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One-step, synthesis of Hantzsch esters and polyhydroquinoline derivatives in fluoro alcohols

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ABSTRACT

Hantzsch 1,4-dihydropyridine, polyhydroquinoline and 1,8-dioxodecahydroacridines derivatives were synthesized in excellent yields in trifluoroethanol (TFE). The solvent (TFE) can be readily separated from reaction products and recovered in excellent purity for direct reuse.

1. Introduction

Multicomponent reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously [1–4]. Such processes are of great interest in diversity-oriented synthesis, especially to generate compound libraries for screening purposes. The Hantzsch [5] reaction and their products 1,4-dihydropyridines (DHP) have attracted immense attention of synthetic chemists due to their pharmacological properties [6,7]. In particular, dihydropyridine drugs such as nifedipine, nicardipine and amlodipine are effective cardiovascular agents for the treatment of hypertension (Fig. 1).

In addition, the dihydropyridine unit has been widely employed as a hydride source for reductive amination [8]. Despite the potential importance of 1,4-dihydropyridyl compounds from a pharmaceutical, industrial, and synthetic point of view [9–11], comparatively few methods for their preparation have been reported. Classical method for the synthesis of 1,4-dihydropyridines is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia in acetic acid or by refluxing in alcohol [5,12]. However, this method involves long reaction time, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally gives low yields. In recent years, several new efficient methods have been developed including the use of microwave [13], TMS iodide [14], ionic liquid [15], $Bu_4N^+HSO_4^-$ [16], in situ generated HCl [17], $K_7[PW_{11}CoO_{40}]$ [18], metal triflates [19], I_2 [20] silica-supported acids [21,22], ceric ammonium nitrate [23], PTSA-SDS [24], tris(pentafluorophenyl)borane [25] and boronic acids [26,27]. These methods, however, suffer from drawbacks such as unsatisfactory yields, acidic or basic catalysts,

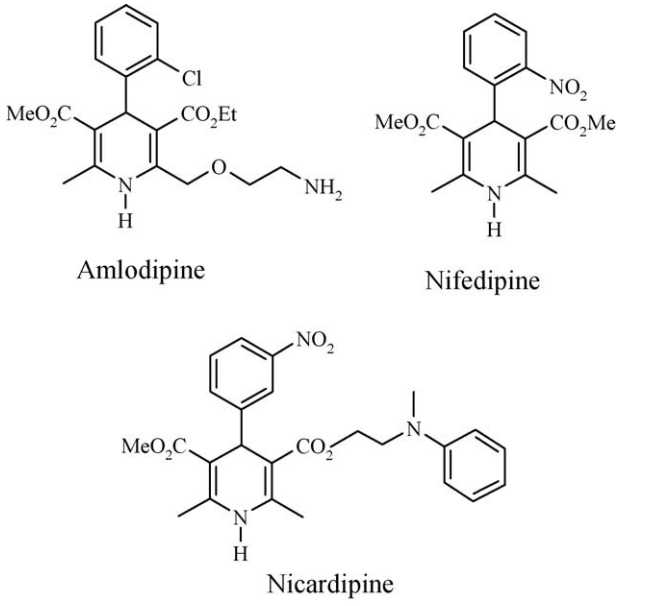

Fig. 1. Typical dihydropyridine drugs.

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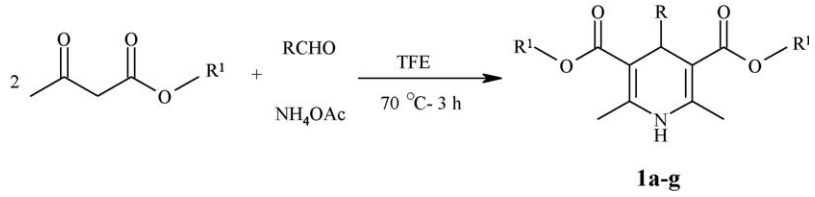
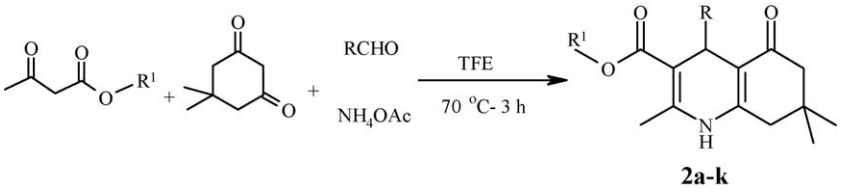
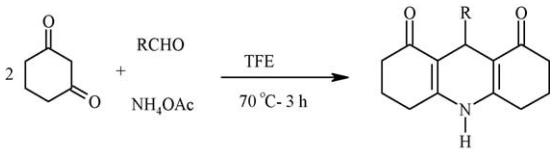


Scheme 1.



Scheme 2.

extended reaction times, elevated temperatures, tedious work-up, anhydrous organic solvents and the use of stoichiometric and/or relatively expensive reagents. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of 1,4-DHPs and polyhydroquinolines in terms of operational simplicity, reusability, economic viability, and greater selectivity. Fluoro alcohols are solvents with peculiar properties [28] such as low nucleophilicity, high polarity, strong hydrogen bond donating ability and ability to solvate water. The most commonly used and cheapest fluorinated alcohols are 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which are available on a commercial scale and with a relatively low toxicity [29–30]. These alcohols display interesting properties, such as solvent, co-solvent, or additives in various catalytic processes and consequently they are often used in studies of peptide and protein structure [31], solvolysis [32–35], their effect on various organic transformations [36–41] and notably the activation of hydrogen peroxide for oxidation, epoxidation and the Baeyer–Villiger rearrangement [42–48]. In continuation of our effort towards the development of efficient synthetic procedures for multicomponent reactions, we turned our attention towards the synthesis of 1,4-dihydropyridines and polyhydroquinoline derivatives. We report herein a practical synthesis of 1,4-dihydropyridines and polyhydroquinoline derivatives in trifluoroethanol at 70 °C.



3a R= Ph 98%

3b R= 4-ClC$_6$H$_4$ 95%

Scheme 3.

2. Results and discussion

In an initial endeavor, the reaction was carried out by simply mixing benzaldehyde, ethyl acetoacetate, and ammonium acetate (Scheme 1, Table 1, entry 1) at 70 °C in trifluoroethanol. The corresponding 1,4-dihydropyridine derivative **1a** was obtained in high yield (97%). The study was extended to α,β-unsaturated (entry 3), heteroaromatic (entry 5) and aliphatic (entries 4 and 10) aldehydes furnishing the products by a smooth cyclocondensation within 3 h. The yields in general are high regardless of the structural variations in aldehyde. The results are summarized in Scheme 1.

After successfully synthesizing a series of Hantzsch esters in excellent yields, we turned our attention towards the synthesis of

Table 1
Synthesis of 1,4-dihydropyridine derivatives through Hantzsch reaction in TFE[a].

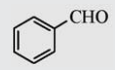
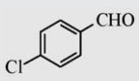
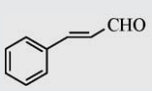
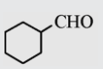
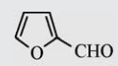
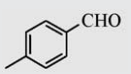
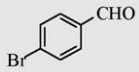
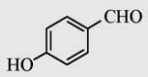
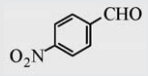
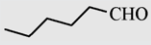
Entry	Aldehyde	R[1]	Yield (%)[b]	Product
1		Et	97	**1a**
2		Et	96	**1b**
3		Me	95	**1c**
4		Et	96	**1d**

Table 1 (*Continued*)

Entry	Aldehyde	R^1	Yield (%)[b]	Product
5		Et	98	**1e**
6		Et	98	**1f**
7		Et	97	**1g**
8		Et	95	**1h**
9		Et	96	**1i**
10		Et	97	**1j**

[a] Reaction condition: aldehyde (1 mmol), acetoacetate ester (2 mmol), NH_4OAc (1 mmol), TFE (2 mL), 3 h.
[b] Isolated yield.

polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction under similar conditions. We carried out the four-component coupling reaction of cyclic 1,3-diketone, aldehyde, acetoacetatic ester, and ammonium acetate in TFE (Scheme 2). Aliphatic, aromatic, heterocyclic and conjugated aldehydes afforded the desired products in high yields under the same reaction conditions as shown in Table 2.

It is noteworthy to mention that the structural variation of the aldehyde and substituents on the aromatic ring did not show any obvious effect on this conversion, because the desired products were obtained in high yields in relatively short reaction times. To further expand the scope of the reaction, we next examined the reactions with 2 equivalents of diketone with aromatic aldehydes (Scheme 3). As expected, these substrates underwent smooth, one-pot conversion to give the corresponding 1,8-dioxodecahydroacridines **3a** and **b** in excellent yields (Scheme 3).

After the reaction, TFE can be easily separated (by distillation) and reused without decrease in its activity. For example, the reaction of benzaldehyde, methyl acetoacetate and ammonium acetate afforded the corresponding 1,4-dihydropyridine derivative in 97%, 95%, and 94% isolated yield over three cycles. When we carried out the reaction in TFE or HFIP at room temperature, the reaction proceeded very slowly to give very poor yields. The result using HFIP at reflux condition was similar to that in TFE at 70 °C.

Table 2
Synthesis of octahydroquinoline derivatives through Hantzsch reaction in TFE[a].

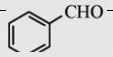
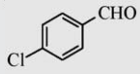
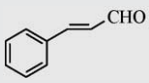
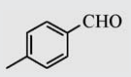
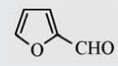
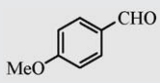
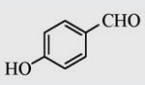
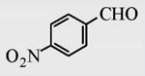
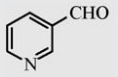
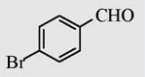
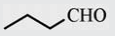
Entry	Aldehyde	R^1	Yield (%)[b]	Product
1		Et	98	**2a**
2		Et	95	**2b**
3		Et	90	**2c**
4		Me	90	**2d**
5		Et	78	**2e**
6		Et	98	**2f**
7		Et	88	**2g**

Table 2 (*Continued*)

Entry	Aldehyde	R^1	Yield (%)[b]	Product
8		Et	90	**2h**
9		Et	75	**2i**
10		Et	95	**2j**
11		Et	90	**2k**

[a] Reaction condition: aldehyde (1 mmol), acetoacetate ester (1 mmol), dimedone (1 mmol), NH_4OAc (1 mmol) (2 mL), 3 h.
[b] Isolated yield.

3. Conclusions

In summary, we have described herein an efficient methodology for Hantzsch reaction using various electronically and structurally divergent aldehydes to give the product in good to excellent isolated yields. In contrast to the existing methods using potentially hazardous catalysts/additives, this new method offers the following competitive advantages: (i) avoiding the use of any base, metal or Lewis acid catalyst (ii) short reaction time, (iii) ease of product isolation/purification by non-aqueous work-up, (iv) high chemoselectivity, (v) no side reaction, and (vi) low costs and simplicity in process and handling. The recovered TFE can be reusable.

4. Experimental

General procedure: Aldehyde (1 mmol), β-keto ester or 1,3-diketone (2 mmol) and NH_4OAc (1 mmol) were dissolved in TFE (2 mL) and stirred at 70 °C. After completion of the reaction as indicated by TLC, the TFE was separated by distillation and the crude product was purified by recrystallization from ethanol to yield the highly pure Hantzsch 1,4-dihydropyridine, polyhydroquinoline and 1,8-dioxodecahydroacridine derivatives. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature [19,20,24,26]. Spectroscopic data for selected examples are shown below.

2,6-Dimethyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1a**) [24,26]: Mp = 156–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 6 H), 2.32 (s, 3 H), 2.33 (s, 3 H), 4.11 (q, J = 7.1 Hz, 4 H), 5.01 (s, 1 H), 5.97 (br s, 1 H, NH), 7.11–7.32 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 19.5, 39.4, 59.3, 104.1, 127.5, 128.8, 135.7, 144.1, 145.9, 167.8. IR (KBr): 3334, 1690, 1654, 1494, 1243, 1127, 721 cm^{-1}.

4-(4-Chloro-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1b**) [26]: Mp = 144–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 6 H), 2.33 (s, 6 H), 4.11 (q, J = 7.2 Hz, 4 H), 4.97 (s, 1 H), 5.88 (br s, 1 H, NH), 7.23–7.19 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 19.6, 39.2, 59.9, 103.8, 127.9, 129.4, 131.7, 144.1, 146.3, 167.5. IR (KBr): 3360, 1695, 1651, 1487, 1212, 1122, 789 cm^{-1}.

2, 6-Dimethyl-4-styryl-1,4-dihydro-pyridine-3,5-dicarboxylic acid dimethyl ester (**1c**) [26]: Solid; Mp = 117–121 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.35 (s, 6 H), 3.72 (s, 6 H), 4.55 (d, J = 7.24 Hz, 1 H), 5.62 (br s, 1 H, NH), 6.17–6.19 (m, 2 H), 7.10–7.40 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 19.3, 36.2, 51.1, 102.2, 126.3, 126.9, 128.0, 128.3, 131.8, 137.7, 145.4, 168.1. IR (KBr): 3335, 2949, 1700, 1650 cm^{-1}.

4-Cyclohexyl-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1d**) [26]: Solid; Mp = 210–212 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.25 (t, J = 6.2 Hz, 6 H), 1.30–1.80 (m, 11 H), 2.25 (s, 6 H), 3.85 (d, J = 5.75 Hz, 1 H), 4.20 (q, J = 8.0 Hz, 4 H), 5.80 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 19.2, 26.2, 26.6, 32.7, 38.3, 45.6, 50.8, 101.5, 144.9, 169.1. IR (KBr): 2994, 1769, 1373, 1242 cm^{-1}.

4-Furan-2-yl-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1e**) [24]: Mp = 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz, 6 H), 2.31 (s, 6 H), 4.17 (q, J = 7.1 Hz, 4 H), 5.20 (s, 1 H), 5.90 (br s, 1 H, NH), 6.11–6.22 (m, 2 H), 7.21–7.23 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 19.4, 33.3, 59.9, 100.4, 104.4, 110.0, 140.8, 145.6, 158.7, 167.5. IR (KBr): 3342, 1697, 1648, 1480, 1361, 1211, 1132, 750 cm^{-1}.

2,6-Dimethyl-4-p-tolyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1f**) [24]: Mp = 135–137 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 6 H), 2.30 (s, 3 H), 2.32 (s, 6 H), 4.14 (q, J = 7.1 Hz, 4 H), 4.98 (s, 1 H), 6.09 (br s, 1 H, NH), 7.04 (d, J = 7.8 Hz, 2 H), 7.23 (d, J = 7.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 19.4, 21.2, 39.1, 59.7, 103.9, 127.8, 128.9, 135.2, 144.3, 145.0, 168.0. IR (KBr): 3343, 1690, 1651, 1491, 1213, 1122, 772 cm^{-1}.

4-(4-Bromo-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1g**) [26]: Mp = 160–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 6 H), 2.34 (s, 6 H), 4.12 (q, J = 7.1 Hz, 4 H), 5.32 (s, 1 H), 5.77 (br s, 1 H, NH), 7.18 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 19.3, 39.4, 59.8, 103.9, 127.9, 130.9, 130.4, 142.3, 148.5, 167.8. IR (KBr): 3340, 1690, 1643, 1492, 1211, 1120, 770 cm^{-1}.

4-(4-Hydroxy-phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1h**) [26]: Mp = 230–232 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 6 H), 2.34 (s, 6 H), 4.12 (q, J = 7.1 Hz, 4 H), 5.32 (s, 1 H), 5.77 (br s, 1 H, NH), 6.65 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 19.3, 39.4, 59.8, 103.9, 127.9, 130.9, 130.4, 142.3, 148.5, 167.8. IR (KBr): 3331, 1689, 1656, 1490, 1244, 1126, 720 cm^{-1}.

2,6-Dimethyl-4-(4-nitro-phenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1i**) [26]: Mp = 130–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 6 H), 2.35 (s, 6 H), 4.13 (q, J = 7.1 Hz, 4 H), 5.10 (s, 1 H), 6.16 (br s, 1 H, NH), 7.50 (d, J = 8.6 Hz, 2 H), 8.14 (d, J = 8.6 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 19.5, 40.1, 60.3, 103.0, 123.6, 128.9, 145.0, 146.2, 155.2, 167.2. IR (KBr): 3317, 1705, 1647, 1521, 1348, 1215, 1122, 707 cm^{-1}.

2,6-Dimethyl-4-pentyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (**1j**) [24]: Syrup. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.86 (t, J = 7.13 Hz, 3 H), 1.20 (t, J = 7.11 Hz, 6H), 1.30–1.70 (m, 8 H), 2.20 (s, 6 H), 3.85 (t, J = 5.23 Hz, 1 H), 4.18 (q, 4 H, J = 7.5 Hz), 5.60 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 14.2,

16.20, 23.24, 29.4, 30.1, 30.5, 40.5, 60.3, 98.6, 143.3, 167.4. IR (KBr): 2993, 1769, 1684, 1241 cm^{-1}.

2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2a**) [19]: Mp = 203–204 °C. ^1H NMR (500 MHz, DMSO-d^6): 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 (br s, 1 H, NH), 7.08–7.33 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 12.9, 17.9, 25.8, 28.1, 31.3, 35.3, 39.6, 49.5, 58.5, 104.7, 110.7, 124.7, 126.5, 126.7, 142.4, 145.8, 147.4, 166.2, 194.4. IR (KBr): 3287, 3078, 2963, 1697, 1611 cm^{-1}.

4-(4-Chloro-phenyl)-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2b**) [22]: Mp = 245–246 °C. ^1H NMR (500 MHz, DMSO-d^6): 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 (br s, 1 H, NH), 7.15–7.19 (d, J = 8.1 Hz, 2 H), 7.24–7.26 (d, J = 8.1 Hz, 2 H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 12.9, 18.0, 25.8, 28.1, 31.3, 34.9, 39.6, 49.4, 58.6, 104.4, 110.4, 126.4, 128.1, 130.3, 142.4, 144.3, 147.2, 165.9, 194.3. IR (KBr): 3276, 3199, 3077, 2964, 1707, 1648, 1604 cm^{-1}.

2,7,7-Trimethyl-5-oxo-4-styryl-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2c**) [19]: Mp = 206–207 °C; ^1H NMR (500 MHz, DMSO-d^6): 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), 4.18 (q, J = 7.1 Hz, 2H), 4.71 (d, J = 6.1 Hz, 1H), 6.16 (dd, J = 16.2, and 6.1 Hz, 1H), 6.58 (d, J = 16.2 Hz, 1H), 6.23 (d, J = 7 Hz, 2H), 7.21–7.32 (m, 5H), 9.03 (br s, 1 H, NH); ^{13}C NMR (125 MHz, DMSO-d^6): δ = 13.1, 18.1, 25.8, 28.3, 31.3, 32.1, 39.7, 49.5, 54.1, 58.5, 102.7, 108.6, 109.5, 119.1, 121.8, 124.9, 125.4, 126.5, 130.8, 143.1, 147.2, 148.1, 166.3, 194.44. IR (KBr): 3335, 3180, 2949, 1700, 1650 cm^{-1}.

2,7,7-Trimethyl-5-oxo-4-p-tolyl-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid methyl ester (**2d**) [19]: Mp = 270 °C. ^1H NMR (500 MHz, DMSO-d^6): 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 (br s, 1 H, NH), 7.00 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 17.4, 19.7, 25.6, 28.3, 31.3, 34.3, 49.4, 49.7, 102.6, 109.3, 126.3, 127.5, 133.7, 143.8, 144.2, 148.5, 166.5, 193.4. IR (KBr): 3283, 3192, 3071, 2956, 1687, 1602, 1491 cm^{-1}.

4-Furan-2-yl-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2e**) [19]: Mp = 248–249 °C; ^1H NMR (500 MHz, DMSO-d^6): δ = 1.01 (s, 3H), 1.10 (s, 3H), 1.25 (t, J = 7 Hz, 3H), 2.21–2.28 (m, 3H), 2.34–2.38 (m, 4H), 4.13 (q, J = 7 Hz, 2H), 5.20 (s, 1H), 5.81 (br s, 1 H, NH), 6.04–7.19 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 14.2, 19.3, 21.1, 27.5, 30.2, 36.9, 59.8, 103.1, 104.7, 110.1, 140.8, 144.2, 150.5, 157.9, 167.2, 195.5. IR (KBr): 3342, 3122, 1697, 1648, 1480, 1361, 1211, 1132, 750 cm^{-1}.

4-(4-Methoxy-phenyl)-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2f**) [19]: Mp = 257–259 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 0.94 (s, 3H), 1.07 (s, 3H), 1.21 (t, J = 7.2 Hz,3H), 2.13–2.36 (m, 7H), 3.74 (s, 3H), 4.06 (q, J = 7.2 Hz, 2H), 5.00 (s, 1H), 6.01 (br s, 1 H, NH), 6.74 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 14.2, 19.4, 27.1, 29.4, 32.6, 35.6, 41.1, 50.7, 55.1, 59.7, 106.3, 112.4, 113.2, 128.9, 139.5, 139.5, 143.1, 147.7, 157.7, 167.4, 195.5. IR (KBr): 3292, 3224, 3087, 2958, 1699, 1605, 1491 cm^{-1}.

4-(4-Hydroxy-phenyl)-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2g**) [19]: Mp = 232–234 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 0.94 (s, 3H), 1.08 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H), 2.08–2.18 (m, 3H), 2.20–2.35 (m, 4H), 4.07 (q, J = 7.6 Hz, 2H), 4.98 (s, 1H), 5.62 (br s, 1 H, NH), 6.65 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 15.1, 19.1, 19.1, 27.4, 33.4, 36.7, 41.1, 51.7, 54.9, 60.2, 106.2, 112.6, 115.5, 130.1, 131.3, 140.4, 145.3, 149.7, 156.6, 168.4, 195.3. IR (KBr): 3331, 3122, 1686, 1656, 1495, 1234, 730 cm^{-1}.

2,7,7-Trimethyl-4-(4-nitro-phenyl)-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2h**) [24]: Mp = 240–242 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 0.89 (s, 3H), 1.09 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H), 2.05–2.25 (m, 4H,), 2.37 (s, 3H), 4.00 (q, J = 7.3 Hz, 2H), 5.05 (s, 1H), 6.01 (br s, 1 H, NH) 7.42 (d, J = 9.2 Hz, 2H), 8.05 (d, J = 9.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 12.9, 18.1, 25.7, 28.1, 31.4, 35.7, 39.5, 49.3, 58.7, 103.7, 109.7, 119.9, 121.5, 127.3, 133.5, 143.4, 146.9, 148.1, 165.7, 194.3. IR (KBr): 3506, 3285, 3193, 2447, 1912, 1678, 1518, 1484, 1306, 1284, 1166, 870, 755 cm^{-1}.

2,7,7-Trimethyl-5-oxo-4-pyridin-3-yl-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2i**) [19]: Mp = 66–67 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 0.80 (s, 3H), 1.03 (s, 3H), 1.08 (t, J = 7.3 Hz, 3H), 1.95–2.49 (m, 4H), 2.29 (s, 3H), 3.51 (q, J = 7.3 Hz, 2H), 4.84 (s, 1H), 7.20–7.48 (m, 2H), 8.26–8.35 (m, 2H), 9.16 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 18.2, 26.3, 28.9, 32.1, 33.8, 50.1, 50.6, 102.3, 109.2, 123.2, 134.5, 142.5, 146.1, 146.8, 148.6, 149.8, 166.9, 194.1. IR (KBr): 3344, 1696, 1652, 1487, 1367, 1211, 1132, 723 cm^{-1}.

4-(4-Bromo-phenyl)-2,7,7-trimethyl-5-oxo-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2j**) [19]: Mp = 253–255 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 0.93 (s, 3H), 1.08 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H), 2.19–2.40 (m, 7H), 4.05 (q, J = 7.1 Hz, 2H), 5.01 (s, 1H), 5.71 (br s, 1H, NH), 7.19 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 13.9, 16.4, 25.8, 28.1, 32.3, 34.9, 39.6, 49.4, 58.6, 97.5, 104.4, 110.4, 126.4, 128.1, 130.3, 142.4, 147.2, 165.9, 197.3. IR (KBr): 3272, 3200, 3070, 2962, 1707, 1648, 1600 cm^{-1}.

2,7,7-Trimethyl-5-oxo-4-propyl-1,4,4a,5,6,7,8,8a-octahydro-quinoline-3-carboxylic acid ethyl ester (**2k**) [19]: Mp = 147–148 °C; ^1H NMR (500 MHz, DMSO-d^6): δ = 0.78 (t, J = 7.2 Hz, 3H), 1.08 (s, 6H), 1.10–1.37 (m, 6H), 2.13–2.32 (m, 7H), 4.01 (t, J = 6.1 Hz, 1H), 4.10–4.23 (m, 2H), 5.59 (s, 1H). 5.58 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 13.3, 14.1, 15.6, 22.1, 29.6, 35.3, 40.1, 44.3, 53.1, 60.1, 99.2, 108.2, 147.2, 149.2, 165.4, 196.4. IR (KBr): 2994, 1770, 1683, 1246 cm^{-1}.

9-Phenyl-3,4,6,7,9,10-hexahydro-2H, 5H-acridine-1,8-dione (**3a**) [25]: White solid; Mp = 279–281 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 1.75–2.48 (m, 12 H), 4.23 (s, 1 H), 7.09–7.31 (m, 2 H), 7.41–7.63 (m, 3H), 9.41 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 200.1, 156.6, 152.5, 132.9, 132.6, 117.6, 41.9, 37.3, 31.5, 25.9. IR (neat): 3413, 1653, 1025, 1004 cm^{-1}.

9-(4-Chloro-phenyl)-3,4,6,7,9,10-hexahydro-2H, 5H-acridine-1,8-dione (**3b**) [25]: White solid; Mp = 268–270 °C. ^1H NMR (500 MHz, DMSO-d^6): δ = 1.68–2.55 (m, 12 H), 4.88 (s, 1H), 7.18–7.19 (d, J = 8 Hz, 2H), 7.21–7.22 (d, J = 8 Hz, 2H), 9.52 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d^6): δ = 20.7, 26.2, 31.9, 36.6, 111.9, 127.5, 127.7, 129.3, 146.2, 151.4, 172.6, 194.6. IR (neat): 3423, 1643, 1045, 1014 cm^{-1}.

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