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Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts☆

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Abstract—A novel and green approach for efficient and rapid synthesis of polyhydroquinoline derivatives via unsymmetric Hantzsch reaction using organocatalysts at room temperature was reported. The process is a simple, environmentally friendly, rapid, and high yielding reaction for the synthesis of polyhydroquinoline derivatives. The catalytic efficiency of various small organocatalysts such as L-proline, *trans*-4-hydroxy-L-proline, L-thiaproline, DL-phenylglycine, and (−)-cinchonidine was studied under aqueous, organic, and solvent free conditions.

1. Introduction

1,4-Dihydropyridyl compounds are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases.[1] Cardiovascular agents such as nifedipine, nicardipine, amlodipine, and other related derivatives are dihydropyridyl compounds, effective in treatment of hypertension.[2] 1,4-Dihydropyridine derivatives possess a variety of biological activities such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic activity.[3] Extensive studies have revealed that these compounds exhibit various medicinal functions such as neuroprotectant, platelet anti-aggregatory activity, cerebral antischemic activity in the treatment of Alzheimer's disease, and chemosensitizer in tumor therapy.[4] These examples clearly indicate the remarkable potential of novel dihydropyridine derivatives as a source of valuable drug candidates. Furthermore, the oxidation of these compounds to pyridines has also been extensively studied.[5] Thus, the synthesis of this heterocyclic nucleus is of much importance.

Numerous methods have been reported for the synthesis of polyhydroquinoline derivatives because of the biological importance associated with these compounds. The classical method involves three-component coupling of an aldehyde with ethyl acetoacetate and ammonia in acetic acid or by refluxing in alcohol.[6] However, these methods suffer from several drawbacks such as long reaction times, use of large quantities of volatile organic solvents, low yields, and harsh reaction conditions. Therefore, it is necessary to develop an efficient and versatile method for the synthesis of these compounds. Recently several methods have been reported comprising the use of microwaves, ionic liquids, TMSCl–NaI, metal triflates, and polymers.[7–14] However, the use of high temperatures, expensive metal precursors, catalysts that are harmful to environment, and longer reaction times limit the use of these methods. Therefore, the search for a better catalyst for the synthesis of polyhydroquinoline derivatives using less hazardous solvents or solvent free conditions is of prime importance.

Organic reactions under aqueous medium and solvent free conditions have attracted much interest from chemists particularly from the viewpoints of green chemistry. Green chemistry approaches are significant due to the reduction in byproducts, a reduction in waste produced, and lowering of energy costs. The possibility of performing multicomponent reactions under solvent free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as ecological point of view. In recent years, heterogeneous catalysis is having more importance due to environmental–economic factors.

Small organic molecules like cinchona alkaloids, L-proline, and its derivatives are readily commercially available catalysts and have been used in various transformations with excellent yields.[15] L-Proline has been found to be very effective in enamine based direct catalytic asymmetric aldol,[16] Mannich,[17] Michael,[18] Diels–Alder,[19] α-amination reactions, and Knoevenagel type reactions.[19,20] More recently, proline and

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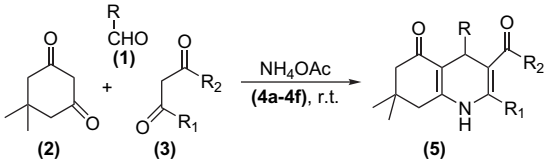
its derivatives have been used in multicomponent Biginelli reactions[21] under solvent free conditions. We, therefore, were interested in exploiting the activity of L-proline as well as other small organocatalysts in the synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction.

2. Results and discussion

Herein, we would like to report the studies of a facile unsymmetric Hantzsch condensation in the presence of a heterogeneous organocatalyst (**4a**–**4f**) at room temperature using substituted aldehyde (**1**), dimedone (**2**), acetoacetate ester or acetyl acetone (**3**), and ammonium acetate to produce polyhydroquinoline derivatives (**5**) in high yields (Scheme 1). We examined this reaction under three different sets of reaction conditions: (i) organic solvents, (ii) water, and (iii) solvent free conditions.



Scheme 1. Organocatalyzed unsymmetric Hantzsch reaction.

In a typical experimental procedure using traditional conditions, a solution of dimedone, a substituted aldehyde, acetoacetate ester, and ammonium acetate in ethanol was stirred in the presence of catalytic amount of L-proline (10 mol %) for a certain period of time required to complete the reaction (TLC), resulting in the formation of polyhydroquinoline. The reaction mixture was then poured into brine and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to give crude product. The pure product was obtained by crystallization from methanol. We also carried out reactions without any catalyst but the polyhydroquinoline derivatives were isolated in poor yields (8–15%) and the major product isolated was a dimedone aldehyde adduct.

In order to study the generality of the reaction a number of polyhydroquinoline derivatives were synthesized in high yields. This method has the ability to tolerate a variety of other functional groups such as methoxy, hydroxyl, nitro, halides, olefins, etc. The results of this study are summarized in Table 1. Both the electron-rich and electron-deficient aldehydes worked well leading to high yields of product. We examined the organocatalyzed reaction with other β-dicarbonyl compounds such as methyl acetoacetate, *tert*-butyl acetoacetate, and 2,4-pentanedione, and similar results were found with these compounds. However, with 2,4-pentanedione yields were somewhat lower than the corresponding esters.

The use of just 10 mol % of L-proline in stirring ethanol is sufficient to push the reaction forward. Higher amounts of L-proline did not lead to significant improvement in the yield of polyhydroquinolines. In stirring ethanol at room temperature the reaction was complete within 2–3 h. Upon refluxing in ethanol the reaction rate was increased and the reaction was complete within 1 h, but the yield was not increased.

We further studied the catalytic efficiency of other organocatalysts (Fig. 1) on the unsymmetric Hantzsch reaction. In all cases the catalyst was taken as 10 mol % and reaction was done under solvent free conditions. The results of this study are shown in Table 2. It was observed that the catalytic

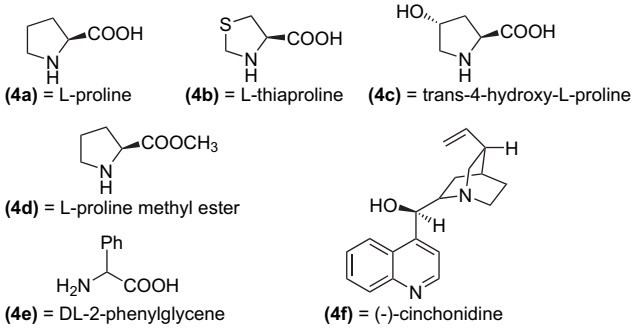


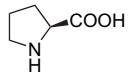
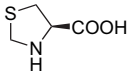
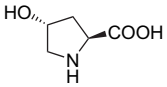
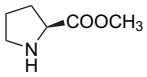
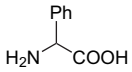
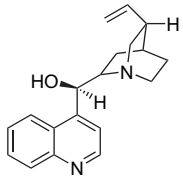
Figure 1. Organocatalysts used for unsymmetric Hantzsch reaction.

Table 1. L-Proline catalyzed synthesis of polyhydroquinoline derivatives[a]

Entry	R	R_1	R_2	Product[b]	EtOH		Water		Solvent free	
					Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	C_6H_5	CH_3	OC_2H_5	**5a**	2.0	85	3.5	72	0.5	95
2	4-CH_3–C_6H_4	CH_3	OC_2H_5	**5b**	2.0	84	3.5	75	0.5	94
3	4-$(CH_3)_2N$–C_6H_4	CH_3	OC_2H_5	**5c**	2.5	86	3.5	79	0.5	96
4	4-Cl–C_6H_4	CH_3	OC_2H_5	**5d**	2.0	81	4.0	75	0.5	91
5	3-NO_2–C_6H_4	CH_3	OC_2H_5	**5e**	1.5	78	3.0	78	0.5	92
6	4-CH_3O–C_6H_4–CH=CH	CH_3	OC_2H_5	**5f**	3.0	79	4.0	68	0.5	89
7	1-Naphthyl	CH_3	OC_2H_5	**5g**	2.0	84	3.0	64	0.5	94
8	3,4-Cl_2–C_6H_3	CH_3	OC_2H_5	**5h**	1.5	82	3.0	71	0.5	92
9	4-CH_3–C_6H_4	CH_3	OCH_3	**5i**	2.0	85	3.0	65	0.5	93
10	3-CH_3O–C_6H_4	CH_3	^{t}OBu	**5j**	2.5	82	3.0	62	0.5	92
11	4-CH_3O–C_6H_4–CH=CH	CH_3	OCH_3	**5k**	2.5	79	3.0	59	0.5	89
12	C_6H_5	CH_3	^{t}OBu	**5l**	2.5	78	4.0	61	0.5	85
13	4-$(CH_3)_2N$–C_6H_4	CH_3	^{t}OBu	**5m**	2.5	76	4.5	64	0.5	88
14	3-CH_3O–C_6H_4	CH_3	CH_3	**5n**	4.0	60	6.0	47	0.5	83

[a] All reactions were carried at room temperature.
[b] Products were characterized by ^1H, ^{13}C, IR, and mass spectroscopy.
[c] Isolated yield.

Table 2. Study of catalytic efficiency of various organocatalyst over unsymmetric Hantzsch reaction[a]

Entry	Catalyst	Yield[b] (%)	
		5a	**5f**
1	None	12	11
2	**4a** 	95	89
3	**4b** 	90	85
4	**4c** 	89	87
5	**4d** 	61	55
6	**4e** 	47	45
7	**4f** 	49	41

[a] Reaction conditions: aldehyde (1 mmol), ethyl acetoacetate (1 mmol), dimedone (1 mmol), and ammonium acetate (1 mmol), catalyst 10 mol %, room temperature, solvent free, stir.
[b] Isolated yield.

effects of **4a**, **4b**, and **4c** were similar, but when **4d**, **4e**, and **4f** were taken as catalysts, the product yields were decreased. The results show that the presence of a secondary nitrogen in the organocatalyst leads to good yields of products. When the methyl ester of L-proline (**4d**) was used as the catalyst the yields of reactions were decreased (94–61% and 88–55%). This clearly shows that the presence of a free carboxylic acid at 2-position makes the catalyst more efficient. It means that acidic hydrogen of carboxylic acid

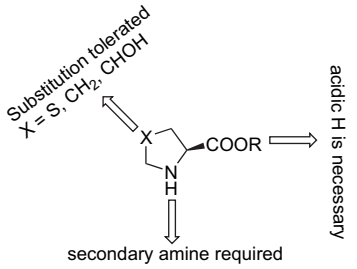
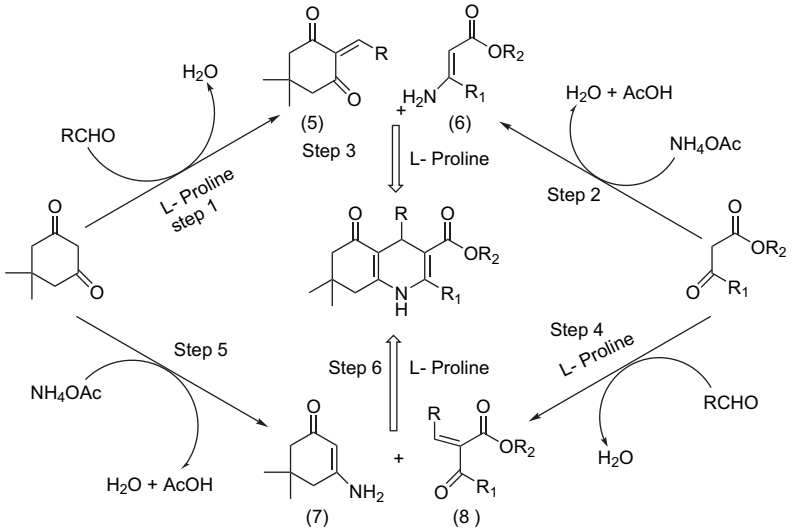


Figure 2. Structure–activity study for successful catalysis.

moiety plays a significant role in the catalysis of the reaction. DL-Phenylglycine (**4e**), which has a primary amino group and (−)-cinchonidine (**4f**), which has a tertiary amino group were used as catalyst but the yields were low. The results shown in Table 2 clearly indicate that the presence of a secondary nitrogen is essential for better catalytic activity. Replacing CH_2 (**4a**) by S (**4b**) and with CHOH (**4c**) did not considerably affect yields. Thus it was concluded that L-proline (**4a**) was the best of all the six catalysts. These results are summarized in Figure 2.

To avoid the use of ecologically suspected organic solvents, we carried out the reaction under solvent free conditions and in aqueous medium. Indeed, water is recognized as an attractive medium for many organic reactions. The reaction was carried out successfully at room temperature leading to good-to-high yields of the products using 10 mol % of L-proline (**4a**).

The reaction under solvent free conditions was found to be the best for the synthesis of polyhydroquinoline derivatives using 10 mol % of L-proline (**4a**) and the products were obtained in excellent yields. In a typical experimental procedure β-ketoester (1 mmol), aldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1 mmol), and L-proline (**4a**) 10 mol % were ground in a porcelain mortar and the reaction was complete within half an hour. The reaction time was decreased and product yield was increased to a remarkable extent. The reaction of acetyl acetone, 3-methoxybenzaldehyde, dimedone, and ammonium acetate in the presence of



Scheme 2. Proposed mechanism for L-proline catalyzed polyhydroquinoline synthesis.

10 mol % of L-proline (**4a**) gave 60% yield in ethanol, 47% in water but under solvent free conditions the yield was 83%. In the majority of instances, the crude product was so pure that it was directly subjected to NMR analysis.

We propose a mechanism for the L-proline catalyzed synthesis of polyhydroquinolines (Scheme 2). As L-proline is well known to catalyze aldol and Michael reactions, polyhydroquinoline **5** may be formed either through step 1→step 2→step 3 or through step 4→step 5→step 6. The role of L-proline comes in steps 1 and 4 where it catalyses the Knoevenagel type coupling of aldehydes with active methylene compounds and in steps 3 and 6 where it catalyses the Michael type addition of intermediates **5**, **6** and **7**, **8** to give product **5**. The isolated products **5** were racemic mixtures.

3. Conclusion

In conclusion, we have developed a simple, rapid, efficient, and green method for the synthesis of a variety of polyhydroquinoline derivatives via an improved Hantzsch reaction catalyzed by small organic molecules. The reaction conditions are mild and the reaction gives excellent yields of products at room temperature. This method does not involve the use of volatile organic solvents, and thus, is an environmentally friendly process.

4. Experimental

4.1. Materials and general

All the reactions were carried out at room temperature, that is, 28–32 °C. Unless otherwise specified, all the reagents were purchased from Sigma–Aldrich Chemical Co, Lancaster and were used directly without further purification. NMR spectra were obtained using the Brucker DRX-300 and 200 MHz spectrometer. Chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (J) in hertz. Mass spectra were obtained using JEOL SX-102 (ESI) instrument. IR spectra were taken on VARIAN FTIR spectrometer as KBr pellets. Elemental analysis was preformed using a Perkin–Elmer Autosystem XL Analyzer. Melting points were measured using a COMPLAB melting point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

4.2. Typical experimental procedure for the synthesis of Hantzsch polyhydroquinoline derivatives (5) under solvent free conditions

When the reaction mixture was oily: in a typical experimental procedure aldehyde **1** (1 mmol), dimedone **2** (1 mmol), acetoacetate ester **3** (1 mmol), ammonium acetate (1 mmol), and L-proline (or other organocatalyst) (0.1 mmol) were taken in a 25 ml round bottom flask and was stirred with a magnetic stirrer until all reactants were consumed (TLC). The reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from methanol.

When reaction mixture was solid: in a typical experimental procedure aldehyde **1** (1 mmol), dimedone **2** (1 mmol), acetoacetate ester **3** (1 mmol), ammonium acetate (1 mmol), and L-proline (or other organocatalyst) (0.1 mmol) were taken in a porcelain dish and were ground by a mortar for 2–3 min. Within 10 min the reaction mixture became oily and within 30 min it became a brown or yellowish solid. The reaction mixture was poured into brine and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from methanol.

4.3. Typical experimental procedure for the synthesis of Hantzsch polyhydroquinoline derivatives (5) under aqueous medium

In a typical experimental procedure aldehyde **1** (1 mmol), dimedone **2** (1 mmol), acetoacetate ester **3** (1 mmol), ammonium acetate (1 mmol), and L-proline (or other organocatalyst) (0.1 mmol) were taken in a 25 ml round bottom flask and 1 ml water was added to it. A small magnet was put in R.B. and was stirred until all reactants were consumed (TLC). The reaction mixture was poured into 10 ml brine and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from methanol.

4.4. Typical procedure for the synthesis of Hantzsch polyhydroquinoline derivatives (5) in ethanol

In a typical experimental procedure aldehyde **1** (1 mmol), dimedone **2** (1 mmol), acetoacetate ester **3** (1 mmol), ammonium acetate (1 mmol), and L-proline (or other organocatalyst) (0.1 mmol) were taken in a 25 ml round bottom flask and 1 ml ethanol was added to it. A small magnet was put in R.B. and was stirred until all reactants were consumed (TLC). The reaction mixture was poured into 10 ml brine and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. A crude solid was obtained. The pure product was obtained through crystallization from methanol.

4.4.1. 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5a). Mp: 203–204 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (s, 3H), 1.07 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 2.13–2.29 (m, 4H), 2.35 (s, 3H), 4.06 (q, J=7.1 Hz, 2H), 5.07 (s, 1H), 6.64 (s, 1H), 7.08–7.13 (m, 1H), 7.18–7.23 (m, 2H), 7.28–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.92, 17.96, 25.84, 28.15, 31.38, 35.33, 39.65, 49.50, 58.52, 104.72, 110.70, 124.74, 126.59, 126.72, 142.41, 145.82, 147.47, 166.24, 194.43. IR (KBr): 3287, 3078, 2963, 1697, 1611 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{21}H_{26}NO_3$: 340.2. Found: 340.2. Analysis calculated for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.27; H, 7.39; N, 4.08.

4.4.2. 2,7,7-Trimethyl-5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl

ester (5b). Mp: 260–262 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.95 (s, 3H), 1.07 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 2.13–2.28 (m, 7H), 2.34 (s, 3H), 4.05 (q, J=7.1 Hz, 2H), 5.03 (s, 1H), 6.66 (s, 1H), 7.00 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.95, 17.97, 19.75, 25.91, 28.15, 31.38, 34.85, 39.64, 49.53, 58.50, 104.86, 110.71, 126.58, 127.32, 134.09, 142.25, 142.98, 147.46, 166.30, 194.46. IR (KBr): 3276, 3079, 2962, 1703, 1648 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{22}H_{28}NO_3$: 354.2. Found: 354.0. Analysis calculated for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.74; H, 7.65; N, 3.91.

4.4.3. 2,7,7-Trimethyl-5-oxo-4-(4-dimethylamino phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5c). Mp: 262–263 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.97 (s, 3H), 1.07 (s, 3H), 1.22 (t, J=7.1 Hz, 3H), 2.13–2.35 (m, 4H), 2.60 (s, 3H), 2.87 (s, 6H), 4.05 (q, J=7.1 Hz, 2H), 5.00 (s, 1H), 6.36 (s, 1H), 6.60 (d, J=8.6 Hz, 2H), 7.16 (d, J=8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.69, 19.66, 27.67, 29.88, 33.03, 35.78, 41.12, 51.23, 60.12, 106.82, 112.60, 112.76, 136.36, 143.61, 149.07, 149.38, 168.19, 196.31. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{23}H_{31}N_2O_3$: 383.2. Found: 383.3. Analysis calculated for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.18; H, 7.85; N, 7.25.

4.4.4. 2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5d). Mp: 245–246 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (s, 3H), 1.08 (s, 3H), 1.18 (t, J=7.1 Hz, 3H), 2.12–2.34 (m, 4H), 2.37 (s, 3H), 4.04 (q, J=7.1 Hz, 2H), 5.04 (s, 1H), 6.46 (s, 1H), 7.15–7.19 (m, 2H), 7.24–7.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.92, 18.05, 25.80, 28.13, 31.39, 34.97, 39.69, 49.42, 58.62, 104.42, 110.46, 126.40, 128.14, 130.32, 142.49, 144.34, 147.26, 165.98, 194.32. IR (KBr): 3276, 3199, 3077, 2964, 1707, 1648, 1604 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{21}H_{25}ClNO_3$: 374.1. Found: 374.1. Analysis calculated for $C_{21}H_{24}ClNO_3$: C, 67.46; H, 6.47; N, 3.75. Found: C, 67.43; H, 6.49; N, 3.69.

4.4.5. 2,7,7-Trimethyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5e). Mp: 177–178 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (s, 3H), 1.08 (s, 3H), 1.22 (t, J=7.1 Hz, 3H), 2.12–2.42 (m, 7H), 3.69 (q, J=7.1 Hz, 2H), 5.16 (s, 1H), 6.85 (s, 1H), 7.36 (t, J=7.9 Hz, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.97 (m, 1H), 7.99 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.90, 18.04, 25.78, 28.09, 31.45, 35.72, 39.54, 49.31, 58.79, 103.71, 109.78, 119.99, 121.59, 127.33, 133.50, 143.42, 146.94, 148.06, 165.72, 194.39. IR (KBr): 3284, 3211, 3079, 2960, 1705, 1607, 1532 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{21}H_{25}N_2O_5$: 385.2. Found: 385.1.

4.4.6. 2,7,7-Trimethyl-5-oxo-4-(4-methoxycinnamyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5f). Mp: 198–200 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 3H), 1.12 (s, 3H), 1.28 (t, J=7.1 Hz, 3H), 2.19–2.33 (m, 4H), 2.37 (s, 3H), 3.76 (s, 3H), 4.12–4.25 (m, 2H), 4.71 (d, J=6.1 Hz, 1H), 6.16 (dd, J=16.2, and 6.1 Hz, 1H), 6.45 (s, 1H), 6.58 (d, J=16.2 Hz, 1H), 6.78–6.87 (m, 2H), 7.11–7.16 (m, 1H), 7.37 (d, J=1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.08, 18.04, 25.87, 28.39, 31.32, 32.13, 39.76, 49.51, 54.08, 58.54, 102.77, 108.61, 109.56, 119.18, 121.89, 124.98, 125.47, 126.58, 130.89, 143.10, 148.23, 155.10, 166.30, 194.44. IR (KBr): 3301, 2964, 1676, 1602, 1483 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{24}H_{30}NO_4$: 396.2. Found: 396.1. Analysis calculated for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.78; H, 7.31; N, 3.43.

4.4.7. 2,7,7-Trimethyl-5-oxo-4-(1-naphthyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5g). Mp: 198–200 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (s, 3H), 1.12 (s, 3H), 1.28 (t, J=7.1 Hz, 3H), 2.19–2.33 (m, 4H), 2.37 (s, 3H), 3.76 (s, 3H), 4.12–4.25 (m, 2H), 4.71 (d, J=6.1 Hz, 1H), 6.16 (dd, J=16.2 and 6.1 Hz, 1H), 6.45 (s, 1H), 6.58 (d, J=16.2 Hz, 1H), 6.78–6.87 (m, 2H), 7.11–7.16 (m, 1H), 7.37 (d, J=1.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.08, 18.04, 25.87, 28.39, 31.32, 32.13, 39.76, 49.51, 54.08, 58.54, 102.77, 108.61, 109.56, 119.18, 121.89, 124.98, 125.47, 126.58, 130.89, 143.10, 148.23, 155.10, 166.30, 194.44. IR (KBr): 3301, 2964, 1676, 1602, 1483 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{24}H_{30}NO_4$: 396.2. Found: 396.1. Analysis calculated for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.78; H, 7.31; N, 3.43.

4.4.8. 2,7,7-Trimethyl-5-oxo-4-(3,4-dichlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5h). Mp: 213–215 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (s, 3H), 1.09 (s, 3H), 1.22 (t, J=7.1 Hz, 3H), 2.14–2.38 (m, 7H), 4.03 (q, J=7.1 Hz, 2H), 5.02 (s, 1H), 6.41 (s, 1H), 7.17 (m, 1H), 7.26 (m, 1H), 7.36 (d, J=2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.59, 19.85, 27.56, 29.75, 33.14, 36.71, 41.41, 51.02, 60.43, 105.65, 111.76, 128.14, 130.19, 130.41, 132.16, 144.43, 147.70, 148.94, 167.40, 195.90. IR (KBr): 3283, 3078, 2962, 1708, 1650, 1603, 1491 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{21}H_{24}Cl_2NO_3$: 408.11. Found: 408.1. Analysis calculated for $C_{21}H_{23}Cl_2NO_3$: C, 61.77; H, 5.68; N, 3.43. Found: C, 61.65; H, 5.56; N, 3.37.

4.4.9. 2,7,7-Trimethyl-5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (5i). Mp: >270 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (s, 3H), 1.09 (s, 3H), 2.15–2.38 (m, 10H), 3.62 (s, 3H), 5.04 (s, 1H), 5.96 (s, 1H), 7.00 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.45, 19.73, 25.64, 28.32, 31.30, 34.38, 49.46, 49.78, 102.62, 109.32, 126.36, 127.57, 133.74, 143.82, 144.22, 148.54, 166.56, 193.46. IR (KBr): 3283, 3192, 3071, 2956, 1687, 1602, 1491 cm^{-1}. MS (ESI) m/z (M+H)$^+$ Calculated for $C_{21}H_{26}NO_3$: 340.2. Found: 340.1. Analysis calculated for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.22; H, 7.35; N, 4.03.

4.4.10. 2,7,7-Trimethyl-5-oxo-4-(3-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid *tert*-butyl ester (5j). Mp: 190–191 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (s, 3H), 1.08 (s, 3H), 1.38 (s, 9H), 2.14–2.35 (m, 7H), 3.78 (s, 3H), 4.98 (s, 1H), 5.86 (s, 1H), 6.65 (m, 1H), 6.88 (m, 2H), 7.10 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.73, 26.90, 26.99, 28.10, 31.30, 35.82, 39.42, 49.58, 53.75, 78.55, 105.98, 109.58, 110.06,

112.95, 119.43, 127.32, 141.57, 147.66, 148.31, 157.94, 165.71, 194.57. IR (KBr): 3292, 3224, 3087, 2958, 1699, 1605, 1491 cm^{-1}. MS (ESI) *m/z* $(M+H)^+$ Calculated for $C_{24}H_{32}NO_4$: 398.2. Found: 398.0. Analysis calculated for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.38; H, 7.76; N, 3.41.

4.4.11. 2,7,7-Trimethyl-5-oxo-4-(4-methoxycinnamyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (5k). Mp: 207–208 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 3H), 1.13 (s, 3H), 2.20–2.38 (m, 7H), 3.72 (s, 3H), 3.76 (s, 3H), 4.69 (d, J=5.8 Hz, 1H), 6.19 (dd, J=16.1 and 5.9 Hz, 1H), 6.36 (s, 1H), 6.55 (d, J=16.4 Hz, 1H), 6.78–6.87 (m, 2H), 7.12–7.16 (m, 1H), 7.36 (d, J=1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.05, 25.90, 28.38, 31.34, 31.91, 39.80, 49.49, 49.82, 54.16, 102.46, 108.80, 109.66, 119.23, 121.80, 125.03, 125.47, 126.60, 130.88, 143.38, 148.03, 155.09, 166.73, 194.38. IR (KBr): 3297, 3080, 2948, 1681, 1604, 1485 cm^{-1}. MS (ESI) *m/z* $(M+H)^+$ Calculated for $C_{23}H_{28}NO_4$: 382.2. Found: 382.3. Analysis calculated for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.35; H, 7.02; N, 3.59.

4.4.12. 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid *tert*-butyl ester (5l). Mp: 222–223 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.93 (s, 3H), 1.07 (s, 3H), 1.37 (s, 9H), 2.11–2.27 (m, 4H), 2.32 (s, 3H), 4.99 (s, 1H), 6.43 (s, 1H), 7.07 (t, J=7.1 Hz, 1H), 7.18–7.23 (m, 2H), 7.28–7.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.84, 25.92, 26.91, 28.05, 31.36, 35.90, 39.74, 49.53, 78.60, 106.34, 110.60, 124.59, 126.45, 126.85, 141.14, 145.92, 147.29, 165.62, 194.32. IR (KBr): 3280, 3216, 3084, 2965, 1678, 1608, 1491 cm^{-1}. MS (ESI) *m/z* $(M+H)^+$ Calculated for $C_{23}H_{30}NO_3$: 368.2. Found: 368.0. Analysis calculated for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.14; H, 7.89; N, 3.72.

4.4.13. 2,7,7-Trimethyl-5-oxo-4-(4-dimethylaminophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid *tert*-butyl ester (5m). Mp: 239–240 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.94 (s, 3H), 1.05 (s, 3H), 1.39 (s, 9H), 2.11–2.24 (m, 7H), 2.86 (s, 6H), 4.88 (s, 1H), 6.42 (s, 1H), 6.58 (m, 2H), 7.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.60, 27.80, 28.09, 28.68, 29.76, 33.07, 36.31, 41.27, 41.42, 51.22, 80.13, 108.46, 112.61, 112.86, 129.08, 136.62, 142.22, 148.63, 149.36, 167.61, 196.17. IR (KBr): 3200, 3077, 2966, 2809, 1688, 1606, 1520 cm^{-1}. MS (ESI) *m/z* $(M+H)^+$ Calculated for $C_{25}H_{35}N_2O_3$: 411.2. Found: 411.2. Analysis calculated for $C_{25}H_{34}N_2O_3$: C, 73.14; H, 8.35; N, 6.82. Found: C, 73.02; H, 8.23; N, 6.68.

4.4.14. 2,7,7-Trimethyl-5-oxo-4-(3-methoxyphenyl)-3-acetyl-1,4,5,6,7,8-hexahydroquinoline (5n). Mp: 205–206 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 0.88 (s, 3H), 1.07 (s, 3H), 2.16–2.39 (m, 10H), 3.49 (s, 3H), 5.08 (s, 1H), 6.29 (s, 1H), 6.68 (m, 1H), 6.87 (m, 2H), 7.13 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.15, 18.95, 25.81, 27.99, 28.32, 31.43, 35.75, 39.79, 49.46, 53.84, 57.17, 110.00, 111.33, 111.67, 112.69, 119.08, 127.99, 142.05, 146.03, 146.51, 158.32, 194.36, 198.00. IR (KBr): 3282, 2954, 1637, 1593, 1469 cm^{-1}. MS (ESI) *m/z* $(M+H)^+$ Calculated for $C_{21}H_{26}NO_3$: 340.2. Found: 340.1. Analysis calculated for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.25; H, 7.33; N, 4.06.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.074.

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