SUPPORTING INFORMATION FOR PUBLICATION

Structure-Activity Relationship of INT131 Analogs for PPARγ-Targeted Antidiabetics

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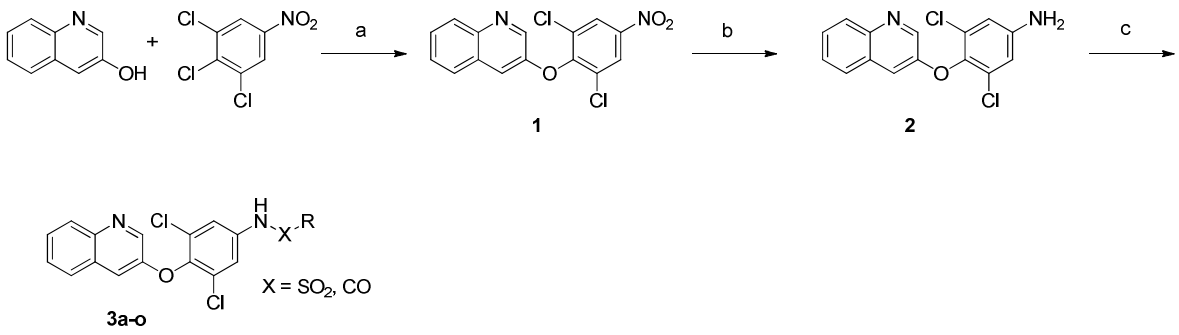
Chemical synthesis.



Reaction Conditions: a) Cs_2CO_3, DMAC, 60 ℃; b) NH_4Cl, Fe, 70 ℃; c) RSO_2Cl or RCOCl, DIEA, CH_2Cl_2

General procedure for determining percent purity of all compounds. Reverse-phase analytical HPLC was used to determine purity for all compounds. All percent purities are located in Table I with all but 5 at or above 95% purity.

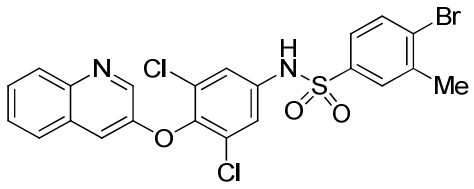
General Procedure: Preparation of 3-(2,6-dichloro-4-nitrophenoxy)quinoline (1). To a solution of 3-hydroxyquinoline (1g) and 1,2,3-trichloro-5-nitrobenzene (1.6g) in DMAC (30mL) was added Cs_2CO_3 (2.5g). The reaction mixture was warmed to 60℃ for 2h, wherein analytical HPLC analysis indicated the reaction was complete. The reaction mixture was poured into ice/water (100mL) and the resulting mixture was stirred for 1h. The light yellow precipitate was collected by filtration to afford **1** which was used without further purification.

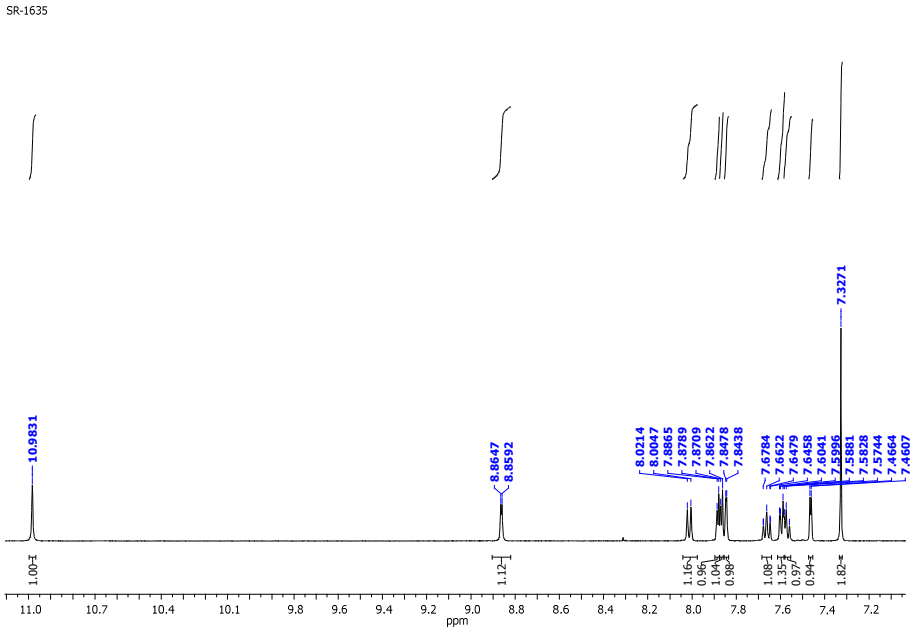
General Procedure: Preparation of 3,5-dichloro-4-(quinolin-3-yloxy)aniline (2). To a solution of crude **1** (1.95g) in ethanol/THF/water (4:2:1 by volume, 28 mL) was added NH_4Cl (0.93g) and powdered iron (0.96g). The mixture was warmed to reflux overnight. After 16h, the hot mixture was

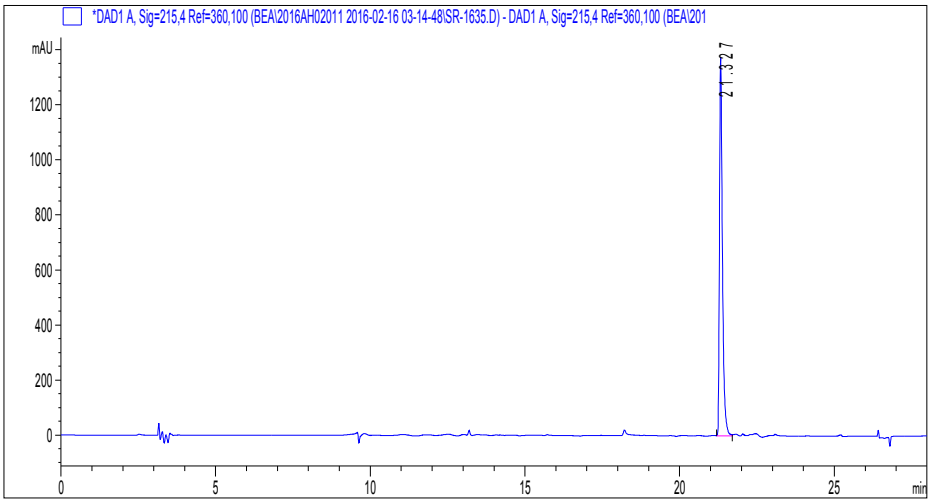
filtered through celite and concentrated *in vacuo*. The residue was dissolved in EtOAc, and washed with sat. aq. $NaHCO_3$, water, brine, and then dried ($MgSO_4$), and concentrated to afford the title compound as a pale red solid which was used without further purification

General Procedure: Preparation of 2,4-dichloro-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)benzenesulfonamide (3a, INT-131). To the solution crude **2** (0.1g) in CH_2Cl_2 was added 2,4-dichlorobenzenesulfonyl chloride (0.16g) followed by DIEA (0.11mL). The reaction mixture was stirred at room temperature for 12h, and then warmed to 40℃ for 3h. After cooling, the reaction was concentrated *in vacuo*, and the crude residue was purified by reverse-phase preparative HPLC, to afford the title compound as a colorless solid.

(1): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-3-methylbenzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 3-methyl-4-bromosulfonyl chloride.





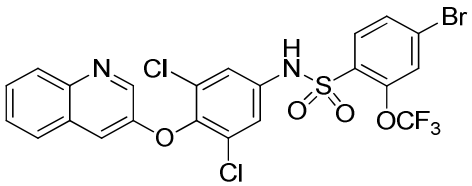


^{1}H NMR (500 MHz, DMSO-*d6*) δ 10.98 (s, 1H), 8.86 (d, *J* = 2.8 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 3.8 Hz, 1H), 7.87 (d, *J* = 4.4 Hz, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.68–7.64 (m, 1H), 7.59 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.57 (t, *J* = 5.7 Hz, 1H), 7.46 (d, *J* = 2.8 Hz, 1H) and 7.33 (s, 2H) ppm.

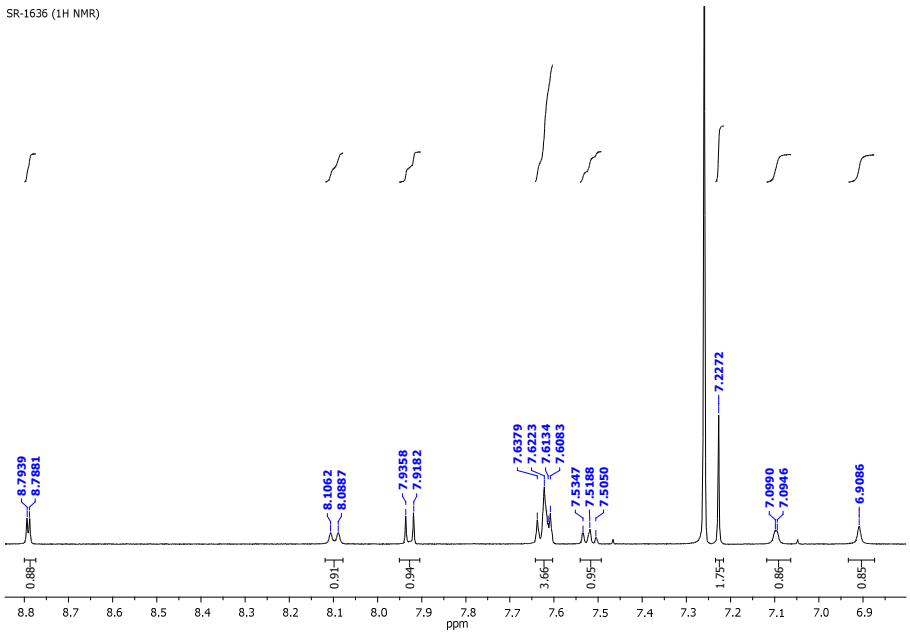
MS HRMS (ESI) calcd for $C_{21}H_{16}BrCl_2N_2O_3S$ ($M-H^+$): 536.9437, found 536.9436.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 21.33 min. Purity 100 %.

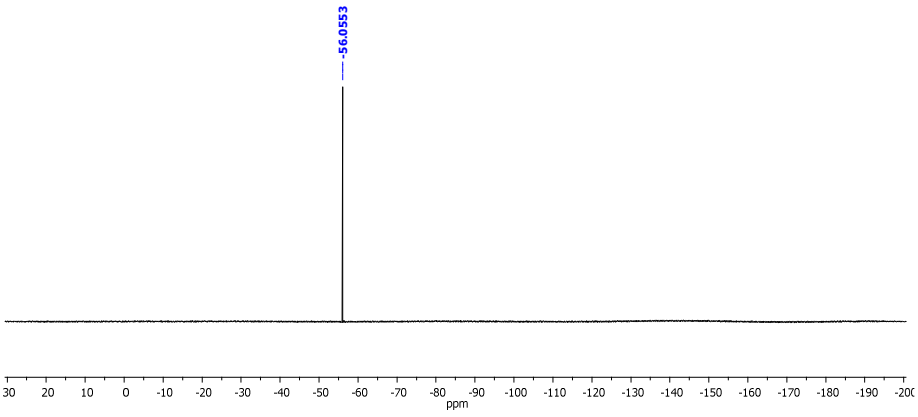
(2): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-2-(trifluoromethoxy)benzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-trifluoromethoxy-4-bromosulfonyl chloride.

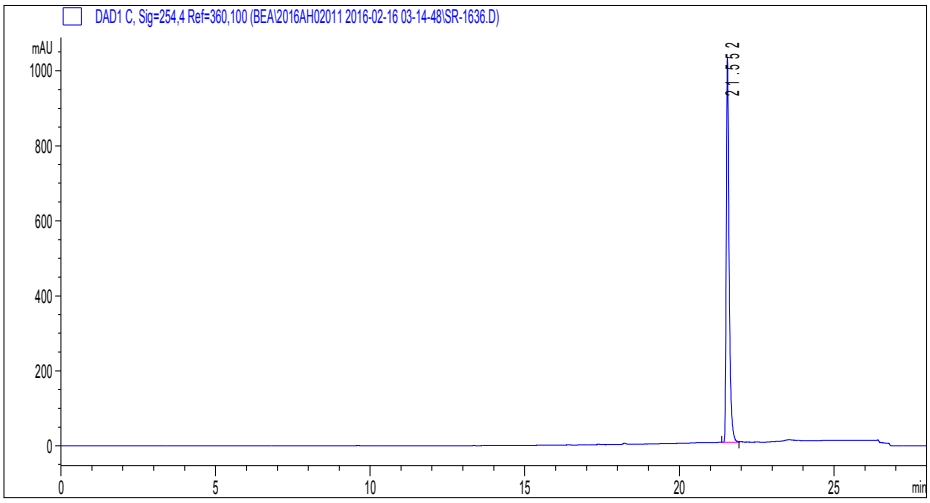


SR-1636 (1H NMR)



SR-1636 (19F NMR)





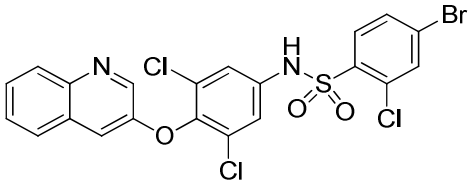
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.9 Hz, 1H), 8.10 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.64–7.60 (m, 4H), 7.54–7.49 (m, 1H), 7.23 (s, *J* = 4.0 Hz, 2H), 7.10 (d, *J* = 2.8 Hz, 1H) and 6.91 (s, 1H) ppm.

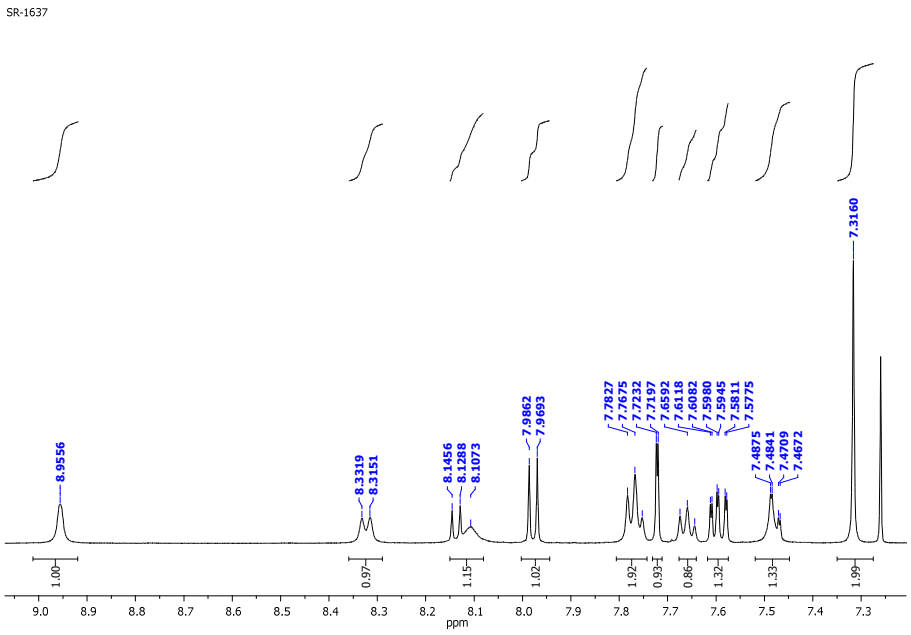
^{19}F NMR (470 MHz, $CDCl_3$) δ –56.06 (s) ppm.

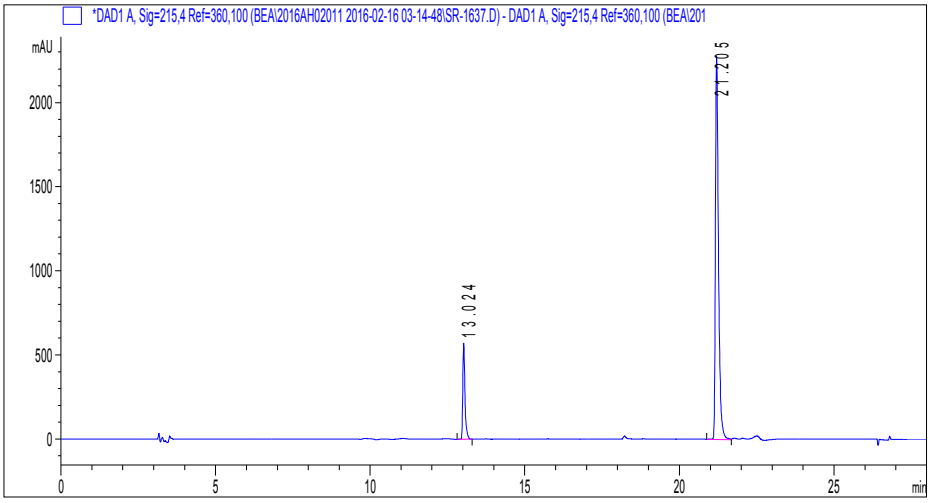
MS HRMS (ESI) calcd for $C_{22}H_{13}BrCl_2F_3N_2O_4S$ ($M-H^+$): 606.9103, found 606.9109.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 254 nm. Retention time 21.55 min. Purity 100 %.

(3): 4-bromo-2-chloro-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)benzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-chloro-4-bromosulfonyl chloride.





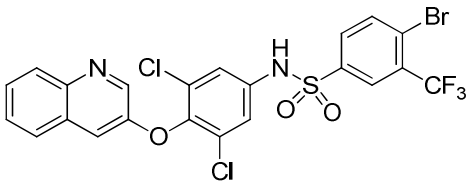


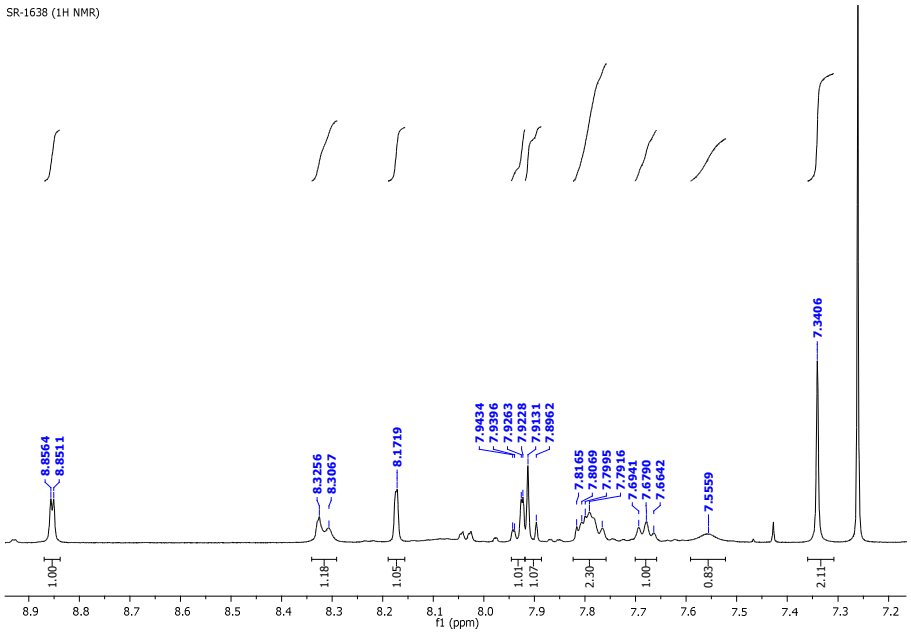
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.13 (m, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.62–7.57 (m, 1H), 7.48 (dd, J = 8.3, 1.8 Hz, 1H) and 7.32 (s, 2H) ppm.

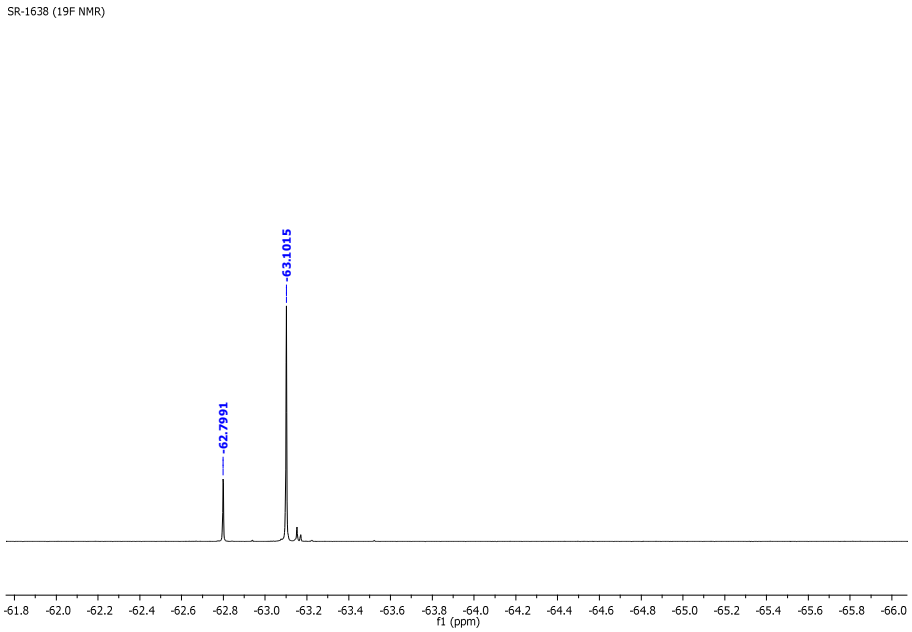
MS HRMS (ESI) calcd for $C_{21}H_{13}BrCl_3N_2O_3S$ ($M-H^+$): 556.8890, found 556.8867.

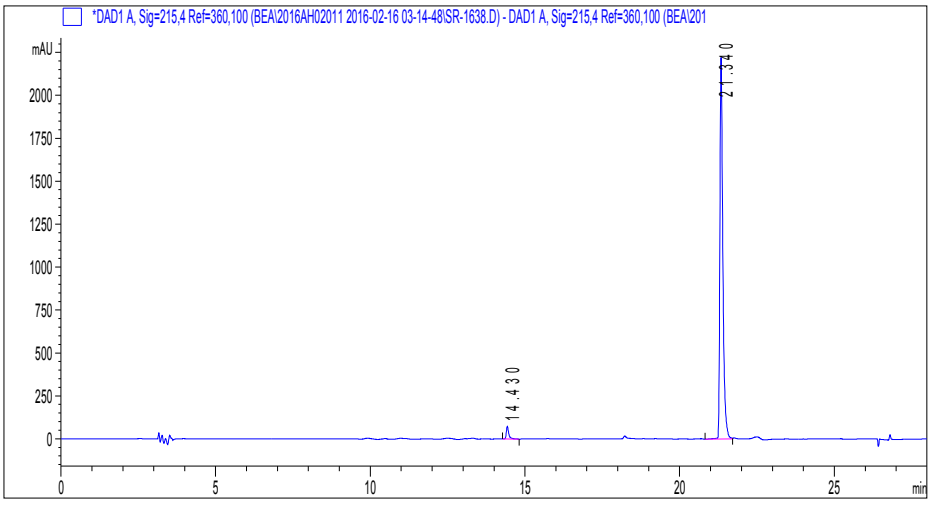
Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 21.20 min. Purity 85 %.

(4): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-3-(trifluoromethyl)benzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 3-trifluoromethyl-4-bromosulfonyl chloride.









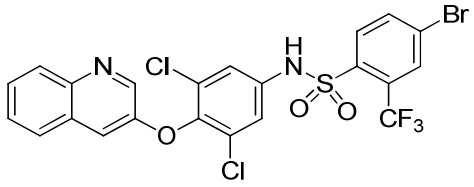
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, *J* = 2.7 Hz, 1H), 8.34–8.29 (m, 1H), 8.17 (s, 1H), 7.93 (dd, *J* = 8.5 and 1.8 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.82–7.76 (m, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.59–7.52 (m, 1H) and 7.34 (s, 2H) ppm.

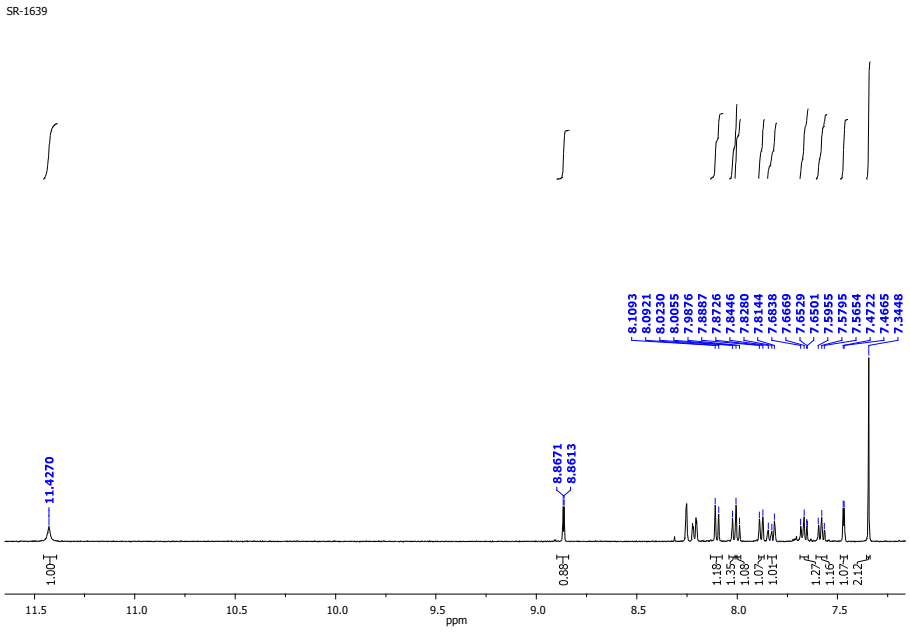
^{19}F NMR (470 MHz, $CDCl_3$) δ −62.80 (s) and −63.10 (s) ppm.

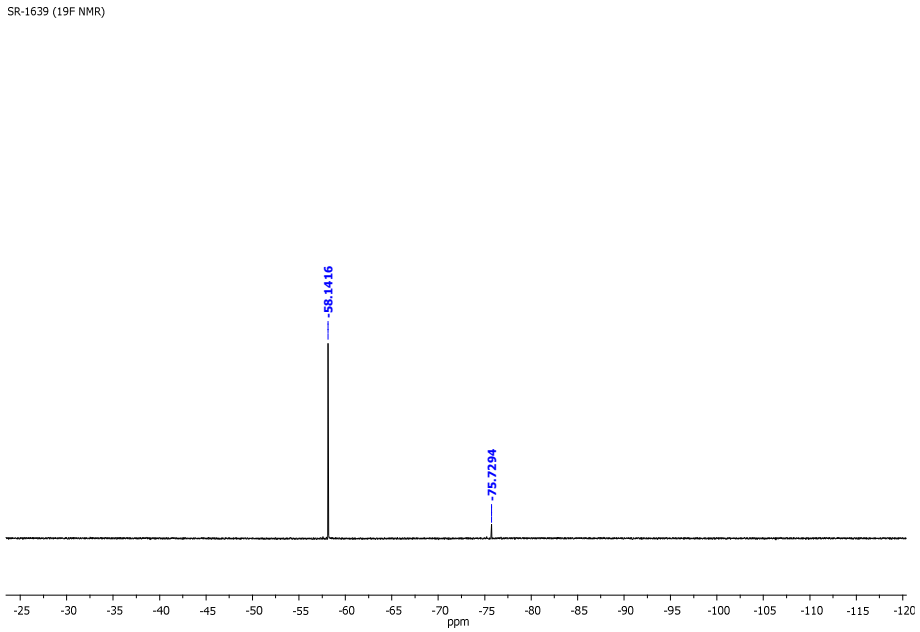
MS HRMS (ESI) calcd for $C_{22}H_{13}BrCl_2F_3N_2O_3S$ ($M-H^+$): 590.9154, found 590.9171.

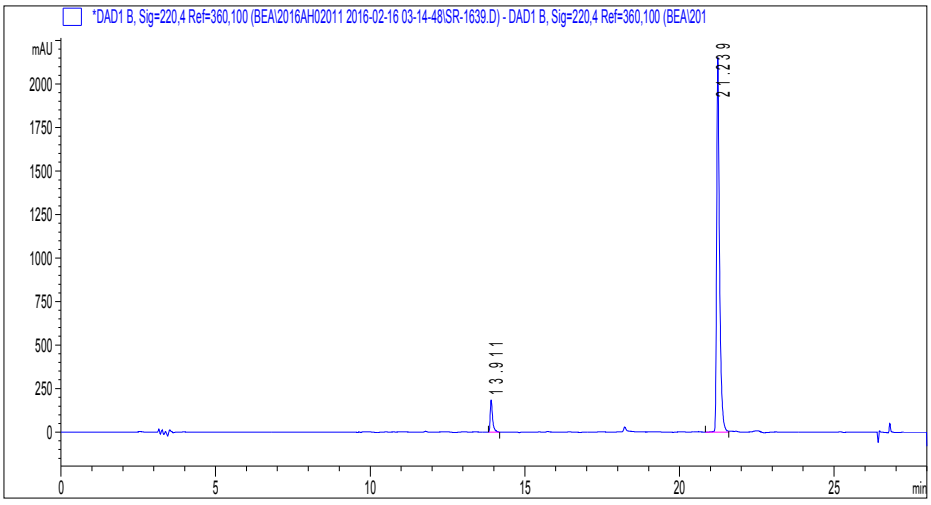
Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 21.34 min. Purity 97 %.

(5): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-2-(trifluoromethyl)benzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-trifluoromethyl-4-bromosulfonyl chloride.









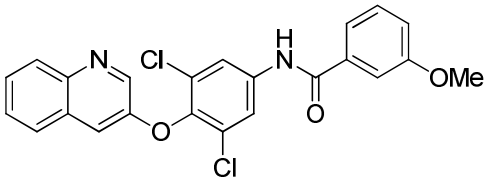
^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.43 (s, 1H), 8.86 (d, *J* = 2.9 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.9 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.85–7.81 (m, 1H), 7.69–7.65 (m, 1H), 7.61–7.55 (m, 1H), 7.47 (d, *J* = 2.8 Hz, 1H) and 7.34 (s, 2H) ppm.

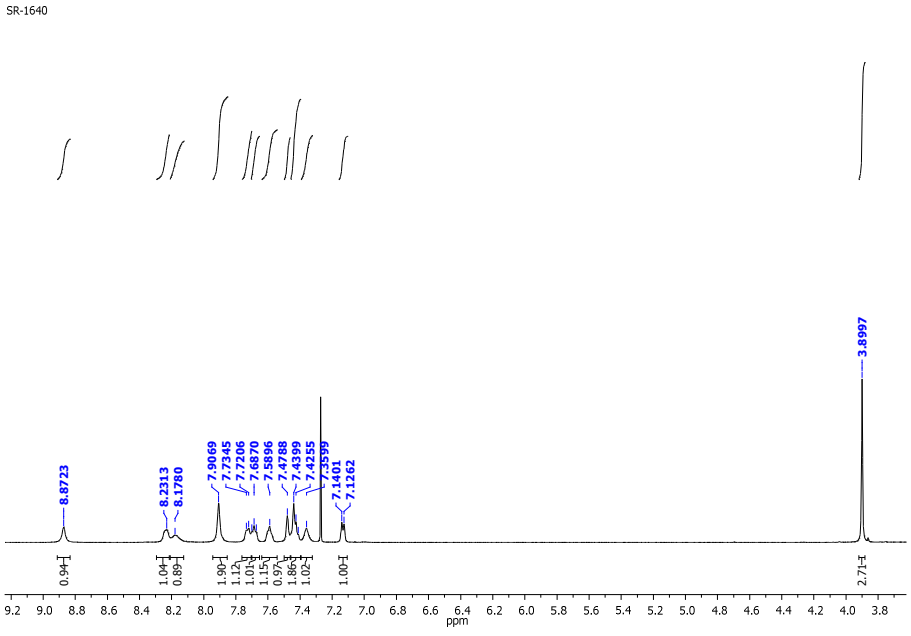
^{19}F NMR (470 MHz, $CDCl_3$) δ −58.14 (s) ppm.

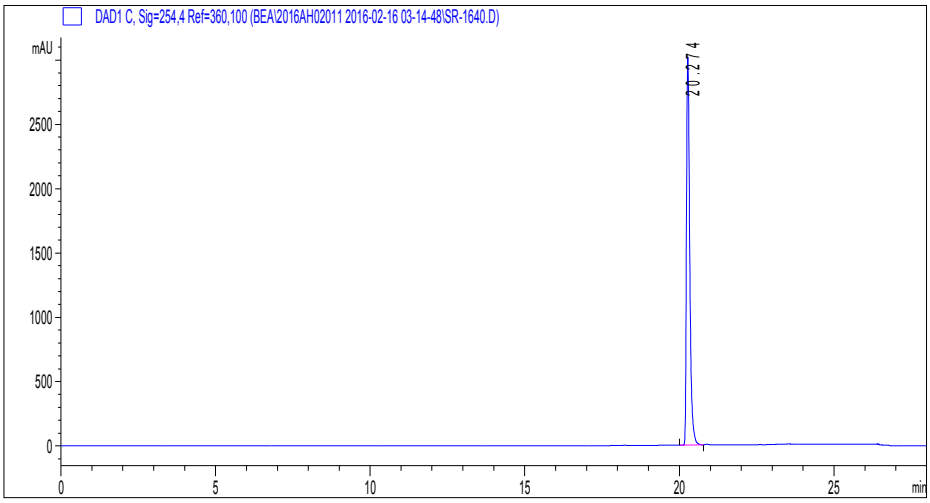
MS HRMS (ESI) calcd for $C_{22}H_{13}BrCl_2F_3N_2O_3S$ ($M-H^+$): 590.9154, found 590.9153.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 220 nm. Retention time 21.24 min. Purity 93 %.

(6): N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)thiophene-2-carboxamide: The title compound was made following the same general protocol as described for **3a**, using 3-methoxybenzoylchloride.





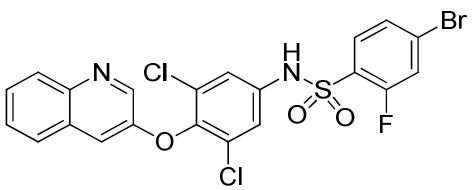


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.24 (d, *J* = 5.9 Hz, 1H), 8.18 (s, 1H), 7.91 (s, 2H), 7.76–7.70 (m, 1H), 7.69 (t, *J* = 7.0 Hz, 1H), 7.59 (t, *J* = 6.3 Hz, 1H), 7.48 (s, 1H), 7.46–7.40 (m, 2H), 7.36 (s, 1H), 7.13 (d, *J* = 6.9 Hz, 1H), 3.90 (s, 3H).

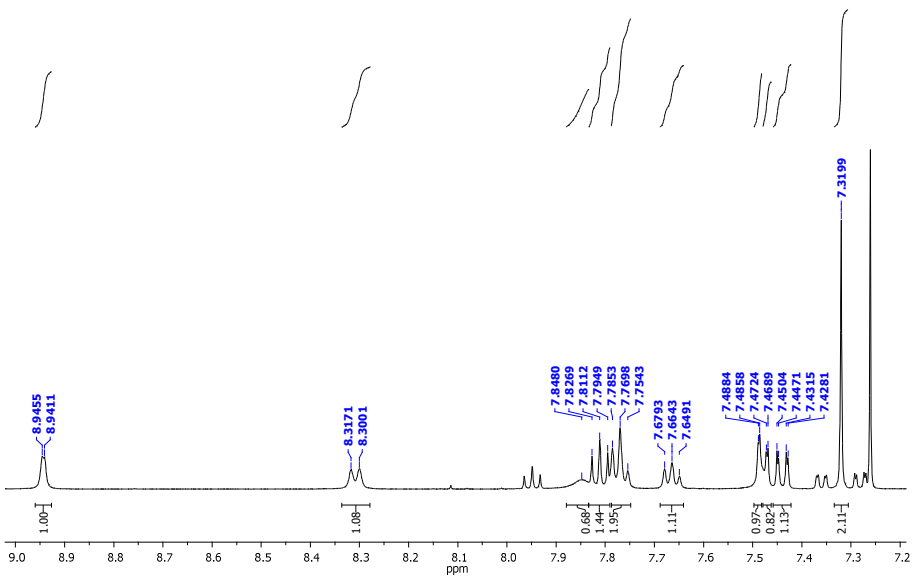
MS HRMS (ESI) calcd for $C_{23}H_{17}Cl_2N_2O_3$ ($M-H^+$): 439.0611, found 439.0635.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 254 nm. Retention time 20.27 min. Purity 100 %.

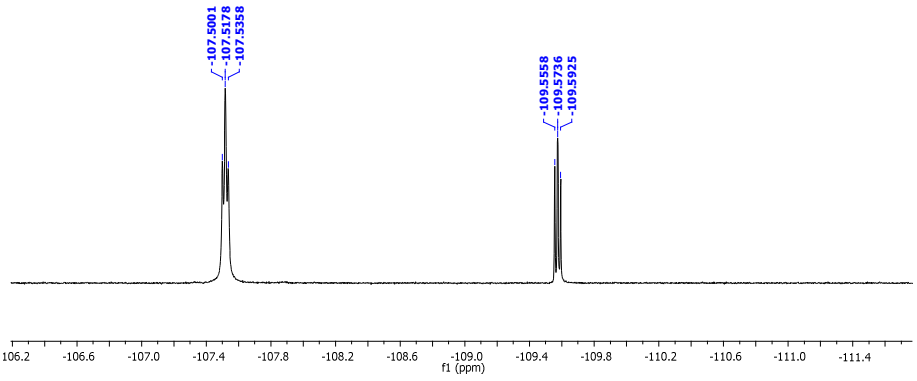
(7): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-2-fluorobenzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-fluoro-4-bromosulfonyl chloride.

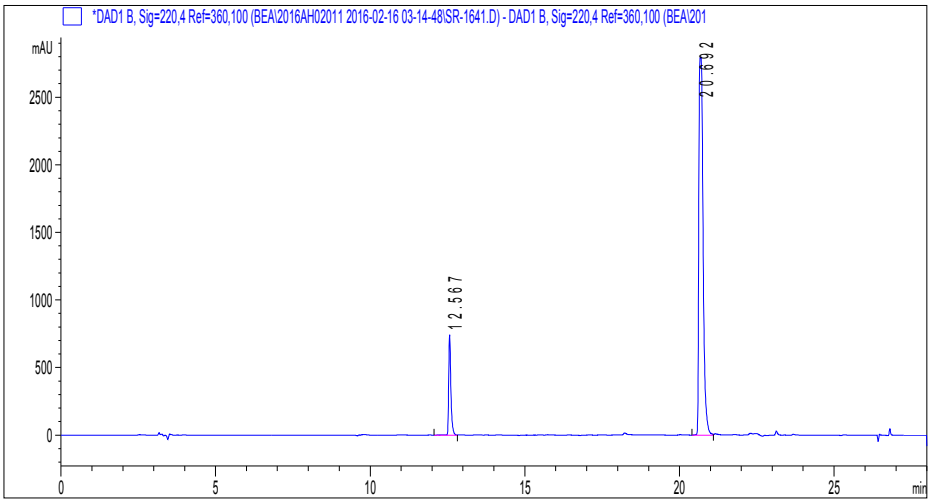


SR-1641 (1H NMR)



SR-1641 (19F NMR)





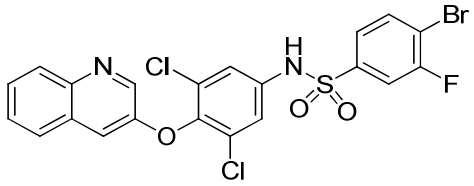
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.2 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.88–7.83 (br s, 1H), 7.83–7.79 (m, 1H), 7.77 (t, *J* = 7.8 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 1.3 Hz, 1H), 7.47 (d, *J* = 1.7 Hz, 1H), 7.44 (dd, *J* = 9.5, 1.7 Hz, 1H) and 7.32 (s, 2H) ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ –107.52 (t, J = 8.4 Hz) ppm.

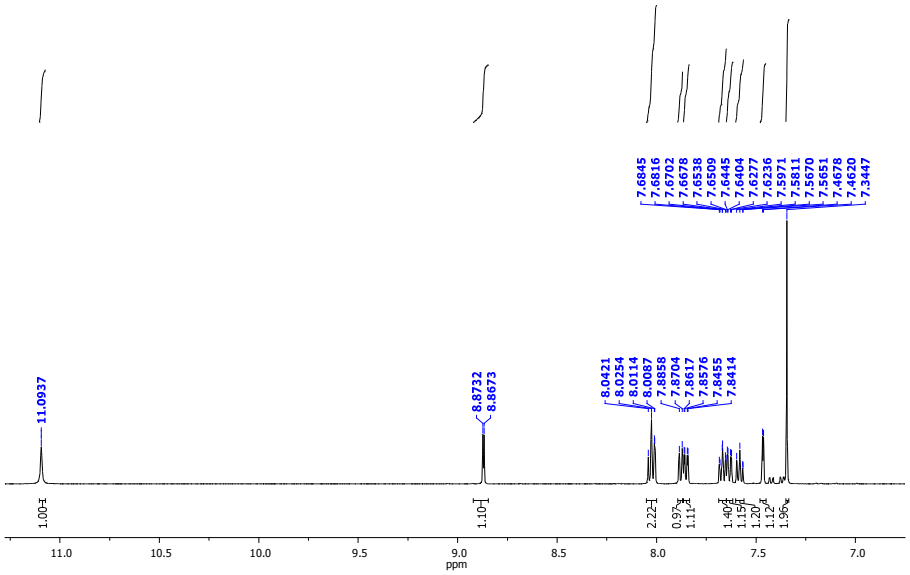
MS HRMS (ESI) calcd for $C_{21}H_{13}BrCl_2FN_2O_3S$ ($M-H^+$): 540.9186, found 540.9197.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 220 nm. Retention time 20.69 min. Purity 88 %.

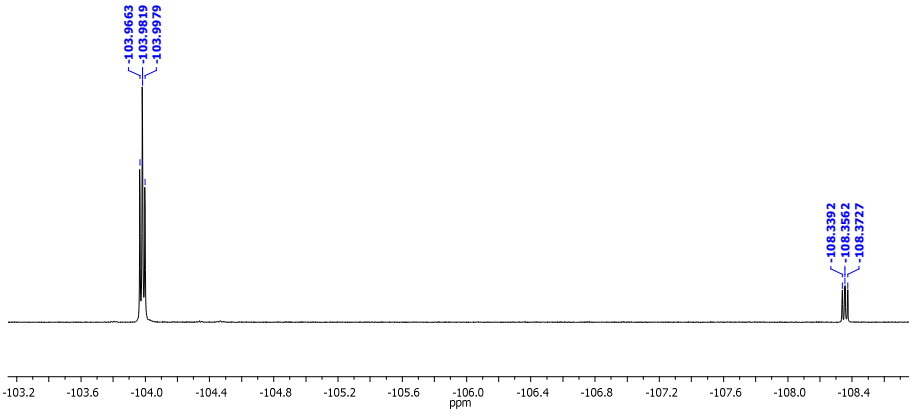
(8): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-3-fluorobenzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 3-fluoro-4-bromosulfonyl chloride.

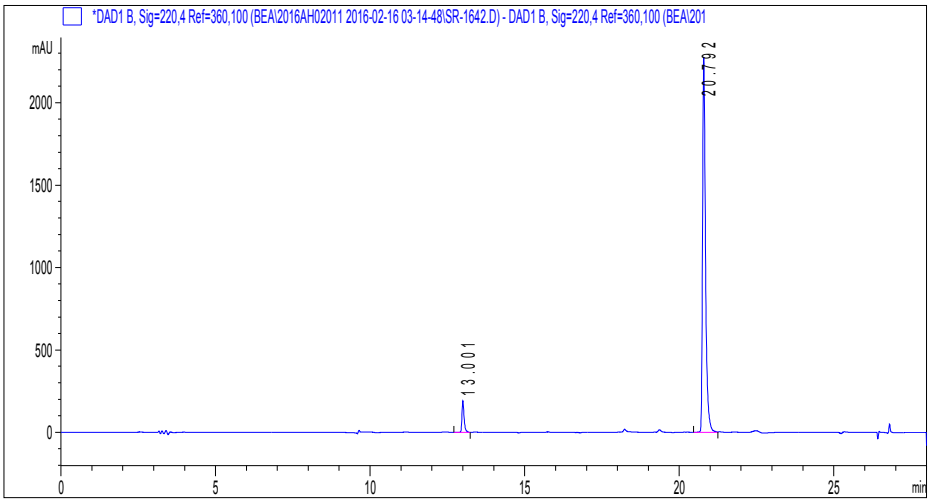


SR-1642



SR-1642 (19F NMR)





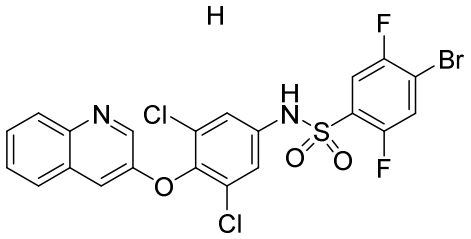
^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.09 (s, 1H), 8.87 (d, *J* = 2.9 Hz, 1H), 8.05–8.00 (m, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.85 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.69–7.65 (m, 1H), 7.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.60–7.56 (m, 1H), 7.46 (d, *J* = 2.9 Hz, 1H) and 7.34 (s, 2H) ppm.

^{19}F NMR (470 MHz, $CDCl_3$) δ –103.98 (t) ppm.

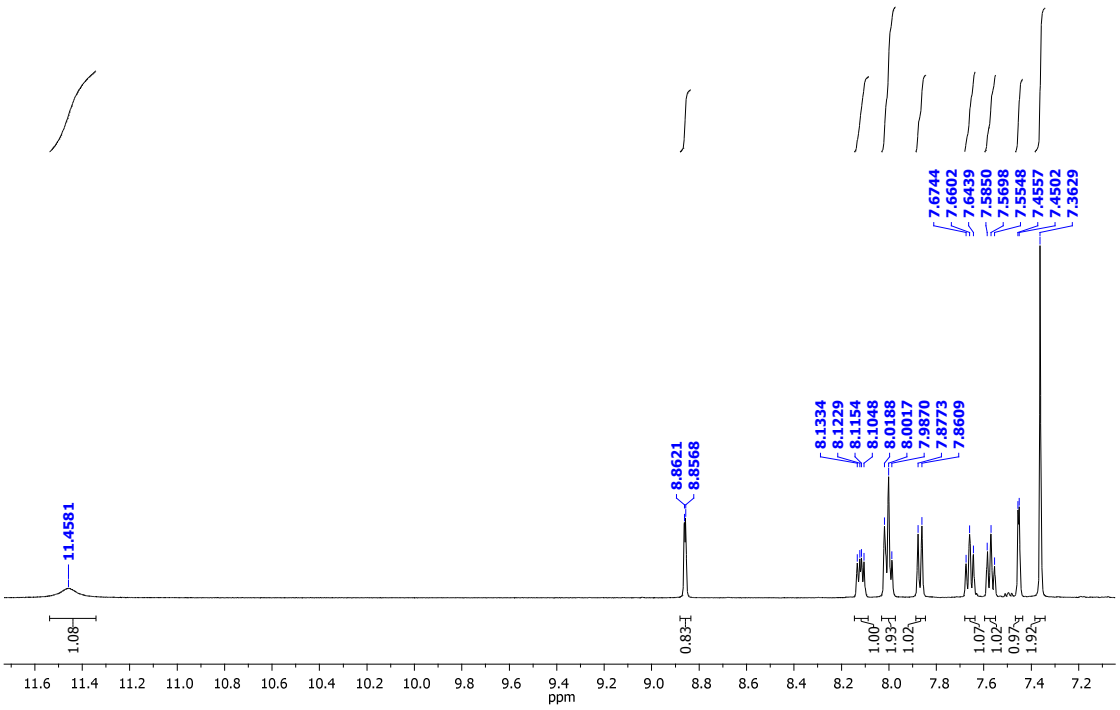
MS HRMS (ESI) calcd for $C_{21}H_{13}BrCl_2FN_2O_3S$ ($M-H^+$): 540.9186, found 540.9198.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 220 nm. Retention time 20.79 min. Purity 94 %.

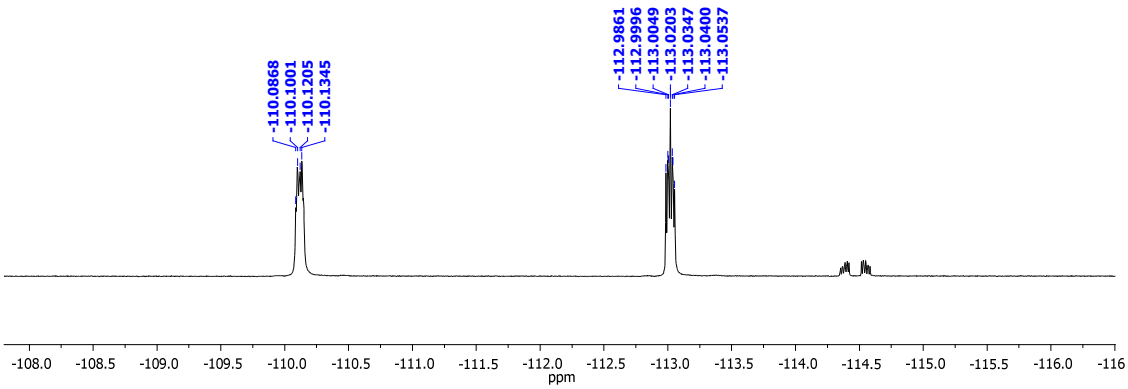
(9): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-2,5-difluorobenzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2,5-difluoro-4-bromosulfonyl chloride.

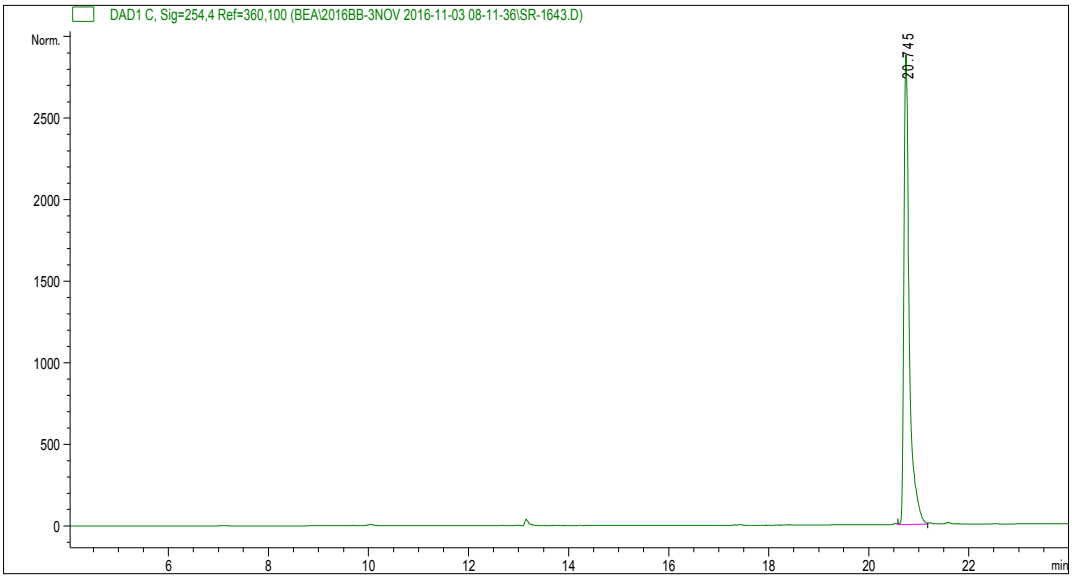


SR-1643 (1H NMR)



SR-1643 (19F NMR)





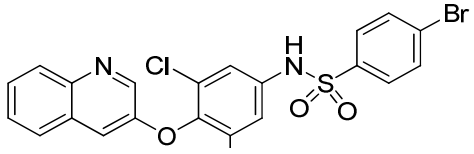
^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.46 (s, 1H), 8.86 (d, *J* = 2.7 Hz, 1H), 8.12 (dd, *J* = 9.0, 5.3 Hz, 1H), 8.00 (t, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 2.7 Hz, 1H) and 7.36 (s, 2H) ppm.

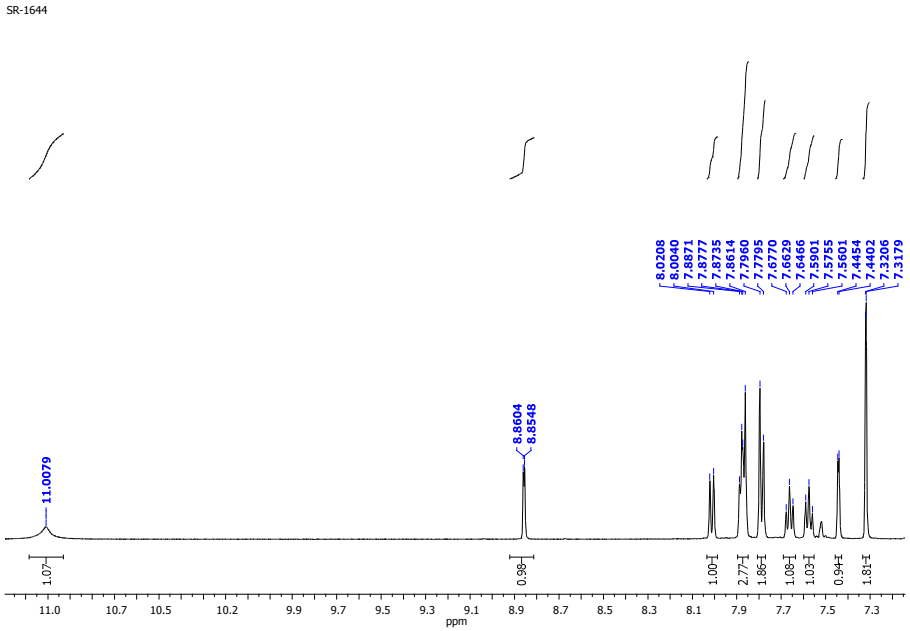
^{19}F NMR (470 MHz, $CDCl_3$) δ –110.12 (m) and -113.01 (m) ppm.

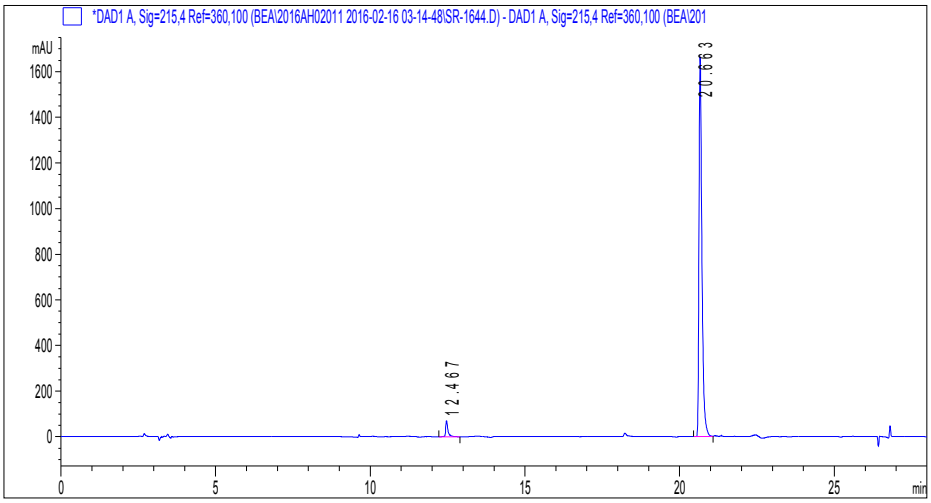
MS HRMS (ESI) calcd for $C_{21}H_{12}BrCl_2F_2N_2O_3S$ ($M-H^+$): 558.9092 / 558.9072, found 558.9048 / 558.9035.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 21.74 min. Purity > 98 %.

(10): 4-bromo-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)benzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2,5-difluoro-4-bromosulfonyl chloride.





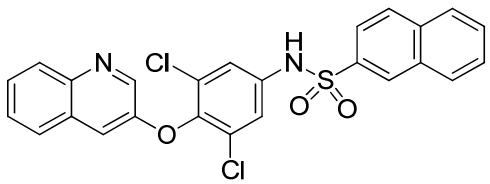


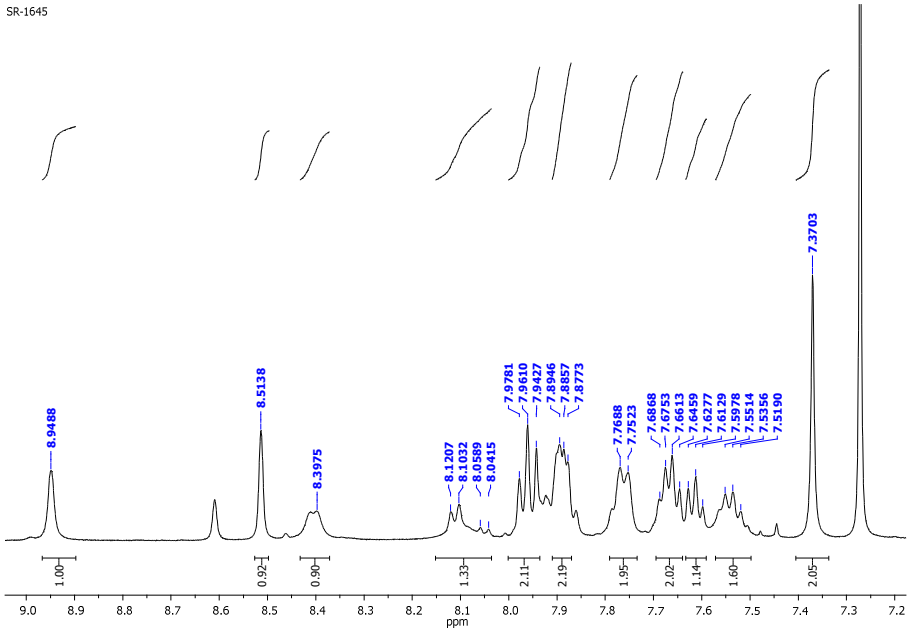
^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.01 (s, 1H), 8.86 (d, *J* = 2.8 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.90–7.85 (m, 3H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.69–7.64 (m, 1H), 7.60–7.55 (m, 1H), 7.44 (d, *J* = 2.6 Hz, 1H) and 7.32 (s, *J* = 1.4 Hz, 2H) ppm.

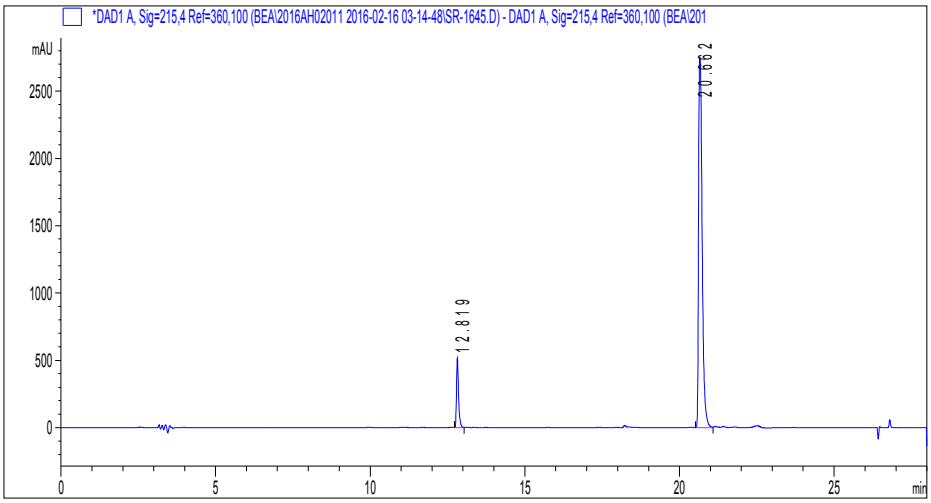
MS HRMS (ESI) calcd for $C_{21}H_{14}BrCl_2N_2O_3S$ ($M-H^+$): 522.9280, found 522.9298.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 20.66 min. Purity 96 %.

(11): N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)naphthalene-2-sulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-naphthylsulfonyl chloride.







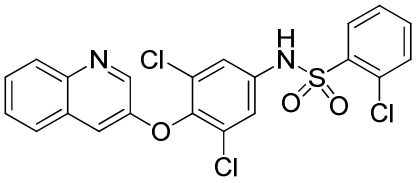
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.51 (s, 1H), 8.43–8.37 (m, 1H), 8.15–8.04 (m, 1H), 8.00–7.94 (m, 2H), 7.91–7.87 (m, 2H), 7.77 (t, *J* = 9.3 Hz, 2H), 7.67 (dd, *J* = 13.7, 6.7 Hz, 2H), 7.63–7.59 (m, 1H), 7.57–7.50 (m, 2H) and 7.37 (s, 2H) ppm.

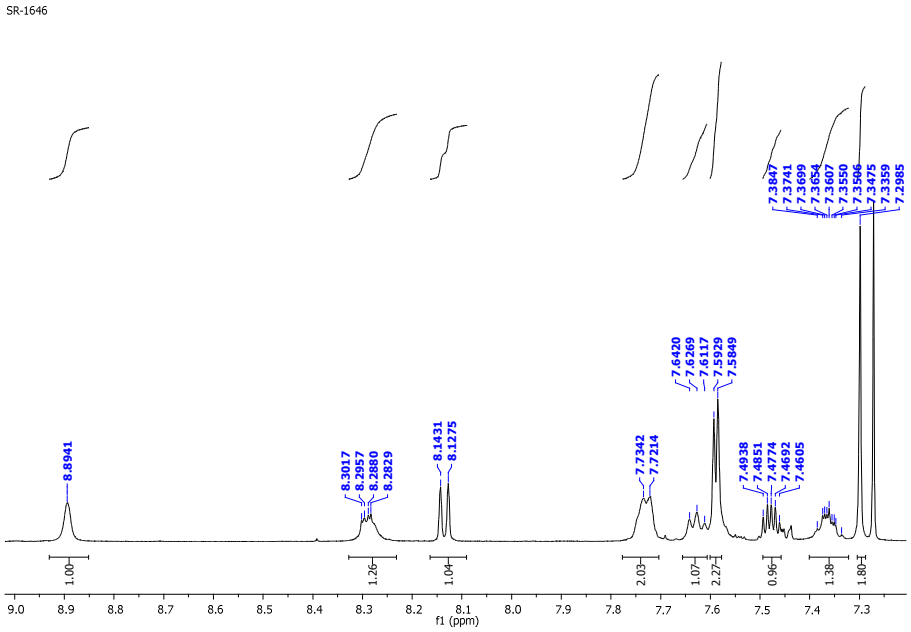
MS HRMS (ESI) calcd for $C_{25}H_{17}Cl_2N_2O_3S$ ($M-H^+$): 495.0331, found 495.0346.

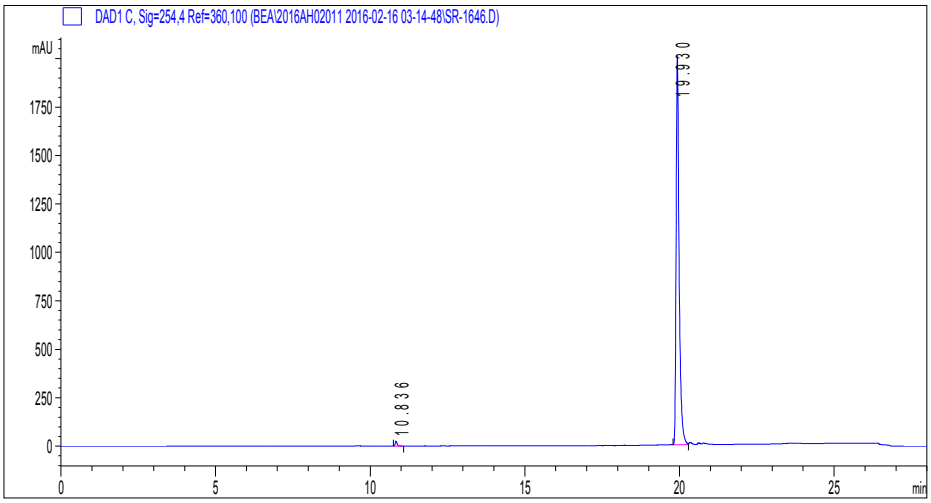
Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18

(2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 20.66 min. Purity 90 %.

(12): 2-chloro-N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)benzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-chlorosulfonyl chloride.





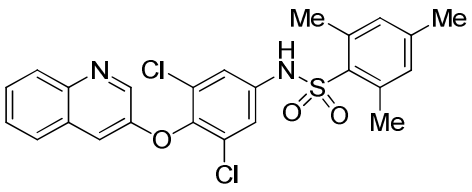


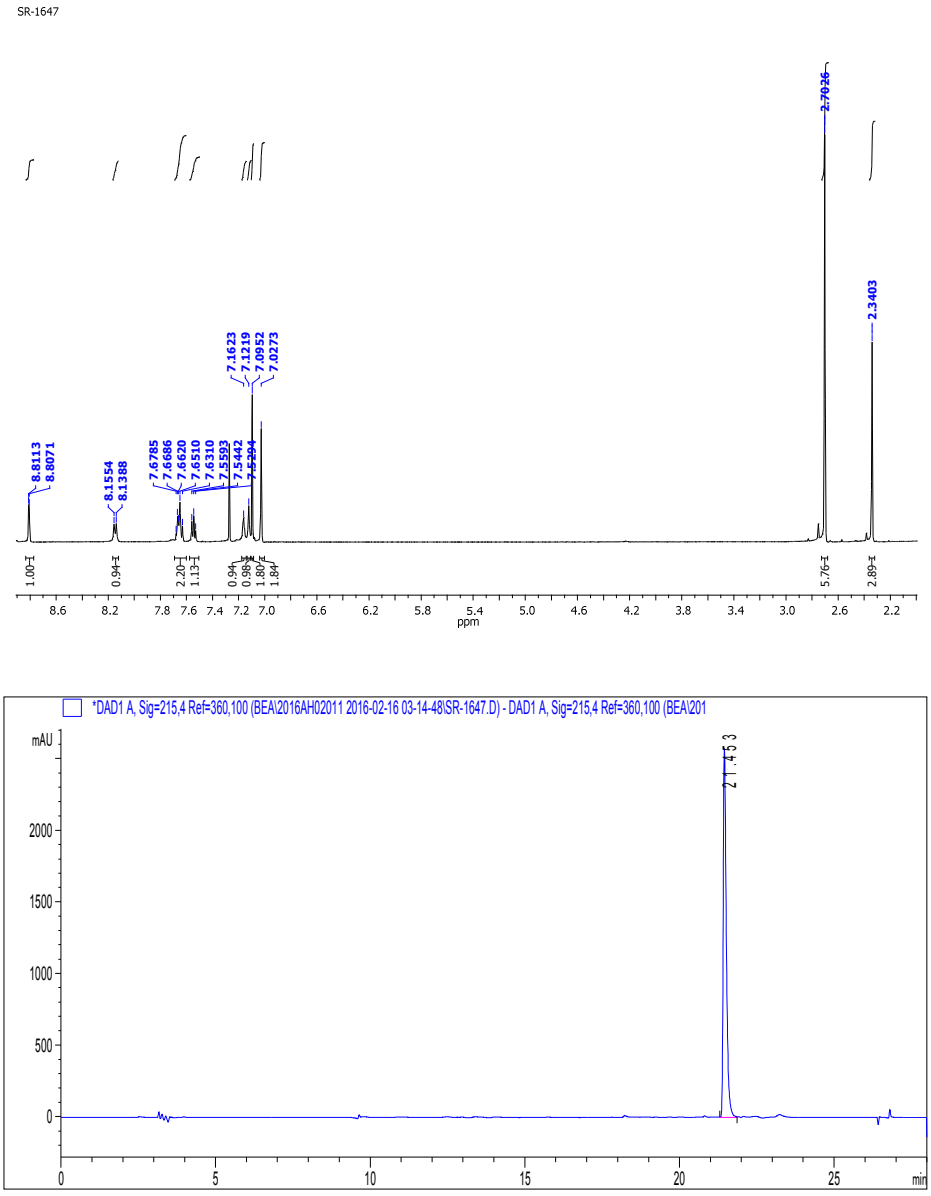
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.33–8.23 (m, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 6.4 Hz, 2H), 7.66–7.60 (m, 1H), 7.59 (d, *J* = 4.0 Hz, 2H), 7.49–7.45 (m, 1H), 7.36 (m, 1H) and 7.30 (s, 2H) ppm.

MS HRMS (ESI) calcd for $C_{21}H_{13}Cl_3N_2O_3S$ ($M-H^+$): 478.9785, found 478.9790.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 254 nm. Retention time 19.93 min. Purity 99 %.

(13): N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)-2,4,6-trimethylbenzenesulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2,4,6-trimethylsulfonyl chloride.





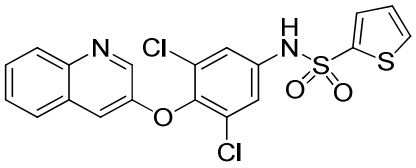
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 2.1 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.69–7.60 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.16 (s, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.10 (s, 2H), 7.03 (s, 2H), 2.70 (s, 6H) and 2.34 (s, 3H) ppm.

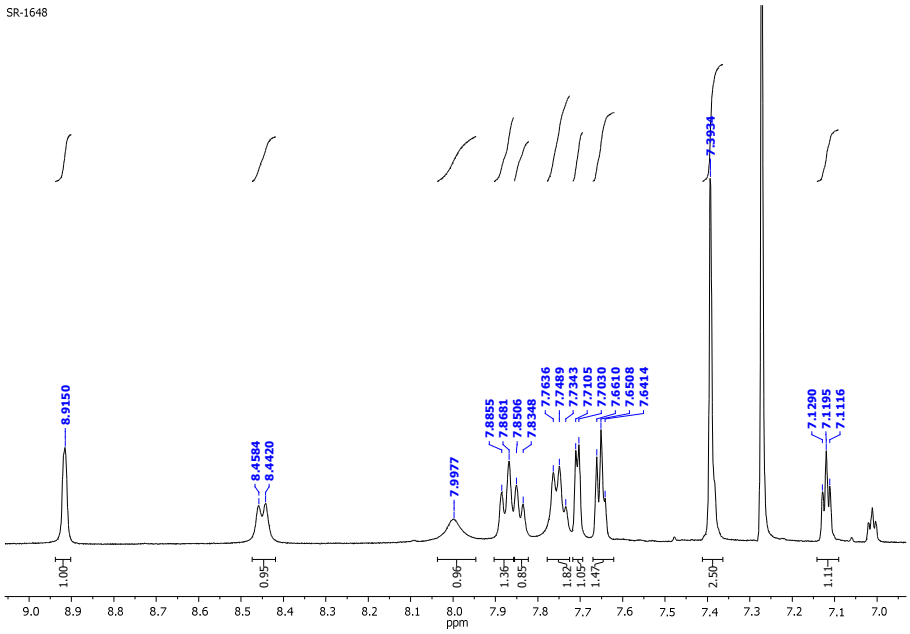
MS HRMS (ESI) calcd for $C_{24}H_{21}Cl_2N_2O_3S$ ($M-H^+$): 487.0644, found 487.0651.

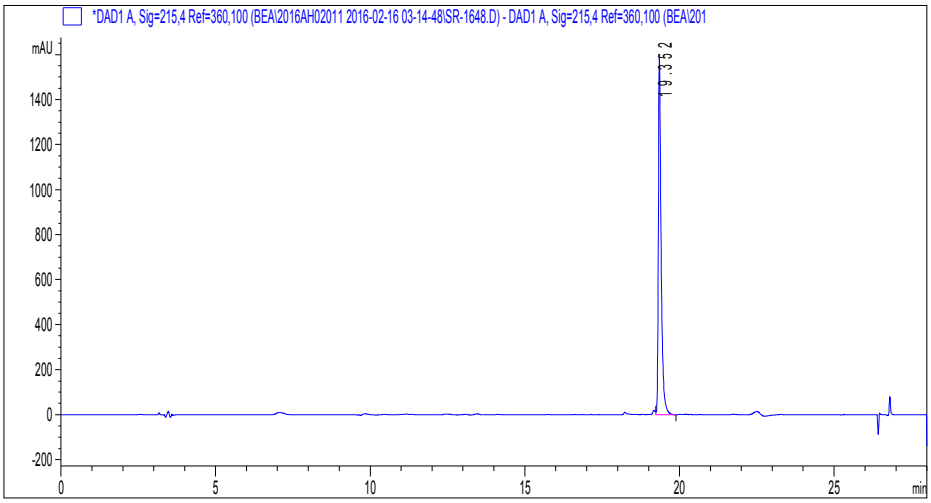
Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2)

(250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 21.45 min. Purity 100 %.

(14): N-(3,5-dichloro-4-(quinolin-3-yloxy)phenyl)thiophene-2-sulfonamide: The title compound was made following the same general protocol as described for **3a**, using 2-thiophenesulfonyl chloride.





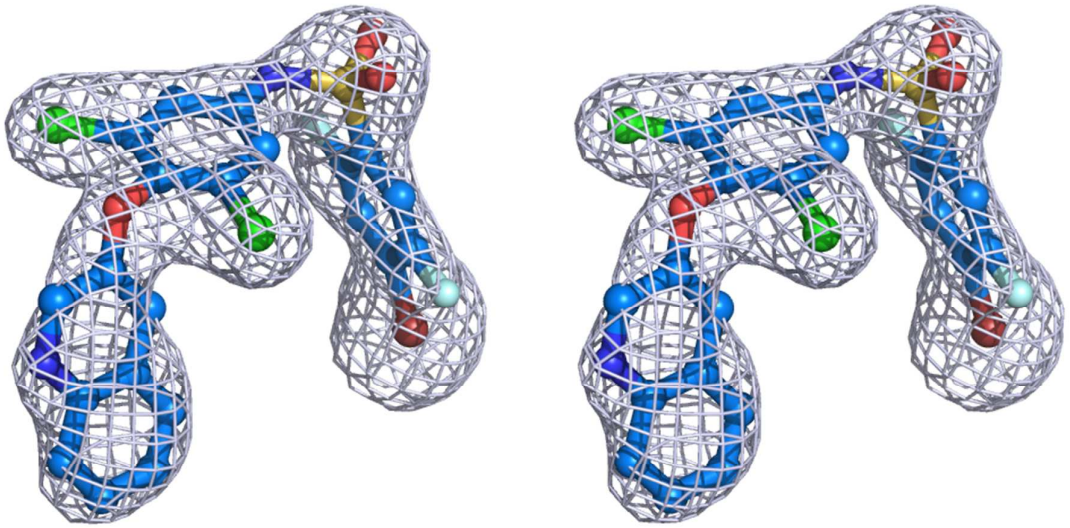


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 2H), 8.45 (d, *J* = 8.0 Hz, 2H), 8.04–7.95 (m, 2H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.78–7.73 (m, 2H), 7.71 (d, *J* = 3.7 Hz, 1H), 7.65 (t, *J* = 4.9 Hz, 1H), 7.39 (s, 2H) and 7.12 (t, *J* = 4.4 Hz, 1H) ppm.

MS HRMS (ESI) calcd for $C_{19}H_{13}Cl_2N_2O_3S_2$ ($M-H^+$): 450.9739, found 450.9743.

Anal HPLC Analytical HPLC: Sample was dissolved in methanol (1 mg/ ml) and eluted with solvent A: 0.1% TFA in Milliq water and solvent B: 0.08% TFA in MeCN on a phenomenex Luna 5 uM C18 (2) (250 x 4.60 mm), flow rate = 1 ml/min, gradient 0–100% of solvent B over 30 min, with UV detection at 215 nm. Retention time 19.35 min. Purity 100 %.

Supplemental Figure 1. . Shown is a wall-eye stereo image of the electron density map (composite omit map) contoured at 1.5σ around **9**.



Supplemental Figure 2. Shown is a superimposition of the published X-ray crystal structure of INT131 bound to the PPARγ LBD (yellow) with the docked model of INT131 (cyan) bound to PPARγ.