

Supporting Information

4-Aryl pyrrolidines as a novel class of orally efficacious antimalarial agents. Part 1:

Evaluation of 4-aryl-*N*-benzylpyrrolidine-3-carboxamides

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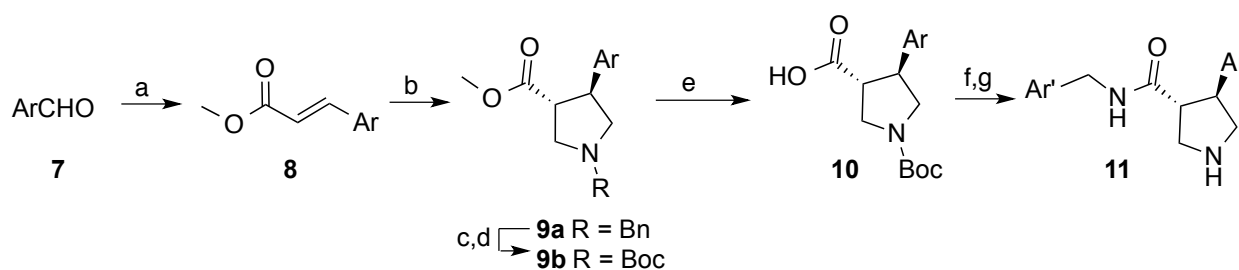
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General. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Chemical structures and IUPAC names were generated using CambridgeSoftChemDraw Ultra 10.0 or CDD Vault (www.collaborativedrug.com). Specific rotation values were recorded on AUTOPOL® μ OJ-H, 4.6mm x 250mm 5 IV-T (λ = 589 nm, 50 mm cell, 20°C). MS analyses were performed on the API 2000 electrospray mass spectrometer in positive/negative ion mode. The scan range was 100–1000d. ^1H NMR spectra were recorded on a Bruker AV-400 or 500 MHz spectrometer. Chemical shifts (δ) are given in relative to tetramethylsilane (δ 0.00 ppm) in CDCl_3 . Coupling constants, J , were reported in hertz unit (Hz). All compounds were $\geq 95\%$ pure by HPLC analysis conducted on an Agilent 1260 system using a reverse phase C18 column with diode array detector and a methanol/water (0.1% NH_4OH) gradient unless stated otherwise. HRMS spectra were recorded on an ABSciex 5600+ instrument.

Synthesis of Compounds. Compounds **6**, **12-44**, and **56-62** were prepared according to the general procedures below or analogous to the procedures for **53**.



Scheme S1: Synthesis of Racemates

Wittig reaction. To a stirred solution of methyl (triphenylphosphoranylidene)acetate (1.05 equiv) in dichloromethane (5 mL/g) was added the corresponding aldehyde (1 equiv) at 0 °C, and

then the resulting mixture was stirred at room temperature for 4 h . The reaction was monitored by TLC (10% ethyl acetate in petroleum ether). The reaction was concentrated *in vacuo*. Flash chromatography afforded the α,β -unsaturated esters **8**.

3+2 Cycloaddition. To a stirred solution of α,β -unsaturated ester **8** (1 equiv) in dichloromethane (10 mL/g) was added N-(methoxymethyl)-N-(trimethylsilylmethyl)-benzylamine (1.3 equiv). The resulting mixture was cooled to 0 °C and a solution of TFA (0.1 eq) in dichloromethane (2.0 mL) was added dropwise. The reaction mixture was allowed to warm to room temp and stirred for 16 h. The solvent was removed by evaporation *in vacuo* and the resulting oil was purified by flash column chromatography to give the racemic *trans* pyrrolidine isomer **9a**.

Sequential benzyl deprotection and Boc protection. To a flask was added **9a** (1 equiv), ammonium formate (3 equiv), 10% Pd/C (~0.1 g/g **9a**) and MeOH (~10 mL/g). The reaction flask was flushed with argon three times and then heated at 70 °C for 30 min. The reaction was cooled to room temp and filtered through Celite®, rinsing with MeOH. To this mixture was added triethylamine (5 equiv), then cooled to 0 °C and di-tert-butyl decarbonate (3 equiv) was added dropwise. The reaction mixture was allowed to warm to room temp and stirred for 16 h. The solvent was removed by evaporation *in vacuo* and the resulting oil was purified by flash column chromatography to give the Boc protected pyrrolidine **9b**.

Hydrolysis. To a flask was added **9b** (15.6 g, 44.4 mmol) and methanol (~10 mL/g). A solution of LiOH (2.5 equiv) in water (~20 mL/g LiOH) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. The most of methanol was removed by evaporation, diluted with water and basified with hydrochloric acid (2M) to pH 4. The mixture was extracted with EtOAc (3 times). The combined organic extracts were washed with water then brine, dried over sodium sulfate, filtered and concentrated to afford racemic **10**.

Amide Coupling and Boc deprotection. To a suspension of **10** (1 equiv), the appropriate amine (1.2 equiv), HATU (1.5 equiv) in dichloromethane (1 mL/40 mg amine) was added triethylamine (2 equiv). The reaction mixture was stirred at room temp for 16 h. The mixture was diluted with dichloromethane and washed with satd sodium carbonate solution then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography to give the Boc-protected carboxamide products.

To a suspension of the Boc-protected carboxamide (1 equiv) in dichloromethane (18 mL/g) was added TFA (9 mL/g). The reaction mixture was stirred at room temp for 2 h. The solvent was removed by evaporation in vacuo and the resulting oil was diluted with dichloromethane and washed with satd sodium carbonate solution then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (DCM/NH₃ in MeOH: 20/1), unless stated otherwise, to give the final products **6**, **12-44**, and **56-62**.

(±)-(3S,4R)-N-[(4-methoxyphenyl)methyl]-4-[4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide trifluoroacetate (6**).** The crude product was purified by reverse phase HPLC (10-65% acetonitrile/water/0.05% TFA) to give a waxy white solid, 21.5 mg (73% yield). MS: $m+1 = 379$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.17 (br. s., 1 H), 8.55 (s, 1 H), 7.74 (d, *J*=8.1 Hz, 2 H), 7.55 (d, *J*=8.0 Hz, 2 H), 6.87 (d, *J*=1.0 Hz, 2 H), 6.75 (d, *J*=1.0 Hz, 2 H), 4.30 (dd, *J*=14.9, 6.7 Hz, 1 H), 3.98 (dd, *J*=15.0, 5.0 Hz, 1 H), 3.69 (s, 3 H), 3.62 - 3.67 (m, 2 H), 3.33 (br. s., 2 H), 3.19 (dd, *J*=8.6 Hz, 2 H).

(±)-(3S,4R)-N-[(4-methylphenyl)methyl]-4-[4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide (12**).** White solid, 90 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.95 (br, 1H), 9.69 (br, 1H), 8.65 (br, 1H), 7.69 (d, *J*= 8.0 Hz, 2H), 7.57 (d, *J*= 7.6 Hz, 2H), 6.97 (d, *J*=7.2 Hz, 2H), 6.81 (d, *J*= 7.6 Hz, 2H), 4.29 (dd, *J*= 14.8, 6.0 Hz, 1H), 3.99 (dd, *J*= 14.8, 4.0 Hz, 1H), 3.84

(m, 3H), 3.27 (m, 3 H), 2.22 (s, 3H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{20}H_{22}F_3N_2O$ 363.1684; found 363.1670.

(±)-(3S,4R)-N-benzyl-4-[4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide

trifluoroacetate (13). The crude product was purified by reverse phase HPLC (10-65% acetonitrile/water/0.05% TFA) to give a white solid, 43.2 mg (49% yield). MS: $m+1=349$. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.62 (t, $J=5.8$ Hz, 1 H), 7.75 (d, $J=1.0$ Hz, 2 H), 7.57 (d, $J=8.1$ Hz, 2 H), 7.16 - 7.24 (m, 3 H), 6.94 (dd, $J=6.5, 3.0$ Hz, 2 H), 4.38 (dd, $J=15.3, 6.8$ Hz, 1 H), 4.06 (dd, $J=15.2, 5.0$ Hz, 1 H), 3.70 - 3.77 (m, 2 H), 3.63 - 3.69 (m, 2 H), 3.33 (br. t, $J=7.3, 7.3$ Hz, 2 H), 3.18 - 3.28 (m, 1 H).

(±)-(3R,4S)-N-{{4-(dimethylamino)phenyl}methyl}-4-[4-

(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide (14). White solid, 60 mg. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 9.96 (br, 1H), 9.67 (br, 1H), 8.75 (br, 1H), 7.74 (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.36 (br, 2H), 7.07 (d, $J=6.8$ Hz, 2H), 4.28 (dd, $J = 15.2, 6.0$ Hz, 1H), 4.01 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.65 (2H, overlapped with the peak of H_2O), 3.44 (t, $J = 7.2$ Hz, 1H), 3.35-3.21 (m, 3H), 3.00 (s, 6H).

(±)-(3S,4R)-N-[(1-methyl-2,3-dihydro-1H-indol-5-yl)methyl]-4-[4-

(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide (15). Yellow solid, 72 mg. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.30 (br, 1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.4$ Hz, 2H), 6.67 (s, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 6.29 (d, $J = 8.0$ Hz, 1H), 4.27 (dd, $J = 14.8, 6.0$ Hz, 1H), 4.13 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.30 (1H, overlapped with the peak of H_2O), 3.24 (m, 3H), 3.20 (t, $J = 8.4$ Hz, 1H), 3.15 (t, $J = 8.4$ Hz, 2H), 2.92 (t, $J = 8.4$ Hz, 1H), 2.84-2.65 (m, 2H), 2.61 (s, 3H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{22}H_{25}F_3N_3O$ 404.1949; found 404.1943.

(±)-(3S,4R)-N-{{4-(diethylamino)phenyl}methyl}-4-[4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide (16). White solid, 120 mg. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 7.54 (d, $J =$

8.4 Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.58 (d, $J = 8.8$ Hz, 2H), 5.53 (br, 1H), 4.31(dd, $J = 14.4, 5.6$ Hz, 1H), 4.31(dd, $J = 14.4, 5.6$ Hz, 1H), 3.56 (m, 2H), 3.41 (dd, $J = 11.6, 5.6$ Hz, 1H), 3.32 (q, $J = 13.6$ Hz, 4H), 3.28 (m, 1H), 2.92 (t, $J = 12.0$ Hz, 1H), 2.66 (q, $J = 13.6$ Hz, 1H), 1.14 (t, $J = 7.2$ Hz, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{23}H_{29}F_3N_3O$ 420.2262; found 420.2244.

(±)-(3S,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-(4-methylphenyl)pyrrolidine-3-carboxamide (17). Yellow solid, 85 mg. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.14 (t, $J = 5.6$ Hz, 1H), 7.10 (dd, $J = 14.4, 8.0$ Hz, 2H), 6.91(d, $J = 8.4$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 2H), 4.14 (dd, $J = 14.8, 6.0$ Hz, 1H), 4.04 (dd, $J = 14.8, 5.6$ Hz, 1H), 3.37 (t, $J = 8.4$ Hz, 1H), 3.25 (q, $J = 16.8$ Hz, 1H), 2.94 (t, $J = 7.6$ Hz, 1H), 2.84 (s, 6H), 2.82 (q, $J = 16.0$ Hz, 1H), 2.69 (t, $J = 10.0$ Hz, 1H), 2.26 (s, 3H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{21}H_{28}N_3O$ 338.2232; found 338.2210.

(±)-(3S,4R)-4-(4-chlorophenyl)-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (18). White solid, 74 mg. 1H NMR (500 MHz, $CDCl_3$) δ ppm 7.27 (d, $J = 8.8$ Hz, 2H), 7.15 (d, $J = 6.4$ Hz, 2H), 7.02 (d, $J = 6.8$ Hz, 2H), 6.66 (d, $J = 6.8$ Hz, 2H), 5.57 (br, 1H), 4.33 (dd, $J = 11.2, 4.4$ Hz, 1H), 4.25 (dd, $J = 11.6, 4.4$ Hz, 1H), 3.50 (t, $J = 8.8$ Hz, 1H), 3.45 (t, $J = 6.4$ Hz, 1H), 3.41 (t, $J = 4.8$ Hz, 1H), 3.25 (dd, $J = 9.2, 6.8$ Hz, 1H), 2.94 (s, 6H), 2.87 (dd, $J = 8.8, 7.2$ Hz, 1H), 2.64 (t, $J = 6.4$ Hz, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{20}H_{25}ClN_3O$ 358.1686; found 358.1673.

(±)-(3S,4R)-4-(4-tert-butylphenyl)-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (19). White solid, 95 mg. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.16 (t, $J = 6.0$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.91(d, $J = 8.8$ Hz, 2H), 6.59 (d, $J = 8.4$ Hz, 2H), 4.17(dd, $J = 14.8, 6.0$ Hz, 1H), 4.01 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.30 (1H, overlapped with the peak of H_2O), 3.24 (t, $J = 10.4$ Hz, 1H), 3.15 (t, $J = 8.4$ Hz, 1H), 2.92 (t, $J = 8.4$ Hz, 1H), 2.83 (s,

6H), 2.74 (t, $J = 9.2$ Hz, 1H), 1.26 (s, 9H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{24}H_{34}N_3O$ 380.2702; found 380.2691. HPLC purity 94.8%.

(±)-(3R,4S)-4-[4-(difluoromethyl)phenyl]-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (20). White solid, 112 mg 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.21 (t, $J = 5.6$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.59 (d, $J = 8.8$ Hz, 2H), 4.17 (dd, $J = 14.8, 6.4$ Hz, 1H), 4.02 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.47 (q, $J = 16.8$ Hz, 1H), 3.32 (dd, $J = 10.8, 8.0$ Hz, 1H), 3.22 (dd, $J = 10.2, 8.0$ Hz, 1H), 3.00-2.86 (m, 2H), 2.83 (s, 6H), 2.78 (d, $J = 10.4$ Hz, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{21}H_{26}F_2N_3O$ 374.2044; found 374.2026.

(±)-(3R,4S)-4-[4-(1,1-difluoroethyl)phenyl]-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (21). White solid, 82 mg. MS: $m+1=388.5$. 1H NMR (500 MHz, $DMSO-d_6$) δ ppm 8.21 (br, 1H), 7.47 (d, $J = 7.5$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.0$ Hz, 2H), 6.59 (d, $J = 8.0$ Hz, 2H), 4.17 (dd, $J = 14.5, 6.0$ Hz, 1H), 4.01 (dd, $J = 15.0, 5.0$ Hz, 1H), 3.44 (q, $J = 17$ Hz, 1H), 3.30 (t, $J = 9.5$ Hz, 1H), 3.20 (t, $J = 9.0$ Hz, 1H), 2.95 (t, $J = 9.0$ Hz, 1H), 2.87 (q, $J = 17$ Hz, 1H), 2.83 (s, 6H), 2.77 (t, $J = 10.0$ Hz, 1H), 1.94 (t, $J = 19.0$ Hz, 3H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{22}H_{28}F_2N_3O$ 388.2200; found 388.2195.

(±)-(3R,4S)-N-{[4-(dimethylamino)phenyl]methyl}-4-[4-(pentafluoro- λ^6 -sulfanyl)phenyl]pyrrolidine-3-carboxamide (22). White solid, 66 mg. 1H NMR (500 MHz, $CDCl_3$) δ ppm 8.25 (t, $J = 6.0$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 2H), 7.48 (d, $J = 7.5$ Hz, 2H), 6.86 (d, $J = 7.5$ Hz, 2H), 6.58 (d, $J = 7.5$ Hz, 2H), 4.22 (m, 1H), 3.96 (m, 1H), 3.48 (t, $J = 8.5$ Hz, 2H), 3.23 (t, $J = 8.5$ Hz, 1H), 3.17 (s, 1H), 2.97 (t, $J = 8.0$ Hz, 1H), 2.89 (t, $J = 8.5$ Hz, 1H), 2.83 (s, 6H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{20}H_{25}F_5N_3OS$ 450.1638; found 450.1624.

(±)-(3R,4S)-N-{{4-(dimethylamino)phenyl}methyl}-4-[3-(pentafluoro- λ^6 -sulfanyl)phenyl]pyrrolidine-3-carboxamide (23). White solid, 75 mg. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.25 (t, $J = 5.6$ Hz, 1H), 7.77 (m, 2H), 7.56 (q, $J = 15.2$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.60 (d, $J = 8.8$ Hz, 2H), 4.17 (dd, $J = 14.8, 6.0$ Hz, 1H), 4.04 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.53 (q, $J = 16.0$ Hz, 1H), 3.34 (d, $J = 10.8$ Hz, 1H), 3.30 (1H, overlapped with the peak of H_2O), 2.97 – 2.86 (m, 2H), 2.83 (s, 6H), 2.73 (m, 1H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{25}\text{F}_5\text{N}_3\text{OS}$ 450.1638; found 450.1624.

(±)-(3S,4R)-N-{{4-(dimethylamino)phenyl}methyl}-4-[3-fluoro-4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide (24). White solid, 62 mg. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ ppm 8.30 (t, $J = 5.5$ Hz, 1H), 7.65 (t, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 12.5$, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 8.5$ Hz, 2H), 6.52 (d, $J = 9.0$ Hz, 2H), 4.22 (dd, $J = 15.0, 7.0$ Hz, 1H), 3.90 (1H, overlapped with the peak of H_2O), 3.43 (q, $J = 18.0$ Hz, 1H), 3.28 (t, $J = 9.5$ Hz, 1H), 3.18 (t, $J = 8.5$ Hz, 1H), 2.94 (m, 1H), 2.77 (s, 6H), 2.77-2.76 (m, 1H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{24}\text{F}_4\text{N}_3\text{O}$ 410.1855; found 410.1854.

(±)-(3S,4R)-N-{{4-(dimethylamino)phenyl}methyl}-4-[2-fluoro-4-(trifluoromethyl)phenyl]pyrrolidine-3-carboxamide (25). White solid, 110 mg. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ ppm 8.54 (br, 1H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.72 (d, $J = 10.5$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 2H), 6.54 (d, $J = 8.5$ Hz, 2H), 4.25 (dd, $J = 15.0, 7.0$ Hz, 1H), 3.89 (m, 2H), 3.68 (t, $J = 11.0$ Hz, 1H), 3.62 (m, 1H), 3.30 (3H, overlapped with the peak of H_2O), 2.82 (s, 6H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{24}\text{F}_4\text{N}_3\text{O}$ 410.1855; found 410.1838.

(±)-(3S,4R)-4-[3-chloro-4-(trifluoromethyl)phenyl]-N-{{4-(dimethylamino)phenyl}methyl}pyrrolidine-3-carboxamide (26). White solid, 78 mg. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.25 (br, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.42 (d, $J = 7.6$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 2H), 6.58 (d, $J = 8.0$ Hz, 2H), 4.22 (dd, $J = 14.4, 6.0$ Hz,

1H), 3.98 (dd, $J = 14.4, 4.0$ Hz, 1H), 3.45 (2H, overlapped with the peak of H₂O), 3.23 (t, $J = 8.0$ Hz, 1H), 2.95-2.83 (m, 2H), 2.83 (s, 6H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for C₂₁H₂₄ClF₃N₃O 426.156; found 426.1544.

(±)-(3S,4R)-4-[2-chloro-4-(trifluoromethyl)phenyl]-N-{{4-(dimethylamino)phenyl}methyl}pyrrolidine-3-carboxamide (27). Brown solid, 85 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.97 (br, 1H), 9.66 (br, 1H), 8.62 (br, 1H), 7.93 (d, $J = 7.6$ Hz, 1H), 7.90 (s, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 6.8$ Hz, 2H), 6.68 (br, 2H), 4.22 (dd, $J = 14.4, 5.6$ Hz, 1H), 4.13 (q, $J = 16.8$ Hz, 1H), 4.00 (dd, $J = 14.4, 5.6$ Hz, 1H), 3.72-3.63 (m, 3H), 3.29-3.10 (m, 2H), 2.85 (s, 6H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for C₂₁H₂₄ClF₃N₃O 426.156; found 426.1565.

(±)-(3S,4R)-4-(3,4-dichlorophenyl)-N-{{4-(dimethylamino)phenyl}methyl}pyrrolidine-3-carboxamide (28). White solid, 56 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.21 (br, 1H), 7.53 (d, $J = 8.0$ Hz, 1H), 7.51 (s, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 2H), 6.60 (d, $J = 8.0$ Hz, 2H), 4.20 (dd, $J = 14.8, 5.6$ Hz, 1H), 4.00 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.45 (1H, overlapped with the peak of H₂O), 3.28 (q, $J = 16.8$ Hz, 1H), 3.18 (t, $J = 8.8$ Hz, 1H), 2.91 (t, $J = 8.0$ Hz, 1H), 2.84 (s, 6H), 2.76 (t, $J = 9.6$ Hz, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for C₂₀H₂₄Cl₂N₃O 392.1296; found 392.1278.

(±)-(3S,4R)-4-(3-chloro-4-methylphenyl)-N-{{4-(dimethylamino)phenyl}methyl}pyrrolidine-3-carboxamide (29). White solid, 130 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.47 (br, 1H), 8.51 (t, $J = 5.6$ Hz, 1H), 7.41 (s, 1H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.20 (d, $J = 6.8$ Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 2H), 6.56 (d, $J = 8.4$ Hz, 2H), 4.23 (dd, $J = 14.8, 6.4$ Hz, 1H), 3.95 (dd, $J = 14.8, 6.4$ Hz, 1H), 3.58 (m, 3H), 3.25 (m, 3H), 2.84 (s, 6H), 2.32 (s, 3H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for C₂₁H₂₇ClN₃O 372.1842; found 372.1842.

(±)-(3S,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-(4-phenoxyphenyl)pyrrolidine-3-carboxamide (30). White solid, 87 mg. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.43 (t, *J* = 5.5 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 10.5 Hz, 2H), 7.13 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 4H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.51 (d, *J* = 10.5 Hz, 2H), 4.28 (dd, *J* = 15.0, 7.0 Hz, 1H), 3.90 (1H, overlapped with the peak of H₂O), 3.60 (m, 2H), 3.52 (q, *J* = 22.0 Hz, 1H), 3.30 (t, *J* = 10.5 Hz, 1H), 3.20 (t, *J* = 11.0 Hz, 1H), 3.12 (q, *J* = 19.0 Hz, 1H), 2.74 (s, 6H). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₀N₃O₂ 416.2338; found 416.2334.

(±)-(3S,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-(3-phenoxyphenyl)pyrrolidine-3-carboxamide (31). White solid, 102 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.47 (t, *J* = 5.2 Hz, 1H), 7.39-7.33 (m, 3H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.88 (m, 3H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.19 (dd, *J* = 14.8, 6.4 Hz, 1H), 4.01 (dd, *J* = 14.8, 4.8 Hz, 1H), 3.62-3.53 (m, 2H), 3.49 (t, *J* = 8.0 Hz, 1H), 3.19-3.10 (m, 3H), 2.82 (s, 6H). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₀N₃O₂ 416.2338; found 416.2329.

(±)-(3S,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-[4-(pyridin-2-yloxy)phenyl]pyrrolidine-3-carboxamide (32). White solid, 78 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.23 (t, *J* = 5.2 Hz, 1H), 8.13 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.83 (t, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.11 (dd, *J* = 7.2, 4.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 4.15 (dd, *J* = 14.8, 4.8 Hz, 1H), 4.07 (dd, *J* = 14.8, 4.8 Hz, 1H), 3.42 (q, *J* = 16.8, 1H), 3.29 (t, *J* = 8.0 Hz, 1H), 3.17 (td, *J* = 10.0, 2.0 Hz, 1H), 2.89 (m, 2H), 2.82 (s, 6H), 2.74 (td, *J* = 10.4, 1.2 Hz, 1H). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₅H₂₉N₄O₂ 417.229; found 417.2275.

(±)-(3S,4S)-N-{[4-(dimethylamino)phenyl]methyl}-4-{2-[4-(trifluoromethyl)phenyl]ethyl}pyrrolidine-3-carboxamide (33). White solid, 96 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.26 (br, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H),

7.05 (d, $J = 8.4$ Hz, 2H), 6.65 (d, $J = 8.4$ Hz, 2H), 4.21(dd, $J = 14.8, 5.6$ Hz, 1H), 4.07 (dd, $J = 14.4, 5.2$ Hz, 1H), 3.03-2.94 (m, 2H), 2.84 (s, 6H), 2.77 (m, 1H), 2.63 (t, $J = 7.6$ Hz, 2H), 2.39 (q, $J = 14.2$ Hz, 2H), 2.11(q, $J = 14.4$, 1H), 1.74-1.68 (m, 1H), 1.67-1.59 (m, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{23}H_{29}F_3N_3O$ 420.2262; found 420.2259.

(±)-N-{{4-(dimethylamino)phenyl}methyl}-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (34). White solid, 130 mg. 1H NMR (500 MHz, $CDCl_3$) δ ppm 8.60 (d, $J = 2.0$ Hz, 1H), 7.71 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.5$ Hz, 2H), 6.65 (d, $J = 8.5$ Hz, 2H), 5.70 (br, 1H), 4.29 (m, 2H), 3.64 (q, $J = 16.0$ Hz, 1H), 3.58 (t, $J = 11.0$ Hz, 1H), 3.38 (dd, $J = 11.5, 5.5$ Hz, 1H), 3.30 (t, $J = 11.5$ Hz, 1H), 2.90 (m, 7H), 2.68 (q, $J = 15.0$ Hz, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{20}H_{24}F_3N_4O$ 393.1902; found 393.1913.

(±)-N-{{4-(dimethylamino)phenyl}methyl}-4-[2-(trifluoromethyl)pyrimidin-5-yl]pyrrolidine-3-carboxamide (35). White solid, 78 mg. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 8.98 (s, 2H), 8.22 (t, $J = 5.2$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 2H), 4.16 (dd, $J = 14.8, 6.0$ Hz, 1H), 4.03 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.46 (q, $J = 16.0$ Hz, 1H), 3.39-3.25 (m, 2H), 3.30-2.87 (m, 3H), 2.83 (s, 6H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{19}H_{23}F_3N_5O$ 394.1854; found 394.1838.

(±)-(3R,4S)-4-(1-benzothiophen-5-yl)-N-{{4-(dimethylamino)phenyl}methyl}pyrrolidine-3-carboxamide (36). White solid, 120 mg. 1H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 7.6$ Hz, 1H), 7.37-7.25 (m, 2H), 7.07 (s, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 6.58 (d, $J = 8.4$ Hz, 2H), 5.74 (br, 1H), 4.35 (dd, $J = 14.4, 5.6$ Hz, 1H), 4.27 (dd, $J = 14.4, 5.2$ Hz, 1H), 3.82 (q, $J = 16.0$ Hz, 1H), 3.57 (dd, $J = 11.6, 7.6$ Hz, 1H), 3.40 (dd, $J = 11.6, 5.2$ Hz, 1H), 3.27 (dd, $J = 11.6, 8.0$ Hz, 1H), 3.01 (dd, $J = 11.6, 8.8$ Hz, 1H), 2.90 (s, 6H), 2.85-2.76 (m, 1H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for $C_{22}H_{26}N_3OS$ 380.1796; found 380.1774.

(±)-(3R,4S)-4-(1-benzothiophen-6-yl)-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (37). White solid, 110 mg. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.75 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 7.34-7.25 (m, 2H), 7.06 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 5.80 (br, 1H), 4.35(dd, *J* = 14.4, 5.6 Hz, 1H), 4.27 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.83 (q, *J* = 16.0 Hz, 1H), 3.57 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.39 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.26 (dd, *J* = 11.6, 8.4 Hz, 1H), 3.00 (dd, *J* = 11.2, 8.8 Hz, 1H), 2.90 (s, 6H), 2.81-2.73 (m, 1H). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₂H₂₆N₃OS 380.1796; found 380.1783.

(±)-(3R,4R)-4-(1-benzofuran-2-yl)-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (38). White solid, 79 mg. MS: *m*+1=364.3. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.47 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24-7.08 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.48 (s, 1H), 6.08 (br, 1H), 4.33 (dd, *J* = 14.4, 5.6 Hz, 1H), 4.27 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.76 (q, *J* = 15.2 Hz, 1H), 3.55 (dd, *J* = 11.2, 8.0 Hz, 1H), 3.44-3.23 (m, 2H), 3.19 (dd, *J* = 11.2, 8.4 Hz, 1H), 3.00 (q, *J* = 13.6, 1H), 2.90 (s, 6H). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₂H₂₆N₃O₂ 364.2025; found 364.2021.

(±)-(3R,4R)-4-(1-benzothiophen-2-yl)-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (39). White solid, 130 mg. MS: *m*+1=380.1. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.34-7.25 (m, 2H), 7.06 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 5.75 (br, 1H), 4.35 (dd, *J* = 14.4, 5.6 Hz, 1H), 4.27 (dd, *J* = 14.4, 5.6 Hz, 1H), 3.84 (q, *J* = 16.0 Hz, 1H), 3.58 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.40 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.27 (dd, *J* = 11.6, 8.0 Hz, 1H), 3.01 (dd, *J* = 11.2, 10.0 Hz, 1H), 2.90 (s, 6H), 3.00 (q, *J* = 15.2 Hz, 1H). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₂H₂₆N₃OS 380.1796; found 380.1795.

(±)-(3S,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-(quinolin-3-yl)pyrrolidine-3-carboxamide (40). White solid, 96mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.84 (d, *J* = 2.0 Hz, 1H), 8.23 (t, *J* = 5.6 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H),

7.71 (t, $J = 7.6$ Hz, 1H), 7.59 (t, $J = 7.2$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 2H), 6.43 (d, $J = 8.4$ Hz, 2H), 4.20 (dd, $J = 14.8, 6.4$ Hz, 1H), 3.98 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.60 (q, $J = 16.0$, 1H), 3.44 (m, 1H), 3.30 (2H, overlapped with the peak of H₂O), 3.02 (t, $J = 5.6$ Hz, 1H), 2.99 -2.90 (m, 2H), 2.78 (s, 6H). HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₃H₂₇N₄O 375.2185; found 375.2180.

(±)-(3R,4R)-4-(5-tert-butylthiophen-2-yl)-N-{[4-(dimethylamino)phenyl]methyl}pyrrolidine-3-carboxamide (41). White solid, 86 mg. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.08 (d, $J = 8.4$ Hz, 2H), 6.66 (d, $J = 8.4$ Hz, 2H), 6.60 (q, $J = 7.2$ Hz, 2H), 5.74 (br, 1H), 4.34 (dd, $J = 14.4, 5.2$ Hz, 1H), 4.28 (dd, $J = 14.4, 5.6$ Hz, 1H), 3.65 (q, $J = 14.2$ Hz, 1H), 3.50 (dd, $J = 11.6, 7.6$ Hz, 1H), 3.36 (dd, $J = 11.6, 5.2$ Hz, 1H), 3.20 (dd, $J = 11.6, 8.4$ Hz, 1H), 2.92 (s, 6H), 2.89 (dd, $J = 11.6, 8.8$ Hz, 1H), 2.67 (q, $J = 15.2$ Hz, 1H), 1.34 (s, 9H). HRMS (ESI) m/z : [M + H]⁺ Calcd for C₂₂H₃₂N₃OS 386.2266; found 386.2251.

(±)-(3R,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-[5-(trifluoromethyl)thiophen-2-yl]pyrrolidine-3-carboxamide (42). Brown solid, 92 mg. MS: $m+1=398.0$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.24 (br, 2H), 8.23 (t, $J = 5.2$ Hz, 1H), 7.64 (d, $J = 2.4$ Hz, 1H), 7.18 (d, $J = 2.4$ Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 2H), 6.64 (d, $J = 8.0$ Hz, 2H), 4.29 (dd, $J = 14.8, 6.4$ Hz, 1H), 4.03 (d, $J = 14.4, 4.4$ Hz, 1H), 3.96 (q, $J = 19.2$ Hz, 1H), 3.78 (1H, overlapped with the peak of H₂O), 3.39-3.30 (m, 2H), 3.17 (q, $J = 17.6$ Hz, 1H), 2.85 (s, 6H). HRMS (ESI) m/z : [M + H]⁺ Calcd for C₁₉H₂₃F₃N₃OS 398.1514; found 398.1514.

(±)-(3R,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]pyrrolidine-3-carboxamide (43). White solid, 56 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.40 (t, $J = 5.6$ Hz, 1H), 7.97 (s, 1H), 6.98 (d, $J = 8.6$ Hz, 2H), 6.63 (d, $J = 8.6$ Hz, 2H), 4.21 (dd, $J = 14.6, 6.0$ Hz, 1H), 4.08 (dd, $J = 14.6, 5.4$ Hz, 1H), 3.84 (q, $J = 15.6$ Hz, 1H), 3.42 (dd, $J = 10.8, 7.6$ Hz, 1H), 3.28 (dd, $J = 10.4, 8.4$ Hz, 1H), 3.03 -2.95 (m, 1H), 2.91 (dd, $J = 16.2, 7.8$ Hz, 2H), 2.84 (s, 6H). HRMS (ESI) m/z : [M + H]⁺ Calcd for C₁₈H₂₂F₃N₄OS 399.1466; found 399.1461.

(±)-(3R,4R)-N-{[4-(dimethylamino)phenyl]methyl}-4-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]pyrrolidine-3-carboxamide (44). White solid, 140 mg. MS: $m+1=396.1$. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.07 (d, $J = 8.8$ Hz, 2H), 6.67 (d, $J = 8.4$ Hz, 2H), 6.30 (s, 1H), 5.92 (br, 1H), 4.30 (m, 2H), 3.81 (s, 3H), 3.68 (q, $J = 15.2$ Hz, 1H), 3.53 (dd, $J = 11.2, 7.6$ Hz, 1H), 3.26 (d, $J = 6.4$ Hz, 2H), 2.93 (s, 6H), 2.86 (dd, $J = 11.6, 8.4$ Hz, 1H), 2.63 (q, $J = 13.6$ Hz, 1H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{25}\text{F}_3\text{N}_5\text{O}$ 396.2011; found 396.2005.

(+)-(3R,4S)-N-{[6-(dimethylamino)pyridin-3-yl]methyl}-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (56). White solid, 130 mg. MS: $m+1=394.1$. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.60 (d, $J = 1.6$ Hz, 1H), 8.00 (d, $J = 2.4$ Hz, 1H), 7.72 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.29 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.45 (d, $J = 8.8$ Hz, 1H), 5.72 (br, 1H), 4.26 (d, $J = 5.6$ Hz, 2H), 3.66-3.57 (m, 2H), 3.39-3.28 (m, 2H), 3.06 (s, 6H), 2.95-2.89 (m, 1H), 2.69 (q, $J = 13.6$ Hz, 1H). $[\alpha]_{\text{D}}^{20} +98.7$ (c 0.16, MeOH). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{23}\text{F}_3\text{N}_5\text{O}$ 394.1854; found 394.185.

(±)-(3S,4R)-N-{[4-(pyrrolidin-1-yl)phenyl]methyl}-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (57). Brown solid, 105 mg. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.74 (s, 1H), 8.46 (t, $J = 5.6$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 2H), 6.36 (d, $J = 8.4$ Hz, 2H), 4.21 (dd, $J = 14.8, 6.8$ Hz, 1H), 3.94 (dd, $J = 14.8, 5.2$ Hz, 1H), 3.67 (m, 2H), 3.58 (t, $J = 10.0$ Hz, 1H), 3.30 (m, 3H), 3.15 (t, $J = 6.4$ Hz, 4H), 1.92 (m, 4H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{26}\text{F}_3\text{N}_4\text{O}$ 419.2058; found 419.2056.

(+)-(3R,4S)-N-{[4-(1H-pyrazol-1-yl)phenyl]methyl}-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (58). White solid, 56 mg. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.69 (s, 1H), 8.45 (t, $J = 6.0$ Hz, 1H), 8.43 (s, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.72 (t, $J = 6.0$ Hz, 3H), 7.21 (d, $J = 8.8$ Hz, 2H), 6.53 (t, $J = 2.4$ Hz, 1H), 4.33 (dd, $J = 15.2, 2.0$ Hz, 1H), 4.20 (dd, $J = 15.2, 2.4$ Hz, 1H), 3.55 (q, $J = 16.0$ Hz, 1H), 3.30 (2H, overlapped

with the peak of H₂O), 2.98 (m, 2H), 2.87 (t, *J* = 8.4 Hz, 1H). [α]D²⁰ +100.0 (*c* 0.19, MeOH). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₁H₂₁F₃N₅O 416.1698; found 416.1678.

(+)-(3R,4S)-4-[6-(trifluoromethyl)pyridin-3-yl]-N-{{6-(trifluoromethyl)pyridin-3-yl}methyl}pyrrolidine-3-carboxamide (59). Yellow solid, 72 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.92 (s, 1H), 8.77 (d, *J* = 26.0 Hz, 1H), 8.50 (s, 1H), 8.10 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 4.51-4.34 (m, 1H), 4.25 (d, *J* = 12.4 Hz, 1H), 3.72 (s, 3H), 3.39 (d, *J* = 42.0 Hz, 3H). [α]D²⁰ +57.5 (*c* 0.26, MeOH). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₇F₆N₄O 419.1306; found 419.1287.

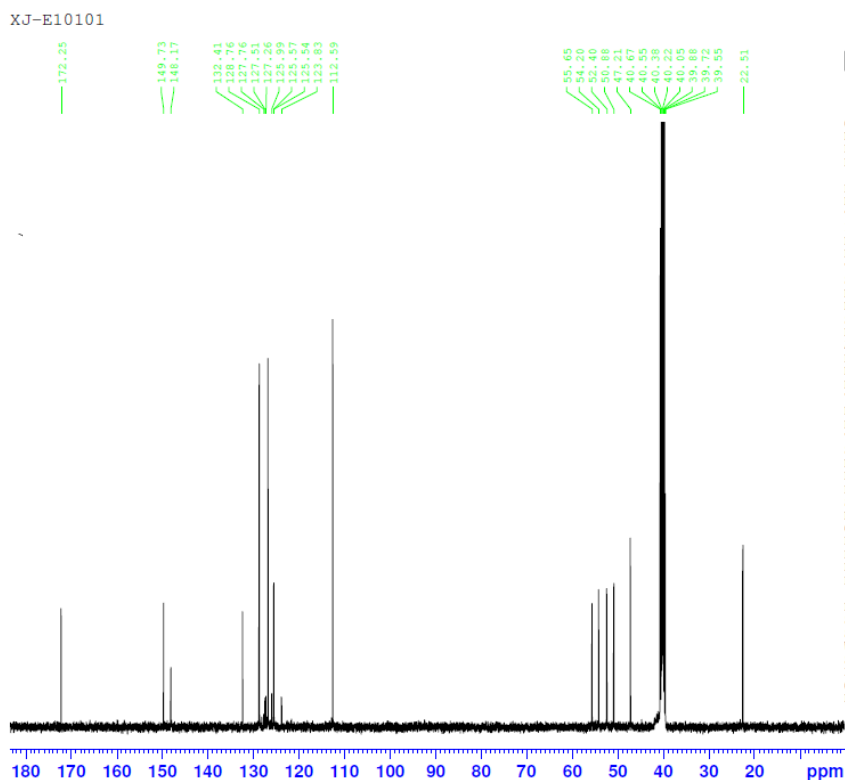
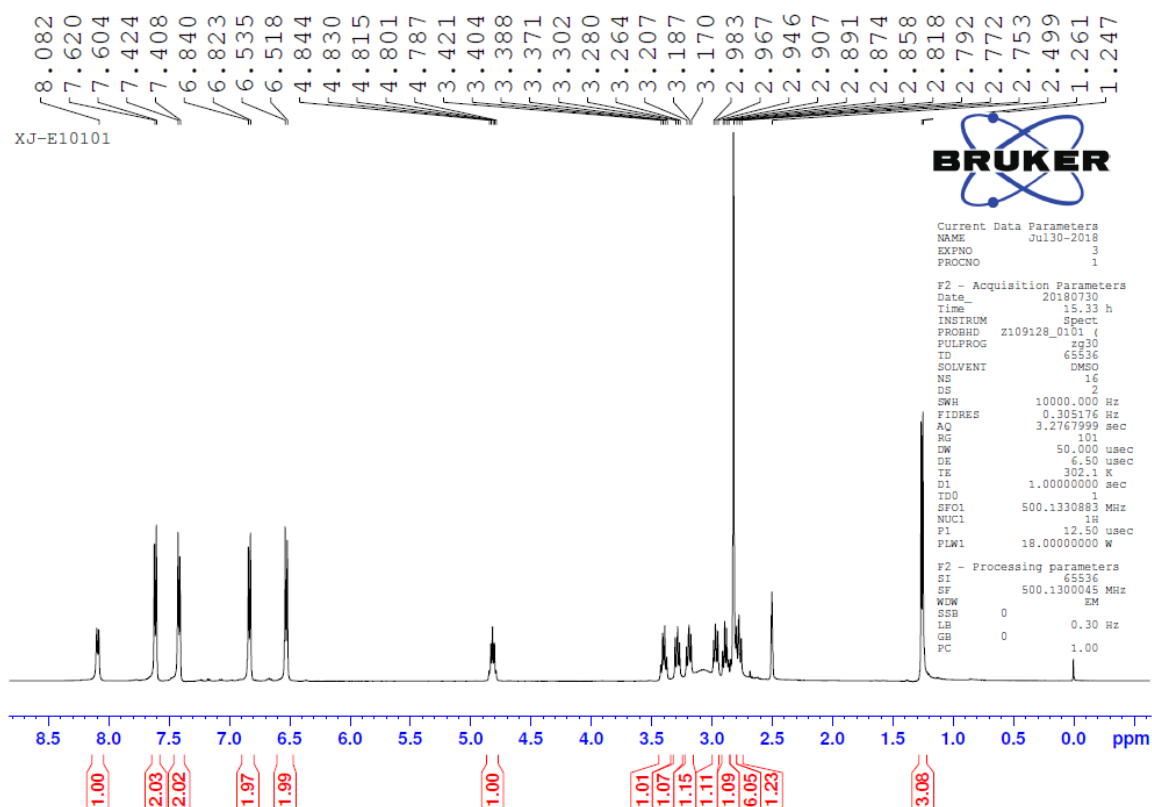
(+)-(3R,4S)-N-[(4-bromophenyl)methyl]-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (60). White solid, 120 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.67 (s, 1H), 8.46 (t, *J* = 5.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.24 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.12 (dd, *J* = 15.6, 5.6 Hz, 1H), 3.52 (t, *J* = 8.0 Hz, 1H), 3.32 (m, 2H), 2.96 (m, 2H), 2.84 (t, *J* = 9.2 Hz, 1H). [α]D²⁰ +91.4 (*c* 0.18, MeOH). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₈BrF₃N₃O 428.0585; found 428.0574.

(+)-(3R,4S)-N-({[1,1'-biphenyl]-4-yl}methyl)-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (61). White solid, 75 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.80 (s, br, 2H), 8.79 (s, 2H), 8.15 (d, *J* = 6.8 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.48 (m, 4H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.39 (dd, *J* = 15.6, 5.6 Hz, 1H), 4.14 (dd, *J* = 15.2, 4.8 Hz, 1H), 3.74 (m, 3H), 3.30 (2H, overlapped with the peak of H₂O), 2.90 (m, 2H). [α]D²⁰ +75.1 (*c* 0.29, MeOH). HRMS (ESI) *m/z*: [M + H]⁺ Calcd for C₂₄H₂₃F₃N₃O 426.1793; found 426.1792.

(±)-(3R,4S)-N-({4-[(dimethylamino)methyl]phenyl}methyl)-4-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidine-3-carboxamide (62). White solid, 132 mg. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.66 (s, 1H), 8.38 (t, *J* = 6.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.82

(d, $J = 8.0$ Hz, 1H), 7.13 (d, $J = 7.6$ Hz, 2H), 7.00 (d, $J = 8.0$ Hz, 2H), 4.27 (dd, $J = 12.4, 6.4$ Hz, 1H), 4.11 (dd, $J = 12.4, 5.6$ Hz, 1H), 3.30 (1H, overlapped with the peak of H₂O), 2.90 (m, 2H), 2.81 (t, $J = 5.6$ Hz, 1H), 2.09 (s, 6H). HRMS (ESI) m/z : $[M + H]^+$ Calcd for C₂₁H₂₆F₃N₄O 407.2058; found 407.2052.

¹H NMR and ¹³C NMR for 54b



X-ray crystallographic data for 54b

Bond precision: C-C = 0.0039 Å

Wavelength=1.54184

Cell: a=4.93147(7) b=21.1977(3) c=21.7467(3)
alpha=90 beta=90 gamma=90

Temperature: 293 K

	Calculated	Reported
Volume	2273.31(6)	2273.31(6)
Space group	P 2 21 21	P 2 21 21
Hall group	P 2bc 2	P 2bc 2
Moiety formula	C22 H27 F3 N3 O, Cl	C22 H27 F3 N3 O, Cl
Sum formula	C22 H27 Cl F3 N3 O	C22 H27 Cl F3 N3 O
Mr	441.92	441.92
Dx, g cm ⁻³	1.291	1.291
Z	4	4
Mu (mm ⁻¹)	1.857	1.857
F000	928.0	928.0
F000'	932.35	
h, k, lmax	5, 25, 25	5, 24, 25
Nref	4028[2374]	3992
Tmin, Tmax	0.895, 0.911	0.585, 1.000
Tmin'	0.395	

Correction method= # Reported T Limits: Tmin=0.585 Tmax=1.000

AbsCorr = MULTI-SCAN

Data completeness= 1.68/0.99

Theta(max)= 66.860

R(reflections)= 0.0412(3805)

wR2(reflections)= 0.1260(3992)

S = 1.072

Npar= 302

