Discovery of 2-Alkyl-1-arylsulfonylprolinamides as 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors

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3T3-L1 cell culture and differentiation

3T3-L1 preadipocytes were maintained at 70% confluence in DMEM supplemented with 10% FBS, 25 mmol/L glucose and antibiotics (DMEM/FBS). Cells were grown for 2 days post-confluence and cultured in DMEM/FBS supplemented with 1 μmol/L insulin, 0.25 μmol/L dexamethasone and 0.5 mmol/L 3-isobutyl-1-methylxanthine for 3 days. The medium was replaced with DMEM/FBS supplemented with only 1 μmol/L insulin for 3 days and then DMEM/FBS alone for 2 days. Cytoplasmic triacylglycerol droplets were visible on day 5 after initiation of differentiation. The differentiated cells were used when ～90% of the cells showed an adipocyte phenotype.

11β-HSD1 enzyme activity assay

The reductase activity of 11β-HSD1 in intact 3T3-L1 adipocytes was determined by measuring the rate of conversion of cortisone to cortisol. 3T3-L1 adipocytes were incubated for 1 h at 37 ℃ in serum-free DMEM containing 6.25 nmol/L [1,2-(N) 3H]-cortisone and different concentrations of compound, and 0.1% DMSO was set as the vehicle control. At the end of the incubation, 80 μL of medium was pipetted into a transparent bottom 96-well plate, and 35 μL of SuperBlock Blocking Buffer containing 10 g/L of protein A-coated yttrium silicate beads and 3 mg/L of anti-cortisol antibodies was added. The mixtures were shaken in the dark for 2 h and then used for liquid scintillation readings.

Material, synthetic procedure and analytical data of intermediates and target molecules

The reagents (chemicals) were purchased from Acros, Admas, Aldrich, Alfa-Aesar, TCI, and Shanghai Chemical Reagent Company (SCRC) and used without further purification. All non-aqueous reactions were performed in dried glassware under an atmosphere of Ar, unless otherwise specified. Yields were not optimized. NMR spectra were performed on Varian Mercury-300 spectrometer. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), and broad (br). The LC-MS was carried out on Thermo Finnigan LCQDECAXP. Low-resolution mass spectra (LRMS) were produced by Finnigan MAT-95 and Finnigan LCQ Deca spectrometers and high resolution mass spectra (HRMS) were measured on Finnigan MAT 95 and MicroMass Q-Tof ultima mass spectrometers.

1. Synthesis of target compounds 4a – g

(*R*)-methyl 2-methylpyrrolidine-2-carboxylate hydrochloride (6)

(*R*)-2-methylpyrrolidine-2-carboxylic acid **5** (1.29 g, 10 mmol) was dissolved in MeOH (100 mL). To this solution, $SOCl_2$ (25 mL) was then added drop-wise and the mixture was refluxed for 2h. The solvent was evaporated at reduced pressure to give **6** as a white solid (1.79 g, yield: 100 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.6 (s, 1H), 9.48 (s, 1H), 3.91 (s, 3H), 3.60 (m, 2H), 2.39 (m, 1H), 1.90-2.42 (m, 3H), 1.78 (s, 3H); LC/MS (ESI): *m/z* 144 $[M+H]^+$.

(*R*)-1-(3-chloro-2-methylphenylsulfonyl)-2-methylpyrrolidine-2-carboxylic acid (7)

To a stirred solution of **6** (1.43 g, 8 mmol) in CH_2Cl_2 (80 mL) was added Et_3N (2 mL) and 3-chloro-2-methylbenzene-1-sulfonyl chloride (1.8g, 8mmol). The resulting mixture was stirred at room temperature for 6h, and washed successively with 1N HCl (20 mL × 2) and brine (20 mL × 2). The organic layer was dried over anhydrous Na_2SO_4,filtered and concentrated to give the crude product. Purification using flash chromatography (hexane / EtOAc; gradient elution) afforded the ester intermediate as a white sold. LC/MS (ESI): *m/z* 332 $[M+H]^+$.

The obtained ester intermediate was dissolved in MeOH/THF (30 mL / 30 mL), which was treated with aq NaOH (5N, 1 mL) and stirred at room temperature overnight. The solvent was evaporated at reduced pressure. The residue was dissolved in H_2O (25 mL), washed with EtOAc (50 mL × 2), acidified with aq HCl, and extracted with EtOAc (60 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give product **7** as a white solid (1.93 g, yield: 76 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 7.8, 8.4 Hz, 1H), 4.52 (s, br, 1H), 3.68 - 3.80 (m, 1H), 3.51 - 3.62 (m, 1H), 2.70 (s, 3H), 2.30 - 2.39 (m, 1H), 1.91 - 2.10 (m, 3H), 1.59 (s, 3H); LC/MS (ESI): *m/z* 318 $[M+H]^+$.

General method of condensation reaction for 4a - g

To a solution of **7** (92 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) was added BOP-Cl （221 mg, 0.87 mmol）, DIPEA（112 mg, 0.87 mmol）and an appropriate amine (RNH_2, 0.29 mmol). The resulting mixture was stirred at room temperature overnight, and then washed successively with 1N HCl (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (CH_2Cl_2/MeOH; gradient elution) to afford target compounds **4a~4g**.

(*2R*)-1-(3-chloro-2-methylphenylsulfonyl)-*N*-cyclohexyl-2-methylpyrrolidine-2-carboxamide (4a)

White solid (77 mg, yield: 67 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.26 (dd, J_1 = 8.1 Hz, J_2 = 8.1 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 3.83-3.69 (m, 1H), 3.65-3.55 (m, 1H), 3.52-3.42 (m, 1H), 2.73 (s, 3H), 2.70-2.62 (m, 1H), 1.97-1.78 (m, 7H), 1.58 (s, 3H), 1.43-1.12 (m, 6H); LC/MS (ESI): *m/z* 399 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{19}H_{28}ClN_2O_3S^+$: 399.1504, found: 399.1510.

(*2R*)-1-(3-chloro-2-methylphenylsulfonyl)-(*trans*)-*N*-(4-hydroxycyclohexyl)-2-methylpyrrolidine-2-carboxamide (4b)

White solid (67 mg, yield: 56 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.26 (dd, J_1 = 8.0 Hz, J_2 = 7.8 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 3.77-3.55 (m,

3H), 3.50-3.40 (m, 1H), 2.72 (s, 3H), 2.68-2.61 (m, 1H), 2.04-1.75 (m, 8H), 1.60 (s, 3H), 1.47-1.25 (m, 4H); LC/MS (ESI): *m/z* 415 [*M*+H] $^{+}$; HRMS-ESI: *m/z* [*M*+Na]$^{+}$ calcd for $C_{19}H_{27}ClN_2NaO_4S^{+}$: 437.1272, found: 437.1278.

(*2R*)-1-(3-chloro-2-methylphenylsulfonyl)-(*trans*)-*N*-(4-methoxycyclohexyl)-2-methyl pyrrolidine-2-carboxamide (4c)

White solid (52 mg, yield: 42 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.25 (dd, J_1 = 8.0 Hz, J_2 = 7.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 3.74-3.69 (m, 1H), 3.64-3.55 (m, 1H), 3.48-3.39 (m, 1H), 3.32 (s, 3H), 3.18-3.10 (m, 1H), 2.70 (s, 3H), 2.67-2.60 (m, 1H), 2.04-1.73 (m, 8H), 1.59 (s, 3H), 1.36-1.17 (m, 4H); LC/MS (ESI): *m/z* 429 [*M*+H] $^{+}$; HRMS-ESI: *m/z* [*M*+H]$^{+}$ calcd for $C_{20}H_{30}ClN_2O_4S^{+}$: 429.1609, found: 429.1632.

(*2R*)-1-(3-chloro-2-methylphenylsulfonyl)-*N*-(2-adamantyl)-2-methylpyrrolidine-2-carboxamide (4d)

White solid (64 mg, yield: 49 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.25 (dd, J_1 = 7.7 Hz, J_2 = 8.1 Hz, 1H), 4.02 (d, *J* = 7.7 Hz, 1H), 3.73-3.66 (m, 1H), 3.56-3.47 (m, 1H), 2.74 (s, 3H), 2.73-2.69 (m, 1H), 1.99-1.63 (m, 17H), 1.63 (s, 3H); LC/MS (ESI): *m/z* 451 [*M*+H]$^{+}$; HRMS-ESI: *m/z* [*M*+Na]$^{+}$ calcd for $C_{23}H_{31}ClN_2NaO_3S^{+}$: 473.1636, found: 473.1632.

(*2R*)-1-(3-chloro-2-methylphenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4e)

White solid (58 mg, yield: 43 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.0 Hz, 1H), 7.26 (dd, J_1 = 8.1 Hz, J_2 = 8.0 Hz, 1H), 3.98 (m, 1H), 3.72-3.66 (m, 1H), 3.55-3.46 (m, 1H) 2.73 (s, 3H), 2.73-2.69 (m, 1H), 2.19 (br s, 2H), 2.08 (br s, 1H), 1.96-1.69 (m, 12H), 1.62 (s, 3H), 1.54 (br s, 1H), 1.49 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 141.5, 137.5, 135.8, 133.6, 126.6, 126.5, 71.8, 67.5, 53.0, 50.5, 45.3, 44.4, 44.4, 40.3, 33.9, 33.6, 30.6, 30.3, 29.7, 22.8, 22.4, 17.3; LC/MS (ESI): m/z 467 [M+H]$^{+}$; HRMS-ESI: m/z [M+Na]$^{+}$ calcd for $C_{23}H_{31}ClN_2NaO_4S^{+}$: 489.1585, found: 489.1593. HPLC: t_R =

2.69 min (99%) with elution at 0.5 ml/min by linear gradient of 10–80% CH_3CN in 0.1% NH_4OH.

(*2R*)-1-(3-chloro-2-methylphenylsulfonyl)-*N*-(1-hydroxyadamant-3-yl)-2-methylpyrrolidine-2-carboxamide (4f)

White solid (41 mg, yield: 30 %). ^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, J = 8.1 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.26 (dd, J_1 = 8.1 Hz, J_2 = 7.8 Hz, 1H), 6.80 (s, 1H), 3.62-3.57 (m, 1H), 3.51-3.45 (m, 1H), 2.74 (s, 3H), 2.65-2.60 (m, 1H), 2.29 (br s, 2H), 2.09-1.73 (m, 10H), 1.72-1.50 (m, 9H); LC/MS (ESI): *m/z* 467 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{23}H_{31}ClN_2NaO_4S^+$: 489.1585, found: 489.1586.

9-{[(2*R*)-1-(3-Chloro-2-methyl-benzenesulfonyl)-2-methyl-pyrrolidine-2-carbonyl]-amino}-3-oxa-bicyclo[3.3.1]nonane-7-carboxylic acid methyl ester (4g)

White solid (37 mg, yield: 26 %). ^{1}H NMR (300 MHz, $CDCl_3$): 7.69 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.26 (dd, J_1 = 8.1 Hz, J_2 = 7.9 Hz, 1H), 4.03-3.71 (m, 5H), 3.67 (s, 3H), 3.66-3.44 (m, 2H), 2.76-2.67 (m, 1H), 2.72 (s, 3H), 2.20-2.16 (m, 2H), 2.02-1.79 (m, 8H), 1.62 (s, 3H); LC/MS (ESI): *m/z* 499 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}ClN_2O_6S^+$: 499.1664, found: 499.1667.

Compounds **8a, 8b** and **8e** were prepared by the same procedure as **4a, 4b** and **4e,** but using (*S*)-2-methylpyrrolidine-2-carboxylic acid (**9**) instead of the (*R*)-acid **5** as starting material.

(*2S*)-1-(3-chloro-2-methylphenylsulfonyl)-N-cyclohexyl-2-methylpyrrolidine-2-carboxamide (8a)

White solid (81 mg, yield: 70 %). HNMR($CDCl_3$): δ = 7.72 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.26 (dd, J_1 = 7.7 Hz, J_2 = 8.1 Hz, 1H), 6.85 (d, J = 7.1 Hz, 1H), 3.77-3.73 (m, 1H), 3.63-3.58 (m, 1H), 3.52-3.43 (m, 1H), 2.73 (s, 3H), 2.70-2.63 (m, 1H), 1.95-1.83 (m, 7H), 1.60 (s, 3H), 1.43-1.21 (m, 6H); LC/MS (ESI): *m/z* 399 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{19}H_{26}ClN_2NaO_3S^+$: 421.1323, found: 421.1338..

(*2S*)-1-(3-chloro-2-methylphenylsulfonyl)-(*trans*)-N-(4-hydroxycyclohexyl)-2-methylpyrrolidine-2-carboxamide (8b)

White solid (78 mg, yield: 65 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.26 (dd, J_1 = 7.8 Hz, J_2 = 8.1 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 3.74 - 3.65 (m, 3H), 3.58 - 3.46 (m, 1H), 2.72 (s, 3H), 2.68 - 2.62 (m, 1H), 2.02 - 1.76 (m, 8H), 1.60 (s, 3H), 1.42 - 1.25 (m, 4H); LC/MS (ESI): *m/z* 415 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{19}H_{28}ClN_2O_4S^+$: 415.1453, found: 415.1442.

(*2S*)-1-(3-chloro-2-methylphenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (8e)

White solid (62 mg, yield: 46 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.26 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H), 4.00 - 3.97 (m, 1H), 3.71 - 3.66 (m, 1H), 3.54 - 3.46 (m, 1H), 2.73 (s, 3H), 2.72 - 2.68 (m, 1H), 2.18 (br s, 2H), 2.07 (br s, 1H), 1.96 - 1.78 (m, 12H), 1.62 (s, 3H), 1.53 (br s, 1H), 1.49 (br s, 1H); LC/MS (ESI): *m/z* 467 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}ClN_2O_4S^+$: 467.1766, found: 467.1768.

2. Synthesis of target compounds 4eb - el

(*R*)-1-(tert-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (12)

To a stirred solution of (*R*)-2-methylpyrrolidine-2-carboxylic acid **5** (1.29 g, 10 mmol) in dioxane/sat. Na_2CO_3 aq. (100 mL, 1:1) was added dropwise at 0ºC a solution of $(Boc)_2O$ (2.17 g, 12 mmol) in dioxane (20 mL). The mixture was stirred at rt. overnight, and washed with EtOAc (50 mL × 3), acidified with 2N HCl to pH = 2. The water phase was extracted with EtOAc (50 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give product **12** as a white solid (1.69 g, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$): 3.59-3.42 (m, 2H), 2.41 and 2.24 (2 × m, 1H), 1.92-1.78 (m, 3H), 1.56 and 1.51 (2 × s, 3H), 1.45 and 1.42 (2 × s, 9H). LC/MS (ESI): *m/z* 230 $[M+H]^+$.

(*2R*)-*tert*-butyl 2-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (13)

To a solution of **12** (1.6 g, 7 mmol) in CH_2Cl_2 (10 mL) was added BOP-Cl（5.08 g, 20 mmol）, DIPEA（3.6 mL, 15 mmol）and (*trans*)-1-hydroxy-4-adamantylamine hydrochloride (1.79 g, 8.8 mmol). The resulting mixture was stirred at rt overnight, and then washed successively with 1N HCl (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (CH_2Cl_2/MeOH; gradient elution) to give product **13** as a white solid (1.4 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (br s, 1H), 3.99 - 3.91 (m, 1H), 3.61 - 3.37 (m, 2H), 2.78 - 2.70 (m, 1H), 2.12 (br s, 2H), 2.04 (br s, 1H), 1.91-1.60 (m, 12H), 1.59 (s, 3H), 1.52-1.46 (m, 2H), 1.46 (s, 9H); LC/MS (ESI): *m/z* 379 $[M+H]^+$.

(*2R*)-1-(3,4-dimethoxyphenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4eb)

To a solution of **13** (189 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added 4N HCl (g) in dioxane (0.5 mL). The resulting mixture was stirred at rt for 2h. The solvent was evaporated at reduced pressure. The residue was dissolved in acetonitrile (5 mL) and then was added Et_3N (0.14 mL, 1 mmol) and 3,4-dimethoxybenzene-1-sulfonyl chloride (120 mg, 0.5 mmol). The mixture was stirred at rt overnight, and then added CH_2Cl_2 (10 mL), washed successively with 1N HCl (2 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography (CH_2Cl_2/MeOH; gradient elution) to give product **4eb** as a white solid (149 mg, 62 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 1H), 7.30 - 7.29 (m, 2H), 6.92 (d, J = 8.8 Hz, 1H), 3.98 - 3.90 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.74 - 3.68 (m, 1H), 3.30 - 3.22 (m, 1H), 2.53 - 2.46 (m, 1H), 2.19 (br s, 2H), 2.08 (br s, 1H), 1.97 - 1.63 (m, 12H), 1.60 (s, 3H), 1.59 - 1.45 (m, 2H); LC/MS (ESI): *m/z* 479 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{24}H_{34}N_2NaO_6S^+$: 501.2030, found: 501.2025.

Compounds 4ec~4el were prepared according to the method described for 4eb.

(*2R*)-1-(4-*tert*-butylphenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ec)

White solid (173 mg, 73 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 7.7 Hz, 1H), 4.01-3.99 (m, 1H), 3.77 - 3.74 (m, 1H), 3.37 - 3.28 (m, 1H), 2.57 - 2.50 (m, 1H), 2.22 (br s, 2H), 2.11 (br s, 1H), 2.00 - 1.74 (m, 12H), 1.61 (s, 3H), 1.60 - 1.51 (m, 4H), 1.35 (s, 9H); LC/MS (ESI): *m/z* 475 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$calcd for $C_{26}H_{39}N_2O_4S^+$: 475.2625, found: 475.2641.

(*2R*)-1-(2-chloro-4-cyanophenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ed)

White solid (132 mg, 55 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.83 (d, *J* = 1.0 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 3.98 - 3.88 (m, 2H), 3.83 - 3.76 (m, 1H), 2.67 - 2.61 (m, 1H), 2.18 (br s, 2H), 2.09 (br s, 1H), 1.97 - 1.72 (m, 12H), 1.55 - 1.50 (m, 2H), 1.42 (s, 3H); LC/MS (ESI): *m/z* 478 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{23}H_{28}ClN_3NaO_4S^+$: 500.1381, found: 500.1398.

(*2R*)-1-(2-cyanophenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ee)

White solid (135 mg, 61 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H), 7.90 (dd, J_1 = 7.5 Hz, J_2 = 1.4 Hz, 1H), 7.80 - 7.68 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 4.01 - 3.90 (m, 2H), 3.77 - 3.68 (m, 1H), 2.60 - 2.54 (m, 1H), 2.20 (br s, 2H), 2.11 (br s, 1H), 1.94 - 1.63 (m, 12H), 1.59 - 1.51 (m, 2H), 1.55 (s, 3H); LC/MS (ESI): *m/z* 444 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{23}H_{30}N_3O_4S^+$: 444.1952, found: 444.1953.

(*2R*)-1-(4-acetylphenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ef)

White solid (154 mg, 67 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.31 - 7.28 (m, 1H), 4.00 - 3.90 (m, 1H), 3.78 - 3.72 (m, 1H), 3.40 - 3.30 (m, 1H), 2.65 - 2.60 (m, 1H), 2.55 (s, 3H), 2.53 - 2.58 (m, 1H), 2.22 (br s, 2H), 2.12 (br s, 1H), 1.97 - 1.77

(m, 11 H), 1.59 (s, 3H), 1.54 - 1.49 (m, 2H); LC/MS (ESI): *m/z* 461 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{24}H_{32}N_2NaO_5S^+$: 483.1924, found: 483.1949.

(*2R*)-1-(biphenyl-4-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4eg)

White solid (127 mg, 51 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.51 - 7.43 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 1H), 4.03 - 4.00 (m, 1H), 3.82 - 3.79 (m, 1H), 3.37 - 3.36 (m, 1H), 2.60 - 2.53 (m, 1H), 2.23 (br s, 2H), 2.13 (br s, 1H), 2.04 - 1.78 (m, 10H), 1.65 (s, 3H), 1.64 - 1.42 (m, 4H); LC/MS (ESI): *m/z* 495 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$calcd for $C_{28}H_{34}N_2NaO_4S^+$: 517.2131, found: 517.2137.

(*2R*)-1-(pyridine-3-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4eh)

White solid (91 mg, 43 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (s, 1H), 8.83 (d, *J* = 4.5 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.49 (dd, J_1 = 4.5 Hz, J_2 = 7.7 Hz, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 4.02 - 3.99 (m, 1H), 3.83 - 3.77 (m, 1H), 3.38 - 3.30 (m, 1H), 2.59 - 2.53 (m, 1H), 2.22 (br s, 2H), 2.13 (br s, 1H), 1.95 - 1.62 (m, 12H), 1.61 (s, 3H), 1.60 - 1.49 (m, 2H); LC/MS (ESI): *m/z* 420 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$calcd for $C_{21}H_{29}N_3NaO_4S^+$: 442.1771, found: 442.1766.

(*2R*)-1-(thiophene-2-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ei)

white solid (136 mg, 64 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 - 7.61 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.13 - 7.10 (m, 1H), 4.00 - 3.96 (m, 1H), 3.79 - 3.73 (m, 1H), 3.47 - 3.39 (m, 1H), 2.61 - 2.54 (m, 1H), 2.20 (br s, 2H), 2.11 (br s, 1H), 1.95 - 1.70 (m, 10H),1.66 (s, 3H), 1.58 - 1.48 (m, 4H); LC/MS (ESI): *m/z* 425 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{20}H_{29}N_2O_4S_2^+$: 425.1563, found: 425.1577.

(*2R*)-1-(5-bromothiophene-2-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ej)

White solid (102 mg, 40 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 4.1 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 4.1 Hz, 1H), 4.00 - 3.97 (m, 1H), 3.77 - 3.71 (m, 1H), 3.43 - 3.35 (m, 1H), 2.61 - 2.54 (m, 1H), 2.19 (br s, 2H), 2.10 (br s, 1H), 1.90 - 1.76 (m, 10H),1.67 (s, 3H), 1.59 - 1.48 (m, 4H); LC/MS (ESI): *m/z* 503 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{20}H_{27}BrN_2NaO_4S_2^+$: 525.0488, found: 525.0496.

(*2R*)-1-(quinoline-8-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4ek)

White solid (57 mg, 24 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (d, *J* = 4.2 Hz, 1H), 8.53 (d, *J* = 7.5 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.84 - 7.80 (m, 1H), 7.63 (dd, J_1 = 7.5 Hz, J_2 = 8.1 Hz, 1H), 7.56 (dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, 1H), 4.98 - 4.88 (m, 1H), 4.02 - 3.97 (m, 1H), 3.89 - 3.83 (m, 1H), 2.58 - 2.51 (m, 1H), 2.23 (br s, 2H), 2.16 (br s, 1H), 2.06 - 1.73 (m, 11H), 1.55 (s, 3H), 1.55 - 1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 151.1, 143.7, 141.1, 136.7, 133.4, 132.4, 129.0, 125.8, 122.2, 70.4, 67.5, 53.0, 51.3, 45.2, 44.3, 39.8, 34.1, 33.6, 30.7, 30.3, 29.6, 22.1, 21.9, 14.0; LC-MS (ESI): 470 $[M+1]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{31}N_3NaO_4S^+$: 492.1927, found: 492.1922. HPLC: t_R = 3.54 min (100%) with elution at 0.3 ml/min by linear gradient of 10 – 60% CH_3CN in 0.1% NH_4OH.

(*2R*)-1-(5-dimethylaminonaphthalene-1-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (4el)

White solid (124 mg, 48 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 7.4 Hz, 1H), 7.57 - 7.48 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.03 - 4.00 (m, 1H), 3.75 - 3.70 (m, 1H), 3.55 - 3.46 (m, 1H), 2.87 (s, 6H), 2.66 - 2.60 (m, 1H), 2.18 (br s, 2H), 2.11 (br s, 1H), 1.98 - 1.75 (m, 12H), 1.65 (s, 3H), 1.53 - 1.48 (m, 2H); LC/MS (ESI): *m/z* 512 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{24}H_{32}N_2NaO_5S^+$: 534.2397, found: 534.2403.

3. Synthesis of target compounds 17a ~ c

(2*R*)-2-methyl-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenylsulfonyl)pyrrolidine-2-carboxylic acid (16)

(*R*)-methyl 1-(4-acetylphenylsulfonyl)-2-methylpyrrolidine-2-carboxylate (**15)** was prepared according to the method described for ester of **7**. To a 50 mL flask containing compound **15** (325 mg, 1 mmol) and 5 mL anhydrous THF was added TMS-CF_3 (426 mg, 3 mmol). The mixture was cooled to 0ºC and added dropwise 1.0 M tetrabutylammonium fluoride in THF (3 mL, 3 mmol). After stirring at rt for 2 h, the solution was diluted with sat. $NaHCO_3$, extracted with CH_2Cl_2 (50 mL × 2), washed with brine (10 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated to give the intermediate as a white solid. The obtained intermediate was dissolved in MeOH/THF (10 mL / 10 mL), treated with aq NaOH (5N, 1 mL) and stirred at rt overnight. Then the solvent was evaporated at reduced pressure, the residue was dissolved in H_2O (10 mL), washed with CH_2Cl_2 (10 mL × 2), acidified with aq HCl, and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to give product **16** as a white solid (190 mg, 50 %), which was used for the next step without further purification. LC/MS (ESI): *m/z* 382 $[M+H]^+$.

Compounds **17a - c** were prepared according to the method described in "General method of condensation reaction for **4a - g**".

(*2R*)-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenylsulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (17a)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 3.92 - 3.90 (m, 1H), 3.75 - 3.72 (m, 1H), 3.34 - 3.26 (m, 1H), 2.42 - 2.39 (m, 1H), 2.15 (br s, 2H), 2.06 (br s, 1H), 1.94 - 1.71 (m, 15H), 1.56 (s, 3H), 1.55 - 1.48 (m, 2H); LC/MS (ESI): *m/z* 531 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{25}H_{34}F_3N_2O_5S^+$: 531.2135, found: 531.2137.

(*2R*)-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenylsulfonyl)-(*trans*)-*N*-(1-cyanoadamant-4-yl)-2-methylpyrrolidine-2-carboxamide (17b)

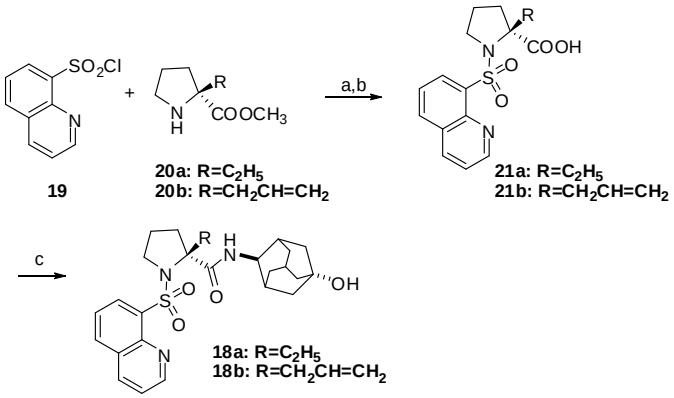
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 4.02 - 4.00 (m, 1H), 3.80 - 3.73 (m, 1H), 3.35 - 3.27 (m, 1H), 2.54 - 2.48 (m, 1H), 2.20 - 1.98 (m, 10H), 1.93 - 1.76 (m, 7H), 1.71 - 1.55 (m, 6H); LC/MS (ESI): *m/z* 540 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$calcd for $C_{26}H_{32}F_3N_3NaO_4S^+$: 562.1958, found: 562.1956.

(*trans*)-methyl 4-(*2R*)-2-methyl-1-(4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)phenylsulfonyl) pyrrolidine-2-carboxamido)adamant-1-carboxylate (17c)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 8.6 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 4.02 - 4.00 (m, 1H), 3.80 - 3.75 (m, 1H), 3.67 (s, 3H), 3.38 - 3.29 (m, 1H), 2.56 - 2.51 (m, 1H), 2.14 (br s, 1H), 2.08 - 1.96 (m, 6H), 1.92 - 1.75 (m, 9H), 1.71 - 1.60 (m, 6H); LC/MS (ESI): *m/z* 573 $[M+H]^+$; HRMS-ESI: *m/z* $[M+Na]^+$calcd for $C_{27}H_{35}F_3N_2NaO_6S^+$: 595.2060, found: 595.2070.

4. Synthesis of target compounds 18a and 18b

Scheme 4. Synthesis of 18a and 18b[a]



[a]Reagents and conditions: (a) Triethylamine, CH_2Cl_2, rt, 2h; (b) NaOH, THF, CH_3OH, H_2O, rt, overnnight; (c) trans-4-aminoadamantan-1-ol hydrochloride, BOP-Cl, DIPEA, CH_2Cl_2, rt, overnight.

Compounds **18a and 18b** were prepared according to the method described for **4ek** using (*R*)-2-ethylpyrrolidine-2-carboxylic acid or (*S*)-2-allylpyrrolidine-2-carboxylic acid as starting material in stead of (*R*)-2-methylpyrrolidine-2-carboxylic acid **5**.

(*2R*)-1-(quinoline-8-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-ethylpyrrolidine-2-carbo xamide (18a)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (dd, J_1 = 1.8 Hz, J_2 = 4.1 Hz, 1H), 8.52 (dd, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 8.27 (dd, J_1 = 1.8 Hz, J_2 = 8.3 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.04 (dd, J_1 = 1.2

Hz, J_2 = 8.2 Hz, 1H), 7.63 (dd, J_1 = 8.2 Hz, J_2 = 7.6 Hz, 1H), 7.55 (dd, J_1 = 4.1 Hz, J_2 = 8.3 Hz, 1H), 4.94 - 4.85 (m, 1H), 4.03 - 4.00 (m, 1H), 3.85 - 3.78 (m, 1H), 2.73 - 2.68 (m, 1H), 2.27 - 2.15 (m, 4H), 2.01 - 1.85 (m, 6H), 1.81 - 1.74 (m, 4H), 1.58 - 1.49 (m, 3H), 0.59 (t, J = 7.6 Hz, 3H); LC/MS (ESI): *m/z* 484 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}N_3O_4S^+$: 484.2265, found: 484.2264.

(*2S*)-1-(quinoline-8-sulfonyl)-(*trans*)-*N*-(1-hydroxyadamant-4-yl)-2-allylpyrrolidine-2-carboxamide (18b)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (dd, J_1 = 1.7 Hz, J_2 = 4.2 Hz, 1H), 8.51 (dd, J_1 = 1.1 Hz, J_2 = 7.6 Hz, 1H), 8.27 (dd, J_1 = 1.7 Hz, J_2 = 8.6 Hz, 1H), 8.05 (dd, J_1 = 1.1 Hz, J_2 = 8.2 Hz, 1H), 7.98 - 7.94 (m, 1H), 7.63 (dd, J_1 = 8.2 Hz, J_2 = 7.6 Hz, 1H), 7.56 (dd, J_1 = 4.2 Hz, J_2 = 8.6 Hz, 1H), 5.25 – 5.38 (m, 1H), 4.80 - 4.69 (m, 3H), 4.00 – 3.97 (m, 1H), 3.87 - 3.84 (m, 1H), 3.84 (s, 2H), 3.04 – 2.90 (m, 1H), 2.62-2.53 (m, 1H), 2.25 – 1.71 (m, 12H), 1.55-1.45 (m, 4H); LC/MS (ESI): *m/z* 496 $[M+H]^+$; HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{27}H_{34}N_3O_4S^+$: 496.2265, found: 496.2262.