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An alternate approach to quinoline architecture via Baylis–Hillman chemistry: $SnCl_2$-mediated tandem reaction toward synthesis of 4-(substituted vinyl)-quinolines

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Abstract—An alternate approach to densely substituted quinolines from the products of S_N2 nucleophilic substitution reaction between the acetyl derivatives of the Baylis–Hillman adducts obtained from 2-nitrobenzaldehydes and the carbonyl group containing carbon nucleophiles is described. Treatment of these compounds with $SnCl_2$, triggers a tandem reaction wherein reduction of the nitro group is followed by a remarkably regioselective intramolecular cyclization and subsequent dehydrogenation to afford 4-(substituted vinyl)-quinolines.

1. Introduction

Substituted quinolines are one of the oldest known classes of pharmaceutical agents and their relevance in chemotherapy especially against malaria is widely known.[1] Beside antimalarials, a spectrum of other pharmacological activities[2] has been the major reason for the development of novel and efficient syntheses of this heterocycle. As a result, the recent past has witnessed the publication of several simple and elegant syntheses of substituted quinolines.[3] Nevertheless, a new mild one-pot method, from readily accessible starting materials, which would permit delivery of this motif decorated with functional groups amenable to further diversification, should be of great synthetic relevance.

In the recent times, Baylis–Hillman adducts have been illustrated as suitable starting materials for the synthesis of variety of heterocyclic systems.[4] The generation of substituted quinolines either directly from the Baylis–Hillman adducts or their derivatives has therefore received considerable attention. Historically, since the first such synthesis reported by Familoni et al. in 1998, several variants of this approach have been demonstrated.[5–16] A summary of these methods is provided in Figure 1.

With our ongoing interest in the synthesis of heterocycles employing derivatives of Baylis–Hillman adducts,[17] it

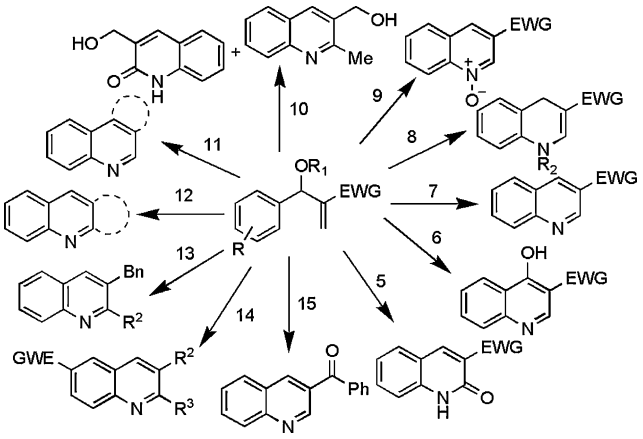

Figure 1. Summary of synthesis of quinoline motif from Baylis–Hillman adducts or their derivatives. Numbers on the arrows indicate the corresponding reference no. (also see Ref. 16).

occurred to us that substrates resulting from the S_N2 nucleophilic substitution reaction between the acetyl derivatives of Baylis–Hillman adducts of 2-nitrobenzaldehydes and a nucleophile containing a keto group or an ester group would represent an interesting carbon framework for the construction of a quinoline architecture. In these compounds beside the three carbon chain originating from the Baylis–Hillman reaction, which generally participates in the intramolecular cyclization toward construction of the quinoline, there would also be another three carbon chain containing a terminal keto or an ester group, which could also undergo cyclization. In the latter case cyclization would result in a dihydroquinoline derivative with a vinyl chain at the 4-position, which could be dehydrogenated to yield the desired quinoline. We have

Keywords: Quinolines; Baylis–Hillman; 2-Nitrobenzaldehyde; Reduction; $SnCl_2$; Regioselective.
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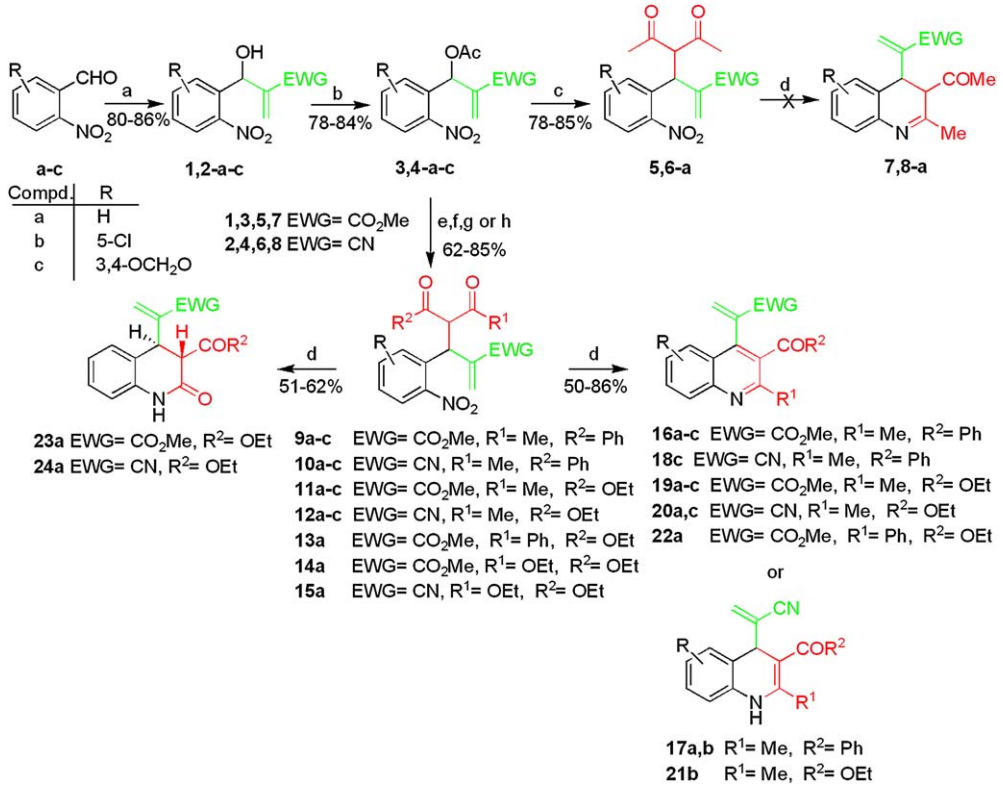
therefore carried out S_N2 reactions of the acetates of the Baylis–Hillman adducts of 2-nitrobenzaldehydes and substituted 2-nitrobenzaldehydes with nucleophiles such as acetyl acetone, benzoyl acetone, methylacetoacetate, and benzoylacetoacetate and subjected the resulting products to chemoselective reduction in the presence of $SnCl_2$. Interestingly, the chemoselective reduction led to a tandem reaction wherein the reduction, a regioselective cyclization involving the carbonyl group of the added nucleophile dehydrogenation occurred in a single step to furnish the 4-(substituted vinyl)-quinolines. This observation prompted us to disclose the details of results of our study in this paper.

2. Results and discussion

Preparation of the starting materials, the acetates **3a–c**,**4a–c**, was accomplished by acetylating the corresponding Baylis–Hillman adducts **1a–c**,**2a–c** in the presence of acetyl chloride and pyridine in dichloromethane at room temperature (Scheme 1). Initially, the S_N2 reaction of acetyl acetone was carried out with the acetate **3a** following the reported procedure to obtain product **5a**.[17d] The chemoselective reduction of the nitro group employing anhydrous $SnCl_2$ in compound **5a**, instead of yielding the desired dihydroquinoline **7a**, resulted in an inseparable mixture of products. It is likely that both the carbonyl group of the added nucleophile and the ester group originally present in the substrate could have participated in the cyclization reaction leading to a complex mixture. In principle, if the acetate **4a** is used as the starting substrate for a similar reaction then the possibility of simultaneous cyclizations could be eliminated. Accordingly, compound **6a** was prepared and subjected to similar reduction. However, instead of the desired product **8a**, a complex mixture of products was formed, which could not be characterized.

In the next step we decided to investigate the same reaction sequence by replacing the nucleophile with benzoyl acetone. Thus, the S_N2 nucleophilic substitution reaction of benzoyl acetone with the acetate **3a** in the presence of DABCO in a THF/H_2O system led to the synthesis of compound **9a** as a diastereoisomeric mixture in good yield. The nitro group in **9a** was then chemoselectively reduced with anhydrous $SnCl_2$. Gratifyingly this reaction proceeded smoothly to yield a product, which was established as the quinoline **16a** via spectroscopic analysis. The change in the chemical shift of the protons of methyl group indicated that the acetyl group of the nucleophile was involved in the intramolecular cyclization with the amino group. The isolation of quinoline **16a** implied that the $SnCl_2$ had triggered a tandem reaction wherein the reduction of the nitro group was followed by cyclization and subsequent dehydrogenation. This reaction was found to be general in nature since substrates **9b**,**c** also furnished the quinolines **16b**,**c**. During optimization it was observed that replacing anhydrous $SnCl_2$ with $SnCl_2\cdot 2H_2O$ did not have any effect on the outcome of the reaction. Encouraged with these results we decided to evaluate the reaction with compounds **10a–c**, which were synthesized from **4a–c**, respectively, following a similar synthetic route to that for the preparation of **9a–c**. Interestingly when **10a** was subjected to $SnCl_2$-promoted reaction, unlike compound **9a–c**, the dihydroquinoline derivative **17a** was isolated. ^{1}H NMR analysis of product **17a** showed



Scheme 1. Reagents and conditions: (a) CH_2=CHEWG, DABCO, rt, 15 min to 1 h; (b) AcCl, pyridine, CH_2Cl_2, rt, 2–3 h; (c) DABCO, $MeCOCH_2COMe$, THF/H_2O (1:1), rt, 30 min; (d) $SnCl_2$, MeOH, reflux, 1 h; (e) DABCO, $PhCOCH_2COMe$, THF/H_2O (1:1), rt, 30 min; (f) DABCO, $MeCOCH_2CO_2Et$, THF/H_2O (1:1), rt, 30 min; (g) DABCO, $PhCOCH_2CO_2Et$, THF/H_2O (1:1), rt, 30 min; (h) DABCO, $CO_2EtCH_2CO_2Et$, THF/H_2O (1:1), rt, 30 min.

the presence of peaks for the NH and the CH protons and ^{13}C NMR exhibited the CH carbon instead of the signal for tertiary carbon. The mass spectrum supported the assigned structure. Treatment of compound **10b** with $SnCl_2$ also yielded the dihydroquinoline **17b** but substrate **10c** gave the usual quinoline **18c**.

The results generated interest in studying the outcome of reactions with other carbonyl group containing carbon nucleophiles in order to further explore the scope of this strategy. Therefore, compounds **11a–c**,**12a–c** were synthesized using ethylacetoacetate as the nucleophile in the S_N2 reaction of the acetates **3a–c**,**4a–c**, respectively. We were pleased to observe that the $SnCl_2$ reduction of the nitro group proceeded smoothly in these compounds to furnish the quinolines **19a–c**, **20a**,**c** in good yields. Like compounds **10a**,**b**, compound **12b** also yielded dihydroquinoline **21b** exclusively. These results indicated that the acetyl carbonyl introduced through the S_N2 reaction reacts in preference to other activated carbonyl moieties present in the molecule with the amine generated during the reduction reaction.

We next examined the reduction in compound **13a**. Gratifyingly treatment with $SnCl_2$ yielded the quinoline **22a** in good yield. This result again indicated that the carbonyl group are more reactive in the cyclization reaction and precedes the ester moiety. In our quest to find out whether the ester group can at all participate in the intramolecular cyclization, diethylmalonate was selected as nucleophile for the S_N2 reaction. Hence, compounds **14a** and **15a** generated by the reaction of compounds **3a** and **4a**, respectively, with diethylmalonate in the presence of DABCO, were treated with $SnCl_2$. The reaction led to isolation of products, which were established to be tetrahydro quinolin-2-ones **23a**, **24a**. Interestingly, this cyclization was found to be diastereoselective in favor of *trans* isomer, as evident from the NOE correlations for H-3 and H-4 protons. Thus in the absence of a ketone moiety, the ester group can also participate in the intramolecular cyclization. However, the subsequent dehydrogenation does not occur.

3. Conclusions

In summary, we have demonstrated a new alternate strategy for the synthesis of highly functionalized quinolines from easily accessible derivatives of Baylis–Hillman adducts, which has general applicability. The $SnCl_2$-mediated reduction of the nitro group initiates a highly regioselective intramolecular cyclization between the amino group and the carbonyl moiety from the nucleophile introduced through the S_N2 substitution reaction. This study indicates that the preference of the activated carbonyl group COR for cyclization has the following order: R=Me>Ph>*O*-alkyl. We believe that the quinoline derivatives generated during the present study would serve as good building blocks for the synthesis of quinoline-annulated ring systems.

4. Experimental

4.1. General

Melting points are uncorrected and were determined using a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin–Elmer RX I FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts are expressed as δ values, *J* in hertz). FABMS were recorded on a JEOL/SX-102 spectrometer and ESMS were recorded using a Micromass LC–MS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL *III* microanalyzer. All yields are the isolated yields from column chromatography. Spectroscopic data of compounds **9–13** are reported as diastereoisomeric mixtures unless otherwise stated.

4.2. General procedure for the S_N2 nucleophilic substitution reaction with the acetyl derivatives

To a stirred solution of appropriate acetate (1.0 equiv) in THF/H_2O (50:50, v/v) was added DABCO (1.5 equiv) at room temperature and the reaction was allowed to continue for 20 min. Thereafter, the appropriate nucleophile (1.2 equiv) was added to the reaction mixture, and was further stirred for 30 min at room temperature. The organic solvent was removed and the residue diluted with water and extracted with EtOAc (3×50 mL). Combined organic layer was washed with brine solution (70 mL), dried (Na_2SO_4), and evaporated to yield a crude product, which was purified via silica gel column chromatography using hexanes/EtOAc (85:15, v/v) as eluent to furnish pure products in 62–85% yield.

4.2.1. 4-Acetyl-2-methylene-3-(2-nitro-phenyl)-5-oxo-hexanoic acid methyl ester (5a). Ref. 17d.

4.2.2. 4-Acetyl-2-methylene-3-(2-nitro-phenyl)-5-oxo-hexanenitrile (6a). Yield 78% (0.9 g from 1.0 g) as a brown solid; mp 135–137 °C; ν_{max} (KBr) 1707 (2×CO), 2227 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.98 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.69 (d, 1H, *J*=11.8 Hz, CH), 5.21 (d, 1H, *J*=11.8 Hz, CH), 6.02 (s, 1H, =CH), 6.19 (s, 1H, =CH), 7.45–7.65 (m, 3H, ArH), 7.87 (d, 1H, *J*=7.4 Hz, CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.3, 30.0, 42.6, 72.0, 117.0, 121.4, 125.8, 129.0, 129.6, 131.3, 135.7, 150.3, 200.0, 200.3; mass (ES+) *m*/*z* 309 (M^++Na); Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.04; H, 4.96; N, 9.65.

4.2.3. 4-Benzoyl-2-methylene-3-(2-nitro-phenyl)-5-oxo-hexanoic acid methyl ester (9a). Yield 81% (1.1 g from 1.0 g) as a brown solid; mp 102–104 °C; ν_{max} (KBr) 1679 (CO), 1724 (CO and CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.57 (s, 3H, CO_2CH_3), 3.71 (s, 3H, CO_2CH_3), 5.55–5.82 (m, 5H, 4×CH and =CH), 5.99 (s, 1H, =CH), 6.18 (s, 1H, =CH), 6.39 (s, 1H, =CH), 7.21–7.72 (m, 16H, ArH), 7.92 (d, 1H, *J*=11.8 Hz, ArH), 8.08 (d, 1H, *J*=11.8 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 27.0, 40.1, 40.8, 50.7, 50.8, 64.8, 65.3, 123.4, 123.6, 126.6, 126.9, 127.4, 127.5, 127.7, 128.3, 128.6, 129.5, 131.0, 131.1, 131.8, 132.6, 132.8, 135.1, 135.3, 136.8, 137.5, 149.0, 149.1, 152.4, 164.7, 165.0, 189.7, 192.5, 200.7, 200.8; mass (ES+) *m*/*z* 382.1 (M^++1), 404.1 (M^++Na); Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.10; H, 4.97; N, 3.66.

4.2.4. 4-Benzoyl-3-(5-chloro-2-nitro-phenyl)-2-methylene-5-oxo-hexanoic acid methyl ester (9b). Yield 63% (0.5 g from 0.6 g) as a brown semisolid; ν_{max} (Neat) 1680 (CO), 1721 (CO and CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.11 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.59 (s, 6H, 2×CO_2CH_3), 5.45–5.60 (m, 4H, 4×CH), 5.65 (s, 2H, 2×=CH), 5.75 (s, 1H, =CH), 6.22 (s, 1H, =CH), 7.34 (d, 2H, J=6.8 Hz, ArH), 7.49–7.76 (m, 10H, ArH), 8.07 (d, 4H, J=7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.6, 30.0, 42.6, 43.2, 53.6, 53.7, 67.2, 67.7, 127.6, 127.7, 129.5, 127.5, 129.3, 129.9, 130.1, 130.3, 130.5, 131.7, 132.2, 135.5, 135.7, 136.3, 138.8, 139.6, 140.1, 149.9, 167.2, 167.5, 195.0, 202.9; mass (ES+) m/z 415.9 (M^++1); Anal. Calcd for $C_{21}H_{18}ClNO_6$: C, 60.66; H, 4.36; N, 3.37. Found: C, 60.69; H, 4.44; N, 3.67.

4.2.5. 4-Benzoyl-2-methylene-3-(6-nitro-benzo[1,3]-dioxol-5-yl)-5-oxo-hexanoic acid methyl ester (9c). Yield 69% (0.9 g from 1.0 g) as a brown solid; mp 127–129 °C; ν_{max} (KBr) 1680 (CO), 1721 (CO and CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.62 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 5.58–5.79 (m, 4H, 3×CH and =CH), 5.96–6.03 (m, 2H, CH and =CH), 6.10 (s, 4H, 2×OCH_2O), 6.20 (s, 1H, =CH), 6.40 (s, 1H, =CH), 7.01 (s, 1H, ArH), 7.06 (s, 1H, ArH), 7.28–7.30 (m, 4H, ArH), 7.43–7.62 (m, 6H, ArH), 7.97 (d, 1H, J=12.0 Hz, ArH), 8.08 (d, 1H, J=12.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.6, 21.4, 28.5, 28.7, 41.5, 42.3, 52.5, 60.8, 66.7, 67.1, 103.2, 103.4, 106.1, 106.3, 109.8, 127.9, 129.2, 129.5, 130.1, 134.6, 136.9, 139.4, 144.8, 151.6, 166.5, 194.2, 202.7; mass (ES+) m/z 425.9 (M^++1), 448.1 (M^++Na); Anal. Calcd for $C_{22}H_{19}NO_8$: C, 62.12; H, 4.50; N, 3.29. Found: C, 62.00; H, 4.41; N, 3.11.

4.2.6. 4-Benzoyl-2-methylene-3-(2-nitro-phenyl)-5-oxo-hexanenitrile (10a). Yield 78% (1.1 g from 1.0 g) as a brown solid; mp 102–104 °C; ν_{max} (KBr) 1674 (CO), 1724 (CO), 2221 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 Hz) δ 1.95 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 5.41–5.53 (m, 4H, 4×CH), 5.91 (s, 1H, =CH), 6.09 (s, 1H, =CH), 6.17 (s, 1H, =CH), 6.30 (s, 1H, =CH), 7.43–8.11 (m, 16H, ArH), 8.12–8.15 (d, 2H, J=7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.9, 29.6, 43.1, 43.5, 65.8, 66.7, 117.4, 117.5, 121.3, 121.7, 125.7, 128.6, 129.1, 129.3, 129.5, 129.6, 131.3, 133.6, 133.7, 134.8, 135.1, 135.7, 135.9, 136.5, 150.4, 192.5, 192.8, 199.9, 200.2; mass (ES+) m/z 349.0 (M^++1); Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.15; H, 4.55; N, 7.90.

4.2.7. 4-Benzoyl-3-(5-chloro-2-nitro-phenyl)-2-methylene-5-oxo-hexanenitrile (10b). Yield 71% (1.1 g from 1.15 g) as a white solid; mp 183–185 °C; ν_{max} (KBr) 1672 (CO), 1723 (CO), 2221 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 Hz) δ 1.99 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 5.36–5.50 (m, 4H, 4×CH), 5.94 (s, 1H, =CH), 6.13 (s, 1H, =CH), 6.18 (s, 1H, =CH), 6.32 (s, 1H, =CH), 7.48–7.91 (m, 14H, ArH), 8.15 (d, 2H, J=7.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.4, 29.9, 42.9, 43.3, 65.5, 66.4, 117.3, 120.6, 121.1, 127.2, 129.1, 129.3, 129.6, 133.9, 134.5, 135.0, 135.2, 136.2, 136.5, 140.0, 140.2, 148.6, 192.3, 192.5, 199.3, 199.7; mass (ES+) m/z 405.0 (M^++Na); Anal. Calcd for $C_{20}H_{15}ClN_2O_4$: C, 62.75; H, 3.95; N, 7.32. Found: C, 62.95; H, 4.02; N, 7.33.

4.2.8. 4-Benzoyl-2-methylene-3-(6-nitro-benzo[1,3]-dioxol-5-yl)-5-oxo-hexanenitrile (10c). Yield 81% (0.75 g from 0.8 g) as a yellow solid; mp 189–191 °C; ν_{max} (KBr) 1676 (CO), 1722 (CO and CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 1.99 (s, 3H, CH_3), 5.42 (d, 1H, J=12.0 Hz, CH), 5.61 (s, 1H, J=12.0 Hz, CH), 5.92 (s, 1H, =CH), 6.17 (s, 3H, =CH, CH_2), 7.14 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.54–7.71 (m, 3H, ArH), 8.13 (d, 2H, J=9.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.5, 29.4, 43.0, 43.4, 66.1, 66.9, 103.6, 103.8, 106.8, 108.2, 117.3, 121.3, 121.7, 127.6, 128.6, 129.1, 129.5, 129.6, 134.8, 135.0, 135.7, 136.6, 144.4, 148.1, 152.3, 192.7, 200.1; mass (ES+) m/z 393.0 (M^++1), 415.0 (M^++Na); Anal. Calcd for $C_{21}H_{16}N_2O_6$: C, 64.28; H, 4.11; N, 7.14. Found: C, 64.21; H, 4.19; N, 7.31.

4.2.9. 2-Acetyl-4-methylene-3-(2-nitro-phenyl)-pentanedioic acid 1-ethyl ester 5-methyl ester (11a). Yield 85% (0.80 g from 0.75 g) as a brown oil; ν_{max} (Neat) 1722 (CO, CO_2Me, CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, 3H, J=7.5 Hz, CH_3), 1.26 (t, 3H, J=7.5 Hz, CH_3), 2.18 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.68 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 3.98 (q, 2H, J=7.0 Hz, CH_2), 4.20 (q, 2H, J=7.0 Hz, CH_2), 4.57 (d, 1H, J=12.0 Hz, CH), 4.63 (d, 1H, J=9.0 Hz, CH), 5.32 (d, 2H, J=12.0 Hz, CH), 5.88 (s, 1H, =CH), 5.92 (s, 1H, =CH), 6.35 (s, 1H, =CH), 6.36 (s, 1H, =CH), 7.35–7.41 (m, 2H, ArH), 7.51–7.62 (m, 4H, ArH), 7.74–7.79 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 14.4, 29.6, 29.8, 41.0, 41.1, 50.5, 52.5, 62.2, 62.3, 63.4, 63.5, 125.0, 125.1, 128.2, 128.6, 129.1, 130.4, 130.6, 132.8, 133.7, 138.8, 139.2, 150.7, 166.3, 166.7, 167.6, 168.1, 210.2, 201.3; mass (ES+) m/z 349.9 (M^++1); Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.36; H, 5.44; N, 3.98.

4.2.10. 2-Acetyl-3-(5-chloro-2-nitro-phenyl)-4-methylene-pentanedioic acid 1-ethyl ester 5-methyl ester (11b). Yield 75% (1.0 g from 0.9 g) as a brown oil; ν_{max} (Neat) 1720 (CO, CO_2Me, CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.24 (t, 3H, J=7.0 Hz, CH_2CH_3), 2.20 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.68 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 3.99–4.21 (2q merged, 4H, 2×CH_2CH_3), 4.15 (d, 1H, J=12.0 Hz, CH), 4.19 (d, 1H, J=12.0 Hz, CH), 5.34 (dd, 2H, J_1=12.0 Hz, J_1=3.4 Hz, 2×CH), 5.90 (s, 1H, =CH), 5.96 (s, 1H, =CH), 6.38 (s, 2H, 2×=CH), 7.32 (d, 2H, J=8.4 Hz, ArH), 7.53 (d, 2H, J=9.6 Hz, ArH), 7.75 (dd, 2H, J_1=8.4 Hz, J_2=2.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 14.4, 26.1, 29.7, 30.0, 40.9, 42.6, 58.1, 61.9, 62.4, 63.0, 63.3, 126.6, 128.6, 128.9, 129.6, 130.4, 131.0, 135.7, 136.1, 138.2, 138.6, 139.1, 148.4, 166.2, 166.5, 167.4, 167.8, 200.7, 200.8; mass (ES+) m/z 383.9 (M^++1); HR-EIMS calculated for $C_{17}H_{18}ClNO_7$: 383.0772, found: 383.0770.

4.2.11. 2-Acetyl-4-methylene-3-(6-nitro-benzo[1,3]-dioxol-5-yl)-pentanedioic acid 1-ethyl ester 5-methyl ester (11c) (single diastereoisomer). Yield 77% (0.75 g from 0.8 g) as a white solid; mp 125–127 °C; ν_{max} (KBr) 1710 (CO, CO_2Me, CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (t, 3H, J=7.0 Hz, CH_2CH_3), 2.28 (s, 3H, CH_3), 3.68 (s, 3H, CO_2CH_3), 4.01 (q, 2H, J=7.0 Hz,

CH_2CH_3), 4.49 (d, 1H, J=11.8 Hz, CH), 5.38 (d, 1H, J=11.8 Hz, CH), 5.86 (s, 1H, =CH), 6.07 (s, 2H, OCH_2O), 6.34 (s, 1H, =CH), 6.97 (s, 1H, ArH), 7.31 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 29.7, 40.9, 52.8, 62.2, 63.4, 103.4, 106.0, 109.0, 128.9, 130.3, 138.9, 144.6, 147.2, 151.6, 166.7, 167.6, 201.3; mass (ES+) m/z 393.9 (M^++1); Anal. Calcd for $C_{18}H_{19}NO_9$: C, 54.96; H, 4.87; N, 3.56. Found: C, 55.12; H, 4.99; N, 3.67.

4.2.12. 2-Acetyl-4-cyano-3-(2-nitro-phenyl)-pent-4-enoic acid ethyl ester (12a). Yield 78% (1.0 g from 1.0 g) as a brown solid; mp 85–87 °C; ν_{max} (KBr) 1723 (CO and CO_2Et), 2226 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.96 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.31 (t, 3H, J=7.0 Hz, CH_2CH_3), 2.12 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.92 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.25 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.41 (d, 1H, J=6.8 Hz, CH), 4.47 (d, 1H, J=6.8 Hz, CH), 5.06 (d, 2H, J=11.8 Hz, 2×CH), 6.05 (s, 1H, =CH), 6.06 (s, 1H, =CH), 6.24 (s, 1H, =CH), 6.28 (s, 2H, 2×=CH), 7.42–7.48 (m, 2H, ArH), 7.56–7.65 (m, 4H, ArH), 7.83–7.88 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.5, 30.1, 42.5, 63.0, 63.1, 117.6, 121.6, 125.7, 128.3, 129.3, 132.1, 133.7, 135.5, 166.6, 199.2; mass (ES+) m/z 317.1 (M^++1), 339.1 (M^++Na); Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.88; H, 5.18; N, 8.99.

4.2.13. 2-Acetyl-3-(5-chloro-2-nitro-phenyl)-4-cyano-pent-4-enoic acid ethyl ester (12b). Yield 64% (0.8 g from 1.0 g) as a white solid; mp 119–121 °C; ν_{max} (KBr) 1708 (CO), 1738 (CO_2Et), 2228 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.03 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.32 (t, 3H, J=7.0 Hz, CH_2CH_3), 2.17 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.97 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.29 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.37 (d, 1H, J=8.2 Hz, CH), 4.43 (d, 1H, J=8.0 Hz, CH), 5.10 (dd, 2H, J_1=11.6 Hz, J_2=3.6 Hz, 2×CH), 6.08 (s, 2H, 2×=CH), 6.25 (s, 1H, =CH), 6.28 (s, 1H, =CH), 7.39–7.44 (m, 2H, ArH), 7.52 (s, 1H, ArH), 7.59 (s, 1H, ArH), 7.85 (dd, 2H, J_1=8.8 Hz, J_2=2.8 Hz, 2×CH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 14.4, 30.1, 30.9, 41.8, 42.2, 62.7, 62.8, 63.0, 63.1, 117.1, 120.7, 121.1, 127.0, 127.2, 128.5, 129.1, 129.4, 134.5, 135.8, 136.6, 140.0, 148.6, 148.7, 165.8, 166.3, 198.8, 199.0; mass (ES+) m/z 351.1 (M^++1), 373.0 (M^++Na); HR-EIMS calculated for $C_{16}H_{15}ClN_2O_5$: 350.0670, found: 350.0671.

4.2.14. 2-Acetyl-4-cyano-3-(6-nitro-benzo[1,3]dioxol-5-yl)-pent-4-enoic acid ethyl ester (12c). Yield 79% (0.68 g from 0.7 g) as a yellow solid; mp 130–132 °C; ν_{max} (KBr) 1710 (CO), 1743 (CO_2Et), 2225 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.32 (t, 3H, J=7.0 Hz, CH_2CH_3), 2.16 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.00 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.26 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.32 (d, 1H, J=9.0 Hz, CH), 4.45 (d, 1H, J=9.0 Hz, CH), 5.19 (d, 2H, J=12.0 Hz, 2×CH), 6.04 (s, 1H, =CH), 6.08 (s, 1H, =CH), 6.14 (s, 4H, 2×OCH_2O), 6.22 (s, 1H, =CH), 6.28 (s, 1H, =CH), 6.95 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.39 (s, 1H, ArH), 7.41 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 14.4, 29.9, 30.8, 41.9, 42.6, 62.9, 63.2, 103.7, 106.4, 106.7, 107.1, 117.3, 121.2, 121.6, 128.3, 135.2, 136.1, 147.8, 152.2, 165.9, 166.6, 199.1; mass (ES+) m/z 383.1 (M^++Na); HR-EIMS calculated for $C_{17}H_{16}N_2O_7$: 360.0958, found: 360.0961.

4.2.15. 2-Benzoyl-4-methylene-3-(2-nitro-phenyl)-pentanedioic acid 1-ethyl ester 5-methyl ester (13a). Yield 82% (1.2 g from 1.0 g) as a brown oil; ν_{max} (Neat) 1691 (CO), 1729 (CO_2Me and CO_2Et) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, J=6.0 Hz, CH_2CH_3), 1.15 (t, 3H, J=6.0 Hz, CH_2CH_3), 3.60 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.82 (q, 2H, J=6.0 Hz, CH_2CH_3), 4.11 (q, 2H, J=6.0 Hz, CH_2CH_3), 5.43–5.63 (m, 3H, 3×CH), 5.72 (d, 1H, J=12.0 Hz, CH), 5.81 (s, 1H, =CH), 6.06 (s, 1H, =CH), 6.26 (s, 1H, =CH), 6.39 (s, 1H, =CH), 7.37–7.62 (m, 11H, ArH), 7.69–7.72 (m, 1H, ArH), 7.76–7.78 (m, 2H, ArH), 7.97–8.00 (m, 2H, ArH), 8.08–8.11 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9; 14.3, 42.1, 43.1, 52.4, 57.6, 60.8, 62.3, 125.0, 125.1, 128.2, 128.5, 128.8, 129.1, 129.2, 130.3, 131.2, 132.7, 133.3, 133.4, 134.3, 136.4, 136.6, 138.1, 138.8, 150.9, 166.6, 167.6, 168.0, 192.7; mass (ES+) m/z 411.9 (M^++1), 434.1 (M^++Na); Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.14; N, 3.40. Found: C, 64.22; H, 5.01; N, 3.32.

4.2.16. 2-Ethoxycarbonyl-4-methoxycarbonyl-3-(2-nitro-phenyl)-pent-4-enoic acid ethyl ester (14a). Yield 74% (1.0 g from 1.0 g) as brown oil; ν_{max} (Neat) 1727 (CO_2Me and 2×CO_2Et) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.05 (t, 3H, J=7.0 Hz, CH_2CH_3), 3.68 (s, 6H, CO_2CH_3), 4.01 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.20 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.41 (d, 1H, J=12.0 Hz, CH), 5.27 (d, 1H, J=12.0 Hz, CH), 5.89 (s, 1H, =CH), 6.38 (s, 1H, =CH), 7.35–7.41 (m, 1H, ArH), 7.51–7.62 (m, 2H, ArH), 7.76 (d, 1H, J=7.5.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 14.3, 41.4, 52.5, 55.9, 62.1, 124.9, 126.7, 128.0, 128.5, 130.4, 132.8, 133.4, 139.4, 150.7, 166.2, 167.4, 167.7; mass (ES+) m/z 379.9 (M^++1), 402.0 (M^++Na); Anal. Calcd for $C_{18}H_{21}NO_8$: C, 56.99; H, 5.58; N, 3.69. Found: C, 57.17; H, 5.66; N, 3.85.

4.2.17. 2-[2-Cyano-1-(2-nitro-phenyl)-allyl]-malonic acid diethyl ester (15a). Yield 85% (1.25 g from 1.0 g) as a white solid; mp 78–80 °C; ν_{max} (KBr) 1739 (2×CO_2Et), 2226 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.99 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.30 (t, 3H, J=7.0 Hz, CH_2CH_3), 3.93 (q, 2H, J=7.0 Hz, CH_2CH_3), 4.10–4.30 (m, 3H, CH_2CH_3 and 1×CH), 5.01 (d, 1H, J=12.0 Hz, CH), 6.07 (s, 1H, =CH), 6.26 (s, 1H, =CH), 7.43–7.51 (m, 1H, ArH), 7.65 (d, 2H, J=4.0 Hz, ArH), 7.87 (m, 1H, J=8.0 Hz, ArH); mass (ES+) m/z 347.2 (M^++1), 369.1 (M^++Na); Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.08; H, 5.49; N, 7.87.

4.3. General procedure for $SnCl_2$-mediated reactions

To a solution of an appropriate nitro derivative (1.0 equiv) in methanol (10 mL) was added anhydrous $SnCl_2$ (5.0 equiv) and the reaction mixture was heated at reflux in a nitrogen atmosphere for 1.0 h. The excess solvent was removed and the residue was made basic with $NaHCO_3$ solution and taken in EtOAc (50 mL). The resultant suspension was passed through a bed of Celite and the organic layer separated, dried (Na_2SO_4), and evaporated to yield the crude product, which

was purified by silica gel column chromatography using hexanes/EtOAc (80–70:20–30, v/v) to yield corresponding products in 50–86% yield.

4.3.1. 2-(3-Benzoyl-2-methyl-quinolin-4-yl)-acrylic acid methyl ester (16a). Yield 67% (0.35 g from 0.6 g) as a white solid; mp 164–166 °C; ν_{max} (KBr) 1661 (CO), 1727 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.61 (s, 3H, CH_3), 3.54 (s, 3H, CO_2CH_3), 5.81 (d, 1H, J=0.6 Hz, =CH), 6.66 (d, 1H, J=0.6 Hz, =CH), 7.43 (t, 2H, J=8.6 Hz, ArH), 7.54–7.59 (m, 2H, ArH), 7.66–7.68 (m, 1H, ArH), 7.74–7.79 (m, 3H, ArH), 8.13 (d, 1H, J=6.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 50.9, 123.7, 124.0, 125.5, 127.4, 127.6, 128.4, 129.1, 131.3, 132.1, 132.8, 134.1, 135.3, 139.8, 145.9, 153.4, 164.0, 195.9; mass (FAB+) m/z 332 (M^++1); HR-EIMS calculated for $C_{21}H_{17}NO_3$: 331.1208, found: 331.1210.

4.3.2. 2-(3-Benzoyl-6-chloro-2-methyl-quinolin-4-yl)-acrylic acid methyl ester (16b). Yield 61% (0.12 g from 0.25 g) as a white solid; mp 134–136 °C; ν_{max} (KBr) 1660 (CO), 1714 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.57 (s, 3H, CH_3), 3.56 (s, 3H, CO_2CH_3), 5.81 (s, 1H, =CH), 6.67 (s, 1H, =CH), 7.40–7.47 (m, 2H, ArH), 7.57–7.77 (m, 5H, ArH), 8.04 (d, 1H, J=9.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.5, 52.8, 126.2, 129.2, 130.1, 131.1, 131.6, 133.1, 133.8, 134.2, 134.7, 135.3, 136.9, 140.6, 146.3, 155.5, 165.4, 197.2; mass (ES+) m/z 366.2 (M^++1); HR-EIMS calculated for $C_{21}H_{16}ClNO_3$: 365.0819, found: 365.0820.

4.3.3. 2-(7-Benzoyl-6-methyl-[1,3]dioxolo[4,5-*g*]quinolin-8-yl)-acrylic acid methyl ester (16c). Yield 50% (0.26 g from 0.6 g) as a white solid; mp 188–189 °C; ν_{max} (KBr) 1665 (CO), 1723 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.51 (s, 3H, CH_3), 3.54 (s, 3H, CO_2CH_3), 5.76 (s, 1H, =CH), 6.12 (s, 2H, OCH_2O), 6.60 (s, 1H, =CH), 6.89 (s, 1H, ArH), 7.39–7.45 (m, 3H, ArH), 7.54–7.60 (m, 1H, ArH), 7.75 (d, 2H, J=7.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.1, 52.6, 101.1, 102.3, 106.0, 122.2, 129.0, 130.1, 134.3, 137.4, 140.3, 146.5, 148.6, 151.6, 152.7, 165.7, 198.0; mass (FAB+) m/z 376 (M^++1); HR-EIMS calculated for $C_{22}H_{17}NO_5$: 375.1107, found: 375.1108.

4.3.4. 2-(3-Benzoyl-2-methyl-1,4-dihydro-quinolin-4-yl)-acrylonitrile (17a). Yield 71% (0.12 g from 0.2 g) as a white solid; mp 188–189 °C; ν_{max} (KBr) 1664 (CO), 2226 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.51 (s, 3H, CH_3), 5.02 (s, 1H, CH), 5.68 (s, 1H, =CH), 5.73 (s, 1H, =CH), 6.76 (s, 1H, NH exchangeable with D_2O), 6.80–6.83 (m, 1H, ArH), 7.08–7.11 (m, 1H, ArH), 7.20–7.24 (m, 2H, ArH), 7.39–7.44 (m, 3H, ArH), 7.45–7.49 (m, 2H, ArH); mass (ES+) m/z 301.1 (M^++1); Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.09; H, 5.45; N, 9.55.

4.3.5. 2-(3-Benzoyl-6-chloro-2-methyl-1,4-dihydro-quinolin-4-yl)-acrylonitrile (17b). Yield 65% (0.28 g from 0.5 g) as a yellow solid; mp 192–194 °C; ν_{max} (KBr) 1665 (CO), 2227 (CN) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.50 (s, 3H, CH_3), 4.92 (s, 1H, CH), 5.74 (s, 1H, =CH), 5.83 (s, 1H, =CH), 6.99 (d, 1H, J=9.0 Hz, ArH), 7.27–7.29 (m, 1H, ArH), 7.35 (d, 1H, J=3.0 Hz, ArH), 7.42–7.52 (m, 5H, ArH), 9.62 (s, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz) δ 20.6, 43.2, 102.4, 107.3, 111.6, 117.1, 118.6, 122.8, 125.9, 126.8, 127.9, 128.3, 128.8, 129.6, 131.0, 136.0, 142.7, 149.7, 194.4; mass (ES+) m/z 335.1 (M^++1); Anal. Calcd for $C_{20}H_{15}ClN_2O$: C, 71.75; H, 4.52; N, 8.37. Found: C, 72.01; H, 4.20; N, 8.55.

4.3.6. 2-(7-Benzoyl-6-methyl-[1,3]dioxolo[4,5-*g*]quinolin-8-yl)-acrylonitrile (18c). Yield 64% (0.36 g from 0.65 g) as a yellow solid; mp 188–190 °C; ν_{max} (KBr) 1664 (CO), 2223 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.53 (s, 3H, CH_3), 6.02 (s, 1H, =CH), 6.17 (s, 2H, OCH_2O), 6.32 (s, 1H, =CH), 7.18 (s, 1H, ArH), 7.42–7.53 (m, 3H, ArH), 7.61–7.64 (m, 1H, ArH), 7.76 (d, 2H, J=9.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.0, 100.2, 102.7, 106.4, 116.9, 117.9, 120.4, 129.6, 130.0, 131.2, 135.0, 136.0, 137.0, 139.1, 146.9, 149.4, 152.2, 153.1, 197.1; mass (ES+) m/z 343.3 (M^++1); HR-EIMS calculated for $C_{21}H_{14}N_2O_3$: 342.1004, found: 342.1009.

4.3.7. 4-(1-Methoxycarbonyl-vinyl)-2-methyl-quinoline-3-carboxylic acid ethyl ester (19a). Yield 86% (0.44 g from 0.6 g) as a brown oil; ν_{max} (Neat) 1727 (CO_2Me and CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.82 (s, 3H, CH_3), 3.73 (s, 3H, CO_2CH_3), 4.34 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.81 (d, 1H, J=0.6 Hz, =CH), 6.81 (s, 1H, =CH), 7.52–7.56 (m, 1H, ArH), 7.70–7.79 (m, 2H, ArH), 8.09 (d, 1H, J=8.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 24.6, 52.9, 62.1, 125.3, 126.1, 126.9, 127.1, 129.3, 131.06, 137.2, 143.1, 147.9, 155.7, 166.0, 168.1; mass (ES+) m/z 300.3 (M^++1), 322.0 (M^++Na); HR-EIMS calculated for $C_{17}H_{17}NO_4$: 299.1158, found: 299.1160.

4.3.8. 6-Chloro-4-(1-methoxycarbonyl-vinyl)-2-methyl-quinoline-3-carboxylic acid ethyl ester (19b). Yield 68% (0.36 g from 0.6 g) as a brown solid; mp 124–126 °C; ν_{max} (KBr) 1729 (CO_2Me and CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.78 (s, 3H, CH_3), 3.75 (s, 3H, CO_2CH_3), 4.35 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.81 (s, 1H, =CH), 6.82 (s, 1H, =CH), 7.65–7.68 (m, 2H, ArH), 7.99 (d, 1H, J=9.6 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8, 24.1, 52.5, 61.7, 124.4, 125.6, 127.1, 130.6, 131.1, 131.4, 132.5, 136.2, 141.6, 145.9, 155.6, 165.2, 167.3; mass (ES+) m/z 334.1 (M^++1); HR-EIMS calculated for $C_{17}H_{16}ClNO_4$: 333.0768, found: 333.0770.

4.3.9. 8-(1-Methoxycarbonyl-vinyl)-6-methyl-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylic acid ethyl ester (19c). Yield 68% (0.36 g from 0.6 g) as a pale yellow oil; ν_{max} (Neat) 1727 (CO_2Me and CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.31 (t, 3H, J=7.0 Hz, CH_2CH_3), 2.73 (s, 3H, CH_3), 3.74 (s, 3H, CO_2CH_3), 4.31 (q, 2H, J=7.0 Hz, CH_2CH_3), 5.76 (s, 1H, =CH), 6.10 (s, 2H, CH_2), 6.74 (s, 1H, =CH), 6.95 (s, 1H, ArH), 7.33 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 24.3, 52.9, 61.9, 101.4, 102.4, 105.9, 122.1, 130.7, 137.8, 144.4, 148.5, 152.0, 153.7, 166.1; mass (ES+) m/z 344.1 (M^++1); Anal. Calcd for $C_{18}H_{17}NO_6$: C, 67.30; H, 4.76; N, 6.20. Found: C, 67.03; H, 4.95; N, 5.95.

4.3.10. 4-(1-Cyano-vinyl)-2-methyl-quinoline-3-carboxylic acid ethyl ester (20a). Yield 65% (0.35 g from 0.65 g) as a brown oil; ν_{max} (Neat) 1728 (CO_2Me), 2228 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.80 (s, 3H, CH_3), 4.45 (q, 2H, J=7.2 Hz, CH_2CH_3), 6.13 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.59–7.66 (m, 1H, ArH), 7.70–7.85 (m, 1H, ArH), 7.93 (d, 1H, J=8.4 Hz, ArH), 8.09 (d, 1H, J=8.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.4, 24.4, 30.1, 62.7, 116.9, 118.6, 123.5, 125.0, 128.1, 129.8, 131.6, 137.3, 148.1, 155.7, 165.6; mass (ES+) m/z 267.2 (M^++1), 289.0 (M^++Na); HR-EIMS calculated for $C_{16}H_{14}N_2O_2$: 266.1105, found: 266.1107.

4.3.11. 8-(1-Cyano-vinyl)-6-methyl-[1,3]dioxolo[4,5-*g*]-quinoline-7-carboxylic acid ethyl ester (20c). Yield 50% (0.07 g from 0.18 g) as a pale yellow solid; mp 128–130 °C; ν_{max} (KBr) 1710 (CO_2Et), 2225 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.72 (s, 3H, CH_3), 4.42 (q, 2H, J=7.2 Hz, CH_2CH_3), 6.07 (s, 1H, =CH), 6.15 (s, 2H, OCH_2O), 6.49 (s, 1H, =CH), 7.15 (s, 1H, ArH), 7.35 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 24.0, 62.5, 100.3, 102.7, 106.2, 117.0, 119.0, 120.5, 125.3, 136.9, 147.0, 149.3, 152.4, 153.5, 167.8, 183.7; mass (ES+) m/z 311.1 (M^++1); Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.77; H, 4.49; N, 8.81.

4.3.12. 6-Chloro-4-(1-cyano-vinyl)-2-methyl-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (21b). Yield 60% (0.15 g from 0.3 g) as a white solid; mp 127–129 °C; ν_{max} (KBr) 1717 (CO_2Me), 2218 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J=7.2 Hz, CH_2CH_3), 2.44 (s, 3H, CH_3), 4.19 (q, 2H, J=7.2 Hz, CH_2CH_3), 4.85 (s, 1H, CH), 5.69 (s, 1H, =CH), 5.75 (s, 1H, =CH), 6.39 (s, 1H, NH exchangeable with D_2O), 6.68 (d, 1H, J=9.0 Hz, ArH), 7.11–7.15 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.8, 20.9, 43.9, 60.23, 93.4, 116.5, 118.8, 122.2, 127.1, 128.4, 128.6, 128.7, 129.2, 135.5, 150.1, 167.4; mass (ES+) m/z 303.1 (M^++1); Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.47; H, 4.99; N, 9.25.

4.3.13. 4-(1-Methoxycarbonyl-vinyl)-2-phenyl-quinoline-3-carboxylic acid ethyl ester (22a). Yield 58% (0.25 g from 0.5 g) as a white solid; mp 107–109 °C; ν_{max} (KBr) 1727 (CO_2Me and CO_2Et) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.79 (s, 3H, CO_2CH_3), 4.10 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.88 (d, 1H, J=0.6 Hz, =CH), 6.87 (d, 1H, J=0.6 Hz, =CH), 7.43–7.50 (m, 3H, ArH), 7.56–7.62 (m, 1H, ArH), 7.64–7.74 (m, 4H, ArH), 8.09 (d, 1H, J=8.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 24.6, 52.9, 62.1, 125.3, 126.1, 126.9, 127.1, 129.3, 131.06, 137.2, 143.1, 147.9, 155.7, 166.0, 168.1; mass (ES+) m/z 362.2 (M^++1); HR-EIMS calculated for $C_{22}H_{19}NO_4$: 361.1314, found: 361.1318.

4.3.14. 4-(1-Methoxycarbonyl-vinyl)-2-oxo-1,2,3,4-tetrahydro-quinoline-3-carboxylic acid ethyl ester (23a). Yield 62% (0.2 g from 0.4 g) as a low melting white solid; ν_{max} (Neat) 1674 (CONH), 1739 (CO_2Et), 3205 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.81 (s, 3H, CO_2CH_3), 4.08 (d, 1H, J=6.0 Hz, CH), 4.13–4.20 (q merged with d, 3H, CH_2CH_3 and CHC–C=CH_2), 5.37 (d, 1H, J=0.6 Hz, =CH), 6.40 (d, 1H, J=0.6 Hz, =CH), 7.05–7.12 (m, 1H, ArH), 7.37–7.45 (m, 2H, ArH), 7.51 (d, 1H, J=7.5 Hz, ArH), 8.98 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.7, 40.0, 50.8, 51.0, 60.8, 112.8, 121.6, 123.4, 126.7, 127.5, 127.9, 135.7, 136.8, 159.4, 166.0, 166.4; mass (ES+) m/z 304 (M^++1); Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.52; H, 5.67; N, 4.70.

4.3.15. 4-(1-Cyano-vinyl)-2-oxo-1,2,3,4-tetrahydro-quinoline-3-carboxylic acid ethyl ester (24a). Yield 51% (0.3 g from 0.85 g) as a brown oil; ν_{max} (Neat) 1671 (CONH), 1739 (CO_2Et), 2227 (CN) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, 3H, J=7.2 Hz, CH_2CH_3), 3.96 (d, 1H, J=7.5 Hz, $CHCO_2Et$), 4.17 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.28 (d, 1H, J=7.5 Hz, CHC–C=CH_2), 5.73 (d, 1H, J=0.6 Hz, =CH), 6.14 (s, 1H, =CH), 7.18–7.21 (m, 2H, ArH), 7.40–7.44 (m, 1H, ArH), 7.52 (d, 1H, J=8.0 Hz, ArH), 9.21 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.7, 42.4, 49.9, 61.3, 113.1, 115.2, 118.3, 119.8, 123.7, 126.5, 128.5, 132.9, 135.4, 158.7, 165.5; mass (ES+) m/z 271.1 (M^++1); Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.68; H, 5.45; N, 10.19.

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References and notes

1. (a) Rosenthal, P. J. *Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery*; Humana: Totowa, NJ, 2001; (b) Bhattacharjee, A. K.; Karle, J. M. *J. Med. Chem.* **1996**, *39*, 4622–4629; (c) De, D.; Krogstad, F. M.; Byers, L. D.; Krogstad, D. J. *J. Med. Chem.* **1998**, *41*, 4918–4926; (d) Stocks, P. A.; Raynes, K. J.; Bray, P. G.; Park, B. K.; O'Neill, P. M.; Ward, S. A. *J. Med. Chem.* **2002**, *45*, 4975–4983; (e) Vennerstrom, J. L.; Ager, A. L., Jr.; Dorn, A.; Andersen, S. L.; Gerena, L.; Ridley, R. G.; Milhous, W. K. *J. Med. Chem.* **1998**, *41*, 4360–4364; (f) Kaschula, C. H.; Egan, T. J.; Hunter, R.; Basilico, N.; Parapini, S.; Taramelli, D.; Pasini, E.; Monti, D. *J. Med. Chem.* **2002**, *45*, 3531–3539; (g) Delarue, S.; Girault, S.; Maes, L.; Debreu-Fontaine, M.-A.; Labaeid, M.; Grellier, P.; Sergheraert, C. *J. Med. Chem.* **2001**, *44*, 2827–2833.
2. (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000; pp 121–150; (b) Roth, H. J.; Fenner, H. *Arzneistoffe*, 3rd ed.; Deutscher Apotheker: Stuttgart, 2000; pp 51–114; (c) Balasubramanian, M.; Keay, J. G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5, pp 245–265; (d) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374–2377; (e) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035; (f) Shinkai, H.; Ito, T.; Iida, T.; Kitao, Y.; Yamada, H.; Uchida, I.

J. Med. Chem. **2000**, *43*, 4667–4677; (g) van Straten, N. C. R.; van Berkel, T. H. J.; Demont, D. R.; Karstens, W.-J. F.; Merkx, R.; Oosterom, J.; Schulz, J.; van Someren, R. G.; Timmers, C. M.; van Zandvoort, P. M. *J. Med. Chem.* **2005**, *48*, 1697–1700; (h) Boschelli, D. H.; Wang, Y. D.; Johnson, S.; Wu, B.; Ye, F.; Barrios Sosa, A. C.; Golas, J. M.; Boschelli, F. *J. Med. Chem.* **2004**, *47*, 1599–1601.

3. (a) Lin, X.-F.; Cui, S.-L.; Wang, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 3127–3130; (b) Sakai, N.; Aoki, D.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2006**, *47*, 1261–1265; (c) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653–3655; (d) Tanaka, S.-y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800–803; (e) Wang, G.-W.; Jia, C.-S.; Dong, Y.-W. *Tetrahedron Lett.* **2006**, *47*, 1059–1063; (f) Wang, X.; Dixon, S.; Kurth, M. J.; Lam, K. S. *Tetrahedron Lett.* **2005**, *46*, 5361–5364; (g) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 1647–1649; (h) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539–4542; (i) Kobayashi, K.; Yoneda, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2004**, *60*, 11639–11645; Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2004**, *7*, 763–766.
4. (a) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, 811–890; (b) Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, *47*, 73–77; (c) Sreedhar, B.; Reddy, P. S.; Kumar, N. S. *Tetrahedron Lett.* **2006**, *47*, 3055–3058; (d) Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I.; Buffon, R. *Tetrahedron* **2006**, *62*, 4563–4572; (e) Chandrasekhar, S.; Basu, D.; Rambabu, Ch. *Tetrahedron Lett.* **2006**, *47*, 3059–3063; (f) Shi, Yong-Ling; Shi, Min *Synlett* **2005**, 2623–2626; (g) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490; (h) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369–3372; (i) Mix, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 2015–2018; (j) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987–1989; (k) Nair, Vijay; Abhilash, K. G. *Synthesis* **2005**, *12*, 1967–1970 (only a few examples are covered herein).
5. Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun.* **1998**, 2563–2564.
6. (a) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343–345; (b) Kim, J. N.; Lee, K. Y.; Ham, H.-S.; Kim, H. R.; Ryu, E. K. *Bull. Korean Chem. Soc.* **2001**, *22*, 135–136.
7. (a) Chung, Y. M.; Lee, H. J.; Hwang, S. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 799–800; (b) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737–3740; (c) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209–6211; (d) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427–6430; (e) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1109–1110.
8. Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341–8344.
9. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385–390.
10. (a) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693–3697; (b) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1493–1494; (c) Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 939–940.
11. Lee, C. G.; Lee, K. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409–7413.
12. Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379–7382.
13. (a) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493–1499; (b) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1001–1004.
14. Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, Ch.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. *Bioorg. Med. Chem.* **2006**, *14*, 4600–4609.
15. See Ref. 4b.
16. These papers appeared after the communication of this manuscript. (a) Hong, W. P.; Lee, K.-J. *Synthesis* **2006**, 963–968; (b) Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. *Synthesis* **2006**, 1953–1960.
17. (a) Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353–356; (b) Pathak, R.; Roy, A. K.; Batra, S. *Synlett* **2005**, 848–850; (c) Pathak, R.; Roy, A. K.; Kanojiya, S.; Batra, S. *Tetrahedron Lett.* **2005**, *46*, 5289–5292; (d) Singh, V.; Batra, S. *Synthesis* **2006**, 63–72; (e) Nag, S. N.; Pathak, R.; Kumar, M.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3824–3828.