hz, 4H), 6.73 (d, *J* = 8.7 Hz, 4H), 3.66 (s, 6H), 3.47 (d, *J* = 13.5 Hz, 2H), 3.08 (d, *J* = 13.6 Hz, 2H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 165.1, 159.0, 148.6, 138.6, 135.9, 133.3, 131.1, 127.6, 126.9, 126.5, 122.6, 121.7, 119.9, 116.5, 113.9, 55.0, 54.9, 42.2; FTIR (neat): 3301, 2932, 2835, 2235, 1683, 1611, 1529, 1511, 1424, 1326, 1245, 1177, 1030, 909, 825, 790 cm^{-1}; MS (ESI): *m/z* 452 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{26}O_3N_3$ $(M+H)^+$: 452.1969, found: 452.1971.

*2-Cyano-2-(4-methoxybenzyl)-5-methyl-N-(quinolin-8-yl)hexanamide (**5h**)*: 129 mg, 81%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (s, 1H), 8.77 (dd, J = 4.2, 1.6 Hz, 1H), 8.72 (dd, J = 5.7, 3.3 Hz, 1H), 8.11 (dd, J = 8.2, 1.6 Hz, 1H), 7.56-7.50 (m, 2H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 3.65 (s, 3H), 3.37 (d, J = 13.6 Hz, 1H), 3.06 (d, J = 13.6 Hz, 1H), 2.22 (td, J = 13.1, 4.6 Hz, 1H), 1.87 (td, J = 13.1, 3.9 Hz, 1H), 1.62-1.49 (m, 2H), 1.40-1.29 (m, 1H), 0.89 (t, d, J = 6.3 Hz, 6H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.6, 159.0, 148.7, 138.7, 136.0, 133.4, 131.0, 127.7, 127.0, 126.4, 122.6, 121.8, 120.4, 116.6, 113.8, 55.0, 53.2, 42.7, 35.4, 34.2, 28.0, 22.3; FTIR (neat): 3304, 2956, 2927, 2873, 2235, 1685, 1528, 1512, 1465, 1325, 1245, 1177, 1033, 9009, 825, 694 cm^{-1}; MS (ESI): *m/z* 402 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}O_2N_3$ $(M+H)^+$: 402.2176, found: 402.2176.

*2-(Bis(4-methoxyphenyl)methyl)-2-cyano-N-(quinolin-8-yl)dodecanamide (**5k**)*: To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added the amide derivative (**3a**, 47 mg, 0.1 mmol), 4-iodoanisole (**2a**, 35 mg, 0.15 mmol), $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), $Mn(OAc)_2$ (35 mg, 0.2 mmol), Na_2CO_3 (21 mg, 0.2 mmol) and *t*-AmOH (2 mL). The mixture was stirred for 40 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc (5 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (5 mL) was added to the crude residue and the product extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 10/1) to afford the desired arylated product as a brown oil (**5k**, 11.5 mg) in 20% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.73 (s, 1H), 8.84 (dd, J = 4.2, 1.6 Hz, 1H), 8.60 (dd, J = 7.3, 1.6 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.58-7.41 (m, 7H), 6.92 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 4.50 (s, 1H), 3.81 (s, 3H), 3.55 (s, 3H), 2.08 (td, J = 12.9, 4.4 Hz, 1H), 1.73 (td, J = 12.5, 4.0 Hz, 1H), 1.27-1.12 (m, 16H), 0.83 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.6, 158.8, 158.4, 148.8, 138.8, 136.0, 133.4, 131.8, 131.1, 130.3, 129.5, 127.7, 127.0, 122.6, 121.8, 121.1, 116.6, 114.2, 113.8, 56.3, 55.8, 55.2, 54.9, 37.4, 31.8, 30.9, 29.4, 29.3, 29.2, 29.2,

25.6, 22.6, 14.1; FTIR (neat): 3309, 2929, 2868, 2237, 1685, 1619, 1552, 1320, 1198, 1022, 901, 799 cm^{-1}; MS (ESI): *m/z* 578 $(M+H)^+$.

*2-Cyano-N-(quinolin-8-yl)-2,3-dihydro-1H-indene-2-carboxamide (**6**)*: To an oven-dried 20 mL sealed tube, amide derivative **1l** (176 mg, 0.4 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), $Mn(OAc)_2$ (138 mg, 0.8 mmol), Na_2CO_3 (85 mg, 0.8 mmol) and *t*-AmOH (4 mL) were added under a N_2 atmosphere. The mixture was stirred for 48 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite and concentrated under reduced pressure. Water (10 mL) was added to the crude residue and the product extracted with ethyl acetate (6 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc= 15/1) to afford the title compound **6** as white solid, 101 mg, 65%, mp = 136-137 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 10.89 (s, 1H), 8.85 (dd, J = 4.2, 1.6 Hz, 1H), 8.70 (dd, J = 7.2, 1.6 Hz, 1H), 7.81 (dd, J = 8.3, 1.6 Hz, 1H), 7.61-7.52 (m, 2H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H), 7.32-7.26 (m, 4H), 3.89 (d, J = 15.8 Hz, 1H), 3.70 (d, J = 15.8 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 165.4, 148.8, 138.6, 138.5, 135.2, 133.5, 127.8, 127.7, 127.1, 124.6, 122.7, 122.0, 121.9, 116.8, 49.8, 43.7; FTIR (neat): 3308, 2922, 2850, 2237, 1682, 1524, 1477, 1323, 1257, 1062, 906, 8323, 796, 611 cm^{-1}; MS (ESI): *m/z* 314 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}ON_3$ $(M+H)^+$: 314.1288, found: 314.1288.

*2,2'-([2,2'-Bithiophene]-5,5'-diylbis(methylene))bis(2-cyano-N-(quinolin-8 yl)dodecanamide) (**7**)*: To an oven-dried 20 mL sealed tube, 5,5'-diiodo-2,2'-bithiophene **2t** (138 mg, 0.33 mmol), amide derivative **1a** (365 mg, 1 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), $Mn(OAc)_2$ (103 mg, 0.6 mmol), Na_2CO_3 (63 mg, 0.6 mmol) and *t*-AmOH (6 mL) were added under a N_2 atmosphere. The mixture was stirred for 48 h at 130 °C followed by cooling. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite and concentrated under reduced pressure. Water was added to the crude residue and the product extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 10/1) to afford the desired product **7** as a pale

yellow oil, 203 mg, 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.77 (s, 1H), 10.75 (s, 1H), 8.78 (dd, J = 4.2, 1.6 Hz, 1H), 8.75 (dd, J = 4.2, 1.6 Hz, 1H), 8.72-8.68 (m, 2H), 8.14-8.07 (m, 2H), 7.58-7.49 (m, 4H), 7.44-7.38 (m, 2H), 6.84 (dd, J = 5.4, 3.7 Hz, 2H), 6.74 (dd, J = 8.9, 3.6 Hz, 2H), 3.55 (dd, J = 14.6, 1.7 Hz, 2H), 3.25 (dd, J = 14.6, 2.8 Hz, 2H), 2.15 (dd, J = 16.3, 7.0 Hz, 2H), 1.89 (td, J = 12.8, 3.9 Hz, 2H), 1.72-1.56 (m, 2H), 1.52-1.40 (m, 2H), 1.37-1.15 (m, 28H), 0.84 (t, J = 6.9 Hz, 6H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 165.2, 148.9, 138.7, 137.1, 137.1, 136.1, 136.0, 134.8, 134.8, 133.3, 133.3, 128.7, 127.8, 127.0, 123.5, 123.5, 122.8, 122.8, 121.9, 121.8, 120.1, 116.8, 116.8, 53.0, 52.9, 37.7, 37.6, 37.4, 31.8, 29.4, 29.4, 29.3, 29.2, 29.2, 25.6, 22.6, 14.1; FTIR (neat): 3301, 2923, 2853, 2235, 1686, 1528, 1485, 1424, 1326, 1170, 908, 825, 789, 756 cm^{-1}; MS (ESI): *m/z* 893 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{54}H_{65}O_2N_6S_2$ $(M+H)^+$: 893.4605, found: 893.4604.

*2-benzyl-3-(4-methoxyphenyl)-N-(quinolin-8-yl)propanamide (**8**)*:[15a, 20] Under an inert atmosphere, to a solution of SmI_2 (6 mL, 0.1 M in THF, 0.6 mmol) in a 2-neck round-bottom flask, was added HMPA (1 mL) at room temperature with stirring for 1 h. To the above solution, amide **4a** (84 mg, 0.2 mmol) in THF (2 mL) was added with stirring for 6 h. After completion of the reaction, the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried over anhydrous magnesium sulfate. The crude product was obtained after evaporation of solvent under reduced pressure using a rotary evaporator. The crude product was purified by column chromatography, providing the product **8** (36 mg, 45%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 8.72 (dd, J = 7.4, 1.5 Hz, 1H), 8.64 (dd, J = 4.2, 1.7 Hz, 1H), 8.09 (dd, J = 8.4, 1.6 Hz, 1H), 7.56-7.42 (m, 2H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H), 7.26-7.09 (m, 8H), 6.73 (d, J = 8.6 Hz, 2H), 3.67 (s, 3H), 3.20-3.07 (m, 2H), 3.03-2.97 (m, 1H), 2.93-2.83 (m, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 173.1, 158.0, 147.8, 139.5, 136.1, 134.2, 131.5, 129.9, 128.9, 128.4, 127.7, 127.2, 126.2, 121.4, 121.3, 116.4, 114.0, 113.8, 55.1, 53.4, 38.6, 37.9; FTIR (neat): 3033, 2955, 2924, 1682, 1510, 1423, 1323, 1245, 1177, 1032, 824, 790 cm^{-1}; MS (ESI): *m/z* 397 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}O_2N_2$ $(M+H)^+$: 397.1911, found: 397.1911.

*Preparation of 2-benzyl-3-(4-methoxyphenyl)propanamide (**9a**)*:[16a] To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added **4a** (84 mg, 0.2 mmol), KOH (45 mg, 0.8 mmol), and *t*-amyl alcohol (1 mL) under a stream of argon. The vessel was sealed, and the mixture was stirred at 120 °C for 24 h. After cooling to room temperature, the mixture was passed through a pad of silica with copious washings with EtOAc (10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:6) to afford **9a** (41 mg, 77%) as a white solid, mp = 137-138 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.23-7.17 (m, 3H), 7.11 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.10 (s, 1H), 4.88 (s, 1H), 3.77 (s, 3H), 3.02-2.89 (m, 2H), 2.83-2.72 (m, 2H), 2.63-2.53 (m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 176.9, 158.1, 139.5, 131.4, 129.9, 128.9, 128.5, 126.4, 113.8, 55.2, 51.9, 38.7, 37.9; FTIR (neat): 3394, 3182, 3025, 2961, 2857, 1644, 1514, 1421, 1251, 1177, 1032, 824, 790 cm^{-1}; MS (ESI): *m/z* 270 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_2N$ $(M+H)^+$: 270.1489, found: 270.1489.

*Preparation of 2-benzyl-3-(4-methoxyphenyl)propanoic acid (**9b**)*:[16a] To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added **4a** (84 mg, 0.2 mmol), KOH (45 mg, 0.8 mmol), and *t*-amyl alcohol (1 mL) under a stream of argon. The vessel was sealed, and the mixture was stirred at 130 °C for 40 h. After cooling to room temperature, the solvent was removed, water (5 mL) was added and pH adjusted to 4 using 2N HCl. The aqueous layer was extracted with EtOAc (5 x 3 mL). The combined organic layers were washed with brine (10 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane = 1:4) to afford **9b** (35 mg, 65%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H), 7.22-7.13 (m, 3H), 7.08 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.00-2.87 (m, 3H), 2.82-2.70 (m, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 180.8, 158.1, 138.8, 130.7, 129.8, 128.9, 128.4, 126.5, 113.8, 55.2, 49.5, 37.6, 36.9; FTIR (neat): 3309, 2931, 1702, 1610, 1584, 1442, 1299, 1244, 1033, 825, 698 cm^{-1}; MS (ESI): *m/z* 269 $(M-H)^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_3$ $(M+H)^+$: 271.1329, found: 271.1328.

General procedure for the preparation of 10a and **10b**:

To an oven-dried 10 mL screw-capped vial, containing a magnetic stir bar were added arylated compound (**3a**, 141 mg, 0.3 mmol) or (**4a**, 126 mg, 0.3 mmol), KOH (67 mg, 1.2 mmol), and *t*-amyl alcohol (2 mL) under a stream of argon. The vessel was sealed, and the mixture was stirred at 90 °C for 3 h. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was dissolved in 5 mL of water and the pH was adjusted to 4 using 1 N HCl. The product was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried over anhydrous magnesium sulfate followed by evaporation of solvent under reduced pressure to give a pale yellow oil. The crude oil was purified by column chromatography on silica gel (EtOAc/hexane = 1:3) to give the corresponding acid.

*2-Cyano-2-(4-methoxybenzyl)dodecanoic acid (**10a**)*: 82 mg, 79%; white solid, mp = 52-53 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.15 (bs, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.17 (d, J = 13.7 Hz, 1H), 3.04 (d, J = 13.7 Hz, 1H), 2.03-1.94 (m, 1H), 1.87-1.78 (m, 1H), 1.68-1.57 (m, 1H), 1.44-1.20 (m, 15H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 174.2, 159.2, 131.0, 125.8, 118.4, 114.0, 55.2, 52.2, 42.2, 37.0, 31.9, 29.5, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1; FTIR (neat): 3035, 2922, 2840, 1695, 1512, 1249, 1030, 828, 698 cm^{-1}; MS (ESI): *m/z* 346 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{32}O_3N$ $(M+H)^+$: 346.2377, found: 346.2373.

*2-Benzyl-2-cyano-3-(4-methoxyphenyl)propanoic acid (**10b**)*: 67 mg, 75%; white solid, mp = 121-122 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 9.49 (bs, 1H), 7.35-7.27 (m, 5H), 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.28 (dd, J = 13.5, 11.0 Hz, 2H), 3.10 (dd, J = 13.8, 12.1 Hz, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 173.4, 159.3, 133.6, 131.1, 129.9, 128.7, 128.0, 125.5, 117.9, 114.1, 55.2, 53.9, 42.7, 42.2; FTIR (neat): 3165, 2954, 2914, 2841, 2248, 1737, 1612, 1514, 1301, 1241, 1018, 819, 721 cm^{-1}; MS (ESI): *m/z* 296 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_3N$ $(M+H)^+$: 296.1281, found: 296.1279.

General procedure for detachment of directing group (**11a** and **11b**):[8f]

To an oven-dried 10 mL screw-capped vial, arylated compound (**3a**, 235 mg, 0.5 mmol) or (**4a**, 210 mg, 0.5 mmol) and 2 M HCl in MeOH (5 mL) were added under a gentle stream of argon. The mixture was

stirred for 20 h at 65 °C followed by cooling. The mixture was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel to afford the corresponding α–cyano methyl ester.

*Methyl 2-cyano-2-(4-methoxybenzyl)dodecanoate (**11a**)*: 129 mg, 72%; Pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.14 (d, J = 13.6 Hz, 1H), 2.99 (d, J = 13.6 Hz, 1H), 1.99 (t, J = 14.6 Hz, 1H), 1.80 (d, J = 12.6 Hz, 1H), 1.66-1.53 (m, 1H), 1.36-1.20 (m, 15H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 169.4, 159.2, 130.9, 126.3, 119.1, 113.9, 55.2, 53.2, 52.0, 42.6, 37.1, 31.9, 29.5, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1; FTIR (neat): 3029, 2924, 1725, 1619, 1519, 1309, 1257, 1031, 835, 704 cm^{-1}; MS (ESI): *m/z* 360 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{34}O_3N$ $(M+H)^+$: 360.2533, found: 360.2531.

*Methyl 2-benzyl-2-cyano-3-(4-methoxyphenyl)propanoate (**11b**)*: 125 mg, 81%; Pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 7.20 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 3.54 (s, 3H), 3.29 (dd, J = 13.5, 10.6 Hz, 2H), 3.06 (t, J = 13.7 Hz, 2H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 168.8, 159.2, 134.1, 31.0, 129.9, 128.6, 127.9, 126.0, 118.6, 114.0, 55.2, 53.7, 53.1, 43.1, 42.6; FTIR (neat): 3022, 2953, 1720, 1613, 1551, 1454, 1321, 1246, 1032, 837, 702 cm^{-1}; MS (ESI): *m/z* 310 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_3N$ $(M+H)^+$: 310.1438, found: 310.1434.

*Synthesis of 2-(((tert-butoxycarbonyl)amino)methyl)-2-(4-methoxybenzyl)dodecanoic acid (**12a**)*: A stirred mixture of α–cyanoacid (**10a**, 35 mg, 0.1 mmol), MeOH (3 mL), $(Boc)_2O$ (24 mg, 0.11 mmol), DIPEA (15 mg, 0.11 mmol) and Pd catalyst (10 wt% on activated charcoal, 1.05 mg, 0.01 mmol) was hydrogenated at ambient temperature at 50 psi for 36 h. The catalyst was then filtered off and washed with MeOH and the solvent evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1:4) to give the *N*-Boc-β–amino acid **12** (26 mg) in 59% yield as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.3 Hz, 2H), 4.93 (bs, 1H), 3.77 (s, 3H), 3.41-3.30 (m, 1H), 3.29-3.16 (m, 1H), 2.97 (d, J = 13.6 Hz, 1H), 2.80 (d, J = 13.9 Hz, 1H), 1.66-1.41 (m, 11H), 1.33-1.18 (m, 16H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 181.8, 158.4, 156.0, 131.0, 128.4, 113.6, 79.4, 55.1, 51.2, 43.4, 39.6, 34.3, 31.9,

30.2, 29.7, 29.6, 29.4, 29.3, 28.4, 24.0, 22.7, 14.1; FTIR (neat): 3324, 3081, 2929, 1732, 1615, 1574, 1422, 1052, 833, 795, 782 cm^{-1}; MS (ESI): *m/z* 448 $(M-H)^+$.

*Synthesis of 2-benzyl-3-((tert-butoxycarbonyl)amino)-2-(4-methoxybenzyl)propanoic acid (**12b**)*: A stirred mixture of α–cyanoacid (**10b**, 30 mg, 0.1 mmol), MeOH (3 mL), $(Boc)_2O$ (24 mg, 0.11 mmol), DIPEA (15 mg, 0.11 mmol) and Pd catalyst (10 wt% on activated charcoal, 1.05 mg, 0.01 mmol) was hydrogenated at ambient temperature at 50 psi for 40 h. The catalyst was then filtered off and washed with MeOH and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1:4) to give the *N*-Boc-β–amino acid **12b** (22 mg) in 55% yield as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30-7.16 (m, 5H), 7.14-7.06 (m, 2H), 6.80 (d, J = 8.5 Hz, 2H), 5.01 (bs, 1H), 3.76 (s, 3H), 3.32-3.03 (m, 4H), 2.79 (dd, J = 13.7, 10.7 Hz, 2H), 1.45 (s, 9H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 180.9, 158.6, 156.2, 136.2, 131.4, 130.3, 128.3, 127.9, 126.8, 113.7, 79.5, 55.1, 53.4, 42.9, 41.2, 40.4, 28.4; FTIR (neat): 3351, 3029, 2921, 1734, 1619, 1578, 1422, 1081, 837, 795, 780 cm^{-1}; MS (ESI): *m/z* 400 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{23}H_{30}O_5N$ $(M+H)^+$: 400.2118, found: 400.2118.

General procedure for the preparation of β–amino esters (**13a** and **13b**):[21]

A stirred mixture of α–cyanoester (**11a**, 108 mg, 0.3 mmol) or (**11b**, 93 mg, 0.3 mmol), MeOH (3 mL), 1 M HCl in diethyl ether (50 μL) and Pd catalyst (10 wt% on activated charcoal, 3.2 mg, 0.03 mmol) was hydrogenated at ambient temperature at 50 psi for 24 h. The catalyst was then filtered off and washed with MeOH and the filtrate was evaporated. To the oily residue, saturated $NaHCO_3$ solution was added and the product extracted with EtOAc (10 mL x 2). The combined organic extracts were dried over Mg_2SO_4 and evaporated. The residue was purified by flash chromatography to give the corresponding β–amino ester.

*Methyl 2-(aminomethyl)-2-(4-methoxybenzyl)dodecanoate (**13a**)*: 89 mg, 82%; Pale yellow oil, ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 2.92 (d, J = 13.8 Hz, 1H), 2.82 (d, J = 13.8 Hz, 1H), 2.77 (bs, 2H), 1.59-1.43 (m, 2H), 1.41-1.19 (m, 18H),

0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 176.5, 158.2, 130.8, 129.4, 113.5, 55.1, 52.8, 44.5, 38.1, 33.1, 31.9, 30.1, 29.6, 29.5, 29.5, 29.3, 24.2, 22.7, 14.1; FTIR (neat): 3391, 3033, 2929, 1722, 1610, 1511, 1454, 1176, 1081, 833, 794, 740 cm^{-1}; MS (ESI): *m/z* 364 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{38}O_3N$ $(M+H)^+$: 364.2846, found: 364.2842.

*Methyl 3-amino-2-benzyl-2-(4-methoxybenzyl)propanoate (**13b**)*: 81 mg, 80%; Pale yellow oil, ^1H NMR (400 MHz, $CDCl_3$): δ 7.29-7.18 (m, 3H), 7.16-7.12 (m, 2H), 7.06 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.77 (s, 3H), 3.64 (s, 3H), 3.09 (dd, J = 16.6, 13.7 Hz, 2H), 2.84 (t, J = 13.7 Hz, 2H)2.71 (bs, 2H), 1.16 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 175.7, 158.2, 137.4, 130.9, 129.9, 129.2, 128.2, 126.5, 113.6, 55.1, 54.0, 51.4, 42.3, 40.7, 39.8; FTIR (neat): 3395, 3029, 2929, 1721, 1618, 1511, 1450, 1300, 1246, 1031, 833, 701 cm^{-1}; MS (ESI): *m/z* 314 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{19}H_{24}O_3N$ $(M+H)^+$: 314.1751, found: 314.1750.

*Synthesis of 3-amino-2,2-dibenzylpropan-1-ol (**14**)*:[22] A suspension of $LiAlH_4$ (0.5 mL, 1 molar solution in THF, 0.5 mmol) in THF (4 mL) was cooled to 0°C and stirred, while a solution of **4c** (78 g, 0.2 mmol) in THF (2 mL) was added dropwise under argon. After addition was completed, the vessel was equipped with a water-jacketed condenser and refluxed for 7.5 h under argon, then quenched by cautious addition of H_2O (1 mL) while cooling in an ice bath. The mixture was filtered through a thin pad of Celite, washed with Et_2O (10 mL), and the combined filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography using (EtOAc: hexanes, 1:3), yielding the title compound as a white solid (37 mg, 72%). mp = 112-113 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.14 (m, 10H), 3.60 (s, 2H), 3.47 (s, 1H), 2.83 (t, J = 6.6 Hz, 4H), 2.57 (d, J = 13.4, 2H), 2.40 (bs, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 137.6, 130.6, 128.0, 126.2, 68.5, 49.3, 41.8, 40.4; FTIR (neat): 3369, 3025, 2916, 2854, 1581, 1494, 1443, 1390, 1114, 1054, 697 cm^{-1}; MS (ESI): *m/z* 256 $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{22}ON$ $(M+H)^+$: 256.1696, found: 256.1696.

Notes

The authors declare no competing financial interest.

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Supporting Information

Copies of ^{1}H and $^{13}C\{^{1}H\}$NMR spectra. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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