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Forward- and reverse-synthesis of piperazino-piperidine amide analogs: a general access to structurally diverse 4-piperazino-piperidine based CCR5 antagonists

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(*S*)-Methyl 2-(2-chloro-*N*-((*S*)-1-(4-(trifluoromethyl)phenyl)ethyl)acetamido)-2-phenylacetate (3d). To the solution of the secondary amine **2d** (586 mg, 1.74 mmol) in 1,2-dichloroethane (15.0 mL) was added chloroacetyl chloride (2.78 mL, 34.8 mmol) at room temperature. The mixture was stirred under refluxing for 3 h. Both the solvent and chloroacetyl chloride were removed under vacuum. The remaining yellow syrup was purified by chromatography using petroleum ether / EtOAc = 5 / 1 to give compound **3d** as glassy solid (603 mg, 84.0% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54-7.07 (m, 7H), 6.84 (d, 2H, *J* = 5.7 Hz), 5.31 (m, 1H), 4.68 (s, 1H), 4.27-4.11 (m, 2H), 3.72 (s, 3H), 1.86 (m, 3H). EI-MS (m/z): 413 $[M]^+$. $[\alpha]_D^{20}$ = +16.8 (*c* = 1.0,

$CHCl_3$).

(*S*)-Methyl 2-(2-chloro-N-((*R*)-1-(4-(trifluoromethyl)phenyl)ethyl)acetamido) propanoate [(1*R*, 2*S*)-3a]. The procedure is similar to the preparation for **3d** to give (1*R*, 2*S*)-**3a** as colorless oil (85% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 8.0 Hz), 5.32 (q, 1H, *J* = 6.8 Hz), 4.22 (q_{AB}, 2H, *J* = 12.4 Hz), 3.72 (s, 3H), 3.48 (q, 1H, *J* = 6.8 Hz), 1.76 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.8 Hz). EI-MS (m/z): 351 $[M]^+$. IR (KBr): 3460, 2989 (m), 1740, 1662, 1460, 1435, 1329, 1225, 1119, 1072 cm^{-1}. $[\alpha]_D^{20}$ = +11.1 (*c* = 0.825, $CHCl_3$).

(*S*)-Methyl 2-(2-chloro-*N*-((*R*)-1-(4-(trifluoromethyl)phenyl)ethyl)acetamido)-3-phenylpropanoate [(1*R*, 2*S*)- 3c]. The procedure is similar to the preparation for **3d** to give (1*R*, 2*S*)-**3c** as colorless oil (88% yield). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.51 (d, 2H, *J* = 7.8 Hz), 7.37 (d, 2H, *J* = 8.3 Hz), 7.05- 6.99 (m, 3H), 6.42 (d, 2H, *J* = 7.3 Hz), 5.27 (q, 1H, *J* = 6.8 Hz), 4.23 (q_{AB}, 2H, *J* = 12.2 Hz), 3.70 (s, 3H), 3.60 (m, 1H), 3.49 (dd, 1H, *J* = 14.2Hz, 7.8 Hz), 2.67 (dd, 1H, *J* = 14.2Hz, 4.9 Hz), 1.67 (d, 3H, *J* = 7.3 Hz). EI-MS (m/z): 429 $[M+2H]^+$, 427 $[M]^+$. IR (film): 2953 (m), 1743, 1653, 1433 (m), 1327, 1167, 1121, 1070, 843, 700 cm^{-1}. $[\alpha]_D^{20}$ = -29.5 (*c* = 1.695, $CDCl_3$).

(*S*)-6-Methoxy-5-phenyl-4-(1-(4-(trifluoromethyl)phenyl)ethyl)-2H-1,4-oxazin-3 (4H)-one (7). Compound **3d** (207 mg, 0.5 mmol) and N-Boc-4-amino-4-methyl piperidine (120 mg, 0.6 mmol) were dissolved in CH_3OH (2.0 mL). Et_3N (0.084 mL, 0.6 mmol) was added at room temperature and the mixture was stirred at reflux overnight. Then the reaction mixture was concentrated and treated with column

chromatography (silica gel, PE / EtOAc = 3 / 1) to afford **7** as white solid (56 mg, 30% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, 2H, J = 8.1 Hz), 7.34 (d, 2H, J = 8.3 Hz), 7.25-7.21 (m, 1H), 7.18-7.14 (m, 2H), 7.05-7.03 (m, 2H), 4.59 (q, 1H, J = 7.1 Hz), 3.89 (s, 3H), 3.58 (d, 1H, J = 15.1 Hz), 3.25 (d, 1H, J = 15.1 Hz), 1.79 (d, 3H, J = 7.1 Hz). EI-MS (m/z): 378 $[M+H]^+$.

***tert*-Butyl 4-(2-(((*S*)-1-methoxy-1-oxopropan-2-yl)((*S*)-1-(4-(trifluoromethyl) phenyl)ethyl)amino)-2-oxoethylamino)-4-methylpiperidine-1-carboxylate (8).** DIPEA (0.22 mL, 1.058 mmol) was added to the solution of **3d** (221 mg, 0.63 mmol) and **4e** (148mg, 0.69mmol) in 5 mL of CH_3CN at rt. The mixture was stirred at reflux overnight. Then the reaction was concentrated and treated with column chromatography (silica gel, PE / EtOAc = 1 / 1) to afford colorless oil (265 mg, 80% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (AB, 2H, J_{AB} = 8.3 Hz), 7.60 (AB, 2H, J_{AB} = 8.3 Hz), 5.19 (q, 1H, J = 6.9 Hz), 3.56 (s, 3H), 3.52-3.40 (m, 7H), 1.97 (br-s, 1H), 1.71 (d, 3H, J = 6.9 Hz), 1.55 (d, 3H, J = 6.9 Hz), 1.49-1.47 (m, 4H), 1.44 (s, 9H), 1.08 (s, 3H). (After exchange with D_2O) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (AB, 2H, J_{AB} = 8.3 Hz), 7.60 (AB, 2H, J_{AB} = 8.3 Hz), 5.19 (q, 1H, J = 6.9 Hz), 3.55 (s, 3H), 3.51-3.36 (m, 7H), 1.70 (d, 3H, J = 7.0 Hz), 1.54 (d, 3H, J = 6.9 Hz), 1.49-1.46 (m, 4H), 1.44 (s, 9H), 1.08 (s, 3H). EI-MS (m/z): 529 $[M]^+$. $[\alpha]_D^{20}$ = -80 (c = 1.65, $CHCl_3$).

(*S*)-Methyl 2-(2-chloro-N-((*R*)-2-methoxy-1-(4-(trifluoromethyl)phenyl)ethyl)acetamido)propanoate (13). To the solution of compound **12** (226 mg, 0.74 mmol) in 10 mL of 1,2-dicloroethane was added chloroacetyl chloride (1.18 mL, 14.8 mmol) at

room temperature. The mixture was stirred at reflux for 3.0 hr. Both the solvent and chloroactyl chloride was removed in vacuo. The remaining yellow syrup was purified by column chromatography using PE / EtOAc = 4 / 1 to give the product (271 mg, 96% yield). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.64 (s, 4H), 5.35 (q, 1H, *J* = 3.9 Hz, 4.8 Hz, 3.9 Hz), 4.48 (d,1H, *J* = 12.6 Hz), 4.17 (d,1H, *J* = 12.3 Hz), 4.03 (q, 1H, *J* = 4.2 Hz, 5.4 Hz, 3.9 Hz), 3.89 (t, 1H, *J* = 12.3 Hz, 12.6 Hz), 3.55 (s, 3H), 3.47 (s, 4H), 1.52 (d, 3H, *J* = 6.9Hz). EI-MS (*m*/*z*): 381 $[M]^+$. $[\alpha]_D^{24}$ = -101.4 (*c* = 1.4, $CHCl_3$)

***tert*-Butyl 4-((*S*)-4-((*R*)-2-methoxy-1-(4-(trifluoromethyl)phenyl)ethyl)-3-methyl-2,5-dioxopiperazin-1-yl)-4-methylpiperidine-1-carboxylate (14).** The solution of compound **13** (459 mg, 1.2 mmol), **4e** (258 mg, 1.2 mmol) and 2-hydroxypyridine (305 mg, 3.12 mmol) in 3 mL of toluene was stirred at reflux overnight. After the removal of the solvent, the residue was purified on a silica gel column with a mixture of petroleum ether and ethyl acetate (2 / 1, v / v) as an eluent to give **14** as white solid (345 mg, 54% yield). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.60-7.58 (d, 2H, *J* = 8.1 Hz), 7.38-7.35 (d, 2H, *J* = 8.1 Hz), 4.07-3.78 (m, 4H), 3.54-3.51 (m, 2H), 3.41 (s, 3H), 3.19 (m, 2H), 2.45-2.20 (m, 2H), 1.79-1.68 (m, 2H), 1.62 (br-s, 2H), 1.45 (s, 9H), 1.45-1.43 (m, 3H), 1.36 (s, 3H).

(*S*)-1-(1-(4,6-Dimethylpyrimidine-5-carbonyl)-4-methylpiperidin-4-yl)-4-((*R*)-2-methoxy-1-(4-(trifluoromethyl)phenyl)ethyl)-3-methylpiperazine-2,5-dione (15). To the solution of compound **14** (52 mg, 0.1 mmol) in methylene chloride (2 mL) was added trifluoroacetic acid (0.2 mL). The mixture was stirred at room temperature for 1.0 h, then evaporated. The residue was dissolved in DMF (2 mL) and treated with

4,6-dimethylpyrimidine-5-carboxylic acid (18 mg, 0.12 mmol), HBTU (77 mg, 0.2 mmol) and DIPEA (0.1 mL). The mixture was stirred at room temperature for 24hr, then diluted with EtOAc. Usual work-up was carried out. The residue was subjected to the chromatography (CH_3OH / CH_2Cl_2 = 1 / 15) to afford compound **15** as light brown foam (53 mg, 95% yield for 2 steps). ^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.96 (s, 1H), 7.62-7.57 (m, 2H), 7.40-7.35 (m, 2H), 5.67-5.63 (m, 1H), 4.02-3.95 (m, 3H), 3.91-3.82 (m, 2H), 3.66-3.56 (m, 1H), 3.42 (s, 3H), 3.22-3.03 (m, 2H), 2.80 (s, 2H), 2.68-2.51 (m, 1H), 2.46 (s, 3H), 2.45 (s, 1H), 1.92-1.69 (m, 2H), 1.47-1.44 (dd, 3H, *J* = 3.0 Hz, 3.9 Hz), 1.42-1.41 (d, 3H, *J* = 3.0 Hz). ESI-MS (*m*/*z*): 562.2 $[M+H]^+$, 563.2 $[M+2H]^+$.

(*S*)-2-Aminopropan-1-ol (16a). Lithium aluminum hydride (5.0 g, 0.13 mol) was suspended in 150 mL of THF at 0 °C. *L*-Alanine (5.88 g, 0.066 mol) was added slowly in small portions. The reaction mixture was heated at reflux overnight and then cooled to room temperature. Saturated K_2CO_3 solution was added slowly. Filtration and evaporation of the solvent gave a light yellowish oil (3.83 g, 77.4% yield), which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.48 (dd, 1H, *J* = 3.6 Hz, 10.4 Hz), 3.18 (dd, 1H, *J* = 7.6 Hz, 10.4 Hz), 3.01-2.92 (m, 1H), 2.51 (br-s, 3H), 0.99 (d, 3H, *J* = 6.4 Hz).

(*S*)-2-Chloro-*N*-(1-hydroxypropan-2-yl)acetamide (17a). The solution of chloroacetyl chloride (5.04 mL, 63.3 mmol) in 20 mL of DCM was added to the solution of **16a** (3.174 g, 42.3 mmol) dissolved in 20 mL of H_2O portionwise (2.5 mL each portion) at 0 °C with stirring, then 1N NaOH solution (6.3 mL) was added at the

same temperature. It was stirred at room temperature for 1.0 hr. After that, CH_2Cl_2 was evaporated and the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford yellow oil (5.0 g, 78.3% yield), which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.84 (br-s, 1H), 4.07-3.99 (m, 1H), 4.01 (s, 2H), 3.60 (dd, 1H, *J* = 5.2 Hz,14.8 Hz), 3.50 (dd, 1H, *J* = 14.8Hz, 7.6 Hz), 3.40 (brs, 1H), 1.18 (d, 3H, *J* = 9.2Hz). $[\alpha]_D^{20}$ = -34.5 (*c* = 1.3, $CHCl_3$).

(*S*)-2-Chloro-*N*-(1-chloropropan-2-yl)acetamide (18a). Sodium borohydride (2.63 g, 69.1 mmol), boron trifluoride etherate (5.3 mL, 33.3 mmol) were added to the solution of compound **17a** (2.15 g, 14.2 mmol) in 50 mL of THF. The mixture was stirred under reflux for 3h and then cooled to 0 ºC. Methanol (60 mL) and concentrated hydrogen chloride (30 mL) were added to the mixture, respectively and stirred for 15 minutes at room temperature, then refluxed for 45 minutes. The mixture was concentrated, and basified with 6N sodium hydroxide, then extracted with EtOAc. Usual work-up was applied to the combined organic layers to give the crude product as glassy solid (1.84 g, 94% yield). Used for next step without further purification. The residue (1.375 g, 10.0 mmol) was dissolved in 50 mL of $CHCl_3$. Then, $SOCl_2$ (1.5 mL, 2.0 mmol) was added .The mixture was stirred at room temperature for 1h then refluxed for 2h. The solvent was evaporated to give **18a** as black oil (1.0 g, 59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.25(m, 1H), 3.72(m, 2H), 3.68-3.56 (m, 3H), 2.96 (br-s, 2H), 1.10 (d, 3H, *J* = 9.2 Hz).

***tert*-Butyl 4-methyl-4-((*S*)-3-methyl-4-((*S*)-1-(4-(trifluoromethyl)phenyl)ethyl) piperazin-1-yl)piperidine-1-carboxylate (20a).** Compound **18a** (976 mg, 6.3 mmol), *tert*-butyl 4-amino-4-methylpiperidine-1-carboxyate **4e** (1.48 g, 6.9 mmol) and DIPEA (2.2 mL, 10.58 mmol) in MeCN (30 mL) was refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether / EtOAc = 1 / 1 to give compound **19a** as white solid (0.897 g, 43.9% yield). This solid (1.285 g, 6.41 mmol) was dissolved in dry 1,2-dichloroethane (15 mL) and added Et_3N (0.5 mL, 3.8 mmol). After stirring at room temperature for 0.5 h, 4'-(trifluoromethyl)acetophenone (0.56 g, 3.0 mmol) was added, then treated with sodium triacetoxyborohydride (0.8 g, 4.2 mmol) and HOAc (0.6 mL, 10 mmol). The mixture was stirred at room temperature for 22 h. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. Usual work-up was conducted, and the residue was purified by chromatography using petroleum ether / EtOAc = 2 / 1 to give compound **20a** as yellow gum (350mg, 25.4% yield) and the other isomer (192mg, 10.3% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.6(s, 4H), 4.3 (br-s, 1H), 3.55-3.48 (m, 2H), 3.45-3.40 (m, 2H), 3.04-2.65 (m,2H), 2.45-2.22 (m, 5H), 1.92-1.84 (m, 2H), 1.46 (s, 9H), 1.50-1.32(m, 2H), 1.29 (d, 3H, *J* = 6.4 Hz), 1.15 (d, 3H, *J* = 6.4 Hz), 0.9 (s, 3H).