Supplementary Information

Synthesis and Biological Evaluation of Selective CXCR4 Antagonists Containing Alkene Dipeptide Isosteres

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General Information

¹H NMR spectra were recorded using a JEOL AL-400 and JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me₄Si (in CDCl₃) as internal standard. ¹³C NMR spectra were recorded using a JEOL AL-400 and JEOL ECA-500, and referenced to the residual CHCl₃ signal. ¹⁹F NMR spectra were recorded using a JEOL AL-400 and JEOL ECA-500, and referenced to the residual CFCl₃ signal (δ 0.00 ppm). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Optical rotations were measured with a JASCO sodium automatic polarimeter P-1020. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S. Melting points (uncorrected) were measured by a hot stage melting point apparatus. For flash chromatography, Wakosil C-300, C-300E and silica gel 60 H (silica gel for thin-layer chromatography, Merck) were employed. For analytical HPLC, a Cosmosil 5C18-ARII column (4.6 x 250 mm, Nacalai Tesque, Inc., Kyoto, Japan) was employed with a linear gradient of CH₃CN containing 0.1% (v/v) TFA at a flow rate of 1 cm³ min⁻¹ on a Shimadzu LC-10ADvp (Shimadzu Corp., Ltd., Kyoto, Japan), and eluting products were detected by UV at 220 nm. Preparative HPLC was performed using a Cosmosil 5C18-ARII column (20 x 250 mm, Nacalai Tesque, Inc.) on a Shimadzu LC-6AD (Shimadzu corporation, Ltd.) in an isocratic mode of CH₃CN solution containing 0.1% (v/v) TFA at a flow rate of 10 cm³ min⁻¹.

Experimental Procedures

(3S,4S)-7-[N-(Benzyloxycarbonyl)amino]-4-[N-(tert-butoxycarbonyl)amino]hept-1-en-3-ol (6a).

To a stirred solution of 5 (9.51 g, 27.0 mmol) in CH₂Cl₂/toluene (1/2, 90 cm³) was added dropwise a solution of DIBAL-H in toluene (0.99 M, 55.6 cm³, 55.0 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. To a stirred solution of ZnCl₂ (10.2 g, 75.0 mmol) and LiCl (3.18 g, 75.0 mmol) in THF (50 cm³) was added dropwise vinyl magnesium chloride in THF (1.1 M, 68.2 cm³, 75.0 mmol) at −78 °C. After being stirred at this temperature for 30 min, the mixture was stirred at 0 °C for 30 min. To this solution was added dropwise the above solution of aldehyde at −78 °C, and the mixture was stirred for 3 h with warming to 0 °C, followed by quenching with 0.25 M Rochelle salt and saturated NH₄Cl. The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was washed with saturated citric acid, saturated NaHCO₃ and brine, and dried over MgSO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc/n-hexane (1/4) gave the diastereomixture of allyl alcohol 6 (4.28 g, 42%). Recrystallization from EtOAc/n-hexane (1/10) gave the title compound 6a as a colorless solid: mp 67-68 °C; [α]²⁴D −27.6 (c 1.13, CHCl₃); δ₁ (500 MHz, CDCl₃, Me₄Si) 1.42 (9 H, s), 1.54–1.61 (4 H, m), 2.52–2.65 (1 H, m), 3.10–3.30 (2 H, m), 3.50–3.65 (1 H, m), 4.04–4.15 (1 H, m), 4.70–4.82 (1 H, m), 4.90–5.00 (1 H, m), 5.09 (2 H, s), 5.19 (1 H, d, J 10.8), 5.30 (1 H, d, J 16.8), 5.86 (1 H, ddd, J 16.8, 10.8 and 5.7) and 7.30–7.35 (5 H, m); δ₇ (125 MHz, CDCl₃, Me₄Si) 26.6, 28.3 (3 C), 28.9, 40.8, 54.3, 66.6, 74.3, 79.3, 116.2, 128.0 (3 C), 128.4 (2 C), 136.6, 138.0, 156.4 and 156.5; HRMS (FAB), m/z calcd for C₂₀H₃₁N₂O₅ ([M+H]+) 379.2227, found 379.2228.
(3S,4S)-7-[N-(Benzyloxy carbonyl)amino]-4-[N-(o-nitrobenzenesulfonyl)amino]hept-1-en-3-ol (7). To a stirred solution of allyl alcohol 6a (3.92 g, 10.3 mmol) in CH$_2$Cl$_2$ (60 cm$^3$) at 0 °C was added TFA (40 cm$^3$), and the mixture was stirred for 1 h. The reaction mixture was diluted with toluene (30 cm$^3$) and concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was washed with saturated NaHCO$_3$ and brine, and dried over MgSO$_4$. Concentration under reduced pressure gave an oily residue of a crude amine, which was dissolved in CH$_2$Cl$_2$ (80 cm$^3$). To this solution were added Et$_3$N (0.740 cm$^3$, 10.3 mmol) and nosyl chloride (2.28 g, 10.3 mmol) at room temperature, and the mixture was stirred at the same temperature for 9 h. After concentration under reduced pressure, the residue was extracted with EtOAc. The extract was washed with saturated citric acid, saturated NaHCO$_3$ and brine, and dried over MgSO$_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc/n-hexane (1/4) gave the title compound 7 (3.51 g, 74%) as a yellow oil: $[\alpha]_{D}^{24} = -70.1$ (c 1.00, CHCl$_3$); $\delta_H$ (500 MHz, CDCl$_3$, Me$_4$Si) 1.53–1.81 (4 H, m), 2.45 (1 H, s), 3.13–3.17 (2 H, m), 3.44–3.59 (1 H, m), 4.02–4.12 (1 H, m), 4.84–4.86 (2 H, m), 5.07–5.14 (3 H, m), 5.56 (1 H, ddd, $J = 17.2$, 10.3 and 5.2), 5.76 (1 H, d, $J = 9.2$), 7.33–7.36 (5 H, m), 7.64–7.70 (2 H, m), 7.78–7.87 (1 H, m) and 8.04–8.15 (1H, m); $\delta_C$ (125 MHz, CDCl$_3$, Me$_4$Si) 26.1, 29.4, 40.4, 58.8, 66.6, 73.8, 116.9, 125.1, 128.0 (2 C), 128.1, 128.5 (2 C), 130.4, 132.8, 133.2, 135.2, 136.5, 137.0, 147.6 and 156.6; HRMS (FAB), $m/z$ calcd for C$_{21}$H$_{26}$N$_3$O$_7$S ([M+H]$^+$) 464.1486, found 464.1483.

(3R,4S)-7-[N-(Benzyloxy carbonyl)amino]-3,4-[N-(o-nitrobenzenesulfonyl)epimino]hept-1-ene (8). To a stirred solution of allyl alcohol 7 (905 mg, 1.95 mmol) in dry THF (20 cm$^3$) at 0 °C were added triphenylphosphine (767 mg, 2.93 mmol) and diethyl azodicarboxylate in toluene solution (2.2 M, 975 cm$^3$, 2.15 mmol), and the reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure and purified by flash chromatography over silica gel with CHCl$_3$ to give the title compound 8 (806 mg, 93%) as a yellow oil: $[\alpha]_{D}^{24} = +4.0$ (c 1.00, CHCl$_3$); $\delta_H$ (500 MHz, CDCl$_3$, Me$_4$Si) 1.55–1.60 (4 H, m), 3.09–3.16 (1 H, m), 3.17–3.25 (2 H, m), 3.56 (1 H, t, $J = 6.9$), 5.00 (1 H, br s), 5.07 (2 H, s), 5.34 (1 H, d, $J = 10.3$), 5.48 (1 H, d, $J = 17.2$ Hz), 5.58–5.65 (1 H, m), 7.29–7.34 (5 H, m), 7.71–7.79 (3 H, m) and 8.16 (1H, d, $J = 7.5$); $\delta_C$ (125 MHz, CDCl$_3$, Me$_4$Si) 24.0, 27.1, 40.1, 46.0, 46.5, 47.6, 66.4, 122.0, 124.2, 127.9, 127.9, 128.4 (2 C), 129.0, 131.0, 131.7, 132.1, 134.4, 136.5, 148.4 and 156.3; HRMS (FAB), $m/z$ calcd for C$_{21}$H$_{22}$N$_3$O$_6$S ([M–H]$^-$) 444.1235, found 444.1235.

tert-Butyl (4R,5S,2E)-8-[N-(benzyloxy carbonyl)amino]-4,5-[N-(o-nitrobenzenesulfonyl)epimino]oct-2-enoate (9). Ozone gas was bubbled through a solution of aziridine 8 (2.79 g, 6.26 mmol) in EtOAc (60 cm$^3$) at –78 °C until a blue color persisted. To the above solution was added Me$_2$S (4.90 cm$^3$, 63.0 mmol), and the mixture was stirred at –78 °C for 10 min. Concentration under reduced pressure gave an oily residue of a crude aldehyde, which was used immediately in the next step without further purification. To a stirred suspension of LiCl (398 mg, 9.39 mmol) in MeCN (40 cm$^3$)
under argon, were added \((\text{EtO})_2\text{P(O)CH}_2\text{CO}_2\text{-Bu}\) (2.37 g, 9.39 mmol) in MeCN (10 cm\(^3\)) and \((\text{i-Pr})_2\text{NEt}\) (1.64 cm\(^3\), 9.39 mmol) at 0 °C. After 30 min, the above aldehyde in MeCN (20 cm\(^3\)) was added to the mixture at 0 °C, and the mixture was stirred at this temperature for 4 h followed by quenching with saturated NH\(_4\)Cl. The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was washed successively with saturated citric acid, saturated NaHCO\(_3\) and brine, and dried over MgSO\(_4\). Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc/n-hexane (1/4) gave the title compound \(9\) (1.93 g, 57%) as a yellow oil: \([\alpha]_24^D –24.3\) (c 1.01, CHCl\(_3\)); \(\delta_H\) (500 MHz, CDCl\(_3\), Me\(_4\)Si) 1.46 (9 H, s), 1.59–1.67 (4 H, m), 3.22–3.24 (3 H, m), 3.67 (1 H, t, \(J = 6.9\)), 4.93 (1 H, br s), 5.08 (2 H, s), 6.12 (1 H, d, \(J = 16.0\)), 6.56 (1 H, dd, \(J = 16.0\) and 7.4), 7.29–7.78 (3 H, m) and 8.19 (1 H, d, \(J = 7.5\)); \(\delta_C\) (125 MHz, CDCl\(_3\), Me\(_4\)Si) 24.3, 27.3, 28.0 (3 C), 40.1, 46.0, 46.9, 66.6, 81.1, 124.4, 128.0 (3 C), 128.5 (2 C), 129.0, 131.4, 131.6, 132.3, 134.7, 136.5, 136.9, 148.5, 156.4 and 164.5; HRMS (FAB), \(m/z\) calcd for C\(_{26}\)H\(_{30}\)N\(_3\)O\(_8\)S (\([\text{M–H}]–\)) 544.1759, found 544.1763.

**tert-Butyl (2R,5S,3E)-8-\[N-(benzyloxycarbonyl)amino]-2-(3-hydroxyprop-1-yl)-5-\[N-(o-nitrobenzenesulfonyl)amino\]oct-3-enoate (11).** To a stirred solution of \(10\) (101 mg, 0.140 mmol) in dry THF (2 cm\(^3\)) at 0 °C were added 1 M tetrabutylammonium fluoride in THF solution (0.210 cm\(^3\), 0.210 mmol), and the reaction mixture was stirred at this temperature for 14 h followed by quenching with saturated aqueous NH\(_4\)Cl. The mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was washed successively with saturated citric acid, saturated NaHCO\(_3\) and brine twice, and dried over MgSO\(_4\). Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc/n-hexane (1/2) gave the title compound \(11\) (62.0 mg, 85%) as a yellow oil: \([\alpha]_24^D –96.1\) (c 1.00, CHCl\(_3\)); \(\delta_H\) (500 MHz, CDCl\(_3\), Me\(_4\)Si) 1.26–1.35 (2 H, m), 1.37 (9 H, s), 1.40–1.56 (6 H, m), 2.12 (1 H, br s), 2.63–2.71 (1 H, m), 3.10–3.20 (2 H, m), 3.48–3.56 (2 H, m), 3.87–3.97 (1 H, m), 4.94–5.03 (1 H, m), 5.09 (2 H, s), 5.29 (1 H, dd, \(J = 15.5\) and 7.4), 5.40 (1 H, dd, \(J = 15.5\) and 8.6), 5.63 (1 H, d, \(J = 8.0\)), 7.32–7.34 (5 H, m), 7.66–7.71 (2 H, m), 7.81 (1 H, d, \(J = 6.7\)) and 8.07 (1 H, d, \(J = 7.5\)); \(\delta_C\) (125 MHz, CDCl\(_3\), Me\(_4\)Si) 25.9, 27.9 (3 C), 28.4, 29.8, 32.9, 40.3, 49.0, 56.4, 62.0, 66.5, 80.8, 125.3, 127.9 (2 C), 128.0, 128.4 (2 C), 130.8, 130.9, 131.2, 132.8, 133.4, 134.6, 136.5, 147.7, 156.4 and 172.7; HRMS (FAB), \(m/z\) calcd for C\(_{29}\)H\(_{38}\)N\(_3\)O\(_9\)S (\([\text{M–H}]–\)) 604.2334, found 604.2343.

**tert-Butyl (2R,5S,3E)-8-\[N-(benzyloxycarbonyl)amino]-2-\{3-\[N-(benzyloxycarbonyl)-N-(o-nitrobenzenesulfonyl)carbamate\]prop-1-yl\}-5-\[N-(o-nitrobenzenesulfonyl)amino\]oct-3-enoate (12).** To a stirred solution of alcohol \(11\) (255 mg, 0.490 mmol) in dry THF (5 cm\(^3\)) at 0 °C were added triphenylphosphine (170 mg, 0.640 mmol), 2.2 M diethyl azodicarboxylate in toluene solution (0.270 cm\(^3\), 0.590 mmol) and benzyl \(N\)-(2-nitrophenylsulfonyl)carbamate (180 mg, 0.540 mmol), and the reaction mixture was stirred at this temperature for 24 h. The mixture was concentrated under reduced pressure and purified by flash chromatography over silica gel with CHCl\(_3\) to give the title compound \(12\) (421 mg, 93%) as a yellow oil: \([\alpha]_24^D –71.0\) (c 1.01, CHCl\(_3\)); \(\delta_H\) (500 MHz, CDCl\(_3\), Me\(_4\)Si) 1.46 (9 H, s), 1.59–1.67 (4 H, m), 3.22–3.24 (3 H, m), 3.67 (1 H, t, \(J = 6.9\)), 4.93 (1 H, br s), 5.08 (2 H, s), 6.12 (1 H, d, \(J = 16.0\)), 6.56 (1 H, dd, \(J = 16.0\) and 7.4), 7.29–7.77 (3 H, m) and 8.19 (1 H, d, \(J = 7.5\)); \(\delta_C\) (125 MHz, CDCl\(_3\), Me\(_4\)Si) 24.3, 27.3, 28.0 (3 C), 40.1, 46.0, 46.9, 66.6, 81.1, 124.4, 128.0 (3 C), 128.5 (2 C), 129.0, 131.4, 131.6, 132.3, 134.7, 136.5, 136.9, 148.5, 156.4 and 164.5; HRMS (FAB), \(m/z\) calcd for C\(_{26}\)H\(_{30}\)N\(_3\)O\(_8\)S (\([\text{M–H}]–\)) 544.1759, found 544.1763.
Me$_4$Si) 1.24–1.29 (2 H, m), 1.38 (9 H, s), 1.53–1.59 (6 H, m), 2.61–2.70 (1 H, m), 3.18–3.20 (2 H, m), 3.70–3.75 (2 H, m), 3.93 (1 H, br s), 4.87 (1 H, br s), 5.09 (2 H, s), 5.11 (2 H, s), 5.27 (1 H, dd, $J$ 15.5 and 7.5), 5.35 (1 H, dd, $J$ 15.5 and 8.0), 5.41 (1 H, d, $J$ 8.6), 7.19–7.23 (2 H, m), 7.29–7.43 (9 H, m), 7.63–7.72 (4 H, m), 7.82–7.86 (1 H, m) and 8.03–8.08 (2 H, m); $\delta_{C}$ (125 MHz, CDCl$_3$, Me$_4$Si) 26.0, 27.1, 27.9 (3 C), 29.0, 33.1, 40.4, 47.6, 48.5, 56.6, 66.6, 69.5, 81.0, 124.3, 125.5, 128.0 (3 C), 128.5 (2 C), 128.6 (2 C), 128.7 (2 C), 128.9, 130.7, 130.8, 131.3, 131.6, 132.6, 132.9, 133.6, 134.0, 134.1, 134.4, 134.7, 136.6, 147.7, 147.8, 151.6, 156.4 and 172.2; HRMS (FAB), $m/z$ calcd for C$_{43}$H$_{48}$N$_5$O$_{15}$S$_2$ ([M–H]$^–$) 922.2645, found 922.2650.

tert-Butyl (2$R$,5$S$,3$E$)-8-[N-(benzyloxy carbonyl)amino]-2-[3-[N-(benzyloxy carbonyl)amino]-prop-1-yl]-5-[N-(fluorenylmethoxycarbonyl)amino]oct-3-enoate (13). To a stirred solution of 12 (750 mg, 0.810 mmol) in DMSO/MeCN (1/49, 10 cm$^3$) were added thiophenol (0.330 cm$^3$, 3.24 mmol) and K$_2$CO$_3$ (0.67 g, 4.86 mmol) at room temperature, and the mixture was stirred at 50 °C for 2 h. The solution was filtered, and the filtrate was concentrated under reduced pressure. The residue was extracted with CHCl$_3$, washed with saturated NaHCO$_3$ and brine, and dried over MgSO$_4$. Concentration under reduced pressure gave an oily residue, which was dissolved in THF/H$_2$O (1/1, 8 cm$^3$). Fmoc-OSu (330 mg, 0.970 mmol) and Et$_3$N (0.120 cm$^3$, 1.62 mmol) were added to the above solution at 0 °C. After being stirred for 4 h, the mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The extract was washed successively with saturated citric acid and saturated NaHCO$_3$ and brine, and dried over MgSO$_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc/n-hexane (1/4) gave the title compound 13 (664 mg, quant.) as a colorless oil: $[\alpha]_{24}^D$ –15.6 (c 0.51, CHCl$_3$); $\delta_{H}$ (500 MHz, CDCl$_3$, Me$_4$Si) 1.41 (9 H, s), 1.44–1.54 (7 H, m), 1.67–1.74 (1 H, m), 2.84–2.86 (1 H, br s), 3.12–3.17 (4 H, m), 4.12 (1 H, br s), 4.17–4.20 (1 H, m), 4.35–4.37 (1 H, m), 4.40–4.46 (1 H, m), 4.92–5.00 (2 H, m), 5.05 (2 H, s), 5.27–5.12 (3 H, m), 5.40–5.45 (1 H, m), 5.52–5.58 (1 H, m), 7.28–7.39 (14 H, m), 7.58 (2 H, d, $J$ 6.9) and 7.75 (2 H, d, $J$ 7.5); $\delta_{C}$ (125 MHz, CDCl$_3$, Me$_4$Si) 26.2, 27.3, 28.0 (3 C), 29.2, 32.1, 40.6, 47.2, 49.2, 52.4, 66.4, 66.5, 80.8, 119.9, 120.0, 124.9 (2 C), 125.0 (2 C), 127.0 (2 C), 127.6 (2 C), 128.0 (3 C), 128.1 (3 C), 128.4 (2 C), 128.4 (2 C), 129.3 (2 C), 132.6, 136.5 (2 C), 141.3, 143.8, 143.9, 155.7, 156.3, 156.4 and 172.9; HRMS (FAB), $m/z$ calcd for C$_{46}$H$_{54}$N$_3$O$_8$ ([M+H]$^+$) 776.3905, found 776.3911.

(2$R$,5$S$,3$Z$)-8-[N-(tert-Butoxycarbonyl)-N-(o-nitrobenzenesulfonyl)amino]-5-[(tert-butoxycarbonyl)amino]-4-fluoro-2-(2-naphthylmethyl)oct-3-enoyl (S)-sultam (17). To a solution of the TBS ether 16 (1.32 g, 1.78 mmol) in MeCN/H$_2$O (1/1, 20 cm$^3$) at 0 °C under argon was added aqueous H$_2$SiF$_6$ (3.26 N, 0.546 cm$^3$), and the mixture was stirred at room temperature for 1 h. After dilution with EtOAc (300 cm$^3$), the reaction mixture was washed with aqueous 5% K$_2$CO$_3$ and dried over MgSO$_4$. Concentration under reduced pressure gave the corresponding alcohol, which was used in the next step without purification. To a solution of the alcohol, triphenylphosphine (934 mg, 3.56 mmol), tert-butyl N-(2-nitrophenylsulfonyl)carbamate (1.15 g, 3.92 mmol) in THF (18 cm$^3$) a
solution of diethyl azodicarboxylate in toluene (2.2 M, 1.62 cm$^3$, 3.56 mmol) were added at 0 °C under argon. After being stirred at room temperature for 12 h, concentration under reduced pressure followed by flash chromatography over silica gel with EtOAc/n-hexane (1/2) gave the title compound 17 (1.59 g, 98%) as a colorless semisolid: $[\alpha]_{D}^{25} = -52.4$ (c 1.10, CHCl$_3$); $\delta$ (500 MHz, CDCl$_3$, Me$_4$Si) 0.27 (3 H, s), 0.75 (3 H, s), 1.15–1.26 (2 H, m), 1.35 (9 H, s), 1.44 (9 H, s), 1.53–1.81 (8 H, m), 1.90 (1 H, dd, $J$ 13.2 and 8.0), 2.99 (1 H, dd, $J$ 13.2 and 6.3), 3.25–3.36 (3 H, m), 3.68–3.77 (3 H, m), 4.49–4.59 (1 H, m), 4.67 (1 H, d, $J$ 9.2), 5.08 (1 H, dd, $J$ 36.1 and 8.6), 6.38–6.51 (1 H, m), 7.38–7.44 (3 H, m), 7.65 (1 H, s), 7.70–7.78 (6 H, m) and 8.24–8.29 (1 H, m); $\delta$ (125 MHz, CDCl$_3$, Me$_4$Si) 14.4, 19.6, 19.8, 26.3, 26.4, 27.8 (3 C), 28.3 (3 C), 32.7, 38.1, 40.5 (d, $J$ 2.4), 43.0, 44.6, 47.3, 47.5, 48.0, 52.8, 62.2, 64.9, 79.7, 84.9, 104.2 (d, $J$ 12.0), 124.3, 125.3, 125.8, 127.5, 127.6, 127.8, 127.9, 131.7, 132.4, 133.1, 133.4, 133.6, 134.0, 135.1, 147.6, 150.3, 154.8, 158.3 (d, $J$ 260.3) and 175.2; $\delta$ (125 MHz, CDCl$_3$, CFCI$_3$) –119.8; HRMS (FAB), $m/z$ calcd for C$_{45}$H$_{57}$FN$_4$NaO$_{11}$S$_2$ ([M+Na]$^+$) 935.3347, found: 935.3358.
HPLC chart of 3E and 4F.

Peptide 3E

HPLC condition: isocratic MeCN (22%) in 0.1% TFA aq., flow rate 1 cm³ min⁻¹

Peptide 4F

HPLC condition: isocratic MeCN (26%) in 0.1% TFA aq., flow rate 1 cm³ min⁻¹