

An alternate approach to quinoline architecture *via* Baylis-Hillman chemistry: SnCl₂-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 SnCl₂, trigger 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 known.¹ Beside antimalarials, a spectrum of other pharmacological activities² 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 have 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.⁵⁻¹⁵ 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,¹⁶ it 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 3 carbon chain originating from the Baylis-Hillman reaction, which generally participates in the intramolecular cyclization towards construction of the quinoline, there would also be another 3 carbon chain containing a terminal keto or an ester group which could also undergo cyclization. In the latter case cyclization would result in a dihydro quinoline derivative with a vinyl chain at the 4-position which could be dehydrogenated to yield the desired quinoline. We have 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 SnCl₂. 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

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observation prompted us to disclose the details of results of our study in this paper.

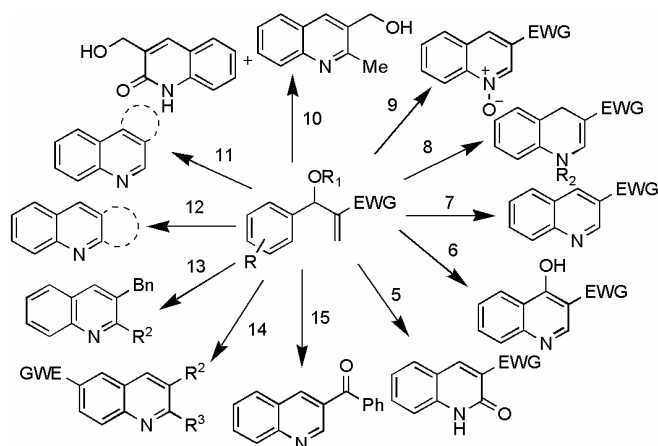


Figure 1. Summary of synthesis of quinoline motif from Baylis-Hillman adducts or their derivatives. Numbers on the arrows indicate the corresponding reference number

2. Results and Discussion

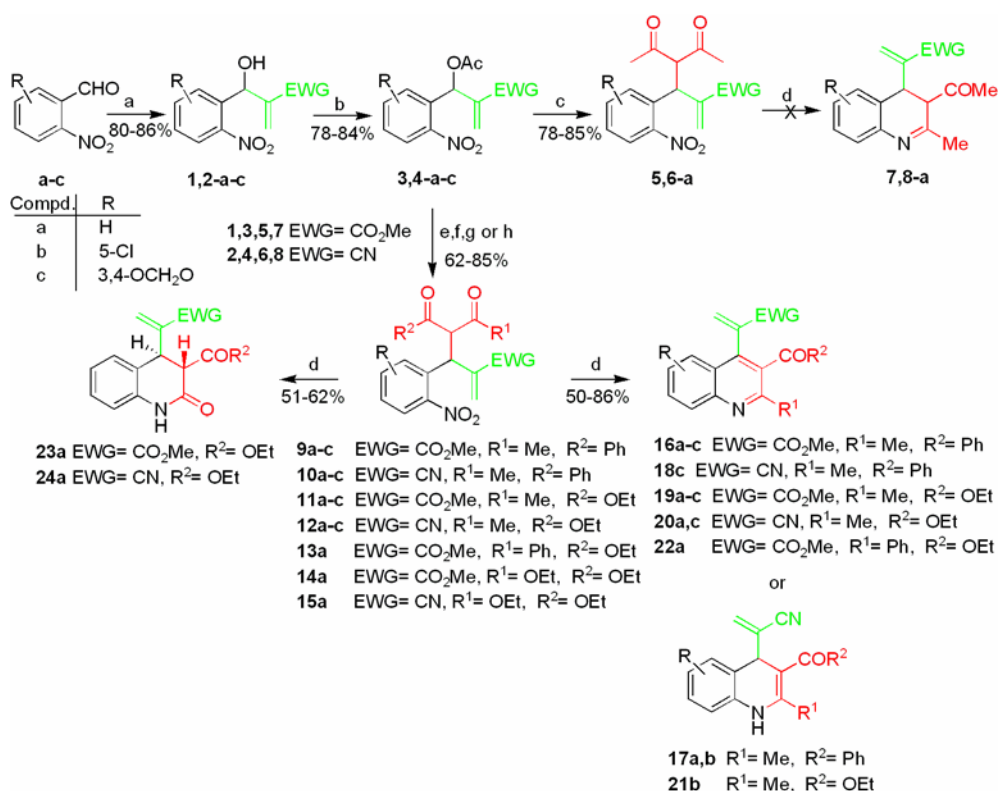
Preparation of the starting materials, the acetates **3,4-a-c**, was accomplished by acetylating the corresponding Baylis-Hillman adducts **1,2a-c** in the presence of acetyl chloride and pyridine in dichloromethane at room temperature (Scheme 1). Initially, the S_N2 reaction of acetyl acetone was carried out with the acetate **3a** following the reported procedure to obtain product **5a** as diastereoisomeric mixture.^{16d} 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 $\text{THF}:\text{H}_2\text{O}$ 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 for 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 $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ 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. Typically the ^1H NMR analysis of product **17a** showed the presence of peaks for the NH and the CH protons and the ^{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 **11-12a-c** were synthesized using ethyl acetoacetate as the nucleophile in the S_N2 reaction of the acetates **3,4a-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 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, compound **14a** and **15a** generated by the reaction of the 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



Scheme 1. Reagents and Conditions: a) CH₂=CHEWG, DABCO, rt, 15min.-1h; b) AcCl, Pyridine, CH₂Cl₂, rt, 2-3 h; c) DABCO, MeCOCH₂COMe, THF:H₂O (1:1), rt, 30 min; d) SnCl₂, MeOH, reflux, 1 h; e) DABCO, PhCOCH₂COMe, THF:H₂O (1:1), rt, 30 min; f) DABCO, MeCOCH₂CO₂Et, THF:H₂O (1:1), rt, 30 min; g) DABCO, PhCOCH₂CO₂Et, THF:H₂O (1:1), rt, 30 min; h) DABCO, CO₂EtCH₂CO₂Et, THF:H₂O (1:1), rt, 30 min.

established to be tetrahydro quinolin-2-ones **23-24a**. Interestingly, this cyclization was found to be diastereoselective in favour 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 SnCl₂-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>Oalkyl. 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 ¹³C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on a JEOL/SX-102 spectrometer and ESMS were recorded using a Micromass LCMS 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 eq) in THF: H₂O (50:50, v/v) was added DABCO (1.5 eq) at room temperature and the reaction was allowed to continue for 20 min. Thereafter, the appropriate nucleophile (1.2 eq) was added to the reaction mixture, and the reaction was further stirred at room temperature for 30 min. The organic solvent was removed and the residue diluted with water and extracted with EtOAc (3 x 50 mL). Combined organic layer was washed with the brine solution (70 mL), dried (Na₂SO₄) 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. 16d

4.2.2. 4-Acetyl-2-methylene-3-(2-nitro-phenyl)-5-oxo-hexanenitrile (6a)-78% (0.9 g from 1.0 g) as a brown solid, mp 135-137 °C; ν_{\max} (KBr) 1707 (2xCO), 2227 (CN) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.98 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 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); ¹³C NMR (CDCl₃, 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 C₁₅H₁₄N₂O₄ 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)- 81% (1.1g from 1.0 g) as a brown solid, mp 102-104 °C; ν_{\max} (KBr) 1679 (CO), 1724 (CO and CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 2.09 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 3.57 (s, 3H, CO₂CH₃), 3.71 (s, 3H, CO₂CH₃), 5.55-5.82 (m, 5H, 4xCH 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); ¹³C NMR (CDCl₃, 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 C₂₁H₁₉NO₆ 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)- 63% (0.5 g from 0.6 g) as a brown semisolid; ν_{\max} (Neat) 1680 (CO), 1721 (CO and CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 2.11 (s, 3H, CH₃), 2.17 (s, 3H, CH₃), 3.59 (s, 6H, 2xCO₂CH₃), 5.45-5.60 (m, 5H, 4xCH), 5.65 (s, 2H, 2x=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); ¹³C NMR (CDCl₃, 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 C₂₁H₁₈ClNO₆ 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)- 69% (0.9 g from 1.0 g) as a brown solid, mp 127-129 °C; ν_{\max} (KBr) 1680 (CO), 1721 (CO and CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 2.12 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 3.62 (s, 3H, CO₂CH₃), 3.75 (s, 3H, CO₂CH₃), 5.58-5.79 (m, 4H, 3xCH and =CH), 5.96-6.03 (m, 2H, CH and =CH), 6.10 (s, 4H, 2xOCH₂O), 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); ¹³C NMR (CDCl₃, 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 C₂₂H₁₉NO₈ 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)- 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 (CDCl₃, 200 Hz) δ = 1.95 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 5.41-5.53 (m, 4H, 4xCH), 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); ¹³C NMR (CDCl₃, 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 C₂₀H₁₆N₂O₄ 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) - 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 (CDCl₃, 200 Hz) δ = 1.99 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 5.36-5.50 (m, 4H, 4xCH), 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); ¹³C NMR (CDCl₃, 50.2 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 C₂₀H₁₅ClN₂O₄ 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)- 81% (0.75 g from 0.8 g) as a yellow solid, mp 189-191 °C; ν_{\max} (KBr) 1676 (CO), 1722 (CO and CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 300 Hz) δ = 1.99 (s, 3H, CH₃), 5.42 (d, 1H, *J*= 12.0 Hz, CH), 5.61 (s, 1H, 1H, *J*= 12.0 Hz, CH), 5.92 (s, 1H, =CH), 6.17 (s, 3H, =CH, CH₂), 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); ¹³C NMR (CDCl₃, 50.2 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)- 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, 663.4, 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)- 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, $2xCH_2CH_3$), 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_2 = 3.4 Hz, $2xCH$), 5.90 (s, 1H, =CH), 5.96 (s, 1H, =CH), 6.38 (s, 2H, $2x=CH$), 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, 2.6, 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)- 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 ($CDCl_3$, 50.2 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)- 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} ; 1H 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, $2xCH$), 6.05 (s, 1H, =CH), 6.06 (s, 1H, =CH), 6.24 (s, 1H, =CH), 6.28 (s, 2H, $2x=CH$), 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)- 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} ; 1H 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, $2xCH$), 6.08 (s, 1H, $2x=CH$), 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, $2xCH$); ^{13}C NMR ($CDCl_3$, 50.2 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) - 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} ; 1H 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, $2xCH$), 6.04 (s, 1H, $2x=CH$), 6.08 (s, 1H, =CH), 6.14 (s, 4H, $2xOCH_2O$), 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)- 82% (1.2 g from 1.0 g) as a brown oil; ν_{max} (Neat) 1691 (CO), 1729 (CO_2Me , CO_2Et) cm^{-1} ; 1H 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, $3xCH$), 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)- 74% (1.0 g from 1.0 g) as brown oil, ν_{\max} (Neat) 1727 (CO₂Me, 2xCO₂Et) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 0.85 (t, 3H, *J*= 7.0 Hz, CH₂CH₃), 1.05 (t, 3H, *J*= 7.0 Hz, CH₂CH₃), 3.68 (s, 6H, CO₂CH₃), 4.01 (q, 2H, *J*= 7.0 Hz, CH₂CH₃), 4.20 (q, 2H, *J*= 7.0 Hz, CH₂CH₃), 4.41 (d, 2H, *J*= 12.0 Hz, CH), 5.27 (d, 2H, *J*= 12.0 Hz, 2xCH), 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); ¹³C NMR (CDCl₃, 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 C₁₈H₂₁NO₈ 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)- 85% (1.25 g from 1.0 g) as a white solid, mp 78-80 °C; ν_{\max} (KBr) 1739 (2xCO₂Et), 2226 (CN) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 0.99 (t, 3H, *J*= 7.0 Hz, CH₂CH₃), 1.30 (t, 3H, *J*= 7.0 Hz, CH₂CH₃), 3.93 (q, 2H, *J*= 7.0 Hz, CH₂CH₃), 4.10-4.30 (m, 3H, CH₂CH₃ and 1xCH), 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 C₁₇H₁₈N₂O₆ C, 58.96; H, 5.24; N, 8.09. Found, C, 59.08; H, 5.49; N, 7.87.

4.3. General procedure for SnCl₂-mediated reactions

To a solution of an appropriate nitro derivative (1.0 eq) in methanol (10 mL) was added anhydrous SnCl₂ (5.0 eq) 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 NaHCO₃ solution and taken in EtOAc (50 mL). The resultant suspension was passed through a bed of celite and the organic layer separated, dried (Na₂SO₄) 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)- 67% (0.35 g from 0.6 g) as a white solid, mp 164-166 °C; ν_{\max} (KBr) 1661 (CO), 1727 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ = 2.61 (s, 3H, CH₃), 3.54 (s, 3H, CO₂CH₃), 5.81 (s, 1H, =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); ¹³C NMR (CDCl₃, 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 C₂₁H₁₇NO₃ 331.1208, found 331.1210.

4.3.2. 2-(3-Benzoyl-6-chloro-2-methyl-quinolin-4-yl)-acrylic acid methyl ester (16b)- 61% (0.12 g from 0.25 g) as a white solid, mp 134-136 °C; ν_{\max} (KBr) 1660 (CO),

1714 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.57 (s, 3H, CH₃), 3.56 (s, 3H, CO₂CH₃), 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); ¹³C NMR (CDCl₃, 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 C₂₁H₁₆ClNO₃ 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)- 50% (0.26 g from 0.6 g) as a white solid, mp 188-189 °C; ν_{\max} (KBr) 1665 (CO), 1723 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.51 (s, 3H, CH₃), 3.54 (s, 3H, CO₂CH₃), 5.76 (s, 1H, =CH), 6.12 (s, 2H, OCH₂O), 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); ¹³C NMR (CDCl₃, 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 C₂₂H₁₇NO₅ 375.1107, found 375.1108.

4.3.4. 2-(3-Benzoyl-2-methyl-1,4-dihydro-quinolin-4-yl)-acrylonitrile (17a)- 71% (0.12 g from 0.2 g) as a white solid, mp 188-189 °C; ν_{\max} (KBr) 1664 (CO), 2226 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.51 (s, 3H, CH₃), 5.02 (s, 1H, CH), 5.68 (s, 1H, =CH), 5.73 (s, 1H, =CH), 6.76 (s, 1H, NH exchangeable with D₂O), 6.80-6.83 (m, 1H, ArH), 7.08-7.11 (m, 1H, ArH), 7.20-7.24 m, 2H, Ar-H), 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 C₂₀H₁₆N₂O 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)- 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-d₆, 300 MHz) δ = 2.50 (s, 3H, CH₃), 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); ¹³C NMR (CDCl₃+DMSO-d₆, 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 C₂₀H₁₅ClN₂O 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)- 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 (CDCl₃, 200 MHz) δ = 2.53 (s, 3H, CH₃), 6.02 (s, 1H, =CH), 6.17 (s, 2H, OCH₂O), 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); ¹³C NMR (CDCl₃, 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 C₂₁H₁₄N₂O₃ 342.1004, found 342.1009.

4.3.7. 4-(1-Methoxycarbonyl-vinyl)-2-methyl-quinoline-3-carboxylic acid ethyl ester (19a)- 86% (0.44 g from 0.6 g) as a brown oil; ν_{\max} (Neat) 1727 (CO₂Me and CO₂Et) cm⁻¹; ¹H NMR (CDCl₃, 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, 2, $J = 7.2$ 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) $\delta = 14.3, 24.6, 52.9, 62.1, 125.3, 126.1, 126.9, 127.1, 129.3, 131.06, 137.2, 143.1, 147.9, 155.7, 166.0, 168.1$; mass (ES+) m/z 300.3 ($\text{M}^+ + 1$), 322.0 ($\text{M}^+ + \text{Na}$); HR-EIMS calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_4$ 299.1158, found 299.1160.

4.3.8. 6-Chloro-4-(1-methoxycarbonyl-vinyl)-2-methyl-quinoline-3-carboxylic acid ethyl ester (19b)- 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) $\delta = 1.33$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.78 (s, 3H, CH_3), 3.75 (s, 3H, CH_2CH_3), 4.35 (q, 2H, $J = 7.2$ Hz, CO_2CH_2), 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) $\delta = 13.8, 24.1, 52.5, 61.7, 124.4, 125.6, 127.1, 130.6, 131.1, 131.4, 132.5, 136.2, 141.6, 145.9, 155.6, 165.2, 167.3$; mass (ES+) m/z 334.1 ($\text{M}^+ + 1$); HR-EIMS calculated for $\text{C}_{17}\text{H}_{16}\text{ClNO}_4$ 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)- 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) $\delta = 1.31$ (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 2.73 (s, 3H, CH_3), 3.74 (s, 3H, CH_2CH_3), 4.31 (q, 2H, $J = 7.0$ Hz, CO_2CH_2), 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) $\delta = 14.3, 24.3, 52.9, 61.9, 101.4, 102.4, 105.9, 122.1, 130.7, 137.8, 144.4, 148.5, 152.0, 153.7, 166.1$; mass (ES+) m/z 344.1 ($\text{M}^+ + 1$); Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}_6$ 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)- 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) $\delta = 1.43$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.80 (s, 3H, CH_3), 4.45 (q, 2, $J = 7.2$ 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) $\delta = 14.4, 24.4, 30.1, 62.7, 116.9, 118.6, 123.5, 125.0, 128.1, 129.8, 131.6, 137.3, 148.1, 155.7, 165.6$; mass (ES+) m/z 267.2 ($\text{M}^+ + 1$), 289.0 ($\text{M}^+ + \text{Na}$); HR-EIMS calculated for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ 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)- 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) $\delta = 1.43$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.72 (s, 3H, CH_3), 4.42 (q, 2, $J = 7.2$ 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) $\delta = 14.3, 24.0, 62.5, 100.3, 102.7, 106.2, 117.0, 119.0, 120.5, 125.3, 136.9, 147.0, 149.3, 152.4, 153.5, 167.8, 183.7$; mass (ES+) m/z 311.1 ($\text{M}^+ + 1$); Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4$ 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)- 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) $\delta = 1.30$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 2.44 (s, 3H, CH_3), 4.19 (q, 2, $J = 7.2$ 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) $\delta = 14.8, 20.9, 43.9, 60.23, 93.4, 116.5, 118.8, 122.2, 127.1, 128.4, 128.6, 128.7, 129.2, 135.5, 150.1, 167.4$; mass (ES+) m/z 303.1 ($\text{M}^+ + 1$); Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2$ 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)- 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) $\delta = 1.05$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 3.79 (s, 3H, CO_2CH_3), 4.10 (q, 2, $J = 7.2$ 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) $\delta = 14.3, 24.6, 52.9, 62.1, 125.3, 126.1, 126.9, 127.1, 129.3, 131.06, 137.2, 143.1, 147.9, 155.7, 166.0, 168.1$; mass (ES+) m/z 362.2 ($\text{M}^+ + 1$); HR-EIMS calculated for $\text{C}_{22}\text{H}_{19}\text{NO}_4$ 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)- 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) $\delta = 1.15$ (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 $\text{CHC}=\text{CH}_2$), 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 (brs, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 12.7, 40.0, 50.8, 51.0, 60.8, 112.8, 121.6, 123.4, 126.7, 127.5, 127.9, 135.7, 136.8, 159.4, 166.0, 166.4$; mass (ES+) m/z 304 ($\text{M}^+ + 1$); Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_5$ 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)- 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) $\delta = 1.18$ (t, 3H, $J = 7.2$ Hz, CH_2CH_3), 3.96 (d, 1H, $J = 7.5$, CHCO_2Et), 4.17 (q, 2, $J = 7.1$ Hz, CH_2CH_3), 4.28 (d, 1H, $J = 7.5$, $\text{CHC}=\text{CH}_2$), 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 (brs, 1H, NH); ^{13}C NMR (CDCl_3 , 75 MHz) $\delta = 12.7, 42.4, 49.9, 61.3, 113.1, 115.2, 118.3, 119.8, 123.7, 126.5, 128.5, 132.9, 135.4, 158.7, 165.5$; mass (ES+) m/z 271.1 ($\text{M}^+ + 1$); Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ C, 66.66; H, 5.22; N, 10.36. Found, C, 66.68; H, 5.45; N, 10.19.

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References

1. a) Rosenthal, P. J. *Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery*, Humana Press, 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.; Labaied, 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 Ltd: Oxford, **2000**; pp 121-150. b) Roth, H. J.; Fenner, H. In *Arzneistoffe*, 3rd ed.; Deutscher Apotheker Verlag, Stuttgart, **2000**; pp 51-114. c) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: 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.; Merckx, 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**, ASAP. 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*, 4539-4532. 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.; Ch. Rambabu *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*, 1987-89. 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. 3. 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. 4. a) Chung, Y. M.; Lee, H. J.; Hwang, S. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 799-780. 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. Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, *47*, 73-77.
16. 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.