Supporting Information

Structure Activity Relationships of α_v Integrin Antagonists for Pulmonary Fibrosis By Variation in Aryl Substituents

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A. General Information

All reagents and solvents used were commercially available and used without further purification. (*R*)- and (*S*)-methyl 3-amino-3-(3-trifluorophenyl)propanoates (enantiomeric purity not independently determined) were purchased from Aurora Fine Chemicals, San Diego, CA, USA and used as supplied.

Anhydrous experiments were carried out in flame dried glassware and under an atmosphere of dry nitrogen. Aluminium-backed Kieselgel 60 F_{254} plates from E. Merck and glass-backed aminopropyl-modified plates from Biotage were used for TLC, and compounds were visualised using u.v. light, anisaldehyde solution or 0.5% aqueous potassium permanganate solution.

Column chromatography was performed on silica gel (50 μ) or aminopropyl-modified silica gel (50 μ) (Biotage Isolute™, Biotage SNAP™ or Interchim HPSI cartridges) in conjunction with an Ismatec solvent pump (typically 10 – 30 mL/min). Chromatography solvents were of technical grade. Waters Oasis™ HLB cartridges were used for the removal of Na^+ and Li^+ to yield final compounds as the free acid. HPLC for reaction monitoring used an Agilent 1200 system, with a standard gradient elution method: Waters Sunfire 30 × 2.1 mm column, stationary phase 5 μm octadecylsilane derivatized silica gel, 0.8 mL/min flow rate, detection at 254 nm; elution with either 5-95% MeCN in 0.1% aqueous TFA over 4 minutes or 5-95% MeCN in 50 mM aqueous ammonium acetate over 4 minutes. For estimation of compound purity an Agilent Zorbax Eclipse XDB-C18 column (150 x 4.6 mm, 5 μm) was used (gradient over 30 min). UPLC was conducted on a Waters Aquity UPLC BEH C18 column (50 mm × 2.1 mm) at 40 °C, eluting with 10 mM ammonium bicarbonate (pH 10):acetonitrile = 99:1 to 0:100 over 2 min, connected to a Waters ZQ mass spectrometer with alternate-scan positive and negative electrospray ionisation mode, with detection by u.v. and ELSD. HPLC on chiral phases was performed by Reach Separations, Nottingham, UK.

Infrared spectra were recorded as solutions in chloroform on a Perkin Elmer 1600 or Bruker Tensor 27 FTIR instruments in the range of 600−4000 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL EX270 (^1H NMR 270 or ^{13}C NMR 67.5 MHz), Bruker DPX300 (^1H NMR 300 or ^{13}C NMR 75 MHz) or Bruker AV400 (^1H NMR 400 or ^{13}C NMR 100 MHz) spectrometers. Chemical shifts were referenced against the residual proton(s) in the deuterated solvents and reported in ppm. Coupling constants (*J* values) are reported in Hertz. Multiplicity is expressed as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br s (broad singlet). DEPT-90 and DEPT-135 spectra were used to assign quaternary, methane, methylene and methyl carbons in ^{13}C NMR. Mass spectra were recorded in both positive and negative electrospray ionisation mode on a Bruker ESI MicroTOF mass spectrometer.

B. Experimental Procedures

Indane-5-carboxaldehyde was prepared from indane in 38% yield (after purification by column chromatography) by the Duff reaction (hexamethylenetetramine/TFA) as described by Arora, *et al.*[1]

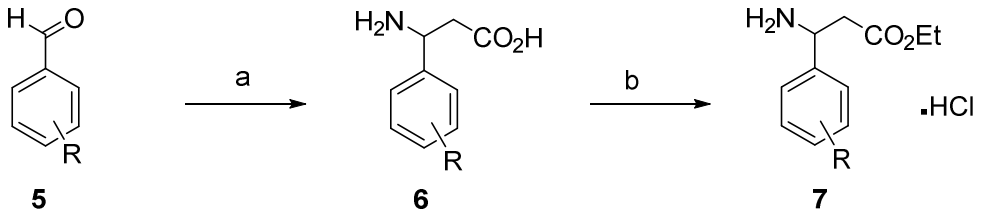
(1,8-Naphthyridin-2-yl)pentanoic acid (**11**) and 5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanoic acid hydrochloride (**14**) were prepared by the method of Coleman *et al.*[2]

5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)pentanoic acid hydrochloride (**14**): yellow powder, mp 120−121 °C. IR ($CHCl_3$) ν (cm^{-1}) 3104, 2870, 1685, 1639, 1540, 1420, 1367, 1247, 1192; ^1H NMR (270 MHz, CD_3OD) δ_H ppm 7.60 (1H, d, *J* 7.5 Hz), 6.64 (1H, d, *J* 7.5 Hz), 3.51 (2H, t, *J* 6.0 Hz), 2.82 (2H, t, *J* 6.0 Hz), 2.73 (2H, t, *J* 7.3 Hz), 2.35 (2H, t, *J* 7.8 Hz), 1.96 (2H, quint, *J* 6.0 Hz), 1.71 (4H, m); ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 175.3, 154.8, 153.4, 143.1, 120.9, 112.1, 42.5, 34.5, 33.5, 29.5, 26.6, 25.4, 20.7; LRMS (ESI^+) 235 $[M + H]^+$.

(i) Ethyl or methyl 3-amino-3-phenylpropanoate derivatives.

Derivatives of ethyl or methyl 3-amino-3-phenylpropanoate were prepared in two steps from the appropriate aldehyde or were purchased commercially (Scheme 1).

Scheme 1



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a: malonic acid (1.5 eq.), ammonium acetate (2.0 eq.), MeOH or EtOH or ^{i}PrOH, reflux; b: $SOCl_2$ (3 eq.), EtOH, −15°C then reflux.

R	Yield a (solvent)	Yield b	Data for aminoester hydrochloride
H[3]	34 (MeOH)	82	solid, mp 128−132 °C; IR (neat) ν (cm^{-1}) : 3008, 2852, 1737, 1596, 1503; ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ_H 8.70 (3H, s), 7.54 (2H, m), 7.41 (1H, m), 4.56 (1H, m), 4.01 (1H, dq, *J* 11, 7 Hz), 3.97 (1H, dq, *J* 11, 7 Hz), 3.20 (1H, dd, *J* 16, 5.8 Hz), 2.98 (1H, dd, *J* 16, 9 Hz), 1.09 (3H, t, *J* 7 Hz). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ_C 169.5, 137.2, 129.3, 129.1, 128.5, 60.9, 51.5, peak ~39 ppm obscured by solvent peaks, 14.3. HRMS (ESI^+): calculated for $C_{11}H_{15}NO_2$ $[M + H]^+$: *m/z* 194.1176, found 194.1170.
2-F[4]	48 (^{i}PrOH)	77	Colourless powder, mp 150−152 °C; IR (neat) ν (cm^{-1}) : 2868, 1585, 1197; ^{1}H NMR δ_H (270 MHz, CD_3OD): 7.52 (2H, m), 7.26 (2H, m), 5.00 (1H, t, *J* 7.3 Hz), 4.15 (1H, q, *J* 7.3 Hz), 3.21 (1H, dd, *J* 16.8, 7.3), 3.06 (1H, dd, *J* 16.8, 7.3 Hz), 1.20 (3H, t, *J* 7.3 Hz); ^{13}C NMR δ_C (67.5 MHz, CD_3OD): 169.6, 131.6 (d, J_{CF} 9 Hz), 128.6, 125.0, 115.9 (d, J_{CF} 22 Hz), 61.3, 45.7, 37.1, 13.0 (peaks for C1′ and C2′ were too weak to be observed); LRMS (ESI^+): *m/z* 212 $[M+H]^+$
2-Cl			Commercial ethyl ester
2-Me			Commercial ethyl ester
2-OMe			Commercial ethyl ester
3-F[4]	24 (^{i}PrOH)	94	Colourless powder, mp 152−154 °C; IR (neat) ν (cm^{-1}): 2849, 1738, 1247; ^{1}H NMR δ_H (270 MHz, CD_3OD) 7.50 (1H, m), 7.32 (2H, m), 7.19 (1H, dt, *J* 3, 8 Hz), 4.77 (1H, t, *J* 7 Hz), 4.15 (2H, q, *J* 7 Hz), 3.14 (1H, dd, *J* 17, 7 Hz), 3.03 (1H, dd, *J* 17, 7 Hz), 1.21 (3H, t, *J* 7 Hz); ^{13}C NMR δ_C (67.5 MHz,CD_3OD): 169.7, C-F peak too weak to be observed, 138.5 (d, J_{CF} 7 Hz), 131.1 (d, J_{CF} 8 Hz), 123.0, 116.1 (d, J_{CF} 21 Hz), 114.2 (d, J_{CF} 23 Hz), 61.1, 51.2, 37.7, 13.0; LRMS (ESI^+): *m/z* 212 $[M+H]^+$.
3-Cl[5]	46 (^{i}PrOH)	56	Colourless solid, mp 45−56 °C; IR (neat) ν (cm^{-1}): 3384, 2980, 2085, 1673, 1378, 1189, 975; ^{1}H NMR δ_H (270 MHz, CD_3CO_2D): 7.61 (1H, s), 7.59-7.55 (1H, m), 7.42-7.40 (2H, m), 4.90 (1H, t, *J* 7 Hz), 4.15 (2H, m), 3.43 (1H, dd, *J* 17, 7 Hz), 3.13 (1H, dd, *J* 17, 7 Hz), 1.20 (3H, t, *J* 7 Hz); ^{13}C NMR δ_c (67.5 MHz, CD_3CO_2D): 170.9, 137.7, 134.4, 130.5, 129.4, 128.1, 126.3, 61.5, 51.8, 37.4, 13.2; HRMS

			(ESI$^+$): *m/z* calculated $C_{11}H_{15}ClNO_2$ $(M + H)^+$ requires 228.0791; found 228.0779.
3-Me	82 (EtOH)	36	Colourless solid, mp 122−124 °C; IR ($CHCl_3$) ν (cm^{-1}) 2875, 1737, 1594, 1509, 1255. ^{1}H-NMR (270 MHz, CD_3CO_2D) δ_H ppm 7.40-7.20 (4H, m), 4.85 (1H, t, *J* 7 Hz) 4.14 (2H, m), 3.40 (1H, dd, *J* 17, 7 Hz) 3.11 (1H, dd, *J* 17, 7 Hz), 2.36 (3H, s), 1.19 (3H, t, *J* 7 Hz). ^{13}C NMR (67.5 MHz, CD_3CO_2D) δ_C ppm 170.8, 138.9, 135.3, 130.0, 128.9, 128.3, 124.6, 61.4, 52.3, 37.7, 20.4, 13.2. HRMS (ESI$^+$): calculated for $C_{12}H_{17}NO_2$ ([M+H]$^+$): *m/z* 208.1338, found 208.1339.
3-OMe			Commercial ethyl ester
4-F [4]			Commercial ethyl ester
4-Cl			Commercial methyl ester
4-Me[6]	40 (EtOH)	80	Mp 160−165 °C; IR ($CHCl_3$) ν (cm^{-1}) 3414, 3354, 1742, 1248, 721; ^{1}H NMR δ_H (400 MHz, CD_3OD) δ_H ppm: 7.35 (2H, d, *J* 8.3 Hz), 7.28 (2H, d, *J* 8.3 Hz), 4.68 (1H, t, *J* 7.2 Hz), 4.15 (2H, m), 3.09 (1H, dd, *J* 17, 7.2 Hz), 2.99 (1H, dd, *J* 17, 7.2 Hz), 2.36 (3H, s), 1.21 (3H, t, *J* 7.3 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm: 169.6, 138.8, 134.3, 129.7, 128.2, 61.0, 51.3, 39.1, 21.3, 14.4; LRMS [ESI$^+$] *m/z* 230 [M + Na]$^+$.
4-OMe			Commercial methyl ester
4-CN[7]	61 (MeOH)	16[§]	Oil, IR ($CHCl_3$) ν (cm^{-1}) : 2985, 2232, 1727, 1611, 1377, 1316, 1187; ^{1}H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 9.03 (3H, br s), 7.91 (2H, d, *J* 8.3 Hz), 7.81 (2H, d, *J* 8.3 Hz), 4.67 (1H, dd, *J* 9, 5.5 Hz), 3.97 (2H, m), 3.25 (1H, dd, *J* 16, 5.5), 3.05 (1H, dd, *J* 16, 9 Hz), 1.06 (3H, t, *J* 7 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$): δ_C ppm 171.4, 152.3, 132.7, 128.1, 119.5, 110.0, 60.4, 53.1, 44.2, 14.6. HRMS (ESI$^+$): calculated for $C_{12}H_{15}N_2O_2$ ([M+H]$^+$): *m/z* = 219.1128, found 219.1130.
4-CF_3	76 (MeOH)	91	Colourless solid, mp 152 °C, IR ($CHCl_3$) ν max (cm^{-1}) 2860, 1732, 1118, 843; ^{1}H NMR (270 MHz, D_2O): δ_H ppm 7.76 (2H, d, *J* 8 Hz), 7.58 (2H, d, *J* 8 Hz), 4.85 (1H, t, *J* 7 Hz), 4.07 (2H, q, *J* 7 Hz), 3.18 (1H, dd, *J* 16.5, 7 Hz), 3.09 (1H, dd, *J* 16.5, 7 Hz), 1.10 (3H, t, *J* 7 Hz). HRMS (ESI$^+$): calculated for $C_{10}H_{11}F_3NO_2$ ([M+H]$^+$): *m/z* = 234.0736, found 234.0738.
4-OCF_3			Commercial methyl ester
4-SO_2Me	62 (MeOH)	41	Beige powder, mp 189 °C; IR (neat) ν max (cm^{-1}) 2986, 2865, 1727, 1601, 1496, 1395, 1323, 1224, 1186, 1151; ^{1}H NMR (270 MHz, CD_3CO_2D) δ_H ppm 8.03 (2H, d, *J* 8.3 Hz,) 7.86 (2H, d, *J* 8.3 Hz), 5.03 (1H, t, *J* 7.0 Hz), 4.15 (2H, m), 3.48 (1H, dd, *J* 17, 7 Hz), 3.19 (1H, dd, *J* 17, 7 Hz), 3.15 (3H, s), 1.19 (3H, t, *J* 7 Hz); ^{13}C NMR (67.5 MHz; CD_3CO_2D) δ_C ppm 170.4, 141.6, 141.2, 129.2, 127.9, 61.6, 51.9, 43.2, 37.4, 13.3. HRMS (ESI$^+$): calculated for $C_{12}H_{18}NO_4S$ ([M+H]$^+$): *m/z* = 272.0951, found 271.0948.
4-Ph	26 (EtOH)	65	Colourless powder, mp 196−198 °C; IR (neat) ν (cm^{-1}) : 2874, 1735, 1028; ^{1}H NMR δ_H (270 MHz, $(CD_3)_2SO$): 8.82 (3H, br s), 7.69 (6H, m), 7.47 (2H, t, *J* 7 Hz), 7.38 (1H, t, *J* 7 Hz), 4.62 (1H, dd, *J* 5.5, 9 Hz), 4.02 (2H, m), 3.25 (1H, dd, *J* 16 Hz, 5.5 Hz), 3.04 (1H, dd, *J* 16, 9 Hz), 1.09 (3H, t, *J* 7 Hz); ^{13}C NMR δ_C (67.5 MHz, $(CD_3)_2SO$): 169.6, 141.1, 140.0, 136.5, 129.6, 129.0, 128.3, 127.4, 127.3, 61.0, 51.3, peak ~38 obscured, 14.4; LRMS (ESI$^+$): *m/z* 270 [M+H]$^+$.

3-CF_3			Commercial methyl esters (racemic, (*S*) and (*R*) enantiomers)
3-OCF_3	64 (^{i}PrOH)	99	Yellow powder, mp 130−133 °C; ^{1}H NMR (270 MHz, CD_3OD) δ_H ppm 7.59 (1H, t, *J* 8 Hz), 7.50 (1H, d, *J* 8 Hz), 7.44 (1H, s), 7.38 (1H, d, *J* 8 Hz), 4.80 (1H, t, *J* 7 Hz), 4.16 (2H, q, *J* 7 Hz), 3.12 (1H, dd, *J* 17, 7 Hz), 3.02 (1H, dd, *J* 17, 7 Hz), 1.21 (3H, t, *J* 7 Hz). ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 171.1, 151.0, 140.0, 132.5, 127.4, 123.3, 121.6, 100.0, 61.7, 52.6, 39.3, 14.5, (O*C*F_3 not observed presumably owing to poor signal/noise). LRMS (ESI$^+$) *m/z* 278 [M + H]$^+$.
2,3-Cl_2	74 (MeOH)	93	Colourless powder, mp 119–121 °C; IR ($CHCl_3$) ν (cm^{-1}): 2986, 2907, 1730, 1604, 1518; ^{1}H-NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 9.09 (3H, br s), 7.91 (1H, d, *J* 8 Hz), 7.68 (1H, d, *J* 8 Hz), 7.47 (1H, t, *J* 8 Hz), 5.03 (1H, br s), 4.10 (1H, q, *J* 7 Hz), 3.28 (1H, dd, *J* 16, 6 Hz), 3.13 (1H, dd, *J* 16, 8.4 Hz, 1.05 (3H, t, *J* 7 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm 168.6, 137.0, 132.1, 131.4, 130.9, 126.7, 127.4, 60.8, 47.7, 41.1, 13.8; HRMS (ESI$^+$): m/z calcd for $C_{11}H_{14}N_1O_2Cl_2$ ([M + H]$^+$), 262.0396; found, 262.0391.
3,4-Cl_2 [8]	62 (^{i}PrOH)	88	Colourless solid. mp 186–188 °C; IR ($CHCl_3$) ν (cm^{-1}) 2869, 1727; ^{1}H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 8.85 (3H, s), 7.91 (1H, d, *J* 2 Hz), 7.72 (1H, d, *J* 8.3 Hz), 7.57 (1H, dd, *J* 8.3, 2 Hz), 4.64 (1H, dd, *J* 5.8, 8.8 Hz), 4.00 (2H, m), 3.21 (1H, dd, *J* 16.3, 5.8 Hz), 3.04 (1H, dd, *J* 16.3, 8.8, Hz), 1.09 (3H, t, *J* 7 Hz); ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 168.9, 137.8, 131.5, 131.1, 130.8, 130.3, 128.4, 60.6, 49.8, 38.1, 13.9; LRMS (ESI$^+$) *m/z* 262 [M + H]$^+$.
3,5-Cl_2 [9]	80 (^{i}PrOH)	90	Colourless solid, mp 183−185 °C; IR ($CHCl_3$) ν (cm^{-1}) 3499, 2904, 1730, 1593, 1571, 1442, 1374, 1223, 1119, 1026, 890, 800, 690; ^{1}H NMR (270 MHz, CD_3OD) δ_H ppm 7.55 (3H, m), 4.76 (1H, t, *J* 7.0 Hz), 4.16 (2H, q, *J* 7.0 Hz), 3.15 (1H, dd, *J* 17, 7.3 Hz), 3.06 (1H, dd, *J* 17, 7.3 Hz), 1.22 (3H, t, *J* 7.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ_C ppm 170.9, 141.2, 137.1, 130.6, 127.6, 62.7, 52.2, 39.1, 14.5; HRMS (ESI$^+$): Calculated for $C_{11}H_{13}Cl_2NO_2$ [M + H]$^+$ *m/z* 262.0396, found 262.0393.
3,4-Me_2	42 (MeOH)	96	Colourless powder, mp 170–171 °C; IR ($CHCl_3$) ν (cm^{-1}): 3168, 2988, 2796, 1710, 1514, 1383, 1276, 831, 751. ^{1}H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 8.71 (3H, br s), 7.30 (1H, s), 7.25 (1H, d, *J* 7.7 Hz), 7.15 (1H, d, *J* 7.7 Hz,), 4.45 (1H, dd, *J* 9.3, 5.5 Hz), 3.97 (2H, m), 3.18 (1H, dd, *J* 16.0, 5.5 Hz), 2.95 (1H, dd, *J* 16, 9.3 Hz), 2.21 (3H, s), 2.20 (3H, s), 1.07 (3H, t, *J* 7 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm 169.6, 137.5, 137.0, 134.6, 130.2, 129.3, 125.5, 61.0, 51.3, 39.2, 20.0, 19.6, 14.4; HRMS (ESI$^+$): *m/z* Calculated for $C_{13}H_{20}NO_2$ ([M + H]$^+$), 222.1489; found, 222.1495.
3,4-$CH_2CH_2CH_2$	26 (MeOH)	54	Colourless powder, mp 109–110 °C; IR ($CHCl_3$) ν (cm^{-1}) 3432, 2845, 1736, 1593, 1508, 1381, 1251, 823; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H ppm 8.54 (3H, br s), 7.37 (1H, s), 7.26 (1H, d, *J* 8 Hz), 7.24 (1H, d, *J* 8 Hz), 4.53 (1H, dd, *J* 5.9, 8.8 Hz), 4.00 (2H, m), 3.14 (1H, dd, *J* 16, 5.9 Hz), 2.93 (1H, dd, *J* 16, 5.9 Hz), 2.85 (4H, m), 2.02 (2H, quint, *J* 7.5 Hz), 1.10 (3H, t, *J* 7.3 Hz); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ_C ppm 169.1, 144.5, 144.2, 134.6, 125.5,

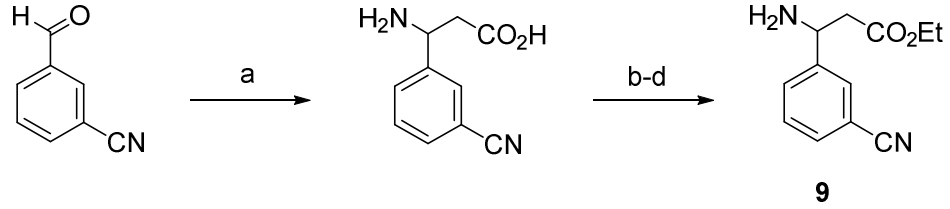
			124.4, 123.4, 60.4, 51.0, 38.8, 32.2, 32.0, 25.1, 13.9; HRMS (ESI_+): m/z calculated for $C_{14}H_{20}NO_2$ ($[M + H]^+$), 234.1489; found, 234.1491.
3,5-Me_2	47 (^{i}PrOH)	80	Colourless solid, mp 123–125 °C; IR ($CHCl_3$) ν (cm^{-1}) 2984, 2922, 1734, 1612, 1519, 1477, 1399, 1381, 1324, 1295, 1240; ^{1}H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 8.78 (3H, br s), 7.16 (2H, s), 7.00 (1H, s), 4.45 (1H, br s), 4.00 (2H, m), 3.20 (1H, dd, *J* 16, 5.5 Hz), 2.95 (1H, dd, *J* 16, 9.4 Hz), 2.26 (6H, s), 1.08 (3H, t, *J* 7.0 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm 169.6, 138.2, 137.2, 130.7, 125.9), 60.9, 51.5, 39.1, 21.5, 14.4; LRMS (ESI^+) 222 $[M + H]^+$
3,4-$(OMe)_2$[10]	49 (^{i}PrOH)	71	Colourless solid, mp 208–210 °C; IR ($CHCl_3$) ν (cm^{-1}): 3154, 2778, 1731, 1516, 1263, 1141, 1016; ^{1}H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 8.36 (3H, s), 7.17 (1H, s), 6.98 (2H, s), 4.53 (1H, dd, *J* 6.5, 8.3 Hz), 4.02 (2H, m), 3.77 (3H, s), 3.75 (3H, s), 3.07 (1H, dd, *J* 16.0, 7.0 Hz), 2.92 (1H, dd, *J* 16.0, 8.0 Hz), 1.11 (3H, t, *J* 7.0 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm 169.7, 149.6, 149.2, 129.5, 120.5, 112.0, 111.9, 60.0, 56.2, 56.1, 39.3, 14.5; LRMS (ESI^+) *m/z* 254 $[M+H]^+$.
3,4-OCH_2O-			Commercial methyl ester
3-CF_3-4-Cl	26 (^{i}PrOH)	70	Colourless crystals, mp 185–186 °C. IR ($CHCl_3$) ν (cm^{-1}) 3112, 3108, 2828, 1737, 1314, 1182, 1131; ^{1}H NMR (270 MHz, CD_3CO_2D) δ_H ppm 8.01 (1H, d, *J* 2 Hz), 7.90 (1H, dd, *J* 8.5, 2 Hz), 7.66 (1H, d, *J* 8.5 Hz), 5.02 (1H, t, *J* 7 Hz), 4.20-4.08 (2H, m), 3.48 (1H, dd, *J* 17.5, 7 Hz), 3.19 (1H, dd, *J* 17.5, 7 Hz), 1.19 (3H, t, *J* 7 Hz); HRMS (ESI^+): m/z calcd for $C_{12}H_{14}ClF_3NO_2$ ($[M + H]^+$), 296.0650; found 296.0647.

§ −10°C then room temperature, 4 days.

Ethyl 3-amino-3-(3-cyclohexyl)propanoate hydrochloride (8). Ethyl 3-amino-3-(3-phenyl)propanoate hydrochloride (1.00 g, 4.37 mmol) was dissolved in EtOH (50 mL) and 5% Rh/Al_2O_3 (200 mg) was added. The reaction vessel was evacuated and flushed with nitrogen 3 times before being charged with hydrogen (4 bar). The reaction vessel was then heated at 80 °C for 24 h. After being cooled, the catalyst was filtered off and the solvent removed under reduced pressure to give ethyl 3-amino-3-(3-cyclohexyl)propanoate hydrochloride as a colourless solid, 684 mg (67%), mp 100-106 °C; IR (neat) ν (cm^{-1}) 2925, 2853, 1729, 1608; ^{1}H NMR δ_H (270 MHz; CD_3OD): 4.90 (3H, br s), 4.21 (2H, q, *J* 7.0 Hz), 3.43 (1H, ddd, *J* 4.3, 5.9, 8.1 Hz), 2.80 (1H, dd, *J* 17.5, 4.3 Hz), 2.65 (1H, dd, *J* 17.5, 8.3 Hz), 1.84-1.63 (6H, m), 1.39-1.02 (5H, m), 1.28 (3H, t, *J* 7 Hz). ^{13}C NMR δ_C (67.5 MHz, CD_3OD): 172.5, 62.5, 54.3, 41.4, 35.1, 29.8, 29.3, 27.1, 14.6; HRMS (ESI^+): calculated for $C_{11}H_{21}NO_2$ $[M+H]^+$: *m/z* 200.1645, found 200.1650.

Ethyl 3-amino-3-(3-cyanophenyl)propanoate (**9**) was prepared as shown in Scheme 2.

Scheme 2



9

a: malonic acid (1.5 eq.), ammonium acetate (2.0 eq.), EtOH, reflux, 20 h; b: *N*-(benzyloxycarbonyloxy)succinimide, $EtNPr^{i}_2$, CH_2Cl_2, room temp., 2 h; c: *N*,*N*'-carbonyldiimidazole, THF, room temp., then EtOH; d: H_2 (1 bar), 10% Pd/C, room temp., 24 h.

A mixture of 3-cyanobenzaldehyde (4.02 g, 30.7 mmol), malonic acid (3.19 g, 30.7 mmol), and ammonium acetate (4.72 g, 61.3 mmol) in EtOH (80 mL) was heated under reflux for 20 h. The reaction mixture was left to cool. The solid was collected by filtration and washed with EtOH (20 mL) and diethyl ether (2 x 10 mL) to afford 3-amino-3-(3-cyanophenyl)propanoic acid as a colourless powder (4.45 g, 76%), mp 228–231 °C, lit.[11] 228–230 °C; IR ($CHCl_3$) ν (cm^{-1}) 3690, 3605, 3424, 1602, 1240. ^{1}H NMR δ_H ppm (270 MHz; CD_3CO_2D) 7.86 (1H, m) 7.74 (1H, m), 7.57 (2H, m), 4.92 (1H, dd, *J* 8.4, 5.5 Hz), 3.35 (1H, dd, *J* 17.5, 8.4 Hz), 3.12 (1H, dd, *J* 17.5, 5.5 Hz); LRMS (ESI^+): 191 $[M + H]^+$.

3-Amino-3-(3-cyanophenyl)propanoic acid (2.50 g, 13.1 mmol) was dissolved in dichloromethane (50 mL). N-(benzyloxycarbonyloxy)succinimide (3.60 g, 14.5 mmol) and ethyldiisopropylamine (4.62 mL, 39.4 mmol) were added and the reaction mixture was stirred at ambient temperature for 2 h. Aqueous sodium hydroxide (2 M, 5 mL) was added and the mixture was stirred for a further 2 h. The mixture was acidified with dilute hydrochloric acid and extracted with dichloromethane (30 mL). The organic layer was washed with brine (30 mL) and dried over $MgSO_4$. The solvent was then removed under reduced pressure to afford 3-(((benzyloxy)carbonyl)amino)-3-(3-cyanophenyl)propanoic acid as a yellow oil (3.47 g, 81%), which was used directly for the next step. LRMS (ESI^+): *m/z* 347 $[M + Na]^+$.

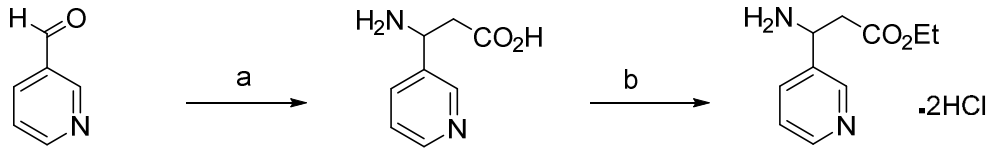
3-(((Benzyloxy)carbonyl)amino)-3-(3-cyanophenyl)propanoic acid (3.47 g, 10.6 mmol) was added to anhydrous THF (25 mL) and cooled to 0 °C in an ice bath. N,N'-carbonyldiimidazole (1.73 g, 10.6 mmol) was added and the mixture was stirred at room temperature for 3 h. Ethanol (0.61 mL, 10.6 mmol) was added and the mixture was stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the product redissolved in EtOAc (30 mL). The organic phase was washed with dilute hydrochloric acid (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford ethyl 3-(((benzyloxy)carbonyl)amino)-3-(3-cyanophenyl) propanoate as a pale yellow oil (3.08 g, 82%). ^{1}H NMR δ_H ppm (270 MHz; $CDCl_3$) 7.53-7.45 (3H, m), 7.35 (1H, m), 7.26 (5H, m), 6.04 (1H,br d, *J* 8.3 Hz), 5.01 (2H, 2), 5.00 (1H, m), 3.98 (2H, q, *J* 7 Hz), 2.75 (2H, m), 1.07 (3H, t, *J* 7 Hz). LRMS (ESI^+): *m/z* 375 $[M + Na]^+$.

Ethyl 3-(((benzyloxy)carbonyl)amino)-3-(3-cyanophenyl)propanoate (2.58 g, 7.33 mmol) was dissolved in EtOH (100 mL). Palladium on charcoal (10%, 0.26 g) was added and the mixture was stirred under a balloon of hydrogen for 24 h. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. Ethyl 3-amino-3-(3-cyanophenyl)propanoate was obtained as a clear oil (0.97 g, 61%). ^{1}H NMR δ_H ppm (270 MHz; $CDCl_3$ 7.67 (1H, s), 7.59 (1H, d, *J* 7.7 Hz), 7.52 (1H, dt, *J* 7.7, 1.5 Hz), 7.40 (1H, t, *J* 7.7 Hz), 4.42 (1H, t, *J* 4.8 Hz), 4.07 (2H, m), 2.62 (2H, m), 1.19

(3H, t, *J* 7 Hz); ^{13}C NMR δ_C ppm (67.5 MHz, $CDCl_3$) 171.3, 146.0, 131.0, 130.9, 130.0, 129.3, 118.6, 112.6, 60.6, 51.9, 43.8, 14.1. LRMS (ESI$^+$): *m/z* 219 [M + H]$^+$.

Ethyl 3-amino-3-(3-pyridyl)propanoate (**10**) was prepared in a similar manner from 3-formylpyridine (Scheme 3).[11]

Scheme 3



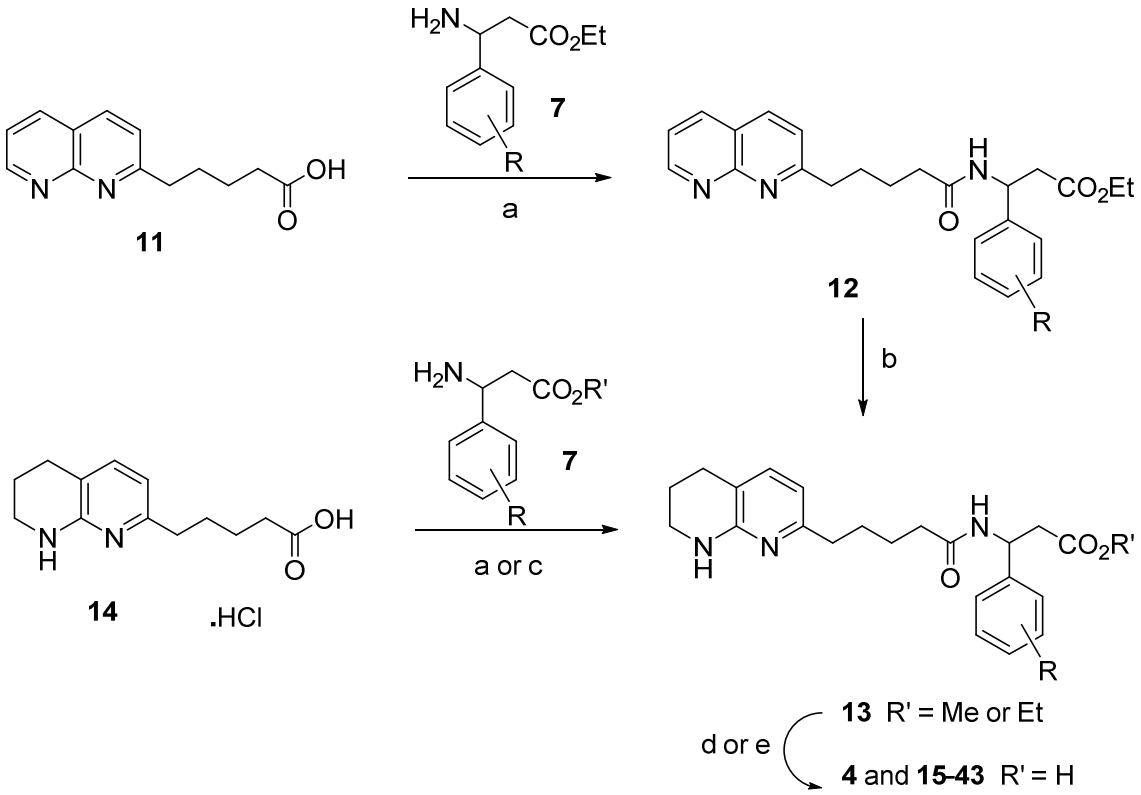
10

3-Amino-3-(pyridin-3-yl)propanoic acid (7.78 g, 99 %) was obtained as a white powder, mp 198–199 °C. IR ($CHCl_3$) ν (cm^{-1}) 3520, 3008, 2929, 1720, 1601, 1410, 1264, 1099; ^{1}H NMR (270 MHz, CD_3CO_2D) δ_H ppm 8.94 (1H, s), 8.77 (1H, d, *J* 5.1 Hz), 8.38 (1H, d, *J* 8.0 Hz), 7.76 (1H, dd, *J* 8.0, 5.1 Hz), 5.06 (1H, dd, *J* 8.8 Hz, 5.7 Hz), 3.38 (1H, dd, *J* 17.6, 8.8 Hz), 3.16 (1H, dd, *J* 17.6, 5.7 Hz); ^{13}C NMR (67.5 MHz, CD_3CO_2D) δ_C ppm 175.5, 147.7, 147.0, 141.1, 134.7, 126.6, 50.9, 38.3; HRMS (ESI$^+$): m/z calc'd for $C_8H_{11}N_2O_2$ ([M + H]$^+$), 167.0815; found, 167.0814.

Ethyl 3-amino-3-(pyridin-3-yl)propanoate dihydrochloride (2.23 g, 69 %) was obtained as a white powder, mp 142–143 °C. IR ($CHCl_3$) ν (cm^{-1}) 2986, 2941, 1727, 1466, 1034**;** ^{1}H-NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 9.30 (3H, br s), 9.16 (1H, s), 8.90 (1H, d, *J* 6.4 Hz), 8.83 (1H, d, *J* 6.4 Hz), 8.05 (1H, t, *J* 6.4 Hz), 4.89 (1H, br s), 4.09 (2H, q, *J* 7.5 Hz), 3.33 (2H, m), 1.08 (3H, t, *J* 7.5 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm 168.9, 144.0, 143.2, 143.0, 126.5, 60.9, 48.0, 41.3, 14.0; HRMS (ESI$^+$): m/z calc'd for $C_{10}H_{15}N_2O_2$ ([M + H]$^+$), 195.1128; found, 195.1130.

Preparation of ester intermediates **13** and carboxylic acids **4** and **14**–**43** as shown in Scheme 4 are described below.

Scheme 4



Reagents and conditions. a: *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide, *N*-methylmorpholine, 1-hydroxybenzotriazole hydrate, 20 °C; b: H_2 (1 bar), 10% Pd/C, EtOH, 20 °C; c: 1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate, Et_3N, CH_2Cl_2, room temp.; d: $NaOH_{(aq.)}$, EtOH, 20 °C; e: LiOH, THF/H_2O, 20 °C.

(ii) Derivatives of ethyl or methyl 3-phenyl-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoate (13).

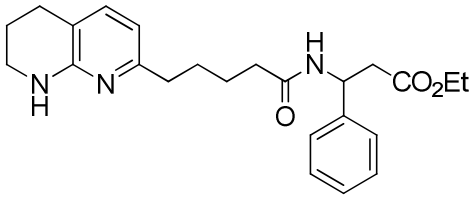
Amide formation – Method A (EDC, HOBt, NMM).
5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)pentanoic acid hydrochloride (284 mg, 1.00 mmol) was added to a stirred solution of the appropriate 3-amino-3-(aryl)propanoic acid ester (1.00 mmol) in dimethylformamide, dichloromethane or (preferably) acetonitrile (5−10 mL) under nitrogen. *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (155 mg, 1.00 mmol), 1-hydroxybenzotriazole hydrate (168 mg, 1.07 mmol) and *N*-methylmorpholine (330 mg, 0.36 mL, 3.00 mmol) were added sequentially and the mixture was stirred for 24 h. The solvent was removed under reduced pressure. The residue was taken up in EtOAc (20 mL) and washed with brine (3 × 20 mL). The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a crude oil. Purification by column chromatography (aminopropyl modified silica cartridge, eluting with a gradient of petrol 100% to petrol:EtOAc = 30:70). Fractions containing product were combined and the solvent removed under reduced pressure to give the product.

Amide formation – Method B (HATU, Et_3N).
HATU (1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate)(1.35 g, 3.55 mmol) was added to a solution of the appropriate 3-amino-3-(aryl)propanoic acid ester (3.55 mmol) and 5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanoic

acid (831 mg, 3.55 mmol) in dichloromethane (30 mL). The reaction mixture was treated with Et_3N (1.50 mL, 10.7 mmol) and left to stir under nitrogen for 24 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with saturated aqueous sodium bicarbonate (2 × 30 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the crude product. Purification as above gave the pure product.

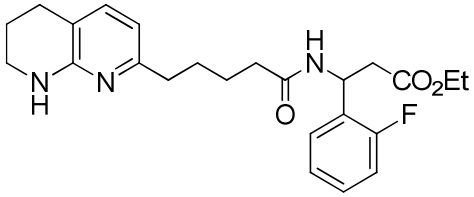
Spectroscopic Data

(*RS*)-Ethyl 3-phenyl-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoate.



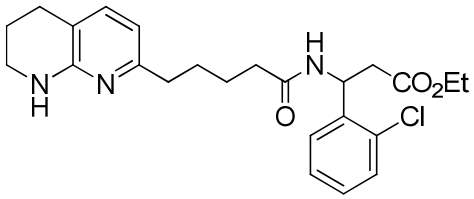
Method A (DMF solvent), yield 146 mg, (19%, from EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.29 (5H, m), 7.08 (1H, d, *J* 7.6 Hz), 6.35 (1H, d, *J* 7.2 Hz), 5.45 (1H, t, *J* 6 Hz), 4.83 (1H, s), 4.05 (2H, q, *J* 7.2 Hz), 3.39 (2H, dt, *J* 8.4, 3.2 Hz), 2.91 (1H, dd, *J* 15.6, 6 Hz), 2.92 (1H dd, *J* 15.6, 6 Hz), 2.21 (2H, t, *J* 6.5 Hz), 2.58 (2H, t, *J* 6.8 Hz), 2.26 (2H, t, *J* 6.8 Hz), 1.93 (2H, m, *J* 5.2 Hz), 1.72 (4H, m), 1.29 (3H, t, *J* 7.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ_C ppm 173.7, 170.7, 157.1, 155.8, 141.4, 137.0, 128.2, 127.1, 126.2, 113.8, 60.3, 50.0, 41.0, 40.5, 36.5, 35.5, 29.3, 26.0, 25.3, 21.0, 13.1. LRMS (ESI^+): 410 $[M + H]^+$.

(*RS*)-Ethyl 3-(2-fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method A. Cream-coloured solid, yield 180 mg (27%); ^{1}H NMR δ_H (400 MHz; CD_3OD) 7.56 (1H, d, *J* 7.3 Hz), 7.42 (1H, t, *J* 7.8 Hz), 7.33 (1H, m), 7.15 (1H, t, *J* 7.5Hz), 7.09 (1H, m), 6.54 (1H, d, *J* 7.3 Hz), 5.56 (1H, m), 4.03 (2H, q, *J* 7 Hz), 3.46 (2H, m), 3.10 (1H, dd, *J* 16.7, 9.7 Hz), 2.91 (1H, dd *J* 16.7*,* 5.6 Hz), 2.77 (2H, m), 2.67, (2H, m), 2.57 (2H, m), 1.88 (2H, m), 1.65 (4H, m), 1.17 (3H, t, *J* 7 Hz). LRMS (ESI^+): *m/z* 428 $[M + H]^+$.

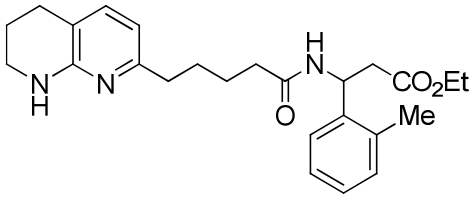
(*RS*)-Ethyl 3-(2-chlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method A (dichloromethane solvent). Light yellow oil, yield 78 mg (16%). ^{1}H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.38-7.26 (2H, m), 7.22-7.12 (2H, m), 7.02 (1H, d, *J* 7 Hz), 6.91 (1H, d, *J* 8 Hz), 6.30 (1H, d, *J* 7 Hz), 5.67 (1H, m), 4.83 (1H, br s), 4.02 (2H, q, *J* 7 Hz), 3.36 (2H, m), 2.93 (1H, dd, *J* 15, 6 Hz),

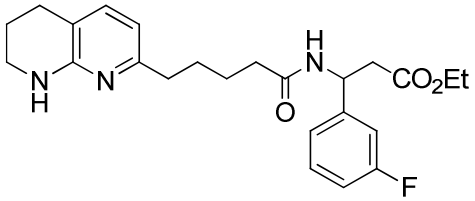
2.82 (1H, dd, *J* 15, 6 Hz), 2.66 (2H, t, *J* 6 Hz), 2.51 (2H, m), 2.23 (2H, t, *J* 7 Hz), 1.87 (2H, quin, *J* 6 Hz), 1.66 (4H, m), 1.12 (3H, t, *J* 7 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.2, 171.4, 157.9, 147.6, 138.0, 136.8, 132.8, 130.1, 128.8, 127.9, 127.0, 113.4, 111.5, 60.9, 47.6, 41.7, 38.4, 37.4, 36.6, 29.4, 26.4, 25.4, 21.6, 14.1. HRMS (ESI$^+$): calculated for $C_{24}H_{31}{}^{35}ClN_3O_3$ $[M + H]^+$: *m/z* 444.2049, found 444.2039.

(*RS*)-Ethyl 3-(2-methylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



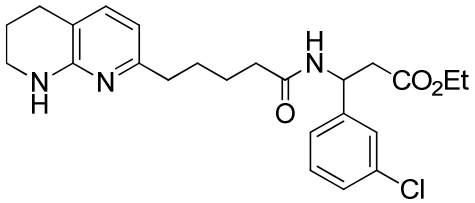
Method A. colourless oil, yield 83 mg, (20%); IR ($CHCl_3$) ν (cm^{-1}) 3623, 3052, 2938, 1727, 1667, 1598, 1587, 1503, 1463, 1387, 1350, 1322, 1300, 1279. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.24 (1H, m), 7.16 (3H, m), 7.07 (1H, d, *J* 7.3 Hz), 6.46 (1H, d, *J* 7.3 Hz), 6.32 (1H, br d, *J* 8 Hz), 5.61 (1H, q, *J* 7 Hz), 5.12 (1H, br s), 4.06 (2H, q, *J* 7 Hz), 3.40 (2H, m), 2.87 (1H, dd, *J* 15.4, 7 Hz), 2.78 (1H, dd, *J* 15.4, 7 Hz), 2.69 (2H, m), 2.55 (2H, m), 2.42 (3H, s), 2.21 (2H, m), 1.91 (2H, m), 1.67 (4H, m), 1.15 (3H, t, *J* 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.0, 171.1, 157.1, 155.3, 138.9, 135.9, 131.1, 130.8, 127.5, 126.2, 125.0, 113.7, 111.3, 60.7, 46.3, 41.6, 39.6, 36.9, 36.4, 29.2, 26.3, 25.2, 21.3, 19.3, 14.1. LRMS (ESI$^+$): 424 $[M + H]^+$.

(*RS*)-Ethyl 3-(3-fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



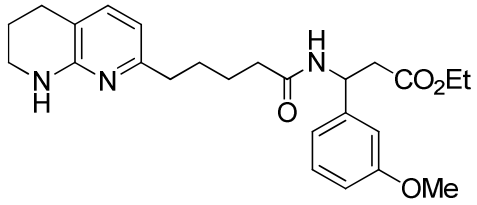
Method B. Colourless solid, yield 291 mg, (19%); IR ($CHCl_3$) ν (cm^{-1}) 3247, 2937, 1728, 1530, 1187, 788; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.11 (2H, m), 7.03 (1H, d, *J* 9 Hz), 6.95 (2H, m), 6.34 (1H, d, *J* 7.3 Hz), 5.44 (1H, dt, *J* 8.3, 6 Hz), 4.02 (2H, q, *J* 7 Hz), 3.42 (2H, m), 2.91 (1H, dd, *J* 16, 6 Hz), 2.83 (1H, dd, *J* 16, 6 Hz), 2.71 (2H, m), 2.58 (2H, m), 2.30 (2H, m), 1.92 (2H, m), 1.71 (4H, m), 1.19 (3H, t, *J* 7 Hz); HRMS (ESI$^+$): calc'd for $C_{24}H_{30}FN_3O_4$ $[M + H]^+$: *m/z* 428.2344, found 428.2331.

(*RS*)-Ethyl 3-(3-chlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



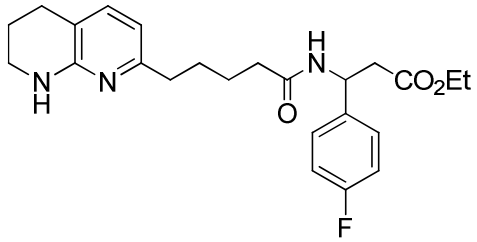
Method A (dichloromethane solvent). Colourless oil, yield 170 mg, (18%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.27-7.22 (3H, m), 7.17 (1H, m), 7.06 (1H, d, *J* 7.3 Hz), 6.69 (1H, br d, *J* 8 Hz), 6.34 (1H, d, *J* 7.5 Hz), 5.40 (1H, dt, *J* 8, 6 Hz), 4.08 (2H, m), 3.40 (2H, m), 2.89 (1H, dd, *J* 16, 6 Hz), 2.82 (1H, dd, *J* 16, 6 Hz), 2.69 (2H, m), 2.56 (1H, m), 2.27 (2H, m), 1.91 (2H, m), 1.70 (4H, m), 1.18 (3H, t, *J* 7.5 Hz); HRMS (ESI$^+$): calc'd for $C_{24}H_{31}ClN_3O_3$ $[M + H]^+$: *m/z* 444.2054, found 444.2043.

(*RS*)-Ethyl 3-(3-methoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



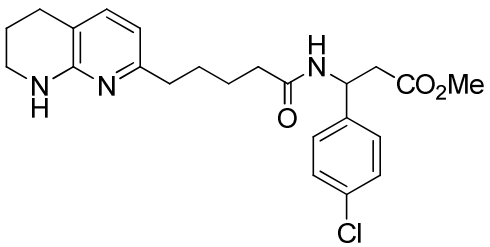
Method A. solid, yield 157 mg, (36%); mp 76 °C; IR ($CHCl_3$) ν (cm^{-1}) 3306-3249, 1241, 1122, 1035, 789. ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.23 (1H, t, *J* 8 Hz), 7.07 (1H, d, *J* 7.3 Hz), 6.87 (1H, d, *J* 8 Hz), 6.84 (1H, s), 6.79 (1H, d, *J* 8 Hz), 6.66 (1H, br d, *J* 8 Hz), 5.40 (1H, dt, *J* 8, 6 Hz), 4.07 (2H, q, *J* 7 Hz), 3.78 (3H, s), 3.39 (2H, m), 2.91 (1H, dd, *J* 15.6, 6 Hz), 2.81 (1H, dd, *J* 15.6, 6 Hz), 2.69 (2H, m), 2.57 (2H, m), 2.26 (2H, m), 1.91 (2H, m), 1.70 (4H, m), 1.17 (3H, t, *J* 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.2, 171.2, 159.8, 156.2, 155.2, 142.4, 137.1, 129.6, 118.5, 113.8, 112.9, 112.2, 111.2, 60.7, 55.2, 49.4, 41.5, 40.1, 36.7, 36.5, 29.2, 26.2, 25.2, 21.4, 14.1. HRMS (ESI^+): calc'd for $C_{25}H_{34}N_3O_4$ $[M + H]^+$: *m/z* 441.2569, found 441.2569.

(*RS*)-Ethyl 3-(4-fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method A (dichloromethane solvent). Colourless oil, yield 140 mg, (34%); IR ($CHCl_3$) ν (cm^{-1}) 3665, 3436, 2937, 1667, 1505, 1239, 866; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.25 (2H, dd, *J* 5, 8.5 Hz), 7.05 (1H, d, *J* 7.5 Hz), 6.99 (2H, t, *J* 8.5 Hz), 6.68 (1H, br d, *J* 8.5), 6.68 (1H, d, *J* 7.5 Hz), 5.40 (1H, dt, *J* 8, 6 Hz), 4.06 (2H, q, *J* 7 Hz), 3.38 (2H, m), 2.89 (1H, dd, *J* 15.5, 6 Hz), 2.79 (1H, dd, *J* 15.5, 6 Hz), 2.69 (2H, m), 2.54 (2H, m), 2.25 (2H, m), 1.90 (2H, m), 1.88 (4H, m), 1.17 (3H, t, *J* 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.3, 171.2, 163.1 (d, J_{CF} 245 Hz), 157.9, 157.7, 136.7, 136.6 (d, J_{CF} 3 Hz), 128.0 (d, J_{CF} 8 Hz), 115.4 (d, J_{CF} 21 Hz), 113.2, 111.4, 60.8, 48.8, 41.6, 40.0, 37.3, 36.6, 29.3, 26.3, 25.3, 21.5, 14.1; HRMS (ESI^+): calc'd for $C_{24}H_{31}FN_3O_3$ $[M + H]^+$: *m/z* 428.2349, found 428.2337.

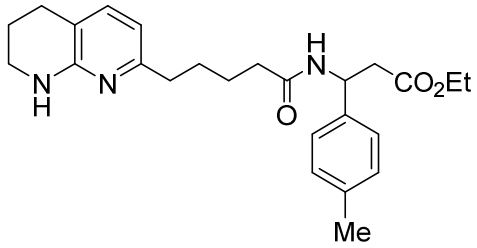
(*RS*)-Methyl 3-(4-chlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method A. Colourless solid, yield 269 mg (61%); IR ($CHCl_3$) ν (cm^{-1}) 3473, 2952, 1720, 1651. ^1H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.28 (4H, m), 7.11 (1H, d, *J* 7.3 Hz), 6.86 (1H, br d, *J* 8.5 Hz), 6.33 (1H, d,

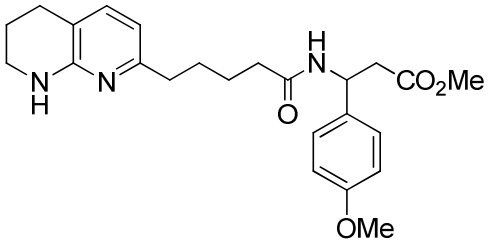
J 7.3 Hz), 5.41 (1H, m), 3.62 (3H, s), 3.41 (2H, m), 2.92 (1H, dd, *J* 16, 6 Hz), 2.83 (1H, dd, *J* 16, 6 Hz), 2.72 (2H, t, *J* 6.3 Hz), 2.57 (2H, m), 2.27 (2H, m), 1.92 (2H, m), 1.69 (4H, m).

(*RS*)-Ethyl 3-(4-methylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



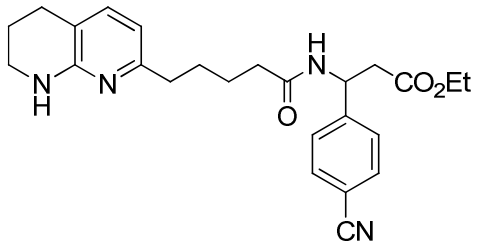
Method A (acetonitrile solvent), colourless oil, 310 mg (30%); IR ($CHCl_3$) ν (cm^{-1}) 3372, 3291, 1739, 1254, 687; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H ppm 8.26 (1H, d, *J* 8.5 Hz), 7.17 (2H, d, *J* 8 Hz), 7.10 (2H, d, *J* 8 Hz), 7.00 (1H, d, *J* 7.3 Hz), 6.21 (1H, d, *J* 7.3 Hz and 1H, br s), 5.17 (1H, q, *J* 8 Hz), 3.97 (2H, m), 3.22 (2H, m), 2.71 (1H, dd, *J* 15, 8 Hz), 2.66 (2H, dd, *J* 15, 8 Hz), 2.59 (2H, t, *J* 6 Hz), 2.39 (2H, t, *J* 7 Hz), 2.25 (3H, s), 2.07 (2H, m), 1.74 (2H, m), 1.51−1.44 (4H, m), 1.10 (3H, t, *J* 7 Hz); ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ_C ppm 171.6, 170.6, 157.7, 156.2, 139.8, 136.6, 136.4 , 129.3 , 126.9, 112.6 , 110.3 , 60.5, 49.4 , 41.5, 41.2 , 37.5, 35.9, 29.3, 26.5, 25.6, 21.5, 21.1, 14.6; LRMS (ESI^+): *m/z* 424 $[M + Na]^+$.

(*RS*)-Methyl 3-(4-methoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



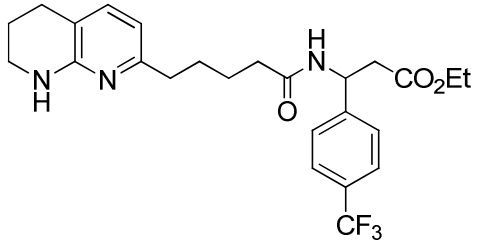
Method A (dichloromethane solvent), yield 350 mg (43%); mp 81–83 °C; IR (state not recorded) ν (cm^{-1}) 3011, 2935, 1733, 1669, 1507; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.23 (2H, d, *J* 8.6 Hz), 7.10 (1H, d, *J* 7.2 Hz), 6.85 (2H, d, *J* 8.6 Hz), 6.31 (1H, d, *J* 7.2 Hz), 5.30 (1H, dd, *J* 8.5, 6.6 Hz), 3.76 (3H, s), 3.59 (3H, s), 3.36 (2H, m), 2.82 (1H, dd, *J* 15.4, 8.5 Hz), 2.75 (1H, dd, *J* 15.4, 6.6 Hz), 2.68 (2H, m), 2.48 (2H, m), 2.20 (2H, m), 1.86 (2H, m), 1.61 (4H, m). ^{13}C NMR (75 MHz, CD_3OD) δ_C ppm 173.7, 171.3, 159.1, 157.2, 157.1, 136.9, 133.3, 127.4 (3C?), 113.8, 110.8, 54.3, 50.8, 49.4, 41.0, 40.3, 36.4, 35.5, 29.1, 26.0, 25.3, 21.1. HRMS (ESI^+): calc'd for $C_{24}H_{31}N_3O_4$ $[M + H]^+$: *m/z* 426.2387, found 426.2390.

(*RS*)-Ethyl 3-(4-cyanophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



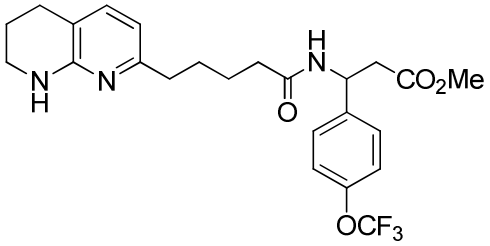
Method A. Colourless powder, yield 230 mg, (32%); mp 140 °C; IR ($CHCl_3$) ν (cm^{-1}) 3436, 2937, 2232, 1723, 1672, 1599, 1503, 1447, 1418, 1322, 1119; ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.59 (2H, d, *J* 8.4 Hz), 7.40 (2H, d, *J* 8.4 Hz), 7.08 (1H, d, *J* 7.3 Hz), 6.96 (1H, br d, *J* 8.3 Hz), 6.32 (1H, d, *J* 7.3 Hz), 5.44 (1H, dt, *J* 8.3, 6 Hz), 5.01 (1H, br s), 4.07 (2H, q, *J* 7.2 Hz), 3.40 (2H, m), 2.90 (1H, dd, *J* 16, 6 Hz), 2.83 (1H, dd, *J* 16, 6 Hz), 2.70 (2H, t, *J* 6.2 Hz), 2.55 (2H, m), 2.28 (2H, m), 1.91 (2H, m), 1.69 (4H, m), 1.17 (3H, t, *J* 7.2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.6, 170.9, 157.2, 155.4, 146.4, 137.0, 132.4, 127.1, 118.6, 113.7, 111.3 (2C), 61.1, 49.1, 41.6, 39.5, 36.9, 29.2, 25.2, 21.3, 14.0. HRMS (ESI^+): calc'd for $C_{25}H_{31}N_4O_3$ $[M + H]^+$: *m/z* 435.2391, found 435.2399.

(*RS*)-Ethyl 3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-3-(4-trifluoromethylphenyl)-pentanamido)propanoate.



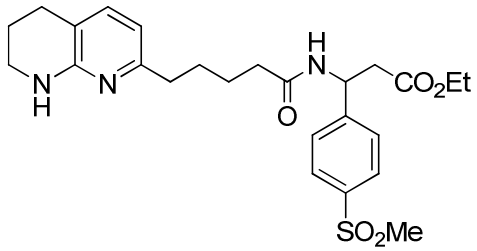
Method A (dichloromethane solvent). Grey gum, yield 253 mg, (28%); IR ($CHCl_3$) ν (cm^{-1}) 3295, 2923, 1727, 1651, 1112. ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.62 (1H, br d, *J* 8.3 Hz), 7.53 (4H, s), 7.25 (1H, presumed d), 6.34 (1H, d, *J* 7.5 Hz), 5.49 (1H, m), 4.05 (2H, q, *J* 7 Hz), 3.48 (2H, m), 2.98 (1H, dd, *J* 15.7, 6.6 Hz), 2.87 (1H, dd, 15.7, 6.6 Hz), 2.75 (2H, m), 2.62 (2H, m), 2.35 (2H, m), 1.70 (4H, m), 1.16 (3H, t, *J* 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.4, 170.7, 155.4, 153.0, 145.3, 139.6, 129.4 (q, J_{CF} 32 Hz, 2C), 127.2 (2C), 125.4 (q, J_{CF} 4 Hz), 116.5, 110.3, 60.8, 49.5, 41.1, 40.1, 35.6, 33.3, 28.7, 25.6, 24.5, 19.9, 14.0, *C*F_3 not observed. HRMS (ESI^+): calc'd. for $C_{24}H_{29}F_3N_3O_3$ ($[M+H]^+$), 464.2156; found, 464.2153.

(*RS*)-Ethyl 3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-3-(4-trifluoromethoxyphenyl) pentanamido)propanoate.



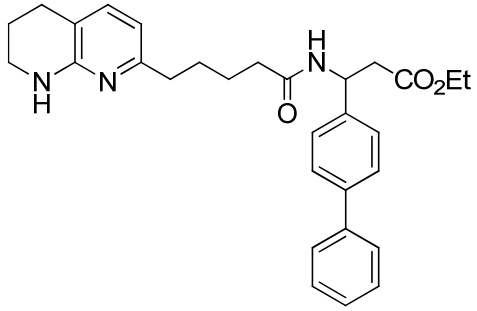
Method A. Colourless solid, yield 160 mg, (48%); mp 76–77 °C; IR ($CHCl_3$) ν (cm^{-1}) 3282, 2934, 2859, 1732, 1648, 1604, 1588, 1510, 1438, 1344, 1155. ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.32 (2H, d, *J* 8.3 Hz), 7.14 (2H, d, *J* 8.3 Hz), 7.05 (1H, d, *J* 7.3 Hz), 6.82 (1H, br d, *J* 8.2 Hz), 6.32 (1H, d, *J* 7.3 Hz), 5.43 (1H, dt, J, 8.2, 6 Hz), 4.95 (1H, br s), 3.61 (3H, s,), 3.38 (2H, m), 2.92 (1H, dd, *J* 15.7, 6 Hz), 2.85 (1H, dd, *J* 15.7, 6 Hz), 2.68 (2H, t, *J* 6 Hz), 2.54 (2H, m), 2.25 (2H, m), 1.89 (2H, m), 1.67 (4H, m). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.4, 171.5, 157.6, 155.6, 139.5, 136.8, 127.7 (2C), 121.0 (2C), 113.4, 111.3, 51.9, 48.7, 41.5, 39.6, 37.1, 36.4, 29.3, 26.3, 25.2, 21.4 (peaks for *C*F_3O*C*) were not observed due to poor signal to noise ratio). HRMS (ESI^+): calc'd for $C_{24}H_{28}F_3N_3O_4$ $[M + H]^+$: *m/z* 480.2105, found 480.2117.

(*RS*)-Ethyl 3-(4-methanesulfonylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



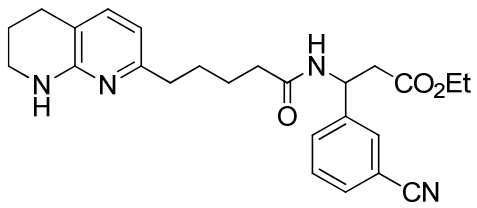
Method A, dichloromethane solvent. Colourless powder, yield 311 mg, (56%); mp 79 °C; IR ($CHCl_3$) ν (cm^{-1}) 3436, 2933, 1723, 1671, 1599, 1503, 1463, 1318, 1151. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.87 (2H, d, *J* 8.3 Hz), 7.51 (2H, d, *J* 8.3 Hz), 7.08 (1H, d, *J* 7.3 Hz), 7.05 (1H, br d, *J* 8 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.47 (1H, dt, J, 8, 6 Hz), 5.07 (1H, br s), 4.08 (2H, q, *J* 7 Hz), 3.41 (2H, m), 3.02 (3H, s), 2.91 (1H, dd, *J* 16, 6 Hz), 2.86 (1H, dd, *J* 16, 6 Hz), 2.70 (2H, t, *J* 6 Hz), 2.55 (2H, m), 2.29 (2H, m), 1.91 (2H, m) 1.69 (4H, m), 1.18 (t, *J* 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.6, 170.9, 157.0, 155.4, 147.4, 139.5, 137.1, 127.8 (2C), 127.4 (2C), 113.8, 111.3, 61.1, 49.2, 44.5, 41.5, 39.6, 36.8, 36.3, 29.2, 26.2, 25.2, 21.3, 14.1. HRMS (ESI$^+$): calc'd for $C_{25}H_{34}N_3O_5S$ $[M + H]^+$: *m/z* 488.2214, found 488.2211.

(*RS*)-Ethyl 3-([1,1'-biphenyl]-4-yl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method A, reaction in dichloromethane solvent. Colourless solid, yield 95 mg (36%); IR ν ($CHCl_3$)/cm^{-1} 3081, 3006, 1724, 1600, 1666, 1503, 948; ^{1}H NMR δ_H (400MHz, $CDCl_3$) 7.55 (4H, m), 7.45-7.33 (5H, m), 7.09 (1H, d, *J* 7.3 Hz), 6.83 (1H, br d, *J* 8 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.49 (1H, dt, *J* 8, 6 Hz), 4.08 (2H, q, *J* 7 Hz), 3.40 (2H, m), 2.97 (1H, dd, *J* 15.5, 6 Hz), 2.87 (1H, dd, *J* 15.5, 6 Hz), 2.68 (2H, m), 2.58 (2H, m), 2.30 (2H, m), 1.90 (2H, m), 1.73 (4H, m), 1.18 (3H, t, *J* 7 Hz); LRMS (ESI$^+$): *m/z* 486 $[M+H]^+$.

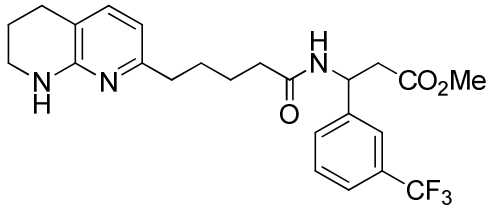
(*RS*)-Ethyl 3-(3-cyanophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method B. Colourless gum, yield 70 mg, (5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.57 (1H, s), 7.55 (1H, m), 7.42 (1H, t, *J* 7.8 Hz), 6.85 (1H, br d, *J* 8 Hz), 6.34 (1H, d, *J* 7.3 Hz), 5.42 (1H, m), 4.09 (2H, q, *J* 7 Hz), 3.39 (2H, m), 2.89 (1H, dd *J* 16, 5.5), 2.83 (1H, dd, *J* 16, 5.5 Hz), 2.69 (2H, m), 2.55

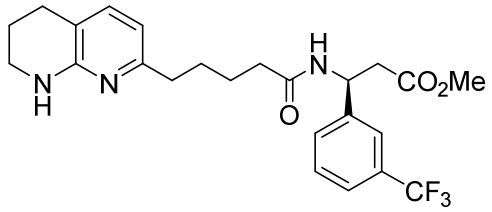
(2H, m), 2.27 (2H, m), 1.90 (2H, m), 1.70 (4H, m), 1.27 (3H, t, *J* 7 Hz); LRMS (ESI^+): *m/z* 435 $[M + H]^+$.

(*RS*)-Methyl 3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethylphenyl)-pentanamido)propanoate.



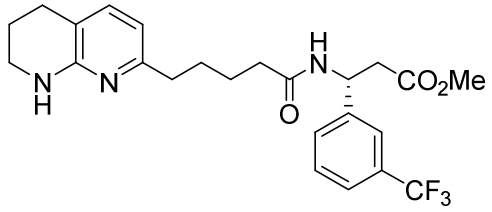
Method A. Colourless gum, yield 238 mg, (60%); IR ($CHCl_3$) ν (cm^{-1}) 3436, 2954, 2359, 1731, 1670, 1503, 1463, 1330, 1169, 1131, 1075; ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.57−7.34 (4H, m), 7.03 (1H, d, *J* 7.2 Hz), 6.79 (1H, d, *J* 8.0 Hz), 6.31 (1H, d, *J* 7.2 Hz), 5.58−5.31 (1H, m), 4.84 (1H, br s), 3.62 (3H, s), 3.44−3.28 (2H, m), 2.97−2.77 (2H, m), 2.72−2.59 (2H, m), 2.57−2.46 (2H, m), 2.24 (2H, m), 1.88 (2H, m), 1.75−1.59 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C ppm 172.5, 171.4, 157.3, 155.5, 141.9, 136.9, 130.9 (q, J_{CF} 32 Hz), 129.4, 124.4 (q, J_{CF} 4 Hz), 124.0 (q, J_{CF} 272 Hz), 122.9 (q, J_{CF} 4 Hz), 113.6, 111.3, 51.9, 49.0, 41.6, 39.6, 37.0, 36.4, 29.2, 26.2, 25.2, 21.4. HRMS (ESI^+): calc'd for $C_{24}H_{29}F_3N_3O_3$ $[M + H]^+$: *m/z* 464.2156, found 464.2161.

(*S*)-Methyl 3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethylphenyl)-pentanamido)propanoate.



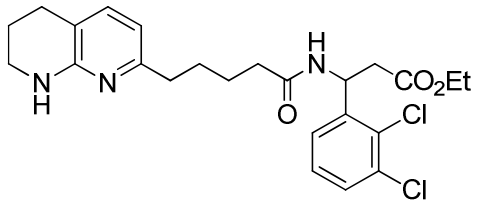
Method A. Colourless solid, yield 176 mg, (42%); mp 72–74 °C.

(*R*)-Methyl 3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethylphenyl)-pentanamido)propanoate



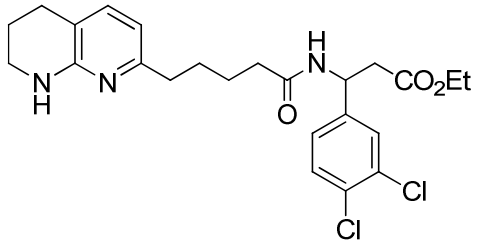
Method A. Colourless solid, yield 272 mg, (63%); mp 75–78 °C.

(*RS*)-Ethyl 3-(2,3-dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



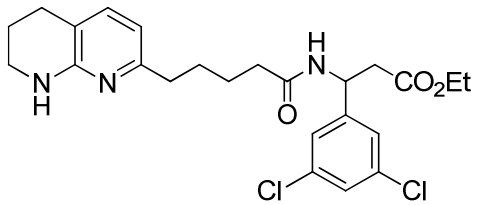
Method A. Colourless solid, yield 289 mg, (39%); Mp 150–151 °C; IR ($CHCl_3$) ν (cm^{-1}) 3438, 3008, 2938, 1721, 1673, 1599, 1503. ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.37 (1H, dd, *J* 8, 1.7 Hz), 7.25 (1H, dd, *J* 8, 1.7), 7.14 (1H, t, *J* 8 Hz), 7.04 (1H, d, *J* 7.3 Hz), 7.02 (1H, br d, *J* 8 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.69 (1H, dt, *J* 8, 5.7 Hz), 4.79 (1H, br s), 4.06 (2H, m), 3.39 (2H, m), 2.92 (1H, dd, *J* 16, 5.7 Hz), 2.87 (1H, dd, *J* 16, 5.7 Hz), 2.69 (2H, t, *J* 6.3 Hz), 2.54 (2H, m), 2.26 (2H, m), 1.90 (2H, m), 1.66 (4H, m), 1.16 (3H, t, *J* 7.2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.2, 171.2, 157.9, 155.7, 140.4, 136.6, 133.5, 129.5, 127.2, 125.9, 113.2, 111.4, 60.9, 48.0, 41.6, 37.9, 37.4, 36.4, 29.3, 26.3, 25.3, 21.5, 14.0. HRMS (ESI^+): calc'd for $C_{24}H_{30}Cl_2N_3O_3$ $[M + H]^+$: *m/z* 478.1659, found 478.1661.

(*RS*)-Ethyl 3-(3,4-dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method A. Colourless solid, yield 490 mg, 73% yield); IR ($CHCl_3$) ν (cm^{-1}) 3463, 2946, 1727, 1668. ^1H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.38 (1H, s), 7.36 (1H, d, *J* 8.3 Hz), 7.13 (1H, dd, *J* 8.3, 1.6 Hz), 7.07 (1H, d, *J* 7.3 Hz), 6.90 (1H, br d, *J* 8.3 Hz), 6.32 (1H, d, *J* 7.3), 5.36 (1H, dt, *J* 8.2, 6 Hz), 4.06 (2H, q, *J* 7.2 Hz), 3.40 (2H, m), 2.86 (1H, dd, *J* 15.8, 6 Hz), 2.79 (1H, dd, *J* 15.8, 6 Hz), 2.70 (2H, m), 2.55 (2H, m), 2.27 (2H, m), 1.90 (2H, m), 1.69 (4H, m), 1.19 (3H, t, *J* 7.2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.4, 170.9, 155.7, 155.4, 141.3, 136.9, 132.6, 131.4, 130.5, 130.3, 128.4, 125.9, 111.3, 61.0, 48.5, 41.5, 39.6, 37.0, 36.4, 29.2, 26.2, 25.2, 21.4, 14.0; LRMS (ESI^+): 478 $[M + H^+]$.

(*RS*)-Ethyl 3-(3,5-dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Method B. Colourless solid, yield 410 mg, (43%); R*f* 0.55 (2% EtOH in EtOAc); mp 99–100 °C; IR ($CHCl_3$) ν (cm^{-1}) 3436, 3084, 3008, 2938, 2863, 1724, 1672, 1598, 1503, 1464, 1446, 1378, 1351, 1298, 859; ^1H NMR (300 MHz, CD_3OD) δ_H ppm 7.33–7.30 (3H, m), 7.10 (1H, d, *J* 7.3 Hz), 6.34 (1H, d, *J* 7.3 Hz), 5.28 (1H, t, *J* 7.3 Hz), 4.08 (2H, q, *J* 7.3 Hz), 3.37 (2H, m), 2.80 (2H, d, *J* 7.3 Hz), 2.68 (2H, m), 2.49 (2H, m), 2.22 (2H, m), 1.86 (2H, m), 1.60 (4H, m), 1.18 (3H, t, *J* 7.3 Hz); ^{13}C NMR (75

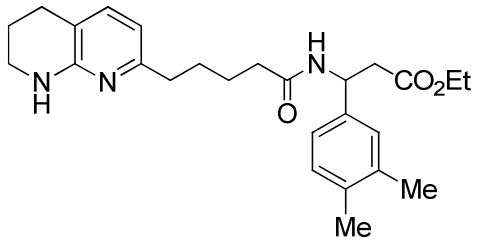
MHz, CD_3OD) δ_C ppm 174.1, 170.2, 157.3, 157.1, 145.7, 137.1, 134.9, 127.1, 125.2, 113.9, 110.8, 60.6, 49.5, 41.1, 39.9, 36.5, 35.4, 29.2, 26.1, 25.5, 21.1, 13.1; HRMS (ESI^+): calculated for $C_{24}H_{30}Cl_2N_3O_3$ $[M + H]^+$: *m/z* 478.1659, found 478.1659. Anal. calcd for $C_{24}H_{30}Cl_2N_3O_3$: C 60.36, H 6.13, N 8.80. Found C 60.27, H 6.17, N 8.68.

Racemic ethyl 3-(3,5-dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoate (340 mg) was dissolved in ethanol (28 mg/mL) and purified by preparative HPLC. Each injection was 1.2 mL (42 mg). The column used was a Lux cellulose-1, (250 x 21.2 mm, 5 µm particle size) and the eluent was heptane/ethanol = 80:20. No modifier was added and the flow rate was 21 mL/min and detection at 220 nm. The solvent was then evaporated and the residue was dried at 40°C / 25mbar to constant weight.
The final determination of chiral purity was performed by HPLC using a Lux cellulose-1 (250 x 4.6 mm, 5 µm particle size). The eluent was heptane:ethanol = 70:30 and the flow rate was 1 ml/min.

Ethyl 3-(3,5-dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoate – enantiomer 1
149 mg, R_t = 5.31 min, ee = 98.6%, achiral purity 98.8%

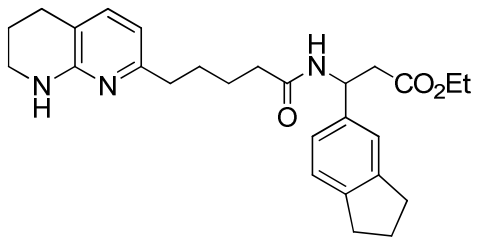
Ethyl 3-(3,5-dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoate – enantiomer 2
155 mg, R_t = 6.26 min, ee = 99.3%, achiral purity 98.7%

(*RS*)-Ethyl 3-(3,4-dimethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate



Method A. Colourless oil, yield 57 mg, (8%); IR ($CHCl_3$) ν (cm^{-1}) 3437, 3011, 2939, 1725, 1667, 1599, 1587, 1504, 1463, 1386, 1024. ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.00 (4H, m), 6.53 (1H, br d, *J* 8.3 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.37 (1H, dt, *J* 8, 6 Hz), 5.07 (1H, br s), 4.09 (2H, q, *J* 7 Hz), 3.39 (2H, m), 2.90 (1H, dd, *J* 15.6, 6.2 Hz), 2.79 (1H, dd, *J* 15.6, 6.2 Hz), 2.69 (2H, t, *J* 5.4 Hz), 2.56 (2H, m), 2.23 (6H, s), 1.90 (2H, quint, *J* 6 Hz), 1.69 (4H, m), 1.27 (2H, m), 1.18 (3H, t, *J* 8.3 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.1, 171.2, 157.6, 155.5, 138.1, 136.6, 135.7, 129.7, 127.6, 123.5, 113.2, 111.1, 77.2, 60.5, 49.1, 41.4, 40.1, 37.1, 36.4, 29.2, 26.2, 25.2, 21.3, 19.7, 19.3, 14.0. HRMS (ESI^+): calculated for $C_{26}H_{36}N_3O_3$ $[M + H]^+$: *m/z* 438.2751, found 438.2758.

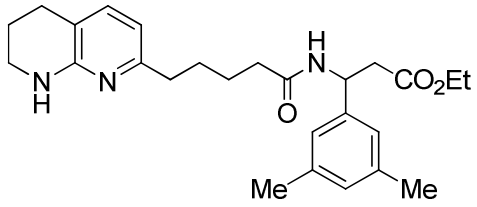
(*RS*)-Ethyl 3-(indan-4-yl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-pentanamido) propanoate.



Method A. Colourless oil, yield 169 mg, (59%); IR ($CHCl_3$) ν (cm^{-1}) 3691, 3438, 3011, 2950, 1726, 1665, 1600, 1588, 1505, 1447, 1386, 1030. ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.13 (2H, m), 7.03 (2H, m), 6.68 (1H, d, *J* 7.9 Hz), 6.29 (1H, d, *J* 7.3 Hz), 5.37 (1H, m), 5.15 (1H, br s), 4.05 (2H, q, *J*

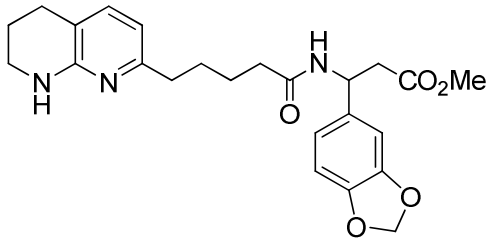
7.5 Hz), 3.34 (2H, m), 2.83 (6H, m), 2.66 (2H, t, *J* 6.3 Hz), 2.51 (2H, m), 2.20 (2H, m), 2.02 (2H, m), 1.87 (2H, m), 1.65 (4H, m), 1.15 (3H, t, *J* 7.5 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 171.6, 170.6, 157.0, 155.0, 144.1, 143.0, 138.1, 136.2, 123.8, 123.6, 121.8, 112.8, 110.6, 60.0, 49.0, 40.9, 39.7, 36.5, 35.9, 32.1, 31.9, 28.7, 25.7, 24.8, 24.7, 20.8, 13.5. HRMS (ESI^+): calcd for $C_{27}H_{35}N_3O_3$ $[M + H]^+$: *m/z* 450.2751, found 450.2761.

(*RS*)-Ethyl 3-(3,5-dimethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



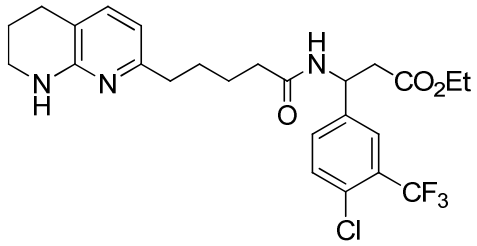
Method A. Yellow oil, yield 373 mg, (46%); IR ($CHCl_3$) ν (cm^{-1}) 3438, 3003, 2938, 2863, 2361, 2342, 1726, 1666, 1599, 1587, 1503, 1463, 1447, 1387, 1377, 1350, 1322, 1300. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.08 (1H, d, *J* 7.5 Hz), 6.89 (2H, s), 6.88 (1H, s), 6.60 (1H, br d, *J* 8.3 Hz), 6.33 (1H, d, *J* 7.5 Hz), 5.36 (1H, m), 4.07 (2H, m), 3.40 (2H, m), 2.89 (1H, dd, *J* 15.5, 6.4 Hz), 2.78 (1H, dd, *J* 15.5, 6 Hz), 2.69 (1H, m), 2.57 (2H, m), 2.27 (6H, s), 2.25 (2H, m), 1.90 (2H, m), 1.70 (4H, m), 1.17 (3H, t, *J* 7 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 175.2, 172.3, 158.6, 157.3, 142.7, 139.3, 138.4, 130.1, 125.5, 115.3, 112.3, 61.8, 51.5, 42.5, 42.2, 38.1, 37.0, 30.6, 27.5, 26.9, 22.6, 21.6, 14.8. LRMS (ESI^+): 438 $[M + H]^+$.

(*RS*)-Methyl 3-(benzo[*d*][1,3]dioxol-4-yl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoate.



Method A. Yellow oil, yield 190 mg, (39%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.07 (1H, d, *J* 7.3 Hz), 6.79 (1H, s), 6.77−6.73 (2H, m), 6.57 (1H, br d, *J* 8 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.95 (2H, s), 5.33 (1H, dt, *J* 8, 6 Hz), 5.01 (1H, br s), 3.63 (3H, s), 3.40 (2H, m), 2.90 (1H, dd, *J* 15.6, 6 Hz), 2.79 (1H, dd, *J* 15.6, 6 Hz), 2.71 (2H, m), 2.56 (2H, m), 2.24 (2H, m), 1.91 (2H, m), 1.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.2, 171.6, 159.9, 155.3, 147.9, 146.9, 137.0, 134.7, 119.5, 113.3, 111.3, 108.3, 107.3, 101.0, 51.8, 49.1, 41.5, 40.0, 36.9, 36.5, 29.2, 26.3, 25.2, 21.3.

(*RS*)-Ethyl 3-(3-chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoate.



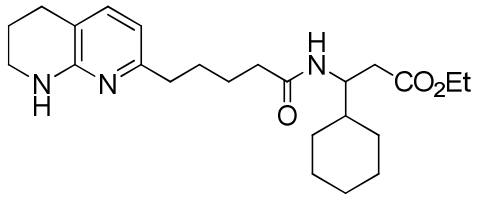
Method A (DMF solvent). Oil, yield 70 mg, (9%); IR ($CHCl_3$) ν (cm^{-1}) 3604, 3433, 3270, 2963, 1656, 1552, 1261, 1087, 823; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.60 (1H, s) 7.47−7.40 (2H, m), 7.07 (1H, d, *J* 7.5 Hz), 6.96 (1H, d, *J* 8.5 Hz), 6.33 (1H, d, *J* 7.5 Hz), 5.42 (1H, q, *J* 7 Hz), 4.91 (1H, br s), 4.09 (2H, m), 3.45 (2H, m), 2.89 (1H, dd, *J* 16, 6 Hz), 2.78 (1H, dd, *J* 16, 6 Hz), 2.72 (2H, m), 2.58 (2H, m), 2.33 (2H, m), 1.93 (2H, m), 1.70 (4H, m), 1.18 (3H, t, *J* 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.6, 170.9, 157.7, 155.6, 140.3, 136.8, 131.7, 131.3, 131.1 (q, J_{CF} 32 Hz), 131.0, 125.4 (q, J_{CF} 5 Hz), 122.7 (q, J_{CF} 273 Hz), 111.3, 61.2, 48.7, 41.5, 39.7, 37.2, 36.4, 29.2, 26.2, 25.3, 21.5, 14.0; HRMS (ESI^+): calc'd for $C_{25}H_{31}ClF_3N_3O_3$ $[M + H]^+$: *m/z* 512.1928, found 512.1897.

(*RS*)-Ethyl 3-(3-chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate (306 mg) was dissolved in ethanol (25 mg/mL) and purified by preparative HPLC. Each injection was 1.0 mL (25 mg). The column used was a Lux cellulose-1, (250 x 21.2 mm, 5 µm particle size) and the eluent was ethanol. No modifier was added and the flow rate was 21 mL/min and detection at 225 nm. The solvent was then evaporated and the residue was dried at 40°C / 25mbar to constant weight.
The final determination of chiral purity was performed by HPLC using a Lux cellulose-1 (250 x 4.6 mm, 5 µm particle size). The eluent was ethanol and the flow rate was 1 ml/min.

Ethyl 3-(3-chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoate – enantiomer 1
90 mg, R_t = 3.81 min, ee = 100%, achiral purity 98.7%

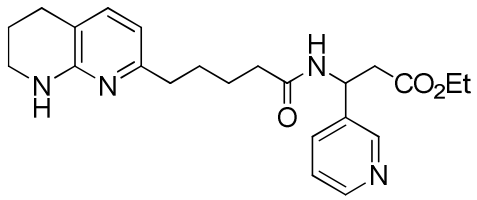
Ethyl 3-(3-chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoate – enantiomer 2
111 mg, R_t = 4.65 min, ee = 97.8%, achiral purity 97.8%

(*RS*)-Ethyl 3-(cyclohexyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoate.



Method A (dichloromethane solvent). Colourless solid, yield 406 mg, (51%); mp 108–110 °C; IR (state not recorded) ν (cm^{-1}) 3019, 2932, 1719, 1661, 1215, 759. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.07 (1H, d, *J* 7.2 Hz), 6.36 (1H, d, *J* 7.2 Hz), 4.15 (3H, m), 3.42 (2H, m), 2.71 (2H, t, *J* 6.4 Hz), 2.54 (1H, m), 2.22 (1H, m), 1.9 (2H, m), 1.73 (6H, m), 1.47 (1H, m), 1.17 (6H, m), 0.99 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.4, 172.3, 157.9, 155.6, 136.7, 113.3, 111.3, 60.6, 50.4, 41.6, 40.9, 37.4, 36.8, 30.9, 29.8, 29.4, 26.3, 25.9, 25.5, 24.0, 21.5, 14.2; HRMS (ESI^+): calc'd for $C_{24}H_{36}N_3O_3$ $[M + H]^+$: *m/z* 416.2908, found 416.2910.

(*RS*)-Ethyl 3-(3-pyridyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoate.

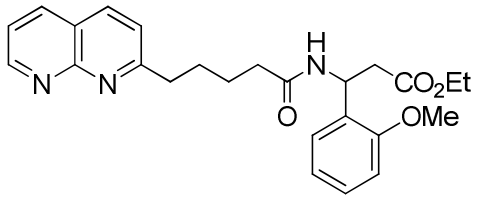


Method A. Pale orange oil, yield 388 mg, (59%); IR ($CHCl_3$) ν (cm^{-1}) 3631, 3436, 3008, 2943, 1725, 1674, 1598, 1503, 1017. ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm 8.58 (1H, d, *J* 1.5 Hz), 8.50 (1H, dd, *J* 4.8, 1.5 Hz), 7.63 (1H, dt, *J* 8, 1.5 Hz), 7.24 (1H, dd, *J* 8, 4.8 Hz), 7.05 (1H, d, *J* 7.3 Hz), 6.94 (1H, br d, *J* 8.3 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.46 (1H, dt, *J* 8.3, 6 Hz), 4.91 (1H, br s), 4.07 (2H, q, *J* 7.2 Hz), 3.38 (2H, m), 2.93 (1H, dd, *J* 16, 6 Hz), 2.84 (1H, dd, *J* 16, 6 Hz), 2.68 (2H, t, *J* 6.2 Hz), 2.54 (2H, m), 2.25 (2H, m), 1.89 (2H, m), 1.68 (4H, m), 1.17 (3H, t, *J* 7.2 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.5, 171.0, 166.3, 157.8, 151.9, 151.4, 148.0, 144.7, 136.7, 134.2, 123.4, 113.3, 61.0, 47.4, 41.6, 39.5, 37.2, 36.4, 29.2, 26.3, 25.2, 21.4, 14.0. HRMS (ESI^+): calc'd for $C_{23}H_{31}N_4O_3$ $[M + H]^+$: *m/z* 411.2391, found 411.2400.

The following compounds (**13**, R = 2-methoxy; 3-methyl; 3-trifluoromethoxy; 3,4-dimethoxy) were prepared via intermediates **12**, as shown in Scheme 4. For amide coupling procedures, see above.

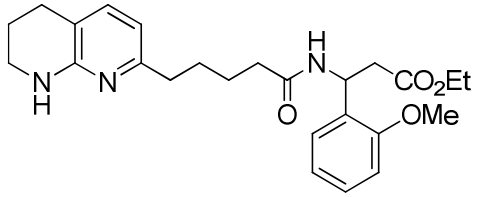
General method for hydrogenation of naphthyridine intermediate: 10% Palladium on charcoal (10% w/w) was added to a solution of the naphthyridine in ethanol (20 mL/g) and hydrogenated (1 bar) for 48 h at room temperature. The catalyst was filtered off and the filtrate concentrated under reduced pressure to give the tetrahydronaphthyridine ester.

(*RS*)-Ethyl 3-(2-methoxyphenyl)-3-(5-(1,8-naphthyridin-2- yl)pentanamido)propanoate.



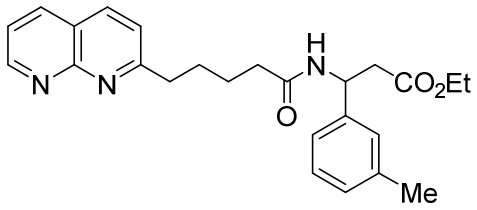
Method A (dichloromethane solvent). Pale pink oil, yield 131 mg, (31%); IR ($CHCl_3$) ν (cm^{-1}) 2927, 2855, 1726, 1667, 1465, 1245; ^1H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 9.03 (1H, dd, *J* 4.5, 2.0 Hz), 8.41 (1H, dd, *J* 8.0, 2.0 Hz), 8.36 (1H, d, *J* 10.0 Hz), 7.58 (1H, dd, *J* 8, 4 Hz), 7.51 (1H, d, *J* 8.0 Hz), 7.25−7.16 (2H, m), 6.96−6.83 (2H, m), 5.64−5.46 (1H, m), 4.01−3.89 (2H, m), 3.76 (3H, s), 2.95 (2H, m), 2.65 (1H, dd, *J* 15.0, 5.0 Hz), ~2.50 (1H, inferred, hidden by DMSO peak), 2.16 (2H, m), 1.79−1.68 (2H, m), 1.61−1.53 (2H, m), 1.05 (3H, t, *J* 7.0 Hz); LRMS (ESI^+): *m/z* 436 $[M + H]^+$.

(*RS*)-Ethyl 3-(2-methoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



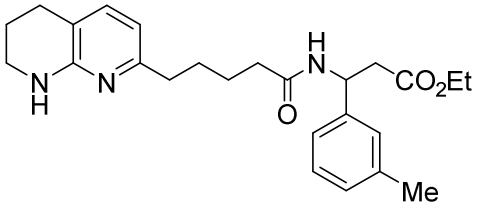
Pale pink oil, yield 99 mg, (76%); ^1H NMR (270 MHz, $CDCl_3$) δ_H ppm ^1H NMR δ_H (270 MHz, $CDCl_3$): 7.21 (1H, d, *J* 6.5 Hz), 7.05 (1H, d, *J* 7.5 Hz), 6.91-6.78 (3H, m), 6.30 (1H, d, *J* 7.5 Hz), 5.62−5.53 (1H, m), 4.01 (2H, q, *J* 7.0 Hz), 3.86 (3H, s), 3.41−3.36 (2H, m), 2.90 (1H, dd, *J* 15.0, 6.5 Hz), 2.78 (1H, dd, *J* 15.0, 6.5 Hz), 2.67 (2H, m), 2.54 (2H, m), 2.21 (2H, m), 1.96−1.84 (2H, m), 1.68−1.61 (4H, m), 1.14 (3H, t, *J* 7.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 171.9, 171.4, 157.2, 156.9, 155.5, 137.1, 128.9, 128.8, 128.2, 120.8, 113.7, 111.3, 110.9, 60.6, 55.4, 47.7, 41.6, 39.5, 37.1, 36.8, 29.4, 26.4, 25.4, 21.4, 14.2; LRMS (ESI^+): *m/z* 440 $[M + H]^+$.

(*RS*)-Ethyl 3-(3-methylphenyl)-3-(5-(1,8-naphthyridin-2-yl)pentanamido)propanoate.



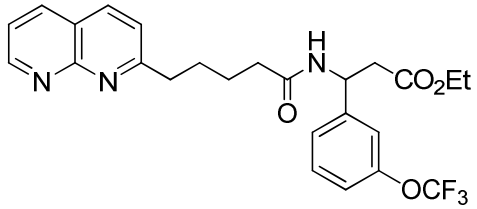
Method A (dichloromethane solvent), yield 459 mg, (67%); ^{1}H NMR (270 MHz, $CDCl_3$) δ_H ppm 9.05 (1H, dd, *J* 4, 2 Hz), 8.14 (1H, dd, *J* 8, 2 Hz), 8.07 (1H, d, *J* 8.4 Hz), 7.42 (1H, dd, *J* 8, 4 Hz), 7.35 (1H, d, *J* 8.4 Hz), 7.16 (1H, m), 7.07-7.00 (3H, m), 6.64 (1H, br d, *J* 8.4 Hz), 5.37 (1H, m), 4.02 (2H, q, *J* 7 Hz), 3.80 (2H, m), 3.05 (2H, m), 2.89 (1H, dd, *J* 16, 6 Hz), 2.77 (1H, dd, *J* 16, 6 Hz), 2.27 (3H, s), 1.93 (2H, m), 1.76 (2H, m), 1.12 (3H, t, *J* 7 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.1, 170.8, 166.6, 155.5, 153.3, 141.1, 140.8, 137.0, 136.8, 128.6, 128.3, 127.3, 123.3, 123.1, 122.7, 121.5, 60.8, 49.6, 38.7, 36.5, 28.5, 25.4, 21.5, 14.1. HRMS (ESI$^+$): calc'd for $C_{25}H_{29}N_3O_3$ $[M + H]^+$: *m/z* 420.2288, found 420.2292.

(*RS*)-Ethyl 3-(3-methylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



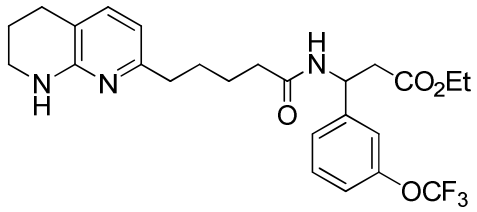
Yield 416 mg, (96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm: 7.21 (1H, t, *J* 7.4 Hz), 7.05−7.14 (4H, m), 6.66 (1H, d, *J* 8.3 Hz), 6.33 (1 H, d, *J* 7.3 Hz), 5.41 (1H, dt, *J* 8, 6 Hz), 4.08 (2 H, q, *J* 7 Hz), 3.39−3.45 (2H, m), 2.92 (1H, dd, *J* 15, 6 Hz), 2.82 (1H, dd, *J* 15, 6 Hz), 2.71 (2H, m), 2.59 (2H, m), 2.33 (3H, s), 2.27 (2H, m), 1.88-1.96 (2H, m), 1.72 (4H, m), 1.18 (3H, t, *J* 7 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm: 172.2, 171.3, 140.8, 138.3, 131.0, 128.9, 128.6, 128.3, 127.3, 123.4, 112.7, 111.0, 60.8, 49.6, 41.5, 40.3, 38.8, 36.4, 30.4, 29.1, 26.1, 21.5, 21.0, 14.2. HRMS (ESI$^+$): calc'd for $C_{25}H_{34}N_3O_3$ $[M+H]^+$: *m/z* 424.2595, found 424.2601.

(*RS*)-Ethyl 3-(5-(1,8-naphthyridin-2-yl)-3-(3-trifluoromethoxyphenyl) pentanamido) propanoate.



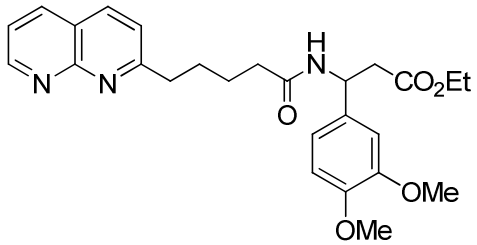
Method A. yellow oil, yield 312 mg, (30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 9.09 (1H, br s), 8.17 (1H, dd, *J 8.3,* 2 Hz), 8.10 (1H, d, *J* 8.3 Hz), 7.46 (1H, dd, *J* 4.2, 8 Hz), 7.37 (1H, d, *J* 8.3 Hz), 7.31 (1H, t, *J* 8 Hz), 7.17 (1H, s), 7.11-7.08 (2H, m), 5.48 (1H, m), 4.074 (2H, q, *J* 7 Hz), 3.07 (2H, t, *J* 7.5 Hz), 2.94 (1H, dd, *J* 16, 6 Hz), 2.85 (1H, dd, *J* 16, 6 Hz), 2.34 (2H, t, *J* 7.5 Hz), 1.95 (2H, m), 1.77 (2H, m), 1.14 (3H, t, *J* 7 Hz). LRMS (ESI$^+$): 490 $[M + H]^+$.

(*RS*)-Ethyl 3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethoxyphenyl) pentanamido)propanoate.



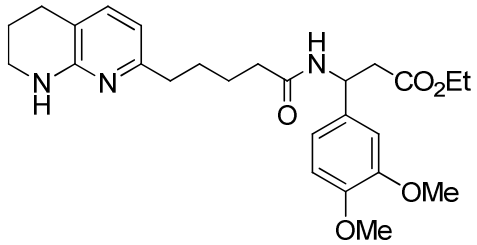
Yellow solid, yield 230 mg, (76%); Mp >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.36 (1H, t, *J* 8 Hz), 7.25 (1H, d, *J* 8 Hz), 7.15 (1H, s), 7.12 (1H, m), 7.08 (1H, d, *J* 7.3 Hz), 6.84 (1H, br d, *J* 10.5 Hz), 6.35 (1H, d, *J* 7.3 Hz), 5.49-5.42 (1H, m), 5.04 (1H, br s), 4.08 (2H, q, *J* 7 Hz), 3.39 (2H, m), 2.92 (1H, dd, *J* 15.5, 7.5 Hz), 2.83 (1H, dd, *J* 15.5, 7.5 Hz), 2.71 (2H, t, *J* 6 Hz), 2.60-2.55 (2H, m), 2.32-2.27 (2H, m), 1.96-1.88 (2H, m), 1.72 (4H, m), 1.18 (3H, t, *J* 7 Hz). LRMS (ESI^+): 494 $[M + H]^+$.

(*RS*)-Ethyl 3-(3,4-dimethoxyphenyl)-3-(5-(1,8-naphthyridin-2-yl)pentanamido)propanoate.



Method A (DMF solvent). Colourless oil, yield 333 mg, (33%); IR ($CHCl_3$) ν (cm^{-1}) 3433, 2928, 2855, 1727, 1670, 1500, 1256; ^{1}H NMR (270 MHz, $(CD_3)_2SO$) δ_H ppm 9.02 (1H, dd, *J* 4.5, 2.0 Hz), 8.41 (1H, dd, *J* 8.3, 2.0 Hz), 8.36 (1H, d, *J* 8.3 Hz), 8.30 (1H, d, *J* 8.7 Hz), 7.57 (1H, dd, *J* 8.3, 4.5 Hz), 7.50 (1H, d, *J* 8.3 Hz), 6.90 (1H, d, *J* 1.5 Hz), 6.84 (1H, d, *J* 8.3 Hz), 6.79 (1H, dd, *J* 8.3, 1.5 Hz), 5.16 (1H, q, *J* 8 Hz), 3.94 (2H, m), 3.69 (3H, s), 3.68 (3H, s), 2.94 (2H, t, *J* 8.0 Hz), 2.68 (2H, d, *J* 8 Hz), 2.14 (2H, m), 1.79−1.68 (2H, m), 1.61−1.50 (2H, m), 1.06 (3H, t, *J* 7.0 Hz); ^{13}C NMR (67.5 MHz, $(CD_3)_2SO$) δ_C ppm 171.1, 170.2, 165.8, 155.3, 153.2, 148.5, 147.8, 137.6, 137.3, 134.8, 122.9, 121.6, 120.9, 118.3, 111.5, 110.3, 59.9, 55.5, 55.4, 49.0, 38.1, 35.3, 28.3, 25.2, 20.8, 14.0; LRMS (ESI^+): *m/z* 466 $[M + H]^+$.

(*RS*)-Ethyl 3-(3,4-dimethoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoate.



Colourless oil, yield 146 mg, (44%) after purification by column chromatography. IR ($CHCl_3$) ν (cm^{-1}) 3436, 2927, 2855, 1726, 1657, 1516, 1257; ^{1}H NMR (270 MHz, $CDCl_3$) δ_H ppm 7.15 (1H, d, *J* 7.3 Hz), 6.89-6.77 (4H, m), 6.32 (1H, d, *J* 7.3 Hz), 5.40 (1H, m), 4.07 (2H, q, *J* 7.2 Hz), 3.86 (3H, s), 3.85 (3H, s), 3.43 (2H, m), 2.94 (1H, dd, *J* 15.5, 6.5 Hz), 2.82 (1H, dd, *J* 15.5, 6.5 Hz), 2.71 (2H, t, *J* 6.0 Hz), 2.60 (2H, m), 2.29 (2H, m), 1.92 (2H, m), 1.71 (4H, m), 1.18 (3H, t, *J* 7.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ_C ppm 172.2, 171.3, (expected peak at ca 156 ppm not observed or overlapped with peak at 155.2), 155.2, 148.9, 148.3, 137.2, 133.4, 125.1, 118.2, 114.0, 111.1, 110.1, 60.7,

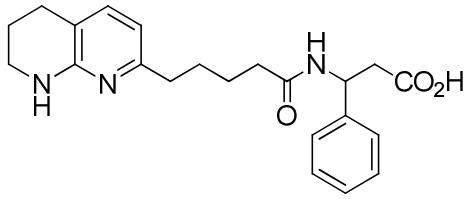
55.9, 55.8, 49.2, 41.5, 40.1, 36.6 (2 x C), 29.2, 26.2, 25.2, 21.2, 14.1; LRMS (ESI^+): *m/z* 470 $[M+H]^+$.

(iii) Derivatives of 3-phenyl-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoic acid (4 and 15−43).

Ester hydrolysis – Method A (NaOH). A solution of the ester (1 eq.) was treated with 1M aqueous NaOH (1.5 eq.) in EtOH at room temperature for 16 h. The solvent was removed under reduced pressure the residue was dissolved in water. The solution was applied to the top of a Waters Oasis™ separation cartridge and eluted with water then MeOH:H_2O (typically 50:50 to 70:30). Fractions containing product were combined and the solvent removed under reduced pressure to give the product. Methanol was used instead of ethanol for methyl esters.

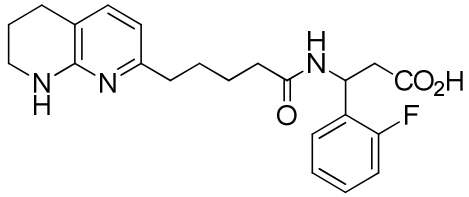
Ester hydrolysis – Method B (LiOH). A solution of the ester (1 eq.) was treated with LiOH (2 eq.) in THF/H_2O (1:1) at room temperature for 16 h. Workup and purification as above gave the product.

(*RS*)-3-Phenyl-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoic acid (15).[12]



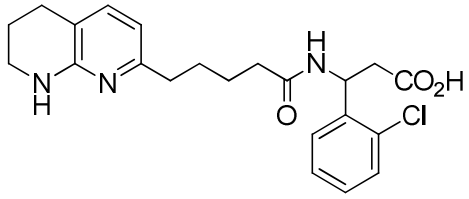
Method A (methanol solvent). Colourless gum, yield 62 mg, (65%); IR (state not recorded) ν (cm^{-1}) 3019, 1519, 1215, 760. ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.31 (2H, d *J* 7 Hz), 7.23 (2H, t, *J* 7.8 Hz), 7.16 (2H, m), 6.33 (1H, d, *J* 7.2 Hz), 5.29 (1H, m), 3.35 (2H, m), 2.67 (2H, m), 2.58-2.47 (4H, m), 2.21 (2H, m), 1.84 (2H, m), 1.61 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_H ppm 175.0 (2C), 156.2, 156.0, 144.6, 139.7, 129.5 (2C), 128.0, 127.6 (2C), 116.9, 112.0, 52.9, 42.3, 36.9, 36.6, 30.3, 27.2, 26.6, 22.0. HRMS (ESI^+): calc'd for $C_{22}H_{27}N_3O_3$ $[M + H]^+$: *m/z* 382.2125, found 382.2130. LCMS purity 100% (ELSD), 382 (MH^+).

(*RS*)-3-(2-Fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (16).



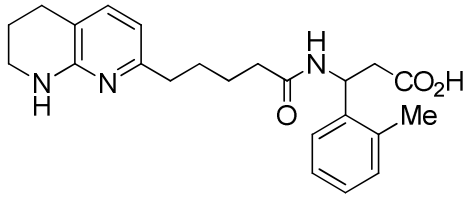
Pale yellow solid, yield 28 mg (17%); ^1H NMR δ_H (400 MHz, CD_3OD) 7.39 (1H, t, *J* 7 Hz), 7.21 (1H, m), 7.10 (1H, d, *J* 7.3 Hz), 7.06 (2H, t, *J* 7.5 Hz), 7.00 (1H, m), 6.32 (1H, d, *J* 7.3 Hz), 5.50 (1H, t, *J* 6.6 Hz), 3.37 (2H, m), 2.69 (2H, m), 2.62 (2H, m), 2.49 (2H, m), 2.24 (2H, m), 1.87 (2H, m), 1.61 (4H, m); ^{13}C NMR δ_C (100 MHz, CD_3OD): 178.6, 175.1, 162.5 (d, J_{CF} 244 Hz), 158.4, 157.2, 138.6, 131.3, 129.7 (d, J_{CF} 8 Hz), 129.5 (d, J_{CF} 4 Hz), 125.2, 125.1, 116.3 (d, J_{CF} 22 Hz), 115.4, 112.3, peak expected at *ca.* 108 not observed, 47.7, 44.0, 42.6, 37.9, 37.1, 30.7, 27.5, 26.8, 22.6; HRMS (ESI^+): *m/z* 400 $[M+H]^+$. LCMS purity 100% (ELSD), 400 (MH^+).

(*RS*)-3-(2-Chlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoic acid (17).



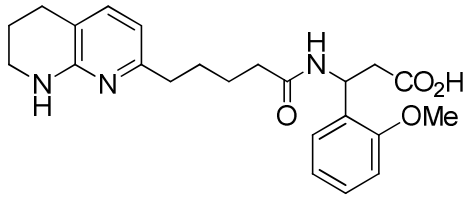
Method A. Colourless powder, yield 40 mg, (59%); Mp 180–182 °C; IR ($CHCl_3$) ν (cm^{-1}) 3293, 3067, 2930, 2865, 1671, 1645, 1394, 1375, 763. ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.56 (1H, d, *J* 7.5 Hz), 7.39 (2H, m), 7.30−7.22 (2H, m), 6.58 (1H, d, *J* 7.5 Hz), 5.71 (1H, dd, *J* 9.5, 5 Hz), 3.49 (2H, m), 2.83−2.73 (4H, m), 2.69 (2H, m), 2.30 (2H, m), 1.95 (2H, m), 1.76−1.61 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 175.1, 174.0, 159.4, 158.9, 143.0, 134.0, 131.0, 128.7, 128.5, 120.8, 112.0, 54.6, 42.4, 40.1, 36.3, 33.4, 29.4, 26.6, 26.0, 20.1. HRMS (ESI^+): calc'd for $C_{22}H_{27}{}^{35}ClN_3O_3$ $[M + H]^+$: *m/z* 416.1736, found 416.1730. LCMS purity 100% (ELSD), 416, 418 (MH^+).

(*RS*)-3-(2-Methylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (18).



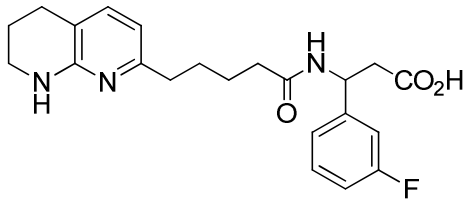
Method A. colourless oil, yield 31 mg, (52%); IR ($CHCl_3$) ν (cm^{-1}) 3693, 3605, 3262, 3066, 3006, 2946, 2866, 2471, 1953, 1666, 1599, 1511, 1463, 1437, 1391, 1323, 1292. ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.43 (1H, d, *J* 7.3 Hz), 7.31 (1H, d, *J* 7.3 Hz), 7.12 (3H, m), 6.48 (1H, d, *J* 7.3 Hz), 5.58 (1H, d, *J* 10, 4.7 Hz), 3.46 (2H, m), 3.20 (2H, t, *J* 6.4), 2.79−2.68 (4H, m), 2.63−2.49 (3H, m), 2.46 (3H, m), 2.36 (1H, s), 2.20 (1H, m), 1.95−1.89 (2H, m), 1.81−1.67 (4H, m). ^{13}C NMR (125 MHz, CD_3OD) δ_C ppm 171.4, 173.4, 157.0, 141.3, 137.0, 135.3, 129.8, 128.2, 125.6, 125.1, 113.8, 110.8, 106.7, 43.1, 41.0, 36.4, 35.5, 29.3, 29.2, 26.0, 25.3, 21.0, 18.0. LCMS purity 88% (ELSD), 396 (MH^+).

(*RS*)-3-(2-Methoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (19).



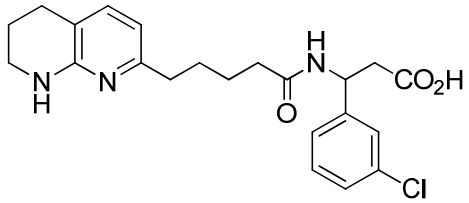
Method A. Colourless solid, yield 48 mg, (51%); Mp 176–178 °C; IR (neat) ν (cm^{-1}) 3249, 2928, 2837, 1642, 1574, 1392, 1237; ^{1}H NMR (270 MHz, CD_3OD) δ_H ppm 7.26−7.11 (3H, m), 6.90 (1H, d, *J* 8 Hz), 6.83 (1H, t, *J* 8 Hz), 6.34 (1H, d, *J* 7.5 Hz), 5.51 (1H, m), 3.82 (3H, s), 3.37 (2H, m), 2.69 (2H, m), 2.60 (2H, m), 2.51 (2H, m), 2.25 (2H, m), 1.87 (2H, m), 1.62 (4H, m); ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 179.4, 174.9, 158.3, 158.2, 157.1, 138.7, 132.1, 129.2, 128.3, 121.4, 115.6, 112.3, 111.8, 55.9, 43.6, 42.5, 37.8, 37.3, 30.7, 27.5, 26.8, 22.5; LRMS (ESI^+) *m/z* 412 $[M+H]^+$; LCMS purity 98% (ELSD), 412 (MH^+).

(*RS*)-3-(3-Fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (4).[13]



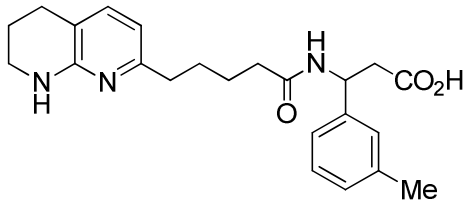
Colourless oil, yield 168 mg, (62%); ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.27 (1H, dt, *J* 6, 8 Hz), 7.17 (2H, m), 7.08 (1H, d, *J* 10 Hz), 6.91 (1H, dt, *J* 3, 8 Hz), 6.36 (1H, d, *J* 7.3 Hz), 5.29 (1H, t, *J* 7 Hz), 3.39 (2H, m), 2.71 (2H, m), 2.59 (2H, d, *J* 7 Hz), 2.53 (2H, m), 2.25 (2H, m), 1.88 (2H, m), 1.64 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 178.9, 175.2, 164.5 (d, J_{CF} 244 Hz), 157.0, 156.6, 147.6 (d, J_{CF} 7 Hz), 139.3, 131.1 (d, J_{CF} 8 Hz), 123.5 (d, J_{CF} 3 Hz), 116.3, 114.6 (d, J_{CF} 13 Hz), 114.4 (d, J_{CF} 14 Hz), 112.1, 52.6, 45.5, 42.4, 37.2, 37.0, 30.5, 27.4, 26.7, 22.3. HRMS (ESI$^+$): calc'd for $C_{23}H_{26}FN_3O_3$ $[M + H]^+$: *m/z* 400.2036, found 400.2045. LCMS purity 100% (ELSD), 400 (MH^+).

(*RS*)-3-(3-Chlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (20).



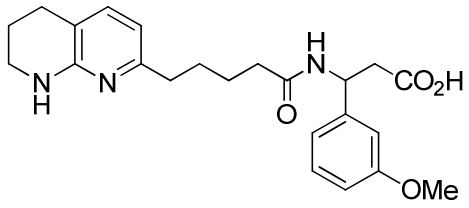
Method A. Colourless solid, yield 40 mg, (28%); Mp 116–117 °C; IR ($CHCl_3$) ν (cm^{-1}) 3256, 2927, 1582, 1395, 1259, 1078, 794; ^{1}H NMR (400 MHz, CD_3OD): δ_H ppm 7.36 (1H, s), 7.29-7.23 (2H, m), 7.20-7.15 (2H, m), 6.35 (1H, d, *J* 7.5 Hz), 5.26 (1H, t, *J* 7 Hz), 3.38 (2H, m), 2.70 (2H, m), 2.58 (2H, d, *J* 7 Hz), 2.53 (2H, m), 2.25 (2H, m), 1.88 (2H, m), 1.63 (4H, m); HRMS (ESI$^+$): calculated for $C_{27}H_{27}ClN_3O_3$ $[M + H]^+$: *m/z* 416.1741, found 416.1740. LCMS purity 100% (ELSD), 416, 418 (MH^+).

(*RS*)-3-(3-Methylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (21).



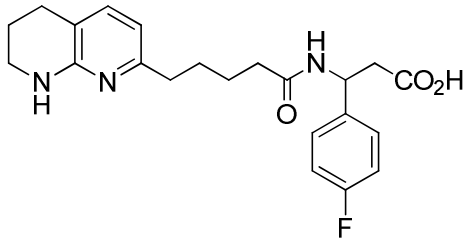
Method A. yellow crystalline solid, yield 143 mg, (38%); mp 230 °C (dec.); IR (neat) ν (cm^{-1}) 3249, 2925, 2857, 1639, 1581. ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.16-7.12 (4H, m), 6.99 (1H, m), 6.34 (1H, d, *J* 7.3 Hz), 5.27 (1H, t, *J* 7 Hz), 3.39 (2H, m), 2.69 (2H, m), 2.58 (2H, d, *J* 7 Hz), 2.52 (2H, m), 2.28 (3H, s), 2.25 (2H, m), 1.87 (2H, m), 1.63 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 179.3, 175.0, 157.3, 156.7, 144.5, 139.1, 139.0, 129.4, 128.6, 128.3, 124.7, 116.1, 112.0, 52.8, 42.5, 37.3, 37.1, 30.5, 27.4, 26.7, 22.3, 21.7, 15.6. HRMS (ESI$^+$): calculated for $C_{23}H_{30}N_3O_3$ $[M + H]^+$: *m/z* 396.2282, found 396.2277. LCMS purity 100% (ELSD), 396 (MH^+).

(*RS*)-3-(3-Methoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (22).



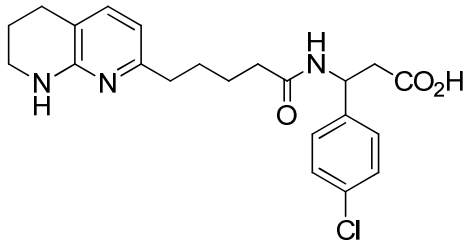
Method A. Colourless solid, yield 36 mg, (44%); IR ($CHCl_3$) ν (cm^{-1}) 3005, 2943, 1667, 1600. ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.17 (2H, m), 6.92 (2H, m), 6.72 (1H, dd, *J* 8, 2.5 Hz), 6.35 (1H, d, *J* 7.3 Hz), 5.27 (1H, t, *J* 7 Hz), 3.75 (3H, s), 2.71 (2H, t, *J* 6.3 Hz), 2.58 (2H, d, *J* 7 Hz), 2.53 (2H, m), 2.26 (2H, m), 1.88 (2H, m), 1.64 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 179.3, 175.1, 161.3, 157.1, 156.7, 146.3, 139.2, 130.4, 119.9, 116.3, 113.6, 113.2, 112.2, 55.7, 52.9, 45.7, 42.5, 37.2, 37.1, 30.5, 27.4, 26.8, 22.3. HRMS (ESI$^+$): calculated for $C_{25}H_{29}N_3O_4$ $[M + Na]^+$: *m/z* 434.2050, found 434.2041. LCMS purity 100% (ELSD), 412 (MH^+).

(*RS*)-3-(4-Fluorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (23).



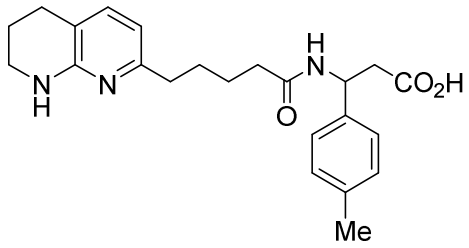
Method A. Colourless oil, yield 48 mg, (39%); IR ($CHCl_3$) ν (cm^{-1}) 3993, 3007, 2934, 1588, 1446, 1261, 1117, 865. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.35 (2H, dd, *J* 8.6, 5 Hz), 7.27 (1H, d, *J* 7.3 Hz), 7.00 (2H, t, *J* 8.6 Hz), 6.40 (1H, d, *J* 7.3 Hz), 6.31 (1H, t, *J* 7 Hz), 3.42 (2H, m), 2.74 (2H, m), 2.64-2.52 (4H, m), 2.33-2.18 (2H, m), 1.90 (2H, m), 1.66 (4H, m). HRMS (ESI$^+$): calc'd for $C_{22}H_{27}FN_3O_3$ $[M + H]^+$: *m/z* 400.2036, found 400.2024. LCMS purity 100% (ELSD), 400 (MH^+).

(*RS*)-3-(4-Chlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (24).



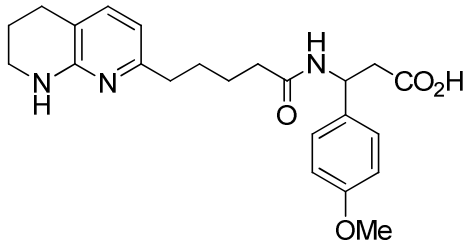
Colourless solid, yield 20 mg (15%); mp 163–165 °C (from MeOH); IR ($CHCl_3$) ν (cm^{-1}) 3256, 3004, 2805, 1724, 1670; ^{1}H NMR (400 MHz, CF_3CO_2D) δ_H ppm 7.65 (1H, d, *J* 7.3 Hz), 7.45 (2H, d, *J* 8.3 Hz), 7.40 (2H, d, *J* 8.3 Hz), 6.66 (1H, d, *J* 7.3 Hz), 5.66 (1H, m), 3.68 (2H, m), 3.29 (1H, dd , *J* 16.8, 8.3 Hz), 3.20 (1H, dd, *J* 16.8, 8.3 Hz), 2.97 (2H, m), 2.78 (4H, m), 2.15 (2H, m), 1.89 (4H, m); ^{13}C NMR (100 MHz, CF_3CO_2D) δ_C ppm 179.0, 174.3, 153.3, 148.9, 144.2, 137.9, 137.3, 131.2 (2C), 129.5 (2C), 122.2, 113.1, 53.5, 43.2, 40.8, 36.4, 34.1, 29.4, 26.9, 26.8, 20.6; LRMS (ESI$^+$) 416 $[M + H]^+$. LCMS purity 100% (ELSD), 416, 418 (MH^+).

(*RS*)-3-(4-Methylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (25).



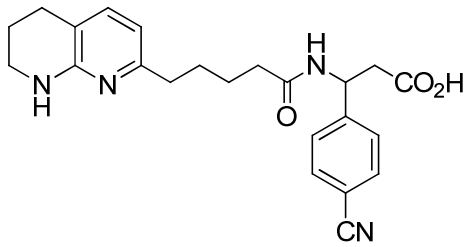
Colourless oil, yield 200 mg (71%); IR ($CHCl_3$) ν (cm^{-1}); 3312, 3285-2751, 2950, 1719, 1417, 1285, 811; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm; 7.28 (1H, d, *J* 7.3 Hz), 7.22 (2H, d, *J* 8 Hz), 7.08 (2H, d, *J* 8 Hz), 6.40 (1H, d, *J* 7.3 Hz), 5.31 (1H, t, *J* 7.3 Hz), 3.41 (2H, m), 2.73 (2H, t, *J* 6 Hz), 2.63 (1H, dd, *J* 14.5, 7 Hz), 2.55 (1H, dd, *J* 15.5, 7 Hz), 2.30 (1H, m), 2.28 (3H, s), 2.21 (1H, m), 1.90 (2H, m), 1.66 (4H, m); ^{13}C NMR (75 MHz, CD_3OD) δ_C ppm; 178.3, 173.4, 154.0, 152.8, 139.9, 138.9, 136.1, 128. 6, 125.9, 116.3, 110.3, 51.1, 44.3, 40.7, 35.3, 34.3, 28.5, 25.5, 25.0, 20.2, 19.8; LRMS (ESI^+): 396 $[M + H]^+$; LCMS purity 100% (ELSD), 396 (MH^+).

(*RS*)-3-(4-Methoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (26).



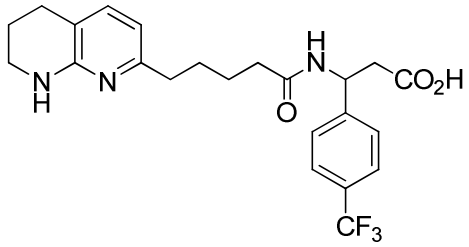
Method A (methanol solvent). Colourless solid, yield 149 mg, (77%); IR (state not recorded) ν (cm^{-1}) 3257, 2929, 1570, 772; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.26 (2H, d, *J* 8.6 Hz), 7.14 (1H, d, *J* 7.3 Hz), 6.81 (2H, d, *J* 8.6 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.25 (1H, t, *J* 7 Hz), 3.74 (3H, s), 3.37 (2H, m), 2.69 (2H, t, *J* 6.4 Hz), 2.59 (2H, d, *J* 7.5 Hz), 2.51 (2H, m), 2.23 (2H, m), 1.87 (2H, m), 1.62 (4H, m); HRMS (ESI^+): calculated for $C_{23}H_{29}N_3O_4$ $[M + H]^+$: *m/z* 412.2231, found 412.2230. LCMS purity 100% (ELSD), 412 (MH^+).

(*RS*)-3-(4-Cyanophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (27).



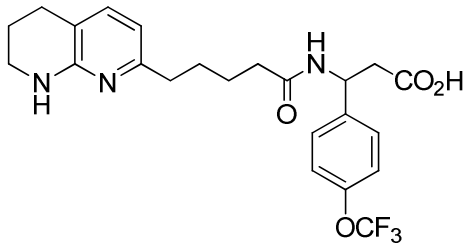
Method B. Colourless solid, yield 70 mg, (37%); mp 140 °C; IR ($CHCl_3$) ν (cm^{-1}) 3271, 2934, 2863, 2231, 1649, 1600, 1507, 1464, 1414, 1323, 1249; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.62 (2H, d, *J* 8.3 Hz), 7.51 (2H, d, *J* 8.3 Hz), 7.17 (1H, d, *J* 7.3 Hz), 6.34 (1H, d, *J* 7.3 Hz), 5.31 (1H, t, *J* 7 Hz), 3.39 (2H, m), 2.71 (2H, t, *J* 6.2 Hz), 2.60 (2H, d, *J* 7 Hz), 2.51 (2H, m), 2.25 (2H, m), 1.88 (2H, m), 1.63 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 176.9, 173.8, 155.8, 155.2, 149.0, 137.6, 131.9, 127.3, 118.4, 114.6, 110.6, 110.1, 51.3, 43.5, 40.9, 35.8, 35.4, 29.0, 25.8, 25.2, 20.8. HRMS (ESI^+): calculated for $C_{23}H_{27}N_4O_3$ $[M + H]^+$: *m/z* 407.2078, found 407.2096.

(*RS*)-3-(5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-3-(4-trifluoromethylphenyl) pentanamido)propanoic acid (28).



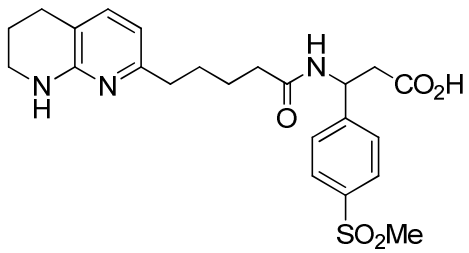
Method A. Colourless solid, yield 28 mg, (28%); IR ($CHCl_3$) ν (cm^{-1}) 3271, 2938, 1653, 1327, 1127. ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.55 (4H, m), 7.16 (1H, d, *J* 7.3 Hz), 6.35 (1H, d, *J* 7.3 Hz), 5.34 (1H, t, *J* 7 Hz), 3.38 (m, obscured by solvent peak), 2.70 (2H, m), 2.62 (2H, d, *J* 7 Hz), 2.53 (2H, m), 2.27 (2H, m), 1.87 (2H, m), 1.63 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 178.7, 175.3, 157.2, 156.7, 149.3, 139.2, 130.1 (q, J_{CF} 32 Hz), 128.4 (2C), 126.3 (q, J_{CF} 4 Hz, 2C), 126.0 (q, J_{CF} 268 Hz), 116.2, 112.1, 52.7, 45.3, 42.5, 37.3, 37.0, 30.5, 27.4, 26.7, 22.3. HRMS (ESI^+): calc'd for $C_{23}H_{26}F_3N_3O_3$ $[M + H]^+$: *m/z* 450.2021, found 450.2021. LCMS purity 100% (ELSD), 450 (MH^+).

(*RS*)-3-(5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-3-(4-trifluoromethoxyphenyl) pentanamido)propanoic acid (29).



Method B. Colourless oil, yield 26 mg, (55%); IR ($CHCl_3$) ν (cm^{-1}) 3634, 3392, 3011, 1638, 1561, 1510, 1262, 1171. ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.58 (1H, d, *J* 7.3 Hz), 7.45 (2H, d, *J* 8.1 Hz), 7.22 (2H, d, *J* 8.1 Hz), 6.59 (1H, d, *J* 7.3 Hz), 5.36 (1H, dd, *J* 8.2, 6.0 Hz), 3.50 (2H, m), 2.81 (4H, m), 2.68 (2H, m), 2.27 (2H, m), 1.96 (2H, m), 1.65 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 175.1, 173.9, 152.8, 149.5, 143.2, 142.6, 129.7, 129.6 (2C), 122.3 (2C), 120.8, 112.1, 51.1, 42.5, 41.5, 36.3, 33.4, 29.3, 26.6, 26.0, 20.7; O*C*F_3 not observed due to poor signal/noise. HRMS (ESI^+): calculated for $C_{23}H_{27}F_3N_3O_4$ $[M + H]^+$: *m/z* 466.1948, found 466.1946. LCMS purity 93% (ELSD), 466 (MH^+).

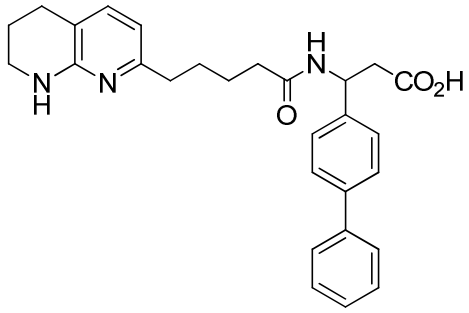
(*RS*)-3-(4-Methanesulfonylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid (30).



Method A. Colourless solid, yield 122 mg, (69%); mp 137 °C; IR (neat) ν (cm^{-1}) 3267, 2926, 2858, 1647, 1583, 1461, 1391, 1302, 1146, 1089; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.84 (2H, d, *J* 8.3 Hz), 7.60 (2H, d, *J* 8.3 Hz), 7.21 (1H, d, *J* 7.3 Hz), 6.37 (1H, d, *J* 7.3 Hz), 5.36 (1H, t, *J* 7 Hz), 3.42

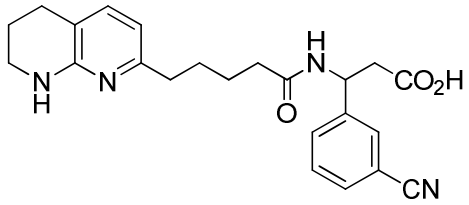
(2H, m), 3.09 (3H, s), 2.72 (2H, t, *J* 6.3 Hz), 2.63 (2H, d, *J* 7 Hz), 2.55 (2H, m), 2.27 (2H, m), 1.90 (2H, m), 1.65 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 178.6, 175.3, 156.44, 156.39, 151.3, 140.6, 139.6, 128.8, 128.7, 116.7, 112.1, 52.9, 45.2, 44.6, 42.4, 36.9, 36.8, 30.4, 27.3, 26.7, 22.1. HRMS (ESI$^+$): calculated for $C_{23}H_{30}N_3O_5S$ $[M + H]^+$: *m/z* 460.1901, found 460.1904. LCMS purity 100% (ELSD), 460 (MH^+).

(*RS*)-3-([1,1′-Biphenyl]-4-yl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid (31).



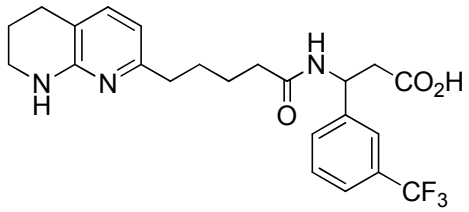
Colourless oil, yield 30 mg (44%); IR ($CHCl_3$) ν (cm^{-1}): 3049, 2868, 1654, 1508, 1192, 887; ^{1}H NMR δ_H (400 MHz, CD_3OD): 7.59–7.53 (4H, m), 7.44–39 (4H, m), 7.31 (1H, t, *J* 7.5 Hz), 6.42 (1H, d, *J* 7 Hz), 5.40 (1H, t, *J* 7.2 Hz), 3.41 (2H, m), 2.73 (2H, t, *J* 6.3 Hz), 2.66 (2H, d, *J* 7.2 Hz), 2.39–2.21 (4H, m), 1.90 (2H, m), 1.68 (4H, m); HRMS (ESI$^+$): calculated for $C_{28}H_{31}N_3O_3$ $[M + H]^+$: *m/z* 458.2438, found 458.2450; LCMS purity 100% (ELSD), 458 (MH^+).

(*RS*)-3-(3-Cyanophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (32).



Method B. Colourless gum, yield 19 mg, (29%); ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.72 (1H, s), 7.68 (1H, d, *J* 7.5 Hz), 7.57 (1H, d, *J* 7.5 Hz), 7.47 (1H, t, *J* 7.5 Hz), 7.14 (1H, d, *J* 7.5 Hz), 6.35 (1H, d, *J* 7.5 Hz), 5.30 (1H, t, *J* 7 Hz), 3.36 (2H, m), 2.69 (2H, m), 2.60 (2H, m), 2.50 (2H, m), 2.49 (2H, m), 1.89 (2H, m), 1.61 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 178.2, 175.3, 158.3, 157.2, 146.6, 138.7, 132.8, 131.8, 131.6, 130.5, 120.0, 115.6, 113.3, 112.3, 52.5, 45.1, 42.5, 37.8, 37.0, 30.7, 27.5, 26.7, 22.5; LRMS (ESI$^+$): *m/z* 407 $[M + H]^+$. LCMS purity 100% (ELSD), 407 (MH^+).

(*RS*)-3-(5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethylphenyl)-pentanamido)propanoic acid (33).



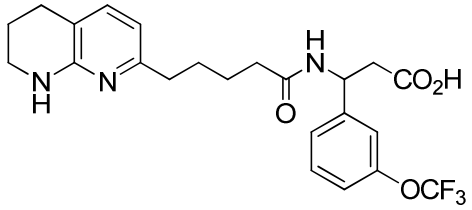
Method A. Colourless solid, yield 132 mg, (58%); mp 76 °C; IR (neat) ν (cm^{-1}) 3067, 2931, 2860, 1645, 1571, 1356, 1326, 1160, 1116, 1073; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.66 (1H, s), 7.62 (1H, d, *J* 7 Hz), 7.52-7.46 (2H, m), 7.23 (1H, d, *J* 7.3 Hz), 6.38 (1H, d, *J* 7.3 Hz), 5.38 (1H, t, *J* 7 Hz),

3.42 (2H, m), 2.73 (2H, m), 2.65 (2H, m), 2.57 (2H, m), 2.39−2.18 (2H, m), 1.95−1.84 (2H, m), 1.75−1.59 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 179.0, 175.2, 156.0, 155.7, 144.5, 139.8, 131.8 (q, J_{CF} 32 Hz), 131.6, 130.2, 125.9 (q, J_{CF} 272 Hz), 124.8 (q, J_{CF} 4 Hz), 124.4 (q, J_{CF} 4 Hz), 117.1, 112.0, 51.1, 43.8, 40.8, 35.3, 34.9, 28.7, 25.6, 25.0, 20.5. HRMS (ESI$^+$): calc'd for $C_{23}H_{27}F_3N_3O_3$ $[M + H]^+$: *m/z* 450.1999, found 450.2009. LCMS purity 100% (ELSD), 450 (MH^+).

(*S*)-3-(5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethylphenyl)-pentanamido)propanoic acid (33S).
Method A. Colourless solid, yield 85 mg, (60%); mp 120–122 °C; LCMS purity 100% (ELSD), 450 (MH^+).

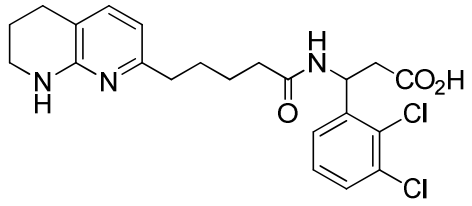
(*R*)-3-(5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethylphenyl)-pentanamido)propanoic acid (33R).
Method A. Colourless solid, yield 137 mg, (54%); mp 130–133 °C; LCMS purity 100% (ELSD), 450 (MH^+).

(*RS*)-3-(5-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)-3-(3-trifluoromethoxyphenyl) pentanamido)propanoic acid (34).



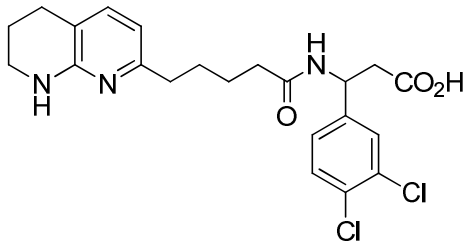
Method A. Yellow solid, yield 138 mg, (67%); IR ($CHCl_3$) ν (cm^{-1}) 3260, 2933, 1645, 1586, 1462, 1396, 1320, 1253, 1212. ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.41−7.35 (2H, m), 7.25 (2H, m), 7.11 (1H, br d, *J* 7.5 Hz), 6.41 (1H, d, *J* 7.3 Hz), 5.34 (1H, t, *J* 7.2 Hz), 3.41 (2H, t, *J* 5.5 Hz), 2.73 (2H, m), 2.65−2.52 (4H, m), 2.35−2.22 (2H, m), 1.90 (2H, m), 1.67 (4H, m); ^{13}C NMR (75 MHz; $(CD_3)_2SO$) δ_C ppm 172.5, 171.2, 157.2, 155.7, 151.4, 148.2, 147.2, 136.0, 129.8, 125.5, 118.8, 118.7, 112.3, 119.9, 49.7, 47.3, 42.9, 40.7, 35.4, 36.7, 26.0, 25.0, 21.5, (OCF_3 not observed owing to poor signal to noise ratio). HRMS (ESI$^+$): calc'd for $C_{23}H_{26}F_3N_3O_4$ ($[M + H]^+$), 466.1948; found, 466.1951. LCMS purity 100% (ELSD), 466 (MH^+).

(*RS*)-3-(2,3-Dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid (35).



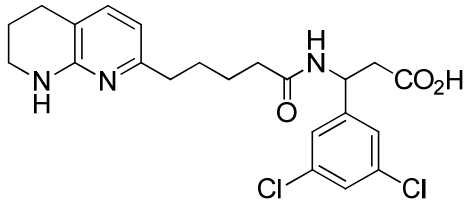
Method A. Colourless solid, yield 81 mg (83%); mp 160–161 °C; IR ($CHCl_3$) ν (cm^{-1}): 3294, 3003, 2937, 1665, 1599, 1509, 1391, 1118. ^{1}H NMR (270 MHz, CD_3OD) δ_H ppm 7.38 (2H, m), 7.20 (2H, m), 6.39 (1H, d, *J* 7 Hz), 5.62 (1H, dd, *J* 10.4 Hz, 5.2 Hz), 3.39 (2H, m), 2.73−2.48 (6H, m), 2.28 (2H, m), 1.88 (2H, m), 1.65 (4H, m). ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 178.1, 174.9, 156.3, 156.1, 149.4, 144.3, 142.7, 139.1, 129.8, 128.5, 127.4, 126.8, 111.8, 51.1, 42.7, 42.1, 38.9, 36.7, 30.1, 27.0, 26.3, 21.9. HRMS (ESI$^+$): m/z calcd for $C_{22}H_{26}Cl_2N_3O_3$ ($[M+H]^+$), 450.1346; found, 450.1353. LCMS purity 100% (ELSD), 450, 452, 454 (MH^+).

(*RS*)-3-(3,4-Dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (36).



Method A. Colourless solid, yield 6 mg (13%); IR ($CHCl_3$) ν (cm^{-1}) 3692, 3000, 1724, 1668; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.50 (1H, d, *J* 2 Hz), 7.41 (1H, d, *J* 8.3 Hz), 7.27 (1H, dd, *J* 8.3, 2 Hz), 7.24 (1H, d, *J* 7.3 Hz), 6.37 (1H, d, *J* 7.3 Hz), 5.27 (1H, t, *J* 7.0 Hz), 3.40 (2H, m), 2.71 (2H, m), 2.61−2.53 (4H, m), 2.31−2.20 (2H, m), 1.88 (2H, m), 1.66 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 173.6 (2C), 154.3, 153.7, 144.0, 138.5, 131.7, 130.2, 130.0, 128.4, 126.2, 115.8, 110.4, 50.6, 43.6, 40.8, 35.2, 34.7, 28.7, 25.6, 25.0, 20.3; LRMS (ESI^+) 450 $[M + H]^+$. LCMS purity 100% (ELSD), 450, 452, 454 (MH^+).

(*RS*)-3-(3,5-Dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (37).

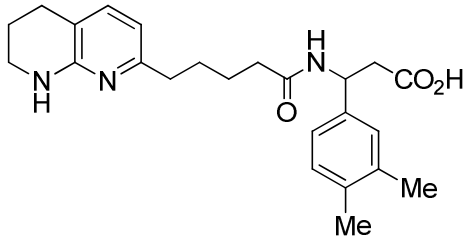


Method A. Colourless glass, yield 66 mg, (73%); IR ($CHCl_3$) ν (cm^{-1}) 3435, 3084, 3008, 2938, 2863, 2468, 1724, 1671, 1589, 1571, 1503, 1463, 1378, 1185, 1119, 859; ^{1}H NMR (400 MHz, CD_3OD) δ_H ppm 7.38−7.36 (2H, m), 7.29−7.24 (1H, m), 7.18 (1H, d, *J* 7.2 Hz), 6.37 (1H, d, *J* 7.2 Hz), 5.25 (1H, t, *J* 7.2 Hz), 3.45−3.37 (2H, m), 2.72 (2H, t, *J* 6.4 Hz), 2.59 (2H, d, *J* 7.2 Hz), 2.57−2.51 (2H, m), 2.32−2.21 (2H, m), 1.93−1.85 (2H, m), 1.70–1.63 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 177.1, 173.1, 155.8, 155.1, 147.3, 137.6, 134.5, 126.4, 125.1, 114.7, 110.6, 50.8, 43.5, 40.9, 35.7, 35.3, 28.9, 25.8, 25.1, 20.7; HRMS (ESI^+): calculated for $C_{22}H_{26}Cl_2N_3O_3$ $[M + H]^+$: *m/z* 450.1346, found 450.1348. LCMS purity 100% (ELSD), 450, 452, 454 (MH^+).

3-(3,5-Dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid, enantiomer 1,(37E1).
Method A. Colourless solid, yield 70 mg, (48%); mp 230 °C; LCMS purity 100% (ELSD), 450, 452, 454 (MH^+).

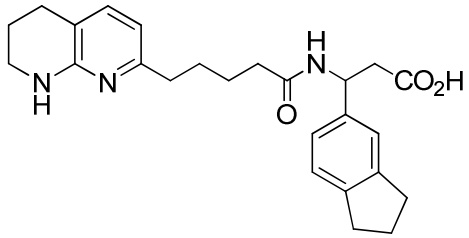
3-(3,5-Dichlorophenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid, enantiomer 2,(37E2).
Method A. Colourless solid, yield 50 mg, (31%); mp 236 °C; LCMS purity 100% (ELSD), 450, 452, 454 (MH^+). This compound was converted to the hydrochloride salt prior to biological testing, to improve aqueous solubility.

(*RS*)-3-(3,4-Dimethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (38).



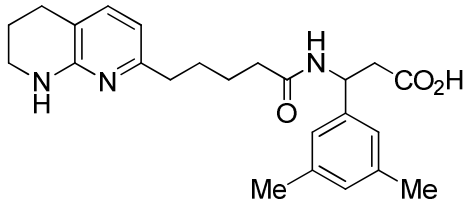
Method A. Colourless oil, yield 28 mg, (53%); IR ($CHCl_3$) ν (cm^{-1}) 3430, 3271, 3057, 2957, 2863, 1719, 1650, 1598, 1588. ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.23 (1H, d, *J* 7.3 Hz), 7.10 (1H, s), 7.02 (2H, m), 6.38 (1H, d, *J* 7.3 Hz), 5.24 (1H, t, *J* 6.2 Hz), 3.40 (2H, m), 2.72 (2H, t, *J* 6.2 Hz), 2.58 (4H, m), 2.27 (2H, m), 2.21 (3H, s), 2.20 (3H, s), 1.90 (2H, m), 1.66 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 174.9, 174.4, 152.9, 149.7, 145.8, 144.6, 142.9, 141.0, 125.7, 125.4, 123.6, 120.6, 111.8, 51.6, 42.3, 42.0, 36.5, 33.8, 33.5, 33.2, 29.3, 26.8, 26.1, 20.6; HRMS (ESI^+): calculated for $C_{24}H_{32}N_3O_3$ $[M + H]^+$: *m/z* 410.2438, found 410.2434**;** LCMS purity 98% (ELSD), 410 (MH^+).

(*RS*)-3-(Indan-4-yl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (39).



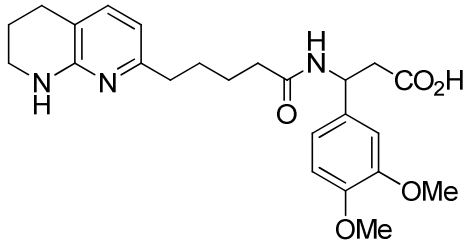
Method A. Viscous yellow oil, yield 25 mg, (28%); IR ($CHCl_3$) ν (cm^{-1}) 3414, 3306, 3006, 2937, 1644, 1589, 1463, 1405, 1118. ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.19 (1H, s), 7.08 (3H, m), 6.30 (1H, d, *J* 7.9 Hz), 5.25 (1H, t, *J* 7.0 Hz), 3.36 (2H, m), 2.84 (4H, m), 2.69 (2H, m), 2.60 (2H, d, *J* 7 Hz), 2.49 (2H, m), 2.23 (2H, m), 2.03 (2H, m), 1.87 (2H, m), 1.61 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 173.4, 172.9, 151.4, 148.2, 144.2, 143.1, 141.4, 139.5, 124.2, 123.9, 122.1, 119.1, 110.3, 50.1, 40.8, 40.5, 34.9, 32.3, 32.0, 31.7, 27.8, 25.2, 25.0, 24.5, 19.1. HRMS (ESI^+): calc'd for $C_{25}H_{32}N_3O_3$ $[M + H]^+$: *m/z* 422.2438, found 422.2426. LCMS purity 100% (ELSD), 422 (MH^+).

(*RS*)-3-(3,5-Dimethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid (40).



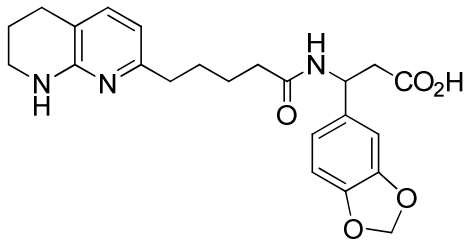
Method A. Yellow oil, yield 116 mg, (42%); IR ($CHCl_3$) ν (cm^{-1}) 3256, 2926, 2858, 1639, 1580, 1481, 1461, 1395, 1320, 1260. ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.09 (1H, d, *J* 7.5 Hz), 6.94 (2H, s), 6.80 (1H, s), 6.31 (1H, d, *J* 7 Hz), 5.20 (1H, t, *J* 7 Hz), 3.36 (2H, m), 2.68 (2H, m), 2.56 (2H, d, *J* 7 Hz), 2.50 (2H, m), 2.22 (2H, m and 6H, s), 1.87 (2H, m), 1.62 (4H, m). ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 177.6, 173.4, 157.1, 155.7, 142.9, 137.3, 137.3, 128.0, 123.9, 113.8, 110.7, 51.2, 44.2, 41.0, 36.5, 35.7, 29.2, 26.0, 25.3, 21.1, 20.0. HRMS (ESI^+): calcd. for $C_{24}H_{32}N_3O_3$ ($[M + H]^+$), 410.2438; found, 410.2448. LCMS purity 100% (ELSD), 410 (MH^+).

(*RS*)-3-(3,4-Dimethoxyphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid (41).



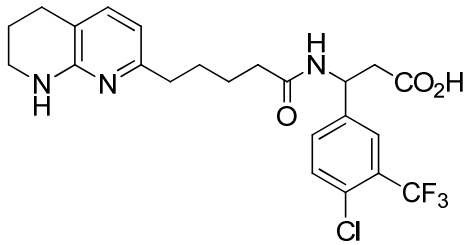
Method A. Colourless solid, yield 47 mg, (35%); mp 218–220 °C; IR ($CHCl_3$) ν (cm^{-1}) 3259, 2929, 1639, 1512, 1258, 1139; ^1H NMR (270 MHz, CD_3OD) δ_H ppm 7.22 (1H, d, *J* 7.3 Hz), 6.97 (1H, d, *J* 1.5 Hz), 6.90 (1H, dd, *J* 8, 1.5 Hz), 6.85 (1H, d, *J* 8 Hz), 6.36 (1H, d, *J* 7.3 Hz), 5.27 (1H, t, *J* 7.0 Hz), 3.79 (6H, s), 3.40 (2H, m), 2.72 (2H, t, *J* 6.0 Hz), 2.61−2.51 (4H, m), 2.25 (2H, m), 1.88 (2H, m), 1.65 (4H, m); ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 179.6, 174.9, 156.2, 155.9, 150.4, 149.5, 139.7, 137.6, 112.0, 117.0, 113.0, 112.0, 111.8, 56.7, 56.5, 52.6, 45.8, 42.4, 37.0, 36.6, 30.3, 27.2, 26.7, 22.0; LRMS (ESI^+): *m/z* 442 $[M + H]^+$. LCMS purity 100% (ELSD), 442 (MH^+).

(*RS*)-3-(Benzo[*d*][1,3]dioxol-4-yl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid (42).[13]



Method A. Colourless oil, yield 71 mg, (67%); ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.26 (1H, d, *J* 7.3 Hz), 6.88 (1H, d, *J* 1.6 Hz), 6.82 (1H, dd, *J* 8, 1.6 Hz), 6.71 (1H, d, *J* 8.5 Hz), 6.39 (1H, d, *J* 7.3 Hz), 5.88 (2H, s), 5.25 (1H, dd, *J* *7.9, 6.*6 Hz), 3.40 (2H, m), 2.72 (1H, m), 2.63−2.50 (4H, m), 2.32−2.18 (2H, m), 1.89 (2H, m), 1.65 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 178.1, 173.3, 154.0, 153.1, 147.7, 146.5, 138.7, 137.1, 119.3, 116.1, 110.4, 107.5, 106.6, 100.8, 51.0, 44.2, 40.7, 35.2, 34.4, 28.6, 25.6, 25.0, 20.2; LRMS (ESI^+) 454 $[M + Na]^+$. LCMS purity 100% (ELSD), 426 (MH^+).

(*RS*)-3-(3-Chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid (43).



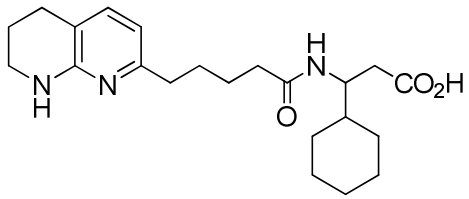
Method A. Colourless oil, yield 28 mg, (36%); IR ($CHCl_3$) ν (cm^{-1}) 3692, 2606, 3271, 2929, 1601, 1463, 1320, 1114; ^1H NMR (400 MHz, CD_3OD) δ_H ppm δ_H (400 MHz, CD_3OD): 7.75 (1H, s), 7.57 (1H, d, *J* 8.5), 7.48 (1H, d, *J* 8.5 Hz), 7.11 (1H, d, *J* 7.5 Hz), 6.32 (1H, d, *J* 7.5 Hz), 5.28 (1H, t, *J* 7 Hz), 3.37 (2H, m), 2.69 (2H, m), 2.63 (1H, dd, *J* 15, 7 Hz), 2.58 (1H, dd, *J* 15, 7 Hz), 2.50 (2H, m), 2.24 (2H, m), 1.87 (2H, m), 1.65−1.58 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 178.1, 175.4, 158.2,

157.1, 144.7, 138.7, 133.1, 132.6, 131.3, 129.0 (q, J_{CF} 30 Hz), 127.2 (q, J_{CF} 5 Hz), 124.4 (q, J_{CF} 272 Hz), 115.6, 112.3, 52.3, 45.1, 42.6, 37.8, 37.0, 30.9, 27.5, 26.7, 22.5; HRMS (ESI^+): calc'd for $C_{23}H_{26}ClF_3N_3O_3$ $[M + H]^+$: *m/z* 484.1615, found 484. 1581; LCMS purity 100% (ELSD), 484, 486 (MH^+).

3-(3-Chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid, enantiomer 1, (43E1)
Method A, Colourless oil, yield 45 mg, (52%); LCMS purity 100% (ELSD), 484, 486 (MH^+).

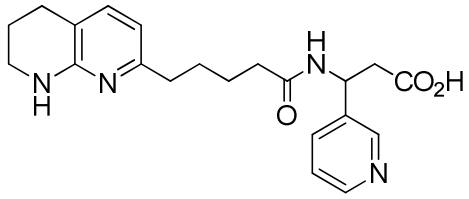
3-(3-Chloro-4-trifluoromethylphenyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl) pentanamido)propanoic acid, enantiomer 2, (43E2)
Method A. Colourless oil yield 96 mg, (91%); LCMS purity 100% (ELSD), 484, 486 (MH^+).

(*RS*)-3-(Cyclohexyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido) propanoic acid.



Method A (methanol solvent). Colourless gum, yield 164 mg, (88%); IR (state not recorded) ν (cm^{-1}) 3297, 2927, 2852, 1628, 1556; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.22 (1H, d, *J* 7.2 Hz), 6.41 (1H, d, *J* 7.2 Hz), 4.02 (1H, m), 3.35 (2H, m), 2.66 (2H, m), 2.51 (2H, m), 2.33 (1H, dd, *J* 14.5, 5 Hz), 2.25 (1H, dd, *J* 14.5, 8 Hz), 2.18 (2H, m), 1.84 (2H, m), 1.70 (4H, m), 1.61 (5H, m), 1.47 (1H, m), 1.23–1.07 (3H, m), 1.01–0.91 (2H, m); ^{13}C NMR (100 MHz, CD_3OD) δ_C ppm 179.1, 173.6, 155.1, 154.9, 137.8, 114.9, 110.5, 51.8, 42.3, 41.1, 39.5, 35.6, 29.5, 29.0, 28.7, 26.0, 25.9, 25.6, 25.1, 20.9; HRMS (ESI^+): calc'd for $C_{22}H_{33}N_3O_3$ $[M + H]^+$: *m/z* 388.2595, found 388.2600. LCMS purity 98% (ELSD), 388 (MH^+).

(*RS*)-3-(3-Pyridyl)-3-(5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamido)propanoic acid.



Method A. pale yellow oil, yield 121 mg, (46%); IR ($CHCl_3$) ν (cm^{-1}) 3413, 3003, 2939, 1673, 1600, 1508, 1390, 1119. ^1H NMR (270 MHz, CD_3OD) δ_H ppm 8.56 (1H, d, *J* 2 Hz), 8.37 (1H, dd, *J* 5, 2 Hz), 7.83 (1H, dt, *J* 8, 2Hz), 7.37 (1H, dd, *J* 8, 5 Hz), 7.15 (1H, d, *J* 7.3 Hz), 6.33 (1H, d, *J* 7.3 Hz), 5.32 (1H, t, *J* 5.3 Hz), 3.38 (2H, m), 2.66 (4H, m), 2.51 (2H, m), 2.24 (2H, m), 1.86 (2H, m), 1.63 (4H, m). ^{13}C NMR (67.5 MHz, CD_3OD) δ_C ppm 178.6, 175.6, 157.9, 157.2, 149.3, 148.8, 141.3, 139.3, 137.0, 125.5, 116.3, 112.5, 50.9, 45.3, 42.8, 37.8, 37.3, 30.9, 27.7, 27.0, 22.7. HRMS (ESI^-): calc'd for $C_{21}H_{25}N_4O_3$ $[M - H]^-$: *m/z* 381.1932, found 381.1921. LCMS purity 92% (ELSD), 383 (MH^+).

Assay details

Adhesion assays were performed broadly as described in (see reference 24 in the main paper), with the following amendments and/or specific details. The cell types used were K562-$\alpha_v\beta_3$, K562-$\alpha_v\beta_5$, K562-$\alpha_v\beta_6$ and K562-$\alpha_v\beta_8$. K562-$\alpha_v\beta_8$ cells have not been described previously, but were generated

and characterised in a similar manner to K562-$\alpha_v\beta_3$, K562-$\alpha_v\beta_5$ and K562-$\alpha_v\beta_6$ (see reference 24 in the main paper). 96-well plates were coated with 1 mg/well GST-LAPb$_1$ for K562-$\alpha_v\beta_3$, K562-$\alpha_v\beta_6$ & K562-K562-$\alpha_v\beta_8$ assays, or 0.25 mg/well vitronectin for K562-$\alpha_v\beta_5$ assays (both ligands as described in reference 24 in the main paper), and 3x10^5 cells per well were used in the assay. Adhesion occurred in the presence of 2 mM $MgCl_2$ as the divalent cation. Before cell addition, cells were labelled with a fluorescent marker (BCECF-AM, Life Technologies) according to the manufacturer's instructions (10 mM BCECF used for labelling 3x10^6 cells per ml). Cell adhesion was subsequently quantified by measuring well fluorescence (Ex 485 nm/Em 535 nM by Envision fluorescence plate reader, PerkinElmer) after removal of un-adhered cells by plate washing, where fluorescence is proportional to adhered cell number. For screening of compounds in dose-response mode, raw data were imported into ActivityBase software (IDBS, Guildford, Surrey), data were normalized according to plate high/low values (8 replicates of data with and without a 100% adhesion blocking concentration of a control compound) as percent inhibition, and individual curves were fitted to a four-parameter logistic equation. Appropriate constraints were applied around the minima (0% ± 30% inhibition), maxima (100% ± 30% inhibition), and Hill slope (0.5–5). A minimum Z' of >0 was applied to pass or fail individual plates.

C. Potential uses of pan α_v and $\alpha_v\beta_6$ antagonists

Although our focus here is IPF, recent data[14] also supports a pan α_v antagonist as being efficacious against a range of fibrotic diseases in animals, such as a carbon tetrachloride model of liver fibrosis and in a bleomycin model of pulmonary fibrosis. Various pan α_v compounds and antibodies have also been widely studied clinically particularly for various forms of cancer.[15,16]

Obtaining an $\alpha_v\beta_6$ antagonist of clinical quality may find use in other fibrotic diseases aside from IPF such as kidney fibrosis,[17] liver fibrosis,[14,18] potentially wound healing[14] and cancer.[19] As already mentioned, antagonists for $\alpha_v\beta_5$ may find a role in treating sepsis.[20]

D. Modelling Hypotheses

The protein sequences for integrin beta subunits of interest (β_1, β_3, β_5, β_6 and β_8) are available from the UniProt database[21] and these sequences were aligned using Muscle within Unipro UGENE (v1.13.2). The residues in the region where the aryl ring is likely to bind are listed (Table 1) based on the published $\alpha_v\beta_3$ crystal structure 1L5G.[22] These amino-acid differences are congruent with the SAR observed – namely aryl substituents having a significant effect on α_v integrin selectivity profiles.

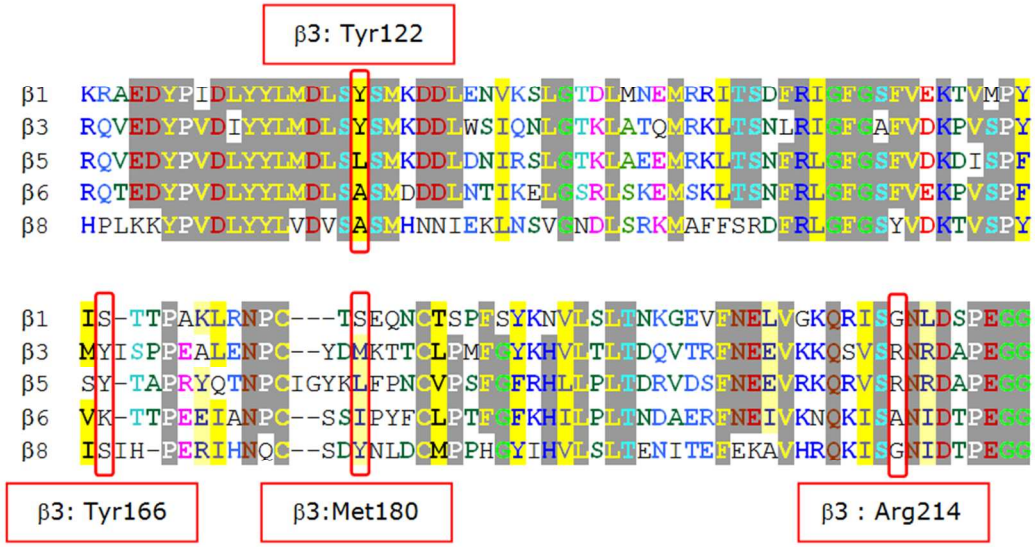


Table 1 Selected sequence alignments for β_1, β_3, β_5, β_6 and β_8 subunits with residues that change in the likely aryl binding region between β_3 and β_6 highlighted.

Key residues in the aryl group binding region that differ between $\alpha_v\beta_3$ and $\alpha_v\beta_6$ are also listed in Table 2. Compounds **42**, **43**, **37** and **33** – differing only in the nature of aryl substituent and with up to a log difference in binding to $\alpha_v\beta_3$ - were then modelled into the $\alpha_v\beta_3$ crystal structure in an attempt to rationalise potency differences. These compounds were selected for study because (i) they have the greatest difference in biological activity for $\alpha_v\beta_3$ and (ii) only the $\alpha_v\beta_3$ crystal structure is known.

$\alpha_v\beta_3$	$\alpha_v\beta_6$
Tyr122	Ala143
Tyr160	Lys187
Met180	Ile200
Arg214	Ala234

Table 2 Residues near the aryl substituent in $\alpha_v\beta_3$ and $\alpha_v\beta_6$

The X-ray structure of $\alpha_v\beta_3$ (PDB code: 1L5G) containing the cyclic pentapeptide ligand Arg-Gly-Asp-{D-Phe}-{N-methyl-Val} was used for modelling purposes. The cyclic peptide is positioned in the crevice between the β-propeller of αV domain and βA subunit of β3 domain with the Arg and Asp side chains positioned towards β-propeller and βA respectively. It is assumed here that this cyclic peptide binding pocket is also the binding site for RGD ligand mimetics.

Modelling was conducted using Maestro, Version 9.8 (Schrödinger, LLC, New York, NY, 2014). The Protein preparation wizard was used to assign ionization states and optimise hydrogen atoms. The binding site for docking was defined using the centroid of the co-crysallised cyclic peptide as starting coordinates for Glide's Grid receptor generation function. Docking was performed using Glide version 6.3 with Standard Precision[23-25]. The preferred poses of docked compounds were selected on the basis of favourable interactions between (i) the tetrahydronapthyridine with α_v-Asp218; (ii) the carboxylic acid motif and the β3-Asn215; and (iii) coordination of the acid with Mn^{2+} (MIDAS). In addition, the preferred poses display acceptable ligand geometry, good shape and surface complementarity with the $\alpha_v\beta_3$ receptor.

The predicted binding mode of **42** in the αvβ3 binding site is shown (Figure 1).

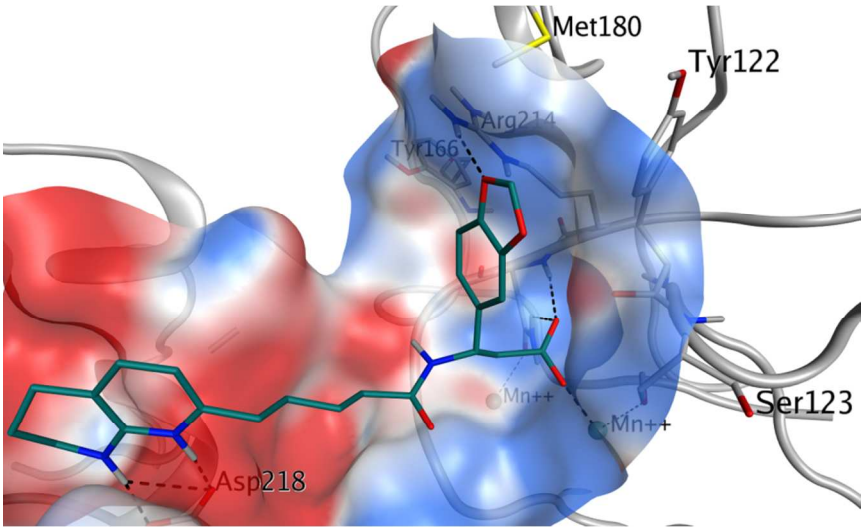


Figure 1. Docking pose for compound **42**. Receptor residues that are nearby the 3,4-dimethoxy aryl substituent are β3-Tyr 166, β3-Arg214, β3-Met180, β3-Tyr122, β3-Ser123. Electrostatic surface potentials are shown with red regions indicating negative potential and blue positive potential.

The tetrahydronaphthyridine moiety interacts with αV-Asp218 whilst the carboxylic acid interacts with the β3-Asn215 and manganese ion in the metal ion dependent adhesion site (MIDAS). Note also the extended alkyl chain. All the changes explored in the discussion that follow are differences in substitution on the carboaromatic and so it is assumed that only the aryl-acid region will show major differences in docking. Thus, zooming in on this region for **42** (Figure 2), there is a H-bond (2.3Å) between β3-Arg214 and one of the oxygen atoms of the cyclic catechol.

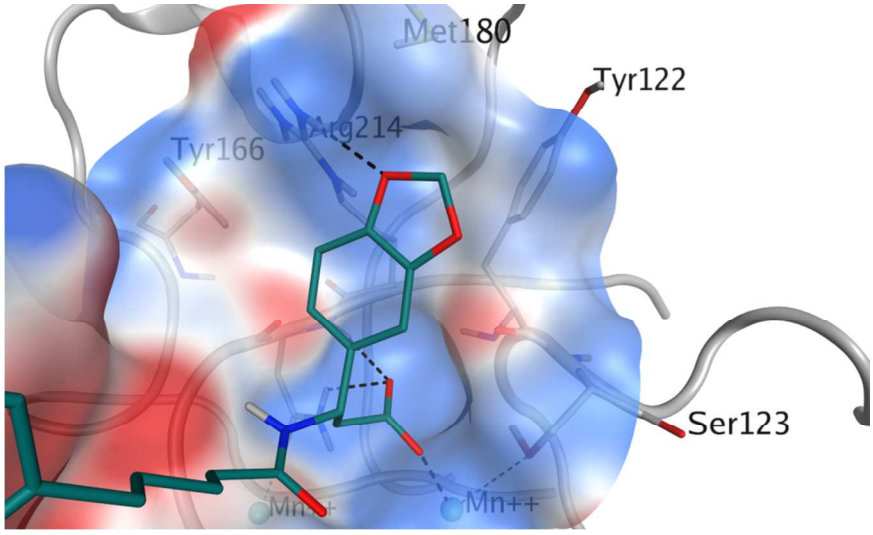


Figure 2. The cyclic catechol of **42** in the aryl binding region of $\alpha_v\beta_3$ with key residues labelled. Note the H-bond to Arg214 (dotted line).

Compound **42** is tenfold more potent than **43** ($\alpha_v\beta_3$ pIC_{50} 7.8 and 6.8 respectively). This may be rationalised by the inability of **43** to form a H-bond with Arg214 (Figure 3). Overlay comparisons of **42** with **37** (0.9 log difference in $\alpha_v\beta_3$ potency) (Figure 4), **42** with **33** (0.8 log difference in $\alpha_v\beta_3$ potency) (Figure 5) are shown and finally with all compounds overlaid together (Figure 6). In each case the decreased $\alpha_v\beta_3$ activity can be rationalised due to the absence of an H-bond. Note the 3-fluoro derivative **4** has a similar activity against $\alpha_v\beta_3$ (pIC_{50} 7.5) to **42** which may indicate the fluorine is acting as a hydrogen bond acceptor. Replacement of the fluorine with a methoxy (**22**, $\alpha_v\beta_3$ 7.4 (not shown in a figure)) or chlorine (**20** $\alpha_v\beta_3$ 7.1 (not shown in a figure)), both in theory capable of some level of electrostatic interaction - show decreased $\alpha_v\beta_3$ values although these are not significant. The presence of the CF_3 groups in **43** and **33** appears to favour positioning away from the Arg214 region (as viewed), suggesting there may be a spatial preference for smaller groups in the vicinity of Arg214. However, the combined overlays (Figure 6) indicate the complexity of predicting relatively minor changes in SAR from subtle structural shifts in the positioning of the aromatic ring and lipophilic group of the ligand. This is further complicated by changes in the binding pocket itself (not observable in Figure 6) from the potential mobility of the specificity-determining loop.[22]

Although a homology model for $\alpha_v\beta_6$ has been described in the literature (see main text) the coordinates have not been released. Obtaining access to a homology model is clearly a major objective for the next phase of our studies but is beyond the scope of this current work. In addition the somewhat idiosyncratic nature of the SAR (see the Table in the main text) may suggest rational explanation of aryl substitution SAR and predicting activity of a particular substituent may not be straightforward.

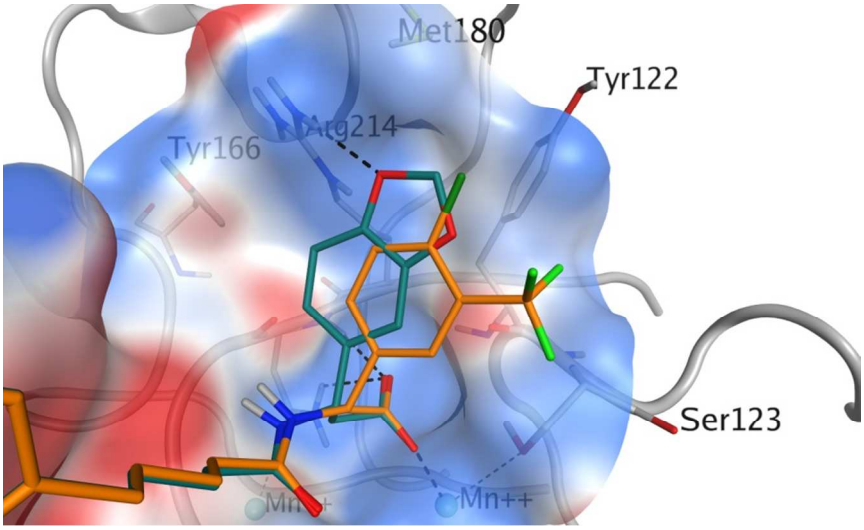


Figure 3 Overlay of the aryl from **42** (green, $\alpha_v\beta_3$ pIC_{50} 7.8) and **43** (orange, $\alpha_v\beta_3$ pIC_{50} 6.8)

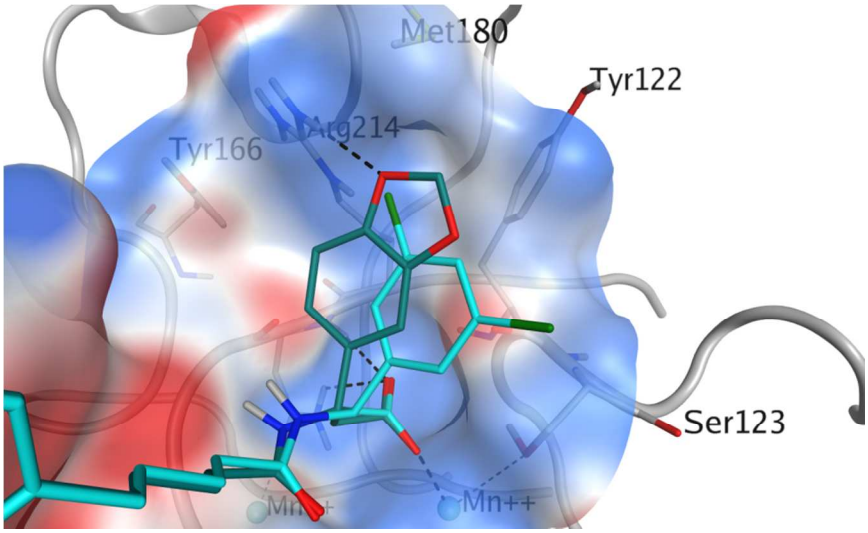


Figure 4 Overlay of the aryl from **42** (green $\alpha_v\beta_3$ pIC_{50} 7.8) and **37** (cyan, $\alpha_v\beta_3$ pIC_{50} 6.9)

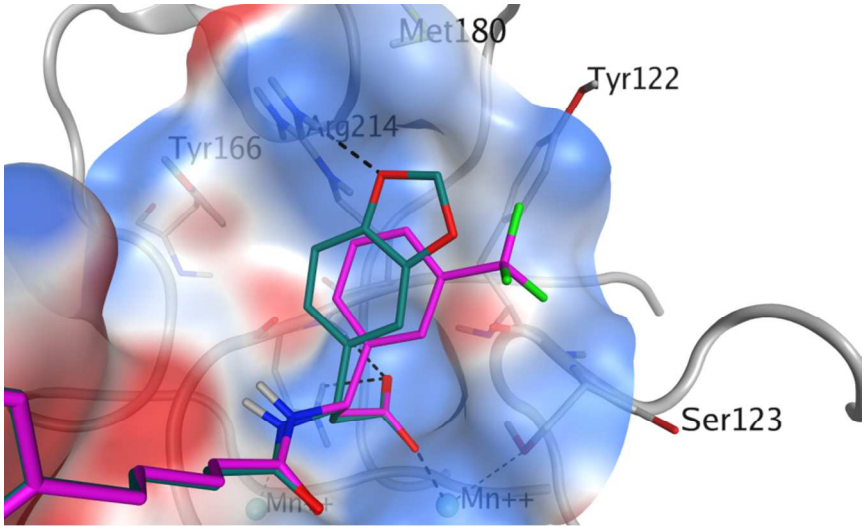


Figure 5 Overlay of the aryl from **42** (green, $\alpha_v\beta_3$ pIC_{50} 7.8) and **33** (magenta, $\alpha_v\beta_3$ pIC_{50} 7.0)

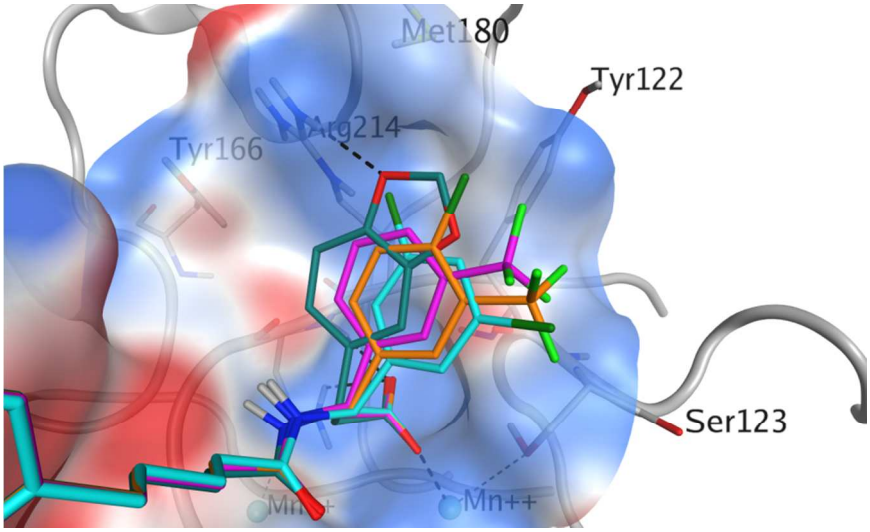


Figure 6 Overlay of **42** (green), **43** (orange), **37** (cyan) and **33** (magenta) together.

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