Supporting Information for

Highly potent, orally-available anti-inflammatory broad-spectrum chemokine inhibitors.

David J. Fox[a, *], Jill Reckless[b], Hannah Lingard[a], Stuart Warren[a] & David J. Grainger[b]

[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK;*

[b] *Department of Medicine, University of Cambridge, Box 157, Addenbrooke's Hospital, Cambridge, CB22QQ UK..*

Contents

* Current Address: Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, U.K. email: d.j.fox@warwick.ac.uk

Synthesis

General Experimental

Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Thin layer chromatography was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$). Proton and carbon NMR spectra were recorded on a Bruker Avance 500 Fourier Transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million down field of tetramethylsilane and values of coupling constants (*J*) are given in Hz. Carbon NMR spectra were recorded with broad band proton decoupling and DEPT. Melting points were measured on a Stuart Scientific melting point apparatus (SMP 1) and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer Spectrum One (FT-IR) spectrophotometer. Electrospray (ES) mass spectra were recorded using a Micromass Q-Toff instrument. Microanalyses were carried out by the staff of the University Chemical Laboratory using a CE440 Elemental Analyser from Exeter Analytical, INC, or by Warwick Analytical Service. Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line; 589 nm). Specific rotations are given in units of 10^{-1} deg dm^2 g^{-1}. Carboxylic acid sidechains were purchased, synthesised according to known procedures, or synthesised as described below. Acid chlorides were used as supplied or made by addition of one equivalent of oxalyl chloride to the relevant carboxylic acid, and used without purification. (*R*)- and (*S*)-3-Amino-caprolactam was synthesised from lysine and isolated as hydrochloride or hydropyroglutamate salts.[1,2] The purty of tested compounds was

confirmed to be greater than 95% by elemental analysis. It some cases a small amount of residual water was present and included in the purity calculations.

(S)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam (*S*)-5

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give (*S*)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam (543 mg; 80%); m.p.: 51-52 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +28.0; $[\alpha]_D^{25}$ (c = 0.87, MeOH) +13.3; ν_{max} (cm^{-1}): 3403, 3265 (NH), 1673, 1641 (CO), 1497 (NH); δ_H, (500 MHz, $CDCl_3$) 7.08 (1H, d, *J* 5.5, CHN*H*), 6.67 (1H, br s, CH_2N*H*), 4.44 (1H, dd, *J* 11, 5.5, C*H*NH), 3.28-3.15 (2H, m, C*H*$_2$NH), 2.01 (1H, br d, *J* 13, ring CH), 1.98-1.89 (1H, m, ring CH), 1.84-1.72 (2H, m, ring CH), 1.47-1.30 (3H, br m, ring CH + C*H*$_2$CMe$_2$CONH), 1.27-1.15 (17H, br m, ring CH +$(CH_2)_8$) 1.13 (3H, s, C*Me*Me), 1.12 (3H, s, CMe*Me*) and 0.82 (3H, t, *J* 7, CH_2C*H*$_3$). δ_C (125 MHz, $CDCl_3$) 177.1, 176.0 (CO), 52.0 (NH*C*HCO), 41.9 (*C*Me$_2$), 42.1, 41.3, 31.8, 31.5, 30.1, 29.6, 29.5 (×2), 29.3, 28.9, 27.9 (CH_2), 25.3, 25.2 (CH_3), 24.8, 22.6 (CH_2) and 14.1 (CH_3). *m/z* ($C_{20}H_{38}N_2O_2Na$ requires 361.2831) found 361.28350; anal. ($C_{20}H_{38}N_2O_2$ requires C 70.96, H 11.31, N 8.28) found C 71.04, H 11.40, N 8.33.

(R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam (*R*)-5

(*R*,*R*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (EtOAc: hexanes 1:3 to EtOAc) to give (*R*)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam (515 mg, 76%); m.p. 50-51 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) -25.7; $[\alpha]_D^{25}$ (c = 0.5, MeOH) -12.2; anal. ($C_{20}H_{38}N_2O_2$ requires C 70.96, H 11.31, N 8.28) found C 71.09, H 11.50, N 8.37.

(S)-3-(2',2',5'-Trimethyl-hexanoyl)amino-caprolactam (*S*)-6

(*S*)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam **(*S*)-7** (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, *ca* 100 mg) was added, and the mixture was stirred at ambient

temperature under an atmostsphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed *in vacuo* to give (*S*)-3-(2',2',5'-yrimethyl-hexanoyl)amino-caprolactam as a waxy solid (400 mg, 98%); m.p. 73-74 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +27.8; ν_{max}/cm^{-1} 3249 (NH), 1654, 1638 (CO), 1502 (NH); δ_H (500 MHz, $CDCl_3$) 7.08 (1H, d, *J* 5.0, CHN*H*), 6.75-6.55 (1H, br m, CH_2N*H*), 4.44 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.29-3.16 (2H, m, C*H*$_2$NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH_2 + C*H*$(CH_3)_2$), 1.13 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.08-1.02 (2H, m, CH_2), 0.82 (3H, s, CH_3), 0.80 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 177.1, 176.1 (CO), 52.1 (NH*C*HCO), 42.1 (CH_2N), 41.9 (CH_2*C*Me_2), 39.0, 33.7, 31.5, 28.9 (CH_2), 28.4 (Me_2*C*H), 27.9 (CH_2), 25.3, 25.2, 22.6, 22.5 (CH_3); *m/z* (MH^+ $C_{15}H_{29}N_2O_2$ requires 269.2229) found 269.2219; anal. ($C_{15}H_{28}N_2O_2$ requires C 67.13, H 10.52, N 10.44) found C 66.99, H 10.50, N 10.41.

(S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam (*S*)-7

Butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 ºC under N_2. The reaction was strirred at -78 ºC for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 ºC for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed *in vacuo*, and the residure was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and hexane (3 × 250 ml). The combined organic layers were dried over Na_2SO_4 and the hexane solvent removed *in vacuo* to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%); ν_{max}/cm^{-1} 1732 (CO); δ_H (400 MHz, $CDCl_3$) 5.04 (1H, tsept, *J* 7.5, 1.5, CH=C), 3.63 (3H, s, OCH_3), 2.20 (2H, d, *J* 7.5, CHC*H*$_2$), 1.68 (3H, br s, CH=C*Me*Me), 1.58 (3H, br s, CH=CMe*Me*), 1.14 (6H, s, $(CH_3)_2$CO); δ_C (125 MHz, $CDCl_3$) 178.4 (CO), 134.1 (Me_2*C*=CH), 119.8 (Me_2C=*C*H), 51.6 (OCH_3), 42.8 (Me_2*C*CO), 38.7 (CH_2), 25.9, 24.7 (× 2), 17.8 (C*C*H_3); *m/z* (MH^+ $C_{10}H_{19}O_2$ requires 171.1385) 171.1388. Methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3 × 150 ml). The combined organic layers were dried over Na_2SO_4 and the ether solvent removed *in vacuo* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 5.12 (1H, tsept, *J* 7.5, 1.5, CH=C), 2.25 (2H, d, *J* 7.5, CHC*H*$_2$), 1.71 (3H, br s, CH=C*Me*Me), 1.60 (3H, br s, CH=CMe*Me*), 1.18 (6H, s, $(CH_3)_2$CO). The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification. (*S*,*S*)-3-amino-caprolactam hydro-

pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na_2CO_3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 50 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (*S*)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%); m.p. 43-44 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +23.2; ν_{max}/cm^{-1} 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ_H (500 MHz, $CDCl_3$) 7.11 (1H, d, *J* 5.0, CHN*H*), 6.65-6.45 (1H, br m, CH_2NH), 5.04 (1H, t, *J* 7.5, CH=C), 4.44 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.24-3.16 (2H, m, CH_2NH), 2.20 (1H, dd, *J* 14.5, 7.5, C=CHCH_2), 2.15 (1H, dd, *J*, 14.5, 7.5, C=CHCH_2), 2.03-1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH_3) and 1.12 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NH*C*HCO), 42.5 (CH_2*C*Me_2), 42.1 (CH_2N), 39.0, 31.5, 28.9, 28.0 (CH_2 lactam), 26.0, 25.0, 24.9, 17.9 (CH_3); *m/z* (MH^+ $C_{15}H_{27}N_2O_2$ requires 267.2073) found 267.2063; anal. ($C_{15}H_{26}N_2O_2$. + 1/3 H_2O requires C 66.14, H 9.87, N 10.28) found C 66.09, H 9.70, N 10.42.

(S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam (*S*)-8

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (20 mmol) and Na_2CO_3 (60 mmol) in water (50 ml) were added to a solution of 2,2-dimethyl-pentanoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was recrystallised from EtOAc / hexane to give **(*S*)-3-(2',2'-dimethyl-pentanoyl)amino-caprolactam** (3.50 g, 77%); m.p. 84-85 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +30.7; ν_{max}/cm^{-1} 3387, 3239 (NH), 1655, 1634 (CO), 1507 (NH); δ_H (500 MHz, $CDCl_3$) 7.08 (1H, d, *J* 5, CHN*H*), 6.53 (1H, br s, CH_2NH), 4.45 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.29-3.16 (2H, m, CH_2NH), 2.00 (1H, br d, *J* 13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.84-1.73 (2H, m, ring CH), 1.47-1.30 (4H, br m, ring CH ×2 + CH_2CMe_2CONH), 1.23-1.15 (2H, m, CH_2CH_3) 1.14 (3H, s, C*Me*Me), 1.13 (3H, s, CMe*Me*) and 0.84 (3H, t, *J* 7, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 177.0, 176.1 (CO), 52.1 (NH*C*HCO), 43.6, 42.0 (×2, one of which is *C*Me_2), 31.5, 28.9, 27.9 (CH_2), 25.3, 25.2 (CH_3), 18.0 (CH_2) and 14.5 (CH_3); *m/z* (M^+ $C_{13}H_{24}N_2O_2$ requires 240.18378) found 240.18437; anal. ($C_{13}H_{24}N_2O_2$ requires C 66.97, H 10.07, N 11.66) found C 65.01, H 10.0, N 11.69.

(*S*)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam (*S*)-9

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (20 mmol) and Na_2CO_3 (60 mmol) in water (50 ml) were added to a solution of 2,2-dimethyl-pent-4-enoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (1:1 EtOAc: hexane to EtOAc) to give **(*S*)-3-(2',2'-dimethyl-pent-4-enoyl)amino-caprolactam** (1.43 g, 32%); m.p. 71-72 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +27.7; ν_{max}/cm^{-1} 3395, 3304 (NH), 1675, 1633 (CO), 1534 (NH); δ_H (500 MHz, $CDCl_3$) 7.10 (1H, d, *J* 4.5, CHN*H*), 6.48 (1H, br s, CH_2N*H*), 5.68 (1H, ddt, *J* 17, 10, 7.5, C*H*=CH_2), 5.02 (1H, br d, *J* 17 CH=C*H*H), 5.00 (1H, br d, *J* 10, CH=CH*H*), 4.45 (1H, dd, *J* 11, 5.5, C*H*NH), 3.30-3.17 (2H, m, C*H*$_2$NH), 2.27 (1H, *J* 14, 7.5, C*H*HCH=CH_2), 2.22 (1H, dd, *J* 14, 7.5, CH*H*CH=CH_2), 2.01 (1H, br d, *J* 13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.85-1.73 (2H, m, ring CH), 1.47-1.30 (2H, br m, ring CH ×2), 1.16 (3H, s, C*Me*Me) and 1.15 (3H, s, CMe*Me*); δ_C (125 MHz, $CDCl_3$) 176.4, 175.9 (CO), 134.2 (*C*H=CH_2), 117.8 (CH=*C*H_2), 52.1 (NH*C*HCO), 45.2, 42.1 (CH_2), 41.9 (*C*Me_2), 31.5, 28.9, 27.9 (CH_2), 25.0 and 24.9 (CH_3); *m/z* (M^+ $C_{13}H_{22}N_2O_2$ requires 238.16813) found 238.16834; anal. ($C_{15}H_{26}N_2O_2$ requires C 65.51, H 9.30, N 11.75) found C 65.42, H 9.33, N 11.76.

(3*S*,2'*R*) and (3*S*,2'*S*)-3-(2'-Methyldodecanoyl)amino-caprolactam (*S*)-10

(*S*)-(*E*)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam **(*S*)-12** (0.5 mmol) and $Pd(OH)_2$ (20% on carbon) were added to methanol (10 ml) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of hydrogen. The reaction was then filtered, and the solvent removed *in vacuo* to give (3*S*,2'*R*) and (3*S*,2'*S*)-3-(2'-methyldodecanoyl)amino-caprolactam as a solid (160 mg, >95%); ν_{max}/cm^{-1} 3313 (NH), 1671, 1636 (CO), 1515 (NH); δ_H (500 MHz, $CDCl_3$) 6.91 (2H, d, *J* 5.5, CHN*H*, both isomers), 6.55 (2H, br s, CH_2N*H*, both isomers), 4.57-4.47 (2H, m, C*H*NH, both isomers), 3.34-3.18 (4H, m, C*H*$_2$NH, both isomers), 2.29-2.14 (2H, CH_3C*H*CO, both isomers), 2.07 (2H, br d, *J* 13.5, lactam ring CH, both isomers), 2.02-1.94 (2H, m, lactam ring CH, both isomers), 1.89-1.76 (4H, m, lactam ring CH ×2, both isomers), 1.67-1.57 (2H, m, chain CH, both isomers), 1.51-1.33 (6H, m, lactam ring CH ×2 + side chain CH_2, both isomers), 1.32-1.18 (32H, m, $(CH_2)_8$, both isomers), 1.13 (3H, d, *J* 7, CHC*H*$_3$, one isomer), 1.11 (3H, d, *J* 7, CHC*H*$_3$, one isomer) and 0.87 (6H, t, *J* 7.5, CH_3, both isomers); δ_C (125 MHz, $CDCl_3$) 175.9 (×2), 175.8 (×2) (CO, both isomers), 52.0, 51.9 (NCH), 42.1 (×2) (NCH_2, both isomers), 41.3, 41.2 (*C*HCH_3), 34.5, 34.1, 31.9 (×2), 31.8, 31.7, 29.6 (×6), 29.5 (×2), 29.3 (×2), 28.9 (×2), 28.0, 27.9, 27.4 (×2), 22.6 (×2) (CH_2) 17.8, 17.6 and 14.1 (×2) (CH_3); *m/z* (MH^+ $C_{19}H_{37}N_2O_2$ requires

325.2855) found 325.2858; anal. ($C_{19}H_{38}N_2O_2$ + 1/6 H_2O) requires C 69.68, H 11.18, N 8.55, found C 69.68, H 11.19, N 8.54.

(*S*)-3-(*trans*-4'-Pentylcyclohexane-1'-carbonyl)amino-caprolactam (*S*)-11

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (7 mmol) and Na_2CO_3 (21 mmol) in water (25 ml) were added to a solution of *trans*-4-pentylcyclohexane-1-carbonyl chloride (6 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc / hexane to give the lactam (977 mg, 53%); m.p. 182-184 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +32.2; ν_{max}/cm^{-1} 3326 (NH), 1670, 1636 (CO), 1511 (NH); δ_H (500 MHz, $CDCl_3$) 6.91 (1H, d, *J* 5.5, CHN*H*), 6.87-6.70 (1H, br m, CH_2N*H*), 4.44 (1H, ddd, *J* 11, 6.0, 1.5, C*H*NH), 3.28-3.15 (2H, m, C*H*$_2$NH), 2.08-1.90 (3H, br m, ring CH ×2 + $(CH_2)_2$C*H*CO), 1.88-1.72 (6H, m, ring CH + chain CH_2 × 4), 1.45-1.28 (4H, br m, ring CH + chain CH_2 ×2 + chain C*H*$(CH_2)_3$), 1.27-1.07 (9H, br m, ring CH + chain CH_2 ×8) and 0.90-0.79 (5H, m, chain CH_2 + CH_3); δ_C (125 MHz, $CDCl_3$) 176.0, 175.3 (CO), 51.8 (NH*C*HCO), 45.4 (CH), 41.0 (CH_2), 37.1 (CH_2), 36.9 (CH), 32.5, 32.4, 32.1, 31.7, 29.6, 29.4, 28.9, 27.9, 26.5, 22.6 (CH_2) and 14.0 (CH_3); *m/z* (M^+ $C_{18}H_{32}N_2O_2$ requires 308.24638) found 308.24566; anal. ($C_{18}H_{32}N_2O_2$ requires C 70.09, H 10.46, N 9.08) found C 70.05, H 10.50, N 9.10.

(*S*)-(*E*)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam (*S*)-12

Decanal (5 mmol) and (carbethoxyethylidene)triphenylphosphorane (10 mmol) were dissolved in CH_2Cl_2 (20 ml)and the reaction was stirred for 18 hours. The solvent was then removed *in vacuo* and the residue was filter through a plug of silica gel with the aid of 5% diethyl ether in hexanes. The collected eluent was reduced *in vacuo* to give (*E*)-ethyl 2-methyldodec-2-enoate as an oil (1.02 g, 88%); ν_{max}/cm^{-1} 1709 (CO), 1651 (C=C); δ_H (500 MHz, $CDCl_3$) 6.73 (1H, tq, *J* 7.5, 1.5, CH=C), 4.16 (2H, q, *J* 7, OCH_2), 2.13 (2H, br q, *J* 7.5, C*H*$_2$CH=C), 1.80 (3H, d, *J* 1.5, C*H*$_3$C=CH), 1.45-1.37 (2H, m, chain CH_2), 1.32-1.19 (15H, m, $(CH_2)_6$ + OCH_2C*H*$_3$) and 0.85 (3H, t, *J* 7, $(CH_2)_8$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 168.3 (CO), 142.4 (*C*H=C), 127.6 (CH=*C*), 60.3 (OCH_2), 31.8, 29.5, 29.4 (×2), 29.3, 28.6, 28.5, 22.6 (CH_2), 14.3, 14.1 and 12.3 (CH_3); *m/z* (MH^+ $C_{15}H_{29}O_2$ requires 241.2168) 241.2165. (*E*)-Ethyl 2-methyldodec-2-enoate (1.43 mmol) was dissolved in ethanol (10 ml), and KOH (10 mmol) in water (5 ml) was added. The reaction was heated at reflux for 18 hours and then cooled. The solvent was removed *in vacuo* and the residue partitioned between water and hexane. The aqueous layer was acidified with aqueous HCl, and was extracted with diethyl ether. The diethyl ether layer was dried over Na_2SO_4 and reduced *in vacuo* to give (*E*)-2-methyldodec-2-enoic acid as a solid (308 mg, >95%); m.p. 28-31 ºC; δ_H (400 MHz, $CDCl_3$) 6.91

(1H, tq, *J* 7.5, 1.5, CH=C), 2.18 (2H, br q, *J* 7.5, C*H*$_2$CH=C), 1.82 (3H, d, *J* 1.5, C*H*$_3$C=CH), 1.48-1.39 (2H, m, chain CH_2), 1.36-1.19 (12H, m, $(CH_2)_6$) and 0.88 (3H, t, *J* 7, $(CH_2)_8CH_3$) (no OH peak observed). (*E*)-2-Methyldodec-2-enoic acid (1.43 mmol) was dissolved in CH_2Cl_2 (20 ml) oxalyl chloride (1 ml) and dimethyl formamide (1 drop) was added. After 1 hour the reaction was reduced *in vacuo* to give crude (*E*)-2-methyldodec-2-enoyl chloride which was used directly in the synthesis of (*S*)-(*E*)-3-(2'-methyldodec-2'-enoyl)amino-caprolactam. (*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (15 ml) were added to a solution of (*E*)-2-methyldodec-2-enoyl chloride (1.43 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. The residue was recrystallised from hexane to give (*S*)-(*E*)-3-(2'-methyldodec-2'-enoyl)amino-caprolactam (297 mg, 65%); m.p. (hexanes) 99-100 ºC; ν_{max}/cm^{-1} 3282 (NH), 1656, 1622 (CO and C=C), 1497 (NH); $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +38.2; δ_H (500 MHz, $CDCl_3$) 7.15 (1H, d, *J* 5.5, N*H*CH), 6.48-6.35 (2H, m, N*H*CH_2 + CH=C), 4.54 (1H, ddd, *J* 11, 5.5, 1.5, NHC*H*), 3.33-3.17 (2H, m, C*H*$_2$NH), 2.14-2.05 (3H, m, C*H*$_2$CH=C + lactam ring CH), 2.02-1.93 (1H, m, lactam ring CH), 1.88-1.77 (5H, m, lactam ring CH ×2 + C*H*$_3$C=CH), 1.47-1.31 (4H, br m, lactam ring CH ×2 + chain CH_2), 1.31-1.17 (12H, m, $(CH_2)_6$) and 0.85 (3H, t, *J* 7, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 175.9, 168.2 (CO), 136.9 (*C*H=C), 130.2 (CH=*C*), 52.3 (NHCH), 42.2 ($NHCH_2$), 31.8, 31.6, 29.5, 29.4 (×2), 29.3, 28.9, 28.7, 28.3, 27.9, 22.6 (CH_2), 14.1 and 12.4 (CH_3); anal. ($C_{19}H_{36}N_2O_2$ requires C 70.76, H 10.63, N 8.69) found C 70.50, H 10.63, N 8.68.

(*S*)-3-(3',3'-Dimethyldodecanoyl)amino-caprolactam (*S*)-13

CuI (2 mmol), trimethylsilyl chloride (24 mmol) and methyl 3,3-dimethylacrylate (20 mmol) in THF (25 mmol) was cooled to –15 ºC, and a solution of nonylmagnesium bromide (24 mmol) in THF (80 ml) was added over one hour. The reaction was allowed to warm to room temperature overnight and it was then quenched by the addition of saturated aqueous ammonium chloride. The THF was removed *in vacuo* and the residue was partitioned between hexanes and water. The organic layer was reduced *in vacuo* and the crude methyl 3,3-dimethyldodecanoate was dissolved in ethanol (50 ml). KOH (100 mmol) in water (10 ml) was added and the reaction was heated at reflux for 18 hours. The reaction was then allowed to cool, and the solvent was removed *in vacuo*. and the resudue was partitioned between hexane and water. The aqueous layer was then acidified to pH 2 with aqueous HCl. and extracted with diethyl ether. The ether layer was dried over Na_2SO_4 and the solution was then reduced in vacuo to give 3,3-dimethyldodecanoic acid as an oil (3.47 g, 76%); ν_{max}/cm^{-1} 1702 (CO); δ_H (500 MHz, $CDCl_3$) 11.12 (1H, br s, OH), 2.21 (2H, s, CH_2CO); 1.32-1.20 (16H, m, $(CH_2)_8$), 1.00 (6H, s, $C(CH_3)_2$) and 0.87 (3H, t, *J* 7, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 179.1 (CO), 45.9, 42.3 (CH_2), 33.2 ($C(CH_3)_2$), 31.9, 30.3, 29.6 (×2), 29.3, 27.1 (×2) ($C(CH_3)_2$), 24.0, 22.6 (CH_2) and 14.1 (CH_3); *m/z* (M^+ $C_{14}H_{28}O_2$ requires 228.2089) 228.2082. 3,3-

dimethyldodecanoic acid (5 mmol) was dissolved in CH_2Cl_2 (20 ml) oxalyl chloride (1 ml) and dimethyl formamide (1 drop) was added. After 1 hour the reaction was reduced *in vacuo* to give crude 3,3-dimethyldodecanoyl chloride which was used directly. (*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (15 ml) were added to a solution of 3,3-dimethyldodecanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. The residue was recrystallised from hexane to give (*S*)-3-(3',3'-dimethyldodecanoyl)amino-caprolactam (1.14 g, 68%); m.p. (hexanes) 123-125 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +28.6; ν_{max}/cm^{-1} 3279 (NH), 1646 (CO), 1498 (NH); δ_H (500 MHz, $CDCl_3$) 6.81 (1H, d, *J* 5.5, CHN*H*), 6.59-6.42 (1H, br m, CH_2NH), 4.50 (1H, ddd, *J* 11, 6, 1.5, C*H*NH), 3.30-3.16 (2H, m, C*H*$_2$NH), 2.08-2.02 (3H, m, CH_2CO + lactam ring CH), 2.00-1.90 (1H, m, lactam ring CH), 1.86-1.75 (2H, m, lactam ring CH ×2), 1.47-1.31 (2H, br m, lactam ring CH ×2), 1.30-1.17 (16H, m, $(CH_2)_8$), 0.89 (6H, s, $C(CH_3)_2$) and 0.84 (3H, t, *J* 7, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 175.8, 170.9 (CO), 52.0 (NH*C*H), 48.4, 42.6, 41.1 (CH_2), 33.3 (*C*Me$_2$), 31.9, 31.7, 30.4, 29.7, 29.6, 29.3, 28.9, 27.9 (CH_2), 27.3 (×2) (CH_3), 24.1, 22.6 (CH_2) and 14.1 (CH_3); *m/z* (M^+ $C_{20}H_{38}N_2O_2$ requires 338.2933) found 338.2928; anal. ($C_{20}H_{38}N_2O_2$ requires C 70.96, H 11.31, N 8.28) found C 70.94, H 11.47, N 8.24.

(*S*)-3-(4'-Pentyl[2,2,2]bicyclo-octane-1'-carbonyl)amino-caprolactam (*S*)-14

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5.5 mmol) and Na_2CO_3 (16.5 mmol) in water (25 ml) were added to a solution of *trans*-4-pentylcyclohexane-1-carbonyl chloride (4.4 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc / hexane to give the lactam (868 mg, 57%); m.p. 195-196 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +28.7; ν_{max}/cm^{-1} 3395, 3254 (NH), 1677, 1626 (CO), 1501 (NH); δ_H (500 MHz, $CDCl_3$) 6.98 (1H, d, *J* 5.5, CHN*H*), 6.77-6.63 (1H, br m, CH_2NH), 4.41 (1H, dd, *J* 11, 5.5, C*H*NH), 3.27-3.15 (2H, m, C*H*$_2$NH), 2.00-1.88 (2H, br m, ring CH ×2), 1.81-1.73 (2H, br m, ring CH ×2), 1.69 (6H, br t, *J* 7.5, chain CCH_2CH_2C × 6), 1.43-1.30 (8H, br m, ring CH ×2 + chain CCH_2CH_2C × 6), 1.24 (2H, sext, *J* 7, C*H*$_2$CH$_3$), 1.19-1.07 (4H, m, C*H*$_2$C*H*$_2$CH$_2$CH$_3$) 1.05-0.98 (2H, m, C*H*$_2$Bu) and 0.82 (3H, t, *J* 7, CH_3); δ_C (125 MHz, $CDCl_3$) 177.4, 176.1 (CO), 51.9 (NH*C*HCO), 42.0, 41.2 (CH_2), 39.0 (C quat), 32.7, 31.6, 30.6 (×3) (CH_2), 30.4 (C quat), 28.9, 28.8 (×3), 27.9, 23.3, 22.6 (CH_2) and 14.0 (CH_3); *m/z* (M^+ $C_{20}H_{34}N_2O_2$ requires 334.26203) found 334.26352; anal. ($C_{20}H_{34}N_2O_2$ requires C 71.81, H 10.25, N 8.37) found C 71.81, H 10.30, N 8.37.

(*S*)-3-(1'-Adamantanecarbonyl)amino-caprolactam (*S*)-15

(*S*)-3-Amino-caprolactam hydrochloride (1 mmol) and Na_2CO_3 (3 mmol) in water (15 ml) were added to a solution of 1-adamantanecarbonyl chloride (1 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was recrystallised from CH_2Cl_2 / hexanes to give (*S*)-3-(1'-adamantanecarbonyl)amino-caprolactam (171 mg, 59%); m.p. 256-258 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +29.5; ν_{max}/cm^{-1} 3411, 3259 (NH), 1678, 1626 (CO), 1505 (NH); δ_H (500 MHz, $CDCl_3$) 7.08 (1H, d, *J* 5.5, CHN*H*), 6.67 (1H, br s, CH_2N*H*), 4.47 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.32-3.17 (2H, m, C*H*$_2$NH), 2.06-1.94 (5H, m, 2 × ring CH + 3 × adamantane CH), 1.90-1.75 (8H, m, 2 × ring CH + 3 × adamantane CH_2), 1.72 (3H, br d, *J* 14.5, 3 × adamantane C*H*H), 1.68 (3H, br d, *J* 14.5, 3 × adamantane C*H*H) and 1.47-1.32 (2H, m, 2 × ring CH); δ_C (125 MHz, $CDCl_3$) 177.2, 175.9 (CO), 51.9 (NH*C*HCO), 42.2 (CH_2N), 40.5 (*C*CO), 39.0 (3 × CH_2 adamantane), 36.5 (3 × CH_2 adamantane), 31.7, 28.9, 28.0 (CH_2 lactam), 28.1 (3 × CH adamantane); *m/z* (MH^+ $C_{17}H_{27}N_2O_2$ requires 291.2073) found 291.1994; anal. ($C_{17}H_{26}N_2O_2$ requires C 70.3, H 9.0, N 9.7) found C 70.0, H 9.0, N 9.6.

(*R*)-3-(1'-Adamantanecarbonyl)amino-caprolactam (*R*)-15

This compound was synthesised in a similar way to the (*S*)-enantiomer but starting from (*R*,*R*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate; m.p. 254-256 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +28.9; anal. ($C_{17}H_{26}N_2O_2$ requires C 70.3, H 9.0, N 9.7) found C 70.0, H 9.0, N 9.5.

(*S*)-3-(1'-Adamantanylmethanecarbonyl)amino-caprolactam (*S*)-16

(*S*)-3-Amino-caprolactam hydrochloride (4 mmol) and Na_2CO_3 (12 mmol) in water (50 ml) were added to a solution of 1-adamantanemethanecarbonyl chloride (4 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 50 ml). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. The residue was recrystallised from EtOAc / hexane to give (*S*)-3-(1'-adamantanylmethanecarbonyl)amino-caprolactam, recrystallised from EtOAc to give white crystals (688 mg, 56%); m.p. 258-260 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +30.7; ν_{max}/cm^{-1} 3409, 3255 (NH), 1682, 1611 (CO), 1539 (NH); δ_H (500 MHz, $CDCl_3$) 6.82 (1H, d, *J* 5.5, CHN*H*), 6.77 (1H, br t, *J* 5.5, CH_2N*H*), 4.48 (1H, ddd, *J* 11, 6, 1.5, C*H*NH), 3.28-3.14 (2H, m, C*H*$_2$NH), 2.04 (1H, br d, *J* 13.5, C-4 H), 1.97-1.86 (6H, m, C-5 H + 3 × adamantane CH + CH_2CO), 1.84-1.72 (2H, m, C-5 H + C-6 H), 1.63 (3H, br d, *J* 12, adamantane 3 × CH_2), 1.60-1.54 (9H, m, 9 × adamantane CH_2) and 1.47-1.27 (2H, m, C-4 H + C-6 H); δ_C (125 MHz, $CDCl_3$) 175.9 (lactam CO), 170.1 (amide CO), 52.0 (NH*C*HCO), 51.4 (*C*H_2CO), 42.6 (3 ×

adamantane CH_2), 42.0 (NCH_2), 36.7 (3 × CH_2 adamantane), 32.7 (C_{quat} adamantane), 31.7 (C-4), 28.8 (C-6), 28.6 (3 × CH adamantane), 28.5 (C-5); *m/z* (M^+ $C_{18}H_{28}N_2O_2$ requires 304.2151) found 304.21430; anal. ($C_{18}H_{28}N_2O_2$ requires C 71.0, H 9.3, N 9.2) found C 70.7, H 9.2, N 9.2.

(*S*)-3-(1'-Methylcyclohexanecarbonyl)amino-caprolactam (*S*)-17

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (25 ml) were added to a solution of 1-methylcyclohexanecarbonyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc / hexane to give the lactam (540 mg, 43%); m.p. (EtOAc / hexanes) 168-169 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +33.0; ν_{max}/cm^{-1} 3380, 3241 (NH), 1674, 1638 (CO), 1501 (NH); δ_H (500 MHz, $CDCl_3$) 7.12 (1H, d, *J* 5, CHN*H*), 6.52 (1H, br s, CH_2N*H*), 4.48 (1H, ddd, *J* 11, 5.5, 1.5 C*H*NH), 3.30-3.16 (2H, m, C*H*$_2$NH), 2.01 (1H, br d, *J* 13, lactam ring CH), 1.98-1.86 (3H, m, lactam ring CH + cyhex CH ×2), 1.85-1.73 (2H, m, lactam ring CH ×2), 1.56-1.47 (2H, m, cyhex CH ×2), 1.47-1.33 (5H, br m, lactam ring CH ×2 + cyhex CH ×3) and 1.33-1.25 (3H, m, cyhex CH ×3); δ_C (125 MHz, $CDCl_3$) 176.9, 167.0 (CO), 52.0 (NH*C*HCO), 42.5 (C quat), 42.1, 35.5 (×2), 31.6, 28.9, 27.9 (CH_2), 26.4 (CH_3), 25.8, 22.9 (×2) (CH_2); *m/z* (M^+ $C_{14}H_{24}N_2O_2$ requires 252.18378) found 252.18323; anal. ($C_{14}H_{24}N_2O_2$ requires C 66.6, H 9.6, N 11.1) found C 66.6, H 9.6, N 11.0.

(*S*)-3-(Cyclohexanecarbonyl)amino-caprolactam (*S*)-18

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (25 ml) were added to a solution of cyclohexanecarbonyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc / hexaneto give the lactam (540 mg, 45%); m.p. (EtOAc / hexanes) 180-181 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +42.0; ν_{max}/cm^{-1} 3294 (NH), 1668, 1614 (CO), 1537 (NH); δ_H (500 MHz, $CDCl_3$) 6.89 (1H, d, *J* 5.5, CHN*H*), 6.51 (1H, br s, CH_2N*H*), 4.48 (1H, dd, *J* 11, 6, C*H*NH), 3.30-3.17 (2H, m, C*H*$_2$NH), 2.11 (1H, tt, *J* 11.5, 3.5, $(CH_2)_2$C*H*CO), 2.01 (1H, br d, *J* 13, lactam ring CH), 1.98-1.92 (1H, m, lactam ring CH), 1.87-1.70 (6H, m, lactam ring CH ×2 + cyhex CH ×4), 1.66-1.59 (1H, m, cyhex CH), 1.47-1.30 (4H, br m, lactam ring CH ×2 + cyhex CH ×2) and 1.23-1.15 (3H, m, cyhex CH ×3); δ_C (125 MHz, $CDCl_3$) 175.9, 175.3 (CO), 51.8 (NH*C*HCO), 45.2 (CH), 42.1, 31.7, 29.6, 29.4, 28.9, 27.9, 25.7 (×2), 25.6

(CH_2); *m/z* (M^+ $C_{13}H_{22}N_2O_2$ requires 238.16813) found 238.16768; anal. ($C_{13}H_{22}N_2O_2$ + 1/6 H_2O requires C 64.7, H 9.3, N 11.6) found C 64.7, H 9.3, N 11.8.

(*S*)-3-(Cyclohex-1'-enecarbonyl)amino-caprolactam (*S*)-19

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (25 ml) were added to a solution of cyclohex-1-ene-1-carbonyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc / hexanes to give the lactam (431 mg, 36%); m.p. (EtOAc / hexanes) 151-152 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +57.5; ν_{max}/cm^{-1} 3219 (NH), 1652, 1628 (C=O, C=C), 1515 (NH); δ_H (500 MHz, $CDCl_3$) 7.12 (1H, d, *J* 5, CHN*H*), 6.67 (1H, qn, *J* 1.5, CH=C), 6.52 (1H, br s, CH_2N*H*), 4.54 (1H, ddd, *J* 11, 5.5, 1.5 C*H*NH), 3.32-3.18 (2H, m, CH_2NH), 2.30-2.17 (2H, m, CH_2CH=C), 2.16-2.10 (2H, m, CH=CCH_2), 2.07 (1H, br d, *J* 15, lactam ring CH), 2.00-1.92 (1H, m, lactam ring CH), 1.87-1.76 (2H, m, lactam ring CH ×2), 1.68-1.60 (2H, m, cyhex CH ×2), 1.60-1.52 (2H, m, cyhex CH ×2) and 1.50-1.31 (2H, br m, lactam ring CH ×2); δ_C (125 MHz, $CDCl_3$) 175.9, 167.4 (CO), 134.0 (*C*H=C), 132.8 (CH=*C*), 52.1 (NH*C*HCO), 42.1, 31.6, 28.9, 27.9, 25.3, 24.0, 22.1, 21.5 (CH_2); *m/z* (M^+ $C_{13}H_{20}N_2O_2$ requires 236.15248) found 236.15208; anal. ($C_{13}H_{20}N_2O_2$ + 1/10 H_2O requires C 65.6, H 8.6, N 11.8) found C 65.6, H 8.6, N 11.6.

(*S*)-3-(2',2'-Dimethyl-butyryl)amino-caprolactam (*S*)-20

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-butyryl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. The residue was recrystallised from EtOAc / hexane to give **(*S*)-3-(2',2'-dimethyl-propionyl)amino-caprolactam** (562 mg, 50%); m.p. 106-107 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +33.6; ν_{max}/cm^{-1} 3400, 3278 (NH), 1677, 1630 (CO), 1500 (NH); δ_H (500 MHz, $CDCl_3$) 7.08 (1H, d, *J* 5.0, CHN*H*), 6.72 (1H, br s, CH_2N*H*), 4.44 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.28-3.16 (2H, m, CH_2NH), 2.04-1.90 (2H, m, 2 × ring CH), 1.83-1.72 (2H, m, 2 × ring CH), 1.57-1.44 (2H, m, CH_2CH_3), 1.44-1.30 (2H, m, 2 × ring CH) 1.12 (3H, s, CH_3) 1.11 (3H, s, CH_3) and 0.78 (3H, t, *J* 7.5, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 177.0, 176.0 (CO), 52.1 (NH*C*HCO), 42.2 (*C*CO), 42.0 (CH_2N), 33.7 (*C*H_2CH_3), 31.6, 28.9, 27.9 (CH_2 lactam), 24.8, 24.7 (C*C*H_3) and 9.1 (CH_2*C*H_3); *m/z* (MH^+ $C_{12}H_{23}N_2O_2$ requires

227.1760) found 227.1767; anal ($C_{12}H_{22}N_2O_2$ + 1/8 H_2O requires C 63.1, H 9.8, N 12.3) found C 63.0, H 9.8, N 12.2.

(*S*)-3-(2',2'-Dimethyl-propionyl)amino-caprolactam (*S*)-21

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-propionyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. The residue was recrystallised from EtOAc / hexane to give **(*S*)-3-(2',2'-dimethyl-propionyl)amino-caprolactam** (645 mg, 61%); m.p. 126-127 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +39.5; ν_{max}/cm^{-1} 3381, 3255 (NH), 1680, 1632 (CO), 1506 (NH); δ_H (500 MHz, $CDCl_3$) 7.10 (1H, d, *J* 5.0, CHN*H*), 6.75 (1H, br s, CH_2N*H*), 4.42 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.27-3.16 (2H, m, C*H*$_2$NH), 2.03-1.89 (2H, m, 2 × ring CH), 1.83-1.71 (2H, m, 2 × ring CH), 1.45-1.28 (2H, m, 2 × ring CH) and 1.15 (9H, s, 3 × CH_3); δ_C (125 MHz, $CDCl_3$) 177.7, 176.1 (CO), 52.1 (NH*C*HCO), 42.0 (CH_2N), 40.5 (*C*CO), 31.5, 28.9, 27.9 (CH_2 lactam), 27.4 (3 × CH_3); *m/z* (MH^+ $C_{11}H_{21}N_2O_2$ requires 213.1602460) found 213.1597543; anal ($C_{11}H_{20}N_2O_2$ requires C 62.2, H 9.5, N 13.2) found C 62.2, H 9.6, N 13.1.

(*S*)-(3'-Chloro-2'-(chloromethyl)-2'-methylpropionyl)amino-caprolactam (*S*)-22

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (15 ml) were added to a solution of 3,3'-dichloropivaloyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. The residue was recrystallised from hexane to give (*S*)-(3'-chloro-2'-(chloromethyl)-2'-methylpropionyl)amino-caprolactam (973 mg, 69%); m.p. (hexanes) 95-96 ºC; $[\alpha]_D^{25}$ (c = 0.5, $CHCl_3$) +16.4; ν_{max}/cm^{-1} 3269 (NH), 1677, 1639 (CO), 1504 (NH); δ_H (500 MHz, $CDCl_3$) 7.33 (1H, d, *J* 5.0, CHN*H*), 6.82-6.62 (1H, br m, CH_2N*H*), 4.49 (1H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.78 (1H, d, *J* 11, C*H*HCl), 3.74 (1H, d, *J* 11, C*H*HCl), 3.69 (1H, d, *J* 11, C*H*HCl), 3.66 (1H, d, *J* 11, C*H*HCl), 3.29-3.17 (2H, m, C*H*$_2$NH), 2.05 (1H, br s, *J* 13.5, ring CH), 2.01-1.93 (1H, m, ring CH), 1.87-1.71 (2H, m, 2 × ring CH) and 1.49-1.31 (5H, m, 2 × ring CH + CH_3); δ_C (125 MHz, $CDCl_3$) 175.4, 170.6 (CO), 52.6 (NH*C*HCO), 49.1 (*C*CO), 48.7, 48.6 (CH_2Cl), 42.1 (CH_2N), 31.1, 28.8, 27.9 (CH_2 lactam) and 18.9 (CH_3); *m/z* (MNa^+ $C_{11}H_{18}N_2O_2Cl_2Na$ requires 303.0643) found 303.0632, (MH^+ $C_{11}H_{19}N_2O_2Cl_2$ requires 281.0824) found 281.0818; anal. ($C_{11}H_{18}N_2O_2Cl_2$ requires C 46.99, H 6.45, N 9.96) found C 46.86, H 6.46, N 9.79.

(*S*,*S*) *N*,*N*'-bis-(2'-oxo-azepan-3'-yl) 2,2,6,6-tetramethylheptadiamide (*S*,*S*)-23

(*S*,*S*)-3-Amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of 2,2,6,6-tetramethyl-heptandioyl dichloride (1 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give **(*S*,*S*)-23** (199 mg, 46%); m.p. 234-236 ºC; $[\alpha]_D^{25}$ (c = 1, $CHCl_3$) +29.4; ν_{max}/cm^{-1} 3379, 3255 (NH), 1683, 1637 (CO), 1507, 1497 (NH); δ_H (500 MHz, $CDCl_3$) 7.07 (2H, d, *J* 5.5, CHN*H*), 6.42 (2H, br s, CH_2NH), 4.44 (2H, ddd, *J* 11, 5.5, 1.5, C*H*NH), 3.31-3.17 (4H, m, CH_2NH), 2.04-1.94 (4H, m, ring CH), 1.86-1.73 (4H, m, ring CH), 1.51-1.31 (8H, br m, 2 × ring CH + CH_2CMe_2) and 1.12 (14H, m, chain $CH_2CH_2CH_2$ + CMe_2); δ_C (125 MHz, $CDCl_3$) 176.9, 175.9 (CO), 52.1 (NH*C*H), 42.0 (CMe_2), 42.1, 41.5, 31.5, 28.9, 28.0 (CH_2), 25.3, 25.1 (CH_3) and 20.0 (CH_2); *m/z* (M^+ $C_{23}H_{40}N_4O_4$ requires 436.30496) found 436.30437; anal. ($C_{23}H_{40}N_4O_4$ requires C 63.27, H 9.23, N 12.83) found C 63.30, H 9.28, N 12.88.

Purity data

Lactam	Formula	Calculated	Found
(*S*)-5	$C_{20}H_{38}N_2O_2$	C 70.96, H 11.31, N 8.28	C 71.04, H 11.40, N 8.33
(*R*)-5	$C_{20}H_{38}N_2O_2$	C 70.96, H 11.31, N 8.28	C 71.09, H 11.50, N 8.37
(*S*)-6	$C_{15}H_{28}N_2O_2$	C 67.13, H 10.52, N 10.44	C 66.99, H 10.50, N 10.41
(*S*)-7	$C_{15}H_{26}N_2O_2$. 1/3 H_2O	C 66.14, H 9.87, N 10.28	C 66.09, H 9.70, N 10.42
(*S*)-8	$C_{13}H_{24}N_2O_2$	C 66.97, H 10.07, N 11.66	C 65.01, H 10.0, N 11.69
(*S*)-9	$C_{15}H_{26}N_2O_2$	C 65.51, H 9.30, N 11.75	C 65.42, H 9.33, N 11.76
(*S*)-10	$C_{19}H_{38}N_2O_2$ 1/6 H_2O	C 69.68, H 11.18, N 8.55	C 69.68, H 11.19, N 8.54
(*S*)-11	$C_{18}H_{32}N_2O_2$	C 70.09, H 10.46, N 9.08	C 70.05, H 10.50, N 9.10
(*S*)-12	$C_{19}H_{36}N_2O_2$	C 70.76, H 10.63, N 8.69	C 70.50, H 10.63, N 8.68
(*S*)-13	$C_{20}H_{38}N_2O_2$	C 70.96, H 11.31, N 8.28	C 70.94, H 11.47, N 8.24
(*S*)-14	$C_{20}H_{34}N_2O_2$	C 71.81, H 10.25, N 8.37	C 71.81, H 10.30, N 8.37
(*S*)-15	$C_{17}H_{26}N_2O_2$	C 70.3, H 9.0, N 9.7	C 70.0, H 9.0, N 9.6
(*R*)-15	$C_{17}H_{26}N_2O_2$	C 70.3, H 9.0, N 9.7	C 70.0, H 9.0, N 9.5

(*S*)-16	$C_{18}H_{28}N_2O_2$	C 71.0, H 9.3, N 9.2	C 70.7, H 9.2, N 9.2
(*S*)-17	$C_{14}H_{24}N_2O_2$	C 66.6, H 9.6, N 11.1	C 66.6, H 9.6, N 11.0
(*S*)-18	$C_{13}H_{22}N_2O_2$ 1/6 H_2O	C 64.7, H 9.3, N 11.6	C 64.7, H 9.3, N 11.8
(*S*)-19	$C_{13}H_{20}N_2O_2$	C 65.6, H 8.6, N 11.8	C 65.6, H 8.6, N 11.6
(*S*)-20	$C_{12}H_{22}N_2O_2$ 1/8 H_2O	C 63.1, H 9.8, N 12.3	found C 63.0, H 9.8, N 12.2
(*S*)-21	$C_{11}H_{20}N_2O_2$	C 62.2, H 9.5, N 13.2	C 62.2, H 9.6, N 13.1
(*S*)-22	$C_{11}H_{18}N_2O_2Cl_2$	C 46.99, H 6.45, N 9.96	C 46.86, H 6.46, N 9.79
(*S*,*S*)-23	$C_{23}H_{40}N_4O_4$	C 63.27, H 9.23, N 12.83	C 63.30, H 9.28, N 12.88

IN VITRO DATA

Compounds were tested for their ability to inhibit chemokine-induced migration using the microtitre format trans-well migration assay, exactly as described previously.[3-6] All migration assays were performed in Gey's balanced salt solution containing 1mg/ml endotoxin-free BSA (in the absence of foetal calf serum), allowing migration to occur for 2 hours at 37ºC. All compounds were solubilised in DMSO and added to both the top and bottom compartments of the trans-well migration plate at a constant final DMSO concentration of 1%. Data for selected compounds (*S*)-**5**, (*R*)-**5**, (*S*)-**15**, (*R*)-**15**, (*S*)-**17** and (*S*)-**21** is shown here (SEM = standard error of the mean).

THP-1 Cell migration inhibition for compound (*S*)-5 vs chemokine CCL2 (MCP-1)

Concentration **(*S*)-5** (nM)	mean % migration inhibition	SEM
1000	97	0
100	93	4
10	96	3
1	81	9
0.1	53.5	3.5
0.01	12	10

THP-1 Cell migration inhibition for compound (*S*)-5 vs chemokine CCL3 (MIP-1α)

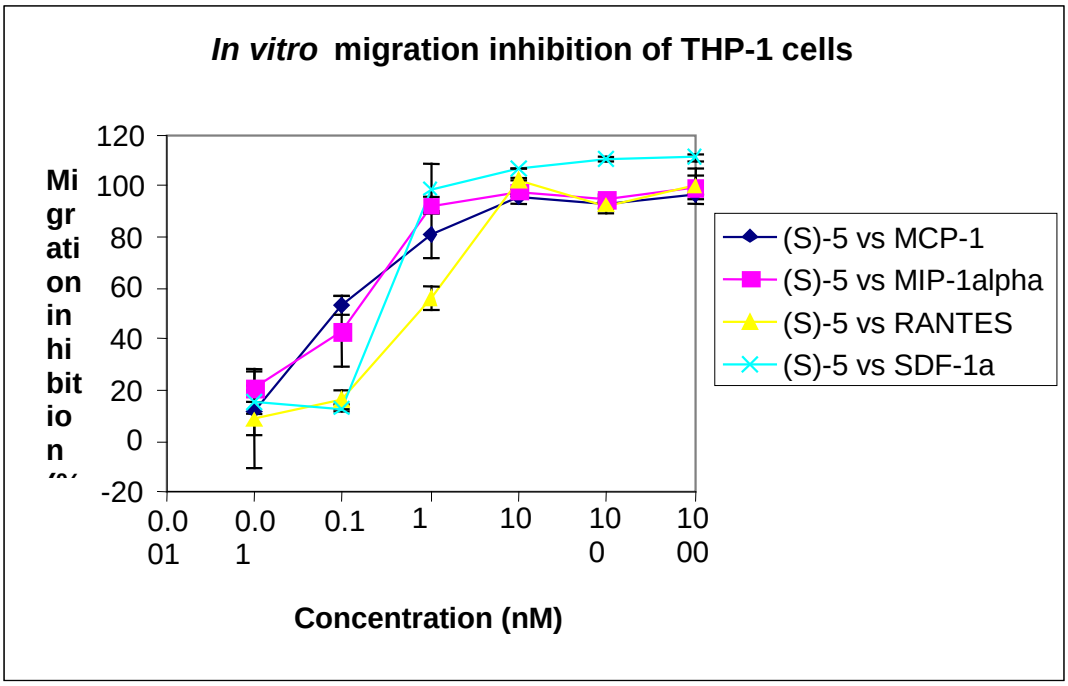
Concentration **(*S*)-5** (nM)	mean % migration inhibition	SEM
1000	99.5	4.5
100	95	1
10	98	1
1	92.5	3.5
0.1	43	14
0.01	21	6

THP-1 Cell migration inhibition for compound (*S*)-5 vs chemokine CCL5 (RANTES)

Concentration **(*S*)-5** (nM)	mean % migration inhibition	SEM
1000	100	7
100	92.5	1.5
10	102.5	0.5
1	56	5
0.1	16.5	3.5
0.01	8.5	19.5

THP-1 Cell migration inhibition for compound (*S*)-5 vs chemokine CXCL12 (SDF1-α)

Concentration **(*S*)-5** (nM)	mean % migration inhibition	SEM
1000	111.5	1.5
100	111	1
10	107	0
1	99	10
0.1	13	1
0.01	15.5	4.5

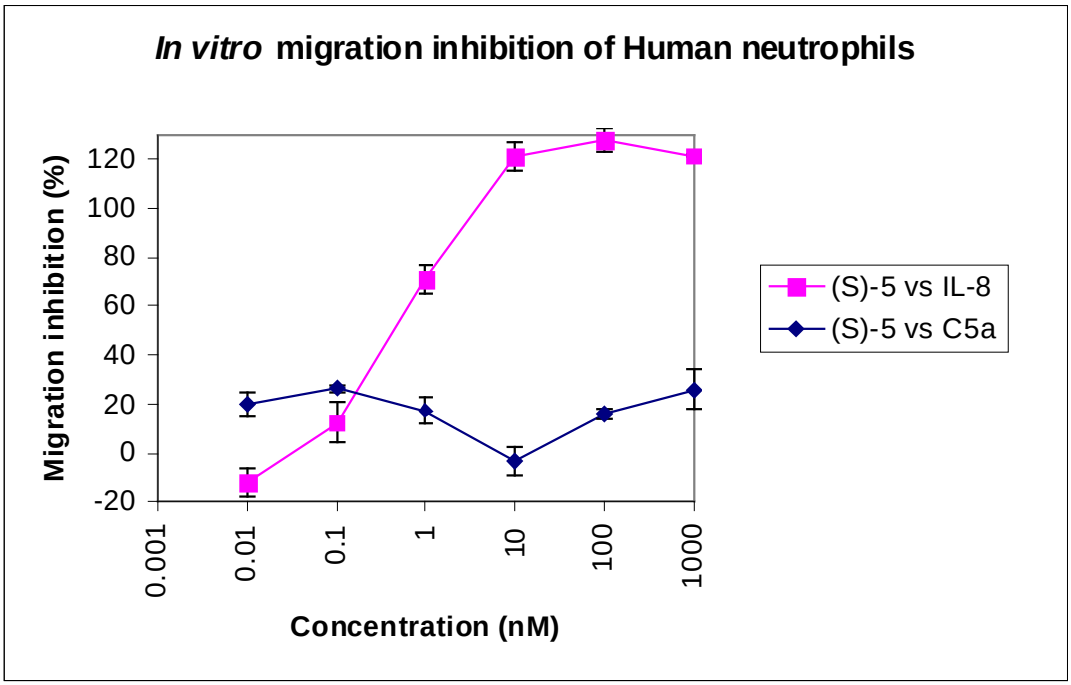


Neutrophil Cell migration inhibition for compound (*S*)-5 vs chemokine CXCL8 (IL-8)

Concentration **(*S*)-5** (nM)	mean % migration inhibition	SEM
1000	121.5	0.5
100	128	5
10	121	6
1	71	6
0.1	12.5	8.5
0.01	-12	6

Neutrophil Cell migration inhibition for compound (*S*)-5 vs C5a

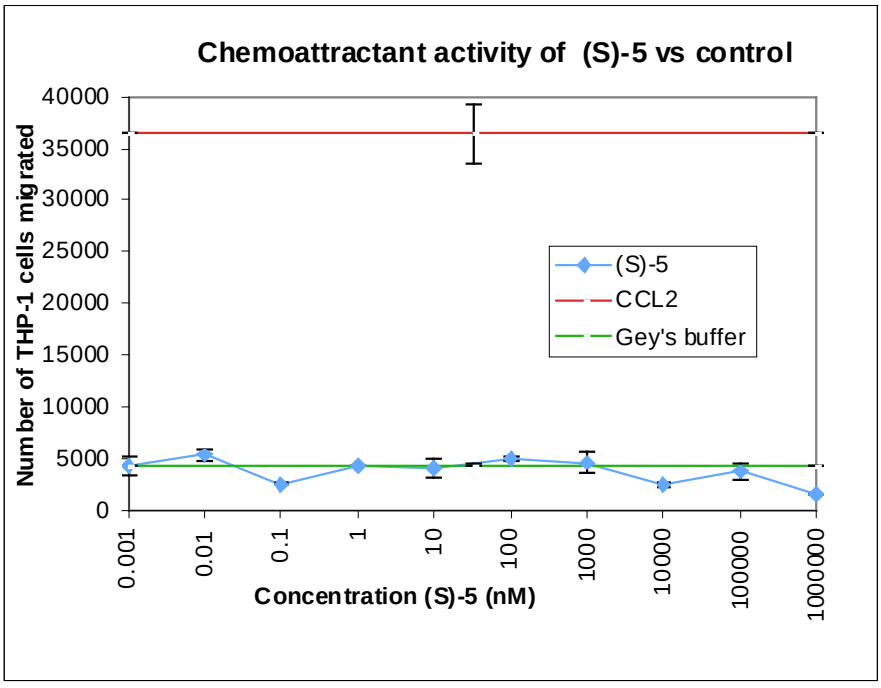
Concentration **(*S*)-5** (nM)	mean % migration inhibition	SEM
1000	26	8
100	16	2
10	-3	6
1	17.5	5.5
0.1	26.5	1.5
0.01	20	5



THP-1 Cell chemoattractant activity of compound (*S*)-5

Compound (S)-5 has absolutely no endogenous chemoattractant activity for THP-1 cells at any concentration tested. The graph shows the number of cells migrated compared to negative control (Gey's buffer) and positive control (CCL2).

Concentration (***R***)-**5** (nM)	mean % cells migrated	SEM
1000000	1602	23
100000	3764	801
10000	2540	266
1000	4626	1052
100	5039	200
10	4093	825
1	4335	69
0.1	2556	97
0.01	5337	461
0.001	4282	895



THP-1 Cell size data for compound (*S*)-5

As with other lactam BSCIs tested to date, compound **(*S*)-5** does not affect cell size measured by forward scatter flow cytometry. This negative control validates the use of the compound in the transwell filter migration assay (which is invalidated when cell size alters).

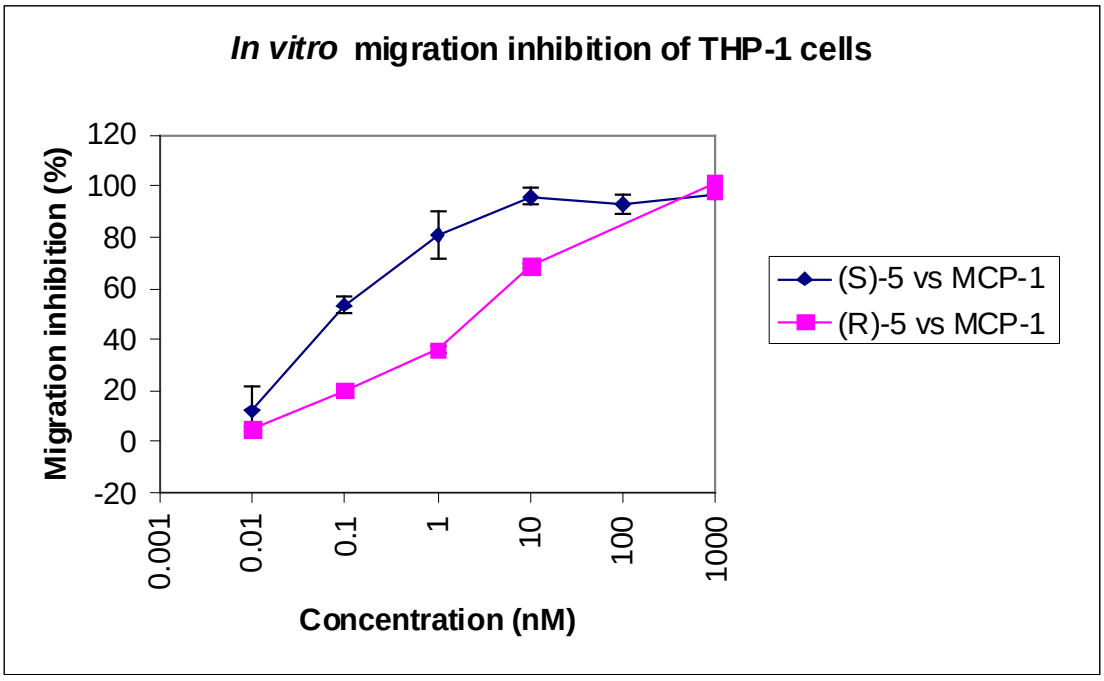
Conc. **(*S*)-5** (nM)	Effect on cell size (fold change)	Mean effect (fold change)
1000	1.06	
1000	1.03	1.05
10	1.05	
10	1.03	1.04
0.1	1.04	
0.1	1.04	1.04

THP-1 Cell toxicity assay for compound (*S*)-5

Compound **(*S*)-5** does not cause cellular toxicity at concentrations up to 100μM, detected by trypan blue dye exclusion assay.

THP-1 Cell migration inhibition for compound (*R*)-5 vs chemokine CCL2 (MCP-1)

Concentration **(*R*)-5** (nM)	mean % migration inhibition	SEM
1000	98.5	0.5
100	101	0
10	69	1
1	36	1
0.1	20	2
0.01	5	1

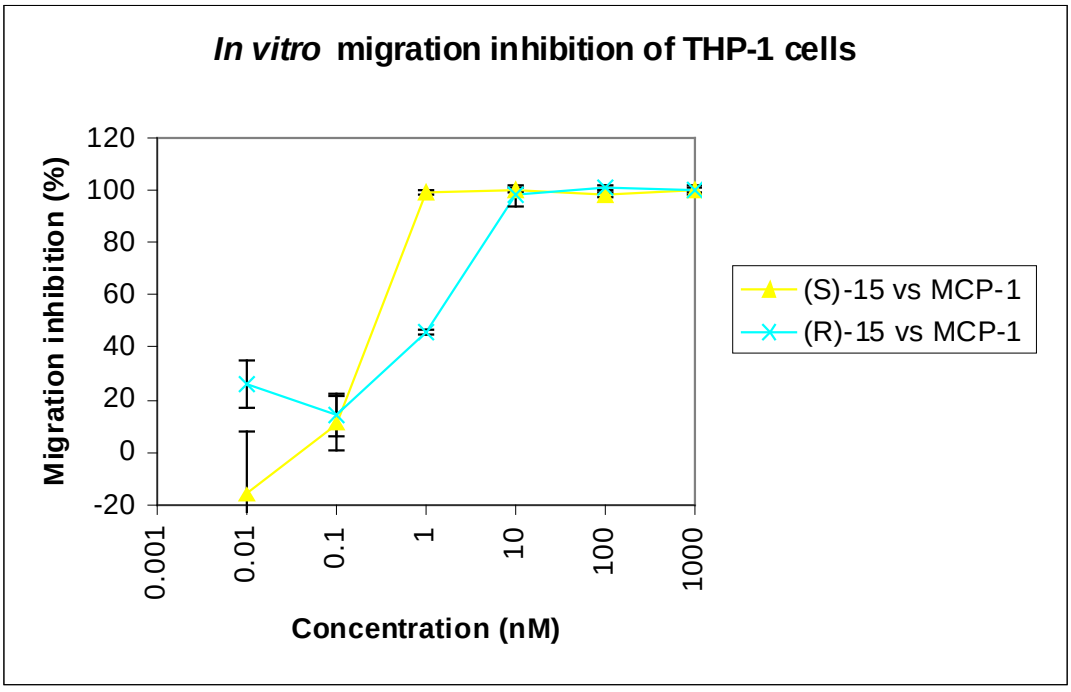


THP-1 Cell migration inhibition for compound (*S*)-15 vs chemokine CCL2 (MCP-1)

Concentration **(*S*)-15** (nM)	mean % migration inhibition	SEM
1000	100	1
100	98	1
10	100	1
1	99	1
0.1	11	10
0.01	-16	24

THP-1 Cell migration inhibition for compound (*R*)-15 vs chemokine CCL2 (MCP-1)

Concentration **(*R*)-15** (nM)	mean % migration inhibition	SEM
1000	100	2
100	101	1
10	98	4
1	46	1
0.1	14	8
0.01	26	9

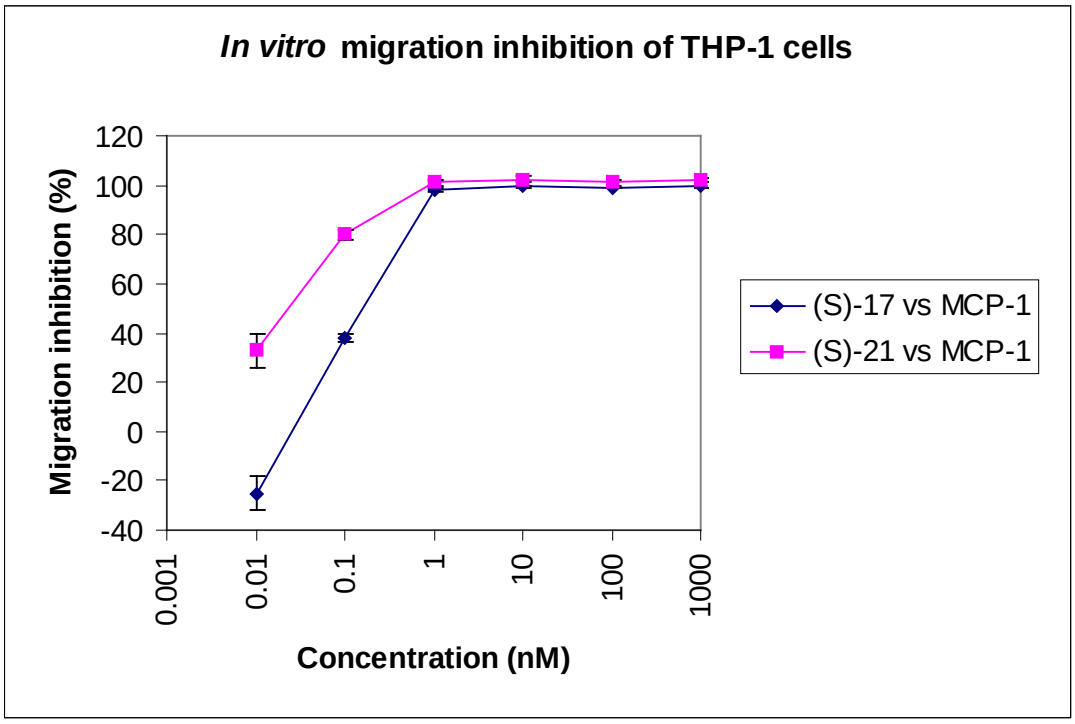


THP-1 Cell migration inhibition for compound (*S*)-17 vs chemokine CCL2 (MCP-1)

Concentration **(*S*)-17** (nM)	mean % migration inhibition	SEM
1000	100	1
100	99	0
10	100	1
1	98	1
0.1	38	2
0.01	-25	7

THP-1 Cell migration inhibition for compound (*S*)-21 vs chemokine CCL2 (MCP-1)

Concentration **(*S*)-21** (nM)	mean % migration inhibition	SEM
1000	102	1
100	101	1
10	102	2
1	101	1
0.1	80	2
0.01	33	7

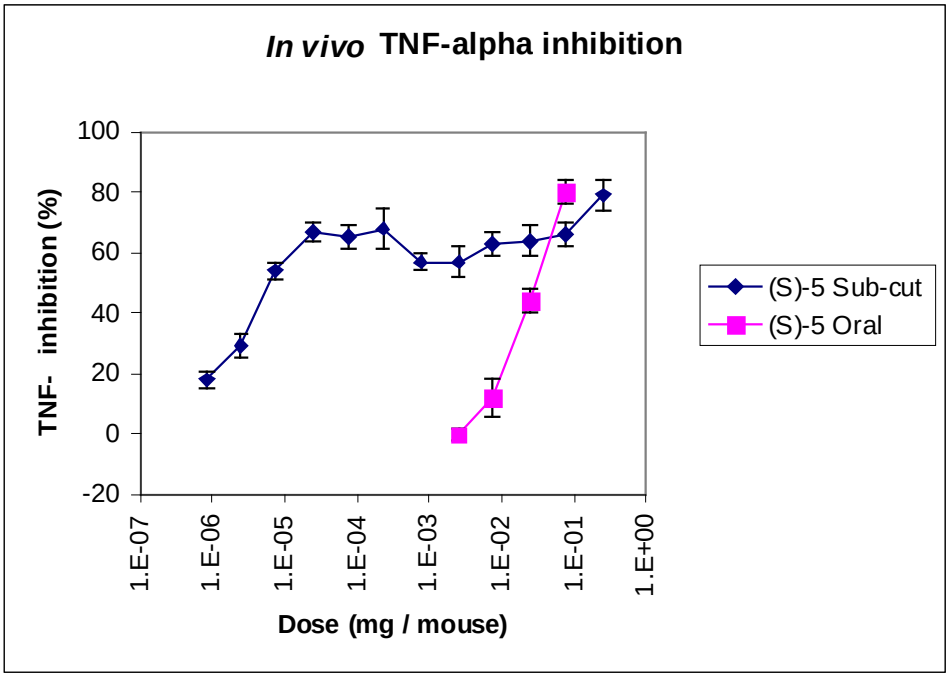


IN VIVO DATA

The effect of the compounds on TNF-α upregulation *in vivo* was determined exactly as previously,[4,5] except that the vehicle used was 0.6% DMSO 1% carboxymethycellulose (final concentrations) in sterile water. Values reported as the mean ± standard error for each group (n=6) (SEM = standard error of the mean).

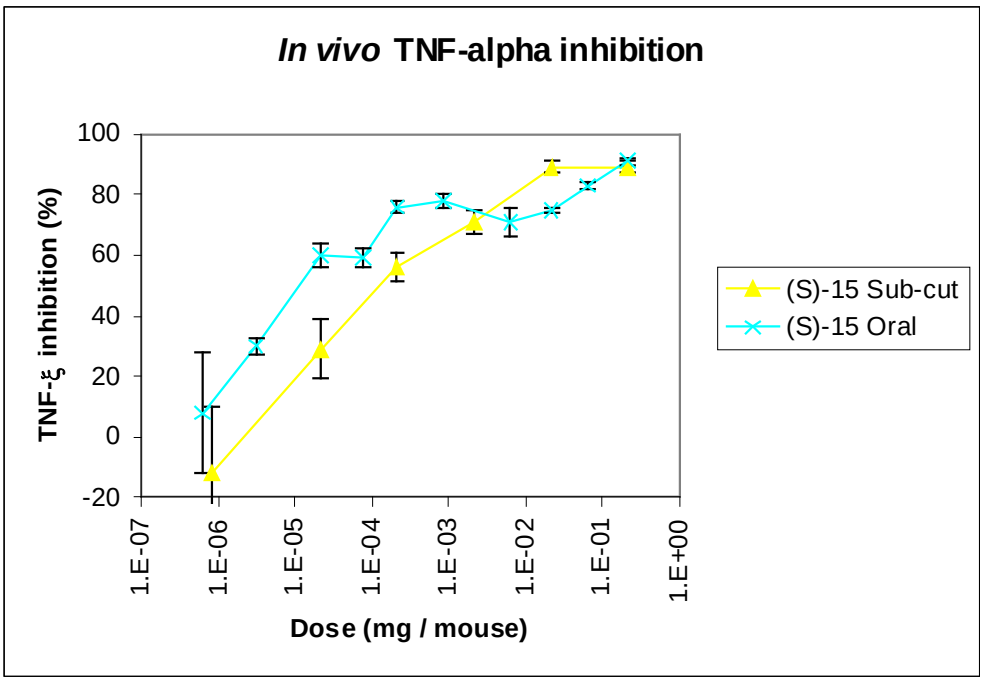
Inhibition of LPS induced TNF-α in vivo compound (*S*)-5

Sub-cut Dose (mg/mouse)	mean % THF-α inhibition	SEM
8.30E-07	18	3
2.50E-06	29	4
7.50E-06	54	3
2.50E-05	67	3
7.50E-05	65	4
0.000225	68	7
0.00075	57	3
0.0025	57	5
0.0075	63	4
0.025	64	5
0.075	66	4
0.25	79	5
Oral Dose (mg/mouse)	mean % THF-α inhibition	SEM
0.0025	0	2
0.0075	12	6
0.025	44	4
0.075	80	4



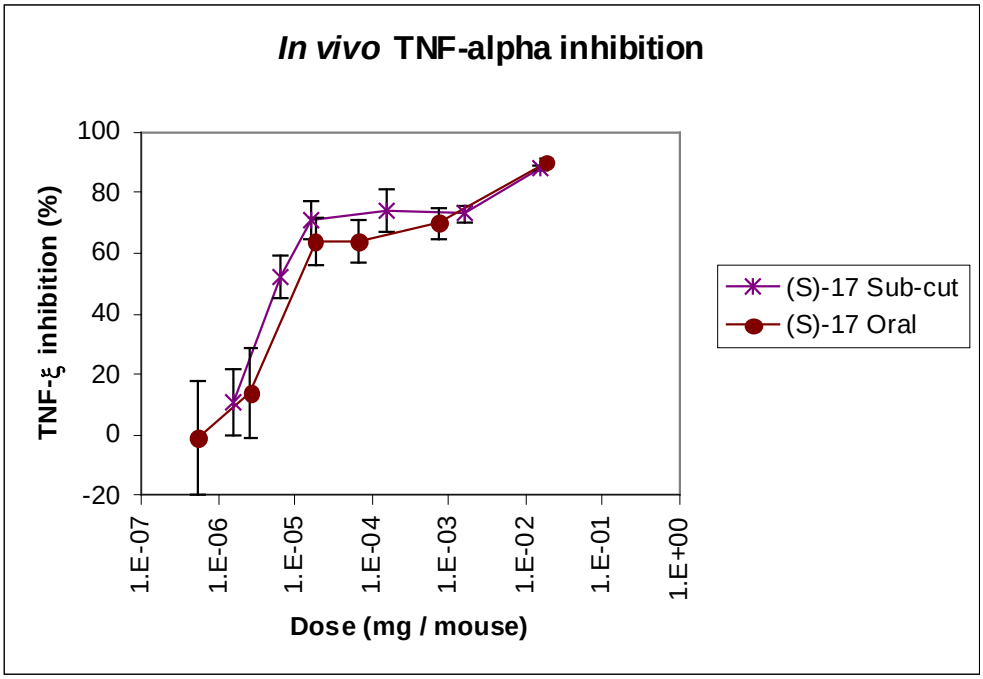
Inhibition of LPS induced TNF-α in vivo: compound (*S*)-15

Sub-cut Dose (mg/mouse)	mean % THF-α inhibition	SEM
8.30E-07	-12	22
2.16E-05	29	10
0.000216	56	5
0.00216	71	4
0.0216	89	2
0.216	89	2
Oral Dose (mg/mouse)	mean % THF-α inhibition	SEM
6.24E-07	8	20
3.12E-06	30	3
2.16E-05	60	4
7.80E-05	59	3
0.000216	76	2
0.000864	78	2
0.0065	71	5
0.0216	75	1
0.065	83	1
0.216	91	1



Inhibition of LPS induced TNF-α in vivo: compound (*S*)-17

Sub-cut Dose (mg/mouse)	mean % THF-α inhibition	SEM
1.60E-06	11	11
6.60E-06	52	7
1.60E-05	71	6
0.00016	74	7
0.0016	73	3
0.016	88	1
Oral Dose (mg/mouse)	mean % THF-α inhibition	SEM
5.40E-07	-1	19
2.70E-06	14	15
1.86E-05	64	8
6.80E-05	64	7
7.50E-04	70	5
0.0186	90	1



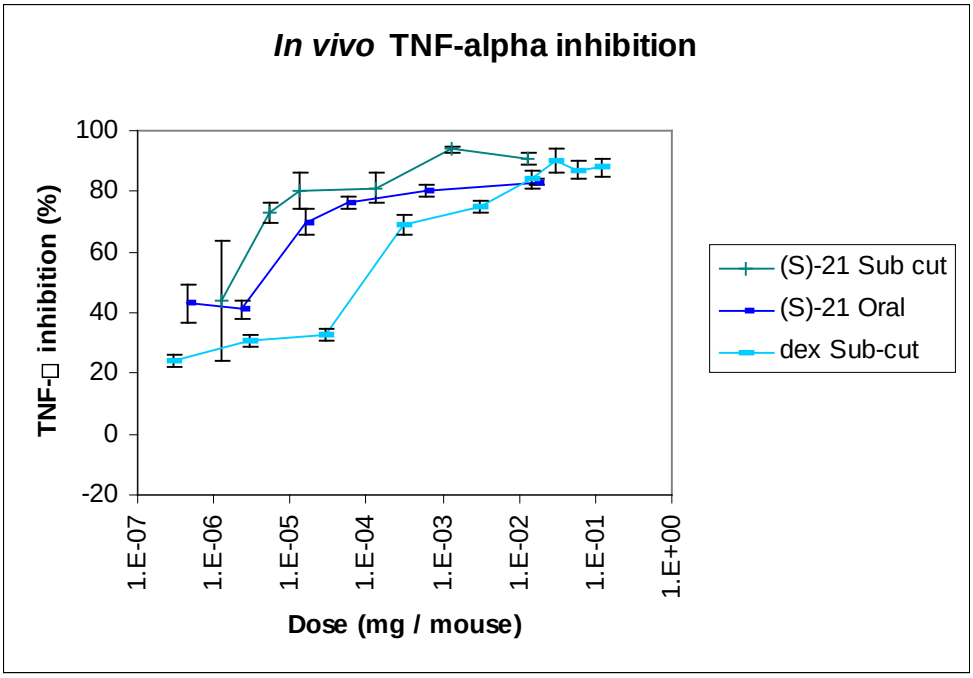
Inhibition of LPS induced TNF-α in vivo: compound (*S*)-21

Sub-cut Dose (mg/mouse)	mean % THF-α inhibition	SEM
1.30E-06	44	20
5.50E-06	73	3
1.30E-05	80	6
0.00013	81	5
0.0013	94	1
0.013	91	2
Oral Dose (mg/mouse)	mean % THF-α inhibition	SEM
4.50E-07	43	6
2.30E-06	41	3
1.60E-05	70	4
5.70E-05	76	2
6.10E-04	80	2
0.016	83	1

Inhibition of LPS induced TNF-α in vivo: dexamethazone

(No oral dose assay performed)

Sub-cut Dose (mg/mouse)	mean % THF-α inhibition	SEM
3E-07	24	2
3E-06	31	2
3E-05	33	2
3E-04	69	3
0.003	75	2
0.015	84	3
0.03	90	4
0.06	87	3
0.12	88	3



References

1) Boyle, W. J.; Sifniades, S. Van Peppen, J. V. *J. Am. Chem. Soc.*, **1979**, *44*, 4841.
2) Rezler, E. M.; Fenton, R. R.; Esdale, W. J.; McKeage, M. J.; Russell, P. J.; Hambley, T. W. *J. Med. Chem.*, **1997**, *40*, 3508.
3) Reckless, J. and Grainger, D. J.; *Biochem. J.*, **1999**, *340*, 803.
4) Fox, D. J.; Reckless, J; Warren, S. G. and Grainger, D. J.; *J. Med. Chem.*, **2002**, *45*, 360.
5) Fox, D. J.; Reckless, J.; Wilbert, S. M.; Greig, I.; Warren, S.; and Grainger, D. J.; *J. Med. Chem.*, **2005**, *48*, 867.
6) Frow, E. K.; Reckless, J. and Grainger, D. J.; *Med. Res. Rev.*, **2004**, *24*, 267.