Supporting Information

Potent and Selective Carboxylic Acid-Based Inhibitors of Matrix Metalloproteinases

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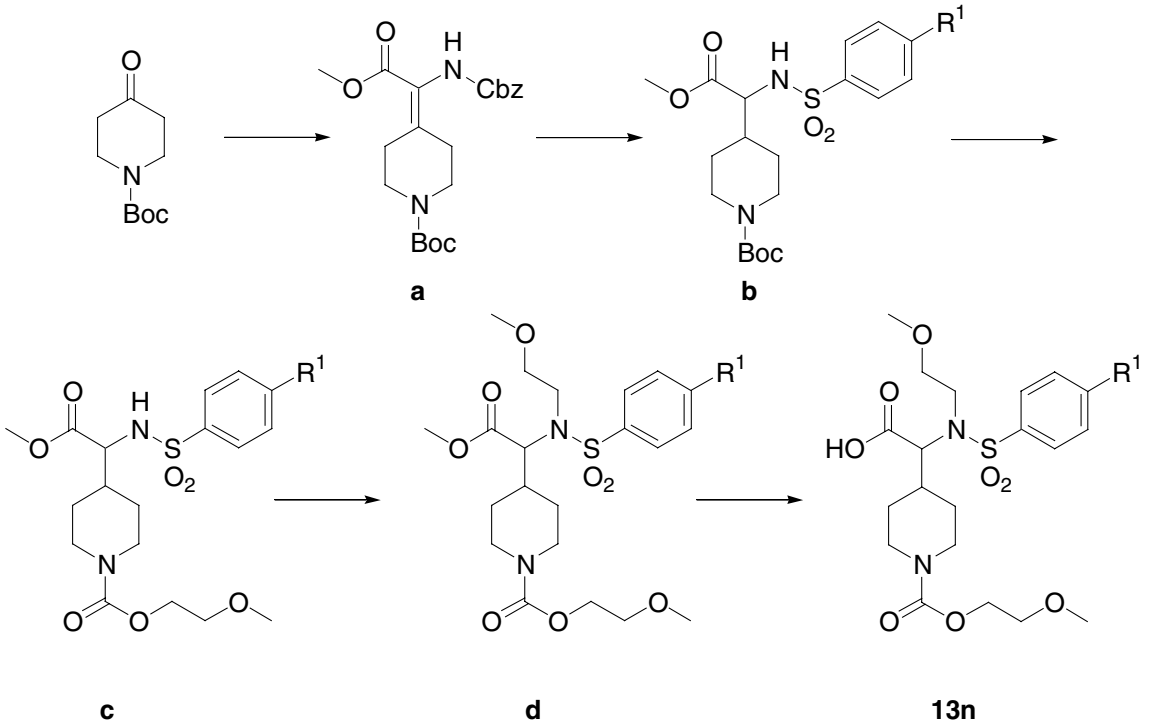
4-{Carboxy-[(4'-methoxy-biphenyl-4-sulfonyl)-(2-methoxy-ethyl)-amino]-methyl}-piperidine-1-carboxylic acid 2-methoxy-ethyl ester (**13n**).



$R^1 = C_6H_4$-4-OMe

a) Benzyloxycarbonylamino-(1-tert-butoxycarbonyl-piperidin-4-ylidene)-acetic acid methyl ester. To a solution of 4-Boc-piperidone (6 g, 30 mmol) and N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (10 g, 30 mmol) in dichloromethane (25 mL) was added dropwise diazabicycloundecane (6.9 g, 42 mmol). The resulting mixture was stirred at room temperature for 2 days when the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and the organic phase was washed with water, 1N hydrochloric acid, saturated sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was purified by silica gel chromatography using 3/2 hexane/EtOAc to give 11.2 g (93.2% yield) of the desired product as a slightly yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 9H), 2.04-2.22 (m, 2H), 2.41-2.49 (m, 2H), 2.90 (s, 2H), 3.52 (s, 2H), 3.79 (s, 3H), 5.17 (s, 2H), 7.37-7.42 (m, 5H). MS m/z 305 [M + H-(*t*-BuCO_2)]$^+$.

b) (1-tert-Butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid methyl ester. Benzyloxycarbonylamino-(1-tert-butoxycarbonyl-piperidin-4-ylidene)-acetic acid methyl ester (11.05 g, 27.3 mmol) was dissolved in methanol (100 mL) and 10% palladium on carbon (0.75 g) was added. The flask was flushed with hydrogen and pressurized to 45 psi, and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through a Celite plug and the solvent was evaporated under reduced pressure to give the crude product that was used in the next step without further purification.

The crude product (5.44 g, 20 mmol) was dissolved in dichloromethane (80 mL) and to the mixture was added triethylamine (3.05 g, 21.8 mmol) followed by 4'-methoxy-biphenyl-4-sulfonyl chloride (5.94 g, 21 mmol). The reaction mixture was stirred overnight at room temperature, washed sequentially with 1N hydrochloric acid, water, 5% aqueous sodium bicarbonate and brine, than dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvent was purified by silica gel chromatography using 3/2 hexane/EtOAc to give 8.22 g (58% combined yield) of the desired product as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.24-1.34 (m, 2H), 1.43-1.59 (m, 10H), 1.65-1.86 (m, 2H), 2.52-2.71 (m, 2H), 3.45 (s, 3H), 3.74-3.88 (m, 1H), 3.94 (s, 3H), 4.11-4.24 (m, 2H), 5.19 (d, J=10.1 Hz, 1H), 7.01 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 7.69 (d, J=8.6 Hz, 2H), 7.86 (d, J=8.6 Hz, 2H). MS m/z 419 $[M + H-(t\text{-}BuCO_2)]^+$.

c) (4'-Methoxy-biphenyl-4-sulfonylamino)-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid methyl ester. To a solution of (1-tert-butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid methyl ester (6.1 g, 11.7 mmol) in dichloromethane (15 mL) at room temperature was added trifluoroacetic acid (8 mL) and the reaction mixture was stirred for 4 hours. Solvents were evaporated under vacuum and the resulting oil was triturated with diethyl ether. The resulting precipitate was collected, washed with diethyl ether and dried under vacuum to give 6.2 g of the crude TFA salt.

The TFA salt was suspended in dichloromethane (30 mL) and triethylamine (3.9 mL, 28 mmol) was added followed by methoxyethylcarbamoyl chloride (1.78 g, 12.9 mmol). The reaction mixture was stirred at room temperature for 4 hour and than concentrated under reduced pressure. The residue was diluted with ethyl acetate and the solution was washed successively with 1N hydrochloric acid, water, brine, and then dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was purified by crystallization from methanol to give 5.24 g (86% combined yield) of the desired product as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.22-1.87 (m, 5H), 2.73 (bs, 2H), 3.41 (s, 3H), 3.47 (s, 3H), 3.62 (t, J=4.8 Hz, 2H), 3.81-3.86 (m, 1H), 3.89 (s, 3H), 4.18-4.32 (m, 4H), 5.20 (d, J=10.1 Hz, 7.03 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H), 7.86 (d, J=8.4 Hz, 2H). MS m/z 521 $[M + H]^+$.

d) [(4'-Methoxy-biphenyl-4-sulfonyl)-(2-methoxy-ethyl)-amino]-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid methyl ester. To a solution of (4'-methoxy-biphenyl-4-sulfonylamino)-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid methyl ester (1.04 g, 2 mmol) in dimethylformamide (8 mL) was added anhydrous cesium carbonate (0.75 g, 2.3 mmol) followed by 2-methoxyethyl bromide (282 μL, 3 mmol). The reaction mixture was stirred at room temperature for 12 hours and than concentrated under reduced pressure. The residue was diluted with methylene chloride and washed successively with water, brine, and then dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was purified by silica gel chromatography using 3/2 hexane/EtOAc to give 1.27 g (91% yield) the desired product as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.22-1.30 (m, 2H), 1.46-1.60 (m, 2H), 2.04-2.08 (m, 1H), 2.79-2.99 (m, 2H), 3.33 (s, 3H), 3.39 (s, 3H), 3.41 (s, 3H), 3.51-3.64 (m, 6H), 3.90 (s, 3H), 4.19-4.28 (m, 5H), 7.04 (d, J=8.8 Hz, 2H), 7.58 (d, J=8.9 Hz, 2H), 7.68 (d, J=8.4 Hz, 2H), 7.87 (d, J=8.2 Hz, 2H). MS m/z 579 $[M + H]^+$.

13n) [(4'-Methoxy-biphenyl-4-sulfonyl)-(2-methoxy-ethyl)-amino]-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid. To a solution of [(4'-methoxy-biphenyl-4-sulfonyl)-(2-

methoxy-ethyl)-amino]-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid methyl ester (323 mg, 0.558 mmol) in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide (67 mg, 2.8 mmol) in methanol-water mixture (0.7 mL, 5:2 v/v) and the reaction mixture was stirred at room temperature for 12 hours. The solvents are removed under reduced pressure and the residue was dissolved in water and washed with diethyl ether. The aqueous layer was than acidified with 1N hydrochloric acid and extracted several times with ethyl acetate. The combined organic extracts were washed with brine and then dried anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was purified using RP-HPLC to give 256 mg (81% yield) of the desired product as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.17-1.29 (m, 2H), 1.65-1.71 (m, 1H), 1.86-2.07 (m, 2H), 2.85 (bs, 2H), 3.33 (s, 3H), 3.39 (s, 3H), 3.49-3.71 (m, 6H), 3.89 (s, 3H), 4.12-4.23 (m, 5H), 7.03 (d, J=9.0 Hz, 2H), 7.58 (d, J=8.8 Hz, 2H), 7.68 (d, J=8.6 Hz, 2H), 7.89 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.6, 36.6, 43.5, 43.8, 44.0, 46.2, 55.8, 59.1, 59.3, 71.3, 72.6, 114.9, 127.2, 128.5, 128.8, 131.8, 137.2, 145.8, 155.7, 160.6, 171.9; MS m/z 565 $[M + H]^+$. Anal. ($C_{27}H_{36}N_2O_9S•0.5H_2O$) C, H, N.

The following analogs were prepared according to the protocol described above for the synthesis of **13n**.

(4'-Methoxy-biphenyl-4-sulfonylamino)-piperidin-4-yl-acetic acid (10a). ^{1}H NMR (CD_3OD) δ 1.54-1.68 (m, 1H), 1.76-1.84 (m, 1H) 1.91-1.96 (m, 2H), 2.11-2.15 (m, 1H), 2.96-3.07 (m, 2H), 3.43-3.47 (m, 2H), 3.87 (s, 3H), 7.06 (d, J=8.8 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.76 (d, J=8.6 Hz, 2H), 7.90 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.3, 25.8, 36.7, 43.7, 54.7, 114.4, 126.6, 127.7, 128.2, 133.23, 140.3, 146.6, 157.5, 173.6; MS m/z 405 $[M + H]^+$. Anal. ($C_{20}H_{24}N_2O_5S$) C, H, N.

(4'-Methoxy-biphenyl-4-sulfonylamino)-(1-methoxycarbonyl-piperidin-4-yl)-acetic acid (13a). ^{1}H NMR ($CDCl_3$) δ 1.12-1.70 (m. 4H), 1.94 (m, 1H), 2.70 (m, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 3.90 (m, 1H), 4.18 (m, 2H), 7.03 (d, J=8.9 Hz, 2H), 7.57 (d, J=8.9 Hz, 2H), 7.68 (d, J=9.0 Hz, 2H), 7.86 (d, J=9.0 Hz, 2H); HRMS $[M + H]^+$ calcd 463.1539, found 463.1542.

(1-Ethoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid (13b). ^{1}H NMR ($CDCl_3$) δ 1.18-1.29 (m, 4H), 1.32-1.42 (m, 1H), 1.60-1.70 (m, 2H), 1.94-1.96 (m, 1H), 2.77 (bs, 2H), 3.79 (d, J=5.8 Hz, 1H), 3.87 (s, 3H), 4.10-4.17 (m, 4H), 7.05 (d, J=8.8 Hz, 2H), 7.65 (d, J=9.0 Hz, 2H), 7.76 (d, J=8.8 Hz, 2H), 7.89 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 15.3, 28.9, 30.2, 40.5, 45.1, 45.1, 115.9, 128.1, 129.2, 129.8, 133.2, 140.3, 146.6, 157.5, 162.1, 173.6; MS m/z 477 $[M + H]^+$. Anal. ($C_{23}H_{28}N_2O_7S \bullet 0.25H_2O$) C, H, N.

(4'-Methoxy-biphenyl-4-sulfonylamino)-[1-(2-propoxy)carbonyl-piperidin-4-yl]-acetic acid (13c). ^{1}H NMR (CD_3OD) δ 1.25 (d, J=6.3 Hz, 6H), 1.25-1.45 (m, 2H), 1.55-1.70 (m, 2H), 1.88-2.00 (m, 1H), 2.70-2.85 (m, 2H), 3.79 (d, J=5.8 Hz, 1H), 3.87 (s, 3H), 4.13 (d, J=13.6 Hz, 2H), 4.87 (m, 1H), 7.05 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H), 7.75 (d, J=8.7 Hz, 2H), 7.89 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.4, 29.3, 39.7, 43.7, 55.7, 59.5, 69.3, 114.8, 127.3, 128.0, 128.7, 137.3, 145.7, 155.5, 160.4, 172.7; MS m/z 491 $[M + H]^+$. Anal. ($C_{24}H_{30}N_2O_7S \bullet 1.5H_2O$) C, H, N.

***(R)*-(1-tert-Butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid (*R*-13d).**

a) *(R)*-Amino-(1-tert-butoxycarbonyl-piperidin-4-yl)-acetic acid methyl ester. To a solution of (R)- [(9H-fluoren-9-ylmethoxycarbonylamino)]-(1--tert-butoxycarbonyl-piperidin-4-yl)-acetic acid methyl ester (402.9 mg, 0.838 mmol) in methanol at room temperature was added trimethylsilyldiazomethane (3.4 mmol) and the solution was stirred until the yellow color faded to colorless. The solvent was removed in vacuo to provide a white solid. The crude ester was than taken up in ethanol, catalytic amount of 10% Pd/C was added and the mixture was placed in a Parr hydrogenation apparatus overnight at a pressure of 40-45 psi. After 24 hours, the reaction mixture was filtered through a pad of Celite, and concentrated to give the crude aminoester as a white solid.

b) *(R)*-(1-tert-Butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid methyl ester. To a solution of methyl *(R)*-amino-(1-tert-butoxycarbonyl-piperidin-4-yl)-acetic

acid methyl ester (10 mL) was added a solution of sodium bicarbonate (214 mg, 2.55 mmol) in water (10 mL). The mixture was cooled to 0°C and to the solution was added 4'-methoxy-biphenyl-4-sulfonyl chloride (270 mg, 0.955 mmol) in tetrahydrofuran (10 mL). The reaction was then allowed to warm to room temperature overnight. The mixture was concentrated under vacuum and the resulting slurry was partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (2x25 mL) and the combined organic phases were washed with 1N hydrochloric acid, water, brine and dried over anhydrous sodium sulfate. The crude product obtained after evaporation of solvents was purified by silica gel chromatography (60:40 hexane:ethyl acetate) to give 180 mg (41% over three steps) of the desired product as a white solid. For NMR data see compound **b** in the synthesis of **13n** above.

c) ***(R)*-(1-tert-Butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid.** To a solution of methyl *(R)*-(1-tert-butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid methyl ester (180 mg, 0.347 mmol) in tetrahydrofuran (15 mL) was added lithium hydroxide hydrate and the solution stirred and heated to 50°C overnight. After cooling the solvents were removed under vacuo and the resulting slurry was diluted with ethyl acetate and acidified to pH=4. The aqueous layer was extracted with ethyl acetate (2x25 mL) and the combined organics were washed with brine and dried. Solvents were evaporated under vacuum to give 80 mg (46% yield) of the desired product as a white solid: α_D -46.9. ^{1}H NMR ($CDCl_3$) δ 1.14-1.46 (m. 2H), 1.47 (s, 9H), 1.62 (t, J = 15.6 Hz, 2H), 1.93 (m, 1H), 2.75 (m, 2H), 3.79 (d, J = 5.9 Hz, 1H), 3.90 (s, 3H), 4.09 (bd, J = 13.6 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.88 (d, 8.6 Hz, 2H); ^{13}C NMR (CD_3OD) δ 29.1, 30.3, 40.6, 56.2, 61.8, 81.5, 115.9, 128.1, 129.2, 129.8, 133.2, 140.3, 146.6, 156.8, 162.1, 174.9. Anal. ($C_{25}H_{31}N_3O_7S$•0.5H_2O) C, H, N.

***(S)*-(1-tert-Butoxycarbonyl-piperidin-4-yl)-(4'-methoxy-biphenyl-4-sulfonylamino)-acetic acid *(S*-13d).** α_D +46.9.

(4'-Methoxy-biphenyl-4-sulfonylamino)-[1-(3-methyl-butyryl)-piperidin-4-yl]-acetic acid (13e). ^{1}H NMR (CD_3OD) δ 0.97 (d, J=6.3 Hz, 6H), 1.18-1.46 (m, 2H), 1.61-1.82 (m, 2H), 1.98-2.10 (m, 2H), 2.27 (d, J=6.2 Hz, 2H), 2.52-2.65 (m, 1H), 3.00-3.15 (m, 1H), 3.77-3.90 (m, 1H), 3.87 (s, 3H), 3.01 (d, J=13.6 Hz, 1H), 4.57 (d, J-12.8 Hz, 1H), 7.05 (d, J=8.8 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.75 (d, J=8.7 Hz, 2H), 7.89 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 22.9, 26.2, 29.1, 39.9, 42.1, 46.4, 55.7, 59.3, 114.8, 127.3, 127.5, 128.7, 131.7, 137.3, 145.7, 155.6, 160.4, 172.1, 172.4; MS m/z 443 $[M + H]^+$. Anal. ($C_{25}H_{32}N_2O_6S$) C, H, N.

(4'-Methoxy-biphenyl-4-sulfonylamino)-[(1-morpholin-4-yl)carbonyl-piperidin-4-yl]-acetic acid (13f). ^{1}H NMR ($CDCl_3$) δ 1.21-1.39 (m, 2H), 1.41-1.47 (m, 2H), 1.56-1.74 (m, 2H), 1.86-2.01 (m, 1H), 3.24 (t, J=4.8 Hz, 4H), 3.62-3.81 (m, 7H), 3.87 (s, 3H), 7.05 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H), 7.76 (d, J=8.7 Hz, 2H), 7.89 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.3, 28.3, 40.1, 55.7, 59.5, 66.8, 114.8, 127.3, 128.0, 128.7, 134.4, 137.3, 145.6, 160.4, 164.3, 172.2; MS m/z 518 $[M + H]^+$. Anal. ($C_{25}H_{31}N_3O_7S$•0.5TFA) C, H, N.

(4'-Methoxy-biphenyl-4-sulfonylamino)-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid (13g). 28.4 % yield; ^{1}H NMR ($CDCl_3$) δ 1.27 (dq, J=12.8, 12.5 Hz, 1H), 1.41 (dq, J=12.8, 12.5 1H), 1.66 (t, J=15.2, 2H), 1.89-2.02 (bs, 1H), 2.71-2.92 (m, 2H), 3.40 (s, 3H), 3.61-3.65 (m, 2H), 3.80 (d, J=6.2 Hz, 1H), 3.88 (s, 3H), 4.15-4.24 (m, 4H), 7.06 (d, J=8.8 Hz, 2H), 7.66 (d, J=8.8 Hz, 2H), 7.77 (d, J=8.8, 2H), 7.90 (d, J=8.8, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2, 39.6, 44.0, 55.7, 59.1, 64.8, 71.1, 114.8, 127.2, 128.7, 131.6, 137.4, 145.6, 155.7, 160.4, 173.0; MS m/z 507 $[M + H]^+$. Anal. ($C_{24}H_{30}N_2O_8S$•0.2H_2O) C, H, N.

[1-(2-Methoxy-ethoxycarbonyl)-piperidin-4-yl]-(4'-methylsulfanyl-biphenyl-4-sulfonylamino)-acetic acid (13h). 92.3%; ^{1}H NMR ($CDCl_3$) δ 1.19-1.50 (m, 2H), 1.57-1.73 (m, 2H), 1.87-2.12 (m, 1H), 2.54 (s, 3H), 2.72-2.90 (bs, 2H), 3.35-3.40 (m, 3H), 3.56-3.68 (m, 2H), 3.76-3.84 (m, 1H), 4.10-4.26 (m, 4H), 7.38 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.6 Hz, 2H), 7.79 (d, J=8.6 Hz, 2H), 7.92 (d, J=8.6

Hz, 2H); ^{13}C NMR (CD_3OD) δ 15.7, 28.9, 30.2, 40.5, 45.2, 45.2, 59.5, 61.8, 66.1, 72.3, 128.1, 128.4, 129.3, 129.8, 137.4, 140.9, 141.5, 146.3, 157.3, 174.5; MS m/z 523 $[M + H]^+$. Anal. ($C_{24}H_{30}N_2O_7S_2$) C, H, N.

(Biphenyl-4-sulfonylamino)-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid (13i). ^{1}H NMR ($CDCl_3$) δ 1.24-1.48 (m, 2H), 1.60-1.70 (m, 2H), 1.92-1.97 (m, 1H), 2.80 (bs, 2H), 3.39 (s, 3H), 3.60-3.63 (m, 2H), 3.81 (d, J=6.1 Hz, 1H), 4.14-4.23 (m, 4H), 7.40-7.53 (m, 3H), 7.70 (d, J=7.0 Hz, 2H), 7.81 (d, J=8.8 Hz, 2H), 7.94 (d, J=8.6 Hz, 2H); ^{13}C NMR (CD_3OD) δ 28.9, 30.2, 40.5, 45.2, 45.2, 59.5, 61.8, 66.1, 72.3, 128.7, 128.8, 129.2, 129.9, 130.5, 141.1, 141.1, 147.0, 157.3, 173.6; MS m/z 477 $[M + H]^+$. Anal. ($C_{23}H_{28}N_2O_7S \bullet 0.25H_2O$) C, H, N.

[1-(2-Methoxy-ethoxycarbonyl)-piperidin-4-yl]-(4-phenoxy-benzenesulfonylamino)-acetic acid (13j). ^{1}H NMR ($CDCl_3$) δ 1.22-1.46 (m, 2H), 1.58-1.69 (m, 2H), 1.90-1.20 (m, 1H), 2.80 (bs, 2H), 3.39 (s, 3H), 3.60-3.64 (m, 2H), 3.75 (d, J=4.0, 1H), 4.14-4.23 (m, 4H), 7.04-7.12 (m, 4H), 7.22-7.28 (m, 1H), 7.42-7.49 (m, 2H), 7.81-7.85 (m, 4H); ^{13}C NMR (CD_3OD) δ 28.8, 30.2, 40.5, 45.2, 45.2, 59.5, 61.7, 66.1, 72.3, 119.0, 121.6, 126.3, 131.0, 131.7, 136.3, 157.3, 163.1, 173.6; MS m/z 493 $[M + H]^+$. Anal. ($C_{23}H_{28}N_2O_8S$) C, H, N.

(4-Butoxy-benzenesulfonylamino)-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid (13k). ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J=7.3 Hz, 3H), 1.21-1.63 (m, 6H), 1.68-1.95 (m, 3H), 2.79 (bs, 2H), 3.39 (s, 3H), 3.60-3.63 (m, 2H), 3.71 (d, J=6.0 Hz, 1H), 4.07 (t, J=6.4 Hz, 2H), 4.13-4.23 (m, 4H), 7.02 (d, J=9.2 Hz, 2H), 7.77 (d, J=8.9 Hz, 2H); ^{13}C NMR (CD_3OD) δ 14.5, 14.8, 20.7, 28.9, 30.2, 32.7, 33.2, 40.5, 45.2, 45.2, 59.5, 61.7, 66.1, 69.6, 72.3, 115.9, 130.8, 133.7, 157.3, 164.3, 173.6; MS m/z 473 $[M + H]^+$. Anal. ($C_{21}H_{32}N_2O_8S \bullet 0.25H_2O$) C, H, N.

[(4'-Methoxy-biphenyl-4-sulfonyl)-methyl-amino]-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid (13l). ^{1}H NMR ($CDCl_3$) δ 1.15-1.35 (m, 2H), 1.75 (t, J=18.1 Hz, 2H), 1.98-2.18 (m, 1H), 2.88 bs, 2H), 2.93 (s, 3H), 3.40 (s, 3H), 3.61-3.64 (m, 2H), 3.87 (s, 3H), 4.11-4.27 (m, 5H), 7.06

(d, J=9.0 Hz, 2H), 7.66 (d, J=9.0 Hz, 2H), 7.78 (d, J=8.8 Hz, 2H), 7.88 (d, J=8.6 Hz, 2H); ^{13}C NMR (CD_3OD) δ 30.5, 31.1, 36.5, 44.9, 45.0, 56.2, 57.1, 59.5, 65.0, 66.1, 72.3, 114.6, 128.2, 129.6, 129.8, 133.2, 138.3, 146.9, 157.4, 162.1, 172.3; MS m/z 521 $[M + H]^+$. Anal. ($C_{25}H_{32}N_2O_8S \bullet 0.5H_2O$) C, H, N.

[(4'-Methoxy-biphenyl-4-sulfonyl)-(pyridin-3-ylmethyl)-amino]-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid (13m). 64.3% yield; ^{1}H NMR ($CDCl_3$) δ 0.82-0.98 (m, 1H), 1.02-1.25 (m, 2H), 1.70-1.55 (m, 2H), 1.78-1.97 (m, 1H), 2.84-2.51 (bs, 1H), 2.68-2.83 (bs, 1H), 3.30-3.42 (m, 4H), 3.56-3.68 (m, 2H), 3.92-3.98 (m, 3H), 3.95-4.10 (m, 2H), 4.15-4.25 (m, 2H), 4.31-4.39 (m, 1H), 4.64-4.72 (m, 1H), 7.07 (d, J=8.8 Hz, 2H), 7.41-7.50 (bs, 1H), 7.66 (d, J=8.8 Hz, 2H), 7.73 (d, J=8.8 Hz, 2H), 7.82 (d, J=8.8 Hz, 2H), 8.01-8.12 (m, 1H); ^{13}C NMR (CD_3OD) δ 30.5, 31.2, 37.6, 44.9, 47.8, 56.2, 59.5, 66.1, 66.4, 72.3, 115.8, 115.9, 127.7, 128.2, 129.6, 129.8, 133.1, 139.4, 140.3, 147.1, 148.9, 150.5, 157.3, 162.2; MS m/z 598 $[M + H]^+$. Anal. ($C_{30}H_{35}N_3O_8S \bullet 0.8EtOAc \bullet 0.1HCl$) C, H, N.

N-Hydroxy-(4'-methoxy-biphenyl-4-sulfonylamino)-[1-(2-methoxy-ethoxycarbonyl)-piperidin-4-yl]-acetic acid amide (14g). ^{1}H NMR ($CDCl_3$) δ 1.13-1.29 (m, 2H), 1.43 (d, J=12.5 Hz, 1H), 1.84 (d, J=13.2 Hz, 1H), 1.95 (bs, 1H), 2.79 (t, J=12.8 Hz, 2H), 3.75 (s, 3H), 3.72 (d, J=7.3 Hz, 1H), 3.78-3.90 (m, 2H), 3.98 (s, 3H), 4.15 (t, J=12.5 Hz, 2H), 4.29-4.39 (m, 2H), 7.10 (d, J=8.4 Hz, 2H), 7.61 (d, J=8.8 Hz, 2H), 7.76 (d, J=8.4 Hz, 2H), 7.85 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.3, 27.7, 38.2, 43.7, 43.9, 56.0, 58.6, 64.8, 70.9, 108.7, 112.5, 115.1, 116.3, 120.0, 127.7, 127.8, 128.9, 132.0, 135.1, 147.0, 156.3, 159.6, 168.8; MS m/z 522 $[M + H]^+$. Anal. ($C_{22}H_{27}N_3O_8S$) C, H, N.

Elemental Analysis

Compound	Mol. Formula	Calcd	Found	HRMS
10a	$C_{20}H_{24}N_2O_5S$	C, 59.39; H, 5.98; N, 6.93	C, 59.095; H, 6.03; N, 6.80	
13a	$C_{22}H_{26}N_2O_7S$			calcd 463.1539, found 463.1542
13b	$C_{23}H_{28}N_2O_7S•0.25H_2O$	C, 57.43; H, 5.97; N, 5.82	C, 57.39; H, 5.86; N, 5.78	
13c	$C_{24}H_{30}N_2O_7S•1.5H_2O$	C, 55.55; H, 6.28; N, 5.28	C, 55.46; H, 6.34; N, 5.25	
***(R)*-13d**	$C_{25}H_{31}N_3O_7S•0.5H_2O$	C, 58.46; H, 6.48; N, 5.45	C, 58.29; H, 6.65; N, 5.38	α_D –46.9^0
***(S)*-13d**	$C_{25}H_{31}N_3O_7S•0.5H_2O$	C, 58.46; H, 6.48; N, 5.45	C, 58.65; H, 6.71; N, 5.14	α_D +42.0^0
13e	$C_{25}H_{32}N_2O_6S$	C, 61.45; H, 6.60; N, 5.73	C, 61.64; H, 6.58; N, 5.48	
13f	$C_{25}H_{31}N_3O_7S•0.5TFA$	C, 54.35; H, 5.53; N, 7.31	C, 54.18; H, 5.68; N, 7.38	
13g	$C_{24}H_{30}N_2O_8S•0.2H_2O$	C, 56.60; H, 6.01; N, 5.49	C, 56.27; H, 5.95; N, 5.47	

13h	$C_{24}H_{30}N_2O_7S_2$	C, 55.16; H, 5.79; N, 5.36	C, 54.91, H, 5.77; N, 5.22
13i	$C_{23}H_{28}N_2O_7S \bullet 0.25H_2O$	C, 57.47; H, 5.97; N, 5.82	C, 57.54; H, 6.19; N, 5.59
13j	$C_{23}H_{28}N_2O_8S$	C, 56.09; H, 5.73; N, 5.69	C, 55.80; H, 5.99; N, 5.42
13k	$C_{21}H_{32}N_2O_8S \bullet 0.25H_2O$	C, 52.87; H, 6.87; N, 5.87	C, 52.69; H, 6.68; N, 5.89
13l	$C_{25}H_{32}N_2O_8S \bullet 0.5H_2O$	C, 56.70; H, 6.28; N, 5.29	C, 56.55; H, 6.16; N, 5.21
13m	$C_{30}H_{35}N_3O_8S \bullet 0.8$EtOAc$\bullet$ 0.1HCl	C, 59.98; H, 6.37; N, 6.21	C, 60.14; H, 6.30; N, 5.82
13n	$C_{27}H_{36}N_2O_9S \bullet 0.5H_2O$	C, 56.53; H, 6.50; N, 4.88	C, 56.25; H, 6.60; N, 4.76
14g	$C_{22}H_{27}N_3O_8S$	C, 54.53; H, 5.90; N, 7.73	C, 54.33; H, 6.08; N, 7.92