Polystyrene-Supported *p*-Toluenesulfonic Acid: A New, Highly Efficient, and Recyclable Catalyst for the Synthesis of Hydropyridine Derivatives under Solvent-Free Conditions

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Abstract: A new environmentally benign method for the preparation of hydropyridine derivatives has been developed by a simple one-pot condensation reaction of dimidine, active methylene compounds with aldehydes, and ammonium acetate in the presence of polystyrene-supported *p*-toluenesulfonic acid as a highly active and reusable heterogeneous acid catalyst under solvent-free conditions at 60 °C. This new protocol has the advantages of easy availability, stability, reusability, and eco-friendliness of the catalyst, high to excellent yields, simple and easy experimental workup procedure.

Key words: polystyrene-supported *p*-toluenesulfonic acid, hydropyridine derivatives, active methylene compounds, solvent-free conditions

Heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Therefore, the interest for developing a new, versatile, and efficient synthesis of heterocycles has always been a thread in the synthetic community.[1] Nitrogen heterocycles containing a hydroquinoline moiety are important because they show biological and pharmacological activities, such as calcium channel blockers, vasodilator, hepatoprotective, antiatherosclerotic, bronchodilator, antitumor, geroprotective, and antidiabetic activity.[2,3] Furthermore, recent studies have revealed several other medicinal applications that include neuroprotectant and platelet antiaggregatory activity, cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and as a chemosensitizer in tumor therapy.[4] Therefore, a number of methods have been reported in the literature for the synthesis of hydroquinoline derivatives.[5–20] Unfortunately, many of these processes suffer from one or other limitations such as harsh reaction conditions, low product yields, tedious workup procedures, relatively long reaction times, and difficulty in recovery and reusability of the catalysts. Moreover, some of the reagents employed are very expensive. Therefore, the search continues for a better catalyst for the synthesis of heterocycles containing hydroquinolines ring fragment in terms of operational simplicity, reusability, economic viability, and greater selectivity.

Organic reactions under solvent-free conditions have attracted much interest from chemists, particularly from the viewpoint of green chemistry. Green chemistry approaches are significant due to the reduction of byproducts, waste, and cost. 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.[21] Although various catalysts have been developed to realize organic transformation under solvent-free conditions,[22,23] it is still difficult to achieve recovery and reuse of the catalysts in many cases. On the other hand, organic reactions using polymer-supported catalysts have received much attention because of their nature; the most important properties are enhanced stability, higher selectivity, easier handling, simple workup procedures, nontoxicity, noncorrosiveness, mildness of the reaction conditions, ease of recovery, and reuse of the catalyst.[24,25] A wide variety of polymer-supported reagents have been used in organic synthesis, like halogenations, condensation, oxidation, and reduction reactions.[24] One of the most important and highly applicable categories of polymer-supported reagents is the polymeric oxidizing agents, which have been used in numerous organic transformations.[26,27] Polystyrene is one of the most widely studied heterogeneous and polymeric supports due to its environmental stability and hydrophobic nature which protects water-sensitive Lewis acids from hydrolysis by atmospheric moisture until it is suspended in an appropriate solvent where it can be used in a chemical reaction.[28] It is well known that *p*-toluenesulfonic acid is a strong organic acid and an important catalyst in organic transformations. However, it hydrolyzes easily in organic solvent, so that its use, reuse, and separation from reaction mixtures are inconvenient and difficult. Polystyrene-supported *p*-toluenesulfonic acid (PS/PTSA), which is a tightly bound and stable complex between PTSA and polystyrenedivinylbenzene copolymer. The use of the PS/PTSA complex catalyst has several advantages over a conventional acid catalyst, such as its ease of handling (as a bench-top catalyst), commercial availability, stability, cost-efficiency, recyclability, and tunable Lewis acidity. Despite its great importance, only a few papers are reported on its catalytic application in organic synthesis.[29,30]

As part of our continuing interest in heterogeneous catalysis in organic synthesis,[31,32] we report herein an efficient and eco-friendly procedure for the synthesis of hydropyridine derivatives from aldehydes with active methylene compounds and ammonium acetate catalyzed by

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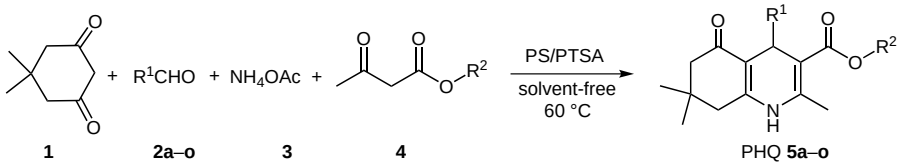


Scheme 1 Synthesis of PHQ derivatives

PS/PTSA as a reusable heterogeneous acid catalyst under solvent-free conditions at 60 °C (Scheme 1 and Scheme 2).[33] Moreover, PS/PTSA has attracted much attention because of its suitable acidity, eco-friendliness, easy availability, and cost-efficiency, thereby acting as a promising table-top reagent.

The typical procedure for polyhydroquinoline (PHQ) involves impregnating the mixture of ammonium acetate (**3**) with dimedone (**1**), 2-fluoro-4-methoxybenzaldehyde (**2a**), and ethyl acetoacetate (**4a**) and was used as a model reaction to optimize the reaction conditions.

To investigate the effects of solvent, the condensation reaction of dimedone (**1**, 1 mmol), 2-fluoro-4-methoxybenzaldehyde (**2a**, 1 mmol), ammonium acetate (**3**, 1.5 mmol), and ethyl acetoacetate (**4**, 1 mmol) in various organic solvents at 60 °C using PS/PTSA as the catalyst was carried out. About 83% of the expected product **5a** was obtained when the solvent was ethanol. Obviously, polar solvents such as ethanol and acetonitrile (Table 1, entries 1 and 3) were much better than nonpolar solvents. It was observed that in the presence of solvent the reaction takes longer time to give even lower yield of product under similar reaction conditions. This may be due to the competitive adsorption of the solvent with the substrate molecule on the catalyst surface; hence reaction under solvent-free conditions gives high yields in less time (Table 1, entry 6). The better yield under solvent-free conditions could be explained by a uniform distribution of the eutectic mixture of reactants, being in closer proximity to react than in conditions using ethanol as the solvent.

To evaluate and optimize the catalytic system, four-component condensations of dimedone (**1**, 1 mmol), 2-fluoro-4-methoxybenzaldehyde (**2a**, 1 mmol), ammonium acetate (**3**, 2.2 mmol), and ethyl acetoacetate (**4**, 1.5 mmol) at 60 °C without catalyst under solvent-free conditions were carried out in order to recognize the capability of the catalyst. The reaction did not proceed even after prolonged reaction time, and no desired product was formed which supported the catalytic activity of PS/PTSA. When the reaction was performed in the presence PS/PTSA, it proceeded effectively to produce the desired product **5a** in high yields. Some other Lewis acid catalysts and supported Lewis acid catalysts such as $GaCl_3$, Li(OTf), TiO_2–SiO_2, CAN–SiO_2, $ZnCl_2$–SiO_2, and also simple PTSA exhibited moderate to good catalytic properties. In most of these cases comparative yields of the desired product were obtained. From these experiments it was clearly demonstrated that the PS/PTSA was indeed an effective catalyst and was convincingly superior to the reported procedures with respect to reaction time, amount of catalyst, and yields under solvent-free conditions. Even though using the PTSA alone took higher reaction time and smaller yields (Table 2, entry 7). All the results are summarized in Table 2. Moreover, we found that the yields were obviously affected by the amount of PS/PTSA loaded. When 10 mg, 20 mg, 30 mg, and 40 mg of PS/PTSA were used, the yields were 75%, 85%, 92%, and 92%, respectively (Table 2, entries 8–11).Therefore, 30 mg of PS/PTSA were sufficient,

Table 1 Effect of Solvent on Polyhydroquinoline Synthesis[a]

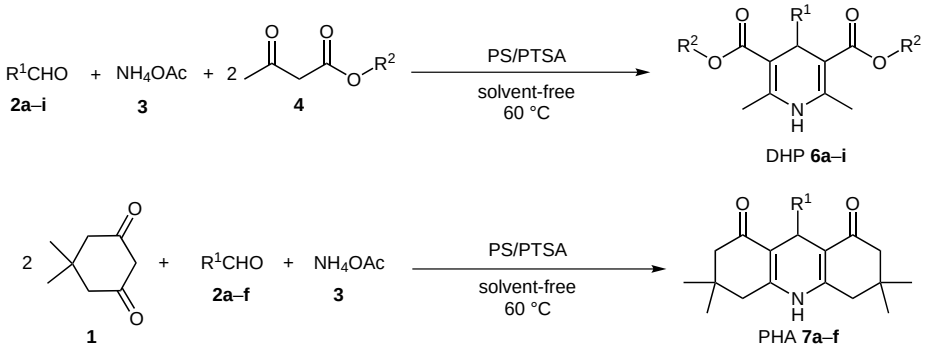
Entry	Solvent (5 mL)	Time (h)	Yield (%)[b]
1	EtOH	1	83
2	$CHCl_3$	4	40
3	MeCN	2	75
4	toluene	3	55
5	CH_2Cl_2	4	40
6	solvent-free	0.25	92

[a] Reaction of 2-fluoro-4-methoxybenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and NH_4OAc (1.5 mmol) using PS/PTSA (30 mg) at 60 °C.
[b] Isolated yield.

Table 2 Influence of the Catalyst on the Synthesis of Polyhydroquinoline Synthesis[a]

Entry	Catalyst (10 mol%)	Time	Yield (%)[b]
1	neat	6.0 h	25
2	$GaCl_3$	2.0 h	65
3	Li(OTf)	3.0 h	69
4	TiO_2–SiO_2	1.5 h	72
5	CAN–SiO_2	1.5 h	88
6	$ZnCl_2$–SiO_2	1.0 h	83
7	PTSA	1.0 h	86
8[c]	PS/PTSA (30 mg)	15 min	92, 91, 90, 88, 87
9	PS/PTSA (10 mg)	45 min	75
10	PS/PTSA (20 mg)	25 min	85
11	PS/PTSA (40 mg)	15 min	92

[a] Reaction of 2-fluoro-4-methoxybenzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and NH_4OAc (1.5 mmol) under solvent-free conditions at 60 °C.
[b] Isolated yield.
[c] Catalyst was used five times.



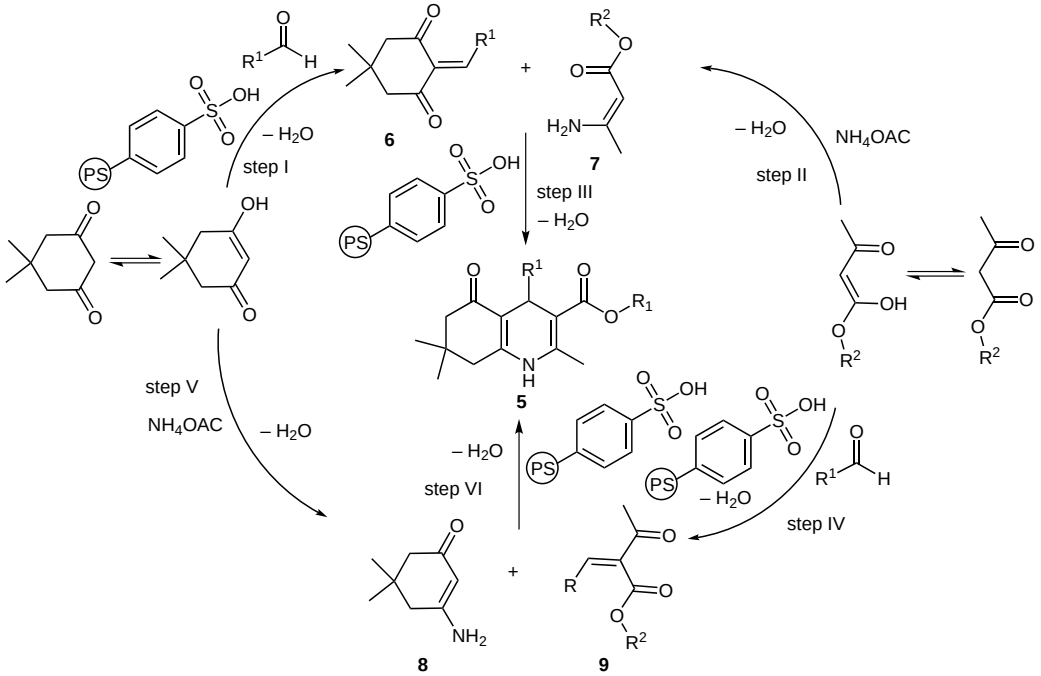
Scheme 2 Synthesis of DHP and PHA derivatives

and an excessive amount of catalyst did not increase the yields significantly (Table 2, entry 8).

The cyclocondensation of active methylene compounds with various aromatic aldehydes bearing electron-withdrawing groups or electron-releasing groups and ammonium acetate was carried out in the presence of PS/PTSA as catalyst. The yields obtained were good to excellent without the formation of any side products. We observed, irrespective of groups on the aromatic ring, that the reaction time and yields are almost close to each other. The acid-sensitive heterocyclic/aliphatic aldehydes were also obtained in good yields and the data coincide with reference compounds (Table 3, entries 8–10).

Other active methylene compounds such as ethyl acetoacetate and methyl acetoacetate also took part in this multicomponent reaction to provide the corresponding PHQ derivatives in good yields under the optimized conditions. The results obtained in the current method are illustrated in Table 3.The simplicity, together with the use of inexpensive, nontoxic, and environmentally benign nature of the PS/PTSA catalyst under solid-state reaction conditions is another remarkable feature of the procedure. From these results, it is clear that a ring substituent like a methoxy group was not affected, and the carbonyl derivative was not oxidized further.

In order to explore the applicability of this method, the same procedure has been extended, and the conditions were applied for the synthesis of dihydropyridine (DHP) and polyhydroacridine (PHA) derivatives (Table 3) via a similar one-pot, four-component condensation of two equivalents of active methylene compounds [dimidine, ethyl acetoacetate, methyl acetoacetate (2 mmol)], aldehydes (1 mmol), and ammonium acetate (1.5 mmol, Scheme 2). We studied the synthesis of PHA **7a** using dimidine (2 equiv), ammonium acetate, and 2-fluoro-4-methoxybenzaldehyde in the presence of a catalytic amount of PS/PTSA at 60 °C under solvent-free conditions (Scheme 2). Compound **7a** was isolated in 95% yield within ten minutes.



Scheme 3 Proposed mechanism of the PS/PTSA-catalyzed synthesis of PHQ

Table 3 PS/PTSA-Catalyzed Multicomponent Synthesis of Hydropyridine Derivatives

Entry	Compd	Aldehyde R	R^1	Yield (%)[a]	Time (min)	Mp (°C)
	PHQ					
1	**5a**	2-F-4-$MeOC_6H_3$	Et	92	15	277–279
2	**5b**	3-F-4-MeC_6H_3	Et	90	16	251–253
3	**5c**	3-NO_2-4-FC_6H_3	Et	88	22	178–180
4	**5d**	2,3-$F_2C_6H_3$	Et	90	18	240–241
5	**5e**	3,5-$F_2C_6H_3$	Et	90	20	208–210
6	**5f**	4-ClC_6H_4	Et	96	18	245–2477
7	**5g**	4-$O_2NC_6H_4$	Et	94	20	242–24419
8	**5h**	*n*-Pr	Et	86	30	147–1497
9	**5i**	Et	Et	88	35	144–1467
10	**5j**	2-thienyl	Et	88	31	239–2418
11	**5k**	2-F-4-$MeOC_6H_3$	Me	91	17	261–263
12	**5l**	3-F-4-MeC_6H_3	Me	89	16	252–254
13	**5m**	3-O_2N-4-FC_6H_3	Me	85	21	192–194
14	**5n**	2,3-$F_2C_6H_3$	Me	89	20	255–257
15	**5o**	3,5-$F_2C_6H_3$	Me	92	21	261–263
	DHP					
16	**6a**	3-F-4-MeC_6H_3	Me	93	14	159–161
17	**6b**	2-F-4-$MeOC_6H_3$	Me	89	15	170–172
18	**6c**	2-Br-4-FC_6H_3	Me	90	20	154–156
19	**6d**	2,3-$F_2C_6H_3$	Me	90	19	150–152
20	**6e**	2,4-$F_2C_6H_3$	Me	91	17	160–162
21	**6f**	3-4-$F_2C_6H_3$	Me	90	20	165–167
22	**6g**	3-O_2N-4-FC_6H_3	Et	90	20	133–135
23	**6h**	3-F-4-MeC_6H_3	Et	93	14	113–115
24	**6i**	3,4-$F_2C_6H_3$	Et	90	16	140–142
	PHA					
25	**7a**	2-F-4-$MeOC_6H_3$	–	95	10	240–242
26	**7b**	3-O_2N-4-FC_6H_3	–	90	16	293–295
27	**7c**	2-Br-4-FC_6H_3	–	91	15	390–392
28	**7d**	3-F-4-MeC_6H_3	–	95	11	345–347
29	**7e**	2,3-$F_2C_6H_3$	–	90	14	167–168
30	**7f**	3,5-$F_2C_6H_3$	–	92	12	172–174

[a] Isolated yields.

A variety of substrates were submitted to the optimum reaction conditions, and the desired products were obtained in excellent yields. As can be seen from the results in Table 3, aromatic aldehydes containing both electron-withdrawing and electron-donating groups reacted smoothly with 1,3-cyclohexanediones and β-keto esters (methyl and ethyl acetoacatete) to produce high yields of products. All the products obtained were fully characterized by spectroscopic methods such as ^{1}H NMR and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.

To check the reusability of the catalyst, the condensation of dimedone, 2-fluoro-4-methoxybenzaldehyde, ethyl acetoacetate, and NH_4OAc to provide the PHQ under the conditions described with PS/PTSA as catalyst was run for five consecutive cycles, furnishing the corresponding PHQ in 92%, 91%, 90%, 88%, and 87% isolated yields, which proved the efficiency of the catalyst for multiple usage (Table 2, entry 8). Even though after five consecutive cycles run for the reaction, the catalytic activity of PS/PTSA did not decrease dramatically. We observed almost a close activity to that of the freshly used catalyst. The gradual decrease in catalytic activity may be due to blocking of some active sites on the catalyst surface by the residues of the reaction.

Similar studies in the synthesis of DHP and PHA also led to the conclusion that the catalyst is reusable without considerable loss in activity.

A possible mechanism to rationalize the product formation is shown in Scheme 3. PHQ **5** may be formed either through steps I–III or through steps IV–VI. The role of PS/PTSA comes in steps I and IV, where it catalyzes the Knoevenagel-type coupling of aldehydes with active methylene compounds and in steps III and VI, where it catalyzes the Michael-type addition of intermediates **6** and **7** and **8** and **9** to give product **5**.

In conclusion, PS/PTSA was found to be an efficient, environmentally benign, and stable heterogeneous polymer-supported solid-acid catalyst for the preparation of hydropyridine derivatives. The mild reaction conditions, high to excellent yields, short reaction times, simple experimental procedure, recyclability of the catalyst with no loss of its activity, low cost, and easy handling of the polymeric catalyst are important features of this new protocol to prepare hydropyridine derivatives.

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(33) **Synthesis of Ethyl-4-(2-fluoro-4-methoxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5a)**

A mixture of dimedone (**1**, 1 mmol), 2-fluoro-4-methoxybenzaldehyde (**2a**, 1 mmol), NH_4OAc (**3**, 1.5 mmol), ethyl acetoacetate (**4**, 1 mmol), and PS/PTSA (30 mg) was stirred at 60 °C under solvent-free conditions for 15 min (Table 3, entry 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with EtOAc and filtered to recover the catalyst. The filtrate was evaporated, and the crude product was recrystallized from EtOH to afford pure **5a** in excellent yield (92%). The spent polymeric catalyst from different experiments was combined, washed with Et_2O, and dried overnight in a vacuum oven and reused. Yield 92%; white solid; mp 277–279 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.20 (q, 1 H), 6.62 (s, 1 H), 6.55 (dd, *J* = 2.5, 11.0 Hz, 1 H), 6.46 (dd, *J* = 2.2, 14.2 Hz, 1 H), 5.14 (s, 1 H), 4.06–4.01 (q, 2 H), 3.71 (s, 3 H), 2.29 (s, 3 H), 2.28 (d, *J* = 16.4 Hz, 2 H), 2.20 (d, *J* = 16.4 Hz, 2 H), 1.20 (t, *J* = 9.0 Hz, 3 H), 1.03 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 167.5, 159.1, 158.9, 148.8, 143.8, 131.6, 126.0, 125.9, 110.5, 109.2, 104.6, 101.2, 59.7, 55.3, 50.6, 40.8, 32.5, 31.7, 29.4, 26.8, 19.1, 14.0 ppm. ESI-HRMS: *m/z* calcd for $C_{22}H_{26}FNO_4$ [M + H$^+$]: 387.1846; found: 387.1844.

Ethyl-4-(3-fluoro-4-methylphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5b)

Yield 90%; white solid; mp 251–253 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (s, 1 H), 6.98 (d, *J* = 5.1 Hz, 2 H), 6.92 (d, *J* = 11.3 Hz, 1 H), 5.01 (s, 1 H), 4.08–4.05 (q, 2 H), 2.30 (s, 3 H), 2.28 (s, 3 H), 2.21 (d, *J* = 16.1 Hz, 2 H), 2.17 (d, *J* = 16.1 Hz, 2 H), 1.21 (t, *J* = 6.9 Hz, 3 H), 1.05 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 167.3, 162.3, 159.8, 149.3, 146.9, 143.6, 130.6, 123.3, 122.1, 114.4, 111.4, 105.5, 59.8, 50.7, 40.7, 36.1, 32.5, 29.3, 27.0, 19.1, 14.5, 14.1 ppm. ESI-HRMS: *m/z* calcd for $C_{22}H_{26}FNO_3$ [M + H$^+$]: 371.1897; found: 371.1897.

Ethyl-4-(4-fluoro-3-nitrophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5c)

Yield 88%; yellow solid; mp 178–180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, *J* = 2.2, 9.5 Hz, 1 H), 7.66–7.64 (m, 1 H), 7.15–7.10 (q, 1 H), 6.73 (s, 1 H), 5.10 (s, 1 H), 4.10–4.05 (q, 2 H), 2.39 (d, *J* = 16.2 Hz, 1 H), 2.38 (s, 3 H), 2.25 (d, *J* = 16.2 Hz, 2 H), 2.18 (d, *J* = 16.1 Hz, 1 H), 1.21 (t, *J* = 6.9 Hz, 3 H), 1.09 (s, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 166.7, 155.2, 152.6, 149.1, 144.6, 144.4, 135.5, 125.1, 117.4, 110.9, 104.7, 104.7, 60.0, 50.5, 40.7, 36.4, 32.7, 29.2, 27.0, 19.3, 14.1 ppm. ESI-HRMS: *m/z* calcd for $C_{21}H_{23}FN_2O_5$ [M + H$^+$]: 402.1591; found: 402.1590.

Ethyl-4-(2,3-difluorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5d)

Yield 90%; white solid; mp 240–242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 7.01–6.98 (m, 1 H), 6.84–6.79 (m, 2 H), 5.15 (s, 1 H), 3.97–3.91 (q, 2 H), 2.29 (s, 3 H), 2.11 (d, *J* = 16.4 Hz, 2 H), 1.99 (d, *J* = 16.4 Hz, 2 H), 1.10 (t, *J* = 7.3 Hz, 3 H), 0.99 (s, 3 H), 0.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 166.7, 149.4, 145.0, 136.5, 136.4, 125.1, 122.4, 113.8, 113.6, 109.1, 102.7, 58.9, 50.1, 39.5, 33.2, 31.2, 28.8, 26.3, 18.1, 13.4 ppm.

Ethyl-4-(3,5-difluorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5e)

Yield 90%; white solid; mp 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (s, 1 H), 6.86–6.81 (m, 2 H), 6.58–6.52 (m, 1 H), 5.06 (s, 1 H), 4.10–4.06 (q, 2 H), 2.30 (s, 3 H), 2.27 (d, *J* = 16.1 Hz, 2 H), 2.19 (d, *J* = 16.4 Hz, 2 H), 1.21 (t, *J* = 6.9 Hz, 3 H), 1.07 (s, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 167.0, 163.9, 161.4, 150.9, 149.6, 144.6, 110.8, 104.8, 101.3, 59.9, 50.6, 40.6, 36.6, 32.5, 29.2, 27.0, 19.0, 14.1 ppm. ESI-HRMS: *m/z* calcd for $C_{21}H_{23}F_2NO_3$ [M + H$^+$]: 375.1646; found: 375.1643.

Ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5f)

Yield 96%; white solid; mp 245–247 °C (244–246 °C).[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 2.2, 12.0 Hz, 2 H), 7.15 (dd, *J* = 2.2, 10.2 Hz, 2 H), 6.91 (s, 1 H), 5.02 (s, 1 H), 4.07–4.03 (q, 2 H), 2.34 (s, 3 H), 2.23 (d, *J* = 16.2 Hz, 2

H), 2.17 (d, *J* = 16.2 Hz, 2 H), 1.20 (t, *J* = 6.9 Hz, 3 H), 1.05 (s, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.56, 167.2, 144.9, 143.5, 131.7, 129.3, 127.9, 116.9, 108.8, 105.4, 53.7, 50.6, 41.0, 37.0, 32.5, 29.5, 27.6, 19.1, 14.5 ppm.

Ethyl-4-(4-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5g)

Yield 94%; white solid; mp 242–244 °C (240–242 °C).[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 6.91 (s, 1 H), 5.16 (s, 1 H), 4.08–4.05 (q, 2 H), 2.38 (s, 3 H), 2.25 (d, *J* = 17.2 Hz, 2 H), 2.14 (d, *J* = 16.2 Hz, 2 H), 1.19 (t, *J* = 6.2 Hz, 3 H), 1.07 (s, 3 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.0, 164.9, 153.3, 149.0, 145.2, 143.0, 128.8, 123.2, 115.9, 106.8, 60.1, 50.5, 40.9, 37.2, 32.6, 29.4, 27.4, 19.4, 14.1 ppm.

Ethyl-2,7,7-trimethyl-5-oxo-4-propyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5h)

Yield 86%; white solid; mp 147–149 °C (148–150 °C).[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (s, 1 H), 4.22–4.11 (m, 2 H), 4.02 (t, *J* = 5.5 Hz, 1 H), 2.36 (d, *J* = 17.2 Hz, 2 H), 2.30 (s, 3 H), 2.23 (d, *J* = 17.2 Hz, 2 H), 1.40–1.32 (m, 2 H), 1.28 (t, *J* = 6.9 Hz, 3 H), 1.23–1.18 (m, 2 H), 1.09 (s, 6 H), 0.82 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 166.4, 149.4, 145.2, 115.8, 108.1, 58.1, 40.6, 38.6, 36.6, 34.4, 32.5, 29.2, 27.0, 20.3, 19.0, 14.5, 14.1 ppm.

Ethyl-4-ethyl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i)

Yield 88%; white solid; mp 144–146 °C (144–146 °C).[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (s, 1 H), 4.22–4.10 (m, 2 H), 4.01 (t, *J* = 5.2 Hz, 1 H), 2.35 (d, *J* = 16.2 Hz, 2 H), 2.31 (s, 3 H), 2.23 (d, *J* = 16.2 Hz, 2 H), 1.48–1.33 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.09 (s, 6 H), 0.74 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 168.6, 148.4, 146.2, 114.8, 105.1, 58.0, 39.6, 36.7, 35.6, 30.5, 29.2, 27.4, 22.3, 19.0, 14.5, 10.3 ppm.

Ethyl-2,7,7-trimethyl-5-oxo-4-(thiophen-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5j)

Yield 88%; white solid; mp 239–241 °C (241–242 °C).[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (s, 1 H), 7.00–6.98 (m, 1 H), 6.80–6.75 (m, 2 H), 5.30 (s, 1 H), 4.12–4.10 (q, 2 H), 2.37 (d, *J* = 16.2 Hz, 2 H), 2.33 (s, 3 H), 2.23 and 2.15 (AB system, *J* = 19.2 Hz, 2 H), 1.25 (t, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 167.4, 150.5, 147.9, 143.8, 125.2, 121.7, 118.2, 111.8, 105.5, 60.4, 50.6, 38.7, 31.3, 30.5, 28.5, 27.5, 19.5, 14.2 ppm.

Methyl-4-(2-fluoro-4-methoxyphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5k)

Yield 91%; white solid; mp 261–263 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 7.16 (t, *J* = 8.4 Hz, 1 H), 6.53 (dd, *J* = 2.5, 10.9 Hz, 1 H), 6.43 (dd, *J* = 2.2, 14.2 Hz, 1 H), 5.07 (s, 1 H), 3.71 (s, 3 H), 3.56 (s, 3 H), 2.35 (d, *J* = 16.8 Hz, 2 H), 2.29 (s, 3 H), 2.03 (d, *J* = 16.2 Hz, 2 H), 1.06 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.0, 167.1, 157.8, 148.8, 144.2, 130.5, 126.0, 109.1, 108.5, 102.7, 100.1, 99.9, 54.4, 49.9, 49.7, 38.2, 31.5, 30.2, 28.7, 26.0, 17.8 ppm.

Methyl-4-(3-fluoro-4-methylphenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5l)

Yield 89%; white solid; mp 252–254 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 7.00–6.94 (q, 2 H), 6.89 (d, *J* = 11.3 Hz, 1 H), 5.10 (s, 1 H), 3.63 (s, 3 H), 2.37–2.30 (m, 5 H), 2.23–2.10 (m, 5 H), 1.06 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 167.1, 161.3, 158.9, 148.8, 146.6, 144.5, 129.8, 122.3, 120.9, 113.4, 110.1, 50.2, 49.5, 39.5, 35.0, 31.6, 28.6, 26.2, 18.0, 13.3 ppm. ESI-HRMS: *m/z* calcd for $C_{21}H_{24}FNO_3$ [M + H$^+$]: 357.1740; found: 357.1745.

Methyl-4-(4-fluoro-3-nitrophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5m)

Yield 85%; yellow solid; mp 192–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, *J* = 2.2, 9.1 Hz 1 H), 7.67–7.64 (m, 1 H), 7.15–7.10 (q, 1 H), 6.68 (s, 1 H), 5.11 (s, 1 H), 3.66 (s, 3 H), 2.35 (s, 3 H), 2.25 (d, *J* = 16.8 Hz, 2 H), 2.11 (d, *J* = 16.2 Hz, 2 H), 1.09 (s, 3 H), 0.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 167.2, 155.2, 153.2, 149.0, 144.8, 135.5, 124.9, 117.6, 110.9, 104.5, 51.1, 50.5, 40.8, 36.2, 32.7, 29.2, 27.0, 19.4 ppm.

Methyl-4-(2,3-difluorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5n)

Yield 89%; white solid; mp 255–257 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 7.06–703 (q, 1 H), 6.92–6.88 (m, 2 H), 5.19 (s, 1 H), 3.56 (s, 3 H), 2.37 (d, *J* = 17.2 Hz, 2 H), 2.31 (s, 3 H), 2.17 (d, *J* = 16.1 Hz, 2 H), 1.06 (s, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 166.7, 149.2, 136.2, 124.7, 123.3, 113.5, 113.3, 108.7, 102.1, 50.2, 49.8, 38.7, 31.5, 30.7, 28.6, 26.0, 17.8 ppm. ESI-HRMS: *m/z* calcd for $C_{20}H_{21}F_2NO_3$ [M + H$^+$]: 361.1489; found: 361.1488.

Methyl-4-(3,5-difluorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (5o)

Yield 92%; white solid; mp 261–263 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 6.82–6.79 (m, 2 H), 6.54–6.52 (m, 1 H), 5.02 (s, 1 H), 3.61 (s, 3 H), 2.37 (s, 3 H), 2.33 (d, *J* = 16.1 Hz, 2 H), 2.19 (d, *J* = 16.3 Hz, 2 H), 1.07 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 167.0, 163.8, 161.0, 151.2, 149.3, 145.4, 109.9, 102.8, 100.4, 50.2, 49.1, 39.6, 35.7, 31.8, 28.8, 26.6, 18.2 ppm.

Dimethyl-4-(3-fluoro-4-methylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6a)

Yield 93%; white solid; mp 159–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (t, *J* = 8.0 Hz, 1 H), 6.94 (dd, *J* = 1.8, 9.5 Hz, 1 H), 6.88 (dd, *J* = 1.4, 12.8 Hz, 1 H), 5.90 (s, 1 H), 4.96 (s, 1 H), 3.65 (s, 6 H), 2.31 (s, 6 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 159.9, 147.2, 144.4, 130.8, 122.8, 114.0, 113.8, 103.4, 51.0, 38.7, 19.4, 14.1 ppm. ESI-HRMS: *m/z* calcd for $C_{18}H_{20}FNO_4$ [M + H$^+$]: 333.1376; found: 331.1378.

Dimethyl-4-(2-fluoro-4-methoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6b)

Yield 89%; yellow solid; mp 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 8.8 Hz, 1 H), 6.56 (dd, *J* = 2.5, 11.0 Hz, 1 H), 6.48 (dd, *J* = 2.5, 14.6 Hz, 1 H), 5.67 (s, 1 H), 5.14 (s, 1 H), 3.74 (s, 3 H), 3.61 (s, 6 H), 2.31 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 144.0, 131.5, 127.1, 109.9, 103.3, 101.4, 57.4, 50.9, 35.3, 19.4 ppm. ESI-HRMS: *m/z* calcd for $C_{18}H_{20}FNO_5$ [M + H$^+$]: 349.1326; found: 349.1325.

Dimethyl-4-(2-bromo-4-fluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6c)

Yield 90%; yellow solid; mp 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.09 (m, 3 H), 5.70 (s, 1 H), 5.18 (s, 1 H), 3.61 (s, 6 H), 2.31 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 144.5, 132.3, 127.3, 119.1, 118.8, 102.3, 50.9, 34.3, 19.4. ppm. ESI-HRMS: *m/z* calcd for $C_{17}H_{17}BrFNO_4$ [M + H$^+$]: 397.0325; found: 397.0328.

Dimethyl-4-(2,3-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6d)

Yield 90%; yellow solid; mp 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 1 H), 6.75–6.63 (m, 2 H),

5.69 (s, 1 H), 5.18 (s, 1 H), 3.61 (s, 6 H), 2.31 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 149.2, 144.4, 141.2, 123.4, 116.4, 103.4, 51.0, 38.8, 19.5 ppm.

Dimethyl-4-(2,4-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6e)

Yield 91%; yellow solid; mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 7.23–7.17 (1, 3 H), 7.02–6.91 (m, 2 H), 5.07 (s, 1 H), 3.49 (s, 6 H), 2.23 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 163.2, 144.5, 131.5, 123.2, 110.9, 110.7, 102.5, 50.9, 34.0, 19.4 ppm. ESI-HRMS: *m/z* calcd for $C_{17}H_{17}F_2NO_4$ [M + H$^+$]: 337.1126; found: 337.1124.

Dimethyl-4-(3,4-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6f)

Yield 90%; yellow solid; mp 165–167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–6.96 (m, 3 H), 5.74 (s, 1 H), 4.97 (s, 1 H), 3.65 (s, 6 H), 2.32 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 148.2, 144.4, 140.2, 123.4, 116.5, 116.3, 103.4, 51.0, 38.8, 19.5 ppm.

Diethyl-4-(4-fluoro-3-nitrophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6g)

Yield 90%; yellow solid; mp 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 2.2, 9.1 Hz, 1 H), 7.58–7.56 (m, 1 H), 7.14–7.10 (m, 1 H), 5.99 (s, 1 H), 5.04 (s, 1 H), 4.14–4.08 (q, 4 H), 2.35 (s, 6 H), 1.23 (t, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 155.3, 152.7, 145.0, 144.8, 135.3, 125.3, 117.4, 103.1, 60.0, 39.3, 19.5, 14.2 ppm. ESI-HRMS: *m/z* calcd for $C_{19}H_{21}FN_2O_6$ [M + H$^+$]: 392.1384; found: 392.1382.

Diethyl-4-(3-fluoro-4-methylphenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6h)

Yield 93%; white solid; mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–6.89 (m, 3 H), 5.86 (s, 1 H), 4.96 (s, 1 H), 4.13–4.08 (q, 4 H), 2.31 (s, 6 H), 2.18 (s, 3 H), 1.23 (t, *J* = 7.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 147.5, 130.6, 123.1, 122.2, 114.3, 103.7, 59.7, 39.1, 19.4, 14.2, 14.1 ppm. ESI-HRMS: *m/z* calcd for $C_{20}H_{24}FNO_4$ [M + H$^+$]: 361.1689; found: 361.1689.

Diethyl-4-(3,4-difluorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (6i)

Yield 90%; white solid; mp 140–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12–7.08 (m, 2 H), 6.92 (d, *J* = 7.3 Hz 1 H), 5.89 (s, 1 H), 5.02 (s, 1 H), 4.10–4.06 (q, 4 H), 2.30 (s, 6 H), 1.22 (t, *J* = 6.9 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 149.2, 144.2, 122.4, 116.9, 115.2, 102.9, 59.2, 39.8, 19.2, 142.2 ppm.

9-(2-Fluoro-4-methoxyphenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (7a)

Yield 95%; yellow solid; mp 240–242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 7.07 (t, *J* = 8.4 Hz, 2 H), 6.74 (d, *J* = 7.6 Hz, 1 H), 4.87 (s, 1 H), 3.67 (s, 3 H), 2.39 and 2.27 (AB system, *J* = 17.2 Hz, 4 H), 2.20 (d, *J* = 16.2 Hz, 2 H), 2.04 (d, *J* = 17.2 Hz, 2 H), 1.02 (s, 6 H), 0.90 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.1, 160.2, 154.9, 149.3, 131.8, 129.4, 118.2, 111.8, 110.5, 55.2, 50.2, 41.8, 32.0, 29.1, 28.0, 26.1 ppm. ESI-HRMS: *m/z* calcd for $C_{24}H_{28}FNO_3$ [M + H$^+$]: 397.2053; found: 397.2053.

9-(4-Fluoro-3-nitrophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (7b)

Yield 90%; yellow solid; mp 293–295 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 7.82 (dd, *J* = 2.2, 9.5 Hz, 1 H), 7.60–7.57 (m, 1 H), 7.44–7.39 (m, 1 H), 4.88 (s, 1 H), 2.47 and 2.37 (AB system, *J* = 17.2 Hz, 4 H), 2.19 (d, *J* = 16.2 Hz, 2 H), 2.01 (d, *J* = 17.2 Hz, 2 H), 1.01 (s, 6 H), 0.87 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 154.0, 151.4, 144.4, 136.0, 135.3, 124.2, 117.8, 110.3, 49.9, 39.6, 32.9, 32.1, 28.9, 26.4 ppm. ESI-HRMS: *m/z* calcd for $C_{23}H_{25}FN_2O_4$ [M + H$^+$]: 412.1798; found: 412.1795.

9-(2-Bromo-4-fluorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (7c)

Yield 91%; yellow solid; mp 390–392 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 7.27–7.21 (m, 2 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 4.91 (s, 1 H), 2.27 and 2.16 (AB system, *J* = 17.2 Hz, 4 H), 2.08 (s, 3 H), 1.93 (d, *J* = 17.2 Hz, 1 H), 1.00 (s, 6 H), 0.84 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6, 161.5, 151.3, 135.5, 133.9, 128.0, 120.2, 119.6, 114.9, 51.9, 39.2, 33.5, 32.5, 30.5, 30.2, 27.7 ppm.

9-(3-Fluoro-4-methylphenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (7d)

Yield 95%; yellow solid; mp 345–347 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (t, *J* = 8.0 Hz, 1 H), 6.86–6.80 (q, 2 H), 4.77 (s, 1 H), 4.66 (s, 1 H), 2.44 and 2.34 (AB system, *J* = 17.2 Hz, 4 H), 2.16 (d, *J* = 16.1 Hz, 2 H), 2.10 (s, 3 H), 1.98 (d, *J* = 16.1 Hz, 2 H), 0.99 (s, 6 H), 0.86 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3, 161.3, 159.0, 149.5, 147.2, 130.5, 123.1, 114.0, 111.0, 50.1, 38.8, 33.2, 32.1, 29.0, 26.4, 13.7 ppm. ESI-HRMS: *m/z* calcd for $C_{24}H_{28}FNO_2$ [M + H$^+$]: 381.2104; found: 381.2102.

9-(2,3-Difluorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (7e)

Yield 91%; white solid; mp 167–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01–6.97 (m, 2 H), 6.89 (d, *J* = 8.8 Hz, 1 H), 5.65 (s, 1 H), 4.74 (s, 1 H), 2.40 and 2.34 (AB system, *J* = 17.2 Hz, 4 H), 2.20 (d, *J* = 16.1 Hz, 2 H), 2.10 (d, *J* = 16.1 Hz, 2 H), 1.01 (s, 6 H), 0.88 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.2, 151.8, 150.2, 149.4, 128.6, 123.6, 123.0, 115.0, 114.8, 46.4, 39.2, 34.5, 31.1, 28.7, 28.0 ppm.

9-(3,5-Difluorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8-(2*H*,5*H*,9*H*,10*H*)-dione (7f)

Yield 92%; white solid; mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64–6.58 (m, 3 H), 5.48 (s, 1 H), 4.88 (s, 1 H), 2.44–2.34 (m, 8 H), 1.22 (s, 6 H), 1.10 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 164.1, 161.8, 142.8, 114.8, 110.0, 109.7, 101.6, 101.1, 46.9, 39.4, 32.8, 31.4, 29.4, 27.3 ppm. ESI-HRMS: *m/z* calcd for $C_{23}H_{25}F_2NO_2$ [M + H$^+$]: 385.1853; found: 385.1857.