

Communication

Supporting Information: Palladium-catalyzed regioselective alkoxylation via C-H bond activation in the dihydrobenzo[*c*]acridine series

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1. General information

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under nitrogen and argon atmosphere with magnetic stirring. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer working at 300 MHz, 75 MHz respectively for ^1H and ^{13}C with chloroform-*d* as solvent. Chemical shifts were reported in δ , parts per million (ppm), relative to chloroform ($\delta = 7.28$ ppm) as international standards unless otherwise stated for proton nuclear magnetic resonance (^1H NMR). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) were reported in δ , parts per million (ppm), relative to the center line of the chloroform triplet ($\delta = 77.07$ ppm). Coupling constants, J , were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. The abbreviations s, d, dd, t, q, br and m stand for resonance multiplicities singlet, doublet, doublet of doublet, triplet, quartet, broad and multiplet, respectively. Allylation diastereoselectivity was determined by ^1H NMR integrations of the methylene signals in the crude products. High resolution Mass Spectrometry data were recorded with an accuracy within 5 ppm on a quadrupole-TOF mass spectrometer (Xevo Q-ToF, Waters) using an electrospray ionization source operating in positive mode. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel plates (Fluka Kiesel gel 60 F254, Merck) and visualized by a 254 nm UV lamp and potassium permanganate. Melting points (Mp) were determined on a System Kofler type WME apparatus. Compounds **1**, **2**, **3**, **4**, **6** and **7** were obtained according to previously reported procedures and show analytical data in agreement with the literature [14, 15].

2. Representative procedure for the preparation of dihydrobenzo[*c*]acridines

A round-bottom flask was charged under argon with chlorovinyl carboxaldehyde (0.5 mmol), amine (2.5 eq.), and dry *isopropanol* (3–5 mL). The reaction mixture was stirred and heated 90 °C for 16h. After cooling down to room temperature, *isopropanol* was evaporated under reduced pressure and the brown organic residue was dissolved in dichloromethane (50mL), extracted successively with water (3 x100 mL) and brine.. The organic layers were separated, dried over magnesium sulfate and the solvent was removed under reduced pressure. Thus residue was subjected to column chromatography purification on silica gel.

3. Characterization data for new dihydrobenzo[*c*]acridines **5** and **8**

2-methoxy-5,6-dihydrobenzo[*c*]acridines 5. Yield: 62%; ^1H NMR (300 MHz, CDCl_3): $\delta = 3.00$ (m, 2H), 3.15 (m, 2H), 6.99 (d, $J = 6.6$ Hz, 1H), 7.23 (d, $J = 10$ Hz, 1H), 7.52 (m, 1H), 7.67 (m, 1H), 7.78 (d, $J = 10$ Hz, 1H), 7.96 (s, 1H), 8.19 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3): $\delta = 27.6, 27.75, 55.6, 109.6, 117.0, 126.1, 126.9, 127.9, 128.7, 129.05, 129.4, 130.7, 131.9, 133.8, 135.7, 147.6, 153.3, 159.1$. HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$ 262.1232, found 262.1224.

11-methyl-5,6-dihydrobenzo[c]acridines 8. Yield: 49%; ^1H NMR (300 MHz, CDCl_3): δ = 2.95 (s, 3H), 3.06 (m, 2H), 3.18 (m, 2H), 7.33 (m, 1H), 7.45 (m, 2H), 7.50 (m, 1H), 7.55 (m, 1H), 7.64 (d, J = 6.6 Hz, 1H), 7.93 (s, 1H), 8.70 (d, J = 6.6 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 17.9, 28.5, 28.7, 124.9, 125.9, 126.4, 127.3, 127.8, 127.95, 128.8, 129.5, 130.1, 133.9, 135.2, 135.2, 137.4, 139.3, 146.5, 152.0. HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{N}$ $[\text{M}+\text{H}]^+$ 246.1283, found 246.1275.

4. Representative procedure for the Pd-catalyzed alkoxylation of dihydrobenzo[c]acridines

The acridine derivative (1 eq.), $\text{PhI}(\text{OAc})_2$ (2 eq.), and $\text{Pd}(\text{OAc})_2$ (0.1 eq.) were placed in a screw capped tube. MeOH (3 mL) was next added and the reaction mixture was stirred for 15 min. The tube was sealed and the suspension was heated with stirring to 100 °C for 16 hours. The crude mixture was filtered through celite and the solvent evaporated. The solid residue was extracted between ethyl acetate and successively water and brine. The organic layers were dried over sodium sulfate and the solvent was removed under vacuum. In all cases the residue was purified by flash column chromatography on silica gel (Petroleum ether/dichloromethane, 6:4) to afford the expected alkoxyacridine derivative.

5. Characterization data for compounds 9 to 15

1-methoxy-5,6-dihydrobenzo[c]acridine 9. Yield: 82%; ^1H NMR (300 MHz, CDCl_3): δ = 2.93 (m, 2H), 3.03 (m, 2H), 4.04 (s, 3H), 6.96 (d, J = 6.6 Hz, 1H), 7.04 (d, J = 6.6 Hz, 1H), 7.38 (m, 1H), 7.54 (m, 1H), 7.68 (m, 1H), 7.76 (d, J = 9 Hz, 1H), 7.95 (s, 1H), 8.20 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 29.7, 30.0, 56.5, 111.7, 120.4, 123.7, 126.2, 126.7, 127.2, 128.4, 129.6, 130.3, 1132.4, 132.85, 143.0, 147.3, 153.5, 158.7. HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{16}\text{NO}$ $[\text{M}+\text{H}]^+$ 262.1232, found 262.1235.

1-chloro-5,6-dihydrobenzo[c]acridine 10. Yield: 63%; ^1H NMR (300 MHz, CDCl_3): δ = 2.96 (m, 2H), 3.07 (m, 2H), 7.26 (m, 4H), 7.52 (m, 1H), 7.57 (m, 1H), 7.72 (m, 1H), 7.84 (d, J = 6 Hz, 1H), 8.00 (s, 1H), 8.22 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 29.35, 30.2, 126.4, 126.7, 126.8, 128.7, 129.5, 129.7, 130.0, 131.0, 132.2, 133.0, 133.25, 133.4, 143.3, 146.9, 152.5. HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{13}\text{NCl}$ $[\text{M}+\text{H}]^+$ 266.0737, found 266.0742.

1-ethoxy-5,6-dihydrobenzo[c]acridine 11. Yield: 61%; ^1H NMR (300 MHz, CDCl_3): δ = 1.50 (t, 3H), 2.84 (m, 2H), 2.95 (m, 2H), 4.15 (q, 2H), 6.85 (d, J = 9 Hz, 1H), 6.93 (d, J = 9 Hz, 1H), 7.23 (m, 1H), 7.42 (m, 1H), 7.58 (m, 1H), 7.67 (d, J = 9 Hz, 1H), 7.87 (s, 1H), 8.07 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 29.35, 30.2, 126.4, 126.7, 126.8, 128.7, 129.5, 129.7, 130.0, 131.0, 132.2, 133.0, 133.25, 133.4, 143.3, 146.9, 152.5. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$ 276.1388, found 276.1390.

1,2-bismethoxy-5,6-dihydrobenzo[c]acridine 12. Yield: 70%; ^1H NMR (300 MHz, CDCl_3): δ = 2.90 (m, 2H), 3.04 (m, 2H), 3.97 (s, 3H), 4.18 (s, 3H), 7.02 (m, 2H), 7.54 (m, 1H), 7.67 (m, 1H), 7.78 (d, J = 9 Hz, 1H), 7.96 (s, 1H), 8.18 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 29.3, 29.95, 56.35, 61.6, 113, 45, 122.7, 126.3, 126.7, 127.3, 128.3, 129.0, 129.9, 132.2, 132.8, 134.1, 147.8, 148.6, 153.1, 153.2. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 292.1338, found 292.1324.

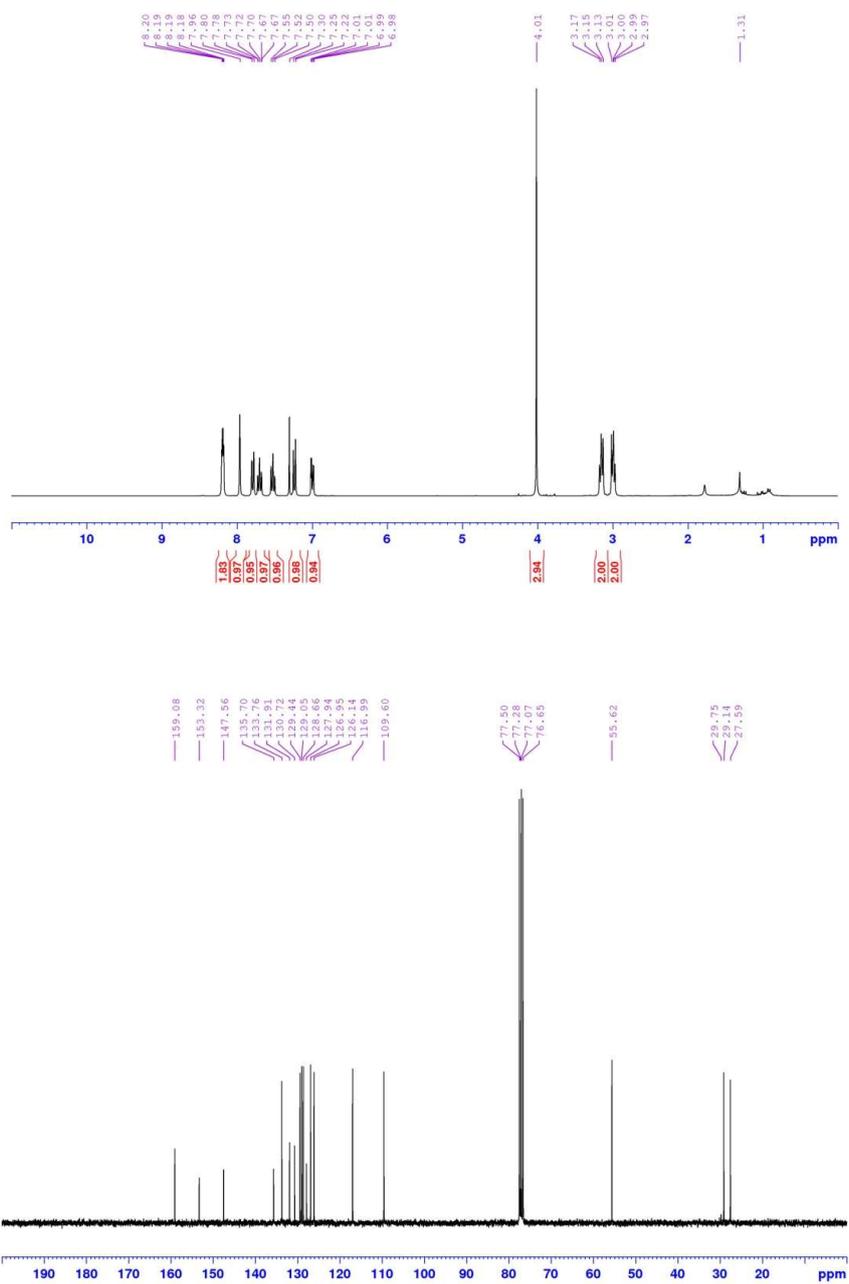
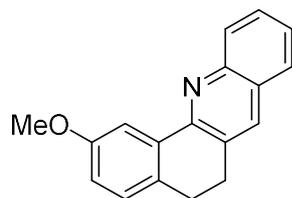
1,3-bismethoxy-5,6-dihydrobenzo[c]acridine 13. Yield: 59%; ^1H NMR (300 MHz, CDCl_3): δ = 3.00 (m, 2H), 3.12 (m, 2H), 4.00 (s, 3H), 4.11 (s, 3H), 6.59 (m, 1H), 6.67 (m, 1H), 7.57 (m, 1H), 7.73 (m, 1H), 7.83 (d, J = 6 Hz, 1H), 8.00 (s, 1H), 8.25 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 29.7, 30.6, 55.4, 56.4, 98.7, 104.8, 117.2, 125.8, 126.6, 126.9, 128.3, 129.4, 131.8, 132.7, 144.4, 147.3, 153.6, 160.2, 161.1. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 292.1338, found 292.1328.

1,9-bismethoxy-5,6-dihydrobenzo[c]acridine 14. Yield: 81%; ^1H NMR (300 MHz, CDCl_3): δ = 3.01 (m, 2H), 3.11 (m, 2H), 4.06 (s, 3H), 4.12 (s, 3H), 7.02 (d, J = 6 Hz, 1H), 7.14 (m, 2H), 7.42 (m, 1H), 8.05 (s, 1H), 8.18 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 29.7, 30.0, 55.5, 56.5, 104.5, 111.7, 120.4, 120.8, 124.5, 125.1, 128.1, 129.8, 131.2, 131.7, 131.8, 132.7, 142.65, 157.7, 158.4. HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 292.1338, found 292.1326.

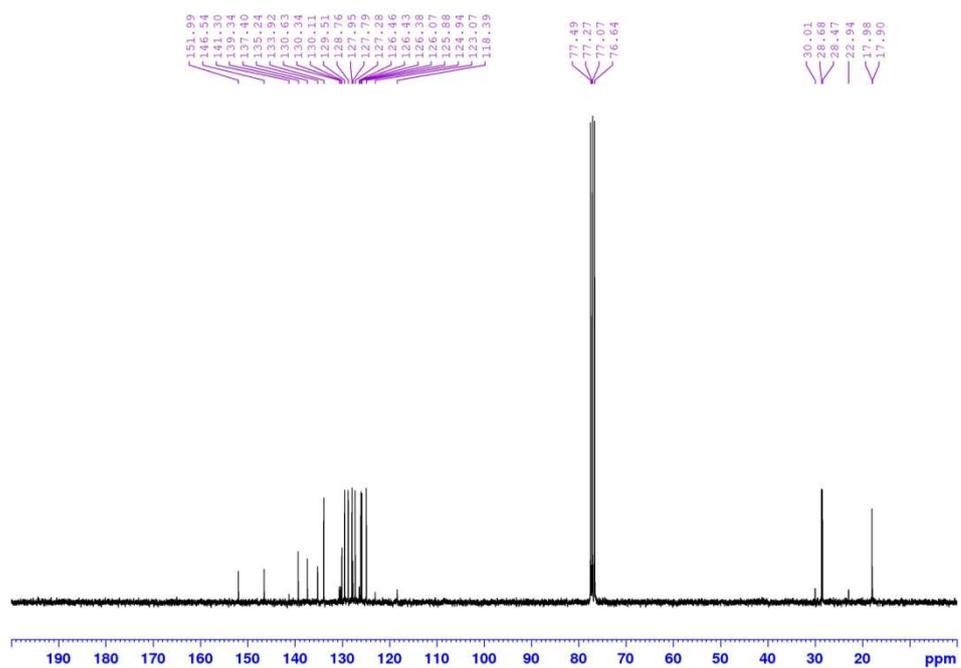
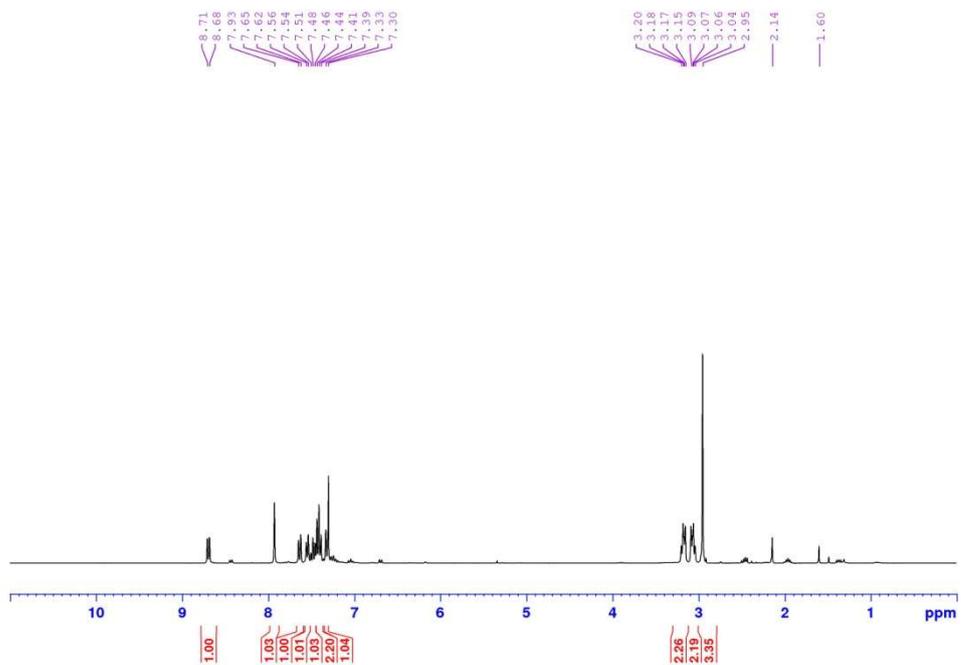
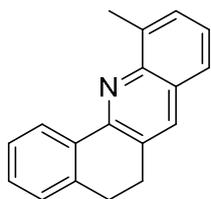
11-acetoxymethylene-5,6-dihydrobenzo[c]acridine 15. Yield: 51%; ^1H NMR (300 MHz, CDCl_3): δ = 2.30 (s, 3H), 3.16 (m, 2H), 3.27 (m, 2H), 6.10 (s, 2H), 7.32 (m, 1H), 7.56 (m, 3H), 7.83 (m, 2H), 8.05 (s, 1H), 8.53 (d, J = 9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ = 21.3, 28.3, 28.7, 63.1, 125.7, 126.3, 127.2, 127.4, 127.6, 127.7, 127.95, 129.8, 130.7, 133.8, 133.9, 134.2, 134.8, 139.3, 145.2, 172.1. HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 304.1338, found 304.1350.

6. ¹H and ¹³C NMR Spectra of new compounds

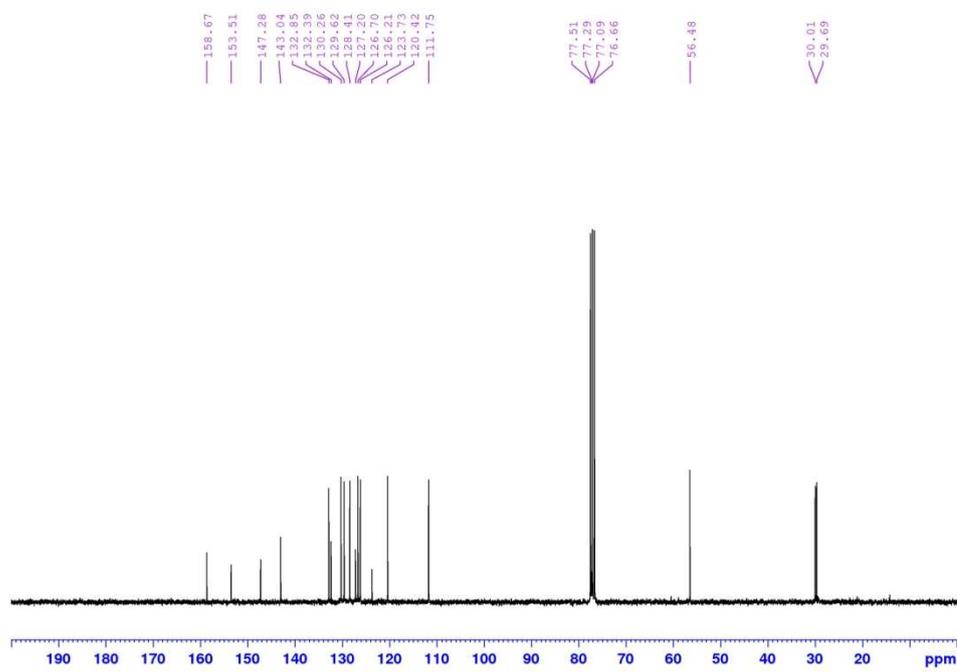
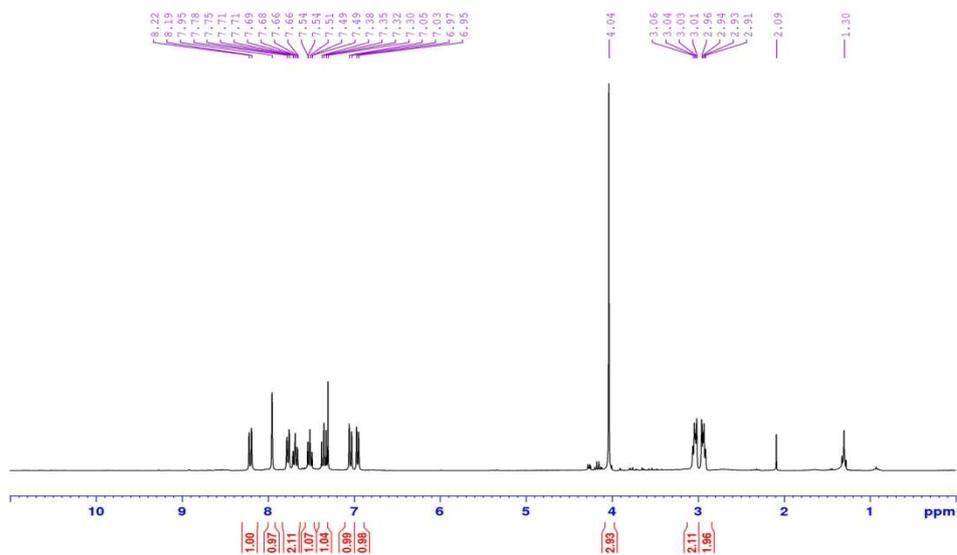
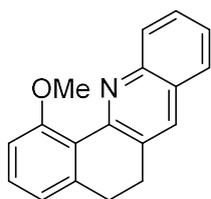
2-methoxy-5,6-dihydrobenzo[c]acridine 5.



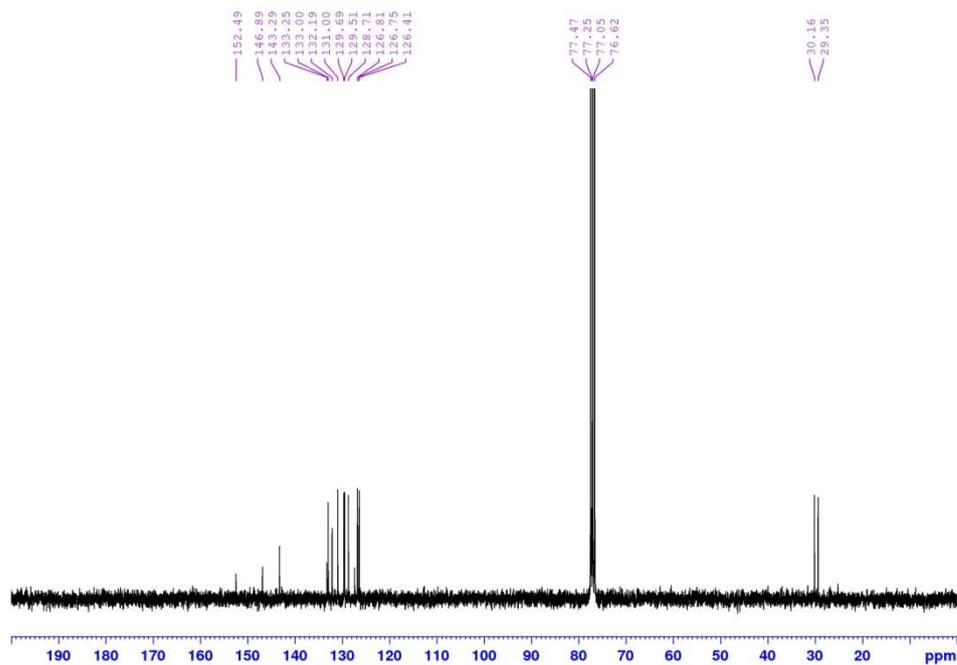
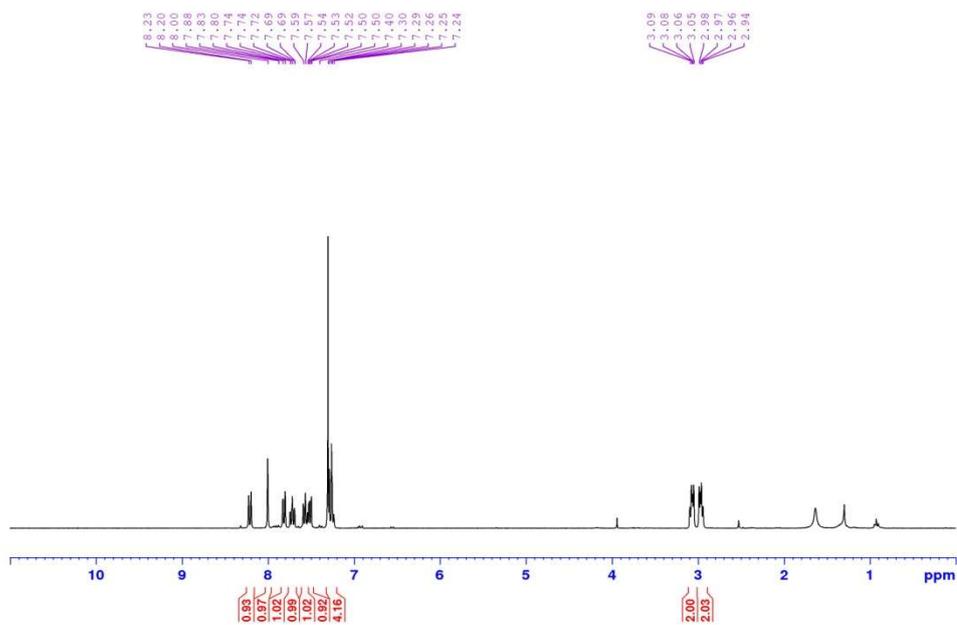
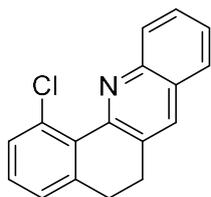
11-methyl-5,6-dihydrobenzo[*c*]acridine 8.



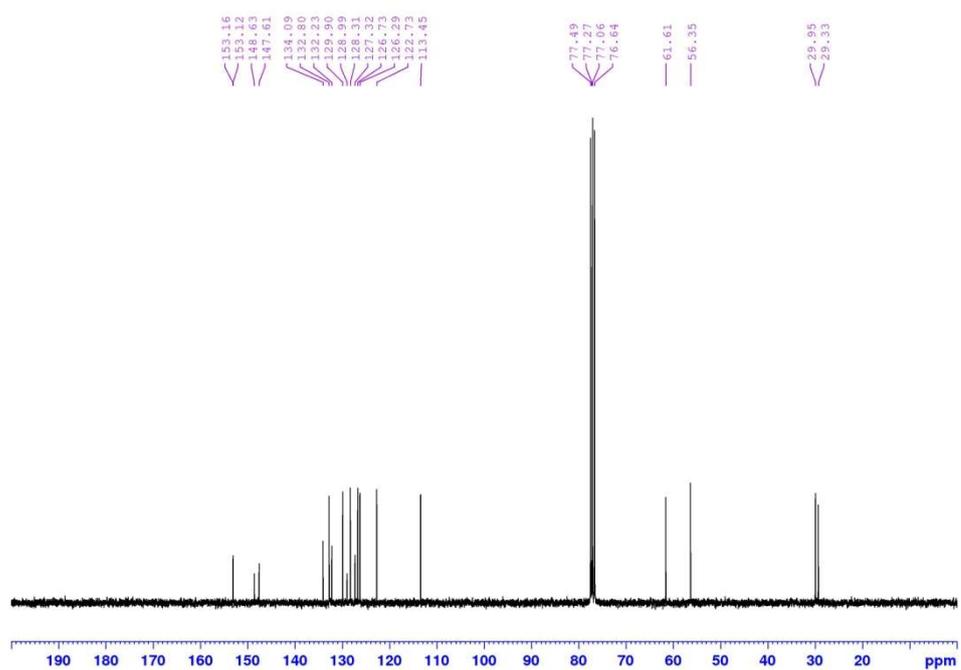
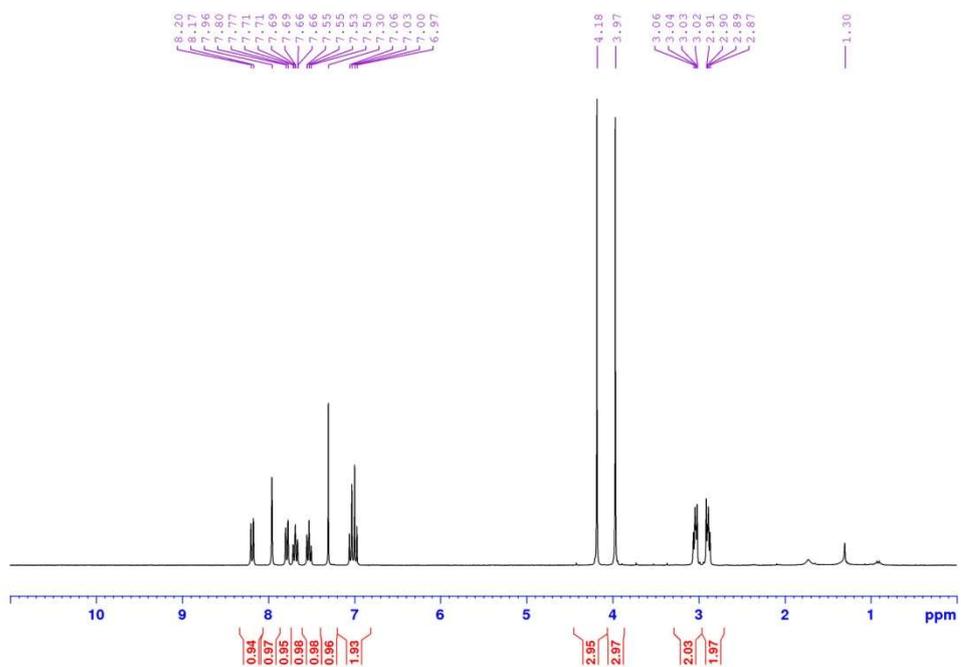
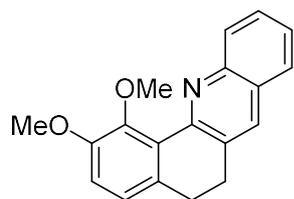
1-methoxy-5,6-dihydrobenzo[c]acridine 9



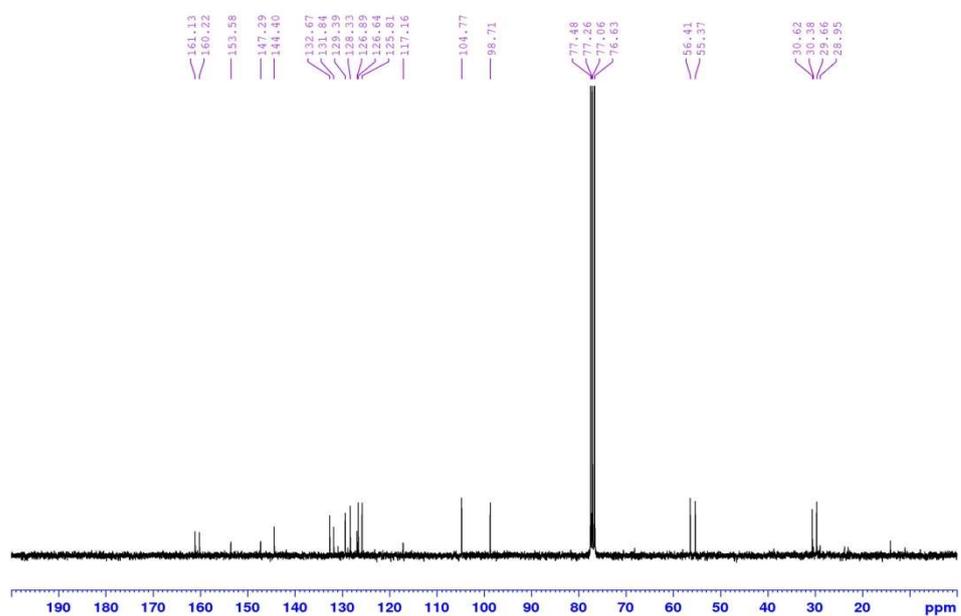
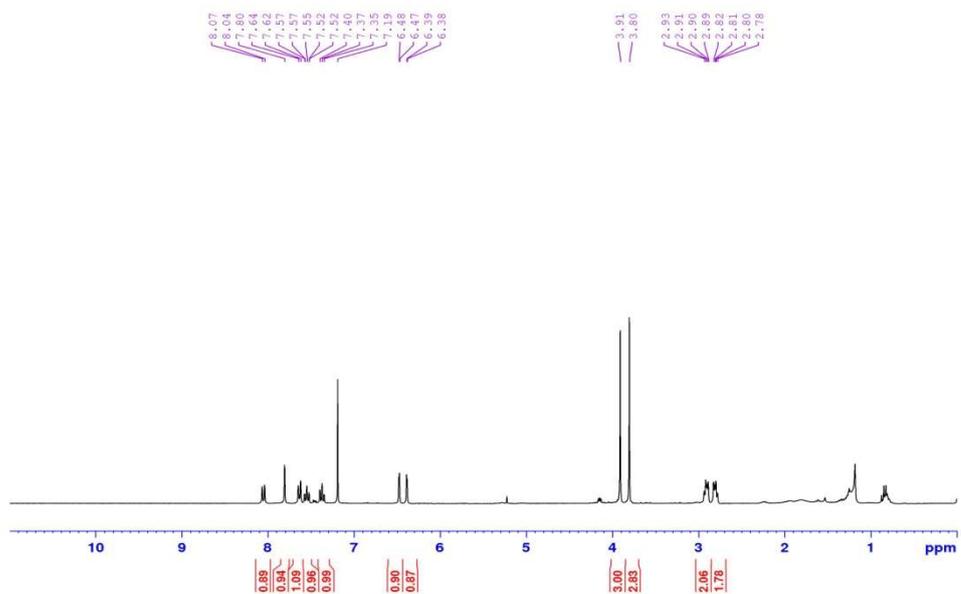
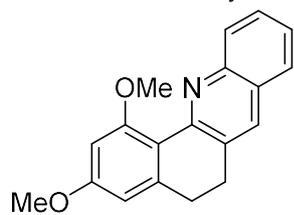
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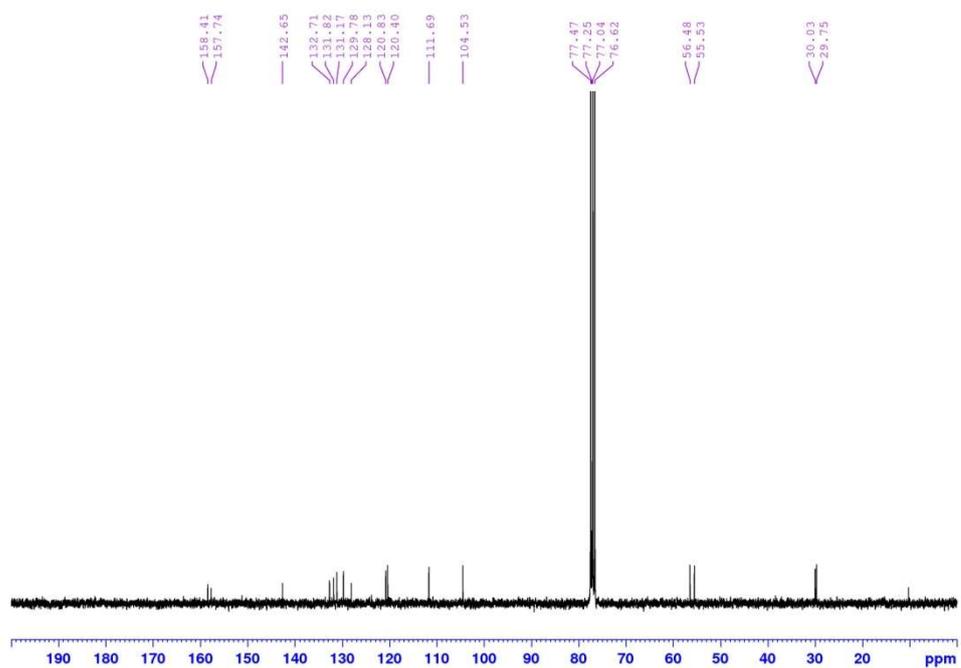
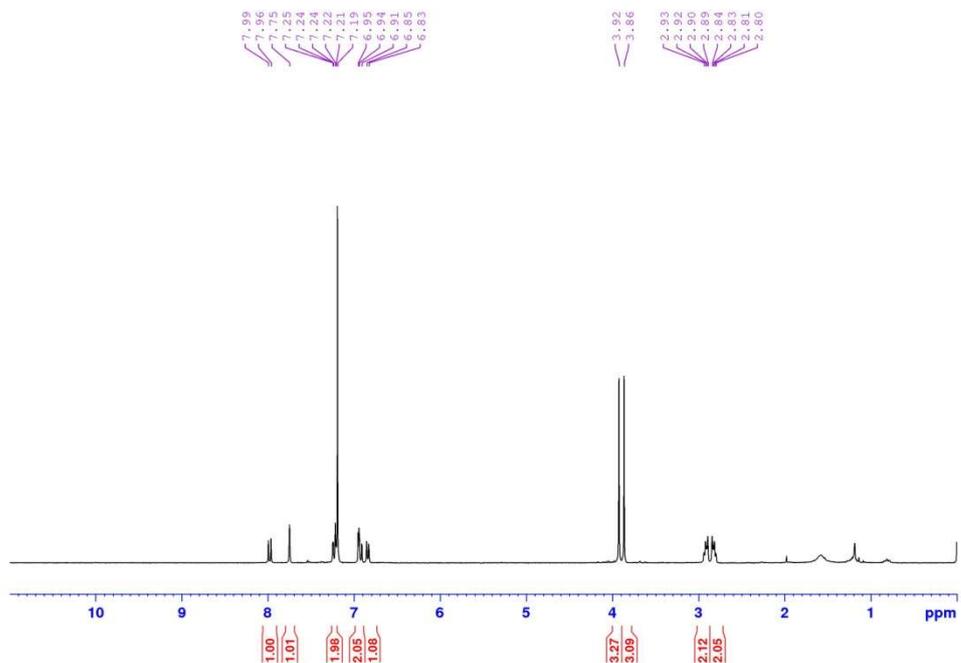
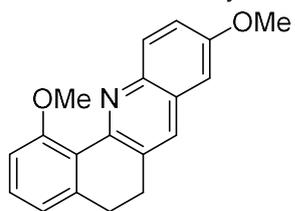
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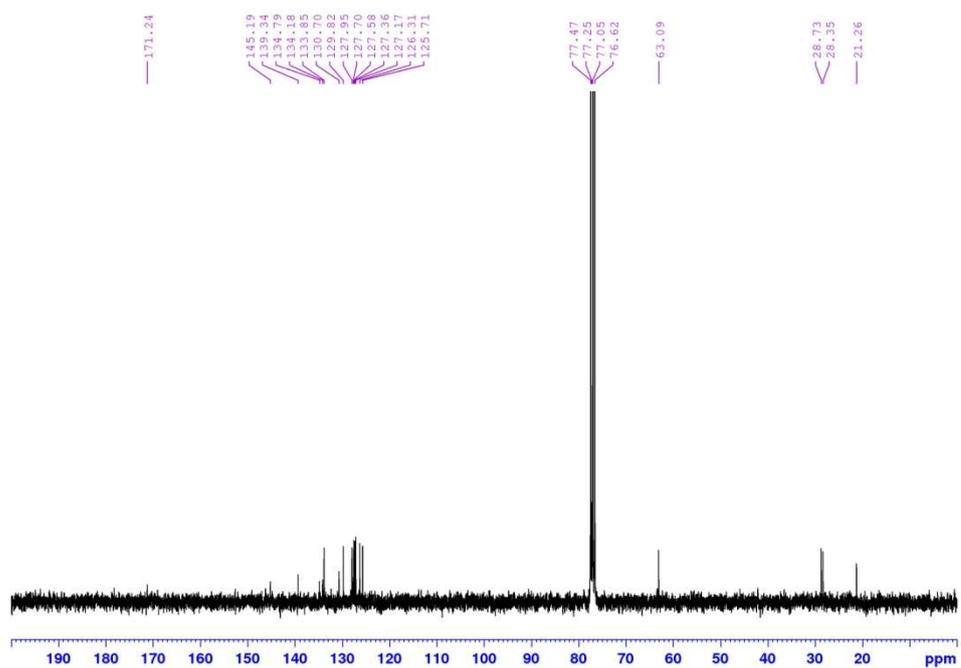
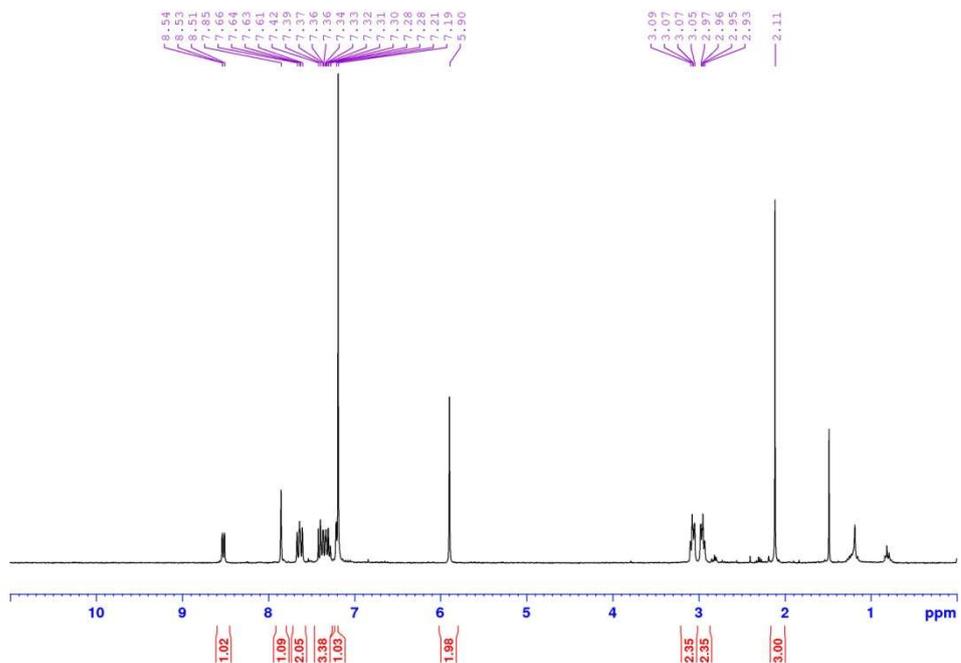
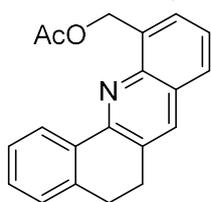
1,3-bis(methoxy)-5,6-dihydrobenzo[*c*]acridine 13

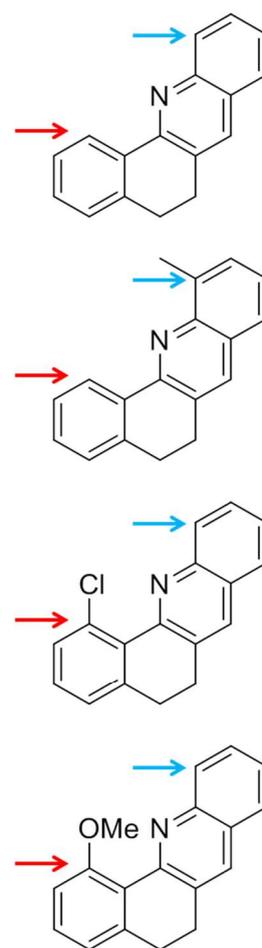
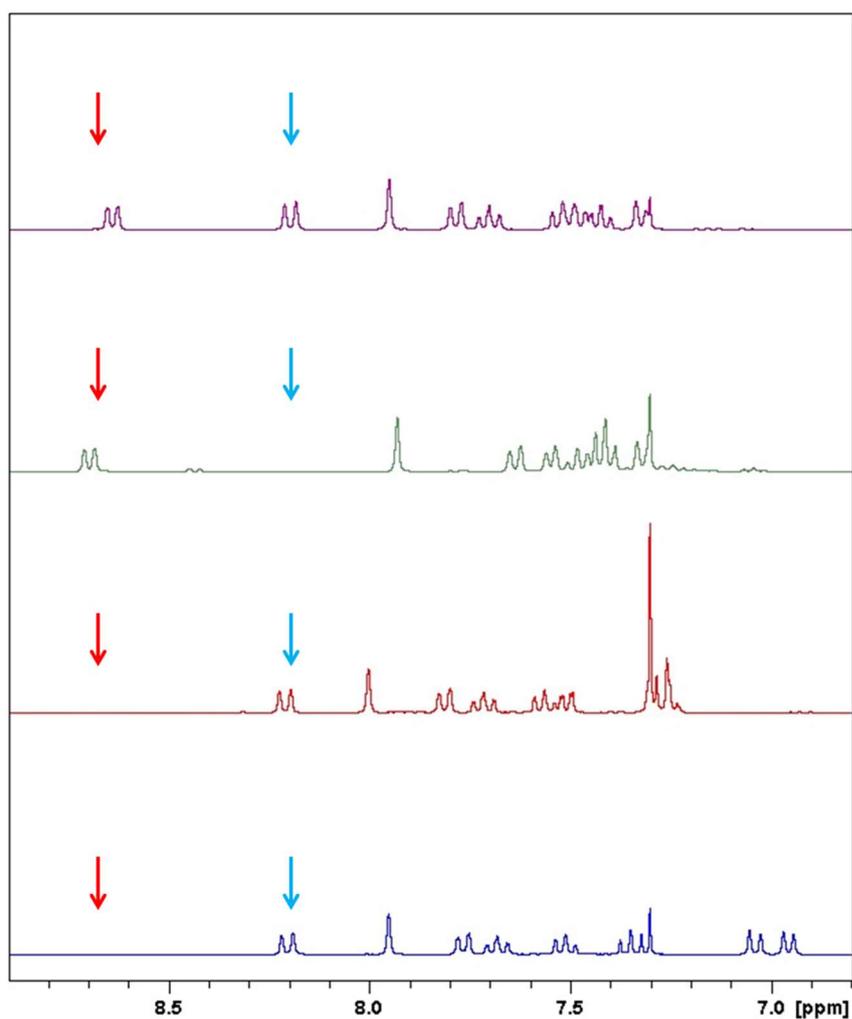


1,9-bis(methoxy)-5,6-dihydrobenzo[*c*]acridine 14



11-acetoxymethylene-5,6-dihydrobenzo[*c*]acridine 15



Compounds 4, 7, 9 and 10 superposition ^1H NMR

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