SUPPLEMENTARY MATERIALS

Asymmetric and Reduced Xanthene Fluorophores: Synthesis, Photochemical Properties, and Application to Activatable Fluorescent Probes for Detection of Nitroreductase

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A. Synthesis Experimental Procedures

General information

All reagents and solvents were purchased from Sigma Aldrich Chemical Co. (St. Louis, USA), Tokyo Chemical Industries (Tokyo, Japan), Daejung Chemicals (Siheung-si, Korea), and Alfa Aesar (Ward Hill, USA) and used without any further purification. Anhydrous solvents were purchased from Aldrich Chemical Co. (St. Louis, USA), and all reactions were performed under nitrogen atmosphere. Silica gel (ZEOpreg 60 40–63 μm, Zeochem AG, Kentucky, USA) was used for flash column chromatography, and silica gel plates (Kieselgel 60F<sub>254</sub>, Merck, Darmstadt, Germany) were used for thin-layer chromatography. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured on a JEOL JNM-ECZ400s/L1 (400 MHz) spectrometer (Jeol, Tokyo, Japan), with CDCl<sub>3</sub> or DMSO-d<sub>6</sub> as the NMR solvent (Cambridge Isotope Laboratories, Tewksbury, USA). Chemical shifts are expressed in parts per million (ppm), and the coupling constant J is reported in hertz (Hz). Chemical shifts (in ppm) in <sup>1</sup>H NMR are based on the chemical shift of tetramethylsilane (δ = 0 ppm) in CDCl<sub>3</sub> as an internal standard. The chemical shifts in <sup>13</sup>C NMR are reported in ppm relative to the centerline of the triplet at 77.0 ppm observed for CDCl<sub>3</sub> or 39.5 ppm for DMSO-d<sub>6</sub>. Known compounds such as compound 1, 2, 3, 4 and 24 are synthesized as per previously known methods and spectral data is in agreement with previously published data.

1. Methyl 2-(6-methoxy-3-oxo-3H-xanthen-9-yl)benzoate (1)[1,2,6]

<image>

Compound 1 (10.3 g, yellow powder) was synthesized in 99% yield via the alkylation of fluorescein (10 g, 28.6 mmol) using methyl iodide (5.34 mL, 85.8 mmol) and K<sub>2</sub>CO<sub>3</sub> (9.88 g, 71.5 mmol) according to general procedure A. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.21 (dd, J = 8.0, 1.1 Hz, 1H), 7.87 (td, J = 7.5, 1.4 Hz, 1H), 7.78 (td, J = 7.5, 1.2 Hz, 1H), 7.50 (dd, J = 7.5, 1.1 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 6.89 (dd, J = 8.7, 2.3 Hz, 1H), 6.84 (d, J = 9.1 Hz, 1H), 6.80 (d, J = 9.6 Hz, 1H), 6.39 (dd, J = 9.6, 1.8 Hz, 1H), 6.24 (d, J = 1.8 Hz, 1H), 3.91 (s, 3H), 3.58 (s, 3H); <sup>13</sup>C-NMR (100 MHz, DMSO-d<sub>6</sub>) δ 184.38, 165.72, 164.42, 158.89, 154.10, 150.58, 133.73, 131.24, 130.89, 130.58, 130.03, 129.91, 129.38, 117.17, 114.82, 114.10, 105.12, 101.11, 56.82, 52.84; HRMS (ESI<sup>+</sup>): m/z Calcd for C<sub>22</sub>H<sub>17</sub>O<sub>5</sub>[M+H]<sup>+</sup>: 361.1076, Found: 361.1072.

2. Methoxymethyl 2-(6-(methoxymethoxy)-3-oxo-3H-xanthen-9-yl)benzoate (2)[10]

<image>

Compound 2 (4.51 g, yellow crystalline powder) was synthesized in 89 % of yield via the alkylation of fluorescein (4 g, 12 mmol) using chloromethyl methyl ether (2.74 mL, 36 mmol) in the presence of K<sub>2</sub>CO<sub>3</sub> (3.12 g, 22.56 mmol) according to general procedure A. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 8.25
(dd, J = 7.8, 0.9 Hz, 1H), 7.89 (td, J = 7.5, 1.3 Hz, 1H), 7.80 (td, J = 7.8, 1.3 Hz, 1H), 7.51 (dd, J = 7.3, 0.9 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 6.96 (dd, J = 8.9, 2.5 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 9.6 Hz, 1H), 6.39 (dd, J = 9.6, 1.8 Hz, 1H), 6.24 (d, J = 1.8 Hz, 1H), 5.35 (s, 2H), 5.14 (q, J = 6.3 Hz, 2H), 3.39 (s, 3H), 3.12 (s, 3H);

13C-NMR (100 MHz, DMSO-d6) δ 183.94, 164.38, 161.03, 158.30, 153.13, 149.62, 133.79, 133.44, 130.83, 130.25, 129.51, 129.02, 117.10, 115.05, 114.41, 104.67, 102.77, 94.05, 91.16, 56.90, 56.05; HRMS (ESI+): m/z Calcd for C24H21O7 [M+H]+: 421.1243, Found: 421.1278.

3. 6'-Methoxy-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-ol (3)[13]

![Compound 3](image3)

Compound 3 was synthesized from compound 1 (1 g, 2.8 mmol) according to general procedure B. The residue was purified by flash column chromatography on silica gel (CH2Cl2/EA = 10:1) to give compound 3 (730 mg, light yellow solid) in 79% yield over two steps. 1H-NMR (400 MHz, DMSO-d6) δ 7.44 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.77 (d, J = 2.7 Hz, 1H), 6.71-6.75 (m, 2H), 6.64 (dd, J = 8.7, 2.3 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.50 (dd, J = 8.8, 2.2 Hz, 1H), 5.22 (s, 2H), 3.76 (s, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 159.81, 158.16, 150.55, 145.36, 138.52, 129.76, 128.09, 123.10, 121.14, 117.35, 115.83, 112.00, 111.04, 101.62, 100.16, 82.59, 71.61, 55.45, 55.18, 54.54; HRMS (ESI+): m/z Calcd for C21H17O4 [M+H]+: 333.1082, Found: 333.1120.

4. 6'-(Methoxymethoxy)-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-ol (4)[10]

![Compound 4](image4)

Compound 4 was synthesized from compound 2 (2.5 g, 6.94 mmol) according to general procedure B. The residue was purified by flash column chromatography on silica gel (CH2Cl2/EA = 9:1) to afford 4 (1.92 g, yellow powder) in 88% yield over two steps. 1H-NMR (400 MHz, DMSO-d6) δ 9.82 (s, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.1 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 6.50 (dd, J = 8.5, 2.5 Hz, 1H), 5.23 (s, 2H), 5.20 (s, 2H), 3.36 (s, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 158.14, 157.13, 150.40, 145.23, 138.50, 129.75, 128.09, 123.10, 121.13, 118.51, 115.73, 112.23, 102.72, 101.61, 93.89, 82.50, 71.63, 55.67; HRMS (ESI+): m/z Calcd for C22H19O5 [M+H]+: 363.1188, Found: 363.1226.

5. 3'-Methoxy-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-yl trifluoromethanesulfonate (5)

![Compound 5](image5)
Compound 5 was synthesized from compound 3 (150 mg, 0.45 mmol) according to general procedure C using triflic anhydride (254 mg, 1.80 mmol) and pyridine (0.145 mL, 0.90 mmol) in CH$_2$Cl$_2$. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/EA = 9:1) to give compound 5 (179 mg, yellow gum) in 86% yield. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.51 (d, $J = 2.7$ Hz, 1H), 7.49 (d, $J = 7.3$ Hz, 1H), 7.39 (td, $J = 7.3$, 0.9 Hz, 1H), 7.31-7.20 (m, 2H), 7.18 (d, $J = 8.7$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 6.85 (d, $J = 7.3$ Hz, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 6.73 (dd, $J = 8.7$, 2.7 Hz, 1H), 5.34 (s, 2H), 3.79 (s, 3H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 160.15, 149.98, 148.63, 144.74, 138.09, 131.02, 129.66, 128.48, 125.96, 122.98, 121.37, 116.66, 111.95, 109.81, 100.26, 81.98, 72.46, 55.53; HRMS (ESI$^+$): m/z Calcd for C$_{22}$H$_{16}$F$_3$O$_6$S [M+H]$^+$: 465.0575, Found: 465.0616.

6. 3'-{(Methoxymethoxy)-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-yl trifluoromethanesulfonate (6)

Compound 6 was synthesized from compound 4 (300 mg, 0.83 mmol) according to general procedure C using triflic anhydride (467 mg, 1.66 mmol) and pyridine (265 mg, 3.32 mmol) in CH$_2$Cl$_2$. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/MeOH = 20:1) to give compound 6 (356 mg, yellow oil) in 86% yield. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.52 (d, $J = 2.3$ Hz, 1H), 7.49 (d, $J = 7.3$ Hz, 1H), 7.39 (t, $J = 7.1$ Hz, 1H), 7.20-7.30 (m, 2H), 7.18 (d, $J = 9.1$ Hz, 1H), 6.94 (d, $J = 2.7$ Hz, 1H), 6.93 (d, $J = 3.7$ Hz, 1H), 6.79-6.84 (m, 2H), 5.35 (s, 2H), 5.23 (s, 2H), 3.37 (s, 3H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 157.54, 150.07, 149.76, 148.69, 144.68, 138.14, 131.04, 129.73, 128.59, 128.51, 125.94, 123.04, 121.43, 117.79, 116.84, 113.41, 109.90, 102.83, 93.99, 81.98, 72.56, 55.75; HRMS (ESI$^+$): m/z Calcd for C$_{23}$H$_{18}$F$_3$O$_7$S [M+H]$^+$: 495.0681, Found: 495.0722.

7. 6'-Methoxy-N-propyl-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-amine (7)

Compound 7 was synthesized via the cross-coupling reaction between compound 5 (100 mg, 0.22 mmol) and n-propylamine (0.36 mL, 4.4 mmol) in the presence of Pd(OAc)$_2$ (14.50 mg, 0.022 mmol), BINAP (21.44 mg, 0.034 mmol), and Cs$_2$CO$_3$ (210 mg, 0.65 mmol) according to general procedure D. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/EA = 30:1) to give compound 7 (16.8 mg, light pink powder) in 20% yield. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.42 (d, $J = 7.8$ Hz, 1H), 7.34 (td, $J = 7.5$, 0.9 Hz, 1H), 7.23 (t, $J = 7.1$ Hz, 1H), 6.79-6.70 (m, 3H), 6.61 (dd, $J = 8.7$, 2.7 Hz, 1H), 6.57 (d, $J = 8.7$ Hz, 1H), 6.52 (dd, $J = 8.7$, 2.3 Hz, 1H), 6.26 (d, $J = 2.3$ Hz, 1H), 5.91 (t, $J = 5.3$ Hz, 1H), 5.17 (s, 2H), 3.76 (s, 3H), 2.96 (q, $J = 6.6$ Hz, 2H), 1.54 (sext, $J = 7.3$ Hz, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 159.68, 150.85, 149.99, 145.46, 138.75, 129.74, 129.19, 128.12, 127.77, 123.16, 121.05, 117.63, 111.68, 110.61, 109.47, 100.12, 96.36, 82.85, 71.25, 55.39, 44.53, 21.76, 11.64; HRMS (ESI$^+$): m/z Calcd for C$_{24}$H$_{24}$NO$_3$ [M+H]$^+$: 374.1711, Found: 374.1750.

8. N,N-Diethyl-6'-methoxy-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-amine (8)
Compound 8 was synthesized via the cross-coupling reaction between compound 5 (650 mg, 1.4 mmol) and diethylamine (1.45 mL, 14 mmol) in the presence of Pd(OAc)$_2$ (94.20 mg, 0.14 mmol), BINAP (131 mg, 0.21 mmol), and Cs$_2$CO$_3$ (1.36 g, 4.20 mmol) according to general procedure D. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/EA = 20:1) to give compound 8 (222 mg, pink powder) in 41% yield. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.43 (d, $J = 7.8$ Hz, 1H), 7.35 (t, $J = 7.1$ Hz, 1H), 7.23 (t, $J = 7.1$ Hz, 1H), 6.84-6.69 (m, 3H), 6.65 (d, $J = 8.7$ Hz, 1H), 6.62 (dd, $J = 8.7$, 2.7 Hz, 1H), 6.41 (dd, $J = 8.7$, 2.7 Hz, 1H), 6.34 (d, $J = 2.7$ Hz, 1H), 5.18 (s, 2H), 3.76 (s, 3H), 3.33 (q, $J = 6.9$ Hz, 4H), 1.07 (t, $J = 6.9$ Hz, 6H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 159.69, 150.93, 148.13, 145.33, 138.80, 129.64, 127.96, 123.19, 121.04, 117.59, 111.40, 110.57, 108.12, 100.15, 96.67, 82.72, 71.25, 55.36, 43.73, 12.37; HRMS (ESI$^+$): m/z Calcd for C$_{25}$H$_{26}$NO$_3$ [M+H]$^+$: 388.1868, Found: 388.1911.

9. $N$-Ethyl-6'-(methoxymethoxy)-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-amine (10)

Compound 10 was synthesized via the cross-coupling reaction between compound 6 (100 mg, 0.20 mmol) and ethylamine (2M solution, 2 mL, 4.05 mmol) in anhydrous toluene (3 mL) in the presence of Pd$_2$(dba)$_3$·CHCl$_3$ (21 mg, 0.02 mmol), Xantphos (18 mg, 0.03 mmol), and Cs$_2$CO$_3$ (201 mg, 0.61 mmol) according to procedure D. The residue was purified by flash column chromatography on silica gel to give compound 10 (79 mg, yellow crystalline powder) in 100% yield. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.40 (d, $J = 7.3$ Hz, 1H), 7.31 (td, $J = 7.5$, 0.9 Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 6.80 (d, $J = 2.7$ Hz, 1H), 6.75 (d, $J = 1.8$ Hz, 2H), 6.29 (dd, $J = 8.2$, 2.3 Hz, 1H), 6.23 (d, $J = 1.8$ Hz, 1H), 6.17 (s, 2H), 5.16 (s, 2H), 3.34 (s, 3H), 3.00 (q, $J = 7.2$ Hz, 2H), 1.11 (t, $J = 7.1$ Hz, 3H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 157.55, 157.55, 151.28, 151.36, 150.44, 145.89, 130.27, 130.28, 129.72, 128.66, 128.33, 123.70, 121.58, 119.32, 112.61, 112.21, 110.10, 103.23, 96.96, 94.41, 83.31, 71.84, 56.18, 37.73, 14.77; HRMS (ESI$^+$): m/z Calcd for C$_{24}$H$_{24}$NO$_4$ [M+H]$^+$: 390.1705, Found: 388.1911.

10. $N,N$-Diethyl-6'-(methoxymethoxy)-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-amine (11)

Compound 11 was synthesized via the cross-coupling reaction between compound 6 (100 mg, 0.20 mmol) and diethylamine (0.418 mL, 4.04 mmol) in the presence of Pd(PPh)$_3$ (23 mg, 0.02 mmol), BINAP
(20 mg, 0.032 mmol), and Cs$_2$CO$_3$ (198 mg, 0.06 mmol) according to procedure D. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/EA = 30:1) to give the desired product (39 mg, light yellow powder) in 47% yield. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.43 (d, $J = 7.3$ Hz, 1H), 7.35 (td, $J = 7.5, 0.9$ Hz, 1H), 7.23 (t, $J = 7.8$ Hz, 1H), 6.83 (d, $J = 2.3$ Hz, 1H), 6.79 (d, $J = 6.9$ Hz, 1H), 6.77 (d, $J = 5.5$ Hz, 1H), 6.69 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.65 (d, $J = 8.7$ Hz, 1H), 6.41 (dd, $J = 8.9, 2.5$ Hz, 1H), 6.35 (d, $J = 2.3$ Hz, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 3.35 (s, 3H), 3.32 (q, $J = 6.9$ Hz, 4H), 1.07 (t, $J = 6.9$ Hz, 6H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 157.60, 151.51, 151.22, 148.70, 145.76, 139.36, 130.31, 130.06, 128.68, 128.37, 123.75, 121.59, 119.30, 112.59, 111.84, 108.69, 103.29, 97.23, 94.45, 83.20, 71.83, 56.19, 44.26, 12.92; HRMS (ESI$^+$): m/z Calcd for C$_{26}$H$_{28}$NO$_4$ [M+H]$^+$: 418.1974, Found: 418.2010.

11. 6'-Methoxy-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-amine (12)

The intermediate imine 9 was synthesized via the cross-coupling reaction between compound 5 (500 mg, 1.08 mmol) and benzophenone imine (236 mg, 1.3 mmol) in the presence of Pd(OAc)$_2$ (74 mg, 0.11 mmol), BINAP (108 mg, 0.17 mmol), and Cs$_2$CO$_3$ (1.06 g, 3.23 mmol) according to general procedure D. The crude product (9) was used to prepare compound 12 without any further purification. Product 9 was dissolved in THF, followed by the addition of 1 N HCl (3 mL). The reaction mixture was stirred at rt for 30 min, and then, the reaction was quenched with 1 N NaOH solution and extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH$_2$Cl$_2$/EA = 30:1) to give compound 12 (200 mg, shiny light yellow crystal) in 55% yield over two steps. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.42 (d, $J = 7.3$ Hz, 1H), 7.33 (t, $J = 7.3$ Hz, 1H), 7.23 (t, $J = 7.1$ Hz, 1H), 6.73-6.76 (m, 3H), 6.60 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.54 (d, $J = 8.7$ Hz, 1H), 6.33 (d, $J = 1.8$ Hz, 1H), 6.29 (dd, $J = 8.7, 2.3$ Hz, 1H), 5.35 (s, 2H), 5.17 (s, 2H), 3.76 (s, 3H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 159.66, 150.73, 149.81, 145.46, 138.73, 129.49, 127.92, 123.13, 121.02, 117.59, 112.18, 110.69, 100.09, 98.96, 82.80, 71.22, 55.38; HRMS (ESI$^+$): m/z Calcd for C$_{21}$H$_{18}$NO$_3$ [M+H]$^+$: 332.1242, Found: 332.1279.

12. 3'-Ethylamino)-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-ol (13)

Compound 13 (264 mg, red powder) was synthesized in 55% yield from compound 10 (543 mg) according to general procedure E. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 9.69 (s, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.30 (td, $J = 7.5, 0.9$ Hz, 1H), 7.19 (t, $J = 7.1$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 6.63 (d, $J = 8.2$ Hz, 1H), 6.52 (d, $J = 8.2$ Hz, 1H), 6.49 (d, $J = 2.3$ Hz, 1H), 6.43 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.26 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.21 (d, $J = 2.3$ Hz, 1H), 5.80 (t, $J = 5.3$ Hz, 1H), 5.12 (s, 2H), 2.99 (sext, $J = 7.3$ Hz, 2H), 1.11 (t, $J = 7.1$ Hz, 3H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 158.43, 151.45, 151.33, 150.34, 146.06, 139.36, 130.28, 129.70, 128.59, 123.13, 121.02, 117.59, 112.18, 110.69, 100.09, 98.96, 82.80, 71.22, 55.38; HRMS (ESI$^+$): m/z Calcd for C$_{21}$H$_{18}$NO$_3$ [M+H]$^+$: 332.1242, Found: 332.1279.
128.19, 123.72, 121.50, 116.74, 112.46, 111.98, 109.98, 102.10, 96.98, 83.47, 71.61, 37.74, 14.79; HRMS (ESI^+): m/z Calcd for C_{22}H_{20}NO_{3} [M+H]^+: 346.1443, Found: 346.1439.

13. 3’-(Diethylamino)-3H-spiro[isobenzofuran-1,9’-xanthen]-6’-ol (14)

Compound 14 (278 mg, red powder) was synthesized in 84% yield from compound 11 (367 mg) according to general procedure E. \(^1{H}\)-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 9.71 (s, 1H), 7.39 (d, \(J = 7.8\) Hz, 1H), 7.31 (td, \(J = 7.3, 0.9\) Hz, 1H), 7.20 (t, \(J = 7.1\) Hz, 1H), 6.73 (d, \(J = 7.3\) Hz, 1H), 6.63 (d, \(J = 8.7\) Hz, 1H), 6.59 (d, \(J = 8.7\) Hz, 1H), 6.51 (d, \(J = 2.3\) Hz, 1H), 6.43 (dd, \(J = 8.7, 2.3\) Hz, 1H), 6.36 (dd, \(J = 8.9, 2.5\) Hz, 1H), 6.31 (d, \(J = 2.1\) Hz, 1H), 5.13 (s, 2H), 3.29 (q, \(J = 6.9\) Hz, 4H), 1.04 (t, \(J = 7.1\) Hz, 6H); \(^13{C}\)-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 157.92, 150.97, 148.07, 145.39, 138.89, 129.63, 127.88, 123.21, 120.98, 116.17, 111.51, 107.96, 101.59, 96.77, 82.82, 71.07, 43.69, 12.40; HRMS (ESI^+): m/z Calcd for C_{24}H_{24}NO_{3} [M+H]^+: 374.1711, Found: 374.1753.

14. 3’-(Ethylamino)-3H-spiro[isobenzofuran-1,9’-xanthen]-6’-yl trifluoromethanesulfonate (15)

Compound 15 was synthesized from compound 13 (264 mg, 0.76 mmol) using \(N\)-phenyl-bis-(trifluoromethanesulfonimide) (546 mg, 1.53 mmol) and K₂CO₃ (423 mg, 3.06 mmol) in CH₃CN according to general procedure C. The residue was purified by flash column chromatography on silica gel (CH₂Cl₂/EA = 20:1) to give 15 (250 mg, pink oil) in 69% yield. \(^1{H}\)-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 7.47-7.41 (m, 2H), 7.35 (td, \(J = 7.3, 0.9\) Hz, 1H), 7.22 (t, \(J = 7.1\) Hz, 1H), 7.13 (dd, \(J = 8.9, 2.5\) Hz, 1H), 7.06 (d, \(J = 8.7\) Hz, 1H), 6.77 (d, \(J = 7.8\) Hz, 1H), 6.61 (d, \(J = 8.7\) Hz, 1H), 6.34 (dd, \(J = 8.7, 2.3\) Hz, 1H), 6.28 (d, \(J = 2.3\) Hz, 1H), 5.95 (s, 1H), 5.23 (s, 2H), 3.01 (q, \(J = 6.7\) Hz, 2H), 1.12 (t, \(J = 7.1\) Hz, 3H); \(^13{C}\)-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 150.96, 150.91, 150.74, 149.01, 145.37, 139.03, 131.59, 129.65, 128.92, 128.72, 126.77, 123.64, 121.78, 116.73, 111.41, 110.73, 110.23, 96.88, 82.90, 72.41, 40.68, 40.47, 40.26, 40.05, 39.84, 39.64, 39.43, 37.70, 14.72; HRMS (ESI^+): m/z Calcd for C_{23}H_{19}F₃NO_{5}S [M+H]^+: 478.0936, Found: 478.0930.

15. 3’-(Diethylamino)-3H-spiro[isobenzofuran-1,9’-xanthen]-6’-yl trifluoromethanesulfonate (16)

Compound 16 was synthesized from compound 14 (10 mg, 0.03 mmol) using \(N\)-phenyl-bis-(trifluoromethanesulfonimide) (21 mg, 0.06 mmol) and K₂CO₃ (17 mg, 0.12 mmol) in CH₃CN according
to general procedure C. The residue was purified by flash column chromatography to give 16 (8.5 mg, pink powder) in 57% yield. 1H-NMR (400 MHz, DMSO-d6) δ 7.44 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.36 (td, J = 7.5, 0.9 Hz, 1H), 7.24 (t, J = 3.9 Hz, 1H), 7.14 (dd, J = 8.7, 2.7 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 6.44 (dd, J = 9.1, 2.7 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 5.22 (s, 2H), 3.31 (q, J = 7.8 Hz, 4H), 1.05 (t, J = 6.9 Hz, 6H); 13C-NMR (100 MHz, DMSO-d6) δ 151.0, 149.05, 148.96, 145.23, 139.12, 131.566, 130.00, 128.95, 128.77, 126.74, 123.69, 121.79, 116.76, 111.02, 110.20, 109.32, 97.13, 82.79, 72.40, 44.29, 12.87; HRMS (ESI+): m/z Calcd for C25H23F3NO5S [M+H]+: 506.1204, Found: 506.1243.

16. N3'-Ethyl-3H-spiro[isobenzofuran-1,9'-xanthene]-3',6'-diamine (17)

The intermediate imine was synthesized via the cross-coupling reaction between compound 15 (63 mg, 0.13 mmol) and benzophenone imine (35 mg, 0.20 mmol) in anhydrous toluene (1.5 mL) in the presence of Cs2CO3 (129 mg, 0.40 mmol), Pd(OAc)2 (9 mg, 0.013 mmol), and BINAP (13 mg, 0.021 mmol) according to general procedure D. The crude imine intermediate was used to prepare compound 17 without any further purification. The crude intermediate was dissolved in THF (2 mL), followed by the addition of 1 N HCl (0.5 mL), and the reaction mixture was stirred at rt for 30 min. The reaction was quenched with 1 N NaOH solution and extracted with CH2Cl2. The organic layer was dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH2Cl2/EA = 20:1) to give 17 (20 mg, dark red powder) in 44% yield. 1H-NMR (400 MHz, DMSO-d6) δ 7.36 (d, J = 7.3 Hz, 1H), 7.29 (td, J = 7.4, 1.1 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 6.70 (d, J = 7.3 Hz, 1H), 6.48 (d, J = 8.7 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 6.29-6.17 (m, 4H), 5.74 (t, J = 5.3 Hz, 1H), 5.26 (s, 2H), 5.08 (s, 2H), 2.99 (sext, J = 7.3 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H); 13C-NMR (100 MHz, DMSO-d6) δ 151.63, 151.48, 150.21, 150.09, 146.20, 139.56, 129.82, 129.69, 128.46, 128.01, 123.69, 121.417, 113.23, 112.83, 110.81, 109.65, 99.59, 97.07, 83.73, 71.29, 37.76, 14.82; HRMS (ESI+): m/z Calcd for C22H21N2O2 [M+H]+: 345.1603, Found: 345.1597.

17. N3',N3'-Diethyl-3H-spiro[isobenzofuran-1,9'-xanthene]-3',6'-diamine (18)

The intermediate imine was synthesized via the cross-coupling reaction between compound 16 (90 mg, 0.18 mmol) and benzophenone imine (39.9 mg, 0.22 mmol) in anhydrous toluene (5 mL) in the presence of Cs2CO3 (176 mg, 0.54 mmol), Pd(OAc)2 (13.5 mg, 0.02 mmol), and BINAP (18.7 mg, 0.03 mmol) according to general procedure D. The crude imine intermediate was used to prepare compound 18, without any further purification. The crude intermediate was dissolved in THF (2 mL) followed by the addition of 1 N HCl (3 mL), and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with 1 N NaOH solution and extracted with CH2Cl2. The organic layer was
dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH2Cl2/EA = 7:3) to give 18 (20 mg, dark red powder) in 30% yield. 1H-NMR (400 MHz, DMSO-d6) δ 7.40 (d, J = 7.8 Hz, 1H), 7.32 (td, J = 7.3, 0.9 Hz, 1H), 7.22 (t, J = 7.1 Hz, 1H), 6.74 (d, J = 7.3 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 6.35 (dd, J = 8.7, 2.7 Hz, 1H), 6.30 (t, J = 2.7 Hz, 2H), 6.25 (dd, J = 8.7, 2.3 Hz, 1H), 5.29 (s, 2H), 5.11 (s, 2H), 3.32 (q, J = 10.7 Hz, 4H), 1.07 (t, J = 7.1 Hz, 6H); 13C-NMR (100 MHz, DMSO-d6) δ 151.79, 151.58, 150.13, 148.51, 146.07, 139.63, 130.03, 129.85, 128.49, 128.06, 123.79, 121.44, 113.20, 112.49, 110.84, 108.21, 99.61, 97.38, 83.62, 71.29, 44.20, 12.96; HRMS (ESI+): m/z Calcd for C_{24}H_{25}N_{2}O_{2}[M+H]+: 373.1871, Found: 373.1911.

18. 3',6'-Dimethoxy-3H-spiro[isobenzofuran-1,9'-xanthene] (19)

To a solution of compound 3 (20 mg, 0.06 mmol) in DMF (1.5 mL) were added K2CO3 (12.5 mg, 0.09 mmol) and methyl iodide (0.01 mL, 0.07 mmol), and the reaction mixture was stirred at rt for 2 h. After completion of the reaction, ice-water was added to the reaction mixture and stirred at 0 °C for 30 min. The resulting yellow solid was filtered and washed with water to completely remove K2CO3. The solid was dried to afford 19 (18 mg, light yellow powder) in 86% yield. 1H-NMR (400 MHz, DMSO-d6) δ 7.42 (d, J = 7.3 Hz, 1H), 7.33 (td, J = 7.4, 1.1 Hz, 1H), 7.21 (t, J = 7.1 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 2.3 Hz, 2H), 6.72 (d, J = 7.8 Hz, 1H), 6.64 (dd, J = 8.7, 2.7 Hz, 2H), 5.23 (s, 2H), 3.74 (s, 6H); 13C-NMR (100 MHz, DMSO-d6) δ 160.38, 151.00, 145.83, 138.92, 130.30, 128.83, 128.56, 123.58, 121.72, 117.77, 111.66, 100.67, 82.97, 72.33, 55.97; HRMS (ESI+): m/z Calcd for C_{22}H_{19}O_{4}[M+H]+: 347.1283, Found: 347.1274.

19. 3'-(Benzyloxy)-6'-methoxy-3H-spiro[isobenzofuran-1,9'-xanthene] (20)

To a solution of compound 3 (20 mg, 0.06 mmol) in acetone (2.5 mL) were added DBU (0.009 mL mg, 0.09 mmol) and benzyl bromide (0.012 mL, 0.07 mmol), and the reaction mixture was stirred at rt for 10 min. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography on silica gel (Hex/EA = 9:1) to afford 20 (25 mg, light yellow powder) in 98% yield. 1H-NMR (400 MHz, DMSO-d6) δ 7.43-7.39 (m, 3H), 7.39-7.27 (m, 4H), 7.21 (t, J = 7.5 Hz, 1H), 6.81 (dd, J = 8.5, 2.5 Hz, 3H), 6.77-6.69 (m, 3H), 6.64 (dd, J = 8.9, 2.5 Hz, 1H), 5.23 (s, 2H), 5.11 (s, 2H), 3.74 (s, 6H); 13C-NMR (100 MHz, DMSO-d6) δ 160.38, 151.00, 145.83, 138.92, 130.30, 128.83, 128.56, 123.58, 121.72, 117.77, 111.66, 100.67, 82.97, 72.33, 55.97; HRMS (ESI+): m/z Calcd for C_{28}H_{23}O_{4}[M+H]+: 423.1596, Found: 423.1587.

20. N-(3'-Methoxy-3H-spiro[isobenzofuran-1,9'-xanthene]-6'-yl)benzamide (21)
To a solution of compound 12 (20 mg, 0.06 mmol) in DMF (1.5 mL) were added EDC (15 mg, 0.08 mmol), HOBt (11 mg, 0.08 mmol), iPrNEt (0.021 mL, 0.12 mmol), and benzoic acid (8.5 mg, 0.07 mmol), and the reaction mixture stirred at rt for 12 h. The reaction mixture was extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (Hex/EA = 1:1) to afford 21 (13 mg, white crystalline powder) in 50% yield.

1H-NMR (400 MHz, DMSO-d₆) δ 10.38 (s, 1H), 7.95-7.88 (m, 2H), 7.84 (d, J = 1.8 Hz, 1H), 7.61-7.54 (m, 1H), 7.43-7.36 (m, 2H), 7.36 (td, J = 7.3, 0.9 Hz, 1H), 7.22 (t, J = 7.1 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.82 (d, J = 2.7 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.65 (dd, J = 8.7, 2.7 Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H);

13C-NMR (100 MHz, DMSO-d₆) δ 166.39, 160.46, 151.04, 150.03, 145.93, 140.46, 138.79, 135.24, 132.30, 130.21, 129.45, 128.97, 128.85, 128.60, 128.25, 123.55, 121.77, 120.70, 117.71, 116.40, 111.84, 107.42, 100.75, 82.94, 72.57, 56.02, 55.44; HRMS (ESI⁺): m/z Calcd for C₂₈H₂₂NO₄ [M+H]⁺: 436.1549, Found: 436.1543.

21. Methyl 2-(6-methoxy-3-oxo-3H-xanthen-9-yl)benzoate (24)

To a solution of compound 22 (20 mg, 0.06 mmol) in DMF (1.5 mL) were added K₂CO₃ (12.5 mg, 0.09 mmol) and methyl iodide (10 mg, 0.07 mmol), and the reaction mixture was stirred at rt for 10 min. After completion of the reaction, ice-water was added to the reaction mixture and stirred at 0 °C for 30 min. The resulting yellow solid was filtered and washed with water to completely remove the K₂CO₃ reagent. The solid was dried to afford 24 (18 mg, yellow powder) in 87% yield. 1H NMR (400 MHz, DMSO-d₆) δ 8.18 (dd, J = 7.8, 1.4 Hz, 1H), 7.83 (td, J = 7.5, 1.4 Hz, 1H), 7.75 (td, J = 7.5, 1.4 Hz, 1H), 7.46 (dd, J = 7.5, 1.1 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 6.86 (dd, J = 9.1, 2.3 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.76 (d, J = 10.1 Hz, 1H), 6.35 (dd, J = 9.6, 1.8 Hz, 1H), 6.21 (d, J = 1.8 Hz, 1H), 3.87 (s, 3H), 3.54 (s, 3H); 13C-NMR (100 MHz, DMSO-d₆) δ 184.41, 165.73, 164.44, 158.92, 154.11, 150.67, 134.42, 133.75, 131.23, 130.91, 130.59, 130.02, 129.89, 129.39, 117.16, 114.82, 114.13, 105.10, 101.11, 56.82, 52.84; HRMS (ESI⁺): m/z Calcd for C₂₂H₁₇O₅ [M+H]⁺: 361.1076, Found: 361.1072.

22. Benzyl 2-(6-methoxy-3-oxo-3H-xanthen-9-yl)benzoate (25)
To a solution of compound 22 (20 mg, 0.06 mmol) in acetone (2.5 mL) were added DBU (13 mg, 0.09 mmol) and benzyl bromide (12 mg, 0.07 mmol), and the reaction mixture was stirred at rt for 10 min. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography on silica gel (Hex/EA = 9:1) to afford 25 (18 mg, yellow powder) in 71% yield.

$^1$H-NMR (400 MHz, DMSO-$_d$6) δ 8.19 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.82 (td, $J = 7.5, 1.4$ Hz, 1H), 7.75 (td, $J = 7.5, 1.4$ Hz, 1H), 7.44 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.30-7.20 (m, 1H), 7.20-7.12 (m, 2H), 7.06 (d, $J = 2.3$ Hz, 1H), 6.99-6.92 (m, 2H), 6.81 (dd, $J = 8.7, 2.3$ Hz, 1H), 6.78 (d, $J = 9.1$ Hz, 1H), 6.75 (d, $J = 9.6$ Hz, 1H), 6.33 (dd, $J = 9.8, 2.1$ Hz, 1H), 6.11 (d, $J = 1.8$ Hz, 1H), 4.94 (dd, $J = 16.2, 12.1$ Hz, 2H), 3.87 (s, 3H); $^{13}$C-NMR (100 MHz, DMSO-$_d$6) δ 184.35, 165.45, 164.36, 158.73, 154.01, 150.16, 135.30, 134.09, 133.73, 131.39, 131.9, 130.81, 130.58, 130.21, 129.93, 129.33, 128.63, 128.32, 117.24, 114.78, 114.03, 105.09, 101.07, 67.32, 56.80; HRMS (ESI$^+$): m/z Calcd for C$_{28}$H$_{21}$O$_5$ [M+H]$^+$: 437.1389, Found: 437.1381.

23. N-(3'-Methoxy-3-oxo-3$^H$-spiro[isobenzofuran-1,9'-xanthene]-6'-yl)benzamide (26)

To a solution of compound 23 (20 mg, 0.06 mmol) in DMF (1.5 mL) were added EDC (15 mg, 0.08 mmol), HOBt (11 mg, 0.08 mmol), $i$PrNEt$_2$ (0.021 mL, 0.12 mmol), and benzoic acid (8.5 mg, 0.07 mmol), and the reaction mixture stirred at rt for 12 h. The reaction mixture was extracted with CH$_2$Cl$_2$, and the organic layer dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (Hex/EA = 1:1) to afford 26 (2 mg, light yellow powder) in 8% yield. $^1$H-NMR (400 MHz, DMSO-$_d$6) δ 10.49 (s, 1H), 8.04-7.97 (m, 2H), 7.97-7.88 (m, 2H), 7.77 (td, $J = 7.5, 1.2$ Hz, 1H), 7.70 (td, $J = 7.5, 0.9$ Hz, 1H), 7.58 (tt, $J = 7.3, 1.8$ Hz, 1H), 7.42 (dd, $J = 8.7, 2.3$ Hz, 1H), 7.26 (d, $J = 7.3$ Hz, 1H), 6.97 (d, $J = 2.3$ Hz, 1H), 6.76 (d, $J = 8.7$ Hz, 1H), 6.70 (dd, $J = 9.1, 2.3$ Hz, 1H), 6.55 (d, $J = 9.1$ Hz, 1H), 3.79 (s, 3H); $^{13}$C-NMR (100 MHz, DMSO-$_d$6) δ 169.22, 166.56, 161.66, 153.11, 152.35, 151.28, 141.93, 136.31, 135.06, 132.43, 130.79, 129.51, 128.99, 128.84, 128.32, 126.31, 125.77, 125.33, 124.52, 116.88, 114.10, 112.68, 111.28, 107.72, 101.41, 82.67, 56.24; HRMS (ESI$^+$): m/z Calcd for C$_{28}$H$_{20}$NO$_5$ [M+H]$^+$: 450.1389, Found: 450.1381.

24. 3'-Methoxy-6'-(4-nitrobenzyl)oxy)-3$^H$-spiro[isobenzofuran-1,9'-xanthene] (27).
To a mixture of compound 3 (50 mg, 0.15 mmol) and 4-nitrobenzyl bromide (39 mg, 0.18 mmol) in toluene (5 mL) was added silver(I) oxide (52 mg, 0.23 mmol). The reaction mixture was heated under reflux with stirring for 5 h. The reaction mixture was filtered through a short pad of Celite, which was subsequently washed with CH$_2$Cl$_2$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (Hex/EA = 3:1) to afford 27 (38 mg, white powder) in 54% yield.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.26 (d, $J = 9.1$ Hz, 2H), 7.72 (d, $J = 9.1$ Hz, 2H), 7.45 (d, $J = 7.8$ Hz, 1H), 7.36 (td, $J = 7.5$, 0.9 Hz, 1H), 7.23 (t, $J = 7.1$ Hz, 1H), 6.83-6.88 (m, 3H), 6.77-6.79 (m, $J = 2.2$ Hz, 2H), 6.75 (d, 1H), 6.67 (dd, $J = 8.9$, 2.5 Hz, 1H), 5.33 (s, 2H), 5.26 (s, 2H), 3.77 (s, 3H);

$^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 159.88, 158.42, 150.41, 147.05, 145.20, 144.71, 138.39, 129.84, 128.04-128.29, 123.67, 123.03, 121.18, 117.87, 117.17, 111.84, 111.20, 101.23, 100.15, 82.38, 71.82, 68.27, 55.45; HRMS (ESI$^+$): m/z Calcd for C$_{28}$H$_{22}$NO$_6$ [M+H]$^+$: 468.1402, Found: 468.1441.

25. N,N-Diethyl-6'-(4-nitrobenzyl)oxy)-3H-spiro[isobenzofuran-1,9'-xanthen]-3'-amine (28)

To a mixture of compound 14 (20 mg, 0.05 mmol) and 4-nitrobenzyl bromide (14 mg, 0.014 mmol) in toluene (5 mL) was added silver(I) oxide (19 mg, 0.08 mmol), and the reaction mixture was heated under reflux with stirring for 5 h. The reaction mixture was filtered through a short pad of Celite, which was subsequently washed with CH$_2$Cl$_2$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (Hex/EA = 3:1) to afford 28 (13 mg, red oil) in 48% yield.

$^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8.23 (d, $J = 8.7$ Hz, 2H), 7.68 (d, $J = 9.1$ Hz, 2H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.32 (td, $J = 7.3$, 0.9 Hz, 1H), 7.20 (t, $J = 7.1$ Hz, 1H), 6.80 (d, $J = 2.3$ Hz, 1H), 6.79-6.68 (m, 3H), 6.62 (d, $J = 8.7$ Hz, 1H), 6.39 (dd, $J = 8.7$, 2.7 Hz, 1H), 6.30 (d, $J = 2.3$ Hz, 1H), 5.29 (s, 2H), 5.15 (s, 2H), 3.29 (q, $J = 6.9$ Hz, 4H), 1.04 (t, $J = 6.9$ Hz, 6H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ 158.80, 151.47, 151.36, 148.70, 147.59, 145.77, 145.34, 139.35, 130.45, 130.07, 128.76, 128.69, 128.37, 124.20, 123.72, 121.60, 118.75, 111.85, 101.78, 97.20, 71.82, 68.76, 44.26; HRMS (ESI$^+$): m/z Calcd for C$_{31}$H$_{29}$N$_2$O$_5$ [M+H]$^+$: 509.2076, Found: 509.2070.

26. 4-Nitrobenzyl (3'-methoxy-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-yl)carbamate (29)
To a solution of compound 12 (20 mg, 0.06 mmol) in CH$_2$Cl$_2$ (4 mL) at 0 °C was added a solution of iPrNEt$_2$ (20.90 mg, 0.12 mmol) in CH$_2$Cl$_2$ (2 mL), followed by a solution of 4-nitrobenzyl chloroformate (15.52 mg, 0.07 mmol) in CH$_2$Cl$_2$ (2 mL), and the reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was allowed to warm to rt and stirred at rt for 5 h. The reaction was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel to afford 29 (27 mg, white crystalline powder) in 86% yield.

$^1$H-NMR (400 MHz, DMSO-d$_6$) δ 10.10 (s, 1H), 8.26 (d, $J$ = 11.4 Hz, 2H), 7.69 (d, $J$ = 8.7 Hz, 2H), 7.45 (t, $J$ = 3.2 Hz, 2H), 7.36 (t, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 7.3 Hz, 1H), 7.13 (dd, $J$ = 8.7, 2.3 Hz, 1H), 6.88 (d, $J$ = 8.7 Hz, 1H), 6.85 (d, $J$ = 8.7 Hz, 1H), 6.82 (d, $J$ = 2.7 Hz, 1H), 6.75 (d, $J$ = 7.8 Hz, 1H), 6.66 (dd, $J$ = 8.7, 2.3 Hz, 1H), 5.31 (s, 2H), 5.27 (s, 2H), 3.77 (s, 3H); $^{13}$C-NMR (100 MHz, DMSO-d$_6$) δ 160.43, 153.55, 150.99, 150.28, 147.65, 145.86, 144.91, 140.27, 138.82, 130.20, 129.75, 129.06, 128.82, 128.56, 124.17, 123.54, 121.73, 119.79, 117.74, 114.55, 111.78, 105.33, 100.76, 82.90, 72.48, 65.20, 56.00; HRMS (ESI$^+$): m/z Calcd for C$_{29}$H$_{23}$N$_2$O$_7$ [M+H]$^+$: 511.1505, Found: 511.1501.

27. 4-Nitrobenzyl (3'-(diethylamino)-3H-spiro[isobenzofuran-1,9'-xanthen]-6'-yl)carbamate (30)

To a solution of compound 18 (20 mg, 0.05 mmol) in anhydrous CH$_2$Cl$_2$ (2.5 mL) were added iPrNEt$_2$ (12.9 mg, 0.1 mmol) and 4-nitrobenzyl chloroformate (12.9 mg, 0.06 mmol), and the reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was allowed to warm to rt and stirred at rt for 6 h. The reaction was quenched with water and extracted with CH$_2$Cl$_2$. The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH$_2$CH$_2$/EA = 9:1) to afford 30 (13 mg, yellow powder) in 47% yield. $^1$H-NMR (400 MHz, DMSO-d$_6$) δ 10.03 (s, 1H), 8.23 (d, $J$ = 9.1 Hz, 2H), 7.66 (d, $J$ = 19.7 Hz, 2H), 7.40 (d, $J$ = 7.8 Hz, 1H), 7.37 (s, 1H), 7.32 (t, $J$ = 7.1 Hz, 1H), 7.20 (t, $J$ = 7.1 Hz, 1H), 7.07 (dd, $J$ = 8.7, 2.3 Hz, 1H), 6.78 (d, $J$ = 8.7 Hz, 1H), 6.72 (d, 1H), 6.63 (d, $J$ = 9.1 Hz, 1H), 6.34-6.39 (m, 2H), 5.28 (s, 2H), 5.17 (s, 2H), 3.26 (q, $J$ = 6.9 Hz, 4H), 1.04 (t, $J$ = 6.9 Hz, 6H); $^{13}$C-NMR (100 MHz, DMSO-d$_6$) δ 153.01, 150.95, 150.16, 148.19, 147.09, 145.33, 144.40, 138.71, 129.34, 128.52, 127.97, 123.62, 123.14, 121.07, 119.59, 113.55, 111.37, 108.12, 104.85, 96.80, 82.62, 71.40, 64.63, 43.68, 12.40; HRMS (ESI$^+$): m/z Calcd for C$_{32}$H$_{30}$N$_3$O$_6$ [M+H]$^+$: 552.2090, Found: 552.2129.

S13
B. Spectral data of all compounds

\(^1\)H NMR

\(^{13}\)C NMR
Mass Spectra

Figure S1: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 1.

$^1$H NMR
Figure S2: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 2.
$^1$H NMR

$^{13}$C NMR
Mass Spectra

Figure S3: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 3.

$^1$H NMR
Figure S4: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 4.
$^1$H NMR

$^{13}$C NMR
Figure S5: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 5.

$^1$H NMR
$^{13}$C NMR

Mass Spectra

Figure S6: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 6.
$^1$H NMR

$^{13}$C NMR
Mass Spectra

Figure S7: Structure, \(^1\)H NMR, \(^{13}\)C NMR and HRMS of Compound 7.

\(^1\)H NMR
$^{13}$C NMR

Mass Spectra

Figure S8: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 8.
$^1$H NMR

$^{13}$C NMR
Figure S9: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 10.

$^1$H NMR
Figure S10: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 11.
$^1$H NMR

$^{13}$C NMR
Figure S11: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 12.

$^1$H NMR
$^{13}$C NMR

Mass Spectra

Figure S12: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 13.
$^1$H NMR

$^{13}$C NMR
Figure S13: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 14.

$^1$H NMR
$^{13}$C NMR

Mass Spectra

Figure S14: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 15.
$^1$H NMR

$^{13}$C NMR
Figure S15: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 16.

$^1$H NMR
Figure S16: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 17.
$^1$H NMR

$^{13}$C NMR
Figure S17: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 18.

$^1$H NMR
Figure S18: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 19.
$^1$H NMR

$^{13}$C NMR
Mass Spectra

Figure S19: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 20.

$^1$H NMR
Figure S20: Structure, 'H NMR, 13C NMR and HRMS of Compound 21.
$^1$H NMR

$^{13}$C NMR
Mass Spectra

Figure S21: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 24.

$^1$H NMR
$^{13}$C NMR

Figure S22: Structure, $^{1}$H NMR, $^{13}$C NMR and HRMS of Compound 25.
Mass Spectra

Figure S23: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 26.

$^1$H NMR
$^{13}$C NMR

Figure S24: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 27.
Mass Spectra

Figure S25: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 28.

$^1$H NMR
13C NMR

Figure S26: Structure, 1H NMR, 13C NMR and HRMS of Compound 29.
Mass Spectra

Figure S27: Structure, $^1$H NMR, $^{13}$C NMR and HRMS of Compound 30.

References

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