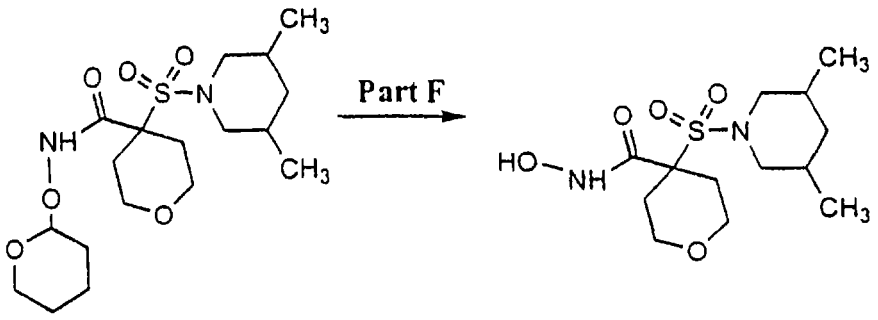
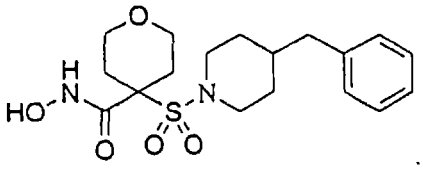


Part F: The crude the THP-protected hydroxamate oil product of Part E (2.7 g, 6.7 mmol) was dissolved in acetonitrile (15 mL) and stirred with 10% HCl (15 mL) for 3 hours, after which time LC showed no more starting material. The solution was reduced to one-half volume, and then acetonitrile (10 mL) and trifluoroacetic acid (1 mL) were added. The solution was filtered and purified by preparatory reverse phase LC (acetonitrile/water) affording title product as a tan solid (1.7 g, 79% yield). ^{1}H-NMR showed the desired compound. HPLC showed product as a mixture of 70% cis and 30% trans. Mass spectroscopy showed M^{+H}_{found} = 321 (M^{+H}_{calc} = 321).

Example 8 : Preparation of tetrahydro-N-hydroxy-4-[[4-(phenylmethyl)-1-piperidinyl]-sulfonyl]-2H-pyran-4-carboxamide



Part A: To a solution of 4-benzylpiperidine (10.55 mL, 60 mmol) and triethylamine (12.5 mL, 90 mmol) in methylene chloride (250 mL) at zero degrees Celsius was added a solution of methanesulfonyl

chloride (7 mL, 60 mmol) in methylene chloride (50 mL). After one hour at ambient temperature, the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as a beige solid (14.2 g, 94%). HRMS (ES+) M+ H^+ calculated for $C_{13}H_{19}N_1O_2S_1$: 254.1215, found 254.1211.

Part B: Preparation of methyl [[4-(phenylmethyl)-1-piperidinyl]sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from Part A (2.53 g, 10 mmol) was dissolved in dry tetrahydrofuran (20 mL), chilled to minus seventy-five degrees Celsius, and a 1M solution of lithium bis(trimethylsilyl)amide (20 mL) was added while maintaining the temperature below minus sixty-five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (0.77mL, 10 mmol) in dry tetrahydrofuran (10 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as a yellow oil (3.05 g, 100%).

Part C: Preparation of methyl tetrahydro-4-[[4-(phenylmethyl)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxylate

To a solution of the methylene sulfonamide from Part B (4.1 g, 13.2 mmol) in dimethylformamide (26 mL) was added potassium carbonate (7.8 g, 56.6 mmol), bis-(2-bromoethyl)ether (1.73 mL, 13.2 mmol) and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours, potassium carbonate (2.0 g, 14 mmol) and bis-(2-bromoethyl)ether (0.2 mL, 1.6 mmol) were added and the reaction stirred at sixty degrees Celsius . After a total of twenty-eight hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP-substituted sulfonamide as a white solid (2.85 g, 57%).

Part D: Preparation of tetrahydro-4-[[4-(phenylmethyl)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxylic acid

In dry equipment under nitrogen, the THP-substituted sulfonamide from Part C (2.8 g, 7.3 mmol) was dissolved in dry tetrahydrofuran 25 mL) and potassium trimethylsilonate (1.4 g, 11.0 mmol) was added at ambient temperature. After sixteen hours, water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was treated with 6 N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was heated in diethyl ether, the solid filtered and dried

to give the carboxylic acid as a white solid (1.96 g, 73%).

Part E: Preparation of tetrahydro-4-[[4-(phenylmethyl)-1-piperidinyl]sulfonyl]-N-[(tetrahydro-2H-pyran-4-carboxamide

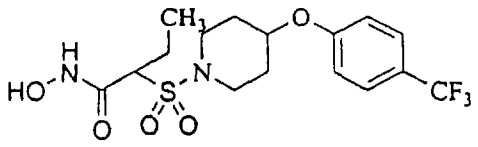
In dry equipment under nitrogen, the carboxylic acid from Part D (1.9 g, 5.18 mmol) was dissolved in dry dimethylformamide (13 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.84 g, 6.2 mmol), N-methylmorpholine (1.71 mL, 15.5 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.88 g, 16.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.39 g, 7.25 mmol). After two hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the TPH hydroxamate as a white foam (2.22 g, 93%).

Part F: Preparation of tetrahydro-N-hydroxy-4-[[4-(phenylmethyl)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide

To a solution of the THP hydroxamate from Part E (2.15 g, 4.6 mmol) in 1,4-dioxane (12 mL) was added 4 N HCl dioxane solution (12 mL) and methanol (12 mL). After thirty minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the depicted compound as a white solid (1.45 g, 82%). HRMS (ES+)

M+ H $^+$ calculated for $C_{18}H_{26}N_2O_5S_1$: 383.1641, found 383.1640.

Example 9: Preparation of N-hydroxy-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]butanamide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-Dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from Part A (6.03 g, 30 mmol) in dimethylformamide (60 mL) were added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The resulting slurry was stirred at ninety degrees

Celsius. After nineteen hours, cesium carbonate (3.26 g, 10 mmol) and 4-fluorobenzotrifluoride (0.95 mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius. After a total of forty-six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxyl]piperidine

To a slurry of the substituted BOC piperidine from Part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4 N HCl dioxane solution (17 mL). After one hour at ambient temperature, the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxyl]piperidine

To a solution of the hydrochloride salt from Part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in methylene chloride (45 mL) at zero degrees Celsius was added a solution of methanesulfonyl chloride (1.97 mL, 25.4 mmol) in methylene chloride (10 mL). After one hour at ambient temperature, the solvent was removed *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of

the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of Methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from Part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added while maintaining the temperature below minus sixty-five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0 mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added while maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as a yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]butanoate

To a solution of the methylene sulfonamide from Part E (6.15 g, 16 mmol) in dimethylformamide (32 mL) were added potassium carbonate (7.8 g, 56.6 mmol), bis-(2-bromoethyl)amine ethyl carbamate (3.0 g, 10.75 mmol; partially purified) and 18-Crown-6 (500 mg). The resulting slurry was stirred at sixty degrees Celsius. After sixteen hours, potassium

carbonate (2.0 g, 14 mmol) was added and the reaction stirred at sixty degrees Celsius. After a total of twenty four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the ethyl sulfonamide as a light yellow oil (0.3 g, 10%).

Part G: Preparation of 2-[[4-[4-(trifluorometyl)-phenoxyl-1-piperidinyl]sulfonyl]butanoic acid

In dry equipment under nitrogen, the ethyl sulfonamide from Part F (0.82 g, 12.0 mmol) was dissolved in dry tetrahydrofuran (5.0 mL) and potassium trimethylsilonate (0.51 g, 4.0 mmol) was added at ambient temperature. After eighteen hours water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate. The combined extracts were concentrated *in vacuo*. The residue was wetted with water and 1N HCl solution (3.0 mL) was added, the resulting slurry was extracted with ethyl acetate and the combined extracts washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the carboxylic acid as an off-white solid (669 mg, 85%).

Part H: Preparation of N-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]butanamide

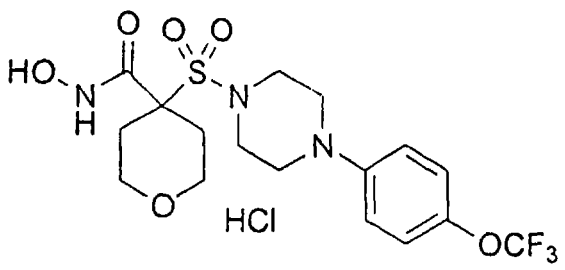
In dry equipment under nitrogen, the carboxylic acid from Part G (0.627 g, 1.59 mmol) was dissolved in dry dimethylformamide (4 mL) and the remaining

reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.26 g, 1.9 mmol), N-methylmorpholine (0.53 mL, 4.84 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.585 g, 5.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.43 g, 2.26 mmol). After fourteen hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white solid (0.666 g, 85%).

Part I: Preparation of N-Hydroxy-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]butanamide

To a solution of the THP hydroxamate from Part H (0.61 g, 1.23 mmol) in 1,4-dioxane (3 mL) were added 4 N HCl dioxane solution (3 mL) and methanol (3 mL). After two hours at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the depicted compound as a white solid (490 mg, 97%). HRMS (ES+) M+ NH_4^+ calculated for $C_{16}H_{21}N_2O_5S_1F_3$: 428.1467, found 428.1451.

Example 10: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenyl]-1-piperazinyl]sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a solution of tert-butyl-piperazine (25.0 g, 134 mmol) in dichloromethane (200 mL), cooled to zero degrees Celsius, was added triethylamine (28.3 mL, 201 mmol) followed by methanesulfonyl chloride (15.5 mL, 201 mmol). Once the addition was complete the cooling bath was removed and the reaction mixture was stirred at ambient temperature. After 1 hour the reaction mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate and the aqueous was further extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the sulfonamide as an off-white solid (36.4 g, >100%).

Part B: To a solution of the sulfonamide of part A (35.0 g, 132 mmol) in tetrahydrofuran (200 mL) was slowly added a solution of lithium bis(trimethylsilyl)amide (66.5 g, 397 mmol) in tetrahydrofuran (300 mL) at such a rate that the temperature never exceeded minus sixty degrees Celsius. After stirring at minus seventy-eight degrees Celsius for 1.5 hours a solution of dimethyl carbonate (10.2 mL, 132 mmol) in tetrahydrofuran (100 mL) was slowly added at such a rate that the temperature of the reaction never exceeded minus sixty degrees Celsius. After stirring for 1 hour at

minus seventy-eight degrees Celsius the reaction was quenched by the addition of saturated NH_4Cl. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with 5% HCl, saturated NH_4Cl, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the sulfonamide ester as an orange oil (34.1 g, 80%).

Part C: To a solution of the sulfonamide ester of part B (15.00 g, 46.53 mmol) in N,N-dimethylformamide (200 mL) was added K_2CO_3 (19.29 g, 139.59 mmol), 18-crown-6 (4.65 g) and bis(2-bromoethyl)ether (10.79 g, 46.53 mmol). The resulting mixture was heated to sixty degrees Celsius for 22 hours and then additional K_2CO_3 (19.3 g, 139.6 mmol) and bis(2-bromoethyl)ether (5.8 mL, 23.2 mmol) was added and stirring was continued at sixty degrees Celsius for 22 hours. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in acetonitrile and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and the residue was partitioned between H_2O and ethyl acetate. The organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the cyclized ester as a pale yellow solid (7.23 g, 40%).

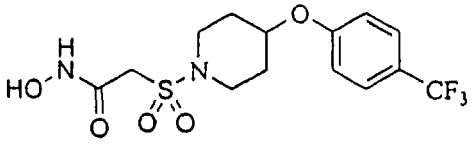
Part D: The cyclized ester of part C (7.23 g, 18.42 mmol) was treated with a solution of 4N HCl in dioxane (46 mL). After stirring at ambient temperature for 1 hour the reaction mixture was concentrated *in vacuo* to provide the piperazine sulfonamide as a tan solid (5.83 g, 96%).

Part E: To a suspension of the piperazine sulfonamide of part D (2.15 g, 6.53 mmol) in toluene (15 mL), precooled to zero degrees Celsius, was added sodium tert-butoxide (1.43 g, 14.93 mmol). Once the addition was complete the cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature at which time 4-(trifluoromethoxy)bromobenzene (1.50 g, 6.22 mmol), BINAP (0.116 g, 0.187 mmol) and tris(dibenzyldeneacetone)dipallidium (0) (0.057 g, 0.062 mmol) were added. The resulting mixture was stirred at eighty degrees Celsius for 12 hours and then concentrated *in vacuo*. The residue was heated in boiling methanol, decanted from the salts and concentrated *in vacuo*. The residue was dissolved in H_2O and acidified (pH-2) with 1N HCl. The aqueous layer was then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 to give the acid as a yellow solid (1.06 g, 39%).

Part F: To a solution of the acid of part E (1.06 g, 2.42 mmol) in N,N-dimethylformamide (5.0 mL) was added 1-hydroxybenzotriazole (0.392 g, 2.90 mmol), N-methylmorpholine (0.790 mL, 7.26 mmol), O-(tetrahydropuranyl) hydroxylamine (0.425 g, 3.63 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.650 g, 3.39 mmol). After stirring at ambient temperature for 7 hours the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate with 5% methanol/hexanes) provided the protected hydroxamate as a white solid (1.02 g, 78%).

Part G: The protected hydroxamate of part F (1.02 g, 1.90 mmol) was treated with a solution of 2N HCl in diethyl ether (9.5 mL) and methanol (0.77 mL, 18.97 mmol). The reaction mixture became gelatinous and a solution of 4 N HCl in dioxane (4.0 mL) was added. After stirring at ambient temperature for 2 hours the solids were collected by filtration, washing with diethyl ether, to give the title compound as a white solid (0.869 g, 93%). MS MH^+ calculated for $C_{17}H_{23}O_6N_3S_1F_3$: 454, found 454.

Example 11: Preparation of N-hydroxy-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetamide



Part A: Preparation of 1,1-Dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) were added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius. After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxylpiperidine

A solution of 4 N HCl dioxane solution (17 mL) was added to a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL). After one hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(Methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

A solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL) was added to a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added while maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of [[4-[4-(trifluoromethyl)-phenoxyl-1-piperidinyl]sulfonyl]acetic acid

In dry equipment under nitrogen, the methylene sulfonamide from part E (1.52 g, 4.0 mmol) was dissolved in dry tetrahydrofuran(10 mL) and potassium trimethylsilonate (1.03 g, 8.0 mmol) was added at ambient temperature. After fifteen hours, water (50 mL) was added, and at 5 degrees Celsius 6 N HCl was added until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was heated in diethyl ether, the solid filtered and dried to give the carboxylic acid as a white solid (1.25 g, 85%).

Part G: Preparation of N-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl] acetamide

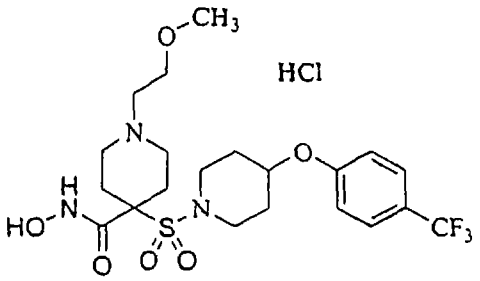
In dry equipment under nitrogen, the carboxylic acid from part F (1.2 g, 3.3 mmol) was dissolved in dry dimethylformamide (8 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.53 g, 3.9 mmol), N-methylmorpholine (1.08 mL, 9.8 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.19 g, 10.1 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.88 g, 4.6 mmol). After two hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in*

vacuo. Chromatography (on silica, ethyl acetate/ hexanes) provided the THP hydroxamate as a white solid (1.16 g, 76%).

Part H: Preparation of N-hydroxy-2-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetamide

To a solution of the THP hydroxamate from part G (1.11 g, 2.4 mmol) in 1,4-dioxane (6 mL) were added 4 N HCl dioxane solution (6 mL) and methanol (6 mL). After ninety minutes at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (0.60 g, 67%). HRMS (ES+) M+ H^+ calculated for $C_{14}H_{17}F_3N_2O_5S_1$: 383.0889, found 383.0885.

Example 12: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl)sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-Dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) were added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius. After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-

phenoxylpiperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4 N HCl dioxane solution (17 mL). After one hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added

maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0 mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part E (1.14 g, 3 mmol) in dimethylformamide (6 mL) were added potassium carbonate (1.24 g, 9 mmol), bis-(2-chloroethyl)benzyl amine (0.7 g, 3 mmol; and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the piperidine sulfonamide as a white solid (950 mg, 59%).

Part G: Preparation of Methyl 1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

To a slurry of the piperidine sulfonamide from part F (420 mg, 0.8 mmol) in methanol (15 mL) was added ammonium formate (147 mg, 2.3 mmol). The system was purged with nitrogen for 10 minutes. The nitrogen stream was removed and palladium on carbon (80 mg of 10 weight % on activated carbon, 50%water) was added. The reaction was refluxed for forty five minutes, cooled, filtered through Celite under nitrogen, and concentrated *in vacuo*. The residue was dissolved in dry dimethylformamide (5 mL) and potassium carbonate (150 mg, 1.07 mmol) and 2-bromoethyl methyl ether (100 uL, 1.07 mmol) were added. The reaction was stirred at thirty five degrees Celsius for thirty hours and then concentrated *in vacuo*. The residue was taken up in ethyl acetate and filtered through Celite. The filtrate washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (methanol) to give the N-methoxyethyl piperidine sulfonamide as an off-white solid (190 mg, 53%).

Part H: Preparation of 1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the N-methoxyethyl piperidine sulfonamide from part G (1.51 g, 2.97 mmol) was dissolved in dry tetrahydrofuran (30 mL) and potassium trimethylsilonate (1.27 g, 8.91 mmol) was added at ambient temperature. After five hours, water (10 mL) was added and at 5 degrees Celsius, 6 N HCl was added until pH=1. The slurry was filtered, washed with water and dried *in vacuo* to

give the carboxylic acid as a white solid (1.47 g, 100%).

Part I: Preparation of 1-(2-methoxyethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide

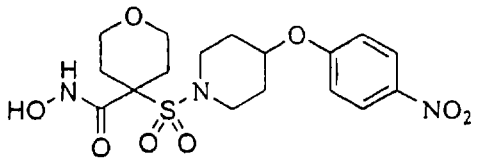
In dry equipment under nitrogen, the carboxylic acid from part H (1.4 g, 2.83 mmol) was dissolved in dry dimethylformamide (12 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.46 g, 3.4 mmol), N-methylmorpholine (0.93 mL, 8.5 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.03 g, 8.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.76 g, 4.0 mmol). The reaction was stirred at forty five degrees Celsius. After forty eight hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white solid (800 mg, 48%).

Part J: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part I (760 mg, 1.28 mmol) in 1,4-dioxane (3 mL) was added 4N HCl dioxane solution (3.2 mL) and methanol (3.5 mL). After thirty minutes at ambient temperature the reaction was poured into 100 mL acetonitrile. The

slurry was filtered under nitrogen, washed with acetonitrile and dried *in vacuo* to give the title compound as an off white solid (0.62 g, 89%). HRMS (ES+) M+ H^+ calculated for $C_{21}H_{30}F_3N_3O_6S_1$: 510.1886, found 510.1862.

Example13: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-nitrophenoxy)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-(4-nitrophenoxy)-1-piperidinyl carboxylate

To a solution of the BOC piperidine from part A (10.05 g, 0.05 mol) in dimethylformamide (100 mL) were added cesium carbonate (16.3 g, 0.05 mol) and 4-fluoronitrobenzene (5.3 mL, 0.05 mol). The slurry was stirred at eighty five degrees Celsius. After eight hours cesium carbonate (1.6g, 5 mmol) was added and the reaction continued at ninety degrees Celsius. After a total of twenty four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as an yellow solid (13.6 g, 84%).

Part C: Preparation of 4-(4-nitrophenoxy)piperidine, monohydrochloride

To a slurry of the substituted BOC piperidine from part B (6.44 g, 20 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl dioxane solution (20 mL). After two hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a light yellow solid (5.2 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-(4-nitrophenoxy)piperidine

To a solution of the hydrochloride salt from part C (5.17 g, 20 mmol) and triethylamine (7.0 mL, 50 mmol) in dichloromethane (80 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (2.32 mL, 30 mmol) in dichloromethane (20 mL). After one hour at ambient temperature, the

solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an yellow solid (4.57 g, 76%).

Part E: Preparation of methyl [[4-(4-nitrophenoxy)-1-piperidinyl]sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.48 g, 14.9 mmol) was dissolved in dry tetrahydrofuran (30 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (30 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.15mL, 14.9 mmol) in dry tetrahydrofuran (15 mL) was added while maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the methylene sulfonamide as a white solid (3.9 g, 73%).

Part F: Preparation of methyl tetrahydro-4-[[4-(4-nitrophenoxy)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxylate

To a solution of the methylene sulfonamide from part E (3.73 g, 10.4 mmol) in dimethylformamide (20

mL) was added potassium carbonate (5.75 g, 41.6 mmol), bis-(2-bromoethyl)ether (1.36 mL, 10.4 mmol) and 18-Crown-6 (500 mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (ethyl acetate) to give the tetrahydropyran sulfonamide as a white solid (2.1 g, 47%).

Part G: Preparation of tetrahydro-4-[[4-(4-nitrophenoxy)-1-piperidinyl)sulfonyl]-2H-pyran-4-carboxylic acid

In dry equipment under nitrogen, the tetrahydropyran sulfonamide from part F (2.04 g, 4.77 mmol) was dissolved in dry tetrahydrofuran (12 mL) and potassium trimethylsilonate (2.04 g, 14.3 mmol) was added at ambient temperature. After five hours water (50 mL) was added and the tetrahydrofuran was stripped off *in vacuo*. The residue was washed with ethyl acetate, the layers were separated, the aqueous was chilled to 5 degrees Celsius and 6 N HCl was added until pH=1. The slurry was filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (1.66 g, 84%).

Part H: Preparation of tetrahydro-4-[[4-(4-nitrophenoxy)-1-piperidinyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide

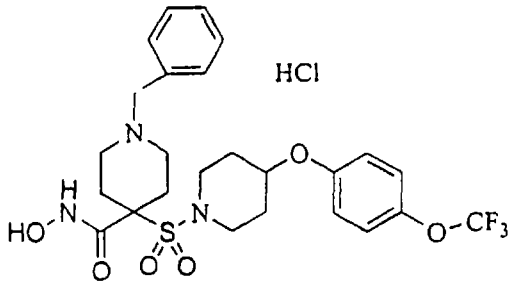
In dry equipment under nitrogen, the carboxylic acid from part G (1.63 g, 3.9 mmol) was dissolved in dry dimethylformamide (10 mL) and the remaining

reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.640 g, 4.7 mmol), N-methylmorpholine (1.3 mL, 11.8 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.43 g, 12.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1 g, 5.5 mmol). The reaction was stirred at forty five degrees Celsius. After forty eight hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the THP hydroxamate as a white solid (1.89 g, 95%).

Part I: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-nitrophenoxy)-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide

To a solution of the THP hydroxamate from part H (1.85 g, 3.6 mmol) in 1,4-dioxane (9 mL) were added 4 N HCl dioxane solution (9 mL) and methanol (1 mL). After fifteen minutes at ambient temperature the product precipitated from the reaction. The reaction was diluted with diethyl ether, the solids filtered under nitrogen and dried *in vacuo* to give the title compound as a white solid (1.4 g, 93%). HRMS (ES+) M+ H^+ calculated for $C_{17}H_{23}N_3O_8S_1$: 430.1284, found 430.1314.

Example 14: Preparation of N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated

sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL) and at minus five degrees Celsius sodium hydride (2.74g, 68.4 mmol of the 60% oil dispersion) was added and the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]piperidine

At fifteen degrees Celsius, 4 N HCl in dioxanes (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]piperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol), and at zero degrees Celsius a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was

quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of Methyl 1-(phenylmethyl)-4-[[4-[4- (trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part F (20.46 g, 51.5 mmol) in dimethylformamide (90 mL) was added potassium carbonate (21.3 g, 154.7 mmol), bis-(2-chloroethyl)benzyl amine (12.0 g, 51.5 mmol; and 18-Crown-6 (700 mg). The slurry was stirred at sixty degrees Celsius. After twenty four hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (methanol) to give the N-benzyl piperidine sulfonamide as a white solid (15 g, 52%).

Part H: Preparation of 1-(Phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the N-benzyl piperidine sulfonamide from part G (1.5 g, 2.7 mmol) was dissolved in dry tetrahydrofuran (30 mL) and potassium trimethylsilonate (1.15 g, 8.1 mmol) was added at ambient temperature. After twenty four hours, water (10 mL) was added and at 5 degrees

Celsius, 6 N HCl was added until pH=7. The slurry was filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (1.24 g, 85%).

Part I: Preparation of 1-(phenylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

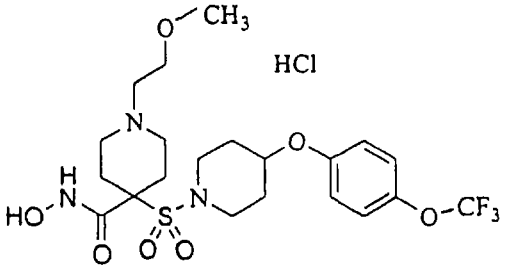
In dry equipment under nitrogen, the carboxylic acid from part H (1.2 g, 2.2 mmol) was dissolved in dry dimethylformamide (6 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.36 g, 2.66 mmol), N-methylmorpholine (0.73 mL, 6.64 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.83 g, 6.86 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.59 g, 3.1 mmol). The reaction was stirred at forty five degrees Celsius. After two hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white solid (1.24 mg, 88%).

Part J: Preparation of N-Hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part I (1.18 g, 1.84 mmol) in 1,4-dioxanes (5 mL) was added 4 N HCl dioxane solution (5 mL) and methanol (1 mL).

After thirty minutes, the reaction was diluted with diethyl ether, the solids filtered under nitrogen and dried *in vacuo* to give the title compound as a white solid (0.96 g, 88%). HRMS (ES+) M+ H^+ calculated for $C_{25}H_{30}F_3N_3O_6S_1$: 558.1886, found 558.1961.

Example 15: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL), and at minus five degrees Celsius sodium hydride (2.74g, 68.4 mmol of the 60% oil dispersion) was added and the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]piperidine

At fifteen degrees Celsius, 4 N HCl in dioxane (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxy]piperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol), and at zero degrees Celsius, a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-

(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part F (20.46 g, 51.5 mmol) in dimethylformamide (90 mL) was added potassium carbonate (21.3 g, 154.7 mmol), bis-(2-chloroethyl)benzyl amine (12.0 g, 51.5 mmol; and 18-Crown-6 (700 mg). The slurry was stirred at sixty degrees Celsius. After twenty four hours the reaction was concentrated *in vacuo*. The

residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (methanol) to give the N-benzyl piperidine sulfonamide as a white solid (15 g, 52%).

Part H: Preparation of 4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylic acid, methyl ester

To a slurry of the N-benzyl piperidine sulfonamide from part G (4.17 g, 7.5 mmol) in methanol (50 mL) was added ammonium formate (1.46 g, 22.5 mmol). The system was purged with nitrogen for 10 minutes. The nitrogen stream was removed and palladium on carbon (1.5 g of 10 weight % on activated carbon, 50%water) was added. The reaction was refluxed for thirty minutes, cooled, filtered through Celite under nitrogen, and concentrated *in vacuo* to give the unsubstituted piperidine sulfonamide as a beige solid (3.15 g, 90%).

Part I: Preparation of methyl 1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

The unsubstituted piperidine sulfonamide from part H (3.0 g, 6.45 mmol) was dissolved in dry dimethylformamide (15 mL) and potassium carbonate (1.3 g, 9.7 mmol) and 2-bromoethyl methyl ether (908 uL, 9.7 mmol) were added. The reaction was stirred at thirty five degrees Celsius for sixteen hours and then concentrated *in vacuo*. The residue was taken up in ethyl acetate and filtered through Celite. The filtrate washed with water two times, saturated

sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the N-methoxyethyl piperidine sulfonamide as a white solid (1.65 g, 50%).

Part J: Preparation of 1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the N-methoxyethyl piperidine sulfonamide from part I (1.6 g, 3.0 mmol) was dissolved in dry tetrahydrofuran (25 mL) and potassium trimethylsilonate (1.3 g, 9.13 mmol) was added at ambient temperature. After twenty four hours, water (10 mL) was added and at 5 degrees Celsius, 6 N HCl was added until pH=7. The slurry was filtered, washed with water and dried *in vacuo* to give the carboxylic acid as an off-white solid (1.39 g, 90%).,

Part K: Preparation of 1-(2-methoxyethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

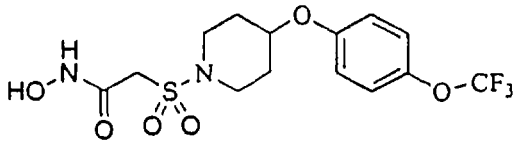
In dry equipment under nitrogen, the carboxylic acid from part J (1.36 g, 2.67 mmol) was dissolved in dry dimethylformamide (9 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.43 g, 3.2 mmol), N-methylmorpholine (0.88 mL, 8.0 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.97 g, 8.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.72 g, 3.7 mmol). The reaction was stirred at forty degrees Celsius. After twenty hours, the reaction was concentrated *in*

vacuo. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white solid (1.42 g, 90%).

Part L: Preparation of N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part K (1.3 g, 2.13 mmol) in 1,4-dioxanes (2 mL) was added 4 N HCl dioxane solution (5.3 mL) and methanol (0.5 mL). After ten minutes, the reaction was diluted with diethyl ether, the solids filtered under nitrogen and dried *in vacuo* to give the title compound as a white solid (1.15 g, 96%). HRMS (ES+) M+ H^+ calculated for $C_{21}H_{30}F_3N_3O_7S_1$: 526.1835, found 526.1805.

Example 16: Preparation of N-hydroxy-2-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]acetamide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL,

0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL) and at minus five degrees Celsius sodium hydride (2.74g, 68.4 mmol of the 60% oil dispersion) was added and

the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-phenoxylpiperidine

At fifteen degrees Celsius, 4 N HCl in dioxanes (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxylpiperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol) and at zero degrees Celsius a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The

residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of [[4-[4-(trifluoromethoxy)-phenoxyl-1-piperidinyl]sulfonyl]acetic acid

In dry equipment under nitrogen, the methylene sulfonamide from part F (1.59 g, 4.0 mmol) was dissolved in dry tetrahydrofuran (10 mL) and

potassium trimethylsilonate (1.2 g, 8.5 mmol) was added at ambient temperature. After fifteen hours water (50 mL) was added and at 5 degrees Celsius 6N HCl was added until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (hexanes/ethyl acetate) to give the carboxylic acid as a white solid (1.15 g, 75%).

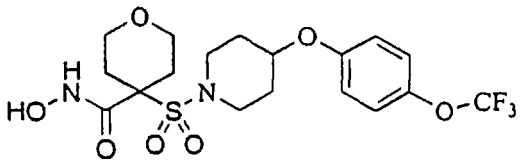
Part H: Preparation of N-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]acetamide

In dry equipment under nitrogen, the carboxylic acid from part G (1.0 g, 2.6 mmol) was dissolved in dry dimethylformamide (7 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.42 g, 3.1 mmol), N-methylmorpholine (0.86 mL, 7.8 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.9 g, 7.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.7 g, 3.7 mmol). After three hours at ambient temperature, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (hexanes/ethyl acetate) to give the THP hydroxamate as a white solid (0.9 g, 71%).

Part I: Preparation of N-hydroxy-2-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]acetamide

To a solution of the THP hydroxamate from part H (0.84 g, 2.4 mmol) in 1,4-dioxane (4.5 mL) was added 4N HCl dioxane solution (4.5 mL) and methanol (64.5 mL). After thirty minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (ethyl acetate/hexanes) to give the title compound as a white solid (0.35 g, 51%). HRMS (ES+) M+ H^+ calculated for $C_{14}H_{17}F_3N_2O_6S_1$: 416.1103, found 416.1117.

Example 17: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5%

$KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL) and at minus five degrees Celsius sodium hydride (2.74g, 68.4 mmol of the 60% oil dispersion) was added and the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in

diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-phenoxyl]piperidine

At fifteen degrees Celsius, 4 N HCl in dioxanes (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxyl]piperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol) and at zero degrees Celsius a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of methyl tetrahydro-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-2H-pyran-4-carboxylate

To a solution of the methylene sulfonamide from part F (5.17 g, 13 mmol) in dimethylformamide (26 mL) was added potassium carbonate (7.2 g, 52.1 mmol), bis-(2-bromoethyl)ether (1.7 mL, 13 mmol) and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours potassium carbonate (2.0 g, 14 mmol) and bis-(2-bromoethyl)ether (0.2 mL, 1.6 mmol) were added and

the reaction stirred at sixty degrees Celsius. After a total of forty hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (ethyl acetate/hexanes) to give the THP substituted sulfonamide as a white solid (1.85 g, 30%).

Part H: Preparation of tetrahydro-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-2*H*-pyran-4-carboxylic acid

In dry equipment under nitrogen, the THP substituted sulfonamide from part G (1.9 g, 40.7 mmol) was dissolved in dry tetrahydrofuran (80.0 mL) and potassium trimethylsilonate (17.4 g, 122.0 mmol) was added at thirty five degrees Celsius. After two hours water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate to remove unreacted starting material. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was heated in diethyl ether, the solid filtered and dried to give the carboxylic acid as a white solid (18.5 g, 100 %).

Part I: Preparation of tetrahydro-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2H-pyran-4-carboxamide

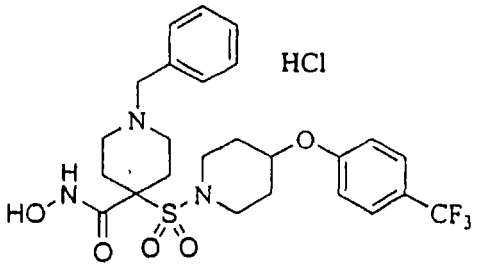
In dry equipment under nitrogen, the carboxylic acid from part H (1.63 g, 3.6 mmol) was dissolved in dry dimethylformamide (7.5 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.97 g, 7.2 mmol), N-methylmorpholine (1.2 mL, 10.8 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.38 g, 7.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.38 g, 7.2 mmol). After one hour at forty five degrees Celsius, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white foam (1.1 g, 55%).

Part J: Preparation of tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-2H-pyran-4-carboxamide

To a solution of the THP hydroxamate from part I (1.0 g, 1.8 mmol) in 1,4-dioxane (5 mL) was added 4N HCl dioxane solution (5 mL) and methanol (5 mL). After thirty minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (acetone/hexanes) to give the title compound as a white solid (0.58 g, 68%). HRMS (ES+) M+ H^+ calculated for $C_{18}H_{23}N_2O_7S_1F_3$: 469.1256, found 469.1287.

Example 18: Preparation of N-hydroxy-1-

(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide monohydrochloride



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) was added cesium carbonate (9.77 g, 30 mmol) and 4-

fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius . After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxylpiperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4N HCl dioxane solution (17 mL). After one hour at ambient temperature, the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken

up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part E (1.14 g, 3 mmol) in dimethylformamide (6 mL)

were added potassium carbonate (1.24 g, 9 mmol), bis-(2-chloroethyl)benzyl amine (0.7 g, 3 mmol, and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the piperidine sulfonamide as a white solid (950 mg, 59%).

Part G: Preparation of 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the piperidine sulfonamide from part F (7.2 g, 13.3 mmol) was dissolved in dry tetrahydrofuran (26 mL) and potassium trimethylsilonate (5.7 g, 40 mmol) was added and stirred at forty degrees Celsius. After twenty four hours water (50 mL) was added and at 5 degrees Celsius, 6N HCl was added until pH=1. The slurry was filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (6.5 g, 93%).

Part H: Preparation of 1-(phenylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide

In dry equipment under nitrogen, the carboxylic acid from part G (6.46 g, 12.2 mmol) was dissolved in dry dimethylformamide (25 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (2.0 g, 14.7

mmol), N-methylmorpholine (4.0 mL, 36.8 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (4.3 g, 36.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.3 g, 17.2 mmol). The reaction was stirred at forty five degrees Celsius. After three hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white solid (6.1 g, 80%).

Part I: Preparation of N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride

To a solution of the THP hydroxamate from part H (6.0 g, 9.6 mmol) in 1,4-dioxane (2.4 mL) was added 4 N HCl dioxane solution (2.4 mL) and methanol (2.4 mL). After thirty minutes at ambient temperature the reaction was poured into diethyl ether (100 mL). The slurry was filtered under nitrogen, washed with diethyl ether, and dried *in vacuo* to give the title compound as an off white solid (5.4 g, 97%). HRMS (ES+) M+ H^+ calculated for $C_{25}H_{30}F_3N_3O_5S_1$: 542.1937, found 542.1938.

Example 19: Preparation of N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius . After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxylpiperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4N HCl dioxane solution (17 mL). After one hour at ambient temperature, the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken

up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part E (1.14 g, 3 mmol) in dimethylformamide (6 mL)

were added potassium carbonate (1.24 g, 9 mmol), bis-(2-chloroethyl)benzyl amine (0.7 g, 3 mmol, and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the piperidine sulfonamide as a white solid (950 mg, 59%).

Part G: Preparation of 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the piperidine sulfonamide from part F (7.2 g, 13.3 mmol) was dissolved in dry tetrahydrofuran (26 mL) and potassium trimethylsilonate (5.7 g, 40 mmol) was added and stirred at forty degrees Celsius. After twenty four hours water (50 mL) was added and at 5 degrees Celsius, 6N HCl was added until pH=1. The slurry was filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (6.5 g, 93%).

Part H: Preparation of 1-(phenylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide

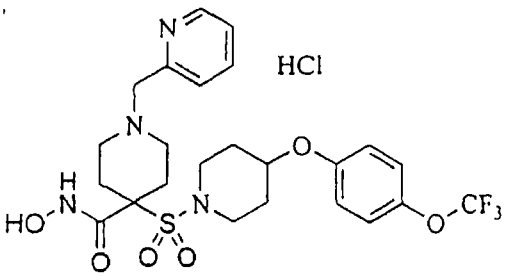
In dry equipment under nitrogen, the carboxylic acid from part G (6.46 g, 12.2 mmol) was dissolved in dry dimethylformamide (25 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (2.0 g, 14.7

mmol), N-methylmorpholine (4.0 mL, 36.8 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (4.3 g, 36.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.3 g, 17.2 mmol). The reaction was stirred at forty five degrees Celsius. After three hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white solid (6.1 g, 80%).

Part I: Preparation of N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride

To a solution of the THP hydroxamate from part H (6.0 g, 9.6 mmol) in 1,4-dioxane (2.4 mL) was added 4 N HCl dioxane solution (2.4 mL) and methanol (2.4 mL). After thirty minutes at ambient temperature the reaction was poured into diethyl ether (100 mL). The slurry was filtered under nitrogen, washed with diethyl ether, and dried *in vacuo* to give the title compound as an off white solid (5.4 g, 97%). HRMS (ES+) M+ H^+ calculated for $C_{25}H_{30}F_3N_3O_5S_1$: 542.1937, found 542.1938.

Example 19: Preparation of N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-fimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours the reaction mixture was

concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL) and at minus five degrees Celsius sodium hydride (2.74g, 68.4 mmol of the 60% oil dispersion) was added and the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]piperidine

At fifteen degrees Celsius, 4 N HCl in dioxanes (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide

solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxyl]piperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol) and at zero degrees Celsius a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus

seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part F (20.46 g, 51.5 mmol) in dimethylformamide (90 mL) was added potassium carbonate (21.3 g, 154.7 mmol), bis-(2-chloroethyl)benzyl amine (12.0 g, 51.5 mmol; and 18-Crown-6 (700mg). The slurry was stirred at sixty degrees Celsius. After twenty four hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (methanol) to give the N-benzyl piperidine sulfonamide as a white solid (15 g, 52%).

Part H: Preparation of 4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylic acid, methyl ester

To a slurry of the N-benzyl piperidine sulfonamide from part G (4.17 g, 7.5 mmol) in methanol (50 mL) was added ammonium formate (1.46 g, 22.5 mmol). The system was purged with nitrogen for 10 minutes. The nitrogen stream was removed and

palladium on carbon (1.5 g of 10 weight % on activated carbon, 50%water) was added. The reaction was refluxed for thirty minutes, cooled, filtered through Celite under nitrogen, and concentrated *in vacuo* to give the unsubstituted piperidine sulfonamide as a beige solid (3.15 g, 90%).

Part I: Preparation of methyl 1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

The unsubstituted piperidine sulfonamide from part H (7.9 g, 16.95 mmol) was dissolved in dry dimethylformamide (35 mL) and potassium carbonate (7.05 g, 51.1 mmol) and 2-picolyl chloride hydrochloride (4.21 g, 25.67 mmol) were added. The reaction was stirred at thirty five degrees Celsius for sixteen hours and then concentrated *in vacuo*. The residue was taken up in ethyl acetate and filtered through Celite. The filtrate washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the N-picolyl piperidine sulfonamide as a white solid (6.8 g, 72%).

Part J: Preparation of 1-(2-pyridinylmethyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide

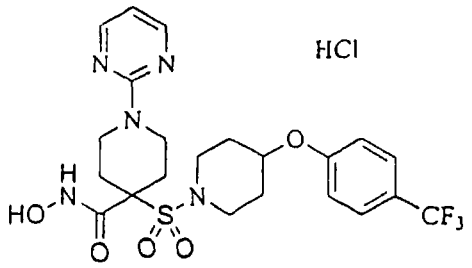
In dry equipment under nitrogen, the N-picolyl piperidine sulfonamide from part I (8.5g, 15.3mmol) was dissolved in dry tetrahydrofuran (30 mL) and potassium trimethylsilonate (6.52 g, 45.8 mmol) was added at ambient temperature. After eighteen hours water (50 mL) was added and at 5 degrees Celsius, 6 N

HCl was added until pH=7. The slurry was filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a off-white solid (6.9 g, 84%). In dry equipment under nitrogen, the carboxylic acid (6.8 g, 12.5 mmol) was dissolved in dry dimethylformamide (25 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (2.03 g, 15.0 mmol), N-methylmorpholine (4.1 mL, 37.6 mmol), O- (tetrahydro-2H-pyran-2-yl)hydroxylamine (4.4 g, 37.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.36 g, 17.5 mmol). The reaction was stirred at forty degrees Celsius. After twelve hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a light yellow foam (7.55 g, 94%).

Part K: Preparation of N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part J (7.4 g, 11.5 mmol) in 1,4-dioxane (2 mL) was added 4N HCl dioxane solution (29 mL, 115.2 mmol) and methanol (2.9 mL). After fifteen minutes, the reaction was diluted with diethyl ether, the solids filtered under nitrogen and dried *in vacuo* to give the title compound as a white solid (1.15 g, 96%). HRMS (ES+) M+ H $^+$ calculated for $C_{24}H_{29}F_3N_4O_6S_1$: 559.1838, found 559.1864.

Example 20: Preparation of N-hydroxy-1-(2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) was

added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius. After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxylpiperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4N HCl dioxane solution (17 mL). After one hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken

up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part E (1.14 g, 3 mmol) in dimethylformamide (6 mL)

was added potassium carbonate (1.24 g, 9 mmol), bis-(2-chloroethyl)benzyl amine (0.7 g, 3 mmol; and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the piperidine sulfonamide as a white solid (950 mg, 59%).

Part G: Preparation of methyl 1-(2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate

To a slurry of the piperidine sulfonamide from part F (6.3 g, 12.0 mmol) in methanol (25 mL) was added ammonium formate (2.2 g, 34.5 mmol). The system was purged with nitrogen for 10 minutes. The nitrogen stream was removed and palladium on carbon (1.2 g of 10 weight % on activated carbon, 50%water) was added. The reaction was refluxed for forty five minutes, cooled, filtered through Celite under nitrogen, and concentrated *in vacuo*. The residue (6.21 g, 13.8 mmol) was dissolved in dry dimethylformamide (28 mL) and potassium carbonate (5.7 g, 41.4 mmol) and 2-chloropyrimidine (3.16 g, 27.6 mmol) were added. The reaction was stirred at eighty five degrees Celsius for one hour and then concentrated *in vacuo*. The residue was taken up in ethyl acetate and filtered through Celite. The filtrate washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered,

and concentrated *in vacuo*. The product was recrystallized (methanol) to give the N- pyrimidinyl piperidine sulfonamide as a white solid (4.94 g, 68%).

Part H: Preparation of 1-(2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the N-pyrimidinyl piperidine sulfonamide from part G (4.9 g, 9.28 mmol) was dissolved in dry tetrahydrofuran (35 mL) and potassium trimethylsilonate (3.97 g, 27.8 mmol) was added at thirty five degrees Celsius. After sixteen hours water (50 mL) was added and at 5 degrees Celsius, 6 N HCl was added until pH=2. The aqueous slurry was extracted with ethyl acetate. The ethyl acetate solution was washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solids were slurried in acetonitrile, filtered under nitrogen, washed with hexanes and dried *in vacuo* to give the carboxylic acid as a white solid (4.7 g, 98%).

Part I: Preparation of 1-(2-pyrimidinyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide

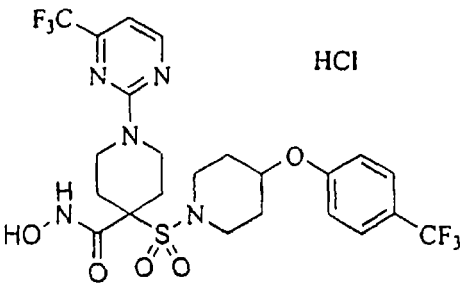
In dry equipment under nitrogen, the carboxylic acid from part H (4.6 g, 8.95 mmol) was dissolved in dry dimethylformamide (18 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (1.45 g, 10.7mmol), N-methylmorpholine (2.95 mL, 26.8 mmol), O- (tetrahydro-2H-pyran-2-yl)hydroxylamine (3.14 g,

26.8 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.4 g, 12.5 mmol). The reaction was stirred at thirty degrees Celsius. After sixteen hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (methanol) to give the THP hydroxamate as a white solid (5.0 g, 91%).

Part J: Preparation of N-hydroxy-1-(2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part I (4.97 g, 8.1 mmol) in 1,4-dioxane (3 mL) was added 4N HCl dioxane solution (20 mL, 81.1 mmol) and methanol (2 mL). After thirty minutes at ambient temperature the reaction was poured into 100 mL acetonitrile. The slurry was filtered under nitrogen, washed with acetonitrile and dried *in vacuo* to give the title compound as a white solid (3.3 g, 72%). HRMS (ES+) M+ H^+ calculated for $C_{22}H_{26}F_3N_5O_5S_1$: 530.1685, found 530.1696.

Example 21: Preparation of N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) was added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees

Celsius. After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxyl]piperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4 N HCl dioxane solution (17 mL). After one hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxyl]piperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part E (1.14 g, 3 mmol) in dimethylformamide (6 mL) was added potassium carbonate (1.24 g, 9 mmol), bis-(2-chloroethyl)benzyl amine (0.7 g, 3 mmol; and 18-Crown-6 (500mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times,

saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the piperidine sulfonamide as a white solid (950 mg, 59%).

Part G: Preparation of methyl 4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxylate

To a slurry of the piperidine sulfonamide from part F (6.3 g, 12.0 mmol) in methanol (25 mL) was added ammonium formate (2.2 g, 34.5 mmol). The system was purged with nitrogen for 10 minutes. The nitrogen stream was removed and palladium on carbon (1.2 g of 10 weight % on activated carbon, 50%water) was added. The reaction was refluxed for forty five minutes, cooled, filtered through Celite under nitrogen, and concentrated *in vacuo*. The residue (4.5 g, 10 mmol) was dissolved in dry dimethylformamide (20 mL) and potassium carbonate (4.14 g, 30 mmol) and 2-chloro-4-trifluoromethylpyrimidine (2.4 mL, 20 mmol) were added. The reaction was stirred at seventy degrees Celsius for three hour and then concentrated *in vacuo*. The residue was taken up in ethyl acetate and filtered through Celite. The filtrate washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (methanol) to give the N-pyrimidinyl piperidine sulfonamide as a white solid (4.51 g, 76%).

Part H: Preparation of 4-[[4-[4-(trifluoromethyl)-

phenoxy]-1-piperidinyl]sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the N-pyrimidinyl piperidine sulfonamide from part G (4.9 g, 9.28 mmol) was dissolved in dry tetrahydrofuran (35 mL) and potassium trimethylsilonate (3.2 g, 22.45 mmol) was added at forty five degrees Celsius. After four hours water (100 mL) was added and at 5 degrees Celsius, 6 N HCl was added until pH=2. The slurry was filtered under nitrogen, the solids washed with hexanes and dried *in vacuo* to give the carboxylic acid as a white solid (4.13 g, 95%).

Part I: Preparation of N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxamide

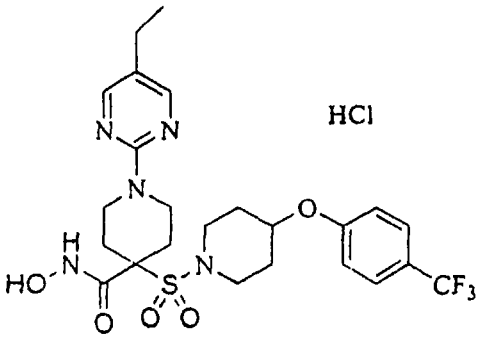
In dry equipment under nitrogen, the carboxylic acid from part H (4.0 g, 6.87 mmol) was dissolved in dry dimethylformamide (20 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (1.1 g, 8.25 mmol), N-methylmorpholine (2.2 mL, 20.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (2.4 g, 20.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.84 g, 9.62 mmol). The reaction was stirred at forty five degrees Celsius. After sixteen hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The

product was recrystallized (methanol) to give the THP hydroxamate as a white solid (4.06 g, 87%).

Part J: Preparation of N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-1-[4-(trifluoromethyl)-2-pyrimidinyl]-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part I (5.0 g, 5.87 mmol) in 1,4-dioxane (3 mL) was added 4N HCl dioxane solution (14.7 mL, 58.7 mmol) and methanol (1.5 mL). After thirty minutes at ambient temperature the reaction was poured into 100 mL acetonitrile. The slurry was filtered under nitrogen, washed with acetonitrile and dried *in vacuo* to give the title compound as a white solid (2.95 g, 80%). HRMS (ES+) M+ H $^+$ calculated for $C_{23}H_{25}F_6N_5O_5S_1$: 598.1559, found 598.1531.

Example 22: Preparation of 1-(5-ethyl-2-pyrimidinyl)-N-hydroxy-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-

piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) was added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius. After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxylpiperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4N HCl dioxane solution (17 mL). After one hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added

maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

To a solution of the methylene sulfonamide from part E (1.14 g, 3 mmol) in dimethylformamide (6 mL) was added potassium carbonate (1.24 g, 9 mmol), bis-(2-chloroethyl)benzyl amine (0.7 g, 3 mmol and 18-Crown-6 (500 mg). The slurry was stirred at sixty degrees Celsius. After sixteen hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the piperidine sulfonamide as a white solid (950 mg, 59%).

Part G: Preparation of methyl 1-(5-ethyl-2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-4-

piperidinecarboxylate

To a slurry of the piperidine sulfonamide from part F (6.3 g, 12.0 mmol) in methanol (25 mL) was added ammonium formate (2.2 g, 34.5 mmol). The system was purged with nitrogen for 10 minutes. The nitrogen stream was removed and palladium on carbon (1.2 g of 10 weight % on activated carbon, 50% water) was added. The reaction was refluxed for forty five minutes, cooled, filtered through Celite under nitrogen, and concentrated *in vacuo*. The residue (4.5 g, 10 mmol) was dissolved in dry dimethylformamide (20 mL) and potassium carbonate (3.45 g, 325mmol) and 2-chloro-5-ethylpyrimidine (1.82 mL, 15 mmol) were added. The reaction was stirred at eighty degrees Celsius for four hour and then concentrated *in vacuo*. The residue was taken up in ethyl acetate and filtered through Celite. The filtrate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (methanol) to give the N-pyrimidinyl piperidine sulfonamide as a white solid (3.33 g, 60%).

Part H: Preparation of 1-(5-ethyl-2-pyrimidinyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylic acid

In dry equipment under nitrogen, the N-pyrimidinyl piperidine sulfonamide from part G (3.3 g, 5.94 mmol) was dissolved in dry tetrahydrofuran (12 mL) and potassium trimethylsilonate (2.54 g, 17.8 mmol) was added at forty five degrees Celsius. After two hours water (100 mL) was added and at 5 degrees

Celsius, 6N HCl was added until pH=2. The slurry was filtered under nitrogen, the solids washed with hexanes and dried *in vacuo* to give the carboxylic acid as a white solid (3.11 g, 97%).

Part I: Preparation of 1-(5-ethyl-2-pyrimidinyl)-N-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide

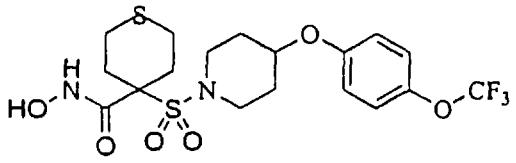
In dry equipment under nitrogen, the carboxylic acid from part H (3.0 g, 5.5mmol) was dissolved in dry dimethylformamide (15 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.9 g, 6.64 mmol), N-methylmorpholine (1.8 mL, 16.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.9 g, 16.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.49 g, 7.75 mmol). The reaction was stirred at forty five degrees Celsius. After three hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was recrystallized (methanol) to give the THP hydroxamate as a white solid (3.34 g, 96%).

Part J: Preparation of 1-(5-ethyl-2-pyrimidinyl)-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

To a solution of the THP hydroxamate from part I (3.3 g, 5.15 mmol) in 1,4-dioxane (3 mL) was added 4 N HCl dioxane solution (13 mL, 51.5 mmol) and methanol (1.3 mL). After thirty minutes at ambient

temperature the reaction was poured into 100 mL acetonitrile. The slurry was filtered under nitrogen, washed with acetonitrile and dried *in vacuo* to give the title compound as a white solid (2.59 g, 85%). HRMS (ES+) M+ H^+ calculated for $C_{24}H_{30}F_3N_5O_5S_1$: 5581998, found 558.1982.

Example 23: Preparation of tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-

piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL) and at minus five degrees Celsius sodium hydride (2.74g, 68.4 mmol of the 60% oil dispersion) was added and the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-

phenoxylpiperidine

At fifteen degrees Celsius, 4 N HCl in dioxanes (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxylpiperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol) and at zero degrees Celsius a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of tetrahydro-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl-2*H*-thiopyran-4-carboxylic acid

To a solution of the methylene sulfonamide from part F (6.0 g, 15 mmol) in dimethylformamide (30 mL) were added potassium carbonate (6.2 g, 45 mmol), bis-(2-bromoethyl)sulfide (3.72 g, 15 mmol; *J.Chem.Soc.*,1948;37) and 18-Crown-6 (500mg). The slurry was stirred at forty degrees Celsius. After twenty hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give impure

tetrahydrothiopyran substituted sulfonamide (4.68 g, 65%). In dry equipment under nitrogen, the tetrahydrothiopyran substituted sulfonamide (4.6 g, 9.52 mmol) was dissolved in dry tetrahydrofuran (20 mL) and potassium trimethylsilonate (4.07 g, 28.6 mmol) was added at fifty degrees Celsius. After four hours water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate to remove impurities. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (acetone/hexanes) to give the carboxylic acid as a white solid (2.62 g, 59%).

Part H: Preparation of tetrahydro-*N*-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide

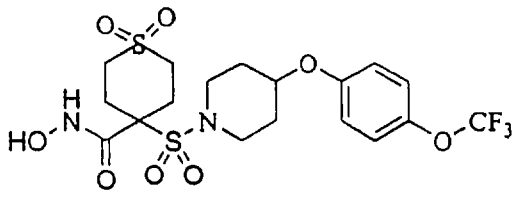
In dry equipment under nitrogen, the carboxylic acid from part G (2.6 g, 5.54 mmol) was dissolved in dry dimethylformamide (11 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.9 g, 6.65 mmol), N-methylmorpholine (1.83 mL, 16.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.95 g, 16.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.49 g, 7.72 mmol). After two hour at thirty five degrees Celsius, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution,

dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white foam (2.69 g, 85%).

Part I: Preparation of tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-2*H*-thiopyran-4-carboxamide

To a solution of the THP hydroxamate from part H (0.99 g, 1.75 mmol) in 1,4-dioxane (3.5 mL) was added 4N HCl dioxane solution (0.9 mL, 3.5 mmol) and methanol (0.14 mL). After thirty minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was slurried in diethyl ether, filtered under nitrogen and dried to give the title compound as a white solid (0.65 g, 77%). HRMS (ES+) M+ H^+ calculated for $C_{18}H_{23}N_2O_6S_2F_3$: 485.1028, found 485.1034.

Example 24: Preparation of tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide, 1,1-dioxide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in

tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

To a solution of the BOC piperidine of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL) at zero degrees Celsius, was added triethylamine (3.81 mL, 27.32 mmol) followed by methane sulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete the cooling bath was removed. After stirring for two hours, the reaction mixture was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the mesylate as an off-white solid (7.34 g, >100%).

Part C: Preparation of 4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

In dry equipment under nitrogen, 4-trifluoromethoxyphenol (10.15 g, 57 mmol) was dissolved in dry dimethylformamide (125 mL), and at minus five degrees Celsius sodium hydride (2.74g,

68.4 mmol of the 60% oil dispersion) was added and the ice bath was removed. After one hour at ambient temperature, the mesylate from part B (15.9 g, 57 mmol) was added and the reaction stirred at eighty degrees Celsius. After stirring at ambient temperature for four hours, the reaction was concentrated *in vacuo*. The residue was taken up in diethyl ether, washed with water, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted BOC-piperidine as a beige solid (20.6 g, 100%).

Part D: Preparation of 4-[4-(trifluoromethoxy)-phenoxylpiperidine

At fifteen degrees Celsius, 4 N HCl in dioxanes (125 mL) was slowly added to the substituted BOC-piperidine from part C (20.6 g, 57 mmol) and stirred for ninety minutes. The reaction was concentrated *in vacuo*. The residue was dissolved in water (150 mL) and washed two times with ethyl acetate. The aqueous solution was cooled to five degrees Celsius and the pH adjusted to eleven with 5 N sodium hydroxide solution and extracted with ethyl acetate. The ethyl acetate was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the substituted piperidine as a beige solid (11.9 g, 80%).

Part E: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethoxy)phenoxylpiperidine

The substituted piperidine from part D (11.5 g, 44.1 mmol) was dissolved in dichloromethane (125 mL) with triethylamine (12.3 mL, 88.1 mmol) and at zero degrees Celsius a solution of methane sulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL) was added. After one hour at ambient

temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (ethyl acetate/hexanes) to give the sulfonamide as an off-white solid (10.77 g, 72%).

Part F: Preparation of methyl [[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxylate

In dry equipment under nitrogen, the sulfonamide from part E (10.77 g, 31.8 mmol) was dissolved in dry tetrahydrofuran (64 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (80 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in dry tetrahydrofuran (32 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride solution (125 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (12.69 g, 100%).

Part G: Preparation of tetrahydro-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-2*H*-thiopyran-4-carboxylic acid

To a solution of the methylene sulfonamide from part F (6.0 g, 15 mmol) in dimethylformamide (30 mL) was added potassium carbonate (6.2 g, 45 mmol), bis-(2-bromoethyl)sulfide (3.72 g, 15 mmol; *J.Chem.Soc.*;1948;37) and 18-Crown-6 (500 mg). The slurry was stirred at forty degrees Celsius. After twenty hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give impure tetrahydrothiopyran substituted sulfonamide (4.68 g, 65%). In dry equipment under nitrogen, the tetrahydrothiopyran substituted sulfonamide (4.6 g, 9.52 mmol) was dissolved in dry tetrahydrofuran (20 mL) and potassium trimethylsilonate (4.07 g, 28.6 mmol) was added at fifty degrees Celsius. After four hours, water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate to remove impurities. The aqueous solution was treated with 6N HCl until pH=1. The slurry was extracted with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized (acetone/hexanes) to give the carboxylic acid as a white solid (2.62 g, 59%).

Part H: Preparation of tetrahydro-*N*-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide

In dry equipment under nitrogen, the carboxylic acid from part G (2.6 g, 5.54 mmol) was dissolved in

dry dimethylformamide (11 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.9 g, 6.65 mmol), N-methylmorpholine (1.83 mL, 16.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.95 g, 16.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.49 g, 7.72 mmol). After two hour at thirty five degrees Celsius, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white foam (2.69 g, 85%).

Part I: Preparation of tetrahydro-*N*-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide, 1,1-dioxide

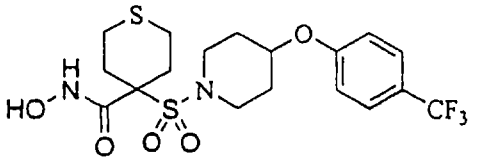
The THP hydroxamate from part H (1.0 g, 1.76 mmol) was dissolved in dichloromethane (10 mL) and 3-chloroperoxybenzoic acid (1.33g, 4.4 mmol, 57-86%) was added at twenty five degrees Celsius. After two hours, a solution of saturated $NaHCO_3$ with 5% sodium thiosulfate (10 mL) was added and the mixture was stirred for ten minutes. The layers were separated and washed with saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the sulfone THP hydroxamate as a white solid (0.907 g, 92%).

Part J: Preparation of tetrahydro-*N*-hydroxy-4-[[4-[4-

(trifluoromethoxy)phenoxy]-1-piperidinyl]-sulfonyl]-2*H*-thiopyran-4-carboxamide, 1,1-dioxide

To a solution of the sulfone THP hydroxamate from part I (0.9 g, 1.5 mmol) in 1,4-dioxane (3. mL) was added 4N HCl dioxane solution (1.9 mL, 7.5 mmol) and methanol (0.5 mL). After ten minutes at ambient temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was slurried in diethyl ether, filtered under nitrogen and dried to give the title compound as a white solid (0.70 g, 90%). HRMS (ES+) M+ NH_4^+ calculated for $C_{18}H_{23}N_2O_8S_2F_3$: 534.1192, found 534.1231.

Example 25: Preparation of tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide



Part A: Preparation of 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate

In dry equipment under nitrogen, 4-hydroxypiperidine (20.2 g, 0.2 mol) was dissolved in tetrahydrofuran (200 mL) and triethylamine (29 mL, 0.21 mol). A solution of di-t-butyldicarbonate (43.65 g, 0.2 mol) was added at such a rate that the temperature remained below thirty degrees Celsius. After stirring at ambient temperature for four hours,

the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, 5% $KHSO_4$, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the BOC piperidine as a white solid (37.7 g, 94%).

Part B: Preparation of 1,1-dimethylethyl 4-[4-(trifluoromethyl)phenoxy]-1-piperidinecarboxylate

To a solution of the BOC piperidine from part A (6.03 g,30 mmol) in dimethylformamide (60 mL) was added cesium carbonate (9.77 g, 30 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30 mmol). The slurry was stirred at ninety degrees Celsius. After nineteen hours cesium carbonate (3.26g, 10 mmol) and 4-fluorobenzotrifluoride (0.95ml mL, 10 mmol) were added and the reaction continued at ninety degrees Celsius. ' After a total of forty six hours, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the substituted BOC piperidine as a white solid (6.0 g, 58%).

Part C: Preparation of 4-[4-(trifluoromethyl)-phenoxylpiperidine

To a slurry of the substituted BOC piperidine from part B (5.95 g, 17.2 mmol) in 1,4-dioxane (10 mL) was added 4 N HCl dioxane solution (17 mL). After one hour at ambient temperature the reaction was concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the

resulting precipitate provided the hydrochloride salt as a white solid (4.6 g, 100%).

Part D: Preparation of 1-(methylsulfonyl)-4-[4-(trifluoromethyl)phenoxylpiperidine

To a solution of the hydrochloride salt from part C (4.6 g, 16.9 mmol) and triethylamine (5.9 mL, 42.4 mmol) in dichloromethane (45 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.97 mL, 25.4 mmol) in dichloromethane (10 mL). After one hour at ambient temperature, the solvent was stripped *in vacuo*. The residue was taken up in ethyl acetate, washed with water two times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was slurried in diethyl ether and vacuum filtration of the resulting precipitate provided the sulfonamide as an off-white solid (5.25 g, 96%).

Part E: Preparation of methyl [[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]acetate

In dry equipment under nitrogen, the sulfonamide from part D (4.2 g, 13 mmol) was dissolved in dry tetrahydrofuran (26 mL), chilled to minus seventy-five degrees Celsius, and a 1 M solution of lithium bis(trimethylsilyl)amide (26 mL) was added maintaining the temperature below minus sixty five degrees. After thirty minutes at minus seventy-five degrees Celsius, a solution of methyl chloroformate (1.0mL, 13 mmol) in dry tetrahydrofuran (13 mL) was added maintaining the temperature below minus sixty degrees. After thirty minutes at minus seventy-five degrees Celsius, the reaction was quenched with

saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate. The combined extracts were washed with saturated ammonium chloride solution, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide as an yellow oil (4.95 g, 100%).

Part F: Preparation of tetrahydro-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-2*H*-thiopyran-4-carboxylic acid

To a solution of the methylene sulfonamide from part E (5.7 g, 15 mmol) in dimethylformamide (30 mL) was added potassium carbonate (6.2 g, 45 mmol), bis-(2-bromoethyl)sulfide (3.72 g, 15 mmol; *J.Chem.Soc.*;1948;37) and 18-Crown-6 (500 mg). The slurry was stirred at forty degrees Celsius. After sixty hours the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give impure tetrahydrothiopyran substituted sulfonamide (3.7 g, 53%). In dry equipment under nitrogen, the tetrahydrothiopyran substituted sulfonamide (3.68 g, 7.88 mmol) was dissolved in dry tetrahydrofuran (15 mL) and potassium trimethylsilonate (3.37 g, 23.6 mmol) was added at fifty degrees Celsius. After ninety minutes water (100 mL) was added and the solution concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate to remove impurities. The aqueous solution was treated with 6 N HCl until pH=1. The slurry was extracted

with ethyl acetate and the combined extracts washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the carboxylic acid as a white foam (1.66 g, 46%).

Part G: Preparation of tetrahydro-*N*-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-2*H*-thiopyran-4-carboxamide

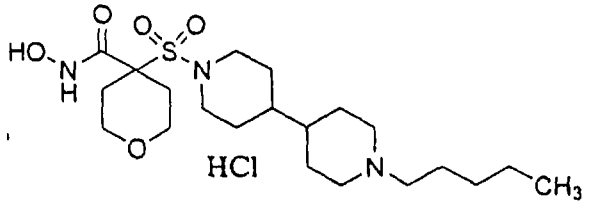
In dry equipment under nitrogen, the carboxylic acid from part F (1.5 g, 3.31 mmol) was dissolved in dry dimethylformamide (7 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.54 g, 3.97 mmol), N-methylmorpholine (1.1 mL, 9.93 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.16 g, 9.93 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.89 g, 4.64 mmol). After ninety minutes at thirty five degrees Celsius, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white foam (0.85 g, 47%).

Part H: Preparation of tetrahydro-*N*-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-2*H*-thiopyran-4-carboxamide

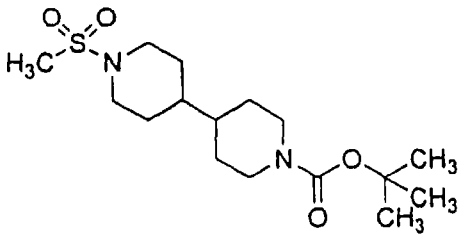
To a solution of the THP hydroxamate from part G (0.7 g, 1.27 mmol) in 1,4-dioxane (2.5 mL) was added 4 N HCl dioxane solution (1.6 mL, 6.34 mmol) and methanol (0.4 mL). After ten minutes at ambient

temperature the reaction was diluted with ethyl acetate and washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Dichloromethane (20 mL) was added and the solution was stripped. The product was slurried in diethyl ether, filtered under nitrogen and dried to give the title compound as a white solid (0.56 g, 94%). HRMS (ES+) M+ H^+ calculated for $C_{18}H_{23}N_2O_5S_2F_3$: 469.1079, found 469.1061.

Example 26: Preparation of *N*-hydroxy-4[[1'-(*n*-pentyl)[4,4'-bipiperidin]-1-yl]-sulfonyl]-tetrahydro-2*H*-pyran-4-carboxamide



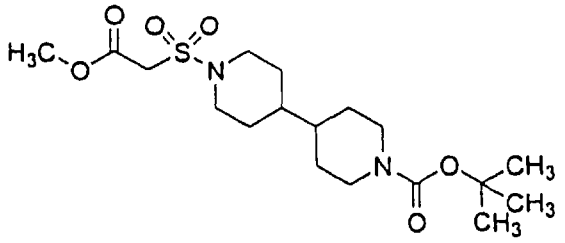
Part 1: Preparation of



To a solution of the N-(t-butoxycarbonyl)-4,4'-bipiperdine (prepared using Preparation 22 in patent application WO 94/14776) (32.3 g, 120.0 mmol) and triethylamine (30.1 mL, 216.0 mmol) in dichloromethane (330 mL) at zero degrees Celsius was

added a solution of methane sulfonyl chloride (16.2 mL, 209.0 mmol) in dichloromethane (100 mL). After 2.5 hours at ambient temperature, the solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (1 L) and water (0.5 L). The aqueous layer was extracted twice with ethyl acetate (300 mL), then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was triturated with diethyl ether to give the methyl sulfonamide N'-t-butoxycarbamate as a white solid (33.31 g, 80%). ^1H NMR and mass spectrum were consistent with the desired compound.

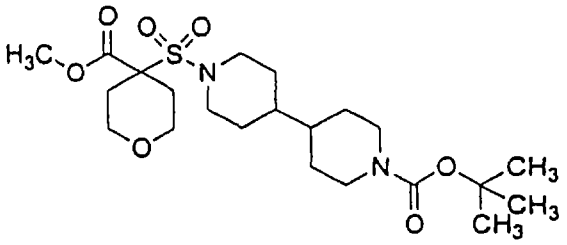
Part 2: Preparation of



In dry equipment under nitrogen, the methyl sulfonamide N'-t-butoxycarbamate from part 1 (28.0 g, 81.0 mmol) was dissolved in dry tetrahydrofuran (160 mL) and cooled to minus seventy-five degrees Celsius. The resulting solution was then treated with a 1 M solution of lithium bis(trimethylsilyl)amide (210 mL, 210.0 mmol) at a rate such that the temperature remained below minus sixty five degrees. After addition was complete, the reaction mixture was allowed to warm to zero degrees Celsius. After 1 hour, the solution was cooled to minus seventy-five degrees Celsius and treated with a solution of methyl chloroformate (8.2 mL, 97.0 mmol) in dry

tetrahydrofuran (50 mL), while maintaining the temperature below minus seventy degrees. After 1 hour at minus seventy-five degrees Celsius, the reaction was quenched with saturated ammonium chloride aqueous solution (60 mL), warmed to ambient temperature and concentrated *in vacuo*. The resulting residue was partitioned between ethyl acetate (500 mL) and 5% aqueous $KHSO_4$ (500 mL). The aqueous layer was extracted with ethyl acetate (250 mL), then the combined organic layers were washed with water (250 mL), twice with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methylene sulfonamide N'-t-butoxycarbamate as a yellow solid (32.6 g, 99.9%). ^1H NMR and mass spectrum were consistent with the desired compound.

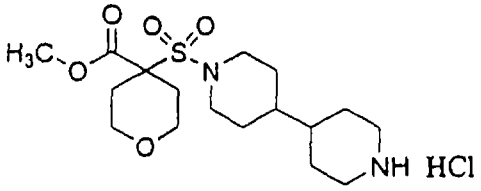
Part 3: Preparation of



To a solution of the methylene sulfonamide N'-t-butoxycarbamate from part 2 (15.0 g, 37.0 mmol) in dimethylformamide (75 mL) was added bis-(2-bromoethyl)ether (10.3 g, 44 mmol), 18-Crown-6 (400 mg), followed by potassium carbonate (15.4 g, 111.0 mmol). The heterogeous mixture was stirred at sixty degrees Celsius. After 48 hours, the reaction was concentrated *in vacuo*, and the resulting oil was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with 5% aqueous $KHSO_4$ (50 mL), twice with water (2 x 50 mL),

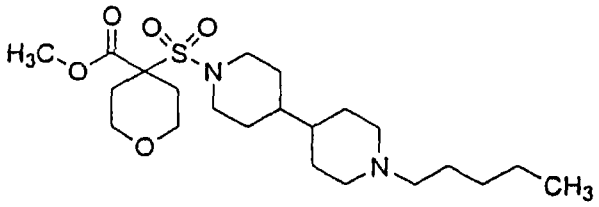
brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the pyran sulfonamide N'-t-butoxycarbamate as a white solid. (18 g, 97%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 4: Preparation of



The pyran sulfonamide N'-t-butoxycarbamate (17 g, 36 mmol) from part 3 was dissolved in 4 N HCl 1,4-dioxane solution (90 mL). After 2 hours at ambient temperature the clear yellow solution began to form a precipitate. After 4 hours, the reaction was diluted with diethyl ether and vacuum filtration of the resulting white suspension provided the pyran sulfonamide hydrochloride salt as a white solid (13.4 g, 91%). ^1H NMR and mass spectrum were consistent with the desired compound.

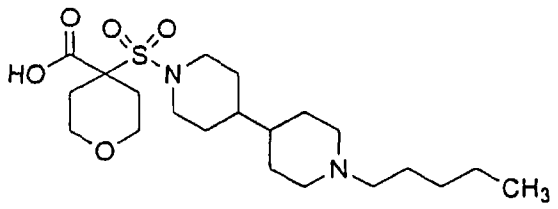
Part 5: Preparation of



A suspension of the pyran sulfonamide hydrochloride salt from part 4 (3.5 g, 8.5 mmol) in tetrahydrofuran (26 mL) was treated with sodium acetate (0.7 g, 8.9 mmol), valeraldehyde (0.9 mL, 8.5 mmol), followed by sodium triacetoxyborohydride (2.2 g, 10.0 mmol). After 96 hours at ambient temperature, the reaction mixture was concentrated *in*

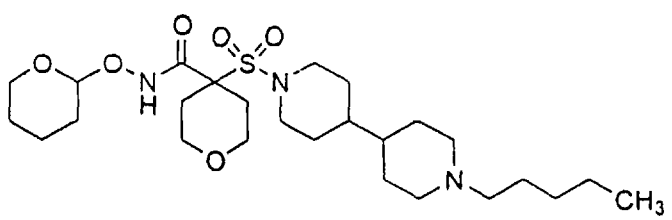
vacuo. The resulting residue was partitioned between ethyl acetate (100 mL) and water (70 mL) and treated with saturated sodium carbonate aqueous solution until pH = 8. The aqueous layer was extracted with ethyl acetate (25 mL) and the combined organic layers were washed with water (20 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the pyran sulfonamide N'-n-pentyl amine as a light yellow solid (3.7 g, 97%). ^{1}H NMR and mass spectrum were consistent with the desired compound.

Part 6: Preparation of



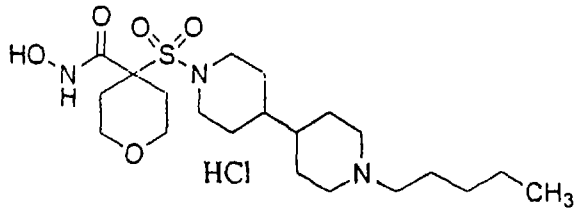
In dry equipment under nitrogen, the pyran sulfonamide N'-n-pentyl amine from part 5 (3.2 g, 7.2 mmol) was dissolved in dry tetrahydrofuran (36 mL) and potassium trimethylsilanolate (3.1 g, 22.0 mmol) was added at ambient temperature. After 21 hours, the reaction was concentrated *in vacuo*, and the resulting residue was dissolved in water (20 mL) and treated with 2N HCl until pH = 7. The white suspension was vacuum filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (2.36 g, 76%). ^{1}H NMR and mass spectrum were consistent with the desired compound.

Part 7: Preparation of



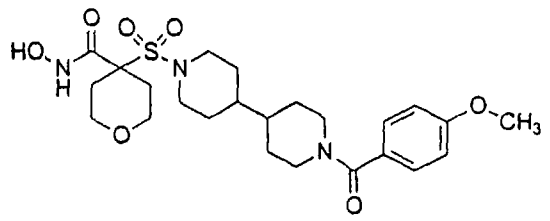
In dry equipment under nitrogen, the carboxylic acid from part 6 (2.2 g, 5.1 mmol) was dissolved in dry dimethylformamide (17 mL) and treated with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.5 g, 7.63 mmol) and N-hydroxybenzo-triazole hydrate (1.03 g, 7.63 mmol). The resulting suspension became a clear amber solution after stirring at fifty degrees Celsius for 1.5 hours. The reaction was then treated with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.9 g, 7.63 mmol), followed by N-methylmorpholine (1.7 mL, 15 mmol) three minutes later. The reaction was stirred at fifty degrees Celsius. After 64 hours, the reaction was treated again with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.49 g, 2.6 mmol), N-hydroxybenzo-triazole hydrate (0.34 g, 2.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.30 g, 2.6 mmol), followed by N-methylmorpholine (0.28 mL, 2.6 mmol). After 98 hours, the reaction was concentrated *in vacuo*. The resulting residue was partitioned between ethyl acetate (100 mL) and water (40 mL). The organic layer was washed three times with saturated sodium bicarbonate aqueous solution (3 x 25 mL), twice with brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was recrystallized in methanol (4 mL) to give the THP hydroxamate as a white solid (1.28 g, 48%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 8: Preparation of

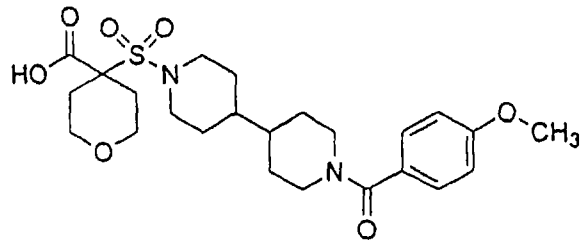


The THP hydroxamate from part 7 (1.1 g, 2.08 mmol) was suspended in methanol (0.5 mL) and the treated with 4 N HCl in 1,4-dioxane solution (5.2 mL, 21 mmol). After 2 hours at ambient temperature, the reaction was concentrated to half the reaction volume and then diluted with diethyl ether (200 mL). The white suspension was filtered under nitrogen and dried *in vacuo* to give the title compound as a white solid (0.94 g, 94%). MS(ES+) m/z calculated for $C_{21}H_{39}N_3O_5S$: 445, found (M+1) 446.

Example 27: Preparation of *N*-hydroxy-4[[1'-(4-methoxybenzoyl)[4,4'-bipiperidin]-1-yl]sulfonyl]-tetrahydro-2*H*-pyran-4-carboxamide



Part 9: Preparation of

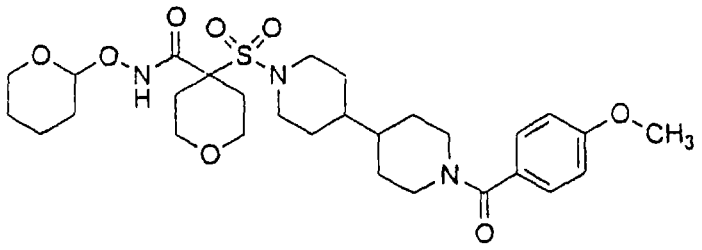


A suspension of the pyran sulfonamide hydrochloride salt from part 4 of Example 26 (3.0 g, 7.3 mmol), in dichloromethane (15 mL) and

triethylamine (1.12 mL, 8.0 mmol) was cooled to zero degrees Celsius and treated with 4-(dimethylamino)pyridine (0.1g) followed by *p*-anisoyl chloride (1.37 g, 8.0 mmol). The cooling bath was removed and the reaction was stirred at ambient temperature for 22 hours. The reaction was again treated with triethylamine (0.51 mL, 3.65 mmol) *p*-anisoyl chloride (0.62 g, 3.65 mmol). After stirring for 8 days, the reaction was diluted with dichloromethane (75 mL) and partitioned with water (50 mL). The aqueous layer was extracted twice with dichloromethane (2 x 25 mL). The combined organic layers were washed twice with 5% aqueous $KHSO_4$ (2 x 30 mL), water (20 mL), saturated sodium bicarbonate aqueous solution (25 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the amide methyl ester as a white solid. (3.7 g, crude).

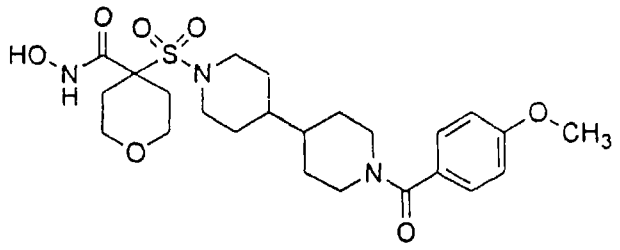
The amide methyl ester was suspended in dry tetrahydrofuran (42 mL) and treated with potassium trimethylsilanolate (2.73 g, 21.0 mmol) and stirred at forty degrees Celsius. After 4.5 days, the reaction was diluted with water (50 mL) and treated with 2 N HCl until pH = 1. The resulting white, yellow suspension was vacuum filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a light yellow solid solid (2.55 g, 82% over 2 steps). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 10: Preparation of



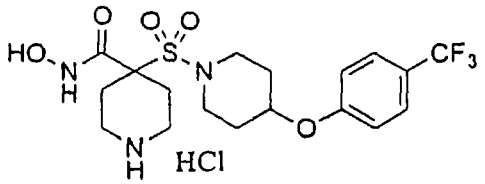
In dry equipment under nitrogen, the carboxylic acid from part 9 (2.2 g, 4.6 mmol) was dissolved in dry dimethylformamide (15 mL) and treated with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.3 g, 6.7 mmol) and N-hydroxybenzotriazole hydrate (0.9 g, 6.7 mmol). The resulting suspension became a clear amber solution after stirring at fifty degrees Celsius for 50 minutes. The reaction was then treated with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.8 g, 6.7 mmol), followed by N-methylmorpholine (1.47 mL, 13 mmol) three minutes later. The reaction was stirred at fifty degrees Celsius. After 25 hours, the reaction was concentrated *in vacuo*. The resulting residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (25 mL), and the combined organic layers were washed twice with saturated sodium bicarbonate aqueous solution (2 x 25 mL), brine (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting yellow oil was recrystallized in methanol (4 mL) to give the THP hydroxamate as a white solid (1.81 g, 69%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 11: Preparation of

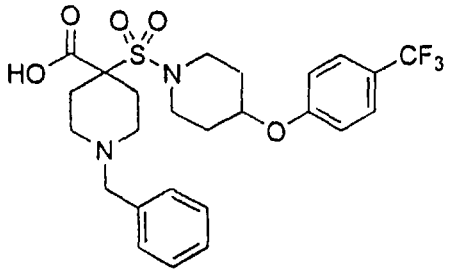


The THP hydroxamate from part 10 (1.44 g, 2.43 mmol) was dissolved in acetonitrile (25 mL), diluted with water (15 mL), and then treated with aqueous 2N HCl (2.5 mL, 4.85 mmol). After 2 hours at ambient temperature, the acetonitrile and excess hydrochloric acid were removed with a stream of nitrogen. The resulting white suspension was filtered under nitrogen, washed with water and dried *in vacuo* to give the title compound as a white solid (0.67 g, 56%). MS(ES+) m/z calculated for $C_{24}H_{35}N_3O_7S$: 509, found (M+1) 510.

Example 28: Preparation of *N*-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride

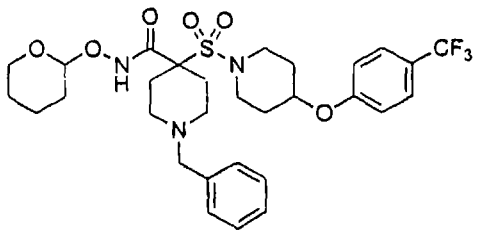


Part 12: Preparation of



In dry equipment under nitrogen, the compound of Example 20, part F (16.51 g, 30.5 mmol) was dissolved in dry tetrahydrofuran (61 mL) and potassium trimethylsilanolate (11.8 g, 91.6 mmol) was added at ambient temperature. After 21 hours, the reaction was concentrated *in vacuo*, and the resulting residue was dissolved in water (100 mL) and treated with 2N HCl until pH = 7. The white suspension was vacuum filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (15.45 g, 96%). ^{1}H NMR and mass spectrum were consistent with the desired compound.

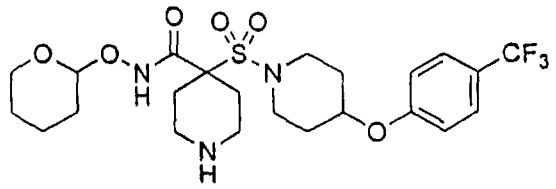
Part 13: Preparation of



In dry equipment under nitrogen, the carboxylic acid from part 12 (15.45 g, 29.3 mmol) was dissolved in dry dimethylformamide (147 mL) and treated with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (8.44 g, 44 mmol) and N-hydroxybenzotriazole hydrate (5.95 g, 44 mmol). After 1 hour and 20 minutes at ambient temperature, the suspension was treated with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (5.15 g, 44 mmol), followed by N-methylmorpholine (9.7 mL, 88 mmol) three minutes later. After stirring for 16 hours at ambient temperature, the reaction was heated to fifty degrees Celsius for 3 hours, and then treated with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.41 g, 7.4 mmol), N-hydroxybenzo-

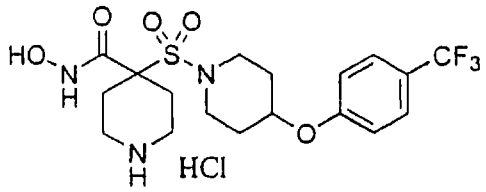
triazole hydrate (0.99 g, 7.3 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.86 g, 7.3 mmol), and N-methylmorpholine (1.61 mL, 14.6 mmol). After 20 hours, the reaction was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate (400 mL) and water (400 mL). The aqueous layer was extracted with ethyl acetate (200 mL), and the combined organic layers were washed with saturated sodium bicarbonate aqueous solution (100 mL), water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the THP hydroxamate piperidine N-benzyl as a brown oil (18.4 g, 100%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 14: Preparation of



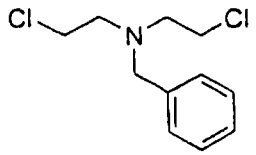
The THP hydroxymate piperidine N-benzyl from part 13 (1.0 g, 1.6 mmol) was dissolved in methanol (4.5 mL) and then treated with ammonium formate (302 mg, 4.8 mmol) followed by palladium on carbon (Degussa catalyst, 400 mg of 10 weight % on activated carbon, 50% water). The black heterogeneous mixture was stirred at ambient temperature for 30 minutes, diluted with methanol (4.5 mL), and then stirred for another 3 hours. The reaction was then filtered through a methanol washed pad of Celite under nitrogen, and the filtrate was concentrated *in vacuo* to give the THP hydroxamate piperidine as a white glassy foam (0.73 g, 85%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 15: Preparation of



The THP hydroxamate piperidine from part 14 (0.34 g, 0.64 mmol) was treated with methanol (0.2 mL) followed by 4 N HCl in 1,4-dioxane solution (2 mL, 8 mmol), which formed a white precipitate. After 1 hour at ambient temperature, the reaction diluted with diethyl ether (5 mL), and the white suspension was filtered under nitrogen, washed with diethyl ether and dried *in vacuo* to give the title compound as a white solid (0.18 g, 58%). MS(FABMS) m/z calculated for $C_{18}H_{24}N_3O_5SF_3$: 451, found (M+1) 452.

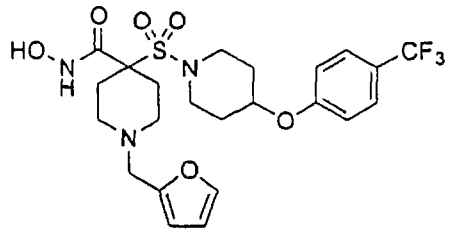
Example 29: Preparation of bis(2-chloroethyl)-benzylamine (Part 16)



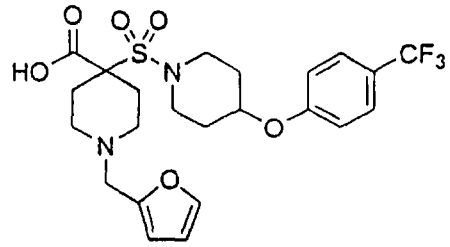
A suspension of bis(2-chloroethyl)amine hydrochloride (Aldrich, 500 g, 2.8 mol), sodium acetate (229.8 g, 2.8 mol), and benzaldehyde (270.5 mL, 2.66 mol), in tetrahydrofuran (2.5 L), was cooled to ten degrees Celsius, and treated with sodium triacetoxyborohydride (712.4 g, 3.36 mol) at a rate such that the temperature did not exceed eighteen degrees Celsius. After stirring the white suspension at ambient temperature for 25 hours, the reaction was quenched with the addition of ethyl acetate (4 L) followed by 2.5 M sodium hydroxide (3.5 L), which

made the mixture pH = 9. The mixture was partitioned with the addition of water (3 L). The aqueous layer was extracted with ethyl acetate (1.5 L). The combined organic layers were washed twice with brine (2 x 1 L), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude yellow oil was purified on silica gel (hexanes) to give a clear, colorless oil (482.6 g, 78%). ^1H NMR and mass spectrum were consistent with the desired compound.

Example 30: Preparation of 1-(2-furanylmethyl)-*N*-hydroxy-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide



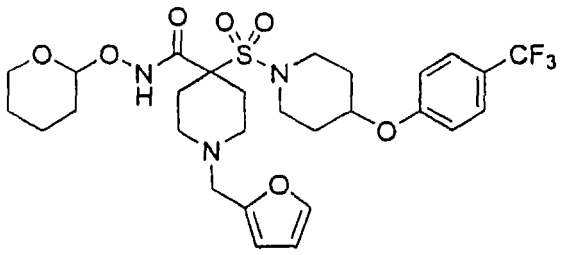
Part 17: Preparation of



To a solution of the piperidine methyl ester from Part 1 of Example 42 (3.91 g, 8.7 mmol) and 2-furaldehyde (0.79 mL, 9.6 mmol) in dichloroethane (58 mL) was added glacial acetic acid (0.5 mL, 8.7 mmol) followed by sodium triacetoxyborohydride (2.4 g, 11.3 mmol). After 64 hours, the reaction was concentrated *in vacuo* and partitioned between ethyl acetate (75

mL) and water (75 mL). The aqueous layer was made basic (pH = 8) with saturated sodium bicarbonate aqueous solution, then extracted three times with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (25 mL), twice with brine (2 x 25 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallization of the crude oil in methanol yielded a brown, tan solid, which was suspended in tetrahydrofuran (17.4 mL) and treated with potassium trimethylsilanolate (3.34 g, 26.0 mmol). After 20 hours at ambient temperature, the reaction was diluted with tetrahydrofuran (10 mL) and charged again with potassium trimethylsilanolate (2.22 g, 17.3 mmol). After 7 hours, the reaction was concentrated *in vacuo*, and the resulting residue was dissolved in water (100 mL) and treated with 2 N HCl until pH = 7. The white suspension was vacuum filtered, washed with water and dried *in vacuo* to give the carboxylic acid as a white solid (4.4 g, 97%). ^1H NMR and mass spectrum were consistent with the desired compound.

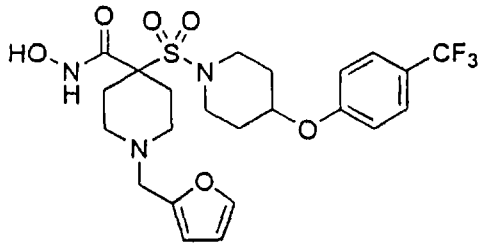
Part 18: Preparation of



In dry equipment under nitrogen, the carboxylic acid from part 17 (3.93 g, 7.61 mmol) was dissolved in dry dimethylformamide (38 mL) and treated with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (2.2 g, 11.4 mmol), N-hydroxybenzo-triazole hydrate (1.54 g, 11.4 mmol), O-(tetrahydro-

2H-pyran-2-yl)hydroxylamine (1.34 g, 11.4 mmol), followed by N-methylmorpholine (2.51 mL, 22.8 mmol). After 17 hours at ambient temperature, the reaction was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate (175 mL) and water (175 mL). The aqueous layer was extracted with ethyl acetate (100 mL), and the combined organic layers were washed with saturated sodium bicarbonate aqueous solution (100 mL), water (100 mL), brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting yellow oil was recrystallized in methanol (6 mL) to give the THP-hydroxamate as a white solid (2.48 g, 53%). ^1H NMR and mass spectrum were consistent with the desired compound.

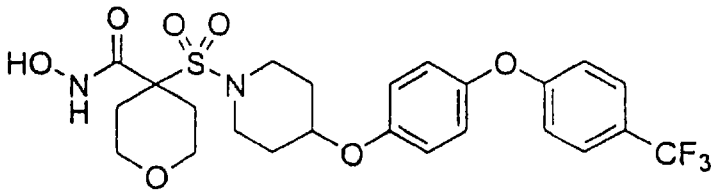
Part 19: Preparation of



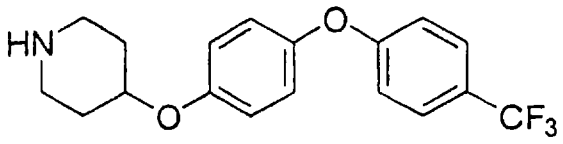
The THP-hydroxamate from part 18 (2.41 g, 3.91 mmol) was dissolved in methanol (1.0 mL) and 1,4-dioxane (15 mL), then treated with 4 N HCl in 1,4-dioxane solution (10 mL, 39 mmol), which formed a tan precipitate. After 1 hour at ambient temperature, the reaction was diluted with acetonitrile (3 mL), and the suspension was filtered under nitrogen, washed with acetonitrile and dried *in vacuo* to give the title compound as a white solid (1.68 g, 81%). MS(EI) m/z calculated for $C_{23}H_{28}N_3O_6SF_3$: 531, found (M+1) 532.

Example 31: Preparation of 4-[[4-[4-[4-

(trifluoromethyl)phenoxy]phenoxy]-1-piperidinyl]sulfonyl]tetrahydro-*N*-hydroxy-2*H*-pyran-4-carboxamide



Part 20: Preparation of

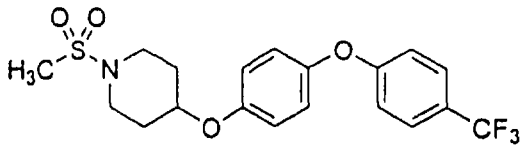


In dry equipment under nitrogen, 4-[4-(trifluoromethyl)phenoxy]phenol (Aldrich, 6.0 g, 23.6 mmol) was added to a dimethylformamide (53 mL) suspension of sodium hydride (60% dispersion in mineral oil, 0.95 g, 23.6 mmol), which was pre-washed in hexanes, while at zero degrees Celsius. After addition, the cold bath was removed and the reaction was warmed to ambient temperature. After 30 minutes, the reaction was cooled to zero degrees Celsius, charged with 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (Example 23, part B) (5.5 g, 19.7 mmol), then heated to eighty degrees Celsius. After 17 hours, the reaction was again treated with sodium hydride (60% dispersion in mineral oil, 0.95 g, 23.6 mmol), and then 10 minutes later with 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (5.5 g, 19.7 mmol). After 47 hours, the reaction was cooled to ambient temperature, quenched with water (10 mL), concentrated *in vacuo*, and partitioned between diethyl ether (100 mL) and water (100 mL).

The aqueous layer was extracted twice with diethyl ether (2 x 25 mL) and then with ethyl acetate (50 mL). The combined organic layers were washed with water (25 mL), twice with brine (2 x 25 mL), dried over Na_2SO_4, filtered, concentrated and dried *in vacuo* to give a brown oil.

The crude oil was treated with 4N HCl in 1,4-dioxane solution (47 mL, 188 mmol) at ambient temperature. After 2 hours, the reaction was concentrated *in vacuo*, and partitioned between ethyl acetate (100 mL) and water (50 mL). The aqueous layer was made pH = 8 with the addition of saturated sodium bicarbonate aqueous solution, then extracted twice with ethyl acetate (2 x 25 mL). The combined organic layers were washed with saturated sodium bicarbonate aqueous solution (50 mL), water (50 mL), brine (25 mL), dried over Na_2SO_4, filtered, concentrated and dried *in vacuo* to give a brown oil. The crude product was purified on silica gel (hexanes/ ethyl acetate) to give the amine as a yellow, orange solid (5.5 g, 69% over 2 steps). ^1H NMR and mass spectrum were consistent with the desired compound.

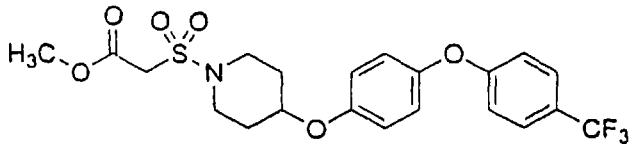
Part 21: Preparation of



To a solution of the amine from part 20 (4.5 g, 13.3 mmol) and triethylamine (3.72 mL, 26.7 mmol) in dichloromethane (12 mL) at zero degrees Celsius was added a solution of methane sulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (15 mL). After 2.5 hours at ambient temperature, the solvent was removed

in vacuo. The residue was partitioned between ethyl acetate (100 mL), water (100 mL), and 10% aqueous hydrochloric acid until pH = 4. The organic layer was washed with saturated sodium bicarbonate aqueous solution (50 mL), brine (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the methyl sulfonamide as a white, yellow solid (5.6 g, 100%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 22: Preparation of

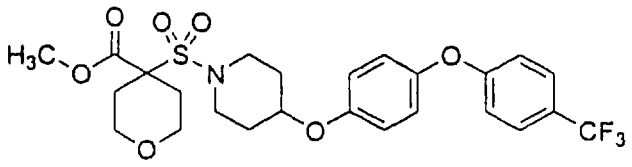


In dry equipment under nitrogen, the methyl sulfonamide from part 21 (5.62 g, 13.5 mmol) was dissolved in dry tetrahydrofuran (27 mL) and cooled to minus seventy-five degrees Celsius. The resulting solution was then treated with a 1M solution of lithium bis(trimethylsilyl)amide (40.6 mL, 41.0 mmol) at a rate such that the temperature remained below minus sixty five degrees. After 30 minutes, the reaction was treated with a solution of methyl chloroformate (1.05 mL, 13.5 mmol) in dry tetrahydrofuran (13 mL), while maintaining the temperature below minus seventy degrees. After 3 hours at minus sixty degrees Celsius, the reaction was quenched with saturated ammonium chloride aqueous solution (100 mL), warmed to ambient temperature and concentrated *in vacuo*. The resulting residue was partitioned between ethyl acetate (150 mL) and water (100 mL).

The organic layer was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and

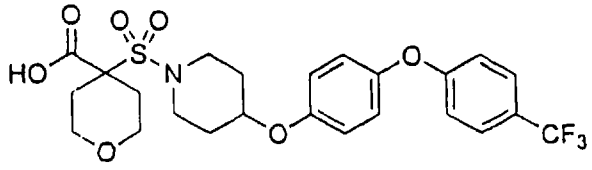
concentrated *in vacuo* to give the methylene sulfonamide as a yellow oil (6.32 g, 98.6%). ^{1}H NMR and mass spectrum were consistent with the desired compound.

Part 23: Preparation of



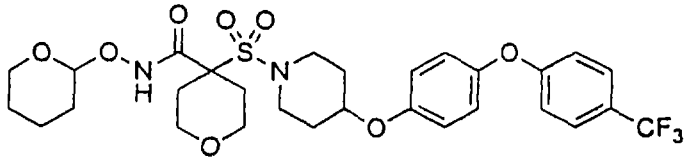
To a solution of the methylene sulfonamide from part 22 (2.56 g, 5.41 mmol) in dimethylformamide (14 mL) was added bis-(2-bromoethyl)ether (1.38 g, 5.95 mmol), 18-Crown-6 (250 mg), followed by potassium carbonate (2.24, 16.2 mmol). After the heterogeous mixture was stirred at sixty degrees Celsius for 22 hours, more potassium carbonate (0.75 g, 5.4 mmol) was added to the reaction. After another 17 hours, the reaction was charged with more potassium carbonate (0.75 g, 5.4 mmol). The reaction was concentrated *in vacuo* after 30 hours, and the resulting oil was partitioned between ethyl acetate (150 mL) and water (150 mL). The aqueous layer was extracted twice with ethyl acetate (2 x 50 mL), then the combined organic layers were washed with water (50 mL), brine (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the pyran methyl ester as a white solid. (2.84 g, 97%). ^{1}H NMR and mass spectrum were consistent with the desired compound.

Part 24: Preparation of



In dry equipment under nitrogen, the pyran methyl ester from part 23 (2.55 g, 4.69 mmol) was suspended in dry tetrahydrofuran (10 mL) and potassium trimethylsilanolate (1.81 g, 14.1 mmol) was added at ambient temperature. After 28 hours, the reaction was charged with more potassium trimethylsilanolate (0.3 g, 2.3 mmol). After 21 hours, the reaction was again charged with more potassium trimethylsilanolate (0.3 g, 2.3 mmol). After 3 hours, the reaction was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted twice with ethyl acetate (2 x 25 mL), then the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated and dried *in vacuo* to give the carboxylic acid as a tan solid (1.71 g, 69%). ^1H NMR and mass spectrum were consistent with the desired compound.

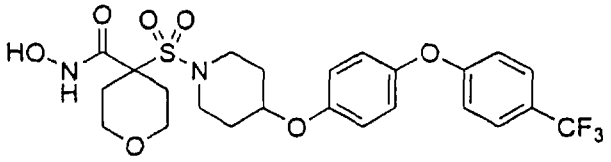
Part 25: Preparation of



In dry equipment under nitrogen, the carboxylic acid from part 24 (1.44 g, 2.72 mmol) was dissolved in dry dimethylformamide (14 mL) and treated with 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.78 g, 4.1 mmol), N-hydroxybenzotriazole hydrate (0.55 g, 4.1 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.48 g, 4.1 mmol), followed by N-methylmorpholine (0.90 mL, 8.16 mmol). After 26 hours at ambient temperature, the reaction

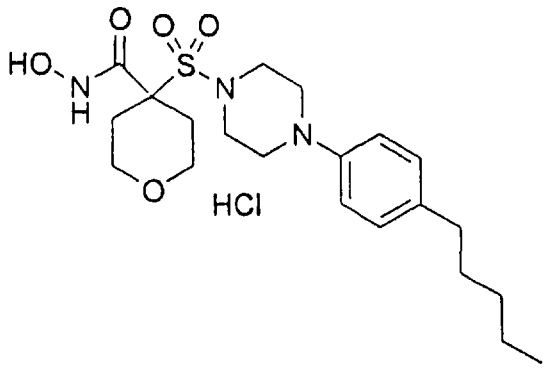
was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (20 mL), and the combined organic layers were washed with 5% $KHSO_4$ aqueous solution (30 mL), brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting yellow oil was purified on silica gel (1:1, hexanes:ethyl acetate) to give the THP hydroxamate as a yellow oil (0.96 g, 56%). ^1H NMR and mass spectrum were consistent with the desired compound.

Part 26: Preparation of



The THP hydroxamate from part 25 (0.82 g, 1.3 mmol) was dissolved in acetonitrile (10 mL) and then treated with aqueous 10% aqueous hydrochloric acid solution (10 mL, 12 mmol). After 25 hours at ambient temperature, the acetonitrile and excess hydrochloric acid were removed with a stream of nitrogen. The resulting white suspension was filtered under nitrogen, washed with water and dried *in vacuo* to give the title compound as a white solid (0.39 g, 55%). HRMS m/z calculated for $C_{24}H_{35}N_3O_7S$: 545.1569, observed 545.1586.

Example 32: Preparation of tetrahydro-N-hydroxy-4-[[4-(4-pentylphenyl)-1-piperazinyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a solution of tert-butyl-piperazine (5.00 g, 26.84 mmol) in toluene (50 mL) was added sodium tert-butoxide (3.01 g, 31.32 mmol). After stirring at ambient temperature for 5 minutes, 1-bromo-4-n-pentylbenzene (5.08 g, 22.37 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (0.418 g, 0.671 mmol) and tris(dibenzyldeneacetone)-dipallidium (0) (0.205 g, 0.224 mmol) were added to the reaction mixture. The resulting mixture was heated to eighty degrees Celsius for 22 hours. After cooling to ambient temperature the reaction mixture was filtered through a pad of Celite®, washing with tetrahydrofuran and methanol. The filtrate was concentrated *in vacuo* to give the aryl Boc-piperazine as an orange oily solid (9.60 g, >100%).

Part B: The aryl Boc-piperazine of part A (9.60 g, ~ 22.37 mmol) was treated with a solution of 4N HCl in dioxane (56 mL). The resulting mixture was stirred at ambient temperature for 2 hours then the reaction was concentrated *in vacuo*. Diethyl ether (50 mL) was added and the precipitate was collected by filtration to give the aryl piperazine as a tan solid (8.49 g, 100 %).

Part C: To a solution of the aryl piperazine of part B (4.00 g, 13.10 mmol) in dichloromethane (50 mL), cooled to zero degrees Celsius, was added

triethylamine (5.48 mL, 39.30 mmol) followed by methanesulfonyl chloride (1.22 mL, 15.72 mmol). Once the addition was complete the cooling bath was removed and the resulting mixture was stirred for 2 hours. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O and ethyl acetate. An emulsion formed and the solids were collected by filtration. The solids were triturated with ethyl acetate to give the methyl sulfonamide as a tan solid (3.99 g, 98 %).

Part D: To a suspension of the methyl sulfonamide of part C (3.35 g, 10.79 mmol) in tetrahydrofuran (50 mL), cooled to minus seventy-eight degrees Celsius, was added lithium bis(trimethylsilyl)amide (24.00 mL, 1.0 M in tetrahydrofuran, 24.00 mmol) at such a rate that the temperature of the reaction mixture never exceeded minus seventy degrees Celsius. Once the addition was complete, the cooling bath was removed. After 30 minutes, the cooling bath was replaced and a solution of dimethyl carbonate (1.09 mL, 12.95 mmol) in tetrahydrofuran (5.0 mL) was added. After 30 minutes additional lithium bis(trimethylsilyl)amide (5.40 mL, 1.0 M in tetrahydrofuran, 5.40 mmol) was added followed by additional dimethyl carbonate (0.273 mL, 3.24 mmol). After stirring at minus seventy-eight degrees Celsius for 1 hour the reaction was quenched by the addition saturated NH_4Cl and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl

acetate/hexanes) provided the sulfonamide ester as a tan solid (1.20 g, 30%).

Part E: To a solution of the sulfonamide ester of part D (1.20 g, 3.26 mmol) in N,N-dimethylformamide (10 mL) was added K_2CO_3 (1.35 g, 9.78 mmol) and dibromoethyl ether (0.430 mL, 3.42 mmol) and the resulting mixture was heated to forty degrees Celsius. After 21 hours additional K_2CO_3 (0.450 g, 3.26 mmol) and dibromoethyl ether (0.102 mL, 0.815 mmol) were added and the resulting mixture was heated to forty degrees Celsius for 4 hours. After cooling to ambient temperature the reaction was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetae/hexanes) provided the ester as a pale yellow solid (1.23 g, 86%).

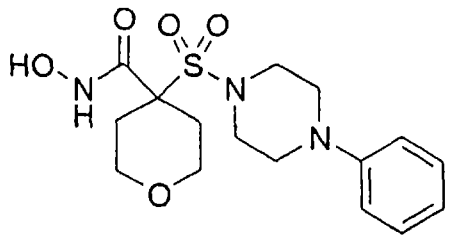
Part F: To a solution of the ester of part E (1.23 g, 2.80 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilanolate (0.718 g, 5.60 mmol). The resulting mixture was stirred at ambient temperature overnight (about 18 hours) and then diluted with H_2O and acidified (pH-7.0) with 1 N HCl. The precipitate was collected by filtration. The solids were suspended in acetonitrile and then concentrated *in vacuo* to give the acid as an off-white solid (0.910 g, 76%).

Part G: To a suspension of the acid of part F (0.910 g, 2.14 mmol) in N,N-dimethylformamide (10 mL) was added 1-hydroxybenzotriazole (0.347 g, 2.57 mmol), N-methylmorpholine (0.701 mL, 6.42 mmol), O-(tetrahydropuranyl) hydroxylamine (0.752 g, 6.42 mmol) and 1-3-[(dimethylamino)propyl]-3-

ethylcarbodiimide hydrochloride (0.574 g, 3.00 mmol). The resulting mixture was stirred at ambient temperature for 22 hours. Then the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with H_2O, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a clear oil (1.11 g, 99%).

Part H: The protected hydroxamate of part G (1.10 g, 2.10 mmol) was treated with a solution of 4N HCl in dixoane (5.25 mL) and methanol (0.851 mL, 21.00 mmol) and the resulting mixture was stirred at ambient temperature for 2 hours. Diethyl ether (20 mL) was added and the precipitate was collected by filtration to provide the title compound as an off-white solid (0.972 g, 97%). MS MH^+ calculated for $C_{21}H_{34}O_5N_3S$: 440, found 440.

Example 33: Preparation of tetrahydro-N-hydroxy-4-[(4-phenyl-1-piperazinyl)sulfonyl]-2H-pyran-4-carboxamide

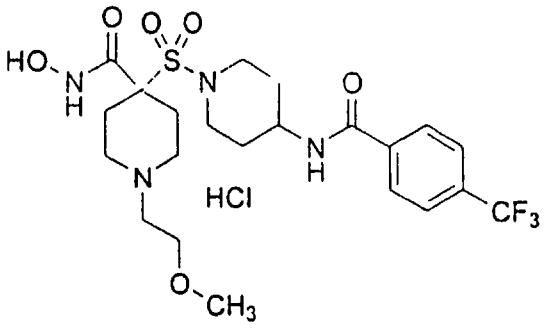


Part A: To a solution of bis(2-bromoethyl)ether (1.55 g, 6.70 mmol) in acetone (30 mL) was added K_2CO_3 (9.26 g, 67.00 mmol), 18-crown-6 (500 mg) and the sulfonamide ester of part B for SC-81434A (2.00 g, 6.70 mmol). The reaction mixture was heated at reflux for 15 hours then filtered through a pad of

Celite® and the filtrate was concentrated *in vacuo*. The residue was dissolved in N,N-dimethylformamide (30 mL) and treated with K_2CO_3 (9.26 g, 67.00 mmol), 18-crown-6 (500 mg) and bis(2-bromoethyl)ether (1.55 g, 6.70 mmol) and the resulting mixture was heated at sixty degrees Celsius for 6 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between H_2O and chloroform. The aqueous layer was further extracted with chloroform. The combined organic layers were washed with H_2O and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate with 5% acetonitrile/hexanes) provided the cyclized ester as a pale yellow oil (1.34 g, 54%).

Part B: To a solution of the cyclized ester of part A (1.34 g, 3.64 mmol) in tetrahydrofuran (15 mL) was added potassium trimethylsilanolate (1.40 g, 10.92 mmol). The resulting mixture was stirred at ambient temperature for 24 hours and then the tetrahydrofuran was removed by blowing N_2 over the reaction mixture. The residue was dissolved in H_2O, washed with diethyl ether, then acidified (pH-3.0) with 1N HCl and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the acid as an off-white solid (1.20 g, 79%).

Part C: To a solution of the acid of part B (1.00 g, 2.82 mmol) in N,N-dimethylformamide (6.0 mL) was added 1-hydroxybenzotriazole (0.457 g, 3.38 mmol), N-methylmorpholine (0.924 mL, 8.46 mmol), O-(tetrahydropuranyl) hydroxylamine (0.469 g, 4.23 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.757 g, 3.95 mmol).



Part A: To a solution of 4-amino-1-benzylpiperidine (10.0 g, 45.82 mmol) in tetrahydrofuran (100 mL) was added di-tert-butyl dicarbonate (30.0 g, 137.46 mmol) and a catalytic amount of N,N-dimethylaminopyridine. The resulting mixture was heated at reflux for 5 hours. After cooling to ambient temperature the reaction mixture was concentrated *in vacuo*. The solids were washed with hexanes to provide the carbamate as a white crystalline solid (13.7 g, >100%).

Part B: To a solution of the carbamate of part A (10.0 g, 34.43 mmol) in methanol (200 mL) was added ammonium formate (6.51 g, 103.29 mmol) and 4% Pd/C. The resulting mixture was heated at reflux for 1.5 hours. After cooling to ambient temperature the reaction mixture was filtered through a pad of Celite®, washing with methanol. The filtrate was concentrated *in vacuo* to provide the piperidine as an off-white solid (6.90 g, 100%).

Part C: To a solution of the piperidine of part B (6.90 g, 34.43 mmol) in dichloromethane (100 mL), cooled to zero degrees Celsius, was added triethylamine (5.28 mL, 37.87 mmol) followed by methanesulfonyl chloride (2.79 mL, 36.12 mmol). Once the addition was complete the cooling bath was removed and the resulting mixture was stirred for 15

hours. After concentration *in vacuo* the residue was partitioned between H_2O and ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. The resulting solids were washed with hexanes to give the sulfonamide as an off-white solid (9.12 g, 95%).

Part D: To a solution of lithium bis(trimethylsilyl)amide (50.0 mL, 1.0M in tetrahydrofuran, 50.00 mmol), cooled to minus seventy-eight degrees Celsius, was added a suspension of the sulfonamide of part C (4.49 g, 16.13 mmol) in tetrahydrofuran (40 mL). Once the addition was complete, the cooling bath was removed and replaced after 0.5 hours. To the resulting mixture was quickly added methyl chloroformate (1.37 mL, 17.74 mmol). After 0.5 hours, the reaction mixture was quenched by the addition of saturated NH_4Cl and then the tetrahydrofuran was concentrated *in vacuo*. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the sulfonamide ester as an off-white solid (5.29 g, 97%).

Part E: The sulfonamide ester of part D (5.27 g, 5.67 mmol) was treated with a solution of 4 N HCl in dioxane (40 mL). After stirring at ambient temperature for 1 hour the reaction mixture was concentrated *in vacuo*. The resulting solids were washed with hexanes to provided the amine as a tan solid (4.19 g, 98%).

Part F: To a solution of the amine of part E (1.50 g, 5.50 mmol) in dichloromethane (10 mL), cooled to zero degrees Celsius, was added

triethylamine (1.61 mL, 11.55 mmol) followed by 4-(trifluoromethyl)benzoyl chloride (0.858 mL, 5.78 mmol). Once the addition was complete the cooling bath was removed and after stirring at ambient temperature for 3.5 hours the reaction mixture was concentrated *in vacuo*. The solids were washed with H_2O and diethyl ether to provide the amide as a tan solid (1.79 g, 80%).

Part G: To a solution of the amide of part F (1.52 g, 3.72 mmol) in N,N-dimethylformamide (10.0 mL) was added K_2CO_3 (1.54 g, 11.16 mmol), 18-crown-6 (0.50 g) and bis(2-chloroethyl)benzyl amine (0.864 g, 3.72 mmol). The resulting mixture was heated to sixty degrees Celsius of 22 hours, at which time additional K_2CO_3 (0.514 g, 3.72 mmol) and bis(2-chloroethyl)benzyl amine (0.216 g, 0.93 mmol) were added. The resulting mixture was heated to sixty degrees Celsius for 14.5 hours at which time additional K_2CO_3 (0.514 g, 3.72 mmol) was added. The resulting mixture was heated to sixty degrees Celsius of 14 hours, at which time additional K_2CO_3 (0.514 g, 3.72 mmol) and bis(2-chloroethyl)benzyl amine (0.216 g, 0.93 mmol Prepared by Darren Kassib) were added. The resulting mixture was heated to sixty degrees Celsius for 24 hours. After cooling to ambient temperature the reaction mixture was diluted with H_2O and extracted with chloroform. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate with 5% methanol/hexanes) followed by trituration with diethyl ether provided the cyclized ester as an off-white solid (0.950 g, 45%).

Part H: To a solution of the cyclized ester of part G (0.950 g, 1.67 mmol) in methanol (10 mL) was added ammonium formate (0.317 g, 5.02 mmol) and 10% Pd/C (0.320 g). The resulting mixture was heated at reflux for 1.5 hours. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite ®, washing with methanol. The filtrate was concentrated *in vacuo* to provide the amine as a gray solid (0.760 g, 95%).

Part I: To a solution of the amine of part H (0.760 g, 1.59 mmol) in N,N-dimethylformamide (5.0 mL) was added K_2CO_3 (0.330 g, 2.39 mmol) and 2-bromoethyl methyl ether (0.225 mL, 2.39 mmol). The resulting mixture was stirred at ambient temperature over the weekend then additional K_2CO_3 (0.055 g, 0.398 mmol) and 2-bromoethyl methyl ether (0.037 mL, 0.398 mmol) was added. After stirring at ambient temperature for 24 hours the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate with 5% methanol/hexanes) provided the alkylated amine as a white solid (0.550 g, 65%).

Part J: To a solution of the alkylated amine of part I (0.540 g, 1.01 mmol) in tetrahydrofuran (5.0 mL) was added potassium trimethylsilanolate (0.388 g, 3.02 mmol). The resulting mixture was stirred at ambient temperature for 18 hours then the tetrahydrofuran was removed by blowing N_2 over the reaction mixture. The reaction mixture was diluted with H_2O and neutralized (pH-7) with 1N HCl. The resulting aqueous reaction mixture was concentrated

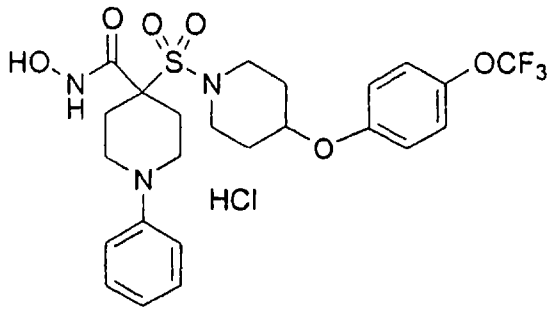
in vacuo to provide the crude acid as a pink solid (0.610 g, >100%).

Part K: To a solution of the crude acid of part J (0.610 g, ~ 1.01 mmol) in N,N-dimethylformamide (5.0 mL) was added 1-hydroxybenzotriazole (0.164 g, 1.21 mmol), N-methylmorpholine (0.331 mL, 3.03 mmol), O-(tetrahydropuranyl) hydroxylamine (0.177 g, 1.52 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.271 g, 1.41mmol). After stirring at ambient temperature for 0.5 hours, additional N,N-dimethylformamide (5.0 mL) was added. After stirring at ambient temperature overnight (about 18 hours) the reaction mixture was heated to forty-five degrees Celsius for 24 hours. The reaction mixture was then diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. The resulting solids were washed with diethyl ether to give the protected hydroxamate as an off-white solid (0.300 g, 49%).

Part L: To a solution of the protected hydroxamate of part K (0.300 g, 0.483 mmol) in dioxane (3.0 mL) and methanol (1.0 mL) was added a solution of 4N HCl in dioxane (1.2 mL). After stirring at ambient temperature for 1.5 hours the solvent was removed by blowing N_2 over the reaction mixture. The resulting solids were washed with diethyl ether to give the title compound as a pink solid (0.193 g, 70%). MS MH^+ calculated for $C_{22}H_{32}O_6N_4S_1F_3$: 537, found 537.

Example 35: Preparation of N-hydroxy-1-phenyl-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-

piperidinyl]sulfonyl]-4-
piperidinecarboxamide, monohydrochloride



Part A: To a solution of commercially available 4-hydroxypiperidine (46.3 g, 458 mmol) in tetrahydrofuran (300 mL) was slowly added triethylamine (67.0 mL, 481 mmol) followed by a solution of di-tert-butyl dicarbonate (100 g, 458 mmol) in tetrahydrofuran (200 mL). After stirring at ambient temperature for 17 hours the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (500 mL) and washed with 5% $KHSO_4$, saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Crystallization with hexanes provided the carbamate as an off-white solid (87.8 g, 95%).

Part B: To a solution of the carbamate of part A (5.00 g, 24.84 mmol) in dichloromethane (50 mL), precooled in an ice-bath, was added triethylamine (3.81 mL, 27.32 mmol) followed by methanesulfonyl chloride (2.02 mL, 26.08 mmol). Once the addition was complete, the cooling bath was removed. After stirring for 2 hours, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and H_2O. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and

dried over Na_2SO_4. Concentration *in vacuo* provided the mesylate as an off-white solid (7.34 g, >100%).

Part C: To a solution of 4-(trifluoromethoxy)-phenol (2.00 g, 11.23 mmol) in N,N-dimethylformamide (25 mL), cooled to zero degrees Celsius, was added sodium hydride (0.449 g, 60% oil dispersion, 11.23 mmol). Once the addition was complete the cooling bath was removed and then replaced after 0.5 hours. To the resulting mixture was added the mesylate of part B (2.61 g, 9.36 mmol). The reaction mixture was then heated to forty degrees Celsius. After stirring at forty degrees Celsius for 15 hours the temperature of the reaction was increased to eighty degrees Celsius. After 8 hours at eighty degrees Celsius the reaction mixture was cooled in an ice-bath and additional sodium hydride (0.225 g, 60% oil dispersion, 5.62 mmol) was added. After 30 minutes additional mesylate of part B (1.31 g, 4.68 mmol) was added and the resulting mixture was heated to eighty degrees Celsius. After 15 hours at eighty degrees Celsius the reaction was cooled to ambient temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and diethyl ether. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. After concentration *in vacuo* the residue was treated with a solution of 4 N HCl in dioxane (30 mL). After stirring at ambient temperature for 2 hours, the reaction mixture was concentrated *in vacuo*. Water was added and the reaction was extracted with ethyl acetate. The aqueous layer was then made alkaline (pH-10) with 2.5 N NaOH and extracted with ethyl acetate. The combined organic layers were washed with saturated

NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the amine as an off-white solid (1.67 g, 68%).

Part D: To a solution of the amine of part C (11.5 g, 44.1 mmol) in dichloromethane (125 mL), precooled in an ice-bath, was added triethylamine (12.3 mL, 88.1 mmol) followed by a solution of methanesulfonyl chloride (5.1 mL, 66.1 mmol) in dichloromethane (20 mL). Once the addition was complete, the cooling bath was removed. After 1 hour at ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Recrystallization from ethyl acetate/hexanes provided the sulfonamide as an off-white solid (10.77 g, 72%).

Part E: To a solution of the sulfonamide of part D (10.77 g, 31.8 mmol) in tetrahydrofuran (64 mL), cooled to minus seventy-five degrees Celsius, was added lithium bis(trimethylsilyl)amide (80 mL, 1M in tetrahydrofuran, 80.0 mmol), at such a rate that the temperature of the reaction never exceeded minus sixty five degrees Celsius. After stirring at minus seventy-five degrees Celsius for 30 minutes, a solution of methyl chloroformate (2.45 mL, 31.8 mmol) in tetrahydrofuran (32 mL) was slowly added at such a rate that the temperature of the reaction never exceeded minus sixty five degrees Celsius. After stirring at minus seventy-five degrees Celsius for 30 minutes the reaction was quenched by the addition of saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with saturated

NaCl and dried over Na_2SO_4. Concentration *in vacuo* gave the sulfonamide ester as a yellow oil (12.69, 100%).

Part F: To a suspension of dibromotriphenylphosphorane (50.0 g, 118.45 mmol) in dichloromethane (200 mL), cooled to zero degrees Celsius, was added N-phenyldiethanol amine (10.0 g, 55.18 mmol). Once the addition was complete, the cooling bath was removed. After stirring at ambient temperature for 17.5 hours, the reaction mixture was concentrated *in vacuo*. The residue was then treated with warm ethyl acetate and the resulting precipitate was removed and the filtrate was concentrated *in vacuo*. Chromatography (on silica, hexanes/dichloromethane) provided the dibromoamine as a light yellow oil (5.85 g, 35%).

Part G: To a solution of the dibromoamine of part F(5.60 g, 18.24 mmol) in N,N-dimethylformamide were added K_2CO_3 (6.87 g, 49.74 mmol), the sulfonamide ester of part E (6.59 g, 16.58 mmol) and 18-crown-6 (1.66 g). The resulting mixture was heated to eighty degrees Celsius for 14.5 hours at which time additional K_2CO_3 (3.44 g, 24.89 mmol) was added. After stirring at eighty degrees Celsius for 7.5 hours the reaction mixture was cooled to ambient temperature and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, filtered through a pad of Celite ® and the filtrate was concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) gave a yellow solid that after washing with hot methanol provided the cyclized ester as an off-white solid (3.15 g, 35%).

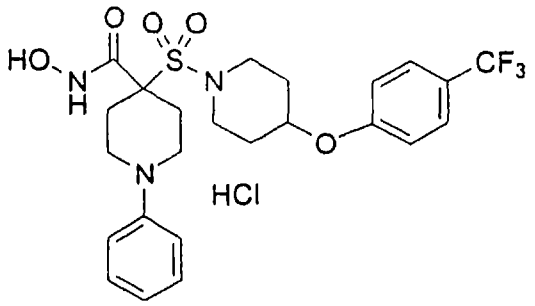
Part H: To a solution of the cyclized ester of part G (3.15 g, 5.81 mmol) in tetrahydrofuran (25 mL) was added potassium trimethylsilanolate (2.24 g, 17.43 mmol). The resulting mixture was stirred at ambient temperature for 24 hours and then H_2O was added. After neutralization (pH-7) with 1 N HCl, the tetrahydrofuran was removed by concentration *in vacuo*. After readjusting the pH of the aqueous reaction mixture (pH = 7) the precipitate was collected by filtration of give the acid as an off-white solid (2.97 g, 97%).

Part I: To a solution of the acid of part H (2.97 g, 5.62 mmol) in N,N-dimethylformamide (20 mL) were added 1-hydroxybenzotriazole (0.911 g, 6.74 mmol), N-methylmorpholine (1.85 mL, 16.86 mmol), O-(tetrahydropuranyl) hydroxylamine (1.98 g, 16.86 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.51 g, 7.87 mmol). After stirring at ambient temperature for 18 hours the reaction mixture was concentrated *in vacuo*. Water was added and the aqueous reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. The resulting solids were washed with hot methanol to give the protected hydroxamate as a white solid (3.09 g, 88%).

Part J: The protected hydroxamate of part I (3.09 g, 4.92 mmol) was treated with a solution of 4 N HCl in dioxane (12.0 mL) and methanol (1.99 mL, 49.23 mmol). After stirring at ambient temperature for several minutes additional dioxane (10 mL) was added. After stirring at ambient temperature for 1.5 hours diethyl ether was added and the precipitate was

collected by filtration to give the title compound as an off-white solid (2.67 g, 94%). MS MH^+ calculated for $C_{24}H_{29}O_6N_3S_1F_3$: 544, found 544.

Example 36: Preparation of N-hydroxy-1-phenyl-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of the carbamate of part A for Example 35 (6.03 g, 30.0 mmol) in N,N-dimethylformamide (60 mL), were added Cs_2CO_3 (9.77 g, 30.0 mmol) and 4-fluorobenzotrifluoride (3.8 mL, 30.0 mmol). After stirring at ninety degrees Celsius for 19 hours, additional Cs_2CO_3 (3.26 g, 10.0 mmol) and 4-fluorobenzotrifluoride (0.95 mL, 10.0 mmol) were added. After stirring at ninety degrees Celsius for 46 hours, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the organic layer was washed with H_2O, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the Boc-amine as a white solid (6.0 g, 58%).

Part B: The Boc-amine of part A (4.10 g, 11.87 mmol) was treated with a solution of 4N HCl in dioxane (20.0 mL). After stirring at ambient

temperature for 1.5 hours, the reaction mixture was concentrated *in vacuo* to provide the amine as a white solid (3.54 g, >100%).

Part C: To a solution of the amine of part B (3.34 g, 11.87 mmol) in dichloromethane (40 mL), cooled in an ice-bath, was added triethylamine (3.31 mL, 23.74 mmol) followed by methanesulfonyl chloride (1.38 mL, 17.81 mmol). Once the addition was complete the cooling bath was removed. After stirring at ambient temperature for 2 hours, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate. The organic layer was washed with 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the sulfonamide as a pale yellow solid (4.25 g, >100%).

Part D: To a solution of the sulfonamide of part C (5.00 g, 15.46 mmol) in tetrahydrofuran (30 mL), cooled to minus forty degrees Celsius, was added lithium bis(trimetylsilyl)amide (31.0 mL, 1 M in tetrahydrofuran, 31.0 mmol) at such a rate that the temperature of the reaction never exceeded minus thirty five degrees Celsius. After stirring at minus forty degrees Celsius for 30 minutes, a solution of dimethyl carbonate (1.56 mL, 18.55 mmol) in tetrahydrofuran (10 mL) was added at such a rate that the temperature of the reaction never exceeded minus thirty five degrees Celsius. After stirring at minus forty degrees Celsius for 30 minutes, the reaction was quenched by the addition of saturated NH_4Cl. The resulting mixture was slowly permitted to warm to ambient temperature and then the tetrahydrofuran was removed *in vacuo*. The aqueous reaction mixture was

diluted with H_2O and extracted with ethyl acetate and diethyl ether. The combined organic layers were washed with 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the sulfonamide ester as a thick yellow oil (5.75 g, 97%).

Part E: To a solution of the dibromoamine of part F of Example 35 (7.00 g, 22.80 mmol) in N,N-dimethylformamide (45 mL), was added K_2CO_3 (9.45 g, 68.40 mmol), the sulfonamide ester of part D (8.70 g, 22.80 mmol) and 18-crown-6 (2.28 g). The resulting mixture was heated to eighty degrees Celsius for 15 hours and then additional K_2CO_3 (4.73 g, 34.22 mmol) was added. The resulting mixture was then heated to eighty degrees Celsius for 6 hours. After cooling to ambient temperature, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) followed by washing of the resulting solids with boiling methanol provided the cyclized ester as an off-white solid (4.50 g, 37%).

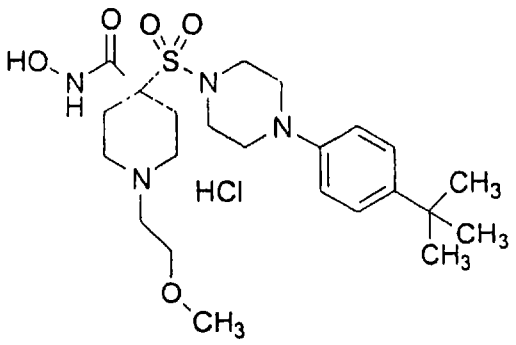
Part F: To a solution of the cyclized ester of part E (4.50 g, 8.55 mmol) in tetrahydrofuran (40 mL) was added potassium trimethylsilanolate (3.29 g, 25.64 mmol). The resulting mixture was stirred at ambient temperature for 22 hours. The reaction mixture was diluted with H_2O and neutralized (pH-7) with 1N HCl. The tetrahydrofuran was removed *in vacuo* and the precipitate was collected by filtration. The solids were suspended in

acetonitrile and concentrated *in vacuo* to provide the acid as a white solid (4.05 g, 92%).

Part G: To a solution of the acid of part F (4.05 g, 7.90 mmol) in N,N-dimethylformamide were added 1-hydroxybenzotriazole (1.28 g, 9.48 mmol), N-methylmorpholine (2.59 mL, 23.70 mmol), O-(tetrahydropuranyl) hydroxylamine (2.78 g, 23.70 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.12 g, 11.06 mmol). After stirring at ambient temperature for 16 hours the reaction mixture was diluted with H_2O and extraced with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. The solids were washed with boiling methanol to provide the protected hydroxamate as a white solid (4.12 g, 85%).

Part H: The protected hydroxamate of part G (4.12 g, 6.74 mmol) was treated with a solution of 4N HCl in dioxane (12.0 mL) and methanol (1.99 mL, 49.23 mmol). After stirring at ambient temperature for several minutes, additional dioxane (10 mL) was added. After stirring at ambient temperature for 1.5 hours, diethyl ether was added and the precipitate was collected by filtration to give the title compound as an off-white solid (3.32 g, 87%). MS MH^+ calculated for $C_{24}H_{29}O_5N_3S_1F_3$: 528, found 528.

Example 37: Preparation of 4-[[4-[4-(1,1-dimethylethyl)phenyl]-1-piperazinyl]-sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide, <u>monohydrochloride</u>



Part A: To a suspension of 4-bromopiperidine hydrobromide (30 g, 122.5 mmol) and N-(benzyloxycarbonyloxy)succinimide in tetrahydrofuran (250 mL) was added N-methylmorphoine (15 g, 148.3 mmol) followed by a catalytic amount of N,N-dimethylaminopyridine. After stirring at ambient temperature for 17 hours, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and H_2O. The organic layer was washed with 10% HCl solution, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the carbamate as a clear oil (33.0 g, 90%).

Part B: To a solution of the carbamate of part A (30.4 g, 101.96 mmol) in N,N-dimethylformamide (200 mL) was added potassium thioacetate (12.75 g, 111.64 mmol) and the resulting mixture was stirred at ambient temperature. After 23 hours, the reaction mixture was heated to sixty degrees Celsius. After heating at sixty degrees Celsius for 3 hour the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and filtered through a pad of Celite®. The filtrate was then concentrated *in vacuo*. The residue was redissolved in ethyl acetate and the organic layer was washed with saturated $NaHCO_3$, saturated NaCl and dried over

Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the thioacetate as an orange oil (22.8 g, 76%).

Part C: Into a solution of the thioacetate of part B (22.8 g, 77.71 mmol) in carbon tetrachloride (240 mL) and ethanol (60 mL) was bubbled Cl_2. Once the exotherm was complete the bubbling of Cl_2 was discontinued. N_2 was bubbled through the reaction mixture for several minutes then the reaction was concentrated *in vacuo* to give the sulfonyl chloride as a brown oil (25.5 g, >100%).

Part D: To a solution of tert-butyl piperazine (5.24 g, 28.15 mmol) in toluene (50 mL) was added sodium tert-butoxide (3.16 g, 32.84 mmol). The resulting mixture was stirred at ambient temperature for several minutes and then 1-bromo-4-tert-butylbenzene (5.00 g, 23.46 mmol), BINAP (0.438 g, 0.704 mmol) and tris(dibenzyldeneacetone)dipallidium (0) (0.215 g, 0.235 mmol) were added. The resulting mixture was heated to eighty degrees Celsius for 16 hours. After cooling to ambient temperature, diethyl ether was added and the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo*. The residue was dissolved in diethyl ether and washed with H_2O, 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. Concentration *in vacuo* provided the phenyl-piperazine as a brown solid (7.80 g, >100%).

Part E: The phenyl-piperazine of part D (7.80 g, 24.49 mmol) was treated with a solution of 4N HCl in dioxane (61 mL). The resulting reaction mixture was stirred at ambient temperature for 1 hour and then concentrated *in vacuo*. The solids were washed

with diethyl ether to give the amine hydrochloride as a mustard colored solid (6.10 g, 98%).

Part F: To a suspension of the amine hydrochloride of part D (1.50 g, 5.89 mmol) and triethylamine (1.81 mL, 12.96 mmol) in dichloromethane (10 mL), cooled in an ice-bath, was added the sulfonyl chloride of part C (1.82 g, 5.73 mmol). Once the addition was complete the cooling bath was removed. After stirring at ambient temperature for 2 hours the reaction mixture was concentrated *in vacuo*. The residue was partitioned between H_2O and ethyl acetate and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. The resulting solids were triturated with methanol to provide the sulfonamide as a light brown solid (1.41 g, 49%).

Part G: To a solution of the sulfonamide of part F (1.40 g, 2.80 mmol) in tetrahydrofuran (10 mL), at ambient temperature, was added lithium bis(trimethylsilyl)amide (6.20 mL, 1 M in tetrahydrofuran, 6.20 mmol). After stirring at ambient temperature for 1 hour, dimethyl carbonate (0.283 mL, 3.36 mmol) was added. The resulting mixture was stirred at ambient temperature for 3 hours and then additional lithium bis(trimethylsilyl)amide (3.10 mL, 1 M in tetrahydrofuran, 3.10 mmol) was added. After 2 hours at ambient temperature additional dimethyl carbonate (0.140 mL, 1.66 mmol) was added. After stirring at ambient temperature overnight (about 18 hours), the reaction was quenched by the addition of saturated NH_4Cl. The reaction was diluted with H_2O and

extracted with ethyl acetate. The combined organic layers were washed with 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. The resulting solids were triturated with methanol to give the sulfonamide ester as a tan solid (1.29 g, 83%).

Part H: To a solution of the sulfonamide ester of part G (1.29 g, 2.31 mmol) in tetrahydrofuran (20 mL) and 10% Pd/C (0.300 g) was bubbled H_2. After bubbling H_2 through the reaction for 17 hours, the mixture was purged with N_2 and filtered through a pad of Celite®, washing with tetrahydrofuran. The filtrate was concentrated *in vacuo* to give the amine as a dark brown sticky solid (0.950 g, 97%).

Part I: To a solution of the amine of Part H (0.940 g, 2.22 mmol) in N,N-dimethylformamide (7.0 mL) was added K_2CO_3 (0.614 g, 4.44 mmol) and 2-bromoethyl methyl ether (0.313 mL, 3.33 mmol). The resulting mixture was stirred at ambient temperature for 3 days. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate and filtered through a pad of Celite®. Chromatography (on silica, ethyl acetate/hexanes) provided the alkylated amine as an off-white solid (0.595 g, 56%).

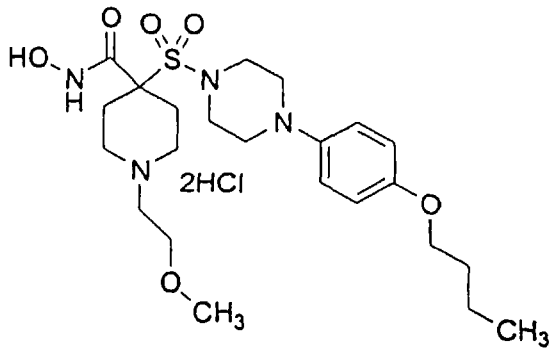
Part J: To a solution of the alkylated amine of part I (0.595 g, 1.24 mmol) in tetrahydrofuran (8.0 mL) was added potassium trimethylsilanolate (0.318 g, 2.48 mmol). After stirring at ambient temperature for 17 hours the tetrahydrofuran was removed by blowing N_2 over the reaction mixture. The residue was dissolved in H_2O and the aqueous reaction mixture was neutralized (pH = 7) with 1 N HCl. The precipitate

was collected by filtration to provide the acid as an off-white solid (0.475 g, 82%).

Part K: To a solution of the acid part J (0.475 g, 1.02 mmol) in N,N-dimethylformamide (5.0 mL) was added 1-hydroxybenzotriazole (0.165 g, 1.22 mmol), N-methylmorpholine (0.334 mL, 3.06 mmol), O-(tetrahydropuranyl) hydroxylamine (0.359 g, 3.06 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.274 g, 1.43 mmol). The resulting reaction mixture was stirred at ambient temperature for 17.5 hours and then heated to sixty degrees Celsius for 6 hours. To the reaction mixture was added triethylamine (0.427 mL, 3.06 mmol) and the resulting mixture was heated to sixty degrees Celsius for 21 hours. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was suspended in H_2O, acidified (pH = 1) with 1 N HCl and then concentrated *in vacuo*. To a solution of the resulting solids in N,N-dimethylformamide (5.0 mL) were added 1-hydroxybenzotriazole (0.119 g, 0.881 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.197 g, 1.03 mmol). After stirring at ambient temperature for 1 hour, N-methylmorpholine (0.400 mL, 3.67 mmol), O-(tetrahydropuranyl) hydroxylamine (0.258 g, 2.20 mmol) were added. After stirring at ambient temperature for 2 days the reaction mixture was diluted with H_2O, then neutralized (pH = 7) and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. The crude protected hydroxamate was treated with a solution of 4 N HCl in dioxane (1.8 mL) and

methanol (0.309 mL). After stirring at ambient temperature for 1.5 hours, diethyl ether was added and the precipitate was collected by filtration. The solids were washed with acetonitrile to give the title compound as a tan solid (0.188 g, 49%). MS MH^+ calculated for $C_{23}H_{39}O_5N_4S_1$: 483, found 483.

Example 38: Preparation of 4-[[4-(4-butoxyphenyl)-1-piperazinyl]sulfonyl]-N-hydroxy-1-(2-methoxyethyl)-4-piperidinecarboxamide, dihydrochloride



Part A: To a solution of n-butyloxybromobenzene (5.00 g, 21.82 mmol) in toluene (50 mL) was added tert-butyl piperazine (4.88 g, 26.18 mmol) and sodium tert-butoxide (2.94 g, 30.55 mmol). After stirring at ambient temperature for several minutes, BINAP (0.408 g, 0.655 mmol) and tris(dibenzyldeneacetone)-dipallidium (0) (0.200 g, 0.218 mmol) were added. The resulting mixture was heated to eighty degrees Celsius for 21 hours. After cooling to ambient temperature, the reaction mixture was filtered through a pad of Celite®, washing with diethyl ether and dichloromethane. Chromatography (on silica, ethyl acetate/hexanes) provided the phenyl-piperazine as a tan solid (5.56 g, 76%).

Part B: The phenyl-piperazine of part A (5.56 g, 16.62 mmol) was treated with a solution of 4 N HCl in dioxane (42 mL). The resulting mixture was stirred at ambient temperature for 1.5 hours and then concentrated *in vacuo*. The resulting solids were washed with diethyl ether to provide the amine hydrochloride as an off-white solid (4.60 g, >100%).

Part C: To a solution of the amine hydrochloride of part B (2.24 g, 8.26 mmol) and triethylamine (2.41 mL, 17.31 mmol) in dichloromethane, cooled to zero degreees Celsius, was slowly added a solution of the sulfonyl chloride of part C of Example 37 (2.50 g, 7.87 mmol) in dichloromethane (20 mL). Once the addition was complete, the cooling bath was removed. After stirring at ambient temperature for 4 hours, additional triethylamine (1.25 mL, 8.97 mmol) was added. The resulting mixture was stirred at ambient temperature for 2.5 hours and then concentrated *in vacuo*. The residue was partitioned between 5% $KHSO_4$ solution and ethyl acetate. The organic layer was washed with saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the sulfonamide as an off-white solid (3.21 g, 75%).

Part D: To a solution of the sulfonamide (3.18 g, 6.17 mmol) in tetrahydrofuran (30 mL), cooled to zero degrees Celsius, was added lithium bis(trimethylsilyl)amide (13.6 mL, 1 M in tetrahydrofuran, 13.6 mmol). Once the addition was complete, the cooling bath was removed and replaced after 1 hour. To the resulting mixture was added dimethyl carbonate (0.624 mL, 7.40 mmol). Once the

addition was complete the cooling bath was removed. After stirring at ambient temperature overnight (about 18 hours), additional dimethyl carbonate (0.260 mL, 3.09 mmol) was added. After stirring at ambient temperature for 2 hours, additional lithium bis(trimethylsilyl)amide (3.09 mL, 1 M in tetrahydrofuran, 3.09 mmol) was added. After stirring at ambient temperature for 2 hours, the reaction mixture was cooled to zero degrees Celsius, and quenched by the addition of saturated NH_4Cl. The tetrahydrofuran was concentrated *in vacuo* and the aqueous reaction mixture was diluted with H_2O and extracted with diethyl ether. The combined organic layers were washed with 5% $KHSO_4$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate/hexanes) provided the sulfonamide ester as a pale yellow gum (1.76 g, 50%).

Part E: To a suspension of the sulfonamide ester of part D (1.76 g, 3.07 mmol) and 10% Pd/C (0.307 g) in tetrahydrofuran (25 mL) was bubbled H_2. After bubbling H_2 through the reaction mixture for 23 hours the mixture was purged with N_2 and filtered through a pad of Celite®, washing with methanol. The filtrate was concentrated *in vacuo* to give the amine as a pale yellow gum (1.19 g, 88%).

Part F: To a solution of the amine of part E (1.19 g, 2.71 mmol) in N,N-dimethylformamide (10 mL) were added K_2CO_3 (0.749 g, 5.42 mmol) and 2-bromoethyl methyl ether (0.382 mmol, 4.07 mmol). The resulting mixture was stirred at ambient temperature for 21 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate and filtered through a pad of Celite®.

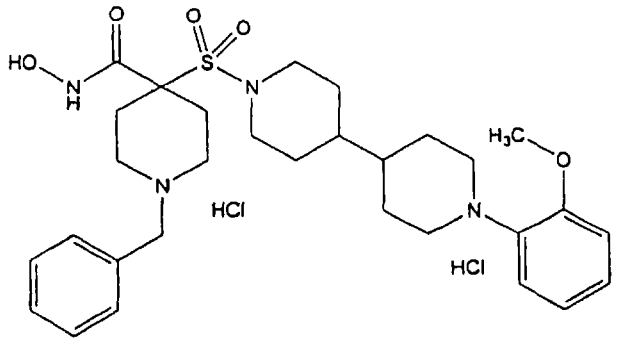
Chromatography (on silica, ethyl acetate with 5% methanol/hexanes) provided the alkylated amine as a tan solid (0.770 g, 57%).

Part G: To a solution of the alkylated amine of part F (0.770 g, 1.55 mmol) in tetrahydrofuran (5.0 mL) was added potassium trimethylsilanolate (0.398 g, 3.10 mmol). After stirring at ambient temperature for 3 hours additional tetrahydrofuran (5.0 mL) was added. The resulting reaction mixture was stirred at ambient temperature for 24 hours and then the tetrahydrofuran was removed by blowing N_2 over the reaction mixture. To the residue was added acetonitrile (20 mL) and 1 N HCl (5 mL). The resulting mixture was stirred at ambient temperature for several minutes and then concentrated *in vacuo* to provide the crude acid as a tan solid (0.806 g, >100%).

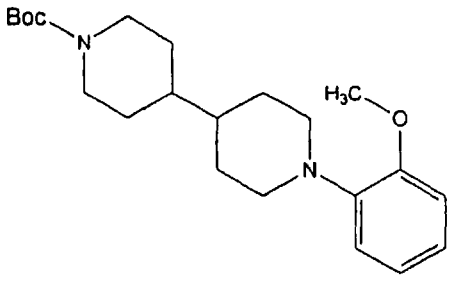
Part H: To a suspension of the crude acid of part G (0.806 g, ~1.55 mmol) in N,N-dimethylformamide (7.0 mL) were added 1-hydroxybenzotriazole (0.251 g, 1.86 mmol) and 1-3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.416 g, 2.17 mmol). After stirring at ambient temperature for 1.5 hours, N-methylmorpholine (0.847 mL, 7.75 mmol) and O-(tetrahydropuranyl) hydroxylamine (0.545 g, 4.65mmol) were added. After stirring at ambient temperature overnight (about 18 hours) the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$, saturated NaCl and dried over Na_2SO_4. Chromatography (on silica, ethyl acetate with 5% methanol/hexanes) provided the protected hydroxamate as a yellow sticky oil (0.687 g, 76%).

Part I: The protected hydroxamate of part H (0.687 g, 1.18 mmol) was treated with a solution of 4 N HCl in dioxane (2.95 mL) and methanol (0.500 mL). The resulting mixture was stirred at ambient temperature for 1.5 hours and then diethyl ether was added. The precipitate was collected by filtration, washing with diethyl ether, to give the title compound as an off-white solid (0.530 g, 79%). MS MH^+ calculated for $C_{23}H_{39}N_4O_6S_1$: 499, found 499.

Example 39: Preparation of N-hydroxy-4-[[1'-(2-methoxyphenyl)[4,4'-bipiperidin]-1-yl]sulfonyl]-1-(phenylmethyl)-4-piperidinecarboxamide, dihydrochloride



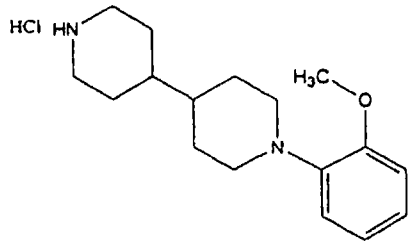
Part 1: Preparation of



To N-(t-butoxycarbonyl)-4,4'-bipiperidine (prepared as described in WO94/14776; preparation 22; (3.5g, 30 mmol) and sodium t-butoxxide (Aldrich, 1.8 mL, 110 mmol), 2-bromoanisole(Aldrich; 2 g, mmol), BINAP (Aldrich; 150 mg), palladium chloride(Aldrich,

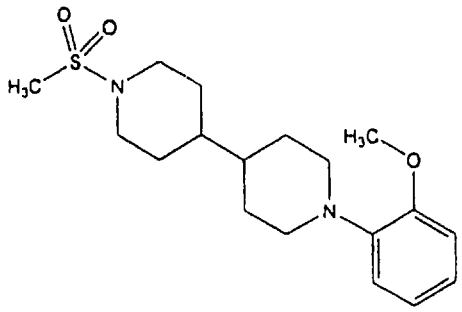
50 mg) were slurried in toluene (22 mL) and heated to 80°C. After the disappearance of the starting material, the solvent wasremoved and the residue was taken up in ethyl acetate (100 mL) and H_2O (30 mL). Once separated, the organic layer was washed with 5% $KHSO_4$ (3x-50 mL) and brine (1x- 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford the N-aryl Boc bipiperidine as an oil (6.5 g). ^1H NMR and mass spectroscopy showed the desired compound.

Part 2: Preparation of



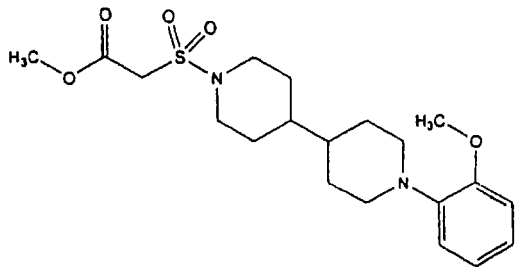
To a solution of the product (6 g) of Part 1 in 1,4-dioxane (10 mL) was added 4 N HCl in dioxane (50 mL, 200 mmol). The mixture was stirred at room temperature until starting material was gone by LC (about 1 hour). The solvents were then removed and the residue was slurried in diethyl ether and filtered. The solid was washed with diethyl ether (2x-50 mL) and dried *in vacuo* to afford the N-aryl bipiperidine as a white solid (6 g). ^1H NMR and mass spectroscopy showed the desired compound as the HCl salt.

Part 3: Preparation of



The HCl salt of Part 2 (5g, 14 mmol) and triethylamine (Aldrich, 4.4 mL, 42 mmol) were slurried in CH_2Cl_2 (50 mL) and cooled to zero°C. A solution of methane sulfonyl chloride (Aldrich, 2 g, 50 mmol) in CH_2Cl_2 (20 mL) was slowly added, maintaining the temperature below 10°C. After the addition, the ice bath was removed and the reaction stirred 1 hour as it warmed to ambient temperature. After the disappearance of the starting material, the solvent was removed and the residue was taken up in ethyl acetate (100 mL) and H_2O (30 mL). Once separated, the organic layer was washed with 5% $KHSO_4$ (3x-50 mL) and brine (1x- 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford an oily solid that was recrystallized from diethyl ether , affording the N-aryl methylsulfonamide bipiperidine as an off-white solid (4 g). ^1H NMR and mass spectroscopy showed the desired compound.

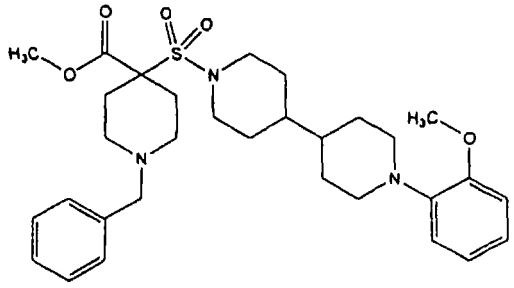
Part 4: Preparation of



Oven-dried glassware was charged with the compound from Part 3 (3.5 g, 10 mmol) and

tetrahydrofuran (20 mL,) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 30 mL, 33 mmol) was slowly added, keeping temperature less than -60°C. The reaction was stirred for 30 minutes after the addition, and was then charged with a solution of methyl chloroformate (Aldrich, 1.1 mmol, 11 mmol) in tetrahydrofuran (1 mL) again keeping the temperature at less than -60°C. After stirring for 1 hour at -75°C, the reaction was quenched with saturated NH_4Cl, keeping temperature less than -20°C. The aqueous portion froze into a solid chunk of ice. After warming to 5°C, the mixture was extracted via ethyl acetate (3x- 200 mL). Organics were washed with saturated NH_4Cl (2x-100 mL) and brine (1x-100mL), then dried over Na_2SO_4 and concentrated to afford the N-aryl bipiperidine methylene as a tan oil(4.0 g, 90% crude yield). ^1H NMR and mass spectroscopy indicated desired compound.

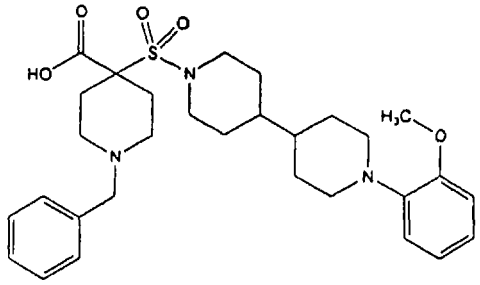
Part 5: Preparation of



To a solution of compound from Part 4 (3 g, 11 mmol) and bis-(2-chloroethyl)benzyl amine (2.7 mL, 15.1 mmol) in dimethylformamide (30 mL) was added 18-Crown-6 (Aldrich, 500 mg, cat.), followed by potassium carbonate (Aldrich, 5 g, 27.4 mmol). The mixture was heated at 60°C for 16 hours. The product was isolated by pouring into water(200 mL) and extraction with ethyl acetate (3x- 300 mL). Organics

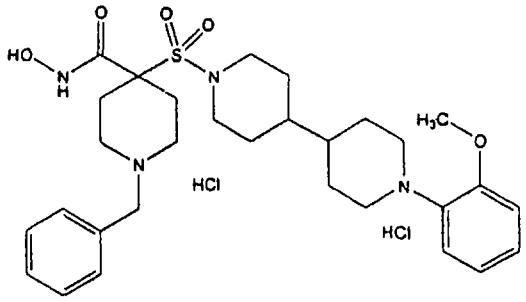
were washed with brine (2x- 200 mL), dried over Na_2SO_4, and concentrated to afford the amino ester an oil (3g) that solidified on standing. ^1H NMR and mass spectroscopy showed the desired compound.

Part 6: Preparation of



To a solution of the compound from Part 5 (2 g, 7 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 2. g, 18 mmol). The reaction stirred overnight (about 18 hours) at room temperazture, at which time LC showed less than 3% starting material remained. Work up comprised removing the tetrahydrofuran and taking the residue up in H_2O (100 mL). The solution was washed with diethylether (50 mL). The aqueous was then cooled to zero°C and 10% HCl_{aq} was slowly added until pH = 3. The acidic mixture was then extracted with ethyl acetate (3x-150 mL). The organics were washed with brine (1x- 100 mL), dried over Na_2SO_4, and concentrated to afford a wet solid. The solid was dried *in vacuo* with phosphorous pentoxide yielding the amino acid as an orange solid (2.4 g, 72% yield). ^1H NMR and mass spectroscopy showed the desired compound.

Part 7: Preparation of



To a solution of the acid product in Part 6 (3 g, 5.2 mmol) in dimethylacetamide (20 mL) was added N-methylmorpholine (Aldrich, 3.0 mL, 15 mmol) followed by by N-hydroxybenzotriazole hydrate (Aldrich,1.0 g, 5 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.1 g, 7.5 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.5 g, 9.4 mmol). The mixture was stirred overnight (about 18 hours) and was then stripped of solvent. The residue was taken up in ethyl acetate (250 mL) and washed with 5% $NaHSO_4$ (1x-150 mL), saturated potassium carbonate (1x-150 mL), and brine (1x-150 mL). The organic layer was then dried over Na_2SO_4 and concentrated to afford a viscous oil. ^1H NMR and mass spectroscopy showed the desired compound.

The viscous crude oil (3.0 g, 6.2 mmol) was dissolved in acetonitrile (10 mL) and stirred with 10% HCl_{aq} (15 mL) for 2 hours, after which LC showed no more starting material. The acetonitrile was removed with N_2 stream over the surface of the solution affording a solid that was collected, washed with H_2O (1x-20 mL), and dried *in vacuo* to afford the product as a tan solid (950 mg, 60% yield). ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{30}H_{42}N_4O_5S$ -2HCl; M^{+H}_{found} = 570 (M^{+H}_{calc} = 570).