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Highly efficient one-pot tandem Friedlander annulation and chemo-selective C_{sp^3}–H functionalization under calcium catalysis†

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A highly efficient and regioselective Friedlander synthesis of 2-methyl-3-acyl quinolines is described, which occurs under solvent-free conditions and employs calcium triflate as a sustainable catalyst. For the first time in the literature, these 2-methyl-3-acyl quinolines undergo an *in situ* chemoselective C_{sp^3}–H functionalization to furnish structurally enriched quinoline heterocycles in high yields and with atom and step economy.

Introduction

Rational drug design based on privileged scaffolds is one of the most powerful concepts in modern drug discovery.[1] A quinoline moiety is one of these privileged scaffolds, and it has been extensively explored owing to its broad biological spectrum.[2] For example, quinoline derivatives serve as anti-malarial drugs (quinine, chloroquine),[2] anti-inflammatories,[3] antibacterials, have antituberculosis properties,[4] are multifunctional agents for Alzheimer's disease,[5] and find uses as other therapeutic agents.[6] In addition, these moieties are an integral part of many biologically active natural products (Fig. 1).[7] Hence, the development of new synthetic methods for quinoline derivatives is an active area of organic synthesis. Among several synthetic methods available, functionalization of 2-methylquinolines has emerged as a new synthetic technique to address the synthesis of quinoline-based new chemical entities (NCE).[8] However, most of these methods utilize 2-methylazaarenes as a starting point for functionalization to generate the new libraries. In general, 2-methyl quinolines can be synthesized starting from easily available *o*-acyl anilines and a suitable carbonyl compound through a Friedlander annulation under acidic or basic conditions.[9] To the best of our knowledge, there are only a couple of reports available in which *in situ*-generated 2-methyl quinolines were functionalized.[10,11] Nevertheless, both of these reports were limited to direct synthesis of styryl quinolines and no chemoselectivity was attained; moreover, the reaction could not even proceed with preformed 2-methyl, 3-acyl quinolines with $In(OTf)_3$.[11] Hence, it is highly desirable to explore the chemoselectivity of these 2-methyl, 3-acyl quinolines through functionalization of their methyl groups to generate useful quinoline derivatives.

On the other hand, one-pot multicomponent reactions (MCRs) have been proven to be efficient alternative green synthetic reactions for some existing classical stepwise reactions.[12] MCRs are well known for the synthesis of complex molecules starting from simple starting materials. Looking at its importance, we have been working on a one-pot, solvent-free/in-water multicomponent approach using calcium triflate as an environmentally benign catalyst.[8i–k,13] As a continuation of our interest in the facile, selective, and sustainable synthesis of biologically important heterocycles, we disclose here a highly efficient one-pot tandem calcium-catalysed Friedlander annulation followed by chemoselective C–H functionalization to generate quinoline-based new chemical entities.

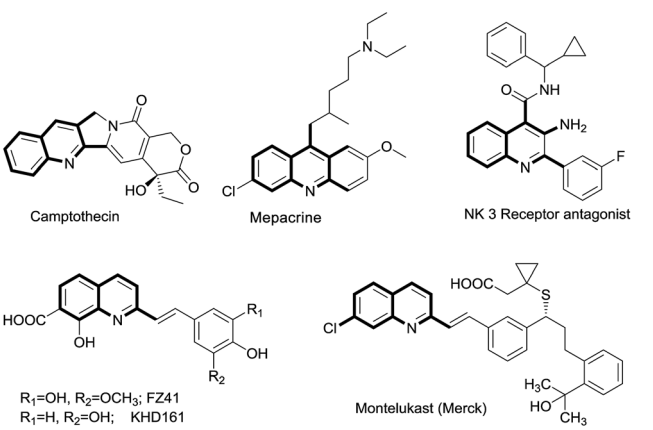

Fig. 1 Representative examples of 2-alkyl quinoline derivatives present in natural products and drug molecules.

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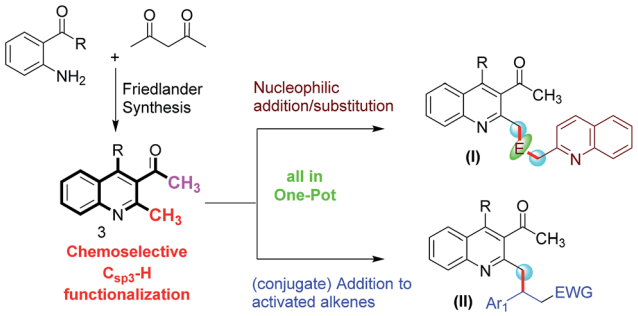


Fig. 2 Schematic representation of our synthetic plan for quinoline derivatives through a one-pot Friedlander annulation followed by chemoselective functionalization (E = electrophile; EWG = electron withdrawing group).

Results and discussion

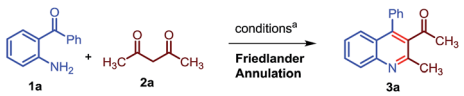
As depicted in Fig. 2, we designed a Friedlander synthesis of quinoline (**3**) which contains two activated methyl groups, the chemoselectivity of which could be differentiated by a suitable combination of reagents and conditions. Based on our expertise in C_{sp^3}–H functionalization, we decided to functionalize the methyl group (C_{sp^3}–H) on the 2nd position in a tandem one-pot multicomponent approach.[8i–k] Thus, compound (**I**) could be achieved by selecting a suitable electrophile (and this can be an aldehyde or isatin) which could accommodate two moles of methyl azaarene. Compound (**II**) was envisaged from the chemoselective and conjugate addition of compound **3** to the activated alkenes in one pot.

In order to implement our concept, initially we decided to look for better conditions for 2-methyl quinoline synthesis and its conjugate (Michael) addition to a chalcone derivative in one pot. 2-Aminobenzophenone (**1a**) and acetylacetone (**2a**) were chosen as starting materials for the Friedlander synthesis of 2-methyl, 3-acetyl, 4-phenyl quinoline (**3a**). As shown in Table 1, stoichiometric amounts of **1a** and **2a** were refluxed in water with 10 mol% of $Ca(OTf)_2/Bu_4NPF_6$ and the reaction gave a positive result with 61% of **3a** after 6 h (entry 1, Table 1). Toluene gave a better result compared to water (Table 1, entry 2) and DCE gave a lower yield of **3a**. However, the reaction yielded excellent results under neat conditions (entry 4, Table 1). After a careful observation of the optimization studies, we found that the Friedlander synthesis was effective at 120 °C under neat conditions with 10 mol% of $Ca(OTf)_2/Bu_4NPF_6$ to furnish a nearly quantitative yield of **3a**.[14]

Encouraged by this observation, we proceeded further and added simple chalcone **4a** to the above reaction to check the possibility of a conjugate addition reaction. Gratifyingly, the reaction gave Michael adduct **5a** in 72% yield after 18 h. Encouraged by this observation, applicability of the reaction condition for the one-pot synthesis of 4-(3-acetyl-4-phenylquinolin-2-yl)-1,3-diphenylbutan-1-one (**5a**) was generalized with different enones bearing different electron-withdrawing and -donating groups. As shown in Table 2, *ortho*-amino benzophenone (**1a**) and acetylacetone (**2a**) were reacted with various chalcones in presence of 10 mol% $Ca(OTf)_2/Bu_4NPF_6$ under neat conditions[15] through a tandem Friedlander annulation followed by Michael addition to give the quinoline derivatives **5a–5d** in good yields. 5-Chloro-2-aminobenzophenone derivative (**1b**) also reacted with acetylacetone and various chalcone derivatives under the same conditions and produced the quinoline derivatives **5e–5i** in good yields. Interestingly, *ortho*-aminobenzophenone bearing an electron-withdrawing group ($-NO_2$) also showed a similar reactivity with acetylacetone and chalcones, to furnish the quinoline derivatives **5j–5l** in moderate to good yields as shown in Table 2.

After a successful demonstration of a three-component calcium-catalyzed tandem Friedlander synthesis of 2-methyl, 3-acyl quinolines and their chemo-selective functionalization through a Michael addition to the chalcone compounds (Table 2), we decided to make dimeric quinoline derivatives. For this, aldehydes were taken as electrophilic partners instead of chalcones, as it is known that 2-methylquinoline adds to aldehydes to yield alcoholic compounds which may further undergo

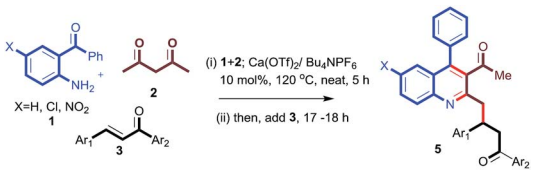
Table 1 Optimization of reaction conditions for the calcium-catalysed Friedlander synthesis of 2-methyl, 3-acyl, 4-phenyl quinoline (**3a**)[a]

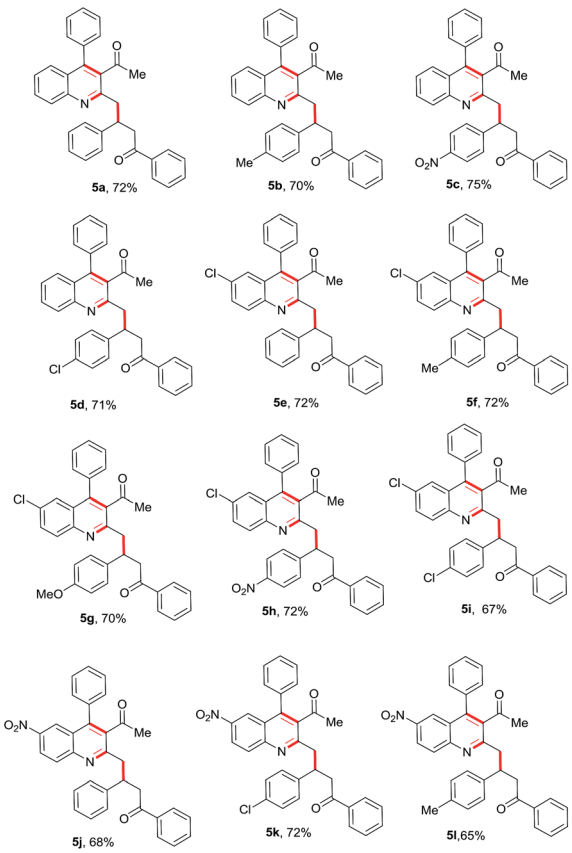


Entry	Catalyst (mol%)	Reaction conditions	Yield (%)
1	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Water, 6 h, 110 °C	61
2	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Toluene, 6 h, 120 °C	73
3	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	1,2-Dichloroethane, 24 h, 80 °C	45
4	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Neat, 5 h, 120 °C	98
5	$Ca(OTf)_2/Bu_4NPF_6$ (10/10)	Neat, 9 h, 100 °C	80
6	$Ca(OTf)_2/Bu_4NPF_6$ (5/5)	Neat, 11 h, 120 °C	93
7	$Ca(OTf)_2/Bu_4NPF_6$ (5/10)	Neat, 10 h, 120 °C	95
8	$Ca(OTf)_2/Bu_4NPF_6$ (10/5)	Neat, 10 h, 120 °C	94

[a] Reaction condition: **1a** (0.50 mmol), **2a** (0.50 mmol) were heated in a closed vessel under neat conditions at 120 °C for 5 h.

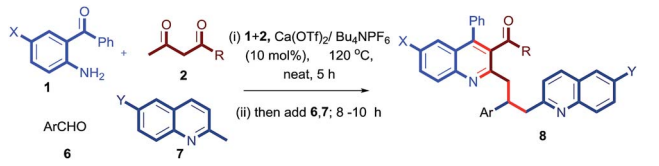
Table 2 Substrate scope for the $Ca(OTf)_2$-catalyzed tandem Friedlander annulation and Michael addition for the synthesis of substituted quinoline derivatives[a]

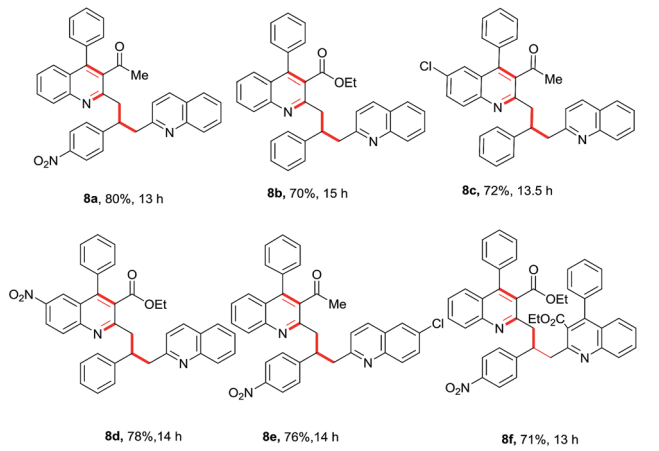




[a] Stoichiometry of reactants: **1** (0.50 mmol), **2** (0.50 mmol) & **3** (0.50 mmol); reaction was performed in a sealed vessel; isolated yields were reported.

Table 3 Substrate scope in the one-pot four-component Ca(II)-catalyzed Friedlander annulation and chemoselective C_{sp^3}–H functionalization for the synthesis of dimeric quinoline derivatives[a]





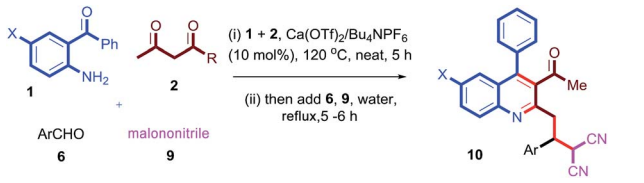
[a] Stoichiometry of reactants: **1** (0.50 mmol), **2** (0.50 mmol), **6** (0.50 mmol) & **7** (0.55 mmol); reaction was performed in a sealed vessel; isolated yields were reported.

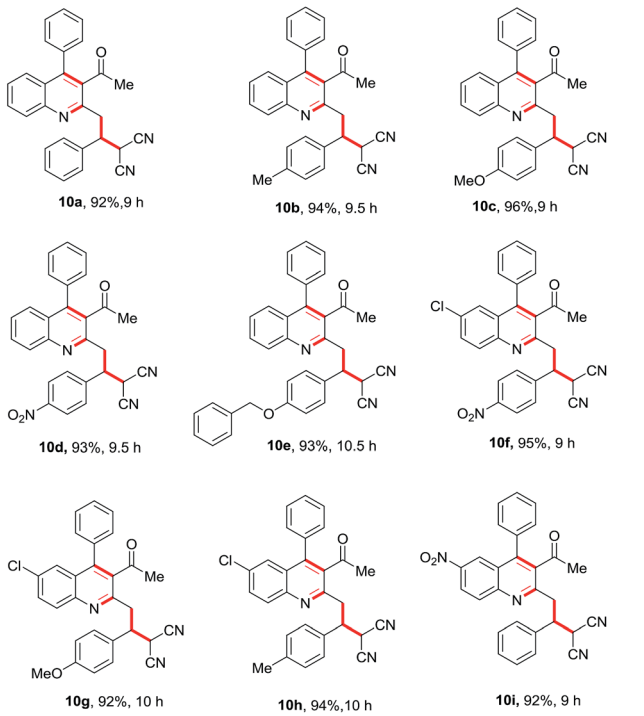
another nucleophilic substitution with a second mole of 2-methylquinoline in the presence of Ca(II).[13f] To implement this idea, we performed the Friedlander annulation and then added 1 equiv. of benzaldehyde and 2-methylquinoline (1 equiv.) in one pot; the reaction was continued for another 8 h to isolate the desired product **8a** in 80% yield. Refreshed by this result, we extended this procedure for the synthesis of other dimeric quinolines **8b–8e** in excellent yields as shown in Table 3. When 4-nitrobenzaldehyde was added alone after the Friedlander annulation, a homodimeric quinoline derivative **8f** was isolated in 71% yield after 13 h.

Having these fruitful results in hand, we investigated another four-component reaction for the synthesis of quinoline derivatives through a tandem Friedlander annulation and C–H functionalization as described in Table 4. Benzaldehyde (**6**) and malononitrile (**9**) were added to the substituted 2-methylquinoline (formed through Friedlander annulation) in one pot and the reaction was further refluxed in water for an additional 5 h to obtain the four-component adduct 2-(2-(3-acetyl-4-phenylquinolin-2-yl)-1-phenylethyl)malononitrile (**10a**) in 92% yield through a simple filtration (Table 4). This compound was so pure that no further recrystallization was required. The substrate scope of this one-pot four-component synthesis was demonstrated by the participation of a large number of aryl aldehydes bearing electron-donating/-withdrawing groups and substituted *ortho*-amino benzophenones to furnish the respective compounds **10a–10i** with excellent yields, as depicted in Table 4. This idea was further extended for the synthesis of biologically important quaternary centered oxindolyl–quinoline derivatives by simply switching the electrophile from aldehyde to isatin (Table 5). Thus, quaternary-centered oxindolyl derivative **12a** was isolated through simple filtration in 92% yield in 5.5 h under similar conditions. Similarly, 1-methylisatin with **3a** yielded **12b** and **12d** in 93% and 91% yields, respectively, whereas 5-methylisatin furnished the product **12c** in 91% yield.

The synthetic utility of this protocol was demonstrated *via* a gram scale synthesis of **5a** (2.65 g) through a tandem Friedlander annulation/C–H functionalization (chemoselective) and 71% yield of the desired product was obtained (Scheme 1).

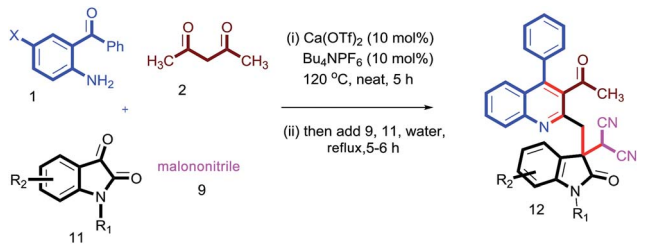
Table 4 Substrate scope for the C_{sp^3}–H functionalisation of substituted quinolines with aldehyde and malononitrile in a one-pot four-component reaction[a]

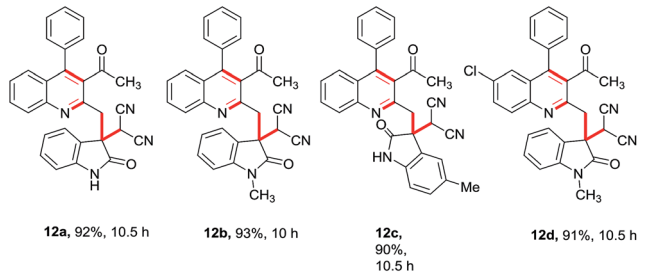




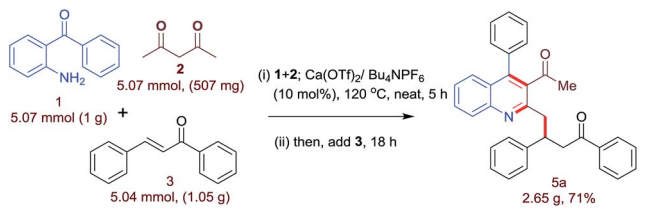
[a] Reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), **6** (0.50 mmol) & **9** (0.50 mmol); isolated yields after filtration were reported.

Table 5 Substrate scope for the synthesis of quaternary centred oxindolyl–quinolines through one-pot 4-component strategy[a]





[a] Reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), **9** (0.50 mmol) & **11** (0.50 mmol); isolated yields after filtration were reported.



Scheme 1 Gram-scale demonstration of calcium-catalyzed three-component synthesis of **5a**.

Conclusions

In summary, we described the first report of tandem Friedlander annulation and chemoselective C_{sp^3}–H functionalization of *in situ*-generated 2-methyl, 3-acyl quinolines under calcium catalysis. The wide substrate scope, high yields, and flexibility to extend to more varieties of quinoline derivatives under calcium catalysis, given the atom and step economy of the method, will attract attention from medicinal chemists wishing to explore further the biological utilities of quinoline derivatives.

Experimental section

General remarks

All chemicals were purchased from commercial sources and were used as received without further purification. ^{1}H, ^{13}C NMR spectra were recorded on an Avance Bruker 500 MHz spectrometer in $CDCl_3$. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) and calibrated to residual chloroform peaks. Coupling constants (J) are reported in Hz and coupling patterns are described as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, m = multiplet. Melting points were measured with a Büchi Melting Point B-540 apparatus. Reactions were monitored by thin layer chromatography (TLC) with aluminium sheets silica gel 60 F254 from Merck with detection by UV light and charring with β-naphthol and ninhydrin stain.

Procedures

General experimental procedure for the synthesis of 4-(3-acetyl-4-phenylquinolin-2-yl)-1,3-diphenylbutan-1-one (5a).[15] 2-Amino benzophenone (0.507 mmol, 100 mg), acetyl acetone (0.65 mmol, 50.7 mg), $Ca(OTf)_2$ (10 mol%), and ^{n}BuNPF$_6$ (10 mol%) were heated at 120 °C under solvent-free conditions for 4–5 h. After completion of the reaction, chalcone (0.507 mmol) was added to the reaction mixture. Then, heating of the reaction was continued for another 16–18 h at 120 °C. After completion, the reaction mass was diluted with water and extracted into ethyl acetate thrice. The solvent was evaporated under reduced pressure. The crude material obtained was purified with

column chromatography to obtain pure **5a** (72% yield) as a light brown solid; mp 132–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.76–7.73 (m, 1H), 7.65–7.61 (m, 2H), 7.53–7.52 (m, 4H), 7.50–7.44 (m, 2H), 7.41–7.38 (m, 2H), 7.28–7.25 (m, 3H), 7.16 (t, J = 7 Hz, 2H), 4.32–4.26 (m, 1H), 3.67 (dd, J = 16.5 Hz, 17 Hz, 1H), 3.47–3.42 (m, 1H), 3.38–3.30 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 198.7, 155.1, 147.4, 144.6, 137.2, 135.3, 135.2, 135.1, 134.8, 130.0, 128.9, 128.7, 128.4, 128.3, 128.0, 127.6, 126.6, 126.5, 126.1, 126.0, 125.1, 125.0, 44.1, 43.6, 40.6, 32.2; HRMS (ESI) m/z calcd for $C_{33}H_{28}O_2N$ $[M + H]^+$ 470.2115; found 470.2118.

4-(3-Acetyl-4-phenylquinolin-2-yl)-1-phenyl-3-(*p*-tolyl)butan-1-one (5b). Yield 70%; brown solid; mp 198–200 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 8 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.53–7.49 (m, 4H), 7.40–7.37 (m, 4H), 7.31–7.29 (m, 2H), 7.21 (d, J = 8 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 4.24–4.21 (m, 1H), 3.64 (dd, J = 16.5 Hz, 16.5 Hz, 1H), 3.43–3.34 (m, 2H), 2.27 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.9, 198.8, 155.2, 147.4, 144.1, 141.5, 137.1, 135.9, 135.3, 135.1, 132.7, 130.3, 130.2, 130.1, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 128.1, 127.4, 126.6, 126.5, 126.2, 126.1, 125.0, 44.1, 43.4, 40.2, 32.2, 23.9, 21.0; HRMS (ESI) m/z calcd for $C_{34}H_{29}O_2N$ [M + H] 483.2198; found 483.2203.

4-(3-Acetyl-4-phenylquinolin-2-yl)-3-(4-nitrophenyl)-1-phenylbutan-1-one (5c). Yield 75%; brown solid; mp 205–206 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7 Hz, 2H), 7.74–7.71 (m, 1H), 7.64 (d, J = 8 Hz, 1H), 7.56–7.53 (m, 6H), 7.49–7.47 (m, 1H), 7.42 (t, J = 8 Hz, 2H), 7.37–7.33 (m, 2H), 4.50–4.45 (m, 1H), 3.69 (dd, J = 17.5 Hz, 17 Hz, 1H), 3.53–3.48 (m, 1H), 3.34–3.32 (m, 2H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 197.2, 153.9, 152.6, 147.4, 146.5, 144.6, 136.7, 135.1, 134.7, 133.1, 130.1, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.0, 126.9, 126.2, 125.0, 123.7, 43.7, 42.4, 40.0, 32.3; HRMS (ESI) m/z calcd for $C_{33}H_{26}O_4N_2$ [M + H] 514.1892; found 514.1896.

3-(3-Acetyl-4-phenylquinolin-2-yl)-2-(4-chlorophenyl)-1-phenylpropan-1-one (5d). Yield 71%; brown solid; mp 214–216 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.71 (t, J = 8.5 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 7.53–7.46 (m, 5H), 7.42–7.39 (m, 1H), 7.32–7.27 (m, 5H), 7.23 (d, J = 8.5 Hz, 2H), 4.30–4.27 (m, 1H), 3.62 (dd, J = 16.5 Hz, 18.5 Hz, 1H), 3.43–3.39 (m, 1H), 3.34–3.32 (d, J = 6.5 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 198.4, 154.6, 143.1, 136.9, 135.2, 134.9, 132.9, 132.0, 130.1, 130.0, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.0, 126.8, 126.1, 125.0, 44.0, 43.0, 39.8, 32.3; HRMS (ESI) m/z calcd for $C_{33}H_{24}O_2NCl$ $[M]^+$ 489.1459; found 489.1463.

3-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-1,2-diphenylpropan-1-one (5e). Yield 72%; brown solid; mp 220–222 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.75 (t, J = 7 Hz, 1H), 7.71 (t, J = 7 Hz, 1H), 7.66–7.62 (m, 2H), 7.54–7.52 (m, 4H), 7.32–7.25 (m, 5H), 7.18–7.15 (m, 1H), 4.31–4.25 (m, 1H), 3.67 (dd, J = 17 Hz, 17 Hz, 1H), 3.48–3.43 (m, 1H), 3.39–3.29 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.9, 198.7, 155.1, 153.5, 147.4, 144.5, 137.1, 132.7, 130.2, 130.1, 130.0, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.0, 127.6, 126.4, 126.2, 125.0, 44.0, 43.2, 40.6, 32.2; HRMS (ESI) m/z calcd for $C_{33}H_{24}O_2NCl$ $[M]^+$ 489.1459; found 489.1463.

3-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-1-phenyl-2-(*p*-tolyl)propan-1-one (5f). Yield 72%; light brown solid; mp 215–217 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.61 (dd, J = 9 Hz, 9 Hz, 1H), 7.57–7.50 (m, 5H), 7.41–7.37 (m, 3H), 7.30–7.28 (m, 1H), 7.21 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 4.24–4.22 (m, 1H), 3.64 (dd, J = 17 Hz, 17 Hz, 1H), 3.42–3.37 (m, 1H), 3.32–3.29 (m, 2H), 2.28 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.4, 198.6, 155.7, 145.6, 143.4, 141.4, 137.0, 136.0, 135.8, 134.6, 132.7, 131.0, 130.7, 130.1, 129.9, 129.2, 129.0, 128.8, 128.4, 128.0, 127.4, 125.8, 124.8, 44.1, 43.2, 40.0, 32.1, 21.0; HRMS (ESI) m/z calcd for $C_{33}H_{27}O_2NCl$ $[M]^+$ 504.1735; found 504.1738.

4-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-3-(4-methoxyphenyl)-1-phenylbutan-1-one (5g). Yield 70%; brown solid; mp 205–207 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 9 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.63 (dd, J = 9 Hz, 9 Hz, 1H), 7.58–7.51 (m, 6H), 7.42–7.39 (m, 3H), 7.24 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.24–4.18 (m, 1H), 3.76 (s, 3H), 3.64 (dd, J = 17 Hz, 17 Hz, 1H), 3.42–3.31 (m, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.4, 155.4, 145.3, 143.5, 141.2, 137.1, 136.2, 135.2, 134.8, 133.1, 132.6, 131.0, 130.4, 130.1, 130.0, 129.3, 129.0, 128.6, 128.1, 127.9, 127.1, 125.6, 124.3, 55.5, 44.2, 43.5, 40.1, 32.4; HRMS (ESI) m/z calcd for $C_{33}H_{28}O_2N$ [M + H] 534.1830; found 534.1833.

4-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-3-(4-nitrophenyl)-1-phenylbutan-1-one (5h). Yield 72%; brown solid; mp 212–214 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 9 Hz, 1H), 7.78–7.76 (m, 2H), 7.54 (dd, J = 9 Hz, 9 Hz, 1H), 7.49–7.44 (m, 5H), 7.33–7.29 (m, 3H), 7.20–7.18 (m, 3H), 7.15–7.13 (m, 2H), 4.20–4.14 (m, 1H), 3.54 (dd, J = 17 Hz, J = 17 Hz, 1H), 3.33–3.28 (m, 1H), 3.21 (d, J = 7 Hz, 2H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 198.2, 155.1, 142.9, 136.8, 135.6, 134.4, 133.0, 132.1, 131.2, 130.4, 130.3, 130.0, 129.9, 129.4, 129.2, 129.1, 129.0, 128.9, 128.6, 128.5, 128.1, 128.0, 126.1, 125.9, 124.9, 44.0, 42.7, 39.7, 32.1; HRMS (ESI) m/z calcd for $C_{33}H_{25}ClO_4N_2$ [M + H] 548.1502; found 548.1506.

3-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-2-(4-chlorophenyl)-1-phenylpropan-1-one (5i). Yield 67%; brown solid; mp 220–222 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 9 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.65–7.63 (m, 1H), 7.63–7.51 (m, 5H), 7.42–7.37 (m, 3H), 7.37–7.27 (m, 4H), 7.23 (d, J = 8.5 Hz, 2H), 4.27–4.23 (m, 1H), 3.64 (dd, J = 17 Hz, 17 Hz, 1H), 3.42–3.37 (m, 1H), 3.31–3.30 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.6, 198.3, 155.1, 142.8, 136.7, 135.6, 133.0, 132.2, 130.0, 129.9, 129.8, 129.5, 129.1, 129.0, 128.9, 128.6, 128.5, 128.0, 125.9, 124.9, 43.9, 42.6, 39.7, 32.1; HRMS (ESI) m/z calcd for $C_{32}H_{23}Cl_2NO_2$ [M + H] 524.4359; found 524.4360.

4-(3-Acetyl-6-nitro-4-phenylquinolin-2-yl)-1,3-diphenylbutan-1-one (5j). Yield 72%; light brown solid; mp 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 9 Hz, 2H), 8.03 (d, J = 8 Hz, 1H), 7.90–7.88 (m, 2H), 7.74–7.71 (m, 1H), 7.65–7.63 (m, 1H), 7.56–7.53 (m, 6H), 7.49–7.46 (m, 1H), 7.42 (t, J = 8 Hz, 2H), 7.38–7.33 (m, 2H), 4.05–4.44 (m, 1H), 3.69 (dd, J = 17.5 Hz, 17.5 Hz, 1H), 3.54–3.48 (m, 1H), 3.34–3.31 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 197.4, 153.9, 152.6, 147.4, 146.5,

144.6, 136.6, 135.1, 134.7, 133.2, 130.3, 130.1, 129.1, 128.9, 128.8, 128.7, 128.6, 128.0, 127.0, 126.2, 125.0, 123.7, 43.7, 42.4, 40.1, 32.3; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{26}N_2O_4$ [M + H] 514.5706; found 514.5708.

General experimental procedure for the synthesis of 1-(4-phenyl-2-(2-phenyl-3-(quinolin-2-yl)propyl)quinolin-3-yl)ethan-1-one (8a). 2-Aminobenzophenone (0.507 mmol, 100 mg), acetylacetone (0.507 mmol, 50.7 mg), $Ca(OTf)_2$ (0.05 mmol), $^nBuNPF_6$ (0.05 mmol) were heated at 120 °C under solvent-free conditions for 4–5 h. After completion of the reaction, 2-methylquinoline (0.507 mmol, 72.6 mg) and benzaldehyde (0.507 mmol, 53.8 mg) were added to the reaction mixture. Heating of the reaction was continued for another 7–8 h at 120 °C. After completion, the reaction mass was diluted with water and extracted into ethyl acetate thrice. The solvent was evaporated under reduced pressure. The crude obtained was purified with column chromatography to obtain pure **8a** (mg, 78% yield) as yellow solid mp 88–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 2H), 8.47–8.44 (m, 2H), 8.15 (d, J = 9.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 7.63–7.57 (m, 8H), 7.32 (d, J = 4.5 Hz, 4H), 4.72 (t, J = 7 Hz, 1H), 3.59–3.54 (m, 2H), 3.43–3.39 (m, 2H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.4, 158.3, 152.1, 149.2, 146.6, 146.1, 145.8, 136.1, 133.5, 130.9, 1230.0, 129.9, 129.8, 129.4, 129.3, 128.9, 128.4, 126.6, 124.3, 124.2, 123.8, 123.7, 123.6, 123.1, 71.7, 42.6, 42.2, 32.1; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{28}O_2N_2$ $[M + H]^+$ 492.2201; found 492.2204.

Ethyl 4-phenyl-2-(2-phenyl-3-(quinolin-2-yl)propyl) quinoline-3-carboxylate (8b). Yield 70%; brown solid; mp 134–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.60 (m, 6H), 7.42–7.40 (m, 2H), 7.37–7.35 (m, 2H), 7.33–7.29 (m, 3H), 7.20–7.19 (m, 5H), 7.16–7.14 (m, 1H), 7.10 (t, J = 7.5 Hz, 3H), 7.05–7.01 (m, 3H), 4.15–4.12 (m, 1H), 3.92–3.84 (m, 2H), 3.45–3.42 (m, 4H), 0.78 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 161.0, 156.0, 147.7, 147.5, 146.2, 144.4, 135.8, 135.5, 130.0, 129.5, 129.3, 129.1, 129.0, 128.8, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.3, 126.5, 126.4, 126.3, 126.1, 125.5, 125.1, 122.1, 61.3, 45.2, 45.1, 43.4, 13.5; HRMS (ESI) *m*/*z* calcd for $C_{36}H_{30}O_2N_2$ $[M + H]^+$ 522.2307; found 522.2309.

1-(6-Chloro-4-phenyl-2-(2-phenyl-3-(quinolin-2-yl)propyl)quinolin-3-yl)ethan-1-one (8c). Yield 72%; light brown solid; mp 132–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 7.5 Hz, 3H), 7.63–7.62 (m, 1H), 7.51–7.48 (m, 2H), 7.45 (d, J = 2 Hz, 2H), 7.28–7.23 (m, 3H), 7.21–7.20 (m, 2H), 7.20–7.18 (m, 2H), 7.16–7.14 (m, 1H), 4.29–4.23 (m, 1H), 3.55–3.50 (m, 1H), 3.42–3.38 (m, 3H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.6, 160.8, 155.8, 147.8, 147.6, 145.6, 144.4, 142.9, 136.2, 135.6, 135.5, 134.5, 132.4, 130.8, 130.7, 130.1, 129.9, 129.8, 129.4, 129.3, 129.2, 129.1, 128.0, 128.8, 128.7, 128.6, 128.3, 127.8, 127.5, 127.4, 126.6, 126.5, 126.3, 125.7, 125.6, 124.7, 122.2, 122.0, 45.2, 45.0, 43.3, 32.1; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{27}ClN_2O$ [M + H] 527.0544; found 527.0548.

Ethyl 6-nitro-4-phenyl-2-(2-phenyl-3-(quinolin-2-yl)propyl) quinoline-3-carboxylate (8d). Yield 78%; yellow solid; mp 133–134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95–7.94 (m, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.61–7.58 (m, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.50–7.47 (m, 3H), 7.43 (d, J = 2.5 Hz, 1H), 7.37–7.35 (m, 1H), 7.32–7.30 (m, 1H), 7.27–7.19 (m, 1H), 7.16–7.10 (m, 2H), 4.30–4.24 (m, 1H), 4.07–3.98 (m, 2H), 3.58–3.48 (m, 2H), 3.46–3.38 (m, 1H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 162.1, 156.4, 148.1, 148.0, 145.8, 145.3, 145.2, 144.8, 144.4, 143.6, 135.5, 135.3, 135.2, 135.1, 134.8, 130.8, 130.7, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 126.7, 126.5, 126.3, 125.8, 125.0, 122.3, 61.4, 45.8, 45.6, 45.2, 44.6, 43.4, 43.3, 42.8, 13.5; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{28}O_2N$ $[M + H]^+$ 567.2228; found 568.2231.

1-(6-Chloro-2-(2-(4-nitrophenyl)-3-(quinolin-2-yl)propyl)-4-phenylquinolin-3-yl)ethan-1-one (8e). Yield 76%; brown solid; mp 128–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.5 Hz, 2H), 7.97–7.93 (m, 2H), 7.89 (d, J = 8.5 Hz, 1H), 7.69–7.61 (m, 3H), 7.51–7.45 (m, 7H), 7.23 (d, J = 6 Hz, 1H), 7.18–7.17 (m, 1H), 7.14 (d, J = 8.5 Hz, 1H), 4.52–4.46 (m, 1H), 3.57–3.53 (m, 3H), 3.42–3.37 (m, 1H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.4, 159.6, 154.5, 152.4, 147.6, 146.4, 145.6, 143.3, 136.0, 135.3, 134.3, 132.8, 131.1, 130.6, 130.0, 129.9, 129.5, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 127.5, 126.5, 125.9, 125.7, 124.8, 123.6, 123.5, 121.9, 44.8, 44.4, 42.3, 32.2; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{26}ClN_3O_3$ $[M + H]^+$ 572.0520; found 572.0526.

Ethyl 2-(3-(3-(ethoxycarbonyl)quinolin-2-yl)-2-phenylpropyl)-4-phenylquinoline-3-carboxylate (8f). Yield 71%; yellow solid; mp 124–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.66 (t, J = 10 Hz, 2H), 7.49–7.46 (m, 7H), 7.38 (d, J = 7 Hz, 3H), 7.25–7.20 (m, 6H), 7.11 (t, J = 7 Hz, 1H), 4.43 (t, J = 7 Hz, 1H), 4.05–3.97 (m, 4H), 3.66–3.56 (m, 4H), 0.89 (t, J = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3, 156.4, 147.3, 146.2, 144.9, 135.9, 133.3, 130.1, 129.9, 129.5, 129.4, 129.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.5, 126.4, 126.3, 126.0, 125.0, 61.2, 43.9, 42.8, 29.7, 13.5; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{28}O_2N$ $[M + H]^+$ 671.2074; found 671.2080.

General experimental procedure for the synthesis of 2-(2-(3-acetyl-4-phenylquinolin-2-yl)-1-phenylethyl)malononitrile (10a). 2-Aminobenzophenone (0.507 mmol, 100 mg), acetylacetone (0.65 mmol, 50.7 mg), $Ca(OTf)_2$ (0.05 mmol), $^nBuNPF_6$ (0.05 mmol) were heated at 120 °C under solvent-free conditions for 4–5 h. After the completion of the reaction, malononitrile (0.507 mmol, 33.5 mg) and benzaldehyde (0.507 mmol, 53.8 mg) were added to the reaction mixture along with water as solvent. The reaction was refluxed for another 5–6 h at 120 °C. After completion, the reaction mass was filtered and washed with cold ethanol. The solid obtained was dried (no further purification was required) as **10a**, white solid, (92% yield); mp 201–202 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, J = 8 Hz, 2H), 8.13 (d, J = 8.5 Hz, 1H), 7.84 (t, J = 7 Hz, 1H), 7.76–7.72 (m, 2H), 7.57 (s, 2H), 7.43 (s, 1H), 7.33 (d, J = 5.5 Hz, 1H), 5.29 (d, J = 4 Hz, 1H), 4.46–4.44 (m, 1H), 3.64–3.59 (m, 1H), 3.45 (dd, J = 17 Hz, 16.5 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 151.4, 148.2, 147.1, 145.7, 144.2, 134.7, 134.2, 131.0, 130.0, 129.9, 129.4, 129.2, 129.1, 128.9, 127.8, 126.5, 125.4, 124.3, 112.0, 111.5, 43.6, 37.1, 32.0, 27.9; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{21}ON_3$ $[M + H]^+$ 415.1684; found 415.1690.

2-(2-(3-Acetyl-4-phenylquinolin-2-yl)-1-phenylethyl)malononitrile (10a). Yield 92%; light brown solid; mp 131–133 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.76–7.73 (m, 1H), 7.65–7.61 (m, 2H), 7.53–7.52 (m, 4H),

7.50–7.44 (m, 2H), 7.41–7.38 (m, 2H), 7.28–7.25 (m, 3H), 7.16 (t, J = 7 Hz, 2H), 4.32–4.26 (m, 1H), 3.67 (dd, J = 16.5 Hz, 17 Hz, 1H), 3.47–3.42 (m, 1H). 3.38–3.30 (m, 2H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.8, 198.7, 155.1, 147.4, 144.6, 137.2, 135.3, 135.2, 135.1, 134.8, 130.0, 128.9, 128.7, 128.4, 128.3, 128.0, 127.6, 126.6, 126.5, 126.1, 126.0, 125.1, 125.0; HRMS (ESI) m/z calcd for $C_{28}H_{21}ON_3$ [M + H]$^+$ 415.1648; found 415.1688.

2-(2-(3-Acetyl-4-phenylquinolin-2-yl)-1-(*p*-tolyl)ethyl)malononitrile (10b). Yield 94%; solid; mp 135–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 7 Hz, 1H), 7.83 (s, 1H), 7.72 (d, J = 6.5 Hz, 1H), 7.56 (s, 4H), 7.42 (s, 4H), 7.27 (m, 2H), 5.27 (s, 1H), 4.26 (s, 1H), 3.63–3.57 (m, 1H), 3.44–3.41 (m, 1H), 2.40 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 152.4, 147.2, 145.1, 138.7, 134.8, 134.6, 134.3, 130.7, 130.1, 129.9, 129.8, 129.3, 129.2, 129.0, 128.8, 128.0, 127.5, 126.3, 125.3, 112.7, 112.1, 43.5, 37.6, 32.0, 28.5, 21.2; HRMS (ESI) m/z calcd for $C_{33}H_{28}O_2N$ [M + H] 430.1914; found 430.1920.

2-(2-(3-Acetyl-4-phenylquinolin-2-yl)-1-(4-methoxyphenyl) ethyl)malononitrile (10c). Yield 96%; white solid; mp 162–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.15 (d, J = 8 Hz, 1H), 7.92 (d, J = 8 Hz, 1H), 7.81 (t, J = 7 Hz, 1H), 7.71–7.66 (m, 2H), 7.55 (s, 1H), 7.45–7.43 (m, 3H), 7.03 (d, J = 8 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 5.21 (d, J = 4 Hz, 1H), 4.24–4.23 (m, 1H), 3.93 (s, 3H), 3.60–3.55 (m, 1H), 3.42–3.39 (m, 1H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 164.8, 159.9, 158.8, 152.4, 147.2, 145.1, 133.4, 129.3, 127.4, 126.3, 125.3, 124.0, 115.1, 114.5, 55.3, 43.3, 37.7, 32.0, 28.7. HRMS (ESI) m/z calcd for $C_{29}H_{23}N_3O_2$ [M + H] 445.5119; found 445.5124.

2-(2-(3-Acetyl-4-phenylquinolin-2-yl)-1-(4-nitrophenyl) ethyl) malononitrile (10d). Yield 93%; white solid; mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, J = 8 Hz, 2H), 8.13 (d, J = 8 Hz, 1H), 7.83 (t, J = 6 Hz, 1H), 7.76–7.72 (m, 3H), 7.57 (s, 4H), 7.43 (s, 1H), 7.33 (d, J = 4.5 Hz, 1H), 5.28 (d, J = 4 Hz, 1H), 4.45 (t, J = 5 Hz, 1H), 3.64–3.59 (m, 1H), 3.48–3.44 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 151.4, 148.2, 147.1, 145.7, 144.2, 134.7, 134.2, 131.0, 130.0, 129.9, 129.4, 129.1, 128.9, 127.7, 126.4, 125.4, 124.3, 112.0, 111.5, 43.7, 37.1, 32.0, 27.9; HRMS (ESI) m/z calcd for $C_{33}H_{28}O_2N$ [M + H]$^+$ 461.1608; found 461.1614.

2-(2-(3-Acetyl-4-phenylquinolin-2-yl)-1-(4-(benzyloxy)phenyl) ethyl)malononitrile (10e). Yield 93%; light brown solid; mp 143–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, J = 2.5 Hz, 1H), 8.57 (d, J = 7 Hz, 1H), 8.29 (d, J = 9.5 Hz, 1H), 7.64–7.60 (m, 3H), 7.45–7.34 (m, 10 H), 7.04 (d, J = 8.5 Hz, 2H), 5.09 (s, 2H), 4.96 (d, J = 5 Hz, 1H), 4.29–4.26 (m, 1H), 3.64–3.59 (m, 1H), 3.49–3.45 (m, 1H), 1.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 159.2, 156.6, 149.1, 146.9, 146.2, 136.6, 136.0, 133.4, 133.3, 131.1, 130.2, 129.9, 129.8, 129.5, 129.4, 129.3, 129.1, 128.6, 128.1, 127.5, 124.7, 124.1, 123.3, 115.5, 112.3, 111.9, 70.1, 43.1, 38.2, 31.8, 28.9; HRMS (ESI) m/z calcd for $C_{33}H_{28}O_2N$ [M + H] 522.2176; found 522.2184.

2-(2-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-1-(4-nitrophenyl) ethyl)malononitrile (10f). Yield 95%; light brown solid; mp 131–133 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 9 Hz, 1H), 7.77–7.72 (m, 3H), 7.67 (d, J = 2 Hz, 1H), 7.60–7.55 (m, 3H), 7.40–7.39 (m, 1H), 7.30 (d, J = 6.5 Hz, 1H), 4.45–4.41 (m, 1H), 3.63–3.57 (m, 1H), 3.46–3.41 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 151.8, 148.2, 145.5, 144.8, 144.1, 134.9, 134.0, 133.9, 131.9, 130.7, 129.9, 129.8, 129.8, 129.4, 129.4, 129.3, 129.2, 128.9, 126.4, 125.2, 124.4, 111.9, 111.4, 43.5, 37.1, 31.9, 28.0; HRMS (ESI) m/z calcd for $C_{28}H_{19}O_3N_4Cl$ [M + H] 494.1145; found 494.1150.

2-(2-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-1-(4-methoxyphenyl) ethyl)malononitrile (10g). Yield 92%; light brown solid; mp 188–190 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 3H), 7.70 (t, J = 8 Hz, 1H), 7.56 (s, 3H), 7.44 (t, J = 8.5 Hz, 2H), 7.04 (d, J = 8.5 Hz, 3H), 5.21 (d, J = 4.5 Hz, 1H), 4.25 (t, J = 5 Hz, 1H), 3.85 (s, 3H), 3.61–3.56 (m, 1H), 3.44–3.40 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 164.8, 159.9, 158.8, 152.4, 133.4, 130.6, 130.1, 129.9, 129.3, 127.4, 126.3, 124.1, 115.1, 114.5, 55.8, 43.3, 37.7, 32.0, 28.6; HRMS (ESI) m/z calcd for $C_{29}H_{22}O_2N_3Cl$ [M + H]$^+$ 479.1400; found 479.1404.

2-(2-(3-Acetyl-6-chloro-4-phenylquinolin-2-yl)-1-(4-methoxyphenyl) ethyl)malononitrile (10h). Yield 94%; white solid; mp 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 1H), 7.85–7.82 (m, 1H), 7.76–7.73 (m, 3H), 7.74 (t, J = 8.5 Hz, 4H), 7.59–7.53 (m, 1H), 7.43–7.32 (m, 1H), 5.29 (d, J = 5 Hz, 1H), 4.47–4.43 (m, 1H), 3.64–3.59 (m, 1H), 3.47–3.43 (m, 1H), 2.46 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.4, 164.8, 151.4, 148.2, 147.1, 145.7, 144.2, 134.7, 134.2, 131.0, 130.0, 129.9, 129.4, 129.1, 128.9, 127.8, 126.5, 125.4, 124.4, 112.0, 111.5, 43.6, 37.1, 32.0, 27.9; HRMS (ESI) m/z calcd for $C_{29}H_{22}N_3ClO$ [M + H]$^+$ 463.9573; found 463.9576.

2-(2-(3-Acetyl-6-nitro-4-phenylquinolin-2-yl)-1-phenylethyl) malononitrile (10i). Yield 92%; white solid; mp 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 1H), 7.85–7.82 (m, 1H), 7.76–7.73 (m, 3H), 7.59–7.53 (m, 4H), 7.43–7.42 (m, 1H), 7.33–7.32 (m, 1H), 5.29 (d, J = 5 Hz, 1H), 4.47–4.43 (m, 1H), 3.64–3.59 (m, 1H), 3.47–3.43 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.3, 151.4, 148.2, 147.1, 145.7, 144.2, 134.7, 134.2, 131.0, 130.0, 129.9, 129.4, 129.2, 129.1, 128.9, 127.8, 126.5, 125.4, 124.4, 112.0, 111.5, 43.6, 37.1, 32.0, 27.9; HRMS (ESI) m/z calcd for $C_{33}H_{28}O_2N$ [M + H]$^+$ 461.1608; found 461.1614.

General experimental procedure for the synthesis of 2-(2-(3-acetyl-4-phenylquinolin-2-yl)-1-(2-oxoindolin-3-yl)ethyl) malononitrile (12a). 2-Aminobenzophenone (0.50 mmol, 100 mg), acetylacetone (0.65 mmol, 50.7 mg), $Ca(OTf)_2$ (0.05 mmol), ^{n}BuNPF$_6$ (0.05 mmol) were heated at 120 °C under solvent free conditions for 4–5 h. After completion of the reaction, malononitrile (0.507 mmol, 33.5 mg) and isatin (0.507 mmol, 84.7 mg) were added to the reaction mixture along with water as solvent. The reaction was refluxed for another 5–6 h at 120 °C. After completion, the reaction mass was filtered and washed with cold ethanol. The solid obtained was dried and characterised without any further purification (**12a**). Yield 91%; light blue solid; mp 186–188 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.34 (t, J = 7 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.53–7.47 (m, 5H), 7.36–7.33 (m, 3H), 7.09–7.04 (m, 2H), 5.23 (s, 1H), 3.72 (q, J = 16.5 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 175.5, 150.2, 146.7, 145.3, 141.1, 134.9, 130.6, 130.4, 130.1, 129.9, 129.3, 129.0, 128.9, 128.8, 127.5, 126.7, 126.3, 125.2, 124.3, 123.4, 110.6, 110.2, 51.6, 38.2,

32.1, 30.2; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{20}O_2N_4$ [M + H] 456.1586; found 470.1590.

2-(3-((3-Acetyl-4-phenylquinolin-2-yl)methyl)-1-methyl-2-oxoindolin-3-yl)malononitrile (12b). Yield 92%; pink solid; mp 215–217 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J = 8 Hz, 1H), 7.73–7.70 (m, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.52–7.48 (m, 5H), 7.41 (d, J = 7.5 Hz, 1H), 7.33–7.31 (m, 2H), 7.09 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 5.12 (s, 1H), 3.72 (dd, J = 16.5 Hz, 16.5 Hz, 2H), 3.14 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 174.1, 150.2, 146.6, 145.1, 144.4, 137.7, 134.9, 134.1, 130.5, 130.4, 130.1, 130.0, 129.2, 128.9, 128.8, 127.4, 126.7, 126.3, 126.1, 125.2, 123.9, 123.8, 123.4, 111.1, 110.2, 109.6, 108.9, 51.2, 38.3, 32.1, 30.4, 26.8; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{22}O_2N_4$ [M + H] 470.1742; found 470.1745.

2-(3-((3-Acetyl-4-phenylquinolin-2-yl)methyl)-5-methyl-2-oxoindolin-3-yl)malononitrile (12c). Yield 92%; pink solid; mp 189–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.94 (d, J = 8 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.53–7.47 (m, 4H), 7.31–7.26 (m, 3H), 7.13 (d, J = 8 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 5.15 (s, 1H), 3.75–3.65 (m, 2H), 2.29 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 175.6, 150.2, 146.7, 145.2, 138.7, 135.0, 134.2, 133.7, 133.1, 130.8, 130.6, 130.2, 130.1, 130.0, 129.2, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 127.4, 127.1, 126.7, 126.6, 126.3, 126.2, 125.2, 124.8, 118.8, 111.3, 111.1, 110.7, 110.3, 51.7, 38.3, 32.1, 30.3, 21.2; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{22}O_2N_4$ [M + H] 470.1742; found 470.1745.

2-(3-((3-Acetyl-6-chloro-4-phenylquinolin-2-yl)methyl)-1-methyl-2-oxoindolin-3-yl)malononitrile (12d). Yield 91%; blue solid; mp 125–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, J = 8.5 Hz, 1H), 7.72 (t, J = 7 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52–7.40 (m, 4H), 7.34–7.30 (m, 3H), 7.10 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 5.11 (s, 1H), 3.79–3.64 (m, 2H), 3.41 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.1, 174.1, 150.2, 146.6, 145.1, 144.4, 134.9, 134.2, 130.5, 130.4, 130.1, 130.0, 129.2, 128.9, 128.8, 127.4, 126.3, 126.1, 125.2, 123.8, 123.3, 111.1, 110.1, 108.9, 51.2, 38.3, 32.1, 30.4, 26.8; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{21}O_2N_4Cl$ [M + H] 504.1725; found 504.1732.

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Notes and references

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14 Though the other conditions found to be reasonably satisfactory for Friedlander synthesis, only entry 4, Table 1 was found to be the best condition for the next step (conjugate addition).
15 See ESI† for more details about optimization of reaction conditions and copies of spectra.