Supporting Information

Discovery of HSD−621 as a Potential Agent for the Treatment of Type 2 Diabetes

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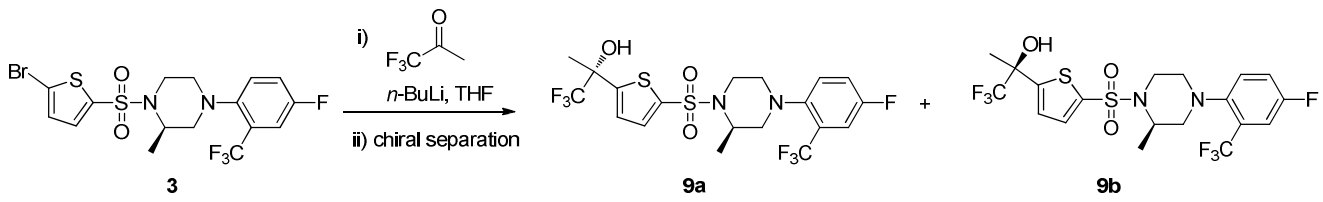
Contents of Supporting Experimental Information:

1. Chemistry.

Commercial reagents and solvents were used as received without further purification. ^{1}H NMR spectra were recorded on a Bruker 400MHz spectrometer. LC–MS data was collected using a Micromass LCT mass spectrometer with electrospray ionization in conjunction with a Waters 2795 LC system. Liquid chromatography (LC–MS) was performed using a Phenomenex C18 column (Mercury MS Luna 5μ C18(2), 20 x 2 mm) with mobile phase of 0.1% formic acid (FA) in H_2O (A) and 0.1% formic acid in MeCN (B) and a gradient of 15–100% B in 3 min followed by 1.5 min at 100% B. HRMS data was recorded on a Bruker APEXIII–7T FTMS spectrometer with electrospray ionization. Purity of compounds was also analyzed by RF–HPLC using the following two conditions: 1) H_2O/MeCN/0.1% FA; 2) H_2O/MeOH/0.1% FA (a gradient of 5–100% B in 7 min followed by 2 min at 100%. A satisfying purity of $\geq$ 95% was achieved with both methods.

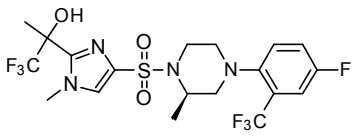
Representative synthesis of 1,1,1-trifluoro-2-(thiophen-2-yl)propan-2-ols:

Method 1**: Synthesis of **9a** and **9b



(2*S*)-1,1,1-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)propan-2-ol (**9a**) and **(2*R*)-1,1,1-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)propan-2-ol** (**9b**): To a solution of (*R*)-1-(5-bromothiophen-2-ylsulfonyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazine **3** (4.0 g, 8.23 mmol) in anhydrous THF (30 ml) was added *n*-butyllithium (5.4 mL, 8.64 mmol, 1.6 M in hexanes) at –78 ^{o}C. The resultant solution was stirred under N_2 for 15 min, then trifluoromethyl ketone (2.7 mL, 30 mmol) was added. After stirring at -78 ^{o}C for 30 min, the mixture was warmed it up to room temperature. Quenched with aq. NH_4Cl, extracted with CH_2Cl_2 (3x). The combined organic layer was dried over $MgSO_4$. The crude product was purified on SiO_2 gel column eluted with CH_2Cl_2/hexane to give 1,1,1-trifluoro-2-(5-(((2*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl-2-methylpiperazin-1-yl)sulfonyl)-2-thienyl)propan-2-ol as a white solid (3.89 g, 91 % yield). This diastereomer mixture was further separated on chiral column to give **9a** and **9b**. **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (d, *J* = 6.82 Hz, 3 H) 1.86 (s, 3 H) 2.69–2.83 (m, 3 H) 2.86–2.94 (m, 1 H) 3.00 (dd, *J* = 11.12, 3.54 Hz, 1 H) 3.36–3.46 (m, 1 H) 3.75 (d, *J* = 12.88 Hz, 1 H) 4.20–4.29 (m, 1 H)

7.11 (d, *J* = 4.04 Hz, 1 H) 7.19–7.28 (m, 2 H) 7.33 (dd, *J* = 8.72, 2.65 Hz, 1 H) 7.49 (d, *J* = 3.79 Hz, 1 H). HRMS: calcd for $C_{19}H_{19}F_7N_2O_3S_2 + H^+$, 521.0798; found $[M+H]^+$, 521.0799. **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.82 Hz, 3 H) 1.86 (s, 3 H) 2.71–2.77 (m, 2 H) 2.84 (s, 1 H) 2.86-2.93 (m, 1 H) 3.02 (dd, *J* = 11.12, 3.54 Hz, 1 H) 3.42 (td, *J* = 12.25, 3.03 Hz, 1 H) 3.73 (d, *J* = 12.88 Hz, 1 H) 4.22–4.30 (m, 1 H) 7.11 (d, *J* = 3.79 Hz, 1 H) 7.18–7.29 (m, 2 H) 7.33 (dd, *J* = 8.84, 2.78 Hz, 1 H) 7.50 (d, *J* = 4.04 Hz, 1 H). HRMS: calcd for $C_{19}H_{19}F_7N_2O_3S_2 + H^+$, 521.0798; found $[M+H]^+$, 521.0820.



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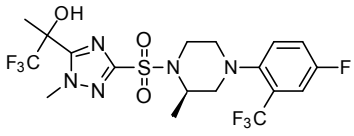
1,1,1-trifluoro-2-(4-(((R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)-1-methyl-1H-imidazol-2-yl)propan-2-ol (**7**): Synthesize in similar fashion as **9a** and **9b** from corresponding aryl halide. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.34 (dd, *J* = 6.69, 4.67 Hz, 3 H) 1.94 (s, 3 H) 2.65–2.88 (m, 3 H) 2.96–3.09 (m, 1 H) 3.46 (t, *J* = 11.87 Hz, 1 H) 3.56–3.69 (m, 1 H) 3.76 (t, *J* = 12.38 Hz, 1 H) 3.89 (s, 3 H) 4.17–4.30 (m, 1 H) 7.17 - 7.25 (m, 2 H) 7.33 (dd, *J* = 8.84, 2.78 Hz, 1 H) 7.42 (s, 1 H). HRMS: calcd for C19H21F7N4O3S + H^+, 519.1295; found (ESI, $[M+H]^+$), 519.1296.



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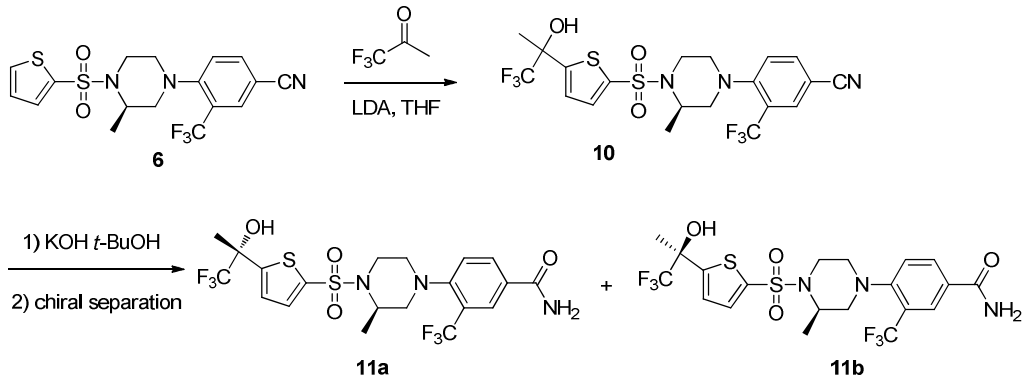
1,1,1-trifluoro-2-(3-(((R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (**8**). Synthesize in similar fashion as **9a** and **9b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (d, *J* = 6.82 Hz, 3 H) 2.61–2.72 (m, 2 H) 2.79 (d, *J* = 10.86 Hz, 1 H) 2.83–2.95 (m, 1 H) 3.35–3.45 (m, 1 H) 3.63–3.78 (m, 1 H) 3.94 (d, *J* = 2.02 Hz, 3 H) 4.05–4.23 (m, 1 H) 7.46–7.70 (m, 3 H) 8.25 (d, *J* = 12.63 Hz, 2 H) 8.60 (br. s., 1 H). HRMS: calcd for C18H19F7N6O4S + H^+, 549.1200; found (ESI, $[M+H]^+$), 549.1146.

Method 2**: Synthesis of **11a** and **11b

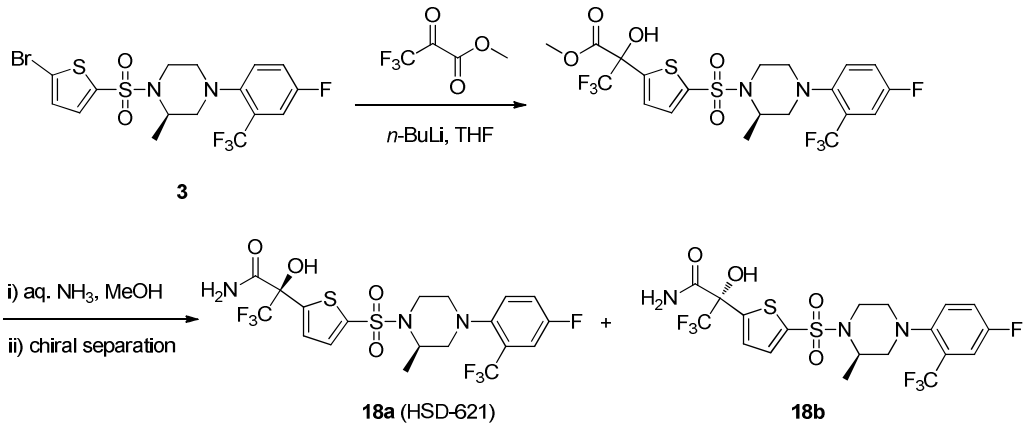


4-((*R*)-3-methyl-4-((5-((*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)thiophen-2-yl)sulfonyl)piperazin-1-yl)-3-(trifluoromethyl)benzamide (**11a**) and **4-((*R*)-3-methyl-4-((5-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)thiophen-2-yl)sulfonyl)piperazin-1-yl)-3-(trifluoromethyl)benzamide** (**11b**): To a solution of (*R*)-4-(3-methyl-4-(thiophen-2-ylsulfonyl)piperazin-1-yl)-3-(trifluoromethyl)benzonitrile **6** (415 mg, 1 mmol, prepared according to similar procedures[7a] in 96% yield) in anhydrous THF (4 mL) was added LDA (0.61 mL, 1.8 M in hexanes/THF, 1.1 mmol). The resultant mixture was stirred at –78 ^{o}C for 15 min. Trifluoroacetione (0.188 mL, 2 mmol) was added dropwise through a syringe. The reaction mixture was warmed to rt slowly, then quenched by a few drops of water. The solvent was removed under vacuum. The crude product was purified on SiO_2 gel column eluted with hexanes/EtOAc to give the desired product 4-((3*R*)-3-methyl-4-((5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)thiophen-2-yl)sulfonyl)piperazin-1-yl)-3-(trifluoromethyl)benzonitrile **10** as white solid (368 mg, 69%).

A reaction mixture of **10** (370 mg, 0.7 mmol) and KOH (196 mg, 3.5 mmol) in *t*-BuOH (5 mL) was heated to 80 ^{o}C for 20 min. Diluted with water and acidified with 10 aq. HCl to pH = 2. The precipitate was collected and washed with water to give the desired product 4-[(3*R*)-3-methyl-4-{[5-(2,2,2-trifluoro-1-hydroxy-1-methylethyl)-2-thienyl]sulfonyl}piperazin-1-yl]-3-(trifluoromethyl)benzamide **7** as a white solid (329 mg, 86%) which was subsequently separated through a chiral column to give 4-[(3R)-3-methyl-4-({5-[(1*S*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]-2-thienyl}sulfonyl)piperazin-1-yl]-3-(trifluoromethyl)benzamide (**11a**) and 4-[(3*S*)-3-methyl-4-({5-[(1*S*)-2,2,2-trifluoro-1-hydroxy-1-methylethyl]-2-thienyl}sulfonyl)piperazin-1-yl]-3-(trifluoromethyl)benzamide (**11b**). **11a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (d, *J* = 6.82 Hz, 3 H) 1.65 (s, 3 H) 2.53–2.71 (m, 2 H) 2.80–2.87 (m, 2 H) 3.15 (td, *J* = 12.25, 2.78 Hz, 1 H) 3.57 (d, *J* = 12.63 Hz, 1 H) 4.02 (d, *J* = 6.57 Hz, 1 H) 7.17 (d, *J* = 4.04 Hz, 1 H) 7.33–7.44 (m, 3 H) 7.52 (d, *J* = 4.04 Hz, 1 H) 7.95–8.07 (m, 3 H). HRMS: calcd for $C_{20}H_{21}F_6N_3O_4S_2 + H^+$, 546.0950; found (ESI, $[M+H]^+$), 546.0973. **11b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (d, *J* = 6.57 Hz, 3 H) 1.78 (s, 3 H) 2.72 (td, *J* = 11.68, 3.16 Hz, 1 H) 2.81 (d, *J* = 11.37 Hz, 1 H) 2.90–3.03 (m, 2 H) 3.28 (td, *J* = 12.32, 2.91 Hz, 1 H) 3.69 (d, *J* = 12.63 Hz, 1 H)

4.12–4.20 (m, 1 H) 4.31–4.40 (m, 1 H) 7.30 (d, *J* = 4.04 Hz, 1 H) 7.50 (d, *J* = 8.34 Hz, 1 H) 7.54 (s, 1 H) 7.66 (d, *J* = 4.04 Hz, 1 H) 8.13 (dd, *J* = 8.34, 1.77 Hz, 1 H) 8.18 (d, *J* = 2.02 Hz, 2 H). HRMS: calcd for $C_{20}H_{21}F_6N_3O_4S_2 + H^+$, 546.0950; found (ESI, $[M+H]^+$), 546.0974.

Representative Synthesis of 3,3,3-trifluoro-2-hydroxy-2-(thiophen-2-yl)propanamides: Synthesis of **18a** and **18b**

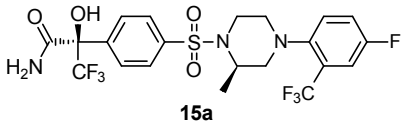


(*R*)-3,3,3-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)-2-hydroxypropanamide (**18a** = HSD-621) and **(*S*)-3,3,3-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)-2-hydroxypropanamide** (**18b**) To a solution of (*R*)-1-(5-bromothiophen-2-ylsulfonyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazine **3** (28.1 g, 57.7 mmol) in anhydrous THF (200 ml) was added butyllithium (28.8 ml, 57.7 mmol) at –78 ^oC. The resultant solution was stirred under N_2 for 15 min., followed by addition of a solution of methyl 3,3,3-trifluoropyruvate (6.07 ml, 57.7 mmol) in THF (20 mL) via a cannula. After stirring for 2 h at -78 ^oC, the reaction mixture was quenched with a few mL of 10% aq. HCl. The temperature was raised to rt and the mixture was dried over $MgSO_4$. The desired product, methyl 3,3,3-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)-2-hydroxypropanoate was purified on SiO_2 column eluted with CH_2Cl_2/hexane (15 - 100%) as a sticky, light yellow solid (22 g, 39.0 mmol, 68% yield).

To a solution of the above compound (21.5 g, 38.1 mmol) in MeOH (200 ml) was added aq. NH_3 (~28-30%, 50 mL). After stirring at room temperature overnight, the reaction mixture was diluted with ice water (700 mL). The white precipitate was collected by filtration, washed with water and dried in oven at 60 ^oC to give the desired product 3,3,3-trifluoro-2-(5-((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)thiophen-2-yl)-2-hydroxypropanamide **18** (15 g). The filtrate was extracted with CH_2Cl_2 (4 x 100 mL) and concentrated. The mixture was purified on column chromatography eluted with EA/DCM (0-40%) to give additional 1.5 g of product **18**. ^1H NMR

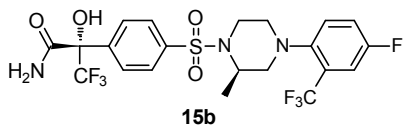
(400 MHz, DMSO-d_6) δ ppm 1.13 (d, J = 6.82 Hz, 3 H) 2.62–2.77 (m, 2 H) 2.79–2.88 (m, 1 H) 2.86–2.98 (m, 1 H) 3.15–3.31 (m, 1 H) 3.67 (d, J = 10.61 Hz, 1 H) 4.10–4.13 (m, 1 H) 7.43 (s, 1 H) 7.49–7.60 (m, 3 H) 7.65 (d, J = 4.04 Hz, 1 H) 8.01 (d, J = 11.12 Hz, 2 H) 8.40 (d, J = 1.77 Hz, 1 H). HRMS: calcd for $C_{19}H_{18}F_7N_3O_4S_2 + H^+$, 550.0700; found (ESI, $[M+H]^+$, 550.0716. Further separation of **18** (13.5 g) with a chiral column gave **18a** (5.7 g) and **18b** (6 g). **18a** (HSD-621)*: $[\alpha]^{25}_D$ = -29.8 (10 mg/mL, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (d, J = 6.57 Hz, 3 H) 2.61–2.76 (m, 2 H) 2.84 (d, J = 11.37 Hz, 1 H) 2.93 (dd, J = 11.24, 3.41 Hz, 1 H) 3.15–3.29 (m, 1 H) 3.66 (d, J = 12.88 Hz, 1 H) 4.01–4.24 (m, 1 H) 7.42 (d, J = 3.79 Hz, 1 H) 7.49–7.59 (m, 3 H) 7.65 (d, J = 4.04 Hz, 1 H) 8.01 (d, J = 10.10 Hz, 2 H) 8.39 (s, 1 H). HRMS: calcd for $C_{19}H_{18}F_7N_3O_4S_2 + H^+$, 550.0700; found (ESI-FTMS, $[M+H]^+$, 550.0697. **18b**: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.28 (d, J = 5.81 Hz, 3 H) 2.68 - 2.83 (m, 2 H) 2.90 (d, J = 11.12 Hz, 1 H) 3.00 (dd, J = 11.12, 3.28 Hz, 1 H) 3.33 - 3.51 (m, 1 H) 3.71 (d, J = 12.63 Hz, 1 H) 4.23 (d, J = 6.06 Hz, 1 H) 6.18 (br. s., 1 H) 6.51 (br. s., 1 H) 7.13–7.30 (m, 2 H) 7.33 (dd, J = 8.72, 2.65 Hz, 2 H) 7.48 (br. s., 1 H). HRMS: calcd for $C_{19}H_{18}F_7N_3O_4S_2 + H^+$, 550.0700; found (ESI-FTMS, $[M+H]^+$, 550.0701.

*Note: the absolute stereochemistry of **18a** (HSD-621) is assigned by single crystal X-ray (see coordinates in Tables 1–4).



15a

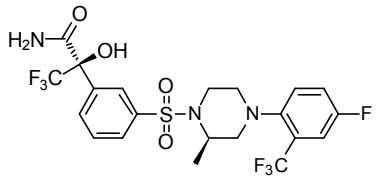
(*R*)-3,3,3-trifluoro-2-(4-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)-phenyl)-2-methylpiperazin-1-yl)sulfonyl)phenyl)-2-hydroxypropanamide (**15a**). Synthesize in similar fashion as **18a** and **18b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (d, J = 6.57 Hz, 3 H) 2.59–2.69 (m, 2 H) 2.78 (d, J = 11.87 Hz, 1 H) 2.86 (d, J = 3.28 Hz, 1 H) 3.21 (t, J = 12.38 Hz, 1 H) 3.68 (d, J = 12.88 Hz, 1 H) 4.12 (t, J = 8.84 Hz, 1 H) 7.45–7.57 (m, 3 H) 7.71 (s, 1 H) 7.77 (s, 1 H) 7.94 (s, 4 H) 7.97 (s, 1 H)**.** HRMS: calcd for $C_{21}H_{20}F_7N_3O_4S + H^+$, 544.11355; found (ESI, $[M+H]^+$), 544.1137.



15b

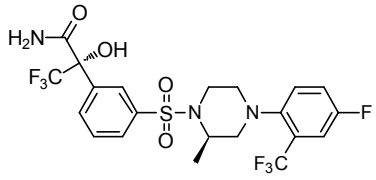
(*S*)-3,3,3-trifluoro-2-(4-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)-phenyl)-2-methylpiperazin-1-yl)sulfonyl)phenyl)-2-hydroxypropanamide (**15a**). Synthesize in similar fashion as **18a** and **18b** Synthesize in similar fashion as **8a** and **8b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (d, J = 6.57 Hz, 3 H) 2.62–2.68 (m, 2 H) 2.75–2.82 (m, 1 H) 2.85–2.92 (m, 1

H) 3.20–3.25 (m, 1 H) 3.67 (d, *J* = 12.88 Hz, 1 H) 4.09 (q, *J* = 5.14 Hz, 1 H) 7.45–7.57 (m, 3 H) 7.72 (s, 1 H) 7.77 (s, 1 H) 7.94 (s, 4 H) 7.97 (s, 1 H)**.** HRMS: calcd for $C_{21}H_{20}F_7N_3O_4S + H^+$, 544.11355; found (ESI, $[M+H]^+$), 544.1134.



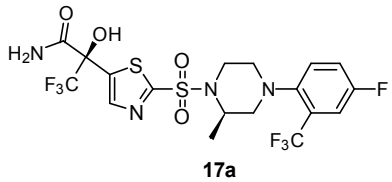
16a

(*R*)-3,3,3-trifluoro-2-(3-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)phenyl)-2-hydroxypropanamide (**16a**). Synthesize in similar fashion as **18a** and **18b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02–1.08 (m, 3 H) 2.61–2.69 (m, 2 H) 2.80 (d, *J* = 12.13 Hz, 1 H) 2.90 (dd, *J* = 11.37, 3.28 Hz, 1 H) 3.14–3.25 (m, 1 H) 3.66 (d, *J* = 12.63 Hz, 1 H) 4.10 (d, *J* = 7.07 Hz, 1 H) 7.47–7.57 (m, 3 H) 7.66 - 7.80 (m, 3 H) 7.90 (d, *J* = 7.83 Hz, 1 H) 8.01 (d, *J* = 7.83 Hz, 1 H) 8.05 (s, 1 H) 8.19 (s, 1 H). HRMS: calcd for $C_{21}H_{20}F_7N_3O_4S + H^+$, 544.11355; found (ESI, $[M+H]^+$), 544.1135.



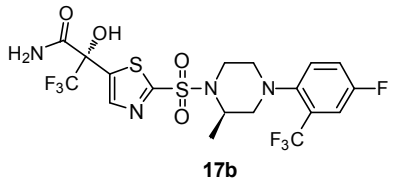
16b

(*S*)-3,3,3-trifluoro-2-(3-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)phenyl)-2-hydroxypropanamide (**16b**). Synthesize in similar fashion as **18a** and **18b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (d, *J*=6.57 Hz, 3 H) 2.61 - 2.71 (m, 2 H) 2.80 (d, *J*=10.86 Hz, 1 H) 2.88 (dd, *J*=11.37, 3.54 Hz, 1 H) 3.17 - 3.24 (m, 1 H) 3.67 (d, *J*=12.63 Hz, 1 H) 4.03 - 4.13 (m, 1 H) 7.48 - 7.57 (m, 3 H) 7.68 - 7.81 (m, 3 H) 7.90 (d, *J*=8.34 Hz, 1 H) 8.01 (d, *J*=7.83 Hz, 1 H) 8.04 (s, 1 H) 8.19 (s, 1 H). HRMS: calcd for $C_{21}H_{20}F_7N_3O_4S + H^+$, 544.11355; found (ESI, $[M+H]^+$), 544.1136;



17a

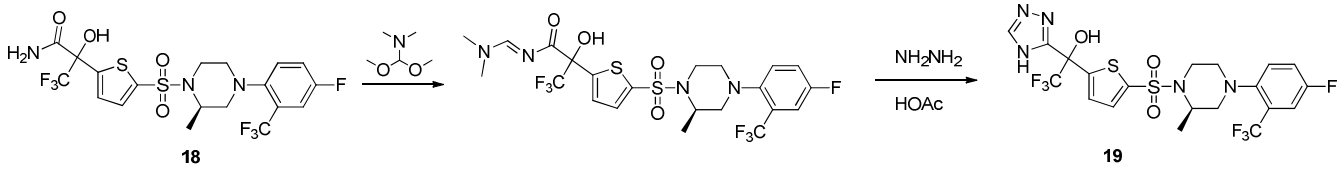
(*R*)-3,3,3-trifluoro-2-(2-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)-phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiazol-5-yl)-2-hydroxypropanamide (**17a**). Synthesize in similar fashion as **18a** and **18b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.15 (d, *J*=6.57 Hz, 3 H) 2.65 - 2.80 (m, 2 H) 2.82 - 2.91 (m, 1 H) 2.96 - 3.05 (m, 1 H) 3.19 - 3.24 (m, 1 H) 3.77 (d, *J*=12.88 Hz, 1 H) 4.17 - 4.25 (m, 1 H) 7.56 (dt, *J*=8.08, 2.27 Hz, 3 H) 8.19 (s, 2 H) 8.26 (s, 1 H) 8.63 (s, 1 H). HRMS: calcd for $C_{18}H_{17}F_7N_4O_4S_2 + H^+$, 551.0652; found (ESI, $[M+H]^+$), 551.0650;



17b

(*S*)-3,3,3-trifluoro-2-(2-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)-phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiazol-5-yl)-2-hydroxypropanamide (**17b**). Synthesize in similar fashion as **18a** and **18b** from corresponding aryl halide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (d, *J*=6.57 Hz, 3 H) 2.65 - 2.81 (m, 2 H) 2.81 - 2.93 (m, 1 H) 2.95 - 3.03 (m, 1 H) 3.34 - 3.39 (m, 1 H) 3.78 (d, *J*=12.88 Hz, 1 H) 4.14 - 4.26 (m, 1 H) 7.49 - 7.61 (m, 3 H) 8.18 (br. s., 2 H) 8.25 (s, 1 H) 8.63 (s, 1 H). HRMS: calcd for $C_{18}H_{17}F_7N_4O_4S_2 + H^+$, 551.0652; found (ESI, $[M+H]^+$), 551.0651.

Synthesis of 8g:



18 19

2,2,2-trifluoro-1-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)-1-(4H-1,2,4-triazol-3-yl)ethanol (**19**):To a 50 mL flask containing 3,3,3-trifluoro-2-(5-((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)thiophen-2-yl)-2-hydroxypropanamide **18** (76.9 mg, 0.14 mmol) was added *N,N*-dimethylformamide dimethylacetal (1 mL). The reaction mixture was stirred at room temperature for 20 min. Reaction was complete as determined by LC/MS. This was concentrated, gave *N*-((dimethylamino)methylene)-3,3,3-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)-2-hydroxypropanamide as a crude oil (96 mg, 100% Yield), which was used in next step directly without purification.

To a solution of hydrazine (8 µL, 0.28 mmol) in 3 mL of acetic acid was added *N*-((dimethylamino)methylene)-3,3,3-trifluoro-2-(5-(((*R*)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonyl)thiophen-2-yl)-2-hydroxypropanamide (96 mg, 0.14 mmol) at room temperature. The reaction mixture was then stirred at room temperature for 1 hour. The reaction was complete as determined by LC/MS. The solvent was evaporated and the resultant crude product was diluted with EtOAc, washed with aq. $NaHCO_3$ solution and extracted with EtOAc (3x). The combined organic layer was dried over Na_2SO_4 and concentrated . The crude was purified on SiO_2 gel column eluted with 0–8% MeOH in DCM to give the titled compound **19** as a light yellow solid (60 mg, 75% Yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 (d, *J* = 1.00 Hz, 3 H) 2.62–2.69 (m, 2 H) 2.80 (d, *J*

= 12.13 Hz, 1 H) 2.90 (dd, *J* = 11.37, 3.28 Hz, 1 H) 3.13–3.26 (m, 1 H) 3.66 (d, *J* = 12.63 Hz, 1 H) 4.11 (br. s., 1 H) 7.49–7.58 (m, 2 H) 7.68–7.81 (m, 2 H) 7.90 (d, *J* = 7.83 Hz, 1 H) 8.01 (d, *J* = 7.83 Hz, 1 H) 8.05 (s, 1 H) 8.19 (s, 1 H). HRMS: calcd for $C_{20}H_{18}F_7N_5O_3S_2 + H^+$, 574.0812; found (ESI, $[M+H]^+$), 574.0808.

2. Cellular Assays.

a. Determination of IC_{50} against human 11β–HSD1

Compounds described herein are tested in a cell-based assay using a stable Chinese Hamster Ovary (CHO) cell line expressing human 11β–HSD1. Cells are plated at 20,000 cells/well in 384 well plates and incubated overnight (12–16 hrs) at 37^{o}C/5% CO_2. Cells are treated with different concentration of compound in 90 microliter serum–free media and incubated for 30 minutes at 37^{o}C/5%CO_2. 10 μL of 5 μM cortisone (final concentration 500nM) is then added to the cells and the plate is incubated at 37 ^{o}C/5%CO_2 for 120 minutes. 15 microliter of media is withdrawn and amount of cortisol in the media is measured using the DiscoverX Hit Hunter Cortisol Assay (DiscoverX corp, CA), following manufacturer's instructions. Briefly, 15 μL media is transferred to a white 384 well assay plate. 5 μL of anti–cortisol antibody and 10 μL of ED complex is added to each well of the assay plate. The assay plate is incubated at room temperature for 60 minutes with gentle shaking. Galacton Star, Emerald Green, and chemiluminescence substrate buffer are mixed 1:5:19. The mixture is then combined in equal parts with EA complex. 20 μL of the mix is added to each well of the assay plate and the assay plate is incubated at room temperature for another 60 minutes. The plate is read in Envision multilabel plate reader (Perkin Elmer, MA) in the enhanced luminescence mode. Background subtracted data is fitted to $y = a + (b/(1+x / IC_{50}))$ and IC_{50} values are calculated using XLFit (IDBS, MA).

b. Determination of IC_{50} against mouse 11β–HSD1

To determine the IC_{50} against mouse 11β–HSD1, a stable CHO cell line expressing mouse 11β–HSD1is used and the above procedure is followed.

c. Determination of IC_{50} against mouse 11β–HSD1 in the presence of serum

To determine the IC_{50} against mouse 11β–HSD1in the presence of serum, 10% defibrinated, delipidized, charcoal stripped human serum (Seracare Life Sciences, CA) was added during the incubation with compound and cortisone. The above procedure is followed.

d. Evaluation of inhibition of human 11β–HSD2

To determine the potency of compounds against mouse 11β–HSD2, a stable CHO cell lilne expressing human 11β–HSD2 is generated. Cells are plated at 20,000 cells/well in 96 well plates and incubated overnight (12–16 hrs) at 37 ^{o}C/5% CO_2. Cells are treated with different concentration of compound in 90 microliter serum–free media and incubated for 30 minutes at 37 ^{o}C/5%CO_2. 10 µL of 500 nM [^{3}H]–Cortisone (ARC Inc, MO) is then added to each well of the plate (final concentration = 50 nM). The plate is incubated for 120 minutes. Cortisone and Cortisol are separated on a PRP–1 (Hamilton Inc, NV) on an Agilent 1100 high pressure liquid chromatography system with a 500TR flow scintillation analyzer (Perkin Elmer, MA). Carbenoxolone (Sigma, MO) is used as a control 11β–HSD2 inhibitor.

3. *Ex vivo* Assays.

a. Evaluation of 11β–HSD1 inhibitors in mouse *ex vivo* assay

To characterize the inhibitors of 11β–HSD1, inhibitors were tested in mouse tissue *ex vivo* assay. Male, C57Bl6 mice 8–10 weeks of age were grouped based on body weight (Taconic Farms on standard chow diet). All mice were orally dosed and sacrificed 2 to 5 hours after dosing (n = 4). Liver and epididymal fat tissues were collected and frozen in liquid nitrogen. Tissue 11β–HSD1 *ex vivo* assay measures the conversion of [3H]–cortisone to [3H]–cortisol and percent inhibition of 11β–HSD1 activity in the liver was determined in reference to vehicle treated mice. 50–60 mg of frozen liver tissue was placed in 48–well plates (kept on dry ice). The tissue/48–well plates were thawed at room temperature for 15 minutes. 250 µL of PBS were added to each well and incubated for additional 15 minutes at room temperature. 48–well plate was placed on a 37 ˚C Eppendorf Thermomixer R plate shaker and 250 µL of PBS containing 2.5 µCi of [3H]–cortisone was added to each well and allowed to incubate for 30 minutes. The reaction was stopped by adding 50 µL of 10% TFA. 20 µL of reaction

aliquot was analyzed by HPLC and percent conversion of [3H]−cortisone to [3H]−cortisol determined (*t*−test, *p < 0.05).

b. Evaluation of 11β–HSD1 inhibitors in mouse *ex vivo* assay with food mix

Prior to implementing long−term efficacy study, we evaluated the properties of 11β–HSD1inhibitor when mixed with high fat diet. We wanted to confirm that the compound did not alter food intake due to taste and maintained tissue *ex vivo* inhibition of 11β–HSD1in the liver. 2 weeks prior to initiation of dosing regimen, 18 weeks old C57B6 DIO mice that have been on high fat diet for 12 weeks from Taconic were placed in reversed light cycle room, where mice were subjected to a 14 hour shift in light cycle (dark cycle began on 08:00 and light cycle began on 20:00). This insured that blood and tissue collection could take place during normal light cycle. C57B6 DIO mice were fed with food mixed with compounds at 0.5 mg/g food for 96 hours. Then mice were sacrificed at 10:00 and 22:00 hour time point. The fat and liver tissues were collected. The drug concentration was determined by HPLC analysis; liver food mix *ex vivo* was conducted as discussed. For all studies, compounds were sent to Research Diet and compound/food mixture was prepared according to Research Diet Standard Operation Procedure.

4. X−ray Crystallographic Studies: Including protocol for getting and resolving X−ray structures

11β–HSD1 residues 24−292 C272S was prepared in the presence of CHAPS as described.[1] Crystals were grown using the hanging drop method with a reservoir solution of 100 mM HEPES pH 6.8−7.1 and 16−18% PEG 3350. Crystals were soaked from 1−3 days in reservoir solution containing compound at 0.5−1 mM. 0.1 % glutaraldehyde was added to the well to stabilize the crystals during soaking. The crystals were cryo−protected in paratone oil and flash frozen in a cryo−stream. X−ray data was collected using a Rigaku FR−E x−ray generator and a Rigaku Saturn92 CCD detector. Data was reduced using HKL2000.[2] The structure was solved by using phenix.refine[3] for rigid body fitting of the published structure of HSD1 with CHAPS (1XU9). Each protein chain was treated as an independent rigid body. The structure was refined through iterative manual rebuilding and reciprocal space refinement using COOT[4] and phenix.refine. The structure was further validated using Molprobity.[5]

5. Pharmacokinetic and Metabolic Stability Studies. Pharmacokinetics (PK) of 11β–HSD1 inhibitors was determined in male C57B6 mice (20 – 30 g, Taconic Farm, NY) after IV or oral administration. The compounds were prepared in DSM/PEG–200/saline solution for the IV administration or in 0.5% MC/2% TW/water as a suspension for the oral administration. Blood samples were collected over a period of 24 hr, and plasma samples were harvested and stored at –80 ^{o}C until assay. The target tissues (liver and muscle) were also collected at selected time points. Tissues were homogenized in saline and the drug concentrations in the homogenates were analyzed. Quantitation of HSD1 inhibitors in plasma and tissue homogenates was carried with a verified LC/MS/MS method. PK of HSD–621 were also determined in male Sprague–Dawley (SD) rats or male Beagle dogs after single IV administration of 2 mg/kg in both species and single oral administration of 10 mg/kg in rats and 3 mg/kg in dogs.

In vitro metabolic half–life ($t_{½}$) and metabolic pathways were determined in liver microsomes from rats, mice and humans using an NADPH regenerating system consisting of $MgCl_2$ (10 mM), glucose-6-phosphate (3.6 mM), $NADP^+$ (1.3 mM) and glucose-6-phosphate dehydrogenase (0.4 units/mL) in sodium phosphate buffer (0.1 M, pH 7.4), UDPGA (4 mM) and substrate (1 μM for metabolic stability and 10 μM for metabolite profiling). Incubations were initiated by the addition of the NADPH generating system and conducted for up to 30 minutes in a shaker–water bath at 37 ^{o}C. For the determination of in vitro metabolic half–life aliquots of the incubation mixture were removed at 0, 10, 20 and 30 min and added to acetonitrile containing the appropriate internal standard. Following centrifugation and evaporation of the supernatant liquid, the samples were reconstituted in 20% methanol in water for analysis by LC/MS.

***6. In vivo study through food mix*:**

26 weeks old male DIO–B6 mice (Taconic, Diet D12492, 60% fat, n = 12) were used to evaluate *in vivo* efficacy of compound HSD–621 in this reversal model. The mice were grouped based on bodyweight and serum insulin levels and placed one per cage, and fed on high fat diet (60% fat kal, 35.5% fat, F1850, BioServ, paste formula of #3282) 7 weeks prior start of the study. A food mix is prepared by mixing 0.5 mg of compound HSD–621 with one gram of the high fat diet (prepared by Research Diet). The mice were fed with this mixture for 31 days. Body weights and food intake were weekly measured; fed glucose and insulin levels were obtained at day 21 and fasting glucose and insulin levels were obtained at day 26 by tail bleeding. Mice were sacrificed under "stress free" condition at the end of study and serum and tissues were collected and frozen in liquid nitrogen. Serum and tissues were collected for analysis.

Table 1. Crystal data and structure refinement for HSD-621.

Identification code	p212121	
Empirical formula	$C_{19}\ H_{18}\ F_7\ N_3\ O_4\ S_2$	
Formula weight	549.48	
Temperature	90(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.1060(6) Å	α= 90°.
	b = 10.0851(7) Å	β= 90°.
	c = 24.2569(2) Å	γ = 90°.
Volume	2227.6(3) $Å^3$	
Z	4	
Density (calculated)	1.638 Mg/m^3	
Absorption coefficient	0.331 mm^{-1}	
F(000)	1120	
Crystal size	0.3 x 0.3 x 0.3 mm^3	
Theta range for data collection	2.39 to 28.33°.	
Index ranges	-12<=h<=12,	
	-13<=k<=13,	
	-31<=l<=32	
Reflections collected	22427	
Independent reflections	5513 [R(int) = 0.0319]	
Completeness to theta = 28.33°	99.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5513 / 0 / 388	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0301, wR2 = 0.0697	
R indices (all data)	R1 = 0.0328, wR2 = 0.0711	
Absolute structure parameter	0.01(5)	
Largest diff. peak and hole	0.419 and -0.221 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for HSD-621. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	15092(2)	4758(2)	2585(1)	23(1)
C(2)	14203(2)	5466(2)	2935(1)	21(1)
C(3)	12946(2)	6060(2)	2724(1)	16(1)
C(4)	12595(2)	5945(2)	2163(1)	16(1)
C(5)	13539(2)	5214(2)	1826(1)	20(1)
C(6)	14792(2)	4612(2)	2034(1)	24(1)
C(7)	11959(2)	6811(2)	3112(1)	18(1)

C(8)	11548(2)	7291(2)	1432(1)	20(1)
C(9)	10249(2)	8189(2)	1332(1)	20(1)
C(10)	10047(2)	5688(2)	1888(1)	15(1)
C(11)	8636(2)	6475(2)	1794(1)	15(1)
C(12)	8104(2)	7216(2)	2304(1)	25(1)
C(13)	8077(2)	6508(2)	327(1)	16(1)
C(14)	8302(2)	4525(2)	-257(1)	15(1)
C(15)	9127(2)	5567(2)	-441(1)	23(1)
C(16)	9000(2)	6704(2)	-103(1)	23(1)
C(17)	8155(2)	3209(2)	-553(1)	14(1)
C(18)	7673(2)	2092(2)	-154(1)	15(1)
C(19)	6934(2)	3327(2)	-994(1)	16(1)
F(1)	16306(1)	4180(1)	2799(1)	35(1)
F(2)	12474(1)	6801(1)	3629(1)	31(1)
F(3)	11787(1)	8084(1)	2977(1)	26(1)
F(4)	10610(1)	6278(1)	3134(1)	24(1)
F(5)	7317(1)	4200(1)	-1384(1)	20(1)
F(6)	6707(1)	2162(1)	-1244(1)	23(1)
F(7)	5665(1)	3724(1)	-782(1)	21(1)
N(1)	11307(2)	6581(1)	1951(1)	15(1)
N(2)	8875(1)	7414(1)	1333(1)	16(1)
N(3)	8434(2)	987(2)	-176(1)	23(1)
O(1)	7847(1)	8911(1)	634(1)	22(1)
O(2)	6269(1)	7199(1)	1076(1)	20(1)
O(3)	9416(1)	2893(1)	-858(1)	17(1)
O(4)	6614(1)	2294(1)	148(1)	22(1)
S(1)	7343(1)	4933(1)	333(1)	16(1)
S(2)	7665(1)	7607(1)	861(1)	15(1)

Table 3. Bond lengths [Å] and angles [°] for HSD-621.

C(1)-F(1)	1.354(2)
C(1)-C(6)	1.371(3)
C(1)-C(2)	1.375(3)
C(2)-C(3)	1.390(2)
C(3)-C(4)	1.403(2)
C(3)-C(7)	1.505(2)
C(4)-C(5)	1.397(2)
C(4)-N(1)	1.433(2)
C(5)-C(6)	1.387(3)
C(7)-F(3)	1.335(2)
C(7)-F(2)	1.3404(19)
C(7)-F(4)	1.3419(19)
C(8)-N(1)	1.465(2)
C(8)-C(9)	1.509(3)
C(9)-N(2)	1.475(2)
C(10)-N(1)	1.466(2)
C(10)-C(11)	1.527(2)
C(11)-N(2)	1.482(2)
C(11)-C(12)	1.524(2)
C(13)-C(16)	1.354(2)
C(13)-S(1)	1.7232(16)
C(13)-S(2)	1.7460(17)
C(14)-C(15)	1.367(2)
C(14)-C(17)	1.515(2)
C(14)-S(1)	1.7255(16)
C(15)-C(16)	1.414(3)
C(17)-O(3)	1.4016(19)
C(17)-C(19)	1.547(2)
C(17)-C(18)	1.549(2)
C(18)-O(4)	1.227(2)
C(18)-N(3)	1.313(2)
C(19)-F(7)	1.3266(19)
C(19)-F(6)	1.3380(19)
C(19)-F(5)	1.3381(18)
N(2)-S(2)	1.6010(13)
O(1)-S(2)	1.4354(12)
O(2)-S(2)	1.4343(12)

F(1)-C(1)-C(6)	119.35(17)
F(1)-C(1)-C(2)	117.83(16)
C(6)-C(1)-C(2)	122.82(17)
C(1)-C(2)-C(3)	118.69(16)
C(2)-C(3)-C(4)	120.66(15)
C(2)-C(3)-C(7)	118.56(15)
C(4)-C(3)-C(7)	120.77(15)
C(5)-C(4)-C(3)	118.11(15)
C(5)-C(4)-N(1)	122.05(15)
C(3)-C(4)-N(1)	119.85(14)
C(6)-C(5)-C(4)	121.65(17)

C(1)-C(6)-C(5)	118.07(17)
F(3)-C(7)-F(2)	106.04(13)
F(3)-C(7)-F(4)	106.75(14)
F(2)-C(7)-F(4)	106.21(13)
F(3)-C(7)-C(3)	113.70(14)
F(2)-C(7)-C(3)	111.85(14)
F(4)-C(7)-C(3)	111.79(14)
N(1)-C(8)-C(9)	108.31(14)
N(2)-C(9)-C(8)	110.29(14)
N(1)-C(10)-C(11)	110.76(13)
N(2)-C(11)-C(12)	110.20(14)
N(2)-C(11)-C(10)	108.73(13)
C(12)-C(11)-C(10)	113.67(14)
C(16)-C(13)-S(1)	112.46(13)
C(16)-C(13)-S(2)	127.75(13)
S(1)-C(13)-S(2)	119.71(9)
C(15)-C(14)-C(17)	124.51(15)
C(15)-C(14)-S(1)	111.47(13)
C(17)-C(14)-S(1)	123.88(12)
C(14)-C(15)-C(16)	112.87(16)
C(13)-C(16)-C(15)	112.26(16)
O(3)-C(17)-C(14)	112.16(13)
O(3)-C(17)-C(19)	104.01(13)
C(14)-C(17)-C(19)	108.89(13)
O(3)-C(17)-C(18)	113.34(13)
C(14)-C(17)-C(18)	111.43(13)
C(19)-C(17)-C(18)	106.49(12)
O(4)-C(18)-N(3)	125.46(15)
O(4)-C(18)-C(17)	118.34(14)
N(3)-C(18)-C(17)	116.19(14)
F(7)-C(19)-F(6)	107.83(13)
F(7)-C(19)-F(5)	107.64(13)
F(6)-C(19)-F(5)	107.28(13)
F(7)-C(19)-C(17)	112.43(13)
F(6)-C(19)-C(17)	110.88(13)
F(5)-C(19)-C(17)	110.58(13)
C(4)-N(1)-C(8)	113.86(13)
C(4)-N(1)-C(10)	113.79(13)
C(8)-N(1)-C(10)	109.14(13)
C(9)-N(2)-C(11)	117.70(12)
C(9)-N(2)-S(2)	121.19(11)
C(11)-N(2)-S(2)	121.10(10)
C(13)-S(1)-C(14)	90.95(8)
O(2)-S(2)-O(1)	120.35(8)
O(2)-S(2)-N(2)	108.36(7)
O(1)-S(2)-N(2)	107.84(7)
O(2)-S(2)-C(13)	106.15(8)
O(1)-S(2)-C(13)	105.77(8)
N(2)-S(2)-C(13)	107.77(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for HSD-621. The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	16(1)	23(1)	32(1)	-4(1)	-7(1)	5(1)
C(2)	21(1)	22(1)	19(1)	-3(1)	-5(1)	1(1)
C(3)	15(1)	14(1)	19(1)	-1(1)	0(1)	-2(1)
C(4)	14(1)	14(1)	19(1)	1(1)	0(1)	-2(1)
C(5)	20(1)	24(1)	17(1)	-3(1)	1(1)	2(1)
C(6)	20(1)	23(1)	27(1)	-7(1)	2(1)	5(1)
C(7)	17(1)	21(1)	16(1)	0(1)	-1(1)	0(1)
C(8)	20(1)	22(1)	18(1)	5(1)	-2(1)	-6(1)
C(9)	23(1)	16(1)	21(1)	6(1)	-7(1)	-7(1)
C(10)	16(1)	13(1)	16(1)	1(1)	-1(1)	-1(1)
C(11)	15(1)	15(1)	14(1)	5(1)	-3(1)	-2(1)
C(12)	22(1)	36(1)	17(1)	1(1)	0(1)	9(1)
C(13)	19(1)	15(1)	14(1)	-2(1)	-2(1)	-4(1)
C(14)	14(1)	21(1)	10(1)	0(1)	-1(1)	-3(1)
C(15)	26(1)	25(1)	18(1)	-4(1)	7(1)	-8(1)
C(16)	29(1)	20(1)	20(1)	-2(1)	5(1)	-10(1)
C(17)	12(1)	17(1)	13(1)	1(1)	1(1)	0(1)
C(18)	16(1)	18(1)	12(1)	2(1)	-4(1)	-4(1)
C(19)	17(1)	16(1)	15(1)	0(1)	1(1)	1(1)
F(1)	28(1)	40(1)	37(1)	-11(1)	-12(1)	19(1)
F(2)	29(1)	49(1)	15(1)	-9(1)	-6(1)	9(1)
F(3)	28(1)	18(1)	32(1)	-4(1)	5(1)	4(1)
F(4)	19(1)	33(1)	20(1)	1(1)	4(1)	-5(1)
F(5)	24(1)	23(1)	14(1)	6(1)	-2(1)	1(1)
F(6)	26(1)	18(1)	23(1)	-6(1)	-9(1)	1(1)
F(7)	15(1)	28(1)	19(1)	-1(1)	-1(1)	3(1)
N(1)	13(1)	15(1)	16(1)	2(1)	-1(1)	-1(1)
N(2)	18(1)	15(1)	16(1)	4(1)	-5(1)	-3(1)
N(3)	22(1)	22(1)	27(1)	9(1)	4(1)	2(1)
O(1)	29(1)	17(1)	20(1)	4(1)	-5(1)	3(1)
O(2)	16(1)	25(1)	19(1)	1(1)	-2(1)	4(1)
O(3)	13(1)	25(1)	14(1)	0(1)	0(1)	2(1)
O(4)	23(1)	23(1)	21(1)	3(1)	7(1)	-2(1)
S(1)	17(1)	17(1)	13(1)	0(1)	3(1)	-4(1)
S(2)	16(1)	14(1)	13(1)	1(1)	-3(1)	2(1)

Table 5. Hydrogen coordinates ($x 10^4$) and isotropic displacement parameters ($Å^2 x 10^3$) for HSD-621.

	x	y	z	U(eq)

H(2)	14480(30)	5560(20)	3291(10)	29(6)
H(3)	10150(30)	2940(20)	-667(10)	33(7)
H(5)	13330(20)	5120(20)	1437(8)	17(5)
H(6)	15470(20)	4090(20)	1807(8)	21(5)
H(11)	7910(20)	5830(20)	1659(8)	16(5)
H(15)	9720(30)	5540(20)	-795(10)	34(6)
H(16)	9500(20)	7490(30)	-164(9)	28(6)
H(3A)	9140(30)	970(30)	-353(10)	34(7)
H(8A)	12460(20)	7846(18)	1464(7)	11(4)
H(9A)	10350(20)	8620(20)	969(9)	24(5)
H(10A)	10190(20)	5120(20)	1582(8)	19(5)
H(12A)	7890(30)	6520(20)	2607(10)	41(7)
H(3B)	8220(30)	380(20)	71(10)	30(6)
H(8B)	11700(20)	6700(20)	1116(8)	18(5)
H(9B)	10170(20)	8830(20)	1614(9)	24(5)
H(10B)	9930(20)	5150(20)	2207(8)	17(5)
H(12B)	8840(30)	7850(20)	2419(9)	31(6)
H(12C)	7190(30)	7640(20)	2234(9)	33(6)

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