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Efficient One-Pot Synthesis of Acridinediones by Indium(III) Triflate-Catalyzed Reactions of β-Enaminones, Aldehydes, and Cyclic 1,3-Dicarbonyls

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An efficient one-pot synthesis of acridinediones by $In(OTf)_3$-catalyzed reactions was developed starting from β-enaminones, aldehydes, and cyclic 1,3-diketones. The key strategies of these reactions involve domino Knoevenagel condensation/Michael addition/cyclodehydration reaction.

Key Words : Acridinedione, Indium(III) triflate, β-Enaminone

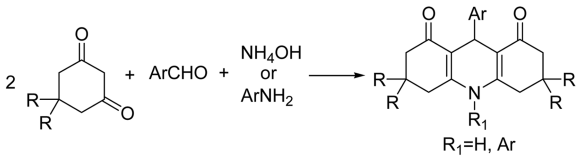
Introduction

Acridinediones and their derivatives possess a wide range of pharmaceutical activities, including antimicrobial,[1] antimalarial,[2] antitumor,[3] anticancer,[4] antibacterial,[5] fungicidal,[6] and DNA binding properties.[7] These derivatives have been used in chemotherapy for the treatment of cancer[2] and in the treatment of cardiovascular diseases, such as angina pectoris and hypertension.[7] In addition, acridinediones exhibit important properties such as high fluorescence efficiency allowing them to be used as laser dyes.[8]

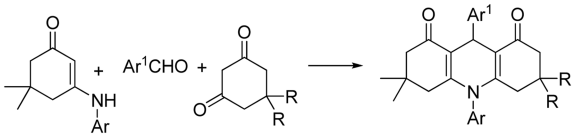
Given the importance of such activities and properties, a number of methods for the synthesis of acridinedione derivatives have been reported. Most of the methods include condensation of cyclic 1,3-dicarbonyls with arylaldehydes and ammonium acetate or anilines in the presence of Amberlyst-15,[9] *p*-dodeccylbenzenesulfonic acid,[10] triethylbenzyl ammonium chloride,[11] ionic liquids,[12] and microwave irradiation (Scheme 1).[13] These reported reactions provided symmetrical compounds which contain two identical cyclohexane rings attached to a dihydropyridine ring.

Other one method for the synthesis of symmetrical and unsymmetrical acridinediones has been developed by the reaction of β-enaminones with arylaldehydes and 1,3-dicarbonyls in ionic liquids (Scheme 2).[14]

Although several methods for the synthesis of acridinedione derivatives have been reported, there is still a demand for simple and cost effective methods. Indium(III) triflate has emerged as a prominent catalyst for the formation of acetals and thioacetals,[15] aromatic electrophilic substitution,[16] Diels-Alder reactions,[17] and the formation of tetrahydrofurans and pyrans.[18] Recently, we developed a new and useful methodology for the synthesis of arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-ones) and xanthenediones *via* an $In(OTf)_3$-catalyzed one-pot multi-component reaction.[19] As part of an ongoing study of the efficacy of this catalyst, we herein describe a facile and general method for the synthesis of acridinedione derivatives by the reaction of β-enaminones with aldehydes and cyclic 1,3-dicarbonyls in the presence of indium (III) triflate as a mild catalyst.



Scheme 1



Scheme 2

Results and Discussion

To produce acridinedione derivatives, we first prepared several β-enaminones **1a-1d** by heating corresponding cyclic 1,3-dicarbonyls and amines in 80-91% yield (Figure 1) according to a known reaction.[20] Reaction of β-enaminone **1a** with benzaldehyde (**2a**) and 1,3-cyclohexanedione (**3a**) in the presence of several Brønsted acid and Lewis acid catalysts was next investigated (Table 1). With 20 mol % of ethylenediamine diacetate (EDDA) in refluxing chloroform for 12 h, only the uncyclized product **4a** was produced in 60% yield. When 20 mol % of EDDA was used as a catalyst in refluxing toluene for 24 h, both **4a** and **5a** were produced in 55 and 5% yield, respectively. With 20 mol % of $FeCl_3$ in refluxing methylene chloride for 12 h, two compounds were obtained in 45 and 4% yield, respectively. When we used

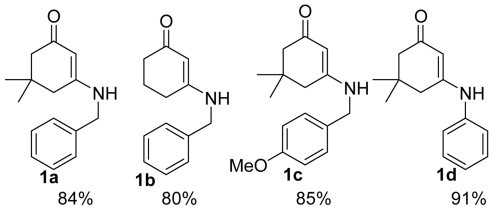
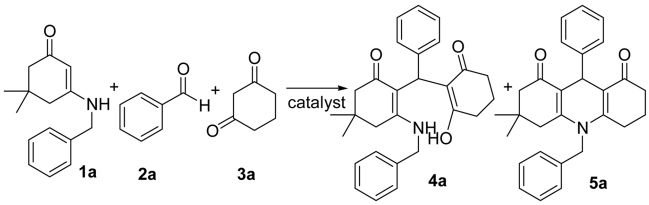


Figure 1

Table 1. Reaction of β-enaminone **1a** with benzaldehyde (**2a**) and 1,3-cyclohexanedione (**3a**) under several catalysts



Catalyst	Solvent	Condition	Yield (%)	
			4a	**5a**
EDDA (20 mol %)	$CHCl_3$	reflux, 12 h	60	0
EDDA (20 mol %)	toluene	reflux, 24 h	55	5
$FeCl_3$ (20 mol %)	CH_2Cl_2	reflux, 12 h	45	4
$Yb(OTf)_3$ (10 mol %)	toluene	reflux, 8 h	22	42
$In(OTf)_3$ (10 mol %)	xylene	reflux, 2 h	15	53
$In(OTf)_3$ (10 mol %)	DMF	100 °C, 2 h	0	85

$Yb(OTf)_3$ and $In(OTf)_3$ as catalysts (10 mol %), yields of the desired cycloadduct **5a** were increased. The two compounds were easily separated by column chromatography and assigned by spectral analysis. The ^{1}H-NMR spectrum of **4a** shows a benzylic methine proton at δ 5.68 ppm, whereas a methine proton of **5a** is exhibited at δ 5.31 ppm. Further, clear assignments come from the hydroxyl and carbonyl absorptions at 3453 and 1670 cm^{-1} for **4a** and carbonyl absorptions at 1636 cm^{-1} for **5a**. Interestingly, treatment with 10 mol % of $In(OTf)_3$ in DMF at 100 °C for 2 h, only **5a** was produced in 85% yield.

To expand the efficiency and generality of this methodology, additional reactions of β-enaminones **1a-1d** with a variety of aldehydes and cyclic 1,3-diketones were next attempted in the presence of 10 mol % of indium (III) triflate in DMF at 100 °C. The results are summarized in Table 2. Reactions of **1a** with benzaldehyde and dimedone, 1,3-cyclopentanedione or 1,3-indandione gave the desired products **5b-5d** in 76, 60, and 82% yield, respectively (entries 1-3). Treatment of **1a** with cyclic 1,3-dicarbonyls and aryl aldehydes including both electron-donating and electron-withdrawing groups on the benzene ring provided the corresponding cycloadducts **5e-5i** in good yields (entries 4-8). Interestingly, reaction of **1a** with 3-furancarboxaldehyde or 3-thiophenecarboxaldehyde gave products **5j** and **5k** in 70

Table 2. Additional reactions for the synthesis of a variety of acridinediones

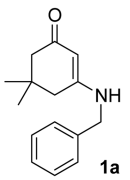
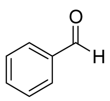
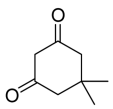
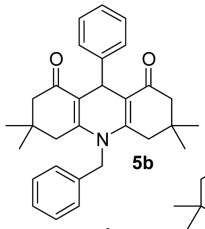
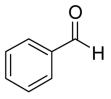
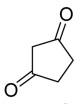
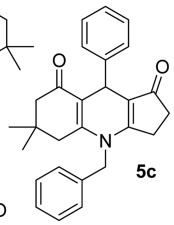
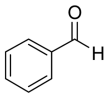
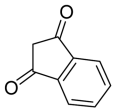
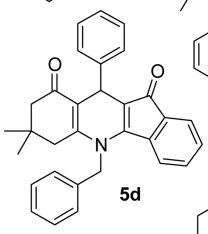
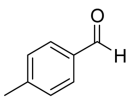
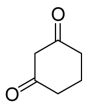
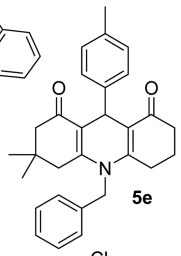
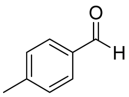
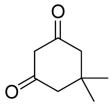
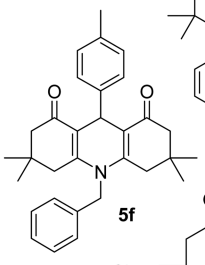
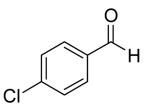
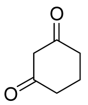
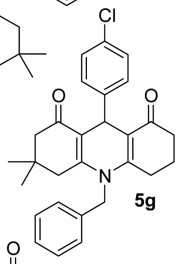
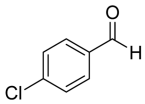
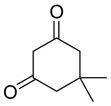
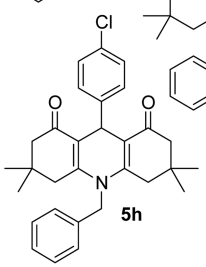
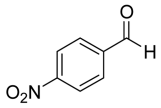
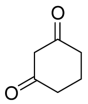
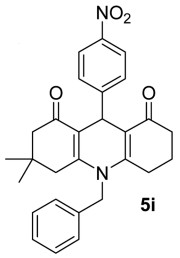
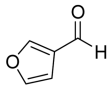
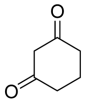
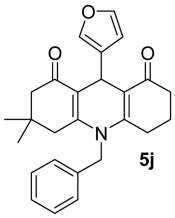
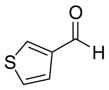
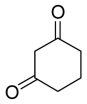
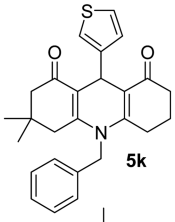
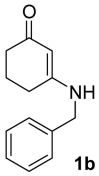
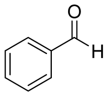
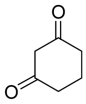
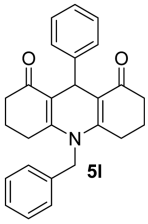
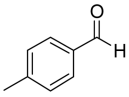
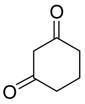
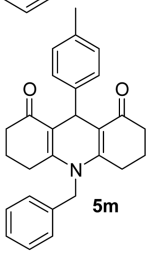
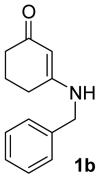
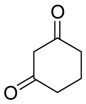
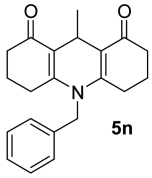
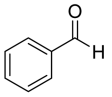
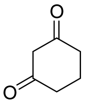
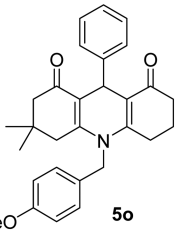
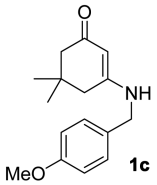
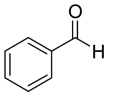
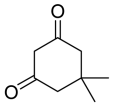
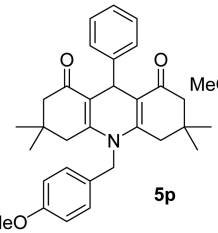
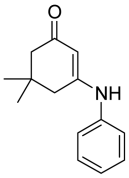
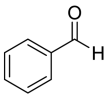
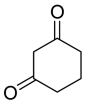
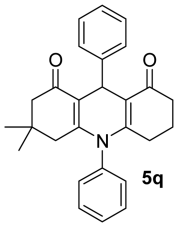
Entry	β-Enaminone	Aldehyde	1,3-Diketone	Time (h)	Product	Yield (%)
1				2		76
2				3		60
3				2		82
4				2		85
5				2		76
6				2		85
7				3		70

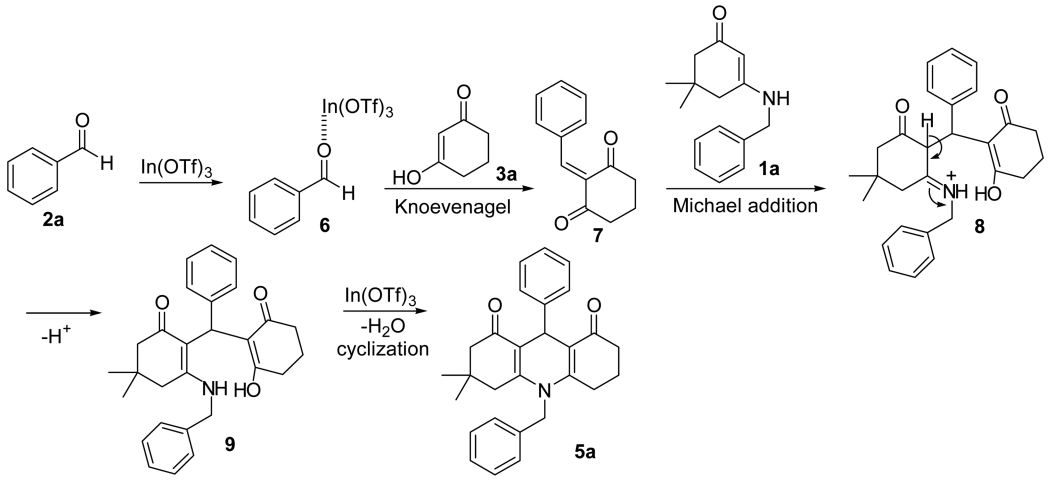
Table 2. Continued

Entry	β-Enaminone	Aldehyde	1,3-Diketone	Time (h)	Product	Yield (%)
8				2	 **5i**	90
9				2	 **5j**	70
10				2	 **5k**	76
11	 **1b**			2	 **5l**	85
12				2	 **5m**	76
13	 **1b**			3	 **5n**	74
14				2	 **5o**	84
15	 **1c**			2	 **5p**	72
16				2	 **5q**	85

and 76% yield, respectively (entries 9 and 10). With β-enaminones **1b-1d**, the desired products **5l-5q** were produced in 72-85% yield (entries 11-16). Importantly, with acetaldehyde, the desired product **5n** was obtained in 76% yield (entry 13).

The formation of **5a** in the presence of $In(OTf)_3$ can be explained by the mechanism shown in Scheme 3. Benzaldehyde (**2a**) forms an oxygen-bonded complex in the presence of indium(III) trifluoromethanesulfonate to give **6**, which is attacked by 1,3-cyclohexanedione (**3a**) to produce the intermediate **7** through Knoevenagel condensation. Michael addition of **1a** to **7** gives another intermediate **8**, which undergoes deprotonation to yield **9**. Cyclodehydration of **9** under $In(OTf)_3$ provides the desired cycloadduct **5a**.

In conclusion, a new and facile method for the synthesis of biologically interesting acridinediones by an $In(OTf)_3$-catalyzed multi-component reaction was developed starting from β-enaminones, aldehydes, and cyclic 1,3-diketones. The key strategies of these reactions were one-pot domino Knoevenagel condensation/Michael addition/cyclodehydration reaction. The method provided several advantages such as low catalyst loading, short reaction time, high yield,



Scheme 3

and convenient synthesis of unsymmetrical acridinediones.

Experimental Section

1,3-Diketones and aldehydes were obtained from Aldrich Chemicals. Merck pre-coated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H and ^{13}C-NMR spectra were recorded using a Bruker Model ARX (300 MHz and 75 MHz, respectively) spectrometer in $CDCl_3$. The IR spectra were measured on a Jasco FTIR 5300 spectrophotometer. All HRMS were carried out at the Korea Basic Science Institute.

General Procedure for the Synthesis of Acridinedione Derivatives (5a-5q). To a mixture of β-enaminones (0.5 mmol), aldehydes (0.5 mmol), and 1,3-diketones (0.5 mmol) in DMF (2 mL) was added $In(OTf)_3$ (28 mg, 0.05 mmol). The reaction mixture was stirred at 100°C for 2-3 h until completion by TLC analysis. After completion, the reaction mixture was cooled to room temperature and was added water (50 mL). The mixture was extracted with ethyl acetate (3 × 30 mL) and washed with brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude residue. Purification of the residue by column chromatography on silica gel gave products.

10-Benzyl-3,3-dimethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5a): A reaction of **1a** (115 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5a** (175 mg, 85%) as a solid: R_f = 0.23 (hexane/ethyl acetate = 1:1); mp 104-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.19 (5H, m), 7.11-6.96 (5H, m), 5.31 (1H, s), 4.85 (2H, s), 2.64-2.55 (1H, m), 2.45-2.18 (5H, m), 2.11 (2H, s), 1.90-1.75 (2H, m), 0.92 (3H, s), 0.80 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 195.9, 152.9, 150.7, 146.1, 137.1, 129.3, 128.0, 127.9, 127.8, 125.9, 125.5, 116.0, 115.4, 50.2, 48.9, 40.2, 36.6, 32.7, 31.8, 28.6, 28.2, 26.8, 21.5; IR (KBr) 2954, 1712, 1636, 1568, 1452, 1376, 1237, 1180, 735, 701 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{28}H_{29}NO_2$: 411.2198. Found: 411.2198.

10-Benzyl-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5b): A reaction of **1a** (115 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (70 mg, 0.5 mmol) in DMF (2 mL) afforded **5b** (167 mg, 76%) as a solid: R_f = 0.33 (hexane/ethyl acetate = 1:1); mp 186-188 °C; lit.[21] mp 184-185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.21 (5H, m), 7.11-6.95 (5H, m), 5.28 (1H, s), 4.84 (2H, s), 2.43 (2H, d, *J* = 16.5 Hz), 2.24 (2H, d, *J* = 16.5 Hz), 2.10 (4H, s), 0.90 (6H, s), 0.79 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 150.8, 145.9, 137.1, 129.2, 127.9, 125.9, 125.5, 115.2, 50.1, 48.8, 40.2, 32.7, 32.1, 28.6, 28.2; IR (KBr) 2958, 1710, 1635, 1568, 1455, 1379, 1240, 1213, 740, 701 cm^{-1}. HRMS *m/z* (M^+) calcd for $C_{30}H_{33}NO_2$: 439.2511. Found: 439.2515.

4-Benzyl-6,6-dimethyl-9-phenyl-2,3,5,6,7,9-hexahydro-1*H*-cyclopenta[*b*]quinoline-1,8(4*H*)-dione (5c): A reaction of **1a** (115 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 1,3-cyclopentanedione (49 mg, 0.5 mmol) in DMF (2 mL) afforded **5c** (119 mg, 60%) as a solid: R_f = 0.20 (hexane/ethyl acetate = 1:1); mp 200-202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m), 7.19-7.12 (5H, m), 5.00 (1H, s), 4.84 (2H, s), 2.58-2.53 (2H, m), 2.47-2.30 (4H, m), 2.11 (2H, s), 0.91 (3H, s), 0.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 195.7, 165.1, 150.8, 145.3, 136.7, 129.5, 128.2, 128.1, 128.0, 126.3, 125.4, 120.6, 115.8, 50.1, 48.9, 39.6, 34.1, 34.0, 32.4, 29.0, 27.8, 25.1; IR (KBr) 2954, 1682, 1641, 1565, 1452, 1398, 1373, 1212, 1163, 798, 735, 701 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{27}H_{27}NO_2$: 397.2042. Found: 397.2044.

5-Benzyl-7,7-dimethyl-10-phenyl-7,8-dihydro-5*H*-indeno-[1,2-*b*]quinoline-9,11(6*H*,10*H*)-dione (5d): A reaction of **1a** (115 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 1,3-indandione (73 mg, 0.5 mmol) in DMF (2 mL) afforded **5d** (182 mg, 82%) as a solid: R_f = 0.62 (hexane/ethyl acetate = 1:1); mp 212-214 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.02 (13H, m), 6.88 (1H, d, *J* = 7.5 Hz), 5.28 (2H, q, *J* = 18.0 Hz), 5.14 (1H, s), 2.53 (1H, d, *J* = 16.5 Hz),

2.33 (1H, d, J = 16.5 Hz), 2.20 (2H, s), 0.96 (3H, s), 0.92 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 191.9, 156.2, 151.8, 145.1, 137.1, 136.9, 134.1, 131.9, 129.6, 128.4, 128.3, 128.0, 126.4, 125.7, 121.8, 121.1, 117.1, 114.6, 50.7, 50.3, 39.6, 33.2, 32.8, 28.3; IR (KBr) 2958, 1685, 1653, 1628, 1588, 1453, 1404, 1373, 1215, 1164, 1139, 727, 698 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{31}H_{27}NO_2$: 445.2042. Found: 445.2043.

10-Benzyl-3,3-dimethyl-9-*p*-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5e): A reaction of **1a** (115 mg, 0.5 mmol), *p*-tolualdehyde (60 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5e** (181 mg, 85%) as a solid: R_f = 0.26 (hexane/ethyl acetate = 1:1); mp 87-90 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.32 (3H, m), 7.17-7.13 (4H, m), 6.97 (2H, d, J = 7.5 Hz), 5.31 (1H, s), 4.89 (2H, s), 2.68-2.56 (1H, m), 2.50-2.26 (5H, m), 2.23 (3H, s), 2.18 (2H, s), 1.98-1.80 (2H, m), 0.98 (3H, s), 0.88 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 195.8, 152.5, 150.4, 143.3, 137.2, 135.3, 129.3, 128.8, 128.0, 127.9, 125.5, 116.4, 115.6, 50.2, 48.9, 40.3, 36.6, 32.8, 31.6, 28.6, 28.3, 26.8, 21.6, 21.2; IR (KBr) 2954, 1633, 1567, 1378, 1241, 1180, 734 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{29}H_{31}NO_2$: 425.2355. Found: 425.2359.

10-Benzyl-3,3,6,6-tetramethyl-9-p-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5f): A reaction of **1a** (115 mg, 0.5 mmol), *p*-tolualdehyde (60 mg, 0.5 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (70 mg, 0.5 mmol) in DMF (2 mL) afforded **5f** (172 mg, 76%) as a solid: R_f = 0.43 (hexane/ethyl acetate = 1:1); mp 105-107 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.32 (3H, m), 7.18-7.14 (4H, m), 6.97 (2H, d, J = 7.8 Hz), 5.27 (1H, s), 4.87 (2H, s), 2.46 (2H, d, J = 16.5 Hz), 2.27 (2H, d, J = 16.5 Hz), 2.22 (3H, s), 2.17 (4H, s), 0.97 (6H, s), 0.87 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 150.7, 143.1, 137.2, 135.1, 129.2, 128.7, 127.9, 127.8, 125.5, 115.3, 50.1, 48.8, 40.2, 32.7, 31.8, 28.5, 28.2, 21.1; IR (KBr) 2956, 1635, 1570, 1460, 1376, 1242, 1205, 1177, 735 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{31}H_{35}NO_2$: 453.2668. Found: 453.2666.

10-Benzyl-9-(4-chlorophenyl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5g): A reaction of **1a** (115 mg, 0.5 mmol), 4-chlorobenzaldehyde (70 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5g** (189 mg, 85%) as a solid: R_f = 0.23 (hexane/ethyl acetate = 1:1); mp 196-198 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.43 (3H, m), 7.35-7.30 (2H, m), 7.24-7.21 (4H, m), 5.40 (1H, s), 5.01 (2H, s), 2.81-2.72 (1H, m), 2.62-2.37 (5H, m), 2.29 (2H, s), 2.10-1.93 (2H, m), 1.09 (3H, s), 0.98 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 195.8, 152.9, 150.7, 144.8, 137.0, 131.6, 129.5, 129.4, 128.2, 125.5, 115.9, 115.1, 50.1, 48.9, 40.3, 36.6, 32.8, 31.8, 28.6, 28.3, 26.8, 21.6; IR (KBr) 2950, 1710, 1635, 1572, 1485, 1379, 1242, 1181, 738 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{28}H_{28}ClNO_2$: 445.1809. Found: 445.1806.

10-Benzyl-9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5h): A reaction of **1a** (115 mg, 0.5 mmol), 4-chlorobenzaldehyde (70 mg, 0.5 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (70 mg, 0.5 mmol) in DMF (2 mL) afforded **5h** (166 mg, 70%) as a solid: R_f = 0.43 (hexane/ethyl acetate = 1:1); mp 217-219 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.32 (3H, m), 7.26-7.22 (2H, m), 7.16-7.11 (4H, m), 5.29 (1H, s), 4.91 (2H, s), 2.51 (2H, d, J = 16.5 Hz), 2.33 (2H, d, J = 16.5 Hz), 2.21 (2H, d, J = 16.5 Hz), 2.15 (2H, d, J = 16.5 Hz), 0.99 (6H, s), 0.88 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 150.9, 144.7, 137.1, 131.6, 129.6, 129.4, 128.2, 128.1, 125.5, 115.1, 50.1, 48.9, 40.4, 32.8, 32.1, 28.6, 28.3; IR (KBr) 2958, 1711, 1635, 1573, 1465, 1373, 1240, 1176, 844, 736 cm^{-1}. HRMS *m/z* (M^+) calcd for $C_{30}H_{32}ClNO_2$: 473.2122. Found: 473.2120.

10-Benzyl-3,3-dimethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5i): A reaction of **1a** (115 mg, 0.5 mmol), 4-nitrobenzaldehyde (76 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5i** (205 mg, 90%) as a solid: R_f = 0.24 (hexane/ethyl acetate = 1:1); mp 205-207 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, d, J = 9.0 Hz), 7.44 (2H, d, J = 9.0 Hz), 7.41-7.35 (3H, m), 7.14 (2H, d, J = 6.9 Hz), 5.39 (1H, s), 4.93 (2H, s), 2.73-2.64 (1H, m), 2.54-2.12 (7H, m), 2.02-1.84 (2H, m), 1.00 (3H, s), 0.88 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 195.7, 153.8, 153.4, 151.3, 146.2, 136.7, 129.5, 129.0, 128.3, 125.4, 123.4, 115.2, 114.3, 50.0, 49.0, 40.3, 36.4, 33.1, 32.8, 28.5, 28.3, 26.8, 21.5; IR (KBr) 2958, 1635, 1568, 1515, 1345, 1243, 1180, 732 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{28}H_{28}N_2O_4$: 456.2049. Found: 456.2051.

10-Benzyl-9-(furan-3-yl)-3,3-dimethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5j): A reaction of **1a** (115 mg, 0.5 mmol), 3-furaldehyde (48 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5j** (140 mg, 70%) as a solid: R_f = 0.26 (hexane/ethyl acetate = 1:1); mp 86-88 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (4H, m), 7.09-7.04 (3H, m), 6.21 (1H, s), 5.25 (1H, s), 4.89 (2H, s), 2.66-2.57 (1H, m), 2.45-2.26 (5H, m), 2.23 (2H, s), 1.97-1.87 (2H, m), 1.00 (3H, s), 0.90 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 195.9, 153.2, 151.0, 142.4, 139.3, 137.1, 129.9, 129.3, 128.0, 125.4, 115.3, 114.7, 110.6, 50.2, 48.8, 40.3, 36.6, 32.8, 28.8, 28.2, 26.8, 23.0, 21.7; IR (KBr) 2954, 1750, 1635, 1568, 1457, 1383, 1243, 1179, 735 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{26}H_{27}NO_3$: 401.1991. Found: 401.1987.

10-Benzyl-3,3-dimethyl-9-(thiophen-3-yl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5k): A reaction of **1a** (115 mg, 0.5 mmol), 3-thiophenecarboxaldehyde (56 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5k** (158 mg, 76%) as a solid: R_f = 0.20 (hexane/ethyl acetate = 1:1); mp 84-86 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.28 (3H, m), 7.10 (1H, dd, J = 5.1, 2.7 Hz), 7.05-7.03 (2H, m), 6.96 (1H, dd, J = 5.1, 1.2 Hz), 6.80-6.79 (1H, m), 5.44 (1H, s), 4.87 (2H, s), 2.68-2.59 (1H, m), 2.48-2.27 (5H, m), 2.24 (2H, s), 2.02-1.84 (2H, m), 1.00 (3H, s), 0.88 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 195.9, 153.2, 151.0, 146.7, 137.0, 129.3, 128.0, 127.9, 125.5, 124.9, 120.4, 115.8, 115.2, 50.2, 48.8, 40.3, 36.6, 32.8, 28.8, 28.2, 27.2, 26.8, 21.6; IR (KBr) 2954, 1634, 1568, 1458, 1383, 1359, 1179, 739 cm^{-1}; HRMS *m/z* (M^+)

calcd for $C_{26}H_{27}NO_2S$: 417.1762. Found: 417.1765.

10-Benzyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5l): A reaction of **1b** (100 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5l** (163 mg, 85%) as solid: R_f = 0.21 (hexane/ethyl acetate = 1:1); mp 289-290 °C; lit.[7] mp 291-294 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.01 (10H, m), 5.34 (1H, s), 4.86 (2H, s), 2.64-2.55 (2H, m), 2.45-2.16 (6H, m), 1.96-1.75 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 152.6, 146.2, 137.0, 129.4, 128.2, 128.0, 127.9, 126.1, 125.5, 116.4, 49.0, 36.7, 31.7, 26.9, 21.6; IR (KBr) 2946, 1631, 1566, 1453, 1382, 1358, 1178, 1134, 940, 741, 707 cm^{-1}. HRMS *m/z* (M^+) calcd for $C_{26}H_{25}NO_2$: 383.1885. Found: 383.1887.

10-Benzyl-9-*p*-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5m): A reaction of **1b** (100 mg, 0.5 mmol), *p*-tolualdehyde (60 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5m** (151 mg, 76%) as a solid: R_f = 0.23 (hexane/ethyl acetate = 1:1); mp 222-224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (3H, m), 7.18-7.12 (4H, m), 6.98 (2H, d, J = 7.8 Hz), 5.35 (1H, s), 4.91 (2H, s), 2.69-2.60 (2H, m), 2.50-2.27 (6H, m), 2.24 (3H, s), 2.01-1.81 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 152.5, 143.4, 137.0, 135.3, 129.3, 128.8, 127.9, 127.7, 125.4, 116.3, 48.9, 36.6, 31.2, 26.7, 21.5, 21.1; IR (KBr) 2948, 1636, 1565, 1368, 1240, 1177, 1135, 938, 818, 747, 702 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{27}H_{27}NO_2$: 397.2042. Found: 397.2043.

10-Benzyl-9-methyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5n): A reaction of **1b** (100 mg, 0.5 mmol), acetaldehyde (22 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5n** (119 mg, 74%) as a solid: R_f = 0.17 (hexane/ethyl acetate = 1:1); mp 201-203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.09 (5H, m), 4.83 (2H, s), 4.12-3.99 (1H, m), 2.57-2.47 (2H, m), 2.39-2.15 (6H, m), 1.93-1.75 (4H, m), 0.87 (3H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 152.7, 137.3, 129.3, 127.8, 125.3, 117.8, 48.7, 36.6, 26.6, 22.4, 21.8, 21.6; IR (KBr) 2957, 1634, 1568, 1384, 1250, 1178, 941, 738, 698 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{21}H_{23}NO_2$: 321.1729. Found: 321.1730.

10-(4-Methoxybenzyl)-3,3-dimethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5o): A reaction of **1c** (130 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5o** (185 mg, 84%) as a solid: R_f = 0.25 (hexane/ethyl acetate = 1:1); mp 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-6.79 (9H, m), 5.30 (1H, s), 4.78 (2H, s), 3.72 (3H, s), 2.65-2.56 (1H, m), 2.47-2.18 (5H, m), 2.10 (2H, s), 1.91-1.72 (2H, m), 0.92 (3H, s), 0.81 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 195.8, 159.2, 152.9, 150.7, 146.1, 128.8, 128.0, 127.8, 126.7, 125.9, 116.0, 115.3, 114.6, 55.4, 50.1, 48.3, 40.3, 36.6, 32.7, 31.8, 28.6, 28.2, 26.7, 21.5; IR (KBr) 2954, 1711, 1636, 1569, 1513, 1377, 1246, 1179, 1032, 821, 702 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{29}H_{31}NO_3$: 441.2304. Found: 441.2307.

10-(4-Methoxybenzyl)-3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5p): A reaction of **1c** (130 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 5,5-dimethyl-1,3-cyclohexanedione (70 mg, 0.5 mmol) in DMF (2 mL) afforded **5p** (169 mg, 72%) as a solid: R_f = 0.39 (hexane/ethyl acetate = 1:1); mp 198-201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-6.83 (9H, m), 5.26 (1H, s), 4.77 (2H, s), 3.76 (3H, s), 2.43 (2H, d, J = 16.5 Hz), 2.24 (2H, d, J = 16.5 Hz), 2.13 (4H, s), 0.93 (6H, s), 0.82 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 159.3, 150.9, 146.0, 128.9, 128.0, 126.8, 126.0, 115.4, 114.7, 55.5, 50.2, 48.4, 40.3, 32.9, 32.2, 28.6, 28.3; IR (KBr) 2957, 1712, 1634, 1570, 1513, 1458, 1377, 1245, 1176, 1034, 826 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{31}H_{35}NO_3$: 469.2617. Found: 469.2621.

3,3-Dimethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (5q): A reaction of **1d** (108 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol), and 1,3-cyclohexanedione (56 mg, 0.5 mmol) in DMF (2 mL) afforded **5q** (168 mg, 85%) as a solid: R_f = 0.38 (hexane/ethyl acetate = 1:1); mp 224-226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.41 (3H, m), 7.37-7.34 (2H, m), 7.20-7.12 (4H, m), 7.03-6.98 (1H, m), 5.27 (1H, s), 2.29-1.89 (7H, m), 1.81-1.57 (3H, m), 0.85 (3H, s), 0.72 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 195.9, 151.8, 149.8, 146.4, 139.0, 129.4, 128.1, 127.8, 125.9, 115.4, 114.5, 50.3, 41.7, 36.8, 32.4, 32.3, 29.7, 28.3, 26.8, 21.1; IR (KBr) 2954, 1712, 1636, 1568, 1452, 1376, 1237, 1180, 735, 701 cm^{-1}; HRMS *m/z* (M^+) calcd for $C_{27}H_{27}NO_2$: 397.2042. Found: 397.2040.

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