Ammonium chloride catalysed one-pot multicomponent synthesis of 1,8-dioxo-octahydroxanthenes and *N*-aryl-1,8-dioxodecahydroacridines under solvent free conditions

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A simple, straightforward and highly efficient protocol has been developed for the one-pot multicomponent synthesis of 1,8-dioxo-octahydroxanthenes from the reaction of aromatic aldehydes and dimedone, and also *N*-aryl-1,8-dioxodecahydroacridines from aromatic aldehydes, dimedone and aromatic amines in excellent yields using ammonium chloride as a low-cost and non-toxic eco-friendly catalyst under solvent-free conditions. The salient features of the present protocol are the operational simplicity, clean reaction profiles, excellent yields, high atom-economy, relatively short reaction-time as well as the use of inexpensive and environmentally benign catalyst.

Keywords: 1,8-dioxo-octahydroxanthenes, *N*-aryl-1,8-dioxodecahydroacridines, ammonium chloride, solvent-free conditions, one-pot multi-component reactions, green protocol

Xanthenes and acridines are important *O*- and *N*-heterocycles, respectively, due to their potent pharmaceutical interest.[1–7] In recent years, 1,8-dioxo-octahydroxanthene and *N*-aryl-1,8-dioxodecahydroacridine moieties, in particular, have been considered as potential lead candidates in drug design and discovery because of their potent pharmacological activities such as antimicrobial, anticancer and enzyme inhibitory properties. Figure 1 offers a glimpse of such potential for some synthetic analogues.[8–10] There have been only a very few reports on the synthetic methodologies claimed to be effective as common techniques in yielding both the scaffolds under the catalysis of 1-methylimidazolium trifluoroacetate ([Hmim]TFA),[11] silica-supported *N*-propyl sulfamic acid,[12] amberlyst-15,[13] ZnO nanoparticles[14] and LiBr.[15] Synthesis of both the scaffolds under single operational conditions is interesting and useful. Although these available methodologies possess notable merits, they suffer from drawbacks such as use of organic solvents and longer reaction time. Thus, the exploration for a more efficient, cost-effective and eco-friendly protocol as a common synthetic tool for both the scaffolds is still warranted. As part of our continuing efforts to develop green synthetic methodologies for useful organic transformations,[16–18] we now report a convenient, straightforward and highly efficient protocol for the one-pot synthesis of 1,8-dioxo-octahydroxanthenes **3** and *N*-aryl-1,8-dioxo decahydroacridines **5** *via* multicomponent reaction (MCR) using a catalytic amount of ammonium chloride (NH_4Cl) under solvent-free conditions (Scheme 1). The process is simple, cost-effective and environmentally benign.

Results and discussion

Ammonium chloride (NH_4Cl) is commercially available, inexpensive, and non-toxic eco-friendly substance that has found applications in organic transformations. It has been reported to act as an effective catalyst in carrying out Claisen rearrangement,[19] Biginelli reaction,[20] one-pot synthesis of diindolymethanes,[21] thia-Michael addition,[22] *etc*.[23] We now wish to extend the synthetic applicability of this unique catalyst in the one-pot synthesis of both 1,8-dioxo-octahydroxanthene (**3**) and *N*-aryl 1,8-dioxo decahydroacridine (**5**) scaffolds of pharmacological interests under the same optimised reaction conditions.

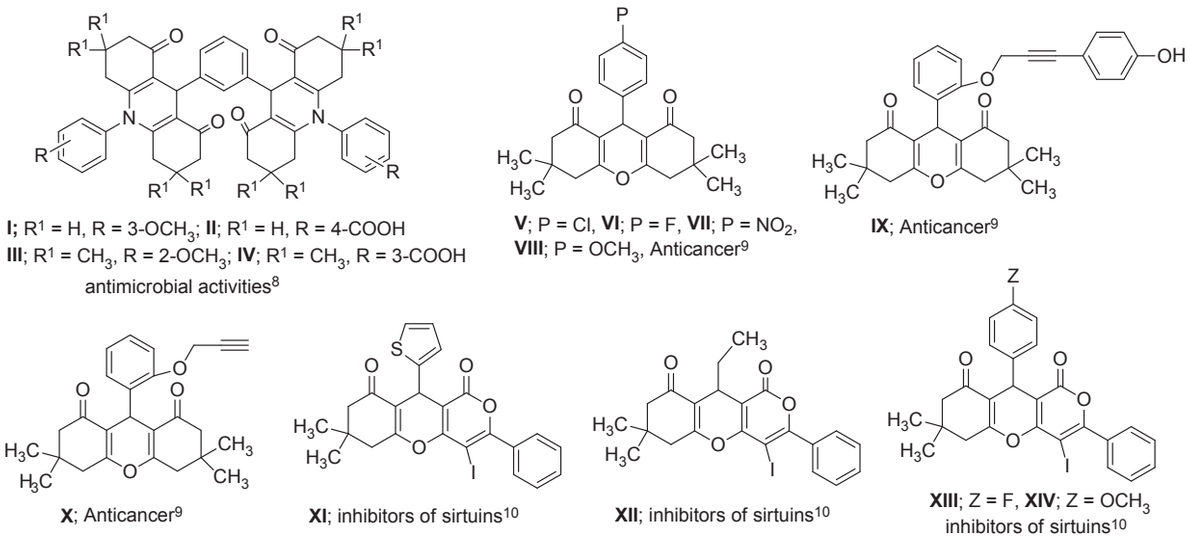

Fig. 1 Examples of pharmacologically active synthetic 1,8-dioxo-octahydroxanthenes and *N*-aryl-1,8-dioxodecahydroacridines.[8–10]

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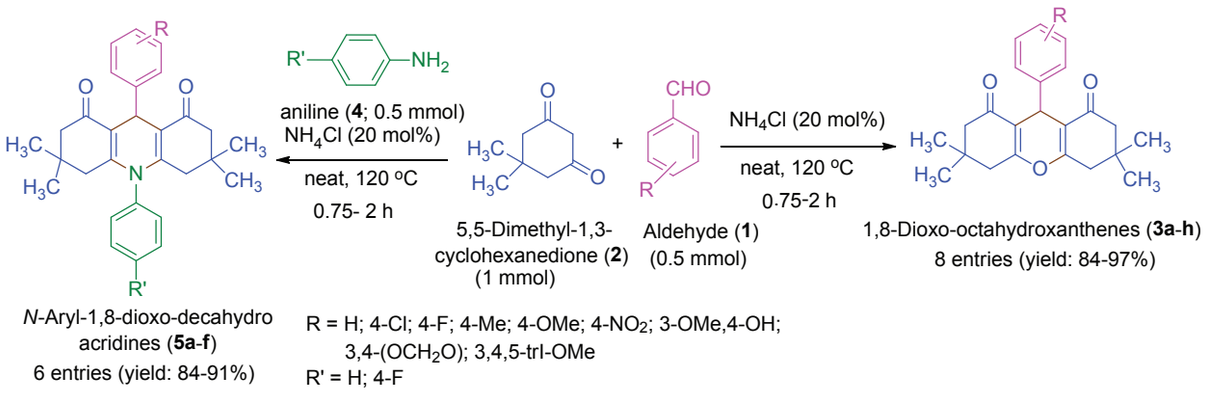
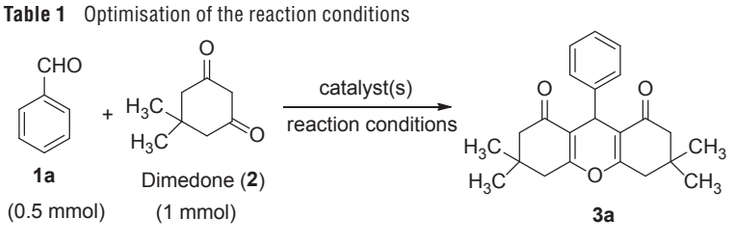


Scheme 1 Synthesis of 1,8-dioxo-octahydroxanthenes and *N*-aryl-1,8-dioxodecahydroacridines.

Initially, we optimised the reaction conditions with the synthesis of 1,8-dioxo-octahydroxanthene moiety (**3**), and for this purpose a set of standard reaction conditions were established on the basis of a series of trial reactions of benzaldehyde (**1a**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone; **2**) in the presence or absence of ammonium, sodium and potassium halides under solvent or neat condition at varying temperatures to obtain 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**3a**) (Table 1). The best result (Table 1, entry 11) was obtained from reaction of these components in the presence of 20 mol% of ammonium chloride under neat conditions at 120 °C; the isolated product **2a** was characterised by its melting point, IR, ^{1}H NMR, ^{13}C NMR, TOF-MS and elemental analysis.

Under the optimised reaction conditions, a range of aromatic aldehydes (**1**) were reacted with 5,5-dimethylcyclohexane-1,3-dione (dimedone; **2**) to furnish a variety of 1,8-dioxo-octahydroxanthenes (**3a**–**h**) in excellent yields (84–97%) within a relatively short reaction-time (0.75–2 h). Both the electron-donating and electron-withdrawing substituents such as hydroxy, methoxy, methylenedioxy, methyl, chloro, fluoro and nitro group present in the aromatic aldehydes underwent the reaction smoothly, thereby establishing the generality and scope of this present method. The optimised reaction conditions worked satisfactorily in generating the *N*-aryl-1,8-dioxodecahydroacridine derivatives (**5a**–**f**) in one-pot when the reaction was carried out in presence of aromatic amines (**4**) with excellent yield of 84–91% within 0.75–2 h. The overall results are described in Table 2. All the isolated products were fully characterised from their physical properties, elemental analyses and spectral studies (IR, ^{1}H NMR, ^{13}C NMR, TOF-MS); all known compounds had physical and spectroscopic data identical to the literature values.[13,24] We have been successful in developing unit crystals for 9,10-bis(4-fluorophenyl)-3,3,6,6-

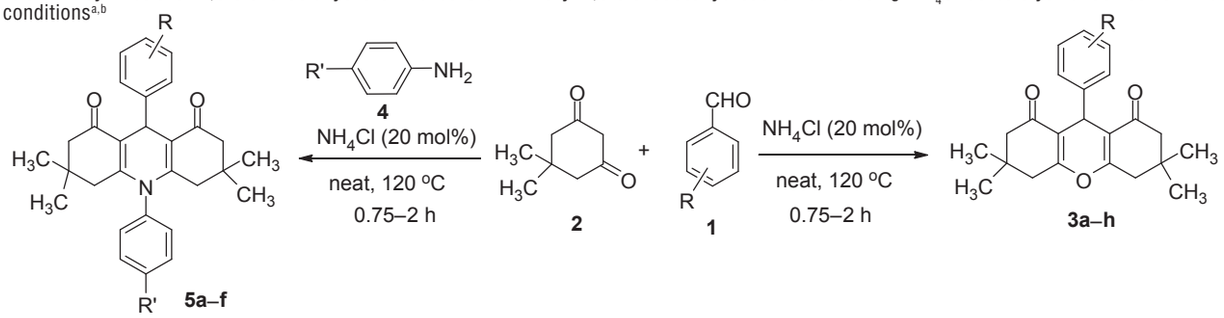
Table 1 Optimisation of the reaction conditions



Entry	Catalyst/mol%	Solvent	Temp/°C	Time /h	Yield/%[a,b]
1	No catalyst	–	120	2	22
2	NH_4F (20)	–	120	2	71
3	NaCl (20)	–	120	2	Trace
4	KBr (20)	–	120	2	Trace
5	KI (20)	–	120	2	Trace
6	NH_4Cl (20)	–	120	1	88
7	NH_4Cl (20)	H_2O	Reflux	2	42
8	NH_4Cl (20)	EtOH	Reflux	2	35
9	NH_4Cl (20)	THF	Reflux	2	Trace
10	NH_4Cl (20)	DCM	Reflux	2	25
11	NH_4Cl (20)	–	120	1	87
12	NH_4Cl (20)	–	110	2	75
13	NH_4Cl (20)	–	50	2	Trace
14	NH_4Cl (20)	–	RT	2	0
15	NH_4Cl (15)	–	120	1.25	82
16	NH_4Cl (10)	–	120	2	79

[a]Experimental conditions: benzaldehyde (0.5 mmol), dimedone (1 mmol) and catalyst(s) in the presence or absence of solvent(s) under heating.
[b]Isolated yield.

Table 2 Synthesis of 1,8-dioxo-octahydroxanthenes **3** and *N*-aryl-1,8-dioxodecahydroacridines **5** using NH_4Cl as catalyst under solvent-free conditions[a,b]



Entry	Aldehyde **1** (R)	Aniline **4** (R')	Product	Time/h	Yield/%[c]	Melting point/°C	
						Found	Reported [Ref.]
1[a]	H	–	**3a**	1	87	200–202	202–204[24]
2[a]	4-Cl	–	**3b**	2	84	228–230	230–232[24]
3[a]	4-F	–	**3c**	1	97	224–226	226–227[24]
4[a]	4-Me	–	**3d**	1.5	93	212–214	215–217[24]
5[a]	4-NO_2	–	**3e**	0.75	92	216–218	219–221[24]
6[a]	3-OMe-4-OH	–	**3f**	2	87	225–226	225–227[24]
7[a]	3,4-O–CH_2–O–	–	**3g**	2	84	221–223	224–225[24]
8[a]	3,4,5-$(OMe)_3$	–	**3h**	2	93	184–185	186–188[24]
9[b]	H	H	**5a**	0.75	84	251–252	254–256[13]
10[b]	4-F	H	**5b**	1.25	87	223–225	–
11[b]	4-OMe	H	**5c**	1.5	91	219–221	220–222[13]
12[b]	3-OMe-4-OH	H	**5d**	1.5	86	224–226	–
13[b]	4-F	4-F	**5e**	1	91	231–233	–
14[b]	3,4,5-$(OMe)_3$	4-F	**5f**	2	89	238–240	–

[a]Reaction conditions: aldehyde (**1**; 0.5 mmol), dimedone (**2**; 1 mmol) and NH_4Cl (20 mol%) at 120 °C under neat conditions.
[b]Reaction conditions: aldehyde (**1**; 0.5 mmol), dimedone (**2**; 1 mmol), aniline (**4**; 0.5 mmol) and NH_4Cl (20 mol%) at 120 °C under neat conditions.
[c]Isolated yield.
Entries **3b**, **3c** and **3e** are identical with anticancer compounds **V**, **VI** and **VII**, respectively, as shown in Fig. 1.

tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (**5e**) (Table 2; entry 13) and performed its X-ray crystallographic studies. Single crystal X-ray analysis for **5e** is also documented in this present paper (Fig. 2).

We propose here a plausible mechanism in Scheme 2 for the reaction resulting 1,8-dioxo-octahydroxanthenes (**3**). On heating, ammonium chloride undergoes decomposition to generate hydrogen chloride *in situ*, which actually participates in the reaction process as an effective catalyst giving rise to 1,8-dioxo-octahydroxanthenes. To validate the proposed mechanism, we isolated the bis-hydroxyenone intermediate (**7**) and characterised in one occasion (see Experimental).

In conclusion, we have developed a simple, straightforward and convenient practical method for one-pot multicomponent synthesis of pharmaceutically-interesting functionalised 1,8-dioxo-octahydroxanthenes from the reaction of aromatic aldehydes and dimedone, and also *N*-aryl-1,8-dioxodecahydroacridines from aromatic aldehydes, dimedone and aromatic amines in excellent yields using ammonium chloride as a low-cost and non-toxic eco-friendly catalyst under solvent-free conditions at 120 °C. Operational simplicity, clean reaction profiles, excellent yields, high atom-economy, relatively shorter reaction-time as well as the use of inexpensive and environmentally benign catalyst are the key advantages of the present method.

Experimental

IR spectra were recorded using a Shimadzu (FTIR 8400S) FTIR spectrophotometer using KBr disc. ^1H and ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz respectively, using Bruker DRX-400 spectrometer and $CDCl_3$ as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 micro-analyser instrument. Melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. TLC was performed using silica gel 60 F_{254} (Merck) plates.

Synthesis of 1,8-dioxo-octahydroxanthenes (**3a**–**h**) *and* N-*aryl-1,8-dioxodecahydroacridines* (**5a**–**f**)*; general procedure*

An oven-dried screw cap test tube was charged with a magnetic stir bar, aldehyde (**1**: 0.5 mmol), 5,5-dimethylcyclohexane-1,3-dione (dimedone; **2**; 1 mmol) and ammonium chloride (20 mol%) The tube was then evacuated and back-filled with nitrogen gas. The evacuation/backfill sequence was repeated twice more. The tube was then placed in a preheated oil bath at 120 °C and the reaction mixture was stirred vigorously for the stipulated time (Table 2). The progress of the reaction was monitored by TLC, and on completion the reaction mixture was cooled to room temperature. The reaction mixture was extracted with dry ethyl acetate (10 mL), and the extract was then concentrated under reduced pressure; the residue was purified *via* column chromatography using silica gel (60–120 mesh) and petrol ether-ethyl acetate (95 : 5) as eluent to obtain pure 1,8-dioxo-octahydroxanthenes (**3a**–**h**). Similar procedure was followed for the preparation of *N*-aryl-1,8-dioxodecahydroacridines (**5**) with an additional addition of aromatic amine (**4**; 0.5 mmol) to the reaction of mixture of aldehyde (0.5 mmol), 5,5-dimethylcyclohexane-1,3-dione (dimedone; 1 mmol) and ammonium chloride (20 mol%); column chromatographic resolution of the crude product using silica gel (60–120 mesh) and petrol ether-ethyl acetate (95 : 5) as eluent furnished pure products of *N*-aryl-1,8-dioxodecahydroacridines (**5a**–**f**;

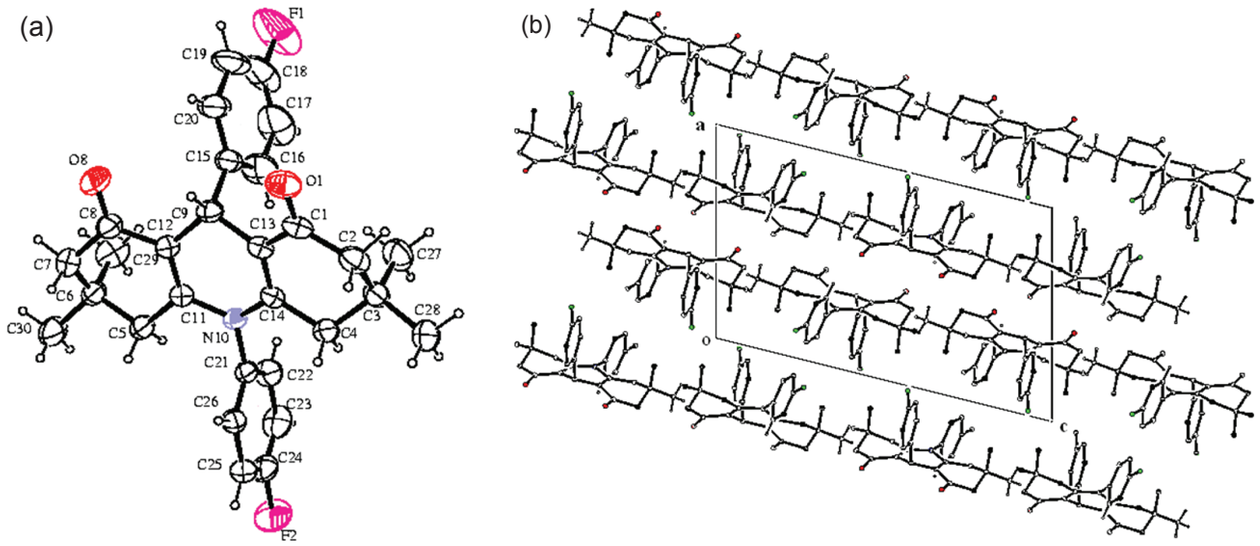


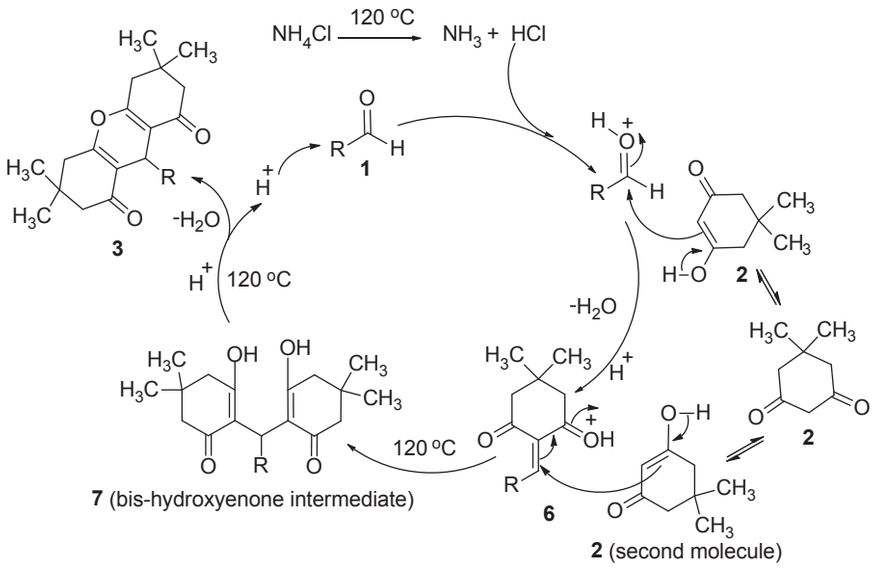
Fig. 2 (a) ORTEP view of compound **5e** (CCDC 971310) with displacement ellipsoids drawn at 40%. H atoms are shown as small spheres of arbitrary radii. (b) The packing arrangement of molecules viewed down the *b*-axis.

Table 2). All the compounds were fully characterised on the basis of physical properties, elemental analyses and spectral studies including FTIR, ^{1}H NMR, ^{13}C NMR and TOFMS.

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3a**): White solid; yield 0.153 g (87%); m.p. 200–202 °C; IR (KBr): ν_{max} = 3045, 2957, 2891, 1664, 1624, 1456, 1196, 1138, 1076, 995, 914, 839, 797, 735, 694, 660, 608, 565, 523, 455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 7.2 Hz, 2H, ArH), 7.21 (t, *J* = 8.0 Hz & 7.2 Hz, 2H, ArH), 7.09 (t, *J* = 7.2 Hz, 1H, ArH), 4.75 (s, 1H, –CH), 2.47 (s, 4H, 2 × –CH_2), 2.24 (d, *J* = 16.4 Hz, 2H, –CH_2), 2.16 (d, *J* = 16.4 Hz, 2H, –CH_2), 1.09 (s, 6H, 2 × –CH_3), 0.99 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.37 (2C), 162.52, 162.32, 160.09, 139.95, 139.92, 129.83, 129.74, 115.42, 114.87, 114.65, 50.67 (2C), 40.78 (2C), 32.13 (2C), 31.17, 29.20 (2C), 27.22 (2C); ESI-TOF-MS: 373.1778 [M + Na]$^{+}$. Anal. calcd for $C_{23}H_{26}O_3$: C, 78.83; H, 7.48; found: C, 78.79; H, 7.46%.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3b**): White solid; yield 0.162 g (84%); m.p. 228–230 °C; IR (KBr): ν_{max} = 3060, 2951, 2700, 2812, 1664, 1622, 1462, 1412, 1360, 1288, 1196, 1159, 1142, 1113, 1090, 1009, 976, 937, 914, 845, 816, 775, 716, 665, 635, 602, 527 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.0 Hz, 2H, ArH), 7.11 (d, *J* = 8.0 Hz, 2H, ArH), 4.64 (s, 1H, –CH), 2.39 (s, 4H, 2 × –CH_2), 2.16 (d, *J* = 16.0 Hz, 2H, –CH_2), 2.07 (d, *J* = 16.4 Hz, 2H, –CH_2), 1.03 (s, 6H, 2 × –CH_3), 0.91 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.36 (2C), 162.44 (2C), 142.66, 131.96, 129.73 (2C), 128.16 (2C), 115.19 (2C), 50.64 (2C), 40.78 (2C), 32.16 (2C), 31.42, 29.23 (2C), 27.23 (2C); ESI-TOF-MS: 407.1378 [M + Na]$^{+}$. Anal. calcd for $C_{23}H_{25}ClO_3$: C, 71.77; H, 6.55; found: C, 71.81; H, 6.53%.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3c**): White solid; yield 0.179 g (97%); m.p. 224–226 °C; IR (KBr): ν_{max} = 3040, 2930, 2813, 2955, 1668, 1653, 1624, 1576, 1504, 1458, 1290, 1218, 1161, 1011, 918, 847, 781, 669, 527, 511, 470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (m, 2H, ArH), 6.82 (t, *J* = 8.8 & 8.4 Hz, 2H, ArH), 4.65 (s, 1H, –CH), 2.39 (s, 4H, 2 × –CH_2), 2.16 (d, *J* = 16.4 Hz, 2H, –CH_2), 2.09 (d, *J* = 16.0 Hz, 2H, –CH_2), 1.03 (s, 6H, 2 × –CH_3), 0.91 (s, 6H, 2 × –CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.37 (2C), 162.52, 162.32 (2C), 160.09, 139.95, 139.92, 129.83, 129.74, 115.42, 114.87, 114.65, 50.67 (2C), 40.78 (2C), 32.13 (2C), 31.17, 29.20 (2C), 27.22 (2C). ESI-TOF-MS: 391.1681 [M + Na]$^{+}$. Anal. calcd for $C_{23}H_{25}FO_3$: C, 74.98; H, 6.84; found: C, 74.95; H, 6.87%.



Scheme 2 Proposed mechanism for the ammonium chloride-catalysed synthesis of 1,8-dioxo-octahydroxanthenes.

*3,3,6,6-Tetramethyl-9-*p*-tolyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione* (**3d**). White solid; yield 0.169 g (93%); m.p. 212–214 °C; IR (KBr): ν_{max} = 3040, 2930, 2887, 2351, 1667, 1649, 1619, 1583, 1576, 1452, 1362, 1302, 1254, 1192, 1157, 1134, 1122, 1049, 914, 895, 878, 860, 841, 806, 660, 582, 563 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 6.99 (d, *J* = 8.0 Hz, 2H, ArH), 5.52 (s, 1H, CH), 2.48 (d, *J* = 18.0 Hz, 2H, –CH_2), 2.41–2.35 (m, 6H, 3 × –CH_2), 2.32 (s, 3H, –CH_3), 1.25 (s, 6H, 2 × –CH_3), 1.12 (s, 6H, 2 × –CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.38, 189.35, 135.22, 134.86, 128.91, 126.62, 115.69, 47.02, 46.40, 32.36, 31.37 (2C), 29.61, 27.34, 20.85. ESI-TOF-MS: 387.1934 [M + Na]$^+$. Anal. calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74; found: C, 79.04; H, 7.72%.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3e**): White solid; yield 0.182 g (92%); m.p. 216–218 °C; IR (KBr): ν_{max} = 3067, 2934, 2878, 2339, 1670, 1661, 1585, 1514, 1366, 1299, 1242, 1149, 1124, 1055, 858, 849, 654, 634, 580, 517, 462 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 2H, ArH), 7.17 (d, *J* = 8.4 Hz, 2H, ArH), 5.48 (s, 1H, –CH), 2.43–2.28 (m, 8H, 4 × –CH_2), 1.16 (s, 6H, 2 × –CH_3), 1.04 (s, 6H, 2 × –CH_3);^{13}C NMR (100 MHz, $CDCl_3$): δ 196.24, 190.96, 189.53, 162.93, 151.47, 146.56, 146.06, 129.31, 127.60, 123.37 (2C), 114.86, 50.54, 46.94, 46.38, 40.78, 33.19, 32.18, 31.42 (2C), 29.45, 29.19, 27.41; ESI-TOF-MS: 418.1634 [M + Na]$^+$. Anal. calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54; found: C, 69.63; H, 6.37; N, 3.51%.

9-(4-Hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3f**): White solid, yield 0.172 g (87%); m.p. 225–226 °C; IR (KBr): ν_{max} = 3404, 3045, 2953, 2881, 1661, 1648, 1597, 1591, 1510, 1460, 1277, 1196, 1026, 995, 920, 860, 806, 758, 629, 567, 486, 459 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (d, *J* = 1.6 Hz, 1H, ArH), 6.65 (d, *J* = 8.4 Hz, 1H, ArH), 6.51 (dd, *J* = 8.4 & 1.6 Hz, 1H, ArH), 4.59 (s, 1H, –CH), 3.81 (s, 3H, –O*C*H_3), 2.38 (br s, 4H, 2 × –CH_2), 2.16 (d, *J* = 16.4 Hz, 2H, –CH_2), 2.01 (d, *J* = 16.0 Hz, 2H, –CH_2),1.03 (s, 6H, 2 × –CH_3), 0.93 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.66 (2C), 162.13 (2C), 145.92, 144.02, 136.42, 120.05 (2C), 115.79, 113.96, 112.25, 55.87, 50.76 (2C), 40.84 (2C), 32.19 (2C), 31.29, 29.30 (2C), 27.27 (2C); ESI-TOF-MS: 419.4619 [M + Na]$^+$. Anal. calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12; found: C, 72.68; H, 7.09%.

9-(Benzo[d][1,3]dioxol-5-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3g**): White solid; yield 0.166 g (84%); m.p. 221–223 °C; IR (KBr): ν_{max} = 3053, 2955, 2928, 2880, 1668, 1659, 1591, 1582, 1479, 1470, 1238, 1190, 1034, 926, 814, 660, 609, 515, 459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, *J* = 1.6 Hz, 1H, ArH), 6.67 (dd, *J* = 8.4, 1.6 & 1.2 Hz, 1H, ArH), 6.58 (d, *J* = 8.0 Hz, 1H, ArH), 5.79 (s, 2H, –CH_2), 4.59 (s, 1H, –CH), 2.38 (s, 4H, 2 × –CH_2), 2.17 (d, *J* = 16.8 Hz, 2H, –CH_2), 2.11 (d, *J* = 16.0 Hz, 2H, –CH_2), 1.03 (s, 6H, 2 × –CH_3), 0.94 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.39 (2C), 162.07 (2C), 147.27, 145.91, 138.25, 121.50, 115.65, 109.07, 107.81 (2C), 100.70, 50.74 (2C), 40.82 (2C), 32.14 (2C), 31.42, 29.16 (2C), 27.41 (2C); ESI-TOF-MS: 417.1684 [M + Na]$^+$. Anal. calcd for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64; found: C, 73.13; H, 6.61%.

3,3,6,6-Tetramethyl-9-(3,4,5-trimethoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3h**): White solid; yield 0.205 g (93%); m.p. 184–185 °C; IR (KBr): ν_{max} = 3076, 2949, 2932, 2881, 1713, 1664, 1587, 1501, 1454, 1230, 1184, 1126, 1007, 933, 879, 839, 760, 717, 673, 615, 577, 511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (s, 2H, ArH), 4.64 (s, 1H, –CH), 3.74 (s, 6H, 2 × –O*C*H_3), 3.70 (s, 3H, –O*C*H_3), 2.40–2.33 (m, 4H, 2 × –CH_2), 2.29–2.16 (m, 4H, 2 × –CH_2), 1.04 (s, 6H, 2 × –CH_3), 0.96 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.43 (2C), 162.30 (2C), 152.74 (2C), 139.68, 136.53, 115.51 (2C), 105.68 (2C), 60.64, 56.05 (2C), 50.69 (2C), 40.85 (2C), 32.74, 32.13, 31.75, 31.05, 29.32 (2C), 27.13; ESI-TOF-MS: 463.2099 [M + Na]$^+$. Anal. calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32; found: C, 70.93; H, 7.34%.

3,3,6,6-Tetramethyl-9,10-diphenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5a**). Yellow solid; yield 0.179 g (84%); m.p. 251–252 °C; IR (KBr): ν_{max} = 3078, 3045, 2955, 2922, 2887, 2853, 1717, 1632, 1578, 1485, 1358, 1265, 1215, 1126, 1074, 1003, 912, 897, 839, 798, 733, 694, 671, 606, 584, 573, 528, 461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 6.4 Hz, 3H, ArH), 7.44 (d, *J* = 7.6 Hz, 2H, ArH), 7.25 (d, *J* = 7.2 Hz, 4H, ArH), 7.10 (t, *J* = 7.2 Hz & 6.8 Hz, 1H, ArH), 5.29 (s, 1H, –CH), 2.24–2.11 (m, 4H, 2 × –CH_2), 2.07 (d, *J* = 17.2 Hz, 2H, –CH_2), 1.82 (d, *J* = 17.6 Hz, 2H, –CH_2), 0.94 (s, 6H, 2 × –CH_3), 0.79 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.73 (2C), 162.19, 159.77, 149.65 (2C), 141.94, 141.91, 138.73, 129.88, 129.31, 129.13 (2C), 129.05, 115.31, 114.65, 114.44, 114.28, 49.96 (2C), 41.59 (2C), 32.19 (2C), 31.95, 29.51 (2C), 26.49 (2C); ESI-TOF-MS: 448.2248 [M + Na]$^+$. Anal. calcd for $C_{29}H_{31}NO_2$: C, 81.85; H, 7.34; N, 3.29; found: C, 81.81; H, 7.31; N, 3.26%.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5b**): Yellow solid; yield 0.193 g (87%); m.p. 223–225 °C; IR (KBr): ν_{max} = 3053, 2957, 1736, 1639, 1605, 1580, 1501, 1456, 1367, 1302, 1227, 1146, 1034, 841, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.45 (m, 3H, ArH), 7.33 (d, *J* = 8.4 Hz, 1H, ArH), 7.32 (d, *J* = 8.4 Hz, 1H, ArH), 7.16 (d, *J* = 8.0 Hz, 1H, ArH), 7.15 (d, *J* = 7.2 Hz, 1H, ArH), 6.85 (t, *J* = 8.8 Hz, 2H, ArH), 5.18 (s, 1H, –CH), 2.13 (d, *J* = 16.0 Hz, 2H, –CH_2), 2.05 (d, *J* = 16.8 Hz, 2H, –CH_2), 2.00 (d, *J* = 17.6 Hz, 2H, –CH_2), 1.74 (dd, *J* = 17.6 & 0.4 Hz, 2H, –CH_2), 0.87 (s, 6H, 2 × –CH_3), 0.72 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.93 (2C), 162.39, 159.97, 149.85 (2C), 142.14, 142.11, 138.93, 130.08, 129.51, 129.34 (2C), 129.25, 114.86 (2C), 114.64, 114.48, 50.16 (2C), 41.79 (2C), 32.40 (2C), 32.16, 29.71 (2C), 26.69 (2C); ESI-TOF-MS: 466.2151 [M + Na]$^+$. Anal. calcd for $C_{29}H_{30}FNO_2$: C, 78.53; H, 6.82; N, 3.16; found: C, 78.59; H, 6.85; N, 3.18%.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5c**). Yellow solid; yield 0.207 g (91%); m.p. 219–221 °C; IR (KBr): ν_{max} = 3059, 2935, 2893, 2860, 1634, 1591, 1363, 1259, 1223, 1134, 1028, 935, 833, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 3H, ArH), 7.19 (dd, *J* = 8.0 & 2.0 Hz, 2H), 7.08 (dd, *J* = 8.0 & 1.6 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 5.06 (s, 1H, –CH), 3.58 (s, 3H, –O*C*H_3), 2.05–1.89 (m, 6H, 3 × –CH_2), 1.65 (d, *J* = 17.2 Hz, 2H, –CH_2), 0.77 (s, 6H, 2 × –CH_3), 0.64 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.83 (2C), 157.57 (2C), 149.47 (2C), 138.99 (2C), 138.66 (2C), 129.29 (2C), 128.69 (2C), 114.67 (2C), 113.36 (2C), 55.01, 50.13 (2C), 41.67 (2C), 32.28 (2C), 31.74, 29.62 (2C), 26.66 (2C); ESI-TOF-MS: 478.2361 [M + Na]$^+$. Anal. calcd for $C_{30}H_{33}NO_3$: C, 79.09; H, 7.30; N, 3.07; found: C, 79.03; H, 7.28; N, 3.09.

9-(4-Hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-10-phenyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5d**): Yellow solid; yield 0.203 g (86%); m.p. 224–226 °C; IR (KBr): ν_{max} = 3470, 2953, 2930, 2870, 1636, 1618, 1591, 1558, 1273, 1221, 1132, 1040, 935, 812, 754, 706, 669, 631, 599, 571, 542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.46 (m, 3H, ArH), 7.15 (dd, *J* = 8.0 & 2.0 Hz, 2H, ArH), 7.06 (s, 1H, ArH), 6.69 (br s, 2H, ArH), 5.13 (s, 1H, –CH), 3.81 (s, 3H, –O*C*H_3), 2.13 (d, *J* = 16.0 Hz, 2H, –CH_2), 2.07 (d, *J* = 16.4 Hz, 2H, –CH_2), 2.00 (d, *J* = 17.6 Hz, 2H, –CH_2), 1.74 (d, *J* = 17.6 Hz, 2H, –CH_2), 0.86 (s, 6H, 2 × –CH_3), 0.74 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.14 (2C), 149.64 (2C), 145.97, 143.74, 139.06, 138.62, 129.41, 129.28, 125.38, 123.75, 119.33, 114.78 (2C), 113.95 (2C), 111.90, 55.84, 50.21 (2C), 41.79 (2C), 32.39 (2C), 32.12, 29.74 (2C), 26.74 (2C); ESI-TOF-MS: 494.2301 [M + Na]$^+$. Anal. calcd for $C_{30}H_{33}NO_4$: C, 76.41; H, 7.05; N, 2.97; found: C, 76.43; H, 7.09; N, 2.94.

9,10-Bis(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5e**): Yellow solid; yield 0.210 g (91%); m.p. 231–233 °C; IR (KBr): ν_{max} = 3024, 2951, 2868, 1637, 1578, 1497, 1452, 1364, 1302, 1259, 1221, 1173, 1136, 1028, 1005, 930, 841, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (td, *J* = 8.0, 6.0, 2.8 Hz, 2H, ArH), 7.20–7.15 (m 4H, ArH), 6.84 (t, *J* = 8.8 & 8.4 Hz, 2H, ArH), 5.17 (s, 1H, –CH), 2.12 (d, *J* = 16.4 Hz, 2H, –CH_2), 2.05 (d, *J* = 16.4 Hz, 2H, –CH_2), 1.99 (d, *J* = 17.6 Hz, 2H, –CH_2), 1.74 (d, *J* = 17.6 Hz, 2H, –CH_2), 0.88 (s, 6H, 2 × –CH_3), 0.74 (s, 6H, 2 × –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.83 (2C), 163.81, 162.42, 161.31, 160.00, 149.63, 141.95, 141.92, 134.92, 134.89, 131.80, 130.92, 129.29, 129.22, 117.28, 114.90, 114.72, 114.68, 50.08 (2C), 41.86 (2C), 32.40 (2C), 32.10, 29.71 (2C), 26.74 (2C); ESI-TOF-MS: 484.2059 [M + Na]$^+$. Anal. calcd for $C_{29}H_{29}F_2NO_2$: C, 75.47; H, 6.33; N, 3.03; found: C, 75.44; H, 6.29; N, 3.06%.

10-(4-Fluorophenyl)-3,3,6,6-tetramethyl-9-(3,4,5-trimethoxyphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (**5f**): Yellow solid; yield 0.237 g (89%); m.p. 238–240 °C; IR (KBr): ν_{max} = 3072, 2993, 2953, 2934, 2818, 1724, 1636, 1580, 1497, 1364, 1312, 1217, 1122, 1009, 856, 815, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20–7.16 (m, 3H, ArH), 7.11–7.07 (m, 1H, ArH), 6.59 (s, 2H, ArH), 5.19 (s, 1H, –CH), 3.76 (s, 6H, 2×–OC*H*$_3$), 3.71 (s, 3H, –OC*H*$_3$), 2.18–2.13 (m, 4H, 2×–CH_2), 2.02 (d, *J* = 17.6 Hz, 2H, –CH_2), 1.74 (d, *J* = 17.2 Hz, 2H, –CH_2), 0.90 (s, 6H, 2×–CH_3), 0.79 (s, 6H, 2×–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.88 (2C), 163.72, 161.22, 152.77 (2C), 149.56 (2C), 141.52, 136.24, 134.93, 126.20, 117.37, 116.25, 114.59 (2C), 104.94 (2C), 60.69, 55.97 (2C), 50.11 (2C), 41.88 (2C), 32.34, 32.29, 29.83 (2C), 28.24, 26.67 (2C); ESI-TOF-MS: 556.2469 $[M+Na]^+$. Anal. calcd for $C_{32}H_{36}FNO_5$: C, 72.02; H, 6.80; N, 2.62; found: C, 72.06; H, 6.79; N, 2.66%.

2,2'-Phenylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**7a**): White solid; m.p. 192–194 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 11.91 (s, 1H, –O*H*), 7.28–7.18 (m, 3H, ArH), 7.01 (d, *J* = 8.0 Hz, 2H, ArH), 5.52 (s, 1H, –CH), 2.41–2.26 (m, 8H, 4×–CH_2), 1.24 (s, 6H, 2×–CH_3), 1.11 (s, 6H, 2×–CH_3). Physical and spectral data of **7a** are in accordance to the values reported in literature.[25]

Crystallographic description

X-ray intensity data were collected on X'calibur, computer-controlled single crystal X-ray diffractometer having CCD Camera equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 × 0.20 × 0.20 mm. The cell dimensions were determined by least-squares fit of angular settings of 18306 reflections in the θ range 3.36 to 29.16°. The intensities were measured by ω scan mode for θ ranges 3.46 to 26.00°. 2985 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarisation and absorption factors. The structure was solved by direct methods using SHELXS97.[26] An ORTEP view of the title compound with atomic labelling is shown in Figure 2.[27] The geometry of the molecule was calculated using the WinGX,[28] PARST[29] and PLATON[30] software. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97.[26] All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms. The final refinement cycles converged to an R = 0.0522 and wR (F^2) = 0.1360 for the observed data. Residual electron densities ranged from –0.168 to 0.177 $eÅ^{-3}$. Compound **5e** (Table 2, entry 13) empirical formula $C_{29}H_{29}F_2NO_2$, white blocked shaped crystal, formula wt 461.53, space group $P2_1/c$ with the unit-cell parameters: *a* = 12.1310(4) Å, *b* = 10.7015(3) Å, *c* = 19.6436(6) Å and β = 104.004(3)° and Z = 4. Complete crystallographic data of 9,10-bis(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-acridine-1,8(2*H*,5*H*)-dione (**5e**) (Table 2, entry 13) for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 971310. Copies of this information may be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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