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Ceric Ammonium Nitrate (CAN) catalyzes the one-pot synthesis of polyhydroquinoline via the Hantzsch reaction

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Abstract—A facile and efficient one-pot synthesis of high yields of polyhydroquinoline derivatives at ambient temperature using Ceric Ammonium Nitrate (CAN) as catalyst via the Hantzsch reaction was reported. The process is simple and environmentally benign and the catalyst is commercially available and inexpensive.

1. Introduction

In recent years, much attention has been focused on the synthesis of 1,4-dihydropyridyl compounds, due to their significant biological activity.[1] Cardiovascular agents such as nifedipine, nicardipine, amlodipine, and other related derivatives are dihydropyridyl compounds, which are effective for the treatment of hypertension.[2] 4-Aryl-1,4-dihydropyridines are analogues of NADH coenzymes, which have been explored for their calcium channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as bronchodilator, antiatherosclerotic, antitumour, vasodilator, antidiabetic, geroprotective, and heptaprotective agents.[3] Extensive studies indicate that these compounds exhibit different medical functions, acting as neuroprotectants, platelet antiaggregators, cerebral antiischemic agents, and chemosensitizers.[4] For these reasons, polyhydroquinoline compounds not only have attracted the attention of chemists to synthesize but also represent an interesting research challenge. Numerous methods have been reported for the synthesis of polyhydroquinoline derivatives, because of the biological importance associated with these compounds. The classical method involves the three-component coupling of an aldehyde with ethyl acetoacetate, and ammonia in acetic acid or in refluxing alcohol.[5,6] However, these methods suffer from several drawbacks such as a long reaction time, an excess of organic solvent, lower product yields, and harsh refluxing conditions. Thus, chemists have developed several alternate and more efficient methods for the synthesis of polyhydroquinoline derivatives, which include the use of microwaves,[7] ionic liquids,[8] refluxing at high temperature,[9] TMSCl–NaI,[10] metal triflates,[11] and I_2.[12] However, the use of high temperatures, expensive metal precursors, catalyst that are harmful to the environment, and long reaction times limits the use of these methods. Thus, the development of a simple and efficient method for the preparation of polyhydroquinoline derivatives is an active area of research and there is scope for further improvement involving milder reaction conditions and higher product yields.

The use of Ceric Ammonium Nitrate (CAN) has recently received considerable attention as an inexpensive, nontoxic, commercially available catalyst for various organic transformations to afford the corresponding products in excellent yields. Due to the numerous advantages associated with this eco-friendly compound, CAN has been explored as a powerful catalyst for different reactions, such as oxidation, nitration, 1,3-dipolar cycloaddition, thiocyanation, protection, esterification, 1,4-addition, and the Biginelli reaction.[13] Because polyhydroquinoline derivatives are important biologically active compounds, which have potential medical applications, improvement and the development of a preparation of this type of compound using CAN are worthy of study.

2. Results and discussion

We had the opportunity to further explore the catalytic activity of CAN in the synthesis of 1,4-dihydropyridines. Herein, we wish to report on a novel synthesis of 1,4-DHP promoted by a catalytic amount of CAN under ambient conditions to give excellent yields. In an initial endeavor, 1 equiv each of benzaldehyde **1a**, 1,3-cyclohexanedione **2**, ethyl acetoacetate **3a**, and ammonium acetate **4** were stirred at ambient temperature in ethanol. After 4 h, only 56% of the expected

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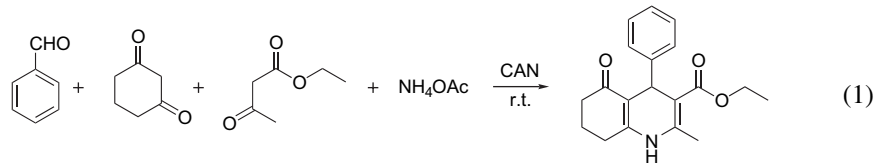
product **5aa** was obtained when after workup and recrystallization of the crude product from ethanol (Eq. 1 and entry 1 of Table 1). To improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of a catalytic amount of 2 mol % of CAN under similar conditions. Surprisingly, a significant improvement was observed and the yield of **5aa** was dramatically increased to 93% after stirring; the mixture was stirred for only 2 h (entry 2). With this optimistic result in hand, we further investigated the best reaction conditions by using different amounts of CAN. An increase in the quantity of CAN from 2 mol % to 5 mol % not only decreased the reaction time from 2 h to 1.5 h, but also increased the product yield slightly from 93% to 98% (entry 3). Although the use of 10 mol % of CAN permitted the reaction time to be decreased to 1 h, the yield unexpectedly decreased to 65% (entry 4). A possible explanation for the low product yield is that the starting material or the product may have been destroyed during the reaction when excess amount (10 mol %) of CAN was used in the exothermic reaction and that 5 mol % CAN was sufficient to catalyze the reaction effectively.

Based on above observations, we conducted the same reactions using aromatic and heteroaromatic aldehydes **1b**–**1k**, **2**, **3a**, and **4** in the presence of 5 mol % of CAN under similar conditions. As expected, satisfactory results were observed and the results are summarized as Eq. 2 and Table 2. Both aromatic (entries 1–9) and heteroaromatic aldehydes (entries 10 and 11) gave the corresponding products in good yields (88–98%). Concerning aromatic aldehyde, it appears that the presence of different or the same substituted groups does not have a significant effect on the final products.

We next tried to observe the effect of substituents in 1,3-cyclohexanedione **2** using 5,5-dimethyl-1,3-cyclohexanedione **6**. Both aromatic and heteroaromatic aldehydes **1** reacted well with **6**, **3a**, and **4** in the presence of 5 mol % of CAN to afford **7** in good to high yields under similar conditions (Table 3). Compared to the results shown in Table 2, the decrease in reaction time can be explained by the assumption that **6** is slightly more reactive than **2** in most cases due to the presence of the methyl groups in the ring.

Finally, we also examined whether other β-keto compounds such as 2,4-pentanedione **3b**, methyl acetoacetate **3c**, and 2-methoxyethyl acetoacetate **3d** also react with these reagents to produce similar results. Aromatic and heteroaromatic aldehydes **1** such as benzaldehyde **1a** and 2-thiophenecarboxaldehyde **1k** were reacted with **2**, **3b**–**3d**, and **4** in the presence of 5 mol % of CAN to afford the expected product

Table 1. Optimizing the reaction conditions[a] **(1)**



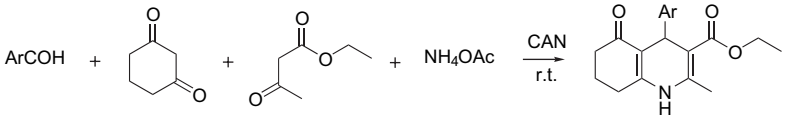
(1)

1a **2** **3a** **4** **5aa**

Entry	CAN (equiv)	Time (h)	Yield (%)[b]
1	0	4	56
2	0.02	2	93
3	0.05	1.5	98
4	0.1	1	65

[a] Benzaldehyde/1,3-cyclohexanedione/ethyl acetoacetate/ammonium acetate = 1:1:1:1.
[b] Isolated yields.

Table 2. CAN catalyzed the synthesis of polyhydroquinoline derivatives through Hantzsch reaction **(2)**



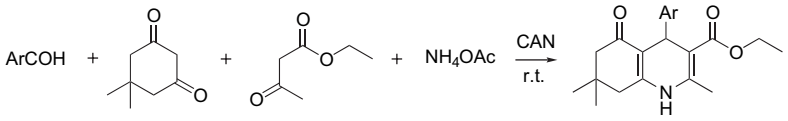
(2)

1 **2** **3a** **4** **5**

Entry	1	Ar	Time	Product	Yield (%)[a]	Mp (°C)
1	**1a**	Ph	1.5 h	**5aa**	98	240–241
2	**1b**	*p*-MeC_6H_4	1.5 h	**5ba**	98	241–242
3	**1c**	*p*-$OMeC_6H_4$	2.5 h	**5ca**	88	193–195
4	**1d**	*p*-FC_6H_4	2 h	**5da**	98	243–244
5	**1e**	*p*-ClC_6H_4	4 h	**5ea**	90	234–235
6	**1f**	*p*-HOC_6H_4	2.5 h	**5fa**	93	220–222
7	**1g**	*o*-$NO_2C_6H_4$	50 min	**5ga**	93	190–191
8	**1h**	*m*-$NO_2C_6H_4$	50 min	**5ha**	98	198–200
9	**1i**	*p*-$NO_2C_6H_4$	25 min	**5ia**	98	204–205
10	**1j**	2-Furyl	35 min	**5ja**	90	210–212
11	**1k**	2-Thienyl	25 min	**5ka**	90	233–234

[a] Isolated yields.

Table 3. CAN catalyzed the synthesis of polyhydroquinoline derivatives through Hantzsch reaction with 5,5-dimethyl-1,3-cyclohexanedione **(3)**



(3)

1 **6** **3a** **4** **7**

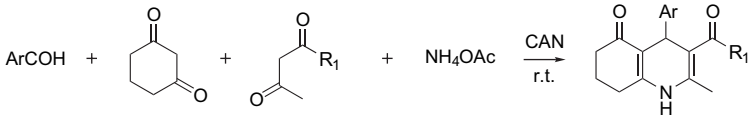
Entry	1	Ar	Time	Product	Yield (%)[a]	Mp (°C)
1	**1a**	Ph	1 h	**7aa**	92	209–210
2	**1c**	*p*-$MeOC_6H_4$	1.75 h	**7ca**	98	243–245
3	**1e**	*p*-ClC_6H_4	35 min	**7ea**	88	230–232
4	**1f**	*p*-HOC_6H_4	2 h	**7fa**	93	237–238
5	**1k**	2-Thienyl	1 h	**7ka**	85	224–226

[a] Isolated yields.

8 in medium to high yields (Table 4). It was surprising to find that the use of **3b** only led to medium yields (60–65%) of products (entries 1 and 4) compared to substrates **3c** and **3d** (entries 2, 3, 5, and 6). A possible explanation of the differences is that **3b** (approximate pK_a value of 9) is much more reactive than **3c** and **3d** (approximate pK_a value of 11) so that the other side reactions might have occurred or side reaction products also could have been formed when **3b** was used.

It is important to understand the role of CAN in the reaction. One possibility is that both Ce(IV) and NH_4^+ in CAN can be used as Lewis acids to catalyze the reaction. To prove this assumption, different Lewis acids such as CeF_4, NH_4Cl, and $CeCl_3\cdot 7H_2O$ were used in the same reactions (Table 5). Surprisingly, CeF_4 and NH_4Cl catalyzed the reaction more efficiently than $CeCl_3\cdot 7H_2O$. The reaction completed more rapidly and the yields were also higher when CeF_4 and NH_4Cl were used (entries 1 and 2). These results indicate that both cerium (IV) ions and ammonium ions, which are present in CAN actually can also catalyze the reaction. Although $CeCl_3\cdot 7H_2O$ can also induce the reaction, the results were not as good as the two other reagents.

Table 4. CAN catalyzed the synthesis of polyhydroquinoline derivatives through Hantzsch reaction with different β-keto compounds **(4)**



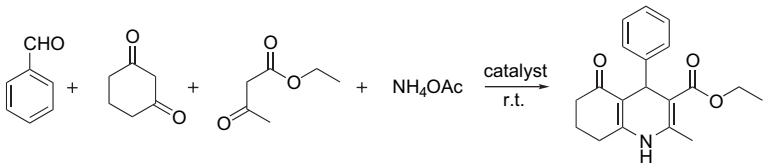
(4)

1 **2** **3b-d** **4** **8**

Entry	1	3	R_1	Time (h)	Product	Yield (%)[a]	Mp (°C)
1	**1a**	**3b**	CH_3	1	**8ab**	65	229–230
2	**1a**	**3c**	OMe	1	**8ac**	85	222–224
3	**1a**	**3d**	OCH_2CH_2OMe	1	**8ad**	87	150–152
4	**1k**	**3b**	CH_3	5	**8kb**	60	218–219
5	**1k**	**3c**	OMe	2	**8kc**	90	216–217
6	**1k**	**3d**	OCH_2CH_2OMe	7	**8kd**	64	207–209

[a] Isolated yields.

Table 5. To address the role of CAN in this reaction[a] **(5)**



(5)

1a **2** **3a** **4** **5aa**

Entry	Catalyst (equiv)	Time (h)	Yield (%)[b]
1	CeF_4 (0.05)	1.75	90
2	NH_4Cl (0.1)	2	85
3	$CeCl_3\cdot 7H_2O$ (0.05)	4	60

[a] Benzaldehyde/1,3-cyclohexanedione/ethyl acetoacetate/ammonium acetate = 1:1:1:1.
[b] Isolated yields.

3. Conclusion

In conclusion, we successfully developed a facile and efficient method for preparing a variety of 4-substituted-1,4-dihydropyridines from the reactions of different aromatic or heteroaromatic aldehydes, β-keto compounds, including 1,3-cyclohexanedione, 5,5-dimethyl-1,3-cyclohexanedione, or 2,4-pentadione, and alkyl acetoacetate, and ammonium acetate in the presence of a catalytic amount of CAN at room temperature. The catalytic activity of CAN is remarkable and the use of the environmentally benign, commercially available CAN as catalyst in the synthesis of 4-substituted-1,4-dihydropyridines in good yields is also significant. The advantages such as shorter reaction times, milder conditions, simplicity of the reaction, good product yields, and the easy procedures involved in the reaction make the inexpensive and commercially available CAN a powerful catalyst for the synthesis of different organic compound.

4. Experimental

4.1. Material and general

All reactions were performed at room temperature. All chemicals were purchased from Aldrich Chemical Co. and the solvent were used directly without further purification. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates. MS or HRMS were measured by JEOL JMS-D300 or JEOL JMS-HX110 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Aavance EX 400.

4.1.1. Typical experimental procedure for the synthesis of Hantzsch polyhydroquinoline derivatives 5, 7, and 8. A typical experimental procedure for the preparation of **5** is described as follows: a 10 mL round-bottomed flask charged with aldehyde **1** (1.0 mmol), 1,3-cyclohexanedione **2** or 5,5-dimethyl-1,3-cyclohexanedione **6** (1.0 mmol), 2,4-pentadione or acetoacetate derivatives **3** (1.0 mmol), ammonium acetate **4** (1.0 mmol), and Ceric Ammonium Nitrate (CAN) (0.05 mmol) followed by 0.5 mL of ethanol. The mixture was then stirred at room temperature until the reaction was completed (monitored by TLC). The reaction mixture was treated with brine solution, extracted with ethyl acetate (2×20 mL). After evaporation of the solvent, the crude yellow product was recrystallized from ethanol to give a yellow or brown solid.

4.1.1.1. 2-Methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5aa). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, 3H, J=6.8 Hz), 1.80–2.10 (m, 2H), 2.30–2.44 (m, 7H), 4.05 (q, 2H, J=6.8 Hz), 5.09 (s, 1H), 6.07 (s, 1H), 7.10 (t, 1H, J=7.6 Hz), 7.20 (t, 2H, J=7.6 Hz), 7.30 (d, 2H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.16, 19.34, 21.01, 27.46, 36.38, 37.00, 59.78, 106.06, 113.46, 125.99, 127.90, 127.98, 143.30, 147.12, 149.58, 167.41, 195.52. MS *m/z* (relative intensity) 311 (M^+, 27), 282 (8), 235 (15), 234 (100), 206 (27). HRMS calcd for $C_{19}H_{21}NO_3$ (M^+) 311.1521; found 311.1526.

4.1.1.2. 2-Methyl-5-oxo-4-(4-methylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ba). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, 3H, J=7.2 Hz), 1.80–2.10 (m, 2H), 2.20–2.51 (m, 10H), 4.07 (q, 2H, J=7.2 Hz), 5.05 (s, 1H), 7.00 (d, 2H, J=7.6 Hz), 7.18 (d, 2H, J=7.6 Hz), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.15, 18.92, 20.93, 26.93, 35.88, 37.03, 59.66, 105.71, 112.68, 127.69, 128.51, 129.56, 135.28, 143.87, 144.42, 151.42, 167.63, 196.29. MS *m/z* (relative intensity) 325 (M^+, 33), 296 (10), 235 (15), 234 (100), 206 (22). HRMS calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1678; found 325.1685.

4.1.1.3. 2-Methyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ca). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H, J=6.8 Hz), 1.80–2.10 (m, 2H), 2.30–2.60 (m, 7H), 3.74 (s, 3H), 4.06 (q, 2H, J=6.8 Hz), 5.04 (s, 1H), 5.95 (s, 1H), 7.10 (d, 2H, J=8.4 Hz), 7.20 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.20, 19.36, 21.05, 27.49, 35.52, 37.02, 55.12, 59.77, 106.33, 113.29, 113.72, 128.94, 139.67, 142.92, 149.20, 157.80, 167.47, 195.71. MS *m/z* (relative intensity) 341 (M^+, 52), 312 (20), 268 (16), 235 (15), 234 (100), 206 (33). HRMS calcd for $C_{20}H_{23}NO_4$ (M^+) 341.1627; found 341.1623.

4.1.1.4. 2-Methyl-5-oxo-4-(4-fluorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5da). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.17 (t, 3H, J=7.2 Hz), 1.80–2.10 (m, 2H), 2.20–2.70 (m, 7H), 4.06 (q, 2H, J=7.2 Hz), 5.07 (s, 1H), 6.03 (s, 1H), 6.85–6.89 (m, 2H), 7.23–7.27 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.60, 18.72, 21.26, 26.58, 35.55, 37.15, 59.54, 103.89, 111.52, 114.78, 114.99, 129.54, 129.62, 144.49, 145.57, 151.90, 167.27, 195.16. MS *m/z* (relative intensity) 329 (M^+, 36), 235 (15), 234 (100), 206 (28). HRMS calcd for $C_{19}H_{20}NFO_3$ (M^+) 329.1427; found 329.1425.

4.1.1.5. 2-Methyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ea). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, 3H, J=7.2 Hz), 1.80–2.10 (m, 2H), 2.30–2.50 (m, 7H), 4.05 (q, 2H, J=7.2 Hz), 5.05 (s, 1H), 6.34 (s, 1H), 7.18 (d, 2H, J=8.8 Hz), 7.24 (d, 2H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.17, 19.33, 20.96, 27.37, 36.07, 36.87, 59.93, 105.77, 112.96, 128.01, 129.40, 131.61, 143.53, 145.63, 150.29, 167.22, 195.92. MS *m/z* (relative intensity) 345 (M^+, 24), 316 (12), 235 (16), 234 (100), 206 (36). HRMS calcd for $C_{19}H_{20}ClNO_3$ (M^+) 345.1132; found 345.1130.

4.1.1.6. 2-Methyl-5-oxo-4-(4-hydroxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5fa). ^{1}H NMR (Acetone-d_6, 400 MHz) δ 1.17 (t, 3H, J=7.2 Hz), 1.70–2.00 (m, 2H), 2.19–2.23 (m, 1H), 2.34 (s, 3H), 2.50–2.54 (m, 2H), 4.02 (q, 2H, J=7.2 Hz), 5.05 (s, 1H), 6.63 (d, 2H, J=8.4 Hz), 7.08 (d, 2H, J=8.4 Hz). ^{13}C NMR (Acetone-d_6, 100 MHz) δ 15.07, 19.12, 22.41, 27.75, 36.57, 38.23, 60.24, 106.30, 113.84, 115.66, 130.14, 140.66, 145.27, 151.47, 156.63, 168.50, 195.72. MS *m/z* (relative intensity) 327 (M^+, 37), 298 (15), 254 (12), 235 (15), 234 (100), 206 (35). HRMS calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1471; found 327.1465.

4.1.1.7. 2-Methyl-5-oxo-4-(2-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ga). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (t, 3H, J=7.2 Hz), 1.70–2.00 (m, 2H), 2.20–2.50 (m, 7H), 4.02–4.09 (m, 2H), 5.87 (s, 1H), 7.22–7.24 (m, 1H), 7.39 (s, 1H), 7.40–7.60 (m, 2H), 7.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.82, 18.66, 20.70, 26.68, 32.23, 36.63, 59.67, 104.55, 111.86, 123.49, 126.41, 131.01, 132.49, 141.75, 145.20, 148.12, 152.27, 167.22, 196.11. MS *m*/*z* (relative intensity) 356 (M^+, 26), 327 (12), 235 (16), 234 (100), 206 (36). HRMS calcd for $C_{19}H_{20}N_2O_5$ (M^+) 356.1372; found 356.1380.

4.1.1.8. 2-Methyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ha). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H, J=7.2 Hz), 1.80–2.10 (m, 2H), 2.30–2.50 (m, 7H), 4.07 (q, 2H, J=7.2 Hz), 5.18 (s, 1H), 6.88 (s, 1H), 7.35–7.40 (m, 1H), 7.72 (d, 2H, J=8.0 Hz), 7.98 (d, 2H, J=8.0 Hz), 8.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.19, 19.30, 21.02, 27.24, 33.01, 36.88, 60.07, 105.77, 112.29, 121.26, 122.89, 128.65, 134.83, 144.63, 148.29, 149.42, 151.03, 167.02, 196.03. MS *m*/*z* (relative intensity) 356 (M^+, 12), 339 (15), 235 (15), 234 (100), 206 (31). HRMS calcd for $C_{19}H_{20}N_2O_5$ (M^+) 356.1372; found 356.1378.

4.1.1.9. 2-Methyl-5-oxo-4-(4-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ia). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, 3H, J=6.8 Hz), 1.80–2.10 (m, 2H), 2.30–2.60 (m, 7H), 4.03–4.09 (m, 2H), 5.18 (s, 1H), 7.30 (s, 1H), 7.48 (d, 2H, J=7.6 Hz), 8.10 (d, 2H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.08, 19.19, 20.94, 27.12, 36.88, 37.13, 60.10, 104.63, 111.89, 123.32, 128.99, 134.83, 144.91, 146.41, 151.62, 154.78, 167.07, 196.23. MS *m*/*z* (relative intensity) 356 (M^+, 12), 339 (40), 235 (17), 234 (100), 206 (50). HRMS calcd for $C_{19}H_{20}N_2O_5$ (M^+) 356.1372; found 356.1365.

4.1.1.10. 2-Methyl-5-oxo-4-(furan-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ja). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 3H, J=7.2 Hz), 1.90–2.10 (m, 2H), 2.30–2.60 (m, 7H), 4.12–4.19 (m, 2H), 5.27 (s, 1H), 5.95–5.99 (m, 1H), 6.02–6.10 (m, 1H), 6.20–6.26 (m, 1H), 7.21 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.27, 19.37, 21.08, 27.56, 30.21, 36.95, 59.88, 103.02, 104.74, 110.10, 140.81, 144.20, 150.56, 157.94, 167.23, 195.56. MS *m*/*z* (relative intensity) 301 (M^+, 50), 272 (22), 256 (19), 245 (29), 228 (100), 200 (19). HRMS calcd for $C_{17}H_{19}NO_4$ (M^+) 301.1314; found 301.1313.

4.1.1.11. 2-Methyl-5-oxo-4-(thiophene-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (5ka). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H, J=7.2 Hz), 1.80–2.10 (m, 2H), 2.30–2.50 (m, 7H), 4.07 (q, 2H, J=7.2 Hz), 5.45 (s, 1H), 6.18 (s, 1H), 6.80–6.90 (m, 2H), 7.13–7.20 (d, 1H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.27, 19.35, 21.08, 27.42, 31.11, 36.98, 59.96, 105.59, 112.81, 123.15, 123.33, 126.46, 143.73, 149.85, 151.18, 167.15, 195.57. MS *m*/*z* (relative intensity) 317 (M^+, 100), 288 (67), 244 (68), 234 (55), 206 (45), 161 (24). HRMS calcd for $C_{17}H_{19}SNO_3$ (M^+) 317.1086; found 317.1084.

4.1.1.12. 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (7aa). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 1.07(s, 3H), 1.20 (t, 3H, J=7.2 Hz), 2.10–2.40 (m, 7H), 4.06 (q, 2H, J=7.2 Hz), 5.06 (s, 1H), 6.22 (s, 1H), 7.10 (t, 1H, J=7.6 Hz), 7.20 (t, 2H, J=7.6 Hz), 7.31 (d, 2H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.18, 19.22, 27.19, 29.33, 32.50, 36.25, 41.27, 50.66, 59.87, 106.16, 112.56, 125.97, 127.88, 127.99, 143.35, 146.52, 148.58, 167.61, 195.97. MS *m*/*z* (relative intensity) 339 (M^+, 12), 263 (16), 262 (100), 234 (28). HRMS calcd for $C_{21}H_{25}NO_3$ (M^+) 339.1834; found 339.1840.

4.1.1.13. 2,7,7-Trimethyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (7ca). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (s, 3H), 1.07 (s, 3H), 1.21 (t, 3H, J=7.2 Hz), 2.13–2.36 (m, 7H), 3.74 (s, 3H), 4.06 (q, 2H, J=7.2 Hz), 5.00 (s, 1H), 6.01 (s, 1H), 6.74 (d, 2H, J=8.4 Hz), 7.22 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.21, 19.40, 27.17, 29.40, 32.69, 35.67, 41.12, 50.72, 55.10, 59.77, 106.36, 112.42, 113.23, 128.95, 139.56, 139.56, 143.02, 147.72, 157.75, 167.49, 195.52. MS *m*/*z* (relative intensity) 369 (M^+, 33), 340 (13), 263 (15), 262 (100), 234 (23). HRMS calcd for $C_{22}H_{27}NO_4$ (M^+) 369.1940; found 369.1931.

4.1.1.14. 2,7,7-Trimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (7ea). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 3H), 1.06 (s, 3H), 1.17 (t, 3H, J=7.2 Hz), 2.10–2.50 (m, 7H), 4.02–4.10 (m, 2H), 5.04 (s, 1H), 6.13 (s, 1H), 7.15–7.20 (m, 2H), 7.25–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.17, 19.30, 27.04, 29.39, 32.64, 36.20, 40.93, 50.65, 59.87, 105.65, 111.71, 127.95, 129.39, 131.56, 143.71, 145.58, 167.21, 195.56. MS *m*/*z* (relative intensity) 373 (M^+, 14), 263 (16), 262 (100), 234 (26). HRMS calcd for $C_{21}H_{24}ClNO_3$ (M^+) 373.1445; found 373.1442.

4.1.1.15. 2,7,7-Trimethyl-5-oxo-4-(4-hydroxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (7fa). ^{1}H NMR (Acetone-d_6, 400 MHz) δ 0.91 (s, 3H), 1.04 (s, 3H), 1.21 (t, 3H, J=7.2 Hz), 2.13–2.36 (m, 7H), 3.74 (s, 3H), 4.06 (q, 2H, J=7.2 Hz), 5.00 (s, 1H), 6.01 (s, 1H), 6.74 (d, 2H, J=8.4 Hz), 7.22 (d, 2H, J=8.4 Hz). ^{13}C NMR (Acetone-d_6, 100 MHz) δ 15.01, 19.09, 19.16, 27.49, 33.40, 36.70, 41.14, 51.77, 54.98, 60.20, 106.29, 112.65, 115.57, 130.13, 131.38, 140.43, 145.31, 149.71, 156.62, 168.41, 195.36. MS *m*/*z* (relative intensity) 356 (M^+, 28), 326 (12), 282 (11), 263 (14), 262 (100), 234 (24). HRMS calcd for $C_{21}H_{25}NO_4$ (M^+) 355.1784; found 355.1776.

4.1.1.16. 2,7,7-Trimethyl-5-oxo-4-(thiophene-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (7ka). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 3H), 1.13 (s, 3H), 1.28(t, 3H, J=7.2 Hz), 2.20–2.55 (m, 7H), 4.17 (q, 2H, J=7.2 Hz), 5.42 (s, 1H), 6.20 (s, 1H), 6.81–6.90 (m, 2H), 7.00–7.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.28, 19.40, 27.25, 29.50, 31.22, 32.69, 41.04, 50.67, 59.96, 105.55, 111.68, 123.05, 123.42, 126.40, 143.87, 148.31, 150.98, 167.17, 195.36. MS *m*/*z* (relative intensity) 345 (M^+, 100), 316 (65), 272 (68), 262

(69), 234 (34). HRMS calcd for $C_{19}H_{23}NSO_3$ (M^+) 345.1399; found 345.1397.

4.1.1.17. 2-Methyl-3-acetyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (8ab).[14] ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80–2.00 (m, 2H), 2.14 (s, 3H), 2.32–2.43 (m, 7H), 5.13 (s, 1H), 6.22 (s, 1H), 7.14 (t, 1H, J=7.6 Hz), 7.22–7.32 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.14, 20.81, 27.42, 29.50, 36.98, 37.01, 113.10, 113.98, 126.37, 127.89, 128.38, 143.04, 145.91, 149.21, 195.78, 199.60.

4.1.1.18. 2-Methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (8ac). ^1H NMR (DMSO-d_6, 400 MHz) δ 1.60–1.75 (m, 1H), 1.85–2.00 (m, 1H), 2.20–2.60 (m, 7H), 3.56 (s, 3H), 4.95 (s, 1H), 7.00–7.30 (m, 5H), 9.19 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.25, 20.78, 26.12, 35.38, 36.71, 50.66, 103.16, 111.12, 125.68, 127.21, 127.91, 145.24, 147.63, 151.41, 167.39, 194.69. MS *m/z* (relative intensity) 297 (M^+, 16), 221 (15), 220 (100). HRMS calcd for $C_{18}H_{19}NO_3$ (M^+) 297.1365; found 297.1366.

4.1.1.19. 2-Methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (2-methoxyethyl) ester (8ad). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.80–2.00 (m, 2H), 2.20–2.50 (m, 7H), 3.31 (s, 3H), 3.52 (t, 2H, J=4.8 Hz), 4.14–4.18 (m, 2H), 5.11 (s, 1H), 6.66 (s, 1H), 7.08–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.24, 20.99, 27.22, 36.39, 37.01, 58.77, 62.75, 70.44, 105.53, 113.16, 125.97, 127.88, 127.95, 144.03, 147.12, 150.20, 167.35, 195.89. MS *m/z* (relative intensity) 341 (M^+, 12), 265 (12), 264 (100). HRMS calcd for $C_{20}H_{23}NO_4$ (M^+) 341.1627; found 341.1620.

4.1.1.20. 2-Methyl-3-acetyl-5-oxo-4-(thiophene-2-yl)-1,4,5,6,7,8-hexahydroquinoline (8kb).[14] ^1H NMR ($CDCl_3$, 400 MHz) δ 1.92–2.01 (m, 2H), 2.22 (s, 3H), 2.34–2.48 (m, 7H), 5.39 (s, 1H), 6.80–6.88 (m, 2H), 7.01–7.03 (m, 1H), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.00, 20.92, 27.05, 29.27, 32.06, 36.87, 112.61, 113.31, 123.68, 123.87, 126.67, 144.18, 150.13, 150.62, 195.85, 199.10.

4.1.1.21. 2-Methyl-5-oxo-4-(thiophene-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (8kc). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.94–2.01 (m, 2H), 2.30–2.55 (m, 7H), 3.72 (s, 3H), 5.42 (s, 1H), 6.79–6.86 (m, 2H), 6.94 (br, 1H), 7.02–7.06 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.14, 21.05, 27.16, 36.97, 51.11, 104.97, 112.42, 123.12, 123.19, 126.53, 144.58, 151.15, 167.68, 196.00. MS *m/z* (relative intensity) 303 (M^+, 90), 288 (25), 244 (57), 220 (100). HRMS calcd for $C_{16}H_{17}NSO_3$ (M^+) 303.0929; found 303.0927.

4.1.1.22. 2-Methyl-5-oxo-4-(thiophene-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid (2-methoxyethyl) ester (8kd). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93–2.01 (m, 2H), 2.32–2.46 (m, 7H), 3.33 (s, 3H), 3.58 (t, 2H, J=4.8 Hz), 4.22–4.27 (m, 2H), 5.51 (s, 1H), 6.80–6.83 (m, 2H), 7.01–7.07 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.18, 21.05, 27.09, 31.12, 36.99, 58.80, 62.89, 70.47, 104.91, 112.40, 123.09, 123.33, 126.50, 144.69, 150.79, 151.27, 167.14, 195.89. MS *m/z* (relative intensity) 347 (M^+, 100), 288 (65), 264 (48), 244 (70). HRMS calcd for $C_{18}H_{21}NSO_4$ (M^+) 347.1191; found 347.1191.

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