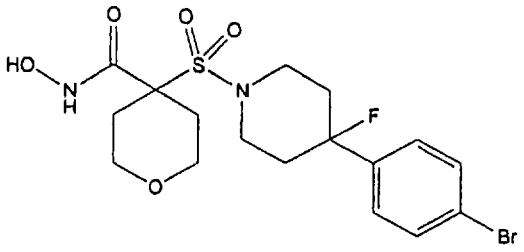
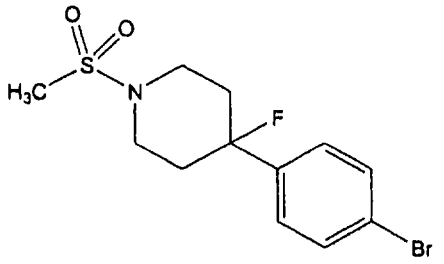
Example 40: Preparation of 4-[[4-(4-bromophenyl)-4-fluoro-1-piperidinyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



G00002

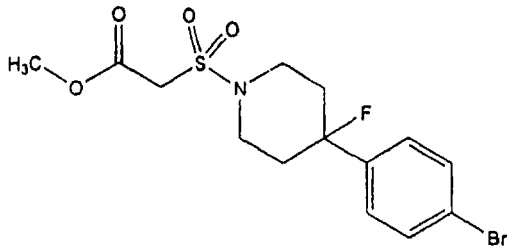
Part 1: Preparation of



166166

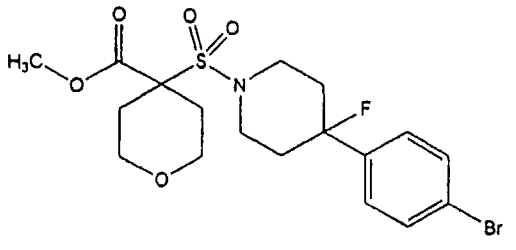
To 4,(4-Bromophenyl)-4-hydroxypiperidine-N-methylsulfonamide (aldrich, 3g, 9 mmol) dissolved in CH_2Cl_2 (75 mL) and cooled to -78°C was added DAST (Aldrich, 1.9g 12 mmol). After the addition, the dry ice bath/reaction was left to warmed to ambient temperature. After the disappearance of the starting material, aqueous ammonium chloride (100 mL) was added and the layers were separated. The organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure to give the methylsulfonamide as a white solid (3 g). ^1H NMR and mass spectroscopy showed the desired compound.

Part 2: Preparation of



Oven-dried glassware was charged with the compound from Part 1 (4.0 g, 1.2 mmol) and tetrahydrofuran (25 mL,) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 35 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, 1.3 mmol, 1.3 mmol) in tetrahydrofuran (17 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 at less than -20°C. The aqueous portion freezes into a solid chunk of ice. After warming to 5°C, the mixture was extracted with ethyl acetate (3x- 200 mL). Organics were washed with saturated NH_4Cl (2x-100 mL) and brine (1x-100 mL), then dried over Na_2SO_4 and concentrated to afford the methylene sulfonamide as an amber oil (4.6 g, 90% crude yield). ^1H NMR and mass spectroscopy indicated desired compound.

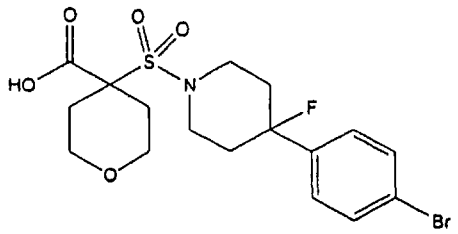
Part 3: Preparation of



To a solution of compound from Part 2 (3.5 g, 1 mmol) and dibromo-diethylether (Lancaster, 3 g, 1.4

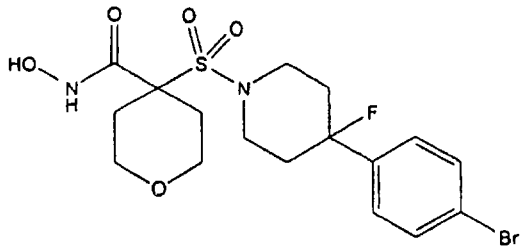
mmol) in dimethylformamide (28 mL) was added 18-Crown-6 (Aldrich, 500 mg, cat.) followed by potassium carbonate (Aldrich, 5 g, 3.6 mmol). The mixture was heated at 60°C for 16 hours. The product was isolated by pouring into stirring 10% HCl_{aq} (200 mL) and extracted with ethyl acetate (3x- 300 mL). Organics were washed with brine (2x- 200 mL), dried over Na_2SO_4, and concentrated to afford an oil. The crystallized to result in 4.8 grams of the ester as a tan solid. ^1H NMR and mass spectroscopy showed the desired compound.

Part 4: Preparation of



To a solution from Part 3 (2 g, 0.4 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 2 g, 1.5 mmol). The reaction was stirred overnight (about 18 hours) at room temperature. 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 diethyl ether (50 mL). The aqueous was then cooled to zero°C and 10% HCl_{aq} was slowly added until pH = 3. The product was filtered and washed with water to result in the acid as a white solid (1.5 g, 72% yield). ^1H NMR and mass spectroscopy showed the desired compound.

Part 5: Preparation of

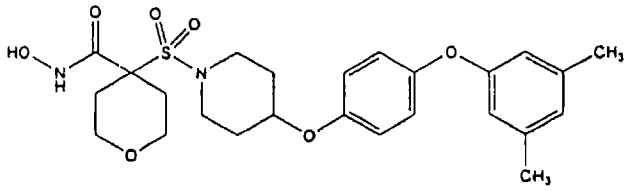


To a solution of the acid product in Part 4 (1 g, 0.2 mmol) in dimethylacetamide (10 mL) was added N-methylmorpholine (Aldrich, 2.0 mL, 2 mmol), followed by by N-hydroxybenzotriazole hydrate (Aldrich,1.0 g, 0.7 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.1 g, 0.9 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.1 g, 0.6 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 was then dried over Na_2SO_4 and concentrated to afford the protected hydroxamate as a viscous oil. ^1H NMR and mass spectroscopy showed the desired compound.

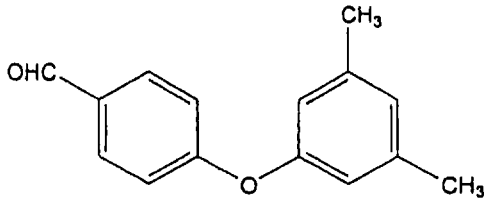
The viscous crude oil from above was dissolved in acetonitrile (10 mL) and stirred with 10% HCl_{aq} (15 mL) for 2 hours, after which LC showed no more starting material. The acetonitrile was removed with a N_2 stream over the surface of the solution affording a solid that was collected, washed with H_20 (1x-20 mL), and dried *in vacuo* to afford the product as a tan solid (755 mg). ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{17}H_{22}FN_2O_5SBrF$ M^{+H}_{found} = 465 (M^{+H}_{calc} = 465).

Example 41: Preparation of 4-[[4-[4-(3,5-

dimethylphenoxy)phenoxy]-1-piperidinyl]-sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide

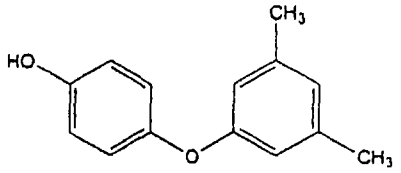


Part 1: Preparation of



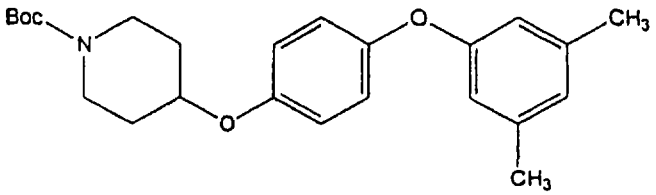
To a slurry of Cs_2CO_3 (Aldrich, 40 g, 12 mmol) and 3,5-dimethyl phenol (Aldrich, 5 g, 4 mmol) in dimethylformamide (60 mL) at 25°C under N_2 was added 4-fluorobenzaldehyde (Aldrich, 5 g, 4 mmol). The mixture was stirred and heated to 90°C for 16 hours. After this time, the solvent was removed by roto-evaporation and taking the residue up in ethyl acetate (150 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2x- 150 mL). The organics were washed with saturated K_2CO_3 (2x-100 mL), H_2O (1x-150 mL), and brine (1x- 150 mL), then dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. The oil was purified on silica gel to give 8 g of the aldehyde as a clear oil. ^1H NMR and mass spectroscopy was consistent with the desired compound.

Part 2: Preparation of



To a solution of aldehyde (8 g, 35 mmol) from part 1 in mehtylene chloride (100 mL) was added meta-chloroperoxybenzoic acid (8 g, 52 mmol). The reaction mixture was stirred at ambient temperature for 16 hours. After complete reaction, the solid meta-chlorobenzoic acid was removed by filtration. The solvent of the filtrate was removed under reduced pressure to give an oil. This oil was dissolved in methanol (100 mL) to which lithium hydroxide (2 g) was added. After 4 hours, the reaction was complete. The solvent was removed by rotory evaporation to give an oil, which was dissolved in ethyl acetate and washed with 10% aqueous hydrochloroic acid, separated and dried over sodium sulfate to result in 5.5 grams of the phenol as an oil. ^{1}H NMR and mass spectroscopy were consistent with the desired compound.

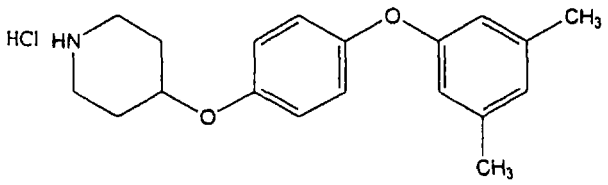
Part 3: Preparation of



Sodium hydride (Aldrich, 2 g, 50 mmol) was added to a solution of 4-(methylsulfonyl)hydroxy-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester of Example 14, B (10 g, 25 mmol) and the phenol from part 2 (5.5 g, 50 mmol) dissolved in dimethylformamide (60 mL) at 25°C and under N_2. The mixture was stirred and heated to 80°C for 16 hours. After this time, the solvent was removed by roto-

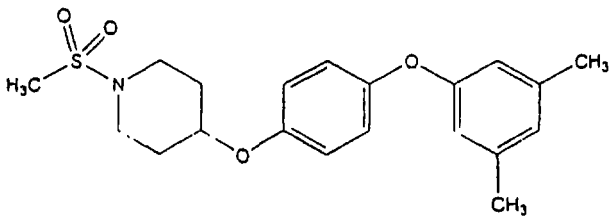
evaporation, followed by taking the residue up in ethyl acetate (150 mL) and H_2O (100 mL). The layers were separated and the aqueous was extracted via ethyl acetate (2x- 150 mL). The organics were washed with saturated K_2CO_3 (2x-100 mL), H_2O (1x-150 mL), and brine (1x- 150 mL), then dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. The oil was purified on silica gel to give 10g of the N-boc piperidine as a clear oil. ^1H NMR and mass spectroscopy was consistent with the desired compound.

Part 4: Preparation of



To a solution of the product (10 g) of Part 3 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 a white solid (3g). ^1H NMR and mass spectroscopy showed the desired compound as the HCl salt.

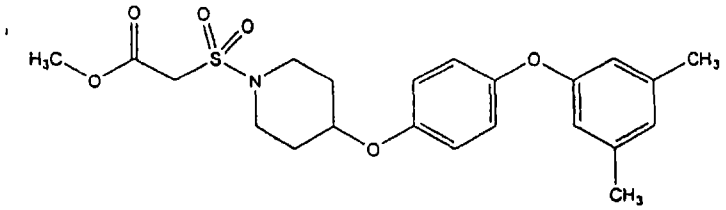
Part 5: Preparation of



The HCl salt of Part 4 (3g, 10 mmol) and triethylamine (Aldrich, 3 mL, 15 mmol) were slurried

in CH_2Cl_2 (50 mL) and cooled to zero°C. A solution of methane sulfonyl chloride (Aldrich, 1.3 g, 13 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 methylsulfonamide as an off-white solid (1.2 g). ^1H NMR and mass spectroscopy showed the desired compound.

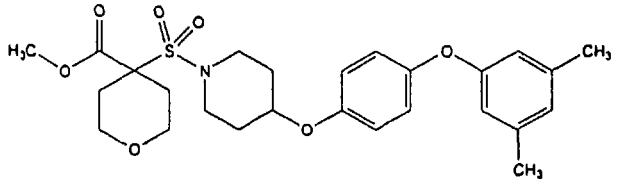
Part 6: Preparation of



Oven-dried glassware was charged with the compound from Part 5 (1.2 g, 3.2 mmol) and tetrahydrofuran (25 mL), and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 9 mL, 6 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, 350mg, 3.5 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 at

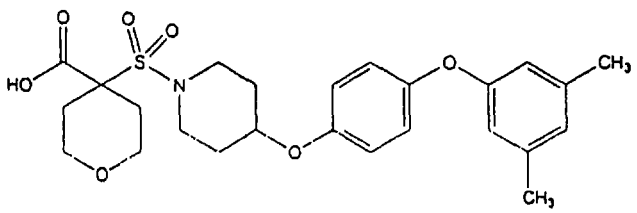
less than -20°C. The aqueous phase froze into a solid chunk of ice. After warming to 5°C, the mixture was extracted with ethyl acetate (3x- 200 mL). Organics were washed with saturated NH_4Cl (2x-100 mL) and brine (1x-100 mL), then dried over Na_2SO_4 and concentrated to afford the methylene sulfonamide as a tan oil (2.0 g, 90% crude yield). ^1H NMR and mass spectroscopy indicated desired compound.

Part 7: Preparation of



To a solution of compound from Part 6 (2 g, 11 mmol) and dibromo-diethylether (Lancaster, 1.8 mL, 15.1 mmol) in dimethylformamide (28 mL) was added 18-Crown-6 (Aldrich, 500mg, cat.) followed by potassium carbonate (Aldrich, 3.8 g, 27.4 mmol). The mixture was heated at 60°C for 16 hours. The product was isolated by pouring the reaction mixture into stirring 10% HCl_{aq} (200 mL), followed by 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 ester as an oil. The oil was crystallized from diethyl ether (2 g). ^1H NMR and mass spectroscopy showed the desired compound.

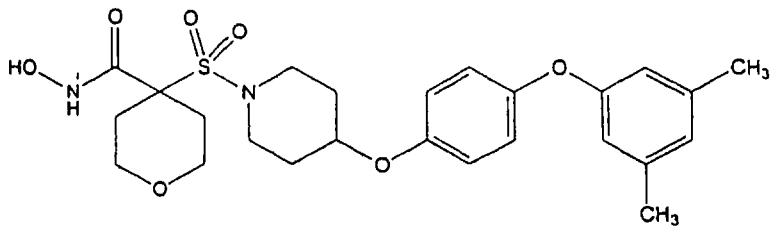
Part 8: Preparation of



To a solution from Part 7 (2 g, 7 mmol) in tetrahydrofuran (20 mL) was added potassium

trimethylsilonate (Aldrich, 2. g, 18 mmol). The reaction was stirred overnight (about 18 hours) at room temperature. LC showed less than 3% starting material remained. Work up comprised remmoving the tetrahydrofuran and taking the residue up in H_2O (100 mL). The solution was washed with diethyl ether (50 mL). The aqueous layer was then cooled to zero°C and 10% HCl_{aq} was slowly added until pH = 3. The acidic mixture was then extracted via 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 acid as an orange solid (2 g, 92% yield). ^1H NMR and mass spectroscopy showed the desired compound.

Part 9: Preparation of

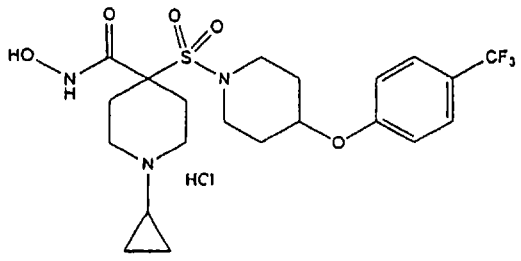


To a solution of the acid product in Part 8 (2 g, 6.2 mmol) in dimethylacetamide (10 mL) was added N-methylmorpholine (Aldrich, 2.0 mL, 18.6 mmol), followed by N-hydroxybenzotriazole hydrate (Aldrich,1.0 g, 7.4 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.1 g, 9.4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.8 g, 9.4 mmol). The mixture 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),

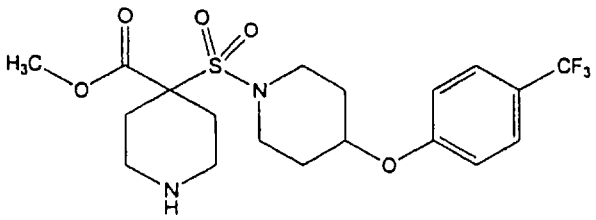
and brine (1x-150 mL). The organic layer was then dried over Na_2SO_4 and concentrated to afford a viscous oil. ^1H NMR and MS showed the desired compound.

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 a N_2 stream over the surface of the solution affording a solid that was collected, washed with H_20 (1x-20 mL), and *dried in vacuo* to afford the product as a tan solid (230 mg, 64% yield). ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{25}H_{32}F_3N_2O_7S$ M^{+H}_{found} = 504 (M^{+H}_{calc} = 504).

Example 42: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



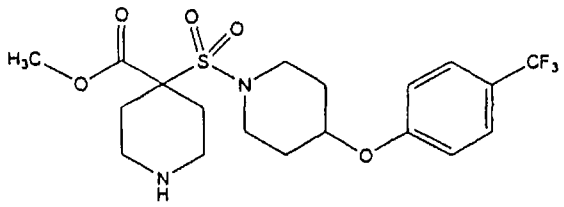
Part 1: Preparation of



To a methanol (160 mL) solution of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate of

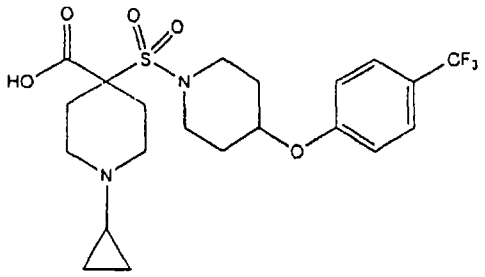
Example 12, Part F (40 g), and ammonium formate (15 g) was added 10%Pd on carbon (16 g, Degussa type catalyst). The black mixture was refluxed for 30-45 minutes. After complete reaction, the mixture was cooled and filtered through a Celite® pad. The solvent was removed under reduced pressure to give the piperidine methyl ester as an oil that solidified on standing (34 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 2: Preparation of



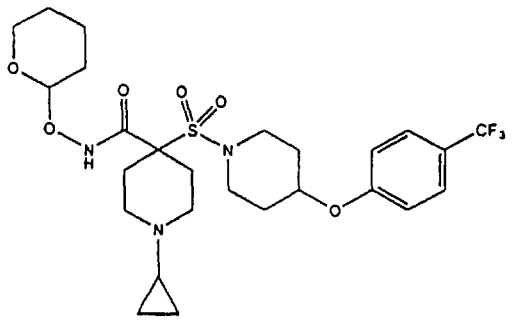
To a solution of compound from Part 1 (5 g, 1 mmol) in methanol (35 mL) were added [(1-ethoxycyclopropyl)oxy]-trimethylsilane (Aldrich, 7 g, 4 mmol), acetic acid (6 g, 10 mmol), sodium cyanoborohydride (1.8 g, 3 mmol) and molecular sieves (2.5 g). The reaction mixture was stirred and heated for 8 hours. The progress of the reaction was monitored by RPHPLC. Work up comprised filtering the reaction mixture through a pad of Celite®, concentrating the methanol and partitioning the residue between in H_2O (50 mL) and ethyl acetate (500 mL). The organics were washed with brine (1x- 100 mL), dried over Na_2SO_4, and concentrated to afford the amino methyl ester as a semi-solid (3 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 3: Preparation of



To a solution from Part 2 (3 g, 5 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 1.5 g, 10 mmol). The reaction was complete overnight (about 18 hours) at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the mixture. Then water was added (20 mL) followed by aqueous 10% HCl until pH = 7. The zwitterion was filtered washed with water (10 mL) and dried *in vacuo* with over phosphorous pentoxide yielding a solid (3 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

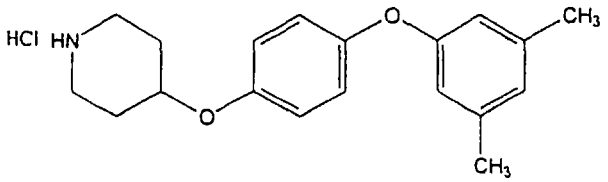
Part 4: Preparation of



To a solution of the zwitterion product in Part 3 (3 g, 5 mmol) in dimethylacetamide (20 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.8 g, 9.4 mmol) and N-hydroxybenzotriazole hydrate (Aldrich, 1.0 g, 7.4 mmol), followed by heating to 50°C for 15 minutes. N-Methylmorpholine (Aldrich, 2.0 mL, 18.6 mmol) was the added, followed by, O-(tetrahydro-2H-pyran-2-yl)

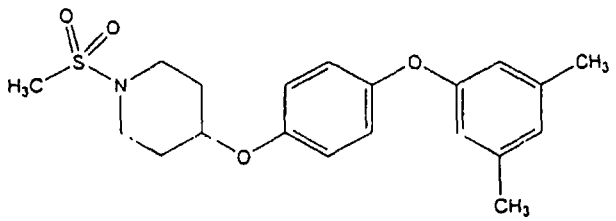
evaporation, followed by taking the residue up in ethyl acetate (150 mL) and H_2O (100 mL). The layers were separated and the aqueous was extracted via ethyl acetate (2x- 150 mL). The organics were washed with saturated K_2CO_3 (2x-100 mL), H_2O (1x-150 mL), and brine (1x- 150 mL), then dried over Na_2SO_4, filtered, and concentrated to afford a crude oil. The oil was purified on silica gel to give 10g of the N-boc piperidine as a clear oil. ^1H NMR and mass spectroscopy was consistent with the desired compound.

Part 4: Preparation of



To a solution of the product (10 g) of Part 3 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 a white solid (3g). ^1H NMR and mass spectroscopy showed the desired compound as the HCl salt.

Part 5: Preparation of

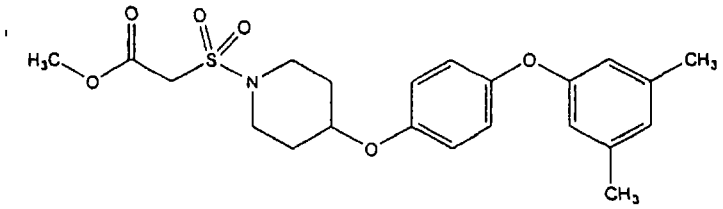


The HCl salt of Part 4 (3g, 10 mmol) and triethylamine (Aldrich, 3 mL, 15 mmol) were slurried

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in CH_2Cl_2 (50 mL) and cooled to zero°C. A solution of methane sulfonyl chloride (Aldrich, 1.3 g, 13 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 methylsulfonamide as an off-white solid (1.2 g). ^1H NMR and mass spectroscopy showed the desired compound.

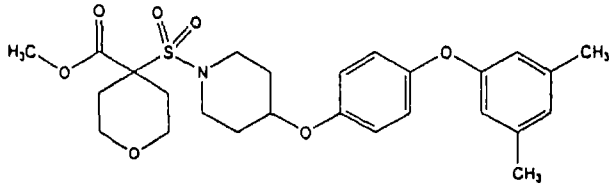
Part 6: Preparation of



Oven-dried glassware was charged with the compound from Part 5 (1.2 g, 3.2 mmol) and tetrahydrofuran (25 mL), and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 9 mL, 6 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, 350mg, 3.5 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 at

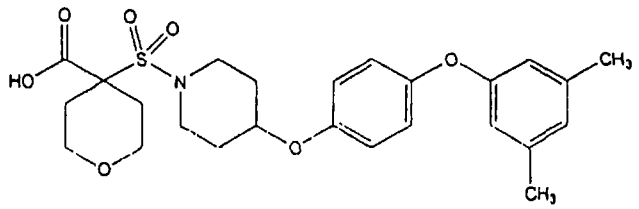
less than -20°C. The aqueous phase froze into a solid chunk of ice. After warming to 5°C, the mixture was extracted with ethyl acetate (3x- 200 mL). Organics were washed with saturated NH_4Cl (2x-100 mL) and brine (1x-100 mL), then dried over Na_2SO_4 and concentrated to afford the methylene sulfonamide as a tan oil (2.0 g, 90% crude yield). ^1H NMR and mass spectroscopy indicated desired compound.

Part 7: Preparation of



To a solution of compound from Part 6 (2 g, 11 mmol) and dibromo-diethylether (Lancaster, 1.8 mL, 15.1 mmol) in dimethylformamide (28 mL) was added 18-Crown-6 (Aldrich, 500mg, cat.) followed by potassium carbonate (Aldrich, 3.8 g, 27.4 mmol). The mixture was heated at 60°C for 16 hours. The product was isolated by pouring the reaction mixture into stirring 10% HCl_{aq} (200 mL), followed by 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 ester as an oil. The oil was crystallized from diethyl ether (2 g). ^1H NMR and mass spectroscopy showed the desired compound.

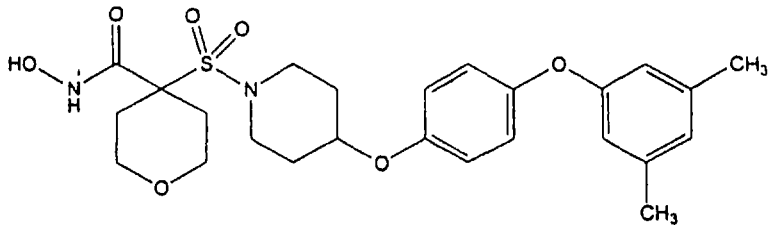
Part 8: Preparation of



To a solution from Part 7 (2 g, 7 mmol) in tetrahydrofuran (20 mL) was added potassium

trimethylsilonate (Aldrich, 2. g, 18 mmol). The reaction was stirred overnight (about 18 hours) at room temperature. LC showed less than 3% starting material remained. Work up comprised remmoving the tetrahydrofuran and taking the residue up in H_2O (100 mL). The solution was washed with diethyl ether (50 mL). The aqueous layer was then cooled to zero°C and 10% HCl_{aq} was slowly added until pH = 3. The acidic mixture was then extracted via 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 acid as an orange solid (2 g, 92% yield). ^1H NMR and mass spectroscopy showed the desired compound.

Part 9: Preparation of

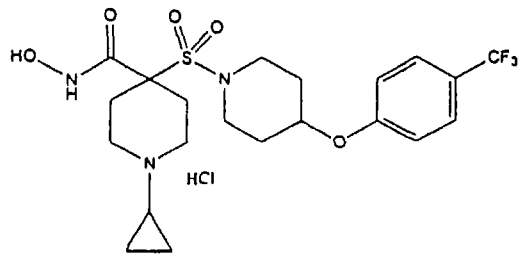


To a solution of the acid product in Part 8 (2 g, 6.2 mmol) in dimethylacetamide (10 mL) was added N-methylmorpholine (Aldrich, 2.0 mL, 18.6 mmol), followed by N-hydroxybenzotriazole hydrate (Aldrich,1.0 g, 7.4 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.1 g, 9.4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.8 g, 9.4 mmol). The mixture 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),

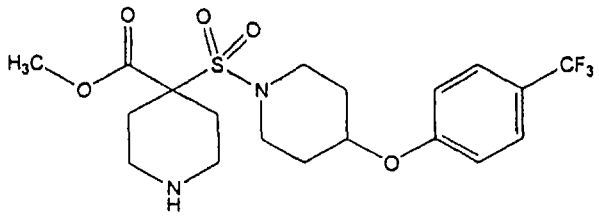
and brine (1x-150 mL). The organic layer was then dried over Na_2SO_4 and concentrated to afford a viscous oil. ^1H NMR and MS showed the desired compound.

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 a N_2 stream over the surface of the solution affording a solid that was collected, washed with H_20 (1x-20 mL), and *dried in vacuo* to afford the product as a tan solid (230 mg, 64% yield). ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{25}H_{32}F_3N_2O_7S$ M^{+H}_{found} = 504 (M^{+H}_{calc} = 504).

Example 42: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



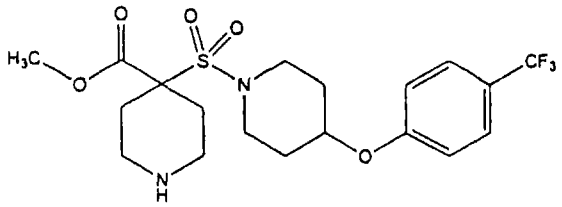
Part 1: Preparation of



To a methanol (160 mL) solution of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate of

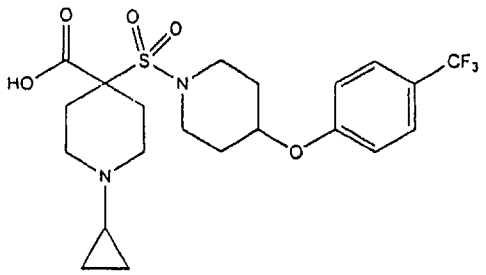
Example 12, Part F (40 g), and ammonium formate (15 g) was added 10%Pd on carbon (16 g, Degussa type catalyst). The black mixture was refluxed for 30-45 minutes. After complete reaction, the mixture was cooled and filtered through a Celite® pad. The solvent was removed under reduced pressure to give the piperidine methyl ester as an oil that solidified on standing (34 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 2: Preparation of



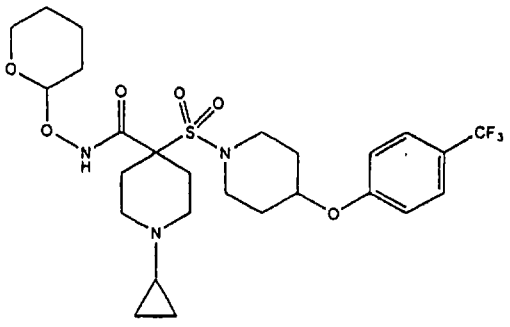
To a solution of compound from Part 1 (5 g, 1 mmol) in methanol (35 mL) were added [(1-ethoxycyclopropyl)oxy]-trimethylsilane (Aldrich, 7 g, 4 mmol), acetic acid (6 g, 10 mmol), sodium cyanoborohydride (1.8 g, 3 mmol) and molecular sieves (2.5 g). The reaction mixture was stirred and heated for 8 hours. The progress of the reaction was monitored by RPHPLC. Work up comprised filtering the reaction mixture through a pad of Celite®, concentrating the methanol and partitioning the residue between in H_2O (50 mL) and ethyl acetate (500 mL). The organics were washed with brine (1x- 100 mL), dried over Na_2SO_4, and concentrated to afford the amino methyl ester as a semi-solid (3 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 3: Preparation of



To a solution from Part 2 (3 g, 5 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 1.5 g, 10 mmol). The reaction was complete overnight (about 18 hours) at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the mixture. Then water was added (20 mL) followed by aqueous 10% HCl until pH = 7. The zwitterion was filtered washed with water (10 mL) and dried *in vacuo* with over phosphorous pentoxide yielding a solid (3 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

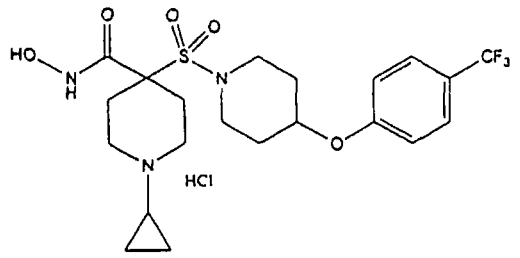
Part 4: Preparation of



To a solution of the zwitterion product in Part 3 (3 g, 5 mmol) in dimethylacetamide (20 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.8 g, 9.4 mmol) and N-hydroxybenzotriazole hydrate (Aldrich, 1.0 g, 7.4 mmol), followed by heating to 50°C for 15 minutes. N-Methylmorpholine (Aldrich, 2.0 mL, 18.6 mmol) was the added, followed by, O-(tetrahydro-2H-pyran-2-yl)

hydroxylamine (1.1 g, 9.4 mmol). The mixture was stirred and heated for 1 hour then left to stir at room temperature overnight (about 18 hours). After complete reaction, the reaction mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate (250 mL) and washed with saturated potassium carbonate (1x-150 mL), and brine (1x-150 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford a viscous oil. The oil was purified on SiO_2 using ethyl acetate in hexane to give 1.8 g of the THP-protected hydroxamate as a clear oil the solidified on standing. ^1H NMR and mass spectroscopy were consistent with the desired structure.

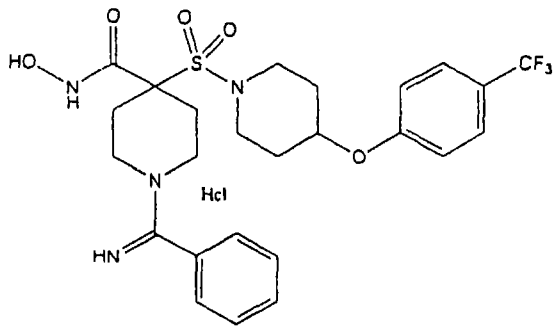
Part 5: Preparation of



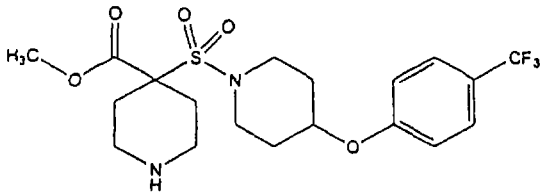
The solid from Part 4 (1.8 g) was slurried in methanol (600 mg) diethyl ether (10 mL). To this was added 4 N HCl in dioxane (10 mL) and stirred for 2 hours, after which, RPHPLC showed complete reaction. The dioxane was concentrated by half, diethyl ether was added (100 mL) and the white solid (1.6 g, 64% yield) filtered and dried under vacuum. ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{21}H_{28}F_3N_3O_5S$-HCl M^{+H}_{found} = 527 (M^{+H}_{calc} = 527).

Example 43: Preparation of N-hydroxy-1-(iminophenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-

piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

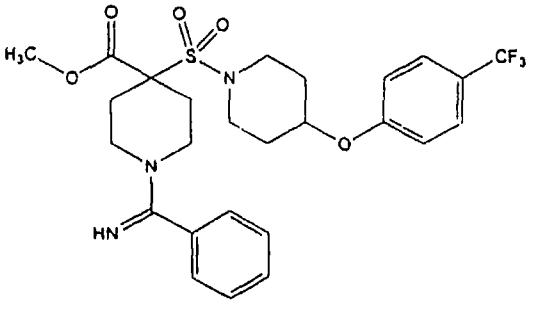


Part 1: Preparation of



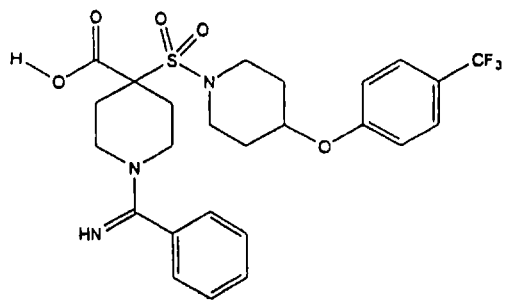
To a methanol (160 mL) solution of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate of Example 12, Part F (40 g), and ammonium formate (15 g) was added 10%Pd on carbon (16 g, Degussa type catalyst). The black mixture was refluxed for 30-45 minuets. After complete reaction the mixture is cooled and filtered through a Celite® pad. The solvent wass removed under reduced pressure to give 34 g of the amino ester as an oil that solidified on standing. ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 2: Preparation of



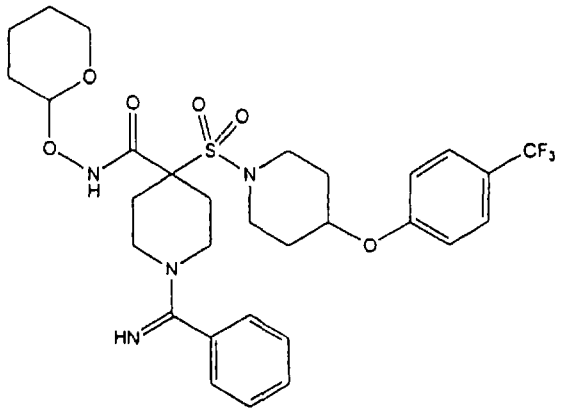
To a solution of compound from Part 1 (5 g, 1.0 mmol) in acetonitrile (50 mL) was added methyl benzimidate HCl (Aldrich, 2.5 g, 1.3 mmol) followed DMAP (100 mg). The reaction mixture was stirred and heated to 60 degrees Celcius for 8 hours. The progress of the reaction was monitored by RPHPLC. Work up comprised removing the solvent under reduced pressure. The resulting solid was triturated with water and filtered to give 7 grams of the amidino ester. ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 3: Preparation of



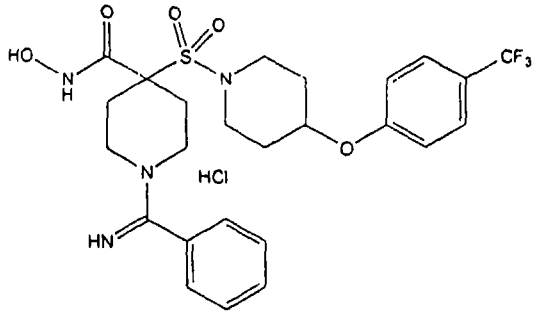
To a solution of the compound from Part 2 (5 g, 1 mmol) in tetrahydrofuran (45 mL) was added potassium trimethylsilonate (Aldrich, 2.5 g, 3 mmol). The reaction was complete overnight (about 18 hours) at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the mixture. Then water was added (20 mL) followed by aqueous 10% HCl until pH = 7. The zwitterion was filtered washed with water (10 mL) and dried *in vacuo* with over phosphorous pentoxide yielding the amidino acid as a solid (3 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 4: Preparation of



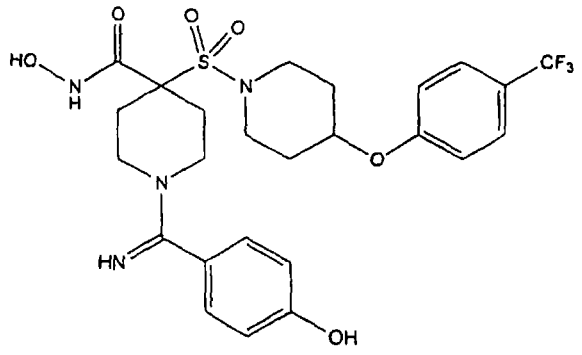
To a solution of the zwitterion product in Part 3 (2.7 g, 5 mmol) in dimethylacetamide (20 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 2.5 g, 9.4 mmol), N-hydroxybenzotriazole hydrate (Aldrich, 1.9 g, 7.4 mmol) and heated to 50°C for 15 minutes. Thereafter, N-methylmorpholine (Aldrich, 4.0 mL, 18.6 mmol) was added, followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (2 g, 9.4 mmol). The mixture was stirred and heated for 1 hour, then left to stir at room temperature overnight (about 18 hours). After complete reaction, the reaction mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate (250 mL) and washed with 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 the THP-protected amidino hydroxamate as a pink solid (1.7 g). ^1H NMR and mass spectroscopy were consistent with the desired structure.

Part 5: Preparation of

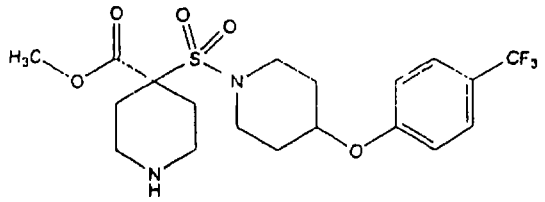


The solid from Part 4 (2.5 g) was slurried in methanol (800 mg) diethyl ether (30 mL). To this was added 4 N HCl in dioxane (10 mL) and the reaction mixture was stirred for 2 hours, after which RPHPLC showed complete reaction. The dioxane was concentrated by half, diethyl ether was added (100 mL) and the white solid (1 g, 70% yield) filtered and dried under vacuum. ^{1}H NMR showed the desired compound. Mass spectroscopy showed: $C_{25}H_{29}F_3N_4O_5S$ - HClM^{+H}_{found} = 591 (M^{+H}_{calc} = 591).

Example 44: Preparation of N-hydroxy-1-[(4-hydroxyphenyl)iminomethyl]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

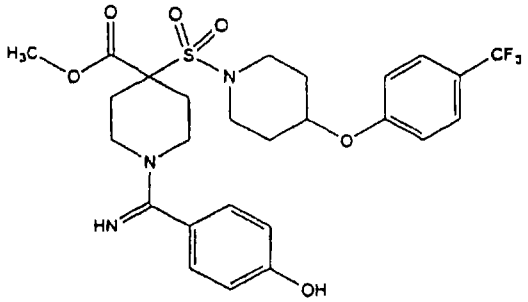


Part 1: Preparation of



To a methanol (160 mL) solution of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate of Example 12, Part F (40 g), and ammonium formate (15 g) was added 10%Pd on carbon (16 g, Degussa type catalyst). The black mixture was refluxed for 30-45 minuets. After complete reaction, the mixture is cooled and filtered through a Celite® pad. The solvent was removed under reduced pressure to give 34 g of the amino ester as an oil that solidified on standing. ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

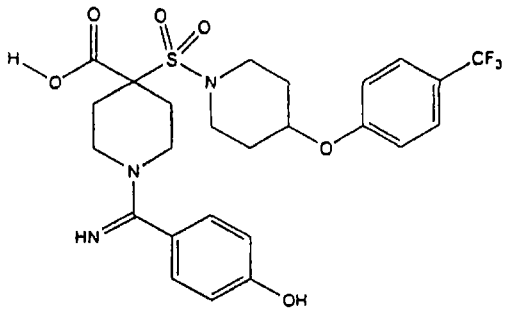
Part 2: Preparation of



To a solution of compound from Part 1 (6 g, 1.2 mmol) in Dimethylformamide (20 mL) was added ethyl 4-hydroxybenzimidate HCl (Aldrich, 3 g, 1.4 mmol) followed by DMAP (150 mg). The reaction mixture was stirred and heated to 50 degrees Celcius for 8 hours. The progress of the reaction was monitored by RPHPLC. Work up comprised removing the solvent under reduced pressure. The resulting solid was triturated with water (50 mL) and filtered to give 5 grams of the amidino ester product. ^{1}H NMR and mass

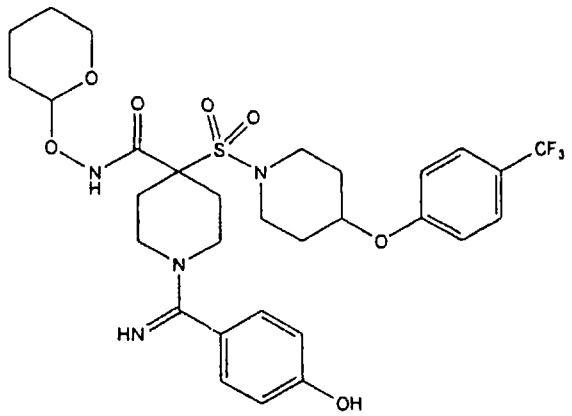
spectroscopy were consistent with the desired structure.

Part 3: Preparation of



To a solution from Part 2 (3 g, 5 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 1.5 g, 10 mmol). The reaction was complete overnight (about 18 hours) at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the mixture. Then water was added (20 mL) followed by aqueous 10% HCl until pH = 7. The zwitterion was filtered, washed with water (10 mL) and dried *in vacuo* with over phosphorous pentoxide yielding the amidino acid as a solid (2.4 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

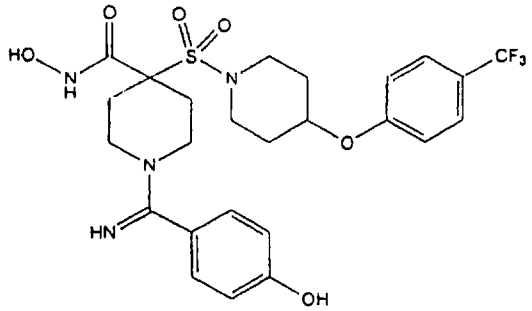
Part 4: Preparation of



To a solution of the zwitterion product in Part 3 (1.1 g, 5 mmol) in dimethylacetamide (20 mL) were

added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.8 g, 9.4 mmol) and N-hydroxybenzotriazole hydrate (Aldrich, 1.0 g, 7.4 mmol), and the mixture was heated to 50°C for 15 minutes. N-methylmorpholine (Aldrich, 2.0 mL, 18.6 mmol) was then added, followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.1 g, 9.4 mmol). The mixture was stirred and heated for 1 hour, then left to stir at room temperature overnight (about 18 hours). After complete reaction, the reaction mixture was concentrated under reduced pressure.. The residue was taken up in ethyl acetate (250 mL) and washed with 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 the THP-protected hydroxamate as a viscous oil. The oil solidified (700 mg) on standing. ^1H NMR and mass spectrosoopy were consistent with the desired structure.

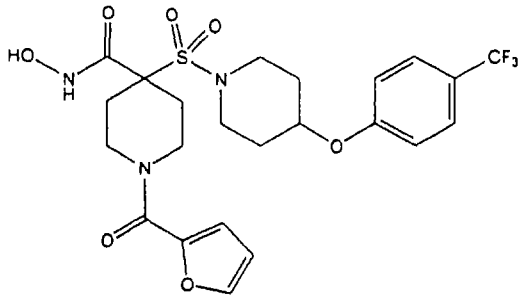
Part 5: Preparation of



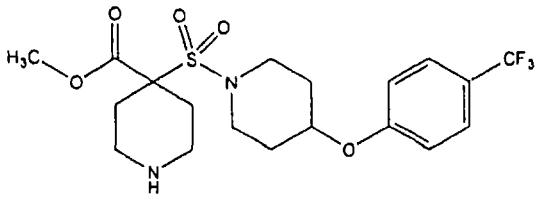
The solid from Part 4 (700 mg) was slurried in methanol (800 mg) and diethyl ether (30 mL). To this was added 4 N HCl in dioxane (10 mL) and stirred for 2 hours, after which RPHPLC showed complete reaction. The dioxane was concentrated by half, diethyl ether was added (100 mL) and the white solid (500 mg, 70% yield) filtered and dried under vacuum. ^1H NMR showed

the desired compound. Mass spectroscopy showed: $C_{25}H_{29}F_3N_4O_6S$ -HCl; M^{+H}_{found} = 607 (M^{+H}_{calc} = 607).

Example 45: Preparation of 1-(2-furanylcarbonyl)-N-hydroxy-4-[[4-[4-(trifluoromethyl)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide

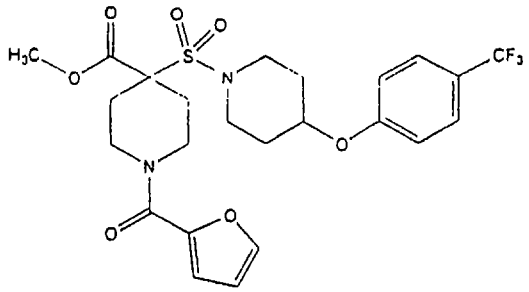


Part 1: Preparation of



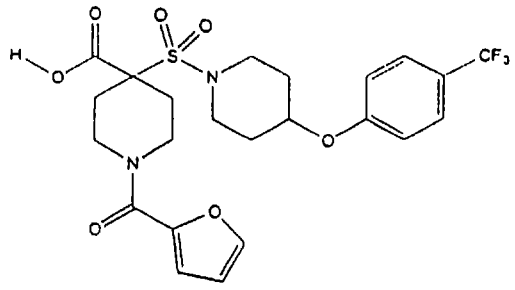
To a methanol (160 mL) solution of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate of Example 12, Part F (40 g), and ammonium formate (15 g) was added 10%Pd on carbon (16 g, Degussa type catalyst). The black mixture was refluxed for 30-45 minuets. After complete reaction the mixture was cooled and filtered through a Celite® pad. The solvent was removed under reduced pressure to give 34 g of the amino ester as an oil that solidified on standing. ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 2: Preparation of



To a solution of the compound from Part 1 (4 g, 0.8 mmol) in methylene chloride (75 mL) was added furfuryl chloride (Aldrich, 1.2 g, 0.8 mmol), followed by N-methylmorpholine (4 mL, 2.3 mmol). The reaction mixture was stirred for 1 hour. The progress of the reaction was monitored by RPHPLC. Work up comprised removing the solvent under reduced pressure. Water (50 mL) was added to the resulting solid and the product as extracted with ethyl acetate (100 mL). The ethyl acetate was washed with brine and dried over sodium sulfate to give the amide ester as a solid (6 grams of product). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

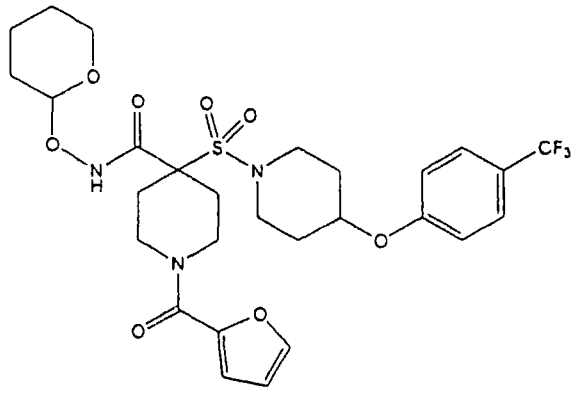
Part 3: Preparation of



To a solution of the compound from Part 2 (6 g, 5 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 5 g, 15 mmol). The reaction was complete overnight (about 18 hours) at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the

mixture. Then water was added (20 mL), followed by aqueous 10% HCl until pH = 7. The product was extracted with methylene chloride (100 mL). The methylene chloride layer was dried over sodium sulfate and the solvent removed under reduced pressure to result in the amide acid as a tan solid (3g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

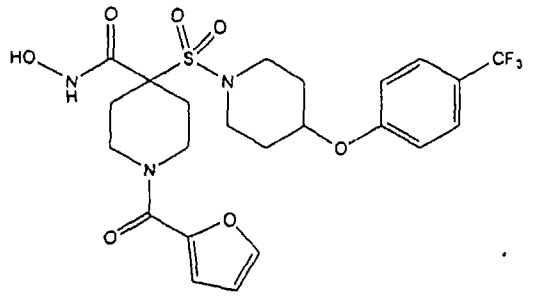
Part 4: Preparation of



To a solution of the product in Part 3 (3 g, 5 mmol) in dimethylformamide (50 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.8 g, 9.4 mmol) and N-hydroxybenzotriazole hydrate (Aldrich,1.0 g, 7.4 mmol), and the mixture was heated to 50°C for 15 minutes. N-methylmorpholine (Aldrich, 2.0 mL, 18.6 mmol) was added, followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.1 g, 9.4 mmol). The mixture was stirred and heated for 1 hour then left to stir at room temperature overnight (about 18 hours). After complete reaction, the reaction mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate (250 mL) and washed with saturated potassium carbonate (1x-150 mL), and brine (1x-150 mL). The organic layer was then dried over

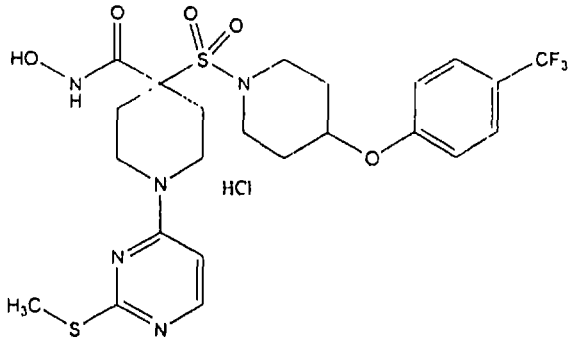
Na_2SO_4 and concentrated to afford THP-protected hydroxamte as a viscous oil. The oil solidified (2.1 g) on standing. ^1H NMR and mass spectroscopy were consistent with the desired structure.

Part 5: Preparation of

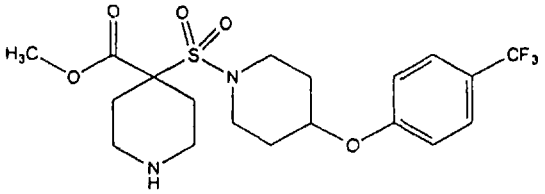


The solid from Part 4 (70 mg) was dissolved in acetonitrile (25mL). To this was added 10% aq. HCl (25 mL), and stirring for 2 hours, after which RPHPLC showed complete reaction. A stream of nitrogen was blown of the surface on the reaction and concentrated by half to result in a precipitate. The white solid was filtered. The solid was crystallized in methanol to give (2.5 g) of a white solid and dried under vacum. ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{23}H_{26}F_3N_3O_7S$; M^{+H}_{found} = 545 (M^{+H}_{calc} = 545).

Example 46: Preparation of N-hydroxy-1-[2-(methylthio)-4-pyrimidinyl]-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

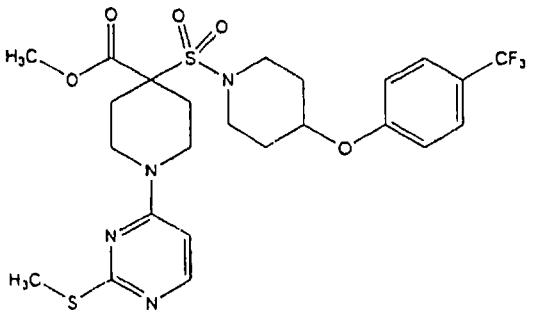


Part 1: Preparation of



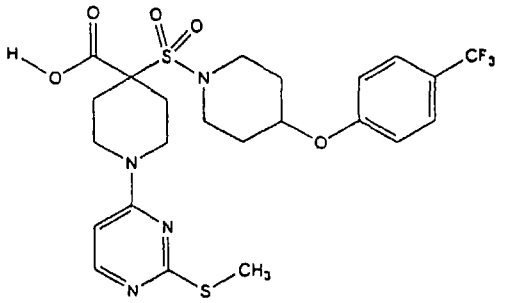
To a methanol (160 mL) solution of methyl 1-(phenylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxylate of Example 12, Part F (40 g), and ammonium formate (15 g) was added 10%Pd on carbon (16 g, Degussa type catalyst). The black mixture was refluxed for 30-45 minuets. After complete reaction the mixture is cooled and filtered through a Celite® pad. The solvent is removed under reduced pressure to give 34 g of the amino ester as an oil that solidified on standing. ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 2: Preparation of



To a solution of the compound from Part 1 (5 g, 0.8 mmol) in dimethylformamide (50 mL) was added chloro-1-methylthiopiperizine (Aldrich, 1.2 g, 1.2 mmol) followed by potassium carbonate (4 g, 2.3 mmol). The reaction mixture was heated to 80 degrees Celsius and stirred for 1 hour, then stirred at room temperature for 12 hours. The progress of the reaction was monitored by RPHPLC. Work up comprised removing the solvent under reduced pressure. Water (50 mL) was added to the resulting solid and the product was filtered to give the N-heteroaryl ester as a solid (6.7 grams of product). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

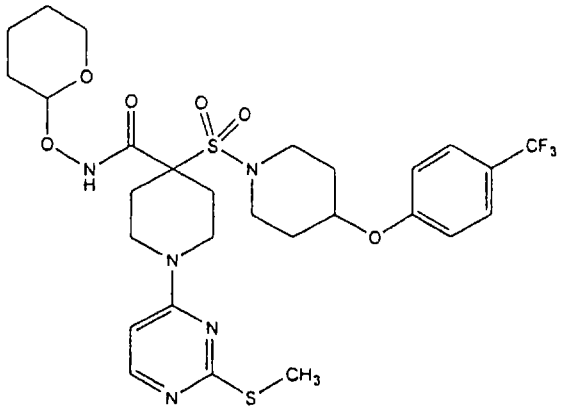
Part 3: Preparation of



To a solution of the compound from Part 2 (6.5 g, 5 mmol) in tetrahydrofuran (50 mL) was added potassium trimethylsilonate (Aldrich, 5 g, 15 mmol). The reaction was complete overnight (about 18 hours) at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the mixture. Then water was added (20 mL) followed by aqueous 10% HCl until pH = 7. The product was extracted with methylene chloride (100 mL). The methylene chloride layer was dried over sodium sulfate and the solvent removed under reduced pressure to result in N-heteroaryl acid as a tan

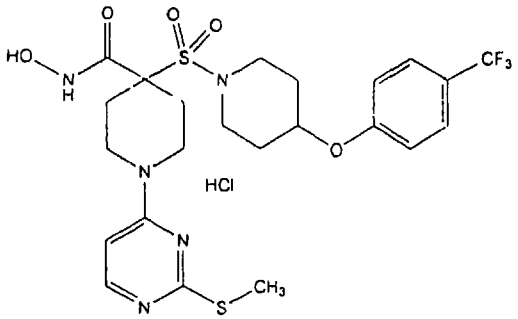
solid (4.2g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 4: Preparation of



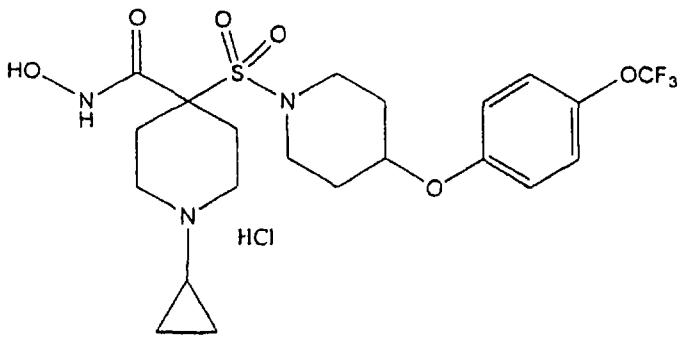
To a solution of the product in Part 3 (4.6 g, 5 mmol) in dimethylformamide (50 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 5 g, 9.4 mmol) and N-hydroxybenzotriazole hydrate (Aldrich,1.0 g, 7.4 mmol), and the mixture was heated to 50°C for 15 minutes. N-methylmorpholine (Aldrich, 4.0 mL, 18.6 mmol) was added, followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (6.1 g, 9.4 mmol). The mixture stirred and heated for 1 hour then left to stir at room temperature overnight (about 18 hours). After complete reaction, the reaction mixture was concentrated under reduced pressure. The residue was taken up in water (75 mL) and filtered to result in the N-heteroaryl THP-protected hydroxamate as a pink solid (4.1 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

Part 5: Preparation of

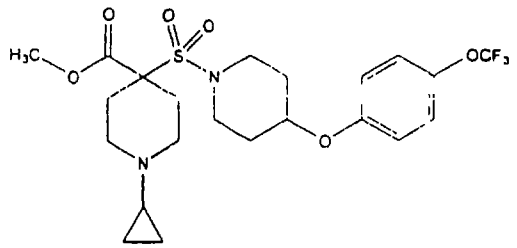


The solid from Part 4 (5.1 g) was dissolved in acetonitrile (25mL). To this was added 10% aq. HCl (25 mL), and the mixture was stirred for 2 hours, after which RPHPLC showed complete reaction. A stream of nitrogen was blown of the surface of the reaction and the volume concentrated by half to result in a precipitate. The white solid was filtered. The solid was crystallized in methanol to give (2.5 g) of a white solid and dried under vacuum. ^{1}H NMR showed the desired compound. Mass spectroscopy showed: $C_{23}H_{28}F_3N_5O_5S_2$ -HCl; M^{+H}_{found} = 612 (M^{+H}_{calc} = ,612).

Example 47: Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[4-(tri-fluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride

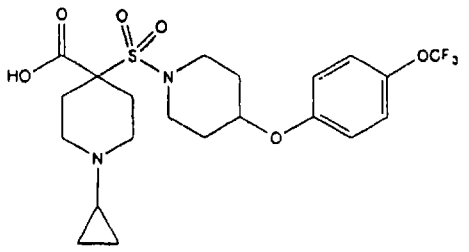


Part 1: Preparation of



To a solution of 4-[[4-[4-(trifluoromethoxy)-phenoxy]-1-piperidinyl]sulfonyl]-4-piperidine-carboxylic acid, methyl ester from Part H of Example 15 (14 g, 30 mmol) in methanol (80 mL) were added [(1-ethoxycyclopropyl)oxy]trimethylsilane (Aldrich, 21 g, 120 mmol), acetic acid (18g, 300 mmol), sodium cyanoborohydride (5.5 g, 90 mmol) and molecular sieves (7 g). The reaction mixture was stirred and heated for 8 hours. The progress of the reaction was monitored by RPHPLC. Work up comprised filtering the reaction mixture through a pad of Celite® then concentrating the methanol and partitioning the residue between in H_2O (50 mL) and ethyl acetate (500 mL). The organics were washed with brine (1x- 100 mL), dried over Na_2SO_4, and concentrated to afford the amino ester as a solid (8 g) after crystallization in methanol. ^1H NMR and mass spectroscopy were consistent with the desired structure.

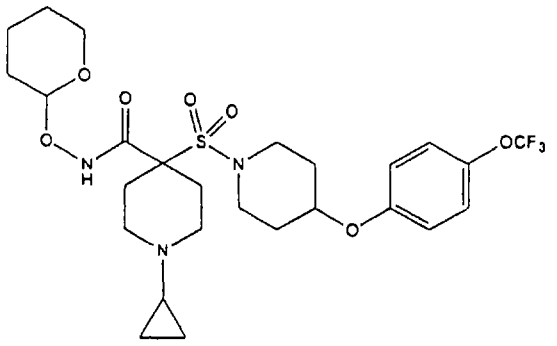
Part 2: Preparation of



To a solution of the compound from Part 1 (8 g, 15 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 4 g, 30 mmol). The reaction was complete overnight (about 18 hours)

at room temperature. A nitrogen stream was blown over the surface of the solution to concentrate the mixture. Then water was added (20 mL) followed by aqueous 10% HCl until pH = 7. The zwitterion was filtered washed with water (10 mL) and dried *in vacuo* with over phosphorous pentoxide yielding the amino acid as a solid (6.8 g). ^{1}H NMR and mass spectroscopy were consistent with the desired structure.

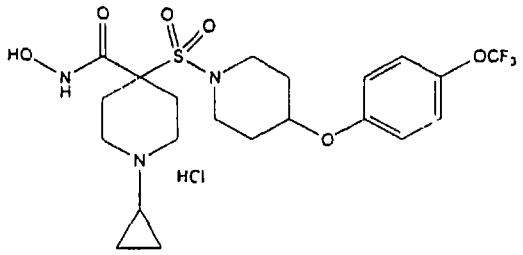
Part 3: Preparation of



To a solution of the zwitterion product in Part 2 (6.8 g, 14 mmol) in dimethylformamide (50 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 5.2 g, 28 mmol) and N-hydroxybenzotriazole hydrate (Aldrich, 3.7 g, 28 mmol), and the mixture was heated to 50°C for 15 minutes. N-methylmorpholine (Aldrich, 2.0 mL, 28 mmol) was added followed by O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (3.2 g, 28 mmol). The mixture stirred and heated for 1 hour then left to stir at room temperature overnight (about 18 hours). After complete reaction, the reaction mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate (250 mL) and washed with 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. The

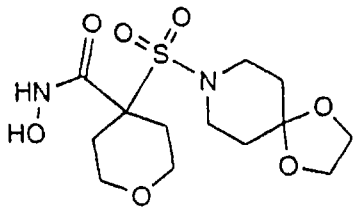
oil was purified on SiO_2 using ethyl acetate in hexane to give 6.5 g of the THP-protected hydroxamate as a clear oil the solidified with addition of methanol. ^1H NMR and mass spectroscopy were consistent with the desired structure.

Part 4: Preparation of



The solid from Part 3 (6.8 g) was slurried in methanol (4.5 mL). To this was added 4 N HCl in dioxane(60 mL), and the mixture stirred for 2 hours, after which RPHPLC showed complete reaction. The dioxane was concentrated by half, diethyl ether was added (100 mL) and the white solid (5.5 g, 90% yield) filtered and dried under vacuum. ^1H NMR showed the desired compound. Mass spectroscopy showed: $C_{21}H_{28}F_3N_3O_6S$ -HCl; M^{+H}_{found} = 543 (M^{+H}_{calc} = 543).

Example 48: Preparation of 4-(1,4-dioxa-8-azaspiro-[4.5]dec-8-ylsulfonyl)tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: 1,4-Dioxa-8-azaspiro[4.5]-decane (Aldrich, 10.0 g, 69.8 mmol) and triethylamine (Aldrich, 14.6 mL, 105 mmol) were slurried in dichloromethane (150 mL) and cooled to zero°C. A

solution of methane sulfonyl chloride (Aldrich, 8.1 mL, 105 mmol) in dichloromethane (60 mL) was slowly added, maintaining the temperature at less than 10°C. After the addition, the ice bath was removed and the reaction stirred 1 hour as it came to ambient temperature. After the disappearance of the starting material, the solvent was removed and the residue was taken up in ethyl acetate (200 mL) and H_2O (50 mL). Once separated, the organic layer was washed with 5% $KHSO_{4\ aq}$ (3x-50 mL) and brine (1x- 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford the sulfonamide as a yellow solid (15.3 g, 99% yield). ^1H NMR showed the desired compound.

Part B: Oven-dried glassware was charged with the sulfonamide of Part A (15.3 g, 69.1 mmol) and tetrahydrofuran (70 mL) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 140 mL, 140 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, 5.4 mL, 69.1 mmol) in tetrahydrofuran (30 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_{aq}, keeping temperature below -20°C. The aqueous phase 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_{aq} (2x-100 mL) and brine (1x-100ml), then dried over Na_2SO_4 and concentrated to afford a yellow oil that slowly solidified. The oily solid was recrystallized from

ethyl acetate and hexanes to afford the methylene ester (8.2 g, 44 % yield). ^{1}H showed the desired compound with some starting material present.

Part C: To a solution of the methylene ester of Part B (3.5 g, 12.5 mmol) and dibromo-diethylether (Lancaster, 1.7 mL, 13.8 mmol) in N,N-dimethylformamide (25 mL) was added 18-Crown-6 (Aldrich, 500 mg, 1.9 mmol), followed by potassium carbonate (Aldrich, 6.0 g, 43.8 mmol). The mixture was heated at 60°C for 4 hours after which more potassium carbonate (1.9 g, 13.7 mmol) was added, and the reaction continued at 60°C for 14 hours. The reaction was worked up by pouring the mixture into stirring 10% HCl_{aq} (200 mL). A gummy solid resulted that was extracted via ethyl acetate (3x- 300 mL). Organics were washed with brine (2x- 200 mL), dried over Na_2SO_4, and concentrated to afford the methyl ester, 9091-157, as a dark brown oil (2.2 g, 50% yield). ^{1}H NMR showed the desired compound.

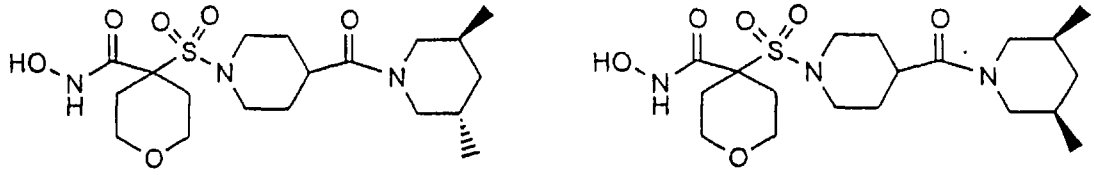
Part D: To a solution of the methyl ester from Part C (2.2 g, 6.3 mmol) in tetrahydrofuran (15 mL) was added potassium trimethylsilonate (Aldrich, 1.9 g, 15.1 mmol). Work up comprised removing the tetrahydrofuran and taking the residue up in H_2O (100 mL). The solution was washed with diethyl ether (50 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 via ethyl acetate (3x-150 mL). The organics were washed with brine (1x- 100 mL), dried over Na_2SO_4, and concentrated to afford the carboxylic acid as a dark oil (1.5 g, 70% yield). ^{1}H NMR showed the desired compound.

Part E: To a solution of the acid of Part D (1.5 g, 4.5 mmol) in dimethylacetamide (10 mL) was added N-methylmorpholine (Aldrich, 1.5 mL, 13.5 mmol), followed by N-hydroxybenzotriazole hydrate (Aldrich, 0.73 g, 5.4 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.77 g, 6.7 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.3 g, 6.7 mmol). The mixture stirred overnight (about 18 hours) and was then stripped of solvent. The residue was taken up in ethyl acetate (300 mL) and water (20 mL). After separation, the organic layer was washed with 5% $KHSO_4$ $_{aq}$ (1x- 200 mL), saturated potassium carbonate (1x-100 mL), and brine (1x-150 mL). The organic layer was then dried over Na_2SO_4 and concentrated to afford the THP-protected hydroxamate, 9091-161, as a brown foam (1.6 g, 76% yield). ^{1}H NMR showed the desired compound.

Part F: The THP-protected hydroxamate of Part E (1.6 g, 3.7 mmol) was dissolved in acetonitrile (15 mL) and stirred with 10% HCl_{aq} (20 mL) for 2 hours. The acetonitrile was removed via N_2 stream giving an oil that was crystallized from t-butylmethylether to afford the hydroxamate as a brown solid (0.82 g, 63% yield). ^{1}H NMR showed the desired compound. HRMS for $C_{13}H_{22}N_2O_7S$ showed M^{+H}_{found} = 351 (M^{+H}_{calc} = 351).

Example 49: Preparation of 4-[[4-[[(3R,5R)-rel-3,5-dimethyl-1-piperidinyl]carbonyl]-1-piperidinyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide and 4-[[4-[[(3R,5S)-rel-3,5-dimethyl-1- piperidinyl]carbonyl]-1-

piperidinyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of N-BOC-isoponic acid (4.0g, 17.4 mmol) in dimethylacetamide (30 mL) were added N-methylmorpholine (Aldrich, 5.7 mL, 52.2 mmol), 3,5-dimethylpiperadine (70% cis, Aldrich, 3.5 mL, 26.1 mmol), N-hydroxybenzotriazole hydrate (Aldrich, 2.8 g, 20.9 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 5.0 g, 26.1 mmol). The mixture was stirred overnight (about 18 hours) at ambient temperature. To work up, the solvent was removed and the residue was taken up in ethyl acetate (300 mL) then washed with 5% $KHSO_{4\ aq}$ (1x 100ml), saturated $K_2CO_{3\ aq}$ (1x 100 mL), and brine (1x 100 mL). After drying over Na_2SO_4, the organic layer was filtered and concentrated to afford the BOC-piperidine as a tan oil that slowly crystallized (5.4 g, 96% yield). ^1H NMR showed the desired compound existing as both the cis- and trans- isomers.

Part B: To a solution of the BOC-piperidine of Part A, (5.4 g, 16.6 mmol) in 1,4-dioxane (20 mL) was added 4 N HCl in 1,4-dioxane (15 mL) and stirred. After 45 minutes, the solvent was removed and the solid was slurried in diethyl ether, filtered, and washed with diethyl ether (2 x 20 mL). Drying

afforded the amine salt as a white solid (2.6 g, 60% yield). ^{1}H NMR showed desired product as both cis- and trans- isomers.

Part C: To a cooled solution (zero°C) of the amine salt of Part B (2.2 g, 9.8 mmol) and triethylamine (Aldrich, 3.4 mL, 24.5 mmol) in dichloromethane (50 mL) was slowly added a solution of methane sulfonyl chloride (Aldrich, 1.1 mL, 14.7 mmol) in dichloromethane (25 mL), maintaining the temperature at less than 10°C. After the addition, the ice bath was removed and the reaction stirred 2 hours as it came to ambient temperature. After the disappearance of the starting material, the solvent was stripped and the residue was taken up in ethyl acetate (100 mL) and H_2O (25 mL). Once separated, the organic layer was washed with 5% $KHSO_{4\ aq}$ (3x-50 mL) and brine (1x- 50 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford the sulfonamide as a dried foamy oil (2.5 g, 83% yield). ^{1}H NMR showed the desired product as both the cis- and trans- isomers.

Part D: Oven-dried glassware was charged with the sulfonamide of Part C (2.5 g, 8.3 mmol) and tetrahydrofuran (17 mL) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 16.5 mL, 16.5 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, 0.64 mL, 8.3 mmol) in tetrahydrofuran (8 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_{aq} (50 mL), keeping temperature at less than -20°C. The aqueous portion froze into a solid chunk of ice. After warming to 5°C, the mixture was extracted with ethyl acetate (3x- 100 mL). Organics were washed with saturated NH_4Cl_{aq} (2x-50 mL) and brine (1x-50 mL), then dried over Na_2SO_4 and concentrated to afford the methylene ester as a brown oil (2.7 g, 90 % crude yield). ^1H showed the desired compound (cis- and trans-).

Part E- To a solution of the methylene ester of Part D (2.7 g, 7.5 mmol) and dibromo-diethylether (Lancaster, 1.0 mL, 8.2 mmol) in N,N-dimethylformamide (15 mL) was added 18-Crown-6 (Aldrich, 200 mg, 1.0 mmol) followed by potassium carbonate (Aldrich, 3.6 g, 26.2 mmol). The mixture was heated at 60°C for 4 hours, after which more potassium carbonate (1.0 g, 7.2 mmol) was added, and the reaction continued at 60°C for 14 hours. The reaction was worked up by pouring the mixture into stirring 10% HCl_{aq} (200 mL). The gummy solid that developed was extracted via ethyl acetate (3x 100 mL). The organics were washed with brine (1x 50 mL), dried over Na_2SO_4, and filtered to afford the methyl ester as a brown oil (3.4 g, quantitative yield). ^1H NMR showed the desired compound (cis- and trans-).

Part F: To a solution of the methyl ester from Part E (3.0 g, 7.0 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 2.2 g, 17.4 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. The work up consisted of stripping the tetrahydrofuran and taking the residue up in H_2O (40 mL). The solution was

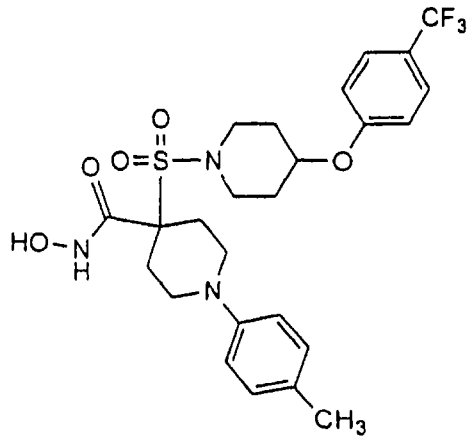
washed with diethyl ether (30 mL). The aqueous composition was then cooled to 0°C and 10% HCl_{aq} was slowly added until pH = 3. The acidic mixture was then extracted via ethyl acetate (3x-100 mL). The organics were washed with brine (1x- 50 mL), dried over Na_2SO_4, and concentrated to give a brown oil (2.4 g). The oil was crystallized from acetone/ diethylether to afford the carboxylic acid as a brown solid (2.2 g, 76% yield). ^1H showed the desired compound as cis- and trans- isomers.

Part G: To a solution of the acid from Part F (2.2 g, 5.3 mmol) in dimethylacetamide (12 mL) were added N-methylmorpholine (Aldrich, 1.7 mL, 15.9 mmol) followed by N-hydroxybenzotriazole hydrate (Aldrich, 0.86 g, 6.4 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.94 g, 8.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.5 g, 8.0 mmol). The mixture stirred overnight and was then stripped of solvent. The residue was taken up in ethyl acetate (250 mL) and washed with 5% $NaHSO_{4\ aq}$ (1x- 150 mL), saturated potassium carbonate (1x-150 mL), and brine (1x-150 mL). The organic was then dried over Na_2SO_4 and concentrated to afford the THP-protected hydroxamate as a brown oil (2.2 g, 81% yield). ^1H NMR showed the desired compound as both isomers.

Part H - The THP-protected hydroxamate of Part G (2.2 g, 3.7 mmol) was dissolved in 1,4-dioxane (10 mL) and stirred with 4 N HCl in 1,4-dioxane (15 mL, 60 mmol) for 2 hours. The solvents were stripped and the residue was taken up in acetonitrile (10 mL) and H_2O (10 mL). This solution was filtered and purified via prep RP LC to afford the cis isomer as a white

solid (0.40 g, 22% yield) and the trans isomer as a white solid (0.20 g, 11%). ^{1}H NMR showed the desired compounds. HRMS for $C_{19}H_{33}N_3O_6S$ showed M^{+H}_{found} = 432 (M^{+H}_{calc} = 432) for both isomers.

Example 50: Preparation of N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A:To a mixture of dibromotriphenylphosphorane (Aldrich, 50 g, 118 mmol) in dichloremethane (200 mL) at zero C was added N,N-bis-(2-hydroxyethyl)-P-toluidine (Fluka, 10.5 g, 54 mmol). A slight exotherm was detected. The ice bath was removed and the reaction stirred eighteen hours at ambient temperature. After completion, the solvent was evaporated affording an oily solid that was purified by silica gel (ethyl acetate) to yield the N,N-bis(2-bromoethyl)-p-toluidine as a white solid (12.6 g, 73% yield). ^{1}H NMR showed the desired compound.

Part B: To a solution of the sulfonamide ester of part D of Example 36 (12.0 g, 31.5 mmol) in N,N-dimethylformamide (63 mL) were added potassium carbonate (Aldrich, 13.0 g, 94.5 mmol), 18-crown-6 (Aldrich, 500 mg, 2.0 mmol), and N,N-bis(2-bromoethyl)-p-toluidine of Part A (10.0 g, 31.5 mmol). The mixture was heated at 80°C for 18 hours after which more potassium carbonate (1.0 g, 7.2 mmol) was added, and the reaction continued at 80°C for 3 hours. The reaction was worked up by removing the solvent by roto-evaporation. The residue was slurried in ethyl acetate and filtered through a Celite® pad. The filtrate was concentrated and the residue crystallized from hot methanol to afford the methyl ester as a yellow solid (9.0 g, 53% yield). ^{1}H and ^{19}F NMR showed the desired compound.

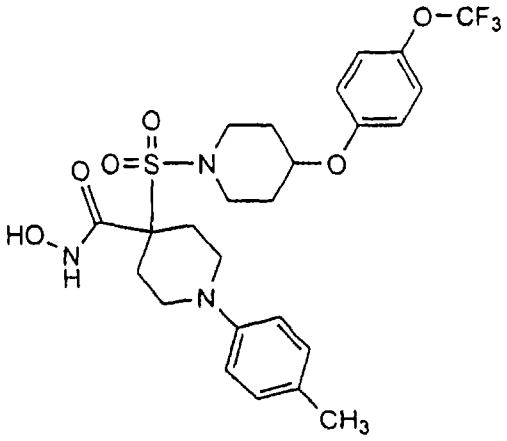
Part C: To a solution of the methyl ester of Part B (9.0 g, 16.6 mmol) in tetrahydrofuran (40 mL) was added potassium trimethylsilonate (Aldrich, 6.4 g, 50 mmol). The reaction stirred overnight (about 18 hours) at ambient temperature. Work up comprised stripping the tetrahydrofuran and taking the residue up in H_2O (5 mL), cooling to zero°C, and titrating to pH 7 via 6 N HCl. Solids formed and were collected then washed with diethyl ether. The solid was dried in vacuo to afford the carboxylic acid as a white solid (8.7 g, 100% yield). ^{1}H and ^{19}F NMR showed the desired compound.

Part D: To a solution of the carboxylic acid of Part C (8.7 g, 16.5 mmol) in N,N-dimethylformamide (35 mL) was added N-methylmorpholine (Aldrich, 5.4 mL, 49.5 mmol) followed by N-hydroxybenzotriazole hydrate (Aldrich, 2.7 g, 19.8 mmol), O-(tetrahydro-

2H-pyran-2-yl) hydroxylamine (3.9 g, 33 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 4.7 g, 24.8 mmol). The mixture stirred at 40 C for 4 hours and was then stripped of solvent. The residue was taken up in ethyl acetate/water (350 mL/50 mL). After separation, the aqueous layer was extracted with ethyl acetate (2x-50 mL). The combined organic layers were washed with 5% $KHSO_{4aq}$ (1x- 30 mL) and brine (1x-30 mL). The organic layer was then dried over Na_2SO_4 and concentrated yielding an orange oily foam that was recrystallized from methanol to afford the THP-protected hydroxamate as a white solid (0.74 g, 64% yield). ^1H and ^{19}F NMR showed the desired compound.

Part E: The THP-protected hydroxamate of Part D (8.9 g,14.2 mmol) was wetted with methanol (3.6 mL) and stirred with 4 N HCl in dioxane (36 mL) for one hour. The solvents were evaporated and the oil slurried in diethyl ether to yield a solid which was filtered and dried. This afforded hydroxamate as a white solid (8.0 g, 98% yield). ^1H and ^{19}F NMR showed the desired compound. HRMS for $C_{25}H_{30}F_3N_3O_5S$ showed M^{+H}_{found} = 542 (M^{+H}_{calc} = 542).

Example 51: Preparation of N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoro-methoxy)phenoxy]-1-piperidinyl]-sulfonyl]-4-piperidinecarboxamide, monohydrochloride



Part A: To a solution of N,N-bis(2-hydroxyethyl)-p-toluidine (Fluka, 30 g, 154 mmol) in dichloromethane (100 mL) was slowly added a solution of thionylchloride (Aldrich, 36 mL, 462 mmol) in dichloromethane (300 mL). The reaction was stirred for 2 hours at ambient temperature then heated for 1 hour at reflux. After removing the solvent, the residue was slurried in ethyl acetate. The ethyl acetate was decanted, then the residue was slurried in hexanes giving a solid precipitate. The solid was filtered and washed with hexanes followed by diethyl ether. The solid was dried to afford the N,N-bis(2-dichloroethyl)-p-toluidine monochloride salt as a gray solid (24 g, 58% yield). ^1H showed the desired compound.

Part B: The N,N-bis(2-dichloroethyl)-p-toluidine monochloride salt of Part A was suspended in water (200 mL) and neutralized (pH 7) with saturated sodium bicarbonate. This was then extracted with a mixture of diethyl ether (200 mL) and ethyl acetate (50 mL) which dissolved all solids. The organic layer was washed with brine (1x-100 mL) then dried over Na_2SO_4, filtered and concentrated to

give the free base amine as a brown oil (6.59 g, 28.39 mmol). The oil was dissolved in 4-methyl-2-pentanone (50 mL) and lithium bromide (Aldrich, 24.66 g, 283.90 mmol) was added. The mixture was heated at reflux for 39 hours. After cooling, the dark mixture was filtered through a Celite pad. After washing the pad, the total filtrate was concentrated. The residue was partitioned between diethyl ether (100 mL) and water (50 mL). The organic layer was washed with water (50ml), brine (50 mL), then dried over Na_2SO_4 and concentrated to afford the dibromo-amine as a brown oil (7.82 g, 86% yield). ^1H showed the desired compound. LCMS showed mixture of dibromo- and monochloro/monobromo compounds.

Part C: To a slurry of 4-hydroxypiperadine (Aldrich, 273 g, 2.7 mol) in tetrahydrofuran (1.8 L) was added triethylamine (Aldrich, 402 mL, 2.9 mol), followed by slow addition of a solution of di-tert-butyl-dicarbonate (Aldrich, 600 g, 2.7 mol) in tetrahyrdofuran (1.2 L). The temperature was monitored and maintained below 32°C. The mixture was stirred for 4 hours before working up. Work up comprised removing the tetrahydrofuran by roto-evaporation and taking the residue up in ethyl acetate (300 mL). The organic was washed with 5% $KHSO_{4\ aq}$ (2x-1 L) and brine (1x-1 L) then dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a crude brown oil. The oil was crystallized from hexanes providing the N-BOC-4-hydroxypiperidine as a tan solid (515 g, 95% yield). ^1H NMR showed the desired compound.

Part D: To a slurry of the N-BOC-4-hydroxypiperidine of Part C (515 g, 2.6 mol) and

triethylamine (390 mL, 2.8 mol) in dichloromethane (1.9 L) cooled to zero°C under N_2 was slowly added a solution of methane sulfonyl chloride (Aldrich, 209 mL, 2.7 mol) in dichloromethane (100 mL). After the addition, the ice bath was removed and the reaction stirred 24 hours. Work up comprised removing the solvent by roto-evaporation and taking the residue up in ethyl acetate (2.0 L) then washing with H_2O (2x- 1 L), brine (1x- 1 L), and drying over Na_2SO_4. The mixture was filtered and concentrated to afford the piperidine mesylate, SC 80998, as a cream colored solid (662 g, 91% crude yield). ^1H NMR showed the desired compound.

Part E: Oven-dried glassware was charged with 4-trifluoromethoxyphenol (Apollo, 100.0 g, 561 mmol) and N,N-dimethylformamide (1.12 L). After cooling to -5 °C, NaH (Aldrich, 60% oil dispersion, 11.2 g, 281 mmol) was slowly added. The ice bath was removed and the reaction stirred for 1.5 hours. The piperidine mesylate of Part D (78.4 g, 281 mmol) was then added and the reaction was heated to 80 °C for 2 hours. This process was repeated until a total of 2.5 equivalents (1.4 moles) of both the piperidine mesylate and NaH were added. Work up consisted of stripping the solvents by roto-evaporation and taking the residue up in diethyl ether (1 L) and H_2O (400 mL). The layers were separated and the organic layer was washed with H_2O (1x-500 mL) and brine (2x- 500 mL) then dried over Na_2SO_4, filtered, and concentrated to afford the BOC-piperidine, SC 83075, as a crude oil (315 g, 100+% crude yield). ^1H NMR showed the desired compound along with the elimination byproduct, 1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridine.

Part F: To an overhead-stirring solution of 4 N HCl in dioxane (1.4 L, 5.6 mol) was poured the crude oil of the BOC-piperidine of Part E (203 g, 561 mmol). The solvents were then stripped and the residue was slurried in diethyl ether and filtered. The solid was dissolved in H_2O (500 mL) and titrated to pH 10 with saturated potassium carbonate aqueous solution. The aqueous was extracted with dichloromethane (3x-800ml). The organics were combined, dried over Na_2SO_4, filtered and concentrated to afford the piperidine, 10507-054, as a foamy solid (136 g, 93% yield). ^1H NMR showed the desired compound.

Part G: The piperidine of Part F (136 g, 520 mmol) and triethylamine (Aldrich, 110 mL, 781 mmol) were slurried in dichloromethane (1.6 L) and cooled to zero°C. A solution of methane sulfonyl chloride (Aldrich,, 60.2 mL, 781 mmol) in dichloromethane (200 mL) was slowly added, maintaining the temperature at less than 10°C. After the addition, the ice bath was removed and the reaction came to ambient temperature. After one hour, the starting material was gone. To work up, the solvent was stripped and the residue was taken up in ethyl acetate (1 L) and H_2O (1 L). Once separated, the aqueous layer was extracted with ethyl acetate (2x- 400 mL). The combined organic layers were washed with 5% $KHSO_{4\ aq}$ (2x-600 mL) and brine (1x-600 mL). The organic layers were then dried over Na_2SO_4, filtered, and concentrated to afford the piperidine mesylate, SC 80766, as a brown solid (139 g, 79% yield. ^1H NMR showed the desired compound.

Part H: Oven-dried glassware was charged with the piperidine mesylate of Part G (92 g, 271 mmol)

and tetrahydrofuran (600 mL) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 705 mL, 705 mmol) was slowly added, keeping temperature below -60°C. The reaction was stirred for 30 minutes after the addition and was then charged with a solution of methyl chloroformate (Aldrich,27.4 mL, 325 mmol) in tetrahydrofuran (100 mL) again keeping the temperature below -60°C. After stirring for 1 hour at -75°C, the reaction was quenched with saturated NH_4Cl_{aq}, keeping temperature below -20°C. The aqueous phase 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_{aq} (2x-100 mL) and brine (1x-100ml), then dried over Na_2SO_4 and concentrated to afford a tan oil. The oil was crystallized from methanol. The solid was collected and washed with hexanes to afford the methylene ester as a tan solid (78 g, 72%). ^1H NMR showed the desired compound with some starting material present.

Part I: To a mixture of the methylene ester of Part H (4.0 g, 10.0 mmol), potassium carbonate (Aldrich, 4.1 g, 30.0 mmol), and 18-crown-6 (Aldrich, 0.1 g, .04 mmol) in N,N-dimethylformamide (20 mL) was added the dibromo-amine of Part B (3.2 g, 10.0 mmol). The mixture was heated at 80°C for 18 hours, after which more potassium carbonate (1.5 g, 12 mmol) was added, and the reaction continued at 80°C for 14 hours. The reaction was worked up by removing the solvent by roto-evaporation. The residue was slurried in acetonitrile and filtered through a Celite pad. The filtrate was concentrated and the residue was purified on silica gel (ethyl

acetate/hexanes) to afford the methyl ester as an orange solid (2.6 g, 46% yield). ^{1}H and ^{19}F NMR showed the desired compound.

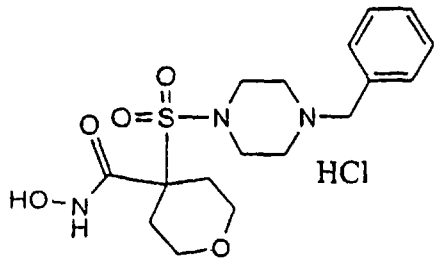
Part J: To a solution of the methyl ester of Part I (2.1 g, 3.8 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilonate (Aldrich, 1.4 g, 11.3 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. Work up comprised removing the tetrahydrofuran and taking the residue up in H_2O (5 mL), cooling to zero°C, and titrating to pH 7 with 6 N HCl. Solids formed and were collected then washed with acetonitrile. The solid was dried in vacuo to afford the carboxylic acid, X14137, as a tan solid (1.0 g, 50% yield). ^{1}H and ^{19}F NMR showed the desired compound.

Part K: To a solution of the carboxylic acid of Part J (1.0 g, 1.8 mmol) in N,N-dimethylformamide (5 mL) was added N-methylmorpholine (Aldrich, 0.6 mL, 5.5 mmol) followed by N-hydroxybenzotriazole hydrate (Aldrich, 0.29 g, 2.2 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.42 g, 3.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 0.52 g, 2.7 mmol). The mixture was stirred at 40 C for 8 hours and was then stripped of solvent. The residue was taken up in ethyl acetate/water (50 mL/10 mL). After separation, the aqueous layer was extracted with ethyl acetate (2x-20 mL). The combined organic layers were washed with 5% $NaHSO_{4\ aq}$ (1x- 30 mL) and brine (1x-30 mL). The organic was then dried over Na_2SO_4 and concentrated yielding an orange oily foam that was recrystallized from methanol to afford the THP-protected hydroxamate

as a white solid (0.74 g, 64% yield). ^{1}H and ^{19}F NMR showed the desired compound.

Part L: The protected hydroxamate of Part K (0.7 g, 1.1 mmol) was dissolved in methanol (0.5 mL) and stirred with 4 N HCl in dioxane (2.8 mL) for one hour. After which, LC showed no more starting material. The solvents were evaporated and the oil slurried in diethyl ether to yield a solid which was filtered and dried. This afforded the hydroxamate, as a white solid (0.6 g, 92% yield). ^{1}H and ^{19}F NMR showed the desired compound. HRMS for $C_{25}H_{30}F_3N_3O_6S$ showed M^{+H}_{found} = 558 (M^{+H}_{calc} = 558).

Example 52 : Preparation of tetrahydro-N-hydroxy-4-[[4-(phenylmethyl)-1-piperazinyl]-sulfonyl]-2H-pyran-4-carboxamide, monohydrochloride



Part A: To a cooled solution, zero C, of N-benzylpiperazine (Aldrich, 10.0 g, 56.7 mmol) in dichloromethane (75 mL) was added triethylamine (Aldrich, 11.9 mL, 85.1 mmol), followed by the slow addition of a solution of methane sulfonyl chloride (Aldrich, 6.6 mL, 85.1 mmol) in dichloromethane (25 mL). After the addition, the ice bath was removed and the reaction stirred at ambient temperature for

1.5 hours. Once completed, the solvent was evaporated and the residue was taken up in ethyl acetate (200 mL) and water (100 mL). The phases were separated and the aqueous phase was treated with 1 N $NaOH_{aq}$ (100 mL), then extracted with ethyl acetate (2x-200 mL). The combined organic layers were washed with 5% $KHSO_{4\ aq}$ (2x- 100 mL) and brine (1x- 100 mL). The ethyl acetate was then dried over Na_2SO_4 and concentrated to afford the piperazine mesylate, as an orange solid (13.0 g, 90% yield). ^1H NMR showed the desired compound.

Part B: Oven-dried glassware was charged with the piperazine mesylate of Part A (12.6 g, 50 mmol) and tetrahydrofuran (160 mL) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 165 mL, 165 mmol) was slowly added, keeping temperature at 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, 3.9 mL, 94.5 mmol) in tetrahydrofuran (80 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_{aq}, keeping temperature below -20°C. The aqueous portion froze into a solid chunk of ice. After warming to 5°C, the mixture was extracted with ethyl acetate (3x- 200 mL). Organics were washed with saturated NH_4Cl_{aq} (2x-100 mL) and brine (1x-100ml), then dried over Na_2SO_4 and concentrated to afford the methylene ester as a brown oil (19.6 g, quantitative yield). ^1H NMR showed the desired compound.

Part C: To a solution of the methylene ester of Part B (10.0 g, 32.0 mmol), potassium carbonate

(Aldrich, 15.5 g, 112 mmol), and 18-crown-6 (Aldrich, 0.5 g, 2.0 mmol) in dimethylformamide (60 mL) was added dibromo-diethylether (Lancaster, 4.4 mL, 35.3 mmol). The mixture was heated at 60°C for 18 hours, after which more potassium carbonate (1.5 g, 12 mmol) was added, and the reaction continued at 60°C for 4 hours. The reaction was worked up by removing the solvent by roto-evaporation. The residue was taken up in ethyl acetate (250 mL) and water (100 mL). The layers were separated and the organic was washed with water (1x-100 mL) and brine (2x- 100 mL) then dried over Na_2SO_4 and concentrated to afford a black oil. The oil was purified via silica gel (ethyl acetate/hexanes) yielding the methyl ester as a yellow oil (7.3 g, 60% yield). ^1H NMR showed the desired compound.

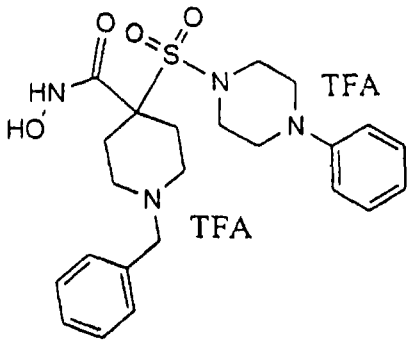
Part D: To a solution of the methyl ester of Part C (3.5 g, 9.2 mmol) in tetrahydrofuran (20 mL) was added potassium trimethylsilonate (Aldrich, 3.5 g, 27.4 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. Work up comprised removing the tetrahydrofuran and taking the residue up in H_2O (8 mL), cooling to zero°C, and titrating to pH 7 with 6 N HCl. Solids formed and were collected and washed with water followed by diethyl ether. The solid was dried in vacuo to afford the carboxylic acid as an off white solid (0.75 g, 22% yield). ^1H NMR showed the desired compound.

Part E: To a solution of the carboxylic acid of Part D (0.75 g, 2.0 mmol) in dimethylacetamide (5 mL) was added N-methylmorpholine (Aldrich, 0.66 mL, 6.0 mmol) followed by N-hydroxybenzotriazole hydrate

(Aldrich, 0.32 g, 2.4 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.35 g, 3.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 0.57 g, 3.0 mmol). The mixture was stirred at 40 C for thirteen hours and was then stripped of solvent. The residue was purified by reverse phase chromatography (carbon-18, acetonitrile/water). The product was hydrolyzed on the column giving the hydroxamate as a white solid (0.54 g, 57% yield). ^{1}H and ^{19}F NMR showed the desired compound but as the trifluoracetic acid salt.

Part F: The hydroxamate of Part E (0.5 g,1.0 mmol) was dissolved in 1,4-dioxane (3.0 mL) and stirred with 4 N HCl in dioxane (4 mL) for one hour. The solvent volume was reduced in half then diethyl ether was added, providing a solid that was filtered and washed with excess diethyl ether. The solid was dried to afford the hydrochloride salt as a white solid (0.4 g, 100% yield). ^{1}H NMR showed the desired compound. HRMS for $C_{17}H_{25}F_3N_3O_5S$ showed M^{+H}_{found} = 384 (M^{+H}_{calc} = 384).

Example 53: Preparation of N-hydroxy-1-(phenylmethyl)-4-[(4-phenyl-1-piperazinyl)sulfonyl]-4-piperidine-carboxamide, bis(trifluoroacetate)



Part A: To a cooled solution, zero C, of N-phenylpiperazine (Aldrich, 10.0 g, 61.6 mmol) in dichloromethane (75 mL) was added triethylamine (Aldrich, 12.9 mL, 92.4 mmol) followed by the slow addition of a solution of methane sulfonyl chloride (Aldrich, 7.1 mL, 92.4 mmol) in dichloromethane (25 mL). After the addition, the ice bath was removed and the reaction stirred at ambient temperature for 1.5 hours. Once completed, the solvent was evaporated and the residue was taken up in ethyl acetate (200 mL) and water (100 mL). The phases were separated and the aqueous phase was treated with 1 N $NaOH_{aq}$ (100 mL) then extracted with ethyl acetate (2x- 200 mL). The combined organic layers were washed with 5% $KHSO_{4\ aq}$ (2x- 100 mL) and brine (1x- 100 mL). The ethyl acetate was then dried over Na_2SO_4 and concentrated to afford the piperazine mesylate, SC 80658, as solid (13.0 g, 88% yield). ^1H NMR showed the desired compound.

Part B: Oven-dried glassware was charged with the piperazine mesylate of Part A (12.6 g, 52.4 mmol) and tetrahydrofuran (160 mL) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 184 mL, 184 mmol) was slowly added, keeping temperature below -60°C. The reaction was stirred for 30 minutes after the addition and was

then charged with a solution of methyl chloroformate (Aldrich, 4.1 mL, 52.4 mmol) in tetrahydrofuran (80 mL) again keeping the temperature below -60°C. After stirring for 1 hour at -75°C, the reaction was quenched with saturated NH_4Cl_{aq} , keeping temperature below -20°C. The aqueous does freeze 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_{aq} (2x-100 mL) and brine (1x-100ml), then dried over Na_2SO_4 and concentrated to afford the methylene ester, 9091-195, as a brown oil (14.1 g, 90%) ^1H NMR showed the desired compound.

Part C: To a solution of the methylene ester of Part B (4.3 g, 14.4 mmol), potassium carbonate (Aldrich, 6.0 g, 43.2 mmol), and 18-crown-6 (Aldrich, 0.5 g, 2.0 mmol) in dimethylformamide (30 mL) was added N,N-bis(2-chloroethyl)-benzylamine, SC 9275A, (3.5 mL, 15.1 mmol). The mixture was heated at 60°C for 18 hours. The reaction was worked up by removing the solvent by roto-evaporation. The residue was taken up in ethyl acetate (250 mL) and washed with water (1x-100 mL) and brine (2x- 100 mL) then dried over Na_2SO_4 and concentrated to afford an orange solid. The solid was purified via silica gel (ethyl acetate/hexanes) yielding the methyl ester as a yellow solid (5.6 g, 85% yield). ^1H NMR showed the desired compound.

Part D: To a solution of the methyl ester of Part C (2.0 g, 4.4 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilonate (Aldrich, 1.7 g, 13.2 mmol). The reaction was stirred overnight (about 18 hours) at ambient temperature. Work up

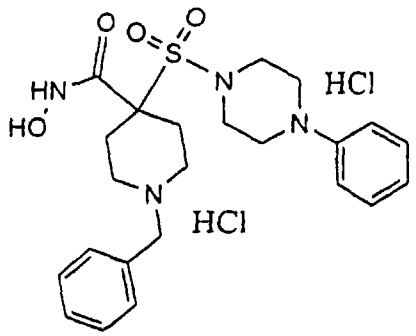
comprised removing the tetrahydrofuran and taking the residue up in H_2O (8 mL), cooling to zero°C, and titrating to pH 6 with 6 N HCl. Solids formed and were collected, then washed with water followed by diethyl ether. The solid was dried in vacuo to afford the carboxylic acid as an off white solid (1.6 g, 84% yield). ^1H NMR showed the desired compound.

Part E: To a solution of the carboxylic acid of Part D (1.6 g, 3.6 mmol) in dimethylacetamide (8 mL) was added N-methylmorpholine (Aldrich, 1.2 mL, 10.8 mmol) followed by by N-hydroxybenzotriazole hydrate (Aldrich, 0.58 g, 4.3 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.84 g, 7.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 1.0 g, 5.4 mmol). The mixture stirred overnight at ambient temperature and was then stripped of solvent. The residue was taken up in ethyl acetate (100 mL) then washed with aqueous saturated sodium bicarbonate (2x-50 mL) and brine (3x-50 mL). The organic was dried over Na_2SO_4 concentrated to afford the tetrahydropyran-protected hydroxamate as an oily foam (1.9 g, 95% yield). ^1H NMR showed the desired compound.

Part F: The tetrahydropyran-protected hydroxamate of Part E (1.6 g, 2.9 mmol) was dissolved in 1,4-dioxane (10.0 mL) and stirred with 4 N HCl in dioxane (12 mL) for 30 minutes. A solid formed that was filtered, washed with diethyl ether and dried. The solid was then purified by reverse phase chromatography (acetonitrile/water) affording the hydroxamate as a tan solid (1.4 g, 70% yield). ^1H

and ^{19}F NMR showed the desired compound. HRMS for $C_{23}H_{30}N_4O_4S$ showed M^{+H}_{found} = 439 (M^{+H}_{calc} = 439).

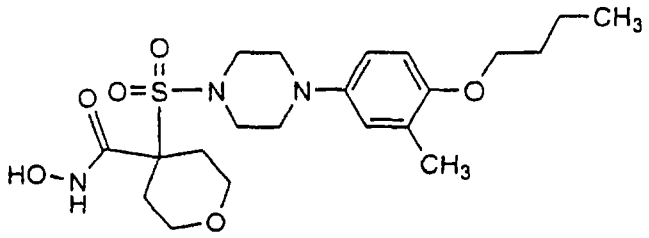
Example 54: Preparation of N-hydroxy-1-(phenylmethyl)-4-[(4-phenyl-1-piperazinyl)sulfonyl]-4-piperidine-carboxamide, dihydrochloride



Part A: The hydroxamate of Example 53 was dissolved in water (10 mL) and titrated to pH 10 via 1.0 N NaOH. The mixture was extracted with ethyl acetate (4x-20 mL). The organics were combined, dried over Na_2SO_4, and concentrated to afford a foamy solid. This solid was dissolved in acetonitrile (5 mL) and then concentrated HCl (1 mL) was dripped in slowly. The mixture was stirred for ten minutes and then was concentrated to a tan oil. The oil was triturated with diethyl ether to form a solid that was dried *in vacuo* to afford the hydrochloride hydroxamate as a yellow solid (0.82 g, 53 % yield). ^1H and ^{19}F NMR showed the desired compound. HRMS for $C_{23}H_{30}N_4O_4S$ showed M^{+H}_{found} = 439 (M^{+H}_{calc} = 439).

Example 55: Preparation of 4-[[4-(4-butoxy-3-methylphenyl)-1-piperazinyl]sulfonyl]-

tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



Part A: To a solution of 4-bromo-2-methylphenol (Transworld, 10.0 g, 53.5 mmol) in acetone (105 mL) was added potassium carbonate (Aldrich, 16.6 g, 120 mmol) followed by 1-iodobutane (7.3 mL, 64.2 mmol). The reaction stirred at reflux for 12 hours. After cooling to ambient temperature, the mixture was filtered through a Celite® pad. The filtrate was concentrated giving a yellow oil which was purified on silica gel (ethyl acetate/hexanes) to afford the bromophenyl ether, SC 83965, as a clear oil (10.8 g, 83 % yield). ^{1}H NMR showed the desired compound. HRMS for $C_{11}H_{15}BrO$ showed M^{+H}_{found} = 244 (M^{+H}_{calc} = 244).

Part B: To a solution of the bromophenyl ether of Part A (10.0 g, 41.1 mmol) in toluene (80 mL) was added 1-tert-butylcarbonylpiperazine (Lancaster, 9.2 g, 49.4 mmol) and sodium tert-butoxide (Fluka, 5.5 g, 57.5 mmol). The reaction stirred at ambient temperature for twenty minutes. BINAP (Aldrich, 0.8 g, 1.2 mmol) and tris(dibenzylideacetone)dipalladium (0) (Aldrich, 0.4 g, 0.4 mmol) were then added and the reaction was stirred at 80°C until the bromide was exhausted. Work up comprised cooling the mixture to ambient temperature, filtering through a Celite® pad,

mesylate as a tan solid (3.1 g, 78% yield). ^{1}H NMR showed the desired compound.

Part E: Oven-dried glassware was charged with the piperazine mesylate of Part D (3.1 g, 9.5 mmol) and tetrahydrofuran (20 mL) and cooled to -75°C. Lithium bis(trimethylsilyl)amide (Aldrich, 1.0 M in tetrahydrofuran, 28.5 mL, 28.5 mmol) was slowly added, keeping temperature below -60°C. The reaction was stirred for 30 minutes after the addition and was then charged with a solution of methyl chloroformate (Aldrich,0.8 mL, 10 mmol) in tetrahydrofuran (10 mL) again keeping the temperature below -60°C. After stirring for 1 hour at -75°C, the reaction was quenched with saturated NH_4Cl_{aq} , keeping temperature less than -20°C. The aqueous phase froze into a solid chunk of ice. After warming to 5°C, the mixture was extracted via ethyl acetate (3x- 100 mL). Organics were washed with saturated NH_4Cl_{aq} (2x-100 mL) and brine (1x-100ml), then dried over Na_2SO_4 and concentrated to give a brown solid that was recrystallized from methanol to afford methylene ester as a yellow solid (1.3 g, 36%) ^{1}H NMR showed the desired compound.

Part F: To a solution of the methylene ester of Part E (1.3 g, 3.4 mmol), potassium carbonate (Aldrich, 1.4 g, 10.2 mmol), and 18-crown-6 (Aldrich, 0.08 g, 8 mmol) in N,N-dimethylformamide (10 mL) was added dibromo-diethylether (Lancaster, 0.5 mL, 3.6 mmol). The mixture was heated at 60°C for 18 hours and then worked up by removing the solvent by roto-evaporation. The residue was dissolved in ethyl acetate (250 mL) and water (100 mL). The layers were separated and the aqueous was extracted with ethyl

acetate (2x-100 mL). The organics were combined and washed with 5% HCl_{aq} (1x- 50 mL), water (1x-100 mL), and brine (2x- 100 mL) then dried over Na_2SO_4 and concentrated to afford a brown oil that was washed with hexanes to afford the methyl ester as an oil (1.5 g, quantitative yield). ^1H NMR showed the desired compound.

Part G: To a solution of the methyl ester of Part F (1.5 g, 3.3 mmol) in tetrahydrofuran (10 mL) was added potassium trimethylsilonate (Aldrich, 1.3 g, 9.9 mmol). The was stirred overnight (about 18 hours) at ambient temperature. Work up comprised removing the tetrahydrofuran and taking the residue up in H_2O (8 mL). The aqueous was washed with diethyl ether, which resulted in an emulsion. The emulsion was filtered affording a gummy solid that was slurried in acetone to give the carboxylic acid as a white powder (0.71 g, 51% yield). ^1H NMR showed the desired compound.

Part H: To a solution of the carboxylic acid of Part G (0.7 g, 1.6 mmol) in N,N-dimethylformamide (5 mL) was added N-methylmorpholine (Aldrich, 0.5 mL, 4.8 mmol), followed by by N-hydroxybenzotriazole hydrate (Aldrich, 0.27 g, 2.0 mmol), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.37 g, 3.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 0.46 g, 2.4 mmol). The mixture was stirred at 40 C for 8 hours, and was then stripped of solvent. The residue was purified by reverse phase chromatography (carbon-18, acetonitrile/water). After removing the acetonitrile from the desired fractions by roto-evaporation, the aqueous layer was extracted with ethyl acetate (2x-100 mL). The

organics were dried over Na_2SO_4 and concentrated to afford the tetrahydropyran(THP)-protected hydroxamate as a white solid (0.57 g, 66% yield). ^1H NMR showed the desired compound.

Part F: To the tetrahydropyran-protected hydroxamate of Part E (0.6 g,1.0 mmol) was added methanol (0.2 mL) and 4 N HCl in dioxane (2.5 mL) and the mixture was stirred for one hour. The solvent was stripped and the residue was slurried in diethyl ether to provide a solid that was filtered and washed with excess diethyl ether. The solid was dried to afford the hydroxamate as a white solid (0.12 g, 26% yield). ^1H NMR showed the desired compound. HRMS for $C_{21}H_{33}N_3O_6S$ showed M^{+H}_{found} = 456 (M^{+H}_{calc} = 456).

Example 56: *In Vitro* Metalloprotease Inhibition

The compounds prepared in the manner described in the Examples above were assayed for activity by an *in vitro* assay. Following the procedures of Knight et al., *FEBS Lett.* 296(3):263 (1992). Briefly, 4-aminophenylmercuric acetate (APMA) or trypsin-activated MMPs were incubated with various concentrations of the inhibitor compound at room temperature for 5 minutes.

More specifically, recombinant human MMP-13 and MMP-1 enzymes were prepared in laboratories of the assignee following usual laboratory procedures. MMP-13 from a full length cDNA clone was expressed as a proenzyme using a baculovirus as discussed in V.A. Luckow, Insect Cell Expression Technology, pages 183-218, in Protein Engineering: Principles and Practice, J.L.Cleland et al eds., Wiley-Liss, Inc., (1996). See, also, Luckow et al., *J. Virol.*, 67:4566-4579

and dimethyl sulfoxide (DMSO) at a final concentration of 1 percent was used to dissolve inhibitor compound.

The assayed inhibitor compound in DMSO/buffer solution was compared to an equal amount of DMSO/buffer with no inhibitor as control using Microfluor™ White Plates (Dynatech). The inhibitor or control solution was maintained in the plate for 10 minutes and the substrate was added to provide a final concentration of 4 μM.

In the absence of inhibitor activity, a fluorogenic peptide was cleaved at the gly-leu peptide bond, separating the highly fluorogenic peptide from a 2,4-dinitrophenyl quencher, resulting in an increase of fluorescence intensity (excitation at 328 nm/emission at 415 nm). Inhibition was measured as a reduction in fluorescent intensity as a function of inhibitor concentration, using a Perkin Elmer L550 plate reader. The IC_{50} values were calculated from those values. The results are set forth in the Inhibition Table below, reported in terms of IC_{50} to three significant figures, where appropriate.

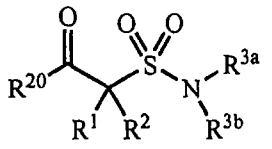
Example	MMP-1	MMP-2	MMP-3	MMP-7	MMP-8	MMP-9	MMP-13	MMP-14
27	<10,000	5,300	-	-	-	-	670	-
28	<10,000	0.3	270	-	4.3	1.8	1.0	360
29	-	-	-	-	-	-	-	-
30	4,000	0.3	28.6		1.6	1.0	0.9	45.5
31	<10,000	1.3	100	-	22.0	100	0.8	2,100
32	<10,000	<0.1	-	-	-	-	<0.1	-
33	2,400	4.4	-	-	-	-	22.2	-
34	<10,000	27.0	-	-	-	-	200	-
35	<10,000	<0.1	210	-	14.8	0.6	<0.1	540
36	<10,000	0.2	-	-	-	-	1.4	-
37	<10,000	300	-	-	-	-	190	-
38	<10,000	3.0	66.4	-	136	2.7	0.8	<10,000
39	<10,000	3,700	-	-	-	-	290	-
40	7,300	8.3	-	-	-	-	13.9	-
41	<10,000	5.0	-	-	-	-	3.7	-
42	5,300	0.1	37.3	<10,000	1.6	1.3	0.3	40.0
43	6,000	0.2	165	-	3.4	1.0	1.4	220
44	7,700	0.2	-	-	-	-	0.7	-
45	-	-	-	-	-	-	-	-
46	<10,000	0.25	-	-	-	-	0.6	-
47	<10,000	<0.1	46.9	<10,000	1.8 1.6	0.48	<0.1	83.1
48	370	200	-	-	-	-	42.5	-
49	<10,000	<10,000	-	-	-	-	<10,000	-
50	<10,000	0.4	-	-	-	-	3.0	-
51	<10,000	<0.1	3,500	-	13.0	9.0	0.3 <0.1	9,000
52	<10,000	115	-	-	-	-	195	-
53	3,500	4.4	-	-	-	-	13.5	-
54	6,000	12.8	-	-	-	-	33.0	-
55	<10,000	2.7	-	-	-	-	4.2	-

5

From the foregoing, it will be observed that numerous modifications and variations can be effected without departing from the true spirit and scope of the novel concepts of the present invention. It is to be understood that no limitation with respect to the specific example presented is intended or should be inferred. The disclosure is intended to cover by the appended claims all such modifications as fall within the scope of the claims.

1. A compound or a pharmaceutically-acceptable salt thereof, wherein:

the compound corresponds in structure to formula II:



II ;

as to R^1 and R^2:

R^1 and R^2, together with the carbon to which they are bonded, form heterocyclo or cycloalkyl, wherein:

the heterocyclo or cycloalkyl optionally is substituted with up to three independently selected R^x substituents, or

R^1 and R^2 are independently selected from the group consisting of hydrido, alkyl, alkyloxyalkyl, alkylthioalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkyloxyalkyl, aryloxyalkyl, arylthioalkyl, arylalkylthioalkyl, cycloalkyl, bicycloalkyl, cycloalkenyl, cycloalkylalkyl, bicycloalkylalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, bicycloalkyloxyalkyl, cycloalkylthioalkyl, bicycloalkylthioalkyl, cycloalkylalkylthioalkyl, bicycloalkylalkylthioalkyl, heterocyclo, heterocycloalkyl, heteroaryl, biarylalkyl, arylalkenyl, arylalkynyl, heterocycloalkylthio, heterocycloalkyloxyalkyl, heteroarylalkenyl, and heteroarylalkyloxyalkyl, wherein:

any such substituent other than hydrido optionally is substituted with up to three independently selected R^x substituents; and

only one of R^1 and R^2 may be hydrido;

each R^x is independently selected from the group consisting of aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, R^cR^d-amino, R^cR^d-aminoalkyl, nitro, nitroso, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, alkoxyalkyl, R^c-oxyalkyl, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, alkyloxycarbonyl-R^c-amino, arylalkyloxycarbonyl-R^c-amino, aryloxycarbonyloxy, carboxy, R^cR^d-aminocarbonyloxy, R^cR^d-aminocarbonyl,

R^cR^d-aminoalkylcarbonyl, hydroxy-R^c-aminocarbonyl, R^cR^d-aminosulfonyl, arylsulfonyl(R^c)amino, R^cR^d-aminoalkoxy, R^cR^d-aminocarbonyl(R^c)amino, trifluoromethylsulfonyl(R^c)amino, heteroarylsulfonyl-(R^c)amino, alkylsulfonyl, arylsulfonyl(R^c)amino, arylsulfonyl(R^c)aminocarbonyl, alkylsulfonyl(R^c)amino, arylcarbonyl(R^c)aminosulfonyl, and alkylsulfonyl (R^c)aminocarbonyl;

each R^c and R^d is independently selected from the group consisting of hydrido, alkylcarbonyl, arylalkyl, arylcarbonyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, thioalkylcarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, and aminosulfonyl, wherein:

any amino nitrogen of R^c or R^d optionally is substituted with up to two independently selected R^y substituents, or

any amino nitrogen of R^c or R^d optionally is substituted with two substituents such that the two substituents, together with the amino nitrogen, form:

a saturated or partially unsaturated heterocyclo optionally substituted with up to three independently selected R^w substituents, or

a heteroaryl optionally substituted with up to three independently selected R^v substituents;

each R^y is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

any such group is optionally substituted by up to two independently selected R^u substituents;

each R^v is independently selected from the group consisting of aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy,

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heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^yR^z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^yR^z-aminocarbonyloxy, R^yR^z-aminocarbonyl, R^yR^z-aminoalkylcarbonyl, hydroxyaminocarbonyl, R^yR^z-aminosulfonyl, R^yR^z-aminocarbonyl(R^y)amino, trifluoromethylsulfonyl(R^y)amino, heteroarylsulfonyl(R^y)amino, arylsulfonyl(R^y)amino, arylsulfonyl(R^y)aminocarbonyl, alkylsulfonyl(R^y)amino, arylcarbonyl(R^y)aminosulfonyl, and alkylsulfonyl(R^y)aminocarbonyl;

each R^w is independently selected from the group consisting of hydrido, aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^yR^z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^yR^z-aminocarbonyloxy, R^yR^z-aminocarbonyl, R^yR^z-aminoalkylcarbonyl, hydroxyaminocarbonyl, R^yR^z-aminosulfonyl, R^yR^z-aminocarbonyl(R^y) amino, trifluoromethylsulfonyl(R^y)amino, heteroarylsulfonyl(R^y)amino, arylsulfonyl(R^y)amino, arylsulfonyl(R^y)aminocarbonyl, alkylsulfonyl(R^y)amino, arylcarbonyl(R^y)aminosulfonyl, and alkylsulfonyl(R^y)aminocarbonyl;

each R^z is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

each such group optionally is substituted by up to two independently selected R^u substituents;

each R^u is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

the aminoalkyl and aminoalkylcarbonyl are optionally substituted with up to two substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, and alkyloxycarbonyl;

as to R^{3a} and R^{3b}:

R^{3a} and R^{3b} are independently selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, heterocyclo, heteroaryl, cycloalkyl, and alkoxyalkyl, wherein:

any such substituent other than hydrido optionally is substituted by -ARE^1Y^1, or

R^{3a} and R^{3b}, together with the nitrogen to which they are bonded, form -$GARE^2Y^2$;

each A is independently selected from the group consisting of:

(1) -O-,

(2) -S-,

(3) -$N(R^e)$-,

(4) -CO-$N(R^e)$,

(5) -$N(R^e)$-CO-,

(6) -CO-O-,

(7) -O-CO-,

(8) -O-CO-O-,

(9) -HC=CH-,

(10) -NH-CO-NH-,

(11) -C≡C-,

(12) -NH-CO-O-,

(13) -O-CO-NH-,

(14) -N=N-,

(15) -NH-NH-,

(16) -CS-$N(R^e)$-,

(17) -$N(R^e)$-CS-,

(18) -CH_2-,

(19) -O-[$(CH_2)_{1-8}$]-,

(20) -[$(CH_2)_{1-8}$]O-,

(21) -S-CH_2-,

(22) -CH_2-S-, and

(23) a bond;

each R is independently selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroaralkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and heterocycloalkylthioalkyl, wherein:

the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl optionally is substituted with up to two substituents independently selected from the group consisting of halo, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkylcarbonylamino, and alkoxycarbonyl;

each E^1 is independently selected from the group consisting of:

(1) -CO(R^w)-,

(2) - (R^w)CO-,

(3) -CON(R^e)-,

(4) -(R^e)NCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) -NH-SO_2-,

(10) -SO_2-NH-, and

(11) a bond;

each Y^1 is independently selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, R^coxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl;

each R^e is independently selected from the group consisting of hydrido, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R^cR^damino carbonyl, R^cR^daminosulfonyl, R^cR^daminoalkylcarbonyl, and R^cR^daminoalkysulfonyl;

G is piperidinyl or piperazinyl;

E^2 is selected from the group consisting of:

(1) -CO(R^w)-,

(2) -(R^w)CO-,

(3) -CONH-,

(4) -HNCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) -NH-SO_2-,

(10) -SO_2-NH-, and

(11) a bond;

Y^2 is selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylaminocarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl;

R^{20} is selected from the group consisting of -O-R^{21}, -NH-O-R^{22}, and -NH-O-R^{14};

R^{21} is selected from the group consisting of hydrido, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, and pharmaceutically-acceptable cation;

R^{22} is a selectively removable protecting group;

R^{14} is selected from the group consisting of hydrido, pharmaceutically-acceptable cation, and C(W)R^{15};

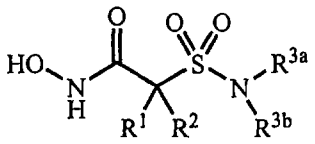
W is selected from the group consisting of O and S; and

R^{15} is selected from the group consisting of C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkylcarbonyl,

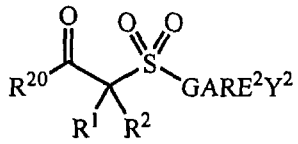
the amino-C_1-C_6-alkyl nitrogen optionally is substituted with two substituents such that the two substituents, together with the nitrogen, form a 5- to 8-membered heterocyclo or heteroaryl.

2. A compound or salt according to claim 1, wherein the compound corresponds in structure to formula I:



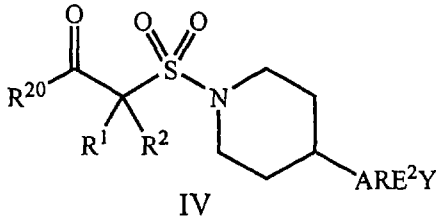
I

3. A compound or salt according to claim 1, wherein the compound corresponds in structure to formula III:



III

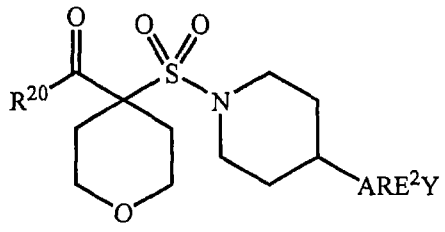
4. A compound or salt according to claim 1, wherein the compound corresponds in structure to formula IV:



IV

5. A compound or salt according to claim 1, wherein the compound corresponds in

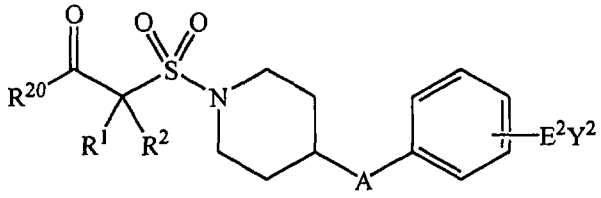
structure to formula V:



V

6. A compound or salt according to claim 1, wherein:

the compound corresponds in structure to formula VI:

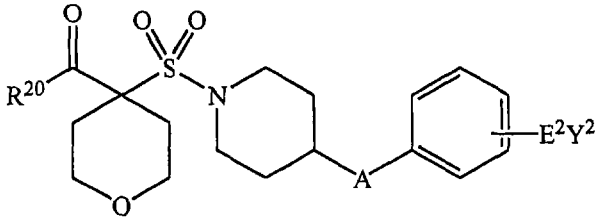


VI ; and

A is selected from the group consisting of -CH_2-, -O-CH_2-, -CH_2-O-, -S-CH_2-, and -CH_2-S-.

7. A compound or salt according to claim 1, wherein:

the compound corresponds in structure to formula VII:

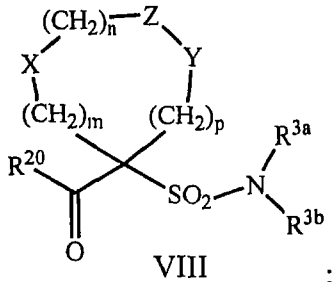


VII ; and

A is selected from the group consisting of -CH_2-, -O-CH_2-, -CH_2-O-, -S-CH_2-, and -CH_2-S-.

8. A compound or a pharmaceutically-acceptable salt thereof, wherein:

the compound corresponds in structure to formula VIII:



VIII ;

m is zero, 1, or 2;

n is zero, 1, or 2;

p is zero, 1, or 2;

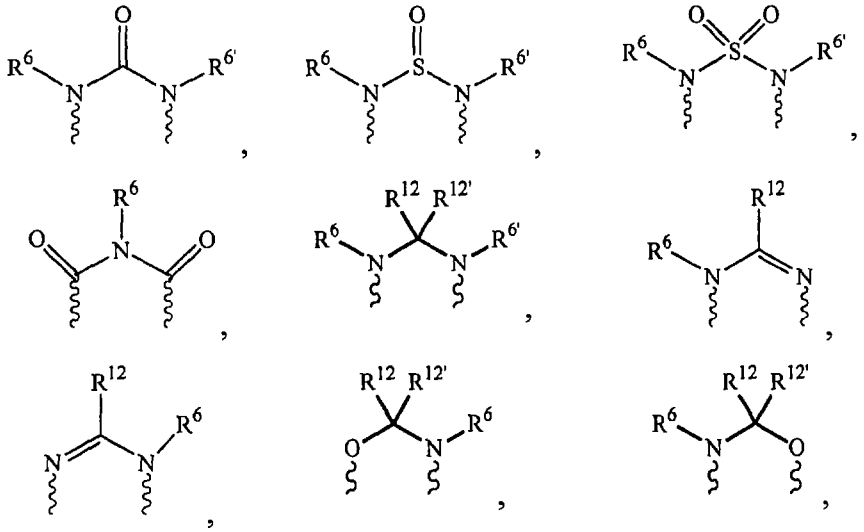
the sum of m + n + p = 1, 2, 3, or 4;

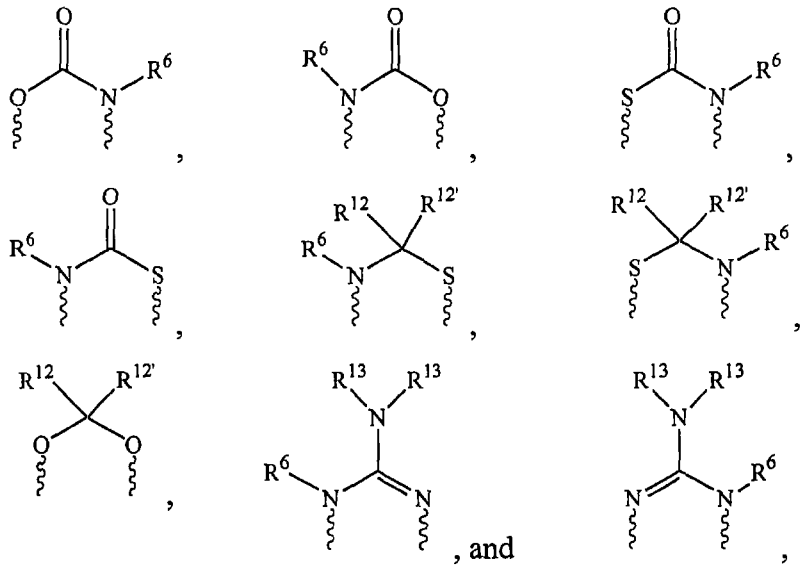
as to X, Y, and Z:

(a) one of X, Y, and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$, and $NS(O)_2R^7$, and the remaining two of X, Y, and Z are CR^8R^9 and $CR^{10}R^{11}$, or

(b) X and Z, or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O, SS, NR^6NR^6, and OC(O), with the remaining one of X and Y being CR^8R^9, or

(c) n is zero and X, Y, and Z together constitute a moiety selected from the group consisting of:





wherein wavy lines are bonds to the atoms of the depicted ring;

each R^6 is independently selected from the group consisting of hydrido, C_1-C_6-alkylcarbonyl, C_6-aryl-C_1-C_6-alkyl, arylcarbonyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, phenyl, 5- to 6-membered heterocyclo, 5- to 6-membered heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenoxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, phenylsulfonyl, C_1-C_6-alkylsulfonyl, 5- to 6-membered heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, phenyliminocarbonyl, 5- to 6-membered heterocycloiminocarbonyl, phenylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, phenylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, 5- to 6-membered heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkylcarbonyl, hydroxy-C_1-C_6-alkylcarbonyl, thiol-C_1-C_6-alkylcarbonyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl, wherein:

the aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl, and C_1-C_6-alkylcarbonyl;

$R^{6'}$ is selected from the group consisting of hydrido, C_1-C_6-alkylcarbonyl,

C_6-aryl-C_1-C_6-alkyl, arylcarbonyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, phenyl, 5- to 6-membered heterocyclo, 5- to 6-membered heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenoxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, phenylsulfonyl, C_1-C_6-alkylsulfonyl, 5- to 6-membered heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, phenyliminocarbonyl, 5- to 6-membered heterocycloiminocarbonyl, phenylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, phenylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, 5- to 6-membered heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkylcarbonyl, hydroxy-C_1-C_6-alkylcarbonyl, thiol-C_1-C_6-alkylcarbonyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl, wherein:

the aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl, and C_1-C_6-alkylcarbonyl;

R^7 is selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl, and C_1-C_6-hydroxyalkyl;

as to R^8:

each R^8 is independently selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^8 and R^9, together with the carbon to which they are bonded, form a carbonyl group, or

R^8 and R^9, or R^8 and R^{10}, together with the atom(s) to which they are bonded, form a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

as to R^9:

each R^9 is independently selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^9 and R^8, together with the carbon to which they are bonded, form:

a carbonyl group, or

a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

as to R^{10}:

R^{10} is selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl,

heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^{10} and R^{11}, together with the carbon to which they are bonded, form a carbonyl group, or

R^{10} and R^{11}, or R^{10} and R^8, together with the atom(s) to which they are bonded, form a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

as to R^{11}:

R^{11} is selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^{11} and R^{10}, together with the carbon to which they are bonded, form:

a carbonyl group, or

a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

only one of R^8 and R^9 or R^{10} and R^{11} may be hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroarylalkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl;

each R^{13} is independently selected from the group consisting of hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, and C_2-C_6-hydroxyalkyl;

as to R^{3a} and R^{3b}:

R^{3a} and R^{3b} are independently selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, heterocyclo, heteroaryl, cycloalkyl, and alkoxyalkyl, wherein:

any such substituent other than hydrido optionally is substituted by -ARE^1Y^1, or

R^{3a} and R^{3b}, together with the nitrogen to which they are bonded, form -$GARE^2Y^2$;

each A is independently selected from the group consisting of:

(1) -O-,

(2) -S-,

(3) -$N(R^e)$-,

(4) -CO-$N(R^e)$,

(5) -N(R^e)-CO-,

(6) -CO-O-,

(7) -O-CO-,

(8) -O-CO-O-,

(9) -HC=CH-,

(10) -NH-CO-NH-,

(11) -C≡C-,

(12) -NH-CO-O-,

(13) -O-CO-NH-,

(14) -N=N-,

(15) -NH-NH-,

(16) -CS-N(R^e)-,

(17) -N(R^e)-CS-,

(18) -CH_2-,

(19) -O-[$(CH_2)_{1-8}$]-,

(20) -[$(CH_2)_{1-8}$]O-,

(21) -S-CH_2-,

(22) -CH_2-S-, and

(23) a bond;

each R is independently selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, cycloalkyloxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and heterocycloalkylthioalkyl, wherein:

the heteroaryl, aryl, cycloalkyl, or heterocycloalkyl optionally is substituted with up to two substituents independently selected from the group consisting of halo, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkylcarbonylamino, and alkoxycarbonyl;

each E^1 is independently selected from the group consisting of:

(1) -CO(R^w)-,

(2) -(R^w)CO-,

(3) -CON(R^e)-,

(4) -(R^e)NCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) -NH-SO_2-,

(10) -SO_2-NH-, and

(11) a bond;

each Y^1 is independently selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, R^coxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl;

each R^e is independently selected from the group consisting of hydrido, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R^cR^damino carbonyl, R^cR^daminosulfonyl, R^cR^daminoalkylcarbonyl, and R^cR^daminoalkysulfonyl;

G is piperidinyl or piperazinyl;

E^2 is selected from the group consisting of:

(1) -CO(R^w)-,

(2) -(R^w)CO-,

(3) -CONH-,

(4) -HNCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) -NH-SO_2-,

(10) -SO_2-NH-, and

(11) a bond;

Y^2 is selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl;

each R^c and R^d is independently selected from the group consisting of hydrido, alkylcarbonyl, arylalkyl, arylcarbonyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, thiolalkylcarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, and aminosulfonyl, wherein:

any amino nitrogen of R^c or R^d optionally is substituted with up to two independently selected R^y substituents, or

any amino nitrogen of R^c or R^d optionally is substituted with two substituents such that the two substituents, together with the amino nitrogen, form:

a saturated or partially unsaturated heterocyclo optionally substituted with up to three independently selected R^w substituents, or

a heteroaryl optionally substituted with up to three independently selected R^v substituents;

each R^y is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl,

arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, halo alkylcarbonyl, and hydroxyalkyl, wherein:

any such group is optionally substituted by up to two independently selected R^u substituents;

each R^v is independently selected from the group consisting of aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^yR^z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^yR^z-aminocarbonyloxy, R^yR^z-aminocarbonyl, R^yR^z-aminoalkylcarbonyl, hydroxyaminocarbonyl, R^yR^z-aminosulfonyl, R^yR^z-aminocarbonyl(R^y) amino, trifluoromethylsulfonyl(R^y)amino, heteroarylsulfonyl(R^y)amino, arylsulfonyl(R^y)amino, arylsulfonyl(R^y)aminocarbonyl, alkylsulfonyl(R^y)amino, arylcarbonyl(R^y)aminosulfonyl, and alkylsulfonyl(R^y)aminocarbonyl;

each R^w is independently selected from the group consisting of hydrido, aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, hetero arylcarbonyl, halogen, cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^yR^z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^yR^z-aminocarbonyloxy, R^yR^z-aminocarbonyl, R^yR^z-aminoalkylcarbonyl, hydroxyaminocarbonyl, R^yR^z-aminosulfonyl, R^yR^z-aminocarbonyl(R^y) amino, trifluoromethylsulfonyl(R^y)amino, heteroarylsulfonyl-(R^y)amino, arylsulfonyl(R^y)amino, arylsulfonyl(R^y)aminocarbonyl, alkylsulfonyl(R^y)amino, arylcarbonyl(R^y)aminosulfonyl, and alkylsulfonyl(R^y)aminocarbonyl;

each R^z is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

each such group optionally is substituted by up to two independently selected R^u substituents;

each R^u is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

the aminoalkyl and aminoalkylcarbonyl are optionally substituted with up to two substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, and alkyloxycarbonyl;

R^{20} is selected from the group consisting of -O-R^{21}, -NH-O-R^{22}, and -NH-O-R^{14};

R^{21} is selected from the group consisting of hydrido, C_1-C_6-alkyl, aryl, and aryl-C_1-C_6-alkyl;

R^{22} is a selectively removable protecting group;

R^{14} is selected from the group consisting of hydrido, pharmaceutically-acceptable cation, and C(W)R^{15};

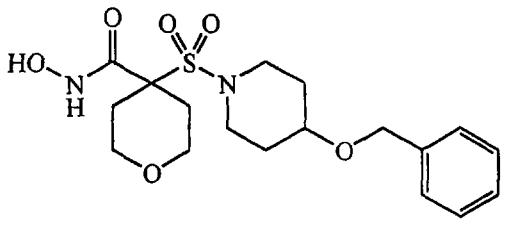
W is selected from the group consisting of O and S; and

R^{15} is selected from the group consisting of C_1-C_6-alkyl, aryl, C_1-C_6-alkoxy, heteroaryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryloxy, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, heteroaryl, and amino-C_1-C_6-alkyl, wherein:

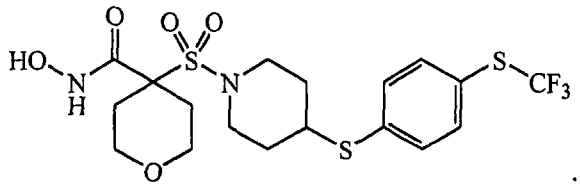
the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl, and C_1-C_6-alkylcarbonyl, or

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with two substituents such that the two substituents, together with the nitrogen, form a 5- to 8-membered heterocyclo or heteroaryl.

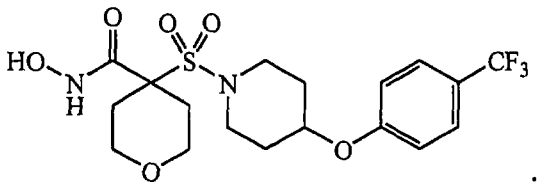
9. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



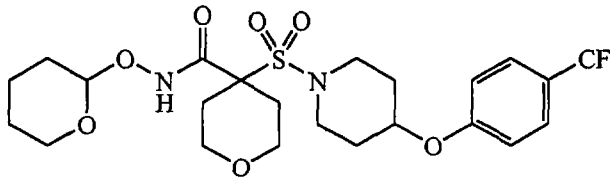
10. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



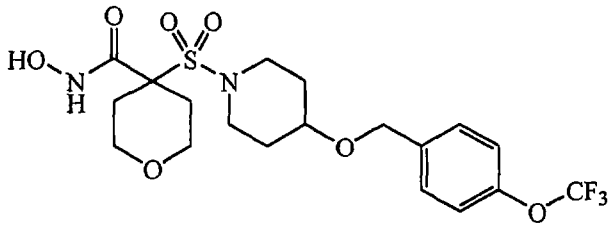
11. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



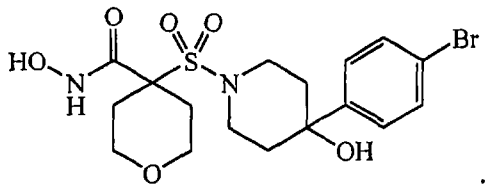
12. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



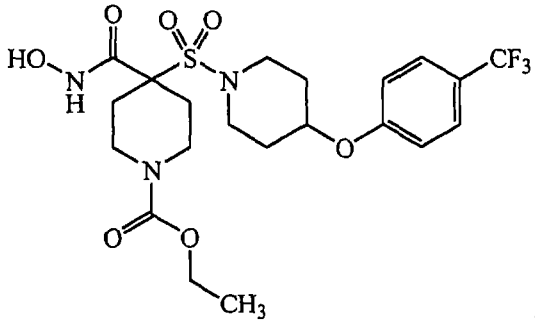
13. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



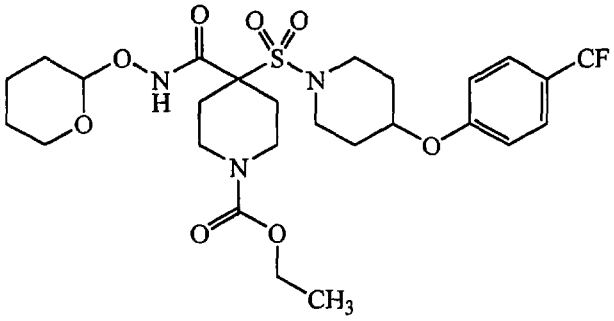
14. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



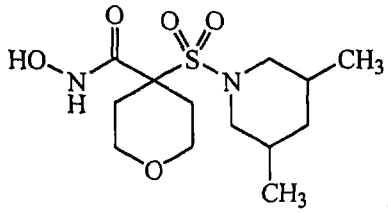
15. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



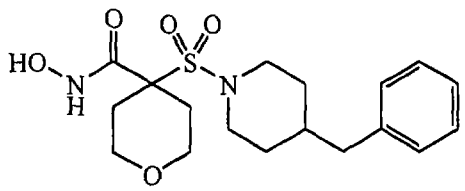
16. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



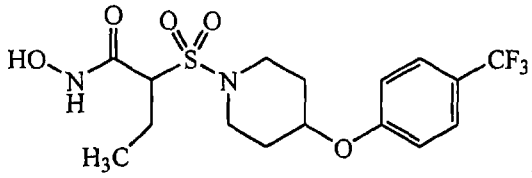
17. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



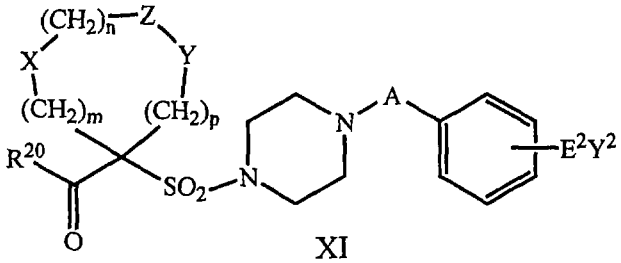
18. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:



19. A compound or salt according to claim 1, wherein the compound corresponds in structure to the formula:

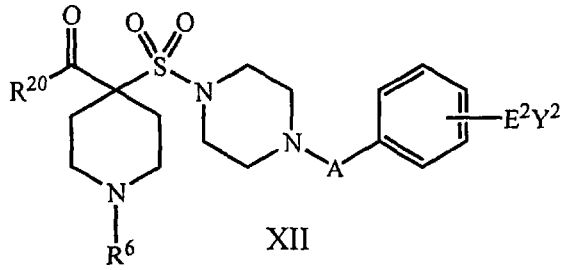


20. A compound or salt according to claim 8, wherein the compound corresponds in structure to formula XI:



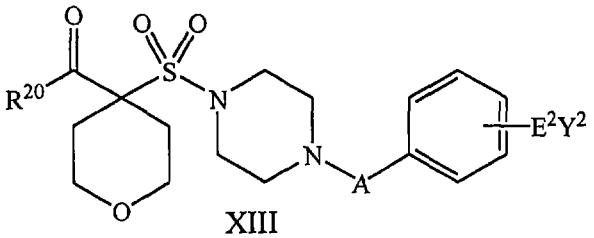
XI

21. A compound or salt according to claim 20, wherein the compound corresponds in structure to formula XII:



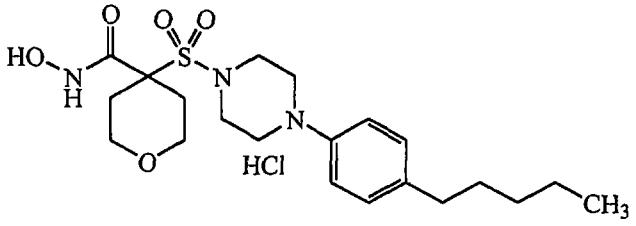
XII

22. A compound or salt according to claim 20, wherein the compound corresponds in structure to formula XIII:

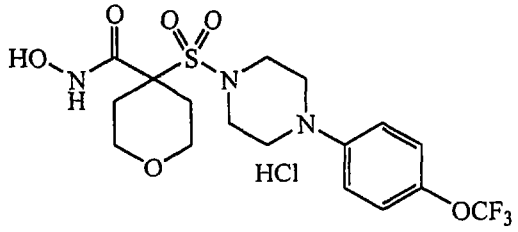


XIII

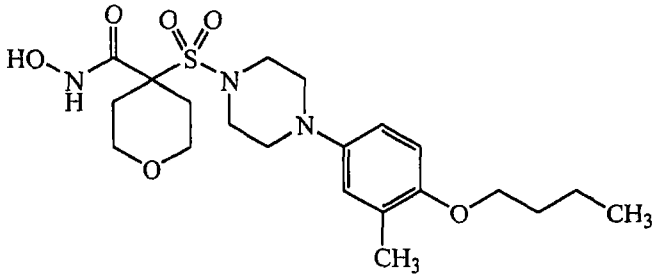
23. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



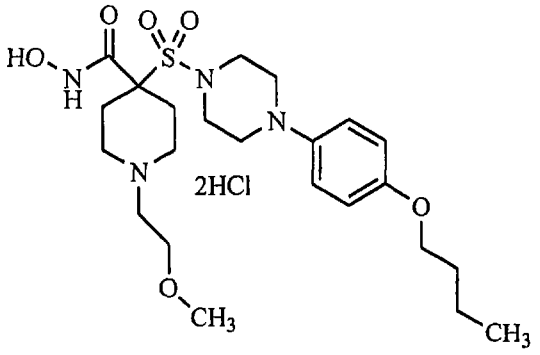
24. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



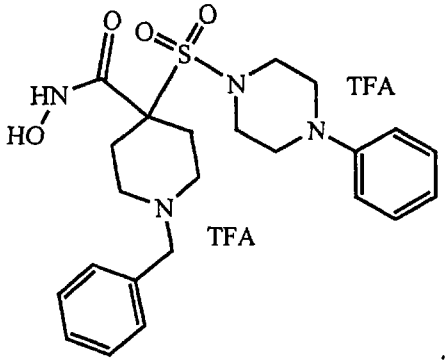
25. A compound or a pharmaceutically-acceptable salt thereof, wherein the compound corresponds in structure to the formula:



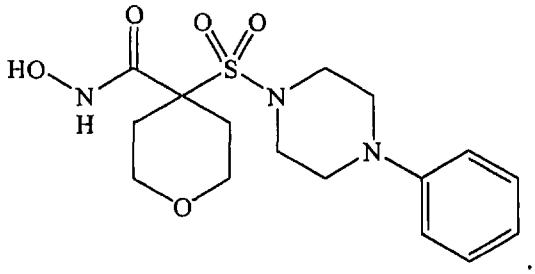
26. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



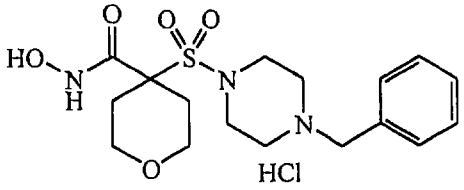
27. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



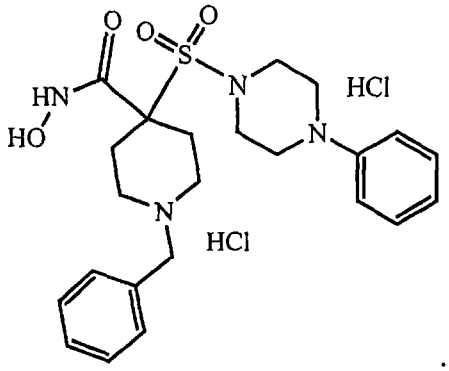
28. A compound or salt according to claim 20, wherein the compound corresponds in structure to the formula:



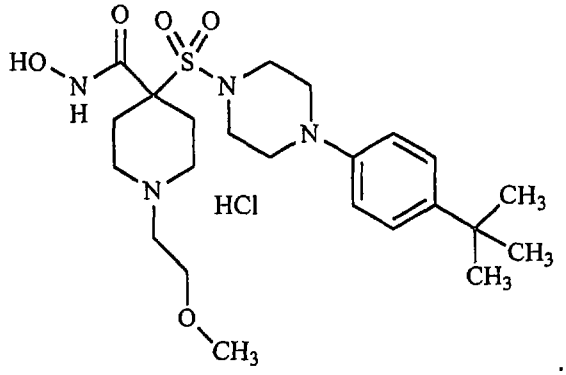
29. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



30. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



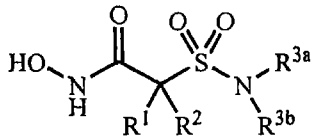
31. A salt according to claim 20, wherein the salt corresponds in structure to the formula:



32. A use of a therapeutically-effective amount of a compound or a pharmaceutically-acceptable salt thereof in the preparation of a pharmaceutical composition for the treatment of a condition associated with pathological matrix metalloprotease (MMP), wherein:

the compound or salt inhibits the activity of one or more of MMP-2, MMP-9, and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1;

the compound corresponds in structure to formula I:



I ;

as to R^1 and R^2:

R^1 and R^2, together with the carbon to which they are bonded, form heterocyclo or cycloalkyl, wherein:

the heterocyclo or cycloalkyl optionally is substituted with up to three independently selected R^x substituents, or

R^1 and R^2 are independently selected from the group consisting of hydrido, alkyl, alkyloxyalkyl, alkylthioalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkyloxyalkyl, aryloxyalkyl, arylthioalkyl, arylalkylthioalkyl, cycloalkyl, bicycloalkyl, cycloalkenyl, cycloalkylalkyl, bicycloalkylalkyl, cycloalkyloxyalkyl, cycloalkylalkyloxyalkyl, bicycloalkyloxyalkyl, cycloalkylthioalkyl, bicycloalkylthioalkyl, cycloalkylalkylthioalkyl, bicycloalkylalkylthioalkyl, heterocyclo, heterocycloalkyl, heteroaryl, biarylalkyl, arylalkenyl, arylalkynyl, heterocycloalkylthio, heterocycloalkyloxyalkyl, heteroarylalkenyl, and heteroarylalkyloxyalkyl, wherein:

any such substituent other than hydrido optionally is substituted with up to three independently selected R^x substituents; and

only one of R^1 and R^2 may be hydrido;

each R^x is independently selected from the group consisting of hydrido, aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, R^cR^d-amino, R^cR^d-aminoalkyl, nitro, nitroso, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, alkoxyalkyl, R^c-oxyalkyl, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, alkyloxycarbonyl-R^c-amino, arylalkyloxycarbonyl-R^c-amino, aryloxycarbonyloxy, carboxy, R^cR^d-aminocarbonyloxy, R^cR^d-aminocarbonyl, R^cR^d-aminoalkylcarbonyl, hydroxy-R^c-aminocarbonyl, R^cR^d-aminosulfonyl, arylsulfonyl(R^c)amino, R^cR^d-aminoalkoxy, R^cR^d-aminocarbonyl(R^c)amino, trifluoromethylsulfonyl(R^c)amino, heteroarylsulfonyl(R^c)amino, alkylsulfonyl, arylsulfonyl(R^c)amino, arylsulfonyl(R^c) aminocarbonyl, alkylsulfonyl(R^c)amino, arylcarbonyl(R^c)aminosulfonyl, and alkylsulfonyl (R^c)aminocarbonyl;

each R^c and R^d is independently selected from the group consisting of hydrido, alkylcarbonyl, arylalkyl, arylcarbonyl, bisalkoxyalkyl, alkyl, haloalkyl, perfluoroalkyl, trifluoromethylalkyl, perfluoroalkoxyalkyl, alkoxyalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, aryl, heterocyclo, heteroaryl, cycloalkylalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroarylalkoxyalkyl, heteroarylthioalkyl, arylsulfonyl, alkylsulfonyl, heteroarylsulfonyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, alkyliminocarbonyl, aryliminocarbonyl, heterocycloiminocarbonyl, arylthioalkyl, alkylthioalkyl, arylthioalkenyl, alkylthioalkenyl, heteroarylalkyl, haloalkylcarbonyl, hydroxyalkylcarbonyl, thiolalkylcarbonyl,

alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, aminoalkylcarbonyl, hydroxyalkyl, aminoalkyl, aminoalkylsulfonyl, and aminosulfonyl, wherein:

any amino nitrogen of R^c or R^d optionally is substituted with up to two independently selected R^y substituents, or

any amino nitrogen of R^c or R^d optionally is substituted with two substituents such that the two substituents, together with the amino nitrogen, form:

a saturated or partially unsaturated heterocyclo optionally substituted with up to three independently selected R^w substituents, or

a heteroaryl optionally substituted with up to three independently selected R^v substituents;

each R^y is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

any such group is optionally substituted by up to two independently selected R^u substituents;

each R^v is independently selected from the group consisting of aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^yR^z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl, alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^yR^z-aminocarbonyloxy, R^yR^z-aminocarbonyl, R^yR^z-aminoalkylcarbonyl, hydroxyaminocarbonyl, R^yR^z-aminosulfonyl, R^yR^z-aminocarbonyl(R^y)amino, trifluoromethylsulfonyl(R^y)amino, heteroarylsulfonyl(R^y)amino, arylsulfonyl(R^y)amino, arylsulfonyl(R^y)aminocarbonyl, alkylsulfonyl(R^y)amino, arylcarbonyl(R^y)aminosulfonyl, and alkylsulfonyl(R^y)aminocarbonyl;

each R^w is independently selected from the group consisting of hydrido, aryl, heteroaryl, heterocyclo, arylcarbonyl, alkylcarbonyl, heteroarylcarbonyl, halogen, cyano, aldehydo, hydroxy, amino, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyaryl, alkoxyheteroaryl, R^yR^z-amino, alkoxyalkyl, alkylenedioxy, aryloxyalkyl, perfluoroalkyl, trifluoroalkyl, alkylthio, arylthio, alkyloxycarbonyl,

alkyloxycarbonyloxy, aryloxycarbonyl, arylalkyloxycarbonyl, arylalkyloxycarbonylamino, aryloxycarbonyloxy, carboxy, R^yR^z-aminocarbonyloxy, R^yR^z-aminocarbonyl, R^yR^z-aminoalkylcarbonyl, hydroxyaminocarbonyl, R^yR^z-aminosulfonyl, R^yR^z-aminocarbonyl(R^y)amino, trifluoromethylsulfonyl(R^y)amino, heteroarylsulfonyl(R^y)amino, arylsulfonyl(R^y)amino, arylsulfonyl(R^y)aminocarbonyl, alkylsulfonyl(R^y)amino, arylcarbonyl(R^y)aminosulfonyl, and alkylsulfonyl(R^y)aminocarbonyl;

each R^z is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

each such group optionally is substituted by up to two independently selected R^u substituents;

each R^u is independently selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, alkyl, alkynyl, alkenyl, alkoxyalkyl, aminoalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, carboxyalkyl, haloalkyl, alkylcarbonyl, arylcarbonyl, aminoalkylcarbonyl, haloalkylcarbonyl, and hydroxyalkyl, wherein:

the aminoalkyl and aminoalkylcarbonyl are optionally substituted with up to two substituents independently selected from the group consisting of alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, and alkyloxycarbonyl;

as to R^{3a} and R^{3b}:

R^{3a} and R^{3b} are independently selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, heterocyclo, heteroaryl, cycloalkyl, and alkoxyalkyl, wherein:

any such substituent other than hydrido optionally is substituted by $-ARE^1Y^1$, or

R^{3a} and R^{3b}, together with the nitrogen to which they are bonded, form $-GARE^2Y^2$;

each A is independently selected from the group consisting of:

(1) -O-,

(2) -S-,

(3) $-N(R^e)-$,

(4) $-CO-N(R^e)$,

(5) -N(R^e)-CO-,

(6) -CO-O-,

(7) -O-CO-,

(8) -O-CO-O-,

(9) -HC=CH-,

(10) -NH-CO-NH-,

(11) -C≡C-,

(12) -NH-CO-O-,

(13) -O-CO-NH-,

(14) -N=N-,

(15) -NH-NH-,

(16) -CS-N(R^e)-,

(17) -N(R^e)-CS-,

(18) -CH_2-,

(19) -O-[$(CH_2)_{1-8}$]-,

(20) -[$(CH_2)_{1-8}$]O-,

(21) -S-CH_2-,

(22) -CH_2-S-, and

(23) a bond;

each R is independently selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, cycloalkoxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and heterocycloalkylthioalkyl, wherein:

the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl optionally is substituted with up to two substituents independently selected from the group consisting of halo, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkylcarbonylamino, and alkoxycarbonyl;

each E^1 is independently selected from the group consisting of:

(1) -CO(R^w)-,

(2) - (R^w)CO-,

(3) -CON(R^e)-,

(4) -(R^e)NCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) -NH-SO_2-,

(10) -SO_2-NH-, and

(11) a bond;

each Y^1 is independently selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, R^coxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl;

each R^e is independently selected from the group consisting of hydrido, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R^cR^damino carbonyl, R^cR^daminosulfonyl, R^cR^daminoalkylcarbonyl, and R^cR^daminoalkysulfonyl;

G is piperidinyl or piperazinyl;

E^2 is selected from the group consisting of:

(1) -CO(R^w)-,

(2) -(R^w)CO-,

(3) -CONH-,

(4) -HNCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) $-NH-SO_2-$,

(10) $-SO_2-NH-$, and

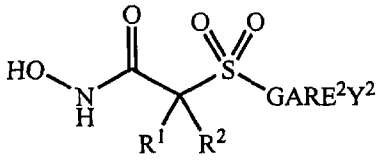
(11) a bond;

Y^2 is selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

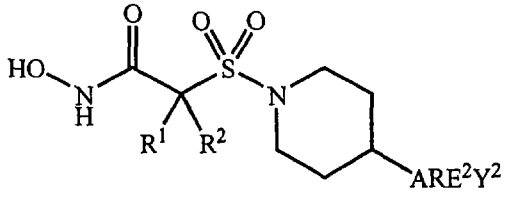
the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl.

33. The use according to claim 32, wherein the compound corresponds in structure to formula IIIA:



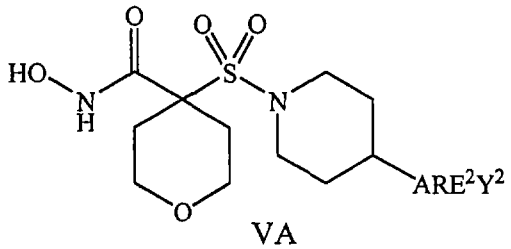
IIIA

34. The use according to claim 32, wherein the compound corresponds in structure to formula IVA:



IVA

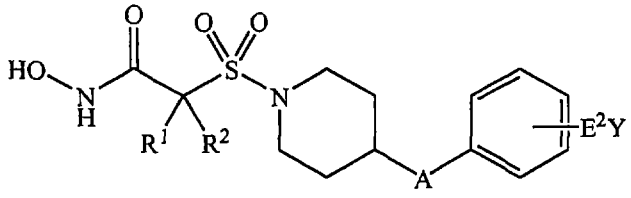
35. The use according to claim 32, wherein the compound corresponds in structure to formula VA:



VA

36. The use according to claim 32, wherein:

the compound corresponds in structure to formula VIA:

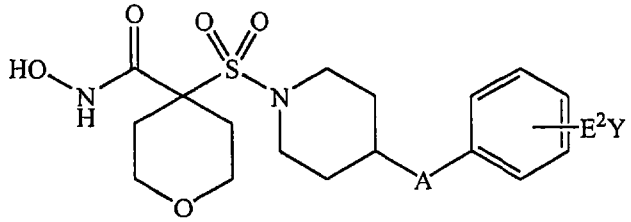


VIA ; and

A is selected from the group consisting of $-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$, and $-CH_2-S-$.

37. The use according to claim 32, wherein:

the compound corresponds in structure to formula VIIA:



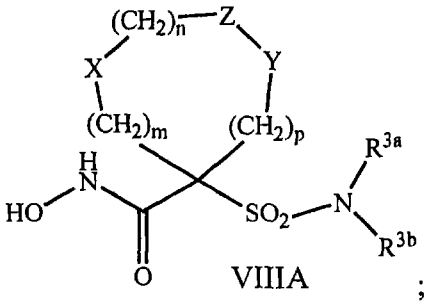
VIIA ; and

A is selected from the group consisting of $-CH_2-$, $-O-CH_2-$, $-CH_2-O-$, $-S-CH_2-$, and $-CH_2-S-$.

38. A use of a therapeutically-effective amount of a compound or a pharmaceutically-acceptable salt thereof in the preparation of a pharmaceutical composition for the treatment of a condition associated with pathological matrix metalloprotease (MMP), wherein:

the compound or salt inhibits the activity of one or more of MMP-2, MMP-9, and MMP-13, while exhibiting substantially less inhibitory activity against MMP-1;

the compound corresponds in structure to formula VIIIA:



VIIIA ;

m is zero, 1, or 2;

n is zero, 1, or 2;

p is zero, 1, or 2;

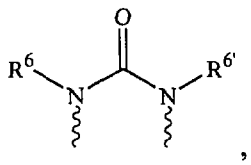
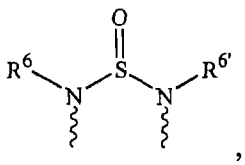
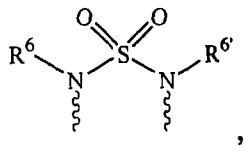
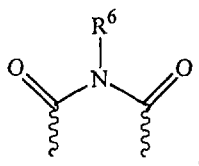
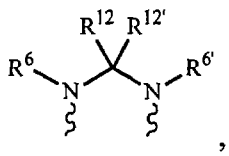
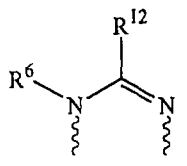
the sum of m + n + p = 1, 2, 3, or 4;

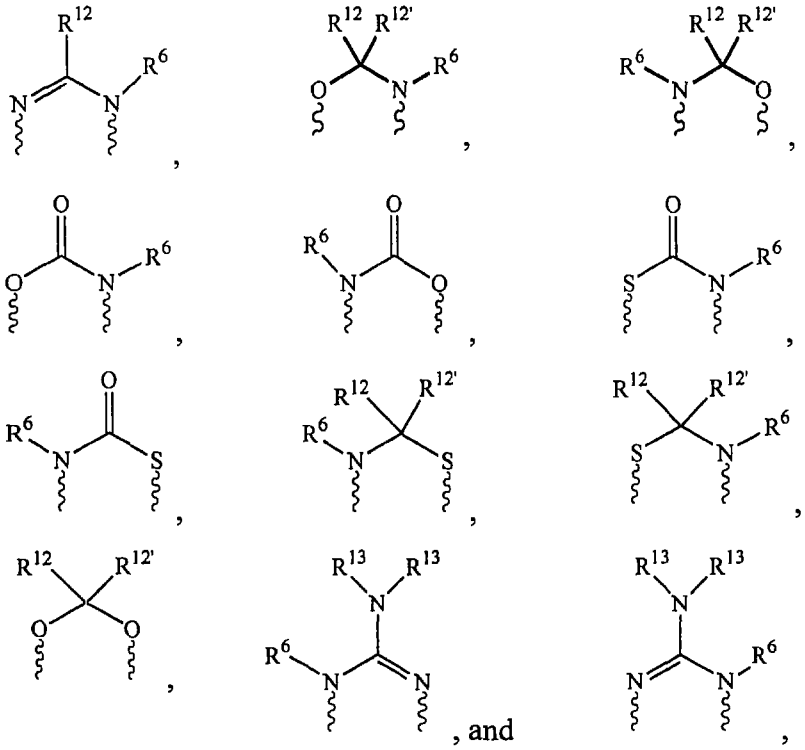
as to X, Y, and Z:

(a) one of X, Y, and Z is selected from the group consisting of C(O), NR^6, O, S, S(O), $S(O)_2$, and $NS(O)_2R^7$, and the remaining two of X, Y, and Z are CR^8R^9 and $CR^{10}R^{11}$, or

(b) X and Z, or Z and Y together constitute a moiety that is selected from the group consisting of $NR^6C(O)$, $NR^6S(O)$, $NR^6S(O)_2$, NR^6S, NR^6O, SS, NR^6NR^6, and OC(O), with the remaining one of X and Y being CR^8R^9, or

(c) n is zero and X, Y, and Z together constitute a moiety selected from the group consisting of:


,

,

,

,

,

,



wherein wavy lines are bonds to the atoms of the depicted ring;

each R^6 is independently selected from the group consisting of hydrido, C_1-C_6-alkylcarbonyl, C_6-aryl-C_1-C_6-alkyl, arylcarbonyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, phenyl, 5- to 6-membered heterocyclo, 5- to 6-membered heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenoxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, phenylsulfonyl, C_1-C_6-alkylsulfonyl, 5- to 6-membered heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, phenyliminocarbonyl, 5- to 6-membered heterocycloiminocarbonyl, phenylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, phenylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, 5- to 6-membered heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkylcarbonyl, hydroxy-C_1-C_6-alkylcarbonyl, thiol-C_1-C_6-alkylcarbonyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl, wherein:

the aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl,

amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl, and C_1-C_6-alkylcarbonyl;

$R^{6'}$ is selected from the group consisting of hydrido, C_1-C_6-alkylcarbonyl, C_6-aryl-C_1-C_6-alkyl, arylcarbonyl, bis(C_1-C_6-alkoxy-C_1-C_6-alkyl)-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-perfluoroalkyl, C_1-C_6-trifluoromethylalkyl, C_1-C_6-perfluoroalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_3-C_8-heterocycloalkyl, C_3-C_8-heterocycloalkylcarbonyl, phenyl, 5- to 6-membered heterocyclo, 5- to 6-membered heteroaryl, C_3-C_8-cycloalkyl-C_1-C_6-alkyl, phenoxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, phenylsulfonyl, C_1-C_6-alkylsulfonyl, 5- to 6-membered heteroarylsulfonyl, carboxy-C_1-C_6-alkyl, C_1-C_4-alkoxycarbonyl-C_1-C_6-alkyl, aminocarbonyl, C_1-C_6-alkyliminocarbonyl, phenyliminocarbonyl, 5- to 6-membered heterocycloiminocarbonyl, phenylthio-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, phenylthio-C_3-C_6-alkenyl, C_1-C_4-alkylthio-C_3-C_6-alkenyl, 5- to 6-membered heteroaryl-C_1-C_6-alkyl, halo-C_1-C_6-alkylcarbonyl, hydroxy-C_1-C_6-alkylcarbonyl, thiol-C_1-C_6-alkylcarbonyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_1-C_5-alkoxycarbonyl, aryloxycarbonyl, NR^8R^9-C_1-C_5-alkylcarbonyl, hydroxy-C_1-C_5-alkyl, aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl, wherein:

the aminocarbonyl, hydroxyaminocarbonyl, aminosulfonyl, amino-C_1-C_6-alkylsulfonyl, and amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, C_3-C_8-cycloalkyl, and C_1-C_6-alkylcarbonyl;

R^7 is selected from the group consisting of arylalkyl, aryl, heteroaryl, heterocyclo, C_1-C_6-alkyl, C_3-C_6-alkynyl, C_3-C_6-alkenyl, C_1-C_6-carboxyalkyl, and C_1-C_6-hydroxyalkyl;

as to R^8:

each R^8 is independently selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-

alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^8 and R^9, together with the carbon to which they are bonded, form a carbonyl group, or

R^8 and R^9, or R^8 and R^{10}, together with the atom(s) to which they are bonded, form a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

as to R^9:

each R^9 is independently selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^9 and R^8, together with the carbon to which they are bonded, form:

a carbonyl group, or

a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

as to R^{10}:

R^{10} is selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^{10} and R^{11}, together with the carbon to which they are bonded, form a carbonyl group, or

R^{10} and R^{11}, or R^{10} and R^8, together with the atom(s) to which they are bonded, form a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

as to R^{11}:

R^{11} is selected from the group consisting of hydrido, hydroxy, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, arylalkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two

substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl, or

R^{11} and R^{10}, together with the carbon to which they are bonded, form:

a carbonyl group, or

a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring containing one or two heteroatoms that are independently selected from the group consisting of nitrogen, oxygen, and sulfur;

only one of R^8 and R^9 or R^{10} and R^{11} may be hydroxy;

R^{12} and $R^{12'}$ are independently selected from the group consisting of hydrido, C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkyl, heteroaryl, heteroarylalkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, thiol-C_1-C_6-alkyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, heterocycloalkyl-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, amino-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, hydroxycarbonyl-C_1-C_6-alkyl, hydroxycarbonylaryl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, aryloxy-C_1-C_6-alkyl, heteroaryloxy-C_1-C_6-alkyl, C_1-C_6-alkylthio-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, heteroarylthio-C_1-C_6-alkyl, a sulfoxide of any said thio substituents, a sulfone of any said thio substituents, perfluoro-C_1-C_6-alkyl, trifluoromethyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, alkoxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl, wherein:

the amino-C_1-C_6-alkyl nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of C_1-C_6-alkyl, aryl-C_1-C_6-alkyl, cycloalkyl, and C_1-C_6-alkylcarbonyl;

each R^{13} is independently selected from the group consisting of hydrido, benzyl, phenyl, C_1-C_6-alkyl, C_2-C_6-alkynyl, C_2-C_6-alkenyl, and C_2-C_6-hydroxyalkyl;

as to R^{3a} and R^{3b}:

R^{3a} and R^{3b} are independently selected from the group consisting of hydrido, alkyl, alkenyl, alkynyl, aryl, heterocyclo, heteroaryl, cycloalkyl, and alkoxyalkyl, wherein:

any such substituent other than hydrido optionally is substituted by $-ARE^1Y^1$, or

R^{3a} and R^{3b}, together with the nitrogen to which they are bonded, form $-GARE^2Y^2$;

each A is independently selected from the group consisting of:

(1) -O-,

(2) -S-,

(3) -N(R^e)-,

(4) -CO-N(R^e),

(5) -N(R^e)-CO-,

(6) -CO-O-,

(7) -O-CO-,

(8) -O-CO-O-,

(9) -HC=CH-,

(10) -NH-CO-NH-,

(11) -C≡C-,

(12) -NH-CO-O-,

(13) -O-CO-NH-,

(14) -N=N-,

(15) -NH-NH-,

(16) -CS-N(R^e)-,

(17) -N(R^e)-CS-,

(18) -CH_2-,

(19) -O-[$(CH_2)_{1-8}$]-,

(20) -[$(CH_2)_{1-8}$]O-,

(21) -S-CH_2-,

(22) -CH_2-S-, and

(23) a bond;

each R is independently selected from the group consisting of alkyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, cycloalkyloxyalkyl, heterocycloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, arylthioalkyl, heteroarylthioalkyl, cycloalkylthioalkyl, and heterocycloalkylthioalkyl, wherein:

the heteroaryl, aryl, cycloalkyl, or heterocycloalkyl optionally is substituted with up to two substituents independently selected from the group consisting of halo, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, amino, alkoxycarbonylalkyl, C_1-C_2-alkylene-dioxy, hydroxycarbonylalkyl, hydroxycarbonylalkylamino, nitro, hydroxy, hydroxyalkyl, alkylcarbonylamino, and

alkoxycarbonyl;

each E^1 is independently selected from the group consisting of:

(1) -CO(R^w)-,

(2) -(R^w)CO-,

(3) -CON(R^e)-,

(4) -(R^e)NCO-,

(5) -CO-,

(6) -SO_2-R^w-,

(7) -R^w-SO_2-,

(8) -SO_2-,

(9) -NH-SO_2-,

(10) -SO_2-NH-, and

(11) a bond;

each Y^1 is independently selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, nitrile, nitro, aryloxy, arylalkoxy, heteroaryloxy, heteroaralkyl, R^coxyalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl;

each R^e is independently selected from the group consisting of hydrido, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxycarbonyl, alkyloxycarbonyl, R^cR^damino carbonyl, R^cR^daminosulfonyl, R^cR^daminoalkylcarbonyl, and R^cR^daminoalkysulfonyl;

G is piperidinyl or piperazinyl;

E^2 is selected from the group consisting of:

(1) -CO(R^w)-,

(2) -(R^w)CO-,

(3) -CONH-,

(4) -HNCO-,

(5) -CO-,

(6) $-SO_2-R^w-$,

(7) $-R^w-SO_2-$,

(8) $-SO_2-$,

(9) $-NH-SO_2-$,

(10) $-SO_2-NH-$, and

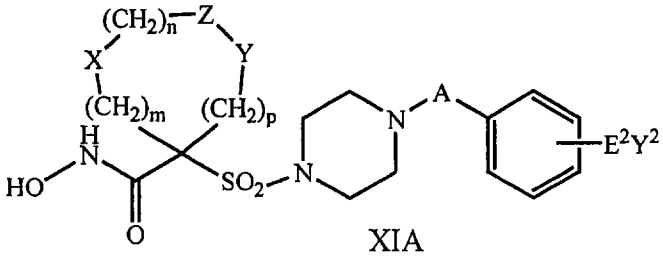
(11) a bond;

Y^2 is selected from the group consisting of hydrido, alkyl, alkoxy, haloalkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, arylalkoxy, heteroaryloxy, heteroarylalkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, trifluoromethyl, alkoxycarbonyl, and aminoalkyl, wherein:

the aryl, heteroaryl, or heterocycloalkyl is optionally substituted with up to two substituents independently selected from the group consisting of alkylcarbonyl, halo, nitro, arylalkyl, aryl, alkoxy, and amino, wherein:

the amino nitrogen optionally is substituted with up to two substituents independently selected from the group consisting of alkyl and arylalkyl.

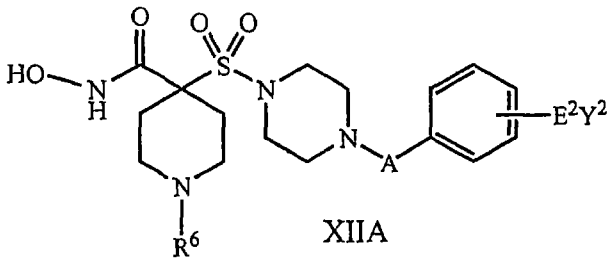
39. The use according to claim 38, wherein the compound corresponds in structure to formula XIA:



XIA

40. The use according to claim 39, wherein A is a bond.

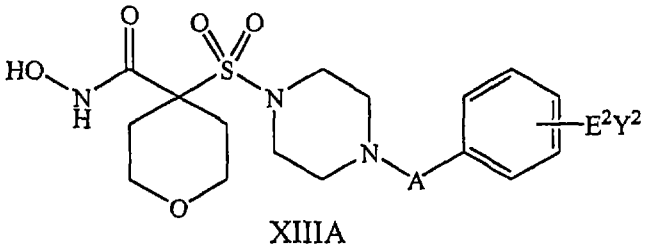
41. The use according to claim 38, wherein the compound corresponds in structure to formula XIIA:



XIIA

42. The use according to claim 41, wherein A is a bond.

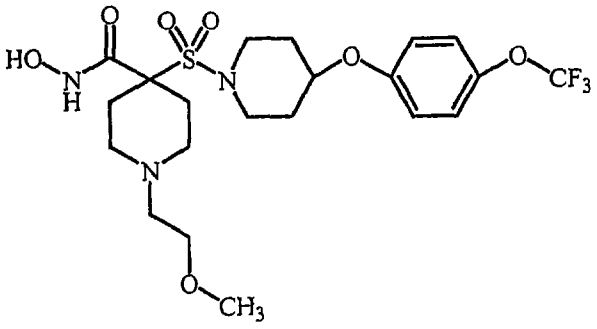
43. The use according to claim 38, wherein the compound corresponds in structure to formula XIIIA:



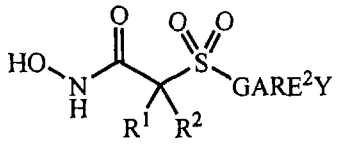
XIIIA

44. The use according to claim 43, wherein A is a bond.

45. A compound or salt according to claim 1, wherein the compound corresponds in structure to the following formula:

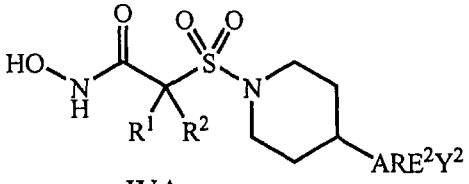


46. A compound or salt thereof according to claim 3, wherein the compound corresponds in structure to formula IIIA:



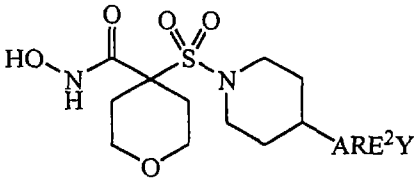
IIIA

47. A compound or salt thereof according to claim 4, wherein the compound corresponds in structure to formula IVA:



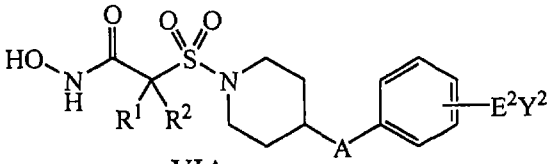
IVA

48. A compound or salt thereof according to claim 5, wherein the compound corresponds in structure to formula VA:



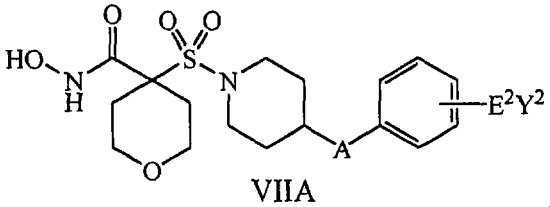
VA

49. A compound or salt thereof according to claim 6, wherein the compound corresponds in structure to formula VIA:



VIA

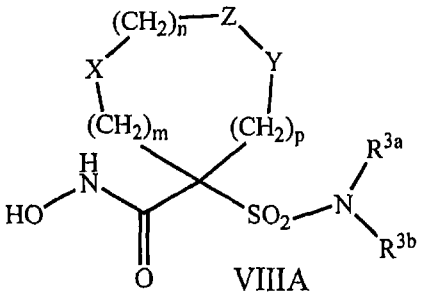
50. A compound or salt thereof according to claim 7, wherein the compound corresponds in structure to formula VIIA:



VIIA

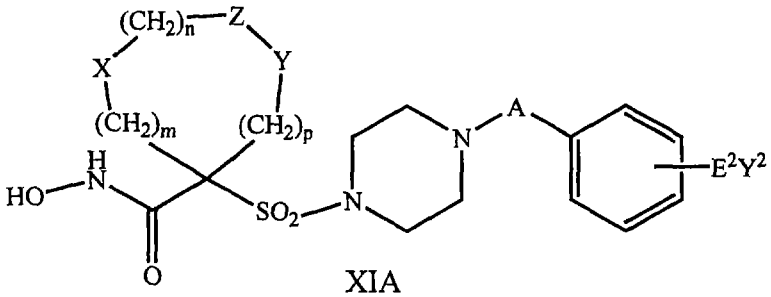
51. A compound or salt thereof according to claim 8, wherein the compound corresponds

in structure to formula VIIIA:



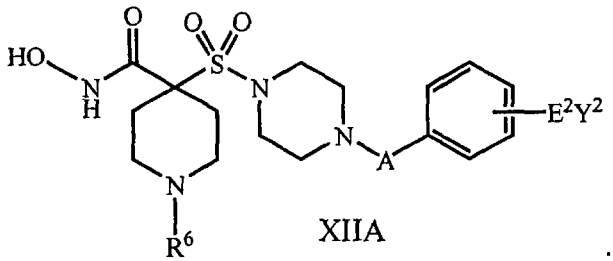
VIIIA

52. A compound or salt according to claim 20, wherein the compound corresponds in structure to formula XIA:



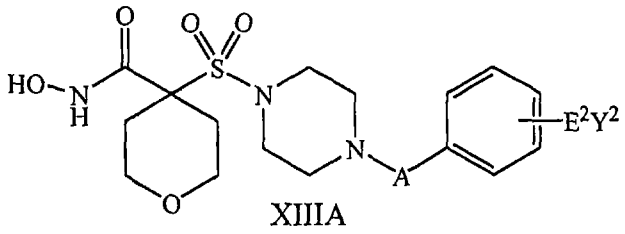
XIA

53. A compound or salt thereof according to claim 21, wherein the compound corresponds in structure to formula XIIA:



XIIA

54. A compound or salt thereof according to claim 22, wherein the compound corresponds in structure to formula XIIIA:



XIIIA

55. The use according to claim 32, wherein the compound corresponds in structure to the following formula:

