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Supporting Information

for

Synthesis of 10-*O*-aryl-substituted berberine derivatives by Chan–Evans–Lam coupling and investigation of their DNA-binding properties

Peter Jonas Wickhorst, Mathilda Blachnik, Denisa Lagumdzija and Heiko Ihmels

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Experimental procedures, syntheses, additional spectroscopic data, ^{1}H NMR and ^{13}C NMR spectra

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1. Synthesis

Generall Procedure for the Chan–Evans–Lam coupling reaction of berberrubine with arylboronic acids (GP 1).

A mixture of berberrubine (**1b**, 240 mg, 750 µmol), $Cu(OAc)_2$ (150 mg, 750 µmol), triethylamine (420 µL, 3.00 mmol), molecular sieves (4 Å) and the respective arylboronic acid (3.00 mmol) in DMF (5 mL) was stirred for 16 h at rt. To the reaction mixture was added CH_2Cl_2 (100 mL) and aq. HBr solution (1 M, 30 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 mL), separated, and dried with Na_2SO_4. The drying agent was filtered off and the solvent was removed by destillation. The crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 0% → 7%) and washed with acetone (20 mL) to obtain the desired product.

10-Phenoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium-9-olate (**4a**).

According to GP 1 the reaction of **1b** (240 mg, 750 µmol) with **3a** (365 mg, 3.00 mmol) gave product **4a** as red solid (74.8 mg, 195 µmol, 26%); mp > 300 °C (dec.). – ^{1}H NMR of **4a** x CF_3COOD (500 MHz, DMSO-d_6 + CF_3COOD): δ = 3.21 (t, ^3J = 6 Hz, 2H, 5-H), 4.93 (t, ^3J = 6 Hz, 2H, 6-H), 6.18 (s, 2H, OCH_2O), 7.42 (d, ^3J = 4 Hz, 4'-H), 7.09 (s, 1H, 4-H), 7.18 (t, ^3J = 9 Hz, 2H, 3'-H, 5'-H), 7.03 (t, ^3J = 9 Hz, 2H, 2'-H, 6'-H), 7.66 (d, ^3J = 4 Hz, 1H, 12-H), 7.80 (s, 1H, 1-H), 7.82 (s, 1H, 11-H), 8.91 (s, 1H, 13-H), 10.00 (s, 1 H, 8-H). – ^{13}C NMR of **4a** x CF_3COOD (125 MHz, DMSO-d_6 + CF_3COOD): δ = 26.3 (C5), 54.9 (C6), 102.1 (OCH_2O), 105.6 (C1), 108.4 (C4), 117.4 (C4'), 118.7 (C12), 119.1 (C13b), 119.9 (C8a), 120.4 (C13), 123.5 (C3', C5'), 130.1 (C2', C6'), 131.0 (C4a), 132.1 (C11), 135.8 (C12a), 138.6 (C13a), 140.6 (C9), 145.9 (C8), 146.8 (C10), 147.7 (C2), 150.0 (C3), 156.9 (C1'). – MS (ESI$^+$): *m/z* (%) = 384 (100) $[M+H]^+$. – El. Anal. for $C_{24}H_{17}NO_4$, calcd. (%): C 75.19, H 4.47, N 3.65, found (%): C 74.86, H 4.22, N 3.67.

10-(4-Chlorophenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium-9-olate (**4b**).

According to GP 1 the reaction of **1b** (240 mg, 750 µmol) with **3b** (469 mg, 3.00 mmol) gave product **4b** as red solid (53.0 mg, 127 µmol, 17%); mp > 286 °C (dec.). – ^{1}H NMR of **4b** (500 MHz, $CDCl_3$): δ = 3.15 (t, ^{3}J = 7 Hz, 1H, 5-H), 4.59 (t, ^{3}J = 7 Hz, 1H, 6-H), 6.09 (s, 1H, OCH_2O), 6.72 (s, ^{3}J = 7 Hz, 1H, 12-H), 6.81 (s, 1H, 4-H), 6.92 (d, ^{3}J = 7, 2H, 2'-H, 6'-H), 7.12 (d, ^{3}J = 7 Hz, 2H, 3'-H, 5'-H), 7.33 (s, 1H, 1-H), 7.57 (d, ^{3}J = 7 Hz, 1H, 11-H), 7.86 (s, 1H, 13-H), 9.30 (s, 1 H, H8). – ^{13}C NMR of **4b** (125 MHz, $CDCl_3$): δ = 28.2 (C5), 54.2 (C6), 102.2 (OCH_2O), 105.0 (C1), 108.6 (C4), 117.9 (C2', C6'), 118.5 (C13), 121.4 (C13b), 126.6 (C4') 129.2 (C4a), 129.3 (C3', C5') 133.1 (C11), 135.9 (C13a), 136.5 (C12a), 144.7 (C10), 146.2 (C8), 148.4 (C2), 150.6 (C3), 157.3 (C1'), 165.8 (C9). – MS (ESI^+): *m/z* (%) = 419 (100) $[M+H]^+$ – El. Anal. for $C_{24}H_{16}NO_4Cl$ x 2/3 H_2O, calcd. (%): C: 67.06; H: 4.06; N: 3.26; found (%): C: 66.76, H: 3.50, N: 3.26.

10-(4-Bromophenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium-9-olate (**4c**).

According to GP 1 the reaction of **1b** (240 mg, 750 µmol) with **3c** (602 mg, 3.00 mmol) gave product **4c** as red solid (65.0 mg, 141 µmol, 19%); mp > 300 °C (dec.). – ^{1}H NMR of **4c** x CF_3COOD (500 MHz, DMSO-d_6 + CF_3COOD): δ = 3.21 (t, ^{3}J = 6 Hz, 2H, 5-H), 4.93 (t, ^{3}J = 6 Hz, 2H, 6-H), 6.18 (s, 2H, OCH_2O), 6.98 (d, ^{3}J = 9 Hz, 2H, 2'-H, 6'-H), 7.09 (s, 1H, 4-H), 7.58 (d, ^{3}J = 9 Hz, 2H, 3'-H, 5'-H), 7.67 (d, ^{3}J = 9 Hz, 1H, 12-H), 7.82 (s, 1H, 1-H), 7.86 (d, ^{3}J = 9 Hz, 1H, 11-H), 8.91 (s, 1H, 13-H), 9.99 (s, 1H, 9-H). – ^{13}C NMR of **4c** x CF_3COOD (100 MHz, DMSO-d_6 + CF_3COOD): δ = 26.3 (C5), 54.9 (C6), 102.1 (OCH_2O), 105.6 (C1), 108.4 (C4), 115.0 (C4'), 118.8 (C12), 119.2 (C8a), 119.4 (C2', C6'), 120.0 (C13), 120.3 (C13b), 131.0 (C4a), 132.3 (C11), 132.7 (C3', C5'), 136.1 (C13a), 138.8 (C12a), 140.0 (C9), 146.0 (C8), 147.0 (C10), 147.7 (C2), 150.1 (C3), 156.4 (C1'). – MS (ESI^+): *m/z* (%) = 462 (100) $[M+H]^+$. – El. Anal. for $C_{24}H_{16}BrNO_4$, calcd. (%): C 62.35, H 3.49, N 3.03, found. (%): C 61.92, H 3.23, N 3.07.

10-(4-Methoxyphenoxy)-5,6-tetradro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium-9-olate (**4d**).

According to GP 1 the reaction of **1b** (240 mg, 750 µmol) with **3d** (455 mg, 3.00 mmol) gave product **4d** as red solid (54.5 mg, 132 µmol, 18%); mp > 300 °C (dec.). – ^{1}H NMR of **4d** x CF_3COOD (500 MHz, DMSO-d_6 + CF_3COOD): δ = 3.21 (t, ^{3}J = 6 Hz, 2H, 5-H), 3.76 (s, 3H, 4´-OCH3), 4.93 (t, ^{3}J = 6 Hz, 2H, 6-H), 6.17 (s, 2H, OCH_2O), 6.99 (d, ^{3}J = 9 Hz, 2H, 2‘-H, 6‘-H), 7.04 (d, ^{3}J = 9 Hz, 2H, 3‘-H, 5‘-H), 7.09 (s, 1H, 4-H), 7.64 (d, ^{3}J = 4 Hz, 1H, 12-H), 7.72 (d, ^{3}J = 4 Hz, 1H, 11-H), 7.82 (s, 1H, 1-H), 8.88 (s, 1H, 13-H), 9.99 (s, 1H, 8-H). – ^{13}C NMR of **4d** x CF_3COOD (125 MHz, DMSO-d_6 + CF_3COOD): δ= 26.3 (C5), 54.9 (C6), 55.5 (OCH_3), 102.1 (OCH_2O), 105.5 (C1), 108.4 (C4), 115.1 (C2‘, C6‘), 118.5 (C12), 118.9 (C3‘, C5‘), 119.5 (C13), 119.9 (C13b), 120.4 (C8a), 130.8 (C4a), 130.9 (C11), 135.1 (C12a), 138.2 (C13a), 142.1 (C9), 145.8 (C8), 145.9 (C10), 149.9 (C4‘), 155.7 (C1‘). – MS (ESI^+): *m/z* (%) = 414 (100) $[M+H]^+$. – El. Anal. for $C_{25}H_{20}NO_5$ x $1.5H_2O$, calcd. (%): C 68.17, H 5.03, N 3.18, found (%): C 68.44, H 4.57, N 3.31.

10-(4-Nitrophenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium-9-olate (**4e**).

According to GP 1 the reaction of **1b** (150 mg, 467 µmol) with **3e** (234 mg, 1.40 mmol) gave product **4e** as red solid (43.4 mg, 101 µmol, 22%); mp > 300 °C (dec.). – ^{1}H NMR of **4e** x CF_3COOD (500 MHz, DMSO-d_6 + CF_3COOD): δ = 3.22 (t, ^{3}J = 6 Hz, 2H, 5-H), 4.94 (t, ^{3}J = 6 Hz, 2H, 6-H), 6.18 (s, 2H, OCH_2O), 7.10 (s, 1H, 4-H), 7.15–7.17 (d, ^{3}J = 9 Hz, 2H, 2‘-H, 6‘-H), 7.72 (d, ^{3}J = 9 Hz, 1H, 12-H), 7.84 (s, 1H, 1-H), 7.97–7.99 (m, 1H, 11-H), 8.28–8.30 (m, 2H, 3´-H, 5´-H), 8.95 (s, 1H, 13-H), 10.03 (s, 1H, 8-H). – ^{13}C NMR of **4e** x CF_3COOD (125 MHz, DMSO-d_6 + CF_3COOD): δ = 26.4 (C5), 54.9 (C6), 102.2 (OCH_2O), 105.7 (C1), 108.5 (C4), 2 x 116.9 (C2’, C6’), 118.9 (C12), 119.5 (C8a), 120.0 (C13), 120.3 (C13b), 126.1 (C3’, C5’), 131.2 (C4a), 133.2 (C11), 137.0 (C9), 138.5 (C12a), 139.3 (13aC), 142.6 (C1’), 147.8 (C2), 150.2 (C3), 158.1 (C10), 162.2 (C4’), 146.2 (C8). – MS (ESI^+): *m/z* (%) = 464 (100) $[M+2H_2O]^+$. – El. Anal. for $C_{25}H_{20}NO_5$ x $1.5H_2O$, calcd. (%): C 63.72, H 4.16, N 6.19, found (%): C 63.39, H 3.57, N 6.01.

10-(4-(Ethoxycarbonyl)phenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium-9-olate (**4f**).

According to GP 1 the reaction of **1b** (240 mg, 750 µmol) with **3f** (579 mg, 3.00 mmol) gave product **4f** as red solid (54.1 mg, 119 µmol, 16%); mp > 278° C (dec.). – ^{1}H NMR of **4f** x CF_3COOD (500 MHz, DMSO-d_6 + CF_3COOD): δ = 1.31 (q, ^{3}J = 6 Hz, 3H C**H**$_3$CH$_2$O), 3.21 (t, ^{3}J = 6 Hz, 2H, 5-H), 4.31 (t, ^{3}J = 6 Hz, 2H CH$_3$C**H**$_2$O), 4.93 (t, ^{3}J = 6 Hz, 2H, 6-H), 6.18 (s, 1 H, OCH$_2$O), 7.09 (s, 1H, 4-H), 7.09 (t, ^{3}J = 6 Hz, 2H, 2'-H, 6'-H), 7.69 (t, ^{3}J = 6 Hz, 1H, 12-H), 7.83 (s, 1H, 1-H), 7.91 (t, ^{3}J = 6 Hz, 11-H), 8.00 (t, ^{3}J = 6 Hz, 3'-H, 5'-H), 8.93 (s, 1H, 13-H), 10.01 (s, 1H, 8-H). – ^{13}C NMR of **4f** x CF_3COOD (125 MHz, DMSO-d_6 + CF_3COOD): δ = 14.19 (**C**H$_3$CH$_2$O), 26.3 (C5), 54.9 (C6), 60.65 (CH$_3$**C**H$_2$O), 102.2 (OCH$_2$O), 105.7 (C1), 108.5 (C4), 116.7 (C2', C6'), 118.9 (C12), 119.4 (C8a), 120.0 (C13), 120.3 (C13b), 124.6 (C4'), 131.1 (C4a), 133.0 (C11), 134.5 (C3', C5'), 136.6 (C9), 139.1 (C13a), 139.1 (C12a), 146.0 (C8), 147.4 (C10), 147.5 (C2), 150.1 (C3), 165.1 (C=O), 165.1 (C1'). – MS (ESI$^+$): *m/z* (%) = 454 (100) [M]$^+$. – El. Anal. for $C_{27}H_{21}NO_6$ x 0.5 H_2O, calcd. (%): C 69.82, H 4.77, N 3.02, found (%): C 69.39, H 4.10, N 2.98.

General Procedure for the *O*-methylation of derivatives 5a–e (GP 2).

A mixture of the respective aryloxyisoquinolinium (36.2–67.5 µmol) and K_2CO_3 (1 molar eq.), and MeI (1.5 ml, 3.42 g, 24.1 mmol) in CH_2Cl_2 (3 ml) was stirred for 2 d at r.t. The mixture was diluted with CH_2Cl_2 (30 ml) and filtered, and the solvent was removed by distillation. The residue was dissolved in MeOH (5 ml) and diluted with water (5 ml). A solution of aq. $NaBF_4$ (sat., 1.0 ml) was added. The yellow precipitate was filtered off and redissolved in CH_2Cl_2 (30 ml). The suspension was filtered and the solvent was removed to give the essentially pure product. Analytical pure samples were obtained by recrystallization from MeOH/EtOAc.

9-Methoxy-10-phenoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium tetrafluoroborate (**5a**).

According to GP 2 the reaction of **4a** (28.1 mg, 73.5 µmol), with MeI (1.5 ml, 3.42 g, 24.1 mmol) and K_2CO_3 (10.2 mg, 73.5 µmol) gave product **5a** as yellow solid (27.2 mg, 56.2 µmol, 76%); mp > 288 °C (dec.). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.23 (t, ^3J= 6 Hz, 2 H, 5-H), 4.15 (s, 3H, OCH_3), 4.96 (t, ^3J = 6 Hz, 2H, 6-H), 6.19 (s, 2H, OCH_2O), 7.42 (d, ^3J = 4 Hz, 1H, 4'-H), 7.09 (d, ^3J = 8 Hz, 2H, 2'-H, 6'-H), 7.11 (s, 1H, 4-H), 7.21 (t, ^3J = 8 Hz, 1H, 4'-H), 7.45 (d, ^3J = 8 Hz, 2H, 3'-H, 5'-H), 7.84 (d, ^3J = 4 Hz, 1H, 1-H), 7.90 (d, ^3J = 9 Hz, 1H, 11-H), 7.95 (s, ^3J = 9 Hz, 1H, 12-H), 9.00 (s, 1H, 13-H), 9.98 (s, 1H, 8-H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.3 (C5), 55.2 (C6), 62.3 (CH_3), 102.2 (OCH_2O), 105.7 (C1), 108.5 (C4), 117.4 (C2', C6'), 120.2 (C13b), 120.3 (C13), 121.9 (C8a), 123.6 (C12), 123.9 (C4'), 130.3 (C3', C5'), 131.2 (C4a), 132.9 (C11), 136.1 (C12a), 139.3 (C13a), 145.1 (C10), 145.8 (C8), 147.2 (C9), 147.8 (C2), 150.2 (C3), 156.5 (C1'). – MS (ESI$^+$): *m/z* (%) = 398 (100) $[M\text{-}BF_4]^+$. – El. Anal. for $C_{25}H_{20}NO_4BF_4$, calcd. (%): C 61.88, H 4.15, N 2.89, found (%): C 61.98, H 3.86, N 2.82.

9-Methoxy-10-(4-chlorophenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium tetrafluoroborate (**5b**).

According to GP 2 the reaction of **4b** (28.2 mg, 67.5 µmol), with MeI (1.5 ml, 3.42 g, 24.1 mmol) and K_2CO_3 (9.33 mg, 67.5 mmol) gave product **5b** as yellow solid (22.4 mg, 43.1 µmol, 64%); mp > 268 °C (dec.). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.21 (t, ^3J = 6 Hz, 2H, 5-H), 4.13 (s, 3H, CH_3), 4.96 (t, ^3J = 6 Hz, 2H, 6-H), 6.19 (s, 2H, OCH_2O), 7.11 (s, 1H, 4-H), 7.13 (d, ^3J = 9 Hz, 2H, 2'-H, 6'-H), 7.50 (d, ^3J = 9 Hz, 2H, 3´-H, 5´-H), 7.85 (s, 1H, 1-H), 7.94 (d, ^3J = 9 Hz, 1H, 11-H), 7.96 (d, ^3J = 9 Hz, 1H, 12-H), 9.01 (s, 1H, 13-H), 9.98 (s, 1H, 8-H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.3 (C5), 55.2 (C6), 62.4 (CH_3), 102.2 (OCH_2O), 105.7 (C1), 108.5 (C4), 119.1 (C2', C6'), 120.2 (C13b), 120.3 (C13), 121.9 (C8a), 123.8 (C12), 127.8 (C4'), 130.1 (C3', C5'), 131.2 (C4a), 132.9 (C11), 136.4 (C12a), 139.5 (C13a), 144.8 (C10), 145.9 (C8), 147.4 (C9), 147.8 (C2), 150.3 (C3), 155.4

(C1'). – MS (ESI$^+$): *m/z* (%) = 432 (100) [M-BF_4]$^+$. – El. Anal. for $C_{25}H_{19}NO_4BClF_4$, calcd. (%): C 57.78, H 3.69, N 2.70, found (%): C 57.84, H 3.37, N 2.72.

9-Methoxy-10-(4-bromophenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium tetrafluoroborate (**5c**).

According to GP 2 the reaction of **4c** (19.2 mg, 41.6 µmol) with MeI (1.5 ml, 3.42 g, 24.1 mmol) and K_2CO_3 (5.75 mg, 41.6 µmol) gave product **5c** as yellow solid (17.6 mg, 31.2 µmol, 75%); mp > 264 °C (dec.). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.22 (t, ^3J = 6 Hz, 2H, 5-H), 4.13 (s, 3H, CH_3), 4.96 (t, ^3J = 6 Hz, 2H, 6-H), 6.19 (s, 2H, OCH_2O), 7.06 (d, ^3J = 9 Hz, 2H, 2'-H, 6'-H), 7.11 (s, 1H, 4-H), 7.62 (d, ^3J = 9 Hz, 2H, 3´-H, 5´-H), 7.83 (s, 1H, 1-H), 7.94 (d, ^3J = 9 Hz, 1H, 12-H), 7.96 (d, ^3J = 9 Hz, 1H, 11-H), 9.01 (s, 1H, 13-H), 9.98 (s, 1H, 8-H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.3 (C5), 55.2 (C6), 62.4 (CH_3), 102.2 (OCH_2O), 105.7 (C1), 108.5 (C4), 115.7 (C4') 119.5 (C2', C6'), 120.2 (C13b), 120.3 (C13), 121.9 (C8a), 123.7 (C12), 131.2 (C4a), 133.0 (C11), 133.0 (C3', C5'), 136.4 (C12a), 139.5 (C13a), 144.6 (C10), 145.9 (C8), 147.4 (C9), 147.8 (C2), 150.3 (C3), 155.9 (C1'). – MS (ESI$^+$): *m/z* (%) = 476 (100) [M-BF_4]$^+$. – El. Anal. for $C_{25}H_{19}BrNO_4BF_4$, calcd. (%): C 52.39, H 3.52, N 2.44, found. (%): C 52.33, H 2.99, N 2.31.

9-Methoxy-10-(4-Methoxyphenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium tetrafluoroborate (**5d**).

According to GP 2 the reaction of **4d** (15.0 mg, 36.2 µmol) with MeI (1.5 ml, 3.42 g, 24.1 mmol) and K_2CO_3 (5.00 mg, 36.2 µmol) gave product **5d** as yellow solid (7.45 mg, 14.5 µmol, 40%); mp > 260 °C (dec.). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.22 (t, ^3J = 6 Hz, 2H, 5-H), 3.77 (s, 3H, 4-OCH_3), 4.17 (s, 3H, 9-OCH_3), 4.95 (t, ^3J = 6 Hz, 2H, 6-H), 6.18 (s, 2H, OCH_2O), 7.01–7.03 (m, 2H, 2'-H, 6'-H), 7.08–7.10 (m, 2H, 3´-H, 5´-H), 7.11 (m, 1H, 4-H), 7.80–7.83 (m, 2H, 1- H, 11-H), 7.92 (d, ^3J = 9 Hz, 1H, 12-H), 8.97 (s, 1H, 13-H), 9.96 (s, 1H, 8-H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.3 (C5), 55.2 (C6), 55.6 (4'-OCH_3), 62.3 (9-OCH_3), 102.2 (OCH_2O), 105.7 (C1), 108.5 (C4), 115.4 (C2', C6'), 119.4 (C3', C5'), 120.0 (C13), 120.3 (C13b), 121.9 (C12a), 123.5 (C12), 131.1 (C4a), 131.7

(C11), 135.5 (C9), 139.0 (C13a), 145.7 (C8), 146.3 (C2), 146.6 (C8a), 147.8 (C10), 149.6 (C1'), 150.2 (C3), 155.9 (C4'). – MS (ESI$^+$): *m/z* (%) = 429 (100) [M-BF_4]$^+$. – El. Anal. for $C_{26}H_{22}BF_4NO_5$, calcd. (%): C 60.61, H 4.30, N 2.72, found (%): C 60.60, H 4.00, N 2.74.

9-Methoxy-10-(4-nitrophenoxy)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium tetrafluoroborate (**5e**).

According to GP 2 the reaction of **4e** (20.0 mg, 46.7 µmol) with MeI (1.5 ml, 3.42 g, 24.1 mmol) and K_2CO_3 (6.45 mg, 46.7 µmol) gave product **5e** as yellow solid (19.1 mg, 36.0 µmol, 77%); mp > 269 °C (dec.). – ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.22 (t, ^3J = 6 Hz, 2H, 5-H), 4.10 (s, 3H, CH_3), 4.94 (t, ^3J = 6 Hz, 2H, 6-H), 6.20 (s, 2H, OCH_2O), 7.12 (s, 1H, 4-H), 7.27 (d, ^3J = 9 Hz, 2H, 2'-H, 6'-H), 7.85 (s, 1H, 1-H), 8.00 (d, ^3J = 9 Hz, 1H, 12-H), 8.08 (d, ^3J = 9 Hz, 1H, 11-H), 8.32 (d, ^3J = 9 Hz, 2H, 3´-H, 5´-H), 9.05 (s, 1H, 13-H), 10.02 (s, 1H, 8-H). – ^{13}C NMR (125 MHz, DMSO-d_6): δ = 26.2 (C5), 55.2 (C6), 62.6 (CH_3), 102.3 (OCH_2O), 105.8 (C1), 108.5 (C4), 117.2 (C2', C6'), 120.1 (C13b), 120.4 (C13), 122.0 (C8a), 123.9 (C12), 126.4 (C3', C5'), 131.4 (C4a), 133.6 (C11), 137.2 (C12a), 139.9 (C13a), 143.0 (C4'), 143.3 (C10), 146.1 (C8), 147.8 (C2), 148.1 (C9), 150.4 (C3), 161.7 (C1'). – MS (ESI$^+$): *m/z* (%) = 443 (100) [M-BF_4]$^+$. – El. Anal. for $C_{25}H_{19}BF_4N_2O_6$, calcd. (%): C 56.63, H 3.61, N 5.28, found (%): C 56.26, H 3.23, N 5.20.

Optimization of reaction parameters for the Chan-Evans-Lam coupling of berberrubine.

Table S1. Optimization of reaction parameters for the synthesis of derivative **4a**.

Entry[a]	Boronic acid	Solvent	Temperature	Base	Yield
1	**3a**	CH_2Cl_2	rt	NEt_3	5%
2	$NaPhBF_3$	CH_2Cl_2	rt	NEt_3	<3%
3	**3a**	MeOH	40 °C	NEt_3	<3%
4	**3a**	MeOH	40 °C	NEt_3	<3%
5	**3a**	DMF	rt	NEt_3	26%
6	**3a**	DMF	40 °C	NEt_3	19%
7	**3a**	DMF	rt	2,2'-Bipyridine	<3%
8	**3a**	DMF	rt	Phenanthroline	<3%
9	**3a**	DMF	rt	DMAP	<3%

[a] All reactions were performed with berberrubine (**1b**, 1.00 mmol), $Cu(OAc)_2$ (1.00 mmol), 4 molar equiv base and molecular sieves (4 Å) in 5 mL of the corresponding solvent. The reaction was stopped when TLC analysis indicated complete consumption of **1b**.

2. Photophysical properties

Solutions were prepared from stock solutions of the derivatives **5a**–**e** in MeOH (c = 1.0 mM). Aliquots of the stock solution were thoroughly evaporated under a stream of nitrogen, and the residue was redissolved in the respective solvent or solvent mixture.

Table S2: Absorption and emission properties of derivatives **5b**, **5c** and **5e** in different solvents.

Compound	Solvent	λ_{abs}[a] / nm	lg ε[b]	λ_{fl}[c] / nm	Φ_{fl}[d]
5b	$CHCl_3$	420	3.88	532	0.03
	EtOH	416	3.87	561	<0.01
	MeOH	413	3.88	576	<0.01
	DMSO	410	3.83	[e]	[e]
	Buffer	410	3.81	[e]	[e]
5c	$CHCl_3$	421	3.85	531	0.03
	EtOH	415	3.85	559	<0.01
	MeOH	414	3.87	568	<0.01
	DMSO	410	3.82	[e]	[e]
	Buffer	410	3.64	[e]	[e]
5e	MeOH	408	3.76	[e]	[e]
	DMSO	405	3.79	[e]	[e]
	Buffer	403	3.78	[e]	[e]

[a] Long-wavelength absorption maximum; c_L = 20 µM. [b] ε = Molar extinction coeff. in cm^{-1} M^{-1}. [c] Fluorescence emission maximum; λ_{ex} = 415 nm. [d] Fluorescence quantum yield relative to coumarin 153 in EtOH (Φ_{fl} = 0.544) [1]. [e] Fluorescence quantum yield too low to be determined.

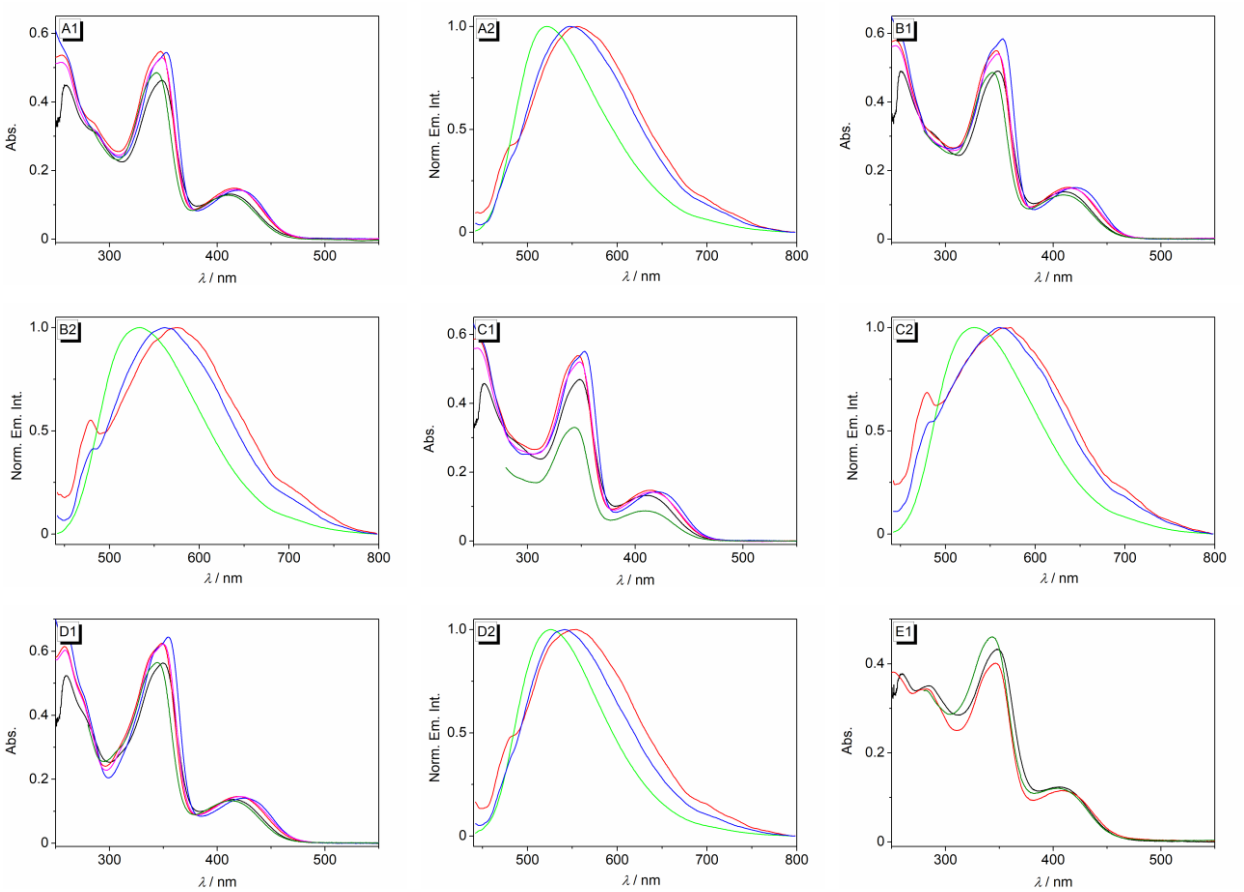

Figure S1. Absorption (1) and emission spectra (2) of **5a** (A), **5b** (B), **5c** (C), **5d** (D) and **5e** (E) (c = 20 µM) in different solvents (red: MeOH, black: DMSO, green: aq. buffer, magenta: EtOH, blue: $CHCl_3$; buffer: 16 mM BPE buffer solution at pH 7, λ_{ex} = 430 nm).

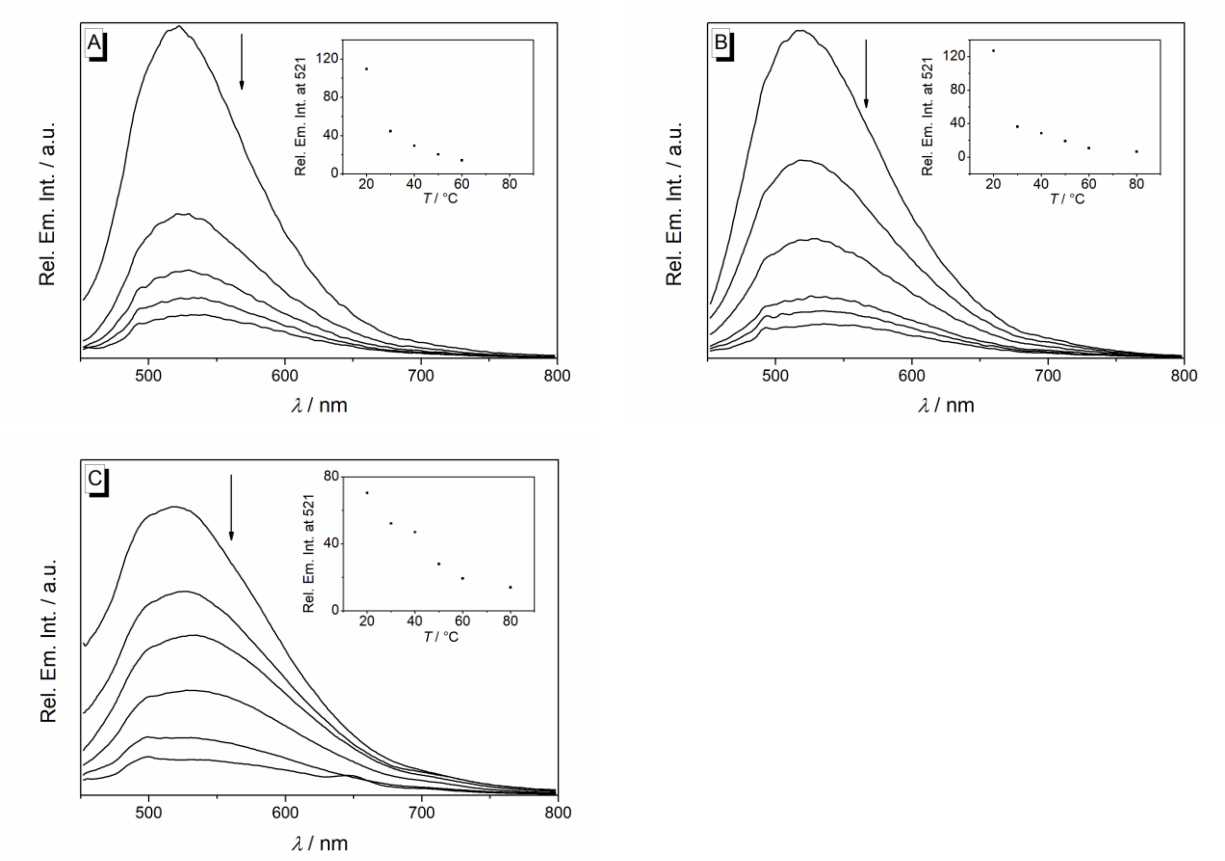

Figure S2. Emission spectra of derivatives **5b** (A), **5c** (B) and **5e** (C) (c = 10 µM, with 0.25% v/v DMSO) in glycerol; λ_{ex} = 430 nm. The arrows indicate the changes of the emission intensity with increasing temperature. Inset: Plot of the relative emission intensity *versus* the temperature of the solution.

3. Determination of the fluorescence quantum yields

Solutions of **5a**–**e** were prepared as described above from stock solutions in MeOH (c = 1.0 mM). The relative fluorescence quantum yields were determined under identical conditions (detection wavelength, excitation wavelength, detector voltage, slit bandwidths, collection rate). excitation and emission slits were adjusted to 5 nm, and the excitation wavelengths were fixed to 340 nm The quantum yield Φ_{fl} was determined according to equation 1. The estimated error is ca. 10% of the given values.

$$\Phi_{\mathrm{fl,X}} = \frac{F_X A_S}{F_S A_X} \cdot \frac{n_X^2}{n_S^2} \cdot \Phi_{\mathrm{fl,s}} \qquad \text{(eq. 1)}$$

The indices X and S indicate the analyte (X) and standard (S, coumarin 153 in ethanol, Φ_{fl} = 0.544 [1]) solution.

Φ_{fl} = Emission quantum yield.

F = Integral of the emission curve.

A = Absorbance at the excitation wavelength.

n = Refractive index.

4. Photometric and fluorimetric DNA titrations

Photometric and fluorimetric titrations with ct DNA and oligonucleotides **22AG** were performed according to published protocols [2]. All titrations were performed with 5% v/v DMSO to ensure a sufficient solubility of the ligand.

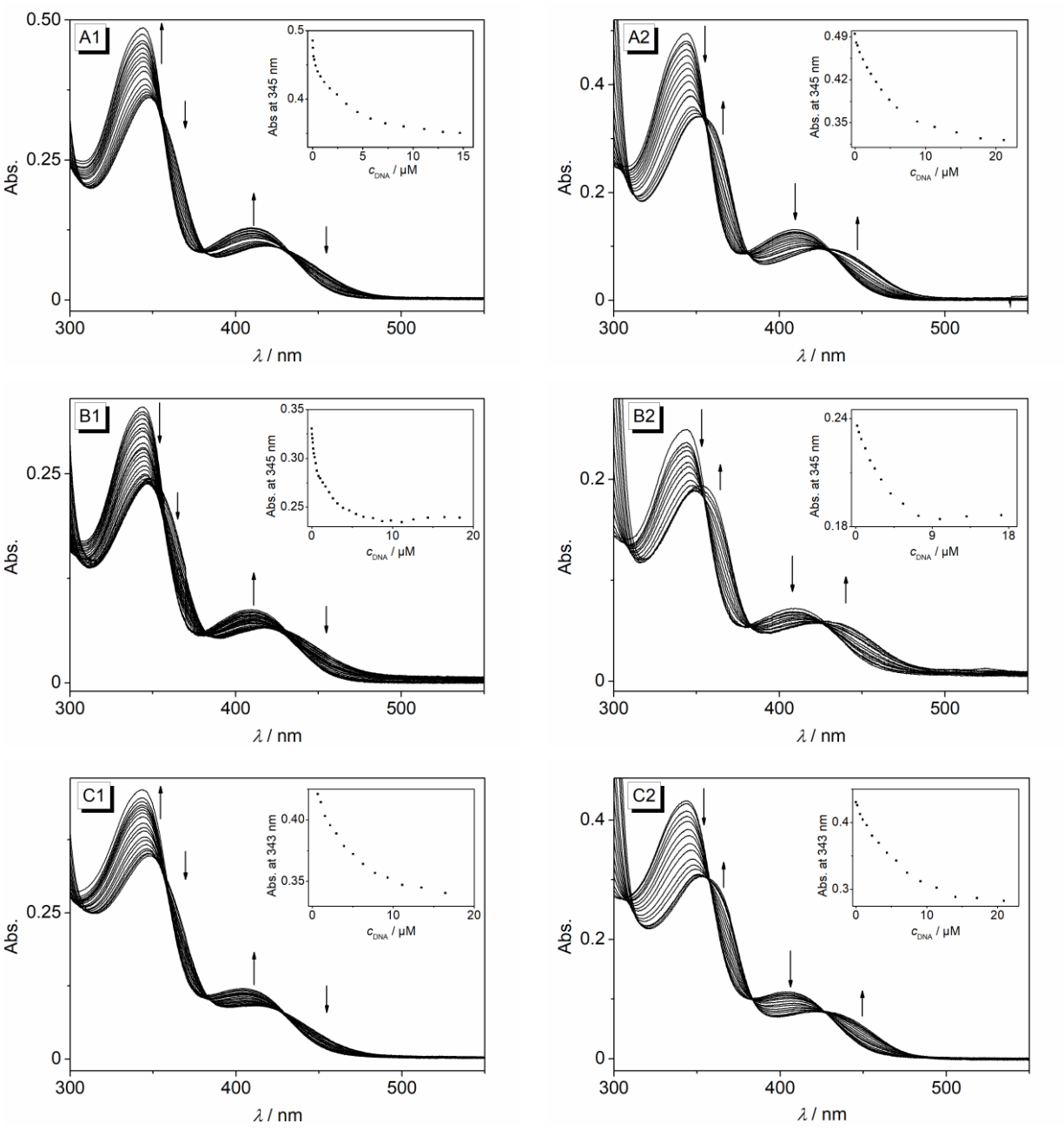

Figure S3. Photometric titration of **5b** (A), **5c** (B) and **5e** (C) (c_{Ligand} = 20 µM) with ct DNA (1) in BPE buffer (c_{Na+} = 16 mM, pH 7.0, with 5% v/v DMSO) and with **22AG** (2) in K-phosphate buffer (c_{K+} = 110 mM, pH 7.0, with 5% v/v DMSO). The arrows indicate the changes of the absorption bands upon addition of DNA. Inset: Plot of the ligand absorption versus c_{DNA} (in base pairs).

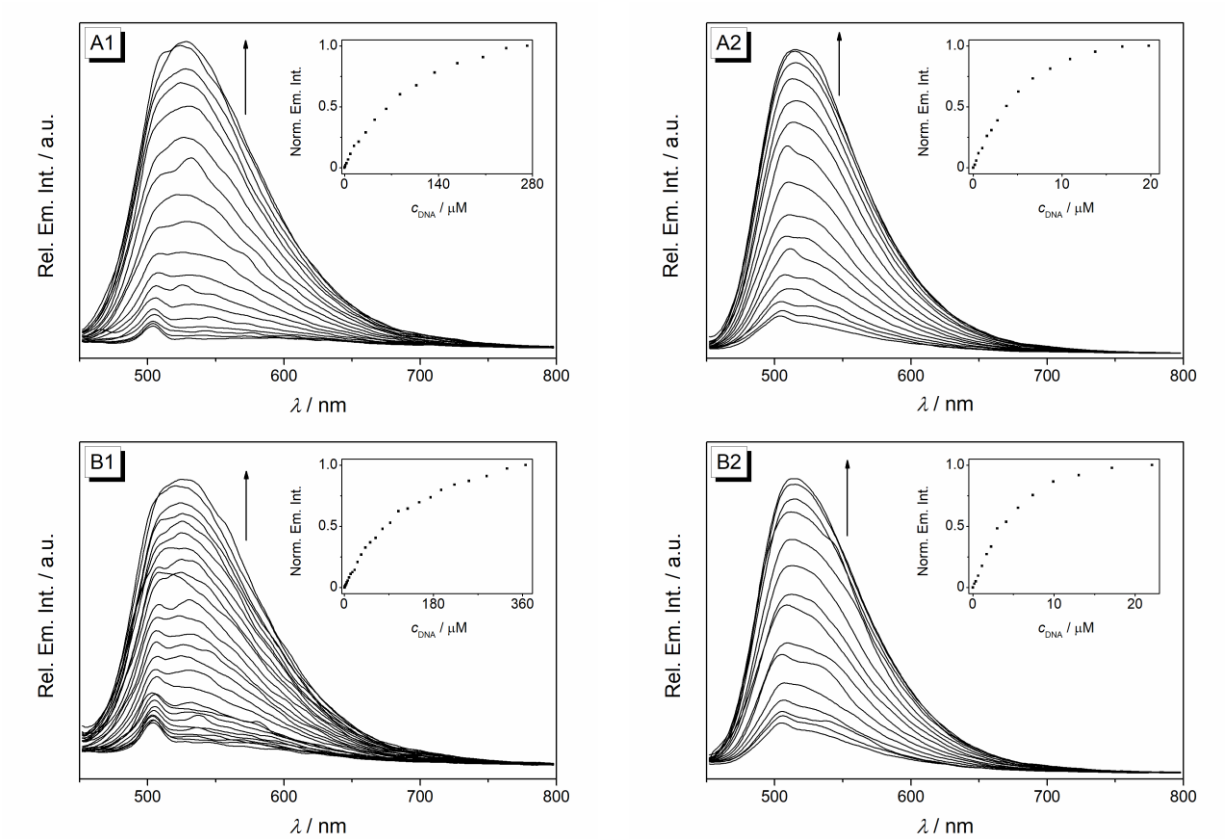

Figure S4. Fluorimetric titration of **5c** (A) and **5d** (B, c_{Ligand} = 20 μM) with ct DNA (1) in BPE buffer (c_{Na+} = 16 mM, pH 7.0, with 5% v/v DMSO) and with **22AG** (2) in K-phosphate buffer (c_{K+} = 110 mM, pH 7.0, with 5% v/v DMSO); λ_{ex} = 430 nm. The arrows indicate the changes of the emission bands upon addition of DNA. Inset: Plot of the relative fluorescence intensity versus c_{DNA} (in base pairs).

The binding constants, K_b, were determined from binding isotherms of the photometric titration spectra (Figure S5) and fitting of the experimental data to the theoretical model according to equation 2 [3].

$$\frac{I}{I_0} = 1 + \frac{Q-1}{2}\left(A + xn + 1 - \sqrt{(Q + xn + 1)^2 - 4xn}\right) \qquad \text{(eq. 2)}$$

$Q = I / I_0$ = Minimal absorbance in the presence of excess ligand

n = Number of independent binding sites per DNA

$A = 1 / (K_b \times c_{Ligand})$

$x = c_{DNA} / c_{Ligand}$ = Titration variable Ligand

Standard derivations (SD) of K_b values were calculated according to equation 3.

$$SD\ (K_b) = \{(SD\ of\ A\ /\ A)\ /\ A\}\ /\ c_{Ligand} \qquad \text{(eq. 3)}$$

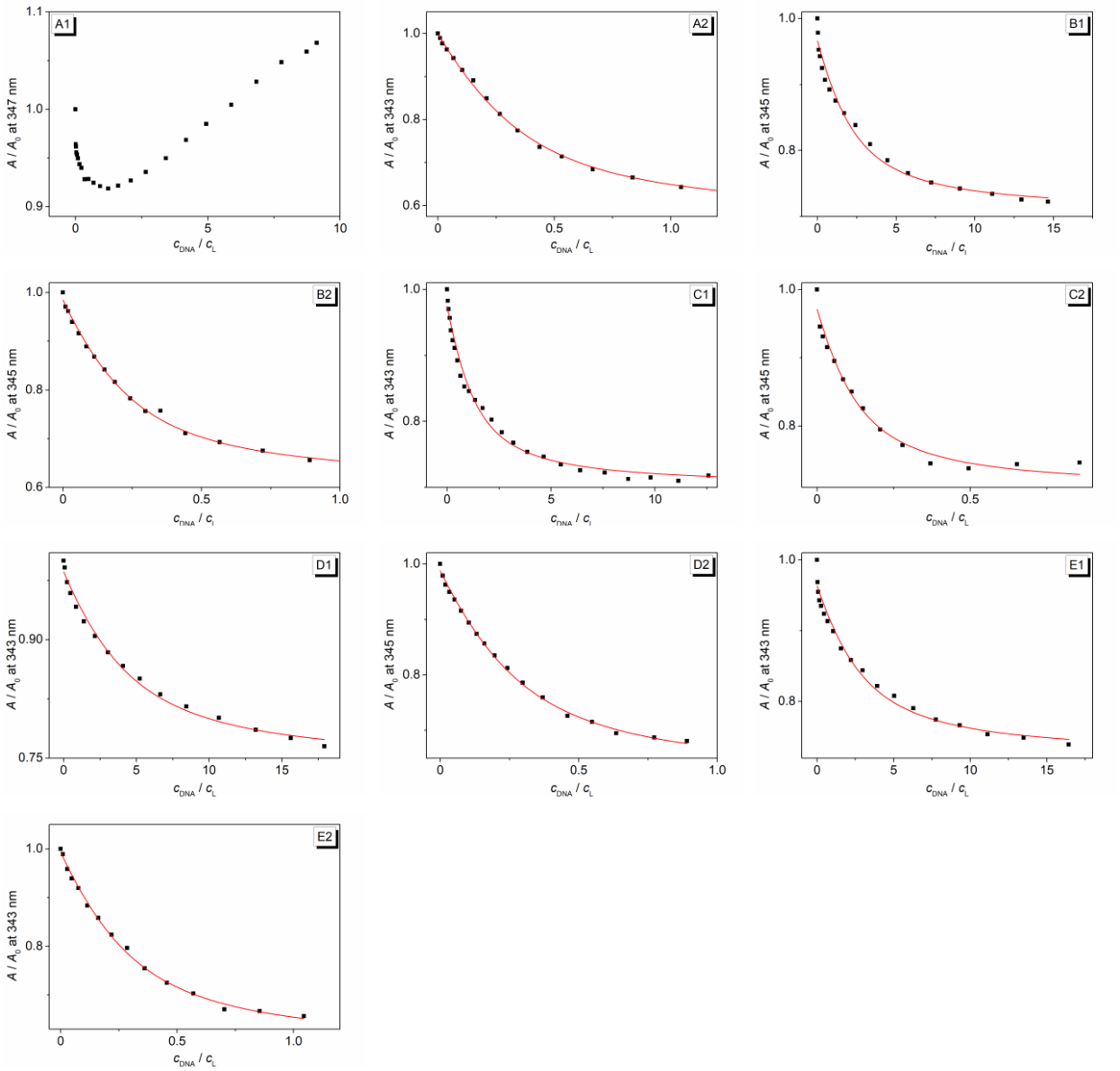

Figure S5. Fitting curves of binding isotherms resulting from spectrophotometric titrations of **5a** (A), **5b** (B), **5c** (C), **5d** (D) and **5e** (E) with ct DNA (1) and with **22AG** (2) for the determination of binding constants (K_b). Red lines represent the best fits of the experimental data to the theoretical model.

5. CD- and LD-spectroscopic analysis

CD and LD spectra were recorded in BPE buffer solution with ct DNA (c_{DNA} = 20.0 µM, 5% v/v DMSO) and in K-phosphate buffer solution with **22AG** (c_{DNA} = 20.0 µM, 5% v/v DMSO) at different ligand-DNA ratios (*LDR*). Measurements with ct DNA were performed at *LDR* = 0, 0.1, 0.2, 0.5, 1.0. CD signals were recorded with band width of 1 nm, recording speed of 1 nm/s and time per data point of 0.5 seconds.

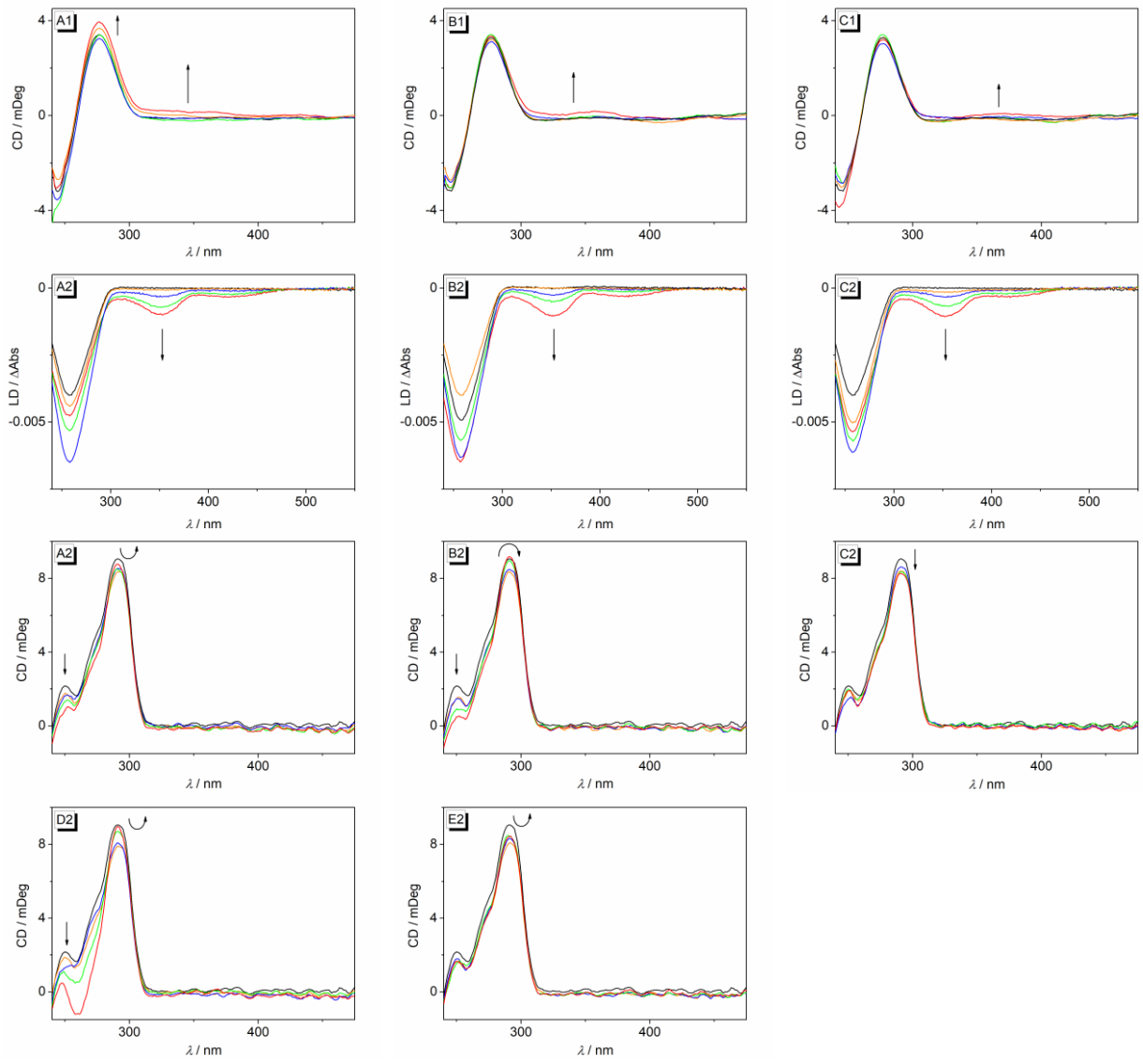

Figure S6. CD (1) and LD spectra (2) of ct DNA (*c* = 20 µM) in the absence and presence of **5a** (A), **5b** (B), **5c** (C), **5d** (D) and **5e** (E) in BPE buffer solution (10 mM, pH 7.0; with 5% v/v DMSO). CD spectra of **22AG** (3, *c* = 20 µM) in the absence and presence of **5a**–**e** in K-phosphate buffer (c_{K+} = 110 mM, pH 7.0, with 5% v/v DMSO) [LDR = 0 (black), 0.05 (orange), 0.2 (blue), 0.5 (green), 1.0 (red)]. The arrows indicate the changes of absorption on addition of DNA.

6. Thermal denaturation experiments

The stock solutions of the oligonucleotide **F21T**, **Fa2T**, **FmycT** and **FkitT** (c = 50 µM) and the ligand (c = 5 µM) were prepared in cacodylate buffer. The solution with the ligand contained 1% v/v DMSO. The samples were mixed according to Table S2. Melting temperatures, ΔT_m, were determined from the maximum of the first derivative of the melting curves. The determined T_m values before addition of ligand resembled the ones reported in literature [4–6].

Table S3. Composition of the samples for Fluorimetric DNA Denaturation Experiments with **F21T**, **Fa2T**, **FmycT** and **FkitT**.

Sample[a]	c_{Ligand} / µM	V_{Ligand} / µL[b]	V_{DMSO} / µL	V_{Puffer} / µL
1	0	0	10.0	996
2	0.25	50	9.50	971
3	0.50	100	9.00	946
4	1.00	200	8.00	896

[a] V_{DNA} = 4 µL c_{DNA} = 0.2 µM. [b] c_{DMSO} = 1 vol% c_{Ligand} = 10 µM.

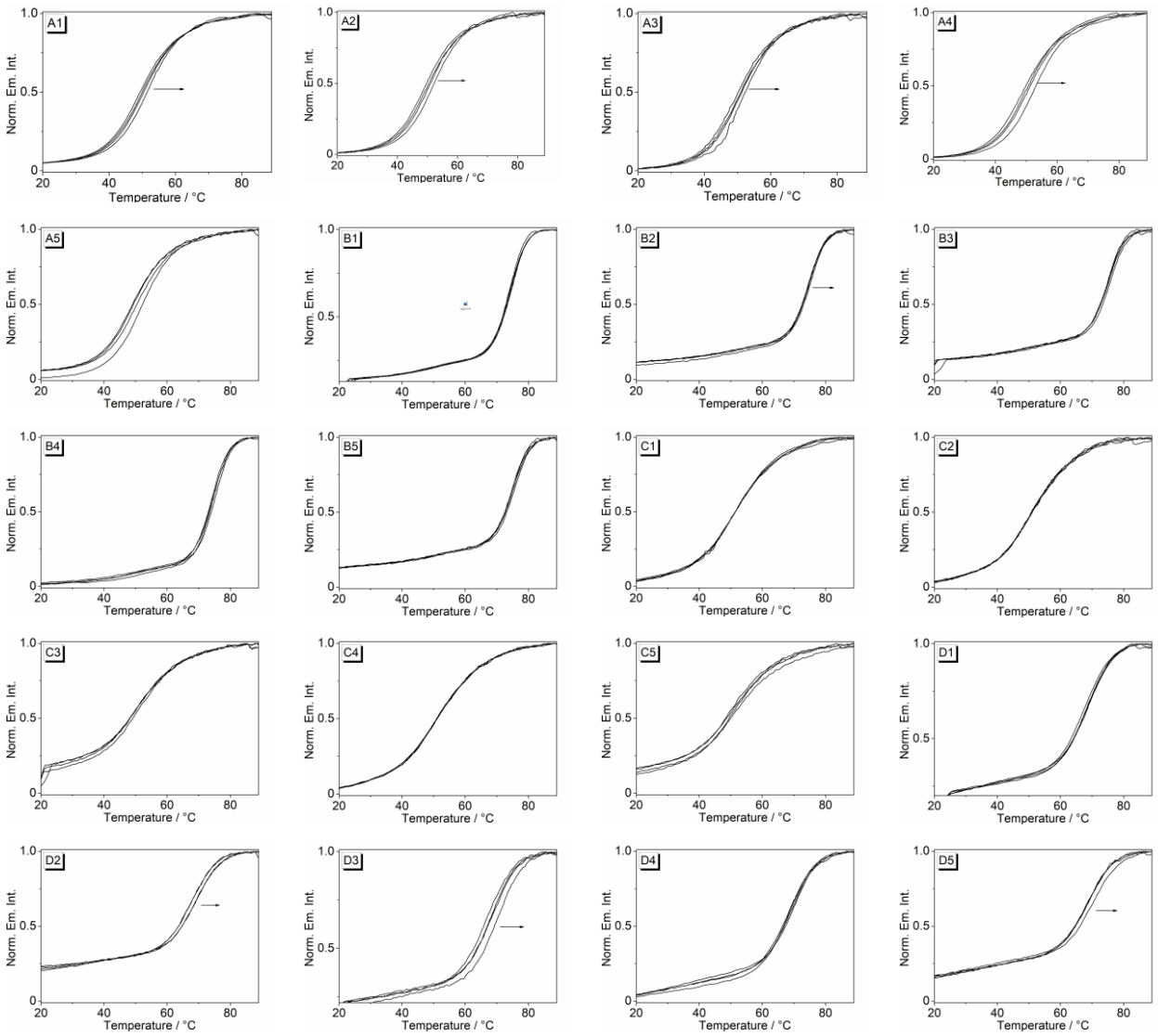

Figure S7. Normalized changes in emission intensity of with the oligonucleotides **F21T** (A), **Fa2T** (B), **FkitT** (C), **FmycT** (D) (0.2 µM, λ_{ex} = 470 nm) at 515 nm between 20 °C and 90 °C in presence of the ligands **5a** (1), **5b** (2), **5c** (3), **5d** (4) and **5e** (5) in aqueous KCl-LiCl-Na-cacolydate buffer (c_{K+} = 10 mM, c_{Na+} = 10 mM, c_{K+} = 90 mM, pH 7.2) at different ligand-DNA ratios (0, 1.3, 2.5, 5.0).

7. NMR spectra

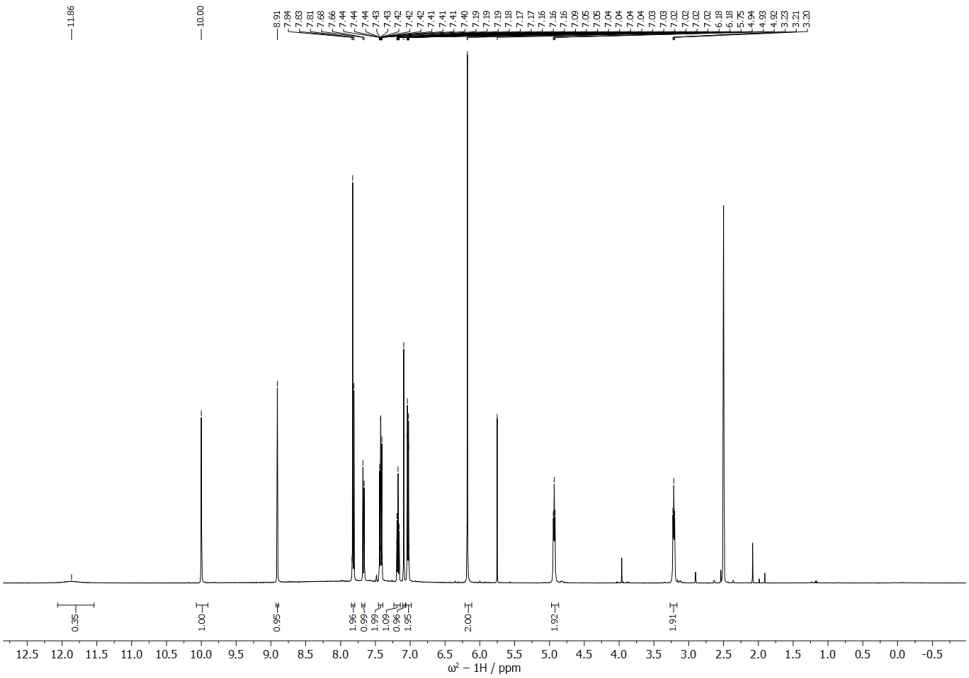

Figure S8. ^{1}H NMR spectrum (500 MHz) of **4a** in DMSO-d_6+ CF_3COOD.

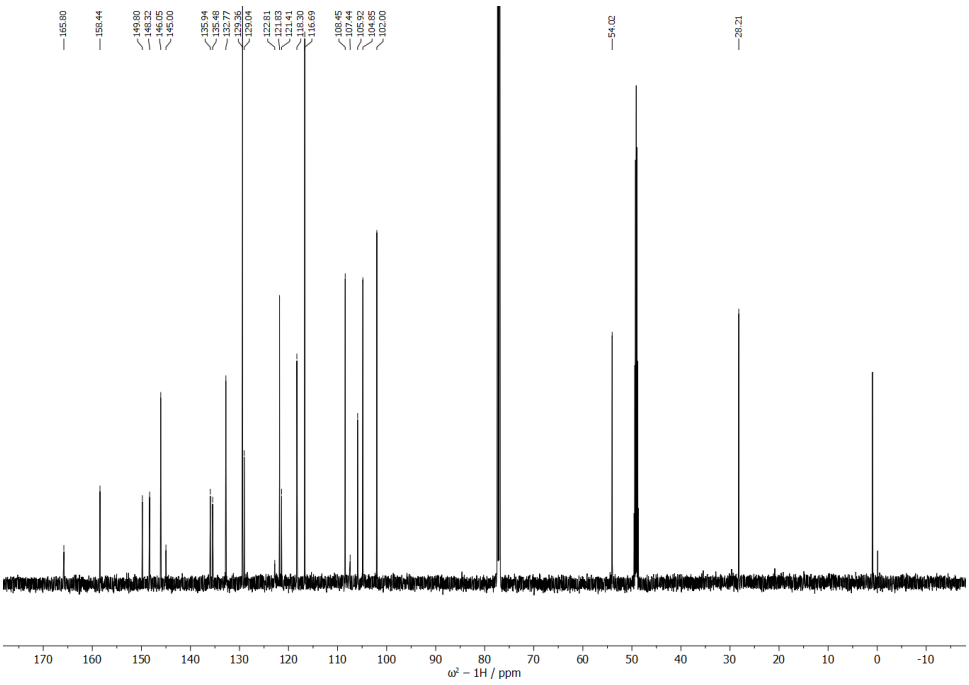

Figure S9. ^{13}C NMR spectrum (125 MHz) of **4a** in DMSO-d_6 + CF_3COOD.

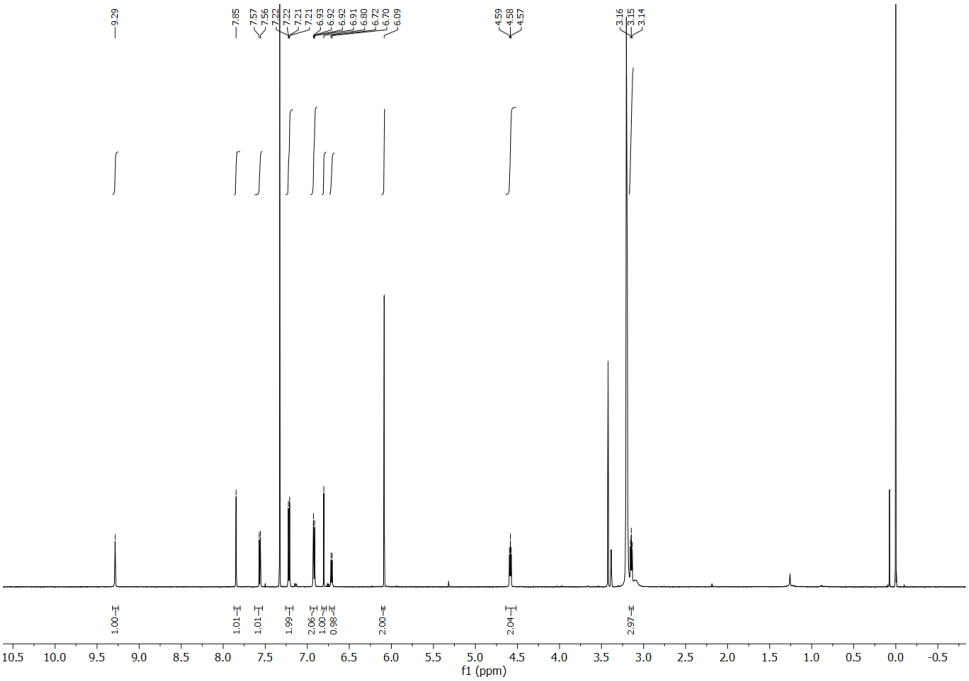

Figure S10. ^{1}H NMR spectrum (500 MHz) of **4b** in $CDCl_3$.

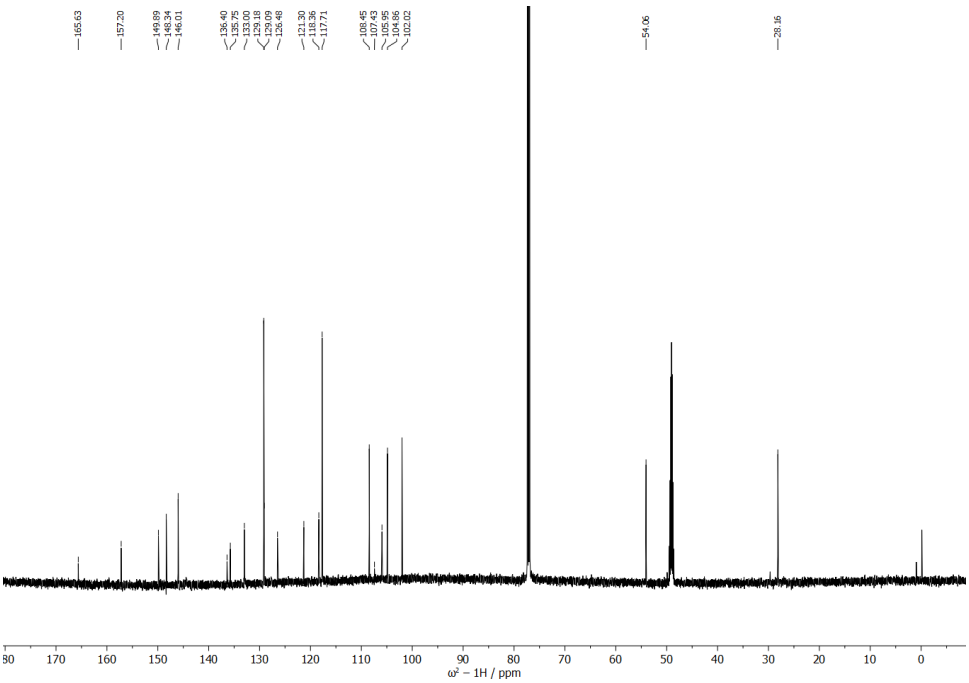

Figure S11. ^{13}C NMR spectrum (125 MHz) of **4b** in $CDCl_3$.

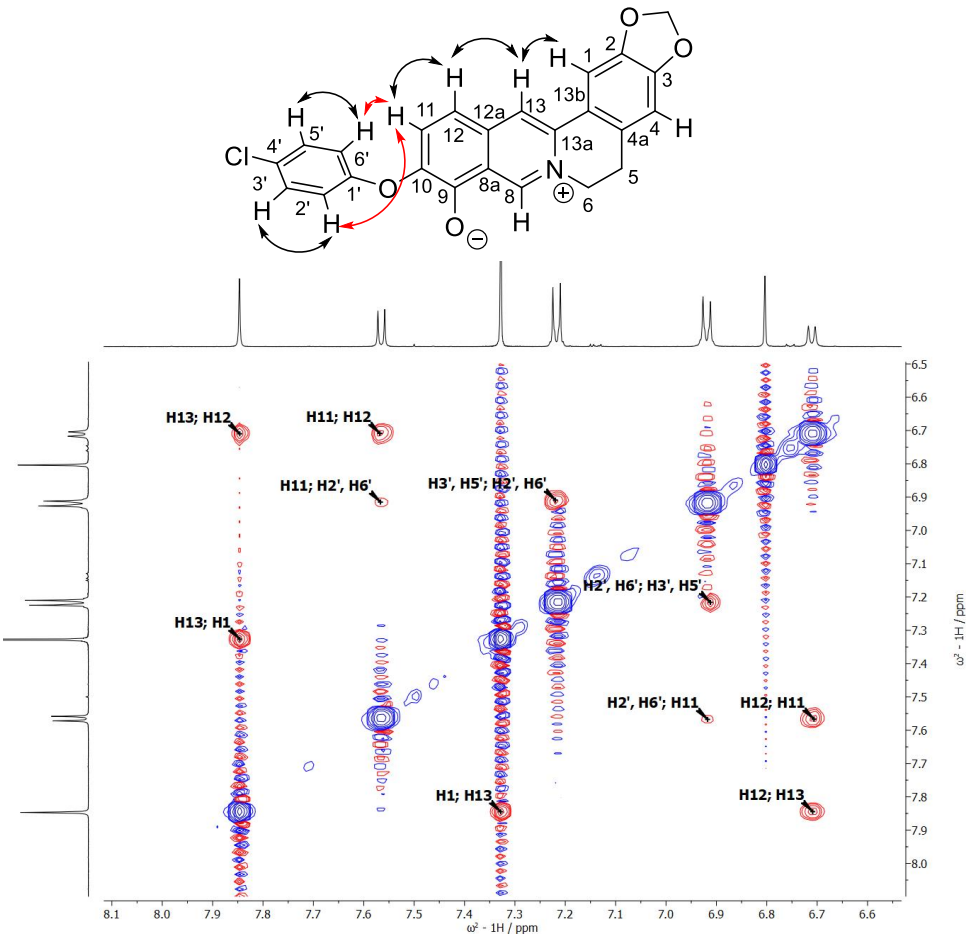

Figure S12. NOESY spectrum (500 MHz) of the aromatic region of **4b** in $CDCl_3$ and schematic representation of the NOE effects.

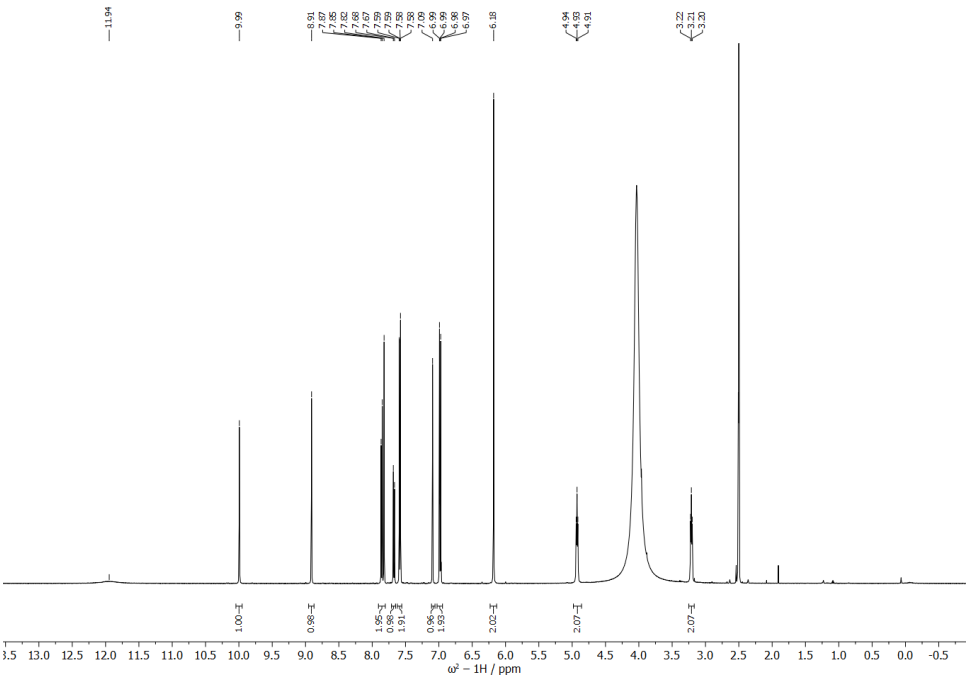

Figure S13. ^{1}H NMR spectrum (500 MHz) of **4c** in DMSO-d_6 + CF_3COOD.

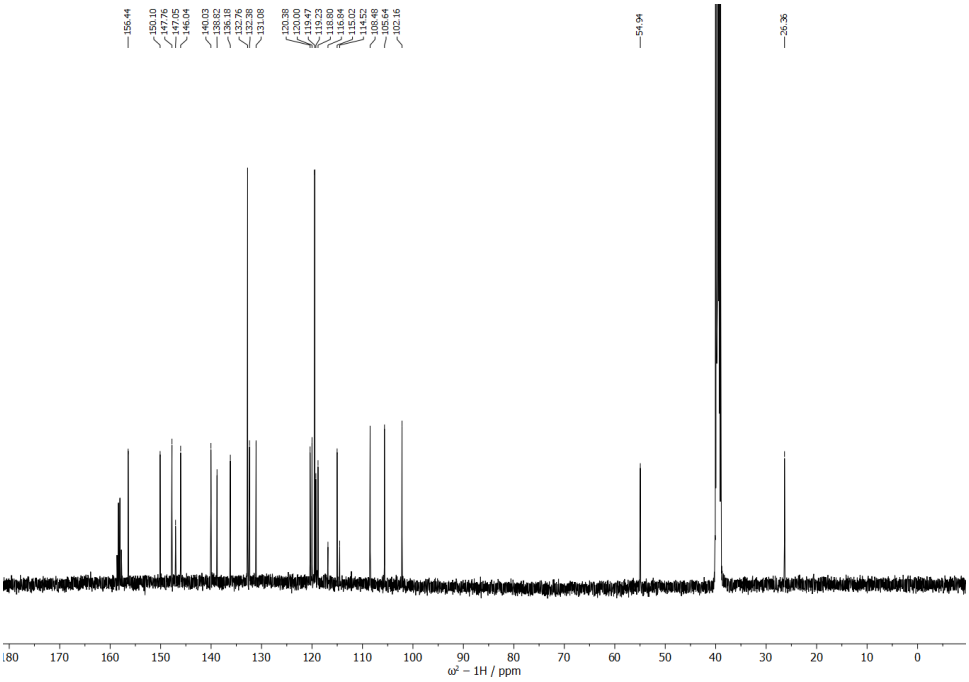

Figure S14. ^{13}C NMR spectrum (125 MHz) of **4c** in DMSO-d_6 + CF_3COOD.

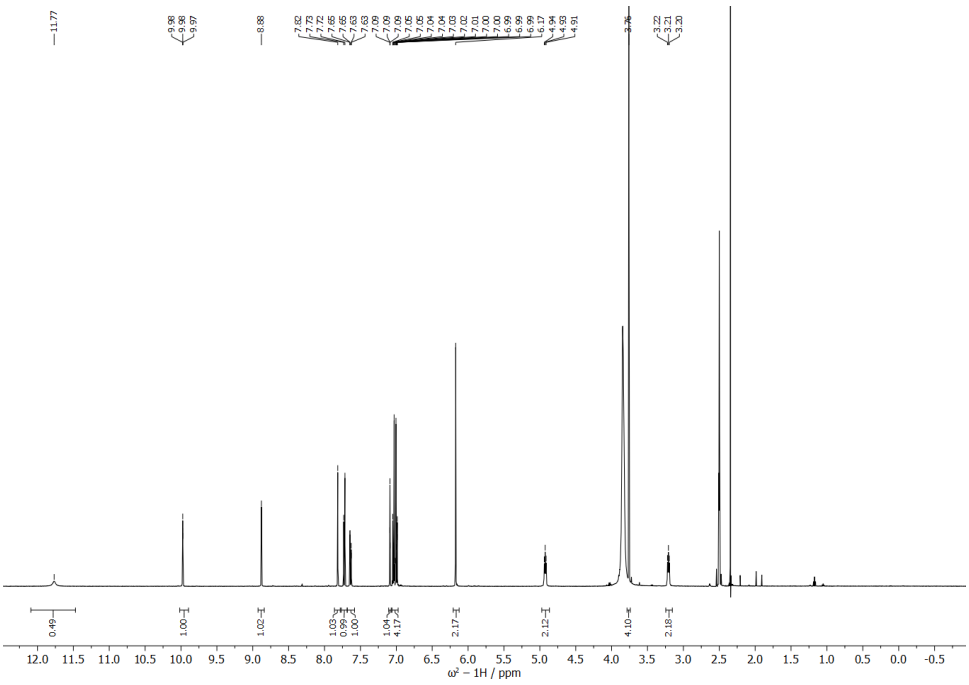

Figure S15. ^{1}H NMR spectrum (500 MHz) of **4d** in DMSO-d_6 + CF_3COOD.

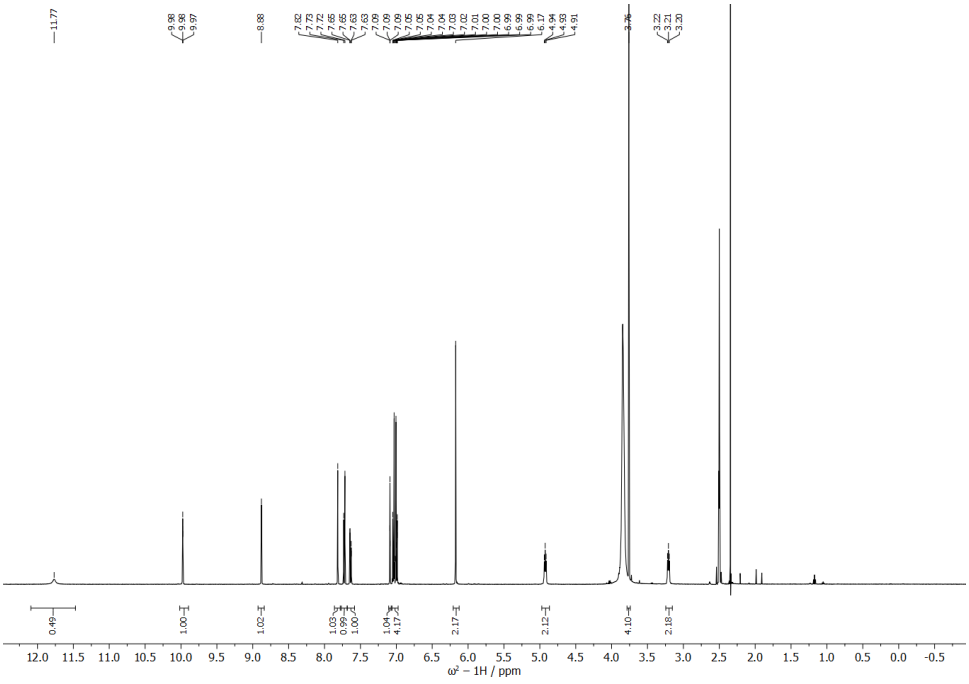

Figure S16. ^{13}C NMR spectrum (125 MHz) of **4d** in DMSO-d_6 + CF_3COOD.

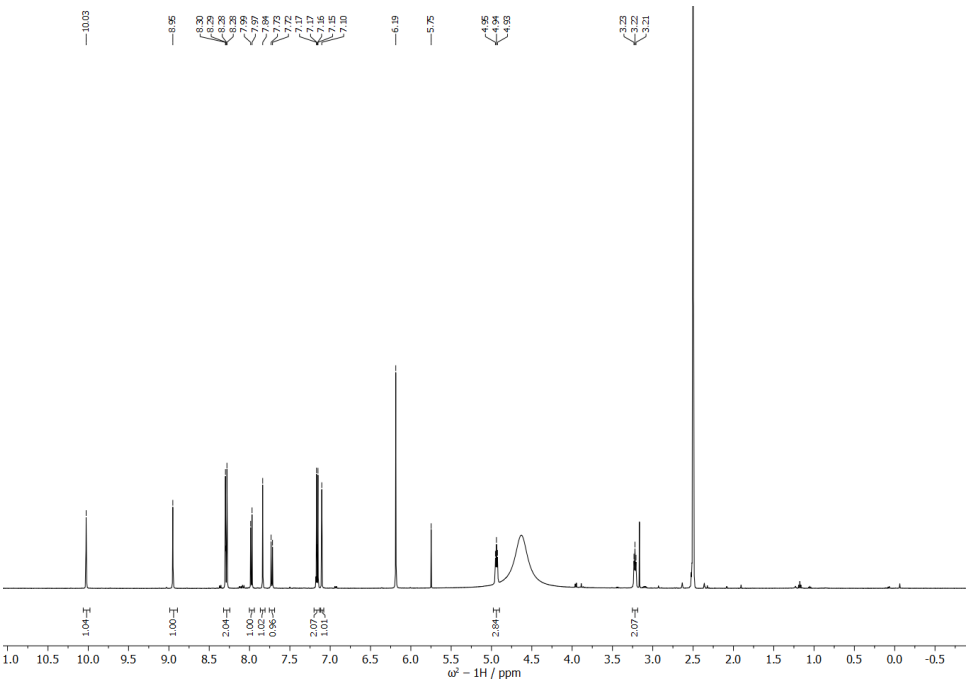

Figure S17. ^{1}H NMR spectrum (500 MHz) of **4e** in DMSO-d_6+ CF_3COOD.

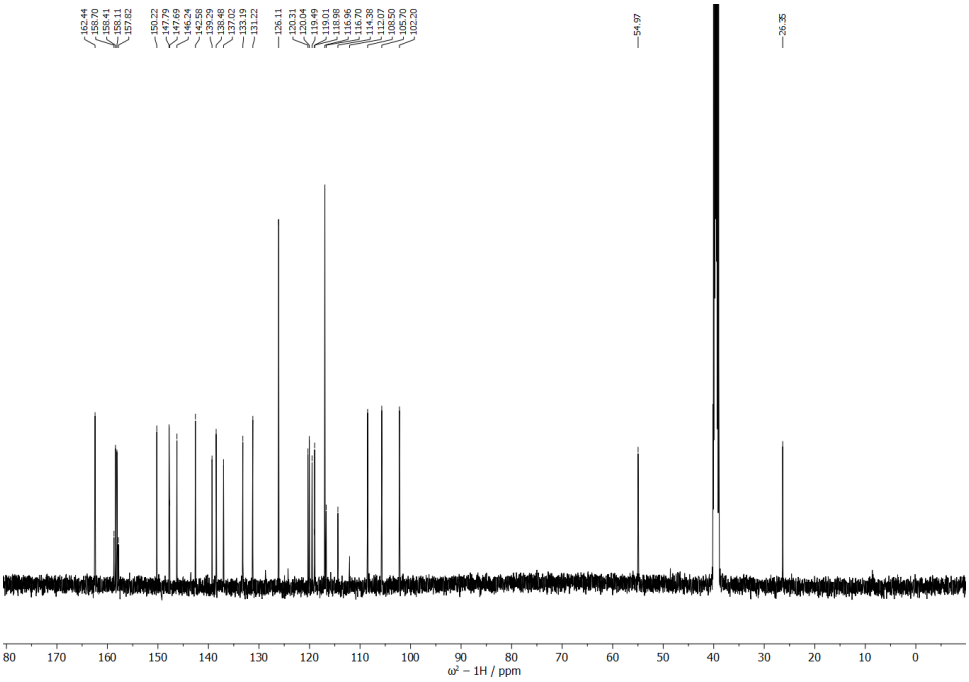

Figure S18. ^{13}C NMR spectrum (125 MHz) of **4e** in DMSO-d_6 + CF_3COOD.

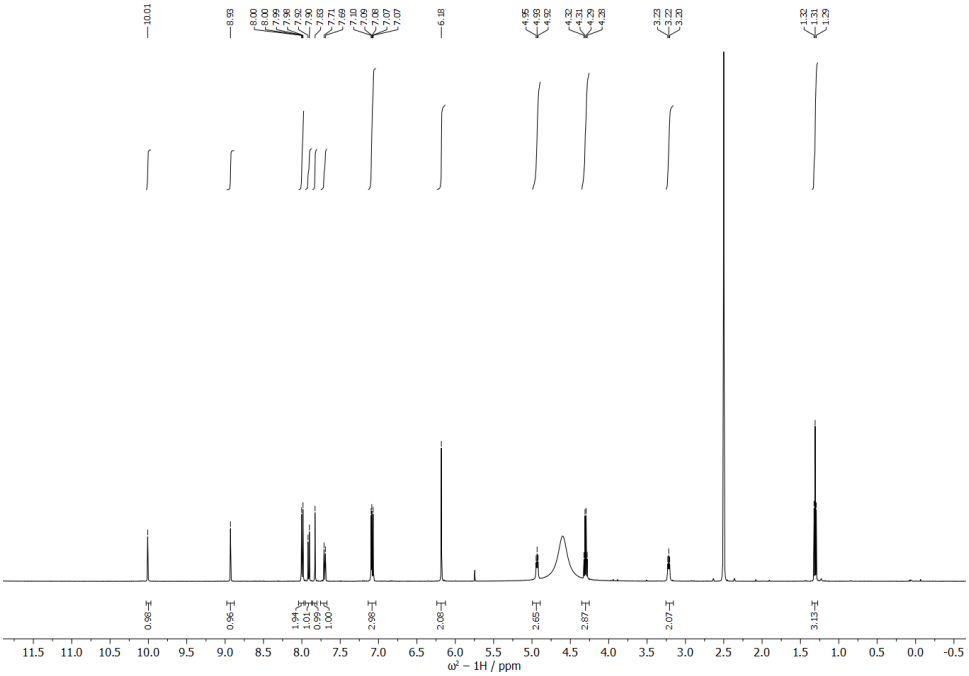

Figure S19. ^{1}H NMR spectrum (500 MHz) of **4f** in DMSO-d_6 + CF_3COOD.

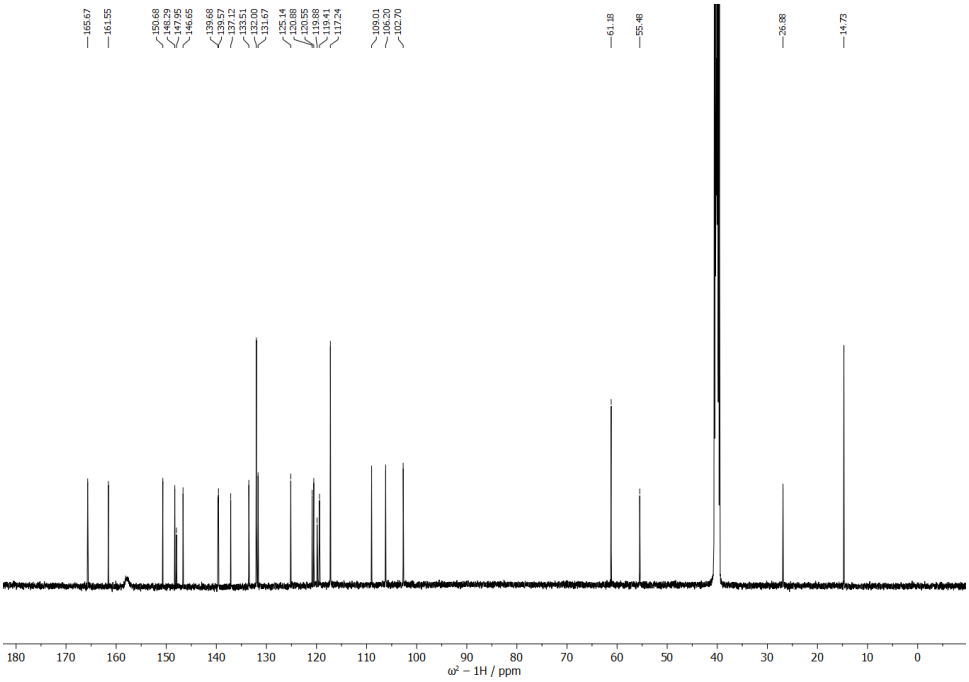

Figure S20. ^{13}C NMR spectrum (125 MHz) of **4f** in DMSO-d_6 + CF_3COOD.

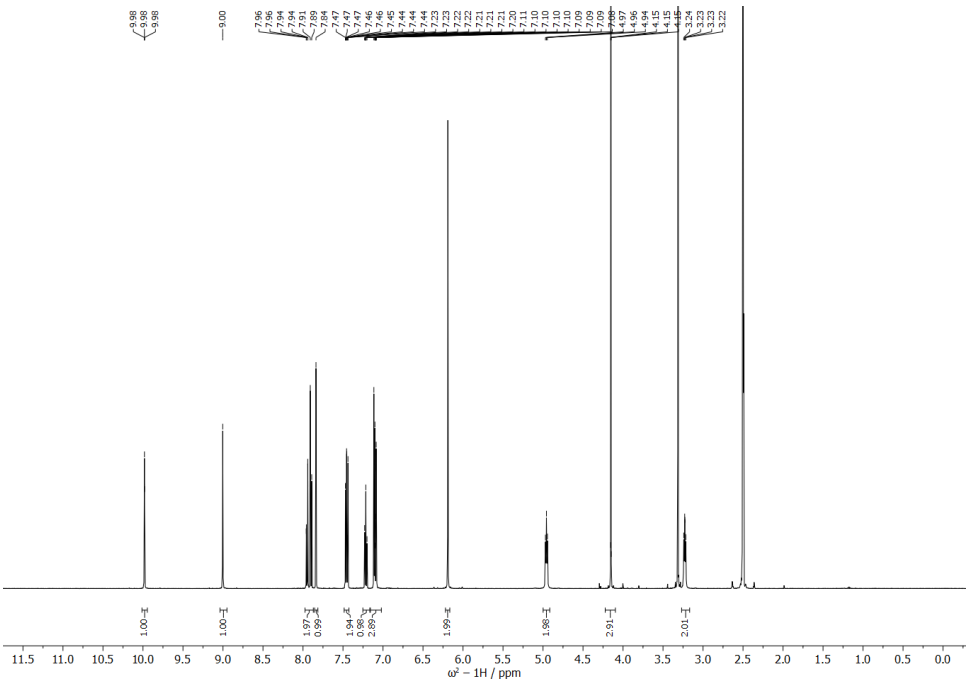

Figure S21. ^{1}H NMR spectrum (500 MHz) of **5a** in DMSO-d_6.

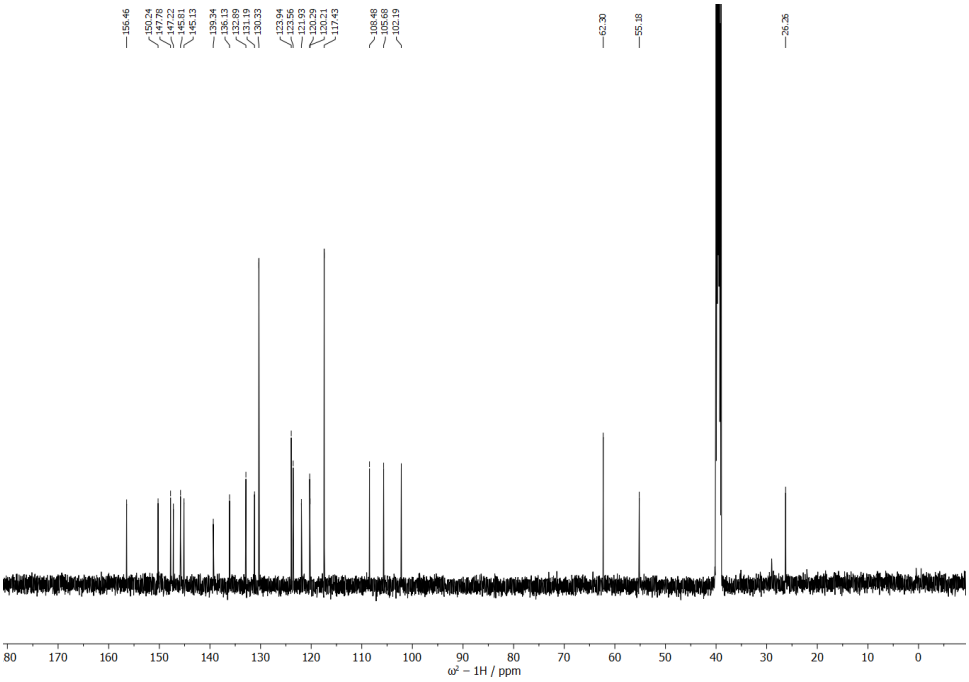

Figure S22. ^{13}C NMR spectrum (125 MHz) of **5a** in DMSO-d_6.

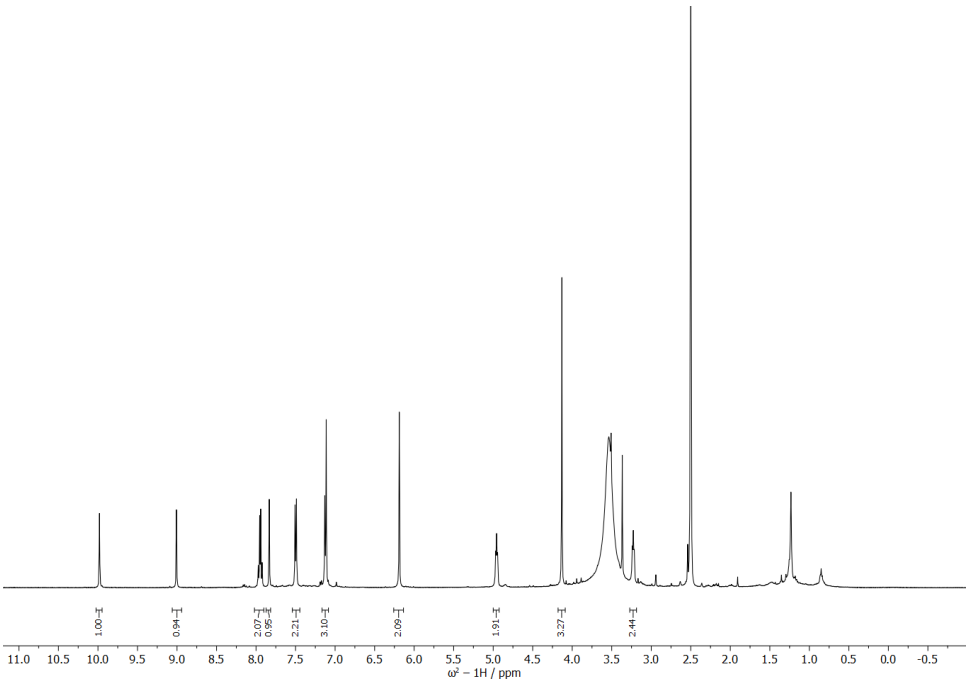

Figure S23. ^{1}H NMR spectrum (500 MHz) of **5b** in DMSO-d_6.

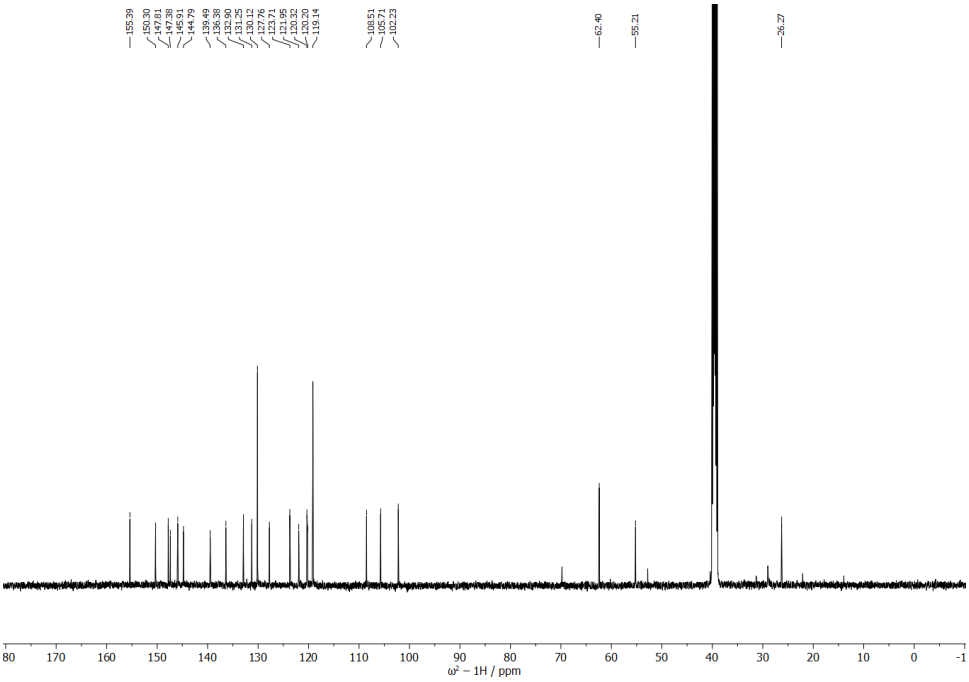

Figure S24. ^{13}C NMR spectrum (125 MHz) of **5b** in DMSO-d_6.

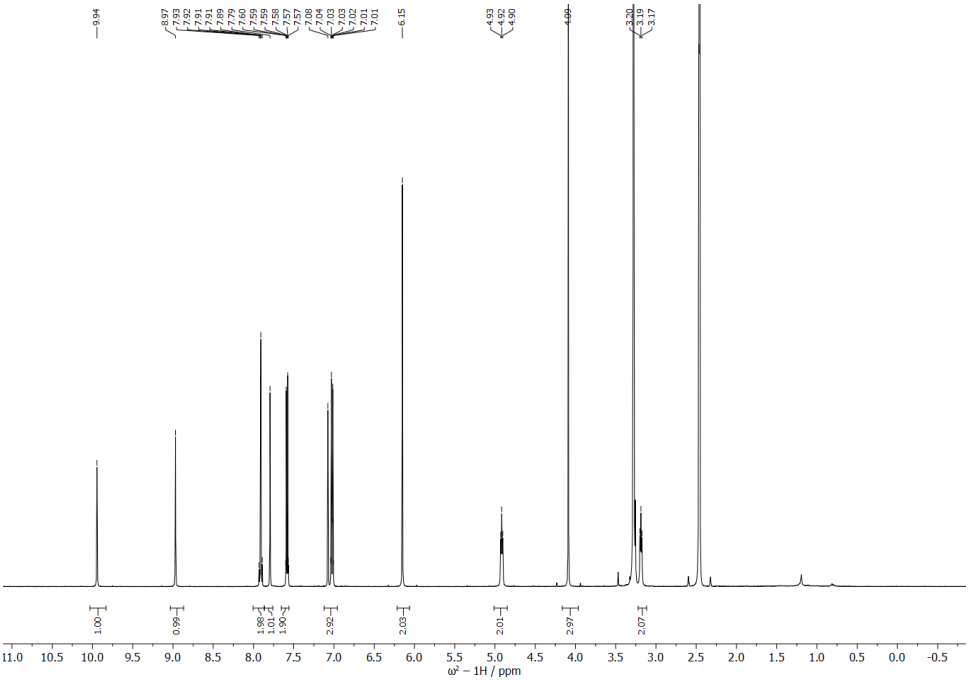

Figure S25. ^{1}H NMR spectrum (500 MHz) of **5c** in DMSO-d_6.

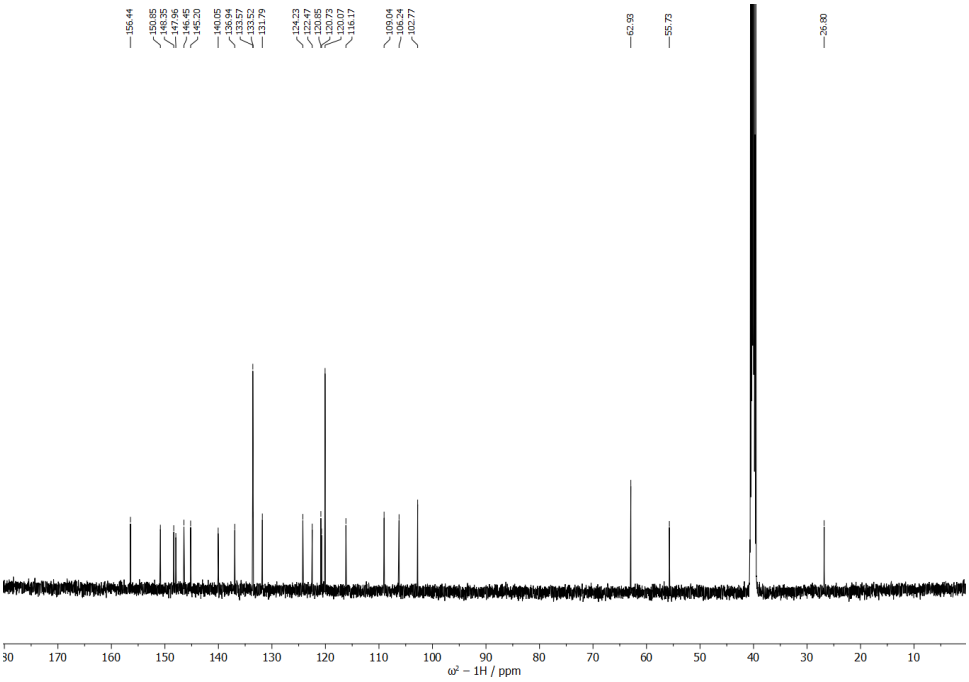

Figure S26. ^{13}C NMR spectrum (125 MHz) of **5c** in DMSO-d_6.

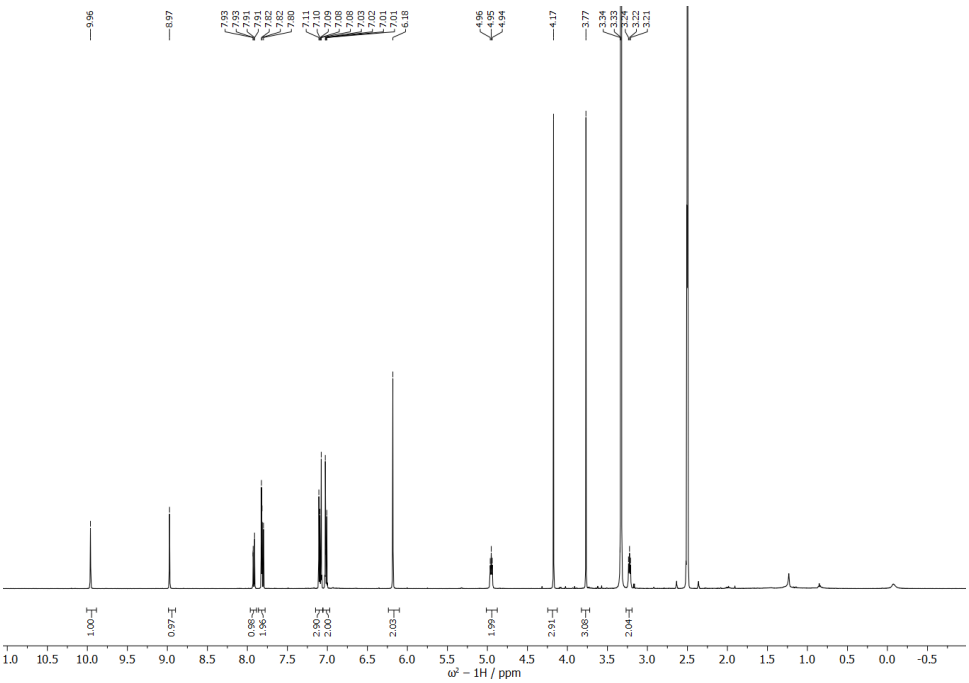

Figure S27. ^{1}H NMR spectrum (500 MHz) of **5d** in DMSO-d_6.

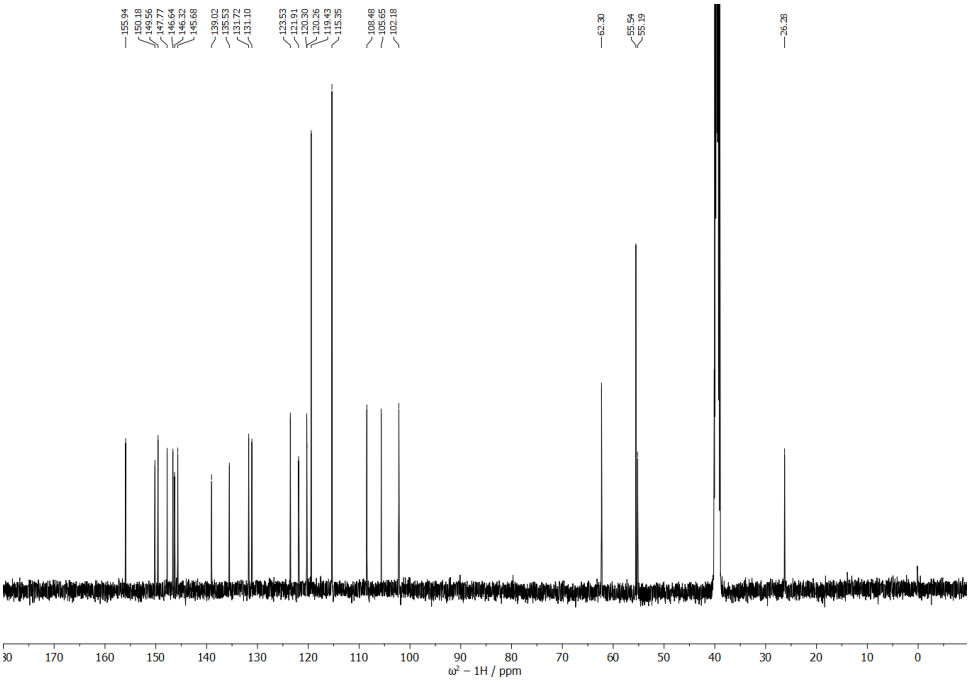

Figure S28. ^{13}C NMR spectrum (125 MHz) of **5d** in DMSO-d_6.

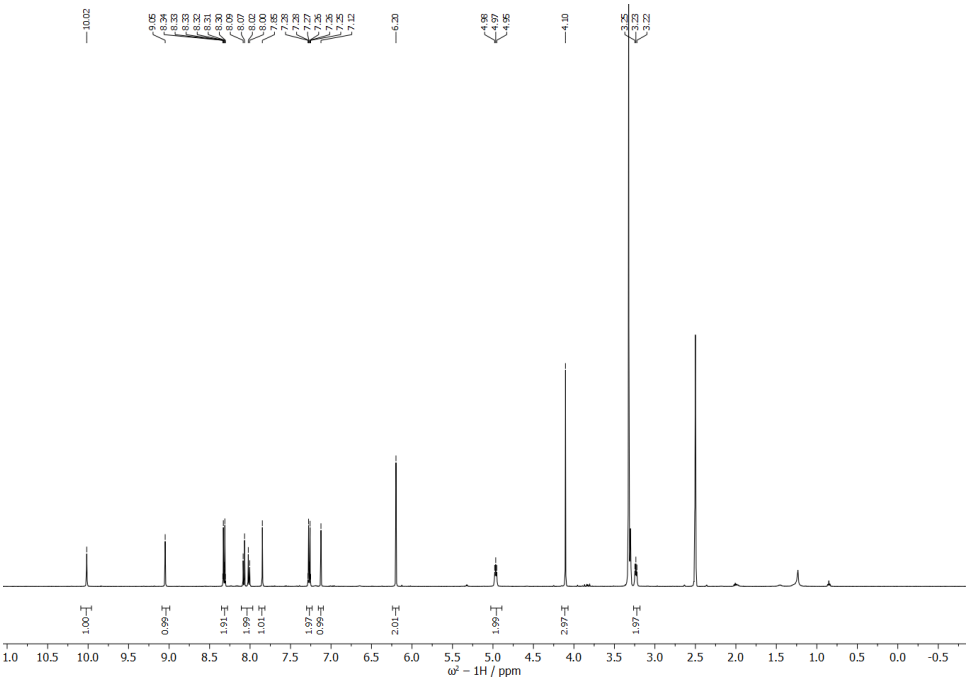

Figure S29. ^{1}H NMR spectrum (500 MHz) of **5e** in DMSO-d_6.

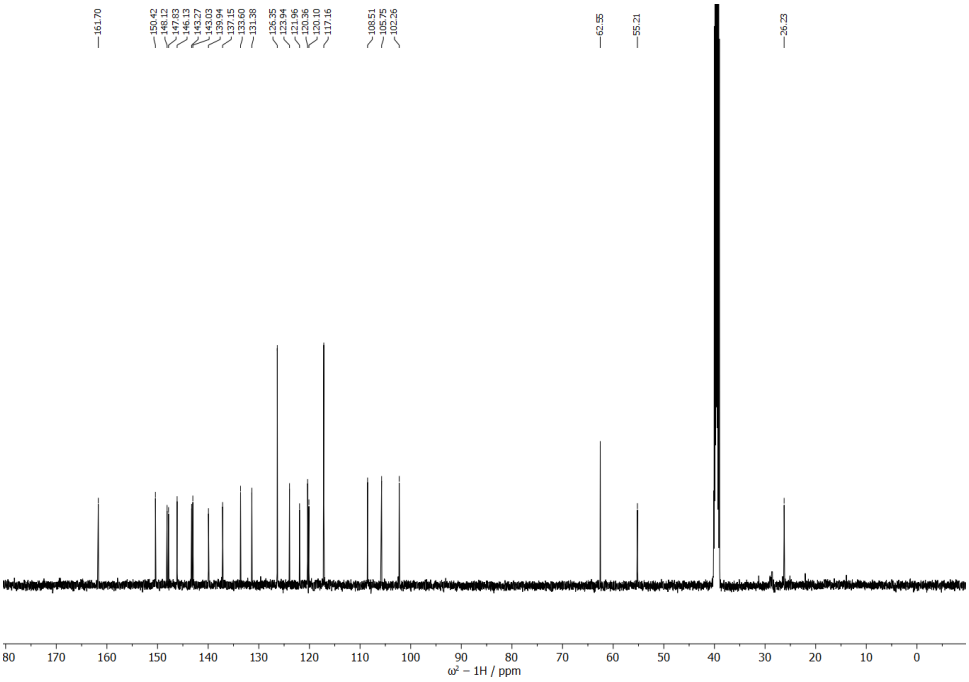

Figure S30. ^{13}C NMR spectrum (125 MHz) of **5e** in DMSO-d_6.

8. References

1. Rurack, K.; Spieles, M. *Anal. Chem.* **2011**, *83*, 1232–1242.

2. Bortolozzi, R.; Ihmels, H.; Thomas, L.; Tian, M.; Viola, G. *Chem. Eur. J.* **2013**, *19*, 8736–8741.

3. Stootman, F. H.; Fisher, D. M.; Rodger, A.; Aldrich-Wright, J. R. *Analyst* **2006**, *131*, 1145–1151.

4. Doria, F.; Nadai, M.; Costa, G.; Sattin, G., Gallati, C.; Bergamaschi, G.; Moraca, F.; Alcaro, S.; Freccero, M.; Richter, S. N. *Eur. J. Org. Chem.* **2016**, 4824–4833.

5. Dzubiel, D.; Ihmels, H.; Mohamed M. A. M.; Thomas, L. *Beilstein J. Org. Chem.* **2014**, *10*, 2963–2974.

6. Carvalho, J.; Quintela, T.; Gueddouda, N. M.; Bourdoncle, A.; Mergny, J.-L.; Salgado, G. F.; Queiroz, J. A.; Cruz, C. *Org. Biomol. Chem.* **2018**, *16*, 2776–2786.