Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Oxidative Cyclization and Enzyme-free Deiodination of Thyroid Hormones

Supporting Information

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1 General Information

Unless otherwise noted, all reactions were carried out under air. Reactions with chemicals sensitive to moisture or oxygen were carried out under a nitrogen atmosphere using standard Schlenk techniques. All chemicals were purchased from commercial suppliers and either used as received or purified according to "Purification of Laboratory Chemicals". All other solvents were dried using standard methods if necessary.[1]

Thin layer chromatography was performed on fluorescence indicator marked precoated silica gel 60 plates (Macherey-Nagel, ALUGRAM Xtra SIL G/UV254) and visualized by UV light (254 nm/366 nm). Flash column chromatography was performed on silica gel (0.040 – 0.063 mm) with the solvents given in the procedures.

NMR spectra were recorded on a Bruker Avance II+ 400 or a Bruker Avance Neo 600. Spectra of compounds **1**, **6** and **7** are recorded with a repetition time of 20 s due to high relaxation times (see. [2]). Chemical shifts for ^{1}H-NMR spectra are reported as δ (parts per million) relative to the residual proton signal of $CDCl_3$ at 7.26 ppm (s), DMSO-d_6 at 2.50 ppm (quint) and CD_3OD at 3.31 ppm (quint). Chemical shifts for ^{13}C-NMR spectra are reported as δ (parts per million) relative to the signal of $CDCl_3$ at 77.0 ppm (t), DMSO-d_6 at 39.5 ppm (sept) and CD_3OD at 49.0 ppm (sept). Chemical shifts for ^{19}F-NMR spectra are reported as δ (parts per million) relative to the signal of $Si(CH_3)_4$ at 0.00 ppm. The following abbreviations are used to describe splitting patterns: br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet. Coupling constants *J* are given in Hz.

Low-resolution ESI mass spectra were recorded on an Agilent 6120 Series LC/MSD system. High-resolution (HR) EI mass spectra were recorded on a double-focusing mass spectrometer ThermoQuest MAT 95 XL from Finnigan MAT. HR-ESI and HR-APCI mass spectra were recorded on a Bruker Impact II. All Signals are reported with the quotient from mass to charge *m/z*.

IR spectra were recorded on a Nicolet Thermo iS10 scientific spectrometer with a diamond ATR unit. The absorption bands $\tilde{\nu}$ are reported in cm^{-1}.

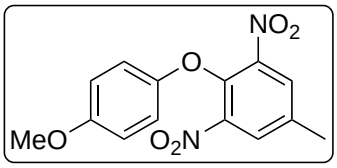
Melting points of solids were measured on a Büchi M-5600 Melting Point apparatus and are uncorrected. The measurements were performed with a heating rate of 2 °C/min and the melting point temperatures *T* are reported in °C.

Intensity data of suitable single crystals were collected on a Bruker Venture D8 diffractometer at 100 K with Mo Kα (0.7107 Å) radiation. All structures were solved by direct methods and refined based on F^2 by the use of the SHELX program package as implemented in Olex2.[3-5] All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms attached to carbon atoms were included in geometrically calculated positions using a rigid model. The ORTEP drawing was made using the program Mercury from the CCDC.[6] Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).

2 Preparation of Starting Materials

2.1 Aryliodides

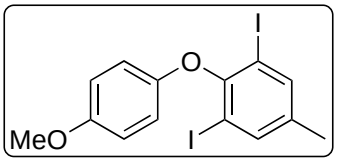
2-(4-methoxyphenoxy)-5-methyl-1,3-dinitrobenzene (S1)



Based on a literature procedure[7] 2,4-dinitro-*p*-cresol (4.95 g, 25.0 mmol) and *p*-TsCl (5.24 g, 27.5 mmol) were dissolved in dry pyridine (40 ml) and stirred for 30 min at 95 °C. *p*-methoxyphenol (6.83 g, 55.0 mmol) was added and the mixture was stirred for 2 h under reflux. After full conv. (TLC) pyridine was removed by reduced pressure and the residue was dissolved in CH_2Cl_2 (80 ml). The solution was washed with aq. HCl (2N, 40 ml), H_2O (40 ml) and aq. NaOH (2N, 2x 40 ml), was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 7:1) afforded the product **S1** (6.92 g, 22.7 mmol, 91%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 0.7 Hz, 2H), 6.80 (s, 4H), 3.76 (s, 3H), 2.52 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 155.8, 151.1, 144.4, 140.2, 136.2, 129.6, 116.5, 114.7, 55.6, 20.7. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3354, 2936, 2837, 1538, 1501, 1229, 1180, 1024, 833, 782. **HRMS (ESI$^+$, MeOH)** *m/z* = 327.0592 $[M+Na]^+$. Calculated for $C_{14}H_{12}N_2NaO_6^+$ *m/z* = 327.0588. **Mp** *T* = 140 – 143 °C.

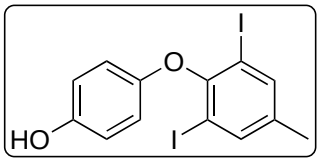
1,3-diiodo-2-(4-methoxyphenoxy)-5-methylbenzene (S2)



In slight deviation from a literature procedure[7] **S1** (988 mg, 3.25 mmol) was suspended under N_2-atmosphere in AcOH (40 ml) and Pd/C (10% w/w, 311 mg, 0.290 mmol) was added. After hydrogenation in a Parr-apparatus ($p(H_2)$ = 3 bar) the suspension was filtered over Celite® and washed with AcOH (2x 20 ml). The filtrate was concentrated to around 15 ml in total and cold aq. H_2SO_4 (50% v/v, 40 ml) was carefully added. Afterwards, a solution of NaNO2 (493 mg, 7.15 mmol) in H2O (7.5 ml) was carefully added over 60 min at 0 °C. After 30 min urea (244 mg, 4.06 mmol) was added and the tetrazonium was added to a vigorously stirred emulsion of NaI (2.44 g, 16.3 mmol), I_2 (2.06 g, 8.13 mmol), H_2O (35 ml) and $CHCl_3$ (15 ml) at 45 °C. The emulsion was stirred for a further 20 min at 45 °C and after cooling to rt the phases were separated. The aqueous phase was extracted with $CHCl_3$ (2x 40 ml) and the combined org. phases were washed with H_2O (2x 20 ml), aq. $Na_2S_2O_3$ (10% w/w, 20 ml) and again H_2O (2x 20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 30:1) afforded the product **S2** (1.18 g, 2.53 mmol, 78%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.68 (s, 2H), 6.83 – 6.87 (m, 2H), 6.72 – 6.76 (m, 2H), 3.78 (s, 3H), 2.31 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 154.7, 152.0, 150.4, 140.6, 138.6, 116.2, 114.6, 90.9, 55.6, 19.8. **FTIR (ATR, neat)** $\tilde{\nu}$ = 2993, 2834, 1502, 1460, 1432, 1240, 1191, 1176, 1028, 822. **HRMS (ESI$^+$, MeOH)** *m/z* = 488.8817 $[M+Na]^+$. Calculated for $C_{14}H_{11}I_3O_2^+$ *m/z* = 488.8819. **Mp** *T* = 106 – 107.5 °C.

4-(2,6-diiodo-4-methylphenoxy)phenol (S3)

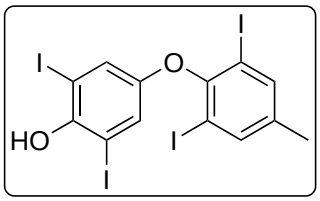


In slight deviation from a literature procedure[7] **S2** (300 mg, 0.640 mmol) was suspended in a mixture of AcOH (1.9 ml) and aq. HI (47%, 1.9 ml) and stirred at 120 °C for 2.5 h. Aft er full conv. the reaction was poured onto ice (5 g) and extracted with toluene (3x 10 ml). The combined org. phases were washed with aq. $Na_2S_2O_3$ (10% w/w, 10 ml) and H_2O (10 ml), were dried

over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 15:1) afforded the product **S3** (262 mg, 0.580 mmol, 91%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 0.6 Hz, 2H), 6.75 – 6.79 (m, 2H), 6.65 – 6.70 (m, 2H), 4.55 (brs, 1H), 2.31 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 152.0, 150.5, 150.4, 140.7, 138.7, 116.4, 116.2, 90.8, 19.8. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3385, 1500, 1433, 1260, 1234, 1193, 1097, 827, 801, 768. **HRMS (ESI$^-$, MeOH)** *m/z* = 450.8702 $[M-H]^-$. Calculated for $C_{13}H_9I_2O_2^-$ *m/z* = 450.8698. **Mp** *T* = 147 – 148.5 °C.

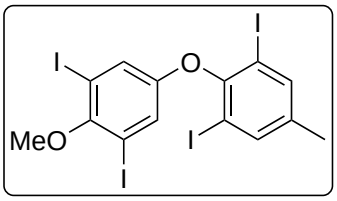
4-(2,6-diiodo-4-methylphenoxy)-2,6-diiodophenol (S4)



In slight deviation from a literature procedure[7] **S3** (4.52 g, 10.0 mmol) was dissolved in a mixture of EtOH (100 ml) and $MeNH_2$ (25% w/w, 100 ml) and a solution of KI (13.3 g, 40 mmol) and I_2 (5.58 g, 22.0 mmol) in H_2O (36 ml) was added dropwise at 0 °C to 5 °C for 1 h. Afterwards, it was stirred for another 90 min and the mixture was acidified at 0 °C by conc. HCl to pH 1. CH_2Cl_2 (150 ml) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x 150 ml). The combined org. phases were washed with aq. $Na_2S_2O_3$ (50 ml, 10% w/w) and H_2O (50 ml), were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/CH_2Cl_2, 3:1) afforded the product **S4** (5.85 g, 8.31 mmol, 83%) as a colourless solid and the side product **S5** (620 mg, 1.07 mmol, 11%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 0.6 Hz, 2H), 7.13 (s, 2H), 5.46 (s, 1H), 2.33 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 151.2, 150.3, 149.2, 140.8, 139.4, 128.9, 90.4, 81.5, 19.8. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3452, 1581, 1550, 1505, 1435, 1316, 1182, 1143, 848, 709. **HRMS (ESI$^-$, MeOH)** *m/z* = 702.6630 $[M]^-$. Calculated for $C_{14}H_{11}I_3O_2^-$ *m/z* = 702.6631. **Mp** *T* = 209 – 210 °C.

2-(3,5-diiodo-4-methoxyphenoxy)-1,3-diiodo-5-methylbenzene (2a)

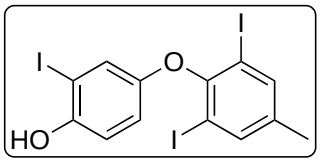


The phenol **S4** (70.4 mg, 100 µmol), MeI (62.5 µl, 142 mg, 1.00 mmol) and K_2CO_3 (1.10 g, 800 µmol) were suspended in acetone (14 ml) and stirred at 55 °C for 1 h. Afterwards, NEt_3 (5 ml) was added and stirred for 1 h at rt. CH_2Cl_2 (20 ml) and H_2O (20 ml) were added, phases were separated and the aq. phase was extracted with CH_2Cl_2 (2x 20 ml), the combined org. phases were washed with aq. HCl (1N, 20 ml) and brine (10 ml), were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 30:1) afforded the product **2a** (67.0 mg, 93.3 µmol, 93%) as a colourless solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.68 (s, 2H), 7.18 (s, 2H), 3.85 (s, 3H), 2.33 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 154.2, 152.9, 151.0, 140.8, 139.5, 126.4, 90.3, 89.8, 60.9, 19.9. **FTIR (ATR, neat)** $\tilde{\nu}$ = 1581, 1565, 1458, 1435, 1410, 1235, 1171, 1002, 912, 851. **HRMS (ESI$^+$, MeOH)** *m/z* = 756.6494 $[M+K]^+$. Calculated for $C_{14}H_{10}I_4KO_2^+$ *m/z* =. **Mp** *T* = 182 – 183.5 °C.

4-(2,6-diiodo-4-methylphenoxy)-2-iodophenol (S5)

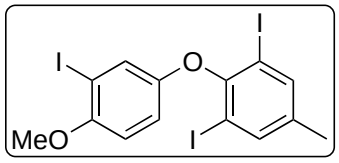
In slight deviation from a literature procedure[7] **S3** (4.52 g, 10.0 mmol) was dissolved in a mixture of EtOH (100 ml) and $MeNH_2$ (25% w/w, 100 ml) and a solution of KI (5.98 g, 36.0 mmol) and I_2 (2.58 g, 10.2 mmol) in H_2O (36 ml) was added dropwise at 0 °C to 5 °C for 1 h. Afterwards, it was stirred for another 90 min and the mixture was acidified at 0 °C by conc. HCl to pH 1. CH_2Cl_2 (150 ml) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x 150 ml). The combined org. phases were washed with aq. $Na_2S_2O_3$ (50 ml, 10% w/w) and H_2O (50 ml), were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/CH_2Cl_2, 3:1) afforded the product **S5** (4.95 g, 8.57 mmol, 86%) as a colourless solid and the side product **S5** (450 mg, 0.639 mmol, 6.3%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 0.5 Hz, 2H), 7.08 (d, *J* = 2.8 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 1H), 6.71 (dd, *J* = 8.9, 2.8 Hz, 1H), 5.05 (bs, 1H), 2.32 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 151.5, 150.3, 150.2, 140.7, 139.0, 124.5, 117.3, 115.1, 90.6, 85.3, 19.8. **FTIR (ATR, neat)** $\tilde{\nu}$ = . **HRMS (ESI$^-$, MeOH)** *m/z* = 576.7665 $[M]^-$. Calculated for $C_{13}H_8I_3O_2^-$ *m/z* = 576.7664. **Mp** *T* = 143 – 144 °C.

1,3-diiodo-2-(3-iodo-4-methoxyphenoxy)-5-methylbenzene (2b)

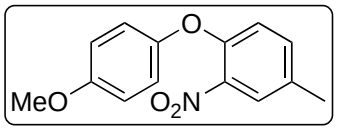
The phenol **S5** (57.8 mg, 100 µmol), MeI (62.5 µl, 142 mg, 1.00 mmol) and K_2CO_3 (1.10 g, 800 µmol) were suspended in acetone (14 ml) and stirred at 55 °C for 1 h. Afterwards, NEt_3 (5 ml) was added and stirred for 1 h at rt. CH_2Cl_2 (20 ml) and H_2O (20 ml) were added, phases were separated and the aq. phase was extracted with CH_2Cl_2 (2x 20 ml), the combined org. phases were washed with aq. HCl (1N, 20 ml) and brine (10 ml), were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 30:1) afforded the product **2b** (57.9 mg, 97.8 µmol, 98%) as a colourless solid.



^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 0.5 Hz, 2H), 7.25 (dd, *J* = 2.1, 0.9 Hz, 1H), 6.73 (m, 2H),3.85 (s, 3H), 2.32 (s, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$)** δ = 153.7, 151.6, 150.6, 140.8, 139.0, 126.5, 115.9, 111.1, 90.6, 86.1, 56.8, 19.8. **FTIR (ATR, neat)** $\tilde{\nu}$ = 2824, 1591, 1477, 1432, 1292, 1265, 1235, 1177, 1043, 800. **HRMS (ESI$^+$, MeOH)** *m/z* = 630.7523 $[M+K]^+$. Calculated for $C_{14}H_{11}I_3KO_2^+$ *m/z* = 630.7525. **Mp** *T* = 138 – 139 °C.

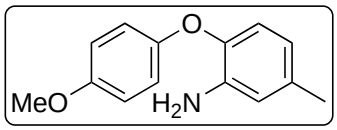
1-(4-Methoxyphenoxy)-4-methyl-2-nitrobenzene (S6)

Dried *p*-methoxyphenol (15.6 g, 126 mmol) and K_2CO_3 (19.9 g, 144 mmol) were suspended in dried DMF (60 ml). 3-nitro-4-chlorotoluene (20.6 g, 120 mmol) was added and the mixture was heated at 120 °C for 24 h under N_2-atmosphere. The mixture was diluted with H_2O (500 ml) and extracted with Et_2O (4x 50 ml). The combined org. phases were washed with H_2O (50 ml) and brine (50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 30:1→6:1) afforded the product **S6** (25.3 g, 97.7 mmol, 81%) as an orange-coloured oil.



^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.71 (dd, *J* = 2.2, 0.4 Hz, 1H), 7.25 (ddd, *J* = 8.5, 2.2, 0.6 Hz, 1H), 7.00 - 6.93 (m, 2H), 6.91 – 6.85 (m, 2H), 6.82 (d, *J* = 8.5 Hz, 1H), 3.79 (s, 2H), 2.36 (s, 3H). **^{13}C-NMR (91 MHz, $CDCl_3$)** δ = 156.3, 149.3, 149.1, 140.3, 134.7, 132.6, 125.5, 120.4, 119.3, 114.9, 55.5, 20.2. **FTIR (ATR, neat)** $\tilde{\nu}$ = 2930, 2836, 1621, 1527, 1502, 1490, 1348, 1031, 821, 810. **HRMS (EI, 70 eV)** *m/z* = 259.0841 $[M]^{+\cdot}$. Calculated for $C_{14}H_{13}NO_4^{+\cdot}$ *m/z* = 259.0839.

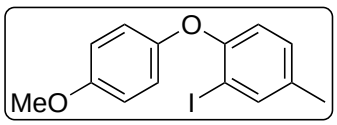
2-(4-Methoxyphenoxy)-5-methylaniline (S7)



Compound **S6** (1.07 g, 4.00 mmol) was dissolved in a mixture of EtOH (8 ml) and AcOH (8 ml), Fe-powder (1.12 g, 20 mmol) was added and the mixture was stirred at 90 °C for 1 h. Afterwards, the mixture was filtered over silica, further washed (Cy/EtOAc, 4:1, 100 ml) and concentrated under reduced pressure to obtain the product **S7** (0.900 g, 3.90 mmol, 98%) as a colourless solid.

^{1}H-NMR (360 MHz, $CDCl_3$) δ = 6.98 - 6.90 (m, 2H), 6.90 - 6.82 (m, 2H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.52 (ddd, *J* = 8.1, 2.0, 0.5 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 2H), 2.28 (s, 3H). **^{13}C-NMR (91 MHz, $CDCl_3$)** δ = 155.1, 151.2, 142.0, 138.0, 133.9, 119.2, 119.0, 118.4, 116.9, 114.7, 55.6, 20.9. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3487, 3391, 2955, 1611, 1497, 1462, 1298, 1207, 1195, 1032, 841. **HRMS (EI, 70 eV)** *m/z* = 229.1096 $[M]^{+\cdot}$. Calculated for $C_{14}H_{15}NO_2^{+\cdot}$ *m/z* = 229.1097. **Mp** *T* = 70 - 70.5 °C.

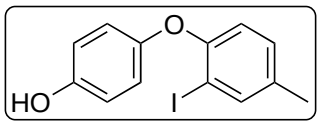
2-Iodo-1-(4-methoxyphenoxy)-4-methylbenzene (S8)



The reaction was based on a literature procedure.[7] The amine **S7** (17.4 g, 75.9 mmol) and *p*-TsOH·H_2O (43.4 g, 228 mmol) were suspended in MeCN (304 ml) and a solution of $NaNO_2$ (10.5 g, 152 mmol) and KI (31.5 g, 190 mmol) in H_2O (46 ml) was added dropwise over 3 h at 10 – 15 °C. After an additional 1 h at rt, the reaction was diluted with aq. Na_2CO_3 (2N, 150 ml) and conc. aq. $Na_2S_2O_3$ (10 ml). The phases were separated and the aqueous phase was extracted with Et_2O. The combined org. phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 200:1) afforded the product **S8** (22.2 g, 65.2 mmol, 86%) as a colourless solid.

^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.67 (dd, *J* = 2.0, 0.6 Hz, 1H), 7.05 (ddd, *J* = 8.3, 2.1, 0.7 Hz, 1H), 6.96 – 6.84 (m, 4H), 6.70 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 2.30 (s, 3H). **^{13}C-NMR (91 MHz, $CDCl_3$)** δ = 155.7, 155.1, 150.5, 139.9, 134.5, 130.1, 119.7, 118.0, 114.7, 87.9, 55.6, 20.1. **FTIR (ATR, neat)** $\tilde{\nu}$ = 2997, 2926, 2832, 1592, 1503, 1474, 1231, 1195, 1035, 811. **HRMS (EI, 70 eV)** *m/z* = 339.9958 $[M]^{+\cdot}$. Calculated for $C_{14}H_{13}IO_2^{+\cdot}$ *m/z* = 339.9955. **Mp** *T* = 50 – 51.5 °C.

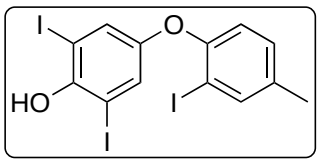
4-(2-Iodo-4-methylphenoxy)phenol (S9)



The iodoarene **S8** (1.02 g, 3.00 mmol) was dissolved in CH_2Cl_2 (30 ml) and BBr_3 (1M in CH_2Cl_2, 6 ml) was added dropwise at 0 °C. The mixture was stirred at rt for 1 h and afterwards, H_2O (20 ml) was added at 0 °C. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2x 30 ml) and the org. phase was dried over Na_2SO_4 concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 4:1) afforded the product **S9** (971 mg, 2.98 mmol, 99%) as a colourless solid.

^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.70 – 7.62 (m, 1H), 7.05 (ddd, *J* = 8.3, 2.1, 0.6 Hz, 1H), 6.90 – 6.76 (m, 4H), 6.70 (d, *J* = 8.3 Hz, 1H), 4.99 (s, 1H), 2.29 (s, 3H). **^{13}C-NMR (91 MHz, $CDCl_3$)** δ = 155.0, 151.4, 150.7, 139.9, 134.7, 130.2, 119.9, 118.1, 116.3, 88.0, 20.1. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3384, 1502, 1477, 1444, 1359, 1219, 1198, 1036, 852, 794. **HRMS (EI, 70 eV)** *m/z* = 325.9797 $[M]^{+\cdot}$. Calculated for $C_{13}H_{11}IO_2^{+\cdot}$ *m/z* = 325.9798. **Mp** *T* = 105 – 106 °C.

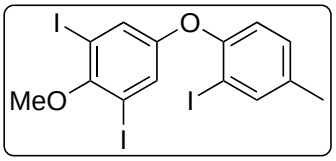
2,6-Diiodo-4-(2-iodo-4-methylphenoxy)phenol (S10)



Based on a literature procedure[7] the phenol **S9** (4.08 g, 12.5 mmol) was dissolved in a mixture of EtOH (62.5 ml) and aq. $MeNH_2$ (25% w/w, 62.5 ml). A solution of KI (10.4 g, 62.5 mmol) and I_2 (6.98 g, 27.5 mmol) in H_2O (100 ml) was added dropwise over 1 h at 0 °C. Afterwards, the mixture was stirred for 1 h at 0 °C and carefully acidified with conc. HCl until pH = 1. The reaction was extracted with CH_2Cl_2 (2x 50 ml) and the org. phases were washed with $Na_2S_2O_3$ (10% w/w, 50 ml). The aq. phase was further extracted with CH_2Cl_2 (2x 50 ml) and the combined org. phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/CH_2Cl_2, 7:1 + 1% AcOH) afforded the product **S10** (6.59 g, 11.4 mmol, 91%) as a colourless solid. During the whole purification process, the solid should be kept acidified with AcOH.

^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.67 (s, 1H), 7.30 (s, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 5.53 (s, 1H), 2.31 (s, 3H). **^{13}C-NMR (91 MHz, $CDCl_3$)** δ = 153.7, 151.1, 149.9, 140.2, 135.8, 130.5, 128.5, 119.0, 88.4, 81.4, 20.2. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3440, 2917, 1580, 1481, 1448, 1308, 1207, 1184, 1141, 807, 796. **HRMS (EI, 70 eV)** *m/z* = 577.7736 $[M]^{+\cdot}$. Calculated for $C_{13}H_9I_3O_2^{+\cdot}$ *m/z* = 577.7731. **Mp** *T* = 117 – 118 °C.

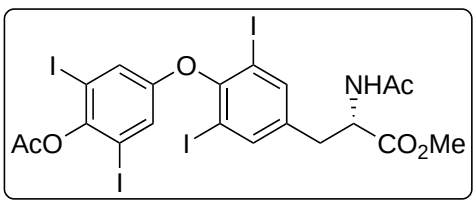
1,3-Diiodo-5-(2-iodo-4-methylphenoxy)-2-methoxybenzene (2c)



KO*t*Bu (2.52 g, 22.5 mmol) was suspended in THF (50 ml). The phenol **S10** (2.26 g, 5.00 mmol) was mixed with AcOH (150 mg, 2.50 mmol) followed by Et_2O (50 ml) and added dropwise over 10 min to the first solution. Afterwards, MeI (3.13 ml, 7.10 g, 50.0 mmol) was added and stirred for 48 h at rt. Et_3N (15 ml) was added and the mixture was stirred for 1 h at rt. H_2O (50 ml) and Et_2O (100 ml) were added and the phases were separated. The aq. phase was extracted with Et_2O (2x 50 ml). The combined org. phases were washed with aq. HCl (1N, 50 ml), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, Cy/EtOAc, 100:1) afforded the product **2c** (2.94 g, 4.97 mmol, 99%) as a colourless solid.

^{1}H-NMR (360 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 1.9 Hz, 1H), 7.32 (s, 2H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 3.83 (s, 3H), 2.32 (s, 3H). **^{13}C-NMR (91 MHz, $CDCl_3$)** δ = 154.5, 154.1, 153.0, 140.2, 136.3, 130.6, 128.2, 119.9, 89.9, 89.0, 60.8, 20.3. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3061, 2932, 1568, 1455, 1407, 1223, 1037, 994, 851, 725. **HRMS (EI, 70 eV)** *m/z* = 591.7886 $[M]^{+\cdot}$. Calculated for $C_{14}H_{11}I_3O_2^{+\cdot}$ *m/z* = 591.7888. **Mp** *T* = 107 – 108.5 °C.

Methyl (*S*)-2-acetamido-3-(4-(4-acetoxy-3,5-diiodophenoxy)-3,5-diiodophenyl)propanoate (Ac-Thx(Ac)-OMe)



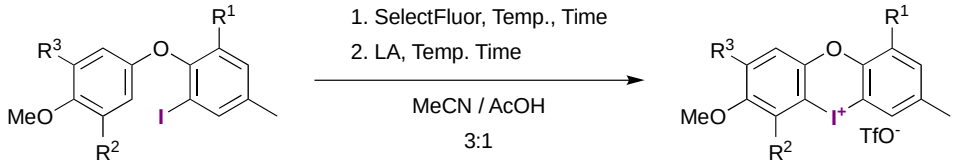
To a solution of L-Thyroxine (1.55 g, 2.00 mmol) in MeOH (10 ml) was added $SOCl_2$ (435 µl, 6.00 mmol) and the mixture is heated to 60 °C for 12 h. After cooling down Et_2O (10 ml) was added and the solution was decanted and washed further with Et_2O (5x 20 ml). The residue was dried under reduced pressure to obtain crude H-Thx-OMe. This

was dissolved in CH_2Cl_2 (10 ml), Ac_2O (11 mmol, 1.04 ml) and pyridine (21 mmol, 1.69 ml) were added and the solution was left to stir overnight at rt. After completion, the reaction mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3x 10 ml). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and purified via column chromatography (silica, EtOAc/Cy, 1:1➞2:1) to give Ac-Thx(Ac)-OMe (1.63 g, 1.86 mmol, 93%) as a beige solid.

^{1}H-NMR (600 MHz, $CDCl_3$) δ = 7.62 (s, 2H), 7.18 (s, 2H), 6.03 (d, *J* = 7.4 Hz, 1H), 4.84 (q, *J* = 6.3 Hz, 1H), 3.77 (s, 3H), 3.11 (dd, *J* = 13.8, 6.1 Hz, 1H), 3.03 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.39 (s, 3H), 2.05 (s, 3H). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ = 171.5, 169.6, 167.5, 153.8, 152.3, 147.0, 141.2, 137.8, 126.2, 90.5, 89.9, 53.1, 52.6, 36.5, 23.2, 21.3. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3270, 3063, 2949, 1738, 1652, 1538, 1427, 1367, 1196, 1163. **HRMS (ESI$^+$, MeOH)** *m/z* = 897.7115 $[M+Na]^+$. Calculated for $C_{20}H_{17}I_4NNaO_6^+$ *m/z* = 897.7127. **Mp** *T* = 152-156 °C.

3 Substrate synthesis

3.1 Optimisation and screening for the synthesis of model substrates 3

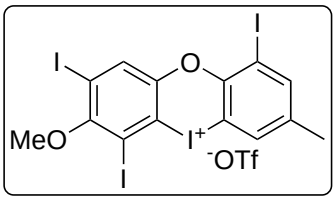


				1st Step			2nd Step			
#[a]	R^1	R^2	R^3	SelectFluor® (eq.)	Temp (°C)	Time (h)	LA (eq.)	Temp (°C)	Time (h)	Yield
1	**I**	**I**	**I**	4	rt	72	TfOH (5)	rt	24	16%
2	**I**	**I**	**I**	2.5	0 - rt	72	**TfOH (2.5)**	0 - 80	1.5	21%
3[b]	**I**	**I**	**I**	2.5	0 - rt	72	**BF_3OEt_2 (2.5)**	0 - 80	1.5	9%
4	**I**	**I**	**I**	2.5	**rt - 50**	**4**	TfOH (2.5)	0 - 80	1.5	35%
5	**I**	**I**	**I**	2.5	**rt - 80**	**1.5**	TfOH (2.5)	0 - 80	1.5	16%
6	**I**	**I**	**I**	**3.5**	**50**	**4**	TfOH (2.5)	rt	64	73%
7	**I**	**I**	**I**	3.5	**50**	**4**	**TfOH (1.5)**	rt - 80	24+1	21%
8[c]	**I**	**I**	**I**	3.5	**50**	**4**	TfOH (2.5)	rt	24	44%
9[d]	**I**	**I**	**I**	3.5	50	4	TfOH (2.5)	rt	72	35%
10	**I**	**H**	**I**	3.5	50	4	TfOH (2.5)	rt	72	0%
11	**I**	**H**	**H**	3.5	50	4	TfOH (2.5)	rt	72	0%
12	**H**	**H**	**I**	3.5	50	4	TfOH (2.5)	rt	72	0%
13	**H**	**I**	**I**	3.5	50	4	TfOH (2.5)	rt	72	23%

[a]All reactions were performed on a 50.0 µmol scale at a conc. of 0.05 M. [b]The corresponding tetrafluoroborate was isolated. [c]Conc. of 0.1 M. [d]500 µmol scale.

3.2 Model Substrates 3 - 5

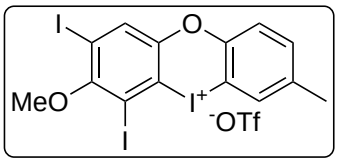
1,6,8-Triiodo-7-methoxy-3-methyldibenzo[*b*,*e*][1,4]iodaoxin-5-ium trifluoromethanesulfonate (3a)



A solution of **2a** (359 mg, 0.500 mmol) and SelectFluor® (620 mg, 1.75 mmol) in MeCN/AcOH (10 ml, 3:1) was heated at 50 °C for 4 h. TfOH (111 µl, 1.25 mmol) was added at 0 °C and the mixture was stirred for 3 d at rt. After dilution with water (40 ml) and extraction with CH_2Cl_2 (3x 20 ml), the organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting solid was washed with Et_2O to obtain **3a** (150 mg, 0.173 mmol, 35%) as a slightly orange solid.

^{1}H-NMR (601 MHz, DMSO-*d*$_6$) δ = 8.09 (s, 1H), 8.00 (s, 1H), 7.91 (s, 1H), 3.76 (s, 3H), 2.35 (s, 3H). **^{13}C-NMR (151 MHz, DMSO-*d*$_6$)** δ = 159.0, 151.1, 149.6, 142.6, 140.2, 133.7, 131.7, 120.7 (q, *J* = 322.1 Hz), 118.8, 106.7, 98.7, 95.9, 89.1, 60.7, 19.7. **^{19}F-NMR (565 MHz, DMSO-*d*$_6$)** δ = -77.7. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3059, 2938, 2857, 1441, 1390, 1272, 1215, 1158, 1034, 926. **HRMS (ESI$^+$, MeOH)** *m/z* = 716.6766 [M-OTf]$^+$. Calculated for $C_{14}H_9I_4O_2^+$ *m/z* = 716.6776. **Mp** decomp. at 250 °C.

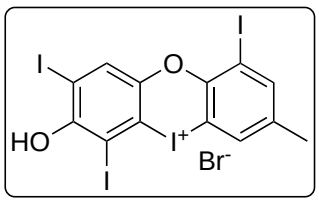
2,4-Diiodo-3-methoxy-7-methyldibenzo[b,e][1,4]iodaoxin-5-ium trifluoromethanesulfonate (3c)



A solution of **2c** (296 mg, 0.500 mmol) and SelectFluor® (620 mg, 1.75 mmol) in MeCN/AcOH (10 ml, 3:1) was heated at 50 °C for 4 h. TfOH (111 µl, 1.25 mmol) was added at 0 °C and the mixture was stirred for 3 d at rt. After dilution with water (40 ml) and extraction with CH_2Cl_2 (3x 20 ml), the organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting solid was washed with Et_2O to obtain **3c** (128 mg, 0.173 mmol, 35%) as a slightly orange solid.

^{1}H-NMR (600 MHz, DMSO-*d*$_6$) δ = 8.30 (s, 1H), 7.91 (d, *J* = 1.9 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.51 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.76 (s, 3H), 2.39 (s, 3H). **^{13}C-NMR (151 MHz, DMSO-*d*$_6$)** δ = 158.6, 151.4, 150.6, 138.5, 134.2, 133.2, 131.5, 120.9, 120.7 (q, *J* = 322.4 Hz), 117.0, 106.4, 98.4, 95.9, 60.7, 20.2. **^{19}F-NMR (565 MHz, DMSO-*d*$_6$)** δ = -77.7. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3085, 2942, 1659, 1519, 1484, 1449, 1393, 1225, 971, 955. **HRMS (ESI$^+$, MeCN/H$_2$O)** *m/z* = 590.7805 [M-OTf]$^+$. Calculated for $C_{14}H_{10}I_3O_2^+$ *m/z* = 590.7810. **Mp** decomp. at 140 °C.

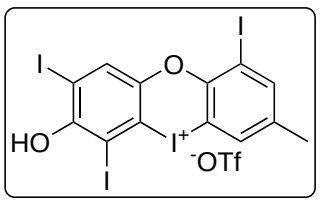
7-Hydroxy-1,6,8-triiodo-3-methyldibenzo[*b*,*e*][1,4]iodaoxin-5-ium bromide (4a)



To a suspension of **3a** (433 mg, 0.500 mmol) in CH_2Cl_2 (5 ml) was added BBr_3 (1.65 ml, 1.50 mmol, 0.91 M in CH_2Cl_2) and the mixture was heated to 60 °C for 1 d. After completion, the mixture was diluted with Et_2O and the resulting solid was washed multiple times with Et_2O to obtain **4a** (321 mg, 0.411 mmol, 82%) as a colourless solid.

^{1}H-NMR (600 MHz, DMSO-*d*$_6$) δ = 10.25 (bs, 1H), 8.18 – 8.15 (m, 1H), 7.95 (s, 1H), 7.94 – 7.93 (m, 1H), 2.33 (s, 3H). **^{13}C-NMR (151 MHz, DMSO-*d*$_6$)** δ = 155.8, 150.2, 148.8, 142.0, 139.7, 134.5, 130.5, 123.5, 108.7, 92.9, 90.4, 88.6, 19.7. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3043, 2115, 1527, 1449, 1412, 1345, 1231, 1063, 1036, 1007. **HRMS (ESI$^+$, MeOH)** *m/z* = 702.6613 [M-Br]$^+$. Calculated for $C_{13}H_7I_4O_2^+$ *m/z* = 702.6620. **Mp** decomp. at 160 °C.

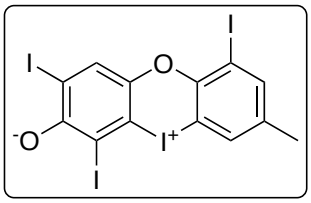
7-Hydroxy-1,6,8-triiodo-3-methyldibenzo[*b*,*e*][1,4]iodaoxin-5-ium trifluoromethanesulfonate (4b)



To a suspension of **4a** (78.3 mg, 0.100 mmol) in MeCN (1 ml) was added AgOTf (28.3 mg, 0.110 mmol) and the mixture was stirred for 14 h. The mixture was filtered through a syringe filter (PTFE, 0.45 µm). The reaction vessel and filter were washed with MeOH (2x 1 ml). The resulting solution was concentrated and precipitated with Et_2O to give **4b** (68.7 mg, 80.7 µmol, 81%) as a beige solid.

^{1}H-NMR (600 MHz, CD_3OD) δ = 8.18 (s, 1H), 8.01 (d, *J* = 1.0 Hz, 1H), 7.86 (d, *J* = 0.9 Hz, 1H), 2.42 (s, 3H). **^{13}C-NMR (151 MHz, CD_3OD)** δ = 156.1, 149.2, 147.0, 142.8, 140.2, 132.1, 131.5, 119.6 (d, *J* = 318.7 Hz), 115.2, 103.5, 88.4, 87.9, 86.7, 18.1. **^{19}F-NMR (565 MHz, CD_3OD)** δ = -80.1. ^{19}F content was checked by the addition of PhF (see spectra Fig. 41). **FTIR (ATR, neat)** $\tilde{\nu}$ = 3419, 1540, 1447, 1414, 1366, 1271, 1212, 1169, 1014, 819. **HRMS (ESI$^+$, MeOH)** *m/z* = 702.6613 [M-OTf]$^+$. Calculated for $C_{13}H_7I_4O_2^+$ *m/z* = 702.6620. **Mp** decomp. at 200 °C.

2,4,9-Triiodo-7-methyldibenzo[*b*,*e*][1,4]iodaoxin-5-ium-3-olate (5)

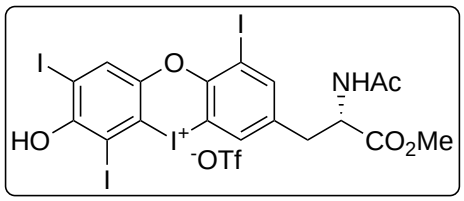


To a solution of iodaoxinium salt **4b** (29.8 mg, 35 µmol) in MeOH (0.7 ml) was added NaOH (38.5 µl, 38.5 µmol, 1 M) to form an orange precipitate. The suspension was stirred for 10 min, Et_2O (10 ml) was added, and the solution was centrifugated (6000 rpm, 10 min) and decanted. The solid was suspended in H_2O (10 ml), centrifugated and decanted. To obtain, after drying, **5** (22.7 mg, 32.4 µmol, 92%) as an orange solid.

^{1}H-NMR (601 MHz, DMSO-d_6) δ = 7.94 (s, 1H), 7.90 (s, 1H), 7.79 (s, 1H), 2.33 (s, 3H). Due to poor solubility and instability of the compound in DMSO the quality of the **^{1}H-NMR** quality is reduced and it was not possible to record a **^{13}C-NMR** spectrum. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3052, 2912, 1541, 1493, 1406, 1236, 1210, 857, 824, 702. **HRMS (ESI$^+$, MeOH)** *m/z* = 702.6613 [M+H]$^+$. Calculated for $C_{13}H_7I_4O_2^+$ *m/z* = 702.6620. **Mp** decomp. at 212 °C.

3.3 Thyroxine-derived Salts 1 and 6

(*S*)-3-(2-Acetamido-3-methoxy-3-oxopropyl)-7-hydroxy-1,6,8-triiododibenzo[*b*,*e*][1,4]iodaoxin-5-ium trifluoromethanesulfonate (6a)

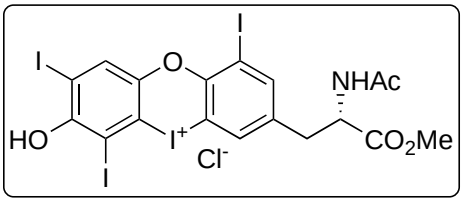


To a solution of Ac-Thx(Ac)-OMe (0.500 mmol, 437 mg) in MeCN/HFIP (10 ml, 1:1) was added mCPBA (0.550 mmol, 112 mg, 85%) at 0 °C. The solution was stirred for 10 min, TfOH (2.50 mmol, 221 µl) was added and the solution was stirred for 3 d. The reaction was monitored via HPLC-MS and after full conversion of the Iodoarene and subsequent *O*-deacylation the mixture was concentrated under reduced pressure and coevaporated with EtOAc (5 x 10 ml). The resulting solid was washed with Et_2O to obtain **6a** (261 mg, 0.266 mmol, 53%) as a colourless to beige solid.

^{1}H-NMR (600 MHz, DMSO-d_6) δ = 10.47 (brs, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.02 (s, 1H), 8.00 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 4.48 (ddd, *J* = 9.5, 7.9, 5.4 Hz, 1H), 3.62 (s, 3H), 3.10 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.91 (dd, *J* = 14.0, 9.4 Hz, 1H), 1.79 (s, 3H). **^{13}C-NMR (151 MHz, DMSO-d_6)** δ = 171.59, 169.46, 156.51, 150.69, 147.91, 143.00, 139.65, 133.95, 131.16, 120.7 (q, *J* = 322.0 Hz), 118.13, 106.84, 93.59, 91.65, 89.05, 53.00, 52.07, 35.15, 22.26. **^{19}F-NMR (565 MHz, DMSO-d_6)** δ = -77.7. **FTIR (ATR, neat)** $\tilde{\nu}$ =

3319, 3064, 1726, 1633, 1542, 1423, 1372, 1219, 1166, 1020, 831. **HRMS (ESI$^+$, MeOH)** *m/z* = 831.7022 [M-OTf]$^+$. Calculated for $C_{18}H_{14}I_4NO_5^+$ *m/z* = 831.7045. **Mp** *T* = 220 °C, with decomp. immediately afterwards.

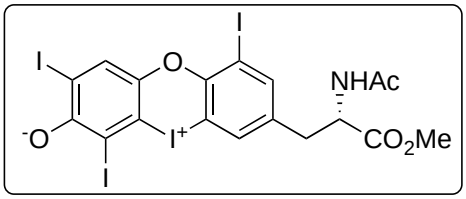
(*S*)-3-(2-Acetamido-3-methoxy-3-oxopropyl)-7-hydroxy-1,6,8-triiododibenzo[*b*,*e*][1,4]iodaoxin-5-ium chloride (6b)



To a solution of iodaoxinium salt **6a** (49.1 mg, 50.0 µmol) in MeOH (0.5 ml) was added HCl (100 µl, 1 M) and the suspension was stirred for 10 min. Et_2O (8 ml) was added and the suspension was centrifugated (6000 rpm, 10 min) and decanted. This was repeated two times to obtain **6b** (40.2 mg, 47.0 mmol, 94%) as a colourless solid.

^{1}H-NMR (601 MHz, DMSO-*d*$_6$) δ = 10.20 (s, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 7.96 – 7.91 (m, 2H), 4.42 (td, *J* = 8.5, 5.4 Hz, 1H), 3.62 (s, 3H), 3.06 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.92 (dd, *J* = 14.0, 9.3 Hz, 1H), 1.80 (s, 3H). **^{13}C-NMR (151 MHz, DMSO-*d*$_6$)** δ = 171.5, 169.5, 155.7, 151.1, 149.0, 142.3, 139.2, 134.7, 130.4, 124.9, 109.9, 92.8, 90.1, 88.7, 53.1, 52.0, 35.1, 22.3. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3250, 3046, 1728, 1644, 1527, 1418, 1530, 1275, 1230, 1194, 929. **HRMS (ESI$^+$, MeOH)** *m/z* = 831.7037 [M-Cl]$^+$. Calculated for $C_{18}H_{14}I_4NO_5^+$ *m/z* = 831.7045 **Mp** decomp at 178 °C.

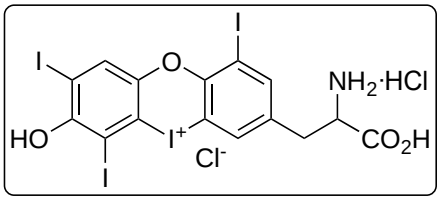
(*S*)-7-(2-Acetamido-3-methoxy-3-oxopropyl)-2,4,9-triiododibenzo[*b*,*e*][1,4]iodaoxin-5-ium-3-olate (7)



To a solution of iodaoxinium salt **6a** (49.1 mg, 50.0 µmol) in MeOH (1 ml) was added NaOH (55 µl, 1 M) to form an orange precipitate. The suspension was stirred for 1 h, H_2O (4 ml) was added and the suspension was washed with H_2O (4 ml) and MeOH (4 ml) to obtain **7** (29.3 mg, 35.9 µmol, 72%) as an orange solid.

^{1}H-NMR (600 MHz, DMSO-*d*$_6$) δ = 8.32 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 2.8 Hz, 2H), 7.80 (s, 1H), 4.46 (td, *J* = 8.5, 5.3 Hz, 1H), 3.61 (s, 3H), 3.06 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.91 (dd, *J* = 14.0, 9.3 Hz, 1H), 1.79 (s, 3H). **^{13}C-NMR** was not possible to record due to poor solubility and instability of the compound in DMSO. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3287, 1716, 1636, 1549, 1411, 1347, 1233, 1043, 838. **HRMS (ESI$^+$, MeOH)** *m/z* = 831.7022 [M+H]$^+$. Calculated for $C_{18}H_{14}I_4NO_5^+$ *m/z* = 831.7045. **Mp** decomp. at 190 °C.

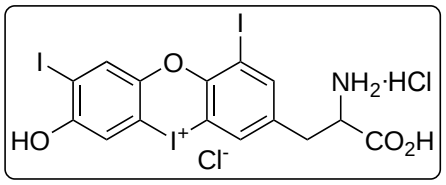
3-(2-Ammonio-2-carboxyethyl)-7-hydroxy-1,6,8-triiododibenzo[*b*,*e*][1,4]iodaoxin-5-ium chloride (1a)



Iodaoxinium salt **6a** (49.1 mg, 50 µmol) was suspended in HCl (7.5 ml, 1 N) and heated to 120 °C for 4 h. The resulting suspension was centrifugated (6000 rpm, 10 min) and decanted. The resulting solid was washed by precipitation from MeOH with Et_2O, centrifugated and decanted. The resulting solid was then extracted from the solid by precipitation with MeCN from a suspension in MeOH, afterwards centrifugated and decanted. The resulting solution was concentrated and dried to obtain **1a** (24.0 mg, 28.3 µmol, 57%) as a colourless solid.

^{1}H-NMR (600 MHz, CD_3OD) δ = 8.39 (s, 1H), 8.11 (s, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 4.33 (t, *J* = 6.7 Hz, 1H), 3.41 (dd, *J* = 14.8, 5.4 Hz, 1H), 3.21 (dd, *J* = 14.7, 7.9 Hz, 1H). **^{13}C-NMR (151 MHz, CD_3OD)** δ = 170.6, 157.8, 153.5, 149.8, 145.0, 138.1, 136.2, 133.2, 122.7, 109.4, 90.1, 89.4, 89.1, 54.6, 35.8. **FTIR (ATR, neat)** $\tilde{\nu}$ = 2845, 2114, 1916, 1727, 1585, 1505, 1416, 1350, 1281, 1195, 1135, 826. **HRMS (ESI$^+$, MeOH)** *m/z* = 775.6775 $[M\text{-}HCl_2]^+$. Calculated for $C_{15}H_{10}I_4NO_4^+$ *m/z* = 775.6783. **Mp** decomp. at 200 °C.

3-(2-Ammonio-2-carboxyethyl)-7-hydroxy-1,8-diiododibenzo[*b*,*e*][1,4]iodaoxin-5-ium chloride (1b)



Iodaoxinium salt **6a** (98.1 mg, 100 µmol) was suspended in HCl (15 ml, 1 N) and heated to 100 °C for 1 d. The resulting suspension was diluted with HCl (5 ml, 1 N), centrifugated (6000 rpm, 10 min) and decanted. The resulting solid was suspended in MeOH (~1 ml) and diluted with Et_2O (9 ml), centrifugated and decanted to obtain **1b** (50.0 mg, 69.3 µmol, 69%) as a colourless solid.

^{1}H-NMR (600 MHz, DMSO-d_6 + 10% D_2O) δ = 8.00 (s, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.84 (s, 1H), 7.66 (s, 1H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.16 – 3.10 (m, 1H), 3.04 (dd, *J* = 14.5, 7.1 Hz, 1H). **^{13}C-NMR (151 MHz, DMSO-d_6)** δ = 170.2, 156.3, 153.2, 147.5, 142.8, 137.0, 135.2, 130.9, 118.0, 108.9, 108.9, 90.0, 88.9, 53.7, 34.7. **FTIR (ATR, neat)** $\tilde{\nu}$ = 3335, 3040, 2860, 2115, 1916, 1724, 1606, 1374, 1229, 1174, 1040, 871, 823. **HRMS (ESI$^+$, MeOH)** *m/z* = 649.7809 $[M\text{-}HCl_2]^+$. Calculated for $C_{15}H_{11}I_3NO_4^+$ *m/z* = 649.7817. **Mp** decomp. at 235 °C.

3.4 Interaction of compound 6a with different amounts of tetra-*n*-butylammonium chloride (TBACl)

To a solution of Iodaoxinium salt **6a** (9.81 mg, 10.0 µmol) in DMSO-d_6 (0.5 ml) were added different amounts of a solution of tetra-*n*-butylammonium chloride in DMSO-d_6 (2 M). Afterwards ^{13}C-NMR spectra of the resulting solutions were measured.

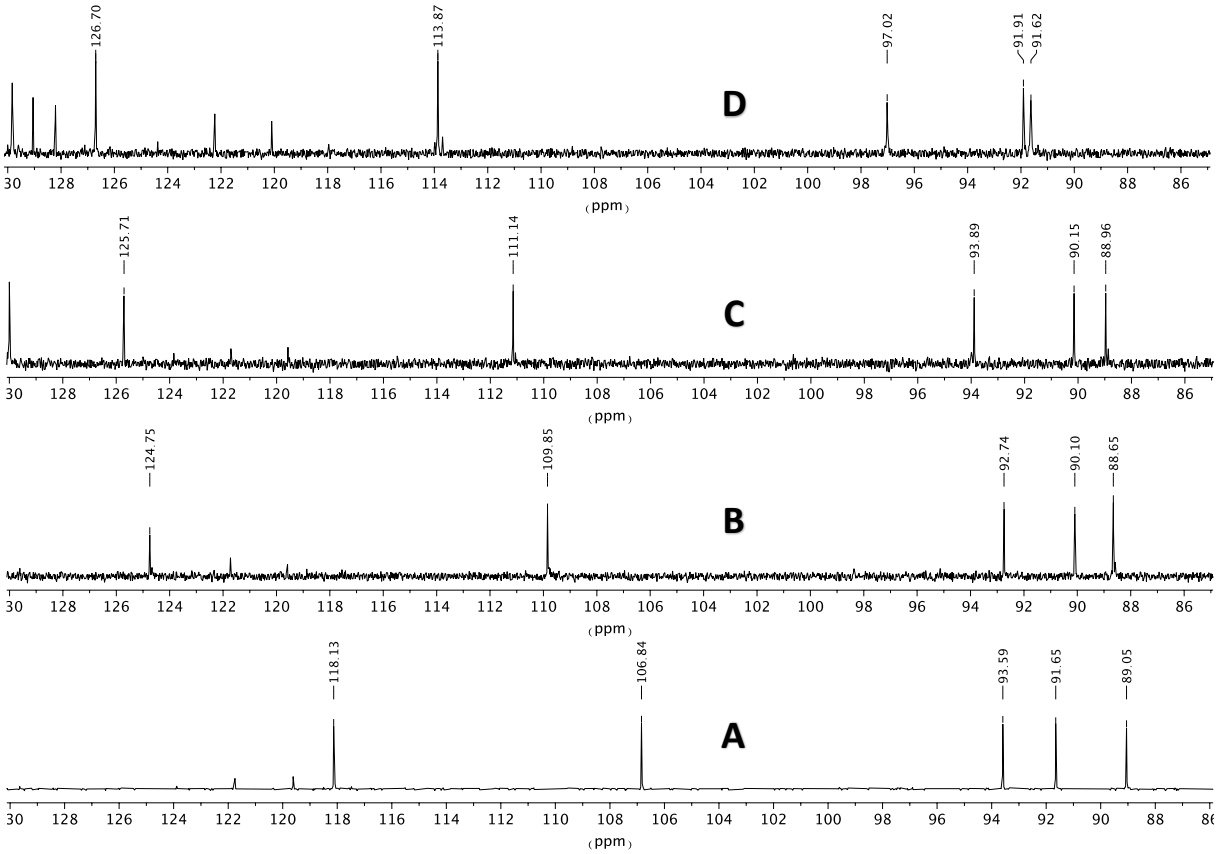


*Figure 1 - NMR Data with annotated peaks for compound **6a** (**A**), **6a** + 1 eq. TBACl (B), **6a** + 5 eq. TBACl (**C**), **6a** + 50 eq. TBACl (**D**) in DMSO-d_6 at 24 °C.*

4 Crystal Structures

Single crystals of **6a** were prepared by dissolving the substance in a minimum amount of methanol. Diethyl ether was introduced via gas-phase diffusion to obtain a suitable crystal. (CCDC 2291802)

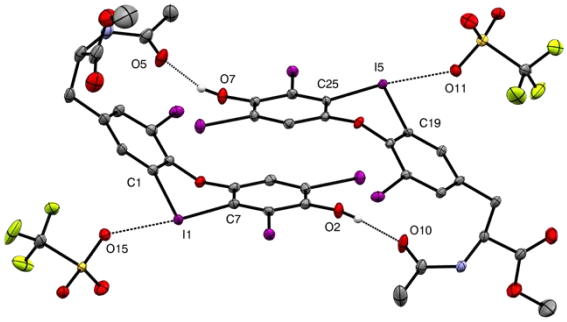


Figure S1: Structure of **6a** showing 50% probability ellipsoids. Selected bond parameters [Å, °]: I1-O15: 2.757(2); I5-O11: 2.752(2); O5-O7: 2.563(4); O2-O10: 2.606(4); C1-I1-C7: 90.0(1); C19-I5-C25: 89.7(1); C7-I1-O15: 175.2(1); C25-I5-O11: 172.69(9).

Table S2: Crystal data and structure refinement for **6a**.

Empirical formula	$C_{19}H_{14}F_3I_4NO_8S$
Formula weight	980.97
Temperature/K	100.00
Crystal system	Trigonal
Space group	R3
a/Å	34.2779(8)
b/Å	34.2779(8)
c/Å	13.8411(5)
α/°	90
β/°	90
γ/°	120
Volume/Å^3	14084.1(8)
Z	18
ρ_{calc}g/cm^3	2.082
μ/mm^{-1}	4.104
F(000)	8172.0
Crystal size/mm^3	0.245 × 0.18 × 0.125
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.024 to 72.87
Index ranges	-57 ≤ h ≤ 57, -57 ≤ k ≤ 57, -23 ≤ l ≤ 23
Reflections collected	262320
Independent reflections	30489 [R_{int} = 0.0460, R_{sigma} = 0.0265]
Data/restraints/parameters	30489/1/669
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0199, wR_2 = 0.0402
Final R indexes [all data]	R_1 = 0.0230, wR_2 = 0.0409
Largest diff. peak/hole / e Å^{-3}	1.42/-0.68
Flack parameter	0.063(4)

5 Computational Details

The DFT calculations were performed with ORCA 5.0.4.[8] Structure optimisations were performed on a PBE0-D3(BJ)/def2-SVP+CPCM level of theory, a combination of the PBE0 functional[9] with Becke-Johnson damping[10, 11], the def2-SVP basis set[12], an auxiliary basis set for the RI approximation[13] and the Conductor-like Polarizable Continuum Model[14]. On the optimised structure single point calculations were performed on a PBE0-D3(BJ)/def2-TZVP+CPCM level of theory, a combination of the PBE0 functional[9] with Becke-Johnson damping[10, 11], the def2-TZVP basis set[12], an auxiliary basis set for the RI approximation[13] and the Conductor-like Polarizable Continuum Model[14]. Transition states were verified by the implemented method of Morokuma et al.[15]. The corresponding geometries are attached as a separate file.

Table S3: PBE0-D3(BJ)/def2-TZVP+CPCM(Water) computed imaginary frequency (ImF), Gibbs free-energy (G) and the energy relative to the corresponding conformer of **1a** (ΔG).

	Conformer	Direction of attack	Im / cm^{-1}	G / Eh	ΔG / kcal mol^{-1}
1a + HCl	**1**		**0**	**-3504.76521948**	**0.00**
	2		**0**	**-3504.76589810**	**0.00**
1a-1-HCl	1	a	0	-3504.74728099	11.26
		b	0	-3504.74980229	9.67
	2	**a**	**0**	**-3504.74918803**	**10.49**
		b	0	-3504.75027868	9.80
TS1	1	a	833.86i	-3504.71854128	29.29
		b	765.90i	-3504.71953144	28.67
	2	**a**	**802.46i**	**-3504.72076594**	**28.32**
		b	756.87i	-3504.72008974	28.75
1b''-1-ICl	1	a	0	-3504.76963102	-2.77
		b	0	-3504.73888234	16.53
	2	**a**	**0**	**-3504.77251990**	**-4.16**
		b	0	-3504.74007346	16.21
1b'' + ICl	1		0	-3504.75404517	7.01
	2		**0**	**-3504.75431142**	**7.27**
1a-6-HCl	**1**	a	0	-3504.75031644	9.35
		b	**0**	**-3504.75051335**	**9.23**
	2	a	0	-3504.75189973	8.78
		b	0	-3504.75209454	8.66
TS6	**1**	a	1062.77i	-3504.72551074	24.92
		b	**530.12i**	**-3504.72656243**	**24.26**
	2	a	1058.97i	-3504.72603908	25.01
		b	458.37i	-3504.72710899	24.34
1b-6-ICl	**1**	a	0	-3504.75400566	7.04
		b	**0**	**-3504.77316283**	**-4.98**
	2	a	0	-3504.75481173	6.96
		b	0	-3504.77422553	-5.23
1b + ICl	**1**		**0**	**-3504.76109736**	**2.59**
	2		0	-3504.76191018	2.50
1a-8-HCl	**1**	**a**	**0**	**-3504.74913224**	**10.09**
		b	0	-3504.74960774	9.80
	2	a	0	-3504.74991549	10.03
		b	0	-3504.75042736	9.71
TS8	**1**	**a**	**1117.63i**	**-3504.71973968**	**28.54**
		b	1113.81i	-3504.71948467	28.70

	2	a	1105.42i	-3504.71964787	29.02
		b	1108.86i	-3504.71990273	28.86
1b'-8-ICl	**1**	**a**	**0**	**-3504.75125351**	**8.76**
		b	0	-3504.75086519	9.01
	2	a	0	-3504.75148539	9.04
		b	0	-3504.75106779	9.31
1b' + ICl	**1**		**0**	**-3504.75505375**	**6.38**
	2		0	-3504.75537039	6.61

6 NMR-Spectra of New Substrates

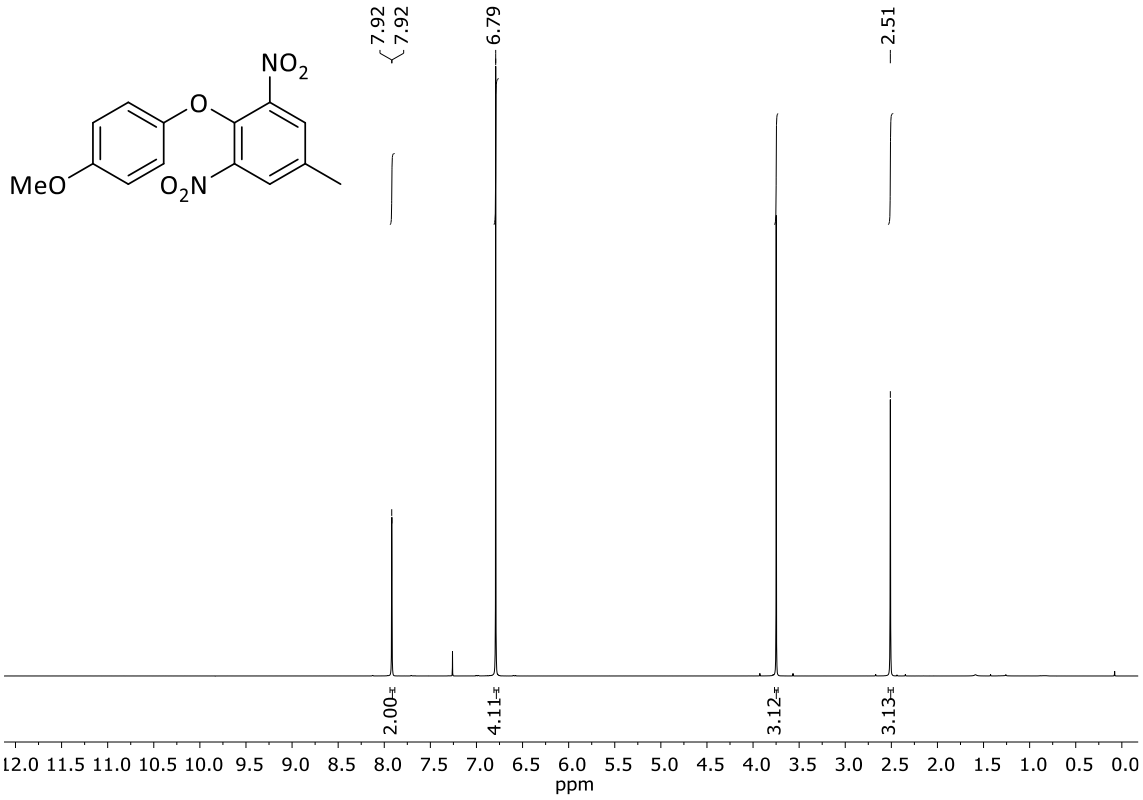


*Figure S2: 400 MHz ^{1}H-NMR spectrum of compound **S1** in $CDCl_3$.*

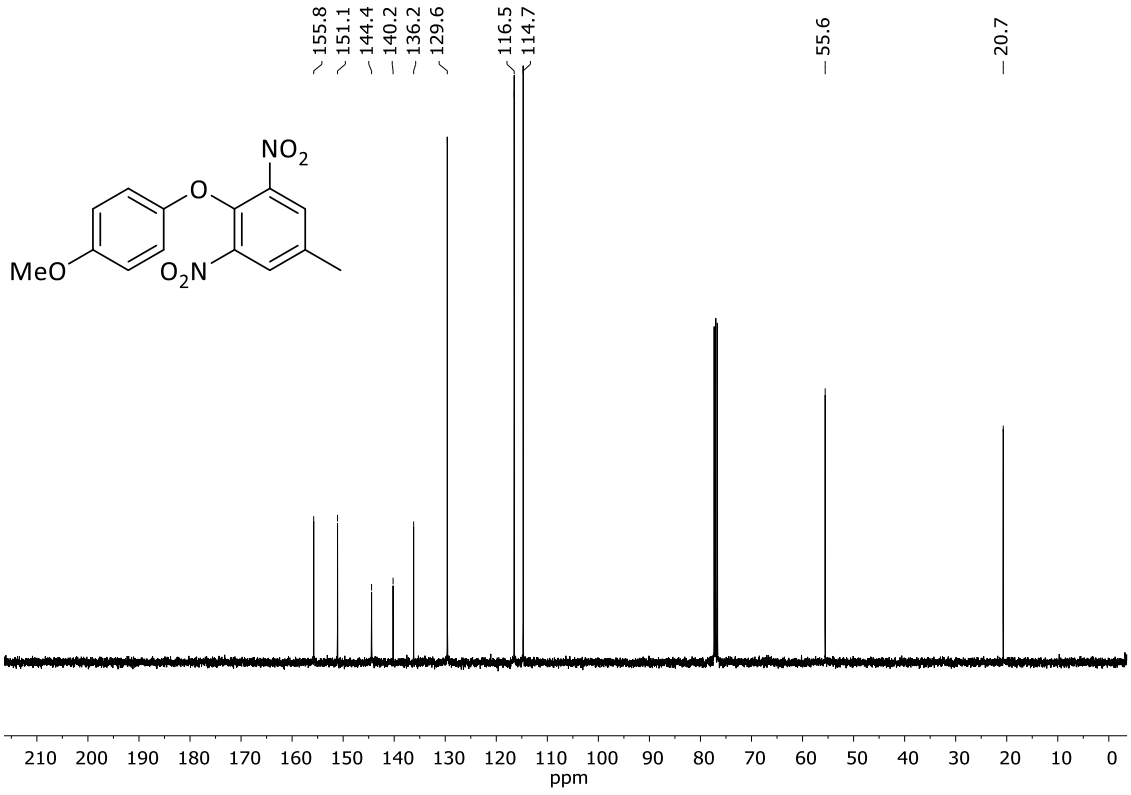


*Figure S3: 100 MHz ^{13}C-NMR spectrum of compound **S1** in $CDCl_3$.*

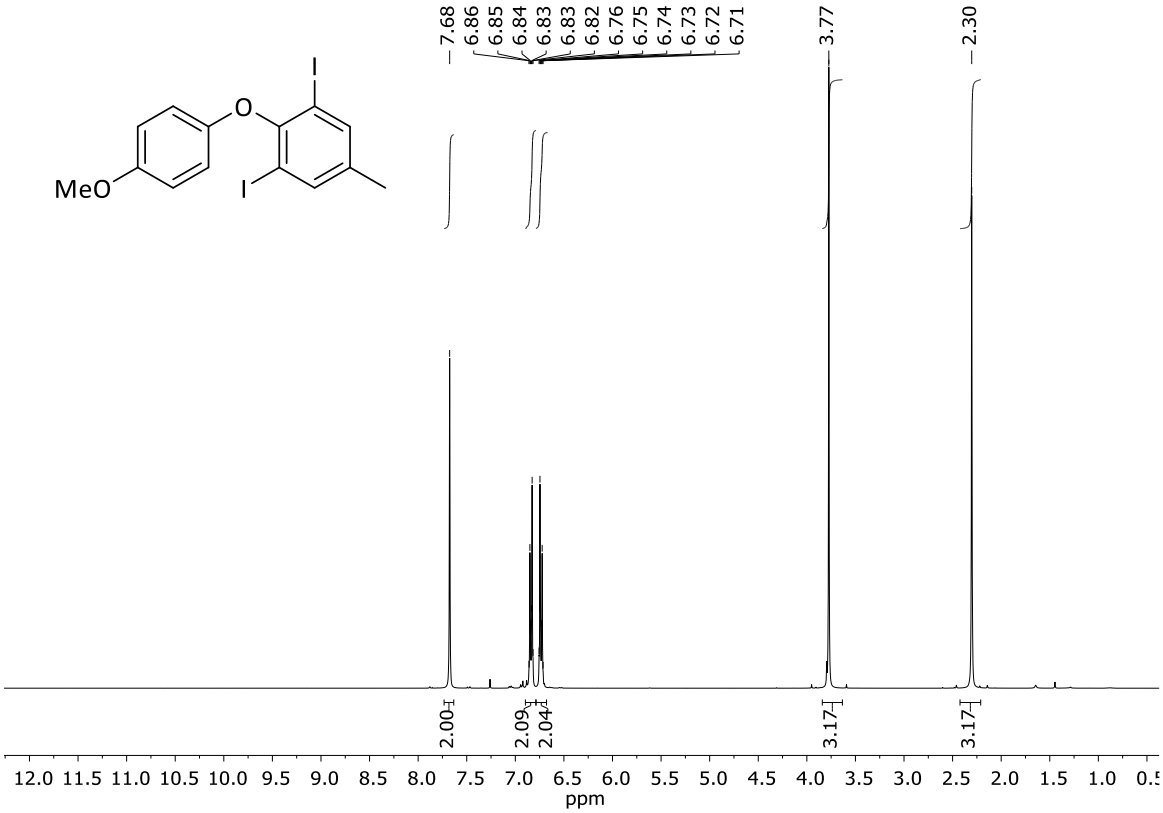


*Figure S4: 400 MHz ^{1}H-NMR spectrum of compound **S2** in $CDCl_3$.*

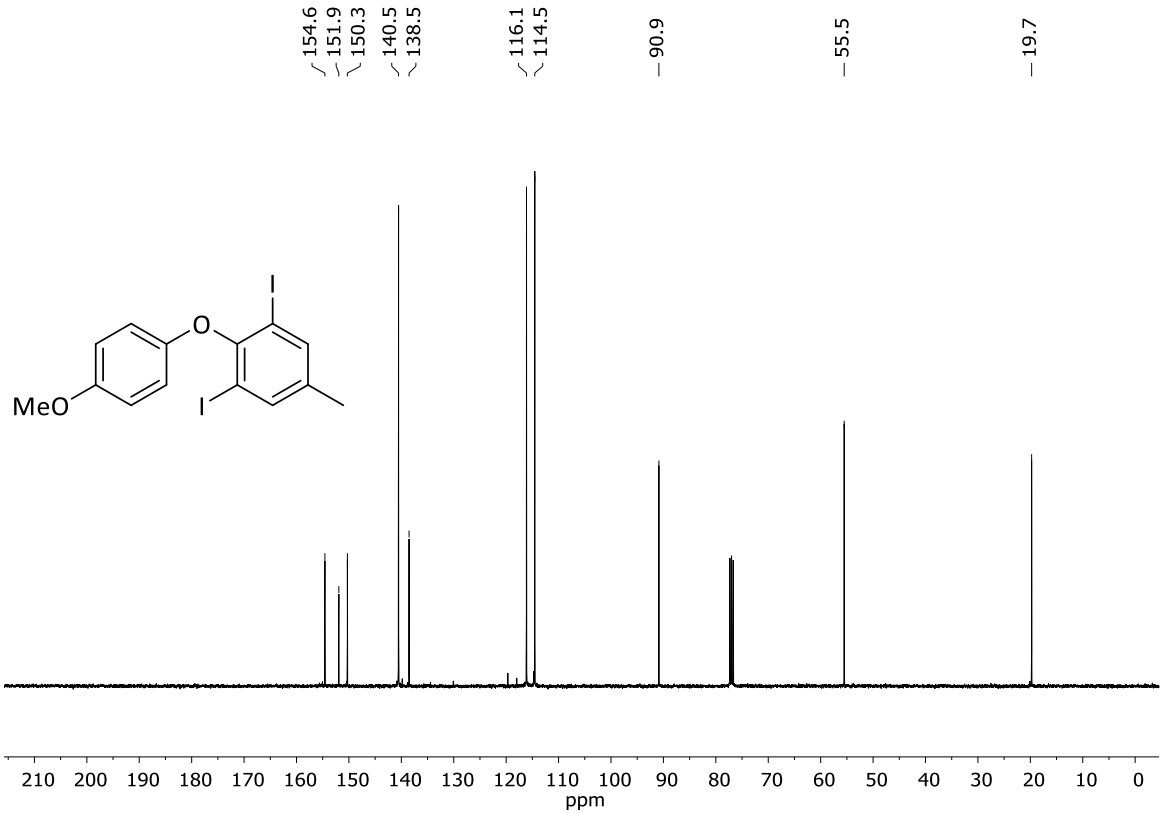


*Figure S5: 100 MHz ^{13}C-NMR spectrum of compound **S2** in $CDCl_3$.*

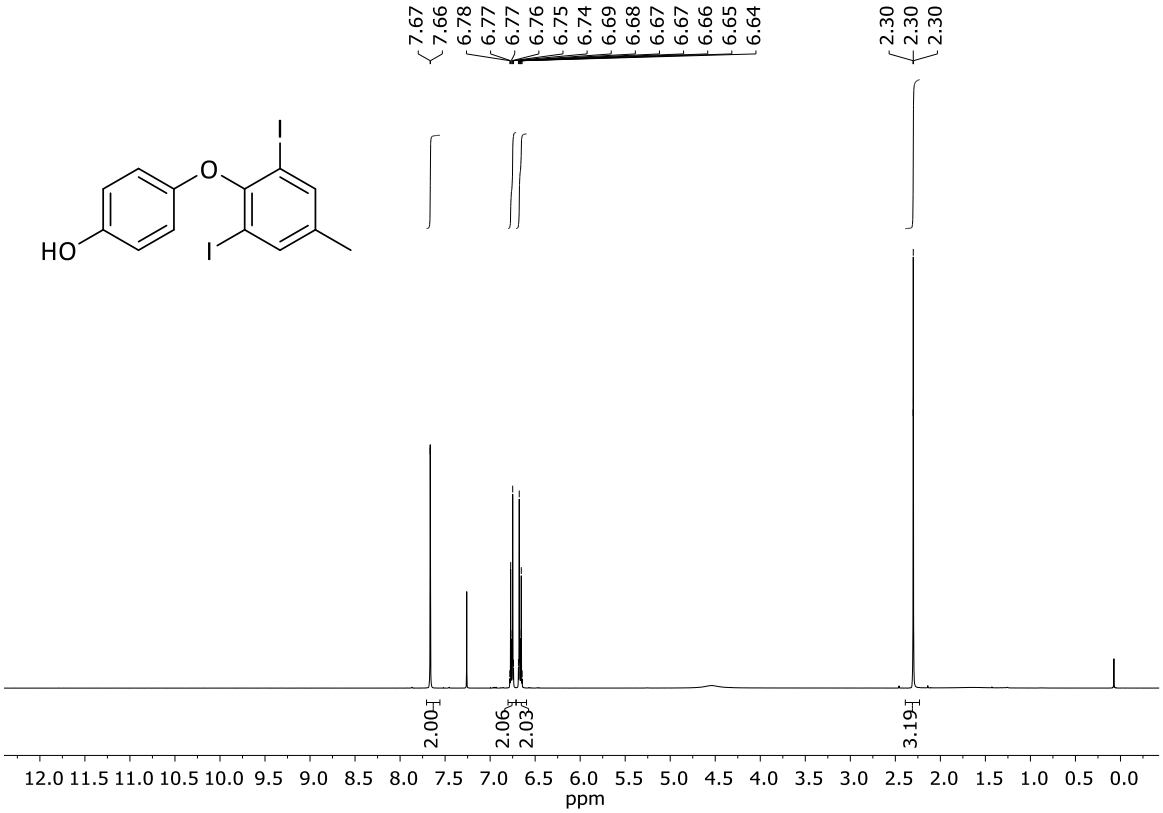


*Figure S6: 400 MHz ^{1}H-NMR spectrum of compound **S3** in $CDCl_3$.*

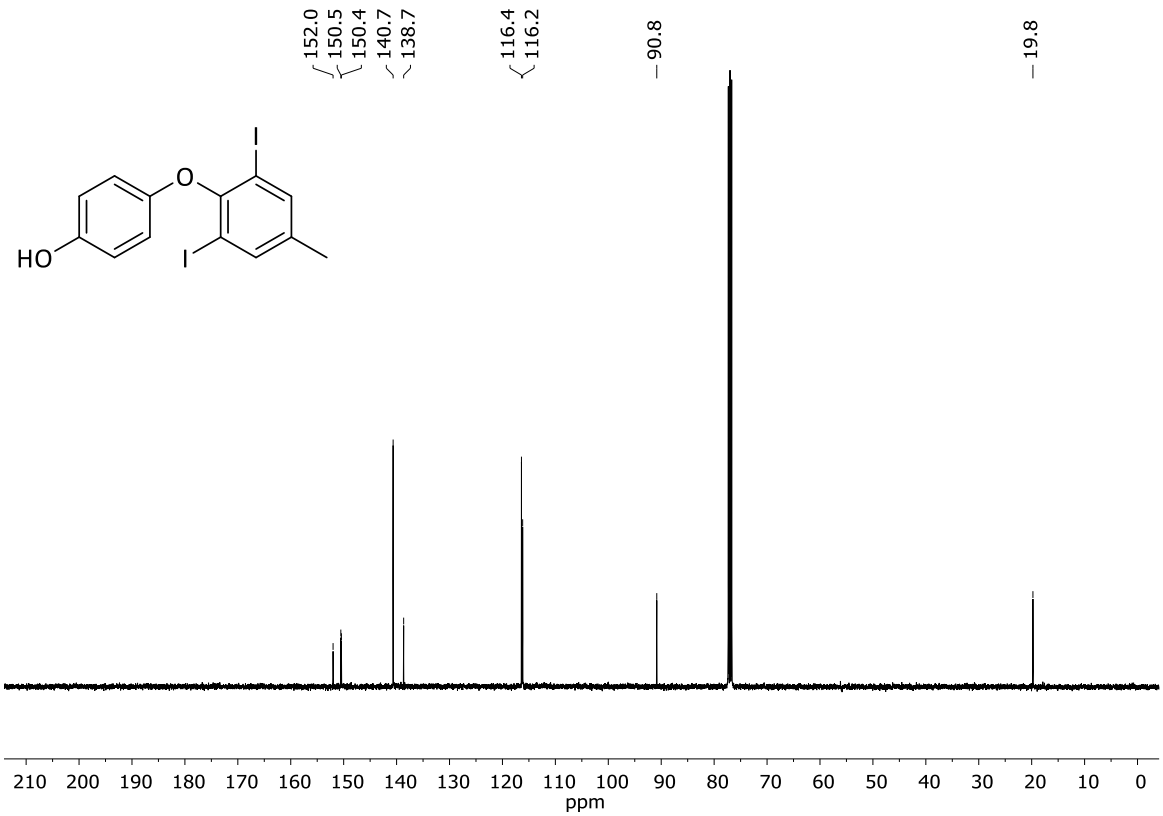


*Figure S7: 100 MHz ^{13}C-NMR spectrum of compound **S3** in $CDCl_3$.*

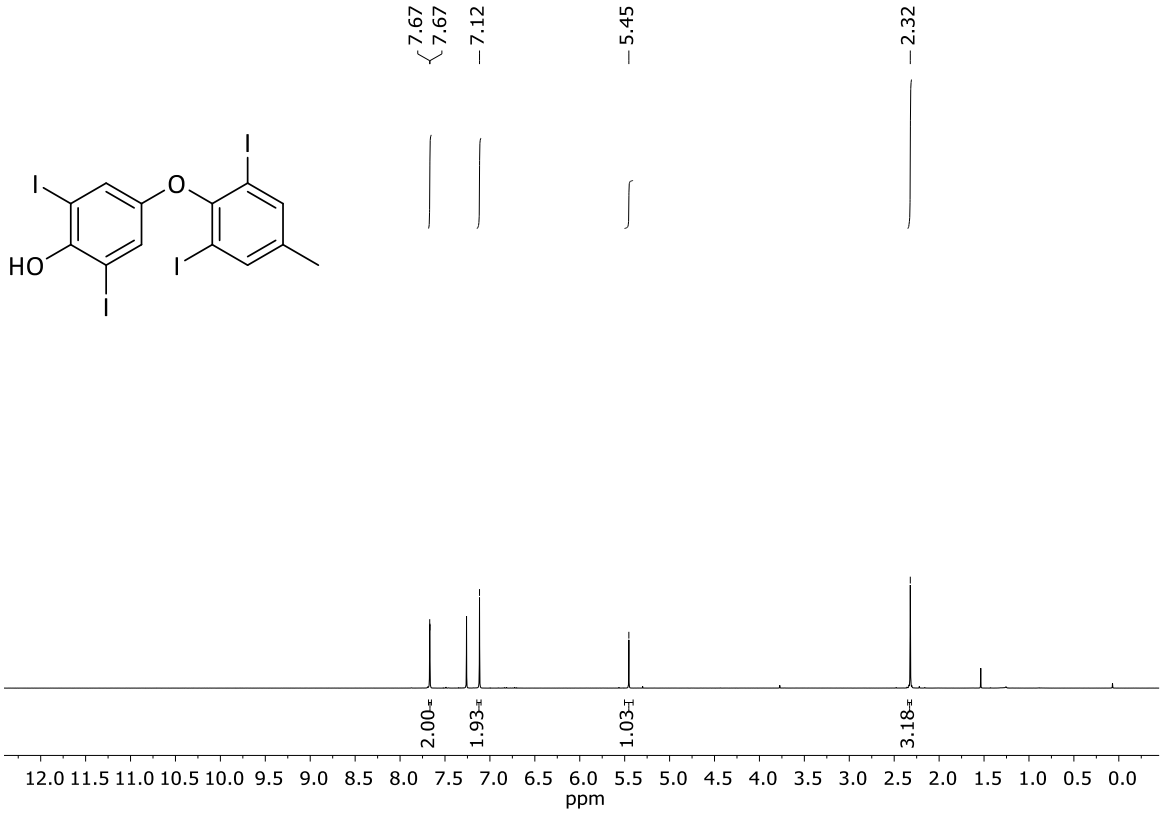


*Figure S8: 400 MHz ^{1}H-NMR spectrum of compound **S4** in $CDCl_3$.*

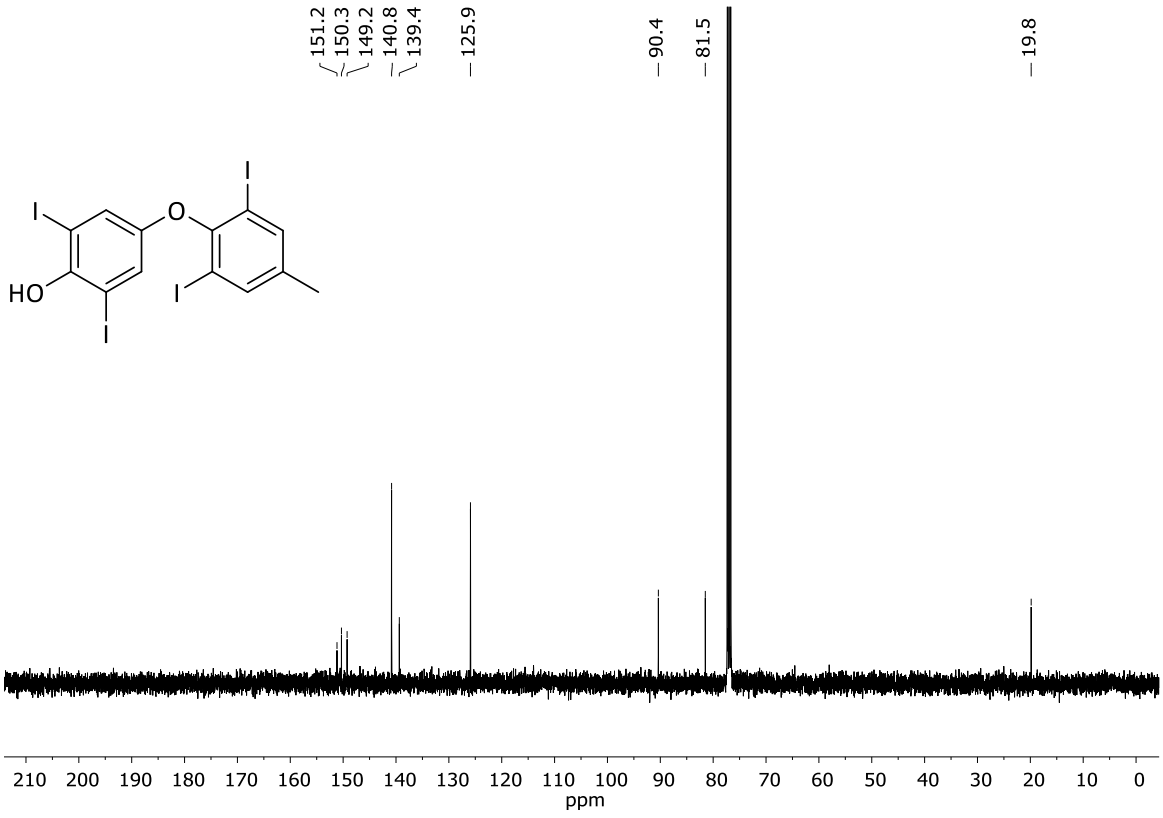


*Figure S9: 100 MHz ^{13}C-NMR spectrum of compound **S4** in $CDCl_3$.*

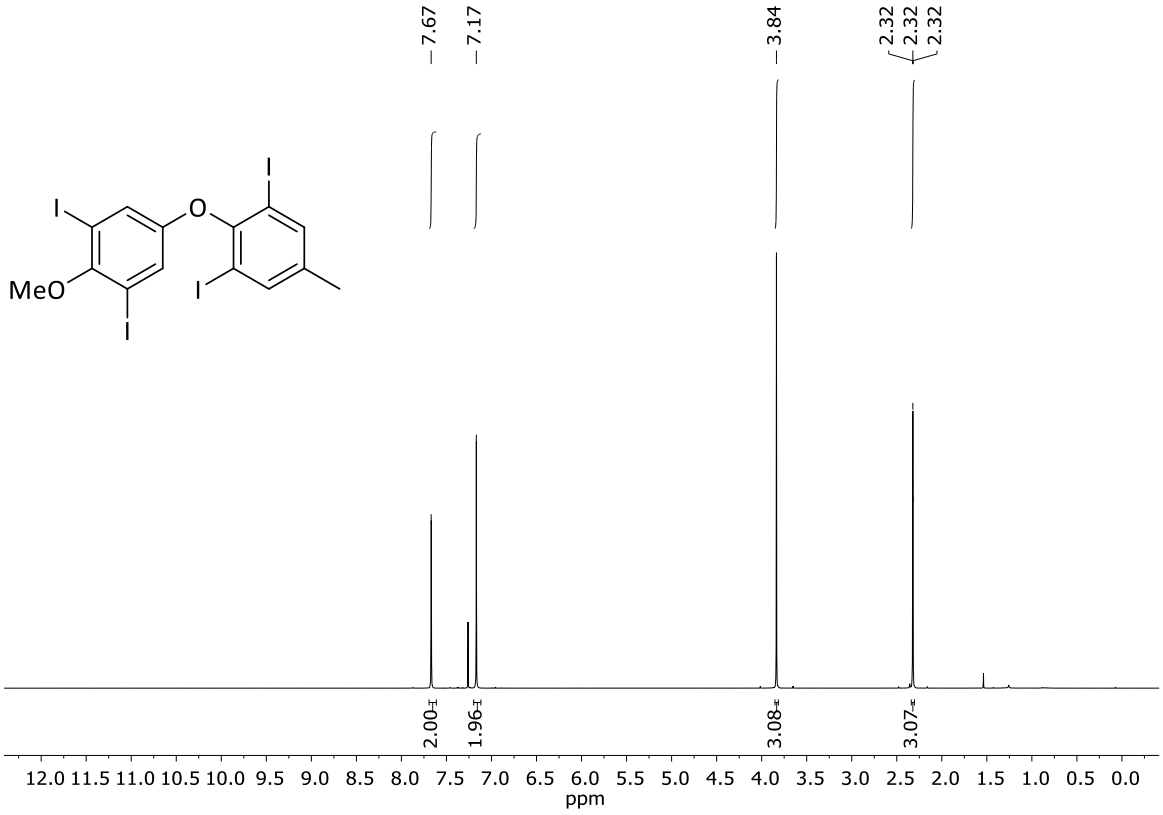


*Figure S10: 400 MHz ^{1}H-NMR spectrum of compound **2a** in $CDCl_3$.*

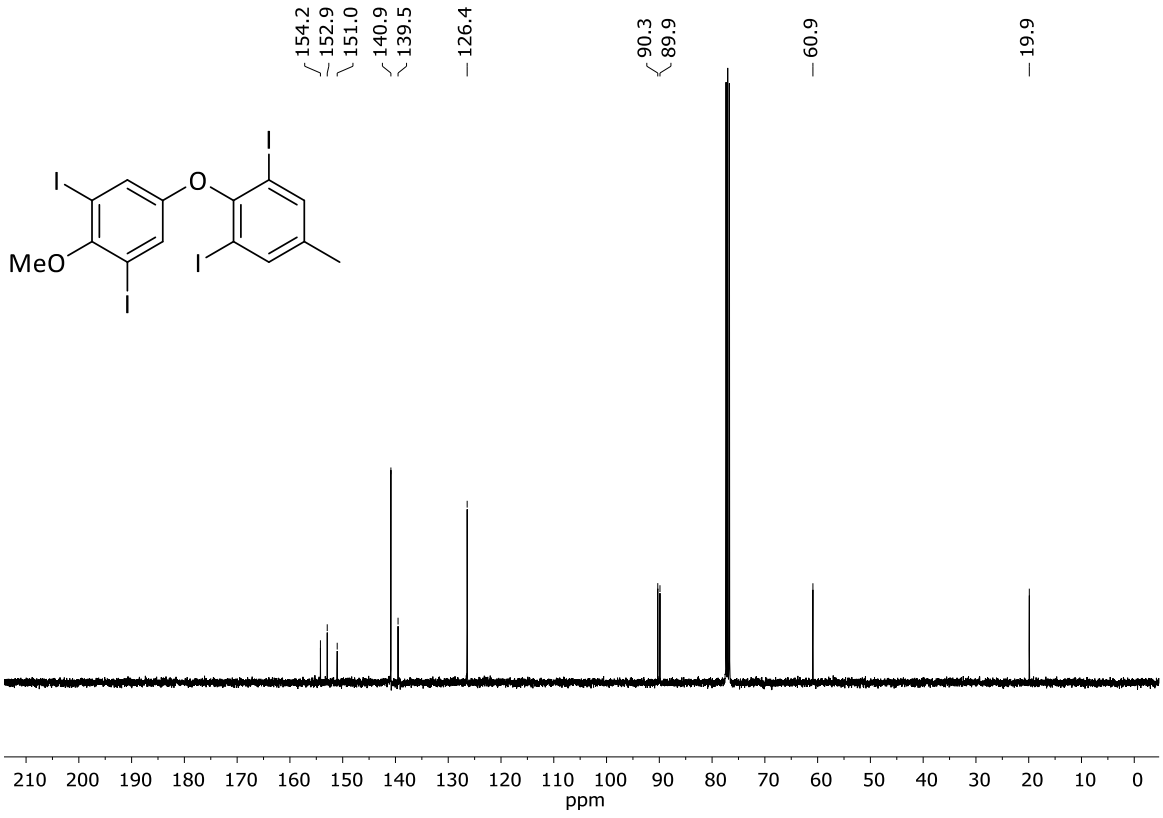


*Figure S11: 100 MHz ^{13}C-NMR spectrum of compound **2a** in $CDCl_3$.*

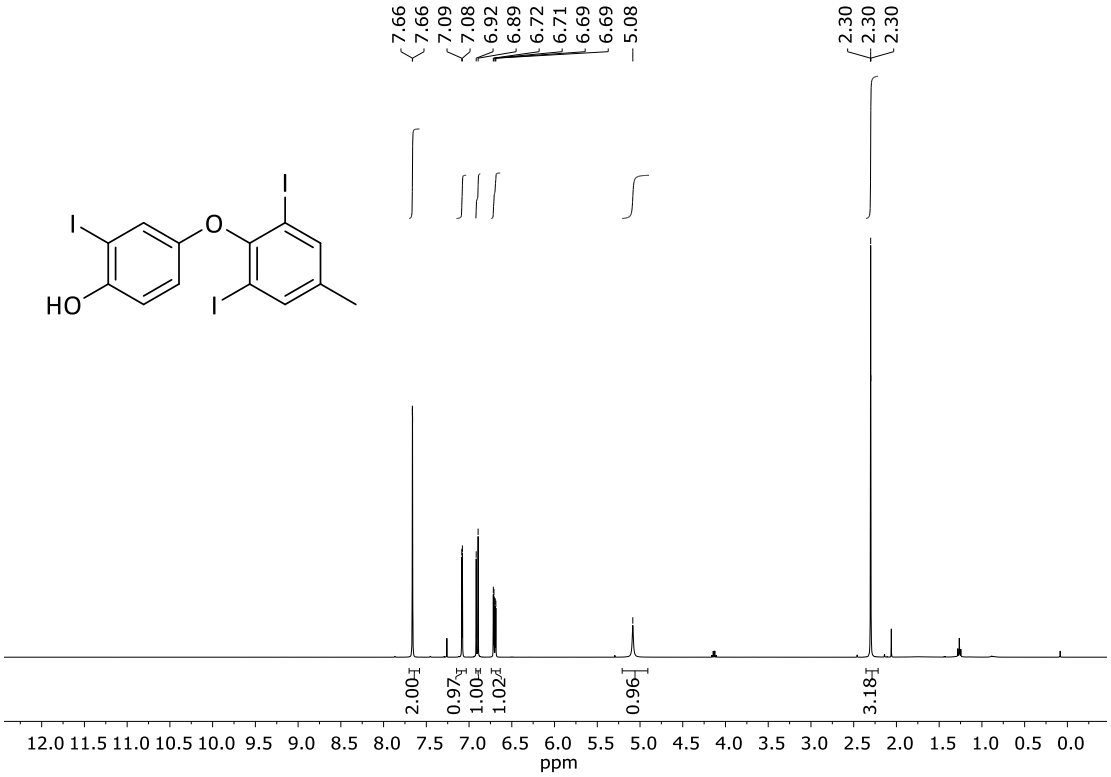


*Figure S12: 400 MHz ^{1}H-NMR spectrum of compound **S5** in $CDCl_3$.*

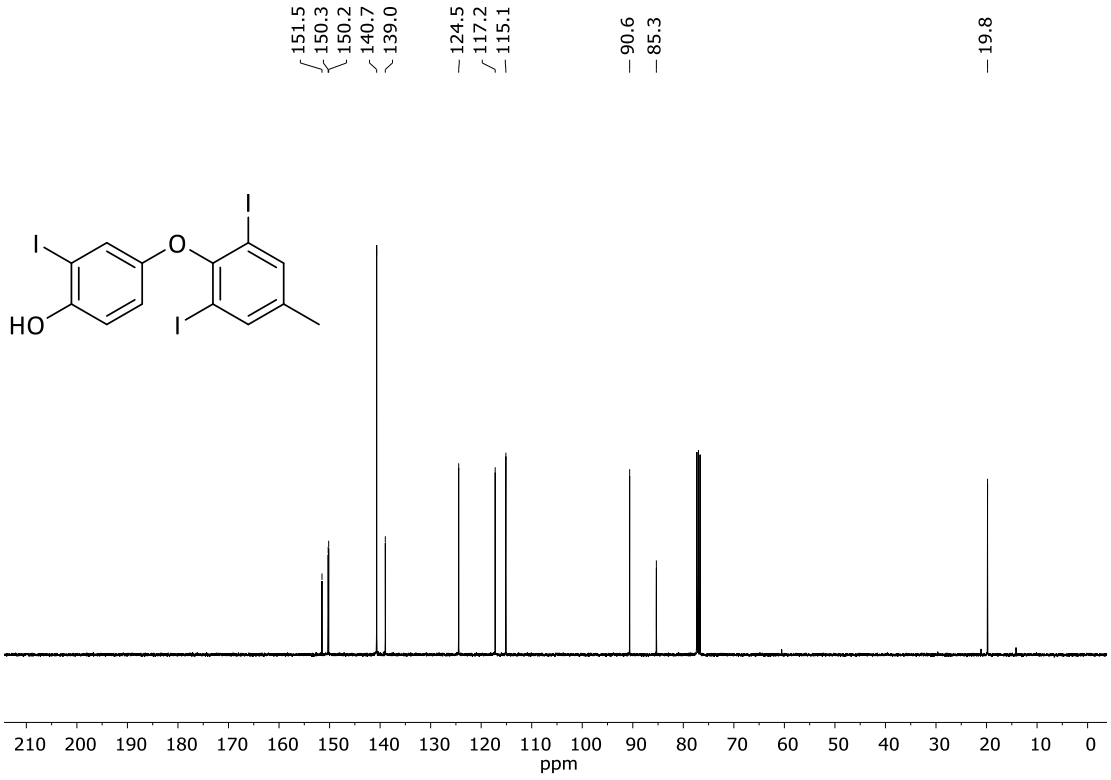


*Figure S13: 100 MHz ^{13}C-NMR spectrum of compound **S5** in $CDCl_3$.*

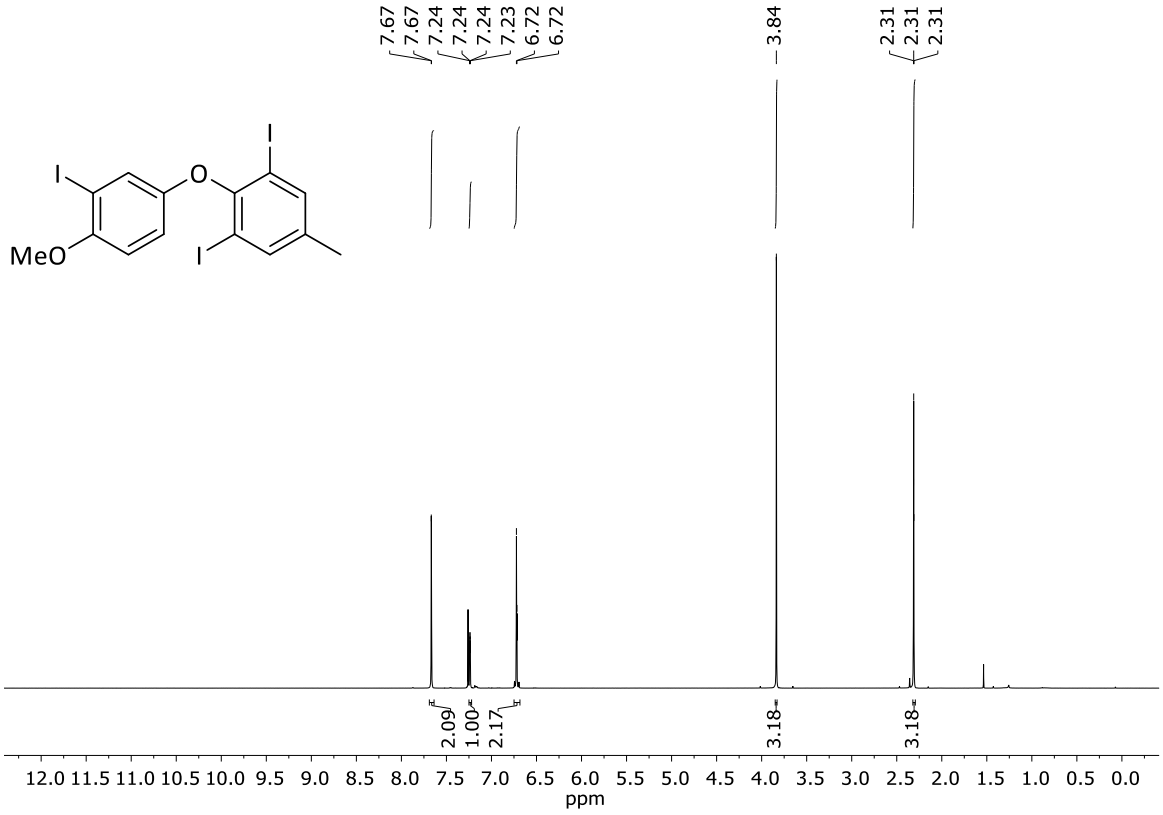


*Figure S14: 400 MHz ^{1}H-NMR spectrum of compound **2b** in $CDCl_3$.*

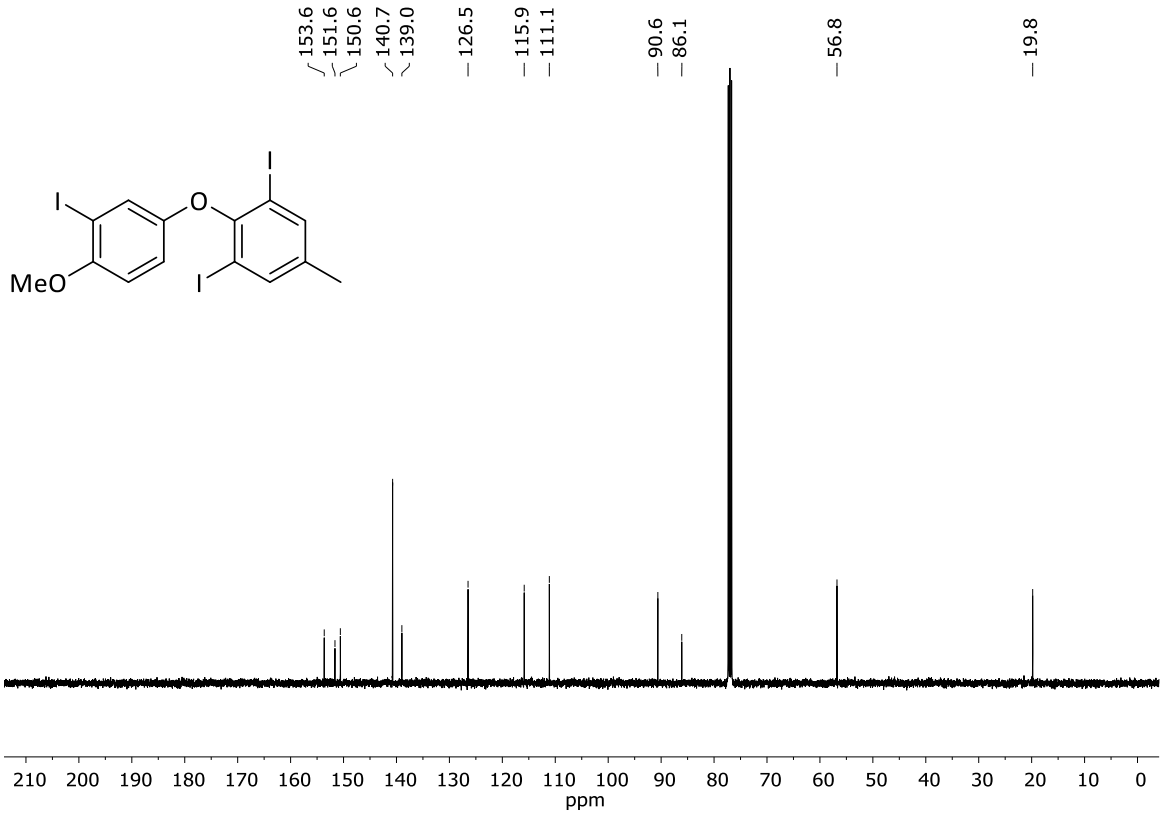


*Figure S15: 100 MHz ^{13}C-NMR spectrum of compound **2b** in $CDCl_3$.*

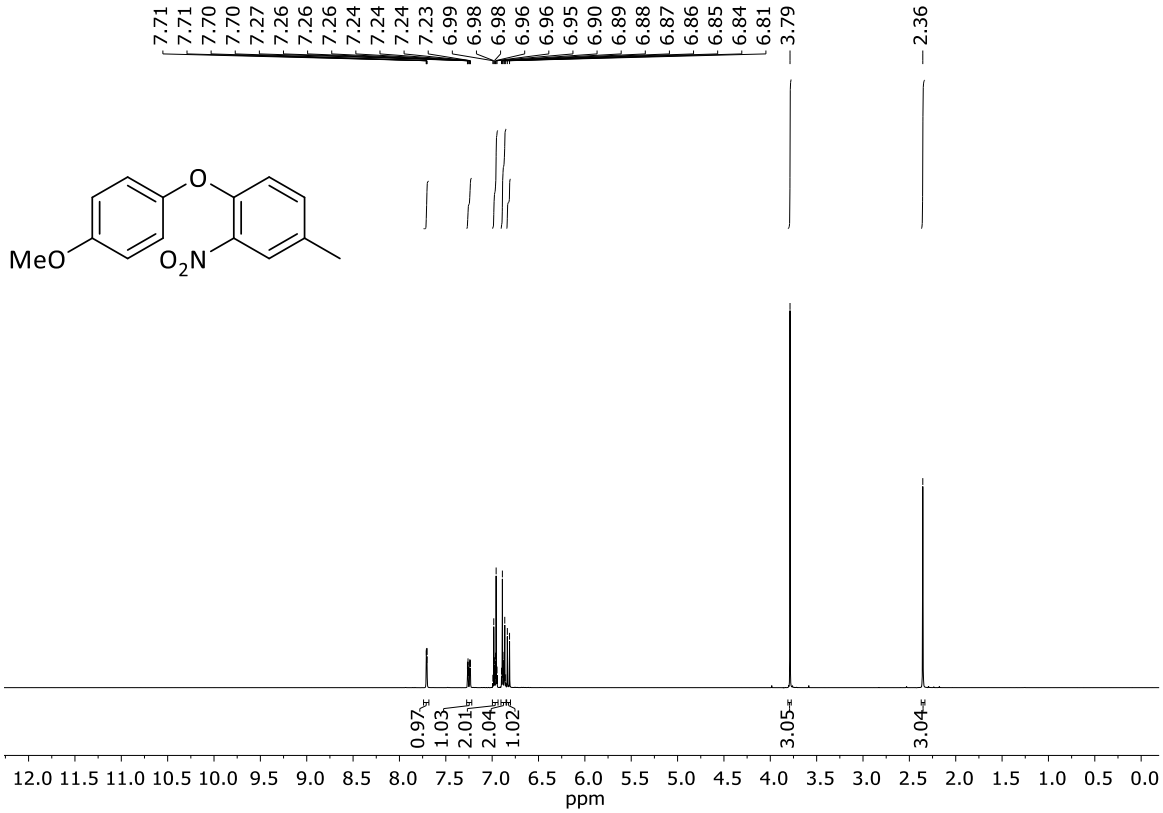


*Figure S16: 360 MHz ^{1}H-NMR spectrum of compound **S6** in $CDCl_3$.*

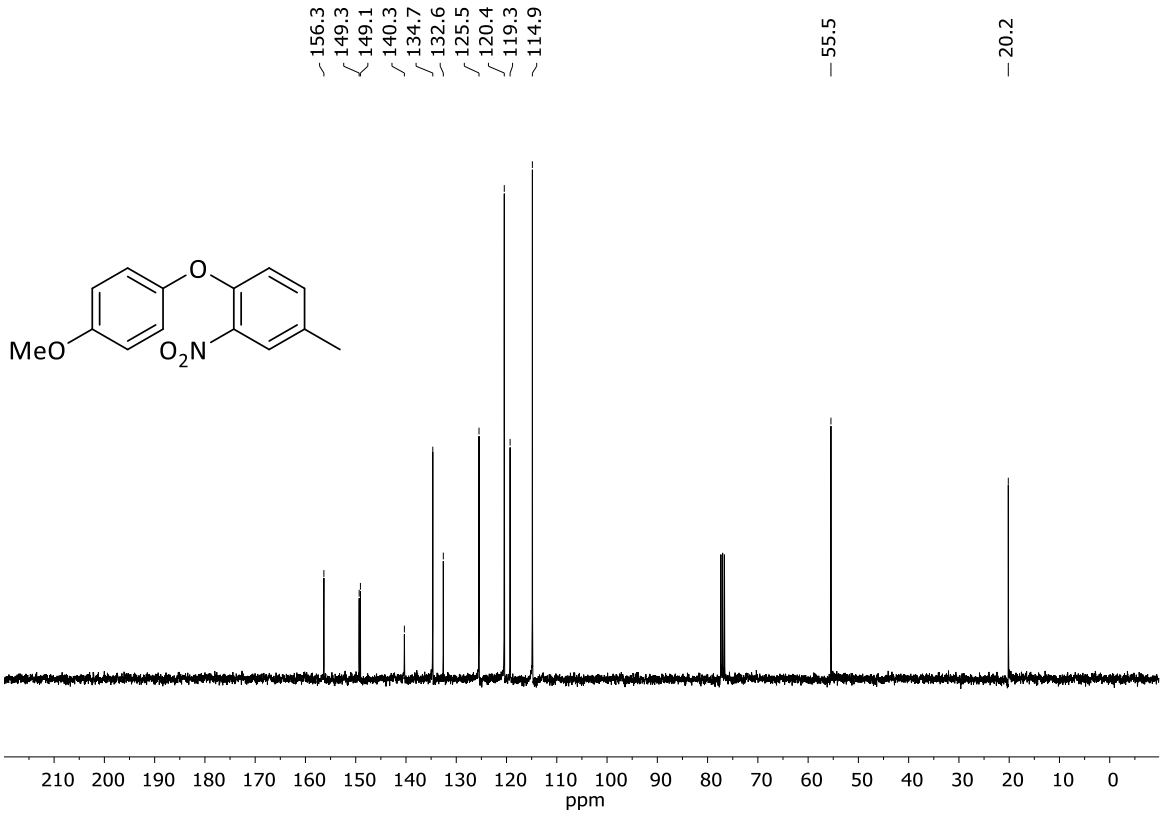


*Figure S17: 90 MHz ^{13}C-NMR spectrum of compound **S6** in $CDCl_3$.*

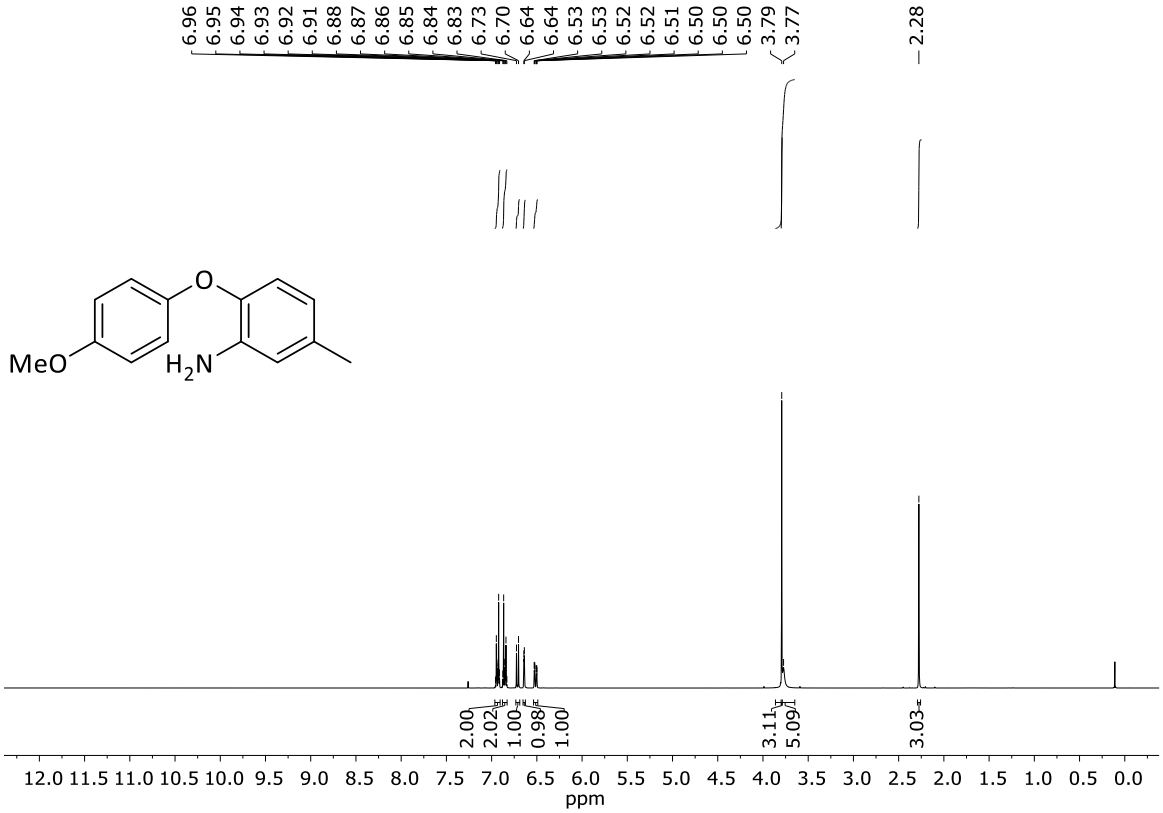


*Figure S18: 360 MHz ^{1}H-NMR spectrum of compound **S7** in $CDCl_3$.*

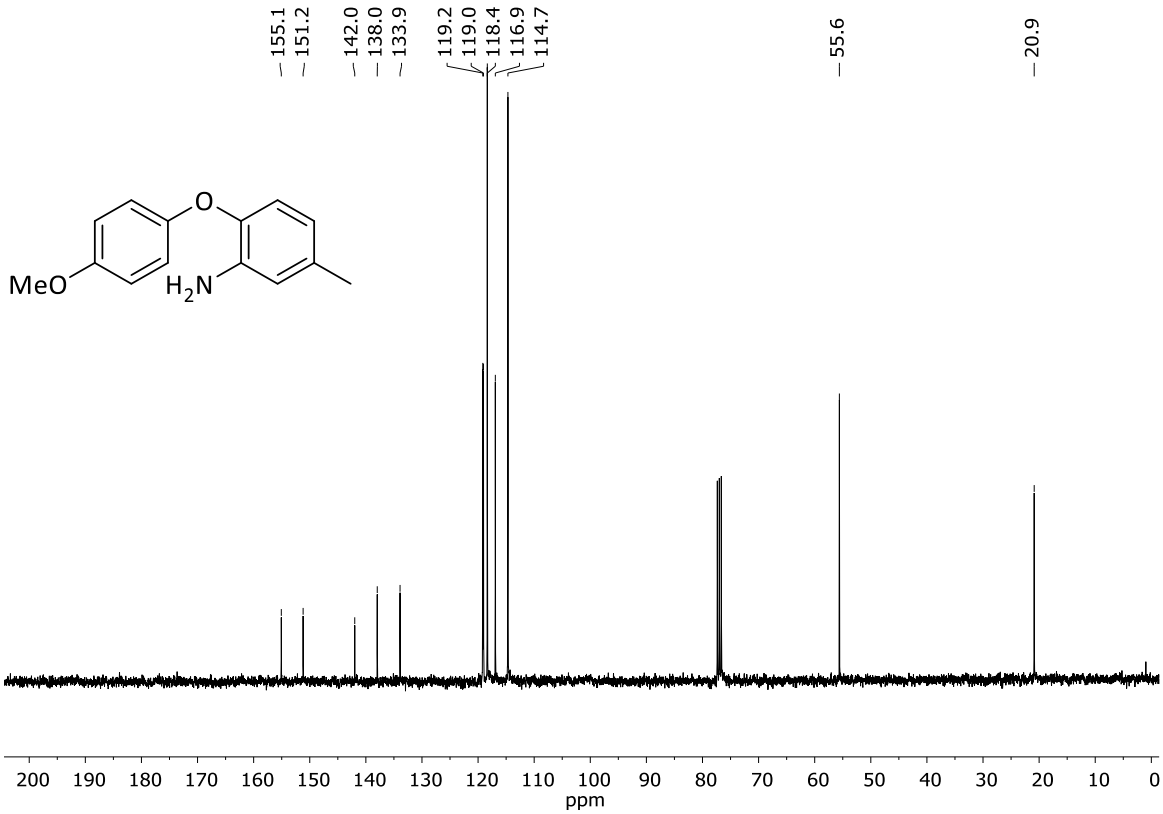


*Figure S19: 90 MHz ^{13}C-NMR spectrum of compound **S7** in $CDCl_3$.*

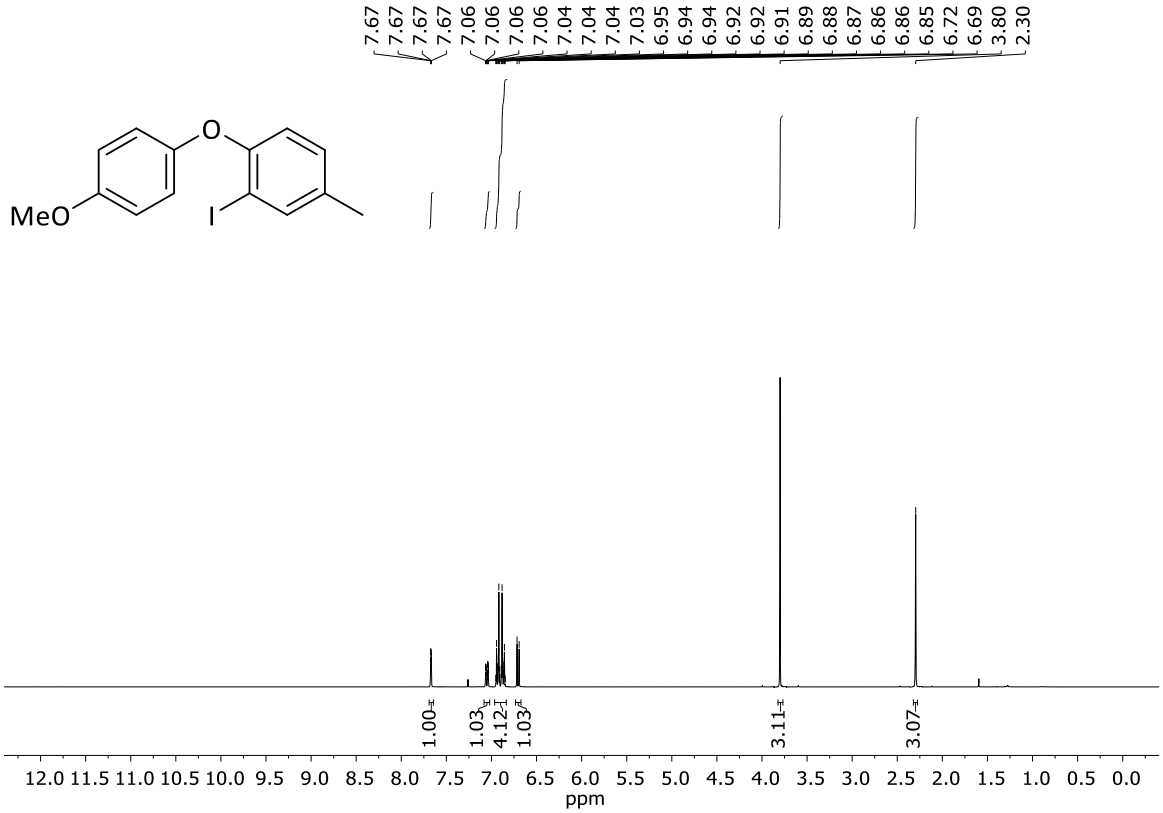


*Figure S20: 360 MHz ^{1}H-NMR spectrum of compound **S8** in $CDCl_3$.*

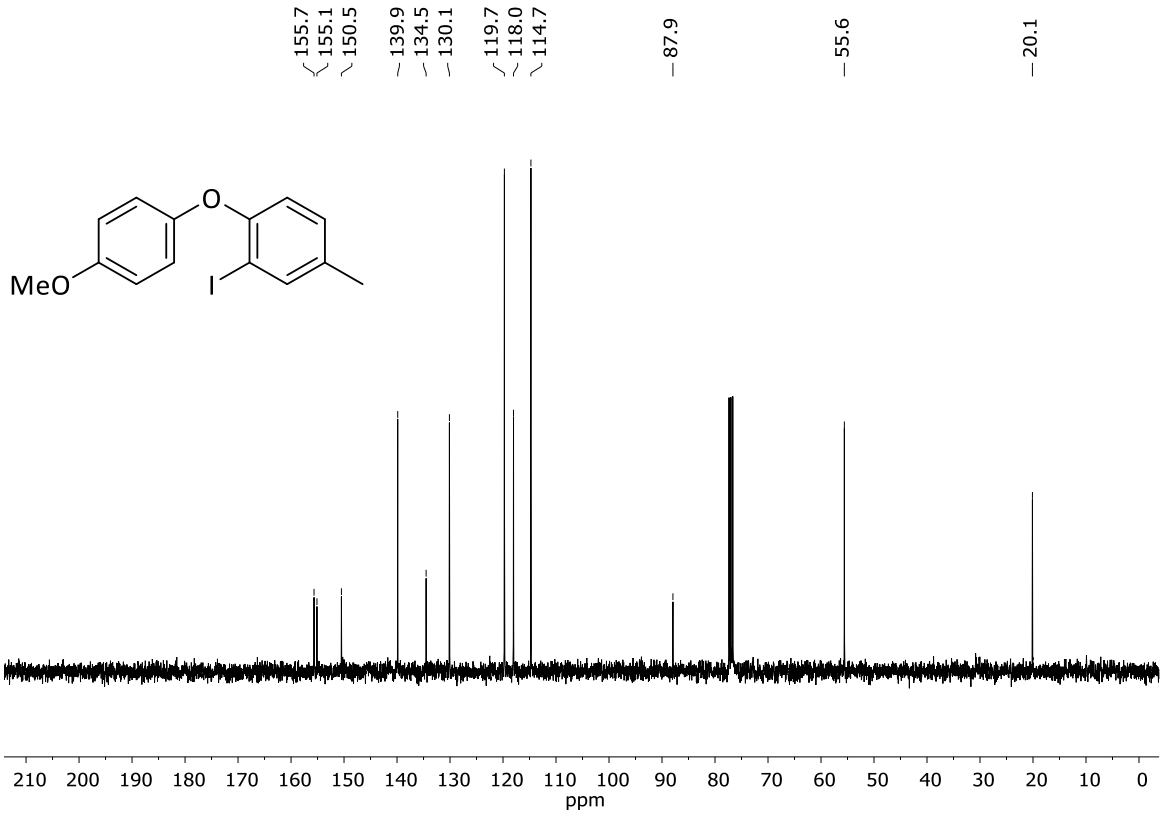


*Figure S21: 90 MHz ^{13}C-NMR spectrum of compound **S8** in $CDCl_3$.*

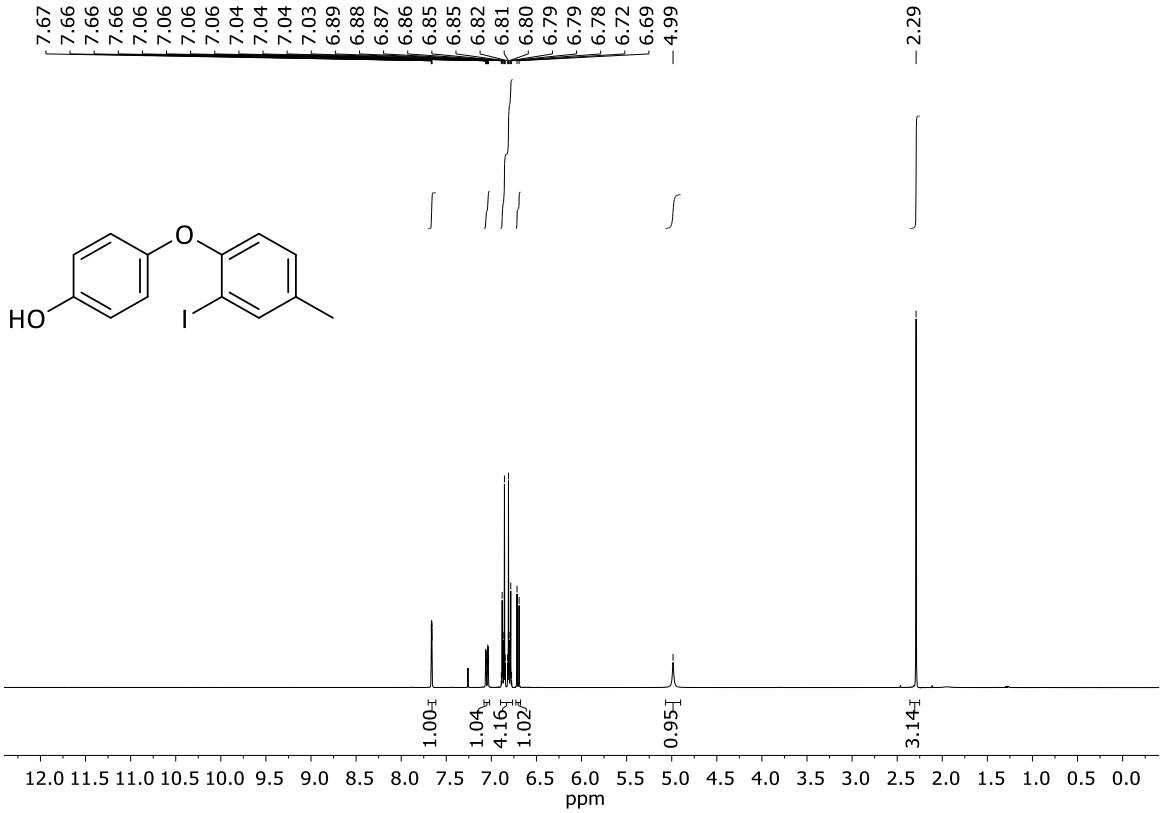


*Figure S22: 360 MHz ^{1}H-NMR spectrum of compound **S9** in $CDCl_3$.*

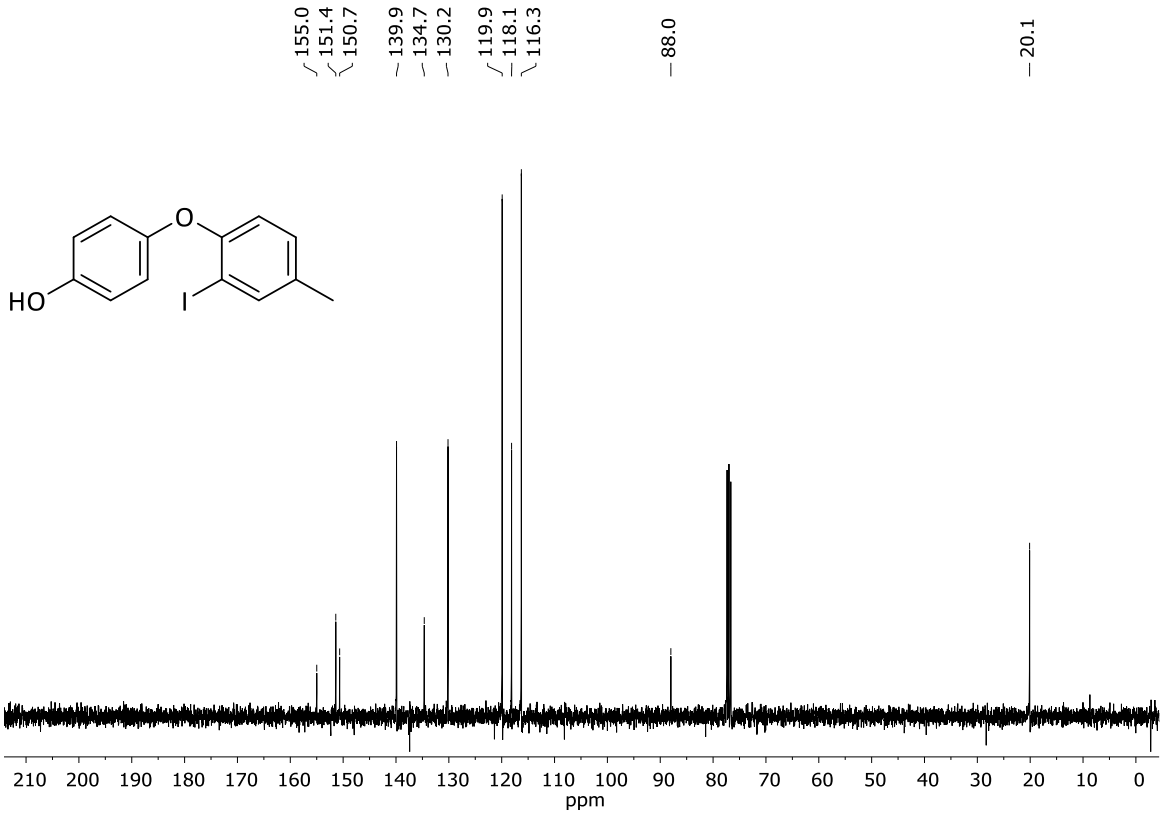


*Figure S23: 90 MHz ^{13}C-NMR spectrum of compound **S9** in $CDCl_3$.*

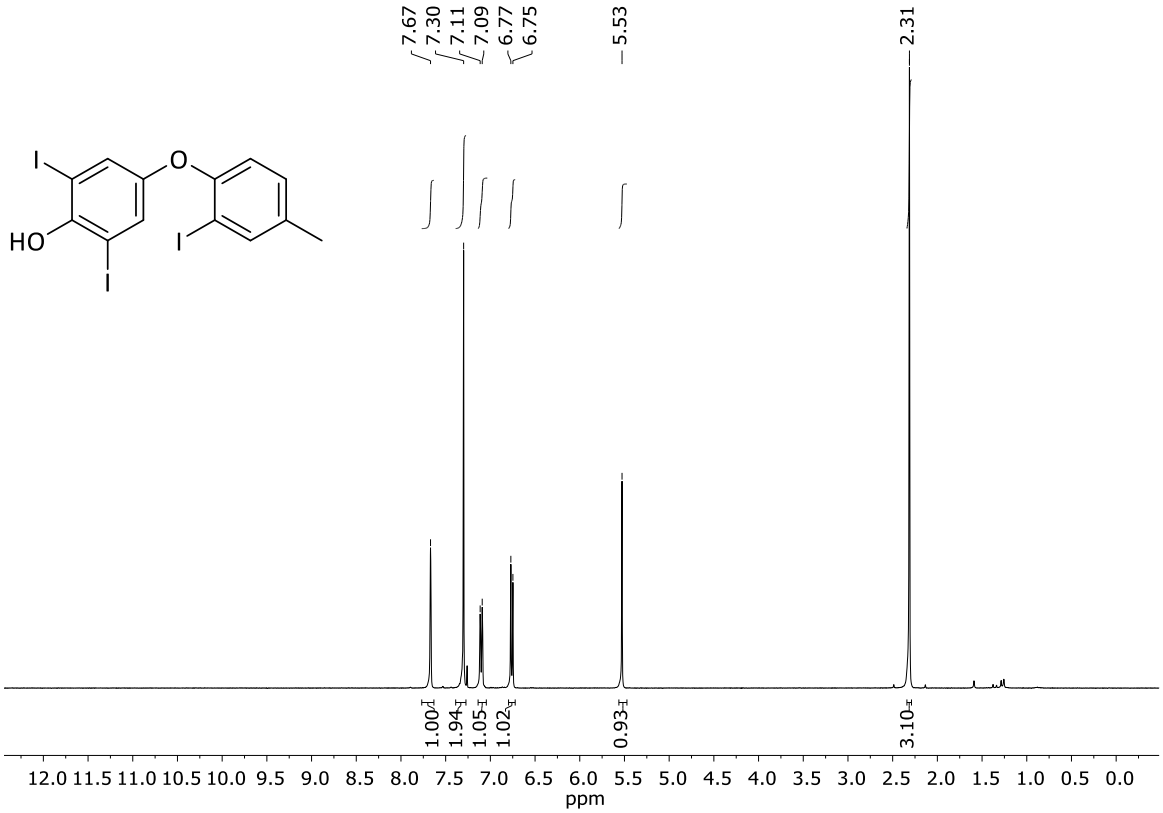


*Figure S24: 360 MHz ^{1}H-NMR spectrum of compound **S10** in $CDCl_3$.*

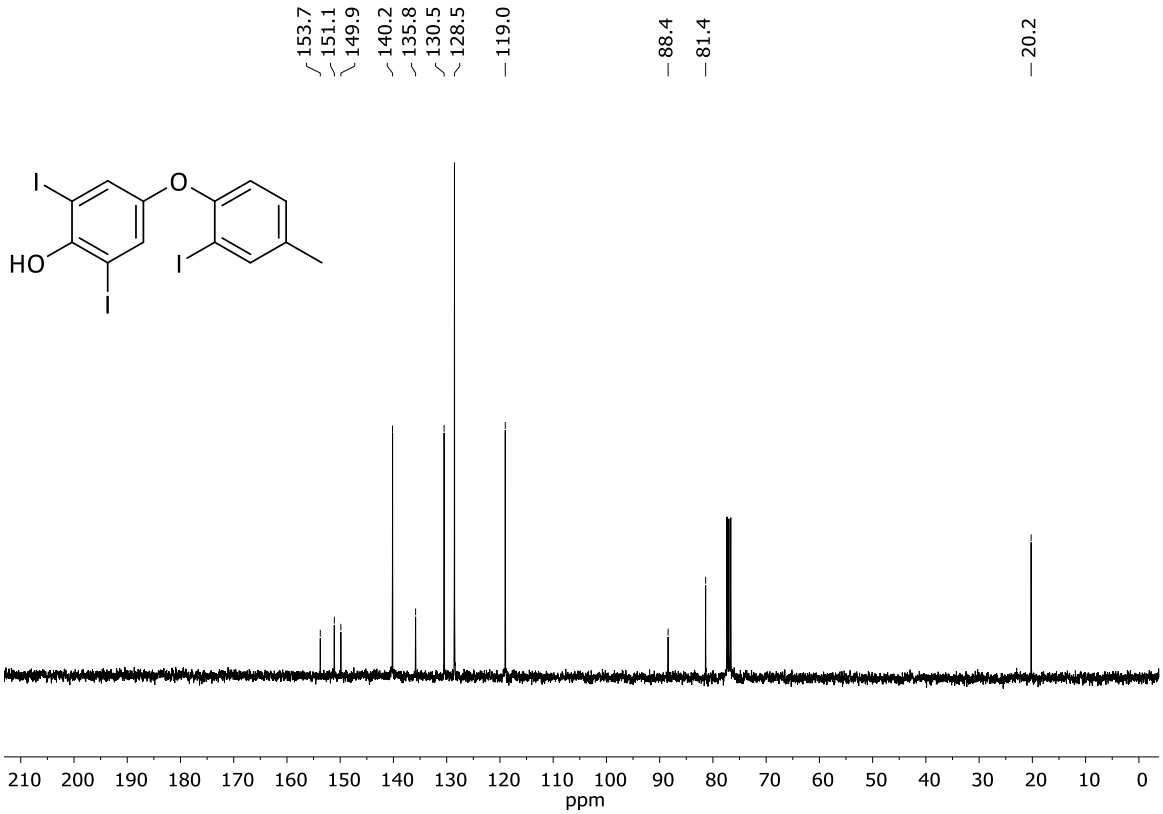


*Figure S25: 90 MHz ^{13}C-NMR spectrum of compound **S10** in $CDCl_3$.*

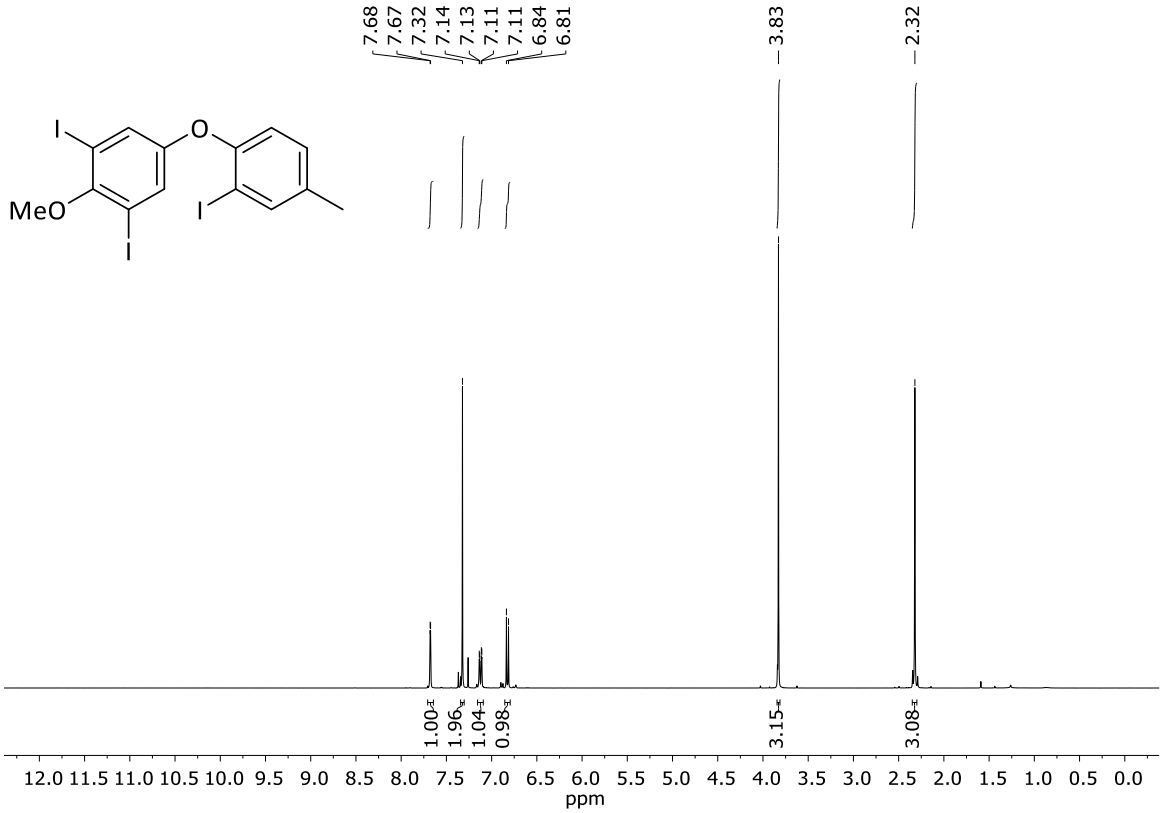


*Figure S26: 360 MHz ^{1}H-NMR spectrum of compound **2c** in $CDCl_3$.*

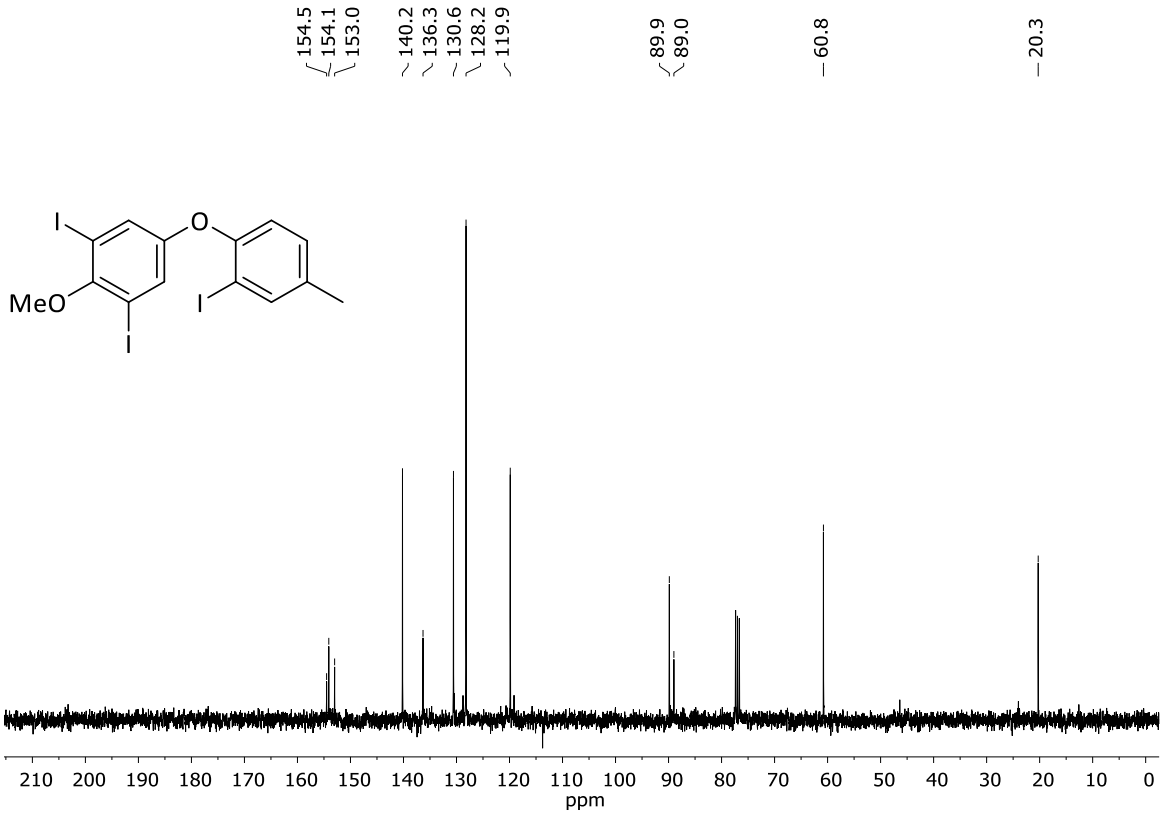


*Figure S27: 90 MHz ^{13}C-NMR spectrum of compound **2c** in $CDCl_3$.*

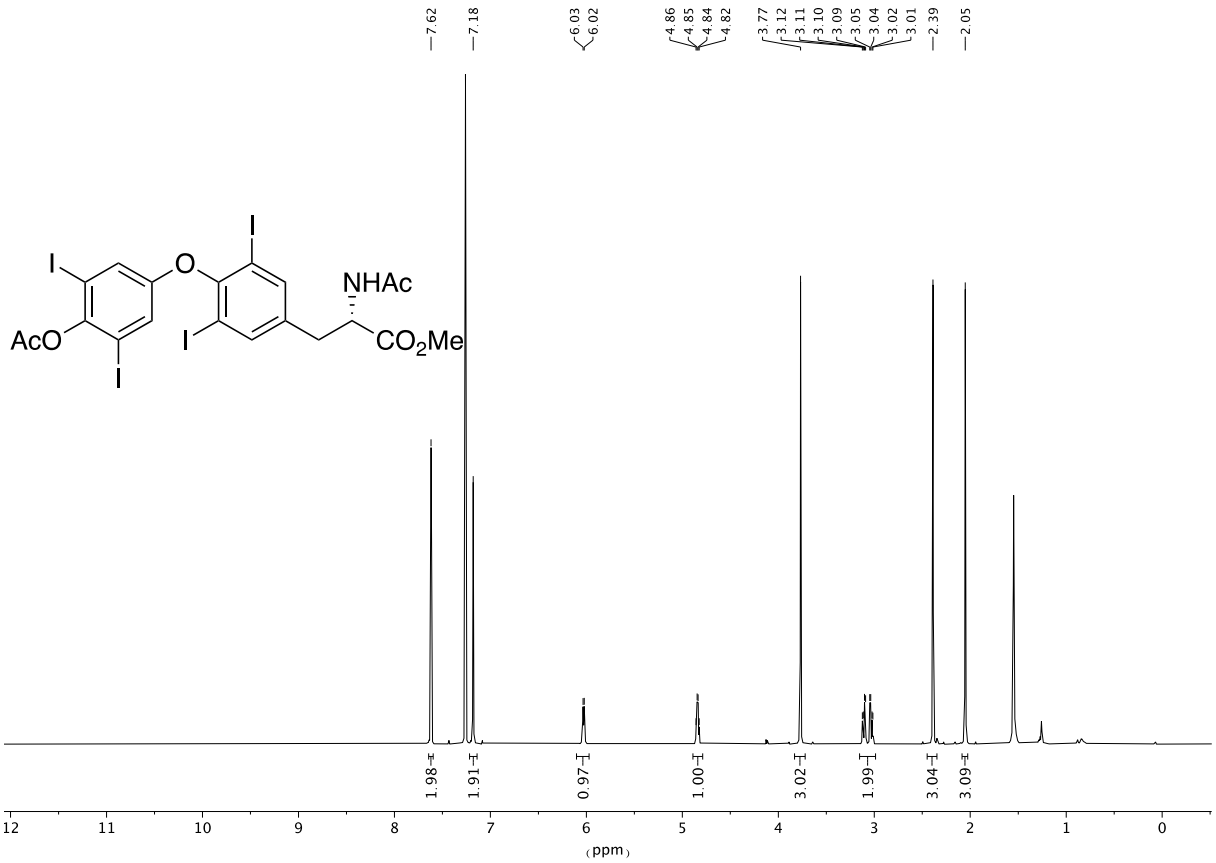


*Figure S28: 600 MHz [1]H-NMR spectrum of compound **Ac-Thx(Ac)-OMe** in $CDCl_3$.*

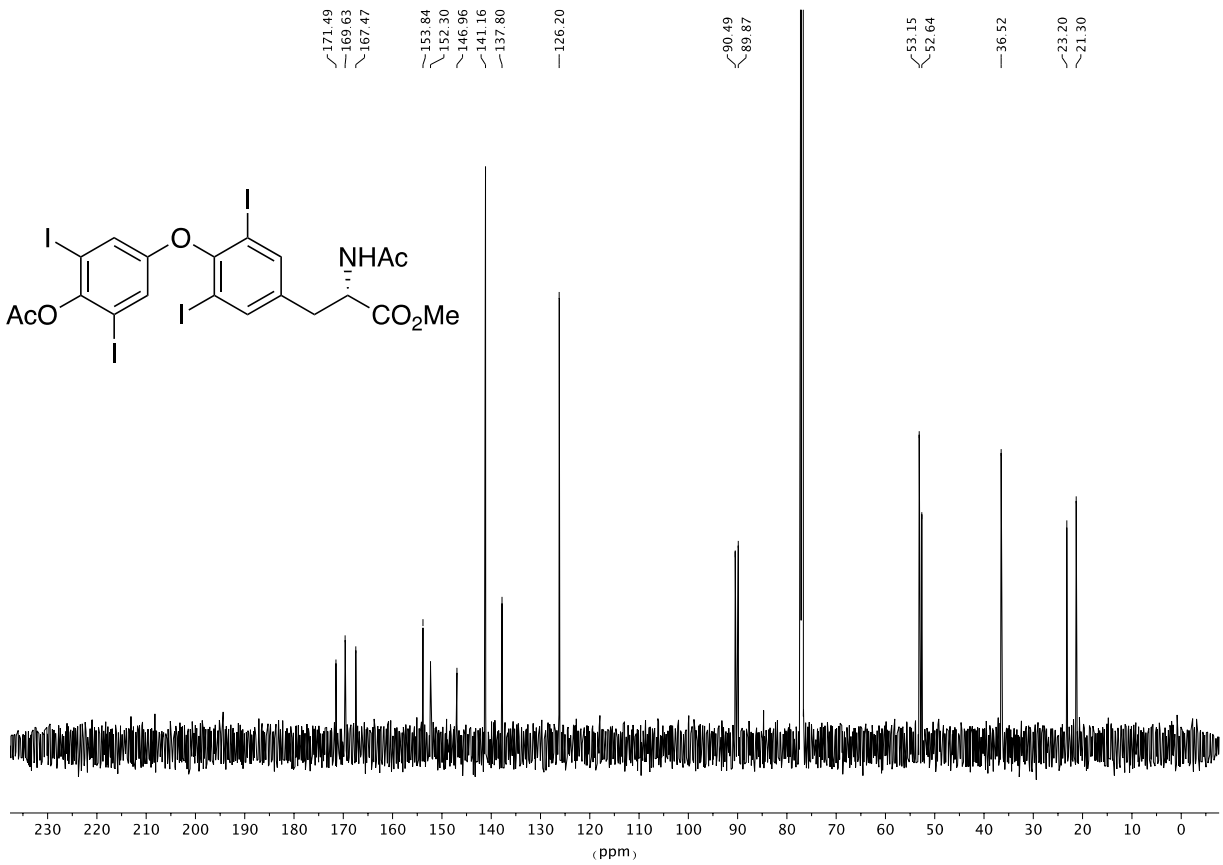


*Figure S29: 151 MHz [13]C-NMR spectrum of compound **Ac-Thx(Ac)-OMe** in $CDCl_3$.*

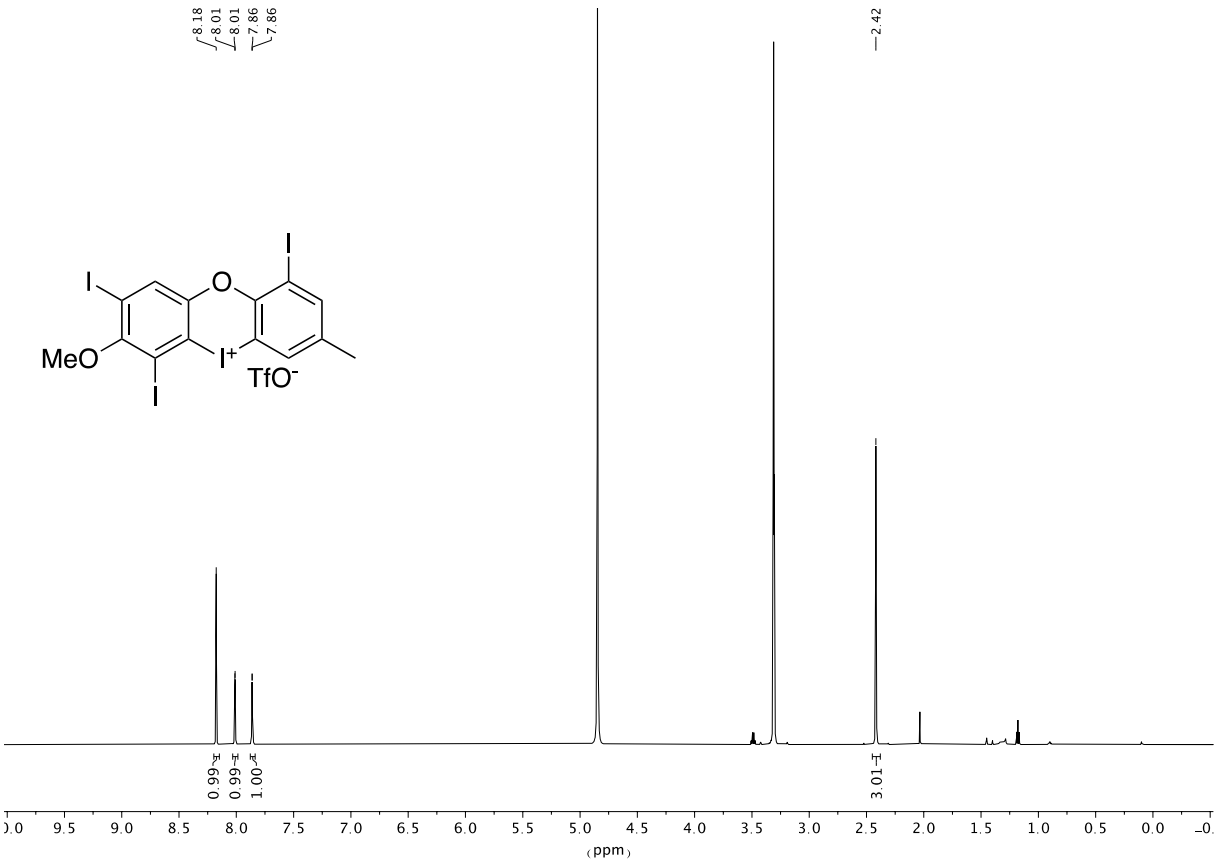


*Figure S30: 600 MHz [1]H-NMR spectrum of compound **3a** in DMSO-d_6.*

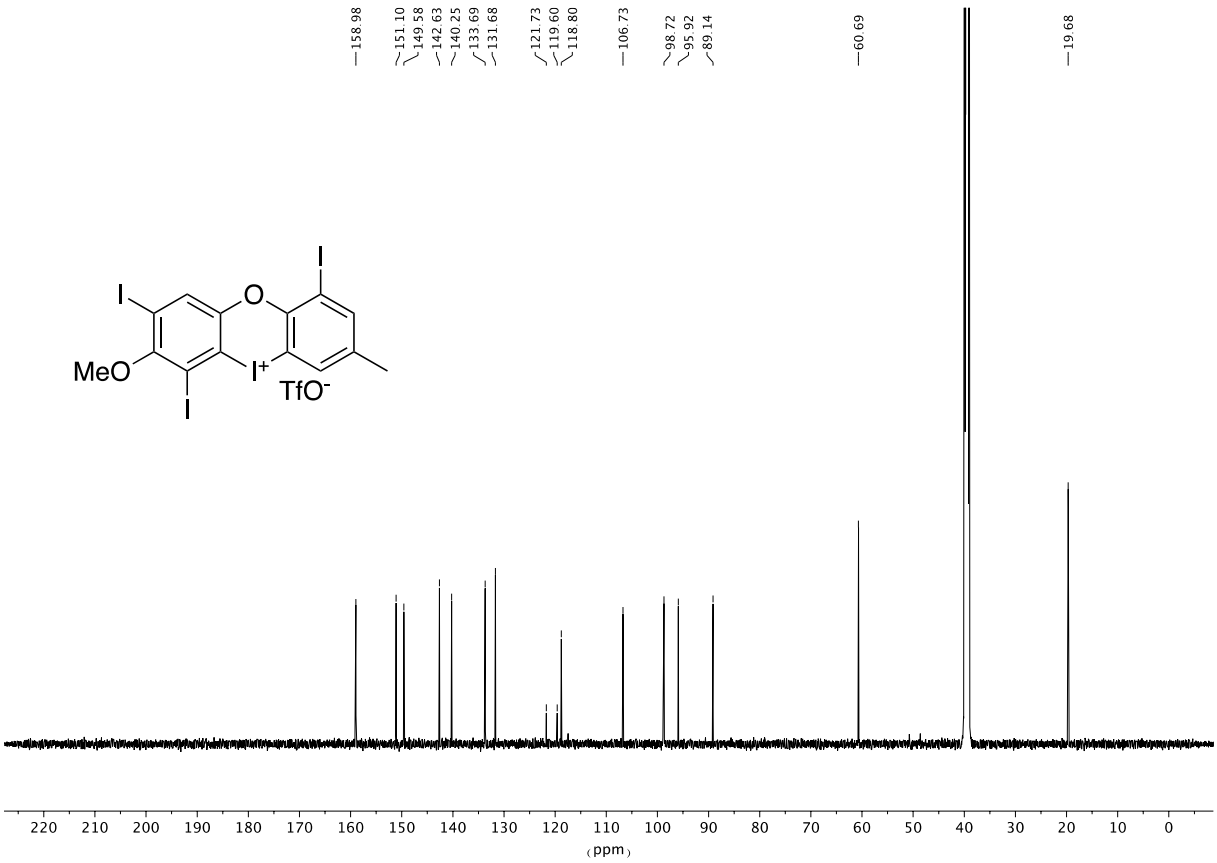


*Figure S31: 151 MHz [13]C-NMR spectrum of compound **3a** in DMSO-d_6.*

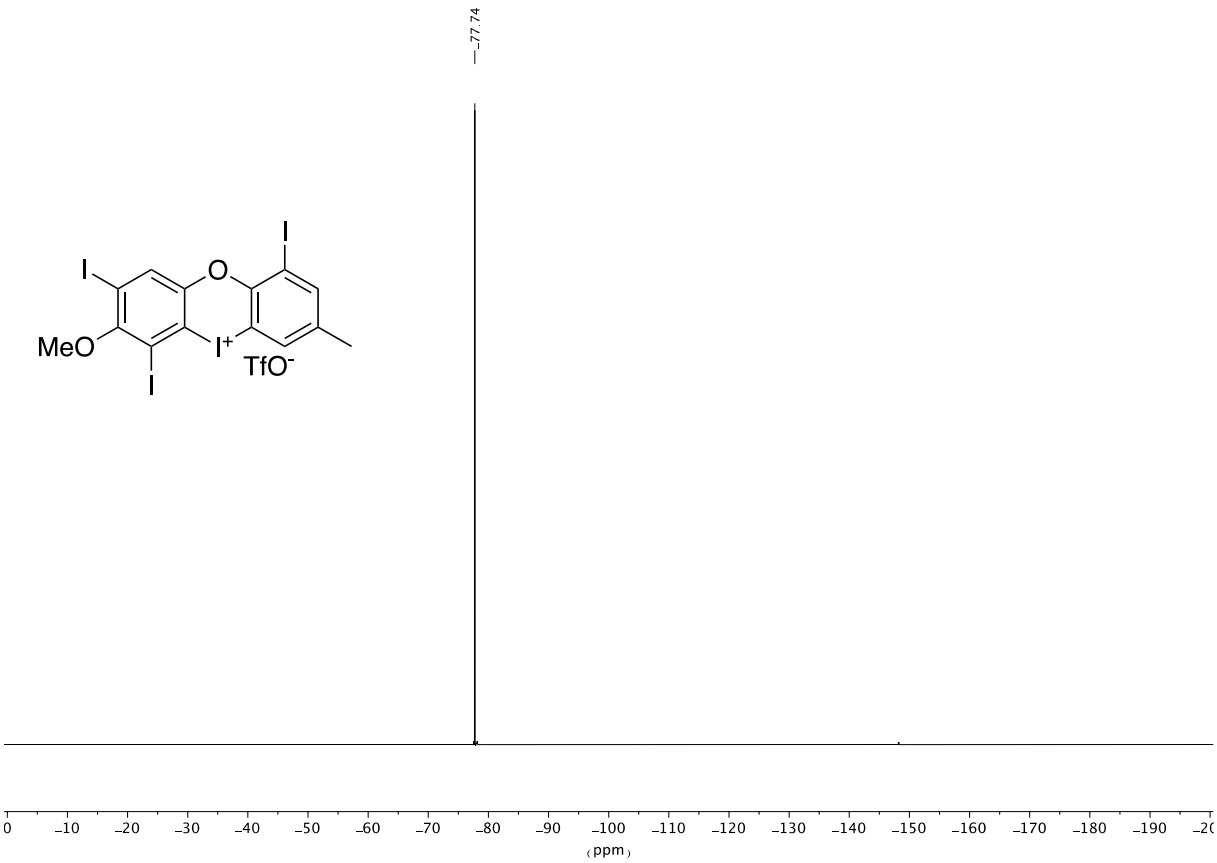


*Figure S32: 565 MHz ^{19}F-NMR spectrum of compound **3a** in DMSO-d_6.*

*Figure S33: 600 MHz [1]H-NMR spectrum of compound **3c** in DMSO-d_6.*

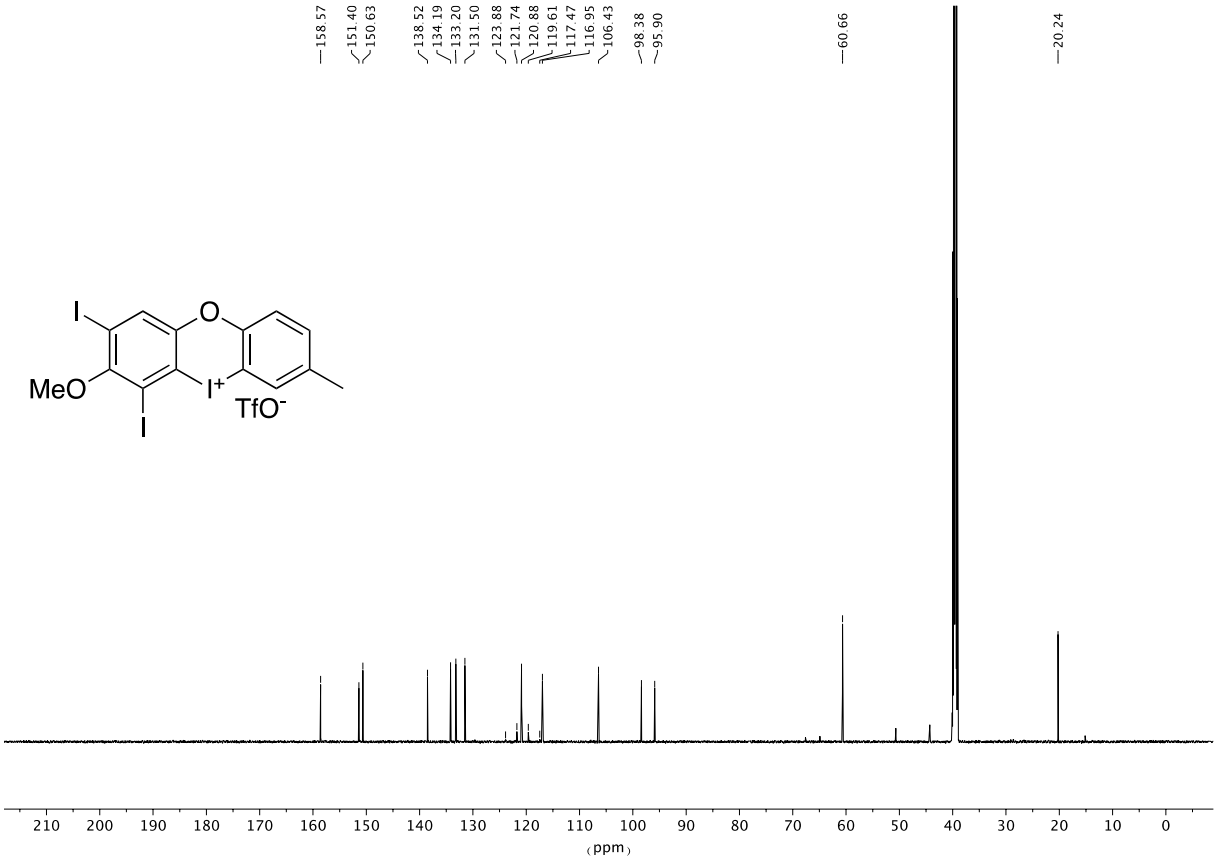


*Figure S34: 151 MHz [13]C-NMR spectrum of compound **3c** in DMSO-d_6.*

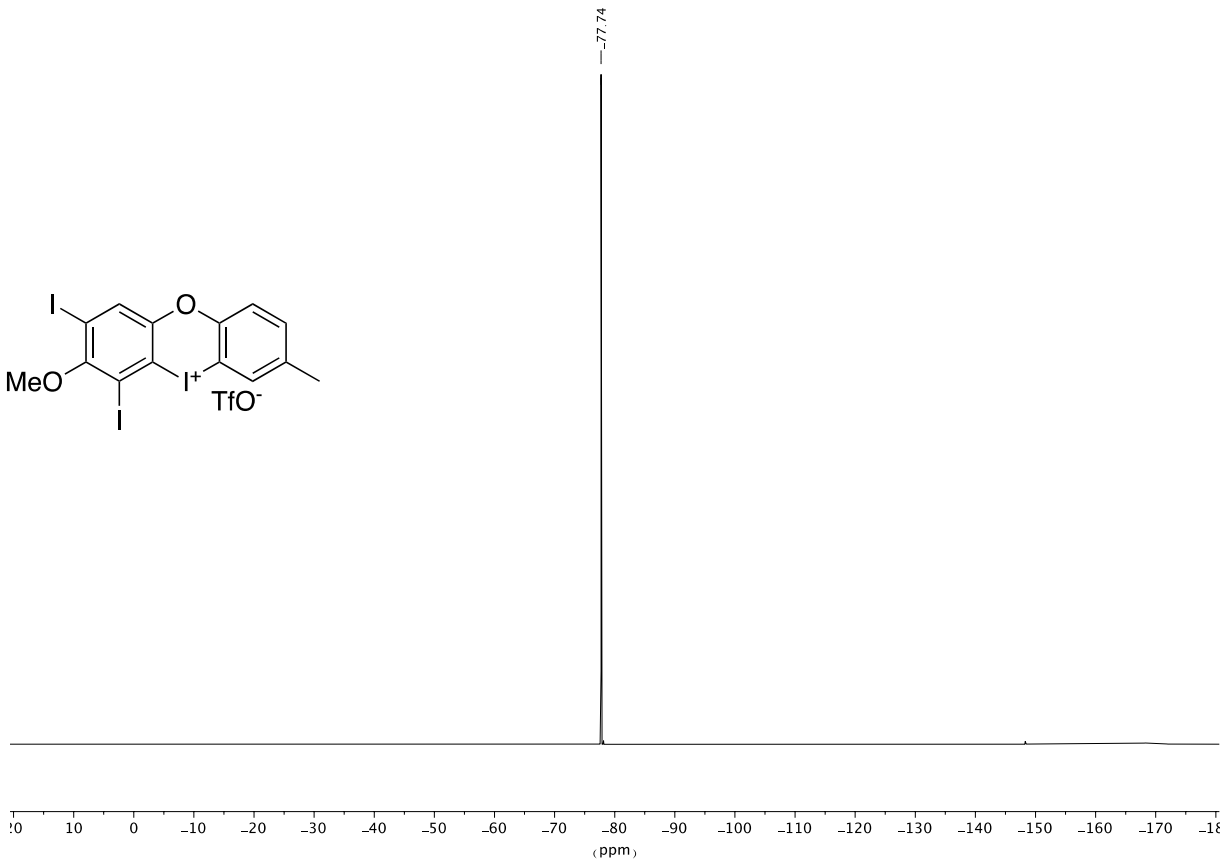


*Figure S35: 565 MHz ^{19}F-NMR spectrum of compound **3c** in DMSO-d_6.*

*Figure S36: 601 MHz ^{1}H-NMR spectrum of compound **4a** in DMSO-d_6.*

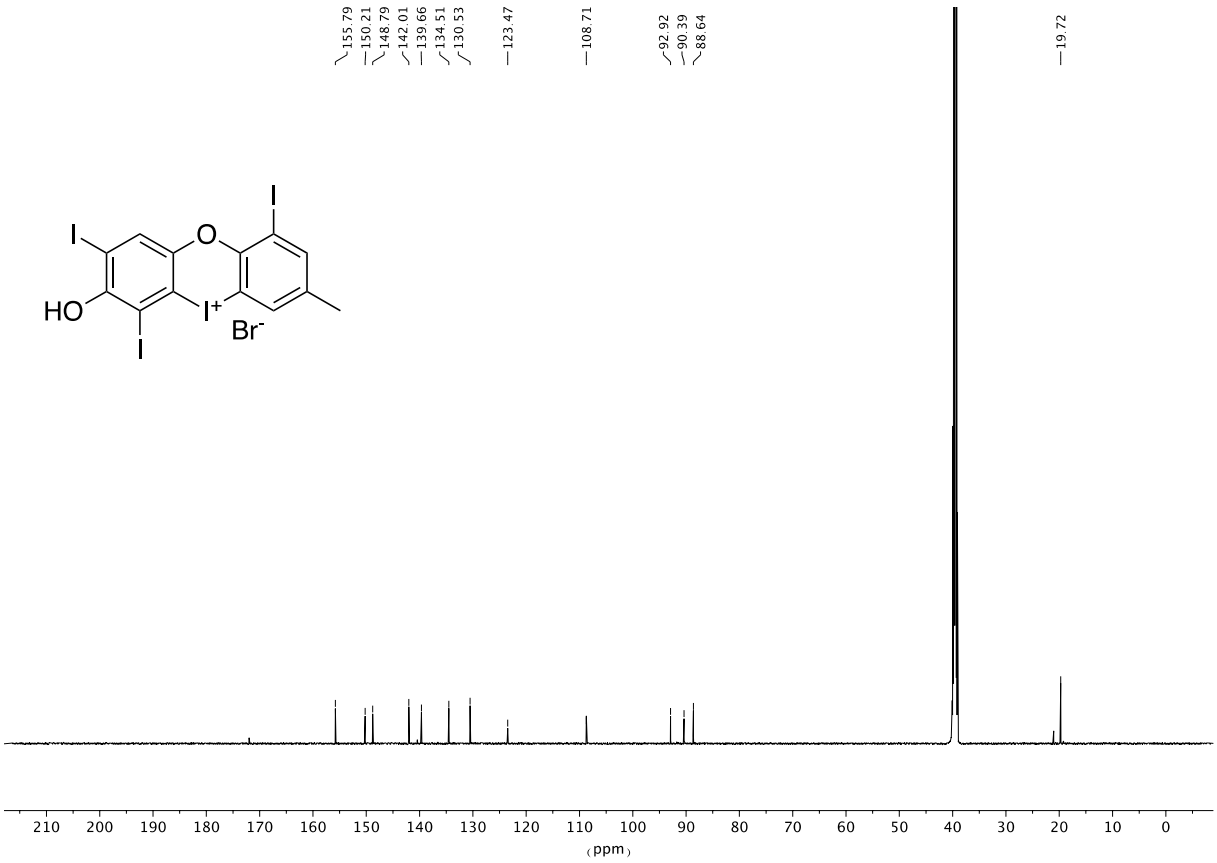


*Figure S37: 151 MHz ^{13}C-NMR spectrum of compound **4a** in DMSO-d_6.*

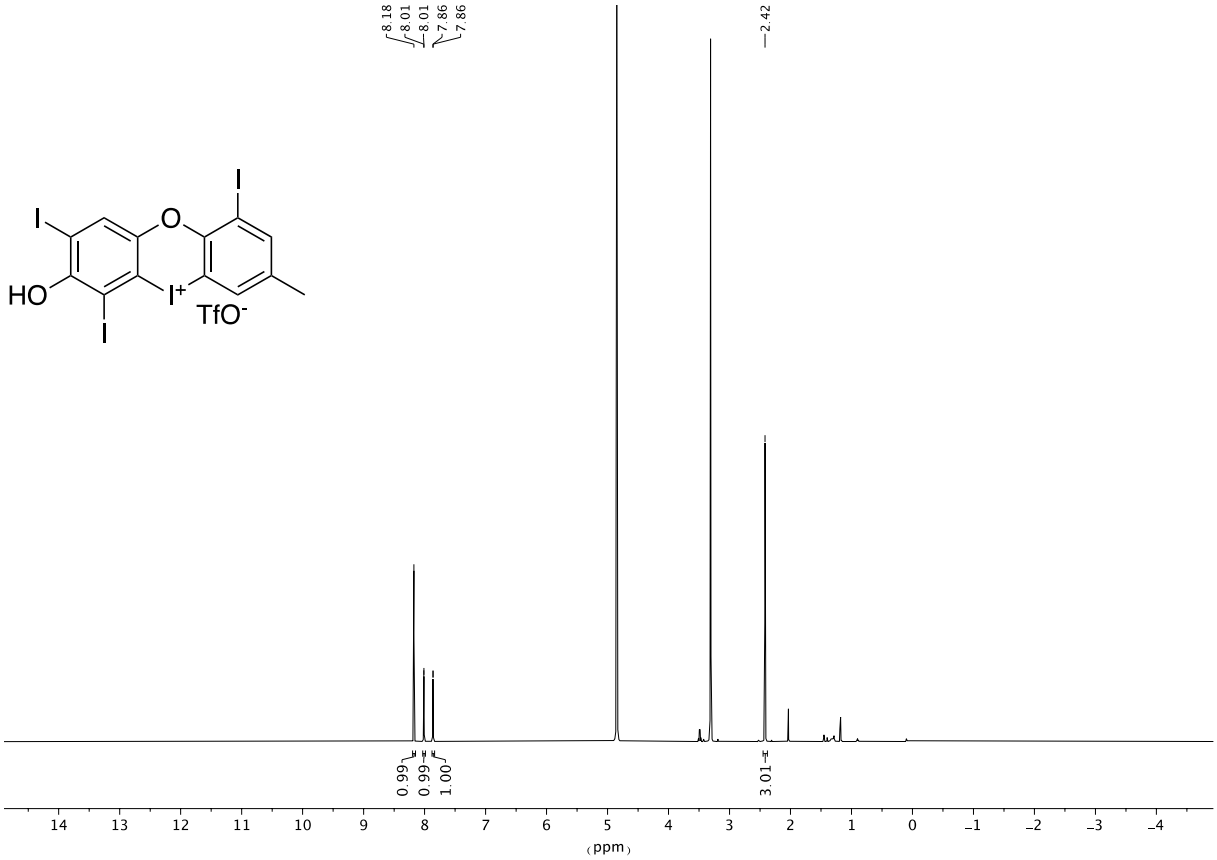


*Figure S38: 600 MHz ^{1}H-NMR spectrum of compound **4b** in CD_3OD.*

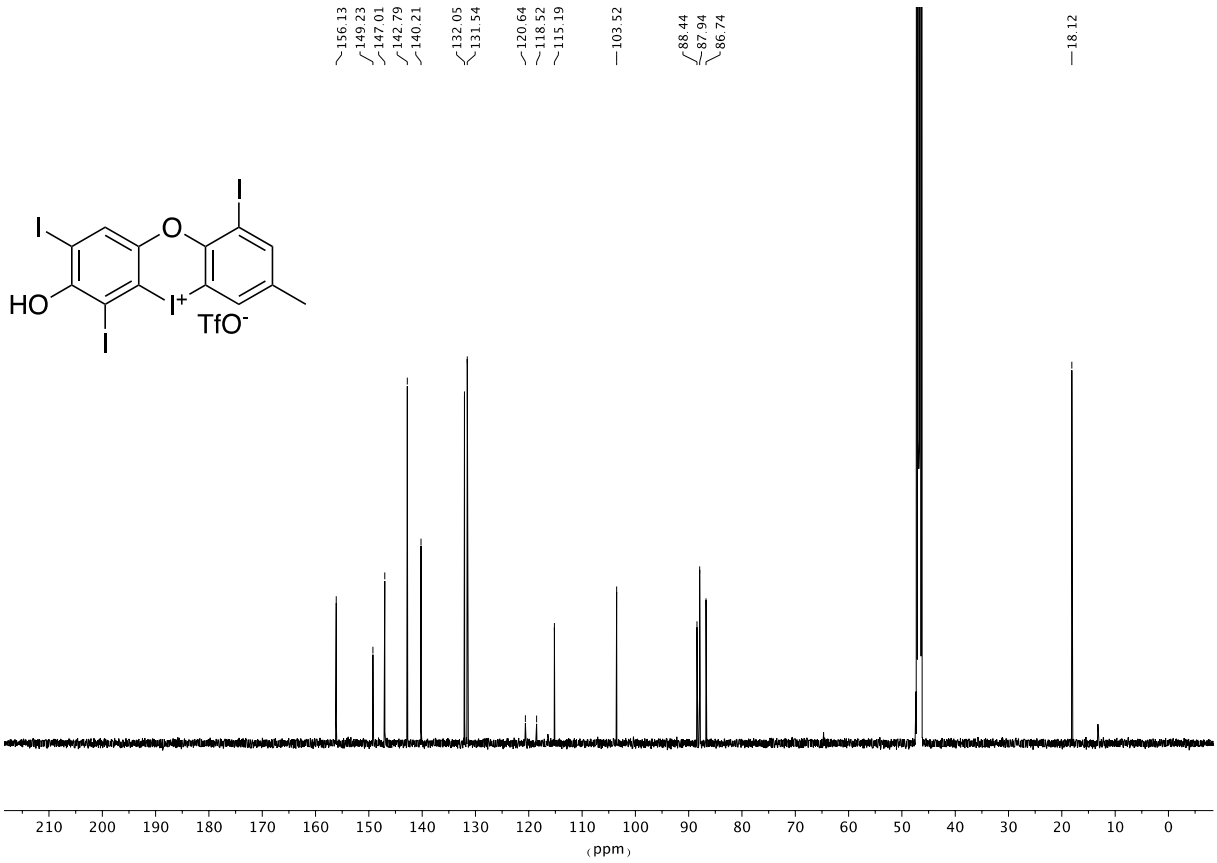


*Figure S39: 151 MHz ^{13}C-NMR spectrum of compound **4b** in CD_3OD.*

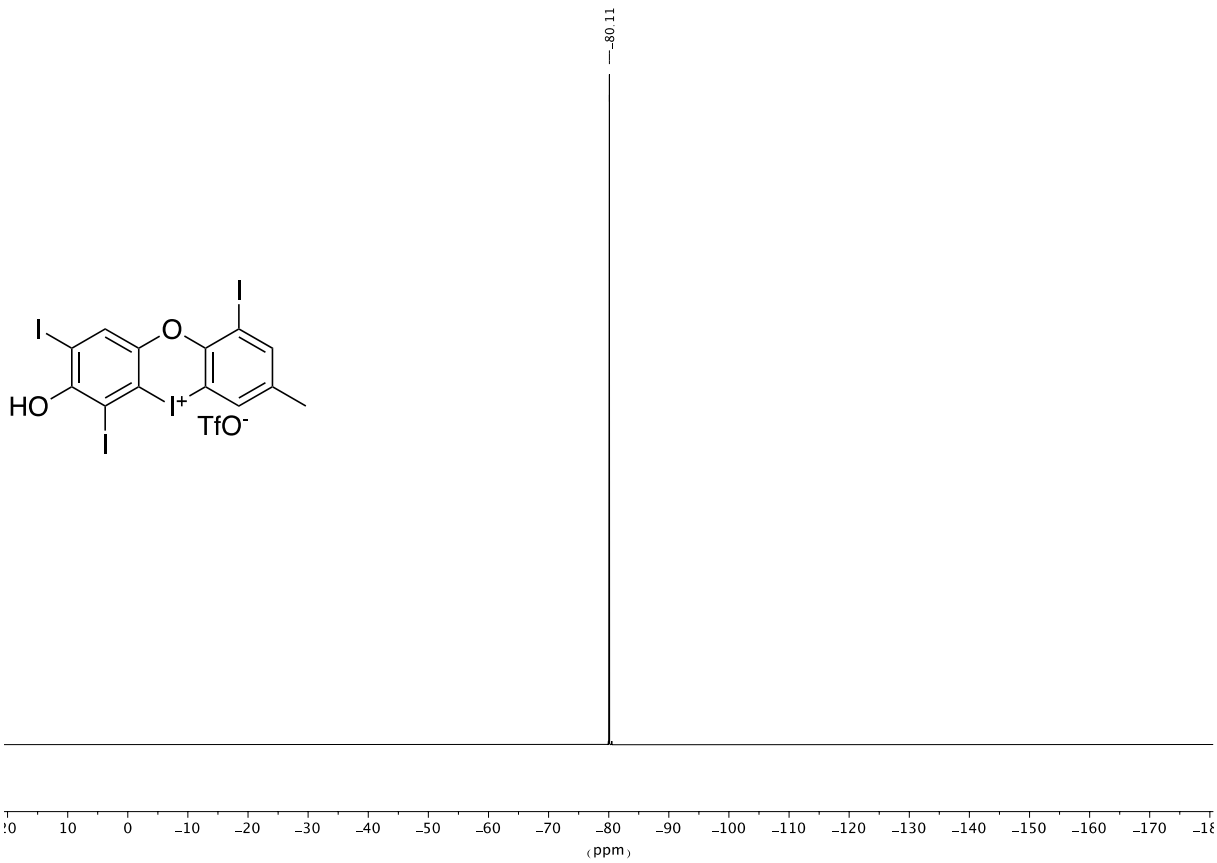


*Figure S40: 565 MHz ^{19}F-NMR spectrum of compound **4b** in CD_3OD.*

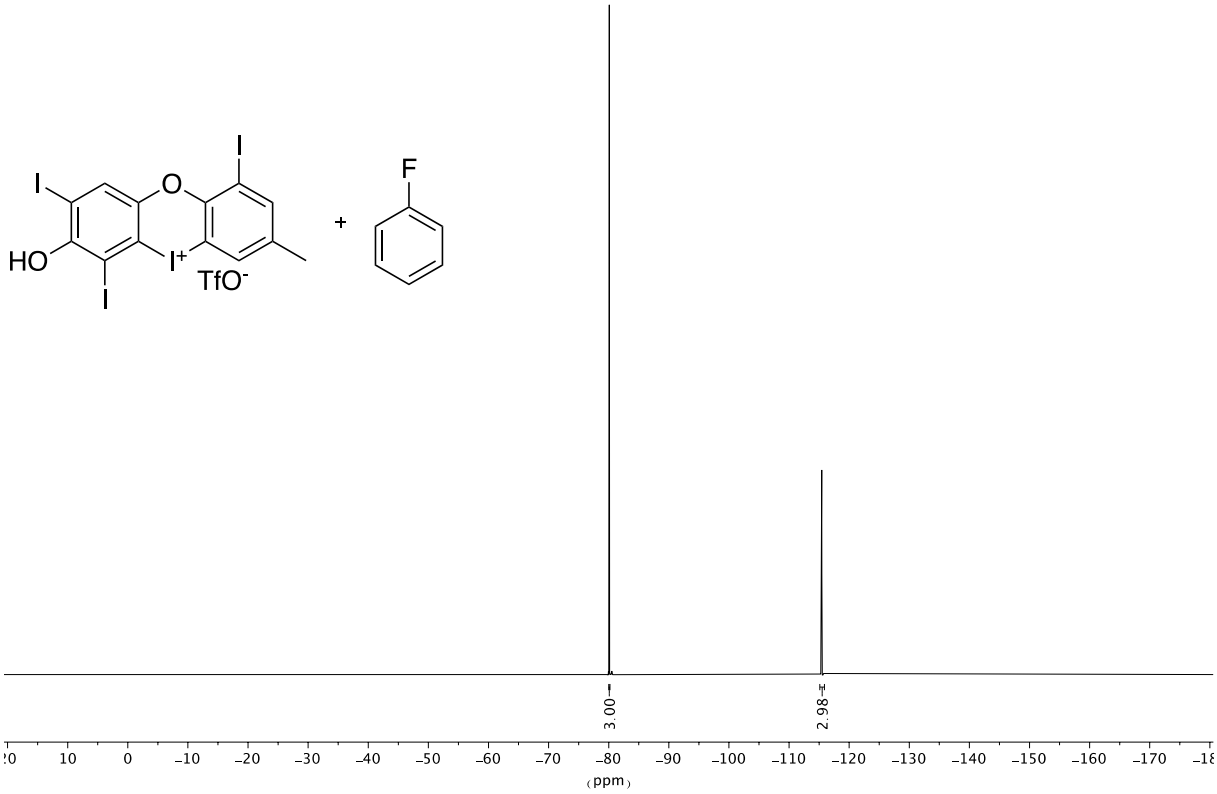


*Figure S41: 565 MHz ^{19}F-NMR spectrum of compound **4b + 3 eq. of PhF** in CD_3OD.*

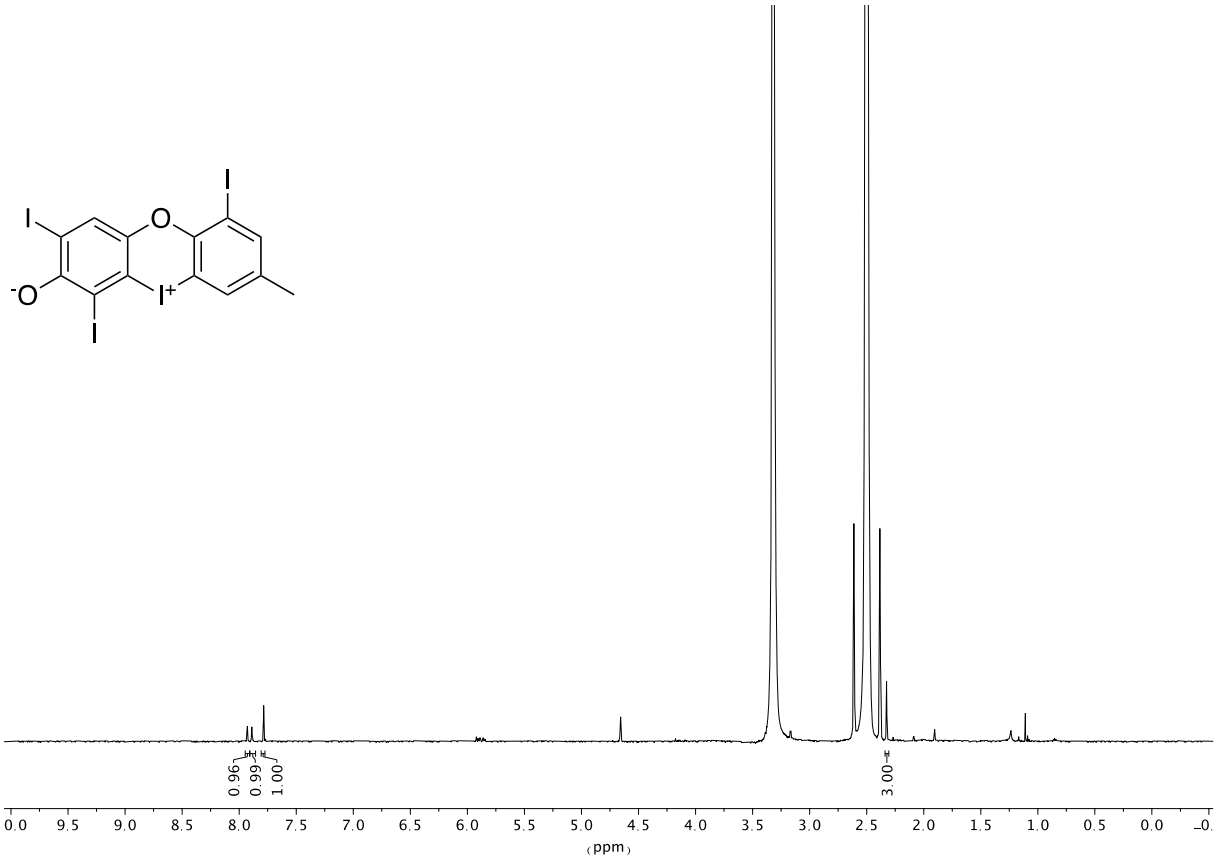


*Figure S42: 600 MHz ^{1}H-NMR spectrum of compound **5** in DMSO-d_6.*

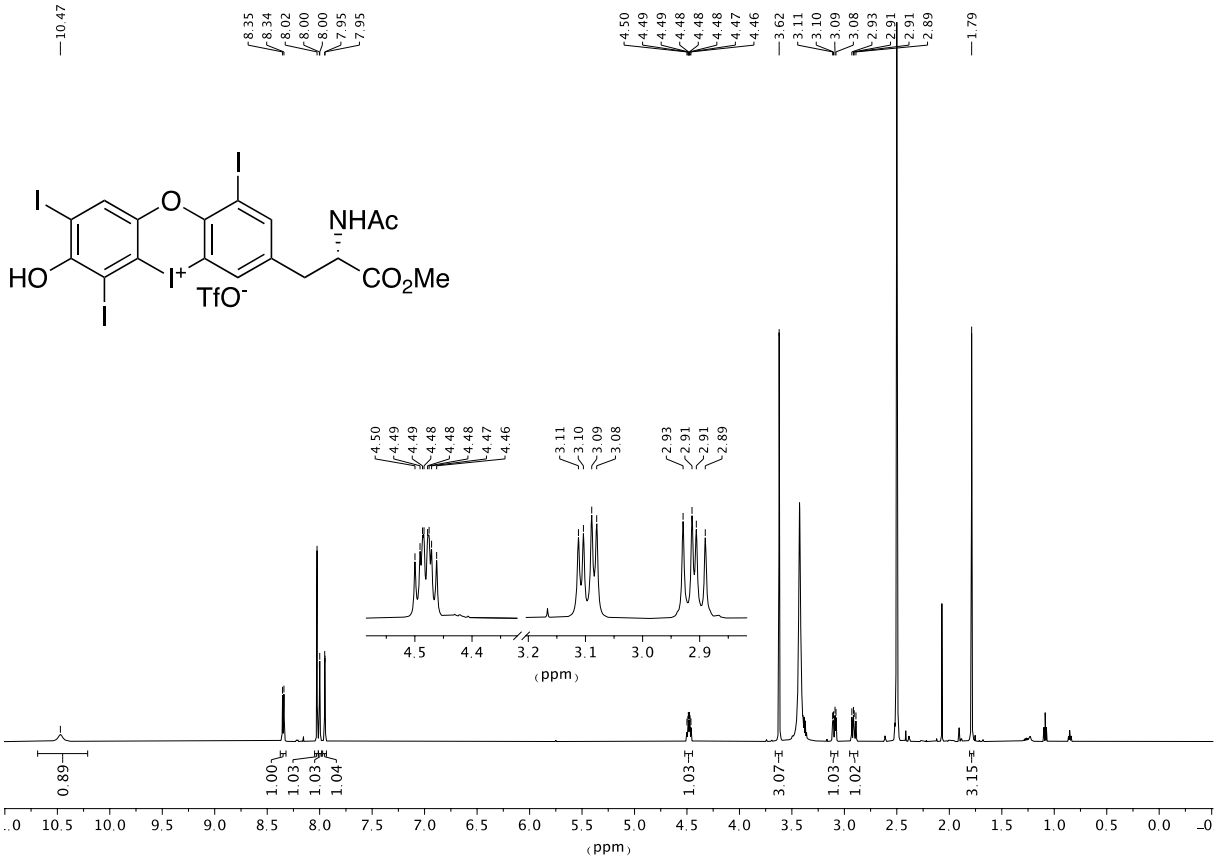


*Figure S43: 600 MHz [1]H-NMR spectrum of compound **6a** in DMSO-d_6.*

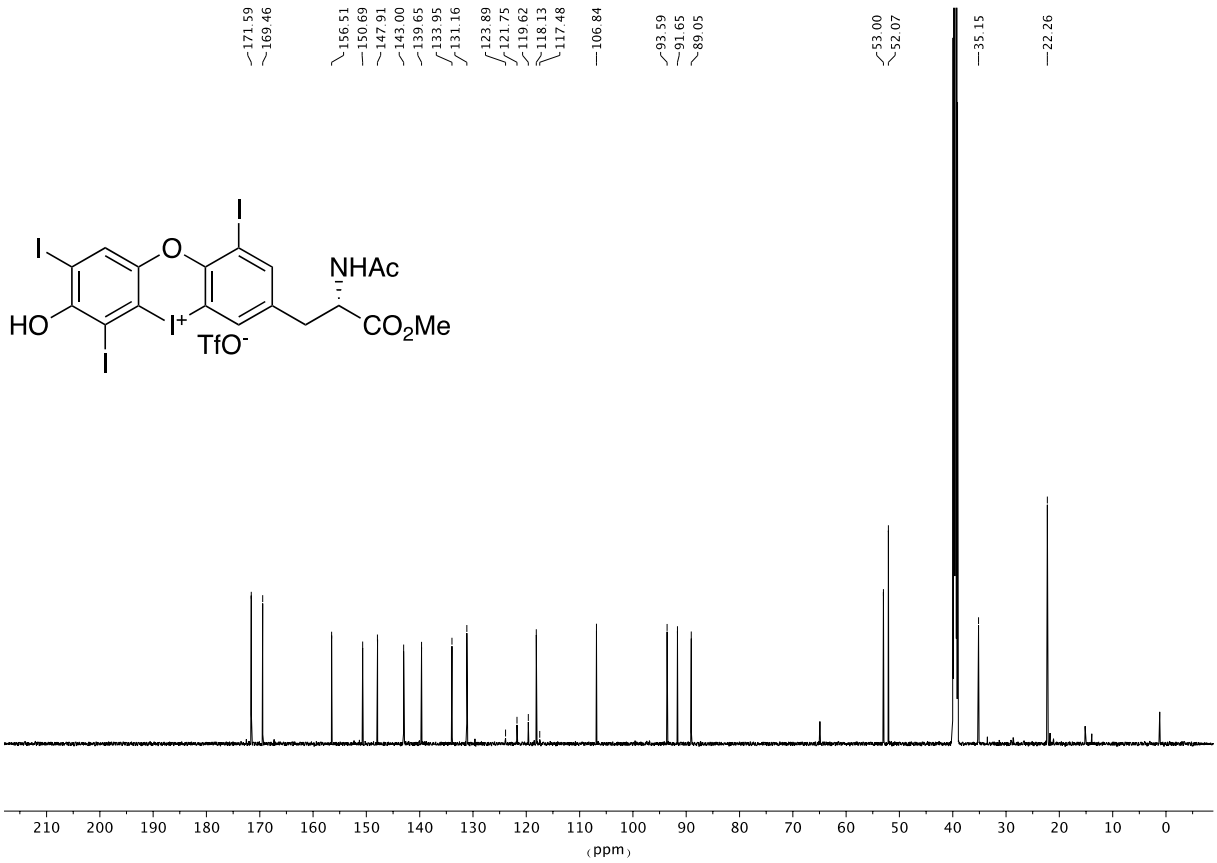


*Figure S44: 151 MHz [13]C-NMR spectrum of compound **6a** in DMSO-d_6.*

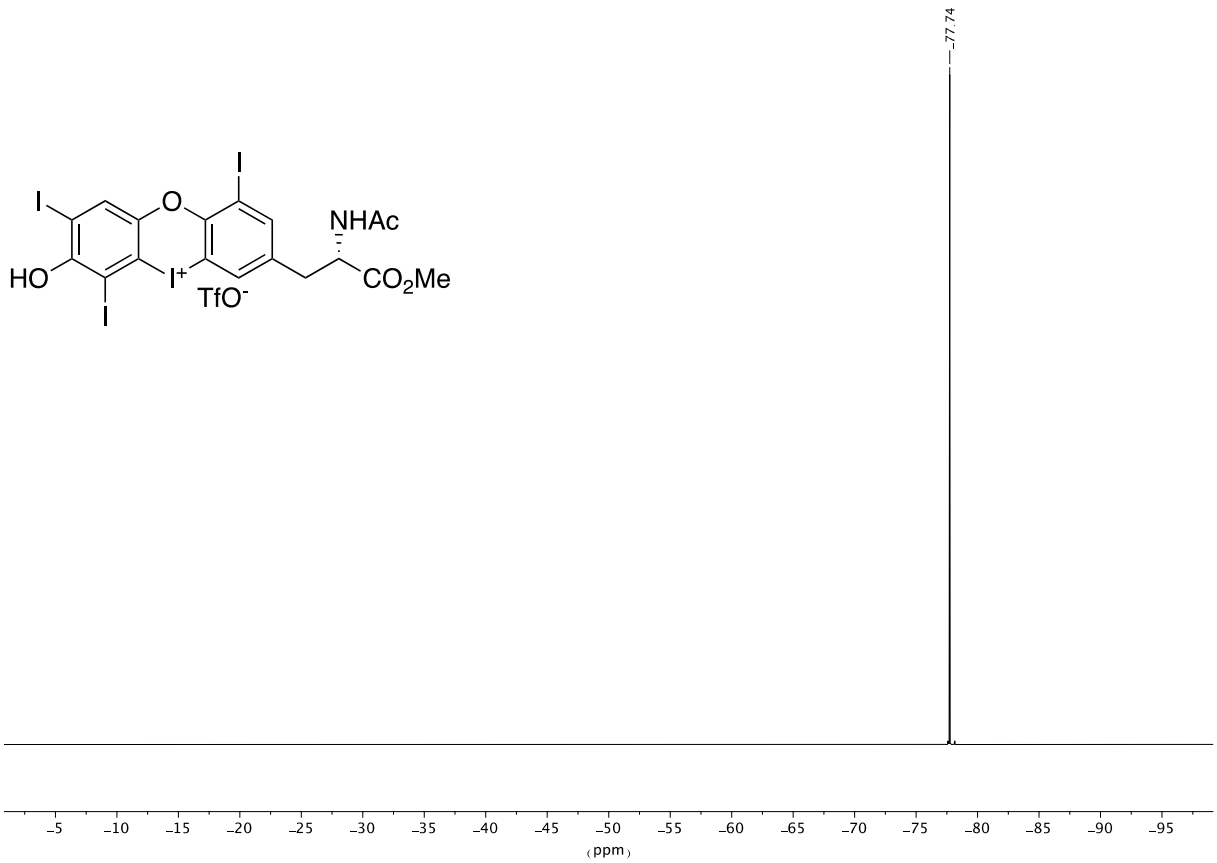


*Figure S45: 565 MHz ^{19}F-NMR spectrum of compound **6a** in DMSO-d_6.*

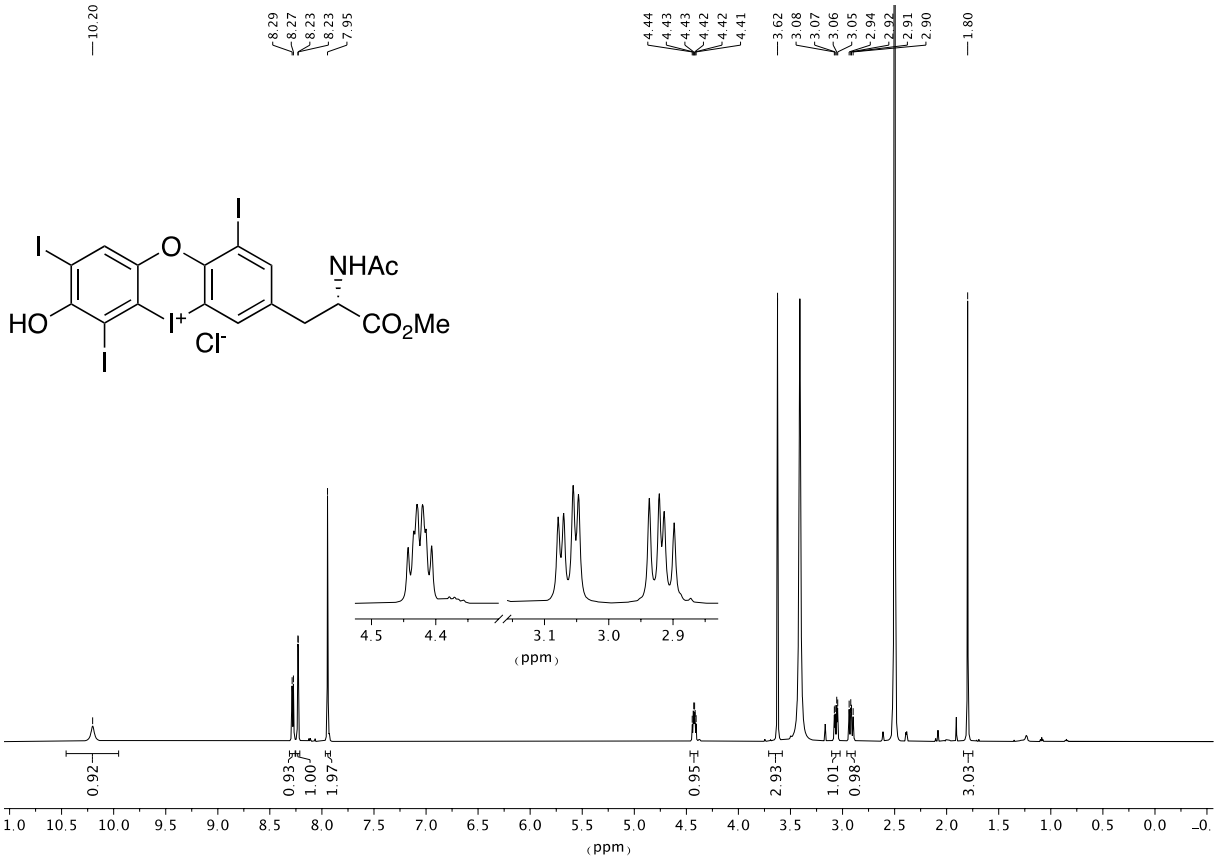


*Figure S46: 600 MHz [1]H-NMR spectrum of compound **6b** in DMSO-d_6.*

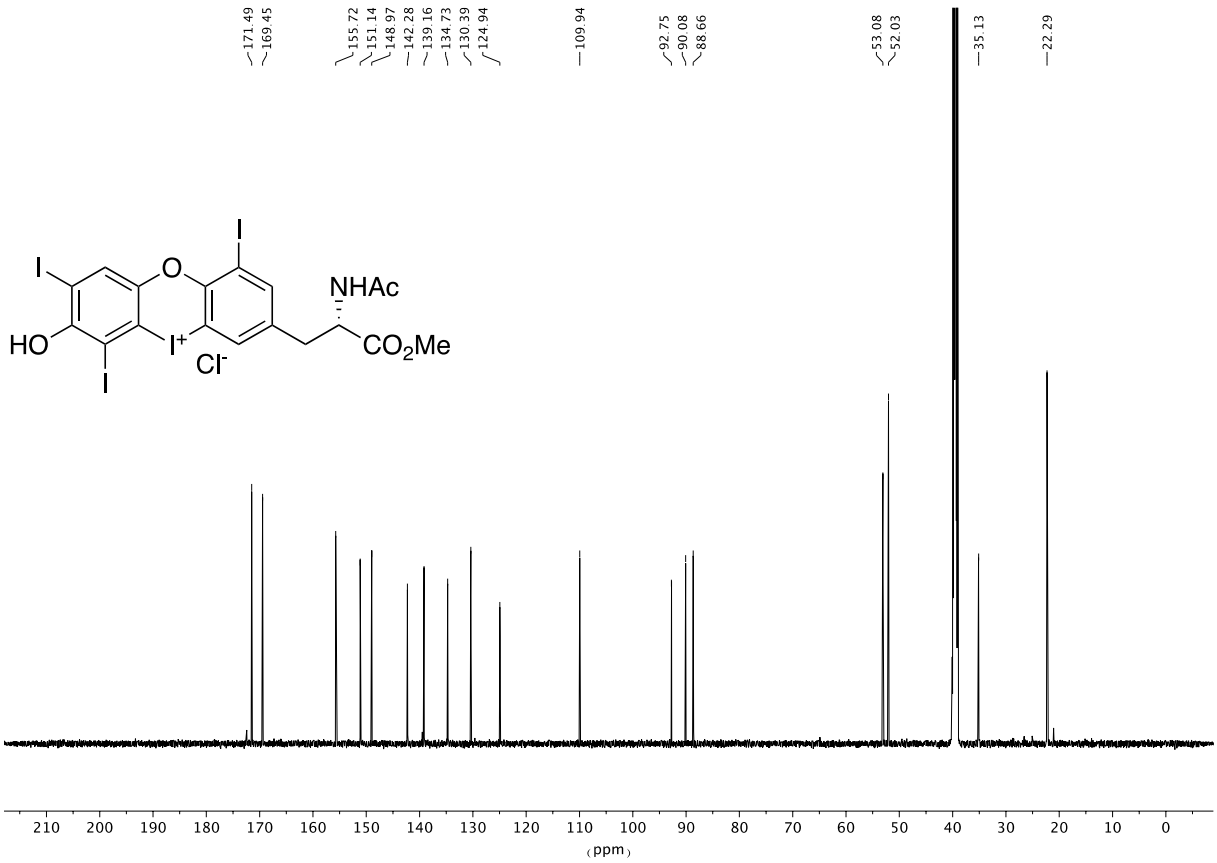


*Figure S47: 151 MHz [13]C-NMR spectrum of compound **6b** in DMSO-d_6.*

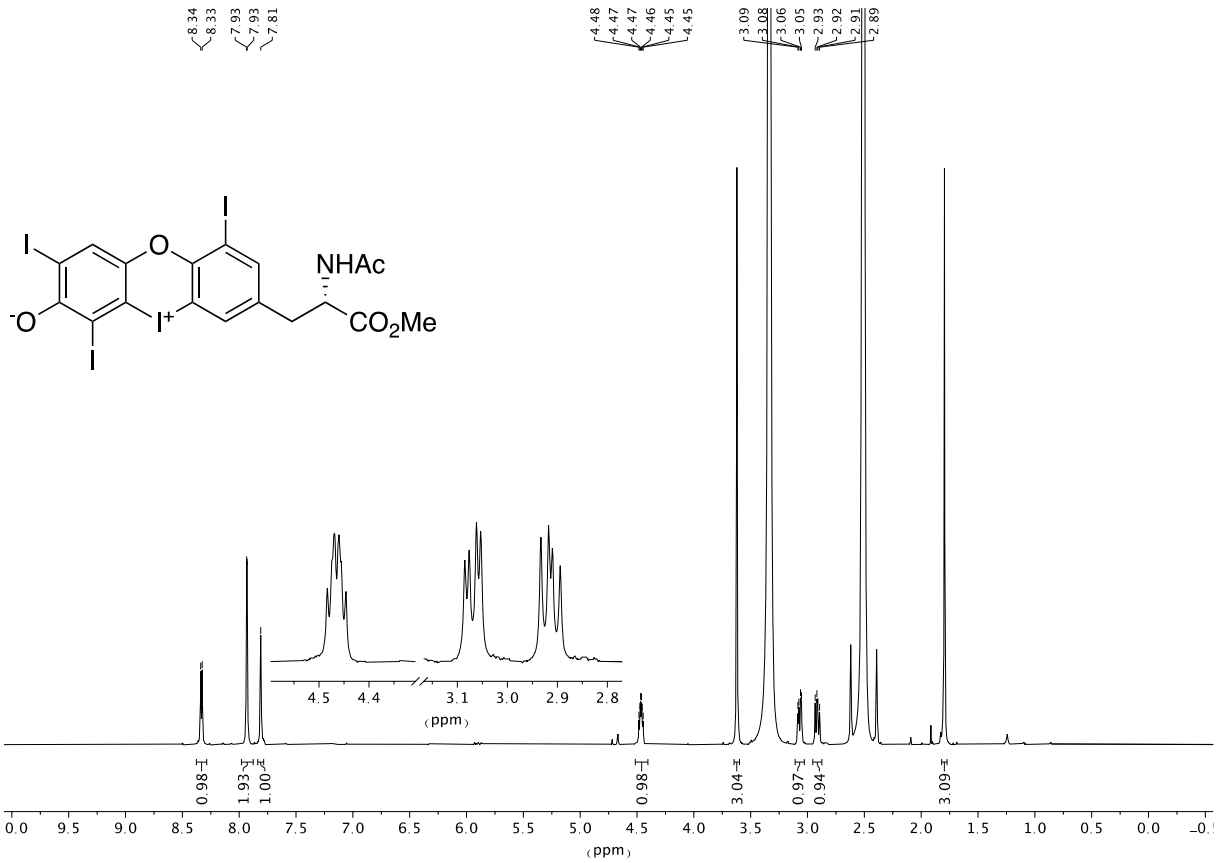


*Figure S48: 600 MHz ^{1}H-NMR spectrum of compound **7** in DMSO-d_6.*

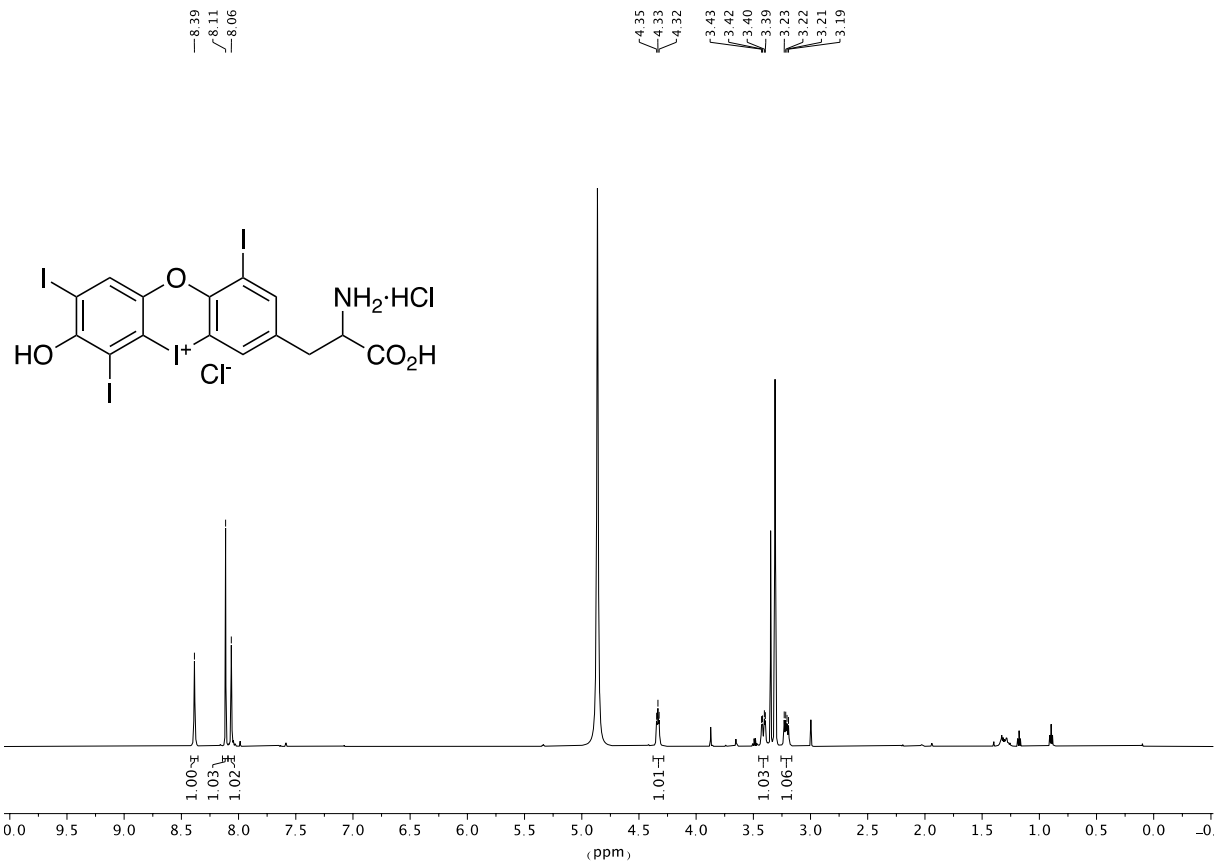


*Figure S49: 600 MHz ^{1}H-NMR spectrum of compound **1a** in CD_3OD.*

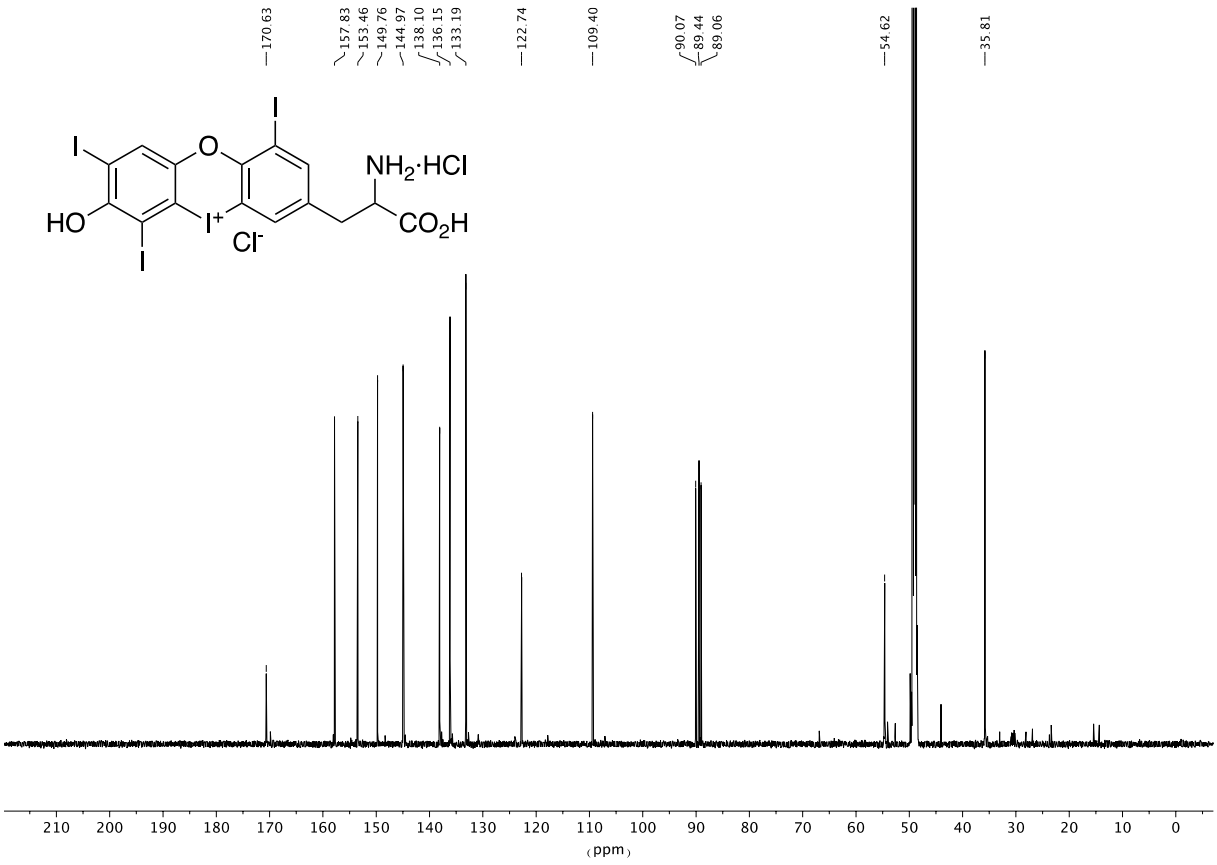


*Figure S50: 151 MHz ^{13}C-NMR spectrum of compound **1a** in CD_3OD.*

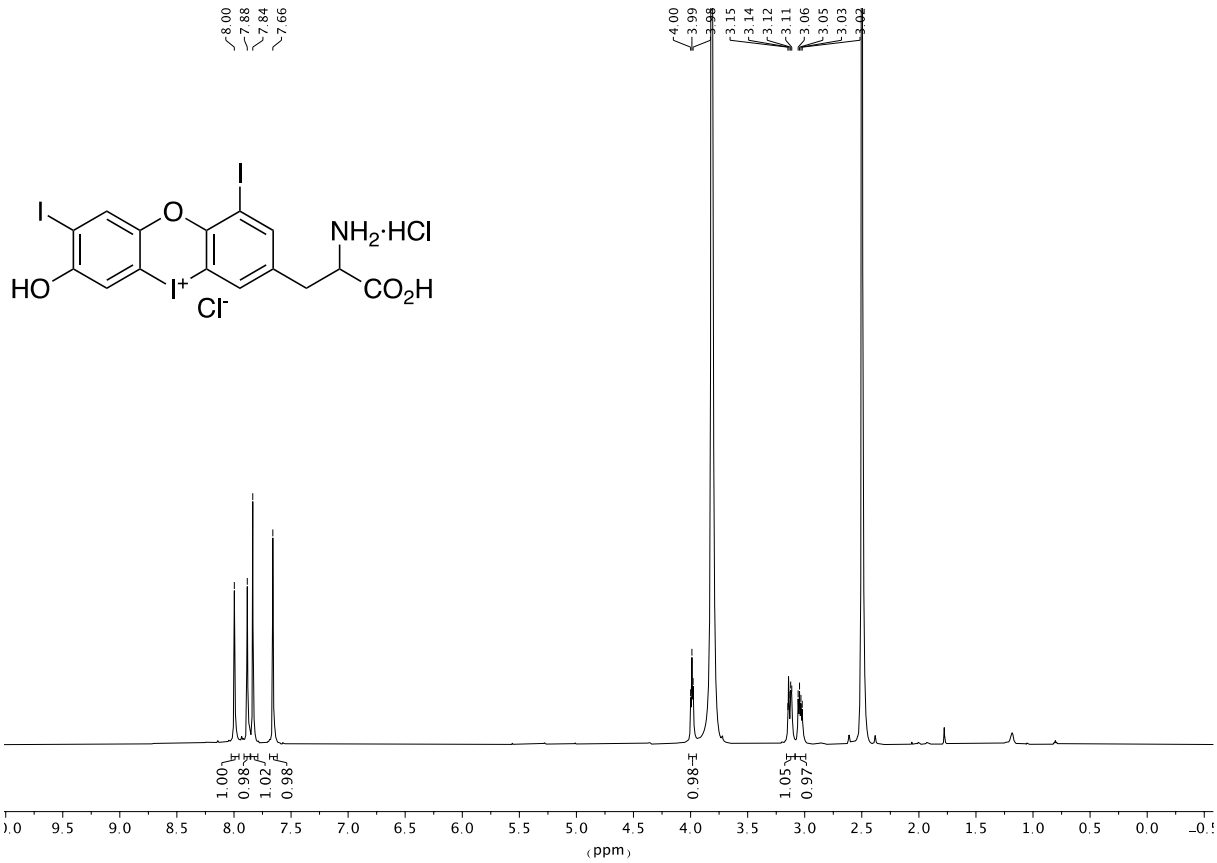


*Figure S51: 600 MHz ^{1}H-NMR spectrum of compound **1b** in DMSO-d_6 + 10% D_2O.*

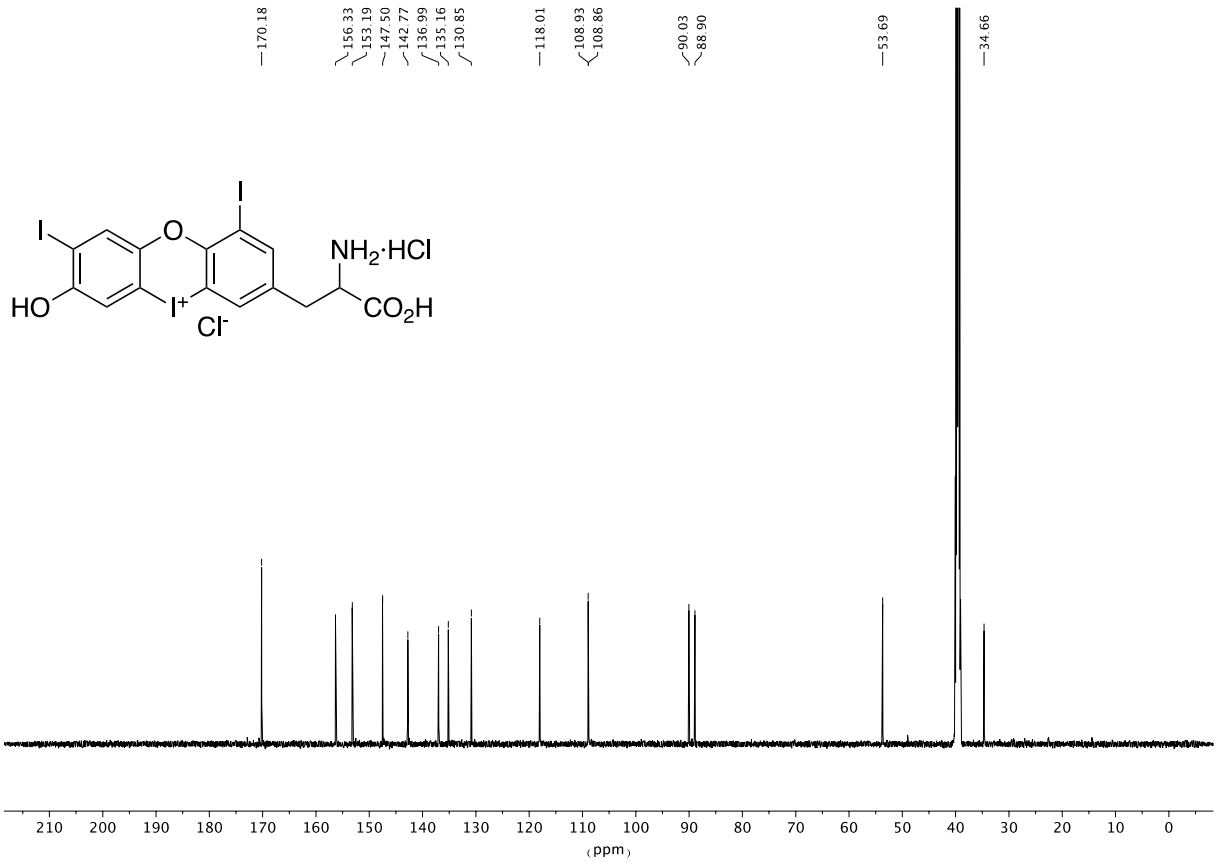


*Figure S52: 151 MHz ^{13}C-NMR spectrum of compound **1b** in DMSO-d_6 + 10% D_2O.*

7 Literature

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