Studies on polycyclic fluoroazaarenes: synthesis of *trans*-9-fluoro- and -11-fluoro 3,4-dihydroxy-3,4-dihydrobenz[*c*]acridines as potential proximate carcinogenic metabolites of fluorobenz[*c*]-acridine

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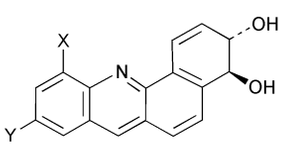
Stereoselective syntheses of the title compounds *trans*-9-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine **1a** and *trans*-11-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine **1b**, as proximate carcinogenic metabolites of 9- and 11-fluorobenz[*c*]acridines, respectively, are described. In order to compare mutagenic activities with their parent fluoroazaarenes, 9-fluorobenz[*c*]acridine **2a** and 11-fluorobenz[*c*]acridine **2b**, have also been synthesised. The dihydrodiols were obtained by the stereoselective reduction of *o*-quinones, which in turn were synthesised by following the protocol of functional group transformation of methoxy ⟶ phenol ⟶ *o*-quinone.

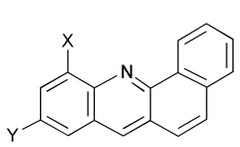
Introduction

Dihydrodiols are putative proximate carcinogenic metabolites that are converted *in vivo* to the corresponding *anti*- and *syn*-diol epoxide metabolites by microsomal mixed function oxidase enzymes.[1] For the last few decades much effort has been directed by various groups, especially by Harvey *et al.*,[1,2] Jerina *et al.*,[3] Lehr *et al.*[4] and various other groups[5] including our laboratory,[6] towards the synthesis and biological evaluation of many suspected mutagenic polyaromatic hydrocarbons (PAH), polycyclic azaarenes (PAA) as well as their oxidative metabolites. PAHs and PAAs are widespread in the biosphere as serious environmental pollutants due to incomplete combustion of fossil fuels mainly from energy industries and automobile exhausts.[7] It is now well established that PAHs or PAAs exert their mutagenic activities not directly but through their oxidative metabolites, formed either by ionic or one-electron oxidation pathways, identified as *syn*- or *anti*-*trans* dihydrodiol epoxides.[1,8]

Carcinogenic activities of polycyclic aromatic hydrocarbons are often strongly affected by the substitution of fluorine at appropriate molecular sites.[1,9] Among the fluoro derivatives of 7,12-dimethylbenz[*a*]anthracene (DMBA), the 10-fluoro-7,12-dimethylbenz[*a*]anthracene exhibits higher tumerogenic and mutagenic activity in mouse skin and human hepatoma (HepG2) cell mediated assay,[10] though the analogous 1-, 2-, 4- or 5-fluoro derivatives were found to be less active [10*a*,11] than 7,12-dimethylbenz[*a*]anthracene. However in the case of other regioisomeric fluoro derivatives of DMBA there is no significant loss of activity compared with the parent hydrocarbons.[10*a*,11] Similar effects have also been observed for 7- and 12-monomethyl analogs of benz[*a*]anthracene.[10*b*,10*c*,12] The presence of fluorine at a suitable position can alter the conformation of two hydroxy groups to affect the mutagenic activity of the *trans* diol epoxide derivatives.[13] To the best of our knowledge, there have been no reports on the synthesis or biological evaluation of dihydrodiols of fluoro derivatives of benz[*c*]acridine. Therefore, we undertook the synthesis of two potential dihydrodiol metabolites of two isomeric fluorobenz[*c*]acridines, **1a**,**b** (see Scheme 1) as well as their parent fluoroazaarenes **2a**,**b** (see Scheme 2).



1a (X = H, Y = F)
1b (X = F, Y = H)



2a (X = H, Y = F)
2b (X = F, Y = H)

Results and discussion

Herein we report the first synthesis of the hitherto unknown *trans*-9-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine **1a** and 11-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine **1b**, as oxidative metabolites of 9- and 11-fluorobenzacridine derivatives, in six high yielding steps starting from 1-chloro-6-methoxy-3,4-dihydro-2-naphthaldehyde **3**,[14] except the last step for which the yield was 35% only (Scheme 1).

Our method involves two key steps—first the construction of a suitable fluoro substituted methoxybenz[*c*]acridine by thermolysis of arylenaminoimine hydrochlorides and second the construction of the *trans* diol moiety by stereoselective reduction of *o*-quinone which in turn was obtained by following the protocol of functional group transformation of methoxy ⟶ phenol ⟶ *o*-quinone.

Thus, treatment of chloroaldehyde **3** with 2.5 equiv. of 4-fluoroaniline **4a** in ethanol in the presence of conc. HCl (catalytic) afforded the arylenaminoimine hydrochloride **5a** in 88% yield. When the arylenaminoimine derivative **5a** was heated at 200–250 °C for 2–3 minutes, 9-fluoro-3-methoxy-5,6-dihydrobenz[*c*]acridine **6a** was obtained in 71% yield. Aromatization (DDQ–chlorobenzene, reflux) followed by demethylation (48% aq. HBr, reflux) of the product generated

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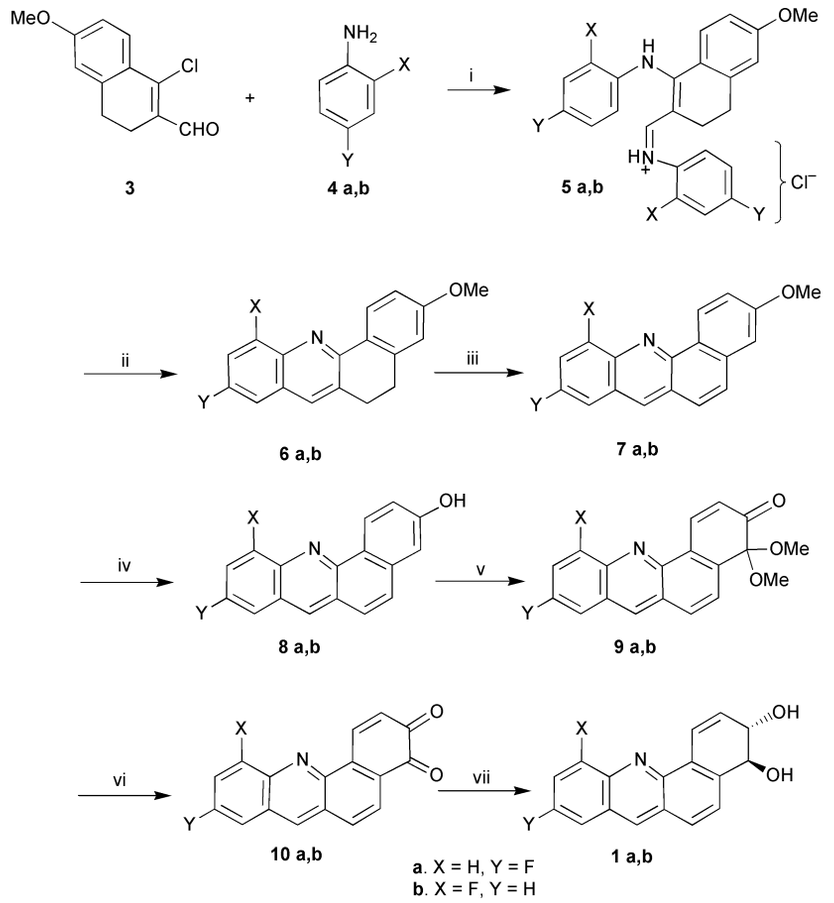
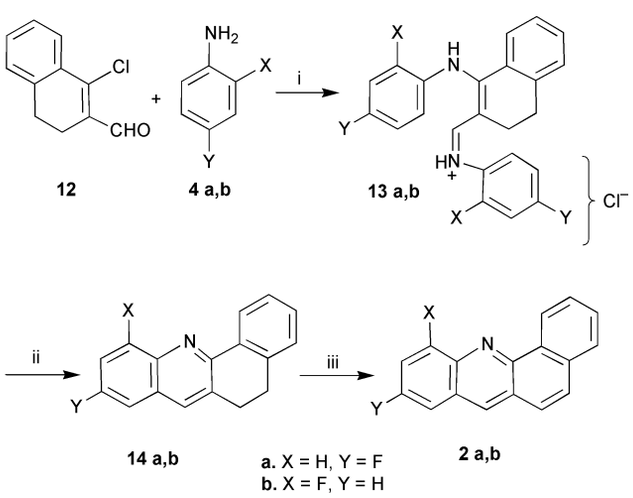


Scheme 1 *Reagents and conditions*: i) EtOH, HCl (catalytic), rt, 3 h; ii) 200–250 °C, 3 min; iii) DDQ, chlorobenzene, reflux, 7 h; iv) 48% aq. HBr, reflux, 6 h; v) PIDA, MeOH, rt, 6 h, under argon; vi) HCl (catalytic), AcOH–H_2O, rt, 1 h; vii) $NaBH_4$, EtOH, O_2, rt, 13 h.



Scheme 2 *Reagents and conditions*: i) EtOH, HCl, (catalytic), rt, 3 h; ii) 200–250 °C, 3 min; iii) DDQ, chlorobenzene, reflux, 6 h.

9-fluoro-3-hydroxybenz[*c*]acridine **8a** in 79% yield. Oxidation[15] of **8a** with phenyliodonium diacetate (PIDA) resulted in the formation of the *o*-quinone monoketal **9a** as a yellow solid, which on hydrolysis with aq. HCl in acetic acid gave the *o*-quinone **10a** as a dark brown solid in 53% yield. Stereoselective reduction[16] of this quinone with excess of sodium borohydride in ethanol under an O_2 atmosphere gave *trans*-9-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine **1a** in a moderate yield, as a light yellow solid. Following a similar sequence of reactions, starting from chloroaldehyde **3** and 2-fluoroaniline **4b**, *trans*-11-fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (**1b**) was obtained also as a light yellow solid. In order to compare the mutagenic and/or carcinogenic activities of these dihydrodiols with their parent fluoroazaarenes, we have also synthesised the 9- and 11-fluoro derivatives of benz[*c*]acridine (Scheme 2).

Thus the reaction of the chloroaldehyde **12**[17] with 2.5 equiv. of 2- or 4-fluoroaniline in EtOH–HCl (cat.) produced the arylenaminoimine hydrochlorides **13a**,**b** in 73–74% yield. Thermolysis of the arylenaminoimine derivatives **13a**,**b**, followed by aromatization (DDQ–chlorobenzene) of the products **14a**,**b** as before, afforded the fluoroazaarenes **2a**,**b** in 74–76% yield.

The compounds were characterised by spectroscopic data. The structures of **14b** and **2b** were also established by single crystal X-ray structure determination and are shown in Fig. 1. The *trans* configuration of the dihydrodiol was assigned based on the relatively large coupling constant of H3 and H4 ($J_{3,4}$) as observed in the ^{1}H NMR spectra of dihydrodiols **1a** and **1b** (Fig. 2). The coupling constants of $J_{3,4}$ = 10.5 and 10.9 Hz respectively clearly suggested that the two hydroxy groups are *trans* to each other.[1,4] The dihydrodiols **1a** and **1b** were found to be more mutagenic than their parent azaarenes **2a** and **2b** on short-term mutagenic assay (Table 1). Although the metabolism of benz[*c*]acridine by rat liver microsomes was conducted earlier by Jacob *et. al.* [18a] who reported that the K-region diol is the predominant product, they did not clearly delineate the pathway through 3,4-diols, thus giving us the rationale to undertake the current study. In our studies, we found that the *trans*-dihydrodiol (**1a** and **1b**) of the respective fluorobenz[*c*]-acridines showed no decrease in mutagenicity compared to their parent fluoroazaarenes **2a** and **2b** respectively. This is expected because the presence of fluorine in the non bay region terminal ring will block the metabolism at this region but the metabolism of the bay region terminal ring will not be affected. Fluorination is merely a tool for metabolism studies. Fluorine atoms present in the terminal ring of **1a** and **1b** are not involved

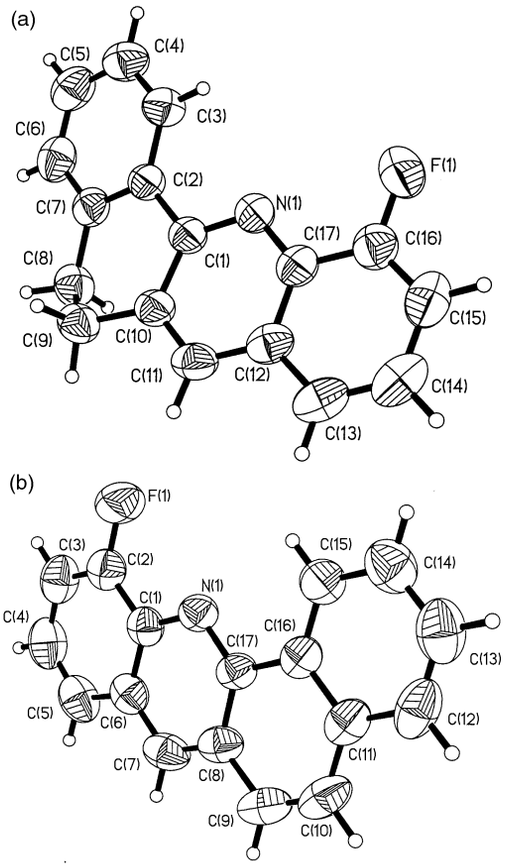


Fig. 1 a) ORTEP plot of compound **14b**. b. ORTEP plot of compound **2b**.

in the metabolism as evidenced by the fact that the mutagenicity of diol **1a** and **1b** does not decline. Therefore it seems that the bay region diol must be involved in the mutagenesis and carcinogenesis of the 9- and 11-fluorobenz[*c*]acridine. Also the presence of a fluorine atom in the non-interactive position of dihydrodiols **1a** and **1b** does not reduce their mutagenicity compared to analogous dihydrodiols of unsubstituted benz[*c*]acridine.[18*b*]

Experimental

General

All the melting points are uncorrected and were obtained in an open glass capillary using a sulfuric acid bath. 2- and 4-Fluoroanilines were purchased from Spectrochem, India Ltd. NMR spectra were recorded on Bruker (300 or 500 MHz) spectrometers with tetramethylsilane as the internal standard. Elemental analyses were obtained from CDRI, Lucknow. The solvents and other reagents used were purified using standard procedures.

General method for the preparation of arylenaminoimine hydrochlorides 5a,b and 13a,b

To a cooled (0–5 °C), stirred solution of 2-/4-fluoroaniline (2.5 equiv.) in 10–15 mL dehydrated ethanol containing a drop of conc. HCl, a solution of the chloroaldehyde (**3** or **12**) (1 equivalent) was slowly added. The mixture was allowed to attain room temperature and stirring was continued at this temperature for another 3 h, the mixture was then cooled in ice and filtered. The dark red residue was washed with a little ice-cold ethanol, dried and was used without further purification.

1-(4-Fluorophenylamino)-2-(4-fluorophenyliminomethyl)-6-methoxy-3,4-dihydronaphthalene hydrochloride (5a). Dark red solid; mp 188–190 °C (decomp.); yield 88%; IR (KBr) ν_{max} 1595, 2980, and 3375 cm^{-1}.

1-(2-Fluorophenylamino)-2-(2-fluorophenyliminomethyl)-6-methoxy-3,4-dihydronaphthalene hydrochloride (5b). Dark red solid; mp 169–171 °C (decomp.); yield 77%; IR (KBr) ν_{max} 1585, 2875, and 3310 cm^{-1}.

1-(4-Fluorophenylamino)-2-(4-fluorophenyliminomethyl)-3,4-dihydronaphthalene hydrochloride (13a). Brick red solid; mp 228–230 °C (decomp.); yield 74%; IR (KBr) ν_{max} 1570, 2900, and 3405 cm^{-1}.

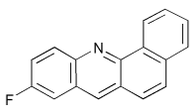
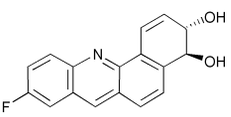
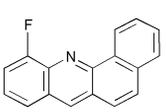
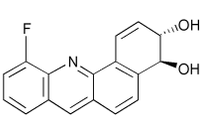
1-(2-Fluorophenylamino)-2-(2-fluorophenyliminomethyl)-3,4-dihydronaphthalene hydrochloride (13b). Dark red solid; mp 155–156 °C (decomp.); yield 73%; IR (KBr) ν_{max} 1565, 2700, and 3305 cm^{-1}.

Thermolysis of arylenaminoimine hydrochlorides: general method for the preparation of 6a,b and 14a,b

The arylenaminoimine derivative **5** or **13** was heated at 200–250 °C for 3–4 minutes in a long necked tube. Arylamine hydrochloride, deposited in the cooler part of the test tube, was removed. The cooled residue was extracted with chloroform, washed with water, and dried (Na_2SO_4), and the solvent was removed to get the crude product which was redissolved in benzene and filtered through a short column of neutral Al_2O_3. Removal of solvent followed by recrystallization from chloroform–petroleum ether (60–80 °C) afforded the desired dihydroazaarene derivatives.

9-Fluoro-3-methoxy-5,6-dihydrobenz[*c*]acridine (6a). Pale yellow solid; mp 96–98 °C (chloroform–petroleum ether, 60–80 °C); yield 71%; ^{1}H NMR ($CDCl_3$) δ 2.95–3.01 (m, 2H, CH_2), 3.07–3.13 (m, 2H, CH_2), 3.88 (s, 3H, CH_3), 6.79 (d, 1H, J = 2.5

Table 1 Mutagenicity tests

Test compound	Concentration (μg/plate)	TA100 (revertants/plate)
DMSO	100 μl pl^{-1}	110 ± 6
2-Aminoacridine	5 μg pl^{-1}	858 ± 26
9-Fluorobenz[*c*]acridine (**2a**) 	1280	503 ± 15
	640	411 ± 16
	320	360 ± 28
	160	306 ± 21
	80	249 ± 18
	40	244 ± 22
	20	248 ± 10
9-Fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (**1a**) 	1280	1137 ± 42
	640	1175 ± 61
	320	1198 ± 91
	160	1269 ± 109
	80	1263 ± 122
	40	1183 ± 66
	20	918 ± 134
11-Fluorobenz[*c*]acridine (**2b**) 	640	408 ± 30
	320	370 ± 29
	160	390 ± 36
	80	398 ± 4
	40	356 ± 18
	20	296 ± 30
11-Fluoro-3,4-dihydroxy-3,4 dihydrobenz[*c*]acridine (**1b**) 	640	1243 ± 70
	320	1180 ± 147
	160	1170 ± 95
	80	1153 ± 65
	40	1066 ± 53
	20	933 ± 62

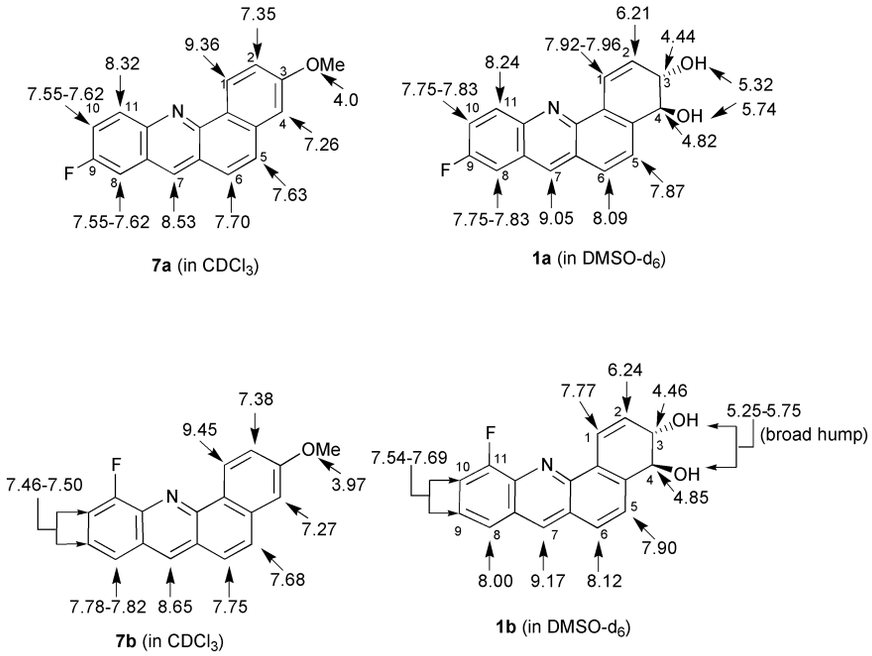


Fig. 2 Representative ^{1}H NMR data of compounds **1a**,**b** and **7a**,**b** in δ ppm.

Hz, aromatic), 6.96 (dd, 1H, J = 2.5 and 8.6 Hz, aromatic), 7.31–7.42 (m, 2H, aromatic), 7.82 (s, 1H, aromatic), 8.07 (dd, 1H, $J_{H11,F}$ = 5.4 Hz, $J_{H10,H11}$ = 9.1 Hz, aromatic), 8.47 (d, 1H, J = 8.6 Hz, aromatic); ^{13}CNMR ($CDCl_3$) δ 28.57, 28.85, 55.32, 109.94 (d, J_{C-F} = 21.7 Hz), 113.00, 113.09, 118.67 (d, J_{C-F} = 25.8 Hz), 127.60, 127.80, 128.06, 130.93, 131.25 (d, J_{C-F} = 9.4 Hz), 133.06, 141.14, 144.01, 152.77, 160.14 (d, J_{C-F} = 245.0 Hz), 161.08 [Calc. for $C_{18}H_{14}NOF$: C, 77.42; H, 5.02; N, 5.02. Found: C, 77.17; H, 4.86; N, 4.81%].

11-Fluoro-3-methoxy-5,6-dihydrobenz[*c*]acridine (6b). Pale yellow solid, mp 65–66 °C (chloroform–petroleum ether, 60–80 °C); yield 68%; ^{1}H NMR ($CDCl_3$) δ 2.92–3.00 (m, 2H, CH_2), 3.09–3.14 (m, 2H, CH_2), 3.88 (s, 3H, CH_3), 6.79 (br s, 1H, aromatic), 6.96 (dd, 1H, J = 2.2 and 8.6 Hz, aromatic), 7.27–7.39 (m, 2H, aromatic), 7.50 (d, 1H, J = 7.0 Hz, aromatic), 7.88 (s, 1H, aromatic), 8.56 (d, 1H, J = 8.6 Hz, aromatic) [Calc. for $C_{18}H_{14}NOF$: C, 77.42; H, 5.02; N, 5.02. Found: C, 77.20; H, 4.79; N, 4.83%].

9-Fluoro-5,6-dihydrobenz[*c*]acridine (14a). White solid; mp 84–85 °C (chloroform–petroleum ether, 60–80 °C); yield 67%; ^{1}H NMR ($CDCl_3$) δ 3.01 (t, 2H, J = 7.4 Hz, CH_2), 3.12 (t, 2H, J = 7.4 Hz, CH_2), 7.27–7.45 (m, 5H, aromatic), 7.85 (s, 1H, aromatic), 8.12 (dd, 1H, $J_{H11,F}$ = 5.4 Hz, $J_{H10,H11}$ = 9.1 Hz, aromatic), 8.54 (d, 1H, J = 7.6 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 28.49, 29.06, 110.20 (d, J_{C-F} = 21.4 Hz), 118.96 (d, J_{C-F} = 25.6 Hz), 126.10, 127.59, 128.22, 128.51, 129.96, 131.69, 132.01 (d, J_{C-F} = 9.2 Hz), 133.26, 133.30, 139.47, 144.90, 153.08, 160.56 (d, J_{C-F} = 245.8 Hz) [Calc. for $C_{17}H_{12}NF$: C, 81.93; H, 4.82; N, 5.62. Found: C, 81.80; H, 4.68; N, 5.49%].

11-Fluoro-5,6-dihydrobenz[*c*]acridine (14b). White solid; mp 95–96 °C (chloroform–petroleum ether, 60–80 °C); yield 65%; ^{1}H NMR ($CDCl_3$) δ 2.99–3.03 (m, 2H, CH_2), 3.11–3.15 (m, 2H, CH_2), 7.25–7.42 (m, 5H, aromatic), 7.51 (d, 1H, J = 8.2 Hz, aromatic), 7.92 (s, 1H, aromatic), 8.62 (d, 1H, J = 7.4 Hz, aromatic) [Calc. for $C_{17}H_{12}NF$: C, 81.93; H, 4.82; N, 5.62. Found: C, 81.75; H, 4.73; N, 5.41%].

Aromatization: general procedure for the preparation of 7a,b and 2a,b

To a solution of dihydroazaarene **6** or **14** (6.9 mmol) in chlorobenzene (10 mL), DDQ (2.3 g, 10 mmol) was added and the mixture was refluxed for 6–7 hours and then filtered directly through a column of neutral alumina. Further elution with benzene followed by removal of solvent under reduced pressure produced the crude product, which was further purified by recrystallization from petroleum ether (60–80 °C)–benzene mixture.

9-Fluoro-3-methoxybenz[*c*]acridine (7a). White solid; mp 127–129 °C (chloroform–petroleum ether, 60–80 °C); yield 87 %; ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 3H, CH_3), 7.26 (d, 1H, J = 2.5 Hz, aromatic), 7.36 (dd, 1H, J = 2.5 and 8.9 Hz, aromatic), 7.55–7.62 (m, 2H, aromatic), 7.64 (d, 1H, J = 9.1 Hz, aromatic), 7.71 (d, 1H, J = 9.1 Hz, aromatic), 8.32 (dd, 1H, $J_{H11,F}$ = 5.7 Hz, $J_{H10,H11}$ = 10.0 Hz, aromatic), 8.53 (s, 1H, aromatic), 9.36 (d, 1H, J = 8.9 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 55.75, 109.43, 110.08 (d, J_{C-F} = 21.4 Hz), 116.97, 120.87 (d, J_{C-F} = 26.9 Hz), 124.99, 125.71, 126.27, 126.91, 126.99, 128.32, 132.32 (d, J_{C-F} = 8.8 Hz), 134.39 (d, J_{C-F} = 6.3 Hz), 135.59, 145.30, 147.45, 159.98 (d, J_{C-F} = 245.0 Hz), 160.65 [Calc. for $C_{18}H_{12}NOF$: C, 77.98; H, 4.33; N, 5.05. Found: C, 77.77; H, 4.12; N, 4.85%].

11-Fluoro-3-methoxybenz[*c*]acridine (7b). Light yellow solid; mp 140–142 °C (chloroform–petroleum ether, 60–80 °C); yield 78%; ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H, CH_3), 7.27 (d, 1H, J = 2.6 Hz, aromatic), 7.38 (dd, 1H, J = 2.6 and 8.9 Hz, aromatic), 7.46–7.50 (m, 2H, aromatic), 7.68 (d, 1H, J = 9.0 Hz, aromatic), 7.75 (d, 1H, J = 9.0 Hz, aromatic), 7.78–7.82 (m, 1H, aromatic), 8.65 (s, 1H, aromatic), 9.45 (d, 1H, J = 8.9 Hz, aromatic).

9-Fluorobenz[*c*]acridine (2a). White solid; mp 144–145 °C (chloroform–petroleum ether, 60–80 °C); yield 76%; ^{1}H NMR ($CDCl_3$) δ 7.57–7.63 (m, 2H, aromatic), 7.71–7.80 (m, 4H, aromatic), 7.86–7.89 (m, 1H, aromatic), 8.37 (br dd, 1H, $J_{H11,F}$ = 5.5 Hz, $J_{H10,H11}$ = 10.2 Hz, aromatic), 8.57 (s, 1H, aromatic), 9.46 (dd, 1H, J = 1.8 and 7.5 Hz, aromatic); ^{13}C NMR ($CDCl_3$) δ 109.79 (d, J_{C-F} = 21.5 Hz), 120.71 (d, J_{C-F} = 26.7 Hz), 125.12, 125.29, 125.47, 127.10, 127.31, 127.43, 128.33, 128.73, 129.09, 132.32 (d, J_{C-F} = 9.3 Hz), 133.79, 134.19, 144.83, 147.17, 160.03 (d, J_{C-F} = 247.0 Hz) [Calc. for $C_{17}H_{10}NF$: C, 82.59; H, 4.05; N, 5.67. Found: C, 82.44; H, 3.86; N, 5.51%].

11-Fluorobenz[*c*]acridine (2b). Pale yellow solid; mp 125–127 °C (chloroform–petroleum ether, 60–80 °C); yield 74%; ^{1}H

NMR ($CDCl_3$) δ 7.46–7.53 (m, 2H, aromatic), 7.75–7.79 (m, 6H, aromatic), 8.67 (s, 1H, aromatic), 9.56 (dd, 1H, J = 1.6 and 7.4 Hz, aromatic) [Calc. for $C_{17}H_{10}NF$: C, 82.59; H, 4.05; N, 5.67. Found: C, 82.41; H, 3.80; N, 5.45%].

Demethylation: general method for the preparation of 8a,b

The methoxyazaarene **7** (120 mg, 0.43 mmol) was refluxed with 48% aq. HBr (10 mL). Initially the compound dissolved in HBr but after about 1 hour, a yellow solid separated out. Refluxing was continued for an additional 6 hours and then the mixture was cooled, diluted with water and neutralized with aqueous $NaHCO_3$. The precipitated solid was filtered, washed well with water and dried. The crude product on recrystallization from petroleum ether (60–80 °C)–ethyl acetate mixture afforded the phenol **8** as a bright yellow solid.

9-Fluoro-3-hydroxybenz[*c*]acridine (8a). Yellow solid; mp 219–221 °C (petroleum ether, 60–80 °C–ethyl acetate); yield 79%; ^{1}H NMR (DMSO-d_6) δ 7.27 (dd, 1H, J = 2.4 and 8.4 Hz, aromatic), 7.36 (br s, 1H, aromatic), 7.74 (d, 1H, J = 9.1 Hz, aromatic), 7.75–7.83 (m, 1H, aromatic), 7.84 (d, 1H, J = 9.1 Hz, aromatic), 7.95 (dd, 1H, $J_{H8,F}$ = 9.5 Hz, $J_{H8,H10}$ = 2.8 Hz, aromatic), 8.29 (dd, 1H, $J_{H11,F}$ = 5.5 Hz, $J_{H10,H11}$ = 9.2 Hz, aromatic), 8.9 (s, 1H, aromatic), 9.16 (d, 1H, J = 8.4 Hz, aromatic), 10.18 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 110.33 (d, J_{C-F} = 21.6 Hz), 111.98, 117.31, 120.77 (d, J_{C-F} = 26.8 Hz), 123.43, 124.24, 125.95, 126.24, 126.49, 127.98, 131.74 (d, J_{C-F} = 9.3 Hz), 134.76 (d, J_{C-F} = 6.3 Hz), 135.54, 144.43, 144.86, 158.76, 159.02 (d, J_{C-F} = 244.0 Hz) [Calc. for $C_{17}H_{10}NOF$: C, 77.57; H, 3.80; N, 5.32. Found: C, 77.43; H, 3.56; N, 4.97%].

11-Fluoro-3-hydroxybenz[*c*]acridine (8b). Yellow solid; mp 202–204 °C (petroleum ether, 60–80 °C–ethyl acetate); yield 70%; ^{1}H NMR (DMSO-d_6) δ 7.28–7.31 (m, 2H, aromatic), 7.58–7.71 (m, 2H, aromatic), 7.77 (d, 1H, J = 9.1 Hz, aromatic), 7.89 (d, 1H, J = 9.1 Hz, aromatic), 8.00 (d, 1H, J = 8.0 Hz, aromatic), 9.01 (s, 1H, aromatic), 9.18 (d, 1H, J = 9.5 Hz, aromatic), 10.24 (s, 1H, OH) [Calc. for $C_{17}H_{10}NOF$: C, 77.57; H, 3.80; N, 5.32. Found: C, 77.39; H, 3.61; N, 5.11%].

General method for the synthesis of *o*-quinone monoketal 9a,b

To a stirred solution of the phenol **8** (170 mg, 0.65 mmol) in dry methanol (40 mL) at 0–5 °C, PIDA (265 mg, 0.82 mmol) was added in two batches in about 20 minutes and the stirring was continued at room temperature under an argon atmosphere for an additional 6 hours. The solvent was removed by rotary evaporator and the crude mass obtained was purified by column chromatography [neutral Al_2O_3/petroleum ether, 60–80 °C–ethyl acetate (9 : 1)].

9-Fluoro-4,4-dimethoxy-3-oxo-3,4-dihydrobenz[*c*]acridine (9a). Yellow solid; mp 105–107 °C; yield 66%; IR (KBr) ν_{max} 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 6H, CH_3), 6.42 (d, 1H, J = 10.3 Hz, vinylic H^2), 7.54–7.74 (m, 2H, aromatic), 7.92 (d, 1H, J = 8.8 Hz, aromatic), 8.11 (d, 1H, J = 8.8 Hz, aromatic), 8.28 (br dd, 1H, $J_{H11,F}$ = 5.4 Hz, $J_{H10,H11}$ = 9.2 Hz, aromatic), 8.72 (s, 1H, aromatic), 9.17 (d, 1H, J = 10.3 Hz, vinylic H^1) [Calc. for $C_{19}H_{14}NO_3F$: C, 70.59; H, 4.33; N, 4.33. Found: C, 70.38; H, 4.12; N, 4.09%].

11-Fluoro-4,4-dimethoxy-3-oxo-3,4-dihydrobenz[*c*]acridine (9b). Yellow solid; mp 99–101 °C; yield 64%; IR (KBr) ν_{max} 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 6H, CH_3), 6.44 (d, 1H, J = 10.2 Hz, vinylic H^2), 7.48–7.56 (m, 2H, aromatic), 7.84 (m, 1H, aromatic), 7.95 (d, 1H, J = 8.7 Hz, aromatic), 8.16 (d, 1H, J = 8.7 Hz, aromatic), 8.84 (s, 1H, aromatic), 9.23 (d, 1H, J = 10.2 Hz, vinylic H^1) [Calc. for $C_{19}H_{14}NO_3F$: C, 70.59; H, 4.33; N, 4.33. Found: C, 70.36; H, 4.07; N, 4.16%].

General method for the synthesis of *o*-quinone 10a,b

To an ice cold solution of the *o*-quinone monoketal **9** (100 mg, 0.31 mmol) in glacial acetic acid (4 mL), 1–2 drops of water and one drop of conc. HCl were added. The color of the solution immediately changed to dark red. The solution was stirred at room temperature for 1 hour, and then poured into ice–water (7–8 mL). After neutralization with $NaHCO_3$, the precipitated *o*-quinone was filtered and washed well with water and dried. This was used, directly for the next step, without further purification.

9-Fluoro-3,4-dioxo-3,4-dihydrobenz[*c*]acridine (10a). Dark brown solid; mp >260 °C; yield 53%; IR (KBr) ν_{max} 1610, 1630, 1662 cm^{-1}.

11-Fluoro-3,4-dioxo-3,4-dihydrobenz[*c*]acridine (10b). Brown solid; mp 218–220 °C; yield 58%; IR (KBr) ν_{max} 1608, 1632, 1654 cm^{-1}.

General method for the preparation of *trans*-dihydrodiol 1a,b

To a stirred suspension of the *o*-quinone **10** (30 mg, 0.11 mmol) in 15 mL of ethanol, sodium borohydride (60 mg, 1.58 mmol) was added in 4–5 batches over a ½ hour period. The mixture was stirred at room temperature (with bubbling of O_2 through the reaction mixture) for an additional 13 hours. Ethanol was then removed under reduced pressure; water was added to the residue and extracted with ethyl acetate. The ethyl acetate layer was thoroughly washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude dihydrodiol thus obtained was purified by preparative TLC [silica gel/petroleum ether (60–80 °C)–ethyl acetate mixture (1 : 2)] to furnish the dihydrodiols **1a** or **1b** as a light yellow solid.

***trans*-9-Fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (1a).** Light yellow solid; mp 219–220 °C; yield 35%; ^{1}H NMR (DMSO-d_6) δ 4.44 (m, 1H, allylic H3), 4.82 (dd, 1H, J = 5.2 and 10.5 Hz, benzylic H4), 5.32 (d, 1H, J = 5.2 Hz, OH), 5.74 (d, 1H, J = 5.9 Hz, OH), 6.21 (dd, 1H, J = 2.6 and 10.0 Hz, vinylic H2), 7.75–7.83 (m, 2H, aromatic), 7.87 (d, 1H, J = 8.7 Hz, aromatic), 7.92–7.96 (m, 1H, vinylic H1), 8.07 (d, 1H, J = 8.7 Hz, aromatic), 8.24 (dd, 1H, $J_{H11,F}$ = 5.6 Hz, $J_{H10,H11}$ = 9.5 Hz, aromatic), 9.05 (s, 1H, aromatic) [Calc. for $C_{17}H_{12}NO_2F$: C, 72.60; H, 4.27; N, 4.98. Found C, 72.37; H, 4.02; N, 4.73%].

***trans*-11-Fluoro-3,4-dihydroxy-3,4-dihydrobenz[*c*]acridine (1b).** Yellow solid; mp 188–190 °C; yield 53%; ^{1}H NMR (DMSO-d_6) δ 4.46 (br d, 1H, J = 10.9 Hz, allylic H3), 4.85 (d, 1H, J = 10.9 Hz, benzylic H4), 5.25–5.75 (broad hump, 2H, 2 × OH), 6.24 (dd, 1H, J = 2.5 and 10.1 Hz, vinylic H2), 7.54–7.69 (m, 2H, aromatic), 7.77 (dd, 1H, J = 1.8 and 10.1 Hz, vinylic H1), 7.90 (d, 1H, J = 8.7 Hz, aromatic), 8.00 (d, 1H, J = 8.2 Hz, aromatic), 8.12 (d, 1H, J = 8.7 Hz, aromatic), 9.17 (s, 1H, aromatic) [Calc. for $C_{17}H_{12}NO_2F$: C, 72.60; H, 4.27; N, 4.98. Found C, 72.31; H, 4.05; N, 4.71%].

Mutagenicity assays

Each compound was dissolved in 100 µL of dimethyl sulfoxide. *S. typhimurium* strain TA 100 was used for the mutagenicity assays with pre-incubation.[19,20] In these studies 500 µL of S-9 mix (32 mg of protein mL^{-1}) was used per plate, and 2-aminoacridine at a dose of 5 µg plate^{-1} was employed as the positive control. Reported mutagenicity values are the means of triplicate assays. Background revertants (110 per plate) have not been subtracted. All test compounds show positive response toward *S. typhimurium* strain TA (threshold greater or equal to two times corresponding solvent).

Crystal structure of compound 14b ‡

$C_{17}H_{12}FN$, $M = 249.28$. Monoclinic $P21/n$, $Z = 4$, $a = 8.5080(3)$, $b = 18.2023(7)$, $c = 8.7856(3)$ Å, $\alpha = 90°$, $\beta = 115.393(1)°$, $\gamma = 90°$, $V = 1229.68(8)$ Å^3, $D_c = 1.347$ g cm^{-3}. Data were collected on a Siemens SMART CCD area detector diffractometer equipped with graphite-monochromatized Mo-Kα in the range of $\theta = 2.2–28.4°$. A total of 8409 independent reflections [R(int) = 0.083] were used in the refinement which converged with $R = 0.079$ and $wR = 0.2378$ (GOF = 0.91).

Crystal structure of compound 2b ‡

$C_{17}H_{10}FN$, M=247.26. Monoclinic $P21/n$, $Z = 4$, $a = 7.1978(2)$, $b = 7.7400$, $c = 21.4206(2)$ Å, $\alpha = 90°$, $\beta = 90.622(1)°$, $\gamma = 90°$, $V = 1193.31(3)$ Å^3, $D_c = 1.376$ g cm^{-3}. Data were collected on a Siemens SMART CCD area detector diffractometer equipped with graphite-monochromatized Mo-Kα in the range of $\theta = 1.9–28.3°$. A total of 7967 independent reflections [R(int) = 0.067] were used in the refinement which converged with $R = 0.057$ and $wR = 0.1170$ (GOF = 0.88).

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‡ CCDC reference numbers 168402 and 168403. See http://www.rsc.org/suppdata/p1/b1/b102750f/ for crystallographic files in .cif or other electronic format.

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