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Short Communication

An efficient ultrasound-promoted method for the one-pot synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives

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ABSTRACT

A new, efficient and general method for preparation of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives using ultrasound irradiation is reported. Under ultrasound, the reaction time is short, the yields are high and the reaction conditions are mild.

1. Introduction

The acridine derivatives have been known since the 19th century where they were first used as pigments and dyes [1]. They are considered to be important chemotherapeutics as they have shown fungicidal, bactericidal, antimalarial effects [2] and multihydroacridineone derivatives have been reported to have high fluorescence efficiency and can be used as fluorescent molecular probes for monitoring of polymerization process [3]. Also the acridine derivatives have been applied for the treatment of protozoal infections caused by *Plasmodium* microorganisms [4]. The importance of those derived of acridines has grown due to recently their antineoplasmic properties [5] as the acridine-4-carboxamides [6], which are in clinical trial [7]. They are also increasingly receiving attention due to their likeness in properties with those of 1,4-dihydropyridines,which have similarities in structure to the biologically important compounds such as NADH and NADPH [8]. As a consequence, the interest of organic chemists in the synthesis or structure modifications of acridinedione derivatives remains high.

Recently, there are many other methods available for the construction of benzoacridine derivatives, for instance, by refluxing appropriate naphthylamine, dimedone and aldehyde in benzene [9], EtOH [10,11], H_2O catalyzed by TEBA [12,13] or under microwave irradiation [14,15]. These methods all have their own merits and shortcomings. Some methods are not very satisfactory due to drawbacks such as low yields, high reaction temperature and long reaction time.

Ultrasound has increasingly been used in organic synthesis. A large number of ultrasonic reactions can be carried out in higher yield, shorter reaction time or milder conditions [16–19]. As we know that the temperature of hot spots caused by the collapse of acoustic caves is generally as high as more than several hundred degrees, this energy can be transferred to the organic molecules and absorbed by them to dramatically raise their intrinsic energy. Due to the thermal effect of ultrasound wave, therefore, much larger amount of molecules can meet the demand for the active energy in a given reaction, leading to the apparent improvement of the reaction efficiency with increased rates and reduced reaction time. It is also observed that reactions under ultrasound irradiation are commonly easier to work-up than those in conventional stirring methods. To our best knowledge, there is no report in literature on preparation of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives using ultrasound irradiation. Herein, we report the results of the synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives from corresponding aldehydes, 1-naphthylamine and dimedone in EtOH under ultrasound irradiation.

2. Results and discussion

In our initial research, 4-chlorobenzaldehyde was selected as a representative reactant in order to optimize the

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Table 1
Effect of different solvents for synthesis of **4a** under ultrasound irradiation at 25–30 °C.

Entry[a]	Solvent	Time (h)	Yield (%)[b]
1	Water	1	36
2	$CHCl_3$	1	53
3	$ClCH_2CH_2Cl$	1	60
4	DMF	1	58
5	THF	1	51
6	CH_3CN	1	63
7	1,4-Dioxane	1	71
8	EtOH	1	91

[a] Reaction conditions: 1 mmol 1-naphthylamine, 1 mmol 4-chlorobenzaldehyde and 1 mmol dimedone and 10 ml solvent.
[b] Isolated yield.

Table 2
Comparison of the yields for the synthesis of **4a** as a model.

Entry	Condition	Time (h)	Yield (%)[a]
1	Ultrasonic in ethanol at 25–30 °C	1	91
2	Stirring in ethanol at 25–30 °C	1	75
3	Stirring in ethanol at 50 °C	1	82
4	Stirring in ethanol at 50 °C	5	87
5	Reflux in ethanol at 80 °C	2	85 [15]

[a] Isolated yield.

reaction conditions. We conducted the one-pot three-component condensation reaction of 1-naphthylamine, 4-chlorobenzaldehyde and dimedone in the presence of various solvents. We examined the effect of different solvents such as water, $CHCl_3$, $ClCH_2CH_2Cl$, DMF, THF, CH_3CN, 1,4-dioxane and EtOH on a model reaction under ultrasound irradiation at 25–30 °C. The results were listed in Table 1. The reaction using EtOH as solvent gave the best result (Table 1, entry 8). The reaction failed to give poor yields in water, $CHCl_3$, $ClCH_2CH_2Cl$, DMF, THF, CH_3CN and 1,4-dioxane (Table 1, entries 1–7).

To demonstrate the effect of ultrasound, the synthesis of **4a** as a model was investigated under stirring and reflux conditions. The results were shown in Table 2. Under stirring and reflux conditions, the reaction can be completed within 1 h, 2 h and 5 h, respectively, to give **4a** in 75%, 82%, 87% and 85% yield. Whereas under ultrasonic irradiation (Table 2, entry 1), **4a** was obtained in 91% yield within 1 h. It was apparent that the ultrasound irradiation accelerates this transformation under milder conditions. The reason may be the phenomenon of cavitations produced by ultrasound [20]. As shown in Tables 1 and 2, we selected the EtOH as solvent under ultrasound irradiation conditions for the one-pot reaction of aldehydes, 1-naphthylamine and dimedone to give corresponding 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives at 25–30 °C.

In order to apply this reaction to a library synthesis, dimedone was treated with 1-naphthylamine and various aldehydes under ultrasound irradiation at 25–30 °C which successfully yielded the corresponding 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives **4a–4l** (Scheme 1). As shown in Table 3, in all cases, 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives were obtained in good yields. In the present procedure, aromatic aldehyde carrying either electron-donating or electron-withdrawing substituents in benzene ring reacted very well. Although the differences in the transformation times are slight, generally the electron-deficient substituents (Table 3, entries 5–8, 11 and 12) were superior to the electron-rich ones (Table 3, entries 9, 10) in this regard. And the longer reaction times were observed for the substrates bearing electron-donating groups (Table 3, entries 7, 8, 11 and 12). The present method was convincingly superior to the reported methods with respect to yield, reaction time, simplicity and safety.

3. Experimental

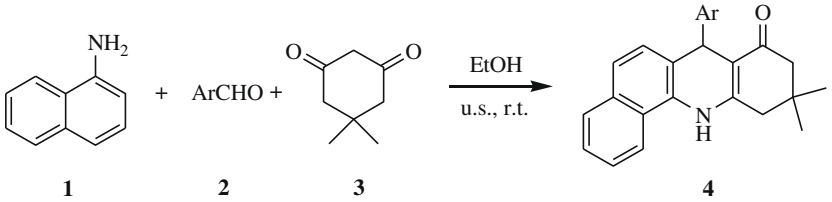
3.1. Materials and methods

All the chemicals were obtained from Tianjin Kermel Chemical Reagent Co., Ltd. and used as received. Melting points were recorded on an electrothermal apparatus and were uncorrected. Sonication was performed in Kunshan KQ-250B ultrasonic cleaner with a frequency of 40 kHz and a power 250 W. The reaction flasks were located in the maximum energy area in the cleaner, and the addition or removal of water controlled the temperature of the water bath.

3.2. General procedure

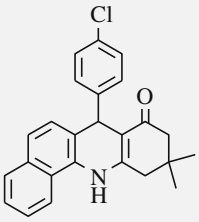
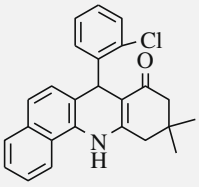
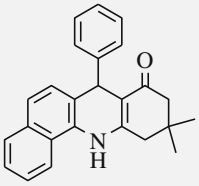
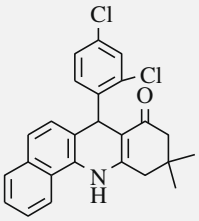
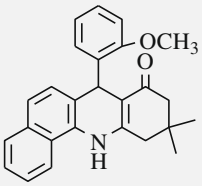
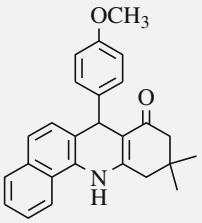
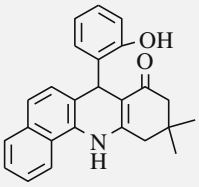
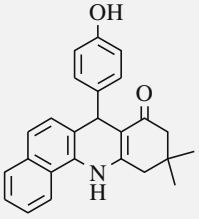
To a mixture of substituted 1-naphthylamine (1 mmol), dimedone (1 mmol) and 4-chlorobenzaldehyde (1 mmol) in 10 ml of ethanol was added and reaction mixture was exposed to ultrasound irradiation a 100 ml conical flask at 25–30 °C, stirring in a 100 ml round flask at 25–30 °C, stirring in a 100 ml round flask at 50 °C or reflux in a 100 ml round flask at 80 °C, respectively. These results were shown in Table 2. The progress of reaction was followed by TLC. After completion of reaction, the mixture was poured into ice-water (50 ml), filtered to give the crude product, which was further purified by recrystallization from EtOH.

A mixture of 1-naphthylamine (1 mmol), dimedone (1 mmol), and respective aldehydes (1 mmol) in 10 ml of ethanol was taken in a 100 ml conical flask and the reaction mixture was irradiated in the water bath of the ultrasonic cleaner at 25–30 °C for a period as indicated in Table 3. The course of the reaction was followed by TLC. After completion of reaction, the mixture was poured into ice-water (50 ml), filtered to give the crude product, which was further purified by recrystallization from EtOH (**4a–4l**). All products were known compounds and were identified by comparison of their physical and spectroscopic data with those reported for authentic samples [21].



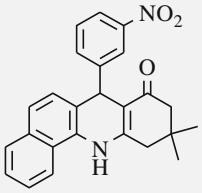
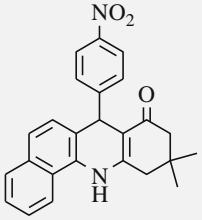
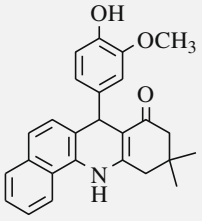
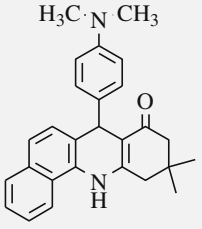
Scheme 1. Synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives.

Table 3
Synthesis of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives under ultrasound irradiation at 25–30 °C.

Entry	Ar	Product		Time (h)	Yield [a](%)	M.p. (°C)	M.p. (Lit) (°C)
1	4-ClC_6H_4		**4a**	1	90	268–270	267–269 [9]
2	2-ClC_6H_4		**4b**	1	91	266–268	265–266 [14]
3	C_6H_5		**4c**	1	85	261–263	258–259 [14]
4	2,4-$Cl_2C_6H_3$		**4d**	1	87	285–287	280–282 [13]
5	2-$CH_3OC_6H_4$		**4e**	1	86	267–269	263–265 [9]
6	4-$CH_3OC_6H_4$		**4f**	1	85	259–261	260–262 [9]
7	2-HOC_6H_4		**4g**	1.5	83	218–220	220–222 [14]
8	4-HOC_6H_4		**4h**	1.5	85	285–287	280–282 [14]

(*continued on next page*)

Table 3 (*continued*)

Entry	Ar	Product		Time (h)	Yield [a](%)	M.p. (°C)	M.p. (Lit) (°C)
9	3-$O_2NC_6H_4$		**4i**	1	90	271–273	267–269 [13]
10	4-$O_2NC_6H_4$		**4j**	1	87	281–283	280–282 [9]
11	3-CH_3O-4-OHC_6H_3		**4k**	1.5	81	274–276	270–273 [15]
12	4-$(CH_3)_2NC_6H_4$		**4l**	1.5	83	281–283	276–278 [13]

[a] Isolated yield.

4. Conclusion

In conclusion, a new, fast, general, and facile method for preparation of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives under ultrasound irradiation is presented. Ultrasounds induce a remarkable acceleration for reactions. The salient features of this protocol were mild reaction conditions, higher yields of products and shorter reaction time.

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[21] Physical and spectroscopic data for **4a–4l**:*10,10-Dimethyl-7-(4-chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4a**):* cM.p. 268–270 °C. IR (KBr, cm^{-1}): 3309, 2951, 1670, 1585, 1520, 1383, 1251, 1154, 1066, 1022, 854, 750; ^{1}H NMR (300 MHz, DMSO-d_6): 0.98 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.03–2.25 (2H, dd, J = 12.5 Hz, J = 12.5 Hz, CH_2), 2.60–2.71 (2H, dd, J = 15.2 Hz, J = 15.2 Hz, CH_2), 5.32 (1H, s, CH), 7.16–7.33 (5H, m, ArH), 7.48–7.61 (2H, m, ArH), 7.48–7.61 (2H, m, ArH), 8.46 (1H, d, J = 8.5 Hz, ArH), 9.38 (1H, s, NH); Ms (m/z): 387; Anal. Calc. for $C_{25}H_{22}NOCl$: C, 77.41; H, 5.72; N, 3.61; Found: C, 77.43; H, 5.75; N, 3.62.
*10,10-Dimethyl-7-(2-chlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin8(9H)-one (**4b**):* White crystal; M.p. 266–268 °C. IR (KBr, cm^{-1}): 3307, 2947, 2864, 1675, 1584, 1511, 1387, 1262, 1151, 1081, 1020, 846, 748; ^{1}H NMR (300 MHz, DMSO-d_6): 1.02 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.05–2.28 (2H, dd, J = 12.5 Hz, J = 12.5 Hz, CH_2), 2.57–2.73 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.83 (1H, s, CH), 6.86–7.65 (8H, m, ArH), 7.88 (1H, d, J = 8.5 Hz, ArH), 8.43 (1H, d, J = 8.5 Hz, ArH), 9.28 (1H, s, NH); Ms (m/z): 387; Anal. Calc. for $C_{25}H_{22}NOCl$: C, 77.41; H, 5.72; N, 3.61; Found: C, 77.45; H, 5.71; N, 3.64.*10,10-Dimethyl-7-phenyl-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4c**):* White crystal; M.p. 261–263 °C. IR (KBr, cm^{-1}): 3309, 2949, 2861, 1674, 1595, 1511, 1380, 1253, 1152, 1088, 1022, 750; ^{1}H NMR (300 MHz, DMSO-d_6): 1.01 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.03–2.27 (2H, dd, J = 12.5 Hz, J = 12.5 Hz, CH_2), 2.57–2.78 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.87 (1H, s, CH), 6.85–7.63 (9H, m, ArH), 7.78 (1H, d, J = 8.5 Hz, ArH), 8.42 (1H, d, J = 8.5 Hz, ArH), 9.22 (1H, s, NH); Ms (m/z): 353; Anal. Calc. for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96; Found: C, 84.93; H, 56.51; N, 3.93.*10,10-Dimethyl-7-(2,4-dichlorophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4d**):* White crystal; M.p. 285–287 °C. IR (KBr, cm^{-1}): 3310, 2949, 1685, 1586, 1517, 1487, 1397, 1261, 1151, 1087, 1023, 856, 760, 742; ^{1}H NMR (300 MHz, DMSO-d_6): 1.01 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.04–2.25 (2H, dd, J = 12.5 Hz, J = 12.5 Hz, CH_2), 2.67–2.75 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.74 (1H, s, CH), 7.16–7.63 (7H, m, ArH), 7.85 (1H, d, J = 8.5 Hz, ArH), 8.46 (1H, d, J = 8.5 Hz, ArH), 9.26 (1H, s, NH); Ms (m/z): 421; Anal. Calc. for $C_{25}H_{21}NOCl_2$: C, 71.10; H, 5.01; N, 3.32; Found: C, 71.11; H, 5.04; N, 3.41.
*10,10-Dimethyl-7-(2-methoxylphenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4e**):* White crystal; M.p. 267–269 °C. IR (KBr, cm^{-1}): 3295, 2952, 2886, 1681, 1589, 1518, 1497, 1412, 1260, 1171, 1143, 1026, 845, 809, 765, 747; ^{1}H NMR (300 MHz, DMSO-d_6): 1.03 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.08–2.23 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.59–2.74 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 3.81 (3H, s, CH_3O),5.84 (1H, s, CH), 6.81–7.65 (8H, m, ArH), 7.83 (1H, d, J = 8.5 Hz, ArH), 8.42 (1H, d, J = 8.5 Hz, ArH), 9.25 (1H, s, NH); Ms (m/z): 383; Anal. Calc. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65; Found: C, 81.41; H, 6.51; N, 3.64.*10,10-Dimethyl-7-(4-methoxylphenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4f**):* White crystal; M.p. 259–261 °C. IR (KBr, cm^{-1}): 3302, 2950, 2885, 1683, 1591, 1510, 1493, 1419, 1385, 1261, 1156, 1020, 835, 809, 762, 749; ^{1}H NMR (300 MHz, DMSO-d_6): 1.01 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.05–2.26 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.63–2.75 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 3.78 (3H, s, CH_3O), 5.76 (1H, s, CH), 6.75–7.65 (8H, m, ArH), 7.86 (1H, d, J = 8.5 Hz, ArH), 8.43 (1H, d, J = 8.5 Hz, ArH), 9.27 (1H, s, NH); Ms (m/z): 383; Anal. Calc. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65; Found: C, 81.48; H, 6.55; N, 3.68.*10,10-Dimethyl-7-(2-hydroxyphenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4g**)*: White crystal; M.p. 218–220 °C. IR (KBr, cm^{-1}): 3305, 3178, 2945, 1685, 1590, 1515, 1491, 1389, 1267, 1154, 1023, 837, 760, 742; ^{1}H NMR (300 MHz, DMSO-d_6): 1.02 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.04–2.26 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.62–2.73 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.86 (1H, s, CH), 6.82–7.69 (8H, m, ArH), 7.76 (1H, d, J = 8.5 Hz, ArH), 8.35 (1H, d, J = 8.5 Hz, ArH), 9.22 (1H, s, NH),13.07 (1H, s, OH); Ms (m/z): 383; Anal. Calc. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79; Found: C, 81.28; H, 6.25; N, 3.73.*10,10-Dimethyl-7-(4-hydroxyphenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4h**)*: White crystal; M.p. 285–287 °C. IR (KBr, cm^{-1}): 3309, 3156, 2942, 1683, 1595, 1522, 1494, 1384, 1265, 1159, 1023, 835, 767, 740; ^{1}H NMR (300 MHz, DMSO-d_6): 1.00 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.06–2.25 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.65–2.74 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.82 (1H, s, CH), 6.84–7.66 (8H, m, ArH), 7.78 (1H, d, J = 8.5 Hz, ArH), 8.34 (1H, d, J = 8.5 Hz, ArH), 9.24 (1H, s, NH),13.04 (1H, s, OH); Ms (m/z): 383; Anal. Calc. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79; Found: C, 81.25; H, 6.22; N, 3.77.*10,10-Dimethyl-7-(3-nitrophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4i**)*: White crystal; M.p. 271–273 °C. IR (KBr, cm^{-1}): 3308, 2952, 1678, 1591, 1526, 1495, 1381, 1354, 1268, 1152, 1087, 1028, 815, 762, 732; ^{1}H NMR (300 MHz, DMSO-d_6): 0.99 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.05–2.28 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.71–2.77 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.74 (1H, s, CH), 7.34–7.86 (7H, m, ArH), 7.98–8.05 (2H, m, ArH), 8.45 (1H, d, J = 8.5 Hz, ArH), 9.31 (1H, s, NH); Ms (m/z): 398; Anal. Calc. for $C_{25}H_{22}N_2O_3$: C 75.36; H 5.57; N 7.03; Found: C, 75.35; H, 5.51; N, 7.09.
*10,10-Dimethyl-7-(4-nitrophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4j**)*: White crystal; M.p. 281–283 °C. IR (KBr, cm^{-1}): 3310, 2957, 1670, 1594, 1523, 1495, 1384, 1352, 1269, 1149, 1083, 1030, 811, 760, 722; ^{1}H NMR (300 MHz, DMSO-d_6): 0.99 (3H, s, CH_3), 1.11 (3H, s, CH_3), 2.06–2.26 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.69–2.75 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 5.76 (1H, s, CH), 7.15–7.74 (7H, m, ArH), 7.95–8.03 (2H, m, ArH), 8.40 (1H, d, J = 8.5 Hz, ArH), 9.29 (1H, s, NH); Ms (m/z): 398; Anal. Calc. for $C_{25}H_{22}N_2O_3$: C 75.36; H 5.57; N 7.03; Found: C, 75.30; H, 5.54; N, 7.06.*10,10-Dimethyl-7-(4-hydroxy-3-methoxyphenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4k**)*: White crystal; M.p. 274–276 °C. IR (KBr, cm^{-1}): 3302, 2959, 1574, 1510, 1498, 1394, 1263, 1144, 1093, 812, 768, 650; ^{1}H NMR (300 MHz, DMSO-d_6): 1.02 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.07–2.28 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.65–2.76 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 3.76 (3H, s, CH_3O), 5.48 (1H, s, CH), 6.98–7.51 (7H, m, ArH), 7.85 (1H, d, J = 8.5 Hz, ArH), 8.43 (1H, d, J = 8.5 Hz, ArH), 8.69 (1H, s, OH), 9.27 (1H, s, NH); Ms (m/z): 399; Anal. Calc. for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.24; H, 6.39; N, 3.42.*10,10-Dimethyl-7-(4-dimethylaminophenyl)-7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one (**4l**):* White crystal; M.p. 281–283 °C. IR (KBr, cm^{-1}): 3298, 2954, 1679, 1578, 1514, 1391, 1261, 1146, 1063, 957, 827, 798, 752; ^{1}H NMR (300 MHz, DMSO-d_6): 1.01 (3H, s, CH_3), 1.09 (3H, s, CH_3), 2.05–2.26 (2H, dd, J = 8.5 Hz, J = 8.5 Hz, CH_2), 2.67–2.75 (2H, dd, J = 15.0 Hz, J = 15.0 Hz, CH_2), 2.86 (6H, s, $2NCH_3$), 5.51 (1H, s, CH), 7.03–7.65 (8H, m, ArH), 7.83 (1H, d, J = 8.5 Hz, ArH), 8.46 (1H, d, J = 8.5 Hz, ArH), 9.22 (1H, s, NH); Ms (m/z): 396; Anal. Calc. for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06. Found: C, 81.70; H, 7.14; N, 6.99.