J. Indian Chem. Soc.,
Vol. 90, October 2013, pp. 1589-1598

Cobalt triflate catalyzed one-pot synthesis of fluorophore 1,4-dihydropyridine derivatives via Hantzsch reaction†

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Manuscript received 04 March 2013, accepted 07 March 2013

Abstract : A wide variety of 1,4-dihydropyridines have been synthesized through one-pot condensation of aromatic aldehydes, β-ketoesters, cyclic 1,3-diones and ammonium acetate using cobalt triflate as a catalyst through Hantzsch reaction. Some of the salient features of the present protocol are shorter reaction time, mild reaction conditions, good yields, non-aqueous work-up, reusability of the catalyst and non-requirement of column chromatographic separation.

Keywords : Cobalt triflate, multicomponent reaction, 1,4-dihydropyridines, cyclic 1,3-diketones, aromatic aldehydes, β-ketoesters, ammonium acetate.

Introduction

1,4-Dihydropyridine (1,4-DHP) skeleton is present in many bioactive compounds and much attention has been paid on the synthesis of these compounds due to their high potential. They are used as antiatherosclerotic, antitumor, antidiabetic, gero-protective, bronchodilator and heptaprotective agents[1]. Some of the highly substituted 1,4-DHPs are already known as valuable drugs for treatment of cardiovascular diseases including hypertension[2], as shown in Fig. 1.

In addition, it has been found that 1,4-DHP pharmacophores show neuroprotectant and platelet antiaggregatory activities[3]. Moreover, they can be used in the treatment of Alzheimer's disease owing to their antiischemic activity and as chemosensitizers in tumor therapy[4]. As a matter of fact, numerous methods have been developed to synthesize these compounds due to their immense medicinal value. They are usually prepared by classical methods[5] using conventional heating or refluxing in the presence of a suitable organic solvent. However, these methods required long reaction time, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally low yields. Over the years numerous synthetic methods have been reported using microwave irradiation[6], ionic liquids[7], polymers[8], Lewis

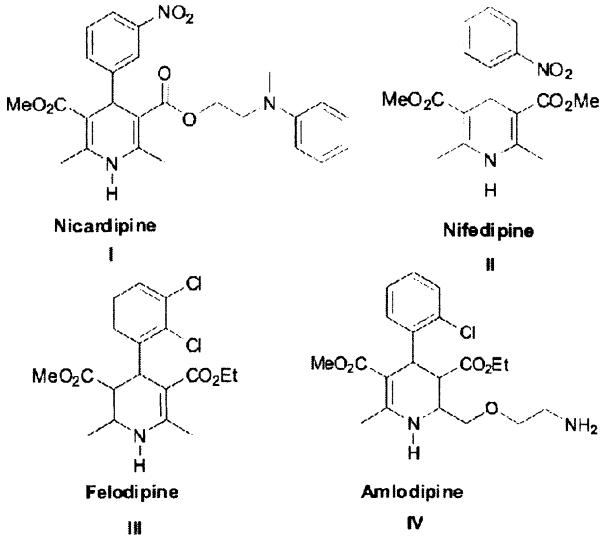


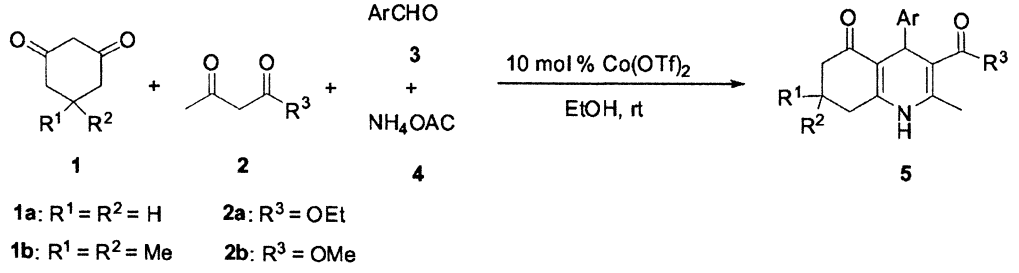
Fig. 1. Biologically active compounds containing dihydropyridine skeleton.

acid[9], Bakers' yeast[10], nickel[11a] or palladium nanoparticle[11b], and metal triflates[12]. Though these methods are quite useful, there is still a further scope to develop newer synthetic methodology which might work under milder reaction conditions. Recently multi-component reactions have been used extensively in the modern drug discovery process and allow fast, automated and high throughput generation of heterocyclic compounds[13].

†**In honour of Professor Sunil Kumar Talapatra on the occasion of his 80th birthday.**

As a part of our ongoing research interest in MCRs for the synthesis of various heterocyclic compounds[14], we perceived that cobalt triflate might be a useful catalyst for the synthesis of 1,4-dihydropyridine derivatives. We have chosen this catalyst as it was not explored earlier, which may reduce reaction time and can be recyclable.

In this paper we report a simple and efficient protocol for the synthesis of 1,4-dihydropyridine derivatives by employing cobalt triflate as a reusable catalyst through one-pot four-component condensation reaction of aromatic aldehydes, β-ketoesters, cyclic 1,3-diketones and ammonium acetate, as shown in Scheme 1.



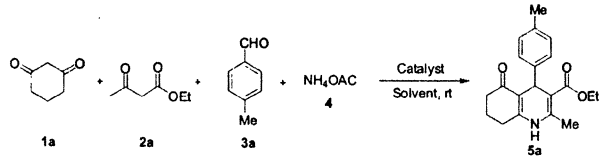
Scheme 1. Synthesis of fused 1,4-dihydropyridine derivatives.

After optimization of the reaction conditions, a mixture of 4-chlorobenzaldehyde, 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate was stirred in presence of 10 mol% $Co(OTf)_2$ at room temperature and the desired product **5b** was obtained in 92% yield (Table 2, entry 2). The reaction of various other aromatic aldehydes was examined with 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate under identical reaction conditions and the resulting product **5c-f** (Table 2, entries 3-6) were obtained in good yields. Similarly, the reaction of 4-methyl benzaldehyde with dimedone, ethyl acetoacetate and ammonium acetate was also carried out

Results and discussion

For the present study, a mixture of 4-methylbenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), 1,3-cyclohexanedione (1 mmol) and ammonium acetate (1 mmol) in 2 mL of ethanol was stirred in the presence of freshly prepared[15] 5 mol% cobalt triflate (0.017 g) at room temperature. After 1 h of stirring, a solid product **5a** precipitated out, which was characterized by recording ^1H NMR and ^{13}C NMR spectra as well as by elemental analysis. It was observed that some unreacted starting materials were present in the filtrate. For complete conversion, a similar reaction was performed in the presence of 10 mol% of cobalt triflate (0.035 g) at room temperature. Interestingly, the reaction was complete within 45 min and the isolated product was obtained in 96% yield (Table 1, entry 3). In order to find out the efficacy of cobalt triflate, similar reactions were examined by using 5 and 10 mol% of $Mn(OTf)_2$ under identical reaction conditions, as shown in Table 1 (entries 4 and 5). The role of solvent was also scrutinized by performing similar reactions in CH_3CN, DCM, MeOH, Et_2O and CH_3CN/DCM, respectively. Among them, EtOH provided the best yield and also required shorter reaction time.

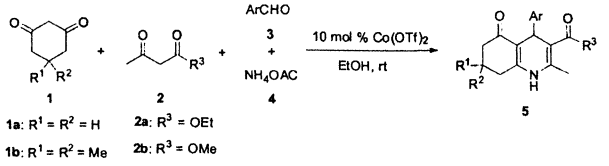
Table 1. Optimization of the reaction conditions[a]



Sl. no.	Catalyst used	Mol%	Solvent	Time (h)	Yield (%)[b]
1.	$Co(OTf)_2$	5	EtOH	1	75
2.	$Co(OTf)_2$	5	CH_3CN	2	55
3.	$Co(OTf)_2$	10	EtOH	0.75	96
4.	$Mn(OTf)_2$	5	CH_3CN	3	45
5.	$Mn(OTf)_2$	10	EtOH	1.5	50
6.	$Co(OTf)_2$	10	CH_3CN	2.5	65
7.	$Co(OTf)_2$	10	DCM	3	40
8.	$Co(OTf)_2$	10	MeOH	2	58
9.	$Co(OTf)_2$	10	Et_2O	1	65
10.	$Co(OTf)_2$	10	CH_3CN/DCM	3	60

[a]The reactions were carried out using (1 mmol) each of aldehyde, cyclic-1,3-dione, β-ketoester and ammonium acetate. [b]Isolated yield.

Table 2. $Co(OTf)_2$ catalyzed synthesis of 1,4-dihydropyridines[a]



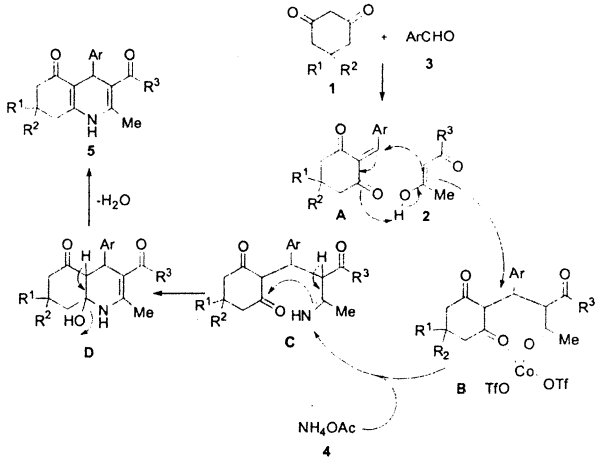
Sl. no.	1	β-Ketoesters (2)	ArCHO (3)	5	Time (min)	Yield (%)[b]
1.	**1a**	**2a**	4-Me-C_6H_4	**5a**	45	96
2.	**1a**	**2a**	4-Cl-C_6H_4	**5b**	40	92
3.	**1a**	**2a**	C_6H_5	**5c**	50	96
4.	**1a**	**2a**	4-NO_2-C_6H_4	**5d**	60	94
5.	**1a**	**2a**	4-OMe-C_6H_4	**5e**	65	96
6.	**1a**	**2a**	4-F-C_6H_4	**5f**	15	96
7.	**1b**	**2a**	4-Me-C_6H_4	**5g**	30	95
8.	**1b**	**2b**	4-Me-C_6H_4	**5h**	40	89
9.	**1b**	**2b**	4-NO_2-C_6H_4	**5i**	60	90
10.	**1b**	**2b**	4-F-C_6H_4	**5j**	15	90
11.	**1b**	**2b**	3-F-C_6H_4	**5k**	20	86
12.	**1b**	**2b**	2-F-C_6H_4	**5l**	15	88
13.	**1b**	**2b**	C_6H_5	**5m**	30	93
14.	**1b**	**2b**	4-OMe-C_6H_4	**5n**	60	87
15.	**1b**	**2b**	2-Naphthyl	**5o**	50	86
16.	**1b**	**2b**	2-Thiophenyl	**5p**	40	88

[a]All the reactions were carried out using (1 mmol) each of aldehyde, cyclic-1,3-dione, β-ketoester and ammonium acetate. [b]Isolated yield.

under identical reaction conditions and the product **5g** was obtained in excellent yield. Next the reaction of various aromatic aldehydes with dimedone, methyl acetoacetate and ammonium acetate in a similar manner and afforded the desired products **5h-n** (Table 2, entries 8–14) in good yields.

The reaction was also carried out by the using 2-naphthaldehyde and 2-thiophenaldehyde, dimedone, methyl acetoacetate and ammonium acetate with 10 mol% $Co(OTf)_2$ at room temperature and the desired products **5o-p** (Table 2, entry 15 and 16) were obtained in good yields.

The formation of 1,4-dihydropyridine can be explained as follows. Initially, cyclic 1,3-diketone (**1**) reacts with aldehyde **3** to give the Knoevenagel product **A**. Then β-ketoester **2** reacts with the intermediate **A** to form Michael adduct **B**, which can also be stabilized through cobalt triflate, as shown in Scheme 2. Subsequently, it is converted into the intermediate **C** on reaction with NH_4OAc (**4**), which undergoes concomitant cyclization to give intermediate **D**. Finally, it gives 1,4-dihydropyridine derivatives **5** with elimination of water molecule from **D**, as shown in Scheme 2.

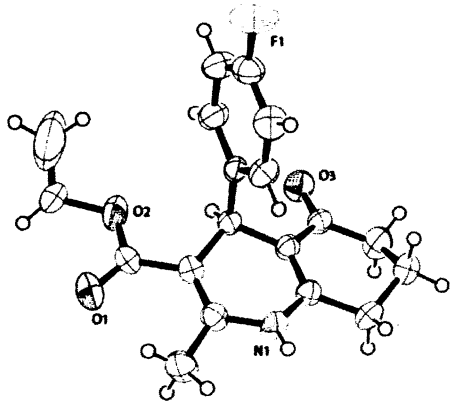


Scheme 2. Plausible mechanism for the formation of 1,4-dihydropyridine (**5**).

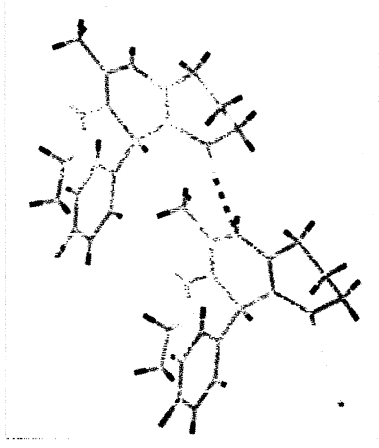
The structure of the compound **5f** was determined by single-crystal X-ray crystallographic data[16] (as shown in Fig. 2a) and their intermolecular H-bonding interaction through N–H···O bonds (H···O = 2.13 Å, N···O = 2.92 Å, < N–H···O = 176°) as shown in Fig. 2b.

The reusability test was accomplished as follows. The mixture of 4-chlorobenzaldehyde (10 mmol), 1,3-cyclohexanedione (10 mmol), ethyl acetoacetate (10 mmol) and ammonium acetate (10 mmol) was stirred in the presence of 0.35 g of $Co(OTf)_2$ under room temperature in ethanol. After completion of reaction, the precipitated solid product was filtered through a Büchner funnel, washed with ethanol and dried under reduced pressure and the desired product **5b** was obtained in 92% yield. The filtrate containing catalyst was reused for second cycle with the same combination of the substrates in a similar manner. Likewise, we have performed another three cycles and the successful results are shown in Fig. 3.

The photophysical properties of the 1,4-dihydropyridine results are summarized in Table 3, Fig. 4. Furthermore, the UV-Visible spectra of the 1,4-dihydropyridine contain intense absorption maxima at 238 ± 5 and at 350 ± 5 nm. Among the 1,4-dihydropyridine



(a)



(b)

Fig. 2. (a) ORTEP diagram of compound **5f** (CCDC no. 886705), (b) H-bonding interactions.

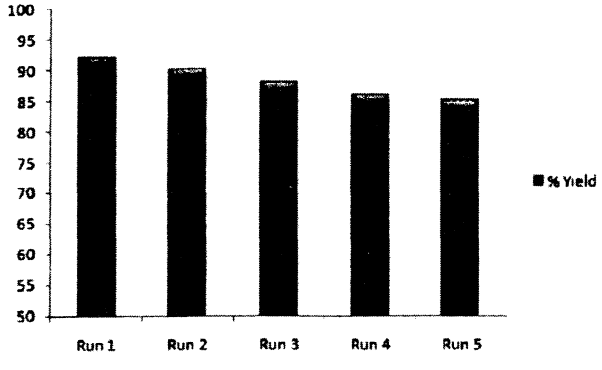


Fig. 3. Reusability of the catalyst $Co(OTf)_2$ in ethanol.

derivatives the substituent which bear a 2-fluorophenyl group at the C3 position **5l** which enhance the shift of the absorption maxima to longer wavelength 355 nm. In the case of the fluorescence spectra results clearly indicates that hetero-aromatic substituent at the C3 position of the 1,4-dihydropyridine **5p** which enhance the fluorescence wavelength maxima 435 nm respectively. In addition to that the fluorescence of the 1,4-dihydropyridine derivatives **5** are shown in Fig. 1.

Next, partial aromatization of the 1,4-dihydropyridines on refluxing with DDQ in toluene provided 5,6,7,8-tetrahydro-quinoline-3-carboxylates (**6a-d**) in good to excellent yield and the reactions were complete within 1 h as shown in Table 4.

Table 3. Photophysical data of 1,4-dihydropyridine derivatives (**5**) in CH_2Cl_2

Entry	1,4-Dihydro pyridine (**5**)	Absorption[a] λ_{abs} (nm)	ϵ (M^{-1} cm^1)	Fluorescence (λ_{em})[b]
1.	**5a**	233	1046410	424
		349	450330	
2.	**5b**	243	2238570	424
		350	1221330	
3.	**5c**	242	2090640	425
		350	1057290	
4.	**5e**	232	1058470	423
		349	404100	
5.	**5f**	234	1272190	429
		354	601550	
6.	**5g**	239	1411190	427
		351	663990	
7.	**5i**	238	756390	427
		350	326070	
8.	**5j**	239	1059040	428
		350	401530	
9.	**5k**	241	1938390	423
		351	908890	
10.	**5l**	242	2129330	428
		355	1088570	
11.	**5m**	233	1362810	424
		353	569170	
12.	**5n**	243	2205050	423
		353	1296530	
13.	**5o**	242	2305360	426
		352	916670	
14.	**5p**	236	1721470	435
		345	630860	

[a]Measured at a concentration of 1.0×10^{-6} mol dm^{-3} at 25 °C. [b]Emission maxima upon excitation at 351 nm.

Subsequently the structure of the compound **6c** was also determined by using single-crystal X-ray data, as shown in the Fig. 5.

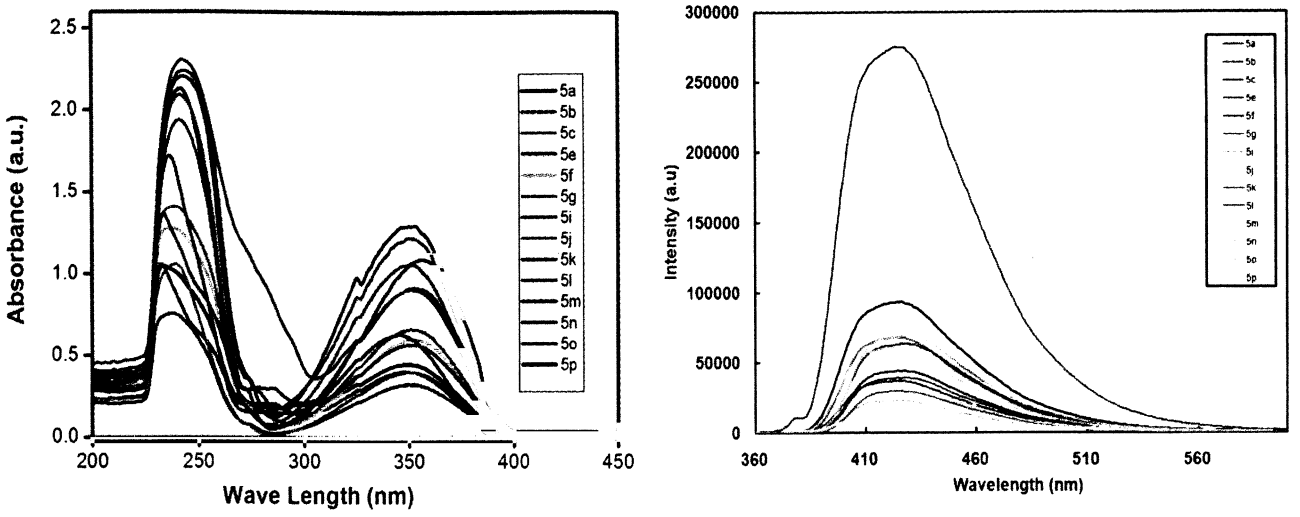


Fig. 4. UV-Visible (a) and fluorescence spectra (b) of 1,4-dihydropyridine (**5**).

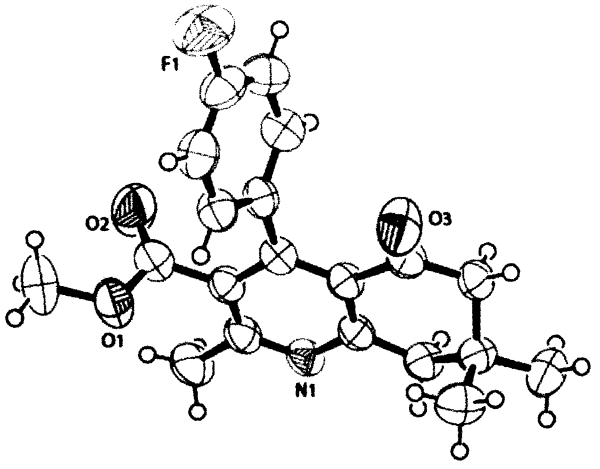
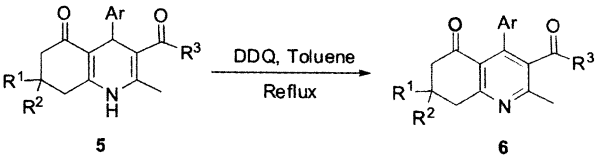


Fig. 5. ORTEP diagram of compound **6c** (CCDC no. 886708).

Table 4. Aromatization of 1,4-dihydropyridines **5**[a]



5 **6**

Entry	5	6	Time (min)	Yield (%)[b]
1	**5a**	**6a**	50	95
2	**5f**	**6b**	50	95
3	**5j**	**6c**	45	95
4	**5o**	**6d**	45	90

[a]The reaction was performed using 1,4-dihydropyridine (**5**), DDQ (1.2 mmol) in toulene under reflux condition. [b]Isolated yield.

In short, we have achieved the synthesis of 1,4-dihydropyridine derivatives using β-ketoester, aromatic aldehyde, cyclic 1,3-diketone and ammonium acetate in the presence of catalytic amount of $Co(OTf)_2$ in ethanol. The advantage of the present protocol was shorter reaction time, simplicity, mild reaction conditions, good yields, no need of chromatographic separation and catalyst recyclability. In addition, the synthesized 1,4-dihydropyridine derivatives can be converted easily into fused pyridine derivatives by refluxing with DDQ in toluene.

General procedure :

IR spectra were recorded on IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on 400 MHz spectrometer using TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^1H NMR spectra are reported in the order : multiplicity, coupling constant (*J* value) in Hertz (Hz) and no. of protons; signals were characterized as s (singlet), d (doublet), t (triplet), q (quatret), and m (multiplet). Elemental analyses were carried out using CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Complete X-ray crystallographic data of **5f** (CCDC no. 886705) and **6c** (CCDC no. 886708) for the structural analysis have been deposited with the Cam-

bridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax : 44-1223-336033, E-mail : deposit@ccdc.cam.ac.uk or via : www.ccdc.cam.ac.uk).

Synthesis of compounds **5a-p** :

To a stirred mixture of aromatic aldehyde (1 mmol), β-ketoester (1 mmol), cyclic 1,3-dione (1 mmol) and ammonium acetate (1 mmol) in 2 mL ethanol was added the catalyst cobalt triflate (0.035 g, 0.1 mmol) at room temperature and stirring was continued until the completion of the reaction as indicated by TLC. The solid product came out after stipulated time indicated in Table 2, which was filtered through a Büchner funnel and the precipitate was washed with ethanol and dried under vaccum.

Ethyl 2-methyl-5-oxo-4-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **(5a)** :

Yield : 0.312 g (96%); white solid; m.p. 242–243 °C (lit.[12b] m.p. 244–245 °C); IR (KBr) ν_{max} : 3283, 3214, 3071, 2951, 2359, 2341, 1696, 1645, 1606, 1481, 1381, 1284, 1223, 1181, 1137, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.2 (3H, t, *J* 7.2 Hz), 1.92–1.98 (2H, m), 2.26 (3H, s), 2.29–2.35 (2H, m), 2.37 (3H, s), 2.39–2.44 (2H, m), 4.07 (2H, q, *J* 7.2 Hz), 5.06 (1H, s), 6.08 (1H, br s), 7.01 (2H, d, *J* 7.6 Hz), 7.19 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.6, 18.1, 20.3, 20.5, 26.2, 35.1, 36.6, 58.7, 104.3, 111.7, 127.1, 127.8, 134.3, 144.0, 144.4, 150.8, 167.0, 195.1 (Found : C, 73.78; H, 7.08; N, 4.25. Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30%).

Ethyl 4-(4-chlorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **(5b)** :

Yield : 0.318 g (92%); white solid; m.p. 235–236 °C (lit.[9b] m.p. 234–235 °C); IR (KBr) ν_{max} : 3284, 3218, 3076, 2977, 2955, 1721, 1625, 1607, 1481, 1381, 1285, 1224, 1182, 1137, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.18 (3H, t, *J* 7.2 Hz), 1.88–1.95 (2H, m), 2.31–2.33 (2H, m), 2.37 (3H, s), 2.46 (2H, s), 4.04 (2H, q, *J* 6.8 Hz), 5.03 (1H, s), 7.14 (2H, d, *J* 8.0 Hz), 7.24 (2H, d, *J* 8.4 Hz), 8.14 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.1, 18.7, 20.9, 26.7, 35.9, 36.9, 59.5, 104.6, 112.0, 127.7, 129.3, 131.1, 144.7, 146.2, 151.5, 167.3, 195.9 (Found : C, 65.94; H, 5.78; N, 3.55. Calcd. for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05%).

Ethyl 2-methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **(5c)** :

Yield : 0.298 g (96%); white solid; m.p. 240–241 °C (lit.[9e] m.p. 238–240 °C); IR (KBr) ν_{max} : 3284, 3214, 3071, 2957, 1691, 1644, 1607, 1479, 1380, 1306, 1284, 1223, 1180, 1137, 1115, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.18 (3H, t, *J* 7.2 Hz), 1.88–1.98 (2H, m), 2.28–2.35 (2H, m), 2.37 (3H, s), 2.40–2.48 (2H, m), 4.04 (2H, q, *J* 7.2 Hz), 5.06 (1H, s), 7.08 (1H, t, *J* 7.2 Hz), 7.18 (2H, t, *J* 7.2 Hz), 7.29 (2H, d, *J* 8.0 Hz), 8.09 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.1, 18.7, 20.9, 26.8, 36.2, 36.9, 59.4, 105.1, 112.5, 125.7, 127.7, 127.9, 144.5, 147.6, 151.4, 167.6, 195.9 (Found : C, 73.24; H, 6.75; N, 4.45. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50%).

Ethyl 2-methyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **(5d)** :

Yield : 0.334 g (94%); yellow solid; m.p. 205–206 °C (lit.[12b] m.p. 201–202 °C); IR (KBr) ν_{max} : 3295, 3222, 3077, 2950, 1703, 1649, 1606, 1552, 1480, 1380, 1350, 1283, 1223, 1183, 1137, 1116, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.17 (3H, t, *J* 7.2 Hz), 1.92–2.02 (2H, m), 2.32–2.39 (2H, m), 2.42 (3H, s), 2.44–2.54 (2H, m), 4.08 (2H, q, *J* 7.2 Hz), 5.19 (1H, s), 6.14 (1H, br s), 7.48 (2H, d, *J* 8.8 Hz), 8.08 (2H, d, *J* 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.4, 19.4, 21.2, 27.3, 37.2, 37.4, 60.3, 104.8, 112.0, 123.5, 129.2, 145.2, 146.3, 151.9, 155.1, 167.3, 196.4 (Found : C, 63.99; H, 5.61; N, 7.81. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86%).

Ethyl 4-(4-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate **(5e)** :

Yield : 0.327 g (96%); white solid; m.p. 195–196 °C (lit.[9b] m.p. 193–195 °C); IR (KBr) ν_{max} : 3283, 3215, 3078, 2952, 2828, 2359, 2341, 1692, 1645, 1607, 1509, 1582, 1380, 1301, 1285, 1259, 1223, 1182, 1137, 1115, 1072, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.20 (3H, t, *J* 6.8 Hz), 1.88–1.98 (2H, m), 2.29–2.38 (7H, m), 3.73 (3H, s), 4.06 (2H, q, *J* 6.8 Hz), 5.03 (1H, s), 6.73 (2H, d, *J* 8.0 Hz), 6.84 (1H, br s), 7.21 (2H, d, *J* 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.3, 19.1, 21.1, 26.9, 35.6, 37.2, 55.1, 59.8, 105.9, 113.3, 128.9, 140.1, 144.1, 151.8, 156.6, 157.9, 167.9, 196.6 (Found : C, 70.31; H, 6.74; N, 4.05. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10%).

Ethyl 4-(4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5f**) :

Yield : 0.316 g (96%); white solid; m.p. 245–246 °C (lit.[9b] m.p. 243–244 °C); IR (KBr) ν_{max} : 3293, 3217, 3077, 2963, 1697, 1646, 1609, 1505, 1481, 1379, 1286, 1222, 1180, 1136, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.17 (3H, t, *J* 7.2 Hz), 1.91–2.04 (2H, m), 2.26–2.37 (2H, m), 2.39 (3H, s), 2.41–2.47 (2H, m), 4.05 (2H, q, *J* 7.2 Hz), 5.07 (1H, s), 5.80 (1H, br s), 6.86–6.90 (2H, m), 7.24–7.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.2, 18.8, 21.0, 26.9, 35.8, 37.1, 59.6, 105.1, 112.6, 114.3, 114.5, 129.4, 129.5, 143.6, 144.5, 151.1, 167.6, 196.0 (Found : C, 69.24; H, 6.07; N, 4.20. Calcd. for $C_{19}H_{20}FNO_3$: C, 69.29; H, 6.12; N, 4.25%).

Ethyl 2,7,7-trimethyl-5-oxo-4-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5g**) :

Yield : 0.335 g (95%); white solid; m.p. 269–270 °C (lit.[12b] m.p. 262–263 °C); IR (KBr) ν_{max} : 3275, 3206, 3077, 2958, 2931, 1701, 1647, 1605, 1494, 1421, 1380, 1310, 1281, 1194, 1167, 1140, 1108, 1072, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.94 (3H, s), 1.06 (3H, s), 1.21 (3H, t, *J* 7.2 Hz), 2.16–2.21 (4H, m), 2.25 (3H, s), 2.34 (3H, s), 4.06 (2H, q, *J* 6.8 Hz), 5.01 (1H, s), 6.28 (1H, br s), 6.99 (2H, d, *J* 8.4 Hz), 7.18 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 14.4, 19.3, 21.2, 27.3, 29.6, 32.8, 36.3, 40.8, 50.9, 59.9, 106.2, 111.9, 128.0, 128.7, 135.5, 143.9, 144.5, 149.5, 167.8, 196.1 (Found : C, 74.71; H, 7.65; N, 3.91. Calcd. for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96%).

Methyl 2,7,7-trimethyl-5-oxo-4-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5h**) :

Yield : 0.275 g (89%); white solid; m.p. 275–276 °C (lit.[9c] m.p. > 270 °C); IR (KBr) ν_{max} : 3282, 3190, 3071, 2957, 2929, 1698, 1643, 1603, 1490, 1452, 1435, 1382, 1333, 1227, 1139, 1114, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.94 (3H, s), 1.07 (3H, s), 2.18–2.22 (4H, m), 2.25 (3H, s), 2.37 (3H, s), 3.61 (3H, s), 5.03 (1H, s), 5.99 (1H, br s), 7.00 (2H, d, *J* 8.0 Hz), 7.18 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.4, 20.5, 26.6, 29.1, 32.0, 35.3, 50.3, 50.4, 104.2, 110.8, 127.2, 128.1, 134.5, 144.2, 144.6, 149.3, 167.7, 195.1 (Found : C, 74.26, H, 7.37; N, 4.08. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13%).

Methyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5i**) :

Yield : 0.333 g (90%); yellow solid; m.p. 271–272 °C; IR (KBr) ν_{max} : 3247, 3189, 3072, 2969, 2945, 2875, 1709, 1649, 1607, 1517, 1493, 1431, 1388, 1377, 1345, 1280, 1187, 1167, 1108, 1074, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.91 (3H, s), 1.09 (3H, s), 2.13–2.27 (4H, m), 2.42 (3H, s), 3.61 (3H, s), 5.17 (1H, s), 6.11 (1H, br s), 7.48 (2H, dd, *J* 0.2, 6.8 Hz), 8.08 (2H, dd, *J* 0.2, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.9, 26.9, 29.4, 32.5, 37.0, 40.5, 50.6, 51.0, 103.8, 110.5, 123.3, 128.8, 145.9, 146.1, 150.0, 154.7, 167.6, 195.6 (Found : C, 64.80; H, 5.92; N, 7.50. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56%).

Methyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5j**) :

Yield : 0.308 g (90%); white solid; m.p. 245–246 °C; IR (KBr) ν_{max} : 3282, 3194, 3072, 2960, 1679, 1643, 1609, 1501, 1436, 1383, 1334, 1227, 1151, 1139, 1115, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.72 (3H, s), 0.88 (3H, s), 1.88–2.01 (2H, m), 2.05–2.15 (2H, m), 2.18 (3H, s), 3.41 (3H, s), 4.82 (1H, s), 6.65–6.69 (2H, m), 7.05–7.08 (2H, m), 8.01 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.0, 26.2, 28.8, 31.7, 34.9, 50.0, 103.6, 110.2, 113.5, 113.7, 128.5, 128.6, 142.9, 144.7, 149.1, 167.2, 194.7 (Found : C, 69.90; H, 6.41; N, 4.03. Calcd. for $C_{20}H_{22}FNO_3$: C, 69.95; H, 6.46; N, 4.08%).

Methyl 4-(3-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5k**) :

Yield : 0.294 g (86%); white solid; m.p. 248–250 °C; IR (KBr) ν_{max} : 3278, 3202, 3078, 2963, 2932, 1713, 1647, 1610, 1486, 1380, 1280, 1213, 1170, 1146, 1124, 1109, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.83 (3H, s), 0.98 (3H, s), 2.08–2.26 (4H, m), 2.29 (3H, s), 3.53 (3H, s), 4.98 (1H, s), 6.69 (1H, t, *J* 8.8 Hz), 6.88 (1H, d, *J* 8.8 Hz), 7.00–7.09 (2H, m), 7.71 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.2, 26.4, 28.9, 31.9, 35.6, 50.2, 103.4, 110.1, 111.9, 112.1, 113.8, 113.9, 122.9, 128.6, 145.1, 149.5, 167.3, 194.9 (Found : C, 69.89; H, 6.40; N, 4.02. Calcd. for $C_{20}H_{22}FNO_3$: C, 69.95; H, 6.46; N, 4.08%).

Methyl 4-(2-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5l**) :

Yield : 0.301 g (88%); white solid; m.p. 264–265 °C;

IR (KBr) ν_{max} : 3289, 3217, 3082, 2966, 2951, 2935, 1706, 1650, 1604, 1485, 1381, 1308, 1282, 1213, 1169, 1111, 1101, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.95 (3H, s), 1.08 (3H, s), 2.15–2.22 (4H, m), 2.34 (3H, s), 3.59 (3H, s), 5.21 (1H, s), 5.92 (1H, br s), 6.88–6.93 (1H, m), 6.97–7.01 (1H, m), 7.06–7.11 (1H, m), 7.33–7.37 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.6, 26.7, 29.3, 31.8, 32.2, 50.4, 50.5, 103.3, 109.8, 114.7, 114.9, 123.3, 127.2, 127.3, 130.9, 133.8, 145.1, 149.6, 167.8, 194.9 (Found : C, 69.90; H, 6.38; N, 4.01. Calcd. for $C_{20}H_{22}FNO_3$: C, 69.95; H, 6.46; N, 4.08%).

Methyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5m**) :

Yield : 0.302 g (93%); white solid; m.p. 265–266 °C; (lit.[9e] m.p. 258–260 °C); IR (KBr) ν_{max} : 3278, 3203, 3078, 2964, 2951, 1708, 1647, 1606, 1488, 1380, 1309, 1280, 1250, 1214, 1168, 1108, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.92 (3H, s), 1.06 (3H, s), 2.13–2.31 (4H, m), 2.37 (3H, s), 3.61 (3H, s), 5.06 (1H, s), 6.14 (1H, br s), 7.11 (1H, t, *J* 7.2 Hz), 7.21 (2H, t, *J* 7.6 Hz), 7.28 (2H, d, *J* 7.6 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.1, 26.4, 28.9, 31.8, 35.6, 50.1, 50.2, 103.8, 110.5, 125.1, 127.1, 127.2, 144.6, 146.9, 149.1, 167.4, 194.7 (Found : C, 73.77; H, 7.07; N, 4.25. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30%).

Methyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5n**) :

Yield : 0.308 g (87%); white solid; m.p. 255–256 °C; IR (KBr) ν_{max} : 3272, 3185, 3068, 2953, 2927, 2939, 1704, 1649, 1605, 1497, 1379, 1280, 1214, 1192, 1167, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.88 (3H, s), 1.02 (3H, s), 1.98 (2H, s), 2.12–2.19 (2H, m), 2.33 (3H, s), 3.57 (3H, s), 3.69 (3H, s), 4.95 (1H, s), 6.68 (2H, d, *J* 8.4 Hz), 6.85 (1H, br s), 7.16 (2H, d, *J* 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.0, 26.3, 28.8, 31.7, 34.5, 49.9, 50.1, 54.3, 103.8, 110.5, 112.4, 127.9, 139.4, 144.2, 148.7, 156.8, 167.3, 194.5 (Found : C, 70.90; H, 7.02; N, 3.89. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94%).

Methyl 2,7,7-trimethyl-4-(naphthalen-2-yl)-5-oxo-1,4,5,6,7,8 -hexahydroquinoline-3-carboxylate (**5o**) :

Yield : 0.322 g (86%); white solid; m.p. 296–298 °C; IR (KBr) ν_{max} : 3286, 3196, 3074, 2950, 2932, 1683, 1643, 1605, 1488, 1381, 1330, 1226, 1140, 1111, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.89 (3H, s), 1.05 (3H, s), 2.15–2.29 (4H, m), 2.44 (3H, s), 3.59 (3H, s), 5.25 (1H, s), 6.02 (1H, br s), 7.35–7.39 (2H, m), 7.50 (1H, d, *J* 8.4 Hz), 7.64–7.71 (2H, m), 7.74 (2H, t, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.3, 26.3, 28.9, 31.8, 35.9, 50.2, 103.8, 110.3, 124.9, 125.2, 126.5, 126.7, 126.8, 127.3, 131.5, 132.7, 144.5, 144.9, 149.3, 167.4, 194.9 (Found : C, 76.70; H, 6.66; N, 3.68. Calcd. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73%).

Methyl 2,7,7-trimethyl-5-oxo-4-(thiophen-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5p**) :

Yield : 0.291 g (88%); white solid; m.p. 218–220 °C; IR (KBr) ν_{max} : 3279, 3206, 3082, 2951, 1705, 1647, 1608, 1488, 1381, 1309, 1281, 1212, 1170, 1123, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.02 (3H, s), 1.09 (3H, s), 2.26 (4H, s), 2.37 (3H, s), 3.68 (3H, s), 5.41 (1H, s), 6.37 (1H, br s), 6.80 (2H, s), 7.02 (1H, d, *J* 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 18.0, 26.3, 28.8, 31.7, 34.5, 49.9, 50.1, 54.3, 103.9, 110.5, 112.4, 127.9, 139.4, 144.2, 148.6, 156.8, 167.3, 194.5 (Found : C, 65.18; H, 6.34; N, 4.18. Calcd. for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23%).

Synthesis of compounds **6a-d** :

Ethyl 2-methyl-5-oxo-4-(p-tolyl)-5,6,7,8-tetrahydroquinoline-3-carboxylate (**6a**) :

Yield : 0.307 g (95%); white solid; m.p. 138–140 °C; IR (KBr) ν_{max} : 2965, 2934, 2877, 1731, 1687, 1549, 1514, 1383, 1324, 1272, 1220, 1175, 1135, 1086, 1076, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.89 (3H, t, *J* 7.2 Hz), 2.06–2.13 (2H, m), 2.30 (3H, s), 2.52 (3H, s) 2.49–2.55 (2H, m), 3.09–3.13 (2H, m), 3.92 (2H, q, *J* 7.2 Hz), 6.94 (2H, d, *J* 8.0 Hz), 7.09 (2H, d, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.7, 21.4, 21.5, 23.3, 33.7, 40.2, 61.5, 124.3, 127.5, 128.6, 130.6, 134.6, 137.5, 149.2, 157.9, 164.5, 167.7, 197.3 (Found : C, 74.23; H, 6.50; N, 4.26. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33%).

Ethyl 4-(4-fluorophenyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**6b**) :

Yield : 0.310 g (95%); white solid; m.p. 105–106 °C; IR (KBr) ν_{max} : 3056, 2950, 2865, 1731, 1682, 1547, 1431, 1401, 1285, 1231, 1210, 1083, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.98 (3H, t, *J* 7.2 Hz), 2.16–2.19 (2H, m), 2.59 (3H, s), 2.56–2.62 (2H, m),

3.18–3.21 (2H, m), 3.99 (2H, q, *J* 7.2 Hz), 7.04–7.12 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 13.9, 21.5, 23.3, 33.7, 40.2, 61.7, 114.9, 115.1, 124.1, 128.6, 129.5, 129.6, 133.5, 148.1, 158.2, 164.7, 167.5, 197.3 (Found : C, 69.65; H, 5.45; N, 4.24. Calcd. for $C_{19}H_{18}FNO_3$: C, 69.71; H, 5.54; N, 4.28%).

Methyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**6c**) :

Yield : 0.324 g (95%); white solid; m.p. 142–143 °C; IR (KBr) ν_{max} : 3030, 2947, 2871, 1732, 1694, 1574, 1511, 1433, 1283, 1231, 1221, 1163, 1151, 1081, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.11 (6H, s), 2.47 (2H, s), 2.59 (3H, s), 3.09 (2H, s), 3.52 (3H, s), 7.06–7.09 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 23.4, 28.3, 32.5, 47.6, 52.4, 53.7, 114.9, 115.1, 123.0, 129.3, 129.4, 130.2, 133.3, 147.7, 158.5, 163.5, 168.1, 197.2 (Found : C, 70.32; H, 5.86; N, 4.04. Calcd. for $C_{20}H_{20}FNO_3$: C, 70.37; H, 5.91; N, 4.10%).

Methyl 2,7,7-trimethyl-4-(naphthalen-2-yl)-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**6d**) :

Yield : 0.335 g (90%); white solid; m.p. 134–135 °C; IR (KBr) ν_{max} : 2978, 2956, 2930, 2869, 1727, 1685, 1549, 1509, 1459, 1266, 1218, 1182, 1162, 1085, 1065, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.12–1.14 (6H, m), 2.47–2.49 (2H, m), 2.62 (3H, s), 3.12 (2H, s), 3.37 (3H, s), 7.25 (1H, d, *J* 8.4 Hz), 7.46–7.49 (2H, m), 7.57 (1H, s), 7.79 (1H, d, *J* 7.6 Hz), 7.84 (2H, t, *J* 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 23.4, 28.2, 28.3, 32.6, 47.6, 52.3, 53.7, 123.2, 125.8, 126.2, 126.3, 126.4, 127.2, 128.0, 128.2, 130.4, 132.8, 133.0, 135.3, 148.7, 158.6, 163.5, 168.2, 197.1 (Found : C, 77.12; H, 6.15; N, 3.70. Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75%).

Acknowledgement

PRB is thankful to UGC, New Delhi. RSB and ML are grateful to CSIR, New Delhi, India for their research fellowship. We also acknowledge to the Department of Science and Technology (DST), New Delhi for financial support for creating single crystal XRD facility in the Department of Chemistry under FIST programme (Sl. No. : SR/FST/CSII-007/2003). The authors are grateful to the Director, IIT Guwahati for providing general laboratory facilities.

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16. Complete crystallographic data of **5f** and **6c** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 886705, 886708 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax : 44-1223-336033, E-mail : deposit@ccdc.cam.ac.uk or via : www.ccdc.cam.ac.uk).