Supporting Information

REGIO-COMPLEMENTARY PREPARATION OF 6- AND 7-FLUORO-1,2,3,4-TETRAHYDROQUINOLINES VIA THE CYCLIZATION OF CATECHOL AMINES FOLLOWED BY DEOXYFLUORINATION

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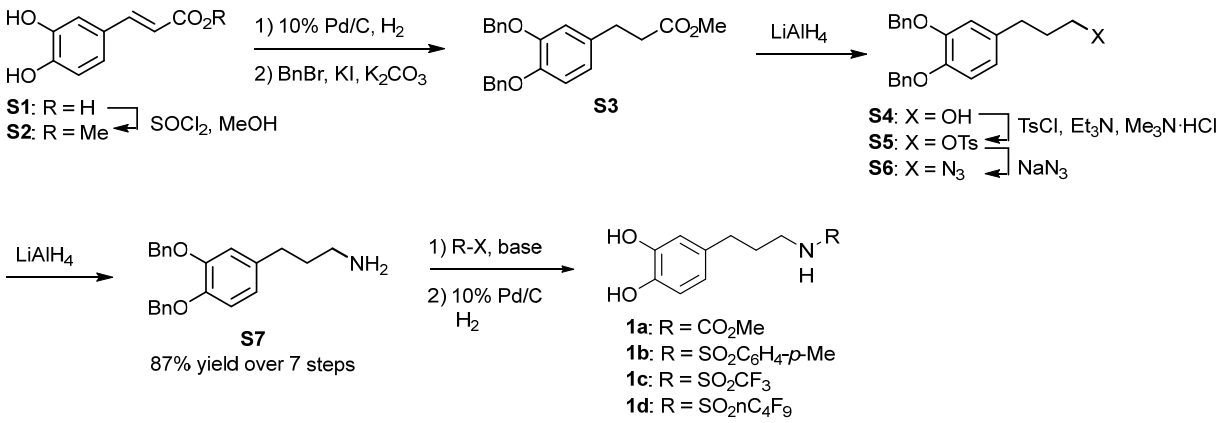
Contents

1. Preparation of catechol amines 1a-1d



Methyl 3-(3,4-dihydroxyphenyl)propanoate (S2)

Under argon atmosphere, $SOCl_2$ (10.0 mL, 139 mmol) was dropwise added to a solution of caffeic acid (**S1**) (25 g, 139 mmol) in MeOH (0.14 L) at ambient temperature. The reaction mixture was stirred at 60 °C for 2.5 h and concentrated in vaccuo. EtOAc (0.10 L) and saturated aqueous $NaHCO_3$ (0.10 L) were added to the residue, and the layers were separated with a separating funnel. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give **S2** (28.6 g), which was directly used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.55 (s, 1H), 5.66 (s, 1H), 6.26 (d, *J* = 16.0 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.07 (d, *J* = 1.5 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H).

Methyl 3-(3,4-bis(benzyloxy)phenyl)propanoate (S3)

Under argon atmosphere, 10% Pd/C (1.4 g, 5% w/w) was added to a solution of crude **S2** (28.6 g) in MeOH (0.14 L) at ambient temperature. Argon atmosphere was replaced by hydrogen gas in a balloon, and the reaction mixture was stirred at the same temperature for 12 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was filthered through a short pad of silica gel, and the filtrate was concentrated in vacuo to give **methyl 3-(3,4-dihydroxyphenyl)propanoate** (29.4 g), which was directly used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (t, *J* = 7.5 Hz, 2H), 2.78-2.90 (m, 2H), 3.67 (s, 3H), 5.65 (s, 2H), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H).

To a solution of crude methyl 3-(3,4-dihydroxyphenyl)propanoate (29.4 g) in DMF (0.20 L) were added KI (69 g, 0.42 mol), K_2CO_3 (58 g, 0.42 mol), and benzyl bromide (41 mL, 0.35 mol), and the mixture was stirred at 70 °C under argon atmosphere overnight. Water (0.20 L) was added, and the reaction mixture was stirred at the same temperature for 1.5 h. After cooling to room temperature, ice-cold Et_2O (0.20 L) was added to the mixture, and the layers were

separated. The aqueous layer was extracted with ice-cold Et_2O (0.20 L x 3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was filtered through a short pad of silica gel to give **S3** (46 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (t, *J* = 8.0 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 3.65 (s, 3H), 5.13 (s, 2H), 5.14 (s, 2H), 6.70 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 7.27–7.40 (m, 6H), 7.41–7.49 (m, 4H).

3-(3,4-Bis(benzyloxy)phenyl)propan-1-ol (S4)

To a flame dried flask, $LiAlH_4$ (4.8 g, 0.126 mmol) and dry THF (0.30 L) were added under argon atmosphere, and the mixture was cooled to 0 °C, to which a solution of **S3** (46 g) in THF (0.30 L) was added through a cannular. The reaction mixture was stirred at 0 °C for 3.5 h, and H_2O (4.8 mL), 15% NaOH (4.8 mL), and H_2O (9.6 mL) were added in this order at 0 °C. Then, Et_2O (0.30 L) was added, and the reaction mixture was stirred for 15 min and filtered through a Celite pad. The filtrate was concentrated in vacuo, and the residue was purified through a short pad of silica gel (hexane/EtOAc = 3:1) to give **S4** (46 g, 95% overall yield from **S1**). A white solid, mp 35–37 °C (reported as a colorless oil[1]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73–1.94 (m, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.60 (t, *J* = 6.5 Hz, 2H), 5.13 (s, 2H), 5.16 (s, 2H), 6.71 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.27–7.41 (m, 7H), 7.41–7.53 (m, 4H). These ^{1}H NMR data are in good agreement with those reported.[1] HRMS (MALDI): *m/z* calcd for $C_{23}H_{24}O_3$ $[M]^+$: 348.1720, found: 348.1717.

3-(3,4-Bis(benzyloxy)phenyl)propyl 4-methylbenzenesulfonate (S5)

Under argon atmosphere, Et_3N (21 mL, 0.151 mol), $Me_3N{\cdot}HCl$ (3.6 g, 38 mmol) and TsCl (30 g, 0.151 mol) were added to an ice-cold solution of **9** (46 g, 0.132 mol) in CH_2Cl_2 (0.25 L). The reaction mixture was stirred at ambient temperature for 4 h. Then, saturated aqueous $NaHCO_3$ (0.20 L) was added, and the mixture was stirred for another 2 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (0.20 L x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified through a short pad of silica gel to give **S5** (60 g), which was directly used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85–1.92 (m, 2H), 2.44 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H), 3.99 (t, *J* = 6.0 Hz, 2H), 5.12 (s, 4H), 6.57 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 7.27–7.40 (m, 8H), 7.40–7.51 (m, 4H), 7.78 (d, *J* = 8.0 Hz, 2H).

3-(3,4-Bis(benzyloxy)phenyl)propyl azide (S6)

NaN_3 (23 g, 0.36 mol) and water (30 mL) were added to a solution of crude **S5** (60 g) in DMF (0.20 L), and the mixture was stirred at 70 °C for 4 h. Ice-cold water (0.20 L) and Et_2O (0.20 L) were added, and the layers were separated. The aqueous layer was extracted with ice-cold Et_2O (0.20 L x 3). The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated in vacuo. The residue was purified through a short pad of silica gel to give **S6** (45 g), which was directly used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77–1.92 (m, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.21 (t, *J* = 7.5 Hz, 2H), 5.14 (s, 2H), 5.16 (s, 2H), 6.69 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.27–7.41 (m, 6H), 7.41–7.52 (m, 4H).

3-(3,4-Bis(benzyloxy)phenyl)propan-1-amine (S7)

To a flame dried flask, $LiAlH_4$ (4.4 g, 0.117 mol) and dry THF (0.50 L) were added under argon atmosphere, and the mixture was cooled to 0 °C. A solution of crude **S6** (44 g, 117 mmol) in THF (0.30 L) was added through a cannula. The reaction mixture was stirred at 0 °C for 3.5 h and worked up as mentioned in the preparation of **S4** to give **S7** (42 g, 91% overall yield from **S4**). A white solid, mp 38–40 °C (reported as a yellowish oil[1]). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (quint, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 5.13 (s, 2H), 5.15 (s, 2H), 6.69 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 7.30–7.37 (m, 6 H), 7.43–7.45 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.7, 35.3, 41.7, 71.4, 71.6, 115.4, 115.7, 121.2, 127.4, 127.76, 127.78, 128.5, 135.7, 137.5, 137.6, 147.2, 148.9. These NMR data are in good agreement with those reported.[1] HRMS (MALDI): *m/z* calcd for $C_{23}H_{26}NO_2$ $[M+H]^+$: 348.1959, found: 348.1958.

***N*-(3-(3,4-Dihydroxyphenyl)propyl)-4-methylbenzenesulfonamide (1b)**

Under argon atmosphere, Et_3N (0.020 mL, 0.14 mmol) and TsCl (26 mg, 0.13 mmol) were added to an ice-cold solution of **S7** (42 mg, 0.121 mmol) in CH_2Cl_2 (1.2 mL). The reaction mixture was stirred at ambient temperature for 2 h, and aqueous $NaHCO_3$ (3 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography of silica gel (EtOAc/hexane = 1:3) to give ***N*-(3-(3,4-bis(benzyloxy)phenyl)propyl)-4-methylbenzenesulfonamide** (37 mg, 60% yield). A white solid, mp 70–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (quint, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.90 (q, *J* = 7.0 Hz, 2H), 5.12 (s, 2H), 5.13 (s, 2H), 6.58 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 7.27–7.40 (m, 8H), 7.44 (d, *J* = 8.0 Hz, 4H), 7.70 (br d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 31.3, 32.2, 42.6, 71.4, 71.6, 115.4, 115.6, 121.2, 127.2, 127.4, 127.9, 128.6, 129.8, 134.3, 137.0, 137.5, 147.4, 149.0. IR (neat): 1511 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{30}H_{31}NO_4NaS$ $[M+Na]^+$: 524.1866, found: 524.1866.

Under argon atmosphere, 10% Pd/C (0.16 g, 10% w/w) was added to a solution of *N*-(3-(3,4-bis(benzyloxy)phenyl)propyl)-4-methylbenzenesulfonamide (1.6 g, 3.1 mmol) in a mixture of MeOH (15 mL) and EtOAc (15 mL). Argon atmosphere was replaced by hydrogen gas in a balloon, and the reaction mixture was stirred at the ambient temperature overnight. The reaction

mixture was filtered through a Celite pad, and a filtrate was concentrated in vacuo. The residue was purified through a short pad of silica gel to give **1b** (0.98 g, 99%). A colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (quint, 2H), 2.43 (s, 3H), 2.49 (t, *J* = 7.0 Hz, 2H), 2.92 (t, *J* = 6.5 Hz, 2H), 4.50 (br s, 1H), 5.31 (br s, 1H), 5.67 (br s, 1H), 6.51 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 31.1, 31.9, 42.6, 115.5, 115.7, 120.8, 127.2, 129.9, 133.8, 136.6, 142.1, 143.7, 143.8. IR (neat): 3409, 3303 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{16}H_{20}NO_4S$ $[M+H]^+$: 322.1108, found: 322.1108.

Methyl (3-(3,4-dihydroxyphenyl)propyl)carbamate (1a)

Similarly to the preparation of **1b**, a mixture of **S7** (3.0 g, 8.6 mmol), $ClCO_2Me$ (0.80 mL, 10.4 mmol), and Et_3N (1.7 mL, 12.1 mmol) were stirred at ambient temperature for 2 h to give **methyl (3-(3,4-bis(benzyloxy)phenyl)propyl)carbamate** (3.7 g), which was directly used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–1.84 (m, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 3.14 (q, *J* = 6.5 Hz, 2H), 3.66 (s, 3H), 4.60 (s, 1H), 5.13 (s, 2H), 5.15 (s, 2H), 6.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.76 (d, *J* = 1.5 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 7.27–7.40 (m, 6H), 7.41–7.48 (m, 4H).

Similarly to the preparation of **1b**, methyl (3-(3,4-bis(benzyloxy)phenyl)propyl)carbamate (3.7 g) was converted into **1a** (1.9 g, >99% overall yield from **S7**). A pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63–1.86 (m, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 3.16 (q, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 4.86 (s, 1H), 6.34 (s, 2H), 6.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.6, 32.3, 40.7, 52.5, 115.4, 115.5, 120.6, 134.0, 142.2, 143.9, 157.8. IR (neat): 3346, 1742 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{11}H_{16}NO_4$ $[M+H]^+$: 226.1074, found: 226.1074.

***N*-(3-(3,4-Dihydroxyphenyl)propyl)trifluoromethanesulfonamide (1c)**

Similarly to the preparation of **1b**, a mixture of **S7** (0.50 g, 1.4 mmol), trifluoromethanesulfonic anhydride (0.31 mL, 1.9 mmol), and Et_3N (0.40 mL) was stirred at –78 °C for 20 min to give ***N*-(3-(3,4-bis(benzyloxy)phenyl)propyl)trifluoromethanesulfonamide** (0.60 g, 87% yield). A colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–1.90 (m, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 3.22 (q, *J* = 6.5 Hz, 2H), 5.14 (s, 2H), 5.16 (s, 2H), 6.66 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.28–7.39 (m, 6H), 7.43–7.45 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.5 (s, 3F).

Similarly to the preparation of **1b**, *N*-(3-(3,4-bis(benzyloxy)phenyl)propyl)trifluoromethanesulfonamide (0.60 g, 1.3 mmol) was converted into **1c** (0.35 g, 93% yield). A white solid, mp 87–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.98 (m, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.31 (q, *J* = 6.5 Hz, 2H), 4.70 (br s, 1H), 5.04 (br s, 1H), 5.21 (br s, 1H), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.78, 31.80,

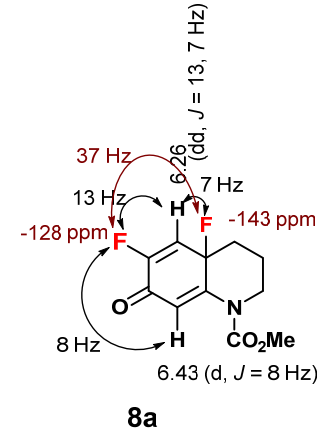
44.0, 115.5, 115.7, 119.7 (q, J = 319 Hz), 120.9, 133.5, 142.0, 143.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ –80.5 (s, 3F). IR ($CHCl_3$): 3492, 3307 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{10}H_{12}NO_4F_3NaS$ $[M+Na]^+$: 322.0331, found: 322.0330.

***N*-(3-(3,4-Dihydroxyphenyl)propyl)nonafluorobutanesulfonamide (1d)**

Similarly to the preparation of **1b**, a mixture of **S7** (3.0 g, 8.6 mmol), nonafluorobutanesolfonyl fluoride (3.0 mL, 17.3 mmol) and K_2CO_3 (4.8 g, 34 mmol) in DMF (40 mL) were stirred at ambient temperature for 1.5 h to give ***N*-(3-(3,4-bis(benzyloxy)phenyl)propyl)nonafluorobutanesulfonamide** (3.0 g, 55% yield). A colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82–1.91 (m, 2H), 2.58 (t, J = 7.5 Hz, 2H), 3.28 (q, J = 6.5 Hz, 2H), 5.14 (s, 2H), 5.16 (s, 2H), 6.67 (dd, J = 8.5, 2.0 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.28–7.38 (m, 6H), 7.43–7.46 (m, 4H). ^{19}F NMR (470 MHz, $CDCl_3$) δ –125.8 (br, 2F), –121.1 (br, 2F), –112.3 (br, 2F), –80.6 (br, 3F).

Similarly to the preparation of **1b**, *N*-(3-(3,4-bis(benzyloxy)phenyl)propyl)nonafluorobutanesulfonamide (3.0 g, 4.8 mmol) was converted into **1d** (1.9 g, 88% yield). A white solid, mp 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84–1.98 (m, 2H), 2.59 (t, J = 7.5 Hz, 2H), 3.35 (q, J = 6.5 Hz, 2H), 4.91 (br s, 1H), 5.19 (br s, 2H), 6.61 (dd, J = 8.0, 2.5 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 32.1, 44.5, 115.5, 115.7, 120.8, 133.5, 142.0, 143.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -129.2– -129.1 (m, 2F), -124.6 – -124.4 (m, 2F), -115.7 (br t, J = 13.0 Hz, 2F), –83.9 (br t, J = 10.0 Hz, 3F). IR (neat): 3306 cm^{-1}. HRMS (MALDI): *m/z* calcd for $C_{13}H_{12}NO_4F_9NaS$ $[M+Na]^+$: 472.0236, found: 472.0239.

2. Characteristic NMR data to support the structures of 5a, 5d, 6d, 8a, 9a, 9d, and 10d



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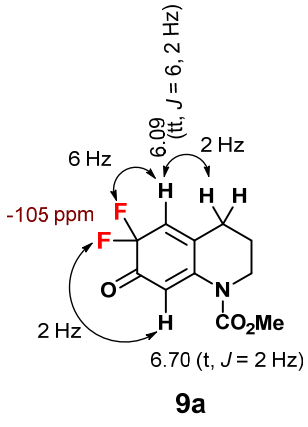

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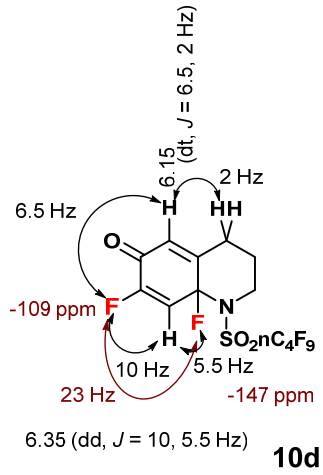

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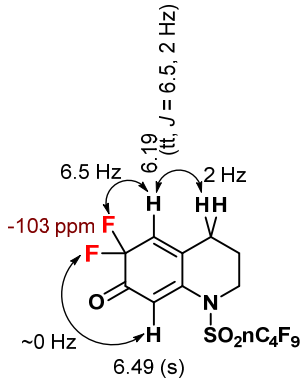

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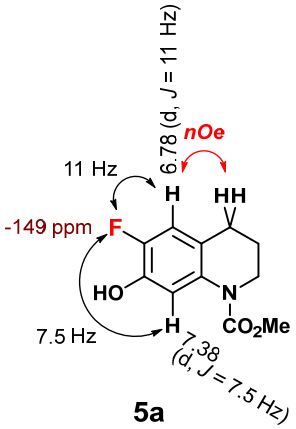

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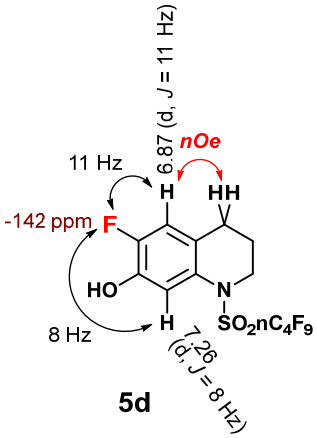

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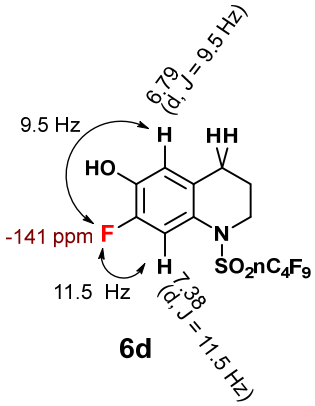

6d

Reference for supporting information

1. G. García, I. Serrano, P. Sánchez-Alonso, M. Rodríguez-Puyol, R. Alajarín, M. Griera, J. J. Vaquero, D. Rodríguez-Puyol, J. Álvarez-Builla, and M. L. Díez-Marqués, *Eur. J. Med. Chem.*, 2012, **50**, 90.